Direct Transformation of Baylis–Hillman Acetates into N-Substituted Quinolones through an $S_N2' \rightarrow S_NAr \rightarrow (\Delta^{3,4}–\Delta^{2,3}$ Shift) $\rightarrow$ Oxidation Sequence

John Victor Napoleon, Muraleedharan Kannoth Manheri*

Department of Chemistry, Indian Institute of Technology Madras, Chennai 600 036, India
Fax +91(44)22574202; E-mail: mkm@iitm.ac.in

Received 18 May 2011; revised 20 July 2011

Abstract: When subjected to tandem S_N2'–S_NAr cyclization in the presence of alkyl or aralkyl amines, Baylis–Hillman acetates gave the corresponding 1,2-dihydroquinolines, which on simple exposure to light and oxygen afforded the corresponding 4- and 2-quinolones through sensitized oxidation or a $\Delta^{3,4}$–$\Delta^{2,3}$ shift $\rightarrow$ oxidation cascade. The mechanism of the oxidation step, the stabilities of the 1,2- and 1,4-dihydroquinolines in solution and in the solid state, and the synthetic elaboration of the key intermediates to known therapeutic agents are discussed.

Key words: antibiotics, cyclizations, quinolines, radical reactions, photooxidations

4-Quinolone moieties are present in several antibiotics, such as ciprofloxacin, levofloxacin, and norfloxacin (Figure 1).[1–3] Ciprofloxacin and levofloxacin dominate this class in terms of sales, and collectively they generate about three billion US dollars a year.[4] The importance of such compounds is reinforced by their promising anti-HIV-1 integrase,[5] anticancer,[6] and antimalarial activities.[7] Like 4-quinolones, 2-quinolones also show potential medicinal properties, as illustrated by their anticancer[8,9] and anti-HIV-1 reverse transcriptase activities.[10]

Most existing methods for preparing 4-quinolones use substituted anilines, anthranilic acids, or *ortho*-haloaroyl compounds as starting materials, and involve Friedel–Crafts acylation, S_NAr, or cyclodehydration as key steps.[11,12] Gould–Jacobs cyclization, the Grohe–Heitzer reaction, and modifications of these reactions are widely used in the preparation of the core skeleton of fluoroquinolone antibiotics. In the Gould–Jacobs cyclization, a substituted aniline is treated with diethyl 2-(ethoxymethylene)malonate at high temperature to effect addition–elimination and cycloacylation reactions to form 4-hydroxyquinoline-3-carboxylate derivative that can be N-alkylated in a subsequent step (Scheme 1).[11,13,14] Problems associated with the scope of N-functionalization can be overcome by the use of the Grohe–Heitzer reaction, in which an *ortho*-haloaroyl halide is converted into an aroylmalonate ester by an acylation reaction.[15] Condensation of the active methylene unit with an *ortho* ester then generates an enol ether that can be treated with the amine to initiate an addition–elimination–cyclization cascade to form the corresponding quinolone (Scheme 1). 4-Quinolones can also be obtained from methyl 2-[hydroxy(2-halophenyl)methyl]-3-iodoacrylate, prepared by Baylis–Hillman-type reactions of arylaldehydes with methyl propiolate in the presence of a zirconium(IV) chloride/tetrabutylammonium iodide system.[16] *N*-Oxides of 4-hydroxyquinolines, prepared by trifluoroacetic acid-mediated cyclization of methyl 2-[hydroxy(2-nitrophenyl)methyl]acrylate (Baylis–Hillman products), can also be used as precursors of 4-quinolones.[17,18] Reduction of the *N*-oxides by using stoichiometric amounts of molybdenum hexacarbonyl in ethanol gave a quinolone precursor that is subsequently alkylated.[19] Notable approaches to the synthesis of 2-quinolones include the reductive cyclization of 2-nitrobenzaldehyde-derived Baylis–Hillman adducts [20,21] or the corresponding *O*-acetates,[22,23] trifluoroacetic acid- mediated tandem Claisen rearrangement and cyclization reactions of aniline-substitution products of Baylis–Hillman acetates,[24] or acid-catalyzed Friedel–Crafts cyclization reactions of *N*-aryl amides prepared from Baylis–Hillman products.[25]

In this report, we describe a strategy for converting Baylis–Hillman acetate-derived dihydroquinolines into 4- and 2-quinolones, useful in studies on structure–activity relationships.[11,13] The overall transformations involve four and five steps, respectively, and can be performed without isolation of intermediates (Scheme 2). As en-

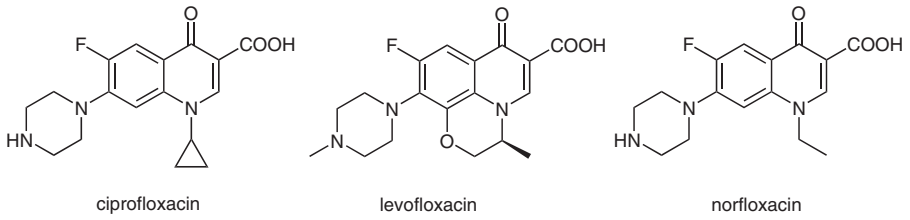
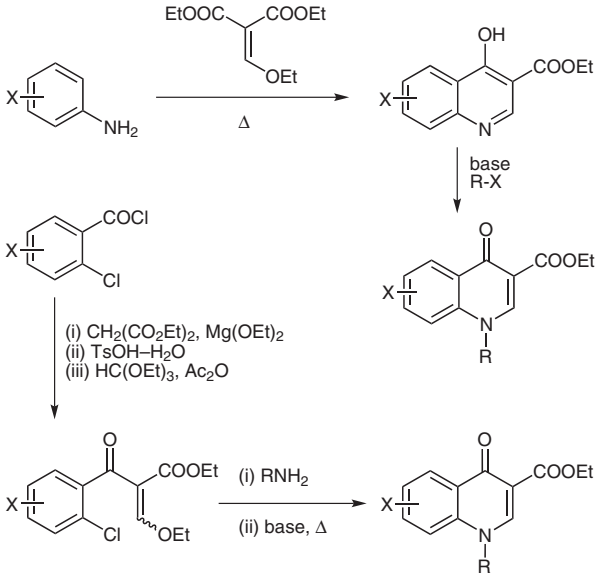


Figure 1 Examples of quinolone-based antibiotics

SYNTHESIS 2011, No. 20, pp 3379–3388
Advanced online publication: 05.09.2011
DOI: 10.1055/s-0030-1260189; Art ID: T52311SS



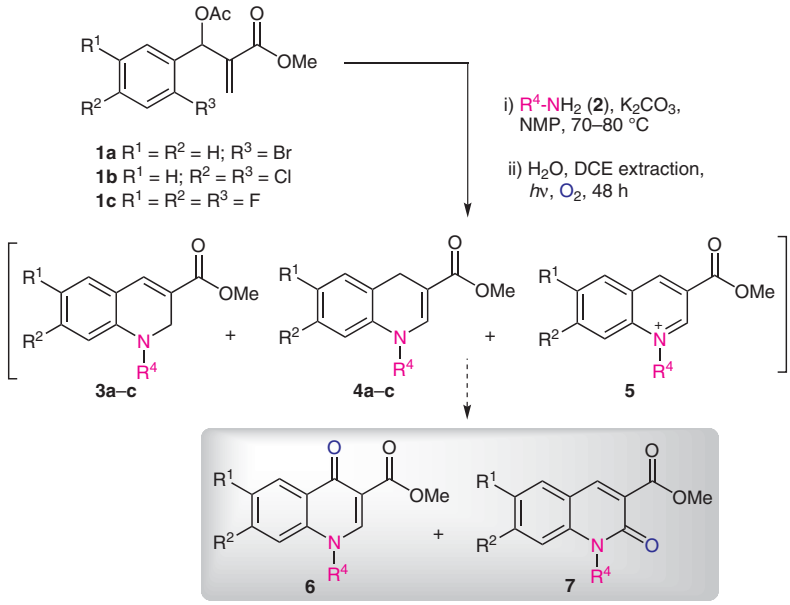
Scheme 1 Some known methods for preparing 4-quinolones

zymes such as aldehyde oxidase are known to convert quinolinium salts into 4- and 2-quinolones, the present observations highlight the possibility of in vivo activation of dihydroquinolines either enzymatically (via the quinolinium salt) or under the conditions of photodynamic therapy.[26–28]

The general experimental procedure involves heating a mixture of the Baylis–Hillman acetate **1a–c** and an amine **2** in *N*-methyl-2-pyrrolidinone (NMP) at 70–80 °C in the presence of potassium carbonate, diluting the mixture with 1,2-dichloroethane, washing with water to remove the *N*-methyl-2-pyrrolidinone and potassium carbonate, and irradiating the organic solution with a 200-W tungsten lamp (or a 354-nm UV light) under an atmosphere of oxygen to give the corresponding quinolone (Scheme 2). Although spots corresponding to 1,4-dihydroquinoline and quinolinium salt initially appeared on the thin-layer chromatograms, they became lighter and new spots corresponding to the quinolones began to appear during irradiation.

Clearly, the S_N2' displacement reaction of the Baylis–Hillman acetate **1a–c** with amine **2** followed by cyclization gives the expected dihydroquinoline **3**; this subsequently undergoes isomerization and oxidation to form the corresponding quinolones **6** and **7**. Results of preliminary studies on the effects of solvents, illumination sources, sensitizers, and quenchers on the outcome of the reaction of **1a** with benzylamine are shown in Table 1. Screening showed that dichloroethane or toluene is the most suitable solvent for this transformation (Table 1, entries 1–5). When acetonitrile was used (entry 2), the thermodynamically more stable 1,4-dihydroquinoline[29] **4a** was isolated in 46% yield, confirming that double-bond isomerization occurred before the oxidation step in **3a**. The structure of the 1,4-dihydroquinoline derivative **4a**, confirmed by X-ray diffraction analysis of crystals prepared from methanolic solution, is shown in Figure 2.[30] Isomerization reactions of this type have been previously observed, and the preparation of 1,4-dihydroquinolines from 1,2-isomers generated in situ from Baylis–Hillman acetates has been reported.[31]

When we performed the reaction in 1,2-dichloroethane as the solvent in darkness or in the absence of oxygen (entries 6 and 7), the reaction stopped at product **4a** (~70% yield), and only traces of products **6.1** and **7.1** were found in the reaction mixture. Although replacing the 200-W tungsten lamp with a 354-nm UV lamp (entry 8) did not have a significant effect on the yields of **6.1** and **7.1**, the introduction of methylene blue gave a consistent improvement (entry 9). There was approximately 50% reduction in yield on adding sodium azide, a $^1O_2$ quencher (entry



Scheme 2 Synthesis of N-substituted 4- and 2-quinolones

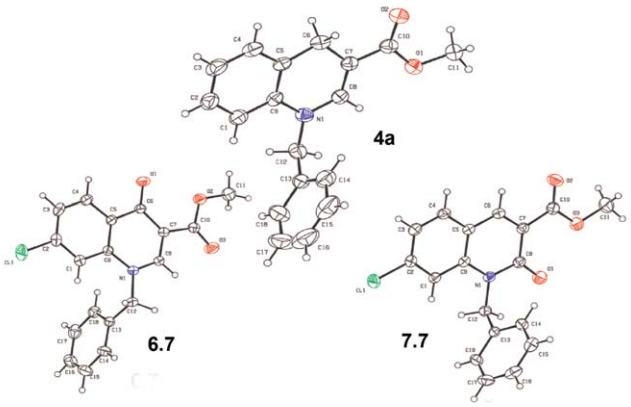


Figure 2 ORTEP diagrams of dihydroquinoline **4a** (R^4 = Bn), 4-quinolone **6.7**, and 2-quinolone **7.7**

10), but a similar effect was not evident in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO; entry 11).

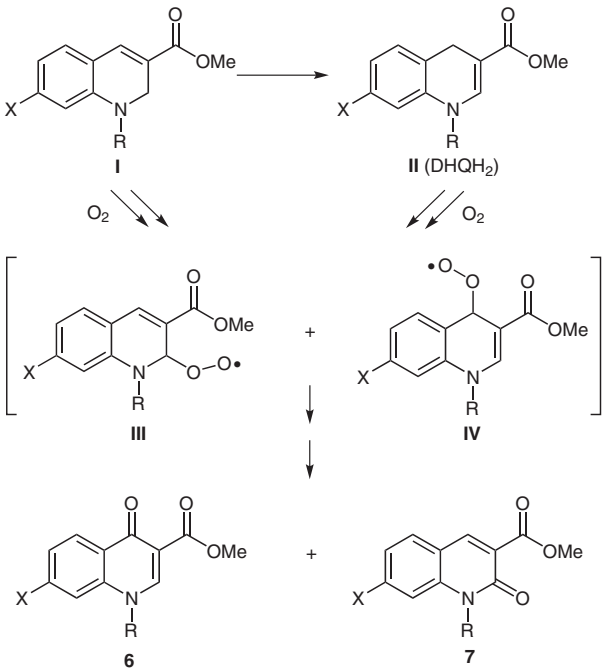
The presence of a reaction in the absence of an external sensitizer suggests that dihydroquinolines are capable of transferring energy or electrons to oxygen,[32,33] but this needs to be verified by detailed experiments. The need for light and oxygen, and the improvement in yield in the presence of methylene blue (which was more prominent in the case of electron-deficient dihydroquinolines; see supporting information) suggest that singlet oxygen is involved in the oxidation step. Other known sensitizers were less effective, either because of solubility problems (Rose Bengal) or because of the formation of intractable reaction mixtures as a result of side reactions (chloranil or tetraphenylporphyrin). Because the formation of a superoxide anion after an electron-transfer process, and its subsequent addition to the 4- or 2-positions of the quinolinium salt[34] to give allyl hydroperoxy intermediates is a possibility, we examined the reactions of dihydroquinolines **3b** (R^1 = H; R^2 = Cl; R^4 = Et) and **3c** (R^1 = R^2 = F; R^4 = Et) as starting materials in the presence of added lithium peroxide. Because no improvement in yield was observed in these cases, it is unlikely that such a pathway is involved.

Table 1 Effects of Solvent, Light, Oxygen, Sensitizers, and Quenchers on the Formation of Quinolones

Entry	Solvent[a]	Time (h)	Yield (%) of **6.1**	Yield (%) of **7.1**	Yield (%) of **4a**
1	MeOH	48	5	2	–
2	MeCN	24	10	–	46
3	THF	48	25	8	–
4	toluene	48	22	17	–
5	DCE	48	29	13	–
6	DCE[b]	120	3	1	70
7	DCE[c]	120	4	3	75
8	DCE[d]	24	26	5	–
9	**methylene blue/DCE**	**48**	**32**	**21**	–
10	DCE/NaN_3	48	16	5	–
11	DCE/DABCO	48	21	17	–

[a] All reactions were carried out under O_2 with irradiation by 200-W tungsten lamp, except as shown. The dihydroquinoline was prepared from **1a** (0.319 mmol) and $BnNH_2$.
[b] In darkness.
[c] Under argon.
[d] Irradiation by a 354-nm UV lamp.

To determine whether an ene-type addition of singlet oxygen[35,36] to the dihydroquinolines occurs, we prepared pure 1,4-dihydroquinoline **II** (X = Cl; R = Bn) (Scheme 3) from the corresponding 1,2-isomer **I**. When a solution of this compound in 1,2-dichloroethane was exposed to the 200-W bulb for 48 hours, both the 4-quinolone **6.7** and the 2-quinolone **7.7** were formed, suggesting that an intramolecular electronic redistribution occurs before the oxygen addition step. 9,10-Dihydro-10-methylacridine, an NADH model system, undergoes photooxidation in the presence of dioxygen through a radical-chain pathway involving an acridinyl peroxyl radical and a hydroperoxy radical as important intermediates.[37] The structural resemblance of dihydroquinolines to such compounds suggested that a similar mechanism might account for the formation of 4- and 2-quinolones. The pathway could start with the transfer of an electron from the dihydroquinoline [$DHQH_2$] to $^1O_2$ to form a dihydroquinoline radical cation–dioxygen radical anion pair, which dissociates to form a dihydroquinolinyl radical [DHQH]• and a hydroperoxyl radical. The C-centered dihydroquinolinyl radical might then undergo addition of dioxygen to give peroxy intermediates **III** and **IV** (Scheme 3), which are



Scheme 3 Probable pathways leading to quinolones **6** and **7** (X = H, halo, etc.; R = alkyl, arylalkyl, etc.)

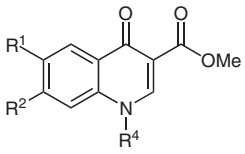
the probable precursors of the quinolones. Isomerization of the C-4 dihydroquinolinyl radical to the corresponding C-2 radical is the likely reason for the formation of the 2-quinolone from 1,4-dihydroquinoline **II** (X = Cl; R = Bn) (Scheme 3). The inefficiency of quenching by sodium azide or DABCO tends to suggest that triplet oxygen might also be involved as an electron acceptor. The mechanistic possibilities outlined here need to be verified by means of detailed experiments. We have initiated some studies with this aim, and our results will be reported in due course.

We next examined the scope of the method by using Baylis–Hillman acetates from other substituted aldehydes and alkyl amines, and our results are presented in Table 2. Linear and branched alkyl amines gave the corresponding quinolones in comparable yields to that obtained from benzylamine. Because the introduction of electron-withdrawing substituents on the aromatic ring might assist in derivatization of the products, chloro- and fluoro-substituted Baylis–Hillman acetates were prepared and treated with selected amines. Although the reaction in these cases proceeded less efficiently than that of **1a**, the ability to prepare quinolones such as **6.12** and **6.13**, which are immediate precursors of known drugs such as ciprofloxacin and norfloxacin (Figure 1) is a definite advantage. Cleavage of a C–N bond in salt **5** (Scheme 2) under the reaction conditions is probably responsible for the formation of aromatized products **8a–c** (entries 6, 10, and 12, respectively).[38,39] The structures of the 7-chloroquinolones **6.7** and **7.7** were confirmed by X-ray diffraction analysis of crystals prepared from methanolic solutions (Figure 2).[30] A characteristic feature in the ^{13}C NMR spectra of the 4-quinolones was the appearance of the keto carbonyl carbon at about δ = 174 ppm, compared with about δ = 159 ppm in the case of 2-quinolones.

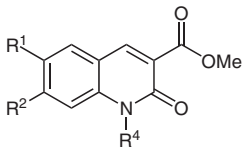
To demonstrate the utility of these quinolone skeletons in the synthesis of known therapeutic agents, we converted intermediates **6.12** and **6.13** into ciprofloxacin and norfloxacin, respectively, through S_NAr and hydrolysis steps, as shown in Scheme 4.[11,40,41] Similarly, the reaction of **7.7** with piperidine in *N*-methyl-2-pyrrolidinone at 120 °C for ten hours gave the 2-quinolone derivative **9** in 78% isolated yield, demonstrating the possibility of using derivatives such as **6.7–6.10** and **7.7–7.10** to prepare new libraries of quinolones (Scheme 4).

Although the 1,2-dihydroquinolines derived from 2-halobenzaldehydes (Table 2) were quite unstable and isomerized to the corresponding 1,4-form, we observed that the introduction of electron-withdrawing substituents on the aromatic ring has a stabilizing effect on these inter-

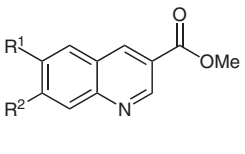
Table 2 Quinolones and Quinolines Prepared from Baylis–Hillman Acetates **1a–c** and Various Amines[a]



6



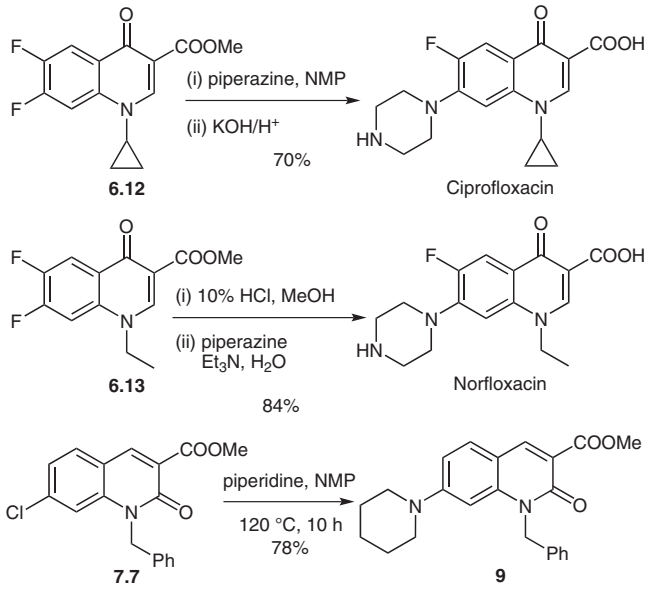
7



8

Entry[a]	R^4	R^2	R^1	Product distribution			Total yield of **6** + **7** (%)
				6	**7**	**8a–c**	
1	Bn	H	H	32	21	–	53
2	***i*-Bu**	**H**	**H**	**40**	**18**	–	**58**
3	Bu	H	H	35	22	–	57
4	Me	H	H	26	25	–	51
5	Cy	H	H	31	–	–	31
6	*c*-Pr	H	H	17	–	17 (**8a**)	17
7	Bn	Cl	H	25	10	–	35
8	*i*-Bu	Cl	H	24	7	–	31
9	Bu	Cl	H	23	10	–	33
10	Et	Cl	H	23	7	7 (**8b**)	30
11	Cy	Cl	H	31	–	–	31
12[b]	*c*-Pr	F	F	14	–	14 (**8c**)	14
13[b]	Et	F	F	26	3	–	29

[a] Irradiation with 200-W tungsten lamp in the presence of methylene blue, except where stated.
[b] Irradiation with 354-nm UV lamp.



Scheme 4 Synthesis of known therapeutic agents from intermediates prepared by the present method

mediates. To understand the extent of isomerization of such systems, we studied the stability of 1,2-dihydroquinoline **3c** (R^4 = Et) in both the solid state and as a solution in deuterochloroform (Figure 3). As evident from its spectrum, a freshly prepared solution of **3c** in deuterochloroform was pure and did not contain any of the 1,4-isomer.

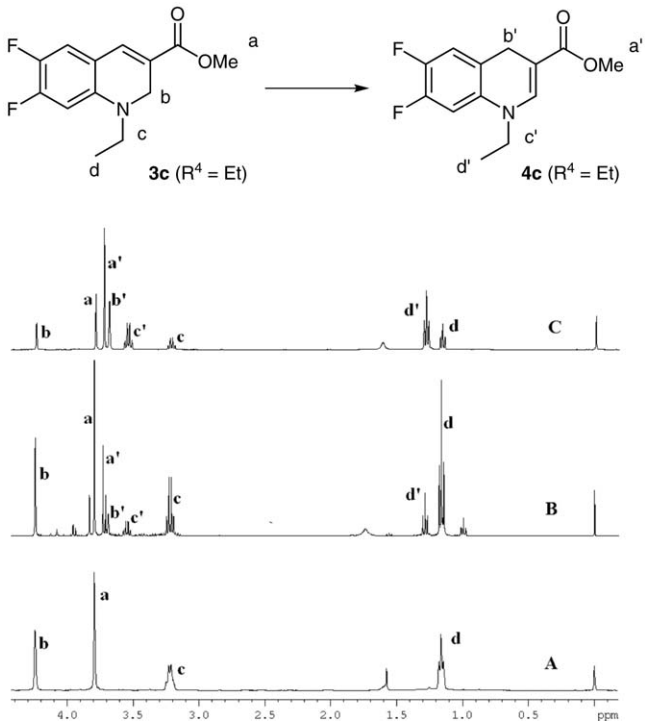


Figure 3 A) ^{1}H NMR spectrum of a $CDCl_3$ solution of **3c** (in the range 0–4.5 ppm); B) the spectrum after exposure of above sample to a 200-W bulb for 1 h; C) the spectrum (in $CDCl_3$) of a crystalline sample of **3c** stored for 60 days at 0–5 °C with protection from light and oxygen.

However, isomerization was observed after exposure of the sample to a 200-W bulb for one hour. The ^{1}H NMR spectrum of this solution clearly showed the presence of 1,2- and 1,4-dihydroquinolines. The ^{1}H NMR spectrum of crystalline **3c** stored for 60 days in a refrigerator at 0–5 °C under oxygen- and light-free conditions, when recorded in $CDCl_3$, showed peaks for the 1,4-dihydroquinoline along with the starting material, suggesting that isomerization may also occur in the solid state. The faster 1,2- to 1,4-isomerization in the presence of light is probably the result of an increase in the electron- and proton transfer rates of 1,2-dihydroquinoline in its excited state.

In conclusion, we have developed a reaction pathway that provides access to 4- and 2-quinolones through the sequence: $S_N2' \rightarrow S_NAr \rightarrow (\Delta^{3,4}–\Delta^{2,3}$ shift) $\rightarrow$ oxidation. Analysis of the effects of light, oxygen, sensitizer, quencher, and the results from experiments involving a pure 1,4-dihydroquinoline suggest the involvement of singlet oxygen and a dihydroquinolinyl peroxyl radical during the oxidation step. This needs to be verified by detailed experiments. ^{1}H NMR studies have shown that the isomerization of 1,2-dihydroquinolines to the 1,4-isomers is feasible both in $CDCl_3$ solution and in the solid state. In addition to providing a new route towards quinolones, our results show the possibility of activation of dihydroquinolines under the conditions of photodynamic therapy.

GR grade solvents and reagents from Merck were used in all the reactions. Melting points were measured by using an electro-thermal apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz instrument at 400 MHz and 100 MHz, respectively, and the chemical shifts are expressed in ppm relative to TMS (δ = 0.00 ppm) for ^{1}H NMR and $CDCl_3$ (δ = 77.1 ppm) for ^{13}C NMR. IR spectra were recorded on a Nicolet 6700 FT-IR spectrophotometer. High-resolution mass spectra (HRMS) were recorded on a Waters Q-Tof *micro*™ spectrometer with lock spray source.

Quinolones; General Procedure

The appropriate amine **2** (1.5–2.0 mmol) and dry K_2CO_3 (1.5–2.0 mmol) were added to a stirred solution of the Baylis–Hillman acetate **1** (1 mmol) in NMP (6 mL) under N_2. The mixture was heated at 70–80 °C until starting materials were completely consumed then cooled to r.t., diluted with DCE (40 mL), and washed with H_2O (3×30 mL) and brine (30 mL). The organic portion was dried (Na_2SO_4) and filtered. Methylene blue (0.7 mmol) was added and the soln was irradiated with a 200-W tungsten lamp under O_2 for 48 h, with the light source 2–3 cm from the reaction vessel. Once all the dihydroquinoline was consumed, the solvents were removed under reduced pressure and the residue was purified by chromatography (silica gel, EtOAc–hexane gradient).

Methyl 1-Benzyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (6.1) and Methyl 1-Benzyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (7.1)

Baylis–Hillman acetate **1a** (0.1 g, 0.319 mmol) was treated with $BnNH_2$ (51 mg, 0.05 mL, 0.478 mmol) in the presence of K_2CO_3 (66 mg, 0.478 mmol) in NMP (2 mL) at 80 °C for 12 h, and the resulting dihydroquinoline was exposed to a 200-W bulb for 48 h according to the general procedure.

Compound 6.1
Crystalline solid; yield: 30 mg (32%); mp 191–193 °C; R_f (EtOAc) = 0.57.

IR (neat): 1726, 1713, 1610, 1596, 1483, 1308, 1225, 1205, 1133, 1090, 995, 765, 738 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.64 (s, 1 H, C_2–H), 8.55 (dd, *J* = 8.0, 1.2 Hz, 1 H, Ar–H), 7.55 (ddd, *J* = 8.8, 7.2, 1.6 Hz, 1 H, Ar–H), 7.43–7.32 (m, 5 H, Ar–H), 7.19–7.15 (m, 2 H, Ar–H), 5.40 (s, 2 H, N–CH_2), 3.94 (s, 3 H, –OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.5, 166.7, 150.1, 139.4, 134.4, 132.8, 129.6 (2C), 129.5, 128.8, 128.2, 126.2 (2C), 125.4, 116.6, 111.2, 57.6, 52.3.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{16}NO_3$: 294.1130; found: 294.1129.

Compound 7.1
Crystalline solid; yield: 20 mg (21%); mp 117–119 °C; R_f (40% EtOAc–hexanes) = 0.4.

IR (neat): 1724, 1637, 1619, 1590, 1566, 1497, 1448, 1436, 1303, 1212, 1159, 1073, 799, 746, 723 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.53 (s, 1 H, C_4–H), 7.67 (dd, *J* = 7.6, 1.2 Hz, 1 H, Ar–H), 7.53 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1 H, Ar–H), 7.33–7.21 (m, 7 H, Ar–H), 5.58 (s, 2 H, N–CH_2), 3.98 (s, 3 H, –OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 159.3, 144.9, 141.1, 136.1, 133.3, 130.7, 128.9 (2C), 127.5, 126.9 (2C), 122.8, 122.3, 119.3, 115.2, 52.8, 46.5.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{16}NO_3$: 294.1130; found: 294.1135.

Methyl 1-Isobutyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (6.2) and Methyl 1-Isobutyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (7.2)
Baylis–Hillman acetate **1a** (0.1 g, 0.319 mmol) was treated with *i*-$BuNH_2$ (47 mg, 0.06 mL, 0.64 mmol) in the presence of K_2CO_3 (88 mg, 0.64 mmol) in NMP (2 mL) at 80 °C for 24 h, and the resulting dihydroquinoline was exposed to a 200-W bulb for 48 h according to the general procedure.

Compound 6.2
Crystalline solid; yield: 33 mg (40%); mp 91–93 °C; R_f (EtOAc) = 0.591.

IR (neat): 2958, 2924, 2849, 1725, 1695, 1610, 1553, 1489, 1316, 1230, 1137, 1096, 767 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.54 (d, *J* = 8.0 Hz, 1 H, Ar–H), 8.45 (s, 1 H, C_2–H), 7.67 (dd, *J* = 7.6, 6.4 Hz, 1 H, Ar–H), 7.50–7.38 (m, 2 H, Ar–H), 3.97 (d, *J* = 7.2 Hz, CH_2–CH, 2 H,), 3.92 (s, 3 H, –OCH_3), 2.32–2.24 (m, 1 H, CH_2–CH), 1.00 [d, *J* = 6.4 Hz, 6 H, $CH(CH_3)_2$)].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.5, 166.8, 149.9, 139.1, 132.6, 129.4, 128.3, 125.3, 116.0, 110.2, 61.5, 52.2, 27.8, 20.0 (2C).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{18}NO_3$: 260.1287; found: 260.1283.

Compound 7.2
Gummy solid; yield: 15 mg (18%); mp 93–95 °C; R_f (40% EtOAc–hexanes) = 0.5.

IR (CH_2Cl_2): 2956, 1739, 1709, 1646, 1593, 1564, 1454, 1433, 1304, 1249, 1210, 1147, 1076, 1009, 798 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.43 (s, 1 H, C_4–H), 7.68–7.60 (m, 2 H, Ar–H), 7.36 (d, *J* = 8.8 Hz, 1 H, Ar–H), 7.24 (d, *J* = 7.2 Hz, 1 H, Ar–H), 4.21 (d, *J* = 7.2 Hz, 1 H, CH_2–CH), 3.95 (s, 3 H, –OCH_3), 2.36–2.19 (m, 1 H, CH_2–CH), 1.01 [d, *J* = 6.8 Hz, 6 H, $CH(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 159.3, 144.3, 141.2, 132.9, 130.8, 122.4 (2C), 119.3, 114.9, 52.8, 49.4, 27.4, 20.4 (2C).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{18}NO_3$: 260.1287; found: 260.1291.

Methyl 1-Butyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (6.3) and Methyl 1-Butyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (7.3)
Baylis–Hillman acetate **1a** (0.1 g, 0.319 mmol) was treated with $BuNH_2$ (37 mg, 0.05 mL, 0.506 mmol) in the presence of K_2CO_3 (66 mg, 0.478 mmol) in NMP (2 mL) at 80 °C for 24 h, and the resulting dihydroquinoline was exposed to a 200-W bulb for 48 h according to the general procedure

Compound 6.3
White solid; yield: 29 mg (35%); mp 93–95 °C; R_f (EtOAc) = 0.5.

IR (neat): 3071, 2959, 1721, 1711, 1610, 1593, 1552, 1485, 1434, 1379, 1311, 1223, 1207, 1181, 1132, 1089, 987, 945, 875, 826, 734 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.54 (d, *J* = 7.6 Hz, 1 H, Ar–H), 8.49 (s, 1 H, C_2–H), 7.68 (t, *J* = 7.2 Hz, 1 H, Ar–H), 7.45–7.40 (m, 2 H, Ar–H), 4.18 (t, *J* = 7.2 Hz, 2 H, N–CH_2), 3.92 (s, 3 H, –OCH_3), 1.87 (quintet, *J* = 7.6 Hz, 2 H, CH_2–CH_2–CH_2–), 1.43 (sextet, *J* = 7.6 Hz, 2 H, –CH_2–CH_2–CH_3), 0.98 (t, *J* = 7.2 Hz, 3 H, CH_2–CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4, 166.8, 149.4, 138.9, 132.7, 129.5, 128.3, 125.2, 115.8, 110.5, 54.0, 52.2, 31.0, 20.0, 13.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{18}NO_3$: 260.1287; found: 260.1285.

Compound 7.3
Gummy solid; yield: 18 mg (22%); mp 153–155 °C; R_f (40% EtOAc–hexanes) = 0.52.

IR (neat): 2957, 2930, 1717, 1653, 1621, 1595, 1567, 1456, 1434, 1290, 1213, 1104, 1082, 801, 750 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.44 (s, 1 H, C_4–H), 7.73–7.63 (m, 2 H, Ar–H), 7.37 (d, *J* = 8.8 Hz, 1 H, Ar–H), 7.31–7.23 (m, 1 H, Ar–H), 4.31 (t, *J* = 8.0 Hz, 2 H, N–CH_2), 3.96 (s, 3 H, –OCH_3), 1.74 (quintet, *J* = 7.6 Hz, 2 H, CH_2–CH_2–CH_2–), 1.51 (sextet, *J* = 7.6 Hz, 2 H, –CH_2–CH_2–CH_3), 1.00 (t, *J* = 7.6 Hz, 3 H, CH_2–CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 158.9, 144.3, 140.9, 133.1, 130.8, 122.4, 122.3, 119.3, 114.4, 52.8, 42.9, 29.5, 20.5, 13.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{18}NO_3$: 260.1287; found: 260.1281.

Methyl 1-Methyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (6.4) and Methyl 1-Methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (7.4)
Baylis–Hillman acetate **1a** (0.1 g, 0.319 mmol) was treated with $MeNH_2$ (40%, 50 mg, 0.05 mL, 0.638 mmol) in the presence of K_2CO_3 (66 mg, 0.479 mmol) in NMP (2 mL) at 70 °C for 5 h, and the resulting dihydroquinoline was exposed to a 200-W bulb for 48 h according to the general procedure.

Compound 6.4
White solid; yield: 18 mg (26%); mp 192–194 °C; R_f (EtOAc) = 0.25. Spectral data for this compound were in agreement with those reported previously.[42]

IR (neat): 1665, 1611, 1587, 1552, 1439, 1342, 1321, 1242, 1123, 1101, 767 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 (dd, *J* = 8.0, 1.6 Hz, 1 H, Ar–H), 8.53 (s, 1 H, C_2–H), 7.73 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 1 H, Ar–H), 7.51–7.43 (m, 2 H, Ar–H), 3.94 (s, 3 H, –OCH_3), 3.90 (s, 3 H, N–CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.5, 166.6, 150.1, 139.8, 132.9, 129.0, 128.0, 125.5, 115.8, 110.6, 52.2, 41.5.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{12}NO_3$: 218.0817; found: 218.0817.

Compound 7.4

Gummy solid; yield: 17 mg (25%); R_f (40% EtOAc–hexanes) = 0.2.

IR (neat): 2943, 1729, 1649, 1615, 1586, 1556, 1435, 1379, 1293, 1269, 1004, 1211, 1150, 1124, 1072, 1004, 942, 799, 773 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (s, 1 H, C_4–H), 7.74–7.64 (m, 2 H, Ar–H), 7.38 (d, *J* = 8.8 Hz, 1 H, Ar–H), 7.33–7.25 (m, 1 H, Ar–H), 3.96 (s, 3 H, –OCH_3), 3.75 (s, 3 H, N–CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 159.2, 144.1, 141.5, 133.2, 130.6, 122.7, 122.5, 119.0, 114.4, 52.8, 29.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{12}NO_3$: 218.0817; found: 218.0816.

Methyl 1-Cyclohexyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (6.5)

Baylis–Hillman acetate **1a** (0.1 g, 0.319 mmol) was treated with $CyNH_2$ (63 mg, 0.07 mL, 0.638 mmol) in the presence of K_2CO_3 (88 mg, 0.638 mmol) in NMP (2 mL) at 80 °C for 48 h, and the resulting dihydroquinoline was exposed to a 200-W bulb for 48 h according to the general procedure to give a white solid; yield: 28 mg (31%); mp 153–155 °C; R_f (EtOAc) = 0.54.

IR (neat): 2928, 2851, 1683, 1635, 1589, 1541, 1444, 1339, 1309, 1205, 1153, 1093, 786 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (s, 1 H, C_2–H), 8.58 (dd, *J* = 8.0, 1.6 Hz, 1 H, Ar–H), 7.69 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 1 H, Ar–H), 7.56 (d, *J* = 8.8 Hz, 1 H, Ar–H), 7.44 (t, *J* = 7.6 Hz, 1 H, Ar–H), 4.48– 4.36 (m, 1 H, –NCH), 3.93 (s, 3 H, –OCH_3), 2.18 (br s, *J* = 13.6, 11.6 Hz, 2 H), 2.04 (br s, 2 H), 1.90–1.71 (m, 3 H), 1.62–1.49 (m, 2 H), 1.40–1.27 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 167.1, 144.9, 139.4, 132.7, 129.7, 128.5, 125.1, 115.0, 110.6, 59.5, 52.2, 32.9 (2C), 26.0 (2C) 25.4.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{20}NO_3$: 286.1443; found: 286.1439.

Methyl 1-Cyclopropyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (6.6) and Methyl Quinoline-3-carboxylate (8a)

Baylis–Hillman acetate **1a**(0.1 g, 0.319 mmol) was treated with cyclopropylamine (27 mg, 0.034 mL, 0.479 mmol) in the presence of K_2CO_3 (66 mg, 0.479 mmol) in NMP (2 mL) at 70 °C for 4 h, and the resulting dihydroquinoline was exposed to a 200-W bulb for 48 h according to the general procedure.

Compound 6.6

White crystalline solid; yield: 13 mg (17%); mp 223–225 °C; R_f (EtOAc) = 0.5.

IR (neat): 1720, 1619, 1606, 1592, 1549, 1479, 1455, 1410, 1350, 1315, 1242, 1213, 1147, 1108, 1091, 1044, 993, 772 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (s, 1 H, C_2–H), 8.49 (dd, *J* = 8.0, 1.6 Hz, 1 H, Ar–H), 7.93 (d, *J* = 8.4 Hz, 1 H, Ar–H), 7.71 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 1 H, Ar–H), 7.49–7.43 (m, 1 H, Ar–H), 3.92 (s, 3 H, –OCH_3), 3.51–3.45 (m, 1 H, N–CH), 1.37–1.31 (m, 2 H, cyclopropyl CH_aCH_b), 1.16–1.11 (m, 2 H, cyclopropyl CH_aCH_b).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6, 166.7, 149.0, 140.6, 132.6, 128.7, 127.8, 125.4, 116.5, 110.7, 52.2, 34.6, 8.3 (2C).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{14}NO_3$: 244.0974; found: 244.0973.

Compound 8a

White crystalline solid; yield: 10 mg (17%); mp 70–73 °C; R_f (20% EtOAc–hexanes) = 0.45. Spectral data for this compound agreed with those reported previously.[43,44]

IR (neat): 2951, 1721, 1677, 1612, 1588, 1552, 1500, 1476, 1437, 1317, 1241, 1224, 1095, 811, 765 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.44 (d, *J* = 2.0 Hz, 1 H, Ar–H), 8.84 (d, *J* = 1.6 Hz, 1 H, Ar–H), 8.16 (d, *J* = 8.4 Hz, 1 H, Ar–H), 7.93 (d, *J* = 8.4 Hz, 1 H, Ar–H), 7.83 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 1 H, Ar–H), 7.62 (apparent dt, *J* = 8.4, 8.4, 1.2 Hz, 1 H, Ar–H), 4.02 (s, 3 H, –OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 150.1, 150.0, 138.9, 132.0, 129.6, 129.2, 127.6, 127.0, 123.1, 52.6.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{10}NO_2$: 188.0712; found: 188.0711.

Methyl 1-Benzyl-7-chloro-4-oxo-1,4-dihydroquinoline-3-carboxylate (6.7) and Methyl 1-Benzyl-7-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate (7.7)

Baylis–Hillman acetate **1b** (0.1 g, 0.33 mmol) was treated with $BnNH_2$ (51 mg, 0.05 mL, 0.478 mmol) in the presence of K_2CO_3 (68 mg, 0.49 mmol) in NMP (2 mL) at 80 °C for 36 h, and the resulting dihydroquinoline was exposed to a 200-W bulb for 48 h according to the general procedure.

Compound 6.7

White crystalline solid; yield: 27 mg, 25% yield; mp 185–187 °C; R_f (EtOAc) = 0.66.

IR (neat): 1673, 1638, 1594, 1542, 1464, 1446, 1434, 1311, 1245, 1233, 1149, 1088, 998, 844, 788 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (s, 1 H, C_2–H), 8.47 (d, *J* = 8.8 Hz, 1 H, Ar–H), 7.42–7.32 (m, 5 H, Ar–H), 7.17 (br s, 2 H, Ar–H), 5.35 (s, 2 H, N–CH_2), 3.94 (s, 3 H, –OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 166.2, 150.4, 140.1, 139.3, 133.7, 129.7, 129.6 (2C), 129.0, 127.7, 126.3 (2C), 126.0, 116.5, 111.6, 57.5, 52.4.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{15}ClNO_3$: 328.0740; found: 328.0740.

Compound 7.7

White crystalline solid; yield: 11 mg (10%); mp 163–165 °C; R_f (40% EtOAc–hexanes) = 0.51.

IR (neat): 1739, 1655, 1620, 1591, 1556, 1437, 1304, 1213, 1088, 764, 750 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (s, 1 H, C_4–H), 7.59 (d, *J* = 8.4 Hz, 1 H, Ar–H), 7.37–7.18 (m, 7 H, Ar–H), 5.52 (s, 2 H, N–CH_2), 3.97 (s, 3 H, –OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 159.0, 144.1, 141.8, 139.7, 135.5, 131.7, 129.1 (2C), 127.8, 126.9 (2C), 123.5, 122.4, 117.7, 115.2, 52.9, 46.6.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{15}ClNO_3$: 328.0740; found: 328.0742.

Methyl 7-Chloro-1-isobutyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (6.8) and Methyl 7-Chloro-1-isobutyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (7.8)

Baylis–Hillman acetate **1b** (0.1 g, 0.33 mmol) was treated with *i*-$BuNH_2$ (37 mg, 0.05 mL, 0.506 mmol) in the presence of K_2CO_3 (91 mg, 0.66 mmol) in NMP (2 mL) at 80 °C for 48 h, and the resulting dihydroquinoline was exposed to a 200-W bulb for 48 h according to the general procedure.

Compound 6.8

White crystalline solid; yield: 23 mg (24%); mp 109–111 °C; R_f (EtOAc) = 0.58.

IR (neat): 2957, 1727, 1698, 1628, 1593, 1542, 1454, 1312, 1224, 1087, 797, 750 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 9.2 Hz, 1 H, Ar–H), 8.42 (s, 1 H, C_2–H), 7.45–7.35 (m, 2 H, Ar–H), 3.93 (br s, 5 H, N–CH_2, and –OCH_3), 2.35–2.20 [m, 1 H, –CH–$(CH_3)_2$], 1.02 [d, *J* = 6.4 Hz, 6 H, $CH(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 166.4, 150.2, 139.9, 139.2, 130.0, 127.8, 125.9, 115.9, 110.9, 61.5, 52.4, 27.7, 20.0 (2C).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{17}ClNO_3$: 294.0897; found: 294.0892.

Compound 7.8

Gummy solid; yield: 7 mg (7%) as a gummy solid; mp 115–117 °C; R_f (40% EtOAc–hexanes) = 0.6.

IR (neat): 2959, 1741, 1709, 1655, 1619, 1591, 1556, 1435, 1303, 1210, 1075, 1016 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.39 (s, 1 H, C_4–H), 7.58 (d, *J* = 8.4 Hz, 1 H, Ar–H), 7.33 (d, *J* = 1.6 Hz, 1 H, Ar–H), 7.22 (dd, *J* = 8.4, 1.6 Hz, 1 H, Ar–H), 4.15 (d, *J* = 7.2 Hz, 2 H, N–CH_2), 3.95 (s, 3 H, –OCH_3), 2.29–2.18 [m, 1 H, –$CH(CH_3)_2$], 1.00 [,*J* = 6.8 Hz, 6 H, CH–$(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 159.1, 143.6, 142.0, 139.4, 131.8, 123.1, 122.4, 117.7, 114.9, 52.9, 49.5, 27.3, 20.3 (2C).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{17}ClNO_3$: 294.0897; found: 294.0901.

Methyl 1-Butyl-7-chloro-4-oxo-1,4-dihydroquinoline-3-carboxylate (6.9) and Methyl 1-Butyl-7-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate (7.9)

Baylis–Hillman acetate **1b** (0.1 g, 0.33 mmol) was treated with $BuNH_2$ (37 mg, 0.05 mL, 0.506 mmol) in the presence of K_2CO_3 (91 mg, 0.66 mmol) in NMP (2 mL) at 80 °C for 12 h, and the resulting dihydroquinoline was exposed to a 200-W bulb for 48 h according to the general procedure.

Compound 6.9

White crystalline solid; yield: 22 mg (23%); mp 73–75 °C; R_f (EtOAc) = 0.58.

IR (neat): 2960, 1686, 1624, 1604, 1588, 1540, 1450, 1432, 1338, 1315, 1235, 1222, 1199, 1087, 976, 911, 854, 846, 794 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.49–8.45 (m, 2 H, Ar–H, C_2–H), 7.43–7.37 (m, 2 H, Ar–H), 4.14 (t, *J* = 7.6 Hz, 2 H, N–CH_2), 3.93 (s, 3 H, –OCH_3), 1.87 (quintet, *J* = 7.6 Hz, 2 H, CH_2–CH_2–CH_2), 1.45 (sextet, *J* = 7.6 Hz, 2 H, –CH_2–CH_2–CH_3), 1.01 (t, *J* = 7.6 Hz, 3 H, CH_2–CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 166.3, 149.8, 139.7, 139.3, 129.9, 127.7, 125.8, 115.7, 111.1, 54.1, 52.3, 30.8, 20.0, 13.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{17}ClNO_3$: 294.0897; found: 294.0889.

Compound 7.9

Gummy solid; yield: 10 mg (10%); R_f (40% EtOAc–hexanes) = 0.6.

IR (neat): 2954, 1741, 1661, 1590, 1436, 1302, 1212, 1078, 913, 743 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.40 (s, 1 H, C_4–H), 7.59 (d, *J* = 8.4 Hz, 1 H, Ar–H), 7.33 (d, *J* = 1.2 Hz, 1 H, Ar–H), 7.23 (dd, *J* = 8.4, 1.6 Hz, 1 H, Ar–H), 4.24 (t, *J* = 7.6 Hz, 2 H, N–CH_2), 3.95 (s, 3 H, –OCH_3), 1.72 (quintet, *J* = 7.6 Hz, 2 H, CH_2–CH_2–CH_2), 1.50 (sextet, *J* = 7.6 Hz, 2 H, CH_2–CH_2–CH_3), 1.01 (t, *J* = 7.6 Hz, 3 H, CH_2–CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 158.6, 143.6, 141.6, 139.6, 131.8, 123.1, 122.3, 117.7, 114.5, 52.9, 43.1, 29.5, 20.4, 13.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{17}ClNO_3$: 294.0897; found: 294.0899.

Methyl 7-Chloro-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (6.10), Methyl 7-Chloro-1-ethyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (7.10), and Methyl 7-chloroquinoline-3-carboxylate (8b)

Baylis–Hillman acetate **1b** (0.1 g, 0.33 mmol) was treated with $EtNH_2$ (70%, 43 mg, 0.05 mL, 0.66 mmol) in the presence of K_2CO_3 (68 mg, 0.49 mmol) in NMP (2 mL) at 70 °C for 12 h, and the resulting dihydroquinoline was exposed to a 200-W bulb for 48 h according to the general procedure.

Compound 6.10

Crystalline solid; yield: 20 mg (23%); mp 181–183 °C; R_f (EtOAc) = 0.44.

IR (neat): 1687, 1680, 1631, 1606, 1591, 1461, 1452, 1316, 1232, 796 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.51 (s, 1 H, C_2–H), 8.47 (d, *J* = 8.4 Hz, 1 H, Ar–H), 7.44 (d, *J* = 1.2 Hz, 1 H, Ar–H), 7.39 (dd, *J* = 8.8, 1.6 Hz, 1 H, Ar–H), 4.22 (q, *J* = 7.2 Hz, 2 H, N–CH_2CH_3), 3.93 (s, 3 H, –OCH_3), 1.55 (t, *J* = 7.2 Hz, 3 H, N–CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 166.3, 149.3, 139.5, 139.4, 129.9, 127.7, 125.9, 115.6, 111.4, 52.3, 49.1, 14.5.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{13}ClNO_3$: 266.0584; found: 266.0582.

Compound 7.10

Gummy solid; yield: 6 mg (7%); R_f (40% EtOAc–hexanes) = 0.4.

IR (neat): 2950, 2934, 1741, 1705, 1651, 1620, 1590, 1557, 1464, 1435, 1305, 1257, 1210, 1075, 913, 803, 743 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.40 (s, 1 H, C_4–H), 7.60 (d, *J* = 8.4 Hz, 1 H, Ar–H), 7.37 (d, *J* = 1.2 Hz, 1 H, Ar–H), 7.23 (dd, *J* = 8.4, 1.6 Hz, 1 H, Ar–H), 4.33 (q, *J* = 7.2 Hz, 2 H, N–CH_2CH_3), 3.95 (s, 3 H, –OCH_3), 1.37 (t, *J* = 7.2 Hz, 3 H, N–CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 158.5, 143.6, 141.4, 139.7, 131.9, 123.1, 122.3, 117.8, 114.3, 52.9, 38.3, 12.6.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{13}ClNO_3$: 266.0584; found: 266.0585.

Compound 8b

Crystalline solid; yield: 5 mg (7%); mp 151–153 °C; R_f (40% EtOAc–hexanes) = 0.4. Spectral data for this compound agreed with those reported previously.[45]

IR (neat): 1711, 1613, 1597, 1479, 1440, 1375, 1279, 1232, 1108, 1064, 941, 878, 808, 774 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.44 (d, *J* = 2.0 Hz, 1 H, Ar–H), 8.82 (d, *J* = 2.0 Hz, 1 H, Ar–H), 8.16 (d, *J* = 1.6 Hz, 1 H, Ar–H), 7.88 (d, *J* = 8.8 Hz, 1 H, Ar–H), 7.58 (dd, *J* = 8.8, 2.0 Hz, 1 H, Ar–H), 4.02 (s, 3 H, –OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 151.2, 150.2, 138.7, 138.1, 130.4, 128.8, 128.7, 125.4, 123.3, 52.8.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{11}H_9ClNO_2$: 222.0322; found: 222.0320.

Methyl 7-Chloro-1-cyclohexyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (6.11)

Baylis–Hillman acetate **1b** (0.1 g, 0.33 mmol) was treated with $CyNH_2$ (49 mg, 0.056 mL, 0.49 mmol) in the presence of K_2CO_3 (91 mg, 0.66 mmol) in NMP (2 mL) at 80 °C for 48 h, and the resulting dihydroquinoline was exposed to a 200-W bulb for 48 h according to the general procedure to give a white crystalline solid; yield: 33 mg (31%); mp 167–169 °C; R_f (20% EtOAc–hexanes) = 0.6.

IR (neat): 2933, 2856, 1731, 1695, 1634, 1595, 1541, 1464, 1340, 1309, 1205, 1150, 1088, 883, 795, 750 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.66 (s, 1 H, C_2–H), 8.51 (d, *J* = 8.4 Hz, 1 H, Ar–H), 7.53 (d, *J* = 1.2 Hz, 1 H, Ar–H), 7.40 (dd, *J* = 8.8, 1.6 Hz, 1 H, Ar–H), 4.36–4.27 (m, 1 H, N–CH), 3.94 (s, 3 H, –OCH_3), 2.17 (br s, 2 H), 2.06 (br s, 2 H), 1.91–1.72 (m, 3 H), 1.66–1.51 (m, 2 H), 1.40–1.27 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 166.7, 145.3, 140.2, 139.3, 130.1, 128.0, 125.7, 115.0, 111.3, 59.8, 52.4, 32.8 (2C), 26.0 (2C), 25.3.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{17}H_{19}ClNO_3$: 320.1053; found: 320.1051.

Methyl 1-Cyclopropyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (6.12) and Methyl 6,7-Difluoroquinoline-3-carboxylate (8c)

Baylis–Hillman acetate **1c** (200 mg, 0.694 mmol) was treated with cyclopropylamine (59 mg, 0.07 mL, 1.04 mmol) in the presence of K_2CO_3 (144 mg, 1.04 mmol) in NMP (4 mL) at 70 °C for 24 h, and the resulting dihydroquinoline was exposed to a 354-nm UV lamp for 48 h according to the general procedure

Compound 6.12

Crystalline solid; yield: 27 mg (14%); mp 224–226 °C; R_f (EtOAc) = 0.51. Spectral data for this compound agreed well those reported previously.[16]

IR (neat): 1728, 1614, 1479, 1286, 1232, 1205, 1188, 1166, 1077, 905, 803 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (s, 1 H, C_2–H), 8.27 (dd, *J* = 10.4, 8.8 Hz, 1 H, Ar–H), 7.73 (dd, *J* = 11.2, 6.4 Hz, 1 H, Ar–H), 3.92 (s, 3 H, –OCH_3), 3.47–3.41 [m, 1 H, NCH(CH_2)$_2$], 1.40–1.33 (m, 2 H, cyclopropyl CH_aCH_b), 1.18–1.13 (m, 2 H, cyclopropyl CH_aCH_b).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 166.0, 153.5 (dd, *J* = 254.0, 16.0 Hz, 1 C), 149.3, 148.8 (dd, *J* = 251.0, 13.0 Hz, 1 C), 137.7 (d, *J* = 8.5 Hz, 1 C), 125.8, 115.5 (dd, *J* = 18.5, 7.3 Hz, 1 C), 110.6 (d, *J* = 10.8 Hz, 1 C), 105.7 (dd, *J* = 22.4, 6.8 Hz, 1 C), 52.3, 35.0, 8.4 (2C).

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{12}F_2NO_3$: 280.0785; found: 280.0751.

Compound 8c

Crystalline solid; yield: 22 mg (14%); mp 153–155 °C; R_f (20% EtOAc–hexanes) = 0.55.

IR (neat): 1710, 1509, 1464, 1434, 1337, 1281, 1249, 1227, 1214, 1127, 1106, 992, 936, 873, 856, 772 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.40 (d, *J* = 1.2 Hz, 1 H, Ar–H), 8.77 (d, *J* = 2.0 Hz, 1 H, Ar–H), 7.90 (dd, *J* = 10.8, 7.6 Hz, 1 H, Ar–H), 7.66 (dd, *J* = 9.6, 8.8 Hz, 1 H, Ar–H), 4.01 (s, 3 H, –OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 153.9 (dd, *J* = 257.2, 16.0 Hz, 1 C), 150.8 (dd, *J* = 253.9, 16.0 Hz, 1 C), 150.5, 147.4 (d, *J* = 10.8 Hz, 1 C), 138.0 (d, *J* = 4.9 Hz, 1 C), 124.0 (d, *J* = 8.0 Hz, 1 C), 123.4, 116.1 (d, *J* = 16.7 Hz, 1 C), 114.3 (d, *J* = 17.5 Hz, 1 C), 52.8.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{11}H_8F_2NO_2$: 224.0523; found: 224.0526.

Methyl 1-Ethyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (6.13) and Methyl 1-Ethyl-6,7-difluoro-2-oxo-1,2-dihydroquinoline-3-carboxylate (7.13)

Baylis–Hillman acetate **1c** (0.200 g, 0.694 mmol) was treated with $EtNH_2$ (70%, 67 mg, 0.1 mL, 1.04 mmol) in the presence of K_2CO_3 (0.144 g, 1.04 mmol) in NMP (4 mL) for 5 h at r.t., and the resulting dihydroquinoline was exposed to 354-nm UV lamp for 48 h according to the general procedure.

Compound 6.13

Crystalline solid; yield: 48 mg (26%); mp 182–184 °C; R_f (EtOAc) = 0.41. Spectral data for this compound agreed with those reported previously.[16]

IR (neat): 3066, 2954, 1684, 1643, 1614, 1598, 1482, 1450, 1321, 1286, 1218, 1087, 909, 862, 803, 742 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (s, 1 H, C_2–H), 8.32 (dd, *J* = 10.4, 9.2 Hz, 1 H, Ar–H), 7.27 (dd, *J* = 11.2, 6.4 Hz, 1 H, Ar–H), 4.20 (q, *J* = 7.2 Hz, 2 H, NCH_2CH_3), 3.93 (s, 3 H, –OCH_3), 1.55 (t, *J* = 7.2 Hz, 3 H, NCH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD): δ = 174.8, 166.3, 155.0 (dd, *J* = 253.1, 15.6 Hz, 1 C), 151.1, 149.8 (dd, *J* = 248.2, 14.2 Hz, 1 C), 137.6 (d, *J* = 10.1 Hz, 1 C), 127.1 (d, *J* = 3.7 Hz, 1 C), 115.3 (d, *J* = 18.6 Hz, 1 C), 110.8, 107.5 (d, *J* = 23.0 Hz, 1 C), 52.1, 50.6, 14.7.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{12}F_2NO_3$: 268.0785; found: 268.077.

Compound 7.13

Gummy solid; yield: 6 mg (3%); R_f (50% EtOAc–hexanes) = 0.43.

IR (neat): 3069, 1742, 1642, 1574, 1519, 1442, 1432, 1411, 1282, 1259, 1239, 1230, 1150, 1123, 1092, 1077, 1016 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (s, 1 H, C_4–H), 7.46 (t, *J* = 8.8 Hz, 1 H, ArH), 7.18 (dd, *J* = 12.0, 6.8 Hz, 1 H, ArH), 4.30 (q, *J* = 7.2 Hz, 2 H, NCH_2CH_3), 3.4 (s, 3 H, –OCH_3), 1.36 (t, *J* = 7.2 Hz, 3 H, NCH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 158.2, 153.8 (d, *J* = 265.2 Hz, 1 C), 146.3 (dd, *J* = 245.6, 15.6 Hz, 1 C), 142.7, 138.1, 122.8, 117.6 (d, *J* = 17.6 Hz, 1 C), 115.5, 103.4 (d, *J* = 22.6 Hz, 1 C), 52.9, 38.7, 12.5.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{13}H_{12}F_2NO_3$: 268.0785; found: 268.0775.

Methyl 1-Benzyl-1,4-dihydroquinoline-3-carboxylate (4a)

$BnNH_2$ (51 mg, 0.05 mL, 0.478 mmol) and dry K_2CO_3 (66 mg, 0.478 mmol) were added to a stirred soln of Baylis–Hillman acetate **1a** (100 mg, 0.319 mmol) in NMP (2 mL) under N_2. The mixture was heated at 80 °C for 24 h until the starting materials were completely consumed then cooled to r.t., diluted with DCE (15 mL), and washed with H_2O (3 × 10 mL) and brine (10 mL). The organic portion was dried (Na_2SO_4) and filtered then kept away from light and O_2 for 5 days. The solvents were then removed in vacuo and the residue was purified by chromatography (silica gel) in darkness; yield: 62 mg (70%); R_f (20% EtOAc–hexanes) = 0.7. Compounds **6.1** [yield: 3 mg (3%)] and **7.1** [yield: 1 mg (1%)] were also obtained as byproducts.

IR (neat): 2624, 2851, 1684, 1668, 1648, 1576, 1495, 1463, 1436, 1396, 1252, 1223, 1091, 1062, 756 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.39 (s, 1 H, C_2–H), 7.36–7.24 (m, 5 H, Ar–H), 7.07 (d, *J* = 7.2 Hz, 1 H, Ar–H), 6.97 (apparent t, *J* = 7.6, 0.8 Hz, 1 H), 6.89 (dt, 1 H), 6.61 (d, *J* = 7.6 Hz, 1 H, Ar–H), 4.78 (s, 2 H, N–CH_2), 3.85 (s, 2 H, C_4–H_2), 3.74 (s, 3 H, –OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 143.2, 138.1, 136.8, 130.0, 129.1 (2C), 127.7, 127.2, 126.3 (2C), 123.3 (2C), 113.9, 98.0, 55.0, 51.2, 26.5.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{17}NNaO_2$: 302.1157, found: 302.1153.

Supporting information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

Acknowledgment

Financial support of this work by CSIR, India (Grants 01(2121)/07/EMR-II) and by DST, India (Grants SR/S1/OC-13/2007) is gratefully acknowledged. We thank Mr. V. Ramkumar (IIT Madras) for performing the X-ray diffraction analyses. J.V. thanks CSIR for a Research Fellowship.

References

(1) Emmerson, A. M.; Jones, A. M. *J. Antimicrob. Chemother.* **2003**, *51*, 13.
(2) Anderson, V. R.; Perry, C. M. *Drugs* **2008**, *68*, 535.
(3) Wolfson, J. S.; Hooper, D. C. *Ann. Intern. Med.* **1988**, *108*, 238.
(4) Raja, A.; Lebbos, J.; Kirkpatrick, P. *Nat. Rev. Drug Discovery* **2004**, *3*, 733.
(5) Sato, M.; Kawakami, H.; Motomura, T.; Aramaki, H.; Matsuda, T.; Yamashita, M.; Ito, Y.; Matsuzaki, Y.; Yamataka, K.; Ikeda, S.; Shinkai, H. *J. Med. Chem.* **2009**, *52*, 4869.
(6) Hadjeri, M.; Peiller, E.-L.; Beney, C.; Deka, N.; Lawson, M. A.; Dumontet, C.; Boumendjel, A. *J. Med. Chem.* **2004**, *47*, 4964.
(7) Mahmoudi, N.; Ciceron, L.; Franetich, J.-F.; Farhati, K.; Silvie, O.; Eling, W.; Sauerwein, R.; Danis, M.; Mazier, D.; Derouin, F. *Antimicrob. Agents Chemother.* **2003**, *47*, 2636.
(8) Ito, C.; Itoigawa, M.; Furukawa, A.; Hirano, T.; Murata, T.; Kaneda, N.; Hisada, Y.; Okuda, K.; Furukawa, H. *J. Nat. Prod.* **2004**, *67*, 1800.
(9) Joseph, B.; Darro, F.; Béhard, A.; Lesur, B.; Collignon, F.; Decaestecker, C.; Frydman, A.; Guillaumet, G.; Kiss, R. *J. Med. Chem.* **2002**, *45*, 2543.
(10) Hopkins, A. L.; Ren, J.; Milton, J.; Hazen, R. J.; Chan, J. H.; Stuart, D. I.; Stammers, D. K. *J. Med. Chem.* **2004**, *47*, 5912.
(11) Boteva, A. A.; Krasnykh, O. P. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2009**, *45*, 757; and references cited therein.
(12) Huang, J.; Chen, Y.; King, A. O.; Dilmeghani, M.; Larsen, R. D.; Faul, M. M. *Org. Lett.* **2008**, *10*, 2609.
(13) Mitscher, L. A. *Chem. Rev.* **2005**, *105*, 559; and references cited therein.
(14) Gould, R. G. Jr.; Jacobs, W. A. *J. Am. Chem. Soc.* **1939**, *61*, 2890.
(15) Bouzard, D.; Di Cesare, P.; Essiz, M.; Jacquet, J. P.; Remuzon, P.; Weber, A.; Oki, T.; Masuyoshi, M. *J. Med. Chem.* **1989**, *32*, 537; and references cited therein.
(16) Hong, W. P.; Lee, K.-J. *Synthesis* **2006**, 963.
(17) Kim, J. N.; Lee, K. Y.; Kim, H. S.; Kim, T. Y. *Org. Lett.* **2000**, *2*, 343.
(18) Kim, J. N.; Lee, K. Y.; Ham, H.-S.; Kim, H. R.; Ryu, E. K. *Bull. Korean Chem. Soc.* **2001**, *22*, 135.
(19) Amarante, G. W.; Benassi, M.; Pascoal, R. N.; Eberlin, M. N.; Coelho, F. *Tetrahedron* **2010**, *66*, 4370.
(20) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 1493.
(21) Lee, K. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 939.
(22) Basavaiah, D.; Reddy, R. M.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron* **2002**, *58*, 3693.
(23) Felpin, F.-X.; Coste, J.; Zakri, C.; Fouquet, E. *Chem. Eur. J.* **2009**, *15*, 7238.
(24) Pathak, R.; Madapa, S.; Batra, S. *Tetrahedron* **2006**, *63*, 451.
(25) Kim, K. H.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 1249.
(26) Taylor, S. M.; Stubley-Beedham, C.; Stell, J. G. P. *Biochem. J.* **1984**, *220*, 67.
(27) Oleinick, N. L.; Morris, R. L.; Belichenko, I. *Photochem. Photobiol. Sci.* **2002**, *1*, 1.
(28) Sissi, C.; Palumbo, M. *Curr. Med. Chem.: Anti-Cancer Agents* **2003**, *3*, 439.
(29) Bunting, J. W.; Fitzgerald, N. P. *Can. J. Chem.* **1985**, *63*, 655.
(30) Crystallographic data for compounds **4a** (R^4 = Bn), **6.7**, and **7.7** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 779998, CCDC 771058, and CCDC 771059, respectively; copies can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223)336033 or email: deposit@ccdc.cam.ac.uk].
(31) Kim, J. N.; Kim, H. S.; Gong, J. H.; Chung, Y. M. *Tetrahedron Lett.* **2001**, *42*, 8341.
(32) Ferroud, C.; Rool, P.; Santamaria, J. *Tetrahedron Lett.* **1998**, *39*, 9423.
(33) Darmanyan, A. P.; Lee, W.; Jenks, W. S. *J. Phys. Chem. A* **1999**, *103*, 2705.
(34) Roberts, R. M. G.; Ostovic, D.; Kreevoy, M. M. *J. Org. Chem.* **1983**, *48*, 2053.
(35) Alberti, M. N.; Orfanopoulos, M. *Chem. Eur. J.* **2010**, *16*, 9414.
(36) Stratakis, M.; Orfanopoulos, M. *Tetrahedron* **2000**, *56*, 1595.
(37) Fukuzumi, S.; Ishikawa, M.; Tanaka, T. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1037.
(38) Raghuvanshi, R. S.; Singh, K. N. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2008**, *47*, 1735.
(39) Memarian, H. R.; Abdoli-Senejani, M.; Tangestaninejad, S. *J. Iran. Chem. Soc.* **2006**, *3*, 285.
(40) Zerbes, R.; Naab, P.; Franckowiak, G.; Diehl, H. US Patent 5639886, **1997**.
(41) Mokrushina, G. A.; Kotovskaya, S. K.; Baskakova, Z. M.; Petrova, G. M.; Kolmakova, T. V.; Charushin, V. N.; Rusinov, V. L.; Chupakhin, O. N. *Khim.-Farm. Zh.* **1996**, *30*, 46.
(42) Volle, J.-N.; Schlosser, M. *Eur. J. Org. Chem.* **2000**, 823.
(43) Han, E.-G.; Kim, H. J.; Lee, K.-J. *Tetrahedron* **2009**, *65*, 9616.
(44) O'Del, D. K.; Nicholas, K. M. *J. Org. Chem.* **2003**, *68*, 6427.
(45) Yoshikawa, K.; Kobayashi, S.; Nakamoto, Y.; Haginoya, N.; Komoriya, S.; Yoshino, T.; Nagata, T.; Mochizuki, A.; Watanabe, K.; Suzuki, M.; Kanno, H.; Ohta, T. *Bioorg. Med. Chem.* **2009**, *17*, 8221.