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·论　著·

新型2,5-二取代-1,3,4-噁二唑化合物的设计、合成及抗真菌活性

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[摘要] **目的**　研究新型2,5-二取代1,3,4-噁二唑化合物的体外抗真菌活性。**方法**　设计合成了16个新型2,5-二取代-1,3,4-噁二唑化合物，所得化合物都经过^{1}HNMR、LC-MS确证；选择6种真菌为实验菌株，进行体外抗真菌活性测试。**结果**　所合成的目标化合物对除熏烟曲霉菌外的所有菌株(白假丝酵母菌、新生隐球菌、热带假丝酵母菌、近平滑假丝酵母菌、红色毛癣菌)均具有一定的体外抗真菌活性，其中化合物**14**、**17**、**18**对白假丝酵母菌和新生隐球菌的MIC_{80}值均为0.25 μg/ml，与氟康唑(0.25 μg/ml)相当；化合物**14**、**17**对红色毛癣菌的MIC_{80}值为0.25 μg/ml，是氟康唑(0.5 μg/ml)的2倍，与酮康唑相当。**结论**　利用1∶3偶极加成反应可在1,3,4-噁二唑化合物的5-位引入1,2,3-三唑取代基。初步体外活性显示，所合成的目标化合物对除熏烟曲霉菌外的所有菌株均具有一定的体外抗真菌活性。1,3,4-噁二唑2-位苯环上连有取代基对化合物的活性影响较大。

[关键词]　合成；1,3,4-噁二唑类；三唑类；抗真菌药
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Design, synthesis and antifungal activity of novel 2,5-disubstituted 1,3,4-oxadiazoles

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[**Abstract**]　**Objective**　To study the *in vitro* antifungal activity of novel 2,5-disubstituted 1,3,4-oxadiazoles. **Methods**　Sixteen novel 2,5-disubstituted 1,3,4-oxadiazoles compounds have been designed, synthesized and characterized by ^{1}HNMR, LC-MS spectra. Their antifungal activities were evaluated with six tested pathogenic fungi *in vitro*. **Results**　All the title compounds exhibited potent antifungal activities against *Candida albicans*, *Cryptococcus neoformans*, *Candida parapsilosis*, *Candida tropicalis*, and *Trichophyton rubrum*, but not *Aspergillus fumigatus*. The activities of compound **14**, **17** and **18** against *Candida atbicans* and *Cryptococcus neoformans* (with the MIC_{80} 0.25 μg/ml) were similar to that of fluconazole. The activities of compound **14** and **17** against *Trichophyton rubrum* (with the MIC_{80} 0.25 μg/ml) were 2 times as high as that of fluconazole and were similar to that of ketoconazole. **Conclusion**　The 1,2,3-triazole can be efficiently introduced to 1,3,4-oxadiazoles compounds by intermolecular 1,3-dipolar cycloaddition. All the title compounds exhibit certain antifungal activities with broad spectrum. The substituent of the benzene plays an important role in improving the antifungal activity of the compound.

[**Key words**]　synthesis; 1,3,4-oxadiazoles, triazoles; antifungal agents
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由于肿瘤放化疗患者、器官移植患者以及介入治疗患者人数的不断增加，临床上广谱抗生素、皮质激素和免疫抑制剂的长期广泛使用，深部真菌感染的发病率和病死率显著增加。深部真菌感染已经成为骨髓移植患者和恶性白血病患者的常见致死原因，严重威胁人类的生命健康[1-2]。目前，临床上用于治疗深部真菌感染的药物较少，主要有两性霉素B和氟康唑、伊曲康唑等氮唑类药物，但两性霉素B的肾毒性较大，氮唑类药物存在抗菌谱窄(尤其是氟康唑对熏烟曲霉菌几乎无效)、耐药性严重两大主要问题[3-4]。因此，临床上迫切需要新型、广谱、高效、低毒、抗耐药的抗真菌药物。

杂环类化合物是药物研究的重要方向之一。在分子中同时引入2个或多个杂环活性中心，能改善化合物的生物活性，从而得到活性更好、应用价值更高的化合物。1,3,4-噁二唑不对称衍生物因其独特

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在关键中间体 2-炔丙基硫醚-5-苯基-1,3,4-噁二唑的制备过程中,我们采用氢氧化钠水溶液(锢)作为反应条件,其产率为 69.5%,高于无催化剂的反应条件;并且采用金属锢作催化剂,大大提高了反应产率,节省了反应时间。另外,我们采用 Click reaction 在分子中引入 1,2,3-三唑基,通过在反应体系中直接加入中间体(**4**)的 N,N-二甲基甲酰胺溶液,以 Cu^{+} 为催化剂,在常温下即可进行,反应副产物较少,后处理简单,产率较高。

本实验拟合成具有较好活性的多杂环新型抗真菌化合物。初步体外活性显示:所合成的目标化合物对除熏烟曲霉菌外的所有菌株均具有一定的体外抗真菌活性。其中化合物 **14**、**17**、**18** 对白假丝酵母菌和新生隐球菌的 MIC_{80} 值均为 0.25 μg/ml,与氟康唑(0.25 μg/ml)相当;化合物 **14**、**17** 对红色毛癣菌的 MIC_{80} 值为 0.25 μg/ml,是氟康唑(0.5 μg/ml)的 2 倍,与酮康唑(0.25 μg/ml)相当。1,3,4-噁二唑 2-位苯环上吸电子基卤素(F,Cl)取代的化合物(**13**～**18**)活性相对较高,吸电子基硝基、氰基取代的化合物(**24**～**27**)活性次之,供电子基甲基、甲氧基取代的化合物(**19**～**23**)活性最低。分析目标化合物的结构与抑菌活性结果,可以初步得到以下构效关系:(1) 从电性效应上分析:2-位苯环上连有吸电子取代基,有利于活性的提高;(2) 从基团大小上分析:取代基较小的化合物有利于活性的提高。综合以上两个因素,具有吸电子效应的较小基团更有利于活性的提高。由于化合物数量有限,更深入的构效关系探讨有待于进一步的研究。

4 利益冲突

所有作者声明本文不涉及任何利益冲突。

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