Research Paper

# Investigating the Effectiveness of Spirocyclopropane-Oxindole Derivatives on Clinical Isolates of *Candida albicans*

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## ABSTRACT

**Objectives:** Given the spread of azole resistance in *Candida albicans* (*C. albicans*), searching for new potent compounds, such as spirocyclopropane-oxindole derivatives is important. This study evaluates the antifungal susceptibility of spirocyclopropane-oxindole derivatives on clinical isolates of *C. albicans*.

**Methods:** Antifungal susceptibility of 50 clinical isolates of *C. albicans* to spirocyclopropane-oxindole derivatives (4a, 4b, and 4c), nystatin, and fluconazole were evaluated according to Clinical Laboratory Standards Institute (M27-S4) guidelines. The medicinal dilution range of the compounds, fluconazole, and nystatin was 0.256 to 128, 0.128 to 64, and 0.032 to 16 µg/mL, respectively. The minimum inhibitory concentration (MIC) was defined as the concentration that caused at least 50% growth inhibition compared to the positive control. Statistical analysis was performed using the SPSS software, version 20. The significance level was set at $P \leq 0.05$.

**Results:** There was a significant difference between the MIC values of spirocyclopropane-oxindole derivatives (4a, 4b, and 4c), nystatin, and fluconazole against *C. albicans*. The comparison of the MICs of the spirocyclopropane-oxindole derivatives (4a, 4b, and 4c) against *C. albicans* showed that derivative 4a had a lower $MIC_{50}$ (8 µg/mL), $MIC_{90}$ (16 µg/mL), and Geometric (G) Mean (10.126) than derivatives 4b ($MIC_{50}$=64, $MIC_{90}$=128, G Mean=76.638), and 4c ($MIC_{50}$=64, $MIC_{90}$=128, G Mean=60.547).

**Discussion:** Antifungal effects of spirocyclopropane-oxindole derivatives (4a, 4b, and 4c) on *C. albicans* isolates were significantly less than nystatin and fluconazole. Therefore, with structural changes, the antifungal effects of these compounds will increase.

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## Introduction

Over the last few decades, fungal diseases have been responsible for an increasing proportion of hospital-acquired infections. Candidiasis is one of the most important infections, accounting for about 25% to 50% of ICU infections and 8% to 15% of all hospital infections, based on recent studies [1, 2]. It is important to be aware of the wide spectrum of Candida infections and the need to have appropriate diagnostic and treatment strategies in place [3-5]. Following several reports on the increasing resistance of *Candida albicans* (*C. albicans*) species to widely use antifungal drugs and the many side effects of these drugs, using some alternative compounds can be important [6, 7]. Cyclopropane as a key intermediates to synthesize dense functional molecules, due to the 27 kcal/mol ring strain in their structure, has posed a major challenge to organic chemists and has led to the development of efficient research methods. The cyclopropane was first observed in chrysanthemic acid in 1909. Since then, many cyclopropane-containing derivatives have been introduced [8, 9]. Otherwise, spiro compounds have varied pharmacological activities; therefore, their synthesis has been a challenge for chemists [10]. The Spirocyclopropane-oxindole is an important structural subunit as a stabilized pharmacophore that is present in the structure of many biologically active natural compounds and small molecules with a wide range of applications in treatment [11]. Various biological activities have been reported for spirocyclopropane-oxindoles, including anti-tumor, analgesic, treating central nervous system disorders, antiviral, etc. [12]. Recently, several studies have evaluated the antifungal effects of oxindole derivatives of spirocyclopropanes with relatively good results, and their findings indicate that by making changes in the skeleton of spirocyclopropane-oxindoles, it is possible to obtain compounds with potential and valuable antifungal effects [13-15]. Accordingly, this study compares the antifungal effects of spirocyclopropane-oxindole derivatives (4a, 4b, and 4c) against clinical *C. albicans* isolates with fluconazole and nystatin.

## Materials and Methods

In this cross-sectional experimental study, 50 *C. albicans* isolates were collected during the years 2021-2023 from patients with candidiasis who were referred to the mycological laboratory of Babol University of Medical Sciences in Babol City, Iran. Identification of the isolates was conducted using traditional mycologic methods, such as culture on sabordextrose agar, chrome agar, germ tube test, chlamydospore formation test, as well as polymerase chain reaction-restriction fragment length polymorphism molecular method using ITS1 (5'-TCCGTAGGTGAACCTGCGG- 3') and ITS4 (5-TCCTCCGCTTATTGATATGC-3) primers and restriction endonuclease MspI digestion in our previous studies [16, 17]. The isolates were cultured under sterile conditions on Sabouraud dextrose agar with chloramphenicol (0.05 mg/mL) and incubated for 48 h at 35˚C.

### Synthesis of spirocyclopropane-oxindole derivatives

Three spirocyclopropane-oxindole derivatives (4a, 4b, and 4c) were prepared based on a sonochemical synthesis of spirocyclopropane-oxindole in our previous study (Figures 1 and 2) [18].

### Antifungal susceptibility testing

Antifungal susceptibility tests were performed to evaluate minimal inhibitory concentrations (MICs) of spirocyclopropane derivatives (4a, 4b, and 4c) against clinical *C. albicans* isolates according to the manufacturer's instructions, which comply with the Clinical and Laboratory Standards Institute (CLSI) guidelines outlined in document M27-S4 [19]. Fluconazole and nystatin were used as control drugs for comparison of the antifungal activity of new derivatives.

For this purpose, serial dilutions were prepared for final concentrations ranging from 0.256 to 128 µg/mL for spirocyclopropane-oxindole derivatives, 0.128 to 64 µg/mL for fluconazole (Sigma-Aldrich, USA), and 0.032 to 16 for nystatin (Sigma-Aldrich USA).

In the next step, 200 µL of spirocyclopropane-oxindole derivatives, fluconazole, and nystatin were seeded into the first column of a flat-bottomed 96-well plate. Then, 100 µL of Roswell Park Memorial Institute (RPMI) medium (Sigma-Aldrich, USA) was added to the remaining wells (except for the first column) and serial dilution was done. Columns 11 and 12 were considered the negative control (drug only, no organism) and the positive control (organism only, no drug). The suspension was adjusted spectrophotometrically to optical densities between 75% to 77% transmission at a 530 nm wavelength. Lastly, 100 µL of the prepared fungal suspensions were added to all columns, except for the negative control column and the plates were incubated at 35˚C for 24-48 h. In each well, the final inoculum density was $0.5–2.5\times10^3$ CFU/mL. The final results were visually read and the well


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with 50% growth compared to the positive control was considered the MIC. The reference strains of *Candida parapsilosis* (ATCC 22019) and *Candida krusei* (ATCC 6258) were used as quality control for each new set of isolates. All antifungal susceptibility tests were replicated to ensure reproducibility.

### Statistical analysis

The data were analyzed using the SPSS software, version 27. The independent t-test was used to analyze quantitative results and the chi-squared test was used to analyze qualitative variables. Meanwhile, P≤0.05 was considered statistically significant.

## Results

The in vitro susceptibility of clinically isolated *C. albicans* to spirocyclopropane-oxindole derivatives (4a, 4b, and 4c), nystatin, and fluconazole is provided in Table 1. All spiro compounds were active against *C. albicans* with $MIC_{50}$ ≥8 µg/mL; however, none of them showed superior activity to nystatin ($MIC_{50}$=0.063 µg/mL) and fluconazole ($MIC_{50}$=0.125 µg/mL). Nystatin has the highest and derivatives 4b and 4c the lowest antifungal activity against *C. albicans* isolates.

The mean MIC of the spirocyclopropane-oxindole derivatives (4a, 4b, and 4c) was higher than the fluconazole and nystatin. In addition, based on the statistical analysis, there was a significant difference between the mean MIC of the two antifungals and the studied derivatives (P<0.001) (Table 2, Figure 3). Also, in comparing the mean MIC of the two antifungals, nystatin had a lower mean MIC than fluconazole; therefore, the difference in their mean is statistically significant. Comparing the MICs of the spirocyclopropane-oxindole derivatives with each other (4a, 4b, and 4c) showed that derivative 4a had a lower mean MIC (12.4 µg/mL) and $MIC_{50}$ (8 µg/mL) than other derivatives. Also, the two derivatives 4b (mean MIC=88) and 4c (mean MIC=76.88) had almost the same mean MIC against *C. albicans* species (P≤0.001).

## Discussion

Considering the growing threat because of the increased multi-drug resistance of Candida in recent years, it is crucial to develop novel derivative compounds with different mechanisms of action. Based on previous studies reported that inhibition activities of several synthesized new derivatives on *C. albicans*, this study investigated the antifungal effects of spirocyclopropane- oxindole derivatives (4a, 4b, and 4c) on clinical *C. albicans* isolates. Oxindole with a fused cyclopropane ring at the C-3 position is one of the new compounds that have several biological activities, such as antiviral, antimicrobial, anticancer and anti-tumor effects, analgesic, antimalarial, anti-inflammatory, treatment of central nervous disorders, etc. [20-23]. Given the limitations of antifungal drugs, the increasing incidence of invasive fungal diseases, and the emergence of antifungal-resistant species, researchers are focusing on the use of different compounds with suitable chemical structures with antifungal activity that can be applied in the future for the formulation and synthesis of new antifungal drugs [12, 24]. The results showed that the difference between MIC means of spirocyclopropane-oxindole derivatives (4a, 4b, and 4c) is significant compared to fluconazole and nystatin. In other words, the antifungal effect of fluconazole and nystatin was higher than spirocyclopropane-oxindole derivatives. Among the three derivatives evaluated, 4a had more antifungal activity, which can be attributed to the presence of the electron-withdrawing chlorine substitution in the para position of the ring (4a), which induces more antifungal activity than when substitution includes the electron-withdrawing group of fluorine or when there is no substitution (H) (4b, 4c) [18]. Rajaraman et al. synthesized a series of seven new spirooxindole derivatives by dipolar 1, 3-cycloaddition and evaluated their antifungal activity against clinical fungal isolates, including *C. albicans*, *Aspergillus niger*, *Aspergillus flavus*, *Cryptococcus neoformans*, and *Fusarium oxysporum* using disc diffusion and broth microdilution methods compare with ketoconazole as a control. 4e derivatives had shown the highest inhibitory activity against *C. albicans* than ketoconazole [25]. In our study, the 4a derivative showed the strongest inhibitory activity against *C. albicans* with mean MIC (12.4 µg/ mL), although the inhibitory activity of the 4a derivative was lower than fluconazole and nystatin (control drugs). Another previous study evaluated the antifungal activity of new polyheterocyclic spiroxindole derivatives against five plant pathogenic fungi (*Rhizoctonia solani*, *Fusarium semitectum*, *Alternaria solani*, *Valsa mali*, and *Fusarium graminearum*) using the mycelial growth rate method in 2015. Polyheterocyclic spiroxindole derivative 53 showed the best inhibitory activity against *F. graminearum* among the evaluated derivatives ($IC_{50}$=3.31 µM) [26]. Similarly, our study confirmed the antifungal activity of spiro-oxindole scaffold derivatives. The difference in the results of the studies can be related to the type of isolates and also the different methodologies.



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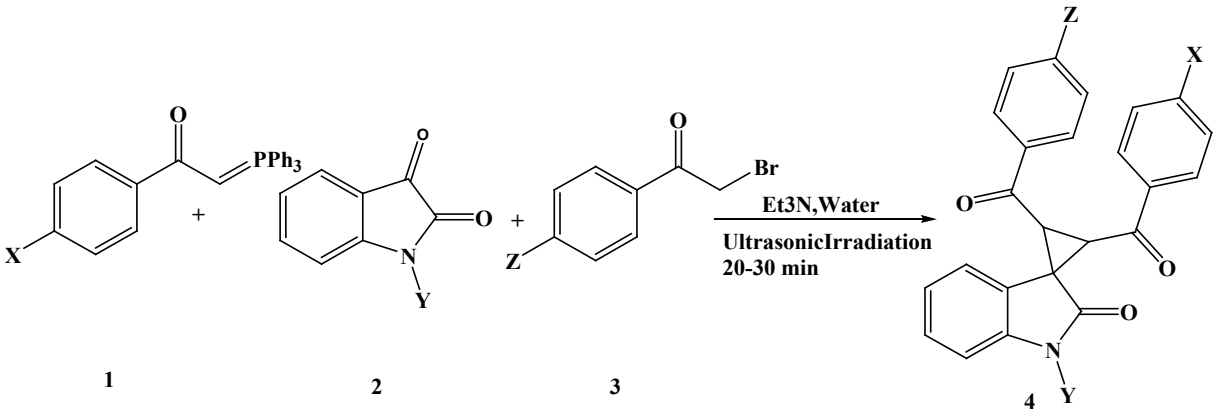



**Figure 1.** Process for synthesis of oxindole-spirocyclopropane derivatives

In vitro, the antifungal activity of eight synthesized spiro-cyclopropane pyrazoles against *C. albicans* and *Saccharomyces cerevisiae* was investigated by Maruoka et al. and the results indicated that all synthesized compounds display moderate to weak antifungal activity against *Candida* and *Saccharomyces*. In line with our study, none of the tested compounds showed superior activity to the antifungal agents as the control drug [10].

There are limited studies that confirmed the antifungal effects of various spiro-oxindole derivatives but other studies also evaluated the anti-bacterial effects of various spiro-oxindole derivatives between 2017 to 2023 that indicated the antibacterial effects of these compounds on various bacteria, including *Mycobacterium tuberculosis*, *Vibrio cholerae*, *Escherichia coli*, *Bacillus subtilis*, *Bacillus licheniformis*, *Pseudomonas fluorescens*, *Salmonella enteric*a, *Shigella flexneri*, and *Shigella boydii* [27-30]. In 2016, Saha et al. demonstrated the anti-leishmanial activity of a spiroxindol scaffold derivative against *Leishmania donovani* in a mouse model [31]. The data of the above studies showed the antifungal, antibacterial, and anti-parasitic activity of the spiro-oxindole scaffold derivatives and some of them exhibited better effects than the standard drugs. However, these results may promise the achievement of medicinal

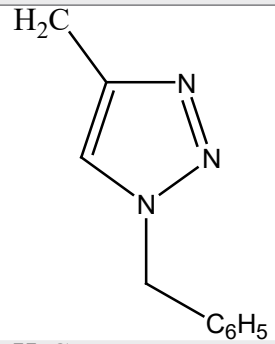
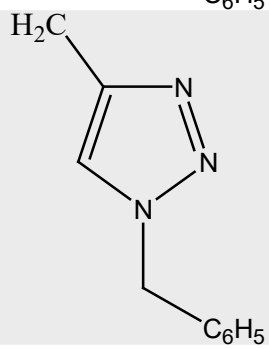
| Structure | y | x | z | Name of the Compound |
|---|---|---|---|---|
| 4a |  | CL | H | 2benzoyl-1-[(1-benzyl-1H-1,2,3-triazol-4yl) methyi]-3-4(4-chlorobenzoyl) spiro[cyclopropane-1,3-indol]-2(1H)-one |
| 4b |  | H | H | 2,3-dibenzoyl-1-[(1-benzyl-1H-1,2,3-TRIAZOL-4yl) methyl] spiro[cyclopropane-1,3-indol]-2(1H)-one |
| 4c | H | F | F | 2-benzoyl-3(4-fluorobenzoyl) spiro[cyclopropane-1,3-indol]-2(1H)-one |

**Figure 2.** Chemical structure of spirocyclopropane-oxindole derivatives (4a, 4b, and 4c)


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**Table 1.** MIC (µg/mL) of fluconazole, nystatin, and spirocyclopropane-oxindole derivatives against clinical *C. albicans* isolates

| Agents | $MIC_{50}$ | $MIC_{90}$ | G Mean | MIC range |
|---|---|---|---|---|
| Fluconazole | 0.125 | 2 | 0.357 | 0.128-8 |
| Nystatin | 0.063 | 0.5 | 0.102 | 0.032-0.5 |
| 4a | 8 | 16 | 10.126 | 4-64 |
| 4b | 64 | 128 | 76.638 | 16-128 |
| 4c | 64 | 128 | 60.547 | 16-128 |

MIC: Minimum inhibitory concentration.

**Table 2.** Central indices and dispersion of MIC in the studied groups

| Agents | Mean±SD | Standard Error Mean | Minimum | Maximum | P |
|---|---|---|---|---|---|
| Fluconazole | 0.778±1.349 | 0.190 | 0.128 | 8 | |
| Nystatin | 0.166±0.166 | 0.023 | 0.032 | 0.5 | |
| 4a | 12.4±10.069 | 1.42 | 4 | 64 | <0.05 |
| 4b | 88.0±40.663 | 5.75 | 16 | 128 | |
| 4c | 76.48±46.314 | 6.54 | 16 | 128 | |

compounds with spiro-oxindole scaffolds for microbial and fungal diseases.

## Conclusion

Even though the antifungal activity of spirocyclopropane-oxindole derivatives (4a, 4b, and 4c) was confirmed against clinical isolates of *C. albicans*, antifungal effects were lower in comparison to fluconazole and nystatin. According to the confirmation of the antimicrobial effects of these derivatives in previous studies, the antifungal activities of these derivatives can be enhanced with further investigations and by constructive changes such as replacing chlorine in Ortho and Meta positions or other positions.

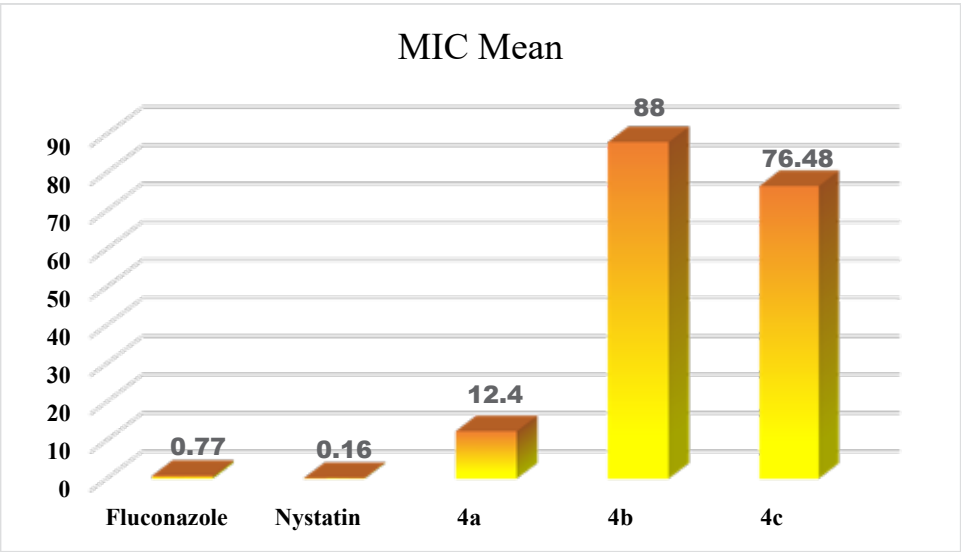


**Figure 3.** MIC mean of fluconazole, nystatin, and spirocyclopropane-oxindole derivatives against *C. albicans* isolates



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## Ethical Considerations

### Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of Babol University of Medical Sciences (Code: IR.MUBABOL.HRI.REC.1402.041).

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### Authors' contributions

Conceptualization and study design: Mojtaba Taghizadeh Armaki, Pouria Rafati and Asieh Khalilpour; Experiments: Pouria Rafati, Jalal Jafarzade, Akbar Hoseinnejad, and Asieh Khalilpour; Data analysis: Akbar Hoseinnejad; Resources: Firoozeh Kermani and Asieh Khalilpour; Writing: Mojtaba Taghizadeh Armaki, Asieh Khalilpour, and Firoozeh Kermani.

### Conflict of interest

The authors declared no conflict of interest.

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