稠环磺酰胺衍生物的合成与抗菌活性研究

杨家强*, 王 越, 周绪容, 吴学姣

(遵义医科大学药学院, 贵州 遵义 563000)

摘要: 为了寻找抗菌候选化合物, 在前期研究基础上, 18个稠环磺酰胺衍生物被设计合成, 经^{1}H NMR、^{13}C NMR和MS确认结构。采用两倍稀释法对目标物进行体外抗菌活性测试, 结果表明: 该类衍生物对所测细菌有不同程度的抑制活性, 尤以化合物**IIi**、**IIr**的抗菌活性最为突出, 其中前者对金葡菌 (*S. aureus*)、大肠埃希菌 (*E. coli*) 和耐甲氧西林金葡菌 (MRSA) 的最小抑菌浓度 (MIC) 分别为8、32和16 μg·mL^{-1}, 后者对*S. aureus*、*E. coli*及MRSA的MIC分别为8、64和32 μg·mL^{-1}, 两者的抗MRSA活性较显著, 值得进一步结构优化和深入研究。

关键词: 磺酰胺; 稠环化合物; 膦酸酯; 合成; 抗菌活性

中图分类号: R916 **文献标识码**: A **文章编号**: 0513-4870(2021)03-0835-06

Synthesis and antibacterial activities of novel sulfonamide derivatives containing a fused-ring

YANG Jia-qiang*, WANG Yue, ZHOU Xu-rong, WU Xue-jiao

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

Abstract: To find antibacterial candidate compounds, eighteen novel sulfonamide derivatives containing a fused-ring were designed and synthesized on the basis of previous studies, with structures confirmed by ^{1}H NMR, ^{13}C NMR and MS. Antibacterial activities of the products were evaluated by the agar dilution method. The results show that these derivatives have different degrees of inhibitory activity on the tested bacteria, with the compounds **IIi** and **IIr** the most potent. The MIC of **IIi** for *S. aureus*, *E. coli* and MRSA was 8, 32 and 16 μg·mL^{-1}, respectively, and the MIC of the **IIr** was 8, 64 and 32 μg·mL^{-1}, respectively. The anti-MRSA activities of the two compounds is significant and is worthy of further structural optimization and study.

Key words: sulfanilamide; fused-ring compound; phosphonate; synthesis; antibacterial activity

随着抗生素耐药性 (AMR) 的不断增加, 已有抗生素对新出现的耐药菌株缺乏有效治疗, 已成为影响人类健康的重要问题。AMR危机涉及各种类型的抗生素, 一些抗生素曾经被认为是对付常见感染的最后手段, 都相继检测出多药耐药性 (MDR), 预计到2050年, 因感染疾病治疗失败而导致的死亡人数将会达到1 000万[1,2]。其中, MRSA作为医院和社区获得性感染的主要病原菌, 被世界卫生组织认定为高度优先的抗生素耐药病原体, MRSA菌株对多种抗菌药物都有抗药性[3,4], 这就对MRSA感染治疗提出了更高的要求。因此, 迫切需要研发安全、高效的抗菌药物来克服多耐药菌株的传播。

磷元素常常被称为“生命活动的调控中心”, 含磷化合物有着良好和广泛的生物活性。研究表明: 膦酸酯类化合物作为有机磷类衍生物, 有着优秀的抗菌活性, 尤其是对耐药性细菌有较好的抑制作用[5,6]。如头孢罗膦[7]和特地唑胺磷酸酯[8], 对包括MRSA及甲氧西林敏感菌株 (MSSA) 等多种细菌感染都有很好治疗作用。课题组前期相继设计合成了多个系列膦酸酯衍生物[9-11], 结果表明部分化合物对MRSA、耐喹诺酮金葡

收稿日期: 2020-11-26; 修回日期: 2020-12-28.
基金项目: 贵州省科技厅国际合作项目 (黔科合外G字 [2014] 7013).
*通讯作者 Tel: 86-851-28642339, E-mail: yjqcn@126.com
DOI: 10.16438/j.0513-4870.2020-1810

菌等有抑制活性。

磺胺类药物作为最早应用于临床的化学合成抗菌药, 自1932年Domagk发现百浪多息能有效治疗由金葡菌和链球菌引起的感染以来, 人们对磺胺类化合物在抗菌方面的应用研究从未停止。近年来, 一些新型磺胺化合物通过多靶标作用, 呈现较好的抗耐药菌活性, 现已成为抗耐药菌药物研究的新方向之一[12,13]。为此, 以前期抗菌类膦酸酯衍生物为基础, 课题组进一步设计合成了含苯磺酰胺、噻吩磺酰胺结构的膦酸酯衍生物[14,15], 其中活性最好的化合物对 *S. aureus* 和MRSA的MIC分别为16和32 μg·mL^{-1}。上述研究表明膦酸酯骨架和磺酰胺结构的杂合体, 可能在抗耐药菌方面发挥重要作用。

稠环结构在抗菌药物的设计和应用十分广泛, 如含萘环的萘夫西林[16]、含喹啉环的头孢喹肟[17]、香豆素类的新生霉素[18]等, 不同稠环的连接, 增强了与靶点的结合力或产生多靶标结合作用, 改善了药物抗菌谱或提高抗菌活性。

基于上述理论依据与研究基础, 为了进一步优化前期研究的系列化合物, 本文运用抗菌药物杂合、活性结构片段组合等药物设计原理, 将不同类的稠环与膦酸酯通过磺酰胺连接在一起, 设计合成系列稠环磺酰胺衍生物进行抗菌活性研究。目标化合物的合成见合成路线1。

结果与讨论

1 化合物的合成与结构表征

中间体**I**的合成: 以**Ia**为例, 参考文献[19]的类似方法合成, 并对制备方法进行优化和改进。反应温度从70 ℃到110 ℃, 收率不断增大, 在110 ℃达最高值64%; 但当温度控制在120 ℃反应, 收率下降至41%, 从TLC跟踪监测来看, 有副产物生成。说明温度对该反应有重要影响, 在反应过程中需控制好温度。

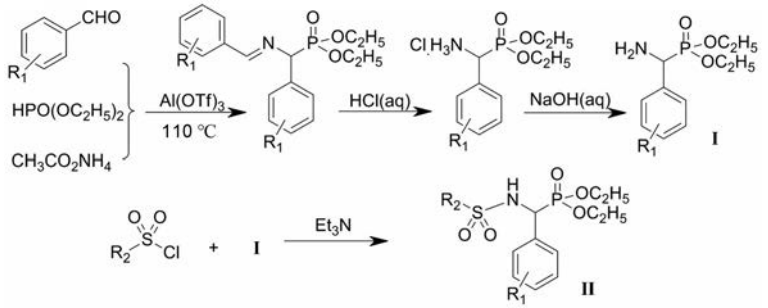
在目标化合物**II**的^{1}H NMR中: δ 6.28～9.02处的多重峰归属于稠环芳香环上的H和phCH=CH-上的H, 其中在7.38～8.55处的二重峰归属于磺酰胺结构中NH上的H, δ 4.59～5.23处的dd双峰归属于P-CH结构上的H, δ 3.44～4.37处的多重峰归属于膦酸二乙酯结构中两个-CH_2O-上的4个H, δ 0.85～1.42处的三重峰归属于膦酸二乙酯结构中-CH_3上的3个H。

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

2 抗菌活性

由表3可知, 目标化合物对所测试细菌有不同程度的抑制活性, 化合物**IIg**、**IIh**、**IIi**、**III**、**IIp**、**IIq**和**IIr**对 *S. aureus* 的MIC分别为64、64、8、64、64、32和8 μg·mL^{-1}, 化合物**IIh**、**IIi**、**IIq**和**IIr**对 *E. coli* 的MIC分别为64、32、32和64 μg·mL^{-1}, 化合物**IIh**、**IIi**、**IIq**和**IIr**对MRSA的MIC分别为64、16、64和32 μg·mL^{-1}。尤以化合物**IIi**和**IIr**的抗菌活性最为显著, 其中**IIi**对 *S. aureus*、*E. coli* 和MRSA的MIC分别为8、32和16 μg·mL^{-1}, 化合物**IIr**对 *S. aureus*、*E. coli* 和MRSA的MIC分别为8、64和32 μg·mL^{-1}, 两个化合物最突出的是抗MRSA活性, 有作为抗MRSA先导化合物的潜质。

构效关系分析: ① 取代基R_1为4-F的化合物抗 *S. aureus* 活性大多优于相同母体的2-F取代或无取代化合物, 如化合物**IIf**优于化合物**IId**和**IIe**, 化合物**IIi**优于化合物**IIg**和**IIh**, 化合物**IIr**优于化合物**IIp**和**IIq**;



Ia: R_1 = H; **Ib**: R_1 = 2-F; **Ic**: R_1 = 4-F

IIa: R_1 = H, R_2 =  ; **IIb**: R_1 = 2-F, R_2 =  ; **IIc**: R_1 = 4-F, R_2 =  ; **IId**: R_1 = H, R_2 =  ; **IIe**: R_1 = 2-F, R_2 =  ; **IIf**: R_1 = 4-F, R_2 =  ; **IIg**: R_1 = H, R_2 =  ; **IIh**: R_1 = 2-F, R_2 =  ; **IIi**: R_1 = 4-F, R_2 =  ; **IIj**: R_1 = H, R_2 =  ; **IIk**: R_1 = 2-F, R_2 =  ; **IIl**: R_1 = 4-F, R_2 =  ; **IIm**: R_1 = H, R_2 =  ; **IIn**: R_1 = 2-F, R_2 =  ; **IIo**: R_1 = 4-F, R_2 =  ; **IIp**: R_1 = H, R_2 =  ; **IIq**: R_1 = 2-F, R_2 =  ; **IIr**: R_1 = 4-F, R_2 = 

Scheme 1 Synthetic route of target compounds

Table 1 Physical property of compounds **Ia**–**Ic and IIa**–**IIr**

Compd.	Appearance	Yield/%	mp/℃
Ia	Colorless liquid	64	–
Ib	Colorless liquid	62	–
Ic	Colorless liquid	68	–
IIa	Yellow solid	53	166.5–168.2
IIb	Yellow solid	57	165.3–166.5
IIc	Yellow solid	62	156.8–158.1
IId	White solid	60	101.2–102.4
IIe	White solid	58	100.6–101.7
IIf	White solid	78	115.3–116.4
IIg	Yellow solid	75	205.3–207.1
IIh	White solid	53	190.4–192.2
IIi	Yellow solid	54	221.3–223.1
IIj	White solid	52	171.9–173.3
IIk	Yellow solid	69	210.1–211.1
IIl	White solid	66	162.5–164.2
IIm	White solid	42	216.8–218.2
IIn	White solid	77	215.3–216.5
IIo	Yellow solid	46	190.4–192.0
IIp	Yellow solid	42	130.8–131.7
IIq	Yellow solid	79	131.4–132.6
IIr	Yellow solid	60	129.9–131.2

② 在苯并六元环的稠环化合物中, 稠杂环类目标物的抗菌活性更优, 如化合物**IId**～**IIi**的活性优于化合物**IIa**～**IIc**, 可能与靶标有更好的结合; ③ 在苯并五元环的稠环化合物中, 含杂原子多的目标物**IIp**、**IIq**的抗菌活性优于目标物**IIj**～**IIo**, 以R_2为香豆素环的目标物有更优的抗菌活性, 如化合物**IIh**、**IIi**、**IIq**和**IIr**的活性明显优于其他化合物, 同时5取代化合物有更好的抗菌活性; ④ 与课题前期研究[14,15]的两类含磺酰胺化合物比较, 该类化合物的抗*S. aureus*和MRSA活性更优, 表明部分稠环 (苯并噻二唑环和香豆素环) 的引入对该类化合物的抗菌活性有促进作用。

3 小结

本文对含膦酸酯结构的磺酰胺衍生物进行结构优化, 设计合成了18个稠环磺酰胺衍生物, 活性测试结果表明: 该类衍生物具有潜在抗菌活性, 尤以含苯并噻二唑环和香豆素环的磺酰胺衍生物的抗MRSA活性更优, 值得进一步结构优化和深入研究其作用机制。

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 (TMS为内标); 质谱数据用Agilent 6460质谱仪测得。

Table 2 Spectral data of compounds **Ia**–**Ic and IIa**–**IIr**

Compd.	^{1}H NMR, ^{13}C NMR and MS
Ia	^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.29–7.46 (m, 5H, ArH), 4.26 (d, 1H, J = 20.0 Hz, CH), 3.83–4.06 (m, 4H, 2CH_2), 2.01 (s, 2H, NH_2), 1.28 (t, 3H, J = 8.0 Hz, CH_3), 1.18 (t, 3H, J = 8.0 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 16.3, 16.5, 54.5, 54.6, 62.8, 62.9, 127.7, 127.8, 127.9, 128.4, 128.5, 137.3.
Ib	^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.05–7.58 (m, 4H, ArH), 4.07 (d, 1H, J = 20.0 Hz, CH), 3.91–4.17 (m, 4H, 2CH_2), 2.04 (s, 2H, NH_2), 1.32 (t, 3H, J = 8.0 Hz, CH_3), 1.17 (t, 3H, J = 8.0 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 16.3, 16.4, 54.2, 54.3, 62.7, 62.8, 115.3, 124.4, 128.1, 128.6, 129.3, 160.7.
Ic	^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.62–7.70 (m, 1H, ArH), 7.41–7.47 (m, 1H, ArH), 7.02–7.13 (m, 2H, ArH), 4.25 (d, 1H, J = 20.0 Hz, CH), 3.89–4.09 (m, 4H, 2CH_2), 2.03 (s, 2H, NH_2), 1.28 (t, 3H, J = 8.0 Hz, CH_3), 1.20 (t, 3H, J = 8.0 Hz, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 16.2, 16.3, 54.2, 54.3, 62.4, 62.5, 115.0, 111.5, 129.5, 129.6, 133.6, 163.9.
IIa	^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 (d, 1H, J = 8.0 Hz, NH), 8.01 (d, 1H, J = 8.0 Hz, ArH), 7.70–7.75 (m, 2H, ArH), 7.45–7.48 (m, 2H, ArH), 7.23–7.25 (m, 1H, ArH), 6.75–6.91 (m, 6H, ArH), 4.61 (dd, 1H, J = 8.0, 8.0 Hz, PCH), 4.06–4.15 (m, 2H, OCH_2), 3.74–3.78 (m, 1H, OCH_2), 3.44–3.50 (m, 1H, OCH_2), 1.20 (t, 3H, J = 20.0 Hz, CH_3), 0.85 (t, 3H, J = 12.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.9, 16.3, 54.3, 63.5, 63.9, 123.7, 124.5, 126.4, 127.5, 127.6, 127.9, 128.6, 129.5, 132.7, 133.8, 133.9, 134.0, 135.0. EI-MS (*m/z*): 434.1 $[M+H]^+$.
IIb	^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55 (d, 1H, J = 8.0 Hz, NH), 8.11 (d, 1H, J = 8.0 Hz, ArH), 7.24–7.76 (m, 5H, ArH), 7.03 (t, 1H, J = 8.0 Hz, ArH), 6.77–6.84 (m, 2H, ArH), 6.37–6.54 (m, 2H, ArH), 4.99 (dd, 1H, J = 12.0, 12.0 Hz, PCH), 4.17–4.23 (m, 2H, OCH_2), 3.81–3.89 (m, 1H, OCH_2), 3.61–3.67 (m, 1H, OCH_2), 1.31 (t, 3H, J = 12.0 Hz, CH_3), 0.95 (t, 3H, J = 12.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.9, 16.3, 48.3, 63.6, 64.2, 114.2, 114.4, 120.4, 120.5, 123.4, 123.7, 124.4, 126.4, 127.9, 128.6, 129.2, 129.8, 133.7, 134.0, 134.3. EI-MS (*m/z*): 452.0 $[M+H]^+$.
IIc	^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55 (d, 1H, J = 16.0 Hz, NH), 8.02 (d, 1H, J = 8.0 Hz, ArH), 7.71–7.81 (m, 2H, ArH), 7.24–7.47 (m, 4H, ArH), 6.86–6.89 (m, 2H, ArH), 6.38–6.42 (m, 2H, ArH), 4.59 (dd, 1H, J = 8.0, 8.0 Hz, PCH), 4.14–4.20 (m, 2H, OCH_2), 3.80-3.85 (m, 1H, OCH_2), 3.52–3.59 (m, 1H, OCH_2), 1.23 (t, 3H, J = 12.0 Hz, CH_3), 0.96 (t, 3H, J = 12.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.0, 16.3, 53.5, 63.5, 64.1, 114.2, 114.4, 123.7, 124.7, 126.5, 127.9, 128.6, 128.9, 129.3, 129.4, 133.8, 133.9, 134.0, 135.3. EI-MS (*m/z*): 452.2 $[M+H]^+$.
IId	^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.01 (s, 1H, ArH), 6.60–8.09 (m, 10H, ArH+NH), 4.73 (dd, 1H, J = 12.0, 12.0 Hz, PCH), 4.23–4.26 (m, 2H, OCH_2), 3.81–3.88 (m, 1H, OCH_2), 3.55–3.63 (m, 1H, OCH_2), 1.35 (t, 3H, J = 16.0 Hz, CH_3), 0.91 (t, 3H, J = 16.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.1, 16.4, 56.2, 63.6, 64.1, 121.9, 125.1, 126.7, 127.2, 127.3, 127.8, 128.0, 128.1, 128.2, 131.0, 132.9, 133.3, 136.5, 147.2, 150.8. EI-MS (*m/z*): 435.1 $[M+H]^+$.
IIe	^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.99 (s, 1H, ArH), 6.43–8.22 (m, 8H, ArH+NH), 6.31–6.35 (m, 2H, ArH), 5.15 (dd, 1H, J = 12.0, 12.0 Hz, PCH), 4.26–4.29 (m, 2H, OCH_2), 3.85–3.91 (m, 1H, OCH_2), 3.69–3.75 (m, 1H, OCH_2), 1.34 (t, 3H, J = 16.0 Hz, CH_3), 0.96 (t, 3H, J = 16.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.2, 16.4, 47.0, 62.6, 63.0, 115.5, 124.6, 126.1, 127.3, 127.5, 128.3, 129.1, 130.3, 132.1, 132.8, 136.1, 138.5, 147.0, 150.7, 159.8. EI-MS (*m/z*): 453.2 $[M+H]^+$.

Continued

Compd.	^{1}H NMR, ^{13}C NMR and MS
IIf	^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.02 (s, 1H, ArH), 7.13−8.13 (m, 6H, ArH+NH), 6.84 (m, 2H, ArH), 6.28−6.32 (m, 2H, ArH), 4.71 (dd, 1H, J = 12.0, 12.0 Hz, PCH), 4.25−4.27 (m, 2H, OCH_2), 3.82−3.88 (m, 1H, OCH_2), 3.61−3.68 (m, 1H, OCH_2), 1.35 (t, 3H, J = 12.0 Hz, CH_3), 0.94 (t, 3H, J = 16.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.0, 16.4, 55.4, 63.7, 64.3, 115.1, 115.3, 127.1, 127.6, 127.8, 129.0, 129.3, 130.0, 131.6, 132.6, 133.8, 136.9, 147.5, 150.2, 160.3. EI-MS (*m/z*): 453.0 $[M+H]^+$.
IIg	^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (d, 1H, J = 12.0 Hz, NH), 7.54 (s, 1H, ArH), 7.39 (d, 1H, J = 8.0 Hz, ArH), 7.23 (s, 1H, PhCH=), 7.00−7.17 (m, 6H, ArH), 6.37 (d, 1H, J = 12.0 Hz, =CH), 4.77 (dd, 1H, J = 8.0, 8.0 Hz, PCH), 4.19−4.24 (m, 2H, OCH_2), 3.79−3.85 (m, 1H, OCH_2), 3.51−3.58 (m, 1H, OCH_2), 1.35 (t, 3H, J = 8.0 Hz, CH_3), 0.97−1.01 (t, 3H, J = 16.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.0, 16.4, 54.2, 63.9, 64.1, 117.1, 117.7, 118.0, 127.4, 128.2, 129.9, 132.8, 136.9, 142.2, 159.3. EI-MS (*m/z*): 452.1 $[M+H]^+$.
IIh	^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, 1H, J = 8.0 Hz, NH), 7.50−7.52 (m, 2H, ArH), 7.35−7.37 (m, 1H, PhCH=), 6.95−7.02 (m, 2H, ArH), 6.72−6.75 (m, 2H, ArH), 6.40 (d, 1H, J = 8.0 Hz, =CH), 5.17 (dd, 1H, J = 8.0, 8.0 Hz, PCH), 4.31−4.37 (m, 2H, OCH_2), 3.90−3.93 (m, 1H, OCH_2), 3.68−3.78 (m, 1H, OCH_2), 1.40 (t, 3H, J = 8.0 Hz, CH_3), 1.03 (t, 3H, J = 8.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.9, 16.5, 54.3, 63.9, 64.5, 109.8, 114.9, 117.2, 117.8, 118.0, 125.6, 127.3, 129.5, 129.9, 130.0, 136.7, 142.2, 155.7, 159.3. EI-MS (*m/z*): 470.1 $[M+H]^+$.
IIi	^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80 (d, 1H, J = 12.0 Hz, NH), 7.71 (d, 1H, J = 12.0 Hz, ArH), 7.58 (s, 1H, PhCH=), 7.42 (d, 1H, J = 8.0 Hz, ArH), 7.08−7.19 (m, 3H, ArH), 6.69 (t, 2H, J = 8.0 Hz, ArH), 6.41 (d, 1H, J = 8.0 Hz, CH=), 4.79 (dd, 1H, J = 12.0, 12.0 Hz, PCH), 4.26−4.30 (m, 2H, OCH_2), 3.83−3.89 (m, 1H, OCH_2), 3.58−3.67 (m, 1H, OCH_2), 1.37 (t, 3H, J = 8.0 Hz, CH_3), 1.04 (t, 3H, J = 8.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.1, 16.4, 53.9, 63.8, 64.4, 115.0, 115.2, 117.1, 118.0, 127.2, 129.1, 129.9, 130.0, 130.1, 137.2, 142.2, 155.7, 159.2. EI-MS (*m/z*): 470.0 $[M+H]^+$.
IIj	^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (d, 1H, J = 8.0 Hz, NH), 6.78−7.24 (m, 7H, ArH), 6.48 (d, 1H, J = 8.0 Hz, ArH), 4.70 (dd, 1H, J = 12.0, 12.0 Hz, PCH), 4.47 (t, 2H, J = 8.0 Hz, OCH_2), 4.20−4.25 (m, 2H, OCH_2), 3.79−3.84 (m, 1H, OCH_2), 3.53−3.57 (m, 1H, OCH_2), 2.90−2.99 (m, 2H, CH_2), 1.33 (t, 3H, J = 8.0 Hz, CH_3), 0.98 (t, 3H, J = 8.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.0, 16.4, 28.7, 54.5, 63.5, 64.0, 72.0, 108.7, 124.4, 127.3, 127.7, 127.9, 128.2, 128.5, 132.2, 133.6, 163.1. EI-MS (*m/z*): 426.1 $[M+H]^+$.
IIk	^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 (d, 1H, J = 8.0 Hz, NH), 7.09−7.34 (m, 3H, ArH), 6.81−6.88 (m, 2H, ArH), 6.46−6.56 (m, 2H, ArH), 5.06 (dd, 1H, J = 12.0, 12.0 Hz, PCH), 4.49 (t, 2H, J = 8.0 Hz, OCH_2), 4.25−4.28 (m, 2H, OCH_2), 3.82−3.90 (m, 1H, OCH_2), 3.72−3.75 (m, 1H, OCH_2), 2.98 (d, 2H, CH_2), 1.31 (t, 3H, J = 20.0 Hz, CH_3), 1.00 (t, 3H, J = 12.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.0, 16.3, 28.8, 56.0, 63.6, 64.5, 72.1, 101.1, 108.9, 115.2, 115.4, 122.5, 124.0, 124.3, 128.3, 129.9, 132.3, 137.3, 163.0. EI-MS (*m/z*): 444.2 $[M+H]^+$.
IIl	^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (d, 1H, J = 12.0 Hz, NH), 7.15−7.25 (m, 3H, ArH), 6.93−6.97 (m, 1H, ArH), 6.75 (t, 2H, J = 8.0 Hz, ArH), 6.53 (t, 2H, J = 8.0 Hz, ArH), 4.70 (dd, 1H, J = 8.0, 8.0 Hz, PCH), 4.49 (t, 2H, J = 8.0 Hz, OCH_2), 4.20−4.26 (m, 2H, OCH_2), 3.85−3.88 (m, 1H, OCH_2), 3.62−3.69 (m, 1H, OCH_2), 2.90−3.00 (m, 2H, CH_2), 1.34 (t, 3H, J = 8.0 Hz, CH_3), 1.04 (t, 3H, J = 8.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.1, 16.4, 28.7, 55.3, 63.5, 64.2, 72.0, 108.8, 114.7, 114.8, 114.9, 124.3, 127.4, 128.5, 129.7, 130.0, 130.1, 132.2, 163.2. EI-MS (*m/z*): 444.1 $[M+H]^+$.
IIm	^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.93 (d, 1H, J = 8.0 Hz, NH), 7.38 (d, 1H, J = 4.0 Hz, ArH), 6.92−7.19 (m, 6H, ArH), 6.41 (d, 1H, J = 16.0 Hz, ArH), 4.66 (dd, 1H, J = 8.0, 8.0 Hz, PCH), 4.05−4.15 (m, 2H, OCH_2), 3.87−3.93 (m, 2H, NCH_2), 3.80−3.86 (m, 1H, OCH_2), 3.52−3.55 (m, 1H, OCH_2), 2.86−2.90 (m, 2H, CH_2), 2.15 (s, 3H, CH_3), 1.16 (t, 3H, J = 8.0 Hz, CH_3), 0.93 (t, 3H, J = 8.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.9, 16.4, 27.3, 55.3, 63.2, 64.1, 121.1, 123.6, 123.7, 124.1, 126.5, 127.5, 127.6, 127.9, 124.7, 131.0, 134.5, 146.2, 169.2. EI-MS (*m/z*): 467.2 $[M+H]^+$.
IIn	^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, 1H, J = 8.0 Hz, NH), 7.44 (d, 1H, J = 8.0 Hz, ArH), 7.04−7.30 (m, 3H, ArH), 6.79−6.84 (m, 2H, ArH), 6.53−6.60 (d, 1H, J = 28.0 Hz, ArH), 5.06 (dd, 1H, J = 12.0, 12.0 Hz, PCH), 4.19−4.24 (m, 2H, OCH_2), 3.96−4.00 (m, 2H, NCH_2), 3.86−3.91 (m, 1H, OCH_2), 3.67−3.72 (m, 1H, OCH_2), 2.93−3.00 (m, 2H, CH_2), 2.14 (s, 3H, CH_3), 1.30 (t, 3H, J = 16.0 Hz, CH_3), 1.01 (t, 3H, J = 12.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.0, 16.3, 24.2, 27.2, 47.2, 48.7, 63.6, 64.2, 114.7, 114.9, 116.2, 121.2, 123.3, 124.0, 127.5, 129.4, 131.3, 134.3, 146.1, 169.1. EI-MS (*m/z*): 485.0 $[M+H]^+$.
IIo	^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, 1H, J = 8.0 Hz, NH), 7.47 (d, 1H, J = 8.0 Hz, ArH), 7.10−7.15 (m, 3H, ArH), 6.83 (d, 1H, J = 8.0 Hz, ArH), 6.72−6.77 (m, 2H, ArH), 4.69 (dd, 1H, J = 8.0, 8.0 Hz, PCH), 4.20−4.24 (m, 2H, OCH_2), 3.94−3.98 (m, 2H, NCH_2), 3.86−3.90 (m, 1H, OCH_2), 3.61−3.68 (m, 1H, OCH_2), 2.86−2.93 (m, 2H, CH_2), 2.13 (s, 3H, CH_3), 1.29 (t, 3H, J = 16.0 Hz, CH_3), 1.05 (t, 3H, J = 16.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.1, 16.4, 24.2, 27.2, 48.9, 53.7, 63.5, 64.1, 114.8, 115.0, 116.1, 123.4, 127.6, 129.9, 130.0, 131.3, 135.0, 145.9, 169.3. EI-MS (*m/z*): 485.1 $[M+H]^+$.
IIp	^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.93−7.95 (d, 1H, J = 8.0 Hz, NH), 7.90 (d, 1H, J = 8.0 Hz, ArH), 7.40−7.42 (m, 1H, ArH), 6.66−6.82 (m, 5H, ArH), 6.33 (q, 1H, J = 12.0 Hz, ArH), 4.64 (dd, 1H, J = 8.0, 8.0 Hz, PCH), 4.18−4.22 (m, 2H, OCH_2), 3.78−3.82 (m, 1H, OCH_2), 3.52−3.62 (m, 1H, OCH_2), 1.32 (t, 3H, J = 8.0 Hz, CH_3), 0.92 (t, 3H, J = 8.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.9, 16.3, 54.6, 63.5, 64.1, 126.1, 127.3, 127.4, 127.5, 127.7, 128.0, 128.1, 130.4, 131.8, 132.1, 148.7, 154.7. EI-MS (*m/z*): 442.1 $[M+H]^+$.
IIq	^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, 1H, J = 4.0 Hz, NH), 7.90 (d, 1H, J = 8.0 Hz, ArH), 7.44 (t, 1H, J = 8.0 Hz, ArH), 6.95 (t, 1H, J = 8.0 Hz, ArH), 6.72 (d, 1H, J = 4.0 Hz, ArH), 6.34−6.41 (m, 3H, ArH), 5.03 (dd, 1H, J = 12.0, 12.0 Hz, PCH), 4.18−4.23 (m, 2H, OCH_2), 3.81−3.84 (m, 1H, OCH_2), 3.64−3.74 (m, 1H, OCH_2), 1.32 (t, 3H, J = 12.0 Hz, CH_3), 0.94 (t, 3H, J = 12.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.8, 16.3, 48.2, 63.4, 64.2, 114.2, 114.4, 120.0, 123.0, 126.1, 127.7, 128.3, 129.6, 130.9, 148.8, 154.5, 157.2. EI-MS (*m/z*): 460.2 $[M+H]^+$.
IIr	^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (d, 1H, J = 8.0 Hz, NH), 7.94 (d, 1H, J = 8.0 Hz, ArH), 7.45−7.47 (m, 1H, ArH), 6.83−6.86 (m, 2H, ArH), 6.32−6.41 (m, 3H, ArH), 4.66 (dd, 1H, J = 12.0, 12.0 Hz, PCH), 4.16−4.20 (m, 2H, OCH_2), 3.79−3.84 (m, 1H, OCH_2), 3.57−3.65 (m, 1H, OCH_2), 1.20 (t, 3H, J = 24.0 Hz, CH_3), 0.90 (t, 3H, J = 24.0 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.0, 16.4, 53.8, 63.4, 64.2, 114.2, 114.4, 126.1, 127.8, 128.5, 129.2, 129.3, 129.4, 130.4, 148.7, 154.7, 161.2. EI-MS (*m/z*): 453.0 $[M+H]^+$.

Table 3 MIC values of different target compounds

Compd.	MIC /μg·mL^{-1}		
	S. aureus	*E. coli*	MRSA
IIa	>1 024	>1 024	>1 024
IIb	512	512	>1 024
IIc	512	512	512
IId	1 024	1 024	>1 024
IIe	256	256	512
IIf	128	256	512
IIg	64	256	256
IIh	64	64	64
IIi	8	32	16
IIj	256	512	>1 024
IIk	128	512	512
IIl	64	256	256
IIm	1 024	>1 024	1 024
IIn	512	1 024	1 024
IIo	>1 024	512	512
IIp	64	128	256
IIq	32	32	64
IIr	8	64	32
Oxacillin	0.25	8	256

醋酸铵、三氟甲磺酸铝、苯甲醛、邻氟苯甲醛、对氟苯甲醛、亚磷酸二乙酯、1-萘磺酰氯、8-喹啉磺酰氯、香豆素-6-磺酰氯、2,3-二氢-1-苯并呋喃-5-磺酰氯、1-乙酰基吲哚啉-5-磺酰氯、1,3-苯并噻二唑-4-磺酰氯购于百灵威化学试剂公司, 其余试剂均为分析纯。反应溶剂CH_2Cl_2需经无水处理。

1 化合物的合成

1.1 中间体I的合成 以**Ia**的合成为例。于50 mL干燥反应瓶中, 加入0.015 mol (1.580 g) 苯甲醛、0.015 mol (1.156 g) 醋酸铵和0.015 mol (2.070 g) 亚磷酸二乙酯, 室温搅拌反应15 min, 再向反应瓶中加入0.075 mmol (0.038 g) 三氟甲磺酸铝, 升温至110 ℃, 搅拌反应, TLC监测反应, 30 min反应完毕。冷却, 加入适量去离子水, 用10%盐酸调节pH为1, 先环己烷 (10 mL×4次) 萃取, 再乙酸乙酯 (10 mL×4次) 萃取。萃取后的水溶液用20%氢氧化钠调节pH为7～8。最后, 用环己烷 (10 mL×6次) 萃取, 合并萃取液, 旋蒸浓缩, 得无色液体, 即为中间体**Ia**。

1.2 目标化合物II的合成 以**IIa**的合成为例。向50 mL干燥反应瓶中加入10 mL无水二氯甲烷、0.001 mol (0.122 g) 中间体**Ia**和0.0011 mol (0.249 g) α-萘磺酰氯、0.002 2 mol (0.222 g) 三乙胺, 加热回流, 搅拌反应, TLC监测反应, 36 h反应完毕。浓缩溶剂, 硅胶柱色谱分离纯化 ($V_{石油醚}$:$V_{乙酸乙酯}$ = 2∶1), 得到白色固体, 即目标化合物**IIa**。

2 体外抗菌活性测试

S. aureus、*E. coli*购自中国食品药品检定研究院; MRSA由遵义医科大学附属医院分离提供。以苯唑西林 (oxacillin) 为对照药, 采用两倍稀释法测定目标化合物的MIC, 测试方法参照文献[20]。测试结果见表3。

作者贡献: 作者杨家强和王越负责化合物的设计合成、活性研究及稿件撰写与修改, 作者周绪容和吴学姣参与化合物的合成及构效关系分析。

利益冲突: 本文作者声明无任何利益冲突。

References

[1] Cui AL, Hu XX, Gao Y, et al. Design, synthesis, and biological evaluation of novel polymyxin B analogues [J]. Acta Pharm Sin (药学学报), 2019, 54: 2031-2038.

[2] Cattoir V, Felden B. Future antibacterial strategies: from basic concepts to clinical challenges [J]. J Infect Dis, 2019, 220: 350-360.

[3] Fan TY, Yang YS, Hu XX, et al. Anti-MRSA activities of cycloberberine derivatives with a novel chemical scaffold [J]. Acta Pharm Sin (药学学报), 2019, 54: 1627-1635.

[4] Guo Y, Bao CN, Li F, et al. Discovery, synthesis, and biological evaluation of dunnianol-based mannich bases against methicillin-resistant staphylococcus aureus (MRSA) [J]. ACS Infect Dis, 2020, 6: 2478-2489.

[5] Subedi YP, Alfindee MN, Shrestha JP, et al. Synthesis and biological activity investigation of azole and quinone hybridized phosphonates [J]. Bioorg Med Chem Lett, 2018, 28: 3034-3037.

[6] Bartee D, Sanders S, Phillips PD, et al. Enamideprodrugs of acetyl phosphonate DXP synthase inhibitors as potent antibacterial agents [J]. ACS Infect Dis, 2019, 5: 406-417.

[7] Poon H, Chang MH, Fung HB. Ceftaroline fosamil: a cephalosporin with activity against methicillin-resistant *staphylococcus aureus* [J]. Clin Ther, 2012, 34: 743-765.

[8] Kisgen JJ, Mansour H, Unger NR, et al. Tedizolid: a new oxazolidinone antimicrobial [J]. Am J Health Syst Pharm, 2014, 71: 621-633.

[9] Yang JQ, Hu YW, Gu Q, et al. Synthesis and antibacterial activities of novel phosphonate derivatives containing quinolinone moiety [J]. Chin J Org Chem (有机化学), 2014, 34: 829-834.

[10] Yang JQ, Che WL, Wang W, et al. Synthesis and antibacterial activity of novel 7-phosphoryl quinolone derivatives [J]. Chin Pharm J (中国药学杂志), 2019, 54: 86-90.

[11] Yang JQ, Zhao SX, An JL, et al. Synthesis and bioactivity of novel ester derivatives of Rhein [J]. Chin Pharm J (中国药学杂志), 2019, 54: 1216-1220.

[12] He SC, Ponmani J, Avula SR, et al. Recent advance in sulfonamide-based medicinal chemistry [J]. Sci China Chem (中国科学: 化学), 2016, 46: 823-847.

[13] Kawai T, Kazuhiko I, Takaya N, et al. Sulfonamide-based non-alkyne *LpxC* inhibitors as Gram-negative antibacterial agents [J]. Bioorg Med Chem Lett, 2017, 27: 1045-1049.

[14] Yang JQ, Lei YY, Yang H, et al. Synthesis and bioactivity of novel phosphonate derivatives containing thiophene and sulfonamide group [J]. Chin Pharm J (中国药学杂志), 2019, 54: 2055-2059.

[15] Yang JQ, Deng L, An JL, et al. Synthesis and antibacterial activity of sulfanilamide derivatives containing phosphonate moiety [J]. Fine Chem (精细化工), 2019, 36: 1869-1873.

[16] Sande MA, Courtney KB. Nafcillin-gentamicin synergism in experimental staphylococcal endocarditis [J]. J Lab Clin Med, 1976, 88: 118-124.

[17] Winther L, Honoré Hansen S, Baptiste KE, et al. Antimicrobial disposition in pulmonary epithelial lining fluid of horses, Part III. Cefquinome [J]. J Vet Pharmacol Ther, 2011, 34: 482-486.

[18] Burlison JA, Neckers L, Smith AB. Novobiocin: redesigning a DNA gyrase inhibitor for selective inhibition of hsp90 [J]. J Am Chem Soc, 2006, 128: 15529-15536.

[19] Sobhani S, Tashrifi Z. $Al(OTf)_3$ as an efficient catalyst for one-pot synthesis of primary diethyl 1-aminophosphonates under solvent-gree conditions [J]. Syn Commun, 2009, 39: 120-131.

[20] Shen GX. Microbiology and Immunology (微生物学与免疫学) [M]. Beijing: People's Medical Publishing House, 2007: 326-328.