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Synthesis, antimycobacterial and antibacterial activity of 1-[(1*R*,2*S*)-2-fluorocyclopropyl]naphthyridone derivatives containing an oxime-functionalized pyrrolidine moiety

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ABSTRACT

A series of novel 1-[(1*R*,2*S*)-2-fluorocyclopropyl]naphthyridone derivatives **21–24** containing an oxime-functionalized pyrrolidine moiety were designed, synthesized and evaluated for their biological activity. Our results reveal that compounds **21a**, **21e** and **21j** show considerable activity against MTB H37Rv ATCC 27294 (MICs: <0.25 μg/mL) and MDR-MTB 6133 (MICs: 0.03–0.054 μg/mL). The target compounds **21–24** are generally poor against the Gram-negative strains, but **21a–j** and **22a–c** have potent potency (MICs: <0.008–32 μg/mL) against all of the tested Gram-positive strains including MRSA and MRSE with a few exceptions, and the most active compounds **21d**, **21e** and **22a–c** (MICs: <0.008–32 μg/mL) were found to be comparable to or better than moxifloxacin, and 2–>250 times more potent than ciprofloxacin and levofloxacin.

Since the discovery of norfloxacin in 1970s, fluoroquinolone (FQ) agents have played an important role in treatment of bacterial infections and have saved countless millions of lives. Targeting two type II bacterial topoisomerase enzymes, DNA gyrase and topoisomerase IV, FQs show their potent bactericidal activity by forming ternary complexes of enzyme–DNA–drug and consequently blocking bacterial replication.[1] However, FQ resistance increases in almost all Gram-negative and Gram-positive species as well as *Mycobacterium tuberculosis* (MTB), due mainly to the high level of use and to some degree of abuse.[2,3] The ideal strategy to such challenges is to find novel agents that inhibit new targets in pathogens, but it now remains extremely difficult. A more practical approach is to modify the structures of existing antibacterial agents to increase potency and to overcome resistance.[4]

Structure activity relationship (SAR) studies of FQs show that it appears evidently that the substituent at C-7 position, the only area that substitution of bulky functional group is permitted, plays an important role in the antibacterial potency, antibacterial spectrum and toxicity of FQs.[5] The presence of five- or six-membered nitrogen heterocycle including pyrrolidine, piperazine and piperidine at this position is a particularly favorable structural feature of important FQs on the market.[6] Moreover, methyloxime-functionalized pyrrolidines/piperidines as novel C-7 substituents have also been proved to be of importance with respect to biological activity and led to the discovery of some new FQ agents, such as gemifloxacin, zabofloxacin (DW224a), DW286 and IMB-070593.[7–10]

As a part of an ongoing program to optimize FQs against bacterial pathogens and MTB, we recently have focused our attention on exploring the effect of introducing an oxime group into side chains at the C-7 position of FQs, and some of them were found to have considerable biological activity.[10–13] For example, a series of 1-[(1*R*,2*S*)-2-fluorocyclopropyl] FQ derivatives containing an oxime-functionalized azetidine, pyrrolidine or piperidine moiety were just synthesized in our lab, and IMB-1402 (Fig. 1) was found

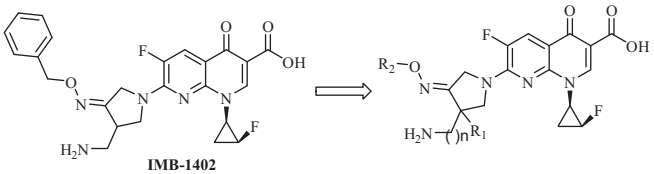

Figure 1. Design of the novel naphthyridone derivatives.

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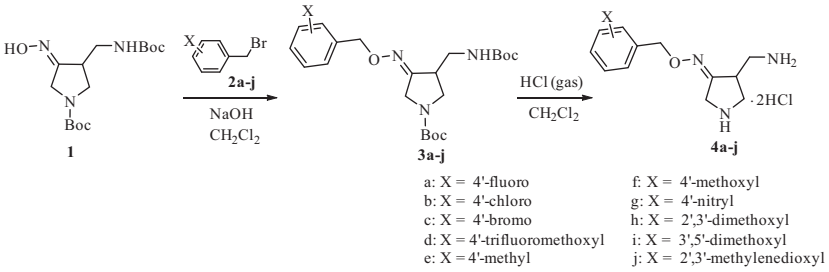
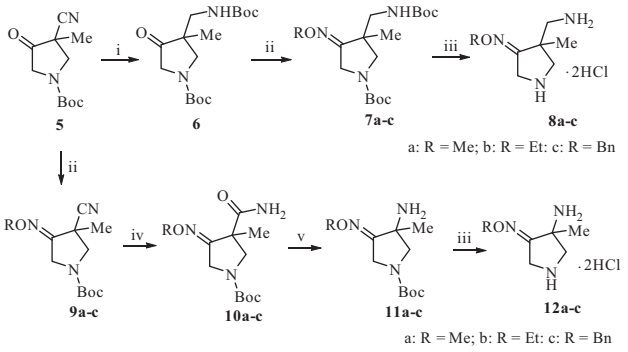


Scheme 1. Synthesis of pyrrolidine derivatives **4a**–**j**.



Scheme 2. Synthesis of pyrrolidine derivatives **8a**–**c** and **12a**–**c**.

to possess excellent in vitro activity against all of the tested Gram-positive strains including methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE) and MTB including multi-drug resistant MTB (MDR-MTB).[2] However, given that only a methyloxime and an ethyloxime analogs of IMB-1402 were synthesized in our previous work,[2] we intended to introduce various related oxime-functionalized pyrrolidine side chains at the C-7 position of IMB-1402. Thus, a series of novel 1-[(1*R*,2*S*)-2-fluorocyclopropyl]naphthyridone derivatives with an 3-aminomethyl-4-substituted benzyloxyiminopyrrolidyl, 3-alkoxyimino-4-aminomethyl-4-methylpyrrolidyl, 3-alkoxyimino-4-amino-4-methylpyrrolidyl or 3-alkoxyimino-4-aminopyrrolidyl group at the C-7 position were designed, synthesized and evaluated for their biological activity in this study (Fig. 1). Our primary objective was to optimize the potency of these naphthyridones against clinically important pathogens (especially Gram-positive ones) and MTB including MDR-MTB. A preliminary SAR study is also explored to facilitate the further development of FQs.

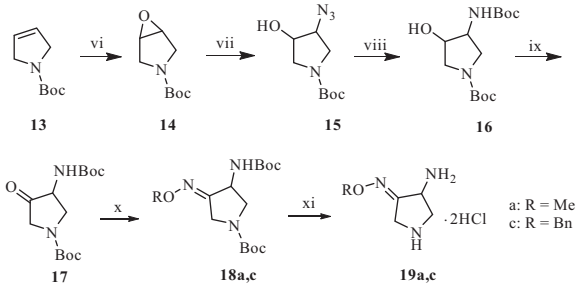
Detailed synthetic pathways to new pyrrolidine derivatives **4a**–**j**, **8a**–**c**, **12a**–**c**, **19a**,**c** and target compounds **21**–**24** are depicted in Schemes 1–4, respectively. Pyrrolidine derivatives containing various substituted benzyl groups **4a**–**j** were easily obtained via condensation of 3-hydroxyiminopyrrolidine **1** and bromomethylbenzenes **2a**–**j** and then removement of the bis-Boc-protecting groups of the resulting **3a**–**j** by pumping hydrogen chloride gas in methylene chloride (Scheme 1).[14]

Selective hydrogenation of the cyano group of N-Boc-pyrrolidinone **5**[15] by Pd/C (5%) gave the primary amine with in situ Boc protection yielded bis-Boc protected ketone **6**. Pyrrolidine derivatives **8a**–**c** were conveniently prepared via oximation of **6** and removement of the bis-Boc-protecting groups of the resulting **7a**–**c** successively (Scheme 2).[15] On the other hand, oximation of ketone **5** and then treatment of the resulting **9a**–**c** with DMSO–H_2O_2–K_2CO_3 system gave amides **10a**–**c**. Hoffmann degradation of **10a**–**c** was conducted successfully using freshly prepared sodium hypobromite instead of sodium hypochlorite to yield primary amines **11a**–**c**. The Boc protecting group on amines **11a**–**c** was removed with HCl gas in methylene chloride to afford pyrrolidine derivatives **12a**–**c** (Scheme 2).[16]

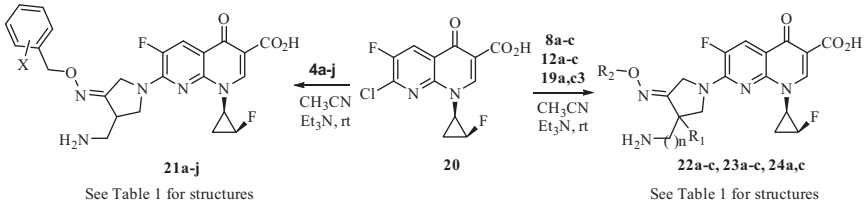
Oxidation of N-Boc-3-pyrroline **13** with *m*-chloroperoxybenzoic acid (*m*-CPBA) yielded the epoxide **14**. And the epoxide ring of **14** was smoothly opened by sodium azide in the presence of ammonium chloride in THF–H_2O. Reduction of the azide group of **15** by triphenylphosphine gave the primary amine with in situ Boc protection produced compound **16**. Pyrrolidine derivatives **19a**,**c** were obtained from the alcohol **16** via oxidation (**17**), oximation (**18a**,**c**) and deprotection successively (Scheme 3).[17]

Finally, the target compounds **21**–**24** were synthesized through direct condensation of naphthyridone carboxylic acid **20** with pyrrolidine derivatives **4a**–**j**, **8a**–**c**, **12a**–**c**, **19a**,**c** in the presence of triethylamine in acetonitrile according to well-established literature procedures (Scheme 4).[2] All of the new synthetic compounds were well characterized by ^{1}H NMR, MS and HRMS.[22]

The target compounds **21**–**24** were initially evaluated for their in vitro activity against MTB H37Rv ATCC 27294 (MTB-1) using

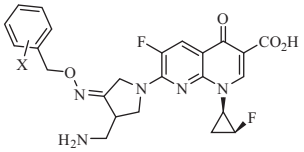


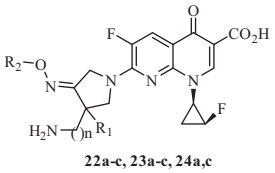
Scheme 3. Synthesis of pyrrolidine derivatives **19a**,**c**.



Scheme 4. Synthesis of naphthyridinone derivatives **21**–**24**.

Table 1
Structures, physical data and antimycobacterial activity of compounds **21**–**24**





Compd	X	Clog*P*[a]	MIC (μg/mL)		Compd	*n*	R1	R2	Clog*P*[a]	MIC (μg/mL)	
			MTB-1	MTB-2						MTB-1	MTB-2
21a	4′-Fluoro	0.75	<0.25	0.043	**22a**	1	Methyl	Methyl	−0.50	0.372	NT
21b	4′-Chloro	1.32	0.342	NT	**22b**	1	Methyl	Ethyl	0.03	0.333	NT
21c	4′-Bromo	1.47	0.375	NT	**22c**	1	Methyl	Benzyl	1.12	0.514	NT
21d	4′-Trifluoromethoxyl	1.63	0.987	NT	**23a**	0	Methyl	Methyl	−0.71	0.392	NT
21e	4′-Methyl	1.10	<0.25	0.030	**23b**	0	Methyl	Ethyl	−0.19	0.420	NT
21f	4′-Methoxyl	0.52	0.353	NT	**23c**	0	Methyl	Benzyl	0.91	0.923	NT
21g	4′-Nitryl	0.35	0.467	NT	**24a**	0	Hydrogen	Methyl	−1.23	0.867	NT
21h	2′,3′-Dimethoxyl	0.26	0.376	NT	**24c**	0	Hydrogen	Benzyl	0.39	1.921	NT
21i	3′,5′-Dimethoxyl	0.61	0.375	NT	INH					0.049	4
21j	2′,3′-Methylnenoxyl	0.57	<0.25	0.054	RFP					0.05	>40
IMB-1402	Hydrogen	0.60	0.5	0.125							

[a] The Clog*P* is calculated by Chemoffice 2010 software; INH: isoniazid; RFP: rifampicin; MTB-1: MTB H37Rv ATCC 27294; MTB-2: MDR-MTB 6133 resistant to INH and RFP. NT = not tested.

Table 2
In vitro antibacterial activity of compounds **21**–**24** against Gram-negative strains

Compd	Strains MIC (μg /mL)																
	E.coli	E.co.1	E.co.2	E.co.3	E.co.4	K.p.1	K.p.2	K.p.3	K.p.4	K.p.5	K.p.6	K.p.7	P.a.	P.a.1	P.a.2	P.a.3	P.a.4	P.a.5
21a	<0.008	8	64	64	64	8	16	64	64	>128	64	128	4	8	16	16	16	16
21b	0.125	4	32	32	32	8	8	64	128	128	64	128	4	4	8	8	8	8
21c	0.125	4	64	64	64	8	8	>128	128	128	128	128	4	8	8	8	8	16
21d	2	8	128	128	128	32	32	128	128	128	128	128	16	16	32	32	32	16
21e	<0.008	2	64	16	32	8	8	128	64	128	64	128	4	8	8	8	8	8
21f	<0.008	<0.008	64	32	32	8	8	128	128	128	128	128	4	8	8	16	8	16
21g	0.25	4	>128	128	128	8	16	128	128	128	128	128	4	4	16	16	16	16
21h	0.03	32	128	2	128	128	16	128	128	128	64	128	2	8	16	16	16	16
21i	2	4	>128	>128	>128	16	16	128	128	>128	64	>128	8	32	32	32	32	16
21j	<0.008	8	64	32	32	8	4	128	128	128	128	128	8	8	8	8	8	8
22a	0.03	4	64	32	32	4	4	128	128	>128	128	64	2	4	8	8	8	8
22b	<0.008	4	128	32	32	4	4	128	128	128	128	128	2	4	8	8	8	8
22c	0.125	8	>128	>128	>128	16	32	64	128	>128	128	>128	8	16	32	32	32	8
23a	0.5	32	>128	>128	>128	16	32	>128	>128	>128	>128	>128	8	16	32	32	32	32
23b	1	32	>128	>128	>128	32	32	128	128	>128	128	>128	16	16	32	32	32	64
23c	2	64	>128	>128	>128	128	128	>128	>128	>128	>128	>128	32	64	64	64	64	64
24a	0.25	16	>128	128	128	8	8	>128	>128	128	>128	128	4	8	8	8	8	8
24c	0.5	128	>128	>128	>128	32	32	>128	>128	>128	>128	>128	16	32	32	32	32	32
CPFX	<0.008	4	16	8	8	4	0.25	64	32	16	128	32	0.25	0.125	0.5	0.5	0.5	0.25
LVFX	0.015	2	8	4	4	4	1	64	16	8	16	8	1	1	2	2	2	2
MXFX	0.06	2	16	8	16	8	1	64	8	16	32	16	2	4	16	16	8	1

E.coli: *E. coli* ATCC 25922. E.co.1: extended-spectrum β-lactamase-producing (ESBL$^+$) *E. coli* 14-1. E.co.2: ESBL$^+$ *E. coli* 14-2. E.co.3: *E. coli* 14-1. E.co.4: *E. coli* 14-2. K.p.1: ESBL$^+$ *K. pneumoniae* 14-17. K.p.2: ESBL$^+$ *K. pneumoniae* 14-18. K.p.3: ESBL$^+$ *K. pneumoniae* 14-19. K.p.4: *K. pneumoniae* 14-1. K.p.5: *K. pneumoniae* 14-2. K.p.6: *K. pneumoniae* 14-3. K.p.7: *K. pneumoniae* 14-4. P.a.: *P. aeruginosa* ATCC 27853. P.a.1: *P. aeruginosa* 14-9. P.a.2: *P. aeruginosa* 14-14. P.a.3: *P. aeruginosa* 14-15. P.a.4: *P. aeruginosa* 14-16. P.a.5: *P. aeruginosa* 14-19. CPFX: ciprofloxacin. LVFX: levofloxacin. MXFX: moxifloxacin.

the Microplate Alamar Blue Assay (MABA).[18,19] The minimum inhibitory concentration (MIC) is defined as the lowest concentration effecting a reduction in fluorescence of ⩾90% relative to the mean of replicate bacterium-only controls and MICs of **21**–**24** along with isoniazid (INH) and rifampicin (RFP) for comparison are presented in Table 1. The data reveal that **21**–**24** have good activity against

Table 3
In vitro antibacterial activity of compounds **21**–**24** against Gram-positive strains

Compd	Strains MIC (μg/mL)																	
	S.a.	MSSA1	MSSA2	MSSA3	MSSA4	MRSA1	MRSA2	MSSE1	MRSE1	MRSE2	MRSE3	MRSE4	S.p.	E. fs. 1	E. fs. 2	E. fm. 1	E. fm. 2	E. fm. 3	E. fm. 4
21a	<0.008	4	<0.008	<0.008	<0.008	32	16	64	8	8	8	16	0.03	64	<0.008	1	2	8	8
21b	<0.008	2	<0.008	0.015	0.03	16	32	16	4	4	8	8	0.015	32	0.125	2	2	4	8
21c	<0.008	2	<0.008	0.015	<0.008	16	16	16	4	2	16	8	<0.008	32	0.125	2	2	8	16
21d	<0.008	4	0.03	0.015	0.06	16	4	16	8	8	8	8	0.015	32	0.5	4	4	8	4
21e	<0.008	2	<0.008	<0.008	0.015	8	4	8	4	2	8	16	<0.008	32	<0.008	0.5	0.5	8	4
21f	<0.008	2	<0.008	0.015	0.03	16	8	32	4	4	16	8	0.015	32	<0.008	2	2	8	8
21g	0.015	4	0.06	0.03	0.125	128	4	128	16	8	4	8	0.015	64	0.25	4	4	8	4
21h	<0.008	4	<0.008	<0.008	0.015	16	2	32	2	1	16	16	0.03	64	0.015	1	1	4	16
21i	<0.008	4	<0.008	0.015	0.015	16	8	16	4	4	16	16	0.06	16	1	2	4	8	16
21j	<0.008	4	<0.008	8	<0.008	16	8	32	4	4	6	8	0.03	16	<0.008	1	1	8	4
22a	<0.008	2	0.015	<0.008	0.015	8	4	16	2	8	8	8	0.015	32	0.125	2	2	4	8
22b	<0.008	2	<0.008	<0.008	<0.008	4	4	8	2	2	8	8	<0.008	8	0.03	2	2	4	8
22c	<0.008	2	<0.008	<0.008	<0.008	8	4	16	4	4	16	16	<0.008	32	0.25	4	4	8	8
23a	0.25	16	0.5	0.5	0.5	128	128	>128	128	32	32	64	0.25	128	2	>128	>128	>128	>128
23b	0.25	64	0.25	0.5	1	64	128	>128	64	32	32	128	0.25	128	2	>128	>128	>128	>128
23c	0.03	16	0.03	0.5	1	32	64	>128	64	32	128	64	0.5	128	2	>128	>128	>128	>128
24a	0.5	32	0.5	1	1	128	64	128	64	32	32	64	0.25	128	2	128	128	128	>128
24c	<0.008	16	<0.008	0.5	1	32	64	64	32	32	64	64	0.5	64	1	64	64	128	>128
CPFX	0.125	16	0.25	0.125	0.5	>128	16	>128	64	128	128	128	2	128	1	64	64	128	>128
LVFX	0.125	8	0.25	0.125	0.5	64	8	128	64	32	64	64	0.5	128	1	16	32	64	64
MXFX	0.06	4	0.06	<0.008	<0.008	16	8	32	32	8	8	8	0.015	32	0.5	8	16	8	8

S.a.: *S. aureus* CMCC 26003. MSSA1: methicillin-sensitive *S. aureus* 14-1. MSSA2: methicillin-sensitive *S. aureus* 14-2. MSSA3: methicillin-sensitive *S. aureus* 14-3. MSSA4: methicillin-sensitive *S. aureus* 14-4. MRSA1: methicillin-resistant *S. aureus* 14-4. MRSA2: methicillin-resistant *S. aureus* 14-5. MSSE1: methicillin-sensitive *S. epidermidis* 14-2. MRSE1: methicillin-resistant *S. epidermidis* 14-21. MRSE2: methicillin-resistant *S. epidermidis* 14-22. MRSE3: methicillin-resistant *S. epidermidis* 14-37. MRSE4: methicillin-resistant *S. epidermidis* 14-39. S.p.: *S. pneumoniae* ATCC 19615. E. fs. 1: *E. faecalis* 14-1. E. fs. 2: *E. faecalis* 14-2. E. fm. 1: *E. faecium* 14-1. E. fm. 2: *E. faecium* 14-2. E. fm. 3: *E. faecium* 14-5. E. fm. 4: *E. faecium* 14-6. CPFX: ciprofloxacin. LVFX: levofloxacin. MXFX: moxifloxacin.

this strain (MICs: <0.25–0.987 μg/mL) except for **24c**. The most active compounds **21a**, **21e** and **21j** (MICs: <0.25 μg/mL) were chosen for further evaluation their in vitro activity against MDR-MTB 6133 (MTB-2) clinical isolate which is resistant to both of INH and RFP. All of the three compounds show excellent activity against MTB-2 (MICs: 0.043, 0.03 and 0.054 μg/mL, respectively), which is much better than IMB-1402 (MIC: 0.125 μg/mL). Although it is generally believed that simply increasing the lipophilicity could improve the anti-MTB and antibacterial activity of FQs,[20] our results suggest that the lipophilicity of these compounds which is expressed in the term of their *Clog*P values (Table 1) seems not to be an important parameter affecting the anti-MTB activity.

The target compounds **21**–**24** were also evaluated for their in vitro antibacterial activity against representative strains using standard techniques.[21] Minimum inhibitory concentration (MIC) is defined as the concentration of the compound required to give complete inhibition of bacterial growth, and MICs of **21**–**24** against Gram-negative and Gram-positive strains along with ciprofloxacin (CPFX), levofloxacin (LVFX) and moxifloxacin (MXFX) for comparison, are listed in Tables 2 and 3, respectively. These data suggest that most of the target compounds **21**––**24** have considerable potency against Gram-positive strains, although they are generally less active than the three reference drugs against the Gram-negative ones. For Gram-positive strains, despite poor activity of **23**–**24**, compounds **21a**–**j** and **22a**–**c** show good activity (MICs: <0.008–32 μg/mL) against all of the tested nineteen strains including methicillin-resistant *S. aureus* (MRSA, two strains) and methicillin-resistant *S. epidermidis* (MRSE, four strains) with a few exceptions, and especially useful activity (MICs: 0.5–4 μg/mL) against CPFX-, LVFX- and MXFX-resistant *Enterococcus faecium* (two strains). Notably, compounds **21d**, **21e** and **22a**–**c** (MICs: <0.008–32 μg/mL) were found to be 2–>250 times more potent than CPFX and LVFX (MICs: 0.125–>128 μg/mL), and comparable to or better than MXFX (MICs: <0.008–32 μg/mL).

In the case of Gram-positive strains, variations (X) on the benzene ring of compounds **21a**–**j** in this study include halogen, methyl, methoxyl, trifluoromethoxyl, nitro, 2,3-/2,5-dimethoxyl and methylenedioxyl (Table 1). The activity impacted to these derivatives by X groups was in the order: 4-bromo (**21c**) ⩾ 4-chloro (**21b**) ⩾ 4-fluoro (**21a**) for halogens and 4-methyl (**21e**) ⩾ 4-trifluoromethoxyl (**21d**) ⩾ 4- methoxyl (**21f**) > 4-nitro (**21g**) for other mono-substitutions; 2,3-dimethoxyl (**21h**) ⩾ 2,5-dimethoxyl (**21i**) ⩾ methylenedioxyl (**21j**) for dimethoxyl substitutions. It is interesting that introduction of an additional methyl group at the 3-position of pyrrolidine ring of **21** while replacement the substituted benzyl moiety of **21** with a methyl, an ethyl or a benzyl group, the activity still remains (**21** vs **22**). It is also obvious that introduction an amino group instead of the aminomethyl one of **22** appears very detrimental to the activity (**22** vs **23**). Moreover, elimination of the methyl moiety at the 3-position of pyrrolidine ring of **23** does not seem to influence the activity when R_2 is a methyl group (**23a** vs **24a**), but it appears to be in favor of the activity when R_2 is a benzyl one (**23c** vs **24c**).

In summary, a series of novel 1-[(1*R*,2*S*)-2-fluorocyclopropyl]-naphthyridone derivatives containing various oxime-functionalized piperidines **21**–**24** were designed, synthesized and evaluated for their biological activity. Our results reveal that compounds **21a**, **21e** and **21j** shows considerable activity against MTB H37Rv ATCC 27294 (MICs: <0.25 μg/mL) and MDR-MTB 6133 (MICs: 0.03–0.054 μg/mL), which is much better than IMB-1402 (MICs: 0.5 and 0.125 μg/mL, respectively). On the other hand, although the target compounds **21**–**24** are generally poor against the Gram-negative strains, **21a**–**j** and **22a**–**c** have potent potency (MICs: <0.008–32 μg/mL) against all of the tested Gram-positive strains including MRSA and MRSE with a few exceptions, and the most active compounds **21d**, **21e** and **22a**–**c** (MICs: <0.008–32 μg/mL) were found to be 2–>250 times more potent than CPFX and LVFX (MIC: 0.125–>128 μg/mL).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.10.027.

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22. To a solution of **13** (17 g, 0.1 mol) in dry $CHCl_3$ (80 mL) was added dropwise *m*-CPBA (19 g, 0.11 m mol) dissolved in dry $CHCl_3$ (100 mL) at 0 °C, then the mixture was stirred for 16 h at room temperature. The reaction mixture was quenched with saturated $Na_2S_2O_3$ and $NaHCO_3$, the organic layer was washed with saturated brine (100 mL), filtrated and dried with anhydrous Na_2SO_4, concentrated under reduced pressure to get crude product **14** as a light yellow oil, which was used directly without further purification. To a solution of the above crude product **14** in THF–H_2O = 4:1 (100 mL) was added NH_4Cl (5.3 g, 0.1 mol) and NaN_3 (7.15 g, 0.11 mol). The reaction mixture was stirred for 4 h at 50 °C, then the mixture was added water (100 mL) and extracted with EtOAc (100 mL × 3), the organic layer was washed with saturated brine (100 mL), filtrated and dried with anhydrous Na_2SO_4, concentrated under reduced pressure to get crude product **15** as a yellow oil. To a solution of the above crude product **15** in THF (100 mL) was added Ph_3P (29.0 g, 0.11 mol). The reaction mixture was stirred for 2 h at 60 °C, then the mixture was added water (20 mL), $(Boc)_2O$ (44 g, 0.2 mol) and $NaHCO_3$ (12.6 g, 0.15 mol). Then the mixture was stirred for 16 h at room temperature. The mixture was added water (100 mL) and extracted with EtOAc (100 mL × 3), the organic layer was washed with saturated brine (100 mL), filtrated and dried with anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography to get **16** (22.3 g, 74% for three steps) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.72 (s, 1H), 4.30–4.24 (m, 1H), 3.96 (s, 1H), 3.88–3.62 (m, 2H), 3.38–3.15 (m, 2H), 1.39 (s, 18H).

To a solution of Py-SO_3 (23.8 g, 0.15 mol) in CH_2Cl_2 (100 ml) was added Et_3N (21 mL, 0.15 mol) at 0 °C. Then the reaction mixture was added DMSO (11 mL, 0.15 mol) in small portion and stirred for 0.5 h and then compound **16** was added. The reaction mixture was stirred for 2 h at room temperature. The mixture was added water (100 mL) and extracted with (100 mL × 3), the organic layer was washed with saturated brine (100 mL), filtrated and dried with anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography to get **17** (4.5 g, 19%) as a white solid. To a solution of *O*-methylhydroxylamine hydrochloride (0.17 g, 2.0 mmol) in methanol (20 mL) was added pyridine (0.16 g, 2.0 mmol), and the mixture stirred at room temperature for 30 min. Compound **17** (0.50 g, 1.7 mmol) was added to the mixture, stirred at 50 °C for 3 h. The reaction mixture was concentrated under reduced pressure and diluted with H_2O (10 mL), extracted with CH_2Cl_2 (10 mL × 3), the organic layer was washed with saturated brine (10 mL), filtrated and dried with anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography to get **18a** (0.502 g, 91.6%) as a colorless oil. Compound **18c** (yield: 63%) was obtained as a colorless oil as the same synthesis route of compound **18a**. To a solution of **18a**,**c** (1.2 mmol) in CH_2Cl_2 (10 mL) was pumped dried hydrochloride gas at room temperature for 30 min. The 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 under vacuum to afford compounds **19a**,**c** (35%, 30% respectively) as white solids.

A mixture of **20** (0.30 g, 1 mmol), pyrrolidine derivatives **4a–j**,[14] **8a–c**,[15] **12a–c**[16] and **19a**,**c** (1.1 mmol) and triethylamine (0.42 mL, 3 mmol) in dry acetonitrile (10 mL) was stirred for 2 h at room temperature under an atmosphere of nitrogen, and concentrated under reduced pressure. The residue was dissolved in 5% NaOH (5 mL) and stirred for 1 h, then filtrated, the filtrate was adjusted to pH 6.5–7.0 with 20% HCl, and extract with $CHCl_3$ (50 mL × 3). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. The solid was washed with ethanol and ether successively to get the targeted compounds **21a–j**, **22a–c**, **23a–c** and **24a**,**c** (38–68%) as off-white or yellow solids.

Compound **21a**, off-white solid (44.2%), mp 151–153 °C, $[\alpha]_D^{20}$ = +17.50 (*c* 0.040, CH_3OH). ^1H NMR (600 MHz, DMSO-d_6) δ: 8.67 (s, 1H), 8.01 (d, *J* = 12.6 Hz, 1H), 7.53–7.35 (m, 2H), 7.24–7.01 (m, 2H), 5.31–4.99 (m, 3H), 4.61 (s, 2H), 4.21–4.08 (m, 1H), 3.92–3.87 (m, 1H), 3.83–3.67 (m, 1H), 3.02 (s, 1H), 2.81–2.71 (m, 2H), 1.90–1.79 (m, 1H), 1.65–1.58 (m, 1H). MS-ESI (*m*/*z*): 502.39 $(M+H)^+$. HRMS-ESI (*m*/*z*): Calcd for $C_{24}H_{22}F_3N_5O_4$ $(M+H)^+$: 502.16967; Found: 502.16971. Compound **21b**, off-white solid (53.9%), mp 148–150 °C, $[\alpha]_D^{20}$ = +32.50 (*c* 0.049, CH_3OH). ^1H NMR (600 MHz, DMSO-d_6) δ: 8.67 (s, 1H), 8.02 (d, *J* = 12.6 Hz, 1H), 7.58–7.23 (m, 4H), 5.25–4.99 (m, 3H), 4.63 (s, 2H), 4.28–4.08 (m, 1H), 3.92–3.89 (m, 1H), 3.75–3.71 (m, 1H), 3.02 (s, 1H), 2.76–2.47 (m, 2H), 1.91–1.79 (m, 1H), 1.65–1.58 (m, 1H). MS-ESI (*m*/*z*): 518.20 $(M+H)^+$. HRMS-ESI (*m*/*z*): Calcd for $C_{24}H_{22}ClF_2N_5O_4$ $(M+H)^+$: 518.14011; Found: 518.14048. Compound **21c**, off-white solid (33.7%), mp 152–154 °C, $[\alpha]_D^{20}$ = −20.00 (*c* 0.023, CH_3OH). ^1H NMR (600 MHz, DMSO-d_6) δ: 8.67 (s, 1H), 8.01 (d, *J* = 12.6 Hz, 1H), 7.60–7.50 (m, 2H), 7.33–7.29 (m, 2H), 5.26–5.01 (m, 3H), 4.63 (s, 2H), 4.29–4.05 (m, 1H), 4.03–3.86 (m, 1H), 3.75–3.71 (dt, m, 1H), 3.01 (s, 1H), 2.85–2.67 (m, 2H), 1.93–1.79 (m, 1H), 1.71–1.56 (m, 1H). MS-ESI (*m*/*z*): 562.12 $(M+H)^+$. HRMS-ESI (*m*/*z*): Calcd for $C_{24}H_{22}BrF_2N_5O_4$ $(M+H)^+$: 562.09278; Found: 562.09326. Compound **21d**, off-white solid (33.7%), mp 142–143 °C, $[\alpha]_D^{20}$ = +37.50 (*c* 0.044, CH_3OH). ^1H NMR (600 MHz, DMSO-d_6) δ: 8.68 (s, 1H), 8.03 (d, *J* = 12.6 Hz, 1H), 7.62–7.44 (m, 2H), 7.43–7.24 (m, 2H), 5.45–4.99 (m, 3H), 4.64 (s, 2H), 4.28–4.12 (m, 1H), 4.03–3.82 (m, 1H), 3.78–3.66 (m, 1H), 3.07 (s, 1H), 2.94–2.72 (m, 2H), 1.88–1.81 (m, 1H), 1.65–1.58 (m, 1H). MS-ESI (*m*/*z*): 568.25 $(M+H)^+$. HRMS-ESI (*m*/*z*): Calcd for $C_{25}H_{22}F_5N_5O_5$ $(M+H)^+$: 568. 16139; Found: 568.16147. Compound **21e**, off-white solid (32.4%), mp 139–140 °C, $[\alpha]_D^{20}$ = +39.30 (*c* 0.046, CH_3OH). ^1H NMR (600 MHz, DMSO-d_6) δ: 8.69 (s, 1H), 8.02 (d, *J* = 12.5 Hz, 1H), 7.23 (dd, *J* = 21.3, 7.2 Hz, 2H), 7.14 (dd, *J* = 21.3, 7.2 Hz, 2H), 5.34–4.97 (m, 3H), 4.60 (s, 2H), 4.30–4.10 (m, 1H), 3.92–3.87 (m, 1H), 3.79–3.66 (m, 1H), 3.11 (s, 1H), 2.98–2.73 (m, 2H), 2.28 (s, 3H), 1.95–1.79 (m, 1H), 1.65–1.58 (m, 1H). MS-ESI (*m*/*z*): 498.30 $(M+H)^+$. HRMS-ESI (*m*/*z*): Calcd for $C_{25}H_{25}F_2N_5O_4$ $(M+H)^+$: 498.19474; Found: 498.19484. Compound **21f**, off-white solid (47.5%), mp 142–144 °C, $[\alpha]_D^{20}$ = +10.25 (*c* 0.049, CH_3OH). ^1H NMR (600 MHz, DMSO-d_6) δ: 8.68 (s, 1H), 8.01 (d, *J* = 12.6 Hz, 1H), 7.29 (dd, *J* = 11.9, 9.1 Hz, 2H), 6.90 (dd, *J* = 11.9, 9.1 Hz, 2H), 5.27–4.98 (m, 3H), 4.58 (s, 2H), 4.26–4.10 (m, 1H), 3.92–3.85 (m, 1H), 3.81–3.66 (m, 4H), 3.03 (s, 1H), 2.91–2.69 (m, 2H), 1.88–1.76 (m, 1H), 1.73–1.55 (m, 1H). MS-ESI (*m*/*z*): 514.25 $(M+H)^+$. HRMS-ESI (*m*/*z*): Calcd for $C_{25}H_{25}F_2N_5O_5$ $(M+H)^+$: 514.18965; Found: 514.18967. Compound **21g**, off-white solid (34.3%), mp 136–138 °C, $[\alpha]_D^{20}$ = +26.74 (*c* 0.019, CH_3OH). ^1H NMR (600 MHz, DMSO-d_6) δ: 8.71 (s, 1H), 8.20 (dd, *J* = 14.0, 8.8 Hz, 2H), 8.06 (d, *J* = 12.6 Hz, 1H), 7.61 (dd, *J* = 14.0, 8.7 Hz, 2H), 5.32–5.08 (m, 3H), 4.70 (s, 2H), 4.32–4.14 (m, 1H), 3.93–3.88 (m, 1H), 3.82–3.70 (m, 1H), 3.13 (s, 1H), 2.88–2.80 (m, 2H), 1.94–1.80 (m, 1H), 1.67–1.60 (m, 1H). MS-ESI (*m*/*z*): 529.25 $(M+H)^+$. HRMS-ESI (*m*/*z*): Calcd for $C_{24}H_{22}F_2N_6O_6$ $(M+H)^+$: 529.16417; Found: 529.16420. Compound **21h**, off-white solid (51.4%), mp 158–160 °C, $[\alpha]_D^{20}$ = −12.50 (*c* 0.016, CH_3OH). ^1H NMR (600 MHz, DMSO-d_6) δ: 8.69 (s, 1H), 8.02 (d, *J* = 12.6 Hz, 1H), 7.13–6.90 (m, 3H), 5.24–5.03 (m, 3H), 4.60 (s, 2H), 4.26–4.12 (m, 1H), 3.91–3.86 (m, 1H), 3.79 (s, 3H), 3.76–3.69 (m, 4H), 3.03 (s, 1H), 2.89–2.67 (m, 2H), 1.93–1.77 (m, 1H), 1.64–1.57 (m, 1H). MS-ESI (*m*/*z*): 544.68 $(M+H)^+$. HRMS-ESI (*m*/*z*): Calcd for $C_{26}H_{27}F_2N_5O_6$ $(M+H)^+$: 544.20022; Found: 544.20023. Compound **21i**, off-white solid (47.6%), mp 130–132 °C, $[\alpha]_D^{20}$ = −29.12 (*c* 0.011, CH_3OH). ^1H NMR (500 MHz, DMSO-d_6) δ: 8.72 (s, 1H), 8.08 (d, *J* = 12.5 Hz, 1H), 7.04–6.81 (m, 3H), 5.18–5.05 (s, 3H), 4.66 (s, 2H), 4.53–4.32 (m, 1H), 3.99–3.82 (m, 2H), 3.75–3.72 (m, 4H), 3.70 (s, 3H), 3.446–3.43 (m, 1H), 3.24–3.04 (m, 2H), 1.93–1.87 (m, 1H), 1.65–1.62 (m, 1H). MS-ESI (*m*/*z*): 544.40 $(M+H)^+$. HRMS-ESI (*m*/*z*): Calcd for $C_{26}H_{27}F_2N_5O_6$ $(M+H)^+$: 544.20022; Found: 544.20036. Compound **21j**, off-white solid (47.6%), mp 141–143 °C, $[\alpha]_D^{20}$ = +10.21 (*c* 0.020, CH_3OH). ^1H NMR (600 MHz, DMSO-d_6) δ: 8.68 (s, 1H), 8.01 (d, *J* = 12.5 Hz, 1H), 6.92 (d, *J* = 6.8 Hz, 1H), 6.90–6.70 (m, 3H), 5.98 (s, 2H), 5.13 (d, *J* = 64.6 Hz, 1H), 5.03–4.96 (m, 2H), 4.59 (s, 2H), 4.31–4.07 (m, 1H), 3.92–3.87 (m, 1H), 3.82–3.68 (m, 1H), 3.03 (s, 1H), 2.83–2.72 (m, 2H), 1.85–1.82 (m, 1H), 1.65–1.58 (m, 1H).MS-ESI (*m*/*z*): 528.37 $(M+H)^+$. HRMS-ESI (*m*/*z*): Calcd for $C_{25}H_{23}F_2N_5O_6$ $(M+H)^+$: 528.16892; Found: 528.16911. Compound **22a**, off-white solid (33.6%), mp 132–134 °C, $[\alpha]_D^{20}$ = +56.07 (*c* .086, CH_3OH). ^1H NMR (600 MHz, DMSO-d_6) δ: 8.71 (s, 1H), 8.05 (d, *J* = 12.6 Hz, 1H), 5.16 (d, *J* = 65.6 Hz, 1H), 4.63 (s, 2H), 4.25–4.18 (m, 1H), 3.78–3.60 (m, 2H), 3.40 (s, 3H), 2.75–2.69 (m, 2H), 1.93–1.80 (m, 2H), 1.65–1.63 (m, 1H), 1.2 (s, 3H) MS-ESI (*m*/*z*): 422.30 $(M+H)^+$. HRMS-ESI (*m*/*z*): Calcd for $C_{19}H_{21}F_2N_5O_4$ $(M+H)^+$: 422.16334; Found: 422.16170. Compound **22b**, off-white solid (42.5%), mp 151–153 °C, $[\alpha]_D^{20}$ = +36.49 (*c* 0.074, CH_3OH). ^1H NMR (400 MHz, DMSO-d_6) δ: 8.76 (s, 1H), 8.02 (d, *J* = 12.6, 1H), 5.17 (d, *J* = 65.7 Hz, 1H), 4.64 (s, 2H), 4.29–3.95 (m, 3H), 3.83–3.55 (m, 2H), 2.79–2.68 (m, 2H), 1.89–1.83 (m, 1H), 1.65–1.63 (m, 1H), 1.32–1.03 (m, 6H). MS-ESI (*m*/*z*): 36.35 $(M+H)^+$. HRMS-ESI (*m*/*z*): Calcd for $C_{20}H_{23}F_2N_5O_4$ $(M+H)^+$: 436.17905; Found: 436.17745. Compound **22c**, off-white solid (33.8%), mp 138–140 °C, $[\alpha]_D^{20}$ = +28.74 (*c* 0.035, CH_3OH). ^1H NMR (600 MHz, DMSO-d_6) δ: 8.68 (s, 1H), 8.03 (d, *J* = 12.5 Hz, 1H), 7.49–7.21 (m, 5H), 5.22–5.04 (m, 3H), 4.67 (s, 2H), 4.18 (m, 1H), 3.72 (m, 2H), 2.83–2.54 (m, 2H), 1.91–1.75 (m, 1H), 1.62–1.59 (m, 1H), 1.19 (s, 3H). MS-ESI (*m*/*z*): 498.27 $(M+H)^+$. HRMS-ESI (*m*/*z*): Calcd for $C_{25}H_{25}F_2N_5O_4$ $(M+H)^+$: 498.19474; Found: 498.19333. Compound **23a**, off-white solid (33.4%), mp 195–197 °C, $[\alpha]_D^{20}$ = +48.78 (*c* 0.049, CH_3OH). ^1H NMR (600 MHz, DMSO-d_6) δ: 8.72 (s, 1H), 8.11 (d, *J* = 12.5, 1H), 5.15 (d, *J* = 63.2 Hz, 1H), 4.78–4.57 (m, 2H), 4.27 (m, 1H), 4.27–4.15 (m, 1H), 3.94 (s, 3H),, 3.74 (s, 1H), 1.92–1.78 (m, 1H), 1.71–1.59 (m, 1H), 1.54 (s, 3H). MS-ESI (*m*/*z*): 408.24 $(M+H)^+$. HRMS-ESI (*m*/*z*): Calcd for $C_{18}H_{19}F_2N_5O_4$ $(M+H)^+$: 408.14779; Found: 408.14784. Compound **23b**, off-white solid (42.6%), mp 171–173 °C, $[\alpha]_D^{20}$ = +32.17 (*c* 0.049, CH_3OH). ^1H NMR (600 MHz, DMSO-d_6) δ: 8.72 (s, 1H), 8.06 (d, *J* = 12.6 Hz, 1H), 5.15 (d, *J* = 64.6 Hz, 1H), 4.86–4.52 (m, 2H), 4.11 (q, *J* = 7.0 Hz, 2H), 4.02–3.96 (m, 1H), 3.89–3.64 (m, 2H), 1.89–1.85 (m, 1H), 1.73–1.55 (m, 1H), 1.40 (s, 3H), 1.23 (t, *J* = 7.0 Hz, 3H). MS-ESI (*m*/*z*): 422.31 $(M+H)^+$. HRMS-ESI (*m*/*z*): Calcd for $C_{19}H_{21}F_2N_5O_4$ $(M+H)^+$: 422.16344; Found: 422.16366. Compound **23c**, off-white solid (47.4%), mp 172–174 °C, $[\alpha]_D^{20}$ = +32.50 (*c* 0.032, CH_3OH). ^1H NMR (500 MHz, DMSO-d_6) δ: 8.73 (s, 1H), 8.10 (d, *J* = 12.6 Hz, 1H), 7.49–7.23 (m, 5H), 5.37–5.04 (m, 3H), 4.88–4.62 (m, 2H), 4.31–4.28 (m, 1H), 3.99–3.94 (m, 1H), 3.79–3.61 (m, 1H), 1.94–1.79 (m, 1H), 1.72–1.57 (m, 1H), 1.54 (s, 3H). MS-ESI (*m*/*z*): 484.21 $(M+H)^+$. HRMS-ESI (*m*/*z*): Calcd for $C_{24}H_{23}F_2N_5O_4$ $(M+H)^+$: 484.17909; Found: 484.17922. Compound **24a**, off-white solid (52.8%), mp 163–165 °C, $[\alpha]_D^{20}$ = +37.70 (*c* 0.051, CH_3OH). ^1H NMR (600 MHz, DMSO-d_6) δ: 8.70 (s, 1H), 8.20–7.93 (d, *J* = 12.6 Hz, 1H), 5.15 (d, *J* = 64.3 Hz, 1H), 4.60–4.53 (m, 2H), 4.32–4.08 (m, 2H), 3.96–3.80 (m, 3H), 3.74 (s, 1H), 1.96–1.82 (m, 1H), 1.61–1.58 (m, 1H). MS-ESI (*m*/*z*): 394.20 $(M+H)^+$. HRMS-ESI (*m*/*z*): Calcd for $C_{17}H_{17}F_2N_5O_4$ $(M+H)^+$: 394.13214; Found: 394.13043. Compound **24c**, yellow solid (33.4%), mp 143–145 °C, $[\alpha]_D^{20}$ = +30.30 (*c* 0.046, CH_3OH). ^1H NMR (500 MHz, DMSO-d_6) δ: 8.75 (s, 1H), 8.14 (d, *J* = 12.5 Hz, 1H), 7.45–7.29 (m, 5H), 5.38–4.99 (m,3H), 4.76–4.72 (m, 1H), 4.66 (m, 2H), 4.43–4.26 (m, 1H), 4.27–4.08 (m, 1H), 3.75 (s, 1H), 1.99–1.81 (m, 1H), 1.76–1.57 (m, 1H). MS-ESI (*m*/*z*): 470.32 $(M+H)^+$. HRMS-ESI (*m*/*z*): Calcd for $C_{23}H_{21}F_2N_5O_4$ $(M+H)^+$: 470.16344; Found: 470.16397.