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Substituted 1,6-diphenylnaphthalenes as FtsZ-targeting antibacterial agents

Yongzheng Zhang [a], Daniel Giurleo [b], Ajit Parhi [a], Malvika Kaul [c], Daniel S. Pilch [c], Edmond J. LaVoie [b,*]

[a] TAXIS Pharmaceuticals Inc., North Brunswick, NJ 08902, USA
[b] Department of Medicinal Chemistry, Rutgers, The State University of New Jersey, Piscataway, NJ 08854-8020, USA
[c] Department of Pharmacology, The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Piscataway, NJ 08854, USA

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ABSTRACT

Bacterial cell division occurs in conjunction with the formation of a cytokinetic Z-ring structure comprised of FtsZ subunits. Agents that disrupt Z-ring formation have the potential, through this unique mechanism, to be effective against several of the newly emerging multidrug-resistant strains of infectious bacteria. Several 1-phenylbenzo[*c*]phenanthridines exhibit notable antibacterial activity. Based upon their structural similarity to these compounds, a distinct series of substituted 1,6-diphenylnaphthalenes were synthesized and evaluated for antibacterial activity against *Staphylococcus aureus* and *Enterococcus faecalis*. In addition, the effect of select 1,6-diphenylnaphthalenes on the polymerization dynamics of *S. aureus* FtsZ and mammalian β-tubulin was also assessed. The presence of a basic functional group or a quaternary ammonium substituent on the 6-phenylnaphthalene was required for significant antibacterial activity. Diphenylnaphthalene derivatives that were active as antibiotics, did exert a pronounced effect on bacterial FtsZ polymerization and do not appear to cross-react with mammalian tubulin to any significant degree.

Bacterial infections associated with drug-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) are recognized worldwide as a major health concern.[1,2] Bacterial resistance to conventional antibacterial drugs has created a critical need for the identification of novel therapeutic antibacterial targets. In this connection, FtsZ has been identified as an appealing new target for antibacterial agents.[10–17] FtsZ is an essential and highly conserved bacterial cytokinesis protein.[3–8] Cell division in bacteria occurs at the site of formation of a cytokinetic Z-ring polymeric structure, which is comprised of FtsZ subunits.[9] The potential for developing agents that target FtsZ and the recent advances in the development of small molecules that target FtsZ have been the subject of several recent reports.[10–24]

Sanguinarine **1** (Fig. 1) is a benzo[*c*]phenanthridine plant alkaloid that has been identified as small molecule that alters FtsZ Z-ring formation and has modest antibacterial activity.[11,25] Studies in our laboratory have also shown that chelerythrine **2** (Fig. 1) has similar effects on *S. aureus* and *Bacillus subtilis*.[26] In addition, the presence of a phenyl functionality at the 1-position of **2** (to yield **3**) was shown to significantly enhance antibacterial activity relative to either **1** or **2**.[25,26] Within the cyclic core structure of **3**, there is a scaffold consisting of a 1,6-diphenylnaphthalene. In light of these results, we examined the relative structure–activity relationships associated with the antistaphylococcal and antienterococcal activity of several 1,6-diphenylnaphthalene derivatives, including those with a constitutive cationic charge, those with basic functionalities that could be protonated to varying degrees at physiological pH, and those without a cationic charge.

The critical intermediate for the preparation of the various 1,6-diphenylnaphthalenes that were synthesized was 5-bromo-2-naphthol, which was prepared from 6-hydroxy-1-naphthylamine as described in the literature (19).[27] Suzuki coupling of 4-*tert*-butylphenylboronic acid to this naphthylbromide provided 5-(4-*t*-butylphenyl)-2-naphthol, which was then converted to its triflate derivative with Tf_2O. This triflate derivative could then be used in a second Suzuki coupling reaction for the preparation of **5**, **6**, and **18** (see Scheme 1).

The triflate of 1-[(4-*t*-butyl)phenyl]-6-hydroxynaphthalene was also used in a Suzuki coupling reaction with 2-formylphenylboronic acid. The resulting aldehyde was reduced with $NaBH_4$ and the hydroxymethyl derivative converted to its benzyl chloride. Treatment of this chloride with either methylamine or dimethylamine provided **7** and **8**, respectively. Treatment of **8** with methyl iodide provided the quaternary ammonium derivative, **9**. The triflate of 1-[(4-*t*-butyl)phenyl]-6-hydroxynaphthalene was also coupled with 4-carboxymethyl-2-methylphenylboronic acid. NBS bromination of **5** and this 6-(2-methyl-4-carboxymethyl)-1-(4-*t*-butylphenylphenyl)naphthalene provided the bromomethyl intermediates

* Corresponding author. Tel.: +1 848 445 2674; fax: +1 732 445 6312.
E-mail address: elavoie@pharmacy.rutgers.edu (E.J. LaVoie).

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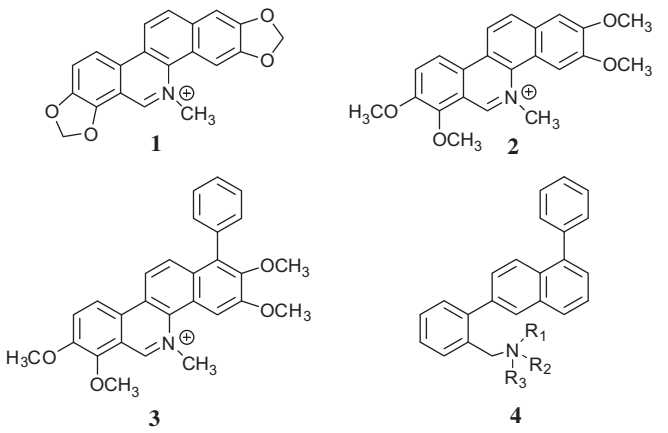


Figure 1. The structures of sanguinarine **1**, chelerythrine **2** and 1-phenyl-5-methyl-2,3,7,8-tetramethoxybenzo[*c*]phenanthridine **3** relative to a generalized structure of a 1,6-diphenylnaphthalene **4**.

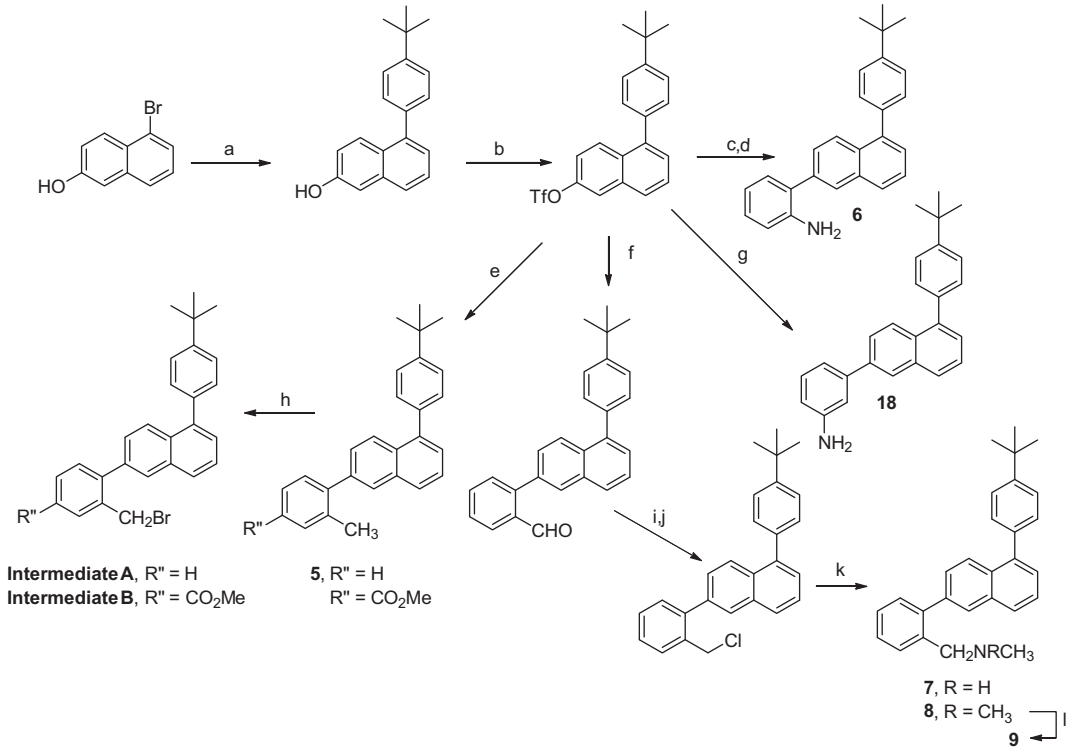
A and **B** that were employed for the preparation of **10**–**17**, as outlined in Scheme 2.

Treatment of these bromomethyl derivatives with 1,3-bis(*t*-butoxycarbonyl)guanidine followed by removal of the *N*-Boc protecting groups provided the guanidinomethyl derivatives **10** and **16**. Treatment of 1-(4-*t*-butyl)phenyl-6-(2-bromomethylphenyl)naphthalene with potassium cyanide followed by reduction of the resulting nitrile with LAH yielded the 2-aminoethyl derivative **11**. 1-(4-*t*-Butyl)phenyl-6-(2-bromomethyl-4-carboxymethylphenyl)naphthalene when treated with either methylamine or dimethylamine provided **13** and **14**, respectively. Compound **14** was methylated using methyl iodide to provide the quaternary ammonium derivative, **15**. Treatment of 1-(4-*t*-butyl)phenyl-6-(2-bromomethyl-4-carboxymethylphenyl)naphthalene with NaN_3 followed by reduction with triphenylphosphine provide the methylamino derivative, **12**. The methyl ester of **12** was hydrolyzed using LiOH in aqueous THF to yield its carboxy derivative, **17**.

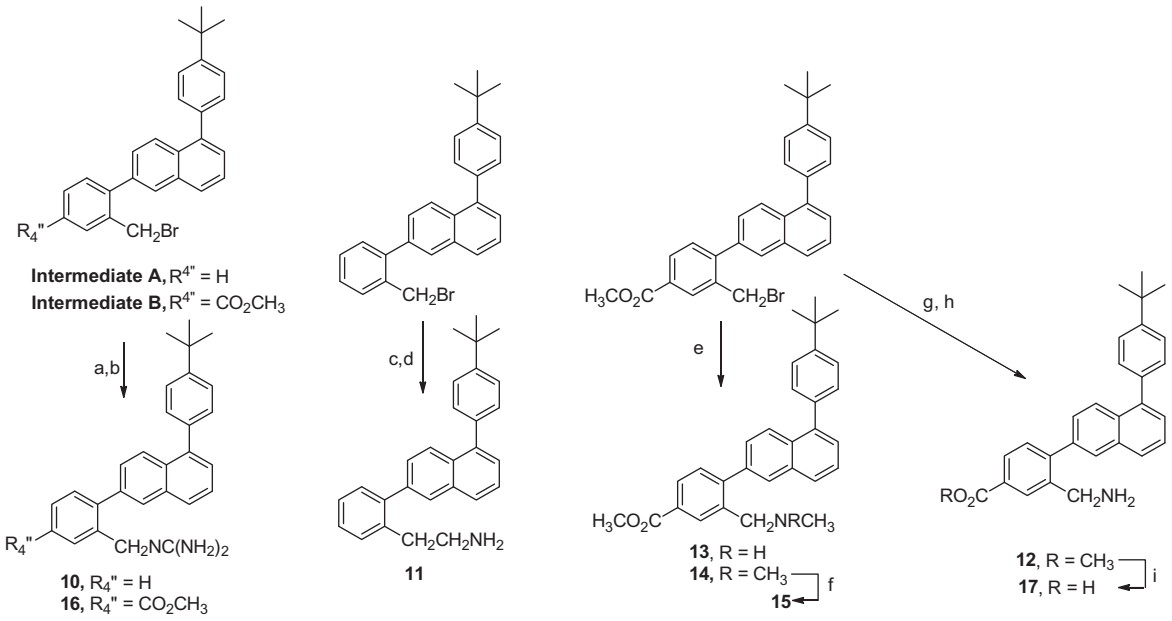
Using the appropriate triflate of 6-hydroxynaphthalene, various 1,6-diphenylnaphthalenes could be synthesized (Scheme 3). Treatment of the requisite *N*,*N*-dimethylamino and *N*,*N*-dimethylanilino derivatives with methyl iodide provided the quaternary ammonium salts, **19–27**. The triflate of 1-(3-[1,1′]-biphenyl)-6-hydroxynaphthalene served as an intermediate for Suzuki coupling with 3-aminophenylboronic acid to give **18**. Alternatively, this triflate intermediate was treated with 3-cyanophenylboronic acid, which was reduced with LAH to give **28**, which in the presence of formaldehyde and formic acid provided the *N*,*N*-dimethyl derivative, **29**. Treatment of **29** with methyl iodide resulted in the formation of the quaternary ammonium derivative, **30**.

Several 1,6-diphenylnaphthalenes (DPNs) were evaluated for antibiotic activity against methicillin-sensitive and methicillin-resistant *S. aureus* (MSSA and MRSA, respectively) and vancomycin-sensitive and vancomycin-resistant *Enterococcus faecalis* (VSE and VRE, respectively), as summarized in Table 1.

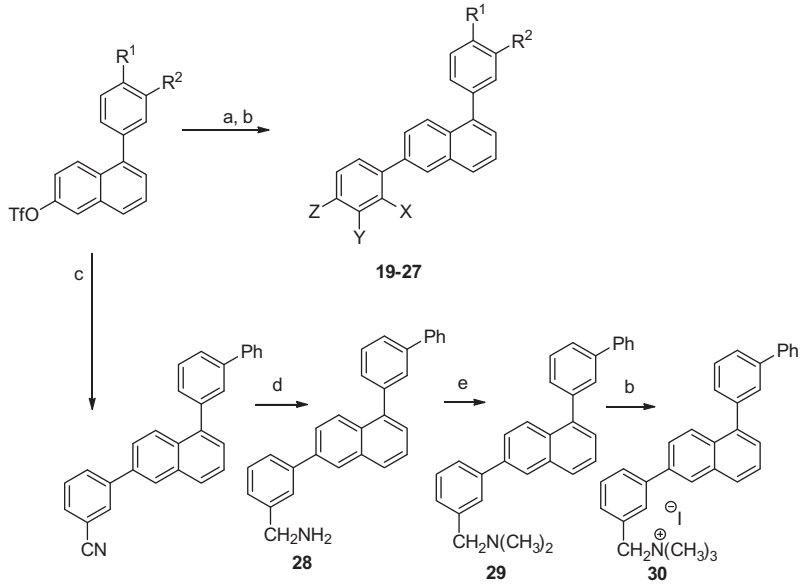
It is evident from the lack of antimicrobial activity for **5** and **6** that the presence of a sufficiently basic functional group, which would be significantly charged at physiological pH, is critical for activity. The first series of DPNs that was studied consisted of 1-[4-(*t*-butyl)phenyl]naphthalene derivatives that had an *o*-aminomethyl substituent on the 6-phenyl moiety. Among the analogs related to 6-(*o*-aminomethyl)phenyl, the presence of a single N-methyl group as in **7** is associated with significant activity against all *S. aureus* and *E. faecalis* strains. However, the *N*,*N*-dimethyl derivative, **8**, is substantially less active. Conversion of



Scheme 1. Methods used for the preparation of 1,6-diphenylnaphthalenes. Reagents and conditions: (a) 4-(*t*-butyl)phenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, dioxane/H_2O, 100 °C ; (b) Tf_2O, Et_3N, DCM, −78 °C; (c) 2-NO_2-phenylboronic acid, $Pd(OAc)_2$, XPhos, K_2CO_3, CH_3CN/H_2O, 100 °C; (d)H_2, Pd/C (10%), EtOH; (e) 2-methylphenylboronic acid-$B(OH)_2$ or 2-methyl-4-carboxymethylphenylboronic acid, $Pd(OAc)_2$, XPhos, K_2CO_3, CH_3CN/H_2O, 100 °C; (f) 2-formylphenylboronic acid, $Pd(OAc)_2$, XPhos, K_2CO_3, CH_3CN/H_2O, 100 °C; (g) 3-aminophenylboronic acid, $Pd(OAc)_2$, XPhos, K_2CO_3, CH_3CH/H_2O (1:1), 100 °C; (h) NBS, AIBN, CCl_4, 85 °C; (i) $NaBH_4$, EtOH; (j) MsCl, Et_3N, CH_2Cl_2, rt; see Ref. [28]; (k) **7**, CH_3NH_2 in THF or **8**, $(CH_3)_2NH$ in THF, 60 °C, sealed tube; (l) MeI, sealed tube 100 °C.



Scheme 2. Methods used for the preparation of 1,6-diphenylnaphthalenes. Reagents and conditions: (a) 1,3-bis(*tert*-butoxycarbonyl)guanidine, K_2CO_3, DMF, 50 °C, acetonitrile; (b) TFA, DCM, 50 °C, sealed vial, (c) KCN, DMF, rt; (d) LAH, toluene/THF(1:1), 100 °C; (e) **13**, CH_3NH_2 in THFor**14**, $(CH_3)_2NH$ in THF, 60 °C, sealed tube; (f) MeI, sealed tube 100 °C; (g) NaN_3, DMF, rt; (h) PPh_3 polymer bound, THF/H_2O, rt; (i) LiOH, THF-H_2O.



Scheme 3. Reagents and conditions: (a) R–$B(OH)_2$, $Pd(OAc)_2$, XPhos, K_2CO_3, CH_3CN/H_2O, 100 °C; (b) MeI, sealed tube 100 °C; (c) 3-cyanophenylboronic acid, $Pd(OAc)_2$, XPhos, K_2CO_3, CH_3CN/H_2O, 100 °C; (d) LAH, THF/toluene, 100 °C; (e) formaldehyde, $NaBH_3CN$, pH 6

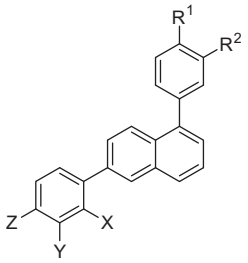
this tertiary amine to its *N*,*N*,*N*,-trimethyl ammonium derivative, **9**, resulted in a significant enhancement of its antibacterial activity against both the MSSA and MRSA strains, with MICs of 0.5 μg/mL. With regard to *E. faecalis*, **9** is slightly less active than **7**, with MICs of 4.0 μg/mL against both VSE and VRE. The guanidinomethyl derivative, **10**, and the 2-aminoethyl analog, **11**, also have similar antibacterial activity to **7**.

The structure–activity relationship among the 6-[(2-aminomethyl)-4-(carboxymethyl)]phenylnaphthalene analogs, **12**–**16**, was similar to that associated with 6-(*o*-aminomethyl)phenylnaphthalene derivatives, **7–11**. The 6-[(2-aminomethyl)-4-(carboxymethyl)]phenylnaphthalene **12** has good antibacterial activity against both MSSA and MRSA, but was notably less active against *E. faecalis*. In contrast, the 6-[(2-aminomethyl)-4-(carboxy)]phenylnaphthalene **17** did not exhibit appreciable antibacterial activity. Within this group of compounds, the most remarkable result, as was observed for **8**, is the loss of antibacterial activity for the *N*,*N*-dimethyl derivative, **14**.

Several DPNs were evaluated that incorporated into their structure a 1-[4-(*t*-butyl)phenyl]naphthalene moiety and either an *m*-amino or *m*-aminomethyl substituent on the 6-phenyl group. While the aniline derivative, **18**, is inactive, its *N*,*N*,*N*-trimethyl ammonium derivative **19** had potent antibacterial activity against all the *S. aureus* and *E. faecalis* strains.

Those DPNs that incorporated within their structure a 6-[3-(trimethylammonium)phenyl]naphthalene and either a 1-[4-

Table 1
Antistaphylococcal and antienterococcal activities of substituted 1,6-diphenylnaphthalenes



	X	Y	Z	R^2	R^1	MIC (μg/mL)			
						S. aureus 8325-4 (MSSA)	*S. aureus* ATCC 33591 (MRSA)	*E. faecalis* ATCC 19433 (VSE)	*E. faecalis* ATCC 51575 (VRE)
5	CH_3	H	H	H	*t*-Butyl	>64	>64	>64	>64
6	NH_2	H	H	H	*t*-Butyl	>64	>64	>64	>64
7	$CH_2NH(CH_3)$	H	H	H	*t*-Butyl	2	2	2	2
8	$CH_2N(CH_3)_2$	H	H	H	*t*-Butyl	32	>64	>64	>64
9	$CH_2N(CH_3)_3$	H	H	H	*t*-Butyl	0.5	0.5	4	4
10	$CH_2NC(NH_2)_2$	H	H	H	*t*-Butyl	1	1	2	2
11	$CH_2CH_2NH_2$	H	H	H	*t*-Butyl	2	2	4	4
12	CH_2NH_2	H	CO_2CH_3	H	*t*-Butyl	2	2	16	16
13	CH_2NHCH_3	H	CO_2CH_3	H	*t*-Butyl	4	4	8	4
14	$CH_2N(CH_3)_2$	H	CO_2CH_3	H	*t*-Butyl	>64	>64	>64	>64
15	$CH_2N(CH_3)_3$	H	CO_2CH_3	H	*t*-Butyl	1	2	4	8
16	$CH_2NC(NH_2)_2$	H	CO_2CH_3	H	*t*-Butyl	1	1	2	4
17	CH_2NH_2	H	CO_2H	H	*t*-Butyl	>64	>64	>64	>64
18	H	NH_2	H	H	*t*-Butyl	>64	>64	>64	>64
19	H	$N(CH_3)_3$	H	H	*t*-Butyl	0.5	1	2	2
20	H	$N(CH_3)_3$	H	H	Phenyl	0.5	1	2	4
21	H	$N(CH_3)_3$	H	H	CF_3	1	4	8	8
22	H	$N(CH_3)_3$	H	H	F	1	4	8	8
23	H	$N(CH_3)_3$	H	phenyl	H	1	1	2	2
24	H	H	$N(CH_3)_3$	H	*t*-Butyl	1	2	4	4
25	H	H	$N(CH_3)_3$	H	Phenyl	1	1	2	2
26	H	H	$N(CH_3)_3$	H	F	4	4	4	4
27	H	H	$N(CH_3)_3$	phenyl	H	1	1	2	2
28	H	CH_2NH_2	H	phenyl	H	2	4	4	8
29	H	$CH_2N(CH_3)_2$	H	phenyl	H	4	8	16	16
30	H	$CH_2N(CH_3)_3$	H	phenyl	H	0.5	1	4	4
1	Sanguinarine					2	2	8	16
2	Chelerythrine					4	4	32	32
Oxacillin						0.063	>64	8	>64
Vancomycin						1	2	1	>64
Erythromycin						0.13	>64	1	>64
Tetracycline						0.063	64	0.5	>64
Clindamycin						0.031	>64	2	>64

[a]Minimum inhibitory concentration (MIC) assays were conducted in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines for broth microdilution.[29] MIC is defined as the lowest compound concentration at which bacterial growth is ⩾90% inhibited.

biphenyl], 1-(4-fluorophenyl), 1-(4-trifluoromethylphenyl), or 1-[3-biphenyl] moiety (**20–23**) had significant antibacterial activity. Unexpectedly, similar activity was observed for 6-[4-(trimethylammonium)phenyl]naphthalenes that had incorporated in their structure a 1-[4-(*t*-butyl)phenyl], 1-[4-biphenyl], 1-(4-fluorophenyl), or 1-[3-biphenyl] moiety (**24–27**). The 6-[4-(trimethylammonium)phenyl]naphthalene analog, **24**, is only slightly less active than **19** against all the *S. aureus* and *E. faecalis* strains.

In a comparison of the 1-[3-biphenyl]-6-(3-aminomethylphenyl)naphthalene derivatives, **28–30**, the primary amine **28** was significantly more active than the tertiary amine **29**. The *N*,*N*,*N*-trimethylammonium derivative, **30,** was as or more potent than **28** against all the *S. aureus* and *E. faecalis* strains.

Stimulation of FtsZ self-polymerization and the concomitant stabilization of FtsZ polymers has been implicated in the antibacterial actions of several distinct classes of small molecules, including substituted benzamides,[10,13,14,20] dibenzoquinoliziniums,[30] isoquinolines,[31] and biaryls.[32] We used a light scattering (turbidity) assay to monitor the impact, if any, of select diphenylnaphthalene compounds on the dynamics of self-polymerization by *S. aureus* FtsZ (SaFtsZ), which was expressed in *Escherichia coli* and purified as previously described.[32] In this assay, FtsZ polymerization is detected in solution by a time-dependent increase in light scattering, as reflected by a corresponding increase in solution absorbance at 340 nm (A_{340}). As illustrative examples, Figure 2 shows the time-dependent A_{340} profiles of SaFtsZ in the presence of vehicle (DMSO) onlyor compounds **9** and **11** at a concentration of 40 μg/mL. Vancomycin was also included as a non-FtsZ-targeting control antibiotic. Note that vancomycin exerts a negligible impact on SaFtsZ polymerization, an expected result given that the antibacterial target of vancomycin is the bacterial cell wall and not FtsZ. By contrast, compounds **9** and **11** increase both the kinetics and extent of SaFtsZ polymerization, with the relative magnitude of these increases correlating with the relative antistaphylococcal potencies of the compounds (see Table 1). Thus, as we have previously indicated for the dibenzoquinoliziniums,[30] isoquinolines,[31] and biaryls,[32]

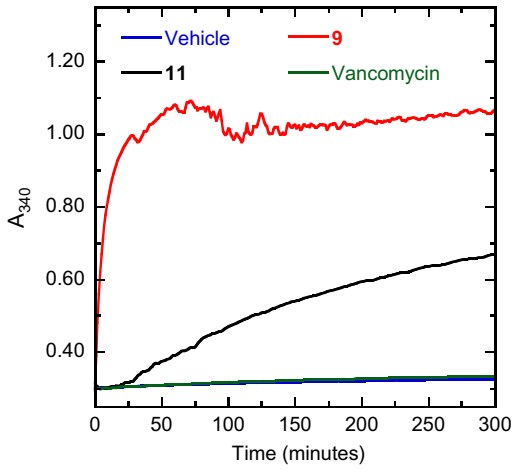


Figure 2. Impact of select diphenylnaphthalenes on the polymerization of *S. aureus* FtsZ (SaFtsZ), as determined by monitoring time-dependent changes in absorbance at 340 nm (A_{340}). Polymerization profiles of SaFtsZ (10 μM) in the presence of DMSO vehicle (blue) or 40 μg/mL of either **9** (red), **11** (black), or the comparator antibiotic vancomycin (green) are depicted. Experiments were conducted at 25 °C in solution containing 50 mM Tris.HCl (pH 7.4), 50 mM KCl, 2 mM magnesium acetate, 1 mM $CaCl_2$, and 1 mM GTP. The reactions (100 μL total volume) were assembled in half-volume, flat-bottom 96-well microtiter plates, and their A_{340} values were continuously monitored using a VersaMax® (Molecular Devices, Inc.) plate reader.

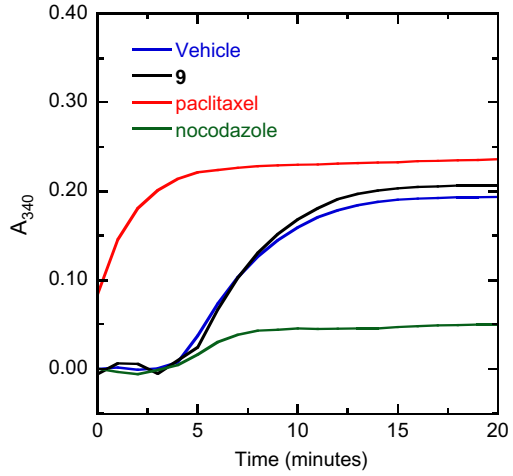


Figure 3. Impact of **9** on the polymerization of microtubule associated protein (MAP)-rich porcine β-tubulin (70% tubulin, 30% MAPs), as determined by monitoring time-dependent changes in A_{340}. Polymerization profiles of tubulin (2 mg/mL) in the presence of DMSO vehicle (blue), 40 μg/mL **9** (black), 25 μg/mL paclitaxel (red), or 10 μg/mL nocodazole (green) are depicted. Experiments were conducted at 37 °C in solution containing 80 mM PIPES.NaOH (pH 7.0), 2 mM $MgCl_2$, 1 mM EGTA, and 1 mM GTP. The reactions (100 μL total volume) were assembled in half-volume, flat-bottom 96-well microtiter plates, and their A_{340} values were continuously monitored using a VersaMax® plate reader.

the antibacterial activities of the diphenylnaphthalenes appear to be related to the impact the compounds have on the polymerization dynamics of FtsZ.

Tubulin is the closest mammalian functional homolog to bacterial FtsZ. We therefore sought to determine whether **9**, which is a potent stimulator of FtsZ polymerization (Fig. 2), would exert a similar effect on mammalian tubulin. To this end, we monitored the impact of **9** on porcine β-tubulin polymerization using a light scattering assay similar to that described above for FtsZ polymerization. We used the antineoplastic drugs paclitaxel (taxol) and nocodazole as positive controls in these assays, the former drug being a known stimulator of tubulin polymerization[33,34] and the latter drug being a known inhibitor of tubulin polymerization.[35] Figure 3 shows the time-dependent A_{340} profiles of porcine β-tubulin in the presence of DMSO vehicle, **9** (at 40 μg/mL), paclitaxel (at 25 μg/mL), or nocodazole (at 10 μg/mL). Both paclitaxel and nocodazole produce their expected impacts on tubulin polymerization dynamics. By contrast, **9** exerts little or no impact. Thus, a diphenylnaphthalene compound that exerts a profound impact on bacterial FtsZ polymerization does not appear to cross-react with mammalian tubulin to any significant degree. This degree of target specificity bodes well for the potential of desirable toxicological properties on the part of the diphenylnaphthalenes.

The structure-activity relationships associated with the antistaphylococcal and antienterococcal activity of several 1,6-diphenylnaphthalenes, including those with a constitutive cationic charge and those with basic functionalities that could be protonated to varying degrees at physiological pH, reveal several derivatives with significant antibacterial activity against *S. aureus* and *E. faecalis*. The presence on the 6-phenyl moiety of a methylaminomethyl-, 2-methylaminoethyl, guanidinomethyl, or (trimethylammonium)methyl at the *o*-position was associated with significant antibacterial activity within a series of 6-phenyl-1-(4-*t*-butylphenyl)naphthalenes. In addition, the presence of a trimethylammonium group at either the *m*- or *p*-position of the 6-phenyl moiety was associated with antibacterial activity for 6-phenyl-1-(4-*t*-butylphenyl)naphthalenes, 6-phenyl-1-(3-[1,1′-phenyl)naphthalenes and 6-phenyl-1-(4-[1,1′-biphenyl)naphthalenes. As was observed with benzo[*c*]phenanthridinium derivatives **1** or **2**, it appears that for the 1,6-diphenylnaphthalenes **9** and **11**, that there antibacterial activity is associated with their ability to effect FtsZ polymerization. While having a pronounced impact on bacterial FtsZ polymerization, they do not affect mammalian tubulin.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.02.016.

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