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Synthesis and *in vitro* antibacterial activities of 7-(4-alkoxyimino-3-hydroxypiperidin-1-yl)quinolone derivatives

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Abstract

A series of novel 7-(4-alkoxyimino-3-hydroxypiperidin-1-yl)quinolone derivatives were designed, synthesized and evaluated for *in vitro* antibacterial activities. Compounds **8f**, **8g**, **8i** and **8j** with the potencies similar to or better than those of levofloxacin and IMB against *Staphylococcus aureus* and *Staphylococcus epidermidis*, worth further investigation.

Keywords: Fluoroquinolone; Synthesis; Antibacterial activities

Fluoroquinolone as chemotherapeutic drugs for the treatment of various bacterial infections in both community and hospital settings have attracted great attention because of their outstanding potency and steady safety [1]. However, most of the fluoroquinolones currently on the market or under development have only moderate activities against many Gram-positive cocci including *staphylococci* and *streptococci*, which has not only limited their use in infections caused by these organisms, but is also believed to be one of the reasons for the rapidly developing fluoroquinolone resistance. Therefore, recent efforts have been directed toward the synthesis of new fluoroquinolones that can provide improved Gram-positive antibacterial activities, while retaining the good Gram-negative activities of early fluoroquinolones, such as ciprofloxacin and ofloxacin [2].

Since the discovery of norfloxacin in the early 1980s, most of the research concerning these drugs has been focused on the basic group at the C-7 position which greatly influences their potency, spectrum, and safety [3]. Generally, 5- or 6-membered nitrogenous heterocycles as side chains such as piperazine, pyrolidine and piperidine ring, have been proven to be the optimal substituents for chemical modification [4]. Of the three, piperidinyl analogs are the least studied [5].

Recently, as part of an ongoing program to find potent and broad-spectrum antibacterial agents that display strong Gram-positive activities, we also have focused on introducing new functional groups to the piperidine ring. Interestingly, IMB (**1**, Fig. 1), a new 8-methoxylfluoroquinolone incorporating a 3-amino-4-methoxyimino-piperidine at C-7 position, shows excellent *in vitro* and *in vivo* antibacterial activities [6]. In addition, nadifloxacin (**2**, Fig. 1) which incorporates a 4-hydroxypiperidine at C-7 exhibits good antibacterial activities to Gram-positive, Gram-negative and anaerobic bacteria [7].

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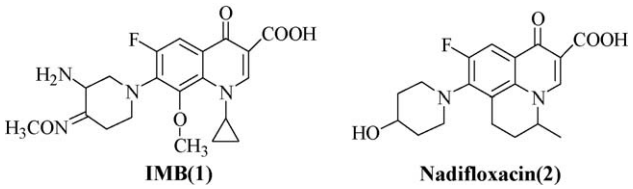


Fig. 1. Chemical structures of IMB and Nadifloxacin.

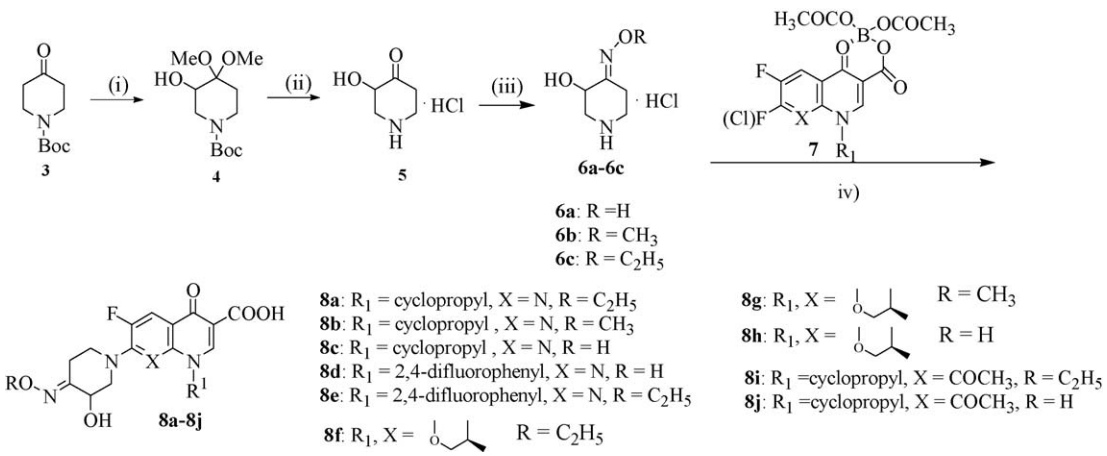
Inspired by those previous research results [6,7], we considered replacement of the 3-aminopiperidinyl with the bioisosteric 3-hydroxylpiperidinyl moiety. In this paper, we report the synthesis and *in vitro* antibacterial activities of a series of 7-(4-alkoxyimino-3-hydroxypiperidin-1-yl)quinolone derivatives.

Synthetic pathways toward substituted piperidines **6a–c** and novel fluoroquinolone derivatives **8a–j** are depicted in Scheme 1. *N*-Boc-4, 4-dimethoxy-3-hydroxypiperidine (**4**) was prepared by the oxidation of *N*-Boc-4-piperidone (**3**) with $PhI(OAc)_2$ in the presence of KOH in MeOH [8]. And then compound **4** was subjected to deprotection via treatment with 6 mol/L HCl, to provide 3-hydroxypiperidin-4-one hydrochloride (**5**), on which the oxime function group was introduced via condensation with hydroxylamine, methoxylamine or ethoxylamine to yield **6a**, **6b** or **6c**, respectively. Finally, the target compounds **8a–j** were obtained by S_N reaction of boric chelating compounds **7** with **6**, and then hydrolysis of chelating groups [9,10]. In addition, as expected, the oxime geometry of compound **6a** has the *E* configuration confirmed by single crystal X-ray diffraction analysis [11].

The target compounds **8a–j** were evaluated for their *in vitro* antibacterial activities against representative Gram-positive and Gram-negative organisms (Table 1) using standard techniques [12]. The minimum inhibitory concentration (MIC) values were compared with those of levofloxacin (LVFX) and IMB.

The *in vitro* activities of compounds **8f**, **8g**, **8i** and **8j** against *Staphylococcus aureus* and *Staphylococcus epidermidis* were comparable to or better than both LVFX and IMB. In particular, activities of compound **8i** (MIC: 0.06 μg/mL) were 4-fold and 8–16-fold times more potent than those of LVFX (MIC: 0.25 μg/mL) and IMB (MIC: 0.5–1 μg/mL) against the two strains, respectively, while the remaining compounds generally showed inferior activities against all the tested strains.

These data suggest that replacement of the amino group in 7-(4-alkoxyimino-3-amino)-8-methoxy-fluoroquinolone with a hydroxyl group could markedly improve the activities against *staphylococci*, but generally decrease the activities against the other strains. The relative contribution of the substituents at C-7 to antibacterial activities was as follows: 4-ethyloxime-3-hydroxypiperidine ≈ 4-methyloxime-3-hydroxypiperidine > 4-oxime-3-hydroxypiperidine.



Scheme 1. Reagents and conditions: (i) $PhI(OAc)_2$, MeOH, KOH, 0–5 °C, 12 h, 57.9%; (ii) EtOH, 6 mol/L HCl, r.t., 1 h; (iii) $RONH_2{\cdot}HCl$, H_2O, $NaHCO_3$, 25–55 °C, 2 h, 59.1–86.3% (from **4**); (iv) a: CH_3CN, Et_3N, 25–50 °C, 1–14 h; b: 5% NaOH/H_2O, 40 °C, 0.5–2 h; c: 2 mol/L HCl, r.t., 40.2–65.6%.

Table 1
In vitro antibacterial activities of target compounds **8a–j** (MIC: μg/mL).

Organism	Compounds											
	8a	**8b**	**8c**	**8d**	**8e**	**8f**	**8g**	**8h**	**8i**	**8j**	LVFX	IMB
S.a.	1	1	2	1	0.5	0.125	0.125	4	0.06	0.25	0.25	1
S.e.	1	1	2	1	1	0.125	0.125	4	0.06	0.25	0.25	0.5
S.p.	8	8	32	32	128	16	8	64	4	8	2	1
S.py.	16	16	16	32	128	16	4	128	32	16	2	8
E.f.	2	2	8	4	4	2	1	32	0.5	0.5	1	0.125
E.c.	2	1	0.5	4	8	1	1	2	1	1	0.06	2
K.p.	2	2	1	2	8	2	1	4	1	1	0.5	0.25
P.a.	16	8	8	16	32	16	8	64	16	16	0.25	2
S.s.	2	2	1	4	16	2	1	4	2	1	0.5	0.25
S.f.	8	4	1	2	16	4	1	4	8	1	1	8

S.a., *Staphylococcus aureus* ATCC29213; *S.e.*, *Staphylococcus epidermidis* ATCC12228; *S.p.*, *Streptococcus pneumoniae* 97100; *S.py.*, *Streptococcus pyogenes* 9619; *E.f.*, *Enterococcus faecalis* ATCC29212; *E.c.*, *Escherichia coli* ATCC 25922; *K.p.*, *Klebsiella pneumoniae* 7; *P.a.*, *Pseudomonas aeruginosa* 17; *S.s.*, *Shigella sonnei* 51592; *S.f.*, *Shigella flexneri* 06-3.

In conclusion, a set of 4-alkoxyimino-3-hydroxypiperindines were prepared and coupled with a variety of quinolone nuclei to produce a series of novel fluoroquinolone derivatives. Compounds **8f**, **8g**, **8i** and **8j** with the potencies similar to or better than those of LVFX and IMB against *S. aureus* and *S. epidermidis*, worth further investigation.

Acknowledgment

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[9] N. Takagi, H. Fubasami, H. Matukubo, EP 464823 (1992).
[10] Synthesis of 1-cyclopropyl-6-fluoro-7-(4-ethyloximino-3-hydroxypiperidine-1-yl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**8a**): a mixture of 6c (0.24 g, 1.2 mmol), 7 (0.41 g, 1 mmol), triethylamine (2.0 mL) and anhydrous acetonitrile (10 mL) was stirred at room temperature for 0.5 h, and then concentrated in vacuo. To the residue was added 5% NaOH solution (6.0 mL), the reaction mixture was stirred at 40 °C for 0.5 h and then adjusted to pH 2 with 2 mol/L HCl. The precipitate was collected by suction to give off-white amorphous product **8a** (0.32 g, 79.2%). mp: 215–218 °C. 1H NMR (400 MHz, $CDCl_3$): δ 1.07–1.11 (m, 2H), 1.25–1.31(m, 5H), 2.48–2.55 (m, 1H), 3.11–3.17 (m, 1H), 3.61–3.78 (m, 3H), 4.10–4.23 (m, 3H), 4.39–4.42 (m, 1H), 4.47–4.53 (m, 1H), 8.09 (d, 1H, *J* = 12.8 Hz), 8.71 (s, 1H), 14.86 (br, 1H); HRMS-ESI *m/z*: 405.15742 (calcd. for $C_{19}H_{22}FN_4O_5$ $[M+H]^+$). **8b** mp: 210–212 °C. 1H NMR (400 MHz, $CDCl_3$): δ 1.07–1.10 (2H, m), 1.25–1.32 (2H, m), 2.45–2.52 (1H, m), 3.09–3.15 (1H, m), 3.61–3.77 (3H, m), 3.92 (3H, s), 4.18–4.22 (m, 1H), 4.39–4.42 (m, 1H), 4.49–4.53 (m, 1H), 8.10 (d, 1H, *J* = 12.8 Hz), 8.95 (s, 1H); HRMS-ESI *m/z*: 413.12219 (calcd. for $C_{18}H_{19}FNaN_4O_5$, $[M+Na]^+$). **8c** mp: 234–236 °C. 1H NMR (400 MHz, $CDCl_3$): δ 1.06–1.10 (m, 2H), 1.13–1.21 (m, 2H), 2.53–2.61 (m, 1H), 2.97–3.01 (m, 1H), 3.15–3.16 (m, 1H), 3.62–3.74 (m, 2H), 4.20 (br, 1H), 4.39–4.43 (m, 1H), 4.55–4.59 (m, 1H), 5.42 (1H, s), 8.04 (d, 1H, *J* = 13.6 Hz), 8.60 (s, 1H), 10.76 (s, 1H), 15.26 (s, 1H). HRMS-ESI *m/z*: 377.12944 (calcd. for $C_{17}H_{18}FN_4O_5$, $[M+H]^+$). **8d** mp: 204–206 °C. 1H NMR (400 MHz, $CDCl_3$): δ 2.08–2.25 (m, 1H), 2.99–3.05 (m, 2H), 3.44–3.48 (m, 1H), 3.87–3.90 (m, 1H), 4.02–4.26 (m, 2H), 5.35–5.39 (m, 1H), 7.34–7.66 (m, 2H), 7.78–7.87 (m, 1H), 8.12 (d, 1H, *J* = 13.2 Hz), 10.75 (s, 1H), 15.03 (br, 1H). HRMS-ESI *m/z*: 449.10888 (calcd. for $C_{20}H_{16}F_3N_4O_5$, $[M+H]^+$). **8e** mp: 210–212 °C. 1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, 3H, *J* = 7.2 Hz), 1.56–1.57 (m, 1H), 2.26–2.34 (m, 1H), 2.88–2.94 (m, 2H), 3.39–3.86 (m, 2H), 4.12 (q, 2H, *J* = 7.2 Hz), 4.19–4.23 (m, 1H), 7.09–7.39 (m, 3H), 8.16 (d, 1H, *J* = 12.8 Hz), 8.69 (s, 1H), 14.66(br, 1H). HRMS-ESI *m/z*: 499.12000 (calcd. for $C_{22}H_{19}F_3NaN_4O_5$, $[M+Na]^+$). **8f** mp: 215–216 °C. 1H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, 3H, *J* = 7.2 Hz), 1.62–1.63 (m, 3H), 2.44–2.54 (m, 1H), 3.09–3.12 (m, 1H), 3.18–3.46 (m, 4H), 3.74–3.77 (m, 1H), 4.16 (q, 2H, *J* = 7.2 Hz), 4.33–4.38 (m, 2H), 4.46–4.49 (m, 2H), 7.78 (d,

1H, J = 12.8 Hz), 8.63 (s, 1H), 14.81(br, 1H). HRMS-ESI *m/z*: 420.15453 (calcd. for $C_{20}H_{23}FN_3O_6$, $[M+H]^+$). **8g** mp: 200–202 °C. 1H NMR (400 MHz, DMSO-*d6*): δ 1.42–1.46 (m, 3H), 2.32 (br, 1H), 3.40–3.48 (m, 3H), 3.79 (s, 3H), 4.26–4.39 (m, 2H), 4.52–4.59 (m, 2H), 4.86–4.91 (m, 2H), 5.19 (br, 1H), 7.56 (d, 1H, J = 12.8 Hz), 7.98 (s, 1H), 15.22 (br, 1H). HRMS-ESI *m/z*: 406.14144 (calcd. for $C_{19}H_{21}FN_3O_6$, $[M+H]^+$). **8h** mp: 176–178 °C. 1H NMR (400 MHz, DMSO-*d6*): δ 1.41–1.44 (m, 3H), 1.92–1.97 (m, 1H), 2.16–2.23 (m, 1H), 2.52–2.54 (m, 1H), 3.45–3.49 (m, 1H), 3.67–3.69 (m, 1H), 4.01–4.07 (m, 1H), 4.14–4.32 (m, 2H), 4.50–4.54(m, 1H), 4.84–4.87 (m, 1H), 7.53 (d, 1H, J = 12.8 Hz), 8.87 (s, 1H), 15.39 (br, 1H). HRMS-ESI *m/z*: 392.12581 (calcd. for $C_{18}H_{19}FN_3O_6$, $[M+H]^+$). **8i** mp: 208–211 °C. 1H NMR (400 MHz, $CDCl_3$): δ 0.98–1.02 (m, 2H), 1.20–1.26 (m, 2H), 1.30 (t, 3H, J = 6.8 Hz), 2.37–2.45 (m, 1H), 3.19–3.35 (m, 3H), 3.49–3.56 (m, 1H), 3.76 (s, 3H), 3.87–3.91 (m, 1H), 4.00–4.03 (m, 1H), 4.17 (q, 2H, J = 6.8 Hz), 4.40–4.43 (m, 1H), 7.91 (d, 1H, J = 11.6 Hz), 8.83 (s, 1H). HRMS-ESI *m/z*: 434.17274 (calcd. for $C_{21}H_{25}FN_3O_6$, $[M+H]^+$). **8j** mp: 194–196 °C. 1H NMR (400 MHz, DMSO-*d6*): δ 1.02–1.15 (m, 4H), 2.66–2.86 (m, 2H), 3.45–3.57 (m, 2H), 3.70–3.79 (m, 2H), 3.86 (s, 3H), 4.08–4.17 (m, 2H), 5.21 (br, 1H), 7.79 (d, 1H, J = 12.8 Hz), 8.64 (s, 1H), 15.12 (br, 1H). HRMS-ESI *m/z*: 406.14144 (calcd. for $C_{19}H_{21}FN_3O_6$, $[M+H]^+$).

[11] X-ray data for **6a**: $C_5H_{11}N_2O_2Cl$ from ethanol and ethyl acetate solution, F.W. 165.60, triclinic, 0.20 mm × 0.40 mm × 0.60 mm, P-1, a = 6.270(1) Å, b = 6.738(1) Å, c = 9.568(1) Å, α = 107.11(1)°, β = 101.06(1)°, γ = 96.01(1)°, V = 373.5(2) Å^3, radiation = Mo Kα (λ = 0.71073 Å), Z = 2, R_f = 0.0494, R_w = 0.1413.

[12] 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.