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Antibacterial activity of quinoxalines, quinazolines, and 1,5-naphthyridines

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ABSTRACT

Several phenyl substituted naphthalenes and isoquinolines have been identified as antibacterial agents that inhibit FtsZ-Zing formation. In the present study we evaluated the antibacterial of several phenyl substituted quinoxalines, quinazolines and 1,5-naphthyridines against methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* and vancomycin-sensitive and vancomycin-resistant *Enterococcus faecalis*. Some of the more active compounds against *S. aureus* were evaluated for their effect on FtsZ protein polymerization. Further studies were also performed to assess their relative bactericidal and bacteriostatic activities. The notable differences observed between nonquaternized and quaternized quinoxaline derivatives suggest that differing mechanisms of action are associated with their antibacterial properties.

Nosocomial infections associated with multidrug-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) represent a major public health concern.[1–4] Increased bacterial resistance to conventional antibiotics has brought attention to the critical need for the identification of novel therapeutic antibacterial targets.[5]

FtsZ is an essential and highly conserved bacterial protein involved in cytokinesis.[6–9] Cell division in bacteria occurs at the site of formation of a cytokinetic Z-ring polymeric structure comprised of FtsZ subunits. FtsZ forms the Z-ring via a process of GTP-dependent self-polymerization.[7–9] The Z-ring plays a key role in constriction of the bacterial cell wall and serves as a scaffold for the recruitment of other components of the cell division machinery.[7,9] Several recent reviews have discussed the potential of antibacterial agents that target FtsZ, as well as recent advances in the discovery of small molecules that perturb processes in which FtsZ is involved.[10–15] FtsZ-targeting antibacterial agents can exert their disruptive effects on the Z-ring by either enhancing or inhibiting FtsZ self-polymerization.[16–25]

Several phenyl substituted naphthalenes and isoquinolines were identified as antibacterial agents that act as stimulators of FtsZ polymerization.[26–28] In the present study, we evaluated of the bactericidal and bacteriostatic potential of phenyl substituted quinoxalines, quinazolines and 1,5-naphthyridines and examined their effect on FtsZ protein polymerization.

The quinoxaline derivatives evaluated in this study are listed in Table 1. Commercially available quinoxaline **1** was converted to 1-methylquinoxalinium iodide **2** by treatment with methyl iodide at 80 °C in a sealed vial. The 2-substituted quinoxalines **2a**–**10a** and the *N*-methylated derivatives **2b**–**9b** were prepared as outlined in Scheme 1. 2-Trifluoromethylsulfonyloxyquinoxaline was prepared as previously described.[29] For the preparation of **7a**, 3-(*t*-butyl)-5-(carbomethoxy)phenylboronic acid pinacol ester was used in the Suzuki coupling. This boronate ester was prepared by treating commercially available methyl 3-bromo-5-iodobenzoate with 4-*t*-butylphenylboronic acid in the presence of $Pd(PPh_3)_4$. The resulting 3-bromo-5-carbomethoxy-4′-(*t*-butyl)biphenyl was converted to it's pinacol ester by standard coupling conditions using bis(pinacolato)diboron and $PdCl_2$(dppf) with KOAc in dioxane.

The assignment of the site of N-methylation in the case of **2b**–**9b** is based upon the literature[30–33] and spectral data from

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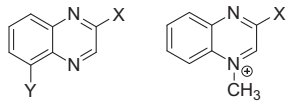
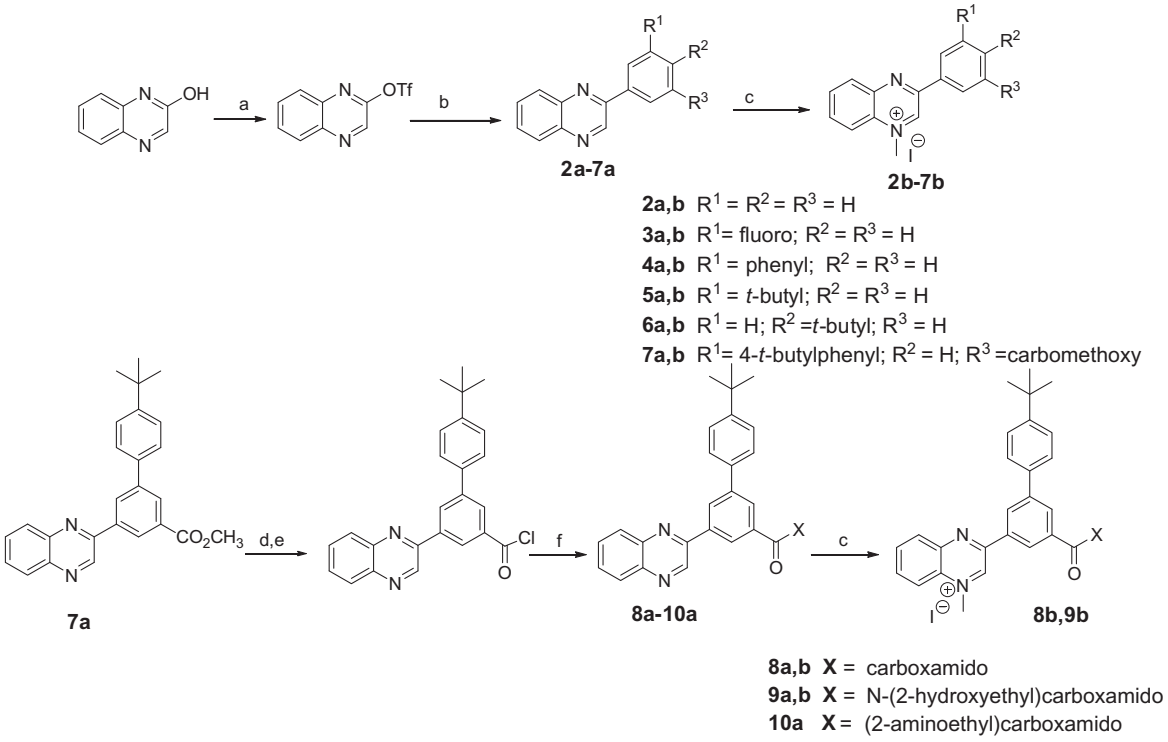
Table 1
Substituted quinoxaline derivatives evaluated for antibacterial activity



Compound	X	Y
1a	H	H
1b	H	H
2a	Phenyl	H
2b	Phenyl	H
3a	3-Fluorophenyl	H
3b	3-Fluorophenyl	H
4a	3-Biphenyl	H
4b	3-Biphenyl	H
5a	3-*t*-Butylphenyl	H
5b	3-*t*-Butylphenyl	H
6a	4-*t*-Butylphenyl	H
6b	4-*t*-Butylphenyl	H
7a	3-(4′-*t*-Butyl-5-carbomethoxybiphenyl)	H
7b	3-(4′-*t*-Butyl-5-carbomethoxybiphenyl)	H
8a	3-(4′-*t*-Butyl-5-carboxamidobiphenyl)	H
8b	3-(4′-*t*-Butyl-5-carboxamidobiphenyl)	H
9a	3-(4′-*t*-butyl-5-[carboxamido-*N*-(2-hydroxyethyl)]biphenyl)	H
9b	3-(4′-*t*-Butyl-5-[carboxamido-*N*-(2-hydroxyethyl)]biphenyl)	H
10a	3-(4′-*t*-Butyl-5-[carboxamido-*N*-(2-aminoethyl)]biphenyl)	H
11a	3-*t*-Butylphenyl	$CH_2NC(NH_2)_2$
12a	4-*t*-Butylphenyl	$CH_2NC(NH_2)_2$



Scheme 1. Synthesis of quinoxalines and *N*-methylquinoxalinium derivatives. Reagents and conditions: (a) triflic anhydride, TEA, DCM, 0 °C, 2 h; (b) dioxane, $Pd((PPh_3)_2)Cl_2$, Cs_2CO_3, phenylboronic acid for **2a**, 4-fluorophenylboronic acid for **3a**, 3-biphenylboronic acid for **4a**, 3-*t*-butylphenylboronic acid for **5a**, 3-*t*-butylphenylboronic acid for **6a**, 3-(*t*-butyl)-5-(carbomethoxy)phenylboronic acid pinacol ester for **7a** with (XPhos, $Pd(OAc)_2$, K_2CO_3, ACN/H_2O (2:1) (c) MeI, 80–90 °C, sealed vial; 12 h; (d) THF/H_2O (2:1), LiOH, 50 °C; (e) Oxalyl chloride, DCM, cat DMF, rt; (f) R-NH_2, DCM, rt.

2D NOESY data that were analyzed for **2b**, **5b** and **6b**, which are detailed in the Supporting information.

The preparation of 2-phenyl-6-methylquinoxalines was performed as outlined in Scheme 2. A mixture of both 5-methyl-2-hydroxyquinoxaline and 8-methyl-2-hydroxyquinoxaline was formed by condensing 3-methyl-1,2-phenylenediamine with ethyl-2-oxaacetate. These hydroxyquinoxalines were converted to their chloro derivatives using $POCl_3$.[34] The mixture of

chloroquinoxalines was then subester by standard coupling conditions usingbisjected to Suzuki coupling conditions using either 3-*t*-butylphenylboronic acid or 4-*t*-butylphenylboronic acid. Isolated from the mixture formed in each instance was 2-(3-*t*-butylphenyl)-6-methylquinoxaline and 2-(4-*t*-butylphenyl)-5-methylquinoxaline, respectively. Each of the isolated 5-methylquinoxalines were treated with NBS to form their bromomethyl derivatives, which subsequently was converted to their respective guanidinomethyl derivatives, **11a** and **12a**.

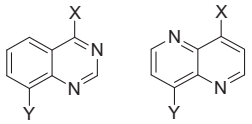
The spectral identification of the 2-phenyl-6-methylquinoxaline was based on a careful analysis of 2D-NOESY and gCOSY spectral data. The position of the phenyl moiety was established unequivocally on the basis of detailed gHMQC and gHMBC spectral analyses, which are detailed in the Supporting information.

The quinazoline and 1,5-naphthyridines synthesized and evaluated for antibacterial activity are listed in Table 2. The substituted 4-phenylquinazoline derivatives **13** and **14** were synthesized as outlined in Scheme 3. 4-Chloro-8-methylquinazoline was prepared as described in the literature.[35] Suzuki coupling of this intermediate using 4-*t*-butylphenylboronic acid provided 4-(4-*t*-butylphenyl)-8-methylquinazoline. Treatment of this intermediate with NBS provided the bromomethyl derivative, which was converted to its azide derivative and subsequently reduced to provide the aminomethyl derivative **13**. Alternative, this bromomethylquinazoline could be treated with 1,3-bis(*t*-butoxycarbonyl)guanidine and the *N*-Boc protecting groups removed using trifluoroacetic acid in dichloromethane.

Compound **16** was prepared as shown in Scheme 4. Conversion of 4-methyl-8-hydroxyquinazoline to its triflate and subsequent Suzuki coupling using 4-*t*-butylphenylboronic acid gave 3-methyl-8-(4-*t*-butylphenyl)quinazoline. This intermediate was converted to its bromomethyl derivative using NBS in CCl_4. Using conditions as previously described for 4-(4-*t*-butylphenyl)-8-bromomethylquinazoline, this bromomethyl derivative could be converted to its guanidinomethyl derivative **16**.

The synthesis of the naphthyridine derivatives **17** and **18** was accomplished as outlined in Scheme 5. Conversion of 4-hydroxy-8-methyl[1,5]naphthyridine to its triflate, followed by Suzuki coupling with 4-*t*-butylphenylboronic acid provided 4-(4-*t*-butylphenyl)-8-methyl[1,5]naphthyridine. The methyl substituent could be converted to its aminomethyl derivative **17** or its guanidinomethyl derivative **18** using methodology previously described in this study for methylquinazolines.

Table 2
Substituted quinazolines and 1,5-naphthyridines synthesized and evaluated for antibacterial activity

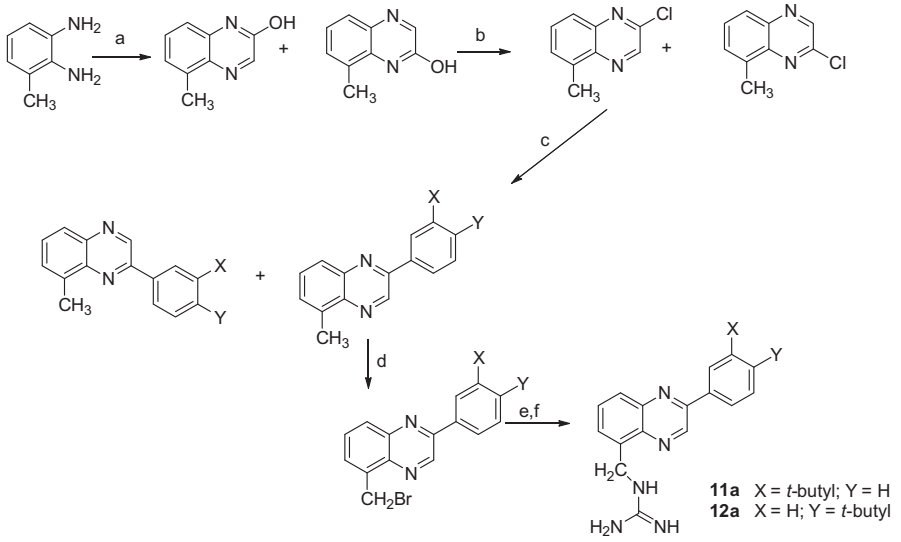


13-16 **17, 18**

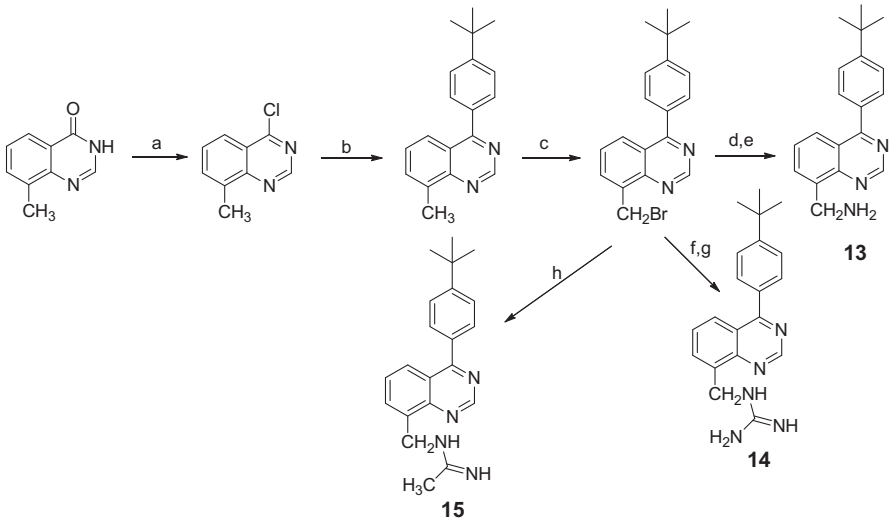
Compd	X	Y
13	4-*t*-Butylphenyl	CH_2NH_2
14	4-*t*-Butylphenyl	$CH_2NC(NH_2)_2$
15	4-*t*-Butylphenyl	$CH_2NC(NH_2)(CH_3)$
16	$CH_2NC(NH_2)_2$	4-*t*-Butylphenyl
17	4-*t*-Butylphenyl	CH_2NH_2
18	4-*t*-Butylphenyl	$CH_2NC(NH_2)_2$

The relative antibacterial activities of these varied quinoxalines and methylquinoxalinium derivatives against methicillin-sensitive *S. aureus* (MSSA), methicilllin-resistant *S. aureus* (MRSA), vancomycin-sensitive *Entercoccus faecalis* (VSE) and vancomycin-resistant *E. faecalis* (VRE) are provided in Table3. Quinoxaline and *N*-methylquinoxalinium iodide did not exhibit notable antibacterial activity against *S. aureus* or *E. faecalis*. The presence of hydrophoblic moieties such as a phenyl, 4-fluorophenyl, 3-biphenyl, or 4-*t*-butylphenyl at the 3-position of 1-methylquinoxalinium iodides **2b**–**6b**, but not at the 2-position of quinoxaline (**2a**–**6a**), resulted in a significant increase in antibacterial activity. A similar trend was observed for quinoxalines structurally-related to **6a** and **6b**, having a 5-carboxymethy substituent (**7a** and **7b**), a 5-carboxyamido substituent (**8a** and **8b**) or a 5-carboxamido-*N*-(2-hydroxyethyl) group (**9a** and **9b**). Only in the case of the related carboxamido derivative with an *N*-(2-aminoethyl) substituent (**10a**) was significant activity observed for a quinoxaline derivative. The placement of a guanidinomethyl substituent at the 5-position of either a 2-(3-*t*-butylphenyl)quinoxaline or 2-(4-*t*-butylphenyl)quinoxaline (**11a** and **12a**) did result in a notable increase in antibacterial activity.

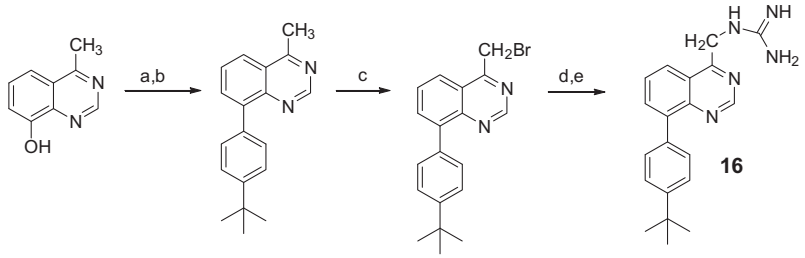
These data tend to suggest that these highly basic substituents that would be protonated at physiological pH could mimic the



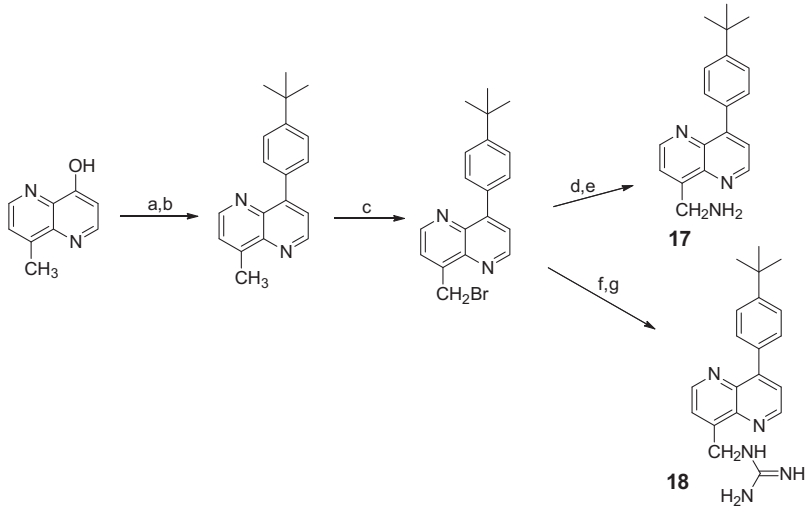
Scheme 2. Synthesis of the 5-guanidinomethyl quinoxaline derivatives **11a** and **12a**. Reagents and conditions: (a) $HCOCOOCH_2CH_3$/EtOH (1:1), reflux; 30 min; (b) $POCl_3$, 110 °C, 1 h; (c) dioxane/H_2O (3:1), $Pd(PPh_3)_4$, K_2CO_3, 3-(*t*-butyl)phenylboronic acid, 100 °C, 2 h; (d) NBS, CCl_4, hν, 30 min; (e) DMF, K_2CO_3, 1,3-bis(*t*-butoxycarbonyl)guanidine, 16 h; (f) trifluoroacetic acid/DCM (1:1), 50 °C, 2 h.



Scheme 3. Synthesis of the quinazoline derivatives **13**–**15**. Reagents and conditions: (a) $POCl_3$, CH_3CN, reflux, 4 h[33]; (b) 4-*t*-butylphenylboronic acid, DME, Na_2CO_3, $Pd(PPh_3)_4$, 85 °C, 1 h; (c) NBS, CCl_4, hν, 3 h; (d) DMF, NaN_3, K_2CO_3; 50 °C, 16 h; (e) THF/H_2O (9:1), $P(Ph_3)$ on solid support, 72 h at rt; (f) DMF, K_2CO_3, 1,3-bis(*t*-butoxycarbonyl)guanidine, 16 h; (g) trifluoroacetic acid/DCM (1:1), 50 °C; (h) acetamidine HCl, K_2CO_3, DMF, 16 h, rt.



Scheme 4. Synthesis of the quinazoline derivative **16**. Reagents and conditions: (a) triflic anhydride, TEA, DCM, −78 °C, 90 min; (b) 4-*t*-butylphenylboronic acid, DME, Na_2CO_3, $Pd(PPh_3)_4$, 80 °C, 1 h; (c) NBS, CCl_4, hν, 1 h; (d) DMF, K_2CO_3, 1,3-bis(*t*-butoxycarbonyl)guanidine, 16 h; (e) trifluoroacetic acid/DCM (1:1), 50 °C.



Scheme 5. Synthesis of the 1,5-naphthyridine derivatives **17** and **18**. Reagents and conditions: (a) triflic anhydride, TEA, DCM, 0 °C, 1 h; (b) 4-*t*-butylphenylboronic acid, DME, Na_2CO_3, $Pd(PPh_3)_4$, 80 °C, 1 h; (c) NBS, CCl_4, hν, 1 h; (d) DMF, NaN_3, K_2CO_3; 50 °C, 16 h; (e) THF/H_2O (9:1), $P(Ph_3)$ on solid support, 72 h at rt; (f) DMF, K_2CO_3, 1,3-bis(*t*-butoxycarbonyl)guanidine, 16 h; (g) trifluoroacetic acid/DCM (1:1), 50 °C.

charge associated with the analogous 1-methylquioxalinium derivatives **5b** and **6b**.

Other diazanaphthalenes were examined including the quinazolines **13**–**16** and 1,5-naphthyridine derivatives (**17** and **18**). In both instances, the less basic aminomethyl derivatives (**13** and **17**) did not exhibit significant antibacterial activity. While the amidinomethyl derivative (**15**) did not exhibit significant activity, in the case of the guanidinomethyl derivatives (**14** and **18**) more pronounced antibacterial activity was observed. Alternating position of the *t*-butylphenyl substituent and the guanidinomethyl

Table 3
Antibacterial activities of quinoxaline, quinazoline and 1,5-naphthyridine derivatives

Compound	[a]MIC (μg/mL)			
	S. aureus 8325-4 (MSSA)	*S. aureus* ATCC 33591 (MRSA)	*E. faecalis* ATCC 19433 (VSE)	*E. faecalis* ATCC 51575 (VRE)
1a	>64	>64	>64	>64
1b	32	>64	>64	>64
2a	>64	>64	>64	>64
2b	4.0	8.0	32	>64
3a	>64	>64	>64	>64
3b	2.0	4.0	32	32
4a	>64	>64	>64	>64
4b	0.5	0.5	8.0	8.0
5a	>64	>64	>64	>64
5b	2.0	2.0	8.0	16
6a	>64	>64	>64	>64
6b	0.5	1.0	16	16
7a	>64	>64	>64	>64
7b	1.0	1.0	4.0	4.0
8a	>64	>64	>64	>64
8b	2.0	2.0	4.0	4.0
9a	>64	>64	>64	>64
9b	4.0	4.0	8.0	8.0
10a	4.0	4.0	8.0	8.0
11a	4.0	4.0	8.0	16
12a	4.0	4.0	8.0	16
13	32	64	64	64
14	4.0	8.0	32	32
15	32	64	64	64
16	16	64	>64	>64
17	>64	>64	>64	>64
18	8.0	8.0	32	64
Oxacillin	0.06	>64	8.0	>64
Vancomycin	1.0	2.0	1.0	>64
Erythromycin	0.13	>64	1.0	>64
Tetracycline	0.06	64	0.5	>64
Clindamycin	0.03	>64	2.0	>64

[a] Minimum inhibitory concentration (MIC) assays were conducted in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines for broth microdilution.[36] MIC is defined as the lowest compound concentration at which bacterial growth is ⩾90% inhibited.

substituent in the case of the quinazoline (**14**) from the 4 and 8 positions, to the 8 and 4 positons as in **16** resulted in a four-fold decrease in activity.

The antibacterial activities of the more potent quinoxaline (**4b**, **5b**, **6b**, **11a**, and **12a**), quinazoline (**14**), and 1,5-naphthyridine (**18**) compounds prompted further investigation as to whether these activities are bactericidal or bacteriostatic in nature. In this connection, values of minimal bactericidal concentration (MBC) for these select compounds in *S. aureus* 8325-4 (MSSA), *S. aureus* ATCC 33591 (MRSA), and *E. faecalis* ATCC 51575 (VRE) were determined and subsequently compared with the corresponding MIC values listed in Table 3. For these determinations, the bactericidal drug vancomycin[37] and the bacteriostatic drug erythromycin[38] were used as comparator controls. Per CLSI guidelines, an MBC/MIC ratio of 1–2 is considered indicative of bactericidal behavior, with a corresponding MBC/MIC ratio ⩾8 being considered indicative of bacteriostatic behavior.[36] The comparator control agents yielded expected results, with an MIC/MBC ratio of 1 being observed for the bactericidal drug vancomycin and an MBC/MIC ratio of 256 being observed for the bacteriostatic drug erythromycin (see Table 4). The nonquaternary quinoxaline (**11a** and **12a**), quinazoline (**14**), and 1,5-naphthyridine (**18**) compounds were all associated with an MBC/MIC ratio of 1–2, indicative of a bactericidal mode of action against MSSA, MRSA, and VRE. In striking contrast to the nonquaternary compounds, the quaternary quinoxaline compounds **4b**, **5b**, and **6b** were associated with MBC/MIC ratios of 8–16 for MSSA and MRSA and 4–8 for VRE, indicative of bacteriostatic behavior on the part of these compounds. Viewed as a whole, these observations suggest that the quaternary and nonquaternary compounds may exert their antibacterial properties through differing mechanisms of action.

To further explore the mechanistic differences between the quaternary and nonquaternary compounds with regard to their antibacterial activities, the impacts of **4b**, **5b**, **11a**, **12a**, **14**, and **18** on the self-polymerization of purified *S. aureus* FtsZ (SaFtsZ) were evaluated using a previously established microtiter plate-based light-scattering assay.[24–28] 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}). Figure 1 shows the time-dependent A_{340} profiles of SaFtsZ in the presence of DMSO vehicle alone or **4b**, **5b**, **11a**, **12a**, **14**, or **18**. Note that the nonquaternary compounds **11a**, **12a**, **14**, and **18** stimulate SaFtsZ polymerization (Fig. 1A and B). We next explored the stability of the SaFtsZ polymers induced by the nonquaternary compounds. In the absence of a polymer-stabilizing agent or compound, addition of GDP has been shown to depolymerize FtsZ polymers formed in the presence of GTP.[16] We examined the impact, if any, of added GDP (10 mM) on the SaFtsZ polymers formed in the presence of both GTP (1 mM) and the compounds (40 μg/mL).

The addition of 10 mM GDP did not exert a significant impact on the A_{340} signal, an observation indicating that SaFtsZ polymers induced by the presence of the compounds are stable to the depolymerizing effects of GDP. These collective results are consistent with the bactericidal activities of the non-quaternary quinoxaline,

Table 4
Comparison of the MIC and MBC values for select quinoxaline, quinazoline, and 1,5-naphthyridine derivatives[a]

Compound or control agent[b]	*S. aureus* 8325-4 (MSSA)			*S. aureus* ATCC 33591 (MRSA)			*E. faecalis* ATCC 51575 (VRE)		
	MIC (μg/mL)	MBC (μg/mL)	MBC/MIC	MIC (μg/mL)	MBC (μg/mL)	MBC/MIC	MIC (μg/mL)	MBC (μg/mL)	MBC/MIC
4b	0.5	4.0	8	0.5	4.0	8	8	64	8
5b	2.0	16	8	2.0	16	8	16	64	4
6b	0.5	8.0	16	1.0	16	16	16	64	4
11a	4.0	4.0	1	4.0	8.0	2	16	32	2
12a	4.0	4.0	1	4.0	8.0	2	16	16	1
14	4.0	8.0	2	8.0	16	2	32	64	2
18	8.0	8.0	1	8.0	16	2	64	64	1
Vancomycin	1.0	1.0	1	2.0	4.0	2	>64	na	na
Erythromycin	0.13	32	256	>64	na	na	>64	na	na

[a] MIC values were determined as described in the footnote to Table 3. Minimum bactericidal concentration (MBC) values were determined as previously described.[24] Na = not applicable.
[b] Vancomycin and erythromycin are included as control bactericidal and bacteriostatic agents, respectively.

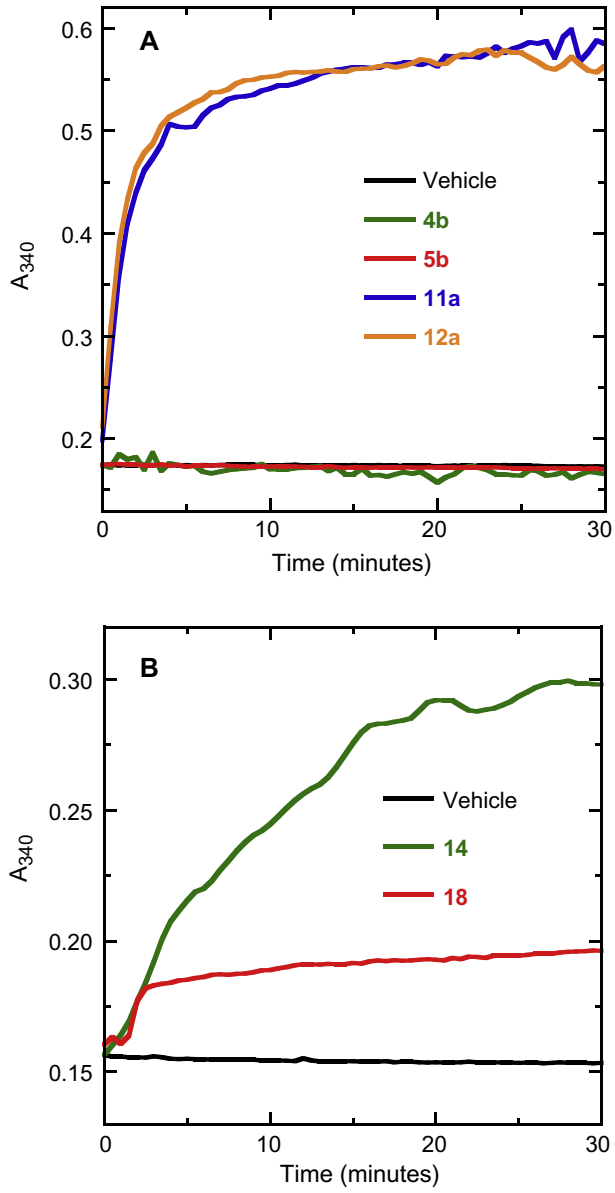


Figure 1. Impact of select quaternary quinoxaline (**4b** and **5b**), nonquaternary quinoxaline (**11a** and **12a**), quinazoline (**14**) and 1,5-naphthyridine (**18**) derivatives on the self-polymerization of *S. aureus* FtsZ (expressed and purified as described previously[24]), as determined by monitoring time-dependent changes in absorbance at 340 nm (A_{340}). The A_{340} profiles of *S. aureus* FtsZ (10 μM) in the presence of DMSO vehicle or the indicated derivatives are depicted. **4b**, **5b**, **11a**, and **12a** were used at a concentration of 40 μg/mL, with **14** and **18** being used at a concentration of 80 μg/mL. 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.

quinazoline, and 1,5-naphthyridine compounds being associated with their disruptive effects on FtsZ function.

In marked contrast to **11a**, **12a**, **14**, and **18**, the quaternary quinoxaline derivatives **4b** and **5b** exert no significant impact on SaFtsZ polymerization (Fig. 1). This observation suggests that the bacteriostatic activities of the quaternary quinoxalines may reflect a mechanism of action unrelated to FtsZ disruption. It is possible that the quaternary compounds may disrupt the bacterial membrane, which, like the basic peptidic drugs polymyxin B and colistin, can result in bacteriostatic behavior.

Acknowledgments

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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.2013.06.048.

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