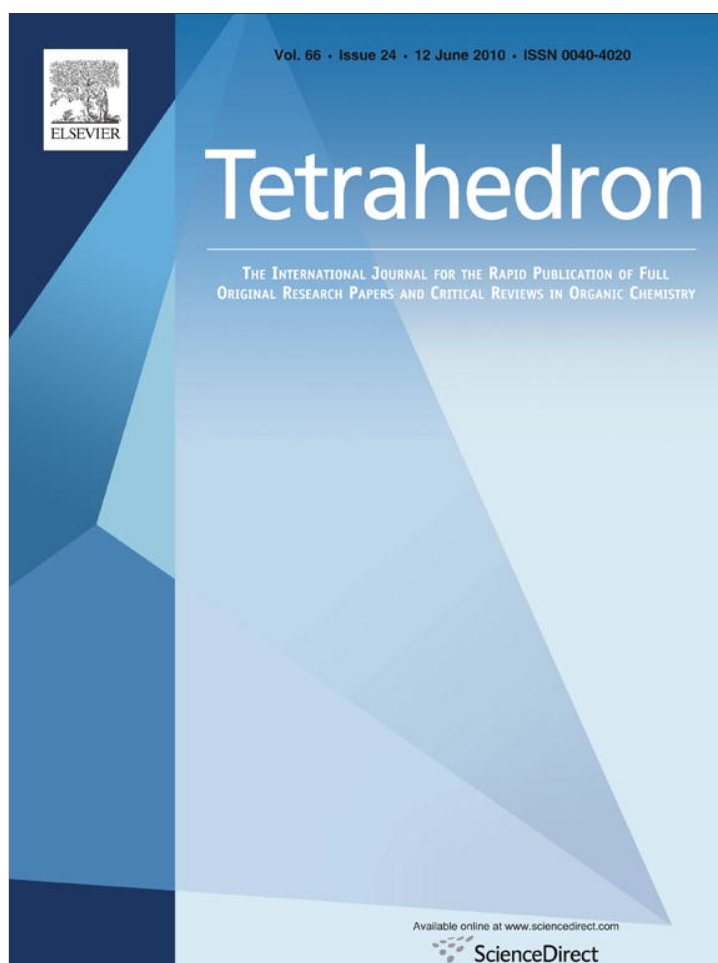


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Mechanism and synthesis of pharmacologically active quinolones from Morita–Baylis–Hillman adducts

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ABSTRACT

The synthesis of quinolones from Morita–Baylis–Hillman (MBH) adducts is reported. The quinolone skeleton is formed via a TFA-mediated cyclization of the MBH adduct, and a mechanism study using ESI (+)-MS(/MS) has indicated the role played by TFA in this key reaction step. The total syntheses of Norfloxacin and a benzyl quinolone carboxylic acid (BQCA) derivative are described. Norfloxacin is a fluoroquinolonic antibacterial drug whereas BQCA is M₁ receptor positive allosteric modulator and seem to provide access to new potential drugs for Alzheimer disease, pain, and sleep disorders. The syntheses of these two important quinolones exemplify the versatility and potentiality of the approach.

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1. Introduction

Quinolones are highly biologically active. They display *anti*-bacterial and *anti*-tumoral activities and its heterocyclic unit is also seen in drugs used to treat neurodegenerative diseases, sleep disorders or pain. Nalidixic acid (**1**, Fig. 1) was the first therapeutically important quinolonic drug,^{1,2} whereas the fluoroquinolones **2–8** (Fig. 1) are the most important result of the SAR (Structure–Activity Relationship) study based on **1**.

Flumequine (**2**) was the first to indicate that modifications of the basic quinolone structure could improve Gram-positive activity,² since earlier modifications had offered no significant improvements over **1**. Norfloxacin (**3**) has been used in genitourinary infections.³

Ciprofloxacin (**4**) is the most potent of the currently available fluoroquinolones against Gram-negative bacteria. Fleroxacin (**5**) is distinguished from its predecessors by its excellent bioavailability, high concentrations in plasma and other body fluids, good tissue penetration and long half-life (10–12 h),⁴ but **5** has displayed some severe side effects.⁵

Moxifloxacin (**6**), gemifloxacin (**7**), and grepafloxacin (**8**) are new antibacterials fluoroquinolones active against all the primary pathogens of typical respiratory diseases.^{6,7}

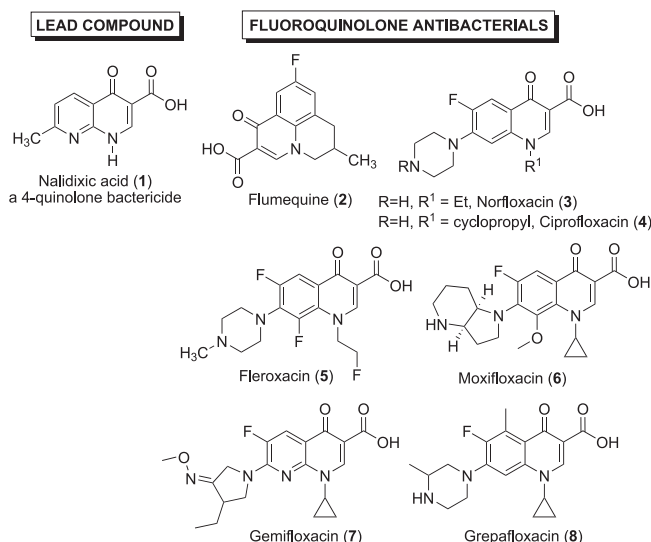


Figure 1. Representative examples of fluoroquinolone antibacterials (2–8) derived from 1.

Quinolones **9** and **10** (Fig. 2) have also shown tubuline polymerization inhibition effects and potential as *anti*-cancer agents.^{8,9} Quinolone **11** has been shown to be useful to prevent tumor cell proliferation, tumor formation, metastasis, inflammatory diseases,

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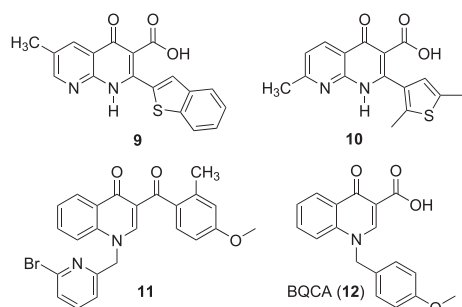


Figure 2. New biologically active quinolones.

treatment of HIV infectivity, stem cell differentiation, and mobilization disorders.^{10,11}

Recently, a benzyl quinolone carboxylic acid (BQCA) **12** has been synthesized and considered as promising drug to the Alzheimer disease (AD) owing the development of selective M₁ activators.^{12–14}

The vast biological relevance of quinolones has therefore stimulated the development of more general and efficient methods for quinolinone synthesis. The current methods (Fig. 3) can be divided into five major groups depending on the bond (i–v) used to close the quinoline ring.^{15,16}

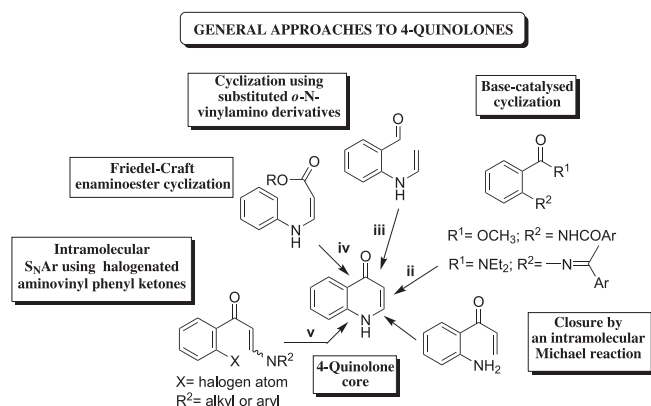
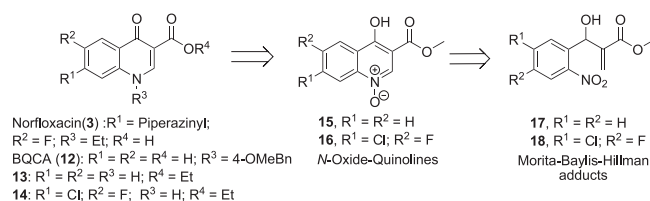


Figure 3. Current approaches to the synthesis of quinolones.

The Morita–Baylis–Hillman (MBH) reaction is an atom-efficient condensation methodology that provides easy access to highly functionalized carbonyl derivatives.^{17,18} MBH adducts are extensively used in synthesis as versatile starting material for many natural products and drugs,¹⁹ and to prepare heterocycles,²⁰ including quinolones.²¹

In a research program focused to develop new biologically active quinolones, particularly those active against human cancers, we were first interested in developing a synthetic strategy to prepare quinolones with great structural diversity. MBH adducts seemed appropriate to this goal owing to the diversity offered by structural variation in the reacting aldehydes and acrylates. We were also interested in developing a method using less expensive reagents than those used by Hong et al.²¹ The use of MBH adducts seemed appropriate considering that Kim et al. have reported the synthesis of *N*-oxide quinoline derivatives from *ortho*-substituted MBH adducts,²² and this method served therefore as the key starting step for our synthetic planning (Scheme 1).

We rationalized that reduction of *N*-Oxide quinolines **15** and **16** should give the corresponding 4-quinolone-esters **13** and **14**, which could be used as substrate for an *N*-alkylation reaction. Ester hydrolysis should provide BQCA (**12**) and Norfloxacin (**3**) could be made, for instance, by using piperazine in a regioselective S_NAr reaction after hydrolysis of **16**. A TFA-mediated cyclization using the MBH adducts **17** and **18**, which could be easily prepared from



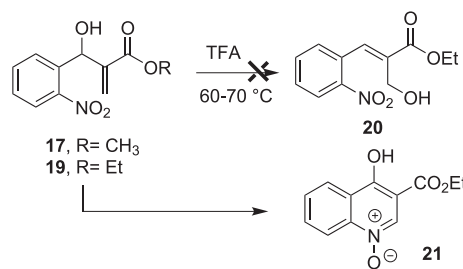
Scheme 1. Retrosynthetic analysis for Norfloxacin (**3**) and BQCA (**12**).

commercially available aldehydes with ethyl or methyl acrylates, would afford the key *N*-oxide quinolines **15** and **16**.

Herein we describe the total synthesis of the fluoroquinolone Norfloxacin (**3**) and BQCA (**12**) using this new method designed from *o*-substituted MBH adducts. To probe the crucial role played by TFA in the cyclization step, a mechanistic study via ESI-MS(/MS) monitoring was also performed.

2. Results and discussion

In order to prepare some allylic derivatives, Kim et al.²² treated *o*-nitrophenyl MBH adducts derived from *o*-nitrobenzaldehyde with TFA. Surprisingly, instead of the desired product **20** from an allylic rearrangement, the *N*-oxide hydroxyquinoline **21** was formed via intramolecular cyclization accompanied by water elimination (Scheme 2).



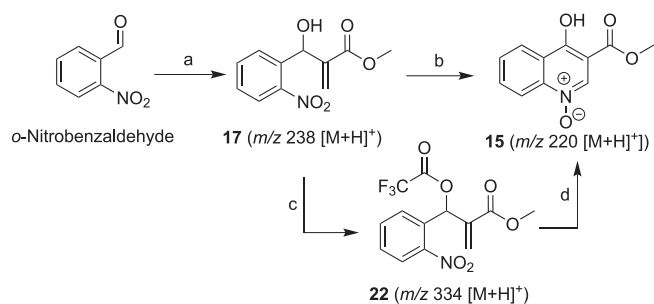
Scheme 2. Kim's TFA-mediated cyclization from MBH adducts.

This synthetically useful reaction seems to work only with TFA, and attempts to use acetic or formic acids failed.²² This unique feature of TFA catalysis intrigued us since, judging from the reaction mechanism proposed by Kim et al.²² (Scheme 2), TFA should work solely as a source of protons.

Electrospray ionization mass spectrometry (ESI(+)-MS) as well as its tandem version (ESI-MS/MS) has been established as a powerful tool to probe mechanisms of major organic reactions^{23,24} such as the MBH reaction^{18a,b,h} via the interception and characterization of their key intermediates. To elucidate therefore this key TFA catalysis, we monitored the reaction outlined in Scheme 2 by ESI(+)-MS(/MS) hoping to intercept and characterize key intermediates that would reveal mechanistic details.^{18a,b,h,25}

The MBH adduct **17** was prepared in 8 h with 98% yield according to a methodology developed in our laboratory.²⁶ Using experimental conditions reported by Kim et al.^{22,27} we treated **17** with TFA at 60–70 °C and monitored the reaction by ESI(+)-MS for 10 h in 1 h intervals (Scheme 3). Aliquots of 10 μL of the reaction solution were taken and diluted with methanol, and directly infused to the ESI source of a tandem mass spectrometer. The mass spectrometer used was a Qtrap (Applied Biosystems, Concord, Ontario, Canada) with a QqQ (linear ion trap) configuration.

As the reaction starts, the ESI-MS (Fig. 4a) showed mainly ions associated with the reactant MBH adduct, that is: [**17**+H]⁺ of *m/z* 238, [**17**+Na]⁺ of *m/z* 260 and [(**17**)₂+Na]⁺ of *m/z* 497. After 150 min (Fig. 4b), however, the ESI-MS was dominated by product ions of *m/z* 334 and *m/z* 220. The ion of *m/z* 334 is a key intermediate and corresponds to the *O*-trifluoroacetylated MBH adduct **22** in its



Scheme 3. Synthesis of *N*-Oxide-hydroxyquinolines from MBH adducts. Reagents and conditions: (a) methyl acrylate, DABCO, ultrasound, 8 h, 98%; (b) TFA, 60–70 °C, 10 h, 80%; (c) (CF₃CO)₂O, NEt₃, 0 °C, 30 min., 80%; (d) CH₃CN, AcOH (cat.), 8 h, 62%.

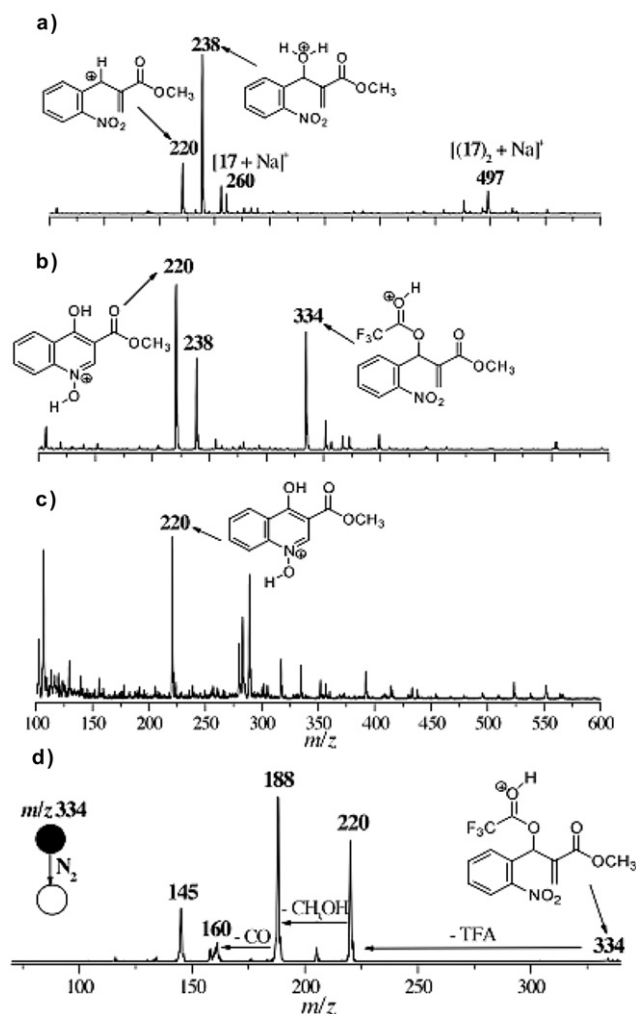


Figure 4. ESI(+)-MS for (a) the reaction solution at the beginning; (b) after 150 min and (c) after 360 min of reaction and (d) ESI(+)-MS/MS for CID of the ion of *m/z* 334.

protonated form. This structural assignment was corroborated by collision induced dissociation (CID) performed via an ESI-MS/MS experiment in which [22+H]⁺ dissociated mainly by the sequential losses of neutral TFA, methanol, and CO (Fig. 4d).

The ion of *m/z* 220 (Fig. 4a) was trickier to assign. At first glance, it was attributed to a fragment of [17+H]⁺ of *m/z* 238 from water loss. Indeed, at the beginning of the reaction, most of the low abundance ions of *m/z* 220 are likely to arise from such loss. However, as Figure 4c and most particularly Figure 5 shows, the abundance of the ion of *m/z* 220 increases steadily as the reaction progresses, even after 17 is totally consumed, as monitored by the abundance of [17+H]⁺ of *m/z* 238 (Fig. 5). This steady increase

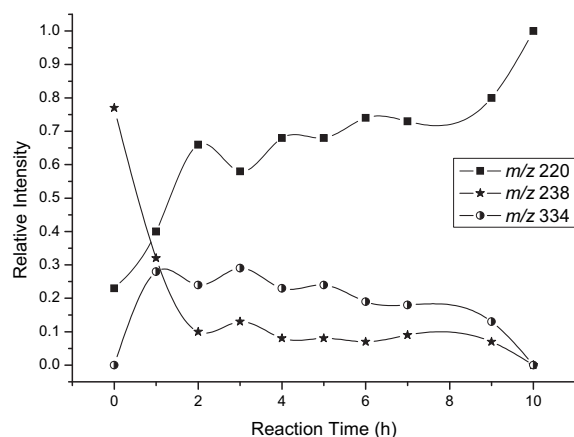


Figure 5. Relative abundances of the ions of *m/z* 220, *m/z* 238, and *m/z* 334 as a function of reaction time.

indicates that, as the reaction progresses, most of the ions of *m/z* 220 correspond to detection of the final product 15 in its protonated form [15+H]⁺.

Note also that, as the abundance of [17+H]⁺ of *m/z* 238 decreases, that of [22+H]⁺ of *m/z* 334 (Fig. 4c) initially raises and then after ca. 3 h falls down slowly.

Based on these ESI-MS data, it seems that the *O*-trifluoroacetylated MBH adduct 22 is a key reaction intermediate, and that its formation is the main factor inducing the reaction deviation from 20 to form instead the *N*-oxide hydroxyquinoline 21 (Scheme 2). We rationalize this role by assuming that, after TFA acetylation, a good leaving group is formed facilitating intramolecular substitution with the participation of the nucleophilic oxygen atom of the nitro group.

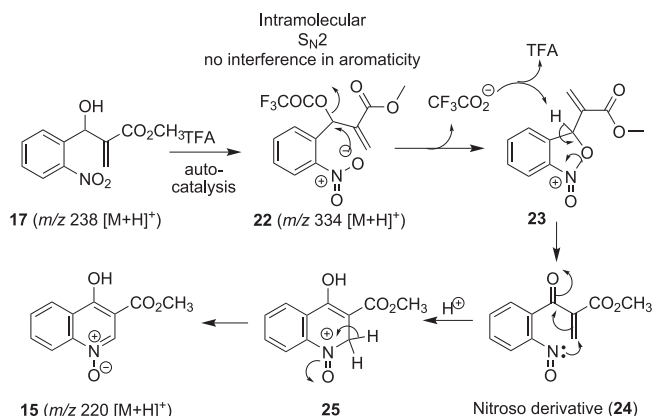
We have also monitored the same reaction replacing TFA by acid acetic as solvent and catalyst. Even after 6 h at 60–70 °C we were unable to see by ESI-MS monitoring any changes in the reaction solution. The predominant ion was that of *m/z* 238 attributed as the starting MBH adduct. Therefore, only TFA (used in excess) seems to be able to auto-catalyze acylation of 17.

We have also prepared an authentic sample of trifluoroacetate 22 to investigate whether it could be directly converted into 15. The MBH adduct 17 was treated at 0 °C with trifluoroacetic anhydride (1.5 equiv) and triethylamine (1.5 equiv) in anhydrous dichloromethane.²⁸ After 30 min, the solvent was evaporated and the residue was quickly purified by flash silica gel column chromatography to afford the corresponding trifluoroacetate 22 in 80% yield (Scheme 3).

Two different experimental conditions were tested: 22 was dissolved and refluxed in acetonitrile (i) without or (ii) with the addition of a catalytic amount (few drops) of acetic acid. After 8 h, we observed for condition (ii) that 22→15 conversion was almost complete and all the spectral data were identical to 15 produced from 17 by direct TFA treatment. This result constitutes therefore evidence of the key role played by the trifluoroacetate MBH adduct 22 in the formation of 15, as revealed by the ESI-MS(/MS) experiments. It is also clear that the presence of an acid is crucial for cyclization of 22.²⁵

Based on these experimental evidences, we propose in Scheme 4 a mechanism to rationalize the formation of *N*-oxide hydroxyquinoline.

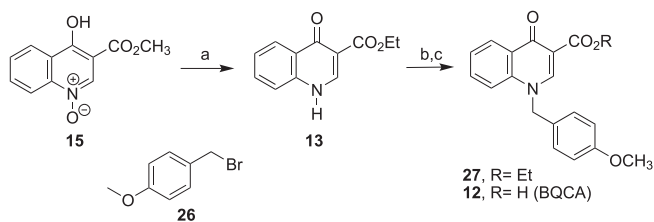
Differently from Kim et al.²², no aromaticity loss occurs in our mechanistic view, since TFA is acid enough to promote a auto-catalytic trifluoroacetylation to 22. An intramolecular S_N2 reaction resulting from the attack of ionic oxygen of the nitro group forms intermediate 23, since now the trifluoroacetate is a very good leaving group. The free trifluoroacetate anion is assumed to abstract the acidic benzylic proton to initiate the rearrangement leading to the nitroso derivative 24.²⁹ An intramolecular Michael addition gives the cyclic intermediate 25, which re-aromatizes to afford



Scheme 4. Mechanistic proposition for the formation of *N*-oxide hydroxyquinoline **15** from **17** catalyzed by TFA.

N-oxide hydroxyquinoline **15**. This sequence rationalizes the role of TFA and corroborates the importance of the trifluoroacetylated species in the reaction mechanism.

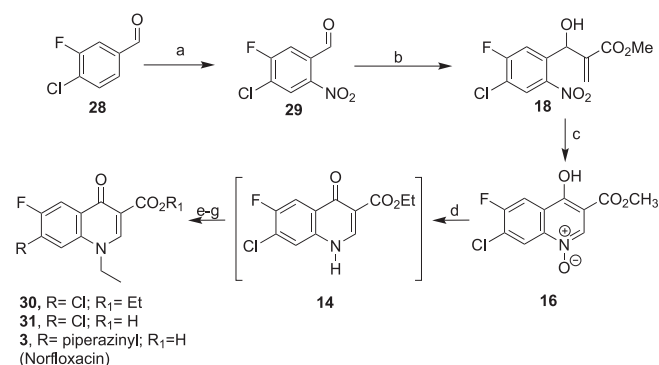
The *N*-oxide quinoline **15** was therefore prepared in 80%. The next step of our sequence was the reduction of the *N*-oxide group. We tested classical methodologies, such as PPh_3 (in different concentrations and temperatures), POCl_3 , and $\text{Zn}(0)$, but all attempts failed or gave **13** in low yield. Recently, Yoo et al. reported a method to reduce *N*-oxide derivatives using molybdenumhexacarbonyl.³⁰ In the presence of a stoichiometric amount of this reagent in ethanol, **15** was smoothly reduced to **13**, after 45 min, in 77% yield. Transesterification has likely occurred due to the use of an excess of ethanol. To finish the synthesis of BQCA (**12**), alkylation of the nitrogen atom of 4-quinolone **13** was required. For that, commercial *p*-anisyl alcohol was treated with $\text{CBr}_4/\text{PPh}_3$ to afford the corresponding bromide **26** in 80% yield after 3 h. Quinolone **13** was then treated with K_2CO_3 in the presence of a catalytic amount of KI and a slight excess of bromide **26** to give the *N*-alkylated product **27** in 65% yield (Scheme 5). The total synthesis of BQCA (**12**) was accomplished through basic hydrolysis of the ethyl ester group, in 85% yield.



Scheme 5. Total synthesis of the selective allosteric M_1 muscarinic acetylcholine receptor potentiator (**12**). (a) $\text{Mo}(\text{CO})_6$, EtOH, reflux, 45 min., 77%; (b) K_2CO_3 , KI, DMF, bromide **26**, 27 h, 65%; (c) LiOH, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1:1), rt, 3 h, 85%.

In summary, benzyl quinolone carboxylic acid (BQCA) **12** was synthesized in five steps using a relatively simple, efficient and easily scalable synthetic sequence from commercially available 2-nitrobenzaldehyde with an overall yield of 33%. To further demonstrate the synthetic feasibility of this approach, we also synthesized norfloxacin **3**. Initially, 4-chloro-3-fluorobenzaldehyde **28** was nitrated in a mixture of H_2SO_4 and HNO_3 to give solely and regioselectively the nitro-aldehyde **29** in 93% yield. The fluorine atom guided efficiently the nitration reaction toward the *para*-position by stabilizing the σ complex formed in the reaction TS (Scheme 6).³¹

Aldehyde **29** was then immediately used to prepare the MBH adduct **18** in 85% after 8 h of reaction. We applied to **18** the same synthetic sequence as described for **13**. That is, **18** was warmed at 70°C in TFA for 30 h to afford the *N*-oxide hydroxyquinoline **16** in 60% yield. Quinolone **14** resulting from the reduction of *N*-oxide quinoline **16** has proved to be unstable. To circumvent this problem,



Scheme 6. Synthesis of Norfloxacin from Morita–Baylis–Hillman adduct. (a) HNO_3 , H_2SO_4 , 80°C , 1 h, 93%; (b) methyl acrylate, DABCO, ultrasound, 8 h, 98%; (c) TFA, 70°C , 30 h, 60%; (d) $\text{Mo}(\text{CO})_6$, EtOH, reflux, 30 min.; (e) EtI, K_2CO_3 , DMF, 95°C , 10 h, 45% (for two steps); (f) LiOH, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1:1), $50\text{--}60^\circ\text{C}$, 10 h, 80%; (g) Piperazine, EtOH, microwaves, 35 min, 80%.

the *N*-alkylation reaction was carried out directly over quinolone **14** without purification, that is, **16** was reduced in the presence of molybdenumhexacarbonyl and the crude product was *N*-alkylated in the presence of ethyl iodide and K_2CO_3 in DMF to provide the *N*-ethyl quinolone **30** in an two steps overall 45% yield. Simultaneously, transesterification also occurred (Scheme 6). Quinolone **30** was then hydrolysed to give the corresponding quinolonic acid derivative **31** in 80%. To complete the synthesis, an ethanolic solution of acid **31** was treated with piperazine under microwave radiation to afford norfloxacin **3** in 85% (Scheme 6).

Fluoroquinolonic antimicrobial Norfloxacin (**3**) was therefore synthesized in seven steps from commercially available 4-fluoro-5-chlorobenzaldehyde with an overall yield of 16%.

3. Conclusion

A synthetic method to prepare quinolines from MBH adducts is described. As proof-of-principle cases, the total synthesis of two pharmacologically active quinolones has been accomplished. The synthetic sequence is relatively simple, uses rather inexpensive reagents, can be easily scalable, and seems to provide access to quinolones with great structural diversity. The MBH adducts used as substrate can be prepared from commercially available and inexpensive starting materials. Via ESI-MS(/MS), a new mechanistic proposition has also been disclosed rationalizing the key role of TFA in the Kim's TFA-mediated method to prepare *N*-oxide hydroxyquinolines.

4. Experimental section

4.1. General

The ^1H and ^{13}C spectra were recorded on a Bruker at 250 MHz and 62.5 MHz, respectively. The ^1H and ^{13}C spectra were also recorded on an Inova instrument at 500 MHz and 125 MHz, respectively. The high resolution mass spectra were recorded using a Q-TOF Micromass equipment (Waters, UK). Manipulations and reactions were not performed under dry atmospheres or employing dry solvents, unless otherwise specified. In those cases CH_2Cl_2 , DMF, and triethylamine were dried over CaH_2 and distilled. Purification and separations by column chromatography were performed on silica gel, using normal or flash chromatography. TLC visualization was achieved by spraying with 5% ethanolic phosphomolybdic acid and heating. All the reactions the Morita–Baylis–Hillman reactions were sonicated in an ultrasonic cleaner (81 W, 40 MHz). Compounds prepared in this manuscript that were

previously known gave spectral data consistent with those reported.

4.1.1. Synthesis of methyl 4-hydroxyquinoline-3-carboxylate 1-oxide (15). A solution of the MBH adduct **17** (0.3 g, 1.26 mmol) in TFA (2 mL) was stirred for 10 h at 70–75 °C. The reaction medium was then dropped in cold water. The mixture was extracted with CHCl₃ (3 × 10 mL). The combined organic phases were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography to provide 0.22 g (80% yield) of *N*-oxide **15** as a white amorphous solid. Mp 187–189 °C; IR (film, ν_{\max}): 3417, 2924, 1702, 1613, 1541, 1454, 1356, 1229, 1143, 1068, 767 cm⁻¹. ¹H NMR (250 MHz, DMSO-*d*₆), δ ppm: 12.8 (s, 1H), 8.70 (s, 1H), 8.19 (d, *J*=7.8 Hz, 1H), 7.81 (m, 2H), 7.49 (m, 1H), 3.73 (s, 3H). ¹³C NMR (62.5 MHz, DMSO-*d*₆), δ ppm: 171.9, 164.6, 145, 139.0, 133.0, 127.4, 126.1, 125.5, 115.3, 107.3, 51.3. HRMS (ESI TOF) calcd for C₁₁H₁₀NO₄ [M+H]⁺ 220.0673. Found 220.0610.

4.1.2. Synthesis of methyl-2-((2-nitrophenyl)((trifluoroacetyl)oxy)methyl)acrylate (22). To a stirred solution of **17** (0.53 g, 2.24 mmol) in 10 mL of dry dichloromethane at 0 °C under argon was added anhydrous triethylamine (0.48 mL, 0.339 g, 3.36 mmol) followed by the careful addition of distilled trifluoroacetic anhydride (0.47 mL, 0.705 g, 3.36 mmol). The reaction was stirred at 0 °C for 30 min. The solvent was evaporated and the residue was quickly purified over a pad of flash silica gel to afford 0.59 g of **22** (80% yield), as a colorless oil. The product proved to be unstable and was kept in dry dichloromethane at 0 °C. IR (ν_{\max} , film): 2958, 1789, 1723, 1634, 1527, 1433, 1348, 1221, 1135 cm⁻¹. ¹H NMR (300 MHz, CDCl₃), δ ppm: 8.12 (d, 1H, *J*=8.4 Hz, 1H), 7.73 (m, 1H), 7.59 (m, 2H), 7.52 (broad s, 1H), 6.53 (s, 1H), 5.59 (s, 1H), 3.78 (s, 3H). ¹³C NMR (75.4 MHz, CDCl₃), δ ppm: 164.2, 155.6 (q, *J*=42.7 Hz, COCF₃), 147.5, 136.7, 133.9, 130.7, 130.0, 129.4, 128.2, 125.3, 114.2 (q, *J*=285.6 Hz, CF₃), 72.0, 52.4; HRMS (ESI, *m/z*) calcd for C₁₃H₁₀F₃NO₆ (M⁺-COCF₃) 333.2168. Found 333.2167.

4.1.3. Synthesis of ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylate (13). To a solution of **15** (0.4 g, 1.83 mmol) under inert gas atmosphere in anhydrous ethanol (10 mL) was added molybdenumhexacarbonyl (0.484 g, 1.83 mmol). The resulting mixture was stirred for 45 min under reflux. The mixture was then cooled to room temperature, filtered, and the solvent removed under reduced pressure to give 0.31 g of **13** (77% yield) as a white solid. The product was pure enough to be used in the next step without purification. Mp 285–287 °C (lit.³² 285–287 °C). ¹H NMR (500 MHz, CF₃CO₂D), δ ppm: 9.84 (s, 1H), 9.23 (d, *J*=8.5 Hz, 1H), 8.75 (t, *J*=7.0 Hz, 1H), 8.67 (d, *J*=8.5 Hz, 1H), 8.53 (t, *J*=7.0 Hz, 1H), 5.22 (q, *J*=7.0 Hz, 2H), 2.08 (t, *J*=7.0 Hz, 3H). ¹³C NMR (125 MHz, CF₃CO₂D), δ ppm: 176.3, 170.2, 147.6, 142, 140.6, 132.9, 127.5, 122.7, 122.5, 107.5, 67.3, 14.8.

4.1.4. Synthesis of ethyl 1-(4-methoxybenzyl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (27). To a solution of **13** (0.125 g, 0.58 mmol) in DMF (4 mL) was added K₂CO₃ (0.16 g, 1.2 mmol), KI (0.015 g, 0.09 mmol), and 4-methoxybenzyl bromide (**26**) (0.17 g, 0.84 mmol). The resulting mixture was warmed at 95 °C for 27 h. The mixture was then filtered and the cake was washed with ethyl acetate (2 × 10 mL). The combined organic phase was washed with distilled water (4 × 5 mL), brine (4 × 5 mL), dried over Na₂SO₄, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexanes—30:70) to provide 0.13 g of **27** (65% yield), as a tinged yellow viscous oil. IR (film, ν_{\max}): 3062, 2979, 2838, 1726, 1688, 1628, 1607, 1515, 1487, 1460, 1416 cm⁻¹. ¹H NMR (250 MHz, CD₃OD) δ ppm: 8.42 (s, 1H), 8.35 (dt, *J*=0.95 and 8 Hz, 1H), 7.84 (m, 2H), 7.5 (m, 1H), 7.34 (d, *J*=8.7 Hz, 2H), 6.94 (d, *J*=8.7 Hz, 2H), 5.28 (s, 2H), 4.23 (q, *J*=7.1 Hz, 2H), 3.79 (s, 3H), 1.29 (t, *J*=7.1 Hz, 3H). ¹³C NMR (62.5 MHz, CD₃OD) δ ppm: 174.3, 163.7, 161.1, 145.5, 137.6,

133.4, 132, 127.4, 126.5, 125.7, 124.9, 114.7, 114.6, 107.5, 79.9, 60.1, 54.4, 13.2; HRMS (ESI *m/z*) calcd for C₂₀H₁₉NO₄K [M+K]⁺ 376.0945. Found 376.0951.

4.1.5. Synthesis of 1-(4-methoxybenzyl)-4-oxo-1,4-dihydroisoquinoline-3-carboxylic acid (12). To a solution of quinolonic ester **27** (0.1 g, 0.3 mmol) in a mixture of CH₃CN/H₂O (1:1, 4 mL) was added lithium hydroxide (0.078 g, 0.25 mmol). The resulting mixture was stirred at room temperature for 3 h. The solvents were removed under reduced pressure. The residue was neutralized with a 10% solution of HCl and extracted with ethyl acetate (2 × 10 mL). The mixture was extracted with ethyl acetate (2 × 10 mL) and the organic phase was washed with brine (10 mL), dried over Na₂SO₄, and concentrated at reduced pressure. No purification was necessary. BQCA **12** was obtained as an amorphous solid (0.079 g), in 85% yield. Mp: 210–212 °C; IR (KBr, ν_{\max}): 3438, 3043, 2961, 2839, 1709, 1611, 1557, 1516, 1458, 1387, 1304 cm⁻¹. ¹H NMR (250 MHz, CDCl₃) δ ppm: 14.8 (br s, 1H, exchangeable with D₂O), 8.74 (s, 1H), 8.50 (dt, *J*=0.7, 8.0 Hz, 1H), 7.91–7.80 (m, 2H), 7.73–7.57 (m, 1H), 7.30 (d, *J*=8.7 Hz, 2H), 6.93 (d, *J*=8.7 Hz, 2H), 5.25 (s, 2H), 3.83 (s, 3H). ¹³C NMR (62.5 MHz, CDCl₃) δ ppm: 177.7, 166.0, 161.3, 144.1, 137.9, 134.4, 131.8, 127.0, 126.8, 125.9, 123.5, 114.8, 114.7, 114.6, 107.3, 81.0, 55.3; HRMS (ESI *m/z*) calcd for C₁₈H₁₅NO₄K [M+K]⁺ 348.0838. Found 348.0744.

4.1.6. Synthesis of (±)-4-chloro-5-fluoro-2-nitro-benzaldehyde (29). To a stirred mixture of 4-chloro-3-fluoro-benzaldehyde **28** (0.5 g, 3.16 mol) in concentrated sulfuric acid (2 mL) at 0 °C, concentrated nitric acid (2 mL) was added dropwise. The resulting mixture was stirred at 80 °C for 1 h. The reaction mixture was then dropped into distilled cold water and the mixture was extracted with ethyl acetate (2 × 25 mL). The combined organic phases were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography (ethyl acetate/hexanes—65:35) to give 0.6 g (93% yield) of **29**, as a yellow tinged viscous oil. IR (film, ν_{\max}): 3072, 1683, 1528, 1340 cm⁻¹. ¹H NMR (300 MHz, CDCl₃), δ ppm: 10.41 (d, *J*=2.1 Hz, 1H), 8.29 (d, *J*=5.7 Hz, 1H), 7.75 (d, *J*=8.1 Hz, 1H). ¹³C NMR (75.4 MHz, CDCl₃), δ ppm: 185.5, 162.9, 159.4, 132.0 (d, *J*=6.5 Hz), 128.0, 127.2 (d, *J*=19.7 Hz), 117.4 (d, *J*=24.4 Hz). HRMS (ESI *m/z*) calcd for C₇H₃O₃ClFNNa [M+Na]⁺: 225.9683. Found: 225.9678.

4.1.7. Synthesis of (±)-methyl-2-[(4-chloro-5-fluoro-2-nitrophenyl)(hydroxy)methyl] acrylate (18). To a solution of nitro-aldehyde **29** (0.37 g, 1.82 mmol) in methyl acrylate (10 mL) was added DABCO (0.13 g, 1.17 mmol). The resulting mixture was kept in an ultrasound bath (ultrasonic cleaner UNIQUE model GA 1000–1000 W) for 8 h. Methyl acrylate was then removed under reduced pressure (92% recovery). The residue was dissolved in ethyl acetate (15 mL) and the organic phase was washed with distilled water (10 mL), brine (2 × 10 mL), dried over anhydrous Na₂SO₄, and the solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography (ethyl acetate/hexanes—1:1) to afford 0.45 g (85% yield) of **18**, as a tinged yellow viscous oil. IR (film, ν_{\max}): 3477, 1716, 1630, 1531, 1348 cm⁻¹. ¹H NMR (300 MHz, CDCl₃), δ ppm: 8.13 (d, *J*=6.6 Hz, 1H), 7.62 (d, *J*=9.6 Hz, 1H), 6.35 (s, 1H), 6.24 (s, 1H), 5.67 (s, 1H), 3.78 (s, 3H). ¹³C NMR (75.4 MHz, CDCl₃), δ ppm: 166.3, 160.9 (d, *J*=258.6 Hz), 140.4, 138.5 (d, *J*=7.4 Hz), 127.9 (d, *J*=1.5 Hz), 126.9, 121.5 (d, *J*=19.5 Hz), 117.2 (d, *J*=24.6 Hz), 67.5, 52.6. HRMS (ESI *m/z*) calcd for C₁₁H₉O₅ClFNNa [M+Na]⁺: 312.0051. Found: 311.9922.

4.1.8. Synthesis of methyl 7-chloro-6-fluoro-4-hydroxyquinoline-3-carboxylate 1-oxide (16). A stirred mixture of the MBH adduct **18** (0.2 g, 0.69 mmol) in TFA (2 mL) was warmed at 70–75 °C for 48 h. The reaction medium was then dropped over cold distilled water (10 mL). The precipitated solid was filtered under reduced pressure,

dried, and use for the next step without purification. *N*-Oxide **16** was obtained in 60% yield (0.11 g). Mp 252–253 °C. IR (film, ν_{\max}): 1720, 1605, 1556, 1458, 1356, 1164, 1025, 796 cm^{-1} . ^1H NMR (250 MHz, $\text{CF}_3\text{CO}_2\text{D}$), δ ppm: 9.40 (s, 1H), 8.59 (d, $J=6.0$ Hz, 1H), 8.32 (d, $J=9.0$ Hz, 1H), 4.16 (s, 3H). ^{13}C NMR (125 MHz, $\text{CF}_3\text{CO}_2\text{D}$), δ ppm: 172.5, 169.6, 161.5 (d, $J=260.7$ Hz), 146.6, 139.2, 138.5 (d, $J=21.4$ Hz), 123.6, 122.7, 113.2 (d, $J=25.3$ Hz), 106.8, 56.4. HRMS (ESI m/z) calcd for $\text{C}_{11}\text{H}_7\text{O}_4\text{ClFN}$ $[\text{M}+\text{H}]^+$: 272.0126. Found: 272.0057.

4.1.9. Synthesis of ethyl 7-chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (30). A stirred mixture of *N*-oxide hydroxyquinoline **16** (0.3 g, 1.1 mmol) in anhydrous methanol (10 mL) and molybdenumhexacarbonyl (0.29 g, 1.83 mmol), under an inert gas atmosphere, was warmed at reflux for 30 min. The resulting mixture was then cooled to room temperature and the solvent was removed under reduced pressure to afford 0.2 g (68% yield) of 4-quinolone **14**. This product revealed to be unstable and was used for the next step without purification. To a solution of quinolone **14** (0.2 g, 0.75 mmol) in anhydrous DMF (1.5 mL) was added K_2CO_3 (0.45 g, 2.91 mmol) and ethyl iodide (0.45 mL, 4.85 mmol). The resulting stirred mixture was warmed at 95 °C under argon atmosphere for 7 h. The reaction was then cooled and filtered. The cake was washed with ethyl acetate (3 \times 7 mL) and the organic phases were combined, washed with distilled water (4 \times 10 mL), brine (10 mL), dried over Na_2SO_4 , and the solvent was removed under vacuum. The residue was purified by silica gel column chromatography (ethyl acetate/hexanes—30:70) to afford 0.213 g of quinolone **30** (65% overall yield), as a white solid. Mp: 139–141 °C. IR (film, ν_{\max}): 2985, 2928, 1718, 1689, 1613, 1527, 1487, 1312, 1218, 1174 cm^{-1} . ^1H NMR (250 MHz, CDCl_3), δ ppm: 8.47 (s, 1H), 8.24 (d, $J=9.1$ Hz, 1H), 7.53 (d, $J=5.8$ Hz, 1H), 4.39 (q, $J=7.1$ Hz, 2H), 4.22 (q, $J=7.2$ Hz, 2H), 1.56 (t, $J=7.2$ Hz, 3H), 1.41 (t, $J=7.1$ Hz, 3H). ^{13}C NMR (62.5 MHz, CDCl_3), δ ppm: 172.7, 165.4, 155.4 (d, $J=250$ Hz), 148.7, 135.3 (d, $J=2.1$ Hz), 129.5 (d, $J=5.8$ Hz), 127.3 (d, $J=20.6$ Hz), 118.0, 114.4 (d, $J=22.7$ Hz), 111.0, 61.1, 49.2, 14.4.

4.1.10. Synthesis of 7-chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (31). To a stirred mixture of quinolone **30** (0.05 g, 0.17 mmol) in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1:1, 5 mL) was added LiOH (0.034 g, 0.85 mmol). The resulting solution was warmed to 50–60 °C for 50 min. The reaction was then cooled to room temperature and the solvents were removed under reduced pressure. The residue was neutralized with a 10% solution of HCl and extracted with ethyl acetate (2 \times 10 mL). The organic phase was then washed with brine (5 mL), dried over Na_2SO_4 , and the solvent was removed under reduced pressure. The residue was filtered on a pad of silica gel (ethyl acetate/methanol—95:5) to give 0.034 g (75% yield) of acid **31**, as a solid. Mp 208–210 °C. IR (film, ν_{\max}): 3433, 3039, 1721, 1613, 1454 cm^{-1} . ^1H NMR (500 MHz, $\text{CF}_3\text{CO}_2\text{D}$), δ ppm: 9.45 (s, 1H), 8.43 (d, $J=7.8$ Hz, 1H), 8.41 (d, $J=5.9$ Hz, 1H), 4.93 (q, $J=7.0$ Hz, 2H), 1.79 (t, $J=7.0$ Hz, 3H). ^{13}C NMR (125 MHz, $\text{CF}_3\text{CO}_2\text{D}$), δ ppm: 174.5, 165.4, 157.4, 153.4, 148.7, 135.3 (d, $J=2.1$ Hz), 129.5, 127.2 (d, $J=20.6$ Hz), 117.9, 114.4, 111.0, 49.1, 14.4. HRMS (ESI m/z) calcd for $\text{C}_{12}\text{H}_9\text{NFCIO}_3$ $[\text{M}+\text{H}]^+$: 270.0333. Found: 270.0281.

4.1.11. Synthesis of 1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (Norfloxacin) (3). To solution of acid **31** (0.03 g, 0.1 mmol) in anhydrous ethanol (1.5 mL) was added freshly distilled piperazine (0.022, 0.25 mmol). This solution was then transferred to a microwave vial and warmed to 120 °C for 35 min. Microwave reactions were conducted on a CEM Discover[®] Microwave synthesizer. The equipment consists of a continuous focused microwave-power delivery system with operator-selectable power output from 0 to 300 W. Reactions were performed in glass vessels (capacity 10 mL) sealed with a septum. Temperature measurements were conducted using an IR temperature sensor

mounted under the reaction vessel. The mixture was then cooled to room temperature and the white precipitate was filtered and dried and purified by crystallisation (methanol/dichloromethane) to furnish 0.025 g (80% yield) of Norfloxacin (**3**), as a white solid. Mp: 220–221 °C (lit.³³ 221 °C); 3600–3250, 2950, 2830, 2500, 1725–1700, 1628, 1619, 1484, 1250 cm^{-1} . ^1H NMR (500 MHz, $\text{CF}_3\text{CO}_2\text{D}$), δ ppm: 9.16 (d, $J=12.2$ Hz, 1H), 8.66 (br s, 1H), 8.32 (d, $J=6.5$ Hz, 1H), 5.69 (q, $J=7.0$ Hz, 2H), 4.80 (s, 4H), 4.62 (s, 4H), 2.61 (t, $J=7.0$ Hz, 3H). ^{13}C NMR (125 MHz, $\text{CF}_3\text{CO}_2\text{D}$), δ ppm: 171.5 (d, $J=3.8$ Hz), 170.6, 157.1, 155.0, 149.3, 149.1 (d, $J=10.4$ Hz), 139.9, 117.1 (d, $J=10$ Hz), 112.9 (d, $J=26$ Hz), 105.8 (d, $J=2.9$ Hz), 104.6, 53.7, 47.1, 47.0, 45.4, 13.8; HRMS (ESI TOF) calcd for $\text{C}_{16}\text{H}_{19}\text{FN}_3\text{O}_3$ $[\text{M}+\text{H}]^+$ 320.1411. Found 320.1453.

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Supplementary data

The ^1H , ^{13}C NMR, and HRMS spectra are available for all compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.04.018. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

- Lescher, G. Y.; Froelich, E. D.; Gruet, M. D.; Bailey, J. H.; Brundage, R. P. *J. Med. Pharm. Chem.* **1962**, *5*, 1063–1065.
- Emmerson, A. M.; Jones, A. M. *J. Antimicrob. Chemother.* **2003**, *51*, 13–20 and references cited therein.
- Wise, R. *J. Antimicrob. Chemother.* **1984**, *13*, 59–64.
- Naber, K. G. *Chemotherapy* **1996**, *42*, 1–9.
- Balfour, J. A.; Todd, P. A.; Peters, D. H. *Drugs* **1995**, *49*, 794–850.
- (a) Jones, R. N.; Pfaller, M. A. *Clin. Infect. Dis.* **2000**, *31*, 16–23; (b) Blondeau, J. M. *J. Antimicrob. Chemother.* **1999**, *43*, 1–11.
- (a) Crumplin, G. C.; Smith, J. T. *Nature* **1976**, *260*, 643–645; (b) Gellert, M.; Mizuuchi, K.; Ódea, M. H.; Nash, H. A. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 3872–3876; (c) Wang, J. C. *Annu. Rev. Biochem.* **1985**, *54*, 665–697; (d) Gootz, T. D.; Brighty, K. E. *Med. Res. Rev.* **1996**, *16*, 433–486.
- Drlaca, K.; Zhao, X. *Microbiol. Mol. Biology Rev.* **1997**, *61*, 377–392.
- (a) Zhang, S.-X.; Feng, J.; Kuo, S.-C.; Brossi, A.; Hamel, E.; Tropsha, A.; Lee, K.-H. *J. Med. Chem.* **2000**, *43*, 167–176; (b) Kuo, S.-C.; Lee, H.-Z.; Juang, J.; Lin, Y.-T.; Wu, T.-S.; Chang, J.-J.; Lednicer, D.; Paull, K. D.; Lin, C. M.; Hamel, E.; Lee, K.-H. *J. Med. Chem.* **1993**, *36*, 1146–1156.
- Melikian, A.; Wright, J.J.; Krasinski, A.; Hu, C.; Novack, A.; Kezer, W.B. WO Patent 2007/059108, May, 24, 2007; *Chem. Abstr.* **2007**, *147*, 9883.
- Muller, A.; Homey, B.; Soto, H.; Ge, N.; Catron, D.; Buchanan, M. E.; McClanahan, T.; Murphy, E.; Yuan, W.; Wagner, S. N.; Barrera, J. L.; Mohar, A.; Verastegui, E.; Zlotnik, A. *Nature* **2001**, *410*, 5–56.
- Geula, C. *Neurobiology* **1998**, *51*, 518–529.
- Ma, L.; Seager, M. A.; Wittmann, M.; Jacobson, M.; Bickel, D.; Burno, M.; Jones, K.; Graufeld, V. K.; Xu, G.; Pearson, M.; McCampbell, A.; Gaspar, R.; Shughrue, P.; Danziger, A.; Regan, C.; Flick, R.; Pascarella, D.; Garson, S.; Doran, S.; Kreatsoulas, C.; Veng, L.; Lindsley, C. W.; Shipe, W.; Kuduk, S.; Sur, C.; Kinney, G.; Seabrook, G. R.; Ray, W. J. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 15950–15955.
- (a) Shipe, W.D.; Lindsley, C.; Hallett, D. WO Patent 2007/100366, September 7, 2007; *Chem. Abstr.* **2007**, *147*, 343962; (b) Shipe, W.D.; Lindsley, C.; Hallett, D. WO Patent 2007/067489, June 14, 2007; *Chem. Abstr.* **2007**, *147*, 72652.
- For a comprehensive review concerning the chemistry of quinolones, see: Boteva, A. A.; Krasnykh, O. P. *Chem. Heterocycl. Compd.* **2009**, *45*, 757–785.
- For some examples concerning the synthesis of Norfloxacin, see: (a) Zhu, S.; Wu, Y.; Yu, Z.; Shen, X.; Xu, C.; Yao, J.; Huang, H.; Jin, S. *Lett. Org. Chem.* **2008**, *5*, 1–2; (b) Bambeke, V. F.; Michot, J.-M.; van Eldere, J.; Tulkens, P. M. *Clin. Microbiol. Infect.* **2005**, *11*, 256–280; (c) Mitscher, L. A. *Chem. Rev.* **2005**, *105*, 559–592; (d) Kalkote, U. R.; Sathe, V. T.; Kharul, R. K.; Chavan, S. P.; Ravindranathan, T. *Tetrahedron Lett.* **1996**, *37*, 6785–6786; (e) Pappalardo, M.; Omodei-Sale, A.; Zanuso, G. *Farmaco* **1988**, *43*, 489–499; (f) Chu, D. T. W. *J. Heterocycl. Chem.* **1985**, *22*, 1033–1034; (g) Koga, H.; Itoh, K.; Murayama, S.; Suzu, S.; Irikura, T. *J. Med. Chem.* **1980**, *23*, 1358–1363.
- For some recent review concerning different aspects of the Morita–Baylis–Hillman reaction, see: (a) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581–1588; (b) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511–4574; (c) Almeida, W. P.; Coelho, F. *Quim. Nova* **2001**, *23*, 98–101.

18. For new insights about the mechanism of this reaction, see: (a) Santos, L. S.; Pavam, C. H.; Almeida, W. P.; Coelho, F.; Eberlin, M. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 4330–4333; (b) Santos, L. S.; da Silveira Neto, B. A.; Consorti, C. S.; Pavam, C. H.; Almeida, W. P.; Coelho, F.; Dupont, J.; Eberlin, M. N. *J. Phys. Org. Chem.* **2006**, *19*, 731–736; (c) Aggarwal, V. K.; Fulford, S. Y.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1706–1708; (d) Robiette, R.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 15513–15525; (e) Price, K. E.; Broadwater, S. J.; Jung, H. M.; McQuade, D. T. *Org. Lett.* **2005**, *7*, 147–150; (f) Price, K. E.; Broadwater, S. J.; Walker, B. J.; McQuade, D. T. *J. Org. Chem.* **2005**, *70*, 3980–3987; (g) Roy, D.; Sunoj, R. B. *Org. Lett.* **2007**, *9*, 4873–4876; (h) Amarante, G. W.; Milagre, H. M. S.; Vaz, B. G.; Ferreira, B. R. V.; Eberlin, M. N.; Coelho, F. *J. Org. Chem.* **2009**, *74*, 3031–3037; (i) Amarante, G. W.; Benassi, M.; Milagre, H. M. S.; Braga, A. C. C.; Maseras, F.; Eberlin, M. N.; Coelho, F. *Chem.—Eur. J.* **2009**, *15*, 12460–12469.
19. For examples for the use of MBH adducts as substrate for natural products synthesis, see: (a) Coelho, F.; Veronese, D.; Pavam, C. H.; de Paula, V. I.; Buffon, R. *Tetrahedron* **2006**, *62*, 4563–4572; (b) Perez, R.; Veronese, D.; Coelho, F.; Antunes, O. A. C. *Tetrahedron Lett.* **2006**, *47*, 1325–1328; (c) Silveira, G. P. D.; Coelho, F. *Tetrahedron Lett.* **2005**, *46*, 6477–6481; (d) Reddy, L. J.; Fournier, J. F.; Reddy, B. V. S.; Corey, E. J. *Org. Lett.* **2005**, *7*, 2699–2701; (e) Almeida, W. P.; Coelho, F. *Tetrahedron Lett.* **2003**, *44*, 937–940; (f) Feltrin, M. A.; Almeida, W. P. *Synth. Commun.* **2003**, *33*, 1141–1146; (g) Dunn, P. J.; Fournier, J. F.; Hughes, M. L.; Searle, P. M.; Wood, A. S. *Org. Process Res. Dev.* **2003**, *7*, 244–253; (h) Rossi, R. C.; Coelho, F. *Tetrahedron Lett.* **2002**, *42*, 2797–2800; (i) Mateus, C. R.; Feltrin, M. P.; Costa, A. M.; Coelho, F.; Almeida, W. P. *Tetrahedron* **2001**, *57*, 6901–6908; (j) Iwabuchi, Y.; Furukawa, M.; Esumi, T.; Hatakeyama, S. *Chem. Commun.* **2001**, 2030–2031; (k) Mateus, C. R.; Coelho, F. *J. Braz. Chem. Soc.* **2005**, *16*, 386–396; (l) McCauley, J. A.; Nagasawa, K.; Lander, P. A.; Mischke, S. G.; Semones, M. A.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 7647–7648; (m) Coelho, F.; Depres, J. P.; Brocksom, T. J.; Greene, A. E. *Tetrahedron Lett.* **1989**, *30*, 565–566.
20. For recent examples of the use of MBH adducts as starting materials for heterocycles synthesis, see: (a) Vaithyanathan, V.; Selvakumar, K.; Shanmugam, P. *Synlett* **2009**, 1591–1596; (b) Ravinder, M.; Sadhu, P.; Sarathi, R.; Vaidya, J. *Tetrahedron Lett.* **2009**, *50*, 4229–4232; (c) Zhong, W.; Lin, F.; Chen, R.; Su, W. *Synthesis* **2009**, 2333–2340; (d) Narender, P.; Ravinder, M.; Sadhu, P. S.; China Raju, B.; Ramesh, C.; Jayathirtha Rao, V. *Helv. Chim. Acta* **2009**, *92*, 959–966; (e) Bakthadoss, M.; Sivakumar, N. *Synlett* **2009**, 1014–1018; (f) Pirovani, R. V.; Ferreira, B. R. V.; Coelho, F. *Synlett* **2009**, 2333–2337; (g) Meng, X.; Huang, Y.; Chen, R. *Org. Lett.* **2009**, *11*, 137–140; (h) Kim, K. H.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 1249–1251; (i) Han, E.-G.; Kim, H. J.; Lee, K.-J. *Tetrahedron* **2009**, *65*, 9616–9625; (j) Lee, H. S.; Kim, S. H.; Gowrisankar, S.; Kim, J. N. *Tetrahedron* **2008**, *64*, 7183–7190; (k) He, L.; Jian, T.-Y.; Ye, S. *J. Org. Chem.* **2007**, *72*, 7466–7468; (l) Lee, H. S.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 4119–4122; (m) Park, D. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1440–1442; *Chem. Abstr.* **2005**, *144*, 350460; (n) Lee, C. G.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron* **2005**, *61*, 1493–1499; (o) Basavaiah, D.; Rao, J. S.; Reddy, R. J. *J. Org. Chem.* **2004**, *69*, 7379–7382; (p) Coelho, F.; Veronese, D.; Lopes, E. C. S.; Rossi, R. C. *Tetrahedron Lett.* **2003**, *44*, 5731–5735; (q) O'Dell, D. K.; Nicholas, K. M. *J. Org. Chem.* **2003**, *68*, 6427–6430; (r) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627–645; (s) Kim, J. N.; Chung, Y. M.; Im, Y. J. *Tetrahedron Lett.* **2002**, *43*, 6209–6221; (t) Basavaiah, D.; Reddy, R. M.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron* **2002**, *58*, 3693–3697; (u) Kim, J. N.; Lee, H. J.; Lee, K. Y.; Kim, H. S. *Tetrahedron Lett.* **2001**, *42*, 3737–3740.
21. Hong, W. P.; Lee, K.-J. *Synthesis* **2006**, 963–968.
22. Kim, J. N.; Lee, K. Y.; Kim, H. S.; Kim, T. Y. *Org. Lett.* **2000**, *2*, 343–345.
23. For examples of ESI-MS monitoring of key organic reactions see: (a) Eberlin, M. N.; Meurer, E. C.; Santos, L. S.; Pilli, R. A. *Org. Lett.* **2003**, *5*, 1391–1394; (b) Sabino, A. A.; Machado, A. H. L.; Correia, C. R. D.; Eberlin, M. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 2514–2518; (c) Pla-Quintana, A. P.; Roglans, A. *ARKIVOC* **2005**, *IX*, 51–62; (d) Furmeier, S.; Griep-Raming, J.; Hayen, A.; Metzger, J. O. *Chem.—Eur. J.* **2005**, *11*, 5545–5554; (e) Masllorens, J.; Moreno-Manas, M.; Pla-Quintana, A.; Roglans, A. *Org. Lett.* **2003**, *5*, 1559–1561; (f) Jayakannan, M.; van Dongen, J. L. J.; Janssen, R. A. J. *Macromolecules* **2001**, *34*, 5386–5393; (g) Aliprantis, A. O.; Canary, J. W. *J. Am. Chem. Soc.* **1994**, *116*, 6985–6986; (h) De Souza, R. O. M. A.; da Penha, E. T.; Milagre, H. M. S.; Garden, S.; Esteves, P. M.; Eberlin, M. N.; Antunes, O. A. C. *Chem.—Eur. J.* **2009**, *15*, 9799–9804.
24. *Reactive Intermediates*; Santos, L. S., Ed.; Wiley-VCH: Weinheim, 2010.
25. Amarante, G. W.; Benassi, M.; Sabino, A. A.; Esteves, P. M.; Coelho, F.; Eberlin, M. N. *Tetrahedron Lett.* **2006**, *47*, 8427–8431.
26. (a) Coelho, F.; Almeida, W. P.; Veronese, D.; Mateus, C. R.; Lopes, E. C. S.; Rossi, R. C.; Silveira, G. P. C.; Pavam, C. H. *Tetrahedron* **2002**, *58*, 7437–7447; (b) Almeida, W. P.; Coelho, F. *Tetrahedron Lett.* **1998**, *39*, 8609–8612.
27. Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron* **2003**, *59*, 385–390.
28. Said, S. A.; Fiksdahl, A. *Tetrahedron: Asymmetry* **2001**, *12*, 893–896.
29. Ordoukhanian, P.; Taylor, J.-S. *J. Am. Chem. Soc.* **1995**, *117*, 9570–9571.
30. Yoo, B. W.; Choi, J. W.; Yoon, C. M. *Tetrahedron Lett.* **2006**, *47*, 125–126.
31. (a) Rosenthal, J.; Schuster, D. I. *J. Chem. Educ.* **2003**, *80*, 679–690; (b) Blanskepoor, R. L.; Pearson, A. J. *J. Chem. Educ.* **2007**, *84*, 697–698.
32. Lager, E.; Andersson, P.; Nilsson, J.; Pettersson, I.; Nielsen, E. Ø.; Nielsen, M.; Sterner, O.; Liljefors, T. *J. Med. Chem.* **2006**, *49*, 2526–2533.
33. Mazuel, C. Norfloxacin. In *Analytical Profiles of Drug Substances*; Florey, K., Ed.; Academic: San Diego, 1991; pp 557–600.