咪唑并[2,1-b][1,3,4]噻二唑及杂环氨曼尼希碱盐酸盐的合成及抗菌活性

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摘要：为了进一步优化由噻二唑核稠合的水溶性稠杂环化合物的合成方法及抗菌活性，本文用2-(4-甲氧苯基)-5-氨基-1,3,4-噻二唑(**2**)与α-氯代-4-氯苯乙酮(**3**)缩合得6-(4-氯苯基)-2-(4-甲氧苯基)-咪唑并[2,1-b][1,3,4]噻二唑(**4**)，**4**与取代哌嗪发生亲核取代反应得到6-(4-取代哌嗪-1-苯基)-2-(4-甲氧苯基)-咪唑并[2,1-b]-[1,3,4]噻二唑(**5**)，**5**与杂环氨进行曼尼希反应并与盐酸成盐得目标化合物6-(4-取代哌嗪-1-苯基)-2-(4-甲氧苯基)-5-杂环氨基甲基-咪唑并[2,1-b][1,3,4]噻二唑盐酸盐(**1**)。用试管二倍稀释法评价了15个新化合物的体外抗菌活性，结果表明，随着极性基团的引入，抗菌活性显著提高，提示该类化合物的结构修饰值得进一步研究。

关键词：咪唑并[2,1-b][1,3,4]噻二唑；曼尼希碱；抗菌活性

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Synthesis and antibacterial activity of imidazothiadiazoles and heterocyclic-amine Mannich-base hydrochloride

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Abstract: To optimize the synthetic method and antibacterial activity of fused heterocyclic thiadiazole compounds, cyclocondensation of 2-(4-methoxyphenyl)-5-amino-1,3,4-thiadiazole (**2**) with α-chloro-4-chloro acetophenone (**3**) resulted in a key intermediate (**4**), 6-(4-chlorophenyl)-2-(4-methoxyphenyl)-imidazo-[2,1-b][1,3,4]thiadiazole, which was carried out an nucleophilic substitution with substituted piperazine to give the corresponding free bases of piperazine (**5a −5c**), then followed by Mannich reaction with heterocyclicamines and formaldehyde to yield the corresponding Mannich bases, (**1a − 1l**) as respective hydrochloride salts. The structures were confirmed by IR, ^{1}H NMR, MS and elemental analysis and the antibacterial activities *in vitro* of fifteen newly synthesized compounds were also tested against Gram positive bacteria and Gram negative bacteria with the standard 2-fold agar dilution method. The antibacterial results showed that the introduction of a polar group resulted in the enhancement of antibacterial activity *in vitro*. Thus, the structures of these fused compounds could further be investigated.

Key words: imidazolo[2,1-b][1,3,4]thiadiazole; Mannich base; antibacterial activity

由1,3,4-噻二唑稠合的双杂环并稠杂环衍生物如均三唑并噻二唑[1]、咪唑并噻二唑[2,3]、噻二唑并均三嗪[4]等因具有广泛的药理活性，其合成方法和活性研究日益受到人们的关注。但这些研究多集中在稠杂环核非功能取代基的变化上，导致了所合成的化合物水溶性差，不利于药效的发挥[5]。为改善稠杂环化合物的水溶性、提高其活性，前期工作已发现在稠杂环骨架周围引入极性哌嗪基团对提高水溶性和活性是有效的修饰方法之一[6]。本文选择咪唑并噻二唑稠环基本骨架，在引入极性哌嗪基团的

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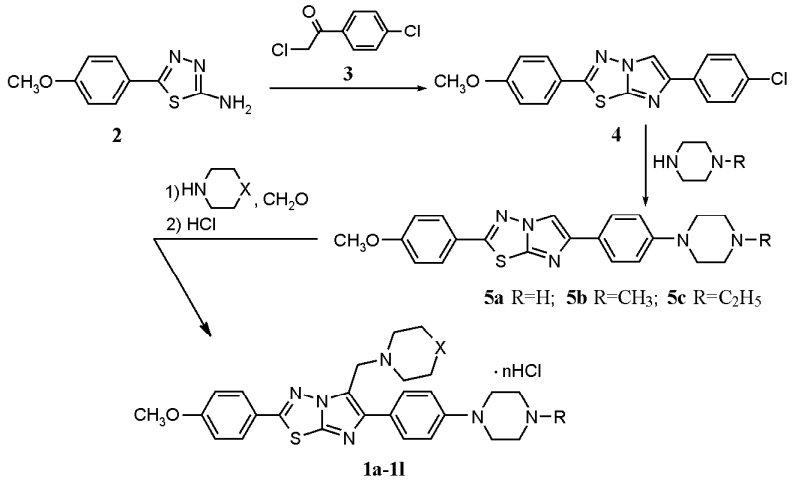
同时，试图通过曼尼希反应引入具有多种活性的曼尼希碱[7,8]，利用活性叠加原理，以期发现有进一步研究价值的修饰方法和先导物。目标化合物**1a**～**1l**的合成路线如图1所示。

2-(4-甲氧苯基)-5-氨基-1,3,4-噻二唑(**2**)与α-氯代-4-氯苯乙酮(**3**)在无水乙醇中发生缩环合反应得到稠杂环中间体6-(4-氯苯基)-2-(4-甲氧苯基)-咪唑并[2,1-b][1,3,4]噻二唑(**4**)。化合物**4**在聚乙二醇600(PEG 600)催化下，其6-位苯环的对位氯原子与(取代)哌嗪发生亲核取代反应生成相应的取代哌嗪衍生物(**5**)。稠核5-位活泼H与胺发生曼尼希反应得到曼尼希碱**1**，最后与盐酸反应得盐酸盐。各中间体及目标化合物的理化性质及光谱数据见表1和表2。

供试化合物**4**、**5a**～**5c**、**1a**～**1l**及对照药诺氟沙星(norfloxacin)预配成128 μg·mL^{-1}的DMSO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*) ATCC27853的体外最低抑菌浓度(MICs)，结果见表3。



	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	1k	1l
X	CH_2	CH_2	CH_2	O	O	O	NCH_3	NCH_3	NCH_3	NC_2H_5	NC_2H_5	NC_2H_5
R	H	CH_3	C_2H_5	H	CH_3	C_2H_5	H	CH_3	C_2H_5	H	CH_3	C_2H_5

Scheme 1 Synthetic route of the target compounds **1a**－**1l**

Table 1 Physical properties of compounds **5a**－**5c** and **1a**－**1l**

No.	Formula	Yield/%	mp/℃	Elemental analysis/% Calcd. (Found)		
				C	H	N
5a	$C_{21}H_{21}N_5OS$	62	232－234	64.43(64.62)	5.41(5.34)	17.89(17.94)
5b	$C_{22}H_{23}N_5OS$	52	224－226	65.16(65.30)	5.72(5.61)	17.27(17.38)
5c	$C_{23}H_{25}N_5OS$	56	218－220	65.85(65.97)	6.01(5.88)	16.69(16.83)
1a	$C_{26}H_{30}N_6OS \cdot 2HCl$	74	266－268	57.03(57.12)	5.89(5.76)	15.36(15.43)
1b	$C_{28}H_{34}N_6OS \cdot 2HCl$	82	263－265	57.75(57.82)	6.10(6.20)	14.96(15.13)
1c	$C_{29}H_{36}N_6OS \cdot 2HCl$	68	257－259	58.43(58.52)	6.30(6.17)	14.60(14.74)
1d	$C_{26}H_{30}N_6O_2S \cdot 2HCl$	77	272－274	54.64(54.80)	5.50(5.61)	15.29(15.36)
1e	$C_{27}H_{32}N_6O_2S \cdot 2HCl$	70	268－270	55.41(55.62)	5.72(5.61)	14.91(15.12)
1f	$C_{28}H_{34}N_6O_2S \cdot 2HCl$	65	261－262	56.15(56.35)	5.93(5.76)	14.55(14.73)
1g	$C_{27}H_{33}N_7OS \cdot 3HCl$	68	296－298	52.13(52.26)	5.72(5.91)	16.37(16.48)
1h	$C_{28}H_{35}N_7OS \cdot 3HCl$	75	288－290	52.90(53.16)	5.92(5.78)	15.99(16.12)
1i	$C_{29}H_{37}N_7OS \cdot 3HCl$	72	286－287	53.63(53.86)	6.11(6.04)	15.64(15.78)
1j	$C_{28}H_{35}N_7OS \cdot 3HCl$	74	284－286	52.90(53.08)	5.92(5.76)	15.99(16.14)
1k	$C_{29}H_{37}N_7OS \cdot 3HCl$	76	280－282	53.63(53.72)	6.11(5.88)	15.64(15.82)
1l	$C_{30}H_{39}N_7OS \cdot 3HCl$	68	272－274	55.17(55.28)	6.17(6.05)	15.01(15.16)

Table 2 Spectral data of compounds **5a -5c** and **1a -1l**

No.	IR/cm^{-1}	^{1}H NMR(DMSO-d_6 for compounds **5** and D_2O for compounds **1**) δ	MS(m/z)
5a	3 358,3 045,1 626, 1 558,1 456	8.38(s,1H,5-H),7.84 -7.45(m,8H,Ph-H),3.93(s,3H,CH_3O),3.88 -3.34(m,8H, piperazine-H)	391[M]$^+$
5b	3 326,3 025,2 897, 1 617,1 557,1 455	8.37(s,1H,5-H),8.06 -7.62(m,8H,Ph-H),3.86(s,3H,CH_3O),3.84 -3.28(m,8H, piperazine-H),2.77(s,3H,NCH_3)	405[M]$^+$
5c	3 336,3 015,1 624, 1 562,1 457	8.37(s,1H,5-H),7.88 -7.54(m,8H,Ph-H),3.92(s,3H,CH_3O),3.78 -3.26(m,8H, piperazine-H),2.76(q,J=7.0 Hz,2H,NCH_2CH_3),1.14(t,J=7.0 Hz,3H,CH_3)	419[M]$^+$
1a	3 345,3 036,1 617, 1 455,1 238	8.15 -7.36(m,8H,Ph-H),4.62(s,2H,5-CH_2),3.86(s,3H,CH_3O),3.66 -3.35(m,8H, piperazine-H),2.86 -1.17(m,10H,piperidine-H)	488[M]$^+$
1b	3 324,1 626,3 007, 1 557,1 224	8.16 -7.33(m,8H,Ph-H),4.57(s,2H,5-CH_2),3.88(s,3H,CH_3O),3.57 -3.18(m,8H, piperazine-H),2.76 -1.15(m,13H,piperidine-H and NCH_3)	502[M]$^+$
1c	3 354,3 015,1 632, 1 557,1 235	8.14 -7.56(m,8H,Ph-H),4.62(s,2H,5-CH_2),3.90(s,3H,CH_3O),3.66 -3.24(m,8H, piperazine-H),2.77 -1.22(m,15H,piperidine-H and NCH_2CH_3)	516[M]$^+$
1d	3 347,3 035,1 618, 1 557,1 224	8.12 -7.54(m,8H,Ph-H),4.68(s,2H,5-CH_2),3.92(s,3H,CH_3O),3.68 -3.32(m,8H, piperazine-H),3.24 -2.88(m,8H,morpholine-H)	490[M]$^+$
1e	3 346,3 005,1 627, 1 563,1 237	8.08 -7.46(m,8H,Ph-H),4.66(s,2H,5-CH_2),3.88(s,3H,CH_3O),3.57 -3.38(m,8H, piperazine-H),3.18 -2.74(m,11H,morpholine-H and NCH_3)	504[M]$^+$
1f	3 317,2 876,1 625, 1 576,1 457	7.86 -7.57(m,8H,Ph-H),4.66(s,2H,5-CH_2),3.90(s,3H,CH_3O),3.66 -3.26(m,8H, piperazine-H),3.17 -1.20(m,13H,morpholine-H and NCH_2CH_3)	518[M]$^+$
1g	3 347,3 027,1 625, 1 555,1 446,1 238	8.12 -7.36(m,8H,Ph-H),4.66(s,2H,5-CH_2),3.92(s,3H,CH_3O),3.47 -3.35(m,16H, 2 × piperazine-H),2.76(s,3H,NCH_3)	503[M]$^+$
1h	3 327,3 017,1 617, 1 562,1 455,1 226	8.06 -7.47(m,8H,Ph-H),4.68(s,2H,5-CH_2),3.89(s,3H,CH_3O),3.45 -3.30(m,16H, 2 × piperazine-H),2.74,2.82(s,6H,2 × NCH_3)	517[M]$^+$
1i	3 325,3 026,1 607, 1 557,1 455,1 228	8.15 -7.52(m,8H,Ph-H),4.64(s,2H,5-CH_2),3.86(s,3H,CH_3O),3.46 -3.28(m,16H, piperazine-H),2.83 -1.16(m,8H,NCH_3 and NCH_2CH_3)	531[M]$^+$
1j	3 357,3 036,1 618, 1 562,1 457,1 236	8.04 -7.55(m,8H,Ph-H),4.66(s,2H,5-CH_2),3.91(s,3H,CH_3O),3.47 -3.35(m,16H, 2 × piperazine-H),2.67(m,2H,NCH_2CH_3),1.17(t,3H,NCH_2CH_3)	517[M]$^+$
1k	3 335,3 028,1 614, 1 558,1 455,1 227	7.86 -7.54(m,8H,Ph-H),4.68(s,2H,5-CH_2),3.88(s,3H,CH_3O),3.38 -3.26(m,16H, 2 × piperazine-H),2.78 -1.15(m,8H,NCH_3 and NCH_2CH_3)	531[M]$^+$
1l	3 328,3 016,1 605, 1 547,1 455,1 226	7.88 -7.42(m,8H,Ph-H),4.65(s,2H,5-CH_2),3.86(s,3H,CH_3O),3.35 -3.22(m,16H, 2 × piperazine-H),2.75 -1.18(m,10H,2 × NCH_2CH_3)	545[M]$^+$

Table 3 *In vitro* antibacterial activities of tested compounds **4**, **5** and **1** (μg · mL^{-1})

No.	Organism			
	S. aureus ATCC25923	*B. substilis* 63501	*E. coli* ATCC25922	*P. aeruginosa* ATCC 27853
4	>64	>128	>64	>64
5a	8	16	8	32
5b	16	16	8	32
5c	32	>32	>16	>16
1a	2	8	2	4
1b	2	8	2	8
1c	4	>16	8	>16
1d	0.5	0.125	2	2
1e	1	0.5	4	2
1f	4	2	8	8
1g	1	0.25	4	4
1h	1	0.5	2	2
1i	8	16	8	16
1j	8	2	8	>16
1k	16	8	8	>32
1l	>16	16	8	>32
Norfloxacin	0.5	4.0	8.0	1.0

上述实验结果表明,非功能化取代的化合物**4**对上述4种试验菌株无抑制活性,然而,当其疏水性氯原子被亲水性哌嗪取代所产生的化合物**5a ~5c**,活性虽不及对照药诺氟沙星,但均较母体化合物**4**有显著的提高。更有意义的是,在稠环骨架上引入亲水性杂环氨基可导致抑菌活性显著增强,目标物**1a ~1l**中的部分化合物的活性高于或相当于对照药诺氟沙星,提示在稠环骨架上引入水溶性取代基可能是咪唑并[2,1-b][1,3,4]噻二唑稠杂环的有效结构修饰策略。

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DMSO-d_6或D_2O);质谱仪为MS HP1100型(EIS源,70 eV);元素分析仪为Carlo Erba 1106。试剂为分析纯,未经处理,直接使用。2-(4-甲氧苯基)-5-氨

基-1,3,4-噻二唑(**2**)和6-(4-氯苯基)-2-(4-甲氧苯基)-咪唑并[2,1-b][1,3,4]噻二唑(**4**)按文献[9]方法制备。

1 6-(4-哌嗪-1-苯基)-2-(4-甲氧苯基)-咪唑并[2,1-b][1,3,4]噻二唑(5a)

化合物**4** (5.0 g, 14.6 mmol)、无水哌嗪(3.2 g, 36.5 mmol)、PEG 600(3.0 mL)、二甲苯(35 mL)与DMSO(15 mL)的混合反应液在120 ℃搅拌反应12 h。减压除去溶剂和未反应的哌嗪,向残留物中加入水(50 mL),用稀醋酸酸化至pH 3、过滤。滤液用氨水碱化至pH 10,析出沉淀,过滤收集沉淀,沉淀用水洗至中性。粗品用无水乙醇-DMF(*v*/*v* 3∶1)重结晶,得**5a**。

用*N*-甲基哌嗪和*N*-乙基哌嗪代替**5a**制备中的无水哌嗪,按上述相同的实验方法可得6-[4-(4-甲基哌嗪)-1-苯基]-2-(4-甲氧苯基)-咪唑并[2,1-b][1,3,4]噻二唑(**5b**)和6-[4-(4-乙基哌嗪)-1-苯基]-2-(4-甲氧苯基)-咪唑并[2,1-b][1,3,4]噻二唑(**5c**)。

2 2-(4-甲氧苯基)-6-(4-哌嗪-1-苯基)-5-哌啶-1-咪唑并[2,1-b][1,3,4]噻二唑二盐酸盐(1a)

化合物**5a** (1.0 g, 2.6 mmol)和40%甲醛溶液(0.3 g, 4.0 mmol)于无水乙醇(20 mL)中回流反应2 h,然后加入哌啶(0.4 g, 4.7 mmol),继续回流反应6 h。减压除去溶剂,用水(20 mL)分散残留物。过滤收集沉淀,水洗至中性。粗品用冰乙酸(2 mL)溶解,加氯化氢饱和乙醇溶液(10 mL),放置,析出结晶。过滤,乙醇洗,真空干燥,得目标物**1a**。按**1a**类似的方法分别制备目标物**1b**~**1l**。

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