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Synthesis and Characterization of Sitafloxacin

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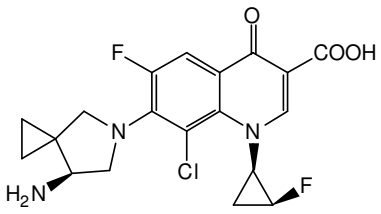
The convenient protocol for the synthesis of sitafloxacin is described. Reaction of ethyl 3-(3-chloro-2,4,5-trifluorophenyl)-3-oxopropanoate with triethylorthoformate and (1R,2S)-(-)-*cis*-1,2-fluorine cyclopropane amino-*p*-toluene sulfonic acid salt by condensation under sodium hydrogen condition. The reaction mixture take place hydrolysis of ester in hydrochloric acid solution. Subsequence reacted with (S)-N-[(oxoboryl)methylene]-5-azaspiro[2,4]heptan-7-amine by condensation. In the end taken off the protection group gives sitafloxacin and total conversion about 52-65 %. The structure of sitafloxacin was characterized by ^{1}H NMR, ^{13}C NMR, IR, MS and elemental analysis.

Keywords: Sitafloxacin, Synthesis, Characterization.

INTRODUCTION

Sitafloxacin[1-3] (Fig. 1) is 7-[(S)-7-amino-5-azas-piro[2,4]heptan-5-yl]-8-chloro-6-fluoro-1-[(1R,2S)-2-fluoro-cyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid. Sitafloxacin (Gracevit®) is a fluoroquinolone with a broad spectrum of antibacterial activity.

Fluoroquinolone antibacterials remain important options in the treatment of bacterial infections. Sitafloxacin is a fluoro-quinolone antibacterial with *in vitro* activity against a broad range of Gram-positive and Gram-negative bacteria, including anaerobicbacteria, as well as against a typical pathogens. Sitafloxacin is approved the treatment of the following bacterial infections: laryngopharyngitis, tonsillitis (including periton-sillitis and peritonsillar abscess), acute bronchitis, pneumonia, secondary infections of chronic respiratory disease, cystitis, pyelonephritis, urethritis, cervicitis, otitis media, sinusitis, periodontitis, pericoronitis and osteitis of the jaw. This article reviews the pharmacological properties, clinical efficacy and tolerability of sitafloxacin, focusing on data from Japan. Sitafloxacin clinical use of its hydrate, synthesis of sitafloxacin containing 1.5 water molecules.



7-[(S)-7-amino-5-azas-piro[2,4]heptan-5-yl]-8-chloro-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

m.f. $C_{19}H_{18}N_3O_3ClF_2$; m.w. 409.81

Fig. 1. Structure of sitafloxacin

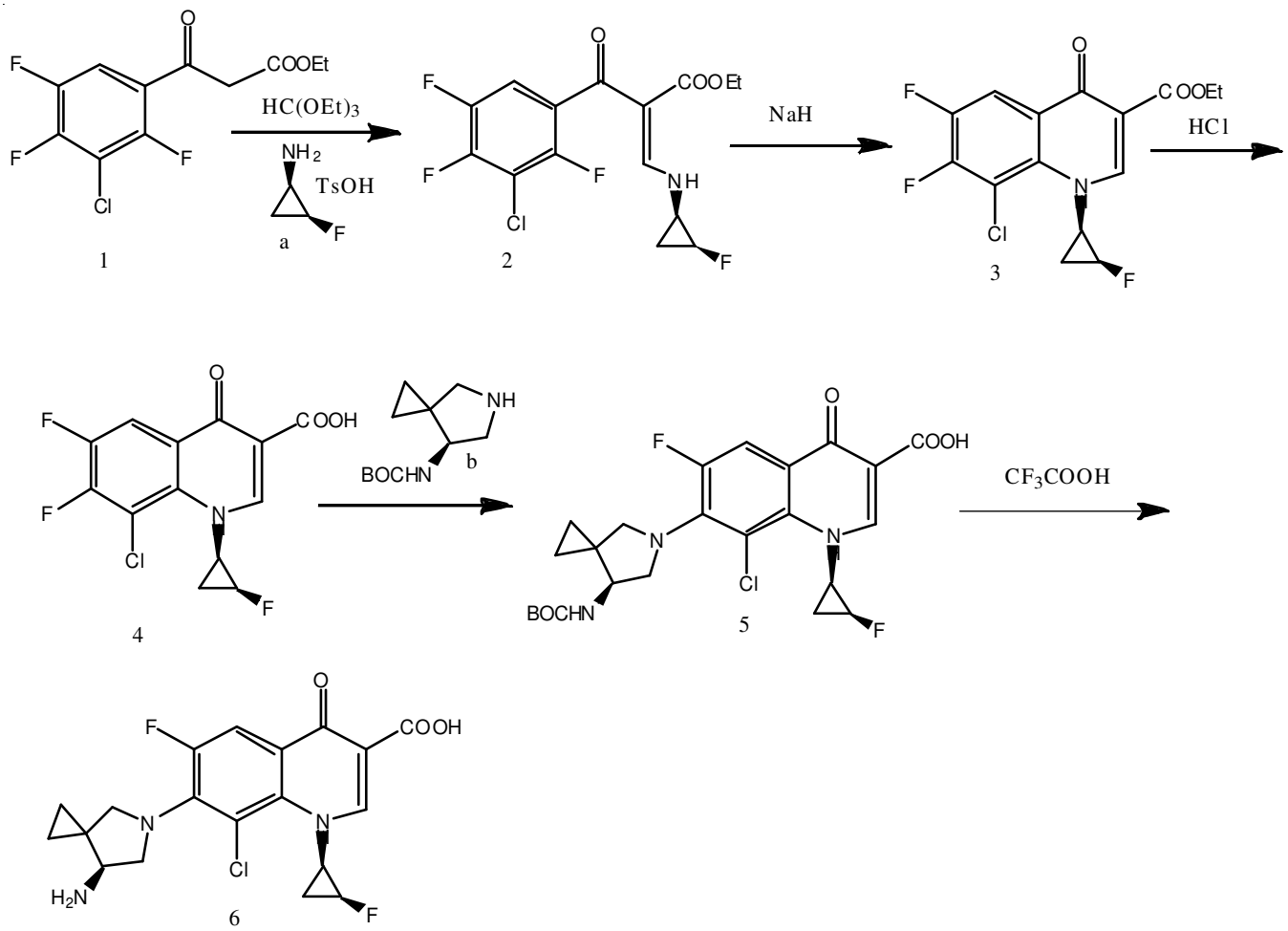
Synthesis of sitafloxacin[4-8]: The research article reported a synthetic method of ethyl 3-(3-chloro-2,4,5-trifluorophenyl)-3-oxopropanoate as the starting material, specific synthetic route shown in **Scheme-I**, finished product structure by ^{1}H NMR, ^{13}C NMR, IR, MS and elemental analysis.

Nicolet 170 SX type infrared spectrometer (KBr tablet); BRUKER AV-500 nuclear magnetic resonance instrument (DMSO-d_6+TFA-d); AGILENT 1200 LC-MSD mass spectro-meter; Elementar Vario EL III type element analyzer. The analytical reagents are used.

EXPERIMENTAL

Preparation of the compound 2: Ethyl 3-(3-chloro-2,4,5-trifluorophenyl)-3-oxopropanoate (15 g, 56.3 mmol, com-pound **1**) and triethylorthoformate (60 mL), anhydrous acetic anhydride (100 mL), after the mixture was stirred at 110-120 °C for 1.5 h and evaporated to dryness under reduced pressure to give concentrated product, it was dissolved in methylene dichloride (50 mL, A).

Trifluoroacetic acid (70 mL) was cooled to 0-5 °C, added (1R, 2S)-(-)-*cis*-1,2-fluorine cyclopropane amino-*p*-toluene sulfonic acid salt. The reaction mixture was stirred at room temperature for 20 min and evaporated to concentrated *in vacuo* and methylene chloride (100 mL) and triethylamine



Scheme-I: Synthesis route of sitafloxacin

(30 mL) under the ice bath were added, the mixture was stirred 20 min. At this time add the A, this mixture was stirred at room temperature for 1 h. The reacted mixture washed with the amount of water, saturated salt water. The solution was dried over $MgSO_4$, filtration and evaporated to dryness under reduce pressure to give oily matter. The product was recrystallized from isopropyl ether to yield (Z)-ethyl 2-(3-chloro-2,4,5-trifluorobenzoyl)-3-[{(1R,2S)-2-fluorocyclopropyl}amino]-acrylate (16.8 g, 82 %, compound **2**).

Preparation of the compound 3: Compound **2** (16.2 g, 44.3 mmol) was dissolved in anhydrous 1,4-dioxane (70 mL) and added NaH (2 g, 60 %). The mixture was stirred for 1 h and extracted with EtOAc (250 mL). The organic layer was washed with 10 % hydrochloric acid, water, dried over sodium sulfate, filtered and evaporated under vacuum, added *n*-hexane under stirring situation, separate out the solid, dried to yield ethyl 8-chloro-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate compound with (1S, 2R)-1-fluoro-2-methylcyclopropane (12.49 g, 78 %, compound **3**).

Preparation of the compound 4: Compound **3** (12.4 g, 34.3 mmol) was added in conc. hydrochloric acid (125 mL) and acetic acid (125 mL). The mixture was stirred at 120-130 °C for 2 h. After diluting with H_2O (500 mL), the precipitate was filtered and washed with H_2O and ether, dryness under reduce pressure to afford target 8-chloro-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid compound with (1S,2R)-1-fluoro-2-methylcyclopropane (8.72 g, 76.2 %, compound **4**) as a colourless solid.

Preparation of the compound 5: Compound **4** (8.2 g, 24.6 mmol) was dissolved in acetonitrile (25 mL), added (S)-N-[(oxoboryl)methylene]-5-azaspiro[2,4]heptan-7-amine (8 g), at reflux for 5 h. The reaction mixture was cooled and filtered. Using acetonitrile-ethanol purified to give (S)-8-chloro-6-fluoro-4-oxo-7-(7-[{(oxoboryl)methylene}amino]-5-azaspiro[2,4]heptan-5-yl0-1,4-dihydroquinoline-3-carboxylic acid compound with (1S, 2R)-1-fluoro-2-methylcyclopropane (8.7 g, 76.5 %, compounds **5**).

Preparation of the compound 6: The flask is charged with compound **5** (8.5, 18.3 mmol) dissolved in phenyl methyl ether (80 mL) and added trifluoroacetic acid (200 mL). The flask is immersed in an ice bath, stirred for 20 min, subsequently at room temperature for 0.5 h. The solvent was evaporated and the residue treated with water, adjust pH = 11, 12 by NaOH solution (1 mol/L), washed with $CHCl_3$, water layer adjust pH = 7 by conc. hydrochloric acid.

The mixture was extracted with $CHCl_3$, washed with water, dried (Na_2SO_4), filtered and evaporated under reduced pressure to obtain the crude as oil. The oil was recrystallized by ethanol and concentrated ammonia to give the desired product 7-((s)-7-amino-5-azaspiro[2,4]heptan-5-yl)-8-chloro-6-fluoro-1-((1R,2S)-2-fluorocyclopropyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (6.7 g, 86 %, compound **6**).

Compound 6 (sitafloxacin): ^{1}H NMR δ: 0.84 (m, 2H, CH_2), 0.95 (m, 1H, CH_2), 1.20 (m, 1H, CH_2), 1.40 (m, H, CH), 1.66 (m, H, CH), 3.23 (d, *J* = 10 Hz, 1H, CH_2), 3.54 (m, H, CH), 3.72 (d, *J* = 11.6 Hz, 1H, CH_2), 4.33 (m, H, CH), 4.38 (m, H, CH_2), 4.47 (m, H, CH_2), 5.13 (d, *J* = 63.9 Hz, 1H, CH), 7.90 (d, *J* = 13.4 Hz, 1H, ArH), 8.24 (m, 2H, NH_2), 8.81 (d, *J* = 3.3 Hz, 1H, CH); ^{13}C NMR δ: 5.96, 14.81, 16.51, 16.59, 25.16, 25.20, 42.14, 42.21, 56.69, 56.74, 56.80, 56.88, 57.19, 57.25, 73.06, 73.85, 108.52, 110.99, 111.18, 114.91, 122.0, 122.06, 139.37, 142.15, 142.25, 154.51; IR (ν_{max}, cm^{-1}): 821, 1039, 1345, 1184, 1452, 1576, 1530, 1609, 1384, 2991, 2890, 3068, 3046, 3440; MS *m/z*: 436.84, 408.1 (M-1.5 H_2O-1)$^-$, 410.0 (M-1.5 H_2O + 1)$^+$, 432.0 (M-1.5 H_2O + Na)$^+$; Anal. Calcd for $C_{19}H_{18}ClF_2N_3O_3 \cdot 1.5H_2O$:C 52.19, H 4.81, N 9.61; Found C 52.08, H 4.90, N 9.68.

RESULTS AND DISCUSSION

In this paper, ethyl 3-(3-chloro-2,4,5-trifluorophenyl)-3-oxopropanoate as the starting material, reacted with triethylorthoformate and (1R, 2S)-(-)-*cis*-1,2-fluorine cyclopropane amino - *p*-toluene sulfonic acid salt by condensation under sodium hydrogen condition. Subsequence take place hydrolysis of ester because of hydrochloric acid, reacted with (S)-N-((oxoboryl) methylene)-5-azaspiro[2,4]heptan-7-amine by condensation. In the end taken off the protection base give to target product sitafloxacin.

Conclusion

The synthesis method as 3 position of the chlorinated intermediates as starting materials. With the traditional ethyl 3-(3-chloro-2,4,5-trifluorophenyl)-3-oxopropanoate as starting materials and original formic acid ethyl ester three condensation and then the (1R, 2S)-(-)-*cis*-1-amino-2-fluorine cyclopropane *p*-toluene sulphonate condensation, cyclization in the presence of sodium hydrogen, in under the condition of free hydrochloric acid ester base and (S)-N-((oxoboryl) methylene)-5-azaspiro[2,4]heptan-7-amine condensation and then reacted with sulfonyl chloride, finally in the presence of three trifluoroacetic acid deprotection method under highly sitaflo-xacin compared. Reduction in (S)-N-((oxoboryl) methylene)-5-azaspiro[2,4]heptan-7-amine condensation generated with fluorine condensation 5 with impurities. From cost considerations, because the process of main cost in (1R, 2S)-(-)-*cis*-1-amino-2-fluorine cyclopropane *p*-toluene sulfonate and (S)-N-((oxoboryl) methylene)-5-azaspiro[2,4]heptan-7-amine. Using the method of using chlorinated good products as intermediates, than the first and (1R, 2S)-(-)-*cis*-1-amino-2-fluorine cyclopropane *p*-toluene sulfonate and (s)-(-)-7-*tert* butoxycarbonylamino-5-aza spiro[2.4] heptane condensation condensation with sulfonyl chloride chlorine than, in the same number of products can be reduced in the two intermediate consumption, cost savings and to obtain a crude product are easy to be purified, the highly purity of sitafloxacin finished.

REFERENCES

1. K. Sato, K. Hoshino, M. Tanaka, I. Hayakawa and Y. Osada, *Antimicrob. Agents Chemother*., **36**, 1491 (1992).
2. R. Nakajima, A. Kitamura, K. Someya, M. Tanaka and K. Sato, *Antimicrob. Agents Chemother.*, **39**, 1517 (1995).
3. N. Shetty and A.P.R. Wilson, *J. Antimicrob. Chemother*., **46**, 633 (2000).
4. Y. Kimura, S. Atarashi, K. Kawakami, K. Sato and I. Hayakawa, *J. Med. Chem*., **37**, 3344 (1994).
5. J. Matsuo, Y. Tani and Y. Hayakawa, *Chem. Lett*., **33**, 464 (2004).
6. Y. Yao, W. Fan, W. Li, X. Ma, L. Zhu, X. Xie and Z. Zhang, *J. Org. Chem*., **76**, 2807 (2011).
7. J. Yukimoto, T. Ehata and T. Tojo, Preparation of 2-Fluorocylo Propanemethanol and 2-Fluorocyclopropane Carboxylic Acid, JP 07 109 237, (1995).
8. K. Satoh, A.Imura, A.Miyadera, K.Kanai and Y.Yukimoto, *Chem. Pharm. Bull. (Tokyo)*, **46**, 587 (1998).