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Synthesis of some 1-(2,4-dihydroxythiobenzoyl)imidazoles, -imidazolines and -tetrazoles and their potent activity against *Candida* species

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Abstract

Various 1-(2,4-dihydroxythiobenzoyl)imidazoles, -imidazolines and -tetrazoles were synthesized and evaluated for their in vitro antifungal activity. Compounds were prepared by the reaction of sulfinyl-bis-(2,4-dihydroxythiobenzoyl) with properly substituted azoles. The MIC values against the *Candida albicans ATCC 10231* strain, the azole-resistant clinical isolates of *C. albicans* and non-*Candida* species were determined. Tetrazole derivatives were the most active against *C. albicans*, imidazoline derivatives against non-*Candida* species. All compounds showed higher activity than that of comparable drugs.

Keywords: 2,4-Dihydroxythiobenzoylderivatives of imidazoles; Imidazolines and tetrazoles; Antimycotic activity; In vitro studies

1. Introduction

During the past two decades, the frequencies of invasive and systemic fungal infections have increased dramatically in the population with altered immunity [1]. Therefore the need for accelerated development of new and more effective as well as less toxic antifungal agents, especially for treating systemic infections has appeared. In antimycotic pharmacotherapy commonly N-substituted azoles are applied. The first group of these drugs were imidazole derivatives like ketoconazole, clotrimazole, bifonazole, miconazole replaced by triazole derivatives (fluconazole, itraconazole, saperconazole). The widespread use of fluconazole for extended periods is responsible for development of fluconazole- and other azole-resistant isolates. For these reasons the effort to synthesize new classes of antifungal agents has been made [2]. At the same time various attempts have been undertaken to modify the structures of so far effective azole drugs in order to improve their antifungal potency and selectivity [3–7]. In this way the newest of the second generation triazole antimycotics were obtained: Voriconazole (UK-109496) and ravuconazole (BMS-207147) as the results of synthetic programme aimed at improving the potency and spectrum of fluconazole and posaconazole (SCH-56592) as analogue of itraconazole [8,9].

Thioamide derivatives obtained by us with 2,4-dihydroxythiobenzoyl moiety like thiobenzanilides substituted in the aniline ring, different N-heterocyclic thiobenzamides, amidrazones, hydrazines, hydrazides, hydrazones, semicarbazides exhibited valuable antimycotic properties against dermatophytes, moulds, yeasts and phytopathogenic fungi [10–14]. Bacteriostatic properties of some chemicals were also confirmed [15].

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Preliminary toxicological studies of some compounds did not show strong toxic actions (acute toxicity, cytotoxicity) [16,17]. Therefore the synthesis of other groups of compounds with 2,4-dihydroxythiobenzoyl moiety including azoles was worked out. Research of new compounds from the *N*-(2,4-dihydroxythiobenzoyl)azoles group also justifies application of *N*-acylimidazoles analogues in order to confine development of various mould fungi (*Aspergillus niger*, *Penicillium italicum*, *Fusarium oxysporum*), yeast-like (*Sacharomyce cerevisiae*) or mildew (*Ustilago maydis*) [18]. As follows from the literature data, properties of this kind of imidazole derivatives depend on geometry of substitution. Usually the electron-acceptor substituent at N-1 of the geometrical formula sp^2 intensifies antifungal properties of the azole ring [19].

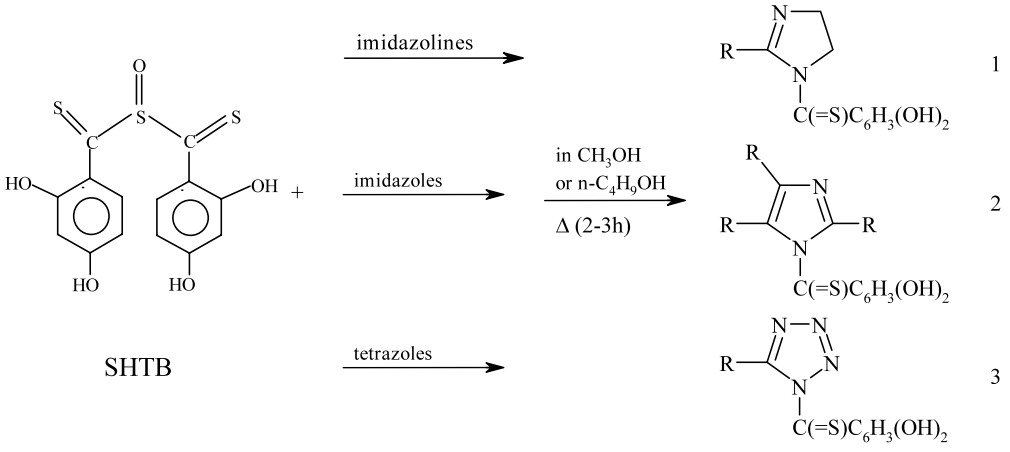
The paper presents synthesis and antimycotic activity of 1-(2,4-dihydroxythiobenzoyl)azoles. In the synthesis made according to the substitution reaction mechanism five-member azole derivatives were used (attack of thioacylating reagent on the nitrogen atom of ring). Heterocyclic chemicals were represented by properly substituted imidazoles, imidazolines or terazoles. Studies of antifungal activity of the compounds in vitro conditions against the reference strain *Candida albicans ATCC 10231*, the azole-resistant clinical isolates of *C. albicans* and non-*C. albicans* species were carried out. As the reference system itraconazole and fluconazole were used. Looking for the SAR dependence, the main aim was to determine the effect of direct binding of thiocarbonyl pharmacophore to the nitrogen atom of heterocyclic ring on the action against the *Candida* species and their partial functions.

2. Chemistry

1-(2,4-Dihydroxythiobenzoyl)imidazoles, imidazolines and tetrazoles were prepared from sulfinyl-bis-(2,4-dihydroxythiobenzoyl) (SHTB) and commercially available heterocyclic compounds (Scheme 1). SHTB was obtained from 2,4-dihydroxythiobenzoic acid and $SOCl_2$ according to patent [19]. Release of 2,4-dihydroxythiobenzoyl carbocations ($C_6H_3(OH)_2CS^{\oplus}$) from SHTB as a result of solvolysis and thioamide bond formation is asynchronic and occurs without the change of carbon atom hybridisation of thiocarbonyl moiety.

Spectroscopic and chromatographic (HPLC) data confirm the fact that despite differentiated nucleophilicity of nitrogen atoms of di- and tetrazoles rings, the attack of electrophilic reagent is unidirectional. Limitation of probable contribution of anular isomers in the reaction depends on property of azole ring and additionally, on effects caused by present substituents in this ring. In the reactions of imidazoles and imidazolines at poor π-electron excessiveness of the rings, the donor effect of pyroline nitrogen atom stabilized with the substituents α is stronger than that of pyridine nitrogen [20]. In the reagents of compounds **3a** and **3b** this does not depend on the kind of substituent at C-5. In one case the 4-chlorophenyl substituent decreases basicity of =N– atom, and in the other tautomeric stabilization of the form 1H– through the hydrogen bond is decisive. Additionally, despite the increased π-acceptor character of 1,2,3,4-azole molecules, there appears greater probability of equilibrium shifts in the substituted rings with the conditional transfer of unstable bonded carbocations $C_6H_3(OH)_2CS^{\oplus}$ from other centres of nucleophilicity to N-1 [21].

Interpretation of ^1H NMR spectra was confined mainly to readable bands of protons at heteroatoms (in the area of low fields) as well as signals of alkyl protons (in the case of their presence). Interpretation of complex multiplets of aromatic and heteroaromatic ring protons was neglected. Independent of conditions of MS spectra recording parent ions M^+ of compounds are unstable. Structure of compounds was confirmed from the course of their fragmentation (line intensities vary



Scheme 1. Synthesis scheme of 1-(2,4-dihydroxythiobenzoyl)imidazoles, -imidazolines and -tetrazoles.

with the change of temperature), elemental analysis and spectroscopic spectra.

3. Experimental

3.1. Analytical investigations

Melting point measures on a Boetius apparatus are given uncorrected. Elemental analysis was performed in order to determine C, H and N contents (Perkin–Elmer 2400 analyser). Analyses (C, N, H) were within ±0.4% of the theoretical values.

^{1}H NMR spectra were made using a Varian 200 or a Bruker 500 spectrometer, with TMS as an internal standard, solutions in DMSO-d_6. All chemical shifts are quoted in δ values (ppm). The infrared spectra were recorded with a Perkin–Elmer FT-IR 1725X spectrophotometer using KBr discs. The spectra were made in the range of 600–4000/cm^{-1}.

The spectra MS (EI-70 eV) were recorded using a AMD-604 spectrometer. The spectra of compound **1a** were taken by means of the ionisation method LSIMA (NBA 80-1300, NaOAc) using the resolving power HR for M^+, $M+H^+$ and $M+Na^+$.

3.2. Chromatography investigations

The purity of the compounds was checked by liquid chromatograph (Knauer) with a dual pump, a 20 μl simple injection valve and UV–Vis detector (320 nm). Hypersil BDS C18 (5 μm, 150 × 4.6 mm) column was used as the stationary phase. The mobile phase consisted of different content of methanol and 10 mM acetate buffer (pH 4) as the aqueous phase. The flow rate was 0.5 ml/min at room temperature. The column dead time was determined by the injection of small amount of acetone dissolved in water.

3.3. Synthesis of compounds

3.3.1. 2-(1-Naphtylmethyl)-1-(2,4-dihydroxythiobenzoyl)-2-imidazoline (*1a*)

0.025 mol 2-(1-naphtylmethyl)-2-imidazolinium nitrate (Aldrich) and 0.01 mol SHTB with addition of 10 ml pyridine were put into 80 ml methanol and heated to boiling (10 h). The mixture was hot filtered, 100 ml water were added to the filtrate. The removed oleiferous product was washed by water and crystallized from methanol (50 ml).

M.p. 113–114 °C; HPLC: $\log k = -0.434$; MS (*m*/*z*): 233 $[M+Na]^+$ 211 $[M+H]^+$ (B = 100%), 209, 197, 185, 176, 167, 153, 137, 121, 107, 95, 81 (lack of molecular ion M^+); ^{1}H NMR (DMSO-d_6), δ (ppm): 11.84 (s, 2C–OH), 10.25 (s, 4C–OH), 4.36 (s, CH_2, 2H), 3.25 (m, CH_2CH_2, 4H); IR (/cm^{-1}): 2925, 1672, 1614, 1440 *v* C=N, 1341, 1259, 1161, 1053 *v* C=S. *Anal.* Calc. for $C_{21}H_{18}N_2O_2S$: N, 7.73. Found: N, 8.00.

3.3.2. 2-Phenyl-1-(2,4-dihydroxythiobenzoyl)-2-imidazoline (*1b*)

0.025 mol 2-phenyl-2-imidazoline (Aldrich) and 0.01 mol SHTB were put into 50 ml methanol and heated to boiling (3 h). The mixture was hot filtered and the filtrate was concentrated to dry. The removed compound was crystallized from diluted (2:1) methanol (75 ml).

M.p. 95–97 °C; HPLC: $\log k = -0.464$; EI MS (*m*/*z*): 184, 153, 135, 146, 137, 117 (B = 100%), 104, 97, 90, 77, 72, 57, 41 (lack of molecular ion M^+); ^{1}H NMR (DMSO-d_6), δ (ppm): 11.20 (s, 2C–OH), 10.60 (s, 4C–OH), 3.40 (m, CH_2CH_2, 4H); IR (/cm^{-1}): 2924, 2360, 1594, 1422*v* C=N, 1285, 1169, 1073 *v* C=S. Anal. calcd. for $C_{16}H_{14}N_2O_2S$: N, 9.38. Found: N, 9.11.

3.3.3. 1-(2,4-Dihydroxythiobenzoyl)-2-undecylimidazole (*2a*)

0.025 mol 2-undecylimidazole (Aldrich) and 0.01 mol SHTB were put into 50 ml methanol and heated to boiling (3 h). The mixture was hot filtered and the filtrate was concentrated to dry. The removed compound was crystallized from diluted (5:1) methanol (60 ml).

M.p. 153–155 °C; HPLC: $\log k = -0.220$; EI MS (*m*/*z*): 305, 263, 235, 222, 193, 179, 153, 137, 123, 109, 95, 82 (B = 100%), 69, 54 (lack of molecular ion M^+); ^{1}H NMR (DMSO-d_6), δ (ppm): 11.01 (s, 2C–OH), 9.92 (s, 4C–OH), 2.64–2.49 (m, CH_2, 2H), 1.61–1.28 (m, $(CH_2)_9$, 18H), 0.83 (t, CH_3, 3H); IR (/cm^{-1}): 1663, 1619, 1462, 1339, 1208, 1060 *v* C=S. *Anal.* Calc. for $C_{21}H_{30}N_2O_2S$: N, 7.48. Found: N, 7.15.

3.3.4. 4,5-Diphenyl-1-(2,4-dihydroxythiobenzoyl)-imidazole (*2b*)

0.025 mol 4,5-diphenylimidazole (Aldrich) and 0.01 mol SHTB were put into 50 ml *n*-butanol and heated to boiling (3 h). The mixture was hot filtered and the filtrate was concentrated to dry. The obtained product was dissolved heated in 100 ml 10% Na_2CO_3 and refiltered. After cooling the product was removed from the solution again by acidification with diluted HCl. The removed thick oil was washed with water several times. The removed compound was crystallized from diluted (5:1) methanol (60 ml).

HPLC: $\log k = -0.191$; EI MS (*m*/*z*): 256, 226, 210, 193, 170, 153, 137 (B = 100%), 108, 97, 79, 69, 57, 55 (lack of molecular ion M^+); ^{1}H NMR (DMSO-d_6), δ (ppm): 11.96 (s, 2C–OH), 10.79 (s, 4C–OH); IR (/cm^{-1}): 1663, 1619, 1462, 1339, 1208, 1060 *v* C=S. *Anal.* Calc. for $C_{22}H_{16}N_2O_2S$: N, 7.52. Found: N, 7.69.

*3.3.5. 4,5-Dichloro-1-(2,4-dihydroxythiobenzoyl)-imidazole (**2c**)*

0.025 mol 4,5-dichloroimidazole (Aldrich) and 0.01 mol SHTB were put into 50 ml methanol and heated to boiling (3 h). The mixture was hot filtered and 100 ml water were added to the filtrate. The removed compound was crystallized from diluted (4:1) methanol (50 ml).

M.p. 150–152 °C; HPLC: $\log k = -0.369$; EI MS (*m/z*): 270, 195, 184, 167, 153, 135, 119 (B = 100%), 97, 92, 77, 65, 57, 41, 38 (lack of molecular ion M^+); ^{1}H NMR (DMSO-d_6), δ (ppm): 11.82 (s, 2C–OH), 10.69 (s, 4C–OH); IR (/cm^{-1}): 1666, 1625, 1591, 1511, 1469, 1440 *v* C=N, 1345, 1265, 1208, 1114, 1050 *v* C=S. *Anal.* Calc. for $C_{10}H_6N_2O_2Cl_2S$: N, 9.68. Found: N, 9.59.

*3.3.6. [5-(4-Chlorophenyl)]-1-(2,4-dihydroxythiobenzoyl)-1H-tetrazole (**3a**)*

0.025 mol 5-(4-chlorophenyl)-1H-tetrazole (Lancaster) and 0.01 mol SHTB were put into 50 ml methanol and heated to boiling (3 h). The mixture was hot filtered and the filtrate was concentrated to dry. 40 ml methanol were added and one of the reagents was separated (crystallization). 20 ml water were added to the filtrate, heated to boiling and filtrated. The removed compound was crystallized from methanol.

M.p. 130–132 °C; HPLC: $\log k = -0.449$; EI MS (*m/z*): 320, 288, 260, 244, 200, 184, 153, 137 (B = 100%), 124, 113, 110, 95, 81, 69, 55, 41 (lack of molecular ion M^+); ^{1}H NMR (DMSO-d_6), δ (ppm): 11.83 (s, 2C–OH), 10.74 (s, 4C–OH); IR (/cm^{-1}): 2693, 1625, 1587, 1512, 1470, 1444 *v* C=N, 1344, 1208, 1114, 1049 *v* C=S. *Anal.* Calc. for $C_{14}H_9N_4O_2ClS$: N, 16.84. Found: N, 16.56.

*3.3.7. Ethyl 1-(2,4-dihydroxythiobenzoyl)-1H-tetrazole-5-acetate (**3b**)*

0.025 mol ethyl 1H-tetrazole-5-acetate (Aldrich) and 0.01 mol SHTB were put into 50 ml methanol and heated to boiling (3 h). The mixture was hot filtered and the filtrate was concentrated to dry. The removed compound was crystallized from diluted (2:1) methanol.

M.p. 100–102 °C; HPLC: $\log k = -0.476$; EI MS (*m/z*): 311, 246, 229, 184 (B = 100%), 168, 153, 137, 124, 108, 96, 85, 69, 59, 55, 39; ^{1}H NMR (DMSO-d_6), δ (ppm): 11.85 (s, 2C–OH), 10.70 (s, 4C–OH), 4.19 (q, OCH_2, 2H), 3.68 (s, CH_2, 2H), 1.21 (t, CH_3, 3H); IR (/cm^{-1}): 1717, 1617, 1588, 1559, 1439 *v* C=N, 1392, 1368, 1345, 1268, 1212, 1178, 1155, 1062 *v* C=S. *Anal.* Calc. for $C_{12}H_{12}N_4O_4S$: N, 18.77. Found: N, 18.82.

3.4. Biological investigations

To determine the antifungal activity of compounds they were tested against *Candida* species. Ten azole-resistant fresh clinical isolates of *C. albicans* were used. 40 strains of *C. albicans* taken from the mouth cavity ontocenosis of patients suffering from tumor diseases were used as the selective material. Itraconazole and fluconazole were administered for prophylactic or due to the symptoms of candidase. Ten isolates resistant to drugs (5-fluorocytosine, ketoconazole, amphotericin B, itraconazole, miconazole, fluconazole) as shown by Fungitest® were chosen for dilution-method testing of the compounds. The drug-resistance was 56.7% but to itraconazole and fluconazole 87.5 and 82.5%, respectively. Additionally, the isolate from the American Type Culture Collection (University Boulevard, Manassas), *C. albicans ATCC 10231* was used as the quality control strain. Six isolates of non-*C. albicans* (two isolates of *C. tropicalis*, *C. glabrata, C. krusei, C. paratropicalis, C. tropicalis)* were tested for which drug-resistance by Fungitest® was also determined. Itraconnazole and fluconazole were used as the reference system.

The yeast isolates were identified to the species level by conventional morphological and biochemical methods using the Candi*Select* (Bio-Rad), Fungiscreen 4H (Bio-Rad), Auxacolor (Bio-Rad) tests.

The compounds were dissolved in 1% DMSO. The susceptibility testing was performed by the agar dilution method. For yeasts MICs were determined by the agar dilution procedure according to the National Committee for Clinical Laboratory Standards (NCCLS) reference document M27 [22]. The Sabouraud's medium—SB (Bio-Rad) was used. Starting inocula were adjusted by the spectrophotometric method densitometre (Bio-Merieux) to 1×10^5 CFU/ml. The concentrations of compounds were ranging from 0.025 to 200 μg/mg. The plates were incubated at 37 °C and read after 24 h of incubation. A solvent control was included in each set of assays; the DMSO solution at the maximum final concentration of 1% had no effect on fungal growth. Each measurement was repeated three times. Itraconazole (Pliva, Krakow, Poland) and fluconazole (Janssen-Cilag) tested under the same experimental conditions were used as the reference system.

The Student's *t*-test (two-tailed) was used to compare the mean MIC values. Significance was defined as a *P* value of 0.05. These analyses were performed using a personal computer with a commercially available statistics program STATISTICA 5.0.

4. Results

The synthetic pathway for the compounds under consideration is illustrated in Scheme 1. The structures of derivatives are presented in Table 1. The analytical data of compounds were in agreement with the proposed structures. The purity of compounds was confirmed by HPLC chromatography in the reversed-phase

Table 1
MIC values of compounds and drugs (itraconazole, fluconazole) against the reference strain *C. albicans ATCC 10231* and mean MIC values against ten *C. albicans* strains isolated from the patients on the Sabouraud's medium after 24 h of incubation (μg/ml)

Substance	R			*C. albicans ATCC 10231* MIC [μg/ml]	*C. albicans* isolates ($n = 10$) MIC [μg/ml]	SD[a]	SE[b]
	C-2	C-4	C-5				
1a	α(−$CH_2C_{10}H_7$)	−H	−H	50	50	0	0
1b	−C_6H_5	−H	−H	100	100	0	0
2a	−$CH_2(CH_2)_9CH_3$	−H	−H	50	25	0	0
2b	−H	−C_6H_5	−C_6H_5	50	25	0	0
2c	−H	−Cl	−Cl	50	50	0	0
3a			4-C_6H_4Cl	25	25	0	0
3b			−$CH_2(C{=}O)OC_2H_5$	50	25	0	0
Itraconazole				200	182.5	55.33	17.5
Fluconazole				200	200	0	0

[a] Standard deviation.
[b] Average deviation.

system RP-18, methanol–water. Log k_w values for methanol–water 8:2 v/v mobile phase were given.

Estimation of compounds inhibition action was expressed by the minimal inhibitory concentration values (Tables 1 and 2). For all compounds MICs against the reference strain *C. albicans ATCC 10231* and against 6 clinical isolates of non-*C. albicans* (5 species) were determined. Mean MIC values against 10 clinical isolates of *C. albicans* and 6 non-*C. albicans* were calculated. Taking into account structure of tested compounds, drug-resistant (including fluconazole and itraconazole) *Candida* clinical isolates were used. A similar procedure was applied for fluconazole and itraconazole, as the reference substances.

The MIC values against the reference strain *C. albicans ATCC 10231* and the mean MIC values against the clinical isolates are in the range 25–100 μg/ml. Analogous MIC values for comparable drugs are within 200 μg/ml (Table 1). The most active are the compounds of tetrazole group, particularly compound **3a**, with the values of MIC 25 μg/ml for both the reference strain and the clinical isolates. This activity is four times as large as that of the drugs used. Activity of 1-(2,4-dihydroxythiobenzoyl)imidazoles (**2a**, **2b**, **2c**) is on the average level (25–50 μg/ml). Imidazoline derivatives, particularly compound **1b** are characterized by the weakest activity. However, their doses are smaller than those for fluconazole and itraconazole.

The mean values of MIC for six non-*C. albicans* species are in the range 17.7–50 μg/ml, but for itraconazole and fluconazole 91.7 and 120.8 μg/ml respectively. Actions of individual groups of compounds are differentiated. Imidazoline derivatives, particularly compound **1b** are the most active. However, action of imidazoles is evidently differentiated. The most active in this group is compound **2a**, with hydrophobic,

Table 2
MIC values of compounds and drugs (itraconazole, fluconazole) against non-*C. albicans* species on the Sabouraud's medium after 24 h of incubation (μg/ml)

Strains	Substance MIC [μg/ml]								
	Itraconazole	Fluconazole	**1a**	**1b**	**2a**	**2b**	**2c**	**3a**	**3b**
Candida krusei	100	200	25	12.5	25	50	50	50	50
Candida tropicalis I	50	25	25	12.5	25	50	50	50	50
Candida tropicalis II	50	50	25	12.5	25	50	50	50	50
Candida paratropicalis	200	200	50	50	25	50	50	25	25
Candida species	100	50	25	6.25	25	12.5	50	12.5	12.5
Candida glabrata	50	200	25	12.5	6.25	12.5	50	12.5	12.5
6 isolates of non-*C. albicans* (mean MIC values)	91.7	120.8	29.2	17.7	21.9	37.5	50	33.3	33.3
SD[a]	58.5	87.2	10.2	16.01	7.7	19.4	0	18.8	18.8
SE[b]	41.7	79.2	6.9	10.8	5.2	16.7	0	16.7	16.7

[a] Standard deviation.
[b] Average deviation.

undecyl chain at C-2. Compound **2c** with the electron-acceptor substituents at C-4 and C-5, is the least active in the whole series. Analogously, phenyls substituted compound **2b**, of weaker electron interaction, is characterized by a slightly higher activity level. Tetrazole derivatives (**3a**, **3b**) are characterized by the average action level, independent of the kind of substitutuent at C-5. It seems that the position of electrodonor substituent at C-2, in the imidazoline and imidazole system exerts a positive effect (**1a**, **1b**, **2a**). Sensitivity of individual non-*C. albicans* species is differentiated. *C. spesiec* and *C. glabrata*, are the most susceptible which seems to be quite interesting taking into consideration high MIC values for fluconazole and itraconazole against *C. species*.

It can be generally stated that the compounds under consideration exhibit much stronger fungistatic activity in vitro conditions expressed by MIC values compared with commonly used azole drugs fluconazole and itraconazole. Taking into account the azole-resistant isolates applied in biological tests, stronger action of the obtained compounds results probably from the function of 2,4-dihydroxythiobenzoyl moiety induced by specific interaction of substituted azole rings (not only from the presence of azolyl moiety). It confirms high level of antimycotic activity of some compounds without heterocyclic rings 2,4-dihydroxythiobenzanilides. Some properly substituted hetrocyclic rings intensify the functions of 2,4-dihydroxythiobenzoyl moiety as pharmacophore of antimycotic activity or probably their partial contributions are summed up.

The compounds with the azole ring obtained recently exhibit, as a rule, smaller activity than the initial structures. Analogues of bifonazole with a phenylisoxazolyl or phenylpyrimidinyl moiety or [α-(1,5-disubstituted 1H-pyrazolyl-4-yl)benzyl]azoles exhibit poor antifungal activity [3,4]. 1,2,3,4-Tetrahydroisoquinoline isomers show lower activity against yeasts than the comparable drugs. Activity towards moulds was at the same level for some derivatives [5]. Azole derivatives of 1,4-benzothiazine exhibit also weaker fungistatic properties than fluconazole [6]. However, sulfur analogues (alkylthio and alkylsulfonyl) of the compound designated as SM-8668 (azole derivative) exhibit several times larger activity than that of the same drug [7].

As follows from the above, the substances obtained by us seem to be a group of compounds characterized by an interesting spectrum of antifungal activity. Whereby direct binding of the thioacyl radical ($C_6H_3(OH)_2CS$) with nitrogen atom of the azole ring is more effective than the use of thioacylaminoheterocyclic derivatives (manuscript in preparation). The effect of 2,4-dihydroxythiobenzoylazole moiety on antimycotic activity seems to be comparable with that of 1-phenylazolylethanol pharmacophore characteristic of most azole drugs including fluconazole [6].

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