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Original article

Synthesis and *in vitro* antibacterial activity of gemifloxacin derivatives containing a substituted benzyloxime moiety

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ABSTRACT

A series of novel gemifloxacin (GMFX) derivatives containing a substituted benzyloxime moiety with remarkable improvement in lipophilicity were synthesized. The target compounds evaluated for their *in vitro* antibacterial activity against representative strains. Our results reveal that most of the target compounds have considerable potency against all of the tested Gram-positive strains including MRSA and MRSE (MIC: <0.008–8 μg/mL), although they are generally less active than the references against the Gram-negative strains. In particular, compound **11l** (MIC: <0.008–4 μg/mL) was found to be 8–2048 and 2–128 times more potent than levofloxacin (LVFX) and GMFX against the Gram-positive strains, respectively. Moreover, against MRSA clinical isolates, **11l** (MIC_{90}: 1 μg/mL) is 8-fold more active than GMFX, and 2-fold more active than GMFX and moxifloxacin against MRSE clinical isolates (MIC_{90}: 4 μg/mL).

1. Introduction

Quinolones, one of the largest classes of antimicrobial agents [1], have been used to treat respiratory tract infections (RTI), urinary tract infections (UTI), sexually transmitted diseases (STD), gastrointestinal and abdominal infections, skin and soft tissue infections and infections of the bone and joints [2]. These antibacterial agents exert their effect by inhibition of two type II bacterial topoisomerase enzymes, DNA gyrase (topoisomerase II) and topoisomerase IV [3,4].

Although the fluoroquinolones currently on the market or under development are generally characterized by a broad antibacterial spectrum, their activity against clinically important Gram-positive pathogens including *staphylococci*, *streptococci*, and *enterococci*, is relatively moderate [5]. Moreover, extensive use and even misuse of fluoroquinolones have brought increasing quinolone resistance to many Gram-positive strains including methicillin-resistant *Staphylococcus aureus* (MRSA) and Gram-negative ones including *Pseudomonas aeruginosa* [6,7]. Thus, there is an urgent need for the discovery and development of new quinolones that can provide improved Gram-positive antibacterial activity, while retaining the good Gram-negative activity of early fluoroquinolones, such as ciprofloxacin [8,9]. Clearly, a more practical strategy is to modify the structures of existing fluoroquinolone agents to increase potency and overcome resistance.

Structure–activity relationship (SAR) studies of fluoroquinolones have indicated that the basic group at the C-7 position, the only an area that substitution of bulky functional group is permitted, greatly influences their antibacterial potency, spectrum and safety [10,11]. It is generally believed that the action of fluoroquinolones increases with an increase in lipophilicity [12]. A large number of existing fluoroquinolone derivatives were synthesized by introduction of an additional functional moiety on the primary or second amino group of the C-7 side chain to increase the lipophilicity, and some of which were found to be stronger antibacterial activity than the corresponding parent fluoroquinolones [13–17]. Moreover, several cephalosporin derivatives possessing a substituted benzyloxime moiety in the C-7 position, such as GR69153 [18], LB10522 [19] and RU-59863 [20], show superior antibacterial activity to the corresponding methyloxime analogs against some bacteria.

Inspired by those research results, we decided to make structural modifications on gemifloxacin (GMFX, Fig. 1), a new fluoroquinolone antibacterial agent possessing extremely potent activity against Gram-positive organisms, and an excellent *in vivo* and *in vitro* efficacy and pharmacokinetic profile [21], by

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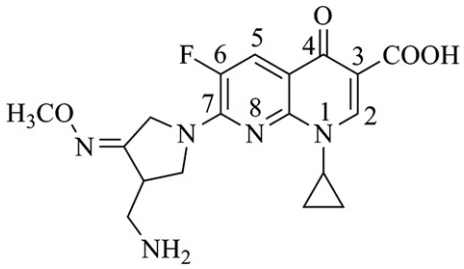


Fig. 1. Chemical structure of gemifloxacin.

introduction of diversified more lipophilic benzyloximes instead of methyloxime of the pyrrolidine ring (Fig. 1) in this study. Our primary object was to optimize the antibacterial (especially Gram-positive bacteria) potency of GMFX.

2. Results and discussion

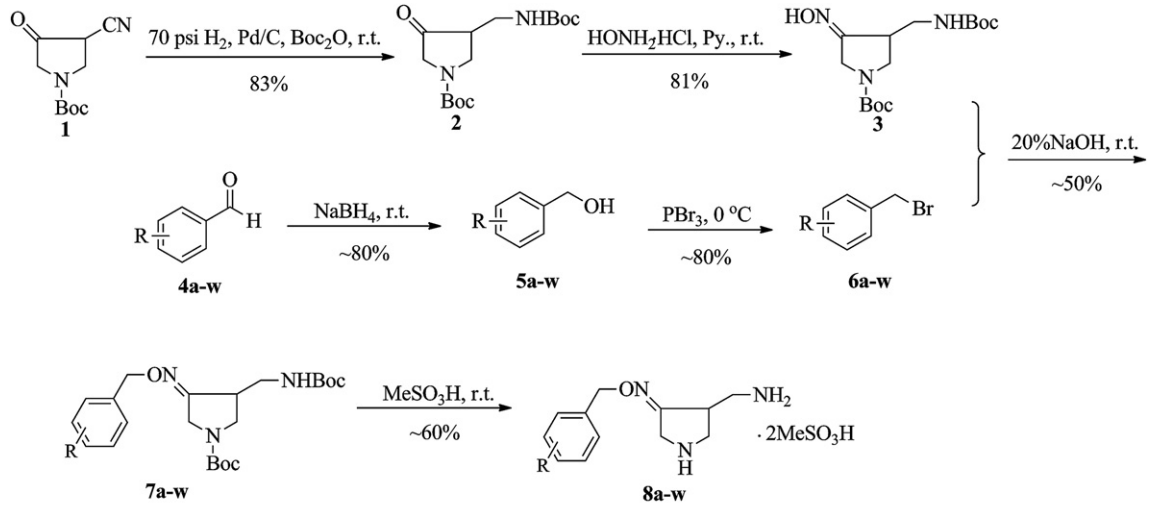
2.1. Chemistry

The new pyrrolidines **8a**–**w** and novel GMFX derivatives **11a**–**w** described herein were synthesized as shown in Schemes 1 and 2, respectively. Catalytic hydrogenation of 4-cyano-1-*N*-*tert*-butoxycarbonyl-pyrrolidin-3-one **1** [22] in methanol employing Boc_2O as an *in situ* protecting agent gave the bis-Boc-protected ketone **2** in 83% yield. The ketone **2** was smoothly converted to the free oxime **3** by reaction with *O*-hydroxyamine hydrochloride in the presence of pyridine in good yield (81%) [23].

On the other hand, reduction of various benzaldehydes **4a**–**w** with sodium borohydride in methanol produced the corresponding phenylmethanols **5a**–**w**, and then nucleophilic substitution of **5a**–**w** with phosphorus tribromide in methylene dichloride yielded the corresponding (bromomethyl)benzenes **6a**–**w**. The resulting bromides **6a**–**w** were reacted with the above oxime **3** in 20% NaOH solution to give the benzyloximes **7a**–**w**, which were then treated with methanesulfonic acid in ethanol to afford the pyrrolidine derivatives **8a**–**w** followed well-established literature procedures (Scheme 1) [23].

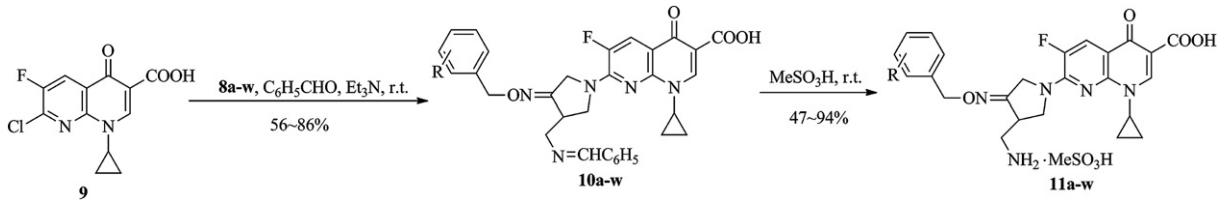
Direct condensation of 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid **9** with the various pyrrolidine derivatives **8a**–**w** according to the routine synthesis of fluoronaphthyridone agents (GMFX, tosufloxacin) [24,25], did not yield the desired products **11a**–**w** in an acceptable yield. This was partly due to the fact that both the primary and second amino groups of **8a**–**w** could attack the fluoronaphthyridone core **9**, simultaneously. Therefore, the primary amino group of **8a**–**w** was protected as its benzaldehyde imine derivatives, and subsequently condensation with **9** in the presence of triethylamine gave compounds **10a**–**w**. Finally, the condensates **10a**–**w** were treated with methanesulfonic acid to give the target GMFX derivatives **11a**–**w** (Scheme 2).

Since the oxime group can exist in the *E* or *Z* configuration, it was necessary to determine the geometries of all the oxime target compounds **11a**–**w**. Preparing X-ray quality single crystals of any oxime intermediate or product met with no success in this study, but the oxime geometry would be expected to have the *Z* configuration, like GMFX [24]. It is also obvious that the target compounds **11a**–**w** and intermediates **8a**–**w** are all racemates.



a: R = 3',4'-methylenedioxyl
b: R = 3',4',5'-trimethoxyl
c: R = 3',4'-dimethoxyl-2'-nitro
d: R = 3',4'-dimethoxyl
e: R = 4'-benzyloxyl-3'-methoxyl
f: R = 2',4'-dimethoxyl
g: R = 2'-chloro-3',4'-dimethoxyl
h: R = 2',3'-dimethoxyl
i: R = 3',4'-dimethoxyl-6'-nitro
j: R = 6'-bromo-3',4'-dimethoxyl
k: R = 3',4'-dimethoxyl-6'-fluoro
l: R = 2',5'-dimethoxyl
m: R = hydrogen
n: R = 4'-methoxyl
o: R = 5-'chloro-3',4'-dimethoxyl
p: R = 2',3',4'-trimethoxyl
q: R = 4'-benzyloxyl
r: R = 3',4'-methylenedioxyl-6'-nitro
s: R = 2',6'-dimethoxyl
t: R = 3',4'-ethylenedioxyl
u: R = 6'-chloro-3',4'-methylenedioxyl
v: R = 3',4'-dimethyl
w: R = 4'-difluoromethoxyl-3'-methoxyl

Scheme 1. Synthesis of new pyrrolidines **8a**–**w**.



Scheme 2. Synthesis of novel gemifloxacin derivatives **11a**–**w** (R groups are equal to those in Scheme 1).

2.2. Lipophilicity

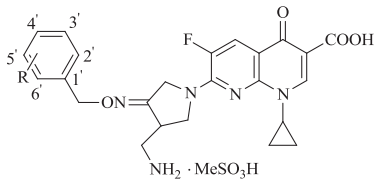
The lipophilicity of the new synthesized derivatives **11a**–**w** and the parent drug GMFX is expressed in the term of their Log *P* values which were calculated with ChemOffice 2009 software. As shown in Table 1, a remarkable improvement in the lipophilicity of the derivatives **11a**–**w** as evidenced by Log *P* values (2.03–4.13) which were much more than that of GMFX (0.80) (statistically significant at $p < 0.001$ using *t* test).

2.3. Antibacterial activity

The target compounds **11a**–**w** were evaluated for their *in vitro* antibacterial activity against representative Gram-positive and Gram-negative strains using standard techniques [26]. Minimum inhibitory concentration (MIC) is defined as the concentration of the compound required to give complete inhibition of bacterial growth, and MICs of the synthesized compounds along with the reference drugs levofloxacin (LVFX) and GMFX for comparison are reported in Tables 2 and 3. These data suggest that most of the target compounds **11a**–**w** have considerable potency against all of the tested Gram-positive strains (MIC: <0.008–8 μg/mL), although they are generally less active than LVFX and GMFX against the Gram-negative strains with few exceptions. The activity of compounds **11g**, **k**, **l**, **n**, **p**, **v**, **w** against *S. aureus* including MRSA (MIC: <0.008–2 μg/mL), compounds **11d**, **h**, **j**, **k**, **l** against *Staphylococcus epidermidis* including MRSE (MIC: <0.03–4 μg/mL), as well as compounds **11h**, **l** against *Enterococcus faecalis*, *Enterococcus faecium* and *Streptococcus pneumoniae* (MIC: <0.015–4 μg/mL) is better than the two reference drugs. In particular, compound **11l** (MIC: <0.008–4 μg/mL) was found to be 8–2048 and 2–128 times more potent than LVFX (MIC: <0.25–128 μg/mL) and the parent GMFX (MIC: <0.06–16 μg/mL) against all of the Gram-positive strains, respectively.

Compounds **11h** and **11l** with better Gram-positive activity were chosen for further evaluation their *in vitro* activity against MRSA, and then **11l** against MRSE clinical isolates. Ranges, MIC_{50}s and MIC_{90}s of **11h** and **11l** along with GMFX and moxifloxacin (MXFX) for comparison are showed in Table 4. Against MRSA clinical isolates, the MIC_{50} (1 μg/mL) and MIC_{90} (4 μg/mL) of **11h** are 2 times less than GMFX, and the MIC_{50} (0.5 μg/mL) and MIC_{90} (1 μg/mL) of **11l** are 4 and 8 times less than GMFX, respectively. Against MRSE clinical isolates, the MIC_{90} (4 μg/mL) of **11l** is 2 times less than GMFX and MXFX, although they are of the same MIC_{50} (0.25 μg/mL).

Table 1
Structures, physical data and lipophilicity of compounds **11a**–**w**.



Compd.	R	Yield (%)	Purity (%)	Mp[a] (°C)	Log *P*[b]
11a	3′,4′-Methylenedioxyl	85	95.6	215–217	2.31
11b	3′,4′,5′-Trimethoxyl	83	94.6	156–158	2.15
11c	3′,4′-Dimethoxyl-2′-nitro	51	88.5	230–231	2.31
11d	3′,4′-Dimethoxyl	93	95.4	210–212	2.27
11e	4′-Benzyloxyl-3′-methoxyl	76	100	195–197	4.01
11f	2′,4′-Dimethoxyl	89	99.8	189–191	2.27
11g	2′-Chloro-3′,4′-dimethoxyl	64	99.2	200–201	2.83
11h	2′,3′-Dimethoxyl	89	97.8	155–156	2.27
11i	3′,4′-Dimethoxyl-6′-nitro	51	97.2	233–235	2.31
11j	6′-Bromo-3′,4′-dimethoxyl	47	97.3	228–230	2.83
11k	3′,4′-Dimethoxyl-6′-fluoro	65	96.7	218–219	2.43
11l	2′,5′-Dimethoxyl	94	99.6	210–211	2.27
11m	Hydrogen	74	99.0	212	2.53
11n	4′-Methoxyl	85	96.8	218–219	2.40
11o	5′-Chloro-3′,4′-dimethoxyl	59	97.2	149–151	2.83
11p	2′,3′,4′-Trimethoxyl	82	97.1	180–182	2.15
11q	4′-Benzyloxyl	81	100	210	4.13
11r	3′,4′-Methylenedioxyl-6′-nitro	63	98.9	222–223	2.34
11s	2′,6′-Dimethoxyl	91	97.9	215	2.27
11t	3′,4′-Ethylenedioxyl	71	94.8	233	2.03
11u	6′-Chloro-3′,4′-methylenedioxyl	78	97.5	218–220	2.87
11v	3′,4′-Dimethyl	66	98.5	181–183	3.50
11w	4′-Difluoromethoxyl-3′-methoxyl	55	98.0	222–227	2.67
GMFX	–	–	–	–	0.80

GMFX, gemifloxacin.
[a] Melting points are uncorrected.
[b] The log *P* is calculated by ChemOffice 2009 software.

3. Conclusion

In summary, a series of novel GMFX derivatives were designed, synthesized and characterized by ^{1}H NMR, MS and HRMS. These derivatives were initially evaluated for their *in vitro* antibacterial activity against representative Gram-positive and Gram-negative strains. Compounds **11h** and **11l** were chosen for further evaluation their activity against MRSA, and then **11l** against MRSE clinical isolates. The results show that most of the target compounds **11a**–**w** with improved lipophilicity have considerable potency against all of the tested Gram-positive strains (MIC: <0.008–8 μg/mL), although they are generally less active than LVFX and GMFX against the Gram-negative strains. The most active compound **11l** (MIC: <0.008–4 μg/mL) was found to be 2–128 times more potent than the parent GMFX against the Gram-positive strains. This partially supports the validity of our strategy that improvement of lipophilicity could be favorable for increasing antibacterial activity of fluoroquinolones, at least for Gram-positive pathogens.

Variations (R) on the benzene ring of the benzyl moiety in this study include methyl, methoxy, difluoromethoxy, benzyloxy, 3,4-methylenedioxy/ethylenedioxy, nitro, fluoro, chloro, bromo and hydrogen substitution (Table 1). The activity imparted to GMFX derivatives by R groups against Gram-positive strains was in the order: methoxy (**11n**) > hydrogen (**11m**) > benzyloxy (**11q**) for mono-substitution; 2′,5′-dimethoxy (**11l**) > 2′,3′-dimethoxy

Table 2
In vitro antibacterial activity of compounds **11a**–**w** against Gram-positive strains.

Compd.	Strains MIC (μg/mL)																
	S.a.	MRSA1[a]	MRSA2[a]	MSSA1[a]	MSSA2[a]	MRSE1[a]	MRSE2[a]	MSSE1[a]	MSSE2[a]	MSSE3[a]	E.fa.1	E.fa.2	E.fa.3	E.fm.1	E.fm.2	S.p. 1[a]	S.p. 2[a]
11a	0.06	1	0.5	0.5	0.03	1	0.5	2	1	4	0.5	2	1	4	4	1	2
11b	0.125	2	0.25	1	0.125	2	0.5	8	2	8	1	4	2	8	8	1	8
11c	0.06	2	1	1	0.06	2	0.5	4	1	4	1	4	2	4	4	1	4
11d	0.03	0.5	0.125	0.5	0.06	0.5	0.25	2	0.5	4	0.5	2	1	4	4	0.5	4
11e	<0.008	4	0.5	4	<0.008	4	1	8	2	8	4	8	4	16	16	4	16
11f	0.06	1	0.25	1	0.06	2	0.5	4	1	4	0.5	4	2	8	8	1	4
11g	0.008	1	0.25	0.015	0.015	0.5	0.5	0.25	0.03	1	0.25	4	2	4	4	0.5	0.06
11h	0.015	1	4	0.03	0.06	0.5	0.25	0.25	0.06	4	0.25	4	1	4	4	0.125	0.06
11i	0.015	2	1	0.125	0.125	1	1	2	0.25	8	0.125	16	2	8	16	1	0.125
11j	<0.008	>128	0.125	0.03	0.5	0.5	0.25	0.5	0.03	2	1	4	2	64	64	1	0.125
11k	0.03	1	0.125	0.03	0.03	0.5	0.25	1	0.03	2	0.25	2	1	4	8	0.25	0.03
11l	<0.008	1	0.125	0.03	0.03	0.25	0.25	0.25	0.03	4	0.25	4	0.25	4	4	0.06	0.015
11m	<0.008	4	0.5	0.015	0.03	1	1	1	0.06	8	1	4	2	4	8	0.25	0.06
11n	0.015	1	0.25	0.015	0.03	0.5	0.5	0.5	0.03	2	0.125	2	1	4	8	0.125	0.125
11o	<0.008	4	0.25	0.015	0.015	2	0.25	2	0.015	4	0.25	4	2	8	16	0.06	0.03
11p	0.015	2	0.25	0.015	0.015	2	0.5	2	0.03	2	1	2	2	4	8	0.5	0.06
11q	2	4	8	1	1	4	4	1	16	4	8	32	16	32	32	2	8
11r	0.008	4	2	0.25	0.25	2	1	0.25	8	2	4	32	8	16	8	0. 5	2
11s	0.03	1	0.5	0.125	0.125	0.25	0.25	0.125	2	0.5	0.5	2	1	8	8	0.125	0.25
11t	0.06	1	0.5	0.06	0.06	0.5	0.5	0.5	2	0.5	0.5	4	1	8	8	0.5	2
11u	0.015	2	1	0.03	0.06	2	2	0.25	8	2	1	8	4	8	8	0.5	2
11v	0.008	2	0.25	0.06	<0.008	1	1	0.25	8	1	0.5	4	4	8	8	0.125	0.5
11w	0.008	2	0.5	0.06	0.03	2	4	0.25	8	4	2	8	4	8	16	0.25	2
LVFX	0.25	32	16	0.5	0.25	8	4	128	4	128	8	64	16	32	32	16	32
GMFX	0.06	4	1	0.25	0.06	2	0.5	16	1	16	1	8	2	8	8	2	2

Abbreviations: *S.a.*, *Staphylococcus aureus* ATCC259223; MRSA1, methicillin-resistant *Staphylococcus aureus* 10–11; MRSA2, methicillin-resistant *Staphylococcus aureus* 10–15; MSSA1, methicillin-sensitive *Staphylococcus aureus* 10–13; MSSA2, methicillin-sensitive *Staphylococcus aureus* 10–14; MRSE1, methicillin-resistant *Staphylococcus epidermidis* 10–10; MRSE2, methicillin-resistant *Staphylococcus epidermidis* 10–13; MSSE1, methicillin-sensitive *Staphylococcus epidermidis* 10–11; MSSE2, methicillin-sensitive *Staphylococcus epidermidis* 10–13; MSSE3, methicillin-sensitive *Staphylococcus epidermidis* 10–15; E.fa.1, *Enterococcus faecalis* 10–5; E.fa.2, *Enterococcus faecalis* 10–6; E.fa.3, *Enterococcus faecalis* 10–7; *E.fm.*1, *Enterococcus faecium* 10–5; *E.fm.*2, *Enterococcus faecium* 10–9; *S.p.*1, *Streptococcus pneumoniae* 10–1; *S.p.*2, *Streptococcus pneumoniae* 10–4.
[a] Extended spectrum beta-lactamases (ESBLs)-producing; LVFX, levofloxacin; GMFX, gemifloxacin.

(**11h**) > 3′,4′-dimethoxy (**11d**) ≈ 2′,6′-dimethoxy (**11s**) > 2′,4′-dimethoxy (**11f**) for dimethoxy substitution. It is also interesting that introduction of an electron-withdrawing group instead of an electron-donating one at the 2′-position of 3′,4′-dimethoxybenzene ring of GMFX derivative (**11d**) seems to be detrimental to the activity. In this case, for example, the relative contribution of R groups to activity is as follows: 2′,3′,4′-trimethoxy (**11p**) > 3′,4′-dimethoxy (**11d**) > 3′,4′-dimethoxy-2′-nitro (**11c**).

4. Experimental protocol

4.1. General

Melting points were determined in open capillaries and uncorrected. ^{1}H NMR spectra were determined on a Varian Mercury-400 spectrometer in DMSO-d_6 or $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. Electrospray ionization (ESI) mass spectra and high resolution mass spectra (HRMS) were obtained on a MDSSCIEX Q-Tap mass spectrometer and AccuTOF CS JMS-T100CS (JEOL) mass spectrometer, respectively. HPLC was preformed using an Agilent 1260 infinity LC with DAD detector and a Class VP 6.x workstation. The column used was an Eclipse Plus C18 reversed phase column, 3.5 μm, 4.6 × 100 mm column. HPLC was performed under the following condition: mobile phase 70/30 methanol/water containing 0.1% TFA, flow rate = 1.0 mL/min, detect wavelength = 254 nm. Unless otherwise noted, the reagents were obtained from commercial suppliers and were used without further purification. 7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro [1,8]naphthyridine-3-carboxylic acid was obtained from Zhejiang Starry Pharmaceutical Co., Ltd. TLC was performed on silica gel plates (Merck, ART5554 60F_{254}).

4.2. Synthesis

4.2.1. General procedure for the preparation of 4-aminomethyl-3-(substituted benzyloxyimino)pyrrolidine dimesylates (**8a**–**w**)

To a solution of various benzaldehydes **4a**–**w** (10 mmol) dissolved in methanol (50 mL) was added sodium borohydride (20 mmol) at room temperature, and the mixture was stirred at the same temperature for 30 min and concentrated under reduced pressure. The residue was diluted with methylene chloride (500 mL) and washed with water, and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the corresponding crude phenylmethanols **5a**–**w** (~80%) which were used directly without further purification.

To a solution of phenylmethanols **5a**–**w** (5 mmol) dissolved in methylene chloride (50 mL) in an ice-water bath was added phosphorus tribromide (5.5 mmol), and the mixture was stirred at the same temperature for 30 min. The mixture was washed with cool water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield (bromomethyl)benzenes **6a**–**w** as off-white solids or light yellow oils (~80%).

To a solution of (bromomethyl)benzenes **6a**–**w** (2 mmol) dissolved in methylene chloride (50 mL) was added 20% NaOH (10 mmol) at room temperature, and the reaction mixture was stirred at the same temperature for 5 min. The oxime **3** [23] was added to the mixture, and stirred overnight at the same temperature. The organic layer was separated and washed with water, and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel) eluted with petroleum ether and ethyl acetate (v:v = 2:1) to give benzyloximes **7a**–**w** (~50%) as colorless or light yellow oils.

Table 3
In vitro antibacterial activity of compounds **11a**–**w** against Gram-negative strains.

Compd.	Strains MIC (μg/mL)																	
	E.co.	E.co.1	E.co.2	E.co.2[a]	E.co.3	E.co.3[a]	E.co.4[a]	K.p.1[a]	K.p.2	K.p.2[a]	K.p.3	K.p.3[a]	K.p.4	P.a.1	P.a.2[a]	P.a.3[a]	P.a.4[a]	P.a.5[a]	P.a.6[a]
11a	0.125	32	2	>128	8	16	2	128	2	>128	2	128	>128	0.06	8	4	4	2	0.25
11b	0.5	128	16	>128	16	16	8	>128	>128	>128	8	>128	>128	0.125	8	8	8	4	0.5
11c	0.5	>128	8	>128	16	>128	8	>128	>128	>128	8	>128	>128	0.06	8	16	4	8	0.25
11d	0.06	16	8	>128	16	16	2	64	128	>128	4	>128	>128	0.03	2	8	1	4	0.06
11e	2	>128	16	>128	>128	>128	32	>128	>128	>128	32	>128	>128	<0.008	16	16	32	16	0.06
11f	0.125	>128	8	>128	16	32	0.25	>128	>128	>128	8	>128	>128	0.06	4	8	8	16	0.25
11g	0.25	>128	32	>128	16	>128	4	>128	>128	>128	8	>128	>128	16	16	8	32	16	16
11h	0.125	>128	16	>128	16	32	2	>128	128	>128	2	>128	>128	8	4	4	8	4	8
11i	0.25	>128	8	>128	32	>128	4	>128	>128	>128	4	>128	>128	16	16	16	32	16	32
11j	0.5	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
11k	0.125	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
11l	0.06	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
11m	0.03	16	4	32	8	32	4	32	32	64	2	32	128	4	8	2	4	1	2
11n	0.06	32	2	128	8	16	2	64	128	128	4	128	128	2	4	4	8	4	2
11o	0.015	>128	16	>128	128	>128	16	>128	128	>128	8	>128	>128	16	16	16	32	16	8
11p	0.03	64	16	128	16	32	4	>128	>128	>128	8	>128	>128	8	8	8	16	8	4
11q	4	0.03	0.25	>128	0.125	>128	0.06	>128	16	>128	2	8	>128	16	16	2	8	2	16
11r	0.008	>128	8	>128	32	32	8	>128	>128	>128	8	>128	>128	8	8	4	8	4	4
11s	0.25	>128	8	>128	8	16	4	64	>128	64	8	>128	>128	4	4	4	4	8	2
11t	0.25	16	4	>128	4	>128	2	>128	16	>128	32	4	128	2	2	2	2	4	2
11u	0.25	>128	16	128	16	>128	8	>128	>128	>128	8	>128	128	8	8	8	32	16	4
11v	0.015	64	8	>128	8	>128	8	>128	>128	>128	8	>128	>128	4	4	4	8	16	8
11w	0.06	>128	16	>128	16	>128	8	>128	>128	>128	8	>128	>128	8	8	8	32	16	8
LVFX	<0.008	4	0.25	16	4	8	1	8	32	8	1	8	32	0.25	0.25	0.25	0.5	1	0.25
GMFX	0.03	8	0.5	16	0.5	2	8	16	0.5	16	8	16	32	0.03	0.5	0.5	1	2	0.5

Abbreviations: *E.co.*, *Escherichia coli* ATCC25922; *E.co.*1, *Escherichia coli* 10−1; *E.co.*2, *Escherichia coli* 10−2; *E.co.*3, *Escherichia coli* 10−3; *E.co.*4, *Escherichia coli* 10−4; *K.*p.1, *Klebsiella pneumoniae* 10−1; *K.*p.2, *Klebsiella pneumoniae* 10−2; *K.*p.3, *Klebsiella pneumoniae* 10−3; *K.*p.4, *Klebsiella pneumoniae* 10−4; *P.a.*1, *Pseudomonas aeruginosa* 10−12; *P.a.*2, *Pseudomonas aeruginosa* 10−5; *P.a.*3, *Pseudomonas aeruginosa* 10−9; *P.a.*4, *Pseudomonas aeruginosa* 10−15; *P.a.*5, *Pseudomonas aeruginosa* 10−18; *P.a.*6, *Pseudomonas aeruginosa* 10−20.

[a] Extended spectrum beta-lactamases (ESBLs)-producing; LVFX, levofloxacin; GMFX, gemifloxacin.

Table 4
Comparative *in vitro* antibacterial activity of **11h** and **11l** against clinical isolates.[a]

Microorganism (no. of isoliates)	Compd.	MIC (μg/mL)		
		Range	MIC_{50}	MIC_{90}
MRSA (37)	**11h**	≤0.03–8	1	4
	11l	≤0.03–8	0.5	1
	GMFX	≤0.03–64	2	8
MRSE (20)	**11l**	<0.008–4	0.25	4
	GMFX	<0.008–8	0.25	8
	MXFX	<0.008–8	0.25	8

GMFX, gemifloxacin; MXFX, moxifloxacin.
MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*.
[a] The clinical isolates were collected from six hospitals in Beijing, Jiangsu and Sichuan, China, during 2009.10-2010.10.

To a solution of benzyloximes **7a**–**w** (3.9 mmol) dissolved in anhydrous ethanol (50 mL) was added methanesulfonic acid (1.0 g, 15.6 mmol) at room temperature, and the reaction mixture was stirred for overnight at the same temperature. The resulting solid was collected by suction, and dried *in vacuo* to give title compounds **8a**–**w** (~60%) as off-white or light yellow solids.

*4.2.1.1. 4-Aminomethyl-3-(3′,4′-methylenedixoybenzyloxyimino)pyrrolidine dimesylate (**8a**).* Yield: 98%, mp: 180–182 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.34 (6H, s, 2× CH_3SO_3), 3.06–4.05 (7H, m, pyrrolidine–H), 5.02 (2H, s, O$\underline{CH_2}$Ar), 6.01 (2H, s, O$\underline{CH_2}$O), 6.84–6.94 (3H, m, Ar–H), 7.89 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 9.05, 9.35 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (*m*/*z*): 264 $(M + H)^+$.

*4.2.1.2. 4-Aminomethyl-3-(3′,4′,5′-trimethxoybenzyloxyimino)pyrrolidine dimesylate (**8b**).* Yield: 88%, mp: 171–174 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.34 (6H, s, 2× CH_3SO_3), 3.04–4.05 (16H, m, pyrrolidine–H and 3× OCH_3), 5.05 (2H, s, O$\underline{CH_2}$Ar), 7.67 (2H, s, Ar–H), 7.89 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 9.06, 9.34 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (*m*/*z*): 310 $(M + H)^+$.

*4.2.1.3. 4-Aminomethyl-3-(3′,4′-dimethxoy-2′-nitrobenzyloxyimino) pyrrolidine dimesylate (**8c**).* Yield: 61%, mp: 219–221 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.35 (3H, s, CH_3SO_3), 2.32 (3H, s, CH_3SO_3), 3.04–4.16 (13H, m, pyrrolidine–H and 2× OCH_3), 5.45 (2H, d, J = 14.8 Hz, O$\underline{CH_2}$Ar), 7.09–7.67 (2H, m, Ar–H), 7.77, 7.84 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 9.25 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (*m*/*z*): 325 $(M + H)^+$.

*4.2.1.4. 4-Aminomethyl-3-(3′,4′-dimethxoybenzyloxyimino)pyrrolidine dimesylate (**8d**).* Yield: 46%, mp: 168–171 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.31 (6H, s, 2× CH_3SO_3), 3.05–4.05 (13H, m, pyrrolidine–H and 2× OCH_3), 5.04 (2H, s, O$\underline{CH_2}$Ar), 6.89–6.95 (3H, m, Ar–H), 7.85 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.97, 9.28 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (*m*/*z*): 280 $(M + H)^+$.

*4.2.1.5. 4-Aminomethyl-3-(4′-benzylxoy-3′-methxoybenzyloxyimino) pyrrolidine dimesylate (**8e**).* Yield: 49%, mp: 186–187 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.32 (6H, s, 2× CH_3SO_3), 3.05–4.05 (10H, m, pyrrolidine–H and OCH_3), 5.02, 5.06 (4H, s, 2× O$\underline{CH_2}$Ar), 6.86–7.44 (8H, m, Ar–H), 7.85 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.98, 9.29 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (*m*/*z*): 356 $(M + H)^+$.

*4.2.1.6. 4-Aminomethyl-3-(2′,4′-dimethxoybenzyloxyimino)pyrrolidine dimesylate (**8f**).* Yield: 64%, mp: 196–198 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.33 (6H, s, 2× CH_3SO_3), 3.06–4.10 (13H, m, pyrrolidine–H and 2× OCH_3), 5.06 (2H, s, O$\underline{CH_2}$Ar), 6.44–6.50 (3H, m, Ar–H), 7.87 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 9.03, 9.33 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (*m*/*z*): 280 $(M + H)^+$.

*4.2.1.7. 4-Aminomethyl-3-(2′-chloro-3′,4′-dimethxoybenzyloxyimino) pyrrolidine dimesylate (**8g**).* Yield: 85%, mp: 175–178 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.33 (6H, s, 2× CH_3SO_3), 3.04–4.05 (13H, m, pyrrolidine–H and 2× OCH_3), 5.14 (2H, s, O$\underline{CH_2}$Ar), 7.04 (1H, d, J = 8.4 Hz, Ar–H), 7.21 (1H, d, J = 8.4 Hz, Ar–H), 7.87 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 9.00, 9.33 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (*m*/*z*): 314 $(M + H)^+$, 316 $(M + H + 2)^+$.

*4.2.1.8. 4-Aminomethyl-3-(2′,3′-dimethxoybenzyloxyimino)pyrrolidine dimesylate (**8h**).* Yield: 77%, mp: 173–175 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.31 (6H, s, 2× CH_3SO_3), 3.06–4.05 (13H, m, pyrrolidine–H and 2× OCH_3), 5.13 (2H, s, O$\underline{CH_2}$Ar), 6.91–7.06 (3H, m, Ar–H), 7.85 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.98, 9.25 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (*m*/*z*): 280 $(M + H)^+$.

*4.2.1.9. 4-Aminomethyl-3-(3′,4′-dimethxoy-6′-nitrobenzyloxyimino) pyrrolidine dimesylate (**8i**).* Yield: 68%, mp: 210–212 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.31 (6H, s, 2× CH_3SO_3), 3.05–4.16 (13H, m, pyrrolidine–H and 2× OCH_3), 5.47 (2H, s, O$\underline{CH_2}$Ar), 7.09–7.77 (2H, m, Ar–H), 7.84 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 9.09, 9.35 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (*m*/*z*): 325 $(M + H)^+$.

*4.2.1.10. 4-Aminomethyl-3-(6′-bromo-3′,4′-dimethxoybenzyloxyimino) pyrrolidine dimesylate (**8j**).* Yield: 79%, mp: 193–195 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.34 (6H, s, 2× CH_3SO_3), 3.05–4.07 (13H, m, pyrrolidine–H and 2× OCH_3), 5.11 (2H, s, O$\underline{CH_2}$Ar), 7.04–7.16 (2H, m, Ar–H), 7.90 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 9.07, 9.36 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (*m*/*z*): 358 $(M + H)^+$, 360 $(M + H + 2)^+$.

*4.2.1.11. 4-Aminomethyl-3-(3′,4′-dimethxoy-6′-fluorobenzyloxyimino) pyrrolidine dimesylate (**8k**).* Yield: 26%, mp: 174–176 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.37 (6H, s, 2× CH_3SO_3), 3.06–3.68 (5H, m, pyrrolidine–H), 3.74, 3.76 (6H, s, 2× OCH_3), 3.95 (1H, q, J = 17.6 Hz, pyrrolidine–H), 5.07 (2H, s, O$\underline{CH_2}$Ar), 6.90 (1H, d, J = 11.6 Hz, Ar–H), 6.99 (1H, d, J = 7.2 Hz, Ar–H), 7.95 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 9.24 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (*m*/*z*): 298 $(M + H)^+$.

*4.2.1.12. 4-Aminomethyl-3-(2′,5′-dimethxoybenzyloxyimino)pyrrolidine dimesylate (**8l**).* Yield: 71%, mp: 166–167 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.31 (6H, s, 2× CH_3SO_3), 3.06–4.08 (13H, m, pyrrolidine–H and 2× OCH_3), 5.10 (2H, s, O$\underline{CH_2}$Ar), 6.86–6.96 (3H, m, Ar–H), 7.83 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.96, 9.29 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (*m*/*z*): 280 $(M + H)^+$.

*4.2.1.13. 4-Aminomethyl-3-benzyloxyiminopyrrolidine dimesylate (**8m**).* Yield: 61%, mp: 157–158 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.31 (6H, s, 2× CH_3SO_3), 3.05–4.08 (7H, m, pyrrolidine–H), 5.17 (2H, s, O$\underline{CH_2}$Ar), 7.30–7.40 (5H, m, Ar–H), 7.84 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.98, 9.27 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (*m*/*z*): 220 $(M + H)^+$.

*4.2.1.14. 4-Aminomethyl-3-(4′-methxoybenzyloxyimino)pyrrolidine dimesylate (**8n**).* Yield: 64%, mp: 176–178 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.32 (6H, s, 2× CH_3SO_3), 3.06–4.03 (10H, m, pyrrolidine–H and OCH_3), 5.05 (2H, s, O$\underline{CH_2}$Ar), 6.91 (2H, d, J = 8.4 Hz, Ar–H), 7.30 (2H, d, J = 8.4 Hz, Ar–H), 7.87 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 9.00, 9.32 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (*m*/*z*): 250 $(M + H)^+$.

*4.2.1.15. 4-Aminomethyl-3-(5′-chloro-3′,4′-dimethxoybenzyloxyimino) pyrrolidine dimesylate (**8o**).* Yield: 85%, mp: 175–178 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.33 (6H, s, 2× CH_3SO_3), 3.04–4.05 (13H, m, pyrrolidine–H and 2× OCH_3), 5.14 (2H, s, O$\underline{CH_2}$Ar), 7.04 (1H, d, J = 8.4 Hz, Ar–H), 7.21 (1H, d, J = 8.4 Hz, Ar–H), 7.87 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 9.00, 9.33 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (m/z): 314 $(M + H)^+$, 316 $(M + H + 2)^+$.

*4.2.1.16. 4-Aminomethyl-3-(2′,3′,4′-trimethxoybenzyloxyimino)pyrrolidine dimesylate (**8p**).* Yield: 83%, mp: 145–147 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.33 (6H, s, 2× CH_3SO_3), 3.04–4.05 (16H, m, pyrrolidine–H and 3× OCH_3), 5.09 (2H, s, O$\underline{CH_2}$Ar), 7.06 (1H, d, J = 8.4 Hz, Ar–H), 7.18 (1H, d, J = 8.4 Hz, Ar–H), 7.88 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 9.01, 9.30 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (m/z): 310 $(M + H)^+$.

*4.2.1.17. 4-Aminomethyl-3-(4′-benzylxoybenzyloxyimino)pyrrolidine dimesylate (**8q**).* Yield: 53%, mp: 153–155 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.33 (6H, s, 2× CH_3SO_3), 3.05–3.66 (5H, m, pyrrolidine–H), 3.95 (2H, q, J = 17.2 Hz, pyrrolidine–H), 5.04, 5.10 (4H, s, 2× O$\underline{CH_2}$Ar), 6.99 (2H, d, J = 8.4 Hz, Ar–H), 7.29–7.44 (7H, m, Ar–H), 7.88 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 9.14 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (m/z): 326 $(M + H)^+$.

*4.2.1.18. 4-Aminomethyl-3-(3′,4′-methylenedixoy-6′-nitrobenzyloxyimino)pyrrolidine dimesylate (**8r**).* Yield: 60%, mp: 176–178 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.31 (6H, s, 2× CH_3SO_3), 3.08–4.15 (7H, m, pyrrolidine–H), 5.18 (2H, s, O$\underline{CH_2}$Ar), 6.09 (2H, s, O$\underline{CH_2}$O), 7.10 (1H, s, Ar–H), 7.18 (1H, s, Ar–H), 7.92 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 9.08, 9.41 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (m/z): 308 $(M + H)^+$.

*4.2.1.19. 4-Aminomethyl-3-(2′,6′-dimethxoybenzyloxyimino)pyrrolidine dimesylate (**8s**).* Yield: 41%, mp: 176–178 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.33 (6H, s, 2× CH_3SO_3), 3.06–4.10 (13H, m, pyrrolidine–H and 2× OCH_3), 5.06 (2H, s, O$\underline{CH_2}$Ar), 6.44–6.50 (3H, m, Ar–H), 7.87 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 9.03, 9.33 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (m/z): 280 $(M + H)^+$.

*4.2.1.20. 4-Aminomethyl-3-(3′,4′-ethylenedixoybenzyloxyimino)pyrrolidine dimesylate (**8t**).* Yield: 72%, mp: 170–172 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.33 (6H, s, 2× CH_3SO_3), 3.06–4.04 (7H, m, pyrrolidine–H), 4.22 (4H, s, OCH_2CH_2O), 4.99 (2H, s, O$\underline{CH_2}$Ar), 6.82 (2H, s, Ar–H), 6.86 (1H, s, Ar–H), 7.87 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 9.01, 9.32 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (m/z): 278 $(M + H)^+$.

*4.2.1.21. 4-Aminomethyl-3-(6′-chloro-3′,4′-methylenedixoybenzyloxyimino)pyrrolidine dimesylate (**8u**).* Yield: 65%, mp: 187–188 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.31 (6H, s, 2× CH_3SO_3), 3.04–4.09 (7H, m, pyrrolidine–H), 5.10 (2H, s, O$\underline{CH_2}$Ar), 6.08 (2H, s, O$\underline{CH_2}$O), 7.05 (1H, s, Ar–H), 7.11 (1H, s, Ar–H), 7.91 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 9.10, 9.40 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (m/z): 298 $(M + H)^+$, 300 $(M + 2 + H)^+$.

*4.2.1.22. 4-Aminomethyl-3-(3′,4′-dimethylbenzyloxyimino)pyrrolidine dimesylate (**8v**).* Yield: 59%, mp: 185–187 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.20 (6H, s, 2× CH_3), 2.34 (6H, s, 2× CH_3SO_3), 3.05–4.04 (7H, m, pyrrolidine–H), 5.04 (2H, s, O$\underline{CH_2}$Ar), 7.06–7.12 (3H, m, Ar–H), 7.88 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 9.10 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (m/z): 248 $(M + H)^+$.

*4.2.1.23. 4-Aminomethyl-3-(4′-difluoromethxoy-3′-methxoybenzyloxyimino)pyrrolidine dimesylate (**8w**).* Yield: 58%, mp: 145–147 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 2.34 (6H, s, 2× CH_3SO_3), 3.06–3.72 (5H, m, pyrrolidine–H), 3.83 (3H, s, OCH_3), 4.01 (2H, q, J = 7.6 Hz, pyrrolidine–H), 5.11 (2H, s, O$\underline{CH_2}$Ar), 6.96 (1H, d, J = 8.0 Hz, Ar–H), 7.05 (1H, t, J = 74.4 Hz, $OCHF_2$), 7.14–7.16 (2H, m, Ar–H), 7.89 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 9.08, 9.24 (2H, s, D_2O exchangeable, $SO_3H_2^+N$). ESI-MS (m/z): 316 $(M + H)^+$.

*4.2.2. General procedure for the synthesis of 7-[3-(benzylideneamino) methyl-4-(substituted benzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids (**10a**–**w**)*

A mixture of compounds **8a**–**w** (1.5 mmol), benzaldehyde (0.18 mL, 1.8 mmol) and dried acetonitrile (15 mL) was stirred at room temperature under an atmosphere of nitrogen for 30 min. Dry triethylamine (11.5 mL, 80 mmol) was added to the reaction mixture and stirred for 3 h at the same temperature. To the reaction mixture was added 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid (**9**, 0.38 g, 1.35 mmol) and stirred at the same temperature under an atmosphere of nitrogen overnight. The reaction mixture was cooled with ice, and the resulting solids were collected by suction, and dried *in vacuo* to give the title compounds as off-white or pale yellow solids.

*4.2.2.1. 7-[3-(Benzylideneamino)methyl-4-(3′,4′-methylenedixoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10a**).* Yield: 75%, mp: 101–103 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.01–1.10 (4H, m, 2× cyclopropylCH$_2$), 3.41–4.60 (8H, m, pyrrolidine–H and cyclopropylCH), 5.02 (2H, s, O$\underline{CH_2}$Ar), 5.99 (2H, s, OCH_2O), 6.85–8.55 (11H, m, Ar–H and N=CH). ESI-MS (m/z): 598 $(M + H)^+$.

*4.2.2.2. 7-[3-(Benzylideneamino)methyl-4-(3′,4′,5′-trimethxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10b**).* Yield: 70%, mp: 93–95 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 0.99–1.10 (4H, m, 2× cyclopropylCH$_2$), 3.41–4.64 (17H, m, pyrrolidine–H, cyclopropylCH and 3× OCH_3), 5.10 (2H, s, O$\underline{CH_2}$Ar), 6.69–8.54 (10H, m, Ar–H and N=CH), 15.27 (1H, s, D_2O exchangeable, COOH). ESI-MS (m/z): 644 $(M + H)^+$, 666 $(M + Na)^+$.

*4.2.2.3. 7-[3-(Benzylideneamino)methyl-4-(3′,4′-dimethxoy-2′-nitrobenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10c**).* Yield: 74%, mp: 133–134 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.02–1.19 (4H, m, 2× cyclopropylCH$_2$), 3.41–4.70 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_3), 5.47 (2H, s, O$\underline{CH_2}$Ar), 7.13–8.83 (10H, m, Ar–H and N=CH), 15.28 (1H, s, D_2O exchangeable, COOH). ESI-MS (m/z): 659 $(M + H)^+$, 681 $(M + Na)^+$.

*4.2.2.4. 7-[3-(Benzylideneamino)methyl-4-(3′,4′-dimethxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10d**).* Yield: 65%, mp: 160 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 0.98–1.09 (4H, m, 2× cyclopropylCH$_2$), 3.42–4.60 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_3), 5.08 (2H, s, O$\underline{CH_2}$Ar), 6.86–8.55 (11H, m, Ar–H and N=CH), 15.28 (1H, s, D_2O exchangeable, COOH). ESI-MS (m/z): 614 $(M + H)^+$, 636 $(M + Na)^+$, 652 $(M + K)^+$.

*4.2.2.5. 7-[3-(Benzylideneamino)methyl-4-(4′-benzylxoy-3′-methxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10e**).* Yield: 86%, mp: 172–173 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.01–1.09 (4H, m, 2× cyclopropylCH$_2$), 3.41–4.60 (11H, m, pyrrolidine–H, cyclopropylCH and OCH_3), 5.11 (4H, s, 2× O$\underline{CH_2}$Ar), 6.89–8.55 (16H, m,

Ar–H and N=CH), 15.28 (1H, s, D_2O exchangeable, COOH). ESI-MS (*m*/*z*): 690 $(M + H)^+$, 712 $(M + Na)^+$, 728 $(M + K)^+$.

*4.2.2.6. 7-[3-(Benzylideneamino)methyl-4-(2′,4′-dimethxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10f**).* Yield: 78%, mp: 92–94 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.01–1.10 (4H, m, 2× cyclopropylCH$_2$), 3.42–4.64 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_3), 5.07 (2H, s, O$\underline{CH_2}$Ar), 6.42–8.56 (11H, m, Ar–H and N=CH), 15.27 (1H, s, D_2O exchangeable, COOH). ESI-MS (*m*/*z*): 614 $(M + H)^+$.

*4.2.2.7. 7-[3-(Benzylideneamino)methyl-4-(2′-chloro-3′,4′-dimethxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10g**).* Yield: 86%, mp: 182–183 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 0.98–1.10 (4H, m, 2× cyclopropylCH$_2$), 3.42–4.61 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_3), 5.13 (2H, s, O$\underline{CH_2}$Ar), 6.94–8.55 (10H, m, Ar–H and N=CH), 15.26 (1H, s, D_2O exchangeable, COOH). ESI-MS (*m*/*z*): 648 $(M + H)^+$, 650 $(M + 2 + H)^+$, 670 $(M + Na)^+$, 672 $(M + 2 + Na)^+$.

*4.2.2.8. 7-[3-(Benzylideneamino)methyl-4-(2′,3′-dimethxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10h**).* Yield: 79%, mp: 182–183 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 0.99–1.09 (4H, m, 2× cyclopropylCH$_2$), 3.42–4.60 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_3), 5.12 (2H, s, O$\underline{CH_2}$Ar), 6.91–8.55 (11H, m, Ar–H and N=CH), 15.28 (1H, s, D_2O exchangeable, COOH). ESI-MS (*m*/*z*): 614 $(M + H)^+$, 636 $(M + Na)^+$.

*4.2.2.9. 7-[3-(Benzylideneamino)methyl-4-(3′,4′-dimethxoy-6′-nitrobenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10i**).* Yield: 67%, mp: 195 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.02–1.14 (4H, m, 2× cyclopropylCH$_2$), 3.41–4.70 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_3), 5.47 (2H, s, O$\underline{CH_2}$Ar), 7.13–8.56 (10H, m, Ar–H and N=CH), 15.27 (1H, s, D_2O exchangeable, COOH). ESI-MS (*m*/*z*): 659 $(M + H)^+$, 681 $(M + Na)^+$.

*4.2.2.10. 7-[3-(Benzylideneamino)methyl-4-(6′-bromo-3′,4′-dimethxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10j**).* Yield: 82%, mp: 189–190 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.01–1.10 (4H, m, 2× cyclopropylCH$_2$), 3.42–4.63 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_3), 5.11 (2H, s, O$\underline{CH_2}$Ar), 7.07–8.55 (10H, m, Ar–H and N=CH), 15.27 (1H, s, D_2O exchangeable, COOH). ESI-MS (*m*/*z*): 692 $(M + H)^+$, 694 $(M + 2 + H)^+$, 714 $(M + Na)^+$, 716 $(M + 2 + Na)^+$.

*4.2.2.11. 7-[3-(Benzylideneamino)methyl-4-(3′,4′-dimethxoy-6′-fluorobenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10k**).* Yield: 79%, mp: 148–149 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 0.99–1.09 (4H, m, 2× cyclopropylCH$_2$), 3.41–4.57 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_3), 5.08 (2H, s, O$\underline{CH_2}$Ar), 6.88–8.54 (10H, m, Ar–H and N=CH), 15.26 (1H, s, D_2O exchangeable, COOH). ESI-MS (*m*/*z*): 632 $(M + H)^+$, 654 $(M + Na)^+$.

*4.2.2.12. 7-[3-(Benzylideneamino)methyl-4-(2′,5′-dimethxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10l**).* Yield: 83%, mp: 169 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 0.99–1.10 (4H, m, 2× cyclopropylCH$_2$), 3.42–4.64 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_3), 5.10 (2H, s, O$\underline{CH_2}$Ar), 6.83–8.55 (11H, m, Ar–H and N=CH), 15.27 (1H, s, D_2O exchangeable, COOH). ESI-MS (*m*/*z*): 614 $(M + H)^+$, 636 $(M + Na)^+$.

*4.2.2.13. 7-[3-(Benzylideneamino)methyl-4-benzyloxyiminopyrrolidin-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10m**).* Yield: 83%, mp: 169 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 0.95–1.10 (4H, m, 2× cyclopropylCH$_2$), 2.19 (6H, s, 2× CH_3), 3.39–4.60 (8H, m, pyrrolidine–H and cyclopropylCH), 5.12 (2H, s, O$\underline{CH_2}$Ar), 7.26–8.54 (1H, s, D_2O exchangeable, COOH). ESI-MS (*m*/*z*): 576 $(M + H)^+$, 592 $(M + Na)^+$.

*4.2.2.14. 7-[3-(Benzylideneamino)methyl-4-(4′-methxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10n**).* Yield: 55%, mp: 179–181 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 0.98–1.11 (4H, m, 2× cyclopropylCH$_2$), 3.41–4.58 (11H, m, pyrrolidine–H, cyclopropylCH and OCH_3), 5.05 (2H, s, O$\underline{CH_2}$Ar), 6.86–8.55 (12H, m, Ar–H and N=CH), 15.26 (1H, s, D_2O exchangeable, COOH). ESI-MS (*m*/*z*): 584 $(M + H)^+$, 606 $(M + Na)^+$, 622 $(M + K)^+$.

*4.2.2.15. 7-[3-(Benzylideneamino)methyl-4-(5′-chloro-3′,4′-dimethxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10o**).* Yield: 63%, mp: 117 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.02–1.10 (4H, m, 2× cyclopropylCH$_2$), 3.30–4.65 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_3), 5.08 (2H, s, O$\underline{CH_2}$Ar), 7.04–8.55 (10H, m, Ar–H and N=CH), 15.28 (1H, s, D_2O exchangeable, COOH). ESI-MS (*m*/*z*): 648 $(M + H)^+$, 650 $(M + 2 + H)^+$.

*4.2.2.16. 7-[3-(Benzylideneamino)methyl-4-(2′,3′,4′-trimethxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10p**).* Yield: 70%, mp: 186–188 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.00–1.09 (4H, m, 2× cyclopropylCH$_2$), 3.40–4.57 (17H, m, pyrrolidine–H, cyclopropylCH and 3× OCH_3), 5.08 (2H, s, O$\underline{CH_2}$Ar), 6.72–8.55 (10H, m, Ar–H and N=CH), 15.28 (1H, s, D_2O exchangeable, COOH). ESI-MS (*m*/*z*): 644 $(M + H)^+$.

*4.2.2.17. 7-[3-(Benzylideneamino)methyl-4-(4′-benzylxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10q**).* Yield: 83%, mp: 169 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 0.95–1.10 (4H, m, 2× cyclopropylCH$_2$), 2.19 (6H, s, 2× CH_3), 3.39–4.60 (8H, m, pyrrolidine–H and cyclopropylCH), 5.12 (2H, s, O$\underline{CH_2}$Ar), 7.26–8.54 (1H, s, D_2O exchangeable, COOH). ESI-MS (*m*/*z*): 576 $(M + H)^+$, 592 $(M + Na)^+$.

*4.2.2.18. 7-[3-(Benzylideneamino)methyl-4-(3′,4′-methylenedixoy-6′-nitrobenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10r**).* Yield: 69%, mp: 208 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.00–1.10 (4H, m, 2× cyclopropylCH$_2$), 3.45–4.61 (8H, m, pyrrolidine–H and cyclopropylCH), 5.12 (2H, s, O$\underline{CH_2}$Ar), 6.08 (2H, s, OCH_2O), 7.08–8.62 (10H, m, Ar–H and N=CH). ESI-MS (*m*/*z*): 643 $(M + H)^+$.

*4.2.2.19. 7-[3-(Benzylideneamino)methyl-4-(2′,6′-dimethxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10s**).* Yield: 72%, mp: 179–180 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.00–1.06 (4H, m, 2× cyclopropylCH$_2$), 3.41–4.50 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_3), 5.14 (2H, s, O$\underline{CH_2}$Ar), 6.67–8.55 (11H, m, Ar–H and N=CH), 15.28 (1H, s, D_2O exchangeable, COOH). ESI-MS (*m*/*z*): 614 $(M + H)^+$.

*4.2.2.20. 7-[3-(Benzylideneamino)methyl-4-(3′,4′-ethylenedixoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10t**).* Yield: 69%, mp: 181 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 0.99–1.10 (4H, m, 2× cyclopropylCH$_2$), 3.41–4.59 (12H, m, pyrrolidine–H, cyclopropylCH and 2× OCH$_2$), 5.00 (2H, s, OCH$_2$Ar), 6.77–8.55 (11H, m, Ar–H and N=CH), 15.28 (1H, s, D$_2$O exchangeable, COOH). ESI-MS (*m*/*z*): 612 (M + H)$^+$.

*4.2.2.21. 7-[3-(Benzylideneamino)methyl-4-(6′-chloro-3′,4′-methylenedixoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10u**).* Yield: 84%, mp: 207–208 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 0.99–1.11 (4H, m, 2× cyclopropylCH$_2$), 3.42–4.63 (8H, m, pyrrolidine–H and cyclopropylCH), 5.10 (2H, s, OCH$_2$Ar), 6.06 (2H, s, OCH$_2$O), 7.03–8.56 (10H, m, Ar–H and N=CH). ESI-MS (*m*/*z*): 632 (M + H)$^+$, 634 (M + 2 + H)$^+$.

*4.2.2.22. 7-[3-(Benzylideneamino)methyl-4-(3′,4′-dimethylbenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10v**).* Yield: 83%, mp: 169 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.01–1.10 (4H, m, 2× cyclopropylCH$_2$), 2.19 (6H, s, 2× CH$_3$), 3.41–4.60 (8H, m, pyrrolidine–H and cyclopropylCH), 5.05 (2H, s, OCH$_2$Ar), 7.07–8.56 (11H, m, Ar–H and N=CH), 15.28 (1H, s, D$_2$O exchangeable, COOH). ESI-MS (*m*/*z*): 582 (M + H)$^+$.

*4.2.2.23. 7-[3-(Benzylideneamino)methyl-4-(4′-difluoromethxoy-3′-methxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (**10w**).* Yield: 56%, mp: 177 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 0.99–1.10 (4H, m, 2× cyclopropylCH$_2$), 3.41–4.64 (11H, m, pyrrolidine–H, cyclopropylCH and OCH$_3$), 5.13 (2H, s, OCH$_2$Ar), 6.84–8.54 (14H, m, Ar–H, N=CH and CHF$_2$O), 15.26 (1H, s, D$_2$O exchangeable, COOH). ESI-MS (*m*/*z*): 650 (M + H)$^+$.

*4.2.3. General procedure for the synthesis of 7-[3-aminomethyl-4-(substituted benzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylates (**11a**–**w**)*

A mixture of compounds **10a**–**w** (1.0 mmol), methanesulfonic acid (4.0 mmol) and anhydrous ethanol (10 mL) was stirred at room temperature for overnight. The reaction mixture was cooled with ice, and the resulting solids were collected by suction, and dried *in vacuo* to give the title compounds **11a**–**w** as off-white or pale yellow solids.

*4.2.3.1. 7-[3-Aminomethyl-4-(3′,4′-methylenedixoybenzyloxyimino) pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11a**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.03–1.22 (4H, m, 2× cyclopropylCH$_2$), 2.31 (3H, s, CH$_3$SO$_3$), 3.11–4.61 (8H, m, pyrrolidine–H and cyclopropylCH), 5.05 (2H, s, OCH$_2$Ar), 5.99 (2H, s, OCH$_2$O), 6.86–6.96 (3H, m, Ar–H), 7.90 (3H, s, D$_2$O exchangeable, SO$_3$H$_3^+$N), 8.06 (1H, d, *J* = 12.4 Hz, C$_5$–H), 8.60 (1H, s, C$_2$–H), 15.24 (1H, s, D$_2$O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 6.75, 6.92, 34.94, 48.51, 48.59, 50.66, 75.57, 100.98, 107.57, 108.05, 108.66, 111.44, 117.98 (d, *J* = 13 Hz), 121.83, 131.23, 146.12 (d, *J* = 257 Hz), 146.87, 146.91, 146.95, 147.27, 148.46 (d, *J* = 12 Hz), 157.05, 165.69, 176.35. ESI-MS (*m*/*z*): 510 (M + H)$^+$. HRMS-ESI (*m*/*z*): $C_{25}H_{25}FN_5O_6$ calcd: 510.17834; found 510.17811.

*4.2.3.2. 7-[3-Aminomethyl-4-(3′,4′,5′-trimethxoybenzyloxyimino) pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11b**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.04–1.21 (4H, m, 2× cyclopropylCH$_2$), 2.30 (3H, s, CH$_3$SO$_3$), 3.17–4.64 (17H, m, pyrrolidine–H, cyclopropylCH and 3× OCH$_3$), 5.09 (2H, s, OCH$_2$Ar), 6.69 (2H, s, Ar–H), 7.91 (3H, s, D$_2$O exchangeable, SO$_3$H$_3^+$N), 8.07 (1H, d, *J* = 12.8 Hz, C$_5$–H), 8.60 (1H, s, C$_2$–H), 15.23 (1H, s, D$_2$O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 6.85, 7.01, 35.02, 48.58, 48.66, 50.76, 55.96, 60.08, 75.97, 105.46, 107.67, 111.50, 118.10 (d, *J* = 20 Hz), 133.11, 137.22, 146.23 (d, *J* = 257 Hz), 147.00, 148.65, 152.93, 165.80, 176.42. ESI-MS (*m*/*z*): 556 (M + H)$^+$. HRMS-ESI (*m*/*z*): $C_{27}H_{31}FN_5O_7$ calcd: 556.22020; found 556.21893.

*4.2.3.3. 7-[3-Aminomethyl-4-(3′,4′-dimethxoy-2′-nitrobenzyloxyimino) pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11c**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.04–1.24 (4H, m, 2× cyclopropylCH$_2$), 2.30 (3H, s, CH$_3$SO$_3$), 3.14–4.69 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH$_3$), 5.50 (2H, s, OCH$_2$Ar), 7.14 (1H, s, Ar–H), 7.68 (1H, s, Ar–H), 7.88 (3H, s, D$_2$O exchangeable, SO$_3$H$_3^+$N), 8.09 (1H, d, *J* = 12.8 Hz, C$_5$–H), 8.61 (1H, s, C$_2$–H), 15.23 (1H, s, D$_2$O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 6.76, 6.90, 34.94, 48.57, 48.62, 50.63, 56.09, 56.19, 72.44, 107.60, 108.06, 111.09, 111.47, 118.10 (d, *J* = 20 Hz), 127.93, 139.78, 146.15 (d, *J* = 257 Hz), 146.91, 146.92, 147.77, 148.46 (d, *J* = 12 Hz), 153.04, 165.69, 176.38. ESI-MS (*m*/*z*): 571 (M + H)$^+$. HRMS-ESI (*m*/*z*): $C_{26}H_{28}FN_6O_8$ calcd: 571.19472; found 571.19521.

*4.2.3.4. 7-[3-Aminomethyl-4-(3′,4′-dimethxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11d**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.03–1.21 (4H, m, 2× cyclopropylCH$_2$), 2.30 (3H, s, CH$_3$SO$_3$), 3.12–4.61 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH$_3$), 5.08 (2H, s, OCH$_2$Ar), 6.93–6.98 (3H, m, Ar–H), 7.90 (3H, s, D$_2$O exchangeable, SO$_3$H$_3^+$N), 8.07 (1H, d, *J* = 12.8 Hz, C$_5$–H), 8.60 (1H, s, C$_2$–H), 15.24 (1H, s, D$_2$O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 6.75, 6.91, 34.93, 48.55, 48.60, 50.65, 55.46, 55.50, 75.77, 107.58, 111.44, 111.54, 112.11, 118.10 (d, *J* = 20 Hz), 120.76, 129.66, 144.87 (d, *J* = 257 Hz), 146.91, 148.45 (d, *J* = 13 Hz), 148.58, 148.64, 165.69, 176.34. ESI-MS (*m*/*z*): 526 (M + H)$^+$. HRMS-ESI (*m*/*z*): $C_{26}H_{29}FN_5O_6$ calcd: 526.20964; found 526.20845.

*4.2.3.5. 7-[3-Aminomethyl-4-(4′-benzylxoy-3′-methxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11e**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.11–1.22 (4H, m, 2× cyclopropylCH$_2$), 2.32 (3H, s, CH$_3$SO$_3$), 3.14–4.62 (11H, m, pyrrolidine–H, cyclopropylCH and OCH$_3$), 5.09, 5.12 (4H, s, 2× OCH$_2$Ar), 7.01–7.43 (8H, m, Ar–H), 7.94 (3H, s, D$_2$O exchangeable, SO$_3$H$_3^+$N), 8.07 (1H, d, *J* = 12.4 Hz, C$_5$–H), 8.60 (1H, s, C$_2$–H), 15.28 (1H, s, D$_2$O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 6.75, 6.91, 34.92, 48.56, 50.66, 55.56, 69.86, 75.72, 107.55, 111.39, 112.37, 113.36, 118.06 (d, *J* = 21 Hz), 120.64, 127.68, 127.79, 128.37, 130.14, 137.11, 144.85, 146.13 (d, *J* = 257 Hz), 146.88, 147.56, 148.50 (d, *J* = 11 Hz), 148.97, 158.27, 165.68, 176.31. ESI-MS (*m*/*z*): 602 (M + H)$^+$. HRMS-ESI (*m*/*z*): $C_{32}H_{33}FN_5O_6$ calcd: 602.24094; found 602.24105.

*4.2.3.6. 7-[3-Aminomethyl-4-(2′,4′-dimethxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11f**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.09–1.22 (4H, m, 2× cyclopropylCH$_2$), 2.31 (3H, s, CH$_3$SO$_3$), 3.10–4.65 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH$_3$), 5.10 (2H, s, OCH$_2$Ar), 6.44 (1H, s, Ar–H), 6.53 (2H, s, Ar–H), 7.91 (3H, s, D$_2$O exchangeable, SO$_3$H$_3^+$N), 8.07 (1H, d, *J* = 12.4 Hz, C$_5$–H), 8.60 (1H, s, C$_2$–H), 15.24 (1H, s, D$_2$O

exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 6.76, 6.92, 34.93, 48.59, 48.64, 50.70, 55.16, 75.52, 99.35, 105.58, 107.57, 111.41, 118.00 (d, J = 20 Hz), 139.88, 145.16 (d, J = 257 Hz), 146.85, 146.90, 148.50 (d, J = 12 Hz), 160.47, 165.70, 176.34. ESI-MS (m/z): 526 $(M + H)^+$. HRMS-ESI (m/z): $C_{26}H_{29}FN_5O_6$ calcd: 526.20964; found 526.20846.

*4.2.3.7. 7-[3-Aminomethyl-4-(2′-chloro-3′,4′-dimethxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11g**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.06–1.21 (4H, m, 2× cyclopropylCH$_2$), 2.30 (3H, s, CH_3SO_3), 3.15–4.62 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_3), 5.17 (2H, s, O$\underline{CH_2}$Ar), 7.05 (1H, d, J = 8.4 Hz, Ar–H), 7.23 (1H, d, J = 8.4 Hz, Ar–H), 7.90 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.07 (1H, d, J = 12.8 Hz, C_5–H), 8.60 (1H, s, C_2–H), 15.23 (1H, s, D_2O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 6.76, 6.92, 34.94, 48.59, 48.63, 50.67, 55.86, 55.88, 75.14, 107.58, 111.45, 112.80, 116.64, 118.02 (d, J = 20 Hz), 120.13, 120.99, 136.22, 138.99, 145.16 (d, J = 257 Hz), 146.91, 148.51 (d, J = 12 Hz), 150.47, 158.82, 165.69, 176.36. ESI-MS (m/z): 560 $(M + H)^+$, 562 $(M + 2 + H)^+$. HRMS-ESI (m/z): $C_{26}H_{28}FClN_5O_6$ calcd: 560.17067, 562.16772; found 560.17001, 562.16784.

*4.2.3.8. 7-[3-Aminomethyl-4-(2′,3′-dimethxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11h**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.06–1.20 (4H, m, 2× cyclopropylCH$_2$), 2.29 (3H, s, CH_3SO_3), 3.10–4.61 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_3), 5.17 (2H, s, O$\underline{CH_2}$Ar), 6.94–7.09 (3H, m, Ar–H), 7.88 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.08 (1H, d, J = 12.8 Hz, C_5–H), 8.61 (1H, s, C_2–H), 15.24 (1H, s, D_2O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 6.74, 6.90, 34.93, 48.53, 48.61, 50.64, 55.69, 60.50, 71.12, 107.56, 111.43, 112.90, 117.98 (d, J = 20 Hz), 121.31, 123.94, 130.71, 145.16 (d, J = 257 Hz), 146.81, 146.87, 146.90, 148.50 (d, J = 12 Hz), 152.34, 165.69, 176.33. ESI-MS (m/z): 526 $(M + H)^+$. HRMS-ESI (m/z): $C_{26}H_{29}FN_5O_6$ calcd: 526.20964; found 526.20922.

*4.2.3.9. 7-[3-Aminomethyl-4-(3′,4′-dimethxoy-6′-nitrobenzyloxyimino)-pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11i**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.04–1.24 (4H, m, 2× cyclopropylCH$_2$), 2.29 (3H, s, CH_3SO_3), 3.14–4.69 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_3), 5.50 (2H, s, O$\underline{CH_2}$Ar), 7.14 (1H, s, Ar–H), 7.68 (1H, s, Ar–H), 7.86 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.10 (1H, d, J = 12.4 Hz, C_5–H), 8.62 (1H, s, C_2–H), 15.23 (1H, s, D_2O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 6.76, 6.90, 34.94, 48.55, 48.62, 50.65, 56.09, 56.19, 72.45, 107.58, 108.05, 111.08, 111.44, 118.05 (d, J = 21 Hz), 127.96, 139.76, 146.15 (d, J = 257 Hz), 146.87, 146.90, 147.77, 148.45 (d, J = 12 Hz), 153.05, 165.68, 176.34. ESI-MS (m/z): 571 $(M + H)^+$. HRMS-ESI (m/z): $C_{26}H_{28}FN_6O_8$ calcd: 571.19472; found 571.19450.

*4.2.3.10. 7-[3-Aminomethyl-4-(6′-bromo-3′,4′-dimethoxybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11j**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.06–1.22 (4H, m, 2× cyclopropylCH$_2$), 2.29 (3H, s, CH_3SO_3), 3.13–4.63 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_3), 5.14 (2H, s, O$\underline{CH_2}$Ar), 7.07 (1H, s, Ar–H), 7.17 (1H, s, Ar–H), 7.89 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.08 (1H, d, J = 12.4 Hz, C_5–H), 8.61 (1H, s, C_2–H), 15.23 (1H, s, D_2O exchangeable, COOH). ESI-MS (m/z): 604 $(M + H)^+$, 606 $(M + 2 + H)^+$. ^{13}C NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 6.76, 6.92, 34.94, 48.58, 48.62, 50.65, 55.76, 55.94, 75.13, 107.58, 111.43, 113.39, 114.05, 115.55, 118.03 (d, J = 20 Hz), 127.98, 145.99 (d, J = 257 Hz), 148.10, 148.47 (d, J = 12 Hz), 149.38, 165.68, 176.36. HRMS-ESI (m/z): $C_{26}H_{28}FBrN_5O_6$ calcd: 604.12015, 606.11810; found 604.12015, 606.11765.

*4.2.3.11. 7-[3-Aminomethyl-4-(3′,4′-dimethxoy-6′-fluorobenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11k**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.03–1.22 (4H, m, 2× cyclopropylCH$_2$), 2.32 (3H, s, CH_3SO_3), 3.12–4.58 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_3), 5.11 (2H, s, O$\underline{CH_2}$Ar), 6.90–7.03 (2H, m, Ar–H), 7.95 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.03 (1H, d, J = 12.8 Hz, C_5–H), 8.57 (1H, s, C_2–H), 15.22 (1H, s, D_2O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 6.74, 6.90, 34.92, 48.44, 48.51, 50.63, 55.94, 56.09, 69.47, 100.32 (d, J = 25 Hz), 107.56, 111.43, 113.78, 114.17 (d, J = 16 Hz), 117.98 (d, J = 20 Hz), 146.16 (d, J = 253 Hz), 146.89, 148.55 (d, J = 12 Hz), 149.88, 149.98, 154.90 (d, J = 237 Hz), 165.69, 176.33. ESI-MS (m/z): 544 $(M + H)^+$. HRMS-ESI (m/z): $C_{26}H_{28}F_2N_5O_6$ calcd: 544.20022; found 544.19960.

*4.2.3.12. 7-[3-Aminomethyl-4-(2′,5′-dimethxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11l**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.04–1.22 (4H, m, 2× cyclopropylCH$_2$), 2.30 (3H, s, CH_3SO_3), 3.16–4.64 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_3), 5.14 (2H, s, O$\underline{CH_2}$Ar), 6.85–6.96 (3H, m, Ar–H), 7.89 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.08 (1H, d, J = 12.8 Hz, C_5–H), 8.61 (1H, s, C_2–H), 15.24 (1H, s, D_2O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 6.75, 6.91, 34.93, 48.59, 48.63, 50.66, 55.35, 55.92, 70.76, 107.56, 111.41, 111.88, 113.02, 115.16, 117.97 (d, J = 20 Hz), 126.29, 146.16 (d, J = 257 Hz), 146.85, 146.90, 148.50 (d, J = 12 Hz), 150.86, 153.01, 165.69, 176.33. ESI-MS (m/z): 526 $(M + H)^+$. HRMS-ESI (m/z): $C_{26}H_{29}FN_5O_6$ calcd: 526.20964; found 526.20835.

*4.2.3.13. 7-[3-Aminomethyl-4-benzyloxyiminopyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11m**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.06–1.22 (4H, m, 2× cyclopropylCH$_2$), 2.30 (3H, s, CH_3SO_3), 3.15–4.64 (8H, m, pyrrolidine–H and cyclopropylCH), 5.17 (2H, s, O$\underline{CH_2}$Ar), 7.31–7.40 (5H, m, Ar–H), 7.90 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.07 (1H, d, J = 12.4 Hz, C_5–H), 8.60 (1H, s, C_2–H), 15.23 (1H, s, D_2O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 6.74, 6.91, 34.94, 48.56, 48.62, 50.68, 75.68, 107.55, 111.40, 117.94 (d, J = 21 Hz), 127.86, 128.35, 137.52, 146.15 (d, J = 257 Hz), 146.82, 146.88, 148.49 (d, J = 12 Hz), 165.68, 176.30. ESI-MS (m/z): 466 $(M + H)^+$. HRMS-ESI (m/z): $C_{24}H_{25}FN_5O_4$ calcd: 466.18851; found 466.18784.

*4.2.3.14. 7-[3-Aminomethyl-4-(4′-methxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11n**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.09–1.21 (4H, m, 2× cyclopropylCH$_2$), 2.29 (3H, s, CH_3SO_3), 3.12–4.59 (11H, m, pyrrolidine–H, cyclopropylCH and OCH_3), 5.08 (2H, s, O$\underline{CH_2}$Ar), 6.92 (2H, d, J = 8.8 Hz, Ar–H), 7.33 (2H, d, J = 8.8 Hz, Ar–H), 7.87 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.08 (1H, d, J = 12.8 Hz, C_5–H), 8.61 (1H, s, C_2–H), 15.24 (1H, s, D_2O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 6.75, 6.91, 34.94, 48.48, 48.55, 50.65, 55.08, 75.50, 107.57, 111.42, 113.72, 117.99 (d, J = 20 Hz), 129.28, 129.81, 146.15 (d, J = 257 Hz), 146.91, 148.52 (d, J = 12 Hz), 159.06, 165.69, 176.35. ESI-MS (m/z): 496 $(M + H)^+$. HRMS-ESI (m/z): $C_{25}H_{27}FN_5O_5$ calcd: 496.19907; found 496.19839.

*4.2.3.15. 7-[3-Aminomethyl-4-(5′-chloro-3′,4′-dimethxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11o**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.10–1.22 (4H, m, 2× cyclopropylCH$_2$), 2.29 (3H, s, CH_3SO_3), 3.13–4.65 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_3), 5.10 (2H, s, O$\underline{CH_2}$Ar), 7.05 (1H, s, Ar–H), 7.06 (1H, s, Ar–H), 7.89 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.09 (1H, d, J = 12.8 Hz, C_5–H), 8.61 (1H, s, C_2–H), 15.24 (1H, s, D_2O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 500 MHz) δ_{ppm}: 6.87, 7.02, 35.04, 48.70, 48.74, 50.74, 56.20, 60.27, 74.82, 107.73, 111.63, 118.18 (d, J = 23 Hz), 120.66, 126.89, 134.64, 144.27, 145.38, 146.26 (d, J = 257 Hz), 147.04, 148.60 (d, J = 11 Hz), 153.54, 165.79, 176.50. ESI-MS (m/z): 560 (M + H)$^+$, 562 (M + 2 + H)$^+$. HRMS-ESI (m/z): $C_{26}H_{28}ClFN_5O_6$ calcd: 560.17067, 562.16772; found 560.17078, 562.16797.

*4.2.3.16. 7-[3-Aminomethyl-4-(2′,3′,4′-trimethxoybenzyloxyimino) pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11p**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.06–1.20 (4H, m, 2× cyclopropylCH$_2$), 2.29 (3H, s, CH_3SO_3), 3.13–4.58 (17H, m, pyrrolidine–H, cyclopropylCH and 3× OCH_3), 5.08 (2H, s, O$\underline{CH_2}$Ar), 6.79 (1H, d, J = 8.4 Hz, Ar–H), 7.07 (1H, d, J = 8.4 Hz, Ar–H), 7.89 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.07 (1H, d, J = 12.4 Hz, C_5–H), 8.61 (1H, s, C_2–H), 15.23 (1H, s, D_2O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 500 MHz) δ_{ppm}: 6.84, 6.99, 35.02, 48.67, 48.71, 50.74, 55.95, 60.42, 61.37, 71.41, 107.69, 107.79, 111.56, 118.10 (d, J = 20 Hz), 122.83, 125.03, 141.82, 146.26 (d, J = 254 Hz), 147.03, 149.23, 152.02, 153.79, 165.78, 176.47. ESI-MS (m/z): 566 (M + H)$^+$. HRMS-ESI (m/z): $C_{27}H_{31}FN_5O_7$ calcd: 556.22020; found 556.22004.

*4.2.3.17. 7-[3-Aminomethyl-4-(4′-benzylxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11q**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.05–1.21 (4H, m, 2× cyclopropylCH$_2$), 2.29 (3H, s, CH_3SO_3), 3.11–4.59 (8H, m, pyrrolidine–H and cyclopropylCH), 5.08, 5.10 (4H, s, 2× O$\underline{CH_2}$Ar), 6.96–7.44 (9H, m, Ar–H), 7.89 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.07 (1H, d, J = 12.8 Hz, C_5–H), 8.61 (1H, s, C_2–H), 15.24 (1H, s, D_2O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 500 MHz) δ_{ppm}: 6.85, 7.02, 35.04, 48.61, 50.73, 69.26, 75.56, 107.69, 111.55, 114.72, 118.10 (d, J = 22 Hz), 127.71, 127.90, 128.51, 129.67, 129.89, 137.13, 146.12 (d, J = 243 Hz), 147.01, 148.56, 158.22, 165.79, 176.45. ESI-MS (m/z): 572 (M + H)$^+$. HRMS-ESI (m/z): $C_{31}H_{31}FN_5O_5$ calcd: 572.23037; found 572.23067.

*4.2.3.18. 7-[3-Aminomethyl-4-(3′,4′-methylenedixoy-6′-nitrobenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11r**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.07–1.23 (4H, m, 2× cyclopropylCH$_2$), 2.25 (3H, s, CH_3SO_3), 3.14–4.71 (8H, m, pyrrolidine–H and cyclopropylCH), 5.45 (2H, s, O$\underline{CH_2}$Ar), 6.25 (2H, s, OCH_2O), 7.19 (1H, s, Ar–H), 7.71 (1H, s, Ar–H), 7.88 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.09 (1H, d, J = 12.8 Hz, C_5–H), 8.61 (1H, s, C_2–H), 15.24 (1H, s, D_2O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 500 MHz) δ_{ppm}: 6.87, 7.02, 35.07, 48.85, 48.90, 50.69, 72.60, 103.61, 105.34, 107.70, 107.82, 111.57, 118.18 (d, J = 22 Hz), 131.20, 141.24, 146.22 (d, J = 245 Hz), 147.03, 147.14, 148.51, 152.29, 165.80, 176.47. ESI-MS (m/z): 555 (M + H)$^+$. HRMS-ESI (m/z): $C_{25}H_{24}FN_6O_8$ calcd: 555.16342; found 555.16388.

*4.2.3.19. 7-[3-Aminomethyl-4-(2′,6′-dimethxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11s**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.03–1.19 (4H, m, 2× cyclopropylCH$_2$), 2.32 (3H, s, CH_3SO_3), 3.14–4.49 (14H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_3), 5.16 (2H, s, O$\underline{CH_2}$Ar), 6.69 (2H, d, J = 8.4 Hz, Ar–H), 7.32 (1H, t, J = 8.4 Hz, Ar–H), 7.94 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.03 (1H, d, J = 12.8 Hz, C_5–H), 8.58 (1H, s, C_2–H), 15.24 (1H, s, D_2O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 500 MHz) δ_{ppm}: 6.80, 6.98, 35.01, 48.50, 48.54, 50.68, 55.97, 65.04, 104.24, 107.66, 111.50, 111.88, 118.03 (d, J = 24 Hz), 130.75, 146.22 (d, J = 257 Hz), 147.01, 148.56, 159.24, 165.80, 176.43. ESI-MS (m/z): 526 (M + H)$^+$. HRMS-ESI (m/z): $C_{26}H_{29}FN_5O_6$ calcd: 526.20964; found 526.20965.

*4.2.3.20. 7-[3-Aminomethyl-4-(3′,4′-ethylenedixoybenzyloxyimino)-pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11t**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.04–1.22 (4H, m, 2× cyclopropylCH$_2$), 2.30 (3H, s, CH_3SO_3), 3.13–4.60 (12H, m, pyrrolidine–H, cyclopropylCH and 2× OCH_2), 5.03 (2H, s, O$\underline{CH_2}$Ar), 6.84 (1H, s, Ar–H), 6.89 (1H, s, Ar–H), 7.90 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.05 (1H, d, J = 12.4 Hz, C_5–H), 8.60 (1H, s, C_2–H), 15.24 (1H, s, D_2O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 500 MHz) δ_{ppm}: 6.85, 7.02, 35.04, 48.65, 48.70, 50.76, 64.10, 64.13, 75.44, 107.67, 111.54, 116.95, 117.08, 118.09 (d, J = 22 Hz), 121.29, 130.48, 143.23, 143,27, 146.25 (d, J = 257 Hz), 146.97, 148.58, 165.79, 176.44. ESI-MS (m/z): 524 (M + H)$^+$. HRMS-ESI (m/z): $C_{26}H_{27}FN_5O_6$ calcd: 524.19399; found 524.19398.

*4.2.3.21. 7-[3-Aminomethyl-4-(6′-chloro-3′,4′-methylenedixoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11u**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.04–1.22 (4H, m, 2× cyclopropylCH$_2$), 2.29 (3H, s, CH_3SO_3), 3.16–4.64 (8H, m, pyrrolidine–H and cyclopropylCH), 5.14 (2H, s, O$\underline{CH_2}$Ar), 6.08 (2H, s, OCH_2O), 7.07 (1H, s, Ar–H), 7.12 (1H, s, Ar–H), 7.89 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.08 (1H, d, J = 12.8 Hz, C_5–H), 8.61 (1H, s, C_2–H), 15.24 (1H, s, D_2O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 500 MHz) δ_{ppm}: 6.86, 7.02, 35.06, 48.70, 48.78, 50.76, 72.93, 102.20, 107.68, 109.71, 109.92, 111.54, 118.12 (d, J = 20 Hz), 124.60, 128.07, 146.26 (d, J = 257 Hz), 146.69, 147.01, 147.96, 148.52 (d, J = 12 Hz), 165.89, 176.46. ESI-MS (m/z): 544 (M + H)$^+$, 546 (M + 2 + H)$^+$. HRMS-ESI (m/z): $C_{25}H_{24}ClFN_5O_6$ calcd: 544.13937, 546.13642; found 544.13928, 546.13637.

*4.2.3.22. 7-[3-Aminomethyl-4-(3′,4′-dimethylbenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11v**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.07–1.21 (4H, m, 2× cyclopropylCH$_2$), 2.21 (6H, s, 2× CH_3), 2.29 (3H, s, CH_3SO_3), 3.12–4.61 (8H, m, pyrrolidine–H and cyclopropylCH), 5.08 (2H, s, O$\underline{CH_2}$Ar), 7.09–7.15 (3H, m, Ar–H), 7.89 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.06 (1H, d, J = 12.8 Hz, C_5–H), 8.61 (1H, s, C_2–H), 15.24 (1H, s, D_2O exchangeable, COOH). ^{13}C NMR (DMSO-d_6, 500 MHz) δ_{ppm}: 6.85, 7.01, 19.20, 19.45, 35.03, 48.62, 48.66, 50.75, 75.82, 107.67, 111.51, 118.08 (d, J = 20 Hz), 125.68, 129.36, 129.40, 134.77, 135.96, 136.18, 146.22 (d, J = 257 Hz), 146.99, 146.99, 148.54, 165.78, 176.43. ESI-MS (m/z): 494 (M + H)$^+$. HRMS-ESI (m/z): $C_{26}H_{29}FN_4O_5$ calcd: 494.21981; found 494.22029.

*4.2.3.23. 7-[3-Aminomethyl-4-(4′-difluoromethxoy-3′-methxoybenzyloxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid dimesylate (**11w**).* ^{1}H NMR (DMSO-d_6, 400 MHz) δ_{ppm}: 1.09–1.22 (4H, m, 2× cyclopropylCH$_2$), 2.30 (3H, s, CH_3SO_3), 3.12–4.65 (11H, m, pyrrolidine–H, cyclopropylCH and OCH_3), 5.15 (2H, s, O$\underline{CH_2}$Ar), 6.86–7.23 (4H, m, Ar–H and CHF_2), 7.91 (3H, s, D_2O exchangeable, $SO_3H_3^+N$), 8.07 (1H, d, J = 12.4 Hz, C_5–H), 8.60 (1H, s, C_2–H), 15.23 (1H, s, D_2O exchangeable, COOH). ESI-MS (m/z): 562 (M + H)$^+$. HRMS-ESI (m/z): $C_{26}H_{27}F_3N_5O_6$ calcd: 562.19079; found 562.19196.

4.3. MIC determination

All the target compounds **11a**–**w** were screened for their *in vitro* antibacterial activity against representative Gram-positive and Gram-negative strains by means of standard twofold serial dilution method using agar media [26]. Minimum inhibitory concentration (MIC) is defined as the minimum concentration of the compound required to give complete inhibition of bacterial growth after incubation at 35 °C for 18–24 h.

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