3-(4哌嗪-1苯基)-6取代-*s*三唑并[3,4-b][1,3,4]噻二唑盐酸盐的合成及抗菌活性

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摘要：为了研究水溶性稠杂环化合物的合成方法及抗菌活性，本研究采用3-(4氯苯基)-6取代-*s*三唑并[3,4-b][1,3,4]噻二唑(**2a** ~ **n**)在相转移催化剂TBAI作用下与哌嗪发生亲核取代，再与盐酸成盐制备了3-(4哌嗪-1苯基)-6取代-*s*三唑[3,4-b][1,3,4]噻二唑盐酸盐(**3a** ~ **n**)。用试管二倍稀释法研究了新化合物的体外抗菌活性。结果表明，合成的28个新化合物极性碱性哌嗪基的引入可提高化合物的抗菌活性。该类稠杂环化合物的结构有待进一步优化。

关键词：相转移催化剂；均三唑并噻二唑；抗菌活性

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Synthesis and antibacterial activity of 3-(4-piperazin-1-yl-phenyl)-*s*-triazolo[3,4-b][1,3,4] thiadiazole hydrochlorides

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Abstract: To study the synthetic method and antibacterial activity of water-soluble fused heterocyclic compounds containing piperazine group, the nucleophilic substitution of 3-(4-chlorophenyl)-6-substituted-*s*-triazolo-[3,4-b][1,3,4]thiadiazoles (**2a** - **n**) with piperazine in the presence of phase transfer catalyst TBAI afforded 3-(4-piperazin-1-yl-phenyl)-6-substituted-*s*-triazolo[3,4-b][1,3,4]thiadiazole and then followed by acid treatment afforded 3-(4-piperazin-1-yl-phenyl)-6-substituted-*s*-triazolo[3,4-b][1,3,4] thiadiazole hydrochlorides (**3a** - **n**). Twenty-eight new compounds were synthesized and their structures were confirmed by IR, ^{1}H NMR, MS and element analysis. The *in vitro* antibacterial activities of all newly synthesized compounds were tested against Gram positive bacteria and Gram negative bacteria with the standard 2-fold agar dilution method. Fourteen title compounds exhibited potential antibacterial activities *in vitro*. The structures of these compounds needed to be further optimized.

Key words: phase transfer catalyst; *s*-triazolo[3,4-b][1,3,4]thiadiazole; antibacterial activity

均三唑并[3,4-b][1,3,4]噻二唑衍生物因具有广泛的生物活性日益受到人们的关注，合成了大量的衍生物用于药学和农学方面的研究[1~4]。然而，目前对其结构的修饰主要集中在3-位和6-位非极性的脂溶性烃基和芳香基上，这导致整个分子的极性降低，水溶性差，脂-水分配系数失调，可能影响配基与配体间的亲和力，不利于药效的发挥。为了寻找新结构的先导化合物，考虑到在许多药物分子如喹诺酮抗菌药诺氟沙星和环丙沙星[5]，抗真菌药伊曲康唑[6]，抗结核药利福平和利福喷丁[7]等分子中引入碱性哌嗪极性基团，有利于提高药物的生理

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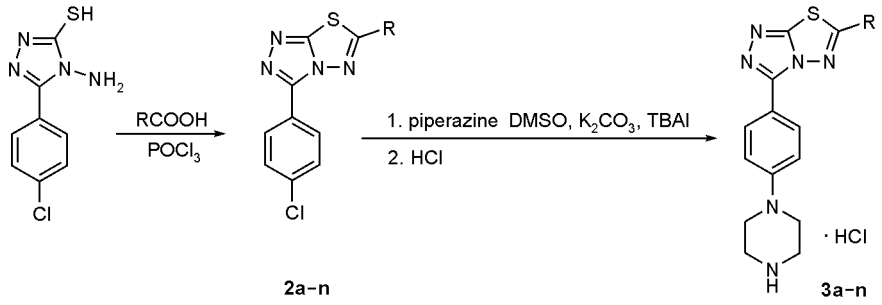
活性。在前文[8]合成及活性研究的基础上,作者设计了在稠杂环 3-(4-氯苯基)-6-取代-*s*-三唑[3,4-*b*][1,3,4]噻二唑 **2a** ~ **n**分子的 3位取代基苯环上通过亲核取代反应引入极性强的碱性哌嗪基,尔后与盐酸成盐,合成了 3-(4-哌嗪-1-苯基)-6-取代-*s*-三唑[3,4-*b*][1,3,4]噻二唑盐酸盐 **3a** ~ **n**(图 1),希望发现有进一步结构修饰价值的先导物,为进一步优化结构提供依据。

3-(4-氯苯基)-4-氨基-5-巯基-1,2,4-均三唑(**1**)与相应的取代羧酸在三氯氧磷作用下经分子内缩环合得中间体 **2a** ~ **n**。实验中发现,在无相转移催化剂存在下,只有当中间体 **2a** ~ **n**的 6位取代基为吸电子杂环取代如化合物 **2l**,**2m**,**2n**时,3位苯环对位的氯原子才能与哌嗪发生亲核取代反应,且收率较低,其余各中间体均不发生反应。如在反应体系中加入四丁基碘化铵(TBAI)相转移催化剂,3位苯环上的氯原子能以理想的收率制得各哌嗪取代化合物 **3a** ~ **n**,其催化机制有待进一步研究。合成中间体及目标化合物的理化性质及光谱数据见表 1 ~3。

供试化合物 **2a** ~ **n**和 **3a** ~ **n**及对照药诺氟沙星(NF)预配成 128 μg·mL^{-1}溶液作为供试样品,采用标准试管二倍稀释法测定其对金葡菌(*S. aureus*) ATCC25923、枯草芽孢杆菌(*B. substilis*) 63501、大肠埃希氏菌(*E. coli*) ATCC25922和铜绿假单孢菌(*P. aeruginosa*) ATCC 27853的体外最低抑制菌浓度(MIC),结果见表 4。

上述实验结果表明,除化合物 **3a**, **3c**, **3g**和 **3m**对大肠埃希氏菌的抑菌活性与对照药相当外,其余化合物对各试验菌均表现较弱的抑菌活性。但哌嗪取代物 **3a** ~ **n**与非取代物 **2a** ~ **n**的抑菌活性相比较发现,哌嗪基的引入能显著提高抑菌活性。



R: **a**: H; **b**: CH_3; **c**: CH_2CH_3; **d**: C_6H_5; **e**: *p*-CH_3-C_6H_4; **f**: *m*-CH_3-C_6H_4; **g**: *p*-CH_3O-C_6H_4; **h**: *o*-CH_3O-C_6H_4; **i**: 3,4-$(CH_3O)_2$-C_6H_3; **j**: 3,4-(OCH_2O)-C_6H_3; **k**: 3,4,5-$(CH_3O)_3$-C_6H_2; **l**: 2-furyl; **m**: 4-pyridyl; **n**: 3-pyridyl

Scheme 1 Synthetic route of piperazine-substituted *s*-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives

Table 1 Physical properties of intermediates **2a - n**

No.	Formula	Yield/%	mp/℃	Elemental analysis/% Calcd. (Found)		
				C	H	N
2a	$C_9H_5ClN_4S$	54	228 - 230	45.67(45.82)	2.13(2.07)	23.67(23.82)
2b	$C_{10}H_7ClN_4S$	48	188 - 190	47.91(47.88)	2.81(2.70)	22.35(22.44)
2c	$C_{11}H_9ClN_4S$	45	172 - 174	49.91(49.82)	3.43(3.38)	21.16(21.28)
2d	$C_{15}H_9ClN_4S$	63	219 - 220	57.60(57.75)	2.90(2.78)	17.91(18.06)
2e	$C_{16}H_{11}ClN_4S$	61	224 - 226	58.80(58.86)	3.39(3.28)	17.14(17.26)
2f	$C_{16}H_{11}ClN_4S$	67	226 - 228	58.80(58.82)	3.39(3.30)	17.14(17.22)
2g	$C_{16}H_{11}ClN_4OS$	68	204 - 206	56.06(56.12)	3.23(3.14)	16.34(16.28)
2h	$C_{16}H_{11}ClN_4OS$	62	212 - 213	56.06(56.16)	3.23(3.24)	16.34(16.45)
2i	$C_{17}H_{13}ClN_4O_2S$	62	221 - 222	54.77(54.80)	3.51(3.48)	15.03(15.17)
2j	$C_{16}H_9ClN_4O_2S$	68	245 - 247	53.86(53.92)	2.54(2.48)	15.70(15.88)
2k	$C_{18}H_{15}ClN_4O_3S$	52	212 - 213	53.67(53.68)	3.75(3.64)	13.91(14.12)
2l	$C_{13}H_7ClN_4OS$	66	235 - 237	51.58(51.62)	2.33(2.26)	18.51(18.72)
2m	$C_{14}H_8ClN_5S$	65	238 - 240	53.59(53.66)	2.57(2.68)	22.32(22.42)
2n	$C_{14}H_8ClN_5S$	61	224 - 225	53.59(53.68)	2.57(2.47)	22.32(22.36)

Table 2 Physical properties of the title compounds **3a - n**

No.	Formula	Yield/%	mp/℃	Elemental analysis/% Calcd. (Found)		
				C	H	N
3a	$C_{13}H_{14}N_6S\cdot HCl$	58	258 - 260	48.37(48.42)	4.68(4.45)	26.03(26.22)
3b	$C_{14}H_{16}N_6S\cdot HCl$	53	234 - 236	49.92(50.12)	5.09(5.05)	24.95(24.88)
3c	$C_{15}H_{18}N_6S\cdot HCl$	47	212 - 214	51.35(51.50)	5.46(5.55)	23.95(24.13)
3d	$C_{19}H_{18}N_6S\cdot HCl$	62	268 - 271	57.21(57.38)	4.80(4.60)	21.07(21.23)
3e	$C_{20}H_{20}N_6S\cdot HCl$	74	226 - 2228	58.17(58.24)	5.13(5.30)	20.35(20.44)
3f	$C_{20}H_{20}N_6S\cdot HCl$	64	228 - 230	58.17(58.21)	5.13(5.27)	20.35(20.44)
3g	$C_{20}H_{20}N_6OS\cdot HCl$	66	257 - 260	56.00(56.22)	4.93(5.13)	19.59(19.62)
3h	$C_{20}H_{20}N_6OS\cdot HCl$	65	238 - 240	56.00(56.20)	4.93(5.12)	19.59(19.77)
3i	$C_{21}H_{22}N_6O_2S\cdot HCl$	57	223 - 224	54.96(55.12)	5.05(5.08)	18.31(18.44)
3j	$C_{20}H_{18}N_6O_2S\cdot HCl$	58	264 - 266	54.23(54.36)	4.32(4.28)	18.97(19.12)
3k	$C_{22}H_{24}N_6O_3S\cdot HCl$	49	218 - 220	54.04(54.16)	5.15(5.03)	17.19(17.26)
3l	$C_{17}H_{16}N_6OS\cdot HCl$	62	264 - 266	52.51(52.68)	4.41(4.28)	21.61(21.74)
3m	$C_{18}H_{17}N_7S\cdot HCl$	76	284 - 286	54.06(54.18)	4.54(4.38)	24.52(24.66)
3n	$C_{18}H_{17}N_7S\cdot HCl$	68	266 - 268	54.06(54.14)	4.54(4.46)	24.52(24.60)

Table 3 Spectral data of the title compounds **3a - n**

No.	IR/cm^{-1}	^{1}H NMR (D_2O) δ	MS(*m/z*)
3a	3 432, 3 025, 1 617, 1 576, 1 457	8.63(s, 1H, 6-H), 8.26 - 7.72(m, 4H, Ph-H), 3.86 - 3.26(m, 8H, piperazine-H)	286[M]$^+$
3b	3 415, 3 017, 1 608, 1 568, 1 457	8.14 - 7.64(m, 4H, Ph-H), 3.88 - 3.34(m, 8H, piperazine-H), 2.46(s, 3H, CH_3)	300[M]$^+$
3c	3 362, 3 007, 1 582, 1 468, 1 457	8.12 - 7.52(m, 4H, Ph-H), 3.84 - 3.18(m, 8H, piperazine-H), 2.38(q, J = 7.2 Hz, 2H, CH_2), 1.18(t, J = 7.2 Hz, 3H, CH_3)	314[M]$^+$
3d	3 326, 1 618, 1 450, 1 267	8.17 - 7.55(m, 9H, Ph-H), 3.68 - 3.45(m, 8H, piperazine-H)	362[M]$^+$
3e	3 314, 1 600, 1 557, 1 264	8.32 - 7.38(m, 8H, Ph-H), 3.88 - 3.45(m, 8H, piperazine-H), 2.37(s, 3H, CH_3)	376[M]$^+$
3f	3 364, 3 012, 1 567, 1 265	8.07 - 7.74(m, 8H, Ph-H), 3.86 - 3.46(m, 8H, piperazine-H), 2.45(s, 3H, CH_3)	376[M]$^+$
3g	3 324, 1 608, 1 264	8.24 - 7.55(m, 8H, Ph-H), 3.94(s, 3H, CH_3O), 3.87 - 3.42(m, 8H, piperazine-H)	392[M]$^+$
3h	3 315, 1 561, 1 267	8.17 - 7.44(m, 8H, Ph-H), 3.88(s, 3H, CH_3O), 3.84 - 3.46(m, 8H, piperazine-H)	392[M]$^+$
3i	3 415, 1 576, 1 456	8.14 - 7.63(m, 7H, Ph-H), 3.93, 3.88(s, 6H, 2 × CH_3O), 3.76 - 3.40(m, 8H, piperazine-H)	422[M]$^+$
3j	3 356, 1 624, 1 575, 1 457	8.14 - 7.48(m, 7H, Ph-H), 6.12(s, 2H, OCH_2O), 3.88 - 3.36(m, 8H, piperazine-H)	406[M]$^+$
3k	3 415, 1 602, 1 457	7.86 - 7.43(m, 6H, Ph-H), 3.96, 3.88, 3.86(s, 6H, 3 × CH_3O), 3.74 - 3.42(m, 8H, piperazine-H)	452[M]$^+$
3l	3 345, 1 627, 1 576, 1 455	8.16 - 7.62(m, 7H, aryl-H), 4.10 - 3.67(m, 8H, piperazine-H);	352[M]$^+$
3m	3 328, 1 617, 1 556, 1 455	9.17(s, 1H, py-H), 8.86 - 7.68(m, 7H, aryl-H), 4.12 - 3.65(m, 8H, piperazine-H)	363[M]$^+$
3n	3 420, 1 634, 1 574, 1 455	9.24(s, 1H, Py-H), 8.84 - 7.58(m, 7H, aryl-H), 3.86 - 3.57(m, 8H, piperazine-H)	363[M]$^+$

Table 4 The *in vitro* antibacterial activities of compounds **2a - n** and **3a - n** (μg·mL^{-1})

No.	Organism				No.	Organism			
	S. aureus	*B. substilis*	*E. coli*	*P. aeruginosa*		*S. aureus*	*B. substilis*	*E. coli*	*P. aeruginosa*
2a/3a	>128/32	>64/16	64/4	>64/32	**2i/3i**	>128/32	>128/>64	>128/16	>128/>128
2b/3b	>64/16	>128/16	>128/16	>64/>64	**2j/3j**	>128/>64	>128/32	>128/32	>128/>64
2c/3c	>128/>64	>128/32	>128/8	>128/>128	**2k/3k**	>128/>64	>128/64	>128/8	>128/>32
2d/3d	>64/16	>64/64	>64/32	>128/>64	**2l/3l**	>64/16	>64/>64	>128/8	>64/16
2e/3e	>64/32	>128/32	>64/16	>64/16	**2m/3m**	>64/32	>128/16	>64/8	>128/>64
2f/3f	>128/32	>128/>64	>128/32	>128/>64	**2n/3n**	>64/32	>128/>64	>128/64	>128/32
2g/3g	>64/16	>128/8	>64/4	>64/16	NF	0.5	4.0	8.0	1.0
2h/3h	>64/32	>128/16	>64/8	>128/>64					

实验部分

熔点用毛细管法测定,温度未校正; IR 由 Nicolet Impact 410 红外光谱仪测定(KBr压片); ^{1}H NMR用 Bruker AM-400 型核磁共振仪测定(溶剂 D_2O);质谱仪为 MS HP1100型(EIS源,70 eV);元素分析仪为 Carlo Erba 1106。试剂除 $POCl_3$ 经干燥重蒸外,其余均为分析纯,未经处理,直接使用。

3-(4-氯苯基)-4-氨基-5-巯基-1,2,4-三唑(1)按文献[9]的方法制备。

1 3-(4-氯苯基)-6-取代-*s*-三唑[1,2,4][3,4-*b*]噻二唑(2a ~ n)

以化合物 1和各种羧酸为原料,按前文[8]的方法分别得到中间体(2a ~ n),其理化性质见表 1。

2 3-(4-哌嗪-1-苯基)-6-取代-*s*-三唑[3,4-*b*][1,3,4]噻二唑盐酸盐(3a ~ n)

中间体 2(10 mmol)、无水哌嗪(25 mmol)、四丁基碘化铵(TBAI)(0.5 mmol)、无水碳酸钾(10 mmol)、二甲苯(10 mL)与 DMSO(10 mL)在 120 ℃搅拌反应 12 h。减压蒸除溶剂和未反应的哌嗪,向残留物中加入水 30 mL,用稀醋酸酸化,过滤。滤液用氨水碱化,滤集产生的沉淀物,水洗呈中性。滤饼用浓盐酸溶解,加入无水乙醇,调醇度为 85%,放置,析出结晶,过滤,乙醇洗,真空干燥,得目标物 3a ~ n,其理化性质见表 2,波谱数据见表 3。

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