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# 薯蓣皂苷元衍生物的合成及其抗肿瘤活性和细胞毒性研究

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**摘　要**:本研究设计并合成了 15 个新的薯蓣皂苷元衍生物,其结构都通过$^{1}$H NMR、$^{13}$C NMR、IR 和 HR-MS 鉴定。所有衍生物采用 MTT 法对 A431 和 H1975 两种细胞株进行体外抗肿瘤活性试验。初步的生物活性测试表明,大多数衍生物都显示出不同程度的抗肿瘤活性。

**关键词**:薯蓣皂苷元;结构修饰;酰化反应;抗肿瘤活性;酰胺类衍生物

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# Synthesis, Antitumor Activity and Cytotoxicity of Diosgenin Amide Derivatives

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**Abstract**: Fifteen novel diosgenin derivatives were designed and synthesized. The structures of all derivatives were confirmed by $^{1}$HNMR, $^{13}$C NMR, IR and HR-MS spectra. The antitumor activities of the fifteen derivatives were evaluated against A431, H1975 cell lines by MTT assay. The preliminary bioassay test suggested that most of these diosgenin derivatives showed different degrees of activities.

**Key words**: diosgenin; structural modification; acylation reaction; antitumor activity; amide derivatives

薯蓣皂苷元是从盾叶薯蓣和穿龙薯蓣提取出的一种重要的甾体皂苷(如图 1),它被广泛用作合成甾体药物的前体,如泼尼松、炔诺酮、氟美松等[1]。同时,薯蓣皂苷元具有抗肿瘤、抗血栓、抗菌、抗炎等药理活性[2,3]。大量研究表明,薯蓣皂苷元具有广谱的抗肿瘤活性,对于 HeLa、K562、HEL、HEP-2 等多种肿瘤细胞,它能有效通过抑制细胞增殖并诱导细胞凋亡的方式来发挥作用[4-6]。但是,薯蓣皂苷元及其衍生物作为潜在的抗肿瘤活性物质,适用范围相对较窄,因此需要进行进一步的结构修饰和药理研究来提高其生物利用度及应用范围。

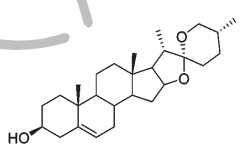


**图 1　薯蓣皂苷元的结构**

Fig. 1　Structure of diosgenin

近年来,薯蓣皂苷元的化学结构修饰主要集中于 A 环 C3-位羟基和 F 环开环后 C26-位的改造,部分改造后的衍生物表现出较好的抗肿瘤活性[7-17]。酰胺结构是重要的功能性基团,具有延长药物在体内的作用时间,降低毒性,提高药物生物利用度等优点,并广泛存在于医药中间体和已知药物中。然而,对于薯蓣皂苷元酰胺类衍生物的报道很少,所以我们设计在薯蓣皂苷元上引入酰胺结构(如图 2)。首先将薯蓣皂苷元 C3-位羟基转变为氨基,然后与不同的酰化试剂反应,得到一系列薯蓣皂苷元 C3-位酰胺类衍生物,并对这些衍生物的抗肿瘤活性及细胞毒性进行初步的研究。

为了在薯蓣皂苷元上引入酰胺结构,我们以薯蓣皂苷元为先导物,三乙胺作为缚酸剂,与甲磺酰氯反应,使 C3-位羟基磺酰化得到化合物 **2**,然后与叠氮化钠发生亲核取代反应得到化合物 **3**,再用三苯基膦将 C3-位叠氮基还原为氨基即得到化合物 **4**[18],最后以得到的薯蓣皂苷元 C3-位氨基衍生物作为共同中间体,分别与不同的酰化试剂反应得到相对应的一系列酰胺类衍生物 **1a ~ 1o**(如图 2)。在这些衍生物的合成中,我们选择了具有不同特征结

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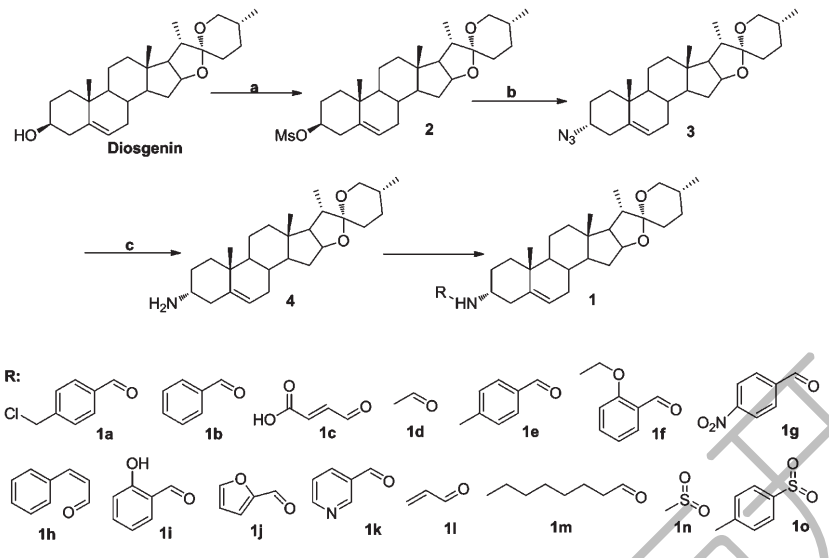


**图 2 化合物 1a-1o 的合成**

Fig. 2 Synthesis of compounds 1a-1o

试剂及反应条件:(a) MsCl, $Et_3N$, THF, 0 ℃, 1 h. (b) $NaN_3$, DMF, 90 ℃, 7 h. (c) $Ph_3P$, THF/$H_2O$, 60 ℃, 24 h.

构的酰化试剂,如杂环类(呋喃环、吡啶环),芳香环类(环上取代基为不同的供电子基或吸电子基),长链烷烃或烯烃类等。所有合成的新化合物结构都经$^1$H NMR,$^{13}$C NMR,IR,HRMS (ESI)确证,并进行了相应的生物活性实验,期望得到生物活性更好的薯蓣皂苷元抗肿瘤衍生物。

## 1 材料与方法

### 1.1 仪器与试剂

实验所用试剂除特别说明外,都为分析纯试剂,且未经纯化直接使用。$^1$H NMR 和$^{13}$C NMR 用 Agilent DD2400-MR(400 MHz)核磁共振波谱仪测定,TMS 作为内标,$CDCl_3$ 作为溶剂;IR 用 FTS 3000 傅里叶变换红外光谱仪(美国 Digilab 公司)测定,KBr 压片;HRMS 用 LCQ Advantage Max 质谱仪测定;旋光用 SGW-1(上海仪电物理光学仪器有限公司)旋光仪测定;熔点用 SGW X-4 显微熔点测试仪(上海精密科学仪器有限公司),温度未经校准。

### 1.2 细胞培养

收集 A431,H1975,HBE 对数生长期细胞,调整细胞悬液浓度,以每孔 $7\times10^3$ 个细胞,每孔体积 100μL 接种到 96 孔板,每孔设 4 个复孔(边缘孔用无菌 PBS 填充)。细胞贴壁后,0% FBS RPMI-1640 饥饿 8 h,对照组用 10% FBS RPMI-1640 培养。37℃,5% $CO_2$ 培养箱中继续培养 48 h。

### 1.3 MTT 检测

在 A431,H1975,HBE 三组细胞分别于培养 48 h 后,加入 100 μL MTT 溶液(5 mg·mL$^{-1}$),4 h 后终止培养,每孔加入 100 μL 三联液,于摇床上低速振荡 10 min,使结晶充分溶解。在酶联免疫检测仪上测定各孔光度值(OD 值),选择 570 nm 波长,以无细胞的即 RPMI-1640 培养液空白孔调零,测各孔的吸光度值。实验重复三次,记录结果:细胞生长抑制率 = (对照组吸光度值一实验组吸光度值)/对照组吸光度值 × 100%。在 GraphPad 软件中的 GraphPad Prism 作图软件中针对抑制剂浓度做图,以便由 log[抑制剂]相对于反应,可变斜率模型估算出 $IC_{50}$ 值。

### 1.4 化学合成

#### 1.4.1 (25*R*)-3α-氨基螺甾烷-5-烯(**4**)

氮气保护下,将薯蓣皂苷元 (3.00 g, 7.24 mmol) 溶于 30 mL 四氢呋喃,加入三乙胺(5.03 mL, 36.2mmol),冰浴下滴加甲磺酰氯(2.24 mL, 28.9 mmol),控制温度不超过 5 ℃,继续搅拌至 TLC 检测反应完全。减压蒸去溶剂,加入水和二氯甲烷萃取,有机相用饱和碳酸氢钠洗涤,无水硫酸钠干燥,减压浓缩,得 3.2 g 淡黄色固体(**2**),粗产率 90%。$^1$H NMR ($CDCl_3$, 400 MHz) $\delta$:5.41 (1 H, d, $J$ = 4.0 Hz, H-6), 4.55 – 4.45 (1 H, m, H-3), 4.40 (1 H, q, $J$ = 7.3 Hz, H-16), 3.46 (1 H, dd, $J$ = 3.2, 2.4 Hz, H-26α), 3.36 (1 H, t, $J$ = 10.8 Hz, H-26$\beta$), 3.0 (3 H, s, $CH_3S$), 1.02 (3 H, s, H-19), 0.96 (3 H, d, $J$ = 6.8 Hz, H-21), 0.79-0.76 (6 H, H-18, H-

27);$^{13}$C NMR ($CDCl_3$,100 MHz) $\delta$:138.81 (C-5), 123.65 (C-6),109.40 (C-22),82.02 (C-3),80.87 (C-16),66.96 (C-26),62.18 (C-17),56.48 (C-14),49.95 (C-9),41.72 (C-20),40.37 (C-13), 39.77 (C-12),39.25 (C-4),38.89 ($CH_3$),36.98 (C-10),36.64 (C-1),32.13 (C-7),31.93 (C-15), 31.50 (C-8),31.45 (C-23),30.40 (C-25),29.07 (C-2),28.91 (C-24),20.93 (C-11),19.34 (C-19),17.26 (C-27),16.39 (C-18),14.64 (C-21); HRMS (ESI) *m/z* 493.2999 [M + H]$^+$ (calcd for $C_{28}H_{44}O_5S$,493.2987)。

取化合物 **2**(3.00 g,6.09 mmol)溶于 20 mL DMF,于 80 ℃下加入 $NaN_3$(0.79 g,12.2 mmol),在 90 ℃继续搅拌 7 h,TLC 检测反应完全。向反应液中加入水,用乙酸乙酯萃取,有机相依次用饱和氯化钠溶液、水、饱和碳酸氢钠溶液洗涤,无水硫酸钠干燥,减压浓缩。经柱色谱(石油醚∶乙酸乙酯 = 200∶1),得 1.82 g 白色固体(3),收率 68%。$^1$H NMR ($CDCl_3$,400 MHz) $\delta$:5.39 (1 H,d,*J* = 4.8 Hz,H-6),4.40 (1 H,q,*J* = 7.5 Hz,H-16),3.89-3.84 (1 H,m,H-3),3.46 (1 H,dd,*J* = 2.8 Hz,4.0,H-26$\alpha$),3.36 (1 H,t,*J* = 11 Hz,H-26$\beta$),1.02 (3 H,s,H-19),0.96 (3 H,d,*J* = 7.2 Hz,H-21),0.78 (6 H,t,H-18,H-27);$^{13}$C NMR ($CDCl_3$,100 MHz) $\delta$:138.25 (C-5),123.01 (C-6),109.40 (C-22),80.94 (C-16),66.97 (C-26),62.20 (C-17),58.30 (C-3),56.60 (C-14),49.96 (C-9),41.75 (C-20),40.37 (C-13),39.87 (C-12),37.35 (C-10),36.18 (C-4),33.73 (C-1),32.10 (C-7),31.95 (C-15),31.53 (C-23),31.45 (C-8),30.45 (C-25),28.96 (C-24),26.23 (C-2),20.65 (C-11),19.16 (C-19),17.29 (C-27),16.43 (C-18),14.67 (C-21); HR-MS (ESI) *m/z* 440.3278 [M + H]$^+$ (calcd for $C_{27}H_{41}N_3O_2$,440.3277)。

将化合物 **3**(2.50 g,5.69 mmol)溶于 20 mL 四氢呋喃中,加入 2 mL 水,加入 $PPh_3$(2.98 g,11.4 mmol),60 ℃下搅拌,TLC 检测反应完全。将反应液减压蒸去溶剂。经柱色谱(二氯甲烷∶甲醇 = 25∶1)得 1.06 g 白色固体(4),产率 45%。$^1$H NMR ($CDCl_3$,400 MHz) $\delta$:5.37 (1 H,d,*J* = 5.2 Hz,H-6),4.41 (1 H,q,*J* = 7.5 Hz,H-16),3.46 (1 H,dd,*J* = 3.6 Hz,4.0,H-26$\alpha$),3.36 (1 H,t,*J* = 10.8 Hz,H-26$\beta$),3.20 (1 H,brs,H-3),1.02 (3 H,s,H-19),0.97 (3 H,d,*J* = 7.2 Hz,H-21),0.79 (6 H,t,H-18,H-27);$^{13}$C NMR ($CDCl_3$,100 MHz) $\delta$:138.92 (C-5),123.36 (C-6),109.42 (C-22),80.97 (C-16),66.97 (C-26),62.23 (C-17),56.65 (C-14),50.46 (C-9),47.07 (C-3),41.75 (C-20),40.38 (C-13),39.92 (C-4),39.87 (C-12),37.69 (C-10),33.16 (C-1),32.27 (C-7),31.97 (C-15),31.53 (C-23),30.44 (C-25),29.84 (C-8),29.35 (C-2),28.95 (C-24),20.71 (C-11),19.01 (C-19),17.28 (C-27),16.42 (C-18),14.67 (C-21);HRMS (ESI) *m/z* 414.3366 [M + H]$^+$ (calcd for $C_{27}H_{43}NO_2$,414.3294)。

化合物 **4** 与不同的酰氯反应得到酰胺衍生物 **1a** 和 **1b**;与不同的酸酐反应得到酰胺类衍生物 **1c** 和 **1d**;与不同的羧酸反应得到酰胺类衍生物 **1e** ~ **1m**;与不同的磺酰氯反应得到酰胺类衍生物 **1n** 和 **1o**。

1.4.2 (25*R*)-3$\alpha$-对氯甲基苯甲酰胺基螺甾烷-5-烯(**1a**)

取化合物 **4**(0.22 g,0.53 mmol)溶于 5 mL $CH_2Cl_2$ 中,加入三乙胺(0.37 mL,2.66 mmol),将对氯甲基苯甲酰氯(0.20 g,1.06mmol)溶于 5mL $CH_2Cl_2$ 中,冰浴下缓慢滴加。2 h 后 TLC 检测原料反应完全,停止反应,将反应液用饱和氯化钠溶液洗涤,无水硫酸钠干燥后浓缩。经柱色谱(石油醚∶乙酸乙酯 = 10∶1)得 0.18 g 白色固体(**1a**),收率 60%。mp. 197.3 ~ 198.9 ℃;$[\alpha]_D^{34}$-104 (*c* 0.003,$CHCl_3$);IR (KBr) $\nu_{max}$ 3427 (N-H),2948,2869,1668 (C = O),1505,1457,1384,1268,1066 cm$^{-1}$;$^1$H NMR ($CDCl_3$,400 MHz) $\delta$:7.69 (2 H,d,*J* = 8.0 Hz,H-Ph),7.45 (2 H,d,*J* = 8.0 Hz,H-Ph),6.20 (1 H,d,*J* = 7.6 Hz,NH),5.47 (1 H,d,*J* = 5.2 Hz,H-6),4.60 (2 H,s,$ClCH_2$),4.42 (1 H,q,*J* = 7.5 Hz,H-16),4.36 ~ 4.29 (1 H,m,H-3),3.48 (1 H,dd,*J* = 4.0,4.0 Hz,H-26$\alpha$),3.38 (1 H,t,*J* = 10.8 Hz,H-26$\beta$),1.08 (3 H,s,H-19),0.97 (3 H,d,*J* = 6.8 Hz,H-21),0.81 ~ 0.77 (6 H,H-18,H-27);$^{13}$C NMR ($CDCl_3$,100 MHz) $\delta$:(140.73,135.27,127.38,128.87,C-Ph),166.03 (C = O),139.31 (C-5),123.66 (C-6),109.44 (C-22),80.90 (C-16),67.00 (C-26),62.21 (C-17),56.58 (C-14),50.79 (C-9),46.18 (C-3),45.57 ($ClCH_2$),41.74 (C-20),40.38 (C-13),39.84 (C-12),37.77 (C-4),37.40 (C-10),34.62 (C-1),32.25 (C-7),31.95 (C-15),31.50 (C-23,8),30.42 (C-25),28.93 (C-

24),26.22 (C-2),20.70 (C-11),19.02 (C-19),17.28 (C-27),16.40 (C-18),14.66 (C-21);HR-MS (ESI) $m/z$ 566.3329 $[M+H]^+$ (calcd for $C_{35}H_{48}ClNO_3$,566.3401)。

1.4.3 (25*R*)-3α-苯甲酰胺基螺甾烷-5-烯(**1b**)

化合物**1b**的合成步骤同**1a**,酰化试剂为苯甲酰氯。经柱色谱(石油醚∶乙酸乙酯=10∶1)得白色固体(1b),收率84%。mp.208.3 ~ 210.3 ℃;$[\alpha]_D^{34}$-115.3 ($c$ 0.003,$CHCl_3$);IR (KBr) $\nu_{max}$ 3437 (N-H),2942,2872,1670 (C=O),1071 $cm^{-1}$;$^1H$ NMR ($CDCl_3$,400 MHz) $\delta$:7.69 (2 H,d,$J$=7.2 Hz,H-Ph),7.51 ~7.39 (3 H,m,H-Ph),6.23 (1 H,d,$J$=7.6 Hz,NH),5.46 (1 H,d,$J$=3.6 Hz,H-6),4.42 (1 H,q,$J$=7.5 Hz,H-16),4.37 ~4.30 (1 H,brs,H-3),3.47 (1 H,d,$J$=8.0 Hz,H-26α),3.38 (1 H,t,$J$=10.8 Hz,H-26$\beta$),1.08 (3 H,s,H-19),0.97 (3 H,d,$J$=6.4 Hz,H-21),0.81 ~0.76 (6 H,H-18,H-27);$^{13}C$ NMR ($CDCl_3$,100 MHz) $\delta$:(135.21,131.39,128.69,126.88,C-Ph),166.59 (C=O),139.32 (C-5),123.55 (C-6),109.42 (C-22),80.89 (C-16),66.97 (C-26),62.18 (C-17),56.56 (C-14),50.75 (C-9),46.09 (C-3),41.72 (C-20),40.35 (C-13),39.82 (C-12),37.75 (C-4),37.39 (C-10),34.60 (C-1),32.24 (C-7),31.93 (C-15),31.48 (C-23,8),30.40 (C-25),28.90 (C-24),26.22 (C-2),20.68 (C-11),19.01 (C-19),17.26 (C-27),16.39 (C-18),14.65 (C-21);HRMS (ESI) $m/z$ 518.3628 $[M+H]^+$ (calcd for $C_{34}H_{47}NO_3$,518.3634)。

1.4.4 (25*R*)-3α-(3-羧基)丁烯酰胺基螺甾烷-5-烯(**1c**)

取化合物**4**(0.08 g,0.20 mmol)溶于4 mL $CH_2Cl_2$,加入顺丁烯二酸酐(0.02 g,0.24 mmol)、三乙胺(0.04 mL,0.30 mmol),室温搅拌14 h,TLC检测原料反应完全后,分别用稀盐酸、水洗反应液,无水硫酸钠干燥后浓缩。经重结晶(石油醚∶乙酸乙酯=3∶1)得0.08 g白色固体(**1c**),收率78%。mp.217.5 ~ 220.3 ℃;$[\alpha]_D^{34}$-168.5 ($c$ 0.003,$CHCl_3$);IR (KBr) $\nu_{max}$ 3307 (N-H),2958,1720 (C=O),1636 (C=O),1556,1251,1061,984,626 $cm^{-1}$;$^1H$ NMR ($CDCl_3$,400 MHz) $\delta$:6.72 (1 H,d,$J$=7.2 Hz,NH),6.32 (2 H,q,$J$=12.4 Hz,CH=CH),5.42 (1 H,brs,H-6),4.39 (1 H,q,$J$=7.5 Hz,H-16),4.22 (1 H,brs,H-3),3.45 (1 H,d,$J$=8.8 Hz,H-26α),3.35 (1 H,t,$J$=10.8 Hz,H-26$\beta$),1.04 (3 H,s,H-19),0.96 (3 H,d,$J$=6.8 Hz,H-21),0.78 (6 H,s,H-18,H-27);$^{13}C$ NMR ($CDCl_3$,100 MHz) $\delta$:165.35 (COOH),165.17 (CON),137.92 (C-5),136.54 (CH=),131.53 (CH=),124.58 (C-6),109.45 (C-22),80.85 (C-16),66.97 (C-26),62.19 (C-17),56.63 (C-14),50.26 (C-9),47.48 (C-3),41.70 (C-20),40.35 (C-13),39.81 (C-12),37.54 (C-4),36.48 (C-10),33.99 (C-1),32.14 (C-7),31.89 (C-15),31.45 (C-8),31.34 (C-23),30.39 (C-25),28.89 (C-24),25.74 (C-2),20.62 (C-11),18.98 (C-19),17.26 (C-27),16.38 (C-18),14.65 (C-21);HRMS (ESI) $m/z$ 534.3196 $[M+Na]^+$ (calcd for $C_{31}H_{45}NO_5$,534.3195)。

1.4.5 (25*R*)-3α-乙酰胺基螺甾烷-5-烯(**1d**)

化合物**1d**的合成步骤同**1c**,酰化试剂为乙酸酐。经柱色谱(石油醚∶乙酸乙酯=10∶1)得白色固体(**1d**),收率35%。mp.206.6 ~ 207.2 ℃;$[\alpha]_D^{34}$-150.7 ($c$ 0.003,$CHCl_3$);IR (KBr) $\nu_{max}$ 3307 (N-H),2945,1645 (C=O),1550,1461,1382,1062,986 $cm^{-1}$;$^1H$ NMR ($CDCl_3$,400 MHz) $\delta$:5.50 (1 H,d,$J$=7.2 Hz,NH),5.39 (1 H,d,$J$=5.2 Hz,H-6),4.42 (1 H,q,$J$=7.5 Hz,H-16),4.13 ~4.10 (1 H,m,H-3),3.47 (1 H,dd,$J$=4.0 Hz,4.0,H-26α),3.37 (1 H,t,$J$=11 Hz,H-26$\beta$),1.04 (3 H,s,H-19),0.97 (3 H,d,$J$=7.2 Hz,H-21),0.79 (6 H,t,H-18,H-27);$^{13}C$ NMR ($CDCl_3$,100 MHz) $\delta$:169.25 (C=O),139.16 (C-5),123.35 (C-6),109.43 (C-22),80.88 (C-16),66.97 (C-26),62.18 (C-17),56.66 (C-14),50.53 (C-9),45.71 (C-3),41.71 (C-20),40.36 (C-13),39.87 (C-12),37.62 (C-4),37.16 (C-10),34.24 (C-1),32.16 (C-7),31.92 (C-15),31.47 (C-8),31.43 (C-23),30.40 (C-25),28.90 (C-24),26.14 (C-2),23.75 ($CH_3$-CO),20.65 (C-11),18.99 (C-19),17.26 (C-27),16.39 (C-18),14.65 (C-21);HRMS (ESI) $m/z$ 478.3291 $[M+Na]^+$ (calcd for $C_{29}H_{45}NO_3$,478.3297)。

1.4.6 (25*R*)-3α-对甲基苯甲酰胺基螺甾烷-5-烯(**1e**)

将**1e**(0.25 g,0.61 mmol)用8 mL $CH_2Cl_2$溶解,依次加入对甲基苯甲酸(0.11 g,0.79 mmol)、EDC·HCl(0.18 g,0.92 mmol)常温搅拌。TLC跟

踪至反应完全,依次用稀盐酸、饱和碳酸氢钠洗涤反应液,无水 $Na_2SO_4$ 干燥后减压浓缩。经柱色谱(石油醚:乙酸乙酯=5:1)得 0.21 g 白色固体(**1e**),收率 65%。mp. 251.5 ~ 252.5 ℃;$[\alpha]_D^{34}$-95.3 (*c* 0.003, $CHCl_3$);IR (KBr) $\nu_{max}$ 3318 (N-H), 2950, 1644 (C = O), 1543, 1462, 1384, 1264, 1061, 809 $cm^{-1}$;$^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$:7.60 (2 H, d, *J* = 7.6, H-Ph), 7.23 (2 H, d, *J* = 7.6, H-Ph), 6.19 (1 H, d, *J* = 7.6, NH), 5.47 (1 H, d, *J* = 4.4, H-6), 4.42 (1 H, q, *J* = 7.5, H-16), 4.33 (1 H, brs, H-3), 3.48 (1 H, d, H-26$\alpha$), 3.38 (1 H, t, *J* = 10.8, H-26$\beta$), 2.39 (3 H, s, $CH_3$-Ph), 1.08 (3 H, s, H-19), 0.97 (3 H, d, *J* = 6.4, H-21), 0.82 ~ 0.77 (6 H, H-18, H-27);$^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$:(141.58, 132.30, 126.72, 120.17, C-Ph), 166.39 (C = O), 139.28 (C-5), 123.33 (C-6), 109.27 (C-22), 80.75 (C-16), 66.84 (C-26), 62.08 (C-17), 56.45 (C-14), 50.65 (C-9), 45.85 (C-3), 41.59 (C-20), 40.22 (C-13), 39.70 (C-12), 37.61 (C-4), 37.30 (C-10), 34.47 (C-1), 32.11 (C-7), 31.80 (C-15), 31.36 (C-23, 8), 30.26 (C-25), 28.77 (C-24), 26.11 (C-2), 21.39 ($CH_3$Ph), 20.55 (C-11), 18.87 (C-19), 17.11 (C-27), 16.23 (C-18), 14.49 (C-21);HRMS (ESI) *m/z* 532.3790 $[M + H]^+$ (calcd for $C_{35}H_{49}NO_3$, 532.3791)。

1.4.7　(25*R*)-3$\alpha$-邻乙氧苯甲酰胺基螺甾烷-5-烯(**1f**)

化合物 **1f** 的合成步骤同 **1e**,酰化试剂为邻乙氧基苯甲酸。经柱色谱(石油醚:乙酸乙酯=8:1)得白色固体(**1f**),收率 52%。mp. 174.2 ~ 175.9 ℃;$[\alpha]_D^{34}$-134.5 (*c* 0.004, $CHCl_3$);IR (KBr) $\nu_{max}$ 3417 (N-H), 2954, 1659 (C = O), 1526, 1460, 1244, 1061, 984, 753 $cm^{-1}$;$^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$:8.21, 8.06 (2 H, d, *J* = 7.6, 6.8 Hz, H-Ph), 7.39, 7.04 (2 H, t, *J* = 7.6 Hz, 6.8, H-Ph), 6.93 (1 H, d, *J* = 8.0 Hz, NH), 5.39 (1 H, brs, H-6), 4.47-4.37 (2 H, m, H-16, H-3), 4.23-4.15 (2 H, m, *J* = 6.4Hz, $OCH_2$), 3.47 (1 H, d, H-26$\alpha$), 3.37 (1 H, t, *J* = 10.8 Hz, H-26$\beta$), 1.07 (3 H, s, H-19), 0.97 (3 H, d, *J* = 6.4 Hz, H-21), 0.82 ~ 0.76 (6 H, H-18, H-27);$^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$:(156.83, 139.92, 132.53, 122.10, 121.18, 112.18, C-Ph), 164.48 (C = O), 139.90 (C-5), 122.53 (C-6), 109.45 (C-22), 80.91 (C-16), 66.99 (C-26), 64.55 ($OCH_2$), 62.24 (C-17), 56.99 (C-14), 50.48 (C-9), 46.35 (C-3), 41.73 (C-20), 40.42 (C-13), 39.96 (C-12), 37.65 (C-4), 37.14 (C-10), 34.23 (C-1), 32.37 (C-7), 31.96 (C-15), 31.50 (C-8), 31.42 (C-23), 30.43 (C-25), 28.93 (C-24), 26.30 (C-2), 20.65 (C-11), 19.12 (C-19), 17.28 (C-27), 16.46 (C-18), 15.51 ($CH_3$), 14.67 (C-21);HRMS (ESI) *m/z* 584.3709 $[M + Na]^+$ (calcd for $C_{36}H_{51}NO_4$, 584.3716)。

1.4.8　(25*R*)-3$\alpha$-对硝基苯甲酰胺基螺甾烷-5-烯(**1g**)

化合物 **1g** 的合成步骤同 **1e**,酰化试剂为对硝基苯甲酸。经乙酸乙酯重结晶得白色固体(**1g**),收率 47%。mp. 235.9 ~ 236.3 ℃;$[\alpha]_D^{34}$-104.7 (*c* 0.003, $CHCl_3$);IR (KBr) $\nu_{max}$ 3428 (N-H), 2943, 1679 (C = O), 1605, 1525, 1347, 1071, 867, 830 $cm^{-1}$;$^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$:8.28 (2 H, d, *J* = 8.8 Hz, H-Ph), 7.84 (2 H, d, *J* = 8.4 Hz, H-Ph), 6.24 (1 H, d, *J* = 7.2 Hz, NH), 5.48 (1 H, d, *J* = 3.6Hz, H-6), 4.40 (1 H, q, *J* = 7.3 Hz, H-16), 4.34 (1 H, brs, H-3), 3.47 (1 H, d, H-26$\alpha$), 3.37 (1 H, t, *J* = 10.8 Hz, H-26$\beta$), 1.08 (3 H, s, H-19), 0.96 (3 H, d, *J* = 6.8 Hz, H-21), 0.80 ~ 0.76 (6 H, H-18, H-27);$^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$:(149.54, 140.71, 128.07, 123.99, C-Ph), 164.54 (C = O), 139.04 (C-5), 123.94 (C-6), 109.44 (C-22), 80.83 (C-16), 66.97 (C-26), 62.11 (C-17), 56.51 (C-14), 50.74 (C-9), 46.55 (C-3), 41.69 (C-20), 40.33 (C-13), 39.77 (C-12), 37.77 (C-4), 37.23 (C-10), 34.59 (C-1), 32.21 (C-7), 31.90 (C-15), 31.43 (C-23, 8), 30.38 (C-25), 28.88 (C-24), 26.09 (C-2), 20.67 (C-11), 18.98 (C-19), 17.28 (C-27), 16.40 (C-18), 14.66 (C-21);HRMS (ESI) *m/z* 601.3041 $[M + K]^+$ (calcd for $C_{34}H_{46}N_2O_5$, 601.3044)。

1.4.9　(25*R*)-3$\alpha$-肉桂酰胺基螺甾烷-5-烯(**1h**)

化合物 **1h** 的合成步骤同 **1e**,酰化试剂为肉桂酸。经重结晶(石油醚:乙酸乙酯=20:1)得白色固体(**1h**),收率 63%。mp. 209.6 ~ 211.6 ℃;$[\alpha]_D^{34}$-105.3 (*c* 0.003, $CHCl_3$);IR (KBr) $\nu_{max}$ 3437 (N-H), 2955, 1670 (C = O), 1628, 1526, 1459, 1063, 985, 768, 718 $cm^{-1}$;$^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$:7.60 (1 H, d, *J* = 15.6, H-3′), 7.51 (2 H, d, H-5′, 9′), 7.39 ~ 7.30 (3 H, m, H-6′, 7′, 8′), 6.38 (1 H,

*d*, *J* = 15.6, H-2′), 5.68 (1 H, d, *J* = 7.2, NH), 5.43 (1 H, d, *J* = 2.0, H-6), 4.42 (1 H, q, *J* = 6.9, H-16), 4.28 (1 H, brs, H-3), 3.47 (1 H, d, H-26α), 3.37 (1 H, t, *J* = 10.8, H-26*β*), 1.06 (3 H, s, H-19), 0.97 (3 H, d, *J* = 6.4, H-21), 0.81 ~ 0.77 (6 H, H-18, H-27); $^{13}$C NMR ($CDCl_3$, 100 MHz) *δ*: (135.04, 129.67, 128.87, 127.90, C-Ph), 164.99 (C=O), 140.90 (CH=), 139.21 (C-5), 123.52 (C-6), 121.13 (CH=), 109.44 (C-22), 80.90 (C-16), 66.98 (C-26), 62.19 (C-17), 56.68 (C-14), 50.53 (C-9), 45.91 (C-3), 41.72 (C-20), 40.37 (C-13), 39.88 (C-12), 37.66 (C-4), 37.25 (C-10), 34.31 (C-1), 32.21 (C-7), 31.94 (C-15), 31.48 (C-8), 31.45 (C-23), 30.41 (C-25), 28.91 (C-24), 26.23 (C-2), 20.66 (C-11), 19.03 (C-19), 17.27 (C-27), 16.41 (C-18), 14.66 (C-21); HRMS (ESI) *m/z* 582.3450 [M + K]$^+$ (calcd for $C_{36}H_{49}NO_3$, 582.3350)。

1.4.10 (25*R*)-3α-水杨酰胺基螺甾烷-5-烯(**1i**)

化合物 **1i** 的合成步骤同 **1e**, 酰化试剂为水杨酸。经柱色谱(石油醚: 乙酸乙酯 = 30∶1)得白色固体(**1i**), 收率 42%。mp. 233.2 ~ 235.0 ℃; [α]$_D^{34}$ -129.3 (*c* 0.003, $CHCl_3$); IR (KBr) $\nu_{max}$ 3450 (N-H), 2951, 1647 (C=O), 1609, 1530, 1494, 1455, 1378, 1255, 1058, 982, 753 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) *δ*: 12.41 (1 H, s, OH), 7.38, 6.84 (2 H, t, *J* = 7.8, 7.6, H-Ph), 7.21, 6.97 (2 H, d, *J* = 8.0, 8.0, H-Ph), 6.41 (1 H, d, *J* = 7.2, NH), 5.52 (1 H, d, *J* = 4.0, H-6), 4.42 (1 H, q, *J* = 7.3, H-16), 4.31 (1 H, brs, H-3), 3.48 (1 H, d, H-26α), 3.38 (1 H, t, *J* = 10.8, H-26*β*), 1.09 (3 H, s, H-19), 0.97 (3 H, d, *J* = 6.8, H-21), 0.81 ~ 0.77 (6 H, H-18, H-27); $^{13}$C NMR ($CDCl_3$, 100 MHz) *δ*: (161.76, 134.17, 125.13, 118.79, 118.72, 114.65, C-Ph), 169.01 (C=O), 139.12 (C-5), 124.03 (C-6), 109.45 (C-22), 80.89 (C-16), 67.00 (C-26), 62.20 (C-17), 56.54 (C-14), 50.80 (C-9), 45.91 (C-3), 41.75 (C-20), 40.37 (C-13), 39.81 (C-12), 37.80 (C-4), 37.26 (C-10), 34.62 (C-1), 32.28 (C-7), 31.96 (C-15), 31.50 (C-23, 8), 30.42 (C-25), 28.93 (C-24), 26.17 (C-2), 20.70 (C-11), 19.01 (C-19), 17.28 (C-27), 16.41 (C-18), 14.67 (C-21); HRMS (ESI) *m/z* 556.3405 [M + Na]$^+$ (calcd for $C_{34}H_{47}NO_4$, 556.3403)。

1.4.11 (25*R*)-3α-呋喃甲酰胺基螺甾烷-5-烯(**1j**)

化合物 **1j** 的合成步骤同 **1e**, 酰化试剂为呋喃甲酸。经柱色谱(石油醚: 乙酸乙酯 = 12∶1)得白色固体(**1j**), 收率 52%。mp. 209.1 ~ 210.7 ℃; [α]$_D^{34}$ -128.0 (*c* 0.004, $CHCl_3$); IR (KBr) $\nu_{max}$ 3425 (N-H), 2956, 1675 (C=O), 1601, 1525, 1477, 1181, 1059, 986, 905, 764 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) *δ*: 7.43 (1 H, s, furyl), 7.07 (1 H, d, *J* = 3.2, furyl), 6.49 ~ 6.46 (1 H, m, furyl), 6.44 (1 H, d, *J* = 8.0, NH), 5.47 (1 H, d, *J* = 4.4, H-6), 4.42 (1 H, q, *J* = 7.5, H-16), 4.31 (1 H, brs, H-3), 3.48 (1 H, d, H-26α), 3.38 (1 H, t, *J* = 10.8, H-26*β*), 1.07 (3 H, s, H-19), 0.98 (3 H, d, *J* = 6.8, H-21), 0.81 ~ 0.77 (6 H, H-18, H-27); $^{13}$C NMR ($CDCl_3$, 100 MHz) *δ*: (148.42, 143.80, 113.95, 112.17, furyl), 157.65 (C=O), 138.95 (C-5), 123.65 (C-6), 109.45 (C-22), 80.93 (C-16), 67.00 (C-26), 62.22 (C-17), 56.60 (C-14), 50.57 (C-9), 45.49 (C-3), 41.74 (C-20), 40.38 (C-13), 39.87 (C-12), 37.69 (C-4), 37.27 (C-10), 34.40 (C-1), 32.22 (C-7), 31.96 (C-15), 31.51 (C-8), 31.49 (C-23), 30.42 (C-25), 28.92 (C-24), 26.39 (C-2), 20.70 (C-11), 19.03 (C-19), 17.27 (C-27), 16.41 (C-18), 14.66 (C-21); HRMS (ESI) *m/z* 530.3248 [M + Na]$^+$ (calcd for $C_{32}H_{45}NO_4$, 530.3246)。

1.4.12 (25*R*)-3α-烟酰胺基螺甾烷-5-烯(**1k**)

化合物 **1k** 的合成步骤同 **1e**, 酰化试剂为烟酸。经柱色谱(石油醚: 乙酸乙酯 = 3∶1)得白色固体(**1k**), 收率 40%。mp. 199.3 ~ 201.0 ℃; [α]$_D^{34}$ -128.5° (*c* 0.004, $CHCl_3$); IR (KBr) $\nu_{max}$ 3444, 2956 (N-H), 1682 (C=O), 1522, 1465, 1262, 1173, 1060, 986, 907 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) *δ*: 8.87 (1 H, s, pyridyl), 8.70 (1 H, d, *J* = 3.6, pyridyl), 8.07 (1 H, d, *J* = 7.6, pyridyl), 7.38 (1 H, t, *J* = 6.0, pyridyl), 6.23 (1 H, d, *J* = 6.8, NH), 5.46 (1 H, d, *J* = 2.8, H-6), 4.41 (1 H, q, *J* = 7.2, H-16), 4.34 (1 H, brs, H-3), 3.47 (1 H, d, H-26α), 3.37 (1 H, t, *J* = 10.8, H-26*β*), 1.07 (3 H, s, H-19), 0.96 (3 H, d, *J* = 6.4, H-21), 0.80 ~ 0.75 (6 H, H-18, H-27); $^{13}$C NMR ($CDCl_3$, 100 MHz) *δ*: (152.21, 147.64, 135.30, 130.83, 123.94, pyridyl), 164.57 (C=O), 139.06 (C-5), 123.73 (C-6), 109.40 (C-22), 80.86 (C-16), 66.96 (C-26), 62.13 (C-17), 56.51 (C-14), 50.73 (C-9), 46.29 (C-3), 41.71

(C-20), 40.34 (C-13), 39.78 (C-12), 37.74 (C-4), 37.30 (C-10), 34.56 (C-1), 32.18 (C-7), 31.91 (C-15), 31.48 (C-8), 31.46 (C-23), 30.39 (C-25), 28.90 (C-24), 26.17 (C-2), 20.67 (C-11), 18.99 (C-19), 17.26 (C-27), 16.39 (C-18), 14.64 (C-21); HRMS (ESI) *m/z* 541.3413 [M + Na]$^+$ (calcd for $C_{33}H_{46}N_2O_3$, 541.3406)。

1.4.13 (25*R*)-3α-丙烯酰胺基螺甾烷-5-烯(**1l**)

化合物 **1l** 的合成步骤同 **1e**,酰化试剂为丙烯酸。经柱色谱(石油醚: 乙酸乙酯 = 6∶1)得白色固体(**1l**),收率 27%。mp. 179.3 ~ 179.9 ℃; $[\alpha]_D^{34}$ -157.3° (*c* 0.003, $CHCl_3$); IR (KBr) $\nu_{max}$ 3442 (N-H), 3298, 2952, 1668 (C = O), 1623, 1548, 1459, 1064, 984, 906 (γ C-H) cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 6.25 (1 H, dd, *J* = 0.8, 1.2, CH = ), 6.07 (1 H, dd, *J* = 10.4, 10.0, $CH_2$ = ), 5.63-5.57 (2 H, m, NH, $CH_2$ = ), 5.40 (1 H, d, *J* = 4.4, H-6), 4.41 (1 H, q, *J* = 7.5, H-16), 4.22 (1 H, brs, H-3), 3.47 (1 H, dd, *J* = 2.0, 2.4, H-26α), 3.37 (1 H, t, *J* = 10.8, H-26*β*), 1.04 (3 H, s, H-19), 0.96 (3 H, d, *J* = 6.8, H-21), 0.80 ~ 0.76 (6 H, H-18, H-27); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 164.62 (C = O), 139.05 (C-5), 131.23 (C-3′), 126.25 (C-2′), 123.50 (C-6), 109.42 (C-22), 80.86 (C-16), 66.94 (C-26), 62.10 (C-17), 56.60 (C-14), 50.47 (C-9), 45.71 (C-3), 41.67 (C-20), 40.32 (C-13), 39.82 (C-12), 37.60 (C-4), 37.12 (C-10), 34.25 (C-1), 32.14 (C-7), 31.89 (C-15), 31.42 (C-8), 31.38 (C-23), 30.37 (C-25), 28.86 (C-24), 26.08 (C-2), 20.62 (C-11), 18.98 (C-19), 17.26 (C-27), 16.39 (C-18), 14.65 (C-21); HRMS (ESI) *m/z* 490.3300 [M + Na]$^+$ (calcd for $C_{30}H_{45}NO_3$, 490.3297)。

1.4.14 (25*R*)-3α-辛酰胺基螺甾烷-5-烯(**1m**)

化合物 **1l** 的合成步骤同 **1e**,酰化试剂为辛酸。经柱色谱(石油醚: 乙酸乙酯 = 3∶1)得白色固体(**1m**),收率 83%。mp. 128.2 ~ 131.1 ℃; $[\alpha]_D^{34}$ -111.3° (*c* 0.003, $CHCl_3$); IR (KBr) $\nu_{max}$ 3431 (N-H), 2949, 1668 (C = O), 1502, 1456, 1382, 1262, 1066, 983, 906, 759 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 5.48 (1 H, d, *J* = 7.6, NH), 5.38 (1 H, d, *J* = 3.6, H-6), 4.41 (1 H, q, *J* = 7.3, H-16), 4.13 (1 H, brs, H-3), 3.47 (1 H, d, H-26α), 3.37 (1 H, t, *J* = 10.8, H-26*β*), 2.13 (2 H, t, *J* = 7.6, $COCH_2$), 1.03 (3 H, s, H-19), 0.97 (3 H, d, *J* = 6.4, H-21), 0.81 ~ 0.78 (6 H, H-18, H-27); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 172.29 (C = O), 139.31 (C-5), 123.30 (C-6), 109.44 (C-22), 80.90 (C-16), 66.99 (C-26), 62.22 (C-17), 56.68 (C-14), 50.69 (C-9), 45.46 (C-3), 41.74 (C-20), 40.38 (C-13), 39.89 (C-12), 37.65 (C-4), 37.28 (C-10), 34.39 (C-1), 32.21 (C-7), 31.95 (C-15), 31.50 (C-8), 31.46 (C-23), 30.42 (C-25), 28.92 (C-24), 26.19 (C-2), 20.68 (C-11), 19.01 (C-19), 17.27 (C-27), 16.41 (C-18), 14.66 (C-21), (37.13, 26.02, 29.19, 29.33, 31.89, 22.77, 14.24, alkyl); HRMS (ESI) *m/z* 540.4408 [M + H]$^+$ (calcd for $C_{37}H_{57}NO_3$, 540.4417)。

1.4.15 (25*R*)-3α-甲磺酰胺基螺甾烷-5-烯(**1n**)

在氮气保护下,将化合物 **4** (0.15 g, 0.36 mmol) 用 12 mL 二氯甲烷搅拌溶解,加入三乙胺(0.10 mL, 0.72 mmol),冰浴下滴加甲磺酰氯 (0.03 mL, 0.43 mmol)。TLC 跟踪反应至完全,反应液经饱和碳酸氢钠溶液洗涤,无水硫酸钠干燥。减压浓缩。经柱色谱(石油醚: 乙酸乙酯 = 3∶1)得白色固体(**1n**),收率 90%。mp. 197.2 ~ 198.1 ℃; $[\alpha]_D^{34}$ -84.7 (*c* 0.003, $CHCl_3$); IR (KBr) $\nu_{max}$ 3296 (N-H), 2963, 1453, 1384, 1321, 1159, 1065, 986, 904, 907, 808 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) δ: 5.39 (1 H, d, *J* = 4.8, H-6), 4.47-4.38 (1 H, m, NH, H-16), 3.78-3.72 (1 H, m, H-3), 3.47 (1 H, dd, *J* = 4.0, 3.2, H-26α), 3.36 (1 H, t, *J* = 10.8, H-26*β*), 2.94 (3 H, s, $CH_3$-S), 1.02 (3 H, s, H-19), 0.97 (3 H, d, *J* = 6.8, H-21), 0.80-0.76 (6 H, H-18, H-27); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 137.77 (C-5), 124.68 (C-6), 109.38 (C-22), 80.85 (C-16), 66.95 (C-26), 62.15 (C-17), 56.53 (C-14), 50.40 (C-9), 50.35 (C-3), 41.81 ($CH_3$), 41.72 (C-20), 40.34 (C-13), 39.77 (C-12), 38.49 (C-4), 37.49 (C-10), 33.66 (C-1), 32.15 (C-7), 31.91 (C-15), 31.49 (C-8), 31.39 (C-23), 30.41 (C-25), 28.92 (C-24), 27.87 (C-2), 20.64 (C-11), 19.06 (C-19), 17.26 (C-27), 16.38 (C-18), 14.65 (C-21); HRMS (ESI) *m/z* 492.3143 [M + H]$^+$ (calcd for $C_{28}H_{45}NO_4S$, 92.3148)。

1.4.16 (25*R*)-3α-对甲苯磺酰胺基螺甾烷-5-烯(**1o**)

化合物 **1o** 的合成步骤同 **1n**,酰化试剂为对甲

苯磺酰氯。经柱色谱(石油醚∶乙酸乙酯 = 8∶1)得白色固体(**1o**),收率 47%。mp. 186.0 ~ 187.7 ℃;$[\alpha]_D^{34}$ -42.7 (*c* 0.003, $CHCl_3$);IR (KBr) $\nu_{max}$ 3288 (N-H), 2937, 1418, 1339, 1162, 1072, 912, 684 $cm^{-1}$;$^1$H NMR ($CDCl_3$, 400 MHz) $\delta$: 7.74, 7.28 (4 H, d, *J* = 7.6, 8.0, H-Ph), 5.20 (1 H, d, *J* = 4.4, H-6), 4.69 (1 H, d, *J* = 8.0, NH), 4.42 (1 H, q, *J* = 7.5, H-16), 3.58 ~ 3.51 (1 H, m, H-3), 3.47 (1 H, dd, *J* = 4.0, 3.6, H-26$\alpha$), 3.37 (1 H, t, *J* = 11, H-26$\beta$), 2.41 (3 H, s, $CH_3$-Ar), 0.97 (3 H, d, *J* = 6.8, H-21), 0.94 (3 H, s, H-19), 0.80 ~ 0.74 (6 H, H-18, H-27);$^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: (143.26, 137.76, 129.74, 127.11, C-Ph), 138.35 (C-5), 124.59 (C-6), 109.38 (C-22), 80.87 (C-16), 66.95 (C-26), 62.16 (C-17), 56.52 (C-14), 50.33 (C-9), 50.06 (C-3), 41.73 (C-20), 40.33 (C-13), 39.77 (C-12), 37.74 (C-4), 37.35 (C-10), 33.71 (C-1), 32.13 (C-7), 31.91 (C-15), 31.50 (C-8), 31.37 (C-23), 30.42 (C-25), 28.93 (C-24), 27.53 (C-2), 21.65 ($CH_3$Ph), 20.62 (C-11), 19.03 (C-19), 17.27 (C-27), 16.37 (C-18), 14.66 (C-21); HRMS (ESI) *m/z* 590.3286 $[M + Na]^+$ (calcd for $C_{34}H_{49}NO_4S$, 590.3280)。

## 2 结果与讨论

所合成的薯蓣皂苷元酰胺类衍生物 **1a ~ 1o**,采用 MTT 法对人皮肤鳞癌细胞 A431 和人肺腺癌细胞 H1975 的抗肿瘤活性进行测定,以及人支气管上皮细胞 HBE 的细胞毒性进行研究。测定结果如表 1 所示。

**表 1 薯蓣皂苷元衍生物的抗肿瘤活性和细胞毒性**

Table 1 Antitumor activities and cytotoxicity of diosgenin derivatives

| Compound | $IC_{50}$ (μM) | | |
|---|---|---|---|
| | A431 | H1975 | HBE |
| **1a** | 40.89 | >40 | >40 |
| **1b** | 42.04 | >40 | >40 |
| **1c** | 41.91 | >40 | >40 |
| **1d** | 41.55 | >40 | >40 |
| **1e** | 42.20 | 36.9 | >40 |
| **1f** | 40.13 | 39.66 | 34.99 |
| **1g** | 44.78 | 36.36 | >40 |
| **1h** | 46.02 | >40 | >40 |
| **1i** | 46.50 | 30.58 | >40 |
| **1j** | 72.36 | >40 | >40 |
| **1k** | 359.4 | >40 | >40 |
| **1l** | 42.55 | 16.63 | >40 |
| **1m** | 41.94 | 33.97 | >40 |
| **1n** | 60.17 | 32.88 | 36.67 |
| **1o** | 44.74 | 25.02 | 24.48 |
| Diosgenin | 64.49 | >40 | 0.0022 |

薯蓣皂苷元酰胺类衍生物的 $IC_{50}$ 值显示,薯蓣皂苷元及其衍生物 **1a ~ 1o** 对 H1975 抑制活性整体上强于 A431。分析 $IC_{50}$ 值,**1j**,**1k** 抗肿瘤活性较弱,大部分衍生物对 A431 的抑制作用强于薯蓣皂苷元,其中 **1f** 抑制作用较强($IC_{50}$ = 40.13 μM)。与薯蓣皂苷元相比 **1e ~ 1g**,**1i**,**1l ~ 1o** 对 H1975 具有好的抑制活性,尤其是 **1l**、**1o**、**1i** 分别含有丙烯酰胺、对甲苯磺酰胺、水杨酰胺基团活性显著强于对照组($IC_{50}$ 分别为 16.63、25.02、30.58 μM)。此外,薯蓣皂苷元酰胺类衍生物除 **1f**、**1n**、**1o**($IC_{50}$ 分别为 34.99、36.67、24.48 μM)外,其余衍生物对 HBE 细胞均显示低毒性。

## 3 结论

本文以薯蓣皂苷元为原料,合成了 15 个新型酰胺类衍生物。所有衍生物的结构经$^{1}$H NMR、$^{13}$C NMR、IR、HRMS 进行鉴定。部分衍生物显示出不同程度的抗肿瘤活性,尤其是含有丙烯酰胺(**1l**)、对甲苯磺酰胺(**1o**)、水杨酰胺基团(**1i**)的化合物($IC_{50}$分别为 16.63、25.02、30.58 μM)与薯蓣皂苷元对照组($IC_{50}$ >40 μM)相比活性较好。除 **1f**、**1n**、**1o** 外的其余衍生物均表现出较低的细胞毒性($IC_{50}$ >40 μM)。当前研究结果对于薯蓣皂苷元的结构修饰具有一定参考价值。同时,对于薯蓣皂苷元 C3-位酰胺类衍生物取代基对于抗肿瘤活性的影响仍有待进一步研究。

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