Macedonian pharmaceutical bulletin, 68 (Suppl 1) 419 - 420 (2022)
Online ISSN 1857 - 8969
DOI:10.33320/maced.pharm.bull.2022.68.03.202
Short communication

A series of 2-pyrazolines endowed with potent anticandidal activity

Mehlika Dilek Altintop[1*], Zerrin Cantürk[2], Ahmet Özdemir[1]

[1]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Anadolu University, 26470 Eskişehir, Turkey*
[2] *Department of Pharmaceutical Microbiology, Faculty of Pharmacy, Anadolu University, 26470 Eskişehir, Turkey*

Introduction

Invasive fungal infections (IFIs) associated with high morbidity and mortality pose a serious threat to human health across the globe. IFIs are estimated to be responsible for almost 1.5-2 million deaths every year (Liu et al., 2018).

Over the last decades, the incidence of IFIs has dramatically increased due to the growing number of patients at risk for IFIs (Liu et al., 2018), particularly those in intensive care units, those with immune systems compromised by human immunodeficiency virus (HIV), post-transplant immunosuppressive therapy or cancer chemotherapy as well as those with severe viral infections such as influenza virus and COVID-19 (Fisher et al., 2022).

Candida species, particularly *Candida albicans*, account for the majority of IFIs (Lopes and Lionakis, 2022). *Candida* spp. are also recognized as the fourth most common cause of nosocomial bloodstream infections (Liu et al., 2018).

Despite tremendous efforts being devoted to the identification of fungal-specific targets and the discovery of selective antifungal drugs, treatment options are rather limited. There are only three classes of antifungal agents (polyenes, azoles, and echinocandins) clinically available for the treatment of IFIs. In addition to these agents, 5-fluorocytosine (5-FC) is frequently used as an adjunctive therapy. Substantial clinical failures associated with these antifungal drugs are attributable to their limited clinical efficacy, narrow antifungal spectrum, significant adverse effects, unfavorable pharmacokinetic features, and drug-drug interactions (Liu et al., 2018). Resistance to antifungal agents, which reduces the clinical success, is also an emerging concern worldwide (Fisher et al., 2022).

Unlike bacteria, eukaryotic fungal cells are similar to mammalian cells (Liu et al., 2018) and therefore the discovery of selective antifungal drugs devoid of severe side effects is an uphill task for researchers.

2-Pyrazoline (also referred to as 4,5-dihydro-1*H*-pyrazole) is an outstanding and highly versatile scaffold extensively used by many researchers for the design of therapeutically active agents to combat various diseases such as bacterial and fungal infections, central nervous system (CNS) disorders, cancer and so on. In particular, antimicrobial activity of pyrazolines predominates over other reported pharmacological activities (Shaaban et al., 2012).

The vast number of scientific reports appearing in the literature related to 2-pyrazolines exerting pronounced antifungal potency (Nehra et al., 2020) motivated us to evaluate the anticandidal effects of 2-pyrazolines, which were previously synthesized and tested for their inhibitory effects on acetylcholinesterase and butyrylcholinesterase by our research group (Altintop *et al*., 2013).

Materials and methods

Chemistry

The synthetic method and the spectral data of 1-[[(4-alkyl/arylpiperazin-1-yl)thiocarbamoylthio]acetyl]-3-(2-furyl)-5-(3,4-methylenedioxyphenyl)-2-pyrazolines (**1-10**) were reported previously by our research team (Altintop et al., 2013).

*mdaltintop@anadolu.edu.tr

Microbiology

The minimum inhibitory concentrations (MICs, µg/mL) of compounds **1-10** were determined by the broth microdilution assay as previously described (Özdemir *et al*., 2015) to evaluate their antifungal effects on *Candida albicans* (ATCC® 90028™), *Candida glabrata* (ATCC® 90030™), *Candida krusei* (ATCC® 34135™), and *Candida parapsilosis* (ATCC® 22019™). Ketoconazole was used as a positive control.

Results and discussion

Compounds **1-10** were tested for their antifungal effects on *C. albicans* (ATCC® 90028™), *C. glabrata* (ATCC® 90030™), *C. krusei* (ATCC® 34135™), and *C. parapsilosis* (ATCC® 22019™). These compounds were found to be more effective on *C. parapsilosis*. Compounds **1**, **3**, **4**, **7** and **8** showed marked antifungal effects on *C. parapsilosis* with a MIC value of 31.25 µg/mL compared to ketoconazole (MIC= 31.25 µg/mL). Taking into account the *in vitro* cytotoxicity data reported previously by our research team (Altintop et al., 2013), only 1-[[(4-(4-methoxyphenyl)piperazin-1-yl)thiocarbamoylthio]acetyl]-3-(2-furyl)-5-(3,4-methylenedioxyphenyl)-2-pyrazoline (**3**) did not show any cytotoxicity towards NIH/3T3 mouse embryonic fibroblast cells (IC_{50}= 191 µg/mL) at its MIC concentration (31.25 µg/mL). Based on this result, it can be concluded that the antifungal activity of compound **3** towards *C. parapsilosis* is selective.

Conclusion

In this paper, we described the *in vitro* evaluation of a series of 2-pyrazolines (**1-10**) as anticandidal agents. Among these compounds, compounds **1**, **3**, **4**, **7** and **8** were the most active compounds against *C. parapsilosis* (MIC= 31.25 µg/mL). However, MTT assay performed previously by our research team (Altintop *et al*., 2013) revealed that only compound **3** did not show any cytotoxic activity towards normal (NIH/3T3) cells at its MIC concentration. In the continuation of this work, further studies are required to provide an insight into the mechanism of action underlying its pronounced anticandidal activity. This work could be the first step towards the development of a new generation of antifungal agents for the treatment of IFIs caused by *Candida* species.

Acknowledgements

This study was supported by Anadolu University Scientific Research Projects Commission under the grant no: 2204S033.

References

Altintop, M.D., Özdemir, A., Kaplancikli, Z.A., Turan-Zitouni, G., Temel, H.E., Akalin Çiftçi, G., 2013. Synthesis and biological evaluation of some pyrazoline derivatives bearing a dithiocarbamate moiety as new cholinesterase inhibitors. Arch. Pharm. Chem. Life Sci. 346, 189–199. https://doi.org/10.1002/ardp.201200384

Fisher, M.C., Alastruey-Izquierdo, A., Berman, J., Bicanic, T., Bignell, E.M., Bowyer, P., Bromley, M., Brüggemann, R., Garber, G., Cornely, O.A., Gurr, S.J., Harrison, T.S., Kuijper, E., Rhodes, J., Sheppard, D.C., Warris, A., White, P.L., Xu, J., Zwaan, B., Verweij, P.E., 2022. Tackling the emerging threat of antifungal resistance to human health. Nat. Rev. Microbiol., 1–15. [Epub ahead of print]. https://doi.org/10.1038/s41579-022-00720-1

Liu, N., Tu, J., Dong, G., Wang, Y., Sheng, C., 2018. Emerging new targets for the treatment of resistant fungal infections. J. Med. Chem. 61, 5484–5511. https://doi.org/10.1021/acs.jmedchem.7b01413

Lopes, J.P., Lionakis, M.S., 2022. Pathogenesis and virulence of *Candida albicans*. Virulence 13, 89–121. https://doi.org/10.1080/21505594.2021.2019950

Nehra, B., Rulhania, S., Jaswal, S., Kumar, B., Singh, G., Monga, V., 2020. Recent advancements in the development of bioactive pyrazoline derivatives. Eur. J. Med. Chem. 205, 112666. https://doi.org/10.1016/j.ejmech.2020.112666

Özdemir, A., Altıntop, M.D., Sever, B., Cantürk, Z., Kaplancıklı, Z.A., 2015. Synthesis and evaluation of tetrazole-based hydrazone derivatives bearing a pyridine moiety as antimicrobial agents, Lett. Drug Des. Discov. 12, 687–693. https://doi.org/10.2174/1570180812666150309235217

Shaaban, M.R., Mayhoub, A.S., Farag, A.M., 2012. Recent advances in the therapeutic applications of pyrazolines. Expert Opin. Ther. Pat. 22, 253–291. https://doi.org/10.1517/13543776.2012.667403