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Original article

2-[2-Substituted-3-(3,4-dichlorobenzylamino)propylamino]-1*H*-quinolin-4-ones as *Staphylococcus aureus* methionyl-tRNA synthetase inhibitors

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Abstract

New analogues of 2-[2-substituted-3-(3,4-dichlorobenzylamino)propylamino]quinolin-4-ones, **26a**, **26b**, **31a–e**, **34**, **35**, **38** and **40**, have been synthesized and evaluated against *Staphylococcus aureus* methionyl-tRNA synthetase. All of the synthesized compounds were less active than the reference compound **2**. The compounds were also screened against various strains of *S. aureus* and *Enterococci* for their antibacterial activities. Among the compounds, **26b**, **31c** and **31e** displayed significant inhibitory properties against various strains of *Enterococci* compared to compound **2**.

Keywords: Antibiotic; Aminoacyl-tRNA synthetase; Methionyl-tRNA synthetase inhibitors

1. Introduction

Aminoacyl-tRNA synthetases (aaRSs) have been identified as promising antibacterial drug targets, since the emergence of drug resistance against the existing antibiotics. The aminoacyl-tRNA synthetases are a family of 20 enzymes that are essential for the translation of the genetic code into proteins. The aaRSs transfer amino acids from the cellular pool to their cognate [1] tRNAs during protein synthesis. The transfer of amino acids to the tRNAs by the aaRSs occurs in two steps. The first step is the formation of an enzyme-bound aminoacyl-adenylate (aa-AMP) active intermediate, by the reaction of the amino acid and ATP. In the second step, either the 2′-OH or 3′-OH of the ribose of the cognate tRNA attacks the aa-AMP intermediate and forms an ester bond with the aminoacyl moiety. The aaRSs have a proof-reading mechanism to check the amino acids attached to their cognate tRNAs, which ensures their functional accuracy [2] of attaching the correct amino acids. The topology of the ATP binding domain and the functions of the human aaRSs differ from those of bacteria, thus providing an opportunity to inhibit them selectively in bacteria. Therefore, the aaRSs have the potential to be exploited as antibacterial drug targets by the synthesis of aaRS inhibitors to treat bacterial infections, including antibiotic resistant strains such as methicillin resistant *Staphylococcus aureus* (MRSA) and *vancomycin resistant Enterococci* (VRE) [3–5].

Previously, several approaches have been reported for the synthesis of aaRS inhibitors, particularly methionyl-tRNA synthetase inhibitors. Among them, the substitution of the hydrolytically unstable acylphosphate and ribose moieties present in methionyl adenylate (Met-AMP, **1**) by their isosteres

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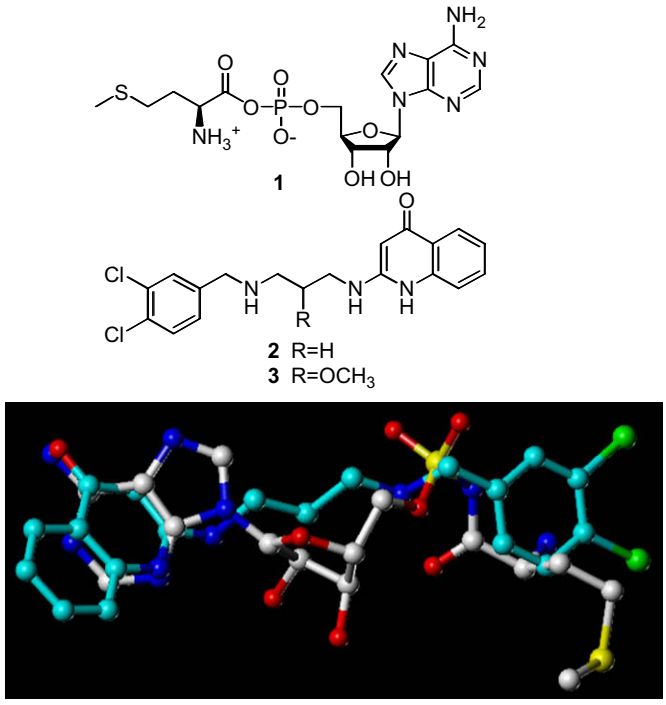


Fig. 1. Molecular superimposition of **1** and **2**.

has provided interesting inhibitors of methionyl-tRNA synthetase. In this respect, alkylphosphate, ester, amide, hydroxamate, sulfamate, sulfamide, *N*-alkoxysulfamide, and *N*-hydroxysulfamide were prepared as stable surrogates to the linear chain acylphosphate [6], and deoxyribosyl surrogates of Met-AMP were also investigated [7]. In addition, a high throughput screening followed by SAR studies provided the quinoline derivative (**2**, $IC_{50} = 16$ nM) as a competitive inhibitor of *S. aureus* methionyl-tRNA synthetase [8–11]. A very potent analogue of **2** has been reported and is in clinical trials [12–14]. Recently, ethanolamine derivatives, a new class of inhibitors of bacterial phenylalanyl-tRNA synthetase [15], have been discovered by high throughput screening. Herein, we report the synthesis and the methionyl-tRNA synthetase inhibitory and antibacterial activities of a new series of 2-substituted-4-quinolones (**26a**, **b**, **39a–e**, **32**, **33**, **36**, **38**). The synthesized compounds were evaluated against strains of *S. aureus*, *Enterococcus faecium*, and *Enterococcus faecalis* for their antibacterial activities. The present work is an extension of our previous report [16] on the study of 3D pharmacophoric superimposition and the synthesis of **1**, **2**, and **3** ($IC_{50} = 2.48$ nM), [16] Fig. 1.

2. Chemistry

The target compounds **26a**, **b**, **29a–e**, **32**, **33**, **36**, **37** were synthesized in two steps by amination of 2-chloro-4-(4-methoxybenzyloxy)quinoline **23** with the 2-substituted 1,3-diamines **6a**, **b**, **10a–d**, **17**, **18**, **22** in the presence of K_2CO_3, followed by the removal of the 4-methoxybenzyl group and reductive alkylation of the resulting intermediates **25**, **28**, **31**, **34**, **35** with 3,4-dichlorobenzaldehyde (Schemes 1–4). The precursor **23** was prepared from aniline according to the published procedure [16,17].

The diamines **6a** and **b** were obtained in five steps from commercially available (hydroxymethyl) propane-1,3-diol. Initially, the two hydroxyl groups of the (hydroxymethyl)-1,3-diol were protected as acetonide **1**, followed by either benzylation or methylation with NaH and a suitable halide at room temperature to provide **2**. The acetonide group of **2** was removed by stirring with a catalytic amount of PTSA·H_2O in methanol. The dihydroxy compound **3** thus obtained was converted into the corresponding diamine **6**, as shown in Scheme 5. The 2-alkoxy-1,3-diamines **10a–d** required for the preparation of **29a–d** were synthesized from commercially available 1,3-diaminopropane-2-ol (**7**), as shown in Scheme 6. The two amino groups of compound **7** were initially protected as carbamates by the reaction of di-*tert*-butyldicarbonyldicarbonate in presence of triethlyamine and DMAP, to yield the biscarbamate **8**. Compound **8**, upon alkylation in a biphasic medium (H_2O:Toluene) in the presence of the phase transfer catalyst Bu_4NHSO_4, provided **9a–d**, which upon hydrolysis with 4M HCl in THF yielded **10a–d**.

Compound **7** was again protected as bisbenzylcarbamate **11**, followed by azide (**13**) substitution and $SnCl_2$ mediated reduction to provide the corresponding amine **14**. Compound **14** was dimethylated with an equimolar mixture of formaldehyde and formic acid in water under reflux conditions to yield **15**. The BOC-protected compound **16** was also synthesized from **14** and di-*tert*-butyldicarbonyldicabonate at room temperature. Compounds **15** and **16** were both debenzylated with 10% Pd–C in methanol under a hydrogen atmosphere to give **17** and **18**, respectively, as shown in Scheme 7.

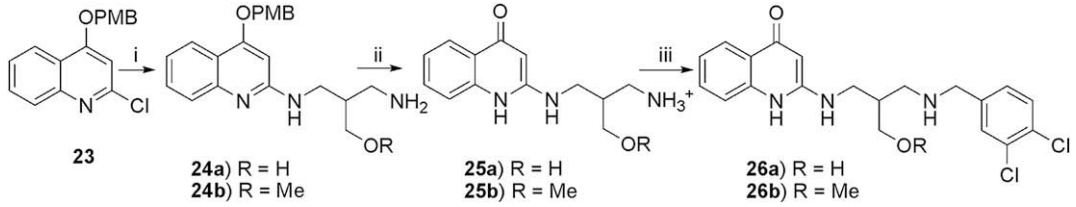
Our effort to synthesize 2-allyloxypropane-1,3-diamine (**22**) from the allylation of **8**, through Scheme 6, provided a very poor yield. This was then synthesized through an alternative route from commercially available 1,3-dibromopropane-2-ol (**19**) in good yield, as shown in Scheme 8. Compound **19** was transformed into the corresponding diazide **20**, which upon allylation with allyl iodide in presence of CsOH·H_2O, tetra *n*-butyl iodide and 4 Å molecular sieves, gave **21**. The diazide groups of **21** were selectively reduced to yield the diamine **22**, Scheme 8, according to the procedure for compound **13**.

3. Results and discussion

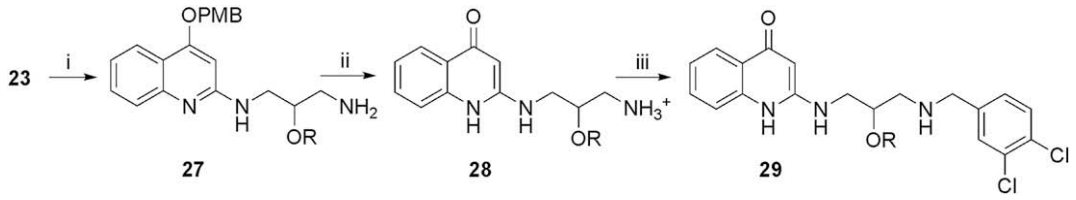
3.1. Methionyl-tRNA synthetase enzyme assay

All of the synthesized compounds, **2**, **26a**, **b**, **29a–e**, **32**, **33**, **36**, and **38**, were evaluated for their *in vitro* inhibitory activity against the *S. aureus* methionyl-tRNA synthetase enzyme. The inhibitory properties of the compounds were determined by measuring the decrease in the generation of the aminoacyl product [^{35}S]methionyl *S. aureus*-tRNA^{Met} in the presence of different chemical concentrations, as reported [7].

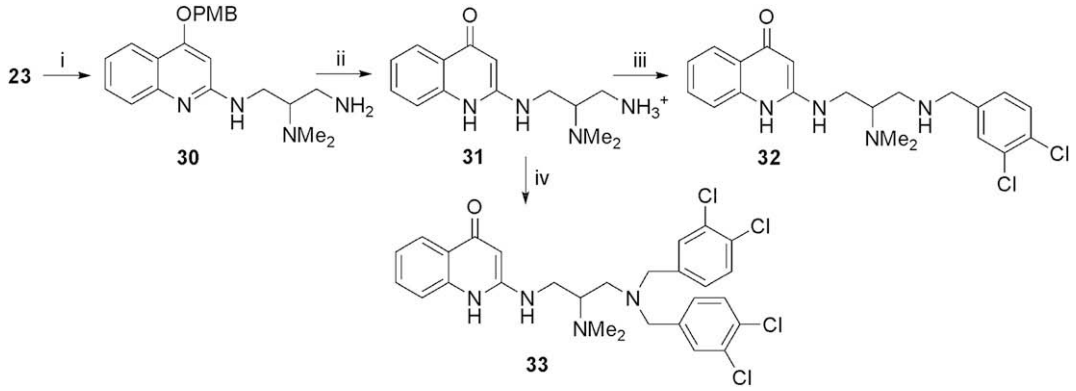
All of the synthesized compounds were less active than the reference compound **2**. A substitution of the hydroxymethyl



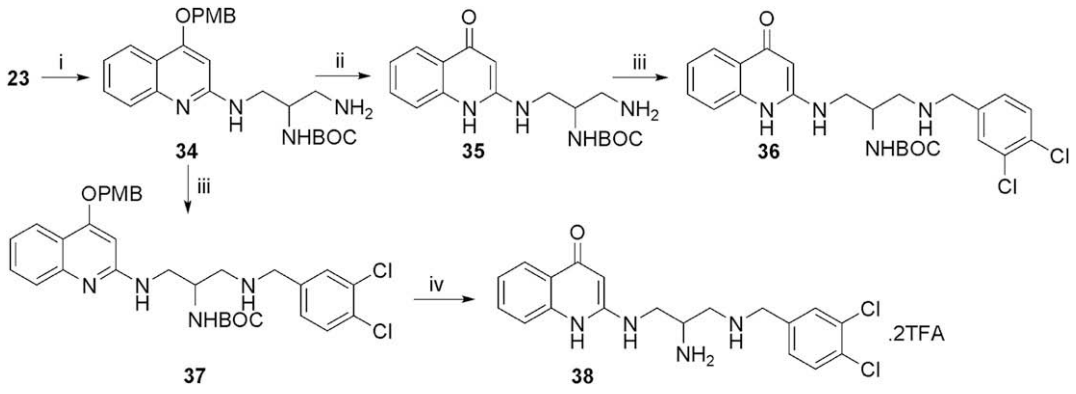
Scheme 1. Reagents and conditions: (i) **6a** or **6b**, K_2CO_3, DMSO, 100 °C, 48 h, **24a**, 44%, **24b**, 45%; (ii) 20% TFA–DCM, 2 h, rt; (iii) 3,4-Cl_2PhCHO, $NaCNBH_3$, MeONa, MeOH, 50 °C, **26a**, 52%, **26b**, 54%.



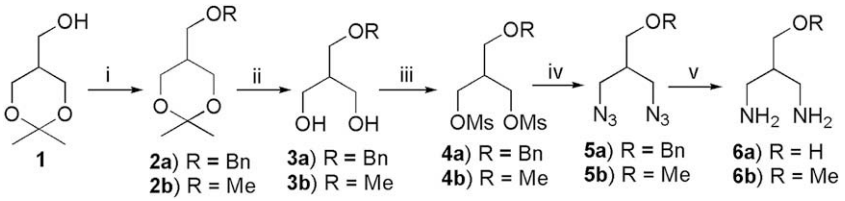
Scheme 2. Reagents and conditions: (i) **10a–d**, or **22**, K_2CO_3, DMSO, 100 °C, 48 h (**27a**, R = C_2H_5, 51%: **27b**, R = $CHMe_2$, 47%: **27c**, R = Bn, 45%: **27d**, R = COPh, 70%: **27e**, R = allyl, 53%); (ii) 20% TFA–DCM, 2 h, rt; (iii) 3,4-Cl_2PhCHO, $NaCNBH_3$, MeONa, MeOH, 6 h, 50 °C (**29a**, R = C_2H_5 50%: **29b**, R = $CHMe_2$, 52%: **29c**, R = Bn, 48%: **29d**, R = COPh, 47%: **29e**, R = allyl, 55%).



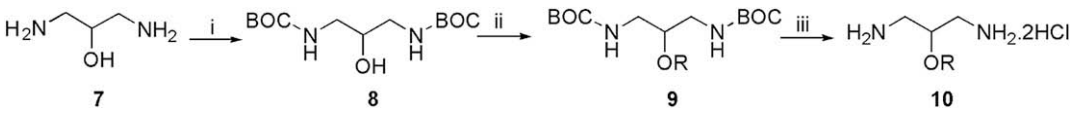
Scheme 3. Reagents and conditions: (i) **17**, K_2CO_3, DMSO, 100 °C, 44%; (ii) 20% TFA–DCM, 2 h, rt; (iii) 3,4-Cl_2PhCHO, $NaCNBH_3$, MeONa, MeOH, 52%; (iv) 3,4-Cl_2PhCHO, $NaCNBH_3$, AcOH, MeOH, 55%.



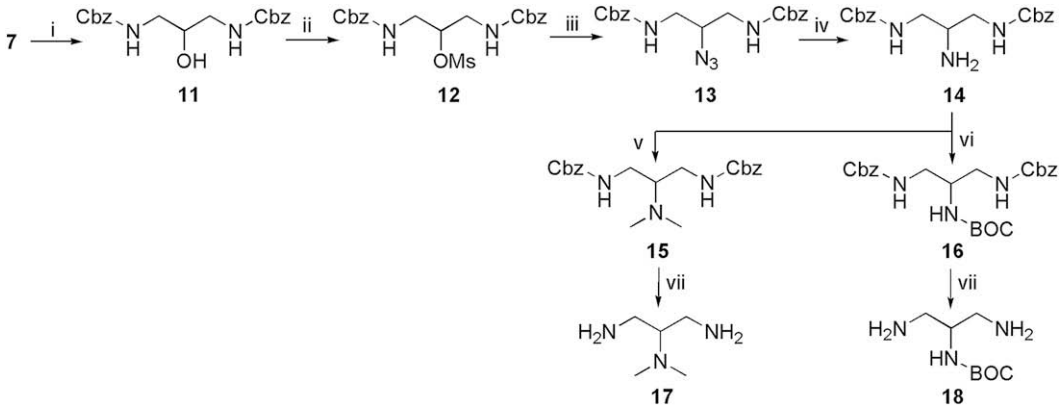
Scheme 4. Reagents and conditions: (i) **18**, K_2CO_3, DMSO, 100 °C, 46%; (ii) 10% Pd–C, H_2 (1 atm), MeOH, 1 h, rt; 100%; (iii) 3,4-Cl_2PhCHO, $NaCNBH_3$, MeONa, MeOH, 54%; (iv) 20% TFA–DCM, 2h.



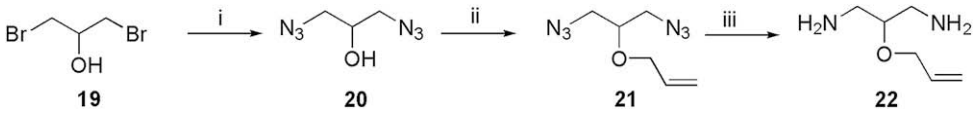
Scheme 5. Reagents and conditions: (i) RX, NaH, THF, 6 h, rt, **2a**, 90%; **2b**, 92% (ii) PTSA.H_2O, MeOH, 1 h, rt, **3a**, 97%, **3b**, 96%; (iii) $MeSO_2Cl$, TEA, DCM, 1.5 h, 0–rt, **4a**, 94%, **4b**, 94%; (iv) NaN_3, DMF, 20 h, 80°C, **5a**, 98%, **5b**, 98%;(v) $Pd(OH)_2$, H_2 (1 atm), MeOH, overnight, rt, 100%.



Scheme 6. Reagents and conditions: (i) $(BOC)_2O$, TEA, DMAP, H_2O–THF (1:1), 14 h, rt, 94%; (ii) **9a–c**, RX, NaOH, Bu_4NHSO_4, $PhCH_3$–H_2O, 18 h, 100 °C, **9d**, C_6H_5COCl, pyridine: DCM (1:1), 6 h, rt (**9a**, R = C_2H_5, 51%: **9b**, R = $CHMe_2$, 47%: **9c**, R = Bn, 45%: **9d**, R = COPh, 70%); (iii) 4M HCl–THF, 4 h, rt (**9a**, R = C_2H_5 95%: **9b**, R = $CHMe_2$, 94%: **9c**, R = Bn, 95%: **9d**, R = COPh, 93%).



Scheme 7. Reagents and conditions: (i) $C_6H_5CH_2OCOCl$ (CbzCl), NaOH, 12 h, 0–rt, 80%; (ii) $MeSO_2Cl$, TEA, DCM, 0–rt, 90%; (iii) NaN_3, DMF, 20 h, 100 °C, 95% (iv) $SnCl_2$, PhSH, TEA, 1 h, rt, 62%; (v) HCO_2H, HCHO, H_2O, 8 h, reflux, 80% (vi) $(BOC)_2O$, C_2H_5OH, 6 h, rt, 96%; (vii) 10% Pd–C, H_2 (1 atm), MeOH, 2 h, rt, **17**, 100%, **18**, 100%.



Scheme 8. Reagents and conditions: (i) NaN_3, DMF, 24 h, 80 °C, 90%; (ii) Allyl iodide, $CsOH·H_2O$, TBAI, 4 Å MS, CH_3CN, 48 h, rt, 80%; (iii) $SnCl_2$/PhSH/TEA/1 h/rt, 66%.

group at the C-2 position of the linear chain yielded the ~4-fold less potent compound **26a**. Its methyl derivative, **26b**, was slightly more active than **26a** and around five times less potent than compound **2**. Thus, hydrogen bond donor and acceptor substitutions at C-2 of the linear chain in **2** do not favor methionyl-tRNA synthetase enzyme inhibitory activity.

Displacement of the oxygen atom while keeping the chain length of the substituent the same as that of compound **26b** resulted in compound **29a**, with a 2-fold decrease in activity as compared to **26b** and 10 times less potency than compound **2**. The isopropyl derivative **29b** displayed a further decrease in inhibitory properties. It was around 30-fold less potent than compound **2**. The allyloxy derivative **29e** also showed less potency, but was more active than the isopropoxy derivative. A change of the alkyl substitution to an aryl group, such as in **29c**, **d**, decreased the potency. Among these, **29c**, an ether derivative, displayed better activity than **29d**, an ester derivative. The difference in the inhibitory activity may be due to the greater hydrophobicity of compound **29c**. The synthesis of more polar and basic derivatives, such as the amino and substituted amino analogues **32**, **33**, **36** and **38**, resulted in a large decrease in the activity. Thus, oxygen analogues with

small carbon chain lengths are favorable for the activity, and amino or substituted amino group substitutions at the C-2 position in the linear chain of **2** are detrimental for the activity.

3.2. Antibacterial assay

Minimum inhibitory concentrations (MIC) of the synthesized compounds shown in Table 2 were determined by the microdilution method with Mueller–Hinton Broth (MH, Difco Laboratories, Detroit, MI) for *Staphylococci* and Brain Heart Infusion Broth (BHI, Difco) for *Enterococci*, according to the Clinical and Laboratory Standards Institute (CLSI) [18]. Seven strains of *S. aureus* (ATCC25923, ATCC6538P, ATCC10537, GIORGIO, Smith, SP-N2, and a methicillin resistant clinical isolate MRSA K2007-6), one *Staphylococcus epidermidis* strain (ATCC12228), two *E. faecalis* strains (ATCC29212, ATCC19433), and one *E. faecium* strain (ATCC10541) were used to determine the MICs of the compounds, as shown in Table 2. The stock solutions of the test compounds were diluted to give a serial, 2-fold series yielding final chemical concentrations ranging from 64 to 0.06 μg/mL. The MIC was defined as the lowest concentration of chemicals that inhibited the development of visible bacterial growth after an incubation for 16–18 h at 36 °C. Mupirocin and amoxicillin antibiotics were used as the reference compounds.

The synthesized molecules **2**, **26a**, **b**, **29a–e**, **32**, **33**, **36**, **38** were screened against various strains of *S. aureus* and *Enterococci*, as shown in Table 2. All of the tested compounds were less potent than both mupirocin and amoxicillin in various strains of *S. aureus*, but displayed significant inhibitory properties in strains of *Enterococci*. Compound **26a**, a hydroxy derivative, displayed low inhibitory activity in all strains of *S. aureus* than both the references and compound **2**, but was more active against *E. faecium* than amoxicillin. Compound **26b**, a methylated derivative of **26a**, displayed interesting inhibitory activity against the *Enterococci* strains and was more potent than both the references and compound **2**. It showed 8-fold more inhibition in *E. faecium* (ATCC10541), 4-fold more in *E. faecalis* (ATCC19433) and 2-fold more in *E. faecalis* (ATCC29212) than amoxicillin. Compound **26b** also displayed 128 times more inhibition against a strain of *E. faecalis* (ATCC19433) and 64 times more against *E. faecium* (ATCC10541) and *E. faecalis* (ATCC29212) than mupirocin, but only 4-fold more inhibition than **2** in all of the strains of *Enterococci*. The oxygen analogues of the synthesized compounds **29a–e** showed interesting inhibition against *Enterococci*. They displayed either similar or better activities against the strains of *E. faecium*, but were less potent in *S. aureus*. Among these compounds, benzyloxy and allyloxy derivatives displayed the best inhibitory activities against the strains of *Enterococci*. Thus, compounds with hydrophobic substituents, such as methoxy (**26b**), benzyloxy (**29c**) and allyloxy (**29e**), are favorable for antibacterial activity, while molecules with polar, hydrophilic substituents, such as **26a**, **32**, **36** and **38**, are not suitable for the inhibitory activity. A certain level of lipophilicity may be required for the antibacterial activities, for permeability of the bacterial membrane.

4. Conclusion

The *S. aureus* methionyl-tRNA enzyme inhibitory activity data (Table 1) of the synthesized compounds suggest that substitutions of the hydroxymethyl, alkoxy or aryloxy group at the C-2 position of compound **2** are not favorable for the activity. However, the antibacterial data presented in Table 2 indicate that the alkoxy substitution at the C-2 position in the linear chain of the parent compound **2** is not detrimental for the activity.

Table 1
In vitro inhibitory activity data of the synthesized compounds against *Staphylococcus aureus* methionyl-tRNA synthetase

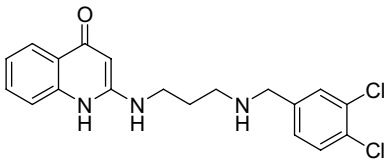
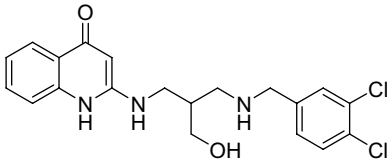
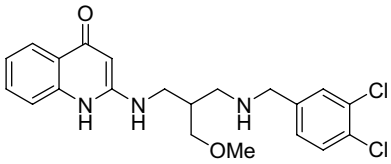
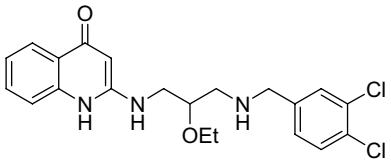
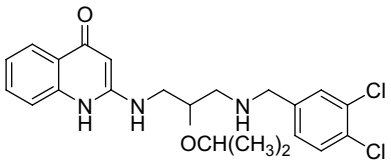
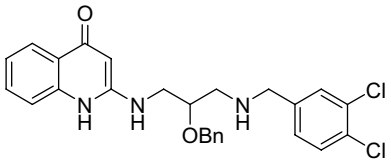
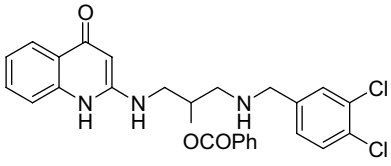
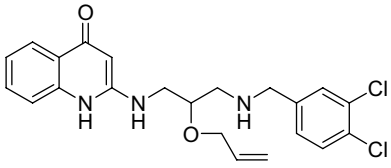
Compound	Structure	IC_{50}[a](nM)
2		3.4 (±0.4)
26a		11.9(±1.6)
26b		15.0(±1.3)
29a		30.3(±3.8)
29b		91.0(±7.8)
29c		24.7(±0.8)
29d		69.4(±5.8)
29e		29.4(±1.6)

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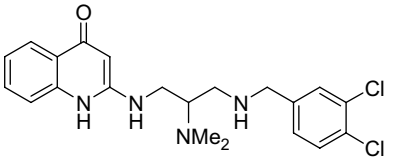
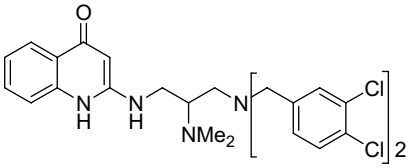
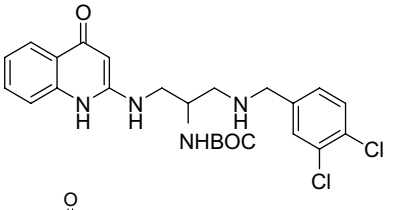
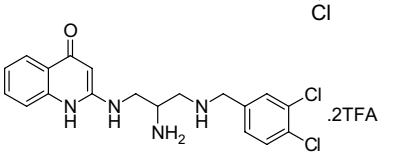
Table 1 (*continued*)

Compound	Structure	IC_{50}[a](nM)
32		39.6(±4.8)
33		131.2(±15.2)
36		102.8(±5.6)
38		136.9(±2.2)

[a] Values represent means of the three experiments.

5. Experimental

5.1. Chemistry

All of the chemical reagents used were either synthesized or commercially available. Melting points were determined on a Melting Point Büchi B-540 apparatus, and are uncorrected. Silica gel column chromatography was performed with 230–400 nm mesh, from Merck. Proton NMR spectra were recorded on a JEOL JNM-LA 300 at 300 MHz. Chemical shifts are reported in ppm units with Me_4Si as an internal reference standard. Infrared spectra were recorded on a Perkin–Elmer 1710 Series FTIR. Mass spectra were recorded on a VG Trio-2 GC–MS.

5.1.1. (2,2-Dimethyl-[1,3]-dioxan-5-yl)methanol (*1*)

2,2-Dimethoxypropane (3.25 mL, 26.45 mmol) was added to a stirred suspension of 2-(hydroxymethyl)propane-1,3-diol (2.5 g, 22.8 mmol) and *p*-toluenesulfonic acid monohydrate (140 mg, 0.73 mmol) in THF (30 mL). The resultant mixture was stirred for 2.5 h at room temperature. The reaction mixture was neutralized with $NaHCO_3$ and evaporated under reduced pressure. The crude product thus obtained was purified by silica gel column chromatography using CH_2Cl_2/MeOH (20:1) as an eluent. Colorless oil; MS (FAB) 147 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.73 (s, 1H, OH), 1.79–1.90 (m, 1H, CH), 3.74–3.81 (m, 4H, CH_2), 4.0–4.05 (m, 2H, CH_2).

5.1.2. 5-Benzyloxymethyl-2,2-dimethyl-[1,3]dioxane (*2a*)

To a mixture of **1** (1.46 g, 100 mmol) and NaH (0.36 g, 150 mmol) in THF was added benzyl bromide (3.42 g, 200 mmol) dropwise at room temperature, and the solution was stirred for 6 h. The reaction mixture was poured into water and extracted with ethyl acetate (20 mL × 3). The ethyl acetate layers were washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using CH_2Cl_2/MeOH (100:1) as an eluent. Colorless oil; MS (FAB) 237 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.96–2.07 (m, 1H, CH), 3.52 (d, $J = 6.7$ Hz, 2H, CH_2), 3.72–3.80 (m, 2H, CH_2), 3.95–4.05 (m, 2H, CH_2), 4.5 (s, 2H, CH_2), 7.28–7.37 (m, 5H, ArH).

5.1.3. 5-Methoxymethyl-2,2-dimethyl-[1,3]dioxane (*2b*)

To a mixture of **1** (1.46 g, 100 mmol) and NaH (0.36 g, 150 mmol) in THF was added methyl iodide (4.26 g, 300 mmol) dropwise at room temperature, and the solution was stirred for 6 h. The workup and purification of the reaction mixture were the same as those for compound **2a**. Colorless

Table 2
In vitro minimum inhibitory concentration (MIC)[a,b] of the synthesized compounds against the strain of *Staphylococcus aureus*, *Enterococcus faecium*, *Enterococcus faecalis*

Strains	Mup/amox	**2**	**26a**	**26b**	**29a**	**29b**	**29c**	**29d**	**29e**	**32**	**33**	**36**	**38**
S. aureus ATCC25923	0.25/0.25	16	64	16	16	16	4	64	8	>64	>64	32	64
S. aureus ATCC6538P	0.125/0.5	4	16	4	8	16	4	32	8	>64	>64	32	64
S. aureus ATCC10537	0.125/0.25	16	32	8	16	16	4	64	16	64	>64	32	64
S. aureus GIORGIO	0.125/0.25	32	64	16	16	32	4	32	16	>64	>64	32	64
S. aureus Smith	0.125/0.25	16	32	8	16	16	4	32	8	64	>64	32	64
S. aureus SP-N2	0.25/>64	8	16	8	16	16	4	32	8	64	>64	32	64
Staphylococcus epidermidis ATCC12228	0.125/2	8	16	4	8	16	2	16	4	32	>64	32	32
MRSA KS2007-6	0.25/>64	8	16	4	8	8	2	32	4	64	>64	32	64
E. faecium ATCC10541	8/1	0.5	2	0.125	1	2	0.5	8	1	8	>64	8	16
E. faecalis ATCC19433	64/1	2	8	0.5	4	4	2	16	2	16	>64	32	64
E. faecalis ATCC29212	64/2	2	8	0.5	4	4	2	16	2	16	>64	32	64

Mup = Mupirocin; amox = Amoxicillin.
[a] Indicates MIC values in μM/mL.
[b] Values represent are means of the three experiments.

oil; MS (FAB) 161 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.31 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.81–1.93 (m, 1H, CH), 3.24 (s, 3H, OCH_3), 3.33 (d, $J = 6.7$ Hz, 2H, CH2), 3.62–3.68 (m, 2H, CH_2), 3.83–3.89 (m, 2H, CH_2).

*5.1.4. 2-Benzyloxymethylpropane-1,3-diol (**3a**)*

Compound **3a** was obtained by stirring a mixture of **2a** (2.8 g, 11.86 mmol) and *p*-toluenesulfonic acid monohydrate (0.22 g, 1.17 mmol) in methanol (15 mL) for 1 h at room temperature. The reaction mixture was neutralized with triethylamine, evaporated and purified by silica gel column chromatography using CH_2Cl_2/MeOH (9:1) as an eluent. Colorless oil; IR (Neat) ν 3390 cm^{-1} (OH); MS (FAB) 197 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.98–2.02 (m, 1H, CH), 2.52 (br s, 2H, OH), 3.62 (d, $J = 5.6$ Hz, 2H, CH_2), 3.80 (d, $J = 5.6$ Hz, 4H, CH_2), 4.5 (s, 2H, CH_2), 7.26–7.37 (m, 5H, PhH).

*5.1.5. 2-Methoxymethylpropane-1,3-diol (**3b**)*

A mixture of **2b** (2.5 g, 15.62 mmol) and i-toluenesulfonic acid monohydrate (0.3 g, 1.56 mmol) was stirred in methanol for 1 h at room temperature. The product was isolated as compound **3a**. Colorless oil; IR (Neat) ν 3400 cm^{-1} (OH); MS (FAB) 121 (MH^+); ^1H NMR (CD_3OD, 300 MHz) δ 1.83–1.95 (m, 1H, CH), 2.36 (s, 2H, OH), 3.32 (s, 3H, OCH_3), 3.43 (d, $J = 5.6$ Hz, 2H, CH_2), 3.63 (d, $J = 5.6$ Hz, 4H, CH_2).

*5.1.6. Methanesulfonic acid 2-benzyloxymethyl-3-methanesulfonyloxypropyl ester (**4a**)*

To a mixture of **3a** (2.0 g, 10.20 mmol) and triethylamine (6.0 mL, 42.85 mmol) in dichloromethane (15 mL) was added methanesulfonic acid (2.56 g, 22.44 mmol) dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 1.5 h, poured into water and extracted with dichloromethane (20 mL × 2). The dichloromethane layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using CH_2Cl_2/MeOH (99:1) as an eluent. Colorless oil; MS (FAB) 353 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.41–2.58 (m, 1H, CH), 3.01 (s, 6H, SO_2Me), 3.56 (d, $J = 5.8$ Hz, 2H, CH_2), 4.27–4.38 (m, 4H, CH_2), 4.51 (s, 2H, CH_2), 7.24–7.39 (m, 5H, PhH).

*5.1.6.1. Methanesulfonic acid 3-methanesulfonyloxy-2-methoxymethylpropyl ester (**4b**).* Compound **4b** was prepared exactly as compound **4a**. Colorless oil; MS (FAB) 277 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.43–2.55 (m, 1H, CH), 3.05 (s, 6H, SO_2Me), 3.35 (s, 3H, OCH_3), 3.46 (d, $J = 6.0$ Hz, 2H, CH_2), 4.25–4.37 (m, 4H, CH_2).

*5.1.7. 1,3-Diazido-2-benzyloxymethylpropane (**5a**)*

A mixture of **4a** (2.0 g, 5.68 mmol) and sodium azide (2.95 g, 45.45 mmol) was stirred in dry DMF at 80 °C for 20 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate (20 mL × 2). The ethyl acetate layer was washed with water, dried over Na_2SO_4 and evaporated under vacuum. The oily product was purified by silica gel column chromatography using hexane/CH_2Cl_2 (9:1) as an eluent. Colorless viscous oil; MS (FAB) 247 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.04–2.15 (m, 1H, CH), 3.37–3.48 (m, 6H, CH_2), 4.50 (s, 2H, CH_2), 7.29–7.39 (m, 5H, PhH).

*5.1.7.1. 1,3-Diazido-2-methoxymethylpropane (**5b**).* A mixture of **4b** (2.0 g, 7.24 mmol) and sodium azide (2.95 g, 57.97 mmol) was stirred in dry DMF at 80 °C for 20 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate (20 mL × 2). The ethyl acetate layer was washed with water, dried over Na_2SO_4 and evaporated under vacuum. The oily product was purified by silica gel column chromatography using hexane/CH_2Cl_2 (9:1) as an eluent. Colorless viscous oil; MS (FAB) 171 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.00–2.12 (m, 1H, CH), 3.34 (s, 3H, OCH3), 3.37–3.46 (m, 6H, CH_2).

*5.1.8. 3-Amino-2-aminomethylpropan-1-ol (**6a**)*

This was obtained by stirring a mixture of **5a** (0.8 g mmol) and 10% $Pd(OH)_2$ (80 mg), under a hydrogen atmosphere in methanol at room temperature for 20 h. The reaction mixture was filtered through celite powder and evaporated under vacuum. The product thus obtained was directly used for the next reaction without purification.

*5.1.8.1. 2-Methoxymethylpropane-1,3-diamine (**6b**).* This was obtained from the reduction of the diazide **5b**, using the procedure for compound **6a**. Compound **6b** was used as such without purification.

*5.1.9. (3-tert-Butoxycarbonylamino-2-hydroxypropyl)-carbamic acid tert-butyl ester (**8**)*

Di-*tert*-butyldicarbonate (45.92 g, 210.64 mmol) was added in portions to a stirred solution of **7** (8.0 g, 88.89 mmol), triethylamine (25 mL, 177.8 mmol) and DMAP (2.4 g, 20 mmol) in THF/H_2O (1:1300 mL). The resulting reaction mixture was stirred at room temperature overnight, acidified with 1 M HCl to pH 2 and extracted with ethyl acetate. The ethyl acetate extract was dried over Na_2SO_4 and evaporated under reduced pressure to yield the desired product. White solid; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.44 (s, 18H, BOC), 3.11–3.28 (m, 4H, CH_2), 3.70–3.78 (m, 1H, CH), 5.14 (br s, 2H, NH).

*5.1.10. (3-tert-Butoxycarbonylamino-2-O-substituted propyl)-carbamic acid tert-butyl ester (**9a–d**): general procedure*

To a stirred solution of **8** (4.0 g, 13.8 mmol) and ethyl iodide (3.34 mL, 41.4 mmol) in toluene (15 mL) was added NaOH (50% aq, 15 mL) followed by Bu_4NHSO_4 (0.88 g, 2.6 mmol) at room temperature. The reaction mixture was stirred at 100 °C for 18 h, diluted with water and extracted with ethyl acetate. The organic extract was washed with brine and with water, and was evaporated under vacuum. The residue thus obtained was purified by silica gel column chromatography using hexane/EtOAc (4:1) as an eluent.

*5.1.10.1. (3-tert-Butoxycarbonylamino-2-ethoxypropyl)-carbamic acid tert-butyl ester (**9a**).* White solid; MS (FAB) 319

(MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19 (t, $J = 6.7$ Hz, 3H, CH_3), 1.44 (s, 18H, BOC), 3.04–3.08 (m, 2H, CH_2), 3.34–3.42 (m, 3H, CH, CH_2), 3.56 (q, $J = 6.7$ Hz, 2H, CH_2), 5.02 (br s, 2H, NH).

*5.1.10.2. (3-tert-Butoxycarbonylamino-2-isopropoxypropyl)-carbamic acid tert-butyl ester (**9b**).* White solid; MS (FAB) 334 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (d, $J = 6.0$ Hz, 6H, CH_3), 1.44 (s, 18H, BOC), 2.99–3.04 (m, 2H, CH_2), 3.29–3.40 (m, 2H, CH_2), 3.47–3.50 (m, 1H, CH), 3.70–3.74 (m, 1H, CH), 5.02 (br s, 2H, NH).

*5.1.10.3. (2-Benzyloxy-3-tert-butoxycarbonylaminopropyl)-carbamic acid tert-butyl ester (**9c**).* White solid; MS (FAB) 381 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s, 18H, BOC), 3.10–3.15 (m, 2H, CH_2), 3.39–3.50 (m, 2H, CH_2), 3.53–3.55 (m, 1H, CH), 4.59 (s, 2H, CH_2), 5.01 (br s, 2H, NH), 7.29–7.34 (m, 5H, PhH).

*5.1.10.4. Benzoic acid 2-tert-butoxycarbonylamino-1-(tert-butoxycarbonylaminomethyl)-ethyl ester (**9d**).* White solid; MS (FAB) 395 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37 (s, 18H, BOC), 3.40–3.43 (m, 4H, CH_2), 5.01–5.02 (m, 1H, CH), 5.01 (br s, 2H, NH), 7.35–7.40 (m, 2H, PhH), 7.49–7.53 (m, 1H, PhH), 7.94–8.01 (m, 2H, PhH).

*5.1.11. 2-Alkoxy-, 2-benzyloxypropane-1, 3-diamine (**10a–d**)*

Compound **9a** (800 mg) was stirred in 4 M HCl (30 mL) in THF at room temperature for 4 h. The precipitate thus formed was filtered and washed with ether to give compound **10a** as a white solid. Similarly, compounds **10b–d** were obtained from their corresponding protected derivatives **9b–d**. The compounds **10a–d** were used as such for the next stage of reactions.

*5.1.12. (3-Benzyloxycarbonylamino-2-hydroxypropyl)-carbamic acid benzyl ester (**11**)*

Benzyl chloroformate (75 g, 440 mmol) was added to a stirred solution of **7** (18.0 g, 200 mmol) in 1 N NaOH (300 mL) at 0 °C, and the mixture was stirred for 12 h at room temperature. The solid product thus formed was filtered, washed with water and crystallized from a mixture of hexane/EtOA (1:1). White solid; MS (FAB) 358 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.25–3.27 (m, 4H, CH_2), 3.80–3.81 (m, 1H, CH), 5.10 (s, 4H, CH_2), 5.52 (br s, 2H, NH), 7.30–7.31 (m, 10H, PhH).

*5.1.13. Methanesulfonic acid 2-benzyloxycarbonylamino-1-(benzyloxycarbonylaminomethyl)-ethyl ester (**12**)*

Methanesulfonyl choride (3.7 g, 32.4 mmol) was added dropwise to a suspension of **11** (10.5 g, 29.3 mmol) and triethylamine (6.9 mL, 48.9 mmol) in dichloromethane (200 mL) at 0 °C. The resultant reaction mixture was allowed to warm to room temperature and was stirred for 1 h. Water was added and the organic phase was separated, washed with water, dried (Na_2SO_4) and evaporated under reduced pressure to yield the desired product in pure form. White solid; MS (FAB) 437 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.03 (s, 3H, SO_2Me), 3.37–3.52 (m, 4H, CH_2), 4.58–4.68 (m, 1H, CH), 5.09 (s, 4H, CH_2), 5.52 (br s, 2H, NH), 7.30–7.33 (m, 10H, PhH).

*5.1.14. (2-Azido-3-benzyloxycarbonyl-aminopropyl)-carbamic acid benzyl ester (**13**)*

A mixture of **12** (4.0 g, 9.17 mmol) and sodium azide (2.38 g, 36.7 mmol) in DMF (30 mL) was stirred at 100 °C for 20 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate (20 mL × 2). The ethyl acetate layer was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure to give the desired compound. White solid; MS (FAB) 384 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.15–3.24 (m, 2H, CH_2), 3.36–3.42 (m, 2H, CH_2), 3.64–3.66 (m, 1H, CH), 5.09 (s, 4H, CH_2), 5.42 (br s, 2H, NH), 7.33–7.34 (m, 10H, PhH).

*5.1.15. (2-Amino-3-benzyloxycarbonyl-aminopropyl)-carbamic acid benzyl ester (**14**)*

To a suspension of $SnCl_2$ (1.11 g, 5.87 mmol) in acetonitrile (10 mL) at room temperature was added thiophenol (2.4 mL, 23.49 mmol) followed by triethylamine (2.47 mL, 17.62 mmol). To the reaction mixture, a solution of **13** (1.5 g, 3.91 mmol) in acetonitrile (10 mL) was added slowly at room temperature, and the mixture was stirred for 1 h and evaporated under reduced pressure. The residue was purified by basic alumina column chromatography using a CH_2Cl_2/MeOH/NH_3 solution (90:10:1) as an eluent. White solid; MS (FAB) 358 (MH^+); ^1H NMR (CD_3OD, 300 MHz) δ 2.84–2.93 (m, 1H, CH), 3.03–3.19 (m, 4H, CH_2), 5.06 (s, 4H, CH_2), 7.33–7.34 (m, 10H, PhH).

*5.1.16. (3-Benzyloxycarbonylamino-2-dimethyl-aminopropyl)-carbamic acid benzyl ester (**15**)*

To an ice-cold suspension of **14** (1.6 g, 4.48 mmol) in water (5 mL), formaldehyde (0.67 mL, 8.96 mmol, 40% aq solution) followed by formic acid (0.41 g, 8.96 mmol) were added with stirring. The reaction mixture was heated under reflux for 8 h, neutralized with a 2 M NaOH solution and extracted with dichloromethane (20 mL × 2). The dichloromethane extract was dried under vacuum and the residue was purified by silica gel column chromatography using CH_2Cl_2/MeOH (19:1) as an eluent. White solid; MS (FAB) 386 (MH^+); ^1H NMR (CD_3OD, 300 MHz) δ 2.31 (s, 6H, CH_3), 2.61–2.67 (m, 1H, CH), 3.11–3.29 (m, 4H, CH_2), 5.06 (s, 4H, CH_2), 7.24–7.33 (m, 10H, PhH).

*5.1.17. [2-Benzyloxycarbonylamino-1-(benzyloxycarbonyl-aminomethyl)-ethyl]-carbamic acid i-butyl ester (**16**)*

A mixture of **14** (2.34 g, 6.55 mmol) and di-*tert*-butyldicarbonate (1.70 g, 7.8 mmol) in ethanol (20 mL) was stirred at room temperature for 6 h. The solvent was evaporated and the residue was purified by silica gel column chromatography, using CH_2Cl_2/MeOH (99:1) as an eluent. White solid; MS (FAB) 458 (MH^+); ^1H NMR (CD_3OD, 300 MHz) δ 1.40 (s,

9H, BOC), 2.96–3.26 (m, 4H, CH), 3.68–3.72 (m, 1H, CH), 5.06 (s, 4H, CH_2), 7.23–7.32 (m, 10H, PhH).

*5.1.18. N,N-Dimethylpropane-1,2,3-triamine (**17**)*

This was obtained by stirring **15** (1.0 g) with 10% Pd–C (100 mg) under a hydrogen atmosphere in methanol at room temperature for 2 h. The reaction mixture was filtered through celite powder and evaporated under reduced pressure to give the desired product in a quantitative yield. Similarly, compound **18** was obtained from debenzylation of **16**. Both compounds **17** and **18** were used directly for the next reaction without purification.

*5.1.19. 1,3-Diazidopropan-2-ol (**20**)*

A mixture of **19** (10.85 g, 50.0 mmol) and sodium azide (9.75 g, 150.0 mmol) in DMF was heated at 80 °C for 24 h. The reaction mixture was allowed to cool to room temperature, diluted with water and extracted with ethyl acetate (25 mL × 3). The organic layer was collected, washed with water and dried under vacuum. The residue thus obtained was purified by silica gel column chromatography using hexane/EtOAc (9:1) as an eluent. Colorless oil; MS (FAB) 143 (MH^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.36–3.37 (m, 4H, CH), 3.66–3.68 (m, 1H, CH).

*5.1.20. 3-(2-Azido-1-azidomethylethoxy)-propene (**21**)*

A mixture of **20** (5.0 g, 35.2 mmol), 4 Å molecular sieves (20 g) and $CsOH\cdot H_2O$ (11.8 g, 70.4 mmol) in acetonitrile (30 mL) was stirred at room temperature for 20 min under a nitrogen atmosphere. Tetra-*n*-butylammonium iodide (12.98 g, 35.2 mmol) and allyl iodide (9.58 mL, 105.6 mmol) were added sequentially, and the resultant mixture was stirred for 48 h at room temperature. The molecular sieves were filtered and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using hexane/EtOAc (19:1) as an eluent. Colorless oil; MS (FAB) 183 (MH^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.37–3.39 (m, 4H, CH), 3.68–3.69 (m, 1H, CH), 4.13–4.15 (m, 2H, allyl), 5.21–5.36 (m, 2H, allyl), 5.87–6.00 (m, 1H, allyl).

*5.1.21. 2-Allyloxypropane-1,3-diamine (**22**)*

To a suspension of $SnCl_2$ (5.67 g, 30.0 mmol) in acetonitrile (30 mL) at room temperature was added thiophenol (12.3 mL, 120 mmol) followed by triethylamine (12.6 mL, 90.12 mmol). To the reaction mixture, a solution of **21** (1.82 g, 10.0 mmol) in acetonitrile (20 mL) was added slowly at room temperature. The mixture was stirred for 1 h and evaporated under reduced pressure. The residue was purified by basic alumina column chromatography using a CH_2Cl_2/MeOH/NH_3 solution (90:10:1) as an eluent. White solid; ^{1}H NMR (CD_3OD, 300 MHz) δ 2.73–2.88 (m, 4H, CH_2), 3.40–3.47 (m, 1H, CH), 4.02–4.10 (m, 2H, allyl), 5.13–5.34 (m, 2H, allyl), 5.89–6.01 (m, 1H, allyl).

*5.1.22. 4-Aryl-2-substituted aminoquinoline (**24a, b, 27a–e, 30, 34**): general procedure*

A mixture of **23** (228 mg, 0.76 mmol) and **6a** (400 mg, 3.84 mmol) in DMSO (15 mL) was stirred in the presence of K_2CO_3 (210 mg, 1.52 mmol) at 100–110 °C for 48 h. The reaction mixture was diluted with water at room temperature and extracted with ethyl acetate (20 mL × 2). The ethyl acetate extract was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography with a CH_2Cl_2/MeOH/NH_3 solution (90:10:1) as an eluent. Similarly, compounds **24b**, **27a–e**, **30** and **34** were prepared from the reactions of diamines **6b**, **10a–d** & **22**, **17** and **18** with **23**, respectively.

*5.1.22.1. 2-Aminomethyl-3-[4-(4-methoxybenzyloxy)-quinolin-2-ylamino]-propan-1-ol (**24a**).* White solid; MS (FAB) 368 (MH^+); ^{1}H NMR (CD_3OD, 300 MHz) δ 1.81–1.89 (m, 1H, CH), 2.64–2.78 (m, 2H, CH_2), 3.49–3.64 (m, 4H, CH_2), 3.80 (s, 3H, OCH_3), 5.14 (s, 2H, CH_2), 6.23 (s, 1H, ArH), 6.95 (d, $J = 8.76$ Hz, 2H, ArH), 7.09–7.16 (m, 1H, ArH), 7.41 (d, $J = 8.76$ Hz, 2H, ArH), 7.46–7.49 (m, 2H, ArH), 7.90 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.22.2. N^1-[4-(4-Methoxybenzyloxy)-quinolin-2-yl]-2-methoxymethylpropane-1,3-diamine (**24b**).* White solid; MS (FAB) 382 (MH^+); ^{1}H NMR (CD_3OD, 300 MHz) δ 1.99–2.07 (m, 1H, CH), 2.65–2.78 (m, 2H, CH_2), 3.36 (s, 3H, OCH_3), 3.42–3.63 (m, 4H, CH_2), 3.80 (s, 3H, OCH_3), 5.15 (s, 2H, CH_2), 6.26 (s, 1H, ArH), 6.95 (d, $J = 8.76$ Hz, 2H, ArH), 7.09–7.14 (m, 1H, ArH), 7.42 (d, $J = 8.76$ Hz, 2H, ArH), 7.46–7.49 (m, 2H, ArH), 7.90 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.23. 2-Ethoxy-N^1-[4-(4-methoxybenzyloxy)-quinolin-2yl]-propane-1,3-diamine (**27a**)*

White solid; MS (FAB) 382 (MH^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (t, $J = 6.9$ Hz, 3H, CH_3), 2.78–2.94 (m, 2H, CH_2), 3.45–3.74 (m, 4H, CH_2), 3.80 (s, 3H, OCH_3), 4.03–4.12 (m, 1H, CH), 5.15 (s, 2H, CH_2), 6.29 (s, 1H, ArH), 6.95 (d, $J = 8.76$ Hz, 2H, ArH), 7.11–7.17 (m, 1H, ArH), 7.42 (d, $J = 8.76$ Hz, 2H, ArH), 7.47–7.53 (m, 2H, ArH), 7.92 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.23.1. 2-Isopropoxy-N^1-[4-(4-methoxybenzyloxy)-quinolin-2yl]-propane-1,3-diamine (**27b**).* White solid; MS (FAB) 396 (MH^+); ^{1}H NMR (CD_3OD, 300 MHz) δ 1.18 (d, $J = 6.0$ Hz, 6H, CH_3), 2.72–2.80 (m, 2H, CH_2), 3.42–3.75 (m, 3H, CH, CH_2), 3.80 (s, 3H, OCH_3), 3.84–3.88 (m, 1H, CH), 5.14 (s, 2H, CH_2), 6.26 (s, 1H, ArH), 6.95 (d, $J = 8.76$ Hz, 2H, ArH), 7.09–7.15 (m, 1H, ArH), 7.41 (d, $J = 8.76$ Hz, 2H, ArH), 7.45–7.51 (m, 2H, ArH), 7.93 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.23.2. 2-Benzyloxy-N^1-[4-(4-methoxybenzyloxy)-quinolin-2yl]-propane-1,3-diamine (**27c**).* White solid; MS (FAB) 444 (MH^+); ^{1}H NMR (CD_3OD, 300 MHz) δ 2.68–2.80 (m, 2H,

CH_2), 3.60–3.61 (m, 3H, CH_2), 3.76 (s, 3H, OCH_3), 4.58–4.68 (m, 2H, CH_2), 5.07 (s, 2H, CH_2), 6.21 (s, 1H, ArH), 6.92 (d, $J = 8.76$ Hz, 2H, ArH), 7.20–7.38 (m, 8H, ArH), 7.42–7.46 (m, 1H, ArH), 7.50–7.51 (m, 1H, ArH), 7.87 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.23.3. Benzoic acid 1-aminomethyl-2-[4-(4-methoxybenzyloxy)-quinolin-2ylamino]-ethyl ester (**29d**).* White solid; MS (FAB) 458 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.45–3.64 (m, 2H, CH_2), 3.75–3.80 (m, 2H, CH_2), 3.82 (s, 3H, OCH_3), 4.00–4.01 (m, 1H, CH), 5.01 (s, 2H, CH_2), 6.05 (s, 1H, ArH), 6.92 (d, $J = 6.2$ Hz, 2H, ArH), 7.15–7.22 (m, 1H, ArH), 7.33–7.56 (m, 7H, ArH), 7.78 (d, $J = 6.2$ Hz, 2H, ArH), 7.87 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.23.4. 2-Allyloxy-N^1-[4-(4-methoxybenzyloxy)-quinolin-2yl]-propane-1,3-diamine (**27e**).* White solid; MS (FAB) 394 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.80–2.87 (m, 2H, CH_2), 3.42–3.73 (m, 3H, CH, CH_2), 3.80 (s, 3H, OCH_3), 4.12–4.14 (m, 2H, allyl), 5.12 (s, 2H, CH_2), 5.18–5.34 (m, 2H, CH_2, allyl), 5.89–6.00 (m, 1H, CH, allyl), 6.02 (s, 1H, ArH), 6.95 (d, $J = 8.76$ Hz, 2H, ArH), 7.13–7.20 (m, 1H, ArH), 7.40 (d, $J = 8.76$ Hz, 2H, ArH), 7.47–7.53 (m, 1H, ArH), 7.58–7.61 (m, 1H, ArH), 7.92 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.23.5. N^1-[4-(4-Methoxybenzyloxy)-quinolin-2-yl]-N^2,N^2-dimethylpropane-1,2,3-triamine (**30**).* White solid; MS (FAB) 381 (MH^+); ^1H NMR (CD_3OD, 300 MHz) δ 2.40 (s, 6H, NCH_3), 2.68–2.81 (m, 2H, CH_2), 3.44–3.53 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 4.08–4.12 (m, 1H, CH), 5.16 (s, 2H, CH_2), 6.26 (s, 1H, ArH), 6.95 (d, $J = 8.76$ Hz, 2H, ArH), 7.09–7.14 (m, 1H, ArH), 7.42 (d, $J = 8.76$ Hz, 2H, ArH), 7.47–7.54 (m, 2H, ArH), 7.92 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.23.6. {1-Aminomethyl-2-[4-(4-methoxybenzyloxy)-quinolin-2-ylamino]ethyl}-carbamic acid tert-butyl ester (**34**).* White solid; MS (FAB) 453 (MH^+); ^1H NMR (CD_3OD, 300 MHz) δ 1.40 (s, 9H, BOC), 2.64–2.78 (m, 2H, CH_2), 3.56–3.58 (m, 2H, CH_2), 3.69–3.76 (m, 1H, CH), 3.80 (s, 3H, OCH_3), 5.15 (s, 2H, CH_2), 6.29 (s, 1H, ArH), 6.95 (d, $J = 8.76$ Hz, 2H, ArH), 7.09–7.14 (m, 1H, ArH), 7.42 (d, $J = 8.76$ Hz, 2H, ArH), 7.47–7.54 (m, 2H, ArH), 7.92 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.24. 3-(4-Oxo-1,4-dihydroquinolin-2-ylamino)-2-substituted-propylammonium trifluoroacetate (**25a**, **b**, **28a–e**, **31**, **35**): general procedure*

The compounds **25a**, **b**, **28a–e**, **31** were prepared from TFA-catalyzed hydrolysis of their 4-methoxybenzyl-protected derivatives, **24a**, **b**, **27a–e**, and **30**. Compound **35** was obtained upon stirring with 10% Pd–C in methanol under a hydrogen atmosphere at room temperature for 2 h. These compounds were directly used for the next stage of the reaction without purification or isolation.

*5.1.25. 2-[3-(3,4-Dichlorobenzylamino)-2-substituted-propylamino]-1H-quinolin-4-one (**26a**, **26b**, **29a–e**, **32**, **32**, **36**, **37**): general procedure*

To a stirred solution of **25a** (100 mg, 0.40 mmol) in methanol (5 mL) was added a 0.5 M methanolic solution of MeONa (1 mL, 0.43 mmol). Additional amounts of the 0.5 M MeONa solution were added to maintain a pH of 12 for the reaction mixture, which was stirred for 10 min at room temperature. 3,4-Dichlorobenzaldehyde (70 mg, 0.40 mmol) was added, and the resultant reaction mixture was stirred at 50 °C for 1 h. To this $NaCNBH_3$ (38 mg, 0.60 mmol) in methanol (2 mL) was added dropwise, and the stirring was continued for an additional 6 h. The solvent was evaporated under reduced pressure, and the residue thus obtained was purified by silica gel column chromatography using a CH_2Cl_2/MeOH/NH_3 solution (95:5:1) as an eluent.

*5.1.25.1. 2-[3-(3,4-Dichlorobenzylamino)-2-hydroxymethyl-propylamino]-1H-quinolin-4-one (**26a**).* White solid; mp 222–224 °C; IR (KBr) ν 3560 cm^{-1} (OH); MS (FAB) 407 (MH^+); ^1H NMR (CD_3OD, 300 MHz) δ 2.26–2.33 (m, 1H, CH), 3.02–3.12 (m, 2H, CH_2), 3.33–3.45 (m, 2H, CH_2), 3.67–3.80 (m, 2H, CH_2), 4.06–4.19 (m, 2H, CH_2), 5.67 (s, 1H, ArH), 7.24–7.28 (m, 1H, ArH), 7.34–7.39 (m, 2H, ArH), 7.52–7.56 (m, 2H, ArH), 7.63–7.65 (m, 1H, ArH), 8.06 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.25.2. 2-[3-(3,4-Dichlorobenzylamino)-2-methoxymethyl-propylamino]-1H-quinolin-4-one (**26b**).* White solid; mp 168–170 °C; MS (FAB) 421 (MH^+); ^1H NMR (CD_3OD, 300 MHz) δ 2.05–2.13 (m, 1H, CH), 2.51–2.69 (m, 2H, CH_2), 3.35 (s, 3H, OCH_3), 3.38–3.45 (m, 4H, CH_2), 3.75 (s, 2H, CH_2), 5.66 (s, 1H, ArH), 7.21–7.27 (m, 3H, ArH), 7.40–7.43 (m, 1H, ArH), 7.46–7.53 (m, 2H, ArH), 8.06 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.25.3. 2-[3-(3,4-Dichlorobenzylamino)-2-ethoxypropylamino]-1H-quinolin-4-one (**29a**).* White solid; mp 110–112 °C; MS (FAB) 421 (MH^+); ^1H NMR (CD_3OD, 300 MHz) δ 1.19 (t, $J = 6.9$ Hz, 3H, CH_3), 2.74 (d, $J = 5.50$ Hz, 2H, CH_2), 3.39–3.66 (m, 5H, CH, CH_2), 3.77–3.88 (m, 2H, CH_2), 5.68 (s, 1H, ArH), 7.23–7.32 (m, 3H, ArH), 7.43–7.46 (m, 1H, ArH), 7.50–7.56 (m, 2H, ArH), 8.06 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.25.4. 2-[3-(3,4-Dichlorobenzylamino)-2-isopropoxy-propylamino]-1H-quinolin-4-one (**29b**).* White solid; mp 120–122 °C; MS (FAB) 435 (MH^+); ^1H NMR (CD_3OD, 300 MHz) δ 1.18 (d, $J = 6.0$ Hz, 6H, CH_3), 2.72 (d, $J = 5.3$ Hz, 2H, CH_2), 3.39–3.56 (m, 2H, CH), 3.75–3.89 (m, 4H, CH_2), 5.72 (s, 1H, ArH), 7.27–7.36 (m, 3H, ArH), 7.46–7.49 (m, 1H, ArH), 7.54–7.59 (m, 2H, ArH), 8.13 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.25.5. 2-[2-Benzyloxy-3-(3,4-dichlorobenzylamino)-propylamino]-1H-quinolin-4-one (**29c**).* White solid; mp 138–140 °C; MS (FAB) 483 (MH^+); ^1H NMR (CD_3OD,

300 MHz) δ 2.72 (d, $J = 5.3$ Hz, 2H, CH_2), 3.42–3.55 (m, 2H, CH), 3.69–3.76 (m, 3H, CH, CH_2), 4.57 (s, 2H, CH_2), 5.65 (s, 1H, ArH), 7.13–7.30 (m, 8H, ArH), 7.37–7.47 (m, 3H, ArH), 8.06 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.25.6. Benzoic acid 1-[(3,4-dichlorobenzylamino)-methyl]-2-(4-oxo-1,4-dihydroquinolin-2ylamino)-ethyl ester (**29d**).* White solid; mp 122–124 °C; MS (FAB) 497 (MH^+); ^1H NMR (CD_3OD, 300 MHz) δ 3.31–3.33 (m, 2H, CH_2), 3.51–3.53 (m, 2H, CH_2), 3.80–3.89 (m, 2H, CH_2), 4.20–4.25 (m, 1H, CH), 5.69 (s, 1H, ArH), 7.21–7.26 (m, 1H, ArH), 7.32–7.35 (m, 1H, ArH), 7.42–7.55 (m, 6H, ArH), 7.83–7.86 (m, 3H, ArH), 8.06 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.25.7. 2-[2-Allyloxy-3-(3,4-dichlorobenzylamino)-propylamino]-1H-quinolin-4-one (**29e**).* White solid; mp 33–135 °C; MS (FAB) 433 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.55–2.68 (m, 2H, CH_2), 3.25–3.40 (m, 2H, CH_2), 3.48–3.60 (m, 3H, CH, CH_2), 3.85–4.05 (m, 2H, allyl), 4.97–5.13 (m, 2H, CH_2, allyl), 5.65 (s, 1H, ArH), 5.66–5.79 (m, 1H, CH, allyl), 6.93–6.98 (m, 2H, ArH), 7.05–7.10 (m, 1H, ArH), 7.17–7.23 (m, 2H, ArH), 7.31–7.37 (m, 1H, ArH), 8.13 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.25.8. 2-[3-(3,4-Dichlorobenzylamino)-2-dimethylamino-propylamino]-1H-quinolin-4-one (**32**).* White solid; mp 110–112 °C; MS (FAB) 420 (MH^+); ^1H NMR (CD_3OD, 300 MHz) δ 2.65 (s, 6H, NCH_3), 3.33–3.36 (m, 1H, CH), 3.62–3.87 (m, 4H, CH_2), 4.21 (s, 2H, CH_2), 6.38 (s, 1H, ArH), 7.40–7.55 (m, 3H, ArH), 7.70–7.79 (m, 3H, ArH), 8.11 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.25.9. 2-{3-[Bis-(3,4-dichlorobenzyl)-amino]-2-dimethylamino-propylamino}-1H-quinolin-4-one (**33**).* White solid; mp 88–90 °C; MS (FAB) 579 (MH^+); ^1H NMR (CD_3OD, 300 MHz) δ 2.90 (s, 6H, NCH_3), 3.66–3.97 (m, 9H, CH), 6.32 (s, 1H, ArH), 7.26–7.29 (m, 2H, ArH), 7.42–7.51 (m, 5H, ArH), 7.74–7.81 (m, 2H, ArH), 8.16 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.25.10. [1-[(3,4-Dichlorobenzylamino)-methyl]-2-(4-oxo-1,4-dihydroquinolin-2-ylamino)ethyl]-carbamic acid tert-butyl ester (**36**).* White solid; mp 202–204 °C; MS (FAB) 492 (MH^+); ^1H NMR (CD_3OD, 300 MHz) δ 1.44 (s, 9H, BOC), 2.63–2.75 (m, 2H, CH_2), 3.34–3.42 (m, 2H, CH_2), 3.74–3.77 (m, 3H, CH, CH_2), 5.65 (s, 1H, ArH), 7.11–7.27 (m, 2H, ArH), 7.33–7.40 (m, 2H, ArH), 7.48–7.54 (m, 2H, ArH), 8.13 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.25.11. {1-[(3,4-Dichlorobenzylamino)-methyl]-2-[4-(4-methoxybenzyloxy)-quinolin-2ylamino]ethyl}-carbamic acid tert-butyl ester (**37**).* White solid; mp 80–82 °C; MS (FAB) 611 (MH^+); ^1H NMR (CD_3OD, 300 MHz) δ 1.45 (s, 9H, BOC), 2.91–2.93 (m, 2H, CH_2), 3.59–3.65 (m, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.93–4.10 (m, 3H, CH, CH_2), 5.28 (s, 2H, CH_2), 6.43 (s, 1H, ArH), 6.98 (d, $J = 6.6$ Hz, 2H, ArH), 7.27–7.62 (m, 8H, ArH), 8.02 (d, $J = 8.10$ Hz, 1H, ArH).

*5.1.25.12. 2-[2-Amino-3-(3,4-dichlorobenzylamino)-propylamino]-1H-quinolin-4-one tri(trifluoroacetic acid) (**38**).* This compound was obtained by incubating **37** (100 mg) in 20% TFA–DCM at room temperature for 2 h. The settled precipitate was filtered and washed with plain dichloromethane. White solid; mp 158–160 °C; MS (FAB) 392 (MH^+); ^1H NMR (CD_3OD, 300 MHz) δ 3.33–3.34 (m, 2H, CH_2), 3.88–3.93 (m, 3H, CH, CH_2), 4.20–4.22 (m, 2H, CH_2), 6.48 (s, 1H, ArH), 7.41–7.56 (m, 3H, ArH), 7.70–7.76 (m, 3H, ArH), 8.02 (d, $J = 8.10$ Hz, 1H, ArH).

6. Biology

MICs were determined by a microdilution method with Mueller–Hinton Broth (MH, Difco Laboratories, Detroit, MI) for staphylococci and Brain Heart Infusion Broth (BHI, Difco) for *Enterococci*, following the National Committee for Clinical Laboratory Standards (NCCLS) (now called the Clinical Laboratory Standards Institute [CLSI]) [18] Six *S. aureus* strains (ATCC25923, ATCC6538P, ATCC10537, GIORGIO, SP-N2 and SMITH), one *S. epidermidis* strain (ATCC12228), two *E. faecalis* strains (ATCC29212 and ATCC19433) and one *E. faecium* strain (ATCC10541) were used. The stock solutions of test compounds were diluted to give a serial, 2-fold series, yielding final chemical concentrations that ranged from 64 to 0.03 μg/mL. The MIC was defined as the lowest concentration of the chemical that inhibited the development of visible bacterial growth after an incubation for 16 h at 36 °C. The MICs of standard antibiotics (mupirocin and amoxicillin) were determined by the same method.

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