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Synthesis of naphthyridone derivatives containing 8-alkoxyimino-1, 6-dizaspiro[3.4]octane scaffolds

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ABSTRACT

The synthesis of naphthyridone derivatives containing 8-alkoxyimino-1,6-dizaspiro[3.4]octane scaffolds, the position isomers of the side chain at the C-7 position of Zabofloxacin, has been achieved in eight steps from *tert*-butyl 3-cyano-4-oxopyrrolidine-1-carboxylate. The possible reaction mechanisms were also proposed. The key spirocyclic carbamate esters, which could be prepared using a modified Hofmann rearrangement strategy, were condensed with naphthyridone nuclei, and the resulting condensates were easily cleaved by TMSI and subsequently cyclized in the presence of K_2CO_3. Moreover, additional N-methylation derivatives were also obtained using the synthetic sequence.

1. Introduction

Since the discovery of nalidixic acid in 1962 by Lesher et al.,[1] quinolone antibacterial agents, one of the few classes that are synthetic in an area where natural products have dominated, are important weapons in our antibacterial arsenal.[2,3] As privileged structures, the 4-quinolone/naphthyridone-3-carboxylic acids containing a good number of points for functionalization have also been proven useful in other therapeutic areas where they have, for example, demonstrated activity as antitumor agents (mammalian topoisomerase II inhibition), anxiolytics, anti-ischemic agents, antivirals (e.g., anti-HIV and anti-herpes simplex virus), cannabinoid type 2 receptor agonists, and antimalarials.[4,5]

Structure–activity relationship (SAR) studies of quinolone antibacterial agents have indicated that the basic group at the C-7 position is the most adaptable site for chemical change and is an area that greatly influences potency, spectrum and safety.[6,7] In fact, almost all the quinolones currently on the market or under development have a nitrogen heterocycle at this position. Among them, five- and six-membered nitrogen heterocycles including piperazinyl, pyrrolidinyl and piperidinyl type side chains have proven to be optimal substituents.[8,9] There is general recognition of the need for the development of both new heterocyclic scaffolds[10] and approaches to modify existing scaffolds in novel ways to confer desirable biological and pharmacological properties.[11] As a result, introduction of nitrogen spirocyclic scaffolds, which are an important class of naturally occurring substances characterized by their highly pronounced biological properties,[12] to the C-7 position of quinolone/naphthyridone cores have led to the discovery of sitafloxacin[13] and DC-159a,[14,15] and both of them generally exhibit good antibacterial activity. However, the goal of modifying existing heterocyclic scaffolds is particularly challenging, because most modifications add molecular weight, which often results in concomitant undesirable changes in physicochemical and ADMET behavior.[16] We are very interested in Zabofloxacin (DW224a, Fig. 1), a novel naphthyridone antibacterial containing an oxime-functionalized spirocycle scaffold as the C-7 substituent. It was reported that Zabofloxacin showed excellent activity against Gram-positive resistant bacteria, associated with very low toxicity and favorable pharmacokinetic profiles.[17] Therefore, it was decided to introduce 8-alkoxyimino-1,6-dizaspiro[3.4]octane scaffolds, the position isomers of the side chain at the C-7 position of Zabofloxacin, to naphthyridone cores, and obtain a series of novel naphthyridone derivatives. The synthetic methods were investigated and the possible mechanisms were proposed.

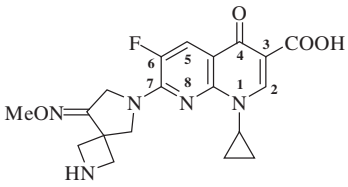

Fig. 1. Chemical structure of Zabofloxacin.

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It is well known that naphthyridone antibacterials, such as Tosufloxacin and Gemifloxacin, are usually synthesized by direct condensation of naphthyridone nuclei and the side-chain compounds.[18,19] Accordingly, 8-alkoxyimino-1,6-dizaspiro[3.4]octane scaffolds are key intermediates for the manufacture of these naphthyridone derivatives. Several potential strategies could be envisioned to access the target derivatives from pyrrolidin-3-ones and the corresponding retrosynthesis is described in Fig. 2.

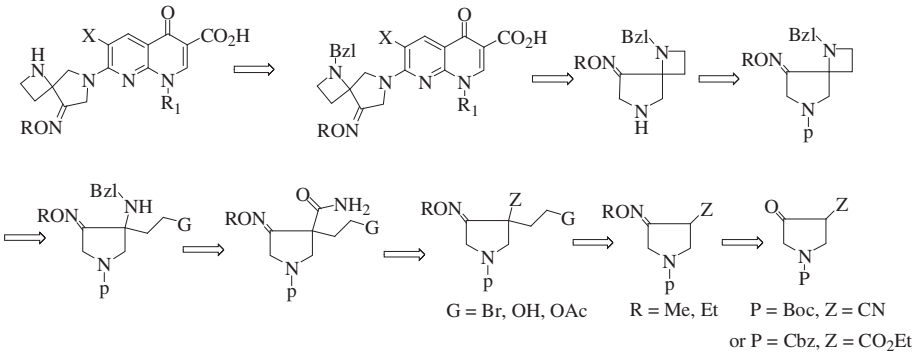


Fig. 2. Retrosynthesis of naphthyridone derivatives.

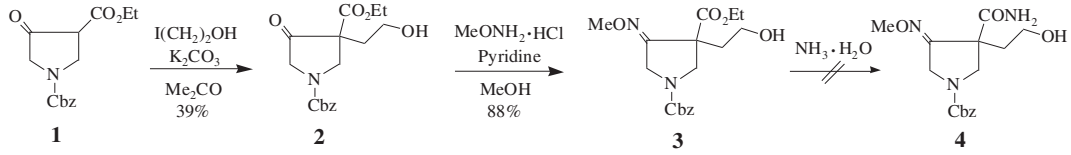
2. Results and discussion

To the best of our knowledge, naphthyridone derivatives containing 8-alkoxyimino-1,6-dizaspiro[3.4]octane scaffolds at the C-7 position are not described so far in the literature. We planned to prepare the spirocyclic scaffolds from 1-benzyl 3-ethyl 4-oxopyrrolidine-1,3-dicarboxylate (**1**) or *tert*-butyl 3-cyano-4-oxopyrrolidine-1-carboxylate (**5**)[20] at hand. The first synthetic route designed, using compound **1** as starting material, is outlined in Scheme 1. Alkylation of **1** with the strong nucleophilic reagent 2-iodoethanol gave 2-hydroxyethyl pyrrolidone **2** in the presence of K_2CO_3. Surprisingly, *O*-alkylated product rather than *C*-alkylated product was obtained under the same condition when 2-chloro/bromoethanol instead of 2-iodoethanol as the reagent. However, the oxime ester **3**, which was obtained easily by coupling **2** with methoxylamine,[21,22] was not converted to the desired amide **4** even though various attempts were made.

The possible mechanism of **13a**,**b**→**15a**,**b** is described in Fig. 4. When treated with Br_2–NaOH, the amides **13a**,**b** were first converted to the isocyanates (–N=C=O), and the ester group was hydrolyzed simultaneously. The resulting **16a**,**b** were cyclized by intramolecular addition, and subsequently proton transfer to give the spirocyclic compounds **15a**,**b**.

In fact, the carbamate ester is usually using to protect the amino group in synthetic chemistry, and the protecting group is easily removed with trimethyl silane iodine (TMSI) in neutral condition.[24–26] However, the Boc-protecting group of **15a**,**b** can be also cleaved when treated with TMSI.[27] In this way, both of the protecting groups of **15a**,**b** are removed simultaneously by TMSI to produce the primary amino iodides **17a**,**b**, and the latter will be cyclized in the presence of a base (such as K_2CO_3) to give the more stable compounds **18a**,**b**, rather than the desired spirocyclic compounds **19a**,**b** (Fig. 5).

On the basis of these considerations, we decided to synthesize naphthyridone derivatives by direct condensation of the naph-



Scheme 1.

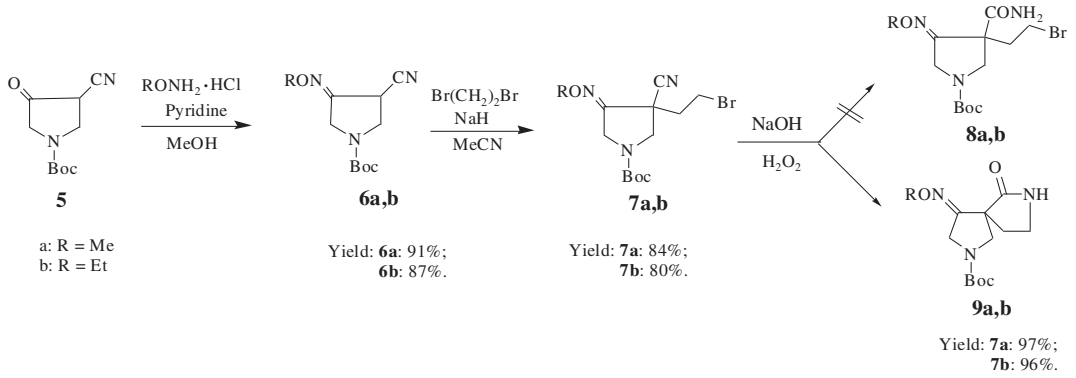
Subsequently, we designed the second synthetic pathway to the spirocyclic scaffolds from Boc-protected cyano ketone **5** (Scheme 2). Introduction of methoxyimino/ethoxyimino group to **5** to yield oximes **6a**,**b**, which then reacted with 1,2-dibromoethane in the presence of NaH to give compounds **7a**,**b**. Hydrolysis of the nitriles **7a**,**b** in NaOH–H_2O_2 system produced the spirocyclic compounds **9a**,**b**, instead of the desired amides **8a**,**b**.

The mechanism of **7a**,**b**→**9a**,**b** may be described in Fig. 3. As a strong nucleophilic reagent, HOO^- attacked the cyano group of **7a**,**b**, and the resulting adducts **10a**,**b** were subsequently cyclized to **11a**,**b**. Finally, the transition states **11a**,**b** accepted a proton from H_2O_2 molecule to provide **9a**,**b**.

To avoid the above undesired cyclization in Scheme 2, 1,2-dibromoethane was replaced with 2-bromoethyl acetate, which was prepared by reaction of 2-bromoethanol and acetyl chloride in a yield of 87%. Nucleophilic substitution of the nitriles **6a**,**b** and 2-bromoethyl acetate in the presence of NaH gave **12a**,**b**, which could be successfully converted to the desired amides **13a**,**b** in DMSO–H_2O_2 system. However, Hofmann degradation of the amides **13a**,**b**, used freshly prepared aqueous NaBrO,[23] did not produce the primary amines **14a**,**b** but the spirocyclic carbamate esters **15a**,**b**, unexpectedly (Scheme 3).

thyridone nuclei **21a**–**e**[19] with the spirocyclic compounds **20a**,**b**, which were obtained easily from **15a**,**b** by treatment with $MeSO_3H$, and subsequently cleavage of the carbamate ester with TMSI and cyclization in the presence of K_2CO_3. Finally, we successfully prepared the target compounds **24a**–**i** based on the synthetic route depicted in Scheme 4.

In this investigation, the condensates **22a**–**h** reacted with TMSI and MeOH, respectively, to provide the amino iodides **23a**–**h**. Interestingly, naphthyridone derivatives **24a**,**b**,**e**–**g** were only the target products when the corresponding amino iodides **23a**,**b**,**d**–**f**, if isolated (in 32–68% yields), were cyclized in the presence of K_2CO_3. However, in the same reaction condition, cyclization of **23c**, if not purified by column chromatography, could yield both of the desired compound **24c** and the corresponding N-methylation



Scheme 2.

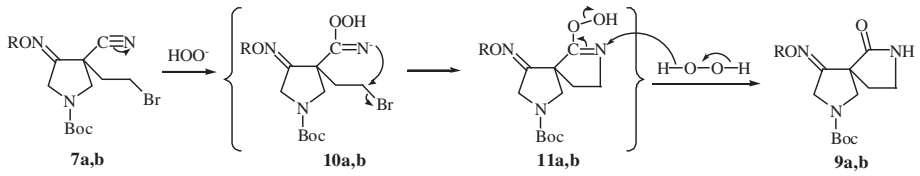
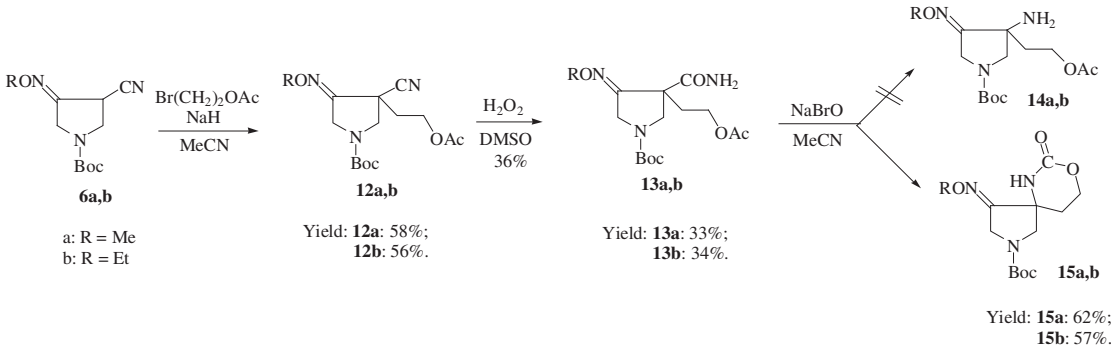


Fig. 3. Possible mechanism of **7a**,**b**→**9a**,**b**.



Scheme 3.

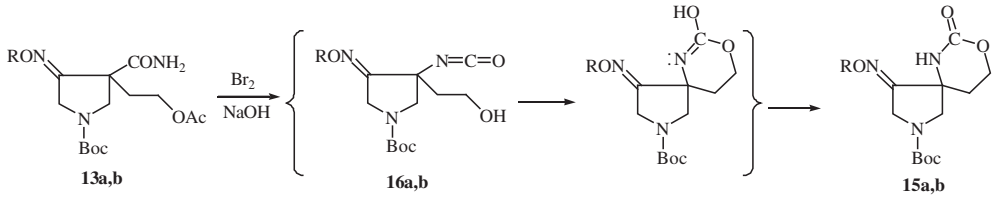


Fig. 4. Possible mechanism of **13a**,**b**→**15a**,**b**.

derivative **24d** simultaneously. This may be due to the existence of MeI in the reaction system resulted from reaction of the excess TMSI with MeOH when **23c** was treated with MeOH (Fig. 6). Surprisingly, only the N-methylation derivatives **24h**,**i**, rather than the corresponding *N*-hydrogen compounds with low percentage, were obtained by isolation techniques from **23g**,**h** although using a similar manner as for the preparation of **24c**,**d**.

3. Conclusion

In summary, the synthesis of naphthyridone derivatives containing 8-alkoxyimino-1,6-dizaspiro[3.4]octane scaffolds, the position isomers of the side chain at the C-7 position of Zabofloxacin, has been achieved through a modified Hofmann rearrangement strategy, in eight steps from *tert*-butyl 3-cyano-4-oxopyrrolidine-1-carboxylate. The possible reaction mechanisms were also proposed. Although the synthetic sequence is inconsistent with the initial design, it has some advantages in synthetic chemistry. First, the spirocyclic compounds **20a**,**b** were reacted with the naphthyridone nuclei **21a**–**e** to yield only condensates **22a**–**h** because there is only one secondary amino group in **20a**,**b**. On the contrary, the designed spirocyclic compounds **19a**,**b** contain two secondary amino groups, so they have no chemoselectivity in condensation with **21a**–**e**, unless the amino group

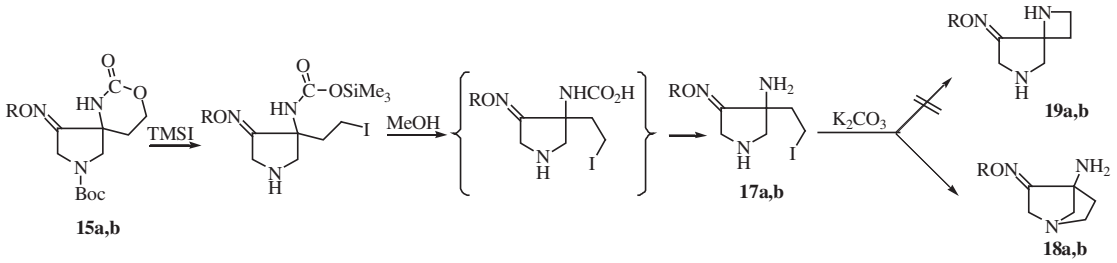
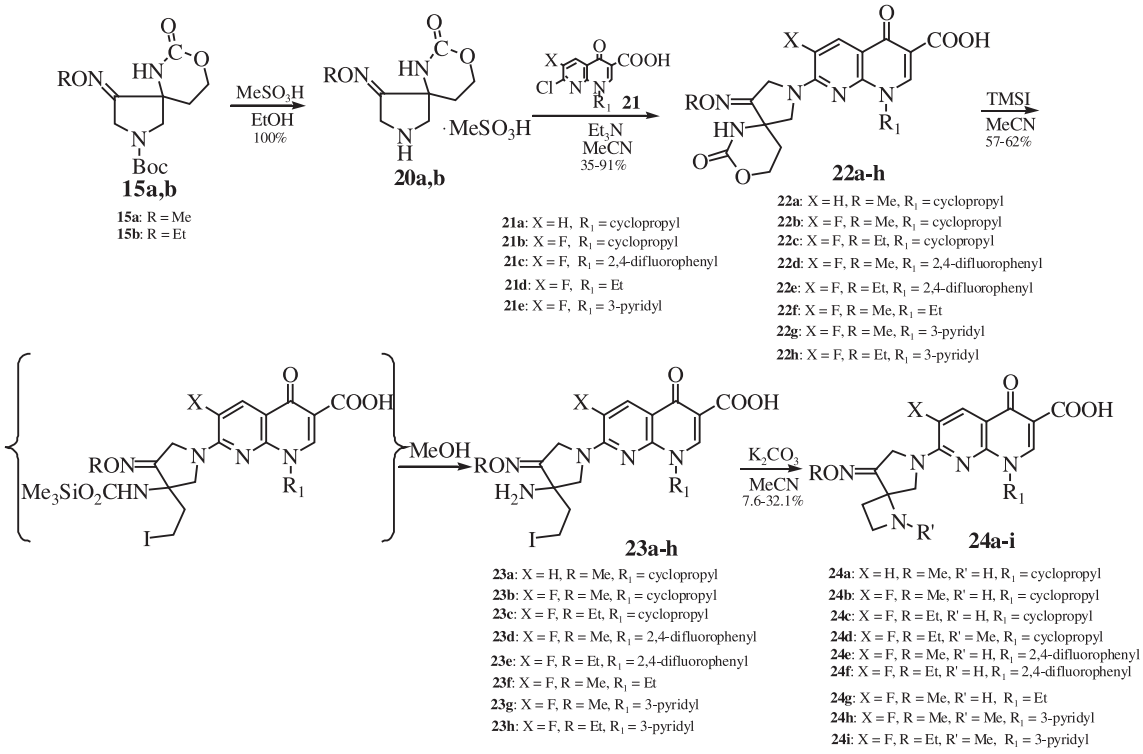


Fig. 5. Possible mechanism of **15a**,**b**→**18a**,**b**.



Scheme 4.

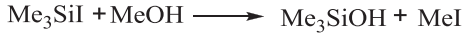


Fig. 6. Possible mechanism of MeI formation.

at the *N*-1 position of **19a**,**b** was previously protected. Second, besides the desired target compounds **24a**,**b**,**e**–**g**, three N-methylation derivatives **24d**,**h**,**i** were also obtained using the synthetic sequence, and this may be important in SAR studies of these naphthyridone derivatives. Further improvement on the reaction conditions of the new sequence is currently in progress.

4. Experimental section

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 an MDSSCIEX Q-Tap mass spectrometer and AccuTOF CS JMS-T100CS (JEOL) mass spectrometer, respectively. Unless otherwise noted, the reagents were obtained from commercial supplier and used without further purification. TLC was performed on silica gel plates (Merck, ART5554 60 F_{254}).

*4.1.1. N-tert-Butoxycarbonyl-3-cyano-4-(methoxyimino/ethoxyimino)pyrrolidine (**6a**,**b**).* To a solution of methoxylamine/ethoxylamine hydrochloride (1.2 mol) and pyridine (80 mL, 1.0 mol) dissolved in MeOH (1000 mL) was added *N-tert*-butoxycarbonyl-3-cyano-4-oxopyrrolidine (**5**, 210 g, 1.0 mol) at room temperature. The reaction mixture was stirred at the same temperature overnight and concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 and washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the title compounds **6a**,**b** as light yellow oils. The crude products were used directly without further purification. Compound **6a**: yield: 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.46 (9H, s, Boc-9H), 3.68–3.90 (3H, m, pyrrolidine), 3.97 (3H, s, OCH_3), 4.06–4.18 (2H, m, pyrrolidine). ESI-MS (*m*/*z*): 262 $(M+Na)^+$. Compound **6b**: yield: 87%. ESI-MS (*m*/*z*): 276 $(M+Na)^+$, 292 $(M+K)^+$.

*4.1.2. N-tert-Butoxycarbonyl-3-(2-acetoxyethyl)-3-cyano-4-(methoxyimino/ethoxyimino)pyrrolidine (**12a**,**b**).* To a solution of **6a**,**b**

(0.9 mol) and 2-bromoethyl acetate[28] (200 g, 1.2 mol) dissolved in MeCN (1000 mL) was added 60% NaH (40 g, 1.0 mol) in batches at 0 °C over 1 h. The reaction mixture was stirred for 4 h at the same temperature, and then adjusted to pH 6.5 with HOAc and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel) eluted with petroleum ether and ethyl acetate to give the title compounds **12a**,**b** as colorless oils. Compound **12a**: yield: 58%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.47 (9H, s, Boc-9H), 2.08 (3H, s, $COCH_3$), 2.10–2.35 (2H, m, CH_2), 3.93 (1H, d, J=10.0 Hz, pyrrolidine–H), 3.94 (3H, s, $NOCH_3$), 4.01–4.41 (5H, m, pyrrolidine–H and OCH_2). ESI-MS (m/z): 348 $(M+Na)^+$, 364 $(M+K)^+$. Compound **12b**: yield: 56%. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.21 (3H, t, J=9.6 Hz, $NOCH_2CH_3$), 1.41 (9H, s, Boc-9H), 2.00 (3H, s, $COCH_3$), 2.20–2.49 (2H, m, CH_2), 3.72–4.27 (8H, m, pyrrolidine–H, $NOCH_2CH_3$ and OCH_2). ESI-MS (m/z): 362 $(M+Na)^+$, 378 $(M+K)^+$.

*4.1.3. N-tert-Butoxycarbonyl-3-(2-acetoxyethyl)-3-carbamoyl-4-(methoxyimino/ethoxyimino)pyrrolidine (**13a**,**b**).* To a stirring solution of **12a**,**b** (0.36 mol) dissolved in DMSO (200 mL) was added K_2CO_3 (40 g, 0.29 mol) at 0 °C, and then added dropwise 30% H_2O_2 (180 mL, 1.6 mol) over 1 h. The reaction mixture was stirred at the same temperature for 3 h, and then overnight at room temperature. The mixture was extracted with ethyl acetate (2×200 mL), and the combined extracts were washed with saturated brine, 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 to afford the title compounds **13a**,**b** as off-white solids. Compound **13a**: yield: 33%, mp: 105–107 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.39 (9H, s, Boc-9H), 1.96 (3H, s, $COCH_3$), 2.04–2.16 (2H, m, CH_2), 3.30–3.33 (1H, m, pyrrolidine–H), 3.83 (3H, s, $NOCH_3$), 3.90–4.14 (5H, m, pyrrolidine–H and OCH_2), 7.12, 7.36 (2H, s, D_2O exchangeable, $CONH_2$). ESI-MS (m/z): 366 $(M+Na)^+$, 382 $(M+K)^+$. HRMS-ESI (m/z): $C_{15}H_{26}N_3O_6$ calcd: 344.18216; found 344.18233. Compound **13b**: yield: 34%, mp: 115–116 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.19 (3H, t, J=7.2 Hz, $NOCH_2CH_3$), 1.39 (9H, s, Boc-9H), 1.96 (3H, s, $COCH_3$), 2.05–2.16 (2H, m, CH_2), 3.30–4.15 (8H, m, pyrrolidine–H, $NOCH_2CH_3$ and OCH_2), 7.09, 7.35 (2H, s, D_2O exchangeable, $CONH_2$). ESI-MS (m/z): 380 $(M+Na)^+$, 396 $(M+K)^+$. HRMS-ESI (m/z): $C_{16}H_{28}N_3O_6$ calcd: 358.19781; found 358.19747.

*4.1.4. **2**-(N-tert-Butoxycarbonyl)-4-methoxyimino/ethoxyimino-7-oxo-8-oxa-2,6-diazaspiro[4.5]decane (**15a**,**b**).* To a solution of **13a**,**b** (0.10 mol) dissolved in MeCN (200 mL) was added dropwise freshly prepared 8% NaBrO (281 mL, 0.20 mol) at 0 °C over 1 h. The reaction mixture was stirred at room temperature overnight. The organic layer was separated, adjusted to pH 6.5 with HOAc, and then concentrated under reduced pressure. The residue was diluted with H_2O (200 mL), and combined with the above water layer. The combined water layers were adjusted to pH 3.0 with 6 N HCl and washed with ethyl acetate (2×100 mL), and then adjusted to pH 9.0 with 6 N NaOH and extracted with ethyl acetate (6×200 mL). The combined extracts were washed with saturated brine, 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 to afford the title compounds **15a**,**b** as off-white solids. Compound **15a**: yield: 62%, mp: 184–186 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.40 (9H, s, Boc-9H), 2.06–2.11 (2H, m, CH_2), 3.36–3.66 (2H, m, pyrrolidine–H), 3.84 (3H, s, $NOCH_3$), 4.01–4.25 (4H, m, pyrrolidine–H and OCH_2), 7.66 (1H, s, D_2O exchangeable, CONH). ESI-MS (m/z): 300 $(M+H)^+$, 322 $(M+Na)^+$. HRMS-ESI (m/z): $C_{13}H_{22}N_3O_5$ calcd: 300.15595; found 300.15621. Compound **15b**: yield: 57%, mp: 114–116 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.19 (3H, t, J=7.2 Hz, $NOCH_2CH_3$), 1.40 (9H, s, Boc-9H), 2.01–2.04 (2H, m, CH_2), 3.30–3.66 (2H, m, pyrrolidine–H), 3.99–4.26 (7H, m, pyrrolidine–H, $NOCH_2CH_3$ and OCH_2), 7.65 (1H, s, D_2O exchangeable, CONH). ESI-MS (m/z): 314 $(M+H)^+$, 336 $(M+Na)^+$. HRMS-ESI (m/z): $C_{14}H_{24}N_3O_5$ calcd: 314.17160; found 314.17148.

*4.1.5. 4-Methoxyimino/ethoxyimino-7-oxo-8-oxa-2,6-diazaspiro[4.5]decane mesylate (**20a**,**b**).* To a solution of **15a**,**b** (60 mmol) dissolved in EtOH (100 mL) was added methanesulfonic acid (7.8 mL, 120 mmol) at room temperature. The reaction mixture was stirred at 50 °C overnight and then concentrated under reduced pressure to afford the crude title compounds **20a**,**b** (60 mmol, 100%) as light yellow oils, which were used directly without further purification.

A mixture of the above crude **20a** and CH_2Cl_2 (100 mL) was stirred for 1 h at room temperature. The resulting precipitate was filtered and dried to give off-white solid (30 mmol, 50%), mp: 155–157 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.06–2.17 (2H, m, CH_2), 2.34 (3H, s, CH_3SO_3), 3.34–4.32 (9H, m, pyrrolidine–H, $NOCH_3$ and OCH_2), 7.62 (1H, s, D_2O exchangeable, CONH), 9.39 (2H, s, D_2O exchangeable, $CH_3SO_3H_2N$). ESI-MS (m/z): 200 $(M+H)^+$. HRMS-ESI (m/z): $C_8H_{14}N_3O_3$ calcd: 200.10352; found 200.10381.

*4.1.6. 1-Cyclopropyl-7-[8-(methoxyimino)-1,6-diazospiro[3.4]oct-6-yl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**24a**).* To a solution of the above crude **20a** (2.9 g, 9.8 mmol) dissolved in MeCN (50 mL) was added Et_3N (14.1 mL, 98 mmol) and 7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**21a**, 1.8 g, 7.3 mmol) at room temperature. The reaction mixture was stirred at 50 °C overnight. The resulting precipitate was filtered, washed with H_2O and CH_3CN, dried to give **22a** (1.5 g, 35%) as an off-white solid, which was used directly without further purification.

To a solution of the above solid **22a** dissolved in MeCN (50 mL) was added TMSI (22.5 mmol) at 50 °C, and stirred at the same temperature for 1 h. After cooled to room temperature, to the reaction mixture was added MeOH (10 mL) and continued to stir at the same temperature for 10 min, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel) eluted with CH_2Cl_2 and MeOH to provide **23a** (0.74 g, 42%) as a yellow solid, which was used directly without further purification.

To a solution of the above solid **23a** dissolved in MeCN (100 mL) was added K_2CO_3 (4.4 g, 32 mmol). The reaction mixture was heated to reflux and stirred at the same temperature for 5 h, and then concentrated under reduced pressure. The residue was diluted with H_2O (50 mL), adjusted to pH 6.0 with 20% HOAc, and then extracted with CH_2Cl_2 (3×100 mL). The combined extracts were washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel) eluted with CH_2Cl_2 and MeOH to afford the title compound **24a** (58.5 mg, 10.6%) as a light yellow solid, mp: 236 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.03–1.19 (4H, m, 2× cyclopropyl CH_2), 2.46–2.52 (2H, m, CH_2), 3.24–3.74 (3H, m, pyrrolidine–H and cyclopropyl–H), 3.93–4.38 (7H, m, pyrrolidine–H, $NOCH_3$ and CH_2N), 6.95 (1H, s, C_6–H), 8.28 (1H, d, J=8.8 Hz, C_5–H), 8.58 (1H, s, C_2–H), 15.40 (1H, br s, D_2O exchangeable, COOH). ESI-MS (m/z): 384 $(M+H)^+$. HRMS-ESI (m/z): $C_{19}H_{22}N_5O_4$ calcd: 384.16663; found 384.16621.

*4.1.7. 1-Cyclopropyl-6-fluoro-7-[8-(methoxyimino)-1,6-diazospiro[3.4]oct-6-yl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**24b**).* The title compound **24b** was obtained from **20a** and 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**21b**) in a similar manner as for the preparation of **24a**. Yield: 7.6%, mp: 227–228 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.04–1.08 (2H, m, cyclopropyl CH_2), 1.28–1.33 (2H, m, cyclopropyl CH_2), 2.62–2.69 (2H, m, CH_2),

3.44–3.49 (1H, m, pyrrolidine–H), 3.64–3.67 (1H, m, cyclopropyl–H), 3.85 (1H, d, J=8.0 Hz, pyrrolidine–H), 4.00 (3H, s, $NOCH_3$), 4.04–4.60 (4H, m, pyrrolidine–H and CH_2N), 8.01 (1H, d, J=12.4 Hz, C_5–H), 8.67 (1H, s, C_2–H). ESI-MS (m/z): 402 $(M+H)^+$. HRMS-ESI (m/z): $C_{19}H_{21}FN_5O_4$ calcd: 402.15721; found 402.15745.

*4.1.8. 1-Cyclopropyl-6-fluoro-7-[8-(ethoxyimino)-1,6-diazospiro[3.4]oct-6-yl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**24c**).* To a solution of **22c** (1.5 g, 3.3 mmol), which was obtained from **20b** and **21b** in a similar manner as for the preparation of **22a**, in MeCN (50 mL) was added TMSI (22.5 mmol) at 50 °C, and stirred at the same temperature for 1 h. After cooled to room temperature, MeOH (10 mL) was added and continued to stir at the same temperature for 10 min. To the reaction mixture was added K_2CO_3 (4.4 g, 32 mmol), stirred at reflex for 5 h and then concentrated under reduced pressure. To the residue was diluted with H_2O (50 mL), adjusted to pH 6.0 with 20% HOAc, and then extracted with CH_2Cl_2 (3×100 mL). The combined extracts were washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel) eluted with CH_2Cl_2 and CH_3OH to afford The title compound **24c**, and its N-methylation compound 1-cyclopropyl-6-fluoro-7-[1-methyl-8-(ethoxyimino)-1,6-diazospiro [3.4]oct-6-yl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**24d**).

Compound **24c**: yield: 14.5%, mp: 192–193 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.04–1.09 (2H, m, cyclopropyl CH_2), 1.30–1.36 (5H, m, $NOCH_2CH_3$ and cyclopropyl CH_2), 1.45–2.00 (1H, br s, D_2O exchangeable, NH), 2.68–2.74 (2H, m, CH_2), 3.56–3.57 (1H, m, pyrrolidine–H), 3.66–3.68 (1H, m, cyclopropyl–H), 3.90 (1H, d, J=8.0 Hz, pyrrolidine–H), 4.18–4.71 (6H, m, pyrrolidine–H, $NOCH_2CH_3$ and CH_2N), 8.02 (1H, d, J=12.0 Hz, C_5–H), 8.69 (1H, s, C_2–H), 15.30 (1H, br s, D_2O exchangeable, COOH). ESI-MS (m/z): 416 $(M+H)^+$. HRMS-ESI (m/z): $C_{20}H_{23}FN_5O_4$ calcd: 416.17286; found 416.17349.

Compound **24d**: yield: 32.1%, mp: 235–236 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.10–1.12 (2H, m, cyclopropyl CH_2), 1.19–1.21 (2H, m, cyclopropyl CH_2), 1.28 (3H, t, J=6.8 Hz, $NOCH_2CH_3$), 2.16 (3H, s, NCH_3), 2.34–2.37 (2H, m, CH_2), 3.07–3.30 (2H, m, pyrrolidine–H), 3.73–3.77 (1H, m, cyclopropyl–H), 3.95 (1H, d, J=12.4 Hz, pyrrolidine–H), 4.18–4.58 (5H, m, pyrrolidine–H, $NOCH_2CH_3$ and CH_2N), 8.05 (1H, d, J=12.8 Hz, C_5–H), 8.60 (1H, s, C_2–H). ESI-MS (m/z): 430 $(M+H)^+$. HRMS-ESI (m/z): $C_{21}H_{25}FN_5O_4$ calcd: 430.18851; found 430.18855.

*4.1.9. 1-(2,4-Difluorophenyl)-6-fluoro-7-[8-(methoxyimino)-1,6-diazospiro[3.4]oct-6-yl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**24e**).* The title compound **24e** was obtained from **20a** and 7-chloro-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**21c**) in a similar manner as for the preparation of **24a**. Yield: 10.6%, mp: 219 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.53–2.64 (2H, m, CH_2), 3.44–3.85 (4H, m, pyrrolidine–H and CH_2N), 3.94 (3H, s, $NOCH_3$), 4.20–4.45 (2H, m, pyrrolidine–H), 7.08–7.15 (2H, m, Ar–H), 7.39–7.43 (1H, m, Ar–H), 8.11 (1H, d, J=12.0 Hz, C_5–H), 8.66 (1H, s, C_2–H). ESI-MS (m/z): 474 $(M+H)^+$. HRMS-ESI (m/z): $C_{22}H_{19}F_3N_5O_4$ calcd: 474.13837; found 474.13834.

*4.1.10. 1-(2,4-Difluorophenyl)-6-fluoro-7-[8-(ethoxyimino)-1,6-diazospiro[3.4]oct-6-yl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**24f**).* The title compound **24f** was obtained from **20b** and **21c** in a similar manner as for the preparation of **24a**. Yield: 10.6%, mp: 193 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.22 (3H, t, J=7.2 Hz, $NOCH_2CH_3$), 2.32–2.54 (2H, m, CH_2), 3.15–4.14 (8H, m, pyrrolidine–H, $NOCH_2CH_3$ and CH_2N), 7.33–7.84 (3H, m, Ar–H), 8.12 (1H, d, J=12.8 Hz, C_5–H), 8.86 (1H, s, C_2–H). ESI-MS (m/z): 488 $(M+H)^+$. HRMS-ESI (m/z): $C_{23}H_{21}F_3N_5O_4$ calcd: 488.15402; found 488.15384.

*4.1.11. 1-Ethyl-6-fluoro-7-[8-(methoxyimino)-1,6-diazospiro[3.4]oct-6-yl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**24g**).* The title compound **24g** was obtained from **20a** and 7-chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**21d**) in a similar manner as for the preparation of **24a**. Yield: 10.5%, mp: 197 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.41 (3H, t, J=7.2 Hz, NCH_2CH_3), 3.22–3.57 (4H, m, pyrrolidine–H and CH_2N), 3.92 (3H, s, $NOCH_3$), 4.05–4.55 (6H, m, pyrrolidine–H and NCH_2CH_3), 8.06 (1H, d, J=12.8 Hz, C_5–H), 8.96 (1H, s, C_2–H). ESI-MS (m/z): 390 $(M+H)^+$. HRMS-ESI (m/z): $C_{18}H_{21}FN_5O_4$ calcd: 390.15721; found 390.15718.

*4.1.12. 1-(Pyridin-3-yl)-6-fluoro-7-[1-methyl-8-(methoxyimino)-1,6-diazospiro[3.4] oct-6-yl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**24h**).* The title compound **24h** was obtained from **20a** and 7-chloroethyl-6-fluoro-1-(pyridin-3-yl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**21e**) in a similar manner as for the preparation of **24d**. Yield: 19.6%, mp: 235–236 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.06 (3H, s, NCH_3), 2.07–2.28 (2H, m, CH_2), 2.98–4.28 (9H, m, pyrrolidine–H, $NOCH_3$ and CH_2N), 7.63–8.82 (6H, m, Ar–H), 15.09 (1H, br s, D_2O exchangeable, COOH). ESI-MS (m/z): 453 $(M+H)^+$. HRMS-ESI (m/z): $C_{22}H_{21}FN_4O_6$ calcd: 453.16811; found 453.16788.

*4.1.13. 1-(Pyridin-3-yl)-6-fluoro-7-[1-methyl-8-(ethoxyimino)-1,6-diazospiro[3.4] oct-6-yl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**24i**).* The title compound **24i** was obtained from **20b** and **21e** in a similar manner as for the preparation of **24d**. Yield: 24.3%, mp: 237–238 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.18–1.26 (3H, m, $NOCH_2CH_3$), 2.06 (3H, s, NCH_3), 2.09–2.25 (2H, m, CH_2), 3.00–4.25 (8H, m, pyrrolidine–H, $NOCH_2CH_3$ and CH_2N), 7.63–8.82 (6H, m, Ar–H), 15.08 (1H, br s, D_2O exchangeable, COOH). ESI-MS (m/z): 467 $(M+H)^+$. HRMS-ESI (m/z): $C_{23}H_{23}FN_4O_6$ calcd: 467.18376; found 467.18414.

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28. Acetyl chloride (96 mL, 3.3 mol) was added dropwise to 2-bromoethanol (213 mL, 3.0 mol) at 0 °C over 1 h. The reaction mixture was stirred at the same temperature for 5 h, and then washed with saturated K_2CO_3 solution, dried over anhydrous Na_2SO_4 to give 2-bromoethyl acetate 432 g (87%)as a light yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.04 (3H, s, $COCH_3$), 3.65 (2H, t, J=6.4 Hz, CH_2Br), 4.31 (2H, t, J=6.4 Hz, CH_2O).