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# 基于薯蓣皂苷元催化合成*N*-甲基吲哚孕烯醇酮化合物及其抗肿瘤活性

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**摘要**　利用*N*-甲基吲哚对类固醇药物的前驱体16-脱氢孕烯醇酮乙酸酯(16-DPA)的D环C16位进行修饰，采用$ZrCl_4$-乙酸乙酯廉价催化体系，合成了16个3*β*-乙酰氧基-16*α*-3′-吲哚孕烯醇酮化合物和6个3*β*-羟基-16*α*-3′-吲哚孕烯醇酮衍生物．该方法具有收率高、立体选择性好和底物适应性强等优点．通过噻唑蓝(MTT)比色法测试了22个化合物对三阴性乳腺癌细胞(MDA-MB-231)的抗肿瘤活性．初步测试结果表明，3*β*-乙酰氧基-16*α*-3′-吲哚孕烯醇酮化合物**6h**和**6i**对MDA-MB-231癌细胞有较好的抑制活性，其半数抑制浓度($IC_{50}$)分别为18.07和23.22 μmol/L；而化合物**7a**~**7f**均对MDA-MB-231癌细胞有较好的抑制活性，其中化合物**7e**的抗肿瘤活性最好，其$IC_{50}$为12.50 μmol/L．目标化合物为药物筛选提供了一定的参考．

**关键词**　16-脱氢孕烯醇酮乙酸酯；孕烯醇酮；*N*-甲基吲哚；抗肿瘤活性
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# Catalytic Synthesis of *N*-methylindopregnenolone Compounds Based on Diosgenin and Their Anti-tumor Activity

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**Abstract**　The D-ring C16 position of 16-dehydropregnenolone acetate (16-DPA), a precursor of steroidal drugs, was modified using *N*-methylindole, and the inexpensive catalytic system of $ZrCl_4$-ethyl acetate was employed to synthesize sixteen (3*β*-acetyloxy-16*α*-3′-indolopregnenolone compounds) as well as to synthesize six 3*β*-hydroxy-16*α*-3′-indolone pregnenolone derivatives. The method has the advantages of high yield, good stereoselectivity and substrate adaptability. Twenty-two compounds were tested for antitumor activity in triple-negative breast cancer cells (MDA-MB-231) by thiazolyl blue (MTT) assay. The preliminary test results showed that among the 3*β*-acetoxy-16*α*-3′-indolopregnenolone compounds, compounds **6h** and **6i** had better cancer inhibitory activities against MDA-MB-231 cancer cells with median inhibition concentration ($IC_{50}$) of 18.07 and 23.22 μmol/L, respectively, whereas all of compounds **7a**—**7f** had better cancer inhibitory activities against MDA-MB-231 cancer cells, among which compound **7e** showed the best antitumor activity with an $IC_{50}$ of 12.50 μmol/L. These compounds provide some references for drug screening.

**Keywords**　16-Dehydropregnenolone acetate; Pregnenolone; *N*-methylindole; Anti-tumor activity

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甾体化合物广泛存在于自然界中，并表现出抗炎和抗肿瘤等生物活性. 基于此，类固醇结构的化学修饰作为药物设计的基本策略被广泛用于药物化学领域[1]. 近年来，由于类固醇药物前体16-脱氢孕烯醇乙酸酯(16-DPA)的D环含有高活性的α，β不饱和酮结构而被重点修饰，包括引入噁唑环[2,3]、咪唑[4~6]、吡唑[7,8]、噻唑[9]、吡啶[10~13]、甲基[14]和哌啶[15]等基团，所得化合物表现出抗肿瘤、抗炎、降病毒、$C_{17(20)}$-裂解酶抑制剂和17α-羟基酶抑制剂等生物活性.

吲哚是天然产物中重要的杂环化合物，其结构作为核心药效基团出现在诸多生物碱中(如色氨酸和植物激素等). 吲哚具有较低的毒性、较高的生物相容性和抑菌、抗炎、抗肿瘤及抗氧化等多种药理活性. 吲哚衍生物在抗肿瘤药物研发方面具有重要地位，如长春瑞滨(Vinorelbine)[16]、芦卡帕利(Rucaparib)[17]及褪黑素(Melatonin)[18]等以吲哚为骨架的临床药物，具有药效良好且愈后副作用小、选择性强等特点. 在吲哚C3位引入一些杂环基团可以改善重要的药学参数，以增强其成药性[19].

鉴于吲哚与甾体均具有潜在的抗肿瘤活性，以及16-DPA的α，β不饱和酮的缺电子性和吲哚的富电子性，因此将吲哚通过迈克尔加成反应修饰在16-DPA的C16位，可能使新合成的甾体化合物有较强的抗肿瘤活性. 本文用16-DPA与3′-吲哚在廉价催化剂$ZrCl_4$作用下反应，以高收率且立体专一地获得16个3′吲哚孕烯醇酮衍生物以及6个C3位乙酰基水解产物；并通过噻唑蓝(MTT)法测试了22个化合物对三阴性乳腺癌细胞(MDA-MB-231)的抗肿瘤活性.

## 1 实验部分

### 1.1 试剂与仪器

吲哚(**1a**，纯度99%)、5-氟-吲哚(**1b**，纯度97%)、5-氯-吲哚(**1c**，纯度98%)、5-溴-吲哚(**1d**，纯度97%)、5-甲基-吲哚(**1e**，纯度98%)、5-甲氧基-吲哚(**1f**，纯度99%)、5-氰基-吲哚(**1g**，纯度99%)、1*H*-吲哚-5羧酸(**1h**，纯度98%)、4-甲基-吲哚(**1i**，纯度98%)、4-甲氧基-吲哚(**1j**，纯度98%)、6-甲基-吲哚(**1k**，纯度98%)、6-甲氧基-吲哚(**1l**，纯度98%)、7-甲基-吲哚(**1m**，纯度98%)、7-甲氧基-吲哚(**1n**，纯度97%)、5-硝基-吲哚(**1o**，纯度98%)、四氯化锆($ZrCl_4$，纯度98%)、*N*-苯基吲哚(纯度98%)、苄基三乙基氯化铵(TEBA，纯度99%)、三氯化铝(纯度99%)和高碘酸钠(纯度99%)，萨恩化学技术有限公司(上海)；甲醇(纯度99.5%)和氢氧化钠(纯度96%)，天津欧博凯化工有限公司；乙酸酐(纯度98.5%)和高锰酸钾，国药集团化学试剂有限公司；薯蓣皂苷元(**4**)，汉中济康生物科技有限公司提供；其它试剂均为分析纯.

AVANCE III-400型核磁共振波谱仪和AVANCE NEO-600型核磁共振波谱仪(NMR)，以$CDCl_3$为溶剂，TMS为内标，德国Bruker公司；VION IMS QTOF型高分辨质谱仪(HRMS)，美国Waters公司；D8 QUEST型X射线单晶衍射仪(XRD)，德国Bruker公司；XT5型显微熔点测试仪，北京科技电光仪器厂；DH5000B型电热恒温培养箱，天津泰斯特仪器有限公司.

### 1.2 实验过程

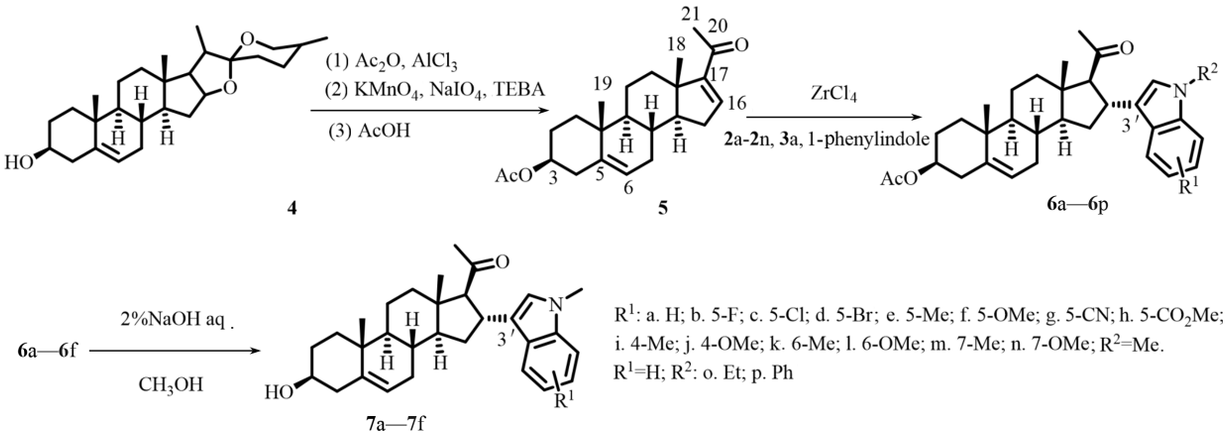
1.2.1 化合物**6**a~**6**p和**7**a~**7**f的合成 合成路线如Scheme 1和Scheme 2所示.


**1**a—**1**o　　**2**a—**2**o, yield 99%　　**1**a　　**3**a, yield 99%

R: a. H; b. 5-Cl; d. 5-Br; e. 5-Me; f. 5-OMe; g. 5-CN; h. 5-$CO_2$Me(**1**f.: $CO_2$H); i. 4-Me; j. 4-OMe; k. 6-Me; l. 6-OMe; m. 7-Me; n. 7-OMe; o. 5-$NO_2$

**Scheme 1 Synthesis of *N*-alkyl indoles**

将1 mmol 16-DPA(**5**)与0.1 mmol催化剂$ZrCl_4$置于50 mL圆底烧瓶中，加入5 mL乙酸乙酯和2 mmol取代吲哚(**2**a~**2**n)或化合物**3**a(*N*-苯基吲哚)，于50 ℃反应10 h，用薄层色谱(TLC)监测反应完成. 粗产品经硅胶柱层析色谱纯化($V_{石油醚}$∶$V_{乙酸乙酯}$=10∶1)，得到化合物**6**a~**6**p.




**Scheme 2　Synthesis of 16-3′ indole pregnenolone derivatives**

在烧瓶中加入0.1 mmol化合物**6**a~**6**f、15 mL甲醇和1 mL质量分数为2%的氢氧化钠水溶液. 将混合物在室温下搅拌12 h. 将反应溶液倒入100 mL冰水中，随后用乙酸乙酯萃取(30 mL×3). 将有机相用无水硫酸镁干燥，然后在真空中除去溶剂，得到化合物**7**a~**7**f. 化合物**6**a~**6**p和**7**a~**7**f的理化性质和表征数据分别列于表1和表2.

**Table 1　Appearance, melting points, yields and HRMS data of compounds 6a—5p and 7a—6f**

| Compd. | Appearance | Yield(%) | m. p./℃ | HRMS, *m/z* |
|---|---|---|---|---|
| **6**a | White solid | 90 | 203—205 | 488.3156[M+H]$^+$ |
| **6**b | White solid | 74 | 190—192 | 506.3051[M+H]$^+$ |
| **6**c | White solid | 71 | 186—198 | 522.2765[M+H]$^+$ |
| **6**d | White solid | 73 | 182—184 | 566.2260[M+H]$^+$ |
| **6**e | White solid | 92 | 215—217 | 502.3294[M+H]$^+$ |
| **6**f | White solid | 96 | 182—184 | 518.3250 [M+H]$^+$ |
| **6**g | White solid | 53 | 206—208 | 513.3117[M+H]$^+$ |
| **6**h | White solid | 80 | 223—224 | 546.3205[M+H]$^+$ |
| **6**i | White solid | 48 | 272—274 | 502.3304[M+H]$^+$ |
| **6**j | White solid | 15 | 215—217 | 518.3259[M+H]$^+$ |
| **6**k | White solid | 93 | 209—211 | 502.3299[M+H]$^+$ |
| **6**l | White solid | 92 | 200—202 | 518.3255[M+H]$^+$ |
| **6**m | White solid | 96 | 220—222 | 502.3304[M+H]$^+$ |
| **6**n | White solid | 98 | 205—207 | 518.3254[M+H]$^+$ |
| **6**o | White solid | 88 | 156—158 | 502.3307[M+H]$^+$ |
| **6**p | Pale yellow solid | 51 | 288—290 | 550.3308[M+H]$^+$ |
| **7**a | White solid | 99 | 150—152 | 446.3054[M+H]$^+$ |
| **7**b | White solid | 99 | 145—147 | 464.2973[M+H]$^+$ |
| **7**c | White solid | 99 | 138—140 | 480.2671[M+H]$^+$ |
| **7**d | White solid | 98 | 135—137 | 524.2170[M+H]$^+$ |
| **7**e | White solid | 99 | 172—174 | 460.3312[M+H]$^+$ |
| **7**f | White solid | 99 | 164—166 | 476.3174[M+H]$^+$ |

**Table 2　$^1$H NMR and $^{13}$C NMR data of compounds 6a—6p and 7a—7f**

| Compd. | $^1$H NMR(400 MHz), $\delta$ | $^{13}$C NMR(101 MHz), $\delta$ |
|---|---|---|
| **6**a | 7.63(d, *J*=7.9 Hz, 1H), 7.31—7.25(m, 1H), 7.21(t, *J*=7.6 Hz, 1H), 7.09(t, *J*=7.4 Hz, 1H), 6.80(s, 1H), 5.39(d, *J*=5.1 Hz, 1H), 4.63(t, *J*=10.6, 6.4, 4.1 Hz, 1H), 4.09(d, *J*=12.8, 9.6, 3.6 Hz, 1H), 3.71(s, 3H), 2.91(d, *J*=9.4 Hz, 1H), 2.34(dd, *J*=9.1, 4.0 Hz, 2H), 2.05(d, *J*=7.9 Hz, 6H), 2.03—1.11(m, 15H), 1.07(s, 3H), 0.82(s, 3H) | 209.23, 170.73, 139.83, 137.60, 126.74, 125.49, 122.44, 121.59, 119.72, 118.73, 109.43, 73.97, 71.42, 56.74, 50.09, 45.62, 39.05, 38.19, 37.11, 36.76, 34.07, 33.31, 32.67, 32.35, 31.96, 31.89, 27.86, 21.59, 21.07, 19.46, 13.92 |

Continued

| Compd. | $^1$H NMR(400 MHz), $\delta$ | $^{13}$C NMR(101 MHz), $\delta$ |
|---|---|---|
| **6**b | 7.28—7.21(m, 1H), 7.15(d, *J*=8.9, 4.3 Hz, 1H), 6.94(t, *J*=9.0, 2.5 Hz, 1H), 6.83(s, 1H), 5.38(d, *J*=4.8 Hz, 1H), 4.68—4.56(m, 1H), 4.08—3.97(m, 1H), 3.69(s, 3H), 2.85(d, *J*=9.4 Hz, 1H), 2.34(d, *J*=7.3 Hz, 2H), 2.05(d, *J*=9.5 Hz, 6H), 2.02—1.08(m, 15H), 1.05(s, 3H), 0.80(s, 3H) | 208.85, 170.68, 139.79, 136.15, 128.56, 126.39, 124.43, 122.36, 122.18, 119.57, 112.20, 110.86, 73.91, 71.27, 56.63, 49.98, 45.52, 38.96, 38.15, 37.05, 36.73, 33.65, 33.43, 32.84, 32.21, 31.91, 31.88, 27.82, 21.56, 21.00, 19.43, 13.85 |
| **6**c | 7.71(d, *J*=1.8 Hz, 1H), 7.30—7.23(m, 1H), 7.11(d, *J*=8.7 Hz, 1H), 6.78(s, 1H), 5.38(d, *J*=5.0 Hz, 1H), 4.68—4.55(m, 1H), 4.02(t, *J*=10.1, 4.2 Hz, 1H), 3.68(s, 3H), 2.83(d, *J*=9.5 Hz, 1H), 2.37—2.26(m, 2H), 2.06(d, *J*=13.8 Hz, 6H), 2.02—1.07(m, 15H), 1.05(s, 3H), 0.80(s, 3H) | 208.87, 170.69, 139.80, 135.93, 127.83, 126.61, 124.60, 122.37, 121.88, 119.56, 119.09, 110.41, 73.92, 71.29, 56.66, 49.99, 45.54, 38.97, 38.15, 37.06, 36.73, 33.70, 33.39, 32.86, 32.23, 31.92, 31.88, 27.82, 21.57, 21.01, 19.43, 13.85 |
| **6**d | 7.71(d, *J*=1.8 Hz, 1H), 7.30—7.23(m, 1H), 7.11(d, *J*=8.7 Hz, 1H), 6.78(s, 1H), 5.38(d, *J*=5.0 Hz, 1H), 4.68—4.55(m, 1H), 4.02(t, *J*=10.1, 4.2 Hz, 1H), 3.68(s, 3H), 2.83(d, *J*=9.5 Hz, 1H), 2.37—2.26(m, 2H), 2.06(d, *J*=13.8 Hz, 6H), 2.02—1.07(m, 15H), 1.05(s, 3H), 0.80(s, 3H) | 208.85, 170.68, 139.79, 136.15, 128.56, 126.39, 124.43, 122.36, 122.18, 119.57, 112.20, 110.86, 73.91, 71.27, 56.63, 49.98, 45.52, 38.96, 38.15, 37.05, 36.73, 33.65, 33.43, 32.84, 32.21, 31.91, 31.88, 27.82, 21.56, 21.00, 19.43, 13.85 |
| **6**e | 7.41—7.37(m, 1H), 7.16(d, *J*=8.3 Hz, 1H), 7.04(d, *J*=8.4, 1.6 Hz, 1H), 6.75(s, 1H), 5.39(d, *J*=5.0 Hz, 1H), 4.63(t, *J*=10.9, 6.9, 4.2 Hz, 1H), 4.06(t, *J*=9.4, 5.3 Hz, 1H), 3.68(s, 3H), 2.89(d, *J*=9.4 Hz, 1H), 2.47(s, 3H), 2.35(d, *J*=7.4 Hz, 2H), 2.06(d, *J*=9.4 Hz, 6H), 2.03—1.09(m, 15H), 1.06(s, 3H), 0.82(s, 3H) | 209.25, 170.70, 139.81, 135.98, 127.85, 127.04, 125.39, 123.20, 122.45, 119.33, 119.23, 109.10, 73.95, 71.27, 56.60, 50.08, 45.54, 39.02, 38.18, 37.08, 36.75, 33.99, 33.48, 32.68, 32.30, 31.92, 27.84, 21.76, 21.56, 21.04, 19.45, 13.91 |
| **6**f | 7.15(d, *J*=8.8 Hz, 1H), 7.07(d, *J*=2.4 Hz, 1H), 6.87(dd, *J*=8.8, 2.4 Hz, 1H), 6.77(s, 1H), 5.38(d, *J*=4.9 Hz, 1H), 4.63(d, *J*=15.9, 10.2, 4.2 Hz, 1H), 4.05(t, *J*=9.7, 4.4 Hz, 1H), 3.87(s, 3H), 3.68(s, 3H), 2.86(d, *J*=9.3 Hz, 1H), 2.34(d, *J*=7.3 Hz, 2H), 2.06(d, *J*=10.4 Hz, 6H), 2.03—1.08(m, 15H), 1.06(s, 3H), 0.81(s, 3H) | 209.29, 170.72, 153.52, 139.82, 132.94, 127.07, 125.85, 122.39, 119.40, 111.59, 110.08, 101.77, 73.92, 71.56, 56.79, 56.09, 50.13, 45.61, 39.07, 38.18, 37.08, 36.75, 33.85, 33.22, 32.84, 32.38, 31.99, 31.93, 27.84, 21.57, 21.05, 19.46, 13.94 |
| **6**g | 7.91(d, *J*=1.5 Hz, 1H), 7.37(d, *J*=8.6, 1.5 Hz, 1H), 7.25(d, *J*=8.3 Hz, 1H), 6.88(s, 1H), 5.33(d, *J*=4.9 Hz, 1H), 4.58(t, *J*=10.8, 5.4 Hz, 1H), 4.02(t, 1H), 3.71(s, 3H), 2.79(d, *J*=9.4 Hz, 1H), 2.33—2.23(m, 2H), 2.02(d, *J*=17.8 Hz, 6H), 1.98—1.05(m, 15H), 1.02(s, 3H), 0.77(s, 3H) | 208.37, 170.57, 139.79, 138.84, 127.33, 126.72, 125.27, 124.54, 122.16, 121.34, 121.12, 110.15, 101.67, 73.84, 71.50, 56.67, 49.86, 45.54, 38.94, 38.09, 36.99, 36.66, 33.50, 33.31, 32.87, 32.08, 31.86, 31.78, 27.76, 21.49, 20.97, 19.36, 13.76 |
| **6**h | 8.39(d, *J*=1.5 Hz, 1H), 7.89(dd, *J*=8.6, 1.6 Hz, 1H), 7.23(d, *J*=8.7 Hz, 1H), 6.83(s, 1H), 5.39—5.33(m, 1H), 4.61(q, *J*=11.4, 9.2 Hz, 1H), 4.10(td, *J*=10.2, 3.8 Hz, 1H), 3.93(s, 3H), 3.71(s, 3H), 2.86(d, *J*=9.5 Hz, 1H), 2.32(d, *J*=7.3 Hz, 2H), 2.07(s, 3H), 2.03(s, 3H), 1.98—1.05(m, 15H), 1.04(s, 3H), 0.80(s, 3H) | 208.71, 170.61, 168.33, 139.90, 139.66, 126.46, 126.44, 123.02, 122.68, 122.35, 121.61, 120.64, 108.95, 73.86, 71.22, 56.51, 51.94, 49.95, 45.43, 38.90, 38.10, 36.99, 36.67, 33.62, 33.54, 32.81, 32.11, 31.85, 31.83, 27.77, 21.50, 20.95, 19.38, 13.81 |
| **6**i | 7.12—7.04(m, 2H), 6.87—6.80(m, 1H), 6.76(s, 1H), 5.33(d, *J*=5.0 Hz, 1H), 4.61(d, *J*=12.0, 8.3, 4.2 Hz, 1H), 4.41—4.32(t, 1H), 3.70(s, 3H), 2.92(d, *J*=9.6 Hz, 1H), 2.77(s, 3H), 2.32(d, *J*=8.1 Hz, 2H), 2.16(s, 3H), 2.04(s, 3H), 2.01—1.07(m, 15H), 1.05(s, 3H), 0.84(s, 3H) | 208.88, 170.68, 139.68, 137.77, 131.34, 126.19, 123.98, 122.44, 121.81, 121.43, 120.82, 107.12, 73.94, 70.36, 55.05, 50.11, 45.11, 39.18, 38.17, 37.22, 37.12, 36.73, 34.62, 32.89, 32.18, 31.73, 27.85, 21.55, 21.05, 20.61, 19.45, 14.00 |
| **6**j | 7.09(d, *J*=15.1, 8.0 Hz, 1H), 6.86(d, *J*=8.2, 6.5 Hz, 1H), 6.68(s, 1H), 6.46(dd, *J*=18.9, 7.8 Hz, 1H), 5.38(dd, *J*=13.0, 5.1 Hz, 1H), 4.68—4.55(m, 1H), 4.15(t, *J*=11.9, 5.9 Hz, 1H), 3.92(s, *J*=4.9 Hz, 3H), 3.66(s, *J*=3.8 Hz, 3H), 2.95(d, *J*=23.6, 10.6 Hz, 1H), 2.36—2.24(m, 2H), 2.07(s, 3H), 2.04(s, *J*=1.5 Hz, 3H), 2.01—1.09(m, 15H), 1.05(s, 3H), 0.83(s, 3H) | 209.99, 170.72, 154.55, 139.89, 139.53, 124.66, 122.64, 119.57, 118.55, 116.99, 102.76, 99.01, 74.04, 70.22, 67.29, 55.45, 50.27, 45.39, 39.20, 38.24, 37.14, 36.82, 35.04, 33.12, 32.90, 32.34, 31.80, 31.07, 27.89, 21.58, 21.07, 19.50, 14.08 |

Continued

| Compd. | $^1$H NMR(400 MHz), $\delta$ | $^{13}$C NMR(101 MHz), $\delta$ |
|---|---|---|
| **6k** | 7.50(d, *J*=8.1 Hz, 1H), 7.06(s, 1H), 6.93(d, *J*=8.1 Hz, 1H), 6.72(s, 1H), 5.39(d, *J*=5.0 Hz, 1H), 4.69—4.57(m, 1H), 4.05(td, *J*=10.2, 3.8 Hz, 1H), 3.67(s, 3H), 2.89(d, *J*=9.4 Hz, 1H), 2.49(s, 3H), 2.38—2.27(m, 2H), 2.05(d, *J*=1.6 Hz, 6H), 2.02—1.09(m, 15H), 1.06(s, 3H), 0.81(s, 3H) | 209.22, 170.68, 139.82, 138.04, 131.44, 124.88, 124.58, 122.44, 120.46, 119.58, 119.36, 109.44, 73.97, 71.40, 56.70, 50.10, 45.60, 39.05, 38.19, 37.11, 36.75, 34.17, 33.30, 32.54, 32.32, 31.96, 31.87, 27.85, 21.93, 21.56, 21.06, 19.44, 13.90 |
| **6l** | 7.52(d, *J*=8.6 Hz, 1H), 6.84—6.74(m, 2H), 6.72(s, 1H), 5.42(d, *J*=5.0 Hz, 1H), 4.66(d, *J*=6.4 Hz, 1H), 4.08(td, *J*=9.9, 4.3 Hz, 1H), 3.91(s, 3H), 3.68(s, 3H), 2.90(d, *J*=9.3 Hz, 1H), 2.38(d, *J*=7.3 Hz, 2H), 2.09(d, *J*=7.0 Hz, 6H), 2.05—1.12(m, 15H), 1.09(s, 3H), 0.84(s, 3H) | 209.19, 170.68, 156.41, 139.83, 138.33, 124.16, 122.42, 121.24, 120.34, 119.91, 108.58, 93.05, 73.96, 71.48, 56.68, 55.85, 50.10, 45.60, 39.06, 38.19, 37.11, 36.75, 34.08, 33.38, 32.65, 32.32, 31.95, 31.88, 27.85, 21.55, 21.07, 19.44, 13.91 |
| **6m** | 7.44(d, *J*=7.8 Hz, 1H), 6.99—6.86(m, 2H), 6.67(s, 1H), 5.38(d, *J*=5.0 Hz, 1H), 4.62(d, *J*=7.5, 3.3 Hz, 1H), 4.04(t, *J*=9.3, 5.3 Hz, 1H), 3.97(s, 3H), 2.89(d, *J*=9.4 Hz, 1H), 2.73(s, 3H), 2.34(d, *J*=7.8 Hz, 2H), 2.05(d, *J*=6.8 Hz, 6H), 2.01—1.08(m, 15H), 1.06(s, 3H), 0.81(s, 3H) | 209.06, 170.59, 139.77, 136.24, 127.92, 126.99, 124.28, 122.38, 121.38, 119.44, 119.04, 117.75, 73.91, 71.06, 56.54, 50.06, 45.50, 39.01, 38.15, 37.07, 36.70, 36.57, 33.88, 33.34, 32.21, 31.89, 31.81, 27.81, 21.50, 21.02, 19.82, 19.39, 13.88 |
| **6n** | 7.19(d, *J*=8.0 Hz, 1H), 6.9(t, *J*=7.9 Hz, 1H), 6.66(s, 1H), 6.60(d, *J*=7.7 Hz, 1H), 5.38(d, *J*=4.9 Hz, 1H), 4.68—4.56(m, 1H), 4.03(td, *J*=9.9, 4.2 Hz, 1H), 3.97(s, 3H), 3.90(s, 3H), 2.88(d, *J*=9.4 Hz, 1H), 2.37—2.27(m, 2H), 2.05(d, *J*=4.5 Hz, 6H), 2.03—1.08(m, 15H), 1.06(s, 3H), 0.81(s, 3H) | 209.20, 170.69, 148.05, 139.82, 129.13, 127.25, 126.56, 122.46, 119.74, 119.25, 112.56, 102.46, 73.98, 71.26, 56.63, 55.50, 50.12, 45.59, 39.05, 38.20, 37.12, 36.76, 36.34, 34.09, 33.37, 32.31, 31.96, 31.87, 27.87, 21.56, 21.07, 19.45, 13.92 |
| **6o** | 7.63(dt, *J*=8.0, 1.0 Hz, 1H), 7.30(d, *J*=8.1 Hz, 1H), 7.20(d, *J*=8.2, 7.0, 1.1 Hz, 1H), 7.08(d, *J*=8.0, 7.0, 1.1 Hz, 1H), 6.86(s, 1H), 5.39(d, *J*=5.2, 1.9 Hz, 1H), 4.69—4.56(m, 1H), 4.09(q, *J*=7.3 Hz, 3H), 2.91(d, *J*=9.4 Hz, 1H), 2.37—2.27(m, 2H), 2.05(d, *J*=4.4 Hz, 6H), 2.02—1.48(m, 13H), 1.42(t, *J*=7.3 Hz, 3H), 1.30—1.09(m, 2H), 1.06(s, 3H), 0.82(s, 3H) | 209.25, 170.72, 139.82, 136.61, 126.87, 123.71, 122.44, 121.41, 119.81, 119.73, 118.65, 109.48, 73.97, 71.36, 56.72, 50.08, 45.62, 40.81, 39.03, 38.18, 37.10, 36.75, 34.17, 33.30, 32.33, 31.96, 31.88, 27.85, 21.58, 21.07, 19.45, 15.54, 13.91 |
| **6p** | 7.68(d, *J*=7.7 Hz, 1H), 7.57—7.44(m, 4H), 7.36—7.29(m, 1H), 7.18(dt, *J*=23.1, 7.3 Hz, 2H), 7.09(s, 1H), 5.39(d, *J*=5.0 Hz, 1H), 4.62(d, *J*=11.2, 5.5, 4.4 Hz, 1H), 4.16(t, *J*=10.3, 3.9 Hz, 1H), 2.96(d, *J*=9.3 Hz, 1H), 2.37—2.26(m, 2H), 2.10(s, 3H), 2.04(s, 3H), 2.02—1.10(m, 15H), 1.07(s, 3H), 0.84(s, 3H) | 208.94, 170.72, 139.87, 136.65, 129.68, 128.02, 126.26, 124.35, 124.30, 122.53, 122.41, 120.02, 119.97, 110.76, 73.97, 71.23, 56.74, 50.10, 45.66, 39.11, 38.20, 37.13, 36.77, 33.94, 33.27, 32.33, 31.98, 31.91, 29.83, 27.87, 21.58, 21.11, 19.47, 13.97 |
| **7a** | 7.62(d, *J*=7.9 Hz, 1H), 7.27(d, *J*=8.0 Hz, 1H), 7.24—7.17(m, 1H), 7.08(t, *J*=7.6 Hz, 1H), 6.79(s, 1H), 5.36(d, *J*=5.1 Hz, 1H), 4.08(td, *J*=10.2, 3.9 Hz, 1H), 3.70(s, 3H), 3.54(tt, *J*=10.7, 4.7 Hz, 1H), 2.90(d, *J*=9.4 Hz, 1H), 2.37—2.18(m, 2H), 2.06(s, 3H), 2.02—1.09(m, 15H), 1.05(s, 3H), 0.82(s, 3H) | 209.13, 140.88, 137.58, 126.68, 125.47, 121.52, 121.44, 119.66, 118.64, 109.37, 71.80, 71.34, 56.79, 50.19, 45.57, 42.32, 39.07, 37.34, 36.61, 34.07, 33.22, 32.58, 32.23, 31.95, 31.83, 31.67, 21.09, 19.48, 13.85 |
| **7b** | 7.24(d, *J*=10.7 Hz, 1H), 7.20—7.12(m, 1H), 6.94(td, *J*=9.0, 2.6 Hz, 1H), 6.82(s, 1H), 5.36(dd, *J*=5.0, 2.3 Hz, 1H), 4.02(q, *J*=8.2 Hz, 1H), 3.69(d, *J*=1.7 Hz, 3H), 3.55(s, 1H), 2.85(d, *J*=9.2 Hz, 1H), 2.32(dd, *J*=13.1, 4.8 Hz, 1H), 2.25(t, *J*=12.0 Hz, 1H), 2.06(d, *J*=1.6 Hz, 3H), 2.03—1.08(m, 15H), 1.04(s, 3H), 0.80(s, 3H) | 208.88, 140.87, 134.22, 127.12, 121.39, 110.00, 109.70, 104.61, 104.38, 71.78, 71.29, 56.88, 50.13, 45.54, 42.31, 39.04, 37.31, 36.60, 33.87, 33.04, 32.86, 32.19, 31.95, 31.82, 31.67, 21.07, 19.48, 13.79 |
| **7c** | 7.59(d, *J*=1.8 Hz, 1H), 7.24—7.14(m, 2H), 6.84(s, 1H), 5.40(d, *J*=4.8 Hz, 1H), 4.06(td, *J*=9.6, 5.3 Hz, 1H), 3.72(s, 3H), 3.59(dq, *J*=11.1, 5.9 Hz, 1H), 2.88(d, *J*=9.5 Hz, 1H), 2.41—2.23(m, 2H), 2.11(s, 3H), 2.08—1.11(m, 15H), 1.08(s, 3H), 0.84(s, 3H) | 208.80, 140.86, 135.95, 127.71, 126.72, 124.55, 121.82, 121.40, 119.42, 110.37, 71.76, 71.20, 56.79, 50.09, 45.51, 42.31, 38.99, 37.29, 36.61, 33.78, 33.22, 32.79, 32.16, 31.95, 31.85, 31.66, 29.76, 21.04, 19.48, 13.79 |

Continued

| Compd. | $^1$H NMR(400 MHz), $\delta$ | $^{13}$C NMR(101 MHz), $\delta$ |
|---|---|---|
| **7**d | 7.71(d, *J*=1.9 Hz, 1H), 7.30—7.23(m, 1H), 7.12(d, *J*=8.7 Hz, 1H), 6.78(s, 1H), 5.36(d, *J*=5.0 Hz, 1H), 4.02(td, *J*=9.9, 4.7 Hz, 1H), 3.68(s, 3H), 3.55(dt, *J*=11.5, 6.3 Hz, 1H), 2.84(d, *J*=9.5 Hz, 1H), 2.36—2.19(m, 2H), 2.07(s, 3H), 2.04—1.06(m, 15H), 1.04(s, 3H), 0.80(s, 3H) | 208.85, 140.85, 136.18, 128.46, 126.50, 124.38, 122.14, 121.40, 119.42, 112.15, 110.84, 71.75, 71.20, 56.75, 50.08, 45.51, 42.29, 38.98, 37.28, 36.62, 33.73, 33.28, 32.78, 32.15, 31.94, 31.86, 31.65, 21.03, 19.47, 13.79 |
| **7**e | 7.42(s, 1H), 7.19(d, *J*=8.3 Hz, 1H), 7.07(dd, *J*=8.0, 1.6 Hz, 1H), 6.78(s, 1H), 5.40(d, *J*=5.1 Hz, 1H), 4.14—4.03(m, 1H), 3.71(s, 3H), 3.58(dq, *J*=10.6, 5.4, 4.5 Hz, 1H), 2.92(d, *J*=9.5 Hz, 1H), 2.50(s, 3H), 2.40—2.22(m, 2H), 2.10(s, 3H), 2.05—1.12(m, 15H), 1.09(s, 3H), 0.85(s, 3H) | 209.18, 140.87, 135.99, 127.78, 126.98, 125.40, 123.14, 121.48, 119.30, 119.17, 109.05, 71.79, 71.18, 56.65, 50.17, 45.51, 42.32, 39.04, 37.31, 36.63, 34.02, 33.40, 32.62, 32.21, 31.95, 31.88, 31.68, 21.70, 21.06, 19.49, 13.86 |
| **7**f | 7.19(d, *J*=8.8 Hz, 1H), 7.11(d, *J*=2.4 Hz, 1H), 6.90(dd, *J*=8.9, 2.4 Hz, 1H), 6.80(s, 1H), 5.39(d, *J*=5.0 Hz, 1H), 4.09(td, *J*=9.7, 4.5 Hz, 1H), 3.90(s, 3H), 3.71(s, 3H), 3.58(dt, *J*=11.4, 6.0 Hz, 1H), 2.90(d, *J*=9.4 Hz, 1H), 2.39—2.23(m, 2H), 2.10(s, 3H), 2.09—1.10(m, 15H), 1.08(s, 3H), 0.85(s, 3H) | 209.20, 153.47, 140.89, 132.96, 127.04, 125.86, 121.40, 119.34, 111.47, 110.01, 101.90, 71.75, 71.44, 56.81, 56.09, 50.19, 45.57, 42.31, 39.07, 37.30, 36.63, 33.87, 33.16, 32.78, 32.29, 31.95, 31.66, 21.06, 19.49, 13.88 |

1.2.2 MTT法测试 参照文献[20~22]方法，将对数生长期的癌细胞用DMEM培养基计数调整细胞浓度至1.0×10$^5$ cell/mL，分别向96孔板中接种100 μL细胞悬液. 将接种好细胞的96孔板放入具有饱和湿度的$CO_2$(5%)恒温培养箱中于37 ℃下培养24 h. 结束后吸去旧培养基，将100 μL无血清培养基溶液加入孔中，随后将100 μL不同浓度梯度的待测化合物和阳性对照化合物溶液分组加入实验组孔中，每组设置3个平行对照，同时设置调零孔(培养基+MTT+DMSO)及对照孔(未经处理的细胞+培养基+MTT+DMSO)，继续培养48 h. 再分别加入20 μL 5 nmol/L MTT溶液继续培养4 h，培养结束后，吸去上层清液，分别加入100 μL DMSO溶液，于摇床上以130 r/min的转速摇晃96孔板10 min，随后用酶标仪测定570 nm处的吸光度(OD). 以抗肿瘤药物阿霉素(DOX)作为阳性对照.

## 2 结果与讨论

### 2.1 化合物6a的合成条件优化及结构确定

参照文献[23]方法，将取代的吲哚(**1**a~**1**o)在*N*-甲基保护下生成化合物**2**a~**2**o和**3**a(Scheme 1)；然后参照文献[24]方法由薯蓣皂苷元(**4**)合成16-DPA中间体(**5**)，并通过Michael加成法将取代的*N*-甲基吲哚引入到16-DPA的C16上. 该合成方法采用廉价易得的催化剂$ZrCl_4$，以EtOAc为溶剂，可高收率(90%)获得立体单一和高区域选择性的*N*-甲基吲哚孕烯醇酮衍生物，最后经NaOH水溶液与甲醇水解得到3*β*-羟基孕酮衍生物(Scheme 2).

首先考察了反应的催化剂. 在Yb(OTf)$_3$[25]，$Br_2$[26]，[Fe(H$_2$O)$_6$](OTs)$_3$[27]，$ZrCl_4$[28]和$SbCl_3$[29]等催化剂中，只有Yb(OTf)$_3$和$ZrCl_4$廉价易得. 将2种催化剂分别用于16-DPA与吲哚的反应中，未检测到目标产物. 随后对吲哚进行*N*-甲基保护后，以相同的反应条件得到了目标产物. 这可能是因为NH结构具有亲核性会争夺电子，使得吲哚C3位富电子性减弱，而*N*-甲基保护后会使吲哚C3位电子富集. 此反应可能是由于给电子基团(—$CH_3$)的存在增加了吲哚分子的电子密度. 而*N*-甲基吲哚分子上C3位的电子密度最为富集，使其能够更好地进攻16-DPA上的*α*，*β*-不饱和酮，因此*N*-甲基化有利于Michael加成. 随后，在确定*N*-甲基吲哚为另一反应物的系列筛选中，以$ZrCl_4$为催化剂高收率地获得了目标产物，但产生了2个副产物. 实验进一步筛选了溶剂、反应时间和催化剂用量等条件，发现以EtOAc为溶剂，反应10 h，催化剂用量(摩尔分数)为10%(50 ℃)时无副产物生成. 最后，考察了扩大反应(5和10 mmol)，发现仍以85%的高收率得到了目标产物.

实验中确定了化合物**6**a的立体构型. 液相色谱(HPLC)测试显示，化合物**6**a的对映体过量(*e.e.*)>99%. 此外，H-H NOESY(C16和C17上的H无耦合信号)和单晶X射线分析结果(图1)证实化合物**6**a的

C16位为α构型．在不添加手性催化剂的情况下也能获得手性化合物．由化合物**4**得到的16-DPA经HPLC测试表明*e.e.* > 80%．这可能是因为16-DPA也是手性化合物，其C18位甲基是β构型从而阻止了吲哚基团从β面攻击16-DPA的C16位，因此只得到了C16位的α-构型产物(**6**a)．此结果与文献[30,31]报道的其它16-DPA迈克尔加成产物的立体化学结构一致．

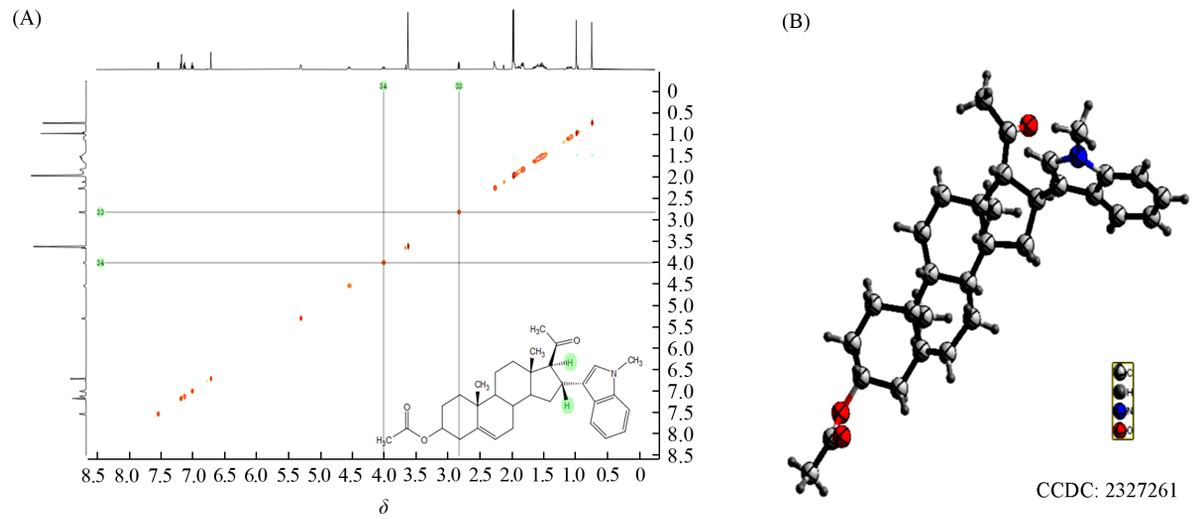



**Fig. 1　H-H NOESY(A) and crystal structure(B) of compound 6a**

### 2.2　化合物6a~6p和7a~7f的生物活性

半数抑制浓度($IC_{50}$)值越低说明化合物对癌细胞的抑制作用越强、活性越好．由表3可见，3β-羟基孕烯醇酮化合物**7**a~**7**f普遍具有较优异的抑制癌细胞活性，化合物**7**b(5-F)和**7**e(5-Me)的活性最好，$IC_{50}$值分别为13.76和12.50 μmol/L．3β-乙酰基孕烯醇酮化合物中只有2个具有较高活性，化合物**6**h(5-$CO_2$Me)和**6**i(4-Me)的$IC_{50}$值分别为18.07和23.22 μmol/L，化合物**6**k，**6**l和**6**m的活性较低，$IC_{50}$值在68~85 μmol/L之间，可见3β-羟基增强了此类化合物的活性．*N*-甲基吲哚上带有—$CO_2$Me，—Me和—OMe基团的抑制癌细胞活性相对较好，而N保护基团则对活性没有影响．此类化合物为药物筛选提供了新的方向．

**Table 3　Anti-tumor activities for MDA-MB-231 of compounds 6a—6p and 7a—7f***

| Compound | $IC_{50}$/(μmol·$L^{-1}$) | Compound | $IC_{50}$/(μmol·$L^{-1}$) |
|---|---|---|---|
| **6**a | >200 | **6**m | 82.67 |
| **6**b | >200 | **6**n | 168.50 |
| **6**c | >200 | **6**o | >200 |
| **6**d | >200 | **6**p | >200 |
| **6**e | >200 | **7**a | 38.20 |
| **6**f | >200 | **7**b | 13.76 |
| **6**g | >200 | **7**c | 21.94 |
| **6**h | 18.07 | **7**d | 27.50 |
| **6**i | 23.22 | **7**e | 12.50 |
| **6**j | >200 | **7**f | 16.89 |
| **6**k | 69.32 | DOX | 1.71 |
| **6**l | 70.55 | | |

* DOX is an anti-tumor drug Adriamycin, >200 indicates no inhibition of cancer cell activity.

## 3　结　　论

以薯蓣皂苷元为原料，首先合成类固醇中间体16-DPA，然后合成了16个3β-乙酰基-16α-3′-吲哚孕烯醇酮化合物和6个3β-羟基孕烯醇酮化合物．采用MTT法进行的体外抗肿瘤实验结果表明，化合物

**6h**, **6i** 和3$\beta$-羟基孕烯醇酮衍生物(**7a~7f**)对三阴性乳腺癌细胞(MDA-MB-231)均具有较好的抑制活性,其中化合物**7e**的抑制癌细胞活性最好, $IC_{50}$值为12.50 μmol/L. 该实验为此类化合物的药物筛选提供了一定的参考.

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