Bioorganic & Medicinal Chemistry Letters 21 (2011) 1728–1730

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Antibacterial activities of imidazolium, pyrrolidinium and piperidinium salts

Noritaka Iwai *, Kyosuke Nakayama, Tomoya Kitazume *

Graduate School of Bioscience and Bioengineering, Tokyo Institute of Technology, 4259 Nagatsuta, Midori-ku, Yokohama 226-8501, Japan

ARTICLE INFO

Article history:
Received 29 November 2010
Revised 17 January 2011
Accepted 19 January 2011
Available online 31 January 2011

Keywords:
Antibacterial activity
Gram-positive bacteria
Two-component system
Ionic liquid

ABSTRACT

The antibacterial activity of various types of imidazolium, pyrrolidinium and piperidinium salts with both propargyl group and alkyl and/or silylalkyl chains of different lengths, are described. Especially, the MIC (μg/ml) of prepared each compound for *Escherichia coli* and other several bacteria was determined.

The development of multi-drug-resistant pathogens has become a serious problem in the chemotherapy of bacterial infections diseases. One of the strategies to overcome this problem is to find a new drug with a new molecular target. Recently, two-component systems are proposed as a new target against drug-resistant bacteria.[1,2] Particularly, *yycG*(*walK*)–*yycF*(*walR*) two-component system is essential and conserved among low G+C Gram-positive pathogen bacteria. In the study of two-component systems, it is known that some kinds of 1-alkyl-2-methy-3-benzylimidazolium salts inhibit the alginate gene activation in *Pseudomonas aeruginosa*[3] and/or histidine protein kinase of *Bacillus subtilis*,[4,5] and that the ionic liquid derived from the antifungal drug miconazole has been prepared.[6] Further, a series of 3-alkoxymethyl-1-methylimidazolium salts have been investigated for antimicrobial activities against *cocci*, *rods* and *fungi*.[7] Based on the results of reported minimum inhibitory concentration (MIC) values, the most active salts against *cocci* and *rods* have an alkoxy group which contains 12 or 14 carbon atoms.[7] However, activity against *fungi* is significantly different result indicating that no optimum activity is clear with the carbon length. These results showed the capability of ionic liquid structure for antibacterial activity, especially for bacterial two-component systems inhibitor. But more details about structure–activity relationships are desired. Furthermore, the emergence and spread of multi-drug-resistant bacteria present a need for new antibiotics with innovative mode of action.[8,9] Consequently, novel approaches for new antibiotics with innovative mode of action are urgently required.

In this Letter, we would like to describe the antibacterial activity of various types of imidazolium, pyrrolidinium and piperidinium salts with propargyl group instead of benzyl group which had the specific activity against Gram-positive bacteria.

Minimal inhibitory concentrations (MIC: μg/ml) of the compounds for several bacteria were determined by the agar-dilution method using Mueller Hinton Broth (Bexton Dickinson and Company, MD). The tested bacterial strains were *B. subtilis* 168, *Staphylococcus aureus* subsp., *aureus* NBRC 15035, *Escherichia coli* MG1655, *Pseudomonas putida* NBRC 14164. The antibacterial activities were determined based on the method of Japanese Society of Chemotherapy.

To study on the antibacterial activity of imidazolium derivatives, we have designed the several kinds of materials based on the 1-cetyl-2-methyl-3-benzylimidazolium iodide (NH125) reported to best derivative by Utsumi and his co-workers. Especially, we aimed at searching for the specific compounds which had the activity against only Gram-positive bacteria with the two-component systems in this study. We first have designed the structure with the electron rich group such as propargyl group instead of benzyl group on one side and alkyl and/or silylalkyl chains of different lengths on other side of the imidazole ring. In order to define the structure–activity relationship of the chain length of alkyl and/or silylalkyl groups on 3rd position of imidazole ring, the biological activities of 17 related compounds were examined.

From the results as shown in Table 1 (Scheme 1) compounds (entries **1**–**5**) showed antibacterial activities toward Gram-positive bacteria *B. subtilis* and *S. aureus* at a relatively low concentration, but those compounds showed similar antibacterial activity against Gram-negative bacteria *E. coli* like NH125. Thereto the compounds with carbon chain lengths of 14 and 16 carbon atoms (entries **6** and **7**) were effective against only Gram-positive bacterias on the basis

* Corresponding authors. Tel.: +81 45 924 5754; fax: +81 45 924 5780 (T.K.).
E-mail addresses: tkitazum@bio.titech.ac.jp, kitazume.t.aa@m.titiech.ac.jp (T. Kitazume).

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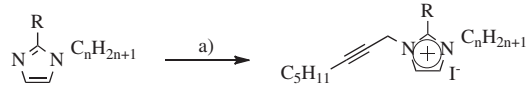
doi:10.1016/j.bmcl.2011.01.081

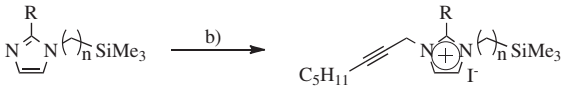
Table 1
Antibacterial activities of propargyl imidazolium derivatives with an alkyl group on 1st position of imidazolium ring (MIC: μg/ml)

Entry	*n*	R	*B. subtilis*	*S. aureus*	*E. coli*	*P. putida*
1	9	Me	0.78	0.78	12.5	50
2	10	Me	0.78	0.39	3.13	50
3	11	Me	0.39	0.39	3.13	50
4	12	H	0.39	0.39	25	50
5	12	Me	0.39	0.39	6.25	50
6	14	Me	0.78	0.78	100	>100
7	16	Me	1.56	1.56	>100	>100

NH125: *B. subtilis* (1.56), *E. coli* (3.13).[4,5]



Scheme 1. Reagents and conditions: (a) $C_5H_{11}{\equiv}CH_2Br$, KI, $CHCl_3$, reflux, 8 h.



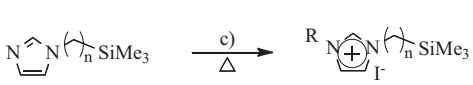
Scheme 2. Reagents and conditions: (b) $C_5H_{11}{\equiv}CH_2Br$, KI, $CHCl_3$, reflux.

Table 2
Antibacterial activities of propargyl imidazolium derivatives with a silylalkyl group on 1st position of imidazolium ring (MIC: μg/ml)

Entry	*n*	R	*B. subtilis*	*S. aureus*	*E. coli*	*P. putida*
8	4	H	1.56	3.13	50	100
9	4	Me	1.56	1.56	50	100
10	5	H	0.39	0.78	25	100
11	5	Me	0.39	0.39	12.5	50
12	6	Me	0.39	0.39	12.5	50
13	7	H	0.39	0.78	25	100
14	7	Me	0.39	0.39	12.5	100
15	9	H	0.39	0.78	100	>100
16	9	Me	0.39	0.78	100	100
17	11	Me	1.56	1.56	>100	>100

Table 4
Activity relationship with both substituted groups on 1st and 3rd positions (MIC: μg/ml)

Entry	R	*n*	*B. subtilis*	*S. aureus*	*E. coli*	*P. putida*
22	HC≡C	4	>100	100	>100	>100
23	C_8H_{17}	4	1.56	3.13	50	>100
24	Biphenyl	4	1.56	0.39	100	100
25	4-$C_5H_{11}C_6H_4$	4	0.39	0.39	50	100
26	4-$Me_3Si(CH_2)_2C_6H_4$	4	0.39	0.39	>100	100
27		5	0.78	0.78	>100	>100
28		6	1.56	1.56	>100	>100
29		7	1.56	1.56	>100	>100
30		9	6.25	>6.25	>100	>100

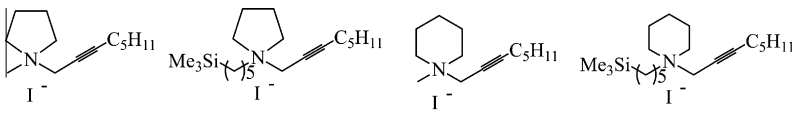


Scheme 4. Reagents and conditions: (c) RX, $CHCl_3$.

of the results in Table 1. These results suggest that the (3-pentyl)propargyl group instead of benzyl group was effective and specific for the activity bear comparison with the reported compound NH125.[4,5] In the next step, we have designed new types of imidazole compounds containing both (3-pentyl)propargyl group and silicone atom instead of carbon atom on the each side of the imidazole ring. All compounds (entries **8**–**17**) have remarkable effect for the bacterial activities against Gram-positive bacteria, and then some of them (entries **15**–**17**) showed the strong specificity. Furthermore, we have designed pyrrolidinium and piperidinium salts with (3-pentyl)propargyl group as shown in Scheme 3, but compounds (entries **18**–**21**) are not effective for the activity as shown in Table 3.

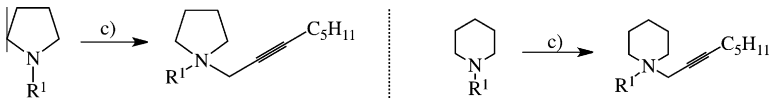
The results shown in Tables 1 and 2(scheme 2) are supports that the long alkyl chain on 1st position of imidazolium ring is an important factor for the specific antibiological activity against Gram-positive bacteria, and that imidazolium ring with methyl group on 2nd position is ineffective (e.g., entries **15** and **16**). Further, we have designed the several types of materials based on the molecular weight. Judging from the results shown in Table

Table 3
Antibacterial activities (MIC: μg/ml)



18 19 20 21

Entry	*B. subtilis*	*S. aureus*	*E. coli*	*P. putida*
18	>50	>50	>50	>50
19	1.56	1.56	>50	>50
20	>50	>50	>50	>50
21	1.56	1.56	50	100



Scheme 3. Reagents and conditions: (b) R^1X, KI, $CHCl_3$, reflux.

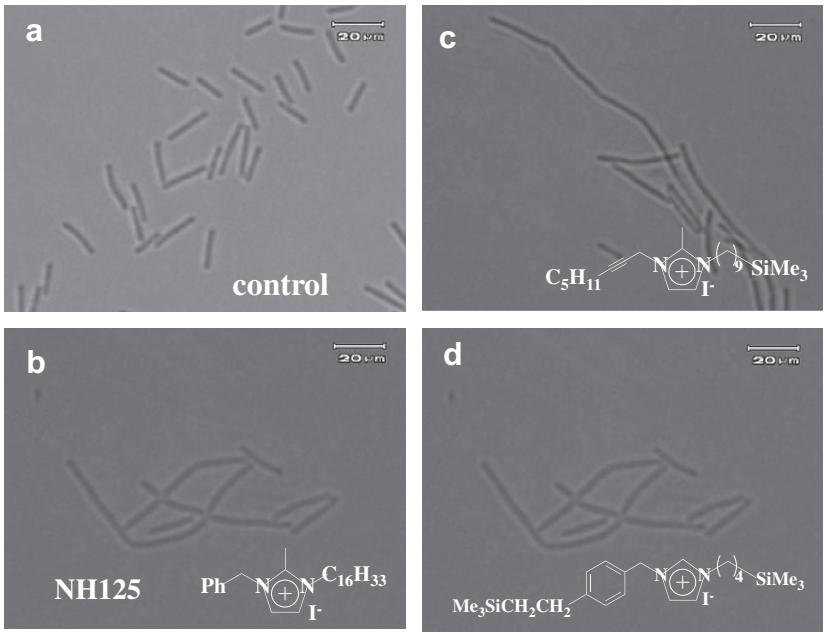


Figure 1. The effect of novel imidazolium salts on *B. subtilis* cell morphology. *B. subtilis* cells were treated with each compound in about three-fold concentration of MIC in Table after pregrowth to log-phase. Cell morphology was observed after 2 h from the treatment.

4(Scheme 4), total carbon chain length on the both sides of imidazole ring and molecular weight are important factors against the specific antibacterial activity of Gram-positive bacterias.

It is reported that the inhibition of *yycG yycF* Gram-positive specific two-component system leads the prevention of cell division in *B. subtilis*. Therefore, imidazolium derivatives were treated to *B. subtilis* cell, and cell morphology was confirmed. NH125 as a positive control led cell elongation through cell division inhibition (Fig. 1b). Compound entries 16 and **26** also led cell elongation, respectively (Fig. 1c and d). These results suggested that synthetic novel imidazolium derivatives shown antibacterial activity reason for the cell division inhibition and the target of these compounds was specific in Gram-positive low G−C bacteria possessed *yycG yycF* two-component system.

In conclusion, we have found that the (3-pentyl)propargyl group is effective for the activity bear comparison with benzyl group, and that silylalkyl group is also useful to generate the antibacterial activity of imidazole salts.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.01.081.

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