Synthesis and Antibacterial Activity of N-[2-(2-naphthyl)ethyl]piperazinyl Quinolones

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A series of N-[2-(2-naphthyl)ethyl]piperazinyl quinolones containing a carbonyl related functional groups (oxo- or oxyimino-) on the ethyl spacer was synthesized and evaluated for antibacterial activity. The synthesis of N-[2-(2-naphthyl)ethyl]piperazinyl quinolones was achieved through the versatile and efficient synthetic route that involved reaction of piperazinyl quinolones with appropriate \(\gamma\)-bromoketone or \(\gamma\)-bromooxime derivatives. The structures of new compounds were confirmed by elemental analysis, IR and NMR spectra. Antibacterial data indicated that some of the new N-[2-(2-naphthyl)ethyl]piperazinyl quinolones showed good antibacterial activity and modification of the position 8 and N-1 substituent on quinolone ring, and ethyl spacer functionality produced significant changes in activity against Gram-positive and Gram-negative bacteria.

**Keywords:** Fluoroquinolones, Piperazinyl quinolones, Antibacterial activity, Structure-activity relationships

**INTRODUCTION**

Increasing multidrug-resistant pathogens have become a serious problem particularly during the last decade. A more controlled usage of these drugs may be a way to partially counterbalance this challenge. However, the design of new agents active against resistant organism remains of critical importance [1].

The fluoroquinolone class of antibacterials is widely used in the treatment of Gram-positive and Gram-negative bacterial infections [2]. Since the development of norfloxacin, many fluoroquinolone antibacterials have been synthesized to improve their antimicrobial activities against various infectious organisms. After the discovery of prototypic norfloxacin, most of the research concerning quinolone antibacterials has been focused on the basic group at the C-7 position, which plays a key role in the improvement of potency, spectrum and pharmacokinetic profile of quinolone antibacterials [3]. As a results, ciprofloxacin, ofloxacin, lomefloxacin, fleroxacin and sparfloxacin have been successfully introduced into the market, all of which contain a piperazine derivative at the C-7 position [4,5]. Whereas, the great majority of the new quinolones under development or in clinical use is incorporated with piperazine, bearing small substitution (e.g., methyl); however, a few of quinolones are substituted at C-7 with bulky substituent on cyclic amine [3].
Recently, we identified a series of \( N \)-substituted piperazinyl quinolones (Fig. 1) in which the \( N \)-4 hydrogen of piperazinyl group of norfloxacin, ciprofloxacin, and enoxacin is replaced with various 2-oxoethyl or 2-oxyiminoethyl moieties and displayed \textit{in vitro} antibacterial activity comparable or higher than respective parent quinolones [6-11]. Therefore our strategy to achieve a better antimicrobial profile has focused on introducing new functionality on the piperazine ring [12]. In the current study, structure 4 was used as starting point for chemical manipulation. Therefore, twelve new analogs 5a-l (Fig. 1), were prepared by replacing aryl with naphthyl ring on 2-oxoethyl or 2-oxyiminoethyl moieties and evaluated for antibacterial activity against Gram-negative and Gram-positive bacteria.

**EXPERIMENTAL**

**Chemistry**

Chemical reagents and all solvents used in this study were purchased from Merck AG and Aldrich Chemicals. 2-Bromo-1-(naphthalen-2-yl)ethanone (7) was prepared according to the literature method [13]. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The IR spectra were obtained on a Shimadzu 470 spectrophotometer (potassium bromide disc). NMR spectra were recorded on a Bruker 500 spectrometer and chemical shifts are reported in parts per million (\( \delta \)) relative to tetramethylsilane (TMS) as an internal standard. Elemental analyses were carried out on a CHN-O rapid elemental analyzer (GmbH-Germany) for C, H and N, and the results were within \( \pm 0.4\% \) of the theoretical values. Merck silica gel 60 F254 plates were used for analytical TLC.

**General procedure for the synthesis of 7-[4-[2-(naphthalen-2-yl)-2-oxoethyl]piperazinyl]quinolones** (5a-c). A mixture of 2-bromo-1-(naphthalen-2-yl)ethanone 7 (0.55 mmol), quinoline 1-3 (0.5 mmol) and NaHCO\(_3\) (0.5 mmol) in DMF (5 ml), was stirred at room temperature for 72 h. After consumption of quinolone, water (20 ml) was added and the precipitate was filtered, washed with water and crystallized from methanol-chloroform (9:1) to give compounds 5a-c.

1-Cyclopropyl-6-fluoro-1,4-dihydro-7-[4-[2-(naphthalen-2-yl)-2-oxoethyl]piperazin-1-yl]-4-oxo-3-quinoline carboxylic acid (5a). Yield: 60\%; m.p.: 175-177 °C; IR (KBr, cm\(^{-1}\)) \( \nu \)\(_{max}\): 1629, 1680 and 1721 (C=O), 3441 (OH); \(^1\)H NMR (DMSO-d\(_6\)) \( \delta \): 1.01-1.31 (m, 4H, cyclopropyl), 2.75-2.89 (m, 4H, piperazine), 3.25-3.38 (m, 4H, piperazine), 3.75-3.86 (m, 1H, cyclopropyl), 4.11 (s, 2H, COCH\(_2\)), 4.11 (s, 2H, COCH\(_2\)), 7.55-7.72 (m, 3H, H-8 quinolone, H-6 and H-7 naphthyl), 7.90 (d, 1H, \( J = 13.32 \) Hz, H-5 quinolone), 7.94-8.07 (m, 3H, H-4, H-5 and H-8 naphthyl), 8.12 (d, 1H, \( J = 8.05 \) Hz, H-3 naphthyl), 8.65 (s, 1H, H-1 naphthyl), 8.72 (s, 1H, H-2 quinolone), 15.20

![Fig. 1.](image-url)