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Article

Complementary Performance of Organoselenides and Organotellurides as Antimicrobials Agents

Felipe G. Borges,[a] Tay Zugman,[a] Pamela T. Bandeira,[a] Mara C. Dalmolin,[a] Débora B. Scariot,[b] Francielle P. Garcia,[b] Alfredo R. M. de Oliveira,[a] Celso V. Nakamura[b] and Leandro Piovan[*,a]

[a]*Laboratório de Síntese Química e Enzimática (LaSQuE), Departamento de Química, Universidade Federal do Paraná, 81531-980 Curitiba-PR, Brazil*

[b]*Laboratório de Inovação Tecnológica no Desenvolvimento de Fármacos e Cosméticos Health Sciences Center, Universidade Estadual de Maringá, 87020-900 Maringá-PR, Brazil*

Fungi and bacteria are well-known pathogens for plants, fruits, and animals, including humans. In this context, the prospection of antimicrobial agents is crucial to provide new alternatives for the treatment of microbial diseases. Hence, selenium- and tellurium-containing compounds are underexploited and herein, antimicrobial activity of several organochalcogenated compounds was evaluated against Gram-negative and Gram-positive bacteria and fungi. A direct comparison between Se- and Te-containing compounds was performed, as well as structure-activity relationship studies. Among assayed compounds, secondary Se-amines **LQ16** and **LQ20** and secondary Te-amine **LQ28** showed excellent results against a variety of fungi, while primary Te-amine **LQ10** demonstrated promising results against bacteria. These results suggest organoselenides and organotellurides may be used for the development of new antimicrobial agents.

Keywords: organochalcogenides, biological activity, fungi, bacteria, chalcogen amines, chalcogen ketones

Introduction

Infectious diseases and food contamination[1,2] caused by bacteria and fungi represent a health risk for plants and animals,[3] including humans.[4] Indeed, some microorganisms have developed resistance to existing antimicrobial agents,[5] mainly due to the indiscriminate use of antimicrobial drugs in human, veterinary, and agricultural applications.[6] Resistance may be caused by intrinsic factors (structural or functional characteristics) or due to a mutation (changing the target site, enzymatic resistance, and efflux pumps),[7] hindering combat and treatment.

Bacteria are especially challenging,[8] such as Gram-positive bacteria *Staphylococcus aureus*, which can cause skin, lung, and heart infections[9] and presents a great capacity to develop antibiotic resistance.[10] In the same way, Gram-negative bacteria *Pseudomonas aeruginosa*, an opportunistic pathogen, is involved in serious respiratory infections in humans.[11] Additionally, Gram-negative bacteria *Escherichia coli*, also used as an indicator of drug resistance in bacterial communities due to its gene coding reservoir, presents remarkably diverse pathogenic forms, ranging from enteric diseases to extra-intestinal infections, such as urinary tract or systemic problems.[12]

Pathogenic fungi are also responsible for billions of infections annually, with ca. 1 million attributable mortalities.[13] The yeasts of *Candida* genus cause mainly opportunistic infections in immunocompromised patients.[14] *Trichophyton* and *Microsporum* genus are also important infectious disease prompters among dermatophyte fungi, being the major cause of superficial mycoses and also an important public health problem, with *Trichophyton rubrum* as one of the most prevalent species.[15]

In this context, there is a room for discovering new antimicrobial compounds either from natural sources[16] or through the development of synthetic compounds such as selenium- and tellurium-containing ones.[17] Thus, the insertion of selenium and tellurium in organic structure allows to achieve a broad diversity of substances according to the oxidation state of chalcogen. This range of possibilities could imply in substances with distinct biological activity. Organochalcogenated substances have

*e-mail: lpiovan@quimica.ufpr.br

already been described as antioxidant,[18] anticancer,[19] cysteine-[20] and threonine-proteases[21] and tyrosine phosphatase inhibitors,[22] antidepressant,[23] neuroprotector,[24] antiviral,[25] antinociceptive,[26,27] anticonvulsant,[28] and anti-inflammatory.[26,29] On the other hand, the antimicrobial activity of organochalcogenated compounds has been scarcely exploited.

To the best of our knowledge, selenides have been reported as active against bacteria such as Gram-negative *Escherichia coli*,[30-34] *Pseudomonas aeruginosa*,[30,34] *Salmonella typhimurium*,[1,30] *Salmonella enteritidis*[2,33] among others,[33,34] and Gram-positive *Listeria monocytogenes*,[1,2,30,31,35] *Staphylococcus aureus*,[1,2,30,33,34,36] *Bacillus cereus*,[30,33-36] *Enterococcus faecalis*[31] among others.[35] Tellurides antibacterial activity are scarce and only *Escherichia coli*,[37,38] *Klebsiella pneumonia*,[37] *Salmonella* spp.[37] (Gram-negatives), *Staphylococcus aureus*,[37] *Streptococcus* sp.,[37] *Bacillus subtilis*,[37] and *Bacillus cereus*[37] (Gram-positives) were assayed.

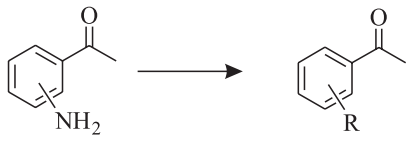
Regarding antifungal activities, selenides have been reported as active against *Candida species*[31-33,36] (*C. albicans*, *C. keyfer*, *C. krusei*, and *C. parapsilosis*), *Cryptococcus neoformans*,[31] *Chrysosporium tropicum*,[36] *Aspergillus niger*,[31-33] *Neurospora crassa*,[31] *Aspergillus fumigatus*,[32] and *Trichophyton rubrum.*[36] For tellurides, once again a small number of microorganisms have been assayed and only *Aspergillus* spp.,[37] *Candida* spp.,[37] and fluconazole-resistant *Candida albicans*[39] strains were reported.

It is also worth mentioning the absence of direct comparative studies between selenium and tellurium-containing congeners in literature. Due to this fact, we decided to carry out this study involving organoselenides and organotellurides to compare their antimicrobial activities against Gram-negative and Gram-positive bacteria and fungi. *Ortho*, *meta*, and *para*-substituted organochalcogen ketones and amines (primary and secondary) were evaluated and structure-activity relationships were identified.

Results and Discussion

Synthesis of compounds

To evaluate and compare the antimicrobial activity of Se- and Te-containing compounds, a series of organochalcogenides was synthesized. The effects of structural changes, such as chalcogen atom (Se or Te), aromatic ring substitution pattern (*ortho*, *meta,* and *para*), and the presence of a second functional group (ketone or amine) were evaluated. All substances were prepared as previously reported by our group.[40] Briefly, organoselenium ketones **LQ13-15** were prepared from the reaction of aryl diazonium salts of *ortho*, *meta*, and *para*-amino acetophenones with lithium butylselenolate at 0 °C (Scheme 1) with 38-57% yield (Table 1). Se-ketones **LQ14-15** were obtained in the form of orange oils, except the *ortho* congener **LQ13**, which showed up as a yellow solid.



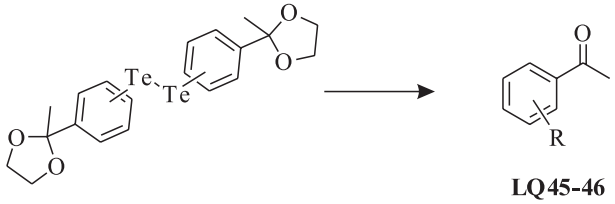
LQ13-15

Scheme 1. Reagents and conditions: (*i*) H_2SO_4, H_2O, $NaNO_2$; (*ii*) $Na_2CO_{3(aq)}$, pH 7; (*iii*) BuSeLi, room temperature, 1 h.

Table 1. Yields for the synthesis of Se-ketones **LQ13-15**

Organochalcogenide	R	Yield / %
LQ13	*o*Se^{n}Bu	55
LQ14	*m*Se^{n}Bu	38
LQ15	*p*Se^{n}Bu	57

Organotellurium ketones **LQ45-46** were synthesized as yellowish oils from the reaction of corresponding diacetal ditellurides with $NaBH_4$ (Te–Te bond cleavage) followed by Te-alkylation with butyl bromide. In the sequence, acetal deprotection reaction with *p*TSA in acetone led to Te-ketones **LQ45-46** (Scheme 2) with 57-73% isolated yield (Table 2).



LQ45-46

Scheme 2. Reagents and conditions: (*i*) ^{n}BuBr, THF, 0 °C; (*ii*) $NaBH_{4(aq)}$, 10 min; (*iii*) acetone, *p*TSA, 3 h.

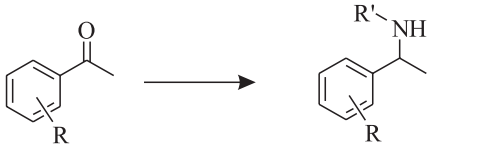
Table 2. Yields for the synthesis of Te-ketones **LQ45-46**

Organochalcogenide	R	Yield / %
LQ45	*m*Te^{n}Bu	73
LQ46	*p*Te^{n}Bu	57

Finally, organochalcogen amines (**LQ9-10**, **LQ16-18**, **LQ20**, **LQ28**, and **LQ30**) were obtained through reductive amination, from the corresponding organochalcogen ketone, in a microwave-assisted reaction with a total reaction time of 5 min (Scheme 3), in a 43-89% yield

(Table 3). Se-amines **LQ16-18**, **LQ20**, and **LQ30** were obtained as yellow liquids, while Te-amines **LQ09-10** were obtained as yellow oils and **LQ28** was obtained as an orange oil.

All substances were characterized by ^{1}H and ^{13}C nuclear magnetic resonance (NMR), Fourier-transform infrared spectroscopy (FTIR), and gas chromatography-mass spectrometry (GC-MS) and their data are in accordance with the literature.[40]



LQ09-10,16-18,20,28,30

Scheme 3. Reagents and conditions: EtOH, amine source, $NaBH_3CN$, AcOH, microwave, 80 ºC, 5 min.

Table 3. Yields for the synthesis of chalcogen amines

Organochalcogenide	R	R'	Yield / %
LQ09	*m*Te^{n}Bu	H	89
LQ10	*p*Te^{n}Bu	H	73
LQ30	*o*Se^{n}Bu	H	67
LQ17	*m*Se^{n}Bu	H	51
LQ18	*p*Se^{n}Bu	H	43
LQ16	*p*Se^{n}Bu	*s*-Bu	56
LQ20	*p*Se^{n}Bu	*i*-Bu	40
LQ28	*p*Te^{n}Bu	*i*-Bu	86

Biological assays

After the synthesis, all organochalcogenides were assayed against the bacteria *Staphylococcus aureus* ATCC 25923 (Gram-positive), *Escherichia coli* ATCC 25922 (Gram-negative), *Pseudomonas aeruginosa* ATCC 27853 (Gram-negative); the yeasts *Candida parapsilosis* ATCC 22019, *Candida tropicalis* ATCC 200958, *Candida krusei* ATCC 6258, *Candida albicans* ATCC 10231; and against dermatophyte fungi *Trichophyton rubrum* ATCC 28189, *Trichophyton mentagrophytes* ATCC 11480, and *Microsporum gypseum* ATCC 14683. The results, expressed as MIC (minimum inhibitory concentration), MBC (minimum bactericidal concentration), and MFC (minimum fungicidal concentration) in μg mL^{-1}, are compilated in Tables 4 and 5. For the analysis of the results, the antimicrobial activities were considered good for MIC < 100 μg mL^{-1}; moderate to MIC between 100 and 500 μg mL^{-1}, weak for MIC between 500 and 1000 μg mL^{-1} and inactive if MIC > 1000 μg mL^{-1}.[41]

Antibacterial activity

The results presented in Table 4 disclosed the Te-ketone **LQ46** (MIC/MBC = 125/1000 μg mL^{-1}) and Te-amines

Table 4. Antibacterial activity of the synthesized compounds

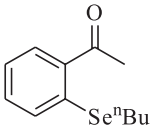
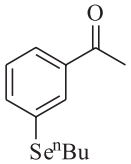
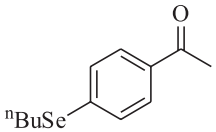
Organochalcogenide	Bacteria MIC/MBC / (μg mL^{-1})		
	S. aureus ATCC 25923	*E. coli* ATCC 25922	*P. aeruginosa* ATCC 27853
 **LQ13**	> 1000	> 1000	> 1000
 **LQ14**	> 1000	> 1000	> 1000
 **LQ15**	> 1000	> 1000	> 1000

Table 4. Antibacterial activity of the synthesized compounds (cont.)

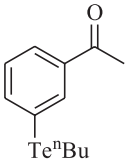
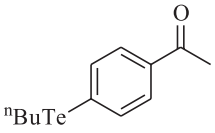
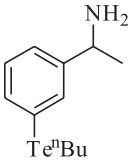
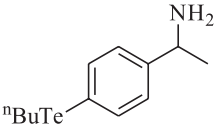
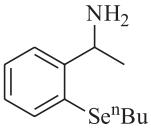
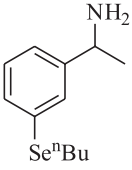
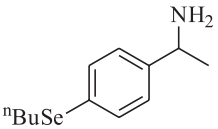
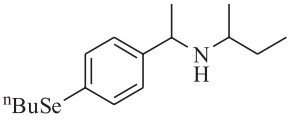
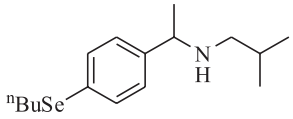
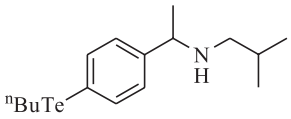
Organochalcogenide	Bacteria MIC/MBC / (μg mL^{-1})		
	S. aureus ATCC 25923	*E. coli* ATCC 25922	*P. aeruginosa* ATCC 27853
 **LQ45**	500/1000	125/250	> 1000
 **LQ46**	125/1000	125/> 1000	> 1000
 **LQ09**	500/500	125/125	125/125
 **LQ10**	250/250	62.5/62.5	62.5/250
 **LQ30**	> 1000	1000/>1000	> 1000
 **LQ17**	> 1000	1000/1000	> 1000
 **LQ18**	1000/1000	1000/1000	> 1000
 **LQ16**	500/500	> 1000	> 1000

Table 4. Antibacterial activity of the synthesized compounds (cont.)

Organochalcogenide	Bacteria MIC/MBC / (μg mL^{-1})		
	S. aureus ATCC 25923	*E. coli* ATCC 25922	*P. aeruginosa* ATCC 27853
 **LQ20**	500/500	> 1000	> 1000
 **LQ28**	125/250	125/125	500/> 1000
Streptomycin	15.6/62.5	7.8/7.8	3.9/62.5

MIC: minimal inhibitory concentration; MBC: minimal bactericidal concentration.

Table 5. Antifungal activity of the synthesized compounds

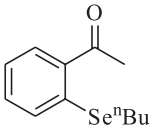
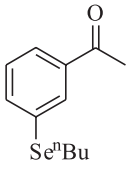
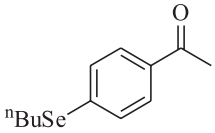
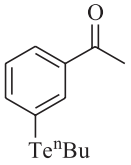
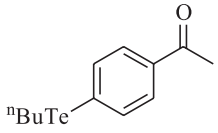
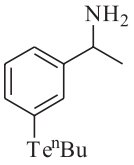
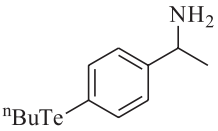
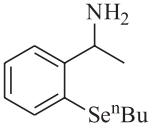
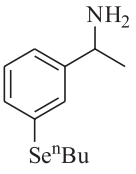
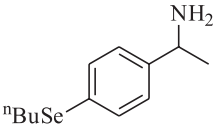
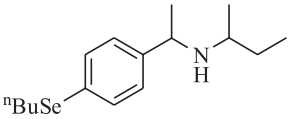
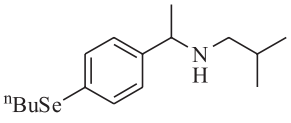
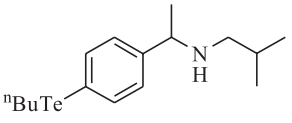
Compound	Fungi MIC/MFC / (μg mL^{-1})						
	T. rubrum ATCC 28189	*T. mentagrophytes* ATCC 11480	*M. gypseum* ATCC 14683	*C. parapsilosis* ATCC 22019	*C. tropicalis* ATCC 200958	*C. krusei* ATCC 6258	*C. albicans* ATCC 10231
 **LQ13**	1000/1000	1000/1000	1000/1000	> 1000	> 1000	> 1000	> 1000
 **LQ14**	> 1000	>1000	> 1000	> 1000	> 1000	> 1000	> 1000
 **LQ15**	500/500	500/1000	1000/1000	> 1000	> 1000	> 1000	> 1000
 **LQ45**	250/250	500/500	500/500	1000/> 1000	1000/> 1000	1000/> 1000	1000/> 1000
 **LQ46**	125/125	500/500	250/250	1000/> 1000	500/1000	500/> 1000	500/1000

Table 5. Antifungal activity of the synthesized compounds (cont.)

Compound	Fungi MIC/MFC / (μg mL^{-1})						
	T. rubrum ATCC 28189	*T. mentagrophytes* ATCC 11480	*M. gypseum* ATCC 14683	*C. parapsilosis* ATCC 22019	*C. tropicalis* ATCC 200958	*C. krusei* ATCC 6258	*C. albicans* ATCC 10231
 **LQ09**	500/500	500/> 1000	500/500	1000/1000	500/1000	500/1000	1000/> 1000
 **LQ10**	500/500	500/1000	500/1000	500/500	500/500	250/1000	1000/1000
 **LQ30**	500/1000	500/1000	1000/> 1000	> 1000	> 1000	1000/1000	1000/1000
 **LQ17**	1000/1000	1000/>1000	1000/1000	1000/1000	1000/> 1000	1000/1000	250/250
 **LQ18**	1000/1000	1000/1000	1000/> 1000	1000/1000	> 1000	500/1000	125/250
 **LQ16**	62.5/125	62.5/125	62.5/62.5	500/1000	500/500	250/500	31.25/125
 **LQ20**	62.5/62.5	31.25/31.25	62.5/62.5	1000/1000	500/1000	500/> 1000	31.25/250
 **LQ28**	62.5/62.5	62.5/62.5	125/125	250/500	250/250	125/250	250/250
Fluconazole	31.25/31.25	125/125	125/125	3.9/7.8	3.9/3.9	62.5/125	7.8/7.8

MIC: minimal inhibitory concentration; MFC: minimal fungicidal concentration.

LQ10 (MIC/MBC = 250/250 μg mL^{-1}) and **LQ28** (MIC/MBC = 125/250 μg mL^{-1}) as the most powerful substances against Gram-positive bacteria *S. aureus*. **LQ10** and **LQ28** were considered more powerful agents than **LQ46** since they were able to cause death of *S. aureus* in a lower concentration. These results highlighted the fact that amine-containing tellurides were more effective than ketone-containing ones.

These Te-amines are both *para*-substituted, which indicates that this pattern was preponderant for this particular biological activity, especially when **LQ10** (MIC = 250 μg mL^{-1}) is directly compared with its *meta* counterpart **LQ09** (MIC = 500 μg mL^{-1}), considered as a weak bactericidal agent for *S. aureus*.

The nature of chalcogen had a strong influence over antibacterial activity against *S. aureus*. This is easily observed by direct comparison of MIC values of **LQ20** (secondary Se-amine, MIC = 500 μg mL^{-1}), **LQ28** (secondary Te-amine, MIC = 125 μg mL^{-1}), **LQ10** (primary Te-amine, MIC = 250 μg mL^{-1}), and **LQ18** (primary Se-amine, MIC = 1000 μg mL^{-1}), which demonstrate that the presence of tellurium led to more effective substances than the presence of selenium.

The ketones synthesized in this work followed a similar behavior, since Te-ketones had better antimicrobial activity than Se-ketones against *S. aureus* and, in addition, the compound **LQ46** showed better MIC value than Se-amines, which highlights the role of the presence of tellurium in the structure. However, MIC/MBC values of the two secondary Se-amines **LQ16** and **LQ20** (MIC/MBC = 500/500 μg mL^{-1} for both) were better than Te-ketones (**LQ45**, MIC/MBC = 500/1000 μg mL^{-1}; **LQ46**, MIC/MBC = 125/1000 μg mL^{-1}), especially through the MBC values, highlighting the relevance of the secondary amine in the structure for this biological activity.

Resembling conclusions can be drawn by comparing tellurium and selenium compounds against Gram-negative *E. coli* and *P. aeruginosa* bacteria, since tellurium compounds presented preeminent antibacterial activity than their selenylated equivalents. This can be seen through the results of the primary Te-amine **LQ10**, which presented the highest activity against the two Gram-negative bacteria tested, with MIC/MBC values of 62.5/62.5 and 62.5/250 μg mL^{-1} against *E. coli* and *P. aeruginosa*, respectively. Primary Te-amine (**LQ09**) showed moderate activities (MIC/MBC = 125/125 μg mL^{-1}) for both *E. coli* and *P. aeruginosa* bacteria. All primary Se-amines (**LQ17**, **LQ18**, and **LQ30**) activities were considered no significant. Secondary Te-amine (**LQ28**), presented moderate activity against *E. coli* (MIC/MBC = 125/125 μg mL^{-1}) and weak activity against *P. aeruginosa* (MIC/MBC = 500/> 1000 μg mL^{-1}), which suggests that the primary amine is preferred to the secondary one for *P. aeruginosa*, not being an evident phenomenon to the *S. aureus*. Secondary Se-amines (**LQ16** and **LQ20**) exhibited no significant activities, showing again that tellurium compounds were better than selenium for these two bacteria. Against *E. coli*, Te-ketones **LQ45** and **LQ46** exhibited weak and moderate activity, respectively, suggesting that the amine functional group led to more active compounds than ketone-containing congeners. Furthermore, the selenylated ketones (**LQ13**, **LQ14**, and **LQ15**) were not considered to be significantly active for these bacteria.

Antifungal activity

In the evaluation of organochalcogenides against fungi (Table 5), the ones with secondary amines were the most powerful antifungal agents, as observed for *T. mentagrophytes* and *M. gypseum* fungi. For *T. mentagrophytes*, MIC/MFC of the secondary chalcogen amines **LQ16**, **LQ20**, and **LQ28** were 62.5/125, 31.25/31.25, and 62.5/62.5 μg mL^{-1}, respectively, these compounds being even more powerful than fluconazole, a reference drug used as control (MIC/MFC = 125/125 μg mL^{-1}). Secondary Se-amine **LQ20** was more efficient than equivalent secondary Te-amine **LQ28**. Similar results were observed in assays with *M. gypseum*, in which secondary Se-amines **LQ16** (MIC/MFC = 62.5/62.5 μg mL^{-1}) and **LQ20** (MIC/MFC = 62.5/62.5 μg mL^{-1}) were better than the control. For secondary Te-amine **LQ28**, MIC/MFC values were equal to fluconazole.

Evaluation against *T. rubrum* presented similar results for the following compounds: **LQ16** (MIC/MFC = 62.5/125 μg mL^{-1}), **LQ20** (MIC/MFC = 62.5/62.5 μg mL^{-1}), and **LQ28** (MIC/MFC = 62.5/62.5 μg mL^{-1}), where it was observed that a change in the position of methyl substituent leads to a tenuous difference in MFC, beneficial for **LQ20** isomer, while the nature of chalcogen did not influence in this case. Antifungal activities of primary organochalcogen amines (**LQ09**, **LQ10**, **LQ17**, **LQ18**, and **LQ30**) were considered weak or no significant for all the tested fungi, except for *C. albicans*. Te-amines performed better as antifungal agents than their respective selenylated equivalents, exception again for the occurrence of *C. albicans*, in which Se-amines **LQ17** and **LQ18** achieved better outcomes.

Organochalcogen ketones (**LQ13**, **LQ14**, **LQ15**, **LQ45**, and **LQ46**) assayed against *T. mentagrophytes* and *M. gypseum*, presented weak or no significant activities, except for **LQ46** against *M. gypseum*, which showed moderate activity (MIC/MFC = 250/250 μg mL^{-1}). As well as in primary organochalcogen amines, the presence of

tellurium improved the biological activity in comparison to selenium. A similar conclusion was reached concerning the activities of these same ketones against *T. rubrum*. It was observed that both Te-ketones (**LQ45** and **LQ46**) showed moderate activity while Se-ketones **LQ13** and **LQ14** showed no significant activities and just a weak activity was observed for **LQ15**. For most of the Se-ketones, results were not significant or worse than Te-ketones. Therefore, for the ketones assayed in this work, it can be concluded that tellurium-containing ones were more active than selenium-containing congeners for both fungi and bacteria.

Another obtained conclusion was that *para* substitution pattern led to more active substances than *meta* or *ortho* substitution pattern against *T. rubrum*. This can be observed by comparing Te-ketones **LQ45** (MIC/MFC = 250/250 μg mL^{-1}) and **LQ46** (MIC/MFC = 125/125 μg mL^{-1}). This also occurred for Se-ketones **LQ13** (MIC/MFC = 1000/1000 μg mL^{-1}), **LQ14** (MIC > 1000 μg mL^{-1}), and **LQ15** (MIC/MFC = 500/500 μg mL^{-1}). Hence, considering the results for these two fungi, *T. mentagrophytes* and *M. gypseum*, it can be said that the secondary amine strongly indulges the biological activity studied in this work, when compared to the primary amine or the ketone function.

Regarding *Candida* strains, the activity of secondary Te-amine **LQ28** was considered moderate for all four species and better than their respective selenylated equivalents, except for *C. albicans*. In this specific case, secondary Se-amines **LQ16** (MIC = 31.25 μg mL^{-1}) and **LQ20** (MIC = 31.25 μg mL^{-1}) activities were considered as good, being better than **LQ28** (MIC = 250 μg mL^{-1}), which suggests that selenium is preferred over tellurium for *C. albicans*. Similar performance was observed for primary amines, since primary Se-amines **LQ17** (MIC = 250 μg mL^{-1}) and **LQ18** (MIC = 125 μg mL^{-1}) showed moderate activity against *C. albicans* while similar primary Te-amines (**LQ09** and **LQ10**) showed no significant activity. Once more, selenium-containing substances were more powerful than tellurium-containing ones for *C. albicans*. Moreover, for primary Se-amines it can be observed that *para* position (**LQ18**) was more active in comparison with *meta* (**LQ17**) and *ortho* (**LQ30**). Organochalcogen ketones showed no significant activity in most of the cases for *Candida* strains. The results for *T. mentagrophytes* and *M. gypseum*, along with results for *Candida* strains led to the conclusion that the presence of secondary amine improves the antifungal activity when compared to the primary amine or the ketone function.

Conclusions

Evaluation of the antimicrobial activity of organochalcogenated ketones and amine disclosed organoselenides as preferential antifungal agents while organotellurides were identified as better antibacterial agents. Organochalcogen ketones were considered inactive. Only primary organotellurium amine **LQ10** showed significant antibacterial activity against *E. coli* and *P. aeruginos*a, but it was inactive against fungi. Secondary organoselenium amines **LQ16** and **LQ20** showed good antifungal activity, mainly against *T. mentagrophyte*s and *M. gypseum*, being even more active than fluconazole. Secondary Te-amine **LQ28** was the unique substance that presented moderate antibacterial activity (*S. aureus* and *E. coli*) and moderate or good antifungal activity for all yeasts and fungi assayed, choosing **LQ28** as a promising structure for the development of antimicrobial agents.

Experimental

General

^{1}H and ^{13}C NMR analyses were carried out at room temperature with a Bruker AVANCE 200 or AVANCE 400 spectrometer operating at 4.7 or 9.4 T, and observing ^{1}H at 200.13 or 400.26 MHz and ^{13}C at 50.03 or 100.06 MHz respectively. Chemical shifts, expressed in ppm, are related to the tetramethylsilane (TMS) signal at 0.00 ppm used as internal reference. ^{1}H NMR data are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and relative intensity (integral). GC-MS spectra were recorded with a Shimadzu QP-2010 Plus apparatus, equipped with an RTX-5 capillary column (30 m × 0.25 mm × 0.25 μm film thickness) and operating in ionization mode by electron impact (70 eV). This was coupled to a Shimadzu GC-2010 gas chromatograph operating with a helium flow rate of 1 mL min^{-1} and an injector temperature set to 200 ºC. The temperature was programmed to 50 ºC for 1 min, increased at 10 ºC min^{-1} up to 250 ºC and kept at 250 ºC for 10 min. Selenium compounds were analyzed by Fourier-transform infrared spectroscopy (FTIR) with a BOMEM Michelson MB100 spectroscope in the spectral range of 4000-400 cm^{-1}, with 64 and 32 scans for solid and liquid samples respectively, and resolution of 4 cm^{-1}. KBr pellets were used for the analysis of solids, while liquid samples were deposited on KBr crystals.

Synthesis of the organoselenium ketones

To a cooled solution (0 ºC) of the appropriate aminoacetophenone (0.405 g, 3 mmol) containing sulfuric acid (0.8 mL) and water (0.8 mL), 1.0 mL of an aqueous

solution of sodium nitrite (0.276 g, 4 mmol) was added dropwise, followed by slow addition of an aqueous solution of Na_2CO_3 until pH 7. This reaction mixture then received the addition of lithium butylselenolate (0.288 g, 4.5 mmol) dissolved in 5 mL of THF, which gave a biphasic mixture that was continuously stirred at room temperature for 1 h. Afterward, the mixture was diluted with brine (20 mL) and extracted with ethyl acetate (5 × 20 mL). The organic phase was separated, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed under reduced pressure and the crude material was purified by flash chromatography using a mixture of hexanes and ethyl acetate (9:1) as eluent.

1-(2-(Butylselanyl)phenyl)ethanone (**LQ13**)

Yield: 55%; yellow solid; FTIR (KBr) ν / cm^{-1} 2957, 2928, 2870, 2123, 1666, 1585, 1454, 1248, 756; ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 7.90 (dd, J_A 7.8, J_B 1.5 Hz, 1H), 7.50 (m, 1H), 7.40 (td, J_A 7.0, J_B 1.5 Hz, 1H), 7.24 (td, J_A 7.0, J_B 1.5 Hz, 1H), 2.84 (t, *J* 7.5 Hz, 2H), 2.62 (s, 3H), 1.73 (m, 2H), 1.50 (m, 2H), 0.95 (t, *J* 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.7, 133.1, 132.2, 131.7, 128.5, 128.3, 124.2, 30.7, 27.5, 24.8, 23.4, 13.6; GC-MS (70 eV), *m/z* (relative abundance): 256 (M^+, 21), 241 (1), 199 (100), 182 (11), 169 (3), 157 (9), 130 (1), 117 (2), 105 (5), 91 (25), 77 (12), 65 (3), 51 (3), 43 (35).

1-(3-(Butylselanyl)phenyl)ethanone (**LQ14**)

Yield: 38%; orange oil; FTIR (KBr) ν / cm^{-1} 2959, 2930, 2870, 1944, 1686, 1568, 1464, 1252, 785; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.89 (dd, J_A 7.7, J_B 1.2 Hz, 1H), 7.48 (d, *J* 7.9 Hz, 1H), 7.39 (dt, J_A 7.4, J_B 1.0 Hz, 1H), 7.23 (m, 1H), 2.83 (t, *J* 7.5 Hz, 2H), 2.61 (s, 3H), 1.74 (m, 2H), 1.50 (m, 2H), 0.95 (t, *J* 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 138.3, 135.5, 132.2, 131.7, 128.4, 124.2, 30.7, 27.5, 24.8, 23.4, 13.7; GC-MS (70 eV), *m/z* (relative abundance): 256 (M^+, 71), 252 (14), 241 (3), 227 (1), 213 (1), 200 (64), 185 (53), 181 (12), 156 (14), 130 (2), 117 (4), 105 (3), 91 (10), 77 (14), 63 (4), 57 (30), 43 (100).

1-(4-(Butylselanyl)phenyl)ethanone (**LQ15**)

Yield: 57%; orange oil; FTIR (KBr) ν / cm^{-1} 2959, 2930, 2872, 1680, 1587, 1464, 1267, 816; ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 7.81 (dt, J_A 8.6, J_B 1.9 Hz, 2H), 7.48 (dt, J_A 8.6, J_B 1.9 Hz, 2H), 3.00 (t, *J* 7.4 Hz, 2H), 2.57 (s, 3H), 1.73 (m, 2H), 1.43 (m, 2H), 0.93 (t, *J* 7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.3, 139.2, 134.8, 133.1, 130.2, 128.7, 128.3, 31.9, 26.7, 26.4, 23.0, 13.5; GC-MS (70 eV), *m/z* (relative abundance): 256 (M^+, 86), 241 (18), 200 (58), 185 (94), 181 (21), 156 (18), 130 (3), 117 (6), 105 (16), 91 (14), 77 (22), 63 (7), 57 (55), 43 (100).

Synthesis of the organotellurium ketone

The solution of appropriate ditelluride (1.74 g, 3 mmol) and butyl bromide (9 mmol, 0.98 mL) in THF (40 mL) was cooled to 0 °C and treated slowly with $NaBH_4$ (15 mmol, 0.567 g) dissolved in water (10 mL). After stirring for 10 min, aqueous NH_4Cl solution was added (20 mL), the resulting mixture extracted with dichloromethane (3 × 20 mL) and concentrated under reduced pressure. The crude product was dissolved in acetone (20 mL), *p*-toluenesulfonic acid (0.03 g) was added and the mixture was refluxed for 3 h. Then, acetone was removed under reduced pressure, water (10 mL) was added and the product extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried over anhydrous magnesium sulfate, concentrated and the product was purified by flash chromatography using hexanes and ethyl acetate (9:1) as eluent.

1-(3-(Butyltellanyl)phenyl)ethanone (**LQ45**)

Yield: 73%; pale oil; FTIR (KBr) ν / cm^{-1} 3051, 2957, 2926, 2870, 2862, 1686, 1678, 1560, 1472, 1356, 1254, 1182, 1171, 1059, 959, 789, 689, 652, 592, 453; ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 8.02 (s, 1H), 7.74-7.93 (m, 2H), 7.28 (t, *J* 7.6 Hz, 1H), 2.95 (t, *J* 7.6 Hz, 2H), 2.59 (s, 3H), 1.79 (quint, *J* 8.0 Hz, 2H), 1.40 (sext, *J* 7.3 Hz, 2H), 0.90 (t, *J* 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.6, 142.4, 137.7, 129.1, 127.3, 112.4, 33.8, 26.6, 25.0, 13.3, 8.9.

1-(4-(Butyltellanyl)phenyl)ethanone (**LQ46**)

Yield: 57%; orange oil; FTIR (KBr) ν / cm^{-1} 3346, 2957, 2926, 2870, 1682, 1582, 1423, 1391, 1358, 1269, 1182, 1080, 1009, 957, 816, 743, 679, 600, 590, 451; ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 7.67-7.78 (s, 4H), 2.97 (t, *J* 7.7 Hz, 2H), 2.57 (s, 3H), 1.82 (quint, *J* 7.7 Hz, 2H), 1.41 (sext, *J* 7.7 Hz, 3H), 0.91 (t, *J* 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.7, 136.6, 135.8, 128.5, 120.9, 33.7, 26.4, 25.1, 13.4, 8.7; GC-MS (70 eV), *m/z* (relative abundance): 306 (M^+, 12), 250 (9), 234 (8), 206 (6), 120 (2), 105 (15), 91 (4), 77 (17), 73 (4), 57 (28), 43 (100).

Synthesis of the organochalcogen amines

To a microwave vial, the appropriate amine (2 equiv.), acetic acid (0.525 g, 8.7 mmol) and sodium cyanoborohydride (1.2 equiv.), were added to a solution of organochalcogen ketone (0.100 g, 0.390 mmol) in ethanol (1 mL). The mixture was heated in a Cem Discovery microwave reactor at 80 ºC for 5 or 10 min under magnetic stirring. Then, the solvent was removed under reduced pressure, the crude material was treated with a 2 mol L^{-1}

sodium hydroxide solution until pH 10 and the product was extracted with dichloromethane (3 × 5 mL). The organic portions were combined, dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure and the crude material was purified by flash chromatography using a mixture of ethyl acetate and ethanol (9:1) as eluent.

1-(2-(Butylselanyl)phenyl)ethanamine (**LQ30**)

Yield: 67%; yellow liquid; FTIR (KBr) ν / cm^{-1} 3360, 3288, 2959, 2928, 2870, 1906, 1591, 1454, 1257, 822; ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 7.46 (m, 2H), 7.27 (m, 1H), 7.18 (dd, J_A 7.4, J_B 1.7 Hz, 1H), 4.58 (q, J 6.6 Hz, 1H), 2.91 (t, J 7.3 Hz, 2H), 1.70 (m, 2H), 1.46 (m, 2H), 1.38 (d, J 6.6 Hz, 3H), 0.92 (t, J 7.3 Hz, 3H);^{13}C NMR (50 MHz, $CDCl_3$) δ 147.9, 131.0, 130.6, 129.6, 129.1, 124.0, 51.2, 32.3, 27.5, 25.3, 22.9, 13.6; GC-MS (70 eV), *m/z* (relative abundance): 257 (M^+, 44), 242 (21), 238 (6), 200 (93), 183 (79), 179 (16), 157 (6), 131 (2), 119 (93), 104 (100), 91 (28), 72 (30), 65 (4), 51 (8), 44 (23).

1-(3-(Butylselanyl)phenyl)ethanamine (**LQ17**)

Yield: 51%; yellow liquid; FTIR (KBr) ν / cm^{-1} 3360, 2959, 2928, 2870, 1940, 1688, 1587, 1464, 1454, 1254, 785; ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 7.47 (s, 1H) 7.34 (dt, J_A 6.4, J_B 1.8 Hz, 1H), 7.20 (m, 2H), 4.08 (q, J 6.6 Hz, 1H), 2.93 (t, J 7.5 Hz, 2H), 1.70 (m, 2H), 1.43 (m, 2H), 1.37 (d, J 6.6 Hz, 3H), 0.91 (t, J 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.6, 130.9, 130.6, 129.7, 129.1, 124.1, 51.2, 32.3, 27.6, 25.6, 23.0, 13.6; GC-MS (70 eV), *m/z* (relative abundance): 257 (M^+, 34), 242 (100), 214 (1), 200 (5), 185 (28), 158 (5), 137 (1), 120 (16), 106 (22), 91 (9), 78 (21), 65 (3), 55 (10), 44 (48).

1-(4-(Butylselanyl)phenyl)ethanamine (**LQ18**)

Yield: 43%; yellow liquid; FTIR (KBr) ν / cm^{-1} 3354, 3288, 2959, 2928, 2870, 1906, 1591, 1493, 1454, 1257, 822; ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 7.45 (dt, J_A 8.3, J_B 1.8 Hz, 2H), 7.23 (dt, J_A 8.3, J_B 1.8 Hz, 2H), 4.08 (q, J 6.6 Hz, 1H), 2.90 (t, J 7.3 Hz, 2H), 1.77 (m, 2H), 1.68 (m, 2H), 1.37 (s, 3H), 0.90 (t, J 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.3, 132.7, 128.6, 126.4, 50.9, 32.2, 27.8, 25.6, 22.9, 13.5; GC-MS (70 eV), *m/z* (relative abundance): 257 (M^+, 22), 241 (100), 214 (1), 200 (5), 186 (20), 158 (4), 133 (1), 120 (22), 106 (23), 91 (6), 78 (17), 65 (2), 55 (4), 42 (15).

1-(3-(Butyltellanyl)phenyl)ethanamine (**LQ09**)

Yield: 89%; yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 7.85 (s, 1H), 7.56 (d, J 7.3 Hz, 1H), 7.08-7.26 (m, 2H), 4.08 (q, J 6.5 Hz, 1H), 2.95 (t, J 7.5 Hz, 3H), 1.72-1.90 (m, 2H), 1.40 (d, J 6.5 Hz, 4H), 1.25-1.53 (m, 2H), 0.93 (t, J 7.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.4, 136.5, 129.2, 124.9, 112.1, 51.1, 33.9, 25.5, 25.0, 13.4, 8.4.

1-(4-(Butyltellanyl)phenyl)ethanamine (**LQ10**)

Yield: 73%; yellow oil; FTIR (KBr) ν /cm^{-1} 3288, 3063, 2959, 2926, 2870, 1655, 1587, 1560, 1487, 1454, 1400, 1375, 1246, 1095, 1011, 887, 920, 700, 540; ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 7.65-7.69 (dd, J_A 8.2, J_B 1.9 Hz, 2H), 7.15-7.19 (dd, J_A 8.2, J_B 1.9 Hz, 2H), 4.08 (q, J 6.6 Hz, 1H), 2.89 (t, J 7.8 Hz, 2H), 1.80-1.60 (m, 3H), 1.23-1.50 (m, 6H), 0.90 (t, J 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.2, 138.5, 126.6, 109.5, 51.0, 33.9, 25.6, 25.0, 13.4, 8.4; GC-MS (70 eV), *m/z* (relative abundance): 307 (M^+, 84), 292 (82), 249 (8), 235 (63), 206 (2), 120 (51), 104 (100), 91 (14), 77 (44), 65 (4), 44 (78), 41 (39).

N-(1-(4-(Butylselanyl)phenyl)ethyl)-2-methylpropan-1-amine (**LQ20**)

Yield: 40%; yellow liquid; FTIR (KBr) ν / cm^{-1} 3321, 2957, 2928, 2870, 1466, 1128, 822; ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 7.43 (dd, J_A 8.3, J_B 1.9 Hz, 2H), 7.20 (dt, J_A 8.1, J_B 1.8 Hz, 2H), 3.69 (q, J 6.6 Hz, 1H), 2.91 (t, J 7.2 Hz, 2H), 2.40-2.15 (m, 2H), 1.78-1.55 (m, 3H), 1.53-1.24 (m, 6H), 0.90 (t, J 7.3 Hz, 3H), 0.88 (dd, J_A 6.6, J_B 0.6 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.8, 132.5, 128.5, 127.3, 58.0, 55.9, 32.3, 28.5, 27.7, 24.4, 22.9, 20.8, 20.6, 13.5; GC-MS (70 eV), *m/z* (relative abundance): 315 (M^+, 1), 298 (39), 270 (4), 241 (100), 207 (2), 185 (22), 157 (2), 132 (2), 104 (39), 78 (10), 65 (1), 57 (11), 44 (5).

N-(1-(4-(Butylselanyl)phenyl)ethyl)butan-2-amine (**LQ16**)

Yield: 56%; yellow liquid; FTIR (KBr) ν / cm^{-1} 3319, 2959, 2928, 2872, 1902, 1485, 1464, 1371, 1014, 824; ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 7.43 (dd, J_A 8.2 and J_B 1.8 Hz, 2H), 7.18 (dd, J_A 8.1 and J_B 1.8 Hz, 2H), 3.86 (m, 1H), 2.90 (t, J 7.3 Hz, 2H), 2.38 (m, 1H), 1.69 (m, 2H), 1.35 (m, 7H), 0.91 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.8, 132.5, 128.4, 127.2, 54.5, 51.2, 32.3, 30.6, 27.7, 25.0, 24.5, 22.9, 20.6, 19.5, 13.5, 10.4, 9.8; GC-MS (70 eV), *m/z* (relative abundance): 313 (M^+, 4), 298 (37), 284 (12), 256 (2), 241 (100), 199 (2), 185 (27), 157 (2), 146 (1), 120 (3), 104 (50), 78 (14), 57 (9), 44 (19).

N-(1-(4-(Butyltellanyl)phenyl)ethyl)-2-methylpropan-1-amine (**LQ28**)

Yield: 86%; orange oil; FTIR (KBr) ν / cm^{-1} 3319, 3063, 2957, 2928, 2870, 2351, 2328, 2174, 1591, 1556, 1481, 1462, 1394, 1180, 1163, 1119, 1011, 822, 723, 554, 467; ^{1}H NMR (200 MHz, $CDCl_3$, TMS) δ 7.67 (dd, J_A 8.1, J_B 1.6 Hz, 2H), 7.20 (dd, J_A 8.1, J_B 1.6 Hz, 2H), 4.85 (sl, NH),

3.84 (q, *J* 6.7 Hz, 1H), 2.90 (t, *J* 7.5 Hz, 2H), 2.32 (m, 2H), 1.78 (quint, *J* 7.5 Hz, 3H), 1.44 (d, *J* 6.7 Hz, 3H), 1.37 (m, 2H), 0.89 (t, *J* 7.2 Hz, 3H), 0.88 (d, *J* 6.6 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.5, 138.3, 127.8, 110.8, 58.5, 55.1, 33.9, 27.7, 25.0, 23.1, 20.7, 20.5, 13.4, 8.4; GC-MS (70 eV), *m/z* (relative abundance): 363 (M^+, 12), 346 (28), 291 (100), 234 (18), 207 (7), 105 (81), 78 (22), 41 (21).

Biological assays

Strains and growth conditions

The tested microorganisms included *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Candida albicans* ATCC 10231, *C. parapsilosis* ATCC 22019, *C. tropicalis* ATCC 200958, and *C. krusei* ATCC 6258. Bacteria were maintained on Mueller Hinton agar and subcultured in Mueller Hinton broth (MHB) at 37 °C for 24 h before each experiment. Yeasts were maintained on Sabouraud dextrose agar plates and subcultured at 37 °C for 24 h in Sabouraud dextrose broth (SDB) before each experiment, to ensure viability and purity.

Broth microdilution assay for bacteria and yeast

The minimum inhibitory concentration (MIC) of all samples were determined by microdilution techniques in Mueller Hinton broth for bacteria,[42] and Rosewell Park Memorial Institute (RPMI) 1640, pH 7.0, plus 0.165 mol L^{-1} 3-(*N*-morpholino) propane sulfonic acid (MOPS) buffer for yeasts.[43] Briefly, 100 µL of broth were distributed in each well of 96-well plates. Then 100 µL of the compounds were added in the first well (initial concentration 1 mg mL^{-1}), proceeding with serial dilution. Inoculates were then prepared in the same medium at a density adjusted to a 0.5 McFarland turbidity standard, which corresponds to 1×10^8 colony-forming unit (CFU) mL^{-1} for bacteria and $1\text{-}5 \times 10^6$ CFU mL^{-1} for yeast and then diluted 1:10 (bacteria) or 1:100 (yeast). Finally, 5 µL of the inoculum were added in each well of the plate. Positive control (wells without compounds) and negative control (wells without compounds and inoculum) were also performed. In addition, the reference drug streptomycin was also tested concomitantly.

The plates were incubated at 37 ºC and the MIC were recorded after 24 h of incubation for bacteria and 48 h for yeast. The MIC was defined as the lowest concentration of compounds at which the microorganism tested did not demonstrate visible growth. For the analysis of the results, the antimicrobial activities were considered good for MIC < 100 µg mL^{-1}; moderate to MIC between 100 and 500 µg mL^{-1}; weak for MIC between 500 and 1000 µg mL^{-1} and inactive if MIC > 1000 µg mL^{-1}.[41]

After MIC determination, the minimal bactericidal or fungicidal concentration (MBC and MFC), was also carried out by subculture technique in Mueller Hinton agar and Sabouraud agar for bacteria and yeasts, respectively. For this, 10 µL was removed from each well where there was growth inhibition and a positive control and transferred to the agar incubating at 37 ºC for an additional 24 h.

Broth microdilution assay for dermatophytes

The dermatophyte strains *Trichophyton rubrum* ATCC 28189, *Trichophyton mentagrophytes* ATCC 11480, and *Microsporum gypseum* ATCC 14683 were used in this study. They were cultured at 28 °C on Sabouraud dextrose agar tubes for 20 days before experiments. Spores were collected in sterile saline and suspensions were adjusted to 1.0×10^5 spores mL^{-1}.

The minimum inhibitory concentrations (MIC) of all samples were determined by microdilution techniques in RPMI medium, described by the Clinical and Laboratory Standards Institute (CLSI).[44] One hundred microliters of the medium were added to each well of a 96-well plate and a volume of 100 µL of the test solution was added to the wells in the first row, and then a serial dilution was performed. Then, 5 µL inoculum (10^5 spores mL^{-1}) were added to wells. Microplates were incubated at 28 °C, and the MICs were recorded after 72 h for yeast of incubation. The MIC was defined as the lowest concentration which resulted in the inhibition of visual growth. Minimal fungicidal concentrations (MFC) were determined by subculturing 10 µL of the culture from each negative well and from the positive control in Sabouraud dextrose agar.

Supplementary Information

Supplementary information (^{1}H NMR, ^{13}C NMR, GC-MS, and FTIR of the synthesized compounds) is available free of charge at http://jbcs.sbq.org.br as PDF file.

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Author Contributions

The synthesis and structural characterizations of orgacochalcogenated compounds were performed by F. G.

Borges, T. Zugman, P. T. Bandeira, and M. C. Dalmolin, supervised by Prof L. Piovan and A. R. M. de Oliveira. Biological assays were carried out by D. B. Scariot and F. P. Garcia, under Prof C. V. Nakamura's supervision. F. G. Borges, T. Zugman, F. P. Garcia, and L. Piovan wrote the manuscript. L. Piovan, A. R. M. de Oliveira and C.V. Nakamura contributed with the laboratories and financial structure for the development of the experiments.

References

1. Victoria, F. N.; Radatz, C. S.; Sachini, M.; Jacob, R. G.; Alves, D.; Savegnago, L.; Perin, G.; Motta, A. S.; da Silva, W. P.; Lenardão, E. J.; *Food Control* **2012**, *23*, 95.
2. Victoria, F. N.; Radatz, C. S.; Sachini, M.; Jacob, R. G.; Perin, G.; da Silva, W. P.; Lenardão, E. J.; *Tetrahedron Lett.* **2009**, *50*, 6761.
3. Guil-Guerrero, J. L.; Ramo, L.; Moreno, C.; Zúñiga-Paredes, J. C.; Carlosama-Yepez, M.; Ruales, P.; *Livest. Sci*. **2016**, *189*, 32.
4. Balouiri, M.; Sadiki, M.; Ibnsouda, S. K.; *J. Pharm. Anal*. **2016**, 71.
5. da Silva, C. M.; da Silva, D. L.; Modolo, L. V.; Alves, R. B.; de Resende, M. A.; Martins, C. V. B.; de Fátima, A.; *J. Adv. Res.* **2011**, *2*, 1; Tahlan, S.; Ramasamy, K.; Lim, S. M.; Shah, S. A. A.; Mani, V.; Narasimhan, B.; *BMC Chem.* **2019**, *13*, 1.
6. Morsy, M. A.; Ali, E. M.; Kandeel, M.; Venugopala, K. N.; Nair, A. B.; Greish, K.; El-Daly, M.; *Antibiotics* **2020**, *9*, 221.
7. Blair, J. M. A.; Webber, M. A.; Baylay, A. J.; Ogbolu, D. O.; Piddock, L. J. V.; *Nat. Rev. Microbiol*. **2015**, *13*, 42; Patil, M.; Poyil, A. N.; Joshi, S. D.; Patil, S. A.; Patil, S. A.; Bugarin, A.; *Bioorg. Chem*. **2019**, *92*, 103217.
8. Xu, Z.-K.; Flavin, M. T.; Flavin, J.; *Expert Opin. Invest. Drugs* **2014**, *23*, 163.
9. Taubes, G.; *Science* **2008**, *321*, 356.
10. Malanovic, N.; Lohner, K.; *Pharmaceuticals* **2016**, *9*, 59.
11. de Oliveira, D. M. P.; Forde, B. M.; Kidd, T. J.; Harris, P. N. A.; Schembri, M. A.; Beatson, S. A.; Paterson, D. L.; Walker, M. J.; *Clin. Microbiol. Rev*. **2020**, *33*, e00181-19.
12. Bucknell, D. G.; Gasser, R. B.; Irving, A.; Whithear, K.; *Aust. Vet. J.* **1997**, *75*, 355; Torres, A. G.; *Pathog. Dis*. **2017**, *75*, ftx012.
13. Li, B.; Wang, K.; Zhang, R.; Li, B.; Shen, Y.; Ji, Q.; *Eur. J. Med. Chem.* **2019**, *182*, 111669; Brown, G. D.; Denning, D. W.; Gow, N. A. R.; Levitz, S. M.; Netea, M. G.; White, T. C.; *Med. Mycol.* **2012**, *4*, 165rv13.
14. Marc, G.; Stana, A.; Pîrnau, A.; Vlase, L.; Vodnar, D. C.; Duma, M.; Tiperciuc, B.; Oniga, O.; *SLAS Discovery* **2018**, *23*, 807.
15. Pinto, S. M. L.; Rivera, Y.; Sandoval, L. V. H.; Lizarazo, J. C.; Rincón, J. J.; Méndez, L. Y. V.; *J. Med. Microbiol.* **2019**, *68*, 1109.
16. Silva, N. C. C.; Júnior, A. F.; *J. Venomous Anim. Toxins Incl. Trop. Dis.* **2010**, *16*, 402.
17. Tsemeugne, J.; Fondjo, E. S.; Tamokou, J.-D.; Rohand, T.; Ngongang, A. D.; Kuiate, J. R.; Sondengam, B. L.; *Int. J. Med. Chem.* **2018**, *2018*, 9197821.
18. Bueno, D. C.; Meinerz, D. F.; Allebrandt, J.; Waczuk, E. P.; dos Santos, D. B.; Mariano, D. O. C.; Rocha, J. B. T.; *BioMed Res. Int*. **2013**, *2013*, ID 537279; Rossato, J. I.; Ketzer, L. A.; Centuriao, F. B.; Silva, S. J. N.; Ludtke, D. S.; Zeni, G.; Braga, A. L.; Rubin, M. A.; Rocha, J. B. T.; *Neurochem. Res*. **2002**, *27*, 297; Meotti, F. C.; Stangherlin, E. C.; Zeni, G.; Nogueira, C. W.; Rocha, J. B. T.; *Environ. Res*. **2004**, *94*, 276; Bandeira, P. T.; Dalmolin, M. C.; Oliveira, M. M.; Nunes, K. C.; Garcia, F. P.; Nakamura, C. V.; de Oliveira, A. R. M.; Piovan, L.; *Bioorg. Med. Chem*. **2019**, *27*, 410; Reich, H. J.; Hondal, R. J.; *ACS Chem. Biol*. **2016**, *11*, 821; Ibrahim, M.; Muhammad, N.; Naeem, M.; Deobald, A. M.; Kamdem, J. P.; Rocha, J. B. T.; *Toxicol. In Vitro* **2015**, *29*, 947; Tanini, D.; Panzella, L.; Amorati, R.; Capperucci, A.; Pizzo, E.; Napolitano, A.; Menichetti, S.; d'Schia, M.; *Org. Biomol. Chem*. **2015**, *13*, 5757; Arai, K.; Kumakura, F.; Takahira, M.; Sekiyama, N.; Kuroda, N.; Suzuki, T.; Iwaoka, M.; *J. Org. Chem.* **2015**, *80*, 5633; Ibrahim, M.; Hassan, W.; Anwar, J.; Deobald, A. M.; Kamdem, J. P.; Souza, D. O.; Rocha, J. B. T.; *Toxicol. In Vitro* **2014**, *28*, 524; Alberto, E. E.; do Nascimento, V.; Braga, A. L.; *J. Braz. Chem. Soc.* **2010**, *21*, 2032.
19. Wang, L.; Yang, Z.; Fu, J.; Yin, H.; Xiong, K.; Tan, Q.; Jin, H.; Li, J.; Wang, T.; Tang, W.; Yin, J.; Cai, G.; Liu, M.; Kehr, S.; Becker, K.; Zeng, H.; *Free Radicals Biol. Med*. **2012**, *52*, 898; Doering, M.; Ba, L. A.; Lilienthal, N.; Nicco, C.; Scherer, C.; Abbas, M.; Zada, A. A. P.; Coriat, R.; Burkholz, T.; Wessjohann, L.; Diederich, M.; Batteux, F.; Herling, M.; Jacob, C.; *J. Med. Chem*. **2010**, *53*, 6954; Seng, H.-L.; Tiekink, E. R. T.; *Appl. Organomet. Chem.* **2012**, *26*, 655; Paschoalin, T.; Martens, A. A.; Omori, Á. T.; Pereira, F. V.; Juliano, L.; Travassos, L. R.; Machado-Santelli, G. M.; Cunha, R. L. O. R.; *Bioorg. Med. Chem*. **2019**, *27*, 2537; Gandin, V.; Khalkar, P.; Braude, J.; Fernandes, A. P.; *Free Radicals Biol. Med*. **2018**, *127*, 80; Garnica, P.; Encío, I.; Plano, D.; Palop, J. A.; Sanmartín, C.; *ACS Med. Chem. Lett*. **2018**, *9*, 306; Silberman, A.; Kalechman, Y.; Hirsch, S.; Erlich, Z.; Sredni, B.; Albeck, A.; *ChemBioChem* **2016**, *17*, 918; Arsenyan, P.; Paegle, E.; Domracheva, I.; Gulbe, A.; Kanepe-Lapsa, I.; Shestakova, I.; *J. Med. Chem.* **2014**, *87*, 471; Du, P.; Saidu, N. E. B.; Intemann, J.; Jacob, C.; Montenarh, M.; *Biochim. Biophys. Acta* **2014**, *1840*, 1808; Sredni, B.; *Semin. Cancer Biol*. **2012**, *22*, 60; Fernandes, A. P.; Gandin, V.; *Biochim. Biophys. Acta* **2015**, *1850*, 1642.
20. Cunha, R. L. O. R.; Urano, M. E.; Chagas, J. R.; Almeida, P. C.; Bincoletto, C.; Tersariol, I. L. S.; Comasseto, J. V.; *Bioorg. Med. Chem. Lett.* **2005**, *15*, 755; Maluf, S. E. C.; Melo, P. M. S.; Varotti, F. P.; Gazarini, M. L.; Cunha, R. L. O. R.; Carmona, A.

K.; *Parasitol. Int.* **2016**, *65*, 20; Cunha, R. L. O. R.; Gouvea, I. E.; Feitosa, G. P. V.; Alves, M. F. M.; Bromme, D.; Comasseto, J. V.; Tersariol, I. L. S.; Juliano, L.; *Biol. Chem.* **2009**, *390*, 1205; Caracelli, I.; Veja-Teijido, M.; Zukerman-Schpector, J.; Cezari, M. H. S.; Lopes, J. G. S.; Juliano, L.; Santos, P. S.; Comasseto, J. V.; Cunha, R. L. O. R.; Tiekink, E. R. T.; *J. Mol. Struct.* **2012**, *1013*, 11; Piovan, L.; Alves, M. F. M.; Juliano, L.; Brömme, D.; Cunha, R. L. O. R.; Andrade, L. H.; *Bioorg. Med. Chem.* **2011**, *19*, 2009; Piovan, L.; Alves, M. F. M.; Juliano, L.; Brömme, D.; Cunha, R. L. O. R.; Andrade, L. H.; *J. Braz. Chem. Soc.* **2010**, *21*, 2108.

21. Piovan, L.; Milani, P.; Silva, M. S.; Moraes, P. G.; Demasi, M.; Andrade, L. H.; *Eur. J. Med. Chem.* **2014**, *73*, 280.
22. Abdo, M.; Liu, S.; Zhou, B.; Walls, C. D.; Wu, L.; Knapp, S.; Zhang, Z.-Y.; *J. Am. Chem. Soc.* **2008**, *130*, 13196; Brondani, P. B.; Guilmoto, N. M. A. F.; Dudek, H. M.; Fraaije, M. W.; Andrade, L. H.; *Tetrahedron* **2012**, *68*, 10431; Piovan, L.; Wu, L.; Zhang, Z.-Y.; Andrade, L. H.; *Org. Biomol. Chem.* **2011**, *9*, 1347.
23. Gai, B. M.; Stein, A. L.; Roehrs, J. A.; Bilheri, F. N.; Nogueira, C. W.; Zeni, G.; *Org. Biomol. Chem.* **2012**, *10*, 798; Sampaio, T. B.; Bilheri, F. N.; Zeni, G. R.; Nogueira, C. W.; *Behav. Brain Res.* **2020**, *386*, ID 32184159; Savegnago, L.; Jesse, C. R.; Pinto, L. G.; Rocha, J. B. T.; Barancelli, D. A.; Nogueira, C. W.; Zeni, G.; *Pharmacol., Biochem. Behav.* **2008**, *88*, 418; da Rocha, J. T.; Gai, B. M.; Pinton, S.; Sampaio, T. B.; Nogueira, C. W.; Zeni, G.; *Psychopharmacology* **2012**, *222*, 709.
24. de Freitas, A. S.; Rocha, J. B. T.; *Neurosci. Lett.* **2011**, *503*, 1; Pinton, S.; da Rocha, J. T.; Zeni, G.; Nogueira, C. W.; *Neurosci. Lett.* **2010**, *472*, 56; Ávila, D. S.; Colle, D.; Gubert, P.; Palma, A. S.; Puntel, G.; Manarin, F.; Noremberg, S.; Nascimento, P. C.; Aschner, M.; Rocha, J. B. T.; Soares, F. A. A.; *Toxicol. Sci.* **2010**, *115*, 194; Okun, E.; Arumugam, T. V.; Tang, S.-C.; Gleichmann, M.; Albeck, M.; Sredni, B.; Mattson, M. P.; *J. Neurochem.* **2007**, *102*, 1232.
25. Gouvea, I. E.; Santos, J. A. N.; Burlandy, F. M.; Tersariol, I. L. S.; da Silva, E. E.; Juliano, M. A.; Juliano, L.; Cunha, R. L. O. R.; *Biol. Chem.* **2011**, *392*, 587; Giurg, M.; Golab, A.; Suchodolski, J.; Kaleta, R.; Krasowska, A.; Piasecki, E.; Pietka-Ottlik, M.; *Molecules* **2017**, *22*, 974; Wójtowicz, H.; Chojnacka, M.; Młochowski, J.; Palus, J.; Syper, L.; Hudecova, D.; Uher, M.; Piasecki, E.; Rybka, M.; *Il Farmaco* **2003**, *58*, 1235; Sartori, G.; Jardim, N. S.; Sari, M. H. M.; Dobrachinski, F.; Pesarico, A. P.; Rodrigues Jr., L. C.; Cargnelutti, J.; Flores, E. F.; Prigol, M.; Nogueira, C. W.; *J. Cell. Biochem.* **2016**, *117*, 1638; Sancineto, L.; Mariotti, A.; Bagnoli, L.; Marini, F.; Desantis, J.; Iraci, N.; Santi, C.; Pannecouque, C.; Tabarrini, O.; *J. Med. Chem.* **2015**, *58*, 9601; Pietka-Ottlik, M.; Wójtowicz-Mlochowska, H.; Kolodziejczyk, K.; Piasecki, E.; Mlochowski, J.; *Chem. Pharm. Bull.* **2008**, *56*, 1423; Sahu, P. K.; Kim, G.; Yu, J.; Ahn, J. Y.; Choi, Y.; Jin, X.; Kim, J.-H.; Lee, S. K.; Park, S.; Jeong, L. S.; *Org. Lett.* **2014**, *16*, 5796; Sahu, P. K.; Umme, T.; Yu, J.; Nayak, A.; Kim, G.; Noh, M.; Lee, J.-Y.; Kim, D.-D.; Jeong, L. S.; *J. Med. Chem.* **2015**, *58*, 8734.
26. Nogueira, C. W.; Quinhones, E. B.; Junhg, E. A. C.; Zeni, G.; Rocha, J. B. T.; *Inflammation Res.* **2003**, *52*, 56; Jesse, C. R.; Savegnago, L.; Nogueira, C. W.; *J. Pharm. Pharmacol.* **2009**, *61*, 623; Chagas, P. M.; Rosa, S. G.; Sari, M. H. M.; Oliveira, C. E. S.; Canto, R. F. S.; da Luz, S. C. A.; Braga, A. L.; Nogueira, C. W.; *Pharmacol., Biochem. Behav.* **2014**, *118*, 87; Pinz, M.; Reis, A. S.; Duarte, V.; da Rocha, M. J.; Goldani, B. S.; Alves, D.; Savegnago, L.; Luchese, C.; Wilhelm, E. A.; *Eur. J. Pharmacol.* **2016**, *780*, 122.
27. Okoronkwo, A. E.; Rosário, A. R.; Alves, D.; Savegnago, L.; Nogueira, C. W.; Zeni, G.; *Tetrahedron Lett.* **2008**, *49*, 3252; Wilhelm, E. A.; Jesse, C. R.; Bortolatto, C. F.; Nogueira, C. W.; Savegnago, L.; *Pharmacol., Biochem. Behav.* **2009**, *93*, 419.
28. Wilhelm, E. A.; Gai, B. M.; Souza, A. C. G.; Bortolatto, C. F.; Roehrs, J. A.; Nogueira, C. W.; *Mol. Cell. Biochem.* **2012**, *365*, 175.
29. Brodsky, M.; Halpert, G.; Albeck, M.; Sredni, B.; *J. Inflammation* **2010**, *7*, 3; Duntas, L. H.; *Horm. Metab. Res.* **2009**, *41*, 443; Martínez-Ramos, F.; Salgado-Zamora, H.; Campos-Aldrete, M. E.; Melendez-Camargo, E.; Márquez-Flores, Y.; Soriano-García, M.; *Eur. J. Med. Chem.* **2008**, *43*, 1432.
30. Ferraz, M. C.; Mano, R. A.; Oliveira, D. H.; Maia, D. S. V.; Silva, W. P.; Savegnago, L.; Lenardão, E. J.; Jacob, R. G.; *Medicines* **2017**, *4*, 39.
31. Sharma, N.; Kumar, S.; Maurya, I. K.; Bhasin, K. K.; Verma, A.; Wangoo, N.; Bhasin, A. K. K.; Mehta, S. K.; Kumar, S.; Sharma, R. K.; *RSC Adv.* **2016**, *6*, 114224.
32. Kumar, S.; Sharma, N.; Maurya, I. K.; Bhasin, A. K.; Wangoo, N.; Brandão, P.; Félix, V.; Bhasin, K. K.; Sharma, R. K.; *Eur. J. Med. Chem.* **2016**, *123*, 916.
33. Bugarčić, Z. M.; Divac, V. M.; Kostić, M. D.; Janković, N. Ž.; Heinemann, F. W.; Radulović, N. S.; Stojanović-Radić, Z. Z.; *J. Inorg. Biochem.* **2015**, *143*, 9.
34. Abdel-Hafez, Sh. H.; *Russ. J. Bioorg. Chem.* **2010**, *36*, 370.
35. Vargas, J.; Narayanaperumal, S.; Gul, K.; Ravanello, B. B.; Dornelles, L.; Soares, L. C.; Alves, C. F. S.; Schneider, T.; Vaucher, R. A.; Santos, R. C. V.; Rodrigues, O. E. D.; *Tetrahedron* **2012**, *68*, 10444.
36. Abdel-Hafez, Sh. H.; Anthonsen, H. W.; Sliwka, H.-R.; Partali, V.; *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180*, 2217.
37. Al-Masoudi, W. A.; Al-Asadi, R. H.; Othman, R. M.; Al-Masoudi, N. A.; *Eur. J. Chem.* **2015**, *6*, 374.
38. Pinheiro, F. C.; Bortolotto, V. C.; Araujo, S. M.; Poetini, M. R.; Sehn, C. P.; Neto, J. S. S.; Zeni, G.; Prigol, M.; *J. Microbiol. Biotechnol.* **2018**, *28*, 1209.
39. de Sá, L. F. R.; Toledo, F. T.; Gonçalves, A. C.; Sousa, B. A.; dos Santos, A. A.; Brasil, P. F.; da Silva, V. A. D.; Tessis, A. C.; Ramos, J. A.; Carvalho, M. A.; Lamping, E.; Ferreira-Pereira, A.; *Antimicrob. Agents Chemother.* **2017**, *61*, 1.

40. Dalmolin, M. C.; Bandeira, P. T.; Ferri, M. S.; Oliveira, A. R. M.; Piovan, L.; *J. Organomet. Chem*. **2018**, *874*, 32.
41. Holetz, F. B.; Pessini, G. L.; Sanches, N. R.; Cortez, D. A.; Nakamura, C. V.; *Mem. Inst. Oswaldo Cruz* **2002**, *97*, 1027.
42. Clinical and Laboratory Standards Institute (CLSI); *M07-A10 Methods for Dilution Antimicrobial Susceptibility Test for Bacteria that Grow Aerobically*, *Approved Standard*, 10th ed.; CLSI: Wayne, USA, 2015, available at https://clsi.org/media/1632/m07a10_sample.pdf, accessed in October 2020.
43. Clinical and Laboratory Standards Institute (CLSI); *M27-A3 Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts*, *Approved Standard*, 3rd ed.; CLSI: Wayne, USA, 2008, available at https://clsi.org/media/1461/m27a3_sample.pdf, accessed in October 2020.
44. Clinical and Laboratory Standards Institute (CLSI); *M38-A2 Reference Method for Broth Dilution Antifungals Susceptibility Testing of Conidium-Forming Filamentous Fungi*, *Approved Standard*, 2nd ed.; CLSI: Wayne, USA, 2008, available at https://clsi.org/media/1455/m38a2_sample.pdf, accessed in October 2020.

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