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Structural, Characterization and Biological Activity of New Ligand N-(Pyrimidin-2-Yl Carbamothioyl) Acetamide and Its Complexes With (VO(II), Mn (II), Cu (II), Zn (II), Cd (II) and Hg (II)

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Abstract
New ligand of N-(pyrimidin-2-yl carbamothioyl)acetamide was synthesized and its complexes with (VO(II), Mn (II), Cu (II), Zn (II), Cd (II) and Hg (II) are formed with confirmation of their structures on the bases of spectroscopic analyses. Antimicrobial activity of new complexes are studied against Gram positive S. aureus and Gram negative E. coli, Proteus, Pseudomonas. The octahedral geometrical structures are proved depending on the outcomes from the preceding procedures.
Keywords: pyrimidin-2-amine, acetyl isothiocyanate, complexes, Antimicrobial activity.

Introduction

Metal Complexation is a branch of organometallic or inorganic chemistry that uses a suitable chelating agent to get a complex from inorganic ions, this complex has higher solubility in the organic extraction solvent.[1] Also, Complexation is a reaction between one or more anions and a cation to afford metal complexes as stable species that are less likely to participate in sorption, precipitation, and even redox reactions.[2-4]

On the other hand, pyrimidine moiety has a broad pharmacological and pharmaceutical activity such as antimicrobial[5], antitumor[6], anti-inflammatory[7], a sleeping aid[8], antidiabtic [9] and antituberculous such as pyrazinamide that is a medication used to treat tuberculosis[10-12](Figure 1). Also pyrimidines used as potent EGFR inhibitor [13], protein kinase inhibitors [14]and 5-HT7 receptors [15].

Besides, amides are one class of organic compounds that have carbonyl group, such as acetamide, ethanamide that used a solvent and a plasticizer in a few cases, and *N*,*N*-dimethylacetamide [16]. Also, ethionamide (ETH) is an important second-line antituberculosis drug used for the treatment of patients infected with multidrug-resistant Mycobacterium and in combination with other medications for treating glaucoma.[17] Also, it has many broad applications in pharmacy and medicine [18-20].

Literature survey revealed that thiourea derivatives are significant compounds in medicinal and pharmaceutical chemistry with several biological applications[21]. Today, they are widely used as antimicrobial agent, chiefly because of their low cost, low toxicity and excellent activity against bacterial diseases

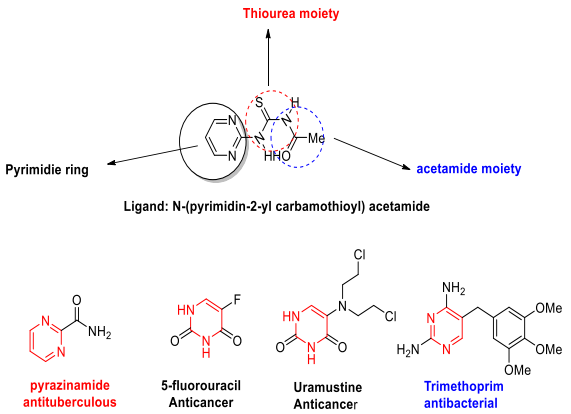

Figure 1: target Ligand and some pyrimidine containing drugs

Antibacterial activities have been investigated more than antifungal activities, due to high resistance of bacteria strains to antibiotics more than fungi

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through biochemical and morphological modifications[22-25] So, new compounds of metal complexes together with ligand were investigated as antibacterial agents via using Mueller-Hinton method[26]

According to above survey, we aimed to synthesize a new metal complexes of a new ligand of N-(pyrimidin-2-yl carbamothioyl)acetamide such as (Co(II), Mn (II), Cu (II), Zn (II), Cd (II) and Hg (II) and investigate them as antimicrobial activity against Gram positive *S. aureus* and Gram negative *E. coli*, *Proteus*, *Pseudomonas*.

Experimental

Chemicals and instrument

All chemicals and solvents were obtained from BDH and Merck. Gallen Kamp capillary melting point apparatus was used to measure melting points. Shimadzu model FT-IR-8400S was used to take FT-IR measurements by using KBr. ^{1}H-NMR spectra were dissolved in deuterated DMSO and measured on a Bruker spectrophotometer ultra-shield at 300 MHz using TMS as an internal standard.

Synthesis of Ligand and its complexes

Pyrimidin-2-amine (**1**, 0.20 g, 2 mol) and acetyl isothiocyanate (**2**, 0.20g, 2 mol) in 20 mL ethanol was reflexed for 3h. The reaction mixture was left to cool, filter, and recrystallized to afford brown crystals of N-(pyrimidin-2-ylcarbamothioyl)acetamide (**3**), yield 50%, m.p. = 196-198^{o}C (Scheme 1).

Ligand **3** (1.5g, 0.08mole) in 20 mL absolute ethanol, and metal chloride (0.04mole); (Mn (II), Co(II), Zn (II), Cu (II), Hg (II) and Cd (II) in absolute ethanol was added. This mix has been refluxed in water bath for 3h (TLC). The mixture was cooled, precipitated, filtered, washed in ethanol and dried under the vacuum (Scheme 1).

Results and Discussion

Pyrimidin-2-amine (**1**) reacted with acetyl isothiocyanate (**2**) in reflux ethanol to afford brown crystals of N-(pyrimidin-2-ylcarbamothioyl) acetamide (**3**). The structure of compound **3** was elucidated according to IR, NMR (Scheme 1). FT-IR (KBr) of compound **3** revealed bands at 3375cm^{-1} of NH group with disappearance of fork-like bands that related to two bands of NH_2 around 3194 and 3444 cm^{-1}. Also, stretching band at 1681 cm^{-1} of C=O, 1228, 1172 cm^{-1} of C=S (Figure 2). In the same manner[25], 1H NMR (500 MHz, $CDCl_3$) of compound **3** has signals at δ 12.80, 11.75 as two singlet for two NHs that exchangeable with D_2O, at δ 8.47 and at δ 6.48 as doublet and triplet for aromatic protons, at δ 2.30 as singlet for methyl protons (Figure 3).

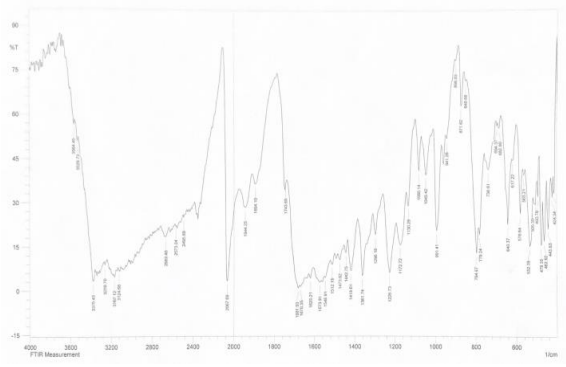


Figure 2: FTIR of ligand 3

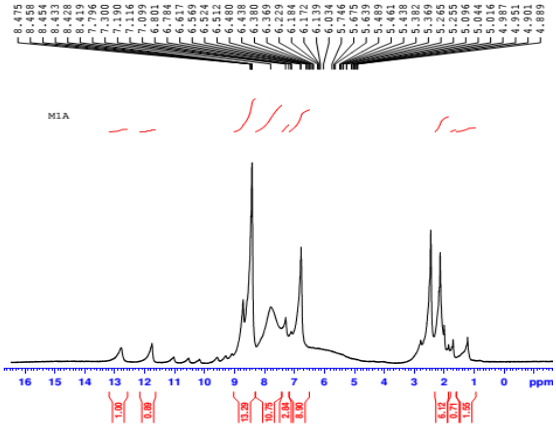
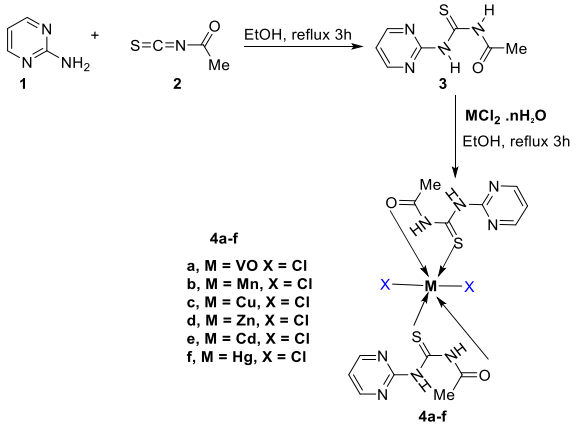


Figure 3: 1HNMR of compound 3

Also, metal complexes **4a-f** were prepared in reflux ethanol via reaction of one mole of metal chloride with two mole equivalent of ligand **3** (Scheme 1). The structures of new complexes were confirmed on their FT-IR, UV-Vis and physical properties.



Scheme1: Ligand 3 and its complexes 4a-f

FT-IR spectra of metal complexes have C=O band at 1627-1656 cm^{-1}, at 408-476 cm^{-1} that related to M-O bond that confirms coordination between metal with donor atoms[25]. Also, appearance of bands at 314-365cm^{-1} that related to M-S bond which afford coordination of metal with donor atoms (Table 1).

Table1: The characteristic FT-IR bands for free Ligand 3 and its metal complexes

Complex	Color	Mp. ^{0}C	υ(N-H)	υ (C=S)	υ(C=O)	υ(M-O)	υ (M-S)
4a	Dark green	300-302	3372	1135	1627	457	314
4b	yellow	320 dec.	3378	1203	1656	476	325
4c	Light green	310-312	3384	1065	1654	441	345
4d	Light brown	325 dec.	3380	1170	1647	459	364
4e	Light brown	290-292	3380	1201	1647	472	365
4f	brown	297 dec.	3379	1139	1662	408	314

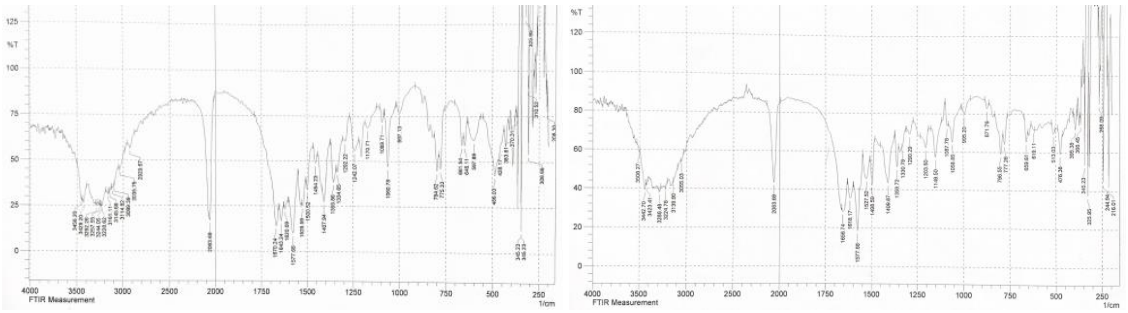


Figure 4: FTIR spectra of VO and Mn complexes

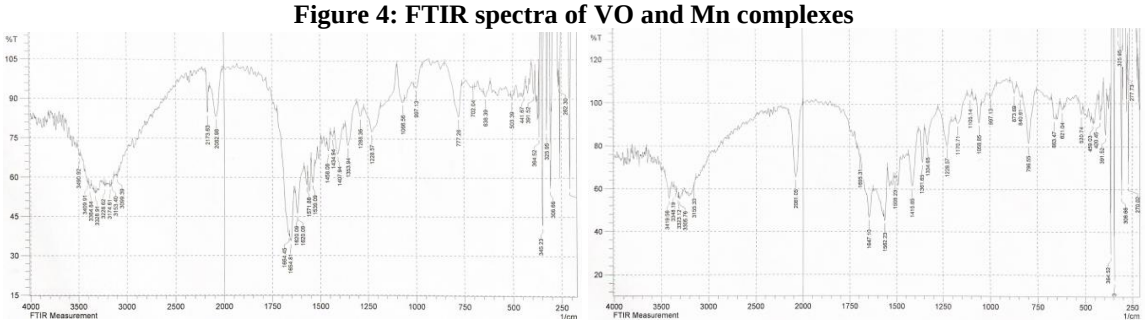


Figure 5: FTIR spectra of Cu and Zn complexes

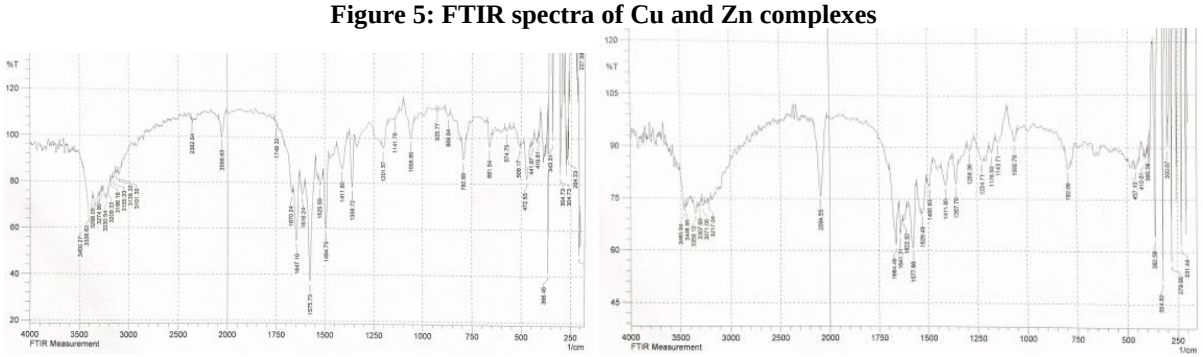


Figure 6: FTIR spectra of Cd and Hg complexes

Besides that, UV spectroscopy (UV-Vis) is used as electronic spectral data to confirm the structures of metal complexes. Ligand **3** UV-Vis. Showed a characteristic absorption peak at 294nm that assigned to ($n \rightarrow \pi^*$).

Also, UV spectroscopy (UV-Vis) of metal complex such as VO (II) complex showed three new absorption peaks at 297nm that confirms the intra-ligand at 584nm which resulted from d-d type of electronic transition $^4A_2g \rightarrow {}^4A_2g(f)$ and at 987nm that indicates $^4T_2g \rightarrow {}^4T_1g(f)$. Those peaks had been in good agreement of octahedral geometry for VO(II) complex (Table 2). UV spectrum (UV-Vis) of Mn (II) complex revealed absorption peak at 293 nm that refers to intra-ligand, a peak at 718nm that indicates d-d type of electronic transition $^6A_1g \rightarrow {}^4T_2g_{(G)}$ and a peak at 865nm that confirms $^6A_1g \rightarrow {}^4T_1g_{(G)}$. These peaks had been in good agreement of octahedral geometry for Mn(II) complex (Table 2). In the same manner[26], UV spectrum (UV-Vis) of Cu(II) complex showed a absorption peak 552 nm that refers to d-d type of electronic transition $^2B_1g \rightarrow {}^2Eg$ and a peak at 888nm that confirms $^2B_1g \rightarrow {}^2A_2g$ together with a peak at 293 nm refers to intra-ligand. These peaks had been in agreement with distorted octahedral geometry for Cu(II) complex (Table 2).

Molar conductivity

Molar conductance of all of the complexes in ethanol lie in a range between (8.92 and 19.15S.cm^{-1}mole^{-1}), determining their non-electrolytic behavior.

Table 2: -The ligand and its chelate complexes electronic spectra

Compound	$\lambda_{Max.}$ nm	Transitions	Suggested structure	$S.cm^{-1}mole^{-1}$
3	294	$n \longrightarrow \pi^*$	-	-
4a	297	Intra-ligand	**Octahedral**	18.82
	584	$^2B_2g \rightarrow {}^2B_1g$		
	987	$^2B_2g \rightarrow {}^2Eg$		
4b	293	Intra-ligand		13.41
	718	$^6A_1g \longrightarrow {}^4T_2g_{(G)}$		
	865	$^6A_1g \rightarrow {}^4T_1g_{(G)}$		
4c	293	Intra-ligand		9.87
	552	$^2B_1g \rightarrow {}^2Eg$		
	888	$^2B_1g \rightarrow {}^2A_2g$		
4d	290	Intra-ligand		8.92
4e	294	Intra-ligand		15.91
4f	279	Intra-ligand		17.10

Table 3. Biological activities of synthesized compounds

	Gram Positive	***Gram negative***		
Compounds	*S. aureus*	*E-coli*	*Pseudomonas*	*Proteus*
control	0	0	0	0
3	3	2	2	3
4a	3	5	0	3
4c	20	17	5	9
4d	8	4	7	7
DMSO	--	--	--	--

Biological activity of prepared compounds

In this section studied the anti-bacterial activities of synthesized compounds against strains of *S. aureus* as a type of Gram positive bacteria and three species of Gram negative bacteria such as *Pseudomonase*, *Proteus* and *E-coli* that are the only available species in our lab. We used Mueller-Hinton method[27] in comparison with DMSO as blank solvent. From our results, complex **4c** has the higher activity than the ligand **3** and complex **4a** and **4d** with inhibition zone equal 20 mm against *S. aureus* and 17mm against *E-coli*, respectively (Table 3).

Conclusion

New series of metal chloride complexes were synthesized and confirmed via their spectroscopic techniques to conform their octahedral shape. The antibacterial activity of the Cu-complex had high inhibition zone.

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