水飞蓟宾衍生物的设计、合成及体外抗肿瘤活性

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摘 要 以天然黄酮类化合物水飞蓟宾为母体，通过氧化脱氢、烷基化、选择性去甲基、酰化等反应共合成了 16 个水飞蓟宾衍生物，其结构均通过^{1}H NMR、^{13}C NMR、MS 确证，确定均为未经文献报道的新化合物。选用胃癌细胞 SGC-7901 和人胶质母细胞瘤细胞 LN-229，采用 MTT 法，以拉帕替尼为阳性对照药测定新型水飞蓟宾衍生物的体外抗肿瘤活性。实验结果表明，合成的新型水飞蓟宾衍生物对两种癌细胞有一定程度的抗增殖作用，其中化合物 **I2** 和 **I14** 对 LN-229 细胞和 SGC-7901 细胞显示较强的抗增殖活性。

关键词 水飞蓟宾衍生物；抗肿瘤；结构修饰

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Design, synthesis, and *in vitro* anti-tumor activity of silybin derivatives

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Abstract This study used the natural flavonoid compound silybin as the parent compound and synthesized 16 silybin derivatives through oxidative dehydrogenation, alkylation, selective demethylation, and acylation. The structures of these derivatives were confirmed by ^{1}H NMR, ^{13}C NMR, and MS. All derivatives were found to be new compounds never reported in previous literature. Using gastric cancer cell line SGC-7901 and human glioblastoma cell line LN-229, the *in vitro* anti-tumor activity of the novel silybin derivative was determined through MTT assay with lapatinib as the positive control. The experimental results indicate that the synthesized novel silybin derivatives have a certain degree of anti-proliferative effect on two types of cancer cells, with compounds **I2** and **I14** showing strong anti-proliferative activity against LN-229 and SGC-7901 cells.

Key words silybin derivatives; antitumor; structural modification

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水飞蓟素是从菊科植物水飞蓟的干燥果实中提取出来的一种天然活性物质，包括水飞蓟宾、异水飞蓟宾、水飞蓟亭、水飞蓟宁等[1]。其中水飞蓟宾为主要活性成分，占水飞蓟素总量的 60%~70%。水飞蓟宾具有抗氧化和抗炎特性，可保护肝细胞免受活性氧（reactive oxygen species, ROS）和有毒物质的侵害[2−4]，并且还具有保肝[5] 和抑制癌细胞增殖[6] 等生物活性。有研究表明，水飞蓟宾可明显降低

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ALDH1A1、RARα、Ets1 和 MMP9 蛋白的表达[7]。在不同的肿瘤疾病中，例如前列腺癌、肝细胞癌、胃癌和胶质母细胞瘤等，水飞蓟宾可以降低细胞活力并抑制失控细胞的增殖[8−10]。

本研究以水飞蓟宾为母体，采用氧化脱氢[11]、烷基化、选择性去甲基、酰化等反应共合成了 16 个新型水飞蓟宾衍生物，以期提高水飞蓟宾的抗肿瘤活性。新型衍生物结构均经 ^{1}H NMR、^{13}C NMR、MS 分析确证，确定均为未经文献报道过的新化合物。采用 MTT 法测定所合成的化合物对胃癌细胞 SGC-7901 和人胶质母细胞瘤细胞 LN-229 的体外抗增殖活性。

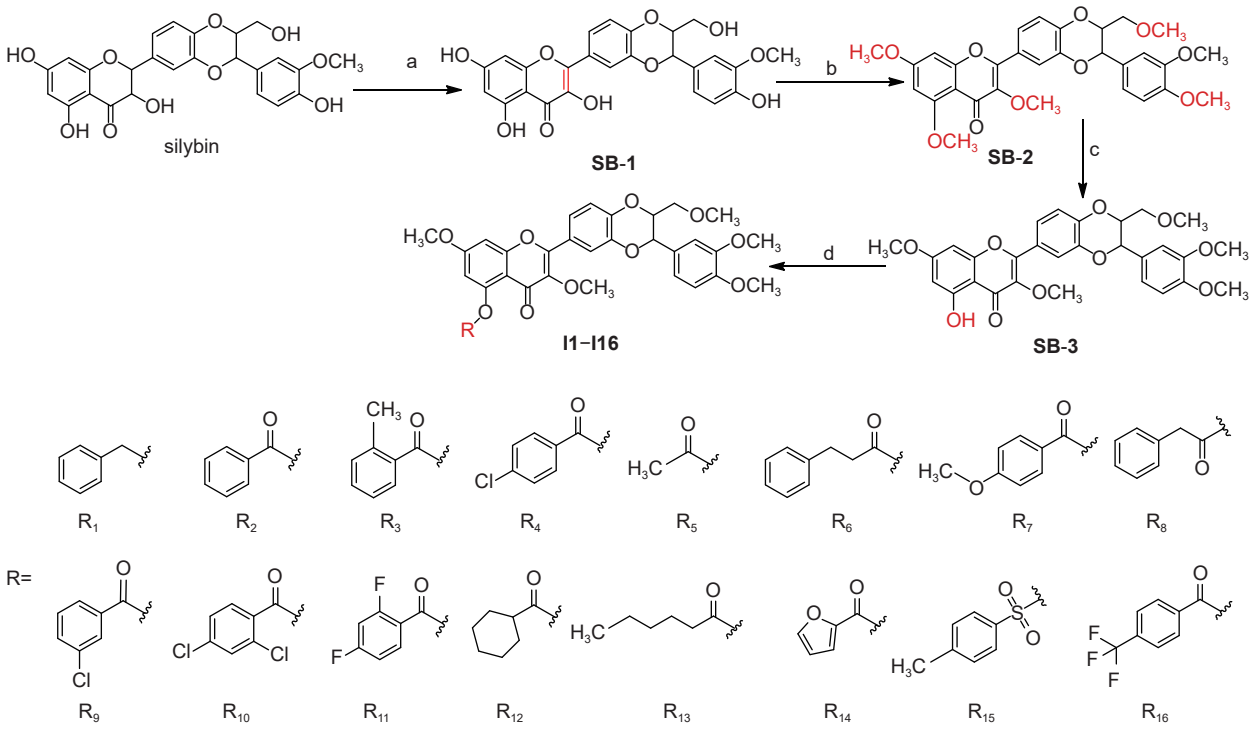
1 实验部分

1.1 主要仪器与试剂

Bruker 500M 核磁共振分析仪（瑞士 Bruker 公司）；B-540 型熔点测定仪、R-200 型旋转蒸发仪（瑞士 Buchi 公司）；水飞蓟宾（辽宁盘锦格林恩生物资源开发有限公司）；*N*,*N*-二甲基甲酰胺（*N*,*N*-dimethylformamide, DMF）、1,2-二氯乙烷（天津市大茂化学试剂厂）；碘甲烷、丙酮、乙腈、四丁基碘化铵（tetrabutylammonium iodide, TBAI）、4-二甲氨基吡啶（4-dimethylaminopyridine, DMAP）、无水三氯化铝（上海麦克林公司）；二氯甲烷（天津市博迪公司）；浓盐酸（天津市凯信公司），所用试剂均为分析纯。人胃癌细胞株 SGC-7901 和人胶质母细胞瘤细胞株 LN-229 来源于中国科学院细胞库。

1.2 合成方法

将水飞蓟宾溶于吡啶中加热回流 24 h 得化合物 **SB-1**。后将化合物 **SB-1** 用 DMF 5 mL 溶解，以 TBAI 为催化剂，和碘甲烷反应得化合物 **SB-2**。之后将化合物 **SB-2** 溶于 1,2-二氯乙烷-乙腈（1∶1）的溶剂中，以 TBAI 为催化剂，通过 $AlCl_3$ 选择性去甲基得化合物 **SB-3**。最后化合物 **SB-3** 以 DMAP 为催化剂，同酰氯或酸酐反应得化合物 **I1~I16**（路线 1）。



Scheme 1 Synthesis route of the target compound **I1−I16**

Reagents and conditions:(a)pyridine, 110 °C, 24 h; (b) ICH_3, NaH, TBAI, DMF, 80 °C, 3 h; (c) $AlCl_3$, TBAI, 1, 2-dichloroethane-acetonitrile(1∶1), 70 °C, 3 h; (d) R-Cl, NaH, DMAP, 0 °C, 1.5 h; R-O-R, DMAP, pyridine, r.t., 1.5 h; R-Br, NaH, TBAI, DMF, 80 °C, 3 h

1.2.1 2,3-脱氢水飞蓟宾（**SB-1**）的合成 水飞蓟宾 3 g 使用吡啶 30 mL 溶解，110 ℃ 加热回流 24 h，通过薄层层析色谱（TLC）监测反应终点。反应结束之后，减压回收吡啶，残余物用乙酸乙酯 40 mL 提取。将提取液静置一夜，用硅胶 10 g 过滤，减压回收乙酸乙酯。最后用甲醇重结晶，得化

合物 **SB-1**。

1.2.2　3,5,7,20,23-五甲氧基-2,3-脱氢水飞蓟宾（**SB-2**）的合成　称取化合物 **SB-1** 0.5 mmol(0.24 g)溶于 DMF 5 mL 中, 加入 NaH 5 mmol(0.12 g), 0 ℃反应 30 min, 之后加入 CH_3I 6.5 mmol(405 μL), 加入 TBAI 0.1 mmol(0.04 g)作为催化剂, 80 ℃反应 3 h, 通过 TLC 监测反应终点。反应结束后加入稀盐酸后抽滤得红色粉末。经硅胶薄层色谱纯化(石油醚-乙酸乙酯, 2∶1)得化合物 **SB-2**。

1.2.3　5-羟基-3,7,20,23-四甲氧基-2,3-脱氢水飞蓟宾（**SB-3**）的合成　称取化合物 **SB-2** 0.5 mmol (0.275 g)溶于 1,2-二氯乙烷-乙腈(1∶1) 5 mL 中, 加入 $AlCl_3$ 1.5 mmol(0.2 g), 以 TBAI 0.1 mmol(0.04 g)为催化剂, 70 ℃加热回流 3 h, 通过 TLC 监测反应终点。反应结束后, 加入稀盐酸搅拌过夜, 用水和二氯甲烷萃取, 旋蒸除去溶剂, 硅胶薄层色谱分离纯化(氯仿-丙酮, 10∶1)得化合物 **SB-3**。

1.2.4　5-*O*-苄基-3,7,20,23 -四甲氧基-2,3-脱氢水飞蓟宾（**I1**）的合成　称取化合物 **SB-3** 0.5 mmol (0.268 g)溶于 DMF 5 mL 中, 加入 NaH 1.5 mmol (0.036 g), 反应 30 min, 之后加入溴化苄 1.5 mmol (171 μL), 以 TBAI 0.1 mmol(0.04 g)为催化剂, 80 ℃反应 3 h。反应结束后加入稀盐酸析出结晶, 经硅胶薄层色谱纯化(石油醚-丙酮, 3∶1)得到化合物 **I1**。

1.2.5　5-酰氧基-3,7,20,23 -四甲氧基-2,3-脱氢水飞蓟宾（**I2~I16**）的合成通法　取化合物 **SB-3** 0.5 mmol 溶于 DCM 5 mL 中, 加入 NaH 2.2 mmol, 反应 30 min 后加入酰氯或酸酐 1.5 mmol, 以 TBAI 0.1 mmol(0.04 g)为催化剂, 0 ℃反应 1.5 h, 通过 TLC 监测反应终点。反应结束后, 用 DCM 和稀盐酸萃取, 减压旋干溶剂, 经硅胶薄层色谱纯化(石油醚-丙酮, 3∶1)得化合物 **I2~I16**。中间体、目标化合物 **I1~I16** 的收率、熔点、质谱数据列于表 1, ^{1}H NMR、^{13}C NMR 数据列于表 2。

2　体外抗肿瘤活性评价

采用四唑盐比色法即 MTT 法对化合物的抗肿瘤活性进行筛选。将生长至对数生长期的细胞消化、离心, 制成细胞悬液并吹匀。将 LN-229 和 SGC-7901 细胞密度调至每毫升 3×10^4 个, 接种于 96 孔板, 各孔 100 μL, 次日给予水飞蓟宾衍生物处理。

Table 1　Yield, melting point and MS data of target compounds

Compd.	Yield%	Melting/°C	ESI-MS *m/z*[M+H]$^+$
SB-1	62.0	230.2−233.5	481.43
SB-2	93.0	98.0−102.0	551.55
SB-3	86.0	114.3−119.5	537.53
I1	94.0	198.6−202.1	613.63
I2	91.1	155.4−158.3	641.64
I3	87.2	148.2−153.0	655.67
I4	89.3	132.1−134.0	676.08
I5	92.3	158.6−162.7	579.57
I6	85.6	223.2−225.1	669.7
I7	88.5	163.2−165.6	671.67
I8	90.1	183.4−186.7	655.67
I9	84.7	127.3−130.6	676.08
I10	91.3	153.4−156.2	710.53
I11	92.4	175.3−178.2	677.62
I12	86.8	241.0−244.3	647.69
I13	91.6	130.9−133.3	635.68
I14	87.1	257.8−259.2	631.6
I15	89.0	130.5−133.6	691.72
I16	96.1	148.5−152.3	709.64

使用细胞级 DMSO 溶解水飞蓟宾衍生物粉末, 充分混后分装到 EP 管中, 放于−80 ℃保存, 避免反复冻融。采用倍比稀释法配制水飞蓟宾衍生物系列梯度浓度的溶液, 以每孔 10 μL 的量加入 96 孔板中, 对照组加入等量溶剂。选用拉帕替尼为阳性对照药。给予化合物处理 48 h 后, 每孔加入 MTT 溶液 20 μL, 反应 2~4 h。从细胞培养箱中取出 96 孔板,吸去培养基(注意不要碰到孔底的结晶),每孔加入 DMSO 200 μL, 包裹锡纸后避光振荡使结晶完全溶解。使用酶标仪测量 490 nm 时的吸收度并记录数据。计算水飞蓟宾衍生物对肿瘤细胞体外增殖的抑制率。本实验独立重复 3 次。使用 Graph Pad Prism 软件计算最大半数抑制浓度(IC_{50})。

两组细胞实验结果表明, 化合物 **I2** 对 LN-229 细胞的抗增殖活性较为显著, IC_{50} 为 8.78 μmol/L, 化合物 **I14** 对 SGC-7901 细胞的抗增殖活性较为显著, IC_{50} 为 9.16 μmol/L, 与阳性对照药拉帕替尼相当。实验结果如表 3 所示。

3　结　论

本研究以水飞蓟宾为母体, 通过氧化脱氢、烷

Table 2 ^{1}H NMR and ^{13}C NMR data of target compounds

Compd.	^{1}H NMR (500 MHz)	^{13}C NMR (125 MHz)
SB-1	(DMSO-d_6) δ: 12.42 (1H, s, 5-OH), 10.81(1H, s, 7-OH), 9.56 (1H, s, 3-OH), 9.16 (1H, s, 20-OH), 7.77 (1H, t, J = 2.1 Hz, Ar-H), 7.75 (1H, d, J = 2.2 Hz, , Ar-H), 7.12 (1H, d, J = 8.5 Hz, Ar-H), 7.05 (1H, d, J =2.0 Hz, , Ar-H), 6.89 (1H, dd, J = 8.2, 2.0 Hz, Ar-H), 6.82 (1H, d, J = 8.0 Hz, Ar-H), 6.46 (1H, d, J = 2.0 Hz, Ar-H), 6.20 (1H, d, J = 2.0 Hz, Ar-H), 4.99 (1H, t, J = 5.6 Hz, 11-H), 4.97 (1H, d, J = 7.9 Hz, 23-OH), 4.28-4.26 (1H, m, 10-H), 3.80 (3H, s, -OCH_3), 3.58 (1H, ddd, J = 12.3, 5.0, 2.5 Hz, 23-H), 3.40−3.35 (1H, m, 23-H)	(Chloroform-d) δ: 176.94, 165.06, 161.65, 157.55, 148.16, 147.30, 145.78, 145.35, 144.51, 136.45, 128.61, 124.54, 122.88, 121.28, 116.85, 116.13, 115.56, 112.00, 102.98, 99.88, 94.59, 78.04, 76.90, 61.51, 56.16
SB-2	(Chloroform-d) δ: 7.77–7.70 (2H, m, Ar-H), 7.10 (1H, d, J = 8.6 Hz, Ar-H), 7.02 (1H, d, J = 8.2 Hz, Ar-H), 6.97–6.91 (2H, m, Ar-H), 6.47 (1H, d, J = 2.3 Hz, Ar-H), 6.32 (1H, d, J = 2.3 Hz, Ar-H), 5.05 (1H, d, J = 8.0 Hz, 11-H), 4.20-4.18 (1H, m, 10-H), 3.95 (3H, s, 5-OCH_3), 3.92 (6H, s, 3-OCH_3, 7-OCH_3), 3.89 (3H, s, 19-OCH_3), 3.87 (3H, s, 20-OCH_3), 3.62 (1H, dd, J = 5.5, 5.0 Hz, 23-H), 3.36 (3H, s, 23-OCH_3), 3.32 (1H, dd, J = 6.4, 4.5Hz, 23-H)	(DMSO-d_6) δ: 178.84, 165.49, 160.95, 156.75, 155.35, 149.76, 149.41, 146.01, 143.75, 139.20, 128.53, 123.69, 122.44, 120.13, 117.47, 111.32, 110.20, 106.09, 97.91, 92.05, 77.28, 76.32, 71.22, 59.77, 59.08, 56.08, 55.97
SB-3	(Chloroform-d) δ: 12.61 (1H, s, 5-OH), 7.77 (1H, d, J = 2.1 Hz, Ar-H), 7.73 (1H, dd, J = 8.6, 2.2 Hz, Ar-H), 7.12 (1H, d, J = 8.6 Hz, Ar-H), 7.02 (1H, d, J = 8.3 Hz, Ar-H), 6.94 (2H, s, Ar-H), 6.41 (1H, d, J = 2.1 Hz, Ar-H), 6.34 (1H, d, J = 2.2 Hz, Ar-H), 5.07–5.04 (1H, m, 11-H), 4.21–4.18 (1H, m, 10-H), 3.92 (6H, s, 3-OCH_3, 7-OCH_3), 3.88 (3H, s, 19-OCH_3), 3.85 (3H, s, 20-OCH_3), 3.62 (1H, dd, J = 5.4, 4.5 Hz, 23-H), 3.37 (3H, s, 23-OCH_3), 3.33 (1H, dd, J = 4.5, 4.0 Hz, 23-H)	(Chloroform-d) δ: 178.84, 165.49, 162.00, 156.75, 155.35, 149.76, 149.40, 146.00, 143.76, 139.19, 128.53, 123.69, 122.44, 120.13, 117.47, 111.32, 110.20, 106.09, 97.91, 92.05, 78.05, 76.30, 71.10, 60.18, 59.55, 56.03, 56.01, 55.79
I1	(DMSO-d_6) δ: 7.69 (2H, d, J = 6.7 Hz, Ar-H), 7.63 (2H, d, J = 7.0 Hz, Ar-H), 7.42 (2H, t, J = 7.5 Hz, Ar-H), 7.33 (1H, t, J = 7.3 Hz, Ar-H), 7.14 (1H, d, J = 9.2 Hz, Ar-H), 7.10 (1H, s, Ar-H), 7.02 (2H, s, Ar-H), 6.86 (1H, d, J = 2.3 Hz, Ar-H), 6.57 (1H, d, J = 2.3 Hz, Ar-H), 5.23 (2H, s, Ar-CH_2-), 5.00 (1H, d, J = 8.0 Hz, 11-H), 4.52–4.48 (1H, m, 10-H), 3.86 (3H, s, 3-OCH_3), 3.79 (6H, s, 7-OCH_3, 19-OCH_3), 3.78 (3H, s, 20-OCH_3), 3.46 (1H, dd, J = 5.0, 5.4 Hz, 23-H), 3.28 (1H, dd, J = 5.0, 5.5 Hz, 23-H), 3.23 (3H, s, 23-OCH_3)	(DMSO-d_6) δ: 172.73, 164.09, 159.46, 158.64, 151.62, 149.77, 149.32, 145.61, 143.93, 141.04, 137.29, 128.86, 128.80, 127.97, 127.31, 123.72, 122.12, 120.82, 117.46, 116.89, 112.04, 111.63, 109.25, 97.79, 93.80, 77.26, 76.31, 71.24, 70.36, 59.80, 59.09, 56.47, 56.08, 55.97
I2	(Chloroform-d) δ: 8.27 (2H, d, J = 4.0 Hz, Ar-H), 8.02 (2H, d, J = 5.2 Hz, Ar-H), 7.80 (1H, d, J = 4.4 Hz, Ar-H), 7.59–7.57 (1H, m, Ar-H), 7.52 (1H, d, J = 1.0 Hz, Ar-H), 7.10(1H, d, J = 8.0 Hz, Ar-H), 7.01–6.98 (1H, m, Ar-H), 6.92 (1H, d, J = 4.5 Hz, Ar-H), 6.89(1H, d, J = 8.0 Hz, Ar-H), 6.85 (1H, d, J = 1.8 Hz, Ar-H), 6.72 (2H, d, J = 1.8 Hz, Ar-H), 5.09 (1H, d, J = 6.1 Hz, 11-H), 4.50–4.47 (1H, m, 10-H), 4.27 (1H, dd, J = 4.4, 4.0 Hz, 23-H), 3.91 (3H, s, 3-OCH_3), 3.87 (3H, s, 7-OCH3), 3.82 (3H, s, 19-OCH_3), 3.77 (3H, s, 20-OCH_3), 3.37 (3H, s, 23-OCH_3), 3.32 (1H, dd, J = 4.5, 4.0 Hz, 23-H)	(DMSO-d_6) δ: 172.42, 163.94, 163.63, 157.69, 157.51, 153.41, 150.13, 149.77, 45.99, 144.00, 140.63, 133.71, 130.73, 130.67, 129.14, 128.81, 127.54, 127.49, 123.42, 122.44, 120.84, 116.58, 116.36, 112.04, 111.63, 111.15, 104.70, 99.92, 77.30, 76.33, 71.23, 59.94, 59.09, 56.92, 56.07, 55.97
I3	(Chloroform-d) δ: 8.33 (1H, dd, J = 7.8, 1.5 Hz, Ar-H), 7.76 (1H, d, J = 2.1 Hz, Ar-H), 7.72 (1H, dd, J = 8.6, 2.2 Hz, Ar-H), 7.46 (1H, dd, J = 7.5, 8.0 Hz, Ar-H), 7.35–7.29 (2H, m, Ar-H), 7.12 (1H, d, J = 8.6 Hz, Ar-H), 7.02 (1H, dd, J = 8.2, 1.9 Hz, Ar-H), 6.97–6.92 (2H, m, Ar-H), 6.84 (1H, d, J = 2.5 Hz, Ar-H), 6.69 (1H, d, J = 2.4 Hz, Ar-H), 5.06 (1H, d, J = 8.1 Hz, 11-H), 4.21–4.18 (1H, m, 10-H), 3.92 (6H, s, 3-OCH_3, 7-OCH_3), 3.91 (3H, s, 19-OCH_3), 3.78 (3H, s, 20-OCH_3), 3.62 (1H, dd, J =5.5, 5.0 Hz, 23-H), 3.37 (3H, s, 23-OCH_3), 3.32 (1H, dd, J = 4.5, 3.0 Hz, 23-H), 2.67 (3H, s, Ar-CH_3)	(DMSO-d_6) δ: 172.49, 165.42, 163.68, 157.73, 157.68, 153.36, 150.24, 149.77, 149.31, 145.98, 144.01,140.65, 140.56, 133.14, 132.10, 131.63, 129.20, 128.82, 126.48, 123.46, 122.44, 120.85, 117.56, 117.17, 112.03, 111.63, 111.31, 99.80, 77.29, 76.33, 71.23, 59.90, 59.09, 56.92, 56.02, 55.97, 21.45
I4	(Chloroform-d) δ: 7.93 (1H, d, J = 8.5 Hz, Ar-H), 7.75 (1H, d, J = 2.0 Hz, Ar-H), 7.49 (3H, dd, J = 8.6, 1.5 Hz, Ar-H), 7.43 (2H, d, J = 8.6 Hz, Ar-H), 7.02 (1H, dd, J = 8.2, 2.0 Hz, Ar-H), 6.96 -6.99 (2H, m, Ar-H), 6.85 (1H, dd, J = 4.5, 4.0 Hz, Ar-H), 6.71 (1H, t, J = 5.6 Hz, Ar-H), 5.04 (1H, d, J = 7.8 Hz, 11-H), 4.24–4.15 (1H, m, 10-H), 3.92 (6H, s, 3-OCH_3, 7-OCH_3), 3.85 (3H, s, 19-OCH_3), 3.76 (3H, s, 20-OCH_3), 3.63 (1H, dd, J = 4.5, 4.1 Hz, 23-H), 3.37 (3H, s, 23-OCH_3), 3.33 (1H, dd, J = 5.5, 4.1 Hz, 23-H)	(DMSO-d_6) δ: 171.34, 162.79, 161.97, 157.67, 157.45, 152.72, 149.77, 149.31, 146.22, 145.98, 143.99, 140.80, 132.30, 130.36, 129.05, 128.79, 123.25, 122.39, 120.85, 117.54, 117.09, 112.03, 111.82, 111.63, 109.25, 101.02, 77.28, 76.32, 71.22, 59.77, 59.09, 56.98, 56.08, 56.04, 55.97

(Continued)

Compd.	^{1}H NMR (500 MHz)	^{13}C NMR (125 MHz)
I5	(Chloroform-*d*) *δ*: 7.75 (1H, d, *J* = 2.1 Hz, Ar-H), 7.71 (1H, d, *J* = 8.7 Hz, Ar-H), 7.12 (1H, d, *J* = 8.7 Hz, Ar-H), 7.02 (1H, dd, *J* = 8.2, 2.0 Hz, Ar-H), 6.98–6.91 (2H, m, Ar-H), 6.79 (1H, d, *J* = 2.4 Hz, Ar-H), 6.58 (1H, d, *J* = 2.5 Hz, Ar-H), 5.06 (1H, d, *J* = 8.1 Hz, 11-H), 4.21–4.17 (1H, m, 10-H), 3.92 (6H, s, 3-OCH_3, 7-OCH_3), 3.88 (3H, s, 19-OCH_3), 3.81 (3H, s, 20-OCH_3), 3.62 (1H, dd, *J* = 5.5, 5.0 Hz, 23-H), 3.37 (3H, s, 23-OCH_3), 3.32 (1H, dd, *J* = 4.5, 4.0Hz, 23-H), 2.45 (3H, s, -$COCH_3$)	(DMSO-d_6) *δ*: 172.73, 169.05, 164.08, 159.46, 159.01, 151.62, 149.77, 149.32, 145.61, 143.93, 137.29, 127.97, 123.72, 122.12, 120.82, 117.47, 116.88, 112.04, 111.63, 111.08, 109.25, 97.79, 77.27, 76.31, 71.24, 59.80, 59.08, 56.46, 56.08, 55.97, 20.62
I6	(Chloroform-*d*) *δ*: 7.71 (1H, dd, *J* = 5.1, 1.6 Hz, Ar-H), 7.33–7.31 (4H, m, Ar-H), 7.24–7.19 (2H, m, Ar-H), 7.12 (1H, dd, *J* =4.4, 3.2 Hz, Ar-H), 7.02 (1H, dd, *J* =4.4 , 2.1 Hz, Ar-H), 6.98–6.90 (3H, m, Ar-H), 6.76 (1H, d, *J* = 1.9 Hz, Ar-H), 5.01 (1H, d, *J* = 6.1 Hz, 11-H), 4.21–4.18 (1H, m, 10-H), 3.92(6H, s, 3-OCH_3, 7-OCH_3), 3.87(3H, s, 19-OCH_3), 3.81(3H, s, 20-OCH_3), 3.63 (1H, dd, *J* = 6.7, 2.0 Hz, 23-H), 3.37(3H, s, 23-OCH_3), 3.33 (1H, dd, *J* = 8.0, 5.3 Hz, 23-H), 3.17–3.09 (4H, m, -CH2-CH_2-)	(DMSO-d_6) *δ*: 172.49, 171.23, 163.57, 157.72, 153.35, 150.18, 149.76, 149.30, 145.98, 143.99, 140.87, 140.67, 128.88, 128.66, 128.53, 125.74, 123.42, 122.44, 120.85, 117.57, 117.17, 112.03, 111.61, 111.09, 105.11, 99.63, 77.28, 76.32, 71.22, 59.96, 59.09, 56.88, 56.07, 55.97, 35.41, 30.34
I7	(Chloroform-*d*) *δ*: 7.97–7.91 (2H, m, Ar-H), 7.76–7.74 (1H, m, Ar-H), 7.48 (3H, dd, *J* = 6.4, 1.2 Hz, Ar-H), 7.02 (1H, dd, *J* = 6.2, 1.5 Hz, Ar-H), 6.98–6.96 (2H, m, Ar-H), 6.87–6.84 (2H, m, Ar-H), 6.71 (1H, t, *J* = 6.1 Hz, Ar-H), 5.04 (1H, d, *J* = 5.8 Hz, 11-H), 4.21-4.19 (1H, m, 10-H), 3.92(6H, s, 3-OCH_3, 7-OCH_3), 3.87(3H, s, 19-OCH_3), 3.84(3H, s, 20-OCH_3), 3.76(3H, s, Ar-OCH_3), 3.62 (1H, dd, *J* = 8.3, 1.7 Hz, 23-H), 3.37(3H, s, 23-OCH_3), 3.33 (1H, dd, *J* = 4.0, 4.4 Hz, 23-H)	(DMSO-d_6) *δ*: 163.73, 163.25, 156.52, 155.90, 153.50, 149.83, 149.40, 149.37, 148.85, 146.09, 140.73, 133.66, 128.88, 123.49, 122.55, 120.94, 120.54, 117.67, 117.26, 114.05, 112.10, 111.69, 109.15, 104.76, 100.16, 77.36, 76.41, 71.31, 60.08, 59.18, 57.04, 56.16, 56.05, 55.86
I8	(DMSO-d_6) *δ*: 7.75 (1H, d, *J* = 1.3 Hz, Ar-H), 7.73 (1H, d, *J* = 1.6 Hz, Ar-H), 7.47 (1H, d, *J* = 5.3 Hz, Ar-H), 7.42 (1H, d, *J* = 1.6 Hz, Ar-H), 7.38–7.35 (2H, m, Ar-H), 7.18 (2H, dd, *J* = 7.0, 1.6 Hz, Ar-H), 7.10(1H, s, Ar-H), 7.02(2H, s, Ar-H), 6.83 (1H, d, *J* = 6.0 Hz, Ar-H), 6.76 (1H, d, *J* = 1.8 Hz, Ar-H), 5.02 (1H, d, *J* = 8.0 Hz, 11-H), 4.56–4.51 (1H, m, 10-H), 3.84 (2H, d, *J* = 9.4 Hz, Ar-CH_2-), 3.79 (6H, s, 3-OCH_3, 7-OCH_3), 3.78 (3H, s, 19-OCH_3), 3.77 (3H, s, 20-OCH_3), 3.47 (1H, dd, *J* = 9.2, 7.5Hz, 23-H), 3.30 (1H, dd, *J* = 6.5, 5.0Hz, 23-OCH_3), 3.23 (3H, s, 23-H)	(DMSO-d_6) *δ*: 172.62, 165.55, 163.81, 157.87, 153.50, 150.37, 149.91, 149.45, 146.12, 144.14, 140.80, 140.70, 131.77, 129.51, 129.40, 126.62, 123.59, 122.57, 120.99, 117.70, 117.31, 112.17, 111.77, 111.45, 109.16, 99.93, 77.43, 76.47, 71.37, 60.04, 59.23, 57.06, 56.22, 56.11, 34.99
I9	(Chloroform-*d*) *δ*: 8.14–8.10 (1H, m, Ar-H), 7.98 (1H, d, *J* = 1.5 Hz, Ar-H), 7.76 (1H, dd, *J* = 8.5, 1.7 Hz, Ar-H), 7.51–7.48 (1H, m, Ar-H), 7.44–7.41 (2H, m, Ar-H), 7.04–6.95 (4H, m, Ar-H), 6.85 (1H, t, *J* = 1.5 Hz, Ar-H), 6.71 (1H, dd, *J* = 5.2, 4.0 Hz, Ar-H), 5.04 (1H, d, *J* = 5.8 Hz, 11-H), 4.21–4.17 (1H, m, 10-H), 3.92(6H, s, 3-OCH_3, 7-OCH_3), 3.87(3H, s, 19-OCH_3), 3.76(3H, s, 20-OCH_3), 3.62 (1H, dd, *J* = 8.2, 1.5 Hz, 23-H), 3.37(3H, s, 23-OCH_3), 3.33 (1H, dd, *J* = 8.2, 1.7 Hz, 23-H)	(DMSO-d_6) *δ*: 172.33, 171.07, 163.41, 157.56, 157.02, 153.19, 149.60, 149.14, 145.82, 143.83, 140.71, 134.33, 132.58, 129.48, 128.72, 128.50, 128.37, 128.10, 123.26, 122.28, 120.69, 117.40, 117.01, 111.87, 111.45, 110.94, 104.95, 99.47, 77.12, 76.16, 71.06, 59.80, 58.93, 56.72, 55.91, 55.81
I10	(DMSO-d_6) *δ*: 8.30 (1H, d, *J* = 6.4 Hz, Ar-H), 7.87 (1H, d, *J* = 1.6 Hz, Ar-H), 7.74 (2H, d, *J* = 1.6 Hz, Ar-H), 7.71 (1H,d, *J* = 1.6 Hz, Ar-H), 7.69 (1H, d, *J* = 1.6 Hz, Ar-H), 7.35 (1H, d, *J* = 1.8 Hz, Ar-H), 7.18–7.16 (1H, m, Ar-H), 7.09 (1H, s, Ar-H), 7.01 (1H, s, Ar-H), 6.95 (1H, d, *J* = 1.8 Hz, Ar-H), 5.01 (1H, d, *J* = 6.0 Hz, 11-H), 4.23–4.16 (1H, m, 10-H), 3.92 (3H, s, 3-OCH_3), 3.78 (6H, s, 7-OCH_3, 19-OCH_3), 3.70 (3H, s, 20-OCH_3), 3.46 (1H, dd, *J* = 5.0, 4.5 Hz, 23-H), 3.29 (1H, dd, *J* = 4.5, 4.0 Hz, 23-H), 3.22 (3H, s, 23-OCH_3)	(DMSO-d_6) *δ*: 172.65, 166.44, 163.85, 157.84, 157.40, 153.73, 149.90, 149.44, 146.17, 144.14, 140.05, 137.72, 134.42, 133.09, 130.43, 128.93, 127.23, 126.52, 123.51, 122.61, 120.97, 117.70, 117.33, 112.15, 111.74, 110.99, 109.08, 100.28, 77.31, 76.33, 71.22, 59.95, 59.09, 56.99, 56.07, 55.96
I11	(DMSO-d_6) *δ*: 8.31 (1H, d, *J* = 8.5 Hz, Ar-H), 7.90–7.84 (2H, m, Ar-H), 7.80–7.77 (1H, m, Ar-H), 7.55 (1H, dd, *J* = 8.4, 2.1 Hz, Ar-H), 7.36 (1H, d, *J* = 2.5 Hz, Ar-H), 7.19 (2H, t, *J* = 8.8 Hz, Ar-H), 7.06 (1H, d, *J* = 8.4 Hz, Ar-H), 6.97 (1H, t, *J* = 2.2 Hz, Ar-H), 6.69 (1H, d, *J* = 8.0 Hz, Ar-H), 5.03 (1H, d, *J* = 8.0 Hz, 11-H), 4.55–4.52 (1H, m, 10-H), 3.79 (6H, d, *J* = 2.3 Hz, 3-OCH_3, 7-OCH_3), 3.75(3H, s, 19-OCH_3), 3.71(3H, s, 20-OCH_3), 3.47 (1H, dd, *J* = 8.5, 4.0 Hz, 23-H), 3.29 (1H, d, *J* = 4.7 Hz, 23-H), 3.23(3H, s, 23-OCH_3)	(DMSO-d_6) *δ*: 172.42, 166.08, 163.92, 163.63, 161.00, 157.69, 157.08, 153.41, 149.77, 149.32, 145.99, 144.00, 140.63, 133.35, 128.81, 123.42, 122.44, 120.84, 116.58, 116.36, 115.22, 112.04, 111.63, 111.15, 109.00, 105.34, 105.12, 99.92, 77.30, 76.33, 71.23, 59.94, 59.09, 56.92, 56.07, 55.97

(Continued)

Compd.	^{1}H NMR (500 MHz)	^{13}C NMR (125 MHz)
I12	(DMSO-d_6) δ: 8.20 (1H, d, J = 3.1 Hz, Ar-H), 7.72 (1H, d, J = 7.3 Hz, Ar-H), 7.47 (2H, t, J = 8.0 Hz, Ar-H), 7.17 (1H, d, J = 9.4 Hz, Ar-H), 7.10 (1H, s, Ar-H), 7.02 (1H, s, Ar-H), 6.95(1H, d, J = 2.5 Hz, Ar-H), 5.02 (1H, d, J = 8.0 Hz, 11-H), 4.56–4.51 (1H, m, 10-H), 3.92 (3H, s, 3-OCH_3), 3.79 (6H, s, 7-OCH_3, 19-OCH_3), 3.67 (3H, s, 20-OCH_3), 3.47 (1H, dd, J = 4.0, 4.5 Hz, 23-H), 3.31 (1H, d, J = 4.0Hz, 23-H), 3.23 (3H, s, 23-OCH_3), 2.08–2.02 (1H, m, -CH-), 1.74–1.59 (4H, m, 2(-CH_2-)), 1.52–1.42 (2H, m, -CH_2-), 1.36–1.20 (4H, m, 2(-CH_2-))	(DMSO-d_6) δ: 172.42, 171.54, 163.63, 157.69, 153.41, 150.13, 149.77, 149.32, 145.99, 144.00, 140.63, 128.81, 123.42, 122.44, 120.84, 116.58, 116.36, 112.04, 111.63, 111.15, 109.00, 99.92, 77.30, 76.33, 71.23, 59.94, 59.09, 56.92, 56.07, 55.97, 43.86, 29.13, 25.58, 25.49
I13	(DMSO-d_6) δ: 7.70-7.71 (2H, m, Ar-H), 7.27 (1H, d, J = 2.4 Hz, Ar-H), 7.17 (1H, d, J = 9.2 Hz, Ar-H), 7.10 (1H, s, Ar-H), 7.02 (2H, s, Ar-H), 6.74 (1H, d, J = 2.4 Hz, Ar-H), 5.02 (1H, d, J = 8.0 Hz, 11-H), 4.53-4.51 (1H, m, 10-H), 3.90 (3H, s, 3-OCH_3), 3.79 (6H, d, J = 2.3 Hz, 7-OCH_3, 19-OCH_3), 3.73 (3H, s, 20-OCH_3), 3.47 (1H, dd, J = 9.5, 5.0 Hz, 23-H), 3.30 (1H, d, J = 6.5 Hz, 23-H), 3.23 (3H, s, 23-OCH_3), 2.66 (2H, t, J=7.5 Hz, -CH_2-), 1.70–1.64 (2H, m, -CH_2-), 1.39–1.35 (4H, m, -CH_2-CH_2-), 0.92 (3H, t, J = 6.9 Hz, -CH_3)	(DMSO-d_6) δ: 172.52, 166.31, 163.72, 162.37, 157.71, 153.60, 149.77, 149.31, 146.04, 144.01, 128.80, 123.38, 122.48, 120.84, 117.57, 117.20, 112.02, 111.61, 110.86, 108.95, 100.15, 77.31, 76.33, 71.22, 59.95, 59.09, 56.07, 55.96, 34.85, 30.88, 24.50, 22.19, 14.03
I14	(Chloroform-d) δ: 8.28 (2H, dd, J = 8.6, 5.5 Hz, Ar-H), 7.76–7.70 (2H, m, Ar-H), 7.18 (2H, t, J = 8.4 Hz, Ar-H), 7.12 (1H, d, J = 8.6 Hz, Ar-H), 7.02 (1H, d, J = 8.2 Hz, Ar-H), 6.97–6.92 (2H, m, Ar-H), 6.84 (1H, d, J = 2.5 Hz, Ar-H), 5.06 (1H, d, J = 8.1 Hz, 11-H), 4.21–4.17 (1H, m, 10-H), 3.92 (6H, s, 3-OCH_3, 7-OCH_3), 3.90 (3H, s, 19-OCH_3), 3.75 (3H, s, 20-OCH_3), 3.62 (1H, dd, J = 11.0, 2.2 Hz, 23-H), 3.37 (3H, s, 23-OCH_3), 3.33 (1H, dd, J = 7.3, 5.0 Hz, 23-H)	(DMSO-d_6) δ: 172.33, 163.64, 157.66, 156.43, 155.81, 153.41, 149.74, 149.31, 149.28, 148.76, 146.00, 144.00, 140.64, 133.57, 128.79, 123.40, 122.46, 120.85, 120.45, 117.58, 117.17, 112.01, 111.60, 109.06, 100.07, 77.27, 76.32, 71.22, 59.99, 59.09, 56.95, 56.07, 55.96
I15	(Chloroform-d) δ: 8.00 (1H, s, Ar-H), 7.98 (1H, s, Ar-H), 7.73 (1H, d, J = 2.1 Hz, Ar-H), 7.69 (1H, dd, J = 8.7, 2.2 Hz, Ar-H), 7.32 (2H, d, J = 8.1 Hz, Ar-H), 7.10 (1H, d, J = 8.6 Hz, Ar-H), 7.04–7.01 (1H, m, Ar-H), 6.96–6.92 (2H, m, Ar-H), 6.83–6.81 (2H, m, Ar-H), 5.05 (1H, d, J = 8.2 Hz, 11-H), 4.20–4.17 (1H, m, 10-H), 3.92 (6H, s, 3-OCH_3, 7-OCH_3), 3.87 (3H, s, 19-OCH_3), 3.79 (3H, s, 20-OCH_3), 3.62 (1H, dd, J = 5.4, 4.5 Hz, 23-H), 3.36 (3H, s, 23-OCH_3), 3.32 (1H, dd, J =5.5, 5.0 Hz, 23-H), 2.42 (3H, s, Ar-CH_3)	(DMSO-d_6) δ: 171.34, 162.79, 157.67, 152.72, 149.77, 149.31, 147.30, 146.22, 145.98, 143.99, 140.80, 132.30, 130.36, 129.05, 128.79, 123.25, 122.39, 120.85, 117.54, 117.09, 112.03, 111.82, 111.63, 109.25, 101.02, 77.28, 76.32, 71.22, 59.77, 59.09, 56.98, 56.04, 56.03, 21.59
I16	(Chloroform-d) δ: 8.38 (1H, d, J = 6.1 Hz, Ar-H), 7.81–7.74 (3H, m, Ar-H), 7.72 (1H, dd, J = 6.5, 1.6 Hz, Ar-H), 7.12 (1H, dd, J = 6.5, 1.8 Hz, Ar-H), 7.02 (1H, dd, J = 6.2, 1.5 Hz, Ar-H), 6.97–6.93 (2H, m, Ar-H), 6.86 (1H, d, J = 1.8 Hz, Ar-H), 6.73 (1H, d, J = 1.8 Hz, Ar-H), 6.38 (1H, dd, J = 6.1, 1.7 Hz, Ar-H), 5.06 (1H, d, J = 6.0 Hz, 11-H), 4.21–4.18 (1H, m, 10-H), 3.92(6H, s, 3-OCH_3, 7-OCH_3), 3.89(3H, s, 19-OCH_3), 3.86(3H, s, 20-OCH_3), 3.63 (1H, dd, J = 4.5, 4.0Hz, 23-H), 3.37(3H, s, 23-OCH_3), 3.33 (1H, dd, J = 5.5, 4.1Hz, 23-H)	(Chloroform-d) δ: 178.84, 165.70, 165.49, 162.00, 156.75, 155.36, 149.76, 149.41, 146.01, 143.75, 139.20, 136.08, 135.65, 135.05, 134.41, 131.04, 131.01, 129.55, 128.53, 126.52, 126.36, 123.69, 122.48, 122.44, 121.58, 120.90, 120.13, 119.60, 117.47, 116.80, 112.06, 111.32, 110.20, 106.09, 97.91, 78.05, 76.30, 71.10, 60.18, 59.55, 56.03, 56.00, 55.78

Table 3 *In vitro* inhibitory activity of target compounds on SGC-7901 and LN-229

Compd.	Inhibition[a]/%		IC_{50}[b]/(μmol/L)	
	LN-229	SGC-7901	LN-229	SGC-7901
I1	18.7	17.4	>50	>50
I2	51.4	48.1	8.78	12.54
I3	48.1	48.7	12.54	16.35
I4	40.1	38.1	16.59	18.03
I5	47.9	43.2	12.98	15.86
I6	20.3	22.4	30.01	29.98
I7	25.1	24.3	27.31	26.79
I8	19.8	18.6	36.47	45.16
I9	48.7	49.5	11.91	11.66
I10	33.9	34.1	20.46	19.81

(Continued)

Compd.	Inhibition[a]/%		IC_{50}[b]/(μmol/L)	
	LN-229	SGC-7901	LN-229	SGC-7901
I11	34.6	35.4	18.33	18.56
I12	39.2	42.8	17.53	15.41
I13	44.8	48.2	14.31	12.03
I14	49.6	50.8	11.59	9.16
I15	38.8	34.2	17.59	15.53
I16	43.3	40.5	17.05	16.71
Silybin	20.1	21.5	30.68	29.88
Lapatinib	57.4	49.8	7.54	8.31

[a]Percentage of cells inhibited by the compound concentration of 10 μmol/L was treated for 48 h; [b]Inhibition rate of LN-229 and SCG-7901 cells reached 50%

基化、选择性去甲基、酰化等反应合成了 16 个新型水飞蓟宾衍生物。两组细胞实验结果显示, 合成的化合物对 SGC-7901 胃癌细胞和 LN-229 人胶质母细胞瘤细胞均有一定程度的抑制作用。其中化合物 **I2** 和 **I14** 分别对 LN-229 细胞和 SGC-7901 细胞显示较强的抗增殖活性。初步构效关系表明, 在 5-OH 上引入吸电子基团有助于提高水飞蓟宾的抗肿瘤活性, 为后续水飞蓟宾相关抗肿瘤药物的研发提供了参考。

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