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Original article

Synthesis and antifungal activity of some substituted phenothiazines and related compounds

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ABSTRACT

Several phenothiazines and related compounds were synthesized and their antifungal activity was evaluated *in vitro*. The results observed for α-chloro-*N*-acetyl phenothiazine led us to choose this compound as a lead in the search of antifungal agents.

1. Introduction

In recent years, the incidence and severity of fungal diseases has increased, particularly in patients with impaired immunity [1]. The growing number of cases of fungi involved in sepsis is a consistent trend [2], being *Candida* the fourth most common isolate in nosocomial bloodstream infections in some developed countries [3]. Furthermore, invasive candidiasis is a problem of growing importance in critically ill patients, such those in intensive care [4]. Besides, the mortality rate due to invasive aspergillosis in neutropenic patients has increased [5]. Superficial mycoses, such dermatophytosis or either infections caused by non dermatophyte agents, are an important cause of morbidity, being more severe in immunocompromised patients. Due to the increase in clinically important fungal infections and the small number of available antifungal agents, as well as to the appearance of antifungal resistance, searching for new, more effective and less toxic drugs is mandatory [6].

Phenothiazines and related compounds, including tranquilizers [7] and drugs with anti-inflammatory [8], antimalarial [9], antipsychotic [10], antimicrobial [11], antitubercular [12,13], antitumor [14–16], antihistaminic [17] and analgesic [18] properties, have found widespread use in medicinal chemistry. Among these, those that act as antihistaminic and antipsychotic agents are the ones most exploited therapeutically. In these compounds, the amino alkyl side chain connected to the nitrogen atom of the heterocyclic unit plays a crucial role in their properties [19,20]. In the last decade, the antifungal properties of some antipsychotic phenothiazine derivatives, such as trifluoroperazine, chlorpromazine and fluphenazine, have been described (Chart 1) [21].

In the course of a research program in medicinal chemistry with the aim to discover phenothiazines with antifungal action alone, we evaluated pipothiazine (PIP), a neuroleptic phenothiazine, promethazine (PMZ), an antihistaminic phenothiazine, and a series of *N*-acyl and *N*-alkyl phenothiazine derivatives. Based on the results observed when evaluating their antifungal activity, some *N*-acyl compounds resulting from isosteric replacements and opening or ring contraction in the phenothiazine core were prepared. Then, with the battery of compounds available, we attempted to establish some structure activity relationships.

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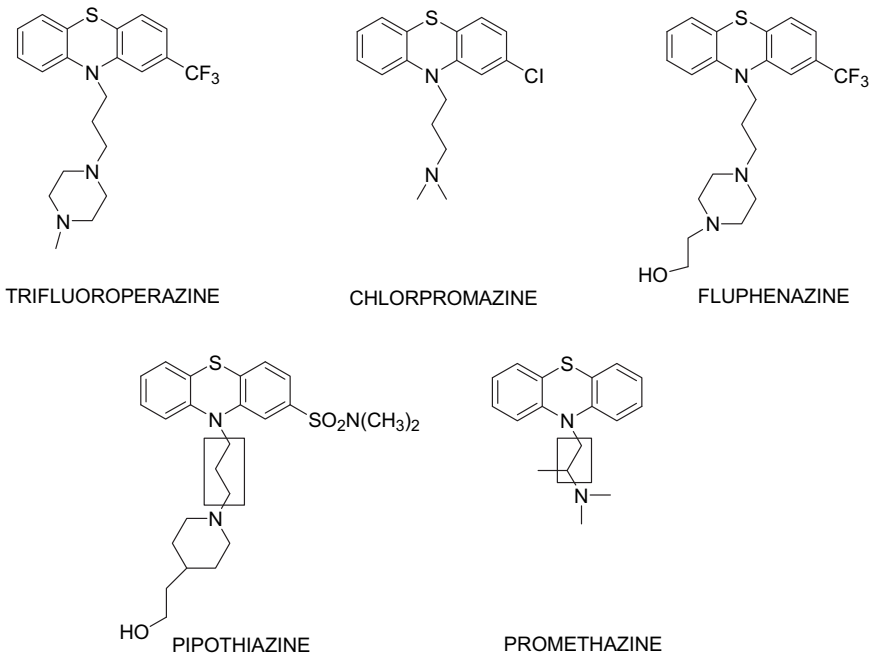


Chart 1. Structures of some antihistaminic and neuroleptic phenothiazines.

2. Chemistry

We have previously described the synthesis of compound **1**, as starting material in the procedure to prepare the neuroleptic compound PIP [22].

Compound **1**, treated with β-Cl-propanoyl chloride, afforded compound **2**, which was reacted with the commercially available compound **3**, to give PIP (Scheme 1).

The *N*-acyl derivatives **2** [22], **4** [22], **6** [23], **7** [24], and **8** (Chart 2) were synthesized using microwave irradiation (MW), with excellent yield and very short times of reaction, starting from the corresponding amines and using β-chloro propanoyl chloride (**2**, **4**), α-chloro acetyl chloride (**6**, **8**) and acetyl chloride (**7**).

N-acyl derivatives **4** and **6** were transformed into the *N*-alkyl compounds **5** and **9** [25] by reduction with borane generated *in situ* (Chart 3).

The *N*-acyl derivatives **10** and **11** [26] were also prepared using MW starting from the corresponding amine and α-chloro acetyl chloride. Compound **12** [27] was synthesized by a conventional procedure using acetyl chloride and carbazole (commercial) (Chart 4).

The nitro compound **13**, previously prepared by us [22], was reduced using $Zn/CaCl_2$, affording compound **14**. Treatment of this amine with α-chloro-acetyl chloride and MW, gave the *N*-acyl derivative **15,** with good yield and very short time of reaction (Scheme 2).

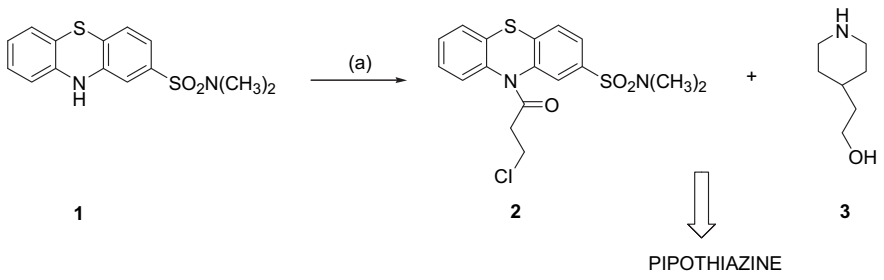
The spectroscopic behavior observed in the ^{1}H-NMR spectra of compounds **2** and **8** showed the diastereotopicity of the hydrogen atoms attached to the methylene carbon in alpha position to the carbonyl group [23], which would indicate the presence of chirality in the phenothiazine system.

3. Results and discussion

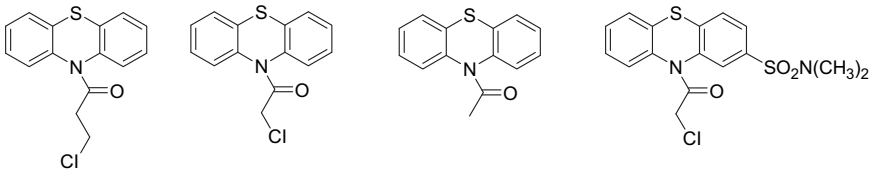
Since the antifungal activity of PIP and PMZ commercially available were evaluated, showed good agreement with that previously described for trifluoperazine, chlorpromazine, and fluphenazine, we decided to evaluate the synthetic precursors of PIP (Scheme 1). Compound **1** showed slight antifungal activity and the synthetic precursors **2** and **3** showed no antifungal properties.

It was observed that the presence of an electron withdrawing group in the 2-position of the tricycle system is essential for neuroleptic activity, so compound **4** was prepared and evaluated as antifungal agent. Neither compound **4** nor its reduced derivative **5** showed antifungal activity.

Given the fact that the length of the carbon chain joined to the N-10 atom is very important in the physiological activity (antihistaminic *vs* antipsychotic) and due to the antifungal activity of PMZ



Scheme 1. Reagents: (a) β-Cl-propanoyl chloride.



4 6 7 8

Chart 2. *N*-acyl phenothiazines prepared.

observed, compound **6** was synthesized and evaluated. Surprisingly, compound **6** was found to be active against different strains of yeasts and molds (Table 1).

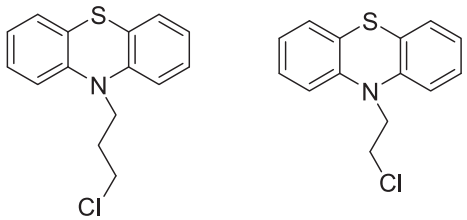
Due to the activity observed in compound **6**, other *N*-acyl (**7** and **8**) and *N*-alkyl (**9**) derivatives were prepared and evaluated. None of these three compounds were active against the strains tested. Finally, with the aim to achieve a better approximation to the structure-activity relationship, some molecules with modifications at different levels of compound **6** were synthesized:

a. Isosteric replacement of sulfur by oxygen atom (**10**).
b. Opening of the phenothiazine system to obtain the corresponding dianiline (**11**) or diphenylthioether (**15**). This compound was obtained from acylation of **14** with α-chloro acetyl chloride.
c. Contraction of the heterocyclic ring (**12**).

The results obtained showed that none of these compounds (**10**, **11**, **12** and **15**) inhibited the growth of the fungi tested.

4. Conclusion

We prepared thirteen phenothiazine derivatives and related compounds and tested the antifungal activity of all the compounds synthesized as well as of commercially available ones, such as PMZ and compound **3**. We found that only PMZ, PIP, and compound **6** showed interesting activity. Compound **6**, the simplest of the compounds tested, showed to be as active as antifungal agents currently used in clinical practice. The open analogs (**11** and **15**) of compound **6** were inactive. Replacement of the sulfur atom by oxygen (**10**) or the elimination of the sulfur atom (**12**) led to loss of activity. We can thus conclude that the phenothiazine ring is necessary for antifungal activity, but only some pattern of substitution in it led to the observed activity. Thus, despite there are not breakpoints for the antifungal drugs, **6** could be a promising drug since the MIC values are some comparable with those observed for the conventional antifungal agents. The most striking finding of this study was the separation of the antifungal effect in compound **6** from the antihistaminic activity of PMZ and from the antipsychotic activity of the PIP, both of which also had antifungal activities.



5 9

Chart 3. *N*-alkyl phenothiazines prepared.

5. Experimental section

5.1. Chemistry

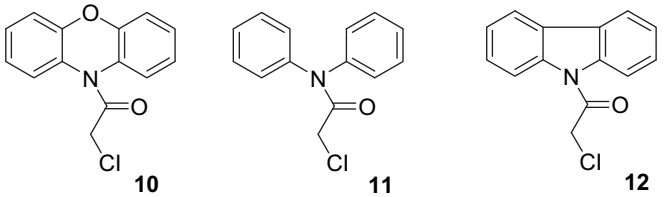
NMR spectra were recorded ($CDCl_3$) on a Bruker AC 300 or on an Avance 500 spectrometers. Shifts reported are relative to the signal of the solvent used in each case and coupling constants are reported in Hz (s: singlet, bs: broad singlet, d: doublet, t: triplet, dd: double doublet, dt: double triplet, m: multiplet). IR spectra were recorded using a Perkin Elmer Spectrum One FT-IR spectrophotometer. High resolution mass spectra were obtained on Bruker micrOTOF-Q II spectrometer. Microwave-assisted reactions were carried out in a household MW oven Electrolux EH-20D. Preparative thin layer chromatography (p-TLC) was done on Merck Silica Gel 60 GF_{254}; and analytical TLC was performed on Merck aluminum sheets Silica Gel 60 GF_{254}. Commercial compounds were purchased Aldrich Chemical Co. THF was distilled from sodium/benzophenone. Melting points are uncorrected and were determined in a Thomas Hoover apparatus. Compound **12**, whose data do not match with those in the literature was described as new compound.

5.1.1. General procedure for obtaining the N-acyl-derivatives (*2*, *4*, *6*, *7*, *8*, *10*, *11*, *15*)

To a solution of 10*H*-phenothiazine (2.62 mmol) in dry toluene (5 mL) was added drop by drop the corresponding acyl chloride (0.5 mL; 6.2 mmol). The reaction was irradiate with MW (500 Watts) during 10 min, then was washed with NaOH 5% (2 × 5 mL) and the organic phase was dry with anhydrous Na_2SO_4. Finally the solvent was remove in vacuo.

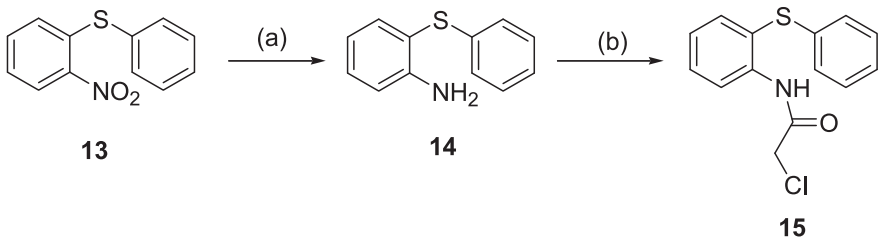
*5.1.1.1. 10-(3-Chloropropionyl)-N,N-dimethyl-10H-phenothiazine-2-sulfonamide **2**.* This compound was obtained as a white solid. It was purified by p-TLC using as eluent hexane:dichloromethane (1:4 v/v). MP: 195–198 °C, yield 62%. The physical and spectroscopic data were consistent with those previously reported in the literature [22].

*5.1.1.2. 10-(3-Chloropropionyl)-10H-phenothiazine **4**.* This compound was obtained as a white solid. It was purified by p-TLC using as eluent hexane:dichloromethane (1:3 v/v). MP: 127–130 °C, yield 91%. The physical and spectroscopic data were consistent with those previously reported in the literature [22].



10 11 12

Chart 4. α-chloro-*N*-acetyl derivatives of phenoxazine, diphenylamine and carbazole.



Scheme 2. Reagents: (a) $Zn/CaCl_2$; (b) α-chloro-acetyl chloride, MW.

*5.1.1.3. 10-(Chloroacetyl)-10H-phenothiazine **6**.* This compound was obtained as a white solid. It was purified by p-TLC using as eluent hexane:dichloromethane (1:3 v/v). Mp: 112-114 C°, yield 92%. The physical and spectroscopic data were consistent with those previously reported in the literature [23].

*5.1.1.4. 10-(Acetyl)-10H-phenothiazine **7**.* It was obtained as a white solid from phenothiazine. It was purified by p-TLC using as eluent hexane:dichloromethane (1:2 v/v). Mp: 196–199 °C; yield 94.5%. The physical and spectroscopic data were consistent with those previously reported in the literature [24].

*5.1.1.5. 10-(Chloroacetyl)-N,N-dimethyl-10H-phenothiazine-2-sulfon amide **8**.* It was obtained as a yellow solid from compound **1** and was purified by p-TLC using as eluent hexane:dichloromethane (1:4 v/v). Mp: 205 °C (d), yield 50%. IR (Nujol, cm^1): 1696 (C═O), 1339 ($SO_2N(CH_3)_2$), 1154 ($SO_2N(CH_3)_2$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.71 (s, 6H, $SO_2N(CH_3)_2$), 4.06 (d, $J = 13.6$ Hz, 1H, -CHHCl), 4.24 (d, $J = 12.8$ Hz, 1H, -CHHCl), 7.27 (dt, $J_o = 7.6$ Hz $J_m = 1.6$ Hz, 1H, Ar), 7.34 (dt, $J_o = 7.6$ Hz $J_m = 1.6$ Hz, 1H, Ar), 7.44 (d, $J = 7.6$ Hz, 2H, Ar), 7.51 (d, $J_o = 8.4$ Hz, 1H, Ar), 7.58 (dd, $J_o = 8.0$ Hz $J_m = 1.6$ Hz, 1H, Ar), 7.97 (d, $J_m = 1.6$ Hz, 1H, Ar) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 165.6, 138.0, 136.9, 134.2, 129.8, 128.6, 128.2, 128.0, 126.6, 126.2, 41.7, 38.1 ppm. HRMS (ESI): calcd for $C_{16}H_{15}O_3S_2N_2ClNa$, 405.0105, found 405.0108.

*5.1.1.6. 10-(Chloroacetyl)-10H-phenoxazine **10**.* It was obtained as a white solid from phenoxazine. It was purified by p-TLC using as eluent hexane:dichloromethane (1:2 v/v). Mp: 140-142 °C, yield 91%. IR (KBr, cm^{-1}): 1675 (C═O).^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.35 (s, 2H, CH_2Cl), 7.14–7.28 (m, 6H, Ar), 7.58 (d, $J = 7.7$ Hz, 2H, Ar) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 41.5, 117.1, 123.7, 124.3, 127.6, 128.5, 150.9, 165.3 ppm. HRMS (ESI): calcd for $C_{14}H_{11}O_2NCl$, 260.0473, found, 260.0482.

Table 1
MICs (μg/mL) values of compounds PIP, PMZ, **6** and those used as reference drugs.

Assayed fungi	Evaluated drugs and calculated MICs (μg/mL)							
	PIP	PMZ	**6**	AMB	FCZ	ITZ	TBF	5FC
C. albicans	256	>512	32	0.5	2	0.125	0.5	2
C. parapsilosis	256	512	32	0.5	1	0.125	0.06	0.5
C. glabrata	256	>512	>512	0.25	1	0.25	0.06	1
C. krusei	512	256	**32**	0.25	**64**	0.06	0.06	0.5
C. guillermondii	256	512	32	1	4	0.5	0.5	1
C. neoformans	256	256	**8**	0.5	**8**	0.25	0.25	0.5
A. fumigatus	>512	256	**16**	0.5	**16**	0.25	0.25	0.5
A. flavus	>512	256	32	0.25	16	0.125	0.25	1
A. niger	>512	256	**2**	0.5	**16**	0.125	0.125	0.5
A. terreus	>512	256	**16**	2	**16**	0.125	0.06	1
C. carrionii	256	512	**4**	1	**8**	0.06	0.25	1
E. spinifera	256	256	**16**	1	**16**	0.06	0.06	2
E. oligosperma	512	256	16	1	8	0.125	0.06	4
E. xenobiotica	512	256	**16**	1	**16**	0.06	0.06	8

*5.1.1.7. 2-Chloro-N,N-diphenylacetamide **11**.* This compound was obtained as a white solid and purified by p-TLC using hexane:dichlorometane (1:3 v/v). Mp: 116–118 °C, yield 90%. The physical and spectroscopic data were consistent with those previously reported in the literature [26].

*5.1.1.8. 2-(N-Chloroacetylamine)-1-phenylthiobenzene **15**.* Compound 2-nitro-diphenylthiobenzene (**13**) [22] (500 mg, 2.16 mmol) was reduced with Zn° (4.6 g) and $CaCl_2$ (155 mg) in ethanol 78% (15.5 mL). The mixture was refluxed during 2 h. Then was filtered and the solvent was removed in vacuo. The amine **14**, obtained as a yellow oil, was purified by p-TLC using as eluent hexane:dichloromethane 1:1, yield 94%. IR (film): 3468 (NH), 3371 (NH). ^{1}H-NMR (300 MHz), $CDCl_3$): δ 4.47 (s, 2H, NH_2), 6.95 (m, 2H, Ar), 7.29 (m, 3H, Ar), 7.41 (m, 3H, Ar), 7.65 (dd, 1H, Ar) ppm. ^{13}C-NMR (75 MHz), $CDCl_3$: δ 114.2, 115.3, 118.7, 125.4, 126.4, 128.9, 131.1, 136.7, 137.4, 148.8 ppm.

The amine **14** was used to prepare compound **15** by the general procedure. Compound **15** was obtained as a white solid and purified by p-TLC using hexane:dichlorometane (1:2 v/v). Mp: 65–66 °C, yield 91%. IR (Nujol, cm^{-1}): 3315 (NH), 1700 (C═O), 1685 (C═N). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.08 (s, 2H, $-CH_2Cl$), 7.09–7.27 (m, 6H, Ar), 7.47 (t, $J = 8.2$ Hz, 1H, Ar), 7.63 (d, $J = 7.7$ Hz, 1H, Ar), 8.4 (d, $J = 8.2$ Hz, 1H, Ar), 9.5 (s, 1H, NH) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 43.0, 120.7, 121.5, 125.2, 126.4, 127.6, 129.2, 130.8, 135.2, 136.6, 138.7, 163.9 ppm. HRMS (ESI): calcd for $C_{14}H_{12}ONSClNa$, 300.0220, found, 300.0231.

*5.1.2. 10-(Chloroacetyl)-10H-carbazole **12***

To a solution of carbazole (400 mg, 2.39 mmol) in dry DMF (4 mL) was added drop by drop α-chloro acetyl chloride (0.95 ml). The reaction was maintaining to 80 °C for 2 d. The solvent was remove in vacuo and the reaction mixture was treated with a solution of NaOH 5% and extracted with dichloromethane (3 × 10 mL). Then the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by p-TLC using as eluent hexane:dichloromethane (1:1 v/v). Compound **12** was obtained as a white solid. Mp: 88–92 °C, yield 90%. IR (KBr, cm^{-1}): 1699 (C═O). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.72 (s, 2H, CH_2Cl), 7.45 (t, $J = 10$ Hz, 2H, Ar), 7.55 (t, $J = 10$ Hz, 2H, Ar), 8.03 (d, $J = 10$ Hz, 2H, Ar), 8.2 (d, $J = 10$ Hz, 2H, Ar) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 44.9, 116.2, 120.0, 124.4, 126.7, 127.6, 137.9, 165.6 ppm. HRMS (ESI): calcd for $C_{14}H_{11}ONCl$, 244.0524, found, 244.0530.

*5.1.3. General procedure for obtaining the N-alkyl-derivatives (**5**, **9**)*

Borane gas was generated from a mixture of $NaBH_4$ (1.6 g) in diethylene glycol dimethyl ether (6 mL) and trifluoroboroetherate (5.4 mL) was bubbled on the corresponding *N*-acyl-derivative (0.91 mmol) in dry THF (10 mL). Then the solution was stirred during 72 h at room temperature. After that, the solution was adjusted to pH = 8 by slowly adding of 1N HCl and the product was

extracted with several portions of dichloromethane. The organic extract was dried with anhydrous Na_2SO_4 and the solvent was removed in vacuo and was purified by p-TLC.

5.1.3.1. 10-(3-Chloropropyl-)-10H-phenothiazine ***5***. It was obtained as a green solid and purified by p-TLC using hexane:dichlorometane (1:1 v/v). Mp: 60–61 °C, yield 88%. IR (KBr, cm^{-1}): 1284 (C–N), 1252 (C–N). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.24 (m, 2H, C–CH_2–C), 3.68 (t, $J = 6.2$ Hz, 2H, –N–CH_2–C), 4.11 (t, $J = 6.6$ Hz, 2H, –CH_2–Cl), 6.93 (m, 4H, Ar), 7.19 (m, 4H, Ar) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ 29.6, 42.4, 44.0, 115.6, 122.8, 125.7, 127.3, 127.6, 145.0 ppm. HRMS (ESI): calcd for $C_{15}H_{14}NSClNa$, 298.0427, found, 298.0428.

5.1.3.2. 10-(2-Chloroetyl)-10H-phenothiazine ***9***. This compound was obtained as a green solid and was purified by p-TLC using as eluent hexane:dichloromethane (1:1 v/v). Mp: 94–95 °C, yield 85%. The physical and spectroscopic data were consistent with those previously reported in the literature [25].

5.2. Antifungal activity

Compounds described above (**1**–**12** and **15**) were evaluated by diffusion methodology as screening. From all, halo of inhibition was observed only for PIP, PMZ, compound **1** and **6**. Then, the antifungal activity of these four compounds and several antifungal agents in clinical use against yeasts and molds were evaluated following the CLSI (Clinical and Laboratory Standards Institute) guidelines (formerly NCCLS), document M27A2 and M38A2 [28,29]. The drugs evaluated were: amphotericin B (AMB), itraconazole (ITZ), fluconazole (FCZ), terbinafine (TBF), flucytosin (5FC), PIP, PMZ, compound **1** and compound **6**. The assayed yeasts were: *Candida albicans*, *Candida parapsilosis*, *Candida glabrata*, *Candida krusei*, *Candida guillermondii*, *Cryptococcus neoformans*. The filamentous fungi included: *Aspergillus fumigates*, *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus nidulans*, *Aspergillus terreus*, *Cladophialophora carrionii* and black yeasts: *Exophiala spinifera*, *Exophiala oligosperma*, *Exophiala xenobiotica*. Briefly fungi were growth onto Saboureaud glucose agar, during 2 days for yeasts and up to 7 days for the molds. For each drug, stock solutions were prepared and diluted in the appropriate solvent to be inoculated into 96-well-flat-bottom micro titer plates. Fungi inoculum was prepared according with the CLSI and inoculated into the plates. Final inoculums for yeasts was $0.5–5 \times 10^3$ CFU/ml, and for filamentous fungi $0.5–5 \times 10^4$ CFU/ml. After incubation at 30 °C, spectrophotometer and visual reading were determined in order to obtain the minimal inhibitory concentration (MIC) for each strain and each drug.

Compound 1 was tested against all strains. Halo of inhibition was observed by diffusion test, but, when microdilution was performed, all strains showed MICs >512 ug/ml, indicating lacking of activity. Activity was observed for PIP and PMZ at concentrations ranged from 128 to 512 ug/ml, with the exception of *Aspergillus* species for PIP showed MIC > 512 ug/ml. Interesting was to observe the higher activity of compound **6** compared with those described above. For this drug the range was from 2 to 32 ug/ml, except for *C. glabrata*, for which MIC of >512 ug/ml was detected. All data is summarized in Table 1.

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