N-[5-(3吡啶基)-1,3,4噻二唑-2-基]-*N*′-芳甲酰基脲的合成及抗菌活性

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Synthesis and antimicrobial activity of *N*-[5-(3-pyridyl)-1,3,4-thiadiazol-2-yl]-*N*′-aroyl urea

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Abstract: To synthesize and evaluate antimicrobial activity of novel heterocyclic compounds, the corresponding title aroyl ureas have been synthesized by the reaction of 2-amino-5-(3-pyridyl)-1,3,4-thiadiazole with aroyl isocyanates. Their antimicrobial activities *in vitro* were tested by disk diffusion methods and broth microdilution according to M-27A protocol recommended by NCCLS. Twelve new compounds were obtained, and their structures were confirmed by MS, IR, ^{1}H NMR and elemental analysis. The biological screening tests showed that most of the compounds have some antifungal activities *in vitro*. Aroyl ureas incorporating pyridyl thiadiazole ring may be developed as novel antifungal candidate drugs and are worthwhile to be further studied.

Key words: aroyl urea; 1,3,4-thiadiazole; synthesis; antibacterial activity

1,3,4噻二唑衍生物具有抗真菌[1]、抗菌[2]、抗惊厥和抗结核等广泛的生物活性,因而该类化合物的研究迄今仍方兴未艾。从生物化学的角度来看,吡啶环中的 N原子可参与生物体中氢键的形成,可以增加药物与受体间的亲和力和选择性[3,4],故吡啶环的引入有望提高化合物的生物活性;且在新药设计中吡啶作为苯环的生物电子等排体常被用作药效团[5],吡啶衍生物已成为近些年来新药设计与开发的热点领域之一[6,7]。而取代脲类化合物具有抗癌[8]等生理活性也倍受关注。但含 3-吡啶基取代噻二唑的芳甲酰基脲的合成及其用于抗菌活性研究尚未见文献报道。根据活性叠加原理和前文研究基础[9],将吡啶环、1,3,4噻二唑环、酰基脲单元等活性基团拼接到同一分子中,可能有加合作用。本文设计并合成出含吡啶基取代的噻二唑环芳甲酰基脲类化合物 **3a** ~ **3l**(其合成路线见图 1),以期获得高抗菌活性的先导化合物,为进一步合成和活性研究提供借鉴。

在三氯氧磷为脱水剂的条件下,烟酸与氨基硫脲直接缩合关环,制得 2-氨基-5-(3-吡啶基)-1,3,4-噻二唑(**1**),再与芳甲酰基异氰酸酯(**2**)发生加成反应得到相应的目标化合物(**3**)。由于芳甲酰基异氰酸酯非常活泼,在空气中室温下很容易发生聚合,所以本文将酰胺→芳甲酰基异氰酸酯(**2**)→芳甲酰基脲(**3**)的两步反应连续进行,其中加成反应的温度选择 40 ~ 50 ℃。所得新化合物 **3**的理化性质见表 1,光谱数据见表 2。

体外抗菌活性首先采用纸片扩散法测定各新化

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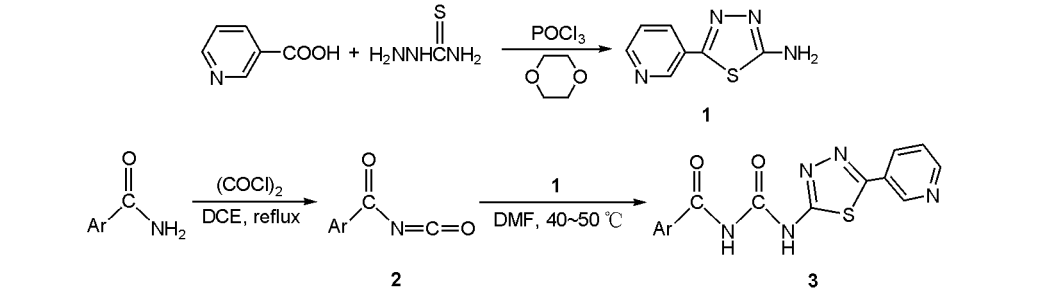

Ar: **3a** C_6H_5 **3b** 3-FC_6H_4 **3c** 4-FC_6H_4 **3d** 2,6-$F_2C_6H_3$ **3e** 3-ClC_6H_4 **3f** 4-ClC_6H_4
3g 2-$O_2NC_6H_4$ **3h** 3-$O_2NC_6H_4$ **3i** 4-$O_2NC_6H_4$ **3j** 3-$CH_3C_6H_4$ **3k** 4-$CH_3C_6H_4$ **3l** 4-$CH_3O\ C_6H_4$

Scheme 1 Synthetic route of compounds **3a - 3l**

Table 1 Physical properties of compounds **3a - 3l**

No.	mp/℃	Yield/%	Appearances	Elemental analysis/% Found (Calcd.)		
				C	H	N
3a	280 - 281	76.2	White crystal	55.49(55.38)	3.27(3.41)	21.70(21.53)
3b	268 - 269	75.6	White crystal	52.68(52.47)	2.75(2.94)	20.64(20.40)
3c	287 - 288	71.5	White crystal	52.62(52.47)	3.10(2.94)	20.28(20.40)
3d	262 - 263	70.2	White crystal	50.13(49.86)	2.36(2.51)	19.52(19.38)
3e	276 - 277	72.6	White crystal	50.22(50.07)	2.95(2.80)	19.61(19.47)
3f	>300	73.7	White crystal	50.31(50.07)	2.66(2.80)	19.29(19.47)
3g	>300	73.8	Yellow crystal	48.78(48.65)	2.87(2.72)	22.46(22.69)
3h	>300	68.6	Yellow crystal	48.63(48.65)	2.51(2.72)	22.82(22.69)
3i	>300	72.0	Yellow crystal	48.81(48.65)	2.56(2.72)	22.75(22.69)
3j	270 - 271	77.3	White crystal	56.87(56.63)	3.67(3.86)	20.72(20.64)
3k	288 - 289	80.1	White crystal	56.82(56.63)	3.65(3.86)	20.76(20.64)
3l	295 - 296	73.5	White crystal	54.37(54.08)	3.55(3.69)	19.84(19.71)

合物对金葡菌 ATCC25923、大肠埃希氏菌 ATCC25922、表皮葡球菌 ATCC12228、痢疾志贺菌 CMCC51252和白假丝酵母菌 ATCC76615的抑菌活性。供试化合物溶于 DMSO中,预配成 0.1%的浓度,用 1%醋酸蒸馏水溶液稀释到所需浓度,阳性对照药为诺氟沙星和氟康唑。结果表明,12个化合物对上述 4株细菌无抑制活性,而化合物 **3b**, **3c**, **3d**, **3e**, **3f**和 **3l**对上述一株真菌白假丝酵母菌 ATCC76615有一定的抑制活性。根据美国临床实验室标准化委员会 (NCCLS)的 M-27A方案[10],采用微量稀释法测定化合物 **3b**, **3c**, **3d**, **3e**, **3f**和 **3l**对以下 3种试验真菌的最低抑菌浓度 (MIC) :白假丝酵母菌 ATCC76615、新生隐球菌 ATCC32609和黑曲霉菌 ATCC16404。结果表明,它们对白假丝酵母菌显示较好的抑制活性, MIC均为 4.0 mg• L^{-1},与氟康唑相似,而对新生隐球菌和黑曲霉菌的抑制活性很低, MIC >128.0 mg• L^{-1}。

实验部分

熔点用 X4型显微熔点测定仪测定,温度未经校正; IR由 NEXUS 470型红外光谱仪测定 (KBr压片) ; ^{1}H NMR用 Mercury Plus-400 MHz核磁共振仪 (TMS为内标,溶剂为 DMSO-d_6) 测定;质谱用 Finnigan TRACE型质谱仪;元素分析采用 Vario EL III CHNSO元素分析仪。

所用试剂均为分析纯。反应溶剂均作无水处理后重蒸备用, $POCl_3$用前新蒸。

1　2-氨基 -5-(3-吡啶基)-1, 3, 4-噻二唑 (1)的合成

氨基硫脲 9.1 g (0.10 mol),烟酸 12.3 g (0.10 mol),二氧六环 60 mL,冰水冷却下边搅拌边缓慢滴加三氯氧磷 9.2 mL (0.10 mol),加完后逐渐升温回流约 4 h,减压蒸去溶剂,冷却后加入冷水 75 mL,然后用 40%氢氧化钠溶液中和至 pH值为 8 ~ 9,抽滤得粗产品,再用乙醇-水重结晶得到淡黄色结晶 **1**, mp 232 ~ 233 ℃ (mp 234 ~ 236 ℃)[11]。

2　芳甲酰基异氰酸酯 (2)的合成

取代的苯甲酰胺 0.01 mol,无水 1, 2-二氯乙烷 (DCE) 8 mL,用冰水浴冷却至 0 ~ 5 ℃,加入草酰氯 2.54 g (0.02 mol),室温搅拌 1 h,再在 50 ~ 55 ℃下反应约 3 h,然后回流至无氯化氢气体放出为止。减

Table 2 Spectral data of compounds **3a - 3l**

No.	IR / cm^{-1}	^1H NMR (400 MHz, DMSO-d_6) δ	MS (*m/z*)
3a	3 134, 3 064, 1 719, 1 676	7.69 - 8.06(m, 5H), 7.59(dd, *J* = 4.8 and 3.2 Hz, 1H), 8.38(d, *J* = 8 Hz, 1H), 8.72(d, *J* = 4.8 Hz, 1H), 9.16(s, 1H), 11.70(s, 1H), 12.28(s, 1H)	325[M]$^+$, 121, 105
3b	3 198, 3 072, 1 724, 1 692	7.62 - 7.91(m, 4H), 7.59(dd, *J* = 4.8 and 3.2 Hz, 1H), 8.37(d, *J* = 8 Hz, 1H), 8.72(d, *J* = 4.8 Hz, 1H), 9.15(s, 1H), 11.73(s, 1H), 12.20(s, 1H)	343[M]$^+$, 324, 139, 123
3c	3 217, 3 112, 1 710, 1 677	7.41 - 8.14(m, 4H), 7.59(dd, *J* = 4.8 and 3.2 Hz, 1H), 8.37(d, *J* = 7.2 Hz, 1H), 8.73(d, *J* = 4.8 Hz, 1H), 9.16(s, 1H), 11.72(s, 1H), 12.23(s, 1H)	343[M]$^+$, 324, 139, 123
3d	3 182, 3 062, 1 721, 1 689	7.26 - 7.68(m, 3H), 7.59(dd, *J* = 4.8 and 3.2 Hz, 1H), 8.36(d, *J* = 8.0 Hz, 1H), 8.72(d, *J* = 4.4 Hz, 1H), 9.14(s, 1H), 11.80(s, 1H), 12.12(s, 1H)	361[M]$^+$, 342, 157, 141, 113
3e	3 145, 3 086, 1 724, 1 690	7.62 - 8.09(m, 4H), 7.59(dd, *J* = 4.4 and 3.2 Hz, 1H), 8.37(d, *J* = 8.0 Hz, 1H), 8.73(d, *J* = 4.8 Hz, 1H), 9.16(s, 1H), 11.75(s, 1H), 12.15(s, 1H)	359[M]$^+$, 155, 139
3f	3 219, 3 093, 1 699, 1 677	7.66 - 8.07(m, 4H), 7.59(dd, *J* = 4.8 and 3.2 Hz, 1H), 8.38(d, *J* = 8.0 Hz, 1H), 8.73(d, *J* = 4.4 Hz, 1H), 9.16(s, 1H), 11.76(s, 1H), 12.20(s, 1H)	359[M]$^+$, 155, 139
3g	3 229, 3 107, 1 718, 1 690	7.77 - 8.28(m, 4H), 7.59(dd, *J* = 4.8 and 3.2 Hz, 1H), 8.36(d, *J* = 7.6 Hz, 1H), 8.72(d, *J* = 4.4 Hz, 1H), 9.16(s, 1H), 11.68(s, 1H), 11.98(s, 1H)	370[M]$^+$, 166, 150
3h	3 178, 3 096, 1 719, 1 693	7.87 - 8.34(m, 4H), 7.60(dd, *J* = 4.8 and 3.2 Hz, 1H), 8.36(d, *J* = 8.0 Hz, 1H), 8.73(d, *J* = 4.4 Hz, 1H), 9.16(s, 1H), 11.96(s, 1H), 12.06(s, 1H)	370[M]$^+$, 166, 150
3i	3 227, 3 045, 1 704, 1 678	7.98 - 8.41(m, 4H), 7.60(dd, *J* = 4.4 and 3.2 Hz, 1H), 8.37(d, *J* = 7.2 Hz, 1H), 8.73(d, *J* = 4.4 Hz, 1H), 9.16(s, 1H), 11.78(s, 1H), 12.05(s, 1H)	370[M]$^+$, 166, 150
3j	3 208, 3 095, 1 720, 1 696	2.42(s, 3H), 7.45 - 7.88(m, 4H), 7.58(dd, *J* = 4.8 and 3.2 Hz, 1H), 8.36(d, *J* = 8.0 Hz, 1H), 8.72(d, *J* = 4.8 Hz, 1H), 9.15(s, 1H), 11.62(s, 1H), 12.27(s, 1H)	339[M]$^+$, 135, 119
3k	3 255, 3 087, 1 698, 1 672	2.41(s, 3H), 7.38 - 7.98(m, 4H), 7.59(dd, *J* = 4.8 and 3.2 Hz, 1H), 8.37(d, *J* = 8.4 Hz, 1H), 8.73(d, *J* = 4.8 Hz, 1H), 9.16(s, 1H), 11.63(s, 1H), 12.32(s, 1H)	339[M]$^+$, 135, 119
3l	3 296, 3 070, 1 697, 1 673	3.87(s, 3H), 7.10 - 8.09(m, 4H), 7.59(dd, *J* = 4.8 and 3.2 Hz, 1H), 8.38(d, *J* = 8.4 Hz, 1H), 8.73(d, *J* = 4.8 Hz, 1H), 9.16(s, 1H), 11.58(s, 1H), 12.40(s, 1H)	355[M]$^+$, 340, 151, 135

压蒸除未反应的草酰氯,得油状芳甲酰基异氰酸酯 **2a ~ 2l**,直接用于下一步反应。

3 芳甲酰基脲 **3a ~ 3l** 的合成

2-氨基-5-(3-吡啶基)-1, 3, 4-噻二唑 (**1**) 1.6 g (0.009 mol), DMF 10 mL,加热使之溶解,慢慢滴加到上述制得的芳甲酰基异氰酸酯中,于 40 ~ 50 ℃反应 2 ~ 3 h, TLC检测至反应完全 (展开剂:乙酸乙酯-石油醚 1∶1),冷却,抽滤,用丙酮 8 mL洗涤两次,抽干得粗产品,用 DMF-丙酮重结晶得目标化合物 **3a ~ 3l**。理化数据见表 1,光谱数据见表 2。

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