Med Chem Res
DOI 10.1007/s00044-017-2126-0

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Thiobarbiturates as potential antifungal agents to control human infections caused by *Candida* and *Cryptococcus* species

Muhammad Shabeer[1] · Luiz C. A. Barbosa[1,2] · Milandip Karak[1,2] · Amanda C. S. Coelho[1] · Jacqueline A. Takahashi[1]

Received: 12 September 2017 / Accepted: 5 December 2017

Abstract Hospitalized patients can suffer from *Candida* and *Crytptococcus* infections, aggravating underlying health conditions. Due to the development of drug-resistant microorganisms, we report here on the potential of some arylidene-thiobarbiturate to control five *Candida* spp. and one *Cryptococcus* species of medical interest. Initially, a bismuth nitrate catalyzed Knoevenagel condensation with thiobarbituric acid and aromatic aldehydes was developed. This new procedure generated seven new and thirteen known arylidene-thiobarbiturate derivatives (**1–20**) with excellent yields (81–95%), with a reaction time within 20 min. The antimicrobial activities of all compounds were evaluated against *Candida albicans*, *C. tropicalis*, *C. parapsilosis*, *C. lusitaniae*, *C. dubliniensis*, and *Cryptococcus neoformans*. Several compounds were as active as the commercially available drugs ($IC_{50} < 1.95\ \mu g\ mL^{-1}$) towards at least one microbial strain. The results suggest that some of the new compounds can serve as leads for new antimicrobial agents for the treatment of human fungal infections.

Keywords Thiobarbituric acid · Knoevenagel condensation · Antimicrobial activity · Antifungal compounds

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00044-017-2126-0) contains supplementary material, which is available to authorized users.

✉ Luiz C. A. Barbosa
lcab@ufmg.br

[1] Department of Chemistry, Universidade Federal de Minas Gerais, Belo Horizonte, MG CEP 31270-901, Brazil

[2] Department of Chemistry, Universidade Federal de Viçosa, Viçosa, MG CEP 36570-900, Brazil

Introduction

Fungal infections have been increasing to alarming levels in all regions of the world, including underdeveloped and developed countries. The mortality rates associated with multidrug resistance fungal infections are unacceptably high (Monk and Goffeau 2008; Mathew and Nath 2009; Rajendran et al. 2016). The emergence of fluconazole resistance among different pathogenic strains (Pfaller et al. 2007) and the high toxicity of amphotericin B (Kullberg and Pauw 1999; Sheehan et al. 1999) intensified the search for newer, safer, and more effective agents to combat serious fungal infections. To search for a lead for a new antifungal compound we focused on barbituric acid derivatives (BAs) among the many classes of small organic molecules with known biological activities (Gurib-Fakim 2006; Bello et al. 2008; Baell and Holloway 2010; Taferner et al. 2011; Nigam et al. 2014).

BAs have contributed to the development of many commercially available hypnotic, sedative and anticonvulsant drugs, such as Veronal (Fig. 1a) (Lemke et al. 2012). More recently, benzylidene-derivatives like **B** (Fig. 1) were shown to be active against *Mycobacterium tuberculosis* ($IC_{50} = 4.71\ \mu g\ mL^{-1}$), (Laxmi et al. 2011) while compound **C** (Fig. 1) was effective against *Candida albicans* (X=O, $IC_{50} = 12.5\ \mu g\ mL^{-1}$) (Faidallah and Khan 2012). Other reported activities of BAs include anticancer (Dhorajiya et al. 2014) and protein tyrosine phosphatase inhibition (Kafle et al. 2011).

In addition to the BAs, the thiobarbiturate derivatives (TBAs, Fig. 1) exhibit highly sought after biological properties such as antifungal (**C**, $IC_{50} = 25\ \mu g\ mL^{-1}$, X=S) (Faidallah and Khan 2012), urease inhibition (**D**, $IC_{50} =$ 1.61 μM) (Khan et al. 2014a), antibacterial (Jin et al. 2012; Khan et al. 2014b; Yan et al. 2009) and anti-inflammatory

Published online: 08 January 2018

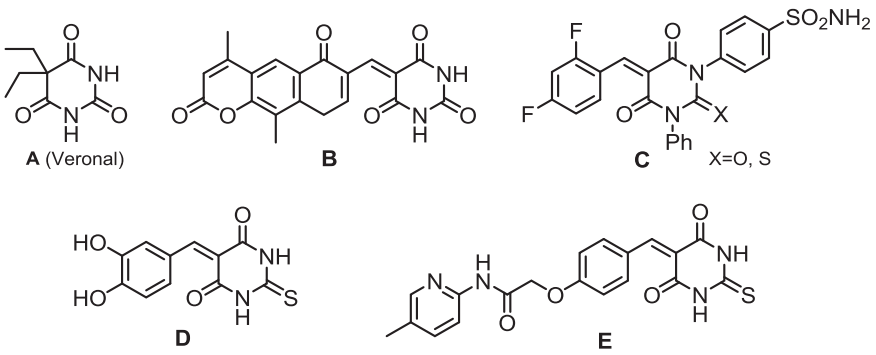


Fig. 1 Structures of commercial BA drug Veronal (**a**) and some biologically active BAs and TBAs (**b–e**)

properties (Kopff et al. 2007). Some studies have also demonstrated that thiobarbiturate derivative **E** is effective for the treatment of non-alcoholic fatty liver disease (Ma et al. 2011).

Despite the large array of biological activities of barbiturates as mentioned above, few reports on the antifungal activities of TBAs are known (Faidallah and Khan 2012; Khan et al. 2014b; Neumann et al. 2014). Thus, we planned to investigate the effect of some known and other new thiobarbiturate derivatives against five *Candida* and one *Cryptococcus* species. Among the investigated species, *C. albicans* is a harmless microorganism present in healthy bodies, which can adapt and generate genetically altered variants, more adapted to the host environment. However, in immunocompromised patients, *C. albicans* can cause serious symptomatic infections; such as oropharyngeal candidiasis in AIDS patients (Morschhäuser 2016) and candidemia associated with high mortality rates in cancer patients (Jung et al. 2015). Nevertheless, the importance of *C. albicans* as a human pathogen, and other species of *Candida* genus like *C. tropicalis* and *C. parapsilosis* are relevant sources of invasive *Candida* infections, especially in surgical patients (Smeekens et al. 2016). On the other hand, *Cryptococcus neoformans*, an opportunistic yeast that causes lung infections, also deserves attention due to its clinical relevance in individuals with compromised host defences (Schmalzle et al. 2016). It is worth mentioning that antifungal multi-drug resistance in *C. neoformans* is of great concern (Perfect and Cox 1999).

Considering the limited reports on the antifungal activities of thiobarbiturate derivatives, and in line with our continuous efforts to synthesize antimicrobial heterocyclic compounds (Pereira et al. 2014a, b; Karak et al. 2016), we report here on the expeditious synthesis of arylidene TBAs and their antifungal activities against five *Candida spp*. and one *Cryptococcus* species. Considering previous reports on anti-*Candida* activities of some benzylidene barbiturates (Fig. 1, R=H, Me or aryl; X=O) (Faidallah and Khan 2012; Khan et al. 2014b; Neumann et al. 2014), we propose the preparation of the corresponding TBAs (Fig. 2, X=S; R=H), and expand the structural diversity of such

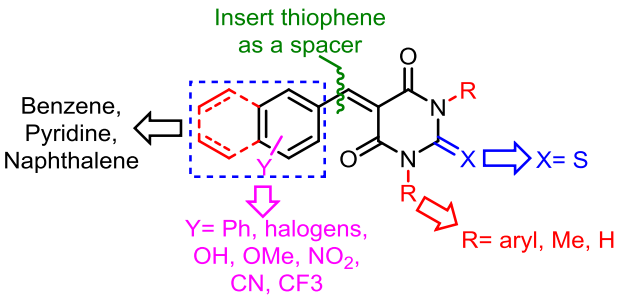


Fig. 2 Proposed structural modifications on thiobarbituric acid derivatives

compounds possessing electron-withdrawing groups (Fig. 2, Y=CN, CF_3, NO_2, and Halogen) and heteroaromatic ring (pyridine). We also included a thiophene unit as a spacer between the TBA core and the arylidene unit.

Experimental

Chemicals and instruments

All chemicals and materials were acquired from Sigma Aldrich Chemicals Ltd. and used without further purification. IR spectra were recorded in KBr on Shimadzu IR Affinity-1 FT-IR spectrophotometer and ^{1}H and ^{13}C NMR spectra were recorded on a BrukerAvance II 300 and 400 MHz NMR spectrometers in DMSO using TMS as an internal standard. Mass spectra were recorded on Waters, Q-TofMicromass (LCMS) spectrometer and Varian Inc. 410 Prostar Binary LC with 500 Mass Spectrophotometer. Melting points are uncorrected and were measured with a MQAPF-301 apparatus.

General procedure for the synthesis of thiobarbituric acid derivatives (1–20)

To a 50 mL round-bottomed flask charged with penta-hydrated bismuth nitrate (0.032 g, 0.065 mmol) in ethanol (20 mL) were added thiobarbituric acid (0.144 g, 1.0 mmol)

and aromatic aldehydes (1.0 mmol). The reaction mixture was stirred for 10–20 min at 80 °C, when thin layer chromatography analyzes revealed it was completed. After completion the precipitated product was separated by filtration, dried, and recrystallized from ethanol. Full physical and spectroscopic data and yields for all compounds are presented in the supporting information (SI).

Biological activity

The bioassays were conducted with six yeast strains (*C. albicans* ATCC 18804, *C. dubliniensis* clinical isolate 28, *C. lusitaniae* CBS 6936, *C. parapsilosis* ATCC 22019, *C. tropicalis* ATCC 750 and *Cryptococcus neoformans* ATCC 24067).

To determine the IC_{50} values for compounds **1–20**, the yeasts were inoculated in Sabouraud broth. Assays were performed according to Clinical and Laboratory Standard Institute guidelines (CSLI 2002). The microorganisms were incubated in an oven at 37 °C for 24 h. The suspensions containing the six yeast strains were transferred to tubes containing sterile distilled water to reach a suspension (inoculum) compatible with the McFarland scale 0.5 (10^8 cells mL^{-1}). To assay the compounds **1–20**, 96-well microtiter plates containing the appropriate broth were used (Brain Heart infusion for yeasts and bacterium and Potato Dextrose Broth for filamentous fungi). The samples were dissolved and microdiluted in DMSO (250.00, 125.00, 62.50, 31.25, 15.63, 7.81, 3.90, and 1.95 μg mL^{-1}) in the microtiter plates. The inoculum was added equally to each well. The plates were incubated in an oven at 37 °C for 24 h. The readings were obtained after 24 h of incubation on a microplate reader at 600 nm. The IC_{50} values were calculated for the samples that showed an inhibition higher than 50% in the highest concentration assayed. Commercially available drugs, i.e., miconazole and nystatin, were used as positive standards. All the tests were performed twice under the same conditions.

Results and discussion

Chemistry

Our synthetic study commenced from the Knoevenagel condensation between aldehydes and thiobarbituric acid (Table 1). Although this condensation can conventionally be carried out under acid or base catalysis (Li et al. 2006; Khan et al. 2014a, b; Rahimov and Avdeev 2009; Mital et al. 2015) or even in an uncatalyzed manner (Ahmed and Karrar 2013; Chen et al. 2014), it normally requires high temperature and a long reaction time. Considering that the use of bismuth (III) nitrate [$Bi(NO_3)_3{\cdot}5H_2O$] as a catalyst has increased considerably over the years due to its thermal stability, low cost, low toxicity and stability to air (Bothwell et al. 2011), we investigated its effect on the condensation of TBA with aldehydes (SI, Table S1). Initially we carried out the condensation of 4-hydroxybenzaldehyde and thiobarbituric acid under a variety of conditions (SI, Table S1) and found that the use of 20 mol% of $Bi(NO_3)_3{\cdot}5H_2O$ in ethanol at 80 °C, efficiently catalyzes the condensation, resulting in the desired products in 10–20 min (Table 1). We envisage that the catalysis takes place via a transition state formed by coordination of bismuth (III) with the formyl group increasing its electrophilicity. Since bismuth (III) can be hydrolyzed producing an acidic solution, a protic catalysis cannot be ruled out without experimental evidence (Aggen et al. 2004). So, a control experiment reacting of 4-hydroxybenzaldehyde with TBA in the presence of 60 mol % of HNO_3 was carried out and no product was formed within 20 min. After one hour only 30% of product **1** was isolated (SI, Table S1), confirming the effect of bismuth (III) as the catalyst. A similar catalytic effect of bismuth (III) on the conversion of aromatic aldehydes to a variety of acylals has been reported (Aggen et al. 2004).

As can be observed from Table 1, the yields were generally high (compounds **1–20**, yields 81–95%). Aldehydes bearing electron donating or electron withdrawing functional groups such as hydroxy (**1–5**), methoxy (**6** and **7**), bromo (**8**), chloro, fluoro (**9**), cyano (**11**), trifluoromethyl (**12**) and nitro (**10**) react well under this procedure. Furthermore, excellent yields were also obtained with the 2-naphthaldehyde (**20**), 4-phenylbenzaldehyde (**19**) and some heteroaromatic aldehydes (**13–18**). The structures of all the new compounds (**9**, **11**, **13**, **14**, **16–18**) were determined by the spectroscopic analysis and the data are reported in the SI. For the known compounds, the spectroscopic data were identical to those from the literature (See the SI).

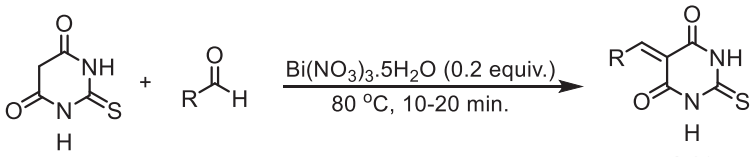
Biological activity

All the synthesized compounds have been screened for their antimicrobial activities against the yeast strains *Candida albicans*, *C. dubliniensis*, *C. tropicalis*, *C. parapsilosis*, *C. lusitaniae*, and *Cryptococcus neoformans*. Positive control experiments were carried out using miconazole and nystatin.

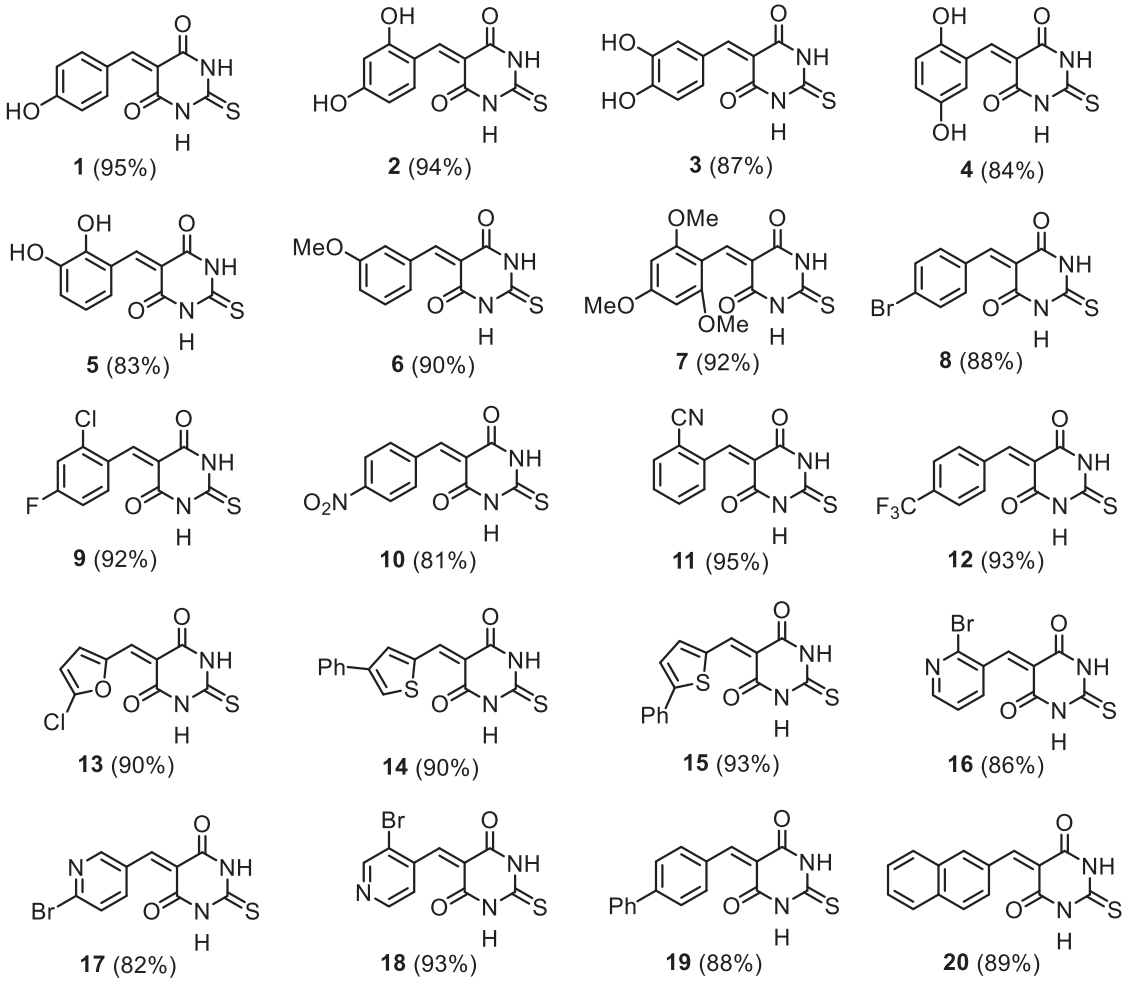
For all yeasts assayed, most of the compounds showed a good correlation between the concentrations tested and the percentage of growth inhibition, indicating that the antimicrobial activity provided by this class of compounds is dose-dependent. Therefore, the IC_{50} values for the active compounds were determined as shown in Table 2.

In general, the activities of this series of compounds on the microorganisms varied according to the structure and the species tested. Among the six yeast strains assayed,

Table 1 Bismuth(III) nitrate facilitated synthesis of thiobarbituric acid derivatives



1-20



C. albicans, *C. dubliniensis*, and *C. lusitaniae* were resistant to most of the compounds, while the growth of *C. parapsilosis*, *C. tropicalis*, and *Cryptococcus neoformans* were more effectively inhibited.

The less sensitive strains, *C. albicans, C. dubliniensis*, and *C. lusitaneae*, were more affected by compounds **14** ($IC_{50} < 1.95$, 9.39, and 6.18 μg mL^{-1}, respectively) and **13** (31.45, 44.33, and 76.83 μg mL^{-1}, respectively). Compound **15** was also significantly active against *C. albicans* ($IC_{50} = 12.77$ μg mL^{-1}). TBAs **14** and **15**, which were active against *C. albicans*, are promising since the corresponding BAs showed weak activity (Neumann et al. 2014). Compound **20** with $IC_{50} = 172.38$ μg mL^{-1}, is slightly less active than its oxo-analog (MIC_{80} of 125 μg mL^{-1}, previously reported by Neumann et al. 2014), suggesting that sulfur could have a restrictive effect on bioactivity. As found by Neumann et al. (2014), our results also showed that the compounds bearing OH or OMe groups (one or more, at various positions) are generally not active against *C. albicans*. This is also consistent for *C. dublinensis* and *C.*

Table 2 IC_{50} for the compounds **1–20** for six yeast strains

Compound	IC_{50} (μg mL^{-1})					
	C. albicans	*C. dubliniensis*	*C. lusitaniae*	*C. parapsilosis*	*C. tropicalis*	*C. neoformans*
1	–[a]	–	–	4.21	–	14.31
2	–	–	–	4.24	–	9.25
3	–	–	–	–	–	155.79
4	218.48	92.64	129.14	–	–	45.61
5	–	–	–	48.49	–	–
6	–	–	–	<1.95	<1.95	27.38
7	214.73	187.31	194.46	<1.95	<1.95	<1.95
8	–	–	–	<1.95	<1.95	123.53
9	–	–	–	8.12	–	17.73
10	–	–	–	3.17	26.27	68.41
11	–	–	–	–	–	–
12	–	–	–	<1.95	<1.95	81.26
13	31.45	44.33	76.83	<1.95	<1.95	6.39
14	<1.95	9.39	6.18	<1.95	<1.95	<1.95
15	12.77	56.21	34.46	<1.95	<1.95	53.58
16	–	–	–	–	–	–
17	–	–	–	–	–	–
18	–	–	–	<1.95	–	12.63
19	221.69	–	166.62	9.78	<1.95	12.36
20	172.38	196.92	192.03	3.60	<1.95	11.35
Miconazole	<1.95	<1.95	<1.95	<1.95	<1.95	<1.95
Nystatin	<1.95	<1.95	<1.95	<1.95	<1.95	<1.95

[a] (–) IC_{50} value was not calculated since inhibition was lower than 50% at the higher concentration assayed

lusitanea that no previous study has been found in this context. Although the inhibitory activities of some *N,N*-dimethylbarbiturates have been reported for *C. albicans* (Khan et al. 2014b), it was not possible to compare these results with ours since a different bioassay (disc diffusion method at a fixed dose of 100 μg) was adopted.

Compounds **13–15** also showed potent activity against *C. parapsilosis*, *C. tropicalis*, and *Cryptococcus neoformans* ($IC_{50} = <1.95$ μg mL^{-1} for most cases), whose IC_{50} values are comparable to those of miconazole and nystatin. The inhibitory activity of BAs and TBAs against *C. parapsilosis*, herein reported for the first time, is especially noteworthy in view of the great demand for effective and selective agents to treat infections of cancer patients (Sabino et al. 2015).

Structurally, **13–15** possess five-membered ring heteroaromatic aldehydes. On the other hand, compounds composed of substituted benzaldehyde, six-membered heteroaromatic aldehydes and naphthalene carbaldehyde were inactive against *C. albicans*, *C. dubliniensis*, and *C. lusitaniae*. Substitution by a phenyl group at α or β position in the thiophene ring makes **14** to be linear, while **15** to be angular-shaped. Such modifications seemed to have a dramatic effect on the activities except for *C. parapsilosis* and *C. tropicalis*, both showing low IC_{50} (1.95 μg mL^{-1}).

As already mentioned, *C. parapsilosis*, *C. tropicalis* and *C. neoformans* were in general more sensitive to TBAs derivatives. The IC_{50} values of compounds **6**, **7**, **8**, **12**, **13**, **14**, **15**, and **18** were lower than the minimum concentration tested (<1.95 μg mL^{-1}) for *C. parapsilosis*. For **6**, **7**, **8**, **12**, **13**, **14**, **15**, **19**, and **20**, the IC_{50} values were <1.95 μg mL^{-1} for *C. tropicallis*, which is also an organism of great concern since it causes invasive candidiasis in hospitalized patients worldwide (Xiao et al. 2014). Moreover, it was noteworthy that compounds **7** and **14** showed $IC_{50} < 1.95$ μg mL^{-1} against *C. neoformans*, which were as potent as the antimicrobial drugs, miconazole and nystatin.

Among the phenolic derivatives (**1-5**), only **1** and **2** were highly active ($IC_{50} = 4.21$ μg mL^{-1}) against *C. parapsitosis*. Derivatives of benzaldehydes bearing electron-donating (OMe) or electron-withdrawing groups at various positions (F, Cl, Br, CN, CF_3, and NO_2) were all active. The naphthalene derivative **20** and the biphenyl derivative **19** were very active against *C. parapsilosis*, *C. tropicalis* and *C. neoformans*. Although we could not determine a clear structure–activity relationship (SAR), we envisaged that the

preparation of other derivatives bearing five-membered heterocyclic, biphenyl, and naphthalene-substituted derivatives would lead to a better understanding of the SAR and to more active substances.

Conclusion

In conclusion, we have described the expeditious synthesis of TBA derivatives via bismuth (III) nitrate catalyzed Knoevenagel condensation between aryl-carbaldehydes and TBA. The reactions proceeded smoothly to afford the desired 5-arylidenethiobarbiturates in high yields within 20 min. Using this methodology, seven new and thirteen known TBAs were prepared and their inhibitory potential was evaluated against five *Candida spp*. and one *Cryptococcus* species. Several compounds had activities comparable to the commercial drugs. The preliminary SAR analysis suggested that (i) the presence of OH/OMe groups on the benzene ring and (ii) the substitution of benzene to naphthalene or pyridine moieties are detrimental for activities. On the other hand, the most active compounds against all *Candida* species had a thiophene spacer between the thiobarbiturate and the benzene ring. The position of the phenyl group on the thiophene also had an impact on the activity, with the linear-shaped compound being more potent. A new furyl derivative (**13**) was also among the most active compounds. The two species *C. parapsilosis* and *C. tropicalis* were most sensitive to the majority of the TBAs tested. These results suggest that such compounds can be further modified for the development of new antimicrobial agents for the treatment of candidiasis.

Acknowledgements We are grateful to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, grant 400746-2014) and Fundação de Amparo à Pesquisa de Minas Gerais (FAPEMIG, grant APQ1557-15) for research fellowships (JAT, LCAB). We also thank the World Academy of Sciences for the advancement of science in developing countries (TWAS) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for PhD fellowships for MS and MK. We would also like to acknowledge the Coleção de Culturas Tropical (CCT, Brazil) for donating some microbial strains.

Compliance with ethical standards

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

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