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Research Article

SYNTHESIS AND CHARACTERIZATION OF METHYL ISOBUTYL DITHIOCARBAMATE COMPLEXES OF Zn(II) AND Te(IV) AND THEIR POTENTIAL AS ANTI-TUBERCULOSIS AGENTS

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ABSTRACT

Tuberculosis (TB) is one of the oldest known human diseases and is still one of the biggest killers of infectious diseases that kill five thousand people every day. New drugs are needed to stem the TB epidemic by studying the synthesis of complex compounds that can be developed as anti-tuberculosis agents. Two new complexes of dithiocarbamate, methyl isobutyl dithiocarbamate zinc(II) and methyl isobutyl dithiocarbamate phenanthroline-tellurium(IV) were synthesized using an 'in situ' method by reaction complexes in a 1:1:3 molar ratio in refluxing ethanol. The complexes were characterized by using Ultra Violet Visible (UV-Vis), Fourier Transform Infra Red (FT-IR), Nuclear Magnetic Resonance (NMR), conductivity, and melting point. The result UV-Vis to methyl isobutyl dithiocarbamate Zn(II) and methyl isobutyl dithiocarbamate phenanthroline-tellurium(IV) each of them is 212 nm and 211 nm electronic transition is $\pi \rightarrow \pi^*$ of CS2 and N=C=S. Infra-Red absorption spectra at wave number Zn(II) methyl isobutyl dithiocarbamate 374^{nm-1} and methyl isobutyl dithiocarbamate phenanthroline-tellurium(IV) 364^{nm-1} is coordination occurred dithiocarbamate ligands and atoms M=S. ^{13}C NMR (ppm) spectra Zn(II) methyl isobutyl dithiocarbamate 20.1, 28.0, 43.3, 64.5. ^{1}HNMR (ppm) 0.976 (d), 0.962 (d), 2.3 (m), 3.770 (d), 3.455 (s), 3.755 (d) and 13C NMR (ppm) methyl isobutyl dithiocarbamate phenanthroline-tellurium(IV) 25.0, 30.3, 64.6, 73.3, 124.0, 126.3, 127.7, 136.9, 146.2, 159.3, 205.0. ^{1}HNMR (ppm) 2.040 (s), 3.25 (d), 4.25 (m), 2.800 (d), 7.556 (d) 7.713 (s), 8.25 (d). Complex characterization using UV-Vis, IR, and NMR showed that complexes are successfully synthesis. The bio-assay results show these complexes are potential as anti-tuberculosis agents.

Keyword: dithiocarbamate, in situ method, anti-tuberculosis assay, characterization, complexes

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. This bacterium is a very strong bacillus bacteria that need years of treatment. The number of tuberculosis patients is increasing, especially with the presence of multi-drug resistance (MDR) to *M. tuberculosis* which makes the situation more worrying. Drugs that have toxicity to *M. tuberculosis* generally have a long treatment period. This can cause problems if the patient treatment is not continuous [1]. Long-term drug use also has side effects. Therefore, the synthesis of new drugs with high inhibition and toxicity to *M. tuberculosis* is needed [2].

Antimicrobial compounds found in nature have been widely studied including those from plants, animals, and microorganisms [3]. Some synthetic compounds, such as those based on dithiocarbamate show biological activity which can be used as antimicrobial agents [4].

Dithiocarbamate is one of the ligands that can stabilize metal complexes in high oxidation numbers [5]. An in-situ method is widely used in the synthesis of dithiocarbamate complexes [6, 7]. More than two hundred different types of new dithiocarbamate compounds have been successfully synthesized and almost fifty crystals structures known. In addition, some of the resulting complex compounds have bioactivity such as anti-microbial, anticancer and antioxidants [8, 9, 10].

In this study, dithiocarbamate complexes were synthesized using Zn (II) and Te (IV) complexed with methyl isobutyl dithiocarbamate ligand. The synthesized compounds were characterized by UV-Vis spectroscopy, FT-IR, NMR, conductometry, and melting point. The bioactivity of the compounds was tested against *M. tuberculosis*.

MATERIAL AND METHODS

The materials used in this study were: N-Methylisobutylamine, CS_2, $ZnCl_2$, $TeCl_4$, 2,9 dimethyl-1,10 Phenanthroline, Test Bacteria (*M. tuberculosis*), Medium Lowenstein Jensen, ethanol PA, methanol PA, acetone PA, methylene chloride PA, chloroform PA, n-hexane PA, acetonitrile PA, KBr.

Synthesis of methyl isobutyl dithiocarbamate ligand

To a (0,6 mL , 5 mmol) N-methyl isobutylamine ethanolic solution was added dropwise a (0,3 mL, 5 mmol) of CS_2 in 10 mL of ethanol, at a temperature below 10 ^{0}C. The solution was stirred for 15 minutes.

A solution of methyl isobutyl dithiocarbamate ligand in ethanol was added to $ZnCl_2$ (0,408 gr; 3 mmol) dissolved in ethanol (10 mL). The solution was stirred for 30 minutes. The precipitate was then filtered and inserted in the desiccator until dried and then crystallized with the appropriate solvent.

Synthesis of Te (IV)MeIsoButDtcPhen

Add solution of methyl isobutyl dithiocarbamate ligand (0,005 mole) to a mixture of 2,9 dimethyl 1-10 phenanthroline (0.208 gr; 1 mmol) and TeCl4 (0.26 gr; 1 mmol) in 10 mL ethanol. The solution was stirred for 30 minutes. The precipitate was then filtered and inserted in the desiccator until dried and then crystallized with the appropriate solvent.

Characterization

Infrared spectra of the compounds were recorded as KBr discs using Infrared SHIMADZU spectrophotometer, in frequency 4000-300 cm^{-1}. ^{1}H and ^{13}C NMR spectra obtained using NMR JEOL spectroscopy. Electronic spectral obtained using UV-Vis Jenwey spectrophotometer 200-1100 nm for 10^{-3} M solutions in ethanolic at 25°C., Melting points were obtained on melting point type WRS-200, and Conductivity measurements were made with ethanolic solutions using a Eutech Con 510.2 at $25^{o}C$ for the complex concentration of 10^{-3} M.

Table 1. UV-Vis Data for Complexes and MeIsoButDtc ligand

Compound	λ (nm)	Electronic transition	Log (ε)
MeIsoButDtc	271	$\pi \rightarrow \pi^*$	5.593
Zn(II)MeIsoButDtc	212	$\pi \rightarrow \pi^*$	1.025
Te(IVMeIsoButDtcPhen	211	$\pi \rightarrow \pi^*$	1.536

Table 2. Characteristic IR band (cm^{-1}) of the synthesized complexes

Compound	v(C=N) aromatik	v(C-N)	v(M-S)	v(C-S)
Zn(II)MeIsoButDtc	-	1510s	374s	983^{m}
Te(IV)MeIsoButDtcPhen	1301^{m}	1490s	364s	985^{m}

s = strong, m = medium

Table 3. ^{13}C and ^{1}H NMR data for complexes

Complexes	^{13}C NMR (ppm)	^{1}H NMR (ppm)
Zn(II)MeIsoButDtc	20.1, 28.0, 43.3,	0.976 (d), 0.962 (d), 2.3 (m), 3.770 (d),
	64.5,	3.455 (s), 3.755 (d)
Te(IV)MeIsoButDtcPhen	25.0, 30.3, 64.6,	2.040 (s), 3.25 (d), 4.25 (m), 2.800 (d),
	73.3, 124.0, 126.3,	7.556 (d) 7.713 (s), 8.25 (d),
	127.7, 136.9, 146.2,	
	159.3, 205.0	

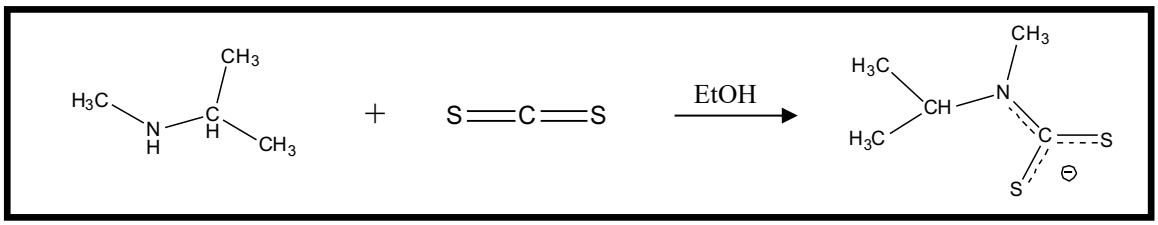

Fig 1. Synthesis reaction of methylisobutyl dithiocarbamate ligand

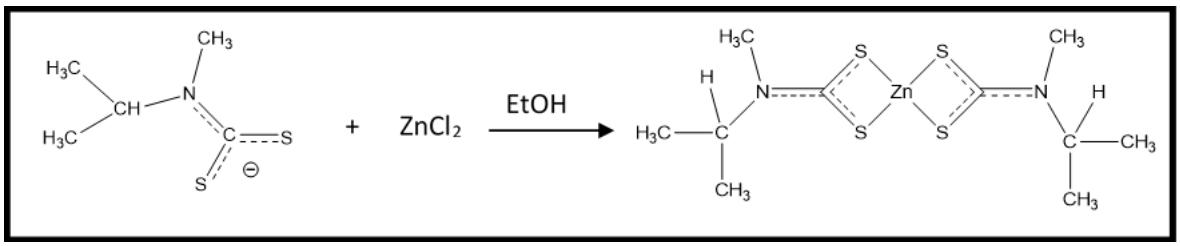

Fig 2. Synthesis reaction of Zn (II) MeIsoButDtc

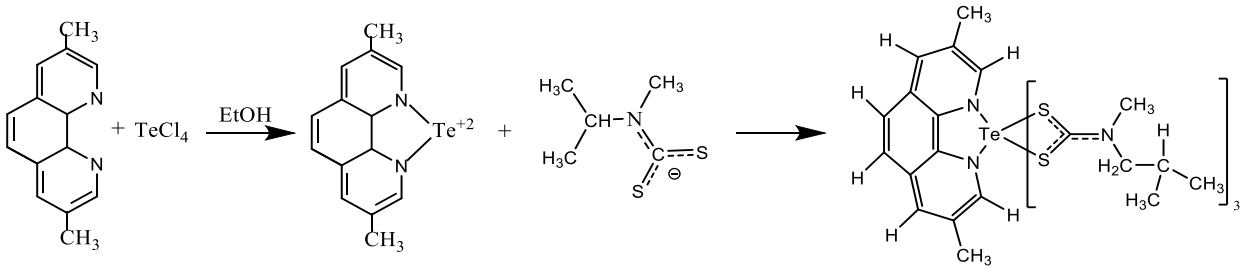

Fig 3. Synthesis reaction of Te (IV) MeIsoButDtcPhen

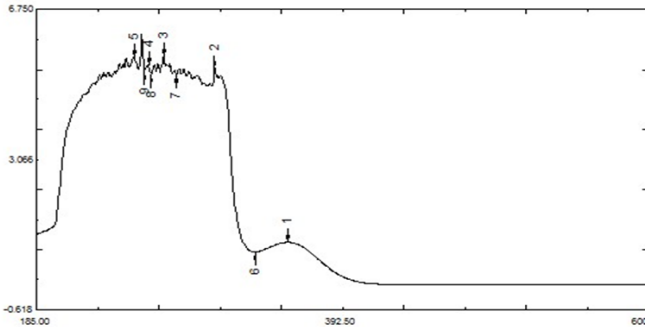

Fig 4. UV-Vis Spectrum of MeIsoButDtc ligan

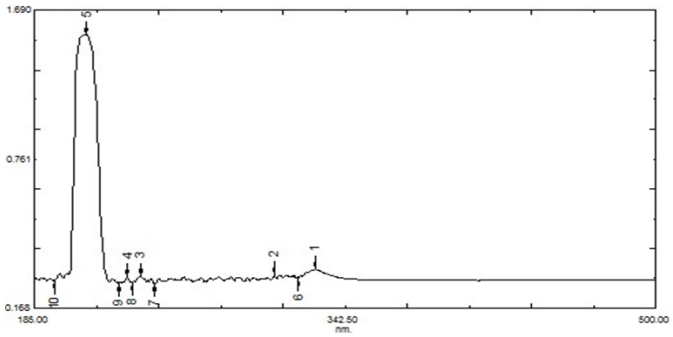

Fig 5. UV-Vis Spectrum of Te (IV) MeIsoButDtcPhen

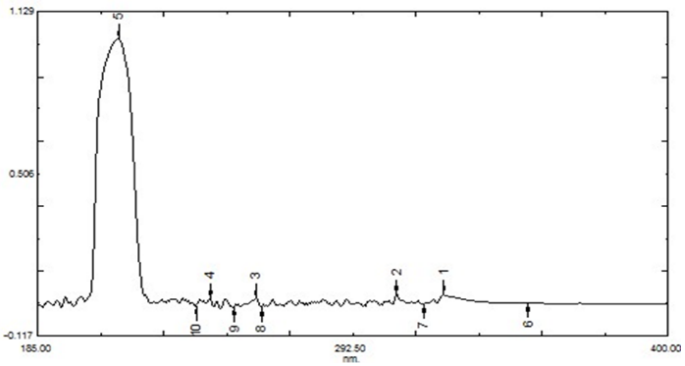

Fig 6. UV-Vis Spectrum of Zn (II) MeIsoButDtc

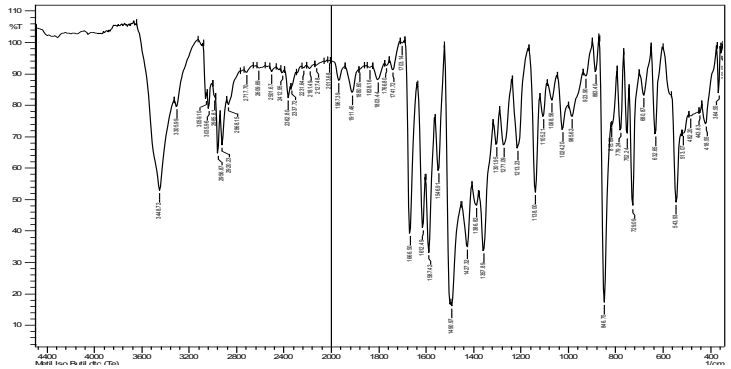

Fig 7. IR Spectrum of Te(IV) MeIsoButDtcPhen

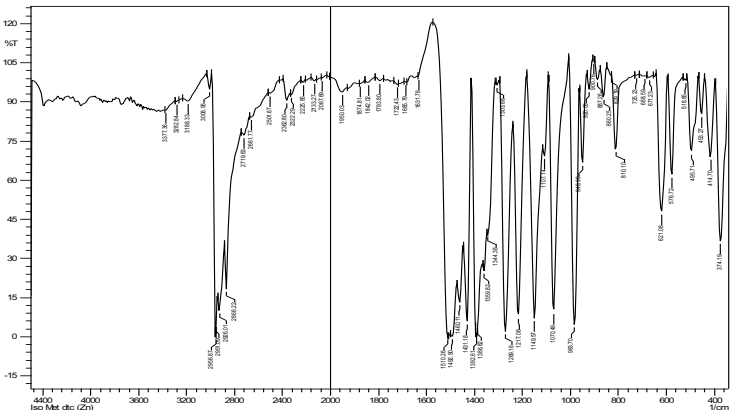

Fig 8. IR Spectrum of Zn (II) MeIsoButDtc

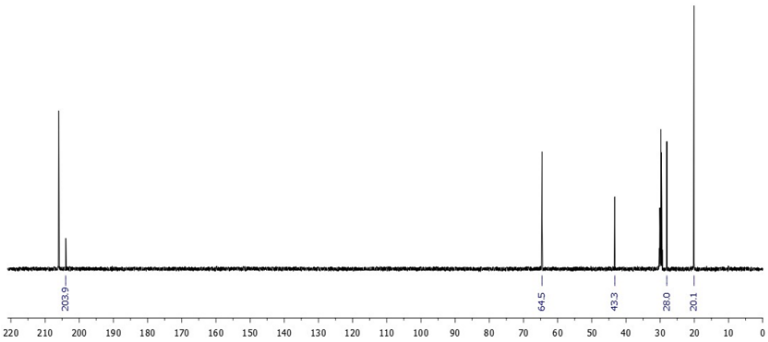

Fig 9. ^{13}C NMR Spectrum of Zn (II) MeIsoButDtc

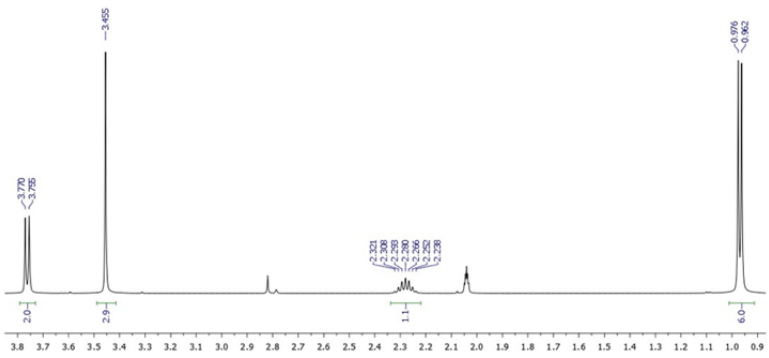

Fig 10. ^{1}H NMR Spectrum of Zn (II) MeIsoButDtc

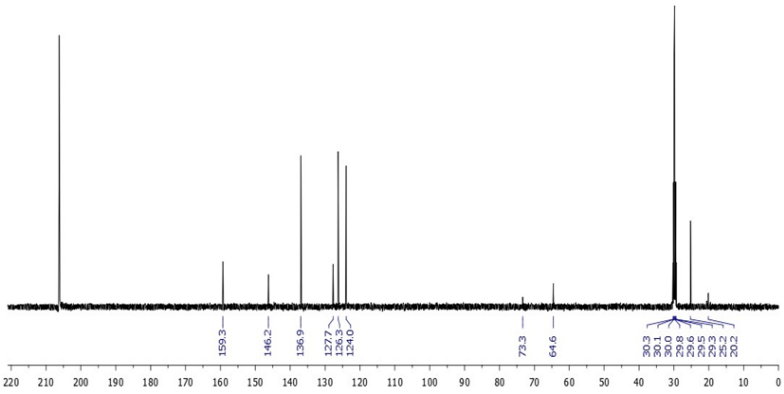

Fig 11. ^{13}C NMR Spectrum of Te (IV) MeIsoButDtcPhen

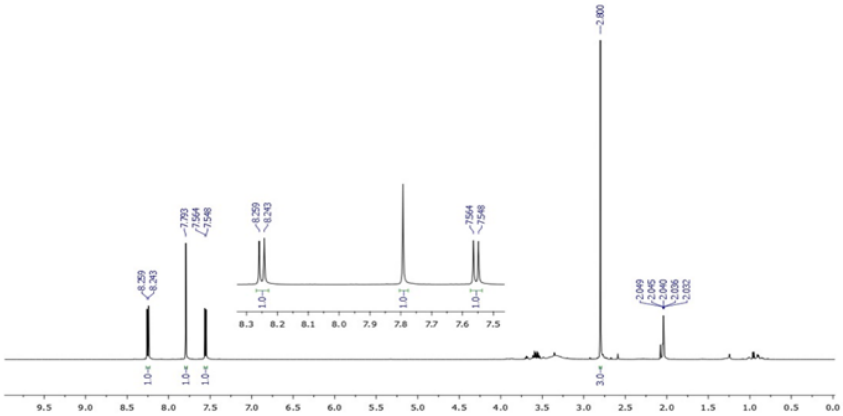

Fig 12. ^{1}H NMR Spectrum of Te (IV) MeIsoButDtcPhen

Fig 13. Antibacterial test result against *M. tuberculosis*, (a) rifampicin, (b) Zn(II)MeIsoButDtc, (c) Te(IV)MeIsoButDtcPhen

RESULT AND DISCUSSION

The yield of synthesized complexes are, Te (IV) MeIsoButDtcPhen is 21.01 % and Zn (II) MeIsoButDtc is 74.47 %. The melting point for Te (IV) MeIsoButDtcPhen is 110-112^{0}C and for Zn (II) MeIsoButDtc is 150-152^{0}C. The conductivity of the synthesized complexes is less than 65 [s/m] which indicates that the complexes are non-electrolytes.

UV-Vis spectra

Dithiocarbamate complexes generally have two main bands. Band I is a transition $\pi \rightarrow \pi^*$, band II occurs due to the transfer of metal charges to ligands [7,11]. The shift in the band I for all complexes have been synthesized detected a wavelength between 210-300 nm which is an intralig and transition $\pi \rightarrow \pi^*$ of the CS_2 group.

Spectroscopy

From the IR spectra data of the dithiocarbamate complexes as known that the important absorption paths are ν(C=N), ν(C=S), and ν (M=S). Infrared spectra of the complexes showed that the ν (C=N) band is in the regions 1450 - 1510 cm^{-1}. The unsplitting band of ν(C=S) in the region 930 - 1000 cm^{-1} indicates the bidentate nature of the chelated dithiocarbamate ligands [4,7]. The ν(M-S) stretching frequency was observed in the range 364-380 cm^{-1} [11].

NMR spectra

The selected NMR chemical shifts of the synthesized complexes are shown in Table 3. In the C-NMR spectrum for the Zn (II) MeIsoButdtc, there are 10 carbon atoms with 8 aliphatic carbon atoms and 2 carbon atom attached to the sulfur group (CS_2) [11]. The presence of isobutyl is showed by presence peak at 20.1, 28.0, 43.3 ppm derived from two methyl carbon (-CH_3), one tertiary carbon (- CH -), and one carbon methylene (-CH_2-). The chemical shifts of N-CH_3 showed by presence peak at 64.5 ppm. The peak at 203.9 derived from carbon bonded to the sulfur group. The H-NMR spectra for Zn (II) MeIsoButDtc presence of isobutyl in the by a high doublet peak at 0.976 and 0.962 ppm derived from the proton resonance of 2 methyl groups (-CH_3) having one proton neighbors. Multiple peaks at 2.3 ppm comes from in tertiary carbon (-CH-), and doublet peak at 3,770 and 3,755 ppm indicates the presence of proton from methylene group (CH_2). The existence of singlet peaks at 3.455 ppm is proton resonance in the methyl (-CH_3) group bonded to the nitrogen atom.

In the C-NMR spectra for Te(IV) MeisoButDtcPhen, there are 19 carbon atoms with 4 aliphatic carbon atoms, 12 conjugated carbon atoms, 2 carbons attached to phenanthroline and 1 carbon atom attached to the sulfur groups (CS_2). The presence of isobutyl is indicated by a peak at 25.0, 64.6 and 73.3 ppm derived from two methyl carbon (-CH_3), one carbon methylene (-CH_2-) and one tertiary carbon (-CH-). The presence of carbon from the methyl group attached to the Nitrogen (N-CH_3) atom is shown at the peak at 30.3 ppm. In addition to the presence of isobutyl compounds, and methyl groups attached to nitrogen atoms, there are 6 peaks which have a fairly high chemical shift such as peaks at 124.0 126.3, 127.7, 136.9, 146.2 and 159.3 ppm. the phenanthroline compound. The peak at 205 ppm comes from the carbon bonded to the sulfur group. The H- NMR spectra of Te (IV) MeIsoButDtcPhen, the isobutyl presence is also known with the doublet peak at 2.040 ppm derived from the proton 2 resonance of the methyl (-CH3) group having one neighboring proton, the very weak peak at 3.25- 4.25 ppm comes from the resonance of the methylene proton (CH2) and the methine proton (CH).The high peak at 7.793 ppm comes from the proton in a methyl group (CH3) binding to the amine group and 2 methyl groups in the phenanthroline. The presence of peaks at 7.564, 7.548, 8.243 and 8.259 ppm indicates the resonance of proton dienicized diene in phenanthroline compounds.

Antimicrobial Activity

The antibacterial action of the complexes on *M. tuberculosis* was studied by LJ method with concentrations of active compounds is 0,003 ppm. The results of the antituberculosis test showed that the complex has potential as a drug of tuberculosis, which is characterized by the absence colonies of *M. tuberculosis* bacteria that grow on the test media. Dithiocarbamates complex is bactericidal in M. tuberculosis cells. This complex can inhibit activity in the cytoplasm thus disturbing the integrity of microbial cell membranes. If the function of the cytoplasmic membrane is disrupted, cell damage or cell death arises, as a result, microbes will die[12].

CONCLUSION

Based on physical measurements the complexes of Zn (II) MeIsoButDtc and Te (IV) MeIsoButDtcPhen can be synthesized using an in-situ method by addition of metals in solution in a secondary amine and carbon disulfide solution. The synthesized complexes have potential as anti-tuberculosis is shown the surface of the medium test did not grow of *M. tuberculosis* colony.

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