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Synthesis and Characterization of New Fluoroquinolones Containing an N Substituted Piperazine Moiety

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N-(Aryl)piperazinyl quinolone derivatives having a hydroxyimino/keto-substituent have been synthesized. Here, intermediate compounds (**1-3**) were synthesized in the presence of bromine in acetic acid. Then these compounds were reacted with ciprofloxacin in the presence of $NaHCO_3$ to give ciprofloxacin derivatives (**4-7**). All the products were confirmed by IR, Mass, ^1H NMR or ^{13}C NMR spectra and elemental analysis.

Key Words: Piperazinyl quinolones, Ciprofloxacin derivatives, Synthesis.

INTRODUCTION

Quinolones are synthetic antibacterial compounds based on a 4-quinolone skeleton. Fluoroquinolones have been clinically successful and are used to treat bacterial infections in both community and hospital settings. Quinolones target bacterial type II topoisomerases, generally DNA gyrase in Gram-negative bacteria and DNA topoisomerase IV in Gram-positive bacteria.l'[1-5]. The most intensive structural variation has been carried out on amines at the 7-position, partially due to the ease of their introduction through a nucleophilic aromatic-substitution reaction on the corresponding halide. Piperazine, aminopyrrolidine and their substituted derivatives have been the most successfully employed side chains, as evidenced by the compounds currently available in the market. Originally, the newer fluoroquinolones arose with the development of 7-piperazinyl quinolones, such as ciprofloxacin and norfloxacin (Fig. 1)[1-5]. Recently, as part of an ongoing program to find potent and broad-spectrum antibacterial agents that display strong Gram-positive activity[5-7], the authors have focused their present attention on modification of the C-7 basic group of the quinolone. Therefore, present strategy to achieve a better antimicrobial profile has focused on introducing new functionality on the piperazine ring. From present research in C-7 piperazine modifications of the quinolones we were able to identify a series of N-substituted piperazinyl quinolones in which the N-4 hydrogen of

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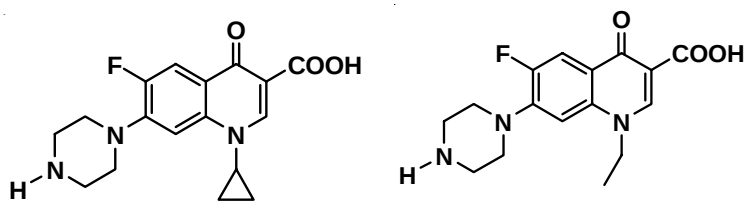
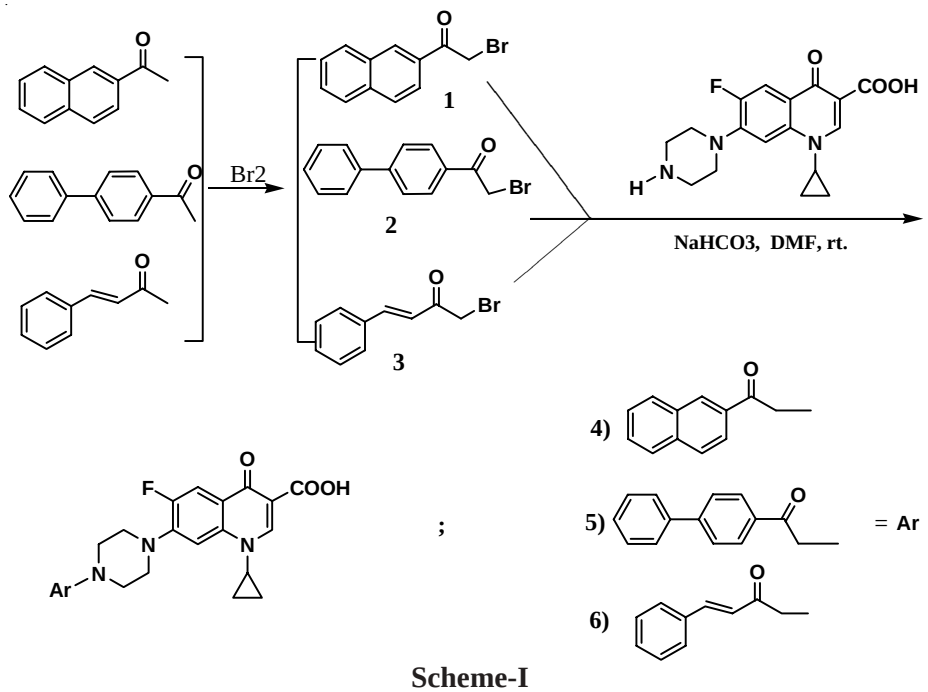
piperazinyl group of ciprofloxacin is replaced with various 2-oxoethyl or 2-hydroxyiminoethyl moieties. The intermediate compounds (**1-3**) were synthesized in the presence of bromine[8]. The N-[2-aryl-2-hydroxyiminoethyl/2-oxoethyl]piperazinyl quinolone analogues **4-7** were prepared by the synthetic route showed in **Scheme-I**. In this case, benzylidene acetone, biphenyl acetone and 2-naphtophenone were converted to a bromo intermediate **1-3** by stirring with bromine in acetic acid at room temperature. Reaction of ciprofloxacine with compounds **1-3** in DMF, in the presence of $NaHCO_3$ at room temperature, afforded N-[2-aryl-2-hydroxyiminoethyl/2-oxoethyl]-piperazinyl quinolone analogues **4-7**[9-11].



Ciprofloxacin Norfloxacin

Fig. 1



Scheme-I

Melting points were determined using a Thomas-Hoover capillary apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker FT-80 spectrometer (Bruker, Rheinstetten, Germany). TMS was used as an internal standard.

Infrared spectra were acquired on a Nicolet 550-FT spectrometer (Medison, WI, USA). Mass spectra were measured with a Finigan TSQ-70 spectrometer (Finnigan Mat, Bremer, Germany) at 70 eV. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus (Perkin-Elmer, Norwalk, CT, USA). The result of the elemental analyses (C, H, N,) were within ± 0.4 % of the calculated amounts.

EXPERIMENTAL

General method for synthesis of α-bromo intermediates: To stirring solution of acetyl compounds (0.133 mol) in 15 mL acetic acid was added bromine (12.613 g, 0.133 mol) in 15 mL acetic acid drop wise then mixed for 1 h. The precipitate was collected and recrystallized from chloform-methanol to give compounds **1-3**.

2-Bromo-1-(naphthalene-2-yl)ethanone (1): Oil; yield *ca.* 86 %; IR (KBr, cm^{-1}): 1692 ν(CO); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.61-4.62 (S, 2H, CH_2), 7.53-7.71 (m, 7H naphtalen) ppm; Mass: M/Z + (%) 249 (3.93), 155 (100), 127 (89.8), 122 (2.36).

1-(Biphenyl-4-yl)-2-bromoethanone (2): m.p. 125-130 °C, yield *ca.* 85 %; IR (KBr, cm^{-1}): 1700 ν(CO); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.9 (S, 2H, CH_2), 7.4-8.0 (m, 9H, biphenyl) ppm; Mass (M/Z +) (%) : 275 (28), 181 (100), 153 (61.4), 76 (31), 69 (5.5), 43 (6).

1-Bromo-4-phenylbut-3-en-2-one (α-bromo benzylidineacetone) (3): m.p. 122-124 ºC; yield *ca.* 81 %; IR (KBr, cm^{-1}): 1720 ν(CO), 1421 ν(C=C), ^{1}H NMR ($CDCl_3$, 90 MHz) δ: 2.46 (S, 2H, CH_2), 4.8-5.3 (dd, 2H, C=C, *J* = 11.7), 7.38 (S, 5H) ppm; Mass (M/Z +) (%): 225 (55.11), 182 (21), 145 (48), 131 (42), 103 (82), 77 (51), 43 (100).

General method for synthesis of ciprofloxacin analogs: A suspension of compound **1-3** (0.584 mol), ciprofloxacin (0.5 mol) $NaHCO_3$ (0.1 g) in 12 mL DMF was mixed for 120 h at room temperature. The product was purified on the column chromatography and was recrystallized in methanol to give **4** and **5** compounds.

1-Cyclopropyl-6-fluoro-7-(4-(2-(naphthalen-2-yl)-2-oxoethyl) piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4): m.p. 310 -312 ºC, yield *ca.* 40 %; IR (KBr, cm^{-1}): 3428 ν(OH), 1730 ν(CO), 1628 ν(CO); ^{1}H NMR (DMSO, 80 MHz) δ: 1.22 (m, 4H, cyclopropyl), 3.5 (m, 8H, piperazin), 4.3 (S, 2H, CH_2), 5.2 (S, 1H, cyclopropyl), 7.2-7.95 (m, 7H Naphthalene and 2H quinolone), 4.8 (S, 1H, COOH) ppm.

1-Cyclopropyl-6-fluoro-7-(4-(2-(biphenyl-4-yl)-2-oxoethyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5): m.p. 320-324 ºC, yield *ca.* 52 %; IR (KBr, cm^{-1}): 3500 ν(OH), 3057 ν(cyclopropyl), 1730 ν(CO), 1479 ν(C=C); ^{1}H NMR (DMSO, 300 MHz) δ: 1.16-1.3 (m, 4H, cyclopropyl), 2.7-3.9 (m, 8H, piperazine), 4.9 (S, 2H, CH_2), 5.63 (S, 1H, cyclopropyl), 7.5-8.5 (m, 9H, biphenyl and 2H, 5,8 quinolone), 8.64 (S, 1H, quinolone), 15.21 (S, 1H, COOH) ppm; Mass M/Z + (%): 525 (3.12), 405 (0.78), 470 (1.5), 237 (7.5), 195 (3.2), 155 (20), 153 (10), 77 (11), 57 (88), 43 (100).

1-Cyclopropyl-6-fluoro-7-(4-(2-(4-phenylbut-3-en)-2-oxoethyl) piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (6): m.p. 330 ºC; yield *ca.* 49 %, ^{1}H NMR (DMSO, 500 MHz) δ: 1.2-1.3 (m, 4H, cyclopropyl), 1.1 (S, 1H, COOH), 2.4-3.1 (m, 8H, piperazine), 2.8 (S, 2H, CH_2), 4.11-4.13 (dd, 2H, C=C), 7.3-7.9 (m, 5H, phenyl and 2H, H5,8 quinolone), 8.9 (S, 1H, H2 quinolone) ppm; Mass M/Z + (%) : 475 (0.78), 384 (7.8), 157 (13.3), 155 (100), 84 (56), 43 (70).

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