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Synthesis and antibacterial activity of pyridinium-tailored aromatic amphiphiles

Peiyi Wang^{a,†}, Manni Gao^{a,†}, Lei Zhou^a, Zhibing Wu^a, Deyu Hu^a, Jun Hu^{b,*}, Song Yang^{a,*}^a State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Center for R&D of Fine Chemicals of Guizhou University, Guiyang 550025, China^b State Key Lab of Polymer Physics and Chemistry, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun 130022, China

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ABSTRACT

In this Letter, the antibacterial activities of pyridinium-tailored aromatic amphiphiles were evaluated by turbidimeter tests in vitro. The bioassays revealed that most of the target compounds exhibit appreciable inhibition activities against the plant pathogenic bacteria *Xanthomonas oryzae* pv. *oryzae*, *Ralstonia solanacearum*, and *Xanthomonas axonopodis* pv. *citri*. The half-maximal effective concentrations (EC₅₀) of **2-NP-10**, **9-AP-10**, and **9-AP-7** against these three bacteria were relatively high, which may be ascribed to the favourable hydrophobicity/hydrophilicity balance in these compounds. Our results suggest that pyridinium-tailored aromatic amphiphiles are promising bactericide candidates against plant bacterial diseases.

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Plant bacterial diseases have attracted the significant attention in the past decades because of the serious threats they pose to agricultural production.^{1–6} Rice bacterial leaf blight, tobacco bacterial wilt, and citrus bacterial canker are the three major diseases caused by the Gram-negative bacteria *Xanthomonas oryzae* pv. *oryzae* (Xoo), *Ralstonia solanacearum* (R. *solanacearum*), and *Xanthomonas axonopodis* pv. *citri* (Xac), respectively.^{7,8} Rice bacterial leaf blight is a vascular disease that occurs at all growth stages of rice, generally resulting in production losses of up to 10%.^{9–11} With typical symptoms of yellowing and wilting of tobacco leaves, tobacco bacterial wilt is always obtained through soil-borne pathogens; this disease causes significant economic losses each year.^{7,12} Citrus bacterial canker, an extremely persistent disease, can cause lesions on the leaves, stems, and fruit of citrus trees, thereby leading to a significant loss in agricultural output every year.^{13,14} To date, a number of commercial bactericides have been developed to address these diseases; however, these agents cannot achieve the desired effect because of their poor efficiency, high phytotoxicity, or bactericide resistance. For example, bismethiazol, one of the bactericides most widely used to control rice bacterial leaf blight, has led to the appearance of bismethiazol-resistant strains of Xoo in Anhui Province, China.⁹ The registered bactericide thiodiazole copper only shows a control efficiency of 37.49% against rice

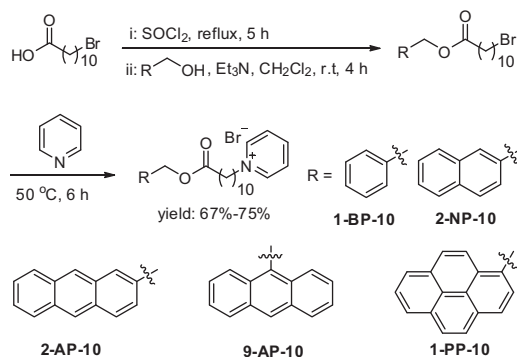
bacterial leaf blight at a high concentration of 200 µg/mL.¹¹ Therefore, exploring and developing new highly efficient bactericides to prevent and control plant bacterial diseases remains a considerable challenge.

Amphiphiles containing hydrophobic and hydrophilic portions can mimic membrane properties and exhibit excellent biocidal activities toward bacteria and fungi by disrupting their innate defense system in microorganisms.^{15–22} Among them, pyridinium-functionalized amphiphiles containing the flat pyridinium cations exert significant antibacterial activities, since their positive charges can facilitate interactions with anionic cell components, thus enhancing the affinity toward biological membranes.^{23–28} For example, Sen and co-workers investigated the antibacterial activity of amphiphilic pyridinium-methacrylate copolymers, and found that polymers with positive charges and hydrophobic tails on spatially separated centres exhibited higher membrane-disrupting ability against Gram-negative (*Escherichia coli*) and Gram-positive (*Bacillus subtilis*) bacteria.²⁹ Bhattacharya and co-workers reported that a triple pyridinium-beard amphiphile showed impressive antibacterial activity against both Gram-positive and -negative bacteria by disrupting the bacterial membrane.³⁰ Obviously, pyridinium-tailored amphiphiles are promising candidates in the development of novel highly efficient bactericides against plant bacterial diseases. The membrane-disrupting activity of amphiphiles depends on their positive charge as well as the overall hydrophobicity/hydrophilicity balance.^{31–33} Inspired by these previous reports, we propose that appreciable

* Corresponding authors.

E-mail addresses: jhu@ciac.ac.cn (J. Hu), jhxx.msm@gmail.com (S. Yang).

† These two authors contribute equally to this work.

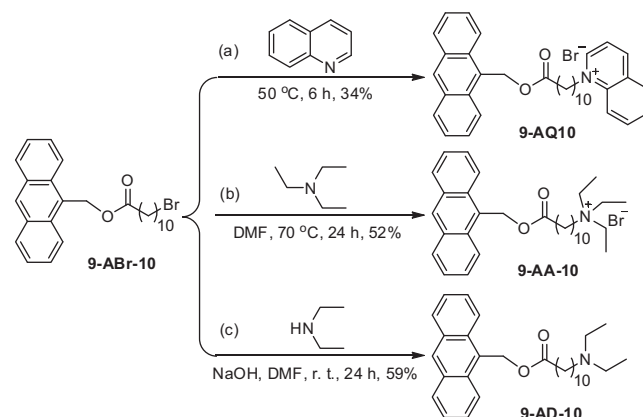


Scheme 1. Synthetic route of **1-BP-10**, **2-NP-10**, **2-AP-10**, **9-AP-10**, and **1-PP-10**.

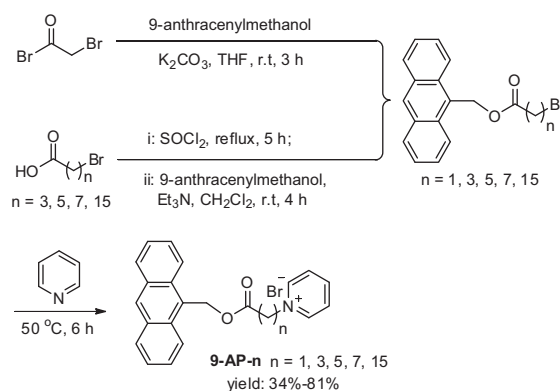
bioactivity can be achieved by manipulating the ratio between the hydrophobic and hydrophilic components of amphiphiles. In this study, we synthesized a series of amphiphilic pyridinium-tailored amphiphiles and investigated their antibacterial activities against *Xoo*, *R. solanacearum*, and *Xac*. Within these amphiphilic molecules, hydrophobic tails with various aromatic areas were linked to the hydrophilic cations by different alkyl chains.

The synthesis routes of 1-[11-benzyloxy-11-oxoundecyl] pyridinium bromide (**1-BP-10**), 1-[11-(2-naphthalenylmethoxy)-11-oxoundecyl]pyridinium bromide (**2-NP-10**), 1-[11-(2-anthracenylmethoxy)-11-oxoundecyl]pyridinium bromide (**2-AP-10**), 1-[11-(9-anthracenylmethoxy)-11-oxoundecyl] pyridinium bromide (**9-AP-10**), and 1-[11-(1-pyrenylmethoxy)-11-oxoundecyl] pyridinium bromide (**1-PP-10**) are shown in Scheme 1.^{34,35} 11-bromoundecanoic acid was treated with aromatic methyl alcohol to afford bromide-tailored intermediates that were subsequently reacted with pyridine at 50 °C to obtain the target molecules **1-BP-10**, **2-NP-10**, **2-AP-10**, **9-AP-10**, and **1-PP-10**. All of the structures were characterised by ¹H NMR, ¹³C NMR, MS, and HRMS (for detailed information, see the Supplementary data).

The turbidimeter test³⁶ was performed to evaluate the antibacterial activities of **1-BP-10**, **2-NP-10**, **2-AP-10**, **9-AP-10**, and **1-PP-10** against *Xoo*, *R. solanacearum*, and *Xac* in vitro. The commercial agricultural antibacterial bismethiazol (**CK₁**) was selected as the positive control for *Xoo*, while thiodiazole copper (**CK₂**) was selected as controls for *R. solanacearum* and *Xac*. As shown in Table 1, **1-BP-10**, **2-NP-10**, **9-AP-10**, and **1-PP-10** showed better bioactivities against these three bacteria than either **CK₁** or **CK₂**. The half-maximal effective concentrations (EC₅₀) of **2-NP-10** against *Xoo*, *R. solanacearum*, and *Xac* are 9.8 ± 0.8, 23.1 ± 4.0, and 8.6 ± 0.4 µg/mL, respectively; **9-AP-10** showed better bioactivity than **2-NP-10** against *Xoo* and *Xac*, with EC₅₀ values of 5.3 ± 0.7 and 6.3 ± 0.5 µg/mL, respectively. Conversely, **1-BP-10** and **1-PP-**



Scheme 2. Synthetic route of **9-AQ-10**, **9-AA-10**, and **9-AD-10**.



Scheme 3. Synthetic route of **9-AP-n**.

10, featuring smaller or larger aromatic areas than naphthalene and anthracene, resulted in a decreased bioactivity toward *R. solanacearum* and *Xac*, although the EC₅₀ value of **1-PP-10** against *Xoo* is 4.6 ± 1.6 µg/mL. This result indicates that even slight changes in the ratio between hydrophobic and hydrophilic parts will affect their bioactivities. The activity of **9-AP-10** against these bacteria is much better than that of its regioisomer **2-AP-10**, although both compounds have the same hydrophobic and hydrophilic ratios. Given the anisotropic feature of the anthracene ring, the alkyl chain of **9-AP-10** orients in a nearly perpendicular direction relative to the anthracene plane, similar to a 'shaver'-like molecular configuration. By contrast, **2-AP-10** orients in a direction parallel to the anthracene ring, as shown in our previous work (Fig. S0).³⁴

Table 1

Antibacterial activity of **1-BP-10**, **2-NP-10**, **2-AP-10**, **9-AP-10**, **1-PP-10**, **9-AQ-10**, **9-AA-10**, **9-ABr-10**, and **9-AD-10** against *Xoo*, *R. solanacearum*, and *Xac* in vitro. The average EC₅₀ values were statistically estimated by probit analysis with the probit package of the SPSS 17.0 software and consequently give an equation (Regression equation)

Compounds	<i>Xoo</i>			<i>R. solanacearum</i>			<i>Xac</i>		
	Regression equation	<i>r</i>	EC ₅₀ (µg/mL)	Regression equation	<i>r</i>	EC ₅₀ (µg/mL)	Regression equation	<i>r</i>	EC ₅₀ (µg/mL)
1-BP-10	y = 3.831x − 0.338	0.96	24.7 ± 1.5	y = 2.567x + 0.710	0.95	46.9 ± 4.2	y = 3.454x + 0.141	0.98	25.5 ± 1.4
2-NP-10	y = 3.746x + 1.289	0.98	9.8 ± 0.8	y = 1.885x + 2.429	0.98	23.1 ± 4.0	y = 2.789x + 2.390	0.91	8.6 ± 0.4
2-AP-10	y = 2.186x + 2.214	0.96	18.8 ± 2.6	/	/	>160	y = 2.083x + 0.852	0.99	98.1 ± 21.0
9-AP-10	y = 3.289x + 2.605	0.93	5.3 ± 0.7	y = 1.005x + 3.496	0.97	31.3 ± 8.2	y = 2.745x + 2.805	0.96	6.3 ± 0.5
1-PP-10	y = 2.836x + 3.126	0.99	4.6 ± 1.6	y = 0.759x + 3.764	0.98	42.4 ± 2.7	y = 1.244x + 2.875	1.00	51.0 ± 7.4
9-AQ-10	y = 3.458x + 1.731	0.95	8.8 ± 2.1	y = 1.207x + 3.501	0.92	17.4 ± 3.4	y = 0.918x + 4.372	0.96	4.8 ± 0.9
9-AA-10	y = 4.941x + 1.868	0.97	4.3 ± 0.7	y = 1.755x + 2.838	0.99	17.1 ± 3.0	y = 2.729x + 2.996	0.98	5.4 ± 0.7
9-ABr-10	/	/	>100	/	/	>100	/	/	>100
9-AD-10	/	/	>100	/	/	>100	/	/	>100
CK₁	y = 1.499x + 2.052	0.98	92.6 ± 2.1	/	/	/	/	/	/
CK₂	/	/	/	y = 1.031x + 2.942	0.99	216.7 ± 5.1	y = 2.153x + 0.938	0.98	77.0 ± 2.0

Table 2
Antibacterial activity of **9-AP-n** ($n = 1, 3, 5, 7, 10, 15$) against *Xoo*, *R. solanacearum*, and *Xac* in vitro

Compounds	<i>Xoo</i>			<i>R. solanacearum</i>			<i>Xac</i>		
	Regression equation	<i>r</i>	EC ₅₀ (μg/mL)	Regression equation	<i>r</i>	EC ₅₀ (μg/mL)	Regression equation	<i>r</i>	EC ₅₀ (μg/mL)
9-AP-1	$y = 1.963x + 0.757$	0.97	144.9 ± 8.3	/	/	>160	$y = 0.632x + 4.313$	0.98	12.2 ± 6.0
9-AP-3	$y = 6.364x - 5.914$	1.00	51.9 ± 3.2	$y = 1.354x + 3.231$	0.99	20.2 ± 3.2	$y = 1.046x + 4.151$	0.99	6.5 ± 2.8
9-AP-5	$y = 8.214x - 6.937$	1.00	28.4 ± 3.1	$y = 1.082x + 3.631$	0.99	18.4 ± 4.8	$y = 5.926x - 1.255$	0.91	11.4 ± 1.1
9-AP-7	$y = 3.001x + 2.234$	0.96	8.3 ± 1.2	$y = 1.022x + 3.629$	0.94	21.9 ± 6.3	$y = 6.094x + 0.746$	1.00	5.0 ± 0.2
9-AP-10	$y = 3.289x + 2.605$	0.93	5.3 ± 0.7	$y = 1.005x + 3.496$	0.97	31.3 ± 8.2	$y = 2.745x + 2.805$	0.96	6.3 ± 0.5
9-AP-15	$y = 2.298x + 0.624$	0.96	80.1 ± 8.9	/	/	>160	/	/	>100
CK₁	$y = 1.499x + 2.052$	0.98	92.6 ± 2.1	/	/	/	/	/	/
CK₂	/	/	/	$y = 1.031x + 2.942$	0.99	216.7 ± 5.1	$y = 2.153x + 0.938$	0.98	77.0 ± 2.0

Thus, the difference in bioactivities between these two regioisomers is attributed to the 'shaver'-like molecular configuration of **9-AP-10**, which may be stuck in the bacterial membrane due to the steric hindrance, and consequently disrupt the functions of bacterial membrane. Based on the above results, **9-AP-10** was selected as the lead compound for further structure optimisation.

To investigate the effect of cation types toward bioactivity, the quinolinium-tailored anthracene **9-AQ-10** and the ammonium-tailored anthracene **9-AA-10** were synthesized.³⁴ As shown in Scheme 2, the intermediate (9-anthracenylmethyl-11-bromoundecanoate) was treated with quinoline (or triethylamine) to afford **9-AQ-10** (or **9-AA-10**); the bioactivities of these compounds were examined under the same conditions (Table 1).

Results revealed that both **9-AQ-10** and **9-AA-10** exhibit bioactivities similar to that of **9-AP-10** against the three bacteria with EC₅₀ values of 8.8 ± 2.1, 17.4 ± 3.4, 4.8 ± 0.9 μg/mL (**9-AQ-10**), and 4.3 ± 0.7, 17.1 ± 3.0, 5.4 ± 0.7 μg/mL (**9-AA-10**), respectively. In order to investigate the effect of positive charge, another two precursors of the amphiphiles (**9-ABr-10** and **9-AD-10**) were synthesized and their antibacterial activities were evaluated. Their high EC₅₀ (>100 μg/mL) strongly verified the crucial role of the positive charge.

In addition, another five pyridinium-tailed anthracenes with different alkyl lengths were synthesized to investigate how linker length affects bioactivity. The synthesis of the pyridinium-tailored anthracene **9-AP-n** is shown in Scheme 3.³⁷ Briefly, 9-anthracenylmethanol was treated with bromoacetyl bromide or bromo-carboxylic acids to obtain bromide-modified intermediates with different alkyl lengths, which were then reacted with pyridine at 50 °C to afford the target compound **9-AP-n** ($n = 1, 3, 5, 7, 15$). All of the structures were characterised by ¹H NMR, ¹³C NMR, MS, and HRMS (for detailed information, see the Supplementary data).

The antibacterial activity of **9-AP-n** against *Xoo*, *R. solanacearum*, and *Xac* was examined using the turbidimeter test under the same conditions. Except for **9-AP-1**, as shown in Table 2, **9-AP-n** exhibited better antibacterial activities against *Xoo* than **CK₁**. The EC₅₀ value decreased with the increase in the length of the alkyl chains and reached a minimum when n was 10. When n was 15, antibacterial activity increased to 80.1 ± 8.9 μg/mL (16-fold higher compared with that of **9-AP-10**). These results revealed that a suitable hydrophobicity/hydrophilicity balance was achieved by **9-AP-10** against *Xoo*.^{24–27} **9-AP-3**, **9-AP-5**, and **9-AP-7** showed better antibacterial activities against *R. solanacearum* than **CK₂**, with EC₅₀ values ranging from 18.4 μg/mL to 21.9 μg/mL. The EC₅₀ values of **9-AP-1**, **9-AP-3**, **9-AP-5**, and **9-AP-7** against *Xac* were 12.2 ± 6.0, 6.5 ± 2.8, 11.4 ± 1.1, and 5.0 ± 0.2 μg/mL, respectively, all of which were lower than that of **CK₂**. **9-AP-7** and **9-AP-10** exhibited the best antibacterial activity against *Xoo*, *R. solanacearum*, and *Xac*, thereby suggesting that a favourable overall hydrophobicity/hydrophilicity balance was attained when n is 7 or 10.

In summary, a series of pyridinium-tailored aromatic amphiphiles were synthesized, and their antibacterial activities against pathogens *Xoo*, *R. solanacearum*, and *Xac* in vitro were evaluated

by a turbidimeter test. After optimising the aromatic areas, substituted positions, cation types, and alkyl length of these pyridinium-tailored aromatic amphiphiles, the bioassay showed that **2-NP-10**, **9-AP-10**, and **9-AP-7** exhibited excellent comprehensive bioactivity against these three bacteria because of the appropriate balance between hydrophobicity and hydrophilicity in these molecules. This finding verifies that pyridinium-tailored aromatic amphiphiles are promising bactericide candidates for treating plant bacterial diseases.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.bmcl.2016.01.053>.

References and notes

- Zou, L. F.; Wang, X. P.; Xiang, Y.; Zhang, B.; Li, Y. R.; Xiao, Y. L.; Wang, J. S.; Walmsley, A. R.; Chen, G. Y. *Appl. Environ. Microbiol.* **2006**, *72*, 6212.
- Gottig, N.; Garavaglia, B. S.; Garofalo, C. G.; Orellano, E. G.; Ottado, J. *PLoS One* **2009**, *4*, 4358.
- Li, Z.; Wu, S.; Bai, X.; Liu, Y.; Lu, J.; Liu, Y.; Xiao, B.; Lu, X.; Fan, L. *J. Bacteriol.* **2011**, *193*, 6088.
- Zou, L.; Li, Y.; Chen, G. *Agric. Sci. China* **2011**, *10*, 1139.
- Gottwald, T. R.; Sun, X.; Riley, T.; Graham, J. H.; Ferrandino, F.; Taylor, E. L. *Phytopathology* **2002**, *92*, 361.
- de Oliveira, A. G.; Murate, L. S.; Spago, F. R.; Lopes, L. D.; Beranger, J. P. D.; Martin, J. A. B. S.; Nogueira, M. A.; de Mello, J. C. P.; Andrade, C. G. T. D.; Andrade, G. *Biol. Control* **2011**, *56*, 125.
- He, K.; Yang, S. Y.; Li, H.; Wang, H.; Li, Z. L. *Eur. J. Plant Pathol.* **2014**, *140*, 665.
- Niño-Liu, D. O.; Ronald, P. C.; Bogdanove, A. J. *Mol. Plant Pathol.* **2006**, *7*, 303.
- Chen, Y.; Yang, X.; Gu, C. Y.; Zhang, A. F.; Zhang, Y.; Wang, W. X.; Gao, T. C.; Yao, J.; Yuan, S. K. *Ann. Appl. Biol.* **2015**, *166*, 129.
- Li, P.; Shi, L.; Yang, X.; Yang, L.; Chen, X.; Wu, F.; Shi, Q.; Xu, W. M.; He, M.; Hu, D. Y.; Song, B. A. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1677.
- Li, P.; Shi, L.; Gao, M.; Yang, X.; Xue, W.; Jin, L. H.; Hu, D. Y.; Song, B. A. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 481.
- Wei, Z.; Huang, J. F.; Tan, S. Y.; Mei, X. L.; Shen, Q. R.; Xu, Y. C. *Biol. Control* **2013**, *65*, 278.
- Piazza, A.; Zimaro, T.; Garavaglia, B. S.; Ficarra, F. A.; Thomas, L.; Marondedze, C.; Feil, R.; Lunn, J. E.; Gehring, C.; Ottado, J.; Gottig, N. *J. Exp. Bot.* **2015**, *66*, 2795.
- Shirai, A.; Sumitomo, T.; Kurimoto, M.; Maseda, H.; Kourai, H. *Biocontrol Sci.* **2009**, *14*, 13.
- Singh, S.; Bhadani, A.; Kataria, H.; Kaur, G.; Kamboj, R. *Ind. Eng. Chem. Res.* **2009**, *48*, 1673.

16. Ventura, S. P. M.; Gurbisz, M.; Ghavre, M.; Ferreira, F. M. M.; Goncalves, F.; Beadham, I.; Quilty, B.; Coutinho, J. A. P.; Gathergood, N. *ACS Sustainable Chem. Eng.* **2013**, *1*, 393.
17. Pernak, J.; Rogoza, J.; Mirska, I. *Eur. J. Med. Chem.* **2001**, *36*, 313.
18. Caruso, E.; Banfi, S.; Barbieri, P.; Leva, B.; Orlandi, V. T. J. *Photochem. Photobiol. B* **2012**, *114*, 44.
19. Patel, A. A.; Lad, H. B.; Pandya, K. R.; Patel, C. V.; Brahmabhatt, D. I. *Med. Chem. Res.* **2013**, *22*, 4745.
20. Bharate, S. B.; Thompson, C. M. *Chem. Biol. Drug Des.* **2010**, *76*, 546.
21. Cole, M. R.; Li, M.; El-Zahab, B.; Janes, M. E.; Hayes, D.; Warner, I. M. *Chem. Biol. Drug Des.* **2011**, *78*, 33.
22. Zasloff, M. *Nature* **2002**, *415*, 389.
23. Wang, L. Y.; Qin, H. L.; Wang, L.; Huo, S. C.; Zhao, B.; Song, B.; Yan, T. J. *Chem. Res.* **2013**, *37*, 205.
24. Brahmachari, S.; Debnath, S.; Dutta, S.; Das, P. K. *Beilstein J. Org. Chem.* **2010**, *6*, 859.
25. Debnath, S.; Shome, A.; Das, D.; Das, P. K. *J. Phys. Chem. B* **2010**, *114*, 4407.
26. Chanawanno, K.; Chantrapromma, S.; Anantapong, T.; Kanjana-Opas, A.; Fun, H. K. *Eur. J. Med. Chem.* **2010**, *45*, 4199.
27. Sundararaman, M.; Kumar, R. R.; Venkatesan, P.; Ilangovan, A. *J. Med. Microbiol.* **2013**, *62*, 241.
28. Kahrman, N.; Yayli, B.; Aktas, A.; Iskefiyeli, Z.; Beris, F. S.; Yayli, N. *Eur. J. Med. Chem.* **2013**, *69*, 348.
29. Sambhy, V.; Peterson, B. R.; Sen, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 1250.
30. Haldar, J.; Kondaiah, P.; Bhattacharya, S. J. *Med. Chem.* **2005**, *48*, 3823.
31. Tew, G. N.; Liu, D.; Chen, B.; Doerksen, R. J.; Kaplan, J.; Carroll, P. J.; Klein, M. L.; DeGrado, W. F. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5110.
32. Kuroda, K.; DeGrado, W. F. *J. Am. Chem. Soc.* **2005**, *127*, 4128.
33. Ilker, M. F.; Nüsslein, K.; Tew, G. N.; Coughlin, E. B. *J. Am. Chem. Soc.* **2004**, *126*, 15870.
34. Hu, J.; Wang, P.; Lin, Y.; Zhang, J.; Smith, M.; Pellechia, P. J.; Yang, S.; Song, B.; Wang, Q. *Chem. Eur. J.* **2014**, *20*, 7603.
35. Wang, P.; Lin, Y.; Smith, M.; Feng, S.; Song, B.; Yang, S.; Hu, J. *Chem. Commun.* **2014**, *50*, 11950.
36. Wang, X.; Yin, J.; Shi, L.; Zhang, G.; Song, B. *Eur. J. Med. Chem.* **2014**, *77*, 65.
37. Wang, P.; Hu, J.; Lin, Y.; Smith, M.; Yang, S.; Song, B.; Wang, Q. *Tetrahedron* **2014**, *70*, 6651.