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Synergism of Fused Bicyclic 2-Aminothiazolyl compounds with polymyxin B against *Klebsiella pneumonia*

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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 pneumonia* (SIPI-KPN-1712). Some of the synthesized compounds exhibited synergistical activity. When 4 μg/ml compound **B1** was combined with PB, it showed potent antibacterial activity, achieving 64-fold reduction for 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 against *E. coli* (ATCC25922 and its clinical isolates), *Acinetobacter baumanii* (ATCC19606 and its clinical isolates), and *Pseudomonas aeruginosa* (Pae-1399).

Introduction

The misuse of antibiotics in clinical and non-clinical field has led to the rapid emergence of widespread multi-drug resistant (MDR) Pathogenic bacteria, especially ESKAPE pathogens *(Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa*) which were highlighted by the Infectious Diseases Society of America. [1-3] *Klebsiella pneumonia*, 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 disease, wound or surgical site infections and so on. [4, 5] More troubling, high antimicrobial resistance rate of *Klebsiella* bacterias was observed for β-lactamase inhibitors and many other antibiotics, which has caused

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serious sequel that 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 pneumonia*.[11-13] Polymyxins are decapeptide antibiotics and mainly include 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 a 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 clinical field is restricted on account of its nephrotoxicity and neurotoxicity. According to the recent clinical studies, above 60% of patients have been found with polymyxins induced nephrotoxicity after administration intravenously. Therefore, the toxicity of polymyxin precludes the use of appropriate dosing for treatment of MDR Gram-negative infections, and even worse is that inferior dosing 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 antibiotic with natural products or peptide antibiotics.[18, 19] For instance, combining chloramphenicol with PB to synergistically kill NDM-producing MDR *Klebsiella pneumonia* and combining curcumin with PB against MDR bacteria associated with traumatic wound infections.[15, 20, 21]Another way to prolong the life span of ineffective antibiotics is to employ adjuvants, mainly include β-lactamase inhibitors, pump inhibitors, outer membrane permeabilizers.[22-24]

Thiazole scaffold are widely used in medicine, pesticides, fine chemicals and other fields due to the unique nitrogen, sulfur heterocyclic structure and wide bioactivities. In medicinal chemistry, many thiazole derivatives have shown effective activities in anti-inflammation[25], anticancer[26], antituberculous[27], anti-HIV[28] and anti-bacterial infection[29].

Enlightened by all of the descriptions above, we tried to screen thiazole compounds synthesized in our group[30] and test their synergistic activities with PB against *Klebsiella pneumonia* (SIPI-KPN-1712). Luckily, we found that compound **1108** exhibited effective synergism with PB，achieving 16-fold reduction for 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

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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 Indice (FICI, the value to predict the synergy).

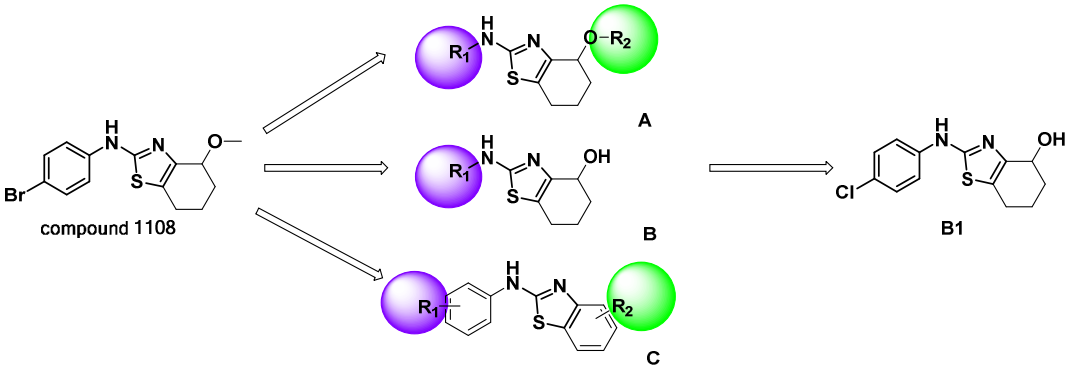

Figure 1. Design strategy of the title thiazole compounds **A**, **B**, **C**

Results and discussion

Chemistry

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

The synthesis of the target compounds **A** were 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 were heated under microwave irradiation to cyclocondensate to get title compounds **A** in 70-90% yield. While, target compounds **B** were gained in moderate yields (60-75%) by the mixture of thioureas **5** and α, β-epoxycyclohexanone **6** in H_2O under the condition of reflux which is shown in Scheme 2b. Then, target compounds **C** was synthesized by route as described by Yao et al[32] shown in Scheme 2c and this method afford compounds **C** in70-90% yields. Compounds **C** could be obtained by a copper-catalyzed tandem reaction of 2-iodoaniline derivatives **7** with isothiocyanates **8** using $CuSO_4$ as catalyst and Bu_3N as a base under ligand- and solvent-free conditions in air.

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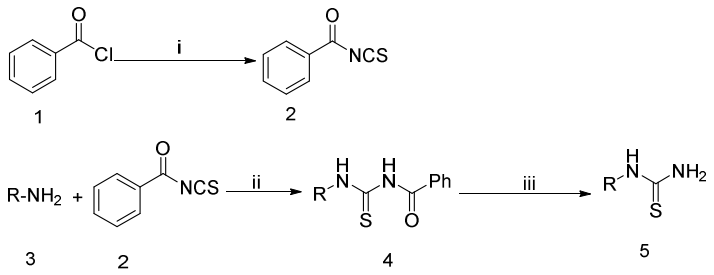
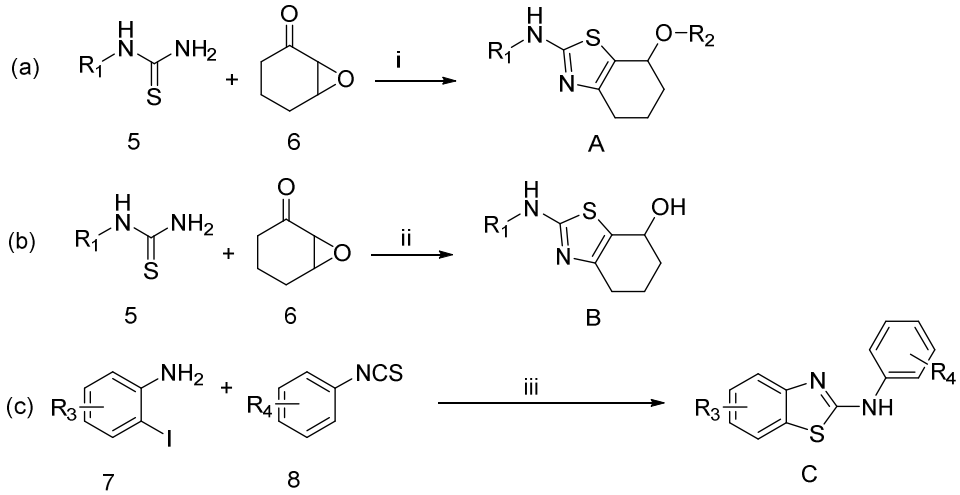


Scheme 1. Synthesis of intermediates. (i) KSCN, acetone, Ar, r.t., 1 h; (ii) EA, reflux, 2h; (iii) NaOH, EtOH, reflux, 2h.



Scheme 2. Synthesis of compounds **A**, **B**, **C**. (i) R_2OH, MW, 15-30 min. (ii) H_2O, reflux, 12 h. (iii) $CuSO_4$, Et_3N, 80℃, 5 h.

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

Antibacterial synergists combined with PB can be used for many Gram-negative bacterias. For example, curcumin combined with PB produced the antimicrobial synergy against MDR bacteria associated with traumatic wound infections, including *E. coli, Acinetobacter baumanii,* and *Pseudomonas aeruginosa.*[15] However, there was no reported synergistic compound combined with PB against *Klebsiella pneumonia* available at present. So we started our study further based on compound **1108**.

To study the structure–activity relationships (SAR) preliminarily, 63 compounds of structure **A,** eight compounds **B** and three compounds of structure **C** with different substituents at R_1, and R_2, 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 is shown in Table 1. Firstly, every synthesized compound individual does not possess any antibacterial effects against the test isolated strain (MICs >128μg ml^{-1}), and the MIC of PB is 32μg ml^{-1} before

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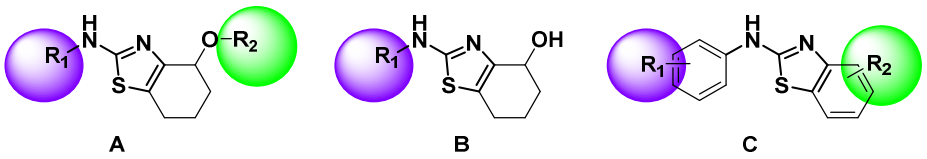
combination. When synthesized compounds combined with PB, the results showed that most of these compounds exhibited synergism or partial synergism with PB against SIPI-KPN-1712, the MICs of PB ranged from 0.5 to 32 μg ml^{-1}. When we tried different groups at R_1 position, it was found that aromatic heterocyclic (**A32-A38**，such as pyridine, thiazole, pyrimidine, quinoline and naphthalene), heterocyclic (**A39**) and benzylated (**A40**) compounds exhibited lower activity than the 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-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 at para-substituted showed a clear preference for the potency among mono-substituted compounds. **A1** and **A3**, *p*-Cl and *p*-CF_3 separately, reduced the MIC of PB to 1 μg ml^{-1} and 8 μg ml^{-1} respectively. Besides, when bis-substituted compounds contained at least one Cl group, the synergistic antibacterial activity were better than that of the others, such as **A13**, **A15**, **A16**. Compound **A13** exhibited the same synergism as compound **A1**. Then, we tried to introduced different substitution for R_2 group including methyl, ethyl, linear alkanes, branched alkanes, cycloalkane and 1H-imidazole-1-carbonyl, but these substituents had no obvious influence on 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 for the MIC of PB, reducing to 0.5 μg ml^{-1}. However, changing tetrahydrobenzothiazole to benzothiazole (structure **C)** did not show any improvement for the synergism. Overall, the relationship between the structure and the synergistic activity exhibited that 4-Cl-phenyl at R_1, no substitution or alkyl substitution at R_2 for structure **A** and **B** was benefit for the synergistic effect.

Table 1

The MICs and FICIs of PB in combination with compounds (4μg ml^{-1}) against SIPI-KPN-1712.



compounds	R_1	R_2	SIPI-KPN-1712	
			MIC	FICI
Compound 1108	4-Br-phenyl	Me	2	0.09
A1	4-Cl-phenyl	Me	1	0.06

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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-$C(CH_3)_3$-phenyl	Me	16	0.53
A24	4-$N(CH_3)_2$-phenyl	Me	16	0.53
A25	1-CH_3-2-phenoxybenzyl	Me	16	0.53
A26	1-F-4-phenoxybenzyl	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-chloropyridyl	Me	16	0.53
A35	1-thiazolyl	Me	32	1.03
A36	1-pyrimidinyl	Me	16	0.53
A37	2-quinolyl	Me	32	1.03
A38	1-naphthyl	Me	32	1.03
A39	1-morpholyl	Me	16	0.53
A40	1-benzyl	Me	32	1.03
A41	1-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

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A46	4-Cl-phenyl	Et	1	0.06
A47	4-CH_3-phenyl	Et	4	0.16
A48	1-CH_3-2-phenoxybenzyl	Et	32	1.03
A49	4-F-phenyl	$CH_2CH_2CH_3$	16	0.53
A50	4-CH_3-phenyl	$CH_2CH_2CH_3$	16	0.53
A51	4-Cl-phenyl	$CH_2(CH_2)_2CH_3$	16	0.53
A52	4-CH_3-phenyl	$CH_2(CH_2)_2CH_3$	32	1.03
A53	4-Cl-phenyl	$CH(CH_3)_2$	1	0.06
A54	4-CH_3-phenyl	$CH(CH_3)_2$	16	0.53
A55	4-CH_3-phenyl	$CH_2CH_2OCH_3$	32	1.03
A56	4-Cl-phenyl	$CH(CH_2CH_2CH_2CH_3)_2$	4	0.16
A57	4-Cl-phenyl	cyclopentyl	8	0.28
A58	4-Cl-phenyl	1*H*-imidazole-1-carbonyl	32	1.03
A59	4-F-phenyl	1*H*-imidazole-1-carbonyl	32	1.03
A60	4-CF_3-phenyl	1*H*-imidazole-1-carbonyl	16	0.53
A61	2-(5-chloropyridyl)	1*H*-imidazole-1-carbonyl	16	0.53
A62	phenyl	1*H*-imidazole-1-carbonyl	16	0.53
A63	4-CH_3-phenyl	1*H*-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_3CO-phenyl	/	16	0.53
B7	2-(5-chloropyridyl)	/	16	0.53
B8	1-naphthyl	/	16	0.53
C1	4-Cl	H	32	1.03
C2	4-Cl	5-Cl	32	1.03
C3	H	4- CF_3	16	0.53
PB			32	1.03

In order to further study the synergism of compound **B1** with PB, we combined PB with different concentrations of **B1** to investigate the changes of the MICs. As seen in Table 2, the MIC of PB alone is 32 μg ml^{-1}, and the MIC sharply decreased with the participation of **B1**. When combined 4 μg ml^{-1} of **B1**, the MIC of PB achieved 0.5 μg ml^{-1}, which means 64 folds reduction. When the dosage of **B1** continuously increased, the MIC slightly decreased. The MICs of PB in combination

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with 8 μg ml^{-1} or 16 μg mL^{-1} of compound **B1** remained the same value at 0.25 μg ml^{-1}, which is equal to 128 folds reduction.

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

Table 2
The MICs of PB in combination with different concentrations of compound **B1**

Compound **B1** concentration	MIC of PB (MIC μg/ml)	Fold reduction
0μg/ml	32	1
1μg/ml	8	4
2μg/ml	2	16
4μg/ml	0.5	64
8μg/ml	0.25	128
16μg/ml	0.25	128

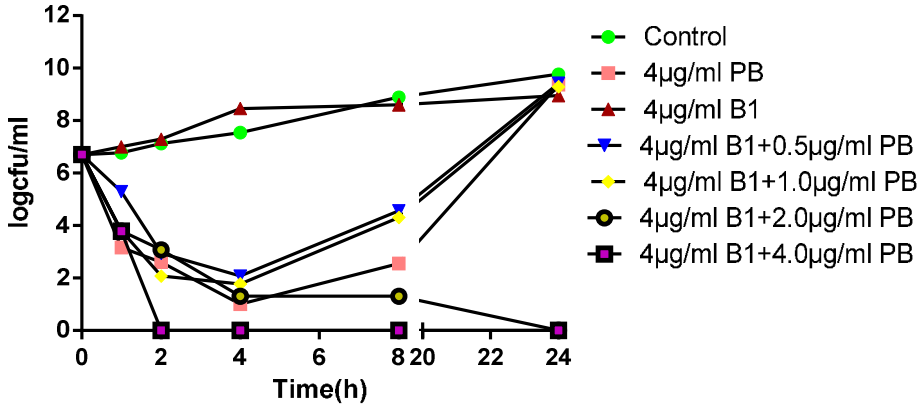

Figure 2. Time–kill curves of PB and **B1** alone and in combination in different concentrations versus SIPI-KPN-1712

Due to the obvious synergistic efficacy of **B1** combined with PB against *Klebsiella pneumonia* (SIPI-KPN-1712), we also tested its synergistic antibacterial activity

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versus other Gram-negative bacterias including *E. coli, Acinetobacter baumanii,* and *Pseudomonas aeruginosa* (containing their clinically isolated strains). The MICs and FICIs of **B1** and PB alone and in combination against these Gram-negative bacterias mentioned were shown in Table 3. Synergistic or partial synergistic effects were observed in most of the tested strains except Pae-ATCC27853 and Pae-1292. As we could see from the Table 3, **B1** alone had no antibacterial activity against these strains which was consistent with previous results. And **B1** showed partial synergistic effects in combination with PB against *Acinetobacter baumanii* (ATCC19606) and its four clinical isolates, the FICIs were ranging from 0.28 to 0.53. Besides, **B1** could markedly decrease the MICs of PB against the other two *Klebsiella pneumonia* clinical isolates, KPN-2677 and KPN-2967, showing the potent synergistic effects and achieving 32 and 8 folds reduction, respectively. When 4μg/ml **B1** combined with PB, it enhanced the activity of PB against *E. coli* (ATCC25922) and its two clinical isolates, the MICs were decreased from 0.5 to 0.25-0.125 μg/ml. While，**B1** showed partial synergistic effect combined with PB against clinical isolate Pae-1399, but no synergism with PB against *Pseudomonas aeruginosa*（ATCC27853）and its clinical isolate Pae-1292. These results demonstrated that **B1** possessed broadly synergism with PB against Gram-negative bacterias. It suggested that the fused bicyclic 2-aminothiazolyl structure was valuable to be modified further.

Table 3

Synergy between **B1** and PB against Gram-negative bacterias

strains[a]	MICs of **B1** alone	MICs of PB alone	MICs of 4μg/ml **B1** in combination 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 baumanii;* KPN, *Klebsiella pneumonia;* Eco, *E. coli*; Pae *Pseudomonas aeruginosa*;

[b]FICI≤0.5=synergy, 0.5-0.75=partial synergy, 0.76-1= an additive effect.

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Conclusions

In conclusion, a series of fused bicyclic 2-aminothiazolyl compounds were synthesized and their synergistic effects with PB against Gram-negative bacterias were evaluated. For *Klebsiella pneumonia* (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 4μg ml^{-1} from 32μg ml^{-1} to 0.5μg ml^{-1}, 64 folds reduction. And time-kill curves also suggested that the combination have significant bactericidal effect and can prevent the regrowth of SIPI-KPN-1712. **B1** also could markedly decrease the MICs of PB against the other two *Klebsiella pneumonia* clinical isolates, KPN-2677 and KPN-2967. In addition, **B1** combined with PB also showed synergistic and partial synergistic against *E. coli (*ATCC25922 and its clinical isolates)*, Acinetobacter baumanii* (ATCC19606 and its clinical isolates)*,* Pae-1399 except *Pseudomonas aeruginosa*（ATCC27853）and Pae-1292. Such combination may be useful in the treatment of infections caused by Gram-negative bacterias. And the dosage reduction of PB through efficacious synergist can provide a new strategy to decline its nephrotoxicity and neurotoxicity. For this reason, further study on this structure is valuable to find the optimized compounds with higher activity *in vivo* and its synergistic mechanism.

Acknowledgments

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Conflict of Interest

The authors declare no competing interests.

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