

树豆叶二苯乙烯类成分的甲醚化和体外抗肿瘤活性

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摘要: 为获得具有抗肿瘤活性的甲醚化先导化合物, 对树豆(*Cajanus cajan*)叶中的二苯乙烯类成分进行甲醚化, 并测定其对肿瘤细胞的细胞毒性。将木豆素 C、树豆酮酸 A、Cajanotone 和木豆素与碘甲烷-碳酸钾反应制备 *O*-甲基产物, 通过波谱数据分析产物结构分别鉴定为: 2-异戊烯基-3,5-二甲氧基二苯乙烯 (**1**)、树豆酮酸 A 甲醚 (**2**)、5-*O*-methyl cajanotone (**3**)和 3-*O*-甲基木豆素 (**4**), 其中化合物 **3** 是新化合物。肿瘤细胞增殖抑制实验(CCK-8 法)结果表明, 木豆素 C 对乳腺癌 MDA-MB-231、宫颈癌 HeLa、肝癌 HepG2、结肠癌 SW480 及 3 种非小细胞肺癌细胞(A549, NCI-H460 和 NCI-H1299)的半数抑制浓度 IC₅₀ 分别为 14.4、16.1、19.6、17.4 和 25.7~29.6 μmol L⁻¹; 木豆素对宫颈癌和结肠癌之外的 5 种肿瘤细胞有弱抑制作用, IC₅₀ 为 44.9~78.3 μmol L⁻¹; 而对照的 3,4',5-三甲氧基二苯乙烯(三-*O*-甲基白藜芦醇)对乳腺癌 MDA-MB-231、宫颈癌 HeLa、结肠癌 SW480 和肝癌 HepG2 细胞有较强抑制作用(IC₅₀ 为 3.0~14.5 μmol L⁻¹)。树豆叶二苯乙烯甲醚化衍生物 **1**~**4** 对 7 种肿瘤细胞系无明显细胞毒活性。

关键词: 树豆; 二苯乙烯; 甲醚化; 细胞毒活性; 化学成分

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Methoxylation of the Stilbenes Originated from Leaves of *Cajanus cajan* and Their Anti-tumor Activities *in vitro*

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Abstract: The aim was to obtain lead compounds with anticancer activity by *O*-methylation of stilbene pheolic derivatives extracted from leaves of *Cajanus cajan*. Four derivatives, such as longistylin C, cajanonic acid A, cajanotone and cajaninstilbene acid, were treated with iodomethane and potassium carbonate under mild condition. The products were purified through silica gel column chromatography and their structures were identified by spectroscopic analysis as 2-isoprenyl-3,5-dimethoxy-stilbene (**1**), *O*-methyl-cajanonic acid A (**2**), 5-*O*-methyl cajanotone (**3**) and 3-*O*-methyl cajaninstilbene acid (**4**), respectively. Among them, compound **3** was a new compound. Effects of **1**–**4** and their reactants, together with resveratrol, 4'-*O*-methyl resveratrol and 3,4',5-*O*-trimethyl resveratrol using as positive controls, on the proliferation of the cell lines of human breast cancer (MDA-MB-231), cervical cancer (HeLa), liver cancer (HepG2), colon cancer (SW480), and non-small cell lung cancer (A549, NCI-H460 and NCI-H1299) were determined by CCK-8 assay. The results showed that

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longistilin C distinctly inhibited the proliferation of all the seven cell lines, with the half inhibitory concentrations (IC_{50}) to MDA-MB-231, HeLa, HepG2, and SW480 at 14.4, 16.1, 19.6, and 17.4 $\mu\text{mol L}^{-1}$ (strong suppression), with IC_{50} values of 25.7–29.6 $\mu\text{mol L}^{-1}$ to other three cell lines of non-small cell lung cancer; cajaninstilbene acid had a weak inhibition to HepG2, A549, NCI-H460, NCI-H1299 and MDA-MB-231 cells with IC_{50} as 44.9–78.3 $\mu\text{mol L}^{-1}$; tri-*O*-methylated resveratrol showed significantly cytotoxicity against MDA-MB-231, HeLa, SW480 and HepG2 cells with IC_{50} of 16.1–17.4 $\mu\text{mol L}^{-1}$; *O*-methylated stilbenes 1–4 did not exhibited obvious cytotoxicity in the cell lines aboved.

Key words: *Cajanus cajan*; Stilbene; Methoxylation; Cytotoxicity; Chemical constituent

癌症是严重威胁人类生命和健康的重大疾病。据统计, 2014 年全国恶性肿瘤估计死亡病例 229.6 万例, 肿瘤死亡率 0.17%, 肺癌和乳腺癌分别位居男女性发病的第 1 位^[1]。寻找新的抗肿瘤先导化合物具有重要意义。一些酚类物质在甲醚化后抗肿瘤活性有所提高, 例如: 黄酮类化合物白杨素甲醚化后生成 5,7-二甲氧基黄酮, 能够降低急性淋巴细胞白血病细胞增殖水平^[2]。二苯乙烯类植物多酚白藜芦醇(3,5,4'-三羟基二苯乙烯)及其类似物的生物活性, 可因结构中甲氧基及其取代位置的不同而变化。Weng 等^[3-4]报道白藜芦醇及其甲氧基类似物如三甲氧基白藜芦醇可抑制肝癌细胞的转移和浸润性质, 还对非小细胞肺癌 A549 细胞增殖有明显抑制作用, 而白藜芦醇对 A549 细胞无效; 白藜芦醇和三甲氧基白藜芦醇在 25 $\mu\text{mol L}^{-1}$ 工作浓度下对乳腺癌 MDA-MB-231 细胞的生长有明显抑制作用^[5]。

豆科植物树豆 [*Cajanus cajan* (Linn.) Mill.] (又名木豆) 叶有多方面的药理作用, 文献报道, 12-羟基木豆萜酸具有良好的自由基清除活性和体外抗肿瘤活性^[6]; 木豆素体外作用于乳腺癌细胞可引起细胞周期停滞并诱导细胞凋亡^[7]; 木豆萜 H 具有体外诱导人骨髓间充质细胞分化为成骨细胞的作用, 并对多种肿瘤细胞表现出中等强度抑制作用^[8]; 木豆素 C 对多种人源肿瘤细胞株的增殖表现出明显抑制作用^[9-10]; 树豆酮酸 A 经动物试验, 具有显著降低糖尿病大鼠的血糖、血脂的作用^[11]。树豆二苯乙烯类成分的结构与白藜芦醇相似, 其甲氧基类似物有可能也具有抗肿瘤生物活性, 所以我们对源自于树豆叶的 4 个二苯乙烯类成分木豆素 C、树豆酮酸 A、Cajanotone 和木豆素进行甲醚化反应^[12], 反应产物经硅胶柱层析纯化和波谱分析确定结构。以白藜芦醇及其甲氧基衍生物为对照, 检测相关化合物的体外抗肿瘤活性。本文报道这类甲醚化衍生物的制备、结构鉴定, 以及体外抗肿瘤活性的测试结果。

1 材料和方法

1.1 仪器、试剂和耗材

DRX-400 核磁共振仪、EQUINOX55 型红外波谱仪(德国 Bruker 公司); TU-1901 双光束紫外可见分光光度计(北京普析通用仪器有限公司); C506-Triple TOF 5600 系统(美国 AB SCIEX 公司); LC6000 型高效制备液相色谱仪、LC3000 型高效制备液相色谱仪(北京创新通恒有限公司); UV D-170U、Chromleon 色谱工作站高效液相色谱仪(美国 Dionex 公司); SHIM-PACK 色谱柱(日本 SHIMADZU 公司); 硅胶(200~300 目)、硅胶 TLC 薄层预制板(青岛海洋化工厂分厂); Sephadex LH-20 葡聚糖凝胶(美国 GE Healthcare 公司); HPLC 分析, 使用 Merck 公司甲醇; 其他溶剂和试剂均为国产分析纯产品。TLC 显色剂为 6% 香兰素乙醇液-12% 高氯酸溶液等体积混合液。

细胞培养基 RPMI 1640 (德国 Biological Industries 公司, 批号 0012118); 胎牛血清(FBS)(澳大利亚 Gibco 公司, 批号 1704206)。

CO₂ 细胞培养箱(上海力申科学仪器有限公司); 垂直超净工作台(上海智城分析仪器制造有限公司); 倒置光学显微镜(日本 Olympus 公司); 低速离心机(科大创新股份有限公司中佳分公司); MK3 型酶标仪(美国 Thermo fisher 公司); Cell Counting Kit-8 (CCK-8) 细胞增殖-毒性检测试剂盒(日本同仁化学研究所)。

1.2 反应原料

木豆素 C, 树豆酮酸 A, Cajanotone 和木豆素均从树豆叶分离得到^[8,10,13]。

1.3 细胞株

人乳腺癌 MDA-MB-231 细胞、人宫颈癌 HeLa 细胞、人肝癌 HepG2 细胞、人结肠癌 SW480 细胞、

人非小细胞肺癌 A549、NCI-H1299 和 NCI-H460 均来自中国科学院上海生命科学研究院细胞资源中心。

1.4 树豆蔗类成分的甲醚化

木豆素 C (500 mg, 1.7 mmol)溶于乙腈(5 mL), 加入无水碳酸钾(400 mg, 2.9 mmol), 于室温(28℃ ~

32℃)下搅拌 20 min, 缓慢滴入 200 μL 碘甲烷(460 mg, 3.2 mmol), 搅拌 3 h (经 TLC 检测反应至终点), 加水 5 mL 淬灭反应; 加乙酸乙酯 15 mL 萃取反应液 3 次, 合并乙酸乙酯溶液, 减压蒸干, 得粗产物; 粗产物经硅胶(200~300 目)柱层析, 以正己烷-乙酸乙酯(50 : 1)洗脱, 得产物 **1** (317 mg, 图 1), 收率 60.6%。

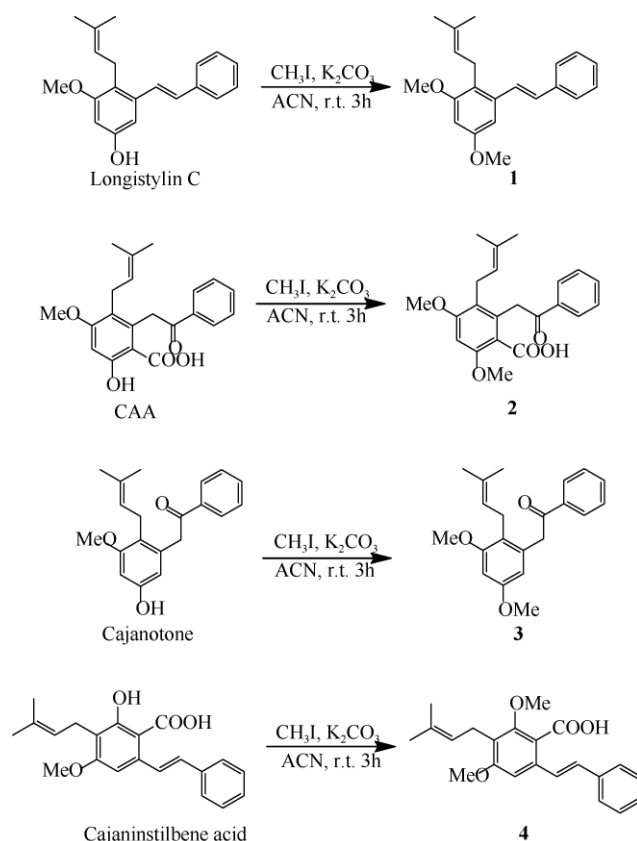


图 1 甲醚化产物 **1**~**4** 的结构

Fig. 1 Structures of methoxylated products **1**~**4**

树豆酮酸 A (93 mg, 0.26 mmol)溶于乙腈(5 mL), 加入无水碳酸钾(120 mg, 0.87 mmol), 缓慢滴入 20 μL 碘甲烷(46 mg, 0.32 mmol), 后续处理过程与制备化合物 **1** 的相同, 硅胶柱层析流动相为正己烷-乙酸乙酯(20 : 1~10 : 1), 得化合物 **2** (35.6 mg, 图 1), 收率 36.8%。

以 Cajanotone (40 mg, 0.13 mmol)溶于乙腈(5 mL), 加入无水碳酸钾(60 mg, 0.44 mmol), 缓慢滴入 10 μL 碘甲烷(23 mg, 0.16 mmol), 后续处理过程与制备化合物 **1** 的相同, 硅胶柱层析流动相为正己烷-乙酸乙酯(20 : 1~10 : 1), 得化合物 **3** (14.3 mg, 图 1), 收率 34.2%。

木豆素(236 mg, 0.70 mmol)溶于乙腈(5 mL), 加入无水碳酸钾(300 mg, 2.17 mmol), 缓慢滴入 80 μL 碘甲烷(184 mg, 1.28 mmol), 后续处理过程与制备化合

物 **1** 的相同, 硅胶柱层析流动相为正己烷-乙酸乙酯(50 : 1~20 : 1), 得化合物 **4** (35 mg, 图 1), 收率 14.8%。

1.5 结构鉴定

化合物 1 白色粉末, ESI-MS m/z : 308.9 $[\text{M} + \text{H}]^+$. ^1H NMR (400 MHz, CDCl_3): δ 7.55 (2H, d, $J = 7.6$ Hz, H-2', H-6'), 7.42 (2H, m, H-3', H-5'), 7.41 (1H, m, H-4'), 7.30 (2H, d, $J = 12$ Hz, H-7, H-8), 6.79 (1H, d, $J = 2.4$ Hz, H-4), 6.46 (1H, d, $J = 2$ Hz, H-6), 5.16 (1H, t, $J = 6.4$ Hz, H-2''), 3.95 (3H, s, 3-OCH₃), 3.88 (3H, s, 5-OCH₃), 3.48 (2H, d, $J = 9.2$ Hz, H-1''), 1.84 (3H, s, H-4''), 1.71 (3H, s, H-5''); ^{13}C NMR (100 MHz, CDCl_3): δ 158.5 (C, C-3), 158.3 (C, C-5), 137.5 (C, C-1, C-1'), 130.9

(CH, C-3''), 130.3 (CH, C-7), 128.6 (CH, C-3', C-5'), 127.6 (CH, C-4''), 126.8 (CH, C-8), 126.5 (CH, C-2', C-6'), 123.4 (CH, C-2''), 121.1 (C, C-2), 101.4 (CH, C-4), 98.1 (CH, C-6), 55.6 (CH₃, 3-OCH₃), 55.3 (CH₃, 5-OCH₃), 25.9 (CH₃, C-4''), 24.4 (CH₂, C-1''), 17.9 (CH₃, C-5''). 以上数据与 5-*O*-methyl-longistilin C 一致^[14]。

化合物 2 白色粉末, ESI-MS *m/z*: (neg.) 367.1 [M - H]⁻. ¹H NMR (400 MHz, CDCl₃): δ 11.59 (1H, s, H-COOH), 8.06 (2H, s, *J* = 7.6 Hz, H-2', H-6'), 7.61 (1H, t, *J* = 7.2 Hz, H-4'), 7.52 (2H, t, *J* = 7.6 Hz, H-3', H-5'), 6.46 (1H, s, H-3), 4.95 (1H, t, *J* = 7.2 Hz, H-7), 3.85 (3H, s, 4-OCH₃), 3.48 (3H, s, 2-OCH₃), 3.27 (2H, d, *J* = 6 Hz, H-1''), 1.61 (3H, s, H-4''), 1.59 (3H, s, H-5''); ¹³C NMR (100 MHz, CDCl₃): δ 197.1 (C, C-8), 171.2 (C, 1-COOH), 163.6 (C, C-4), 162.5 (C, C-2), 137.0 (C, C-1'), 136.7 (C, C-6), 133.0 (C, C-4'), 131.6 (C, C-3''), 128.7 (CH, C-3', C-5'), 123.1 (C, C-5), 122.7 (CH, C-2''), 105.2 (C, C-1), 98.6 (CH, C-3), 55.7 (CH₃, 4-OCH₃), 51.9 (CH₃, 2-OCH₃), 41.6 (CH₂, C-7), 25.6 (CH₃, C-5''), 24.9 (CH₂, C-1''), 17.8 (CH₃, C-4''). 以上数据与 5-*O*-methyl-cajanonic acid A 的一致^[15]。

化合物 3 白色粉末, ESI-MS *m/z*: (pos.) 347.0 [M + Na]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.01 (2H, d, *J* = 7.6 Hz, H-2', H-6'), 7.57 (1H, t, *J* = 7.2 Hz,

H-4'), 7.46 (2H, t, *J* = 7.2 Hz, H-3', H-5'), 6.41 (1H, d, *J* = 2 Hz, H-6), 5.00 (1H, t, *J* = 6.4 Hz, H-2''), 4.26 (2H, s, H-7), 3.78 (3H, s, 3-OCH₃), 3.74 (3H, s, 5-OCH₃), 3.26 (2H, d, *J* = 6.4 Hz, H-1''), 1.59 (3H, s, H-4''), 1.51 (3H, s, H-5''); ¹³C NMR (100 MHz, CDCl₃): δ 197.8 (C, C-8), 158.4 (C, C-3, C-5), 136.7 (C, C-1'), 134.9 (C, C-1), 133.1 (CH, C-4'), 131.2 (C, C-3''), 128.6 (CH, C-2', C-6'), 123.2 (CH, C-2''), 121.1 (C, C-2), 106.6 (CH, C-4), 97.5 (CH, C-6), 55.6 (CH₃, 3-OCH₃), 55.2 (CH₃, 5-OCH₃), 43.2 (CH₂, C-7), 25.6 (CH₃, C-5''), 24.8 (CH₂, C-1''), 17.8 (CH₃, C-4''). 因此, 化合物 3 的结构确定为 5-*O*-methyl-cajanotone (表 1, 图 2)^[16]。

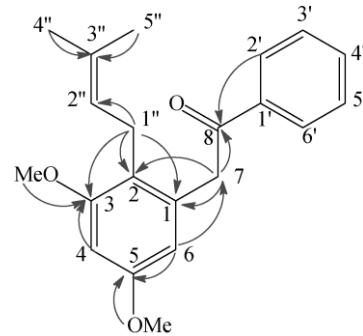


图 2 化合物 3 主要的 HMBC 相关

Fig. 2 Key HMBC correlations of compound 3

表 1 Cajanotone 与化合物 3 的核磁数据(溶剂为 CDCl₃)

Table 1 NMR data of cajanotone and compound 3 (in CDCl₃)

C/H	Cajanotone ^[13]		3		
	δ _H (<i>J</i> in Hz)	δ _C	δ _H (<i>J</i> in Hz)	δ _C , type	HMBC (¹ H→ ¹³ C)
1		135.1		134.9, C	
2		121.0		121.2, C	
3		158.7		158.4, C	
4	6.34 (d, 2.2 Hz)	98.1	6.41 (d, 2 Hz)	97.5, CH	C-3
5		154.5		158.4, C	
6	6.19 (d, 2.2 Hz)	109.0	6.27 (d, 2 Hz)	106.6, CH	C-5,7
7	4.21 (s)	42.8	4.26 (s)	43.2, CH ₂	C-1,2,8
8		198.1		197.8, C	
1'		136.7		136.7, C	
2', 6'	7.96 (d, 7.5 Hz)	128.4	8.00 (d, 7.6 Hz)	128.3, CH	C-8,4'
3', 5'	7.44 (t, 7.5 Hz)	128.6	7.46 (t, 8 Hz)	128.6, CH	C-1'
4'	7.56 (t, 7.5 Hz)	133.2	7.57 (t, 7.6 Hz)	133.1, CH	C-2',6'
1''	3.24 (d, 6.5 Hz)	24.8	3.26 (d, 6.4 Hz)	24.8, CH ₂	C-1,2,3,2''
2''	5.00 (t, 6.5 Hz)	123.2	5.00 (t, 6.4 Hz)	123.1, CH	
3''		131.2		131.2, C	
4''	1.59 (s)	17.8	1.59 (s)	17.8, CH ₃	C-2'',3''
5''	1.59 (s)	25.6	1.59 (s)	25.6, CH ₃	C-2'',3''
3-OCH ₃	3.76 (s)	56.6	3.80 (s)	55.6, CH ₃	C-3
5-OCH ₃			3.78 (s)	55.2, CH ₃	C-5

癌 LNCaP 细胞、人结肠腺癌 HT-29 细胞、人肝癌 HepG2 细胞的抑制作用显著增强^[18]。由此推测, 甲氧基数目和取代位置对树豆叶二苯乙烯类成分的抗肿瘤活性有显著影响。我们的试验为树豆叶二苯乙烯类成分通过结构修饰改变体外抗肿瘤活性提供了参考依据。

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