

· 论著 ·

新型二氢呋喃类化合物的合成及抑制血小板聚集活性研究

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[摘要] 目的 研究 2-(4-甲氧基苯基)-4-乙烯基-2,5-二氢呋喃-3-羧酸及其衍生物的合成及抗血小板凝集活性。方法 设计合成未见报道的目标化合物 17 个, 应用 ¹H-NMR、MS 对得到的目标化合物进行结构鉴定, 采用 Born 方法对目标化合物进行体外抗凝血活性测试。结果 合成得到 2-(4-甲氧基苯基)-4-乙烯基-2,5-二氢呋喃-3-羧酸及其衍生物 17 个, 所有目标化合物均具有优于对照药 MCI-154 的抗血小板凝集活性。结论 2-(4-甲氧基苯基)-4-乙烯基-2,5-二氢呋喃-3-羧酸及其衍生物具有较好的抗凝血药理活性, 其中化合物 (3)、(6) 和 (10) 的活性分别是到对照药 MCI-154 的 22.2、12.8 和 8.6 倍, 具有很强的开发应用前景。

[关键词] 3-取代呋喃羧酸类化合物; 合成; 抗凝血

[中图分类号] R973⁺.2, R914.5 **[文献标志码]** A **[文章编号]** 1006-0111(2014)02-0102-05

[DOI] 10.3969/j.issn.1006-0111.2014.02.007

Synthesis and anti-platelet aggregative activity of novel 2, 5-dihydrofuran derivatives

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[Abstract] **Objective** To study the synthesis and anti-platelet aggregative activity of 2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxylic acid derivatives. **Methods** 17 target compounds were designed, synthesized and determined *via* ¹H-NMR spectra and MS. The anti-platelet aggregative activities of the target compounds *in vitro* were assessed by Born method. **Results** The results of preliminary pharmacological test showed that all the target compounds had good anti-platelet aggregative activity *in vitro* and compounds 3, 6 and 10 were the best candidates, which had 22.2, 12.8 and 8.6 times than positive control, respectively. **Conclusion** 2-(4-methoxyphenyl)-4-vinyl-2,5-dihydrofuran-3-carboxylic acid derivatives had a pharmacological activity of anti-coagulation. The anti-platelet aggregative activities of compounds 3, 6 and 10 could be worth to further research.

[Key words] pyridazinones; synthesis; antiplatelet aggregation activity

近年来, 脑血栓、心肌梗死、外周动脉血栓、深静脉血栓等一系列血栓栓塞疾病严重威胁着人类健康, 其发病率、致残率和致死率都居各类疾病之首, 成为危害人类健康的头号杀手, 而大多数心脑血管疾病都与凝血异常所导致的血栓和血栓栓塞有着密切的联系^[1,2]。血小板在止血、血栓形成、动脉粥样硬化等过程中起着重要作用, 因此阻止血小板凝集就可以达到抗凝的目的。抗血小板治疗是通过药物阻滞血小板聚集而起到预防血栓形成, 减少缺血性卒死事件的发生; 同时也是缺血性卒死一级和二级

预防的重要组成部分^[3,4]。

木脂素类化合物具有多种结构类型, 体外活性测试表明, 该类型的化合物体外具有抗肿瘤、保肝、调节中枢神经、松弛平滑肌、抗菌、抗病毒等多种生物学活性^[5]。本课题组首次以 2-(4-甲氧基苯基)-4-乙烯基-2,5-二氢呋喃为母核, 对该类木脂素化合物进行抗凝血活性研究, 在此基础上设计合成了结构为 2-(4-甲氧基苯基)-4-乙烯基-2,5-二氢呋喃-3-羧酸的前体化合物, 并在其 3 位侧链引入不同的杂环基团共设计合成了 17 个新目标化合物, 并对所合成的目标化合物进行抑制血小板凝集的抗凝血活性测试。

1 实验部分

1.1 仪器及材料 RY-2 型熔点仪, 温度未经过校

[基金项目] 国家自然科学基金(30973640)。

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正;核磁共振氢谱用 Bruker Spectmspin AC-P300 型核磁共振测定, CDCl_3 为溶剂, TMS 为内标;对对照品 MCI-154^[6] 由第二军医大学药学院有机教研室合成;合成过程中所用原料及试剂均为市售分析纯。

1.2 2-(4-甲氧基苯基)-4-乙烯基-2,5-二氢咪喃-3-羧酸的合成 见图1。

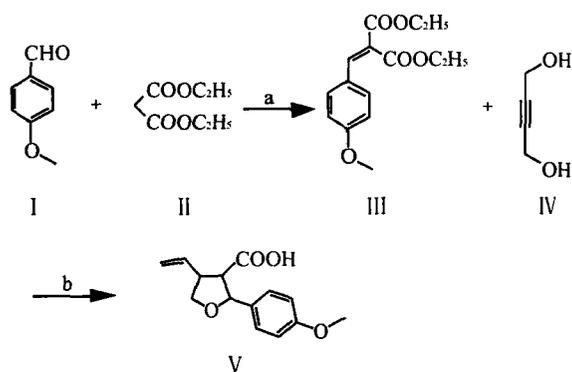


图1 中间体 V 的合成方法

a. 吡啶, 乙酸, 甲苯, 回流, 6 h, 产率: 85%;

b. 钠氢, 碘化亚铜, 四氢呋喃, 40 °C, 6 h, 产率: 90%

1.2.1 芳基次甲基丙二酸二乙酯(III)的合成 将 60.75 ml 对甲氧基苯甲醛、90 ml 丙二酸二乙酯及 15 ml 冰乙酸、6 ml 吡啶加入 500 ml 无水甲苯中, 加热至回流, 用分水器和分水器分出反应过程中生成的水。9 h 后终止反应, 减压蒸去甲苯, 油泵蒸去丙二酸二乙酯得油状粗产品。在粗产品中加乙醇 50 ml 于冰箱中冰冻结晶, 得到白色固体 III (129.6 g, 收率 80%), mp: 145.1 ~ 145.5 °C。

1.2.2 4-乙烯基-2-对甲氧基苯基-2,5-二氢咪喃-3-羧酸(V)的合成 在冰浴条件下, 将 NaH (17.28 g, 0.72 mol) 加入 100 ml 的无水的 THF 中, 搅拌 30 min 后将 1,4-丁炔二醇 (23.24 g, 0.27 mol) 溶解于 60 ml 无水 THF 中, 用恒压滴液漏斗滴入上述 NaH 的无水 THF 中, 剧烈搅拌; 将芳基次甲基丙二酸二乙酯(III) 用 100 ml 无水 THF 溶解, 缓慢滴入反应液中, 继而将研细的 CuI 一次加入到反应瓶中。将反应烧瓶油浴加热至 40 °C, 恒温下搅拌 6 h。用 TLC 监测至反应结束, 向反应液中缓慢加入 100 ml 水, 用稀盐酸调 pH 值至 2 ~ 3。减压回收 THF, 用 100 ml 二氯甲烷反复萃取 3 次, 合并二氯甲烷相, 用 MgSO_4 干燥后进行硅胶柱色谱分离, 以 PE : EA = 10 : 1 洗脱, 得关键中间体 V。

1.3 目标化合物的合成

1.3.1 苯胺、苄胺及苯乙胺类衍生物的合成(图2) 将 2-(4-甲氧基苯基)-4-乙烯基-2,5-二氢咪喃-3-羧酸(0.5 g, 1.89 mmol) 加入 5 ml 无水 CH_2Cl_2 中, 加入 1 ml 的 SOCl_2 。加热回流 4 h, 减压蒸去溶剂, 用少量无水 CH_2Cl_2 除去过量 SOCl_2 , 得到固体粗产物。将粗产物加入 10 ml 的无水 CH_2Cl_2 中, 将溶液置于冰盐浴中使反应瓶温度降低至 0 °C 以下, 向 CH_2Cl_2 溶液中缓慢加入 1.1 倍量苄胺 (2.12 mmol) 和 1 ml 吡啶, 搅拌 3 h 后撤去冰盐浴常温搅拌过夜。加入 3 ml 冰乙酸终止反应, 浓缩反应液后倒入冰水中, 有固体析出, 过滤, 洗涤, 干燥, 得到目标产物。

1.3.2 哌嗪类衍生物的合成(图3) 将 2-(4-甲氧基苯基)-4-乙烯基-2,5-二氢咪喃-3-羧酸 (0.2 g, 0.5 mmol) 加入到 5 ml 无水 CH_2Cl_2 中, 搅拌, 加入 1 ml 的 SOCl_2 , 加热回流 4 h, 减压蒸去溶剂, 用少量无水 CH_2Cl_2 除去过量 SOCl_2 , 得到固体粗产物。将此固体加入 10 ml 的无水 CH_2Cl_2 中, 将溶液置于冰盐浴中使反应瓶温度降低至 0 °C 以下, 向 CH_2Cl_2 溶液中缓慢加入 1.5 倍量 2,3-二氯苯基哌嗪和 NaH (0.2 g, 8.3 mmol), 搅拌 3 h 后撤去冰浴常温搅拌过夜。加入 3 ml 冰乙酸终止反应, 浓缩反应液后倒入冰水中, 有固体析出, 过滤, 洗涤, 干燥, 得到目标产物。

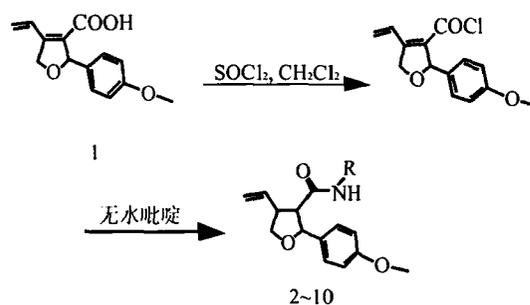


图2 苯胺、苄胺、苯乙胺衍生物系列的合成

1.3.3 其他目标化合物均按以上方法合成 17 个目标化合物经光谱确证结构, 其数据见表 1。

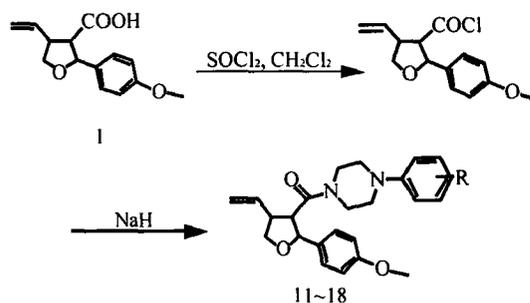
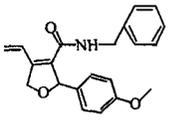
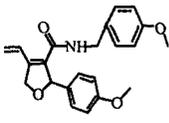
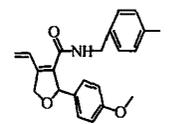
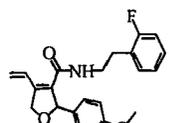
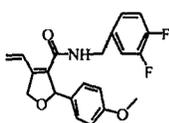
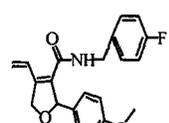
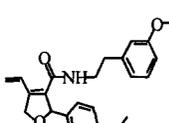
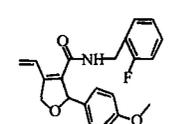
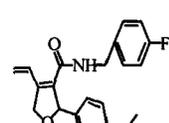
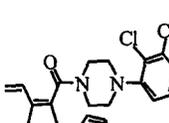
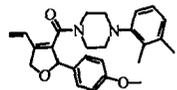
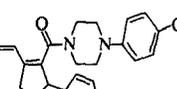
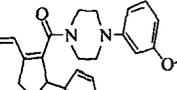
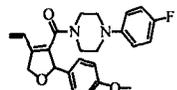
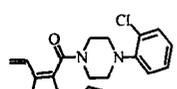
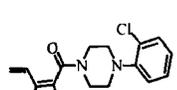
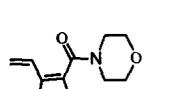


图3 哌嗪衍生物系列的合成

表1 合成目标化合物结构,理化常数及氢谱数据

化合物编号	R 基团	mp(°C)	产量 (%)	¹ H-NMR (CDCl ₃)
2		165.1 ~ 165.5	94	7.40 (q, 1H, C = CH-); 7.26 (d, 2H, J = 7.2 Hz, Ph-H); 6.88 (d, 2H, J = 6.9 Hz, Ph-H); 5.92 (m, 1H, -CH-Ph); 5.50 (d, 1H, J = 6.9 Hz, CH ₂ = C-); 5.41 (s, 1H, -CONH); 5.34 (d, 1H, J = 12.5 Hz, CH ₂ = C-); 5.11 (dd, 1H, J ₁ = 6 Hz, J ₂ = 6 Hz, -CH ₂ -O); 4.94 (dd, 1H, J = 6 Hz, J = 6 Hz, -CH ₂ -O); 4.36 (m, 2H, -N-CH ₂ -); 3.80 (s, 3H, -OCH ₃).
3		157 ~ 157.5	75	7.37 (q, 1H, C = CH-); 7.25 (m, 2H, Ph-H); 6.85 (d, 2H, J = 9 Hz, Ph-H); 6.78 (d, 2H, J = 9 Hz, Ph-H); 6.74 (d, 2H, J = 12 Hz, Ph-H); 5.90 (t, 1H, -CH-Ph); 5.50 (d, 1H, J = 9 Hz, CH ₂ = C-); 5.36 (s, 1H, -CONH); 5.31 (s, 1H, CH ₂ = C-); 5.10 (dd, 1H, J ₁ = 9 Hz, J ₂ = 9 Hz, -CH ₂ -O); 4.94 (dd, 1H, J = 12 Hz, J = 12 Hz, -CH ₂ -O); 4.25 (m, 2H, -N-CH ₂ -); 3.76 (m, 6H, -OCH ₃).
4		150.4 ~ 150.7	92	7.40 (q, 1H, C = CH-); 7.25 (m, 2H, Ph-H); 7.02 (t, 2H, Ph-H); 6.86 (m, 2H, Ph-H); 6.77 (d, 2H, J = 12 Hz, Ph-H); 5.91 (t, 1H, -CH-Ph); 5.50 (d, 1H, J = 12 Hz, CH ₂ = C-); 5.51 (s, 1H, -CONH); 5.49 (d, 1H, J = 7.2 Hz, CH ₂ = C-); 5.11 (dd, 1H, -CH ₂ -O); 4.94 (dd, 1H, J ₁ = 12.5 Hz, J ₂ = 12.5 Hz, -CH ₂ -O); 4.29 (m, 2H, -N-CH ₂ -); 3.81 (s, 3H, -OCH ₃); 2.31 (s, 3H, -CH ₃).
5		123.3 ~ 123.6	88	7.30 (q, 1H, C = CH-); 7.20 (m, 2H, Ph-H); 7.00 (m, 2H, Ph-H); 6.90 (m, 1H, Ph-H); 6.84 (m, 2H, Ph-H); 5.82 (t, 1H, -CH-Ph); 5.46 (d, 1H, J = 2.4 Hz, CH ₂ = C-); 5.30 (d, 1H, J = 6 Hz, CH ₂ = C-); 5.19 (s, 1H, -CONH); 5.06 (dd, 1H, J ₁ = 2.4 Hz, J ₂ = 2.4 Hz, -CH ₂ -O); 4.90 (dd, 1H, J ₁ = 2.4 Hz, J ₂ = 2.4 Hz, -CH ₂ -O); 3.80 (s, 3H, -OCH ₃); 3.42 (m, 2H, -N-CH ₂ -); 2.68 (m, 2H, -CH ₂ -Ph).
6		170.7 ~ 170.8	86	7.40 (q, 1H, C = CH-); 7.26 (m, 2H, Ph-H); 6.99 (m, 1H, Ph-H); 6.89 (m, 2H, Ph-H); 6.60 (m, 2H, Ph-H); 5.91 (t, 1H, -CH-Ph); 5.53 (d, 1H, J = 9 Hz, CH ₂ = C-); 5.45 (s, 1H, -CONH); 5.36 (d, 1H, J = 15 Hz, CH ₂ = C-); 4.32 (dd, 1H, J ₁ = 6 Hz, J ₂ = 6 Hz, -CH ₂ -O); 4.23 (dd, 1H, J ₁ = 6 Hz, J ₂ = 6 Hz, -CH ₂ -O); 3.81 (s, 3H, -OCH ₃).
7		112.9 ~ 114.1	80	7.34 (q, 1H, C = CH-); 7.20 (m, 2H, Ph-H); 6.89 (m, 6H, Ph-H); 5.80 (t, 1H, -CH-Ph); 5.48 (d, 1H, J ₁ = 9 Hz, J ₂ = 9 Hz, CH ₂ = C-); 5.32 (m, 1H, CH ₂ = C-); 5.12 (s, 1H, -CONH); 5.06 (dd, 1H, J ₁ = 9 Hz, J ₂ = 9 Hz, -CH ₂ -O); 4.90 (dd, 1H, J ₁ = 9 Hz, J ₂ = 9 Hz, -CH ₂ -O); 3.81 (s, 3H, -OCH ₃); 3.40 (m, 2H, -N-CH ₂ -); 2.61 (m, 2H, -CH ₂ -Ph).
8		145.5 ~ 145.7	90	7.30 (q, 1H, C = CH-); 7.20 (m, 2H, Ph-H); 7.00 (m, 2H, Ph-H); 6.90 (m, 1H, Ph-H); 6.84 (m, 2H, Ph-H); 5.82 (t, 1H, -CH-Ph); 5.46 (d, 1H, J = 6.9 Hz, CH ₂ = C-); 5.30 (d, 1H, J = 12 Hz, CH ₂ = C-); 5.19 (s, 1H, -CONH); 5.06 (dd, 1H, J ₁ = 9 Hz, J ₂ = 9 Hz, -CH ₂ -O); 4.90 (dd, 1H, J ₁ = 9 Hz, J ₂ = 9 Hz, -CH ₂ -O); 3.80 (s, 3H, -OCH ₃); 3.42 (m, 2H, -N-CH ₂ -); 2.68 (m, 2H, -CH ₂ -Ph).
9		142.3 ~ 142.9	87	7.37 (q, 1H, C = CH-); 7.27 (m, 2H, Ph-H); 7.20 (m, 1H, Ph-H); 6.98 (m, 2H, Ph-H); 6.88 (m, 2H, Ph-H); 5.90 (t, 1H, -CH-Ph); 5.50 (d, 1H, CH ₂ = C-); 5.34 (d, 1H, J = 12.5 Hz, CH ₂ = C-); 5.10 (dd, 1H, -CH ₂ -O); 4.93 (dd, 1H, J ₁ = 6 Hz, J ₂ = 6 Hz, -CH ₂ -O); 4.37 (d, 2H, J = 7.2 Hz, -N-CH ₂ -); 3.85 (s, 3H, -OCH ₃).
10		138.1 ~ 139.2	81	7.40 (q, 1H, C = CH-); 7.25 (m, 3H, Ph-H); 6.86 (m, 5H, Ph-H); 5.90 (t, 1H, -CH-Ph); 5.51 (d, 1H, J = 15 Hz, CH ₂ = C-); 5.38 (s, 1H, -CONH); 5.32 (s, 1H, CH ₂ = C-); 5.11 (dd, 1H, -CH ₂ -O); 4.94 (dd, 1H, J ₁ = 6 Hz, J ₂ = 6 Hz, -CH ₂ -O); 4.30 (m, 2H, -N-CH ₂ -); 3.85 (s, 3H, -OCH ₃).
11		149.1 ~ 149.3	91	7.32 (m, 2H, Ph-H); 7.28 (m, 1H, Ph-H); 7.12 (m, 1H, Ph-H); 6.89 (m, 2H, Ph-H); 6.67 (m, 1H, Ph-H); 6.39 (q, 1H, C = CH-); 6.14 (t, 1H, -CH-Ph); 5.39 (m, 1H, CH ₂ = C-); 5.25 (m, 1H, CH ₂ = C-); 5.19 (dd, 1H, J ₁ = 9 Hz, J ₂ = 9 Hz, -CH ₂ -O); 4.99 (dd, 1H, J ₁ = 9 Hz, J ₂ = 9 Hz, -CH ₂ -O); 4.20 (d, 2H, J = 6 Hz, N-CH ₂ -); 3.77 (s, 3H, -OCH ₃); 3.37 (m, 2H, N-CH ₂ -); 3.05 (d, 2H, J = 6 Hz, N-CH ₂ -); 2.69 (d, 2H, J = 7.2 Hz, N-CH ₂ -).

续表 1

化合物编号	R 基团	mp(°C)	产量 (%)	¹ H-NMR (CDCl ₃)
12		176.3 ~ 176.5	91	7.32 (m, 2H, Ph-H); 7.06 (m, 1H, Ph-H); 6.92 (m, 1H, Ph-H); 6.89 (m, 2H, Ph-H); 6.61 (m, 1H, Ph-H); 6.40 (q, 1H, C=CH-); 6.15 (t, 1H, -CH-Ph); 5.39 (d, 1H, J=9 Hz, CH ₂ =C-); 5.25 (m, 1H, CH ₂ =C-); 5.20 (m, 1H, -CH ₂ -O); 4.99 (dd, 1H, J ₁ =9 Hz, J ₂ =9 Hz, -CH ₂ -O); 3.79 (s, 3H, -OCH ₃); 3.37 (m, 4H, N-CH ₂ -); 2.84 (m, 2H, N-CH ₂ -); 2.52 (d, 2H, J=15.6 Hz, N-CH ₂ -); 2.25 (s, 3H, CH ₃); 2.18 (s, 3H, CH ₃).
13		138.4 ~ 138.8	90	7.28 (m, 2H, Ph-H); 7.20 (m, 2H, Ph-H); 6.85 (m, 2H, Ph-H); 6.69 (d, 2H, J=12 Hz, Ph-H); 6.38 (q, 1H, C=CH-); 6.12 (t, 1H, -CH-Ph); 5.39 (m, 1H, CH ₂ =C-); 5.25 (m, 1H, CH ₂ =C-); 5.19 (m, 1H, -CH ₂ -O); 4.99 (dd, 1H, J ₁ =9 Hz, J ₂ =9 Hz, -CH ₂ -O); 4.05 (d, 2H, J=6 Hz, N-CH ₂ -); 3.74 (m, 3H, -OCH ₃); 3.33 (m, 2H, N-CH ₂ -); 3.16 (m, 2H, N-CH ₂ -); 2.83 (m, 2H, N-CH ₂ -).
14		105.8 ~ 106.9	80	7.28 (m, 2H, Ph-H); 7.26 (m, 1H, Ph-H); 6.85 (m, 2H, Ph-H); 6.41 (m, 3H, Ph-H); 6.33 (m, 1H, C=CH-); 6.12 (t, 1H, -CH-Ph); 5.38 (m, 1H, CH ₂ =C-); 5.25 (m, 1H, CH ₂ =C-); 5.19 (dd, 1H, J ₁ =9 Hz, J ₂ =9 Hz, -CH ₂ -O); 4.99 (dd, 1H, J ₁ =5.6 Hz, J ₂ =5.6 Hz, -CH ₂ -O); 4.02 (d, 2H, J=12 Hz, N-CH ₂ -); 3.79 (s, 3H, -OCH ₃); 3.71 (s, 3H, -OCH ₃); 3.30 (m, 4H, N-CH ₂ -); 2.88 (d, 1H, J=6 Hz, N-CH ₂ -); 2.73 (m, 2H, N-CH ₂ -).
15		101.6 ~ 102.2	85	7.32 (m, 2H, Ph-H); 7.28 (m, 1H, Ph-H); 7.12 (m, 1H, Ph-H); 6.89 (m, 2H, Ph-H); 6.67 (m, 1H, Ph-H); 6.39 (q, 1H, C=CH-); 6.14 (t, 1H, -CH-Ph); 5.39 (m, 1H, CH ₂ =C-); 5.25 (m, 1H, CH ₂ =C-); 5.01 (dd, 1H, J ₁ =6 Hz, J ₂ =6 Hz, -CH ₂ -O); 4.96 (dd, 1H, J ₁ =6 Hz, J ₂ =6 Hz, -CH ₂ -O); 4.20 (d, 2H, J=15 Hz, N-CH ₂ -); 3.77 (s, 3H, -OCH ₃); 3.37 (m, 2H, N-CH ₂ -); 3.05 (d, 2H, J=12 Hz, N-CH ₂ -); 2.69 (d, 2H, J=6 Hz, N-CH ₂ -).
16		118.7 ~ 119.4	84	7.32 (m, 2H, Ph-H); 7.28 (m, 1H, Ph-H); 7.12 (m, 1H, Ph-H); 6.89 (m, 2H, Ph-H); 6.67 (m, 1H, Ph-H); 6.39 (q, 1H, C=CH-); 6.14 (t, 1H, -CH-Ph); 5.39 (m, 1H, CH ₂ =C-); 5.25 (m, 1H, CH ₂ =C-); 5.01 (dd, 1H, J ₁ =9 Hz, J ₂ =9 Hz, -CH ₂ -O); 4.96 (dd, 1H, J ₁ =8.9 Hz, J ₂ =8.9 Hz, -CH ₂ -O); 4.20 (d, 2H, J=12 Hz, N-CH ₂ -); 3.77 (s, 3H, -OCH ₃); 3.37 (m, 2H, N-CH ₂ -); 3.05 (d, 2H, J=6 Hz, N-CH ₂ -); 2.69 (d, 2H, N-CH ₂ -).
17		105.4 ~ 106.2	80	7.28 (m, 2H, Ph-H); 7.16 (m, 1H, Ph-H); 6.86 (m, 3H, Ph-H); 6.72 (m, 1H, Ph-H); 6.65 (m, 1H, Ph-H); 6.38 (q, 1H, C=CH-); 6.12 (t, 1H, -CH-Ph); 5.38 (m, 1H, CH ₂ =C-); 5.28 (m, 1H, CH ₂ =C-); 5.20 (m, 1H, -CH ₂ -O); 4.99 (dd, 1H, J ₁ =6.3 Hz, J ₂ =6.5 Hz, -CH ₂ -O); 4.07 (m, 2H, N-CH ₂ -); 3.71 (s, 3H, -OCH ₃); 3.30 (m, 4H, N-CH ₂ -); 2.87 (d, 1H, J=9 Hz, N-CH ₂ -); 2.74 (m, 1H, N-CH ₂ -).
18		133.6 ~ 134.3	85	7.27 (m, 2H, Ph-H); 6.87 (m, 2H, Ph-H); 6.35 (q, 1H, C=CH-); 6.10 (t, 1H, -CH-Ph); 5.38 (m, 1H, CH ₂ =C-); 5.28 (m, 1H, CH ₂ =C-); 5.20 (m, 1H, -CH ₂ -O); 4.99 (dd, 1H, J ₁ =6 Hz, J ₂ =6 Hz, -CH ₂ -O); 4.07 (m, 2H, N-CH ₂ -); 3.71 (s, 3H, -OCH ₃); 3.30 (m, 4H, N-CH ₂ -); 2.87 (d, 1H, J=12 Hz, -CH ₂ -O); 2.74 (m, 1H, -CH ₂ -O).

2 药理实验

参考 Born 比浊法,测定所有目标化合物对 ADP 诱导的新西兰大白兔血小板凝集活性,以 MCI-154 (由本教研室合成)为阳性对照物, MCI-154, [6-]4-(4-吡啶氨基)苯基]-4,5-二氢-3(2H)吡嗪酮,是一种新型强心剂,它能通过增加心脏对 Ca²⁺的敏感性来促进心脏收缩功能^[7,8]。取新西兰大白兔心脏血,离心制备富含血小板血浆 (PRP) 和贫血小板血

浆 (PPP)。接通聚集仪电源,使之预热 30 min,恒温 (37 ± 0.1) °C,取 2 只比色杯,一只加入 PPP 200 ml,另一只加入 PRP 200 ml,置聚集仪中预热 5 min,分别向两杯中加入空白溶剂 DMSO 1 ml,用 PPP 杯调节透光率为 100%,用 PRP 杯调节透光率为 0。于装有 PRP 杯中加入配制好的不同浓度的 ADP 溶液,搅拌下观察 3 min 血小板的最大聚集程度,从而得出诱导剂的阈剂量,将目标化合物配成不同浓度的 DMSO 溶液,加入含 200 LPRP 的比色管中,同上条件观察血

小板的最大聚集程度,计算血小板聚集的抑制百分率,并用回归法求出各目标化合物的50%抑制活性。体外抑制血小板聚集的活性数据见表2。

$$\text{聚集抑制率} = (\text{对照聚集率} - \text{样品聚集率}) / \text{对照聚集率} \times 100\%$$

表2 化合物2~10抗血小板聚集活性

编号	IC ₅₀ (μmol/L)	编号	IC ₅₀ (μmol/L)
2	2.42	11	2
3	0.63	12	2.15
4	23.84	13	30.1
5	8.36	14	5.42
6	1.09	15	31.99
7	11.1	16	4.86
8	1.91	17	3
9	2.21	18	4.82
10	1.62	MCI-154	13.95

3 结果与讨论

经初步的体外抗血小板凝集实验表明,所合成的目标化合物对ADP引起的血小板聚集有不同程度的抑制作用。其中大部分化合物的活性均优于对照药MCI-154,化合物3,6和10的IC₅₀值分别为0.63,1.09和1.62μmol/L,分别是对照药的22.2,12.8和8.6倍。从上面的药理活性数据来看,R基团的引入对抗血小板凝集有一定的影响,其中取代苄胺的引入可以增强其血小板聚集的抑制作用,特别是对位为F取代的化合物对药效提高有帮助,而供电子的引入会降低抗血小板凝集作用。对于杂化

和苄乙胺的引入对于药效影响不显著。但由于目标化合物的数目有限,尚难得出全面的构效关系讨论,有待于进一步的研究。

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【收稿日期】 2012-04-24 【修回日期】 2013-01-06

【本文编辑】 陈静 李睿旻

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【收稿日期】 2013-03-29 【修回日期】 2013-09-07

【本文编辑】 李睿旻