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A new class of anti-MRSA and anti-VRE agents: Preparation and antibacterial activities of indole-containing compounds

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Abstract—A new class of indole-containing compounds were prepared by the use of three component reaction and their in vitro antibacterial activities (MIC) were evaluated against *Staphylococcus aureus* and *Enterococcus faecium* including MRSA and VRE.

Drug-resistant Gram-positive bacterial pathogens including methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VRE) have caused serious chemotherapeutic problem in hospitals.[1] Thus, new anti-MRSA and anti-VRE agents are strongly sought and research on the agents has been carried out in the recent decade.

In the course of our research to find the new antibacterial agents, we were interested in the indole-containing compounds, because some indole-containing compounds were known to have antibacterial activities.[2] Screening of indole-containing compounds in our compound collection led to identification of **1** (Fig. 1) as an antibacterial agent, which was inactive against Gram-negative bacteria but active against Gram-positive bacteria including MRSA and VRE. We therefore started the preparation of the analogs of compound **1** to investigate the structure activity relationship (SAR) and to improve the antibacterial activities against Gram-positive bacteria. In this paper, we describe the preparation of the indole-containing compounds and antibacterial activity of these compounds.

Indole-containing compounds were prepared from coumarine or quinolone I, aldehydes II, and indole derivatives III in acetic acid in the same manner as described in Ref. 3 (Scheme 1). The pyrone-containing compound **6** was prepared from 4-hydroxy-6-methyl-2-pyrone, 3-bromo-benzaldehyde, and 2-(1*H*-indol-3-yl)-ethyl 2-methoxy-benzoate.[4] Compound **7** was prepared from 4-hydroxycoumarine, 5-bromo-pyridine-3-carbaldehyde, and 2-(1*H*-indol-3-yl)-ethyl 2-methoxy-benzoate. And compound **23** was prepared from 6-chloro-4-hydroxy-coumarine, 4-trifluoromethoxy-benzaldehyde, and 2-(1*H*-indol-3-yl)-ethyl benzoate. The synthetic yields and MS analysis data of compounds **2**–**33** are also shown in Scheme 1. Antibacterial activity of these compounds was evaluated in vitro against Gram-positive bacteria with vancomycin (VCM) and linezolid[5] as the reference compounds. Minimum inhibitory concentrations (MICs) were determined by an agar dilution method according to the recommendation in the National Committee for Clinical Laboratory Standards.[6]

At the beginning of our research, we designed and prepared the diversified analogs of compound **1** to obtain its SAR information. Antibacterial activity of compounds **2**, **3**, **4**, **6**, **7**, **8**, **10**, **11**, and **12** was weaker than that of compound **1** (Table 1). A difference in antibacterial activity between 2-methoxybenzoate analog and benzoate analog (**1** vs **5** and **8** vs **9**) was observed (Table 1).

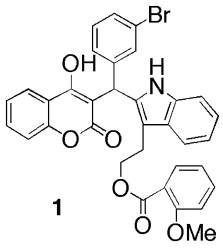

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Figure 1. Structure of a new antibacterial agent **1**.

Keywords: MRSA; VRE; Indole-containing compounds.
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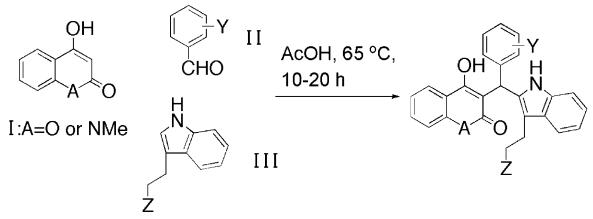
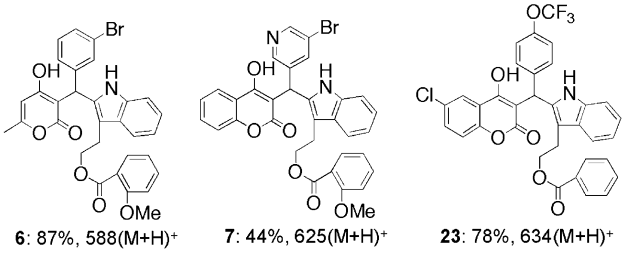


compound	yield, MS(m/z)
2: A=O, Y=3-Br, Z=NHC(O)–(2-MeO-Ph)	90%, 622(M+H)$^+$
3: A=O, Y=3-Br, Z=NHAc	53%, 529(M+H)$^+$
4: A=O, Y=3-Br, Z=OAc	69%, 531(M+H)$^+$
5: A=O, Y=3-Br, Z=OBz	85%, 593(M+H)$^+$
8: A=NMe, Y=3-Br, Z=OC(O)–(2-MeO-Ph)	93%, 636(M+H)$^+$
9: A=NMe, Y=3-Br, Z=OBz	87%, 606(M+H)$^+$
10: A=NMe, Y=3-Br, Z=OC(O)BzI	96%, 621(M+H)$^+$
11: A=NMe, Y=3-Br, Z=NHAc	94%, 543(M+H)$^+$
12: A=NMe, Y=3-Br, Z=OAc	60%, 544(M+H)$^+$
13: A=O, Y=H, Z=OBz	81%, 515(M+H)$^+$
14: A=O, Y=3-F, Z=OBz	98%, 533(M+H)$^+$
15: A=O, Y=3-Me, Z=OBz	97%, 592(M+H)$^+$
16: A=O, Y=3-CF_3, Z=OBz	85%, 584(M+H)$^+$
17: A=O, Y=4-Br, Z=OBz	62%, 545(M+H)$^+$
18: A=O, Y=4-SMe, Z=OBz	86%, 562(M+H)$^+$
19: A=O, Y=4-Me, Z=OBz	88%, 528(M-H)$^-$
20: A=O, Y=4-CF_3, Z=OBz	84%, 584(M+H)$^+$
21: A=O, Y=4-OMe, Z=OBz	87%, 593(M+H)$^+$
22: A=O, Y=4-OCF_3, Z=OBz	85%, 599(M+H)$^+$
24: A=NMe, Y=4-CF_3, Z=OBz	90%, 595(M-H)$^-$
25: A=NMe, Y=4-CF_3, Z=NHBz	82%, 594(M-H)$^-$
26: A=NMe, Y=4-CF_3, Z=OC(O)BzI	86%, 610(M+H)$^+$
27: A=NMe, Y=4-CF_3, Z=OC(O)–(Ph)	79%, 602(M+H)$^+$
28: A=NMe, Y=4-CF_3, Z=NHSO$_2$Ph	89%, 630(M-H)$^-$
29: A=NMe, Y=4-CF_3, Z=NHCON(Me)Ph	84%, 623(M-H)$^-$
30: A=NMe, Y=4-OCF_3, Z=OBz	82%, 612(M+H)$^+$
31: A=NMe, Y=4-OCF_3, Z=NHBz	87%, 612(M+H)$^+$
32: A=NMe, Y=4-OCF_3, Z=OC(O)BzI	82%, 627(M+H)$^+$
33: A=NMe, Y=4-OCF_3, Z=OC(O)–(Ph)	78%, 619(M+H)$^+$



Scheme 1.

Demethoxylation of 2-methoxy-benzoate in the side chain of compounds **1** and **8** was effective to improve antibacterial activity. Compound **9** did not exhibit anti-*E. faecium* activity, although the compound exhibited good anti-*S. aureus* activity. It was noteworthy that anti-MRSA activity of compound **9** was comparable to that of VCM.

In order to improve antibacterial activities of coumarine type compound **5**, we next investigated the substituent effect on the benzene ring derived from aldehyde II. Antibacterial activities of compounds **13**–**23** are shown in Table 2. Substituents at the *meta*-position, such as

Table 1. MICs (μg/ml) of compounds **1**–**12**

Compound	*S.a.*[a]	*S.a.*[b]	*E.f.*[c]	*E.f.*[d]
1	4	8	8	8
2	8	16	32	32
3	>128	>128	>128	>128
4	32	32	64	32
5	4	4	4	4
6	32	64	64	64
7	64	128	128	128
8	>128	>128	>128	>128
9	1	2	>128	>128
10	64	>128	>128	>128
11	32	32	>128	>128
12	16	16	64	32
VCM	0.5	2	1	>128
Linezolid	1	1	2	2

[a] Methicillin-susceptible *S. aureus* 209P.
[b] Methicillin-resistant *S. aureus* MF535.
[c] *E. faecium* ATCC19434.
[d] VCM-resistant [c]*E. faecium* VRA.

Table 2. MICs (μg/ml) of compounds **5** and **13**–**23**

Compound	*S.a.*[a]	*E.f.*[b]	*E.f.*[c]	*E.f.*[d]
5	4	4	4	4
13	8	8	16	16
14	4	8	8	8
15	8	8	8	4
16	4	4	2	1
17	2	2	2	2
18	4	8	4	4
19	4	4	8	8
20	2	2	2	2
21	8	8	16	16
22	2	2	0.5	0.5
23	2	2	1	1
VCM	0.5	2	1	>128
Linezolid	1	1	2	2

Strains: see Table 1.

hydrogen (unsubstituted) **13**, fluorine **14**, and methyl **15**, decreased the antibacterial activities moderately. On the other hand, *para*-bromo substituted analog **17** was more potent than the corresponding *meta*-bromo compound **5**. Among the *para* substituted analogs, compounds **20**, **22**, and **23** exhibited the best potency. Furthermore, compound **22** was much more active than linezolid (LZD) against *E. faecium* including VRE.

We sought the quinolone type compounds with anti-*E. faecium* activity and designed the new compounds. From the study of coumarine type compound, we selected both *para*-trifluoromethyl and *para*-trifluoromethoxy phenyl group and prepared the new analogs of quinolone type compound **9**. All the derivatives were highly active against *S. aureus*, except compounds **25** and **31** (Table 3). Anti-*E. faecium* activity of compounds **27**, **28**, **29**, and **33** was much more potent than that of compound **9**. Especially, anti-MRSA activities of compounds **27** and **29** were more potent than that of VCM, and anti-VRE activities of these compounds were superior to that of LZD.

Table 3. MICs (μg/ml) of compounds **9** and **24–33**

Compound	*S.a.*[a]	*S.a.*[b]	*E.f.*[c]	*E.f.*[d]
9	1	2	>128	>128
24	0.5	1	8	8
25	8	16	16	16
26	1	1	>128	>128
27	1	1	2	1
28	1	1	4	2
29	1	1	2	1
30	0.5	1	>128	>128
31	8	128	>128	>128
32	1	1	32	2
33	1	1	2	2
VCM	0.5	2	1	>128
Linezolid	1	1	2	2

Strains: see Table 1.

In conclusion, we found a new indole-containing antibacterial agent **1** and we prepared its analogs **2–33** by the use of three component reaction to improve antibacterial activities. We successfully developed compounds **22**, **27**, and **29** which were much more potent than hit compound **1**. It is a new example that the compounds synthesized by one-pot reaction exhibit good to excellent in vitro activities against *S. aureus* and *E. faecium* including MRSA and VRE.

References and notes

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4. Experimental procedure: 4-hydroxy-6-methyl-2-pyrone (0.25 mmol, 32 mg), 3-bromo-benzaldehyde (0.40 mmol, 74 mg), and 2-(1*H*-indol-3-yl)-ethyl 2-methoxy-benzoate (0.25 mmol, 74 mg) were added to the reaction vessel and suspended in acetic acid (3.0 ml). The mixture was stirred at 55 °C for 20 h. The reaction mixture was evaporated and the residual mixture was purified by silica gel thin layer chromatography (chloroform/methanol 30:1) to provide 119 mg (0.202 mmol) of compound **6**.
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