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# A novel approach to Finafloxacin hydrochloride (BAY35-3377)

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ABSTRACT

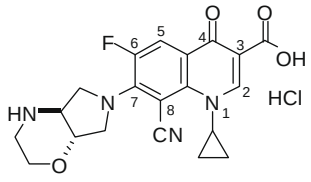
Finafloxacin hydrochloride, an important clinical compound was synthesized by a novel synthetic approach. An active intermediate ethyl 7-chloro-8-cyano-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate **19** was prepared by a new route. The chiral (*S*,*S*′)-*N*-Boc **10** was derived from protected pyrrolidine and the absolute stereochemistry was established by X-ray analysis.



*Helicobacter pyroli* (*H. pyroli*) is a microaerophilic Gram-negative bacterium that lives on the lining of the stomach and infects 50% of the human population worldwide. Infection of the bacterium causes chronic superficial gastritis, chronic gastritis, gastric ulcers and also gastric cancer in humans.[1] *H. pyroli* is only bacterium designated as a Class I carcinogen by International Agency for Research in Cancer.[2]

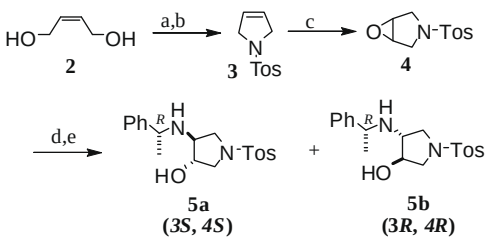
Since the discovery of quinolone antibiotics[3] for Gram-negative bacteria, constant efforts were paid for the structural modification of the basic quinolone scaffolds to new analogues with improved antibacterial activity.[4] In common the newer and more potent quinolones are modified at C-6 fluorine, C-7 amino functional.[5] The fluoroquinolones (FQs)[6] such as ciprofloxacin and norfloxacin are modified[7] quinolone antibiotics which are widely used for the treatment of various bacterial infections. The mode of action of the FQs antibiotics involves inhibition of two bacterial enzymes: DNA gyrase and topoisomerase IV enzymes. DNA gyrase[8] (topoisomerase II) is an essential enzyme involved in the replication, transcription, and reparation of the bacterial DNA and topoisomerase IV is an enzyme responsible for the separation of daughter DNA strands during bacterial cell division. In Gram-negative organisms DNA gyrase is the primary target, in the case of topoisomerase IV the Gram-positive bacteria are the most affected ones.

Recently, finafloxacin hydrochloride (**1**, BAY35-3377)[9] was identified as a novel fluoroquinolone antibiotic for eradication of *H. pyroli.*



**1**

Most antimicrobials are effective against *H. pyroli* in vitro, but in vivo at lower pH environment[10] of the gastric mucosa the activity reduces dramatically for most of the drugs. Finafloxacin hydrochloride is 'pH activated' antibiotic and stabilized under pH condition below neutral. Finafloxacin hydrochloride is currently under clinical development. In this Letter, we report a novel synthesis of finafloxacin hydrochloride in multi-gram quantity. In our method, a new synthetic route was designed for making the core quinolone ester unit. Instead of using chiral chromatographic resolution[9] step on silica gel bonded poly (*N*-methacrylolyl-L-leucine-d-menthylamide) for making the chiral pure desired bicyclic amine, we used commer-



**Scheme 1.** Reagents and conditions: (a) $SOCl_2$, 87%; (b) NaH, $TsNH_2$, DMF, 55%; (c) *m*-CPBA, DCM, 90%; (d) (*R*)-1-phenylethanamine, water, 85%; (e) crystallization.

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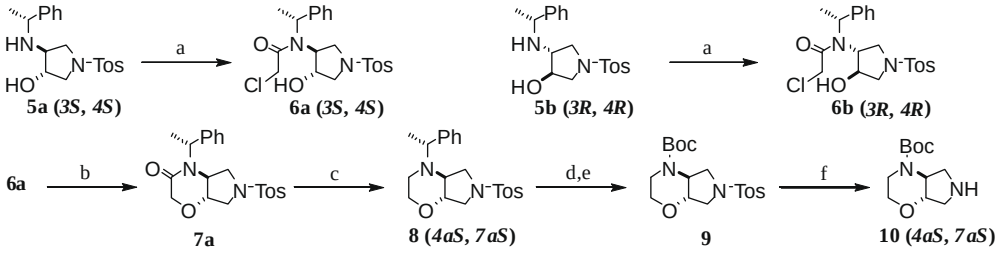
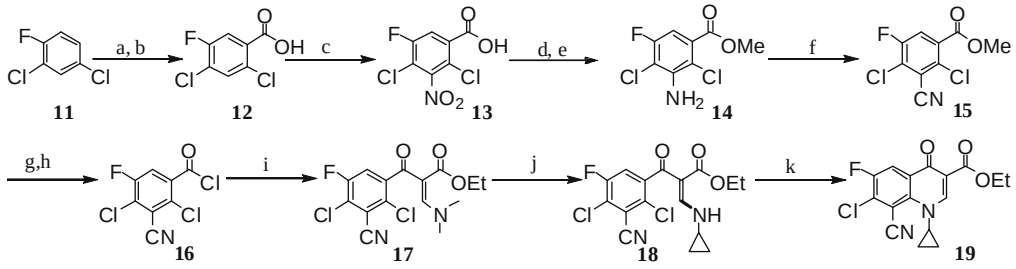


**Scheme 2.** Synthesis of Boc-*SS*-10. Reagents and conditions: (a) chloroacetyl chloride, DIPEA, THF, 80%; (b) $^{t}$BuOK, DCM, 84%; (c) $LiAlH_4$, THF, 60%, (d) Pd/C, $H_2$,MeOH, 90%; (e) $(Boc)_2O$, DCM, 90%; (f) Na, naphthalene, DME, 55%.



**Scheme 3.** Synthesis of 7-chloro-8-cyano-1-cyclopropyl-6-fluoroquinolone **19**. Reagents and conditions: (a) AcCl, $AlCl_3$, 52%; (b) NaClO, 1,4-dioxane, 98%; (c) $HNO_3$, $H_2SO_4$, 90%; (d) MeOH, $SOCl_2$, 95%; (e) Raney Ni, $H_2$ (120PSI); MeOH, 80%; (f) CuCN, *t*-$BuNO_2$, DMF, 60 °C, 43%; (g) LiOH; THF:$H_2O$ (1:1), 86%; (h) $SOCl_2$, toluene 95%; (i) ethyl 3-(dimethylamino)-acrylate, $Et_3$ N, toluene, 60–80 °C, 80%; (j) cyclopropanamine, EtOH:ether (1:1), 80%; (k) $K_2CO_3$, $CH_3CN$, 90%.

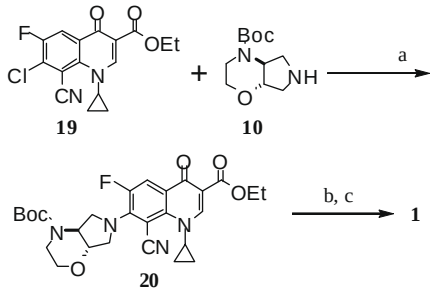
cially available less expensive (*R*)-1-phenyl-ethanamine and the diastereomers were purified by using crystallization technique.

As shown in Scheme 1, our synthesis began with the synthesis of chiral pure (*S,S′*)-*N*-Boc-**10**. 4-(toluene-4-sulfonyl)-2,5-dihydro-1H-pyrol (**3**) was easily prepared[11] from dihydroxy butane **2** in two steps. Epoxidation of the double bond led to the racemate mixture of the syn-epoxide **4** in 90% yield.[12] Opening of the epoxide with chiral (*R*)-phenylethanamine gave the mixture of the two diastereomers (**5a**, **5b**, Scheme 1). The both diastereomers were initially purified by chromatography. As our goal was to develop an easy handling process for large scale synthesis of the amine subunit, alternative techniques were investigated. After checking several solvents, it was found that the minor diastereomer was more soluble in ethyl acetate than the major one. Therefore, the isomers were separated by solvent extractions followed by crystallization. The purity of the separated diastereomers was checked by HPLC and chiral HPLC analysis. In both cases, excellent purities were observed. $^1$H NMR data and NOE study of the both compounds (**5a**, **5b**) were not sufficient to establish the absolute configuration of the newly generated chiral centers. In order to determine the absolute stereochemistry of the chiral centers at amino alcohols, both **5a** and **5b** were converted to the corresponding chloroacetyl derivatives **6a** and **6b,** respectively, and crystallized. Luckily, a suitable crystal of compound **6a** derived from **5a** was obtained for X-ray studies.[13]

Analysis of the X-ray data[13] revealed that the absolute configuration of **6a** was confirmed as **R, S, S**. It was the desired absolute configuration for our synthesis. Chloroacetyl compound **6b** derived from **5b** did not have the desired stereochemistry and was not further pursued. The cyclization of **6a** was achieved using $^{t}$BuOK as the base and the amide was subsequently reduced in moderate yield to afford **8**. Finally deprotection of **8** followed Boc protection and detosylation led to *N*-Boc **10**[14] in moderate yield (Scheme 2). Analysis of **10** with chiral HPLC revealed that there was no racemization during the deprotection of the ethylphenyl unit.

We then turned to synthesize the quinolone ester **19**[15] as shown in Scheme 3. The 6-fluoro-quinolone[16] esters were usually prepared by classical method of Gould–Jacobs[16a] synthesis through preparation of enamine malonate from anilines followed by the thermal cyclization to the ring structure and the alkylation of quinoline nitrogen. But the 6-fluoro-7-chloro-*N*-alkyl substituted quinolones were made in different ways.[17] Because the corresponding aniline for making quinoline **19** was not easily available, the Gould–Jacobs method of quinoline synthesis was not adopted. The synthesis of quinoline ester unit began with commercially available dichlorofluorobenzene (**11**). The dichloro-fluoro-benzoic acid (**12**) was prepared from **11** by a two-step reaction sequence (Friedel–Craft's acetylation, followed by the oxidation) in moderate yield. The nitro-group of **13** was introduced smoothly. The aniline **14** was prepared by reduction of the corresponding nitro-unit. A mild Sandmayer reaction condition[18] was used to install cyano-moiety in ester **15**. The ester hydrolysis followed by thionyl chloride treatment led to the acid chloride **16** in 95% yield. The reaction[19] of this acid chloride with *N,N*-dimethyl ethyl acrylate in presence of triethyl amine at elevated temperature (80 °C) led to the acrylate intermediate **17** in 80% yield. The addition of the cyclopropyl amine led to the β-ketoacrylate ester **18** at room temperature and it was easily cyclized[20] to the quinolone structure **19** in the presence of $K_2CO_3$ with an overall yield of 89% for two steps.

Fluoroquinolones antibiotics were usually prepared by the direct amination of 7-halo-6-flurorquinolone-3-carboxylic acids with piperazine and pyrrolidine derivatives under thermal conditions. But the substituted pyrrolidines were not nucleophilic enough to displace the 7-halo to the desire products and modified esters methods were reported.[21] Therefore, **19** was coupled with




**Scheme 4.** Reagent and conditions: (a) DMP, DIPEA, 100 °C, 76%; (b) LiOH, 75%; (c) HCl/ether, 85%.

chiral pyrrolidine *N*-Boc **10** to give the 7-substituted quinolone ester **20** in 76% yield (Scheme 4). Hydrolysis of the ester followed by Boc-deprotection was completed in two steps with good yield to afford the desired final product finafloxacin hydrochloride.[22]

In summary, a novel convergent synthesis of finafloxacin hydrochloride (**1**, BAY35-3377) was achieved on a multi-gram scale. The core quinolone ester unit **19** was synthesized by a new route. The chiral *N*-Boc **10** was prepared and the absolute configuration was confirmed by X-ray analysis. The isolation of the chiral amine **5a** and **5b** by solvent extraction and crystallization was demonstrated for the first time as per our knowledge.

## Acknowledgment

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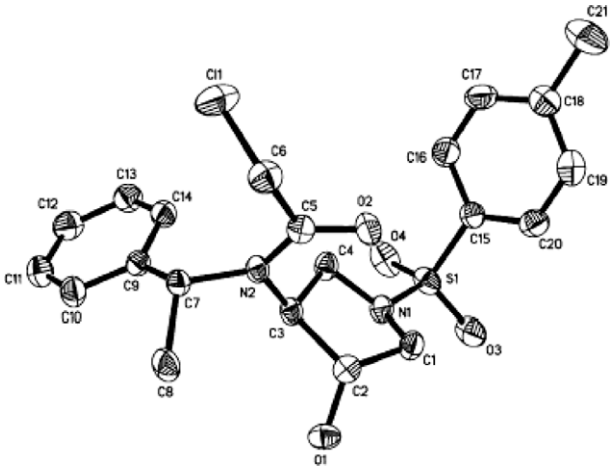
13. ORTEP diagram of **6a**:




14. (a) *N*-Boc **10**: $^1$H NMR (400 MHz, $CDCl_3$, $\delta$ ppm) 1.1 (s, 3H), 3.13–3.47 (m, 3H), 3.49–3.5.3 (m, 2H), 3.62–3.67 (m, 1H), 3.71–3.3.75 (m, 1H), 3.83–3.9 (m, 1H), 4.01–4.07 (m, 1H), 4.15–4.19 (m, 1H); EIMS 229.2 (M+1).
15. *Synthesis of* **19**: Stage 1: A solution of the acid of the corresponding ester **15** (100 g, 0.43 mol) in toluene (800 mL) was treated with $SOCl_2$ (100 mL) and then stirred under reflux for 3 h. The solvent was removed under reduced pressure to dryness and azeotrop with toluene to remove excess $SOCl_2$ to give acid chloride **16**. Then a solution of **16** in toluene (200 mL) was added into a solution of 3-dimethylamino-acrylic acid ethyl ester (68 g, 0.47 mol) and triethylamine (87 g, 0.86 mol) in toluene (1.0 L) at 50 °C. After completion of addition, the reaction mixture was stirred at 70–80 °C for 4 h. Then the solvent was removed completely to dryness under reduced pressure and redissolved in ethyl acetate (500 mL). The solid was filtrated off and washed with ethyl acetate. The filtrate was concentrated to dryness under reduced pressure. The residue was purified by column to give compound **17** (107 g, 70% yield). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$ ppm) 1.03 (t, 3H, $J$ = 7.2 Hz), 3.03 (s, 3H), 3.43 (s, 3H), 4.01 (q, 2H, $J$ = 7.2 Hz), 7.4 (d, 1H, $J$ = 8 Hz), 7.91 (s, 1H). Stage 2: A solution of 16 (100 g, 0.28 mol) in ethanol (500 mL) and ether (500 mL) was treated with cyclopropylamine (32 g, 0.56 mol) at room temperature. After stirring for 1.5 h, the solvent was removed under reduced pressure to give crude compound **18** which was used in next step without purification. Stage 3: A solution of **18** in $CH_3CN$ (1.0 L) was treated with $K_2CO_3$ (193 g, 1.4 mol) at room temperature and then heated to 70–80 °C for 1 h. The $K_2CO_3$ was filtrated off while hot. The solvent was concentrated to half amount and standby overnight. The precipitate was collected by filtrating to give compound **19** (83 g, 89% yield for 2 steps). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$ ppm) 1.03 (t, 3H, $J$ = 7.2 Hz), 1.21–1.33 (m, 4H), 4.01 (q, 2H, $J$ = 7.2 Hz), 4.23–4.26 (m, 1H), 8.5 (d, 1H, $J$ = 8 Hz), 8.78 (s, 1H); EI-MS 371.1 (M+1).
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18. *Sandmayer condition*: A solution of CuCN (75 g, 0.84 mol) in DMSO (400 mL) was heated to 60 °C for 1 h and then *tert*-butyl-nitrite (173 g, 1.7 mol) was added at once. To this mixture, a solution of amine **14** (100 g, 0.42 mmol) in DMSO (150 mL) was added while maintaining the reaction temperature between 60 and 70 °C. After complete addition and stirring for additional 3 h, the reaction mixture was poured onto ice-water and was extracted with ethyl acetate (1.0 L × 3). The combined organic layer was washed with brine. The solvent was removed under reduced pressure. The residue was purified by column to give cyano compound **15** (45 g, 43% yield).
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22. *Synthesis of finafloxacin hydrochloride*: A mixture of **10** (22.8 g, 0.1 mol) and **19** (33.4 g, 0.1 mol) and DIPEA (26 g, 0.2 mol) in DMP (100 mL) was heated to 60 °C for 6 h. The reaction mixture was cooled to room temperature and then diluted with water. The resultant mixture was extracted with ethyl acetate (200 mL × 3). The combined organic layer was washed with 0.5 M HCl and brine. The solvent was evaporated under reduced pressure to give **20** (32.5 g,

76% yield). To a solution of **20** (32.5 g, 76 mmol) in THF (200 mL) and $H_2O$ (200 mL) was added LiOH (20 g) and stirred for 2 h. The reaction mixture was washed with ether twice. The aqueous layer was acidified to pH 3 by adding 1 M HCl at 0 °C and then was extracted with ethyl acetate (150 mL × 3). The solvent was evaporated under reduced pressure to give acid (28 g, 75% yield) The acid was dissolved in ethanol (200 mL) and 2 M ethereal HCl (50 mL) was added drop wise and stirred at room temperature overnight. The solid was collected by filtrating and dried to give **1** (21 g, 85% yield). $^1$H NMR (400 MHz, DMSO-$d_6$, $\delta$ ppm) 1.06–1.08 (m, 1H), 1.19–1.24 (m, 2H), 1.410–1.42 (m, 1H), 2.99–3.03 (m, 1H), 3.08–3.15 (m, 2H), 3.73–3.95 (m, 7H), 3.97–4.11(m, 1H), 4.12–4.14 (m, 1H), 7.92 (d, 1H, $J$ = 14.4 Hz), 8.7 (s, 1H); EI-MS 399.2 (M+1).