A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Sulfonium, an underestimated moiety for structural modification, alters antibacterial profile of vancomycin against multidrug-resistant bacteria

Authors: Dongliang Guan, Feifei Chen, Yunguang Qiu, Bofeng Jiang, Likun Gong, Lefu Lan, and wei huang

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201902210
Angew. Chem. 10.1002/ange.201902210

Link to VoR: http://dx.doi.org/10.1002/anie.201902210
http://dx.doi.org/10.1002/ange.201902210

WILEY-VCH

10.1002/anie.201902210

WILEY-VCH

COMMUNICATION

Sulfonium, an underestimated moiety for structural modification, alters antibacterial profile of vancomycin against multidrug-resistant bacteria

Dongliang Guan[a,b], Feifei Chen[a], Yunguang Qiu[a,b], Bofeng Jiang[a], Likun Gong[a], Lefu Lan[a,b]*, Wei Huang[a,b]*

Abstract: In the antibiotics arsenal, vancomycin was no doubt the last resort to treat the intractable infections clinically. However, this situation is under grave menace because of the increasing appearance of vancomycin-resistant bacteria (VRB). Herein, we reported a series of novel vancomycin derivatives carrying a sulfonium moiety, which was an underestimated modification in previous studies and rarely reported in literature. The sulfonium-vancomycin analogues exhibited enhanced antibacterial activity against VRB both *in vitro* and *in vivo* potently. More interestingly, sulfonium can alter the innate feature of vancomycin and tune its antibacterial activity against Gram-negative bacteria. The mechanism studies illustrated that sulfonium modification enhances the interaction of vancomycin with bacteria cell membrane and disrupts membrane integrity. In addition, *in vivo* pharmacokinetic profile, stability, and toxicity of these derivatives demonstrated good druggability of sulfonium modification. This work provides a promising strategy for combating drug-resistant bacterial infection, and also advances the knowledge on sulfonium derivatives for structural optimization and drug development.

Multidrug-resistant bacterial infection has become a life-threatening disease for human health worldwide[1]. Among them, resistant Gram-positive *Enterococcus faecium* and *Staphylococcus aureus* are listed as high priority for new treatments in "ESKAPE pathogens" and in "the list of drug-resistant bacteria" released by WHO recently[2]. Vancomycin was awarded as "the last resort" against Gram-positive bacteria especially for methicillin-resistant *Staphylococcus aureus* (MRSA)[3-5]. However, after over 50-year clinic medication, vancomycin-resistant bacteria including vancomycin resistant *S. aureus* (VRSA) and *Enterococci* (VRE) have emerged and become new challenges in anti-infective treatment[6]. To tackle the bacterial resistance, various modification strategies have been applied to novel vancomycin derivatives, such as lipophilic modification on vancosamine[7], ligand binding enhancement[8], attachment of membrane disruption fragments[8c, 9], pyrophosphate-targeting designs[10], vancomycin core-structure modification by total synthesis[9e, 11], etc. Recently, a combined modification of lipophilic and cationic motifs on vancomycin has been used to enhance the permeability towards bacterial membrane, including vancomycin derivatives carrying C-terminal lipophilic quaternary ammonium moieties from Halder group[9d] and carrying lysine-rich lipo-peptides from Cooper group[9f]. The concept of the lipo-cation modification is that the lipid penetrates into the bilayer of bacterial cell membrane and the cation interacts with the negative charge of phospholipids, resulting in membrane destruction of bacteria[9][12]. Ammonium, a common moiety of positive charge for chemical modification, is widely used in structural optimization during drug discovery and development. However, for glycopeptide antibiotics, it was reported that the ammonium-based positive charge on vancomycin may lead to low urinary clearance and high accumulation in liver and kidney[13]. In the case of lipopeptide antibiotics such as polymyxin, it consists of a multi-ammonium structure, which is the major cause of its nephrotoxicity.[14]

Sulfonium, as a cationic moiety, is largely underestimated in structural optimization for drug development and is rarely reported. In fact, sulfonium occurs naturally in plants[15], animals[16], and also in therapeutic reagents such as adenosylmethionine[16, 17], bleomycin[18], and modified-echinomycin[19]. In a comparison study, alkylsulfonium compounds indicated less toxic than their ammonium and phosphonium analogues[20]. On the other hand, the stability property, pharmacokinetic profile, and safety evaluation on sulfonium compounds is still ambiguous, which limits its wide application in medicinal chemistry. Herein, for the first time we designed and synthesized a series of sulfonium-containing vancomycin analogues, which exhibited enhanced antibacterial activities against drug-resistant MRSA, VISA, VRE, and even certain Gram-negative bacteria. Furthermore, stability, pharmacokinetic, and safety assays of these derivatives were also investigated.

We designed a series of sulfonium-vancomycin derivatives by assembly of sulfonium moiety on four peripheral positions of vancomycin at resorcinol (**5a-k**), vancosamine (**8a-g** and **11a-d**), C-terminal (**13a-g**), and N-terminal (**15a-b**) respectively (Scheme 1, Scheme S1-S4). We employed a regioselective reaction between an epoxide and a methylthio group to synthesize the sulfonium as previous reported for methionine modification on proteins[21]. The resulted beta-hydroxyl sulfonium indicated better stability based on the energy computation (Table S8, Figure S6). In a general procedure, a methylthio group was loaded onto these four modification sites via Mannich reaction, reductive amination, or amide condensation, followed by S-alkylation with various

[a] D. Guan, F. Chen, Y. Qiu, B. Jiang, Prof. Dr. L. Lan, Prof. Dr. W. Huang
CAS Key Laboratory of Receptor Research, CAS Center for Excellence in Molecular Cell Science, Center for Biotherapeutics Discovery Research
Shanghai Institute of Materia Medica, Chinese Academy of Sciences
555 Zuchongzhi Road, Pudong, Shanghai, China 201203
E-mail: huangwei@simm.ac.cn
llan@simm.ac.cn

[b] D. Guan, Y. Qiu, Prof. Dr. L. Lan, Prof. Dr. W. Huang
Department
University of Chinese Academy of Sciences
No.19A Yuquan Road, Beijing 100049, China

Supporting information for this article is given via a link at the end of the document.

Accepted Manuscript

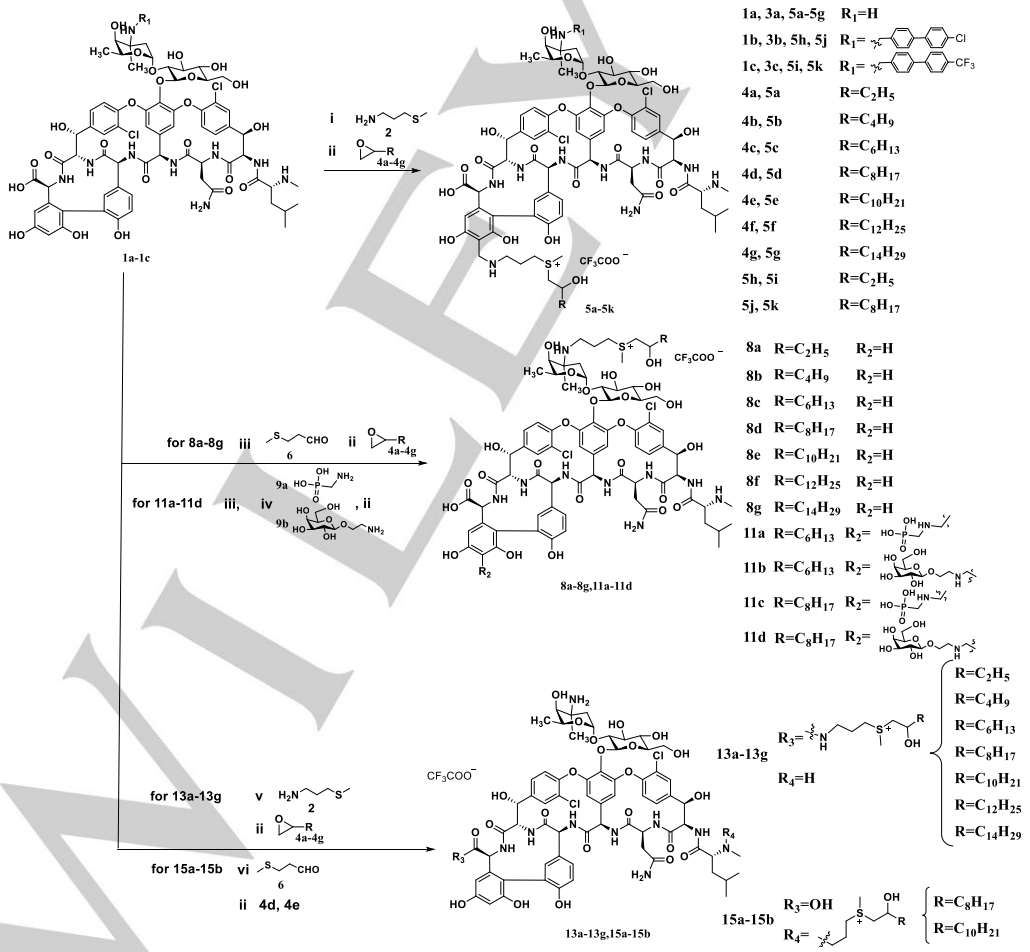
This article is protected by copyright. All rights reserved.

10.1002/anie.201902210

lipophilic epoxides to achieve corresponding lipo-sulfonium derivatives. Beside single-site modification, we also prepared dual-site derivatives including compounds **5h-k**, (combined modification of sulfonium on resorcinol and biphenyl on vancosamine) and compounds **11a-d** (combined modification of sulfonium on vancosamine and extra sugar or phosphonate on resorcinol). For comparison purpose, corresponding thioether (**16**, **17**, Scheme S7) and ammonium (**18**, **19**, Scheme S8) compounds were synthesized as control groups to explore the unique features of sulfonium moiety.

Then, we sought to investigate how sulfonium modification may affect the *in vitro* and *in vivo* antibacterial efficacy, pharmacokinetic profile, toxicity, and mechanism of action. Table 1 summarized the *in vitro* antibacterial activities of the optimal analogues against various drug-resistant Gram-positive bacteria including MSSA, VISA (MRSA), VRE strains (more details in Table S1-S4). These data clearly demonstrated that lipo-sulfonium modification strategy dramatically alters the antibacterial profile of vancomycin with up to more than 2048-fold enhanced activity against certain strains. The structure-activity relationship (SAR) analysis revealed that: (1) the optimal modification positions of sulfonium on vancomycin were resorcinol or vancosamine rather than C-terminus or N-terminus (**5**/**8** vs **13**/**15**); (2) dual-site modification (**5h-k**/**11a-d**) does not show further advantage in enhanced activity compared with single-site modified derivatives; (3) length of S-lipophilic chains indicated importance in tuning of activity; For MSSA and VISA, C6-C8 carbon chains (**5d**/**8c**/**8d**) showed better activity. For VRE strains, longer chains of C10-C12 compounds (**5d-f**/**8d-f**) indicated the best activity with over 512 to 2048-fold enhanced activity than vancomycin; (4) compared to thioether and ammonium derivatives (**16-19**), sulfonium compounds (**5d**/**8c**/**13d**) indicated better activity especially for VRE with up to 32-fold enhancement.

Furthermore, we chose **5d** and **8c** to test their activities against 49 strains of 8 types of clinically isolated Gram-positive bacteria, including *S. aureus*, *S. epidermidis*, *E. faecium*, *E. faecalis*, and *S. Pneumoniae* (Table S3). Overall, these two sulfonium derivatives indicated excellent antibacterial activity (MIC 0.03-0.06 ug/mL for most strains) compared with vancomycin (MIC 1-2 ug/mL). Compare to Telavancin or Oritavancin, **5d** and **8c** also demonstrated 2-32 fold enhanced activity against *S. aureus*, *S. epidermidis*, and *S. Pneumoniae*, and comparable activity against *E. faecium* and *E. faecalis*.



Scheme 1. Reagents and conditions: (i) HCHO, DIPEA, H_2O:MeCN=1:1,-10˚C, 12h; (ii) AcOH, 37˚C, 24h; (iii) a, DIPEA, DMF, 50˚C, 1.5h; b, NaCNBH3, TFA, MeOH, r.t, 1h; (iv) HCHO, DIPEA, H_2O:MeCN=1:1, -10˚C, 12h; (v) HATU, DIPEA, DMSO:DMF=1:1, r.t., 2h; (vi) $NaCNBH_3$, H_2O: ACN: AcOH =2:2:1, r.t., 48h.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

Table 1. *In vitro* Activities of Vancomycin Derivatives against MSSA, VISA and VRE*.

Compound	MIC(μg/mL)				
	MSSA[a]	VISA[b]	VRE(VanA)[c]	VRE(VanM)[d]	VRE(VanB)[e]
5d	⩽0.0625	0.25	8	2	≤0.0625
5e	0.25	0.5	2	1	≤0.0625
5f	4	2	1	0.125	0.5
8c	⩽0.0625	0.25	2	0.25	1
8d	⩽0.0625	0.125	2	0.25	≤0.0625
8e	0.5	2	0.5	0.25	0.25
8f	4	2	0.25	0.125	0.25
13d	0.125	1	16	2	8
13e	0.5	1	8	4	8
15b	1	2	32	2	1
16	⩽0.0625	0.5	16	8	32
17	⩽0.0625	0.25	8	8	≤0.0625
18	⩽0.0625	0.5	16	8	≤0.0625
19	0.5	2	16	2	16
Vancomycin	2	8	>128	>128	>128
Telavancin	0.25	2	8	8	≤0.0625

*Strains used: [a] MSSA (Methicillin-susceptible *S. aureus*): Newman strain, ATCC 25904; [b] VISA (vancomycin intermediate resistant *S. aureus*): Mu 50, a Healthcare associated MRSA isolated in Japan; [c] VRE (VanA phenoype): Efm-HS-0649, Glycopeptide-resistant *E.faecium*, isolated in China; [d] VRE (VanM phenoype): Efm-HS-08257, Glycopeptide-resistant *E.faecium*, isolated in China; [e] VRE (VanB phenoype): Van B(R), Glycopeptide-resistant *E.faecium*.

Table 2. *In vitro Antibacterial Activity against 5 Types of Gram-negative Bacteria**

Compound	MIC(μg/mL)				
	Eco[a]	Kpo[b]	Aba[c]	Pae[d]	Mca[e]
5f	8	>16	4-8	>16	0.25-0.5
Polymyxin B	0.06-1	2-4	0.06	0.25-0.5	32-64
Vancomycin[r]	>100	>100	>100	>100	resistant

*[a] Eco, *E. coli*, 5 strains; [b] Kpn, *K. pneumoniae*, 3 strains; [c] Aba, *A. baumannii*, 3 strains; [d] Pae, *P. aeruginosa*, 4 strains; [e] Mca, *M. catarrhalis*, 2 strains; [r], date from literature report.

Lipo-ammonium complex in polymyxin[22] and vancomycin derivatives[23] was reported with antibacterial activity against Gram-negative bacteria by disrupting the outer membrane. To investigate whether lipo-sulfonium moiety could achieve similar effect, we examined their antibacterial activity against *E. coli* and *P. aeruginosa* (Table S4). Compounds **5d-g** indicated moderate activity against *E. coli*. The optimal compound **5f** was assessed on its activity against 17 strains of 5 types of clinically isolated Gram-negative bacteria, including *E. coli*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *M. catarrhalis* (Table 2). Interestingly, **5f** exhibited moderate activity against *E. coli* and *A. baumannii*, but very potent antibacterial effect against *M. catarrhalis* with even 128-fold enhanced activity than polymyxin B. These data clearly demonstrated that sulfonium modification significantly alters the antibacterial profiles of vancomycin with enhanced activity and a broader spectrum.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/anie.201902210

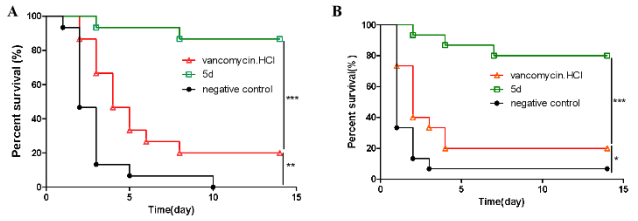


Figure 1. *In vivo* lethal challenge assay of **5d** on infected mice models. Survival rates of mice (15 mice each group) infected by (panel A) USA400 MW2 (MRSA) and (panel B) XN108 (VISA) were recorded after treatment with 5d or vancomycin at a single dose of 7 mg/kg (A) or 14 mg/kg (B) via i.v. injection at the first day of infection. Statistical significance determined by the log-rank (Mantel-Cox) test: **p < 0.01, *** p < 0.001.

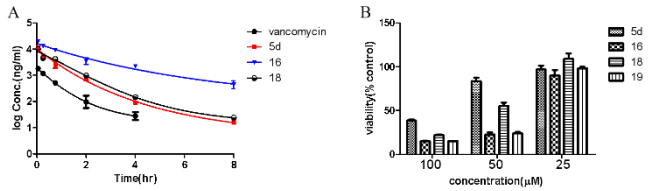


Figure 2. Panel A: Single-dose (5 mg/kg) concentration-versus-time pharmacokinetic profiles of **5d**, **16**, **18**, and vancomycin in CD-1 mice. The abscissa shows the time and the ordinate shows the plasma drug concentration (Conc.) (n=3 per group). Panel B: Cytotoxicity assays of compounds **5d**, **16**, **18**, **19** on HK-2 cell line (human renal proximal tubule epithelial cells).

The *in vivo* efficacy was tested *via* a lethal challenge assay of mice infected with the MRSA strain USA400 MW2 or VISA strain XN108 respectively. As shown in Fig. 1, the survival rates of the **5d** group were 86.7% for USA400 infection and 80% for XN108 infection, much higher than those of vancomycin group (20%). These results verified the enhanced antibacterial activity of sulfonium modification strategy.

Sulfonium modification was rarely used in previous research that could be partially due to the poor knowledge on druggable properties of sulfonium derivatives. Here, we sought to understand how sulfonium moiety affects pharmacokinetics, toxicity, stability, and mechanism of action of vancomycin derivatives. The *in vivo* pharmacokinetics of **5d** were tested on normal CD-1 mice, compared to **16** (thioether), **18** (ammonium), and vancomycin (Fig. 2A and Table S5). Sulfonium **5d** exhibited similar properties as ammonium **18**, with increased half-life and AUC compared to vancomycin but reduced half-life compared to thioether **16**, that may alleviate the accumulation toxicity as reported in other lipo-vancomycin derivatives[13]. The cytotoxicity assay was performed on HK-2 cell line since nephrotoxicity is the major safety concern of vancomycin-type antibiotics. The results (Fig. 2B) implicated that sulfonium **5d** was significantly less toxic than its thioether and ammonium analogues **16**, **18**, and **19** at 50 and 100 μM. These data demonstrated that sulfonium moiety is a good fragment for optimization of *in vivo* PK profile and toxicity.

Thereafter, we investigated the stability of the sulfonium derivatives. In an 8-day stability assay by incubation of **8c** in a phosphate buffer (pH 7.5) at 37 ºC (Table S6), the compound indicated excellent stability with an estimated half-life of 12.3 days. In another experiment of the antibacterial assay in a solution containing human serum albumin (HSA), the results implicated that binding with plasma protein (like HSA) does not significantly affect the MIC values of sulfonium **5d** and **8c** (Table S7).

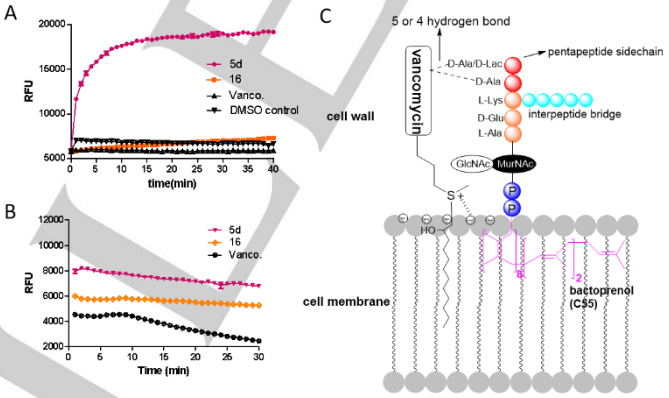


Figure 3. Elucidation on mechanism of action (MOA) of sulfonium-vancomycin derivatives against VRE. Panel A: cytoplasmic membrane permeability assay of vancomycin analogues at 10 μg/mL; Panel B: cytoplasmic membrane depolarization assay of vancomycin analogues at 21.5 μg/mL; Panel C: schematic diagram of proposed MOA for these novel sulfonium-vancomycin derivatives.

Nextly, to explore the mechanism of action (MOA) of these sulfonium derivatives, we tested membrane disruptive potential of compounds **5d**, **8c**, **13d**, **15b** and their thioether analogues **16** and **17** against VRE and MRSA (Fig. 3, S3-S5). Bacterial cytoplasmic membrane permeabilization and depolarization, as two types of mechanisms for disrupting membrane integrity, were measured. In membrane permeability assay, all tested sulfonium compounds exhibited better permeabilization than vancomycin and its thioether derivatives (Fig. 3A, S3, S4). The permeabilization of sulfonium compounds was concentration-dependent and **5d** indicated excellent activity even at a concentration as low as 5 ug/mL. In membrane depolarization assay, sulfonium derivatives also demonstrated enhanced effect on dissipating bacterial membrane potential at a higher level

Accepted Manuscript

This article is protected by copyright. All rights reserved.

compared to vancomycin and thioethers (Fig. 3B and S5). Based on these data, we proposed a possible MOA of lipo-sulfonium-vancomycin derivatives as shown in Fig. 3C. As the vancomycin skeleton approaches bacterial cell wall, sulfonium cationic ion interacts with the negative charges on bacterial membrane while the hydrophobic aliphatic tail inserts into the bilayer. The enhanced interaction between lipo-sulfonium moiety and membrane of vancomycin-resistant bacteria may result in disruption of membrane integrity and cell lysis, thus causing bacterial death.

In summary, we present a new strategy of sulfonium modification for vancomycin-based structure optimization, which alters the antibacterial profile of vancomycin against multi-drug resistant bacteria and demonstrates good druggable properties of pharmacokinetics, stability, toxicity, and MOA. This strategy represents a rational, effective, and promising design of sulfonium derivatives which was underestimated in medicinal chemistry. In a practical application, sulfonium-vancomycin compounds enable disruption of bacterial membrane to tackle the crisis of drug-resistant bacterial infection, including both Gram-positive and Gram-negative bacteria resistant to vancomycin. The optimal PK and safety property of sulfonium derivative also render it a prospective candidate for further development.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (NNSFC, No. 21572244, 21877116), National Science & Technology Major Project “Key New Drug Creation and Manufacturing Program” of China (No. 2018ZX09711002-006), and the Youth Innovation Promotion Association of CAS (No. 2017328). We thank Dr. Houchao Tao, Dr. Fei Zhao in ShanghaiTech University and Dr. Jingjing Shi in SIMM for their kind help in MS determination.

Keywords: sulfonium• vancomycin • antibacterial • multi-drug resistance bacteria

[1] a) C. International, *Antibiotic resistance threats in the United States*, 2013, **2013**. https://stacks.cdc.gov/view/cdc/20705.; b) D. M. Brogan, E. Mossialos, *Global. Health* **2016**, *12*, 8.

[2] a) J. N. Pendleton, S. P. Gorman, B. F. Gilmore, *Expert Rev. Anti-Infect. Ther.* **2013**, *11*, 297-308; b) C. Willyard, Nature 2017, 543, 15; c) L. B. Rice, *J. Infect. Dis.* **2008**, *197*, 1079-1081. d) B. Mat, K. A. Hansford, M. S. Butler, Z. Jia, A. E. Mark, M. A. Cooper, *ACS Infect. Dis.* **2018**, *4*, 715-735; e) M. S. Butler, M. A. T. Blaskovich, M. A. Cooper, *J. Antibiot.* **2016**, *70*, 3-24.

[3] D. Kahne, C. Leimkuhler, W. Lu, C. Walsh, *Chem. Rev.* **2005**, *105*, 425-448.

[4] a) M. P. Lechevalier, *Int. J. Syst. Bacteriol.* **1986**, *36*, 29-37; b) K. C. Nicolaou, C. N. C. Boddy, S. Bräse, N. Winssinger, *Angew. Chem. Int. Ed.* **1999**, *38*, 2096-2152; *Angew. Chem.* **1999**, *111*, 2230-2287; c) M. H. Mccormick, J. M. Mcguire, G. E. Pittenger, R. C. Pittenger, W. M. Stark, *Antibiot. Annu.* **1955**, *3*, 606.

[5] a) B. K. Hubbard, C. T. Walsh, *Angew. Chem. Int. Ed*. **2003**, *42*, 730-765; *Angew. Chem.* **2003**, *115*, 752-789.

[6] a) C. T. Walsh, S. L. Fisher, I. S. Park, M. Prahalad, Z. Wu, *Chem. Biol.* **1996**, *3*, 21-28; b) J. Pootoolal, J. Neu, G. D. Wright, *Annu. Rev. Pharmacol.* **2002**, *42*, 381-408; c) C. C. McComas, B. M. Crowley, D. L. Boger, *J. Am. Chem. Soc.* **2003**, *125*, 9314-9315.

[7] a) M. S. Butler, K. A. Hansford, M. A. T. Blaskovich, R. Halai, M. A. Cooper, *J. Antibiot.* **2014**, *67*, 631-644; b) G. G. Zhanel, D. Calic, F. Schweizer, S. Zelenitsky, H. Adam, P. R. S. Lagacé-Wiens, E. Rubinstein, A. S. Gin, D. J. Hoban, J. A. Karlowsky, *Drugs* **2010**, *70*, 859-886.

[8] a) V. Yarlagadda, M. M. Konai, G. B. Manjunath, C. Ghosh, J. Haldar, *J. Antibiot.* **2015**, *68*, 302-312; b) D. Guan, F. Chen, L. Xiong, F. Tang, Faridoon, Y. Qiu, N. Zhang, L. Gong, J. Li, L. Lan, W. Huang, *J. Med. Chem.* **2018**, *61*, 286-304; c) V. Yarlagadda, S. Samaddar, K. Paramanandham, B. R. Shome, J. Haldar, *Angew. Chem. Int. Ed.* **2015**, *54*, 13644-13649; *Angew. Chem.* **2015**, *127*, 13848-13853.

[9] a) O. Domenech, G. Francius, P. M. Tulkens, F. Van Bambeke, Y. Dufrêne, M.-P. Mingeot-Leclercq, *Biochim. Biophys. Acta, Biomembr.* **2009**, *1788*, 1832-1840; b) D. L. Higgins, R. Chang, D. V. Debabov, J. Leung, T. Wu, K. M. Krause, E. Sandvik, J. M. Hubbard, K. Kaniga, D. E. Schmidt, Q. Gao, R. T. Cass, D. E. Karr, B. M. Benton, P. P. Humphrey, *Antimicrob. Agents Chemother.* **2005**, *49*, 1127-1134; c) G. A. McKay, S. Beaulieu, F. F. Arhin, A. Belley, I. Sarmiento, J. T. Parr, G. Moeck, *J. Antimicrob. Chemother.* **2009**, *63*, 1191-1199; d) V. Yarlagadda, P. Akkapeddi, G. B. Manjunath, J. Haldar, *J. Med. Chem.* **2014**, *57*, 4558-4568; e) A. Okano, N. A. Isley, D. L. Boger, *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114*, 5052-5061; f) M. A. T. Blaskovich, K. A. Hansford, Y. Gong, M. S. Butler, C. Muldoon, J. X. Huang, S. Ramu, A. B. Silva, M. Cheng, A. M. Kavanagh, Z. Ziora, R. Premraj, F. Lindahl, T. A. Bradford, J. C. Lee, T. Karoli, R. Pelingon, D. J. Edwards, M. Amado, A. G. Elliott, W. Phetsang, N. H. Daud, J. E. Deecke, H. E. Sidjabat, S. Ramaologa, J. Zuegg, J. R. Betley, A. P. G. Beevers, R. A. G. Smith, J. A. Roberts, D. L. Paterson, M. A. Cooper, *Nat. Commun.* **2018**, *9*, 22.

[10] a) V. Yarlagadda, P. Sarkar, S. Samaddar, J. Haldar, *Angew. Chem. Int. Ed.* **2016**, *55*, 7836-7840; *Angew. Chem.* **2016**, *128*, 7967-7971; b) D. Guan, F. Chen, Faridoon, J. Liu, J. Li, L. Lan, W. Huang, *ChemMedChem* **2018**, *13*, 1644-1657.

[11] A. Okano, A. Nakayama, A. W. Schammel, D. L. Boger, *J. Am. Chem. Soc.* **2014**, *136*, 13522-13525.

[12] F. Van Bambeke, M.-P. Mingeot-Leclercq, M. J. Struelens, P. M. Tulkens, *Trends Pharmacol. Sci* **2008**, *29*, 124-134.

[13] M. R. Leadbetter, S. M. Adams, B. Bazzini, P. R. Fatheree, D. E. Karr, K. M. Krause, B. M. Lam, M. S. Linsell, M. B. Nodwell, J. L. Pace, *J. Antibiot.* **2004**, *57*, 326-336.

[14] Z. Ma, J. Wang, R. L. Nation, J. Li, J. D. Turnidge, K. Coulthard, R. W. Milne, *Antimicrob. Agents. Ch* **2009**, *53*, 2857-2864.

[15] D. Rhodes, A. Hanson, *Annu. Rev. Plant Biol.* **1993**, 44, 357-384.

[16] G. L. Cantoni, *J. Am. Chem. Soc.* **1952**, *74*, 2942-2943.

[17] Q. M. Anstee, C. P. Day, *J. Hepatol.* **2012**, *57*, 1097-1109.

[18] J. Chen, J. Stubbe, *Nat. Rev. Cancer* **2005**, *5*, 102.

[19] Y. S. Park, Y. H. Kim, S. K. Kim, S.-J. Choi, *Bioorg. Med. Chem. Lett* **1998**, *8*, 731-734.

[20] M. Hirayama, *Biocontrol Sci.* **2011**, *16*, 23-31.

[21] E. G. Gharakhanian, T. J. Deming, *Biomacromolecules* **2015**, *16*, 1802-1806.

[22] F. Rabanal, Y. Cajal, *Nat. Prod. Rep.* **2017**, *34*, 886-908.

[23] V. Yarlagadda, G. B. Manjunath, P. Sarkar, P. Akkapeddi, K. Paramanandham, B. R. Shome, R. Ravikumar, J. Haldar, *ACS Infect. Dis.* **2016**, *2*, 132-139.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

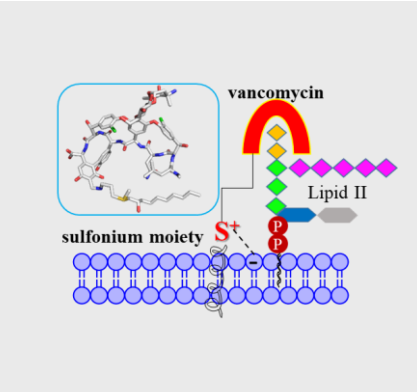
10.1002/anie.201902210

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

COMMUNICATION

Sulfonium moiety was modified onto vancomycin, which enhanced the antibacterial activity against vancomycin-resistant bacteria *in vitro* and *in vivo* potently. The further evaluation including toxicity, stability, PK and MOA demonstrated the good druggability of these sulfonium derivatives. This strategy is beneficial for combating drug-resistant bacterial infection, and also advances the knowledge on sulfonium derivatives for drug development.



Dongliang Guan, Feifei Chen, Yunguang Qiu, Bofeng Jiang, Likun Gong, Lefu Lan, Wei Huang**

Page No. – Page No.

Sulfonium, an underestimated moiety for structural modification, alters antibacterial profile of vancomycin against multidrug-resistant bacteria

WILEY-VCH

Accepted Manuscript

This article is protected by copyright. All rights reserved.