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SYNTHESIS AND ANTIFUNGAL ACTIVITY OF 3-OXO-2-PIPERAZINYLACETAMIDES

Aim. *Synthesis of 3-oxo-2-piperazinylacetamides and investigation of their antifungal activity.* ***Methods.*** *Organic synthesis, spectral methods (NMR), pharmaceutical screening.* ***Results.*** *A series of new 3-oxo-2-piperazinylacetamides has been synthesized and the screening of their antifungal activity has been performed. N-butyl-3-oxo-2-piperazineacetamide shows antifungal activity against Cryptococcus neoformans comparable with amphotericin B and fluconazole (MIC = 2μg/mL).* ***Conclusions.*** *3-oxo-2-piperazineacetamide moiety has been identified as a promising template to search for novel antimicrobials against Cryptococcus neoformans.*

Keywords: *3-oxo-2-piperazinylacetamides, N-butyl-3-oxo-2-piperazinylacetamide, antifungal activity, Cryptococcus neoformans.*

Introduction

Fungal infections are becoming a growing public health issue, as common pathogens like Candida are developing greater resistance to the available treatments.

Although invasive fungal infections primarily affect severely ill patients and individuals with weakened immune systems, such as people receiving cancer chemotherapy, living with HIV or having undergone organ transplants — recent report estimates a global number of infections in 6.5 million per year resulting in 3.8 million deaths from which approximately 68% are directly caused by these infections [1, 2]. At-risk population is projected to further expand due to conflicts, natural

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disasters, displacement of people and poverty, which all affect individuals and communities on a growing scale [3].

Cryptococcus neoformans, *Candida auris, Aspergillus fumigatus* and *Candida albicans* have been classified as "critical" fungal pathogens based on their resistance to antifungal drugs, lack of scientifically proven diagnostic and therapeutic methods, mortality rates, annual incidence, complications and consequences [4]. Invasive disease mainly occurs in immunocompromised individuals and typically manifests as meningoencephalitis as well as pulmonary cryptococcosis occurring less commonly. Cryptococcal meningitis is estimated to affect 194 000 people annually, resulting in 147 000 deaths (75.8% mortality) [2], and is a major health problem in countries with high HIV prevalence and limited health care facilities.

To date, antifungal drugs of three various classes — polyenes, flucytosine and azoles have found application in clinical practice of treatment of invasive fungal infections caused by *Cryptococcus neoformans* (Fig. 1) [5, 6]. Amphotericin B from the polyenes — the subgroup of macrolide antibiotics was the first antifungal agent isolated in the late 50-ies. It binds with the ergosterol component of the cell wall and forms pores through which monovalent ions: K^+, Na^+, H^+ and Cl^- leak from the cell causing cell death. 5-fluorocytosine (flucytosine) penetrates through the fungal cell with the help of cytosine permease and disrupts both DNA and RNA metabolism being partially converted into 5-fluorouracil. Azoles like fluconazole have a common mechanism of action, which targets ergosterol biosynthesis in the fungal cells by inhibiting a fungal cytochrome P 450-dependent enzyme — lanosterol 14α-sterol-demethylase.

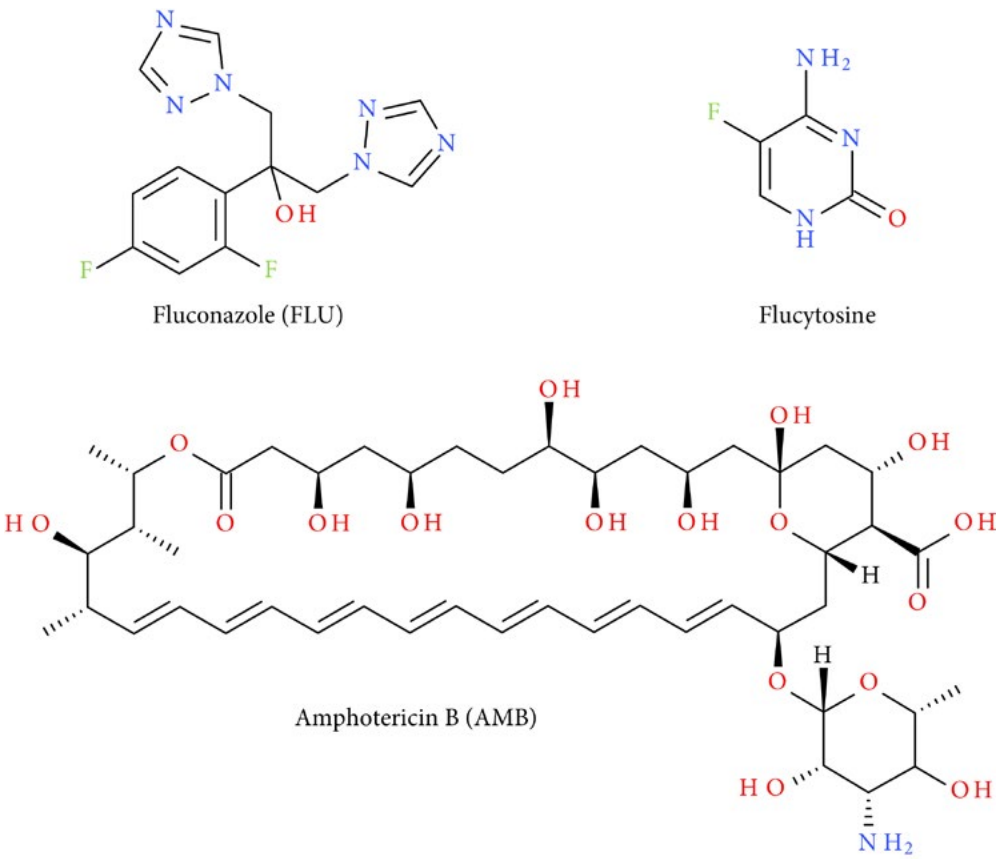
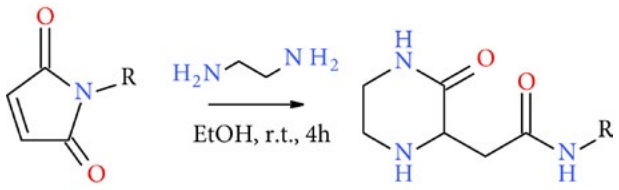


Fig. 1. Basic anticryptococcal drugs



2a-g **1a-g**

a: R = Bu; **b**: R = iBu; **c**: R = 2-BuOC$_6$H$_4$; **d**: R = 2-CF$_3$C$_6$H$_4$;
e: R = CH$_2$CH$_2$C$_6$H$_5$; **f**: R = 2-EtC$_6$H$_4$; **g**: R = 3-MeOC$_6$H$_4$

Fig. 2. General method of syntheses of 3-oxo-2-piperazinylacetamides.

Despite the availability of the other polyenes and azoles in current clinical practice is generally recommended to use for treatment of infections caused by *Cryptococcus neoformans* only the set of three drugs — amphotericin B, flucytosine and fluconazole, that is often even more limited in poor countries. Wide-spread use of limited number of antifungal agents in medicine and agriculture surely leads to development of antifungal resistance [5, 6] and causes the need to search for novel classes of drugs with the other mechanisms of action.

This investigation, planned in the framework of the search for new antifungal agents, is focused on the 3-oxo-2-piperazinylacetamides that demonstrate antibacterial activity [7], but their antifungal activity has not been studied previously.

Materials and Methods

Chemistry

All reagents were purchased from Merck KGaA company (Germany). The solvents were purchased from Macrochim (Ukraine).

Melting points were measured on a Kofler melting point-device and are uncorrected.

Thin layer chromatography was performed on DC-Alufolien Kieselgel 60 F_{254} plates (Merck, Germany) in $CHCl_3$-MeOH 19:1.

^{1}H-NMR spectra were recorded in DMSO-d_6 on Varian Gemini-2000 instrument (400 MHz, Varian, USA) using tetramethylsilane as an internal standard; chemical shifts are given in ppm.

Liquid chromatography — mass spectrometry analysis (LC-MS) was performed on Agilent 1100LC/MSD SL instrument (Agilent Technologies, USA) equipped with Zorbax SB-C18 Rapid Resolution HT Cartridge (2.1 × 30 mm, 1.8 μm) using a 0—100% gradient (2 min) of CH_3CN in 0.1% formic acid.

General procedure for the synthesis of N-substituted 2-(3-oxopiperazin-2-yl)acetamides 1a-g.

These compounds were synthesized by a modified procedure following the general method described previously [8]. To a solution of ethylenediamine (24 mmol) in absolute ethanol (30 mL) was added corresponding N-substituted maleimides **2a-g** (20 mmol) at room temperature and resulting reaction mixture was refluxed for 4 hours. After disappearing of spot of starting **2a-g** on a TLC plate — boiling was stopped and the reaction mixture was cooling at 5 °C overnight. Then crystalline precipitates of N-R-3-oxo-2-piperazinylacetamides **1a-g** were filtered and washed twice with 10 ml ethyl acetate. Recrystallization from 20 ml of mixture: carbon tetrachloride-ethyl acetate (2:1) gave **1a-g** as white crystals.

N-butyl-2-(3-oxopiperazin-2-yl)acetamide (**1a**)

Yield 65%. M.p. 116—118 °C. R_f 0.55. ^{1}H NMR ($CDCl_3$): δ 6.54 (1H, br s, -NH-oxopiperazine), 6.21 (1H, br s, -NH- (Bu)), 3.66 (1H, dd, J_1 = = 5.7 Hz, J_2 = 1.1 Hz, N-CH-CO (oxopiperazine)), 3.15 (2H, q, J = 5.8 Hz, N-CH_2- (Bu)), 2.96 (2H, m, CH_2 (oxopiperazine)), 2.64 (1H, dd, J_1 = 6.4 Hz, J_2 = = 4.5 Hz, CH (oxopiperazine)), 2.47 (4H, m, NH + + 3CH (oxopiperazine)), 1.29 (2H, q, J = 5.4 Hz, -CH_2- (Bu)), 1.21 (2H, q, J = 6.7 Hz, -CH_2- (Bu)), 0.82 (3H, t, J = 5.9 Hz, -CH_3 (Bu)). LC-MS: r.t. 0.18 min *m/z* 214.3 $[M+1]^+$.

N-isobutyl-2-(3-oxopiperazin-2-yl) acetamide (**1b**)

Yield 66%. M.p. 146—148 °C. R_f 0.55. ^{1}H NMR (DMSO-D_6): δ 7.95 (1H, m, -NH- iBu), 7.60 (1H, s, -NH- (oxopiperazine)), 3.43 (1H, dd, J_1 = 4.7 Hz, J_2 = 1.0 Hz, N-CH-CO (oxopiperazine)), 3.08 (2H, m, -CH- (oxopiperazine)), 2.87 (3H, m, N-CH_2

(iBu) + -CH- (oxopiperazine)), 2.72 (2H, m, -CH_2- (oxopiperazine)), 2.58 (3H, m, 3(-CH-) (oxopiperazine)), 2.34 (1H, dd, J_1 = 6.5 Hz, J_2 = 4.7 Hz, -CH- (oxopiperazine)), 1.66 (1H, p, J = 6.4 Hz, -CH- (iBu)), 0.84 (6H, d, J = 6.5 Hz, 2(-CH_3) (iBu)). LC-MS: r.t. 0.18 min *m/z* 214.3 $[M+1]^+$.

N-(2-butoxyphenyl)-2-(3-oxopiperazin-2-yl)acetamide (**1c**)

Yield 64%. M.p. 113—115 °C. R_f 0.53. ^{1}H NMR (DMSO-D_6): δ 10.13 (1H, s, -NHAr), 8.1 (1H, d, J = 8.2 Hz, 3-CH (Ar)), 7.62 (1H, s, -NH- (oxopiperazine)), 6.88 (2H, m, 4,6-CH (Ar)), 6.83 (1H, t, J = 7.4 Hz, 5-CH (Ar)), 3.97 (2H, m, O-CH_2- (OBu)), 3.31 (1H, t, J = 4.7 Hz, -CH- (oxopiperazine)), 3.17 (1H, d, J = 4.5 Hz, -CH- (oxopiperazine)), 3.04 (1H, m, -CH- (oxopiperazine)), 2.87 (1H, t, J = 4.8 Hz, -CH- (oxopiperazine)), 2.72 (1H, dd, J_1 = 4.8 Hz, J_2 = 1.1 Hz, -CH- (oxopiperazine)), 2.66 (1H, dd, J_1 = 4.7 Hz, J_2 = 4.4 Hz, -CH- (oxopiperazine)), 1.78 (2H, p, J = 7.2 Hz, -CH_2- (OBu)), 1.53 (2H, q, J = 6.4 Hz, -CH_2- (OBu)), 0.98 (3H, t, J = 5.9 Hz, -CH_3 (OBu)). LC-MS: r.t. 0.61 min *m/z* 306.4 $[M+1]^+$.

N-[2-(trifluoromethyl)phenyl]-2-(3-oxopiperazin-2-yl)acetamide (**1d**)

Yield 62%. M.p. 133—135°C. R_f 0.64. ^{1}H NMR (DMSO-D_6): δ 10.44 (1H, s, -NHAr), 7.76 (1H, d, J = 8.2 Hz, 3-CH (Ar)), 7.72 (2H, d, J = 8.0 Hz, 6-CH (Ar) + -NH- (oxopiperazine)), 7.65 (1H, t, J = 7.6 Hz, 5-CH (Ar)), 7.38 (1H, t, J = 7.4 Hz, 4-CH (Ar)), 3.56 (1H, m, -CH- (oxopiperazine)), 3.18 (1H, m, -CH- (oxopiperazine)), 3.14 (1H, m, -CH- (oxopiperazine)), 2.84—2.73 (2H, m, 2(-CH-) (oxopiperazine)), 2.67 (1H, m, -CH- (oxopiperazine)). LC-MS: r.t. 0.59 min *m/z* 302.2 $[M+1]^+$.

N-(2-phenylethyl)-2-(3-oxopiperazin-2-yl) acetamide (**1e**)

Yield 66%. M.p. 106—108 °C. R_f 0.59. ^{1}H NMR (DMSO-D_6): δ 8.054 (1H, br s, -NH-phenetyl), 7.59 (1H, s, -NH- (oxopiperazine), 7.29 (2H, d, J = 8.4 Hz, 2(-CH-) (Ar)), 7.22 (3H, m, 3(-CH-) (Ar)), 3.44 (1H, dd, J_1 = 5.8 Hz, J_2 = 1.0 Hz, N-CH-CO (oxopiperazine)), 3.27 (2H, d, J = 6.0 Hz, -CH_2- (phenetyl)), 3.08 (2H, m, 2(-CH-) (oxopiperazine)), 2.90 (2H, d, J = 6.4 Hz, 2(-CH-) (oxopiperazine)), 2.71 (3H, t, J = 6.2 Hz, -CH_2- (phenetyl) + -CH- (oxopiperazine)), 2.56 (1H, dd, J_1 = 6.7 Hz, J_2 = = 1.3 Hz, -CH- (oxopiperazine)), 2.30 (1H, dd, J_1 = = 4.7 Hz, J_2 = 4.3 Hz, -CH- (oxopiperazine)). LC-MS: r.t. 0.59 min *m/z* 262.3 $[M+1]^+$.

N-(2-ethylphenyl)-2-(3-oxopiperazin-2-yl) acetamide (**1f**)

Yield 62%. M.p. 137—139 °C. R_f 0.64. ^{1}H NMR (DMSO-D_6): δ 9.83 (1H, s, -NHAr), 7.71 (1H, s, -NH (oxopiperazine), 7.57 (1H, d, J = 7.8 Hz, 3-CH (Ar), 7.19 (1H, d, J = 7.6 Hz, 6-CH (Ar), 7.14 (1H, t, J = 8.0 Hz, 6-CH (Ar)), 6.88 (1H, t, J = 7.5 Hz, 5-CH (Ar)), 3.56 (1H, d, J = 4.0 Hz, N-CH-CO (oxopiperazine)), 3.21 (H, m, -CH- (oxopiperazine)), 3.14 (1H, m, -CH- (oxopiperazine)), 3.01 (H, m, -CH- (oxopiperazine)), 2.80 (2H, m, -CH- (oxopiperazine)), 2.54 (3H, q, J = 7.6 Hz, -CH_2- (EtAr) + -CH- (oxopiperazine)), 1.14 (3H, t, J = = 7.4 Hz, -CH_3 (EtAr)). LC-MS: r.t. 0.58 min *m/z* 262.3 $[M+1]^+$.

N-(3-methoxyphenyl)-2-(3-oxopiperazin-2-yl)acetamide (**1g**)

Yield 68%. M.p. 163—165 °C. R_f 0.52. ^{1}H NMR (DMSO-D_6): δ 10.04 (1H, s, -NHAr), 7.65 (1H, s, -NH (oxopiperazine), 7.32 (1H, d, J = 3.2 Hz, 2-CH (Ar), 7.19 (1H, t, J = 7.5 Hz, 5-CH (Ar), 7.11 (1H, d, J = 7.8 Hz, 6-CH (Ar)), 6.63 (1H, dd, J_1 = 7.4 Hz, J_2 = 2.6 Hz, 4-CH (Ar)), 3.72 (1H, s, -OCH_3), 3.58 (1H, dd, J_1 = 4.8 Hz, J_2 = 4.0 Hz, N-CH-CO (oxopiperazine)), 3.21 (1H, m, -CH- (oxopiperazine)), 3.10 (1H, m, -CH- (oxopiperazine)), 2.95 (1H, m, -CH- (oxopiperazine)), 2.79 (2H, m, 2(-CH-) (oxopiperazine)), 2.57 (1H, dd, J_1 = 4.4 Hz, J_2 = 4.1 Hz, -CH- (oxopiperazine)). LC-MS: r.t. 0.59 min *m/z* 264.3 $[M+1]^+$.

Antifungal assays

Determination of antifungal activity of the newly synthesized 3-oxo-2-piperazinylacetamides was carried out according to the standard protocols of the Community for Open Antimicrobial Drug Discovery laboratory at The University of Queensland (Australia) with the determination of the minimum inhibitory concentration (MIC) at which complete/partial inhibition of the growth and reproduction of fungi is observed. The experiments used reference test strains of yeast-like fungi (*Cryptococcus neoformans* ATCC 208821). The work was performed using 384-well nonbinding polystyrene plates (Fisher Scientific). Such antimicrobial agents as amphotericin B and fluconazole served as references.

The cultures of yeast-like fungi *C. neoformans* were grown on pure live medium YPD for 72 hours at 30 °C. The culture inoculations were prepared from some (2—5) isolated colonies. The density of the suspension was measured spectrophotometrically (OD_{530}) and adjusted to $1—5 \times 10^6$ CFU/ml.

The minimal inhibitory concentration of the solutions of the tested compounds was determined by serial twofold dilutions. The concentrations of the substances were in the range of 32—0.25 μg/ml. Inoculates of yeast-like fungi in Mueller-Hinton liquid medium with a final suspension density of 2.5×10^3 CFU/ml were added to plates containing appropriate concentrations of compounds. The cultures were incubated without aeration (mixing) for 24 hours at 37 °C.

After 24 hours of incubation, 0.001% resazurin solution was added to the plates with the C. neoformans fungal culture and placed in a thermostat for 2 hours at 35 °C. After incubation, the difference in absorption of light waves by the wells was determined on a Biotek Synergy HTX plate reader at 570—600 nm.

The determination of antimicrobial activity was carried out according to CLSI recommendations, by determining the minimum inhibitory concentration (MIC), at which complete/partial inhibition of fungal growth and reproduction was observed.

In the experiments, antimicrobial agents such as amphotericin B and fluconazole served as comparators. The antibiotics under study were dissolved in water for injection in the appropriate concentrations.

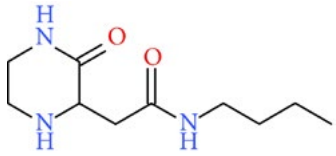
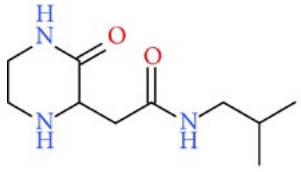
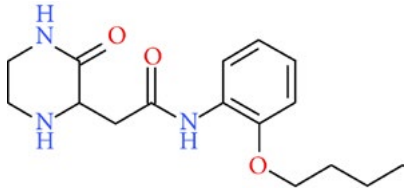
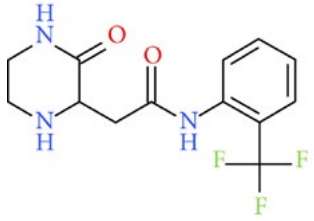
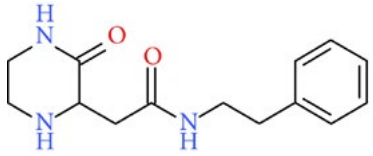
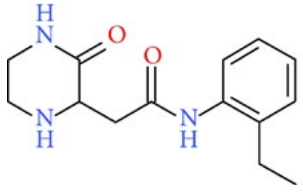
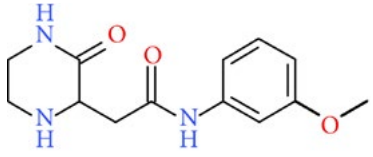
Cytotoxicity assay

HEK293 (human embryonic kidney) cells ATCC CRL-1573 were counted manually in a Neubauer hemocytometer and then plated in 384-well tissue culture plates (Corning 3712) containing compounds to obtain a density of 500 cells/well in a final volume of 50 μl. DMEM supplemented with 10% FBS was used as the culture medium and the cells were incubated with the compounds for 20 hours at 37 °C in 5% CO_2. Cytotoxicity (or cell viability) was measured by fluorescence, ex: 560/10 nm, em: 590/10 nm (F560/590), after addition of 5 μl of resazurin at a concentration of 25 μg/ml (final concentration 2.3 μg/ml) and incubation for an additional 3 hours at 37 °C in 5% CO_2. Fluorescence intensity was measured with a Tecan M1000 Pro plate reader monochromator using automatic gain calculation. CC_{50} (concentration at 50% cytotoxicity) was calculated by fitting the inhibition values against logarithm (concentration) using a sigmoidal dose-response function with variable fit values for the bottom, top and slope.

Hemolysis assay

Human whole blood was washed three times with 3 equal volumes of 0.9% NaCl and then resuspended in it to a concentration of $0,5 \times 10^8$ cells/ml, as determined by manual cell counting in a Neubauer hemocytometer. The washed cells were then added to 384-well polystyrene plates (Corning 3657) to a final volume of 50 μl. After 10 min of shaking on a shaker, the plates were incubated for 1 h at 37 °C. After incubation, the plates were centrifuged at 1000 g for 10 min to pellet cells and other undissolved particles, then 25 μl of the supernatant was transferred to a 384-well polystyrene assay plate (Corning 3680). Hemolysis was determined by measuring the absorbance of the supernatant at 405 mm (OD405).

Antifungal activity (MIC), cytotoxicity (CC_{50}) and hemolytic activity (HC_{10}) of 3-oxo-2-piperazinylacetamides 1a-g

Number	Compound structure	MIC, μg/mL Cn	CC_{50}, μg/mL, Hek	HC_{10}, μg/mL RBC
1a		2	>32	>32
1b		>64	n.d.	n.d.
1c		>64	n.d.	n.d.
1d		>64	n.d.	n.d.
1e		>64	n.d.	n.d.
1f		>64	n.d.	n.d.
1g		>64	n.d.	n.d.
	AMB	1.56		
	FLU	8		

Cn — *Cryptococcus neoformans* H99 ATCC 208821; Hek — HEK293, human embryonic kidney cells ATCC CRL-1573; RBC — human red blood cells; n.d. — not determined; AMB — amphotericin B; FLU — fluconazole.

Absorbance was measured using a Tecan M1000 monochromator for plate reading. HC10 (concentration causing 10% haemolysis) was calculated by fitting the inhibition values against logarithm (concentration) using a sigmoidal dose-response function with variable fit values for the top, bottom and slope. The use of human blood (obtained from the Australian Red Cross Blood Service) for haemolysis assays was approved by The University of Queensland Institutional Human Research Ethics Committee, Approval Number 2014000031.

Results and Discussion

Chemistry

We have synthesized seven new 3-oxo-2-piperazinylacetamides **1a-g** by reaction of ethylenediamine with N-substituted maleimides **2a-g** with a yield of 62—68% following a general method described earlier [8]. Addition of ethylenediamine to a double bond of maleimide proceeds readily with immediate recyclization of pyrrolidine-2,5-dione ring into the 3-oxo-2-piperazine ring (Fig. 2).

Antifungal activity

The biological activity of the synthesized 3-oxo-2-piperazinylacetamides **1a-g** was assessed through primary screening against *Cryptococcus neoformans*. The obtained data are shown in Table.

The study demonstrates that only *N*-butyl-3-oxo-2-piperazinylacetamide **1a** inhibits the growth and reproduction of *C. neoformans*, with a recorded MIC of 2 μg/ml, surpassing the effectiveness of the reference drug fluconazole, which has a MIC of 8 μg/ml. Besides, *N*-butyl-3-oxo-2-piperazinylacetamide **1a** has no cytotoxic or hemolytic effects, suggesting minimal side effects on the host organism. The other six tested 3-oxo-2-piperazinylacetamides **1b-g** do not demonstrate anticryptococcal activity showing MIC less than 64 μg/ml.

Conclusions

The preliminary screening of the newly synthesized 3-oxo-2-piperazinylacetamides having been performed to assess their antifungal and toxic properties revealed one promising compound, N-butyl-3-oxo-2-piperazinylacetamide **1a**. This compound exhibits significant antifungal activity against *C. Neoformans* and has no cytotoxic or hemolytic effects.

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СИНТЕЗ ТА ПРОТИГРИБКОВА АКТИВНІСТЬ
3-ОКСО-2-ПІПЕРАЗИНІЛАЦЕТАМІДІВ

Мета. Синтез 3-оксо-2-піперазинілацетамідів та дослідження їхньої протигрибкової активності. ***Методи.*** Органічний синтез, спектральні методи (ЯМР), фармацевтичний скринінг. ***Результати.*** Синтезовано серію нових 3-оксо-2-піперазинілацетамідів та проведено скринінг їхньої протигрибкової активності. N-бутил-3-оксо-2-піперазиналацетамід виявив протигрибкову активність відносно *Cryptococcus neoformans* (МІК = 2 мкг/мл) порівнювану з амфотерицином Б та флуконазолом. ***Висновки.*** 3-оксо-2-піперазиналацетамідний фрагмент було ідентифіковано як перспективну основу для пошуку нових антимікробних засобів проти *Cryptococcus neoformans*.

***Ключові слова*:** 3-оксо-2-піперазиналацетаміди, N-бутил-3-оксо-2-піперазиналацетамід, протигрибкова активність, *Cryptococcus neoformans*.