6-取代二氢哒嗪酮类化合物的合成及血小板聚集抑制作用

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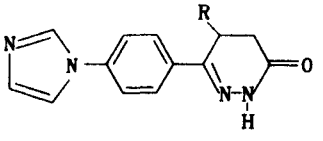
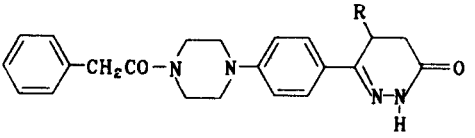
近年报道,6-苯基-4,5-二氢-3(2H)-哒嗪酮类化合物可特异地抑制细胞 CAMP 磷酸二酯酶 III(PDE III)提高 CAMP 水平,具有较强的正性肌力及抗血小板聚集作用[1,2]。如 CI 914(1),CI 930(2)是这类化合物效果较好的代表[3,4]。CCI 17810(3)可抑制多种诱导剂如胶原、ADP 和凝血酶等引起的血小板聚集[5],蒋勤等在改造其结构时发现5-位甲基衍生物4作用比前者强二十多倍[6],其结构如下。

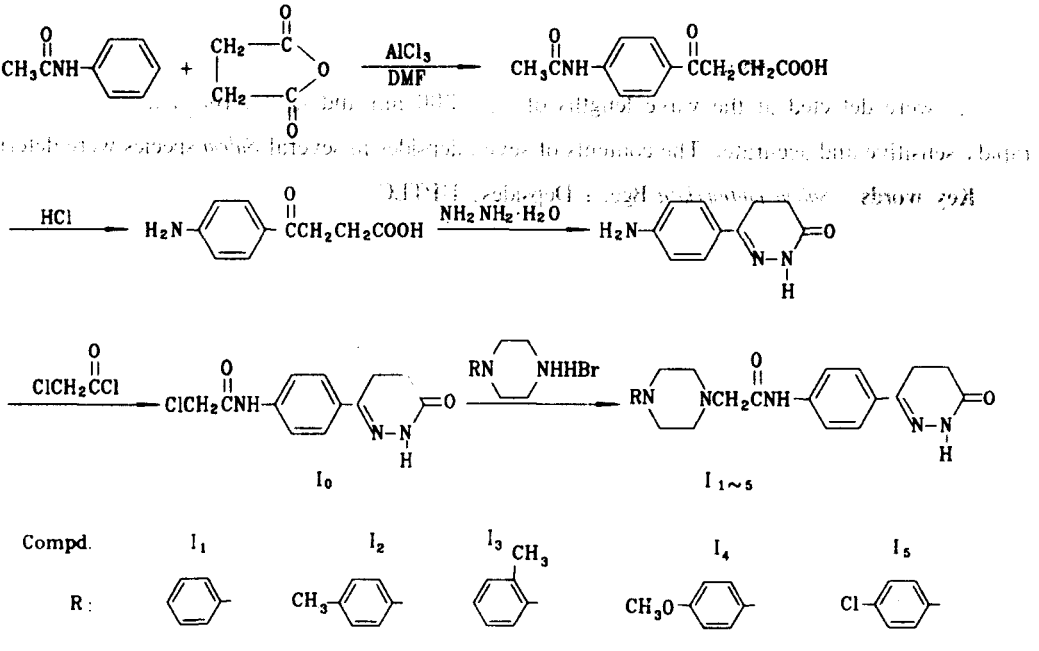


1 R=H
2 R=CH_3



3 R=H
4 R=CH_3

设想在这类化合物中寻找优良的抗血小板药较有希望。因此本文设计合成了一类新的6-取代苯基哒嗪酮类化合物10个,以期得到理想的抗血栓药物。化学结构及合成路线如图1和2。



Scheme 1 Route of synthesis of compounds I_1～I_5.

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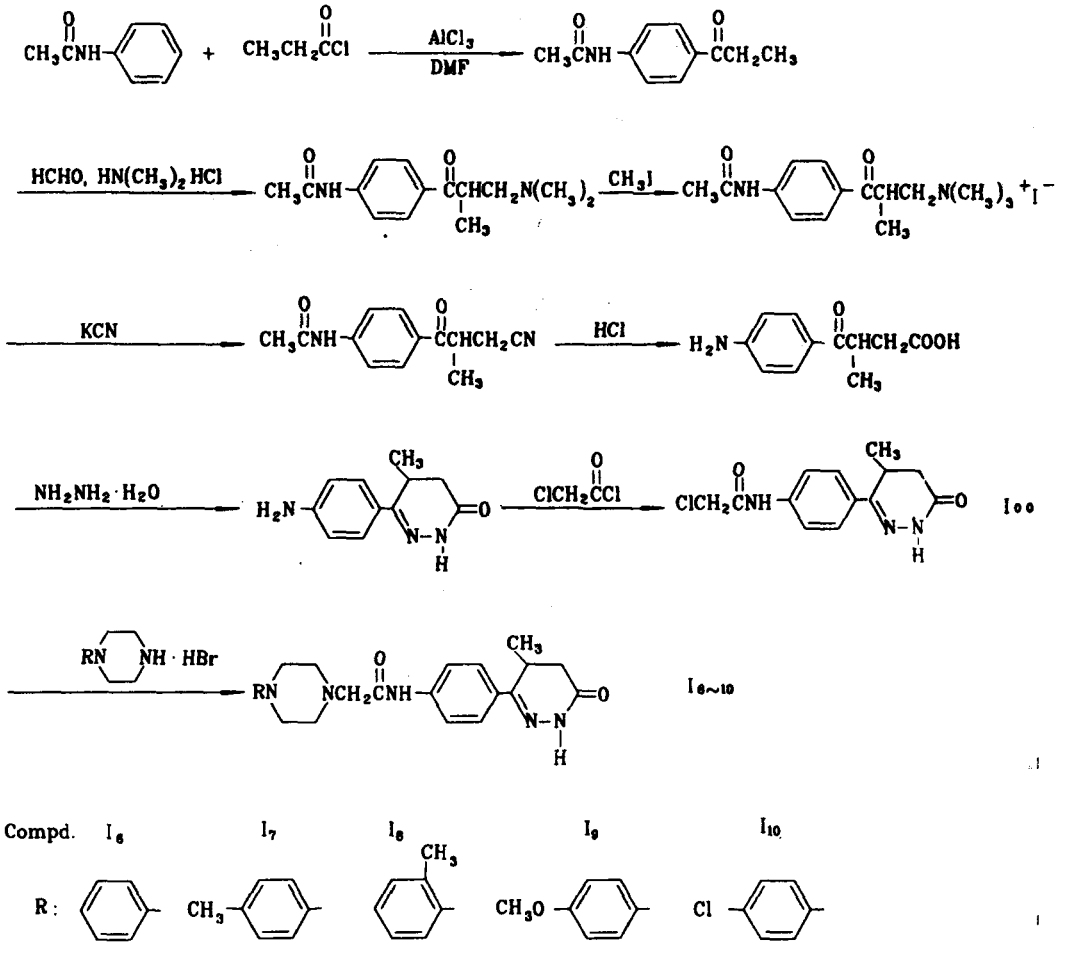

Scheme 2 Route of synthesis of compounds I_6～I_{10}.

所合成的10个化合物均未见报道，其结构根据元素分析及波谱解析证实(见表1)，以 CI 930为对照进行体外抗血小板聚集实验，发现所有化合物对 ADP 诱导大鼠血小板聚集均有抑制作用，其中 I_6～I_{10}作用较强，其 IC_{50}分别为2.62，1.45，1.45，0.99，5.12 μmol/L 与 CI 930(IC_{50} 2.12 μmol/L)相近；另外还测定了 I_2，I_4，I_5，I_7，I_9，I_{10}，CI 930对血小板活化因子(PAF)诱导家兔血小板聚集的抑制作用，发现 I_9作用最强，IC_{50}为3.7 μmol/L，比 CI 930(IC_{50} 7.15 μmol/L)强1.93倍(见表2)。

实验结果进一步证明哒嗪酮5-位甲基确能增强活性，且因6-位取代基的不同活性，增强的程度不同；化合物中哌嗪4-位以含有给电子取代基的苯环取代，活性较强。是否为这类化合物的一般规律，以及这类化合物的作用机制，值得进一步研究。

Tab 1 Physical data of the title compounds

Compd[a]	MP(℃)	Yield[b] (%)	IR(KBr) cm^{-1}	^{1}HNMR (DMSO-D_6,TMS)	MS (m/z)
I_1	218～219.5	55.5	1670,1350,815, 690,750		
I_2	258.5～260.5	57.1	1670,1350,840, 805		105(M^+), 189(100)
I_3	187.0～189.0	50.7	1690,1620,850, 820,765,725		105(M^+), 189(100)
I_4	217.5～218.5	51.8	1675,1620,840, 815	2.13(m,2H,5-H),2.92(m,2H,1-H),3.33～3.36 [m,8H,2(-CH_2CH_2-)],3.68(s,3H,CH_3O-),3.21 (s,2H,N-CH_2CO-),6.86(m,1H,Ph-H),7.72 (s,1H,Ph-H),10.88(s,2H,-NH-,-CO-NH)	
I_5	228～229.0	46.6	1690,1625,820		
I_6	198.5～199.5	60.0	1670,1620,840	1.06(d,3H,J=7.3 Hz,5-CH_3),2.25(m,1H,5-H), 2.61～2.71(m,2H,1-H),3.31～3.4[m,8H, 2(-CH_2CH_2-)],3.21(s,2H,NCH_2CO-),6.67～ 7.21(m,5H,Ph-H),7.70～7.77(m,1H,Ph-H), 10.92(s,2H,-NH-,-CONH-)	105(M^+), 175(100)
I_7	249.5～250.5	40.8	1680,1620,845, 810	1.06(d,3H,J=7.3 Hz,5-CH_3),2.25(m,1H,5-H), 2.19(s,3H,CH_3-Ph),2.72(m,2H,1-H),3.31～ 3.38[m,8H,2(-CH_2CH_2-)],3.21(br.s,2H, NCH_2CO-),6.81(d,2H,J=8.1 Hz,Ph-2′,6′-H), 6.91(d,2H,J=8.4 Hz,Ph-3′,5′-H),7.72(d,2H, J=9.2 Hz,Ph-3′,5′-H),7.75(d,2H,J=9.2 Hz, Ph-2′,6′-H),10.92(s,2H,-NH-,-CONH-)	
I_8	179～180	53.2	1680,1618,840, 760,720	1.06(d,3H,J=7.3 Hz,5-CH_3),2.23～2.25(m, 1H,5-H)2.61～2.72(m,2H,1-H),3.31～3.38 [m,8H,2(-CH_2CH_2-)],3.23(2H,s,NCH_2CO-), 6.95～7.17(m,1H,Ph-3′,5′1′6′-H),7.71(m,1H, Ph-2′,3′,5′,6′-H),10.92(s,2H,-NH-,-CONH-)	
I_9	212.5～213.5	58.5	1675,1620,840 820	1.06(d,3H,J=7.2 Hz,5-CH_3),2.22(m,1H,5-H), 2.72(m,2H,1-H),3.31～3.38[m,8H, 2(CH_2CH_2-)],3.21(br.s,2H,NCH_2CO-),3.68(s, 3H,CH_3O-),6.8～6.9(m,1H,Ph-H),7.73～ 7.77(m,1H,Ph-H),10.92(s,2H,-NH-,-CONH-)	
I_{10}	222.5～223.5	57.1	1680,1620,845, 815	1.06(d,3H,J=7.3 Hz,5-CH_3),2.2～2.27(m, 1H,5-H),2.61～2.72(m,2H,1-H),3.31～3.4 [8H,m,2(CH_2CH_2-)],3.21(br.s,2H,NCH_2CO-), 6.96(d,2H,J=9.0 Hz,Ph-2′,6′-H),7.21(d,2H, J=9.0 Hz,Ph-3′,5′-H),7.72(d,2H,J=9.2 Hz, Ph-3′,5′-H),7.75(d,2H,J=9.2 Hz,Ph-2′,6′-H), 10.92(s,2H,-NH-,-CONH-)	111(M^++2), 139(M^+)

a. C, H, N analyses were within ±0.5% of calculated values.

b. Yield of substitution reaction.

Tab 2 Platelet aggregation inhibitory activity of the title compounds

Compd.	IC_{50}^{c} (μ mol/L X±SD)[e]	IC_{50}^{d} (μ mol/L X±SD)[e]	Compd.	IC_{50}^{c} (μ mol/L X±SD)[e]	IC_{50}^{d} (μ mol/L X±SD)[e]
I_1	43.06±4.06		I_7	1.45±0.39	5.8±1.4
I_2	13.30±0.71	60.4±12.1	I_8	1.45±0.16	
I_3	14.45±1.31		I_9	0.99±0.27	3.7±0.3
I_4	14.83±1.98	25.6±4.4	I_{10}	5.12±0.09	16.6±3.5
I_5	19.28±3.34	64.3±3.5	CI 930	2.12±0.15	7.15±1.2
I_6	2.62±0.08				

c. ADP-induced rat platelet aggregation.

d. PAF-induced rabbit platelet aggregation.

e. The number of experimental animal was 3.

实 验 部 分

熔点用 ZMD 83-1型熔点仪测定，温度未校正；元素分析仪为 MOD-1106型；红外光谱仪为 Hitachi 270-50型，KBr 压片法测定；质谱仪为 JMS-D 300型；核磁共振仪为 AC-300P 型，TMS 为内标。

6-(4-氯乙酰氨基苯基)-4,5-二氢-3(2H)-哒嗪酮(I_o)

参考文献[7]方法制备，产品用 DMF—H_2O 重结晶，产率72.0%，mp 224.5～227.5℃(产率71.0%，mp 227～229℃)[7]。

6-(4-氯乙酰氨基苯基)-5-甲基-4,5-二氢-3(2H)-哒嗪酮(I_{oo})

参考文献[8]方法制备，产品用 DMF—H_2O 重结晶，产率43.5%，mp 235.5～236.5℃(产率43.0%，mp 235.5～236.5℃)[8]。

6-[4(4-取代苯基哌嗪乙酰氨基)苯基]-5-甲基(或无取代)-4,5-二氢-3(2H)-哒嗪酮

I_o 1.06 g 或 I_{oo} 1.12 g(0.004 mol)，N-取代哌嗪氢溴酸盐0.86～1.0 g(0.004 mol)，三乙胺1.3 g(0.013 mol)，置于无水乙醇50 ml 中，搅拌回流6 h，DMF—H_2O 重结晶，得目标化合物 I_1～I_{10}，产率40.8～72.0%，物理数据、波谱结果及药理活性见表1和2。

关键词 血小板聚集抑制剂；哒嗪酮

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SYNTHESIS AND PLATELET AGGREGATION INHIBITORY ACTIVITY OF 6-SUBSTITUTED DIHYDROPYRIDAZINONES

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ABSTRACT In order to develop more potent and less toxic antithrombotic agents, ten 6-(4-substituted piperazinyl acetyl aminophenyl)-4,5-dihydro-3(2H)-pyridazinones were synthesized. The title compounds were tested *in vitro* for platelet aggregation inhibitory activity with ADP-induced rat platelets and PAF-induced rabbit platelets. Preliminary tests showed that all of the pyridazinones could inhibit ADP-induced rat platelet aggregation. I_7, I_8, I_9 were more potent than the control compound CI 930. I_9 was the most potent compound with IC_{50} of 0.99 μmol/L. Pertaining to PAF-induced rabbit platelet aggregation, I_9 was the most potent inhibitor with IC_{50} of 3.7 μmol/L.

Key words Platelet aggregation inhibitor; Pyridazinones