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17-[5-(取代肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素新颖衍生物的合成

徐洪蛟 李震宇 王 贞 郝慧琳
鲁春华 朱 敬 沈月毛*
(山东大学药学院 天然产物化学生物学教育部重点实验室 济南 250012)

摘要 格尔德霉素(geldanamycin, GA)是第一个天然产物来源的强效热休克蛋白 90 (heat shock protein 90, Hsp90)抑制剂, 但临床应用受到其肝毒性的限制. 前期构效关系研究表明, 在GA的C-17位通过一个烷二胺基连接基团, 引入保肝基团肉桂酰基可以降低肝毒性. 报道以戊二胺为连接基团, 26 个 17-[5-(取代肉桂酰基)戊二胺]-17-去甲氧基 GA 新颖衍生物的合成和活性评价. 活性测试结果表明, 所有的化合物都有较强的抗乳腺癌细胞株 MDA-MB-231 活性, IC_{50} 值在 0.12～1 μmol•L^{-1} 之间. 其中, **3a** 和 **3u** 是抗肿瘤活性最高的化合物, IC_{50} 值均为 0.12 μmol•L^{-1}, 优于阳性对照 17-*N*-烯丙基氨基-17-去甲氧基 GA (17-AAG) (IC_{50}=0.27 μmol•L^{-1}), 并且 **3u** 的肝细胞毒性较低. 该类衍生物的初步构效关系研究, 为 GA 类 Hsp-90 抑制剂和抗肿瘤先导化合物的结构优化提供了有参考价值的基础.

关键词 热休克蛋白 90; 格尔德霉素; 结构优化; 抗肿瘤

Synthesis and Preliminary Antitumor Activity Evaluation of 17-(5-(Substituted cinnamamido)pentylamino)-17-demethoxygeldanamycin Derivatives as Potent Hsp90 Inhibitors

Xu, Hongjiao Li, Zhenyu Wang, Zhen Hao, Huilin Lu, Chunhua
Zhu, Jing Shen, Yuemao*
(*Key Laboratory of Chemical Biology* (*Ministry of Education*), *School of Pharmaceutical Sciences*, *Shandong University*, *Shandong 250012*)

Abstract Geldanamcyin (GA) is the first potent inhibitor of heat shock protein 90 (Hsp90) from natural products. However, its clinical application was limited by the unwanted hepatotoxicity. Our previous studies on the structure-activity relationships of GA derivatives indicated that the introduction of hepatoprotective cinnamyol group via an alkyldiamino linker decreased the hepatotoxicity evidently. In this study, using pentyldiamine as the linker, twenty-six 17-(5-(substituted cinnamamido)pentylamino)-17-demethoxygeldanamycins were designed and synthesized as the inhibitors of Hsp90. All the compounds showed potent antitumor activities against human breast cancer cell line MDA-MB-231 with IC_{50} ranging from 0.12 to 1 μmol•L^{-1}. Particularly, 17-(5-(cinnamamido)pentylamino)-17-demethoxygeldanamycin (**3a**) and 17-(5-(2,5-methoxycinnamamido)pentylamino)-17-demethoxygeldanamycin (**3u**) were proved to be the most potent compounds (IC_{50} = 0.12 μmol•L^{-1}), more active than the positive control 17-*N*-allylamino-17-demethoxygeldanamycin (17-AAG) (IC_{50}=0.27 μmol•L^{-1}) and showed lower hepatotoxicity. Additionally, the preliminary structure-activity relationships among these newly synthesized congeners are briefly discussed, which should provide valuable basis for the structure optimization of GA-type Hsp90 inhibitors and antitumor lead compounds.

Keywords heat shock protein 90 (Hsp90); geldanamycin (GA); structure optimization; antitumor activity

* E-mail: yshen@sdu.edu.cn
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格尔德霉素(Geldanamycin, GA)是1970年从吸水链霉菌(*Streptomyces hygroscopicus*)发酵液中分离得到的苯醌安莎霉素, 是第一个天然产物来源的热休克蛋白90 (Heat shock protein 90, Hsp90)抑制剂[1,2]. GA通过竞争性结合Hsp90 N末端ATP/ADP结构域, 特异性地抑制Hsp90所必需的ATP酶活性, 改变Hsp90构象, 从而抑制Hsp90的分子伴侣功能. Hsp90被抑制后, 依赖Hsp90的众多蛋白, 包括信号转导系统的许多重要成员被泛素化和降解, 产生抑制肿瘤细胞增殖、诱导细胞凋亡等效应[3-4].

尽管GA有广谱抗肿瘤作用, 但是在有效浓度下显示出的高肝毒性, 严重影响了其新药开发[5]. 为了增加药效、提高成药性、降低毒性, 药物化学家对GA进行了多方面的结构优化[6~11], 发现了比GA毒性更低、活性更强的衍生物, 例如17-*N*-烯丙基氨基-17-去甲氧基GA (17-AAG)和17-[2-(二甲氨基)乙烷]胺-17-去甲氧基GA (17-DMAG) (图1)[12,13]. 虽然二期临床中17-AAG对乳腺癌有显著疗效, 但是其肝毒性使临床试验被迫中止[14]. 因此, 寻找新一代低肝毒性的GA衍生物具有重要意义.

在前期工作中, 我们设计并合成了两个系列GA衍生物, 17-苯甲胺基-17-去甲氧基GA和17-苯乙胺基-17-去甲氧基GA[15,16]. 生物活性评价结果表明, 17-{[6-(三氟甲基)吡啶-3-基]甲胺}-17-去甲氧基GA (**A**)和17-(3-三氟甲基苯乙胺)-17-去甲氧基GA (**B**)(图1)的肝毒性均低于GA, 有望成为癌症治疗药物的先导化合物; 进一步用3种二元胺(4-氨甲基哌啶、1,4-丁二胺、1,6-己二胺)作为GA C-17位的连接基团, 合成了3个系列GA衍生物[17]. 小鼠体内实验结果表明, **C**～**E**诱导天冬氨酸转氨酶(Aspartate aminotransferase, AST)和丙氨酸转氨酶(Alanine aminotransferase, ALT)的作用水平显著低于GA (P＜0.05), 表明1,6-己二胺的长度适合衍生物与Hsp90结合. 然后, 我们在GA的C-17引入一个更长的连接基团3,6-二氧杂-1,8-辛二胺[18], 然而与GA相比, 所有衍生物的体外抗肿瘤活性均显著降低. 为了进一步考查连接基团链长对化合物抗肿瘤活性和肝毒性的影响, 我们在GA的C-17位引入1,5-戊二胺, 合成了26个17-[5-(取代肉桂酰胺基)戊二胺]-17-去甲氧基GA, 并筛选了其体外抗MDA-MB-231细胞的毒性(Scheme 1).

1 结果与讨论

1.1 化合物的合成

以GA为起始原料, 根据文献实验条件[15-17], 与1,5-戊二胺反应得到中间体**2**. 接着将中间体**2**分别与取代的肉桂酸反应得到目标化合物**3a**～**3z** (Scheme 1). 目标化合物的结构由质谱、^{1}H NMR和^{13}C NMR确证.

1.2 细胞毒性构效关系

采用MTT法检测化合物**3a**～**3z**对人乳腺癌MDA-MB-231细胞株的生长抑制作用, 以17-AAG和GA为阳性对照. 结果表明, 除了**3z**以外, 其余GA衍生物均显示出较强的抗肿瘤活性. 其中有14个GA衍生物(表1)显示出比17-AAG更强的体外抗肿瘤活性.

在单取代衍生物中, 吸电子基团取代的衍生物与供

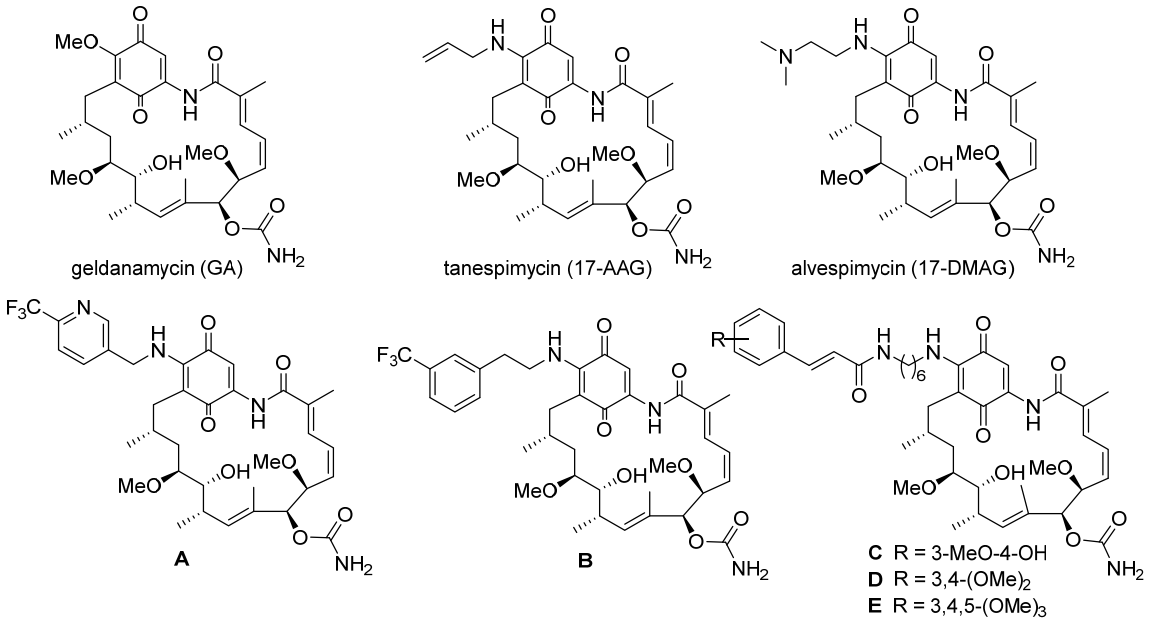
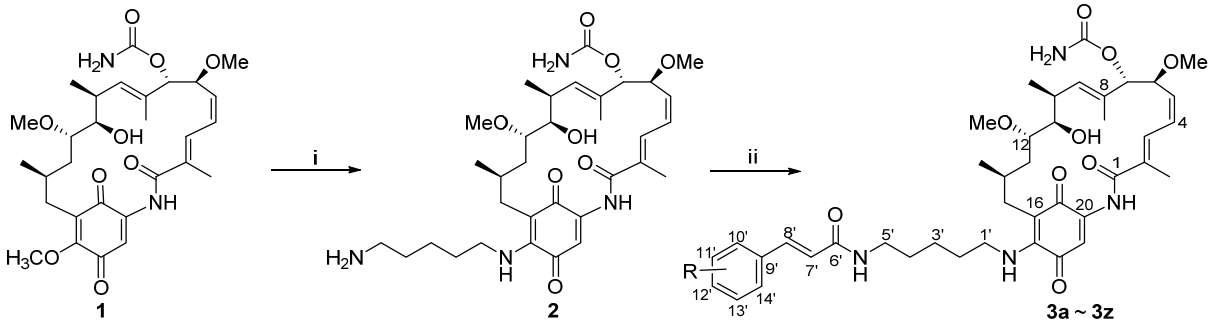


图1 代表性GA类Hsp90抑制剂的结构

Figure 1 Structures of representative GA-type of Hsp90 inhibitors



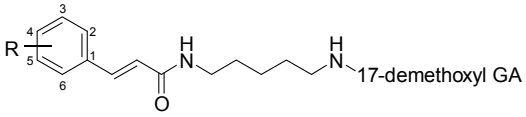
Reagents and conditions: (i) 1,5-pentyldiamine, dichloromethane, r.t., 3.5 h; (ii) substituted cinnamic acid, NHS, EDC·HCl, DMF, r.t., 24 h

图式 1 化合物 **3a**～**3z** 的合成路线

Scheme 1 The synthesis of compounds **3a**～**3z**

表 1 化合物 **3a**～**3z** 对人乳腺癌 MDA-MB-231 细胞株的生长抑制作用 [a]

Table 1 The cytotoxicities of compounds **3a**～**3z** against the growth of MDA-MB-231 cells



Compd.	R	IC_{50}/(μmol•L^{-1})	Compd.	R	IC_{50}/(μmol•L^{-1})
3a	H	0.12	**3o**	4-$N(Me)_2$	0.28
3b	2-NO_2	0.35	**3p**	4-CF_3	0.24
3c	3-NO_2	0.18	**3q**	4-OCF_3	0.46
3d	4-NO_2	0.17	**3r**	3-OH-4-OMe	0.14
3e	2-Cl	0.38	**3s**	3-OMe-4-OH	0.36
3f	3-Cl	0.15	**3t**	2,3-$(OMe)_2$	0.28
3g	4-Cl	0.21	**3u**	2,5-$(OMe)_2$	0.12
3h	2-Me	0.48	**3v**	3,4-$(OMe)_2$	0.13
3i	3-Me	0.21	**3w**	3,5-$(OMe)_2$	0.21
3j	4-Me	0.23	**3x**	2,3,4-$(OMe)_3$	0.41
3k	2-OH	0.28	**3y**	3,4,5-$(OMe)_3$	0.34
3l	3-OH	0.26	**3z**	3,5-$(OMe)_2$-4-OH	＞1
3m	2-OMe	0.28	17-AAG		0.27
3n	4-OMe	0.21	GA		0.05

电子基团取代的衍生物活性差异不大, 但取代基团的位置对活性影响显著. 对于以 1,5-戊二胺为连接基团的衍生物, 间位取代的化合物活性相对较好, 邻位取代的衍生物活性相对较差. 例如, 吸电子基团硝基取代的衍生物 **3b**～**3d** 显示出不同的抗肿瘤活性, 邻硝基取代的衍生物 **3b** 的活性低于衍生物 **3c** 和 **3d**. 氯代衍生物 **3e**～**3g** 和甲基取代的化合物 **3h**～**3j** 也符合这个规律. 同样, 给电子基团甲氧基取代对位取代衍生物活性强于邻位取代, 间位羟基取代衍生物活性强于邻位. 二取代化合物的衍生物活性较强, 二甲氧基取代的衍生物整体活性较好, 取代位置对化合物活性有较大影响, 其中 **3v** 的细胞毒性(IC_{50}＝0.13 μmol•L^{-1})仅次于 **3a** 和 **3u** (IC_{50}＝0.12 μmol•L^{-1}). 有趣的是, 衍生物 **3r** 的抗肿瘤活性优于 **3s**, 暗示甲氧基和羟基的位置对抗肿瘤活性有较大的影响. 三取代衍生物的活性明显降低. 二甲氧基取代的衍生物 **3t**～**3w** 比三甲氧基取代的衍生物 **3x**～**3y** 的活性强, **3z** 活性降低尤为明显. 此外, 17-[5-(肉桂酰胺基)戊二胺]-17-去甲氧基 GA (**3a**)和 17-(5-[(2,5-甲氧基苯基)丙烯酰胺]戊二胺)-17-去甲氧基 GA (**3u**)是该系列中抗肿瘤活性最好的化合物(IC_{50}＝0.12 μmol•L^{-1}), 均优于阳性药 17-AAG 的活性(IC_{50}＝0.27 μmol•L^{-1}). 总体来看, 以 1,5-戊二胺为连接基团的衍生物活性相对其他已报道的连接基团衍生物较强.

1.3 肝细胞 HL7702 毒性测定

以 17-AAG 和 GA 为阳性对照, 采用 SRB 法检测细胞毒性最高的化合物 **3a** 和 **3u** 对肝细胞 HL7702 的毒性. 实验数据表明, 与阳性对照相比, 具有良好抗癌活性的衍生物 **3a** 在细胞肝毒性实验中显示出比阳性对照更强的肝毒性, 具有与 **3a** 相当抗肿瘤活性的衍生物 **3u**

(IC_{50}＝368.15 nmol•L^{-1})对肝细胞毒性低，可以进一步发展为治疗乳腺癌的药物(表 2).

表 2 化合物 **3a** 和 **3u** 对人肝细胞 HL7702 细胞株的毒性

Table 2 *In vitro* hepatotoxicity of compounds **3a** and **3u** against HL7702 cells

Compd.	IC_{50}/(nmol•L^{-1})
3a	230.17
3u	368.15
GA	350.28
17-AAG	270.09

1.4 Hsp90 靶点亲和力测定

为了验证该类衍生物的作用靶点，我们选取抗肿瘤细胞活性最高的化合物 **3a** 进行其体外抑制 Hsp90 实验. 采用荧光偏振法测得 **3a** 与 Hsp90 亲和作用 K_d 值为 0.36 μmol•L^{-1}，比 17-AAG (IC_{50}＝0.72 μmol•L^{-1})的活性更好，表明 17-[5-(取代肉桂酰胺)戊二胺]-17-去甲氧基 GA 是 Hsp90 抑制剂.

1.5 3u 分子对接至 Hsp90

为了从分子水平阐明化合物 **3u** 的作用机制，将其对接至 Hsp90 的活性口袋中. 本课题采用 Autodock vina 1.1.2 进行分子对接研究. 由图 2 可以看出，化合物 **3u** 显示出与 GA 类似的结合模式. **3u** 采用紧凑的构象结合至 Hsp90 的 ATP/ADP 结合口袋. **3u** 安莎环顶端的 6-位甲氧基、7-位氨基甲酸酯基、8-位和 10-位的甲基与 Hsp90 口袋底部结合，形成强烈的范德华力相互作用；而苯醌环位于 Hsp90 结合口袋的开口区，只有少量的作用力. 重要的是，氨基甲酸酯基的氨基和羰基分别与氨基酸残基 Asp83 和 Thr174 形成氢键. 在活性口袋的入口处，苯醌环上 18-位的羰基氧和 17-位的氮原子与 Asp44 形成双重氢键作用. 安莎环 1-位羰基氧可以与氨基酸残基 Phe128 形成氢键. 最值得一提的是，17-位侧链末端的 2,5-二甲氧基肉桂酰基的苯环可以与氨基酸残基 Gln123 的氨基形成阳离子-π 相互作用.

总之，以上的分子模拟为戊二胺连接的 17-芳酰基-17-去甲氧基 GA 衍生物与 Hsp90 在分子水平的相互作用给予了合理的解释，为进一步设计新一代以 GA 为骨架的 Hsp90 抑制剂提供了有用的信息.

2 结论

本研究中，我们以 GA 为母核，1,5-戊二胺为连接基团，引入取代的肉桂酰基，共合成了 26 个 GA 衍生物，并且评价其对人乳腺癌细胞株 MDA-MB-231 的抑制活性. 除了化合物 **3z** 以外，其它衍生物均显示出较强的细胞毒性，IC_{50} 值在 0.12～0.48 μmol•L^{-1} 之间. 其中，17-[5-(肉桂酰胺)戊二胺]-17-去甲氧基 GA (**3a**)和 17-[5-(2,5-甲氧基肉桂酰胺)戊二胺]-17-去甲氧基 GA (**3u**)抗肿瘤活性最好，均优于阳性药 17-AAG，为以 GA 为母核的 Hsp90 抑制剂结构优化提供了新的方向.

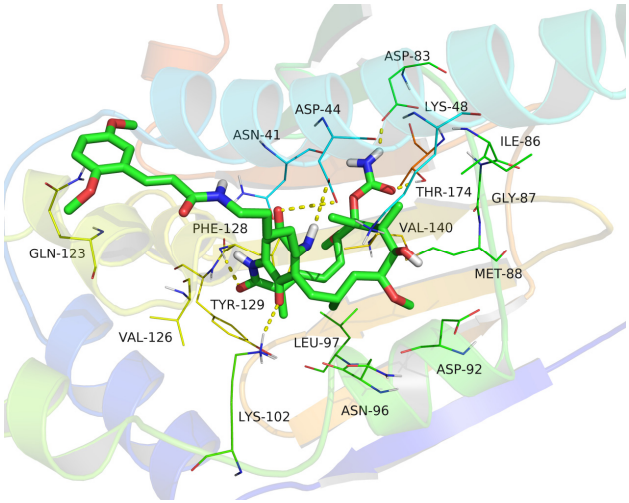


图 2 化合物 **3u** 对接至 Hsp90 的活性口袋

Figure 2 Docking of compound **3u** binding to the ATP site of yeast Hsp90

3 实验部分

3.1 仪器与试剂

熔点用 X4 型显微熔点仪测定 (温度未校正)；核磁共振仪为 Brucker Avance-600 和 Brucker Avance-300 型，TMS 为内参；质谱仪为 LTQ-Orbitrap XL 型 (Thermo Fisher)，离子源采用电喷雾离子化(ESI)；柱色谱用 200～300 目硅胶和薄层层析硅胶 GF_{254} 均为青岛海洋化工厂生产. 所有试剂均为国产或进口分析纯，除特别说明外，一般均直接使用.

3.2 实验方法

3.2.1 化学合成

化合物 **3a**～**3z** 的制备合成步骤以 **3a** 为例. GA (56 mg, 0.10 mmol, 1.0 equiv.)溶于二氯甲烷 (10 mL)中，加入 1,5-戊二胺(73 μL, 1.00 mmol, 10.0 equiv.)，反应液在室温下搅拌 3.5 h 后，分别用水(25 mL×3)和饱和食盐水(25 mL×3)洗涤，有机相用无水硫酸钠干燥，过滤，浓缩后所得中间体 **2** 直接用于下一步. 将中间体 **2** 溶于 *N*,*N*-二甲基甲酰胺(10 mL)中，加入 1-乙基-(3-二甲基氨基丙基)碳二亚胺盐酸盐(EDC•HCl, 1.2 equiv.)、*N*-羟基琥珀酰亚胺(NHS, 1.2 equiv.). 反应液室温下搅拌过夜，反应结束后用乙酸乙酯萃取(20 mL×3)，合并有机相，用饱和食盐水洗涤(30 mL×3)，无水硫酸钠干燥，抽滤，浓缩后粗品用硅胶柱层析分离[*V*(乙酸乙酯)：*V*(石油醚)=2：1 洗脱]，得紫色固体化合物 **3a**. 采用相同的方法制备得到化合物 **3b**～**3z**.

17-[5-(肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3a**): 收率 65.9%. m.p. 125～127 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.16 (s, 1H, CONH-1), 8.01 (s, 1H, CONH-6'), 7.64 (d, J=15.4 Hz, 1H, H-7'), 7.50 (d, J=6.3 Hz, 2H, H-10' and H-14'), 7.41～7.31 (m, 3H, H-11', H-12' and H-13'), 7.26 (s, 1H, H-19), 6.94 (d, J=11.4 Hz, 1H, H-3), 6.59 (t, J=11.3 Hz, 1H, H-4), 6.41 (d, J=15.6 Hz, 1H, H-8'), 6.28 (s, 1H, NH-17), 5.90 (d, J=9.6 Hz, 1H, H-9), 5.87 (t, J=10.3 Hz, 1H, H-5), 5.17 (s, 1H, H-7), 4.92 (br s, 2H, $CONH_2$-7), 4.30 (d, J=9.8 Hz, 1H, H-6), 3.61～3.52 (m, 2H, H-11, H-12), 3.48～3.38 (m, 4H, H-1' and H-5'), 3.34 (s, 3H, MeO-12), 3.26 (s, 3H, MeO-6), 2.77～2.69 (m, 1H, H-10), 2.66 (d, J=13.9 Hz, 1H, H-15), 2.42 (t, J=12.2 Hz, 1H, H-15), 2.01 (s, 3H, Me-2), 1.83～1.76 (m, 5H, Me-8, H-13), 1.74～1.66 (m, 3H), 1.66～1.59 (m, 2H), 1.51～1.44 (m, 2H), 0.99 (d, J=6.2 Hz, 3H, Me-10), 0.95 (d, J=5.9 Hz, 3H, Me-14); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 183.9 (C-18), 180.6 (C-21), 168.4 (C-1), 166.1, 156.2 ($CONH_2$-7), 144.8 (C-17), 141.4 (C-20), 141.2, 135.8 (C-5), 135.0 (C-2), 134.8, 133.8 (C-9), 132.7 (C-8), 129.7, 128.8, 127.8, 126.9 (C-4), 126.6 (C-3), 120.5, 108.6 (C-19), 108.4 (C-16), 81.7 (C-7), 81.5 (C-6), 81.2 (C-12), 72.6 (C-11), 57.1 (MeO-6), 56.7 (MeO-12), 45.7, 39.3, 35.0 (C-13), 34.4 (C-15), 32.3 (C-10), 29.5, 28.5 (C-14), 24.1, 22.9 (Me-14), 12.8 (Me-8), 12.7 (Me-2), 12.4 (Me-10); HRESIMS calcd for $C_{42}H_{56}N_4NaO_9$ $[M+Na]^+$: 783.3940, found 783.3915.

17-[5-(2-硝基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3b**): 紫色固体, 收率 74.9%. m.p. 116～118 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.17 (s, 1H), 8.02 (d, J=7.9 Hz, 1H), 7.97 (d, J=15.5 Hz, 1H), 7.67～7.57 (m, 2H), 7.52 (t, J=7.4 Hz, 1H), 7.26 (s, 1H), 6.96 (d, J=10.9 Hz, 1H), 6.60 (t, J=11.4 Hz, 1H), 6.35 (d, J=15.6 Hz, 1H), 5.94～5.81 (m, 3H), 5.18 (s, 1H), 4.31 (d, J=9.8 Hz, 1H), 3.64～3.52 (m, 2H), 3.51～3.38 (m, 4H), 3.36 (s, 3H), 3.27 (s, 3H), 2.78～2.70 (m, 1H), 2.68 (d, J=13.8 Hz, 1H), 2.47～2.35 (m, 1H), 2.02 (s, 3H), 1.83～1.77 (m, 5H), 1.76～1.69 (m, 3H), 1.68～1.61 (m, 2H), 1.54～1.43 (m, 2H), 1.00 (d, J=6.9 Hz, 3H), 0.97 (d, J=6.6 Hz, 3H); HRESIMS calcd for $C_{42}H_{55}N_5NaO_{11}$ $[M+Na]^+$: 828.3790, found 828.3765.

17-[5-(3-硝基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3c**): 紫色固体, 收率 88.0%. m.p. 123～124 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.16 (s, 1H), 8.38 (s, 1H), 8.19 (d, J=8.1 Hz, 1H), 7.78 (d, J=7.6 Hz, 1H), 7.69 (d, J=15.5 Hz, 1H), 7.57 (t, J=7.9 Hz, 1H), 7.25 (s, 1H), 6.94 (d, J=11.5 Hz, 1H), 6.59 (d, J=11.2 Hz, 1H), 6.28 (s, 1H), 5.97 (s, 1H), 5.90～5.82 (m, 2H), 5.19 (s, 1H), 4.98 (s, 2H), 4.31 (d, J=9.9 Hz, 1H), 3.59～3.52 (m, 2H), 3.51～3.40 (m, 4H), 3.35 (s, 3H), 3.26 (s, 3H), 2.77～2.70 (m, 1H), 2.67 (d, J=13.8 Hz, 1H), 2.42 (d, J=11.4 Hz, 1H), 2.02 (s, 3H), 1.83～1.76 (m, 5H), 1.76～1.68 (m, 3H), 1.69～1.62 (m, 2H), 1.55～1.45 (m, 2H), 1.00 (d, J=6.9 Hz, 3H), 0.96 (d, J=6.5 Hz, 3H); HRESIMS calcd for $C_{42}H_{55}N_5NaO_{11}$ $[M+Na]^+$: 828.3790, found 828.3761.

17-[5-(4-硝基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3d**): 紫色固体, 收率 75.6%. m.p. 136～138 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.16 (s, 1H), 8.23 (d, J=8.5 Hz, 2H), 7.72～7.68 (m, 1H), 7.68～7.61 (m, 2H), 7.26 (s, 1H), 6.94 (d, J=11.5 Hz, 1H), 6.60 (t, J=11.4 Hz, 1H), 6.53 (d, J=15.6 Hz, 1H), 6.26 (s, 1H), 5.93～5.84 (m, 2H), 5.18 (s, 1H), 4.89 (s, 2H), 4.31 (t, J=7.6 Hz, 1H), 3.63～3.54 (m, 2H), 3.51～3.39 (m, 4H), 3.37 (s, 3H), 3.35 (s, 3H), 2.78～2.70 (m, 1H), 2.67 (t, J=12.6 Hz, 1H), 2.42 (d, J=11.2 Hz, 1H), 2.01 (d, J=15.9 Hz, 3H), 1.83～1.76 (m, 5H), 175～1.68 (m, 3H), 1.68～1.61 (m, 2H), 1.55～1.42 (m, 2H), 1.00 (d, J=6.9 Hz, 3H), 0.96 (d, J=6.42 Hz, 3H); HRESIMS calcd for $C_{42}H_{55}N_5NaO_{11}$ $[M+Na]^+$: 828.3790, found 828.3762.

17-[5-(2-氯肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3e**): 紫色固体, 收率 69.6%. m.p. 129～131 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.17 (s, 1H), 7.98 (d, J=15.6 Hz, 1H), 7.56 (d, J=5.9 Hz, 1H), 7.40 (dd, J=7.6, 1.6 Hz, 1H), 7.30～7.26 (m, 1H), 7.26～7.22 (m, 2H), 6.95 (d, J=11.3 Hz, 1H), 6.59 (t, J=11.4 Hz, 1H), 6.42 (d, J=15.6 Hz, 1H), 6.26 (s, 1H), 5.95～5.81 (m, 2H), 5.18 (s, 1H), 4.84 (br s, 1H), 4.31 (d, J=9.8 Hz, 1H), 3.63～3.52 (m, 2H), 3.50～3.39 (m, 4H), 3.35 (s, 3H), 3.26 (s, 3H), 2.78～2.70 (m, 1H), 2.67 (d, J=13.5 Hz, 1H), 2.45～2.37 (m, 1H), 2.02 (s, 3H), 1.82～1.76 (m, 5H), 1.76～1.68 (m, 3H), 1.68～1.59 (m, 2H), 1.54～1.43 (m, 2H), 1.00 (d, J=6.9 Hz, 3H), 0.96 (d, J=6.4 Hz, 3H); HRESIMS calcd for $C_{42}H_{55}ClN_4NaO_9$ $[M+Na]^+$: 817.3550, found 817.3527.

17-[5-(3-氯肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3f**): 紫色固体, 收率 74.1%. m.p. 120～122 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.14 (s, 1H), 8.00 (s, 1H), 7.54 (d, J=15.5 Hz, 1H), 7.44 (s, 1H), 7.40～7.26 (m, 3H), 7.22 (s, 1H), 6.93 (d, J=10.8 Hz, 1H), 6.57 (t, J=11.2 Hz, 1H), 6.43 (d, J=15.5 Hz, 1H), 6.26 (br s, 1H), 5.96～5.79 (m, 2H), 5.15 (s, 1H), 5.01 (br s, 2H), 4.29 (d,

J=9.5 Hz, 1H), 3.65～3.50 (m, 2H), 3.49～3.36 (m, 4H), 3.33 (s, 3H), 3.24 (s, 3H), 2.78～2.67 (m, 1H), 2.67～2.58 (m, 1H), 2.39 (t, *J*=12.2 Hz, 1H), 2.00 (s, 3H), 1.84～1.73 (m, 5H), 1.73～1.65 (m, 3H), 1.65～1.57 (m, 2H), 1.46 (s, 2H), 0.97 (d, *J*=6.4 Hz, 3H), 0.94 (d, *J*=5.5 Hz, 3H); HRESIMS calcd for $C_{42}H_{55}ClN_4NaO_9$ $[M+Na]^+$: 817.3550, found 817.3542.

17-[5-(4-氯肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3g**): 紫色固体, 收率 40.4%. m.p. 127～129 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 9.16 (s, 1H), 8.01 (s, 1H), 7.60 (d, *J*=15.5 Hz, 1H), 7.43 (d, *J*=8.3 Hz, 2H), 7.34 (d, *J*=8.3 Hz, 2H), 7.27 (s, 1H), 6.95 (d, *J*=11.4 Hz, 1H), 6.60 (t, *J*=11.4 Hz, 1H), 6.37 (d, *J*=15.6 Hz, 1H), 6.27 (s, 1H), 5.91 (d, *J*=9.4 Hz, 1H), 5.88 (t, *J*=10.5 Hz, 1H), 5.73 (t, *J*=5.1 Hz,1H), 5.19 (s, 1H), 4.31 (d, *J*=9.8 Hz, 1H), 3.61～3.52 (m, 2H), 3.50～3.38 (m, 4H), 3.35 (s, 3H), 3.27 (s, 3H), 2.77～2.70 (m, 1H), 2.67 (d, *J*=13.8 Hz, 1H), 2.42 (t, *J*=12.4 Hz, 1H), 2.02 (s, 3H), 1.76～1.84 (m, 5H), 1.76～1.67 (m, 3H), 1.67～1.59 (m, 2H), 1.54～1.43 (m, 2H), 1.00 (d, *J*=6.9 Hz, 3H), 0.96 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 183.9, 180.6, 168.4, 165.7, 156.1, 144.8, 141.4, 139.9, 135.9, 135.5, 135.0, 133.8, 133.3, 132.7, 129.1, 129.0, 126.9, 126.6, 120.9, 108.6, 108.5, 81.7, 81.5, 81.2, 72.6, 57.2, 56.7, 45.7, 39.3, 35.0, 34.4, 32.3, 29.4, 28.5, 24.0, 23.0, 12.8, 12.7, 12.4; HRESIMS calcd for $C_{42}H_{55}ClN_4NaO_9$ $[M+Na]^+$: 817.3550, found 817.3529.

17-[5-(2-甲基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3h**): 紫色固体, 收率 67.3%. m.p. 118～120 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 9.17 (s, 1H), 7.93 (d, *J*=15.4 Hz, 1H), 7.50 (d, *J*=7.6 Hz, 1H), 7.26 (s, 1H), 7.25～7.22 (m, 1H), 7.22～7.15 (m, 2H), 6.95 (d, *J*=11.4 Hz, 1H,), 6.60 (t, *J*=11.4 Hz, 1H), 6.35～6.23 (m, 2H), 5.90 (d, *J*=9.4 Hz, 1H), 5.88～5.79 (m, 2H), 5.18 (s, 1H), 4.90 (s, 2H), 4.31 (d, *J*=9.9 Hz, 1H), 3.61～3.52 (m, 2H), 3.50～3.39 (m, 4H), 3.35 (s, 3H), 3.26 (s, 3H), 2.79～2.69 (m, 1H), 2.70 (d, *J*=13.9 Hz, 1H), 2.43 (s, 3H), 2.41 (d, *J*=13.1 Hz, 1H), 2.04 (d, *J*=13.4 Hz, 3H), 1.82～1.76 (m, 5H), 1.76～1.67 (m, 3H), 1.67～1.59 (m, 2H), 1.53～1.44 (m, 2H), 1.00 (d, *J*=6.8 Hz, 3H), 0.96 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 183.9, 180.6, 168.4, 166.1, 156.1, 144.8, 141.4, 139.1, 137.6, 135.8, 135.0, 133.8, 132.7, 130.8, 129.5, 126.9, 126.6, 126.2, 126.0, 121.5, 108.67, 108.4, 81.7, 81.5, 81.2, 72.6, 57.1, 56.7, 45.8, 39.3, 35.0, 34.4, 32.3, 29.5, 28.5, 24.1, 22.9, 19.9, 12.8, 12.7, 12.4; HRESIMS calcd for $C_{43}H_{58}N_4NaO_9$ $[M+Na]^+$: 797.4096, found 797.4068.

17-[5-(3-甲基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3i**): 紫色固体, 收率 62.4%. m.p. 114～116 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 9.16 (s, 1H), 7.61 (d, *J*=15.5 Hz, 1H), 7.30 (s, 1H), 7.29 (s, 1H), 7.26 (s, 1H), 7.25～7.22 (m, 1H), 7.16 (d, *J*=7.4 Hz, 1H), 6.94 (d, *J*=11.5 Hz, 1H), 6.60 (t, *J*=11.4 Hz, 1H), 6.39 (d, *J*=15.6 Hz, 1H), 6.27 (s, 1H), 5.91 (d, *J*=9.4 Hz, 1H), 5.87 (t, *J*=10.5 Hz, 1H), 5.29 (s, 1H), 5.16 (s, 1H), 4.87 (br s, 2H), 4.31 (d, *J*=9.9 Hz, 1H), 3.63～3.51 (m, 2H), 3.51～3.38 (m, 4H), 3.35 (s, 3H), 3.28 (s, 3H), 2.76～2.69 (m, 1H), 2.67 (d, *J*=13.8 Hz, 1H), 2.44～2.37 (m, 1H), 2.35 (s, 3H), 2.02 (s, 3H), 1.84～1.76 (m, 5H), 1.74～1.67 (m, 3H), 1.67～1.59 (m, 2H), 1.55～1.43 (m, 2H), 1.00 (d, *J*=6.9 Hz, 3H), 0.96 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 183.9, 180.6, 168.4, 166.1, 156.1, 144.8, 141.4, 141.3, 138.5, 135.8, 135.0, 134.7, 133.8, 132.7, 130.6, 128.7, 128.5, 126.9, 126.6, 124.9, 120.2, 108.7, 108.4, 81.7, 81.5, 81.2, 72.6, 57.2, 56.7, 45.8, 39.3, 35.0, 34.4, 32.3, 29.5, 28.5, 24.1, 22.9, 21.4, 12.8, 12.7, 12.4; HRESIMS calcd for $C_{43}H_{58}N_4NaO_9$ $[M+Na]^+$: 797.4096, found 797.4065.

17-[5-(4-甲基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3j**): 紫色固体, 收率 63.1%. m.p. 130～132 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 9.16 (s, 1H), 7.60 (d, *J*=15.5 Hz, 1H), 7.39 (d, *J*=7.8 Hz, 2H), 7.26 (s, 1H), 7.17 (d, *J*=7.7 Hz, 2H), 6.94 (d, *J*=11.5 Hz, 1H), 6.59 (t, *J*=11.4 Hz, 1H), 6.36 (d, *J*=15.6 Hz, 1H), 6.27 (s, 1H), 5.90 (d, *J*=9.3 Hz, 1H), 5.85 (t, *J*=10.6 Hz, 2H), 5.18 (s, 1H), 4.90 (s, 2H), 4.31 (d, *J*=9.9 Hz, 1H), 3.60～3.51 (m, 2H), 3.49～3.38 (m, 4H), 3.34 (s, 3H), 3.26 (s, 3H), 2.77～2.69 (m, 1H), 2.66 (d, *J*=13.9 Hz, 1H), 2.42 (t, *J*=11.6 Hz, 1H), 2.35 (s, 3H), 2.02 (s, 3H), 1.84～1.75 (m, 5H), 1.75～1.66 (m, 3H), 1.66～1.58 (m, 2H), 1.53～1.42 (m, 2H), 1.00 (d, *J*=6.9 Hz, 3H), 0.96 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 183.9, 180.6, 168.4, 166.3, 156.1, 144.8, 141.4, 141.1, 140.0, 135.8, 135.0, 133.79, 132.74, 132.0, 129.6, 127.8, 126.9, 126.6, 119.4, 108.6, 108.4, 81.7, 81.4, 81.2, 72.6, 57.2, 56.7, 45.8, 41.0, 39.3, 35.0, 34.4, 32.3, 29.5, 28.5, 24.1, 22.9, 21.5, 12.8, 12.7, 12.4; HRESIMS calcd for $C_{43}H_{58}N_4NaO_9$ $[M+Na]^+$: 797.4096, found 797.4067.

17-[5-(2-羟基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3k**): 紫色固体, 收率 44.0%. m.p. 139～

141 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.11 (s, 1H), 7.93 (d, J=15.8 Hz, 1H), 7.37 (d, J=7.5 Hz, 1H), 7.26 (s, 1H), 7.18 (s, 1H), 7.15 (t, J=7.6 Hz, 1H), 6.90 (d, J=11.9 Hz, 1H), 6.82 (t, J=7.4 Hz, 1H), 6.57 (t, J=11.3 Hz, 1H), 6.31 (s, 1H), 5.92 (d, J=9.1 Hz, 1H), 5.88 (t, J=10.3 Hz, 1H), 5.17 (s, 1H), 4.97 (s, 2H), 4.31 (d, J=9.7 Hz, 1H), 3.58～3.37 (m, 6H), 3.34 (s, 3H), 3.27 (s, 3H), 2.78～2.69 (m, 1H), 2.66 (d, J=13.6 Hz, 1H), 2.40～2.32 (m, 1H), 1.98 (s, 3H), 1.82～1.77 (m, 3H), 1.77～1.71 (m, 3H), 1.70～1.64 (m, 2H), 1.64～1.53 (m, 2H), 1.46～1.39 (m, 2H), 1.00 (d, J=6.9 Hz, 3H), 0.94 (d, J=5.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 184.1, 180.4, 168.2, 167.7, 156.4, 156.0, 144.9, 141.5, 137.3, 136.1, 134.9, 133.9, 132.6, 130.8, 128.8, 126.9, 126.6, 121.9, 120.4, 120.1, 116.5, 108.6, 108.4, 82.1, 81.3, 72.6, 57.3, 56.7, 45.5, 39.3, 34.7, 34.4, 32.3, 29.2, 29.1, 28.2, 23.7, 23.0, 12.8, 12.6, 12.5; HRESIMS calcd for $C_{42}H_{56}N_4NaO_{10}$ $[M+Na]^+$: 799.3889, found 799.3861.

17-[5-(3-羟基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3l**): 紫色固体, 收率 24.9%. m.p. 140～142 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.11 (s, 1H), 7.56 (d, J=14.6 Hz, 1H), 7.22～7.12 (m, 2H), 7.05 (s, 1H), 6.99 (s, 1H), 6.91 (d, J=11.5 Hz, 1H), 6.83 (d, J=7.9 Hz, 1H), 6.58 (t, J=11.1 Hz, 1H), 6.41～6.19 (m, 1H), 5.91～5.82 (m, 2H), 5.19 (s, 1H), 4.92 (br s, 1H), 4.32 (d, J=9.3 Hz, 1H), 3.61～3.54 (m, 1H), 3.53～3.40 (m, 4H), 3.35 (s, 3H), 3.27 (s, 3H), 2.79～2.69 (m, 1H), 2.63 (d, J=12.4 Hz, 1H), 2.35 (s, 1H), 2.00 (s, 3H), 1.83～1.51 (m, 10H), 1.44 (s, 2H), 1.00 (d, J=6.8 Hz, 3H), 0.97～0.91 (m, 3H); HRESIMS calcd for $C_{42}H_{56}N_4NaO_{10}$ $[M+Na]^+$: 799.3889, found 799.3861.

17-[5-(2-甲氧基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3m**): 紫色固体, 收率 67.1%. m.p. 116～118 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.16 (s, 1H), 7.87 (d, J=15.8 Hz, 1H), 7.46 (d, J=7.6 Hz, 1H), 7.32 (t, J=7.8 Hz, 1H), 7.26 (s, 2H), 7.27 (s, 1H), 6.96～6.91 (m, 2H), 6.90 (d, J=8.3 Hz, 1H), 6.59 (t, J=11.4 Hz, 1H), 6.54 (d, J=15.8 Hz, 1H), 6.27 (s, 1H), 5.90 (d, J=9.3 Hz, 1H), 5.87～5.78 (m, 2H), 5.17 (s, 1H), 4.91 (s, 2H), 4.30 (d, J=10.0 Hz, 1H), 3.87 (s, 3H), 3.62～3.51 (m, 2H), 3.49～3.38 (m, 4H), 3.34 (s, 3H), 3.26 (s, 3H), 2.78～2.69 (m, 1H), 2.66 (d, J=13.9 Hz, 1H), 2.43 (t, J=12.1 Hz, 1H), 2.01 (s, 3H), 1.83～1.75 (m, 5H), 1.74～1.66 (m, 3H), 1.66～1.57 (m, 2H), 1.52～1.44 (m, 2H), 0.99 (d, J=6.8 Hz, 3H), 0.96 (d, J=6.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 183.9, 180.6, 168.4, 166.7, 158.2, 156.2, 144.8, 141.4, 136.6, 135.8, 135.0, 133.8, 132.7, 130.8, 129.1, 126.9, 126.6, 123.7, 121.5, 120.7, 111.1, 108.6, 108.4, 81.7, 81.5, 81.2, 72.6, 57.1, 56.7, 55.4, 45.8, 39.3, 36.6, 35.0, 34.4, 32.3, 29.5, 28.5, 24.1, 22.9, 12.8, 12.7, 12.4; HRESIMS calcd for $C_{43}H_{58}N_4NaO_{10}$ $[M+Na]^+$: 813.4045, found 813.4019.

17-[5-(4-甲氧基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3n**): 紫色固体, 收率 63.4%. m.p. 126～128 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.16 (s, 1H), 8.01 (s, 1H), 7.59 (d, J=15.5 Hz, 1H), 7.44 (d, J=8.4 Hz, 2H), 7.25 (s, 1H), 6.94 (d, J=11.5 Hz, 1H), 6.88 (d, J=8.4 Hz, 2H), 6.59 (t, J=11.4 Hz, 1H), 6.33～6.21 (m, 2H), 5.90 (d, J=9.4 Hz, 1H), 5.87 (t, J=10.41 Hz, 2H). 5.17 (s, 1H), 4.99 (br s, 2H), 4.30 (d, J=9.9 Hz, 1H), 3.81 (s, 3H), 3.61～3.51 (m, 2H), 3.46～3.38 (m, 4H), 3.35 (s, 3H), 3.25 (s, 3H), 2.76～2.69 (m, 1H), 2.66 (d, J=13.9 Hz, 1H), 2.42 (t, J=11.9 Hz, 1H), 2.01 (s, 3H), 1.82～1.75 (m, 5H), 1.74～1.65 (m, 3H), 1.65～1.58 (m, 2H), 1.50～1.42 (m, 2H), 0.99 (d, J=6.9 Hz, 3H), 0.95 (d, J=6.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 183.9, 180.6, 168.4, 166.5, 160.9, 156.3, 144.8, 141.4, 140.8, 135.8, 135.0, 133.8, 132.7, 129.4, 127.5, 126.9, 126.6, 118.0, 114.2, 108.6, 108.4, 81.7, 81.5, 81.2, 72.6, 57.1, 56.7, 55.4, 45.7, 39.3, 35.0, 34.4, 32.3, 29.5, 28.5, 24.1, 22.9, 20.7, 12.8, 12.7, 12.4; HRESIMS calcd for $C_{43}H_{58}N_4NaO_{10}$ $[M+Na]^+$: 813.4045, found 813.4014.

17-[5-(4-(*N*,*N*-二甲基氨基]肉桂酰胺基)戊二胺)-17-去甲氧基格尔德霉素(**3o**): 紫色固体, 收率 44.9%. m.p. 127～129 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.17 (s, 1H), 7.56 (d, J=15.5 Hz, 1H), 7.39 (d, J=7.5 Hz, 2H), 7.26 (s, 1H), 6.95 (d, J=10.6 Hz, 1H), 6.68 (s, 2H), 6.59 (t, J=11.0 Hz, 1H), 6.27 (s, 1H), 6.20 (d, J=15.4 Hz, 1H), 5.95～5.81 (m, 2H), 5.68 (s, 1H), 5.18 (s, 1H), 4.88 (br s, 1H), 4.31 (d, J=9.0 Hz, 1H), 3.66～3.52 (m, 2H), 3.51～3.37 (m, 4H), 3.35 (s, 3H), 3.26 (s, 3H), 2.99 (s, 6H), 2.79～2.69 (m, 1H), 2.67 (d, J=14.4 Hz, 1H), 2.42 (t, J=11.8 Hz, 1H), 2.02 (s, 3H), 1.85～1.75 (m, 5H), 1.75～1.67 (m, 3H), 1.66～1.58 (m, 2H), 1.51～1.41 (m, 2H), 1.00 (d, J=6.1 Hz, 3H), 0.96 (d, J=4.8 Hz, 3H); HRESIMS calcd for $C_{44}H_{61}N_5NaO_9$ $[M+Na]^+$: 826.4361, found 826.4331.

17-[5-(4-三氟甲基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3p**): 紫色固体, 收率 74.8%. m.p. 118～120 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.16 (s, 1H), 7.67

(d, *J*=15.6 Hz, 1H), 7.63～7.56 (m, 4H), 7.26 (s, 1H), 6.94 (d, *J*=11.5 Hz, 1H), 6.59 (t, *J*=11.4 Hz, 1H), 6.48 (d, *J*=15.6 Hz, 1H), 6.27 (s, 1H), 5.94～5.82 (m, 3H), 5.18 (s, 1H), 4.96 (s, 2H), 4.31 (d, *J*=9.6 Hz, 1H), 3.61～3.52 (m, 2H), 3.50～3.39 (m, 4H), 3.35 (s, 3H), 3.26 (s, 3H), 2.77～2.70 (m, 1H), 2.67 (d, *J*=13.8 Hz, 1H), 2.42 (t, *J*=12.3 Hz, 1H), 2.01 (s, 3H), 1.81～1.75 (m, 5H), 1.75～1.67 (m, 3H), 1.67～1.58 (m, 2H), 1.53～1.44 (m, 2H), 1.00 (d, *J*=6.9 Hz, 3H), 0.96 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 183.93, 180.59, 168.41, 165.40, 156.26, 144.79, 141.44, 139.54, 138.20, 135.88, 134.94, 133.71, 132.77, 127.93, 126.95, 126.59, 125.82, 125.80, 122.97, 122.92, 108.63, 108.47, 81.71, 81.44, 81.19, 72.62, 57.15, 56.73, 45.70, 39.41, 35.02, 34.40, 32.31, 29.42, 29.38, 28.52, 24.04, 22.94, 12.83, 12.64, 12.41; HRESIMS calcd for $C_{43}H_{55}F_3N_4NaO_9$ $[M+Na]^+$: 851.3813, found 851.3776.

17-[5-(4-三氟甲氧基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3q**): 紫色固体, 收率 66.4%. m.p. 126～128 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 9.17 (s, 1H), 7.62 (d, *J*=15.5 Hz, 1H), 7.53 (d, *J*=8.5 Hz, 2H), 7.26 (s, 1H), 7.21 (d, *J*=8.3 Hz, 2H), 6.95 (d, *J*=11.5 Hz, 1H), 6.60 (t, *J*=11.4 Hz, 1H), 6.38 (d, *J*=15.6 Hz, 1H), 6.27 (s, 1H), 5.93～5.78 (m, 3H), 5.18 (s, 1H), 4.88 (s, 2H), 4.31 (d, *J*=9.9 Hz, 1H), 3.63～3.52 (m, 2H), 3.52～3.38 (m, 4H), 3.35 (s, 3H), 3.26 (s, 3H), 2.79～2.69 (m, 1H), 2.67 (d, *J*=13.7 Hz, 1H), 2.42 (t, *J*=11.2 Hz, 1H), 2.02 (s, 3H), 1.87～1.76 (m, 5H), 1.75～1.67 (m, 3H), 1.67～1.59 (m, 2H), 1.54～1.41 (m, 2H), 1.00 (d, *J*=6.9 Hz, 3H), 0.96 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 183.9, 180.6, 168.4, 165.6, 156.1, 150.0, 144.8, 141.4, 139.6, 135.9, 135.0, 133.7, 133.4, 132.8, 129.2, 126.9, 126.6, 121.3, 121.2, 119.5, 108.6, 108.5, 81.7, 81.4, 81.2, 72.6, 57.2, 56.7, 45.7, 39.4, 35.0, 34.4, 32.3, 29.4, 28.5, 24.0, 22.9, 12.8, 12.6, 12.4; HRESIMS calcd for $C_{43}H_{55}F_3N_4NaO_{10}$ $[M+Na]^+$: 867.3762, found 867.3738.

17-[5-(3-羟基-4-甲氧基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3r**): 紫色固体, 收率 33.3%. m.p. 131～133 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 9.16 (s, 1H), 7.53 (d, *J*=15.5 Hz, 1H), 7.25 (s, 1H), 7.10 (d, *J*=1.6 Hz, 1H), 7.00～6.96 (m, 1H), 6.94 (d, *J*=11.4 Hz, 1H), 6.82 (d, *J*=8.3 Hz, 1H), 6.59 (t, *J*=11.4 Hz, 1H), 6.30～6.20 (m, 2H), 5.90 (d, *J*=9.4 Hz, 1H), 5.87 (t, *J*=10.3 Hz, 2H), 5.18 (s, 1H), 4.89 (br s, 2H), 4.31 (d, *J*=9.4 Hz, 1H), 3.90 (s, 3H), 3.60～3.51 (m, 2H), 3.48～3.39 (m, 4H), 3.35 (s, 3H), 3.26 (s, 3H), 2.79～2.69 (m, 1H), 2.66 (d, *J*=13.6 Hz, 1H), 2.42 (t, *J*=11.0 Hz, 1H), 2.01 (s, 3H), 1.81～1.75 (m, 5H), 1.75～1.66 (m, 3H), 1.66～1.56 (m, 2H), 1.51～1.41 (m, 2H), 1.00 (d, *J*=6.9 Hz, 3H), 0.95 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 183.9, 180.5, 168.4, 166.4, 156.2, 148.2, 145.8, 144.8, 141.4, 141.0, 135.9, 134.9, 133.8, 132.7, 128.3, 126.9, 126.6, 121.6, 118.5, 112.6, 110.6, 108.6, 108.4, 81.8, 81.4, 81.2, 72.6, 57.2, 56.7, 56.0, 45.7, 39.3, 35.0, 34.4, 32.3, 29.4, 29.4, 28.5, 24.0, 22.9, 12.8, 12.6, 12.4; HRESIMS calcd for $C_{43}H_{58}N_4NaO_{11}$ $[M+Na]^+$: 829.3994, found 829.3969.

17-[5-(4-羟基-3-甲氧基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3s**): 紫色固体, 收率 24.9%. m.p. 118～120 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 9.14 (s, 1H), 7.54 (d, *J*=15.3 Hz, 1H), 7.25 (s, 1H), 7.04 (d, *J*=8.1 Hz, 1H), 6.98 (s, 1H), 6.94 (d, *J*=11.5 Hz, 1H), 6.89 (d, *J*=8.2 Hz, 1H), 6.59 (t, *J*=11.3 Hz, 1H), 6.35～6.17 (m, 2H), 5.91～5.82 (m, 2H), 5.79 (s, 1H), 5.18 (s, 1H), 4.90 (br s, 1H), 4.34～4.26 (m, 1H), 3.90 (s, 3H), 3.59～3.51 (m, 2H), 3.50～3.36 (m, 4H), 3.35 (s, 3H), 3.26 (s, 3H), 2.77～2.69 (m, 1H), 2.66 (d, *J*=13.6 Hz, 1H), 2.42 (t, *J*=11.1 Hz, 1H), 2.01 (s, 3H), 1.83～1.75 (m, 5H), 1.74～1.67 (m, 3H), 1.65～1.59 (m, 2H), 1.51～1.43 (m, 2H), 1.00 (d, *J*=6.9 Hz, 3H), 0.96 (d, *J*=6.5 Hz, 3H); HRESIMS calcd for $C_{43}H_{58}N_4NaO_{11}$ $[M+Na]^+$: 829.3994, found 829.3964.

17-[5-(2,3-二甲氧基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3t**): 紫色固体, 收率 56.2%. m.p. 114～116 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 9.17 (s, 1H), 8.01 (s, 1H), 7.87 (d, *J*=15.8 Hz, 1H), 7.26 (s, 1H), 7.10 (d, *J*=7.9 Hz, 1H), 7.05 (t, *J*=7.9 Hz, 1H), 6.98～6.88 (m, 2H), 6.59 (t, *J*=11.3 Hz, 1H), 6.50 (d, *J*=15.8 Hz, 1H), 6.28 (s, 1H), 5.89 (d, *J*=9.4 Hz, 1H), 5.85 (t, *J*=10.6 Hz, 1H), 5.17 (s, 1H), 4.97 (br s, 2H), 4.31 (d, *J*=9.9 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.61～3.51 (m, 2H, H-11), 3.50～3.38 (m, 4H), 3.35 (s, 3H), 3.26 (s, 3H), 2.95 (s, 3H), 2.88 (s, 3H), 2.77～2.69 (m, 1H), 2.66 (t, *J*=14.0 Hz, 1H), 2.43 (t, *J*=12.4 Hz, 1H), 2.02 (s, 3H), 1.84～1.75 (m, 5H), 1.75～1.67 (m, 3H), 1.66～1.60 (m, 2H), 1.52～1.43 (m, 2H), 0.99 (d, *J*=6.8 Hz, 3H), 0.96 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) *δ*: 183.9, 180.6, 168.4, 166.4, 156.3, 153.1, 148.2, 144.8, 141.4, 135.8, 135.0, 133.8, 132.7, 128.9, 126.9, 126.6, 124.1, 122.2, 119.4, 113.3, 108.6, 108.4, 81.7, 81.5, 81.2, 72.6, 61.2, 57.1, 56.7, 55.8, 45.8, 39.4, 35.0, 34.4, 32.3, 29.5, 29.5, 28.5, 24.1, 22.9, 12.8, 12.7, 12.4; HRESIMS calcd for $C_{44}H_{60}N_4NaO_{11}$

[M+Na]$^+$: 843.4151, found 843.4118.

17-[5-(2,5-甲氧基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3u**): 紫色固体, 收率 67.3%. m.p. 131～133 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.16 (s, 1H), 8.01 (s, 1H), 7.83 (d, J=15.7 Hz, 1H), 7.26 (s, 1H), 7.00 (s, 1H), 6.95 (d, J=11.4 Hz, 1H), 6.89～6.80 (m, 2H), 6.60 (t, J=11.3 Hz, 1H), 6.52 (d, J=15.7 Hz, 1H), 6.27 (s, 1H), 5.90 (d, J=9.3 Hz, 1H), 5.87 (t, J=10.5 Hz, 1H), 5.80 (s, 1H), 5.18 (s, 1H), 4.89 (s, 2H), 4.31 (d, J=9.9 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.61～3.52 (m, 2H), 3.50～3.37 (m, 4H), 3.35 (s, 3H), 3.26 (s, 3H), 2.77～2.70 (m, 1H), 2.67 (d, J=13.9 Hz, 1H), 2.43 (t, J=12.4 Hz, 1H), 2.02 (s, 3H), 1.82～1.75 (m, 5H), 1.75～1.67 (m, 3H), 1.66～1.57 (m, 2H), 1.48 (d, J=7.0 Hz, 2H), 1.00 (d, J=6.8 Hz, 3H), 0.96 (d, J=6.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 183.9, 180.6, 168.4, 166.6, 156.2, 153.4, 152.7, 144.8, 141.4, 136.4, 135.8, 135.0, 133.8, 132.7, 126.9, 126.6, 124.3, 121.8, 116.1, 113.9, 112.3, 108.7, 108.4, 81.7, 81.5, 81.2, 72.6, 57.2, 56.7, 56.1, 55.8, 45.8, 39.3, 35.0, 34.4, 32.3, 29.5, 28.5, 24.1, 22.9, 12.8, 12.7, 12.4; HRESIMS calcd for $C_{44}H_{60}N_4NaO_{11}$ [M+Na]$^+$: 843.4151, found 843.4120.

17-[5-(3,4-二甲氧基肉桂酰胺基)戊二胺)-17-去甲氧基格尔德霉素(**3v**): 紫色固体, 收率 59.4%. m.p. 124～126 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.16 (s, 1H), 8.01 (s, 1H), 7.57 (d, J=15.5 Hz, 1H), 7.26 (s, 1H), 7.09 (d, J=8.3 Hz, 1H), 7.01 (s, 1H), 6.94 (d, J=11.5 Hz, 1H), 6.85 (d, J=8.3 Hz, 1H), 6.59 (t, J=11.4 Hz, 1H), 6.32～6.22 (m, 2H), 5.89 (d, J=9.4 Hz, 1H), 5.87 (t, J=10.6 Hz, 1H), 5.79 (s, 1H), 5.17 (s, 1H), 4.97 (s, 2H), 4.30 (d, J=9.8 Hz, 1H), 3.89 (s, 6H), 3.62～3.51 (m, 2H), 3.50～3.38 (m, 4H), 3.35 (s, 3H), 3.26 (s, 3H), 2.95 (s, 3H), 2.87 (s, 3H), 2.77～2.70 (m, 1H), 2.67～2.62 (m, 1H), 2.42 (t, J=12.3 Hz, 1H), 2.01 (s, 3H), 1.81～1.75 (m, 5H), 1.75～1.65 (m, 3H), 1.65～1.58 (m, 2H), 1.52～1.43 (m, 2H), 0.99 (d, J=6.9 Hz, 3H), 0.95 (d, J=6.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 183.9, 180.6, 168.4, 166.4, 156.3, 150.6, 149.1, 144.8, 141.5, 141.1, 135.8, 135.0, 133.8, 132.7, 127.7, 126.9, 126.6, 122.0, 118.3, 111.0, 109.6, 108.6, 108.4, 81.7, 81.5, 81.2, 72.6, 57.1, 56.7, 56.0, 55.9, 45.7, 39.3, 35.0, 34.4, 32.3, 29.5, 28.5, 25.4, 24.0, 22.9, 12.8, 12.6, 12.4; HRESIMS calcd for $C_{44}H_{60}N_4NaO_{11}$ [M+Na]$^+$: 843.4151, found 843.4117.

17-[5-(3,5-二甲氧基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3w**): 紫色固体, 收率 33.9%. m.p. 128～130 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.16 (s, 1H, CONH-1), 7.55 (d, J=15.5 Hz, 1H), 7.26 (s, 1H), 6.95 (d, J=11.4 Hz, 1H), 6.64 (s, 2H, H-10'), 6.60 (t, J=11.4 Hz, 1H), 6.45 (s, 1H), 6.37 (d, J=15.5 Hz, 1H), 6.27 (s, 1H), 5.90 (d, J=9.3 Hz, 1H), 5.87 (t, J=10.5 Hz, 1H), 5.78 (s, 1H), 5.18 (s, 1H), 4.84 (br s, 2H), 4.31 (d, J=9.9 Hz, 1H), 3.80 (s, 6H), 3.60～3.52 (m, 2H), 3.49～3.38 (m, 4H), 3.35 (s, 3H), 3.26 (s, 3H), 2.77～2.69 (m, 1H), 2.66 (d, J=13.8 Hz, 1H), 2.42 (t, J=11.7 Hz, 1H), 2.02 (s, 3H), 1.83～1.75 (m, 5H), 1.75～1.66 (m, 3H), 1.66～1.58 (m, 2H), 1.53～1.42 (m, 2H), 1.00 (d, J=6.8 Hz, 3H), 0.96 (d, J=6.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 183.9, 180.6, 168.4, 165.9, 161.0, 156.1, 144.8, 141.4, 141.2, 136.7, 135.8, 135.0, 133.8, 132.7, 126.9, 126.6, 121.0, 108.6, 108.4, 105.8, 101.8, 81.7, 81.5, 81.2, 72.6, 57.2, 56.7, 55.4, 45.7 (C-1'), 39.3, 35.0, 34.4, 32., 29.5, 28.5, 24.1, 22.9, 12.8, 12.7, 12.4; HRESIMS calcd for $C_{44}H_{60}N_4NaO_{11}$ [M+Na]$^+$: 843.4151, found 843.4121.

17-[5-(2,3,4-三甲氧基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3x**): 紫色固体, 收率 54.9%. m.p. 127～129 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.17 (s, 1H), 7.76 (d, J=15.7 Hz, 1H), 7.26 (s, 1H), 7.21 (d, J=8.6 Hz, 1H), 6.95 (d, J=11.4 Hz, 1H), 6.67 (d, J=8.7 Hz, 1H), 6.59 (t, J=11.3 Hz, 1H), 6.44 (d, J=15.7 Hz, 1H), 6.28 (s, 1H), 5.90 (d, J=9.1 Hz, 1H), 5.87 (t, J=10.6 Hz, 1H), 5.77 (s, 1H), 5.18 (s, 1H), 4.93 (s, 2H), 4.31 (d, J=9.8 Hz, 1H), 3.95～3.82 (m, 9H), 3.61～3.53 (m, 2H), 3.49～3.37 (m, 4H), 3.35 (s, 3H), 3.26 (s, 3H), 2.77～2.69 (m, 1H), 2.66 (d, J=14.0 Hz, 1H), 2.43 (t, J=12.3 Hz, 1H), 2.02 (s, 3H), 1.79 (s, 5H), 1.75～1.66 (m, 3H), 1.66～1.56 (m, 2H), 1.53～1.42 (m, 2H), 0.99 (d, J=6.5 Hz, 3H), 0.96 (d, J=5.6 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 183.9, 180.6, 168.4, 166.7, 156.2, 155.0, 153.1, 144.8, 142.4, 141.4, 136.2, 135.8, 135.0, 133.8, 132.7, 126.9, 126.61 123.4, 121.8, 119.9, 108.7, 108.4, 107.5, 81.7, 81.5, 81.2, 72.6, 61.3, 60.9, 57.1, 56.7, 56.0, 45.8, 39.3, 35.0, 34.4, 32.3, 29.5, 28.5, 24.1, 22.9, 12.8, 12.7, 12.4; HRESIMS calcd for $C_{45}H_{62}N_4NaO_{12}$ [M+Na]$^+$: 873.4256, found 873.4231.

17-[5-(3,4,5-三甲氧基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3y**): 紫色固体, 收率 22.5%. m.p. 97～99 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.17 (s, 1H), 7.56 (d, J=15.4 Hz, 1H), 7.27 (s, 1H), 6.95 (d, J=11.5 Hz, 1H), 6.73 (s, 2H), 6.60 (t, J=11.3 Hz, 1H), 6.37～6.20 (m, 2H), 5.90 (d, J=9.3 Hz, 1H), 5.87 (t, J=10.5 Hz, 1H),

5.72 (s, 1H), 5.18 (s, 1H), 4.32 (d, J=9.9 Hz, 1H), 3.92～3.84 (m, 9H), 3.61～3.54 (m, 2H), 3.51～3.39 (m, 4H), 3.35 (s, 3H), 3.27 (s, 3H), 2.77～2.71 (m, 1H), 2.68 (d, J=13.8 Hz, 1H), 2.43 (t, J=12.3 Hz, 1H), 2.02 (s, 3H), 1.82～1.77 (m, 5H), 1.76～1.67 (m, 3H), 1.67～1.59 (m, 2H), 1.52～1.45 (m, 2H), 1.00 (d, J=6.9 Hz, 3H), 0.96 (d, J=6.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 183.9, 180.6, 168.4, 166.1, 156.2, 153.4, 144.8, 141.5, 141.3, 139.6, 135.8, 135.0, 133.8, 132.7, 130.3, 126.9, 126.6, 119.7, 108.6, 108.5, 104.9, 81.7, 81.5, 81.2, 72.6, 61.0, 57.2, 56.7, 56.2, 45.7, 39.4, 35.0, 34.4, 32.3, 29.4, 28.5, 25.4, 24.1, 22.9, 12.8, 12.7, 12.4; HRESIMS calcd for $C_{45}H_{62}N_4NaO_{12}$ $[M+Na]^+$: 873.4256, found 873.4228.

17-[5-(4-羟基-3,5-二甲氧基肉桂酰胺基)戊二胺]-17-去甲氧基格尔德霉素(**3z**): 紫色固体, 收率44.9%. m.p. 124～126 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.15 (s, 1H), 7.54 (d, J=15.4 Hz, 1H), 7.26 (s, 1H), 6.95 (d, J=11.7 Hz, 1H), 6.74 (s, 2H), 6.59 (t, J=11.4 Hz, 1H), 6.32～6.19 (m, 2H), 5.83～5.94 (m, 2H), 5.77 (s, 1H), 5.66 (s, 1H), 5.18 (s, 1H), 4.30 (d, J=9.9 Hz, 1H), 3.91 (s, 6H), 3.62～3.52 (m, 2H), 3.50～3.38 (m, 4H), 3.35 (s, 3H), 3.26 (s, 3H), 2.80～2.70 (m, 1H), 2.68 (d, J=13.5 Hz, 1H), 2.44～2.34 (m, 1H), 2.02 (s, 3H), 1.83～1.76 (m, 5H), 1.74～1.68 (m, 3H), 1.65～1.59 (m, 2H), 1.52～1.45 (m, 2H), 1.00 (d, J=6.9 Hz, 3H), 0.96 (d, J=6.6 Hz, 3H); HRESIMS calcd for $C_{44}H_{60}N_4NaO_{12}$ $[M+Na]^+$: 859.4100, found 859.4068.

3.2.2 体外抗肿瘤活性试验

体外抗肿瘤活性测定采用 MTT 法, 具体实验方法和实验数据处理方法见相应参考文献[15～17]. 抑制率按下式计算: $(A570_{\text{control cells}}-A570_{\text{treated cells}})/(A570_{\text{control cells}}-A570_{\text{blank cells}})\times100\%$. IC_{50} 值用软件 Prism 5 (GraphPad Software, Inc., USA)计算.

3.2.3 肝细胞 HL7702 毒性试验

肝细胞 HL7702 毒性试验采用 SRB 法, 具体实验方法和实验数据处理方法见相应参考文献[15～17].

3.2.4 荧光偏振法检验 Hsp90 靶点亲和力

化合物 **3a** 对 Hsp90 靶点亲和力测定采用荧光偏振法, 具体实验方法和实验数据处理方法见参考文献[15～17]. Hsp90 靶点亲和力测定以 17-AAG 为阳性对照.

3.2.5 分子对接步骤

采用 ChemBioDraw Ultra 12.0 画出化合物 **3u** 的结构, 然后用 ChemBio3D Ultra 12.0 将其转化为三维结构. Hsp90 的三维结构(PDB ID: 1YET)从 Protein Data Bank (http://www.rcsb.org/pdb/home/home.do)下载得到. Hsp90 和 **3u** 使用 AutodockTools 1.5.6 转化为 PDBQT 格式. 本文采用 Autodock vina 1.1.2 进行分子对接研究. Hsp90 的活性口袋坐标为: center_x=41.067, center_y=－46.783, center_z=65.506; size_x=15, size_y=15, size_z=15. 参数 exhaustiveness 设置为 20. 除了特别说明, 其他参数均采用默认值, 对接结果用 PyMoL 软件显示.

辅助材料 (Supporting Information) 化合物 **3a**～**3z** 的质谱、^{1}H NMR 和 ^{13}C NMR 谱图. 这些材料可以免费从本刊网站 (http://sioc-journal.cn/)上下载.

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