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Synthesis and antibacterial activity of pyridinium-tailored aromatic amphiphiles

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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 (EC_{50}) 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, bismerthiazol, one of the bactericides most widely used to control rice bacterial leaf blight, has led to the appearance of bismerthiazol-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

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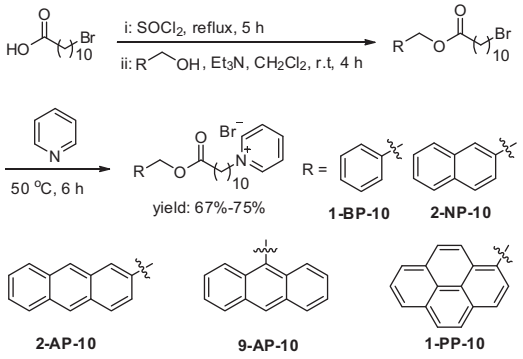
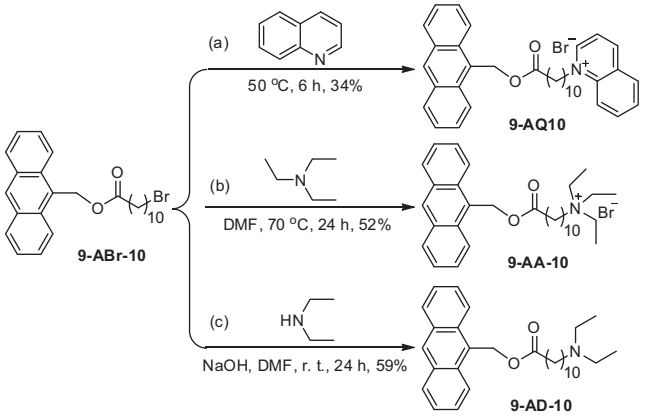
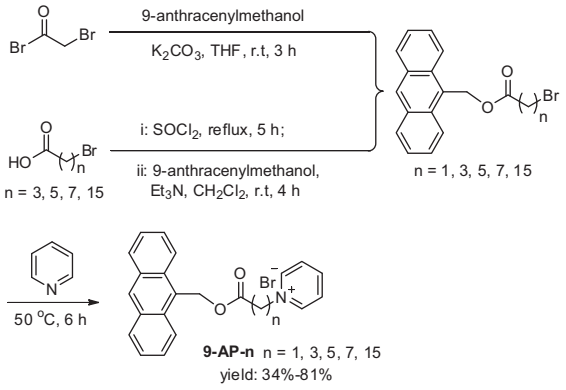


Scheme 1. Synthetic route of **1-BP-10**, **2-NP-10**, **2-AP-10**, **9-AP-10**, and **1-PP-10**.



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



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

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-anthracenyl methoxy)-11-oxoundecyl]pyridinium bromide (**2-AP-10**), 1-[11-(9-anthracenyl methoxy)-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 ^{1}H NMR, ^{13}C NMR, MS, and HRMS (for detailed information, see the Supplementary data).

The turbidimeter test[36] 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 bismerthiazol (**CK_1**) was selected as the positive control for *Xoo*, while thiodiazole copper (**CK_2**) 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 **CK_1** or **CK_2**. The half-maximal effective concentrations (EC_{50}) 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 EC_{50} values of 5.3 ± 0.7 and 6.3 ± 0.5 μg/mL, respectively. Conversely, **1-BP-10** and **1-PP-10**, featuring smaller or larger aromatic areas than naphthalene and anthracene, resulted in a decreased bioactivity toward *R. solanacearum* and *Xac*, although the EC_{50} 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 EC_{50} 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	*Xoo*			*R. solanacearum*			*Xac*		
	Regression equation	*r*	EC_{50} (μg/mL)	Regression equation	*r*	EC_{50} (μg/mL)	Regression equation	*r*	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
CK_1	y = 1.499x+2.052	0.98	92.6 + 2.1	/	/	/	/	/	/
CK_2	/	/	/	y = 1.031x+2.942	0.99	216.7 ± 5.1	y = 2.153x+0.938	0.98	77.0 ± 2.0

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