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RESEARCH ARTICLE

Synthesis, Characterization and Biological Activity of Himdazole-2-carboaldehyde Thiosemicarbazone and its Cd (II), Hg (II) and Zn (II) Complexes

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Abstract

Equimolar amounts of Himdazole-2-carboaldehyde and thiosemicarbazide were combined together and Himdazole-2-carboaldehyde thiosemicarbazone was prepared. The synthesized lingad was reacted with Cd (II), Hg (II) and Zn (II) ions yielding stable color complexes. For quantification and characterization purpose, elemental analysis, molar conductivity, infrared spectra, electronic spectra, proton nuclear magnetic resonance spectra, and mass spectra were carried out. The magnetic moment was also used for characterization. The ligand of IR spectrum showed that thiosemicarbazone coordinates to the metal ions via sulfur and azomethine nitrogen atom. The measurements of magnetic moment for all complexes were found to be (0.00). In range of normal for octahedral geometry and indicated all complexes were diamagnetic. An in vitro antimicrobial have been tested against a number of bacteria and fungal strains for the free ligand and its metal complexes, to assess their antimicrobial properties by diffusion technique. The ligand and its complexes exhibit higher activity against bacteria and fungi in compared with standard.

Key Words: Biological activity, diffusion technique, Potato dextrose agar.

INTRODUCTION:

Thiosemicarbazones are compounds that have been studied for a considerable period of time for their biological properties. Traces of interest date back to the beginning of the 20th century but the first reports on their medical applications began to appear in the fifties as drugs against tuberculosis (Bavin et al, 1950), and leprosy (Koch and Stuttgen, 1950). In the sixties the antiviral properties were discovered (Kune .1964) and a huge amount of research was carried out that eventually led to the commercialization of thiosemisazone. Recently Triapine 3-aminopyridine-2-carboxaldehyde thiosemicarbazone has been developed as an anticancer drug (Nutting, et al, 2009, Goh and Tan; 2008). Presently, the areas in which thiosemicarbazones are receiving more attention can be classified according to their antitumor (Blanz, 1968), antifungal (Mitral et al, 1981), antibacterial (Dobek et al, 1980) and antiviral activities (Pirrung et al, 2005), and in all cases their action has been shown to involve interaction with metal ions (Finch et al., 1999).

Transition metal complexes of thiosemicarbazones are widely studied, especially because of their chemical and biological properties. According to the transition metal and the parent aldehyde or ketone associated to the thiosemicarbazide moiety, the thiosemicarbazone complexes are developed for analytical chemistry (Sarma et al., 2005), can be engaged in catalysis or pre-catalysis,(Pandiarajan et al., 2013) in addition to their biological properties. All these peculiar properties prompt many authors to study transition metal complexes of thiosemicarbazone in order to understand the relationship between these activities and their molecular structures.

Experimental

• Materials and measurements

Organic solvents (absolute ethyl alcohol (SDFCL, India dimformamide (DMF, 99%, GC-Lab Tech Chemical), dimetheylsulfoxide (DMSO, Laba Chemie PVT. Ltd) used without purification. $ZnCl_2$, $PdCl_2$ provided by CDH, extra pure), 1Himdazole-2-carboaldahyde (Sigma,USA), Sodiumhydroxide (SDFCL, India), glacial acetic acid (Scharlau,European Union) and ammonium hydroxide are of analytical grade and used. Double distilled water was used in all preparations.

• Instrumentations

The magnetic susceptibility was measured on powdered samples using Gouy balance at Cairo University, Egypt.Elemental analyses were carried out in the Micro Analytical

Unit, Cairo University, using chemical analyzer, Carlo-Erba1106. UV-vis spectra were carried out using Shimadzu model 3101 spectrophotometer. Infrared spectra of solid samples were recorded on Perkin-Elmer model 1650 and Shimadzu model 8400S spectrophotometer. 1 H NMR spectra were recorded in a Varian Mercury VX-300 NMR

spectrometer operating at 300 MHz using DMSO-d 6. Mass chromatograms were recorded on a Shimadzu GCMS-QP2010.The electrical conductivity was measured using

Conductivity.

• Synthesis of the ligand (HL)

Thiosemicarbazide (0.0911g (0.001 mol) was placed in 100 ml round bottomed flask. Absolute ethanol (20 ml) was added and the mixture was heated until the dissolution was completed. Of [1]Himdazole -2-carboxaldehyde (0.096g (0.001mol) dissolved in 20ml hot absolute ethanol and added to solution, followed by addition of few drops of Sodium hydroxide (IM). The mixture was then refluxed on water bath for two hours. On cooling, yellow powder was precipitated. The precipitate was filtered, washed with ethanol and left to dry in air. The product was recrystallized from ethanol. The yield obtained was 72.18% melting point was 200 ^{0}C.

• Synthesis of complexes

• Synthesis of [Cd ($C_5H_7N_5S)_2$],[Cd $(HL)_2$]

1Himdazole -2-carboxaldeydethiosemicarbazone –Palladium complex was prepared by following method. $CdCl_2$ (0.177 g (0.001mol) placed in 100 ml beaker dissolved in 20 ml of warm absolute ethanol to a solution of 1Himdazole -2-carboxaldeydethiosemicarbazone (0.338g (0.002mol) in 20 ml ethanol. The mixture was refluxed for two hours. On partial evaporation of the solvent, the reddish yellow precipitate separated out was filtered, washed with ethanol and left under shadow.

• Synthesis of [Zn ($C_5H_7N_5S)_2$],[Zn$(HL)_2$]

1Himdazole -2-carboxaldeydethiosemicarbazone –Zinc complex was prepared by following method. $ZnCl_2$ (0. 162g (0.001mol) placed in 100 ml beaker dissolved in 20 ml of warm absolute ethanol to a solution of 1Himdazole -2-carboxaldeydethiosemicarbazone (0.338g (0.002mol) in 20 ml ethanol followed by addition of few drops of sodium hydroxide (to adjust the reaction, as well as neutralize remaining hydrochloric acid). The mixture was refluxed for two hours. On partial evaporation of the solvent, the green powder precipitate separated out was filtered, washed with ethanol and left under shadow.

• Synthesis of [Hg ($C_5H_7N_5S$)2 Cl_2],[Hg $(HL)_2$ Cl_2]

Himdazole -2-carboxaldeydethiosemicarbazone –Zinc complex was prepared by following method. $HgCl_2$ (0. 271 g (0. 001mol) placed in 100 ml beaker dissolved in 20 ml of warm absolute ethanol to a solution of 1Himdazole -2-carboxaldeydethiosemicarbazone (0.338g (0.002mol) in 20 ml ethanol. The mixture was refluxed for two hours. On partial evaporation of the solvent, the white powder precipitate separated out was filtered, washed with ethanol and left under shadow.

• **Biological Screening**

Antifungal activity of the synthesized ligand (HL) and its complexes in term of their inhibition to the linear growth of Aspergillus fumigates, and Candida albicans was investigated. Potato dextrose agar (PDA) was used to evaluate the effect of the compounds under investigation on the mycelia linear growth of the two tested fungi. 50 ml of the medium were poured into 150 ml conical flasks and autoclaved at 121° C for 20 minutes. Three drops of 25% lactic acid were added to prevent bacterial contamination. Dilutions of each of the tested compounds were carried out (v/v) by dissolving

appropriate amounts of each compound in 10 ml DMSO. Equal volumes of DMSO containing diluted compounds were added to sterile molten (40C) PDA to get a series of different concentrations for each compound in PDA. A zero concentration treatment was prepared for each fungus which contains equivalent volume of DMSO only and used as control. Compounds amended PDA was dispensed aseptically into 9 centimeter Petri dishes. Plugs of mycelium were cut from the margins of actively grow thing cultures of the fungi and placed in the center of compound-amended and amended PDA plates with four replicate plates for each fungus. All plates were incubated at 25C. Colony diameter in (mm) was measured after three days and the inhibition zone was calculated for each compound. The growth inhibition percentage diameter of the fungal colony using the equation (C-T) x 100/C, where C is the diameter of the fungus colony in the control plate after three days and T is the diameter of the fungus colony in the tested plates after the same period of time. The antibacterial activity of the ligand and its complexes were tested using diffusion method against Staphylococcus aureus as gram positive bacteria and Esherichia coli as gram negative bacteria. Nutrient agar (NA) medium was used. The test compounds were dissolved in DMSO. 25 ml of nutrient agar (NA) were placed in Petri plates. After solidification, the test bacteria were spread over the medium using a spreader. Discs of What-mann no. 1 filter paper saturated with the test compounds were placed at four equidistant places from the center in the incubated Petri plates. Filter paper discs treated with DMSO served as control and Tetracycline was used as standard drug. The Petri dishes were kept in a refrigerator for 24 hours for pre-diffusion and then incubated for 72 hours at 38 $^{\circ}$ C and the inhibition zone around each disc was measured. The zone of inhibition was carefully calculated in millimeters.

Results and discussion

• Spectral studies

The analytical data of the ligand and its complexes was given in experimental section, coincide with empirical formula.

Table:1 Analytical data of HL and its metal complexes using Elemental analysis

		Elemental analysis (found) and calculated (%) Percentage of elements detected			
Compound	Color	C	N	H	S
[HL]	white	35.49 (34.7)	41.39 (40.2)	4.17 (3.9)	18.9 (18.8)
$[Cd(C_5H_7N_5S)_2]Cl_2$	Pale yellow	26.64 (26.13)	26.85 (25.32)	3.13 (2.6)	14.22 (13.2)
$[Hg(C_5H_7N_5S)_2]Cl_2$	white	19.69 (18.5)	22.97 (21.7)	2.31 (2.31)	10.63(11.52)
$[Zn(C_5H_7N_5S)_2]^{+2}$	Green	29.74 (28.7)	34.69 (34.3)	3.49 (3.4)	15.88 (14.98)

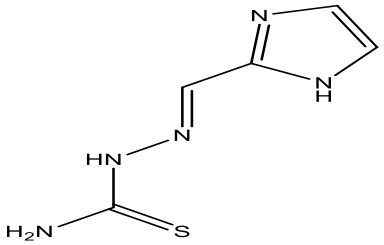

Fig. 1 Postulated structure of Himdazole -2-carboxaldeydethiosemicarbazone

Table (2): IR spectral data (4000-400cm-1) of the ligand HL and its complexes. Complexes and negative control (DMSO) measured by agar diffusion test (Unit, mm)

Sample	ν(NH_2)	ν (C=N)	ν (NH)	ν (C=S)
[HL]	3375-3328	1616	3153	840
[Cd $(C_5H_7N_5S)_2]Cl_2$	3342-3152	1523	3171	613
[Hg$(C_5H_7N_5S)_2]Cl_2$	3344-3231	1523	3179	833
[Zn$(C_5H_7N_5S)_2]^{+2}$	3345-3248	1556	3120	756

Newly formed (C=N) bond.

The Infrared spectral data of Cd (II) complex with the ligand HL is shown in table (2)

Cd (II) complex shown band at 1616 cm-1 assigned to ν (C=N) in the free ligand is shifted to 1523 cm^{-1} in the spectrum of the complex. This indicates complexation of the ligand through the azomethine nitrogen to the Cd (II) ion. The band at 840 cm-1 assigned to ν (C=S) in the free ligand is shifted to 613 cm-1. This suggests coordination of the ligand via the ν (C=S) sulfur atom. Hg (II) complex a band at 1616 cm-1 assigned to ν(C=N) in the free ligand is shifted to 1535 cm-1 in the spectrum of the complex. This indicates complexation of the ligand through the azomethine nitrogen to the Hg(II) ion. The band at 840 cm-1 assigned to ν (C=S) in the free ligand is shifted to 833 cm-1. This suggests coordination of the ligand via the ν (C=S) sulfur atom.

. Zn(II) complex with the ligand (1Himidazole-2-carboxaldehyde) thiosemicarbazone is shown the band at 1616 cm-1 assigned to ν (C=N) in the free ligand is shifted to lower frequency, 1556 cm-1 in the spectrum of the complex. This indicates complexation of ligand through the azomethine nitrogen to the Zn (II).The band at 840 cm-1 assigned to ν (C=S) in the free ligand is shifted to 756 cm-1 indicating the involvement of sulfur in complexation.

Table (3) UV-vis spectral (nm) of band, molar Conductivity and magnetic moment of complexes of the ligand H

Sample	Electronic spectra (nm) Molar	ConductivityOhm $^{-1}$ cm^2 mol^{-1}	B.M
[Cd $(C_5H_7N_5S)_2]Cl_2$	232, 353	0.00	diamagnetic [Hg
$(C_5H_7N_5S)_2]Cl_2$	223,351, 420	0.00	diamagnetic
[Zn $(C_5H_7N_5S)_2]^{+2}$	3261, 349	0.00	diamagnetic

Electronic spectra

The electronic spectra data of the Complex $[Cd(C_5H_7N_5S)_2]Cl_2$, in the solid state show bands at 43103 cm-1 (232 nm) , and 28328 cm-1 (353 nm) . On the basis of analytical, conductance and spectral data octahedral geometry is suggested (Mohammad et al, 2003). The electronic absorption spectral data of the complex [Hg $(C_5H_7N_5S)_2Cl_2$], in the solid state of Complex [Zn $(C_5H_7N_5S)_2$], in the solid state show bands at 37134.72 cm-1 (261 nm) 29229 cm-1 (349 nm) . The band at 349 nm is assigned to Zn(II) →S transitions. No appreciable absorptions occurred above 500 nm, indicating the absence of d→d bands which is in accordance with d10 configuration of Zn(II) ion. ow bands at 44843 cm-1 (223 nm), 28490 cm-1 (351 nm) and 23805 cm-1 (420 nm).

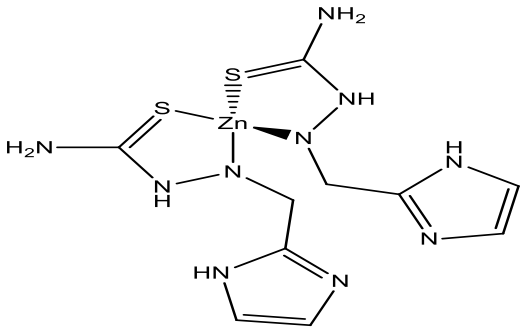

Fig .2 The probable structure of complex [Zn $(C_5H_7N_5S)_2$]

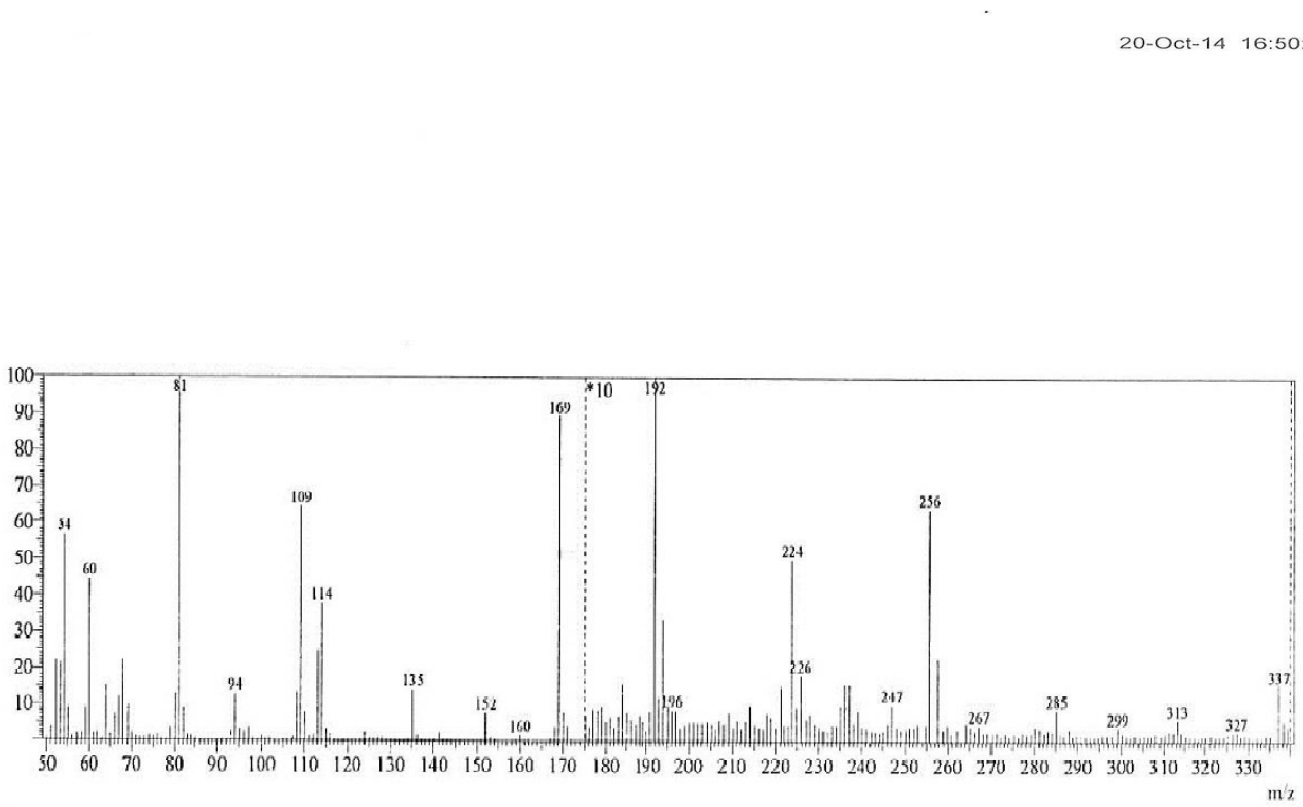

Fig .3 mass spectrum of the ligand HL

Results of the microbial studies

The antimicrobial screening data for the ligand and its complexes are shown in Tables (5) and (6)

The ligand and its some complexes exhibit activity against bacteria than fungi. The experimental results show that nearly some complexes exhibit antibacterial activity compare with free ligand, but less than the standard. This fact can be understood in terms of the chelation theory which states that upon complexation the polarity of the metal ion is reduced which increase the lipophilicity of the metal complex enabling them to cross the cell membrane easily (Mohamed G, 2009). The free ligand was active against Aspergillus fumigates, but less than the standard drug, but its complexes activity showed very least antifungal activity, Hg(II), Cd(II), Zn(II).

Table: 4 Antibacterial activity of ligand, its metal complexes, positive control (Ampicillin and Gentamicin) and negative control (DMSO) measured by agar

Sample	Gram positive bacteria S. pneumoniae	E. coli
[HL]	11.2	10.2
$[Cd\ (C_5H_7N_5S)_2]Cl_2$	13.5	13.4
$[Hg(C_5H_7N_5S)_2]Cl_2$	14.3	15.2
$[Zn(C_5H_7N_5S)_2]^{+2}$	13.7	9.6
Ampicillin (Positive)	23.8	--
Gentamicin (negative)	--	27.3

Table:5 Antifungal activity of Himdazole -2-carboxaldeydethiosemicarbazone and its complexes and negative control (DMSO) measured by agar diffusion test (Unit, mm).

	Zone of inhibition	
Sample	*Aspergillus flavus*	*Candida albicans*
[HL]	16.5	13
$[Cd\ (C_5H_7N_5S)_2]Cl_2$	13.6	15.3
$[Hg(C_5H_7N_5S)_2]Cl_2$	14	16.3
$[Zn(C_5H_7N_5S)_2]^{+2}$	11.7	17.9
Amphotericin B	23.7	25.4

Conclusion

In conclusion, this study reports a new ligand from the reaction between 2-Chloro-3-phenylpropanal and thiosemicarbazone. Two stable colored metal ion complexes

were synthesized from the reaction between the prepared complexing agent and three ions namely Hg (II), Zn(II), and Cd(II). The ligand and its complexes were characterized using different spectroscopic analytical techniques such as MS, IR and 1 H NMR spectra. In vitro antimicrobial potential of the ligand complexes were also investigated. Higher antifungal and antibacterial activities were observed from the metal ion compared to that of the free ligand bioactivity. The complexes may be developed to drugs in the future for treatment of diseases caused by the tested pathogenic fungal and bacterial strain

REFERENCES

1- Amna Qasem Ali , Siang Guan Teoh ,Naser Eltaher Eltayeb , Mohamed B. Khadeer Ahamed , A.M.S. Abdul Majid,(2014). Synthesis of copper(II) complexes of isatin thiosemicarbazone derivatives: In vitro anti-cancer, DNA binding, and cleavage activities, Polyhedron 74 – pp 6–15

2- Bavin EM, Rees RJW, Robson JM, Seiler M, Seymour DE, Suddaby D.(1950), The tuberculostatic activity of some thiosemicarbazones. J Pharm Pharmacol 2: 764-72.

3- Blanz Jr., F. French,(1968) Cancer Res.

4- Dobek, D. 1. Klavrnan, E.J. Dickson Jr., J. P. Scovill, E. C. Trarnont,

5- Finch RA, Liu MC, Cory AH, Cory JG, Sartorelli AC (1999), Triapine (3-aminopyridine-2-carboxaldehyde thiosemicarbazone; 3-AP): an inhibitor of ribonucleotide reductase with antineoplastic activity. Adv Enzyme Regul 39: 3-12

6- Koch O, Stuttgen G.(1950),Clinical and experimental studies on the effects of thiosemicarbazones. Naunyn Schmiedebergs Arch Exp Pathol Pharmakol Vol 210: 409-23.

7- Kune GA. (1964).To-day's drugs: methisazone. Br Med J 2: 621

8- Mitral, Sharma, Singh, J. P. Tandon,(1981). Curr. Sci, 50, and the references therein

9- Mohamed G., Ibrahim N.A. and Attia H.A. (2009). Synthesis an antifungicidal activity of some transition metal complexes with benzimidazole dithiocarbamate ligand. Spectrochimica Actra part A 72:pp 610-615.

10- Mohammad Akbar Ali a, Aminul Huq Mirza a, Mohammad Nazimuddin b, Raju Ahmed b, Lawrence R. Gahan c, Paul V. Bernhardt (2003). Synthesis and characterization of mono- and bis-ligand zinc(II) and cadmium(II) complexes of the di-2-pyridylketone Schiff base of Sbenzyl dithiocarbazate (Hdpksbz) and the X-ray crystal structures of the [Zn(dpksbz)2] and [Cd(dpksbz)NCS]2 complexes. Polyhedron 22 pp 1471-1479

11- Nutting CM, van Herpen CML, Miah AB, (2009). Phase II study of 3-AP Triapine in patients with recurrent or metastatic head and neck squamous cell carcinoma. Ann Oncol 20:pp 1275-9

12- Pandiarajan, Ramesh, Liu, R. Suresh, (2013), Inorg. Chem. Commun. pp:33 -33

13- Pirrung, M.C.;Pansare, S.V.; Sarma, K.D.; Keith, K.A.; Kern, E.R (2005). Combinatorial optimization of isatin-β-thiosemicarbazones as anti-poxvirus agents. J. Med. Chem, 48, pp 3045-3050

14- Sarma, Kumar, Reddy, Reddy, (2005) , J. Agric. Food Chem. 53 -5492

15- Suni V, M.R. Prathapachandra Kurup, Munirathinam Nethaji, (2007). Studies on Co(II) and Co(III) complexes of di-2-pyridyl ketone N(4)-cyclohexyl and N(4)-phenyl thiosemicarbazones. Polyhedron 26 –pp 5203–5209

16- Goh BC, Tan EH, et al. A (2008),multicenter phase II trial of 3- aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP, Triapine) and gemcitabine in advanced non-small-cell lung cancer with pharmacokinetic evaluation using peripheral blood mononuclear cells. Invest New Drugs 26: pp 169-73