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Bioorganic & Medicinal Chemistry Letters 17 (2007) 4523–4526
Bioorganic & Medicinal Chemistry Letters

Synthesis and antibacterial activity of novel fluoroquinolones containing substituted piperidines

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Received 15 April 2007; revised 16 May 2007; accepted 31 May 2007
Available online 6 June 2007

Abstract—The design and synthesis of new fluoroquinolone antibacterial agents having substituted piperidine rings at the C-7 position are described. Most of the new compounds demonstrated high in vitro antibacterial activity. Several of them exhibited significant activities against Gram-positive organisms, which were more potent than those of gemifloxacin, Linezolid, and vancomycin.

Quinolone antibacterial agents are among the most attractive drugs in the anti-infective chemotherapy field. These antibiotics exert their effect by inhibition of two type II bacterial topoisomerase enzymes, DNA gyrase and Topoisomerase IV.[1]

The structure–activity relationship (SAR) study of quinolone antibacterial agents showed that substituents at the C-7 position greatly influenced their potency, spectrum, and safety.[2] In general, the optimal substituents have proven to be 5- and 6-membered nitrogen heterocycles that contain peripheral nitrogens.[3] The majority of quinolone C-7 substituents can be arranged into three main categories: the piperazinyl, pyrrolidinyl, and piperidinyl type side chains. It is worth noting that the piperidinyl-based quinolone antibacterial agents reported in the literature were significantly fewer than that of piperazinyl- and pyrrolidinyl-based analogues.

In our continuous efforts to develop new fluoroquinolones, we have focused on introducing new functional groups to the piperidine ring. The structural modifications were made on the basis of balofloxacin **1**, a well-known 3-amino-piperidinyl-based fluoroquinolone, and gemifloxacin **2**, possessing a methoxyimino group attached to the pyrrolidine ring at the C-7 position (Fig. 1).[4] New piperidine derivatives and a series of fluoroquinolone compounds derivatized from these amines at the C-7 position were designed and synthesized. These piperidine derivatives are structurally novel, having an alkyloxime group and a substituted amino substituent. Our primary objective was to optimize the potency of these compounds against Gram-positive and Gram-negative organisms. A SAR study was also explored to facilitate the further development of the new fluoroquinolone compounds.

The novel fluoroquinolone derivatives described herein were synthesized as shown in Schemes 1 and 2. Compound **3** was prepared by quaternization of pyridine with benzyl chloride followed by reduction with sodium borohydride following a modified procedure developed by Oediger and Joop.[5] Catalytic hydrogenation of 1-benzyl-1,2,3,6-tetrahydropyridine **3** did not afford the expected 1,2,3,6-tetrahydropyridine **5**.[6]

Therefore, compound **3** was converted to 1-ethoxycarbonyl-1,2,3,6-tetrahydropyridine **4** by refluxing it

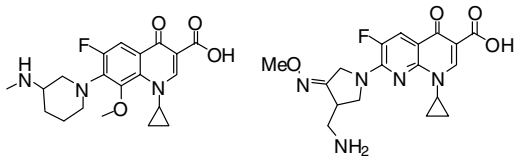

Figure 1.

Keywords: Fluoroquinolone; Antibacterial activity; Piperidine.
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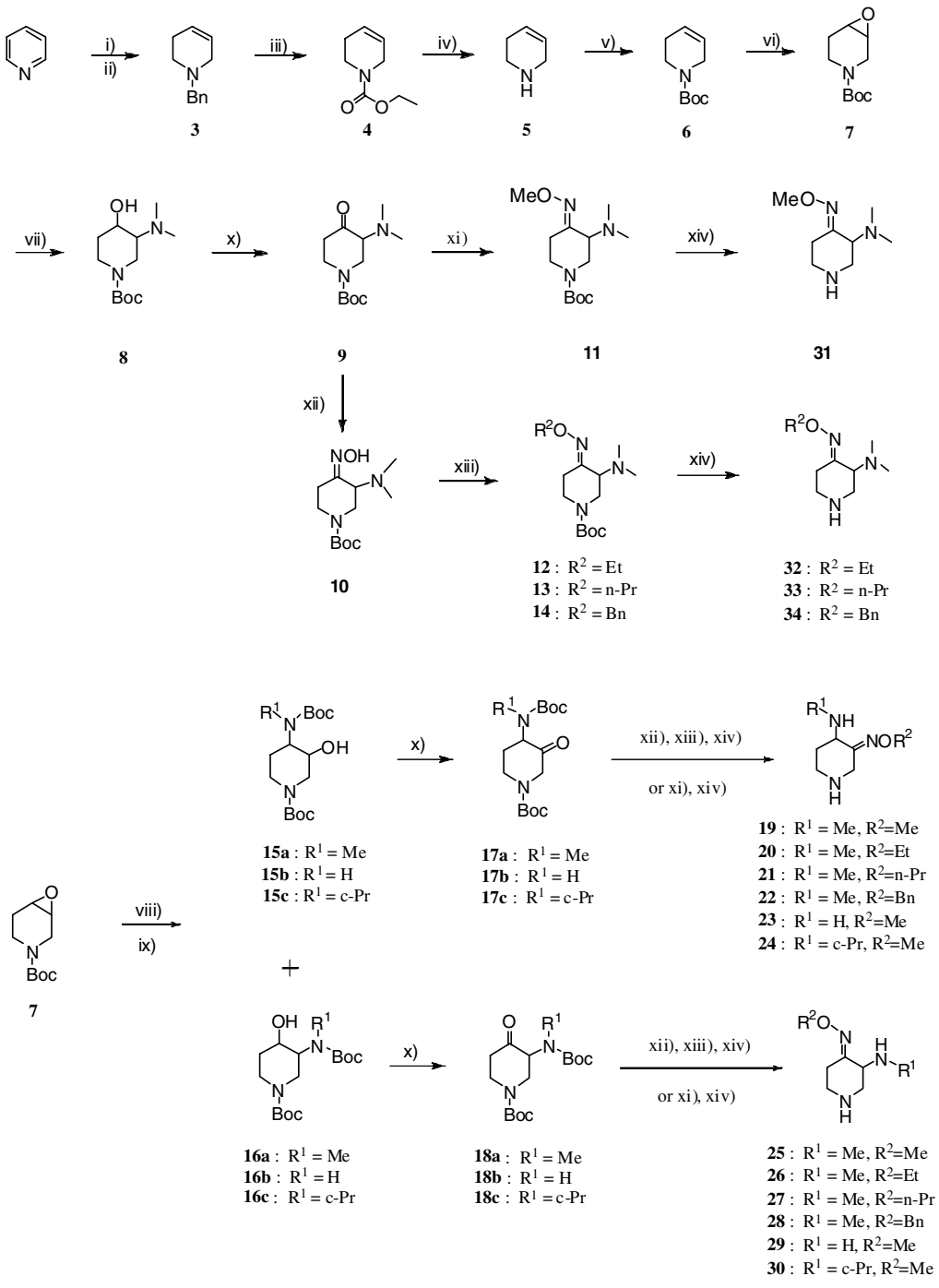
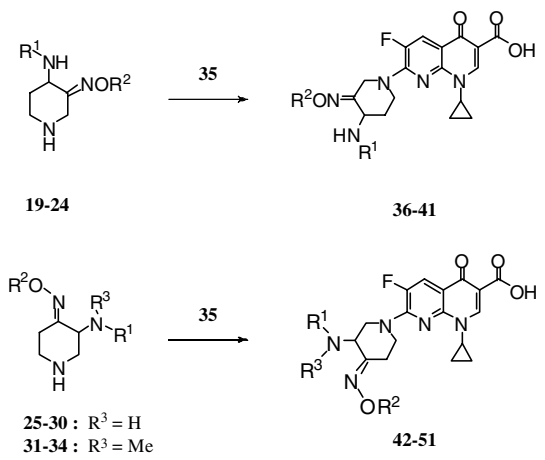
doi:10.1016/j.bmcl.2007.05.093



Scheme 1. Reagents and conditions: (i) BnCl, 140 °C, 1 h; (ii) $NaBH_4$, EtOH, rt, 6 h, 46% (two-step yield); (iii) $ClCO_2Et$, C_6H_6, reflux, 1 h, 93%; (iv) NH_2NH_2–H_20, KOH, Ethylene glycol, reflux, 1.5 h; (v) $(Boc)_2O$, $CHCl_3$, rt, 12 h, 82% (two-step yield); (vi) *m*-CPBA, CH_2Cl_2, rt, 18 h, 92%; (vii) $HN(CH_3)_2$, EtOH, reflux, 6 h, 27%; (viii) R^1NH_2, EtOH, reflux, 6 h; (ix) $(Boc)_2O$, $CHCl_3$, rt, 6 h, 55–65% (two-step yield, **15a**:**16a** = 3:4); (x) Pyridine–SO_3, Et_3N, DMSO, 5 °C, 3 h, 82%; (xi) $MeONH_2$ HCl, $NaHCO_3$, EtOH–THF, 40 °C, 1 h, 85%; (xii) $HONH_2$ HCl, $NaHCO_3$, EtOH–THF, 40 °C, 1 h, 81%; (xiii) R^2Br, TBAB, CH_2Cl_2/aq NaOH, rt, 5 h, 80–86%; (xiv) $MeSO_3H$, THF, rt, 18 h, 85–95%.

with ethyl chloroformate. Deprotection of ethoxycarbonyl group was carried out by the method using NH_2NH_2–H_2O[7] and 1,2,3,6-tetrahydropyridine **5** was obtained. Compound **5** was treated with di-*tert*-butyl dicarbonate to produce Boc-protected tetrahydropyridine **6**, which was reacted with *m*-chloroperoxybenzoic acid (*m*-CPBA) in chloroform to furnish the epoxide **7**.[8]

Tert-butyl 3-(dimethylamino)-4-hydroxypiperidine-1-carboxylate **8** was the only product when compound **7** was treated with dimethylamine in refluxing ethanol.[9] However, treatment of the key intermediate **7** with methylamine and subsequent protection of the resulting amine by a Boc group gave a chromatographically separable mixture of *tert*-butyl 1-(*tert*-butoxycarbonyl)-3-hydroxypiperidin-4-ylmethylcarbamate **15a** (27%) and



Scheme 2. Reagents and condition: DBU, CH_3CN, rt, 50–65%.

tert-butyl 1-(*tert*-butoxycarbonyl)-4-hydroxypiperidin-3-ylmethylcarbamate **16a** (34%).[10]

Reaction of **7** with cyclopropylamine or ammonia and subsequent protection of the resulting amine yielded **15b**, **16b**, **15c**, and **16c**, respectively. Parikh–Doering oxidant[11] was a suitable reagent for the oxidation of the alcohol **8**. Thus, alcohol **8** was cleanly converted to the ketone **9** by treatment with sulfur trioxide–pyridine complex in DMSO. Similarly, compounds **17a**, **17b**, **17c**, **18a**, **18b**, and **18c** were obtained.[10]

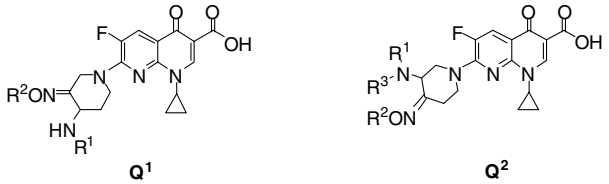
The oxime functional group was introduced into the ring by coupling **9** with hydroxylamine in EtOH–THF–H_2O to afford **10**. The methyloxime **11** was obtained by reacting the ketone **9** with methoxylamine instead of hydroxylamine. Compounds **12**, **13**, and **14** were synthesized simply by alkylating **10** with bromoethane, 1-bromopropane or benzyl bromide. The Boc protective groups of the oxime **11**, **12**, **13**, and **14** were removed by methane sulfonic acid in THF to give the new piperidine derivatives **31**–**34**. Following the each chemical modification described above, compounds **17a**, **17b**, **17c**, **18a**, **18b**, and **18c** were converted to the corresponding new piperidine derivatives **19**–**30.**

Finally, The novel fluoroquinolones **36**–**51** were obtained by coupling the 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3- carboxylic acid **35**[12] with the new piperidine derivatives **19**–**34**.[13]

The new fluoroquinolones **36**–**51** were tested against Gram-positive and Gram-negative organisms (Table 1) using standard techniques.[14] The minimum inhibitory concentration (MIC) values were compared with those of gemifloxacin, Linezolid, and vancomycin.

The activities of the novel fluoroquinolones **36**, **37**, **39**, **42**, and **43** against methicillin-sensitive *Staphylococcus aureus* (MSSA), *Streptococcus pneumoniae*, and *Enterococcus faecalis* (MICs < 0.001 μg/mL) were four times more potent than those of gemifloxacin and vancomycin,

Table 1. In vitro antibacterial activities of the new fluoroquinolones **36**–**51**



Compound	Structure	Substitutions on the structure	MICs (μg/mL)						
			MSSA	MRSA	S.p.	E.f.	E.co.	K.p.	Ps.a.
36	Q^1	R^1 = Me, R^2 = Me	<0.001	0.5	<0.001	<0.001	1	1	0.06
37	Q^1	R^1 = Me, R^2 = Et	<0.001	2	<0.001	<0.001	4	1	0.06
38	Q^1	R^1 = Me, R^2 = *n*-Pr	0.06	2	0.03	0.06	4	4	0.06
39	Q^1	R^1 = Me, R^2 = Benzyl	<0.001	2	<0.001	<0.001	8	4	0.5
40	Q^1	R^1 = H, R^2 = Me	2	4	2	2	1	1	1
41	Q^1	R^1 = Cyclopropyl, R^2 = Me	0.015	2	0.004	0.004	16	16	1
42	Q^2	R^1 = Me, R^2 = Me, R^3 = H	<0.001	4	<0.001	<0.001	4	2	1
43	Q^2	R^1 = Me, R^2 = Et, R^3 = H	<0.001	4	<0.001	<0.001	8	16	1
44	Q^2	R^1 = Me, R^2 = *n*-Pr, R^3 = H	0.03	16	0.015	0.015	8	8	2
45	Q^2	R^1 = Me, R^2 = Benzyl, R^3 = H	0.125	16	0.25	0.125	16	16	2
46	Q^2	R^1 = H, R^2 = Me, R^3 = H	4	16	4	8	8	2	4
47	Q^2	R^1 = Cyclopropyl, R^2 = Me, R^3 = H	0.015	2	0.004	0.004	16	16	8
48	Q^2	R^1 = Me, R^2 = Me, R^3 = Me	0.004	1	0.015	0.015	8	1	0.125
49	Q^2	R^1 = Me, R^2 = Et, R^3 = Me,	0.015	1	0.002	0.004	8	2	1
50	Q^2	R^1 = Me, R^2 = *n*-Pr, R^3 = Me	0.5	2	0.125	0.25	16	16	2
51	Q^2	R^1 = Me, R^2 = Benzyl, R^3 = Me	0.015	4	0.015	0.06	16	16	2
Gemifloxacin			0.004	0.004	0.004	0.004	0.125	0.125	0.125
Linezolid			0.5	1	0.5	0.125			
Vancomycin			0.004	0.5	0.004	0.004			

Abbreviations: MSSA, methicillin-sensitive *Staphylococcus aureus* 04-4; MRSA, methicillin-resistant *Staphylococcus aureus* 05-3; S.p., *Streptococcus pneumoniae* 05-9; E.f., *Enterococcus faecalis* 03-4; E.co., *Escherichia coli* ATCC25922; K.p., *Klebsiella pneumoniae* 05-4; Ps.a., *Pseudomonas aeruginosa* ATCC2785.

and 100 times superior to that of Linezolid. The most active compound tested against methicillin-resistant *Staphylococcus aureus* (MRSA) was **36**, with a MIC value of 0.5 μg/mL. Compounds **37**, **38**, **39**, **41**, **47**, **48**, **49**, and **50** exhibited moderate activity against MRSA (MICs $\leqslant$ 2 μg/mL). Compounds **36**, **37**, and **38** exhibited excellent activity against Pseudomonas aeruginosa (MICs = 0.06 g/mL). Compounds **36**, **37**, **38**, **40**, and **42** showed mild activity against *Escherichia coli* and Klebsie pneumoniae (MICs $\leqslant$ 4 μg/mL).

The 4-methylamino-3-methyloxime piperidine derivative **36** showed the most potent antibacterial activity against Gram-positive and Gram-negative organisms. For Gram-positive bacteria, there was no significant difference between the activities of 4-(substituted) amino-3-alkyloxime piperidine series (Q^1) and the 3-(substituted) amino-4-alkyloxime piperidine series (Q^2); but for Gram-negative bacteria, the Q^1 series displayed better activity than the Q^2 series.

The size of the alkyl group of the amine moiety might be important in determining antibacterial activity. The methyl group seems to be optimal; however, introduction of another methyl group to the methylamine or replacement of the methyl by a cyclopropyl group caused reduced antibacterial activity. Compounds **40** and **46** which have an unsubstituted amine group showed relatively low potency against Gram-positive pathogens.

The new fluoroquinolones featuring methyloxime-incorporated piperidino-substitution at C-7 were more potent than the analogues containing ethyloxime, *n*-propyloxime or benzyloxime. The antibacterial activity decreased generally in the order methyloxime < ethyloxime < benzyloxime, *n*-propyloxime.

In conclusion, new piperidine derivatives, which bear an oxime substituent and a substituted amino substituent in the piperidine ring, have been synthesized and coupled with naphthyridine acid to produce a series of novel fluoroquinolone derivatives. Most of the new compounds demonstrated high in vitro antibacterial activity. Several of them exhibited significant activities against Gram-positive organisms, which were more potent than those of gemifloxacin, Linezolid, and vancomycin. These compounds may serve as useful lead molecules for new antibiotic drug discoveries.

References and notes

1. (a) Hooper, D. C. *Drugs* **1995**, *49*(Suppl. 2), 10; (b) Hoshino, K.; Kitamura, A.; Morrissey, I.; Sato, K.; Kato, J.-I.; Ikeda, H. *Antimicrob. Agents Chemother.* **1994**, *38*, 2623.
2. Bryskier, A.; Chantot, J. F. *Drugs* **1995**, *49*(Suppl. 2), 16.
3. Domagala, J. M. *J. Antimicrob. Chemother.* **1994**, *33*, 685.
4. (a) Sanchez, J. P.; Gogliotti, R. D.; Domagala, J. M.; Gracheck, S. J.; Huband, M. D.; Sesnie, J. A.; Cohen, M. A.; Shapiro, M. A. *J. Med. Chem.* **1995**, *38*, 4478; (b) Zhanel, G. G.; Ennis, K.; Vercaigne, L.; Walkty, A.; Gin, A. S.; Embil, J.; Smith, H.; Hoban, D. J. *Drugs* **2002**, *62*, 13.
5. Takemura, S.; Miki, Y.; Uono, M.; Yoshimura, K.; Kuroda, M.; Suzuki, A. *Chem. Pharm. Bull.* **1981**, *29*, 3026.
6. Grishina, G. V.; Borisenko, A. A.; Nosan, Z. G.; Veselov, I. S.; Ashkinadze, L. D.; Karamov, E. V.; Kornilaeva, G. V.; Zefirov, N. S. *Dokl. Chem.* **2003**, *391*, 195.
7. Shono, T.; Matsumura, Y.; Uchida, K.; Tsubata, K.; Makino, A. *J. Org. Chem.* **1984**, *49*, 300.
8. Boto, A.; Hernández, R.; de León, Y.; Murguía, J. R.; Rodríguez-Afonso, A. *Tetrahedron Lett.* **2004**, *45*, 6841.
9. Tichy, M.; Sipos, J.; Sicher, J. *Collect. Czech. Chem. Commun.* **1962**, *27*, 2907.
10. The proposed structures are supported by the ^{1}H NMR experiment and mass spectra. Selected NMR and MS data are given. Compound **15a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 (1H, m), 4.18 (1H, m), 3.99 (1H, m), 3.56 (1H, m), 2.79 (3H, s), 2.70 (1H, m), 1.66 (2H, m), 1.48(9H, s), 1.47 (9H, s); MS: M^+ (*m*/*e*) 330. Compound **16a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (2H,m), 3.80 (1H, m), 3.68 (1H, m), 2.85 (3H, s), 2.79 (1H, m), 2.68 (1H, m), 2.05 (1H, m), 1.88 (2H, m), 1.48 (9H, s), 1.47 (9H, s); MS: M^+ (*m*/*e*) 330. Compound **17a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (1H, m), 4.36 (1H, m), 4.28 (1H, d, J = 17.6 Hz), 4.12 (1H, m), 3.82 (1H, d, J = 17.6 Hz), 3.33 (1H, m), 2.79 (3H, s), 2.11 (2H, m), 1.48 (18H, s); MS: M^+ (m/e) 328. Compound **18a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (1H, m), 4.41 (2H, m), 3.55 (1H, m), 3.19 (1H, m), 2.88 (3H, s), 2.51 (2H, m), 1.48 (18H, s); MS: M^+ (*m*/*e*) 328.
11. Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
12. Mich, T.F.U.S. Patent 4, 663, 457, 1987.
13. Hong, C. Y.; Kim, Y. K.; Lee, Y. H.; Kwak, J. H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 221.
14. MICs were determined as described by the NCCLS (see National Committee for Clinical Laboratory Standards. 2001. Performance standards for antimicrobial susceptibility testing: 11th informational supplement. Vol. 21, M100-S11. National Committee for Clinical Laboratory Standards, Wayne, PA). The MIC was defined as the lowest concentration of each compound resulting in inhibition of visible growth of bacteria after incubation at 37 °C for 18–24 h.