含苯丙氨酸残基的拟肽衍生物的设计、合成与抗菌活性研究

汪 晴, 钱春丽, 佘慧娴, 杨家强*

(遵义医科大学药学院, 贵州 遵义 563000)

摘要: 运用分子杂合策略, 将药效片段氨基噻唑肟与苯丙氨酸组合, 设计合成了17个含苯丙氨酸残基的拟肽衍生物进行抗菌活性研究。结果表明, 该类化合物对所测试细菌有不同程度的抑制作用, 尤以化合物**8p**最为突出, 对大肠埃希菌 (*E. coli*)、绿脓杆菌 (*P. aeruginosa*) 和耐氟喹诺酮大肠杆菌 (fluoroquinolone-resistant *E. coli*, FREC) 的最小抑菌浓度 (minimum inhibitory concentration, MIC) 均为2 μg·mL^{-1}, 抗*E. coli*、*P. aeruginosa*与对照药环丙沙星相当, 抗FREC活性远优于对照药; 同时, 化合物**8p**与部分抗菌药物联用, 具有协同作用。其较显著的抗菌及增效作用具有进一步开发的潜力。

关键词: 氨基噻唑肟; 苯丙氨酸残基; 拟肽衍生物; 合成; 抗菌活性

中图分类号: R914 **文献标识码**: A **文章编号**: 0513-4870(2026)09-3442-06

Design, synthesis and antibacterial activities of peptidomimetic derivatives containing phenylalanine

WANG Qing, QIAN Chun-li, SHE Hui-xian, YANG Jia-qiang*

(*College of Pharmacy, Zunyi Medical University, Zunyi 563000, China*)

Abstract: Using a molecular hybridization strategy, 17 peptidomimetic derivatives of phenylalanine were designed and synthesized by combining an aminothiazole oxime scaffold with phenylalanine for antibacterial activity studies. The results showed that these compounds exhibited varying degrees of inhibitory activity against the tested bacterial strains, with compound **8p** being particularly outstanding. It demonstrated minimal inhibitory concentrations (MIC) of 2 μg·mL^{-1} against *E. coli*, *P. aeruginosa*, and fluoroquinolone-resistant *E. coli* (FREC). Its activity against *E. coli* and *P. aeruginosa* was comparable to that of the reference drug ciprofloxacin, while its efficacy against FREC was significantly superior to the reference drug. Meanwhile, compound **8p** exhibited synergistic effects when combined with certain antibacterial agents. Its relatively significant antibacterial activities and synergistic enhancement warrant further investigation.

Key words: aminothiazole oxime; phenylalanine; peptidomimetic derivative; synthesis; antibacterial activity

天然抗菌肽是宿主防御系统的一部分, 具有广谱抗菌、作用快速且不易产生耐药性等优点, 但存在稳定性差、成本高和生物利用度低等缺陷[1,2]。而拟肽类化合物旨在模仿天然抗菌肽的优势, 通过保留或模拟其关键的药效团, 来克服其局限性[3-5]。其中, 含苯丙氨酸残基的拟肽衍生物近年在抗菌药物的设计中呈现巨大潜力[6]。2017年, Su等[7]设计合成的含苯丙氨酸残基的共聚肽, 对金黄色葡萄球菌 (*S. aureus*) 的MIC值达到2 μg·mL^{-1}; 2021年, Peng等[8]用疏水性苯丙氨酸取代质子凝集素肽中的氨基酸, 能显著提高对*S. aureus*和枯草芽孢杆菌 (*B. subtilis*) 的抑制作用, MIC值达4 μg·mL^{-1}; 2025年, 本课题组[9]设计合成的含苯丙氨酸残基的拟肽类蛇床子素衍生物对*E. coli*、耐甲氧西林金黄色葡萄球菌 (methicillin-resistance *S. aureus*, MRSA) 和耐氟喹诺酮大肠杆菌 (fluoroquinolone-resistant

收稿日期: 2026-02-25; 修回日期: 2026-03-20.
基金项目: 贵州省科技计划项目 (黔科合基础-ZK [2024] 一般265).
*通讯作者 Tel: 86-851-28642339, E-mail: yjqcn@126.com
DOI: 10.16438/j.0513-4870.2026-0196

E. coli, FREC) 的 MIC 值分别达 2、16 和 4 μg·mL^{-1}, 苯丙氨酸残基的引入有助于提高抗革兰阴性菌活性。

2-氨基噻唑可分别作为氢键供体或受体与靶标结合, 存在于多种药物中[10]。尤其是在抗菌药物结构中, 能增强细胞膜的通透性, 提高与靶点的亲和力, 进而提升抗菌活性、扩大抗菌谱, 尤其是克服细菌耐药性的重要结构单元[11-14], 如头孢匹罗、氨曲南和磺胺噻唑等。肟醚作为一种抗菌药效团, 其独特的电子效应和立体取向, 有助于药物分子更精确地与细菌靶点结合, 增强亲和力, 避免被耐药菌产生的灭活酶识别, 在抗菌药物的设计中扮演着重要角色[15,16]。如在半合成 β-内酰胺类抗生素中引入肟醚结构, 提高了对酶的稳定性[17]; 在喹诺酮类抗菌药物中引入肟醚片段, 增强了与靶标的亲和力[18]。

基于此, 运用分子杂合策略, 将 2-氨基噻唑肟与苯丙氨酸通过酰胺键杂合 (设计思路见图 1), 设计系列新型含苯丙氨酸残基的拟肽衍生物进行抗菌活性评价。目标物的合成如路线 1 所示。

结果与讨论

1　化合物的合成

在合成中间体 **1** 时, 以亚硝酸叔丁酯做肟化剂, 替代亚硝酸钠[19], 操作简便, 反应易控制, 更绿色环保。在合成中间体 **5** 时, 以 $(C_2H_5O)_3P$ 代替传统的脱水剂浓硫酸[20], 反应更温和, 收率更高。在合成目标物 **8** 时, 以 HBTU/DIPEA 为缩合剂比以 HOBT/EDCI/DMAP 为缩合剂有更好的收率。

目标化合物 **8** 的相关理化数据见表 1、2。

2　目标化合物的抗菌活性

该类化合物对所测细菌有不同程度的抑制作用 (表 3), 化合物 **8d**、**8f**、**8g**、**8h**、**8i**、**8j**、**8l**、**8n** 和 **8p** 对 *S. aureus* 的 MIC 分别为 32、16、8、32、32、16、32、16 和 16 μg·mL^{-1}, 尤以 **8g** 最为突出; 化合物 **8d**、**8e**、**8g**、**8h**、**8j**、**8n**、**8o** 和 **8p** 对 *E. coli* 的 MIC 分别为 32、16、4、32、8、32、16 和 2 μg·mL^{-1}, 其中, **8g** 和 **8o** 与对照药环丙沙星相当; 化合物 **8e**、**8g**、**8h**、**8j**、**8o** 和 **8p** 对 *P. aeruginosa* 的 MIC 分别为 32、4、32、8、32 和 2 μg·mL^{-1}, 其中, **8o** 优于对照药; 同时, 该类化

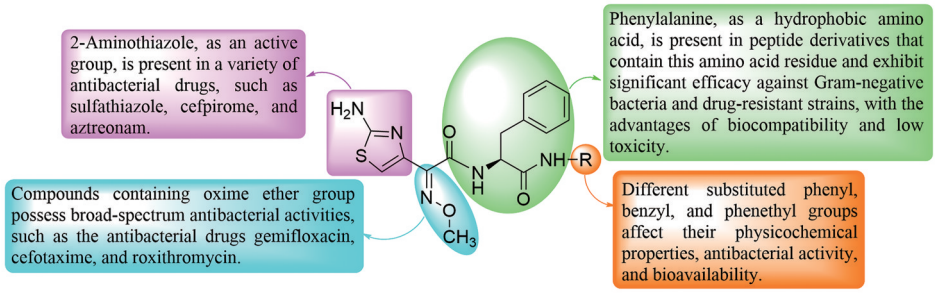
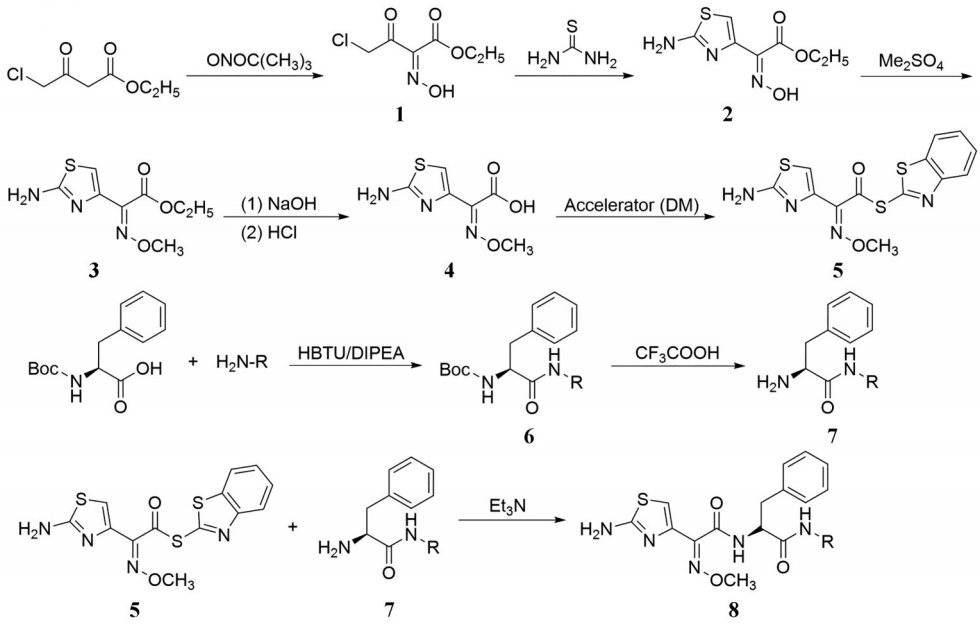


Figure 1　Design strategy for target compounds



Scheme 1　Synthetic route of target compounds

Table 1 The structures and physical property of compounds **8a**−**8q**

Compd.	R	Appearance	Yield/%	mp/℃
8a	Ph	White solid	67	101−102
8b	2-CH_3Ph	White solid	79	100−101
8c	3-CH_3Ph	White solid	72	102−103
8d	4-CH_3Ph	White solid	71	103−104
8e	2-FPh	White solid	63	104−106
8f	3-FPh	White solid	61	107−109
8g	4-FPh	White solid	55	98−99
8h	2-ClPh	White solid	58	108−110
8i	3-ClPh	White solid	56	100−102
8j	4-ClPh	White solid	48	185−186
8k	2-BrPh	White solid	52	102−103
8l	3-BrPh	White solid	49	103−104
8m	4-BrPh	White solid	43	121−122
8n	$PhCH_2$	White solid	73	116−118
8o	2-$FPhCH_2$	White solid	41	188−190
8p	4-$FPhCH_2$	White solid	55	214−215
8q	$PhCH_2CH_2$	White solid	73	114−115

合物抗耐药菌FREC活性较显著, 化合物**8d**、**8e**、**8g**、**8h**、**8j**、**8n**、**8o**和**8p**对FREC的MIC分别为32、16、4、32、8、32、16和2 μg·mL^{-1}, 均优于对照药。综合来看, 该类化合物抗革兰阴性菌活性更优。

构效关系分析如下, ① 取代基的位置: 对位取代普遍能获得更好的抗菌活性, 尤其是化合物**8g** (4-FPh)和**8p** (4-$FPhCH_2$) 呈现出较显著的抗菌效果, 可能是氟原子在对位实现了亲脂性、膜穿透性与靶点亲和力的最优平衡; 邻位取代导致抗菌活性大幅降低; 而间位取代对革兰阴性菌几乎无活性; ② 取代基的电子效应: 吸电子基取代的抗菌活性更优, 大多遵循F > Cl > Br, 给电子基使其活性降低; ③ 取代基的长度: 适中长度的苄基取代对革兰阴性菌活性最好 (如**8p**优于**8g**), 而连接链延长至苯乙基 (**8q**), 活性降低, 可能是靶点结合口袋对连接链长度较为敏感。

Table 2 Spectral data of target compounds **8a**−**8q**

Compd.	^{1}H NMR, ^{13}C NMR and MS
8a	^{1}H NMR (400 MHz, DMSO) δ_H: 10.05 (s, 1H), 9.00 (d, *J* = 8.3 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.23−7.31 (m, 6H, ArH), 7.18 (d, *J* = 7.8 Hz, 1H), 7.15 (s, 2H), 7.01−7.06 (m, 1H), 6.13 (s, 1H), 4.75−4.81 (m, 1H) , 3.71 (s, 3H), 2.83−3.11 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ_C: 37.5, 55.2, 62.3, 110.7, 119.8, 124.0, 126.8, 128.5, 129.2, 129.7, 137.9, 139.0, 143.2, 149.6, 162.8, 168.6, 170.0; ESI MS (*m*/*z*): 424.3 $[M+H]^+$
8b	^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.14 (s, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.26−7.29 (m, 5H), 7.13−7.17 (m, 2H), 7.05−7.09 (m, 1H), 6.45 (s, 1H), 5.37 (s, 2H), 5.03−5.08 (m, 1H), 3.88 (s, 3H), 3.24−3.39 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 17.5, 37.2, 55.2, 62.8, 110.9, 124.0, 126.0, 126.5, 127.1, 128.8, 129.4, 130.6, 131.0, 134.9, 136.3, 142.3, 147.7, 162.8, 168.1, 169.3; ESI MS (*m*/*z*): 438.5 $[M+H]^+$
8c	^{1}H NMR (400 MHz, DMSO) δ_H: 9.96 (s, 1H), 8.99 (d, *J* = 8.2 Hz, 1H), 7.30−7.37 (m, 4H), 7.24−7.27 (m, 2H), 7.17−7.20 (m, 2H), 7.16 (s, 2H), 6.85−6.87 (m, 1H), 6.12 (s, 1H), 4.75−4.80 (m, 1H), 3.71 (s, 3H), 2.85−3.10 (m, 2H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ_C: 21.6, 37.5, 55.1, 62.3, 110.7, 117.0, 120.2, 124.6, 126.8, 128.5, 129.0, 129.7, 138.0, 138.4, 138.9, 143.2, 149.7, 162.7, 168.6, 169.9; ESI MS (*m*/*z*): 438.3 $[M+H]^+$
8d	^{1}H NMR (400 MHz, DMSO) δ_H: 9.94 (s, 1H), 8.99 (d, *J* = 7.5 Hz, 1H), 7.42−7.44 (m, 2H), 7.19−7.29 (m, 5H), 7.16 (s, 2H), 7.09−7.11 (m, 2H), 6.13 (s, 1H), 4.77−4.82 (m, 1H), 3.71 (s, 3H), 2.86−3.09 (m, 2H), 2.22 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ_C: 20.9, 37.6, 55.1, 62.3, 110.7, 119.7, 126.7, 128.5, 129.6, 129.7, 132.8, 136.5, 138.0, 143.2, 149.7, 162.7, 168.6, 169.8; ESI MS (*m*/*z*): 438.0 $[M+H]^+$
8e	^{1}H NMR (400 MHz, DMSO) δ_H: 8.39 (s, 1H), 8.04 (d, *J* = 10.2 Hz, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.19−7.27 (m, 5H), 6.99−7.04 (m, 3H), 6.31 (s, 1H), 5.06−5.12 (m, 1H), 3.84 (s, 3H), 3.13−3.42 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ_C: 18.3, 37.3, 55.1, 62.9, 111.6, 115.0, 115.2, 122.8, 124.4, 125.3, 127.1, 128.8, 129.2, 136.2, 142.0, 147.6, 151.9, 154.3, 162.8, 168.2, 169.3; ESI MS (*m*/*z*): 442.4 $[M+H]^+$
8f	^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.02 (s, 1H), 7.88 (d, *J* = 9.8 Hz, 1H), 7.19−7.26 (m, 5H), 6.45 (s, 1H), 6.39−6.41 (m, 2H), 5.84 (s, 2H), 4.96−5.01 (m, 1H), 3.86 (s, 3H), 3.18−3.36 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 37.7, 55.4, 62.8, 98.5, 103.6, 111.3, 120.0, 121.5, 126.9, 128.6, 129.3, 136.4, 142.1, 147.5, 149.9, 156.9, 162.4, 168.3, 168.5; ESI MS (*m*/*z*): 442.1 $[M+H]^+$
8g	^{1}H NMR (400 MHz, DMSO) δ_H: 10.19 (s, 1H), 9.03 (d, *J* = 8.2 Hz, 1H), 7.55−7.58 (m, 2H), 7.24−7.37 (m, 5H), 7.11−7.20 (m, 4H), 6.21 (s, 1H), 4.73−4.79 (m, 1H), 3.72 (s, 3H), 2.87−3.10 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ_C: 37.6, 55.2, 62.4, 110.8, 115.7, 115.9, 121.5, 121.6, 126.8, 128.6, 129.7, 135.5, 137.9, 149.2, 157.4, 159.7, 162.5, 168.8, 169.9; ESI MS (*m*/*z*): 441.9 $[M+H]^+$
8h	^{1}H NMR (400 MHz, DMSO) δ_H: 9.59 (s, 1H), 9.06 (d, *J* = 8.4 Hz, 1H), 7.73−7.69 (m, 1H), 7.39 (d, *J* = 5.6 Hz, 1H), 7.26−7.30 (m, 2H), 7.15−7.18 (m, 3H), 7.12 (s, 2H), 7.04−7.07 (m, 2H), 5.09−4.79 (m, 1H), 3.69 (s, 3H), 2.91−3.19 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ_C: 37.3, 54.7, 56.5, 62.3, 110.8, 126.1, 126.6, 126.8, 126.9, 127.9, 128.6, 129.8, 129.9, 134.9, 138.1, 143.1, 149.7, 162.9, 168.7, 170.4; ESI MS (*m*/*z*): 458.2 $[M+H]^+$
8i	^{1}H NMR (400 MHz, DMSO) δ_H: 10.30 (s, 1H), 9.03 (d, *J* = 8.1 Hz, 1H), 7.77 (s, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.24−7.34 (m, 5H), 7.18 (d, *J* = 9.0 Hz, 1H), 7.16 (s, 2H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.18 (s, 1H), 4.73−4.78 (m, 1H, CH), 3.71 (s, 3H), 2.87−3.09 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ_C: 37.5, 55.2, 62.3, 110.7, 118.2, 119.2, 122.7, 126.8, 128.6, 129.7, 130.9, 133.5, 137.9, 140.6, 143.3, 149.7, 162.8, 168.7, 170.5; ESI MS (*m*/*z*): 458.3 $[M+H]^+$
8j	^{1}H NMR (400 MHz, DMSO) δ_H: 10.22 (s, 1H), 9.03 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 7.7 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.23−7.27 (m, 2H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.17 (s, 2H), 6.18 (s, 1H), 4.74−4.79 (m, 1H), 3.71 (s, 3H), 2.87−3.08 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ_C: 37.5, 55.2, 62.3, 110.7, 126.9, 127.5, 128.6, 129.2, 129.7, 137.9, 138.1, 143.3, 149.7, 162.8, 168.7, 170.3; ESI MS (*m*/*z*): 458.3 $[M+H]^+$

Continued

Compd.	^{1}H NMR, ^{13}C NMR and MS
8k	^{1}H NMR (400 MHz, DMSO) δ_H: 9.61 (s, 1H), 9.05 (d, J = 8.6 Hz, 1H), 7.59−7.66 (m, 2H), 7.34−7.39 (m, 3H), 7.25 (t, J = 15.6 Hz, 2H), 7.18−7.22 (m, 1H), 7.16 (s, 2H), 7.11−7.13 (m, 1H), 6.05 (s, 1H), 4.90−4.96 (m, 1H), 3.69 (s, 3H), 2.89−3.24 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ_C: 37.3, 54.6, 62.3, 110.8, 117.9, 126.8, 127.1, 127.6, 128.6, 129.8, 133.2, 136.2, 138.1, 143.1, 149.7, 162.9, 168.6, 170.33; ESI MS (*m*/*z*): 504.2 $[M+H]^+$
8l	^{1}H NMR (400 MHz, DMSO) δ_H: 10.28 (s, 1H), 9.04 (d, J = 8.3 Hz, 1H), 7.89 (s, 1H), 7.43−7.45 (m, 1H), 7.29 (d, 2H), 7.24−7.27 (m, 4H), 7.18 (d, J = 7.8 Hz, 1H), 7.16 (s, 2H), 6.17 (s, 1H), 4.72−4.77 (m, 1H), 3.71 (s, 3H), 2.87−3.09 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ_C: 37.4, 55.2, 62.3, 118.5, 121.9, 122.0, 126.6, 126.9, 128.6, 129.7, 131.3, 137.8, 140.7, 143.3, 149.7, 162.8, 168.7, 170.5; ESI MS (*m*/*z*): 503.9 $[M+H]^+$
8m	^{1}H NMR (400 MHz, DMSO) δ_H: 10.22 (s, 1H), 9.02 (d, J = 8.2 Hz, 1H), 7.47−7.54 (m, 4H), 7.23−7.30 (m, 4H), 7.18 (d, J = 7.8 Hz, 1H), 7.16 (s, 2H), 6.17 (s, 1H), 4.72−4.78 (m, 1H), 3.71 (s, 3H), 2.87−3.07 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ_C: 37.5, 55.2, 62.3, 110.7, 111.5, 121.7, 126.8, 128.6, 129.7, 132.1, 137.9, 138.5, 143.3, 149.7, 162.8, 168.6, 170.3; ESI MS (*m*/*z*): 504.3 $[M+H]^+$
8n	^{1}H NMR (400 MHz, DMSO) δ_H: 8.94 (d, J = 7.6 Hz, 1H), 8.26 (t, J = 12.0 Hz, 1H), 7.24−7.28 (m, 6H), 7.17−7.22 (m, 4H), 7.13 (s, 2H), 6.08 (s, 1H), 4.61−4.66 (m, 1H), 4.30 (d, J = 8.6 Hz, 2H), 3.63 (s, 3H), 2.78−3.12 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ_C: 37.3, 42.6, 54.5, 62.2, 110.5, 126.7, 127.3, 127.6, 128.6, 128.7, 129.7, 138.3, 139.4, 143.0, 149.8, 162.7, 168.7, 170.9; ESI MS (*m*/*z*): 438.5 $[M+H]^+$
8o	^{1}H NMR (400 MHz, DMSO) δ_H: 8.94 (d, J = 7.8 Hz, 1H), 8.29 (t, J = 12.2 Hz, 1H), 7.24−7.25 (m, 4H), 7.19−7.22 (m, 3H), 7.07−7.12 (m, 4H), 6.11 (s, 1H), 4.59−4.64 (m, 1H), 4.28 (d, J = 3.6 Hz, 2H), 3.65 (s, 3H), 2.74−3.08 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ_C: 37.3, 41.9, 54.5, 62.3, 110.4, 115.3, 115.5, 126.7, 128.6, 129.5, 129.6, 129.7, 135.6, 135.7, 138.3, 143.1, 149.8, 160.4, 162.7, 168.7, 170.9; ESI MS (*m*/*z*): 456.3 $[M+H]^+$
8p	^{1}H NMR (400 MHz, DMSO) δ_H: 8.93 (d, J = 8.0 Hz, 1H), 8.28 (t, J = 12.4 Hz, 1H), 7.22−7.25 (m, 4H), 7.18−7.20 (m, 3H), 7.07−7.13 (m, 4H), 6.11 (s, 1H), 4.58−4.64 (m, 1H), 4.28 (d, J = 4.0 Hz, 2H), 3.65 (s, 3H), 2.78−3.10 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ_C: 37.3, 41.9, 54.5, 62.3, 110.4, 115.3, 115.5, 126.7, 128.6, 129.5, 129.6, 129.7, 135.6, 138.2, 143.1, 149.8, 160.4, 162.7, 168.7, 170.9; ESI MS (*m*/*z*): 456.0 $[M+H]^+$
8q	^{1}H NMR (400 MHz, DMSO) δ_H: 8.84 (d, J = 8.4 Hz, 1H), 7.92 (t, J = 6.6 Hz, 1H), 7.25−7.27 (m, 1H), 7.23−7.24 (m, 5H), 7.18 (d, J = 4.2 Hz, 2H), 7.16−7.17 (m, 4H), 6.13 (s, 1H), 4.51−4.57 (m, 1H), 3.69 (s, 3H), 3.26 (d, J = 5.9 Hz, 2H), 2.97−3.00 (m, 2H), 2.64−2.77 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ_C: 35.6, 37.4, 54.4, 55.3, 62.3, 63.5, 110.5, 126.6, 126.7, 128.5, 128.7, 129.1, 129.7, 138.4, 139.7, 143.1, 149.9, 162.7, 168.7, 170.9; ESI MS (*m*/*z*): 452.5 $[M+H]^+$

3　化合物8p与抗菌药物联合的抗菌效果及协同作用

化合物**8p**与不同抗菌药物的联合使用对MIC的影响结果如表4所示, 化合物**8p**与环丙沙星联合使用, 对*E. coli*、*P. aeruginosa*和FREC有协同作用; 与苯唑西林联合使用, 对*S. aureus*有协同作用; 与庆大霉素联合使用, 则对所测细菌均有一定的协同作用; 而与替加环素联合使用时, 无协同作用。

Table 3　The minimal inhibitory concentrations (MIC) values of target compounds. FREC: Fluoroquinolone-resistant *E. coli*

Compd.	MIC/μg·mL^{-1}			
	S. aureus	*E. coli*	*P. aeruginosa*	FREC
8a	128	64	128	64
8b	> 128	128	128	128
8c	64	> 128	> 128	> 128
8d	32	32	64	32
8e	64	16	32	16
8f	16	> 128	> 128	> 128
8g	8	4	4	4
8h	32	32	32	32
8i	32	128	128	128
8j	16	8	8	8
8k	64	128	64	128
8l	32	> 128	> 128	> 128
8m	64	128	64	> 128
8n	16	32	64	32
8o	128	16	32	16
8p	16	2	2	2
8q	> 128	128	64	128
Ciprofloxacin	0.5	2	4	> 128

4　小结

依据分子杂合原理, 设计合成的部分含苯丙氨酸残基的拟肽衍生物有较显著抗菌活性, 该类化合物的活性受取代基的位置、电子效应和长短等因素的影响较大, 其中, 以化合物**8p**的抗革兰阴性菌效果最突出, 可作为先导化合物深入研究。

实验部分

用SGW X-显微熔点仪测定熔点 Agilent 6460质谱仪; NMR用Brker Avance 400型核磁共振仪测定; 质谱数据用Agilent 6460质谱仪测得。

溴乙酰乙酸乙酯、亚硝酸叔丁酯、硫脲、吡啶、四丁基溴化铵、硫酸二甲酯、亚膦酸三乙酯、三乙胺、促进剂DM、*L*-苯丙氨酸、苯胺、取代苯胺、取代苄胺、苯乙胺、*O*-苯并三氮唑-四甲基脲六氟磷酸盐 (HBTU)、*N*,*N*-二异丙基乙胺 (DIPEA)、三氟乙酸均为化学纯, 购于百灵威试剂有限公司, 其余试剂均为分析纯。

1　化合物的合成

1.1　化合物5的合成　在反应瓶中加入8.2 g (0.05 mol)溴乙酰乙酸乙酯、10 mL丙醇、5.2 g (0.05 mol) 亚硝酸叔丁酯、0.3 mL浓盐酸, 于5～10 ℃下搅拌反应20 h, 完毕, 通氮气除去未反应的亚硝酸叔丁酯, 浓缩溶剂, 得黄色液体, 即化合物**1**。接着, 将化合物**1**、3.8 g (0.1 mol)

Table 4 Fractional inhibitory concentration index (FICI) of compound **8p** combined with antibiotics. Note: FICI index of < 0.5 indicates synergistic effect, 0.5−1 indicates additive effect, 1−2 indicates indifferent effect, > 2 indicates antagonistic effect

Bacterial species		Ciprofloxacin + **8p**	Oxacillin + **8p**	Gentamicin + **8p**	Tigecycline + **8p**
S. aureus	MIC	1/16MIC + 1/2MIC	1/16MIC + 1/2MIC	1/8MIC + 1/2MIC	1/16MIC + 1/2MIC
	FICI	1.7	0.4	0.5	1.2
E. coli	MIC	1/4MIC + 1/2MIC	1/2MIC + 1/2MIC	1/8MIC + 1/2MIC	1/16MIC + 1/2MIC
	FICI	0.4	1.3	0.4	0.9
P. aeruginosa	MIC	1/2MIC + 1/2MIC	1/2MIC + 1/2MIC	1/4MIC + 1/2MIC	1/4MIC + 1/2MIC
	FICI	0.4	1.4	0.5	0.8
FREC	MIC	1/2MIC + 1/2MIC	1/2MIC + 1/2MIC	1/4MIC + 1/2MIC	1/4MIC + 1/2MIC
	FICI	0.4	0.8	0.5	1.2

硫脲、20 mL 蒸馏水和 4.5 mL 吡啶加至反应瓶, 室温搅拌反应 3.5 h, 减压过滤, 得浅黄色固体, 即化合物 **2**。然后, 将化合物 **2**、4.8 g (0.046 mol) 碳酸钠、0.1 g 四丁基溴化铵和 9.8 g (0.046 mol) Me_2SO_4 加至反应瓶, 于 10～15 ℃搅拌反应 4 h; 冰水浴冷却, 减压过滤, 得淡黄色固体, 即化合物 **3**。接下来, 将化合物 **3**、30 mL 乙醇和 40 mL 1.5 mol·L^{-1} 的 NaOH 溶液加入反应瓶, 室温搅拌反应 2 h, 用 10% HCl 调 pH 至 7, 减压蒸出乙醇, 乙酸乙酯萃取, 水溶液用 10% HCl 调节 pH 至 2～3, 冰水浴冷却, 析出固体, 减压过滤, 得白色固体, 即化合物 **4**。最后, 将 11.6 g (0.035 mol) 促进剂 DM、50 mL 1,2-二氯乙烷、5.24 g (0.026 mol) 化合物 **4**、0.013 mol 三乙胺和 0.035 mol 亚磷酸三乙酯加至反应瓶中, 于 10～15 ℃搅拌反应 5 h, 减压过滤, 得淡黄色粉末, 即化合物 **5**。mp 129～131 ℃。^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.11～8.13 (m, 1H), 7.93～7.95 (m, 1H), 7.51～7.57 (m, 2H), 6.90 (s, 1H), 5.75 (s, 2H), 4.11 (s, 3H)。

1.2 化合物 7 的合成 以化合物 **7a** 为例, 依次称取 0.297 g (1.12 mmol) *L*-苯丙氨酸、0.885 g (2.34 mmol) HBTU、0.56 mL (3.27 mmol) DIPEA、3.5 mL *N*,*N*-二甲基甲酰胺和 0.085 g (0.93 mmol) 苯胺于反应瓶中, 在 0～5 ℃搅拌反应, 薄层色谱跟踪, 2 h 反应完毕, 加适量蒸馏水, 过滤, 得白色固体, 即化合物 **6**。再将化合物 **7**、3 mL 二氯甲烷和 0.68 mL (1.5 mmol) 三氟乙酸加入反应瓶中, 5～10 ℃搅拌反应, 薄层色谱跟踪, 4 h 反应完毕, 加适量饱和碳酸氢钠, 析出浅棕色固体, 过滤, 硅胶柱色谱 ($V_{石油醚}$∶$V_{乙酸乙酯}$ = 5∶1) 分离纯化, 得白色固体, 即化合物 **7a**。mp 75～77 ℃。^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.42 (brs, 1H), 7.61～1.58 (m, 2H), 7.36～7.25 (m, 7H), 7.13～7.09 (m, 1H), 3.74 (dd, *J* = 9.6, 4.0 Hz, 1H), 3.39～2.80 (m, 2H), 1.46 (brs, 2H)。

1.3 化合物 8 的合成 以化合物 **8a** 为例, 依次称取 0.085 g (0.24 mmol) 化合物 **6**、0.2 mL (0.1 mmol) 三乙胺、10 mL 二氯甲烷和 0.029 g (0.12 mmol) 化合物 **7a** 于反应瓶中, 薄层色谱监测反应, 4 h 反应完毕, 浓缩溶剂, 硅胶柱色谱 ($V_{石油醚}$∶$V_{乙酸乙酯}$ = 3∶1) 分离纯化, 得化合物 **8a**。

2 体外抗菌活性测试

S. aureus、*E. coli* 和 *P. aeruginosa* 源于北京北纳创联生物技术研究院; 耐药菌株 FREC 由遵义医科大学附属医院分离提供。以环丙沙星 (Oxacillin) 对照药, 采用两倍稀释法测定目标物的 MIC, 测试方法参照文献[21]。

3 联合抗菌活性测试

采用微量稀释法, 调整细菌浓度为 10^5 CFU·mL^{-1}, 接种于 96 孔板, 加入不同的抗菌药, 依次倍比稀释, 使其终浓度自 32～0.062 5 μg·mL^{-1}; 再加入相应浓度的目标物, 使其浓度范围为 64～0.125 μg·mL^{-1}; 置 37 ℃培养箱孵育 24 h, 记录联合使用时的 MIC, 并计算抑菌浓度指数 (fractional inhibitory concentration index, FICI)。

作者贡献: 汪晴负责理化与活性数据整理、分析及论文撰写等; 钱春丽负责化学合成; 佘慧娴参与构效关系分析; 杨家强负责论文指导与修改等工作。

利益冲突: 本文所有作者声明不存在利益冲突关系。

References

[1] Boparai JK, Sharma PK. Mini review on antimicrobial peptides, sources, mechanism and recent applications [J]. Protein Pept Lett, 2020, 27: 4-16.

[2] Rezende SB, Oshiro KGN, Júnior NGO, et al. Advances on chemically modified antimicrobial peptides for generating peptide antibiotics [J]. Chem Commun, 2021, 57: 11578-11590.

[3] Zhong C, Zhang FY, Zhu NY. Ultra-short lipopeptides against Gram-positive bacteria while alleviating antimicrobial resistance [J]. Eur J Med Chem, 2021, 212: 113138.

[4] Yang HX, Cui AL, Wang YJ, et al. Synthesis and antibacterial activity evaluation of octapeptin derivatives [J]. Acta Pharm Sin (药学学报), 2024, 59: 152-160.

[5] Zhu X, Ma XC, Zhang XT, et al. Synthesis of ornithine peptidomimetic efflux pump inhibitors and synergistic antibiotic activity against *Pseudomonas aeruginosa* [J]. Acta Pharm Sin (药学学报), 2024, 59: 1720-1729.

[6] Gao Y, Cui JL, Cao S, et al. Recent advances in peptoids as promising antimicrobial agents to target diverse microbial species [J]. Eur J Med Chem, 2024, 280: 116982.

[7] Su XK, Zhou XY, Tan ZZ, et al. Highly efficient antibacterial diblock copolypeptides based on lysine and phenylalanine [J]. Biopolymers, 2017, 107: 3-4.

[8] Peng JX, Qiu S, Jia FJ, et al. The introduction of *L*-phenylalanine into antimicrobial peptide protonectin enhances the selective antibacterial activity of its derivative phe-Prt against Gram-positive bacteria [J]. Amino Acids, 2021, 53: 23-32.

[9] Zhou XR, Chen YM, She HX, et al. Synthesis and antibacterial activities of osthole derivatives containing *L*-phenylalanine [J]. Chin Pharm J (中国药学杂志), 2025, 60: 326-333.

[10] Das D, Sikdar P, Bairagi M. Recent developments of 2-amino-thiazoles in medicinal chemistry [J]. Eur J Med Chem, 2016, 109: 89-98.

[11] Tabei A, Ejtemaei R, Mahboubi A, et al. Synthesis of new 2-[5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-ylimino] thiazolidin-4-one derivatives as anti-MRSA and anti-*H. pylori* agents [J]. BMC Chem, 2022, 16: 38.

[12] Chen YM, An Y, Dong XT, et al. Synthesis and antibacterial activities of phosphonate derivatives containing aminothiazoloxime fragment [J]. Acta Pharm Sin (药学学报), 2024, 59: 161-165.

[13] Yang JQ, Wu XJ, Lu ZC, et al. Design, synthesis and antibacterial activities of osthole derivatives containing thiazole fragment [J]. Chin J Org Chem (有机化学), 2024, 44: 3541-3549.

[14] She HX, Chen YM, Yang JQ. Design, synthesis and antibacterial activities of thioxime amide derivatives containing thiopeptide [J]. Chem J Chin Univ (高等学校化学学报), 2025, 46: 20240548.

[15] Chen JP, Battini N, Ansari MF, et al. Membrane active 7-thiazoxime quinolones as novel DNA binding agents to decrease the genes expression and exert potent anti-methicillin-resistant *Staphylococcus aureus* activity [J]. Eur J Med Chem, 2021, 217: 113340.

[16] Chen YM, She HX, Wang Q, et al. Synthesis and antibacterial activities of osthole oxime ether derivatives [J]. Chem J Chin Univ (高等学校化学学报), 2025, 46: 20250147.

[17] Alfei S, Zuccari G. Recommendations to synthetize old and new β-lactamases inhibitors: A review to encourage further production [J]. Pharmaceuticals (Basel), 2022, 15: 384.

[18] Feng LS, Lv K, Liu ML, et al. Synthesis and *in vitro* antibacterial activity of gemifloxacin derivatives containing a substituted benzyloxime moiety [J]. Eur J Med Chem, 2012, 55: 125-136.

[19] Adkins H, Reeve EW. A synthesis of *DL*-threonine [J]. J Am Chem Soc, 1938, 60: 1329.

[20] Ascher G. New process for producing cephalosporin antibiotics, and novel intermediates for use in such process and their production: US, 4767852 [P]. 1988-08-30.

[21] CLSI. Performance Standards for Antimicrobial Susceptibility Testing. CLSI Supplement M100 [M]. 29th ed. Wayne: Clinical and Laboratory Standards Institute, 2019.