Medicinal Chemistry Research
https://doi.org/10.1007/s00044-020-02636-y

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Antifungal activity of aminoalcohols and diamines against dermatophytes and yeast

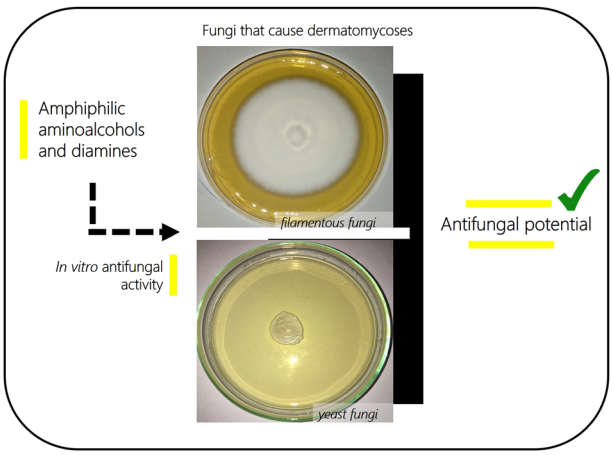
César A. Caneschi[1] · Bruno A. de Oliveira[2] · Angelina M. de Almeida[2] · Renata P. do Carmo[1] · Francislene J. Martins[1] · Mauro V. de Almeida[2] · Nádia R. B. Raposo[1]

Received: 4 June 2020 / Accepted: 12 September 2020

Abstract

Dermatomycoses are infections caused by fungi and yeasts and the drug treatment is considered expensive and extensive. Researchers are synthesizing new organic compounds in order to obtain more effective molecules that provide reduced adverse effects. Our research group has synthesized and evaluated the biological activities of aminoalcohol and diamine derivatives, which were considered active against human pathogenic fungi. Therefore, the objective of this study was to evaluate the in vitro antifungal activity of aminoalcohols and diamine derivatives against fungi and yeasts that cause dermatomycoses. The minimum inhibitory concentrations (MICs) and the minimum fungicidal concentration (MFC) of aminoalcohol (**1–4**) and diamine (**5–13**) derivatives was determined against *Trichophyton mentagrophytes*, *T. rubrum*, *Epidermophyton floccosum*, and *Candida albicans* according to protocols from the Clinical and Laboratory Standards Institute. All molecules exhibited fungicidal activity against the evaluated fungal strains, with the MIC and MFC ranging between 0.12 and 1000 µg/mL for filamentous fungi and 0.6 and 1250 µg/mL for yeasts. The best activity was attributed to diamines compared to aminoalcohols, with an emphasis on molecules 6 and 7. These results demonstrate the antifungal potential of the evaluated aminoalcohols and diamines against the four primary fungal species that cause dermatomycoses.

Graphical Abstract



Keywords Aminoalcohols · Diamines · Antifungal activity · Dermatomycoses

✉ César A. Caneschi
Cacaneschi@yahoo.com.br

[1] Núcleo de Pesquisa e Inovação em Ciências da Saúde (NUPICS), Faculdade de Farmácia, Universidade Federal de Juiz de Fora, Rua José Lourenço Kelmer, s/n, Juiz de Fora, MG 36036-330, Brazil

[2] Departamento de Química, Instituto de Ciências Exatas, Universidade Federal de Juiz de Fora, Rua José Lourenço Kelmer, s/n, Juiz de Fora, MG 36036-330, Brazil

Published online: 23 September 2020

Introduction

Dermatomycoses are superficial infections that can trigger inflammatory conditions and ulcerations [1–5]. This type of mycosis is associated with several predisposing factors, such as climatic conditions, sports activities, prolonged contact with water, lifestyle, immunological status, chronic diseases, and older age [6].

The main etiological agents of these infections are the microorganisms oh the genera *Trichophyton*, *Microsporum*, and *Epidermophyton*, which include the species *T. rubrum*, *T. mentagrophytes*, *E. floccosum*, and *M. canis* [1, 4–7]. In contrast, the genus *Candida* comprises opportunistic yeast fungi whose representatives are responsible for causing candidiasis, but it is also directly associated with dermatomycosis, with *C. albicans* being its primary representative [8]. This species is also responsible for causing several hospital infections from catheters and drains and complications of bacterial sepsis and the urinary system [9].

This type of mycosis is widely distributed among humans and it is considered a serious health problem due to the difficulty of treatment that is attributed to the reduced efficacy of available drugs, prolonged treatment, and high cost, in addition to causing hepatotoxicity. These factors result in low adhesion to the drug therapy and consequently the emergence of relapse cases and the selection of strains more resistant to the antifungals [3, 10–12].

The search for compounds with biological activities from natural sources, biomolecules, metals, etc. has been going on for a long time [12]. In this context, organic synthesis plays a fundamental role in the development of new compounds such as aminoalcohols and diamines with potential antibacterial as was verified by [13–20]. In this way new aminoalcohols and diamines were synthesized and described by [15] and [21]. These compounds are the target of this study, have already been evaluated against *Mycobacterium tuberculosis* and *Leishmania* species [14, 15, 19], *Escherichia coli*, and *Pseudomonas aeruginosa*; *Trichomonas vaginalis* [22], *Staphylococcus aureus, S. epidermidis, Escherichia coli, Pseudomonas aeruginosa* [23], and antifungal activity against fungi of the genera *Trichophyton*, *Epidermophyton*, and *Candida* [24].

The severals studies were carried out and promising results for the mentioned molecules and their derivatives arouse greater interest in the evaluation of their antifungal activity in vitro against the primary species of dermatophytic and yeast fungi responsible for causing dermatomycoses.

Results and discussion

All aminoalcohols and diamines exhibited fungicidal activity against the five fungal strains evaluated in this study, with the minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) values ranging between 0.12 and 1000 µg/mL for filamentous fungi and 0.6 and 1250 µg/mL for yeasts (Table 1), which corroborates data from the literature attributing the antimicrobial action to these classes of compounds [15, 17, 19, 25]. The lowest MIC and MFC values were provided by diamine **6**, whose antifungal action could be attributed to its amphiphilic property, since it favors its interaction with the cells, as described in previous studies [21–23, 26, 27]. Among the molecules evaluated, diamine **6** with a lateral aliphatic chain bearing 12 carbon atoms exhibited better antifungal action against the tested microbial strains, with the MIC value in the range of 0.12–4.8 µg/mL.

Diamine **6** also presented the lowest MIC value (0.12 µg/mL) against *T. rubrum* CCT 5507 URM 1666 strain and this MIC value was less than the value obtained with the reference drugs (terbinafine, ketoconazole, itraconazole, and amorolfine). This result deserves attention since Lima et al. [28] have considered this specie as the main responsible for dermatomycoses in humans. In addition, the existence of antifungals-resistant clinical isolates of this species is common, which may be related to the presence of transporters associated with cellular efflux identified as TruMDR1 and TruMDR2 [29].

As shown in Table 1, the diamines **5**–**13** exhibited the best activity (MICs: 0.97–3.9 µg/mL) compared with the aminoalcohols **1**–**4** (MICs: 0.462–500 µg/mL). There was a reduction in the antifungal activity of the diamines with the increase in the number of carbon atoms present in the spacers between the functional groups. The presence of two- and four-carbon spacers provided MICs of 0.24–15.62 and 0.6–312 µg/mL, respectively. These results suggest a decrease in the biological response due to the increased lipophilicity (longer than 12 carbon atoms in the lateral alkyl chain). Krauss et al. [30] evaluated the antimicrobial activity of *N*-alkyl-trans-decahydroisoquinoline molecules and observed that the biological action was related to the length of the alkyl chain, with the best activity being attributed to the presence of chains composed of 10–12 carbon atoms. Tang et al. [31] evaluated the antifungal potential of quinazolinones, quinoxalines, and benzopyrans and found that the size of the lipophilic chain presents a strong correlation with the biological response.

The highest MIC and MFC values (250 and 2500 µg/mL) were provided by compound **1**. As this aminoalcohol has the shortest carbon chain (eight carbons) among the molecules described in this study, it could be suggested that the increase in the lipophilic characteristic can hamper the described pharmacological action, as demonstrated by [23]. In contrast, compound **3** exhibited the best activity among the described aminoalcohols (MICs: 0.462–500 µg/mL) and has 12 carbon atoms in its side chain; the result may be

Table 1 In vitro antifungal activity of amphiphilic aminoalcohols and diamines

Compounds	Fungal strains									
	Trichophyton mentagrophytes ATCC 11481		*Trichophyton-rubrum* CCT 5507 URM 1666		*Epidermophyt-onfloccosum-* CCF -IOC-3757		*Candidaalbi-cans* ATCC 10231		*Candida albicans* Clinical isolated	
	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC
1	500	1000	250	500	1000	1000	1250	2500	312.5	625
2	1.85	7.4	125	250	500	1000	78	78	39	78
3	0.462	7.4	7.81	7.81	500	1000	19	19	4.8	19
4	250	250	3.9	3.9	15.62	31.25	4.8	4.8	4.8	4.8
5	3.9	7.8	3.9	7.8	15.62	15.62	9.7	9.7	9.7	19
6	0.24	0.48	0.12	0.97	1.95	1.95	4.8	4.8	4.8	4.8
7	0.97	0.97	0.487	0.97	1.95	1.95	1.2	1.2	2.4	2.4
8	1.95	3.90	3.9	7.81	31.25	250	19	78	19	78
9	500	500	125	125	125	250	19	19	19	1250
10	3.9	3.9	0.97	1.95	3.9	3.9	2.4	2.4	2.4	2.4
11	3.9	250	62.5	125	125	125	78	78	78	156
12	31.25	125	31.25	31.25	125	500	39	156.2	19	312
13	1.95	1.95	3.9	7.81	15.62	125	9	19	0.6	78
Terbinafine	0.03	0.03	0.19	0.19	>480	ND	NE	NE	NE	NE
Ketoconazole	0.25	0.25	1	4	>640	ND	NE	NE	NE	NE
Itraconazole	8	64	2	64	>64	ND	NE	NE	NE	NE
Amorolfine	2	4	0,5	1	>16	ND	NE	NE	NE	NE
Amphotericin B	NE	NE	NE	NE	NE	NE	125	500	78	312.5
Nystatin	NE	NE	NE	NE	NE	NE	0.33	3.33	0.08	0.8

Results are expressed as $\mu g\ mL^{-1}$

ND not determined (MIC > 1000 $\mu g\ mL^{-1}$ or MIC > 5000 $\mu g\ mL^{-1}$), *NE* not evaluated, *MIC* minimum inhibitory concentration, *MFC* minimum fungicidal concentration

associated with the synergism between the lipophilic chain and the aminoalcohol functional group [21].

All the molecules evaluated in this study exhibited fungicidal action against *E. floccosum* CCF-IOF-3757 (MFC ≤ 1000 μg/mL), a fact that indicates their great significance, since this strain was considered resistant to the reference drugs (ketoconazole [>640 μg/mL], itraconazole [>64 μg/mL], terbinafine [>480 μg/mL] and amorolfine [>16 μg/mL]) [32] used in the treatment of dermatomycosis. However, this fact is consistent with the studies of [7], which mention that cases of resistance to antifungals are not common.

According to studies conducted by Ouf et al. [33] and Miron et al. [34], the MIC values of terbinafine against the clinical isolates of *T. rubrum* and *E. floccosum* were 4–8 and 0.25–4 μg/mL, respectively. In our work, we check that *T. rubrum* CCT 5507 URM 1666 was more susceptible to the same drug described (MIC = 0.19 μg/mL), whereas *E. floccosum* CCF-IOF-3757 was resistant to the above-mentioned allylamine (MIC > 480 μg/mL). The results are not contradictory, since clinical strains were used [33, 34], so it is expected that the MIC values are higher when compared to standard strains. This fact was evidenced for *T. rubrum* CCT 5507 URM 1666; however, the *E. floccosum* CCF-IOF-3757 strain showed unexpected behavior when presenting MIC > 480 μg/mL.

The antifungal activities of compounds 1–13 against *C. albicans* were analyzed. Results showed that compounds 2–13 presented lower MIC and MFC values than amphotericin B (125 and 500 μg/mL, respectively) when tested against *C. albicans* ATCC 10231. Conversely, all compounds (1–13) presented higher MIC and MFC values than nystatin. This experiment was performed in triplicate to confirm the results which repeat the values described in the Table 1.

When tested against the clinical isolate, compounds 2–8, 10, 11, and 13 showed lower MIC and MFC values than amphotericin B. These results are of great significance due the current scenario wherein there is an increase in the number of *C. albicans* isolates resistant to available drug therapy [35]. Compared to nystatin antifungal activity, all the molecules presented higher MIC and MFC values.

Therefore, the results shown in Table 1 are important because these compounds may contribute to the development of a candidate prototype for treating infections caused by resistant fungal strains.

Conclusion

This study demonstrated the fungicidal activity of a series of aminoalcohols **1–4** and diamines **5–13** against *T. mentagrophytes* ATCC 11481, *T. rubrum* CCT 5507 URM 1666, *E. floccosum* CCF-IOF-3757, *C. albicans* ATCC 10231, and a clinical isolate of *C. albicans*. Among the evaluated compounds, diamine **6** and **7** presented the lowest MIC and MFC values against dermatophytes and yeast, respectively. These results can contribute to the synthesis and evaluation of compounds with fungicidal potential against both filamentous fungi and yeasts that cause dermatomycoses.

Material and methods

Chemistry

N-alkylated aminoalcohols **1–4** and diamines **5–13** (Scheme 1) were prepared using a methodology previously described by [15, 25] (Scheme 1).

Fungal strains

Three strains of filamentous fungi, *T. mentagrophytes* ATCC 11481, *T. rubrum* CCT 5507 URM 1666, and *E. floccosum* CCF-IOF-3757, were obtained from the Collection of Tropical Crops (CCT) provided by the André Tosello Foundation (Campinas-SP, Brazil). *C. albicans* ATCC 10231 was provided by the National Institute of Quality Control in the Health-Oswaldo Cruz Foundation (Rio de Janeiro-RJ, Brazil) and a clinical isolate of this species was obtained from a patient form Maurílio Baldi Laboratory at the UFJF University Hospital.

The authenticity of the lineages *T. mentagrophytes* ATCC 11481, *T. rubrum* CCT 5507 URM 1666, *C. albicans* ATCC 10231, and the clinical isolate of *C. albicans* was confirmed through molecular analysis as described previously [24, 36, 37]. The strain of *E. floccosum* exhibited pleomorphism; however, its authenticity was certified through macroscopic and microscopic analyses.

Antifungal activity

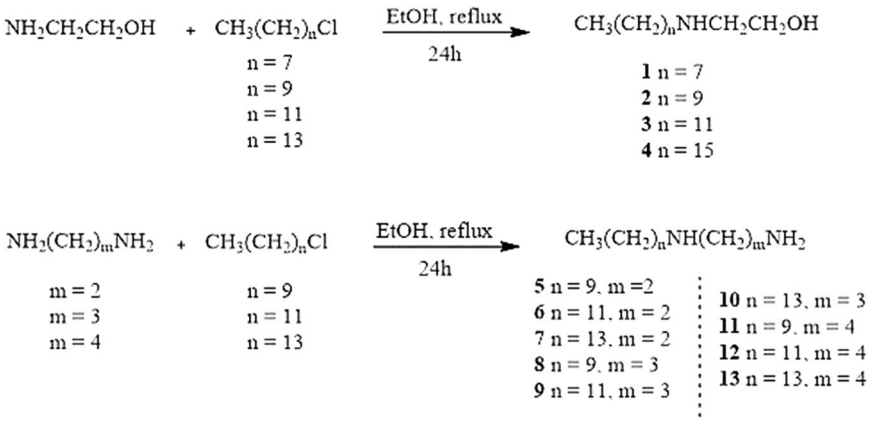
The MIC and the MFC values were established as described by Clinical and Laboratory Standards Institute (CLSI) [32, 38, 39].

Minimum inhibitory concentration

The MIC value was established according to the CLSI protocols M38-A2, M27-A3, and M27-S4 [32, 38, 39], and the analyses were performed in triplicate. Initially, the filamentous fungi and yeasts were cultivated on Sabouraud dextrose agar for 7 days (filamentous fungi) e 2 days (yeasts). These colonies were used to prepare fungal suspension from successive washes of the surface on the culture medium where the growth microorganism occurred.

The number of viable fungal structures (conidia, blastoconidia, and chlamydoconidia) in the suspensions was analyzed using a spectrophotometer (Libra S12; Biochrom, Cambourne, UK) at a wavelength of 530 nm and a transmittance of 68–70% for filamentous fungi and 89–90% for yeast [32, 38–40]. These transmittance ranges corresponded to $2 \times 10^5 - 2.5 \times 10^6$ CFU/mL for filmamentous fungi and $1–5 \times 10^6$ CFU/mL for yeasts. Subsequently, the suspension was diluted in RPMI-1640 culture medium (Sigma, St. Louis, MO, USA) buffered with 3-(*N*-morpholino)propanesulfonic acid (MOPS; JT Baker, Griesheim, Germany), at a ratio of 1:50 (final concentration of $0.4–5.0 \times 10^4$ CFU/mL for filamentous fungi) and 1:2000 (final concentration of $1–5 \times 10^3$ CFU/mL for yeast).

The aminoalcohols **1–4** and the diamines **5–13** were solubilized in RPMI-1640 culture medium, buffered with MOPS, and tested at the final concentrations of 7.8–1000 and 39.06–5000 μg mL^{-1} for filamentous fungi and yeasts, respectively. Fungal growth was evaluated by adding 100 μL RPMI-1640 culture medium buffered with MOPS



Scheme 1 Synthesis of aminoalcohols **1–4** and diamines **5–13**

containing the fungal inoculum. The 96-well sterile plates were incubated at 28 ± 2 °C for 7 days (dermatophytes) or at 37 ± 2 °C for 48 h (yeasts) according to the CLSI. The growth of the fungi was analyzed visually using a SMZ800 microscope (Nikon, Melville, NY). Terbinafine, ketoconazole, itraconazole, amorolfine, amphotericin B, and nystatin were used as reference drugs and assessed according to the M38-A2, M27-A3, and M27-S4 protocols [32, 38, 39].

Minimum fungicidal concentration

The MFC analysis for filamentous fungi was performed by transferring 10 µL volume from the wells where no fungal growth was observed to the wells of another microtiter plate containing 200 µL of Sabouraud dextrose broth (SDB) sterile and without antifungal SDB as described previously [41]. The MFC was determined as the lowest concentration of the molecule that resulted in fungal death. The MFC for *C. albicans* was evaluated using 5 µL from wells without fungal growth, which was transferred to cryotubes containing 1000 µL SDB. The analysis was conducted as described above [42].

Acknowledgements This research was supported by Coordination for the Improvement of Higher Education Personnel (CAPES), National Council for Scientific and Technological Development (CNPq), Research Support Foundation of the State of Minas Gerais (FAPEMIG), Carlos Chagas Filho Foundation for Research Support of the State of Rio de Janeiro (FAPERJ-E-26/202.447/2019), and Pro-Rectorate of Graduate Studies and Research at the Federal University of Juiz de Fora (PROPESQ/UFJF).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Achterman RR, White TC. Dermatophytes. Curr Biol. 2013;23:551–2. https://doi.org/10.1016/j.cub.2013.03.026.
2. Chen J, Yi J, Liu L, Yin S, Chen R, Li M, et al. Substrate adaptation of *Trichophyton rubrum* secreted endoproteases. J Micro Path. 2010;48:57–61. https://doi.org/10.1016/j.micpath.2009.12.001.
3. Sadeghi-Nejad B, Rezaei-Matehkolaei A, Naanaie SY. Isolation and antifungal activity evaluation of *Satureja khuzestanic*a Jamzad extract against some clinically important dermatophytes. J Myco Med. 2017;27:554–60. https://doi.org/10.1016/j.mycmed.2017.08.002.
4. Trocoli Drakensjö I, Vassilaki I, Bradley MM. Granuloma caused by *Trichophyton mentagrophytes* in 2 immunocompetent patients. Actas Dermo-Sifiliogr. 2017;108:e6–8. https://doi.org/10.1016/j.ad.2015.05.020.
5. Zhang J, Tan J, He Y. Tacrolimus, not triamcinolone acetonide, interacts synergistically with itraconazole, terbinafine, bifonazole, and amorolfine against clinical dermatophyte isolates. J Med Mycol. 2018;28:612–6. https://doi.org/10.1016/j.mycmed.2018.09.003.
6. Silva-Rocha WP, De Azevedo MF, Chaves GM. Epidemiology and fungal species distribution of superficial mycoses in Northeast Brazil. J Med Mycol. 2017;27:57–64. https://doi.org/10.1016/j.mycmed.2016.08.009.
7. Achterman RR, White TC. A foot in the door for dermatophyte research. PLoS Pathog. 2012;8:6–9. https://doi.org/10.1371/journal.ppat.1002564.
8. Silva RAC, Da Silva CR, Neto JBA, Da Silva AR, Campos RS, Sampaio LS, et al. In-vitro anti-*Candida* activity of selective serotonin reuptake inhibitors against fluconazole-resistant strains and their activity against biofilm-forming isolates. J Micro Path. 2017;107:341–8. https://doi.org/10.1016/j.micpath.2017.04.008.
9. Wiebusch L, Almeida-Apolonio AA, Rodrigues LMC, Bicudo BP, Silva DBS, Lonchiati DF, et al. *Candida albicans* isolated from urine: phenotypic and molecular identification, virulence factors and antifungal susceptibility. Asian Pac J Trop Biomed. 2017;7:624–8. https://doi.org/10.1016/j.apjtb.2017.06.006.
10. Millsop JW, Fazel N. Oral candidiasis. Clin Dermatol. 2016;34:487–94. https://doi.org/10.1016/j.clindermatol.2016.02.022.
11. Carmello JC, Alves F, Mima EGO, Jorge JH, Bagnato VS, Pavarina AC. Photoinactivation of single and mixed biofilms of *Candida albicans* and non-*albicans Candida* species using Phorodithazine®. Photodiagnosis Photodyn Ther. 2017;17:194–9. https://doi.org/10.1016/j.pdpdt.2016.11.013.
12. Rehman S, Gunday ST, Alsalem ZH, Bozkurt A. Synthesis and characterization of novel azole functionalized poly(glycidyl methacrylate)s for antibacterial and anticandidal activity. Curr Org Synth. 2019;16:1002–9. https://doi.org/10.2174/1385272823666190828112113.
13. Almeida AM, Oliveira BA, Castro PP, Mendonça CC, Furtado RA, Nicolella HD, et al. Lipophilic gold (I) complexes with 1, 3, 4-oxadiazol-2-thione or 1, 3-thiazolidine-2-thione moieties: synthesis and their cytotoxic and antimicrobial activities. Biometals. 2017;30:841–57. https://doi.org/10.1007/s10534-017-0046-6.
14. Coimbra ES, Santos JÁ, Lima LL, Machado PA, Campos DL, Pavan FR, et al. Synthesis, antitubercular and leishmanicidal evaluation of resveratrol analogues. J Braz Chem Soc. 2016;27:2161–9. https://doi.org/10.5935/0103-5053.20160107.
15. Rezende CO Jr, Le Hyaric M, Da Costa CF, Corrêa TA, Taveira AF, Araújo DP, et al. Preparation and antitubercular activity of lipophilic diamines and amino alcohols. Mem do Inst Oswaldo Cruz. 2009;104:703–5. https://doi.org/10.1590/S0074-02762009000500006.
16. Rezende CO Jr, Alves RO, Rezende CAM, Da Costa CF, Silva H, Le Hyaric M, et al. Trypanocidal activity of lipophilic diamines and amino alcohols. Biomed Pharmacother. 2010;64:624–6. https://doi.org/10.1016/j.biopha.2010.06.002.
17. Giordani RB, De Almeida MV, Fernandes E, Costa CF, De Carli GA, Tasca T, et al. Anti-*Trichomonas vaginalis* activity of synthetic lipophilic diamine and amino alcohol derivatives. Biomed Pharmacother. 2009;63:613–7. https://doi.org/10.1016/j.biopha.2008.10.002.
18. Popadyuk II, Markov AV, Babich VO, Salomatina OV, Logashenko EB, Zenkova MA, et al. Novel derivatives of deoxycholic acid bearing aliphatic or cyclic diamine moieties at the C-3 position: synthesis and evaluation of anti-proliferative activity. Bioorg Med Chem Lett. 2017;27:3755–9. https://doi.org/10.1016/j.bmcl.2017.06.072.

19. Taveira AF, Le Hyaric M, Reis EFC, Araújo DP, Ferreira AP, De Souza MA, et al. Preparation and antitubercular activities of alkylated amino alcohols and their glycosylated derivatives. Bioorg Med Chem Lett. 2007;15:7789–94. https://doi.org/10.1016/j.bmc.2007.08.045.
20. Wang D, Liu W, Tang M, Yu N, Yang X. Atroposelective synthesis of biaryl diamines and amino alcohols via chiral phosphoric acid catalyzed para-aminations of anilines and phenols. iScience. 2019;22:195–205. https://doi.org/10.1016/j.isci.2019.11.024.
21. Fernandes FS, Fernandes TS, Silveira LS, Caneschi W, Lourenço MCS, Diniz CG, et al. Synthesis and evaluation of antibacterial and antitumor activities of new galactopyranosylated amino alcohols. Eur J med Chem. 2016;108:203–10. https://doi.org/10.1016/j.ejmech.2015.11.037.
22. Rigo GV, Trein MR, Trentin DS, Macedo AJ, De Olivera BA, De Almeida AM, et al. Diamine derivative anti-*Trichomonas vaginalis* and anti-*Tritrichomonas foetus* activities by effect on polyamine metabolism. Biomed Pharmacother. 2017;95:847–55. https://doi.org/10.1016/j.biopha.2017.09.007.
23. De Almeida AM, Nascimento T, Ferreira BS, Castro PP, Silva VL, Diniz CG, et al. Synthesis and antimicrobial activity of novel amphiphilic aromatic amino alcohols.Bioorg Med Chem Lett. 2013;23:2883–7. https://doi.org/10.1016/j.bmcl.2013.03.078.
24. Caneschi CA, Almeida AM, Martins FJ, Le Hyaric M, Oliveira MME, Macedo GC, et al. In vitro antifungal activity of organic compounds derived from amino alcohols against onychomycosis. Braz J Microbiol. 2017;48:476–82. https://doi.org/10.1016/j.bjm.2016.12.008.
25. Sales PA Jr, Júnior COR, Le Hyaric M, De Almeida MV, Romanha AJ. The in vitro activity of fatty diamines and amino alcohols against mixed amastigote and trypomastigote *Trypanosoma cruzi* forms. Mem do Inst Oswaldo Cruz. 2014;109:362–4. https://doi.org/10.1590/0074-0276130496.
26. Du P, Viswanathan UM, Xu Z, Ebrahimnejad H, Hanf B, Burkholz T, et al. Synthesis of amphiphilic seleninic acid derivatives with considerable activity against cellular membranes and certain pathogenic microbes. J Hazard Mater. 2014;269:74–82. https://doi.org/10.1016/j.jhazmat.2014.01.014.
27. Schreier S, Malheiros SVP, De Paula E. Surface active drugs: self-association and interaction with membranes and surfactants. Physicochemical and biological aspects. Biochim et Biophys Acta. 2000;1508:210–34. https://doi.org/10.1016/s0304-4157(00)00012-5.
28. Lima MIO, Medeiros ACA, Silva KVS, Cardoso GN, Lima EO, Pereira FO. Investigation of the antifungal potential of linalool against clinical isolates of fluconazole resistant *Trichophyton rubrum*. J Mycol Med. 2017;27:195–202. https://doi.org/10.1016/j.mycmed.2017.01.011.
29. Peres NT, Maranhão FCA, Rossi A, Martinz-Rossi NM. Dermatófitos: Interação patógeno-hospedeiro e resistência a antifúngicos. Bras Dermatol. 2010;85:657–67. https://doi.org/10.1590/S0365-05962010000500009.
30. Krauss J, Muller C, Kiebling J, Richter S, Staudacher V, Bracher F. Synthesis and biological evaluation of novel *N*-alkyl tetra- and decahydroisoquinolines: novel antifungals that target ergosterol biosynthesis. Arch Pharm. 2014;347:283–90. https://doi.org/10.1002/ardp.201300338.
31. Tang H, Wu J, Zhang W, Zhao L, Zhang Y, Shen C. Design, synthesis and biological evaluation of novel non-azole derivatives as potential antifungal agents. Chin Chem Lett. 2015;26:2–6. https://doi.org/10.1016/j.cclet.2015.04.030.
32. Clinical and Laboratory Standards Institute (CLSI). Reference method for broth dilution antifungal susceptibility testing of filamentous fungi: approved standard. 2nd edn. (M38-A2). Wayne, PA, USA: Clinical and Laboratory Standards Institute; 2008. p. 1–35.
33. Ouf SA, Abu Taleb AM, Tharwat NA, Geweely NS. Efficacy of some synthesized thiazoles against dermatophytes. J Mycol Med. 2013;23:230–23. https://doi.org/10.1016/j.mycmed.2013.07.056.
34. Miron D, Battisti F, Silva FK, Lana AD, Pippi B, Casanova B, et al. Antifungal activity and mechanism of action of monoterpenes against dermatophytes and yeasts. Braz J Pharmacogn. 2014;24:660–7. https://doi.org/10.1016/j.bjp.2014.10.014.
35. Szczepaniak J, Cieslik W, Romanowicz A, Musiol R, Krasowska A. Blocking and dislocation of *Candida albicans* Cdr1p transporter by styrylquinolines. Int J Antimicrob Agents. 2017;50:171–6. https://doi.org/10.1016/j.ijantimicag.2017.01.044.
36. Bisha B, Kim HJ, Brehm-Stecher BF. Improved DNA-FISH for cytometric detection of *Candida* spp. J Appl Microbiol. 2011;110:881–92. https://doi.org/10.1111/j.1365-2672.2011.04936.x.
37. Rivas L, Mühlhauser M. Complejo *Trichophyton mentagrophytes*. Rev Chil Infect. 2015;32:319–20. https://doi.org/10.4067/S0716-10182015000400009.
38. Clinical and Laboratory Standards Institute (CLSI). Reference method for broth dilution antifungal susceptibility testing of yeasts; Third informational supplement. CLSI document M27-S3. Wayne, PA, USA: Clinical and Laboratory Standards Institute; 2008.
39. Clinical and Laboratory Standards Institute (CLSI). Reference method for broth dilution antifungal susceptibility testing of yeast; fourth informational supplement. CLSI document M27-S4. Wayne, PA, USA: Clinical and Laboratory Standards Institute; 2012.
40. Falahati M, Nozari S, Makhdoomi A, Ghasemi Z, Nami S, Assadi M. Comparison of antifungal effect of nanosilver particles alone and in combination with current drugs on candida species isolated from women with recurrent vulvovaginal candidiasis. Eur J Exp Biol. 2014;4:77–82.
41. Magagnin CM, Stopiglia CDO, Vieira FJ, Daiane H, Machado M, Vetoratto G, et al. Perfil de suscetibilidade a antifúngicos de dermatófitos isolados de pacientes com insuficiência renal crônica. Bras Dermatol. 2011;86:694–701. https://doi.org/10.1590/S0365-05962011000400011.
42. Espinel-Ingroff A, Fothergill A, Peter J, Rinaldi MG, Walsh TJ. Testing conditions for determination of minimum fungicidal concentrations of new and established antifungal agents for *Aspergillus spp.*: NCCLS Collaborative Study. J Clin Microbiol. 2002;40:3204–8. https://doi.org/10.1128/jcm.40.9.3204-3208.2002.