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2,5-二取代-1,3,4-封二唑类杂环化合物的合成、表征

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摘　要:分别以水杨酸和邻氨基苯甲酸为起始原料,设计合成了6个未见文献报道的2,5-二取代-1,3,4-封二唑类杂环化合物.其结构经^{1}H NMR、EI-MS和元素分析表征.

关键词:2,5-二取代-1;3,4-封二唑;合成;表征

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0　引言

1,3,4-封二唑杂环,具有杀虫、消炎、杀菌等作用[1-4],在农药、医药等领域有着广泛应用.研究发现,某些2,5-二取代-1,3,4-封二唑杂环化合物具有抗肿瘤活性[5-7],或抗惊厥活性[8-9].

本实验以图1所示的化合物为先导化合物,根据电子等排原理对其进行结构修饰[10].分别以水杨酸和邻氨基苯甲酸为起始原料,合成了6个未见文献报道的2,5-二取代-1,3,4-封二唑类化合物,以期从中寻找到具有一定抗肿瘤活性的杂环化合物.合成路线如图2所示.

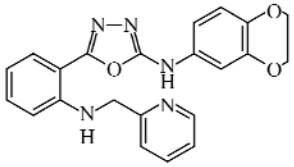


图1　先导化合物

Fig.1　leading compound

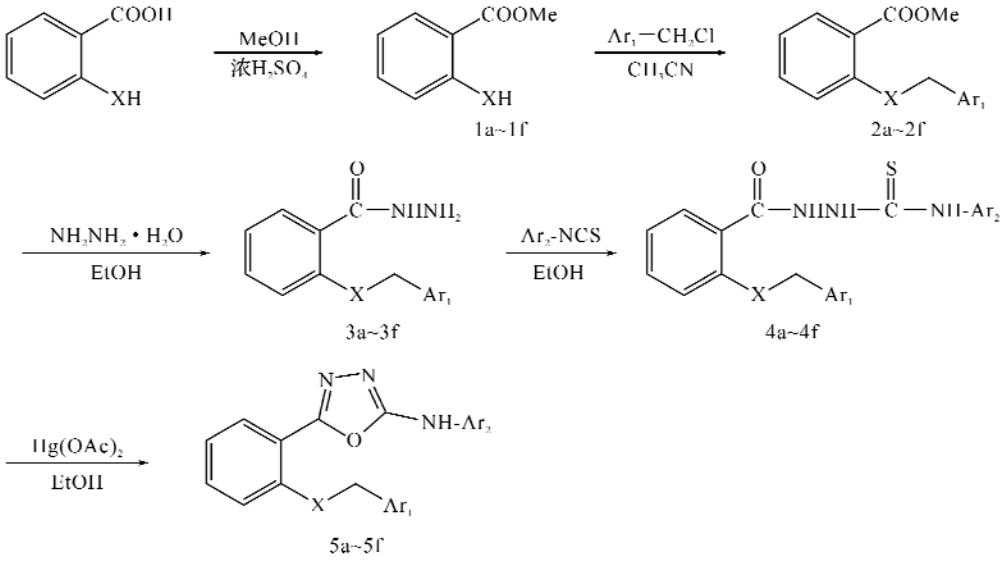
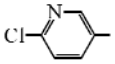


图2　目标化合物的合成

Fig.2　Synthesis of 5a to 5f

注:

Comp	a	b	c	d	e	f
Ar_1	Ph	Ph			Ph	Ph
Ar_2	Ph	o-MeC6H4-	Ph	Ph	Ph	o-MeC6H4-

X:O或NH.

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1 实验部分

1.1 仪器与试剂

RY-1 型熔点仪;Varian Mercury-Vx300 型核磁共振仪(TMS 为内标,300 MHz);FINNIGAN TRACE GC-MS 型质谱仪;Vario EL Ⅲ型元素分析仪.

水杨酸,分析纯,国药集团化学试剂有限公司生产;邻胺基苯甲酸,分析纯,国药集团化学试剂有限公司生产;异硫氰酸苯酯和异硫氰酸对甲苯酯按文献[11]合成;柱层析硅胶,孔径 45 ~ 75 μm,青岛海洋化工厂;实验中所用试剂均为化学纯或分析纯,除特别注明外,未经进一步处理.

1.2 合成(以化合物 5a 为例)

1.2.1 中间体 1a 的合成 于 100 mL 烧瓶中加入 6.9 g (50 mmol) 水杨酸和 40 mL 甲醇,搅拌使固体溶解. 滴加 2 mL 浓硫酸后,升温至回流. TLC 跟踪反应(展开剂为 $V_{乙酸乙酯}$: $V_{正己烷}$ = 1∶1). 反应结束后,减压脱溶. 加入 30 mL 水,用乙酸乙酯萃取(20 mL×3),收集油层,用饱和 $NaHCO_3$ 溶液洗涤至中性,用饱和食盐水洗涤,用无水 $MaSO_4$ 干燥,过滤,蒸干溶剂. 产品为无色油状物 4.996 g(1a),产率 60%.

1.2.2 中间体 2a 的合成[12] 于 50 mL 三口烧瓶中投入 0.56 g (10 mmol) KOH 和 20 mL 乙腈溶液,加热使固体尽量溶解. 稍冷,投入 1.64 g (10 mmol) 水杨酸甲酯,搅拌片刻. 将 2.53 g (20 mmol) 苄氯溶入 10 mL 乙腈中,缓慢滴入三口烧瓶. 滴毕,升温至回流,TLC 跟踪反应(展开剂为 $V_{乙酸乙酯}$∶$V_{石油醚}$ = 1∶8). 反应结束后,减压脱溶. 加入 20 mL 水,用乙酸乙酯萃取(20 mL×3),收集油层,用饱和食盐水洗涤,用无水 $MaSO_4$ 干燥,过滤,蒸干溶剂. 柱层析提纯分离(洗脱剂为 $V_{乙酸乙酯}$∶$V_{石油醚}$ = 1∶10),产物为无色透明状液体 0.847 g (2a),产率 33%.

1.2.3 中间体 3a 的合成 于 50 mL 三口烧瓶中投入 1.28 g (5 mmol)2a 和 25 mL 乙醇溶液,搅拌升温至 60 ℃,将 1.25 g(25 mmol)水合肼溶入 10 mL 乙醇溶液中,缓慢滴入三口烧瓶. 滴毕,升温至回流,TLC 跟踪反应(展开剂为 $V_{乙酸乙酯}$∶$V_{石油醚}$ = 1∶1). 反应结束后,减压脱溶. 反应物为油状,加入 10 mL 水,过滤,用石油醚淋洗固体,烘干,得白色固体 0.653 g (3a),收率 54%.

1.2.4 中间体 4a 的合成 将 0.65 g (2.7 mmol) 中间体 3a 与 0.4 g(3 mmol)异硫氰酸苯酯投入 50 mL 烧瓶中,投入乙醇 25 mL,回流 1 h,冷却至室温,静置过夜后,有白色针状晶体析出,过滤,滤饼用乙醇淋洗,得中间体 0.892 g (4a),产率 88%.

1.2.5 目标化合物 5a 的合成[13] 将 0.377 g (1 mmol) 中间体 4a 与 0.32 g(1 mmol) $Hg(OAc)_2$ 投入到 50 mL 烧瓶中. 加入 30 mL 乙醇,回流 3 h,待反应混合物完全变成黑色,趁热过滤,直到黑色固体全部滤出,滤液冷却至室温,有固体析出,用乙醇重结晶,得到目标化合物 155 mg (5a),产率 45%.

以相同的路线制得 5b-5f.

2-苯氨基-5-(2-苄氧基苯基) -1,3,4-㗁二唑(5a):白色晶体,收率 45.3%. 熔点:160 ~ 162 ℃. ^{1}H NMR(DMSO-d_6,300 MHz):δ = 5.36 (s, 2H, CH_2), 7.03 (t, 1H, NHph-H_4), 7.19 (d, 2H, ph-H_3,H_5), 7.31 (t, 2H, NHph-H_3,H_5), 7.38 (t, 2H, NHph-H_2,H_6), 7.52 (t, 1H, ph-H_4), 7.62 (m, 4H, CH_2ph-H_2, H_3, H_5, H_6), 7.85 (d, 1H, ph-H_6), 10.59 (s, 1H, NH). MS m/z (%): 343(M +, 16), 225(24), 120(98), 92(63), 91 (100), 77 (66). Anal. calcd for $C_{21}H_{17}N_3O_2$: C 73.45, H 4.99, N 12.24. found C 73.18, H 4.39, N 12.07.

2-对甲苯基氨基-5-(2-苄氧基苯基) -1,3,4-㗁二唑(5b):白色晶体,收率 57.1%. 熔点:159 ~ 161 ℃. ^{1}H NMR(Acetone-d_6,300MHz):δ = 2.29 (s, 3H, CH_3), 5.63 (s, 2H, CH_2), 7.12 (t, 1H, CH_2ph-H_4), 7.18 (d, 2H, ph-H_3,H_5), 7.31 (t, 2H, NHph-H_3,H_5), 7.38 (t, 2H, NHph-H_2, H_6), 7.52 (t,1H, ph-H_4), 7.61 (m, 4H, CH_2ph-H_2,H_3,H_5,H_6), 7.85 (d, 1H, ph-H_6), 10.54 (s, 1H, NH). MS m/z (%): 357 (M^+, 16), 251 (44), 225 (13), 106 (63), 91 (100), 77 (48). Anal. calcd for $C_{22}H_{19}N_3O_2$: C 73.97, H 5.36, N 11.76. found C 73.79, H 5.12, N 11.73.

2-苯氨基-5-[2-(4-氯-3-吡啶基)苄氧基]苯基 -1,3,4-㗁二唑(5c):白色絮状固体,收率 67.0%. 熔点:199 ~ 200 ℃. ^{1}H NMR (DMSO-d_6, 300MHz):δ = 5.36 (s, 2H, CH_2), 7.03 (t, 1H, NHph-H_4), 7.19 ~ 7.34 (t, 3H, Ph-H_5, NHph-H_3,H_5), 7.54 ~ 7.61 (m,4H, NHph-H_2,H_6, pyrimidine-H_3, ph-H_4), 7.79 (dd, 1H, pyrimidine-H_4), 8.05 (dd,1H, ph-H_6), 8.65 (d, 1H, pyrimidine-H_5), 10.59 (s, 1H, NH). MS m/z (%):378(M^+, 16), 286 (34), 260(53), 126 (17), 92 (100), 77 (72). Anal. calcd for $C_{20}H_{15}$

ClN_4O_2: C 63.41, H 3.99, N 14.79. found C 63.88, H 3.79, N 14.73.

2-苯氨基-5-[2-(2-吡啶基)苄氧基]-1,3,4-𫫇二唑(5d):白色针状晶体,收率 37.9%. 熔点:174~175 ℃. 1H NMR($CDCl_3$,300MHz):δ=5.37(s, 2H, CH_2), 7.06~7.11 (q,3H, NHph-H_4, ph-H_3,H_5), 7.21 (t, 1H, ph-H_4), 7.36 (t, 2H, NHph-H_3,H_5), 7.45 (t, 1H, pyrimidine-H_5), 7.55 (d, 2H, NHph-H_2, H_6), 7.67 (t, 1H, pyrimidine-H_3), 7.84 (t, 2H, ph-H_6, pyrimidine-H_4), 7.91 (t, 1H, py-H_6), 8.58 (d, 1H, NH); MS m/z (%):344 (M^+, 57), 252 (23), 226 (40), 134 (76), 92 (100), 77 (58); Anal. calcd for $C_{20}H_{16}N_4O_2$: C 69.76, H 4.68, N 16.27. found C 69.24, H 4.79, N 16.59.

2-苯氨基-5-(2-苄氨基苯基)-1,3,4-𫫇二唑(5e):白色晶体,收率 27.4%. 熔点:225~227 ℃. ^{1}H NMR(DMSO-d_6,300MHz):δ=4.56 (d, 2H, CH_2), 5.75 (s, 1H, NH), 6.74 (t, 1H, ph-H_5), 6.83 (d, 1H, ph-H_3), 7.02 (t, 1H, NHph-H_4), 7.27~7.38 (m, 7H, NHph-H_3,H_5, NHCH2ph-H), 7.62 (d, 3H, NHph-H_2,H_6, ph-H_3), 7.84 (bs, 1H, ph-H_6), 10.69 (s, 1H, NH). MS m/z (%):342 (M^+, 34), 249 (12), 207 (17), 193 (100), 91 (90), 77 (33). Anal. calcd for $C_{21}H_{18}N_4O$: C 73.67, H5.30, N 16.36. found C 72.98, H 5.10, N 16.30.

2-对甲苯基氨基-5-(2-苄氨基苯基)-1,3,4-𫫇二唑(5f):白色絮状固体,收率 29.2%. 熔点:233~235 ℃. ^{1}H NMR(DMSO-d_6,300MHz):δ=2.31 (s, 3H, CH_3), 4.61 (d, 2H, CH_2), 5.80 (s, 1H, NH), 6.78 (t, 1H, ph-H_5), 6.88 (d, 1H, ph-H_3), 7.23 (d, 2H, CH_2ph-H_2,H_6), 7.34 (d, 2H, CH_3ph-H_2,H_6), 7.41 (m, 3H, CH_2ph-H_3,H_4,H_5), 7.56 (d, 2H, CH_3ph-H_3,H_5), 7.67 (d, 1H, ph-H_4), 7.89 (bs, 1H, ph-H_6), 10.62 (s, 1H, NH). MS m/z (%):356 (M^+, 27), 249 (16), 207 (35), 193 (81), 107 (75), 92 (98)77 (58). Anal. calcd for $C_{22}H_{20}N_4O$: C 74.14, H 5.66, N 15.72. found C 73.94, H 5.41, N 15.75.

2 结果与讨论

本实验以水杨酸和邻氨基苯甲酸为起始原料,经过酯化,威廉反应,肼解,取代,环合五步反应合成了 6 个 2,5-二取代-1,3,4-𫫇二唑类杂环化合物. 化合物未见文献报道. 其中,第二步威廉反应,反应时间最长,并且要用到柱层析的方法来提纯,产率最低,因此是整条路线的关键步骤. 该步反应的碱选用 KOH,乙腈做溶剂产率较高. 笔者期望通过结构修饰发现具有一定抗肿瘤活性的化合物.

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Synthesis and characterization of 2,5-disubstituted-1,3,4-oxadiazoles heterocyclic compounds

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Abstract: Six novel 2,5-disubstituted-1,3,4-oxadiazoles were designed and synthesized by starting materials of salicylic acid and ortho-aminobenzoic acid. Target structures were characterized by ^{1}H NMR, EI-MS and elemental analysis.

Key words: 2,5-disubstituted-1,3,4-oxadiazole; synthesis; characterization

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Synthesis of phenylpyrazole derivatives

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Abstract: 9 Phenylpyrazole derivatives(7 new compounds) were synthesized by Scheme 1, starting with 2,6-dichloro-4-trifluoromethyl aniline as material, via cyclization, synthesis of the intermediate 1-(2,6-dichloro-4-trifluoromethyl-phenyl)-3-Cyano-5-amino-pyrazole, then introducing alkyl or acyl to 4-NH_2 of pyrazole ring. And all the target compounds were confirmed by melting point, ^{1}H NMR and MS.

Key words: phenylpyrazole derivatives; alkylation; amidation; lewis acid

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