1-[2-(取代苯基甲硫基)-2-(2,4-二氟苯基)乙基]-1H-1,2,4-三唑类化合物的合成及抗真菌活性*

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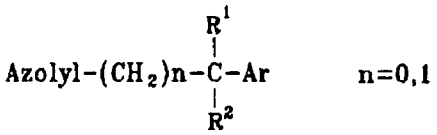
摘要 设计合成了21个1-[2-(取代苯基甲硫基)-2-(2,4-二氟苯基)乙基]-1H-1,2,4-三唑类化合物，其中19个为首次报道。体外抑菌试验表明：所有目标化合物对8种试验真菌均有不同程度的抗菌活性，其中化合物1,2,5对絮状表皮癣菌的活性为硫康唑的512倍以上；化合物5对白色念株菌的活性为硫康唑的32倍；化合物2对申克孢子丝菌的活性为硫康唑的32倍；化合物2,14对新型隐球菌的活性分别为硫康唑的64倍,32倍；化合物1,5对熏烟色曲菌的活性分别为硫康唑的16倍以上。

关键词 三唑类；抗真菌活性

真菌病是常见病、多发病，近年来，由于临床上广泛应用广谱抗菌素、皮质激素、免疫抑制剂、抗肿瘤药物等，降低了机体抵抗力，使真菌病发病率大幅度上升，已成为许多疾病的主要死亡原因之一。因此，临床迫切需要高效、低毒、广谱的抗真菌新药。

自60年代末发现咪唑有抗真菌作用后，氮唑类抗真菌药物发展很快，先后研究成功克霉唑[1]、咪康唑[2]、益康唑[3]、氟康唑[4]、伊曲康唑[5]等几十个药物，成为目前临床应用的主要用药。这类药物抗真菌作用强，抗真菌谱广，但亦存在毒性大，抗深部真菌作用弱的问题，急待解决。

构效关系分析表明[6]绝大多数氮唑类抗真菌化合物有如下基本结构：



在抗深部真菌活性和毒性方面三唑类化合物优于咪唑类化合物；Ar以二氟苯基取代的化合物优于其他卤素取代化合物。近年来，硫醇、硫醚、砜类等含硫抗真菌化合物的研究，日益受到重视，发现了一些抗真菌活性很强的药物，如硫康唑[7]，SM8668[8]等。

据此，我们以硫康唑为先导化合物，用三唑替换咪唑基团，以2,4-二氟苯基替换2,4-二氯苯基，同时改变分子中苯环上取代基(R)，设计合成了21个1-[2-(取代苯基甲硫基)-2-(2,4-二氟苯基)乙基]-1H-1,2,4-三唑类化合物(图1及表1)。用2倍稀释法测定了它们对8种常见致病真菌的体外抑菌活性，并与硫康唑、氟康唑对照(表2)。

为目标化合物的合成，设计了三种方法：a. 磺原酸酯与卤代烷(4)反应，该法收率低，后处理困难；b. 硫醇与卤代烷(4)反应，该法气味难闻；最后改用相应的异硫脲盐碱性水解后不经分离，直接与卤代烷(4)反应生成目标物，该法操作简单，收率高，避免了硫醇的难闻气味。设计合成的关键中间体(3)和(4)均为首次报道。

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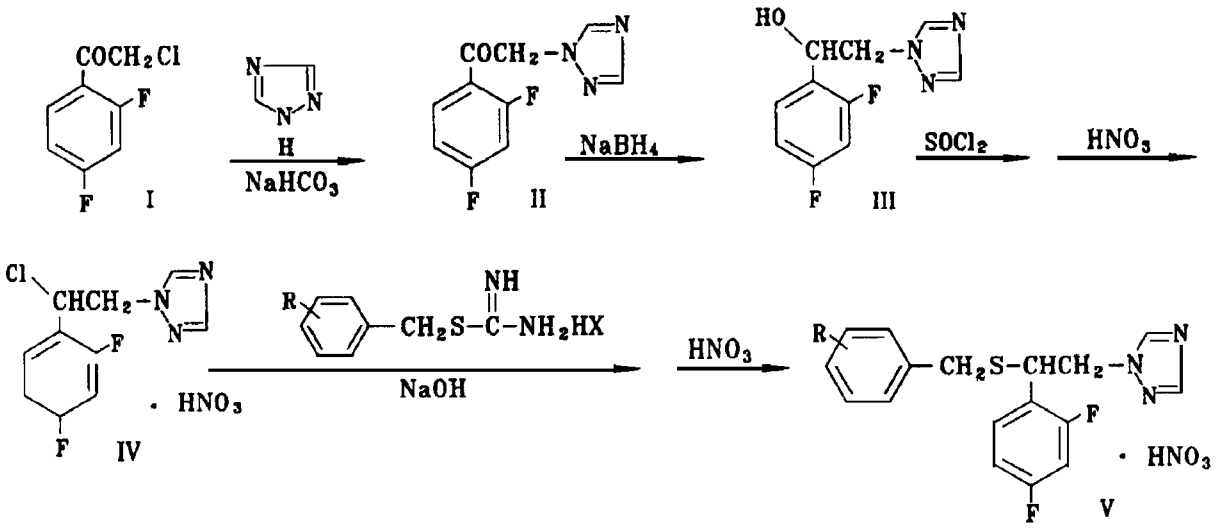
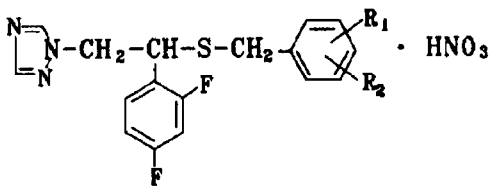


Fig 1 Route of synthesis of the title compounds 1～21.

Tab 1 Structure and physical properties of the title compounds



Compd	R^1	R^2	MP (℃)	Yield (%)	IR(KBr) (cm^{-1})	^{1}HNMR (δ ppm, DMSO-d_6)
1	P-CH_2CH_3	H	113～114	72.4	862,846,825	8.61(1H,s),8.07(1H,s),7.47～7.04(7H,m),4.71 (2H,d,J=7.74 Hz),4.47(1H,t,J=7.74 Hz),3.66 (2H,dd,J=13.02 Hz),2.55(2H,q,J=7.58 Hz),1.13 (3H,t,J=7.58 Hz)
2	m-Cl	H	122～123	87.3	878,840,787	8.82(1H,s),8.21(1H,s),7.48～7.04(7H,m),4.75 (2H,d,J=7.74 Hz),4.47(1H,t,J=7.74 Hz),3.73 (2H,dd,J=13.55 Hz)
3	m-F	H	119～119.5	69.1	884,843,825	8.81(1H,s),8.20(1H,s),7.60～7.04(7H,m),4.75 (2H,d,J=7.75 Hz),4.47(1H,t,J=7.75 Hz),3.74 (2H,dd,J=13.52 Hz)
4	P-CN	H	130～130.5	65.1	2229,868,837	8.65(1H,s),8.09(1H,s),7.80～7.00(7H,m),4.78 (2H,d,J=7.75 Hz),4.47(1H,t,J=7.75 Hz),3.81 (2H,dd,J=13.75 Hz)
5	P-Br	H	110.5～112	84.4	906,859	8.88(1H,s),8.27(1H,s),7.60～7.04(7H,m),4.78 (2H,d,J=7.78 Hz),4.47(1H,t,J=7.78 Hz),3.72 (2H,dd,J=13.40 Hz)
6	2-Cl	4-Cl	117～118.5	71.4	928,843	8.73(1H,s),8.15(1H,s),7.60～7.04(6H,m),4.77 (2H,d,J=7.75 Hz),4.57(1H,t,J=7.75 Hz),3.84 (2H,dd,J=13.25 Hz)
7	H	H	110～111	82.5	843,825,768	8.63(1H,s),8.10(1H,s),7.60～7.00(8H,m),4.74 (2H,d,J=7.75 Hz),4.47(1H,t,J=7.75 Hz),3.71 (2H,dd,J=13.09 Hz)

Continued

Compd	R^1	R^2	MP ℃	Yield (%)	IR(KBr) cm^{-1}	^{1}HNNR (δ ppm, DMSO-d_6)
8	P-C(=O)-C_6H_5	H	121～122	45.4	1650,856,818	8.82(1H,s),8.21(1H,s),7.70～7.01(12H,m),4.75(2H,d,J=7.73 Hz),4.52(1H,t,J=7.73 Hz),3.83(2H,dd,J=13.47 Hz)
9	P-CH_2-CH=CH_2	H	93～94	51.7	931,865,853	8.91(1H,s),8.30(1H,s),7.60～7.00(3H,m),5.70～5.62(1H,m),5.13～5.06(2H,m),4.76(2H,d,J=7.75 Hz),4.50(1H,t,J=7.75 Hz),3.11(2H,m)
10	P-F	H	120～120.5	75.3	853,834	8.96(1H,s),8.33(1H,s),7.60～7.05(7H,m),4.81(2H,m,J=7.76 Hz),4.48(1H,t,J=7.76 Hz),3.74(2H,dd,J=13.28 Hz)
11	m-Br	H	121～122.5	81.2	840,812,790	8.69(1H,s),8.13(1H,s),7.51～7.00(7H,m),4.75(2H,d,J=7.75 Hz),4.50(1H,t,J=7.75 Hz),3.72(2H,dd,J=13.54 Hz)
12	m-CH_3	H	123～124	56.6	926,843,793	8.72(1H,s),8.15(1H,s),7.52～6.90(7H,m),4.72(2H,d,J=7.71 Hz),4.47(1H,t,J=7.71 Hz),3.66(2H,dd,J=13.05 Hz),2.23(3H,s)
13	O-Cl	H	120～121	68.2	853,812	8.83(1H,s),8.21(1H,s),7.60～7.00(7H,m),4.78(2H,d,J=7.66 Hz),4.60(1H,t,J=7.66 Hz),3.80(2H,dd,J=13.07 Hz)
14	**	H	134～135	85.9	843,790,781	8.68(1H,s),8.11(1H,s),8.00～7.00(10H,m),4.77(2H,d,J=7.64 Hz),4.61(1H,t,J=7.64 Hz),4.20(2H,dd,J=12.76 Hz)
15	P-Cl	H	108～109	81.4	921,850	8.68(1H,s),8.11(1H,s),7.50～7.00(7H,m),4.73(2H,d,J=7.80 Hz),4.45(1H,t,J=7.80 Hz),3.71(2H,dd,J=13.41 Hz)
16	P-CH_3	H	105.5～107	76.3	912,843	8.68(1H,s),8.12(1H,s),7.52～7.00(7H,m),4.72(2H,d,J=7.53 Hz),4.50(1H,t,J=7.53 Hz),3.65(2H,dd,J=13.12 Hz),2.25(3H,s)
17	O-F	H	114.5～116	51.2	878,846,821	8.87(1H,s),8.27(1H,s),7.60～7.00(7H,m),4.78(2H,d,J=7.72 Hz),4.57(1H,t,J=7.72 Hz),3.77(2H,dd,J=13.44 Hz)
18	P-NO_2	H	120～121	21.1	884,859	8.68(1H,s),8.14(1H,s),8.09～7.00(7H,m),4.75(2H,d,J=7.78 Hz),4.47(1H,t,J=7.78 Hz),3.87(2H,dd,J=13.73 Hz)
19	P-C(CH_3)$_3$	H	101～102	79.8	921,850	8.69(1H,s),8.13(1H,s),7.60～7.20(7H,m),4.70(2H,d,J=7.44 Hz),4.48(1H,t,J=7.44 Hz),3.64(2H,dd,J=12.99 Hz),1.12(9H,s)
*20	P-Cl	H	129～130	81.5	859,787	8.69(1H,s),8.13(1H,s),7.60～7.20(7H,m),4.80(2H,d,J=7.44 Hz),4.60(1H,t,J=7.44 Hz),3.71(2H,dd,J=13.25 Hz)
*21	2-Cl	4-Cl	136～136.5	78	865,831	8.73(1H,s),8.14(1H,s),7.60～7.30(6H,m),4.80(2H,d,J=6.95 Hz),4.68(1H,t,J=6.95 Hz),3.80(2H,dd,J=13.37 Hz)

* 2,4-Difluoropheny group is replaced by 2,4-dichlorophenyl group; compounds 20 and 21 were reported in form of B. HCl in Ger off 2724684, 14 Dec, 1978; ** the benzene ring in substituted benzyl group is replaced by 1-naphthyl group.

Tab 2 Antifungal activities of the title compounds

Compd	MIC($\mu g \cdot ml^{-1}$)							
	Candida albicans 9505052	*Cryptococcus neoformans* 9406204	*Sporotrichum schenckii* 940516	*Aspergillus fumigatus* 9508214	*Epidermophyton floccosum* 9505110	*Trichophyton rubrum* 9503068	*Microsporum lanosum* 9505115	*Trichophyton mentagrophytes* 9503045***
1	10	1.25	40	<0.156	<0.156	5	40	10
2	80	0.31	2.5	1.25	<0.156	10	40	10
3	80	1.25	20	1.25	0.625	5	40	10
4	10	20	20	1.25	0.625	10	20	10
5	2.5	2.5	80	<0.156	<0.156	10	20	5
6	80	2.5	40	1.25	10	10	20	10
7	80	2.5	80	1.25	0.31	20	20	<0.156
8	>80	80	>80	40	0.31	40	>40	20
9	>80	20	80	1.25	2.5	20	10	20
10	>80	20	80	1.25	0.31	10	10	20
11	>80	2.5	40	1.25	40	5	40	10
12	>80	2.5	40	1.25	>80	20	40	10
13	>80	10	20	1.25	>80	5	20	5
14	>80	0.625	20	2.5	20	2.5	10	5
15	20	2.5	5	0.31	40	5	10	5
16	80	5	80	0.31	80	10	20	10
17	80	2.5	40	1.25	80	10	20	2.5
18	80	20	80	20	>80	5	20	20
19	>80	>80	20	0.625	>80	5	>40	20
20	>80	2.5	80	10	>80	2.5	>40	0.156
21	>80	2.5	80	10	>80	2.5	>40	10
22*	80	20	80	2.5	80	2.5	10	2.5
23**	>80	20	80	>40	>80	>80	>40	>40

* Sulconazole; ** fluconazole; *** strain number.

体外抑菌试验表明:所有目标化合物对 8 种致病真菌均有不同程度的抗菌活性,且均相当于或优于氟康唑,化合物 1～7,11～17 对大部分真菌的活性优于或相当于硫康唑,引人注目的是部分化合物对深部真菌有较好的活性。如化合物 1,2,5 对絮状表皮癣菌的活性为硫康唑的 512 倍以上;化合物 5 对白色念株菌活性为硫康唑的 32 倍;化合物 2,4 对新型隐球菌的活性为硫康唑 64 倍和 32 倍;化合物 2,15 对申克孢子丝菌的活性为硫康唑的 32 倍和 16 倍;化合物 1,5 对熏烟色曲菌的活性为硫康唑的 16 倍以上。

实 验 部 分

熔点用 ZMD83-1 型熔点测定仪测定,温度计未校正,元素分析仪为 MOD-1106 型,红外光谱仪为 Hitachi 270-50 型,KBr 压片,核磁共振仪为 AC-300P 型,TMS 为内标,DMSO-d_6 为溶剂。

1 2′,4′-二氟-2-(1H-1,2,4-三唑-1-基)苯乙酮(II)的合成

取 1H-1,2,4-三唑 27.6 g(0.4 mol)及碳酸氢钠 16.8 g(0.20 mol)置于 500 ml 三颈瓶中,加甲苯 180 ml,剧烈搅拌回流下,滴加 2-氯-2′,4′-二氟苯乙酮 38.1 g(0.20 mol)的甲苯溶液,加毕,回流搅拌 5 h。冷却,用水洗甲苯溶液,用无水硫酸钠干燥,回收甲苯,乙酸乙酯—环己烷重结晶,得产品 18.2 g,收率 40.8%, mp 105～106℃,文献值 mp 103～105℃[9]。

2 1-(2,4-二氟苯基)-2-(1H-1,2,4-三唑-1-基)乙醇(III)的制备

取 II 22.3 g(0.10 mol)溶于无水乙醇 150 ml 中,在冰浴冷却并搅拌下分批加入 $NaBH_4$ 3.78 g(0.1 mol),加毕,继续搅拌 1 h,然后升温至沸腾,回流搅拌反应 1 h,回收乙醇,加入 H_2O 200 ml,析出固体。水洗数次,95%乙醇重结晶得 III 19.5 g,收率 86.6%,mp 122℃。元素分析 $C_{10}H_9F_2N_3O$,理论值%: C 53.33, H 4.03, N 18.66; 实测值%: C 53.41, H 4.11, N 18.52。

3 1-氯-1-(2,4-二氟苯基)-2-(1H-1,2,4-三唑-1-基)乙烷硝酸盐(IV)的制备

取 III 22.5 g(0.1 mol)及氯化亚砜 119 g(1 mol)置于 250 ml 园底烧瓶中,加热回流搅拌 4 h 后,蒸去氯化亚砜,残留物加 10% $NaHCO_3$ 溶液使呈碱性。二氯甲烷提取,提取液用水洗,无水硫酸钠干燥,蒸去溶剂,加乙醚溶解,滴加 HNO_3,析出固体。用异丙醇—丙酮重结晶,得 IV 20.8 g,收率 67.8%,mp 136.5～138℃。元素分析 $C_{10}H_9ClF_2N_4O_3$,理论值%: C 39.17, H 2.96, N 18.27; 实测值%: C 39.03, H 2.87, N 18.38。

4 1-[2-(苯基甲硫基)-2-(2,4-二氟苯基)乙基]-1H-1,2,4-三唑硝酸盐(V)

取苄基异硫脲盐酸盐 1.6 g(0.008 mol), NaOH 1.3 g,二氧六环 20 ml 和水 5 ml,混合后,搅拌回流 1 h,加入 IV 2 g(0.0065 mol),继续反应 4 h,反应毕,回收溶剂,加水 20 ml,乙醚提取,无水硫酸钠干燥,滴加 HNO_3,析出白色固体。异丙醇重结晶,得产品 2.1 g,收率 82%, mp 110～111℃。元素分析 $C_{17}H_{16}F_2N_4O_3S$,理论值%: C 51.77, H 4.09, N 14.21; 实测值%: C 51.65, H 4.03, N 14.10。

化合物 1～21 均按此法合成。

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SYNTHESIS AND ANTIFUNGAL ACTIVITIES OF 1-{2-[(SUBSTITUTED-PHENYL) METHYL]THIO} -2-(2,4-DIFLUOROPHENYL)ETHYL-1H-1,2,4-TRIAZOLES

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ABSTRACT Twenty-one 1-[2-[[(substituted-phenyl)methyl]thio]-2-(2,4-difluorophenyl)ethyl]-1H-1,2,4-triazoles were synthesized and 19 compounds are reported for the first time. Results of biological tests *in vitro* showed that the antifungal activities of all title compounds were better than or comparable to the activities of fluconazole. The antifungal activities of compounds 1～7 and 11～17 were better than or comparable to the activities of sulconazole. Compounds 1, 2 and 5 were 512 times more active than sulconazole against epidermophyton floccosum; compound 5 was 32 times more active against *Candida albicans*, compound 2 was 32 times more active against *Sporotrichum schenckii*; compounds 2 and 14 were shown to be 64 and 32 times more active against *Cryptococcus neoformans*; compounds 1 and 5 were 16 times more active against *Aspergillus fumigatus*.

KEY WORDS Triazoles; Antifungal activity