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Synthesis, structure and biological properties of a series of dicopper(bis-thiosemicarbazone) complexes†

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Fifteen new coordination binuclear compounds of copper(II) were synthesized based on substituted 4-*tert*-butyl-2,6-bis(*N*⁴-thiosemicarbazonyl)phenol (H₃L¹⁻³) ditopic ligands. The complexes were characterized using FT-IR spectroscopy, elemental analysis, MALDI-TOF analysis and X-ray diffraction studies highlighting the formation of dinuclear species with various bridging ligands between the two copper(II) atoms and in some cases the dimerization of these species into tetranuclear complexes. The antioxidant, antimicrobial and antifungal activities of ligands and their copper(II) coordination complexes have been investigated. In particular, the complexes show similar or better antimicrobial and antifungal properties than the drugs commonly used in this field. The structure–biological activity relationship is discussed based on the nature of the ligand and the copper salt used in the synthesis of the complexes.

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Introduction

Discovered in the 1950s, thiosemicarbazone molecules are a fascinating class of ligands displaying interesting properties and applications in many domains.^{1–4} Thiosemicarbazones and bis-thiosemicarbazones have a broad pharmacological profile and, thanks to their donor atoms, possess a high affinity for transition metal ions. Due to their huge structural and compositional diversity, thiosemicarbazone-based transition metal complexes are of interest for application in molecular

magnetism,^{5,6} catalysis^{7–9} and medicinal chemistry because of their promising antiviral,¹⁰ antiproliferative, antitumor,^{11–20} antimicrobial, antifungal,^{21–25} antioxidant,^{26–28} and anti-inflammatory²⁹ properties and also as diagnostic and therapeutic radiopharmaceutical drug candidates.²

Among thousands of complexes, thiosemicarbazone-based copper(II) complexes have received particular attention. Copper is the third most abundant transition metal in the human body, with a normal content of 1.4–2.1 mg kg^{−1}. It is essential for several biological processes, such as iron transport, metabolism and respiration.³⁰ Various thiosemicarbazone-based copper(II) complexes revealed a wide range of efficient biological activities. For example copper(II)-diacetylbis(*N*⁴-methylthiosemicarbazone) (CuATSM) is a clinical candidate for the treatment of Parkinson's disease,³¹ amyotrophic lateral sclerosis (ALS)³² and ischemic stroke.³³

Great attention is paid to the research into mono-thiosemicarbazone-based copper(II) complexes while the research into bis-thiosemicarbazone compounds is more scarce. We can mention for instance a mononuclear bis-thiosemicarbazone-based Cu(II) complex reported by Orio *et al.* for oxygen catalytic reduction.⁸ On the other hand, dinuclear copper(II) complexes are of interest for their biological properties and especially as tyrosinase models. For this purpose, ditopic ligands designed around a phenol group appear perfectly adapted for obtaining dinuclear copper(II) complexes.^{34,35} In the 1970s, Robson and coworkers reported dicopper(II) bis(thiosemicarbazone) complexes but to our knowledge their biological properties were not

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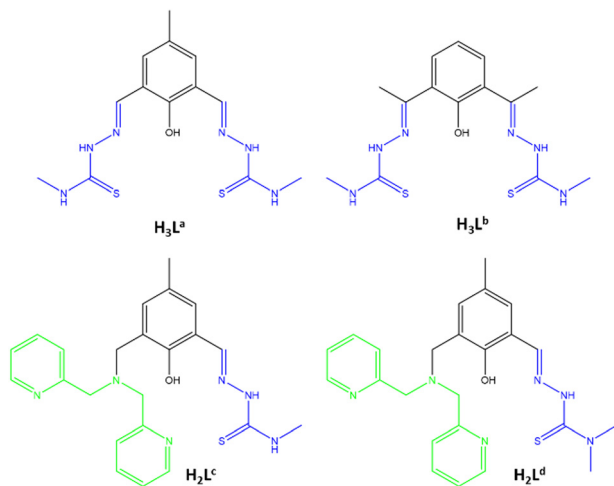
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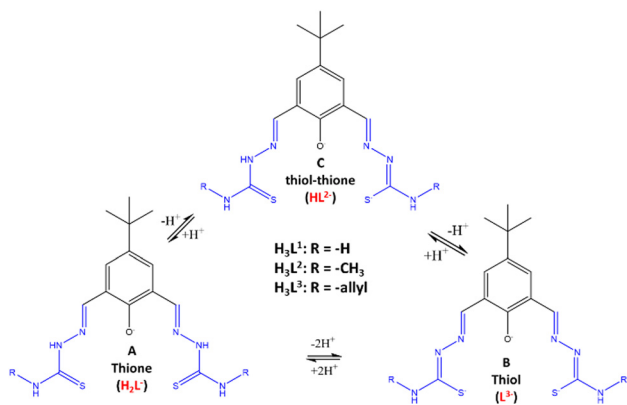
† Electronic supplementary information (ESI) available: Experimental section (Part 1), materials and methods, syntheses, IR spectra and table of important bands (Part 2, Fig. S1–S3 and Table S2); ESI-MS and MALDI-TOF spectra (Part 3, Fig. S4–S17); crystallographic data and pictures of disorders (Table S3 and Fig. S18–S23); NMR spectra of ligands (Part 5, Fig. S24–S29); antioxidant tests (Part 6, Fig. S30) and stability studies (Part 7, Fig. S31–S33). CCDC 2299430(4'), 2299431(8'), 2299432(9'), 2299433(13'), 2299434 (14') and 2299435(15'). For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4nj00342j>



Scheme 1 Some bis(thiosemicarbazones) and unsymmetrical thiosemicarbazone ligands reported in the literature for the synthesis of dinuclear and tetranuclear copper complexes.

studied.^{36–38} More recently, Bermejo, Casella *et al.* reported the magnetic properties, kinetic studies, and the formation of dicopper(II) complexes based on bis-*N*-methyl-thiosemicarbazone ligands (see Scheme 1, ligands H_3L^{a-b}).³⁹ Furthermore, Belle *et al.* have reported dinuclear and tetranuclear copper(II) complexes obtained from unsymmetrical thiosemicarbazone ligands (see Scheme 1, ligands H_2L^{c-d}).⁴⁰

In our recent work, we reported the synthesis and characterization of bis-thiosemicarbazone-based $[Mo_2^V O_2 S_2]^{2+}$ complexes containing flexible or rigid (only aromatic) spacers between the two thiosemicarbazone units.⁴¹ Replacing the central aromatic ring by a phenol leads to bis-thiosemicarbazone ligands well suited to form di-copper(II) complexes.^{34,36,39,40,42–44} In this context, the aim of this study is to develop a new series of dicopper(II) complexes and investigate their antioxidant, antifungal and antimicrobial properties. In the first part of this paper, the syntheses and the characterisation of 15 di-copper(II) complexes from three different bis-thiosemicarbazone ligands depicted in Scheme 2 and different copper salts are reported. The complexes were



Scheme 2 Representation of the three bis-thiosemicarbazone ligands used in this study, with $R = H$ (H_3L^1), $R = Me$ (H_3L^2) and $R = allyl$ (H_3L^3), in their three possible protonation states.

characterized by routine techniques as well as MALDI-TOF and single crystal X-ray diffraction. In the second part, the structure–biological activity relationship is discussed based on the nature of the ligands and the counter-anions.

Results and discussion

Synthesis

As shown in Scheme 2, the bis-thiosemicarbazone ligands can exist in different forms depending on their protonation state. The non-coordinated ligands are usually in the di-thione form (A). Their coordination to metal ions usually involves the *N*-imino group and the sulfur atom. This process contributes to deprotonation of the ligand, generally on the azomethine nitrogen atom of the thiosemicarbazone moieties to give a coordinated thiolate group, but the coordination of the sulfur atom to metals can also occur in its neutral thione form.⁶ If so, the coordination of bis-thiosemicarbazone ligands can occur either in the di-thiolate form (B) or in the di-thione form (A) or in the mixed thione–thiolate form (C), depending on pH, the solvent and the nature of the copper salt.

In this study, we synthesized 15 complexes of copper(II), denoted 1–15, in powder form, which were characterized by FT-IR, elemental analysis, EDX, and MALDI-TOF experiments (see Table 1 and parts 1–3 in the ESI†). In all cases, two Cu(II) atoms are found per ligand and the two Cu(II) atoms are bridged by the deprotonated phenolate group and by an additional external bridging ligand which can be either Cl^- , Br^- , or EtO^- depending on the nature of the salt and the solvent used (see Table 1). The presence of Cl^- and Br^- is confirmed by EDX studies and the MALDI-TOF spectra (see Table 1), while the formation of an ethoxo bridge agrees with the results of elemental analyses and is mainly confirmed by X-ray diffraction studies. This bridging ligand seems less stable than the two others since MALDI-TOF experiments evidenced the replacement of EtO^- by OH^- or MeO^- bridges in some cases.

Depending on the copper salt used in the synthesis, bis-thiosemicarbazones behave as mono or doubly deprotonated, ligands, thus leading to neutral complexes of general formula $[Cu_2(L)(Bridge)]$ and monocationic species of general formula $[Cu_2(HL)(Bridge)](anion)$. Interestingly, as seen in Table 1, when perchlorate or nitrate salts are used, the bridge is an ethanolate ligand and the complexes are monocationic species. In these cases, the counter anion nitrate or perchlorate, is easily identified by FT-IR spectroscopy (see Part 2, ESI†). In contrast, the use of chloride, bromide and acetate salts of Cu(II) leads to the complete deprotonation of the ligand and neutral complexes with Cl^- , Br^- or EtO^- bridges, respectively.

FT-IR spectroscopy (see Part 2, Fig. S1–S3 and Table S2, ESI†) brings additional elements to confirm the protonation state of the ligand. The thione form is confirmed by the presence of vibration bands in the wavenumber range of $821–822\text{ cm}^{-1}$, which corresponds to the data from the literature.^{45,46} In particular, the thione/thiolate forms of the coordinated

Table 1 Summary of complexes prepared in this study. MALDI-TOF data obtained for the copper(II) complexes. Since perchlorate salts can be explosive, the complexes with perchlorate anions (complexes **4**, **9**, and **14**) have not been studied using MALDI-TOF spectrometry

Complex ^a	Salt of Cu(II) used in the synthesis	Bridging ligand	Synthesis/formula	MALDI-TOF experiments		
			Formula from elemental analysis	Exp. <i>m/z</i>	Assignment	Calc. <i>m/z</i>
[Cu ₂ (L ¹)Cl] (1)	CuCl ₂ ·2H ₂ O	Cl ⁻	[Cu ₂ (C ₁₄ H ₁₇ N ₆ OS ₂)Cl](H ₂ O) _{4.1} (CH ₃ OH) _{0.6}	511.0	[Cu ₂ L ¹ Cl + H] ⁺	511.0
[Cu ₂ (L ¹)Br] (2)	CuBr ₂	Br ⁻	[Cu ₂ (C ₁₄ H ₁₇ N ₆ OS ₂)Br](H ₂ O) ₇ (C ₂ H ₆ O) _{0.5}	554.9	[Cu ₂ L ¹ Br + H] ⁺	554.9
[Cu ₂ (HL ¹)OC ₂ H ₅]NO ₃ (3)	Cu(NO ₃) ₂ ·3H ₂ O	EtO ⁻	[Cu ₂ (C ₁₄ H ₁₈ N ₆ OS ₂)(OC ₂ H ₅)]NO ₃ (H ₂ O) ₆	491.9	[Cu ₂ HL ¹ OH] ⁺	492.0
[Cu ₂ (HL ¹)OC ₂ H ₅]ClO ₄ (4)	Cu(ClO ₄) ₂ ·6H ₂ O	EtO ⁻	[Cu ₂ (C ₁₄ H ₁₈ N ₆ OS ₂)(OC ₂ H ₅)]ClO ₄ (H ₂ O) ₄	—	—	—
[Cu ₂ (L ¹)OC ₂ H ₅] (5)	Cu(CH ₃ COO) ₂ ·H ₂ O	EtO ⁻	[Cu ₂ (C ₁₄ H ₁₇ N ₆ OS ₂)(OC ₂ H ₅)](H ₂ O) _{1.1}	563.2	[Cu ₂ L ¹ (H ₂ O) ₅] ⁺	565.0
[Cu ₂ (L ²)Cl] (6)	CuCl ₂ ·2H ₂ O	Cl ⁻	[Cu ₂ (C ₁₆ H ₂₁ N ₆ OS ₂)Cl](H ₂ O) ₅	538.9	[Cu ₂ L ² Cl + H] ⁺	539.0
[Cu ₂ (L ²)Br] (7)	CuBr ₂	Br ⁻	[Cu ₂ (C ₁₆ H ₂₁ N ₆ OS ₂)Br](C ₂ H ₅ OH)(H ₂ O) ₁₁	582.9	[Cu ₂ L ² Br + H] ⁺	582.9
[Cu ₂ (HL ²)OC ₂ H ₅]NO ₃ (8)	Cu(NO ₃) ₂ ·3H ₂ O	EtO ⁻	[Cu ₂ (C ₁₆ H ₂₂ N ₆ OS ₂)(OC ₂ H ₅)]NO ₃ (H ₂ O) ₂	534.0	[Cu ₂ HL ² (OCH ₃)] ⁺	535.0
[Cu ₂ (HL ²)OC ₂ H ₅]ClO ₄ (9)	Cu(ClO ₄) ₂ ·6H ₂ O	EtO ⁻	[Cu ₂ (C ₁₆ H ₂₂ N ₆ OS ₂)(OC ₂ H ₅)]ClO ₄ (H ₂ O) ₄	—	—	—
[Cu ₂ (L ²)OC ₂ H ₅] (10)	Cu(CH ₃ COO) ₂ ·H ₂ O	EtO ⁻	[Cu ₂ (C ₁₆ H ₂₁ N ₆ OS ₂)(OC ₂ H ₅)](H ₂ O)	548.0	[Cu ₂ L ² (OC ₂ H ₅) + H] ⁺	549.0
[Cu ₂ (L ²)Cl] (11)	CuCl ₂ ·2H ₂ O	Cl ⁻	[Cu ₂ (C ₂₀ H ₂₅ N ₆ OS ₂)Cl](H ₂ O) ₇	590.9	[Cu ₂ L ² Cl + H] ⁺	591.0
[Cu ₂ (L ³)Br] (12)	CuBr ₂	Br ⁻	[Cu ₂ (C ₂₀ H ₂₅ N ₆ OS ₂)Br](H ₂ O) _{13.8}	1246.7	[(Cu ₂ L ³ Cl) ₂ (CH ₃ OH) ₂ + H] ⁺	1247.3
[Cu ₂ (HL ³)OC ₂ H ₅]NO ₃ (13)	Cu(NO ₃) ₂ ·3H ₂ O	EtO ⁻	[Cu ₂ (C ₂₀ H ₂₆ N ₆ OS ₂)(OC ₂ H ₅)]NO ₃ (H ₂ O) ₂	634.9	[Cu ₂ L ³ Br + H] ⁺	635.0
[Cu ₂ (HL ³)OC ₂ H ₅]ClO ₄ (14)	Cu(ClO ₄) ₂ ·6H ₂ O	EtO ⁻	[Cu ₂ (C ₂₀ H ₂₆ N ₆ OS ₂)(OC ₂ H ₅)]ClO ₄ (H ₂ O)	573.0	[Cu ₂ HL ³ OH] ⁺	573.0
[Cu ₂ (L ³)OC ₂ H ₅] (15)	Cu(CH ₃ COO) ₂ ·H ₂ O	EtO ⁻	[Cu ₂ (C ₂₀ H ₂₅ N ₆ OS ₂)(OC ₂ H ₅)](H ₂ O) _{1.1}	886.2	[Cu ₂ L ³ OC ₂ H ₅ - (C ₂ H ₅ OH) ₅ (H ₂ O) ₃] ⁺	886.1

^a Solvent molecules are omitted from the formula for clarity.

ligands are indicated by the C–S (583–621 cm⁻¹) and C=S (817–846 cm⁻¹) vibration bands.

MALDI-TOF studies

MALDI-TOF mass spectrometry has been proven to be a very effective analytical research method for the characterization of thiosemicarbazone complexes.^{41,47} The results obtained for the synthesized complexes are collected in Table 1. Fig. 1 shows an example of the spectrum obtained for the neutral complex [Cu₂(L¹)Cl], while the spectra obtained for the other complexes are shown in Fig. S7–S17 (ESI⁺). The main peak corresponds to a monocationic adduct formed with a proton, *i.e.* [Cu₂(L¹)Cl + H]⁺ and simulations performed with IsoPro freeware confirm the isotopic distribution expected for the dinuclear complex of

Cu(II). As shown in Table 1, this is a common feature for all the complexes studied in this paper for which two Cu(II) centers, one bis-thiosemicarbazone ligand and one bridging ligand Cl⁻, Br⁻, OH⁻ or MeO⁻ are identified. Interestingly, in some cases, the ethoxy bridges identified by elemental analyses are not preserved by MALDI-TOF experiments and are replaced by methoxy or hydroxy bridges. Besides, in some cases tetranuclear, and even hexanuclear, species resulting from the dimerization and trimerization of dinuclear complexes are also observed, notably for H₃L² and H₃L³ based complexes with nitrate as counter anions. The formation of such tetranuclear complexes is relatively common for this class of complexes. For instance, Belle *et al.* reported dinuclear and tetranuclear phenoxido bridged copper(II) complexes for which DFT calcula-

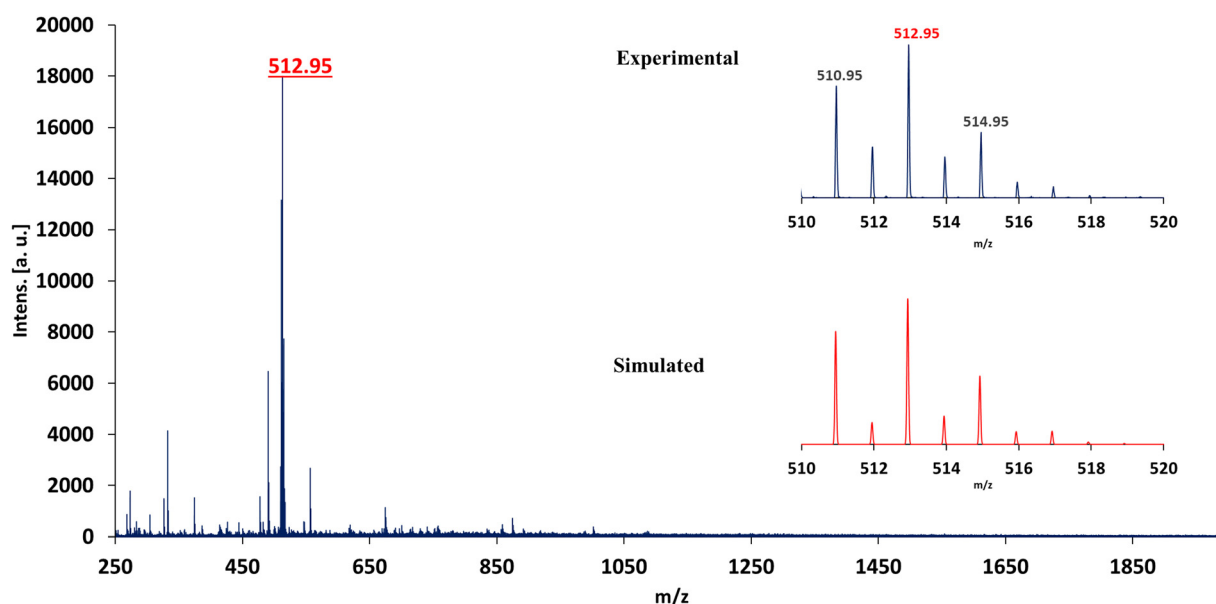


Fig. 1 MALDI-TOF mass spectrum of the compound [Cu₂(L¹)Cl] (**1**). The simulated spectrum is obtained with IsoPro3 freeware.

tions evidence close energies and a possible equilibrium between the two forms, in agreement with our results.⁴⁰ These species display a typical isotopic distribution of tetranuclear or hexanuclear species (see Fig. S12, S14, S16 and S17, ESI†) but the ligands are probably partially decomposed, which renders difficult a confident attribution of the peaks. Besides, in these cases, the bridging ligand may disappear, providing clues as to the mode of dimerization.

Crystallography

Single crystals were obtained for six copper(II) complexes, denoted **4'**, **8'**, **9'**, **13'**, **14'** and **15'** using the micro-synthesis method in ethanol and slow evaporation of the solvent in air. The crystallographic data are gathered in Table S3 (ESI†), while selected distances are given in Table 2. Dinuclear Cu(II) complexes are obtained in all cases, in agreement with elemental analyses and MALDI-TOF studies. Conversely to the powders **1–15** obtained previously, X-ray analysis shows that the bis-thiosemicarbazone ligands can be found in the form of single, double or triple deprotonated ligands, named A: (H₂L)²⁻, C: (HL)²⁻ and B: (L)³⁻, respectively (see Scheme 2) for giving dicationic, monocationic or neutral complexes, respectively. Perchlorate or nitrate ensures the neutrality of the whole system. The copper(II) atoms are coordinated to the thiosemicarbazone arms through the imino N atoms and sulfur atoms found in the thione or thiolate form. The two Cu(II) centers are bridged by a phenolato O atom from the ligand and an oxygen atom coming from an external bridging ligand, which can be either hydroxo or ethoxo anionic ligands.

Structures of dicationic complexes [Cu₂(H₂L¹)(OH)](ClO₄)₂ (4'**) and [Cu₂(H₂L²)(OC₂H₅)](NO₃)₂ (**8'**).** The molecular structures of complexes [Cu₂(H₂L¹)(OH)](ClO₄)₂ (**4'**) and [Cu₂(H₂L²)(OC₂H₅)](NO₃)₂ (**8'**) are depicted in Fig. 2A and B, respectively. According to literature data, complex compounds based on 2,6-diformyl-4-*R*-phenol are known to have methoxy, ethoxy or hydroxy bridging molecules between Cu(II) atoms.^{36,48–51} In these cases, the authors report Cu–O distances

between 1.8 and 1.9 Å that are characteristic for Cu-methoxy or ethoxy ligands, while these distances increase up to 2.5–2.6 Å for Cu–OH₂, Cu–OHMe or Cu–OHET bonds. For complex **4'**, [Cu₂(H₂L¹)(OH)](ClO₄)₂, the external bridge between the two Cu(II) atoms is identified as a hydroxo ligand (*d*Cu–O = 1.907–1.911 Å), while it was an ethoxo ligand in the complex **4** synthesized in powder form. In contrast, for the complex [Cu₂(H₂L²)(OC₂H₅)](NO₃)₂ (**8'**), the bridge between Cu(II) centers is an ethoxo ligand (*d*Cu–O = 1.898–1.899 Å). For both complexes, the ligands are found to be in their monodeprotonated form A (see Scheme 2). The CS bond lengths are found to be equivalent in both arms of ligands and in both complexes. The range 1.71–1.72 Å agrees with that of thione groups C=S. The coordination spheres of both Cu(II) atoms in [Cu₂(H₂L²)(OC₂H₅)](NO₃)₂ (**8'**) are filled by a monodentate nitrate ligand to give pentacoordinated Cu(II) atoms in a square-based pyramid environment, with the distances between Cu(II) and nitrate being longer (Cu–O(NO₃⁻): 2.454 and 2.747 Å). In contrast, the perchlorate anions in [Cu₂(H₂L¹)(OH)](ClO₄)₂ (**4'**) are found as counter anions, but a connection with the neighbouring complex is identified through a long bond between one Cu(II) atom and a hydroxo bridging ligand of the second complex (*d*Cu–O = 2.561 Å) to give a tetranuclear assembly in the crystal structure, a feature commonly observed for such type of complexes.³⁹ Cu(II) atoms are either in a square-base pyramid or in a square planar environment.

Structures of mono-cationic complexes [Cu₂(HL²)OC₂H₅]-ClO₄ (9'**) and [Cu₂(HL³)OC₂H₅]-NO₃ (**13'**).** Similar tetranuclear assembly is found with the structure of [Cu₂(HL²)OC₂H₅]-ClO₄ (**9'**, see Fig. 2C) with an intermolecular distance Cu–O(ethoxo) of 2.691 Å. Interestingly, for this complex, the ligand is in the di-deprotonated form C but one anionic charge is delocalized over the two arms of the ligand, which translates into CS bond lengths intermediate between C–S and C=S bonds: 1.718 Å for both arms. The neutrality is ensured by one perchlorate anion, which bridges the two Cu(II) atoms (*d*Cu–O = 2.719 and 2.862 Å) to give an octahedral coordination sphere for Cu1 and a

Table 2 Selected bond lengths (Å). Solvents are omitted in the formulas for clarity

Complexes	Label	C–S	(N)N=C(S)	Cu–N	Cu–S _{ligand}	Cu–O _{bridge}	Cu–O _{Phenolate}	Cu–O _{anion}
(4') [Cu ₂ (H ₂ L ¹)(OH)](ClO ₄) ₂	Cu1	1.717	1.328	1.909	2.255	1.911	1.978	—
	Cu2	1.711	1.331	1.922	2.256	1.907	1.972	—
(8') [Cu ₂ (H ₂ L ²)(OC ₂ H ₅)](NO ₃) ₂	Cu1	1.718	1.346	1.938	2.233	1.899	1.952	2.747
	Cu2	1.710	1.351	1.938	2.241	1.898	1.968	2.454
(9') [Cu ₂ (HL ²)OC ₂ H ₅]-ClO ₄	Cu1	1.718	1.350	1.929	2.245	1.940	1.946	2.862
	Cu2	1.718	1.325	1.936	2.251	1.930	1.945	2.719
(13') [Cu ₂ (HL ³)OC ₂ H ₅]-NO ₃	Cu1	1.757	1.304	1.926	2.216	1.931	1.959	—
	Cu2	1.701	1.338	1.934	2.255	1.921	1.961	—
(15') [Cu ₂ (L ³)OC ₂ H ₅]	Cu1	1.763	1.305	1.945	2.235	1.944	1.970	—
	Cu2	1.749	1.298	1.934	2.219	1.952	1.960	—
(14') [Cu ₂ (L ³)OC ₂ H ₅][Cu ₂ (HL ³)OC ₂ H ₅]-ClO ₄	Cu1	1.738	1.331	1.934	2.194	1.916	1.962	—
	Cu2	1.718	1.324	1.923	2.234	1.875	1.959	—
	Cu3	1.753	1.308	1.933	2.216	1.913	1.961	—
	Cu4	1.752	1.310	1.933	2.221	1.907	1.960	—

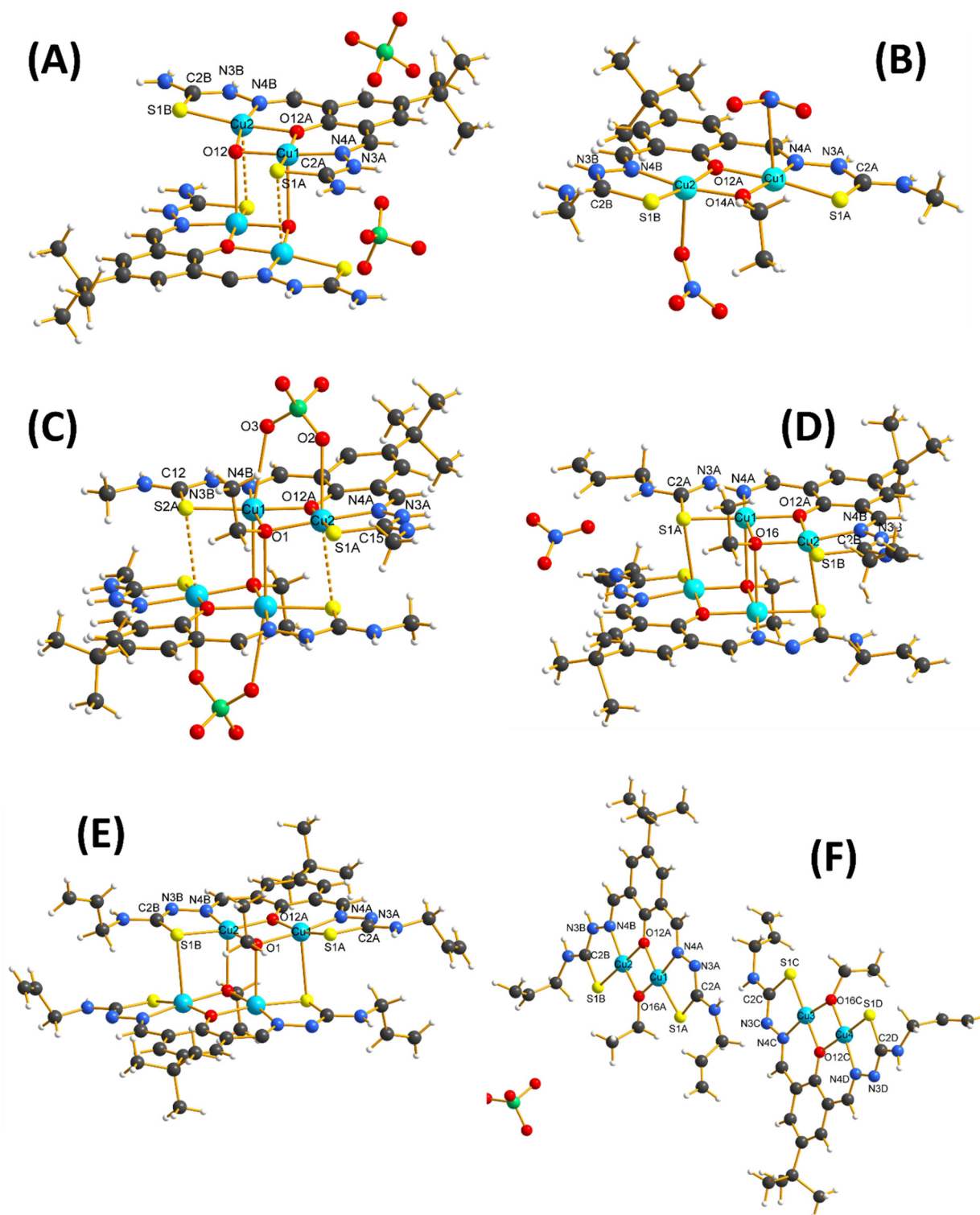


Fig. 2 Molecular structure of complexes (**4'**) $[\text{Cu}_2(\text{H}_2\text{L}^1)\text{OH}](\text{ClO}_4)_2$ (A), (**8'**) $[\text{Cu}_2(\text{H}_2\text{L}^2)\text{OC}_2\text{H}_5](\text{NO}_3)_2$ (B), (**9'**) $[\text{Cu}_2(\text{HL}^2)\text{OC}_2\text{H}_5]\text{ClO}_4$ (C), (**13'**) $[\text{Cu}_2(\text{H}^1\text{L}^3)\text{OC}_2\text{H}_5]\text{NO}_3$ (D), (**15'**) $[\text{Cu}_2(\text{L}^3)\text{OC}_2\text{H}_5]$ (E), and (**14'**) $[\text{Cu}_2(\text{L}^3)\text{OC}_2\text{H}_5][\text{Cu}_2(\text{HL}^3)\text{OC}_2\text{H}_5]\text{ClO}_4$ (F). Figures with ellipsoids, solvents, and disorders are given in the ESI† (Fig. S18–S23).

square-base pyramid geometry for Cu2 with a Jahn–Teller effect in both cases. Conversely, the structure of $[\text{Cu}_2(\text{HL}^3)\text{OC}_2\text{H}_5]\text{NO}_3$ (**13'**, Fig. 2D) reveals the formation of a tetranuclear assembly

with both Cu–O and Cu–S intermolecular contacts ($d_{\text{Cu1–O}} = 2.700 \text{ \AA}$; $d_{\text{Cu2–S}} = 2.811 \text{ \AA}$), a nitrate as a counter anion and a ligand in the di-deprotonated form C with a clear position of

the proton and two CS bond lengths typical of the C=S bond (1.701 Å) and the C–S bond (1.757 Å), respectively.

Structures of the neutral complex [Cu₂(L³)OC₂H₅] (15'). The structure of complex [Cu₂(L³)OC₂H₅] completes the series of complexes with a neutral complex depicted in Fig. 2E. The ligand is triply deprotonated and the form B of the ligand is confirmed by long distances C–S = 1.749 and 1.763 Å typical of thiolate groups. As seen for previous complexes, the propensity to give tetranuclear assembly is confirmed once again through Cu1–O and Cu2–S intermolecular bonds (2.515 and 2.904 Å, respectively). Both Cu(II) are in square base pyramid geometry.

Structures of mixed complexes

[Cu₂(L³)OC₂H₅][Cu₂(HL³)OC₂H₅]ClO₄ (14'). Finally, the structure of [Cu₂(L³)OC₂H₅][Cu₂(HL³)OC₂H₅]ClO₄ depicted in Fig. 3F reveals the co-crystallization of a neutral dinuclear complex [Cu₂(L³)OC₂H₅] (Cu3, Cu4) with a monocationic one [Cu₂(HL³)OC₂H₅]ClO₄ (Cu1, Cu2). The distances C–S agree well with the deprotonation states of the ligands and no intermolecular interactions between complexes are identified in such a case.

In summary, this series of structures highlight the variety of structures and complexes that we can obtain in the solid state with bis-thiosemicarbazone ligands, the ligand being deprotonated once, twice or three times, the anions being either counter-anions or ligands and the dinuclear complexes being either connected to a neighbouring complex or not.

Biological properties of complexes 1–15. Before the biological tests, it is interesting to look at the stability of the complexes in solution. 3 complexes were chosen at random, one with each ligand: **1**, **8** and **11**. For these complexes, the UV-Vis spectra were measured in DMSO and in DMSO/water mixtures at different concentrations up to 2 μM (see Part 7, Fig. S31–S33, ESI[†]). The studies show little change in the spectra between 10^{−4} and 2 × 10^{−6} M, indicating that these complexes are very stable in solution in this range.

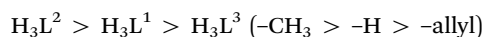
In vitro antibacterial and antifungal tests

The antimicrobial activity of the 15 synthesized dicopper(II) complexes obtained as powders numbered 1–15 was tested against G(+) bacteria: *Staphylococcus aureus* ATCC 25923, *Bacillus cereus* ATCC 11778 and G(−) bacteria: *Escherichia coli* ATCC 25922, *Acinetobacter baumannii* ATCC BAA-747 bacteria and the antifungal activity against *Candida albicans* ATCC 10231 fungal strains. The antibacterial and antifungal activity of the 15 complexes is evaluated using the microdilution broth test, which allows the determination of the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) or fungicidal concentration (MFC).^{52,53} The results are gathered in Table 3.

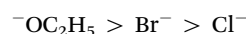
As can be seen from Table 3, the coordination of bis-thiosemicarbazones to the copper ion contributes to the increase of biological activity, unlike the free ligands, which are inactive. Similarly, the copper salts used do not show significant biological activity. The results obtained for dicopper(II) complexes show that G(−) bacteria *Escherichia coli* and *Acinetobacter baumannii* are more resistant to most of these complexes. The MIC values against G(+) bacteria are represented as histograms in Fig. 3. The most active dicopper(II) complex against *S. aureus* is [Cu₂L²Br] (7) with a MIC of 0.28 μM and [Cu₂L²OC₂H₅] (10) with a MIC of 0.12 μM. Considering that the ligands alone and the copper salts alone are not active and that the complexes exhibit a good stability at least to 2 μM, we can reasonably suppose that these complexes are still stable at these low concentrations.

From Table 3, it appears that the nature of the ligand, the nature of the bridge and the nature of the counter-anion play a role in the activity of the complexes. Behind all these parameters, the size and the charge of the complexes can or cannot make a complex chaotropic and therefore more or less able to penetrate biological membranes.⁵⁹ Further investigations are needed to elucidate this point for such a class of complexes but it could explain some differences, between [Cu₂L²Cl] (6), [Cu₂L²Br] (7), and [Cu₂L²OC₂H₅] (10) for instance, the former being 10 times less active than the two others. The structure–antibacterial activity relationship of dicopper(II) complexes can be highlighted by the following structural parameters:

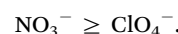
- Nature of the ligand:



- Nature of the anion in the inner sphere:



- Nature of the anion in the external sphere



Therefore, the dicopper(II) complexes based on the H₃L² ligand show bactericidal activity while others containing H₃L¹ and H₃L³ ligands are bacteriostatic. The activity against G(+) *S. aureus* of dicopper(II) complexes **4–8**, **10** and **13** is from 1.2 to

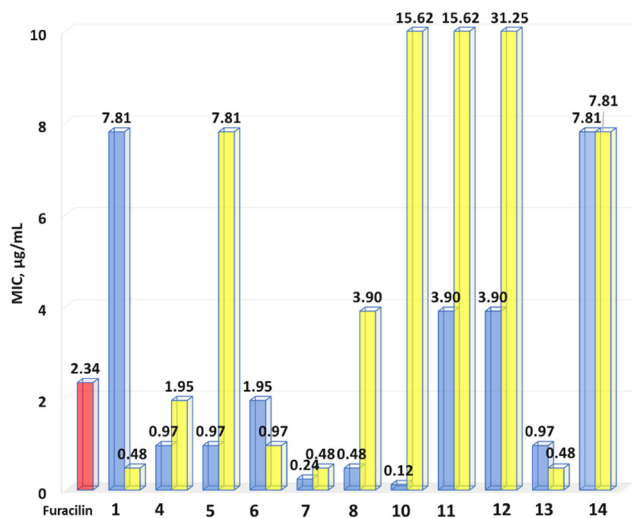


Fig. 3 Inhibition activity of dicopper(II) compounds on *S. aureus* (blue) and *B. subtilis* (yellow) bacteria in comparison with the activity of Furacilin.

Table 3 Activity of copper bis-thiosemicarbazone complexes against G(+) and G(−) bacteria

Compound	Gram positive G(+)		Gram negative G(−)		
	Minimum inhibitory concentration, MIC $\mu\text{g mL}^{-1}$ (μM)				
	<i>S. aureus</i> ATCC 25923	<i>B. cereus</i> ATCC 11778	<i>E. coli</i> ATCC 25922	<i>A. baumannii</i> ATCC BAA-747	
Copper(II) salts	$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}^{54,55}$	> 500	> 1000	> 1000	> 1000
	CuBr_2^{55}	> 500	NA	> 500	NA
	$\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}^{54}$	> 1000	> 1000	> 1000	> 1000
	$\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}^{55}$	> 1000	NA	> 1000	NA
	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}^{55}$	> 1000	NA	> 1000	NA
Thiosemicarbazone ligands (see Fig. 4 for ligands from the literature)	H_3L^1	NA	NA	NA	NA
	H_3L^2	NA	NA	NA	NA
	H_3L^3	NA	500	NA	500
	4-MeSalH ₂ Th ⁵⁶	NA	NA	NA	NA
	SalH ₂ Th ⁵⁷	NA	NA	NA	NA
Complexes (see Fig. 4 for ligands from the literature)	$[\text{Cu}_2\text{L}^1\text{Cl}]$ (1)	7.81 (12.90)	0.48 (0.79)	NA	NA
	$[\text{Cu}_2(\text{HL}^1)\text{OC}_2\text{H}_5]\text{ClO}_4$ (4)	0.97 (1.39)	1.95 (2.80)	500	125
	$[\text{Cu}_2(\text{L}^1)\text{OC}_2\text{H}_5]$ (5)	0.97 (1.79)	7.81 (14.42)	NA	NA
	$[\text{Cu}_2\text{L}^2\text{Cl}]$ (6)	1.95 (3.09)	0.97 (1.53)	NA	NA
	$[\text{Cu}_2\text{L}^2\text{Br}]$ (7)	0.24 (0.28)	0.48 (0.57)	NA	100
	$[\text{Cu}_2(\text{HL}^2)\text{OC}_2\text{H}_5]\text{NO}_3$ (8)	0.48 (0.73)	3.90 (6.01)	NA	NA
	$[\text{Cu}_2\text{L}^2\text{OC}_2\text{H}_5]$ (10)	0.12 (0.21)	15.62 (27.51)	NA	500
	$[\text{Cu}_2\text{L}^3\text{Cl}]$ (11)	3.90 (5.42)	15.62 (21.74)	NA	NA
	$[\text{Cu}_2\text{L}^3\text{Br}]$ (12)	3.90 (4.40)	31.25 (35.30)	NA	NA
	$[\text{Cu}_2(\text{HL}^3)\text{OC}_2\text{H}_5]\text{NO}_3$ (13)	0.97 (1.38)	0.48 (0.68)	NA	NA
	$[\text{Cu}_2(\text{HL}^3)\text{OC}_2\text{H}_5]\text{ClO}_4$ (14)	7.81 (10.84)	7.81 (10.84)	NA	500
	$[\text{Cu}(\text{MeSalTh})\text{Py}]^{56}$	4.67 (13.34)	NA	300	NA
	$[\text{Mo}_2\text{O}_2\text{S}_2(\text{SalHTh})_2]^{58}$	125.0 (165.34)	125.0 (165.34)	NA	NA
	$[\text{Cu}(\text{SalallylTsc})\text{H}_2\text{O}]^{57}$	1.50 (4.76)	3.00 (9.52)	15	NA
Reference compound	Furacilin	2.34 (11.8)	4.67 (23.58)	2.34 (11.8)	4.67 (23.58)

“NA” means that no activity was measured; MeSalTh – salicylaldehyde *N*(4)-methyl-3-thiosemicarbazone; SalHTh – salicylaldehyde thiosemicarbazone; and allylTsc – *N*(4)-allyl-3-thiosemicarbazone (see Fig. 4).

38.9 times higher than the Furacilin activity used for the prophylaxis and treatment of various infections. Furthermore, the dicopper(II) complexes inhibit the growth and multiplication of G(+) *Bacillus cereus* in the concentration range 0.48–125 $\mu\text{g mL}^{-1}$ (0.57–165.34 μM). The most active complexes being **1**, **7** and **13**. In this case, the complexes **1**, **4**, **6–8**, **13** are 1.2 to 9.7 times more active than Furacilin. Thus, the activity of the complexes against G(+) *Bacillus cereus* depending on the ligand type decreases as follows: $\text{H}_3\text{L}^1 > \text{H}_3\text{L}^2 > \text{H}_3\text{L}^3$ ($-\text{H} > -\text{CH}_3 > -\text{allyl}$). The influence of the anion type from inner and external spheres remains the same as that observed for *S. aureus*. It is important to make a comparison of bioactivity of dicopper(II) bis-thiosemicarbazone complexes described in this work with that of mononuclear copper(II) compounds based on similar mono thiosemicarbazone ligands (Fig. 4). Thus, the dicopper(II) complexes have a stronger activity than the reported mononuclear copper(II) compounds $[\text{Cu}(\text{MeSalTh})\text{Py}]$ based on salicylaldehyde thiosemicarbazones (Fig. 4). Moreover, the dicopper(II) complexes are more active even if $[\text{Cu}(\text{MeSalTh})\text{Py}]$ compounds contain in the inner sphere, pyridine, a ligand well-known to increase the biological activity.⁵⁶ Besides, we have to compare the mononuclear $[\text{Cu}(\text{allylTsc})\text{H}_2\text{O}]^{57}$ complex with the terminal allyl substituent (Fig. 4, SalH₂allylTh ligand) with dicopper(II) complexes based on a similar ligand (H_3L^3). $[\text{Cu}(\text{allylTsc})\text{H}_2\text{O}]$ has a relatively

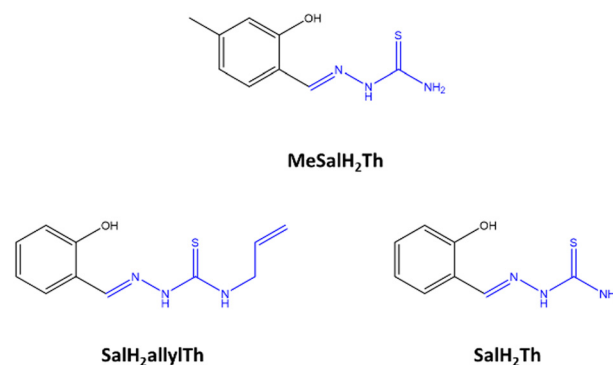


Fig. 4 Drawing of thiosemicarbazone ligands mentioned in Table 3.

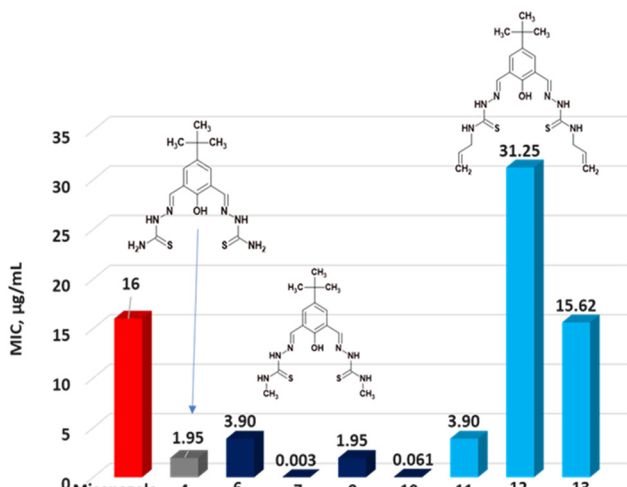
good biological activity compared to the dicopper(II) complexes **11–12** and **14**, but is lower than that of the complex **13**.

On the other hand, it is interesting to compare the biological activity of dicopper(II) complexes with that of bis-thiosemicarbazone-based $[\text{Mo}_2\text{O}_2\text{S}_2]^{2+}$ compounds containing two Mo^{V} metal ions previously reported by our group.⁵⁸ Thus, dicopper(II) complexes containing the H_3L^1 ligand show stronger activity than the $[\text{Mo}_2\text{O}_2\text{S}_2(\text{MeSalTh})_2]^{58}$ complex based on the salicylaldehyde thiosemicarbazone SalH₂Th ligand (Fig. 4). This result shows the importance of the metal ion type on antibacterial activity.

Table 4 Activity of copper bis-thiosemicarbazone complexes against *C. albicans* ATCC 10231

Compound	MIC $\mu\text{g mL}^{-1}$, (μM) <i>Candida albicans</i>	MFC $\mu\text{g mL}^{-1}$ (μM)	MFC/MIC
$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}^{54}$	> 1000	> 1000	—
CuBr_2^{55}	—	—	—
$\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}^{60}$	> 500	> 500	—
$\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}^{54}$	> 1000	> 1000	—
$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}^{55}$	—	—	—
H_3L^1	—	—	—
H_3L^2	—	—	—
H_3L^3	—	—	—
$[\text{Cu}_2\text{L}^1\text{Cl}]$ (1)	—	—	—
$[\text{Cu}_2(\text{HL}^1)\text{OC}_2\text{H}_5]\text{ClO}_4$ (4)	1.95 (2.80)	3.90 (5.61)	2**
$[\text{Cu}_2(\text{L}^1)\text{OC}_2\text{H}_5]$ (5)	—	—	—
$[\text{Cu}_2\text{L}^2\text{Cl}]$ (6)	3.90 (6.19)	15.62 (24.79)	4**
$[\text{Cu}_2\text{L}^2\text{Br}]$ (7)	0.003 (0.003)	0.007 (0.008)	2**
$[\text{Cu}_2(\text{HL}^2)\text{OC}_2\text{H}_5]\text{NO}_3$ (8)	1.95 (3.00)	31.20 (48.09)	16**
$[\text{Cu}_2\text{L}^2\text{OC}_2\text{H}_5]$ (10)	0.061 (0.10)	0.240 (0.42)	4**
$[\text{Cu}_2\text{L}^3\text{Cl}]$ (11)	3.90 (5.42)	15.62 (21.74)	4**
$[\text{Cu}_2\text{L}^3\text{Br}]$ (12)	31.25 (35)	250.00 (282)	8**
$[\text{Cu}_2(\text{HL}^3)\text{OC}_2\text{H}_5]\text{NO}_3$ (13)	15.62 (21.68)	500.00 (694)	32***
$[\text{Cu}(\text{allylTsc})\text{H}_2\text{O}]^{57}$	7.00 (22)	60.00 (190)	9**
$[\text{Mo}_2\text{O}_2\text{S}_2(\text{SalHTh})_2]^{58}$	250.0 (330)	250.0 (330)	—
Miconazole	16 (38.46)	16 (38.46)	1*

MIC – minimum inhibiting concentration ($\mu\text{g mL}^{-1}$); MFC – minimum fungicidal concentration; * – fungicide; ** – fungistatic; *** – resistant. If $\text{MFC/MIC} < 2$: fungicidal activity; $\text{MFC/MIC} > 2$: fungistatic activity; and $\text{MFC/MIC} \geq 32$ fungus resistant to compound's action.

**Fig. 5** Inhibition activity of copper (ii) compounds against *Candida albicans*.

The antifungal activity against *Candida albicans* is shown in Table 4 and in the histograms of Fig. 5. Through the method of successive dilutions, it was established that the free bis-thiosemicarbazone H_3L^{1-3} ligands did not show antifungal activity. The coordination of these ligands to the copper(II) ion give mostly fungicidal and fungistatic dicopper(II) complexes. The Cu(II) salts do not possess any significant activities.

Once again, the best antifungal activities against *Candida albicans* were observed for dicopper(II) complexes containing the methyl group as the terminal substituent on the bis-thiosemicarbazone ligand. A lower activity is observed for the

complexes with allyl as the terminal group on the ligand. By comparing the MIC (minimum inhibitory concentration) and MFC (minimum fungicidal concentration) values, we can determine the fungicidal activity (FA) of the compounds (see Table 4). If $\text{MFC/MIC} < 2$, we speak of fungicidal; for $\text{MFC/MIC} > 2$, we speak of a fungistatic compound and if $\text{MFC/MIC} \geq 32$ we speak of a resistant compound. These classes are given in Table 4.

Mostly dicopper(II) complexes have stronger antifungal activity than the $[\text{Cu}(\text{allylTsc})\text{H}_2\text{O}]^{57}$ complex reported in the literature. Besides, the $[\text{Mo}_2\text{O}_2\text{S}_2(\text{SalHTh})_2]^{58}$ complex based on salicylaldehyde thiosemicarbazone ligand reported by our group in a previous work⁵⁸ has a very weak activity compared to dicopper(II) complexes. The structure–antifungal activity relationship of dicopper(II) complexes appears to be influenced by

Table 5 Antioxidant activities of bis-thiosemicarbazone ligands

Product	Structure	IC_{50} (μM)	TEAC^a
H_3L^1		20.31 ± 1.69	1.29
H_3L^2		4.83 ± 0.45	5.44
H_3L^3		51.13 ± 0.48	0.51
Trolox		26.30 ± 0.70	1
Rutin		20.7 ± 0.12	1.27

^a TEAC = ratio of the activity of Trolox to the activity of a ligand; $\text{TEAC} = 1$ means similar activity; $\text{TEAC} > 1$ means “more active than Trolox”; and $\text{TEAC} < 1$ means “less active than Trolox”.

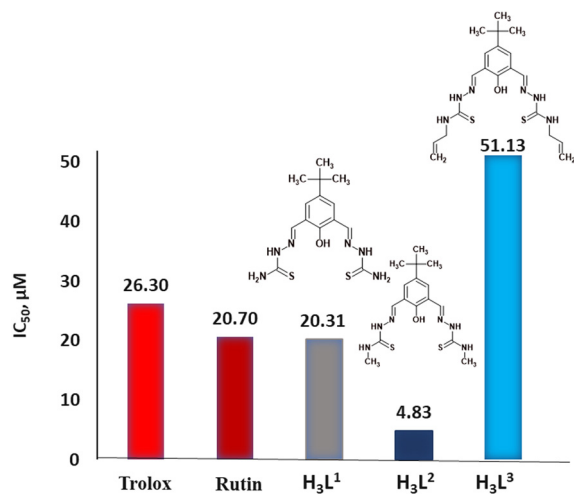
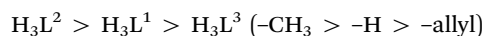


Fig. 6 Antioxidant activities (ABTS) of ligands H₃L¹⁻³ in comparison with TROLOX and RUTIN references.

- The nature of the ligand



- The nature of the anion in the inner sphere:



In vitro antioxidant tests

Free radicals are secondary chemical compounds involved in various vital biological processes in the human body. Free radicals can lead to cancer, stroke, diabetes, heart attack, and Alzheimer's or Parkinson's disease.⁶¹⁻⁶⁶ Therefore, the investigation of the antioxidant activity of dicopper(II) complexes and the thiosemicarbazone ligands is of interest. The mononuclear copper complexes reported in the literature have lower antioxidant activity than the free ligands.^{26,45,67} The antioxidant study using the ABTS method of dicopper(II) complexes revealed a lack of antioxidant activity. Conversely, the bis (thiosemicarbazones) ligands alone show an interesting antioxidant activity (Table 5 and Fig. 6), which decreases as follows: H₃L² > H₃L¹ > H₃L³ (-CH₃ > -H > -allyl). The terminal allyl ligand with IC₅₀ of 51.13 μM is less active than the Rutin and Trolox references with values of 20.7 μM and 26.30 μM, respectively. The antioxidant activity of the ligands and their lack of dicopper(II) complexes can be explained by the blocking through coordination of some functional groups involved in the redox processes.

Conclusions

15 dicopper(II) complexes based on N⁴-bis-thiosemicarbazone ligands were synthesized and characterized by elemental analysis, FT-IR, and MALDI-TOF experiments. 6 of them were characterized by X-ray diffraction, showing an influence of

the nature of the salts on the nature of the bridging external ligands and the protonation state of the ligands. The solid molecular structures of dicopper(II) complexes show a variety of coordination modes: the bis-thiosemicarbazone ligands can act as thiol-thiol, thiol-thione and thione-thione forms, the anions being either counter-anions or ligands and the dicopper(II) complexes being either connected or not connected to their neighbouring complex.

The biological activity of dicopper(II) complexes is influenced by the N⁴-substituent and anion type. The dicopper(II) complexes exhibit antimicrobial and antifungal activity, unlike bis-thiosemicarbazones, which do not show any activity. The activity of dicopper(II) complexes is 1.2 to 38.9 times higher than that of Furacilin, currently used as an antibacterial drug. The [Cu₂L²Br] (7) complex shows the best antifungal activity, 5000 times higher than that of antifungal drug Miconazole. The bis(thiosemicarbazone) ligands revealed excellent as antioxidants, while the corresponding copper(II) complexes do not exhibit any antioxidative activity. Most likely the ligand coordination led to the blocking of the groups involved in the free radical neutralization mechanism.

Author contributions

Dr Diana Cebotari: synthesis and characterization and writing of the manuscript; Dr Sergiu Calancea: characterization of complexes; Dr Jérôme Marrot and Dr Sergiu Shova: X-ray diffraction studies; Dr Vincent Guérineau and Dr David Touboul: MALDI-TOF experiments; Dr Olga Garbuz, Dr Greta Balan, and Dr Victor Tsapkov: biological tests; and Prof. Dr Aurelian Gulea and Prof. Dr Sébastien Floquet: supervision of the work, funding acquisition and writing of the manuscript.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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