An alternative synthesis of temafloxacin, a potent antibacterial agent

DANIEL T. W. CHU,[1] ISABELLA M. LICO, AKIYO K. CLAIBORNE, AND HERMANN FAUBL
Anti-infective Research Division, Abbott Laboratories, One Abbott Park Road, Abbott Park, IL 60064-3500 U.S.A.

Received July 3, 1991

This paper is dedicated to Professor Zdenek (Denny) Valenta on the occasion of his 65th birthday

DANIEL T. W. CHU, ISABELLA M. LICO, AKIYO K. CLAIBORNE, and HERMANN FAUBL. Can. J. Chem. **70**, 1323 (1992).

An alternative synthesis of (±)-7-(3-methylpiperazin-1-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid hydrochloride **4**, a potent antibacterial agent, was developed. The method was characterized by regiospecific displacement of the 4-fluoro of the 2,4,5-trifluoroacetophenone by 2-methylpiperazine to produce the key intermediate, 2,5-difluoro-4-(3-methylpiperazin-1-yl)acetophenone **12**, which was subsequently converted to **4** via an intramolecular nucleophilic displacement cyclization reaction.

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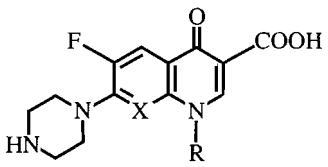
On a mis au point une nouvelle méthode de synthèse du chlorhydrate de l'acide (±)-7-(3-méthylpipérazin-1-yl)-6-fluoro-1-(2,4-difluorophényl)-1,4-dihydro-4-oxoquinoléine-3-carboxylique (**4**), un agent antibactérien très puissant. La méthode est caractérisée par une substitution régiospécifique du fluor en position 4 de la 2,4,5-trifluoroacétophénone par une 2-méthylpipérazine pour préparer l'intermédiaire clé, la 2,5-difluoro-4-(3-méthylpipérazin-1-yl)acétophénone (**12**), que l'on peut transformer subséquemment en **4** par le biais d'une réaction de cyclisation impliquant un substitution nucléophilique intramoléculaire.

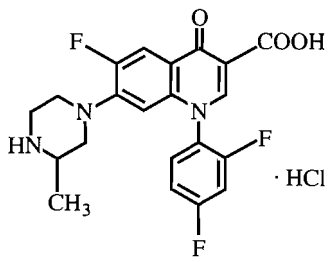
[Traduit par la rédaction]

Introduction

Recently many potent clinically important antibacterial agents having the 1,4-dihydro-4-oxoquinoline-3-carboxylic acid moiety, collectively known as quinolones, have been discovered. Representative examples of these are norfloxacin **1** (1), ciprofloxacin **2** (2), and enoxacin **3** (3). An excellent and comprehensive review of the synthetic chemistry associated with these antibacterial agents has been published (4). The most common synthetic methodology used to prepare ethyl 1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylate is the reaction of an arylamine with diethyl ethoxymethylene malonate to yield an anilinomethylene malonate that may be cyclized by heating (the Gould–Jacobs reaction) or by the use of a Friedel–Crafts catalyst to yield the 4-hydroxyquinoline-3-carboxylate. Alkylation of this derivative with an alkyl halide followed by hydrolysis yields the desired quinolone. Another approach requires the reaction of an isatoic anhydride with sodio ethyl formylacetate, leading efficiently to the quinolone ester (5).



1 $R = C_2H_5$ $X = CH$
2 $R = c\text{-}C_3H_5$ $X = CH$
3 $R = C_2H_5$ $X = N$



4

Temafloxacin hydrochloride **4** ((±)-7-(3-methylpiperazin-1-yl) - 6-fluoro-1-(2,4 - difluorophenyl)-1,4 - dihydro-4-oxoquinoline-3-carboxylic acid hydrochloride) is a potent quinolone antibacterial agent. It is currently under clinical development and an NDA has been filed in the United States. An approval for clinical use has been obtained in Italy and it will be in market shortly. It possesses excellent activity against both Gram-positive and Gram-negative bacteria (6). The general synthetic methods for the introduction of an N-1 substituent require the alkylation of 1,4-dihydro-4-oxoquinoline-3-carboxylic ester with a reactive alkyl halide. This process, however, makes the introduction of a 2,4-difluorophenyl group at the N-1 position difficult. Temafloxacin was synthesized via an intramolecular nucleophilic displacement cyclization reaction as illustrated in Scheme 1 (7–9).

Although this reported synthesis of temafloxacin hydrochloride is fairly efficient, it provides some problems during commercial production. Our manufacturing facility is not well equipped for the low-temperature reaction required in the preparation of the β-ketoester **8**. The oxidation of 2,4,5-trifluoroacetophene **6** to the 2,4,5-trifluorobenzoic acid **7** by the use of commercial bleach offers a physical problem since the reaction conditions required high dilution with vigorous agitation. The reaction time may not be constant due to the variations in agitation. While the above problems may be solved by engineering and modification of reaction conditions, the low yield (between 42 and 49%) of the displacement of **11** with 2-methylpiperazine to afford the desired product prompted us to investigate an alternative synthesis. This paper deals with a new and efficient route for the synthesis of temafloxacin hydrochloride.

Results and discussion

Our previous reported synthetic pathway to temafloxacin was designed to generate a common intermediate having the basic ring skeleton with a leaving group at the 7-position, such as **11**. Displacement at the 7-position with different amines would generate many derivatives for biological testing. A fluorine atom was chosen as the leaving group since aromatic fluorine groups are very susceptible to nucleophilic displacement. Unfortunately, the displacements of the fluorine atom with 2-methylpiperazine did not give a high-

[1]Author to whom correspondence may be addressed.

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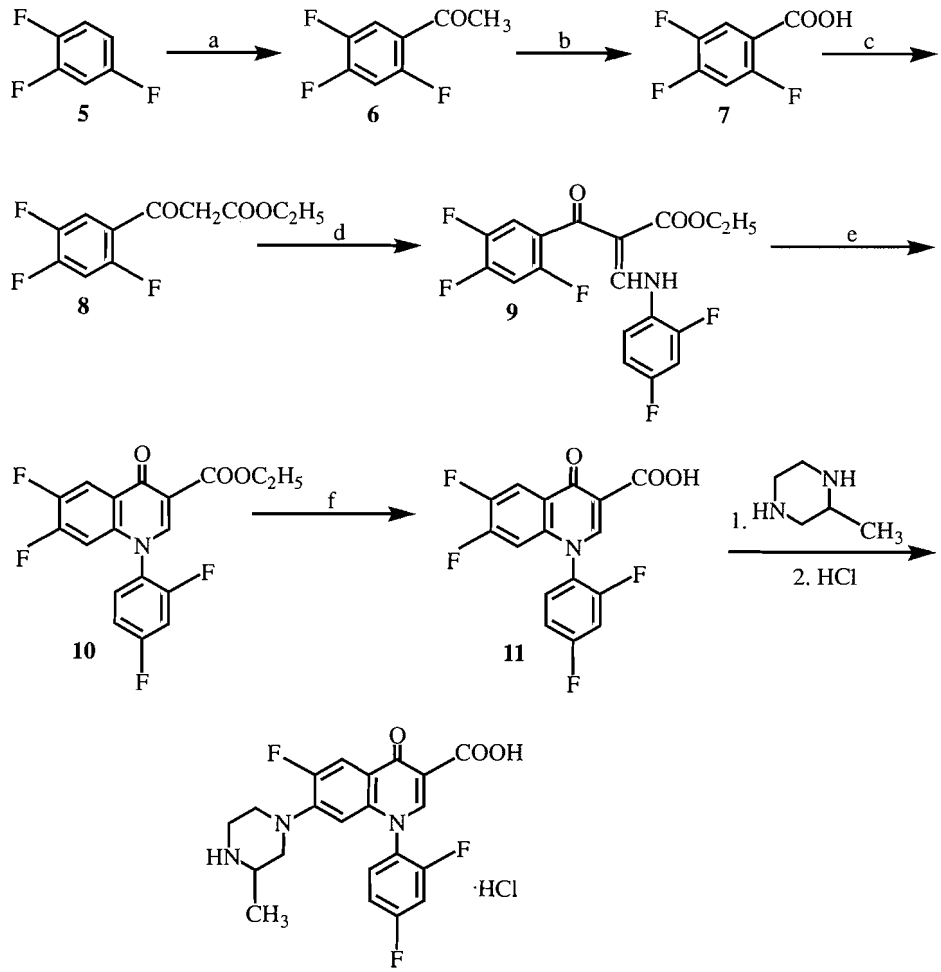

(a) $CH_3COCl/AlCl_3$; (b) NaOCl/NaOH; HCl; (c) $SOCl_2$; $CH_2(COOC_2H_5)COOH/n$-BuLi; HCl; (d) $CH(OC_2H_5)_3/Ac_2O$; *o,p*-difluoroaniline; (e) NaH/THF; (f) H^+

SCHEME 1

yield reaction. To avoid this low-yield reaction, as well as the other manufacturing problems mentioned above, we investigated a synthetic route that required an intermediate which could allow for addition of the C-7 amino group prior to the formation of the bicyclic nucleus. The 2,4,5-trifluoroacetophenone **6** was chosen as the appropriate intermediate since it is readily available.

Displacement of the C-4 fluoro moiety of **6** with 2-methylpiperazine in pyridine in the presence of excess triethylamine followed by precipitation with hydrochloric acid yielded the 2,5-difluoro-4-(3-methylpiperazin-1-yl)acetophenone hydrochloride (**12**) in 92% yield. The fluoro groups at C-2 or C-4 of **6** are both activated by the electron-withdrawing character of the carbonyl group and could be replaced by an appropriate amine. However, the displacement reaction proceeded regioselectively to give the desired key intermediate **12** as a single product. The signal of the critical acetyl proton in the ^1H NMR of **12** in DMSO-d_6 was obscured by the solvent peak. Since **12** is not soluble in $CDCl_3$, a small amount was converted to the free base by neutralization for detailed NMR analysis. The ^1H NMR spectrum of 2,5-difluoro-4-(3-methylpiperazin-1-yl)acetophenone in $CDCl_3$ shows a doublet at δ 2.57 (J_{H-F} = 5 Hz) (corresponding to the acetyl group), due to the long-range coupling[2] with the *ortho* fluorine atom on the benzene ring. Hence, the site of the displacement was assigned as position 4. Additional confirmation of this assignment was provided by the conversion of **12** to temafloxacin hydrochloride by the synthetic route outlined in Scheme 2.

Protection of the secondary amino group as a *tert*-butoxycarbonyl group was achieved by reaction of **12** with di-*tert*-butyl dicarbonate in methylene dichloride in the presence of triethylamine, yielding **13** (mp 100–102°C, 87%). Condensation of 2,5-difluoro-4-(3-methyl-4-*tert*-butoxycarbonylpiperazin-1-yl)acetophenone (**13**) with two molar equivalents of sodium hydride in diethylcarbonate in the presence of a catalytic amount of ethanol yielded the ethyl 2,5-difluoro- 4 -(3-methyl- 4 -*tert*-butoxycarbonylpiperazin-1-yl)benzoylacetate (**14**) (mp 105–108°C, 63%), which existed in both keto and enol forms in approximately 2:1 ratio. Its ^1H NMR spectrum showed the presence of a doublet at δ 2.91 (J_{H-F} = 4 Hz) corresponding to the two keto methylene protons and a singlet at δ 5.81 corresponding to the enol

[2]Long-range coupling was observed with 2,4,6-trifluoroacetophenone (9).

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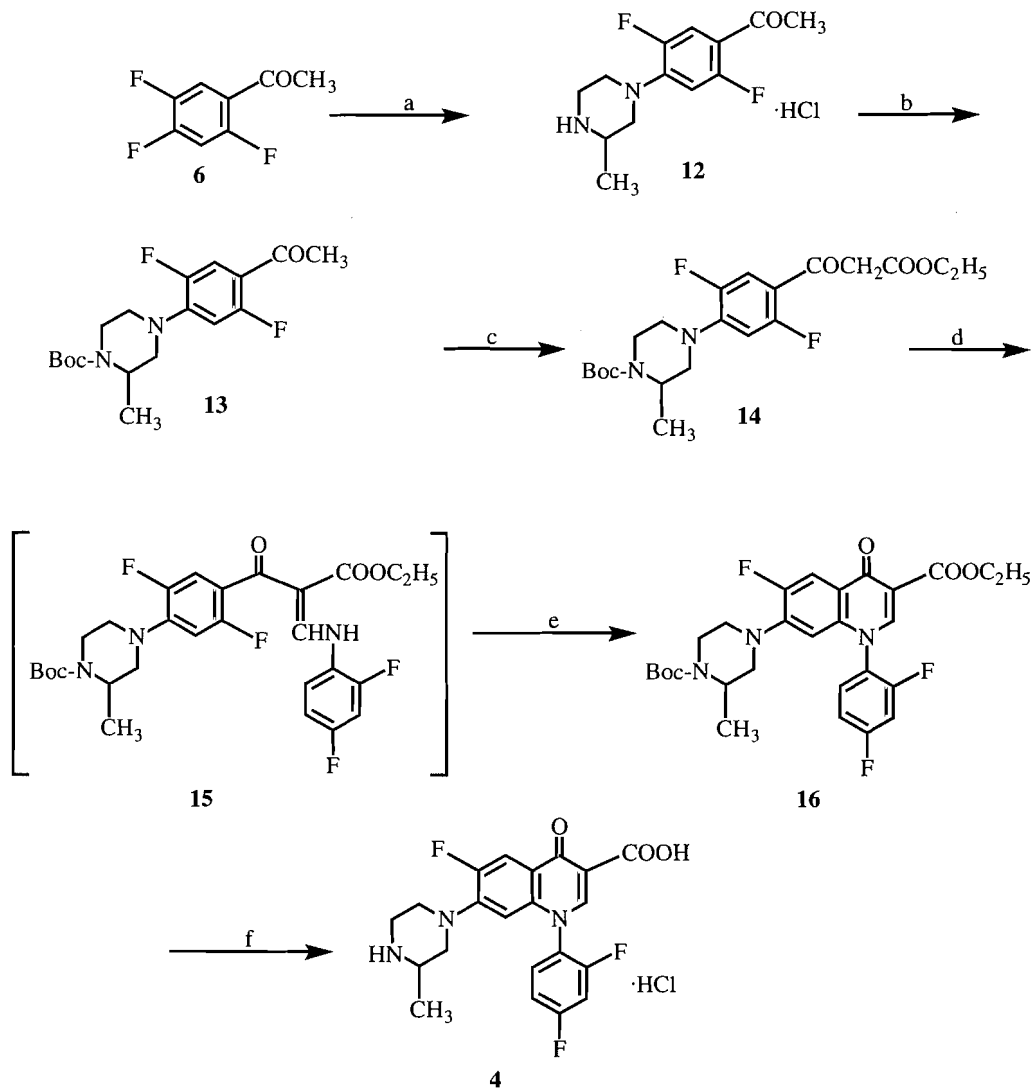

(a) 2-Methylpiperazine/pyridine/TEA; (b) Di-*tert*-butyl dicarbonate/TEA/CH_2Cl_2; (c) NaH/$CO(OC_2H_5)_2$/cat. C_2H_5OH; (d) 1. $CH(OC_2H_5)_3$/Ac_2O; 2. *o*,*p*-difluoroaniline/CH_2Cl_2; (e) NaH/THF; (f) 6 N HCl

SCHEME 2

olefinic proton. The ratio of intensities of these two signals was about 4:1. The long-range coupling with the *ortho* fluorine atom on the benzene ring observed for the methylene protons of the ketoester moiety[3] further confirmed our assignment of the substitution at position 4. Reaction of the ketoester (**14**) with triethylorthoformate in acetic anhydride gave the one-carbon homolog enol ether intermediate, which, upon evaporation of solvent, was allowed to react with a slight excess of 2,4-difluoroaniline in methylene chloride at room temperature to give ethyl 3-(2,4-difluoroanilino)-2-[2,5-difluoro- 4 -(3-methyl- 4 -*tert* - butoxycarbonylpiperazin-1-yl)]benzoylacrylate (**15**). Without purification, **15** was converted to ethyl 7-(3-methyl-4-*tert*-butoxycarbonylpiperazin-1-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate (**16**) (mp 120–123°C, 72%) upon treatment with 1 molar equivalent of sodium hydride in refluxing tetrahydrofuran. Hydrolysis of **16** with 6 N hydrochloric acid yielded temafloxacin hydrochloride (**4**) in 98% yield. The structure of **4** was confirmed by direct comparison with authentic samples prepared by reported methods (9, 11).

In summary, we have developed an alternative synthesis of temafloxacin hydrochloride with an overall yield of 35.6% compared to 20.8% with the reported synthesis. The requirement for low-temperature reactions was also avoided. The key features for this synthesis are the use of easily accessible 2,4,5-trifluoroacetophenone as starting material and the regiospecific displacement of the 4-fluoro of the above acetophenone with 2-methylpiperazine to produce key intermediate **12** in high yield.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were taken in a Thomas–Hoover capillary apparatus and was uncorrected. NMR spectra were determined on a General Electric

[3]Similar long-range couplings were reported for ethyl 2,3,4,5,6-pentafluorobenzoylacetate (10*a*) and for ethyl 2,3,5-trifluoro-4-(4-methyl-1-piperazinyl)benzoylacetate (10*b*).

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GN-300 spectrometer operating at 300.1 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^{1}H NMR data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad; dd, double doublet), coupling constants, number of protons, and designation. The IR spectra were recorded on a Perkin–Elmer model 710A infrared spectrometer. Mass spectra were obtained with a Hewlett–Packard 5985A mass spectrometer or a Kratos MS-50 instrument with EI source (70 eV). The IR, NMR, and mass spectral data of all compounds were consistent with the assigned structures. Solutions were dried over magnesium sulfate. E. Merck silica (230–400 mesh) obtained from VWR Scientific was used for column chromatography, and yields of the reactions were not optimized. Elemental analyses were performed by the Abbott analytical department and IR, NMR, and mass spectra were recorded by the Abbott structural chemistry department.

2,5-Difluoro-4-(3-methylpiperazin-1-yl)acetophenone hydrochloride (**12**)

To a stirring solution of 2,4,5-trifluoroacetophenone (**6**) (8.7 g, 50 mmol) in pyridine (25 mL) and triethylamine (21 mL) was added 2-methylpiperazine (5.5 g, 55 mmol). After 2 days, the mixture was concentrated to an orange solid, which was dissolved in water (150 mL). Concentrated hydrochloric acid was added until the mixture became acidic, yielding a precipitate. The solid was collected by filtration and washed with small amounts of water, ethanol, and ether. The filtrate was basified with dilute sodium hydroxide solution and extracted with ethyl acetate, and dried and concentrated to give a red oil. 1 N Hydrochloric acid was added and the solid was collected as above. The combined solid was dried to yield **12** (mp >250°C, 13.4 g, 92%). IR (KBr): 1660 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6)δ: 1.39 (d, J = 6.5 Hz, 3H, CH_3), 2.53 (d, J_{H-F} = 4.8 Hz, 3H, $COCH_3$: this signal is partly covered by solvent peak), 3.14 (m, 4H, NCH_2) 3.40 (m, 1H, NCH), 3.68 (m, 2H, NCH_2), 7.08 (dd, 1H, aromatic H), 7.54 (dd, 1H, aromatic H), 9.45 (bs, 1H, NH). Anal. calcd. for $C_{13}H_{17}ClF_2N_2O$: C 53.71, H 5.89, N 9.64; found: C 53.48, H 5.77, N 9.50.

A small amount of **12** was shaken with dilute sodium hydroxide solution and extracted with methylene chloride to yield the free amine of **12**. mp 86–89°C. ^{1}H NMR ($CDCl_3$) δ: 1.12 (d, J = 6.5 Hz, 3H, CH_3), 1.74 (bs, 1H, NH), 2.47 (m, 1H, NCH_2), 2.57 (d, J_{H-F} = 5 Hz, 3H, $COCH_3$), 2.83 (m, 1H, NCH_2), 3.04 (m, 3H, NCH_2 and NCH), 6.56 (dd, 1H, aromatic H), 7.55 (dd, 1H, aromatic H). Anal. calcd. for $C_{13}H_{16}F_2N_2O \cdot 1/5\ H_2O$: C 60.56, H 6.29, N 10.87; found: C 60.76, H 6.29, N 10.76.

*2,5-Difluoro-4-(3-methyl-4-*tert*-butoxycarbonylpiperazin-1-yl)acetophenone* (**13**)

To a suspension of **12** (12.45 g, 42.9 mmol) in methylene chloride (100 mL) in an ice bath was added triethylamine (18 mL, 129 mmol). After the addition of di-*tert*-butyl dicarbonate, the ice bath was removed and the reaction was allowed to warm up slowly to room temperature. After 3 h, the mixture was washed with 1 M H_3PO_4, saturated $NaHCO_3$, and brine solution in sequence. The organic solvent was dried and concentrated. The residue was crystallized from hexane, yielding **13** (13.18 g, 87%), mp 100–102°C. IR ($CDCl_3$): 1620, 1680 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$) δ: 1.31 (d, J = 6.5 Hz, 3H, CH_3), 1.50 (s, 9H, $C(CH_3)_3$), 2.58 (d, J_{H-F} = 4.8 Hz, 3H, $COCH_3$), 2.55 (m, 1H, NCH_2), 2.99 (m, 1H, NCH_2), 3.27 (m, 1H, NCH_2), 3.45 (m, 2H, NCH_2), 3.96 (m, 2H, NCH_2), 4.34 (m, 1H, NCH), 6.53 (dd, 1H, aromatic H), 7.57 (dd, 1H, aromatic H). Anal. calcd. for $C_{18}H_{24}F_2N_2O_3$: C 61.00, H 6.83, N 7.90; found: C 60.97, H 6.82, N 7.87.

*2,5-Difluoro-4-(3-methyl-4-*tert*-butoxycarbonylpiperazin-1-yl)benzoylacetate* (**14**)

To a solution of **13** (3.6 g, 10.17 mmol) in diethyl carbonate (50 mL) was added sodium hydride (60% in oil suspension) (0.853 g, 21.3 mmol) at room temperature under nitrogen atmosphere. The temperature was raised to 80°C and 1 drop of ethanol was added. After 1 h, the mixture was cooled and acetic acid (2 mL) was added. It was concentrated to a red oily residue, which was partitioned between ether and water. The organic layer was separated and dried and concentrated. Flash chromatography of the residue (200 g silica, 1:7 ethyl acetate/hexane as eluent) yielded **14** (2.72 g, 63%). This oil solidified after standing a few days, mp 105–108°C. IR (thin film): 1620, 1695, 1740 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$) δ: 1.27 and 1.33 (each t, J = 7 Hz, 3H, ethyl CH_3), 1.30 (d, J = 6.5 Hz, CH_3), 1.48 (s, 9H, $C(CH_3)_3$), 2.91 (m, 2H, NCH_2), 3.26 (m, 1H, NCH_2), 3.42 (m, 2H, NCH_2), 3.91 (d, J_{H-F} = 4 Hz, 2H × 2/3, $COCH_2COO$), 3.96 (m, 1H, NCH_2), 4.21 (q, J = 7 Hz, 2H × 2/3, ethyl CH_2), 4.21 (q, J = 7 Hz, 2H × 1/3, ethyl CH_2), 4.33 (m, 1H, NCH), 5.81 (s, 1H × 1/3, vinyl H), 6.51 (dd, 1H × 2/3, aromatic H), 6.57 (dd, 1H × 1/3, aromatic H), 7.54 (dd, 1H × 1/3, aromatic H), 7.61 (dd, 1H × 2/3, aromatic H), 12.72 (s, 1H × 1/3, enol OH). Anal. calcd. for $C_{21}H_{28}F_2N_2O_5$: C 59.14, H 6.62, N 6.57; found: C 59.43, H 6.69, N 6.55.

*Ethyl 7-(3-methyl-4-*tert*-butoxycarbonylpiperazin-1-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxoquinoline-3-carboxylate* (**16**)

A mixture of **14** (1 g, 2.3 mmol), acetic anhydride (0.96 g, 9.4 mmol), and triethylorthoformate (0.7 g, 4.7 mmol) was heated at 110°C for 2 h with the removal of the ethyl acetate formed during the reaction. The mixture was evaporated under reduced pressure to an oil, which was then dissolved in methylene chloride (25 mL). 2,4-Difluoroaniline (0.33 g, 2.6 mmol) in methylene chloride (5 mL) was then added to the solution. After 1.5 h, the solution was evaporated to dryness. The residue was dissolved in ether and washed with 1 N acetic acid to remove excess difluoroaniline and then water. The organic layer was dried and concentrated. A small amount of this residue was purified by flash chromatography on silica (using 5% ethyl acetate in methylene chloride as eluent) to yield pure **15**. The remaining residue was dissolved in tetrahydrofuran. To this cold solution was slowly added a 60% sodium hydride-in-oil suspension (0.105 g, 2.6 mmol). The mixture was heated at reflux for 2 h under nitrogen atmosphere and was cooled. A few drops of acetic acid were added. The mixture was concentrated. The residue was dissolved in methylene chloride and washed with water and dried. Upon evaporation of the solvent to dryness, the residue was purified by column chromatography on silica using 3% methanol in methylene chloride as eluent, yielding **16** (0.92 g, 72% from **14**), mp 120–123°C. IR (KBr): 1625, 1725 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$) δ: 1.29 (d, J = 6.5 Hz, 3H, CH_3), 1.39 (t, J = 7 Hz, 3H, ethyl CH_3), 1.45 (s, 9H, $C(CH_3)_3$), 2.63 (m, 1H, NCH_2), 2.81 (m, 1H, NCH_2), 3.24 (m, 3H, NCH_2), 3.91 (m, 1H, NCH_2), 4.30 (m, 1H, NCH), 4.38 (q, J = 7 Hz, 2H, ethyl CH_2), 4.30 (m, 1H, NCH), 4.38 (q, J = 7 Hz, 2H, ethyl CH_2), 6.11 (d, J_{H-F} = 7 Hz, 1H, C_8-H), 7.17 (m, 2H, aromatic H), 7.51 (m, 1H, aromatic H), 8.08 (d, J_{H-F} = 13 Hz, 1H, C_5-H), 8.31 (s, 1H, olefinic H). Anal. calcd. for $C_{28}H_{30}F_3N_3O_5$: C 61.64, H 5.54, N 7.70; found: C 61.48, H 5.52, N 7.62.

Difluoroanilinobenzoylacrylate (**15**): IR ($CDCl_3$): 1625, 1675, 1685 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$), 2 sets of signals, δ: 1.04, 1.15 (each t, J = 7 Hz, 3H, ethyl CH_3), 1.33, 1.34 (each d, J = 6.5 Hz, 3H, CH_3), 1.49 (s, 9H, $C(CH_3)_3$), 2.80 (m, 1H, NCH_2), 2.92 (m, 1H, NCH_2), 3.25 (m, 1H, NCH_2), 3.38 (m, 2H, NCH_2), 3.96 (m, 1H, NCH_2), 4.14, 4.15 (each q, J = 7 Hz, 2H, ethyl CH_2), 4.84 (m, 1H, NCH), 6.49 (m, 1H, aromatic H), 6.96 (m, 2H, aromatic H), 7.34 (m, 1H, aromatic H), 8.25, 8.43 (each d, J_{H-J} = 13 Hz, 1H, aromatic H), 10.90, 12.30 (each bd, J = 13 Hz, 1H, NH). Anal. calcd. for $C_{28}H_{31}F_4N_3O_5$: C 59.46, H 5.52, N 7.43; found: C 59.28, H 5.79, N 7.24.

Temafloxacin hydrochloride (**4**)

To a solution of **16** (0.26 g, 0.47 mmol) in acetic acid (1 mL) at 100°C under nitrogen atmosphere added 6 N HCl (10 mL). The mixture was heated at 100°C for 2.5 h. It was concentrated. The residue was crystallized from ethanol–water to yield temafloxacin hydrochloride (**4**) (0.212 g, 98%), mp > 300°C. IR (KBr): 1625, 1725 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6) δ: 1.26 (d, J = 7 Hz, 3H,

CH_3), 2.95 (m, 1H, NCH), 3.11 (m, 2H, NCH_2), 3.48 (m, 2H, 2 NCH_2), 6.41 (d, J_{H-F} = 7 Hz, 1 H, C_8-H), 7.46 (m, 1H, aromatic H), 7.75 (m, 1H, aromatic H), 7.95 (m, 1H, aromatic H), 8.04 (d, J_{H-F} = 12 Hz, 1H, C_5-H), 9.52 (bs, 1H, NH), 14.87 (bs, 1H, OH). Anal. calcd. for $C_{21}H_{19}ClF_3N_3O_3 \cdot 1/2\ H_2O$: C 54.49, H 4.36, N, 9.08; found: C 54.64, H 4.25, N 9.03. **4** is identical in TLC and HPLC to the authentic samples prepared by the reported method.

Acknowledgements

We wish to thank the analytical research and structural chemistry departments of Abbott Laboratories for elemental analysis and spectral measurements, respectively, and Ms. Cynthia Shepherd for typing the manuscript.

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