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4-Substituted 4-(1*H*-1,2,3-triazol-1-yl)piperidine: Novel C7 moieties of fluoroquinolones as antibacterial agents

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ABSTRACT

A series of 4-substituted 4-(1*H*-1,2,3-triazol-1-yl)piperidine building blocks was synthesized and introduced to the C7 position of the quinolone core, 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid, to afford the corresponding fluoroquinolones in 40–83% yield. The antibacterial activity of these new fluoroquinolones was evaluated using a standard broth microdilution technique. Among them, the quinolone 1-cyclopropyl-6-fluoro-7-(4-(4-formyl-1*H*-1,2,3-triazol-1-yl)piperidin-1-yl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (**34.15**) exhibited comparable antibacterial activity against quinolone-susceptible and multidrug-resistant strains, especially to *Staphylococcus aureus* and *Staphylococcus epidermidis*, in comparison with ciprofloxacin and vancomycin.

Quinolones are one of the most important synthetic medicines used in the treatment of community or hospital acquired infectious diseases. Their excellent pharmacokinetic properties, high antibacterial activity, and few side effects make quinolone antibiotics widespread use in clinical practice.[1] Generally, most quinolones have good activity against Gram-negative bacteria, but the activity against clinical important Gram-positive pathogens is relatively moderate. This characteristic of quinolones has resulted not only in their limited use in some infections but is also believed to be one of the reasons for the rapid development of quinolone resistance. For example, the life-threatening infections caused by multiple drug-resistant Gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and recently identified vancomycin-resistant *enterococci* (VRE) are serious health concerns and are widespread throughout the world.[2] In addition, certain adverse events during treatment with quinolones, such as 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) can lead to potentially fatal torsades.[1,3] Thus, although there have been many advances in the fluoroquinolone field, there is a continuous need for novel quinolones to overcome the limitations of existing drugs.

Structure–activity relationship (SAR) studies have 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.[4]

1,2,3-Triazole and its derivatives have received much attention from medicinal chemists in the past few decades due to their chemotherapeutic value.[5] Many 1,2,3-triazoles are found to be potent antimicrobial,[6] antimalarial,[7] anticonvulsant,[8] antitumor,[9] and anti HIV agents,[10] and help to avert platelet aggregation.[11] Some 1,2,3-triazole derivatives have been used as potassium channel activators.[12] Very recently, disubstituted 1,2,3-triazole analogues have been reported as antitubercular agents[13] and cannabinoid CB1 receptor antagonists.[14]

Piperidine and its analogues, an important pharmacophore of many drug molecules, are reported to act as antibacterials,[15] antitubercular agents[16] and AChE inhibitors.[17] We wanted to investigate whether there would some new beneficial properties if piperidine and 1,2,3-triazole like cores were combined in one molecule. To the best of our knowledge, there is no evidence in the literature of the development of a molecular scaffold containing core 1,2,3-triazole and piperidine at the C7 moiety of fluoroquinolone antibiotics. In our previous work, we have synthesized a series of new quinolones based on (2*S*,4*R*)-methyl 4-hydroxypyrrolidine-2-carboxylate and (*S*)-pyrrolidin-2-ylmethanol. The in vitro potency assay results indicated that some of these compounds exhibited good to excellent activities against all the Gram-positive and Gram-negative strains tested.[18] Herein, we report the synthesis of a series of 4-substituted 4-(1*H*-1,2,3-triazol-1-yl)piperidine as the C7 building blocks of quinolone core **32** and their antibacterial activities.

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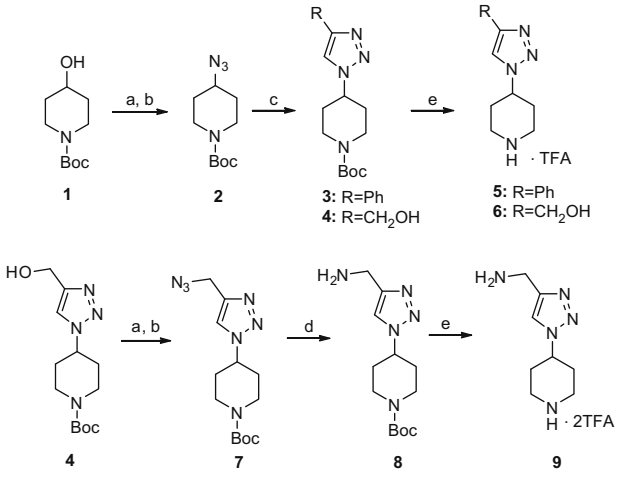
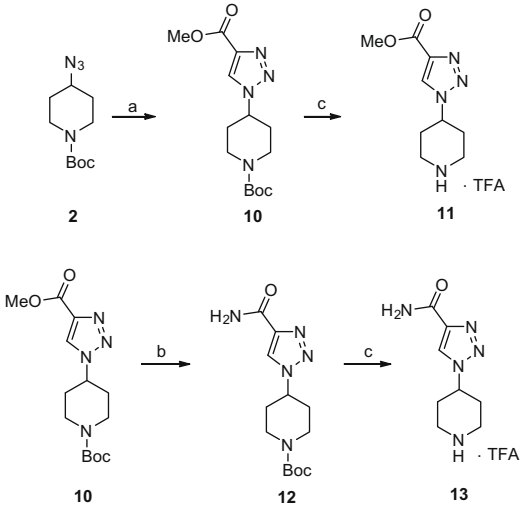


Scheme 1. Reagents and conditions: (a) MsCl, Et_3N, DCM 0 °C to rt; (b) NaN_3, DMF, 80 °C (93% two steps); (c) 1-ethynylbenzene or prop-2-yn-1-ol, CuI, DIPEA, MeOH (92% and 86%, respectively); (d) Pd/C, H_2 (quantitative); (e) TFA, DCM (quantitative).

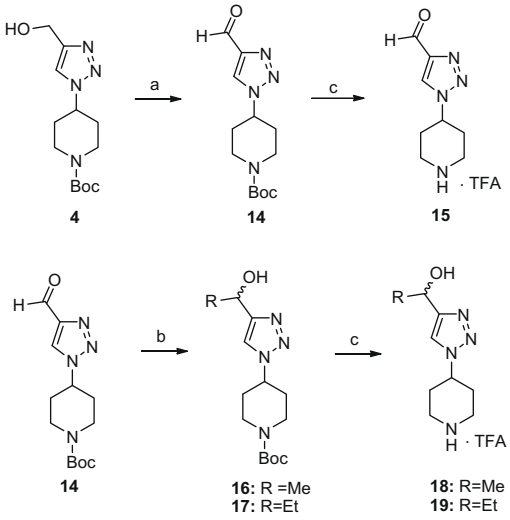
On the base of our previous work, we used the less lipophilic naphthyridine acid **32** as the quinolone core as the scaffold for the addition of novel building blocks at the C7 position instead of a diamine to avoid QT prolongation adverse effects,[18] as this quinolone core has less mammalian cell cytotoxicity, good activity against resistant organisms,[19] superior pharmacokinetics, pharmacodynamics, and ADME properties.[20]

The synthesis of the C7 position building block series started from *N*-Boc protected 4-hydroxypiperdine (**1**). The reaction of **1** with methanesulfonyl chloride followed by azidation provided intermediate **2**. Compound **2** reacted with ethynylbenzene or prop-2-yn-1-ol catalyzed by CuI in the presence of DIPEA, to give the corresponding 1,2,3-triazole intermediates **3** and **4** with 92% and 86% yields, respectively[21] (Scheme 1), which were then treated with TFA to provide the corresponding salt, which could be directly used in the coupling step (Scheme 5).

Starting from intermediate **4**, intermediate **9** was also synthesized by mesylation and azidation to afford the intermediate **7**. Hydrogenation of **7** catalyzed by Pd/C gave the corresponding primary amine **8** with quantitative yield, followed by deprotection in the presence of TFA to get the corresponding diamine **9** (Scheme 1).



Scheme 2. Reagents and conditions: (a) methyl propiolate, CuI, CH_3CN, rt (77%); (b) ammonia, MeOH, 50 °C (quantitative); (c) TFA, DCM (quantitative).

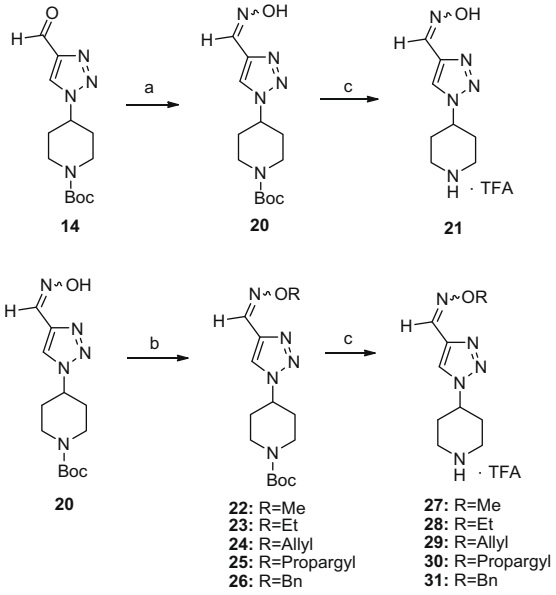


Scheme 3. Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, −78 °C (95%); (b) Mg, CH_3I or CH_3CH_2Br, THF (80% and 85%, respectively); (c) TFA, DCM (quantitative).

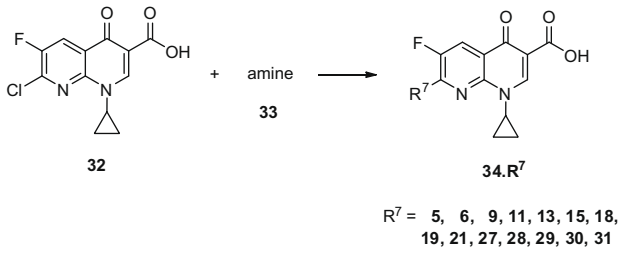
The other building blocks varied at 4-position of triazole are the corresponding methyl ester and amide (**11** and **13**), which were synthesized from intermediate **2**. First, **2** was reacted with methyl propiolate in the presence of CuI to give **10** with 77% yield.[22] When reacted with ammonia at 50 °C, intermediate **10** was converted to the corresponding amide **11** with nearly quantitative yield. Then, deprotection of compounds **10** and **12** gave **11** and **13**, respectively (Scheme 2).

Formyl substituted intermediate **15** was synthesized starting from intermediate **4**, which underwent Swern oxidation and deprotection to afford the target compound. The reaction of Swern oxidation product **14** with Grignard reagents generated in situ gave two chiral moieties **16** and **17**,[23] followed by deprotection to provide the corresponding salts **18** and **19** in quantitative yields, respectively (Scheme 3).

The C7 position building block series with the oxime and alkyloxime, **21** and **27–31**, were also synthesized starting from inter-



Scheme 4. Reagents and conditions: (a) hydroxylamine hydrochloride, CH_2Cl_2/aq NaOH, (96%); (b) RBr, TBAI, CH_2Cl_2/aq NaOH, rt, 70–85%; (c) TFA, DCM (quantitative).



Scheme 5. Reagents and conditions: Et_3N, CH_3CN, 50–80 °C, 40–83%.

mediate **14** (Scheme 4), as oximes and alkyloximes are common in antibiotic design including cephalosporins and the recently launched fluoroquinolone gemifloxacin.[24] The reaction of **14** with hydroxylamine hydrochloride in the presence of sodium hydroxide solution give oxime intermediate **20**, which reacted with a series of alkylation reagents to get corresponding alkyloximes **22–26**. The deprotection of **20** and **22–26** provided the corresponding salts **21** and **27–31** (Scheme 4).

With the 14 4-substituted 4-(1*H*-1,2,3-triazol-1-yl)piperidine building blocks in hand,[25] a series of new fluoroquinolone compounds were synthesized by the reaction of these building blocks with quinolone core **32** in the presence of triethylamine with 40–83% yields (Scheme 5).

The minimal inhibitory concentrations (MICs) or the lowest drug concentration that prevents visible growth of bacteria, were determined by a standard broth microdilution technique according to Clinical and Laboratory Standards Institute guidelines.[26] As can be deduced from these data, all of the synthesized compounds exhibited potent antibacterial activity.[27] This activity seems to be modulated through the 4-substituted 4-(1*H*-1,2,3-triazol-1-yl)piperidine.

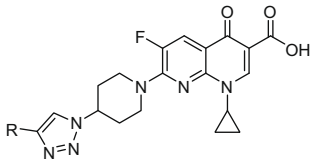
The in vitro antibacterial activity results listed in Table 1 revealed that the phenyl substituted quinolone **34.5** and hydroxymethyl substituted quinolone **34.6** showed equal activities against *Staphylococcus epidermidis*. The quinolone **34.6** exhibited superior activity against *Staphylococcus aureus* (MIC = 0.125 μg/mL) and *Escherichia coli* (0.5 μg/mL), and compound **34.5** displayed good activity against multidrug-resistant *Staphylococcus aureus* (0.5 μg/mL) clinical isolates and *Enterococcus faecalis* (1 μg/mL). In contrast, the quinolone **34.5** exhibited low potency against *Pseudomonas aeruginosa* and multidrug-resistant *Pseudomonas aeruginosa* clinical isolates (MIC >32 μg/mL).

Aminomethyl substituted quinolone **34.9**, compared with phenyl and hydroxymethyl substituted quinolones **34.5** and **34.6**, significantly decreased the activity of most bacterial strains except *P. aeruginosa* and multidrug-resistant *P. aeruginosa,* for which quinolone **34.6** was 32–64-fold more potent than quinolone **34.9**.

Quinolones **34.11** and **34.13**, with both a 4-substituted methyl ester and an amide at the triazole, had similar activities against *S. aureus*, *P. aeruginosa* and multidrug-resistant *P. aeruginosa*. Quinolone **34.11** had superior activity against *E. coli* (1 μg/mL), whereas quinolone **34.13** displayed superior activity against *E. faecalis* (4 μg/mL). However, the two quinolones were less potent than quinolone **34.6**.

Formyl at the triazole substituted quinolone **34.15** displayed good activities against most pathogens. It exhibited excellent in vitro antibacterial activities against *S. epidermidis* (0.031 μg/mL), which is 16-fold more potent than that of ciprofloxacin (0.5 μg/mL), and showed equal potency against *S. aureus* to ciprofloxacin (0.125 μg/mL). It is very interesting that quinolone **34.15** maintained good antibacterial activity against both Gram-positive and Gram-negative strains. For example, the MIC against *S. epidermidis* (0.031 μg/mL) was superior to that of ciprofloxacin (0.5 μg/mL), while the MIC against *E. coli* (0.25 μg/mL) was comparable to that of ciprofloxacin (0.125 μg/mL). In addition, it also demonstrated potency against *P. aeruginosa* (16 μg/mL) although it was less potent than that of ciprofloxacin (0.5 μg/mL). This results was similar with that of Srivastava, B. K. reported, a series of quinolones bearing the 4,5,6,7-tetrahydro-thieno[3,2-*c*]pyridine moiety attached at the C7 position, especially the formyl derivative 1-cyclopropyl-6-fluoro-7-(2-formyl-6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid showed excellent activity in vitro antibacterial test against all

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



Compound	R	Gram-positive				Gram-negative		
		S.a.1	S.a.2	S.e	E.f.	E.c.	P.a.1	P.a.2
34.5	–Ph	0.5	0.5	0.5	1	32	>32	>32
34.6	$-CH_2OH$	0.125	>32	0.5	2	0.5	32	32
34.9	$-CH_2NH_2$	16	>32	32	>32	16	32	32
34.11	$-COOCH_3$	1	>32	1	16	1	32	32
34.13	$-CONH_2$	1	>32	2	4	4	32	32
34.15	–CHO	0.125	>32	0.031	2	0.25	16	32
34.18	$-CH(CH_3)OH$	2	>32	2	8	1	32	32
34.19	$-CH(C_2H_5)OH$	2	>32	2	8	1	32	32
34.21	–CHNOH	1	>32	1	4	2	32	32
34.27	$-CHNOCH_3$	0.25	>32	0.5	4	2	32	32
34.28	$-CHNOC_2H_5$	0.5	32	1	4	4	32	32
34.29	$-CHNOCH_2CHCH_2$	0.5	8	2	8	4	32	32
34.30	$-CHNOCH_2CCH$	0.5	32	1	8	4	32	32
34.31	–CHNOBn	1	4	1	4	8	32	32
Ciprofloxacin		0.125	>32	0.5	1	0.125	0.5	16
Vancomycin		1	1	2	0.5			

[a] MIC 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 *Staphylococcus aureus* clinical isolates; S.e., *Staphylococcus epidermidis* **ATCC12228**; E.f., *Enterococcus faecalis* **ATCC29212**; E.c., *Esche-*

the bacteria strains, which exhibited 4–8-folds superior antibacterial activity than ciprofloxacin.[28]

Two chiral quinolones **34.18** and **34.19** have equal activities against all bacteria, and displayed moderate activities against *S. aureus* (2 μg/mL), *S. epidermidis* (2 μg/mL) and *E. coli* (1 μg/mL).

The oxime and alkyloxime substituted quinolones **34.21**, **34.27**, **34.28**, **34.29**, **34.30** and **34.31** all showed good activities against Gram-positive pathogens, such as *S. aureus* and *S. epidermidis*. Among them, quinolone **34.27** exhibited superior potency against *S. aureus* (0.25 μg/mL) and *S. epidermidis* (0.5 μg/mL) than the other quinolones, which was comparable to that of ciprofloxacin (0.125 and 0.5 μg/mL, respectively). Quinolones **34.28**, **34.29**, **34.30** and **34.31** exhibited good activity against multidrug-resistant *S. aureus*. Benzyloxyimino substituted quinolone **34.31** exhibited good antibacterial activities against multidrug-resistant *S. aureus* (4 μg/mL) than any other alkyloxime substituted quinolone and ciprofloxacin (MIC >32 μg/mL). In contrast, the oxime and alkyloxime substituted quinolones **34.21**, **34.27**, **34.28**, **34.29**, **34.30**, **34.31** all displayed moderate potency against *E. coli* and *P. aeruginosa*.

In conclusion, we have synthesized a series of new quinolones based on 4-substituted 4-(1*H*-1,2,3-triazol-1-yl)piperidine as the C7 building blocks of quinolone core **32**.[29] The in vitro antibacterial activity assay demonstrated that the quinolones exhibited good antibacterial activities to most organisms. The phenyl substitute quinolone **34.5** displayed superior antibacterial activities against multidrug-resistant *S. aureus*, *S. epidermidis* and *E. faecalis*, whereas it exhibited mild potency to Gram-negative strains. Quinolone **34.6** displayed excellent antibacterial activities against *S. aureus*, *S. epidermidis* and *E. coli*, which is comparable to the reference drug. The formyl substitute quinolone **34.15** displayed good and balanced activities against both Gram-positive and Gram-negative organisms, especially against *S. epidermidis*. The oxime and alkyloxime substituted quinolones exhibited good antibacterial activities against the Gram-positive strains. In particular the methoxyimino substituted quinolone **34.27** displayed the highest inhibitory activities against *S. aureus* and *S. epidermidis*. In the light of the increasing need for treatments against infections caused by Gram-positive pathogens, this series of quinolones may be a potential scaffold for the exploration of new quinolone antibacterials. 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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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.03.044.

References and notes

1. Mitscher, L. A. *Chem. Rev.* **2005**, *105*, 559.
2. (a) Emami, S.; Shafiee, A.; Foroumadi, A. *Mini-Rev. Med. Chem.* **2006**, *6*, 109; (b) Paterson, D. L. *Curr. Opin. Pharmacol.* **2006**, *6*, 486; (c) Bradbury, B. J.; Pucci, M. J. *Curr. Opin. Pharmacol.* **2008**, *8*, 1.
3. Ball, P.; Mandell, L.; Niki, Y.; Tillotson, G. *Drug Safety* **1999**, *21*, 407.
4. Murphy, S. T.; Case, H. L.; Ellsworth, E.; Hagen, S.; Huband, M.; Joannides, T.; Limberakis, C.; Marotti, K. R.; Ottolini, A. M.; Rauckhorst, M.; Starr, J.; Stier, M.; Taylor, C.; Zhu, T.; Blaser, A.; Denny, W. A.; Lu, G.; Smaill, J. B.; Rivault, F. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2150.
5. Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128.
6. Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953.
7. Jilino, M.; Stevens, F. G. *J. Chem. Soc, Perkin Trans.* **1998**, *1*, 1677.
8. Kadaba, P. K.; Stevenson, P. J.; P-Nnane, I.; Damani, L. A. *Bioorg. Med. Chem.* **1996**, *4*, 165.
9. Passannanti, A.; Diana, P.; Barraja, P.; Mingoia, F.; Lauria, A.; Cirrincione, G. *Heterocycles* **1998**, *48*, 1229.
10. Velarquez, S.; Alvarez, R.; Perez, C.; Gago, F.; De, C.; Balzarini, J.; Camarasa, M. J. *Antiviral Chem. Chemother.* **1998**, *9*, 481.
11. Cunha, A. C.; Figueiredo, J. M.; Tributino, J. L. M.; Miranda, A. L. P.; Castro, H. C.; Zingali, R. B.; Fraga, C. A. M.; de Souza, M. C. B. V.; Ferreirac, V. F.; Barreiroa, E. J. *Bioorg. Med. Chem.* **2003**, *11*, 2051.
12. Biagi, G.; Calderone, V.; Giorgi, I.; Livi, O.; Martinotti, E.; Martelli, A.; Nardi, A. *Farmaco* **2004**, *59*, 397.
13. Gill, C.; Jadhav, G.; Shaikh, M.; Kale, R.; Ghawalkar, A.; Nagargoje, D.; Shiradkar, M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6244.
14. Hou, D. R.; Alam, S.; Kuan, T. C.; Ramanathan, M.; Lin, T. P.; Hung, M. S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1022.
15. Weis, R.; Schweiger, K.; Faist, J.; Rajkovic, E.; Kungl, A. J.; Walter, M. F.; Schunack, F. W.; Seebacher, W. *Bioorg. Med. Chem.* **2008**, *16*, 10326.
16. Aridoss, G.; Amirthaganesan, S.; Ashok Kumar, N.; Kim, J. T.; Lim, K. T.; Kabilan, S.; Jeong, Y. T. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6542.
17. Sheng, R.; Xu, Y.; Hu, C.; Zhang, J.; Lin, X.; Li, J.; Yang, B.; He, Q.; Hu, Y. *Eur. J. Med. Chem.* **2009**, *44*, 7.
18. Huang, X.; Chen, D.; Wu, N.; Zhang, A.; Jia, Z.; Li, X. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4130.
19. Suto, M. J.; Domagala, J. M.; Roland, G. E.; Mailloux, G. B.; Cohen, M. A. *J. Med. Chem.* **1992**, *35*, 4745.
20. Brighty, K. E.; Gootz, T. D. *J. Antimicrob. Chemother.* **1997**, *39*, 1.
21. Fuwa, H.; Takahashi, Y.; Konno, Y.; Watanabe, N.; Miyashita, H.; Sasaki, M.; Natsugari, H.; Kan, T.; Fukuyama, T.; Tomita, T.; Iwatsubo, T. *ACS Chem. Biol.* **2007**, *2*, 408.
22. Sangshetti, J. N.; Nagawade, R. R.; Shinde, D. B. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3564.
23. Datta, A.; Veeresa, G. *J. Org. Chem.* **2000**, *65*, 7609.
24. Dang, Z.; Yang, Y.; Ji, R.; Zhang, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4523.
25. *General synthetic procedure for selected compounds*: Reactions were conducted using oven-dried glassware under an atmosphere of nitrogen. NMR spectra were recorded on Bruker 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm related to tetramethylsilane as the internal standard. The mass spectra were recorded on Agilent 6120 quadrupole LC/MS system under electron spray impact (ESI) ionization condition or otherwise specified. The preparation of *tert-butyl 4-(4-phenyl-1H-1,2,3-triazol-1-yl)piperidine-1-carboxylate (compound **3**)*: A dried flask containing *tert*-butyl 4-azidopiperidine-1-carboxylate (0.600 g, 2.65 mmol) and ethynylbenzene (0.271 g, 2.65 mmol) in 5 mL of methanol, *N*-ethyl-*N*-isopropylpropan-2-amine (1.712 g, 13.30 mmol) and CuI (1.151 g, 0.80 mmol) were added at room temperature. The mixture was stirred at the same temperature for 32 h, and then filtered. The filtrate was concentrated under reduced pressure and the residue were added ethyl acetate (30 mL) and HCl solution (0.1 M, 30 mL). The organic phase was separated and the aqueous solution was extracted with ethyl acetate. The combined organic phase was washed with saturated $NaHCO_3$ solution (60 mL), brine (60 mL), dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to afford the crude product which was purified by column chromatography (petroleum ether/ethyl acetate = 4:1) to give compound **3** (0.801 g, 2.44 mmol), yield 92%. The preparation of *tert-butyl 4-(4-(methoxycarbonyl)-1H-1,2,3-triazol-1-yl)piperidine-1-carboxylate (compound **10**)*: A dried flask containing *tert*-butyl 4-azidopiperidine-1-carboxylate (1.929 g, 8.52 mmol), CuI (1.624 g, 8.52 mmol) and methyl propiolate (1.074 g, 12.79 mmol) in 16 mL of acetonitrile. The mixture was stirred at room temperature for 48 h and then concentrated under reduced pressure. The residue was added ethyl acetate (80 mL) and water (80 mL). The mixture was separated and the aqueous phase was extracted with ethyl acetate (80 mL). The combined organic phase was washed with brine (150 mL) and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (Petroleum ether/ethyl acetate = 6:1) to give compound **10** (2.033 g, 6.55 mmol), yield 77%. The preparation of *tert-butyl 4-(4-(1-hydroxyethyl)-1H-1,2,3-triazol-1-yl)piperidine-1-carboxylate (compound **16**)*: A dried flask containing magnesium powder (0.312 g, 12.84 mmol), 10 mL of THF was added under an atmosphere of nitrogen at the room temperature. Methyl iodine was added to the suspension of magnesium at a suitable rate. When the reaction started, the solution of methyl iodine was added dropwise at a rate which is sufficient to maintain a gentle reflux. After the reaction was completed, the gray solution was stirred for another 4 h at room temperature and then cooled by an ice/water bath. A solution of *tert*-butyl 4-(4-formyl-1*H*-1,2,3-triazol-1-yl)piperidine-1-carboxylate (0.600 g, 2.14 mmol) in 5 mL of THF was added to the Grignard reagent above, and the mixture was warmed to room temperature. After the reaction mixture was stirred overnight, saturated NH_4Cl solution (50 mL) was added in ice/water bath. Ethyl acetate (50 mL) was added, separated and the aqueous phase was extracted with ethyl acetate (50 mL). The combined organic phase was washed with brine (100 mL) and dried over $MgSO_4$. Concentrated under reduced pressure to give the crude produc which was purified by column chromatography (Petroleum ether/ethyl acetate = 2:3) to get compound **16** (0.508 g, 1.71 mmol), yield 80%. The preparation of *tert-butyl 4-(4-((methoxyimino)methyl)-1H-1,2,3-triazol-1-yl)piperidine-1-carboxylate (compound **22**)*: A mixture of *tert*-butyl 4-(4-((hydroxyimino)methyl)-1*H*-1,2,3-triazol-1-yl)-piperidine-1-carboxylate (0.591 g, 2.00 mmol), methyl iodine (1.278 g, 9.00 mmol), 4 M sodium hydroxide solution (0.75 mL) and tetrabutylammonium iodide (0.222 g, 0.60 mmol) in THF (8 mL) was stirred at room temperature for

48 h. DCM (20 mL) and saturated NH_4Cl solution (20 mL), were added and then the organic phase was separated the aqueous phase was extracted with DCM (20 mL) and the combined organic phase washed with brine (50 mL), dried over $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (Petroleum ether/ethyl acetate = 4:1) to get compound **22** (0.433 g, 1.40 mmol), yield 70%.

26. Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) guidelines. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, 5th ed.; Approved standard: NCCLS Document M7-A5, 2000.
27. 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. MIC data for selected strains are expressed in μg/mL. For comparison, ciprofloxacin and vancomycin were employed as reference drugs.
28. Srivastava, B. K.; Solanki, M.; Mishra, B.; Soni, R.; Jayadev, S.; Valani, D.; Jain, M.; Patel, P. R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1924.
29. The proposed structures are supported by the ^1H NMR and mass spectra. Selected NMR and LC–ESIMS data see Supplementary data.