# SYNTHESIS OF 3-SUBSTITUTED 4-HYDROXYQUINOLIN-2-ONES *VIA* *C*-ACYLATION REACTIONS OF ACTIVE METHYLENE COMPOUNDS WITH FUNCTIONALIZED 3,1-BENZOXAZIN-4-ONES

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Abstract- A general protocol for the construction of 4-hydroxyquinolin-2-ones is described. Benzoxazinones react with the anion of active methylene compounds to produce the functionalized *C*-acylation compounds in very good yields. These key intermediates are cyclized to the desired quinolinones (**25-40**) under basic conditions. Spectral data and physical characteristics for all compounds are reported.

Quinolin-2,4-dione derivatives represent an important class of compounds that have widespread biological action. Many naturally occurring quinolinone derivatives exhibit antimicrobial activity and cytotoxicity against animal and plant tumors.[1] Quinolinone alkaloids (**I**) and (**II**), extracted from *Euodia roxburghiana*, protect CEM-SS cells from the cytopathic effects of HIV-1 *in vitro*.[2]


I   II
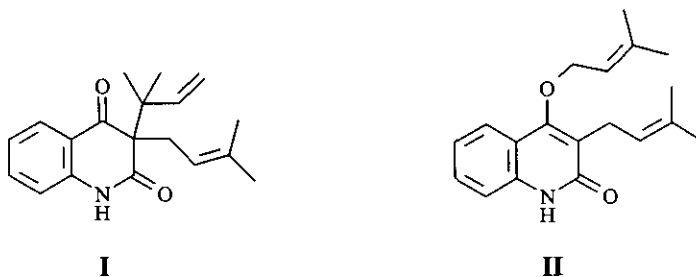
During recent years attention has increasingly been given to the synthesis of quinolinone and naphthyridinone antibacterials, collectively known as "quinolones", as a source of new chemotherapeutic agents. Noteworthy examples are kynurenic acid (**III**),[3] 3-methoxycarbonyl- and 3-benzoyl-4-hydroxyquinolin-2(1*H*)-ones (**IV**)[4] and L-701,324 (**V**).[5]

Recently, a class of quinolone carboxylic acids have been shown to inhibit DNA gyrase, a key enzyme in bacterial DNA replication.[6] It is reported that blood-brain barrier transport of "quinolone" derivatives is characterized by its dependence on lipophilicity.[7] Moreover, 2-oxoquinoline-3-carboxylic acid derivatives were designed and synthesized as 5-HT$_3$ receptor antagonists.[8]

The influence of the structure-activity relationship of varying substituents on the aromatic ring and N-1 was also investigated.[9] Compounds with a 7-chloro substituent are selective antagonists at NMDA
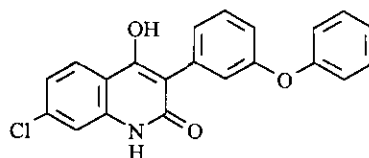
receptors; Leeson et al.[4] reported that 3-alkoxycarbonyl- and 3-benzoylquinolones (**IV**) with a small electron-withdrawing group at position 7 showed anticonvulsant activity.
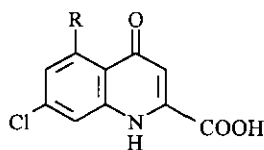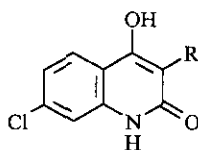
III (Kynurenic acid)   **IV** (R = CO$_2$Me, COPh)   **V** (L - 701,324)

Hitherto, synthetic work directed towards the development of new and improved synthesis of "quinolones" continues to be a challenging topic to the organic chemists. Our interest in the chemistry of "quinolone" derivatives possessing the "enolic β-dicarbonyl moiety", was to develop a simple and efficient route to highly functionalized 4-hydroxyquinolin-2-ones with different substituents at one or two positions on the aromatic ring. It is well known that, many "quinolone" derivatives with biochemical interest possess a substituent on the aromatic ring. Moreover, the nature and position of the substituents can change the biochemical properties of these molecules. Then, it appeared worthwhile to investigate the tandem C-acylation - cyclization reaction (Scheme 1) in order to open a route to highly functionalized "quinolones" endowed with a large synthetic potential.

The substituted 4-hydroxyquinolin-2-ones and congeners were generally prepared by treatment of anthranilic esters with an appropriate acylating agent to produce the corresponding N-substituted compound, which was converted to the 4-hydroxyquinolinone under basic conditions.[4,5,10,11] Alternatively, condensation of substituted malonates with anilides gave the corresponding 3-substituted quinolinones.[12] Coppola and co-workers[13] have synthesized similar compounds using isatoic anhydrides as precursors. Recently, Ganesan et al.[14] have reported a solid-phase combinatorial synthesis of 3-cyano-4-hydroxyquinolin-2(1H)-ones.

As part of our program on the chemistry of heterocyclic systems as potential pharmacological agents,[15,16] we report here an improved methodology for the synthesis of 7-chloro- and 6,7-dimethoxy-3-substituted 4-hydroxyquinolin-2-ones (**32-40**) using a suitably substituted benzoxazinone (**5** or **6**) as starting material. The C-acylation intermediates used in this study have been prepared in our laboratory. These products are promising precursors for the synthesis of polyfunctional "quinolone" derivatives. The preparation of the C-acylation intermediates and their subsequent cyclization chemistry are summarized in Scheme 1.

The performance of the C-acylation reaction was first explored using as acylating agent an anthranilic acid derivative, the 2-ethoxy-3,1-benzoxazin-4-one (**4**), available in a single step from anthranilic acid (**1**).[17] Modification of the phenyl in **1** to 4-chlorophenyl in **2** and 4,5-dimethoxyphenyl in **3** was well evaluated

leading to 7-chloro-2-ethoxy-3,1-benzoxazin-4-one (**5**) and 6,7-dimethoxy-2-ethoxy-3,1-benzoxazin-4-one (**6**) in good yields (69-91%).

1 - 3

4 $X_1 = X_2 = H$
5 $X_1 = H, X_2 = Cl$
6 $X_1 = X_2 = OMe$

7 - 24   **25 - 40**
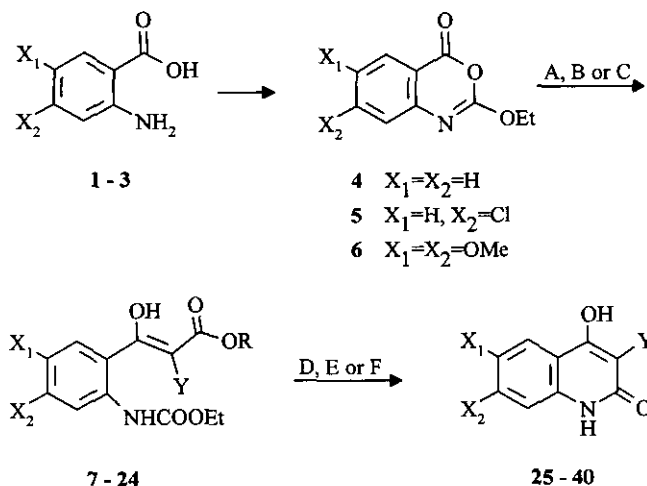
Scheme 1

In a typical C-acylation reaction, 2 or 3 equiv. of an active methylene compound were treated with 2 equiv. of sodium hydride in benzene (method A), or 2 equiv. of potassium *tert*-butoxide in *tert*-butanol (method B), or tetrahydrofuran (method C) at ambient temperature. After 1 hour, 1 equiv. of the requisite benzoxazinone was added to the mixture which was stirred for 2-4 hours before treatment with water and ether; the aqueous layer in acidification gave the C-acylation compounds (**7-24**) as pure solids in good yields (50-99%). Cyclization of these intermediates was affected by refluxing with 2.2 equiv. of sodium hydride in alcohol-benzene (method D), sodium alkoxide in alcohol (method E), or potassium *tert*-butoxide in tetrahydrofuran (method F). Work up of the reaction mixture gave the functionalized 4-hydroxyquinolin-2-ones (**25-40**) as pure solids in good yields (76-100%). The isolated C-acylation compounds and the 4-hydroxyquinolin-2-ones prepared with this methodology are listed in Tables 1 and 2, respectively.

Table 1. C-Acylation Compounds (**7 - 24**).

	X_1	X_2	R	Y		X_1	X_2	R	Y
7	H	H	Me	CN	**16**	H	Cl	Et	CN
8	H	H	Et	CN	**17**	H	Cl	Me	CO_2Me
9	H	H	Me	CO_2Me	**18**	H	Cl	Et	CO_2Et
10	H	H	Et	CO_2Et	**19**	H	Cl	Et	SO_2Me
11	H	H	Et	SO_2Me	**20**	H	Cl	Et	COPh
12	H	H	Et	COMe	**21**	OMe	OMe	Me	CN
13	H	H	Et	$COPr^n$	**22**	OMe	OMe	Me	CO_2Me
14	H	H	Et	COPh	**23**	OMe	OMe	Et	SO_2Me
15	H	Cl	Me	CN	**24**	OMe	OMe	Et	COMe

Table 2. 4-Hydroxy-quinolin-2(1H)-ones (**25** - **40**).

	X_1	X_2	Y		X_1	X_2	Y		X_1	X_2	Y
25	H	H	CN	**31**	H	H	COPh	**37**	OMe	OMe	CN
26	H	H	CO_2Me	**32**	H	Cl	CN	**38**	OMe	OMe	CO_2Me
27	H	H	CO_2Et	**33**	H	Cl	CO_2Me	**39**	OMe	OMe	SO_2Me
28	H	H	SO_2Me	**34**	H	Cl	CO_2Et	**40**	OMe	OMe	COMe
29	H	H	COMe	**35**	H	Cl	SO_2Me				
30	H	H	$COPr^n$	**36**	H	Cl	COPh				

The key control element of this approach to "quinolone" heterocycles was the utilization of 2-substituted benzoxazinones (**4-6**) as acylating agents. Benzoxazinones represent unique species of anthranilic acid derivatives where both the carboxylate activation and the amino group protection are achieved simultaneously. Several features of the proposed methodology make it synthetically useful: the starting materials are inexpensive, stable and readily available; the yields of the C-acylation and cyclization reactions are very good; the reactions are relatively rapid and proceed at ambient temperature and under mild conditions.

The structures of the obtained C-acylation compounds (**7-24**) were confirmed by elemental analysis and their spectral data (Tables 3 and 4). The ^{1}H NMR spectra of the newly obtained C-acylation compounds indicate that the N-ethoxycarbonylanthranyl cyanoacetates (**7, 8, 15, 16, 21**) exist in their enol form showing an enol proton at δ 14.52-14.80 (exchangeable). On the other hand the N-ethoxycarbonylanthranyl malonates (**9, 10, 17, 18, 22**), and methylsulfonyl esters (**11, 19, 23**) were found to exist in the keto form showing a methine proton at δ 5.29-5.85. In CDCl$_3$ solution, the N-ethoxycarbonylanthranyl acylacetates (**12, 13, 24**) exist as a mixture of the keto form and two different enol forms (Scheme 2).
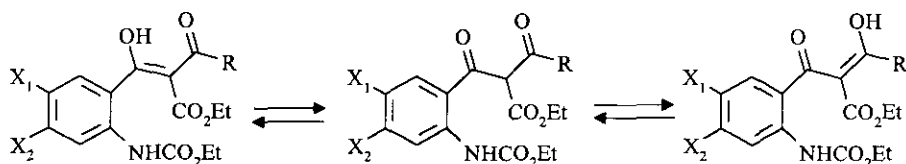
Scheme 2

The N-ethoxycarbonylanthranyl benzoylacetates (**14**) and (**20**) exist as a mixture of the keto and one enol form showing the methine proton at δ 6.20 and 6.27, and the enol proton at δ 13.48. The keto/enol ratio is 55:45 and 45:55 for compounds (**14**) and (**20**), respectively.

Table 3. ^{1}H NMR Chemical Shifts for the *C*-Acylation Compounds (**7 - 24**) (CDCl$_3$).[†]
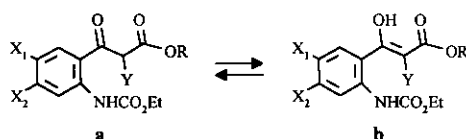
	NCOOCH$_2$CH$_3$	R	ArH and X$_1$, X$_2$	CH / OH	NH
7	4.22 (2 H, q, J 7), 1.31 (3 H, t, J 7)	3.97 (3 H, s, OCH_3)	8.11 (1 H, d, J_{34} 8, 3-H), 7.69 (1 H, dd, J_{56} 8, J_{46} 2, 6-H), 7.54 (1 H, pseudotriplet, 4-H), 7.17 (1 H, pseudotriplet, 5-H)	14.52 (OH)	7.74
8	4.21 (2 H, q, J 7), 1.30 (3 H, t, J 7)	4.41 (2 H, q, J 7, OCH_2), 1.40 (3 H, t, J 7, CH_3)	8.10 (1 H, d, J_{34} 8, 3-H), 7.68 (1 H, dd, J_{56} 8, J_{46} 2, 6-H), 7.52 (1 H, pseudotriplet, 4-H), 7.15 (1 H, pseudotriplet, 5-H)	14.66 (OH)	7.76
9	4.22 (2 H, q, J 7), 1.31 (3 H, t, J 7)	3.82 (6 H, s, OCH_3)	8.57 (1 H, dd, J_{34} 8, J_{35} 1, 3-H), 7.65 (1 H, dd, J_{56} 8, J_{46} 1, 6-H), 7.60 (1 H, pseudotriplet, 4-H), 7.06 (1 H, pseudotriplet, 5-H)	5.41 (CH)	10.80
10	4.23 (2 H, q, J 7), 1.30 (3 H, t, J 7)	4.28 (4 H, q, J 7, OCH_2), 1.27 (6 H, t, J 7, CH_3)	8.56 (1 H, dd, J_{34} 8, J_{35} 1, 3-H), 7.66 (1 H, dd, J_{56} 8, J_{46} 1, 6-H), 7.58 (1 H, pseudotriplet, 4-H), 7.06 (1 H, pseudotriplet, 5-H)	5.36 (CH)	10.79
11	4.25 (2 H, q, J 7), 1.34 (3 H, t, J 7)	4.31 (2 H, m, OCH_2), 1.30 (3 H, t, J 7, CH_3)	8.58 (1 H, dd, J_{34} 9, J_{35} 1, 3-H), 7.91 (1 H, dd, J_{56} 8, J_{46} 1, 6-H), 7.65 (1 H, pseudotriplet, 4-H), 7.14 (1 H, pseudotriplet, 5-H)	5.85 (CH)	10.64
12[‡]	4.24 (2 H, q, J 7), 1.33 (3 H, t, J 7)	4.12 (2 H, q, J 7, OCH_2), 1.03 (3 H, t, J 7, CH_3)	8.47 (1 H, dd, J_{34} 9, J_{35} 1, 3-H), 7.65 (1 H, dd, J_{56} 8, J_{46} 1, 6-H), 7.53 (1 H, pseudotriplet, 4-H), 7.00 (1 H, pseudotriplet, 5-H)	13.12 (OH)	10.78
13[‡]	4.24 (2 H, q, J 7), 1.34 (3 H, t, J 7)	4.11 (2 H, q, J 7, OCH_2), 1.02 (3 H, t, J 7, CH_3)	8.48 (1 H, dd, J_{34} 9, J_{35} 1, 3-H), 7.66 (1 H, dd, J_{56} 8, J_{46} 1, 6-H), 7.53 (1 H, pseudotriplet, 4-H), 6.99 (1 H, pseudotriplet, 5-H)	13.11 (OH)	10.82
14a	4.15 - 4.35 (4 H, m, OCH_2), 1.05 - 1.35 (6 H, m, CH_3)		8.57 (1 H, dd, J_{34} 9, J_{35} 1, 3-H), 7.68 (1 H, dd, J_{56} 8, J_{46} 1, 6-H), 7.62 (1 H, pseudotriplet, 4-H), 7.04 (1 H, pseudotriplet, 5-H)	6.27 (CH)	10.81
14b	4.15 - 4.35 (4 H, m, OCH_2), 1.05 - 1.35 (6 H, m, CH_3)		8.41 (1 H, d, J_{34} 8, 3-H), 7.76 (1 H, dd, J_{56} 8, J_{46} 2, 6-H), 7.58 (1 H, pseudotriplet, 4-H), 6.94 (1 H, pseudotriplet, 5-H)	13.48 (OH)	10.79
15	4.23 (2 H, q, J 7), 1.32 (3 H, t, J 7)	3.98 (3 H, s, OCH_3)	8.27 (1 H, d, J_{35} 2, 3-H), 7.64 (1 H, d, J_{56} 8, 6-H), 7.13 (1 H, dd, J_{56} 8, J_{35} 2, 6-H)	14.60 (OH)	7.86
16	4.23 (2 H, q, J 7), 1.32 (3 H, t, J 7)	4.43 (2 H, q, J 7, OCH_2), 1.42 (3 H, t, J 7, CH_3)	8.28 (1 H, d, J_{35} 2, 3-H), 7.64 (1 H, d, J_{56} 8, 6-H), 7.13 (1 H, dd, J_{56} 8, J_{35} 2, 6-H)	14.77 (OH)	7.88
17	4.23 (2 H, q, J 7), 1.32 (3 H, t, J 7)	3.81 (6 H, s, OCH_3)	8.66 (1 H, d, J_{35} 2, 3-H), 7.55 (1 H, d, J_{56} 9, 6-H), 7.02 (1 H, dd, J_{56} 9, J_{35} 2, 6-H)	5.32 (CH)	10.86
18	4.23 (2 H, q, J 7), 1.30 (3 H, t, J 7)	4.28 (4 H, q, J 7, OCH_2), 1.27 (6 H, t, J 7, CH_3)	8.65 (1 H, d, J_{35} 2, 3-H), 7.57 (1 H, d, J_{56} 9, 6-H), 7.02 (1 H, dd, J_{56} 9, J_{35} 2, 6-H)	5.27 (CH)	10.85
19	4.23 (2 H, q, J 7), 1.32 (3 H, t, J 7)	4.31 (2 H, m, OCH_2), 1.29 (3 H, t, J 7, CH_3)	8.68 (1 H, d, J_{35} 2, 3-H), 7.83 (1 H, d, J_{56} 9, 6-H), 7.10 (1 H, dd, J_{56} 9, J_{35} 2, 6-H)	5.75 (CH)	10.72
20a	4.15 - 4.35 (4 H, m, OCH_2), 1.10 - 1.35 (6 H, m, CH_3)		8.66 (1 H, d, J_{35} 2, 3-H), 7.59 (1 H, d, J_{56} 9, 6-H), 6.99 (1 H, dd, J_{56} 9, J_{35} 2, 6-H)	6.20 (CH)	10.89
20b	4.15 - 4.35 (4 H, m, OCH_2), 1.10 - 1.35 (6 H, m, CH_3)		8.51 (1 H, d, J_{35} 2, 3-H), 7.69 (1 H, d, J_{56} 9, 6-H), 6.90 (1 H, dd, J_{56} 9, J_{35} 2, 6-H)	13.48 (OH)	
21	4.21 (2 H, q, J 7), 1.31 (3 H, t, J 7)	3.96 (3 H, s, OCH_3)	8.14 (1 H, s, 3-H), 7.27 (1 H, s, 6-H), 3.95 (3 H, s, 4-OCH_3), 3.90 (3 H, s, 5-OCH_3)	14.80 (OH)	7.85
22	4.21 (2 H, q, J 7), 1.31 (3 H, t, J 7)	3.82 (6 H, s, OCH_3)	8.26 (1 H, s, 3-H), 7.26 (1 H, s, 6-H), 3.98 (3 H, s, 4-OCH_3), 3.84 (3 H, s, 5-OCH_3)	5.29 (CH)	11.07
23	4.23 (2 H, q, J 7), 1.34 (3 H, t, J 7)	4.31 (2 H, m, OCH_2), 1.30 (3 H, t, J 7, CH_3)	8.27 (1 H, s, 3-H), 7.26 (1 H, s, 6-H), 4.00 (3 H, s, 4-OCH_3), 3.90 (3 H, s, 5-OCH_3)	5.70 (CH)	10.98
24[‡]	4.23 (2 H, q, J 7), 1.34 (3 H, t, J 7)	4.16 (2 H, q, J 7, OCH_2), 1.11 (3 H, t, J 7, CH_3)	8.22 (1 H, s, 3-H), 7.06 (1 H, s, 6-H), 4.00 (3 H, s, 4-OCH_3), 3.79 (3 H, s, 5-OCH_3)	13.00 (OH)	11.23

[†] Y shift values: **11**, 3.40 (3 H, s, SO$_2$CH_3); **12**, 2.01 (3 H, s, COCH_3); **13**, 2.23 (2 H, t, J 7.0, COCH_2), 1.64 (2 H, m, COCH$_2$CH_2CH$_3$), 0.89 (3 H, t, J 7.3, COCH$_2$CH$_2$CH_3); **14**, 7.88-7.94 (1 H, m, 4′-H), 7.42-7.53 (2 H, m, 2′-H), 7.22-7.40 (2 H, m, 3′-H); **19**, 3.39 (3 H, s, SO$_2$CH_3); **20**, 7.87-7.92 (1 H, m, 4′-H), 7.41-7.53 (2 H, m, 2′-H), 7.24-7.40 (2 H, m, 3′-H); **23**, 3.40 (3 H, s, SO$_2$CH_3); **24**, 1.98 (3 H, s, COCH_3).

[‡] Chemical shifts for the predominant enol form

Table 4. ^{13}C NMR Chemical Shifts for the C-Acylation Compounds (7 - 24) (CDCl$_3$).

	NCOOCH$_2$CH$_3$	C-1	C-2	C-3	C-4	C-5	C-6	COH	CY
7	153.4 (C=O), 61.6 (CH$_2$), 14.3 (CH$_3$)	120.8	137.1	121.8	133.9	123.3	130.2	183.5	81.8
8	153.4 (C=O), 61.6 (CH$_2$), 14.3 (CH$_3$)	120.9	137.0	121.7	133.8	123.2	130.1	183.5	81.9
9	153.8 (C=O), 61.3 (CH$_2$), 14.3 (CH$_3$)	119.7	142.8	119.7	136.3	121.6	130.6	192.4	62.3
10	153.8 (C=O), 61.3 (CH$_2$), 14.3 (CH$_3$)	119.9	142.6	119.7	136.1	121.6	130.6	192.8	62.8
11	153.9 (C=O), 61.6 (CH$_2$), 14.3 (CH$_3$)	119.9	143.3	119.8	137.2	121.9	132.0	189.7	74.6
12 [a]	154.0 (C=O), 61.2 (CH$_2$), 14.3 (CH$_3$)	123.4	141.6	119.1	135.1	121.3	132.9	178.1	105.8
13 [a]	154.1 (C=O), 61.2 (CH$_2$), 14.4 (CH$_3$)	123.6	141.6	119.1	135.1	121.2	133.0	180.9	105.6
14 [b]	153.9 (C=O), 61.3 (CH$_2$), 14.3 (CH$_3$)	120.0	142.8	119.8	136.1	121.6	130.7	190.5	64.8
[c]	154.0 (C=O), 61.5 (CH$_2$), 14.3 (CH$_3$)	123.5	141.7	118.9	135.1	121.3	131.4	174.6	105.5
15	153.1 (C=O), 61.9 (CH$_2$), 14.3 (CH$_3$)	118.3	140.5	121.4	138.5	123.3	131.1	182.3	81.9
16	153.1 (C=O), 61.9 (CH$_2$), 14.3 (CH$_3$)	118.4	140.4	121.3	138.5	123.3	131.2	182.3	82.1
17	153.6 (C=O), 61.7 (CH$_2$), 14.2 (CH$_3$)	118.0	143.8	119.7	143.0	122.0	131.7	191.7	62.4
18	153.6 (C=O), 61.6 (CH$_2$), 14.2 (CH$_3$)	118.2	143.6	119.6	142.7	121.9	131.7	192.0	62.8
19	153.4 (C=O), 61.9 (CH$_2$), 14.2 (CH$_3$)	118.1	144.2	119.6	144.1	122.2	133.1	189.0	74.6
20 [b]	153.6 (C=O), 61.6 (CH$_2$), 14.2 (CH$_3$)	118.2	143.8	119.6	142.7	121.9	131.8	190.3	64.9
[c]	153.7 (C=O), 61.7 (CH$_2$), 14.3 (CH$_3$)	121.6	142.8	118.9	141.5	121.5	131.6	174.8	105.1
21	153.6 (C=O), 61.5 (CH$_2$), 14.3 (CH$_3$)	111.2	133.5	104.8	153.9	144.3	112.3	183.0	79.6
22	154.2 (C=O), 61.3 (CH$_2$), 14.3 (CH$_3$)	111.9	140.0	102.1	156.1	143.4	112.0	189.9	62.8
23	154.0 (C=O), 61.5 (CH$_2$), 14.3 (CH$_3$)	112.2	141.0	102.0	157.1	143.6	112.9	186.8	75.1
24 [a]	154.3 (C=O), 61.2 (CH$_2$), 14.3 (CH$_3$)	115.3	138.8	101.9	155.3	143.0	115.1	177.0	105.7

	COOR	Y and X$_1$, X$_2$
7	171.7 (CO$_2$Me), 53.5 (OCH$_3$)	114.7 (CN)
8	171.4 (CO$_2$Et), 63.2 (OCH$_2$), 13.9 (CH$_3$)	114.8 (CN)
9	165.2 (CO$_2$Me), 53.3 (OCH$_3$)	165.2 (CO$_2$CH$_3$), 53.3 (CO$_2$CH$_3$)
10	164.8 (CO$_2$Et), 62.5 (OCH$_2$), 13.8 (CH$_3$)	164.8 (CO$_2$CH$_2$CH$_3$), 62.5 (OCH$_2$), 13.8 (CH$_3$)
11	161.9 (CO$_2$Et), 63.6 (OCH$_2$), 13.7 (CH$_3$)	40.3 (SO$_2$CH$_3$)
12 [a]	170.9 (CO$_2$Et), 61.1 (OCH$_2$), 13.7 (CH$_3$)	197.2 (COCH$_3$), 19.9 (COCH$_3$)
13 [a]	171.0 (CO$_2$Et), 61.0 (OCH$_2$), 13.7 (CH$_3$)	197.3 (COCH$_2$CH$_2$CH$_3$), 35.1 (COCH$_2$), 19.9 (CH$_2$), 13.6 (CH$_3$)
14 [b]	165.6 (CO$_2$Et), 62.6 (OCH$_2$), 13.8 (CH$_3$)	194.5 (COPh), 135.5 - 134.2 - 129.2 - 128.6 (COPh)
[c]	171.3 (CO$_2$Et), 61.2 (OCH$_2$), 13.8 (CH$_3$)	197.2 (COPh), 133.6 - 133.0 - 128.5 - 128.1 (COPh)
15	171.7 (CO$_2$Me), 53.7 (OCH$_3$)	114.5 (CN)
16	171.4 (CO$_2$Et), 63.5 (OCH$_2$), 13.9 (CH$_3$)	114.6 (CN)
17	165.0 (CO$_2$Me), 53.5 (OCH$_3$)	165.0 (CO$_2$CH$_3$), 53.5 (CO$_2$CH$_3$)
18	164.6 (CO$_2$Et), 62.6 (OCH$_2$), 13.8 (CH$_3$)	164.6 (CO$_2$CH$_2$CH$_3$), 62.6 (OCH$_2$), 13.8 (CH$_3$)
19	161.8 (CO$_2$Et), 63.7 (OCH$_2$), 13.7 (CH$_3$)	40.3 (SO$_2$CH$_3$)
20 [b]	165.4 (CO$_2$Et), 62.7 (OCH$_2$), 13.8 (CH$_3$)	193.8 (COPh), 135.3 - 134.4 - 129.2 - 128.6 (COPh)
[c]	171.1 (CO$_2$Et), 61.5 (OCH$_2$), 13.8 (CH$_3$)	196.4 (COPh), 133.5 - 134.2 - 128.6 - 128.0 (COPh)
21	172.4 (CO$_2$Me), 53.4 (OCH$_3$)	115.6 (CN), 56.3 and 56.1 (4- and 5-OCH$_3$)
22	165.4 (CO$_2$Me), 53.3 (OCH$_3$)	165.4 (CO$_2$CH$_3$), 53.3 (OCH$_3$), 56.2 (4- and 5-OCH$_3$)
23	162.2 (CO$_2$Et), 63.6 (OCH$_2$), 13.8 (CH$_3$)	40.5 (SO$_2$CH$_3$), 56.4 and 56.3 (4- and 5-OCH$_3$)
24 [a]	170.8 (CO$_2$Et), 61.1 (OCH$_2$), 13.9 (CH$_3$)	195.1 (COCH$_3$), 19.8 (COCH$_3$), 56.4 and 56.1 (4-, 5-OCH$_3$)

[a] Chemical shifts for the predominant enol form, [b] Keto form, [c] Enol form

Detailed assignments of ^{1}H and ^{13}C NMR spectra were accomplished by analysis of 2D NMR, including COSY, HETCOR and long-range HETCOR data.

The spectral assignments for compound (**11**) (Figure 1) are representative for the series of *C*-acylation compounds (**7-14**). The correlation between the quaternary carbon at δ 189.7 (C-7) and H-6 at δ 7.91 distinguishes C-7 from C-9 and fixes the H-6 position. The other aromatic ring protons are assigned by a COSY experiment. Moreover, long-range correlations are observed between the methine proton (H-8) resonating at δ 5.85 and carbons at 161.9 (C-9) and 189.7 (C-7). The HETCOR experiment establishes the proton and carbon one-bond connectivities in the structure of **11**. In particular, correlations were observed between carbons resonating at δ 137.2 (C-4), 132.0 (C-6), 121.9 (C-5), 119.8 (C-3), 74.6 (C-8) and 40.3 (SO$_2$CH$_3$), and protons resonating at δ 7.65 (H-4), 7.91 (H-6), 7.14 (H-5), 8.58 (H-3), 5.85 (H-8) and 3.40 (SO$_2$C*H*$_3$), respectively.
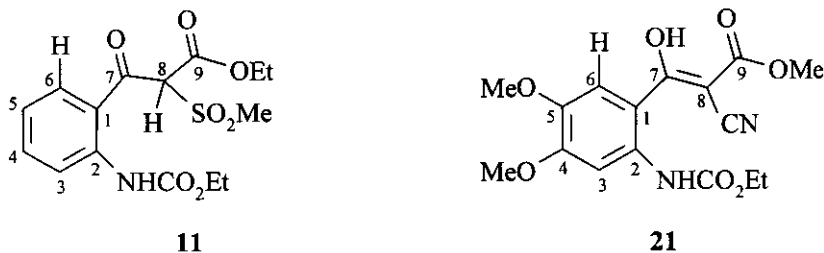
Figure 1

Similar experiments enabled the complete assignment of ^{1}H and ^{13}C resonances of compound (**21**) (Figure 1). The long range correlation between H-6 and C-7 distinguishes H-6 from H-3. Proton H-6 also correlates to the quaternary C-2 and C-4, though the latter is distinguished through its connectivity to the protons of 4-OCH$_3$ group. Such correlation is also observed for C-5 which also correlates to H-3. Carbons C-3 and C-6 are assigned through the one bond connectivities to H-3 and H-6. In the case of the 4-chloro compounds (**15-20**), the assignment of the aromatic protons is straight and their one bond connectivities designate the positions of C-3, C-5 and C-6.

The structures of 3-substituted 4-hydroxyquinolin-2(1*H*)-ones were identified by ^{1}H and ^{13}C NMR spectral results. The chemical shifts are given in Tables 5 and 6. It is possible to assign all protons by comparison with the model system referred to in the literature.[18,19] These compounds were found to exist in the enol form as their ^{1}H and ^{13}C NMR spectra lacked any signals corresponding to an sp^3-CH group for the quinoline-2,4-dione system. Moreover, only one set of signals can be observed for these compounds in DMSO-d$_6$ solutions, indicating that any possible tautomeric equilibrium between different enol forms is fast on the NMR time scale.

Table 5. ^{1}H NMR Chemical Shifts for 4-Hydroxyquinolin-2($1H$)-ones (**25 - 40**) (DMSO-d$_6$).

	5,6 - H and X$_1$, X$_2$	NH and OH	Y
25	7.98 (1 H, d, J_{56} 8.0, 5-H), 7.60 (1 H, pseudotriplet, 7-H), 7.27 (1 H, d, J_{78} 8.3, 8-H), 7.20 (1 H, pseudotriplet, 6-H)	11.76 (NH)	
26	7.89 (1 H, dd, J_{56} 8.1, J_{57} 1.5, 5-H), 7.59 (1 H, pseudotriplet, 7-H), 7.23 (1 H, d, J_{78} 8.1, 8-H), 7.17 (1 H, pseudotriplet, 6-H)	11.52 (NH), 13.40 (OH)	3.83 (3 H, s, CO$_2$CH_3)
27	7.90 (1 H, dd, J_{56} 8.1, J_{57} 1.4, 5-H), 7.60 (1 H, pseudotriplet, 7-H), 7.25 (1 H, d, J_{78} 8.1, 8-H), 7.18 (1 H, pseudotriplet, 6-H)	11.48 (NH), 13.42 (OH)	4.32 (2 H, q, J 7.1, CO$_2$CH_2), 1.28 (3 H, t, J 7.1, CH_3)
28	7.92 (1 H, dd, J_{56} 8.2, J_{57} 1.1, 5-H), 7.69 (1 H, pseudotriplet, 7-H), 7.31 (1 H, d, J_{78} 8.5, 8-H), 7.26 (1 H, pseudotriplet, 6-H)	11.96 (NH)	3.48 (3 H, s, SO$_2$CH_3)
29	7.96 (1 H, d, J_{56} 7.7, 5-H), 7.66 (1 H, pseudotriplet, 7-H), 7.27 (1 H, d, J_{78} 8.4, 8-H), 7.21 (1 H, pseudotriplet, 6-H)	11.52 (NH), 17.02 (OH)	2.69 (3 H, s, COCH_3)
30	7.96 (1 H, dd, J_{56} 7.8, J_{57} 1.2, 5-H), 7.65 (1 H, pseudotriplet, 7-H), 7.26 (1 H, d, J_{78} 8.2, 8-H), 7.21 (1 H, pseudotriplet, 6-H)	11.52 (NH), 17.07 (OH)	3.16 (2 H, t, J 7.2, COCH_2), 1.61 (2 H, m, CH_2Me), 0.92 (3 H, t, J 7.4, CH_3)
31	7.96 (1 H, dd, J_{56} 8.0, J_{57} 1.1, 5-H), 7.60 (1 H, pseudotriplet, 7-H), 7.31 (1 H, d, J_{78} 8.1, 8-H), 7.21 (1 H, pseudotriplet, 6-H)	11.56 (NH), 12.42 (OH)	7.76 (2 H, d, J 7.0, 2′-H), 7.59 (1 H, t, J 7.6, 4′-H), 7.47 (2 H, pseudotriplet, 3′-H)
32	7.96 (1 H, d, J_{56} 8.5, 5-H), 7.27 (1 H, d, J_{68} 2.1, 8-H), 7.23 (1 H, dd, J_{56} 8.5, J_{68} 2.1, 6-H)	11.74 (NH)	
33	7.91 (1 H, d, J_{56} 8.4, 5-H), 7.26 (1 H, d, J_{68} 1.8, 8-H), 7.23 (1 H, dd, J_{56} 8.4, J_{68} 1.8, 6-H)	11.60 (NH), 13.25 (OH)	3.83 (3 H, s, CO$_2$CH_3)
34	7.91 (1 H, d, J_{56} 8.5, 5-H), 7.27 (1 H, d, J_{68} 1.8, 8-H), 7.23 (1 H, dd, J_{56} 8.5, J_{68} 1.8, 6-H)	11.57 (NH), 13.34 (OH)	4.31 (2 H, q, J 7.1, CO$_2$CH_2), 1.28 (3 H, t, J 7.1, CH_3)
35	7.93 (1 H, d, J_{56} 8.5, 5-H), 7.33 (1 H, d, J_{68} 1.8, 8-H), 7.31 (1 H, dd, J_{56} 8.5, J_{68} 1.8, 6-H)	12.02 (NH)	3.47 (3 H, s, SO$_2$CH_3)
36	7.95 (1 H, d, J_{56} 8.7, 5-H), 7.33 (1 H, d, J_{68} 1.8, 8-H), 7.26 (1 H, dd, J_{56} 8.5, J_{68} 2.1, 6-H)	11.65 (NH), 13.30 (OH)	7.78 (2 H, d, J 7.0, 2′-H), 7.60 (1 H, t, J 7.6, 4′-H), 7.47 (2 H, pseudotriplet, 3′-H)
37	7.41 (1 H, s, 5-H), 6.77 (1 H, s, 8-H), 3.80 (3 H, s, 7-OCH_3), 3.76 (3 H, s, 6-OCH_3)	11.55 (NH)	
38	7.24 (1 H, s, 5-H), 6.76 (1 H, s, 8-H), 3.83 (3 H, s, 7-OCH_3), 3.81 (3 H, s, 6-OCH_3)	11.33 (NH), 13.64 (OH)	3.79 (3 H, s, CO$_2$CH_3)
39	7.21 (1 H, s, 5-H), 6.81 (1 H, s, 8-H), 3.84 (3 H, s, 7-OCH_3), 3.79 (3 H, s, 6-OCH_3)	11.76 (NH)	3.46 (3 H, s, SO$_2$CH_3)
40	7.26 (1 H, s, 5-H), 6.78 (1 H, s, 8-H), 3.83 (3 H, s, 7-OCH_3), 3.79 (3 H, s, 6-OCH_3)	11.31 (NH), 17.12 (OH)	2.66 (3 H, s, COCH_3)

Total assignments on the ^{1}H and ^{13}C NMR spectra were accomplished by utilizing COSY, HETCOR and long-range HETCOR experiments. For example, the carbonyl assignments for the 3-methoxycarbonyl-4-hydroxyquinolin-2-one (**26**) (Figure 2) were based on the long-range HETCOR data. A clear correlation can be seen from C-9 (CO_2CH_3) at δ 171.0 to the methyl protons at δ 3.83, distinguishing C-9 from C-4 at δ 169.2, which shows a correlation to the proton H-5 at δ 7.89.
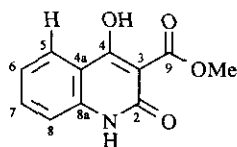

Figure 2

Table 6. ^{13}C NMR Chemical Shifts for 4-Hydroxyquinolin-2(1H)-ones (**25 - 39**) (DMSO-d_6).

	C - 2	C - 3	C - 4	C - 4a	C - 5	C - 6	C - 7	C - 8	C - 8a	other shift values
25	161.0	86.5	169.7	114.1	124.1	122.1	133.8	116.1	139.8	115.2 (*C*N)
26	159.5	99.8	169.2	113.5	124.3	121.9	134.0	115.4	140.1	171.0 (*C*O$_2$Me), 52.4 (*C*H$_3$)
27	159.5	100.0	169.1	113.5	124.2	121.8	133.9	115.4	140.0	170.5 (*C*O$_2$Et), 61.4 (*C*H$_2$), 14.0 (*C*H$_3$)
28	158.9	106.8	165.2	113.4	124.5	122.6	134.6	115.9	140.0	43.1 (SO$_2$*C*H$_3$)
29	161.5	105.9	175.0	113.6	124.9	122.2	135.2	115.6	140.9	206.3 (*C*OMe), 30.6 (*C*H$_3$)
30	161.3	105.6	175.0	113.6	124.9	122.1	135.2	115.6	140.8	208.7 (*C*OPr^n), 43.7 (*C*OCH$_2$), 17.1 (*C*H$_2$), 13.7 (*C*H$_3$)
31	161.7	109.9	163.8	114.8	124.0	121.9	132.9	115.6	139.7	196.1 (*C*OPh), 138.3 - 132.8 - 128.8 - 128.4 (CO*Ph*)
32	161.3	86.3	169.7	113.6	126.3	122.3	138.2	115.2	140.7	115.3 (*C*N)
33	159.6	100.7	167.8	112.7	126.4	122.2	138.2	114.6	140.8	170.2 (*C*O$_2$Me), 52.5 (*C*H$_3$)
34	159.6	100.8	167.8	112.6	126.4	122.1	138.2	114.6	140.7	169.8 (*C*O$_2$Et), 61.4 (*C*H$_2$), 13.9 (*C*H$_3$)
35	158.9	107.2	164.8	112.5	126.7	122.9	139.0	115.1	140.8	43.1 (SO$_2$*C*H$_3$)
36	161.7	110.5	162.4	113.9	126.1	122.0	138.0	114.8	140.4	195.3 (*C*OPh), 137.0 - 133.1 - 128.9 - 128.5 (CO*Ph*)
37	161.0	84.3	168.9	106.1	104.2	136.3	154.6	98.0	145.2	115.7 (*C*N), 55.8 (6- and 7-O*C*H$_3$)
38	159.3	96.7	170.1	105.5	104.1	136.9	155.3	97.4	145.2	172.1 (*C*O$_2$Me), 55.7 (6- and 7-O*C*H$_3$), 52.5 (CO$_2$*C*H$_3$)
39	158.7	104.6	164.6	105.5	103.9	136.7	155.4	97.8	145.6	55.9 and 55.7 (6- and 7-O*C*H$_3$), 43.0 (SO$_2$*C*H$_3$)

CONCLUSION

The proposed methodology appears to be general for the construction of "quinolone" derivatives in good yields. Of particular importance is its applicability to the synthesis of the useful key "intermediates" (**7-24**), inaccessible *via* previous methodologies. The mild conditions employed and the wide availability of the starting materials are attractive features.

EXPERIMENTAL

Melting points were determined on a Gallenkamp MFB-595 melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 267 photometer. The NMR spectra were recorded on a Gemini-2000 300 MHz spectrometer. Chemical shifts are quoted in ppm (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets); *J* values are given in Hz. The MS spectra were recorded on a VG 7070E mass spectrometer. Elemental analyses were obtained from the University of Liverpool, Chemistry Department.

General procedure for the preparation of 2-ethoxy-4H-3,1-benzoxazin-4-ones.

The 2-ethoxy-4H-3,1-benzoxazin-4-ones (**4-6**) were prepared following the procedure of Krantz *et al.*[17] with minor modifications. A solution of the substituted 2-aminobenzoic acid (0.020 mol) in pyridine (20 mL) was cooled at below 5 °C and ethyl chloroformate (0.080 mol, 7.6 mL) was added dropwise over a period of 15 min. The reaction

mixture was stirred at rt for 2-4 h, then the solvent was evaporated *in vacuo* and the solid residue stirred with 50 ml of ice-cold water. The insoluble solid was collected by filtration and washed with cold water.

2-Ethoxy-4H-3,1-benzoxazin-4-one (4). A mixture of anthranilic acid (**1**) (0.020 mol, 2.74 g), pyridine (20 mL) and ethyl chloroformate (0.080 mol, 7.6 mL) was stirred for 2 h and then worked-up as described above. After recrystallisation (ethyl acetate-light petroleum) the pure product was obtained as pale yellow crystals (3.47 g, 91%), mp 91-93 °C (lit.,[17] mp 88-90 °C); v_{max}(Nujol)/cm^{-1} 1750 (C=O), 1630 (C=N and C=C ring stretching); δ_H(300 MHz; CDCl$_3$) 1.44 (3 H, t, J 7, CH_3), 4.50 (2 H, q, J 7, CH_2), 7.32 (1 H, pseudotriplet, 6-H), 7.39 (1 H, d, $J_{7,8}$ 8, 8-H), 7.70 (1 H, pseudotriplet, 7-H), 8.09 (1 H, dd, $J_{5,6}$ 8, $J_{5,7}$ 2, 5-H); δ_C(75 MHz; CDCl$_3$) 13.9 (CH$_3$), 65.9 (CH$_2$), 114.5 (C-4α), 125.4 (C-8), 125.8 (C-6), 129.0 (C-5), 136.8 (C-7), 148.5 (C-8α), 154.8 (C-2), 159.6 (C-4).

7-Chloro-2-ethoxy-4H-3,1-benzoxazin-4-one (5). A mixture of 2-amino-4-chlorobenzoic acid (**2**) (0.025 mol, 4.30 g), pyridine (25 mL) and ethyl chloroformate (0.10 mol, 9.5 mL) was stirred for 3 h and then worked-up as described above. The crude product was dissolved in chloroform-light petroleum, the solution filtered through silica gel (Merck Kieselgel 60) and the filtrate evaporated *in vacuo* to afford the title compound as a white solid (5.10 g, 90%), mp 85-87 °C (from ether-light petroleum). Anal. Calcd for C$_{10}$H$_8$NO$_3$Cl : C, 53.23; H, 3.57; N, 6.21; M$^+$ 225.0193. Found: C, 53.33; H, 3.62; N, 6.16; M$^+$ 225.0196. v_{max}(Nujol)/cm^{-1} 1760 (C=O), 1630 (C=N and C=C ring stretching); δ_H(300 MHz; CDCl$_3$) 1.44 (3 H, t, J 7, CH_3), 4.50 (2 H, q, J 7, CH_2), 7.28 (1 H, dd, $J_{5,6}$ 9, $J_{6,8}$ 2, 6-H), 7.39 (1 H, d, $J_{6,8}$ 2, 8-H), 8.01 (1 H, d, $J_{5,6}$ 9, 5-H); δ_C(75 MHz; CDCl$_3$) 13.8 (CH$_3$), 66.3 (CH$_2$), 112.9 (C-4α), 125.2 (C-8), 126.4 (C-6), 130.2 (C-5), 143.2 (C-7), 149.6 (C-8α), 155.6 (C-2), 158.8 (C-4); m/z (EI) 225 (M$^+$, 32%), 197 (38), 180 ([M - OCH$_2$CH$_3$]$^+$, 100), 153 (65), 124 (31).

6,7-Dimethoxy-2-ethoxy-4H-3,1-benzoxazin-4-one (6). The reaction mixture containing 2-amino-4,5-dimethoxybenzoic acid (**3**) (0.050 mol, 9.90 g), pyridine (50 mL) and ethyl chloroformate (0.20 mol, 19.0 mL) was stirred for 4 h and then 150 mL of ice-cold water were added. The mixture was filtered and the solid washed with ice-cold water and air-dried. The crude product was dissolved in dichloromethane-light petroleum, the solution filtered through silica gel (Merck Kieselgel 60) and the filtrate evaporated *in vacuo* to afford compound (**6**) as a white solid (8.70 g, 69%), mp 171-172 °C (from ethyl acetate). Anal. Calcd for C$_{12}$H$_{13}$NO$_5$: C, 57.37; H, 5.22; N, 5.58; M$^+$ 251.0794. Found: C, 57.39; H, 5.22; N, 5.54; M$^+$ 251.0790. v_{max}(Nujol)/cm^{-1} 1750 (C=O), 1620 (C=N and C=C ring stretching); δ_H(300 MHz; CDCl$_3$) 1.46 (3 H, t, J 7, CH$_2$CH_3), 3.95 (3 H, s, 6-OCH_3), 4.00 (3 H, s, 7-OCH_3), 4.48 (2 H, q, J 7, CH_2), 6.85 (1 H, s, 8-H), 7.43 (1 H, s, 5-H); δ_C(75 MHz; CDCl$_3$) 13.9 (CH$_2$CH$_3$), 56.2 (6-OCH$_3$), 56.3 (7-OCH$_3$), 65.7 (CH$_2$), 106.4 (C-4α), 106.5 (C-5), 108.0 (C-8), 145.0 (C-6), 147.9 (C-8α), 154.7 (C-2), 156.9 (C-7), 159.5 (C-4); m/z (EI) 251 (M$^+$, 100%), 223 (19), 206 ([M - OCH$_2$CH$_3$]$^+$, 32), 179 (26), 164 (28), 150 (23).

General procedures for the reactions of 2-ethoxy-4H-3,1-benzoxazazin-4-ones (4, 5 and 6) with active methylene compounds.

Method A: The active methylene compound (7.5 mmol) was added dropwise to a dispersion of sodium hydride (55-60% sodium hydride in oil; 5.0 mmol, 0.22 g) in anhydrous benzene (30 mL) and the thick slurry thus formed

was stirred at rt for 1 h. The appropriate 3,1-benzoxazin-4-one (2.5 mmol) was then added to the mixture and stirring continued at rt for 2-4 h. Water (*ca.* 5 mL) was added to the reaction mixture, the aqueous layer was separated and the organic phase extracted with water. The combined aqueous extracts were acidified with 10% hydrochloric acid, in an ice-water bath, to give a solid product which was filtered off and washed with ice-cold water.

Method B: The active methylene compound (4.0 mmol) was added dropwise to a solution of potassium *tert*-butoxide (4.0 mmol, 0.45 g) in *tert*-butanol (10 mL) and the mixture stirred at rt for 1 h. The appropriate 3,1-benzoxazin-4-one (2.0 mmol) was then added to the mixture and stirring continued at rt for 2-4 h. Water (*ca.* 5 mL) and ether (*ca.* 10 mL) were added to the reaction mixture, the aqueous layer was separated and the organic phase extracted with water. The combined aqueous extracts were acidified with 10% hydrochloric acid, in an ice-water bath, to give a solid product which was filtered off and washed with ice-cold water.

Method C: The active methylene compound (5.0 mmol) was added dropwise to a solution of potassium *tert*-butoxide (5.0 mmol, 0.56 g) in anhydrous tetrahydrofuran (15 mL) and the mixture stirred at rt for 30 min. The appropriate 3,1-benzoxazin-4-one (2.5 mmol) was then added to the mixture and stirring continued at rt for 2-4 h. The solvent was removed at reduced pressure and the residue was dissolved in water (10 mL). The solution was washed with a small amount of ether and then acidified with 10% hydrochloric acid, in an ice-water bath, to give a solid product which was filtered off and washed with ice-cold water.

Methyl [(2-ethoxycarbonylaminophenyl)hydroxymethylidene]cyanoacetate (7). Following method C. The reaction mixture [compound (**4**) (2.5 mmol, 0.48 g), methyl cyanoacetate (5.0 mmol, 0.50 g) and potassium *tert*-butoxide (5.0 mmol, 0.56 g) in anhydrous tetrahydrofuran (15 mL)] was stirred for 2 h and worked up as usual. The title compound was obtained as a white solid (0.65 g, 90%), mp 136-137 °C (from dichloromethane-light petroleum). Anal. Calcd for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65. Found: C, 57.93; H, 4.86; N, 9.67. ν_{max}(Nujol)/cm^{-1} 3400 (NH), 2220 (CN), 1740 (C=O, amide I), 1660 (C=O, ester), 1600 (C=C), 1530 (amide II).

Ethyl [(2-ethoxycarbonylaminophenyl)hydroxymethylidene]cyanoacetate (8). Following method C. The reaction mixture [compound (**4**) (2.5 mmol, 0.48 g), ethyl cyanoacetate (5.0 mmol, 0.56 g) and potassium *tert*-butoxide (5.0 mmol, 0.56 g) in anhydrous tetrahydrofuran (15 mL)] was stirred for 2 h and worked up as usual. The title compound was obtained as a white solid (0.67 g, 88%), mp 119-120 °C (from dichloromethane-light petroleum). Anal. Calcd for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.30; N, 9.21; M$^+$, 304.1059. Found: C, 59.13; H, 5.25; N, 9.17; M$^+$, 304.1058. ν_{max}(Nujol)/cm^{-1} 3400 (NH), 2230 (CN), 1740 (C=O, amide I), 1660 (C=O, ester), 1600 (C=C), 1520 (amide II); *m/z* 304 (M$^+$, 24%), 258 ([M - H - OCH$_2$CH$_3$]$^+$, 14), 232 (11), 212 (16), 186 (100), 160 (24), 146 (60).

Dimethyl 2-(2-ethoxycarbonylaminobenzoyl)malonate (9). Following method A. The reaction mixture [compound (**4**) (2.5 mmol, 0.48 g), dimethyl malonate (7.5 mmol, 0.99 g) and sodium hydride (55-60% sodium hydride in oil; 5.0 mmol, 0.22 g) in anhydrous benzene (30 mL)] was stirred for 2 h and worked up as usual. The title compound was obtained as a white solid (0.76 g, 94%), mp 101-104 °C (from dichloromethane-light

petroleum). Anal. Calcd for $C_{15}H_{17}NO_7$: C, 55.73; H, 5.30; N, 4.33; M^+, 323.1005. Found: C, 55.47; H, 5.29; N, 4.29; M^+, 323.1004. v_{max}(Nujol)/cm^{-1} 3270 (NH), 1730 (C=O, ester and amide I), 1640 (C=O, ketone), 1580 (C=C), 1520 (amide II); m/z (EI) 323 (M^+, 5), 291 ([M - H - OCH$_3$]$^+$, 4), 192 (10), 187 (60), 146 (100).

Diethyl 2-(2-ethoxycarbonylaminobenzoyl)malonate (10). Following method A. The reaction mixture [compound (4) (2.5 mmol, 0.48 g), diethyl malonate (7.5 mmol, 1.20 g) and sodium hydride (55-60% sodium hydride in oil; 5.0 mmol, 0.22 g) in anhydrous benzene (30 mL)] was stirred for 2 h and worked up as usual. The title compound was obtained as a white solid (0.73 g, 83%), mp 86-88 °C (from dichloromethane-light petroleum). Anal. Calcd for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.02; N, 3.99; M^+, 351.1318. Found: C, 58.11; H, 6.01; N, 3.96; M^+, 351.1318. v_{max}(Nujol)/cm^{-1} 3280 (NH), 1730 (C=O, ester and amide I), 1650 (C=O, ketone), 1580 (C=C), 1520 (amide II); m/z (EI) 351 (M^+, 4), 305 ([M - H - OCH$_2$CH$_3$]$^+$, 3), 278 ([M - COOCH$_2$CH$_3$]$^+$, 3), 192 (13), 187 (73), 146 (100).

Ethyl 2-(2-ethoxycarbonylaminobenzoyl)methylsulfonylacetate (11).
(i) Following method A. The reaction mixture [compound (4) (2.5 mmol, 0.48 g), ethyl methylsulfonylacetate (7.5 mmol, 1.25 g) and sodium hydride (55-60% sodium hydride in oil; 5.0 mmol, 0.22 g) in anhydrous benzene (30 mL)] was stirred for 2 h and worked up as usual. The title compound was obtained as a white solid (0.45 g, 50%).
(ii) Following method B. The reaction mixture [compound (4) (2.5 mmol, 0.48 g), ethyl methylsulfonylacetate (5.0 mmol, 0.83 g) and potassium *tert*-butoxide (5.0 mmol, 0.56 g) in *tert*-butanol (15 mL)] was stirred for 2 h and worked up as usual. The title compound was obtained as a white solid (0.67 g, 75%), mp 111-116 °C (from dichloromethane-light petroleum). Anal. Calcd for $C_{15}H_{19}NO_7S$: C, 50.41; H, 5.36; N, 3.92; M^+, 357.0882. Found: C, 50.55; H, 5.21; N, 3.98; M^+, 357.0885. v_{max}(Nujol)/cm^{-1} 3280 (NH), 1730 (C=O, ester and amide I), 1640 (C=O, ketone), 1580 (C=C), 1530 (amide II); m/z (EI) 357 (M+, 8), 311 ([M - H - OCH$_2$CH$_3$]$^+$, 7), 239 (11), 192 (9), 175 (40), 146 (100).

Ethyl [(2-ethoxycarbonylaminophenyl)hydroxymethylidene]acetoacetate (12). Following method A. The reaction mixture [compound (4) (2.5 mmol, 0.48 g), ethyl acetoacetate (7.5 mmol, 0.98 g) and sodium hydride (55-60% sodium hydride in oil; 5.0 mmol, 0.22 g) in anhydrous benzene (30 mL)] was stirred for 2 h and worked up as usual. The title compound was obtained as a white solid (0.74 g, 92%), mp 95-96 °C (from dichloromethane-light petroleum). Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.80; H, 5.96; N, 4.36. Found: C, 59.71; H, 5.95; N, 4.33. v_{max}(Nujol)/cm^{-1} 3280 (NH), 1740 (C=O, amide I), 1630 (C=O, ketone and ester), 1580 (C=C), 1510 (amide II).

Ethyl [(2-ethoxycarbonylaminophenyl)hydroxymethylidene]butanoylacetate (13). Following method A. The reaction mixture [compound (4) (2.5 mmol, 0.48 g), ethyl butanoylacetate (7.5 mmol, 1.20 g) and sodium hydride (55-60% sodium hydride in oil; 5.0 mmol, 0.22 g) in anhydrous benzene (30 mL)] was stirred for 2 h and worked up as usual. The title compound was obtained as a white solid (0.75 g, 86%), mp 66-68 °C (from diethyl ether-light petroleum). Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 61.90; H, 6.67; N, 3.97. v_{max}(Nujol)/cm^{-1} 3270 (NH), 1720 (C=O, amide I), 1640 (C=O, ketone and ester), 1580 (C=C), 1520 (amide II).

Ethyl [(2-ethoxycarbonylaminophenyl)hydroxymethylidene]benzoylacetate (14). Following method A. The reaction mixture [compound (**4**) (2.5 mmol, 0.48 g), ethyl benzoylacetate (7.5 mmol, 1.46 g) and sodium hydride (55-60% sodium hydride in oil; 5.0 mmol, 0.22 g) in anhydrous benzene (30 mL)] was stirred for 2 h and worked up as usual. The title compound was obtained as a white solid (0.96 g, 99%), mp 119-121 °C (from dichloromethane-light petroleum). Anal. Calcd for $C_{21}H_{21}NO_6$: C, 65.78; H, 5.52; N, 3.65. Found: C, 65.87; H, 5.54; N, 3.66. v_{max}(Nujol)/cm^{-1} 3270 (NH), 1720 (C=O, amide I), 1680 (C=O, ketone), 1640 (C=O, ester), 1580 (C=C), 1520 (amide II).

Methyl [(4-chloro-2-ethoxycarbonylaminophenyl)hydroxymethylidene]cyanoacetate (15).

(i) Following method B. The reaction mixture [compound (**5**) (2.0 mmol, 0.46 g), methyl cyanoacetate (4.0 mmol, 0.40 g) and potassium *tert*-butoxide (4.0 mmol, 0.45 g) in *tert*-butanol (10 mL)] was stirred for 2.5 h and worked up as usual. The title compound was obtained as a white solid (0.42 g, 65%).

(ii) Following method C. The reaction mixture [compound (**5**) (2.0 mmol, 0.46 g), methyl cyanoacetate (4.0 mmol, 0.40 g) and potassium *tert*-butoxide (4.0 mmol, 0.45 g) in anhydrous tetrahydrofuran (15 mL)] was stirred for 3 h and worked up as usual. The title compound was obtained as a white solid (0.63 g, 97%), mp 161-162 °C (from dichloromethane-light petroleum). Anal. Calcd for $C_{14}H_{13}N_2O_5Cl$: C, 51.78; H, 4.04; N, 8.63; M$^+$, 324.0513. Found: C, 51.80; H, 4.02; N, 8.61; M$^+$, 324.0513. v_{max}(Nujol)/cm^{-1} 3420 (NH), 2220 (CN), 1740 (C=O, amide I), 1660 (C=O, ester), 1590 (C=C), 1520 (amide II); *m/z* (EI) 324 (M$^+$, 22), 292 ([M - H - OCH$_3$]$^+$, 8), 266 (10), 246 (15), 233 (14), 220 (100), 194 (28), 180 (73).

Ethyl [(4-chloro-2-ethoxycarbonylaminophenyl)hydroxymethylidene]cyanoacetate (16).

(i) Following method B. The reaction mixture [compound (**5**) (2.0 mmol, 0.46 g), ethyl cyanoacetate (4.0 mmol, 0.45 g) and potassium *tert*-butoxide (4.0 mmol, 0.45 g) in *tert*-butanol (10 mL)] was stirred for 2.5 h and worked up as usual. The title compound was obtained as a white solid (0.46 g, 68%).

(ii) Following method C. The reaction mixture [compound (**5**) (2.0 mmol, 0.46 g), ethyl cyanoacetate (4.0 mmol, 0.45 g) and potassium *tert*-butoxide (4.0 mmol, 0.45 g) in anhydrous tetrahydrofuran (15 mL)] was stirred for 3 h and worked up as usual. The title compound was obtained as a white solid (0.61 g, 90%), mp 141-142 °C (from dichloromethane-light petroleum). Anal. Calcd for $C_{15}H_{15}N_2O_5Cl$: C, 53.19; H, 4.46; N, 8.27; M$^+$, 338.0669. Found: C, 53.30; H, 4.43; N, 8.27; M$^+$, 338.0668. v_{max}(Nujol)/cm^{-1} 3400 and 3420 (NH), 2220 (CN), 1740 (C=O, amide I), 1660 (C=O, ester), 1590 (C=C), 1520 (amide II); *m/z* (EI) 338 (M$^+$, 17), 292 ([M - H - OCH$_2$CH$_3$]$^+$, 22), 266 (16), 246 (36), 220 (100), 194 (32), 180 (72).

Dimethyl 2-(4-chloro-2-ethoxycarbonylaminobenzoyl)malonate (17). Following method A. The reaction mixture [compound (**5**) (2.0 mmol, 0.46 g), dimethyl malonate (6.0 mmol, 0.79 g) and sodium hydride (55-60% sodium hydride in oil; 4.1 mmol, 0.18 g) in anhydrous benzene (25 mL)] was stirred for 4 h and worked up as usual. The title compound was obtained as a white solid (0.47 g, 66%), mp 101-104 °C (from dichloromethane-light petroleum). Anal. Calcd for $C_{15}H_{16}NO_7Cl$: C, 50.36; H, 4.51; N, 3.92. Found: C, 50.26; H, 4.48; N, 3.89.

v_{max}(Nujol)/cm^{-1} 3260 (NH), 1730 (C=O, ester and amide I), 1640 (C=O, ketone), 1570 (C=C), 1510 (amide II).

Diethyl 2-(4-chloro-2-ethoxycarbonylaminobenzoyl)malonate (18). Following method A. The reaction mixture [compound (5) (2.0 mmol, 0.46 g), diethyl malonate (6.0 mmol, 0.96 g) and sodium hydride (55-60% sodium hydride in oil; 4.1 mmol, 0.18 g) in anhydrous benzene (25 mL)] was stirred for 4 h and worked up as usual. The title compound was obtained as a white solid (0.69 g, 89%), mp 112-115 °C (from dichloromethane-light petroleum). Anal. Calcd for C$_{17}$H$_{20}$NO$_7$Cl : C, 52.93; H, 5.23; N, 3.63; M$^+$, 385.0928. Found: C, 52.94; H, 5.21; N, 3.57; M$^+$, 385.0929. v_{max}(Nujol)/cm^{-1} 3260 (NH), 1730 (C=O, amide I), 1720 (C=O, ester), 1650 (C=O, ketone), 1570 (C=C), 1520 (amide II); m/z (EI) 385 (M$^+$, 2), 221 (59), 195 (15), 180 (100).

Ethyl 2-(4-chloro-2-ethoxycarbonylaminobenzoyl)methylsulfonylacetate (19). Following method C. The reaction mixture [compound (5) (2.0 mmol, 0.46 g), ethyl methylsulfonylacetate (4.0 mmol, 0.67 g) and potassium *tert*-butoxide (4.0 mmol, 0.45 g) in anhydrous tetrahydrofuran (15 mL)] was stirred for 3 h and worked up as usual. The title compound was obtained as a white solid (0.71 g, 91%), mp 126-128 °C (from dichloromethane-light petroleum). Anal. calcd for C$_{15}$H$_{18}$NO$_7$ClS : C, 45.98; H, 4.63; N, 3.57. Found: C, 45.92; H, 4.61; N, 3.57. v_{max}(Nujol)/cm^{-1} 3260 (NH), 1730 (C=O, ester and amide I), 1640 (C=O, ketone), 1570 (C=C), 1510 (amide II).

Ethyl [(4-chloro-2-ethoxycarbonylaminophenyl)hydroxymethylidene]benzoylacetate (20). Following method B. The reaction mixture [compound (5) (2.0 mmol, 0.46 g), ethyl benzoylacetate (4.0 mmol, 0.77 g) and potassium *tert*-butoxide (4.0 mmol, 0.45 g) in *tert*-butanol (10 mL)] was stirred for 2 h and worked up as usual. Compound (20) was obtained as a white solid (0.78 g, 93%), mp 137-141 °C (from diethyl ether-light petroleum); v_{max}(Nujol)/cm^{-1} 3260 (NH), 1730 (C=O, amide I), 1680 (C=O, ketone), 1650 (C=O, ester), 1580 (C=C), 1520 (amide II).

Methyl [(4,5-dimethoxy-2-ethoxycarbonylaminophenyl)hydroxymethylidene]cyanoacetate (21). Following method B. The reaction mixture [compound (6) (2.5 mmol, 0.63 g), methyl cyanoacetate (5.0 mmol, 0.50 g) and potassium *tert*-butoxide (5.0 mmol, 0.56 g) in *tert*-butanol (12 mL)] was stirred for 3.5 h and worked up as usual. The title compound was obtained as a yellow solid (0.80 g, 91%), mp 134-135 °C (from dichloromethane-light petroleum). Anal. Calcd for C$_{16}$H$_{18}$N$_2$O$_7$: C, 54.86; H, 5.18; N, 8.00; M$^+$, 350.1114. Found: C, 54.74; H, 5.16; N, 8.00; M$^+$, 350.1111. v_{max}(Nujol)/cm^{-1} 3440 (NH), 2220 (CN), 1740 (C=O, amide I), 1650 (C=O, ester), 1600 (C=C), 1530 (amide II); m/z (EI) 350 (M$^+$, 26), 318 ([M - H - OCH$_3$]$^+$, 67), 246 (36), 231 (47), 217 (22), 206 (100).

Dimethyl 2-(4,5-dimethoxy-2-ethoxycarbonylaminobenzoyl)malonate (22). Following method A. The reaction mixture [compound (6) (2.0 mmol, 0.51 g), dimethyl malonate (6.0 mmol, 0.79 g) and sodium hydride (60% sodium hydride in oil; 4.0 mmol, 0.16 g) in anhydrous benzene (25 mL)] was stirred for 3 h and worked up as usual. The title compound was obtained as a yellow solid (0.51 g, 67%), mp 135-136 °C (from dichloromethane-light petroleum). Anal. Calcd for C$_{17}$H$_{21}$NO$_9$: C, 53.26; H, 5.52; N, 3.65. Found: C, 53.20; H, 5.48; N, 3.62. v_{max}(Nujol)/cm^{-1} 3260 (NH), 1730 (C=O, ester and amide I), 1630 (C=O, ketone), 1590 (C=C), 1530 (amide II).

Ethyl 2-(4,5-dimethoxy-2-ethoxycarbonylaminobenzoyl)methylsulfonylacetate (23). Following method B. The reaction mixture [compound (**6**) (2.5 mmol, 0.63 g), ethyl methylsulfonylacetate (5.0 mmol, 0.83 g) and potassium *tert*-butoxide (5.0 mmol, 0.56 g) in *tert*-butanol (10 mL)] was stirred for 4 h and worked up as usual. The title compound was obtained as a yellow solid (0.70 g, 67%), mp 140-143 °C (from dichloromethane-light petroleum). Anal. Calcd for $C_{17}H_{23}NO_9S$: C, 48.91; H, 5.55; N, 3.36; M^+, 417.1093. Found: C, 48.81; H, 5.33; N, 3.28; M^+,417.1099. ν_{max}(Nujol)/cm^{-1} 3250 (NH), 1740 (C=O, ester and amide I), 1620 (C=O, ketone), 1580 (C=C), 1530 (amide II); *m/z* (EI) 417 (M^+, 11), 371 ([M - H - OCH_2CH_3]$^+$, 21), 206 (100).

Ethyl [(4,5-dimethoxy-2-ethoxycarbonylaminophenyl)hydroxymethylidene]acetoacetate (24). Following method A. The reaction mixture [compound (**6**) (2.0 mmol, 0.51 g), ethyl acetoacetate (6.0 mmol, 0.78 g) and sodium hydride (60% sodium hydride in oil; 4.0 mmol, 0.16 g) in anhydrous benzene (25 mL)] was stirred for 4 h and worked up as usual. The title compound was obtained as a yellow solid (0.40 g, 52%), mp 127-128 °C (from dichloromethane-light petroleum). Anal. Calcd for $C_{18}H_{23}NO_8$: C, 56.68; H, 6.08; N, 3.67. Found: C, 56.66; H, 6.06; N, 3.66. ν_{max}(Nujol)/cm^{-1} 3240 (NH), 1720 (C=O, amide I), 1620 (C=O, ketone and ester), 1590 (C=C), 1520 (amide II).

General procedures for the formation of 3-substituted 4-hydroxyquinolin-2(1*H*)-ones.

Method D: Methanol was added dropwise to a dispersion of sodium hydride (55-60% sodium hydride in oil; 2.2 mmol, 0.09 g) in anhydrous benzene (15 mL) until the evolution of hydrogen ceased. The *C*-acylation compound (1.0 mmol) was added, the mixture heated at reflux for 5 h and after cooling to rt the solvent was evaporated *in vacuo.* The solid residue was dispersed in water (*ca.* 10 mL) and acidified with 10% hydrochloric acid under cooling in an ice-water bath. The precipitate formed was collected by filtration and washed with ice-cold water.

Method E: To a solution of sodium alkoxide in alcohol [prepared by the addition of sodium (2.2 mmol, 0.05 g) to methanol (10 mL)] was added the *C*-acylation compound (1.0 mmol). The reaction mixture was refluxed for 5 h and after cooling to rt the solvent was evaporated *in vacuo*. The solid residue was dispersed in water (*ca.* 10 mL) and acidified with 10% hydrochloric acid under cooling in an ice-water bath. The solid product was collected by filtration and washed with ice-cold water.

Method F: The *C*-acylation compound (1.0 mmol) was added to a solution of potassium *tert*-butoxide (2.2 mmol, 0.25 g) in anhydrous tetrahydrofuran (15 mL) and the mixture heated at reflux for 3 h. The solvent was evaporated *in vacuo* and the solid residue dispersed in water (*ca.* 10 mL) and acidified with 10% hydrochloric acid under cooling in an ice-water bath. The solid product was filtered off and washed with ice-cold water.

3-Cyano-4-hydroxyquinolin-2(1*H*)-one (25). Following method E. A mixture of compound (**7**) (1.0 mmol, 0.29 g) and sodium methoxide in methanol [prepared from sodium (2.2 mmol, 0.05 g) and methanol (10 mL)] was refluxed for 5 h and worked up as described above to afford compound (**25**) as a white solid (0.18 g, 96%), mp 298-299 °C (from methanol) (lit.,[15] mp 293-296 °C); ν_{max}(Nujol)/cm^{-1} 2230 (CN), 1660 (C=O, amide I), 1600 (C=C).

3-Methoxycarbonyl-4-hydroxyquinolin-2(1H)-one (26).

(i) Following method D. A mixture of compound (9) (1.5 mmol, 0.48 g) and sodium methoxide [prepared from sodium hydride (55-60% sodium hydride in oil; 3.2 mmol, 0.14 g) and methanol] in anhydrous benzene (15 mL) was heated at reflux for 5 h and worked up as usual. Compound (26) was obtained as a white solid (0.33 g, 100%).

(ii) Following method F. The reaction mixture [compound (9) (0.65 mmol, 0.21 g) and potassium *tert*-butoxide (1.4 mmol, 0.16 g) in anhydrous tetrahydrofuran (9 mL)] was heated at reflux for 3 h and worked up as usual to afford the title compound as a white solid (0.13 g, 93%), mp 228-230 °C (from methanol) (lit.,[15] mp 226-228 °C); v_{max}(Nujol)/cm^{-1} 1670 (C=O, ester and amide I), 1600 (C=C).

3-Ethoxycarbonyl-4-hydroxyquinolin-2(1H)-one (27).

(i) Following method D. A mixture of compound (10) (1.0 mmol, 0.36 g) and sodium ethoxide [prepared from sodium hydride (55-60% sodium hydride in oil; 2.3 mmol, 0.10 g) and absolute ethanol] in anhydrous benzene (10 mL) was heated at reflux for 5 h and worked up as usual. Compound (27) was obtained as a white solid (0.21 g, 95%).

(ii) Following method E. A mixture of compound (10) (1.0 mmol, 0.36 g) and sodium ethoxide in ethanol [prepared from sodium (2.2 mmol, 0.05 g) and absolute ethanol (10 mL)] was refluxed for 4 h and worked up as usual to afford the title compound as a white solid (0.18 g, 78%).

(iii) Following method F. The reaction mixture [compound (10) (0.60 mmol, 0.21 g) and potassium *tert*-butoxide (1.3 mmol, 0.15 g) in anhydrous tetrahydrofuran (10 mL)] was heated at reflux for 3 h and worked up as usual to afford the title compound as a white solid (0.12 g, 86%), mp 214-215 °C (from ethanol) (lit.,[15] mp 212-215 °C); v_{max}(Nujol)/cm^{-1} 1670 (C=O, ester and amide I), 1610 (C=C).

3-Methylsulfonyl-4-hydroxyquinolin-2(1H)-one (28).

(i) Following method D. A mixture of compound (11) (1.0 mmol, 0.36 g) and sodium methoxide [prepared from sodium hydride (55-60% sodium hydride in oil; 2.3 mmol, 0.10 g) and methanol] in anhydrous benzene (12 mL) was heated at reflux for 3 h and worked up as usual. The title compound was obtained as a white solid (0.24 g, 97%).

(ii) Following method E. A mixture of compound (11) (1.0 mmol, 0.36 g) and sodium methoxide in methanol [prepared from sodium (2.2 mmol, 0.05 g) and methanol (10 mL)] was heated at reflux for 5 h and worked up as usual. The title compound was obtained as a white solid (0.22 g, 92%), mp 292-293 °C (from methanol) (lit.,[15] mp 290-292 °C); v_{max}(Nujol)/cm^{-1} 1650 (C=O, amide I), 1600 (C=C).

3-Acetyl-4-hydroxyquinolin-2(1H)-one (29). Following method D. A mixture of compound (12) (2.0 mmol, 0.65 g) and sodium methoxide [prepared from sodium hydride (55-60% sodium hydride in oil; 4.4 mmol, 0.19 g) and methanol] in anhydrous benzene (25 mL) was heated at reflux for 5 h and worked up as usual. The title compound was obtained as a white solid (0.36 g, 89%), mp 261-263 °C (from methanol) (lit.,[15] mp 261-263 °C); v_{max}(Nujol)/cm^{-1} 1660 (C=O, ketone and amide I), 1600 (C=C).

3-Butanoyl-4-hydroxyquinolin-2(1H)-one (30). Following method D. A mixture of compound (**13**) (1.0 mmol, 0.35 g) and sodium methoxide [prepared from sodium hydride (55-60% sodium hydride in oil; 2.2 mmol, 0.09 g) and methanol] in anhydrous benzene (12 mL) was heated at reflux for 5 h and worked up as usual. The title compound was obtained as a white solid (0.21 g, 91%), mp 223-226 °C (from methanol) (lit.,[20] mp 217-219 °C); v_{max}(Nujol)/cm^{-1} 1660 (C=O, ketone and amide I), 1600 (C=C).

3-Benzoyl-4-hydroxyquinolin-2(1H)-one (31). Following method D. A mixture of compound (**14**) (1.1 mmol, 0.46 g) and sodium methoxide [prepared from sodium hydride (55-60% sodium hydride in oil; 2.5 mmol, 0.11 g) and methanol] in anhydrous benzene (15 mL) was heated at reflux for 5 h and worked up as usual. The title compound was obtained as a white solid (0.31 g, 97%), mp 265-266 °C (from methanol) (lit.,[21] mp 258 °C); v_{max}(Nujol)/cm^{-1} 1660 (C=O, ketone and amide I), 1600 (C=C).

7-Chloro-3-cyano-4-hydroxyquinolin-2(1H)-one (32). Following method E. A mixture of compound (**15**) (1.0 mmol, 0.33 g) and sodium methoxide in methanol [prepared from sodium (2.2 mmol, 0.05 g) and methanol (10 mL)] was refluxed for 4 h and worked up as usual to afford compound (**32**) as a white solid (0.20 g, 90%), mp 306-307 °C (from methanol) (lit.,[5] mp 314-316 °C); v_{max}(Nujol)/cm^{-1} 2240 (CN), 1660 (C=O, amide I), 1590 (C=C).

7-Chloro-3-methoxycarbonyl-4-hydroxyquinolin-2(1H)-one (33). Following method D. A mixture of compound (**17**) (1.0 mmol, 0.36 g) and sodium methoxide [prepared from sodium hydride (55-60% sodium hydride in oil; 2.3 mmol, 0.10 g) and methanol] in anhydrous benzene (15 mL) was heated at reflux for 3 h and worked up as usual. Compound (**33**) was obtained as a white solid (0.22 g, 87%), mp >300 °C (from methanol) (lit.,[5] mp 240 °C). Anal. Calcd for $C_{11}H_8NO_4Cl$: C, 52.09; H, 3.18; N, 5.52; M$^+$, 253.0142. Found: C, 51.83; H, 3.17; N, 5.49; M$^+$, 253.0139. v_{max}(Nujol)/cm^{-1} 1680 (C=O, amide I), 1650 (C=O, ester), 1600 (C=C); m/z (EI) 253 (M$^+$, 17), 221 ([M - H - OCH$_3$]$^+$,78), 195 (10), 153 (100).

7-Chloro-3-ethoxycarbonyl-4-hydroxyquinolin-2(1H)-one (34). Following method D. A mixture of compound (**18**) (1.0 mmol, 0.39 g) and sodium methoxide [prepared from sodium hydride (55-60% sodium hydride in oil; 2.3 mmol, 0.10 g) and absolute ethanol] in anhydrous benzene (12 mL) was heated at reflux for 2 h and worked up as usual. Compound (**34**) was obtained as a white solid (0.22 g, 88%), mp >300 °C (from ethanol) (lit.,[5] mp >340 °C); v_{max}(Nujol)/cm^{-1} 1680 (C=O, amide I), 1650 (C=O, ester), 1600 (C=C).

7-Chloro-3-methylsulfonyl-4-hydroxyquinolin-2(1H)-one (35). Following method F. The reaction mixture [compound (**19**) (0.51 mmol, 0.20 g) and potassium *tert*-butoxide (1.1 mmol, 0.12 g) in anhydrous tetrahydrofuran (8 mL)] was heated at reflux for 3 h and worked up as usual. The title compound was obtained as a white solid (0.13 g, 93%), mp 289-291 °C (from methanol) (lit.,[5] mp 238-240 °C); v_{max}(Nujol)/cm^{-1} 1650 (C=O, amide I), 1590 (C=C).

3-Benzoyl-7-Chloro-4-hydroxyquinolin-2(1H)-one (36). Following method D. A mixture of compound (**20**) (0.6

mmol, 0.25 g) and sodium methoxide [prepared from sodium hydride (60% sodium hydride in oil; 1.5 mmol, 0.06 g) and methanol] in anhydrous benzene (7 mL) was heated at reflux for 5 h and worked up as usual. The title compound was obtained as a white solid (0.17 g, 94%), mp 303-304 °C (from methanol) (lit.,[5] mp 240 °C); v_{max}(Nujol)/cm^{-1} 1670 (C=O, ketone and amide I), 1600 (C=C).

3-Cyano-6,7-dimethoxy-4-hydroxyquinolin-2(1*H*)-one (37). Following method E. A mixture of compound (**21**) (1.0 mmol, 0.36 g) and sodium methoxide in methanol [prepared from sodium (2.2 mmol, 0.05 g) and methanol (10 mL)] was refluxed for 5 h and worked up as usual. Compound (**37**) was obtained as a white solid (0.20 g, 82%), mp 303-304 °C (from methanol). Anal. Calcd for $C_{12}H_{10}N_2O_4$: C, 58.53; H, 4.09; N, 11.38; M$^+$, 246.0641. Found: C, 57.97; H, 4.03; N, 11.18; M$^+$, 246.0640. v_{max}(Nujol)/cm^{-1} 2230 (CN), 1650 (C=O, amide I), 1600 (C=C); m/z (EI) 246 (M$^+$, 100), 231 (57), 203 (17), 186 (17).

6,7-Dimethoxy-3-methoxycarbonyl-4-hydroxyquinolin-2(1*H*)-one (38). Following method F. The reaction mixture [compound (**22**) (0.76 mmol, 0.29 g) and potassium *tert*-butoxide (1.7 mmol, 0.19 g) in anhydrous tetrahydrofuran (15 mL)] was heated at reflux for 3 h and worked up as usual. The title compound was obtained as a yellow solid (0.16 g, 76%), mp >320 °C (from methanol); v_{max}(Nujol)/cm^{-1} 1670 (C=O, amide I), 1630 (C=C and C=O, ester).

6,7-Dimethoxy-3-methylsulfonyl-4-hydroxyquinolin-2(1*H*)-one (39). Following method E. A mixture of compound (**23**) (1.0 mmol, 0.42 g) and sodium methoxide in methanol [prepared from sodium (2.2 mmol, 0.05 g) and methanol (10 mL)] was refluxed for 5 h and worked up as usual. Compound (**39**) was obtained as a white solid (0.24 g, 80%), mp 316-317 °C (from methanol); v_{max}(Nujol)/cm^{-1} 1640 (C=O, amide I), 1610 (C=C).

3-Acetyl-6,7-dimethoxy-4-hydroxyquinolin-2(1*H*)-one (40). Following method D. A mixture of compound (**24**) (0.76 mmol, 0.29 g) and sodium methoxide [prepared from sodium hydride (60% sodium hydride in oil; 1.7 mmol, 0.07 g) and absolute methanol] in anhydrous benzene (8 mL) was heated at reflux for 5 h and worked up as usual. The title compound was obtained as a yellow solid (0.20 g, 100%), mp 307-308 °C (from methanol); v_{max}(Nujol)/cm^{-1} 1650 (C=O, amide I and ketone), 1600 (C=C).

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