

Short Note

(*R*)-7-(Azepan-3-ylamino)-8-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid Hydrochloride

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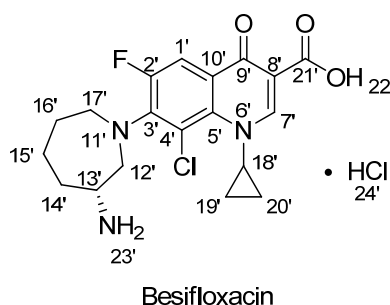
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Abstract: In this paper (*R*)-7-(azepan-3-ylamino)-8-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride **1** was isolated and identified as the *N*-substituted regioisomer of besifloxacin, which has been synthesized from the reaction of 8-chloro-1-cyclopropyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **3** with (*R*)-tert-butyl 3-aminoazepane-1-carboxylate **2** in acetonitrile as solvent in 37% yield. The chemical structure of compound **1** was established on the basis of ¹H-NMR, ¹³C-NMR, mass spectrometry data and elemental analysis.

Keywords: besifloxacin; *N*-substituted regioisomer

Besifloxacin, (+)-7-[(3*R*)-3-aminoheptahydro-1*H*-azepin-1-yl]-8-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride, developed by SS Pharmaceutical (SSP) Co. Ltd. (Figure 1), was a fourth-generation fluoroquinolone antibiotic [1–5]. Besifloxacin hydrochloride eye drop was used to treat bacterial conjunctivitis caused by aerobic and facultative Gram-positive microorganisms and aerobic and facultative Gram-negative microorganisms.

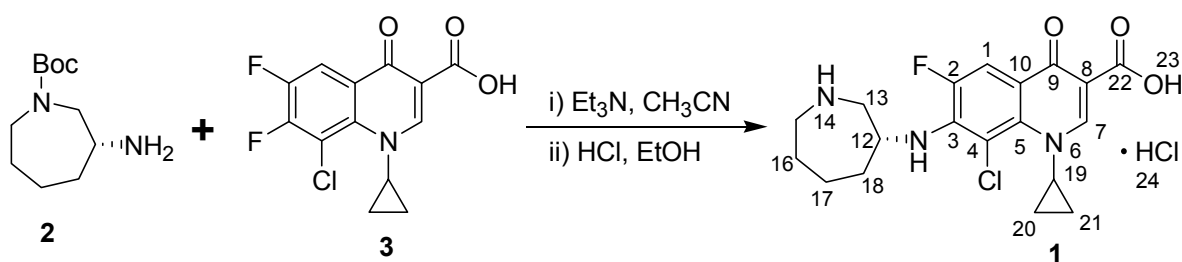
Figure 1. The structure of besifloxacin.



Recently, we found a new compound **1**, (*R*)-7-(azepan-3-ylamino)-8-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride was always present during the synthesis of besifloxacin. It was found that **1** was the *N*-substituted regioisomer of besifloxacin.

As a part of our research programme on besifloxacin, we report herein the synthesis of the compound **1** through 8-chloro-1-cyclopropyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **3** with (*R*)-tert-butyl 3-aminoazepane-1-carboxylate **2** in acetonitrile in the presence of catalytic amounts of triethylamine (Scheme 1). And then it was deprotected with hydrochloric acid to get the target compound **1** [6–8]. The total yield was 37%.

Scheme 1. Synthesis of (*R*)-7-(azepan-3-ylamino)-8-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride.



The ¹H-NMR spectrum of compound **1** was different from besifloxacin. The ¹H-NMR spectrum of compound **1** showed a doublet located at δ 6.20 ppm (*J* = 9.1 Hz) which was assigned to the one H-11 proton of -NH-. A singlet was located at δ 9.72 ppm indicated two H-14 protons of the amine hydrochloride. The ¹H-NMR spectrum of besifloxacin showed a singlet located at δ 8.23 ppm which was assigned to the three H-23' protons of the amine hydrochloride.

Experimental

¹H-NMR and ¹³C-NMR spectra were obtained using a Bruker Avance AV-500 spectrometer (Bruker BioSpin GmbH, Karlsruhe, Germany) and were recorded at 500 MHz and 125 MHz respectively. All the experiments were carried out in DMSO-*d*₆. Chemical shifts are expressed in ppm (δ) with tetramethylsilane (TMS) as an internal standard.

The 8-chloro-1-cyclopropyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **3** [9] and (*R*)-tert-butyl 3-aminoazepane-1-carboxylate **2** [10] were obtained by R&D Center, Jiangsu Yabang Pharmaceutical Group.

To a solution of 8-chloro-1-cyclopropyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **3** (3.00 g, 10 mmol), in dry acetonitrile (15 mL) was added to triethylamine (2.00 g, 20 mmol) at 0 °C. After 15 min, a solution of (*R*)-tert-butyl 3-aminoazepane-1-carboxylate **2** (2.14 g, 10 mmol) in anhydrous acetonitrile (5 mL) was added and the mixture was refluxed for 5 h. Then the mixture was concentrated to dryness, dissolved in CH₂Cl₂ (30 mL), washed with brine (15 mL × 3), followed by concentrated and recrystallized from 95% ethanol to give a white solid. The white solid dissolved in 4 mol/L HCl-ethanol solution, then heated at 37 °C for 2 h. After concentrated to dryness and recrystallized by 95% ethanol to give compound **1** as pale yellowish-white powder.

Yield: 37%; m.p.: 224–225 °C pale yellowish-white powder.

Structural Characterization

¹H-NMR (500 MHz, DMSO-*d*₆): δ ppm: 14.73 (H-23, s, 1H), 9.72 (H-14, s, 2H), 8.69 (H-7, s, 1H), 7.79 (H-1, d, *J* = 13.1 Hz, 1H), 6.20 (H-11, d, *J* = 9.1 Hz, 1H), 4.37 (H-12 and H-19, m, 2H), 3.38 (H-13, m, 2H), 3.23 (H-15, m, 1H), 3.09 (H-15, m, 1H), 2.14 (H-18, m, 1H), 1.94 (H-16 and H-18, m, 2H), 1.84 (H-16 and H-17, m, 2H), 1.60 (H-17, m, 1H), 1.23 (H-20 or H-21, m, 2H), 1.03 (H-20 or H-21, m, 2H).

¹³C-NMR(125 MHz, DMSO-*d*₆): δ ppm: 175.6 (C-9), 165.4 (C-22), 151.7 (C-7), 150.6 (C-2), 148.7 (C-3), 139.0 (C-5), 137.3 (C-4), 117.8 (C-10), 110.3 (C-1), 107.0 (C-8), 52.9 (C-12), 50.1 (C-13), 46.2 (C-15), 41.3 (C-19), 34.0 (C-18), 24.9 (C-16), 21.6 (C-17), 10.9 (C-20 or C-21).

FAB-MS, *m/z* = 394.1 (M⁺).

Elemental analysis: Calculated for C₁₉H₂₁ClFN₃O₃·HCl: C, 53.03%; H, 5.15%; N, 9.77%; found: C, 52.82%; H, 5.39%; N, 9.50%.

Acknowledgements

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