# 4-S-(5″-烃基-4″-氨基-1″,2″,4″-三唑-3″-基)-4-去氧-4′-去甲基表鬼臼毒素衍生物的合成及抗肿瘤活性

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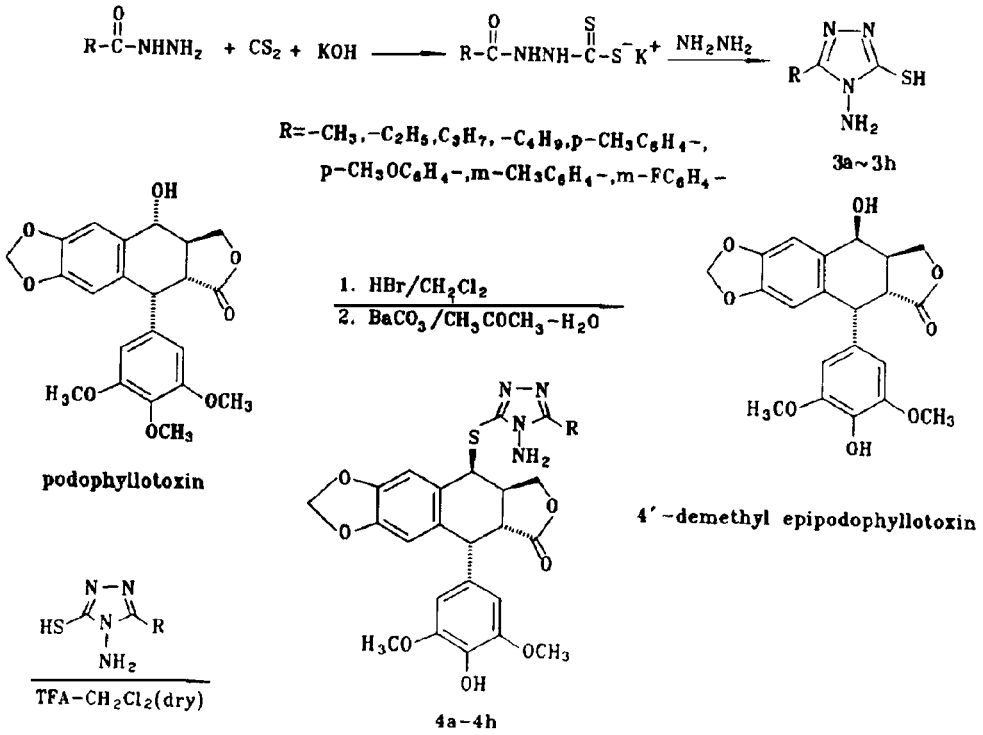
许多有显著抗肿瘤活性的鬼臼毒素类化合物,其母核 C-4 侧链上往往连接有刚性较强的脂环或芳香环结构,而且侧链多含有一定数量的杂原子[1～3]。另外,三氮唑类化合物大都有广泛的生物活性,如抗菌[4～5]、抗病毒[6]、抗肿瘤[7]等,据此,我们设计并合成了 8 个三氮唑杂环取代的表鬼臼毒素衍生物,以期寻找活性高、毒副作用小的鬼臼毒素类药物,并进一步考察此类化合物的构效关系。

合成路线如图 1 所示,三氮唑 **3a～3h** 和 4′-去甲基-表鬼臼毒 **2** 分别按文献[8,9]方法合成;我们选择三氟乙酸作为缩合剂,基于它不仅能催化缩合反应,而且能保护三唑上的氨基官能团,使其不能充当进攻基团;最后一步缩合反应显然经历了一个 $S_{N1}$ 历程,4′-去甲基-表鬼臼毒的 C-4 位上很容易形成一个苄基型碳正离子,由于 C-1 位有庞大的芳环,加之,进攻的基团也较大,可以预料,这个反应有很强的立体选择性,使 C-4β-构型成为主要产物,事实确实如此,在 TLC 上几乎看不到 C-4α-构型的产物。




Scheme 1 Route of synthesis of compounds **4a～4h**.

对表 1 所列的化合物进行了体外人白血病 HL-60、人红白血病 $K_{562}$、人胃癌 BGC-823、人乳腺癌 Bcap、人鼻咽癌 KB 等肿瘤细胞株活性实验,结果(表 2)表明,这些化合物对人红白血病 $K_{562}$ 的活性较强,而对其他肿瘤细胞的活性一般或较弱,对人红白血病 $K_{562}$ 肿瘤细胞来说,三氮唑环上的取代基对标题化合物的抗肿瘤活性影响较大,含烷基的化合物的活性高于含芳香基的化合物。对人白血病 HL-60 肿瘤细胞来说,正好相反;对其他肿瘤细胞来说,三氮唑环上的取代基对抗肿瘤活性影响较小。

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**Tab 1　Physical data of compounds 4a～4h**

| Compd | R | Formula | MP/℃ | $J_{3,4}$ | Elemental analysis / % | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | | H | | N | |
| | | | | | Calc | Found | Calc | Found | Calc | Found |
| **4a** | $-CH_3$ | $C_{24}H_{24}N_4O_7S\cdot 1.5H_2O$ | 161～162 | 3.6 | 47.78 | 47.72 | 4.31 | 4.01 | 8.57 | 8.62 |
| **4b** | $-C_2H_5$ | $C_{25}H_{26}N_4O_7S$ | 167～169 | 3.4 | 50.62 | 50.92 | 4.25 | 4.22 | 8.75 | 8.60 |
| **4c** | $-C_3H_7$ | $C_{26}H_{28}N_4O_7S$ | 168～169 | 3.3 | 51.37 | 51.16 | 4.46 | 4.31 | 8.56 | 8.65 |
| **4d** | $-C_4H_9$ | $C_{27}H_{30}N_4O_7S$ | 165～168 | 3.3 | 52.09 | 52.31 | 4.67 | 4.77 | 8.37 | 8.30 |
| **4e** | *p*-$CH_3C_6H_4$- | $C_{30}H_{28}N_4O_7S\cdot H_2O$ | 200～204 | 4.0 | 59.68 | 59.85 | 4.66 | 4.48 | 9.60 | 9.44 |
| **4f** | *p*-$CH_3OC_6H_4$- | $C_{29}H_{34}N_4O_7S\cdot H_2O$ | 194～197 | – | 58.09 | 58.41 | 4.54 | 4.38 | 9.34 | 9.14 |
| **4g** | *m*-$CH_3C_6H_4$- | $C_{29}H_{34}N_4O_7S\cdot H_2O$ | 118～120 | 4.2 | 59.40 | 59.50 | 4.98 | 5.17 | 9.23 | 9.20 |
| **4h** | *m*-$FC_6H_4$- | $C_{29}H_{34}N_4O_7S$ | 188～190 | 4.1 | 58.78 | 58.66 | 4.25 | 4.49 | 9.45 | 9.08 |

**Tab 2　Inhibition of *in vitro* tumor cell growth by epipodophyllotoxin derivatives (4a～4h)**

| Compd | Concentration/mol·L$^{-1}$ | Inhibition rate / %* | | | | |
|---|---|---|---|---|---|---|
| | | HL-60 | $K_{562}$ | BGC-823 | $Bca_P$ | KB |
| **4a** | $10^{-6}$ | 37.9 | 68.76 | −1.05 | 40.6 | 29.14 |
| | $10^{-5}$ | 48.2 | 69.24 | 11.58 | 42.8 | 53.64 |
| | $10^{-4}$ | 58.6 | 80.24 | 16.84 | 49.6 | 64.90 |
| **4b** | $10^{-6}$ | 48.2 | 76.15 | 1.05 | 37.5 | 23.18 |
| | $10^{-5}$ | 55.1 | 83.10 | 30.53 | 43.6 | 52.98 |
| | $10^{-4}$ | 58.6 | 86.83 | 40.00 | 54.1 | 74.83 |
| **4c** | $10^{-6}$ | 24.1 | 68.32 | −10.53 | 38.3 | −17.88 |
| | $10^{-5}$ | 55.1 | 73.95 | 2.11 | 40.6 | 28.48 |
| | $10^{-4}$ | 55.1 | 86.32 | 20.00 | 51.8 | 29.14 |
| **4d** | $10^{-6}$ | 22.3 | 60.71 | 48.31 | – | 47.02 |
| | $10^{-5}$ | 49.6 | 72.86 | 50.56 | – | 67.55 |
| | $10^{-4}$ | 58.6 | 79.07 | 56.18 | – | 74.83 |
| **4e** | $10^{-6}$ | 63.04 | 35.5 | 40.45 | 31.9 | 25.12 |
| | $10^{-5}$ | 64.39 | 47.83 | 56.18 | 36.2 | 24.64 |
| | $10^{-4}$ | 67.39 | 68.06 | 70.79 | 40.1 | 22.22 |
| **4f** | $10^{-6}$ | 47.82 | 6.07 | 50.56 | 25.1 | 8.21 |
| | $10^{-5}$ | 47.82 | 45.23 | 51.69 | 28.5 | 19.32 |
| | $10^{-4}$ | 76.08 | 64.88 | 82.02 | 36.0 | 25.60 |
| **4g** | $10^{-6}$ | 43.47 | 14.09 | 64.04 | 23.1 | 31.88 |
| | $10^{-5}$ | 63.04 | 26.30 | 66.29 | 35.3 | 35.75 |
| | $10^{-4}$ | 67.39 | 57.23 | 69.27 | 39.4 | 49.76 |
| **4h** | $10^{-6}$ | 41.3 | 51.01 | 43.82 | 26.6 | 17.39 |
| | $10^{-5}$ | 50.0 | 53.61 | 61.80 | 28.6 | 20.29 |
| | $10^{-4}$ | 56.5 | 76.16 | 65.17 | 35.9 | 38.16 |

a) Results obtained after 72 h; b) – No activity.

## 实　验　部　分

熔点在 Kofler 显微熔点仪上测定(温度未校正); IR 在 NICOLET-5DX 型红外光谱仪上测定(KBr 压片); $^1$HNMR 在 Bruker-80A 型核磁共振仪上测定,TMS 内标;元素分析在 Carlo-Erba 元素自动分析仪上测定;旋光在 J-20C 型分光偏振仪上测定。

**4a～4h** 的合成通法

4′-去甲基表鬼臼毒 **2**(200 mg,0.5 mmol)溶于干燥的二氯甲烷(8 ml)中,冰盐浴至 −10℃,在搅拌下加入三氮唑 **3**(0.5 mmol),然后,滴入几滴 $CF_3COOH$,搅拌 1～3 h,反应完全后(TLC 检测),减压蒸去溶剂,残留物经乙醇重结晶或硅胶柱分离得产物 **4**。它们的波谱数据如下:

**4a**　收率:89%,mp 161℃ ～ 162℃,$[\alpha]_{20}^{D}$ −5.04°; IR(KBr): 3360 ～ 3008(b,-$NH_2$,-OH), 1784.1, 1671.1, 1516.3, 1483.1, 1229.2, 1191.8, 1115.5, 1034.5, 935.33 cm$^{-1}$; $^1$HNMR(acetone-$d_6$): 7.02(s, 1H, 5-H), 6.51(s, 1H, 8-H), 6.36(s,

2H,2′-H,6′-H),6.00(s,2H,$OCH_2O$),5.43(d,1H,J=3.6 Hz,4-H),4.56(d,1H,J=4.0 Hz,1-H),3.97～4.4(m,2H,11-H),3.71(s,6H,3′-$OCH_3$,5′-$OCH_3$),3.0～3.3(m,2H,2-H,3-H),2.6(t,2H,-$NH_2$),1.9(s,3H,-$CH_3$)。

**4b** 收率:92%,mp 167℃～169℃,$[\alpha]_{20}^{D}$ +46.2°;IR(KBr):3346.1,3310.9(双峰,-$NH_2$),3212.5～3135(b,OH),1784.1,1673.41,1610.7,1516.7,1483.3,1232.7,1192.5,1114.1,1036.2,937.68 $cm^{-1}$;$^1$HNMR(acetone-$d_6$):7.04(s,1H,5-H),6.51(s,1H,8-H),6.38(s,2H,2′-H,6′-H),6.01(s,2H,$OCH_2O$),5.46(d,1H,J=3.4 Hz,4-H),4.60(d,1H,J=4.5 Hz,1-H),4.0～4.4(m,2H,11-H),3.71(s,6H,3′-$OCH_3$,5′-$OCH_3$),3.1～3.5(m,2H,2-H,3-H),2.6(t,2H,-$NH_2$),1.76(q,2H,-$CH_2$),0.96(t,3H,-$CH_3$)。

**4c** 收率:89%,mp 168℃～169℃,$[\alpha]_{20}^{D}$ +1.97°;IR(KBr):3346.1,3310.9(双峰,-$NH_2$),3212.5(b,-OH),1785.1,1671.7,1611.9,1517.3,1483.4,1225.8,1192.0,1035.7,937.23 $cm^{-1}$;$^1$HNMR(acetone-$d_6$):7.04(s,1H,5-H),6.51(s,1H,8-H),6.36(s,2H,2′-H,6′-H),6.01(s,2H,$OCH_2O$),5.40(d,1H,J=3.3 Hz,4-H),4.60(d,1H,J=4.4 Hz,1-H),3.95～4.30(m,2H,11-H),3.70(s,6H,3′-$OCH_3$,5′-$OCH_3$),3.2～3.6(m,4H,2-H,3-H,$CH_2$),2.5～2.9(m,4H,-$NH_2$,$CH_2$),1.76(q,2H,-$CH_2$),1.27(t,3H,-$CH_3$)。

**4d** 收率:76%,mp 165℃～168℃,$[\alpha]_{20}^{D}$ −3.46°;IR(KBr):3367.2,3360～3212.5(双峰,-$NH_2$),1780.9,1670.6,1482.6,1226.7,1191.2,1115.2,1035.0,936.36 $cm^{-1}$;$^1$HNMR(acetone-$d_6$):7.04(s,1H,5-H),6.51(s,1H,8-H),6.38(s,2H,2′-H,6′-H),6.01(s,2H,$OCH_2O$),5.41(d,1H,J=3.4 Hz,4-H),4.59(d,1H,J=4.4 Hz,1-H),4.10～4.40(m,2H,11-H),3.71(s,6H,3′-$OCH_3$,5′-$OCH_3$),3.3～3.4(m,2H,2-H,3-H),2.62(t,2H,-$NH_2$),1.2～1.9(m,6H,-$CH_2CH_2CH_2$-),0.95(t,3H,-$CH_3$)。

**4e** 收率:85%,mp 200℃～204℃,$[\alpha]_{20}^{D}$ −202.6°;IR(KBr):3430.5,3318,3170.3～3149.2(双峰,-NH2),1759.1,1614.0,1456.0,1218.7,1118.9,1032.7,921.22 $cm^{-1}$;$^1$HNMR(CDCl$_3$):7.86(d,2H,J=7.8 Hz,2″-H,6″-H),7.33(d,2H,J=7.8 Hz,3″-H,5″-H),6.96(s,1H,5-H),6.51(s,1H,8-H),6.33(s,2H,2′-H,6′-H),5.98(s,2H,$OCH_2O$),5.59(d,1H,J=4.0 Hz,4-H),4.4～4.8(m,4H,1-H,11-H,4′-OH),4.01(m,1H,2-H),3.81(s,6H,3′-$OCH_3$,5′-$OCH_3$),3.63(m,1H,3-H),3.26(s,2H,-$NH_2$),2.44(s,3H,$CH_3$)。

**4f** 收率:88%,mp 194℃～197℃,$[\alpha]_{20}^{D}$ +364.8°;IR(KBr):3430.5～3156.2(b,-$NH_2$,-OH),1761.7,1613.2,1515.4,1481.0,1243.9,1118.5,1032.2,921.79 $cm^{-1}$;$^1$HNMR(CDCl$_3$):7.97(d,2H,J=8.5 Hz,2″-H,6″-H),7.02(d,2H,J=8.5 Hz,3″-H,5″-H),7.01(s,1H,5-H),6.51(s,1H,8-H),6.33(s,2H,2′-H,6′-H),5.98(s,2H,$OCH_2O$),5.56(s,1H,4′-OH),4.4～4.9(m,4H,4-H,1-H,11-H),4.05(m,1H,2-H),3.88(s,3H-$OCH_3$),3.81(s,6H,3′-$OCH_3$,5′-$OCH_3$),3.56(m,1H,3-H),3.29(s,2H,-$NH_2$)。

**4g** 收率:85%,mp 118℃～120℃,$[\alpha]_{20}^{D}$ −214.0°;IR(KBr):3353.1(b,-$NH_2$,-OH),1763.8,1611.6,1517.4,1481.5,1223.9,1112.6,1035.9,932.43 $cm^{-1}$;$^1$HNMR(CDCl$_3$):7.6～7.2(m,4H,苯环氢),7.05(s,1H,5-H),6.50(s,1H,8-H),6.26(s,2H,2′-H,6′-H),6.02(s,2H,$OCH_2O$),5.42(d,1H,J=4.21 Hz,4-H),4.6～4.2(m,3H,1-H,11-H),3.63(s,6H,3′-$OCH_3$,5′-$OCH_3$),3.36(s,3H,$CH_3$),5.03(s,1H,4′-OH),3.25(s,2H,-$NH_2$),3.15～3.05(m,2H,2-H,3-H)。

**4h** 收率:82%,mp 188℃～190℃,$[\alpha]_{20}^{D}$ −108.2°;IR(KBr):3353.1(b,-$NH_2$,-OH),1764.1,1611.4,151.8,1480.9,1224.6,1112.0,1036.2,932.15 $cm^{-1}$;$^1$HNMR(acetone-$d_6$):8.0～7.4(m,4H,苯环氢),7.12(s,1H,5-H),6.53(s,1H,8-H),6.41(s,2H,2′-H,6′-H),6.01(s,2H,$OCH_2O$),5.55(s,1H,4′-OH),4.64(d,1H,J=4.1 Hz,4-H),4.32(d,1H,J=6.7 Hz,1-H),3.68(s,6H,3′-$OCH_3$,5′-$OCH_3$),3.66～3.20(m,4H,11-H,2-H,3-H),3.05(2H,-$NH_2$)。

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关键词 鬼臼毒素;1,2,4三唑;抗肿瘤活性

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# SYNTHESIS AND ANTITUMOR ACTIVITIES OF 4β-S-(5″-ALKYL-4″-AMINO-1″,2″,4″-TRIAZOLE-3″-YL)-4-DEOXY-4′-O-DEMETHYL-EPIPODOPHYLLOTOXIN DERIVATIVES

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**ABSTRACT** **AIM:** In order to search for podophyllotoxin analogue agents with fewer side effects and improved activity, the podophyllotoxin derivatives are to be synthesized. **METHODS:** Eight 4′-demethyl-podophyllotoxin analogues with 4β-S-triazoles have been synthesized from 4′-demethyl-podophyllotoxin. **RESULTS:** Eight 4′-demethyl-podophyllotoxin derivatives possessing 4β-S-triazoles have been synthesized and their antitumor activities were screened *in vitro* against HL-60, BGC-823, BcaP, KB and $K_{562}$ cells. **CONCLUSION:** The results indicated that these compounds showed high biological activity only towards $K_{562}$ cells.

**KEY WORDS** podophyllotoxin analogues; triazoles; antitumor activity