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Synthesis and Characterization of New Derivative of Norfloxacin Containing an N Substituted Piperazine Moiety

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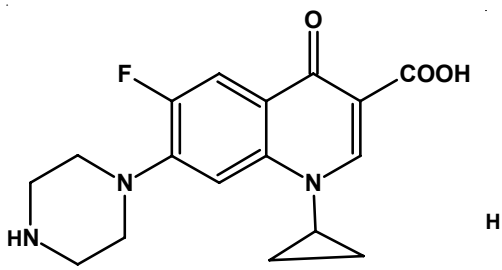
N-(Aryl) norfloxacin derivative that bear a hydroxyimino-substituent has been synthesized. Here, intermediate compound **2** was synthesized from benzylidineacetone in presence of bromine in acetic acid. Then this compound was reacted with hydroxyamine to give compound **3**. The reaction of this compound with norfloxacin in the presence of $NaHCO_3$ gave norfloxacin analog **4**. The products were confirmed by IR, mass or ^1H NMR spectra.

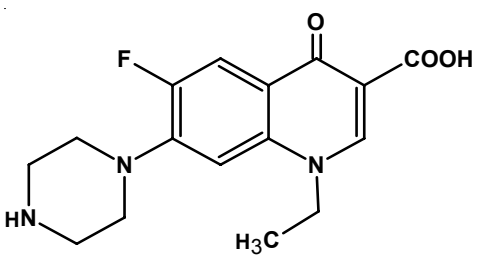
Key Words: Piperazinyl quinolones, Norfloxacin derivative, Synthesis.

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[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 on 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 attention has been focussed on the modification of the C-7 basic group of the norfloxacin. Therefore, an attempt has been made on N-substituted piperazinyl quinolone in which the N-4 hydrogen of piperazinyl group of norfloxacin was replaced with 2-hydroxyiminoethyl moiety. The intermediate compound **2** was synthesized from benzylidineacetone in the presence of Br_2[8]. The bromohydroxyiminoethyl intermediate **3** was prepared by stirring of **2** with excess of hydroxylamine hydrochloride in methanol at room temperature[9]. The N-[2-aryl-2-hydroxyiminoethyl]piperazinyl quinolone analogue **4** was prepared by the synthetic route showed in **Scheme-I**, in which the compound **3** was reacted

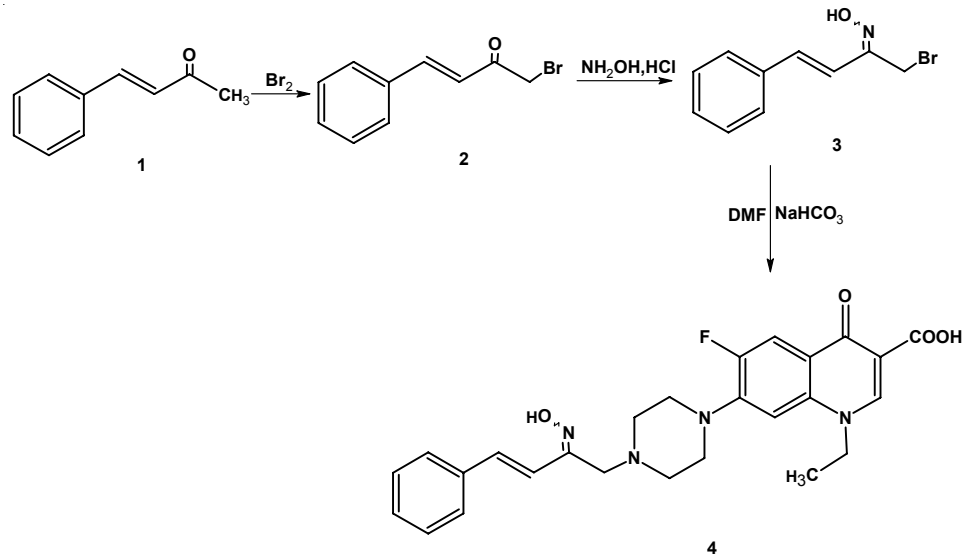


Ciprofloxacin



Norfloxacin

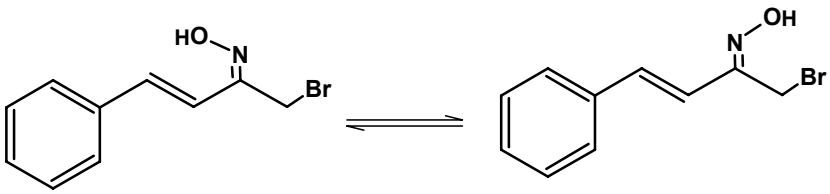
Fig. 1



Scheme-I

with norfloxacin in the presence of $NaHCO_3$ in DMF[9-11]. The purity of the compounds was checked by TLC. The spectral data (^{1}H NMR, IR and Mass) of all the synthesized compounds were in full agreement with the proposed structure. The infrared spectra of compound **2**, revealed the presence of C=O, C=C and CH_2Br infrared peaks at 1720, 1421 and 1200 cm^{-1}. Compound **3** showed (OH), (C=N) infrared peaks at 3292 and 1653 cm^{-1}, respectively. For the compound **4**, OH, oxime and OH (COOH), (CO, COOH) and C=O infrared peaks appear at, 3500-3440, 1725, 1670 cm^{-1}. In the nuclear magnetic resonance spectra (^{1}H NMR) the signals of the respective protons of the synthesized derivatives of norfloxacin were verified on the basis of their chemical shifts, multiplicities and coupling constants. The spectra of compound **2** showed singlet at δ 2.46 ppm corresponding to CH_2Br group; doublet of doublet at δ 4.8-5.3 ppm corresponding to olifin group, multiplet at δ 7.38 ppm corresponding to phenyl group. The spectra of compound **3** indicated the presence of two rotational

isomers in a 0.54: 0.46 ratio (**Scheme-II**), therefore, singlet at δ 2.12 and 2.16 ppm for the CH_2Br group for two isomers; doublet of doublet at δ 5.12 and 5.25 ppm corresponding to olifin group for two isomers, multiplet at δ 7.3-7.5 ppm corresponding to phenyl group, singlet at δ 7.70 ppm corresponding to OH group. The ^1H NMR spectra of compound **4** indicated the protons of olefin and phenyl groups, also showed triplet at 1.16 for the ethyl group of quinolone, multiplet at 2.73-3.62 corresponding to piperazin, singlet at δ 8.6 ppm for the H_2-quinolon. The ^1H NMR of this compound showed one isomer, because of inter-molecular hydrogen bonding. The mass spectra of the compounds displayed molecular ion peak of them.



Scheme-II

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary apparatus and were uncorrected. ^1H 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.

Synthesis of 1-bromo-4-phenylbut-3-en-2-one (α-bromo benzylidine acetone) (2): To stirring solution of 4-phenylbut-3-en-2-one (α-bromo benzylidineacetone) (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 crystallized from chloroform-methanol to give compound **2**; m.p. 122-124 ºC; yield 81 %; IR (KBr, ν_{max}, cm^{-1}): 1720 (CO), 1421 (C=C), ^1H NMR ($CDCl_3$, 90 MHz): δ 2.46 (S, 2H, CH_2), δ 4.8-5.3 (dd, 2H, C=C, *J* = 11.7), δ 7.38 (m, 5H, ph) ppm; Mass (M/Z^+) (%): 225 (55.11), 182 (21), 145 (48), 131 (42), 103 (82), 77 (51), 43 (100).

Synthesis of 1-bromo-4-phenylbut-3-en-2-one oxime (3): A solution of compound **2** (1 g, 0. 584 mol) and hydroxylamine hydrochloride (78.6 g, 0.62 mol) in 12 mL methanol was mixed for 120 h at room temperature. The product was purified on the column chromatography and was crystallized in methanol to give compound **3**; m.p. 148-150 ºC, yield 75 %, IR (KBr, ν_{max}, cm^{-1}): 3292 (OH), 1653 (C=N); ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.12 (S, 2H, CH_2, ferst isom.), 2.16 (S, 2H, CH_2, second isom.), 5.12 (dd, 2H, C=C, ferst isom.), 5.25 (dd, 2H, C=C, second isom.), 7.3-7.5 (m, 5H, Ph), 7.70 (S, 1H, OH) ppm; Mass: (M/Z^+) (%) 240 (46.5), 224 (16.5), 196 (70.8), 160 (100), 102 (40.9), 85 (31.5), 77 (54), 43 (41.7).

Synthesis of 1-ethyl-6-fluoro-7-(4-(2-(phenylbut-3-en-2-one oxime)-2-oxoethyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (4): A suspension of compound **3** (0.584 mol), norfloxacin (0.5 mol) $NaHCO_3$ (0.5 g) in 12 mL DMF was mixed for 72 h at room temperature. The product was purified on the column chromatography and was crystallized in methanol to give compounds **4**. m.p. 330-335 ºC, yield 58 %; IR (KBr, ν_{max}, cm^{-1}): 3500-3440 (OH, oxime and OH (COOH)), 1725, (CO, COOH) 1670 (CO), 1630 (C=N). 1400 (C=C); ^1H NMR (DMSO, 500 MHz) δ: 1.16 (t, *J* = 10.42 Hz, 3H ethyl), 2.73 (S, 2H, CH_2), 2.73-3.62 (m, 8H, piperazin), 3.8 (m, 2H, ethyl), 5.5-5.8 (dd, 2H, C=C), 7.59-8.6 (m, 5H, Ph), 8.6 (S, 1H (H2 quinolon)), 10.33 (S, 1H, OH) ppm.

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