Journal of Inorganic Biochemistry 225 (2021) 111620

Contents lists available at ScienceDirect

Journal of Inorganic Biochemistry

journal homepage: www.elsevier.com/locate/jinorgbio

Review Article

Antifungal activity of thiosemicarbazones, bis(thiosemicarbazones), and their metal complexes

Kritika Bajaj, Robert M. Buchanan *, Craig A. Grapperhaus *

Department of Chemistry, University of Louisville, 2320 South Brook Street, Louisville, KY 40292, United States of America

ARTICLE INFO

Keywords:
Thiosemicarbazone
Bis(thiosemicarbazone)
Metal complexes
Antifungal activity
Pathogens
Drug resistance

ABSTRACT

Fungi are ubiquitous in nature, and typically cause little or no environmental or pathogenic damage to their plant, animal, and human hosts. However, a small but growing number of pathogenic fungi are spreading world-wide at an alarming rate threatening global ecosystem health and proliferation. Many of these emerging pathogens have developed multi-drug resistance to front line therapeutics increasing the urgency for the development of new antifungal agents. This review examines the development of thiosemicarbazones, bis(thiosemicarbazones), and their metal complexes as potential antifungal agents against more than 65 different fungal strains. The fungistatic activity of the compounds are quantified based on the zone of inhibition, minimum inhibitory concentration, or growth inhibition percentage. In this review, reported activities were standardized based on molar concentrations to simplify comparisons between different compounds. Of all the fungal strains reported in the review, *A. niger* in particular was very resistant towards a majority of tested compounds. Our analysis of the data shows that metal complexes are typically more active than non-coordinated ligands with copper(II) and zinc(II) complexes generally displaying the highest activity.

1. Introduction

Fungi are among the most widely distributed and biodiverse organisms with an estimated 1.5–5.9 million species [1,2] some of which display great environmental and medical importance. Part of the eukaryote family of organisms that includes algae, plants, and humans, fungi are ubiquitous in nature. The approximately 148,000 known species of fungi [3] include diverse organisms such as rusts, mildews, molds, and mushrooms. Over 8000 fungi species are known to cause diseases in plants and more than 300 appear to be pathogenic to humans and animals [4].

Many fungi are benign. They colonize and thrive on plant and animal hosts through parasitic and symbiotic relationships and are integral to normal metabolic processes. They cause little or no environmental or pathogenic damage. However, other fungi cause irreparable harm including disease in immunocompromised hosts. It is estimated that nearly 40% of food world-wide is spoiled by *Aspergillus, Penicillium, Fusarium* and *Alternaria genra* fungi, which produce toxins such as

Abbreviations: *A. alternata*, *Alternaria alternata*; *A. corymbifera*, *Absidia corymbifera*; *A. flavus*, *Aspergillus flavus*; *A. fumigatus*, *Aspergillus fumigatus*; *A. niger*, *Aspergillus niger*; *A. nomius*, *Aspergillus nomius*; *A. ochraceous*, *Aspergillus ochraceus*; *A. parasiticus*, *Aspergillus parasiticus*; *Aspergillus sp.*, *Aspergillus species*; *ABCC1*, *ATP binding cassette subfamily C member 1*; *C. albicans*, *Candida albicans*; *C. auris*, *Candida auris*; *C. dubliniensis*, *Candida dubliniensis*; *C. glabrata*, *Candida glabrata*; *C. globosum*, *Chaetomium globosum*; *C. krusei*, *Candida krusei*; *C. lusitaniae*, *Candida lusitaniae*; *C. neoformans*, *Cryptococcus neoformans*; *C. parapsilosis*, *Candida parapsilosis*; *C. tropicalis*, *Candida tropicalis*; *C. gattii*, *Cryptococcus gattii*; *E. floccosum*, *Epidermophyton floccosum*; *F. moniliforme*, *Fusarium moniliforme*; *F. odum*, *Fusarium odum*; *F. oxysporum*, *Fusarium oxysporum*; *F. verticillioides*, *Fusarium verticillioides*; *G. candidum*, *Geotrichum candidum*; *H. oryzae*, *Heterodera oryzae*; *M. canis*, *Microsporum canis*; *M. phaseolina*, *Macrophomina phaseolina*; *Paecilomyces sp.*, *Paecilomyces species*; *P. brasiliensis*, *Paracoccidioides brasiliensis*; *P. citrinum*, *Penicillium citrinum*; *Pestalotia sp.*, *Pestalotia species*; *P. italicum*, *Penicillium italicum*; *P. variotii*, *Paecilomyces variotii*; *R. bataticola*, *Rhizoctonia bataticola*; *S. brevicaulis*, *Spoculariopsis brevicaulis*; *S. cerevisiae*, *Saccharomyces cerevisiae*; *T. rubrum*, *Trichophyton rubrum*; ala, alanine; bipy, 2,2′-bipyridine; BTSC, bis(thiosemicarbazone); Cp, cyclopentadienyl; Etz, etridiazole; gly, glycine; GSH, glutathione; hexim, azepane; 8-HQ, 8-hydroxyquinoline; IC_{50}, half maximal inhibitory concentration; Mepy, methylpyridine; MFC, minimum fungicidal concentration; MIC, minimum inhibitory concentration; MOA, mechanism of action; mor, morpholine; phen, 1,10-phenanthroline; Pht, phthaloyl; pic, picoline; pip, piperidine; py, pyridine; ROS, reactive oxygen species; TSC, thiosemicarbazone; val, valine; PET/CT, positron emission tomography/computed tomography.

* Corresponding author.
E-mail address: grapperhaus@louisville.edu (C.A. Grapperhaus).

https://doi.org/10.1016/j.jinorgbio.2021.111620
Received 29 July 2021; Received in revised form 6 September 2021; Accepted 18 September 2021
Available online 25 September 2021

mycotoxins and aflatoxins that can lead to neurotoxic and carcinogenic effects in humans and animals [5]. The most devastating plant disease pathogens of commercial significance include wheat stem rust [6], soybean rust [7], and potato late blight [8]. Others cause devastating loss to fruit orchards and forests [9]. Further, recent wildlife extinction [10,11] and high mortality in bee [9] and bat [12,13] populations has been attributed to fungal infections.

Very few fungi are able to infect healthy people. As established by Casadevall, pathogenic fungi that parasitize humans must have a tolerance of temperatures above 37 °C, the ability to penetrate tissue and absorb nutrients, and resistance to human immune responses [14,15]. The most prevalent disease-causing fungi in humans are *Candida*, *Aspergillus*, *Pneumocystis* and *Cryptococcus sp.* [4,16,17]. Collectively, they contribute to more than 1.6 million world-wide deaths [18]. These disease-causing pathogens are frequently found in hospitals and assisted care facilities and are particularly lethal to immunocompromised patients. Eradication of entrenched colonies is difficult and costly due to their rapid growth and expanding multidrug resistance [19–21]. This is particularly true for the multidrug resistant *Candida* group of fungi, which include *Candida auris*, *Candida albicans*, *Candida krusei* and *Candida glabrata*. First identified in 2009 in health-care facilities, the rapidly spreading *Corynebacterium auris* has a reported morality rate exceeding 30% in immunocompromised patients [22]. Another emerging pathogen is the rapidly spreading azole-resistant *Aspergillus* reported to have mortality rates as high as 90% [23].

The emergence and global spread of highly contagious and transmittable pathogenic fungi presents a significant threat to human, animal, and ecosystem health and proliferation [20,24,25]. This has stimulated the urgent need for the development of new antifungal therapeutics as highlighted in the 2019 Centers for Disease Control and Preventions (CDC) report entitled “Antibiotic Resistance Threats in the United States.” [26,27]. To date, most clinical antifungal agents are organic based. There are six classes of antifungal drugs and their therapeutic application is based on their respective structure and mechanism of action. They consist of polyenes, azoles, allylamines, pyrimidines, echinocandins, and flucytosine [21,28–31]. These compounds either target the membrane (polyenes, allylamines, pyrimidines, and azoles), the fungal cell-wall complex β-(1,3)-glucan synthase (echinocandins) or inhibit DNA and RNA synthesis (flucytosine) [32–34]. However, *Aspergillus fumigatus* is reported to be completely resistant to all classes of antifungal agents [35]. Likewise, more than 90% of *C. auris* isolates are resistant to front-line therapies [36] with several types completely resistant [17,21]. The growing drug resistance to azoles and echinocandins, and the high toxicity of polyenes provides unique opportunities to develop new antifungal therapeutics [32,37,38]. The mechanism of antifungal resistance varies between species and antifungal agents [17,39]. Over expression of drug targets and efflux pumps are major contributors to drug resistance development. For example, *C. auris* shows resistance to fluconazole (azole class) and amphotericin B (polyene class) by increasing the copy numbers of the gene *ERG11* and by instilling mutations within *ERG3*, respectively, the genes required for ergosterol biosynthesis. With respect to echinocandins, *C. auris* resists by installing mutations at S639F in *FKS1*, a gene responsible for glucan synthase. In contrast, for *A. fumigatus* azole resistance is obtained through modification and overexpression of Cyp51A (azole drug target) and by overexpression of efflux pumps Cdr1B and AtrF. Echinocandin resistance, on the other hand, is quite rare in *A. fumigatus*. Hence, diminishment of the number of clinically effective antifungal drugs has stimulated interest in development of new drug classes.

There is a long-standing interest in the exploration of metal containing antifungal agents as future therapeutics. The fungicidal and fungistatic activities of various organic compounds and their metal complexes have been evaluated. Well-explored classes of compounds include Schiff base ligands [40,41], amine ligands [42], and their related metal complexes [42,43]. In general, metal salts have very poor antifungal activity [44–46]. Another important class of compounds with extensive reports of antifungal activity are thiosemicarbazones (TSCs), bis(thiosemicarbazones) (BTSCs), and their metal complexes.

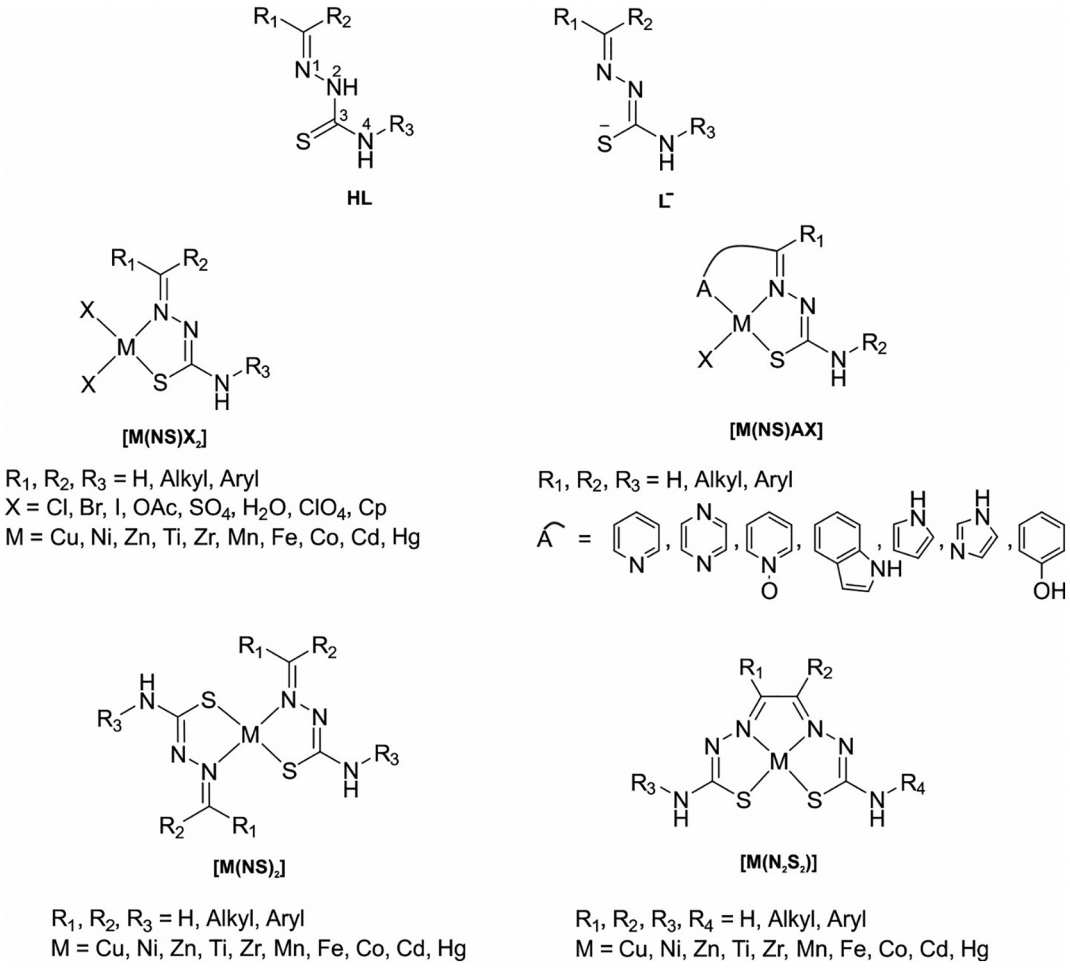
TSCs constitute a group of compounds with well-established medicinal and pharmacological properties including antifungal, antitumor, antiviral, antimicrobial, and antiparasitic activities [47]. The general structure of TSCs and common binding motifs of deprotonated TSCs are shown in Scheme 1. The TSC framework consists of hydrazino nitrogens N1 and N2, the amino nitrogen N4, the thiocarbonyl S, and variable substituent groups R1, R2, and R3. As a ligand, TSC can coordinate as a neutral, bidentate NS chelate or more commonly as an anionic bidentate NS chelate upon deprotonation of the azomethinic nitrogen. The TSC ligand motif can be modified to include an additional heteroatom donor expanding its denticity from two to three, often as N_2S or ONS chelates. BTSCs result from either metal ion coordination of two individual bidentate NS TSC chelates or coordination of a single N_2S_2 tetradentate chelate. The resulting metal complexes exhibit important medicinal and pharmacological properties. For example, the Cu(II) complex of the N_2S_2 chelate diacetyl-bis(N-4-methylthiosemicarbazone) (ATSM) is in Phase II trials as a PET/CT (positron emission tomography/computed tomography) imaging agent for hypoxic lung cancer cells [48], and in Phase III trials as an oral therapeutic against amyotrophic lateral sclerosis (ALS) [49]. This review examines the development of TSCs, BTSCs, and their metal complexes as antifungal agents.

2. Evaluating antifungal activity

Several methods have been developed over the years to quantify antifungal activity [50–59]. The evaluation of antifungal activity for TSCs, BTSCs, and their metal complexes has largely focused on their fungistatic activity, which is the ability to inhibit the growth of fungi. The activity of an individual compound can vary widely between different fungi. So, it is important to compare activity values for different compounds against the same fungi species. The three main techniques employed to quantify fungistatic activity are zone of inhibition, minimum inhibitory concentration (MIC), and growth inhibition percentage. Ideally, studies should report activities against multiple fungi to demonstrate breadth of activity. The MIC values are the most quantitatively reliable metric for comparison between different studies as they reflect the minimum inhibitory concentration that prevents visible growth of the fungus. In the current review, all MICs are reported in units of mM, although individual references may use other concentration units based on mass/volume rather than moles/volume ratios. Antifungal activities reported using zone of inhibition and growth inhibition percentage are more difficult to compare between studies as there is no standard dosage and the quantity of compound tested significantly impacts reported values. When using these methods, best practices are to report antifungal activity at multiple concentrations over a large range as exemplified by West and coworkers [47,60–63]. Additional details concerning methodology can be found in the supplementary material file.

3. Mechansim of action

At this time, the mechanism of action (MOA) associated with TSCs and their metal complexes is largely underexplored. While this is true for the antifungal activity of the TSCs and their metal complexes, the MOA of TSCs for other biomedical applications has been extensively studied. For instance, in cancer cells various targets disrupting biological function have been identified. Some of these targets include inhibition of ribonucleotide reductase, topoisomerase inhibition, mitochondrial disruption, lysosomal membrane permeabilization, inhibition of proteasomal activity, disruption of cellular pathways, induction of oxidative stress and cell apoptosis [65–73]. Target sites like ribonucleotide reductase, mitochondria, lysosomes, mitogen-activated protein kinase (MAPK) cellular pathway are known to be common to animal and fungal cells [74]. It is possible that the TSCs and their metal complexes may



Scheme 1. Protonated and deprotonated forms of TSC and different coordination modes of TSCs and BTSCs with metals.

target these sites in fungi with a MOA similar to that in mammalian cells. In studies specifically addressing the antifungal MOAs of TSCs, the most commonly proposed are dependent on the targeted sites mainly including inhibition of ergosterol synthesis, physiochemical interaction with fungal membrane sterols, and inhibition of macromolecular synthesis, various components of fungi responsible for important biological processes such as plasma membrane biogenesis, regulation of permeability and fluidity, exostructure rigidity, and shape [31,32,76,77]. Various groups have tried to establish the structure activity relationships through theoretical investigations that suggests an inverse correlation between dipole moment of the molecule and its antifungal activity [78–80]. Additionally, in order to combat the development of drug resistance in pathogenic fungi, there is a need for a better understanding of the origin of the resistance mechanism(s). Drug resistance can be manifested through various cellular processes including modified sterol synthesis, reduced intercellular concentration of enzyme targets, alteration, and overexpression of efflux mechanisms. Irrespective of the depth of research focused on the development of antifungal agents to date, there is a serious need to develop antifungals that target alternative cellular processes or operate under different mechanisms in order to circumvent drug resistance associated with current therapeutics.

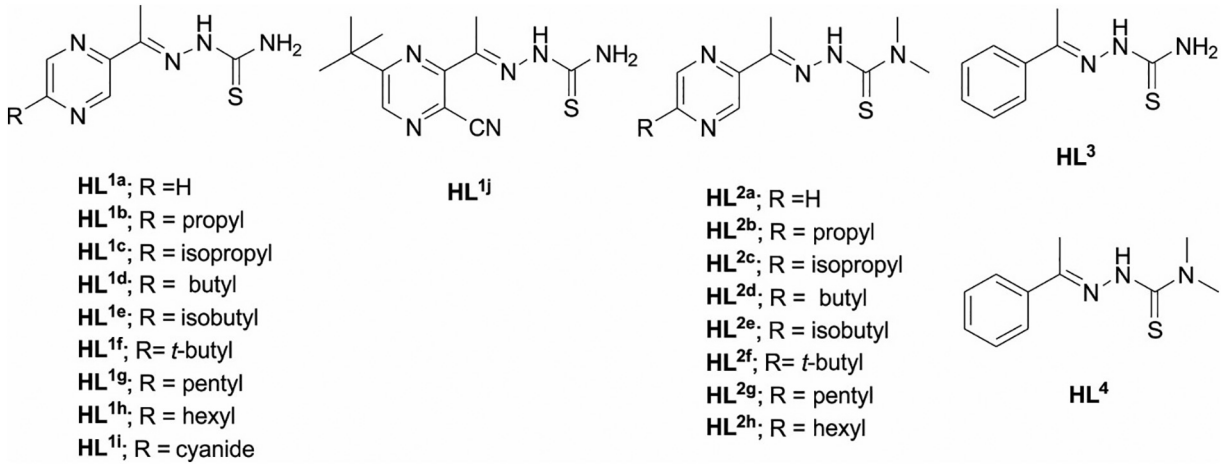
4. Thiosemicarbazone activity

4.1. Metal free

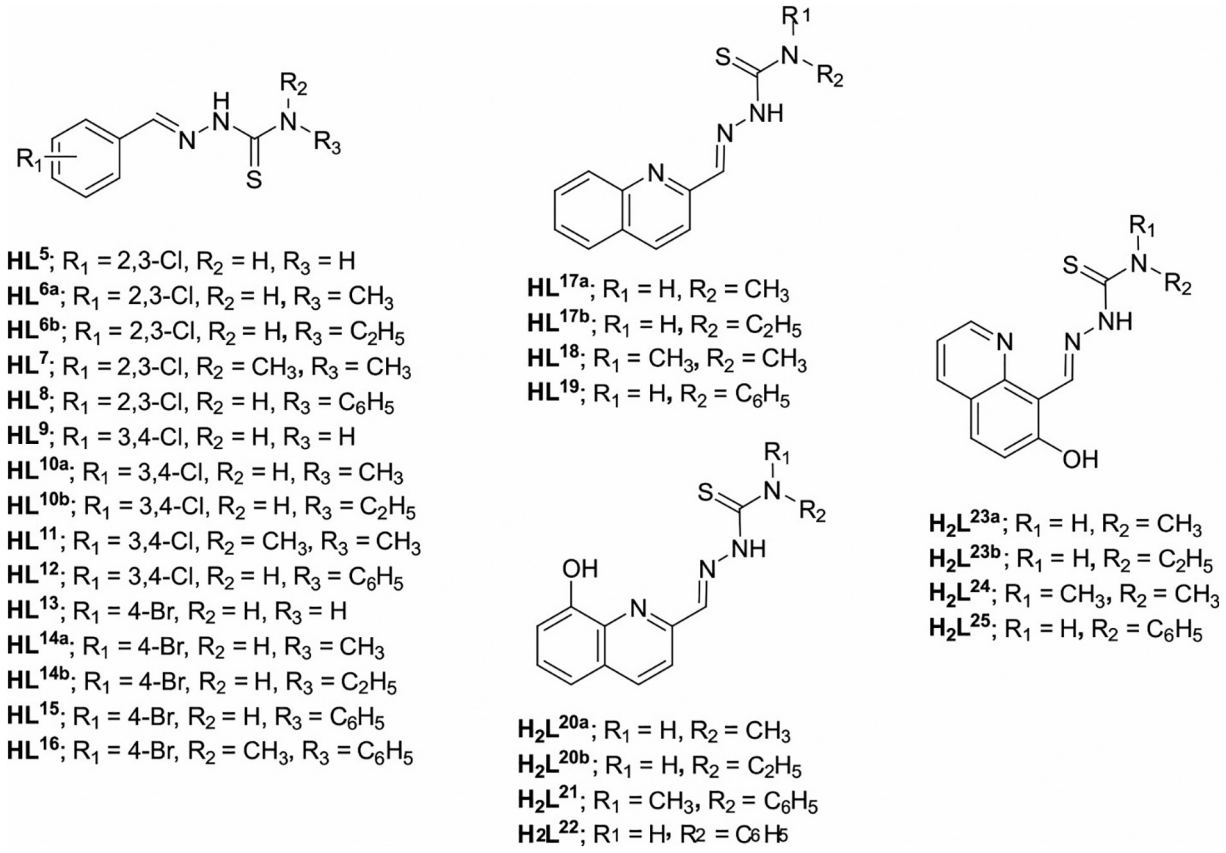
The antifungal activities of ~250 metal free TSC compounds, Table S1, have been reported in the literature. Of these, a select number demonstrating significant activity and/or providing insight into the MOA are further described below. Activities of organic compounds that were also evaluated as ligands in discrete metal complexes are reported along with the metal complex activity in subsequent sections.

A library of TSCs (HL^1–HL^2) derived from acetylpyrazines were prepared, characterized, and tested for antifungal effects on eight strains of fungi by Opletalova and coworkers (Scheme 2) [81,82]. For HL^1, which has a primary amino group, the most lipophilic compounds HL^{1g} and HL^{1h} possessed the highest antifungal activities with MIC_{80} values of 0.004 ± 0.001 mM to 0.026 ± 0.007 mM and 0.002 ± 0.001 mM to 0.022 ± 0.013 mM after 24 h, respectively. This is consistent with the general expectation that higher lipophilicity increases intercellular access. However, for the N,N-dimethyl TSC derivatives, HL^{2a} – HL^{2h}, the most hydrophilic member of the series had the highest activity with MIC_{80} values of 0.00098 ± 0.00001 mM to 0.01172 ± 0.00391 mM after 24 h indicating that lipophilicity was not the only factor influencing activity. The ability to coordinate metal ions was also cited as a contributing factor. This is supported by the poor activity of the acetophenyl derivatives HL^3 and HL^4 (MIC_{80} value ≥0.05 mM at 24 h), which lack the additional heteroatom donor in HL^3 and HL^4 that is essential for tridentate coordination.

Similarly, benzylidene, $HL^{5–16}$, and quinolinylvinyl TSCs, $HL^{17–25}$ (Scheme 3) were evaluated for antifungal activity against eight fungal strains by Serda et al. [83]. Although the majority of the compounds were weakly active (MIC >0.125 – > 0.500 mM), the quinolinylvinyl TSCs were generally better antifungals than the benzylidene TSCs. In particular, HL^{18} displayed the highest antimicrobial activity (MIC ˆ 0.002–0.004 mM at 24 h) among all of the tested compounds and is more



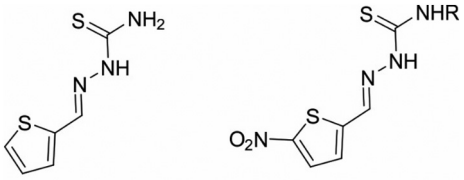
Scheme 2. Structure of ligands HL^1 – HL^4.



Scheme 3. Structure of ligands HL^5 – HL^{25}.

active (MIC ˆ 0.004 mM) than fluconazole (MIC >0.125 mM) against *A. fumigatus* and *Absidia corymbifera*.

The thiophene TSC HL^{26} prepared by Paiva and coworkers displayed moderate activity with an MIC of 0.676 mM against *Aspergillus nomius, Aspergillus ochraceus* and *Aspergillus parasiticus* and MIC values of 1.351 mM and 2.703 mM against *Aspergillus flavus* and *Fusarium verticillioides* [84]. Neto et al. prepared twelve amino N-substituted 2-(5-nitro-thiophene) TSCs derivatives (HL^{27a} – HL^{27l}, Scheme 4) and evaluated them for potential antifungal activity against *Candida* species and *Cryptococcus neoformans* [76]. While all of the compounds showed good to excellent activity against *C. neoformans* (minimum fungicidal concentration, MFC ˆ 0.0002–0.059 mM), only the 3-pyridyl derivative HL^{27j} and the electron withdrawing derivatives $HL^{27k\text{-}l}$ were active against *Candida* strains. In evaluations of the MOA, ergosterol assays showed that the compounds do not bind to the ergosterol in the membrane and sorbitol assays suggested the compounds do not act by inhibiting the synthesis of fungal cell walls. Further studies on HL^{27j} against *C. albicans* showed an increase in MIC values in ascorbic acid and glutathione protection tests and an interaction between HL^{27j} and GSH (glutathione) was observed by nuclear magnetic resonance spectroscopy [86]. Further, changes were observed in ROS (reactive oxygen species) production and mitochondrial membrane potential that were associated with apoptosis suggesting the MOA of HL^{27j} involves changes in cellular redox balance, ROS production, and apoptosis.



HL^{26}

HL^{27a}; R =4-methoxyphenyl
HL^{27b}; R = 4-bromophenyl
HL^{27c}; R = naphthlene
HL^{27d}; R = allyl
HL^{27e}; R = phenyl
HL^{27f}; R= 4-chlorophenyl
HL^{27g}; R = phenethyl
HL^{27h}; R = *p*-tolyl
HL^{27i}; R = 4-ethylphenyl
HL^{27j}; R = 3-pyridinyl
HL^{27k}; R = 4-florophenyl
HL^{27l}; R = 4-nitrophenyl

Scheme 4. Structure of ligands HL^{26} and HL^{27}.

Souza and colleagues prepared a TSC derivative (HL^{28}, Scheme 5) of the known antifungal agent lapachol and compared their antifungal activities against *C. albicans, Candida tropicalis, Cryptococcus gattii* and *Paracoccidioides brasiliensis* [87]. It was observed that the TSC derivative (MIC ˆ 0.02 – >0.80 mM) performed superior to the lapachol (MIC ˆ 0.26–1.03 mM) in all fungal strains. Kulandaivelu and coworkers synthesized a series of *p*-aminobenzoic acid and amino N-substituted TSCs (HL$^{29–34}$, Scheme 5) and tested them for antifungal activity against *C. albicans* and *Aspergillus niger* [88]. The hydroxamate derivatives HL$^{32–34}$ were found to have slightly better antifungal activity (half maximal inhibitory concentration, IC$_{50}$ ˆ 0.0008–0.003 mM) than their acid counterparts, HL$^{29–31}$ (IC$_{50}$ ˆ 0.0013–0.003 mM). Notably, all compounds showed better activity than the antifungal drug fluconazole (IC$_{50}$ > 0.010 mM) against *A. niger* and HL^{34b} (IC$_{50}$ ˆ 0.0013 mM) has comparable activity as fluconazole (IC$_{50}$ ˆ 0.00098 mM) against *C. albicans*.

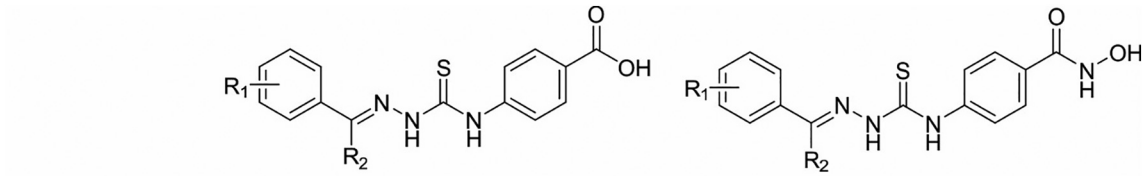
Thanh et al. prepared compounds HL^{35a-n} (Scheme 6) derived from N-(tetra-*O*-acetyl-β-D-glucopyranosyl)TSCs and 4-formylsydnones and compared their antifungal activity to nystatin, a standard antifungal drug [89]. Most compounds exhibited moderately higher to similar antifungal activity against *C. albicans, Fusarium oxysporum* and *A. niger* when compared to nystatin (MIC ˆ 0.0002–0.001 mM vs. MIC ˆ 0.0001 mM of nystatin). The TSCs HL^{35k-n} showed significant antifungal activity (MIC ˆ 0.0002–0.0003 mM) against all tested strains.

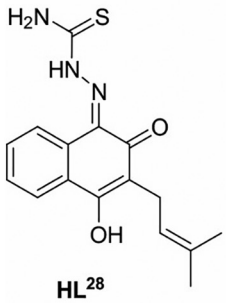
4.2. Copper complexes

The antifungal activities of more than 200 copper TSC compounds, Table S2, have been reported in the literature. In the majority of the studies, the activities of both the free ligand and the copper complexes are reported for comparison with the copper complex showing higher activity than the ligand and/or activity at lower concentration than the ligand. A selected number of ligand classes that provide insight into the structure activity relationship are further described in this section. Several of the ligands in this section were also evaluated with other coordinated metal ions and the activities of those complexes are described in subsequent sections.

In one of the early works evaluating the antifungal activity of TSCs and their copper complexes, Benns et al. prepared 40 TSCs (only a few shown here, HL$^{36–40}$, Scheme 7) and tested them against *A. niger* and *Chaetomium globosum* [90]. The HL$^{36–40}$ ligands all have a primary amine at N4 and hydrogen at N2. Only a few of the compounds showed activity at concentrations of 4.142–7.622 mM in the metal free form and all of the copper complexes were inactive. A series of similar ligands HL$^{41–46}$ studied by Gingras and coworkers included derivatives with hydrogen or methyl at N2 and primary amines, alkylamine, or dialkylamines at N4 [91]. It was found that an N2—H atom was essential for the formation of copper complexes. Of these, the copper complex of HL^{42} was most active with an MIC of 0.040 mM against *A. niger* and *C. globosum*, which is an order magnitude lower than the free ligand value of 0.464 mM. Notably, copper complexes of the phenyl derivatives with methylamine (HL^{44a}) and dimethylamine (HL^{45a}) at N4 displayed similar MIC values of 0.391 mM and 0.371 mM that were only ~25% lower than the free ligand values of 0.517 and 0.482 mM.

Chandra and coworkers studied the effect of the 2-pyridinecarboxadehyde TSC HL^{47} (Scheme 8) and its copper complexes (Cu(HL^{47})$_2$Cl$_2$, Cu(HL^{47})$_2$(NO$_3$)$_2$ and Cu(HL^{47})$_2$SO$_4$) on the growth of three fungal strains, *Rhizoctonia Bataticola, Alternaria alternata* and *Fusarium odum* [92]. The copper complexes were active at lower concentrations than the ligand with (CuL^{47})$_2$Cl$_2$ having a growth inhibition percentage of 76.6% at 0.509 M compared to 84.4% at 1.387 mM for the free ligand against *R. Bataticola*. Similar activities were observed against the other



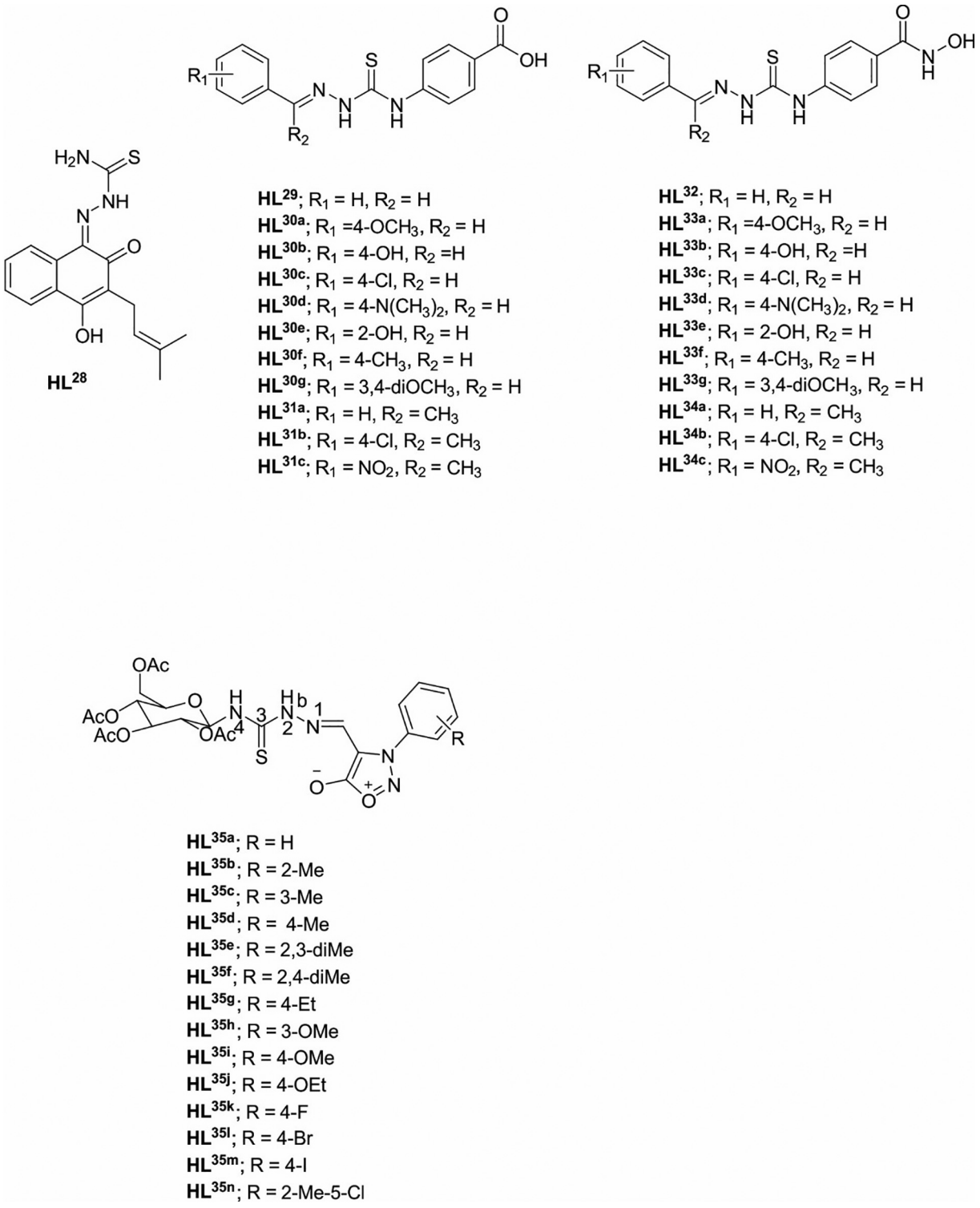


HL^{28}

HL^{29}; R$_1$ = H, R$_2$ = H
HL^{30a}; R$_1$ =4-OCH$_3$, R$_2$ = H
HL^{30b}; R$_1$ = 4-OH, R$_2$ =H
HL^{30c}; R$_1$ = 4-Cl, R$_2$ = H
HL^{30d}; R$_1$ = 4-N(CH$_3$)$_2$, R$_2$ = H
HL^{30e}; R$_1$ = 2-OH, R$_2$ = H
HL^{30f}; R$_1$ = 4-CH$_3$, R$_2$ = H
HL^{30g}; R$_1$ = 3,4-diOCH$_3$, R$_2$ = H
HL^{31a}; R$_1$ = H, R$_2$ = CH$_3$
HL^{31b}; R$_1$ = 4-Cl, R$_2$ = CH$_3$
HL^{31c}; R$_1$ = NO$_2$, R$_2$ = CH$_3$

HL^{32}; R$_1$ = H, R$_2$ = H
HL^{33a}; R$_1$ =4-OCH$_3$, R$_2$ = H
HL^{33b}; R$_1$ = 4-OH, R$_2$ =H
HL^{33c}; R$_1$ = 4-Cl, R$_2$ = H
HL^{33d}; R$_1$ = 4-N(CH$_3$)$_2$, R$_2$ = H
HL^{33e}; R$_1$ = 2-OH, R$_2$ = H
HL^{33f}; R$_1$ = 4-CH$_3$, R$_2$ = H
HL^{33g}; R$_1$ = 3,4-diOCH$_3$, R$_2$ = H
HL^{34a}; R$_1$ = H, R$_2$ = CH$_3$
HL^{34b}; R$_1$ = 4-Cl, R$_2$ = CH$_3$
HL^{34c}; R$_1$ = NO$_2$, R$_2$ = CH$_3$

Scheme 5. Structure of ligands HL^{28} – HL^{34}.

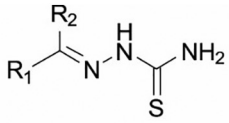


Scheme 6. Structure of ligand HL[35].

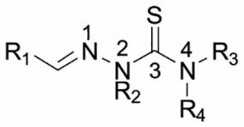
fungal strains and there was no substantial effect upon change of the anion.

Work by West and coworkers, Ibrahim and coworkers, and Mendes et al. evaluated three classes of ligands related to HL[47] including additional 2-pyridinecarboxadehyde compounds HL[48–51] with alkylamines, dialkylamines, cyclic amines, and aromatic amines at the N4 position and their 2-acetylpyridine (HL[42–57]) and 2-benzoylpyridine (HL[58–62]) analogues (Scheme 8) [47,60,61,93–99]. Coordination of copper yielded the neutral ligand derivatives Cu(*HL*)X_2 or the anionic ligand derivatives CuLX depending on reaction conditions (X ˆ Cl, Br). Most of the ligands and their copper complexes were evaluated by measuring the growth inhibition of *A. niger* and *Paecilomyces variotii*. For compounds with measurable activity, the copper complexes generally showed activity at lower concentrations than the free ligands and both the ligand and the metal complexes were generally more active against *P. variotii* than *A. niger*.

For the N4-alkylamine and N4-dialkylamine derivatives of HL[47] the anti-fungal activity is dependent on the ligand series and the



HL^{36a}; R_1 = *n*-propyl, R_2 = H
HL^{36b}; R_1 = *n*-butyl, R_2 = H
HL^{36c}; R_1 = *iso*-butyl, R_2 = H
HL^{36d}; R_1 = *n*-hexyl, R_2 = H
HL^{36e}; R_1 = *n*-heptyl, R_2 = H
HL^{36f}; R_1 = *n*-octyl, R_2 = H
HL^{36g}; R_1 = *n*-nonyl, R_2 = H
HL^{36h}; R_1 = *n*-decyl, R_2 = H
HL^{36i}; R_1 = 9-decyl, R_2 = H
HL^{36j}; R_1 = -C=$CH_2(CH_3)$-CH_2-CH_2-CH=$C(CH_3)_2$, R_2 = H
HL^{36k}; R_1 = -CH_2-$CH(CH_3)$-CH_2-CH_2-CH=$C(CH_3)_2$, R_2 = H
HL^{37a}; R_1 = phenyl, R_2 = H
HL^{37b}; R_1 = *o*-fluorophenyl, R_2 = H
HL^{37c}; R_1 = *m*-fluorophenyl, R_2 = H
HL^{37d}; R_1 = *p*-fluorophenyl, R_2 = H
HL^{37e}; R_1 = *o*-chlorophenyl, R_2 = H
HL^{37f}; R_1 = *p*-chlorophenyl, R_2 = H
HL^{38}; R_1 = methyl, R_2 = CH_3
HL^{39a}; R_1 = phenyl, R_2 = CH_3
HL^{39b}; R_1 = *p*-bromophenyl, R_2 = CH_3
HL^{39c}; R_1 = *p*-chlorophenyl, R_2 = CH_3
HL^{40}; R_1 = C_6H_5CO, R_2 = Ph



HL^{41a}; R_1 = hexyl, R_2 = Me, R_3 = H, R_4 = H
HL^{41b}; R_1 = heptyl, R_2 = Me, R_3 = H, R_4 = H
HL^{41c}; R_1 = octyl, R_2 = Me, R_3 = H, R_4 = H
HL^{41d}; R_1 = nonyl, R_2 = Me, R_3 = H, R_4 = H
HL^{41e}; R_1 = decyl, R_2 = Me, R_3 = H, R_4 = H
HL^{41f}; R_1 = 9-decyl, R_2 = Me, R_3 = H, R_4 = H
HL^{42}; R_1 = heptyl, R_2 = H, R_3 = Me, R_4 = H
HL^{43}; R_1 = phenyl, R_2 = Me, R_3 = H, R_4 = H
HL^{44a}; R_1 = phenyl, R_2 = H, R_3 = Me, R_4 = H
HL^{44b}; R_1 = *p*-chlorophenyl, R_2 = Me, R_3 = Me, R_4 = H
HL^{45a}; R_1 = phenyl, R_2 = H, R_3 = Me, R_4 = Me
HL^{45b}; R_1 = *p*-chlorophenyl, R_2 = H, R_3 = Me, R_4 = Me
HL^{46}; R_1 = phenyl, R_2 = Me, R_3 = Me, R_4 = H

Scheme 7. Structure of ligands HL^{36} – HL^{46}.

coordination mode. For free ligands, only the N4-alkylamine derivatives within the 2-acetylpyridine TSC series were consistently active at concentrations of 3.590–4.668 mM, whereas for N4-dialkylamine derivatives the 2-pyridinecarboxadehyde and 2-acetylpyridine TSCs typically showed similar activities that were higher than the 2-benzoylpyridine TSCs at similar concentrations, Fig. 1A. For neutral ligand complexes Cu(*HL*)Cl_2 at concentrations of 2.981–4.868 mM, the activities of the dialkyl derivatives followed the same general trends, however most of the alkylamine derivatives were inactive or not reported, Fig. 1B [47,60,61,93–99].

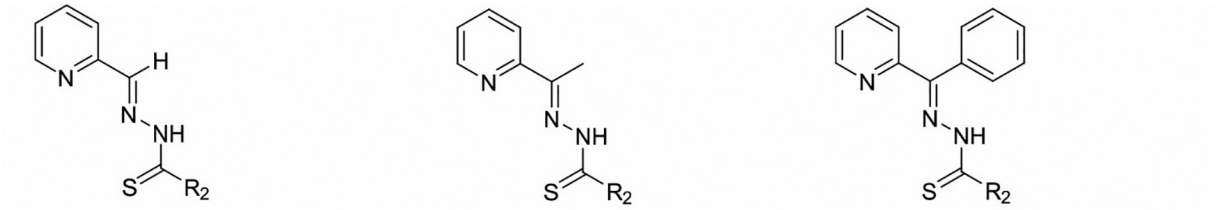
An effect of halogen ion as an auxiliary ligand on the reduction potential and the antifungal activity of the copper complexes of HL^{54b} was observed by Kumbhar et al. on six fungal strains, *A. niger, Aspergillus fumigatus, C. albicans, Cryptococcus neoformans, Trichophyton rubrum, Epidermophyton floccosum* and *Microsporum canis* [97]. An anodic shift in the $Cu^{II/I}$ reduction potential in the presence of Br^- (−0.36 V) as compared to Cl^- (−0.46 V) lead to the bromo-copper complex displaying better activity (inhibition zone diameter ˆ 11–17 mm at 0.508 mM) than the chloro-copper complex (inhibition zone diameter ˆ 9–12 mm at 0.574 mM). This trend was however not observed for the copper complexes derived from HL^{50a-c} where the more easily reduced bromo-copper complexes are less active (inhibition zone diameter ˆ 6.0–31.7 mm at 3.126–3.392 mM) than the chloro analogues (inhibition zone diameter ˆ 6.0–33.5 mm at 3.784–4.180 mM) [99].

For most CuLCl type of compounds based on derivatives of HL^{47}, copper complexes derived from the 2-acetylpyridine TSCs HL^{54a-c} and HL^{55a-d} were observed to be more active than the ones derived from 2-pyridinecarboxaldehyde TSCs HL^{49a-c} against *A. niger* (Fig. 2A). An opposite trend was observed against *P. variotiii* where the copper complexes derived from 2-pyridinecarboxaldehyde TSCs HL^{49a-c} were more active against *P. variotii* than the ones derived from 2-acetylpyridine TSCs HL^{54a-c} and HL^{55a-d} (Fig. 2B).

An effect of bulkiness of the TSC ligand was observed in the antifungal activity of copper complexes derived from the 2-pyridinecarboxadehyde TSC with methylamine and dialkylamine at N4 position, HL^{48a} and HL^{49a-c} (Scheme 8) respectively and 2-acetylpyridine TSCs with cyclic groups at N4 position, HL^{55a-d} (Scheme 8) against *P. variotii* [47,61,93,94]. It was observed that the copper complexes derived from ligand groups with bulkier substitutions at N4 were more active in inhibiting the fungal growth in comparison to the copper complexes with less bulky substitutions. Whereas an opposite trend was observed with copper complexes derived from the 2-pyridinecarboxadehyde TSCs with N4-cyclic groups, HL^{50a-c} (Scheme 8) and 2-acetylpyridine TSC N4-dialkyl groups, HL^{54a-d} (Scheme 8) against *A. niger* and *P. variotiii* [96,99].

Ibrahim and coworkers synthesized two tridentate ligands, $HL^{51d,e}$ (Scheme 8), and their copper complexes ($CuL^{51d,e}Cl$) to evaluate their antifungal activity against *A. flavus, C. albicans, F. oxysporum, Geotrichum candidum, Scopulariopsis brevicaulis* and *T. rubrum* [100]. An increase in the biological activity was observed on complexation with copper. The copper complex $CuL^{51d}Cl$ produced the best inhibition zones (8–25 mm at 2.572 mM) for all the fungal strains among the tested compounds and it was the only active compound against *Scapania brevicaulis* and *T. rubrum* with inhibition zones of 13 mm for both. Compounds similar to the previous study ($HL^{51f,g}$, Scheme 8) and their copper complexes, $[Cu(L^{51f,g})Cl]_2$ were prepared by the same group and investigated against *A. flavus, C. albicans, F. oxysporum, G. candidum, S. brevicaulis* and *T. rubrum* [101]. All tested compounds except $[Cu(L^{51f})Cl]_2$ (inhibition zone diameter ˆ 8–20 mm at 1.252 mM) were inactive against the tested fungal strains.

The antimicrobial activity of pyridine derived N4-tolyl TSCs (HL^{51a-c}, HL^{57a-c} and HL^{62b-d}, Scheme 8) and their respective copper complexes



HL^{48a}; R_1 = H, R_2 = NHMe
HL^{48b}; R_1 = H, R_2 = NHPr
HL^{49a}; R_1 = H, R_2 = $N(Me)_2$
HL^{49b}; R_1 = H, R_2 = $N(Et)_2$
HL^{49c}; R_1 = H, R_2 = $N(Pr)_2$
HL^{50a}; R_1 = H, R_2 = hexim
HL^{50b}; R_1 = H, R_2 = pip
HL^{50c}; R_1 = H, R_2 = azabicyclononane
HL^{51a}; R_1 = H, R_2 = *o*-tolyl
HL^{51b}; R_1 = H, R_2 = *m*-tolyl
HL^{51c}; R_1 = H, R_2 = *p*-tolyl
HL^{51d}; R_1 = H, R_2 = 2-chlorophenyl
HL^{51e}; R_1 = H, R_2 = 2-methoxyphenyl
HL^{51f}; R_1 = H, R_2 = 2,5-dimethoxyphenyl
HL^{51g}; R_1 = H, R_2 = 3-nitrophenyl

HL^{52}; R_1 = Me, R_2 = NH_2
HL^{53a}; R_1 = Me, R_2 = NHMe
HL^{53b}; R_1 = Me, R_2 = NHEt
HL^{53c}; R_1 = Me, R_2 = NHPr
HL^{53d}; R_1 = Me, R_2 = NHt-Bu
HL^{54a}; R_1 = Me, R_2 = $N(Me)_2$
HL^{54b}; R_1 = Me, R_2 = $N(Et)_2$
HL^{54c}; R_1 = Me, R_2 = $N(Pr)_2$
HL^{55a}; R_1 = Me, R_2 = pip
HL^{55b}; R_1 = Me, R_2 = hexim
HL^{55c}; R_1 = Me, R_2 = pyrrolidine
HL^{55d}; R_1 = Me, R_2 = azabicyclononane
HL^{55e}; R_1 = Me, R_2 = morpholine
HL^{56a}; R_1 = Me, R_2 =
HL^{56b}; R_1 = Me, R_2 =
HL^{56c}; R_1 = Me, R_2 =
HL^{57a}; R_1 = Me, R_2 = NHPh
HL^{57b}; R_1 = Me, R_2 = *o*-tolyl
HL^{57c}; R_1 = Me, R_2 = *m*-tolyl
HL^{57d}; R_1 = Me, R_2 = *p*-tolyl
HL^{57e}; R_1 = Me, R_2 = 2-chlorophenyl
HL^{57f}; R_1 = Me, R_2 = 4-flourophenyl
HL^{57g}; R_1 = Me, R_2 = 4-chlorophenyl
HL^{57h}; R_1 = Me, R_2 = 4-iodophenyl
HL^{57g}; R_1 = Me, R_2 = 2-flourophenyl
HL^{57h}; R_1 = Me, R_2 = 2-nitrophenyl

HL^{58}; R_1 = Ph, R_2 = NH_2
HL^{59a}; R_1 = Ph, R_2 = NHMe
HL^{59b}; R_1 = Ph, R_2 = NHEt
HL^{59b}; R_1 = Ph, R_2 = NHPr
HL^{60a}; R_1 = Ph, R_2 = $N(Me)_2$
HL^{60b}; R_1 = Ph, R_2 = $N(Et)_2$
HL^{60c}; R_1 = Ph, R_2 = $N(Pr)_2$
HL^{61a}; R_1 = Ph, R_2 = piperidine
HL^{61b}; R_1 = Ph, R_2 = azepane
HL^{62a}; R_1 = Ph, R_2 = NHPh
HL^{62b}; R_1 = Ph, R_2 = *o*-tolyl
HL^{62c}; R_1 = Ph, R_2 = *m*-tolyl
HL^{62d}; R_1 = Ph, R_2 = *p*-tolyl
HL^{62e}; R_1 = Ph, R_2 = 2-chlorophenyl
HL^{62f}; R_1 = Ph, R_2 = 2-flourophenyl
HL^{62g}; R_1 = Ph, R_2 = 2-nitrophenyl

Scheme 8. Structure of ligands HL^{47} – HL^{62}.

($Cu(HL^{51a})Cl_2$, $CuL^{51b}Cl$, $CuL^{51c}Cl$, $CuL^{57a}Cl$, $CuL^{57b}Cl$, $CuL^{57c}Cl$, $Cu(HL^{62b})Cl_2$, $Cu(HL^{62c})Cl_2$ and $Cu(HL^{62d})Cl_2$) was evaluated by Mendes et al. against *C. albicans* [102,103]. Quite low MIC values were obtained for the free ligands, $HL^{51a\text{-}c}$, $HL^{57a\text{-}c}$ and $HL^{62b\text{-}d}$ (0.0007–0.026 mM), Fig. 3. When comparing the activities of the 2-benzoylpyridine TSC $HL^{62b\text{-}d}$, the much lower activity of the meta derivative (HL^{62c}, MIC ˆ 0.023 mM) was attributed to an unfavorable resonance involving N4 and the tolyl ring [103]. However, for the 2-acetylpyridine TSCs $HL^{57a\text{-}c}$ the meta isomer had the highest activity and the 2-pyridinecarboxadehyde TSCs $HL^{51a\text{-}c}$ did not display a dependence on the position of the methyl group. An increase in activity was observed when the ligands $HL^{62b\text{-}d}$ were complexed to copper with the trend in activity as follows: $Cu(HL^{62d})Cl_2 > Cu(HL^{62c})Cl_2 > Cu(HL^{62b})Cl_2$. Similarly, for $HL^{57a\text{-}c}$, the antifungal activity was observed to increase on complexation (MIC ˆ 0.005–0.026 mM for $HL^{57a\text{-}c}$ and 0.004–0.007 mM for the copper complexes of $HL^{57a\text{-}c}$). However, the antifungal activity of $HL^{51a\text{-}c}$ (MIC ˆ 0.003 mM) was less affected by complexation with copper (MIC ˆ 0.002–0.004 mM).

4.3. Nickel, palladium and platinum complexes

The antifungal activities of the 90 nickel, 17 palladium, and 5 platinum TSC compounds reported in the literature are summarized in Table S3. In the majority of the studies, the complexes reported employ ligands that were also evaluated with copper. For ligands evaluated with both nickel and copper, nickel generally has similar or lower activity than copper. In comparison to their copper and nickel analogues, palladium and platinum complexes are generally less active or inactive. A select number of compounds are further described in this section.

Numerous studies have been reported employing nickel(II) complexes based on 2-pyridinecarboxaldehyde TSC (HL^{47}, Scheme 8) and its related derivatives. Coordination yields neutral ligand $Ni(HL)X_2$ and anionic ligands NiLX complexes (X ˆ Cl, Br) similar to those reported for copper along with *bis*-chelate $Ni(L)_2$ complexes. Against *R. bataticola, A. alternata*, and *F. odum* the complexes $Ni(L^{47})_2Cl_2$, $Ni(L^{47})_2(NO_3)_2$ and $Ni(L^{47})_2SO_4$ were found to be active at lower concentrations than the ligand, but less active (growth inhibition percentage ˆ 33.0–61.2%, at 0.460–0.510 mM) than the copper complexes at similar concentrations [92]. Nickel complexes of 2-pyridinecarboxadehyde TSCs with methylamine (HL^{48a}), dialkylamines (HL^{49}), and cyclic amines (HL^{50}) at the N4 position were inactive versus *A. niger*, but activity was observed against *P. variotii* with HL^{49} (inhibition zone ˆ 19.0–34.7 mm at 3.980–4.372 mM) and HL^{50} (inhibition zone ˆ 13.3–25.2 mm at 3.389–4.139 mM). Moderate activity was observed versus *A. niger* for the 2-acetylpyridine TSC complexes (HL^{54}) that was dependent of the size of the dialkyl substituent with inhibition zones of 8.0, 10.8, and 12.5 mm for $NiL^{54a}Br$, $NiL^{54b}Br$, and $NiL^{54c}Br$, respectively at ~4 mM. In contrast, the shorter chain derivatives $NiL^{54a}Br$ and $NiL^{54b}Br$ were more active than $NiL^{54c}Br$

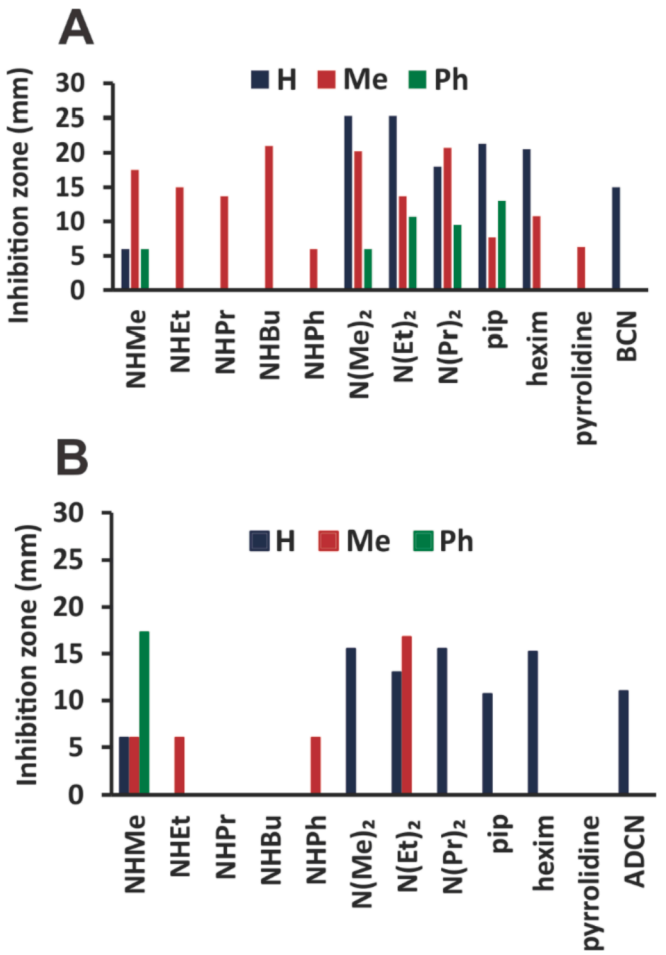


Fig. 1. A. Comparison of antifungal activities of 2-pyridinecarboxaldehyde (R_1 ^ H, blue), 2-acetylpyridine (R_1 ^ Me, red) and 2-benzoylpyridine TSCs (R_1 ^ Ph, green) derivatives of HL^{47} with alkylamine, dialkylamine and cyclic pendent R_2 groups against *A. niger*. B. Comparison of the activities of neutral ligand complexes Cu(*HL*)Cl_2 derived from 2-pyridinecarboxaldehyde (R_1 ^ H, blue), 2-acetylpyridine (R_1 ^ Me, red) and 2-benzoylpyridine TSCs (R_1 ^ Ph, green) derivatives of HL^{47} with alkylamine, dialkylamine and cyclic pendent R_2 groups against *A. niger*.

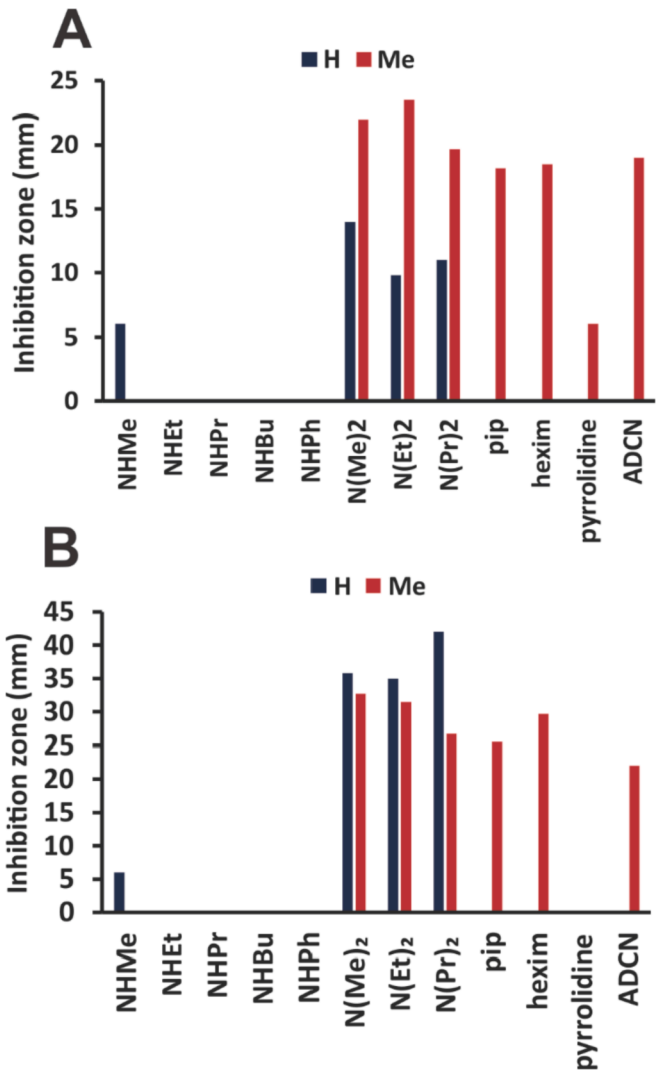


Fig. 2. Comparison of antifungal activities of 2-pyridinecarboxaldehyde (R_1 ^ H, blue) and 2-acetylpyridine (R_1 ^ Me, red) CuLCl derivatives of HL^{47} with alkylamine, dialkylamine and cyclic pendent R_2 groups against *A. niger* (A) and *P. variotii* (B).

against *P. variotii* with inhibition zones of 31.7, 31.7, and 9.5 mm, respectively. The 2-benzoylpyridine TSC complexes $NiL^{58}Cl$, $Ni(HL^{59a})Cl_2$, and $[Ni(L^{62a})_2]Cl_2$ were screened against *C. albicans* and found to be inactive even at high concentrations of 14–16 mM.

A series of related 2-pyridinecarboxaldehyde TSC palladium complexes ($PdL^{48b}Cl$, $PdL^{48b}Br$, $PdL^{49c}Cl$, $PdL^{49c}Br$, $Pd(L^{49c})_2$, $PdL^{50a}Cl$, $PdL^{50a}Br$ and $Pd(L^{50a})_2$) synthesized by Demertzi et al. were evaluated for potential antifungal properties against *A. niger* and *P. variotii* [63]. Although the metal-free ligands HL^{48b} and HL^{50a} yielded substantial growth inhibition zones at concentrations of 0.450 and 0.381 mM, respectively, none of the palladium complexes were active at the tested concentrations of 0.157–0.275 mM, which is contrary to copper complexes that were active against both fungi and nickel complexes that were active against only *P. variotii*. Likewise, the 2-acetylpyridine TSC complexes $PdL^{53a}Cl$ and $PtL^{53a}Cl$ were screened against *A. niger* and *P. variotii* by Bermejo and coworkers [104]. Whereas the free ligand HL^{53a} was active at 7.682 mM with a zone of inhibition of 17.5 and 17.7 mm for *A. niger* and *P. variotii*, neither complex was active at the tested concentration of 4.583 mM.

Another study by Demertzi and coworkers with HL^{52} (Scheme 8) and its palladium complexes ($PdL^{52}Cl$, $[Pd(L^{52})_2]Cl_2$ and $Pd(L^{52})_2$) described their role in inhibiting the growth of *C. albicans* [105]. Only compounds HL^{52} and $Pd(L^{52})_2$ showed significant antifungal activity (MIC <0.002 mM), while the remaining complexes were inactive (MIC >0.002 mM). Similarly, of three platinum complexes studied only $Pt(L^{52})_2$ showed significant antifungal activity (MIC <0.002 mM), which is similar to the palladium derivative. Notably, all nickel complexes of HL^{52} possessed much lower activity than $Pd(L^{52})_2$ and $Pt(L^{52})_2$. This may be due to differences in coordination environment. Whereas $Ni(L^{52})_2$ is a six-coordinate complex with two N_2S chelates, $Pd(L^{52})_2$ and $Pt(L^{52})_2$ are proposed to be four-coordinate with one tridentate N_2S L^{52} and one monodentate S bound L^{52} [105,106].

A series of nickel(II) complexes based on tridentate 2-phenylhydrazono-propan-2-ylidene TSC ligands (HL^{67a-c}, Scheme 9) were prepared and their antifungal activity was evaluated against *A. flavus, Penicillium italicum, C. albicans*, and *G. candidum* [79]. The highest activity was observed against *A. flavus* with MIC values of 0.045, 0.091, and 0.154 mM for $[Ni(L^{67a})Cl]\cdot H_2O$, $[Ni(L^{67b})Cl]\cdot H_2O$, and $[Ni(L^{67c})Cl]\cdot H_2O$, respectively, with the complexes showing a two to six times increase in activity relative to the free ligand. Similar trends were observed against *P. italicum* and *G. candidum* with $[Ni(L^{67a})Cl]\cdot H_2O$ showing the highest activity, but all complexes and ligands were inactive against *C. albicans*. A series of tridentate 1-hydroxypropan-2-ylidene TSCs (HL^{68a-c}, Scheme 9) and their bis-chelate nickel(II) complexes ($[Ni(HL^{68a-c})_2]Cl_2\cdot H_2O$)

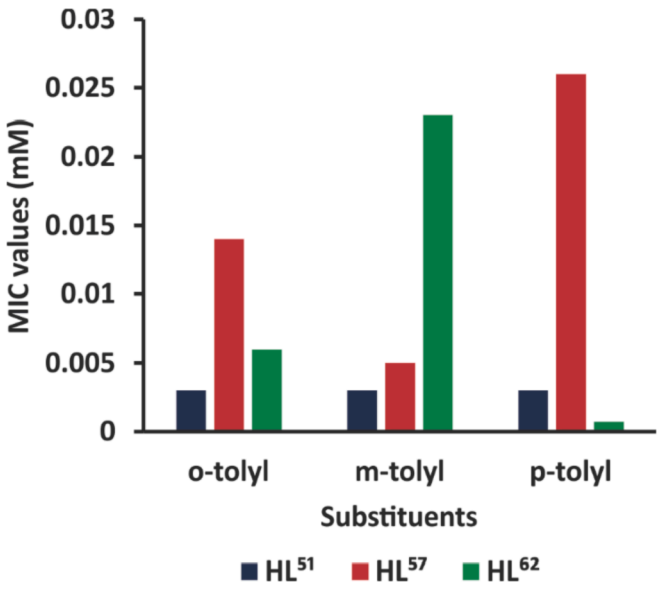


Fig. 3. Comparison of activities of TSCs HL^{51a-c}, HL^{57a-c} and HL^{62b-}.

were prepared by Netalkar and coworkers and screened for antifungal activity against *C. albicans* and *A. niger* [107]. For the free ligands, the N4-bromophenyl derivative HL^{68c} (MIC ˆ 0.041 mM) was more active than the fluoro- and chlorophenyl derivatives HL^{68a} and HL^{68b}, which had MIC values 0.207 and 0.194 mM, respectively. Coordination of nickel(II) substantially enhanced the activity of the complexes resulting in MIC values of 0.002–0.008 mM.

4.4. Zinc, cadmium and mercury complexes

The antifungal activities of the 50 zinc, 14 cadmium, and 20 mercury TSC compounds reported in the literature are summarized in Table S4. Most of the ligands evaluated with zinc, cadmium and mercury were also tested with copper and nickel. Typically, the zinc complexes are as active or more active than their copper analogues and the cadmium complexes had similar activities to zinc. A notable exception is HL^{26} where cadmium yielded the most active complexes of any metal. In most cases, mercury complexes were found to be more active than their corresponding zinc derivatives. In cases where the same ligand was evaluated for mercury and copper, the two metals displayed similar activity. A select number of compounds are further described in this section.

Alomar et al. prepared the zinc(II) ($Zn(HL^{26})_2Cl_2$) and cadmium(II) ($Cd(HL^{26})Cl_2$, $Cd(HL^{26})Br_2$, and $Cd(HL^{26})_2Br_2$) complexes of 3-thiophenealdehyde TSC, HL^{26} (Scheme 4) to evaluate their antifungal activity against *C. albicans, C. glabrata*, and *A. fumigatus* [108]. The cadmium complexes exhibited the highest activity against *C. albicans* and *C. glabrata* and were the only complexes with activity against *A. fumigatus.* At a concentration of 15.56 mM, $Cd(HL^{26})_2Br_2$ yielded zones of inhibition of 27, 40, and 52 mm versus *C. albicans, C. glabrata*, and *A. fumigatus*, respectively. The other cadmium complexes had consonant activity at similar concentrations. At 19.73 mM, $Zn(HL^{26})_2Cl_2$ was less active (zone of inhibition ˆ 17 and 18 mm versus *C. albicans* and *C. glabrata*) than the cadmium complexes, whereas the free ligand required higher concentrations of 53.98 mM to achieve a zone of inhibition of 18 mM against *C. glabrata* and 27 mm for *C. albicans.*

Chandra et al. prepared the zinc complexes ($[Zn(L^{47})_2]Cl_2$, $[Zn(L^{47})_2](NO_3)_2$, $[Zn(L^{47})_2]SO_4]$) and mercury complexes ($[Hg(L^{47})_2]Cl_2$, $[Hg(L^{47})_2](NO_3)_2$, $[Hg(L^{47})_2]SO_4]$) derived from 2-pyridinecarboxaldehyde TSC (HL^{47}, Scheme 8) to investigate their antimicrobial properties against *C. albicans* and *A. niger* [109]. Against *C. albicans*, $[Cd(L^{47})_2]Cl_2$ displayed higher activity (zone of inhibition ˆ 20 mm at 200 μg/disc) than $[Zn(L^{47})_2]Cl_2$ (15 mm) and the free ligand (14 mm) with the same loading. The $[Cd(L^{47})_2]Cl_2$ complex was also more active (22 mm) than $[Zn(L^{47})_2]Cl_2$ (14 mm) and the ligand (0 mm) against *A. niger*. For each metal, the nitrate salts had similar activity as the chloride and the sulfate salts had lower activity. Parwana and Singh compared the antimicrobial activities of $[Zn(HL^{47})Cl_2]\cdot C_2H_5OH$ and $[Zn(HL^{64})_2Cl_2]$ against *C. albicans* and *A. fumigatus* [110]. The ligands differ by the position of the TSC substituent on pyridine at the 2- (HL^{47}) or 3-position (HL^{64}). For *C. albicans*, $[Zn(HL^{47})Cl_2]\cdot C_2H_5OH$ (MIC ˆ 1.474 mM) was slightly more active than $[Zn(HL^{64})_2Cl_2]$ (2.013 mM). The same trend was observed for *A. fumigatus*.

A series of $M(HL^{53a-c})X_2$ (M ˆ Zn, Cd, Hg; X ˆ Cl, Br, I) complexes with 2-acetylpyridine TSC ligands with methyl (HL^{53b}, Scheme 8) [104], ethyl (HL^{53c}, Scheme 8) [111], or propyl (HL^{53d}, Scheme 8) [112] substituents at the N4 position were prepared and evaluated for antifungal activity against *A. niger* and *P. variotii*. Like the Cu(II), Pd(II), and Pt(II) complexes of HL^{53a}, most of the complexes were inactive. Only the zinc complexes of HL^{53a} and HL^{53b} (inhibition zone diameter ˆ 10.2–13.8 mm) and the mercury complexes of HL^{53b} (8.1–19.0 mm) showed activities at concentrations of 2–3 mM against *P. variotii* with the highest activity observed for $Hg(HL^{53b})I_2$. Versus *A. niger*, only the Hg (HL^{53b})X_2 series were active (11.3–16.3 mm) with the iodo complex again having the highest activity. A series of 2-benzoylpyridine TSC complexes ($Zn(L^{58})_2Cl_2$, $Zn(L^{59a})_2Cl_2$, and $Zn(HL^{62a})Cl_2$) investigated for antimicrobial activity against *C. albicans* by Costa were also found to inactive [113].

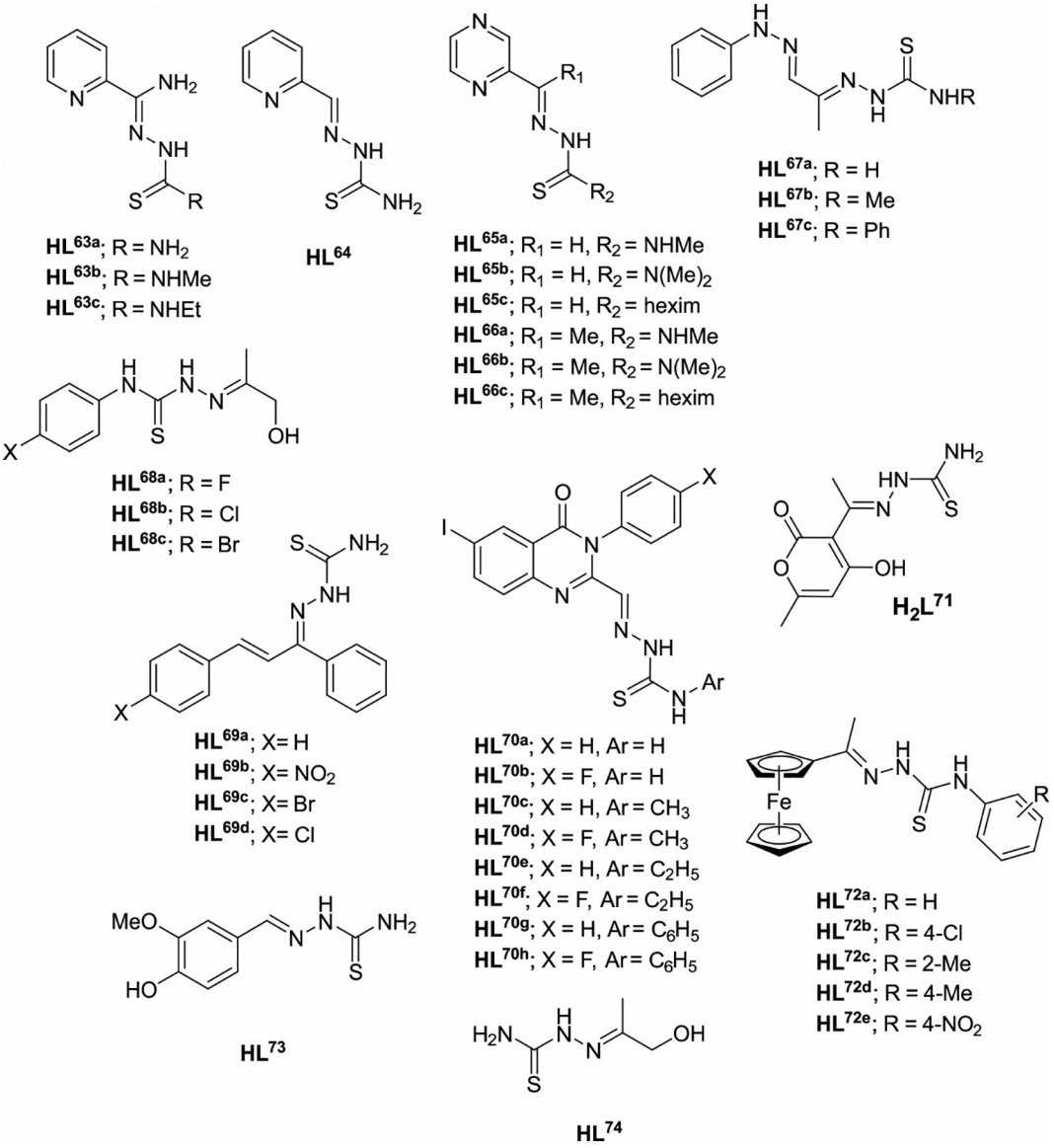
The antimicrobial activities of chalcone derived TSCs HL^{69a-d} (Scheme 9) and their respective zinc complexes ($Zn(L^{69a})_2$, $Zn(L^{69b})_2$, $Zn(L^{69c})_2$ and $Zn(L^{69d})_2$) were examined by Silva and coworkers against *C. albicans* [114]. The series represents an atypical example were activity decreases upon coordination of zinc. The MIC values for HL^{69a}, HL^{69c} and HL^{69d} (MIC ˆ 0.011 mM, 0.020 mM, and 0.009 mM, respectively) increase at least two-fold upon coordination to Zn(II) (MIC ˆ 0.023 mM, > 0.068 mM, and 0.019 mM, respectively). For the nitro derivative HL^{69b}, the activity was observed to increase from MIC >0.157 mM for the metal-free ligand to MIC >0.069 mM for the zinc complex.

Aly et al. prepared various 4(3*H*)-quinazoline-2-carboxaldehyde TSCs HL^{70a-h} (Scheme 9) and some of their zinc complexes ($ZnL^{70b}Cl$, $ZnL^{70d}Cl$, $ZnL^{70h}Cl$, $Zn(L^{70b})_2$, $Zn(L^{70d})_2$, and $Zn(L^{70h})_2$) to study their antimicrobial activity against *Aspergillus species* and *Fusarium sp*. [115]. Out of all tested TSCs, only HL^{70a}, HL^{70e}, and HL^{70h} (inhibition zone diameter ˆ 23, 15, and 25 mm, respectively) were found to be active against *Fusarium sp.,* and no activity was shown towards *Aspergillus* sp. The zinc complexes on the other hand showed moderate to good activity against both fungi (inhibition zone diameter ˆ 14–28 mm). $Zn(L^{70d})_2$ showed some activity against *A. niger* and *Fusarium sp.* (inhibition zone diameter ˆ 14 mm and 28 mm). $Zn(L^{70d})_2$ and $Zn(L^{70h})_2$ on the other hand were found to be active only against *Fusarium sp.* (inhibition zone diameter ˆ 16 and 24 mm).

4.5. Other transition metal complexes

The antifungal activities of approximately 80 TSC other transition metal complexes with Ti, Zr, Cr, Mn, Co, Fe, or Ru are summarized in Table S5 of the supplementary material. The majority of the complexes are Co compounds that employ ligands also evaluated with Cu and Ni. In general, Co complexes displayed similar or less activity than the Cu and Ni analogues. Similarly, the studies with Cr, Mn, and Fe employ ligands that were also evaluated with Cu and Ni and they display similar or lower activities. The ruthenium complexes were inactive. Data for the titanium and zirconium complexes are limited to a family of cyclopentadienyl derivatives unique to these metals.

Sharma and coworkers investigated the antimicrobial properties of various mixed ligand cobalt complexes that combined long chain alkyl TSCs $HL^{36j,k}$ (Scheme 5) with N-phthaloyl (N-Pht) protected amino acids



Scheme 9. Structure of ligands HL^{63} – HL^{74}.

against *Fusarium moniliforme* and *Macrophomina phaseolina* [116]. The complexes (CoL^{36j}-N-Pht-gly, CoL^{36j}-N-Pht-ala, CoL^{36j}-N-Pht-val, CoL^{36k}-N-Pht-gly, CoL^{36k}-N-Pht-ala, and CoL^{36k}-N-Pht-val) were found to have better activity (growth inhibition percentage ˆ 78.42–88.98% at 0.753 mM–0.821 mM) than the metal-free TSCs (growth inhibition percentage ˆ 75.15–85.63% at 1.775 mM and 1.759 mM) against both of the tested fungal strains. These complexes were reported to restrict growth by disturbing the respiratory processes of the cell and blocking protein synthesis.

West and Carlson reported the antifungal properties of Co and Fe complexes with the 2-acetylpyridine TSC ligands $HL^{54b,c}$ (Scheme 8) with dialkyl substituents at the N4 position against the growth of *A. niger* and *P. variotii* [117]. The cobalt complexes ($[Co(L^{54b})_2]BF_4$, $CoL^{54b}Cl$, $CoL^{54b}Br$, $[Co(L^{54c})_2]BF_4$, $CoL^{54c}Cl$, and $CoL^{54c}Br$) and the iron complexes ($[Fe(L^{54b})_2]ClO_4$, $[Fe(L^{54b})_2]FeCl_4$, $[Fe(HL^{54c})(L^{54c})ClO_4]ClO_4{\cdot}H_2O$, and $[Fe(L^{54c})_2]FeCl_4$) possess little, if any activity, and there was no difference between the activity of the complexes with HL^{54b} and HL^{54c}. Six-coordinate bis-chelate iron complexes ($[Fe(L^{58})_2]Cl_2$, $[Fe(L^{59a})_2]Cl_2$ and $[Fe(HL^{62a})_2]Cl_2$) with 2-benzoylpyridine TSC ligands were synthesized and investigated for antimicrobial activity against *C. albicans* by Costa [113]. Like the nickel complexes, the activity of the ligand was lost upon coordination to Fe(II) (zone of inhibition ˆ 6.0–7.0 mm at 8.106–17.746 mM). Parwana and Singh reported the antimicrobial activities of 2- and 3-acetylpyridine iron complexes $[Fe(HL^{47})_2]Cl$ and $[Fe(HL^{64})_2Cl_2]Cl$ against *C. albicans* and *A. fumigatus* [110]. With *C. albicans*, both iron complexes (MIC ˆ 1.913 mM) displayed good antifungal activity by decreasing the concentration of the fungus (8.8×10^6 CFU/ mL to 1×10^6 CFU/ mL) by eight-fold in comparison to just the metal-free ligand that displayed no activity. With *A. fumigatus*, only $[Fe(HL^{47})_2]Cl$ showed any activity (zone of inhibition ˆ 15 and 20 mm at 1.660 mM and 2.214 mM, respectively).

Sengupta and colleagues prepared titanocene ($Cp_2TiCl(L)$; L ˆ $L^{72a\text{-}e}$) and zirconocene ($Cp_2ZrCl(L)$; L ˆ $L^{72a\text{-}e}$) chelates of acetylferrocenyl TSCs, $HL^{72a\text{-}e}$ (Scheme 9) to study their effect in inhibiting the growth of *A. niger, A. alternata*, and *Heterodera oryzae* [118]. All compounds showed significant toxicity at higher concentration (1.497–2.650 mM) against all the fungi and the complexes were found to be more active (growth inhibition percentage ˆ 44.8–88.6%) than the metal-free ligands (growth inhibition percentage ˆ 40.2–52.8%). The activity was seen to decrease on dilution. Complex $Cp_2TiCl(L^{72b})$ was found to be the most active of all the tested complexes with growth inhibition percentage of 88.6%.

4.6. Post transition metal complexes

The antifungal activities of 28 TSC complexes with post transition metals including Ga, In, Sn, and Sb have been reported as summarized in Table S6 of the supplementary material. Bastos et al. prepared gallium complexes ($[Ga(L^{63a})_2]NO_3$, $[Ga(L^{63b})_2]NO_3$ and $[Ga(L^{63c})_2]NO_3$) with the 2-aminomethylpyridine ligands HL^{63a-c} (Scheme 9) to study their effect on the growth of *C. gattii* [119]. Among the TSCs, HL^{63a} exhibited the best antifungal activity (MIC ˆ 0.026 mM), HL^{63b} showed moderate activity (MIC ˆ 0.052–0.104 mM), and HL^{63c} exhibited weak activity (MIC >0.417 mM). Coordination to gallium(III) significantly improved the activity of HL^{63a-c} (MIC ˆ 0.013 mM, 0.002 mM and 0.013 mM, respectively). In contrast, coordination of the ligand family HL^{69a-d} to gallium to yield $Ga(L^{69a-d})_2$ had only a small impact on the activity of the ligands against *C. albicans* for HL^{69a}, HL^{69c} and HL^{69d} (MIC ˆ 0.017 mM, 0.014 mM and 0.0135 mM, respectively) [114]. Notably, the nitro derivative HL^{69b} was found to be inactive as the free ligand but had similar activities to the other compounds upon coordination to Ga(III) (MIC ˆ 0.015 mM). In general, the gallium complexes for HL^{69} displayed better antifungal activities than the respective zinc analogues.

Oliveira et al. reported antimicrobial effects of indium(III) complexes ($[In(L^{57a})Cl_2(MeOH)]$, $[In(L^{57b})Cl_2(MeOH)]$, $[In(L^{57c})Cl_2(MeOH)]$ and $[In(L^{57d})Cl_2(MeOH)]$) of 2-acetylpyridine derived TSCs, HL^{57a-d} (Scheme 8) against *C. albicans, Candida dubliniensis, Candida lusitaniae*, and *Candida parapsilosis* [120]. An increase in antimicrobial activity of the free ligands (IC_{50} ˆ 0.017 ± 0.001 to 0.294 ± 0.025 mM) was observed on complexation with indium (IC_{50} ˆ 0.0014 ± 0.0001 to 0.016 ± 0.001 mM) in most of the cases. All complexes were observed to be very active especially against *C. dubliniensis* and *C. lusitaniae* (IC_{50} ˆ 0.0014 ± 0.0001 to 0.0038 ± 0.0004 mM). $[In(L^{57a})Cl_2(MeOH)]$ (IC_{50} ˆ 0.0014 ± 0.0001 μM) was found to be as active as nystatin (IC_{50} ˆ 0.002 ± 0.0003 mM) and 100 times more active than the metal-free ligand, HL^{57a} (IC_{50} ˆ 0.138 ± 0.001 mM).

Pyridine derived TSCs HL^{57e-g} and HL^{62e-g} (Scheme 8) and their tin (IV) complexes ($(n\text{-Bu})Sn(L^{57e-g})Cl_2$ and $(n\text{-Bu})Sn(L^{62e-g})Cl_2$) were analyzed for antifungal activity against *C. albicans, C. krusei, C. glabrata*, and *C. parapsilosis* by Parrilha et al. [80]. For the free ligands, the 4-chlorophenyl derivative HL^{57g} (MIC ˆ 0.006 mM) was more active than the 2-chlorophenyl (HL^{57e}, MIC ˆ 0.013–0.026 mM) and 4-fluorophenyl (HL^{57f}, MIC ˆ 0.007–0.028 mM) derivatives. Coordination of Sn (IV) had no significant effect on the activity of HL^{57g}, but it slightly increased the activities of HL^{57f} and slightly decreased the activities of HL^{57e}. For the 2-benzoylpyridine TSCs, HL^{62e-g} both the 2-chlorophenyl and 4-chlorophenyl derivatives had similar activities (MIC ˆ 0.021–0.042 mM) that increased by a factor of 4–7 upon coordination of Sn(IV) to HL^{62g}, but slightly decreased upon coordination to HL^{62e}. Mendes and coworkers developed organotin(IV) complexes ($(n\text{-Bu})Sn(L^{63a})Cl_2$, $(n\text{-Bu})Sn(L^{63b})Cl_2$ and $(n\text{-Bu})Sn(L^{63c})Cl_2$) of 2-pyridinecarboxaldehyde TSCs HL^{63a-c} (Scheme 9), to investigate their antimicrobial effects on *C. albicans* [122]. The activity of the TSCs (MIC ˆ 1.312–2.448 mM) was observed to increase on complexation with tin (IV), although all complexes bore similar activity (MIC ˆ 0.273–0.290 mM) that was less active than the gallium counterparts.

Kasuga and coworkers investigated the antimicrobial activities of antimony(III) complexes, $SbL^{55e}Cl_2$ and $SbL^{55e}Br_2$ of the 2-acetylpyridine TSC HL^{55e} (Scheme 8) against *C. albicans, Saccharomyces cerevisiae, A. niger*, and *Penicillium citrinum* [123]. The complex $Sb(L^{55e})Cl_2$ exhibited superior antifungal activity (MIC ˆ 0.137 mM) than the parent TSC (MIC ˆ 0.473 mM) against *A. niger* and *P. citrinum*. Whereas, for *C. albicans* and *S. cerevisiae*, the ligand exhibited higher antifungal activity (MIC ˆ 0.118 mM) than $Sb(L^{55e})Cl_2$ (MIC ˆ 0.137 mM and 0.274 mM). On the other hand, complex $Sb(L^{55e})Br_2$ possessed the same antimicrobial activity against all fungi (MIC ˆ 0.229 mM). The antimony complexes of HL^{55e} performed superior to both nickel and zinc complexes.

4.7. Comparison of the antifungal activities of various metal complexes

For the sake of comparison, the influence of the metal ion on the activity of two ligand families that have been studied with a variety of metal ions are highlighted in Figs. 4 and 5.Fig. 4 compares the activities of various metal complexes of the vanillin TSC HL^{73} in inhibiting the growth of *Alternaria sp., Paecilomyces species*, and *Pestalotia species*. Overall, the metal complexes of HL^{73} follow the trend observed with many other TSC ligands. The highest growth inhibition percentage with the HL^{73} ligand against all fungal strains is observed for $[Cu(HL^{73})Cl_2]H_2O$. The activity of the corresponding zinc(II) complex is substantially lower than copper, with some activity restored upon substitution of zinc with cadmium and mercury. Compared to Cu(II), the anti-fungal activity of the HL^{73} complexes decreases systematically with Cu(II) > Ni(II) > Fe (II) > Mn(II). All of the complexes displayed enhanced activity relative to the metal-free ligand [124].

Fig. 5 compares the MIC values for metal complexes of (E)-1-(1-hydroxypropan-2-ylidene) thiosemicarbazide HL^{74} for *C. albicans* and *A. niger*. Interestingly, of the four metal ions evaluated with HL^{74} the copper complex $[Cu(HL^{74})Cl_2]\cdot H_2O$ had the lowest activity (highest MIC values). This can be attributed to differences in the coordination mode of HL^{74} with copper as compared to Co, Ni, and Zn. In the former case, a single bidentate TSC ligand is coordinated, while in the latter cases each metal ion coordinates two bidentate TSC ligands. Against *C. albicans* the greatest activity is observed for $[Co(L^{74})_2]Cl$ followed by $[Zn(HL^{74})_2]\cdot 2Cl$ and $[Ni(HL^{74})_2]Cl_2\cdot 2H_2O$. Versus *A. niger* the order of activity with HL^{74} is Zn(II) > Ni(II) > Co(III) [44].

5. Bis(thiosemicarbazones)

The antifungal activities for four families of BTSC N_2S_2 chelates and their respective metal complexes have been reported in Table S7 in the supplementary material. In comparison to TSCs, metal complexes of BTSC N_2S_2 chelates are understudied. Currently there is not enough data to make general conclusions about the relative activities of different metals.

West and coworkers synthesized four different BTSC ligands (H_2L^{75a-d}, Scheme 10) and their respective neutral, square planar copper, CuL^{75a-d}, and nickel complexes, NiL^{75a-d} and tested them against the fungus *P. variotii* for antifungal activity [125]. Although the N4-methylamine derivative H_2L^{75a} showed no activity, the N4-dimethylamine ligand H_2L^{75b} yielded a small zone of inhibition (8.0 mm at 3.467 mM), and the N4-cyclic amine ligands H_2L^{75c} and H_2L^{75d} gave large inhibition zones of

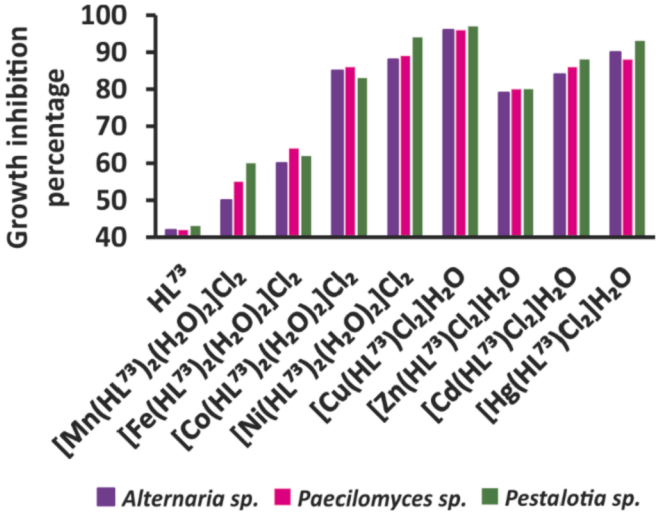


Fig. 4. Comparison of the growth inhibition percentage of TSC HL^{73} and its various metal complexes. The ligand activity was tested at 4.439 mM and the metal complexes were tested over a concentration range of 1.622–2.719 mM.

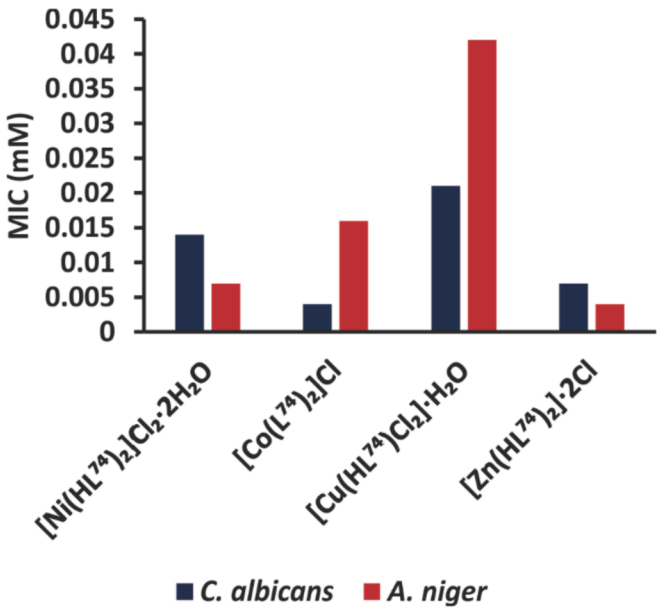


Fig. 5. Comparison of the MIC values of various complexes of TSC HL^{74}.

32.6 mm and 21.8 mm at 2.713 mM and 2.521 mM, respectively. Upon complexation with Cu, the N4-methylamine CuL^{75a} and the N4-dimethylamine CuL^{75b} showed small inhibition zones (9.1 mm and 10.1 mm, at 3.106 mM and 2.857 mM, respectively), whereas CuL^{75c} and CuL^{75d} were found to be inactive. All four Ni complexes were inactive.

A series of Cu(II) and Ni(II) six-coordinate $M(H_2L^{76})X_2$ (M ˆ Ni, Cu; X ˆ Cl^-, NO_3^-, CH_3COO^-) were prepared by coordination of the benzil BTSC, H_2L^{76} (Scheme 10) and evaluated for antifungal activity against *R. Bataticola, A. alternata, and F. odum*. It was observed that all the Cu complexes had better activity (growth inhibition percentage ˆ 30.0–49.2% at 0.230–0.255 mM) in comparison to the parent ligands (growth inhibition percentage ˆ 22.0–30.2% at 0.351 mM). There was no significant effect upon changing the X ligand. The nickel complexes were slightly less active (growth inhibition percentage ˆ 23.4–45.2% at 0.232–0.257 mM) than the copper complexes, but more active than the free ligands. Refat and colleagues prepared the corresponding Co(II) and Mn(II) complexes [126]. The compounds showed fungal growth inhibition in the following order: Cu(II) > Ni(II) > Co(II) > Mn(II) ≈ H_2L^{76}.

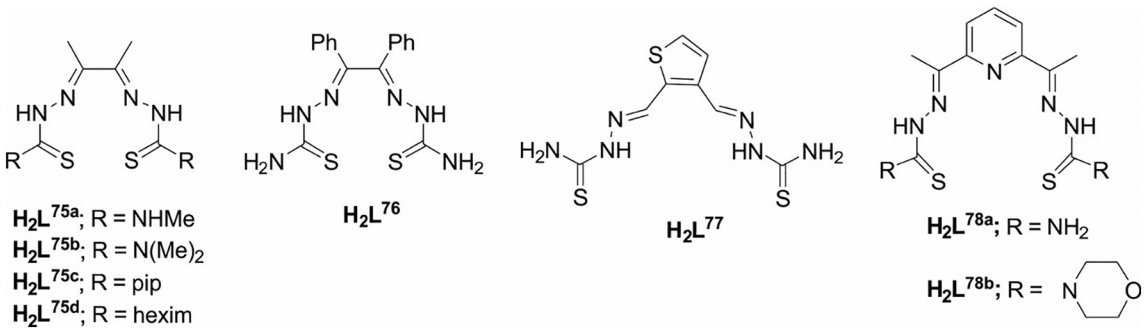
The thiophen-2,3-dicarboxaldehyde BTSC (H_2L^{77}, Scheme 10) and its square planar Cu, CuL^{77}, and Ni, $[Ni(HL^{77})]Cl$, complexes were synthesized by Alomar and coworkers to study their effect on *C. albicans, C. glabrata, and A. fumigatus* fungi [127]. Only weak activity was shown by both the ligand (MIC >0.775 mM) and the respective Cu complex (MIC >0.719 mM), whereas the Ni complex was slightly active against *C. albicans* (MIC ˆ 0.659 mM) and more active against *C. glabrata* (MIC ˆ 0.163 mM). Coordination of H_2L^{77} as the neutral ligand to Ni yielded the six-coordinate complexes $[Ni(H_2L^{77})Cl(H_2O)]Cl$ and $[Ni(H_2L^{77})Br(H_2O)]Br$ [128]. Compared to $[Ni(HL^{77})]Cl$, activity with the fully protonated ligand was slightly improved against *C. glabrata* for the chloro derivative (MIC ˆ 0.144 mM) and more so for the bromo derivative (MIC ˆ 0.060 mM). A similar trend was observed for *C. albicans*. The corresponding Cd complexes $(Cd(H_2L^{77})Cl_2$ and $Cd(H_2L^{77})Br_2)$ were found to be highly active (MIC ˆ 0.014–0.111) mM against all *Candida* [127].

Kasuga and colleagues investigated the antifungal activity of compounds with the pentadentate ligands H_2L^{78a} and H_2L^{78b} (Scheme 10) and their respective zinc complexes ($[Zn(L^{78a})]_n$ and $[Zn(L^{78b})]_n$) against *C. albicans, S. cerevisiae, A. niger*, and *P. citrinum* [129]. Only the free ligand H_2L^{78b} was observed to show any activity against *C. albicans* and *S. cerevisiae* (MIC ˆ 0.278 mM). The related Ni complex NiL^{78b} was found to be inactive (MIC >1.975 mM) against the same fungi [130]. Tyagi and Chandra explored the biocidal properties of the same ligand in the protonated form with various metals as the chloride salts, $[M(H_2L^{78a})Cl]Cl_2]$ (M ˆ Rh, Ir) and $[M(L^{78a})]Cl_2]$ (M ˆ Pd, Pt), against *A. niger*, *A. fumigatus*, and *F. odum* [131]. Metal complexes were found to have higher inhibitory effect (growth inhibition percentage ˆ 45.0%–56.0%) than the free ligand (growth inhibition percentage ˆ 29.0%–38.0%) and the respective metal salts, with the Pd complex consistently showing the highest activity.

6. Summary

In this review, we have summarized the anti-fungal activities of TSCs and BTSCs and their respective metal complexes. The ligand structures differ by incorporating different substituents at various positions in the TSC framework resulting in observed changes in their biological activity. It has often been observed that the metal complexes outperform the metal-free ligands in inhibiting the fungal growth. This has been attributed to charge dispersion upon chelation, which enhances the lipophilicity of the complex favoring its permeation through the fungal cell wall. Further, the anti-fungal activity is dependent on the identity of the metal ion. Of the most commonly studied metals, copper(II) and zinc (II) complexes typically display the highest activity. While this is generally the case, it is not universally observed. It is noteworthy that the copper complexes are redox active with biologically accessible reduction potentials and is likely related to their MOA. In contrast, zinc complexes have no metal centered redox activity suggesting they operate via a different MOA. For zinc, transmetalation with copper under physiological condition is known to occur and needs to be considered [132,133]. In a few examples explored in this review the metal free ligand was evaluated at a higher concentration than the corresponding metal complexes. In these cases, a direct comparison of the activities is difficult.

In conclusion, several TSC, BTSC, and their metal complexes show promise as potential antifungal agents. However, the development of new antifungal agents faces a number of challenges currently including



Scheme 10. Structure of ligands HL^{75} – HL^{78}.

the various methods of recording the data, making it difficult to compare of different studies. Because every fungi behaves differently towards a potential drug candidate, this contributes as another issue in comparing results. Another major challenge faced by this field is the development of resistance mechanism(s) by fungi. In particular, on comparing the different fungal strains, *A. niger* was observed to be resistant towards many drug candidates. This challenge poses as a threat of a potential global pandemic. As noted by a reviewer, an important aspect that is often overlooked in this field is the effect of complex stability on the biological activity. For example, COTI-2, an anticancer TSC forms a stable ternary copper(II)-glutathione complex that is effluxed by ATP binding cassette subfamily C member 1 (ABCC1), contributing to drug resistance [134]. Similar effects could also become prominent in the antifungal resistance and hence, it is advisable to determine the complex stabilities in future work. Additionally, in the development of TSCs as therapeutic drugs the antifungal activity needs to be considered relative to other biological activities of the host, such as cell proliferation. For example, the copper, palladium and platinum complexes derived from HL^{80} were evaluated for biological activity against both *C. albicans* fungal strain and human leukemia (HL-60) cells. The compounds are much more active against the leukemia cell line (IC_{50} ˆ 1.6 ± 3 to ≥10 μM) than against *C. albicans* (MIC values ˆ 0.237 to >12.33 mM) [45]. Overall, there is an urgent need to further explore and develop this class of compounds through more detailed and systematic studies of their antifungal activities and MOAs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

K.B. is indebted to the Dorothy Gibson Fellowship awarded by the Department of Chemistry for its support. This research was supported in part by the National Science Foundation CHE-1955268 (CAG) and CHE-1800245 (RMB).

Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jinorgbio.2021.111620.

References

[1] H.E. O'Brien, J.L. Parrent, J.A. Jackson, J.M. Moncalvo, R. Vilgalys, Fungal community analysis by large-scale sequencing of environmental samples, Appl. Environ. Microbiol. 71 (2005) 5544–5550, https://doi.org/10.1128/aem.71.9.5544-5550.2005.
[2] D.L. Hawksworth, R. Lücking, Fungal diversity revisited: 2.2 to 3.8 million species, Microbiol. Spectrum 5 (2017), https://doi.org/10.1128/microbiolspec.FUNK-0052-2016.
[3] M. Cheek, E. Nic Lughadha, P. Kirk, H. Lindon, J. Carretero, B. Looney, B. Douglas, D. Haelewaters, E. Gaya, T. Llewellyn, A.M. Ainsworth, Y. Gafforov, K. Hyde, P. Crous, M. Hughes, B.E. Walker, R. Campostrini Forzza, K.M. Wong, T. Niskanen, New scientific discoveries: plants and fungi, Plants People Planet 2 (2020) 371–388, https://doi.org/10.1002/ppp3.10148.
[4] Nature, Stop neglecting fungi, Nat. Microbiol. 2 (2017), 17120, https://doi.org/10.1038/nmicrobiol.2017.120.
[5] V.H. Tournas, Spoilage of vegetable crops by Bacteria and Fungi and related health hazards, Crit. Rev. Microbiol. 31 (2005) 33–44, https://doi.org/10.1080/10408410590886024.
[6] G.L. Schumann, K.J. Leonard, Stem rust of wheat (black rust), Plant Health Instr. (2000), https://doi.org/10.1094/phi-i-2000-0721-01.
[7] J.T. Yorinori, W.M. Paiva, R.D. Frederick, L.M. Costamilan, P.F. Bertagnolli, G. E. Hartman, C.V. Godoy, J. Nunes Jr., Epidemics of soybean rust (Phakopsora pachyrhizi) in Brazil and Paraguay from 2001 to 2003, Plant Dis. 89 (2005) 675–677, https://doi.org/10.1094/PD-89-0675.
[8] A.C. Saville, M.D. Martin, J.B. Ristaino, Historic Late Blight Outbreaks Caused by a Widespread Dominant Lineage of *Phytophthora infestans* (Mont.) de Bary, PLoS One 11 (2016), e0168381, https://doi.org/10.1371/journal.pone.0168381.
[9] M.C. Fisher, D.A. Henk, C.J. Briggs, J.S. Brownstein, L.C. Madoff, S.L. McCraw, S. J. Gurr, Emerging fungal threats to animal, plant and ecosystem health, Nature 484 (2012) 186–194, https://doi.org/10.1038/nature10947.
[10] P. Daszak, A.A. Cunningham, A.D. Hyatt, Emerging infectious diseases of wildlife–threats to biodiversity and human health, Science 287 (2000) 443–449, https://doi.org/10.1126/science.287.5452.443.
[11] K.F. Smith, D.F. Sax, K.D. Lafferty, Evidence for the role of infectious disease in species extinction and endangerment, Conserv. Biol. 20 (2006) 1349–1357, https://doi.org/10.1111/j.1523-1739.2006.00524.x.
[12] A. Gargas, M.T. Trest, M. Christensen, T.J. Volk, D. Blehert, Geomyces destructans sp. nov. associated with bat white-nose syndrome, Mycotaxon 108 (2009) 147–154.
[13] J.M. Lorch, C.U. Meteyer, M.J. Behr, J.G. Boyles, P.M. Cryan, A.C. Hicks, A. E. Ballmann, J.T. Coleman, D.N. Redell, D.M. Reeder, D.S. Blehert, Experimental infection of bats with Geomyces destructans causes white-nose syndrome, Nature 480 (2011) 376–378, https://doi.org/10.1038/nature10590.
[14] A. Casadevall, Fungal virulence, vertebrate endothermy, and dinosaur extinction: is there a connection? Fungal Genet. Biol. 42 (2005) 98–106, https://doi.org/10.1016/j.fgb.2004.11.008.
[15] A. Casadevall, Fungi and the rise of mammals, PLoS Pathog. 8 (2012), e1002808, https://doi.org/10.1371/journal.ppat.1002808.
[16] J.R. Köhler, A. Casadevall, J. Perfect, The spectrum of fungi that infects humans, Cold Spring Harbor Perspect. Med. 5 (2014) a019273, https://doi.org/10.1101/cshperspect.a019273.
[17] A. Arastehfar, T. Gabaldón, R. Garcia-Rubio, J.D. Jenks, M. Hoenigl, H.J.F. Salzer, M. Ilkit, C. Lass-Flörl, D.S. Perlin, Drug-resistant fungi: an emerging challenge threatening our limited antifungal Armamentarium, Antibiotics 9 (2020), https://doi.org/10.3390/antibiotics9120877.
[18] Leading International Fungal Education, The Burden of Fungal Disease: New Evidence to Show the Scale of the Problem Across the Globe. http://www.life-worldwide.org/media-centre/article/the-burden-of-fungal-disease-new-evidence-to-show-the-scale-of-the-problem, 2017 (February 28, 2017).
[19] A.H. Fairlamb, N.A. Gow, K.R. Matthews, A.P. Waters, Drug resistance in eukaryotic microorganisms, Nat. Microbiol. 1 (2016) 16092, https://doi.org/10.1038/nmicrobiol.2016.92.
[20] D.Z.P. Friedman, I.S. Schwartz, Emerging Fungal Infections: New Patients, New Patterns, and New Pathogens, J. Fungi 5 (2019), https://doi.org/10.3390/jof5030067.
[21] J. Berman, D.J. Krysan, Drug resistance and tolerance in fungi, Nat. Rev. Microbiol. 18 (2020) 319–331, https://doi.org/10.1038/s41579-019-0322-2.
[22] A. Chowdhary, A. Voss, J.F. Meis, Multidrug-resistant Candida auris: 'new kid on the block' in hospital-associated infections? J. Hosp. Infect. 94 (2016) 209–212, https://doi.org/10.1016/j.jhin.2016.08.004.
[23] J.V. Paassen, A. Russcher, A.W.M. Wingerden, P. Verweij, E.J. Kuijper, Emerging aspergillosis by azole-resistant Aspergillus fumigatus at an intensive care unit in the Netherlands, 2010 to 2013, Eurosurveillance 21 (30) (2016), https://doi.org/10.2807/1560-7917.ES.2016.21.30.30300.
[24] M.L. Rodrigues, J. Nosanchuk, Fungal diseases as neglected pathogens: A wake-up call to public health officials, PLoS Neglected Trop. Dis. 14 (2020), https://doi.org/10.1371/journal.pntd.0007964.
[25] M. Nucci, K.A. Marr, Emerging fungal diseases, Clin. Infect. Dis. 41 (2005) 521–526, https://doi.org/10.1086/432060.
[26] Centers for Disease Control and Prevention, Biggest Threats and Data. https://www.cdc.gov/drugresistance/Biggest-Threats.html, 2019.
[27] R. Garcia-Rubio, M. Cuenca-Estrella, E. Mellado, Triazole resistance in Aspergillus species: an emerging problem, Drugs. 77 (2017) 599–613, https://doi.org/10.1007/s40265-017-0714-4.
[28] D.S. Perlin, Current perspectives on echinocandin class drugs, Future Microbiol. 6 (2011) 441–457, https://doi.org/10.2217/fmb.11.19.
[29] K.S. Barker, P.D. Rogers, Recent insights into the mechanisms of antifungal resistance, Curr. Infect. Dis. Rep. 8 (2006) 449–456, https://doi.org/10.1007/s11908-006-0019-3.
[30] F.C. Odds, A.J. Brown, N.A. Gow, Antifungal agents: mechanisms of action, Trends Microbiol. 11 (2003) 272–279, https://doi.org/10.1016/s0966-842x(03)00117-3.
[31] G. Wall, J.L. Lopez-Ribot, Current antimycotics, new prospects, and future approaches to antifungal therapy, Antibiotics (Basel) 9 (2020) 445, https://doi.org/10.3390/antibiotics9080445.
[32] M.A. Ghannoum, L.B. Rice, Antifungal agents: mode of action, mechanisms of resistance, and correlation of these mechanisms with bacterial resistance, Clin. Microbiol. Rev. 12 (1999) 501–517, https://doi.org/10.1128/CMR.12.4.501.
[33] M.V. Castelli, E. Butassi, M.C. Monteiro, L.A. Svetaz, F. Vicente, S.A. Zacchino, Novel antifungal agents: a patent review (2011 – present), Expert Opin. Ther. Pat. 24 (2014) 323–338, https://doi.org/10.1517/13543776.2014.876993.
[34] C. Kauffman, J. Sobel, P. Pappas, W. Dismukes, Essentials of Clinical Mycology, 2011.
[35] J.-Y. Kim, Human fungal pathogens: why should we learn? J. Microbiol. 54 (2016) 145–148, https://doi.org/10.1007/s12275-016-0647-8.
[36] Centers for Disease Control and Prevention, Drug-Resist and *Candida auris*. https://www.cdc.gov/drugresistance/pdf/threats-report/candida-auris-508.pdf, 2019.
[37] J.B. Anderson, Evolution of antifungal-drug resistance: mechanisms and pathogen fitness, Nat. Rev. Microbiol. 3 (2005) 547–556, https://doi.org/10.1038/nrmicro1179.
[38] L.A. Walker, N.A.R. Gow, C.A. Munro, Fungal echinocandin resistance, Fungal Genet. Biol. 47 (2010) 117–126, https://doi.org/10.1016/j.fgb.2009.09.003.

[39] L. Marquez, C.L. Quave, Prevalence and therapeutic challenges of fungal drug resistance: role for plants in drug discovery, Antibiotics 9 (2020), https://doi.org/10.3390/antibiotics9040150.

[40] C. Bonaccorso, T. Marzo, D.L. Mendola, Biological applications of thiocarbohydrazones and their metal complexes: a perspective review, Pharmaceuticals 13 (2019), https://doi.org/10.3390/ph13010004.

[41] K.S.A. Melha, In-vitro antibacterial, antifungal activity of some transition metal complexes of thiosemicarbazone Schiff base (HL) derived from N^4-(7′-chloroquinolin-4′-ylamino) thiosemicarbazide, J. Enzyme Inhib. Med. Chem. 23 (2008) 493–503, https://doi.org/10.1080/14756360701631850.

[42] K. Turecka, A. Chylewska, A. Kawiak, K.F. Waleron, Antifungal activity and mechanism of action of the co(iii) coordination complexes with diamine chelate ligands against reference and clinical strains of Candida spp, Front. Microbiol. 9 (2018), https://doi.org/10.3389/fmicb.2018.01594.

[43] F. Gomes da Silva Dantas, A. Araújo de Almeida-Apolonio, R. Pires de Araújo, L. Regiane Vizolli Favarin, P. Fukuda de Castilho, F. De Oliveira Galvão, T. Inez Estivalet Svidzinski, G. Antônio Casagrande, K. Mari Pires de Oliveira, A promising copper(II) complex as antifungal and antibiofilm drug against yeast infection, Molecules 23 (2018), https://doi.org/10.3390/molecules23081856.

[44] P.P. Netalkar, S.P. Netalkar, V.K. Revankar, Transition metal complexes of thiosemicarbazone: synthesis, structures and invitro antimicrobial studies, Polyhedron. 100 (2015) 215–222, https://doi.org/10.1016/j.poly.2015.07.075.

[45] E. Pahontu, C.C. Paraschivescu, D. Ilig, D. Poirier, C. Oprean, V. Paunescu, A. Gulea, Tudor Roșu, O. Bratu, Synthesis and characterization of novel Cu(II), Pd (II) and Pt(II) complexes with 8-ethyl-2-hydroxytricyclo(7.3.1.02,7)tridecan-13-one-thiosemicarbazone: antimicrobial and in vitro antiproliferative activity, Molecules 21 (2016), https://doi.org/10.3390/molecules21050674.

[46] M. Montazerozohori, S. Zahedi, M. Nasr-Esfahani, A. Naghiha, Some new cadmium complexes: antibacterial/antifungal activity and thermal behavior, J. Ind. Eng. Chem. 20 (2014) 2463–2470, https://doi.org/10.1016/j.jiec.2013.10.027.

[47] A.E. Liberta, D.X. West, Antifungal and antitumor activity of heterocyclic thiosemicarbazones and their metal complexes: current status, Biometals 5 (1992) 121–126, https://doi.org/10.1007/BF01062223.

[48] A. Challapalli, L. Carroll, E.O. Aboagye, Molecular mechanisms of hypoxia in cancer, Clin. Transl. Imaging 5 (2017) 225–253, https://doi.org/10.1007/s40336-017-0231-1.

[49] P.S. Donnelly, A. Caragounis, T. Du, K.M. Laughton, I. Volitakis, R.A. Cherny, R. A. Sharples, A.F. Hill, Q.X. Li, C.L. Masters, K.J. Barnham, A.R. White, Selective intracellular release of copper and zinc ions from bis(thiosemicarbazonato) complexes reduces levels of Alzheimer disease amyloid-beta peptide, J. Biol. Chem. 283 (2008) 4568–4577, https://doi.org/10.1074/jbc.M705957200.

[50] N.G. Heatley, A method for the assay of penicillin, Biochem. J. 38 (1944) 61–65, https://doi.org/10.1042/bj0380061.

[51] M. Wikler, Clinical, Performance Standards for Antimicrobial Disk Susceptibility Tests: Approved Standard, Clinical and Laboratory Standard Institute, 2006.

[52] S. Arikan, V. Paetznick, J.H. Rex, Comparative evaluation of disk diffusion with microdilution assay in susceptibility testing of caspofungin against Aspergillus and Fusarium isolates, Antimicrob. Agents Chemother. 46 (2002) 3084–3087, https://doi.org/10.1128/aac.46.9.3084-3087.2002.

[53] J. Rex, Clinical, Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts: Approved Standard, Clinical and Laboratory Standard Institute, 2008.

[54] P. Gupta, V. Khare, D. Kumar, A. Ahmad, G. Banerjee, M. Singh, Comparative evaluation of disc diffusion and E-test with broth Micro-dilution in susceptibility testing of Amphotericin B, Voriconazole and Caspofungin against clinical Aspergillus isolates, J. Clin. Diagn. Res. 9 (2015) DC04–07, https://doi.org/10.7860/JCDR/2015/10467.5395.

[55] A. Imhof, S.A. Balajee, K.A. Marr, New methods to assess susceptibilities of Aspergillus isolates to caspofungin, J. Clin. Microbiol. 41 (2003) 5683–5688, https://doi.org/10.1128/jcm.41.12.5683-5688.2003.

[56] A. Espinel-Ingroff, V. Chaturvedi, A. Fothergill, M.G. Rinaldi, Optimal testing conditions for determining MICs and minimum fungicidal concentrations of new and established antifungal agents for uncommon molds: NCCLS collaborative study, J. Clin. Microbiol. 40 (2002) 3776–3781, https://doi.org/10.1128/jcm.40.10.3776-3781.2002.

[57] S. Arikan, Current status of antifungal susceptibility testing methods, Med. Mycol. 45 (2007) 569–587, https://doi.org/10.1080/13693780701436794.

[58] Y. Liu, G. Tortora, M.E. Ryan, H.M. Lee, L.M. Golub, Potato dextrose agar antifungal susceptibility testing for yeasts and molds: evaluation of phosphate effect on antifungal activity of CMT-3, Antimicrob. Agents Chemother. 46 (2002) 1455–1461, https://doi.org/10.1128/aac.46.5.1455-1461.2002.

[59] M. Balouiri, M. Sadiki, S. Ibnsouda, Methods for in vitro evaluating antimicrobial activity: a review, J. Pharm. Anal. 6 (2016) 71–79, https://doi.org/10.1016/j.jpha.2015.11.005.

[60] D. West, C.S. Carlson, A. Liberta, J. Scovill, The chemical and antifungal properties of the copper(II) complexes of 2-acetylpyrazine4N-methyl-,4N-dimethyl-, and 3-hexamethyleneiminylthiosemicarbazone, Transit. Met. Chem. 15 (1990) 383–387, https://doi.org/10.1007/BF01177467.

[61] D.X. West, D.L. Huffman, J.S. Saleda, A.E. Liberta, Chemical and antifungal properties of the copper(II) complexes of 2-formylpyridine4N-methyl-,4N-dimethyl,4N-diethyl and4N-dipropylthiosemicarbazones, Transit. Met. Chem. 16 (1991) 565–570, https://doi.org/10.1007/BF01024187.

[62] D.X. West, A.C. Whyte, F.D. Sharif, H. Gebremedhin, A.E. Liberta, Nickel(II) and copper(II) complexes of 2-acetylpyridine 4 N-(2-methylpyridinyl)-, 4 N-(2-ethylpyridinyl)- and 4 N-methyl(2-ethylpyridinyl) thiosemicarbazones, Transit. Met. Chem. 18 (1993) 238–242, https://doi.org/10.1007/bf00139963.

[63] D. Kovala-Demertzi, A. Domopoulou, M.A. Demertzis, A. Papageorgiou, D. X. West, Palladium(II) complexes of 2-acetylpyridine N(4)-propyl, N(4)-dipropyl- and 3-hexamethyleneiminylthiosemicarbazones with potentially interesting biological activity. Synthesis, spectral properties, antifungal and in vitro antitumor activity, Polyhedron 16 (1997) 3625–3633, https://doi.org/10.1016/S0277-5387(97)00107-1.

[65] M.A. Cater, H.B. Pearson, K. Wolyniec, P. Klaver, M. Bilandzic, B.M. Paterson, A. I. Bush, P.O. Humbert, S. La Fontaine, P.S. Donnelly, Y. Haupt, Increasing intracellular bioavailable copper selectively targets prostate cancer cells, ACS Chem. Biol. (2013) 1621–1631, https://doi.org/10.1021/cb400198p.

[66] D. Palanimuthu, S.V. Shinde, K. Somasundaram, A.G. Samuelson, In vitro and in vivo anticancer activity of copper bis(thiosemicarbazone) complexes, J. Med. Chem. (2013) 722–734, https://doi.org/10.1021/jm300938r.

[67] R. Anjum, D. Palanimuthu, D.S. Kalinowski, W. Lewis, K.C. Park, Z. Kovacevic, I. U. Khan, D.R. Richardson, Synthesis, characterization, and in vitro anticancer activity of copper and zinc bis(thiosemicarbazone) complexes, Inorg. Chem. 58 (2019) 13709–13723, https://doi.org/10.1021/acs.inorgchem.9b01281.

[68] P. Heffeter, V.F.S. Pape, E.A. Enyedy, B.K. Keppler, G. Szakacs, C.R. Kowol, Anticancer thiosemicarbazones: chemical properties, interaction with Iron metabolism, and resistance development, Antioxid. Redox Signal. 30 (2019) 1062–1082, https://doi.org/10.1089/ars.2017.7487.

[69] K.M. Acevedo, D.J. Hayne, L.E. McInnes, A. Noor, C. Duncan, D. Moujalled, I. Volitakis, A. Rigopoulos, K.J. Barnham, V.L. Villemagne, A.R. White, P. S. Donnelly, Effect of structural modifications to Glyoxal-bis (thiosemicarbazonato)copper(II) complexes on cellular copper uptake, copper-mediated ATP7A trafficking, and P-glycoprotein mediated efflux, J. Med. Chem. 61 (2018) 711–723, https://doi.org/10.1021/acs.jmedchem.7b01158.

[70] Z. Xiao, P.S. Donnelly, M. Zimmermann, A.G. Wedd, Transfer of copper between bis(thiosemicarbazone) ligands and intracellular copper-binding proteins. insights into mechanisms of copper uptake and hypoxia selectivity, Inorg. Chem. 47 (2008) 4338–4347, https://doi.org/10.1021/ic702440e.

[71] C. Stefani, Z. Al-Eisawi, P.J. Jansson, D.S. Kalinowski, D.R. Richardson, Identification of differential anti-neoplastic activity of copper bis (thiosemicarbazones) that is mediated by intracellular reactive oxygen species generation and lysosomal membrane permeabilization, J. Inorg. Biochem. 152 (2015) 20–37, https://doi.org/10.1016/j.jinorgbio.2015.08.010.

[72] G. Pelosi, Thiosemicarbazone metal complexes: from structure to activity, Open Crystallogr. J. 3 (2010) 16–28, https://doi.org/10.2174/1874846501003010016.

[73] A.S. Dhillon, S. Hagan, O. Rath, W. Kolch, MAP kinase signalling pathways in cancer, Oncogene 26 (2007) 3279–3290, https://doi.org/10.1038/sj.onc.1210421.

[74] D. Martinez-Soto, J. Ruiz-Herrera, Functional analysis of the MAPK pathways in fungi, Rev. Iberoam. Micol. 34 (2017) 192–202, https://doi.org/10.1016/j.riam.2017.02.006.

[76] L.N. de Araújo Neto, M. do Carmo Alves de Lima, J.F. de Oliveira, E.R. de Souza, M.D.S. Buonafina, M.N. Vitor Anjos, F.A. Brayner, L.C. Alves, R.P. Neves, F.J. B. Mendonça-Junior, Synthesis, cytotoxicity and antifungal activity of 5-nitro-thiophene-thiosemicarbazones derivatives, Chem. Biol. Interact. 272 (2017) 172–181, https://doi.org/10.1016/j.cbi.2017.05.005.

[77] H. Pervez, M.S. Iqbal, M.Y. Tahir, F.U.H. Nasim, M.I. Choudhary, K.M. Khan, In vitro cytotoxic, antibacterial, antifungal and urease inhibitory activities of some N4-substituted isatin-3-thiosemicarbazones, J. Enzyme Inhib. Med. Chem. 23 (2008) 848–854, https://doi.org/10.1080/14756360701746179.

[78] M. Aljahdali, A.A. El-Sherif, Synthesis, characterization, molecular modeling and biological activity of mixed ligand complexes of cu(II), Ni(II) and co(II) based on 1,10-phenanthroline and novel thiosemicarbazone, Inorg. Chim. Acta 407 (2013) 58–68, https://doi.org/10.1016/j.ica.2013.06.040.

[79] M.S. Aljahdali, Nickel(II) complexes of novel thiosemicarbazone compounds: synthesis, characterization, molecular modeling and in vitro antimicrobial activity, Eur. J. Chem. 4 (2013) 434–443, https://doi.org/10.5155/eurjchem.4.4.434-443.838.

[80] G.L. Parrilha, J.G. da Silva, L.F. Gouveia, A.K. Gasparoto, R.P. Dias, W.R. Rocha, D.A. Santos, N.L. Speziali, H. Beraldo, Pyridine-derived thiosemicarbazones and their tin(IV) complexes with antifungal activity against Candida spp, Eur. J. Med. Chem. 46 (2011) 1473–1482, https://doi.org/10.1016/j.ejmech.2011.01.041.

[81] V. Opletalova, D.S. Kalinowski, M. Vejsova, J. Kunes, M. Pour, J. Jampilek, V. Buchta, D.R. Richardson, Identification and characterization of thiosemicarbazones with antifungal and antitumor effects: cellular iron chelation mediating cytotoxic activity, Chem. Res. Toxicol. 21 (2008) 1878–1889, https://doi.org/10.1021/tx800182k.

[82] V. Opletalova, J. Dolezel, J. Kunes, V. Buchta, M. Vejsova, M. Kucerova-Chlupacova, Synthesis and antifungal screening of 2-{[1-(5-alkyl/arylalkylpyrazin-2-yl)ethylidene]hydrazono}-1,3-thiazolidin-4-ones, Molecules 21 (2016), https://doi.org/10.3390/molecules21111592.

[83] M. Serda, A. Mrozek-Wilczkiewicz, J. Jampilek, M. Pesko, K. Kralova, M. Vejsova, R. Musiol, A. Ratuszna, J. Polanski, Investigation of the biological properties of (hetero)aromatic thiosemicarbazones, Molecules 17 (2012) 13483–13502, https://doi.org/10.3390/molecules171113483.

[84] R.D. Paiva, L.F. Kneipp, C.M. Goular, M.A. Albuquerque, A. Echevarria, Antifungal activities of thiosemicarbazones and semicarbazones against mycotoxigenic fungi, Cienc. Agrotecnol. 38 (2014) 531–537, https://doi.org/10.1590/S1413-70542014000600001.

[86] L.N.D. Neto, M.D.A. de Lima, J.F. de Oliveira, E.R. de Souza, S.E.F. Machado, G. M.D. Lima, M.D.S. Buonafina, F.A. Brayner, L.C. Alves, J.M. Sandes, M.V. da Silva, M.C.A.B. de Castro, R.P. Neves, F.J.B. Mendonca, Thiophene-thiosemicarbazone derivative (L10) exerts antifungal activity mediated by oxidative stress and apoptosis in *C. albicans*, Chem. Biol. Interact. 320 (2020), 109028, https://doi.org/10.1016/j.cbi.2020.109028.

[87] M.A. Souza, S. Johann, L.A. Lima, F.F. Campos, I.C. Mendes, H. Beraldo, E. M. Souza-Fagundes, P.S. Cisalpino, C.A. Rosa, T.M. Alves, N.P. de Sa, C.L. Zani, The antimicrobial activity of lapachol and its thiosemicarbazone and semicarbazone derivatives, Mem. Inst. Oswaldo Cruz 108 (2013), https://doi.org/10.1590/S0074-02762013000300013.

[88] U. Kulandaivelu, V.G. Padmini, K. Suneetha, B. Shireesha, J.V. Vidyasagar, T. R. Rao, K.N. Jayaveera, A. Basu, V. Jayaprakash, Synthesis, antimicrobial and anticancer activity of new thiosemicarbazone derivatives, Arch. Pharm. 344 (2011) 84–90, https://doi.org/10.1002/ardp.201000201.

[89] N.D. Thanh, H.T. Duc, V.T. Duyen, P.M. Tuong, N.V. Quoc, Synthesis and antibacterial and antifungal activities of N-(tetra-O-acetyl-β-d-glucopyranosyl) thiosemicarbazones of substituted 4-formylsydnones, Chem. Cent. J. 9 (2015), https://doi.org/10.1186/s13065-015-0138-8.

[90] B.G. Benns, B.A. Gingras, C. Bayley, Antifungal activity of some thiosemicarbazones and their copper complexes, Appl. Microbiol. 8 (1960) 353–356, https://doi.org/10.1128/am.8.6.353-356.1960.

[91] B.A. Gingras, G. Colin, C.H. Bayley, Antifungal activity of thiosemicarbazones, J. Pharm. Sci. 54 (1965) 1674–1675, https://doi.org/10.1002/jps.2600541127.

[92] S. Chandra, S. Raizada, M. Tyagi, P.K. Sharma, Spectroscopic and biological approach of Ni(II) and Cu(II) complexes of 2-pyridinecarboxaldehyde thiosemicarbazone, Spectrochim. Acta Pt A 69 (2008) 816–821, https://doi.org/10.1016/j.saa.2007.05.033.

[93] A. Kumbhar, S. Padhye, D. West, A. Liberta, Electrochemical studies of transition metal complexes of 2-acetyl-pyridine thiosemicarbazones. Part 2. Correlations with spectral and antifungal properties of copper(II) complexes of 2-acetylpyridine 3-azacyclothiosemicarbazones, Transit. Met. Chem. 17 (1992) 247–249, https://doi.org/10.1007/BF02910848.

[94] D.X. West, C.S. Carlson, K.J. Bouck, A.E. Liberta, Transition metal ion complexes of tiosemicarbazones derived from 2-acetylpyridine. Part 10. A comparison of the chemical and antifungal properties of the copper(II) complexes of 2-acetylpyridine 3-pyrrolidinyl-, 3-piperidinyl-, 3-hexamethyleneiminyl- and 3-azabicyclo [3,2,2]-nonylthiosemicarbazones, Transit. Met. Chem. 16 (1991) 271–275, https://doi.org/10.1007/bf01032851.

[95] A.S. Kumbhar, S.B. Padhye, D.X. West, A.E. Liberta, Electrochemical studies of copper(II) 2-acetylpyridine4N-dialkylthiosemicarbazones. Relation to their spectral, magnetic, and biological properties, Transit. Met. Chem. 16 (1991) 276–279, https://doi.org/10.1007/BF01032852.

[96] D. West, C.S. Carlson, C.P. Galloway, A. Liberta, C. Daniel, Transition metal ion complexes of thiosemicarbazones derived from 2-acetylpyridine. Part 6. The chemical and antifungal properties of 2-acetylpyridine4N-diethyl- and4N-dipropylthiosemicarbazones and their copper(II) complexes, Transit. Met. Chem. 15 (1990) 91–95, https://doi.org/10.1007/BF01023893.

[97] A.S. Kumbhar, S.B. Padhye, A.P. Saraf, H.B. Mahajan, B.A. Chopade, D.X. West, Novel broad-spectrum metal-based antifungal agents. Correlations amongst the structural and biological properties of copper (II) 2-acetylpyridine N4-dialkylthiosemicarbazones, Biol. Met. 4 (1991) 141–143, https://doi.org/10.1007/BF01141304.

[98] D. West, C.S. Carlson, A.C. Whyte, A. Liberta, Transition metal ion complexes of thiosemicarbazones derived from 2-acetylpyridine. Part 7. Chemical and antifungal properties of 2-acetylpyridine4N-ethylthiosemicarbazone and its metal complexes, Transit. Met. Chem. 15 (1990) 43–47, https://doi.org/10.1007/BF01032230.

[99] D.X. West, C.E. Ooms, J.S. Saleda, H. Gebremedhin, A.E. Liberta, Copper(II) and nickel(II) complexes of 2-formylpyridine 3-piperidinyl-, 3-hexamethyleneiminyl- and 3-azabicyclo[3.2.2]nonylthiosemicarbazones, Transit. Met. Chem. 19 (1994) 553–558, https://doi.org/10.1007/bf00136373.

[100] A.S.M. Ibrahim, M.K. Farh, S.A. El-Gyar, M.A. El-Gahami, D.M. Fouad, F. Silva, I. C. Santos, A. Paulo, Synthesis, structural studies and antimicrobial activities of manganese, nickel and copper complexes of two new tridentate 2-formylpyridine thiosemicarbazone ligands, Inorg. Chem. Commun. 96 (2018) 194–201, https://doi.org/10.1016/j.inoche.2018.08.023.

[101] A.B.M. Ibrahim, M.K. Farh, P. Mayer, Copper complexes of new thiosemicarbazone ligands: synthesis, structural studies and antimicrobial activity, Inorg. Chem. Commun. 94 (2018) 127–132, https://doi.org/10.1016/j.inoche.2018.06.019.

[102] I.C. Mendes, J.P. Moreira, A.S. Mangrich, S.P. Balena, B.L. Rodrigues, H. Beraldo, Coordination to copper(II) strongly enhances the in vitro antimicrobial activity of pyridine-derived N(4)-tolyl thiosemicarbazones, Polyhedron. 26 (2007) 3263–3270, https://doi.org/10.1016/j.poly.2007.03.002.

[103] I.C. Mendes, J.P. Moreira, N.L. Speziali, A.S. Mangrich, J.A. Takahashi, H. Beraldo, N(4)-tolyl-2-benzoylpyridine thiosemicarbazones and their copper(II) complexes with significant antifungal activity. Crystal structure of N(4)-para-tolyl-2-benzoylpyridine thiosemicarbazone, J. Braz. Chem. Soc. 17 (2006) 1571–1577, https://doi.org/10.1590/S0103-50532006000800013.

[104] E. Bermejo, R. Carballo, A. Castiñeiras, R. Domínguez, A. Liberta, C. Maichle-Mössmer, M.M. Salberg, D. West, Synthesis, structural characteristics and biological activities of complexes of ZnII, CdII, HgII, PdII, and PtII with 2-acetylpyridine 4-methylthiosemicarbazone, Eur. J. Inorg. Chem. (1999), https://doi.org/10.1002/(SICI)1099-0682(199906)1999:6<965::AID-EJIC965>3.0.CO;2-A.

[105] D. Kovala-Demertzi, A. Domopoulou, M.A. Demertzis, J. Valdés-Martínez, S. Hernández-Ortega, G. Espinosa-Pérez, D.X. West, M.M. Salberg, G.A. Bain, P. D. Bloom, Structures and spectral properties of palladium(II) complexes of 2-acetylpyridine N(4)-dimethylthiosemicarbazone, Polyhedron 15 (1996) 2587–2596, https://doi.org/10.1016/0277-5387(95)00538-2.

[106] D. Kovala-Demertzi, M. Demertzis, J. Miller, C. Papadopoulou, C. Dodorou, G. Filousis, Platinum(II) complexes with 2-acetyl pyridine thiosemicarbazone. Synthesis, crystal structure, spectral properties, antimicrobial and antitumour activity, J. Inorg. Biochem. 86 (2–3) (2001) 555–563.

[107] P.P. Netalkar, S.P. Netalkar, V.K. Revankar, Nickel(II) complexes of thiosemicarbazones: synthesis, characterization, X-ray crystallographic studies and in vitro antitubercular and antimicrobial studies, Transit. Met. Chem. 39 (2014) 519–526, https://doi.org/10.1007/s11243-014-9827-8.

[108] K. Alomar, A. Landreau, M. Kempf, M.A. Khan, M. Allain, G. Bouet, Synthesis, crystal structure, characterization of zinc(II), cadmium(II) complexes with 3-thiophene aldehyde thiosemicarbazone (3TTSCH). Biological activities of 3TTSCH and its complexes, J. Inorg. Biochem. 104 (2010) 397–404, https://doi.org/10.1016/j.jinorgbio.2009.11.012.

[109] S. Chandra, S. Parmar, Y. Kumar, Synthesis, spectroscopic, and antimicrobial studies on bivalent zinc and mercury complexes of 2-formylpyridine thiosemicarbazone, Bioinorg. Chem. Appl. 2009 (2009) 851316, https://doi.org/10.1155/2009/851316.

[110] H.K. Parwana, G. Singh, P. Talwar, Antifungal activity of metal complexes of thiosemicarbazones, Inorg. Chim. Acta 108 (1985) 87–89, https://doi.org/10.1016/S0020-1693(00)81618-7.

[111] E. Bermejo, R. Carballo, A. Castiñeiras, R. Domínguez, C. Maichle-Mössmer, J. Straehle, D. West, Synthesis, characterization and antifungal activity of group 12 metal complexes of 2-acetylpyridine-4N-ethylthiosemicarbazone (H4EL) and 2-acetylpyridine-N-oxide-4N-ethylthiosemicarbazone (H4ELO), Polyhedron 18 (1999) 3695–3702, https://doi.org/10.1016/S0277-5387(99)00309-5.

[112] E. Bermejo, A. Castiñeiras, R. Domínguez, R. Carballo, C. Maichle-Mössmer, J. Straehle, D. West, Preparation, structural characterization, and antifungal activities of complexes of group 12 metals with 2-Acetylpyridine- and 2-Acetylpyridine-N-oxide-4N-phenylthiosemicarbazones, Z. Anorg. Allg. Chem. 625 (1999) 961–968, https://doi.org/10.1002/(SICI)1521-3749(199906)625:6<961::AID-ZAAC961>3.0.CO;2-J.

[113] R.F.F. Costa, A.P. Rebolledo, T. Matencio, H.D.R. Calado, J.D. Ardisson, M. E. Cortes, B.L. Rodrigues, H. Beraldo, Metal complexes of 2-benzoylpyridine-derived thiosemicarbazones: structural, electrochemical and biological studies, J. Coord. Chem. 58 (2005) 1307–1319, https://doi.org/10.1080/00958970500213307.

[114] J.G.d. Silva, C.C.H. Perdigão, N. Speziali, H. Beraldo, Chalcone-derived thiosemicarbazones and their zinc(II) and gallium(III) complexes: spectral studies and antimicrobial activity, J. Coord. Chem. 66 (2013) 385–401, https://doi.org/10.1080/00958972.2012.757762.

[115] M.M. Aly, Y.A. Mohamed, K.A.M. El-Bayouki, W.M. Basyouni, S.Y. Abbas, Synthesis of some new 4(3H)-quinazolinone-2-carboxaldehyde thiosemicarbazones and their metal complexes and a study on their anticonvulsant, analgesic, cytotoxic and antimicrobial activities - Part-1, Eur. J. Med. Chem. 45 (2010) 3365–3373, https://doi.org/10.1016/j.ejmech.2010.04.020.

[116] R. Sharma, M. Nagar, M. Agarwal, H. Sharma, Synthesis, characterization and antimicrobial activities of some mixed ligand complexes of Co(II) with thiosemicarbazones and N-protected amino acids, J. Enzyme Inhib. Med. Chem. 24 (2009) 197–204 (Pii 903299110), 1080/14756360802051263.

[117] D. West, C.S. Carlson, A. Liberta, Transition metal ion complexes of thiosemicarbazones derived from 2-acetylpyridine. Part 9. The chemical and antifungal properties of the iron(III) and cobalt(II, III) complexes of 2-acetylpyridine4N-diethyl-and4N-diopropylthiosemicarbazones, Transit. Met. Chem. 16 (1991) 53–56, https://doi.org/10.1007/BF01127871.

[118] S.K. Sengupta, O.P. Pandey, B.K. Srivastava, V.K. Sharma, Synthesis, structural and biochemical aspects of titanocene and zirconocene chelates of acetylferrocenyl thiosemicarbazones, Transit. Met. Chem. 23 (1998) 349–353, https://doi.org/10.1023/A:1006986131435.

[119] T.D. Bastos, B.M. Soares, P.S. Cisalpino, I.C. Mendes, R.G. dos Santos, H. Beraldo, Coordination to gallium(III) strongly enhances the potency of 2-pyridineformamide thiosemicarbazones against Cryptococcus opportunistic fungi, Microbiol. Res. 165 (2010) 573–577, https://doi.org/10.1016/j.micres.2009.10.005.

[120] A.A. Oliveira, G.M.C. Perdigão, L.E. Rodrigues, J.G. da Silva, E.M. Souza-Fagundes, J.A. Takahashi, W.R. Rocha, H. Beraldo, Cytotoxic and antimicrobial effects of indium(iii) complexes with 2-acetylpyridine-derived thiosemicarbazones, Dalton Trans. 46 (2017) 918–932, https://doi.org/10.1039/C6DT03657K.

[122] I.C. Mendes, J.P. Moreira, J.D. Ardisson, R.G. Santos, P.R. da Silva, I. Garcia, A. Castineiras, H. Beraldo, Organotin(IV) complexes of 2-pyridineformamide-derived thiosemicarbazones: antimicrobial and cytotoxic effects, Eur. J. Med. Chem. 43 (2008) 1454–1461, https://doi.org/10.1016/j.ejmech.2007.09.016.

[123] N.C. Kasuga, K. Onodera, S. Nakano, K. Hayashi, K. Nomiya, Syntheses, crystal structures and antimicrobial activities of 6-coordinate antimony(III) complexes with tridentate 2-acetylpyridine thiosemicarbazone, bis(thiosemicarbazone) and semicarbazone ligands, J. Inorg. Biochem. 100 (2006) 1176–1186, https://doi.org/10.1016/j.jinorgbio.2006.01.037.

[124] K.N. Thimmaiah, G.T. Chandrappa, W.D. Lloyd, C. Parkanyi, Synthesis and chemical characterization of biologically important complexes of vanillin Thiosemicarbazone with manganese(ii), Iron(ii), cobalt(ii), nickel(ii), copper(ii),

zinc(ii), cadmium(ii), and mercury(ii), Transit. Met. Chem. 10 (1985) 299–302, https://doi.org/10.1007/Bf00619014.
[125] D.X. West, J.S. Ives, G.A. Bain, A.E. Liberta, J. Valdes Martinez, K.H. Ebert, S. Hernandez Ortega, Copper(II) and nickel(II) complexes of 2,3-butanedione bis (N(3)-substituted thiosemicarbazones), Polyhedron (1997) 1895–1905, https://doi.org/10.1016/S0277-5387(96)00468-8.
[126] M. Refat, S. Chandra, M. Tyagi, Transition metal complexes of dis (thiosemicarbazone): synthesis and spectral, and antifungal studies, Phosphorus Sulfur Silicon 185 (2009) 22–33, https://doi.org/10.1080/10426500802713234.
[127] K. Alomar, A. Landreau, M. Allain, G. Bouet, G. Larcher, Synthesis, structure and antifungal activity of thiophene-2,3-dicarboxaldehyde bis(thiosemicarbazone) and nickel(II), copper(II) and cadmium(II) complexes: unsymmetrical coordination mode of nickel complex, J. Inorg. Biochem. 126 (2013) 76–83, https://doi.org/10.1016/j.jinorgbio.2013.05.013.
[128] K. Alomar, V. Gaumet, M. Allain, G. Bouet, A. Landreau, Synthesis, crystal structure, characterisation, and antifungal activity of 3-thiophene aldehyde semicarbazone (3STCH), 2,3-thiophene dicarboxaldehyde bis(semicarbazone) (2,3BSTCH2) and their nickel (II) complexes, J. Inorg. Biochem. 115 (2012) 36–43, https://doi.org/10.1016/j.jinorgbio.2012.04.022.
[129] N.C. Kasuga, K. Sekino, M. Ishikawa, A. Honda, M. Yokoyama, S. Nakano, N. Shimada, C. Koumo, K. Nomiya, Synthesis, structural characterization and antimicrobial activities of 12 zinc(II) complexes with four thiosemicarbazone and two semicarbazone ligands, J. Inorg. Biochem. 96 (2003) 298–310, https://doi.org/10.1016/s0162-0134(03)00156-9.
[130] N.C. Kasuga, K. Sekino, C. Koumo, N. Shimada, M. Ishikawa, K. Nomiya, Synthesis, structural characterization and antimicrobial activities of 4- and 6-coordinate nickel(II) complexes with three thiosemicarbazones and semicarbazone ligands, J. Inorg. Biochem. 84 (2001) 55–65, https://doi.org/10.1016/s0162-0134(00)00221-x.
[131] M. Tyagi, S. Chandra, Synthesis, characterization and biocidal properties of platinum metal complexes derived from 2,6-diacetylpyridine (bis thiosemicarbazone), Open J. Inorg. Chem. 02 (2012) 41–48, https://doi.org/10.4236/ojic.2012.23007.
[132] J.P. Holland, F.I. Aigbirhio, H.M. Betts, P.D. Bonnitcha, P. Burke, M. Christlieb, G. C. Churchill, A.R. Cowley, J.R. Dilworth, P.S. Donnelly, J.C. Green, J.M. Peach, S. R. Vasudevan, J.E. Warren, Functionalized Bis(thiosemicarbazonato) complexes of zinc and copper: synthetic platforms toward site-specific radiopharmaceuticals, Inorg. Chem. (2007) 465–485, https://doi.org/10.1021/ic0615628.
[133] S.A. Andres, K. Bajaj, N.S. Vishnosky, M.A. Peterson, M.S. Mashuta, R. M. Buchanan, P.J. Bates, C.A. Grapperhaus, Synthesis, characterization, and biological activity of hybrid Thiosemicarbazone–Alkylthiocarbamate metal complexes, Inorg. Chem. 59 (2020) 4924–4935, https://doi.org/10.1021/acs.inorgchem.0c00182.
[134] J.H. Bormio Nunes, S. Hager, M. Mathuber, V. Posa, A. Roller, E.A. Enyedy, A. Stefanelli, W. Berger, B.K. Keppler, P. Heffeter, C.R. Kowol, Cancer cell resistance against the clinically investigated Thiosemicarbazone COTI-2 is based on formation of intracellular copper complex glutathione adducts and ABCC1-mediated efflux, J. Med. Chem. 63 (2020) 13719–13732, https://doi.org/10.1021/acs.jmedchem.0c01277.