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Synthesis and in vitro antibacterial activity of quinolone/naphthyridone derivatives containing 3-alkoxyimino-4-(methyl)aminopiperidine scaffolds

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ABSTRACT

We report herein the synthesis of a series of 7-[3-alkoxyimino-4-(methyl)aminopiperidin-1-yl]quinolone/naphthyridone derivatives. In vitro antibacterial activity of these derivatives was evaluated against representative strains, and compared with ciprofloxacin (CPFX), levofloxacin (LVFX) and gemifloxacin (GMFX). The results reveal that all of the target compounds **19a**–**c** and **20** have considerable Gram-positive activity, although they are generally less active than the reference drugs against the Gram-negative strains with some exceptions. Especially, novel compounds **19a2**, **19a4** and **19a5** were found to show strong antibacterial activity (MICs: <0.008–0.5 μg/mL) against all of the tested 15 Gram-positive strains including MRSA, LVFX- and GMFX-resistant MRSE, and CPFX-, LVFX- and GMFX-resistant MSSA.

Since the discovery of norfloxacin (NFLX) by Koga et al. in the early 1980s,[1] fluoroquinolones/naphthyridones, as important weapons in our antibacterial arsenal,[2] have been used mainly to fight both community-acquired and serious hospital-acquired infections.[3] These antibiotics depict several properties such as excellent bioavailability, good tissue penetrability, and a relatively low incidence of adverse and toxic effects.[4] During the past 30 years, a great number of fluoroquinolone/naphthyridone derivatives have been designed and synthesized, and a large body of structure–activity relationship (SAR) has been accumulated. The C-4 carbonyl and C-3 carboxylic groups are known to be essential for antibacterial activity. Cyclopropyl and methoxyl (or hydrogen) groups are generally accepted as the optimal substituents at the N-1 and C-8 positions of fluoroquinolones, respectively.[5] And for fluoronaphthyridones, the optimal substituent at the N-1 position can be cyclopropyl [gemifloxacin (GMFX)] or 2,4-diflurophenyl group (tosufloxacin, trovafloxacin). Moreover, the basic group at the C-7 position is the most adaptable site for chemical change and an area that greatly influences their potency, spectrum and safety, and the presence of a five- or six-membered nitrogen heterocycle including pyrrolidine, piperazine and piperidine at this position is particularly structural feature of important fluoroquinolones/naphthyridones on the market,[6] such as ciprofloxacin (CPFX), levofloxacin (LVFX), GMFX and moxifloxacin, and so on.

Recently, oxime-functionalized pyrrolidines as novel C-7 substituents have attracted great attention and led to the discovery of some new fluoronaphthyridones, such as GMFX, zabofloxacin (DW224a) and DW286. All of the three show excellent antibacterial activity and pharmacokinetic profiles which emphasize the importance of the oxime group with respect to biological activity.[7–9]

As part of an ongoing program to develop novel fluoroquinolones/naphthyridones, we have focused our attention on introduction of an oxime functional group to azetidine or piperidine ring containing an amino/aminomethyl moiety, as side chains at the C-7 position.[10–12] IMB-070593 (Fig. 1), a candidate discovered in

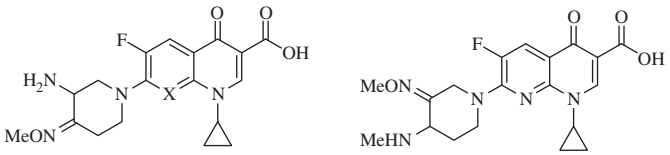

Figure 1. Structures of some fluoroquinolones/fluoronaphthyridones.

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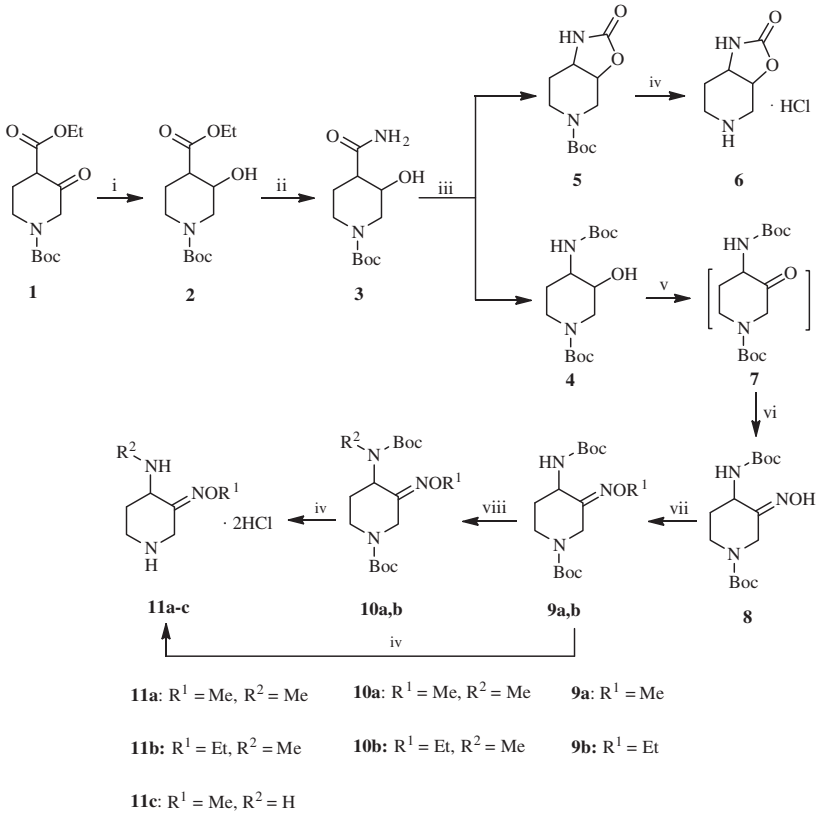
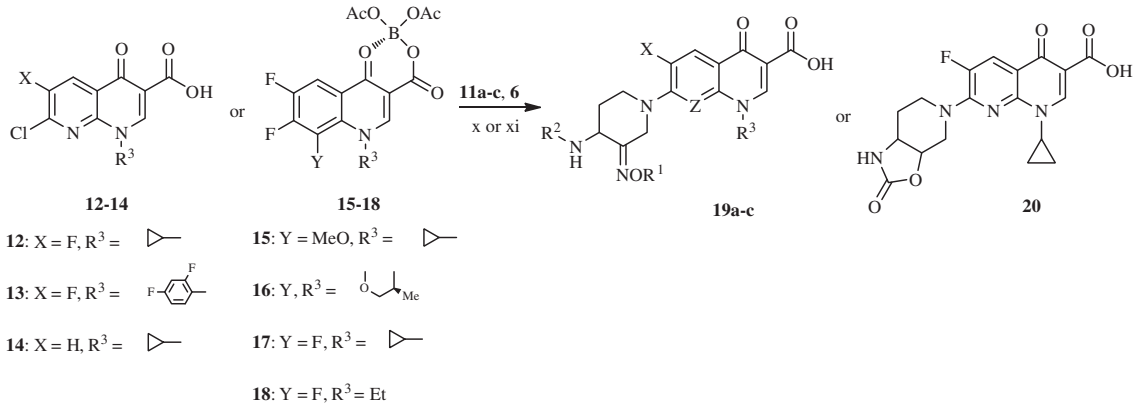


Scheme 1. Synthesis of piperidine derivatives **6** and **11a–c**. Reagents and conditions: (i) KBH_4, EtOH, rt, 2 h; (ii) $NH_3{\cdot}H_2O$, DMF, H_2O, rt, 36 h; (iii) NaBrO, $(Boc)_2O$, H_2O, EtOH, 4 h, 80 °C; (iv) HCl gas, CH_2Cl_2, rt, 3 h; (v) DPCP, Et_3N, DMSO, CH_2Cl_2, −25 °C, 5 h; (vi) $HONH_2{\cdot}HCl$, pyridine, rt, 5 h; (vii) R^1I, K_2CO_3, DMF, rt, 5 h; (viii) R^2I, NaH, MeCN, rt, 4 h.



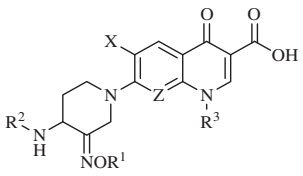
Scheme 2. Synthesis of the target compounds **19a–c** and **20** (See Table 1 for structures). Reagents and conditions: (x) Et_3N, CH_3CN, 50 °C, 5 h; (xi) (1) Et_3N, CH_3CN, 50 °C, overnight. (2) 5% NaOH, 50 °C, 1 h.

our lab, was found to have better in vitro antibacterial activity than LVFX and GMFX, and good in vivo activity comparable to GMFX and MXFX against Gram-positive strains including methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE).[11] IMB-070593 in late pre-clinical stage of development currently, was also observed to possess extremely low phototoxicity, hepatotoxicity and cardiac toxicity (unpublished). Moreover, a preliminary SAR study shows that oxime-containing fluoroquinolones have significantly increased activity, when directly compared to the corresponding fluoronaphthyridones (IMB-070593 vs IMB-070595, Fig. 1).[11]

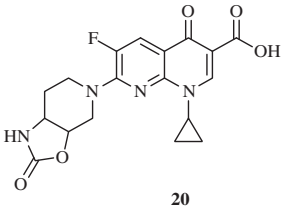
Dang et al. reported a series of fluoronaphthyridone derivatives containing 3-alkoxyimino-4-(methyl)aminopiperidine moieties. The most active compound DZH Figure 1 shows excellent in vitro antibacterial activity against some important pathogens such as methicillin-sensitive *S. aureus* (MSSA), *Staphylococcus pneumoniae*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa*, which is even better than vancomycin and GMFX. However, it is a pity that 1-cyclopropyl fluoronaphthyridone was chosen as the only nucleus in this study.[13]

The above research results intensified our interest, and considering the fact small structural changes of quinolone/naphthyridone nuclei usually cause dramatic improvement in antibacterial activity (such as NFLX vs CPFX and ofloxacin vs LVFX), it was decided to synthesize a series of 3-alkoxyimino-4-(methyl)aminopiperidine-containing derivatives in which the selected nuclei were common

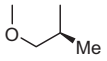
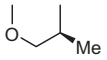
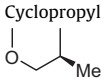
Table 1
Structures and physical data of compounds **19a–c** and **20**



19a-c



20

Compd	R^1	R^2	X	R^3	Z	Yield (%)	Mp[a] (°C)
19a1	Me	Me	F	Cyclopropyl	N	18.6	201–203
19a2	Me	Me	F	Cyclopropyl	C–OMe	23.4	179–180
19a3	Me	Me	F			25.8	156–159
19a4	Me	Me	F	Cyclopropyl	C–F	33.4	134–135
19a5	Me	Me	F	2,4-Diflurophenyl	N	25.2	151–153
19a6	Me	Me	H	Cyclopropyl	N	22.0	203–204
19a7	Me	Me	F	Ethyl	C–F	17.5	135–137
19b1	Et	Me	F	Cyclopropyl	N	27.4	200–202
19b2	Et	Me	F	Cyclopropyl	C–OMe	20.6	130–131
19b3	Et	Me	F			22.5	140–142
19b4	Et	Me	F	Cyclopropyl	C–F	25.0	159–161
19c1	Me	H	F	Cyclopropyl	N	31.4	172–174
19c2	Me	H	F	Cyclopropyl	C–OMe	29.3	109–110
19c3	Me	H	F			34.0	125–127
20					47.5	296–299	

[a] Melting points are uncorrected.

quinolones and other naphthyridones instead of the 1-cyclopropyl fluoronaphthyridone in Dang's study. It could be anticipated that some of these derivatives (such as 8-methoxylfluoroquinolone) should have superior antibacterial activity to DZH. Our primary objective was to optimize the potency of these compounds against clinical familiar pathogens (especially Gram-positive ones). A preliminary SAR study is also explored to facilitate the further development of the quinolones/naphthyridones.

Dang et al. reported a synthetic route of piperidine derivatives **11a–c** via a 12-step procedure with low total yield.[13] To overcome its disadvantages, a simpler route for synthesis of **11a–c** was developed in this work.

Detailed synthetic pathways to **11a–c** and quinolones/naphthyridones **19a–c** are depicted in Schemes 1 and 2, respectively. By the way, three known compounds **19a1** (**DZH**), **19b1** and **19c1**[13] were also prepared in this work for the purpose of comparing antibacterial activity and exploring SAR.

Reduction of readily available 1-*tert*-butyl 4-ethyl 3-oxopiperidine-1,4-dicarboxylate **1** with KBH_4 in ethanol gave hydroxyl ester **2**, which upon aminolysis in $NH_3{\cdot}H_2O$–DMF (catalytic amount) solution yielded hydroxyl amide **3**. However, Hoffmann degradation of the amide **3** used commercially sodium hypochlorite met no success.

Degradation of **3** was then conducted successfully by freshly prepared sodium hypobromite instead of sodium hypochlorite, and subsequent protection of the resulting primary amine by treatment with di-*tert*-butyl dicarbonate (Boc_2O) gave the desired *bis*-Boc protected amino alcohol **4**. Unexpectedly, a new compound containing a lactam ester moiety was simultaneously separated and its chemical structure (shown as **5**) was established by ^1H NMR and MS. Compound **6** was prepared from **5** via deprotection of the Boc group by pumping dry hydrogen chloride gas in dichloromethane

Table 2
In vitro antibacterial activity of compounds **19a–c** and **20** against Gram-positive strains

Strains	Compd MIC (μg/mL)																
	19a1	**19a2**	**19a3**	**19a4**	**19a5**	**19a6**	**19a7**	**19b1**	**19b2**	**19b3**	**19b4**	**19c1**	**19c2**	**19c3**	**20**	GMFX	LVFX	CPFX
S. a ATCC259233	0.5	0.25	0.25	0.25	0.125	0.5	0.125	0.5	0.125	0.5	0.5	0.25	0.06	0.5	1	<0.008	0.125	0.25
MSSA 12-6	0.25	0.06	0.25	0.03	0.03	2	0.5	0.25	0.25	1	0.5	0.25	0.25	0.5	1	0.03	0.125	0.125
MSSA 12-7	0.5	0.125	1	0.06	0.06	4	1	32	32	128	128	32	8	64	128	4	32	64
MSSA 12-10	0.25	0.06	0.25	0.03	0.03	2	0.5	0.5	0.125	>128	0.125	2	0.125	0.25	0.5	0.03	0.06	0.25
MRSA 12-3	1	0.25	1	0.06	0.03	4	1	4	0.25	1	0.5	0.25	0.25	1	2	0.03	0.125	0.125
MRSA 12-13	1	0.25	1	0.06	0.03	4	1	4	0.25	1	0.5	0.25	0.25	1	2	0.015	0.125	0.125
MRSA 12-15	1	0.25	1	0.06	0.03	4	1	4	0.25	1	0.5	0.25	0.25	1	2	0.03	0.125	0.125
MSSE 12-1	0.5	0.25	0.5	0.25	0.125	8	0.5	1	0.5	0.5	0.5	0.5	0.25	0.5	1	0.06	0.25	0.06
MSSE 12-2	2	0.5	2	0.5	0.5	16	16	4	1	2	1	2	0.5	1	2	0.25	0.25	0.5
MSSE 12-3	0.5	0.25	0.5	0.25	0.125	8	0.5	1	0.5	0.5	0.5	0.5	0.25	0.5	1	0.06	0.25	0.06
MRSE 12-5	0.25	0.06	0.125	0.015	0.015	2	0.5	1	1	0.5	1	2	0.25	0.5	0.5	0.015	0.125	0.015
MRSE 12-33	0.06	0.125	<0.008	<0.008	0.015	4	8	0.25	1	8	1	4	2	0.5	1	4	8	0.015
MRSE 12-35	0.25	0.06	0.125	0.015	0.015	2	0.5	1	1	0.5	1	2	0.25	0.5	0.5	0.008	0.125	0.015
S. p. 12-2	0.5	0.125	1	0.06	0.06	4	1	0.25	0.25	1	0.5	0.25	0.25	0.5	2	0.25	0.125	0.5
S. p. 12-5	0.5	0.125	1	0.06	0.06	4	1	0.25	1	8	1	4	2	0.5	0.5	0.25	0.125	0.5

GMFX, gemifloxacin; LVFX, levofloxacin; CPFX, ciprofloxacin; *S. a.*, *Staphylococcus aureus*; MSSA, Methicillin-sensitive *Staphylococcus aureus*; MRSA, Methicillin-resistant *Staphylococcus aureus*; MSSE, Methicillin-sensitive *Staphylococcus epidermidis*; MRSE, Methicillin-resistant *Staphylococcus epidermidis*; *S. p.*, *Streptococcus pneumonia*.

(Scheme 1). Given the oxazolidinone moiety of **5** is one of the key constituents of linezolid, it was also decided to synthesized a naphthyridone derivative **20** containing lactam ester **6** (Scheme 2) so that more SAR could be explored.

The oxime **8** was obtained using 'one-pot' method from the alcohol **4** via Swern oxidation[14] involving phenyl dichlorophosphate (DPCP) as the electrophilic activator, and subsequent condensation of the resulting ketone **7** with hydroxylamine hydrochloride in the presence of pyridine. Nucleophilic substitution of **8** with iodoalkanes in the presence of anhydrous K_2CO_3 gave alkyloximes **9a–b**, which upon methylation by reaction with iodomethane in the presence of NaH produced compounds **10a–b**. Deprotection of the *bis*-Boc groups on the amines **10a–b** and **9a** was carried out in a similar manner as for the preparation of **6** to afford the piperidine derivative dihydrochlorides **11a–b** and **11c**, respectively (Scheme 1).[15]

Finally, the target compounds **19a–c** and **20** were obtained by coupling piperidine derivatives **11a–c** and **6** with various compounds containing naphthyridone and quinolone cores according to well-established literature procedures.[16] In the case of quinolone/naphthyridone derivatives **19a1**, **19a5**, **19a6**, **19b1**, **19c1** and **20**, condensations of **12–14** with **6** and **11a–c** were performed in the presence of triethylamine. However, for **19a2–4**, **19a7**, **19b2–4**, **19c2** and **19c3**, boric chelates **15–18** were required to increase reactivity (Scheme 2). Table 1 shows structures and physical data of compounds **19a–c** and **20**.[17]

Because the oxime group is present in the *E* or *Z* configuration, it was necessary to determine the geometries of all the oxime target compounds **19a–c**. Unfortunately, we were unable to prepare X-ray-quality single crystals of any oxime intermediate or product. Nonetheless, we can speculate that the oxime group of the target compounds is present in a single configuration of *E* or *Z* isomer due to signal singleness of the piperidine ring of the compounds observed in the ^{1}H NMR spectra.

The target compounds **19a–c** and **20** were evaluated for their in vitro antibacterial activity against representative strains using standard techniques.[18] Minimum inhibitory concentration (MIC) is defined as the compound concentration required to give complete inhibition of bacterial growth, and MIC values of **19a–c** and **20** against Gram-positive and Gram-negative strains, along with those of the three standard drugs GMFX, LVFX and CPFX for comparison, are listed in Tables 2 and 3, respectively.

Our results indicate that the derivatives **19a–c** and **20**, like the reference drugs, have potential broad-spectrum antibacterial activity. Their MIC values against Gram-positive strains are generally smaller than those against Gram-negative ones. Although **19a–c** and **20** are less active than GMFX, LVFX and CPFX against the Gram-negative strains with some exceptions, all of them have considerable activity against the Gram-positive ones. Novel compounds **19a2**, **19a4** and **19a5** exhibit strong activity (MICs: <0.008–0.5 μg/mL) against all of the tested fifteen Gram-positive strains including MSSA, MRSA, methicillin-susceptible *S. epidermidis* (MSSE), MRSE, and *S. pneumoniae*. It is especially worth to note that **19a2**, **19a4** and **19a5** also display excellent activity (MICs: <0.008–0.125 μg/mL) against GMFX-, LVFX- and CPFX-resistant MSSA (MICs: 4–64 μg/mL), and GMFX- and LVFX-resistant MRSE (MICs: 4–8 μg/mL).

In the case of Gram-positive strains, the activity of the nuclei in this study is in the order 2,4-difluorophenyl-1,8-naphthyridone ≈ 1-cyclopropyl-6,8-difluoroquinolone > 1-cyclopropyl-8-methoxylfluoroquinolone > LVFX nucleus > 1-ethyl-6,8-difluoroquinolone when 3-alkoxyimino-4-(methylamino)piperidines serve as the C-7 side chains. Introduction of a methyl group on the amino moiety of the piperidine ring seems to contribute to the antibacterial activity (**19a1** vs **19c1**, **19a2** vs **19c2**, **19a3** vs **19c3**), while replacement of the fluorine with hydrogen at C-6 position results in decreased activity (**19a1** vs **19a6**). Moreover, fluoroquinolones featuring methyloxime-incorporated piperidino-substitution at C-7 position are more active than the corresponding analogs containing ethyloxime (**19a1** vs **19b1**, **19a2** vs **19b2**, **19a3** vs **19b3**, **19a4** vs **19b4**). It is interesting that 1-cyclopropylfluoronaphthyridones do show significantly decreased activity when compared to the corresponding 8-methoxylfluoroquinolones (**19a1** vs **19a2**, **19b1** vs **19b2**, **19c1** vs **19c2**), which is consistent with the SAR in our previous study.[11] Anyway, the validity of our strategy has been supported by the data listed in Table 2, especially two quinolone derivatives (**19a2**, **19a4**) and one naphthyridone derivatives (**19a5**) possessing better Gram-positive activity than the most active compound DZH (**19a1**) reported in Dang's study.[13]

Notably, the naphthyridone derivative containing a lactam ester moiety at C-7 position (**20**) has also good activity with the MIC values of 0.5–2 μg/mL against all of the Gram-positive strains except MSSA 12-7. Furthermore, it was found to be comparable to or slightly less active than the corresponding compounds with the same naphthyridone nulei (**19a1**, **19b1**, **19c1**). This implies the existence of a free amino group on the piperidine ring at C-7 position is not always essential for antibacterial activity of the naphthyridones.

Table 3
In vitro antibacterial activity of compounds **19a–c** and **20** against Gram-negative strains

Strains	Compd MIC (μg/mL)																	
	19a1	**19a2**	**19a3**	**19a4**	**19a5**	**19a6**	**19a7**	**19b1**	**19b2**	**19b3**	**19b4**	**19c1**	**19c2**	**19c3**	**20**	GMFX	LVFX	CPFX
E. co. ATCC25922	0.125	0.125	0.25	0.03	0.125	0.5	0.5	4	16	16	16	32	4	8	1	0.015	0.015	0.008
E.co. 12-1	4	4	8	2	8	64	8	32	8	4	8	2	2	4	16	0.125	0.5	0.125
E.co. 12-4	>128	>128	128	>128	>128	>128	>128	>128	>128	>128	>128	>128	128	>128	>128	16	8	8
E.co. 12-5	>128	128	128	>128	>128	>128	>128	>128	>128	>128	>128	>128	64	128	>128	16	8	2
E. co.[a]12-1	>128	>128	128	>128	>128	>128	>128	>128	>128	>128	>128	>128	64	128	>128	8	16	32
E.co. [a] 12-2	>128	>128	>128	>128	>128	128	>128	>128	>128	>128	>128	64	64	>128	>128	16	16	16
E.co. [a] 12-4	16	32	16	128	32	64	128	32	32	64	16	32	16	16	64	2	0.5	2
K. p. 12-1	0.5	1	1	0.5	1	2	4	4	4	2	2	0.25	2	8	2	0.03	0.06	0.03
K. p. 12-2	0.5	2	1	0.5	1	2	4	4	4	1	1	0.25	2	1	2	0.06	0.06	0.125
K. p. 12-4	0.125	0.5	0.5	0.5	1	2	1	2	2	1	1	0.125	0.5	1	32	0.06	0.25	0.125
K. p. [a]12-1	16	16	16	8	64	128	16	64	32	8	16	8	8	0.5	128	2	1	2
K. p. [a]12-2	16	16	16	8	32	>128	32	>128	32	32	16	8	16	16	>128	2	8	4
K. p. [a]12-4	0.125	0.5	0.5	0.5	1	2	1	>128	>128	>128	>128	>128	64	128	128	2	4	4
P. a. ATCC27853	2	8	4	4	8	8	8	4	16	32	16	32	4	32	8	1	1	0.5
P. a. 12-1	16	16	8	8	4	16	8	128	16	16	16	8	16	16	16	8	4	0.125
P. a. 12-2	16	16	8	8	8	8	8	128	16	8	16	8	16	16	16	16	16	16

GMFX, gemifloxacin; LVFX, levofloxacin; CPFX, ciprofloxacin; *E. co.*, *Escherichia coli*; *K. p.*, *Klebsiella pneumoniae*; *P. a.*, *Pseudomonas aeruginosa*.
[a] Extended-spectrum β-lactamase-producing.

In summary, a new synthetic route of 3-alkoxyimino-4-(methyl)aminopiperidine derivatives **11a–c** was developed in this study. A series of quinolone/naphthyridone derivatives containing these heterocyclic amines were synthesized and evaluated for their in vitro antibacterial activity, and a preliminary SAR was also explored. All of the target compounds **19a–c** and **20** have considerable Gram-positive activity, although they are generally less active than the reference drugs against the Gram-negative strains with some exceptions. In especial, compounds **19a2**, **19a4** and **19a5** were found to have strong activity (MICs: <0.008–0.5 μg/mL) against all of the fifteen Gram-positive strains including MRSA, GMFX- and LVFX-resistant MRSE, and GMFX-, LVFX- and CPFX-resistant MSSA.

Acknowledgments

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15. To a stirring solution of **1** (13.55 g, 50 mmol) in ethanol (50 mL) was added potassium borohydride (1.10 g, 20 mmol) at room temperature. The reaction mixture was stirred for 2 h at the same temperature, quenched with distilled water (100 mL), and extracted with ethyl acetate. The combined extracts were washed successively with water and saturated saline solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography eluted with petroleum ether and ethyl acetate (V:V = 2:1) to afford **2** (12.28 g, 90.2%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 4.21–4.00 (5H, m), 2.97 (1H, d, J = 13 Hz), 2.88–2.81 (1H, m), 2.53 (1H, d, J = 11 Hz), 2.06–2.03 (1H, m), 1.73 (1H, dd, J_1 = 13 Hz, J_2 = 2 Hz), 1.45 (9H, s) ,1.27 (3H, t, J = 7 Hz). MS-ESI (m/z): 274 $(M+H)^+$, 296 $(M+Na)^+$. To a stirring solution of **2** (81.90 g, 300 mmol) in 25% ammonia solution (250 mL) was added dimethyl formamide (25 mL) at room temperature. The reaction mixture was stirred for 36 h at the same temperature, then cooled to 0 °C. The precipitate was filtered, washed with distilled water, and dried in vacuo to afford **3** (23.42 g, 32.5%) as a white solid, mp:133–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 5.63 (2H, s), 4.16–4.09 (3H, m), 2.94–2.81 (2H, m), 2.41 (1H, d, J = 11 Hz), 2.07 (1H, qd, J_1 = 12 Hz, J_2 = 3 Hz), 1.75–1.72 (1H, m), 1.46 (9H, s). MS-ESI (m/z): 245 $(M+H)^+$, 267 $(M+Na)^+$. To a stirring suspension of **3** (29.28 g, 120 mmol) in distilled water (300 mL) was added dropwise 10% sodium hypobromite solution (300 mL) at 5 °C for 1 h. The reaction mixture was stirred for 3 h at room temperature, and then 4 h at 80 °C. A solution of $(Boc)_2O$ (30.52 g, 140 mmol) in ethanol (50 mL) was added to the reaction mixture over a period of 30 min at 50 °C. The reaction mixture was stirred for 3 h at the same temperature. The precipitate was filtered, washed with distilled water, and dried in vacuo to afford **4** (9.5 g, 30.8%) as a white solid, mp: 133–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 4.96 (1H, s), 4.16 (1H, d, J = 14 Hz), 4.01 (1H, d, J = 14 Hz), 3.88 (1H, br s), 3.65 (1H, br s), 2.97 (1H, d, J = 14 Hz), 2.86–2.79 (1H, m), 1.97 (1H, br s), 1.72–1.65 (2H, m) ,1.45 (18H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ_{ppm}: 155.86, 155.43, 80.06, 79.47, 67.09, 50.61, 42.97, 28.33, 26.53. MS-ESI (m/z): 339 $(M+Na)^+$. The filtrate was extracted with ethyl acetate. The combined extracts were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by chromatography eluted with petroleum ether and ethyl acetate (V:V = 3:1) to afford **5** as a white solid, mp: 169–171 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ_{ppm}: 7.50 (1H, s), 4.70–4.62 (1H, m), 3.96–3.94 (1H, m), 3.78–3.76 (1H, m), 3.25–3.13 (3H, m), 1.87–1.81 (1H, m), 1.59–1.56 (1H, m), 1.38 (9H, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ_{ppm}: 158.62, 155.22, 79.29, 73.47, 47.81, 42.30, 37.68, 28.54, 25.59. MS-ESI (m/z): 260 $(M+NH_4)^+$. To a stirring solution of **5** (2.42 g, 10 mmol) in dichloromethane (80 mL) was pumped dried hydrochloride gas at room temperature for 30 min. The reaction mixture was stirred for 3 h at the same temperature, and then filtered. The precipitate was washed with dichloromethane, and dried in vacuo to yield **6** (1.01 g, 47.0%) as a white solid, mp: 232–234 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ_{ppm}: 9.55 (1H, br s), 8.87 (1H, br s), 7.89 (1H, s), 4.74–4.71 (1H, m), 3.93–3.89 (1H, m), 3.40–3.37 (1H, m), 3.25–3.28 (1H, m), 3.03–2.95 (2H, m), 2.05–1.98 (1H, m), 1.64–1.57 (1H, m). MS-ESI (m/z): 143 $(M+H)^+$. To a stirring solution of DMSO (23.40 g, 300 mmol) in anhydrous dichloromethane (150 mL) was added dropwise phenyl dichlorophosphate (38.00 g, 180 mmol) at −25 °C over a period of 30 min. The mixture was stirred for 1 h at the same temperature. Triethylamine (30.30 g, 300 mmol) was added dropwise to the reaction mixture at −20 to −25 °C over a period of 2 h, and then the mixture was stirred for 3 h at the same temperature. A solution of **4** (19.01 g, 60 mmol) in dichloromethane (400 mL) was added dropwise to the reaction mixture over a period of 3 h at −20 to −25 °C, and then was stirred at room temperature for 10 h to produce a mixture containing **7**. To the above mixture were added hydroxylamine hydrochloride (5.56, 80 mmol) and pyridine (12.66 g, 160 mmol) at room temperature. The reaction mixture was stirred for 5 h at the same temperature, and concentrated under reduced pressure. The residue was treated with ethyl acetate, washed successively with water and saturated saline solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was treated with petroleum ether to afford **8** (8.49 g, 43.8%) as a white solid, mp: 124–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 7.26 (1H, br s), 5.35 (1H, br s), 5.20 (1H, d, J = 16 Hz), 4.33 (1H, br s), 3.98 (1H, br s), 3.59–3.57 (1H, m), 3.20 (1H, br s), 2.44-2.42 (1H, br s), 1.60–1.51 (19H, m). MS-ESI (m/z): 330 $(M+H)^+$. To a stirring solution of **8** (9.87 g, 30 mmol) in DMF was added potassium carbonate (16.58 g, 120 mmol) and methyl iodide (12.77 g, 90 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 5 h, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel) eluted with petro ether and ethyl acetate (V:V = 2:1) to give **9a** as a light yellow oil (75.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 5.39 (1H, br s), 5.01 (1H, d, J = 16 Hz), 4.20 (1H, m), 3.85 (4H, m), 3.49 (1H, d, J = 16 Hz), 3.15–3.09 (1H, m), 2.38 (1H, d, J = 12 Hz), 1.58–1.47 (18H, m). MS-ESI (m/z): 366 $(M+Na)^+$. The compound **9b** was obtained from ethyl iodide as a colorless oil (70.0%) in a similar manner as for the preparation of **9a**. Compound **9b**, ^{1}H NMR (500 MHz, $CDCl_3$) δ_{ppm}: 5.40 (1H, br s), 5.04 (1H, br s), 4.22 (1H, br s), 4.13 (2H, q, J = 7 Hz), 3.98 (1H, br s), 3.53 (1H, br s), 3.17 (1H, br s), 2.48 (1H, br s), 1.60 (1H, br s), 1.48 (18H, s), 1.33 (3H, t, J = 7 Hz). MS-ESI (m/z): 358 $(M+H)^+$. To a solution of **9a** (5.49 g, 16 mmol) in acetonitrile (50 mL) was added 60% sodium hydride (1.92 g, 48 mmol) and methyl iodide (6.81 g, 48 mmol) at room temperature. The reaction mixture was stirred for 4 h at the same temperature, quenched with distilled water (3 mL), and concentrated under reduced pressure. The residue was treated with ethyl acetate, washed successively with water and saturated saline solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was treated with petroleum ether at −20 °C. The precipitate was filtered, and washed with petroleum ether to afford **10a** as a light yellow solid (47.5%), mp: 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 4.99 (1H, d, J = 16 Hz), 4.82 (1H, br s), 4.01 (1H, m), 3.82 (3H, s), 3.56 (1H, d, J = 16 Hz), 3.09–3.04 (1H, m), 2.75 (3H, s), 2.00–1.80 (2H, m), 1.45 (18H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ_{ppm}: 156.15, 154.58, 149.93, 80.24, 79.80, 62.06, 54.50, 42.07, 37.58, 28.44, 22.66. MS-ESI (m/z): 375 $(M+NH_4)^+$, 380 $(M+Na)^+$. The compound **10b** was obtained from **9b** as a light yellow solid (58.3%) in a similar manner as for the preparation of **10a**. Compound **10b**, mp: 95–97 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ_{ppm}: 5.02 (1H, d, J = 16 Hz), 4.95 (1H, br s), 4.06 (2H, 7 Hz), 4.02 (1H, br s), 3.54 (1H, br s), 3.07 (1H, br s), 2.75 (3H, s), 2.00–1.82 (2H, m), 1.45 (18H, s), 1.23 (3H, t, J = 7 Hz). MS-ESI (m/z): 372 $(M+H)^+$, 389 $(M+NH_4)^+$, 394 $(M+Na)^+$. To a stirring solution of **10a** (0.50 g, 1.4 mmol) in dichloromethane (10 mL) was pumped dried hydrochloride gas at 0–5 °C for 30 min. The reaction mixture was stirred for another 1 h at room temperature, and concentrated under reduced pressure. The residue was treated with ethyl acetate. The precipitate was collected by suction, and dried in vacuo to give **11a** as a white solid (0.15 g, 66.5%), mp: 76–78 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ_{ppm}: 9.60 (4H, br s), 4.35 (1H, d, J = 15 Hz), 4.10–4.08 (1H, m), 3.92 (3H, s), 3.82 (1H, d, J = 15 Hz), 3.51–3.47 (1H, m), 3.20–3.15 (1H, m), 2.55 (3H, s), 2.42–2.38 (1H, m), 2.13–2.11 (1H, m). ^{13}C NMR (100 MHz, DMSO-d_6) δ_{ppm}: 145.06, 62.57, 53.79, 46.58, 37.35, 30.50, 24.17. MS-ESI (m/z): 158 $(M+H)^+$. The compounds **11b** and **11c** were obtained in a similar manner as for the preparation of **11a**. Compound **11b**, yield: 47.0% (from **10b**), white solid. mp: 80–82 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ_{ppm}: 9.75 (4H, br s), 4.46 (1H, d, J = 15 Hz), 4.17 (2H, q, J = 7 Hz), 4.15–4.05 (1H, m), 3.85 (1H, d, J = 15 Hz), 3.40–3.10 (2H, m), 2.53 (3H, s), 2.49–2.48 (1H, m), 2.22–2.12 (1H, m), 1.24 (3H, t, J = 7 Hz). MS-ESI (m/z): 172 $(M+H)^+$. Compound **11c**, yield: 39.7% (from **9a**), off-white solid easily absorbing moisture.
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17. To a solution of **11a** (0.23 g, 1 mmol) and triethylamine (0.42 mL, 3 mmol) in anhydrous acetonitrile (10 mL) was added **12** (0.23 g, 0.8 mmol) at room

temperature. The reaction mixture was stirred for 5 h at 50 °C, and concentrated under reduced pressure. The residue was dissolved in 20% acetic acid (10 mL), stirred for 0.5 h at 50 °C, and filtered. The filtrate was adjusted to pH 6.5–7.5 by 15% sodium hydroxide and extracted by dichloromethane. The combined extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel), eluting with dichloromethane and methanol (V:V = 10:1) to afford the target compound **19a1** as a off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ_{ppm}: 8.63 (1H, s), 8.13 (1H, d, J = 13 Hz), 5.12 (1H, d, J = 14 Hz), 4.57 (1H, d, J = 16 Hz), 4.25–4.22 (1H, m), 4.07 (1H, br s), 3.87 (3H, s), 3.82-3.79 (1H, m), 3.70 (1H, m), 2.49 (3H, s), 1.12 (1H, br s), 1.99–1.97 (1H, m), 1.20–1.19 (2H, m), 1.13–1.11 (2H, m). MS-ESI (m/z): 404 $(M+H)^+$. HRMS-ESI (m/z): Calcd for $C_{19}H_{23}O_4N_5F$ $(M+H)^+$: 404.1728; Found 404.1732. The other target compounds **19a5**, **19a6**, **19b1**, **19c1** and **20** were obtained as off-white or light yellow solids in a similar manner as for the preparation of **19a1**. Compound **19a5** (from **11a** and **13**), ^{1}H NMR (600 MHz, $CDCl_3$) δ_{ppm}: 8.67 (1H, s), 8.11 (1H, d, J = 13 Hz), 7.43–7.37 (1H, m), 7.11–7.06 (2H, m), 4.41 (1H, d, J = 14 Hz), 4.12–4.08 (1H, m), 3.97 (1H, d, J = 14 Hz), 3.86 (1H, br s), 3.81 (3H, s), 3.62–3.55 (1H, m), 2.36 (3H, s), 1.90–1.86 (1H, m), 1.78-1.70 (1H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ_{ppm}: 177.65, 166.32, 157.09 (d, J = 250 Hz), 153.72, 149.99, 147.19 (d, J = 258 Hz), 147.09, 145.85, 129.96, 123.98, 119.05 (d, J = 22 Hz), 112.92, 112.27, 110.11, 105.36 (d, J = 21 Hz), 61.85, 50.29, 46.64, 42.67, 33.98, 29.14. MS-ESI (m/z): 476 $(M+H)^+$. HRMS-ESI (m/z): Calcd for $C_{22}H_{21}O_4N_5F_3$ $(M+H)^+$: 476.1540; Found 476.1552. Compound **19a6** (from **11a** and **14**), ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 8.66 (1H, s), 8.38 (1H, d, J = 9 Hz), 6.86 (1H, d, J = 9 Hz), 4.80–4.67 (2H, m), 3.98–3.86 (5H, m), 3.62 (1H, br s), 3.46 (1H, br s), 2.50 (3H, s), 2.21 (1H, br s), 2.04 (1H, br s), 1.28–1.25 (2H, m), 1.08–1.03 (2H, m). ^{13}C NMR (150 MHz, $CDCl_3$) δ_{ppm}: 177.36, 167.25, 158.76, 152.43, 151.31, 146.87, 136.38, 111.82, 108.78, 106.97, 62.18, 56.82, 41.19, 40.27, 34.41, 33.71, 29.03, 7.43, 7.35. MS-ESI (m/z): 386 $(M+H)^+$. HRMS-ESI (m/z): Calcd for $C_{19}H_{24}O_4N_5$ $(M+H)^+$: 386.1723; Found 386.1771. Compound **19b1** (from **11b** and **12**), ^{1}H NMR (600 MHz, $CDCl_3$) δ_{ppm}: 8.73 (1H, s), 8.08 (1H, d, J = 13 Hz), 4.90 (1H, d, J = 16 Hz), 4.75 (1H, d, J = 16 Hz), 4.16–4.14 (3H, m), 3.96–3.93 (1H, m), 3.64–3.60 (1H, m), 3.49–3.46 (1H, m), 2.48 (3H, s), 2.28–2.26 (1H, m), 1.98–1.97 (1H, m), 1.34–1.26 (5H, m), 1.18–1.14 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ_{ppm}: 177.05, 166.83, 151.97, 150.06, 149.97, 147.35 (d, J = 258 Hz), 146.65, 119.89, 113.40, 108.86, 69.88, 57.20, 43.63, 42.31, 34.74, 33.70, 30.26, 14.51, 7.42. MS-ESI (m/z): 418 $(M+H)^+$. HRMS-ESI (m/z): Calcd for $C_{20}H_{25}O_4N_5F$ $(M+H)^+$: 418.1885; Found 418.1893. Compound **19c1** (from **11c** and **12**), ^{1}H NMR (500 MHz, DMSO-d_6) δ_{ppm}: 8.74 (1H, s), 8.09 (1H, d, J = 13 Hz), 5.24 (1H, d, J = 16 Hz), 4.33 (1H, d, J = 16 Hz), 4.32–4.30 (1H, m), 3.88 (3H, s), 3.78–3.72 (2H, m), 3.66–3.63 (1H, m), 2.28–2.25 (1H, m), 1.83–1.78 (1H, m), 1.31–1.29 (2H, m), 1.10–1.07 (2H, m). ^{13}C NMR (100 MHz, DMSO-d_6) δ_{ppm}: 176.41, 165.64, 154.84, 149.46, 147.22, 146.62 (d, J = 254 Hz), 146.49, 119.50 (d, J = 22 Hz), 112.50, 107.66, 61.49, 48.83, 43.67, 41.81, 34.95, 31.87, 6.88. MS-ESI (m/z): 390 $(M+H)^+$. HRMS-ESI (m/z): Calcd for $C_{18}H_{21}O_4N_5F$ $(M+H)^+$: 390.1572; Found 390.1563. Compound **20** (from **6** and **12**), ^{1}H NMR (400 MHz, DMSO-d_6) δ_{ppm}: 15.24 (1H, s), 8.58 (1H, s), 8.04 (1H, d, J = 16 Hz), 7.72 (1H, s), 4.94 (1H, d, J = 9 Hz), 4.46 (1H, d, J = 15 Hz), 4.16–4.12 (2H, m), 3.82–3.67 (2H, m), 2.15–2.06 (1H, m), 1.82–1.77 (1H, m), 1.22–1.07 (4H, m). ^{13}C NMR (100 MHz, DMSO-d_6) δ_{ppm}: 176.84, 166.23, 158.53, 150.74, 147.49, 147.15, 146.80 (d, J = 250 Hz), 119.40 (d, J = 22 Hz), 73.50, 47.74, 44.18, 41.47, 35.93, 25.93, 7.34, 7.25. MS-ESI (m/z): 387 $(M-H)^-$. HRMS-ESI (m/z): Calcd for $C_{18}H_{16}O_5N_4F$ $(M-H)^-$: 387.1099; Found 387.1100. To a solution of **11a** (0.23 g, 1 mmol) and triethylamine (0.42 mL, 3 mmol) in acetonitrile (10 mL) was added **15** (0.34 g, 0.8 mmol) at room temperature. The reaction mixture was stirred overnight at 50 °C, and concentrated under reduced pressure. The residue was dissolved in a solution of 5% sodium hydroxide solution (8 mL) and stirred for 1 h at 50 °C. After cooling to room temperature, the mixture was adjusted to pH 7.0–7.5 with 5% acetic acid, and extracted with dichloromethane. The combined extracts were concentrated under reduced pressure. The residue was dissolved in 20% acetic acid (10 mL), stirred for 0.5 h at 50 °C, and filtered. The filtrate was adjusted to pH 6.5–7.5 by 15% sodium hydroxide and extracted by dichloromethane. The combined extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel), eluting with dichloromethane and methanol (V:V = 10:1) to afford the target compound **19a2** as a light yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ_{ppm}: 8.82 (1H, s), 7.88 (1H, d, J = 13 Hz), 4.37 (1H, d, J = 15 Hz), 4.10 (1H, d, J = 15 Hz), 4.05–4.02 (1H, m), 3.87 (3H, s), 3.76 (3H, s), 3.70–3.63 (1H, m), 3.40–3.37 (2H, m), 2.50 (3H, s), 2.33–2.27 (1H, m), 1.90–1.86 (1H, m), 1.24–1.19 (2H, m), 1.03–1.00 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ_{ppm}: 177.03, 166.69, 164.93, 156.60 (d, J = 250 Hz), 149.96, 138.68, 133.70, 122.53, 108.10, 107.83, 62.17, 61.89, 57.80, 47.90, 45.62, 40.61, 33.77, 31.99, 9.53, 9.47. MS-ESI (m/z): 433 $(M+H)^+$. HRMS-ESI (m/z): Calcd for $C_{21}H_{26}O_5N_4F$ $(M+H)^+$: 433.1892. The other target compounds **19a3**, **19a4**, **19a7**, **19b2**–**4**, **19c2** and **19c3** were obtained as light yellow solids in a similar manner as for the preparation of **19a2**. Compound **19a3** (from **11a** and **16**), ^{1}H NMR (600 MHz, $CDCl_3$) δ_{ppm}: 8.61 (1H, s), 7.74 (1H, d, J = 12 Hz), 4.47–4.33 (2H, m), 4.36–4.27 (2H, m), 4.07 (1H, d, J = 16 Hz), 3.87 (3H, s), 3.60-3.53 (1H, m), 3.37–3.30 (2H, m), 2.47 (3H, s), 2.23–2.20 (1H, m), 1.90–1.88 (1H, m), 1.61 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ_{ppm}: 177.05, 167.14, 156.24 (d, J = 246 Hz), 153.79, 144.80, 140.07, 132.11, 124.59, 121.16, 107.99, 105.12 (d, J = 24 Hz), 68.24, 61.81, 57.41, 55.44, 47.74, 46.34, 33.80, 31.21, 18.31. MS-ESI (m/z): 419 $(M+H)^+$. HRMS-ESI (m/z): Calcd for $C_{20}H_{24}O_5N_4F$ $(M+H)^+$: 419.1725; Found 419.1734. Compound **19a4** (from **11a** and **17**), ^{1}H NMR (600 MHz, C_5D_5N) δ_{ppm}: 8.91 (1H, s), 8.04 (1H, d, J = 12 Hz), 4.82 (1H, d, J = 15 Hz), 4.25 (1H, d, J = 15 Hz), 4.18–4.16 (1H, m), 3.89 (3H, s), 3.87 (1H, br s), 3.82–3.79 (1H, m), 3.42–3.39 (1H, m), 2.82 (3H, s), 2.77–2.73 (1H, m), 2.35–2.30 (1H, m), 1.10–1.07 (2H, m), 1.03–1.01 (2H, m). ^{13}C NMR (100 MHz, DMSO-d_6) δ_{ppm}: 175.82, 165.30, 153.28 (d, J = 253 Hz), 150.24, 149.53, 146.33 (d, J = 248 Hz), 132.54, 126.33, 121.08, 107.45, 106.78, 62.08, 55.37, 47.78, 45.91, 30.78, 28.27, 8.43. MS-ESI (m/z): 421 $(M+H)^+$. HRMS-ESI (m/z): Calcd for $C_{19}H_{23}O_4N_4F_2$ $(M+H)^+$: 421.1681; Found 421.1690. Compound **19a7** (from **11a** and **18**), ^{1}H NMR (600 MHz, $CDCl_3$) δ_{ppm}: 8.61 (1H, s), 7.98 (1H, d, J = 12 Hz), 4.49–4.45 (2H, m), 4.36 (1H, d, J = 15 Hz), 4.16 (1H, d, J = 15 Hz), 3.89 (3H, s), 3.67–3.64 (1H, m), 3.45–3.43 (1H, m), 3.38–3.34 (1H, m), 2.52 (3H, s), 2.32 (1H, m), 1.98–1.94 (1H, m), 1.57 (3H, t, J = 7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ_{ppm}: 176.20, 166.57, 154.25 (d, J = 251 Hz), 152.47, 150.06, 146.25 (d, J = 254 Hz), 133.88, 127.05, 121.98, 108.34 (d, J = 24 Hz), 108.16, 61.93, 57.30, 54.68, 47.86, 45.99, 33.56, 31.36, 16.33. MS-ESI (m/z): 409 $(M+H)^+$. HRMS-ESI (m/z): Calcd for $C_{19}H_{23}O_4N_4F_2$ $(M+H)^+$: 409.1681; Found 409.1690. Compound **19b2** (from **11b** and **15**), ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 8.81 (1H, s), 7.87 (1H, d, J = 12 Hz), 4.45 (1H, d, J = 15 Hz), 4.17–4.11 (3H, m), 4.06–4.02 (1H, m), 3.77 (3H, s), 3.72 (1H, br s), 3.50 (1H, br s), 3.45–3.40 (1H, m), 2.57 (2H, s), 2.35–2.32 (1H, m), 2.05–2.03 (1H, m), 1.27–1.21 (5H, m), 1.07–0.99 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ_{ppm}: 177.00, 166.66, 156.42 (d, J = 251 Hz), 149.99, 146.50, 138.42, 133.70, 122.49, 108.10 (d, J = 23 Hz), 107.84, 69.86, 62.23, 57.73, 47.76, 45.83, 40.60, 33.25, 31.47, 14.54, 9.56, 9.48. MS-ESI (m/z): 447 $(M+H)^+$. HRMS-ESI (m/z): Calcd for $C_{22}H_{28}O_5N_4F$ $(M+H)^+$: 447.2038; Found 447.2046. Compound **19b3** (from **11b** and **16**), ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 8.64 (1H, s), 7.71 (1H, d, J = 12 Hz), 4.52–4.30 (4H, m), 4.18–4.10 (3H, m), 3.62–3.57 (1H, m), 3.43–3.32 (2H, m), 2.52 (3H, s), 2.28–2.24 (1H, m), 2.01–1.98 (1H, m), 1.61 (3H, d, J = 6 Hz), 1.25 (3H, t, J = 7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ_{ppm}: 177.13, 167.04, 157.61, 153.83 (d, J = 259 Hz), 144.65, 140.11, 132.19 (d, J = 14 Hz), 124.60, 121.24, 108.01, 105.23 (d, J = 24 Hz), 69.70, 68.28, 57.55, 55.47, 47.62, 46.40, 33.52, 30.98, 18.30, 14.57. MS-ESI (m/z): 433 $(M+H)^+$. HRMS-ESI (m/z): Calcd for $C_{21}H_{26}O_5N_4F$ $(M+H)^+$: 433.1881; Found 433.1889. Compound **19b4** (from **11b** and **17**), ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 8.79 (1H, s), 7.93 (1H, d, J = 12 Hz), 4.35 (1H, d, J = 15 Hz), 4.19 (1H, d, J = 15 Hz), 4.13 (2H, q, J = 7 Hz), 4.00–3.98 (1H, m), 3.67–3.62 (1H, m), 3.47–3.41 (2H, m), 2.49 (3H, s), 2.29–2.24 (1H, m), 1.95–1.88 (1H, m), 1.33–1.24 (5H, m), 1.22–1.18 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ_{ppm}: 176.82, 165.29, 153.10 (d, J = 250 Hz), 150.18, 149.33, 145.33 (d, J = 247 Hz), 132.44, 126.30, 121.08, 107.45, 106.78, 68.40, 61.83, 43.63, 42.31, 34.74, 33.70, 30.26, 14.51, 7.42. MS-ESI (m/z): 435 $(M+H)^+$. HRMS-ESI (m/z): Calcd for $C_{21}H_{25}O_4N_4F_2$ $(M+H)^+$: 435.1838; Found 435.1846. Compound **19c2** (from **11c** and **15**), ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 8.82 (1H, s), 7.88 (1H, d, J = 12 Hz), 4.68 (1H, d, J = 15 Hz), 4.04–3.98 (1H, m), 3.89 (3H, s), 3.88–3.79 (1H, m), 3.74 (3H, m), 3.70–3.61 (1H, m),3.52–3.41 (2H, m), 2.39–2.34 (1H, m), 1.99–1.90 (1H, m), 1.24–1.19 (2H, m), 1.06–1.01 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ_{ppm}: 177.07, 166.58, 158.37, 155.91 (d, J = 250 Hz), 150.08, 146.38, 138.39, 133.66, 121.65, 108.13 (d, J = 23 Hz), 107.90, 62.35, 62.19, 50.22, 46.49, 40.58, 33.29, 32.53, 9.46, 9.40. MS-ESI (m/z): 419 $(M+H)^+$. HRMS-ESI (m/z): Calcd for $C_{20}H_{24}O_5N_4F$ $(M+H)^+$: 419.1725; Found 419.1732. Compound **19c3** (from **11c** and **16**), ^{1}H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 8.63 (1H, s), 7.77 (1H, d, J = 12 Hz), 4.53–4.40 (4H, m), 3.87 (3H, s), 3.80–2.93 (4H, m), 2.40–2.01 (2H, m), 1.62 (3H, d, J = 6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ_{ppm}: 176.48, 166.35, 155.48 (d, J = 248 Hz), 152.68, 144.20, 139.47, 134.09, 128.64, 121.29, 108.15, 107.90, 69.58, 57.48, 47.87, 46.01, 40.14, 33.92, 31.77, 14.54. MS-ESI (m/z): 404 $(M+H)^+$. HRMS-ESI (m/z): Calcd for $C_{19}H_{22}O_5N_4F$ $(M+H)^+$: 405.1574; Found 405.1576.

18. Performance standards for antimicrobial susceptibility testing: 17th informational supplement, Clinical and Laboratory Standards Institute, Wayne, PA, 2007, M100eS17.