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Antifungal and antitumor activity of heterocyclic thiosemicarbazones and their metal complexes: current status

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More than 75 substituted thiosemicarbazones and a number of metal complexes of each have been assayed for their antifungal activity. Their activity is significantly affected by the substituted groups attached at both ^{1}N and ^{4}N of the thiosemicarbazone moiety. Greatest activity occurs for 2-substituted pyridine thiosemicarbazones with differences observed for 2-formylpyridine, 2-acetylpyridine and 2-benzoylpyridine derivatives and their metal complexes. Further, there are activity differences for ^{4}N-alkyl-, ^{4}N-aryl-, ^{4}N-dialkyl- and 3-azacyclothiosemicarbazones and their metal complexes as well as changes in the substituent size among each of these subgroups. Cu(II) complexes are often more active than the uncomplexed thiosemicarbazones, with the latter showing similar activity to Ni(II) complexes in many instances. The reduction potential of the thiosemicarbazone ligand in a Cu(II) complex, the strength of the ligand field and various spectral properties can be correlated to the inhibitory activity.

Keywords: *Apergillus niger, Paecilomyces variotii*, antifungal, antitumor, thiosemicarbazones

Introduction

Transition metal ion complexes of thiosemicarbazones have been the subject of a recent review article (West *et al.* 1991c). These compounds possess a range of biological applications that include antitumor (Antholine *et al.* 1977), antifungal (Mittal *et al.* 1981), antiviral (Shipman *et al.* 1981), antibacterial (Dobek *et al.* 1980), antifilarial (Klayman *et al.* 1991) and antimalarial activities (Klayman *et al.* 1979).

Thiosemicarbazones exercise their biological activity in mamalian cells by inhibiting ribonucleotide reductase, a necessary enzyme in the synthesis of DNA precursors (Frence *et al.* 1970). The non-heme subunit of the enzyme has been shown to be inhibited/inactivated by these thiosemicarbazones (Cory & Fleischer 1979). This inhibitory action is thought to be due to coordination of iron via a heterocyclic thiosemicarbazone's N–N–S tridentate ligating system (Figure 1), either by a preformed iron complex binding to the enzyme or by the free ligand complexing with the iron-charged enzyme (Sartorelli *et al.* 1977). Studies of iron and copper complexes have shown that they can be more active in the inhibition of DNA synthesis than the uncomplexed parent thiosemicarbazone (Saryan *et al.* 1981). Evidence has also been presented that a thiosemicarbazone may cause lesions in DNA, suggesting a second site of action (Karon & Benedict 1972), Structural alterations that hinder a thiosemicarbazone's ability to function as a chelating agent with metal ions tend to destroy or reduce its medicinal activity (Scovill *et al.* 1984).

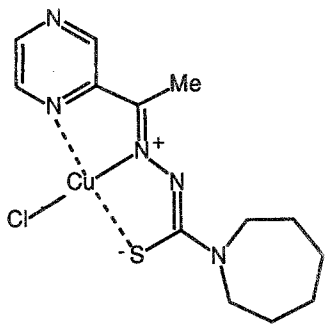

Figure 1. Tridentate N–N–S coordination of an anionic heterocyclic thiosemicarbazone ligand in a planar Cu(II) complex.

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A systematic study of formylthiosemicarbazones of 16 different heterocyclic ring systems by Blanz & French (1968) revealed that the thiosemicarbazone side chain must be adjacent to the heterocyclic nitrogen, and that a conjugated N–N–S tridentate ligand system is essential for anticancer activity. Recently, Wengel *et al.* (1990) reported that several assayed thiosemicarbazones had no effect on the synthesis of fungal chitin, one of the major fungal cell wall constituents.

Compound preparation and assessment of antifungal activity

Using the procedures previously described for synthesizing thiosemicarbazones and their metal complexes as well as measuring their antifungal activity (West *et al.* 1990), we have assessed the activity of a substantial number of compounds (West *et al.* 1990a–d, 1991a). The two fungal isolates most frequently used in our assay are *Aspergillus niger* and *Paecilomyces variotii*. *P. variotii* displays the greater degree of sensitivity to the compounds thus far tested. The reason for this differential response is not yet known, although it may simply be a matter of greater uptake of compounds by *P. variotti* or metabolic detoxification of compounds by *A. niger*. Using the 'poison food technique' of Grover & Moore (1962), we have determined that the compounds thus far tested are fungistatic rather than fungicidal, since hyphae or spores will resume growth or germination, respectively, upon removal from poisoned agar media.

Structural characteristics versus antifungal activity

Heterocyclic thiosemicarbazones having a hydrogen and either an alkyl or aryl group attached at ^4N are relatively inactive antifungal agents. Figure 2 shows representations of each type of thiosemicarbazone and Table 1 shows fungal growth inhibition results for the uncomplexed thiosemicarbazones as well as example Cu(II) and Ni(II) complexes against *A. niger*.

The information in Table 1 can be summarized as follows: (i) none of the compounds have activity at the lowest concentration, 200 $\mu g\,ml^{-1}$, (ii) the thiosemicarbazones are more active than their Cu(II) and Ni(II) complexes, which have minimal or no activity against *A. niger*, (iii) the thiosemicarbazones derived from 2-acetylpyridine are the only ones that have activity, and (iv) the increased size of the ^4N-alkyl substituent seems to lower the activity

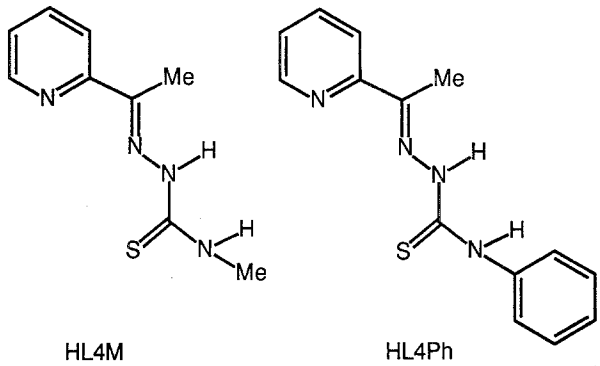


Figure 2. *E* isomers of 2-acetylpyridine ^4N-methyl- and ^4N-phenylthiosemicarbazones (HL4M and HL4Ph).

Table 1. Growth inhibition of *A. niger* by heterocyclic ^4N-alkyl- and ^4N-arylthiosemicarbazones, and examples of their Cu(II) and Ni(II) complexes

Compound	200[a]	400	600	1000	1600
H4M[b]	6.0	6.0	6.0	6.0	6.0
HL4M[c]	6.0	9.8	12.2	16.2	17.5
HBz4M[d]	6.0	6.0	6.0	6.0	6.0
HPz4M[e]	6.0	6.0	6.0	6.0	6.0
HL4E	6.0	6.0	7.5	11.5	15.0
HL4P	6.0	6.5	6.0	13.5	13.7
HL4tB	6.0	11.0	17.0	19.7	21.0
HL4Ph	6.0	6.0	6.0	6.0	6.0
HL4mT	6.0	6.0	7.8	10.5	11.5
$[Cu(H4M)Cl_2]$	6.0	6.0	6.0	6.0	6.0
$[Cu(HL4M)Cl_2]$	6.0	6.0	6.0	6.0	6.0
$[Cu(HLBz4M)Cl_2]$	6.0	6.0	6.0	6.0	6.0
$[Cu(HPz4M)Cl_2]$	6.0	6.0	6.0	6.0	6.0
$[Cu(HL4Ph)Cl_2]$	6.0	6.0	6.0	6.2	6.0
$[Ni(H4M)Cl_2]$	6.0	6.0	6.0	6.0	6.0
[Ni(Pz4M)Cl]	6.0	6.0	6.0	6.0	7.2

[a]Concentration in $\mu g\,ml^{-1}$; an inhibition zone of 6.0 mm in diameter is indicative of no inhibitory activity.
[b]Compounds having H followed by 4 are derived from 2-formylpyridine.
[c]Compounds having HL followed by 4 are derived from 2-acetylpridine.
[d]Compounds having HBz followed by 4 are derived from 2-benzoylpyridine.
[e]Compounds having HPz followed by 4 are derived from acetylpyrazine.

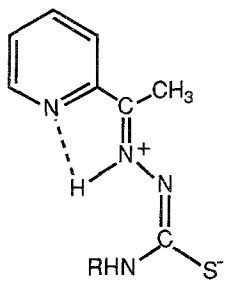
(e.g. HL4M > HL4E > HL4P), but the most active thiosemicarbazone is 2-acetylpyridine ^4N-*tert*-butylthiosemicarbazone.

This latter observation can be explained as follows: it has previously been shown that 2-acetylpyridine ^4N-methylthiosemicarbazone (HL4M) exists exclusively as the *E* isomer (Figure 2). No isomerism was noted on heating in the presence of silica gel

and we have recorded ^{1}H- and ^{13}C-NMR spectra of freshly prepared chloroform solutions that agree with this finding and confirm the absence of intramolecular hydrogen bonding. However, based on the assumption that the bulkiness of the substituents attached at ^{4}N may have an effect on the isomeric purity, or the antifungal activity, of heterocyclic ^{4}N-alkylthiosemicarbazones, we have synthesized members of the series having larger ^{4}N-alkyl groups. As with HL4M, ^{1}H-NMR spectral studies of 2-acetylpyridine ^{4}N-ethylthiosemicarbazone (HL4E) show it to be 100% *E* isomer, but thiosemicarbazones with larger alkyl groups show a second isomer which reaches a maximum of 35% of the sample based on integration of NMR signals. The spectral differences in the *E* and new isomer (Figure 3), which we termed *E″*, respectively, are as follows: acetyl(CH_3): $\delta = 2.400$ and 2.350 and the appearance of low field signal indicating hydrogen bonding of ^{2}NH for *E″*. HL4tB solutions contain about 35% E″.

Table 2 shows growth inhibition results against *P. variotii*. Although the activity against this fungus is greater by certain compounds, they are not generally as active as ^{4}N-dialkylthiosemicarbazones or 3-azacyclothiosemicarbazones (*vide infra*). Again, those thiosemicarbazones which possess the *E″* isomer (i.e. hydrogen bonding involving the ^{2}NH) possess greater activity than those thiosemicarbazones that do not (i.e. H4M, HL4M, HL4E). For *P. variotii* a number of the compounds also have activity at 200 $\mu g\,ml^{-1}$, indicating the greater susceptibility of this fungus to these compounds. Finally, their Ni(II) complexes show little growth inhibition; the Cu(II) complexes of the most active thiosemicarbazones, while showing activity, have less than the uncoordinated thiosemicarbazone.

Both the ^{4}N-dialkylthiosemicarbazones and the 3-azacyclothiosemicarbazones have as many as three isomers in chloroform solution (two involve hydrogen bonding; Figure 4) and at least two in dimethylsulfoxide solution. Their ^{1}H- and ^{13}C-NMR spectra have been discussed in more detail elsewhere, but it suffices to indicate that the pyridyl ring's ^{6}CH, the acetyl methyl, and the low field hydrogens of ^{1}H spectra as well as the ring carbons, and the acetyl methyl group in the ^{13}C spectra all confirm this observation. We seem to be able to directly correlate the extent of the *E′* isomer's presence with the thiosemicarbazone's activity against *A. niger*. The inhibitory activity of a group of these thiosemicarbazones and their Cu(II) and Ni(II) complexes against this fungus are shown in Table 3.



E'

Figure 3. *E″* isomer formed in solutions of ^{4}N-alkylthiosemicarbazones.

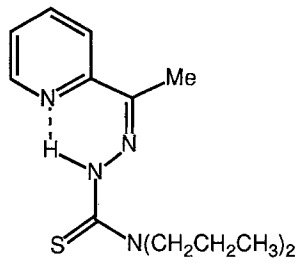
Table 2. Growth inhibition of *P. variotti* by heterocyclic ^{4}N-alkyl- and ^{4}N-arylthiosemicarbazones, and examples of their Cu(II) and Ni(II) complexes

Compound[a]	200	400	600	1000	1600
H4M	6.0	6.0	6.0	6.0	6.0
HL4M	6.0	8.3	10.0	14.4	17.7
HBz4M	6.0	6.0	6.0	6.0	6.0
HPz4M	6.0	6.0	6.0	10.0	10.3
HL4E	6.0	6.0	12.2	29.0	30.0
HL4P	24.8	25.8	26.7	27.5	28.0
HL4tB	14.3	20.3	25.3	30.2	30.5
HL4Ph	6.0	6.0	6.0	6.0	6.0
HL4mT	16.5	19.7	22.2	22.5	24.8
$[Cu(H4M)Cl_2]$	6.0	6.0	6.0	6.0	6.0
$[Cu(HL4M)Cl_2]$	6.0	6.0	6.0	6.0	6.0
$[Cu(HL4P)Cl_2]$	15.5	16.0	16.8	16.7	17.5
$[Cu(HLBz4M)Cl_2]$	7.0	10.5	11.0	16.3	17.3
$[Cu(HPz4M)Cl_2]$	6.0	6.0	6.0	6.0	6.0
$[Cu(HL4Ph)Cl_2]$	12.7	14.0	15.7	15.5	16.7
$[Ni(H4M)Cl_2]$	6.0	6.0	6.0	6.0	6.0
[Ni(Pz4M)Cl]	6.0	6.0	6.0	6.0	7.6

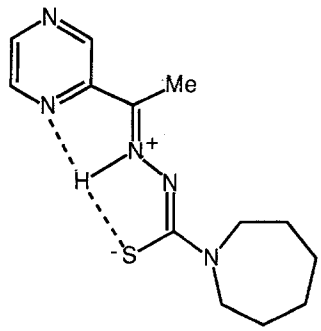
[a]See footnote to Table 1.

The 2-acetylpyridine thiosemicarbazones have proven to be most effective compared to thiosemicarbazones prepared from 2-formylpyridine, 2-benzoylpyridine and acetylpyrazine against *A. niger*. There appears to be a trend to greater activity of the thiosemicarbazone with increase of the bulkiness of the ^{4}N substituent. Further, the Cu(II) complexes are often more active than the uncomplexed thiosemicarbazones and some (e.g. [Cu(L4DP)Cl] and [Cu(Lhexim)Cl] are active at 10–20 $\mu g\,ml^{-1}$). Also, the Ni(II) complexes of these thiosemicarbazones show some activity. It should be noted that most of these complexes involve coordination in the anionic form (i.e. loss of ^{2}NH) of the thiosemicarbazone (Figure 1) rather than the neutral ligand.

With a few exceptions, these compounds are all



HL4DP, Z-isomer



HPzhexim, E'-isomer

Figure 4. *Z* and *E'* hydrogen bonding isomers of heterocyclic ^4N-dialkyl- and 3-azacyclothiosemicarbazones.

more active against *P. variotii* than they are against *A. niger* and most of them are active at much lower concentrations, particularly the metal complexes. In this instance the 2-formylpyridine ^4N-dimethylaminothiosemicarbazone, H4DM, has essentially the same activity as its 2-acetylpyridine analog, HL4DM, and both are considerably more active than either HBz4DM or HPz4DM. However, the 3-hexamethyleneiminylthiosemicarbazones of 2-formylpyridine, Hhexim, 2-acetylpyridine, HLhexim and acetylpyrazine, HPzhexim have essentially the same activity except at the lowest concentration where Hhexim in the most active. The Cu(II) complexes of 2-acetylpyrdine thiosemicarbazones are invariably more active and the Ni(II) complexes are as active against *P. variotii* as the uncomplexed ligands. However, the 2-formylpyridine thiosemicarbazones are often more active than their Cu(II) complexes. Of interest is that [Cu(L4DM)Cl] ≫ [Cu(4DM)Cl], but [Cu(4DP)Cl] ≫ [Cu(L4DP)Cl]. [Cu(4DP)Cl] has the most activity against *P. variotii* of any compound that we have tested to date.

Antifungal activity versus antitumor activity

Various metallic complexes that have shown active antifungal activity have now been screened for *in*

Table 3. Growth inhibition of *A. niger* by heterocyclic ^4N-dialkyl- and 3-azacyclothiosemicarbazones, and examples of their Cu(II) and Ni(II) complexes

Compound[a]	200	400	600	1000	1600
H4DM	6.0	9.2	15.0	20.3	25.2
HL4DM	11.7	13.7	16.3	19.8	21.5
HBz4DM	6.0	6.0	6.0	6.0	6.0
HPz4DM	6.0	12.5	15.5	19.5	26.2
HL4DE	7.3	7.5	9.7	14.4	15.2
HL4DP	14.0	16.4	17.8	18.4	20.1
HLpip	6.0	6.0	6.0	7.3	7.7
HLhexim	7.7	8.3	9.5	10.5	10.8
Hhexim	6.0	8.2	12.7	16.5	20.5
HPzhexim	6.0	6.0	8.7	11.0	15.7
[Cu(4DM)Cl]	6.0	6.0	8.2	11.2	14.0
[Cu(L4DM)Cl]	14.2	16.5	19.3	20.5	23.3
[Cu(Pz4DM)Cl]	6.0	6.0	6.0	10.7	13.2
[Cu(4DP)Cl]	7.8	8.2	8.2	8.2	11.0
[Cu(L4DP)Cl]	14.1	17.8	17.9	19.5	19.3
[Cu(Lhexim)Cl]	17.7	17.8	19.2	20.3	18.5
[Ni(L4DM)Cl]	6.0	6.0	6.0	8.0	8.0
[Ni(L4DP)Cl]	8.0	10.3	10.8	11.2	11.3
[Ni(Lhexim)Cl]	8.5	9.3	10.2	12.0	11.8

[a]See footnote to Table 1.

Table 4. Growth inhibition of *P. variotii* by heterocyclic ^4N-dialkyl- and 3-azacyclothiosemicarbazones, and examples of their Cu(II) and Ni(II) complexes

Compound[a]	200	400	600	1000	1600
H4DM	21.8	27.5	29.2	30.0	30.0
HL4DM	18.5	26.0	29.2	31.5	32.5
HBz4DM	6.0	6.0	6.0	6.0	6.0
HPz4DM	6.0	6.0	6.0	11.5	17.8
HL4DE	25.6	29.7	31.0	36.7	37.7
HL4DP	13.2	12.2	19.7	22.8	24.5
HLpip	6.0	6.0	6.0	9.8	16.8
HLhexim	7.8	12.2	16.5	17.3	19.2
Hhexim	13.5	18.3	21.5	24.3	25.0
HPzhexim	11.2	12.3	19.3	24.2	29.7
[Cu(4DM)Cl]	10.3	17.0	22.5	30.2	35.8
[Cu(L4DM)Cl]	27.7		30.8		32.7
[Cu(Pz4DM)Cl]	7.0	13.2	14.0	21.4	22.5
[Cu(4DP)Cl]	32.5	38.7	37.7	40.0	42.0
[Cu(L4DP)Cl]	21.0	19.7	25.5	27.5	26.7
[Cu(Lhexim)Cl]	25.8	28.3	28.5	29.5	29.7
[Ni(L4DM)Cl]	27.7	28.3	29.0	29.5	29.5
[Ni(L4DP)Cl]	12.7	12.5	12.7	12.8	13.7
[Ni(Lhexim)Cl]	10.7	14.3	17.2	19.0	18.0

[a]See footnote to Table 1.

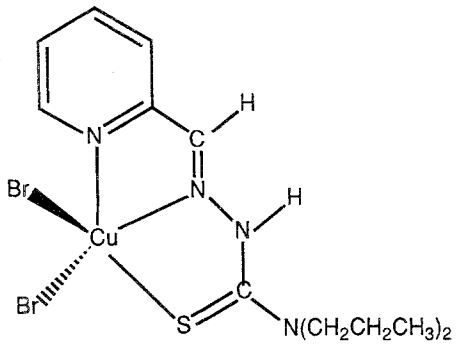


Figure 5. Proposed bonding for a $[Cu(HL)Br_2]$ complex with tridentate, neutral heterocyclic thiosemicarbazone.

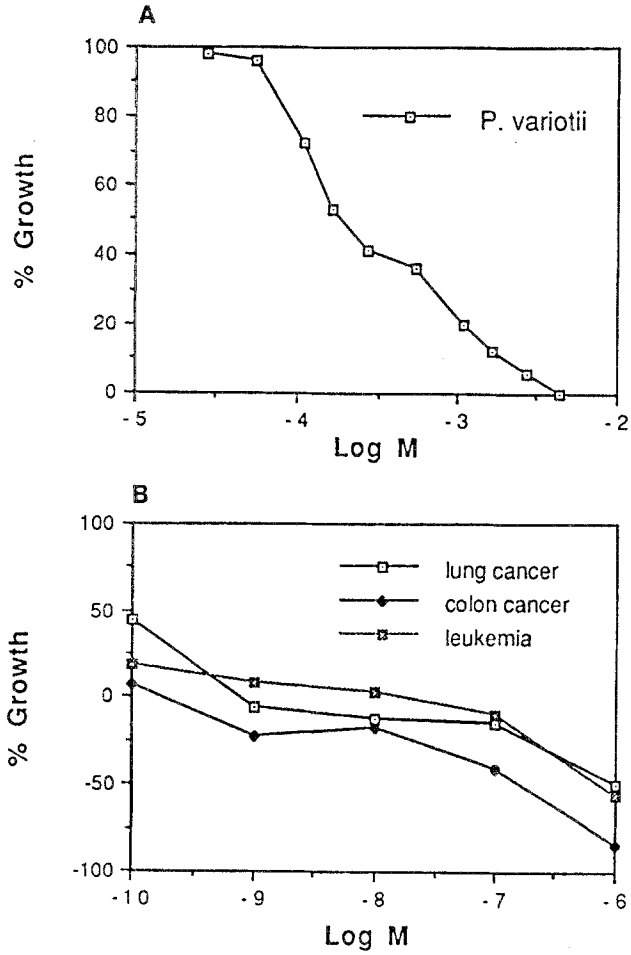


Figure 6. Effect of [Cu(4DP)Cl] on growth of *P. variotii* (A) and *in vitro* growth (B) of three tumor cell lines. Specific cell lines are: lung cancer (non-small cell lung cancer, HOP 62), colon cancer (COLO 205) and leukemia (K562).

vitro antitumor activity by the National Cancer Institute's Research and Development Center, using the 'Preclinical Antitumor Drug Discovery Screen' (Boyd 1989). The Screen currently consists of 60 distinct cell lines that are distributed among eight 'panels' of cell types.

Cu(II) complexes that have thus far been found to be highly active as both antifungal and antitumor agents are [Cu(L4DM)Br], [Cu(L4DP)Cl], $[Cu(H4DP)Br_2]$, [Cu(4DP)Cl] and [Cu(Pzhexim)Cl]. Of this group all have N–N–S coordination and only $[Cu(H4DP)Br_2]$ is five-coordinate (Figure 5) while the other four compounds are four-coordinate and all have the planar Cu(II) arrangement shown in Figure 1. Among the five complexes noted above, we have selected the latter two (i.e. [Cu(4DP)Cl] and [Cu(Pzhexim)Cl] which are depicted in Figure 4) to illustrate the combined antifungal and antitumor activities displayed by the complexes (Figures 6 & 7). The figures show that compounds capable of reducing fungal growth are also capable of causing comparable *in vitro* growth reductions in various types of tumor cells. The figures illustrate an observation that we have made for all five complexes: compounds that reduce fungal growth by

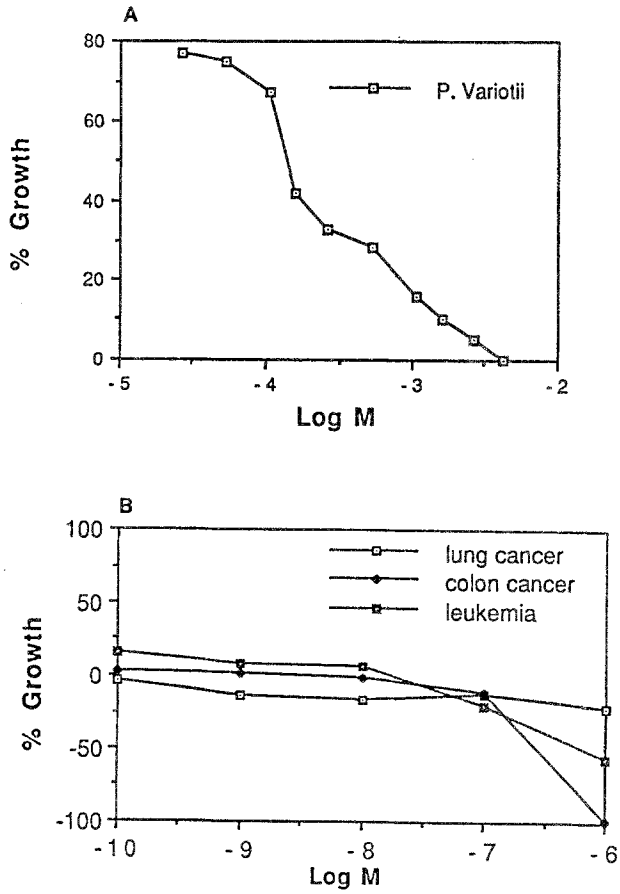


Figure 7. Effect of [Cu(Pzhexim)Cl] on growth of *P. variotii* (A) and *in vitro* growth (B) of three tumor cell lines as described in Figure 6.

50% or more at 10^{-4} to 10^{-5} M concentrations, will also cause comparable growth reductions in tumor cells at 10^{-9} to 10^{-10} M concentrations. These observations suggest that antifungal assay system may become useful as an inexpensive, rapid method for initially screening organic compounds and their metal complexes for potential antitumor activity.

Acknowledgements

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References

Antholine WE, Knight J, Petering DH. 1977 Some properties of copper and zinc complexes of 2-formylpyridine thiosemicarbazones. *Inorg Chem* **16**, 569–574.

Blanz EJ Jr, French FA. 1968 The carsinostatic activity of 5-hydroxy-2-formylpyridine thiosemicarbazone. *Cancer Res* **28**, 2419–2422.

Boyd MR. 1989 Status of the NCI preclinical antitumor drug discovery screen. *Princip Pract Oncol* **3**, 1–12.

Cory JG, Fleischer AE. 1979 Specific inhibitors directed at the individual components of ribonucloetide reductase as an approach to combination chemotherapy. *Cancer Res* **39**, 4600–4604.

Dobek AS, Klayman DL, Dickson ET, Scovill JP, Tramont EC. 1980 Inhibition of clinically significant bacterial organisms *in vitro* by 2-acetylpyridine thiosemicarbazones. *Antimicrob Agents Chemother* **18**, 27–36.

French FA, Blanz EJ Jr. 1970 Carcinostatic activity of thiosemicarbazones of formyl heterocyclic compounds. 6. 1-formylisoquinoline derivatives bearing additional ring substituents with notes on mechanism of action. *J Med Chem* **13**, 1117–1123.

Grover RK, Moore JD. 1962 Toximetric studies of fungicides against brownrot organism *Sclerotinia fruticola* and *S. laxa*. *Phytopathology* **52**, 876–880.

Karon M, Benedict WF. 1972 Chromatid breakage: differential effect of inhibitors of DNA synthesis during G_2 phase. *Science* **178**, 62.

Klayman DL, Bartosevich JF, Griffin TS, Mason CJ, Scovill JP. 1979 2-acetylpyridine thiosemicarbazones. A new class of potential antimalarial agents. *J Med Chem* **22**, 855–862.

Klayman DL, Lin AJ, McCall JW, *et al.* 1991 2-acetylpyridine thiosemicarbazones. 13. Derivatives with antifilarial activity. *J Med Chem* **34**, 1422–1425.

Mittal SP, Sharma SK, Singh RV, Tandon JP. 1981 Antifungal activity of some novel lanthanon thiosemicarbazone complexes. *Curr Sci* **50**, 483–484.

Sartorelli AC, Agrawal KC, Tsiftsoglou AS, Moore EC. 1977 Characterization of biochemical mechanism of action of alpha(*N*)-heterocyclic carboxaldehyde thiosemicarbazones. *Adv Enzyme Reg* **15**, 117–139.

Saryan LA, Mailer K, Krishnamurti C, Antholine W, Petering DH. 1981 Interaction of 2-formylpyridine thiosemicarbazonato copper(II) with Ehrlich ascites tumor-cells. *Biochem Pharmacol* **30**, 1595–1604.

Scovill JP, Klayman DL, Lambrose C, Childs GE, Notsch JD. 1984 2-acetylpyridine thiosemicarbazones. 4. Complexes with transition metals as antimalarial and antileukemic agents. *J Med Chem* **27**, 87–91.

Shipman C, Smith SH, Drach JC, Klayman DL. 1981 Antiviral activity of 2-acetylpyridine thiosemicarbazones against herpes simplex virus. *Antimicrob Agents Chemother* **19**, 682–685.

Wengel A, Jacobsen N, Kolind-Anderson H, Bjerregaard P. 1990 Chitin biosynthesis inhibition and fungicidal effect of thiosemicarbazones of 2-formyl- and 2-acetylpyridine, their hydrogenated derivatives and copper complexes thereof. *Pesticide Sci* **30**, 223–233.

West DX, Carlson CS, Whyte AC, Liberta AE. 1990a Transition metal ion complexes of thiosemicarbazones derived from 2-acetylpyridine. Part 7. Chemical and antifungal properties of 2-acetylpyridine ^4N-ethylthiosemicarbazone and its metal complexes. *Transition Met Chem* **15**, 43–47.

West DX, Carlson CS, Galloway CP, Liberta AE, Daniel CR. 1990b Transition metal ion complexes of thiosemicarbazones derived from 2-acetylpyridine. Part 6. Chemical and antifungal properties of 2-acetylpyridine ^4N-diethyl- and ^4N-dipropylthiosemicarbazones and their copper(II) complexes. *Transition Met Chem* **15**, 91–95.

West DX, Carlson CS, Liberta AE, Albert JN, Daniel CR. 1990c Transition metal ion complexes of thiosemicarbazones derived from 2-acetylpyridine. Part 8. The chemical and antifungal properties of nickel(II) complexes of 2-acetylpyridine ^4N-diethyl- and ^4N-dipropylthiosemicarbazones and their copper(II) complexes. *Transition Met Chem* **15**, 341–344.

West DX, Carlson CS, Liberta AE, Scovill JP. 1990d The chemical and antifungal properties of the copper(II) complexes of 2-acetylpyrazine ^4N-methyl-, ^4N-dimethyl-, and 3-hexamethyleneiminylthiosemicarbazones. *Transition Met Chem* **15**, 383–387.

West DX, Carlson CS, Bouck KJ, Liberta AE. 1991a Transition metal ion complexes of thiosemicarbazones derived from 2-acetylpyridine. Part 10. A comparison of the chemical and antifungal properties of the copper(II) complexes and 2-acetylpyridine 3-pyrrolidinyl, 3-piperidinyl-, 3-hexamethyleneiminyl and 3-azabicyclo[3.2.2] nonylthiosemicarbazones. *Transition Met Chem* **165**, 271–275.

West DX, Padhye SB, Sonawane PB. 1991b Structure and physical correlations in the biological properties of transition metal heterocyclic thiosemicarbazone and *S*-alkyldithiocarbazates. *Struct Bond* **76**, 1–50.