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新型泰乐菌素衍生物的设计合成和活性评价

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摘要 泰乐菌素作为 16 元大环内酯类抗生素的重要成员之一, 被广泛用于治疗由革兰氏阳性菌和支原体引起的感染性疾病, 对革兰氏阴性菌和耐药菌引起的感染性疾病没有明显治疗效果. 目前扩大泰乐菌素的抗菌谱是对其进行结构改造的目的之一. 以泰乐菌素以及其水解产物脱碳霉糖泰乐菌素(Desmycosin)和 5-*O*-碳霉胺糖泰乐内酯(OMT)为母核, 对其 C-20 位修饰改造, 并引入含 3-喹啉或 3-吡啶的侧链, 设计合成了 18 个新型泰乐菌素半合成衍生物. 目标化合物均经核磁共振氢谱(^{1}H NMR)、核磁共振碳谱(^{13}C NMR)和高分辨质谱仪(HRMS)进行了结构确证. 体外抗敏感菌活性表明, 化合物 20-脱氧-20-{*N*-对氟苄基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三唑-4-基]甲氨基}-5-*O*-碳霉胺糖基泰乐内酯(**4g**)表现最为突出, 化合物 **4g** 对金黄色葡萄球菌和大肠杆菌的最小抑菌浓度(MIC)为＜0.0625 和 4 μg•mL^{-1}; 体外抗耐药菌活性表明, 化合物 **4g** 对溶血性葡萄球菌和大肠杆菌的最小抑菌浓度分别为＜0.0625 和 8 μg•mL^{-1}. 这为进一步结构优化和发现抗菌谱更广、抗菌活性更高的新型泰乐菌素衍生物提供了理论依据.

关键词 泰乐菌素衍生物; 5-*O*-碳霉胺糖泰乐内酯; 3-喹啉; 合成; 抗菌活性

Design, Synthesis and Activity Evaluation of New Tylosin Derivatives

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Abstract Tylosin, as one of the important members of 16 membered macrolide antibiotics, has been widely used in the treatment of infectious diseases caused by gram-positive bacteria and mycoplasma, but has little therapeutic effect on infectious diseases caused by gram-negative bacteria and drug-resistant bacteria. At present, one of the purposes modifying tylosin is to expand its antibacterial spectrum. In this paper, using tylosin and its hydrolysate decarbomycin tylosin (desmycosin) and 5-*O*-mycaminosyltylonolide (OMT) as mother nucleus, 18 new tylosin semisynthetic derivatives were designed and synthesized by modifying the C-20 position, introducing side chain containing 3-quinoline or 3-pyridine, and then their antibacterial activities were evaluated. The target compounds were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS. The *in vitro* anti-sensitive bacteria activity showed that 20-deoxy-20-(*N*-*p*-fluorobenzyl-*N*-(1-(3-quinolyl)-1*H*-1,2,3-triazol-4-yl)methylamino)-5-*O*-mycaminosyltylonolide (**4g**) performed the most prominently. Minimum inhibitory concentration (MIC) values of compound **4g** against *S. aureus* and *E. coli* were ＜ 0.0625 and 4 μg•mL^{-1}. The *in vitro* anti-drug resistant bacteria activity showed that MIC values of compound **4g** against *S. hemolyticus* and *E. coli* were ＜ 0.0625 and 8 μg•mL^{-1}. This provides a theoretical basis for further structural optimization and discovery of novel tylosin derivatives with wider antibacterial spectrum and better antibacterial activity.

Keywords tylosin derivatives; 5-*O*-mycaminosyltylonolide; 3-quinoline; synthesis; antibacterial activity

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大环内酯类抗生素作为使用最广泛的抗生素之一，被用于治疗由金黄色葡萄球菌、肺炎链球菌和大肠杆菌等引起的感染性疾病[1-2]. 与14, 15元大环内酯类抗生素相比，16元大环内酯类抗生素具有很高的生物学潜力，如具有胃肠道刺激小、结构灵活性高、药物之间的相互作用小、无诱导耐药和泵出耐药等优点，从而促使16元大环内酯类抗生素的研发方兴未艾[3-4]. 目前用于临床的16元大环内酯类抗生素有以下药物：天然存在的交沙霉素、螺旋霉素、泰乐菌素和麦迪霉素，以及半合成的米卡霉素、罗他霉素、替米考星和泰地罗新等[5-6]. 其中泰乐菌素专门用于促进动物的生长，并于1970年在欧洲被批准作为猪和仔猪的饲料添加剂[7]，其不仅对各种革兰氏阳性菌和部分革兰氏阴性菌有抗菌活性，对支原体、螺旋体、弯曲杆菌、球虫和真菌等也有很强的抑制作用，但对革兰氏阴性菌和耐药菌引起的感染性疾病基本没有治疗效果[8-10].

为了提高对革兰氏阴性菌和耐药菌的治疗效果，研究者们对泰乐菌素及其衍生物进行了结构改造. Tsutsui等[11]采用烷基肟的形式在烷基链的末端引入大体积基团，如苯环、喹啉环等，其中化合物**I**和**II**(图1)对金黄色葡萄球菌和粪肠球菌均有较强抑制作用. Hong课题组[12]基于5-*O*-碳霉胺糖泰乐内酯(OMT)和替米考星合成新型9-*O*-芳基烷基肟衍生物，与泰乐菌素和OMT相比，化合物**III**和**IV**(图1)对敏感菌表现出相似或更好的抗菌活性，并且提高对大环内酯类耐药菌的抗菌活性. 通过对衍生物**III**和**IV**进行核糖体结合研究，结果表明这些化合物与大肠杆菌核糖体50S大亚基结构域V的A2058和结构域II的A752存在相互作用，这些相互作用力可能是化合物具有高抗菌活性的原因.

基于本课题组的研究和文献调研，三氮唑是芳香族化合物且富含电子，易与各种不同的酶或受体结合，并且表现出广泛的生物活性. 其中1*H*-1,2,3-三氮唑不仅用作抗生素的侧链结构，也是许多抗生素的重要中间体[13]，Kolb和Sugawara等[14-16]将*Anti*-1*H*-1,2,3-三氮唑和*Syn*-1*H*-1,2,3-三氮唑两种构型引入OMT的C-20位，结果发现反式三氮唑表现出更好的抗菌活性，因此本工作采用*Anti*-1*H*-1,2,3-三氮唑进一步研究. 在泰乐菌素、Desmycosin和OMT的C-20位引入*Anti*-1*H*-1,2,3-三氮唑，设计合成了18个新型泰乐菌素衍生物，并采用微量肉汤稀释法测试其对8种细菌的抗菌活性. 抗菌实验结果表明，大部分化合物对金黄色葡萄球菌具有较好的抗菌活性，其中化合物**4e**和**4g**对金黄色葡萄球菌、大肠杆菌和部分耐药菌都具有良好的抗菌活性. 通过考察化合物在C-20位引入不同基团对抗菌活性的影响，分析其构效关系的规律，以获得抗菌活性更好的目标化合物，同时为从事抗菌活性筛选的药物工作者提供有价值的信息.

1 结果与讨论

1.1 目标化合物的合成

基于以上研究，以泰乐菌素、Desmycosin和OMT

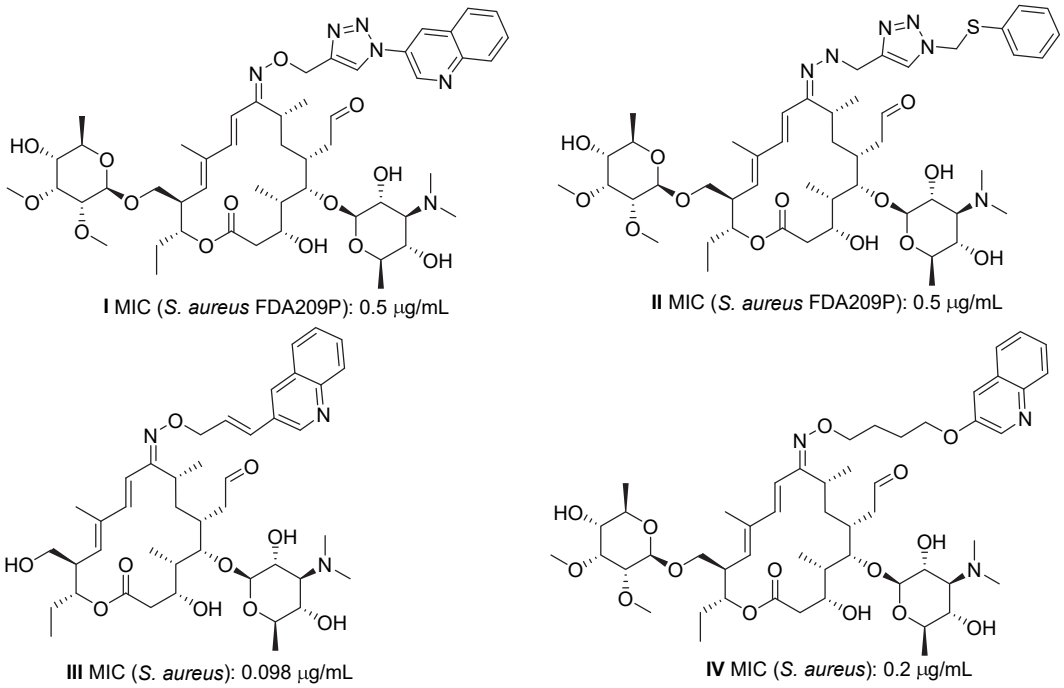


图1 化合物**I**～**IV**的结构

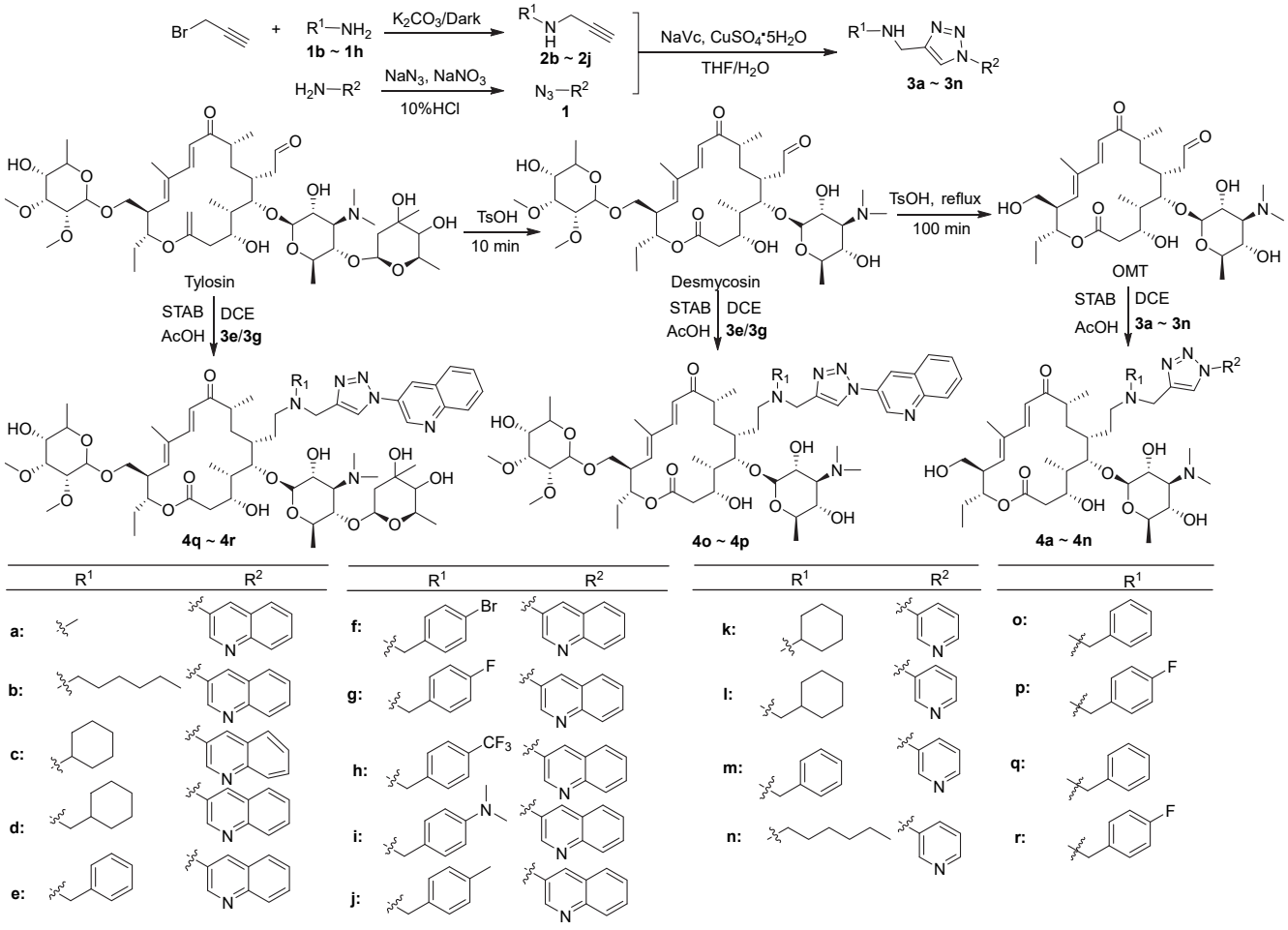
Figure 1 Structures of compounds **I**～**IV**

为母环, 在其C-20位引入含喹啉或吡啶侧链结构, 设计合成了 **4a**～**4r** 目标化合物(Scheme 1), 并且评价了这一系列化合物的抗菌活性.

目标化合物 **4a**～**4r** 的合成如 Scheme 1 所示, 中间体 **2b**～**2j** 的合成采用文献报道的方法进行[15]. 将伯胺分别溶于甲苯、乙腈或者无溶剂中, 并以碳酸钾为缚酸剂, 于 0 ℃下缓慢滴加溴代丙炔, 反应过夜即得化合物 **2a**～**2j**. 以 3-氨基喹啉或 3-氨基吡啶为起始原料, 在10%盐酸溶液中与 $NaNO_2$ 水溶液发生重氮化反应, 在室温下与叠氮化钠发生反应, 经二氯甲烷−正己烷(V∶V=1∶4, V∶V)重结晶得 3-叠氮喹啉或 3-叠氮吡啶. 化合物 **3a**～**3n** 的合成采用 click 点击反应[16], 以四氢呋喃或叔丁醇和水作为溶剂, 抗坏血酸钠和五水硫酸铜为体系提供亚铜离子, **2a**～**2j** 与 3-叠氮喹啉或 3-叠氮吡啶在室温下 1 h 即可反应完全, 粗产物用乙酸乙酯打浆抽滤即可得到白色固体, 且收率高, 如 **2h**(产率 86%). 接着以乙酸为催化剂促进化合物 **3a**～**3n** 与泰乐菌素、Desmycosin 和 OMT 形成席夫碱, 经 $NaBH(OAc)_3$(STAB)发生还原胺化得到目标产物 **4a**～**4r**.

1.2 体外抗菌活性

本实验敏感菌以泰乐菌素(*Tylosin*, Tyl)、5-*O*-碳霉胺糖泰乐内酯(OMT)、泰地罗新(*Tildipirosin*, Til)、脱碳霉糖泰乐菌素(*Desmycosin*, Des)作为阳性对照药, 耐药菌以替米考星(*Timicosin*, Tim)、泰地罗新(*Tildipirosin*, Til)为阳性对照药物. 采用微量肉汤稀释法对 18 个目标化合物进行了抗菌活性测试, 分别测定了 2 种敏感菌[金黄色葡萄球菌(*Staphylococcus aureus* ATCC25923, *S. aureus*)、大肠杆菌(*Escherichia coli* ATCC25922, *E. coli*)]和 6 种耐药菌[溶血葡萄球菌(*Staphylococcus haemolyticus*, *S. hl*)、大肠杆菌(*Escherichia coli*, *E. coli*)、链球菌(*Streptococcus*, SC181)、肠球菌(*Enterococcus*, Fbc35), 肠球菌(*Enterococcus* P254)和金黄色葡萄球菌(*Staphylococcus aureus*, *S. aureus*)]的抗菌活性和部分衍生物对巴氏杆菌(*Pasteurella*)和猪肺炎支原体(*Mycoplasma*)抑制活性测试. 测试结果如表 1～3 所示.



图式 1 目标化合物 **4a**～**4r** 的合成路线

Scheme 1 Synthetic route of target compounds **4a**～**4r**

表 1 化合物 **4a**～**4r** 的抗菌活性

Table 1 Antimicrobial activity of compounds **4a**～**4r**

Compd.	MIC/(μg•mL^{-1})	
	E. coli	*S. aureus*
Til	1	1
Tyl	＞32	4
OMT	＞32	0.5
Des	＞32	4
4a	8	＜0.0625
4b	16	0.5
4c	8	0.5
4d	32	1
4e	8	＜0.0625
4f	8	0.125
4g	4	＜0.0625
4h	16	＜0.0625
4i	8	0.25
4j	16	0.5
4k	32	32
4l	16	4
4m	16	8
4n	16	8
4o	＞32	2
4p	＞32	2
4q	＞32	1
4r	＞32	1

[a] "—" as no antibacterial activity.

由表 1 可知, 大部分化合物对 *S. aureus* 和 *E. coli* 均表现出一定的抗菌活性. 其中, 泰乐菌素衍生物(**4o**、**4p**)和 Desmycosin 衍生物(**4q**、**4r**)最小抑菌浓度与对照药泰乐菌素相比, 对 *S. aureus* 的抗菌活性提高 2～4 倍, 但对 *E. coli* 的抗菌活性没有变化; OMT 衍生物(**4e**、**4g**)与 **4o**、**4p** 和 **4q**、**4r** 相比, 对 *S. ureus* 和 *E. oli* 的抗菌活性均大幅度提高, 可能是泰乐菌素以及 Desmycosin 结构中糖环的存在会降低化合物对 *E. oli* 和 *S. ureus* 抗菌活性. **4a**～**4n** 系列中引入含喹啉侧链的衍生物表现出了优异的抗革兰氏阴性菌和革兰氏阳性菌的活性, 其中化合物 **4e** 和 **4g** 对 *S. aureus* 的最小抑菌浓度(MIC)＜0.0625 μg•mL^{-1}, 优于泰地罗新等对照药, 而引入含吡啶侧链的衍生物未能提高抗革兰氏阳性菌的活性.

表 2 化合物 **4e** 和 **4g** 对四株耐药菌株的抗菌活性 [a]

Table 2 Antimicrobial activities of compounds **4e** and **4g** against four resistant strains

Compd.	MIC/(μg•mL^{-1})					
	S. hl	*E. coli*	SC181	Fbc35	P254	*S. aureus*
Tim	1	32	＞32	32	＞32	＞32
Til	—	—	16	32	＞32	＞32
4e	0.125	8	＞32	＞32	＞32	＞32
4g	＜0.0625	8	＞32	＞32	＞32	＞32

[a] "—" as no antibacterial activity.

由表 2 可知, 化合物 **4g** 对无乳链球菌、肠球菌和金黄色葡萄球菌的抗菌活性无明变化; 但增加了对部分耐药性菌株的抑制活性, 如对大肠杆菌的抑制活性(8 μg•mL^{-1})优于对照药替米考星(32 μg•mL^{-1}), 对溶血性葡萄球菌的抗菌活性最好(MIC＜0.0625 μg•mL^{-1}), 优于所有对照药. 因此化合物 **4e** 和 **4g** 在抗菌药物研究方面具有潜在的应用价值.

表 3 部分衍生物抗巴氏杆菌和猪肺炎支原体结果 [a]

Table 3 Partial derivatives of *Pasteurella* and *Mycoplasma* hyopneumoniae results

Compd.	MIC/(μg•mL^{-1})	
	Pasteurella	*Mycoplasma*
Tyl	＞32	25
Tim	＞32	1.56
OMT	32	—
4a	8	—
4c	8	1.77
4d	16	2.19
4e	16	0.175
4g	4	0.125

[a] "—" as no antibacterial activity.

经过抑菌活性的初步筛选, 进一步测试抗菌活性突出的化合物对巴氏杆菌和猪肺炎支原体的抑制活性, 与对照药相比, 化合物 **4a** 和 **4c** 均提高了对巴氏杆菌的抑制活性, 其 MIC 均为 8 μg•mL^{-1}, 而化合物 **4g** 的 MIC 为 4 μg•mL^{-1}, 并且化合物 **4g** 对猪肺炎支原体也具有优良的抑制作用, 明显优于对照药泰乐菌素和替米考星.

1.3 构效关系

通过对目标化合物抗菌活性的分析, 其构效关系如图 2 所示.

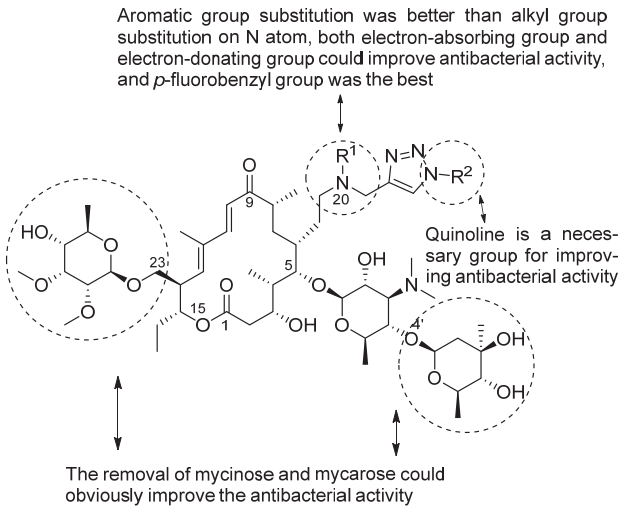


图 2 目标化合物的构效关系

Figure 2 Structure activity relationships of target compounds

通过目标化合物的抗菌活性构效关系分析表明, 泰乐菌素中 C-23 位阿洛糖和 C-4'位碳霉糖的脱去大大提

高了对抗革兰氏阴性菌和革兰氏阳性菌的活性；在C-20位引入3-喹啉侧链比3-吡啶侧链更有利于扩大抗菌谱；另外，C-20位引入的3-喹啉侧链上*N*-芳香取代优于*N*-烷基取代，其中苯环上引入吸电子基如三氟甲基，给电子基如二甲胺基都可以提高对敏感菌的抗菌活性，其中引入*N*-对氟苄基明显提高了对临床菌、支原体和巴氏杆菌的抑制作用，并且提高对耐药菌株的抗菌活性更为明显，如大肠杆菌(8 μg•mL^{-1})和溶血性葡萄球菌(<0.0625 μg•mL^{-1}).

1.4 分子对接研究

为了阐明化合物 **4g** 具有高抗菌活性的原因，以及为进一步结构优化提供理论依据，选取 **4g** 与大肠杆菌核糖体50S大亚基的晶体结构(PDB:3ofr)[17]进行分子对接.

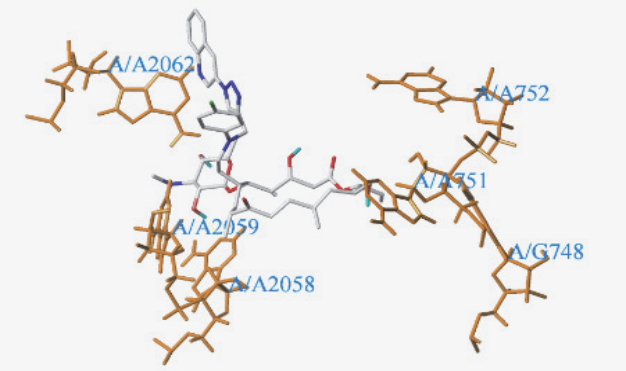


图3 化合物**4g**与大肠杆菌核糖体50S大亚基晶体结构(PDB: 3ofr)的分子对接图

Figure 3 Molecular docking diagram of compound **4g** with the crystal structure of *E. coli* ribosomal 50S large subunit (PDB: 3ofr)

使用SYBYL-2.0进行分子对接如图3所示，目标化合物**4g**的碳霉氨糖上C-2'位羟基与核糖体结构域V的核苷酸残基A2058形成氢键作用. 此外，C-20位侧链氮原子与A2062形成氢键作用；C-23位羟基向结构域II由A752、A751和G748形成的空腔延伸. 对接结果表明，化合物能够增加与细菌核糖体的结合位点，增强与细菌核糖体的结合力，这些相互作用力可能是化合物具有高抗菌活性的原因.

2 结论

设计合成了18个含有三氮唑取代的新型泰乐菌素半合成衍生物，测试了化合物的抗菌活性，发现在OMT的C-20位上引入含喹侧链的化合物**4a**～**4j**比含吡啶侧链的化合物**4k**～**4n**对大肠杆菌标准株、金黄色葡萄球菌标准株有更高度的抑制作用，其中化合物**4g**对耐药菌株溶血性葡萄球菌和大肠杆菌抗菌效果突出，其最小抑菌浓度分别为<0.0625和8 μg•mL^{-1}，对猪肺炎支原体的最小抑菌浓度为0.125 μg•mL^{-1}，明显优于所有对照药. 该研究结果为探索新泰乐菌素半合成衍生物提供了重要的参考信息.

3 实验部分

3.1 仪器与试剂

X-5型显微数字熔点测定仪、85-1型强磁力搅拌器、DF-101S型集热式恒温磁力搅拌器、高分辨质谱仪、DZF-6050AB型真空干燥箱、UV-2550型紫外分析仪、400 M Hz超导核磁共振仪、BHC-1300A$_2$生物洁净安全柜、GNP-905C型隔水式恒温培养箱、XK96-8振荡器；其它试剂和溶剂未经特别说明均为国产或进口分析纯与生物级，无水试剂均按常规方法处理.

3.2 实验方法

3.2.1 化合物**1**的合成

3-叠氮喹啉的合成：将3-氨基喹啉(6.936 mmol)溶于10%的盐酸溶液(10 mL)中，冰浴条件下将亚硝酸钠溶液(6.824 mmol)缓慢滴加入反应液中，搅拌1 h后，自然升至室温，将叠氮化钠(13.86 mmol)溶于10 mL水中，缓慢滴加，室温下反应1 h，薄层色谱(TLC)跟踪检测. 反应完全后，加入饱和碳酸氢钠水溶液调pH至8，加入二氯甲烷萃取水相，有机相用无水$NaSO_4$干燥抽滤，减压蒸干得粗品. 用二氯甲烷-正己烷重结晶得白色固体，收率87%. m.p. 79.2～81.7 ℃；^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63 (d, J=2.5 Hz, 1H, quinoline-H-2), 8.09 (d, J=8.4 Hz, 1H, quinoline-H-8), 7.77 (t, J=4.9 Hz, 2H, quinoline-H-4, quinoline-H-5), 7.70～7.64 (m, 1H, quinoline-H-7), 7.61～7.54 (m, 1H, quinoline-H-6); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 147.3, 143.6, 130.8, 129.4, 129.1, 128.5, 127.6, 126.0, 121.9. 与文献[19]所述一致.

3-叠氮吡啶的合成：3-叠氮吡啶的合成方法同3-叠氮喹啉，得到白色固体，收率83%. m.p. 83.6～85.3 ℃；^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (dd, J=4.6, 1.4 Hz, piperidine-H-2, 1H), 8.30 (d, J=2.4 Hz, piperidine-H-6, 1H), 7.28 (ddd, J=8.2, 2.6, 1.5 Hz, piperidine-H-4, 1H), 7.25～7.19 (m, piperidine-H-5, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 145.0, 140.3, 136.1, 124.9, 123.1. 与文献[20]所述一致.

3.2.2 化合物**2b**～**2j**的合成

N-甲基丙炔胺(**2a**)于上海贤鼎生物科技有限公司购买.

N-(丙-2-炔-1-基)己-1-胺(**2b**)：将**1b** (1.2 mmol)溶于乙腈(10 mL)中，避光下于0 ℃下缓慢滴加溴代丙炔(0.2 mmol)，并以碳酸钾为缚酸剂，室温下反应过夜，反应

结束后, 将乙腈蒸除, 加入水和二氯甲烷, 水相用二氯甲烷萃取两次后, 合并有机相, 有机相用无水 $NaSO_4$ 干燥后, 抽滤, 旋转蒸发除去溶剂. 粗产品经硅胶色谱柱[展开剂: 石油醚(PE)/乙酸乙酯(EA), V∶V=3∶1～5∶1]分离得淡黄色液体 **2b**, 收率 75%, 直接进行下一步反应.

化合物 **2c**～**2j** 的合成方法同 **2b**, 得到淡黄色液体, 收率 62%～75%, 直接进行下一步反应.

3.2.3 化合物 **3a**～**3n** 的合成

将 **2a** (1.67 mmol)溶于叔丁醇−水的混合溶液中, 随后依次加入硫酸铜(0.166 mmol)及 *L*-抗坏血酸钠(0.833 mmol), 搅拌完全溶解后, 加入 3-叠氮喹啉或 3-叠氮吡啶(1.66 mmol), 室温搅拌至反应完全后, 将体系蒸干后加入适量二氯甲烷溶解, 用水洗涤至有机相无色, 有机相用无水 $NaSO_4$ 干燥后抽滤, 旋转蒸发除去溶剂, 粗产品用二氯甲烷−正己烷重结晶得淡黄色固体 *N*-甲基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三氮唑-4-基]甲胺(**3a**), 收率 95%. m.p. 126.6～129.0 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.48 (d, J=2.6 Hz, 1H, quinoline-H-2), 8.93 (d, J=2.4 Hz, 1H, quinoline-H-4), 8.87 (s, 1H, triazole-H-5), 8.13 (d, J=8.4 Hz, 2H, quinoline-H-5,8), 7.88～7.84 (m, 1H, quinoline-H-7), 7.77～7.68 (m, 1H, quinoline-H-6), 3.83 (s, 2H, NH-**CH$_2$**-triazole), 3.49～3.07 (m, 1H, NH), 2.36 (s, 3H, **CH$_3$**-NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 148.4, 147.3, 143. 6, 130.8, 130.8, 129.4, 129.1, 128.5, 127.6, 126.0, 121.9, 46.6, 36.2. HRMS (ESI) calcd for $C_{13}H_{14}N_5$ [M+H]$^+$ 240.1249, found 240.1247. 与文献[19]所述一致.

化合物 **3b**～**3n** 的合成方法同化合物 **3a**.

N-{[1-(喹啉-3-基)-1*H*-1,2,3-三氮唑-4-基]甲基}己胺(**3b**): 淡黄色固体, 收率 87%. m.p. 126.8～127.5 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.33 (d, J=2.5 Hz, 1H, quinoline-H-2), 8.51 (d, J=2.4 Hz, 1H, quinoline-H-4), 8.19 (d, J=8.5 Hz, 1H, quinoline-H-8), 8.12 (s, 1H, triazole-H-2), 7.93 (d, J=8.0 Hz, 1H, quinoline-H-5), 7.81 (ddd, J=8.4, 7.0, 1.4 Hz, 1H, quinoline-H-7), 7.72～7.59 (m, 1H, quinoline-H-6), 4.05 (s, 2H, N-CH_2-triazole), 2.73 (t, J=7.2 Hz, 2H, *n*-hexyl- H-1), 1.88 (s, 1H, NH), 1.64～1.47 (m, 2H, *n*-hexyl-H-2), 1.45～1.19 (m, 6H, *n*-hexyl-H-3,4,5), 0.89 (t, J=6.9 Hz, 3H, *n*-hexyl-H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 148.4, 147.7, 143.0, 130.5, 130.5, 129.6, 128.2, 128.2, 127.4, 126.1, 120.0, 49.8, 44.8, 31.8, 30.0, 27.0, 22.6, 14.1. HRMS (ESI) calcd for $C_{18}H_{24}N_5$ [M+H]$^+$ 310.2032, found 310.2032.

N-{[1-(喹啉-3-基)-1*H*-1,2,3-三氮唑-4-基]甲基}环己胺(**3c**): 淡黄色固体, 收率 91%. m.p. 127.8～128.9 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.25 (d, J=2.4 Hz, 1H, quinoline-2-H), 8.42 (d, J=1.9 Hz, 1H, quinoline-4-H), 8.11 (d, J=8.5 Hz,1H, quinoline-8-H), 8.10～8.07 (m, 1H, triazole-5-H), 7.85 (d, J=8.1 Hz, 1H, quinoline-5-H), 7.77～7.65 (m, 1H, quinoline-7-H), 7.58 (t, J=7.5 Hz, 1H, quinoline-6-H), 4.01 (s, 2H, N-**CH$_2$**-triazole), 2.52 (t, J=10.2 Hz, 1H, N-**CH**), 2.10 (s, 1H, CH_2-**NH**), 1.91 (d, J=11.3 Hz, 2H, cyclohexyl-H-2, cyclohexyl-H-6), 1.69 (d, J=12.7 Hz, 2H, cyclohexyl-H-2, cyclohexyl-H-6), 1.57 (d, J=12.3 Hz, 1H, cyclohexyl-H), 1.29～0.99 (m, 5H, cyclohexyl-H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.7, 146.9, 142.0, 129.5, 129.4, 128.6, 127.2, 127.1, 126.3, 125.1, 119.1, 55.4, 40.7, 32.3, 25.0, 23.9. HRMS (ESI) calcd for $C_{18}H_{22}N_5$ [M+H]$^+$ 308.1875, found 308.1876.

N-环己基-*N*-{[1-(喹啉-3-基)-1*H*-1,2,3-三氮唑-4-基]甲基}甲胺(**3d**): 淡黄色固体, 收率 83%. m.p. 126.9～127.8 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.33 (d, J=2.2 Hz, 1H, quinoline-H-2), 8.51 (s, 1H, quinoline-H-4), 8.19 (d, J=8.5 Hz, 1H, quinoline-H-8), 8.16 (s, 1H, triazole-H-5), 7.93 (s, 1H, quinoline-H-5), 7.86～7.74 (m, 1H, quinoline-H-7), 7.67 (s, 1H, quinoline-H-6), 4.05 (s, 2H, triazole-**CH$_2$**), 2.58 (s, 2H, NH-**CH$_2$**), 2.31 (s, 1H, NH), 1.89～1.61 (m, 5H, cyclohexyl-H), 1.54 (s, 1H, NH-CH_2-**CH**), 1.21～1.18 (m, 3H, cyclohexyl-H), 0.99～0.94 (m, 2H, cyclohexyl-H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.1, 146.7, 142.0, 129.5, 129.4, 128.6, 127.2, 127.1, 126.3, 125.1, 119.2, 55.3, 43.8, 36.8, 30.4, 25.6, 24.9. HRMS (ESI) calcd for $C_{19}H_{18}N_5$ [M+H]$^+$ 322.2032, found 322.2013.

N-苄基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三氮唑-4-基]甲胺(**3e**): 淡黄色固体, 收率 83%. m.p. 126.1～128.5 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.49 (d, J=2.6 Hz, 1H, quinoline-H-2), 8.94 (d, J=2.4 Hz, 1H, quinoline-H-4), 8.90 (s, 1H, triazole-H-5), 8.14 (d, J=8.4 Hz, 2H, quinoline-H-5,8), 7.88～7.84 (m, 1H, quinoline-H-7), 7.80～7.69 (m, 1H, quinoline-H-6), 7.40 (d, J=7.2 Hz, 2H, Ph-H-2,6), 7.34 (dd, J=10.2, 4.7 Hz, 2H, Ph-H-3,5), 7.24 (t, J=7.2 Hz, 1H, Ph-H-4), 3.88 (s, 2H, NH-**CH$_2$**-triazole), 3.80 (s, 2H, Ph-**CH$_2$**-NH), 2.70 (s, 1H, NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 148.5, 147.3, 143.6, 140.9, 130.8, 130.8, 129.4, 129.1, 128.6, 128.5, 127.6, 127.1, 126.0, 122.0, 52.8, 43.9. HRMS (ESI) calcd for $C_{19}H_{18}N_5$ [M+H]$^+$ 316.1562, found 316.1565. 与文献[19]所述一致.

N-对溴苄基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三氮唑-4-

基]甲胺(**3f**): 淡黄色固体, 收率 84%. m.p. 126.6～129.0 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.32 (d, J=2.4 Hz, 1H, quinoline-H-2), 8.49 (d, J=2.2 Hz, 1H, quinoline-H-4), 8.19 (d, J=8.5 Hz, 1H, quinoline-H-8), 8.07 (s, 1H, triazole-H-5), 7.93 (d, J=8.2 Hz, 1H, quinoline-H-5), 7.86～7.74 (m, 1H, quinoline-H-7), 7.67 (t, J=7.5 Hz, 1H, quinoline-H-6), 7.46 (d, J=8.2 Hz, 2H, Ph-H-3,5), 7.26 (d, J=8.5 Hz, 2H, Ph-H-2,6), 4.04 (s, 2H, NH-**CH$_2$**-triazole), 3.87 (s, 2H, Ph-**CH$_2$**-NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 148.1, 147.7, 143.0, 138.8, 131.6, 130.5, 130.5, 129.9, 129.6, 128.3, 128.2, 127.4, 126.1, 120.9, 120.1, 52.7, 43.9. HRMS (ESI) calcd for $C_{19}H_{17}BrN_5$ $[M+H]^+$ 394.0687, found 394.0689.

N-(4-氟苄基)-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三氮唑-4-基]甲胺(**3g**): 淡黄色固体, 收率 95%. m.p. 126.0～127.6 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.32 (d, J=2.5 Hz, 1H, quinoline-H-2), 8.50 (d, J=2.3 Hz, 1H, quinoline-H-4), 8.19 (d, J=8.5 Hz, 1H, quinoline-H-8), 8.08 (s, 1H, triazole-H-5), 7.94 (d, J=8.0 Hz, 1H, quinoline-H-5), 7.81 (ddd, J=8.4, 7.0, 1.3 Hz 1H, quinoline-H-7), 7.72～7.63 (m, 1H, quinoline-H-6), 7.35 (dd, J=8.4, 5.6 Hz, 2H, Ar-H-2,6), 7.03 (t, J=8.7 Hz, 2H, Ar-H-3,5), 4.05 (s, 2H, NH-**CH$_2$**-triazole), 3.88 (s, 2H, Ar-**CH$_2$**-NH), 1.89 (s, 1H, CH_2-**NH**); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.1, 147.7, 142.9, 135.4, 130.5, 130.5, 129.9, 129.6, 128.3, 128.2, 127.4, 126.1, 120.1, 115.3, 52.7, 43.9. HRMS (ESI) calcd for $C_{19}H_{17}FN_5$ $[M+H]^+$ 334.1468, found 334.1467.

N-(4-三氟甲基苄基)-*N*-[1-(喹啉-3-基)-1*H*-1,2,3-三氮唑-4-基]甲胺(**3h**): 淡黄色固体, 收率 84%. m.p. 127.0～128.5 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.32 (d, J=2.5 Hz, 1H, quinoline-H-2), 8.51 (d, J=2.3 Hz, 1H, quinoline-H-4), 8.20 (d, J=8.5 Hz, 1H, quinoline-H-8), 8.08 (s, 1H, triazole-H-5), 7.94 (d, J=8.0 Hz, 1H, quinoline-H-5), 7.86～7.78 (m, 1H, quinoline-H-7), 7.71～7.64 (m, 1H, quinoline-H-6), 7.61 (d, J=8.1 Hz, 2H, Ar-H-3,5), 7.51 (d, J = 8.0 Hz, 2H, Ar-H-2,6), 4.05 (s, 2H, NH-**CH$_2$**-triazole), 3.98 (s, 2H, Ar-**CH$_2$**-NH), 1.83 (s, 1H, CH_2-**NH**); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.9, 147.8, 143.8, 130.5, 142.9, 135.9, 130.6, 130.5, 129.7, 128.4, 128.3, 128.2, 127.4, 126.2, 125.4, 120.1, 52.9, 44.0. HRMS (ESI) calcd for $C_{20}H_{17}F_3N_5$ $[M+H]^+$ 384.1436, found 384.1434.

N-(4-*N*,*N*-二甲氨基)苄基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三氮唑-4-基]甲胺(**3i**): 淡黄色固体, 收率 86%. m.p. 126.6～129.0 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.32 (d, J=2.5 Hz, 1H, quinoline-H-2), 8.49 (d, J=2.3 Hz, 1H, quinoline-H-4), 8.19 (d, J=8.5 Hz, 1H, quinoline-H-8), 8.06 (s, 1H, triazole-H-5), 7.93 (d, J=8.0 Hz, 1H, quinoline-H-5), 7.92～7.81 (m, 1H, quinoline-H-7), 7.72～7.62 (m, 1H, quinoline-H-6), 7.23 (d, J=8.6 Hz, 2H, Ph-H-2,6), 6.72 (d, J=8.7 Hz, 2H, Ph-H-3,5), 4.05 (s, 2H, NH-**CH$_2$**-triazole), 3.82 (s, 2H, Ph-**CH$_2$**-NH), 2.93 (s, 6H, N(**CH$_3$**)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 149.9, 148.5, 147.7, 143.0, 130.5, 130.5, 129.6, 129.3, 128.3, 128.2, 127.6, 127.4, 126.1, 120.1, 112.7, 53.1, 43.9, 40.7. HRMS (ESI) calcd for $C_{21}H_{22}N_6Na$ $[M+Na]^+$ 381.1804, found 381.1807.

N-对甲基苄基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三氮唑-4-基]甲胺(**3j**): 淡黄色固体, 收率 81%. m.p. 126.6～129.0 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.48 (d, J=2.6 Hz, 1H, quinoline-H-2), 8.94 (d, J=2.5 Hz, 1H, quinoline-H-4), 8.88 (s, 1H, triazole-H-5), 8.14 (d, J=8.4 Hz, 2H, quinoline-H-5,8), 7.86 (m, 1H, quinoline-H-7), 7.78～7.71 (m, 1H, quinoline-H-6), 7.28 (d, J=7.9 Hz, 2H, Ph-H-2,6), 7.14 (d, J=7.8 Hz, 2H, Ph-H-3,5), 3.86 (s, 2H, NH-**CH$_2$**-triazole), 3.75 (s, 2H, Ph-**CH$_2$**-NH), 2.63 (s, 1H, NH), 2.28 (s, 3H, **CH$_3$**); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 148.5, 147.3, 143.6, 137.9, 136.0, 130.8, 130.8, 129.4, 129.2, 129.1, 128.5, 127.6, 126.0, 121.9, 52.5, 43.8, 21.2. HRMS (ESI) calcd for $C_{20}H_{20}N_5$ $[M+H]^+$ 330.1719, found 330.1712.

N-{[1-(吡啶-3-基)-1*H*-1,2,3-三氮唑-4-基]甲基}环己胺(**3k**): 淡黄色固体, 收率 91%. m.p. 126.5～127.0 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.04 (d, J=2.5 Hz, 1H, pyridine-H-2), 8.70 (dd, J=4.8, 1.3 Hz, 1H, pyridine-H-6), 8.31 (s, 1H, triazole-H-5), 8.14 (ddd, J=8.3, 2.5, 1.5 Hz, 1H, pyridine-H-4), 7.50 (dd, J=8.3, 4.8 Hz, 1H, pyridine-H-5), 4.57 (s, 1H, NH), 4.19 (s, 2H, triazole-**CH$_2$**-NH), 2.70 (td, J=10.1, 3.6 Hz, 1H, cyclohexyl-H-1), 2.07 (d, J=8.8 Hz, 2H, cyclohexyl-H-2, 6), 1.83～1.73 (m, 2H, cyclohexyl-H-2,6), 1.37～1.15 (m, 6H, cyclohexyl-H-3,4,5); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 149.9, 145.3, 141.6, 133.6, 128.0, 124.3, 121.3, 56.0, 40.4, 31.8, 25.6, 24.7. HRMS (ESI) calcd for $C_{14}H_{20}N_5$ $[M+H]^+$ 258.1719, found 258.1721.

N-环己基-*N*-{[1-(吡啶-3-基)-1*H*-1,2,3-三氮唑-4-基]甲基}甲胺(**3l**): 淡黄色固体, 收率 88%. m.p. 127.9～128.5 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.94 (d, J=2.4 Hz, 1H, pyridine-H-2), 8.63 (dd, J=4.7, 1.3 Hz, 1H, pyridine-H-5), 8.07 (ddd, J=8.3, 2.6, 1.5 Hz, 1H, pyridine-H-4), 7.95 (s, 1H, triazole-H-5), 7.43 (dd, J=8.3, 4.8 Hz,

1H, pyridine-H-5), 3.96 (s, 2H, triazole-**CH$_2$**), 2.50 (d, *J*=6.7 Hz, 2H, NH-**CH$_2$**-cyclohexyl), 1.75～1.56 (m, 5H, NH, cyclohexyl-H), 1.54～1.40 (m, 1H, cyclohexyl-H-1), 1.25～1.05 (m, 7H, cyclohexyl-H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 148.9, 146.9, 140.5, 132.8, 127.0, 123.2, 119.0, 55.1 43.7, 36.8, 30.4, 25. 6, 24.9. HRMS (ESI) calcd for $C_{15}H_{22}N_5$ $[M+H]^+$ 272.1875, found 272.1878.

N-苄基-*N*-[1-(吡啶-3-基)-1*H*-1,2,3-三氮唑-4-基]甲胺(**3m**): 淡黄色固体, 收率 85%. m.p. 127.9～128.8 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.91 (d, *J*=2.5 Hz, 1H, pyridine-H-2), 8.62 (dd, *J*=4.8, 1.3 Hz, 1H, pyridine-H-6), 8.05 (ddd, *J*=8.3, 2.6, 1.5 Hz, 1H, pyridine-H-4), 7.96 (s, 1H, triazole-H-5),7.50 (dd, *J*=8.3, 4.8 Hz, 1H, pyridine-H-5), 7.37～7.32 (m, 4H, Ar-H), 7.29～7.27 (m, 1H, Ar-H-4), 4.03 (s, 2H, triazole-**CH$_2$**-NH), 3.89 (s, 2H, Ar-**CH$_2$**-NH), 1.95 (s, 1H, **NH**); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 148.8, 147.2, 140.5, 138.7, 132.7, 127.5, 127.2, 126.9, 126.2, 123.2, 118.8, 52.4, 42.9. HRMS (ESI) calcd for $C_{15}H_{16}N_5$ $[M+H]^+$ 266.1406, found 266.1408.

N-{[1-(吡啶-3-基)-1*H*-1,2,3-三氮唑-4-基]甲基}己胺(**3n**): 淡黄色固体, 收率 86%. m.p. 126.5～127.9 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.93 (d, *J*=2.4 Hz, 1H, pyridine-6-H), 8.62 (dt, *J*=6.3, 3.1 Hz, 1H, pyridine-2-H), 8.06 (ddd, *J*=8.3, 2.5, 1.5 Hz, 1H, triazole-5-H), 7.96 (s, 1H, pyridine-4-H), 7.43 (dd, *J*=8.1, 4.7 Hz, 1H, pyridine-5-H), 3.96 (s, 2H, hexylamine-H), 2.90 (s, 2H, NH-**CH$_2$**), 2.65 (t, *J*=7.3 Hz, 2H, hexylamine-H), 1.23 (tdd, *J*=15.2, 8.7, 6.5 Hz, 7H, hexylamine-H), 0.81 (t, *J*=6.8 Hz, 3H, hexylamine-H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 149.9, 147.79, 141.6, 133.8, 128.0, 124.3, 120.0, 49.5, 44.4, 31.7, 29.7, 26.9, 22.6, 14.0. HRMS (ESI) calcd for $C_{14}H_{22}N_5$ $[M+H]^+$ 260.1875, found 260.1882.

3.2.4 化合物 **4a～4r** 的合成

5-*O*-碳霉胺糖泰乐内酯(OMT): 取 1 g 酒石酸泰乐菌素溶于 30 mL 0.6 mol/L 的对甲苯磺酸水溶液中, 100 ℃回流 1.5 h, 高效液相色谱仪跟踪反应. 反应结束后, 立即冰浴至室温, 加入碳酸氢钠固体调 pH=8, 加入 1%活性炭除杂 40 min, 过滤, 滤液用二氯甲烷萃取至无色, 有机相用无水 $NaSO_4$ 干燥抽滤, 旋转蒸发除去溶剂, 粗产品经硅胶色谱柱分离[展开剂: *V*(EA)∶*V*(二乙胺)=39∶1], 得淡黄色固体, 收率 39%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.70 (s, 1H, CHO), 7.32 (d, *J*=15.5 Hz, 1H, H-11), 6.29 (d, *J*=15.5 Hz, 1H, H-10), 5.86 (d, *J*=10.6 Hz, 1H, H-13), 4.96～4.85 (m, 1H, H-15), 4.26 (d, *J*=7.4 Hz, 1H, H-1'), 3.85 (d, *J*=10.4 Hz, 1H, H-3), 3.79～3.69 (m, 3H, H-23, 5), 3.57 (s, 1H, H-2'), 3.49 (dd, *J*=10.4, 7.4 Hz, 1H, H-4'), 3.27 (s, 2H, N-CH_2-triazole), 3.05 (t, *J*=9.4 Hz, 1H, H-14), 3.00～2.83 (m, 2H, H-5', 20), 2.80～2.64 (m, 1H, H-8), 2.57～2.51 (m, 1H, H-2), 2.50 (s, 7H, H-7', 8', OH), 2.36 (t, *J*=10.1 Hz, 2H, H-3', 20), 2.16 (s, 1H, OH), 1.95 (d, *J*=16.5 Hz, 1H, H-2), 1.91～1.84 (m, 1H, H-16), 1.83 (d, *J*=1.0 Hz, 3H, H-22), 1.81～1.54 (m,7H, H-4, 6, 7, 16, 19), 1.27 (d, *J*=6.1 Hz, 3H, H-21), 1.22 (d, *J*=6.8 Hz, 3H, H-6'), 1.01 (d, *J*=6.8 Hz, 3H, H-18), 0.95 (t, *J*=7.3 Hz, 3H, H-17); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 203.6, 203.1, 174.0, 148.0, 141.7, 136.1, 104.0, 81.1, 75.0, 73.3, 71.0, 70.8, 70.1, 62.5, 47.3, 43.7, 41.7, 39.5, 25.6, 17.9, 17.4, 13.1, 9.7, 9.0. 与文献[18, 19]所述一致.

20-脱氧-20-{*N*-甲基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三唑-4-基]甲氨基}-5-*O*-碳霉胺糖基泰乐内酯(**4a**): 将 **3a** (0.1478 mmol)溶于 1,2-二氯乙烷中, 室温下搅拌溶解, 加入中间体 OMT、泰乐菌素或 Desmycosin (0.1478 mmol)后, 加入冰醋酸(0.4425 mmol), 室温搅拌 30 min, 分批加入三乙酰氧基硼氢化钠(0.443 mmol), TLC 跟踪反应, 反应结束后, 加入饱和 $NaHCO_3$ 水溶液淬灭反应, 并用二氯甲烷萃取至体系无色, 有机相用无水 $NaSO_4$ 干燥抽滤, 旋转蒸发除去溶剂, 得粗产品经硅胶色谱柱分离[展开剂: *V*(EA)∶*V*(甲醇)∶*V*(三乙胺)=30∶1∶0.5～10∶1∶0.5]得白色固体 **4a**, 收率 74%. m.p. 125～127 ℃; $[\alpha]_D^{25}$ −121.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.58 (d, *J*=2.2 Hz, 1H, quinoline-2-H), 8.84 (d, *J*=1.6 Hz, 1H, triazole-5-H), 8.84 (s, 1H, quinoline-4-H), 8.19 (d, *J*=8.5 Hz, 1H, quinoline-8-H), 7.98 (d, *J*=7.8 Hz, 1H, quinoline-5-H), 7.80～7.77 (m, 1H, quinoline-7-H), 7.65 (t, *J*=15.0 Hz, 1H, quinoline-6-H), 7.19 (d, *J*=15.3 Hz, 1H, H-11), 6.31 (d, *J*=15.4 Hz, 1H, H-10), 5.98 (d, *J*=10.8 Hz, 1H, H-13), 4.97 (td, *J*=10.0, 2.1 Hz, 1H, H-15), 4.30 (d, *J*=7.3 Hz, 1H, H-1'), 4.12 (q, *J*=7.1 Hz, 1H, H-3), 3.92 (d, *J*=13.2 Hz, 2H, N-**CH$_2$**-triazole), 3.73 (d, *J*=2.8 Hz, 2H, H-23), 3.61 (d, *J*=10.3 Hz, 1H, H-5), 3.51 (dd, *J*=15.2, 7.1 Hz, 2H, N-**CH$_2$**, H-2'), 3.34～3.34～3.30 (m, 2H, N-**CH$_2$**), 3.12 (t, *J*=9.4 Hz, 1H, H-5), 2.82～2.75 (m, 3H, H-4',5', OH), 2.67～2.53 (m, 2H, H-14, 8), 2.51 (s, 6H, H-7', H-8'), 2.44～2.35 (m, 2H, H-3', H-2), 2.31～2.84 (m, 1H, H-2), 2.21 (s, 3H, N-**CH$_3$**), 2.04 (s, 2H, H-16), 1.85～1.83 (m, 3H, H-22), 1.77 (s, 3H, H-4, H-7), 1.72～1.52 (m, 5H, H-2,6,7,19, OH), 1.31～1.22 (m, 6H, H-21, H-19, OH), 1.19 (d, *J*=6.8 Hz, 3H, H-6'), 1.02 (d, *J*=6.6 Hz, 3H, H-18), 0.85 (t, *J*=7.2 Hz, 3H, H-17);

^{13}C NMR (101 MHz, $CDCl_3$) δ: 203.6, 173.3, 171.2, 148.1, 147.2, 146.0, 144.0, 143.0, 131.1, 130.5, 128.8, 128.5, 128.0, 127.7, 122.3, 117.7, 104.3, 80.0, 74.9, 73.3, 71.0, 70.9, 66.9, 61.7, 60.4, 55.3, 52.1, 46.9, 45.3, 42.4, 41.9, 41.7, 39.3, 33.9, 31.9, 24.9, 21.0, 17.9, 17.6, 14.2, 12.9, 9.8, 9.4; HRMS (ESI) calcd for $C_{44}H_{65}N_6O_9$ $[M+H]^+$ 821.4768, found 821.4814.

化合物 **4b**～**4r** 的合成方法同化合物 **4a**.

20-脱氧-20-{*N*-正己基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三唑-4-基]甲氨基}-5-*O*-碳霉胺糖基泰乐内酯(**4b**): 白色固体, 收率 67%. m.p. 138.6～141.2 ℃; $[\alpha]_D^{20}$ −89.3 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.26 (s, 1H, quinoline-2-H), 9.26 (s, 2H, triazole-5-H, quinoline-4-H), 8.12 (d, *J*=8.4 Hz, 1H, quinoline-8-H), 8.07 (d, *J*=8.1 Hz, 1H, quinoline-5-H), 7.87 (t, *J*=7.4 Hz, 1H, H-11), 7.74 (t, *J*=7.4 Hz, 1H, H-10), 7.63～7.56 (d, *J*=15.3 Hz, 1H, H-13), 6.22 (d, *J*=15.1 Hz, 1H, H-1'), 5.78 (d, *J*=10.4 Hz, 1H, H-15), 4.87 (t, *J*=9.1 Hz, 1H, H-3), 4.19 (d, *J*=7.0 Hz, 1H, N-**CH$_2$**-triazole), 4.01 (d, *J*=7.1 Hz, 1H, N-**CH$_2$**-triazole), 3.67 (t, *J*=8.9 Hz, 2H, H-23), 3.27 (dd, *J*=12.4, 6.5 Hz, 2H, N-**CH$_2$**), 3.16～3.04 (m, 2H, H-5, H-2'), 2.95 (s, 2H, H-4'), 2.81 (dd, *J*=14.4, 7.1 Hz, 3H, H-5, H-4'), 2.57～2.47 (m, 2H, N-CH_2), 2.48～2.36 (m, 7H, H-7', H-8', H-3'), 2.03～1.92 (m, 2H, H-19), 1.91～1.68 (m, 10H, **CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$**), 1.61 (s, 4H, H-22), 1.56 (dd, *J*=21.6, 13.0 Hz, 4H, CH_2-CH_2), 1.31 (d, *J*=5.8 Hz, 3H, H-4, H-7), 1.26 (t, *J*=6.9 Hz, 3H, H-21), 1.17 (t, *J*=7.4 Hz, 6H, H-6', CH_2-**CH$_2$-CH$_2$**), 0.98～0.90 (m, 3H, H-18), 0.83 (ddd, J=20.3, 13.3, 6.3 Hz, 6H, H-17, CH_2-**CH$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 203.3, 173.3, 148.1, 147.1, 145.7, 144.0, 142.9, 134.5, 131.2, 130.5, 128.8, 128.1, 127.8, 125.2, 122.3, 117.6, 104.4, 81.1, 77.2, 75.0, 73.4, 71.0, 70.9, 70.2, 66.9, 61.9, 58.0, 47.2, 45.7, 45.2, 44.8, 41.7, 39.1, 34.1, 32.5, 29.7, 29.4, 26.5, 27.4, 26.4, 26.0, 25.3, 25.1, 24.6, 22.6, 17.9, 17.6, 14.1, 12.9, 9.4; HRMS (ESI) calcd for $C_{49}H_{75}N_6O_9$ $[M+H]^+$ 891.5517, found 891.5596.

20-脱氧-20-{*N*-环己基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三唑-4-基]甲氨基}-5-*O*-碳霉胺糖基泰乐内酯(**4c**): 白色固体, 收率 73%. m.p. 129.4～131.5 ℃; $[\alpha]_D^{20}$ −44.5 (*c* 0.03, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.54 (s, 1H, quinoline-2-H), 8.80 (s, 2H, triazole-5-H, quinoline-4-H), 8.19 (d, *J*=8.4 Hz, 1H, quinoline-8-H), 7.97 (d, *J*=8.1 Hz, 1H, quinoline-5-H), 7.79 (t, *J*=7.4 Hz, 1H, H-11), 7.64 (t, *J*=7.4 Hz, 1H, H-10), 7.22 (d, *J*=15.3 Hz, 1H, H-13), 6.31 (d, *J*=15.1 Hz, 1H, H-1'), 5.91 (d, *J*=10.4 Hz, 1H, H-15), 4.94 (t, *J*=9.1 Hz, 1H, H-3), 4.20 (d, *J*=7.0 Hz, 2H, N-CH_2-triazole), 3.50 (t, *J*=8.9 Hz, 2H, H-23), 3.27 (dd, *J*=12.4, 6.5 Hz, 2H, N-**CH$_2$**-triazole), 3.16～3.04 (m, 2H, H-5, H-2'), 2.95 (s, 2H, H-4'), 2.81 (dd, *J*=14.4, 7.1 Hz, 3H, H-5, H-14'), 2.70 (s, 1H), 2.53～2.40 (m, 9H, H-7', H-8', H-2), 2.34 (t, *J*=10.0 Hz, 1H, H-3'), 2.10 (d, *J*=18.6 Hz, 1H, H-2), 2.03～1.92 (m, 2H, H-19), 1.91～1.68 (m, 1H, N-**CH$_2$**), 1.61 (s, 4H, H-22), 1.31 (d, *J*=5.8 Hz, 4H, H-4, H-7), 1.26 (t, *J*=6.9 Hz, 3H, H-21), 1.18 (t, *J*=7.4 Hz, 7H, H-6', CH_2-**CH$_2$**-CH_2), 1.00 (d, *J*=6.1 Hz, 3H, H-18), 0.84 (t, *J*=6.7 Hz, 3H, H-17); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 203.5, 173.2, 148.0, 147.2, 146.7, 144.0, 142.6, 134.9, 131.0, 130.4, 128.9, 128.4, 128.0, 127.7, 127.3, 126.1, 117.9, 104.7, 80.8, 77.3, 75.0, 73.4, 71.0, 70.9, 70.2, 66.9, 61.9, 47.2, 45.7, 45.2, 44.8, 41.7, 39.1, 34.1, 29.7, 29.5, 26.5, 26.4, 26.0, 25.3, 25.1, 24.8, 21.1, 17.9, 17.6, 13.0, 9.9; HRMS (ESI) calcd for $C_{49}H_{73}N_6O_9$ $[M+H]^+$889.5494, found 889.5493.

20-脱氧-20-{*N*-环己甲基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三唑-4-基]甲氨基}-5-*O*-碳霉胺糖基泰乐内酯(**4d**): 白色固体, 收率 71%. m.p.136.1～138.9 ℃; $[\alpha]_D^{20}$ −13.6 (*c* 0.167, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.55 (s, 1H, quinoline-2-H), 8.78 (s, 2H, triazole-5-H, quinoline-4-H), 8.19 (d, *J*=8.4 Hz, 1H, quinoline-8-H), 7.96 (d, *J*=8.1 Hz, 1Hquinoline-5-H), 7.79 (t, *J*=7.4 Hz, 1H, H-11), 7.64 (t, *J*=7.4 Hz, 1H, H-10), 7.22 (d, *J*=15.3 Hz, 1H, H-13), 6.28 (d, *J*=15.1 Hz, 1H, H-1'), 5.91 (d, *J*=10.4 Hz, 1H, H-15), 4.94 (t, *J*=9.1 Hz, 1H, H-3), 4.20 (d, *J*=7.0 Hz, 2H, N-**CH$_2$**-triazole), 3.50 (t, *J*=8.9 Hz, 2H, H-23), 3.27 (dd, *J*=12.4, 6.5 Hz, 2H, N-**CH$_2$**-triazole, N-**CH$_2$**), 3.16～3.04 (m, 2H, H-5, H-2'), 2.95 (s, 2H, H-4'), 2.81 (dd, *J*=14.4, 7.1 Hz, 3H, H-5, H-14'), 2.53～2.40 (m, 9H, H-7', H-8', H-2), 2.34 (t, *J*=10.0 Hz, 1H, H-3'), 2.10 (d, *J*=18.6 Hz, 1H, N-**CH$_2$**), 2.03～1.92 (m, 2H, H-19), 1.91～1.68 (m, 10H, CH_2-**CH$_2$**CH_2-**CH$_2$**-CH_2), 1.61 (s, 4H, H-22), 1.31 (d, *J*=5.8 Hz, 4H, H-4, H-7), 1.26 (t, *J*=6.9 Hz, 3H, H-21), 1.18 (t, *J*=7.4 Hz, 7H, H-6', CH_2-**CH$_2$**-CH_2), 1.00 (d, *J*=6.1 Hz, 3H, H-18), 0.84 (t, *J*=6.7 Hz, 3H, H-17); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 203.5, 173.2, 148.0, 147.2, 146.7, 144.0, 142.6, 134.9, 131.0, 130.4, 128.9, 128.4, 128.0, 127.7, 127.3, 126.3, 117.9, 1047, 80.8, 77.3, 75.0, 73.4, 71.0, 70.9, 70.2, 66.9, 61.9, 58.0, 47.2, 45.7, 45.2, 44.8, 41.7, 39.1, 34.1, 29.7, 29.4, 26.5, 26.4, 26.0, 25.3, 25.1, 24.8, 21.1, 17.9, 17.6, 13.0,

9.9; HRMS (ESI) calcd for $C_{50}H_{75}N_6O_9$ [M + H]$^+$ 903.5517, found 903.5551.

20-脱氧-20-{*N*-苄基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三氮唑-4-基]甲胺}-5-*O*-碳霉氨糖泰乐内酯(**4e**): 白色固体, 收率 91%. m.p. 122.4～123.8 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.57 (d, J=2.0 Hz, 1H, quinoline-H-2), 8.82 (s, 2H, quinoline-H-4, triazole-H-5), 8.20 (d, J=8.5 Hz, 1H, quinoline-H-8), 7.98 (d, J=7.6 Hz, 1H, quinoline-H-5), 7.79 (ddd, J=8.4, 7.0, 1.3 Hz, 1H, quinoline-H-7), 7.69～7.57 (m, 1H, quinoline-H-6), 7.42 (d, J=7.0 Hz, 2H, Ph-H-2, 6), 7.36～7.20 (m, 4H, Ph-H-3, 4, 5, H-11), 6.35 (d, J=15.4 Hz, 1H, H-10), 6.09 (d, J=10.6 Hz, 1H, H-13), 4.99 (td, J=9.9, 2.2 Hz, 1H, H-15), 4.49 (s, 1H, OH), 4.09 (d, J=13.7 Hz, 1H, N-**CH$_2$**-triazole), 4.01～3.69 (m, 5H, H-3,1', Ph-**CH$_2$**-N, H-23), 3.42～3.39 (m, 3H, H-5, 2', N-CH_2-triazole), 3.28 (d, J = 12.9 Hz, 1H, Ph-**CH$_2$**-N), 2.99 (t, J=9.4 Hz, 2H, H-4', OH), 2.83～2.76 (m, 3H, H-14,5', 20), 2.73 (s, 1H, H-8), 2.51～2.39 (m, 8H, H-2,7',8', OH), 2.24 (t, J=10.1 Hz, 1H, H-3'), 2.16～2.07 (m, 1H, H-20), 2.01 (d, J=17.0 Hz, 2H, H-2, OH), 1.88 (ddd, J=14.2, 7.3, 2.4 Hz, 1H, H-16), 1.80 (s, 3H, H-22), 1.73～1.44 (m, 7H, H-4,6,7,16,19), 1.20 (d, J=6.8 Hz, 3H, H-21), 1.09 (d, J=6.0 Hz, 3H, H-6'), 1.00 (d, J=6.6 Hz, 3H, H-18), 0.84 (t, J=7.2 Hz, 3H, H-17); ^{13}C NMR (101M Hz, $CDCl_3$) δ: 203.7, 173.4, 148.1, 147.2, 145.9, 144.1, 142.7, 137.1, 134.9, 131.0, 130.4, 128.9, 128.5, 128.2, 128.0, 127.7, 127.4, 127.3, 122.8, 117.9, 104.3, 80.0, 75.2, 73.0, 70.9, 70.8, 70.2 , 67.2, 61.9, 59.5, 51.0, 49.0, 47.1, 45.2, 41.7, 39.0, 34.0, 31.7, 25.1, 24.9, 17.7, 17.6, 13.0, 9.9, 9.3; HRMS (ESI) calcd for $C_{50}H_{68}N_6O_9$ [M+H]$^+$ 897.5126, found 897.5119. 与文献[16]所述一致.

20-脱氧-20-{*N*-对溴苄基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三氮唑-4-基]甲胺}-5-*O*-碳霉氨糖泰乐内酯(**4f**): 白色固体, 收率 85%. m.p. 124.3～126.7 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.53 (s, 1H, quinoline-H-2), 8.78～8.76 (m, 2H, quinoline-H-4,triazole-H-5), 8.22～8.14 (m, 1H, quinoline-H-8), 7.97 (dd, J=8.1, 3.1 Hz, 1H, quinoline-H-5), 7.79 (ddd, J=8.3, 5.0, 1.3 Hz, 1H, quinoline-H-7), 7.64 (dd, J=9.9, 5.0 Hz, 1H, quinoline-H-6), 7.49～7.43 (m, 2H, Ph-H-3, 5), 7.33 (d, J=8.2 Hz, 2H, Ph-H-2,6), 7.20 (d, J=15.3 Hz, 1H, H-11), 6.32 (d, J=15.3 Hz, 1H, H-10), 5.99 (d, J=10.1 Hz, 1H, H-13), 4.97 (t, J=8.6 Hz, 1H, H-15), 4.36 (s, 1H, OH), 4.01 (t, J = 12.0 Hz, 1H, N-**CH$_2$**-triazole), 3.97～3.92 (m, 3H, H-3,1', Ph-**CH$_2$**-N), 3.78 (d, J=2.9 Hz, 2H, H-23), 3.56～3.37 (m, 3H, H-5,2', N-**CH$_2$**-triazole), 3.25 (d, J=13.2 Hz, 1H, Ph-**CH$_2$**-N), 3.02 (t, J=9.3 Hz, 1H, H-4'), 2.93～2.76 (m, 4H, H-14, 5', 20, OH), 2.71 (s, 2H, H-8, OH), 2.55～2.50 (m, 1H, H-2), 2.47 (s, 6H, H-7',8'), 2.26 (t, J=10.1 Hz, 1H, H-3'), 2.16 (d, J=7.7 Hz, 1H, H-20), 2.00 (d, J=17.0 Hz, 1H, H-2), 1.90～1.83 (m, 1H, H-16), 1.79 (d, J=5.8 Hz, 3H, H-22), 1.80～1.66 (m, 5H, H-4,6,7,19), 1.60～1.56 (m, 1H, H-16), 1.51 (d, J=10.6 Hz, 1H, H-19), 1.19 (d, J=6.5 Hz, 3H, H-21), 1.11 (d, J=6.0 Hz, 3H, H-6'), 1.03 (d, J=6.5 Hz, 3H, H-18), 0.87 (t, J=7.2 Hz, 3H, H-17); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 203.7, 173.7, 147.9, 147.2, 146.0, 143.7, 142.5, 136.8, 135.2, 131.8, 131.4, 130.9, 130.4, 129.0, 128.4, 128.1, 127.7, 127.1, 122.5, 123.0, 118.0, 104.4, 79.8, 75.2, 73.3, 70.9, 70.2, 67.2, 62.0, 58.3, 51.0, 49.1, 47.1, 45.2, 41.7, 41.5, 39.1, 33.8, 31.9, 25.2, 25.0, 17.7, 17.6, 13.1, 9.9, 9.5; HRMS (ESI) calcd for $C_{50}H_{68}N_6O_9$ [M+H]$^+$ 975.4231, found 975.4231.

20-脱氧-20-{*N*-对氟苄基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三唑-4-基]甲氨基}-5-*O*-碳霉胺糖基泰乐内酯(**4g**): 白色固体, 收率 63%. m.p. 141.8～144.1 ℃; $[\alpha]_D^{20}$ −108.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.47 (s, 1H), 8.70 (d, J=22.0 Hz, 2H), 8.13 (d, J=8.4 Hz, 1H), 7.90 (d, J=8.1 Hz, 1H), 7.72 (t, J=7.5 Hz, 1H)7.58 (t, J=7.4 Hz, 1H), 7.40～7.25 (m, 2H), 7.15 (s, 1H), 6.94 (t, J=8.5 Hz, 2H), 6.26 (d, J=15.2 Hz, 1H), 5.95 (d, J=10.3 Hz, 1H), 5.23 (s, 1H), 4.92 (t, J=8.9 Hz, IH), 3.89 (ddd, J=32.9, 23.3, 13.7 Hz, 4H), 3.72 (s, 2H), 3.39 (dd, J=20.3, 11.1 Hz, 3H), 3.23 (d, J=12.9 Hz, 1H), 3.07～2.94 (m, 1H), 2.87 (s, 1H), 2.76 (d, J=9.8 Hz.2H), 2.64 (s.1H), 2.55～2.36 (m, 6H), 2.31 (s, 1H), 2.10 (s, 1H), 192 (d, J=17.5 Hz, 2H), 1.83～1.77 (m, 1H), 1.72 (s, 3H), 1.58 (d, J=12.5 Hz, 4H), 1.52～1.47 (m, 1H), 1.47～1.29 (m, 2H), 1.20 (d, J=11.9 Hz, 2H), 1.07 (d, J=5.1 Hz, 3H), 0.93 (d, J=6.0 Hz, 3H), 0.80 (t, J=6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 202.6, 172.6, 162.3, 147.0, 146.2, 145.1, 142.8, 141.5, 134.0, 132.0, 130.7, 129.9, 129.4, 128.0, 127.4, 127.1, 126.7, 126.2, 121.5, 116.9, 114.4, 114.0, 103.1, 78.9, 74.2, 72.1, 69.8, 69.6, 66.1, 60.9, 57.1, 52.4, 49.9, 47.7, 46.0, 44.2, 40.7, 40.5, 38.0, 32.9, 28.7, 24.1, 23.9, 16.7, 16.5, 13.1, 12.0, 8.8; HRMS (ESI) calcd for calcd for $C_{50}H_{68}FN_6O_9$ [M + H]$^+$ 915.4987, found 915.5034.

20-脱氧-20-{*N*-4-氟苄基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三唑-4-基]甲氨基}-5-*O*-碳霉胺糖基泰乐内酯(**4h**): 黄色

固体, 收率 83%. m.p. 129～132 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.51 (s, 1H, H36), 8.76 (d, J=13.3 Hz, 2H, H-33, H-35), 8.19 (d, J=8.5 Hz, 1H, H-42), 7.97 (d, J=8.0 Hz, 1H, H-39), 7.79 (dd, J=11.3, 4.1 Hz, 1H, H-41), 7.66 (d, J=7.4 Hz, 1H, H-40), 7.64～7.54 (m, 4H, H-25, H-29, H-11, H-26), 7.17 (d, J=15.4 Hz, 1H, H-28), 6.32 (d, J=15.3 Hz, 1H, H-10), 5.94 (d, J=10.5 Hz, 1H, H-13), 4.97 (t, J=8.9 Hz, 1H, H-15), 4.07～3.87 (m, 4H, H-1', H-3, H-31, H-24), 3.76 (d, J=3.3 Hz, 3H, H-23), 3.45 (ddd, J=30.8, 25.4, 15.1 Hz, 8H, H-5, H-2', H-31), 3.06 (dd, J=12.6, 5.4 Hz, 2H, H-4'), 2.94～2.77 (m, 3H, H-14), 2.71 (s, 1H, H-8), 2.63～2.43 (m, 7H, H-7', H-8'), 2.39～2.29 (m, 1H, H-3'), 2.22 (d, J=8.5 Hz, 1H, H-2), 2.03 (d, J=8.8 Hz, 1H, H-16), 1.98 (d, J=4.6 Hz, 1H, H-2), 1.89 (ddd, J=14.4, 13.4, 7.2 Hz, 1H, H-4), 1.78 (s, 3H, H-22), 1.73～1.54 (m, 2H, H-7), 1.50 (d, J=11.3 Hz, 1H, H-6), 1.26 (t, J=7.1 Hz, 2H, H-19), 1.18 (d, J=6.6 Hz, 3H, H-21), 1.10 (d, J=5.9 Hz, 3H, H-6'), 1.03 (d, J=6.3 Hz, 3H, H-18), 0.89 (t, J=7.2 Hz, 3H, H-17); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 203.8, 173.8, 147.9, 147.3, 146.1, 143.5, 142.5, 135.3, 130.8, 130.5, 130.0, 129.4, 129.1, 129.0, 128.4, 128.1, 127.6, 127.0, 125.7, 125.2, 123.0, 122.3, 79.8, 75.3, 73.1, 70.6, 67.2, 61.9, 60.4, 58.4, 51.1, 49.1, 47.1, 45.8, 45.2, 41.7, 41.3, 39.1, 33.7, 32.1, 29.7, 22.7, 21.1, 17.6, 13.1, 9.5, 8.7; HRMS (ESI) calcd for $C_{51}H_{68}F_3N_6O_9$ $[M+H]^+$ 965.4922, found 965.5002.

20-脱氧-20-{*N*-(4-*N*,*N*-二甲氨基)苄基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三氮唑-4-基]甲胺}-5-*O*-碳霉氨糖泰乐内酯(**4i**): 黄色固体, 收率 88%. m.p. 128.3～130.2 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.55 (s, 1H, quinoline-H-2), 8.88 (s, 1H, quinoline-H-4), 8.81 (s, 1H, triazole-H-5), 8.18 (d, J=8.5 Hz, 1H, quinoline-H-8), 7.98 (d, J=8.0 Hz, 1H, quinoline-H-5), 7.78 (t, J=7.3 Hz, 1H, quinoline-H-7), 7.64 (t, J=7.5 Hz, 1H, quinoline-H-6), 7.28～7.24 (m, Ph-H-2, 6, H-11), 6.70 (d, J=8.5 Hz, 2H, Ph-H-3,5), 6.33 (d, J=15.3 Hz, 1H, H-10), 6.03 (d, J=10.6 Hz, 1H, H-13), 4.95 (t, J=8.9 Hz, 1H, H-15), 4.05 (d, J=13.7 Hz, 1H, N-**CH$_2$**-triazole), 3.89～4.02 (m, 3H, H-3,1', Ph-**CH$_2$**-N), 3.78～3.69 (m, 2H, H-23), 3.38～3.27 (m, 5H, H-5,2', N-**CH$_2$**-triazole, Ph-**CH$_2$**-N), 3.07 (t, J=9.3 Hz, 1H, H-4'), 2.94～2.82 (m, 8H, (**CH$_3$**)$_2$-N-Ph, H-14,5'), 2.81 (d, J=10.2 Hz, 2H, H-20, OH), 2.71 (s, 1H, H-8), 2.55 (s, 6H, H-7',8'), 2.47 (dd, J=17.0, 10.1 Hz, 1H, H-2), 2.32 (t, J=9.9 Hz, 1H, H-3'), 2.10 (d, J=8.8 Hz, 2H, H-20, OH), 2.01～1.98 (m, 1H, H-2), 1.90～1.81 (m, 1H, H-16), 1.78 (s, 3H, H-22), 1.73～1.44 (m, 8H, H-4, 6, 7, 16, 19), 1.19 (d, J=6.7 Hz, 3H, H-21), 1.13 (d, J=5.9 Hz, 3H, H-6'), 1.02 (d, J=6.5 Hz, 3H, H-18), 0.83 (t, J=7.1 Hz, 3H, H-17); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 203.8, 173.3, 150.0, 148.1, 147.1 145.7, 144.1, 142.7, 134.8, 131.4, 131.0, 130.4, 128.9, 128.5, 128.0, 127.7, 127.4, 124.6, 122.9, 117.9, 112.7, 104.4, 80.6, 75.1, 73.0, 70.9, 70.6, 70.5, 67.3, 61.8, 58.5, 50.8, 49.0, 47.0, 45.1, 41.7, 40.9, 39.0, 34.1, 31.7, 25.1, 24.8, 17.7, 17.6, 13.0, 9.9, 9.3; HRMS (ESI) calcd for $C_{52}H_{74}N_7O_9$ $[M+H]^+$ 940.5548, found 940.5549.

20-脱氧-20-{*N*-对甲基苄基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三氮唑-4-基]甲胺}-5-*O*-碳霉氨糖泰乐内酯(**4j**): 黄色固体, 收率 88%. m.p. 129.6～130.5 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.57 (d, J=1.8 Hz, 1H, quinoline-H-2), 8.83 (s, 2H, quinoline-H-4, triazole-H-5), 8.19 (d, J=8.5 Hz, 1H, quinoline-H-8), 7.98 (d, J=7.8 Hz, 1H, quinoline-H-5), 7.86～7.70 (m, 1H, quinoline-H-7), 7.64 (t, J=7.2 Hz, 1H, quinoline-H-6), 7.37～7.28 (m, 3H, Ph-H-2,6, H-11), 7.12 (d, J=7.8 Hz, 2H, Ph-H-3,5), 6.34 (d, J=15.4 Hz, 1H, H-10), 6.09 (d, J=10.7 Hz, 1H, H-13), 4.99 (td, J=9.9, 2.1 Hz, 1H, H-15), 4.60 (s, 1H, OH), 4.06 (d, J=13.6 Hz, 1H, N-CH$_2$-triazole), 3.98 (d, J=9.5 Hz, 1H, H-3), 3.94～3.84 (m, 2H, H-1', Ph-**CH$_2$**-N), 3.79 (d, J=11.7 Hz, 2H, H-23), 3.54～3.35 (m, 3H, H-5,2', N-**CH$_2$**-triazole), 3.28 (d, J=12.8 Hz, 1H, Ph-**CH$_2$**-N), 2.99 (t, J=9.3 Hz, 2H, H-4', OH), 2.97～2.82 (m, 3H, H-14,5',20), 2.72 (s, 1H, H-8), 2.56～2.39 (m, 8H, H-2,7',8', OH), 2.32 (s, 3H, **CH$_3$**-Ph), 2.21 (t, J=10.1 Hz, 1H, H-3'), 2.09 (d, J=12.4 Hz, 1H, H-20), 2.01 (d, J=17.0 Hz, 1H, H-2), 1.97～1.91 (s, 1H, OH), 1.88 (ddd, J=14.2, 7.4, 2.3 Hz, 1H, H-16), 1.80 (s, 3H, H-22), 1.75～1.45 (m, 7H, H-4,6,7,16,19), 1.20 (d, J=6.8 Hz, 3H, H-21), 1.10 (d, J=5.8 Hz, 3H, H-6'), 1.02 (d, J=6.6 Hz, 3H, H-18), 0.83 (t, J=7.2 Hz, 3H, H-17); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 203.6, 173.4, 148.1, 147.2, 145.9, 144.2, 142.6, 136.8, 134.9, 133.7, 131.0, 130.5, 130.4, 128.9, 128.5, 128.0, 127.7, 127.5, 122.8, 117.9, 104.5, 80.2, 75.1, 73.1, 71.0, 70.8, 70.3, 67.2, 61.9, 59.0, 51.0, 48.9, 47.0, 45.2, 41.8, 39.0, 34.0, 31.6, 25.1, 24.8, 21.1, 17.7, 17.6, 13.0, 9.9, 9.3; HRMS (ESI) calcd for $C_{51}H_{71}N_6O_9$ $[M+H]^+$ 911.5283, found 911.5284.

20-脱氧-20-{*N*-环己基-*N*-[1-(3-吡啶基)-1*H*-1,2,3-三唑-4-基]甲氨基}-5-*O*-碳霉胺糖基泰乐内酯(**4k**): 白色固体, 收率 72%. m.p. 133.3～136.7 ℃; $[\alpha]_D^{20}$ −33.3 (*c*

0.03, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 9.23 (s, 1H, pyridine-2-H), 8.72 (s, 1H, triazole-5-H), 8.63 (d, J=4.5 Hz, 1H, pyridine-4-H), 8.37 (d, J=6.8 Hz, 1H, pyridine-5-H), 7.52 (dd, J=8.3, 4.8 Hz, 1H, pyridine-6-H), 7.28 (s, 1H, H-11), 6.31 (d, J=15.3 Hz, 1H, H-10), 5.99 (d, J=8.3 Hz, 1H, H-13), 4.99 (t, J=9.7 Hz, 1H, H-1'), 4.22 (d, J=6.7 Hz, 1H, N-**CH₂**-triazole), 4.01～3.93 (m, 1H, N-**CH₂**-triazole), 3.89 (s, 1H, H-5), 3.77 (d, J=11.4 Hz, 2H, H-2', H-3), 3.57～3.46 (m, 2H, H-23), 3.32～3.23 (m, 1H, H-4'), 3.15 (t, J=9.3 Hz, 1H, H-5), 3.04 (q, J=7.3 Hz, 2H, H-14), 2.91 (s, 1H, H-2), 2.81 (s, 1H, H-2), 2.58 (s, 5H, H-20), 2.53～2.38 (m, 3H, H-7'), 2.08 (s, 1H, H-19), 2.00 (s, 3H, H-8'), 1.97 (s, 1H, H-19), 1.80 (s, 7H, N-**CH**, CH_2-CH_2-CH_2), 1.67～1.49 (m, 5H, H-4, H-7), 1.31 (t, J=7.3 Hz, 10H, H-21, CH_2-CH_2-CH_2), 1.20 (d, J=6.4 Hz, 3H, H-6'), 0.99 (d, J=6.2 Hz, 3H, H-18), 0.91 (t, J=7.2 Hz, 3H, H-17); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 203.8, 177.2, 149.0, 148.1, 142.7, 141.9, 134.2, 128.8, 126.3, 124.4, 122.4, 117.9, 104.4, 80.8, 77.3, 75.1, 73.3, 70.7, 67.0, 61.9, 58.3, 66.9, 61.9, 47.1, 45.9, 45.4, 45.1, 44.7, 41.7, 29.7, 29.4, 26.4, 26.3, 25.9, 25.1, 24.8, 22.9, 21.1, 17.9, 17.6, 9.9, 8.7; HRMS (ESI) calcd for for $C_{45}H_{71}N_6O_9$ $[M+H]^+$ 839.5294, found 839.5281.

20-脱氧-20-{*N*-环己甲基-*N*-[1-(3-吡啶基)-1*H*-1,2,3-三唑-4-基]甲氨基}-5-*O*-碳霉胺糖基泰乐内酯(**4l**): 白色固体, 收率 74%. m.p. 127.3～129.6 ℃; $[\alpha]_D^{20}$ −20.0 (*c* 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 9.23 (s, 1H, pyridine-2-H), 8.65 (d, J=4.2 Hz, 2H, triazole-5-H, pyridine-4-H), 8.39 (d, J=5.4 Hz, 1H, pyridine-5-H), 7.52 (dd, J=8.2, 4.8 Hz, 2H, pyridine-6-H, H-11), 7.18 (d, J=15.5 Hz, 1H, H-10), 6.30 (d, J=15.2 Hz, 1H, H-13), 5.85 (dd, J=41.9, 9.8 Hz, 1H, H-1'), 5.02 (s, 1H, H-15), 4.23 (d, J=7.1 Hz, 1H, H-3), 4.12 (d, J=7.1 Hz, 1H, N-**CH₂**-triazole), 3.93 (d, J=14.1 Hz, 1H, H-5'), 3.73 (s, 1H, H-3), 3.66 (d, J=5.3 Hz, 1H, H-3'), 3.60 (d, J=9.2 Hz, 2H, N-**CH₂**-triazole), 3.54～3.45 (m, 2H, H-23), 3.31 (s, 3H, N-**CH₂**, CH_2-**CH**-CH_2), 3.25～3.20 (m, 2H, H-20), 2.56 (d, J=15.5 Hz, 7H, H-7', H-8'), 2.50～2.42 (m, 2H, H-5, H-4'), 2.29 (dd, J=12.6, 7.4 Hz, 2H, H-2), 2.25～2.16 (m, 1H, H2, H-19), 1.79 (s, 4H, CH_2-**CH₂**-CH_2), 1.76～1.67 (m, 6H, CH_2-**CH₂**-CH_2), 1.63 (s, 6H, H-22, H-4, H-7), 1.50 (d, J=7.7 Hz, 3H, H-21), 1.19 (d, J=6.5 Hz, 6H, H-6', CH_2-**CH₂**-CH_2), 1.00 (d, J=6.6 Hz, 3H, H-18), 0.93 (t, J=7.2 Hz, 3H, H-17); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 203.6, 173.7, 149.9, 149.1, 147.9, 146.6, 142.2, 141.6, 134.3, 128.7, 128.1, 126.3, 124.4, 118.1, 80.4, 77.3, 74.9, 73.3, 71.0, 70.4, 67.0, 63.7, 61.6, 55.9, 49.4, 47.2, 47.0, 45.2, 41.7, 39.4, 31.3, 29.7, 29.4, 26.6, 26.3, 26.2, 25.9, 25.5, 22.7, 17.9, 14.2, 14.1, 13.0, 9.5; HRMS (ESI) calcd for $C_{46}H_{73}N_6O_9$ $[M+H]^+$ 853.5394, found 853.5479.

20-脱氧-20-{*N*-苄基-*N*-[1-(3-吡啶基)-1*H*-1,2,3-三唑-4-基]甲氨基}-5-*O*-碳霉胺糖基泰乐内酯(**4m**): 白色固体, 收率 71%. m.p. 127.1～128.5 ℃; $[\alpha]_D^{20}$ −43.6 (*c* 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 9.56 (s, 1H, pyridine-2-H), 8.81 (s, 2H, pyridine-4-H, H-33), 8.20 (d, J=8.5 Hz, 1H, pyridine-5-H), 7.98 (d, J=8.1 Hz, 1H, pyridine-6-H), 7.42 (d, J=7.2 Hz, 2H, H-25), 7.36～7.19 (m, 5H, H-26,27,28,29, H-11), 6.34 (d, J=15.4 Hz, 1H, H-10), 6.05 (d, J=10.4 Hz, 1H, H-13), 4.97 (t, J=9.2 Hz, 1H, H-15), 4.12 (q, 3H, N-**CH₂**-triazole, H-3,1'), 3.98～3.91 (m, 3H, Ph-**CH₂**-N, H-23), 3.78 (s, 3H, H-5,2', N-**CH₂**-triazole), 3.61 (d, J=13.6 Hz, 1H, Ph-**CH₂**-N), 3.55～3.35 (m, 5H, H-4', OH, H-14,5',20), 3.18 (d, J=12.8 Hz, 1H, H-8), 3.11～2.92 (m, 2H, H-2), 2.58～2.43 (m, 6H, , 7', 8'), 2.34～2.20 (m, 1H, H-3'), 2.08～2.00 (m, 3H, H-20,2, OH), 1.54 (s, 4H, H-16,22), 1.27 (q, J=7.2 Hz, 7H, H-4,6,7,16,19), 1.18 (dd, J=15.0, 6.7 Hz, 3H, H-21), 1.10 (d, J=6.0 Hz, 3H, H-6'), 1.05～0.92 (m, J=6.8 Hz, 3H, H-21), 0.85 (t, J=7.1 Hz, 3H, H-17); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 203.6, 171.2, 148.0, 147.2, 146.0, 144.0, 142.6, 131.0, 130.4, 128.9, 128.4, 128.2, 128.0, 127.7, 127.2, 122.7, 117.9, 104.3, 77.2, 75.2, 73.1, 70.8, 70.1, 61.9, 60.4, 49.0, 47.1, 45.2, 43.3, 41.7, 39.0, 33.7, 24.9, 22.4, 21.0, 18.1, 17.7, 14.2, 13.0, 9.9; HRMS (ESI) calcd for $C_{46}H_{67}N_6O_9$ $[M+H]^+$ 847.4925, found 847.4969.

20-脱氧-20-{*N*-己基-*N*-[1-(3-吡啶基)-1*H*-1,2,3-三唑-4-基]甲氨基}-5-*O*-碳霉胺糖基泰乐内酯(**4n**): 白色固体, 收率 69%. m.p. 119.2～121.7 ℃; $[\alpha]_D^{20}$ −36.4 (*c* 0.11, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 9.23 (s, 1H, pyridine-2-H), 8.66 (s, 1H, triazole-5-H), 8.56 (d, J=4.6 Hz, 1H, pyridine-4-H), 8.39 (d, J=7.7 Hz, 1H, pyridine-5-H), 7.46 (dt, J=9.6, 4.9 Hz, 1H, pyridine-6-H), 7.06 (d, J=15.4 Hz, 1H, H-11), 6.22 (d, J=15.4 Hz, 1H, H-10), 5.96 (d, J=10.3 Hz, 1H, H-13), 5.00 (t, J=9.3 Hz, 1H, H-1'), 4.20 (d, J=7.3 Hz, 1H, H-15), 3.88～3.76 (m, 4H, H3, N-**CH₂**-triazole), 3.64～3.52 (m, 2H, H-23), 3.43 (dd, J=21.3, 11.4 Hz, 4H, H-5, H-2', H-14), 2.79～2.66 (m, 3H, N-CH_2), 2.56 (d, J=6.9 Hz, 1H, H-3'), 2.45 (s, 7H, H-7', H-8'), 2.32 (t, J=10.1 Hz, 4H, CH_2-**CH₂**), 1.57～1.38 (m, 7H, H-20, CH_2-**CH₂**-CH_2), 1.23 (d, J=5.8

Hz, 2H, H-19), 1.18 (s, 8H, H-21), 1.11 (d, *J*=6.8 Hz, 6H, H-6', CH_2-**CH_2**-CH_2), 0.94 (d, *J*=6.5 Hz, 3H, H-18), 0.81 (dd, *J*=12.7, 7.0 Hz, 6H, H-17, CH_2-**CH_3**); ^{13}C NMR (101M Hz, $CDCl_3$) *δ*: 202.3, 172.3, 148.8, 147.9, 147.1, 144.7, 133.4, 133.4, 128.3, 127.0, 123.5, 122.6, 123.3, 103.4, 80.0, 76.2, 74.0, 72.4, 70.0, 69.8 (C-3), 69.2, 65.8, 62.7, 60.8, 53.2, 50.8, 47.9, 46.0, 41.0, 40.7, 38.1, 33.0, 31.4, 30.7, 28.7, 26.3, 23.9, 23.8, 23.5, 21.6, 16.9, 16.6, 13.1, 11.8, 8.4; HRMS (ESI) calcd for $C_{45}H_{73}N_6O_9$ [M+H]$^+$ 841.5494, found 841.5446.

20-脱氧-20-{*N*-苄基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三唑-4-基]甲氨基}-泰乐菌素(**4o**): 将 **3a** 换成 **3e** 同化合物 **4a** 制备, 得到白色固体, 收率 80%. m.p. 138.3～139.6 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.53 (s, 1H, H36), 8.78 (d, *J*=41.5 Hz, 2H, H-33, H-35), 8.20 (d, *J*=8.5 Hz, 1H, H-42), 7.95 (d, *J*=8.0 Hz, 1H, H-39), 7.84～7.75 (m, 1H, H-41), 7.65 (t, *J*=7.5 Hz, 1H, H-40), 7.41 (d, *J*=7.2 Hz, 2H, H-25, H-29), 7.34 (t, *J*=7.4 Hz, 2H, H-11, H-26), 7.24 (dd, *J*=15.9, 11.4 Hz, 2H, H-28, H-10), 6.31 (d, *J*=15.0 Hz, 1H, H-13), 5.75 (d, *J*=10.4 Hz, 1H, H-15), 5.03 (d, *J*=3.2 Hz, 1H, H-1'), 4.81 (s, 1H, H-3), 4.03 (dd, *J*=10.0, 6.1 Hz, 3H, H-31), 3.92 (dd, *J*=13.3, 9.4 Hz, 5H, H-24, H-23), 3.72 (t, *J*=2.7 Hz, 1H, H-5"), 3.61 (d, *J*=6.4 Hz, 4H, H-7"', H-8"'), 3.55～3.42 (m, 4H, H-5, H-2', H-31), 3.39 (s, 4H, H-4"'), 3.25 (d, *J*=19.7 Hz, 2H, H-2"', H-5"'), 3.22～3.13 (m, 2H, H-4"), 3.01～2.90 (m, 4H, H-4', H-14), 2.77～2.66 (m, 3H, H-8, H-2"), 2.58 (q, *J*=7.2 Hz, 11H, H-7', H-8'), 2.50 (dd, *J*=10.7, 6.2 Hz, 2H, H-20), 2.00 (s, 2H, H-19), 1.98～1.93 (m, 2H, H-2"), 1.70～1.55 (m, 5H, H-6", H-7"), 1.26 (dd, *J*=12.0, 6.1 Hz, 6H, H-6"', H-5'), 1.21 (d, *J*=6.6 Hz, 4H, H-21), 1.12～1.01 (m, 18H, H-6'), 0.99 (d, *J*=6.6 Hz, 4H, H-18), 0.91 (t, *J*=7.2 Hz, 4H, H-17); ^{13}C NMR (101M Hz, $CDCl_3$) *δ*: 203.6, 178.1, 173.2, 147.9, 147.5, 146.0, 143.7, 143.3, 137.9, 134.6, 130.9, 130.1, 129.9, 129.6, 128.3, 128.3, 127.9, 127.5, 127.2, 126.2, 122.4, 117.9, 104.0, 101.1, 81.8, 80.1, 79.9, 77.4, 77.3, 75.0, 72.9, 72.7, 71.7, 70.6, 69.5, 69.1, 68.7, 67.1, 66.0, 61.8, 59.6, 58.9, 51.1, 49.1, 46.0, 45.3, 42.0, 41.6, 40.9, 39.2, 34.1, 32.1, 29.7, 29.3, 25.4, 25.1, 24.0, 19.0, 18.2, 17.8, 9.8, 9.5; HRMS (ESI) calcd for $C_{58}H_{83}N_6O_{13}$ [M＋H]$^+$ 1215.4930, found 1215.4933.

20-脱氧-20-{*N*-对氟苄基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三唑-4-基]甲氨基}-泰乐菌素(**4p**): 将 **3a** 换成 **3g** 同化合物 **4a** 制备, 白色固体, 收率 84%. m.p. 136.1～139.5 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.53 (s, 1H, H-36), 8.78 (d, *J*=41.5 Hz, 2H, H-33, H-35), 8.20 (d, *J*=8.5 Hz, 1H, H-42), 7.95 (d, *J*=8.0 Hz, 1H, H-39), 7.84～7.75 (m, 1H, H-41), 7.65 (t, *J*=7.5 Hz, 1H, H-40), 7.41 (d, *J*=7.2 Hz, 2H, H-25, H-29), 7.34 (t, *J*=7.4 Hz, 2H, H-11, H-26), 7.24 (dd, *J*=15.9, 11.4 Hz, 2H, H-28, H-10), 6.31 (d, *J*=15.0 Hz, 1H, H-13), 5.75 (d, *J*=10.4 Hz, 1H, H-15), 5.03 (d, *J*=3.2 Hz, 1H, H-1'), 4.81 (s, 1H, H-3), 4.03 (dd, *J*=10.0, 6.1 Hz, 3H, H-31), 3.92 (dd, *J*=13.3, 9.4 Hz, 5H, H-24, H-23), 3.72 (t, *J*=2.7 Hz, 1H, H-5"), 3.61 (d, *J*=6.4 Hz, 4H, H-7"', H-8"'), 3.55～3.42 (m, 4H, H-5, H-2', H-31), 3.39 (s, 4H, H-4"'), 3.25 (d, *J*=19.7 Hz, 2H, H-2"', H-5"'), 3.22～3.13 (m, 2H, H-4"), 3.01～2.90 (m, 4H, H-4', H-14), 2.77～2.66 (m, 3H, H-8, H-2"), 2.58 (q, *J*=7.2 Hz, 11H, H-7', H-8'), 2.50 (dd, *J*=10.7, 6.2 Hz, 2H, H-20), 2.00 (s, 2H, H-19), 1.98～1.93 (m, 2H, H-2"), 1.70～1.55 (m, 5H, H-6", H-7"), 1.26 (dd, *J*=12.0, 6.1 Hz, 6H, H-6"', H-5'), 1.21 (d, *J*=6.6 Hz, 4H, H-21), 1.12～1.01 (m, 18H, H-6'), 0.99 (d, *J*=6.6 Hz, 4H, H-18), 0.91 (t, *J*=7.2 Hz, 4H, H-17); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 203.6, 178.1, 163.3, 160.9, 147.9, 147.5, 146.0, 143.7, 143.3, 137.9, 134.6, 131.3, 131.2, 130.9, 130.1, 129.9, 129.6, 128.3, 127.9, 127.5, 127.2, 126.2, 122.4, 117.9, 104.0, 101.1, 81.8, 80.1, 79.9, 77.4, 77.3, 75.0, 72.9, 72.7, 71.7, 70.6, 69.5, 69.1, 68.7, 67.1, 66.0, 61.8, 59.6, 58.9, 51.1, 49.1, 46.0, 45.3, 42.0, 41.6, 40.9, 39.2, 34.1, 32.1, 29.7, 29.3, 25.4, 25.1, 24.0, 19.0, 18.2, 17.8, 9.8, 9.5; HRMS (ESI) calcd for $C_{58}H_{82}FN_6O_{13}$ [M＋H]$^+$ 1233.6632, found 1233.6634.

20-脱氧-20-{苄基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三唑-4-基]甲氨基}-脱霉菌糖泰乐菌素(**4q**): 将 **3a** 换成 **3e** 同化合物 **4a** 制备, 白色固体, 收率 81%. m.p. 138.9～139.8 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.54 (s, 1H, H-36), 8.85 (s, 1H, H-33), 8.72 (s, 1H, H-35), 8.20 (d, *J*=8.5 Hz, 1H, H-42), 7.94 (d, *J*=7.9 Hz, 1H, H-39), 7.78 (ddd, *J*=8.4, 7.0, 1.3 Hz, 1H, H-41), 7.64 (dd, *J*=11.1, 4.0 Hz, 1H, H-40), 7.41 (d, *J*=7.2 Hz, 2H, H-25, H-29), 7.34 (t, *J*=7.4 Hz, 3H, H-11, H-26), 7.25 (d, *J*=7.1 Hz, 1H, H-28), 7.21 (s, 1H, H-10), 6.31 (d, *J*=16.2 Hz, 1H, H-13), 5.73 (d, *J*=10.4 Hz, 1H, H-15), 4.79 (s, 1H, H-1'), 4.51 (d, *J*=7.8 Hz, 1H, H-3), 3.93 (dd, *J*=9.2, 4.1 Hz, 4H, H31, H23), 3.72 (t, *J*=2.8 Hz, 1H, H5, H-24), 3.63～3.56 (m, 6H, H-7"', H-8"'), 3.53 (dd, *J*=11.0, 4.7 Hz, 2H, H-2'), 3.50～3.47 (m, 2H, H-4"', H-1"'), 3.42 (s, 2H, H-2"', H-5"'), 3.14 (d, *J*=3.2 Hz, 1H, H-14), 3.02 (s, 1H, H-4'),

3.01～2.92 (m, 4H, H-8, H-3'''), 2.70 (dd, *J*=14.4, 7.2 Hz, 5H, H-5'''), 2.51 (d, *J*=6.9 Hz, 3H, H-20), 2.46 (d, *J*=5.1 Hz, 8H, H-7', H-8'), 2.22 (t, *J*=9.5 Hz, 2H, H-19), 1.55 (dd, *J*=13.6, 9.4 Hz, 3H, H-2''), 1.26 (d, *J*=6.3 Hz, 8H, H-6''', H-5'), 1.23～1.16 (m, 5H, H-21), 1.12 (t, *J*=7.3 Hz, 3H, H-6'), 1.01 (t, *J*=5.8 Hz, 4H, H-18), 0.91 (dd, *J*=14.3, 7.2 Hz, 3H, H-17); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 203.6, 178.1, 173.1, 147.9, 147.5, 146.0, 143.9, 143.4, 137.8, 134.6, 130.9, 130.1, 130.0, 129.6, 128.3, 127.9, 127.5, 127.2, 126.3, 122.4, 117.9, 104.3, 101.1, 81.9, 79.8, 75.0, 70.8, 70.6, 70.1, 69.1, 67.2, 61.8, 59.8, 59.6, 59.1, 51.1, 49.3, 45.9, 45.4, 41.7, 39.2, 38.2, 34.1, 32.1, 31.2, 25.4, 25.1, 22.7, 17.8, 17.7, 9.7, 9.4; HRMS (ESI) calcd for $C_{65}H_{95}N_6O_{16}$ $[M+H]^+$ 1071.5940, found 1071.5939.

20-脱氧-20-{*N*-对氟苄基-*N*-[1-(3-喹啉基)-1*H*-1,2,3-三唑-4-基]甲氨基}-脱霉菌糖泰乐菌素(**4r**): 将 **3a** 换成 **3g** 同化合物 **4a** 制备, 白色固体, 收率 82%. m.p. 137.1～139.5 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.50 (s, 1H, H36), 8.77 (s, 1H, H-33), 8.70 (s, 1H, H-35), 8.19 (d, *J*=8.5 Hz, 1H, H-42), 7.94 (d, *J*=8.1 Hz, 1H, H-39), 7.79 (t, *J*=7.7 Hz, 1H, H-41), 7.65 (t, *J*=7.5 Hz, 1H, H-40), 7.39 (dd, *J*=7.8, 5.8 Hz, 2H, H-25, H-29), 7.21 (d, *J*=15.4 Hz, 1H, H-11), 7.06 (t, *J*=8.5 Hz, 2H, H-26, H-28), 6.31 (d, *J*=15.2 Hz, 1H, H-10), 5.80 (d, *J*=10.4 Hz, 1H, H-13), 4.89 (t, *J*=8.9 Hz, 1H, H-15), 4.53 (d, *J*=7.8 Hz, 1H, H-1'), 4.02～3.87 (m, 5H, H-3, H-24), 3.73 (s, 2H, H-23), 3.61 (s, 4H, H-31), 3.58～3.46 (m, 4H, H-5, H-2', H-4''', H-1'''), 3.43 (d, *J*=12.3 Hz, 7H, H-7''', H-8'''), 3.28～3.13 (m, 3H, H-2''', H-5''', H-14), 3.08～2.98 (m, 3H, H-4', H-8, H-3'''), 2.99～2.81 (m, 4H, H-5'''), 2.52 (dd, *J*=16.8, 10.3 Hz, 2H, H-20), 2.45 (s, 7H, H-7', H-8'), 2.22 (t, *J*=9.6 Hz, 2H, H-19), 1.74～1.62 (m, 4H, H-2''), 1.13 (d, *J*=7.3 Hz, 11H, H-21), 1.10 (s, 3H, H-6'), 1.00 (d, *J*=6.6 Hz, 3H, H-18), 0.92 (t, *J*=7.2 Hz, 4H, H-17); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 203.6, 173.4, 163.3, 160.9, 147.9, 147.6, 146.1, 143.5, 143.1, 134.5, 133.8, 131.4, 130.8, 130.2, 129.6, 128.2, 128.0, 127.5, 126.1, 122.2, 118.0, 115.2, 115.0, 104.3, 101.1, 81.8, 79.9, 79.7, 75.1, 73.3, 72.7, 70.9, 70.5, 70.1, 68.9, 67.2, 59.6, 57.8, 51.0, 49.1, 46.0, 45.2, 41.7, 39.2, 34.0, 32.1, 25.4, 25.3, 25.1, 25.1, 17.8, 17.7, 9.8, 9.5; HRMS (ESI) calcd for $C_{65}H_{94}FN_6O_{16}$ $[M+H]^+$ 1089.5879, found 1089.5882.

3.3 抗菌活性测定

3.3.1 菌种及菌悬液的制备

实验所用菌株: 大肠杆菌(*Escherichia coli* ATCC-25922, *E. coli*)和金黄色葡萄球菌(*Staphylococcus aureus* ATCC25923, *S. aureus*)的标准菌株, 由郑州大学药学院秦上尚老师惠赠; 巴氏杆菌(*Pasteurella*)和猪肺炎支原体(*Mycoplasma*)由中国农业大学惠赠; 溶血葡萄球菌(*Staphylococcus haemolyticus*, *S. hl*)、大肠杆菌(*Escherichia coli*, *E.coli*)、链球菌(*Streptococcus*, *SC181*)、肠球菌(*Enterococcus*, *Fbc35*), 肠球菌(*Enterococcus* P254)和金黄色葡萄球菌(*Staphylococcus aureus*, *S. aureus*)等耐药菌株由兰州畜牧兽医所及河南农业大学惠赠.

按照 CLSI 实验方法, 用划线法在 Mueller-Hinton Agar (MHA)培养基上接种供试菌, 放入恒温培养箱中, 在 37 ℃下倒置培养 24 h. 挑取形态相同单菌落, 接种至 Mueller-Hinton Broth (MHB, 4 mL)肉汤中, 于恒温摇床中 37 ℃, 200 r/min 震荡下培养 8 h. 与比浊管对照, 调整菌落数为 1×10^8 CFU/mL, 然后用 MHB 肉汤培养基将此菌液按 1∶100 进行稀释.

以泰乐菌素(Tylosin, Tyl)、替米考星(Timicosin, Tim)、泰地罗新(Tildipirosin, Til)作为阳性对照, 化合物均配置成 2.56 mg•mL^{-1}, 然后用 MHB 稀释成浓度为 64 μg•mL^{-1}.

3.3.3 最低抑菌浓度的测试

采用微量肉汤稀释法对进行抗菌活性测试, 具体测试方法参照文献[21], 在 96 孔板中第 1 孔各加入 200 μL 目标化合物溶液, 在第 2～10 孔加入 100 μL 的 MHB 肉汤培养基, 在第 12 孔加入 200 μL 的 MHB 肉汤培养基. 用微量加样器从第 1 孔中吸出 100 μL 目标化合物溶液, 加入到第 2 列中并吹打均匀, 然后从第 2 列中吸出 100 μL, 于第 3 列中吹打均匀, 依次进行倍比稀释, 至第 10 列稀释后, 弃去 100 μL 剩余液体, 向第 1～10 孔加 100 μL 菌液, 向第 11 孔加 200 μL 菌液, 即得 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.125 和 0.0625 μg•mL^{-1} 等 10 个浓度. 37 ℃恒温箱培养 18～24 h 后查看结果, 肉眼观察到阴性对照组的细菌生长良好, 选择溶液透明的孔所对应的浓度即为该样品的最小抗菌浓度(MIC), 记录下 MIC 值, 最小抑菌浓度通过三次试验取平均值得出.

辅助材料(Supporting Information) 化合物 **3a**～**3n**、**4a**～**4r** 的 ^{1}H NMR 谱图、^{13}C NMR 和 HRMS 谱图, 以及 **4e** 的 ^{19}F NMR. 这些材料可以免费从本刊网站(http://sioc-journal.cn/)上下载.

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