STUDIA UNIVERSITATIS MOLDAVIAE, 2020, nr.6(136)
Seria "Științe reale și ale naturii" ISSN 1814-3237 ISSN online 1857-498X p.101-112

CZU: 547.497:542.913 **DOI: http://doi.org/10.5281/zenodo.4431691**

SYNTHESIS AND CHARACTERISATIONS OF SIX NEW BIS-THIOSEMICARBAZONE LIGANDS

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Six new bis-thiosemicarbazones ligands were synthesized with rigid or flexible organic chemical links between the two thiosemicarbazones moieties. Such ligands have been designed for the synthesis of polymetallic coordination complexes. They were synthesised by the condensation reaction between aldehydes and substituted thiosemicarbazides in alcohol, using acetic acid as a catalyst. To determine the composition, the products were characterised by ^{1}H, ^{13}C and ^{15}N nuclear magnetic resonance, mass spectrometry and elemental analysis.

Keywords: *bis-thiosemicarbazone, synthesis methods, NMR characterisation, polymetallic complexes.*

SINTEZA ȘI CARACTERIZAREA A ȘASE NOI LIGANZI BIS-TIOSEMICARBAZONICI

Au fost sintetizați șase noi liganzi bis-tiosemicarbazonici cu legături organice rigide sau flexibile între cele două fracțiuni tiosemaicarbazonice. Astfel de liganzi au fost proiectați pentru sinteza complecșilor de coordonare polimetalică. Ei au fost obținuți prin reacția de condensare dintre aldehide și tiosemicarbazide substituite, în mediul alcoolic, folosind acidul acetic în calitate de catalizator. Pentru determinarea compoziției și purității, produșii au fost caracterizați cu ajutorul ^{1}H, ^{13}C și ^{15}N rezonanță magnetică nucleară, spectroscopia de masă și analiza elementală.

Cuvinte-cheie: *bis-tiosemicarbazone, metode de sinteză, caracterizarea RMN, compuși polimetalici.*

INTRODUCTION

The thiosemicarbazone derivatives represent an important class of basic Schiff ligands with application in various fields, especially when associated with transition metals [1–3]. In coordination chemistry, the thiosemicarbazone ligands coordinate metals with sulphur, nitrogen and/or oxygen donor atoms for giving a very wide family of complexes exhibiting a considerable interest because of their magnetic [4,5], catalytic [6], analytical [1], biological and medicinal properties [7–9]. Among these properties, the biological properties are by far the most studied and thiosemicarbazone complexes display a very large plan of properties including their antibacterial, antitumor, antimalarial, antitrypanosomal, antiviral and antifungal properties. In the Republic of Moldova, the pioneer of thiosemicarbzone coordination chemistry was the young scientist, who later became an academician of the ASM, Antonie Ablov [2]. Since the first work published in 1953, some thousands of thiosemicarbazone complexes have been reported in the literature and this work is still under development worldwide, thus demonstrating the interest towards such class of ligands.

Some experimental evidence has supported the relationship between the chemical structures and biological activities of (N)-heterocyclic thiosemicarbazones and their metal compounds [3]. Experimental results have shown that changes in the ligand backbone can significantly alter the biological activity of thiosemicarbazones as ligands and complexes[10]. Among this very wide family of ligands, the bis-thiosemicarbazones ligands offer the possibility to get polymetallic coordination complexes. These ligands possess two branches of thiosemicarbazide derivatives, allowing to accommodate two or more metals, and lead to complexes with improved biological properties[11,12]. The aim of this study was thus to investigate the synthesis of new ligands of this type for developing new classes of coordination compounds with 3d and 4d metals. The properties and the activity of coordinating complexes depending on the nature of the bis-thiosemicarbazone ligands used in the synthesis, a family rich of 6 new bisthiosemicarbazone ligands have been developed by varying the nature of the chemical link between the two thiosemicarbazide moieties (rigid or flexible) and the nature of substituents on linker or on the terminal amino groups. In connection with this, the aim of this paper is to find the synthesis conditions and to stabilise the composition of the new rigid or flexible ligands for polymetallic syntheses. A particular attention is also paid to the NMR and ESI-MS characterisations of the ligands, notably by ^{15}N NMR, which remains rarely used in this domain so far.

RESULTS AND DISCUSSIONS

Syntheses

The synthesis of some substituted bis-thiosemicarbazones is already described in the literature [13]. Nevertheless, the compounds obtained by condensing 5-tert-butylbenzene-1,3-dicarbaldehyde or 2,2 '- [butane-1,4-

diylbis (oxy)]dibenzaldehyde with substituted thiosemicarbazides are poorly known. In this study, these two aldehydes will constitute our two chemical linkers for designing bis thiosemicarbazone ligands, the first one being rigid, while the second offers some flexibility and increased solubility properties in solvents as alcohols for instance. The synthetic protocols are given in the experimental part.

The first ligand, **bis-(4-methyl-3-thiosemicarbazone) of isophthalaldehyde**, noted hereafter **H_2L^1** was obtained with a good yield (see experimental section) by condensing isophtalaldehyde with 4-methyl-3-thiosemicarbazone, in a 1:2 molar ratio, in alcoholic solution, see Fig.1.

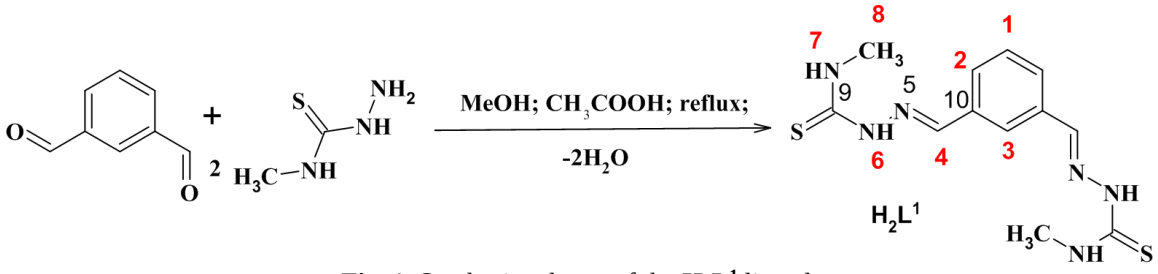


Fig. 1. Synthesis scheme of the **H_2L^1** ligand.

The carbonyl compounds used for the syntheses of **H_2L^2-H_2L^6** ligands were prepared using different precursors. 5-Tert-butylbenzene-1,3-dicarbaldehyde was synthesized in 2 steps, as shown in Fig.2. 5-Tert-butylisophthalic acid was used as a precursor, which was reduced to (5-(tert-butyl)-1,3-phenylene)-dimethanol with sodium borohydride and $BF_3 \cdot OEt_2$. In the second step, MnO_2 was used as the oxidant and the alcohol was oxidised to the carbonyl compound.

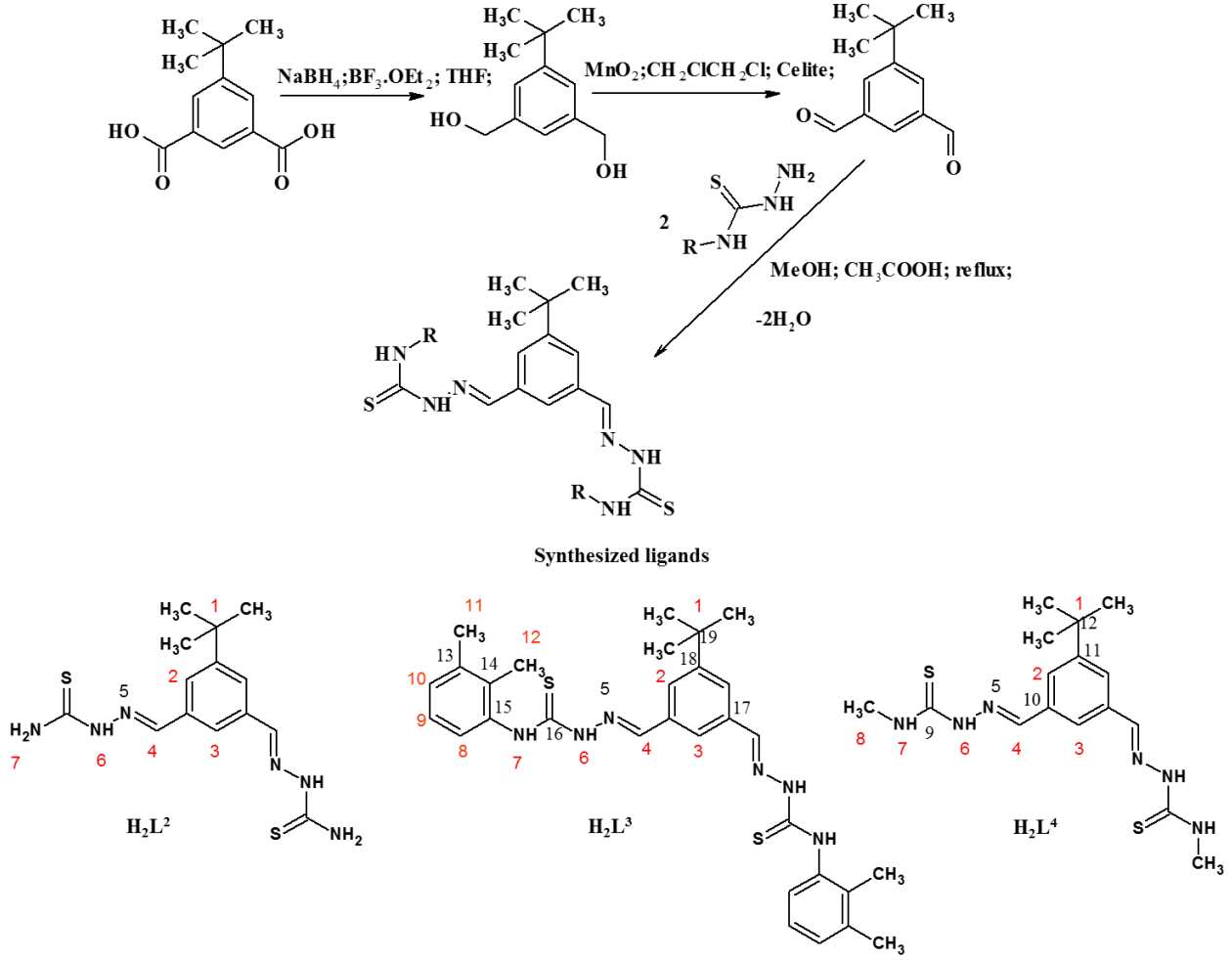


Fig.2. Synthesis scheme of the **H_2L^{2-4}** ligands.

For the synthesis of 2,2 '-[butane-1,4-diylbis(oxy)]dibenzaldehyde, salicylaldehyde was used as a precursor, as shown in Fig.3. As a result of the interaction with 1,4-dibromobutane we obtain dibenzaldehyde, containing a flexible etheric bridge.

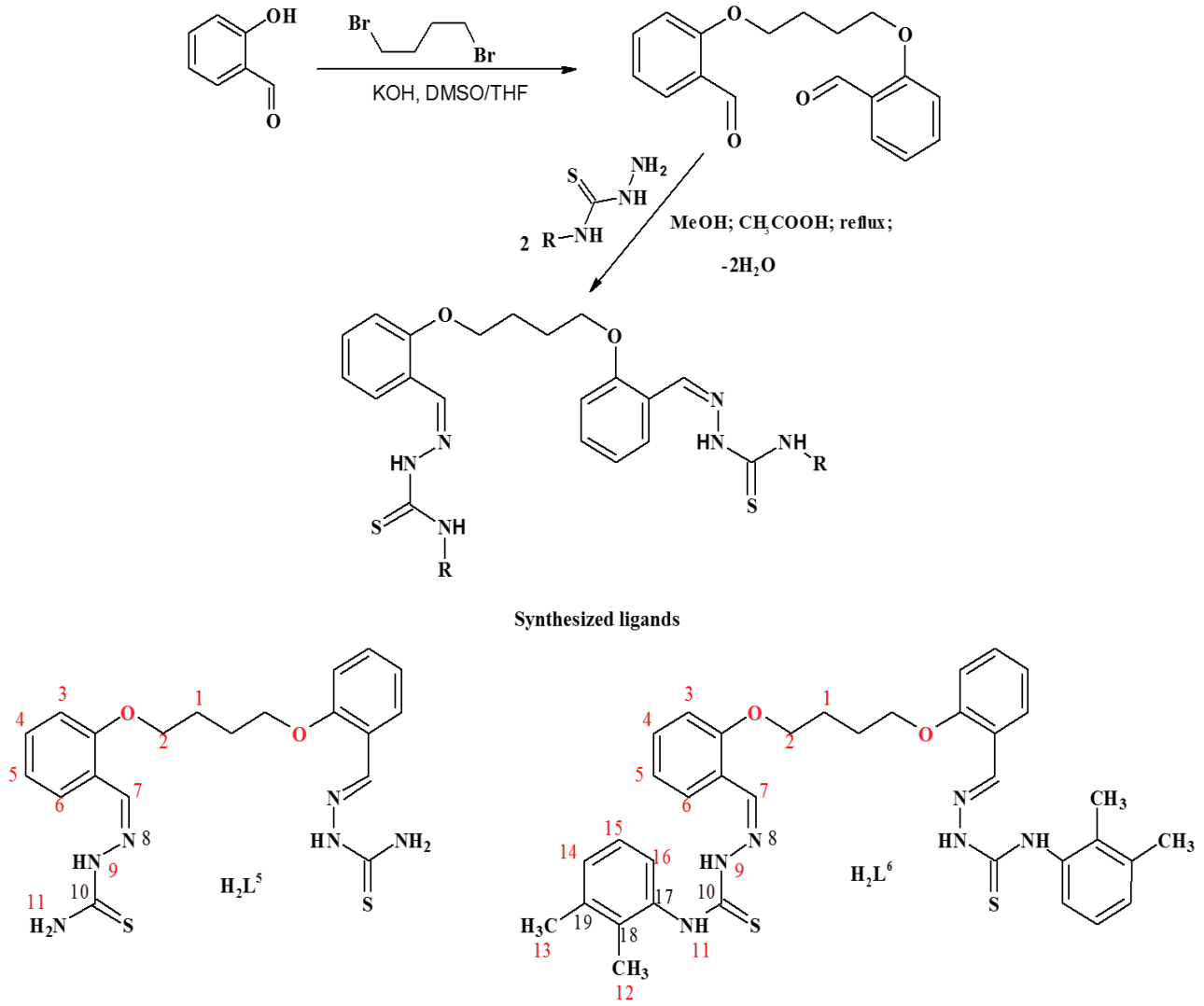


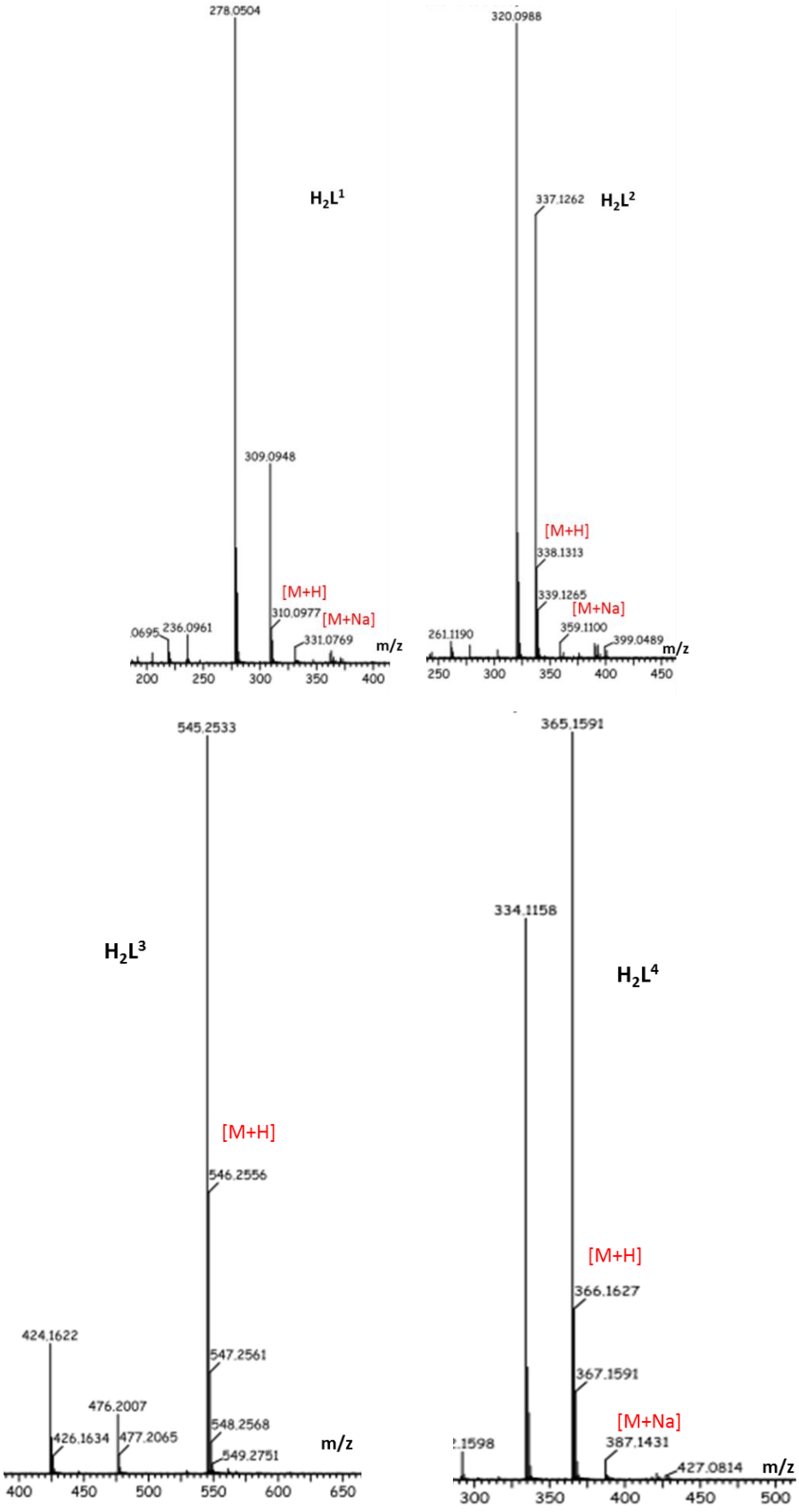
Fig.3. Synthesis scheme of the H_2L^{5-6} ligands.

The six new ligands are isolated as solids with good yields (see experimental section for further details) and were characterized by FT-IR (ATR Diamond), Elemental analysis, ESI-MS and NMR (^1H, ^{13}C and ^{15}N). The results of FT-IR and elemental analysis are given in the experimental section, while ESI-MS and NMR studies are discussed below.

Mass spectroscopy analysis

Mass spectrometry is a destructive method, which allows both to access the measurement of the molecular mass of a substance as well as to obtain structural data: the ionized substance is in an excited state which causes its fragmentation. The analysis of these fragments informs about the structure of the molecule. Each of the ions formed is characterized by its mass/charge ratio (m / z) and the device is able to separate these ions (by a magnetic field) and to detect/characterize them (qualitatively and quantitatively).

The six ligands were first analysed by ESI-MS in positive mode in CH_3CN (10^{-4} M). The corresponding spectra are depicted in Figure 4, while results are gathered in Table 1.


278.0504
H_2L^1
309.0948
[M+H]
310.0977
[M+Na]
236.0961
331.0769
m/z
200 250 300 350 400
320.0988
337.1262
H_2L^2
[M+H]
338.1313
339.1265
[M+Na]
359.1100
399.0489
261.1190
m/z
250 300 350 400 450
545.2533
H_2L^3
[M+H]
546.2556
424.1622
547.2561
476.2007
426.1634
477.2065
548.2568
549.2751
m/z
400 450 500 550 600 650
365.1591
334.1158
H_2L^4
[M+H]
366.1627
367.1591
[M+Na]
387.1431
427.0814
m/z
300 350 400 450 500

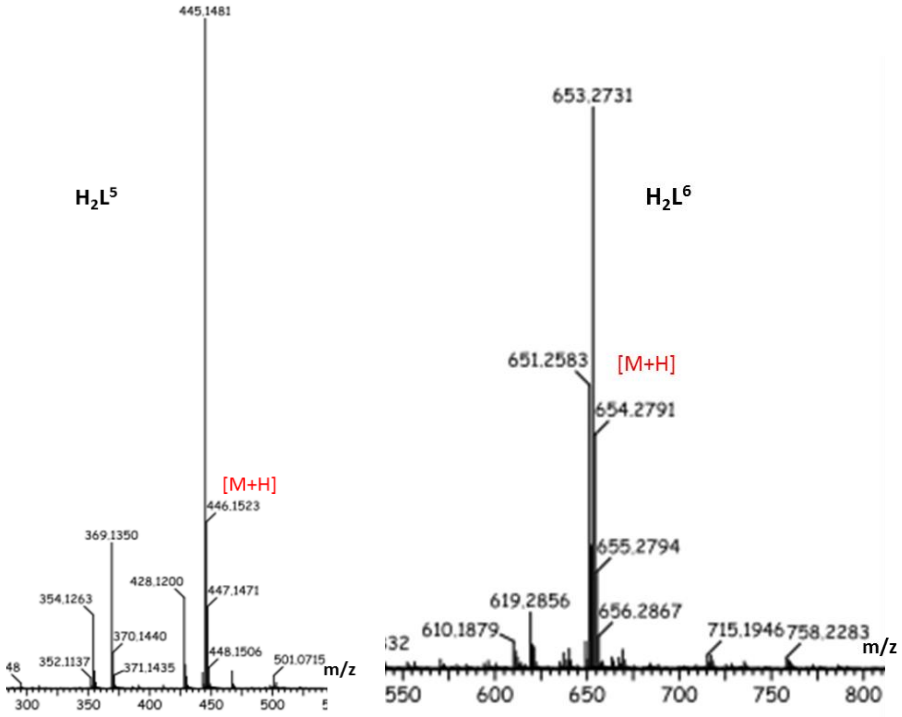


Fig.4. Mass spectroscopy analysis of the H_2L^{1-6} ligands.

Table 1

Summarised ESI-MS data

Compounds	Exp. m/z	Assignments	Calc. m/z
H_2L^1	310.09	$[C_{12}H_{16}N_6S_2]+H^+$	309.44
H_2L^2	338.13	$[C_{14}H_{20}N_6S_2]+H^+$	337.49
H_2L^3	546.26	$[C_{30}H_{36}N_6S_2]+H^+$	545.80
H_2L^4	366.16	$[C_{16}H_{24}N_6S_2]+H^+$	365.54
H_2L^5	446.15	$[C_{20}H_{24}N_6O_2S_2]+H^+$	445.59
H_2L^6	654.28	$[C_{36}H_{40}N_6O_2S_2]\ H^+$	653.89

As shown in Figure 4 and in the Table 1, the peaks attributed to the ligands are detected as major species associated with one proton (noted $[M+H]^+$) or one sodium cation (noted $[M+Na]^+$) to give positive species. It demonstrates unambiguously the formation of the expected ligands. Besides, as expected with this technique, some degradation compounds are also detected, still in full agreement with the expected formula of the ligands. For instance, in the case of H_2L^1 and H_2L^4, the peak detected at m/z lower than that assigned to $[M+H]^+$ species correspond to the loss of the two methyl groups of the terminal amine functions or to one aminomethyl fragment; for H_2L^2, the lower peak can be assigned to $[M+H]^+$ with the loss of one terminal amine functions; or for H_2L^3, the m/z loss of 122 can be assigned to the loss of one aromatic group with the amine of one thiosemicarbazide branch of the ligand.

NMR Studies

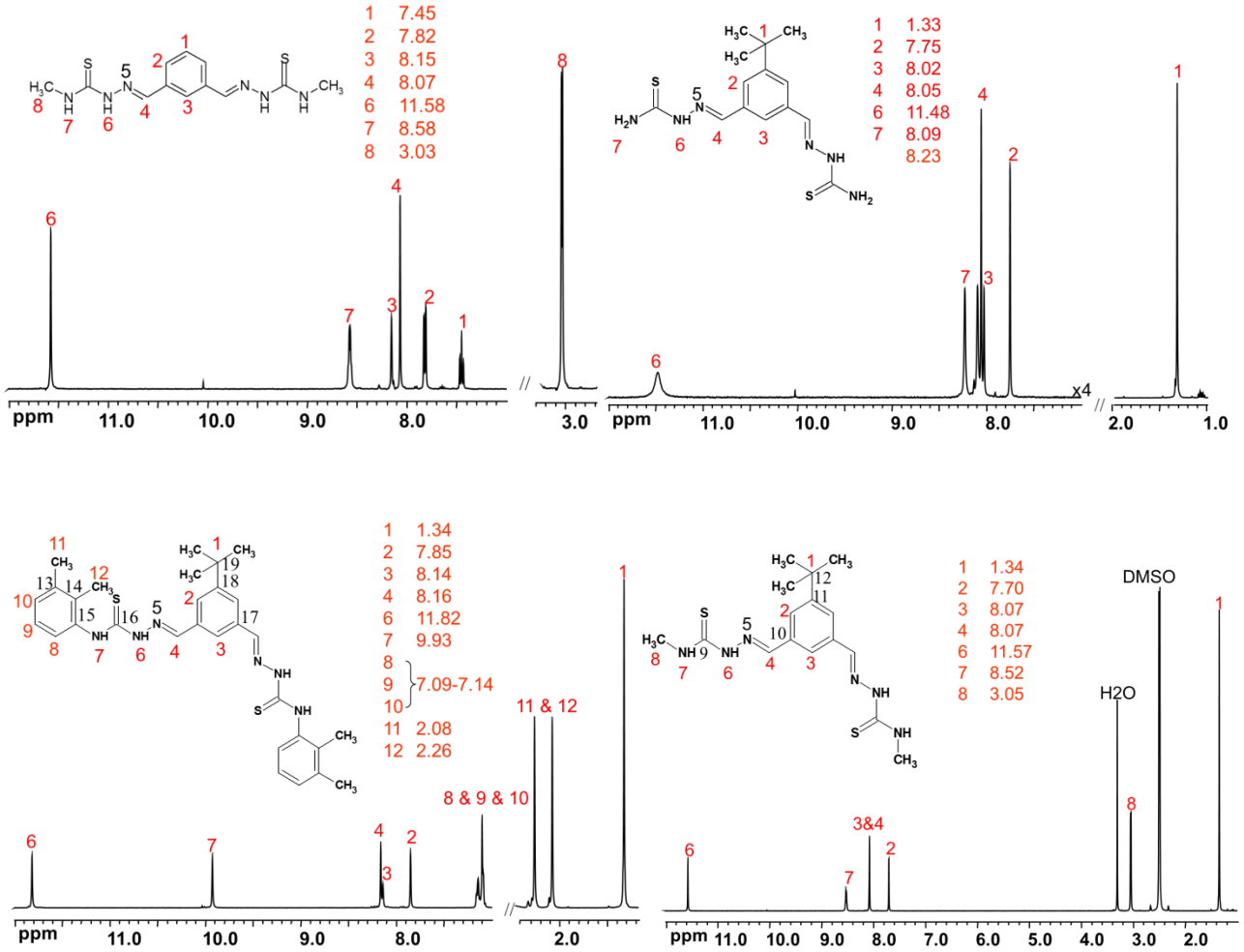
The NMR technique is a powerful technique for characterisation of ligands and complexes in solution. For thiosemicarbazone ligands, ^1H and ^{13}C are usual NMR probes but, to our knowledge, ^{15}N NMR spectra are rarely recorded. The six ligands synthetised in this paper were studied by the three techniques. The resulting spectra are displayed in Figures 5-7 while the chemical shifts of each ligands are summarized in Table 2.

The ^1H and ^{13}C NMR spectra (Figures 5 and 6, respectively) are in perfect agreement with spectra reported in the literature for many other thiosemicarbazone ligands [14]. The assignments and the chemical shifts are gathered in Table 2.

According to the results obtained in the case of ^{1}H NMR, it was established that the most shielded are the alkyl groups. All proton signals that appear in the left spectrum of DMF-d7 or DMSO–d6 refer to less and less shielded protons, whose absorption takes place at lower and lower frequencies and magnetic field values of weak intensity. Therefore, the least shielded is proton 6 in case of **H_2L^{1-4}** and proton 9 in case of **H_2L^{5-6}**. In the case of ^{13}C, the least shielded is the carbon from the C = S group, which has a chemical displacement between 179.0-177.69 ppm. These spectra display only signals expected for the ligands with sometimes only traces of solvents. Therefore, we can conclude that our six ligands have been isolated with a good or very good purity.

In addition, we decided to investigate the ^{15}N NMR, which is much less common. The recording of a direct ^{15}N NMR spectrum is not trivial. To reach to goal, we used HMBC (Heteronuclear Multiple Bond Correlation) experiment which gives correlations between nitrogen and protons that are separated by two, three, and, sometimes in conjugated systems, four bonds. Direct one-bond correlations are suppressed. This method allows obtaining information about the N atoms in a reasonable acquisition time and this information will be very informative when the coordination complexes will be formed, especially if we are not able to get structural data. In this case, the ^{15}N NMR data will permit to evidence the N atoms coordinated to the metal. This 2D experiment gives connectivity information much like a proton-proton COSY. Using this, we identified the peaks corresponding to each nitrogen atom and their chemical displacements. As shown in Figure 7, the ^{15}N NMR spectra are in the wide range -300 to -50 ppm and the three types of the N atoms of the thiosemicarbazides moieties are well defined and perfectly identified thanks to the correlation with the proton NMR spectra. The terminal amino groups are found in the range -251 to -274 ppm, while the N imino atom are found in -58 to -63 ppm range. The thioamido N atom is found in -205 to -208 ppm range, accordingly to its closer chemical proximity with the terminal thioamido N atoms (see Table 2).

The ^{15}N confirms once again the good purity of the 6 new ligands studied here.



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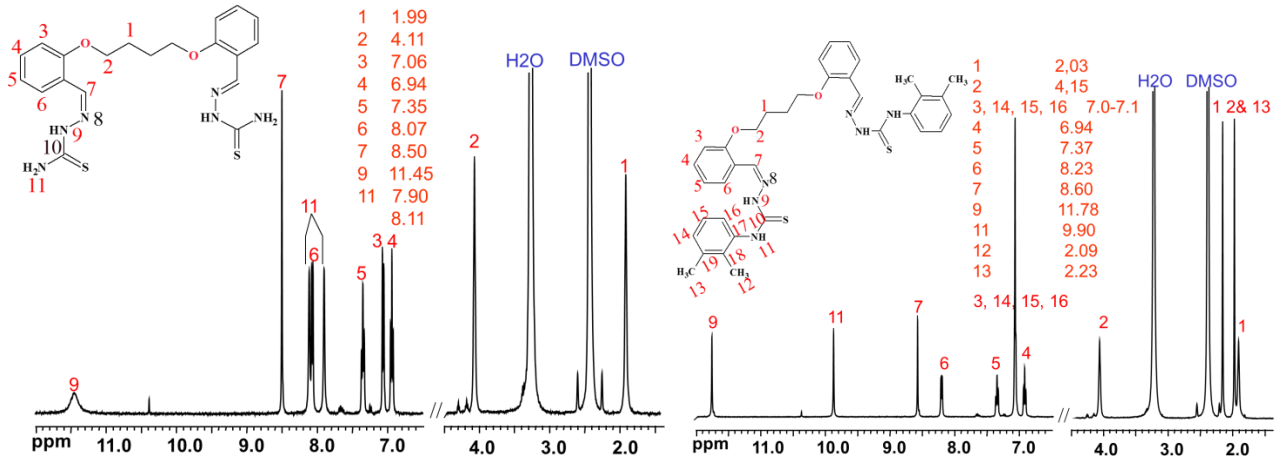
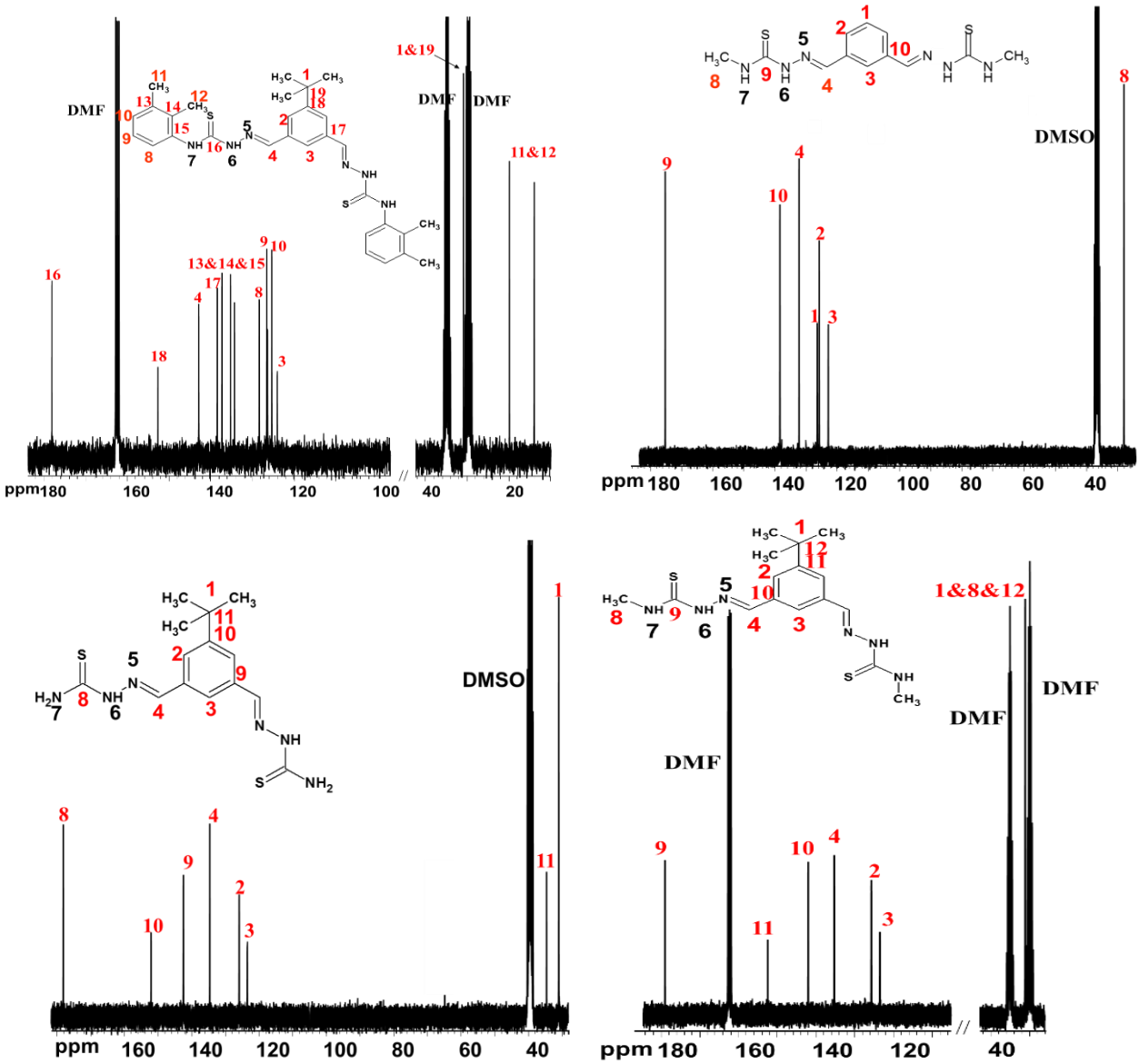


Fig.5. ^{1}H NMR, δ ppm (400 MHz/DMSO-d_6) spectra of the synthesized ligand (**H_2L^{1-6}**).



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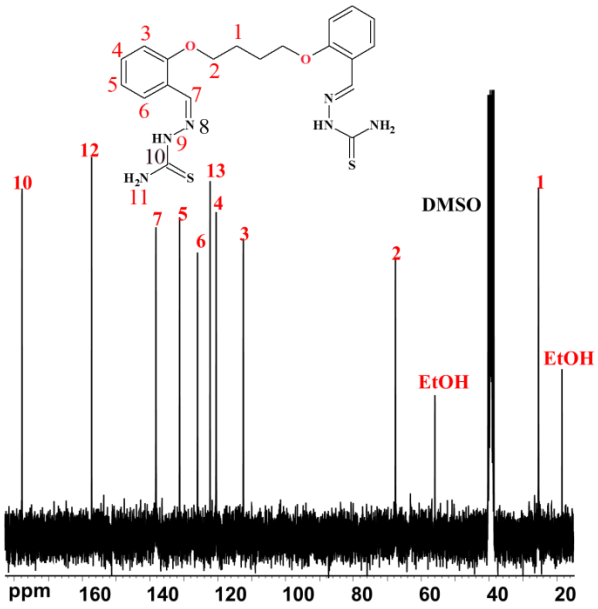
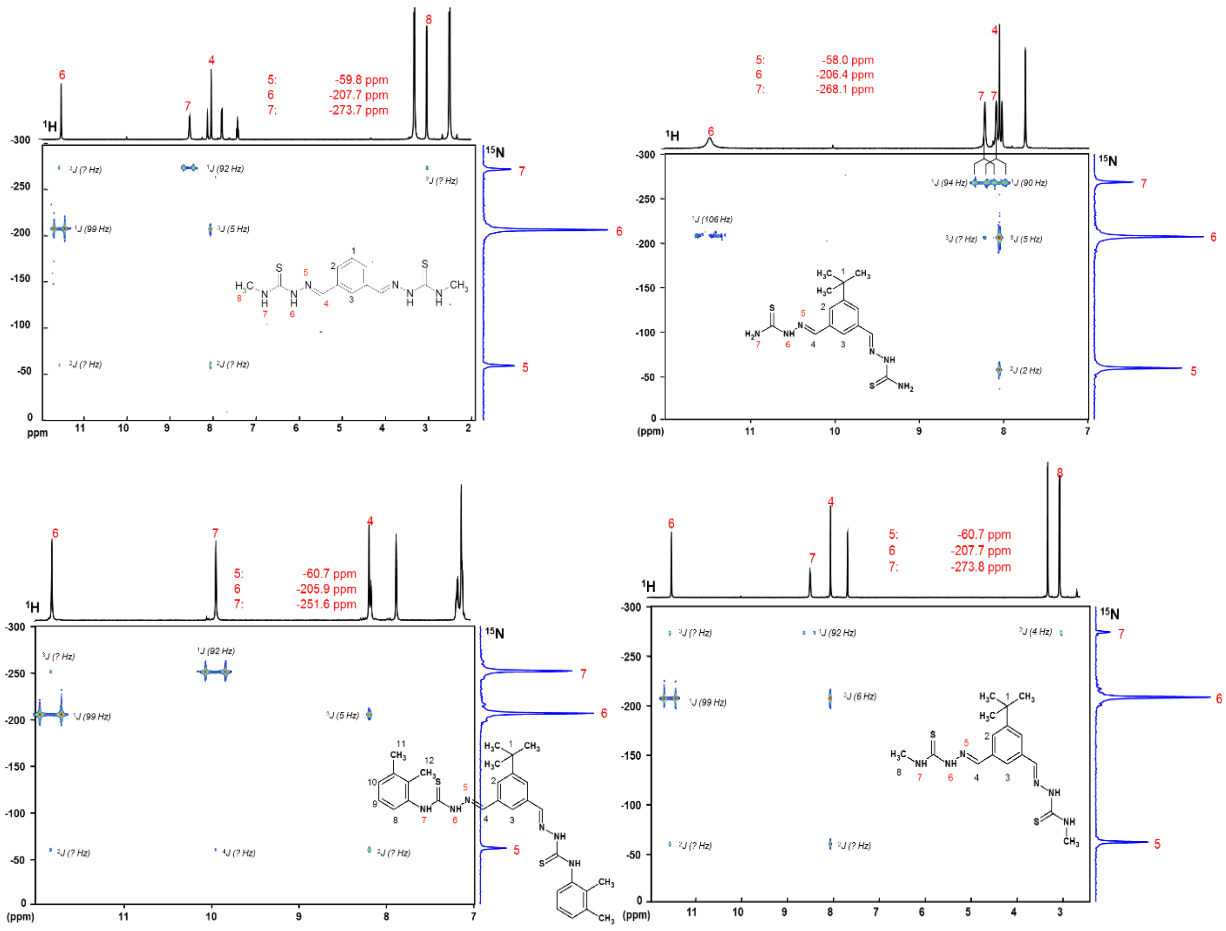


Fig.6. ^{13}C NMR, δ ppm (DMSO-d6 or DMF-d7) spectra of the synthesized ligand (**H_2L^{1-5}**).



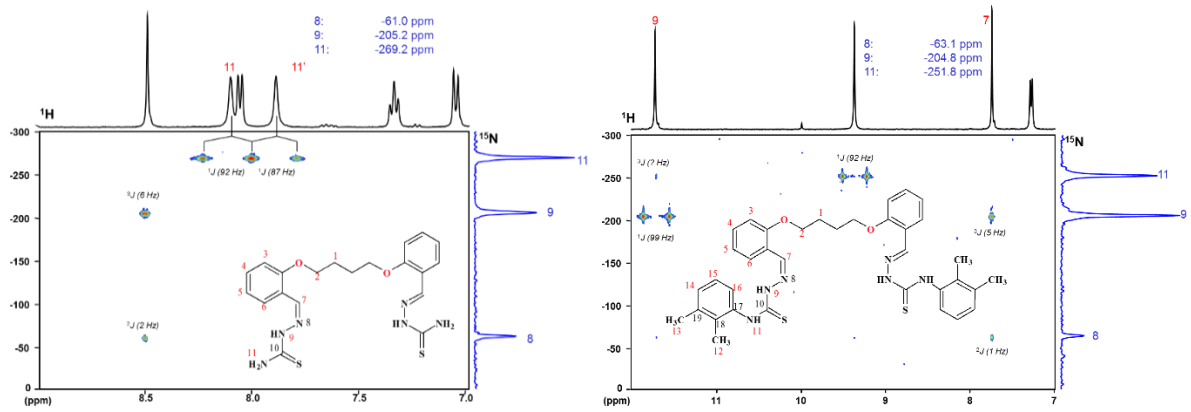


Fig.7. ^{1}H {^{15}N} HMBC NMR correlation of H_2L^{1-6} ligands, δ ppm (DMSO-d6).

Table 2

^{1}H, ^{13}C and ^{15}N NMR chemical shifts of H_2L^{1-6} in DMSO-d6 or DMF-d7(*)

Experiment	Compounds	Main Chemical shifts/ppm
^{1}H	H_2L^1	11.58(s, 2H); 8.58(m, 2H); 8.15(s, 1H); 8.07(s, 2H); 7.82(d, 2H); 7.45(t, 1H); 3.03 (d, 6H)
	H_2L^2	11.48(s, 2H); 8.23(s, 2H); 8.09-8.02(m, 5H); 7.75(s, 2H); 1.33 (s, 9H)
	H_2L^3	11.82(s, 2H); 9.93(s, 2H); 8.16(s, 2H); 8.14(s, 1H); 7.85(s, 2H); 7.09-7.14(m 6H); 2.26(s, 6H); 2.08(s, 6H); 1.31(s, 9H)
	H_2L^4	11.57(s, 2H); 8.52(m, 2H); 8.07(s, 2H); 8.07(s, 1H); 7.70(s 2H); 3.05(d, 6H); 1.34 (s, 9H)
	H_2L^5	11.45(s, 2H); 8.50(s, 2H); 8.11/7.90(s, 4H); 8.07(d, 2H); 7.35(t,2H) 7.06(d, 2H); 6.94(t, 2H); 4.11(s, 4H); 1.99 (s, 4H)
	H_2L^6	11.78(s, 2H); 9.90(s,2H); 8.60(s, 2H); 8.23(d, 2H); 7.37(t, 2H); 7.00-7.10(m, 8H); 6.94(t, 2H); 4.15(s, 4H); 2.23(s, 6H); 2.09(s, 6H); 2.03(s, 4H)
^{13}C	H_2L^1	177.70; 140.94; 134.79; 128.96; 128.33; 125.42; 30.82.
	H_2L^2	177.86; 151.79; 142.10; 134.40; 125.65; 123.24; 34.65; 31.00.
	H_2L^{3*}	178.06; 152.46; 142.86; 138.39; 137.23; 135.24; 134.27; 128.31; 126.53; 125.29; 124.00; 30.92; 19.91; 13.90.
	H_2L^{4*}	179.00; 152.50; 142.07; 135.31; 125.70; 123.50; 30.90.
	H_2L^5	177.69; 157.17; 138.22; 131.25; 125.97; 122.26; 120.47; 112.46; 67.64; 25.47.
^{15}N	H_2L^1	-273.7; -207.7; -59.8.
	H_2L^2	-268.1; -206.4; -58.0.
	H_2L^3	-251.6; -205.9; -60,7.
	H_2L^4	-273.8; -207.7; -60.7.
	H_2L^5	-269.2; -205.2; -61.0.
	H_2L^6	-251.8; -204.8; -63.1.

Experimental Part

Fourier Transform Infrared (FT-IR) spectra were recorded on a 6700 FT-IR Nicolet spectrophotometer, using diamond ATR technique. The spectra were recorded on non-diluted compounds and ATR correction was applied.

Elementary analyses were performed by BioCIS laboratory at Chatenay-Malabry, France. Analyses of synthesized ligands were performed on a PERKIN ELMER 2400 apparatus, a proven instrument for the rapid determination of the carbon, hydrogen, nitrogen, sulphur or oxygen content in organic and other types of materials. Based on the classical Pregl-Dumas method, samples are combusted in a pure oxygen environment, with the resultant combustion gases measured in an automated fashion.

Electrospray Ionization Mass Spectrometry (ESI-MS) spectra were collected using a Q-TOF instrument supplied by WATERS. Samples were solubilised in water at a concentration of 10^{-4} M and were introduced into the spectrometer via an ACQUITY UPLC WATERS system whilst a Leucine Enkephalin solution was co-injected via a micro pump as internal standard.

Nuclear magnetic resonance (NMR) solution spectra were recorded at 298 K. ^{1}H and ^{15}N NMR spectra were measured with a Bruker Avance 400 MHz spectrometer equipped with a 5mm BBI probe head and operated at a magnetic field strength of 9.4 T. DMSO-d_6 or DMF-d_7 were used as deuterated solvent. Typically, ^{1}H spectra were recorded with one pulse sequence at 30° flip angle (pulse duration 2.7 μs), using 10 s recycle delay, 1.6 s acquisition time, and 8 number of scans. 2D $^{1}H\{^{15}N\}$ HMBC spectra were carried out on all samples using standard Bruker pulse sequences. The recycle period was shortened to 2 s, and a mixing time of 50 ms corresponding to $1/2J_{H\text{-}N}$ ($J_{H\text{-}N}$ = 10 Hz) was employed. The ^{13}C NMR spectra were obtained with a Bruker Avance 300 MHz spectrometer equipped with a 5mm BBI probe head. DMSO-d_6 or DMF-d_7 were used as deuterated solvents and number of scans ranging from 2000 to 66000. Chemical shifts are reported relative to 1% Me_4Si in $CDCl_3$ for both ^{1}H and ^{13}C, and neat $MeNO_2$ for ^{15}N, according to conventional standards.

MATERIALS AND METHODS

All reagents and solvents were of the highest quality available from commercial sources. The reagents, 5-tert-butylisophthalic acid, thiosemicarbazide, 4-methyl-3-thiosemicarbazide, isophthalaldehyde, 5-(tert-butyl)isophthalaldehyde, tetrahydrofuran, $BF_3{\cdot}OEt_2$, sodium hydrogen carbonate, anhydrous sodium sulphate, MnO_2, dichloromethane, 1,2-dichroloethane, hexane, methanol, ethanol, acetic acid, AcOEt, DMSO, Celite, SiO_2 were obtained from Sigma-Aldrich. The 4-(2,3-dimethylphenyl)-3-thiosemicarbazide was synthesized according to the method reported in literature [14] .

1. *Synthesis of (5-(tert-Butyl)-1,3-phenylene)-dimethanol* [15]

To tetrahydrofuran (THF) (50 mL), 5-tert-butylisophthalic acid (2.22 g, 10.0 mmol) and sodium borohydride (1.17 g, 30.9 mmol) were added. To this suspension, $BF_3.OEt_2$ (3.70 mL, 30.0 mmol) was gradually added at 0° C., followed by stirring at room temperature for 23 hours. The reaction was quenched by adding water, followed by extraction with ethyl acetate. The obtained organic layer was washed with 1 M aqueous hydrochloric acid and saturated aqueous sodium hydrogen carbonate in this order, and dried over anhydrous sodium sulphate. The solvent was evaporated, and then the obtained crude product was purified by flash column chromatography (CH_2Cl_2/MeOH=30/1 to 20/1) to obtain the target product as a colourless solid in a yield of 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 2H, Ar), 7.20 (s, 1H, Ar), 4.70 (s, 4H, CH_2), 1.33 (s, 9H, CH_3).

2. *Synthesis of 5-(tert-Butyl)isophthalaldehyde* [16]

To a suspension of MnO_2 (2.76 g, 31.8 mmol) in 1,2-dichroloethane (11 mL) was added (5-(tert-butyl)-1,3-phenylene)dimethanol (617.2 mg, 3.18 mmol). The reaction mixture was refluxed for 3 h. After being cooled to room temperature, the reaction mixture was filtered through Celite and washed with AcOEt. The filtrate was concentrated in vacuo, and the residue was purified by SiO_2 column chromatography (hexane/AcOEt=3/1) to give the product (470.0 mg, 78%) as colourless solid. ^{1}H NMR (300 MHz $CDCl_3$): δ=10.1 (s, 2H), 8.19 (s, 3H), 1.41 ppm (s, 9H).

3. *Synthesis of 2,2 '-[butane-1,4-diylbis(oxy)]dibenzaldehyde* [17]

10,45 mL of salicylaldehyde (100 mmol), 6,72 g of KOH (120 mmol), 25 mL THF, and 5 mL DMSO was refluxed for 30 min. continuous stirring. A solution of 50 mmol of 1,4-dibromobutan (10,8 g or 5,93 mL) was dissolved in 5 mL of THF/DMSO (9:1) and added slowly to the reaction mixture. After the addition, the mixture was kept under reflux for 16 h. After completion of the reaction, the resulting mixture was cooled to room temperature and washed with 125 cm^3 water. The pale-yellow precipitate was filtered off and recrystallised in ethanol to afford pure products (yield: 80%).

4. *Synthesis of bis-(thiosemicarbazones) of 5-(tert-Butyl)isophthalaldehyde* [18]

The ligands $H_2L^{1\text{-}6}$ were prepared by dissolving 4.0 mmol of either of the thiosemicarbazide, 4-methyl-3-thiosemicarbazide or 4-(2,3-dimethylphenyl)-3-thio-semicarbazide, with 2.0 mmol of the isophthalaldehyde, 5-(tert-butyl)isophthalaldehyde or 2,2 '-[butane-1,4-diylbis(oxy)]dibenzaldehyde in 20 mL of methanol or ethanol. Five drops of acetic acid were added to catalyse the reaction and the mixture was refluxed at 75˚C for

4 h. After reflux, the mixture was allowed to cool to room temperature. The precipitate was collected by filtration and was washed with methanol, diethyl ether and dried under vacuum.

Bis-(4-methyl-3-thiosemicarbazone) of isophthalaldehyde, abbreviated H_2L^1 White power (yield =94.3 %). ^{1}H NMR: δ ppm (400 MHz/DMSO-d_6): 11.58(s, 2H); 8.58(m, 2H); 8.15(s, 1H); 8.07(s, 2H); 7.82(d, 2H); 7.45(t, 1H); 3.03 (d, 6H). ^{13}C NMR: δ ppm (300 MHz/DMSO-d_6): 177.7; 140.94; 134.79; 128.96; 128.33; 125.42; 30.82. ***Anal. Calc.*** for $C_{12}H_{16}N_6S_2$ (found): C 46.73(46.84); H 5.23(5.09); N 27.25(26.32); S 20.79(20.89). ***Mass spectrum:*** m/z 310.09 ([M+H]$^+$); 331.07 ([M+Na]$^+$).

Bis-(thiosemicarbazone) of 5-(tert-Butyl)isophthalaldehyde, abbreviated H_2L^2 White power (yield = 94.0%). ^{1}H NMR: δ ppm (400 MHz/DMSO-d_6): 11.48(s, 2H); 8.23(s, 2H); 8.09-8.02(m, 5H); 7.75(s, 2H); 1.33 (s, 9H). ^{13}C NMR: δ ppm (300 MHz/DMSO-d_6): 177.86; 151.79; 142.10; 134.40; 125.65; 123.24; 34.65; 31.00. ***Anal. Calc.*** for $C_{14}H_{20}N_6S_2(CH_4O)_{0.9}(H_2O)_{0.5}$ (found): C 47.81(47.45); H 6.61(5.85); N 22.45(21.93); S 17.13(17.62). ***Mass spectrum:*** m/z 338.13 ([M+H]$^+$); 359.11 ([M+Na]$^+$).

Bis-(4-(2,3-dimethylphenyl)-3-thiosemicarbazone) of 5-(tert-Butyl)isophthalaldehyde, abbreviated H_2L^3 White power (yield = 86.6%). ^{1}H NMR: δ ppm (400 MHz/DMF-d_6): 11.82(s, 2H); 9.93(s, 2H); 8.16(s, 2H); 8.14(s, 1H); 7.85(s, 2H); 7.09-7.14(m 6H); 2.26(s, 6H); 2.08(s, 6H); 1.31(s, 9H). ^{13}C NMR: δ ppm (300 MHz/DMSO-d_6): 178.06; 152.46; 142.86; 138.39; 137.23; 135.24; 134.27; 128.31; 126.53; 125.29; 124.00; 30.92; 19.91; 13.90. ***Anal. Calc.*** for $C_{30}H_{36}N_6S_2$ $(CH_4O)_{0.15}$(found): C 65.89(65.99); H 6.71(6.09); N 15.29(14.75); S 11.67(11.57). ***Mass spectrum:*** m/z 546.25 ([M+H]$^+$).

Bis-(4-methyl-3-thiosemicarbazone) of 5-(tert-Butyl)isophthalaldehyde, abbreviated H_2L^4 White power (yield = 82.6%). ^{1}H NMR: δ ppm (400 MHz/DMSO-d_6): 11.57(s, 2H); 8.52(m, 2H); 8.07(s, 2H); 8.07(s, 1H); 7.70(s 2H); 3.05(d, 6H); 1.34 (s, 9H). ^{13}C NMR: δ ppm (300 MHz/DMSO-d_6): 179.00; 152.50; 142.07; 135.31; 125.70; 123.50; 30.90. ***Anal. Calc.*** for $C_{16}H_{24}N_6S_2(CH_4O)_{0.19}$ (found): C 52.47(52.92); H 6.73(5.91); N 22.68(22.22); S 17.30(17.74). ***Mass spectrum:*** m/z 366.16 ([M+H]$^+$); 387.14 ([M+Na]$^+$).

Bis-(thiosemicarbazone) of 2,2 '-[butane-1,4-diylbis(oxy)]dibenzaldehyde, abbreviated H_2L^5 White power (yield = 86.5%). ^{1}H NMR: δ ppm (400 MHz/DMSO-d_6): 11.45(s, 2H); 8.50(s, 2H); 8.11/7.90(s, 4H); 8.07(d, 2H); 7.35(t,2H) 7.06(d, 2H); 6.94(t, 2H); 4.11(s, 4H); 1.99 (s, 4H). ^{13}C NMR: δ ppm (300 MHz/DMSO-d_6): 177.69; 157.17; 138.22; 131.25; 125.97; 122.26; 120.47; 112.46; 67.64; 25.47. ***Anal. Calc.*** for $C_{20}H_{24}N_6O_2S_2$ $(H_2O)_{0.7}(C_2H_5OH)_{0.1}$ (found): C 52.54(52.58); H 5.67(5.10); N 18.2(17.69); S 13.89(14.24). ***Mass spectrum:*** m/z 446.15([M+H]$^+$).

Bis-(4-(2,3-dimethylphenyl)-3-thiosemicarbazone) of 2,2'-[butane-1,4-diylbis(oxy)] dibenzaldehyde, abbreviated H_2L^6 White-yellow power (yield = 83.5%). ^{1}H NMR: δ ppm (400 MHz/DMSO-d_6): 11.78(s, 2H); 9.90(s,2H); 8.60(s, 2H); 8.23(d, 2H); 7.37(t, 2H); 7.00-7.10(m, 8H); 6.94(t, 2H); 4.15(s, 4H); 2.23(s, 6H); 2.09(s, 6H); 2.03(s, 4H). ***Mass spectrum:*** m/z 654.28([M+H]$^+$).

CONCLUSION

In this paper, we presented the synthesis of six new bis-thiosemicarbazone ligands. These ligands were fully characterized by different techniques and especially by ^{15}N NMR. This technique is, to our knowledge, rarely performed for the characterisation of coordination complexes in solution and the data acquired in this study open the route towards new methods for studying the coordination complexes of thiosemicarbazones. We aim now to study the reactivity of these ligands with 3d and 4d metal, especially with $[Mo_2O_2S_2]^{2+}$ clusters, which are known to be biomimetic models of Mo-based enzymes. This work is in progress

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Acknowledgments:

Ms. Aurelie Damond is gratefully acknowledged for ESI-MS experiments. University of Versailles, the "Institut Universitaire de France, IUF" and the CNRS are gratefully acknowledged for financial support. This work is supported by the "ADI 2019" project funded by the IDEX Paris-Saclay, ANR-11-IDEX-0003-02. DC gratefully acknowledges Campus France for Excellence Eiffel grant as well as University State of Moldova for funding her PhD thesis.

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Prezentat la 01.12.2020