Graphical Abstract

Discovery of new azole derivatives containing the 2,4-dienone motif with broad-spectrum antifungal and antibacterial activity

Chunli Liu,a,† Ce Shi,b,c,† Fei Mao,a,* Yong Xu,d Jinyan Liu,b Bing Wei,b,c Jin Zhu,a Mingjie Xiang,b,c,* and Jian Li a,*

a Shanghai Key Laboratory of New Drug Design, School of Pharmacy, East China University of Science and Technology, 130 Mei Long Road, Shanghai 200237, China
b Radioimmunology and Clinical Laboratory, Luwan Branch, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200020, China
c Department of Clinical Microbiology Laboratory, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200025, China
d Humanwell Healthcare (Group) Co, Ltd., 666 Gaoxin Road, East Lake High-Tech Development Zone, Wuhan 430075, Hubei, China
† These authors made equal contributions to this work.
* To whom all correspondence should be addressed: jianli@ecust.edu.cn; mjxiang123456@126.com; maofei6517@163.com.

A compound containing an imidazole moiety and a 2,4-dienone motif with significant activity toward several fungi was discovered in a screen for new antifungal compounds. Then, a total of 26 derivatives of this compound were designed, synthesized and evaluated through in vitro and in vivo antifungal activity assays. Several compounds exhibited improved antifungal activities compared to the lead compound. Of the derivatives, compounds 31 and 42 exhibited strong, broad-spectrum inhibitory effects toward Candida spp. In particular, the two derivatives exhibited potent antifungal activities toward the fluconazole-resistant isolate C. albicans 64110 (MIC = 8 μg/mL) and S. epidermidis UF843 (compound 31: MIC = 8 μg/mL; compound 42: MIC = 8 μg/mL). The results of an animal experiment indicated that both compounds could improve the survival rate of model mice infected with ATCC 90028 (fluconazole-susceptible isolate). More importantly, the two compounds exhibited notable effects toward the fluconazole-resistant C. albicans isolate in vivo, which is promising with regard to the clinical problem posed by fluconazole-resistant Candida species.