含氨基噻唑肟结构的膦酸酯衍生物的合成与抗菌活性研究

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摘要: 采用分子杂合原理, 将氨基噻唑肟与膦酸酯片段组合, 设计合成了15个目标物进行抗菌活性研究。结果显示: 该类衍生物对所测试细菌有较好的抑制作用, 尤以化合物**III f**和**III i**的抗金葡菌 (*S. aureus*)、大肠杆菌 (*E. coli*)、耐甲氧西林金葡菌 (MRSA) 和耐氟喹诺酮大肠杆菌 (FREC) 活性最为显著, 前者的最小抑菌浓度 (MIC) 分别为1、8、4和16 $\mu g\cdot mL^{-1}$, 后者的MIC分别为4、4、16和8 $\mu g\cdot mL^{-1}$, 抗*S. aureus*活性略低于苯唑西林, 抗*E. coli*、MRSA和FREC活性优于对照药苯唑西林, 值得进一步深入研究。

关键词: 氨基噻唑肟; 膦酸酯; 分子杂合; 合成; 抗菌活性

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Synthesis and antibacterial activities of phosphonate derivatives containing aminothiazoloxime fragment

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Abstract: Based on the principle of molecular hybridization, fifteen compounds were designed and synthesized through the combination of aminothiazoloxime and phosphonate fragment. The results showed that these compounds had better inhibitory effects on the tested bacteria. In particular, the activities of compounds **III f** and **III i** against *S. aureus*, *E. coli*, methicillin-resistant *S. aureus* (MRSA) and fluoroquinolone-resistant *E. coli* (FREC) were the most significant, the minimal inhibitory concentration (MIC) of **III f** was 1, 8, 4, 16 $\mu g\cdot mL^{-1}$ respectively, and the MIC of **III i** was 4, 4, 16, 8 $\mu g\cdot mL^{-1}$ respectively, which were slightly lower than that of the control drug oxacillin, and their anti-*E. coli*, MRSA and FREC activities were superior to that of the control drug oxacillin. Their activities to *S. aureus* were close to that of oxacillin, and to *E. coli*, MRSA and FREC were superior to that of oxacillin, which is worthy of further study.

Key words: aminothiazole oxime; phosphonate; molecular hybridization; synthesis; antibacterial activity

在有机磷化学中, α-氨基膦酸酯作为天然氨基酸的结构类似物, 具有抗菌[1]、抗真菌[2]、抗肿瘤[3]、抗病毒[4]、抗氧化[5]和抗阿尔茨海默病[6]等多种生物活性, 在医学、制药及农业等领域应用广泛[7,8], 受到化学家和生物学家的极大关注。研究表明, α-氨基膦酸酯衍生物对革兰阳性菌、革兰阴性菌和耐药菌等多种细菌有抑制作用。2020年, Poola等[9]设计合成了含不同官能团的α-氨基膦酸酯衍生物, 一些化合物对金葡菌、枯草芽孢杆菌、肺炎克雷伯菌和大肠杆菌的活性显著, 有望成为新的抗菌候选化合物; 2022年, K'tir等[10]设计合成了含噁噻唑烷的新型α-氨基膦酸酯, 对革兰阳性菌和阴性菌有较优的活性, 作用机制研究表明对YpDHPS靶点有潜在抑制作用, 可进一步开发为抑制DHPS的候选化合物; 另外, 2023年, Yang等[11]报道含香豆素结构的α-氨基膦酸酯衍生物对金葡菌也有显著的抑制活性, 能够破坏细菌细胞膜的完整性, 从而导致蛋白质的

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在药物分子结构中, 氨基噻唑常作为一种优势骨架[12-14], 已上市的药物中, 有许多以其为核心结构, 如法莫替丁、头孢替安、美洛司康等。其中, 2-氨基噻唑肟作为氨基噻唑的衍生结构, 近年来, 在抗菌药物研发中具有明显优势[15-17], 尤其是在第三、四代半合成头孢菌素类抗生素的设计和改造中, 通过引入2-氨基噻唑肟片段, 能扩大抗菌谱、增强活性、改善耐药性等作用, 对其药效学和动力学均有着重要影响, 如头孢噻肟、头孢匹罗、头孢喹肟等。

基于此, 本文采用分子杂合策略, 将优势骨架“2-氨基噻唑肟”与“α-氨基膦酸酯”活性片段结合, 设计合成系列含氨基噻唑肟结构的新型膦酸酯衍生物进行抗菌活性研究。目标物的合成路线如路线1所示。

结果与讨论

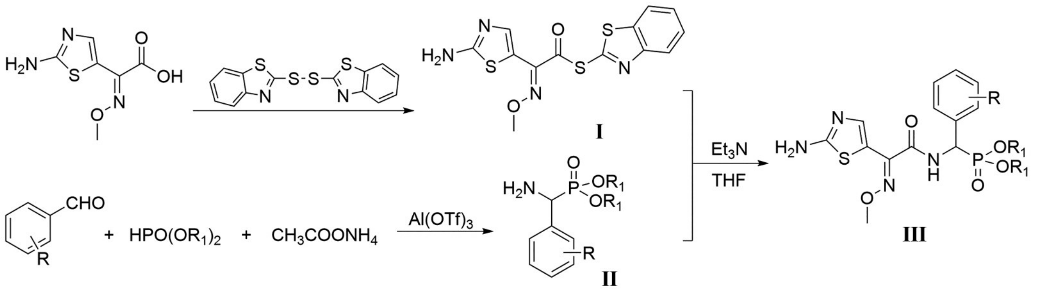
1　化合物的合成

按实验部分“1.1”方法, 优化中间体**I**的合成方法。首先, 考察溶剂对其收率的影响, 以乙腈和二氯甲烷为溶剂, 收率分别为73%和79%; 以四氢呋喃和1,2-二氯乙烷为溶剂, 收率分别为85%和88%。接着, 考察反应温度对其收率的影响, 在−5 ℃, 无反应, 在0 ℃和5 ℃, 收率较低, 分别为41%和66%; 随着温度由10 ℃升高到15 ℃, 收率由76%逐渐达到88%; 但当温度超过20 ℃, 溶液就会变稠, 颜色也会有所加深, 生成的副产物较多, 收率明显降低。最后, 考察脱水剂对其收率的影响, 以无机酸浓硫酸和浓磷酸为脱水剂, 收率较低, 约50%左右, 而采用有机脱水剂三苯基膦和亚磷酸三乙酯, 收率分别为84%和88%, 收率有很大提高。综上, 中间体**I**的最优合成条件为: 在15 ℃下, 以亚磷酸三乙酯为催化剂, 1,2-二氯乙烷为溶剂。

目标物结构经^{1}H NMR、^{13}C NMR及MS得以确证, 理化数据见表1和表2。

Table 1　Physical property of compounds **IIIa−IIIo**

Compd.	Appearance	Yield/%	mp/℃
IIIa	White solid	66	161−162
IIIb	White solid	68	165−166
IIIc	White solid	70	179−180
IIId	White solid	75	171−172
IIIe	White solid	80	167−169
IIIf	White solid	87	169−170
IIIg	White solid	78	222−224
IIIh	White solid	65	213−214
IIIi	White solid	80	214−215
IIIj	White solid	61	192−193
IIIk	White solid	90	187−188
IIIl	White solid	89	182−183
IIIm	White solid	68	185−187
IIIn	White solid	69	188−189
IIIo	White solid	60	188−190



Scheme 1　Synthetic route of target compounds

Table 2　Spectral data of target compounds **IIIa−IIIo**

Compd.	^{1}H NMR, ^{13}C NMR and MS
IIIa	^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.28 (s, 1H, CONH), 7.49 (d, 2H, J = 8.0 Hz, ArH), 7.32−7.37 (m, 3H, ArH), 6.63 (s, 1H, ArH), 6.30 (s, 2H, NH$_2$), 5.70 (dd, 1H, J = 8.0, 8.0 Hz, PCH), 3.88 (s, 3H, CH$_3$), 3.73 (d, 3H, J = 8.0 Hz, CH$_3$), 3.65 (d, 3H, J = 12.0 Hz, CH$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 169.9, 163.3, 160.7, 148.3, 142.3, 133.7, 132.6, 128.2, 128.0, 127.9, 110.1, 61.5, 53.2, 53.0, 48.4. ESI MS (m/z): 399.1 [M+H]$^+$.
IIIb	^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.21 (s, 1H, CONH), 7.62 (t, 1H, J=12.0 Hz, ArH), 7.33-7.36 (m, 1H, ArH), 7.18−7.23 (m, 2H, ArH), 6.62 (s, 1H, ArH), 6.32 (s, 2H, NH$_2$), 5.84 (dd, 1H, J = 12.0, 12.0 Hz, PCH), 3.73 (s, 3H, CH$_3$), 3.65 (d, 3H, J = 12.0 Hz, CH$_3$), 3.53 (d, 3H, J = 12.0 Hz, CH$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 168.8, 162.6, 160.7 ($J_{\text{C-F}}$ = 77 Hz), 158.4, 149.4, 143.3, 130.5, 125.0, 122.7, 115.7, 115.6, 109.8, 62.3, 55.3, 54.2, 53.7. ESI MS (m/z): 417.1 [M+H]$^+$.
IIIc	^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.29 (s, 1H, CONH), 7.51 (d, J = 16.0 Hz, 2H, ArH), 7.08−7.13 (m, 2H, ArH), 6.65 (s, 1H, ArH), 6.28 (s, 2H, NH$_2$), 5.70 (dd, 1H, J = 12.0, 12.0 Hz, PCH), 3.88 (s, 3H, CH$_3$), 3.74 (d, 3H, J = 12.0 Hz, CH$_3$), 3.67 (d, 3H, J = 12.0 Hz, CH$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 170.0, 163.9, 163.2 ($J_{\text{C-F}}$ = 12 Hz), 161.4, 148.3, 142.3, 130.1, 130.0, 115.1, 114.9, 110.0, 61.5, 53.3, 53.0, 49.3. ESI MS (m/z): 417.1 [M+H]$^+$.

Continued

Compd.	^{1}H NMR, ^{13}C NMR and MS
IIId	^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.26 (s, 1H, CONH), 7.49 (d, 2H, J = 8.0 Hz, ArH), 7.34−7.37 (m, 3H, ArH), 6.63 (s, 1H, ArH), 6.32 (s, 2H, NH$_2$), 5.64 (dd, 1H, J = 8.0, 8.0 Hz, PCH), 3.92−4.01 (m, 4H, 2CH$_2$), 3.89 (s, 3H, CH$_3$), 1.25 (t, 3H, J = 12.0 Hz, CH$_3$), 1.18 (t, 3H, J = 16.0 Hz, CH$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 169.8, 163.3, 161.6, 148.3, 142.4, 133.9, 132.8, 128.2, 128.1, 127.9, 110.2, 63.5, 63.3, 61.5, 50.6, 15.3, 15.1. ESI MS (m/z): 427.1 [M+H]$^+$.
IIIe	^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.23 (s, 1H, CONH), 7.62 (t, 1H, J = 8.0 Hz, ArH), 7.33−7.35 (m, 1H, ArH), 7.11−7.20 (m, 2H, ArH), 6.59 (s, 1H, ArH), 6.33 (s, 2H, NH$_2$), 5.79 (dd, 1H, J = 12.0, 12.0 Hz, PCH), 3.82−4.02 (m, 4H, 2CH$_2$), 3.72 (s, 3H, CH$_3$), 1.16 (t, 3H, J = 12.0 Hz, CH$_3$), 1.03 (t, 3H, J = 16.0 Hz, CH$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 168.8, 162.7, 160.9 ($J_{\text{C-F}}$ = 98 Hz), 158.5, 149.4, 143.4, 130.6, 124.9, 122.8, 115.6, 115.4, 109.9, 63.3, 63.0, 62.3, *53.7*, 16.7, 16.5. ESI MS (m/z): 445.2 [M+H]$^+$.
IIIf	^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.28 (s, 1H, CONH), 7.50−7.54 (m, 2H, ArH), 7.08−7.13 (m, 2H, ArH), 6.65 (s, 1H, ArH), 6.31 (s, 2H, NH$_2$), 5.64 (dd, 1H, J = 12.0, 12.0 Hz, PCH), 3.99−4.12 (m, 4H, 2CH$_2$), 3.90 (s, 3H, CH$_3$), 1.25 (d, 3H, J = 16.0 Hz, CH$_3$), 1.20 (d, 3H, J = 16.0 Hz, CH$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 168.7, 163.2, 162.5 ($J_{\text{C-F}}$ = 9 Hz), 160.6, 149.5, 143.5, 130.8, 130.7, 115.5, 115.3, 109.9, 63.1, 62.9, 62.3, 48.2, 16.6, 16.5. ESI MS (m/z): 445.1 [M+H]$^+$.
IIIg	^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.66 (s, 1H, CONH), 7.46−7.48 (m, 2H, ArH), 7.27−7.34 (m, 3H, ArH), 6.61 (s, 1H, ArH), 6.33 (s, 2H, NH$_2$), 5.49 (dd, 1H, J = 16.0, 16.0 Hz, PCH), 4.63−4.75 (m, 1H, CH), 4.49−4.57 (m, 1H, CH), 3.75 (s, 3H, CH$_3$), 1.07−1.36 (m, 12H, 4CH$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 168.7, 162.6, 161.4, 143.6, 135.4, 128.8, 128.7, 128.5, 128.1, 114.9, 109.9, 72.8, 72.6, 61.5, 56.5, 23.0, 22.9, 22.7, 22.2. ESI MS (m/z): 455.2 [M+H]$^+$.
IIIh	^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.25 (s, 1H, CONH), 7.58−7.62 (m, 1H, ArH), 7.33−7.37 (m, 1H, ArH), 7.11−7.21 (m, 2H, ArH), 6.62 (s, 1H, ArH), 6.31 (s, 2H, NH$_2$), 5.94 (dd, 1H, J = 12.0, 12.0 Hz, PCH), 4.69-4.73 (m, 1H, CH), 4.50−4.55 (m, 1H, CH), 3.85 (s, 3H, CH$_3$), 1.07−1.34 (m, 12H, 4CH$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 169.9, 163.3, 161.3 ($J_{\text{C-F}}$ = 74 Hz), 158.8, 148.4, 142.3, 130.0, 129.7, 124.0, 114.9, 110.2, 72.8, 72.5, 61.5, 56.5, 23.0, 22.9, 22.7, 22.2. ESI MS (m/z): 473.2 [M+H]$^+$.
IIIi	^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.01 (s, 1H, CONH), 7.58−7.61 (m, 2H, ArH), 6.95−6.99 (m, 2H, ArH), 6.65 (s, 1H, ArH), 6.22 (s, 2H, NH$_2$), 5.60 (dd, 1H, J = 16.0, 16.0 Hz, PCH), 4.68−4.74 (m, 1H, CH), 4.24−4.32 (m, 1H, CH), 3.69 (s, 3H, CH$_3$), 1.18−1.38 (m, 12H, 4CH$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 168.2, 163.8, 161.6 ($J_{\text{C-F}}$ = 7 Hz), 161.3, 147.0, 143.6, 131.4, 129.6, 115.3, 115.1, 110.5, 73.2, 72.3, 61.9, 58.3, 24.2, 24.1, 23.9, 22.9. ESI MS (m/z): 473.2 [M+H]$^+$.
IIIj	^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.25 (s, 1H, CONH), 7.63 (d, 2H, J = 8.0 Hz, ArH), 7.22−7.30 (m, 3H, ArH), 6.63 (s, 1H, ArH), 6.26 (s, 2H, NH$_2$), 5.70 (dd, 1H, J = 16.0, 16.0 Hz, PCH), 4.05−4.27 (m, 2H, CH$_2$), 3.46−3.75 (m, 2H, CH$_2$), 3.22 (s, 3H, CH$_3$), 1.65−1.72 (m, 2H, CH$_2$), 1.38−1.45 (m, 2H, CH$_2$), 1.30−1.35 (m, 2H, CH$_2$), 1.09−1.22 (m, 2H, CH$_2$), 0.89 (t, 3H, J = 16.0 Hz, CH$_3$), 0.74 (t, 3H, J = 12.0 Hz, CH$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 168.2, 163.3, 161.9, 146.9, 143.8, 133.0, 128.2, 126.6, 125.3, 122.6, 110.1, 67.5, 67.3, 61.9, 49.0, 32.4, 32.2, 18.7, 18.4, 13.6, 13.4. ESI MS (m/z): 483.2 [M+H]$^+$.
IIIk	^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.17 (s, 1H, CONH), 7.31−7.46 (m, 1H, ArH), 7.21−7.26 (m, 1H, ArH), 7.10−7.14 (m, 1H, ArH), 6.98−7.02 (m, 1H, ArH), 6.67 (s, 1H, ArH), 6.16−6.23 (m, 3H, PCH+NH$_2$), 4.08−4.36 (m, 2H, CH$_2$), 3.60−3.72 (m, 2H, CH$_2$), 3.31 (s, 3H, CH$_3$), 1.67−1.74 (m, 2H, CH$_2$), 1.33−1.46 (m, 4H, 2CH$_2$), 1.11−1.23 (m, 2H, CH$_2$), 0.90 (t, 3H, J = 16.0 Hz, CH$_3$), 0.75 (t, 3H, J = 16.0 Hz, CH$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 168.2, 162.2, 161.9 ($J_{\text{C-F}}$ = 81 Hz), 154.4, 143.6, 129.7, 126.6, 125.3, 122.6, 114.7, 110.3, 67.7, 67.3, 62.0, 53.4, 32.4, 32.2, 18.4, 18.3, 13.6, 13.4. ESI MS (m/z): 501.2 [M+H]$^+$.
IIIl	^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.31 (s, 1H, CONH), 7.64 (d, 2H, J = 8.0 Hz, ArH), 6.96−6.98 (m, 2H, ArH), 6.62 (s, 1H, ArH), 6.31 (s, 2H, NH$_2$), 5.69 (dd, 1H, J = 16.0, 16.0 Hz, PCH), 4.04−4.28 (m, 2H, CH$_2$), 3.52−3.78 (m, 2H, CH$_2$), 3.23 (s, 3H, CH$_3$), 1.65−1.72 (m, 2H, CH$_2$), 1.33−1.45 (m, 4H, 2CH$_2$), 1.11−1.22 (m, 2H, CH$_2$), 0.89 (t, 3H, J = 16.0 Hz, CH$_3$), 0.76 (t, 3H, J = 12.0 Hz, CH$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 168.3, 163.7, 161.9 ($J_{\text{C-F}}$ = 10 Hz), 146.9, 143.7, 131.4, 126.6, 125.3, 115.4, 115.2, 110.1, 67.6, 67.5, 61.9, 48.2, 32.4, 32.2, 18.7, 18.4, 13.6, 13.4. ESI MS (m/z): 501.2 [M+H]$^+$.
IIIm	^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.29 (s, 1H, CONH), 7.63 (d, 2H, J = 4.0 Hz, ArH), 7.22−7.32 (m, 3H, ArH), 6.62 (s, 1H, ArH), 6.30 (s, 2H, NH$_2$), 5.71 (dd, 1H, J = 16.0, 16.0 Hz, PCH), 3.80−4.12 (m, 2H, CH$_2$), 3.50-3.71 (m, 2H, CH$_2$), 3.42 (s, 3H, CH$_3$), 1.94−2.00 (m, 1H, CH), 1.58−1.65 (m, 1H, CH), 0.94−0.96 (m, 6H, 2CH$_3$), 0.67 (t, 6H, J = 16.0 Hz, 2CH$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 168.2, 161.9, 146.9, 143.7, 128.3, 128.1, 126.6, 125.3, 122.6, 121.3, 110.0, 73.5, 73.3, 61.9, 49.0, 29.2, 29.0, 18.8, 18.7, 18.4, 18.3. ESI MS (m/z): 511.2 [M+H]$^+$.
IIIn	^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.26 (s, 1H, CONH), 8.01−8.03 (m, 1H, ArH), 7.19−7.23 (m, 1H, ArH), 7.08−7.11 (m, 1H, ArH), 6.96−7.00 (m, 1H, ArH), 6.64 (s, 1H, ArH), 6.30 (s, 2H, NH$_2$), 6.17 (dd, 1H, J = 16.0, 16.0 Hz, PCH), 4.12−4.18 (m, 1H, CH$_2$), 3.83−3.88 (m, 1H, CH$_2$), 3.55−3.61 (m, 1H, CH$_2$), 3.33−3.39 (m, 1H, CH$_2$), 3.27 (s, 3H, CH$_3$), 1.93−2.01 (m, 1H, CH), 1.60−1.67 (m, 1H, CH), 0.95−0.97 (m, 6H, 2CH$_3$), 0.69 (t, 6H, J = 12.0 Hz, 2CH$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 168.3, 161.9 ($J_{\text{C-F}}$ = 89 Hz), 158.4, 146.9, 143.6, 131.9, 129.8, 125.3, 121.3, 114.7, 110.1, 73.7, 73.2, 61.9, 42.1, 29.2, 29.0, 18.8, 18.7, 18.3, 18.2. ESI MS (m/z): 529.2 [M+H]$^+$.
IIIo	^{1}H NMR (400 MHz, CDCl$_3$) δ: 9.25 (s, 1H, CONH), 7.62−7.65 (m, 2H, ArH), 6.96−7.00 (m, 2H, ArH), 6.62 (s, 1H, ArH), 6.26 (s, 2H, NH$_2$), 5.69 (dd, 1H, J = 16.0, 16.0 Hz, PCH), 4.07−4.12 (m, 1H, CH$_2$), 3.80−3.85 (m, 1H, CH$_2$), 3.54−3.60 (m, 1H, CH$_2$), 3.29−3.33 (m, 1H, CH$_2$), 3.26 (s, 3H, CH$_3$), 1.94−2.02 (m, 1H, CH), 1.62−1.69 (m, 1H, CH), 0.95−0.97 (m, 6H, 2CH$_3$), 0.71 (t, 6H, J = 12.0 Hz, 2CH$_3$). ^{13}C NMR (101 MHz, CDCl$_3$) δ: 168.3, 163.8, 161.8 ($J_{\text{C-F}}$ = 7 Hz), 161.3, 146.9, 143.6, 131.3, 129.0, 115.4, 115.2, 110.1, 73.6, 73.4, 61.8, 48.2, 29.2, 29.0, 18.8, 18.7, 18.4, 18.3. ESI MS (m/z): 529.2 [M+H]$^+$.

2　活性评价

由表3可知, 该类衍生物具有潜在抗菌活性, 部分化合物的活性较为显著。其中, 化合物**IIIc**、**IIId**、**IIIe**、**IIIf**、**IIIh**和**IIIi**对*S. aureus*的MIC分别为32、32、8、1、32和4 μg·mL^{-1}, **IIIf**和**IIIi**的活性略低于苯唑西林(MIC = 0.5 μg·mL^{-1}); 化合物**IIIe**、**IIIf**、**IIIh**和**IIIi**对

Table 3 Minimal inhibitory concentration (MIC) values of different target compounds. MRSA: Methicillin-resistant *S. aureus*; FREC: Fluoroquinolone-resistant *E. coli*

Compd.	R	R_1	MIC/μg·mL^{-1}			
			S. aureus	*E. coli*	MRSA	FREC
IIIa	H	CH_3	256	256	1 024	512
IIIb	2-F	CH_3	128	128	128	512
IIIc	4-F	CH_3	32	64	128	64
IIId	H	C_2H_5	32	128	32	128
IIIe	2-F	C_2H_5	8	16	8	32
IIIf	4-F	C_2H_5	1	8	4	16
IIIg	H	$CH(CH_3)_2$	64	64	64	64
IIIh	2-F	$CH(CH_3)_2$	32	16	32	32
IIIi	4-F	$CH(CH_3)_2$	4	4	16	8
IIIj	H	$(CH_2)_3CH_3$	1 024	1 024	>1 024	>1 024
IIIk	2-F	$(CH_2)_3CH_3$	512	1 024	1 024	1 024
IIIl	4-F	$(CH_2)_3CH_3$	256	512	256	512
IIIm	H	$(CH_2)_2CH(CH_3)_2$	>1 024	1 024	>1 024	>1 024
IIIn	2-F	$(CH_2)_2CH(CH_3)_2$	1 024	512	>1 024	512
IIIo	4-F	$(CH_2)_2CH(CH_3)_2$	1 024	256	>1 024	1 024
Oxacillin			0.5	16	256	64

E. coli 的MIC分别为16、8、16和4 μg·mL^{-1}, **IIIe**和**IIIh**的活性与苯唑西林 (MIC = 16 μg·mL^{-1}) 相当, **IIIf**和**IIIi**的活性优于苯唑西林; 化合物**IIId**、**IIIe**、**IIIf**、**IIIh**和**IIIi**对MRSA的MIC分别为32、8、4、32和16 μg·mL^{-1}, 优于苯唑西林 (MIC = 256 μg·mL^{-1}); 化合物**IIIe**、**IIIf**、**IIIh**和**IIIi**对FREC的MIC分别为32、16、32和8 μg·mL^{-1}, 优于苯唑西林 (MIC = 64 μg·mL^{-1})。综合来看, 在所设计合成的衍生物中, 目标物**IIIf**和**IIIi**对*S. aureus*、*E. coli*、MRSA和FREC的活性最为突出, 且具有广谱性。

构效关系分析: ① R为氟原子取代且位于苯环对位的目标物通常有更好的抗菌活性, 可能与靶标的结合位点或作用力有关; ② 取代基R_1为甲基、丁基和异戊基时, 抗菌活性都不佳, 为乙基和异丙基时, 抗菌活性较为显著, 推测取代基R_1需要合适的大小, 可能与空间效应有关。

3 小结

依据分子杂合策略, 设计合成的含氨基噻唑肟结构的膦酸酯衍生物有较好的抗菌活性, 尤其是化合物**IIIf**和**IIIi**对*S. aureus*和*E. coli*的活性与对照药相当, 对MRSA和FREC的活性优于对照药。后续有必要以此结合体为基础, 进一步丰富取代基或官能团的类型和位置, 进行结构优化与深入研究。

实验部分

用SGW X-4显微熔点仪测定熔点; NMR用Bruker Avance 400型核磁共振仪测定; 质谱数据用Agilent 6460质谱仪测得。

氨基噻肟酸、二硫化二苯并噻唑、亚磷酸三乙酯、三乙胺、苯甲醛、邻氟苯甲醛、对氟苯甲醛、三氟甲磺酸铝、亚磷酸二甲酯、亚磷酸二乙酯、亚磷酸二异丙酯、亚磷酸二丁酯、亚磷酸二异戊酯、三苯基膦均为化学纯, 购于百灵威试剂有限公司; 其余溶剂或试剂均为分析纯, 购于安徽优昇生物科技有限公司。

1 化合物的合成

1.1 中间体I的合成 在15 ℃下, 依次将二硫化二苯并噻唑6.75 mmol和1,2-二氯乙烷20 mL加入50 mL反应瓶中, 反应20 min, 再加入氨基噻肟酸5 mmol, 反应30 min, 再加入三乙胺2.5 mmol, 反应60 min, 再加入亚磷酸三乙酯6.75 mmol, 反应4 h, 减压过滤, 干燥, 得淡黄色粉末, 即中间体**I**。

1.2 中间体II的合成 依次称取芳香甲醛2.4 mmol、乙酸铵2 mmol和亚磷酸酯2 mmol于50 mL反应瓶中, 室温反应10 min, 再加入三氟甲磺酸铝0.01 mmol, 在95 ℃下反应, 薄层色谱法跟踪, 完毕, 加20 mL蒸馏水; 接着, 用1 mol·L^{-1}的盐酸酸化至pH 1, 用环己烷萃取4次, 乙酸乙酯萃取4次, 1 mol·L^{-1}的氢氧化钠碱化至pH 7～8; 最后, 用乙酸乙酯萃取6次, 合并萃取液, 减压浓缩, 得中间体**II**。

1.3 目标物III的合成 取中间体**II** 0.5 mmol、四氢呋喃20 mL和三乙胺0.3 g于50 mL反应瓶中, 搅拌下, 将中间体**I** 0.6 mmol加至反应瓶中, 室温反应, 薄层色谱法跟踪, 完毕, 减压过滤, 再用四氢呋喃重结晶, 制得目标物**III**。

2 体外抗菌活性测试

金葡菌、大肠埃希菌源于北京北纳创联生物技术研究院; 耐药菌株: 耐甲氧西林金葡菌和耐氟喹诺酮大肠杆菌, 由遵义医科大学附属医院分离提供。以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[18]。

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