

芳烷酮哌嗪衍生物的设计合成及镇痛活性

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摘要: 以中枢兴奋性氨基酸 NMDA 受体多胺调节位点为靶点, 设计合成芳烷酮哌嗪类全新化合物并研究它们的镇痛活性。哌嗪经甲酰基保护后, 与相应的卤代芳烃进行烷基化反应, 制备目标化合物。以小鼠扭体法、大鼠热板法、大鼠光热甩尾法等动物体内镇痛模型测试目标化合物的镇痛活性。共合成 64 个未见文献报道的新化合物, 其结构经质谱、核磁共振谱及元素分析确证。镇痛药理试验显示: 该类化合物具有较好的镇痛作用及作为新型非阿片类镇痛药开发的潜在价值。化合物 **I₂**, **I₄**, **I₁** 和 **I₇** 在三种镇痛模型上均显示很强的镇痛活性, 具有深入研究的价值。

关键词: 芳烷酮哌嗪类化合物; 合成; 镇痛活性

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Design and synthesis of aralkyl-ketone piperazine derivatives and their antalgic activities

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Abstract: To synthesize aralkyl-ketone piperazine derivatives as analgesic agents, the N atom of the one side of piperazine ring is protected by formyl group firstly, then the unprotected N atom is alkylated to prepare aralkyl-ketone piperazine derivatives. Their analgesic biological activities were well studied by mice writhing model, rat hot plate model and rat tail flick model. Sixty four compounds were synthesized and pharmacological tests *in vivo* revealed these compounds have potent analgesic activities, especially compound **I₂**, **I₄**, **I₁** and **I₇**. These four compounds are more worthy for further research.

Key words: aralkyl-ketone piperazine derivatives; synthesis; analgesic activity

严重的急慢性疼痛包括肿瘤疼痛、术后疼痛等困扰着数以万计的患者, 是目前临床一大难题。由于现有阿片类镇痛剂具有药物成瘾性及呼吸抑制、胃蠕动减少等副作用, 限制了它们的广泛使用, 因此寻找既能保持强镇痛效应, 又能克服上述弊端, 安全用于临床的非阿片类中枢镇痛类药物是镇痛领域的主要目标。其中, 中枢兴奋性氨基酸 NMDA 受体拮抗剂是寻找新型非成瘾性镇痛剂的重要途径之一^[1]。

作用于 NMDA 受体 NR2B 亚单位选择性 NMDA 受体拮抗剂, 在各种临床前和临床实验中, 被证明具有镇痛作用强、毒副作用小等多方面优点^[2]。多胺位点主要分布在 NR2B 亚单位, 因此 NMDA 多胺位点拮抗剂多为 NR2B 选择性 NMDA 受体拮抗剂, 其作用位点比较明确, 对中枢其他部位的影响较小, 毒副作用也相对温和, 对记忆和识别功能无影响, 更为重要的是在动物成瘾性实验中, 没有体现依赖性^[3]。因此该类化合物很有可能开发成为副作用温和的镇痛新药。

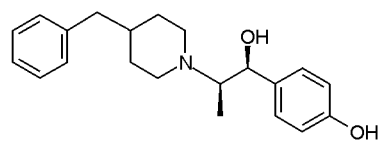
苄哌酚醇 (ifenprodil) 为第一代的 NR2B 选择性 NMDA 受体拮抗剂, 于 1972 年在法国首次上市, 之

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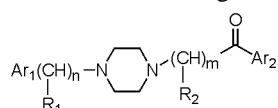
后在希腊、菲律宾等 21 个国家上市主要作为神经保护剂和外周血管扩展药,用于神经性疼痛和中枢眩晕等病的治疗^[4]。



苄哌酚醇 (ifenprodil)

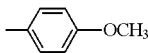
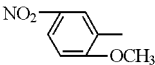
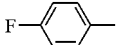
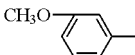
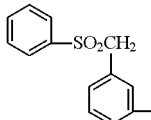
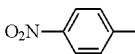
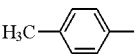
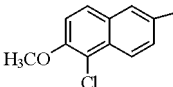
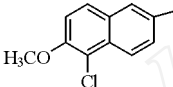
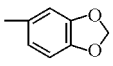
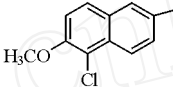
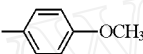
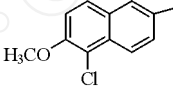
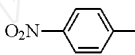
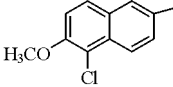
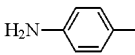
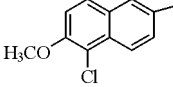
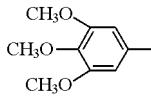
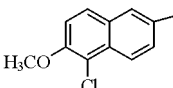
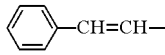
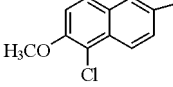
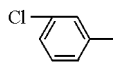
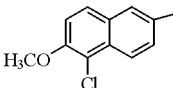
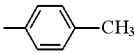
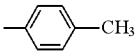
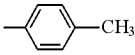
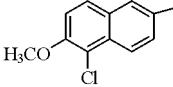
本研究参考苄哌酚醇的结构信息,根据生物电子等排原理设计合成了芳烷酮哌嗪类化合物^[5],共 64 个 **I**₁₋₆₄ (化合物的结构见表 1),以考察该类化合物的镇痛活性及作为非阿片类新型镇痛剂开发的可能性。由于手性化合物的合成具有较大的难度,本文考虑先对消旋体化合物的活性进行考察。合成的 64 个化合物中除 **I**₈, **I**₉, **I**₁₁, **I**₁₂, **I**₄和 **I**₅ 6 个化合物为手性体外,其他均为消旋体化合物。

Table 1 Structures of target compounds



Compd	Ar ₁	Ar ₂	R ₁	R ₂	n	m
I ₁	Ph	Ph	H	H	1	1
I ₂		Ph	H	CH ₃	1	1
I ₃		Ph	H	H	1	1
I ₄		Ph	H	H	1	1
I ₅	Ph	Ph	COOC ₂ H ₅	H	1	1
I ₆	Ph		H	H	1	1
I ₇	Ph		H	H	1	1
I ₈	Ph		H	H	1	1
I ₉	Ph		H	H	1	1
I ₁₀		Ph	H	H	1	1
I ₁₁		Ph	H	H	1	1
I ₁₂		Ph	H	H	1	1
I ₁₃		Ph	H	CH ₃	1	1
I ₁₄	Ph	Ph	H	H	2	1
I ₁₅		Ph	H	H	1	1
I ₁₆	Ph		H	H	1	1
I ₁₇	Ph	Ph	H	H	1	2
I ₁₈			H	H	1	1
I ₁₉		Ph	H	H	1	1
I ₂₀			H	H	1	1
I ₂₁		Ph	H	H	1	1

Continued

Compd	A _{R1}	A _{R2}	R ₁	R ₂	n	m
I ₂	Ph		OH	H	1	1
I ₃		Ph	H	H	1	1
I ₄		Ph	CH ₃	H	1	1
I ₅		Ph	H	H	1	1
I ₆		Ph	H	H	1	1
I ₇			CH ₃	H	1	1
I ₈	Ph		H	H	1	1
I ₉	Ph		H	CH ₃	1	1
I ₁₀			H	CH ₃	1	1
I ₁₁			H	CH ₃	1	1
I ₁₂			H	CH ₃	1	1
I ₁₃			H	CH ₃	1	1
I ₁₄			H	CH ₃	1	1
I ₁₅			H	CH ₃	1	1
I ₁₆			0	CH ₃	0	1
I ₁₇	Ph	Ph	CH ₃	H	1	1
I ₁₈	Ph	Ph	CH ₃ (R)	H	1	1
I ₁₉	Ph	Ph	CH ₃ (S)	H	1	1
I ₂₀	Ph		CH ₃	H	1	1
I ₂₁	Ph		CH ₃ (R)	H	1	1
I ₂₂	Ph		CH ₃ (S)	H	1	1
I ₂₃	Ph		CH ₃	CH ₃	1	1

Continued						
Compd	A _{R1}	A _{R2}	R ₁	R ₂	n	m
I ₄₄	Ph		CH ₃ (R)	CH ₃	1	1
I ₄₅	Ph		CH ₃ (S)	CH ₃	1	1
I ₄₆	Ph	Ph	H	CH ₃	1	1
I ₄₇		Ph	H	CH ₃	1	1
I ₄₈	Ph	Ph	CH ₃	CH ₃	1	1
I ₄₉		Ph	H	H	1	1
I ₅₀			H	H	1	1
I ₅₁	Ph	Ph	COOH	H	1	1
I ₅₂	Ph	Ph	COOC ₂ H ₅	CH ₃	1	1
I ₅₃		Ph	H	H	1	1
I ₅₄	Ph		H	H	1	1
I ₅₅	Ph		H	H	1	1
I ₅₆	Ph		H	0	1	0
I ₅₇	Ph	Ph	H	Ph	1	1
I ₅₈		Ph	H	H	1	1
I ₅₉		Ph	H	H	1	1
I ₆₀		Ph	CH ₃	H	1	1
I ₆₁	Ph	Ph	CH ₂ CH ₃	H	1	1
I ₆₂			H	H	1	1
I ₆₃		Ph	H	H	1	1
I ₆₄			H	H	1	1

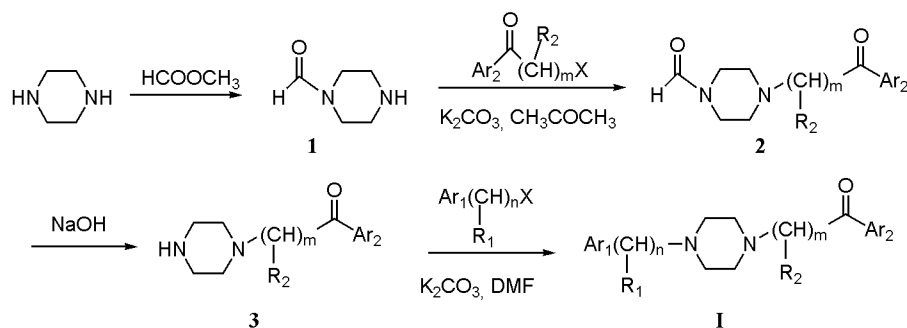
1 化学合成

以哌嗪为起始原料,与甲酸甲酯在 80 反应,可得到哌嗪环单侧甲酰基保护的化合物 1^[6],1再经烷基化,碱水解甲酰基后,可得到纯度和收率较高的化合物 3,三步总收率可达 40%左右。该反应亦可用哌嗪直接与相应的卤代物进行烷基化反应,经一步得到化合物 3,其合成路线虽短,但哌嗪的两个氮原子可同时发生反应,生成较多对称的双烷基化副产物,难以去除,严重影响目标化合物的纯度。

化合物 3是制备目标化合物 I的主要中间体,

与相应的卤代物进行 N⁺的烃基化反应得到目标化合物 I,采用对亲核试剂很少溶剂化的极性非质子溶剂 DMF为反应溶媒, K₂CO₃为去酸剂,反应可在室温进行,收率达 80%左右,若以 K₂CO₃/CH₃COCH₃, NaHCO₃/C₂H₅OH及 Et₃N/CHCl₃为反应系统,需长时间回流(8~24 h),反应颜色随时间延长而加深,影响产物的质量和收率。目标化合物 I溶解在乙醇中,用 5 mol·L⁻¹盐酸乙醇溶液调 pH=4,有固体析出,过滤,乙醇重结晶,采用上述步骤,可获得目标化合物 I₁₋₆₄的盐酸盐(合成路线见图 1)。

合成的 64 个目标化合物未见文献报道, 其结构 化常数和元素分析数据见表 2, 波谱数据见表 3。均通过 $^1\text{H NMR}$ 、MS 和元素分析验证, 各化合物的理



Scheme 1 Synthetic route of target compounds

Table 2 Physical properties of target compounds **I** - **64**

No	Formula	Yield/%	mp/	Elemental analysis/%		
				Found (Calcd)		
				C	H	N
I ₁	C ₁₉ H ₂₂ N ₂ O · 2HCl · H ₂ O	75.0	238 - 239	59.13 (59.22)	6.59 (6.80)	7.30 (7.27)
I ₂	C ₂₀ H ₂₃ CN ₂ O · 2HCl · H ₂ O	59.5	260 - 262	55.01 (55.37)	6.05 (6.27)	6.41 (6.46)
I ₃	C ₁₉ H ₂₁ CN ₂ O · 2HCl · H ₂ O	57.3	256 - 258	54.61 (54.41)	5.95 (5.97)	5.81 (5.70)
I ₄	C ₁₉ H ₂₁ N ₃ O ₃ · 2HCl · H ₂ O	62.1	236 - 238	53.98 (54.16)	5.53 (5.74)	9.91 (9.97)
I ₅	C ₂₂ H ₂₆ N ₂ O ₃ · 2HCl · H ₂ O	60.4	182 (dec)	57.54 (57.15)	5.90 (6.00)	6.83 (6.67)
I ₆	C ₁₉ H ₂₁ CN ₂ O · 2HCl	56.6	231 - 233	56.61 (56.79)	5.73 (5.73)	6.98 (6.97)
I ₇	C ₂₃ H ₂₄ N ₂ O · 2HCl · H ₂ O	74.8	241 (dec)	63.40 (63.45)	6.41 (6.48)	6.38 (6.43)
I ₈	C ₂₀ H ₂₄ N ₂ O ₂ · 2HCl · 2H ₂ O	70.3	228 - 230	55.12 (55.43)	6.90 (6.93)	6.34 (6.47)
I ₉	C ₁₉ H ₂₁ N ₃ O ₃ · 2HCl · 1/2H ₂ O	70.2	236 - 238	54.23 (54.16)	5.56 (5.70)	9.90 (9.98)
I ₁₀	C ₂₀ H ₂₄ N ₂ O ₂ · 2HCl · 1/2H ₂ O	70.3	222 - 224	59.47 (59.12)	6.78 (6.70)	7.19 (6.89)
I ₁₁	C ₁₈ H ₂₁ N ₃ O · 3HCl · H ₂ O	65.8	225 - 226	50.55 (51.14)	6.00 (6.20)	9.77 (9.94)
I ₁₂	C ₁₉ H ₂₃ N ₃ O · 3HCl	68.3	194 - 196	52.10 (52.24)	6.59 (6.46)	9.72 (9.58)
I ₁₃	C ₂₀ H ₂₅ N ₃ O · 2HCl · H ₂ O	65.1	244 - 246	57.82 (57.97)	7.14 (7.05)	10.33 (10.14)
I ₁₄	C ₂₁ H ₂₆ N ₂ O · 2HCl · H ₂ O	60.3	238 - 240	61.14 (61.02)	7.24 (7.31)	6.55 (6.78)
I ₁₅	C ₂₁ H ₂₆ N ₂ O ₃ · 2HCl · 1/2H ₂ O	62.1	238 - 240	57.54 (57.80)	6.71 (6.71)	6.32 (6.33)
I ₁₆	C ₁₉ H ₂₃ N ₃ O · 3HCl · 2H ₂ O	61.4	286 - 288	49.44 (49.35)	6.61 (6.54)	9.13 (9.09)
I ₁₇	C ₂₁ H ₂₆ N ₂ O · 2HCl · H ₂ O	72.1	230 - 232	60.89 (61.02)	7.20 (7.31)	6.65 (6.78)
I ₁₈	C ₂₁ H ₂₄ N ₄ O ₄ · 2HCl · 3/2H ₂ O	74.3	228 - 230	50.65 (50.81)	5.68 (5.89)	11.54 (11.35)
I ₁₉	C ₂₀ H ₂₂ N ₂ O ₃ · 2HCl · 1/2H ₂ O	68.4	240 - 241	57.59 (57.15)	5.87 (6.00)	6.39 (6.67)
I ₂₀	C ₁₉ H ₂₀ ClFN ₂ O · 2HCl · H ₂ O	54.9	246 - 248 (dec)	65.79 (65.80)	5.89 (5.81)	7.99 (8.08)
I ₂₁	C ₂₁ H ₂₅ N ₃ O ₂ · 2HCl · 1/2H ₂ O	65.3	238 - 240	57.81 (58.20)	6.44 (6.51)	9.45 (9.70)
I ₂₂	C ₂₀ H ₂₄ N ₂ O ₃ · 2HCl · 2H ₂ O	54.2	240 - 243	46.28 (46.17)	5.90 (5.81)	5.35 (5.38)
I ₂₃	C ₂₀ H ₂₃ N ₃ O ₄ · 2HCl	61.2	214 - 215	49.02 (49.28)	5.93 (6.20)	8.76 (8.62)
I ₂₄	C ₂₀ H ₂₃ FN ₂ O · 2HCl · 1/2H ₂ O	60.7	198 - 199	58.70 (58.83)	6.53 (6.42)	6.66 (6.86)
I ₂₅	C ₂₀ H ₂₄ N ₂ O ₂ · 2HCl	54.2	174 - 176	60.22 (60.45)	6.43 (6.66)	7.26 (7.05)
I ₂₆	C ₂₆ H ₂₈ N ₂ O ₃ S · 2HCl	50.7	189 - 191	60.02 (59.88)	5.98 (5.80)	5.46 (5.37)
I ₂₇	C ₂₁ H ₂₅ N ₃ O ₃ · 2HCl	65.8	214 - 215	57.02 (57.27)	5.98 (6.18)	10.26 (10.42)
I ₂₈	C ₂₄ H ₂₅ CN ₂ O ₂ · 2HCl	63.1	217 - 219	59.95 (59.83)	5.70 (5.65)	5.51 (5.81)
I ₂₉	C ₂₅ H ₂₇ CN ₂ O ₂ · 2HCl · H ₂ O	60.2	252 - 253	59.60 (59.46)	5.81 (5.49)	5.44 (5.55)
I ₃₀	C ₂₆ H ₂₇ CN ₂ O ₄ · 2HCl	70.2	230 - 232	57.63 (57.84)	5.37 (5.04)	5.41 (5.19)
I ₃₁	C ₂₆ H ₂₉ CN ₂ O ₃ · 2HCl · H ₂ O	57.9	222 - 224	59.10 (59.38)	5.66 (5.94)	5.39 (5.33)
I ₃₂	C ₂₅ H ₂₆ CN ₃ O ₄ · 2HCl	65.4	203 - 205	55.42 (55.52)	5.46 (5.22)	7.59 (7.77)
I ₃₃	C ₂₅ H ₂₈ CN ₃ O ₂ · 2HCl	61.2	206 - 208	59.01 (58.77)	5.96 (5.91)	8.39 (8.23)
I ₃₄	C ₂₈ H ₃₃ CN ₂ O ₅ · 2HCl	72.7	219 - 222	57.10 (57.39)	5.99 (6.04)	4.73 (4.80)
I ₃₅	C ₂₇ H ₂₉ CN ₂ O ₂ · 2HCl	70.2	197 - 199	62.10 (62.13)	5.98 (5.99)	5.33 (5.37)

Continued

No	Formula	Yield/%	mp/	Elemental analysis/%		
				Found (Calcd)		
				C	H	N
I ₃₆	C ₂₄ H ₂₄ Cl ₂ N ₂ O ₂ · 2HCl	64.9	185 - 187	55.60 (55.83)	5.28 (5.08)	5.39 (5.43)
I ₃₇	C ₂₀ H ₂₄ N ₂ O · 2HCl	67.5	230 - 237	62.43 (62.99)	6.88 (6.82)	6.91 (7.35)
I ₃₈	C ₂₀ H ₂₄ N ₂ O · 2HCl	85.2	230 - 232	62.40 (62.99)	6.78 (6.82)	6.96 (7.35)
I ₃₉	C ₂₀ H ₂₄ N ₂ O · 2HCl	81.7	236 - 238	62.56 (62.99)	6.79 (6.82)	7.11 (7.35)
I ₄₀	C ₂₁ H ₂₆ N ₂ O · 2HCl · H ₂ O	74.2	230 - 232	62.11 (61.02)	7.24 (7.31)	6.56 (6.78)
I ₄₁	C ₂₁ H ₂₆ N ₂ O · 2HCl · H ₂ O	74.9	231 - 232	60.77 (61.02)	7.44 (7.31)	6.97 (6.78)
I ₄₂	C ₂₁ H ₂₆ N ₂ O · 2HCl · H ₂ O	73.9	236 - 238	60.77 (61.02)	7.29 (7.31)	6.74 (6.78)
I ₄₃	C ₂₆ H ₂₉ CN ₂ O ₂ · 2HCl · 2H ₂ O	65.7	231 - 232	57.37 (57.20)	6.37 (6.46)	5.06 (5.13)
I ₄₄	C ₂₆ H ₂₉ CN ₂ O ₂ · 2HCl	65.4	232 - 233	61.47 (61.24)	5.47 (5.73)	5.36 (5.50)
I ₄₅	C ₂₆ H ₂₉ CN ₂ O ₂ · 2HCl	65.1	235 - 236	61.31 (61.24)	5.42 (5.73)	5.41 (5.50)
I ₄₆	C ₂₀ H ₂₄ N ₂ O · 2HCl · 2H ₂ O	72.3	215 - 217	57.39 (57.55)	7.16 (7.24)	6.70 (6.71)
I ₄₇	C ₂₀ H ₂₃ N ₃ O ₃ · 2HCl	65.3	223 - 225	56.39 (56.34)	5.69 (5.87)	9.79 (9.86)
I ₄₈	C ₂₁ H ₂₆ N ₂ O · 2HCl · 2H ₂ O	69.8	209 - 211	58.39 (58.47)	7.19 (7.48)	6.71 (6.49)
I ₄₉	C ₁₉ H ₂₁ Cl ₂ N ₂ O · 2HCl · H ₂ O	57.0	257 - 258	48.51 (48.22)	5.83 (5.75)	5.90 (5.92)
I ₅₀	C ₁₉ H ₂₁ Cl ₂ N ₂ O · 2HCl · H ₂ O	53.1	249 - 250	48.03 (48.22)	5.63 (5.75)	5.87 (5.92)
I ₅₁	C ₂₀ H ₂₂ N ₂ O ₃ · 2HCl	49.8	198 - 199	58.03 (58.40)	5.79 (5.88)	6.83 (6.81)
I ₅₂	C ₂₃ H ₂₈ N ₂ O ₃ · 2HCl · H ₂ O	72.3	203 - 205	58.53 (58.60)	6.89 (6.84)	5.87 (5.94)
I ₅₃	C ₁₉ H ₂₁ FN ₂ O · 2HCl	58.3	220 - 221	59.47 (59.23)	6.14 (6.02)	7.20 (7.27)
I ₅₄	C ₁₉ H ₂₃ N ₃ O · 2HCl	49.8	174 - 176	59.76 (59.69)	6.62 (6.59)	10.92 (10.99)
I ₅₅	C ₂₁ H ₂₅ N ₃ O ₂ · 2HCl	56.9	189 - 190	59.32 (59.44)	6.18 (6.41)	9.79 (9.90)
I ₅₆	C ₂₅ H ₃₅ N ₄ O · 2HCl	72.1	147 - 149	62.01 (62.49)	7.49 (7.76)	11.53 (11.66)
I ₅₇	C ₂₅ H ₂₆ N ₂ O · 2HCl	67.8	214 - 216	67.81 (67.72)	6.29 (6.36)	6.25 (6.32)
I ₅₈	C ₂₃ H ₂₄ N ₂ O · 2HCl	57.9	238 (dec)	66.07 (66.19)	6.34 (6.28)	6.59 (6.71)
I ₅₉	C ₂₃ H ₂₄ N ₂ O · 2HCl	63.5	232 (dec)	66.12 (66.19)	6.19 (6.28)	6.57 (6.71)
I ₆₀	C ₂₀ H ₂₃ N ₃ O ₃ · 2HCl · H ₂ O	72.1	230 - 231	54.00 (54.06)	6.23 (6.12)	9.41 (9.46)
I ₆₁	C ₂₁ H ₂₆ N ₂ O · 2HCl	73.2	235 - 236	60.97 (61.02)	7.37 (7.31)	6.69 (6.78)
I ₆₂	C ₂₀ H ₂₄ N ₄ O ₃ · 2HCl	56.9	211 - 212	54.21 (54.43)	5.79 (5.94)	12.63 (12.69)
I ₆₃	C ₂₆ H ₂₈ N ₂ O ₂ · 2HCl · H ₂ O	49.8	198 - 199	63.47 (63.54)	6.39 (6.56)	5.74 (5.70)
I ₆₄	C ₂₀ H ₂₆ N ₄ O · 2HCl	63.5	201 - 202	58.27 (58.39)	6.59 (6.86)	13.47 (13.62)

Table 3 Spectral data of target compounds I₁₋₆₄

No	MS m/z	¹ H NMR (400 MHz, DMSO-d ₆)
I ₁	294[M] ⁺	3.58 - 3.62 (m, 8H, A-H), 4.50 (s, 2H, PhCH ₂), 5.22 (br, 2H, NCH ₂ CO), 7.40 - 8.10 (m, 10H, A-H)
I ₂	342[M] ⁺	1.32 - 1.35 (d, 3H, CHCH ₃), 3.59 (m, 8H, A-H), 4.53 (s, 2H, PhCH ₂), 5.24 - 5.26 (m, 1H, COCHN), 7.00 - 8.02 (m, 9H, A-H)
I ₃	328[M] ⁺	3.60 - 3.62 (m, 8H, A-H), 4.55 (s, 2H, PhCH ₂), 5.20 (br, 2H, NCH ₂ CO), 7.20 - 8.09 (m, 9H, A-H)
I ₄	339[M] ⁺	3.55 - 3.60 (m, 8H, A-H), 4.52 (s, 2H, PhCH ₂), 5.19 (br, 2H, NCH ₂ CO), 7.32 - 8.17 (m, 9H, A-H)
I ₅	366[M] ⁺	1.30 (m, 3H, CH ₃), 3.58 - 3.60 (m, 8H, A-H), 4.12 - 4.14 (m, 2H, OCH ₂), 4.74 (s, 2H, PhCH), 5.24 (br, 2H, NCH ₂ CO), 7.06 - 8.12 (m, 10H, A-H)
I ₆	328[M] ⁺	3.56 - 3.59 (m, 8H, A-H), 4.46 (s, 2H, PhCH ₂), 5.18 (br, 2H, NCH ₂ CO), 7.25 - 7.96 (m, 9H, A-H)
I ₇	344[M] ⁺	3.57 - 3.60 (m, 8H, A-H), 4.48 (s, 2H, PhCH ₂), 5.33 (br, 2H, NCH ₂ CO), 7.46 - 8.14 (m, 12H, A-H)
I ₈	308[M] ⁺	3.62 - 3.64 (m, 8H, A-H), 3.96 (s, 3H, OCH ₃), 4.62 (s, 2H, PhCH ₂), 5.26 (br, 2H, NCH ₂ CO), 7.08 - 7.90 (m, 9H, A-H)
I ₉	339[M] ⁺	3.46 - 3.52 (m, 8H, A-H), 4.46 (s, 2H, PhCH ₂), 5.16 (br, 2H, NCH ₂ CO), 7.25 - 8.30 (m, 9H, A-H)
I ₁₀	324[M] ⁺	3.40 - 3.45 (m, 8H, A-H), 3.72 (s, 3H, OCH ₃), 4.42 (s, 2H, PhCH ₂), 5.10 (br, 2H, NCH ₂ CO), 6.65 - 8.09 (m, 9H, A-H)
I ₁₁	295[M] ⁺	3.33 - 3.54 (m, 8H, A-H), 4.33 (s, 2H, CH ₂ N), 5.00 (s, 2H, COCH ₂ N), 7.46 - 8.96 (m, 9H, A-H, pyridine-H)
I ₁₂	309[M] ⁺	3.58 - 3.60 (m, 8H, A-H), 4.45 (s, 2H, PhCH ₂ N), 5.25 (s, 2H, COCH ₂ N), 7.40 - 8.05 (m, 9H, A-H)
I ₁₃	323[M] ⁺	1.42 - 1.43 (d, 3H, CHCH ₃), 3.39 - 3.42 (m, 8H, A-H), 4.45 (s, 2H, PhCH ₂ N), 5.10 - 5.12 (m, 1H, COCHN), 7.40 - 8.07 (m, 9H, A-H)
I ₁₄	308[M] ⁺	3.07 - 3.10 (m, 4H, PhCH ₂ CH ₂ N), 3.60 - 3.63 (m, 8H, A-H), 5.16 (s, 2H, NCH ₂ CO), 7.26 - 8.02 (m, 10H, A-H)

Continued

No	MS <i>m/z</i>	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆)
I ₁₅	354[M] ⁺	3.56 - 3.60 (m, 8H, A-H), 4.54 (s, 2H, PhCH ₂), 4.62 (s, 6H, OCH ₃ ×2), 5.22 (s, 2H, COCH ₂ N), 6.46 - 8.12 (m, 8H, A-H)
I ₁₆	309[M] ⁺	3.46 - 3.50 (m, 8H, A-H), 4.46 (s, 2H, PhCH ₂), 5.10 (s, 2H, COCH ₂ N), 5.86 (s, 2H, NH ₂), 6.57 - 7.78 (m, 9H, A-H)
I ₁₇	308[M] ⁺	3.37 (m, 4H, NCH ₂ CH ₂ CO), 3.55 - 3.59 (m, 8H, A-H), 4.05 (s, 2H, PhCH ₂ N), 7.43 - 7.95 (m, 10H, A-H)
I ₁₈	396[M] ⁺	2.03 (s, 3H, CH ₃), 3.38 - 3.40 (m, 8H, A-H), 4.32 (s, 2H, PhCH ₂), 5.22 (s, 2H, COCH ₂ N), 7.32 - 8.17 (m, 8H, A-H)
I ₁₉	338[M] ⁺	3.32 - 3.35 (m, 8H, A-H), 4.40 (s, 2H, PhCH ₂), 5.08 (s, 2H, COCH ₂ N), 6.14 (s, 2H, OCH ₂ O), 6.51 - 8.09 (m, 8H, A-H)
I ₂₀	346[M] ⁺	3.64 - 3.66 (m, 8H, A-H), 4.45 (s, 2H, PhCH ₂), 5.12 (br, 2H, NCH ₂ CO), 7.29 - 8.03 (m, 8H, A-H)
I ₂₁	351[M] ⁺	2.03 (s, 3H, CH ₃), 3.46 - 3.50 (m, 8H, A-H), 4.46 (s, 2H, PhCH ₂), 5.26 (s, 2H, COCH ₂ N), 7.04 - 8.08 (m, 9H, A-H)
I ₂₂	368[M] ⁺	3.69 - 3.71 (m, 8H, A-H), 3.82 (s, 3H, OCH ₃), 5.10 (s, 1H, PhCH), 7.10 - 7.13 (d, 4H, A-H)
I ₂₃	369[M] ⁺	3.58 - 3.60 (m, 8H, A-H), 3.83 (m, 3H, OCH ₃), 4.48 (s, 2H, PhCH ₂), 5.26 (s, 2H, COCH ₂ N), 7.22 - 8.12 (m, 8H, A-H)
I ₂₄	326[M] ⁺	1.52 - 1.56 (d, 3H, CHCH ₃), 3.46 - 3.50 (m, 8H, A-H), 4.30 - 4.32 (m, 1H, PhCH), 5.12 (s, 2H, COCH ₂ N), 6.92 - 8.12 (m, 9H, A-H)
I ₂₅	324[M] ⁺	3.42 - 3.45 (m, 8H, A-H), 4.40 (s, 2H, PhCH ₂), 4.60 (m, 3H, OCH ₃), 5.26 (s, 2H, COCH ₂ N), 6.57 - 8.10 (m, 9H, A-H)
I ₂₆	448[M] ⁺	3.30 - 3.33 (m, 8H, A-H), 4.46 (s, 2H, PhCH ₂), 5.24 (s, 2H, COCH ₂ N), 5.40 (s, 2H, SO ₂ CH ₂), 6.86 - 8.12 (m, 14H, A-H)
I ₂₇	369[M] ⁺	1.44 - 1.48 (d, 3H, CHCH ₃), 2.41 (s, 3H, PhCH ₃), 3.44 - 3.46 (m, 8H, A-H), 4.60 - 4.62 (m, 1H, PhCH), 5.12 (s, 2H, COCH ₂ N), 6.75 - 8.24 (m, 8H, A-H)
I ₂₈	408[M] ⁺	3.20 - 3.23 (m, 8H, A-H), 4.12 (s, 2H, PhCH ₂), 5.08 (s, 3H, OCH ₃), 5.32 (s, 2H, COCH ₂ N), 7.10 - 8.34 (m, 10H, A-H)
I ₂₉	423[M] ⁺	1.32 - 1.33 (d, 3H, CHCH ₃), 3.30 - 3.33 (m, 8H, A-H), 4.22 (s, 2H, PhCH ₂), 4.68 (s, 3H, PhOCH ₃), 5.08 - 5.10 (m, 1H, COCHN), 7.10 - 8.34 (m, 10H, A-H)
I ₃₀	466[M] ⁺	1.62 - 1.64 (d, 3H, CHCH ₃), 3.30 - 3.32 (m, 8H, A-H), 4.19 (s, 2H, PhCH ₂), 4.46 (s, 3H, OCH ₃), 5.08 - 5.11 (m, 1H, COCHN), 6.06 (s, 2H, OCH ₂ O), 6.51 - 8.34 (m, 8H, A-H)
I ₃₁	452[M] ⁺	1.42 - 1.44 (d, 3H, CHCH ₃), 3.36 - 3.40 (m, 8H, A-H), 4.32 (s, 2H, PhCH ₂), 4.42 - 4.46 (m, 6H, OCH ₃ ×2), 5.12 - 5.14 (m, 1H, COCHN), 6.65 - 8.24 (m, 9H, A-H)
I ₃₂	467[M] ⁺	1.56 - 1.58 (d, 3H, CHCH ₃), 3.46 - 3.50 (m, 8H, A-H), 4.43 (s, 2H, PhCH ₂), 4.46 (s, 3H, OCH ₃), 5.22 - 5.23 (m, 1H, COCHN), 6.75 - 8.22 (m, 9H, A-H)
I ₃₃	437[M] ⁺	1.48 - 1.50 (d, 3H, CHCH ₃), 3.56 - 3.60 (m, 8H, A-H), 4.52 (s, 2H, PhCH ₂), 4.88 (s, 3H, OCH ₃), 5.08 - 5.10 (m, 1H, COCHN), 5.58 (s, 2H, NH ₂), 7.10 - 8.34 (m, 9H, A-H)
I ₃₄	512[M] ⁺	1.68 - 1.69 (d, 3H, CHCH ₃), 3.36 - 3.40 (m, 8H, A-H), 4.30 (s, 2H, PhCH ₂), 4.68 - 4.71 (m, 12H, PhOCH ₃ ×4), 5.16 - 5.18 (m, 1H, COCHN), 6.58 - 8.44 (m, 7H, A-H)
I ₃₅	449[M] ⁺	1.56 - 1.58 (d, 3H, CHCH ₃), 3.66 - 3.40 (m, 8H, A-H), 4.78 (s, 3H, PhOCH ₃), 5.18 - 5.20 (m, 1H, COCHN), 5.48 (s, 1H, PhCH), 5.98 (m, 1H, NCH), 7.30 - 8.14 (m, 10H, A-H)
I ₃₆	444[M] ⁺	1.64 - 1.66 (d, 3H, CHCH ₃), 2.59 - 3.26 (m, 8H, A-H), 3.78 (s, 3H, OCH ₃), 4.60 - 4.63 (m, 1H, COCHN), 6.60 - 8.38 (m, 9H, A-H)
I ₃₇	308[M] ⁺	1.62 - 1.68 (d, 3H, CHCH ₃), 2.98 - 3.01 (m, 8H, A-H), 4.22 - 4.24 (m, 1H, PhCH), 4.98 (s, 1H, COCH ₂ N), 7.02 - 8.14 (m, 10H, A-H)
I ₃₈	308[M] ⁺	1.70 - 1.72 (d, 3H, CHCH ₃), 3.37 - 3.55 (m, 8H, A-H), 4.60 - 4.65 (m, 1H, NCH), 5.03 (s, 2H, NCH ₂ CO), 7.48 - 7.97 (m, 10H, A-H)
I ₃₉	308[M] ⁺	1.71 - 1.72 (d, 3H, CHCH ₃), 3.39 - 3.57 (m, 8H, A-H), 4.67 - 4.69 (m, 1H, NCH), 5.09 (s, 2H, NCH ₂ CO), 7.52 - 7.99 (m, 10H, A-H)
I ₄₀	322[M] ⁺	1.67 - 1.72 (d, 3H, CH ₃), 2.34 (s, 3H, PhCH ₃), 3.27 - 3.51 (m, 8H, A-H), 4.49 - 4.56 (m, 1H, NCH), 4.93 (s, 2H, NCH ₂ CO), 7.39 - 7.84 (m, 9H, A-H)
I ₄₁	322[M] ⁺	1.67 - 1.68 (d, 3H, CH ₃), 2.37 (s, 3H, PhCH ₃), 3.29 - 3.54 (m, 8H, A-H), 4.52 - 4.57 (m, 1H, NCH), 4.88 (s, 2H, NCH ₂ CO), 7.37 - 7.85 (m, 9H, A-H)
I ₄₂	322[M] ⁺	1.65 - 1.67 (d, 3H, CH ₃), 2.34 (s, 3H, PhCH ₃), 3.22 - 3.49 (m, 8H, A-H), 4.51 - 4.59 (m, 1H, NCH), 4.93 (s, 2H, NCH ₂ CO), 7.42 - 7.79 (m, 9H, A-H)
I ₄₃	437[M] ⁺	1.32 - 1.72 (d, 3H, CH ₃ ×2), 2.41 (s, 3H, PhCH ₃), 2.68 - 3.28 (m, 8H, A-H), 4.08 - 4.26 (m, 1H, NCH), 4.63 (m, 1H, NCHCO), 6.82 - 7.64 (m, 9H, A-H)
I ₄₄	437[M] ⁺	1.67 - 1.72 (d, 3H, CH ₃ ×2), 2.34 (s, 3H, PhCH ₃), 3.27 - 3.41 (m, 8H, A-H), 4.49 - 4.53 (m, 1H, NCH), 4.93 (m, 1H, NCHCO), 7.39 - 7.84 (m, 9H, A-H)

Continued

No	MS <i>m/z</i>	¹ H NMR (400 Hz, DMSO- <i>d</i> ₆)
I ₄₅	437[M] ⁺	1.69 - 1.73 (d, 3H, CH ₃ ×2), 2.36 (s, 3H, PhCH ₃), 3.30 - 3.45 (m, 8H, A-H), 4.31 - 4.40 (m, 1H, NCH), 4.73 (m, 1H, NCHCO), 7.20 - 7.79 (m, 9H, ArH)
I ₄₆	308[M] ⁺	1.30 (d, 3H, CHCH ₃), 3.59 - 3.62 (m, 8H, A-H), 4.53 (s, 2H, PhCH ₂), 5.24 (m, 1H, COCHN), 7.00 - 8.02 (m, 10H, ArH)
I ₄₇	353[M] ⁺	1.42 (d, 3H, CHCH ₃), 3.80 - 3.82 (m, 8H, A-H), 4.86 (s, 2H, PhCH ₂), 5.46 (m, 1H, COCHN), 7.32 - 8.17 (m, 9H, ArH)
I ₄₈	322[M] ⁺	1.69 - 1.74 (d, 3H, CH ₃ ×2), 3.27 - 3.51 (m, 8H, A-H), 4.49 - 4.56 (m, 1H, NCH), 4.93 (m, 1H, NCHCO), 7.12 - 8.02 (m, 10H, ArH)
I ₄₉	363[M] ⁺	3.20 - 3.22 (m, 8H, A-H), 4.45 (s, 2H, PhCH ₂), 5.12 (br, 2H, NCH ₂ CO), 6.94 - 8.09 (m, 8H, ArH)
I ₅₀	363[M] ⁺	3.64 - 3.66 (m, 8H, A-H), 4.26 (s, 2H, PhCH ₂), 5.22 (br, 2H, NCH ₂ CO), 7.29 - 8.20 (m, 8H, ArH)
I ₅₁	338[M] ⁺	3.48 - 3.50 (m, 8H, A-H), 4.42 (s, 1H, PhCH), 5.26 (br, 2H, NCH ₂ CO), 7.09 - 8.10 (m, 10H, ArH)
I ₅₂	380[M] ⁺	1.06 - 1.10 (m, 3H, CH ₂ CH ₃), 1.32 (m, 3H, CH ₃), 2.68 - 2.70 (m, 8H, A-H), 2.76 (m, 2H, CH ₂), 4.74 (s, 1H, PhCH), 5.24 (m, 1H, NCHCO), 7.06 - 8.12 (m, 10H, ArH)
I ₅₃	312[M] ⁺	3.44 - 3.46 (m, 8H, A-H), 4.35 (s, 2H, PhCH ₂), 5.02 (br, 2H, NCH ₂ CO), 7.19 - 8.13 (m, 9H, ArH)
I ₅₄	309[M] ⁺	3.58 - 3.60 (m, 8H, A-H), 4.50 (s, 2H, PhCH ₂), 5.22 (br, 2H, NCH ₂ CO), 7.40 - 8.10 (m, 10H, ArH)
I ₅₅	351[M] ⁺	2.63 (s, 3H, COCH ₃), 3.58 - 3.62 (m, 8H, A-H), 4.47 (s, 2H, PhCH ₂), 5.27 (br, 2H, NCH ₂ CO), 7.42 - 8.19 (m, 9H, ArH)
I ₅₆	407[M] ⁺	2.46 - 3.30 (m, 16H, A-H), 3.62 (m, 4H, PhCH ₂ ×2), 3.72 (s, 2H, COCH ₂), 7.10 - 7.31 (m, 10H, ArH)
I ₅₇	370[M] ⁺	3.59 - 3.62 (m, 8H, A-H), 4.53 (s, 2H, PhCH ₂), 5.24 - 5.26 (m, 1H, COCHN), 7.06 - 8.02 (m, 15H, ArH)
I ₅₈	344[M] ⁺	2.88 - 2.92 (m, 8H, A-H), 3.73 (s, 2H, PhCH ₂), 4.50 (s, 2H, COCH ₂ N), 7.10 - 8.27 (m, 12H, ArH)
I ₅₉	344[M] ⁺	2.69 - 2.71 (m, 8H, A-H), 3.86 (s, 2H, PhCH ₂), 4.62 (s, 2H, COCH ₂ N), 7.18 - 8.10 (m, 12H, ArH)
I ₆₀	353[M] ⁺	1.67 - 1.72 (d, 3H, CH ₃), 3.27 - 3.51 (m, 8H, A-H), 4.49 - 4.56 (m, 1H, NCH), 4.93 (s, 2H, NCH ₂ CO), 7.55 - 8.24 (m, 9H, ArH)
I ₆₁	322[M] ⁺	1.10 (m, 3H, CH ₂ CH ₃), 1.62 - 1.68 (d, 2H, CH ₂ CH ₃), 2.98 - 3.02 (m, 8H, A-H), 4.22 (m, 1H, PhCH), 4.98 (s, 1H, COCH ₂ N), 7.02 - 8.14 (m, 10H, ArH)
I ₆₂	368[M] ⁺	2.46 - 2.48 (m, 8H, A-H), 3.25 (s, 2H, NCH ₂ CONH), 3.62 (m, 2H, PhCH ₂), 4.46 (s, 2H, NHCH ₂ Ph), 7.25 - 8.17 (m, 9H, ArH)
I ₆₃	400[M] ⁺	2.50 - 2.53 (m, 8H, A-H), 3.62 (s, 2H, PhCH ₂ N), 3.73 (s, 2H, NCH ₂ CO), 5.14 (m, 2H, PhCH ₂ O), 7.37 - 8.17 (m, 14H, ArH)
I ₆₄	338[M] ⁺	2.66 - 2.68 (m, 8H, A-H), 3.25 (s, 2H, PhCH ₂ N), 3.72 (m, 2H, NCH ₂ CO), 4.46 (m, 2H, CONCH ₂ Ph), 5.85 (s, 2H, NH ₂), 6.34 - 7.31 (m, 9H, ArH)

Note: A = Piperazine

2 药理试验

实验动物均由中国科学院上海动物中心提供。

2.1 小鼠扭体法镇痛作用

采用昆明种小鼠,雌雄各半,体重 22 ~ 26 g,随机分组,每组 10 只。小鼠先 sc 测试药物 (20 mg · kg⁻¹),对照组 sc 生理盐水 (20 mL · kg⁻¹), 30 min 后 ip 0.7% 乙酸 10 mL · kg⁻¹, 5 min 后记录各组小鼠在 10 min 内出现的扭体反应次数,计算各给药组的抑制扭体频率百分率 [抑制 % = (生理盐水组的扭体次数 - 测试组的扭体次数) / 生理盐水组的扭体次数 × 100%]。39 个化合物的药理结果见表 4,其中有 7 个化合物的抑制扭体频率达到 100%,另有 3 个化合物的抑制扭体频率大于 90%。

2.2 大鼠热板法镇痛作用

雌性大白鼠,体重 80 ~ 120 g,随机分组,每组 10 只。采用 55 热板测痛仪 (宁海白石电子医药

Table 4 Analgesic effect of 39 compounds in mice writhing model

Group	Inhibitory rate / %	Group	Inhibitory rate / %	Group	Inhibitory rate / %
I ₁	68.2	I ₅	56.6	I ₄	93.2
I ₂	14	I ₆	43	I ₇	25
I ₃	39	I ₉	74	I ₁₀	100
I ₁₁	86	I ₁₂	100	I ₁₃	100
I ₁₄	94	I ₁₅	80	I ₁₆	63
I ₁₇	45	I ₁₈	64	I ₁₉	97
I ₂₀	45	I ₂₁	100	I ₂₂	100
I ₂₃	87	I ₂₄	64	I ₂₅	100
I ₂₇	57	I ₃₁	45	I ₃₇	100
I ₃₈	51	I ₃₉	42	I ₄₁	60
I ₄₂	44	I ₄₃	42	I ₄₇	28.8
I ₅₅	21	I ₅₈	49	I ₅₉	45
I ₆₀	37	I ₆₁	6	I ₆₂	64

仪器厂生产) 测试大鼠用药前后痛阈变化。大鼠试验前用酒精棉球将后脚趾擦洗干净。各大鼠先测试二次正常痛反应,以出现舔后趾为痛反应终止时间,

二次间隔 20 ~ 30 min。痛反应稳定的大鼠用于药物试验。ip 给药, 剂量为 $20 \text{ mg} \cdot \text{kg}^{-1}$, 观察大鼠痛反应时间比之用药前延长 1 倍以上的时间及痛反应时间超过 60 s 以上的为阳性。9 个化合物的药理结果见表 5, 有 4 个化合物的镇痛百分率达到 100%。

Table 5 Analgesic effect of 9 compounds in rat hot plate model

Group	Analgesic ratio /% (pain threshold increased > 100%)	Analgesic ratio /% (pain threshold > 60 s)
I ₀	90	70
I ₂	100	80
I ₄	100	70
I ₉	70	50
I ₁₁	100	50
I ₂₅	40	10
I ₂₇	20	0
I ₃₇	100	100
I ₄₀	10	10

2.3 大鼠光热甩尾法镇痛结果

SD 大鼠, 体重 250 ~ 300 g, 雌雄各半, 随机分组, 每组 10 只。用 8.75 mm 放映灯泡 (12 V, 50 W) 发出光热, 照射于大鼠尾的近尾端 3 cm 处, 通过调压变压器调节光热强度, 使痛反应 (甩尾离开光源) 时间在 3 ~ 5 s 之间。大鼠先预测 2 ~ 3 次, 各次痛

反应时间稳定者用于药物镇痛作用测试。大鼠分别口服测试药物 $20 \text{ mg} \cdot \text{kg}^{-1}$, 测定药物作用高峰时 (给药后 30 ~ 45 min) 痛阈延长百分比。9 个化合物的药理结果见表 6。

以上研究表明: I₂、I₄、I₁₁、I₂₇ 在大、小鼠三种致痛模型上, 均显示很强的镇痛活性, 具有深入研究的价值。

2.4 纳洛酮翻转试验

通过纳洛酮翻转试验来验证化合物 I₂ 镇痛途径, 以评价该类化合物属非阿片类镇痛药。

雌性小鼠 18 ~ 22 g, 随机分组, 每组 10 只。分组及给药剂量: 吗啡组 (Mor $10 \text{ mg} \cdot \text{kg}^{-1}$); 吗啡 + 纳洛酮组 (Mor $10 \text{ mg} \cdot \text{kg}^{-1}$; Nal $1 \text{ mg} \cdot \text{kg}^{-1}$); I₂ 组 (I₂ $60 \text{ mg} \cdot \text{kg}^{-1}$); I₂ + 纳洛酮组 (I₂ $60 \text{ mg} \cdot \text{kg}^{-1}$; Nal $1 \text{ mg} \cdot \text{kg}^{-1}$); 强痛定组 (QTD $23 \text{ mg} \cdot \text{kg}^{-1}$); 强痛定 + 纳洛酮组 (QTD $23 \text{ mg} \cdot \text{kg}^{-1}$, Nal $1 \text{ mg} \cdot \text{kg}^{-1}$)。sc 给药, 55 热板测痛仪测试。

各组均取 ED₉₅ 剂量。正常测痛二次 (取二次的平均数), 以舔后趾为痛反应终止时间。给药后 5, 15, 30, 60, 90, 150, 210 和 270 min 测痛阈 (结束)。药后痛阈限制 60 s 内。加纳洛酮组给药途径也是皮下, 与受试药物同时给药, 只是给药部位不在一处。实验结果见表 7。

Table 6 Analgesic effect of 9 compounds in rat tail flick model

Group	Pain threshold before administration / s	Pain threshold after administration / s	Pain threshold increased / s	Pain threshold increased / %	P
I ₀	8.05	8.81	0.76	9.4	0.173
I ₂	7.84	10.05	2.21	34	0.005
I ₄	7.70	10.62	2.92	37.9	0.005
I ₉	8.04	8.58	0.54	6.7	0.366
I ₁₁	7.63	9.72	2.09	28	0.001
I ₂₅	7.49	8.37	0.88	12	0.096
I ₂₇	8.58	9.37	0.79	9.2	0.233
I ₃₇	8.43	10.54	2.11	25	0.101
I ₄₀	7.30	7.88	0.58	8	0.183

Table 7 Drug dependence test of compound I₂

Time/min	Mor	Mor+Nal	QTD	QTD+Nal	I ₂	I ₂ +Nal
5	89.6 ±23.3	6.7 ±10.5	100 ±0	5.2 ±11.6	100 ±0	100 ±0
15	100 ±0	0	80.0 ±44.7	1.3 ±2.9	100 ±0	100 ±0
30	100 ±0	0	27.3 ±48.6	0	100 ±0	100 ±0
60	94.8 ±11.6	39.5 ±39.5	10 ±17.3	1.9 ±4.2	100 ±0	100 ±0
90	49.1 ±39.6	38.9 ±41.5	-	-	100 ±0	100 ±0
150	-	-	-	-	100 ±0	100 ±0
210	-	-	-	-	93.8 ±13.9	87.6 ±27.7
270	-	-	-	-	43.1 ±25.9	50.2 ±30.5

研究表明:加纳洛酮可以翻转吗啡和强痛定的镇痛作用,但不能翻转化合物 I_2 的镇痛作用,预示化合物 I_2 属非阿片类镇痛途径,有可能避免阿片类镇痛剂的药物成瘾性。

3 结论

本研究以 NMDA 受体靶位点和化合物的生物活性为导向,设计合成了未曾报道的芳烷醇哌嗪系列化合物 64 个,其结构经质谱、核磁共振谱及元素分析确证。镇痛药理试验显示:该类化合物具有较好镇痛作用。其中,化合物 I_2 , I_4 , I_1 和 I_7 在 3 种镇痛模型上均显示很强的镇痛活性,值得进一步深入研究。化合物 I_2 的纳洛酮翻转试验研究表明,该类化合物可能属非阿片类镇痛途径,是否可发展成为镇痛作用强、毒副反应温和、非成瘾性的新型镇痛剂,有待进一步深入研究。

合成实验部分

熔点用毛细管法测定,温度未经校正。核磁共振仪为 Varian NOVA-400 型, TMS 为内标;质谱仪为 Finnigan-MAT 212 型;元素分析仪为 Carlo Erba-1106。

通法一: N 芳烷甲酰烷基哌嗪 (3) 盐酸盐的合成

将无水哌嗪 (258 g, 3 mol) 置于甲酸甲酯 (180 g, 3 mol) 中,加热至 80 °C,回流 8 h,冷至室温,减压除去未反应的哌嗪,收集 130 ~ 134 /8 mmHg 馏份,得 N-甲酰基哌嗪化合物 240 g,收率 70%, $D_{(20)}^{20}$ 1.514 0 (文献^[6] 140 ~ 170 /10 mmHg, $D_{(20)}^{20}$ 1.510 0)。

将上述 N-甲酰基哌嗪 (35.34 g, 310 mmol), 卤代芳烷甲酰烷基 (372 mmol), 无水碳酸钾 (64.17 g, 465 mmol) 及碘化钾 (4.4 g, 30 mmol) 置于丙酮 (320 mL) 中,剧烈搅拌加热回流 8 ~ 16 h,冷至室温,过滤,用少许丙酮洗,合并滤液减压蒸干为桔红色油状物。在油状物中加入 5% 氢氧化钠水溶液 350 mL,回流反应 10 h,冷至室温,用 6 mol · L⁻¹ HCl 调反应液 pH = 8,再用 CHCl₃ (200 mL ×3) 萃取水层,合并氯仿层,用水 50 mL,饱和 NaCl 水溶液 50 mL 洗, MgSO₄ 干燥。过滤,减压蒸干溶媒,用乙醇 50 mL 溶

解油状物, HCl/C₂H₅OH (5 mol · L⁻¹) 调 pH = 3,析出固体,用无水乙醇重结晶,得 N 芳烷甲酰烷基哌嗪双盐酸盐 (3),收率 55 ~ 60%。

通法二: N¹ 芳烷甲酰烷基-N⁴ 芳烷基哌嗪 (I) 盐酸盐的合成

将 N 芳烷甲酰烷基哌嗪双盐酸盐 (3) (10 mmol), 卤代芳烷基 (12 mmol), 碘化钾 (0.15 g, 1 mmol) 和无水碳酸钾 (4.8 g, 35 mmol) 置于 DMF (50 mL) 中,室温搅拌反应 8 ~ 12 h,过滤,减压蒸干溶剂,加水 50 mL,用乙酸乙酯 (100 mL ×3) 提取,合并酯层,依次用水 20 mL,饱和 NaCl 水溶液 30 mL 洗, MgSO₄ 干燥。过滤,蒸去溶剂,加乙醇 30 mL 溶解,用 HCl/C₂H₅OH (5 mol · L⁻¹) 调 pH = 2,过滤析出的固体,乙醇/水或甲醇重结晶,得目标化合物 (I),收率 50 ~ 85%。

参照通法一、二合成目标化合物 I_{1-64} 。

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