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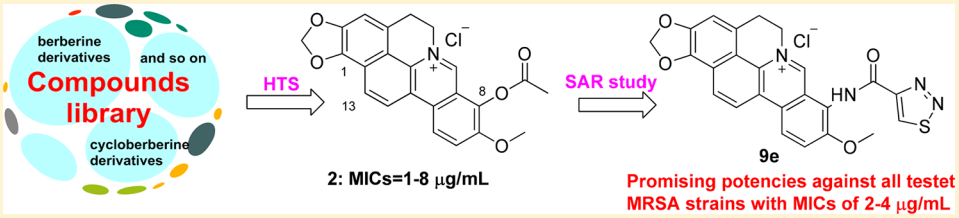
Discovery and Development of 8-Substituted Cycloberberine Derivatives as Novel Antibacterial Agents against MRSA

Tianyun Fan,[†] Xinxin Hu,[†] Sheng Tang, Xiaojia Liu, Yanxiang Wang, Hongbin Deng, Xuefu You, Jiandong Jiang, Yinghong Li,* and Danqing Song*

Beijing Key Laboratory of Antimicrobial Agents, Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100050, China

Supporting Information



ABSTRACT: 8-Acetoxycycloberberine (**2**) with a unique skeleton was first identified to display a potent activity profile against Gram-positive bacteria, especially methicillin-resistant *S. aureus* (MRSA) with minimum inhibitory concentration (MIC) values of 1−8 μg/mL, suggesting a possible novel mechanism of action against bacteria. Taking **2** as the lead, 23 new 8-substituted cycloberberine (CBBR) derivatives including ether, amine, and amide were synthesized and evaluated for their antibacterial effect. The structure−activity relationship revealed that the introduction of a suitable substituent at the 8-position could greatly enhance the potency against MRSA. Among them, compounds **5d** and **9e** demonstrated equally effective anti-MRSA potency as lead **2**, with an advantage of having a more stable pharmacokinetics feature. A preliminary mechanism study indicated that compound **9e** acted upon bacteria partly through catalyzing the cleavage of bacterial DNA. Therefore, we consider that 8-substituted CBBR derivatives constitute a promising class of antibacterial agents in the treatment of MRSA infections.

KEYWORDS: *Cycloberberine, berberine, structure−activity relationship, antibacterial, MRSA*

Antimicrobial resistance is a major global health concern, and of the Gram-positive bacteria, drug-resistant *Staphylococcus aureus* (*S. aureus*) is a serious threat.[1] Over a period of decades, *S. aureus* isolated from patients has developed increasing resistance to several classes of clinical antibacterials, such as β-lactam, fluoroquinolone, macrolide, glycopeptide, and oxazolidinone.[2,3] Especially, the challenge of treating methicillin-resistant *S. aureus* (MRSA) was highlighted in a recent report published by the U.S. Centers for Disease Control and Prevention (CDC).[4] Vancomycin, as one of the last resort therapies for MRSA infection, has issues that restrict its utility including slow bactericidal activity, low tissue penetration, and increasing reports of vancomycin-intermediate *S. aureus* (VISA).[5−7] Although daptomycin remains as one of the main treatment options for MRSA, resistance cases in patients treated with daptomycin are a growing concern.[8,9] This situation has resulted in a very pressing need for the discovery of novel antibacterial candidates for the treatment of infections arising from MRSA.

To explore and discover new chemical entity (NCE) against MRSA, a library of berberine (**1**, Figure 1) derivatives constructed in our lab was screened for their antibacterial activity using phenotype screening assay.[10] Surprisingly, cycloberberine (CBBR, Figure 1) derivatives,[11] such as 8-acetoxycyclo-berberine (**2**, Figure 1), were first identified to display satisfactory activity profile against both methicillin-susceptible *S. aureus* (MSSA) and MRSA strains with minimum inhibitory concentration (MIC) values ranging from of 1−8 μg/mL (Table 1), suggesting a possible novel mechanism of action against bacteria. The unique chemical scaffold and antibacterial activity profile of compound **2** against MRSA organisms, high-level resistant pathogens across the world, spurred us to further carry out structural modifications and optimization so as to develop them into a novel family of antimicrobial agents against MRSA.

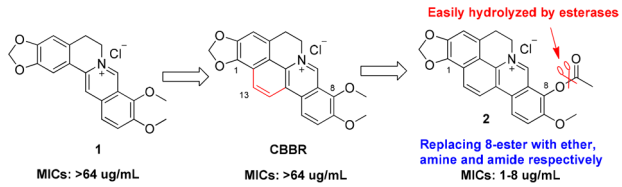


Figure 1. Structures and antibacterial activities of **1**, CBBR, and **2**, as well as the modification strategy.

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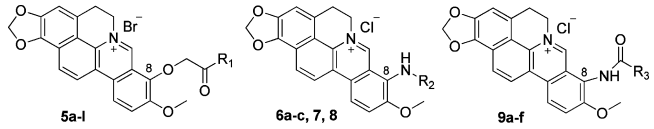
Table 1. Antimicrobial Activities of the Target Compounds against Drug-Susceptible Gram-Positive Strains



Code	R1	MIC (μg/mL)[a]									
		MSSA						MSSE		*S.s*	*S.h*
		ATCC 29213[b]	15[c]	13-17[c]	13-19[c]	13-20[c]	13-21[c]	ATCC 12228	13-1[c]	ATCC15305	ATCC 35982
2		1	2	1	8	2	4	1	2	4	2
4		0.25	4	0.25	0.5	0.25	0.5	0.5	0.5	>64	0.5
5a	ethyl	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
5b	tert- butyl	32	64	32	32	32	32	32	32	32	16
5c	cyclopropyl	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
5d	1'-adamantyl	4	2	2	4	4	2	2	2	2	2
5e	C_6H_5	16	32	16	16	32	16	8	64	16	32
5f	*p*-FC_6H_4	64	8	16	8	16	8	8	8	32	32
5g	*p*-$CF_3C_6H_4$	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
5h	*o*-$CF_3OC_6H_4$	8	16	8	8	8	8	4	16	4	4
5i	*m*-$CF_3OC_6H_4$	32	16	16	16	16	16	16	32	16	32
5j	*m*-CF_3-*p*-$CH_3OC_6H_3$	4	4	4	4	4	8	4	8	4	4
5k	*m*-$CH_3OC_6H_4$	16	32	4	4	8	16	16	8	8	64
5l	*p*-$CH_3C_6H_4$	4	8	4	4	8	4	2	8	4	4
6a	benzyl	64	64	64	64	64	64	8	64	8	8
6b	*p*-CH_3OPh	64	64	64	64	64	64	8	64	16	8
6c	furfuryl	32	32	32	16	32	32	32	64	32	32
7	*o,p*-di-CH_3OPh	8	8	8	8	8	8	4	8	8	8
8	H	4	4	4	8	4	8	8	8	8	8
9a	1'-adamantyl	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
9b	cyclopentyl methyl	8	8	8	8	8	8	8	8	32	8
9c	2'-pyridyl	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
9d		16	16	16	8	8	16	32	>64	>64	>64
9e		2	4	2	2	2	2	4	2	4	2
9f		>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Lev		0.06	0.125	0.125	0.5	0.125	0.25	0.06	0.125	0.5	0.125

[a]MIC (μg/mL), minimum inhibitory concentration. [b]The American Type Culture Collection (ATCC). [c]Strains isolated from patients in Chinese hospitals.

However, as shown in Figure 1, it is well-known that the ester bond at the 8-position of compound **2** could be easily hydrolyzed by esterases resulting in a poor *in vivo* pharmacokinetic (PK) profile. Therefore, a series of new 8-substituted CBBR ether, amine, and amide derivatives was then constructed and synthesized, aiming at overcoming PK instability of compound **2**. In the present study, taking compound **2** as the lead, we describe 23 new 8-substituted CBBR analogues for their synthesis, *in vitro* effects against MSSA and MRSA, structure−activity relationship (SAR) analysis, and stability in blood as well as primary mechanism of action of the representative compound.

The synthetic route used for the preparation of the CBBR analogues is described in Scheme 1 with commercially available

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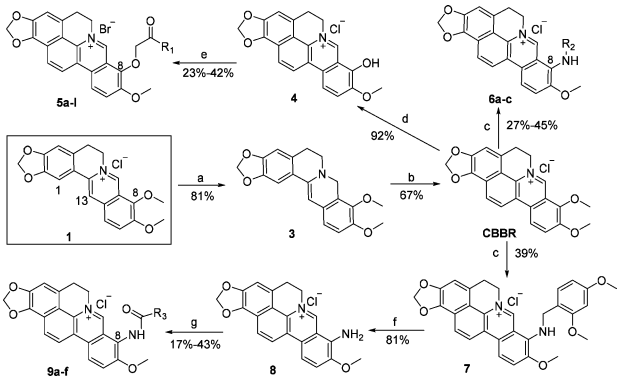
Scheme 1. Synthesis of All the Target Compounds[a]



[a]Reagents and conditions: (a) $NaBH_4$, 5% $NaOH/K_2CO_3$, CH_3OH, rt, 3 h; (b) (1) 40% glyoxal, $HOAc/CH_3CN$, reflux, 6 h; (2) methanol/HCl (2:1 by vol.), rt, 24 h; (c) 2,4-dimethoxybenzylamine/R_2NH_2, 100−116 °C, 4−32 h; (d) 20−30 mmHg, 195−210 °C, 40 min; (e) R_1COCH_2Br, KOH, DMF, 68−75 °C, 4−24 h; (f) 1:1 HCl/CH_3OH, rt, 24 h; (g) R_3COCl, pyridine, CH_3CN, 40−91 °C, 3−72 h.

1 as the starting material. Compound **1** was selectively reduced to the dihydroberberine (**3**) using $NaBH_4$ as a reductive agent in the presence of 5% $NaOH/K_2CO_3$ in 81% yield. Glyoxal (40%) was added to the mixture of **3** and $HOAc/CH_3CN$ to give 13-acetaldehyde berberine, which was used for the next step without purification.[11] A cyclization reaction took place on the addition of methanol/HCl (2:1 by vol.), and the desired CBBR was obtained with a combined yield of 67%, much higher than our previous report (38%).[12] Then, CBBR was heated at 195−210 °C under vacuum (20−30 mmHg) and acidified in concentrated HCl/ethanol (5:95 by vol.) to get the key intermediate **4** in 92% yield using the previous procedures.[11,12] Compound **4** was etherified to provide the final products **5a−l** in 23−42% yield.

Compounds **6a−c** were prepared using the corresponding amines in 27−45% yield. Similarly, intermediate **7** was prepared with 2,4-dimethoxybenzylamine as the nucleophilic reagent as well as the solvent. Free amine was then obtained by the removal of 2,4-dimethoxybenzyl using HCl/CH_3OH in 81% yield. The desired products **9a−f** were obtained by amidation with corresponding acyl chloride using pyridine as the base with 17−43% yield. All the final products were purified with flash column chromatography on silica gel using CH_2Cl_2 and MeOH as eluent.

All of the newly synthesized compounds were initially examined for their activities using standard techniques[13] against drug-susceptible Gram-positive strains including MSSA, methicillin-susceptible *S. epidermidis* (MSSE), *S. saprophyticus* (*S. s*), and *S. hominis* (*S. h*) taking levofloxacin (Lev) as a reference drug. Structures of the 23 CBBR analogues and their MIC values against Gram-positive bacteria are summarized in Table 1.

The SAR study was mainly focused on the influence of the substituent at the 8-position, and then a series of 8-substituted CBBR derivatives was obtained. First, 8-acetoxy in compound **2** was respectively replaced with several ether groups, by which

Table 2. Antibacterial Activities of the Target Compounds against Drug-Resistant Gram-Positive Strains

	MIC (μg/mL)[a]									
	MRSA								VISA	
Code	ATCC 33591	13−18	13−23	12−3	12−8	12−13	12−16	ATCC-BAA-1708[b]	ATCC 700698	ATCC 700699
2	4	1	2	4	8	4	2	8	16	32
4	0.25	0.25	0.25	0.25	0.5	1	0.5	0.5	0.5	0.25
5a	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
5b	32	32	32	32	64	32	32	32	>64	>64
5c	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
5d	2	4	2	4	4	4	2	4	8	8
5e	16	32	16	16	16	32	32	32	>64	>64
5f	8	16	8	8	8	8	16	64	>64	>64
5g	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
5h	8	8	8	16	8	4	4	32	>64	>64
5i	16	16	16	16	8	32	16	64	>64	>64
5j	4	8	4	4	8	4	8	16	>64	>64
5k	4	4	16	16	16	8	8	64	>64	>64
5l	4	4	4	4	8	4	4	8	>64	>64
6a	64	64	64	64	64	64	64	64	32	>64
6b	32	32	32	32	32	32	32	64	16	>64
6c	64	64	64	32	64	32	64	>64	>64	>64
7	8	8	8	8	8	8	8	16	4	8
8	4	8	8	8	4	4	4	4	64	4
9a	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
9b	8	8	8	8	8	16	8	4	64	4
9c	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
9d	64	32	8	32	32	16	16	16	>64	4
9e	2	2	2	2	2	4	2	2	16	8
9f	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Lev	0.125	32	32	32	32	32	32	16	32	2

[a]MIC (μg/mL), minimum inhibitory concentration. [b]mupA positive (isolates with mupirocin resistance).

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CBBR ether analogues **5a−l** were then generated and tested. Compounds **5a−c** with small aliphatic chains or rings lost their antimicrobial activities completely; while compound **5d** with large adamantyl[14] exhibited activities with MICs ranging from 2 to 4 μg/mL, similar to that of lead **2**. The results suggested that large volume at position 8 might be helpful for maintaining good activities. Based on the results, various benzenes with electron-withdrawing or electron-donating groups were respectively attached, and then new compounds **5e−l** were created and tested. Compound **5g** is much weaker than other analogs with similar phenyl substitutions, while compounds **5f**, **5h**, and **5i−l** exhibited comparable antimicrobial activities with MICs values of 2−32 μg/mL, regardless of electron-withdrawing or electron-donating groups on the benzene ring.

Then, we moved our SAR investigation onto the amine or amide moiety at the 8-position. With an introduction of a free amine group, 2-furanmethanamine, and substituted benzylamines at position 8, respectively, five new CBBR amine analogues (**6a−c**, **7**, and **8**) were generated and measured. However, as described in Table 1, all of them abolished the activity completely or partially, suggesting that introduction of an amine substituent at the 8-position might not be helpful for potency. The potencies of compounds **7** and **8** reduced slightly, and the MIC values ranged from 4 to 8 μg/mL compared with the lead **2**. Introduction of amide resulted in compounds **9a−f** that were tested for activity. The activity of compound **9a** with adamantyl was abolished, while the potencies of compounds **9b−d** and **9f** with cyclic or heterocyclic dropped obviously. Both compound **9a** and **5d** contain 1-adamantyl moiety, while the activity is quite different. Surprisingly, compound **9e** with 1,2,3-thiadiazole[15,16] attached exhibited comparable activity to the lead **2** (MICs = 1−8 μg/mL), suggesting that a thiadiazole group might be beneficial for antibacterial activity. The results illustrated that introducing a suitable substituent at the 8-position might be helpful for potency.

All of the target compounds were measured for their antibacterial activity using standard methods[13] against ten drug-resistant *S. aureus* strains (MRSA/VISA) with Lev as a reference drug as summarized in Table 2. Their potencies against MRSA/VISA were basically consistent with that of drug-susceptible strains, suggesting a different mechanism of action from the current antibacterial drugs. Among them, most of compounds showed potential anti-MRSA effect on not only ATCC strains but also isolated ones from Chinese patients, with MIC values between 2 and 64 μg/mL. More importantly, compounds **5d**, **7**, **8**, **9b**, and **9e** displayed promising effects against both MRSA and VISA strains with MICs values ranging from 2−64 μg/mL, similar to reference drug Lev. Especially, compounds **5d** and **9e** with different structures displayed excellent potencies with MIC of 2−4 μg/mL, and thus, both of them were selected as representative compounds for the next investigation. In addition, the key intermediate **4** was also tested for the activity, and results showed that it displayed a promising effect against both MRSA and VISA.

Thus, compound **4** could be selected as a parent structure to make prodrugs for potential antibacterial agents against MRSA.

As displayed in Figure 2, CBBR ether **5d** and amine **9e** were chosen to further explore the *in vitro* stability in whole blood taking enalapril containing an ester bond (Figure 2) as the control.[17,18] Compounds **2**, **5d**, and **9e** and enalapril were incubated with blood isolated from the Sprague-Dawly (SD) rats, and samples were taken out at 0, 30, 60, 120, 240, and 420 min, respectively. As expected, after 420 min, the remaining

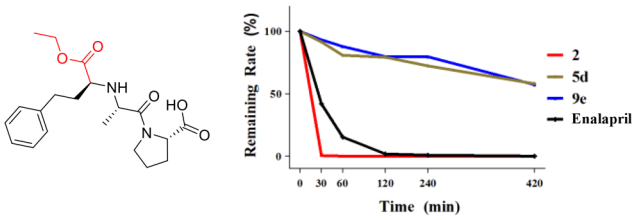

Figure 2. Structure of enalapril and metabolic stability of key compounds in whole blood.

ratios of the compounds **5d** and **9e** in blood were still 58.0 and 57.2%, respectively, much higher than that of lead **2** and enalapril, as described in Figure 2. The results suggested that compounds **5d** and **9e** possessed much more stable *in vitro* blood stability than lead **2**.

To evaluate the safety of this kind of compounds, the cytotoxic effects of the representative compounds **2**, **5d**, and **9e** on A549 cells were carried out using MTT assay.[19] As displayed in Figure 3, lead **2** had no cytotoxic activity in A549 cells with

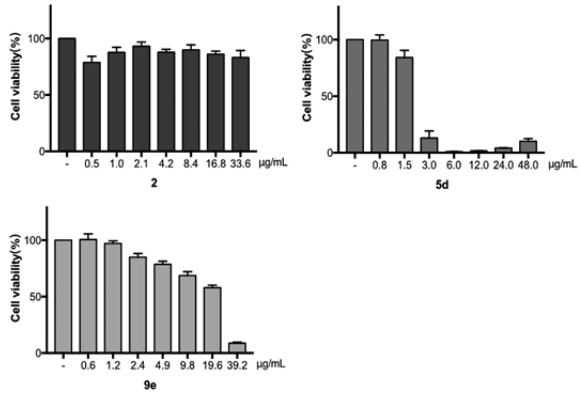

Figure 3. Cytotoxic effects of compounds **2**, **5d**, and **9e** on A549 cells. Following pretreatment with compounds **2**, **5d**, and **9e** at the indicated concentrations for 24 h, the cell viability of A549 cells were determined by MTT assay. Control cells were treated with 0.4% (v/v) DMSO.

CC_{50} value over 33.6 μg/mL, while compound **9e** demonstrated the moderate cytotoxicity with a CC_{50} of 16.1 μg/mL, much lower than that of compound **5d** of 2.0 μg/mL. The quaternary ammonium structure at the 6-position in compound **9e** made itself not easy to traverse the cellular membrane;[20] therefore, compound **9e** showed a moderate selectivity toward bacteria versus cells with the MIC values of 2−4 μg/mL.

In order to further understand the mechanism of action of this kind of compounds, the preliminary mechanism of action of the representative compound **9e** was carried out. Based on its plane rigid structure, we speculated that this kind of compounds might act upon microorganisms by intercalating into DNA of bacteria.[21] Therefore, the activity of compound **9e** toward supercoiled pET-32a (bacterial expression vector) DNA was conducted under physiological conditions (4 h, 37 °C) using agarose gel electrophoresis (GE). As shown in Figure 4, a strong dependence on the concentration (lanes 2−5), converting pET-32a DNA from CCC form (Form I) into open circular form (OC, Form II), could be detected on their cleaving activity. This result indicated that compound **9e** acted upon bacteria partly through catalyzing the cleavage of bacterial DNA. Furthermore, compound **9e** exerted the potent

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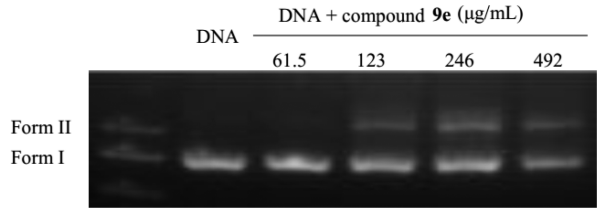

Figure 4. Agarose GE patterns for the cleavage of pET-32a DNA by compound **9e** of increasing concentrations at 37 °C (4 h).

antibacterial activity with MIC values of 2−4 μg/mL, possibly due to other antibacterial mechanisms of this kind of compounds.[22−24]

Twenty-three new 8-substituted CBBR derivatives with a unique chemical scaffold were synthesized and examined for their activity against Gram-positive bacteria including MRSA and VISA. SAR revealed that a suitable substituent at the 8-position could greatly enhance the antibacterial potency. Among them, compounds **5d** and **9e** exhibited potent activities against all tested drug-susceptible and drug-resistant strains with MICs ranging from 2 to 4 μg/mL, suggesting a possible novel mechanism of action against bacteria. Moreover, compound **9e** showed much better stability in whole blood than that of lead **2**. A preliminary mechanism study indicated that compound **9e** acted upon bacteria partly through catalyzing the cleavage of bacterial DNA. Therefore, we consider 8-substituted CBBR derivatives to be a promising class of anti-MRSA agents, and compound **9e** has been chosen for the further investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.8b00094.

Synthetic procedures, analytical data, and antibacterial and cytotoxic assays (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*Tel: +86 10 63033012. Fax: +86 10 63165268. E-mail: liyinghong@imb.pumc.edu.cn.

*Tel: +86 10 63165268. Fax: +86 10 63165268. E-mail: songdanqing@imb.pumc.edu.cn.

ORCID

Danqing Song: 0000-0002-2557-5009

Author Contributions

†T.F. and X.H. contributed equally.

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

MRSA, methicillin-resistant *S. aureus*; VISA, vancomycin-intermediate *S. aureus*; MSSE, methicillin-susceptible *S. epidermidis*

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