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Synergism of fused bicyclic 2-aminothiazolyl compounds with polymyxin B against *Klebsiella pneumoniae*†

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A series of fused bicyclic 2-aminothiazolyl compounds were synthesized and evaluated for their synergistic effects with polymyxin B (PB) against *Klebsiella pneumoniae* (SIPI-KPN-1712). Some of the synthesized compounds exhibited synergistic activity. When 4 $\mu\text{g ml}^{-1}$ compound **B1** was combined with PB, it showed potent antibacterial activity, achieving 64-fold reduction of the MIC of PB. Furthermore, compound **B1** showed prominent synergistic efficacy in both concentration gradient and time-kill curves *in vitro*. In addition, **B1** combined with PB also exhibited synergistic and partial synergistic effect against *E. coli* (ATCC25922 and its clinical isolates), *Acinetobacter baumannii* (ATCC19606 and its clinical isolates), and *Pseudomonas aeruginosa* (Pae-1399).

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Introduction

The misuse of antibiotics in clinical and non-clinical fields has led to the rapid emergence of widespread multi-drug resistant (MDR) pathogenic bacteria, especially ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*), which were highlighted by the Infectious Diseases Society of America.^{1–3} *Klebsiella pneumoniae*, as a representative of antibiotic-resistant Gram-negative bacteria, has caused many kinds of infections which threaten the global public health, including pneumonia, bloodstream infections, food-borne diseases, wound or surgical site infections and so on.^{4,5} More troubling, the high antimicrobial resistance rate of *Klebsiella* bacteria was observed for β -lactamase inhibitors and many other antibiotics, which has caused a serious problem, that is a variety of traditional antibiotics are not able to achieve a therapeutic effect.^{6–10}

This trend has driven the use of polymyxins as the ultimate weapon due to their effective antibacterial activity against MDR Gram-negative bacteria, such as *Acinetobacter baumannii*, *E. coli*, and *Klebsiella pneumoniae*.^{11–13} Polymyxins

are decapeptide antibiotics and mainly have five different types, polymyxin A–E. Among these polymyxins, polymyxin B (PB) is widely used. The only difference between polymyxin B and polymyxin E is that D-Leu (D-leucine) replaced the position of D-Phe (D-phenylalanine) in polymyxin B.¹⁴ PB can effectively treat some diseases caused by microorganisms, such as skin diseases in combination with B-bacitracin-neomycin, and it can also suppress the growth of *Enterobacteriaceae* when it is used in selective decontamination regimes.¹⁵ However, the use of PB in the clinical field is restricted on account of its nephrotoxicity and neurotoxicity. According to recent clinical studies, above 60% of patients have been found with polymyxin induced nephrotoxicity after intravenous administration. Therefore, the toxicity of polymyxins precludes the use of an appropriate dosage for the treatment of MDR Gram-negative infections, and even worse is that the inferior dosage may promote the emergence of polymyxin resistance.^{16,17} Thus, it is necessary to find new strategies to reduce the dose of polymyxin in order to make these antibiotics effective.

Combination therapies have been proposed as good options. Nowadays, the hot directions of combination therapies include combining two ‘old’ antibiotics, traditional antibiotics with natural products or peptide antibiotics,^{18,19} for instance, combining chloramphenicol with PB to synergistically kill NDM-producing MDR *Klebsiella pneumoniae* and combining curcumin with PB against MDR bacteria associated with traumatic wound infections.^{15,20,21} Another way of prolonging the life span of ineffective antibiotics is to employ adjuvants, which mainly include β -lactamase inhibitors, pump inhibitors, and outer membrane permeabilizers.^{22–24}

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Thiazole scaffolds are widely used in medicine, pesticides, fine chemicals and other fields due to their unique nitrogen, sulfur heterocyclic structure and wide bioactivities. In medicinal chemistry, many thiazole derivatives have shown effective activities in anti-inflammation,²⁵ anticancer,²⁶ anti-tuberculous,²⁷ anti-HIV²⁸ and anti-bacterial treatments.²⁹

Enlightened by all of the descriptions above, we tried to screen thiazole compounds synthesized in our group³⁰ and tested their synergistic activities with PB against *Klebsiella pneumoniae* (SIPI-KPN-1712). Luckily, we found that compound **1108** exhibited effective synergism with PB, achieving a 16-fold reduction of the MIC of PB against SIPI-KPN-1712. Then, we designed and synthesized three series of fused bicyclic 2-aminothiazolyl compound derivatives (A, B, C) on the basis of the structure of compound **1108** and studied their synergistic effects with PB against SIPI-KPN-1712 *in vitro* by evaluating the Minimum Inhibitory Concentration (MIC, the lowest concentration of a drug, preventing visible growth of a bacterium) and Fractional Inhibitory Concentration Index (FICI, the value for synergy prediction) (Fig. 1).

Results and discussion

Chemistry

Intermediate thioureas **5** were synthesized referring to the method by Rödl *et al.*³¹ As described in Scheme 1, benzoyl isothiocyanate **2** was prepared by the reaction of benzoyl chloride and KSCN in acetone at room temperature under inert atmosphere conditions, followed by the reaction with aniline derivatives **3** in ethyl acetate under reflux conditions to get compounds **4**. Finally, following the debenzoylation of **4**, intermediate thioureas **5** were obtained in 80–90% yield.

The synthesis of the target compounds **A** are outlined in Scheme 2a, according to the method by Liu *et al.*³⁰ The mixture of thioureas **5** and α,β -epoxycyclohexanone **6** in alcohol was heated under microwave irradiation to cyclocondense to get target compounds **A** in 70–90% yield. Meanwhile, target compounds **B** were obtained in moderate yields (60–75%) using the mixture of thioureas **5** and α,β -epoxycyclohexanone **6** in H₂O under reflux conditions, which is shown in Scheme 2b. Then, target compounds **C** were synthesized by a

route described by Yao *et al.*,³² as shown in Scheme 2c, and this method afforded compounds **C** in 70–90% yields. Compounds **C** could be obtained by a copper-catalyzed tandem reaction of 2-iodoaniline derivatives **7** with isothiocyanates **8** using CuSO₄ as a catalyst and Bu₃N as a base under ligand- and solvent-free conditions in air.

Synergistic activities with polymyxin B (PB) against *Klebsiella pneumoniae* and the SAR study

Antibacterial synergists combined with PB can be used for many Gram-negative bacteria. For example, curcumin combined with PB produced antimicrobial synergy against MDR bacteria, which are associated with traumatic wound infections, including *E. coli*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*.¹⁵ However, there is no reported synergistic compound combined with PB against *Klebsiella pneumoniae* available at present. So, we started our study further using compound **1108**.

To study the structure–activity relationships (SAR) preliminarily, 63 compounds of structure **A**, eight compounds of structure **B** and three compounds of structure **C** with different substituents at R₁ and R₂ were synthesized, and the synergistic effects between these compounds and PB against SIPI-KPN-1712 were studied by the determination of MICs and the calculation of FICIs, which are shown in Table 1. Firstly, every synthesized compound does not individually possess any antibacterial effects against the test isolated strain (MICs > 128 $\mu\text{g ml}^{-1}$), and the MIC of PB is 32 $\mu\text{g ml}^{-1}$ before the combination. When the synthesized compounds were combined with PB, the results showed that most of these compounds exhibited synergism or partial synergism with PB against SIPI-KPN-1712, and the MICs of PB ranged from 0.5 to 32 $\mu\text{g ml}^{-1}$. When we tried different groups at R₁ position, it was found that the aromatic heterocyclic (A32–A38, such as pyridine, thiazole, pyrimidine, quinoline and naphthalene), heterocyclic (A39) and benzylated (A40) compounds exhibited lower activity than their corresponding phenylated counterparts (A1–A31). Then, we focused on the effect of various substituents for benzene ring. As shown in Table 1, the activity data revealed that when the substituents were electron-

Fig. 1 Design strategy for the target thiazole compounds A–C.

Scheme 1 Synthesis of intermediates. (i) KSCN, acetone, Ar, r.t., 1 h; (ii) EA, reflux, 2 h; (iii) NaOH, EtOH, reflux, 2 h.

Scheme 2 Synthesis of compounds A–C. (i) $R_2\text{OH}$, MW, 15–30 min. (ii) H_2O , reflux, 12 h. (iii) CuSO_4 , Et_3N , 80°C , 5 h.

withdrawing groups (A1–A17), compounds exhibited better activity than the compounds bearing electron-donating groups (A18–A31). Further investigations were performed for compounds A1–A17, and we found that halogen groups on *para*-substituted compounds showed a clear preference for the potency among mono-substituted compounds. A1 and A3, *p*-Cl and *p*-CF₃ separately, reduced the MIC of PB to $1\ \mu\text{g ml}^{-1}$ and $8\ \mu\text{g ml}^{-1}$ respectively. Besides, when bis-substituted compounds contained at least one Cl group, the synergistic antibacterial activity was better than that of the others, such as A13, A15, and A16. Compound A13 exhibited the same synergism as compound A1. Then, we tried to introduce different substitution for the R_2 group including methyl, ethyl, linear alkanes, branched alkanes, cycloalkane and 1*H*-imidazole-1-carbonyl, but these substituents had no obvious influence on the synergistic effect. And then, when the R_2 group was replaced with H to generate structure B, it was inspiring that compound B1 (the substitution of *p*-Cl of benzene ring) can cause a 64-fold reduction of the MIC of PB to $0.5\ \mu\text{g ml}^{-1}$. However, changing tetrahydrobenzothiazole to benzothiazole (structure C) did not show any improvement in the synergism. Overall, the relationship between the structure and the synergistic activity exhibited that the 4-Cl-phenyl substitution at R_1 and the no substitution or alkyl substitution at R_2 for structure A and B were beneficial to the synergistic effect.

In order to further study the synergism of compound B1 with PB, we combined PB with different concentrations of B1

to investigate the changes in the MICs. As seen in Table 2, the MIC of PB alone is $32\ \mu\text{g ml}^{-1}$, and the MIC sharply decreased with the participation of B1. When it was combined with $4\ \mu\text{g ml}^{-1}$ of B1, an MIC of PB of $0.5\ \mu\text{g ml}^{-1}$ was achieved, indicating a 64-fold reduction. When the dosage of B1 was continuously increased, the MIC slightly decreased. The MICs of PB combined with $8\ \mu\text{g ml}^{-1}$ or $16\ \mu\text{g ml}^{-1}$ of compound B1 remained the same at $0.25\ \mu\text{g ml}^{-1}$, which is equal to 128-fold reduction.

As shown in Fig. 2, $4\ \mu\text{g ml}^{-1}$ of PB alone exhibited a strong bactericidal effect within 4 h, showing a decrease of $\geq 4\ \log\ \text{cfu ml}^{-1}$. Despite the great initial effect, significant bacterial regrowth was observed. Within 8 h, a regrowth of $\geq 1\ \log\ \text{cfu ml}^{-1}$ was observed, and the regrowth approached a higher amount than the original at 24 h. Meanwhile, $4\ \mu\text{g ml}^{-1}$ of B1 alone had no appreciable antibacterial activity against SIPI-KPN-1712, and its growth curve was similar to that of the no-drug control. When $4\ \mu\text{g ml}^{-1}$ of B1 was combined with $0.5\ \mu\text{g ml}^{-1}$ and $1\ \mu\text{g ml}^{-1}$ PB respectively, it showed a similar trend to that of PB alone. However, when an amount of PB was added up to $2\ \mu\text{g ml}^{-1}$, the antibacterial activity was markedly enhanced, and complete cell death was observed at 24 h. Besides, $4\ \mu\text{g ml}^{-1}$ of B1 combined with $4\ \mu\text{g ml}^{-1}$ of PB exhibited a complete inhibition of bacterial growth within 2 h, and no regrowth was observed at 24 h. These results suggested that this combination of both $4\ \mu\text{g ml}^{-1}$ of B1 and $2.0\ \mu\text{g ml}^{-1}$ or $4.0\ \mu\text{g ml}^{-1}$ PB produced synergistic bactericidal effects.

Table 1 The MICs and FICIs of PB combined with the compounds ($4 \mu\text{g ml}^{-1}$) against SIPI-KPN-1712

			SIPI-KPN-1712	
Compounds	R_1	R_2	MIC	FICI
Compound 1108	4-Br-phenyl	Me	2	0.09
A1	4-Cl-phenyl	Me	1	0.06
A2	4-I-phenyl	Me	16	0.53
A3	4- CF_3 -phenyl	Me	8	0.28
A4	4- NO_2 -phenyl	Me	16	0.53
A5	4-CN-phenyl	Me	16	0.53
A6	4- CH_3CONH -phenyl	Me	32	1.03
A7	3-Cl-phenyl	Me	8	0.28
A8	3-Br-phenyl	Me	16	0.53
A9	3-F-phenyl	Me	32	1.03
A10	3- CF_3 -phenyl	Me	16	0.53
A11	2-Cl-phenyl	Me	32	1.03
A12	2- CF_3 -phenyl	Me	16	0.53
A13	2,6-(Cl) $_2$ -phenyl	Me	1	0.06
A14	2,6-(F) $_2$ -phenyl	Me	32	1.03
A15	2-Cl-4- CF_3 -phenyl	Me	4	0.16
A16	2,4-(Cl) $_2$ -phenyl	Me	8	0.28
A17	3- CF_3 -4-CN-phenyl	Me	16	0.53
A18	Phenyl	Me	32	1.03
A19	4- CH_3 -phenyl	Me	16	0.53
A20	4- CH_2CH_3 -phenyl	Me	32	1.03
A21	4-OH-phenyl	Me	32	1.03
A22	4- OCH_3 -phenyl	Me	16	0.53
A23	4- $\text{C}(\text{CH}_3)_3$ -phenyl	Me	16	0.53
A24	4- $\text{N}(\text{CH}_3)_2$ -phenyl	Me	16	0.53
A25	4-(<i>o</i> -Tolyloxy)phenyl	Me	16	0.53
A26	4-(4-Fluorophenoxy)phenyl	Me	32	1.03
A27	4- CH_3CO -phenyl	Me	16	0.53
A28	2- CH_3 -phenyl	Me	32	1.03
A29	3- CH_3 -phenyl	Me	32	1.03
A30	2,3-(CH_3) $_2$ -phenyl	Me	32	1.03
A31	3,4,5-(OCH_3) $_3$ -phenyl	Me	16	0.53
A32	4-(2-Chloropyridyl)	Me	4	0.16
A33	2-(5-Chloropyridyl)	Me	16	0.53
A34	3-Pyridyl	Me	16	0.53
A35	2-Thiazolyl	Me	32	1.03
A36	2-Pyrimidinyl	Me	16	0.53
A37	2-Quinolyl	Me	32	1.03
A38	2-Naphthyl	Me	32	1.03
A39	4-Morpholyl	Me	16	0.53
A40	1-Benzyl	Me	32	1.03
A41	2-Pyrimidinyl	Et	16	0.53
A42	2-Quinolyl	Et	32	1.03
A43	2-(5-Chloropyridyl)	Et	16	0.53
A44	4-Br-phenyl	Et	2	0.09
A45	4-F-phenyl	Et	16	0.53
A46	4-Cl-phenyl	Et	1	0.06
A47	4- CH_3 -phenyl	Et	4	0.16
A48	4-(<i>o</i> -Tolyloxy)phenyl	Et	32	1.03
A49	4-F-phenyl	$\text{CH}_2\text{CH}_2\text{CH}_3$	16	0.53
A50	4- CH_3 -phenyl	$\text{CH}_2\text{CH}_2\text{CH}_3$	16	0.53
A51	4-Cl-phenyl	$\text{CH}_2(\text{CH}_2)_2\text{CH}_3$	16	0.53
A52	4- CH_3 -phenyl	$\text{CH}_2(\text{CH}_2)_2\text{CH}_3$	32	1.03
A53	4-Cl-phenyl	$\text{CH}(\text{CH}_3)_2$	1	0.06
A54	4- CH_3 -phenyl	$\text{CH}(\text{CH}_3)_2$	16	0.53
A55	4- CH_3 -phenyl	$\text{CH}_2\text{CH}_2\text{OCH}_3$	32	1.03
A56	4-Cl-phenyl	$\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$	4	0.16
A57	4-Cl-phenyl	Cyclopentyl	8	0.28
A58	4-Cl-phenyl	1 <i>H</i> -imidazole-1-carbonyl	32	1.03

Table 1 (continued)

Compounds	R_1	R_2	SIPI-KPN-1712	
			MIC	FICI
A59	4-F-phenyl	1 <i>H</i> -imidazole-1-carbonyl	32	1.03
A60	4-CF ₃ -phenyl	1 <i>H</i> -imidazole-1-carbonyl	16	0.53
A61	2-(5-Chloropyridyl)	1 <i>H</i> -imidazole-1-carbonyl	16	0.53
A62	Phenyl	1 <i>H</i> -imidazole-1-carbonyl	16	0.53
A63	4-CH ₃ -phenyl	1 <i>H</i> -imidazole-1-carbonyl	32	1.03
B1	4-Cl-phenyl	—	0.5	0.05
B2	4-F-phenyl	—	32	1.03
B3	4-CF ₃ -phenyl	—	16	0.53
B4	Phenyl	—	32	1.03
B5	4-CH ₃ -phenyl	—	32	1.03
B6	4-CH ₃ CO-phenyl	—	16	0.53
B7	2-(5-Chloropyridyl)	—	16	0.53
B8	2-Naphthyl	—	16	0.53
C1	4-Cl	H	32	1.03
C2	4-Cl	6-Cl	32	1.03
C3	H	6-CF ₃	16	0.53
PB			32	1.03

Due to the obvious synergistic efficacy of **B1** combined with PB against *Klebsiella pneumoniae* (SIPI-KPN-1712), we also tested its synergistic antibacterial activity against other Gram-negative bacteria including *E. coli*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* (containing their clinically isolated strains). The MICs and FICIs of **B1** and PB alone and in combination against these Gram-negative bacteria mentioned are shown in Table 3. The synergistic or partial synergistic effects were observed in most of the tested strains except Pae-ATCC27853 and Pae-1292. As we could see from Table 3, **B1** alone had no antibacterial activity against these strains, which was consistent with previous results. In addition, **B1** combined with PB showed partial synergistic effects against *Acinetobacter baumannii* (ATCC19606) and its four clinical isolates, and the FICIs ranged from 0.28 to 0.53. Besides, **B1** could markedly decrease the MICs of PB against the other two *Klebsiella pneumoniae* clinical isolates, KPN-2677 and KPN-2967, showing potent synergistic effects and achieving 32 and 8-folds reduction, respectively. When 4 $\mu\text{g ml}^{-1}$ **B1** was combined with PB, it enhanced the activity of PB against

E. coli (ATCC25922) and its two clinical isolates, and the MICs were decreased from 0.5 to 0.25–0.125 $\mu\text{g ml}^{-1}$. Meanwhile, **B1** combined with PB showed partial synergistic effect against the clinical isolate Pae-1399, but no synergism against *Pseudomonas aeruginosa* (ATCC27853) and its clinical isolate Pae-1292. These results demonstrated that **B1** with PB possessed a broad synergism against Gram-negative bacteria. It suggested that the fused bicyclic 2-aminothiazolyl structure is valuable to be modified further.

Conclusions

In conclusion, a series of fused bicyclic 2-aminothiazolyl compounds were synthesized and their synergistic effects with PB against Gram-negative bacteria were evaluated. For *Klebsiella pneumoniae* (SIPI-KPN-1712), significant synergistic and partial synergistic interactions were observed by the determination of MICs and the calculation of FICIs. A potent synergist **B1** was found, which can reduce the MIC of PB at 4 $\mu\text{g ml}^{-1}$ from 32 $\mu\text{g ml}^{-1}$ to 0.5 $\mu\text{g ml}^{-1}$, which is a 64-fold reduction. And time-kill curves also suggested that the combination has significant bactericidal effect and can prevent the regrowth of SIPI-KPN-1712. **B1** could also markedly decrease the MICs of PB against the other two *Klebsiella pneumoniae* clinical isolates, KPN-2677 and KPN-2967. In addition, **B1** combined with PB also showed synergistic and partial synergistic effects against *E. coli* (ATCC25922 and its clinical isolates), *Acinetobacter baumannii* (ATCC19606 and its clinical isolates), and Pae-1399 except *Pseudomonas aeruginosa* (ATCC27853) and Pae-1292. Such a combination may be useful in the treatment of infections caused by Gram-negative bacteria. And the

Table 2 The MICs of PB combined with compound **B1** at different concentrations

Compound B1 concentration	MIC of PB (MIC $\mu\text{g ml}^{-1}$)	Fold reduction
0 $\mu\text{g ml}^{-1}$	32	1
1 $\mu\text{g ml}^{-1}$	8	4
2 $\mu\text{g ml}^{-1}$	2	16
4 $\mu\text{g ml}^{-1}$	0.5	64
8 $\mu\text{g ml}^{-1}$	0.25	128
16 $\mu\text{g ml}^{-1}$	0.25	128

Fig. 2 Time-kill curves of PB and B1 alone and in combination at different concentrations against SIPI-KPN-1712.

Table 3 Synergy between B1 and PB against Gram-negative bacteria

Strains ^a	MICs of B1 alone	MICs of PB alone	MICs of 4 µg ml ⁻¹ B1 combined with PB	FICI ^b
Aba-ATCC19606	>64	1	0.5	0.53
Aba-1	>64	4	2	0.53
Aba-2	>64	4	1	0.28
Aba-3	>64	1	0.5	0.53
Aba-4	>64	1	0.5	0.53
KPN-2677	>64	16	0.5	0.06
KPN-2967	>64	4	0.5	0.16
Eco-ATCC25922	>64	0.5	0.25	0.53
Eco-2944	>64	0.5	0.125	0.28
Eco-2945	>64	0.5	0.125	0.28
Pae-ATCC27853	>64	1	1	1.03
Pae-1399	>64	2	1	0.53
Pae-1292	>64	2	2	1.03

^a Aba, *Acinetobacter baumannii*; KPN, *Klebsiella pneumoniae*; Eco, *E. coli*; Pae *Pseudomonas aeruginosa*. ^b FICI ≤ 0.5 = synergy, 0.5–0.75 = partial synergy, 0.76–1 = an additive effect.

dosage reduction of PB through an efficacious synergist can provide a new strategy to reduce its nephrotoxicity and neurotoxicity. For this reason, a further study on this structure is valuable to find the optimized compounds with higher activity *in vivo* and its synergistic mechanism.

Conflicts of interest

The authors declare no competing interests.

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