Molbank **2010**, M669; doi:10.3390/M669

OPEN ACCESS

molbank

ISSN 1422-8599

www.mdpi.com/journal/molbank

Short Note

7-(3-Chlorophenylamino)-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid

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Received: 8 March 2010 / Accepted: 22 March 2010 / Published: 24 March 2010

Abstract: 7-(3-Chlorophenylamino)-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**2**) was prepared and fully characterized by NMR, IR, and MS. Compound **2** exhibited good antibacterial activity against gram-positive standard and resistant strains.

Keywords: 7-anilinofluoroquinolone; fluoroquinolone; antibacterial

1. Introduction

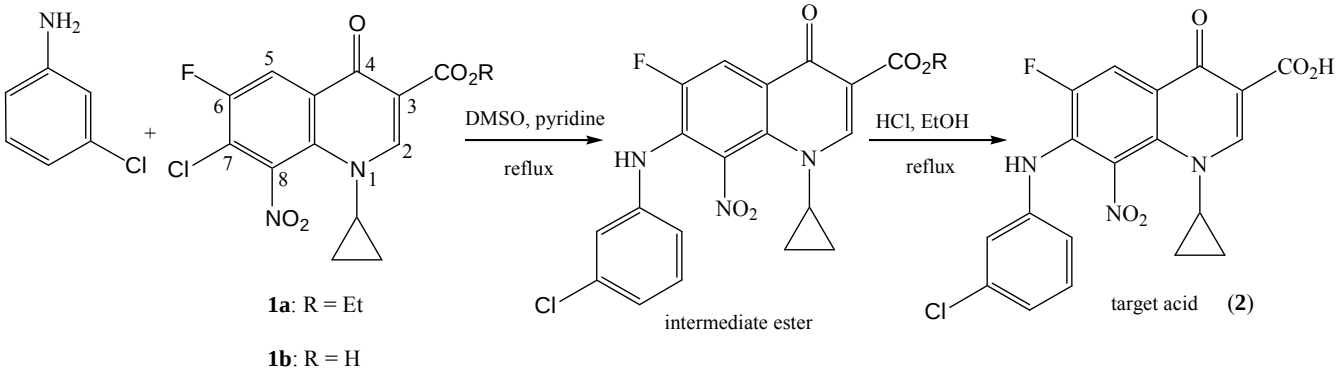
To date, fluoroquinolones represent successful synthetic antibacterial agents [1–5]. However, increased prescribing has led to the recent emergence of fluoroquinolone-resistant bacteria which has necessitated the search for newer drugs with efficacy against resistant strains [6,7]. The present work aims at the synthesis of a new fluoroquinolone derivative (**2**) and screening of its activity.

2. Results and Discussion

An earlier study carried out by our team [4] revealed that substitution of lipophilic groups such as aniline at C-7 of 8-nitrofluoroquinolone (**1**) produced noticeable increase in gram-positive activity, especially against resistant strains with significant loss of gram-negative activity [4]. This research aims at further investigation of halogenated aniline derivatives exemplified by compound **2**. Synthon **1** involved introducing an electron-withdrawing nitro group at C-8 to facilitate coupling of the chloro-

aniline [4]. Although compound **2** was prepared by direct coupling of 7-chloro-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**1b**) with a 2 molar excess of 3-chloroaniline in DMF/pyridine (7:3 V/V), the yield was very low after chromatographic separation from many side products. Alternatively, the chloroaniline was reacted with the correspondent ester (**1a**) to produce the target acid **2** in satisfactory yield upon hydrolysis of the ester intermediate (Scheme 1).

Scheme 1. Synthesis of target compound **2**.



The *in vitro* antibacterial activity of **2** was evaluated against standard and resistant isolates of gram-positive *Staphylococcus aureus* and gram-negative *Escherichia coli* bacteria, using broth dilution method. Compound **2** revealed excellent antimicrobial activity against standard *S. aureus* strains (ATCC6538) with minimum inhibitory concentrations (MIC) of 0.88 µg/mL. Interestingly, it showed good activity against resistant isolates of *S. aureus* gram-positive bacteria with MIC value of 7.0 µg/mL. These data are comparable to ciprofloxacin reference which showed MIC values of 2.9 µg/mL and 1.4 µg/mL, respectively, against both gram-positive strains.

These findings are in correlation with literature findings that more lipophilic quinolones can better penetrate the lipophilic cell membrane of gram-positive bacteria [8,9].

3. Experimental

Two molar equivalents of 3-chloroaniline (0.36 g) were gradually added to a solution of ethyl 7-chloro-1-cyclopropyl-6-fluoro-8-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**1a**) (0.5 g) in 10 mL of DMSO and a few drops of pyridine. The mixture was heated at 70–80 °C under anhydrous conditions. The reaction mixture was left to crystallize, then filtered and the product was left to dry in a dark place. The resulting solid was recrystallized from methanol/chloroform (3x) to give fairly pure ester intermediate (0.15 g, 24%). The intermediate was then hydrolyzed upon dissolving the solid in ethanol and adding conc. HCl (10 mL). The mixture was heated at 70–80 °C for 5 h, then compound **2** was collected by filtration and dried to give a yellow solid (0.13 g, 93%).

M.p.: 240–243 °C (decomp).

IR (KBr, cm^{-1}): *v* 3434, 3390, 2942, 1735, 1640, 1535, 1467, 1365, 1210, 1225.

^{1}H-NMR (300 MHz, DMSO-d_6): δ 0.95, 1.02 (2m, 4H, H_2-2′/H_2-3′), 3.71 (m, 1H, H-1′), 7.16 (dd, J = 1.0, 7.8 Hz, 1H, Ar-H), 7.39 (dd, J = 7.8, 8.1 Hz, 1H, Ar-H), 7.49 (d, J = 8.4 Hz, 1H, Ar-H), 7.98

(m, $J_{H5\text{-}F}$ = 11.2 Hz, 2H, Ar-H and H-5), 8.50 (br s, 1H, NH, D_2O exchangeable), 8.76 (s, 1H, H-2), 12.95 (br s, 1H, CO_2H).

MS (CI/ESI-ve): *m/z* (% rel. int.): calcd. for $C_{19}H_{13}ClFN_3O_5$ (417.8): 419 (5), 418 (34), 417 (21), 416 (78), 383 (4), 360 (5), 359 (35), 339 (7), 325 (6), 311 (8), 293 (12), 265 (100), 191 (6), 161 (6).

Elemental Analysis: Calcd. for $C_{19}H_{13}ClFN_3O_5$, C, 54.62; H, 3.14; N, 10.06. Found: C, 54.61; H, 3.20; N, 9.97.

Acknowledgements

We wish to thank the University of Jordan represented by the Deanship of Academic Research and Hamdi Mango Research Center.

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