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The synthesis and biological evaluation of a novel series of C7 non-basic substituted fluoroquinolones as antibacterial agents

Xiaoguang Huang, Dongliang Chen, Ning Wu, Aiqin Zhang, Zhenhua Jia, Xingshu Li *

School of Pharmaceutical Science, Sun Yat-Sen University, Guangzhou 510006, China

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ABSTRACT

A series of non-basic building blocks was synthesized and introduced to the C7 position of the quinolone nucleus 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid to afford the corresponding fluoroquinolones in 46–85% yield. The antibacterial activity of these new fluoroquinolones was evaluated using a standard broth microdilution technique. The sulfur-containing quinolone, 7-(2-thia-5-azabicyclo[2.2.1]heptan-5-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid exhibited a superior antibacterial activity against quinolone-susceptible and multidrug-resistant strains in comparison with the clinically used fluoroquinolones ciprofloxacin and vancomycin, especially to the *Streptococcus pneumonia* and multidrug-resistant *S. pneumonia* clinical isolates.

There is an urgent medical need for novel antibacterial agents to treat community-acquired infections, especially community-acquired pneumonia (CAP) caused by multidrug-resistant Gram-positive pathogens. It has become difficult to treat community-acquired infections because on a worldwide basis, nosocomial multidrug-resistant Gram-positive staphylococcal and enterococcal pathogenic isolates are found to display resistance to frontline antimicrobial agents such as methicillin and more recently vancomycin.[1] *Streptococcus pneumoniae* is one of the most significant causes of CAP, meningitis, otitis media, sinusitis, and acute exacerbations of chronic bronchitis, and it is also responsible for substantial morbidity and mortality worldwide.[2] The fluoroquinolones are one of the most important groups of antibiotics against CAP therapy in the clinic. For example, ciprofloxacin, which was introduced in 1986, has become one of the most potent and widely used antibacterial agents today.[3] However, some of these drugs currently on the market or under development have insufficient activity which has resulted not only in their limited use in infections caused by Gram-positive cocci, including Staphylococci and Streptococci, but is also believed to be one of the reasons for the rapid development of quinolone resistance.[4] Additionally, some recently approved fluoroquinolones have had cardiovascular safety issues, in particular the possibility of QT interval prolongation (The QT interval is defined as the time interval between the start of the Q wave and end of the T wave on an electrocardiogram associated with each heartbeat), which can lead to potentially fatal *torsades de pointes*.[1a,5] These concerns led to sparfloxacin and grepafloxacin being removed from the market and bolded warnings added to the package inserts for moxifloxacin and gatifloxacin.[6] From both fundamental and practical standpoints, it is highly desirable to develop new antibacterial agents which are more safe, highly potent and with a possible broad antibacterial spectrum for both multidrug-resistant Gram-positive and Gram-negative pathogens.

As there are serious consequences as a result of inducing QT interval prolongation from drug treatment, much research has been performed to understand the effect, and several methods have been identified for predicting it. Some results have indicated that a basic nitrogen and two or three aromatic components at appropriate distances from the amine confer an increased risk of QT interval prolongation.[7] A structure–activity relationship (SAR) study has shown that substituents at the C7 position of the quinolone core greatly influence their potency, spectrum, and safety. Murphy et al. found that QT interval prolongation was dramatically decreased by reducing the C7 amine basicity and reducing the lipophilicity of the quinolone core, while at the same time maintaining activity against resistant organisms.[8]

Although many marketed quinolones bearing side chains at the C7 position have a secondary amine basic functionality, there are some molecules which exhibit excellent antibacterial potency without this characteristic structure. For example, nadifloxacin[9] (Fig. 1 (**1**)), which contains a 4-hydroxypiperidine moiety at the C8 position without a distal basic functionality, was introduced only for topical use as a liniment against *Propionibacterium acnes*.[10] It exhibited excellent antibacterial potency against both Gram-positive and Gram-negative strains, especially for the *Staphylococcus*

* Corresponding author.
E-mail address: lixsh@mail.sysu.edu.cn (X. Li).

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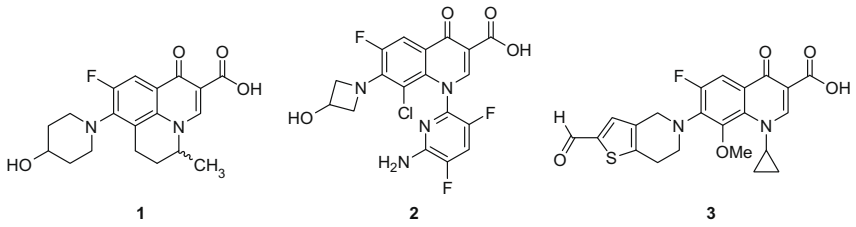
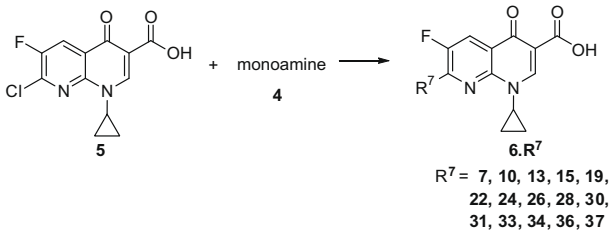


Figure 1. Some quinolones containing a C7 monoamine moiety.



Scheme 1. Reagents and conditions: Et_3N, CH_3CN, 50–80 °C (46–85%).

aureus strains isolated from skin infections.[11] The other new quinolones bearing a C7 non-secondary amine moiety are ABT-492 (WQ-3034) (**2**)[12] and a sulfur-containing quinolone (**3**) (Fig. 1), which exhibited excellent activities against many Gram-positive and Gram-negative organisms during in vitro activity assays.[13] Based on these research results, we set out to develop new fluoroquinolones using the less lipophilic naphthyridine acid **5** as the quinolone core and a monoamine moiety at the C7 position instead of a diamine to avoid severe adverse effects. In addition, this quinolone core has less mammalian cell cytotoxicity, good activity against resistant organisms,[14] and superior pharmacokinetics (PK), pharmacodynamics (PD), and ADME properties.[15] Herein, we report our studies based on C7 non-basic substituted quinolones, in particular compound **6.24**, which exhibited excellent in vitro antibacterial potencies against Gram-positive, Gram-negative, and resistant strains.

The synthesis of quinolone core **5** was carried out according to a known procedure.[16] We chose the cyclopropanamine for the preparation of the quinolone core **5**, because this group was widely used as an N1 substituent for other quinolone antibiotics which have exhibited good antibacterial activities.[14] With the quinolone core **5**, a series of new quinolones **6** could be prepared by the reaction of **5** with different monoamine intermediates (Scheme 1).

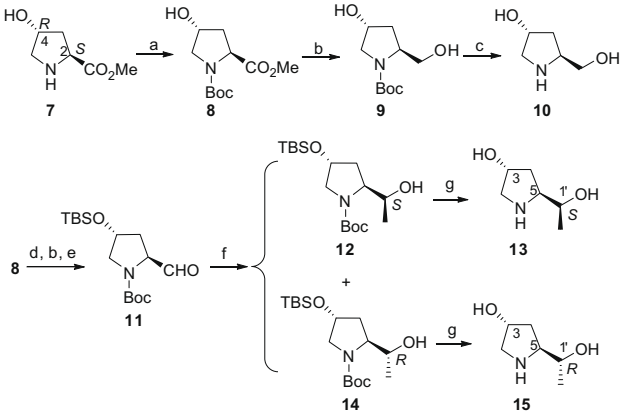
We first chose (2*S*,4*R*)-methyl 4-hydroxypyrrolidine-2-carboxylate **7**, which was cheap and commercially available as the starting material for the preparation of C7 intermediates **10**, **13**, and **15** (Scheme 2).[17]

Another diol-containing amine, (*R*,*R*)-pyrrolidine-3,4-diol (**19**),[18] which has two adverse hydroxy groups in configuration at the 3rd and 4th position of the pyrrolidine ring was synthesized starting from the L-tartaric acid **16** (Scheme 3).

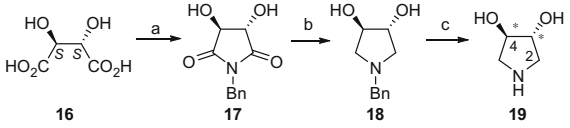
Some bridged intermediates such as **22**, **24**, **26**, **28**, and **30** were synthesized from compound **9** (Scheme 4).[19–21]

The 1,2,3-triazole intermediates **33**, **34**, **36**, and **37**, were also prepared from **31**(Scheme 5).[22]

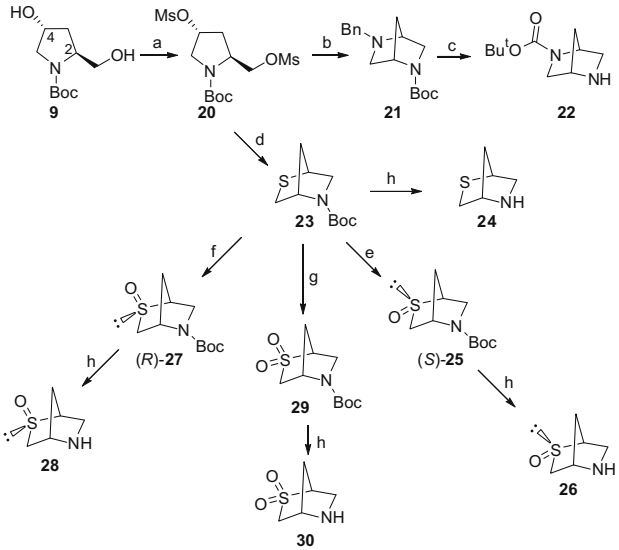
The minimal inhibitory concentrations (MICs) or the lowest drug concentration that prevents visible growth of bacteria, were determined by a standard broth microdilution technique using the National Committee for Clinical and Laboratory Standards method.[23] The bacterial strains used for susceptibility studies were either clinical isolates from the hospital culture collection or reference strains from the American Type Culture Collection. The in vitro assay results are listed in Table 1.



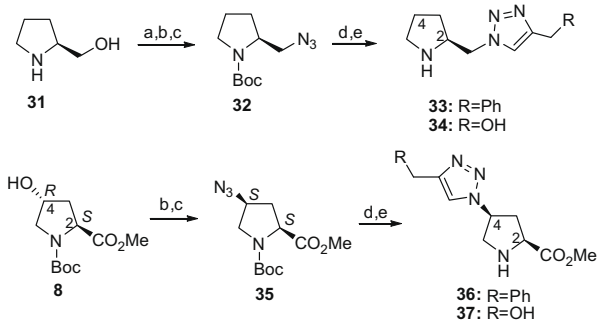
Scheme 2. Reagents and conditions: (a) $(Boc)_2O$, NaOH, rt (96%); (b) $LiAlH_4$, THF, 0 °C–rt (78%); (c) HCl(g) (83%); (d) TBSCl, imidazole, DMF, 0 °C–rt (92%); (e) SO_3·pyridine, Et_3N, DMSO, 0 °C–rt (90%); (f) Mg, CH_3I, rt (42% **12** and 30% **14**); (g) TFA/H_2O (9:1), rt (quantitative).



Scheme 3. Reagents and conditions: (a) phenylmethanamine, toluene, reflux (76%); (b) $LiAlH_4$, THF, reflux (68%); (c) Pd/C, H_2, MeOH (quantitative).



Scheme 4. Reagents and conditions: (a) MsCl, Et_3N, DCM, 0 °C–rt (93%); (b) phenylmethanamine, toluene, reflux (82%); (c) Pd/C, H_2 (76%); (d) $Na_2S·9H_2O$, DMSO, 110 °C (70%); (e) $Ti(O^iPr)_4$-(*S*,*S*)-(−)-DET-H_2O (1:2:1), ^{t}BuOOH, DCM, −25 °C (89%); (f) $Ti(O^iPr)_4$-(*R*,*R*)-(+)-DET-H_2O(1:2:1), ^{t}BuOOH, DCM, −25 °C (77%); (g) *m*-CPBA, DCM, rt (81%); (h) TFA, DCM (quantitative).



Scheme 5. Reagents and conditions: (a) $(Boc)_2O$, NaOH, THF/H_2O, rt (94%); (b) MsCl, Et_3N, DCM, 0 °C–rt (85%); (c) NaN_3, DMF, 80 °C (92%); (d) 1-ethynylbenzene or prop-2-yn-1-ol, CuI, DIPEA, MeOH, rt (91% and 85%, respectively); (e) TFA, DCM (quantitative).

In vitro assay results revealed that the antibacterial potency of target quinolone **6.7** was moderate for Gram-positive strains, and mild for Gram-negative strains. These results indicated that the new chiral center of quinolone **6.13** and **6.15** at the 1′ position did not play an important role in the antibacterial potency as the two new compounds had similar activities against both Gram-positive and Gram-negative strains which were less than that of **6.7**. However, the antibacterial potencies of the three quinolones were all superior to that of quinolone **6.10**.

The activities of quinolones **6.19** were comparable to quinolone **6.7**, and the results indicated that the chiral hydroxy group at the 4th position of the pyrrolidine ring did not play an essential role in influencing the potency. However, quinolone **6.19** exhibited enhanced potency against *Escherichia coli*.

The quinolone **6.22** exhibited almost equivalent antibacterial activities to most organisms as quinolone **6.19**, with the exception of *S. aureus* (0.25 μg/mL). Interestingly, the four sulfur-containing quinolones, **6.24**, **6.26**, **6.28**, and **6.30** exhibited good to excellent activities. Especially, quinolone **6.24** provided excellent potency against all the pathogens except the multidrug-resistant *S. aureus* clinical isolates. It provided the most effective antibacterial activity against *S. aureus* (MIC = 0.016 μg/mL), excellent potency against *S. pneumonia* (0.031 μg/mL), and multidrug-resistant *S. pneumonia* clinical isolates (0.031 μg/mL), but was somewhat less potent than the reference drug ciprofloxacin (0.008 and 0.008 μg/mL, respectively). However, the activities of **6.24** against *Staphylococcus epidermidis* (0.125 μg/mL) and *Enterococcus faecalis* (0.125 μg/mL) were superior to ciprofloxacin (0.5 μg/mL and 0.5 μg/mL, respectively). It should be noted that quinolone **6.24** maintained good antibacterial activity against both the Gram-positive and Gram-negative strains. For example, the MIC against *S. aureus* (0.016 μg/mL) was superior to ciprofloxacin (0.125 μg/mL), and it had the same activity against *E. coli* (0.125 μg/mL) as ciprofloxacin (0.125 μg/mL). The activities of **6.24** against *Pseudomonas aeruginosa* (2 μg/mL) and multidrug-resistant *P. aeruginosa* (32 μg/mL) were also good, although less than ciprofloxacin (0.5 μg/mL and 16 μg/mL, respectively). On the other hand, the sulfone-containing quinolone **6.30** displayed comparable potency to quinolone **6.24** across the strains with the exception of *P. aeruginosa* (8 μg/mL). The two chiral sulfoxide-containing quinolones **6.26** and **6.28** also exhibited excellent activities against *S. pneumoniae* (0.125 μg/mL and 0.5 μg/mL, respectively) and multidrug-resistant *S. pneumonia* (0.125 μg/mL and 0.25 μg/mL, respectively). However, all four quinolones were inactive against multidrug-resistant *S. aureus* (MIC >32 μg/mL).

Quinolone **6.31** (Scheme 5) from **31** and quinolone nucleus **5** exhibited good activities against *S. aureus*, *S. pneumonia*, multidrug-resistant *S. pneumonia* and *E. faecalis* (MICs all 0.5 μg/mL), and was more potent (8–16-fold) than quinolones **6.10** against the other pathogens except *P. aeruginosa* and multidrug-resistant *P. aeruginosa*. The results indicated that the chiral center at C4 of the pyrrolidine may be obstructed during the interaction with some bacteria.

Two quinolones **6.33** and **6.34**, derived from 1,2,3-triazoles, only displayed mild potency against all the strains. Quinolones **6.37** exhibited moderate activities against most strains with an exception of *E. faecalis* (0.5 μg/mL). In addition, **6.37** was more effective than **6.36** against all the strains, which was comparable to that of quinolone **6.7**. The results indicated that the 1,2,3-triazole structure at the 4th position of the pyrrolidine was not an effective moiety to influence the potency although the stereocenter was inverted to the adverse configuration.

In conclusion, we have synthesized a series of new quinolones based on (2*S*,4*R*)-methyl 4-hydroxypyrrolidine-2-carboxylate and (*S*)-pyrrolidin-2-ylmethanol. From in vitro potency assay results, it

Table 1
In vitro MIC values of novel quinolones in various Gram-positive and Gram-negative bacteria[a]

Compound	Gram-positive						Gram-negative		
	S.a.1	S.a.2	S.p.1	S.p.2	S.e.	E.f.	E.c.	P.a.1	P.a.2
6.7	2	>32	0.5	0.5	16	1	8	32	32
6.10	16	>32	8	8	>32	4	32	32	32
6.13	16	>32	1	2	32	4	8	32	32
6.15	32	>32	2	8	>32	2	16	32	32
6.19	4	>32	2	2	>32	2	4	32	32
6.22	0.25	>32	2	0.5	4	0.5	4	32	32
6.24	0.016	>32	0.031	0.031	0.125	0.125	0.125	2	32
6.26	1	>32	0.125	0.125	1	0.25	0.5	16	32
6.28	4	>32	0.5	0.25	4	1	1	32	32
6.30	0.016	>32	0.063	0.031	0.5	0.063	0.125	8	32
6.31	0.5	>32	0.5	0.5	8	0.5	2	32	32
6.33	1	>32	2	2	>32	4	>32	>32	>32
6.34	32	>32	8	4	32	4	32	32	32
6.36	>32	>32	4	8	>32	16	32	32	32
6.37	4	>32	1	1	8	0.5	4	32	>32
Ciprofloxacin	0.125	>32	0.008	0.008	0.5	0.5	0.125	0.5	16
Vancomycin	1	1	1	2	2	0.5			

[a] MICs were determined by microbroth dilution technique and values reported in the table represent the values obtained in triplicate. S.a.1, *Staphylococcus aureus* **ATCC25923**; S.a.2, multidrug-resistant *S. aureus* clinical isolates; S.p.1, *Streptococcus pneumoniae* **ATCC49619**; S.p.2, multidrug-resistant *S. pneumonia* clinical isolates; S.e., *Staphylococcus epidermidis* **ATCC12228**; E.f., *Enterococcus faecalis* **ATCC29212**; E.c., *Escherichia coli* **ATCC25922**; P.a.1, *Pseudomonas aeruginosa* **ATCC27853**; P.a.2, multidrug-resistant *P. aeruginosa* clinical isolate.

was determined that 7-(5-thia-2-aza-bicyclo[2.2.1]heptan-2-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**6.24**), the corresponding sulfoxides (**6.26** and **6.28**), and sulfone (**6.30**) exhibited good to excellent activities against all the Gram-positive and Gram-negative strains tested.[24] Quinolones **6.24** and **6.30** displayed superior activities against all the strains, whereas quinolones **6.26** and **6.28** had comparatively low potency against all the pathogens. In general, they were all effectively potent against strains of *S. pneumoniae* and multidrug-resistant *S. pneumonia*, which are the most significant strains of CAP. Further work on the antibacterial activity of these compounds using an expanded panel of organisms and in vivo efficacy models are in progress.

Acknowledgments

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24. *The proposed structures are supported by the ^{1}H NMR experiments and mass spectra*. Selected NMR and LC–ESIMS data are as follows. Compound **6.24**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 15.10 (s, 1H), 8.68 (s, 1H), 8.00 (d, J = 12.4 Hz, 1H), 5.29 (s, 1H), 4.12 (s, 1H), 4.06 (s, 1H), 3.77 (s, 1H), 3.61 (m, 1H), 3.36 (s, 1H), 3.21 (s, 1H), 2.39 (d, J = 8.4 Hz, 1H), 2.10 (d, J = 10.0 Hz, 1H), 1.65 (s, 1H), 1.25 (d, J = 6.4 Hz, 2H), 1.07 (d, J = 3.2 Hz, 1H). LC–ESIMS for $C_{17}H_{16}FN_3O_3S$ [M+H$^+$] calcd 361.1 found 362.0 (M+H); compound **6.26**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.83 (s, 1H), 8.74 (s, 1H), 8.10 (d, J = 12.4 Hz, 1H), 5.35 (s, 1H), 4.08 (d, J = 10.8 Hz, 1H), 3.97 (d, J = 4.0 Hz, 1H), 3.70 (d, J = 12.8 Hz, 1H), 3.60 (m, 1H), 3.40 (d, J = 11.6 Hz, 1H), 2.88 (d, J = 12.0 Hz, 1H), 2.62 (d, J = 12.4 Hz, 1H), 2.50 (d, J = 11.6 Hz, 1H), 1.28 (d, J = 7.6 Hz, 2H), 1.26 (s, 2H). LC–ESIMS for $C_{17}H_{16}FN_3O_4S$ [M+H$^+$] calcd 377.1 found 378.0 (M+H); compound **6.28**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.89 (s, 1H), 8.66 (s, 1H), 8.03 (d, J = 12.4 Hz, 1H), 5.28 (s, 1H), 4.66 (d, J = 8.8 Hz, 1H), 4.02 (t, J = 12.8 Hz, 1H), 3.64 (d, J = 12.8 Hz, 1H), 3.53 (s, 1H), 3.21 (d, J = 12.4 Hz, 1H), 2.55 (d, J = 13.2 Hz, 1H), 2.45 (t, J = 12.8 Hz, 1H), 1.91 (d, J = 11.6 Hz, 1H), 1.19 (s, 4H). LC–ESIMS for $C_{17}H_{16}FN_3O_4S$ [M+H$^+$] calcd 377.1 found 378.0 (M+H); compound **6.30**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 15.23 (s, 1H), 8.63 (s, 1H), 8.14 (d, J = 12.0 Hz, 1H), 5.29 (s, 1H), 4.17 (s, 1H), 4.11 (d, J = 8.8 Hz, 1H), 3.71 (s, 1H), 3.47 (s, 1H), 3.09 (q, J = 6.4 Hz, 1H), 2.59 (d, J = 7.6 Hz, 1H), 2.34 (s, 1H), 1.25 (d, J = 14.4 Hz, 1H), 1.18 (t, J = 7.2 Hz, 2H), 1.11 (d, J = 7.2 Hz, 2H). LC–ESIMS for $C_{17}H_{16}FN_3O_5S$ [M+H$^+$] calcd 393.1 found 394.1 (M+H).