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The synthesis and SAR study of phenylalanine-derived (*Z*)-5-arylmethylidene rhodanines as anti-methicillin-resistant *Staphylococcus aureus* (MRSA) compounds

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ABSTRACT

A focused library of rhodanine compounds containing novel substituents at the C5-position was synthesized and tested in vitro against a panel of clinically relevant MRSA strains. The present SAR study was based on our lead compound **1** (MIC = 1.95 μg/mL), with a focus on identifying optimal C5-arylidene substituents. In order to obtain this objective, we condensed several unique aromatic aldehydes with phenylalanine-derived rhodanine intermediates to obtain C5-substituted target rhodanine compounds for evaluation as anti-MRSA compounds. These efforts produced three compounds with significant efficacy: **23**, **32** and **44**, with MIC values ranging from 0.98 to 1.95 μg/mL against all tested MRSA strains as compared to the reference antibiotics penicillin G (MIC = 15.60–250.0 μg/mL) and ciprofloxacin (MIC = 7.80–62.50 μg/mL) and comparable to that of vancomycin (MIC = 0.48 μg/mL). In addition, compounds **24**, **28**, **37**, **41**, **46** and **48** (MIC = 1.95–3.90 μg/mL) were efficacious against all MRSA strains. The majority of the synthesized compounds had bactericidal activity at concentrations only two to fourfold higher than their MIC. Overall, the results suggest that compounds **23**, **32** and **44** may be of potential use in the treatment of MRSA infections.

In the last two decades, methicillin-resistant *Staphylococcus aureus* (MRSA) has become one of the major health threats in the United States as well as globally. It has been estimated that >50% of all staphylococcus infections are due to MRSA. The death toll from MRSA infections in 2005 exceeded those from HIV/AIDS in the United States. MRSA infection is typically classified into two major types, hospital (HA)- and community-acquired (CA) MRSA, which differ in their epidemiology, DNA sequence, populations infected and sites of infection.[1–3] HA-MRSA occurs in patients with specific risk factors,[4–6] whereas CA-MRSA can occur in healthy individuals that do not have predisposing factors.[7–9] Typically, HA-MRSA infections occur in the urine, lungs, bloodstream and surgical sites, whereas CA-MRSA primarily produces skin and skin structure infections, as well as invasive infections, although to a lesser extent.[3,10] Until the mid-1990s, MRSA infections primarily occurred in individuals in health care facilities (HA-MRSA).[11,12] Subsequently, the CA-MRSA strains have become widespread in the community[11,13] and the USA300 strain has been found on all continents except Antarctica.[14] Recent data indicates that CA-MRSA strains have become successfully established as nosocomially.[15–17] The CA-MRSA strains, like HA-MRSA, are broadly resistant to β-lactam and macrolide/azalide antibiotics; however, CA-MRSA infections, particularly those in skin and skin structures, can be treated with minocycline, doxycycline, sulfamethoxazole + trimethoprim and clindamycin.[2,18,19] Nonetheless, resistance rates are increasing and there are limited treatment options for invasive MRSA infections. Therefore, the development of new and potent anti-MRSA drugs is imperative.

Previously, we reported that the L-phenylalanine-derived rhodanine lead compound **1** was active against various MRSA strains, with MIC values ranging from 1.95 to 3.90 μg/mL. Recently we[20] and others have reported that the rhodanine class of compounds possesses antibacterial action.[21–24] Here, we report the subsequent optimization of lead compound **1** with respect to identifying optimal C5-arylidene substituents and determining the influence of stereo-configuration on various MRSA strains. A variety of strains of *Staphylococcus aureus* were used for this study and were obtained from the American Type Culture Collection (ATCC). Strains were selected to represent the scope of *Staphylococcus* variants that might be present in a number of clinical, community and quality control situations. The ATCC strain 34404 is commonly used as a quality control organism for susceptibility testing. Strains 700698, 700787 and BAA39 represent nosocomial or hospital-acquired strains from distant global locations and body sites (i.e., pneumonia patient from Japan, blood culture from New York and

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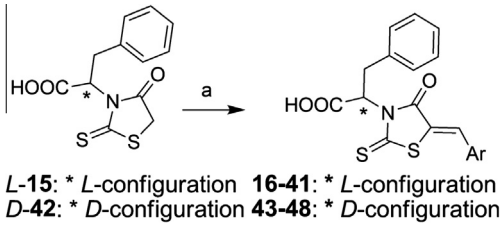
nasal culture from Hungary, respectively). Strain BAA1680 is a community-acquired MRSA (CA-MRSA) strain from the skin of a patient from Michigan, U.S.A. In addition, a *sas*X-positive MRSA strain was tested (ST239 HS770). *Sas*X is a mobile genetic element that plays a key role in MRSA colonization and pathogenesis.[25] The strains chosen, while all resistant to methicillin, have varying resistance to other antimicrobial agents as well. ATCC 700698 is susceptible to vancomycin, strain ATCC 700787 has reduced susceptibility to vancomycin and ATCC BAA-39 is a strain resistant to numerous antibiotics (tetracycline, erythromycin, clindamycin, tobramycin, gentamicin, imipenem, various first- and second-generation cephalosporins, penicillin, oxacillin and amoxicillin). The variety of strains used present a cross-section of MRSA that might be present in given populations with varying susceptibility to currently available antibacterial drugs and underscores the urgent need for additional effective drugs in the event of potential multi-resistance.

To explore the SAR around the phenoxy group of compound **1**, we had to synthesize unique benzaldehydes as these compounds were either commercially expensive or unavailable. The synthesis of a few of the intermediate benzaldehydes has been recently reported by us.[26] The other intermediates were prepared according to Scheme 1, adhering to the procedures described in the above mentioned report. The alkyloxy benzaldehydes **2** and **3** were made by alkylating 3-hydroxybenzaldehyde with propargyl chloride and cyclopropylmethyl bromide, respectively, in the presence of potassium carbonate in acetonitrile. The substituted 2-phenoxybenzaldehyde **4** was prepared using the Ullmann condensation, where 2-bromobenzaldehyde was coupled with 3,4-dichlorophenol in the presence of cupric oxide and potassium carbonate. To prepare the isosteric analogs, the requisite benzaldehydes **5**–**10** were synthesized by palladium catalyzed cross-coupling of the appropriate formylphenyl boronic acid. Intermediates **5** and **7** were prepared starting from 2-formylphenyl boronic acid and benzaldehydes **6**, **8**, **9** and **10** were made beginning with 3-formylphenyl boronic acid. The 2-hydroxybenzaldehyde and the 3-hydroxybenzaldehyde were treated with corresponding arylalkyl bromides or chlorides in the presence of potassium carbonate to prepare 2-substituted intermediates **11**, **14** and 3-substituted intermediate **13**, respectively. Compound **12** was synthesized by alkylating 2-hydroxybenzaldehyde with phenylethyl bromide using cesium carbonate as base. As shown in Scheme 2, the target compounds were synthesized by Knoevenagel condensation of rhodanine intermediates

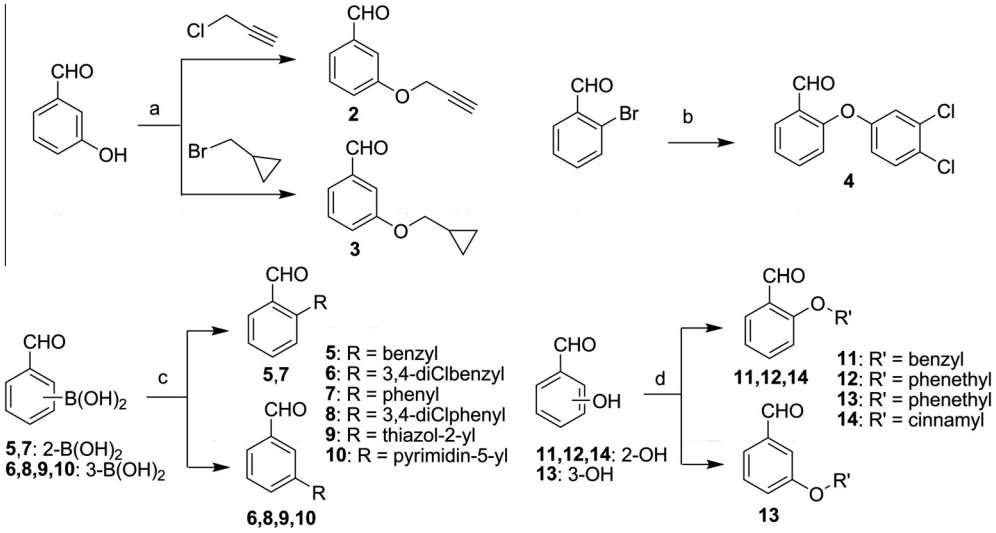


Scheme 2. Reagents and conditions: (a) ArCHO, ammonium acetate, toluene, reflux, 4–6 h.

L-**15** and *D*-**42** with the prepared benzaldehydes. The synthesis of phenylalanine-derived *L*-**15** and *D*-**42**, as well as target compounds **18**–**25**, **28**–**29**, **32**, **37**, **41**, **43**–**47**, was described in our recent report.[26] The enantiomeric excess values for selected L- and D-isomers were also stated in that report. As previously demonstrated,[27,28] the Knoevenagel condensation reaction with aromatic aldehydes provided only the *Z*-isomer, as determined by the chemical shift of the methine proton ranging from 7.7–8.5 ppm as a singlet (chemical shift for corresponding methine proton of *E*-isomer is calculated to be 6.8 ppm). The target compounds **16**–**41** (*L*-isomers) and **43**–**48** (*D*-isomers) were subjected to evaluation against various strains of MRSA.

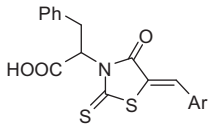
All synthesized rhodanine analogs were tested for their in vitro activity against a panel of MRSA strains (MRSA ATCC 34404, MRSA ATCC 700787, MRSA ATCC 700698, MRSA ATCC BAA-39, MRSA CA ATCC BAA-1680 and MRSA ST239 HS770), together with reference antibiotics ciprofloxacin, vancomycin and penicillin G in a microdilution minimum inhibition concentration (MIC) assay. The assay was performed in a sterile 96 well plates in triplicate. Briefly, the assay involves observing the turbidity in a media containing the bacterial strain cell suspension and the compound being tested. The cells in the control wells were incubated only with the vehicle for the test compounds. The MIC value was recorded based on the visual absence of turbidity when compared to control wells. The MBC values (data not shown) indicating 0.1% survival in subculture on suitable agar plates were also determined to evaluate bactericidal activity. The results are presented in Table 1.

In our earlier study, we observed that the phenylalanine at the N3 position and the 3-phenoxy benzylidene group at C5 position of the rhodanine ring (compound **1**, MIC = 1.95 μg/mL) significantly



Scheme 1. Reagents and conditions: (a) K_2CO_3, CH_3CN, rt, 3–6 h; (b) 3,4-dichlorophenol, CuO, K_2CO_3, pyridine, quinoline, 170 °C, overnight; (c) RBr, $Pd(PPh_3)_4$, K_2CO_3, THF, 80 °C, overnight; (d) (a) R'Br or R'Cl, K_2CO_3 or Cs_2CO_3, CH_3CN, rt, 14–18 h.

Table 1
Anti-MRSA activity of compounds **1, 16–41** and **43–48** (MIC μg/mL)[b]



Compd[a]	Ar	MIC μg/mL[b]					
		MRSA ATCC 34404	MRSA ATCC 700787	MRSA ATCC 700698	MRSA ATCC BAA-39	MRSA CA ATCC BAA-1680	MRSA ST239 HS770
1	3-Phenoxyphenyl	1.95	3.90	3.90	3.90	1.95	ND[c]
16	3-(3-Prop-2-ynyloxy)phenyl	15.60	31.25	62.50	31.25	31.25	62.50
17	3-(3-Cyclopropylmethoxy)phenyl	15.60	15.60	15.60	15.60	15.60	15.60
18	3-(3-Chloro)phenoxyphenyl	15.60	15.60	15.60	15.60	15.60	ND
19	3-(3-Fluoro)phenoxyphenyl	15.60	31.25	15.60	15.60	31.25	ND
20	3-(4-Methoxy)phenoxyphenyl	7.80	7.80	7.80	7.80	15.60	ND
21	3-(4-Chloro)phenoxyphenyl	7.80	15.60	7.80	7.80	15.60	ND
22	3-(4-Fluoro)phenoxyphenyl	7.80	7.80	7.80	7.80	7.80	ND
23	3-(3,4-Dichloro)phenoxyphenyl	0.98	3.90	1.95	1.95	1.95	ND
24	2-Phenoxyphenyl	1.95	1.95	1.95	3.90	1.95	ND
25	4-Phenoxyphenyl	1.95	7.80	1.95	3.90	1.95	7.80
26	2-(3,4-Dichloro)phenoxyphenyl	3.90	3.90	7.80	3.90	3.90	1.95
27	2-Benzylphenyl	15.60	7.80	7.80	7.80	3.90	15.60
28	3-Benzylphenyl	1.95	3.90	3.90	1.95	1.95	ND
29	3-Benzoylphenyl	3.90	7.80	7.80	3.90	3.90	ND
30	3-(3,4-Dichlorobenzyl)phenyl	31.25	62.50	31.25	15.60	31.25	15.60
31	2-Biphenyl	7.80	15.60	15.60	7.80	7.80	7.80
32	3-Biphenyl	0.98	1.95	1.95	0.98	1.95	1.95
33	3-(3,4-Dichlorophenyl)phenyl	3.90	3.90	7.80	3.90	7.80	1.95
34	3-(Thiazol-2-yl)phenyl	15.60	31.25	31.25	7.80	31.25	3.90
35	3-(Pyrimidin-5-yl)phenyl	125.0	125.0	125.0	125.0	125.0	125.0
36	2-Benzyloxyphenyl	7.80	15.60	7.80	15.60	7.80	7.80
37	3-Benzyloxyphenyl	1.95	3.90	3.90	1.95	1.95	1.95
38	2-Phenethyloxyphenyl	15.60	15.60	7.80	15.60	7.80	15.60
39	3-Phenethyloxyphenyl	31.25	31.25	31.25	31.25	15.60	15.60
40	2-Cinnamyloxyphenyl	15.60	31.25	31.25	15.60	31.25	15.60
41	3-Cinnamyloxyphenyl	1.95	1.95	1.95	1.95	1.95	1.95
43	3-Phenoxyphenyl	3.90	3.90	1.95	3.90	1.95	3.90
44	3-(3-chloro)phenoxyphenyl	0.98	3.90	3.90	1.95	1.95	1.95
45	3-(4-Chloro)phenoxyphenyl	1.95	3.90	3.90	1.95	1.95	1.95
46	3-(4-Fluoro)phenoxyphenyl	1.95	1.95	1.95	1.95	1.95	1.95
47	3-(3,4-Dichloro)phenoxyphenyl	1.95	15.60	1.95	1.95	3.90	3.90
48	3-Benzylphenyl	1.95	3.90	3.90	1.95	1.95	1.95
Cipro		⩽0.48	62.50	15.60	7.80	7.80	62.50
Vanco		⩽0.48	1.95	⩽0.48	⩽0.48	⩽0.48	⩽0.48
Pen-G		31.25	62.50	15.60	62.50	125.0	250.0

[a] Compounds **1**, **18**–**25**, **28**–**29**, **32**, **37**, **41**, and **43**–**47** were synthesized previously[26] whereas compounds **16**–**17**, **26**–**27**, **30**–**31**, **33**–**36**, **38**–**40**, and **48** were synthesized in this Letter.
[b] Results of average values obtained from two independent experiments in duplicate; Cipro = ciprofloxacin, Vanco = vancomycin, Pen-G = penicillin G.
[c] ND = not determined.

enhanced *anti*-MRSA activity across all strains. In this letter, 32 rhodanine analogues based on lead compound **1** were assessed in the MRSA inhibition assay with the aim to optimize the phenoxy group as well as to determine the effect of configurational isomerism in the phenylalanine segment. Foremost, we wanted to validate that an aromatic ring substitution is required in the benzylidene moiety for anti-bacterial activity. Two compounds with aliphatic substitutions on the benzylidene moiety, the alkyne derivative 3-(3-prop-2-ynyloxy)phenyl (compound **16**, MIC = 15.60–62.50 μg/mL) and the cyclopropyl ring analog (compound **17**, MIC = 15.60 μg/mL) were tested for *anti*-MRSA activity. The data clearly indicates the importance of the terminal aromatic ring on the benzylidene fragment. Continuing with the phenoxy ring as in compound **1**, attempts to further enhance the activity with 3-chloro (compound **18**, MIC = 15.60 μg/mL) and 3-fluoro (compound **19**, MIC = 15.60–31.25 μg/mL) substitutions on the phenoxy group were unsuccessful. Similarly, 4-position substitutions with methoxy (compound **20**, MIC = 7.80–15.60 μg/mL), chloro (compound **21**, MIC = 7.80–15.60 μg/mL) and fluoro (compound **22**, MIC = 7.80 μg/mL) groups also decreased the antibacterial action. Interestingly, replacement of the phenoxy ring with 3,4-dichlorophenoxy group (compound **23**) improved the overall efficacy, with the lowest MIC value of 0.98 μg/mL against the MRSA strain ATCC 34404. Based on this finding, we decided to optimize the position of the phenoxy ring on the benzylidene fragment. The transfer of the phenoxy ring to the 2nd position (compound **24**) of the benzylidene function maintained the activity against MRSA ATCC 34404 (MIC = 1.95 μg/mL), MRSA ATCC BAA-39 (MIC = 3.90 μg/mL) and MRSA CA ATCC BAA-1680 (MIC = 1.95 μg/mL), with improved inhibition against MRSA ATCC 700787 (MIC = 1.95 μg/mL) and MRSA ATCC 700698 (MIC = 1.95 μg/mL) as compared to antimicrobial profile of compound **1**. In contrast, the 4-phenoxy analog (compound **25**, MIC = 1.95–7.80 μg/mL) was not more efficacious when compared to the 3-phenoxy

counterpart (**1**). Also, the 4-phenoxy analog had a MIC of 7.80 μg/mL against the newly available MRSA strain ST239 HS770. As a result of a slight increase in the overall inhibition profile for 2-phenoxy compound, we incorporated a 3,4-dichloro substitution on the phenoxy ring (compound **26**) in an attempt to obtain enhanced activity against the various MRSA strains. However, this replacement (MIC = 1.95–7.80 μg/mL) proved to be less active.

Thereafter, we sought to understand the importance of the linker atom in addition to the length of the linker between the two aromatic rings. The ether linkage was replaced with $-CH_2-$ in 2-benzylbenzylidene and 3-benzylbenzylidene analogs and –C(=O)– in the 3-benzoylbenzylidene analog in order to identify the role of the oxygen atom as a linker. The 2-benzylbenzylidene (compound **27**, MIC = 3.90–15.60 μg/mL) and 3-benzoylbenzylidene (compound **29**, MIC = 3.90–7.80 μg/mL) derivatives were found to be ineffective, whereas the 3-benzylbenzylidene analog (compound **28**, MIC = 1.95–3.90 μg/mL) had similar antimicrobial efficacy as that of compound **1**. Subsequently, the 3-benzyl ring was substituted with 3,4-dichloro (compound **30**, MIC = 15.60–62.50 μg/mL), but this lead to a decrease in efficacy. Continuing the aforementioned strategy, we removed the linker and attached the terminal phenyl ring directly on the benzylidene moiety. This resulted in 2-phenylbenzylidene analog (compound **31**, MIC = 7.80–15.60 μg/mL), which was not favorable for activity. However, the 3-phenylbenzylidene (compound **32**, MIC = 0.98–1.95 μg/mL) analog was more efficacious in terms of overall anti-MRSA activity, with an MIC of 0.98 μg/mL against MRSA ATCC 34404 and MRSA ATCC BAA39. Based on this, we synthesized the 3,4-dichlorophenyl analog (compound **33**, MIC = 1.95–7.80 μg/mL), which displayed decreased efficacy. We hypothesized that the space occupied by the phenyl ring in the 3-phenylbenzylidene compound was producing 'steric crowding' for further substitution. Therefore, we replaced the phenyl ring with aromatic heterocycles viz. thiazole (compound **34**, MIC = 3.90–31.25 μg/mL) and pyrimidine (compound **35**, MIC = 125.0 μg/mL) to grasp the nature of the enunciated vicinity. In general, these modifications produced a significant decrease in the efficacy against the MRSA strains. These results suggest that aromaticity, coupled with hydrophobic nature of the terminal phenyl ring, is required for activity against MRSA. Furthermore, to ascertain the extent of the binding pocket, we assayed six compounds (**36**–**41**) with two, three or four atom length linkers between the two aromatic rings of compound **1**. Of these compounds, only 3-benzyloxybenzylidene (compound **37**, MIC = 1.95–3.90 μg/mL) and 3-cinnamyloxybenzylidene (compound **41**, MIC = 1.95 μg/mL) retained the original activity, thus indicating the tolerance of two and four-atom linkers between the two aryl rings. To further identify the importance of chirality, we tested the D-counterparts 3-phenoxybenzylidene (compound **43**, MIC = 1.95–3.90 μg/mL, ee = 84%), 3-(3-chlorophenoxy)benzylidene (compound **44**, MIC = 0.98–3.90 μg/mL, ee = 75%), 3-(4-chlorophenoxy)benzylidene (compound **45**, MIC = 1.95–3.90 μg/mL, ee = 78%), 3-(4-fluorophenoxy)benzylidene (compound **46**, MIC = 1.95 μg/mL, ee = 85%), 3-(3,4-dichlorophenoxy)benzylidene (compound **47**, MIC = 1.95 –15.60 μg/mL, ee = 93%), 3-benzylbenzylidene (compound **48**, MIC = 1.95–3.90 μg/mL) of compounds **1** (MIC = 1.95–3.90 μg/mL, ee = 85%), **18** (MIC = 15.60 μg/mL, ee = 93%), **21** (MIC = 7.80–15.60 μg/mL, ee = 86%), **22** (MIC = 7.80 μg/mL, ee = 84%), **23** (MIC = 0.98–3.90 μg/mL, ee = 77%) and **28** (MIC = 1.95–3.90 μg/mL), respectively. It seems that a configurational effect is present only when the terminal ring is substituted and that the selectivity switches based on the substitution pattern, with the D-analog being preferred if monosubstituted and the L-analog upon disubstitution of the terminal phenyl ring. Furthermore, to probe the effect of serum protein binding, we determined the MIC values (data not shown) of the most potent compounds, **23**, **32** and **44** against all MRSA strains in the presence of 10% fetal bovine serum (FBS). These results indicated only a twofold increase in the MIC values with 10% FBS as compared to MIC values obtained in the absence of 10% FBS. These findings suggest that these compounds do not significantly bind to serum proteins.

Based on the present data, it is evident that (i) a hydrophobic aromatic group is essential at the third-position of the benzylidene ring, (ii) the distance between the two aromatic rings is critical, and (iii) stereochemistry plays a role in the potent anti-MRSA activity of the tested rhodanine derivatives.

In our future studies, we will optimize the antibacterial activity of compounds **37** and **41** with respect to the substitution pattern on the terminal phenyl ring as well as evaluate the influence of D-stereochemistry. Furthermore, compound **29**, a benzophenone analog, will be explored for optimal substituents at the terminal phenyl ring. Compound **29** and its derivatives could serve as photophores to understand the antibacterial mechanism of action. These data will be reported in a future publication.

Compounds **23**, **24**, **28**, **32**, **37**, **41, 44**, **46**, **47** and **48** were found to be active against globally widespread strains used in this study including the *sas*X-positive MRSA strain ST239 HS770. Several arylalkylidene rhodanines have been reported to interact with PBPs[29] and all MRSA strains harbor the SCCmec gene that codes for the PBP2a protein.[30–32] Hence, it is possible that these compounds may produce their *anti*-MRSA action by inhibiting PBP2a, although this remains to be proven experimentally.

In summary, lead optimization was attempted using our previously reported phenylalanine derived rhodanine analogue **1**. The SAR data clearly emphasizes the importance of a hydrophobic aromatic substituent on the benzylidene moiety. However, the effect of the configurational isomerism requires further study. Several compounds were significantly more efficacious than the reference antibiotics penicillin G and ciprofloxacin against a panel of MRSA strains. Among these, three compounds **23**, **32**, and **44** were highly efficacious against MRSA ATCC 34404 and MRSA ATCC BAA-39. Currently, the mechanism of action of the compounds tested in this study is unknown. Typically, antibiotics can produce a bactericidal effect by inhibiting cell wall synthesis or DNA synthesis. Thus, it is possible that the bactericidal compounds in this study could produce their anti-MRSA activity via these targets, although this remains to be proven.

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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.2013.08.059.

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