Synthesis and Biological Evaluation of New 1,2-Dihydro-4-hydroxy-2-oxo-3-quinolinecarboxamides for Treatment of Autoimmune Disorders: Structure−Activity Relationship

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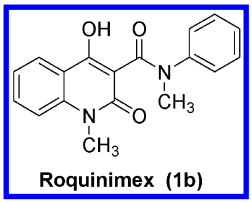
Roquinimex-related 3-quinolinecarboxamide derivatives were prepared and evaluated for treatment of autoimmune disorders. The compounds were tested in mice for their inhibitory effects on disease development in the acute experimental autoimmune encephalomyelitis model and selected compounds in the beagle dog for induction of proinflammatory reaction. Structure−activity relationships are discussed. Compound **8c**, laquinimod, showed improved potency and superior toxicological profile compared to the lead compound roquinimex (**1b**, Linomide) and was selected for clinical studies (currently in phase II).

Introduction

Multiple sclerosis (MS) is a common autoimmune disease that affects the central nervous system (CNS). The etiology of the disease is unknown, but the pathophysiological mechanism is similar to other autoimmune diseases where there is an infiltration of mononuclear cells into the target tissue. Although the driving autoantigen has not been defined, a number of candidates have been postulated. Thus, myelin basic protein, proteolipid protein, and myelin oligodendrocyte globulin are known to induce acute or chronic experimental autoimmune encephalomyelitis (EAE) in genetically susceptible animals by active immunization. The disease in these experimental models is similar to MS in human with cell infiltration and demyelination. A number of immune-modulating compounds used in MS therapy have been documented for efficacy in this animal model, and therefore, the EAE model has been considered as a reliable tool in screening for new drugs.[1]

Proinflammatory cytokines most probably contribute to the autodestruction and demyelination in MS. Thus, TNF-α production correlates positively with MS exacerbation while IL-10 and TGF-β correlate with MS remission.[2] Also, in animal models of MS the cytokine spectrum and production seem to to be a major determinant for the disease outcome. Roquinimex (Linomide, Chart 1), a synthetic immunomodulator, has been shown to inhibit both acute and chronic relapsing EAE in both rats and mice.[3−6] Interestingly, it has been shown that roquinimex dose-dependently inhibited EAE in the rat by suppression of the proinflammatory cytokines IFN-γ and TNF-α as well as up-regulation of IL-4, IL-10, and TGF-β.[7,8] On the basis of these experimental observations, it has been hypothesized that roquinimex exerts an immunomodulatory effect resulting in a change from a Th1 type of cytokine profile into a regulatory type of immune response also relevant for treatment of human MS.

Chart 1



Roquinimex (1b)

In phases II and III clinical trials in MS, Linomide (roquinimex) treated patients had fewer clinical relapses and showed fewer active MR images in comparison to those on placebo.[9,10] However, the phase III trial had to be discontinued because of unacceptable toxicity.[9] The mechanism of action of these adverse effects is unknown, but preclinical studies in a dog model indicate that roquinimex induces a proinflammatory reaction, observed as an increase in the plasma level of acute-phase reactants and inflammation on serosal surfaces.

The objective of the present study was to optimize the lead compound roquinimex by chemical modifications for determining structure−activity relationship (SAR) in order to obtain more efficient compounds for treatment of MS. To accomplish this, a screening program was established in order to select new quinoline-based compounds with an improved therapeutic window. The acute EAE model was used in screening for structure-related efficacy, and a selected number of active compounds were screened for structure-related proinflammatory effects in the beagle dog model.

Chemistry

In the present study, we focused on optimizing the lead structure roquinimex (**1b**) via aromatic substitution (R_1 and R_4, Figure 1) and variation of alkyl substituents on the nitrogens (R_2 and R_3, Figure 1).

Synthesis. The syntheses of the target compounds required access to a number of different substituted 3-quinolinecarboxylic ester derivatives (**1a**−**34a**). These

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Table l. Yields and Spectroscopic Data of the 3-Quinolinecarboxylic Ethyl Esters

					^{1}H signals ($CDCl_3$), δ, ppm				
compd	R_1	R_2	method	yield, %[a]	5	6	7	8	substituent[c] R_1 or R_2
1a	H	CH_3	B	86	8.13 d	7.23 t	7.66 t	7.27 d	
2a	6-MeO	H	B	14		7.20−7.45 m (3H)[b]			3.38 s (3H)[b]
3a	H	*c*-C_3H_5	B	59	8.06 d	7.15 t	7.58 t	7.70 d	0.8 m, 1.2 m, 2.8 m (5H)
4a	H	C_5H_5	B	54	8.18 d	6.60 d (2H), 7.18−7.27 m (3H), 7.39−7.58 (3H)			
5a	5-CH_3	CH_3	B	88		7.09 d	7.35 t	7.24 d	2.82 s (3H)
6a	5-C_2H_5	CH_3	B	61		7.04 d	7.53 t	7.18 d	1.28 t, 3.25 q (5H)
7a	5-F	CH_3	B	54		6.90 dd	7.58 dt	7.08 d	
8a	5-Cl	CH_3	B	74		7.27 d	7.49 t	7.23 d	
9a	5-Br	CH_3	D	48		7.52 d	7.37 t	7.26 d	
10a	5-CF_3	CH_3	D	40		7.58 m	7.71 m	7.71 m	
11a	5-MeO	CH_3	B	74		6.70 d	7.55 t	6.92 d	3.96 s (3H)
12a	5-EtO	CH_3	D	42		6.72 d	7.57 t	6.92 d	1.50 t, 4.15 q (5H)
13a	5-(pF-PhO)	CH_3	D	56		6.59 d	7.50 t	7.01 d	6.95 m (4H)
14a	5-MeS	CH_3	D	42		6.98 d	7.52 t	7.05 d	2.48 s (3H)
15a	5-NO_2	CH_3	B	78		7.47 d	7.72 t	7.21 d	
16a	5-$N(CH_3)_2$	CH_3	B	88		7.17 d	7.54 t	7.21 d	2.78 s (6H)
17a	5-OCH_2O-6	CH_3	C	41			6.71d	7.14 d	6.17 s (2H)
18a	6-CH_3	CH_3	A	58	7.93 s		7.46 d	7.18 d	2.41 s (3H)
19a	6-C_2H_5	CH_3	A	54	7.97 s		7.51 d	7.22 d	1.27 t, 2.72 q (5H)
20a	6-F	CH_3	B	40	7.82 dd		7.39 ddd	7.27 d	
21a	6-Cl	CH_3	A	35	8.14 s		7.63 d	7.26 d	
22a	6-CF_3	CH_3	C	81	8.26 s		7.84 dd	7.48 d	
23a	6-MeO	CH_3	A	85	7.56 d		7.28 dd	7.22 d	3.88 s (3H)
24a	6-EtO	CH_3	A	63	7.54 d		7.27 dd	7.22 d	1.46 t, 4.10 q (5H)
25a	6-CF_3O	CH_3	A	10	8.02 s		7.52 d	7.32 d	
26a	6-$N(CH_3)_2$	CH_3	B	44	7.35 s		7.19 s	7.19 s	2.98 s (6H)
27a	7-CH_3	CH_3	A	17	8.02 d	7.04 d		7.07 s	2.48 s (3H)
28a	7-Cl	CH_3	B	83	8.08 d	7.19 d		7.28 s	
29a	7-CF_3	CH_3	C	90	8.29 d	7.47 d		7.52 s	
30a	7-MeO	CH_3	A	46	8.08 d	6.81 d		6.67 s	3.93 s (3H)
31a	7-PhO	CH_3	A	67	7.90 d[b]	6.53 d[b]		6.74 s[b]	7.01−7.39 m (5H)[b]
32a	8-F	CH_3	C	45	7.96 d	7.14 dt	7.36 dd		3.8 d
33a	8-CF_3	CH_3	B	35	8.37 d	7.31 t	8.00 d		
34a	8-MeO	CH_3	B	49	7.60 d	7.20 t	7.32 d		3.91 s (3H)

[a] Yields are calculated from starting material depicted in Schemes 1−4. [b] NMR solvent was DMSO-d_6. [c] Representative signals: −N−CH_3, 3.6 ppm; OCH_2, 4.5 ppm; CH_3, 1.5 ppm ($CDCl_3$).

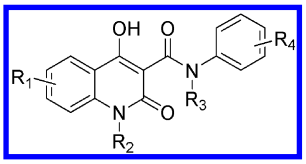


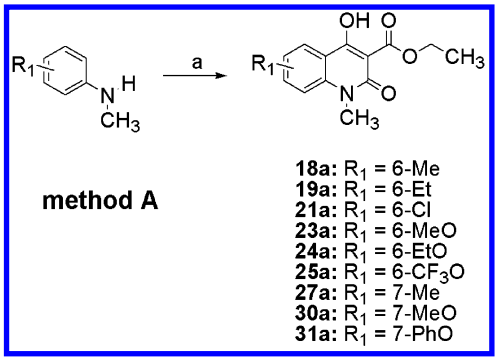
Figure 1. Structural modifications of the lead compound roquinimex (**1b**).

were prepared by methods outlined in Schemes 1−4, and the yields along with spectroscopic data are listed in Table 1.

The 3-quinolinecarboxylic ester derivatives **18a**, **19a, 21a**, **23a-25a**, **27a**, **30a**, **31a** were prepared by heating the appropriate *N*-methylaniline with triethyl methanetricarboxylate[11] in Dowterm A at 220 °C (method A, Scheme 1). Para-substituted anilines yielded the 6-substituted ester derivatives, while the meta-substituted anilines gave exclusively the 7-substituted derivatives. This method involves few synthetic steps and worked well for electron-rich anilines such as methoxyanilines, but it was impractical as a general method because of low yields for other substituents.

A more general method with overall high yields but with more synthetic steps is method B (Scheme 2). Commercially available anthranilic acids were treated with phosgene to give corresponding isatoic anhydrides.[12] These were N-alkylated with iodomethane in the presence of sodium hydride in dimethylformamide (when R_2 = methyl; Table 1). The isatoic anhydride derivatives were then condensed with ethyl malonate[13]

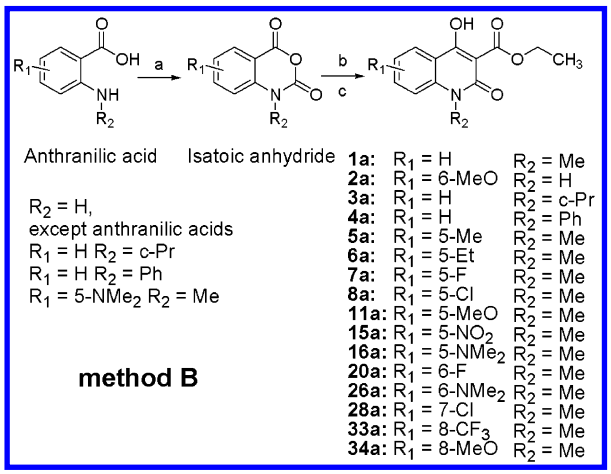
Scheme 1[a]



[a] Reagents and conditions: (a) triethyl methanetricarboxylate, Dowterm A, 220 °C, 3 h.

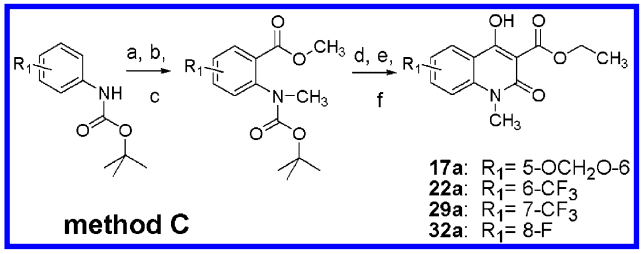
to give 3-quinolinecarboxylic ester derivatives **1a**, **2a**, **4a**, **5a**, **7a**, **8a**, **20a**, **28a**, **33a**, **34a**. Anthranilic acids, which are not commercially available, were prepared using known or modified literature procedures and converted to 3-quinolinecarboxylic esters in the same way. Thus, nitroisatoic anhydride used in the preparation of ester **15a** was obtained by oxidation of protected 2-methyl-3-nitroaniline, 6-ethylanthranilic acid[14] (ester **6a**) by oxidation of 4-ethylisatin, and 5-dimethylaminoanthranilic acid[15] (ester **26a)** by reductive alkylation of 5-amino-2-nitrobenzoic acid. The *N*-cyclopropyl-, 6-methoxy-, and 6-(dimethylamino)anthranilic acids used for the synthesis of esters **3a**, **11a**, and **16a** were prepared by hydrolysis of corresponding benzonitriles.

Scheme 2[a]



[a] Reagents and conditions: (a) phosgene, dioxane; (b) when R_2 = Me, MeI, NaH, DMF; (c) NaH, diethyl malonate, DMF, 85 °C, 5 h.

Scheme 3[a]



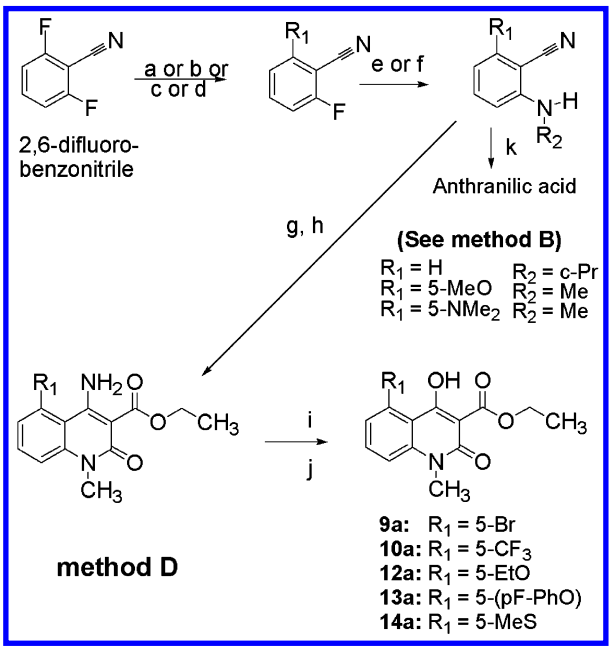
[a] Reagents and conditions: (a) di-*tert*-butyl dicarbonate, THF, reflux; (b) *t*-BuLi, THF, −40 °C, when R_1 = 5-OCH_2O-6, *sec*-BuLi; (c) MeI, NaH, DMF; (d) HCl/methanol; (e) ethyl malonylchloride, NEt_3, CH_2Cl_2; (f) NaOEt, ethanol.

The substituted benzonitriles were obtained by nucleophilic displacement, which is further explored in method D.

Ortho-directed metalation was applied successfully for the preparation of some anthranilic acid (method C, Scheme 3). The anilines were *t*-Boc protected and metalated with *t*-BuLi at −40 °C.[16] Quenching of these metalated intermediates with dry ice gave pure *N*-*t*-Boc protected anthranilic acids. These derivatives were then alkylated using iodomethane and base followed by deprotection of the *t*-Boc group and afforded the corresponding N-methylated anthranilic acid esters. These could then easily be treated with ethyl malonylchloride followed by cyclization to give the 3-quinolinecarboxylic esters **17a**, **22a**, **29a**, and **32a** in good yields.

An alternative approach, especially versatile for 3-quinolinecarboxylic esters substituted in the 5-position, was carried out by introduction of the 5-substituents by nucleophilic aromatic substitution (method D, Scheme 4). Starting from commercially available 2,6-difluorobenzonitrile, substituents such as methoxy, dimethylamino, and thiol were introduced selectively by monosubstitution of one of the fluoro groups. The other fluoro group was then at slightly elevated temperature replaced by a methylamino group. Attempts to hydrolyze the nitrile group to the carboxylic acid functionality for these derivatives were, however, quite a challenging task. Since the nitrile group was surrounded with two ortho groups, the hydrolysis was hampered by steric reasons. The intermediate carboxamide was easily formed, but the yield of carboxylic acid was low because

Scheme 4[a]

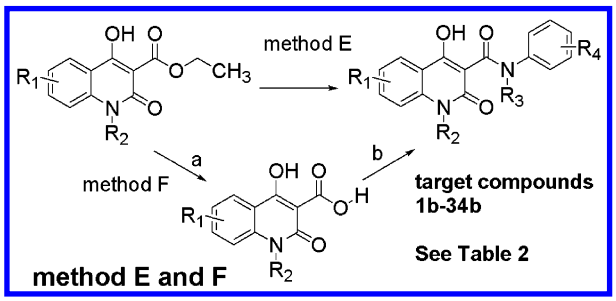


[a] Reagents and conditions: (a) (1) sodium sulfide, DMF, (2) MeI, NaH, DMF; (b) NaOMe, methanol; (c) NaOEt, ethanol; (d) dimethylamine, 2-propanol, 110 °C; (e) methylamine, 2-propanol, 110 °C; (f) cyclopropylamine, 2-propanol, 110 °C; (g) ethyl malonylchloride, NEt_3, CH_2Cl_2; (h) NaOMe, methanol; (i) MeI, NaH, THF, reflux; (j) HCl/ethanol, 80 °C; (k) hydrolysis when R_1 = H, R_2 = *c*-Pr, KOH/aqueous ethanol, reflux, 48 h, yield 34% when R_1 = MeO, R_2 = Me, KOH/aqueous glycol, 145 °C, 8 h, yield 60% when R_1 = NMe_2, R_2 = Me, aqueous H_2SO_4, 120 °C 3 h, yield 42%.

of competing decarboxylation of the formed carboxylic group. Several methods were evaluated, involving acidic and alkaline hydrolysis, and moderate yields were obtained for the 6-methoxy- and 6-(dimethylamino)-anthranilic acids. A better alternative was to proceed by amidification of the aniline nitrogen position with ethyl malonylchloride. The intermediates were then cyclized as for the derivatives in Scheme 3. The NH_2 group in the 4-position was alkylated to transform it into a better leaving group. Acidic hydrolysis yielded the 3-quinolinecarboxylic esters **12a** and **14a** in overall good yields. Esters **10a** and **13a** were prepared with this method from the commercially available 2-fluoro-6-trifluoromethylbenzonitrile and 2-fluoro-(*p*-fluorophenoxy)benzonitrile. Ester **9a** was prepared from 2-amino-6-fluorobenzonitrile by diazotation, followed by copper-assisted bromination.[17]

Two methods were employed for the preparation of the target 3-quinolinecarboxamides derivatives **1b**−**34b** as depicted in Scheme 5. Amidification could be performed either by direct condensation of the 3-quinolinecarboxylic ester derivative with the appropriate aniline or by acidic cleavage of the ester into a 3-quinolinecarboxylic acid followed by amide coupling.[18] In the first method, the 3-quinolinecarboxylic ester derivative was heated with the N-alkylated aniline in dry toluene while the formed ethanol is distilled off. The method works especially well for electron-rich N-alkylated anilines (e.g., unsubstituted anilines or anilines with electron-donating groups). When this methodology was used, it was important to prevent moisture from entering the reaction mixture, which would otherwise result in contamination of the product with byproducts. In the second method the 3-quinolinecarboxylic ester was first

Scheme 5[a]



[a] Reagents and conditions: method E; N-alkylated aniline, toluene, azeotropic distillation, 4−6 h; method F; (a) HCl in HOAc, 60 °C, 6 h; (b) N-alkylated aniline and $NEt_3/SOCl_2$, 0−5 °C, 4 h.

hydrolyzed to acid by cleavage in anhydrous HCl/acetic acid solution and then treated with thionyl chloride/triethylamine in the presence of the appropriate N-alkylated aniline. The second coupling method was more general than the direct ester-coupling method and worked well even for N-alkylated anilines substituted with electron-withdrawing groups. All the N-alkylated anilines used in this study were either commercially available or prepared by N-alkylation of commercially available anilines.[19]

The physicochemical properties of the obtained target 3-quinolinecarboxamides could be characterized as slightly acidic compounds with pK_a values typically in the range 4.2−5.0. They are readily water-soluble and chemically stable in buffered aqueous solutions at neutral or alkaline pH (solubility of >1 mg/mL). However, in their neutral protonated form, the target compounds are generally unstable in solution and could therefore not be purified by recrystallization. Melting point determinations were excluded because of decomposition during heating. More data on the properties of 3-quinolinecarboxamides will be presented in due course.

Results and Discussion

Inhibition of Disease Development in Acute Experimental Autoimmune Encephalomyelitis (aEAE) Induced in SJL/N Mice. (a) Dose-Related Inhibition of aEAE by the Lead Compound Roquinimex. Roquinimex (**1b**), the lead structure in the present study, dose-dependently inhibits disease development in the aEAE mouse model.[5,6] In Figure 2, it can be seen that onset of clinical symptoms in the control group appears at day 9 after immunization. There is a progressive disease development to the end of the experimental period. Roquinimex treatment dose-dependently decreased the severity of the disease. At the highest dose tested (25 (mg/kg)/day), there was almost a complete inhibition of clinical symptoms.

(b) Screening for a Structure−Activity Relationship (SAR) of New Compounds in the aEAE Model. The synthesized 3-quinolinecarboxamide derivatives were tested for their ability to inhibit aEAE in mice following treatment at different doses. Treatment was initiated 3 days after immunization and continued with daily treatments: days 3−7 and 10−12. The mean clinical score for days 9−14 was calculated for each animal and used to determine the therapeutic effect of the tested compounds. Disease development for each animal was compared with the control group (vehicle treated) and is presented as the percent inhibition of

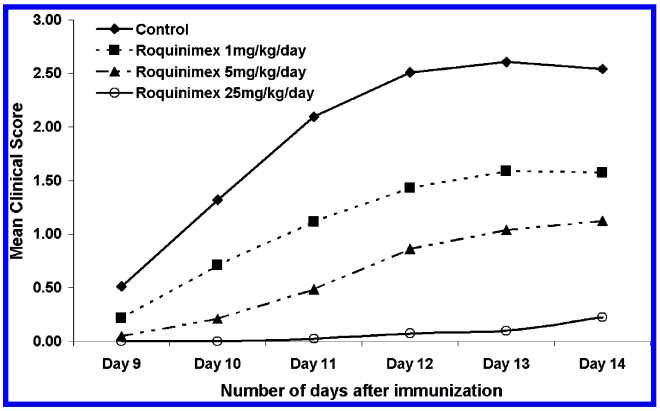


Figure 2. Dose-related inhibition of aEAE development in female SJL/N mice by daily treatment (from day 3 pi) with various doses of roquinimex (**1b**). Control mice received vehicle alone (n = 487 mice). Results from ABR-212616 treated mice are obtained from several experiments: 1 (mg/kg)/day (n = 223 mice), 5 (mg/kg)/day (n = 375 mice), and 25 (mg/kg)/day (n = 40 mice).

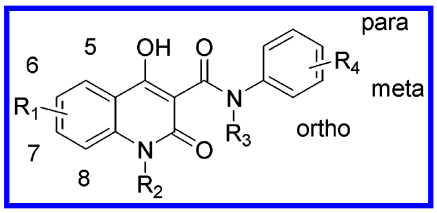
the mean clinical score. Table 2 summarizes the screening data for the various test compounds.

Structure−Activity Relationship aEAE. To explore the structure−activity relationship for this series of 3-quinolinecarboxamides, we have systematically varied the aromatic substitution with regard to substituent classes and positions. With the aim to modify in a systematic manner, we have selected substituents from substituent classes as defined by Alluni et al.[20] In their work a large number of aromatic substituents were clustered by multivariate data analysis according to their physicochemical properties, describing steric, electronic, and lipophilic properties considered to be relevant to protein−ligand interactions,[21] to give four substituent classes, i.e., alkyls (e.g., Me, Et, Ph), halogens (F, Cl, Br), acceptors (CF_3, NO_2), and donors (OMe, NMe_2).

Consequently, in the first stage of exploring the SAR, we decided to study the influence of a substituent in the 5-, 6-, 7-, and 8-position of the quinoline ring (R_1, Table 2) by introducing substituents from the four classes, compounds **5b**, **8b**, **10b**, **11b**, **18b**, **21b**, **22b**, **23b**, and **27b**−**34b**. The screening results of the studied compounds clearly demonstrated that the position of a substituent was very important; i.e., the aEAE potency was enhanced with the introduction of substituents to the 5- and 6-position while it did not contribute to potency in the 7- and 8-position, compared to the unsubstituted roquinimex (**1b**). However, analysis of the substituent effects in the 5- and 6-position did not distinguish between activity and substituent classes. For this reason a number of diverse substituents from the classes were further introduced to the positions associated with high potency, i.e., positions 5 and 6, compounds **12b**−**16b**, **20b**, **24b**−**26b**. The result showed that all 5-substituted derivatives, except **13b**, demonstrated increased potency when compared to roquinimex (**1b**). Similar substituent effects, but with less impact on activity, were observed in the 6-position. Disubstitution in the 5- and 6-position with introduction of a methylenedioxy ring **17b** did not further enhance activity compared to monosubstitution.

The observed substituent effects in the 5- or 6-position might be attributed to the steric factor. Introduction of

Table 2. Substituted 3-Quinolinecarboxamides and Their Effects on aEAE Development in SJL/N Mice



compd	R_1	R_2	R_3	R_4	prep method	yield, %[a]	dose, (mg/kg)/day[b] 0.2	1	5	administration[c]
1b	H	CH_3	CH_3	H	E	83	35 ± 30 (6)	43 ± 24 (29)	71 ± 21 (49)	po/sc
2b	6-MeO	H	CH_3	*p*-F	F	47	nd	nd	in.	sc
3b	H	*c*-C_3H_5	CH_3	*p*-MeO	F	58	nd	in.	in.	po/sc
4b	H	C_6H_5	CH_3	H	F	80	nd	nd	in.	sc
5b	5-CH_3	CH_3	CH_3	H	F	74	95	100	97	po/sc
5c	5-CH_3	CH_3	C_2H_5	H	E	76	in. (4)	65 ± 12 (4)	85 ± 01 (2)	po
6b	5-C_2H_5	CH_3	C_2H_5	H	F	85	81 ± 10 (3)	100 ± 0 (3)	nd	po
7b	5-F	CH_3	C_2H_5	H	E	78	nd	60	nd	po
8b	5-Cl	CH_3	CH_3	H	F	77	91 ± 12 (2)	99 ± 08 (2)	100 (4)	po/sc
8c	5-Cl	CH_3	C_2H_5	H	F	79	66 ± 24 (16)	92 ± 15 (53)	96 ± 15 (3)	po/sc
8d	5-Cl	CH_3	*n*-C_3H_7	H	F	54	49 ± 36 (3)	94± 7 (4)	100	po
8e	5-Cl	CH_3	*i*-C_3H_7	H	F	72	in. (2)	54 ± 26 (4)	70	po
8f	5-Cl	CH_3	$CH_2CH_2{=}CH_2$	H	F	68	nd	59 ± 37 (4)	81 ± 15 (3)	po
9b	5-Br	CH_3	C_2H_5	H	F	74	57 ± 23 (2)	95 ± 3 (2)	nd	po
10b	5-CF_3	CH_3	CH_3	H	E	90	nd	99	100	po
10c	5-CF_3	CH_3	C_2H_5	H	E	69	49	80	nd	po
11b	5-MeO	CH_3	CH_3	H	E	83	79 ± 14 (4)	95 ± 52 (4)	96 ± 4 (3)	po/sc
11c	5-MeO	CH_3	C_2H_5	H	E	79	69 ± 11 (4)	73 ± 6 (4)	86 ± 11 (4)	po/sc
11d	5-MeO	CH_3	CH_3	*o*-F	E	61	94	82 ± 18 (2)	100	po
11e	5-MeO	CH_3	CH_3	*o*,*o*′-F_2	E	83	28	43	nd	po
11f	5-MeO	CH_3	CH_3	*o*,*m*-F_2	F	69	in.	in.	nd	po
11g	5-MeO	CH_3	CH_3	*o*,*m*′-F_2	F	84	62	90 ± 10 (2)	95	po
11h	5-MeO	CH_3	CH_3	*o*,*p*-F_2	F	75	76 ± 6 (2)	88 ± 10 (2)	nd	po
11i	5-MeO	CH_3	CH_3	*o*-Cl	F	72	in.	50	68	po
11j	5-MeO	CH_3	CH_3	*o*-MeO	F	59	in.	in.	nd	po
11k	5-MeO	CH_3	CH_3	*m*-Cl	E	82	54	85	71 ± 6 (2)	po
11l	5-MeO	CH_3	CH_3	*m*-CF_3	F	71	38	60	84 ± 10 (2)	po
11m	5-MeO	CH_3	CH_3	*m*-MeO	E	47	35	90	85 ± 16 (2)	po/sc
11n	5-MeO	CH_3	CH_3	*m*-PhO	E	80	47	63 ± 27 (2)	90 ± 10 (2)	po
11o	5-MeO	CH_3	CH_3	*p*-F	F	71	92	nd	93	po/sc
11p	5-MeO	CH_3	CH_3	*p*-Cl	E	50	77	70	89 ± 16 (2)	po/sc
11q	5-MeO	CH_3	CH_3	*p*-CF_3	E	60	60 ± 17 (2)	84 ± 4 (2)	98 ± 2 (2)	po
11r	5-MeO	CH_3	CH_3	*p*-MeO	E	89	78	84	nd	po
12b	5-EtO	CH_3	CH_3	H	F	32	44	40 ± 17 (3)	76 ± 34 (2)	po
13b	5-(pF-PhO)	CH_3	CH_3	H	E	39	nd	in.	in.	po
14b	5-MeS	CH_3	CH_3	H	E	21	94 ± 2 (2)	100 (3)	100	po
14c	5-MeS	CH_3	C_2H_5	H	F	85	51 ± 14 (2)	73 ± 11 (2)	99	po
15b	5-NO_2	CH_3	CH_3	H	F	62	46	96	100	po
16b	5-$N(CH_3)_2$	CH_3	CH_3	H	E	71	58	93	100	po
17b	5-OCH_2O-6	CH_3	C_2H_5	H	F	83	58 ± 13 (3)	75 ± 24 (5)	99 ± 1 (2)	po
18b	6-CH_3	CH_3	CH_3	H	E	73	62	79	100	po/sc
18c	6-CH_3	CH_3	C_2H_5	H	E	69	in.	in.	nd	po
19b	6-C_2H_5	CH_3	C_2H_5	H	E	79	nd	in.	in.	po
20b	6-F	CH_3	CH_3	*p*-F	F	82	nd	77	93 (2)	po/sc
21b	6-Cl	CH_3	CH_3	H	E	80	81 ± 18 (2)	100 (2)	100 (3)	po/sc
21c	6-Cl	CH_3	C_2H_5	H	E	83	in.	62	83 ± 11 (2)	po/sc
22b	6-CF_3	CH_3	CH_3	H	F	68	67	100	100 ± 04 (3)	po/sc
22c	6-CF_3	CH_3	C_2H_5	H	E	81	in.	57	nd	po
23b	6-MeO	CH_3	CH_3	H	E	84	83 ± 11 (3)	100 (2)	100 (2)	po/sc
23c	6-MeO	CH_3	C_2H_5	H	E	77	39	37	84 ± 6 (2)	po/sc
24b	6-EtO	CH_3	CH_3	*p*-F	F	50	nd	nd	53	sc
25b	6-CF_3O	CH_3	CH_3	H	F	74	63	72	96 ± 6 (3)	po/sc
26b	6-$N(CH_3)_2$	CH_3	CH_3	H	E	62	nd	nd	in.	po
27b	7-CH_3	CH_3	CH_3	H	E	75	nd	nd	53	sc
28b	7-Cl	CH_3	CH_3	H	E	69	nd	nd	in.	sc
29b	7-CF_3	CH_3	CH_3	*p*-F	F	64	nd	nd	35	sc
30b	7-MeO	CH_3	CH_3	H	E	71	nd	nd	in.	sc
31b	7-PhO	CH_3	CH_3	*p*-F	F	55	nd	nd	in.	sc
32b	8-F	CH_3	CH_3	*p*-F	F	62	in.	in.	55	sc
33b	8-CF_3	CH_3	CH_3	*m*,*p*-Cl_2	F	64	nd	nd	in.	sc
34b	8-MeO	CH_3	CH_3	H	E	70	nd	nd	in. (2)	sc

[a] Yields are calculated from starting material as depicted in Scheme 5 and not optimized. [b] Percent inhibition of mean clinical score ± standard deviation (see Experimental Section). The number of experiments run is indicated in parentheses (*n*). Inactive (in.) is defined as <35%. nd = not determined. [c] See Experimental Section.

small or medium-sized substituents (e.g., methoxy) to these positions enhances activity; however, larger-sized substituents such as ethoxy in the 5- and 6-position resulted in a pronounced decrease in activity, in particular for the 6-substituted analogue (**24b**). This may reflect that introduction of steric bulk is more tolerated in the 5-position. Introduction of a larger sized substituent to the 5-position with the size of phenoxy (**13b**) was detrimental to activity and confirmed the existence of a size-limited tolerance for steric bulk also in this position. With electronic effects, no real differences were noted between the 5- and 6-position except when comparing the dimethylamino group (compounds **16b** and **26b**), the former being highly potent and the latter inactive. This might be interpreted in terms of electronic properties, possibly caused by intramolecular electrostatic interaction of the substituent with the acidic 4-enolic proton.

Methyl substitution in the 1-position of the quinoline ring (R_2, Table 2) was found to be a prerequisite for efficacy. Thus, substitution with other groups (H, cyclo-Pr, Ph) resulted in no activity in the aEAE model (compounds **2b**−**4b**).

We also extended the methyl group on the *N*-carboxamide position (R_3, Table 2) to higher alkyls such as ethyl, *n*-propyl, isopropyl, and allyl (compounds **8c**−**f** (R_1 = 5-Cl)). This substitution resulted in compounds with lower potency compared to the *N*-methyl-substituted reference compound **8b** but showed that larger alkyl groups are sterically tolerated in this position. In this context, the importance of the position of the quinoline ring substitution also becomes quite evident. The introduction of an *N*-ethyl group to the *N*-carboxamide position of the 5-substituted molecules (Me, Cl, CF_3, MeO, MeS), compounds (**5c**, **8c**, **10c**, **11c**, **14c**), retained high aEAE potency compared to the *N*-methyl analogues (**5b**, **8b**, **10b**, **11b**, **14b**). In contrast, when the *N*-ethyl group was introduced into 6-substituted molecules (**18c**, **21c**−**23c**, also **19b**), there was a dramatic loss of aEAE activity when compared to the corresponding *N*-methyl derivatives (**18b**, **21b**−**23b**). These findings further confirm position specificity in the quinoline part; i.e., the 5-position possesses more steric tolerance than the 6-position when combined with additional ligand bulk in the *N*-carboxamide position.

An examination of 3-carboxamide phenyl-ring substitution (R_4, Table 2) was undertaken to study the importance of aromatic substitution in this part of the molecule. In the same manner as described for the quinoline-ring substitution, substituents with different properties (e.g., MeO, Cl, CF_3) were introduced into the ortho, meta, and para positions. In this series, compound **11b** (R_1 = 5-MeO, Table 2) was selected as the reference compound. As can be seen from Table 2, introduction of substituents to the phenyl ring of **11b** was tolerated in the meta and para positions but did not affect the aEAE potency in a significant way (compounds **11d**−**r**). The rank order of potency was found to be para > meta > ortho substitution. Substitution in the ortho position had an adverse influence on potency. In this position halogens such as a fluoro or even a chloro group was accepted but not a methoxy group. In this context, it is also interesting to note that when introducing fluoro substituents to the 3-carboxamide phenyl-ring, the substitution pattern was important in order to retain activity. Thus, the presence of a fluoro substituent in the ortho position **11d** or difluoro substitutions in positions ortho/para-F_2 **11h** or ortho/meta′-F_2 **11g** are tolerated. However, ortho/ortho-F_2 **11e** and ortho/meta-F_2 **11f** disubstitutions resulted in poorly active compounds.

Pharmacokinetic studies with this group of compounds in the aEAE mouse model have shown good oral bioavailability similar to that of the lead compound roquinimex (**1b**). Furthermore, the studies indicated that there was no correlation between exposure of the compounds and efficacy in the aEAE model (unpublished results).

Recently, a SAR study of roquinimex-related 3-quinolinecarboxamides was reported by Tsuji et al.[22] In that study, it was found that chemical modifications of **1b** resulted in analogues highly effective in two nephritis models: chronic graft-versus-host disease (GVHD) and autoimmune MRL/l mice. Comparison of the findings of Tsuji et al. with our results indicates a similar SAR. Introduction of substituents in the 6-position of the quinoline ring (e.g., R1 = 6-MeS) was reported to increase the activity in the GVHD model compared to **1b**. R_2 and R_3 = Me was found optimal, and R_4 = para substitution retained high activity. These data support the SAR observations made in our study.

Side Effect Evaluation of Proinflammatory Responses. It has earlier been observed that roquinimex (**1b**), at doses that inhibit aEAE in the mouse, induces a proinflammatory reaction in the beagle dog. Its main characteristics are fever, neutrophilia, and an increase in acute-phase reactant levels. Thus, it was found that after 5 days of roquinimex treatments (1 and 5 (mg/kg)/day iv), the white blood cell (WBC) count increased by $7.2 \times 10^3/mm^3$ and $10.8 \times 10^3/mm^{-3}$, and the erythrocyte sedimentation rate (ESR) was increased by 14 and 32 mm/h, respectively. The no observed adverse effect level (NOAEL) for roquinimex was determined to 0.1 (mg/kg)/day (unpublished observation).

In this study, roquinimex (**1b**) was compared to two derivatives substituted in the 6-position of the quinoline ring, i.e., the 6-chloro **21b** and 6-methoxy **23b** derivatives. Both compounds, at a dosage of 1 (**21b**) and 5 (**23b**) (mg/kg)/day, respectively, caused an inflammatory reaction. The WBC count increased by $10.3 \times 10^3/mm^3$ and $18.3 \times 10^3/mm^3$, and the ESR increased by 17 and 39 mm/h, respectively. These results clearly demonstrate that 6-substitution does not reduce the proinflammatory response.

Therefore, it was considered to be of great importance to monitor the effects of selected 5-substituted compounds in the beagle dog. To study the structural influence on the proinflammatory response in the dog, we selected a group of five 5-substituted analogues. The compounds were selected on basis of their high aEAE potency combined with a structural diversity consideration in an attempt to deduce a SAR. The compounds were structurally varied by substituent class (R_1 = chloro, methoxy, and methyl) and 3-carboxamide substitution (R_3 = methyl and ethyl). The compounds were infused into beagle dogs at 1 (mg/kg)/day iv for 5 consecutive days. In this study the mean body temperature of untreated dogs was 38.5 ± 0.4 °C. One male

Table 3. Effects of Various 3-Quinolinecarboxamide Derivatives on WBC Count, ESR, and Body Temperature (Mean Δ-Values) in the Beagle Dog

compd	body temp (°C)	ESR (mm/h)	WBC count (10^3/mm^3)
11b	1.4	20	13.2
8b	1.0	15	7.2
11c	0.5	0	9.0
8c	0.3	2	4.1
5c	0.2	0	4.0

and one female dog were allocated to each treatment group. No difference in response between male and female dogs was recorded. The effects on WBC count, ESR, and body temperature of the studied compounds are shown in Table 3. The compounds were ranked in relation to increased body temperature. As can be seen, the body temperature increase was accompanied by an increase in WBC count and ESR. Derivatives wherein R_3 is methyl (**11b** and **8b**) caused a proinflammatory response similar to that from roquinimex and was not affected by the quinoline 5-substitution. On the other hand, the result showed a clear difference between the compounds wherein R_3 is methyl and R_3 is ethyl. All compounds wherein R_3 is ethyl, compounds **11c**, **8c**, and **5c**, only slightly affected body temperature and proinflammatory markers. Hence, while the position (5 or 6) and type of substituent (chloro, methoxy, and methyl) in the quinoline ring were not found to affect the proinflammatory response when being compared to **1b**, the replacement of methyl with an ethyl group in the *N*-carboxamide moiety strongly influenced the response. Further structural conclusions are difficult to draw because of the limited extent of the present study.

Conclusion

We have disclosed the synthesis and SAR of a series of novel and potent immunomodulating 3-quinolinecarboxamide derivatives. Prominent improvements over prior art, i.e., roquinimex (**1b**), in both aEAE activity and safety aspects have been accomplished through introduction of substitution in the 5-position of the quinoline ring and replacement of methyl for higher alkyl in the *N*-carboxamide moiety. The SAR of the compounds described here demonstrate that the type and position of the quinoline ring substitution play an important role in the aEAE potency and, furthermore, the *N*-carboxamide substitution in avoiding unacceptable toxicity. Further detailed pharmacological and drug/metabolism/pharmacokinetic studies on this series are in progress, and the results will be presented elsewhere. New 3-quinolinecarboxamide derivatives available from this study will be investigated for their clinical activity in the treatment of autoimmune/inflammatory diseases. In a recent study on one member of this series, **8c**, it was confirmed that this compound modulated the immune response and cytokine balance similar to the lead compound roquinimex.[23] Thus, the basic pharmacological profile, relevant for immune modulation in MS according to our original hypothesis, was retained during the optimization program. In fact, **8c** (laquinimod) was selected for studies in man (currently in phase II) in order to determine its potential as a therapeutic agent for the treatment of multiple sclerosis.

Experimental Section

Pharmacology. Animals and Animal Care. The 8−10 week-old female SJL/N and 11−14 week-old female C57BL/6 mice were purchased from Taconic M&B (Denmark). The mice were fed RM1 Expanded (Special Diet Services Ltd., U.K.) and water ad libitum and were allowed an acclimatization period to the new environment for at least 1 week before the experiments were started.

Antigens. Mouse spinal cord homogenate (MSCH) was prepared from spinal cords obtained from 11−14 week old female C57BL/6 mice for the induction of aEAE in SJL/N mice. The spinal cords were dissected from the mice, homogenized, and diluted (500 mg/mL) in phosphate-buffered saline. The whole preparation procedure was done on ice. The homogenate was stored in aliquots at −70 °C until use.

Immunization. aEAE was induced in female SJL/N mice by immunization with 1 mg of MSCH emulsified in complete Freund's adjuvant (Difco, Detroit, MI). The mice were immunized under enflurane anesthesia by an intradermal injection at the base of the tail with 0.1 mL of the emulsion. Immediately following and 72 h after immunization, the mice were given an intraperitoneal injection of 0.1 mL of 4 μg/mL pertussis toxin (Sigma, St. Louis, MO).

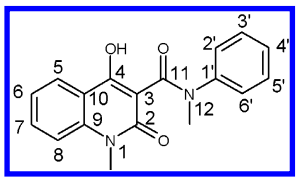
Compound Administration. The compounds were administered orally (po) or subcutaneously (sc) in a volume of 0.2 mL. Doses are indicated in the results section. The aEAE experiments were conducted with seven to eight mice in each treatment group. The investigated compounds or vehicle was administered once a day on the following days after immunization: days 3−7 and 10−12.

Clinical Evaluation. Onset of clinical signs in the aEAE model was around day 9 postimmunization (pi). The mice were weighed and scored for clinical signs of aEAE on days 0 and 9−14 pi according to the scale described below. The experiments were terminated on day 14 pi. Clinical signs of aEAE were scored as follows: 0, no signs of clinical disease; 1, tail weakness to tail paralysis; 2, paresis of hind limbs and gait disturbance; 3, total hind limb paralysis with hind body paresis, with severely impaired mobility; 4, quadriplegia, no mobility or moribund state; 5, dead. For ethical reasons the animals were killed when a clinical score of 4 was obtained.

Chemistry. General. Mass spectra were recorded by use of a TSQ 700 quadrupole tandem instrument (FinniganMAT) with an electrospray ion source (ESI) interfaced with an HP1050 HPLC system (Hewlett-Packard). Elemental analyses (CHN) were performed on a Fison EA 1108 instrument. Water was determined by use of a DL37 Karl Fischer coulometer (Mettler Toledo). HPLC analyses were performed by use of an SP8800 gradient pump (Spectra Physics) or a 616 pump (Waters), a Wisp 717plus (Waters), a DAD 996 photodiode array detector (Waters), and a Symmetry Shield column (Waters). NMR spectra on target compounds were recorded on a DRX-500 instrument (Bruker), with an operating frequency of 500.13 MHz for ^{1}H NMR and 125.8 MHz for ^{13}C NMR. Spectra were recorded at room temperature (296−297 K) unless otherwise stated, and the shift scale was referenced to TMS, defined as 0.00 ppm. The spectra were obtained in $CDCl_3$ and DMSO-d_6 or in mixtures of $CDCl_3$ and DMSO-d_6 or $CDCl_3$ and trifluoroacetic acid (TFA). Abbreviations used in the description of NMR spectra were the following: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, dt = double triplet, m = multiplet, and br = broad signal. Signals from two rotameric forms were obtained for some compounds; in these cases only signals from the larger form were reported. The fact that an equilibrium exists was demonstrated in the 2D-NOESY spectrum by the correlations obtained between the signals from two forms. The interpretation of NMR spectra was performed by use of 2D-NMR techniques such as HSQC and HMBC experiments and by comparison with spectra from related compounds. The designation of carbon atoms is in accordance with the structure in Chart 2.

Target compound purity was evaluated from elemental analysis and the ^{1}H NMR spectra, and compounds that agree

Chart 2



within 0.4% from theoretical CHN values and did not demonstrate extra signals larger than 5% in ^{1}H NMR spectra were accepted without further analysis. Those compounds that disagree more than 0.4% from theoretical CHN values were also evaluated by means of HPLC, and here, the minimum purity for the reported compounds was 95% estimated from HPLC and ^{1}H NMR spectra unless otherwise stated.

Solvents for syntheses were used as received or dried with molecular sieves when appropriate. Thin-layer chromatography was performed with 0.25 mm silica gel 60-F plates (Merck) and visualized by ultraviolet light. Solvent systems for TLC were $CHCl_3$/MeOH/acetic acid (10/1/0.1) or heptane/EtOAc/acetic acid (1/3/0.1). Organic extracts were dried with sodium sulfate unless otherwise noted and concentrated at reduced pressure using a rotary evaporator (35 °C). Most of the 3-quinolinecarboxamide compounds (target compounds) decompose slowly in solution in organic solvents and could not be recrystallized from solvents without decomposition. They also decompose during melting point determination, and hence, these values are omitted. Yields are not optimized.

Chemistry. General Synthetic Methods for the Preparation of Esters in Table 1: Methods A−D. Method A. Ethyl 1,2-Dihydro-4-hydroxy-6-methoxy-1-methyl-2-oxo-3-quinolinecarboxylate (23a). *N*-Methyl-4-(methoxy)aniline (13.7 g, 0.1 mol) was added to a solution of methanetricarboxylic acid triethyl ester (68 mL, 0.32 mol) in Dowtherm A (eutectic mixture of diphenyl and diphenyl oxide, 300 mL) under a nitrogen atmosphere at 180 °C. The temperature was slowly raised to 220−225 °C, while the formed ethanol was distilled off. The solution was heated for 3 h and then cooled. After the mixture stood overnight, a formed crystalline precipitate was filtered off, washed with pentane, and dried to afford the title compound: yield 23.5 g (85%). ^{1}H NMR ($CDCl_3$) δ 1.47 (t, 3H), 3.65 (s, 3H), 4.50 (q, 2H), 7.22 (d, 1H), 7.28 (dd, 1H), 7.56 (d, 1H), 14.2 (s, 1H).

The following esters were also prepared by method A. Yields and characteristic signals in their ^{1}H NMR spectra are reported in Table 1. Addition of heptane fascilitated precipitation of some of the products.

Ethyl 1,2-Dihydro-4-hydroxy-1,6-dimethyl-2-oxo-3-quinolinecarboxylate (18a).

Ethyl 6-Ethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylate (19a).

Ethyl 6-Chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylate (21a).

Ethyl 6-Ethoxy-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylate (24a).

Ethyl 1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-6-trifluoromethoxy-3-quinolinecarboxylate (25a).

Ethyl 1,2-Dihydro-4-hydroxy-1,7-dimethyl-2-oxo-3-quinolinecarboxylate (27a).

Ethyl 1,2-Dihydro-4-hydroxy-7-methoxy-1-methyl-2-oxo-3-quinolinecarboxylate (30a).

Ethyl 1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-7-phenoxy-3-quinolinecarboxylate (31a).

Method B. Ethyl 5-Chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylate (8a). A solution of phosgene (13.0 g, 0.13 mol) in 1,4-dioxane (100 mL) was added dropwise to a slurry of 2-amino-6-chlorobenzoic acid (17.0 g, 0.1 mol) in 1,4-dioxane (100 mL), keeping the temperature below 20 °C. After the mixture was stirred for 1 h at room temperature, the resulting precipitate was collected, washed with water, and dried under reduced pressure to furnish the isatoic anhydride: yield 24.1 g (93%). This anhydride (18.7 g, 0.093 mol) was dissolved in DMF (170 mL) and cooled on an ice bath, and sodium hydride (75% dispersion in oil, 3.5 g, 0.11 mol) followed by methyl iodide (7.6 mL, 0.12 mol) was added at a rate to keep the temperature below 5 °C. After stirring at room temperature for 5 h, excess methyl iodide was removed by evacuating the reaction vessel for 30 min at approximately 15−20 mbar. Sodium hydride (75% dispersion in oil, 3.5 g, 0.11 mol) followed by diethyl malonate (17.3 g, 0.11 mol) was added, and the mixture was heated at 85 °C for 5 h, then cooled, and quenched with water (700 mL). The aqueous solution was acidified with 1 M HCl, and the resulting crystalline mass was collected by filtration, washed with water, and dried to afford the pure title compound: yield 20.8 g (overall 74%). ^{1}H NMR ($CDCl_3$) δ 1.46 (3H, t), 3.63 (3H, s), 4.49 (2H, q), 7.23 (1H, d), 7.27 (1H, d), 7.49 (1H, t), 15.0 (1H, s).

The following esters were also prepared by method B.

Ethyl 1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylate (1a).

Ethyl 1,2-Dihydro-4-hydroxy-6-methoxy-1-methyl-2-oxo-3-quinolinecarboxylate (2a).

Ethyl 1-Cyclopropyl-1,2-dihydro-4-hydroxy-2-oxo-3-quinolinecarboxylate (3a).

Ethyl 1,2-Dihydro-4-hydroxy-1-phenyl-2-oxo-3-quinolinecarboxylate (4a).

Ethyl 1,2-Dihydro-4-hydroxy-1,5-dimethyl-2-oxo-3-quinolinecarboxylate (5a).

Ethyl 5-Ethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylate (6a).

Ethyl 5-Fluoro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylate (7a).

Ethyl 1,2-Dihydro-4-hydroxy-1-methyl-5-methoxy-2-oxo-3-quinolinecarboxylate (11a).

Ethyl 1,2-Dihydro-4-hydroxy-1-methyl-5-nitro-2-oxo-3-quinolinecarboxylate (15a).

Ethyl 1,2-Dihydro-4-hydroxy-1-methyl-5-(dimethylamino)-2-oxo-3-quinolinecarboxylate (16a). Starting from *N*-methyl-6-(dimethylamino)anthranilic acid, treatment with phosgene and subsequent sodiumhydride/diethylmalonate did not give a crystalline mass upon acidification. Instead, the product was isolated using a CH_2Cl_2 extraction.

Ethyl 6-Fluoro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylate (20a).

Ethyl 1,2-Dihydro-4-hydroxy-1-methyl-6-(dimethylamino)-2-oxo-3-quinolinecarboxylate (26a). Following the synthetic procedure described above, a crystalline mass was not obtained upon acidification. Instead, the product was isolated using a CH_2Cl_2 extraction.

Ethyl 7-Chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylate (28a).

Ethyl 1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-8-trifluoromethyl-3-quinolinecarboxylate (33a).

Ethyl 1,2-Dihydro-4-hydroxy-1-methyl-8-methoxy-2-oxo-3-quinolinecarboxylate (34a).

Method C. Ethyl 1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-6-trifluoromethyl-3-quinolinecarboxylate (22a). A solution of di-*tert*-butyl dicarbonate (26.0 g, 0.11 mol) and *p*-trifluoromethylaniline (13.0 mL, 0.1 mol) in anhydrous THF (50 mL) was refluxed for 18 h. The solution was evaporated to dryness, and the residue was dissolved in anhydrous THF (250 mL) and cooled to −40 °C. Then a hexane solution of 1.3 M *t*-BuLi (190 mL, 0.24 mol) was added dropwise with maintained temperature. After 2.5 h at −40 °C, dry ice pellets (15.0 g) were added. The temperature was raised to 0 °C, and water (250 mL) was added carefully. The two layers were separated, and the aqueous layer was acidified with HCl to pH 3 and extracted with diethyl ether (3 × 30 mL). The extracts were dried and concentrated to give crude *N*-*t*-Boc protected 6-trifluoromethylanthranilic acid as a solid residue: yield 23 g (0.075 mol). ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 9H), 7.72 (d, 1H), 8.33 (s, 1H), 8.60 (d, 1H), 10.2 (bs, 1H). This crude acid was added portionwise to an ice-cooled mixture of sodium hydride (75% dispersion in oil, 5.4 g, 0.17 mol) in DMF (100 mL) and stirred for 1 h before addition of methyl iodide (11.0 mL, 0.17 mol). The mixture was then stirred at room temperature overnight and quenched with water (150 mL), and the methylated intermediate was extracted with diethyl ether.

Concentration under reduced pressure gave a brown oil, which was dissolved in methanol (150 mL) and concentrated HCl (30 mL). The solution was stirred overnight at room temperature and neutralized with 5 M NaOH, water was added, and the product was extracted with diethyl ether (3 × 50 mL). Concentration gave isomerically pure *N*-methyl-6-trifluoromethylanthranilic methyl ester: yield 15.0 g (0.064 mol). ^{1}H NMR ($CDCl_3$) δ 2.94 (d, 3H), 3.88 (s, 3H), 6.68 (d, 1H), 7.55 (d, 1H), 8.0 (bs, 1H), 8.15 (s, 1H). This ester was dissolved in CH_2Cl_2 (200 mL), cooled on an ice bath, and ethyl malonylchloride (14.0 g, 0.09 mol) was added. After 30 min, triethylamine (9.0 mL, 0.06 mol) was added. The mixture was stirred for 1 h at room temperature and then washed with 0.5 M HCl and saturated $NaHCO_3$, and the organic phase was dried and concentrated under reduced pressure. The residue was then dissolved in dry ethanol (75 mL), and sodium methoxide (7.0 g, 0.13 mol) was added. The mixture was stirred for 1 h, and water (100 mL) was added. The solution was washed with ethyl acetate, and the aqueous phase was then acidified with concentrated HCl. The precipitate was collected by filtration and dried under reduced pressure to give the title compound as pure white crystals: yield 16.0 g (overall yield from *p*-trifluoromethylaniline 53%). ^{1}H NMR ($CDCl_3$) δ 1.45 (t, 3H), 3.62 (s, 3H), 4.50 (q, 2H), 7.48 (d, 1H), 7.84 (dd, 1H), 8.26 (s, 1H).

The following esters were also prepared by method C.

Ethyl 1,2-Dihydro-4-hydroxy-1-methyl-5,6-methylenedioxy-2-oxo-3-quinolinecarboxylate (17a). *sec*-BuLi was used instead of *t*-BuLi.

Ethyl 1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-7-trifluoromethyl-3-quinolinecarboxylate (29a).

Ethyl 8-Fluoro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylate (32a).

Method D. Ethyl 1,2-Dihydro-4-hydroxy-1-methyl-5-methylthio-2-oxo-3-quinolinecarboxylate (14a). 2,6-Difluorobenzonitrile (13.2 g, 0.10 mol) was slowly added to a solution of sodium sulfide nonahydrate (26.4 g, 0.11 mol) in DMF (300 mL). After the solution was stirred overnight, diethyl ether and 1 M HCl were added, and the organic phase was dried and concentrated under reduced pressure. The residue (12.5 g) was added in portions to a solution of sodium hydride (75% dispersion in oil, 3.8 g, 0.12 mol) in DMF (300 mL), followed by addition of methyl iodide (10.0 mL, 0.15 mol). The mixture was stirred for 6 h at room temperature and poured onto ice/water, and the resulting precipitate, 2-fluoro-6-thiomethylbenzonitrile, was filtered off and dried under reduced pressure. This was dissolved in a solution of anhydrous methylamine (9 g, 0.3 mol) in 2-propanol (200 mL) and heated at 110 °C in an autoclave for 14 h. The solvents were thereafter removed under reduced pressure to give a yellow solid of 2-methylamino-6-thiomethylbenzonitrile: yield 16.0 g (0.09 mol). ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 2.91 (d, 3H), 4.7 (bs, 1H), 6.42 (d, 1H), 6.53 (d, 1H), 7.30 (t, 1H). This nitrile was dissolved in CH_2Cl_2 (200 mL) together with 4-aminopyridine (0.1 g, 0.001 mol) and triethylamine (5.6 mL, 0.045 mol). The solution was cooled to 0 °C, and ethyl malonylchloride (15.0 g, 0.10 mol) was added slowly. After 4 h, the reaction mixture was washed with 0.5 M HCl and saturated $NaHCO_3$, and the organic phase was concentrated to give a yellowish syrup. The syrup was dissolved in anhydrous ethanol (100 mL), and sodium methoxide (7.5 g, 0.14 mol) was added. After 1 h, the solvent was removed and the residue was neutralized under cooling with 2 M HCl (70 mL) and thereafter extracted with CH_2Cl_2 to give ethyl 4-amino-1,2-dihydro-1-methyl-5-methylthio-2-oxo-3-quinolinecarboxylate: yield 19.0 g (0.065 mol). ^{1}H NMR ($CDCl_3$) δ 1.41 (t, 3H), 2.52 (s, 3H), 3.59 (s, 3H), 4.41 (q, 2H), 7.24 (d, 1H), 7.32 (d, 1H), 7.43 (t, 1H). This crude syrup was suspended at 0 °C in anhydrous THF (250 mL), and sodium hydride (75% dispersion in oil, 5.3 g, 0.175 mol) was slowly added, followed by addition of methyl iodide (13.0 mL, 0.21 mol). The mixture was heated under reflux for 6 h, quenched with water, and extracted with diethyl ether. The solvents were removed, and the residue (17.3 g) was dissolved in a mixture of ethanol (100 mL) and concentrated HCl (5.0 mL). The solution was warmed at 80 °C for 4 h and cooled and the precipitate was collected and purified by silica gel chromatography (CH_2Cl_2/MeOH, 20:1) to give the title compound: yield 12.0 g (overall 42%). ^{1}H NMR ($CDCl_3$) δ 1.46 (t, 3H), 2.48 (s, 3H), 3.62 (s, 3H), 4.48 (q, 2H), 6.98 (d, 1H), 7.05 (d, 1H), 7.52 (t, 1H), 15.5 (bs, 1H).

The following esters were prepared essentially as outlined in method D.

Ethyl 5-Bromo-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylate (9a). 2-Bromo-6-fluorobenzonitrile was prepared from 2-amino-6-fluorobenzonitrile by diazotization, followed by copper-assisted bromination.[17]

Ethyl 1,2-Dihydro-4-hydroxy-1-methyl-2-oxo-5-trifluoromethyl-3-quinolinecarboxylate (10a). 10a was from commercially available 2-fluoro-6-trifluoromethylbenzonitrile.

Ethyl 5-Ethoxy-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylate (12a). 12a was obtained by reaction of 2,6-difluorobenzonitrile with 1.0 equiv of sodium ethoxide in ethanol as described.[18]

Ethyl 5-(*p*-Fluorophenoxy)-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylate (13a). 13a was from commercially available 2-fluoro-6-(*p*-fluorophenoxy)benzonitrile.

General Synthetic Methods for the Preparation of Target Compounds in Table 2. Methods E and F. Method E. Condensation of Esters in Table 1 with N-Alkylated Anilines. 1,2-Dihydro-4-hydroxy-*N*,1-dimethyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (1b). *N*-Methylaniline (2.7 mL, 24.2 mmol) and ethyl 1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylate (**1a**, 3.0 g, 12.1 mmol) were dissolved in 80 mL of dry toluene under a nitrogen atmosphere, and an amount of approximately 60 mL of the volatiles was distilled off at atmospheric pressure for 6 h. The reaction vessel was kept under nitrogen during the distillation. After cooling and addition of heptane (20 mL), the crystalline suspension was filtered to give the title compound: yield 3.1 g (83%). ^{1}H NMR ($CDCl_3$) δ 3.28 (s, br, 3H, 1-NCH_3), 3.50 (s, 3H, 12-NCH_3), 7.1−7.3 (m, 7H, 6,8,2′,3′,4′,5′,6′-aromatic CH), 7.56 (dt, J_{HCCH} = 7.5 and 8.5 Hz, J_{HCCCH} = 1.5 Hz, 1H, 7-aromatic CH), 8.09 (dd, J_{HCCH} = 8.0 Hz, J_{HCCCH} = 1.5 Hz, 1H, 5-aromatic CH), 12.3 (s, br, 1H, 4-OH). ^{13}C NMR ($CDCl_3$) δ 28.7 (1C, 1-NCH_3), 38.3 (1C, br, 12-NCH_3), 104.6 (1C, 3-C), 113.5 (1C, 8-CH), 115.3 (1C, 10-C), 121.4 (1C, 6-CH), 124.6 (1C, 5-CH), 125.5 (2C, 2′,6′-CH), 126.7 (1C, 4′-CH), 128.5 (2C, 3′,5′-CH), 132.3 (1C, 7-CH), 140.1 (1C, 9-C), 143.8 (1C, 1′-C), 158.8 (1C, 2-CO), 164.3 (1C, 4-C), 169.4 (1C, 11-CO). MS-ESI: *m*/*z* 309 $[MH]^+$. Anal. ($C_{18}H_{16}N_2O_3$) C, H, N.

The following target compounds were also prepared by method E (yields are given in Table 2). In some cases the product did not crystallize properly from the reaction mixture. The product was then extracted from the reaction mixture using 0.5 M NaOH(aq) and isolated as described in method F below.

***N*-Ethyl-1,2-dihydro-4-hydroxy-1,5-dimethyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (5c).** ^{13}C NMR ($CDCl_3$) δ 12.9 (CH_3), 24.4 (CH_3), 29.5 (CH_3), 45.9 (CH_2), 102.8 (C), 112.2 (CH), 114.3 (C), 125.5 (CH), 126.4 (2CH), 126.4 (CH), 128.4 (2CH), 131.7 (CH), 139.6 (C), 142.0 (C), 142.4 (C), 158.1 (C), 169.7 (C), 170.1 (C). MS-ESI: *m*/*z* 337 $[MH]^+$. Anal. ($C_{20}H_{20}N_2O_3$) C, H, N.

***N*-Ethyl-5-fluoro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (7b).** ^{13}C NMR ($CDCl_3$ + TFA) δ 12.6 (CH_3), 31.4 (CH_3), 46.6 (CH_2), 104.4 (C, d, J_{CCF} = 9.2 Hz), 108.7 (C), 110.4 (CH, d, J_{CCF} = 22.8 Hz), 112.8 (CH, d, J_{CCCCF} = 3.3 Hz), 126.8 (2 CH), 129.7 (CH), 129.8 (2CH), 134.2 (CH, d, J_{CCCF} = 12.3 Hz), 139.9 (C), 141.0 (C, d, J_{CCCF} = 4.0 Hz), 158.0 (C), 160.3 (CF, d, J_{CF} = 247 Hz), 161.4 (C), 166.8 (C). MS-ESI: *m*/*z* 341 $[MH]^+$. Anal. ($C_{19}H_{17}N_2O_3F$) C, H, N.

1,2-Dihydro-4-hydroxy-*N*,1-dimethyl-2-oxo-*N*-phenyl-5-(trifluoromethyl)-3-quinolinecarboxamide (10b). ^{13}C NMR ($CDCl_3$ + TFA) δ 31.2 (CH_3), 39.0 (CH_3), 105.5 (C), 113.1 (C), 119.5 (CH), 123.2 (CF_3, q, J_{CF} = 274 Hz), 123.5 (CH, q, J_{CCCF} = 7.7 Hz), 125.5 (2CH), 128.0 (CH), 128.3 (C, q, J_{CCF} = 33.3 Hz), 129.2 (2CH), 132.2 (CH), 141.5 (C), 142.4 (C), 159.4

(C), 164.5 (C), 168.4 (C). MS-ESI: *m/z* 377 $[MH]^+$. Anal. ($C_{19}H_{15}N_2O_3F_3$) C, H, N.

***N*-Ethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-5-(trifluoromethyl)-3-quinolinecarboxamide (10c).** ^{13}C NMR ($CDCl_3$ + TFA) δ 12.5 (CH_3), 31.1 (CH_3), 46.2 (CH_2), 106.4 (C), 113.0 (C), 119.5 (CH), 123.3 (CF_3, q, $J_{CF} = 273$ Hz), 123.4 (CH, q, $J_{CCCF} = 7.8$ Hz), 126.6 (2CH), 128.1 (CH), 128.2 (C, q, $J_{CCF} = 33.1$ Hz), 129.1 (2CH), 132.1 (CH), 140.5 (C), 141.4 (C), 159.3 (C), 163.7 (C), 167.8 (C). MS-ESI: *m/z* 391 $[MH]^+$. Anal. ($C_{20}H_{17}N_2O_3F_3$) C, H, N.

1,2-Dihydro-4-hydroxy-5-methoxy-*N*,1-dimethyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (11b). ^{13}C NMR ($CDCl_3$) δ 29.7 (CH_3), 36.8 (CH_3), 56.8 (CH_3), 103.3 (CH), 104.2 (C), 108.4 (CH), 110.2 (C), 126.2 (2CH), 127.2 (CH), 128.6 (2CH), 131.4 (CH), 141.2 (C), 143.6 (C), 157.0 (C), 157.4 (C), 160.3 (C), 165,1 (C). MS-ESI: *m/z* 339 $[MH]^+$. Anal. ($C_{19}H_{18}N_2O_4$) C, H, N.

***N*-Ethyl-1,2-dihydro-4-hydroxy-5-methoxy-1-methyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (11c).** ^{13}C NMR ($CDCl_3$) δ 13.0 (CH_3), 29.6 (CH_3), 43.8 (CH_2), 56.8 (CH_3), 103.2 (CH), 104.2 (C), 108.3 (CH), 110.5 (C), 127.3 (2CH), 127.4 (CH), 128.5 (2CH), 131.2 (CH), 141.1 (C), 141.9 (C), 156.9 (C), 157.1 (C), 160.2 (C), 164.4 (C). MS-ESI: *m/z* 353 $[MH]^+$. Anal. ($C_{20}H_{20}N_2O_4 \cdot 0.1H_2O$) C, H, N.

***N*-(2-Fluorophenyl)-1,2-dihydro-4-hydroxy-5-methoxy-*N*,1-dimethyl-2-oxo-3-quinolinecarboxamide (11d).** ^{13}C NMR ($CDCl_3$) δ 29.8 (CH_3), 36.0 (CH_3), 56.9 (CH_3), 103.4 (CH), 104.3 (C), 108.5 (CH), 109.4 (C), 116.2 (CH, d, $J_{CCF} = 20.0$ Hz), 123.8 (CH, d, $J_{CCCCF} = 3.4$ Hz), 129.0 (CH, d, $J_{CCCF} = 7.8$ Hz), 129.2 (CH), 131.0 (C, d, $J_{CCF} = 11.9$ Hz), 131.7 (CH), 141.4 (C), 157.2 (C), 158.1 (CF, d, $J_{CF} = 252$ Hz), 158.4 (C), 160.4 (C), 165.5 (C). MS-ESI: *m/z* 357 $[MH]^+$. Anal. ($C_{19}H_{17}N_2O_4F$) C, H, N.

***N*-(2,2-Difluorophenyl)-1,2-dihydro-4-hydroxy-5-methoxy-*N*,1-dimethyl-2-oxo-3-quinolinecarboxamide (11e).** ^{13}C NMR ($CDCl_3$ + TFA) δ 31.3 (CH_3), 37.1 (CH_3), 57.3 (CH_3), 104.5 (C), 104.9 (C), 105.3 (CH), 109.6 (CH), 112.2 (2CH, dd, $J_{CCF} = 19.7$ Hz, $J_{CCCCF} = 3.4$ Hz), 119.1 (C, t, $J_{CCF} = 15.5$ Hz), 130.0 (CH, t, $J_{CCF} = 10.1$ Hz), 134.3 (CH), 141.0 (C), 157.8 (C), 158.5 (2CF, dd, $J_{CF} = 254$ Hz, $J_{CCCF} = 3.8$ Hz), 161.8 (C), 162.9 (C), 168.4 (C). MS-ESI: *m/z* 375 $[MH]^+$. Anal. ($C_{19}H_{16}N_2O_4F_2$) C, H, N.

***N*-(3-Chlorophenyl)-1,2-dihydro-4-hydroxy-5-methoxy-*N*,1-dimethyl-2-oxo-3-quinolinecarboxamide (11k).** ^{13}C NMR ($CDCl_3$) δ 29.8 (CH_3), 36.8 (CH_3), 57.0 (CH_3), 103.5 (CH), 104.3 (C), 108.6 (CH), 109.9 (C), 124.7 (CH), 126.5 (CH), 127.5 (CH), 129.7 (CH), 131.7 (CH), 133.9 (C), 141.4 (C), 144.8 (C), 157.2 (C), 157.7 (C), 160.3 (C), 165.0 (C). MS-ESI: *m/z* 373 $[MH]^+$. Anal. ($C_{19}H_{17}N_2O_4Cl$) C, H, N.

1,2-Dihydro-4-hydroxy-5-methoxy-*N*-(3-methoxyphenyl)-*N*,1-dimethyl-2-oxo-3-quinolinecarboxamide (11m). ^{13}C NMR ($CDCl_3$) δ 29.8 (CH_3), 36.9 (CH_3), 55.3 (CH_3), 56.8 (CH_3), 103.4 (CH), 104.4 (C), 108.6 (CH), 110.6 (C), 111.4 (CH), 113.6 (CH), 118.4 (CH), 129.3 (CH), 131.5 (CH), 141.3 (C), 144.8 (C), 157.1 (C), 157.4 (C), 159.5 (C), 160.4 (C), 165.1 (C). MS-ESI: *m/z* 369 $[MH]^+$. Anal. ($C_{20}H_{20}N_2O_5 \cdot 1.8H_2O$) C, H, N.

1,2-Dihydro-4-hydroxy-5-methoxy-*N*,1-dimethyl-2-oxo-*N*-(3-phenoxyphenyl)-3-quinolinecarboxamide (11n). ^{13}C NMR ($CDCl_3$) δ 29.8 (CH_3), 36.7 (CH_3), 56.9 (CH_3), 103.4 (CH), 104.3 (C), 108.6 (CH), 110.1 (C), 117.6 (CH), 118.0 (2CH), 118.5 (CH), 121.6 (CH), 122.9 (CH), 129.5 (2CH), 129.7 (CH), 131.6 (CH), 141.4 (C), 145.0 (C), 156.6 (C), 157.2 (C), 157.3 (C), 157.5 (C), 160.2 (C), 165.0 (C). MS-ESI: *m/z* 431 $[MH]^+$. Anal. ($C_{25}H_{22}N_2O_5$) C, H, N.

***N*-(4-Chlorophenyl)-1,2-dihydro-4-hydroxy-5-methoxy-*N*,1-dimethyl-2-oxo-3-quinolinecarboxamide (11p).** ^{13}C NMR ($CDCl_3$) δ 29.8 (CH_3), 36.8 (CH_3), 56.8 (CH_3), 103.4 (CH), 104.2 (C), 108.6 (CH), 110.0 (C), 127.6 (2CH), 128.9 (2CH), 131.6 (CH), 132.8 (C), 141.3 (C), 142.2 (C), 157.1 (C), 157.5 (C), 160.3 (C), 165.0 (C). MS-ESI: *m/z* 373 $[MH]^+$. Anal. ($C_{19}H_{17}N_2O_4Cl$) C, H, N.

1,2-Dihydro-4-hydroxy-5-methoxy-*N*,1-dimethyl-2-oxo-*N*-[4-(trifluoromethyl)phenyl]-3-quinolinecarboxamide (11q). ^{13}C NMR ($CDCl_3$) δ 29.8 (CH_3), 36.9 (CH_3), 56.9 (CH_3), 103.5 (CH), 104.2 (C), 108.7 (CH), 109.5 (C), 123.8 (CF_3, q, $J_{CF} = 272$ Hz), 125.9 (2CH, q, $J_{CCCF} = 3.7$ Hz), 126.3 (2CH), 128.6 (C, q, $J_{CCF} = 30$ Hz), 131.8 (CH), 141.4 (C), 146.7 (C), 157.2 (C), 158.0 (C), 160.3 (C), 165.0 (C). MS-ESI: *m/z* 407 $[MH]^+$. Anal. ($C_{20}H_{17}N_2O_4F_3$) C, H, N.

1,2-Dihydro-4-hydroxy-5-methoxy-*N*-(4-methoxyphenyl)-*N*,1-dimethyl-2-oxo-3-quinolinecarboxamide (11r). ^{13}C NMR ($CDCl_3$), two rotameric forms in equilibrium, δ 29.8 (CH_3), 37.1 (CH_3), 55.3 (CH_3), 56.8 (CH_3), 103.3 (CH), 104.4 (C), 108.6 (CH), 110.5 (C), 113.8 (2CH), 127.5 (2CH), 131.3 (CH), 136.7 (C), 141.3 (C), 157.1 (C), 157.2 (C), 158.5 (C), 160.3 (C), 165.3 (C). MS-ESI: *m/z* 369 $[MH]^+$. Anal. ($C_{20}H_{20}N_2O_5$) C, H, N.

5-(4-Fluorophenoxy)-1,2-dihydro-4-hydroxy-*N*,1-dimethyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (13b). ^{13}C NMR ($CDCl_3$) δ 29.9 (CH_3), 37.0 (CH_3), 110.6 (C), 105.6 (C), 108.7 (CH), 109.8 (CH), 117.1 (2CH, d, $J_{CCF} = 23.8$ Hz), 122.3 (2CH, d, $J_{CCCF} = 8.5$ Hz), 126.3 (2CH), 127.2 (CH), 128.7 (2CH), 131.4 (CH), 141.5 (C), 143.6 (C), 149.7 (C, d, $J_{CCCCF} = 2.9$ Hz), 156.3 (C), 157.3 (C), 160.1 (C), 160.2 (CF, d, $J_{CF} = 246$ Hz), 165.2 (C). MS-ESI: *m/z* 419 $[MH]^+$. Anal. ($C_{24}H_{19}N_2O_4F \cdot 0.2H_2O$) C, H, N.

1,2-Dihydro-4-hydroxy-*N*,1-dimethyl-5-(methylthio)-2-oxo-*N*-phenyl-3-quinolinecarboxamide (14b). ^{13}C NMR ($CDCl_3$) δ 18.3 (CH3), 29.8 (CH3), 38.4 (CH3), 104.6 (C), 112.0 (CH), 113.2 (C), 121.5 (CH), 125.7 (2CH), 126.8 (CH), 128.7 (2CH), 131.5 (CH), 139.1 (C), 142.3 (C), 144.2 (C), 158.7 (C), 166.0 (C), 169.1 (C). MS-ESI: *m/z* 355 $[MH]^+$. Anal. ($C_{19}H_{18}N_2O_3S \cdot 0.9H_2O$) C, H, N.

5-(Dimethylamino)-1,2-dihydro-4-hydroxy-*N*,1-dimethyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (16b). ^{13}C NMR ($CDCl_3$), two rotameric forms in equilibrium, δ 29.5 (CH_3), 36.7 (CH_3), 45.2 (CH_3), 46.4 (CH_3), 109.5 (C), 110.0 (C), 113.0 (CH), 114.0 (CH), 126.4 (2CH), 127.1 (CH), 128.4 (2CH), 130.9 (CH), 140.8 (C), 144.0 (C), 150.6 (C), 160.0 (C), 160.6 (C), 165.7 (C). MS-ESI: *m/z* 352 $[MH]^+$. Anal. ($C_{20}H_{21}N_3O_3 \cdot 0.07i\text{-PrOH} \cdot 0.5H_2O$) C, H, N.

1,2-Dihydro-4-hydroxy-*N*,1,6-trimethyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (18b). ^{13}C NMR ($CDCl_3$) δ 20.7 (CH_3), 28.9 (CH_3), 38.7 (CH_3), 103.5 (C), 113.8 (CH), 115.2 (C), 124.5 (CH), 125.5 (2CH), 126.6 (CH), 128.7 (2CH), 131.3 (C), 134.0 (CH), 138.7 (C), 144.3 (C), 158.5 (C), 166.1 (C), 170.1 (C). MS-ESI: *m/z* 323 $[MH]^+$. Anal. ($C_{19}H_{18}N_2O_3$) C, H, N.

***N*-Ethyl-1,2-dihydro-4-hydroxy-1,6-dimethyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (18c).** ^{13}C NMR ($CDCl_3$) δ 13.0 (CH_3), 20.7 (CH_3), 28.8 (CH_3), 45.9 (CH_2), 103.7 (C), 113.7 (CH), 115.1 (C), 124.4 (CH), 126.5 (2CH), 126.6 (CH), 128.5 (2CH), 131.2 (C), 133.9 (CH), 138.6 (C), 142.4 (C), 158.4 (C), 165.9 (C), 169.6 (C). MS-ESI: *m/z* 337 $[MH]^+$. Anal. ($C_{20}H_{20}N_2O_3$) C, H, N.

***N*,6-Diethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (19b).** ^{13}C NMR ($CDCl_3$) δ 12.9 (CH_3), 15.6 (CH_3), 28.0 (CH_2), 28.8 (CH_3), 45.8 (CH_2), 103.8 (C), 113.7 (CH), 115.2 (C), 123.2 (CH), 126.4 (2CH), 126.6 (CH), 128.4 (2CH), 132.7 (CH), 137.5 (C), 138.7 (C), 142.3 (C), 158.4 (C), 165.7 (C), 169.5 (C). MS-ESI: *m/z* 351 $[MH]^+$. Anal. ($C_{21}H_{22}N_2O_3$) C, H, N.

6-Chloro-1,2-dihydro-4-hydroxy-*N*,1-dimethyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (21b). ^{13}C NMR ($CDCl_3$) δ 29.1 (CH_3), 38.5 (CH_3), 105.1 (C), 115.1 (CH), 116.6 (C), 124.1 (CH), 125.5 (2CH), 127.0 (CH), 127.2 (C), 128.7 (2CH), 132.4 (CH), 138.7 (C), 143.7 (C), 158.7 (C), 163.3 (C), 169.3 (C). MS-ESI: *m/z* 343 $[MH]^+$. Anal. ($C_{18}H_{15}N_2O_3Cl$) C, H, N.

6-Chloro-*N*-ethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (21c). ^{13}C NMR ($CDCl_3$ + TFA) δ 12.4 (CH_3), 30.7 (CH_3), 46.6 (CH_2), 106.5 (C), 116.7 (CH), 116.7 (C), 124.4 (CH), 126.5 (2CH), 129.1 (CH), 129.5 (2CH), 130.1 (C), 134.0 (CH), 137.9 (C), 139.5 (C), 160.5 (C), 161.4 (C), 167.5 (C). MS-ESI: *m/z* 357 $[MH]^+$. Anal. ($C_{19}H_{17}N_2O_3Cl$) C, H, N.

***N*-Ethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-6-(trifluoromethyl)-3-quinolinecarboxamide (22c).** ^{13}C NMR ($CDCl_3$ + TFA) δ 12.5 (CH_3), 30.4 (CH_3), 46.3 (CH_2), 106.4 (C), 115.3 (C), 115.6 (CH), 122.8 (CH, q, $J_{CCCF} = 3.9$ Hz),

123.6 (CF_3, q, J_{CF} = 272 Hz), 125.9 (C, q, J_{CCF} = 34.0 Hz), 126.5 (2CH), 128.7 (CH), 129.3 (2CH), 129.8 (CH, q, J_{CCCF} = 3.3 Hz), 139.3 (C), 141.3 (C), 160.5 (C), 162.5 (C), 167.4 (C). MS-ESI: *m/z* 391 $[MH]^+$. Anal. ($C_{20}H_{17}N_2O_3F_3$·0.035 toluene) C, H, N.

1,2-Dihydro-4-hydroxy-6-methoxy-*N*,1-dimethyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (23b). ^{13}C NMR ($CDCl_3$) δ 28.9 (CH_3), 38.6 (CH_3), 56.7 (CH_3), 104.4 (C), 105.5 (CH), 115.2 (CH), 115.9 (C), 122.1 (CH), 125.6 (2CH), 126.6 (CH), 128.6 (2CH), 135.1 (C), 144.0 (C), 154.4 (C), 158.3 (C), 164.8 (C), 169.9 (C). MS-ESI: *m/z* 339 $[MH]^+$. Anal. ($C_{19}H_{18}N_2O_4$) C, H, N.

***N*-Ethyl-1,2-dihydro-4-hydroxy-6-methoxy-1-methyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (23c).** ^{13}C NMR ($CDCl_3$) δ 12.9 (CH_3), 28.8 (CH_3), 45.6 (CH_2), 55.6 (CH_3), 105.3 (CH), 106.0 (C), 115.0 (CH), 116.0 (C), 121.6 (CH), 126.6 (2CH), 126.9 (CH), 128.5 (2CH), 134.7 (C), 141.9 (C), 154.2 (C), 158.4 (C), 163.0 (C), 169.1 (C). MS-ESI: *m/z* 353 $[MH]^+$. Anal. ($C_{20}H_{20}N_2O_4$·0.04CH_2Cl_2) C, H, N.

6-(Dimethylamino)-1,2-dihydro-4-hydroxy-6-methoxy-*N*,1-dimethyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (26b). ^{13}C NMR ($CDCl_3$) δ 28.9 (CH_3), 38.7 (CH_3), 41.1 ($2CH_3$), 103.7 (C), 106.2 (CH), 114.8 (CH), 116.0 (C), 119.8 (CH), 125.6 (2CH), 126.5 (CH), 128.6 (2CH), 132.9 (C), 144.4 (C), 145.9 (C), 158.1 (C), 165.9 (C), 170.3 (C). MS-ESI: *m/z* 352 $[MH]^+$. Anal. ($C_{20}H_{21}N_3O_3$) C, H, N.

1,2-Dihydro-4-hydroxy-*N*,1,7-trimethyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (27b). ^{13}C NMR ($CDCl_3$) δ 22.4 (CH_3), 28.9 (CH_3), 38.7 (CH_3), 102.4 (C), 113.0 (C), 114.1 (CH), 123.1 (CH), 124.9 (CH), 125.5 (2CH), 126.5 (CH), 128.7 (2CH), 140.8 (C), 143.9 (C), 144.4 (C), 158.8 (C), 166.7 (C), 170.2 (C). MS-ESI: *m/z* 323 $[MH]^+$. Anal. ($C_{19}H_{18}N_2O_3$·0.3H_2O) C, H, N.

7-Chloro-1,2-dihydro-4-hydroxy-*N*,1-dimethyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (28b). ^{13}C NMR ($CDCl_3$) δ 29.1 (CH_3), 38.6 (CH_3), 103.6 (C), 113.8 (CH), 113.9 (C), 122.1 (CH), 125.5 (2CH), 126.3 (CH), 126.8 (CH), 128.7 (2CH), 139.1 (C), 141.3 (C), 144.1 (C), 158.6 (C), 165.6 (C), 169.7 (C). MS-ESI: *m/z* 343 $[MH]^+$. Anal. ($C_{18}H_{15}N_2O_3Cl$) C, H, N.

1,2-Dihydro-4-hydroxy-7-methoxy-*N*,1-dimethyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (30b). ^{13}C NMR ($CDCl_3$) δ 28.9 (CH_3), 38.6 (CH_3), 55.5 (CH_3), 98.0 (CH), 101.3 (C), 109.0 (C), 109.2 (CH), 125.4 (2CH), 126.4 (CH), 126.7 (CH), 128.6 (2CH), 142.4 (C), 144.3 (C), 159.1 (C), 163.4 (C), 166.2 (C), 170.2 (C). MS-ESI: *m/z* 339 $[MH]^+$. Anal. ($C_{19}H_{18}N_2O_4$) C, H, N.

1,2-Dihydro-4-hydroxy-8-methoxy-*N*,1-dimethyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (34b). ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 34.2 (CH_3), 37.5 (CH_3), 55.8 (CH_3), 105.2 (C), 114.5 (CH), 116.0 (CH), 117.4 (C), 121.7 (CH), 125.2 (2CH), 126.3 (CH), 128.1 (2CH), 131.2 (C), 143.2 (C), 147.6 (C), 160.0 (C), 161.5 (C), 167.5 (C). MS-ESI: *m/z* 339 $[MH]^+$. Anal. ($C_{19}H_{18}N_2O_4$·0.8H_2O) H, N. C calcd, 64.69; found, 64.2. Purity = 93% (contains 6% of the corresponding decarboxylated quinoline acid).

Method F. Acidic Cleavage of Esters in Table 1 into 3-Quinolinecarboxylic Acids and Coupling to N-Alkylated Anilines with Thionyl Chloride. 5-Chloro-*N*-ethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (8c). To a solution of acetic anhydride (450 mL) at 0 °C was slowly added (very exothermic!) concentrated HCl (138 mL, 37%). This yields an approximately 2.8 M solution of HCl in acetic acid with a low water content, and the solution can be kept in a refrigerator for several years. To ethyl 5-chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylate (**8a**, 5.0 g, 17.7 mmol) was added 50 mL of the above solution of 2.8 M HCl in acetic acid, and the mixture was heated for 6 h at 60 °C using a reflux condenser. Volatile methyl chloride is formed during the reaction. After the mixture was cooled to room temperature and diluted with 2-propanol, the crystals were filtered off, washed with 2-propanol, and dried in a vacuum to furnish the product 5-chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-3-quinolinecarboxylic acid: yield 4.1 g (91%). ^1H NMR ($CDCl_3$) δ 3.75 (3H, s), 7.42 (1H, d), 7.46 (1H, d), 7.65 (1H, t), 15.77 (1H, s), 15.78 (1H, s).

To this acid (3.8 g, 15 mmol) was added CH_2Cl_2 (38 mL), triethylamine (7.4 mL, 53 mmol), and *N*-ethylaniline (2.2 mL, 16.5 mmol). The mixture was stirred under nitrogen and cooled to 0 °C, and a solution of thionyl chloride (1.3 mL, 18 mmol) in CH_2Cl_2 (10 mL) was added during 30 min. The stirring was continued at 0 °C for 4 h and then at room temperature for 30 min. The reaction mixture was diluted with $CHCl_3$ and quickly washed with cold 1 M H_2SO_4. It is important not to leave the separatory funnel for prolonged times because the product slowly decomposes in the organic phase. The organic phase was then immediately extracted with 60 mL of 0.5 M NaOH. The aqueous phase was treated under vacuum on a rotary evaporator in order to remove traces of chlorinated organic solvents, and the pH was adjusted to the point where the desired product started to precipitate (approximately 6.5 for this compound, depending on the pK_a of target compound!). The solution was filtered through Celite, and the product was precipitated by acidification with 1 M HCl until the pH was approximately 1−2. After the mixture stood for 2 h, the precipitate was collected by filtration, washed with water, and dried under reduced pressure to give the title compound **8c**: 4.7 g (13.2 mmol, 87% yield, 79% overall yield from ester **8a**). ^1H NMR ($CDCl_3$) δ 1.22 (t, J_{HCCH} = 7.1 Hz, 3H, 12-NCH_2CH_3), 3.30 (s, 3H, 1-NCH_3), 3.98 (q, J_{HCCH} = 6.8 Hz, 2H, 12-NCH_2-CH_3), 7.08−7.26 (m, 7H, 6,8,2′,3′,4′,5′,6′-aromatic CH), 7.41 (t, J_{HCCH} = 8.2 Hz, 1H, 7-aromatic CH), 12.6 (s, br, 1H, 4-OH). ^{13}C NMR ($CDCl_3$): δ 12.9 (1C, 12-NCH_2CH_3), 29.8 (1C, 1-NCH_3), 45.7 (1C, 12-NCH_2CH_3), 105.1 (1C, 3-C), 112.8 (1C, 10-C), 113.3 (1C, 8-CH), 125.4 (1C, 6-CH), 126.7 (2C, 2′,6′-CH), 126.9 (1C, 4′-CH), 128.5 (2C, 3′,5′-CH), 131.7 (1C, 7-CH), 132.8 (1C, 5-C), 142.1 (1C, 1′-C), 142.7 (1C, 9-C), 157.9 (1C, 2-CO), 165.7 (1C, 4-C), 168.8 (1C, 11-CO). MS-ESI: *m/z* 357 $[MH]^+$. Anal. ($C_{19}H_{17}N_2O_3Cl$) C, H, N.

The following target compounds were also prepared by method F (yields are given in Table 2).

***N*-(4-Fluorophenyl)-1,2-dihydro-4-hydroxy-6-methoxy-*N*-methyl-2-oxo-3-quinolinecarboxamide (2b).** ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 37.3 (CH_3), 55.4 (CH_3), 104.4 (CH), 108.5 (C), 115.0 (C), 115.2 (2CH, d, J_{CCF} = 22.4 Hz), 116.7 (CH), 120.9 (CH), 127.8 (2CH, d, J_{CCCF} = 8.6 Hz), 133.3 (C), 139.2 (C), 154.2 (C), 159.5 (C), 160.3 (C), 161.0 (CF, d, J_{CF} = 246 Hz), 166.5 (C). MS-ESI: *m/z* 343 $[MH]^+$. Anal. ($C_{18}H_{15}N_2O_4F$·0.1H_2O) C, H, N.

1,2-Dihydro-4-hydroxy-*N*-(4-methoxyphenyl)-*N*-methyl-1-cyclopropyl-2-oxo-3-quinolinecarboxamide (3b). ^{13}C NMR ($CDCl_3$) δ 9.8 ($2CH_2$), 25.4 (CH), 38.6 (CH_3), 55.6 (CH_3), 103.2 (C), 113.8 (2CH), 114.9 (CH), 115.4 (C), 121.6 (CH), 124.9 (CH), 127.1 (2CH), 132.3 (CH), 137.4 (C), 141.5 (C), 158.2 (C), 159.9 (C), 166.7 (C), 170.1 (C). MS-ESI: *m/z* 365 $[MH]^+$. Anal. ($C_{21}H_{20}N_2O_4$·0.1TEA·0.7H_2O) C, H, N.

1,2-Dihydro-4-hydroxy-*N*-methyl-2-oxo-*N*,1-diphenyl-3-quinolinecarboxamide (4b). ^{13}C NMR ($CDCl_3$) δ 38.3 (CH_3), 102.9 (C), 114.9 (CH), 115.5 (C), 121.8 (CH), 124.5 (CH), 125.8 (2CH), 126.6 (2CH), 128.5 (CH), 128.6 (CH), 128.8 (2CH), 129.8 (2CH), 132.3 (CH), 137.2 (C), 141.5 (C), 144.2 (C), 158.5 (C), 167.2 (C), 169.7 (C). MS-ESI: *m/z* 371 $[MH]^+$. Anal. ($C_{23}H_{18}N_2O_3$) C, H, N.

1,2-Dihydro-4-hydroxy-*N*,1,5-trimethyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (5b). ^{13}C NMR ($CDCl_3$) δ 24.4 (CH_3), 29.6 (CH_3), 38.8 (CH_3), 102.4 (C), 112.3 (CH), 114.4 (C), 125.6 (1+2CH), 126.5 (CH), 128.7 (2CH), 132.0 (CH), 139.8 (C), 142.1 (C), 144.4 (C), 158.3 (C), 170.2 (C), 170.7 (C). MS-ESI: *m/z* 323 $[MH]^+$. Anal. ($C_{19}H_{18}N_2O_3$) C, H, N.

***N*,5-Diethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (6b).** ^{13}C NMR ($CDCl_3$) δ 13.2 (CH_3), 16.8 (CH_3), 29.8 (CH_3), 30.2 (CH_2), 46.1 (CH_2), 103.3 (C), 112.5 (CH), 113.9 (C), 124.6 (CH), 126.7 (CH), 126.7 (2CH), 128.6 (2CH), 132.1 (CH), 142.3 (C), 142.6 (C), 146.2 (C), 158.3 (C), 169.3 (C), 170.4 (C). MS-ESI: *m/z* 351 $[MH]^+$. Anal. ($C_{21}H_{22}N_2O_3$) C, H, N.

5-Chloro-1,2-dihydro-4-hydroxy-*N*,1-dimethyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (8b). ^{13}C NMR ($CDCl_3$) δ 29.9 (CH_3), 38.5 (CH_3), 104.7 (C), 112.8 (C), 113.3 (CH), 125.5 (CH), 125.6 (2CH), 126.8 (CH), 128.7 (2CH), 131.8 (CH), 132.9

(C), 142.6 (C), 143.9 (C), 158.0 (C), 166.1 (C), 169.3 (C). MS-ESI: *m/z* 343 $[MH]^+$. Anal. ($C_{18}H_{15}N_2O_3Cl \cdot 0.038CH_2Cl_2$) C, H, N.

5-Chloro-*N*-ethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (8c). See method F above.

5-Chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-*N*-propyl-3-quinolinecarboxamide (8d). ^{13}C NMR ($CDCl_3$) δ 11.3 (CH_3), 20.9 (CH_2), 29.8 (CH_3), 52.1 (CH_2), 105.5 (C), 112.7 (C), 113.3 (CH), 125.4 (CH), 126.6 (2CH), 126.8 (CH), 128.5 (2CH), 131.6 (CH), 132.7 (C), 142.3 (C), 142.6 (C), 157.9 (C), 165.2 (C), 168.8 (C). MS-ESI: *m/z* 371 $[MH]^+$. Anal. ($C_{20}H_{19}N_2O_3Cl$) C, H, N.

5-Chloro-1,2-dihydro-4-hydroxy-1-methyl-*N*-(1-methylethyl)-2-oxo-*N*-phenyl-3-quinolinecarboxamide (8e). ^{13}C NMR ($CDCl_3$) δ 21.0 (CH_3), 29.9 (CH_3), 48.2 (CH), 109.4 (C), 112.4 (C), 113.5 (CH), 125.1 (CH), 127.9 (2CH), 129.6 (2CH), 131.1 (CH), 131.6 (C), 137.9 (C), 142.1 (C), 158.6 (C), 160.6 (C), 167.5 (C). MS-ESI: *m/z* 371 $[MH]^+$. Anal. ($C_{20}H_{19}N_2O_3Cl$) C, H, N.

5-Chloro-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-*N*-(2-propenyl)-3-quinolinecarboxamide (8f). ^{13}C NMR ($CDCl_3$) δ 29.8 (CH_3), 53.3 (CH_2), 105.0 (C), 112.7 (C), 113.3 (CH), 117.8 (CH_2), 125.5 (CH), 126.0 (2CH), 126.8 (CH), 128.5 (2CH), 131.8 (CH), 132.5 (C), 132.8 (C), 142.7 (C), 142.9 (C), 157.9 (C), 165.7 (C), 168.9 (C). MS-ESI: *m/z* 369 $[MH]^+$. Anal. ($C_{20}H_{17}N_2O_3Cl \cdot 0.1H_2O$) C, H, N.

5-Bromo-*N*-ethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (9b). ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 12.9 (CH_3), 29.7 (CH_3), 45.1 (CH_2), 106.4 (C), 113.9 (C), 114.0 (CH), 119.5 (C), 126.8 (2CH), 127.0 (CH), 128.5 (2CH), 129.3 (CH), 131.7 (CH), 141.8 (C), 142.5 (C), 158.3 (C), 163.0 (C), 167.7 (C). MS-ESI: *m/z* 401 $[MH]^+$. Anal. ($C_{19}H_{17}N_2O_3Br \cdot 0.3H_2O$) H, N. C calcd, 56.11; found, 55.0.

***N*-(2,3-Difluorophenyl)-1,2-dihydro-4-hydroxy-5-methoxy-*N*,1-dimethyl-2-oxo-3-quinolinecarboxamide (11f).** ^{13}C NMR ($CDCl_3$) δ 29.8 (CH_3), 35.9 (CH_3), 57.0 (CH_3), 103.5 (CH), 104.2 (C), 108.5 (CH), 109.0 (C), 116.4 (CH, d, J_{CCF} = 17.0 Hz), 123.1 (CH), 124.1 (CH), 131.9 (CH), 133.0 (C, d, J_{CCF} = 8.7 Hz), 141.4 (C), 146.8 (CF, dd, J_{CF} = 253 Hz, J_{CCF} = 13.2 Hz), 150.8 (CF, dd, J_{CF} = 249 Hz, J_{CCF} = 11.6 Hz), 157.3 (C), 158.6 (C), 160.4 (C), 165.3 (C). MS-ESI: *m/z* 375 $[MH]^+$. Anal. ($C_{19}H_{16}N_2O_4F_2$) C, H, N.

***N*-(2,5-Difluorophenyl)-1,2-dihydro-4-hydroxy-5-methoxy-*N*,1-dimethyl-2-oxo-3-quinolinecarboxamide (11g).** ^{13}C NMR ($CDCl_3$ + TFA), two rotameric forms in equilibrium, δ 31.0 (CH_3), 37.2 (CH_3), 57.2 (CH_3), 104.4 (C), 105.0 (CH), 105.7 (C), 109.5 (CH), 115.4 (CH, d, J_{CCF} = 25.2 Hz), 116.8 (CH), 117.4 (CH, dd, J_{CCF} = 23.0 Hz), J_{CCCCF} = 7.9 Hz), 130.0 (C, dd, J_{CCF} = 22.9 Hz, J_{CCCF} = 14.3 Hz), 133.9 (CH), 141.0 (C), 153.9 (CF, d, J_{CF} = 244 Hz), 157.6 (C), 157.7 (CF, d, J_{CF} = 240 Hz), 161.4 (C), 161.7 (C), 167,6 (C). MS-ESI: *m/z* 375 $[MH]^+$. Anal. ($C_{19}H_{16}N_2O_4F_2$) C, H, N.

***N*-(2,4-Difluorophenyl)-1,2-dihydro-4-hydroxy-5-methoxy-*N*,1-dimethyl-2-oxo-3-quinolinecarboxamide (11h).** ^{13}C NMR ($CDCl_3$), two rotameric forms in equilibrium, δ 29.9 (CH_3), 36.0 (CH_3, d, J_{CNCCF} = 2.2 Hz), 56.9 (CH_3), 103.5 (CH), 104.2 (C), 104.6 (CH, dd, J_{CCF} = 23.9 and 26.0 Hz), 108.6 (CH), 109.2 (C), 111.0 (CH, dd, J_{CCF} = 22.0 Hz, J_{CCCCF} = 3.6 Hz), 127.4 (C, dd, J_{CCF} = 12.5 Hz, J_{CCCCF} = 4.0 Hz), 130.0 (CH, d, J_{CCCF} = 9.9 Hz), 131.8 (CH), 141.4 (C), 157.2 (C), 158.4 (CF, dd, J_{CF} = 254 Hz, J_{CCCF} = 12.6 Hz), 158.5 (C), 160.3 (C), 161.7 (CF, dd, J_{CF} = 249 Hz, J_{CCCF} = 11.2 Hz), 165.5 (C). MS-ESI: *m/z* 375 $[MH]^+$. Anal. ($C_{19}H_{16}N_2O_4F_2$) C, H, N.

***N*-(2-Chlorophenyl)-1,2-dihydro-4-hydroxy-5-methoxy-*N*,1-dimethyl-2-oxo-3-quinolinecarboxamide (11i).** ^{13}C NMR ($CDCl_3$), two rotameric forms in equilibrium, δ 29.8 (CH_3), 35.9 (CH_3), 56.9 (CH_3), 103.4 (CH), 104.3 (C), 108.4 (CH), 109.4 (C), 127.0 (CH), 128.9 (CH), 129.6 (CH), 130.1 (CH), 131.7 (CH), 132.4 (C), 140.7 (C), 141.3 (C), 157.2 (C), 158.6 (C), 160.5 (C), 165.5 (C). MS-ESI: *m/z* 373 $[MH]^+$. Anal. ($C_{19}H_{17}N_2O_4Cl \cdot 0.4H_2O$) C, H, N.

1,2-Dihydro-4-hydroxy-5-methoxy-*N*-(2-methoxyphenyl)-*N*,1-dimethyl-2-oxo-3-quinolinecarboxamide (11j). ^{13}C NMR ($CDCl_3$) δ 29.8 (CH_3), 35.8 (CH_3), 55.7 (CH_3), 56.9 (CH_3), 103.3 (CH), 104.4 (C), 108.5 (CH), 110.0 (C), 111.6 (CH), 120.0 (CH), 128.5 (CH), 128.6 (CH), 131.3 (CH), 132.1 (C), 141.3 (C), 155.3 (C), 157.1 (C), 158.1 (C), 160.3 (C), 165.7 (C). MS-ESI: *m/z* 369 $[MH]^+$. Anal. ($C_{20}H_{20}N_2O_5$) C, H, N.

1,2-Dihydro-4-hydroxy-5-methoxy-*N*,1-dimethyl-2-oxo-*N*-[3-(trifluoromethyl)phenyl]-3-quinolinecarboxamide (11l). ^{13}C NMR ($CDCl_3$) δ 29.6 (CH_3), 36.5 (CH_3), 56.9 (CH_3), 103.5 (CH), 104.0 (C), 108.5 (CH), 109.5 (C), 123.6 (CF_3, q, J_{CF} = 272 Hz), 123.3 (CH), 123.8 (CH), 129.2 (CH), 129.6 (CH), 130.8 (C, q, J_{CCF} = 33.0 Hz), 131.7 (CH), 141.2 (C), 144.0 (C), 157.1 (C), 157.7 (C), 160.2 (C), 165.1 (C). MS-ESI: *m/z* 407 $[MH]^+$. Anal. ($C_{20}H_{17}N_2O_4F_3$) C, H, N.

***N*-(4-Fluorophenyl)-1,2-dihydro-4-hydroxy-5-methoxy-*N*,1-dimethyl-2-oxo-3-quinolinecarboxamide (11o).** ^{13}C NMR ($CDCl_3$), two rotameric forms in equilibrium, δ 29.8 (CH_3), 36.9 (CH_3), 56.8 (CH_3), 103.3 (CH), 104.2 (C), 108.6 (CH), 110.1 (C), 115.4 (2CH, d, J_{CCF} = 22.5 Hz), 128.0 (2CH, d, J_{CCCF} = 8.7 Hz), 131.5 (CH), 139.6 (C), 141.3 (C), 157.0 (C), 157.4 (C), 160.2 (C), 161.5 (CF, d, J_{CF} = 246 Hz), 165.1 (C). MS-ESI: *m/z* 357 $[MH]^+$. Anal. ($C_{19}H_{17}N_2O_4F$) C, H, N.

5-Ethoxy-1,2-dihydro-4-hydroxy-*N*,1-dimethyl-2-oxo-*N*-phenyl-3-quinolinecarboxamide (12b). ^{13}C NMR ($CDCl_3$) δ 14.6 (CH_3), 29.8 (CH_3), 36.9 (CH_3), 66.2 (CH_2), 104.3 (CH), 104.5 (C), 108.4 (CH), 110.3 (C), 126.3 (2CH), 127.2 (CH), 128.6 (2CH), 131.4 (CH), 141.3 (C), 143.7 (C), 156.5 (C), 157.7 (C), 160.3 (C), 165.2 (C). MS-ESI: *m/z* 353 $[MH]^+$. Anal. ($C_{20}H_{20}N_2O_4 \cdot 0.1H_2O$) C, H, N.

***N*-Ethyl-1,2-dihydro-4-hydroxy-1-methyl-5-(methylthio)-2-oxo-*N*-phenyl-3-quinolinecarboxamide (14c).** ^{13}C NMR ($CDCl_3$) δ 13.0 (CH_3), 18.4 (CH_3), 29.7 (CH_3), 45.4 (CH_2), 105.1 (C), 112.1 (CH), 113.2 (C), 121.7 (CH), 126.7 (2CH), 126.8 (CH), 128.5 (2CH), 131.4 (CH), 138.8 (C), 142.3 (2C), 158.5 (C), 165.6 (C), 168.5 (C). MS-ESI: *m/z* 369 $[MH]^+$. Anal. ($C_{20}H_{20}N_2O_3S$) C, H, N.

1,2-Dihydro-4-hydroxy-*N*,1-dimethyl-5-nitro-2-oxo-*N*-phenyl-3-quinolinecarboxamide (15b). ^{13}C NMR ($CDCl_3$) δ 29.8 (CH_3), 38.8 (CH_3), 104.7 (C), 106.8 (C), 116.1 (CH), 116.3 (CH), 125.5 (2CH), 127.0 (CH), 128.8 (2CH), 132.2 (CH), 141.3 (C), 143.7 (C), 148.4 (C), 157.8 (C), 163.8 (C), 169.1 (C). MS-ESI: *m/z* 354 $[MH]^+$. Anal. ($C_{18}H_{15}N_3O_5 \cdot 0.1H_2O$) C, H, N.

***N*-Ethyl-*N*-(2,4-difluorophenyl)-6,7-dihydro-9-hydroxy-6-methyl-7-oxo-1,3-dioxolo[4,5-*f*]quinoline-8-carboxamide (17b).** ^{13}C NMR ($CDCl_3$) δ 29.7 (CH_3), 38.5 (CH_3), 102.4 (C), 102.8 (CH_2), 104.6 (C), 106.1 (CH), 112.5 (CH), 125.7 (2CH), 126.8 (CH), 129.2 (2CH), 135.6 (C), 142.6 (C), 144.1 (C), 144.7 (C), 158.5 (C), 163.7 (C), 169.0 (C). MS-ESI: *m/z* 367 $[MH]^+$. Anal. ($C_{20}H_{18}N_2O_5 \cdot 1H_2O$) C, H, N.

6-Fluoro-*N*-(4-fluorophenyl)-1,2-dihydro-4-hydroxy-*N*,1-dimethyl-2-oxo-3-quinolinecarboxamide (20b). ^{13}C NMR ($CDCl_3$) δ 29.2 (CH_3), 38.8 (CH_3), 104.3 (C), 110.2 (CH, d, J_{CCF} = 24.0 Hz), 115.6 (CH, d, J_{CCCF} = 7.7 Hz), 115.6 (2 CH, d, J_{CCF} = 22.8 Hz), 116.3 (C, d, J_{CCCF} = 8.3 Hz), 120.6 (CH, d, J_{CCF} = 24.0 Hz), 127.4 (2CH, d, J_{CCCF} = 8.4 Hz), 137.0 (C, d, J_{CCCCF} = 1.6 Hz), 139.8 (C), 157.6 (CF, d, J_{CF} = 243 Hz), 158.4 (C), 161 2 (CF, d, J_{CF} = 247 Hz), 164.7 (C), 169.6 (C). MS-ESI: *m/z* 345 $[MH]^+$. Anal. ($C_{18}H_{14}N_2O_3F_2$) C, H, N.

1,2-Dihydro-4-hydroxy-*N*,1-dimethyl-2-oxo-*N*-phenyl-6-(trifluoromethyl)-3-quinolinecarboxamide (22b). ^{13}C NMR ($CDCl_3$) δ 29.2 (CH_3), 37.7 (CH_3), 105.5 (C), 114.3 (CH), 117.1 (C), 122.8 (CH), 123.6 (C, q, J_{CCF} = 33.2 Hz), 124.0 (CF_3, q, J_{CF} = 271.6 Hz), 125.6 (2CH), 127.1 (CH), 128.3 (CH), 128.8 (2CH), 141.9 (C), 143.8 (C), 160.5 (C), 164.3 (C), 169.3 (C). MS-ESI: *m/z* 377 $[MH]^+$. Anal. ($C_{19}H_{15}N_2O_3F_3$) H, N. C calcd, C 60.64; found, C 57.3.

6-Ethoxy-*N*-(4-fluorophenyl)-1,2-dihydro-4-hydroxy-*N*,1-dimethyl-2-oxo-3-quinolinecarboxamide (24b). ^{13}C NMR ($CDCl_3$) δ 14.7 (CH_3), 29.1 (CH_3), 38.8 (CH_3), 64.0 (CH_2), 103.8 (C), 106.4 (CH), 115.4 (CH), 115.5 (2CH, d, J_{CCF} = 22.8 Hz), 115.8 (C), 122.7 (CH), 127.4 (2CH, d, J_{CCCF} = 8.6 Hz), 135.1 (C), 140.1 (C), 153.9 (C), 158.3 (C), 161.1 (CF, d, J_{CF} = 247 Hz), 165.4 (C), 170.1 (C). MS-ESI: *m/z* 371 $[MH]^+$. Anal. ($C_{20}H_{19}N_2O_4F$) N. C, H calcd, C 64.85, H 5.17; found, C 61.4, H 4.71. Purity = 90% (contains 5% of the 6-hydroxy analogue).

1,2-Dihydro-4-hydroxy-6-methoxy-*N*,1-dimethyl-2-oxo-*N*-phenyl-6-(trifluoromethoxy)-3-quinolinecarboxamide (25b). ^{13}C NMR ($CDCl_3$) δ 29.2 (CH_3), 38.7 (CH_3), 104.0 (C), 115.4 (CH), 116.1 (C), 117.2 (CH), 120.4 (CF_3, q, J_{CF} = 258 Hz), 125.5 (2CH), 126.0 (CH), 126.8 (CH), 128.7 (2CH), 139.0 (C), 143.4 (C), 144.1 (C), 158.3 (C), 165.5 (C), 169.5 (C). MS-ESI: *m*/*z* 393 $[MH]^+$. Anal. ($C_{19}H_{15}N_2O_4F_3 \cdot 0.3H_2O$) C, H, N.

***N*-(4-Fluorophenyl)-1,2-dihydro-4-hydroxy-*N*,1-dimethyl-2-oxo-7-(trifluoromethyl)-3-quinolinecarboxamide (29b).** ^{13}C NMR ($CDCl_3$ + TFA) δ 30.6 (CH_3), 39.3 (CH_3), 106.6 (C), 112.4 (CH, q, J_{CCCF} = 4.0 Hz), 116.7 (2CH, d, J_{CCF} = 23.1 Hz), 117.8 (C), 120.2 (CH, q, J_{CCCF} = 3.3 Hz), 123.3 (CF_3, q, J_{CF} = 273 Hz), 126.3 (CH), 127.6 (CH, d, J_{CCCF} = 8.6 Hz), 135.4 (C, q, J_{CCF} = 32.8 Hz), 137.7 (C), 139.3 (C), 160.7 (C), 162.1 (C), 162.4 (CF, d, J_{CF} = 248 Hz), 168.1 (C). MS-ESI: *m*/*z* 395 $[MH]^+$. Anal. ($C_{19}H_{14}N_2O_3F_4 \cdot 1H_2O$) C, H, N.

***N*-(4-Fluorophenyl)-1,2-dihydro-4-hydroxy-*N*,1-dimethyl-2-oxo-7-phenoxy-3-quinolinecarboxamide (31b).** ^{13}C NMR ($CDCl_3$) δ 29.1 (CH_3), 38.9 (CH_3), 101.6 (C), 102.3 (CH), 110.4 (C), 112.0 (CH), 115.5 (2CH, d, J_{CCF} = 22.6 Hz), 120.2 (2CH), 124.9 (CH), 127.0 (CH), 127.3 (2CH, d, J_{CCCF} = 7.1 Hz), 130.1 (2CH), 140.3 (C), 142.4 (C), 155.3 (C), 158.9 (C), 161.0 (CF, d, J_{CF} = 246 Hz), 162.1 (C), 166.5 (C), 170.2 (C). MS-ESI: *m*/*z* 419 $[MH]^+$. Anal. ($C_{24}H_{19}N_2O_4F \cdot 0.9H_2O$) C, H, N.

8-Fluoro-*N*-(4-fluorophenyl)-1,2-dihydro-4-hydroxy-*N*,1-dimethyl-2-oxo-3-quinolinecarboxamide (32b). ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 32.8 (CH_3, d, J_{CNCCF} = 15.5 Hz), 37.7 (CH_3), 107.3 (C), 115.6 (2CH, d, J_{CCF} = 22.6 Hz), 118.7 (C, d, J_{CCCF} = 3.0 Hz), 119.1 (CH, d, J_{CCF} = 23.3 Hz), 120.4 (CH, d, J_{CCCCF} = 3.6 Hz), 121.9 (CH, d, J_{CCCF} = 8.2 Hz), 127.8 (2CH, d, J_{CCCF} = 8.6 Hz), 129.2 (C, d, J_{CCF} = 7.3 Hz), 139.6 (C), 150.0 (CF, d, J_{CF} = 245.7 Hz), 159.8 (C), 160.0 (C), 161.2 (CF, d, J_{CF} = 246.5 Hz), 167.2 (C). MS-ESI: *m*/*z* 345 $[MH]^+$. Anal. ($C_{18}H_{14}N_2O_3F_2 \cdot 0.6H_2O$) C, H, N.

***N*-(3,4-Dichlorophenyl)-1,2-dihydro-4-hydroxy-*N*,1-dimethyl-2-oxo-8-(trifluoromethyl)-3-quinolinecarboxamide (33b).** ^{13}C NMR ($CDCl_3$) δ 37.3 (CH_3, q, J_{CNCCCF} = 7.1 Hz), 38.9 (CH_3), 101.5 (C), 118.0 (C, q, J_{CCF} = 32.1 Hz), 119.0 (C), 121.8 (CH), 124.8 (CH), 123.7 (CF_3, q, J_{CF} = 273 Hz), 127.2 (CH), 128.8 (CH), 130.5 (CH), 130.9 (C), 132.7 (C), 133.2 (CH, q, J_{CCCF} = 6.0 Hz), 141.0 (C), 143.3 (C), 160.0 (C), 168.0 (C), 169.7 (C). MS-ESI: *m*/*z* 445 $[MH]^+$. Anal. ($C_{19}H_{13}N_2O_3Cl_2F_3$) C, N. H calcd, 2.94; found 3.42. Purity = 90%.

Preparation of Not Commercially Available Starting Materials Used in Methods A−F for the Syntheses of Esters and Target Compounds in Tables 1 and 2. All the N-alkylated anilines used in this study are either commercially available or prepared by N-alkylation of commercially available anilines.[19] The 6-ethylanthranilic acid used for preparation of quinoline ester **6a** was prepared from 3-ethylaniline.[14] 5-Dimethylaminoanthranilic acid was used for the preparation of ester **26a** from 5-amino-2-nitrobenzoic acid.[15] 6-Methoxyanthranilic acid (ester **11a**) was prepared from 2,6-difluoronitrile.[18] 2-Bromo-6-fluorobenzonitrile was used for the preparation of quinoline ester **9a** from 2-amino-6-fluorobenzonitrile.[17]

4-Nitroisatoic Anhydride (Preparation of Ester 15a, Method B). A mixture of 2-methyl-3-nitroaniline (54.8 g, 0.36 mol) and ethyl chloroformiate (100 mL, 1 mol) in 1,4-dioxane (500 mL) was heated at 65 °C for 24 h. The clear solution was evaporated to dryness to give white crystals in quantitative yield. This was dissolved in pyridine (250 mL) and water (250 mL) and warmed to 80 °C. Then $KMnO_4$ (142 g, 0.9 mol) was added portionwise during 4 h, maintaining the temperature at 80−95 °C. After another 1 h, the black mixture was filtered through Celite and the MnO_2 cake was carefully washed with hot water (800 mL). The collected yellowish filtrate was acidified with concentrated HCl to pH 3−4 and then extracted with CH_2Cl_2. The organic extract was concentrated to dryness, the residue was dissolved in aqueous Na_2CO_3 (100 mL), the undissolved material was filtered off, and the solution was acidified to give first a tar and then pure orange crystals: yield 10.0 g (0.04 mol). ^{1}H NMR ($CHCl_3$) δ 1.33 (t, 3H), 4.27 (q, 2H), 7.50 (d, 1H), 7.58 (t, 1H), 8.48 (d, 1H), 8.83 (bs, 1H). This acid was dissolved in 1,4-dioxane (40 mL), and thionyl chloride (7.2 g, 0.06 mol) was added. The mixture was heated at 40 °C overnight and then cooled, and the formed pure title compound was collected by filtration and dried under reduced pressure: yield 6.4 g (overall 9%). ^{1}H NMR (DMSO-d_6) δ 7.31 (d, 1H), 7.53 (d, 1H), 7.85 (t, 1H).

***N*-Methyl-6-(dimethylamino)anthranilic Acid (Preparation of Ester 16a, Method B).** A solution of 2,6-difluorobenzonitrile (35.7 g, 0.26 mol) and dimethylamine (17.5 g, 0.39 mol) in anhydrous 2-propanol (100 mL) was heated at 110 °C for18 h in an autoclave. After the mixture was cooled, the solvent was evaporated, the residue was worked up with aqueous $NaHCO_3$ and diethyl ether, and the ether extract was dried and concentrated to give a yellowish oil of 2-(dimethylamino)-6-fluorobenzonitrile contaminated with 2−4% of 2,6-di(dimethylamino)benzonitrile: yield 41.0 g. ^{1}H NMR ($CHCl_3$) δ 3.10 (s, 6H), 6.52 (t, 1H), 6.58 (d, 1H), 7.30 (q, 1H). This crude mixture was treated as above with 40% aqueous methylamine (130 mL, 1.5 mol) and gave 2-(dimethylamino)-6-methylaminobenzonitrile: yield 44 g (>95% pure). ^{1}H NMR ($CHCl_3$) δ 2.88 (d, 3H), 2.96 (s, 6H), 6.12 (d, 1H), 6.17 (d, 1H), 7.20 (t, 1H). This was hydrolyzed in concentrated H_2SO_4 (170 mL) and water (34 mL) at 120 °C for 3 h. The resulting brown solution was cooled and neutralized with 5 M NaOH. The resulting cloudy mixture was filtered through Celite and washed with diethyl ether (30 mL). Then the aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL) and the extracts were washed with water, dried, and concentrated to give the title compound as pure gray-reddish crystals: yield 21.5 g (overall 42%). ^{1}H NMR ($CDCl_3$) δ 2.75 (s, 6H), 2.89 (d, 3H), 6.54 (d, 1H), 6.57 (d, 1H), 7.30 (t, 1H).

***N*-Cyclopropylanthranilic Acid (Preparation of Ester 3a, Method B).** A solution of 2-fluorobenzonitrile (24.2 g, 0.2 mol) and cyclopropylamine (21 mL, 0.3 mol) in anhydrous 2-propanol (100 mL) was heated at 110 °C for 48 h in an autoclave. After the mixture was cooled, the solvent was evaporated and the residue was worked up with aqueous $NaHCO_3$ and diethyl ether. The organic phase was then evaporated to give a viscous paste, which upon trituration with petroleum ether gave a solid residue: yield 22.0 g. ^{1}H NMR (DMSO-d_6) δ 0.41−0.45 (m, 2H), 0.60−0.67 (m, 2H), 2.29−2.35 (m, 1H), 6.33 (b s, 1H), 6.62 (t, 1H), 6.98 (d, 1H), 7.37 (dt, 2H). This was dissolved in a solution of KOH (36.0 g, 0.64 mol) in ethanol (100 mL) and water (20 mL). The clear yellow solution was refluxed for 24 h, cooled, and acidified with concentrated HCl. The precipitate was filtered, washed with water, and dried to give the title compound as white pure crystals: yield 24.0 g (overall 68%). ^{1}H NMR (DMSO-d_6) δ 0.36−0.41 (m, 2H), 0.69−0.74 (m, 2H), 2.36−2.40 (m, 1H), 6.56 (t, 1H), 7.02 (d, 1H), 7.33 (t, 1H), 7.74 (1d, H).

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