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研究论文

含(杂)芳磺酰基哌嗪的蛇床子素衍生物的合成及抗菌活性

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摘要 设计合成了25个含(杂)芳磺酰基哌嗪的蛇床子素衍生物，经核磁共振波谱(^{1}H NMR和^{13}C NMR)及元素分析确证了其结构. 抗菌活性测试结果表明，化合物**4**q对金黄色葡萄球菌(*S. aureus*)、大肠杆菌(*E. coli*)、耐甲氧西林金黄色葡萄球菌(MRSA)和耐氟喹诺酮大肠杆菌(FREC)的最小抑菌浓度(MIC)分别为0.5, 1, 2和2 μg/mL，化合物**4**s对*S. aureus*, *E. coli*, MRSA和FREC的MIC分别为0.25, 0.5, 1和2 μg/mL，化合物**4**u对*S. aureus*, *E. coli*, MRSA和FREC的MIC分别为0.5, 2, 1和4 μg/mL，3个化合物的抗*S. aureu*活性与对照药苯唑西林相似，且优于诺氟沙星；抗*E. coli*, MRSA和FREC活性优于对照药苯唑西林和诺氟沙星. 研究结果表明，(杂)芳磺酰基哌嗪的引入能有效提高抗菌活性，扩大抗菌谱.

关键词 蛇床子素衍生物；哌嗪；磺酰胺；抗菌活性
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Synthesis and Antibacterial Activities of Osthole Derivatives Containing (Hetero)arylsulfonylpiperazine

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Abstract In order to obtain antibacterial candidate compounds, the strategy of pharmacophore hybridisation was adopted to optimize the structure of the previously obtained active compound. Twenty-five osthole derivatives were designed and synthesized, and confirmed by means of nuclear magnetic resonance hydrogen spectroscopy (^{1}H NMR), nuclear magnetic resonance carbon spectroscopy (^{13}C NMR) and elemental analysis. The antibacterial activities against *S. aureus*, *E. coli*, methicillin-resistant *S. aureus* (MRSA) and fluoroquinolone-resistant *E. coli* (FREC) were evaluated, the results showed that the minimum inhibitory concentration (MIC) of compound **4**q was 0.5, 1, 2, 2 μg/mL respectively, the MIC of compound **4**s was 0.25, 0.5, 1, 2 μg/mL respectively, and the MIC of compound **4**u was 0.5, 2, 1, 4 μg/mL respectively. The inhibitory activities of these compounds against *S. aureus* were comparable to the control drug oxacillin, and superior to norfloxacin, and against *E. coli*, MRSA, and FREC were superior to the control drugs oxacillin and norfloxacin. The combination of (hetero)arylsulfonylpiperazine and osthole can effectively enhance antibacterial activities and expand the antibacterial spectrums.

Keywords Osthole derivative; Piperazine; Sulfonamide; Antibacterial activity

目前，抗生素的耐药性已成为全球主要的医疗卫生问题[1~3]，不同耐药菌的相继出现导致各种感染

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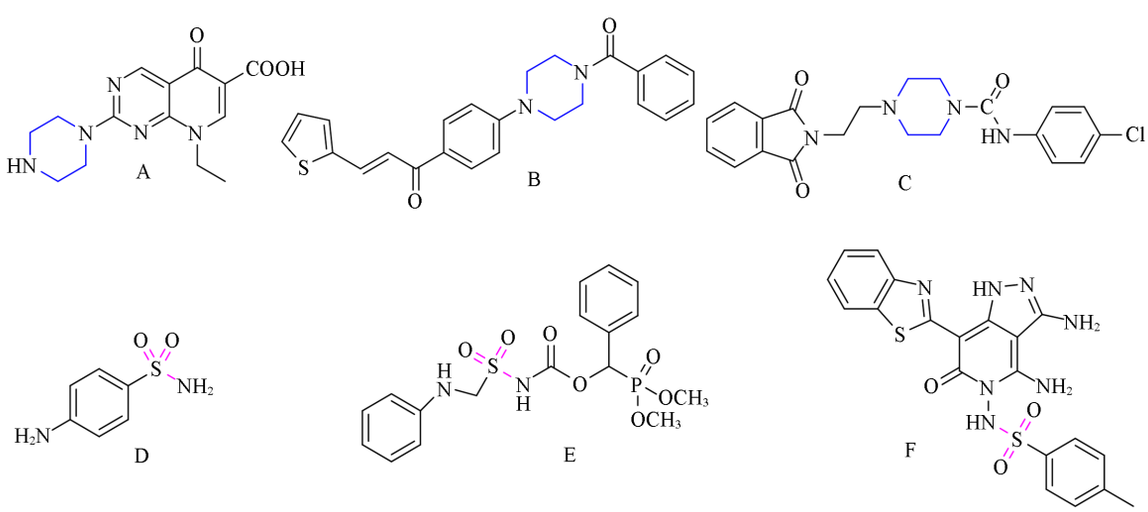
疾病患者的发病率和死亡率不断增加，给临床治疗带来了巨大挑战[4,5]. 因此，迫切需要新的抗菌药物来应对这些问题.

天然来源化合物由于结构新颖独特及生物活性多样，一直是抗菌药物研发领域关注的重点[6~9]. 2019年美国食品药品监督管理局(FDA)批准上市的Lefamulin[10]源于对截短侧耳素结构的改造，具有抗菌谱广、活性高、作用机制新和不耐药等优点. 前期工作中，本课题组以蛇床子素为原料，运用天然产物改造策略，对其7号位进行修饰，先后设计合成了醚类[11]、羧酸酯及磺酸酯类[12]衍生物，发现修饰后的醚类化合物对大肠杆菌(*E. coli*)有较好的抑制活性，值得进一步结构改造与优化.

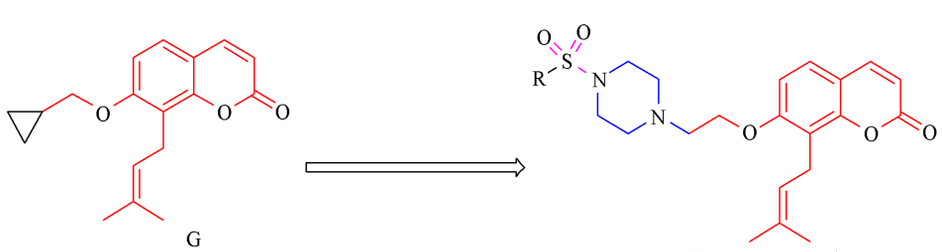
当药物分子中引入哌嗪环时，能有效改善脂水分配系数、药代动力学性质及蛋白结合力等，从而表现出更强的生物活性[13~16]. 最早将哌嗪引入到喹诺酮类抗菌药物中得到的吡哌酸(化合物A，结构见Scheme 1)能有效改善组织渗透性，增强与靶标的亲和力[17]；2020年，Li等[18]将哌嗪引入到噻吩查尔酮结构中得到的化合物B(结构见Scheme 1)对金黄色葡萄球菌(*S. aureus*)、枯草芽孢杆菌(*B. subtilis*)和*E. coli*具有显著的抑制作用；2021年，Prasad等[19]设计合成的哌嗪酰胺(化合物C，结构见Scheme1)的抗耐甲氧西林金黄色葡萄球菌(MRSA)活性优于对照药.



Scheme 1　Chemical structures of compounds A—F

自Domagk[20]发现磺胺类抗菌药物对氨基苯磺酰胺(化合物D，结构见Scheme 1)以来，该类衍生物在抗菌领域受到关注和广泛应用[21~23]. 2018年，Bouzina等[24]设计合成了含磺酰胺结构的膦酸酯(化合物E，结构见Scheme 1)，其对*E. col*和铜绿假单胞菌(*P. aeruginosa*)的最小抑菌浓度(MIC)分别为1.00和0.50 μg/mL，优于对照药磺胺甲噁唑和甲氧苄啶. 2020年，Azzam等[25]发现吡啶酮类磺酰胺(化合物F，结构见Scheme 1)对*E. coli*和*S. aureus*的活性优于对照药氨苄青霉素.

基于此，本文以前期研究[11,12]为基础，对由蛇床子素7位改造获得的活性化合物G(结构见Scheme 2)进行结构优化，保留有效醚键片段，运用药效团拼合原理，与哌嗪和磺酰胺进行三组分结合，设计合成了一系列含(杂)芳磺酰基哌嗪的蛇床子素衍生物，并进行了抗菌活性与构效关系研究.



Scheme 2　Design strategy for target compounds

1 实验部分

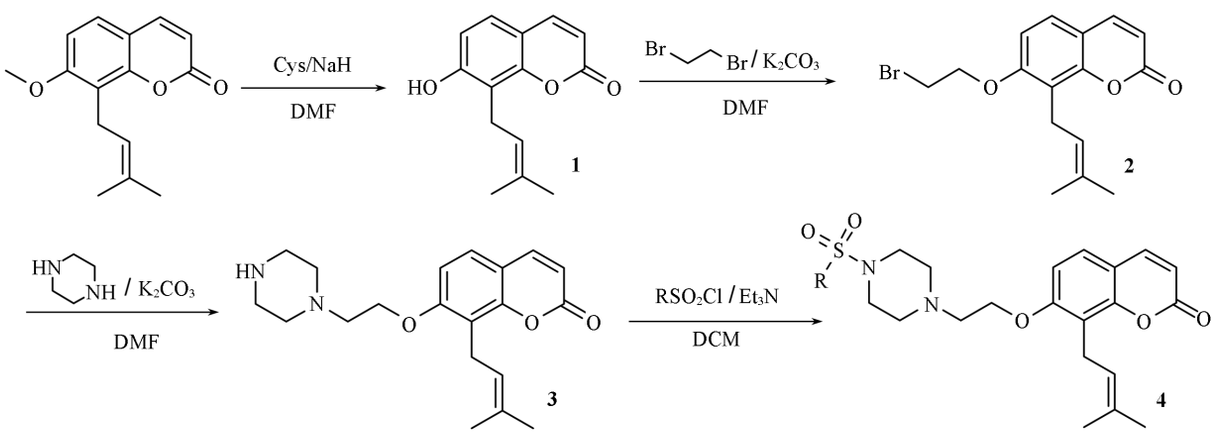
1.1 试剂与仪器

蛇床子素、半胱氨酸、二溴乙烷、哌嗪和不同取代的磺酰氯，纯度99%，北京百灵威科技有限公司；氢化钠(纯度60%)，*N*,*N*-二甲基甲酰胺、碳酸钾、三乙胺、碳酸氢钠、氯化钠、乙酸乙酯和石油醚均为分析纯，安庆泽升科技股份有限公司.

X-4B型显微熔点仪，上海仪电物理光学仪器有限公司；Agilent-400型核磁共振波谱仪(NMR)，美国安捷伦公司；Vario EL III型元素分析仪，德国Elementar公司.

1.2 实验过程

目标化合物**4**a~**4**y的合成路线如Scheme 3所示.



R: **4**a, Ph; 4b, 2-CH_3Ph; **4**c, 3-CH_3Ph; **4**d, 4-CH_3Ph; **4**e, 2-OCH_3Ph; **4**f, 3-OCH_3Ph; **4**g, 4-OCH_3Ph; **4**h, 2-FPh; **4**i, 4-FPh; **4**j, 2-CF_3Ph; **4**k, 3-CF_3Ph; **4**l, 4-CF_3Ph; **4**m, 2-NO_2Ph; **4**n, 3-NO_2Ph; **4**o, 4-NO_2Ph; **4**p, naphthalen-1-yl; **4**q, quinolin-8-yl; **4**r, 2,3-dihydrobenzofuran-6-yl; **4**s, coumarin-6-yl; **4**t, benzo[1,2,5]thiadiazol-4-yl; **4**u, 1-acetylindolin-5-yl; **4**v, thiophen-2-yl; **4**w, 2-(methoxycarbonyl) thiophene-3-yl; **4**x, 5-chlorothiophen-2-yl; **4**y, 3,5-dimethylisoxazol-4-yl.

Scheme 3 Synthetic routes of target compounds 4a—4y

1.2.1 中间体**1**的合成 将6.00 g(24.56 mmol)蛇床子素、8.93 g(73.68 mmol)半胱氨酸、5.89 g(147.37 mmol)氢化钠(质量分数60%)和100 mL DMF加入250 mL反应瓶中，加热至回流，用薄层色谱(TLC)跟踪反应进程. 待反应结束，冷却至室温，加入蒸馏水稀释，以1 mol/L盐酸调节pH值至5.5，用乙酸乙酯萃取3次，合并有机层，用饱和氯化钠水溶液洗涤2次，以无水硫酸钠干燥，经过滤、浓缩及硅胶柱层析分离纯化，得中间体**1**白色固体，m. p. 90~91 ℃，与文献[26]报道一致.

1.2.2 中间体**2**的合成 将1.50 g(6.51 mmol)中间体**1**、3.60 g(26.06 mmol)无水碳酸钾和20 mL DMF加入50 mL反应瓶中，室温下反应0.5 h后，升温至80 ℃，缓慢滴加2.25 mL(26.06 mmol)1,2-二溴乙烷，用TLC跟踪反应进程. 待反应结束，冷却至室温，加入蒸馏水稀释，用乙酸乙酯萃取3次，合并有机层，依次用1 mol/L盐酸、饱和碳酸氢钠溶液和饱和氯化钠水溶液洗涤有机相，以无水硫酸钠干燥，经过滤、浓缩及硅胶柱层析分离纯化，得中间体**2**白色固体，m. p. 110~112 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.60(d, J=9.4 Hz, 1H), 7.25(d, J=3.7 Hz, 1H), 6.77(d, J=8.6 Hz, 1H), 6.24(d, J=9.4 Hz, 1H), 5.24(t, J=7.3 Hz, 1H), 4.37(t, J=6.1 Hz, 2H), 3.67(t, J=6.1 Hz, 2H), 3.56(d, J=7.4 Hz, 2H), 1.83(s, 3H), 1.65(s, 3H).

1.2.3 中间体**3**的合成 将1.69 g(5 mmol)中间体**2**、2.76 g(20 mmol)无水碳酸钾和20 mL DMF加入50 mL反应瓶中，室温下反应0.5 h后，升温至50 ℃，加入1.72 g(20 mmol)无水哌嗪，反应1 h. 停止反

应，冷却至室温，加入适量蒸馏水，用乙酸乙酯萃取3次，合并有机层，依次用蒸馏水和饱和氯化钠水溶液洗涤，以无水硫酸钠干燥，经过滤、浓缩及硅胶柱层析分离纯化，得到白色固体中间体**3**，m. p. 104~106 ℃. ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.59(d, J=9.4 Hz, 1H), 7.25(d, J=8.6 Hz, 1H), 6.79(d, J=8.6 Hz, 1H), 6.21(d, J=9.5 Hz, 1H), 5.18(t, J=7.5 Hz, 1H), 4.17(t, J=5.7 Hz, 2H), 3.50(d, J=7.3 Hz, 2H), 2.96(t, J=4.8 Hz, 4H), 2.84(t, J=5.7 Hz, 2H), 2.63(t, J=4.7 Hz, 4H), 1.81(s, 3H), 1.63(s, 3H), 1.22(dt, J=9.3, 7.1 Hz, 1H).

1.2.4 目标化合物**4**a~**4**y的合成 将0.05 g(0.15 mmol)中间体**3**和10 mL二氯甲烷加入50 mL反应瓶中，滴加0.06 mL(0.45 mmol)三乙胺和0.04 mL(0.30 mmol)苯磺酰氯，室温下进行反应，用TLC跟踪反应进程. 待反应结束，浓缩溶剂，经硅胶柱层析分离纯化，得到化合物**4**a. 采用类似方法合成化合物**4**b~**4**y. 目标化合物**4**a~**4**y的理化数据列于表1，^{1}H NMR和^{13}C NMR数据列于表2.

Table 1 Physical properties of compounds 4a—4y

Compd.	Appearance	Yield(%)	m. p./℃	Elemental analysis calcd.(%, found)		
				C	H	N
4a	White solid	85	154—155	64.71(64.60)	6.27(6.44)	5.80(5.65)
4b	White solid	88	109—110	65.30(65.24)	6.50(6.56)	5.64 (5.55)
4c	White solid	88	116—117	65.30(65.27)	6.50(6.54)	5.64 (5.62)
4d	White solid	88	148—149	65.30(65.07)	6.50(6.61)	5.64 (5.63)
4e	White solid	82	165—166	63.26(63.21)	6.29(6.29)	5.46(6.28)
4f	White solid	81	88—90	63.26(63.35)	6.29(6.50)	5.46(6.37)
4g	White solid	83	126—127	63.26(63.22)	6.29(6.37)	5.46(6.44)
4h	White solid	73	134—135	62.38(62.37)	5.84(5.91)	5.60 (5.55)
4i	White solid	73	135—136	62.38(62.28)	5.84(5.88)	5.60 (5.47)
4j	White solid	79	142—143	58.90(58.96)	5.31(5.46)	5.09(4.98)
4k	White solid	84	84—86	58.90(58.85)	5.31(5.49)	5.09(5.02)
4l	White solid	78	160—161	58.90(58.72)	5.31(5.30)	5.09(5.00)
4m	White solid	75	150—151	59.19(59.22)	5.54(5.71)	7.96(8.00)
4n	White solid	76	135—136	59.19(59.02)	5.54(5.54)	7.96(7.91)
4o	White solid	76	121—122	59.19(59.10)	5.54(5.66)	7.96(7.78)
4p	White solid	94	138—139	67.65(67.48)	6.06(6.16)	5.26(5.22)
4q	White solid	70	110—111	65.27(65.49)	5.86(5.81)	7.87(7.85)
4r	White solid	63	154—155	64.10(64.16)	6.15(6.18)	5.34(5.31)
4s	White solid	66	139—140	63.26(63.25)	5.49(5.54)	5.09(5.04)
4t	White solid	71	133—134	57.76(57.67)	5.22(5.41)	10.36(10.22)
4u	White solid	50	96—97	63.70(63.65)	6.24(6.49)	7.43(7.34)
4v	White solid	69	169—170	59.00(59.06)	5.78(5.91)	5.73(5.65)
4w	White solid	74	108—109	57.13(56.98)	5.53(5.53)	5.12(5.00)
4x	White solid	80	129—130	55.11(54.99)	5.20(5.23)	5.36(5.24)
4y	White solid	78	144—145	59.86(59.94)	6.23(6.35)	8.38(8.23)

Table 2 ^{1}H NMR and ^{13}C NMR data of compounds 4a—4y

Compd.	^{1}H NMR(400 MHz, $CDCl_3$), δ	^{13}C NMR(101 MHz, $CDCl_3$), δ
4a	7.71—7.75(m, 2H, ArH), 7.55—7.62(m, 2H, ArH), 7.49—7.53(m, 2H, ArH), 7.18—7.28(m, 1H, ArH), 6.72(d, J=8.5 Hz, 1H, ArH), 6.20(d, J=9.4 Hz, 1H, ArH), 5.11(t, J=7.0 Hz, 1H, HC=C), 4.08—4.11(m, 2H, OCH_2), 3.45(d, J=7.1 Hz, 2H, CH_2C=), 3.03(s, 4H, piperazine-H), 2.84(s, 2H, NCH_2), 2.68(s, 4H,piperazine-H), 1.77(s, 3H, CH_3), 1.58(s, 3H, CH_3)	161.26, 159.06, 152.82, 143.68, 132.95, 132.55, 129.08, 127.78, 126.22, 121.10, 118.00, 113.17 (d, J=5.4 Hz), 108.02, 66.82, 56.68, 52.69, 46.03, 25.79, 22.01, 18.08

Continued

Compd.	^{1}H NMR(400 MHz, $CDCl_3$), δ	^{13}C NMR(101 MHz, $CDCl_3$), δ
4b	7.84(dd, *J*=8.2, 1.6 Hz, 1H, ArH), 7.53—7.61(m, 1H, ArH), 7.40—7.44(m, 1H, ArH), 7.25—7.32(m, 2H, ArH), 7.23(d, *J*=10.1 Hz, 1H, ArH), 6.68—6.78(m, 1H, ArH), 6.17—6.20(m, 1H, ArH), 5.11(t, *J*=7.4 Hz, 1H, HC═C), 4.08—4.13(m, 2H, OCH_2), 3.43(d, *J*=7.0 Hz, 2H, CH_2C═), 3.23—2.99(m, 4H, piperazine-H), 2.81—2.85(m, 2H, NCH_2), 2.62—2.67(m, 4H, piperazine-H), 2.38(s, 3H, CH_3), 1.76(s, 3H, CH_3), 1.56(s, 3H, CH_3)	161.32, 159.10, 152.80, 143.78, 138.02, 135.06, 132.93(d, *J*=8.5 Hz), 132.50, 130.29, 129.66, 127.83, 126.28, 126.13, 121.15, 117.91, 113.10, 108.08, 66.88, 56.77, 52.92, 45.26, 25.78(d, *J*=1.2 Hz), 22.00, 20.88, 18.07
4c	7.51—7.59(m, 3H, ArH), 7.33—7.40(m, 2H, ArH), 7.21(d, *J*=8.6 Hz, 1H, ArH), 6.71(d, *J*=8.6 Hz, 1H, ArH), 6.18—6.22(m, 1H, ArH), 5.11(t, *J*=7.1 Hz, 1H, HC═C), 4.07(t, *J*=5.3 Hz, 2H, OCH_2), 3.44(d, *J*=7.2 Hz, 2H, CH_2C═), 3.01(s, 4H, piperazine-H), 2.81(t, *J*=5.4 Hz, 2H, NCH_2), 2.60—2.70(m, 4H, piperazine-H), 2.38(s, 3H, CH_3), 1.75(s, 3H, CH_3), 1.57(s, 3H, CH_3)	161.28, 159.09, 152.79, 143.72, 139.28, 134.90, 133.73, 132.48, 128.92, 128.04, 126.25, 124.98, 121.13, 117.93, 113.10, 108.04, 66.84, 56.67, 52.69, 46.05, 25.76, 22.00, 21.36, 18.07
4d	7.54—7.62(m, 3H, ArH), 7.20—7.30(m, 3H, ArH), 6.71(d, *J*=8.6 Hz, 1H, ArH), 6.16—6.23(m, 1H, ArH), 5.11(t, *J*=7.3 Hz, 1H, HC═C), 4.07(t, *J*=5.5 Hz, 2H, OCH_2), 3.44(d, *J*=7.2 Hz, 2H, CH_2C═), 3.00(s, 4H, piperazine-H), 2.81(d, *J*=5.6 Hz, 2H, NCH_2), 2.66(d, *J*=5.9 Hz, 4H, piperazine-H), 2.39(s, 3H, CH_3), 1.76(s, 3H, CH_3), 1.57(s, 3H, CH_3)	161.31, 159.08, 152.80, 143.73, 132.54, 132.02, 129.67, 127.85, 126.24, 121.10, 117.96, 113.14, 108.03, 66.79, 56.67, 52.68, 46.02, 25.77, 22.00, 21.52, 18.08
4e	7.83(dd, *J*=7.8, 1.8 Hz, 1H, ArH), 7.57(d, *J*=9.4 Hz, 1H, ArH), 7.49—7.51(m, 1H, ArH), 7.23(d, *J*=6.5 Hz, 1H, ArH), 6.94—7.03(m, 2H, ArH), 6.74(d, *J*=8.6 Hz, 1H, ArH), 6.20(d, *J*=9.4 Hz, 1H, ArH), 5.10—5.20(m, 1H, HC═C), 4.11(t, *J*=5.5 Hz, 2H, OCH_2), 3.88(s, 3H, OCH_3), 3.47(d, *J*=7.2 Hz, 2H, CH_2C═), 3.22(d, *J*=5.1 Hz, 4H, piperazine-H), 2.83(t, *J*=5.5 Hz, 2H, NCH_2), 2.62(d, *J*=5.2 Hz, 4H, piperazine-H), 1.78(d, *J*=1.3 Hz, 3H, CH_3), 1.60(s, 3H, CH_3)	161.32, 159.15, 156.96, 152.82, 143.73, 134.64, 132.54, 131.82, 126.23, 125.68, 121.12, 120.37, 118.01, 113.12(d, *J*=3.4 Hz), 112.20, 108.08, 66.88, 56.87, 55.90, 53.36, 45.97, 25.80, 22.02, 18.09
4f	7.56(dd, *J*=9.5, 1.3 Hz, 1H, ArH), 7.38—7.43(m, 1H, ArH), 7.28—7.31(m, 1H, ArH), 7.20—7.24(m, 2H, ArH), 7.07—7.10(m, 1H, ArH), 6.72(dd, *J*=8.6, 1.2 Hz, 1H, ArH), 6.19(dd, *J*=9.5, 2.2 Hz, 1H, ArH), 5.11(t, *J*=7.4 Hz, 1H, HC═C), 4.03—4.12(m, 2H, OCH_2), 3.82(s, 3H, OCH_3), 3.46(d, *J*=7.1 Hz, 2H, CH_2C═), 3.04(s, 4H, piperazine-H), 2.84(s, 2H, NCH_2), 2.68(s, 4H, piperazine-H), 1.77(s, 3H, CH_3), 1.59(s, 3H, CH_3)	161.26, 159.89, 152.81, 143.69, 136.27, 132.55, 130.13, 126.23, 121.10, 119.90, 118.97, 117.99, 113.18, 112.66, 108.02, 66.83, 56.68, 55.64, 52.69, 46.04, 25.78, 22.01, 18.08
4g	7.63—7.68(m, 2H, ArH), 7.56—7.59(m, 1H, ArH), 7.21(d, *J*=8.7 Hz, 1H, ArH), 6.90—7.02(m, 2H, ArH), 6.72(d, *J*=8.5 Hz, 1H, ArH), 6.14—6.25(m, 1H, ArH), 5.11(t, *J*=7.2 Hz, 1H, HC═C), 4.08(t, *J*=5.4 Hz, 2H, OCH_2), 3.83(s, 3H, OCH_3), 3.46(d, *J*=7.3 Hz, 2H, CH_2C═), 3.00(s, 4H, piperazine-H), 2.83(s, 2H, NCH_2), 2.67(s, 4H, piperazine-H), 1.76(s, 3H, CH_3), 1.58(s, 3H, CH_3)	163.11, 161.28, 159.10, 152.82, 143.69, 132.52, 129.92, 126.70, 126.22, 121.11, 118.00, 114.19, 113.15(t, *J*=2.7 Hz), 108.04, 66.81, 56.67, 55.62, 52.67, 46.02, 25.76, 22.01, 18.07
4h	7.78(t, *J*=7.5 Hz, 1H, ArH), 7.53—7.59(m, 2H, ArH), 7.16—7.28(m, 3H, ArH), 6.74(d, *J*=8.6 Hz, 1H, ArH), 6.20(d, *J*=9.3 Hz, 1H, ArH), 5.12(t, *J*=7.4 Hz, 1H, HC═C), 4.11(t, *J*=5.4 Hz, 2H, OCH_2), 3.46(d, *J*=7.2 Hz, 2H, CH_2C═), 3.21(s, 4H, piperazine-H), 2.86(t, *J*=5.4 Hz, 2H, NCH_2), 2.68(s, 4H, piperazine-H), 1.78(s, 3H, CH_3), 1.59(s, 3H, CH_3)	161.27, 159.08, 157.73, 152.82, 143.69, 135.19(d, *J*=8.7 Hz), 132.55, 131.31, 126.23, 124.50, 121.12, 118.02, 117.45, 117.23, 113.17, 108.05, 66.79, 56.73, 52.88, 45.74, 25.76, 22.01, 18.08
4i	7.72—7.77(m, 2H, ArH), 7.56(d, *J*=9.4 Hz, 1H, ArH), 7.16—7.25(m, 3H, ArH), 6.72(d, *J*=8.6 Hz, 1H, ArH), 6.20(dd, *J*=9.4, 1.4 Hz, 1H, ArH), 5.12(t, *J*=7.0 Hz, 1H, HC═C), 4.10(t, *J*=5.5 Hz, 2H, OCH_2), 3.46(d, *J*=7.2 Hz, 2H, CH_2C═), 3.03(s, 4H, piperazine-H), 2.84(d, *J*=6.6 Hz, 2H, NCH_2), 2.68(s, 4H, piperazine-H), 1.77(s, 3H, CH_3), 1.58(s, 3H, CH_3)	166.55, 164.01, 161.27, 152.81, 143.69, 132.55, 131.30(d, *J*=3.2 Hz), 130.47(d, *J*=9.4 Hz), 126.24, 121.11, 117.97, 116.47, 116.25, 113.17(d, *J*=4.9 Hz), 108.00, 66.79, 56.65, 52.61, 46.00, 25.78, 22.01, 18.09

Continued

Compd.	^{1}H NMR(400 MHz, $CDCl_3$), δ	^{13}C NMR(101 MHz, $CDCl_3$), δ
4j	7.97—8.12(m, 1H, ArH), 7.84—7.91(m, 1H, ArH), 7.67(dd, *J*=6.6, 2.9 Hz, 2H, ArH), 7.57(d, *J*=9.5 Hz, 1H, ArH), 7.23(d, *J*=8.6 Hz, 1H, ArH), 6.75(d, *J*=8.6 Hz, 1H, ArH), 6.19(d, *J*=9.5 Hz, 1H, ArH), 5.13(t, *J*=7.2 Hz, 1H, HC═C), 4.12(t, *J*=5.5 Hz, 2H, OCH_2), 3.46(d, *J*=7.2 Hz, 2H, CH_2C═), 3.25(t, *J*=4.7 Hz, 4H, piperazine-H), 2.86(t, *J*=5.4 Hz, 2H, NCH_2), 2.66(t, *J*=5.0 Hz, 4H, piperazine-H), 1.78(s, 3H, CH_3), 1.59(s, 3H, CH_3)	161.30, 159.10, 152.82, 143.73, 137.08, 132.77, 132.54, 132.19, 131.96, 128.54(d, *J*=6.8 Hz), 126.26, 123.77, 121.14, 117.99, 113.14, 108.08, 66.81, 56.79, 52.98, 45.65, 25.75, 22.01, 18.06
4k	7.97(s, 1H, ArH), 7.91(d, *J*=7.9 Hz, 1H, ArH), 7.83(d, *J*=7.8 Hz, 1H, ArH), 7.66(t, *J*=7.9 Hz, 1H, ArH), 7.56(d, *J*=9.6 Hz, 1H, ArH), 7.21(d, *J*=8.6 Hz, 1H, ArH), 6.71(d, *J*=8.6 Hz, 1H, ArH), 6.18(dd, *J*=9.5, 3.2 Hz, 1H, ArH), 5.11(t, *J*=7.4 Hz, 1H, HC═C), 4.09(t, *J*=5.4 Hz, 2H, OCH_2), 3.45(d, *J*=7.2 Hz, 2H, CH_2C═), 3.05(s, 4H, piperazine-H), 2.84(t, *J*=5.3 Hz, 2H, NCH_2), 2.69(t, *J*=4.9 Hz, 4H, piperazine-H), 1.76(s, 3H, CH_3), 1.57(s, 3H, CH_3)	161.26, 159.04, 152.80, 143.71, 136.62, 132.52, 131.98, 131.64, 130.97, 129.96, 129.58(d, *J*=3.6 Hz), 126.25, 124.65(d, *J*=4.0 Hz), 121.76, 121.11, 117.94, 113.15(d, *J*=2.2 Hz), 108.00, 66.83, 56.65, 52.58, 46.03, 25.73, 22.00, 18.06
4l	7.85(d, *J*=8.2 Hz, 2H, ArH), 7.77(d, *J*=8.2 Hz, 2H, ArH), 7.55(d, *J*=9.5 Hz, 1H, ArH), 7.21(d, *J*=8.8 Hz, 1H, ArH), 6.71(d, *J*=8.6 Hz, 1H, ArH), 6.19(d, *J*=9.5 Hz, 1H, ArH), 5.11(t, *J*=7.4 Hz, 1H, HC═C), 4.08(t, *J*=5.6 Hz, 2H, OCH_2), 3.45(d, *J*=7.1 Hz, 2H, CH_2C═), 3.06(s, 4H, piperazine-H), 2.85(t, *J*=5.4 Hz, 2H, NCH_2), 2.69(s, 4H, piperazine-H), 1.76(s, 3H, CH_3), 1.57(s, 3H, CH_3)	161.20, 159.02, 152.83, 143.64, 139.08, 134.76, 134.43, 132.51, 128.24, 126.21(d, *J*=1.8 Hz), 124.50, 121.78, 121.12, 117.99, 113.18(d, *J*=4.0 Hz), 107.99, 66.82, 56.63, 52.60, 45.99, 25.72, 22.00, 18.04
4m	7.91(dd, *J*=7.5, 1.7 Hz, 1H, ArH), 7.63—7.73(m, 2H, Ar-H), 7.55—7.60(m, 2H, ArH), 7.23(d, *J*=8.6 Hz, 1H, ArH), 6.75(d, *J*=8.9 Hz, 1H, ArH), 6.19(dd, *J*=9.4, 1.6 Hz, 1H, ArH), 5.13(t, *J*=7.3 Hz, 1H, HC═C), 4.12(t, *J*=5.5 Hz, 2H, OCH_2), 3.46(d, *J*=7.2 Hz, 2H, CH_2C═), 3.29(t, *J*=4.9 Hz, 4H, piperazine-H), 2.84(t, *J*=5.5 Hz, 2H, NCH_2), 2.65(t, *J*=5.0 Hz, 4H, piperazine-H), 1.78(s, 3H, CH_3), 1.59(s, 3H, CH_3)	161.33, 159.12, 152.81, 148.45, 143.78, 133.86, 132.54, 131.50, 130.89, 130.61, 126.29, 124.06, 121.15, 117.97, 113.12, 108.11, 66.80, 56.73, 52.87, 45.96, 25.78, 22.02, 18.09
4n	8.54(q, *J*=2.1 Hz, 1H, ArH), 8.41—8.44(m, 1H, ArH), 8.04(dd, *J*=7.9, 1.7 Hz, 1H, ArH), 7.73—7.77(m, 1H, ArH), 7.55(dd, *J*=9.4, 1.6 Hz, 1H, ArH), 7.21—7.24(m, 1H, ArH), 6.71(dd, *J*=8.6, 1.4 Hz, 1H, ArH), 6.18—6.21(m, 1H, ArH), 5.11(t, *J*=7.0 Hz, 1H, HC═C), 4.07(t, *J*=5.5 Hz, 2H, OCH_2), 3.43(d, *J*=7.2 Hz, 2H, CH_2C═), 3.08(s, 4H, piperazine-H), 2.83(t, *J*=5.5 Hz, 2H, NCH_2), 2.68(t, *J*=5.1 Hz, 4H, piperazine-H), 1.76(s, 3H, CH_3), 1.57(s, 3H, CH_3)	161.25, 159.03, 152.78, 148.28, 143.71, 137.76, 133.22, 132.50, 130.59, 127.38, 126.27, 122.75, 121.12, 117.91, 113.16(d, *J*=4.0 Hz), 107.99, 66.83, 56.61, 52.52, 46.12, 25.77, 22.01, 18.08
4o	8.34—8.36(m, 2H, ArH), 7.90(d, *J*=8.7 Hz, 2H, ArH), 7.56(d, *J*=9.5 Hz, 1H, ArH), 7.21(d, *J*=8.6 Hz, 1H, ArH), 6.71(d, *J*=8.6 Hz, 1H, ArH), 6.19(d, *J*=9.5 Hz, 1H, ArH), 5.10(t, *J*=7.3 Hz, 1H, HC═C), 4.08(t, *J*=5.2 Hz, 2H, OCH_2), 3.44(d, *J*=7.2 Hz, 2H, CH_2C═), 3.08(s, 4H, piperazine-H), 2.84(dd, *J*=7.2, 3.9 Hz, 2H, NCH_2), 2.69(t, *J*=5.0 Hz, 4H, piperazine-H), 1.76(s, 3H, CH_3), 1.58(s, 3H, CH_3)	161.20, 159.01, 152.81, 150.19, 143.66, 141.54, 132.51, 128.92, 126.24, 124.32, 121.13, 117.94, 113.19(d, *J*=5.7 Hz), 107.97, 66.86, 56.60, 52.55, 46.05, 25.76, 22.01, 18.08
4p	8.74(d, *J*=8.6 Hz, 1H, ArH), 8.14(dd, *J*=7.4, 1.3 Hz, 1H, ArH), 8.02(d, *J*=8.2 Hz, 1H, ArH), 7.87(dd, *J*=8.1, 1.6 Hz, 1H, ArH), 7.46—7.64(m, 4H, ArH), 7.17(d, *J*=8.6 Hz, 1H, ArH), 6.68(d, *J*=8.6 Hz, 1H, ArH), 6.11—6.20(m, 1H, ArH), 5.08(t, *J*=7.3 Hz, 1H, HC═C), 4.03(t, *J*=5.4 Hz, 2H, OCH_2), 3.40(d, *J*=7.2 Hz, 2H, CH_2C═), 3.15(t, *J*=4.8 Hz, 4H, piperazine-H), 2.76(t, *J*=5.4 Hz, 2H, NCH_2), 2.58(t, *J*=4.9 Hz, 4H, piperazine-H), 1.71(s, 3H, CH_3), 1.52(s, 3H, CH_3)	159.08, 143.73, 134.56, 134.33, 132.42, 132.10, 130.62, 129.05, 128.90, 128.06, 126.87, 126.25, 125.16, 124.10, 121.15, 117.87, 113.05, 113.02, 108.05, 66.84, 56.67, 52.84, 45.67, 25.72, 21.97, 18.03

Continued

Compd.	^{1}H NMR(400 MHz, $CDCl_3$), δ	^{13}C NMR(101 MHz, $CDCl_3$), δ
4q	9.01—9.03(m, 1H, ArH), 8.38—8.50(m, 1H, ArH), 8.18(dd, *J*=8.4, 2.0 Hz, 1H, ArH), 7.99(dd, *J*=8.1, 1.7 Hz, 1H, ArH), 7.55—7.62(m, 2H, ArH), 7.46—7.50(m, 1H, ArH), 7.18—7.27(m, 1H, ArH), 6.72(d, *J*=8.6 Hz, 1H, ArH), 6.17(dd, *J*=9.5, 2.4 Hz, 1H, ArH), 5.11(t, *J*=7.2 Hz, 1H, HC═C), 4.09(t, *J*=5.6 Hz, 2H, OCH_2), 3.43—3.45(m, 6H, piperazine-H+CH_2C═), 2.81(d, *J*=5.7 Hz, 2H, NCH_2), 2.64(s, 4H, piperazine-H), 1.74(s, 3H, CH_3), 1.54(s, 3H, CH_3)	161.32, 159.12, 152.79, 151.22, 144.22, 143.74, 136.39(d, *J*=7.7 Hz), 133.58, 133.21, 132.50, 128.98, 126.23, 125.48, 122.04, 121.11, 117.97, 113.08, 108.08, 66.75, 56.86, 53.52, 46.31, 25.75, 21.99, 18.06
4r	7.55(dd, *J*=9.5, 2.1 Hz, 1H, ArH), 7.47—7.54(m, 2H, ArH), 7.19—7.26(m, 1H, ArH), 6.81(dd, *J*=8.3, 2.0 Hz, 1H, ArH), 6.72(dd, *J*=8.6, 2.0 Hz, 1H, ArH), 6.18—6.22(m, 1H, ArH), 5.13(t, *J*=7.4 Hz, 1H, HC═C), 4.62—4.67(m, 2H, CH_2), 4.09(t, *J*=5.7 Hz, 2H, OCH_2), 3.45(d, *J*=7.2 Hz, 2H, CH_2C═), 3.21(t, *J*=8.7 Hz, 2H, CH_2), 3.00(s, 4H, piperazineH), 2.82(d, *J*=5.9 Hz, 2H, NCH_2), 2.68(s, 4H, piperazine-H), 1.77(s, 3H, CH_3), 1.58(s, 3H, CH_3)	164.04, 161.28, 159.09, 152.81, 143.70, 132.53, 129.45, 128.33, 126.52, 126.23, 124.98, 121.13, 117.98, 113.16, 109.50, 108.03, 72.28, 66.84, 56.68, 52.70, 46.05, 29.05, 25.75, 22.01, 18.08
4s	7.90(d, *J*=2.1 Hz, 1H, ArH), 7.84(dd, *J*=8.7, 2.1 Hz, 1H, ArH), 7.72(d, *J*=9.7 Hz, 1H, ArH), 7.55(dd, *J*=9.4, 1.9 Hz, 1H, ArH), 7.42(dd, *J*=8.7, 1.9 Hz, 1H, ArH), 7.21(dd, *J*=8.6, 1.8 Hz, 1H, ArH), 6.70(d, *J*=8.6 Hz, 1H, ArH), 6.51(dd, *J*=9.6, 2.0 Hz, 1H, ArH), 6.19(dd, *J*=9.4, 2.2 Hz, 1H, ArH), 5.10(t, *J*=7.2 Hz, 1H, HC═C), 4.08(t, *J*=5.2 Hz, 2H, OCH_2), 3.44(d, *J*=7.2 Hz, 2H, CH_2C═), 3.06(s, 4H, piperazine-H), 2.84(s, 2H, NCH_2), 2.69(s, 4H, piperazine-H), 1.76(s, 3H, CH_3), 1.57(s, 3H, CH_3)	161.22, 159.08(d, *J*=19.4 Hz), 156.47, 152.80, 143.67, 142.33, 132.51, 131.81, 130.65, 128.00, 126.25, 121.12, 118.95, 118.53, 117.93, 113.19(d, *J*=6.1 Hz), 107.96, 56.61, 52.57, 25.76, 22.01, 18.08
4t	8.17—8.24(m, 2H, ArH), 7.66—7.72(m, 1H, ArH), 7.55(d, *J*=9.5 Hz, 1H, ArH), 7.20—7.24(m, 1H, ArH), 6.70(d, *J*=8.6 Hz, 1H, ArH), 6.18(d, *J*=9.4 Hz, 1H, ArH), 5.11(t, *J*=7.6 Hz, 1H, HC═C), 4.07(t, *J*=5.4 Hz, 2H, OCH_2), 3.43(d, *J*=7.2 Hz, 2H, CH_2C═), 3.34(t, *J*=4.8 Hz, 4H, piperazine-H), 2.81(t, *J*=5.3 Hz, 2H, NCH_2), 2.64(t, *J*=5.0 Hz, 4H, piperazine-H), 1.75(s, 3H, CH_3), 1.54(s, 3H, CH_3)	161.23, 159.05, 155.52, 152.80, 149.79, 143.65, 132.49, 132.34, 130.05, 128.14, 126.59, 126.20, 121.11, 117.98, 113.15(d, *J*=4.9 Hz), 108.02, 66.79, 56.74, 53.11, 46.15, 25.72, 22.00, 18.05
4u	8.24(d, *J*=8.5 Hz, 1H, ArH), 7.45—7.60(m, 3H, ArH), 7.20(d, *J*=8.6 Hz, 1H, ArH), 6.70(d, *J*=8.6 Hz, 1H, ArH), 6.16(d, *J*=9.4 Hz, 1H, ArH), 5.09(t, *J*=7.2 Hz, 1H, HC═C), 4.04—4.14(m, 4H, OCH_2+CH_2), 3.43(d, *J*=7.2 Hz, 2H, CH_2C═), 3.18(t, *J*=8.6 Hz, 2H, CH_2), 2.98(s, 4H, piperazine-H), 2.79(t, *J*=5.4 Hz, 2H, NCH_2), 2.62(t, *J*=4.9 Hz, 4H, piperazine-H), 2.22(s, 3H, CH_3), 1.75(s, 3H, CH_3), 1.57(s, 3H, CH_3)	169.48, 161.27, 159.14, 152.79, 146.83, 143.73, 132.45, 132.20, 129.30, 128.44, 126.24, 124.07, 121.14, 117.95, 116.52, 113.07(d, *J*=1.9 Hz), 108.10, 66.88, 56.64, 52.64, 49.10, 46.08, 27.57, 25.74, 24.28, 22.00, 18.06
4v	7.55—7.62(m, 2H, ArH), 7.49(d, *J*=3.7 Hz, 1H, ArH), 7.22(d, *J*=8.8 Hz, 1H, ArH), 7.10(t, *J*=4.4 Hz, 1H, ArH), 6.73(d, *J*=8.6 Hz, 1H, ArH), 6.19(d, *J*=9.4 Hz, 1H, ArH), 5.12(t, *J*=7.2 Hz, 1H, HC═C), 4.10(t, *J*=5.4 Hz, 2H, OCH_2), 3.45(d, *J*=7.2 Hz, 2H, CH_2C═), 3.07(t, *J*=4.8 Hz, 4H, piperazine-H), 2.84(t, *J*=5.4 Hz, 2H, NCH_2), 2.69(t, *J*=5.0 Hz, 4H, piperazine-H), 1.77(s, 3H, CH_3), 1.59(s, 3H, CH_3)	161.26, 159.10, 152.82, 143.70, 135.47, 132.57(d, *J*=7.4 Hz), 132.31, 127.73, 126.24, 121.13, 118.01, 113.15, 108.07, 66.84, 56.65, 52.55, 46.07, 25.79, 22.02, 18.08
4w	7.56(dd, *J*=9.5, 1.1 Hz, 1H, ArH), 7.46(d, *J*=5.3 Hz, 1H, ArH), 7.39(dd, *J*=5.2, 1.5 Hz, 1H, ArH), 7.22(s, 1H, ArH), 6.74(d, *J*=8.6 Hz, 1H, ArH), 6.18—6.21(m, 1H, ArH), 5.12(t, *J*=7.1 Hz, 1H, HC═C), 4.07—4.17(m, 2H, OCH_2), 3.85(s, 3H, CH_3), 3.46(d, *J*=7.2 Hz, 2H, CH_2C═), 3.30(t, *J*=4.9 Hz, 4H, piperazine-H), 2.83(t, *J*=5.2 Hz, 2H, NCH_2), 2.65(t, *J*=5.0 Hz, 4H, piperazine-H), 1.77(s, 3H, CH_3), 1.59(s, 3H, CH_3)	161.31, 159.90, 159.12, 152.81, 143.76, 139.92, 133.99, 132.52, 131.28, 129.18, 126.27, 121.15, 117.98, 113.11, 108.09, 66.82, 56.79, 53.04(d, *J*=3.1 Hz), 46.14, 25.77, 22.02, 18.08
4x	7.56(d, *J*=9.5 Hz, 1H, ArH), 7.28(d, *J*=4.0 Hz, 1H, ArH), 7.24(d, *J*=8.3 Hz, 1H, ArH), 6.94(d, *J*=4.0 Hz, 1H, ArH), 6.73(d, *J*=8.6 Hz, 1H, ArH), 6.19(d, *J*=9.4 Hz, 1H, ArH), 5.12(t, *J*=7.2 Hz, 1H, HC═C), 4.10(t, *J*=5.4 Hz, 2H, OCH_2), 3.46(d, *J*=7.2 Hz, 2H, CH_2C═), 3.07(t, *J*=4.8 Hz, 4H, piperazine-H), 2.84(t, *J*=5.4 Hz, 2H, NCH_2), 2.69(t, *J*=5.0 Hz, 4H, piperazine-H), 1.78(s, 3H, CH_3), 1.60(s, 3H, CH_3)	161.25, 159.09, 152.83, 143.69, 137.56, 133.59, 132.53, 131.98, 127.14, 126.24, 121.14, 118.00, 113.15, 108.04, 66.84, 56.61, 52.49, 46.07, 25.77, 22.02, 18.09

Continued

Compd.	^{1}H NMR(400 MHz, $CDCl_3$), δ	^{13}C NMR(101 MHz, $CDCl_3$), δ
4y	7.56(d, *J*=9.4 Hz, 1H, ArH), 7.23(d, *J*=8.9 Hz, 1H, ArH), 6.74(d, *J*=8.6 Hz, 1H, ArH), 6.14—6.24(m, 1H, ArH), 5.13(t, *J*=7.1 Hz, 1H, HC═C), 4.12(t, *J*=5.3 Hz, 2H, OCH_2), 3.46(d, *J*=7.1 Hz, 2H, CH_2C═), 3.12(t, *J*=5.0 Hz, 4H, piperazine-H), 2.86(t, *J*=5.2 Hz, 2H, NCH_2), 2.60(t, *J*=5.2 Hz, 4H, piperazine-H), 2.60(s, 3H, CH_3), 2.36(s, 3H, CH_3), 1.78(s, 3H, CH_3), 1.60(s, 3H, CH_3)	173.76, 161.23, 159.02, 157.94, 152.82, 143.69, 132.54, 126.26, 121.14, 117.95, 113.18, 112.90, 108.01, 66.91, 56.64, 52.57, 45.45, 25.77, 22.03, 18.08, 12.99, 11.38

1.2.5 目标化合物的抗菌活性测试 标准菌株为*S. aureus*和*E. coli*，耐药菌株为MRSA和耐氟喹诺酮大肠杆菌(FREC)，由遵义医科大学附属医院分离提供. 以苯唑西林(*Oxacillin*)和诺氟沙星(*Norfloxacin*)为对照药，参照文献[27]方法，采用两倍稀释法测定目标化合物的MIC.

2 结果与讨论

2.1 合成与表征

目标化合物合成的关键步骤为中间体**1**的合成，在*n*(氢化钠)∶*n*(半胱氨酸)∶*n*(蛇床子素)=6∶3∶1条件下回流3 h，中间体**1**收率可达78%；合成中间体**2**的最优条件：以DMF为溶剂，在80 ℃下反应3 h，收率可达79%；合成中间体**3**的最优条件：以DMF为溶剂，于50 ℃反应1 h，收率为88%. 核磁共振波谱数据解析以化合物**4**a为例，在其^{1}H NMR谱图中，δ 7.75~6.20处为苯环和香豆素环的H吸收峰，δ 5.11处的三重峰为异戊烯基双键上的H吸收峰，δ 4.08处的多重峰为—OCH_2，δ 3.45处的双峰为异戊烯基侧链的—CH_2，δ 3.03~2.68处为—NCH_2上的H吸收峰，δ 1.77和1.58处为2个—CH_3单峰；在其^{13}C NMR谱图中，δ 161.2处为羰基吸收峰，芳基碳和双键碳的信号峰位于δ 108.02~159.06处，—NCH_2与—OCH_2上的碳吸收峰位于δ 46.03~66.82处，δ 25.79处为异戊烯基上—CH_2的信号峰，δ 22.01和18.08处为2个—CH_3的信号峰.

2.2 晶体结构解析

通过室温溶剂缓慢挥发法，从乙酸乙酯中获得化合物**4**i的结晶，晶体结构见图1. 该晶体属于单斜晶系，空间群为$P2_1/n$. 晶胞参数：a=1.11483(7) nm，b=1.84930(9) nm，c=11.4073(7) nm，α=90°，β=113.208(7)°，γ=90°，μ=0.195 mm^{-1}，V=2.1615(2) nm^3，Z=4，D_c=1.427 g/cm^3，F(000)=968.0. 晶体结构分析表明，分子结构中除了香豆素环中的2个环共平面，其余环均不在同一平面；哌嗪环成稳定的椅式.

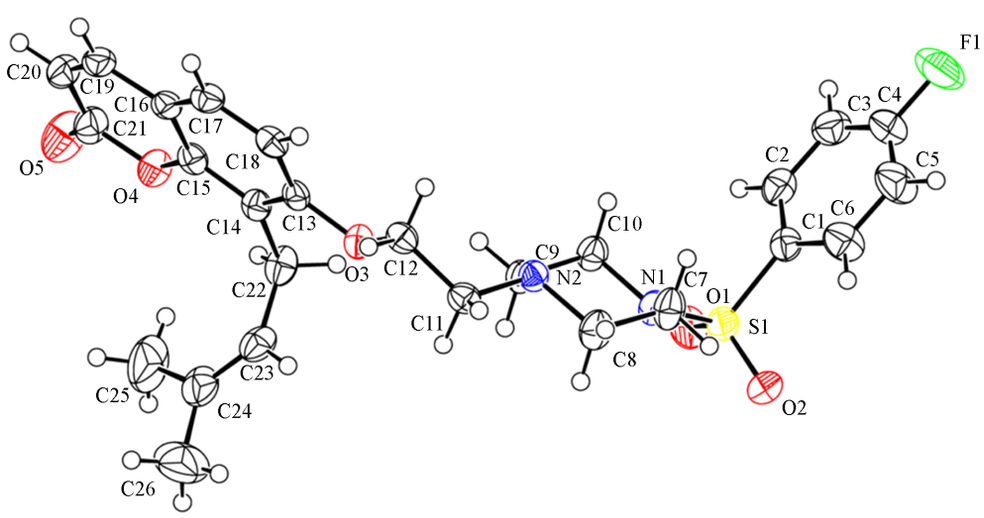


Fig. 1 Crystal structure of compound 4i

2.3 抗菌活性与构效关系

由表3可知，目标化合物**4**对所测细菌均有不同程度的抑制作用. 其中，化合物**4o**，**4q**，**4s**和**4u**对*S. aureus*的MIC值分别为0.5，0.5，0.25和0.5 μg/mL，与苯唑西林(0.5 μg/mL)相似，优于诺氟沙星(1 μg/mL)；化合物**4q**，**4s**和**4u**对*E. coli*的MIC值分别为1，0.5和2 μg/mL，远优于苯唑西林(16 μg/mL)和诺氟沙星(4 μg/mL). 另外，大多数目标化合物对耐药菌MRSA和FREC有较显著的抑制作用，抗菌活性远远优于对照药，以化合物**4o**，**4q**，**4s**，**4u**和**4y**最突出.

Table 3 MIC values of different target compounds

Compd.	R	MIC/(μg·mL^{-1})			
		S. aureus	*E. coli*	MRSA	FREC
4a	Ph	128	128	>128	128
4b	2-CH_3Ph	>128	>128	>128	>128
4c	3-CH_3Ph	128	128	>128	>128
4d	4-CH_3Ph	32	64	64	64
4e	2-OCH_3Ph	>128	128	>128	>128
4f	3-OCH_3Ph	>128	>128	>128	>128
4g	4-OCH_3Ph	16	32	32	128
4h	2-FPh	>128	>128	>128	>128
4i	4-FPh	32	128	64	>128
4j	2-CF_3Ph	128	128	>128	>128
4k	3-CF_3Ph	64	64	64	64
4l	4-CF_3Ph	16	16	16	32
4m	2-NO_2Ph	>128	>128	>128	>128
4n	3-NO_2Ph	64	32	64	64
4o	4-NO_2Ph	0.5	4	2	16
4p	Naphthalen-1-yl	>128	>128	>128	>128
4q	Quinolin-8-yl	0.5	1	2	2
4r	2,3-Dihydrobenzofuran-6-yl	128	64	128	64
4s	Coumarin-6-yl	0.25	0.5	1	2
4t	Benzo[1,2,5]thiadiazol-4yl	32	32	32	32
4u	1-Acetylindolin-5-yl	0.5	2	1	4
4v	Thiophen-2-yl	128	128	128	128
4w	2-(Methoxycarbonyl) thiophene-3-yl	128	>128	>128	>128
4x	5-Chlorothiophen-2-yl	64	64	64	128
4y	3,5-Dimethylisoxazol-4-yl	8	8	16	16
Oxacillin		0.5	16	256	64
Norfloxacin		1	4	128	>128

构效关系研究表明，苯环上不同取代位置的化合物表现出不同的抗菌活性，对位取代的化合物抗菌活性大多优于邻位、间位取代，如化合物**4d**优于**4b**和**4c**，化合物**4o**优于**4n**和**4m**，推测可能在对位有靶标的结合位点；苯环上吸电子基取代的化合物抗菌活性大多优于给电子基取代的，如化合物**4o**(4-NO_2)和**4l**(4-CF_3)；当R为稠环或单杂环时，大多含稠杂环化合物的抗菌活性显著，如化合物**4q**(喹啉环)、**4s**(香豆素环)和**4u**(吲哚啉)，这可能与稠杂环的空间结构有关；与前文[11]报道的醚类活性化合物G(对*E. coli*的MIC为32 μg/mL)相比，含(杂)芳磺酰基哌嗪的蛇床子素衍生物的抗菌活性更显著、抗菌谱更广.

3 结　论

运用药效团拼合原理，对前期得到的活性化合物进行结构优化，设计合成了25个含(杂)芳磺酰基哌嗪的蛇床子素衍生物. 结果表明，该类化合物对*S. aureus*，*E. coli*，MRSA和FREC均表现出潜在的抗菌活性，在(杂)芳磺酰基哌嗪结构中，取代基的位置、电子效应及空间效应对抗菌活性具有重要影响. 其中，化合物**4q**，**4s**和**4u**的活性尤为显著，抗*S. aureus*活性与对照药相当，抗*E. coli*活性优于对

照药，抗MRSA和FREC活性远优于对照药，可作为抗菌候选化合物进一步研究.

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