



Antifungal Activity of New Acetophenone Derivatives

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Abstract

The emergence of antifungal resistance among *Candida* species has created an urgent need to develop new antifungal agents. In this study, four newly synthesized organic compounds: 4-(3-methoxyphenyl)-2,6-diphenylpyridine (I), 4''Nitro-5'-oxo-N-phenyl-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxamide (II), (2,4-bis(3-methoxyphenyl)-6-phenylcyclohexane-1,3-diyl)bis(phenylmethanone) (III) and 4''-methoxy-5'-oxo-N-phenyl-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxamide (IV) were evaluated for their antifungal activity against three clinically relevant *Candida species*: *Candida albicans* BDU MI – 44 and *C. guilliermondii*. BDU-217, *C. tropicalis* BDU LK-30. Antifungal efficacy was assessed by agar well diffusion method, and results were expressed as zones of inhibition (mm). All tested compounds exhibited inhibitory activity against *C. albicans*. Compounds I, II, and IV exhibited 1.2-1.3-fold greater inhibitory activity than compound III. Compound III was also active against *C. guilliermondii*, while the remaining compounds were inactive. None of the compounds exhibited inhibitory activity against *C. tropicalis*. These results indicate that acetophenone derivatives I, II, and IV possess selective antifungal activity, offering potential for further development as inhibitory agents against *Candida albicans* infections.

Keywords: Antifungal Activity; Acetophenone Derivatives; *Candida* Species

Introduction

The genus *Candida* comprises a group of opportunistic fungi that causes a wide range of infections, from superficial mucosal candidiasis to life-threatening systemic candidemia [1]. *Candida albicans*, the most common species isolated from clinical specimens, causes mild to severe infections of the skin, nails, and mucous membranes in individuals with normal immune defenses and serious deep-seated infections in debilitated hosts [2]. The increasing prevalence of antibiotic resistance, coupled with a limited arsenal of effective antifungal agents, highlights the urgent need for new compounds with potent and specific activity against

Candida species [3]. For this purpose, derivatives of furan [4], pyrazoline [5], chalcone and hydroxychalcone [6,7], dihydroxypyridine [8], cyanodioxypentene [9], monocyclic and spirocyclic cyclohexane [10], phospholipids [11], etc. were tested. Acetophenone derivatives are effective synthons for the development of new heterocycles and cyclohexane derivatives with valuable pharmaceutical properties, including antimicrobial, antibacterial, antifungal, anticancer, antituberculosis, antiviral, anti-inflammatory, and antihyperglycemic activities, among others [12]. Evaluation of the antifungal activity of new acetophenone derivatives against *Candida* species is crucial for identifying potential drug development candidates.

This study is devoted to the evaluation of the antifungal activity of four new acetophenone derivatives: 4-(3-methoxyphenyl)-2,6-diphenylpyridine (I), 4''nitro-5'-oxo-N-phenyl-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxamide (II), (2,4-bis(3-methoxyphenyl)-6-phenylcyclohexane-1,3-diyl)bis(phenylmethanone) (III) and 4''-methoxy-5'-oxo-N-phenyl-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxamide (IV) against strains of the genus *Candida*.

Materials and Methods

New acetophenone derivatives: 4-(3-methoxyphenyl)-2,6-diphenylpyridine (I), 4''nitro-5'-oxo-N-phenyl-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxamide (II), (2,4-bis(3-methoxyphenyl)-6-phenylcyclohexane-1,3-diyl)bis(phenylmethanone) (III) and 4''-methoxy-5'-oxo-N-phenyl-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxamide (IV) were obtained from the Department of Petrochemical Synthesis of Baku State University. Fungal strains: *Candida albicans* BDU MI-44, *Candida guilliermondii* BDU-217, and *Candida tropicalis* BDU LK-30 were obtained from the culture collection of the Microbiology and Virology Laboratory of Baku State University. The fungi were cultivated on Sabouraud dextrose agar medium (Biolab, Hungary).

The antifungal activity of these compounds was tested in vitro at a concentration of 0.3% using the agar diffusion method [13]. Dimethyl sulfoxide (DMSO) was used as a solvent for organic compounds. One hundred microliters of a fresh 24-hour culture suspension (3.5 McFarland) of each test strain were aseptically distributed over the surface of the agar medium. Then, 8-mm diameter wells were made in the agar, each filled with 150 microliters of a 0.3% solution of the test compound. Antifungal activity was assessed by

measuring the diameter (in millimeters) of the inhibition zone formed around the wells after incubation at 30°C for 24-48 hours. Fluconazole and DMSO were used as positive and negative controls, respectively.

Zones of inhibition are presented as mean \pm SD for each *Candida* species. Differences among treatments (compound I- IV and fluconazole) were assessed separately for each species using one-way ANOVA followed by Tukey's post hoc test. P values <0.01 were considered statistically significant.

Results and Discussion

The results showed that acetophenone derivatives I, II, and IV specifically inhibited the growth of *Candida albicans* only. Compound III inhibited the growth of both *Candida albicans* and *C. guilliermondii* to the same extent. The tested compounds had no effect on the growth of *C. tropicalis* (Table 1). Consequently, *Candida albicans* were sensitive to all tested compounds. The antimicrobial activity of compounds I, II, and IV was 1.2-1.3 times greater than compound III. *Candida guilliermondii* was sensitive only to compound III, while *C. tropicalis* was not sensitive to the tested compounds. It should be noted that DMSO, as a negative control, had no effect on the tested yeast strains. Fluconazole, used as a positive control, demonstrated broad-spectrum activity, inhibiting the growth of all three fungal species. Thus, it was shown that the acetophenone derivatives 4-(3-methoxyphenyl)-2,6-diphenylpyridine, 4''nitro-5'-oxo-N-phenyl-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxamide, and 4''-methoxy-5'-oxo-N-phenyl-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxamide have a narrow substrate specificity, in comparison with the antibiotic fluconazole and can be used as a specific inhibitory agent against the fungus *Candida albicans* [14].

Yeasts <i>Candida</i>	№ compounds and zone of inhibition in mm, M \pm m				
	I	II	III	IV	Fluconazole
<i>C. albicans</i>	20.0 \pm 0.7	21.0 \pm 0.3	17.0 \pm 0.7	22.0 \pm 0.8	20.0 \pm 0.8
<i>C. guilliermondii</i>	0	0	17.0 \pm 0.8	0	19.0 \pm 0.8
<i>C. tropicalis</i>	0	0	0	0	16.0 \pm 0.7

Note: I-4-(3-Methoxyphenyl)-2,6-diphenylpyridine; II - 4''Nitro-5'-oxo-N-phenyl-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxamide; III - (2,4-Bis(3-methoxyphenyl)-6-phenylcyclohexane-1,3-diyl)bis(phenylmethanone); IV- 4''-Methoxy-5'-oxo-N-phenyl-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxamide.

Table 1: Antifungal activity of new acetophenone derivatives.

Conclusion

All tested compounds exhibited inhibitory activity against *C. albicans*. The inhibitory activity of compounds I, II, and IV was 1.2-1.3 times greater than compound III. Compound III was also active against *C. guilliermondii*.

None of the tested compounds exhibited inhibitory activity against *C. tropicalis*. Therefore, acetophenone derivatives: 4-(3-methoxyphenyl)-2,6-diphenylpyridine, 4''nitro-5'-oxo-N-phenyl-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxamide and 4''-methoxy-5'-oxo-N-phenyl-2',3',4',5'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxamide specifically

inhibited the growth of the opportunistic yeast fungus *C. albicans* and can be used as a selective inhibitory agent.

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