

## · 论 文 ·

# 含 1,2-苯并噻嗪结构的[1,3,4]噻二唑并[3,2-a][1,3,5]三嗪衍生物的合成及其抗肿瘤活性

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**摘要** 以吡罗昔康合成中间体(CAS:35511-15-0)为原料,利用活性拼接等药物设计原理,设计并合成了9个结构新颖的目标化合物,其结构经<sup>1</sup>H NMR、MS等表征。通过测定对胰腺癌细胞 Capan-1、白血病细胞 L1210 和人肝癌细胞 SMMC-7721 的抑制活性,评价目标化合物的体外抗肿瘤活性。结果表明,化合物 **6f** ( $IC_{50} = 2.4 \pm 0.5 \mu\text{mol/L}$ ) 对胰腺癌细胞 Capan-1 表现出较好的抑制活性;化合物 **6h** ( $IC_{50} = 5.4 \pm 0.2 \mu\text{mol/L}$ ) 对白血病细胞 L1210 表现出较好的抑制活性;化合物 **6g** ( $IC_{50} = 3.8 \pm 0.2 \mu\text{mol/L}$ ) 对人肝癌细胞 SMMC-7721 表现出较好的抑制活性。初步的抗肿瘤活性实验结果表明,将吡罗昔康3位的侧链替代为噻二唑并三嗪侧链,对提高该类化合物的抗肿瘤活性有一定的作用。

**关键词** [1,3,4]噻二唑并[3,2-a][1,3,5]三嗪;合成;抗肿瘤活性

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## Synthesis and antitumor activities of 1,2-benzothiazines[1,3,4]thiadiazolo[3,2-a][1,3,5]triazin derivatives

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**Abstract** Based on the drug design principle of reactive functional group splicing, nine novel title compounds were designed and synthesized with piroxicam intermediate as the starting material. Their structures were characterized by <sup>1</sup>H NMR and MS analysis. The *in vitro* antitumor activity evaluation suggested that compounds **6f**, **6h** and **6g** exhibited good inhibitory reactivity on pancreatic cancer cell line Capan-1 ( $IC_{50} = 2.4 \pm 0.5 \mu\text{mol/L}$ ), leukemia cell line L1210 ( $IC_{50} = 5.4 \pm 0.2 \mu\text{mol/L}$ ), and human liver cancer cell line SMMC-7721 ( $IC_{50} = 3.8 \pm 0.2 \mu\text{mol/L}$ ), respectively. The introduction of thiadiazolo[3,2-a]triazine side chain could improve the antitumor activity of these compounds.

**Key words** [1,3,4] thiadiazolo[3,2-a][1,3,5]triazin; synthesis; antitumor activity

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恶性肿瘤是一种严重危害人类健康的疾病,对于肿瘤疾病的预防和治疗是世界各国所面临的共

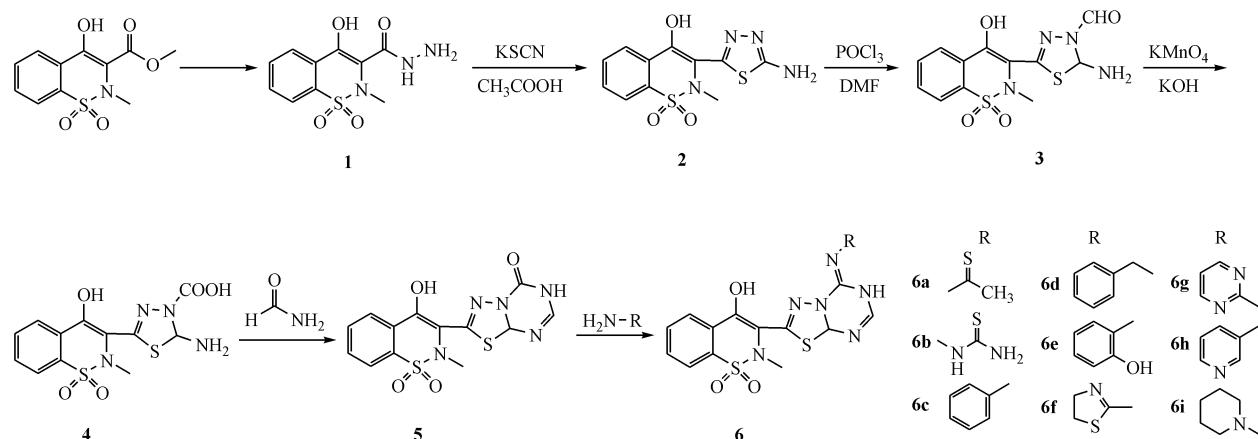
同问题,研究并开发有效的抗肿瘤药物是药学领域一直以来的热点。基于机制的药物设计是发现先

导化合物的有效途径<sup>[1]</sup>。肿瘤相关因子 NF-κB 既是免疫和炎症反应重要的调节因子, 又是肿瘤疾病重要的启动因子。目前, 有研究表明<sup>[2]</sup>, 炎症有促进肿瘤发展的趋势, 炎症与肿瘤之间的关系的研究将会为新型抗肿瘤药物的研究提供新的思路。

吡罗昔康是第 1 个上市的 1,2-苯并噻嗪类药物, 通过抑制 COX-2 的活性, 从而抑制花生四烯酸的生成, 导致前列腺素的合成受阻, 进而发挥抗炎作用。

1,3,5-三嗪类化合物具有广泛的生物活性, 常

常出现在具有生物活性的农药、医药等化合物中。该类化合物具有抗肿瘤<sup>[3-5]</sup>、杀菌<sup>[6-7]</sup>、降血糖<sup>[8]</sup>、抑制乙酰胆碱酯酶<sup>[9-10]</sup>、保护心脏功能<sup>[11]</sup>、抗癫痫<sup>[12-13]</sup>、抗抑郁<sup>[14-16]</sup>等效用, 因而受到研究者的广泛关注。基于此, 本研究以吡罗昔康合成中间体(2-甲基-4-羟基-2H-1,2-苯并噻嗪-3-甲酸甲酯-1-1-二氧化物, CAS:35511-15-0)为原料, 用稠杂环在1,2-苯并噻嗪环 C-3 进行活性拼接, 经多步反应合成一系列含 1,2-苯并噻嗪结构的[1,3,4]噻二唑并[3,2-a][1,3,5]三嗪的衍生物, 合成见路线 1。



Scheme 1 Synthetic route of the target compounds

## 1 化学合成部分

### 1.1 试剂与仪器

吡罗昔康(湖北鸿鑫瑞宇精细化工有限公司);化合物 1(2-甲基-4-羟基-2H-1,2-苯并噻嗪-3-甲酰胺-1-1-二氧化物)按文献<sup>[17]</sup>的方法制备。其余试剂均为市售分析纯, 未经处理, 直接使用。

熔点用毛细管法测定, 温度未校正; AM2400 型核磁共振仪(德国 Bruker 公司); HP1100 型质谱仪(美国 Agilent 公司); PE2400-II 元素分析仪(美国 PE 公司)。

### 1.2 实验步骤

1.2.1 化合物 2(3-(5-氨基-1,3,4-噻二唑-2-基)-2-甲基-4-羟基-2H-1,2-苯并噻嗪-1,1-二氧化物)的合成 将化合物 1 26.9 g(0.1 mol), KSCN 19.5 g(0.2 mol), 乙酸 135 mL(2.36 mol)依次加入到 250 mL 的三口瓶中, 搅拌均匀后, 加热, 回流反应 8

h, TLC 检测, 反应完全后, 冷却, 过滤, 干燥得化合物 23.3 g, 收率 75%; mp:244~245 °C。

1.2.2 化合物 3(2-氨基-5-(2-甲基-4-羟基-2H-1,2-苯并噻嗪-1,1-二氧化物)-1,3,4-噻二唑-3(2H)-甲醛)的合成 在装有温度计的 500 mL 四口瓶中, 加入二甲基甲酰胺(DMF)45 mL, 冰浴条件下, 缓慢滴加三氯氧磷 130 mL(1.4 mol), 控制温度小于 10 °C, 滴毕, 将化合物 2(22.1 g, 0.07 mol), 分批加入到四口瓶中, 控制温度小于 15 °C, 加毕, 自然升温至室温, 反应 1 h 后, 加热至 80~90 °C, 并反应 5 h。反应结束后, 将反应液倒入冰水中, 搅拌, 得化合物 3。采用乙醇和水的混合溶剂对产物进行重结晶, 过滤, 干燥, 得黄色化合物 12.4 g, 收率 51%; mp:252~254 °C。

1.2.3 化合物 4(2-氨基-5-(2-甲基-4-羟基-2H-1,2-苯并噻嗪-1,1-二氧化物)-1,3,4-噻二唑-3(2H)-羧酸)的合成 取化合物 3(11.3 g, 0.03 mol), 纯化水 300 mL, 依次加入到 1 000 mL 三口瓶中, 加热至 70~80 °C, 剧烈搅拌下, 滴加 5%

$\text{KMnO}_4$ 水溶液360 mL,约30 min滴完。反应过程中,用1 mol/L KOH水溶液控制反应液的pH范围为8~9,反应8 h。TLC检测,原料反应完全后,自然冷却至室温,析出结晶,过滤,得黄色粉末状化合物**4** 7.2 g。收率61%,mp:286~288 °C。

1.2.4 化合物**5**(2-(2-甲基-4-羟基-2H-1,2-苯并噻嗪-1,1-二氧化-3-基)-6,8a-二氢-5H-[1,3,4]噻二唑并[3,2-a][1,3,5]三嗪-6-酮)的合成 向100 mL三口瓶中,依次加入化合物**4**(5.3 g,0.014 mol)、甲酰胺(5.6 mL,0.141 mol),升温至120~130 °C反应3 h后,再升温至160~170 °C并保温反应2 h,反应结束后,自然冷却至50 °C左右,加入300 mL水,充

分搅拌,过滤,干燥得黄色化合物**5** 2.1 g。收率39%,mp:253~255 °C。

1.2.5 化合物**6a**(*N*-(2-(2-甲基-4-羟基-2H-1,2-苯并噻嗪-1,1-二氧化-3-基)-6,8a-二氢-5H-[1,3,4]噻二唑并[3,2-a][1,3,5]三嗪-5-亚基)硫代乙酰胺)的合成 向100 mL三口瓶中,加入化合物**5**(1.1 g,0.003 mol),硫代乙酰胺(0.3 g,0.004 mol),无水乙醇20 mL,加热至回流,反应6 h,TLC检测,反应结束后,自然冷却至室温,过滤,得黄色化合物**6a** 0.8 g。收率62%,mp:237~239 °C。

按化合物**6a**类似的方法分别制备目标化合物**6b~6i**。理化性质和光谱数据见表1和表2。

Table 1 Physical properties of compounds **6a~6i**

Compd.	Formula	Yield/%	mp/°C	Elemental analysis/(%,Calcd.)		
				C	H	N
<b>6a</b>	$\text{C}_{15}\text{H}_{14}\text{N}_6\text{O}_3\text{S}_3$	62	237~239	42.56(42.64)	3.64(3.34)	19.92(19.89)
<b>6b</b>	$\text{C}_{14}\text{H}_{14}\text{N}_8\text{O}_3\text{S}_3$	58	224~226	38.45(38.35)	3.43(3.22)	25.57(25.55)
<b>6c</b>	$\text{C}_{19}\text{H}_{16}\text{N}_6\text{O}_3\text{S}_2$	55	233~235	51.92(51.81)	3.56(3.66)	19.14(19.08)
<b>6d</b>	$\text{C}_{20}\text{H}_{18}\text{N}_6\text{O}_3\text{S}_2$	57	236~238	52.74(52.85)	4.03(3.99)	18.46(18.49)
<b>6e</b>	$\text{C}_{19}\text{H}_{16}\text{N}_6\text{O}_4\text{S}_2$	60	230~232	50.72(49.99)	3.74(3.53)	18.58(18.41)
<b>6f</b>	$\text{C}_{16}\text{H}_{15}\text{N}_7\text{O}_3\text{S}_3$	53	242~244	42.65(42.75)	3.32(3.36)	21.84(21.81)
<b>6g</b>	$\text{C}_{17}\text{H}_{14}\text{N}_8\text{O}_3\text{S}_2$	50	231~233	46.23(46.15)	3.24(3.1)	25.33(5.32)
<b>6h</b>	$\text{C}_{18}\text{H}_{15}\text{N}_7\text{O}_3\text{S}_2$	50	243~245	49.02(48.97)	3.45(3.42)	22.18(22.21)
<b>6i</b>	$\text{C}_{18}\text{H}_{21}\text{N}_7\text{O}_3\text{S}_2$	49	238~240	48.32(48.31)	4.78(4.73)	21.96(21.91)

Table 2 Spectral data of compounds **2~5** and **6a~6i**

Compd.	$^1\text{H}$ NMR (DMSO- $d_6$ ) $\delta$	$^{13}\text{C}$ NMR (DMSO- $d_6$ ) $\delta$	MS( $m/z$ )
<b>2</b>	12.23(1H,s,-OH),7.42~7.85(4H,m,Ph-H),7.68(2H,s,-NH <sub>2</sub> ),2.87(3H,s,-NCH <sub>3</sub> )	163,157,135,132,129,127,122,108,37	311[M+H] <sup>+</sup>
<b>3</b>	12.15(1H,s,-OH),8.23(2H,s,-NH <sub>2</sub> ),8.11(1H,s,-CHO),7.56~7.94(4H,m,Ph-H),5.75(1H,s,-CH-S),2.82(3H,s,-NCH <sub>3</sub> )	160,156,150,134,132,128,127,124,68,42	341[M+H] <sup>+</sup>
<b>4</b>	13.43(1H,s,-COOH),12.02(1H,s,-OH),8.14(2H,s,-NH <sub>2</sub> ),7.44~7.85(4H,m,Ph-H),5.68(1H,s,-CH-S),2.74(3H,s,-NCH <sub>3</sub> )	158,156,150,134,132,129,127,124,104,40	357[M+H] <sup>+</sup>
<b>5</b>	11.98(1H,s,-OH),9.43(1H,s,-CONH),7.64(1H,s,-N=CH),7.35~7.84(4H,m,Ph-H),5.68(1H,s,-N-CH-N),2.76(3H,s,-NCH <sub>3</sub> )	157,155,151,149,134,132,129,126,123,1,04,41	366[M+H] <sup>+</sup>
<b>6a</b>	12.13(1H,s,-OH),10.33(1H,s,-N=C-NH),7.52(1H,s,-N=CH),7.52~7.78(4H,m,Ph-H),4.62(1H,s,-N-CH-N),2.64(3H,s,-NCH <sub>3</sub> ),1.26(3H,s,-CH <sub>3</sub> )	216,158,156,153,150,149,136,134,132,128,127,124,105,40,32	423[M+H] <sup>+</sup>
<b>6b</b>	12.08(1H,s,-OH),10.87(1H,s,-CSNH),10.46(1H,s,-N=C-NH),7.72(2H,s,-CSNH <sub>2</sub> ),7.58(1H,s,-N=CH),7.43~7.75(4H,m,Ph-H),4.48(1H,s,-N-CH-N),2.64(3H,s,-NCH <sub>3</sub> )	183,158,155,146,135,134,132,129,127,124,104,70,39	439[M+H] <sup>+</sup>
<b>6c</b>	12.21(1H,s,-OH),10.46(1H,s,-N=C-NH),7.58(1H,s,-N=CH),7.29~7.74(9H,m,Ph-H),4.36(1H,s,-N-CH-N),2.69(3H,s,-NCH <sub>3</sub> )	159,155,150,138,137,134,132,130,129,127,124,104,41	441[M+H] <sup>+</sup>
<b>6d</b>	12.33(1H,s,-OH),10.42(1H,s,-N=C-NH),7.62(1H,s,-N=CH),7.25~7.83(10H,m,Ph-H),4.22(1H,s,-N-CH-N),2.67(3H,s,-NCH <sub>3</sub> ),2.52(2H,s,-C=N-CH <sub>2</sub> )	158,155,153,5,1,135,132,129,128,127,126,124,115,106,55,40	455[M+H] <sup>+</sup>

(Continued)

Compd.	<sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ) $\delta$	<sup>13</sup> C NMR (DMSO- <i>d</i> <sub>6</sub> ) $\delta$	MS (m/z)
<b>6e</b>	12.28 (1H, s, -OH), 11.63 (1H, s, Ph-OH), 10.54 (1H, s, -N = C-NH), 7.63 (1H, s, -N = CH), 7.14–7.83 (8H, m, Ph-H), 4.25 (1H, s, -N-CH-N), 2.68 (3H, s, -NCH <sub>3</sub> )	158, 155, 152, 150, 138, 136, 134, 129, 127, 124, 115, 104, 72, 41	457 [M + H] <sup>+</sup>
<b>6f</b>	12.24 (1H, s, -OH), 10.38 (1H, s, -N = C-NH), 7.52 (1H, s, -N = CH), 7.42–7.74 (4H, m, Ph-H), 4.35 (1H, s, -N-CH-N), 3.82 (2H, s, -C = N-CH <sub>2</sub> ), 3.28 (2H, s, -S-CH <sub>2</sub> ), 2.67 (3H, s, -NCH <sub>3</sub> )	174, 157, 153, 150, 133, 132, 129, 127, 124, 104, 71, 55, 41, 32	450 [M + H] <sup>+</sup>
<b>6g</b>	12.32 (1H, s, -OH), 10.34 (1H, s, -N = C-NH), 7.72–8.56 (3H, m, pyrimidine-H), 7.61 (1H, s, -N = CH), 7.42–7.86 (4H, m, Ph-H), 4.32 (1H, s, -N-CH-N), 3.82 (2H, s, -C = N-CH <sub>2</sub> ), 3.28 (2H, s, -S-CH <sub>2</sub> ), 2.67 (3H, s, -NCH <sub>3</sub> )	163, 160, 158, 137, 134, 132, 129, 127, 124, 115, 104, 72, 40	443 [M + H] <sup>+</sup>
<b>6h</b>	12.22 (1H, s, -OH), 10.36 (1H, s, -N = C-NH), 7.36–8.52 (4H, m, pyridine-H), 7.53 (1H, s, -N = CH), 7.46–7.78 (4H, m, Ph-H), 4.37 (1H, s, -N-CH-N), 2.69 (3H, s, -NCH <sub>3</sub> )	157, 156, 150, 149, 139, 138, 134, 132, 129, 127, 124, 104, 72, 39	442 [M + H] <sup>+</sup>
<b>6i</b>	12.26 (1H, s, -OH), 10.42 (1H, s, -N = C-NH), 7.48 (1H, s, -N = CH), 7.44–7.83 (4H, m, Ph-H), 4.34 (1H, s, -N-CH-N), 2.66 (3H, s, -NCH <sub>3</sub> ), 1.52–2.94 (10H, m, piperidine-H)	158, 155, 149, 140, 134, 132, 129, 127, 124, 106, 71, 51, 41, 25, 24	448 [M + H] <sup>+</sup>

## 2 抗肿瘤活性实验

采用 MTT 法测定合成的目标化合物对人胰腺癌细胞 Capan-1(中国医学科学院协和细胞库)、鼠

白血病细胞 L1210(中国医学科学院协和细胞库)和人肝癌细胞 SMMC-7721(中国医学科学院协和细胞库)的半数抑制浓度( $IC_{50}$ )，结果见表 3。

Table 3 Anti-proliferative activity of the tested compounds against Capan-1 SMMC-7721 and L1210 tumor cells ( $\bar{x} \pm s, n = 3$ )

Compd.	IC <sub>50</sub> /( $\mu$ mol/L)		
	Capan-1	SMMC-7721	L1210
<b>6a</b>	12.7 $\pm$ 1.3	14.8 $\pm$ 1.6	15.2 $\pm$ 1.6
<b>6b</b>	14.6 $\pm$ 1.8	12.1 $\pm$ 1.3	13.4 $\pm$ 1.3
<b>6c</b>	15.8 $\pm$ 1.6	12.6 $\pm$ 1.4*	13.8 $\pm$ 1.4
<b>6d</b>	10.2 $\pm$ 1.1*	11.4 $\pm$ 1.2	10.4 $\pm$ 1.0*
<b>6e</b>	15.6 $\pm$ 1.8	16.9 $\pm$ 1.8	15.2 $\pm$ 1.6
<b>6f</b>	2.6 $\pm$ 1.1*	8.7 $\pm$ 0.7*	9.2 $\pm$ 0.9*
<b>6g</b>	7.8 $\pm$ 1.0	8.4 $\pm$ 0.9	2.2 $\pm$ 0.3
<b>6h</b>	9.2 $\pm$ 1.0*	3.1 $\pm$ 0.2*	8.7 $\pm$ 0.8*
<b>6i</b>	11.3 $\pm$ 1.2	10.7 $\pm$ 1.2*	9.8 $\pm$ 1.0*
Doxorubicin	3.5 $\pm$ 0.6	2.7 $\pm$ 0.2	1.4 $\pm$ 0.2
Piroxicam intermediate	>100	>100	>100
<b>1</b>	>100	>100	>100
<b>2</b>	80.2 $\pm$ 8.1	78.5 $\pm$ 7.3	77.4 $\pm$ 7.3
<b>3</b>	75.5 $\pm$ 7.1	72.7 $\pm$ 7.0	74.6 $\pm$ 7.5
<b>4</b>	68.2 $\pm$ 6.3	67.3 $\pm$ 6.5	69.5 $\pm$ 7.0
<b>5</b>	20.2 $\pm$ 2.3	22.5 $\pm$ 2.4	26.4 $\pm$ 2.6

\*  $P < 0.05$  vs doxorubicin

体外抗肿瘤实验结果显示,9个目标化合物对人胰腺癌细胞 Capan-1、鼠白血病细胞 L1210 和人肝癌细胞 SMMC-7721 呈现出不同程度的抑制作用( $IC_{50}$ 均小于 20  $\mu$ mol/L),其中化合物 **6f**、**6g** 和 **6h** 对 Capan-1、L1210 和 SMMC-7721 的  $IC_{50}$  与对照药多柔比星的活性相当。

结果表明,噻二唑并三嗪侧链的引入,对提高该类化合物的抗肿瘤活性有一定的作用。在噻二唑并三嗪的基础上,引入芳环或芳杂环取代时,化合物的抗肿瘤活性较烷基取代时更强,尤其是引入芳香杂环侧链时,有利于化合物电荷的分散而稳定,进一步增强了化合物的抗肿瘤活性,具有进一

步研究的价值,这也预示着1,2-苯并噻嗪类药物C-3位的结构修饰在治疗肿瘤方面将会有更广阔的研究前景。

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