Research Paper Medical Science

Synthesis and Bio-Evaluation of Ni (II) Complexes Derived From 5-Aminothiabendazole and Heterocyclic Bases

Dr. J. R. Gujarathi | Associate Prof. *Pratap College, Amalner (M.S.)

ABSTRACT

Ni (II) complexes were synthesized by the reaction of NiCl2.6H2O with and 5-aminothiabendazole in ethanol and heterocyclic bases in the ratio 1:1:1. The synthesized compound 5-aminothiabendazole was characterized by elemental analysis, 13C-NMR,1H NMR,ESI-MS,IR and UV-visible spectra The complexes were characterized by elemental analysis, IR,UV-visible spectra, magnetic measurements, conductivity measurements. Screenings of antimicrobial activity of synthesized metal complexes were also carried out against different bacterial species such as Citrobactor, Acinetobactor, and fungal species such as Aspergillus Nigar, Candida Albicans, Yields of the synthesized compounds were found adequate and some of them also exhibited potent activity against bacterial and fungal species.

KEYWORDS 5-aminothiabendazole, NiCl2.6H2O, antimicrobial assay.

Introduction:

The utility of thiazoles in curative treatment has been firmly established. Sulfur and nitrogen hetero cycles are important, as these possess pharmaceutical activities and pest management potency. They are occurred in the nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cells. They show anti-bacterial, anti-hypertensive, anti-anginal, anti-arrhythmetic, anti-histaminic, narcotic antagonist activities [1].The benzimidazole compounds have ability to control a large number of fungal diseases. Because of their systematic activity, they can help to control some diseases after infection. Benzimidazole fungicides are also used to prevent post-harvest rots and in soil-drench treatments [2].

Nickel is the most abundant element in the earth's crust. Nickel is most toxic metal among transition metals. Its toxicity is observed even in low doses to both plants and animals [3, 4]. The refining of nickel is associated with excess nasal and lung cancers. Crystalline nickel compounds are carcinogenic, while amorphous nickel compounds are weak or non-carcinogenic. Nickel helps in transport of metal in eukaiyotic algae. Nickel shows oxidation states from (+1) to (+IV), but its stable oxidation state is (+II). Nickel is divalent and ionic in simple compounds, and exists as Ni (II) in its complexes. Nickel forms four coordinate square planar, tetrahedral five coordinate trigonal bipyramidal, square pyramidal and six coordinate octahedral complexes. Four coordinate square planar complexes of Ni (II) are more common.

Six coordinate octahedral complexes of Ni (II) have been reported [5, 6]. Ni (II) square planar complexes are generally diamagnetic and some are paramagnetic [7]. Square pyramidal complexes of Ni (II) are unusual and when encountered exists as a result of particular circumstances in the complex rather than any intrinsic tendency on the part of Ni (II) ion to attain the structure.

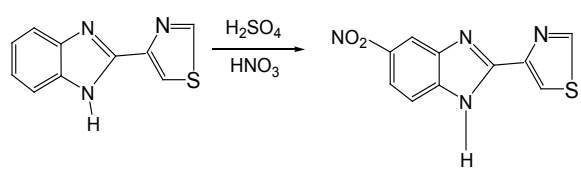
In present work 5-aminothiabendazole, is selected as a chelate ligand because it is structurally similar to compounds such as 2, 2' bipyridine and 1, 10 phenanthroline.

MATERIALS AND METHODS

Thiabendazole (A.R.Grade), Nickel Chloride (A.R.Grade), zinc dust, methanol, formic acid, chloroform, sodium bicarbonate, super saturated solution of NaCl (A.R.Grade).

Synthesis : Thiabendazole to 5-Nitrothiabendazole

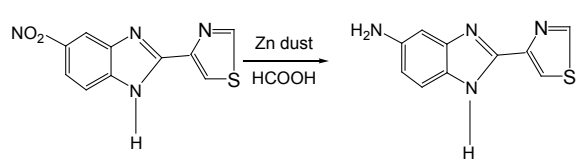
Ice cold conc.H_2SO_4 was added to thiabendazole with constant stirring .The reaction mixture was then warmed at 50° C for 10 min till thiabendazole dissolved completely. In ice bath below - 4° C. Nitrating mixture (ice cold 1.5 ml conc.H_2SO_4 and 10.2 ml of conc. HNO_3) was added with constant stirring. The reaction mixture was kept aside for 45 min. The reaction mixture was then warmed at 90° C for 90 min. After cooling at room temperature crushed ice was added with constant stirring, faint yellowish white product was then separated out. Sodium bicarbonate was added to it till the effervesces of CO_2 completely stopped and product became neutral. The product was then filtered off, washed with water and finally with diethyl ether and dried under IR lamp.



Scheme I

Synthesis: 5-Nitrothiabendazole to 5-Aminothiabendazole

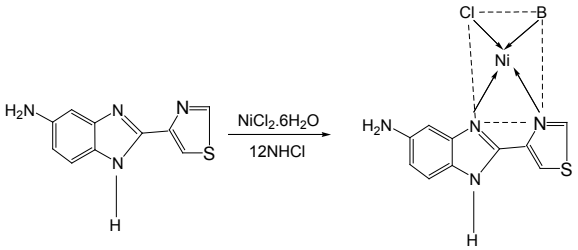
Methanol was added to homogeneous mixture of nitro thiabendazole and Zn dust. To this solution formic acid was added slowly with constant stirring. The solution was filtered. The filtrate was then warmed to evaporate the organic solvent completely.Formic acid was removed completely by the addition of few drops of chloroform and hot supersaturated solution of NaCl. Sticky product obtained, washed with methanol to convert to the powdered form. It was filtered filtered, dried under IR lamp and stored in vacuum.



Scheme II

Synthesis of complexes:

This complex of the type Ni.L.B (where B is heterocyclic bases pyridine,α-picoline,β- picoline,γ-picoline)was prepared by mixing 5-Aminothiabendazole in 40 ml of boiling ethanol containing 0.3 ml of 12N HCl, nickel chloride and heterocyclic bases in the mole ratio 1:1:1 in 25 ml of ethanol. The mix was refluxed for 2 hrs on a steam bath. The reddish brown complex which separated out by centrifugation, washed with hot water, cold ethanol, dried under IR lamp and stored in vacuum.



scheme III

(B= pyridine, α-picoline, β- picoline, γ-picoline)

Physical measurements-

Magnetic moments were measured by Faraday method. IR spectra were recorded in the range 4000-200 cm^{-1} range. NMR spectra were recorded in the mixture of $CDCl_3$ and DMSO-d_6 (1:1 v/v) with a Bruker AC-300F 300MHz spectrometer. Thermo gravimetric analysis was carried out in the temp range 30-800°C. UV-Visible spectra were measured on Jasco UV-visible double beam spectrophotometer. Metal in the complexes was estimated by standardized E.D.T.A using muroxide as an indicator and PH-10 buffer solution. Chloride in the complex was determined by Mohr's method.

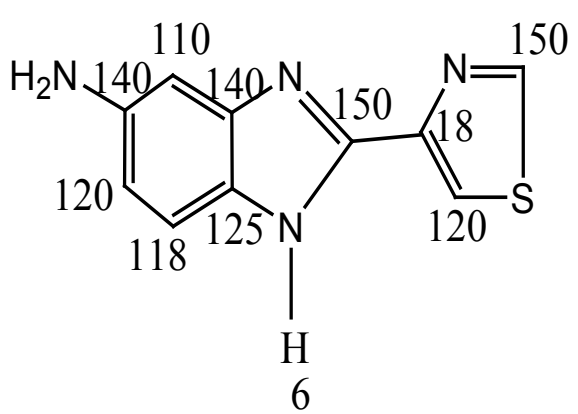
Table 1 Physical property:

Compounds	Colour	Empirical Formula	Molar conductance Ohm^{-1}cm^{2}mole^{-1}	Magnetic Moment B.M.
L	Yellow	$C_{10}H_8N_4S$	-	-
Ni-L.Cl_2	Reddish brown	$C_{10}H_8N_4SNiCl_2$	29.5	Diamagnetic
Ni.L.Cl.Py	Reddish brown	$C_{15}H_{13}N_5SNiCl$	28.6	Diamagnetic
Ni.L.Cl.α-Pico	Reddish brown	$C_{16}H_{15}N_5SNiCl$	24.7	Diamagnetic
Ni.L.Cl. β-Pico	Reddish brown	$C_{16}H_{15}N_5SNiCl$	20.5	Diamagnetic
Ni.L.Cl.γ-Pico	Reddish brown	$C_{16}H_{15}N_5SNiCl$	21.4	Diamagnetic

^{1}H-NMR

Signals at 4.4 δ-ppm corresponds to-NH_2, 8.20 δ-ppm corresponds to N=C-H, 7.25 δ ppm corresponds to C=C-H-S, 5.3 δ-ppm corresponds to N-H. The aromatic protons show multipletes at 6.4, 6.8, 7.40 δ-ppm.

^{13}C-NMR (DMSO-D_6): δppm - 110 (C=C), 140 (C=C), 120 (C=C), 118 (C=C), 125 (C=C), 140 (C=C), 150 (N=C), 150 (N=C), 18 (C=C), 120 (C=C).6 (N-H).



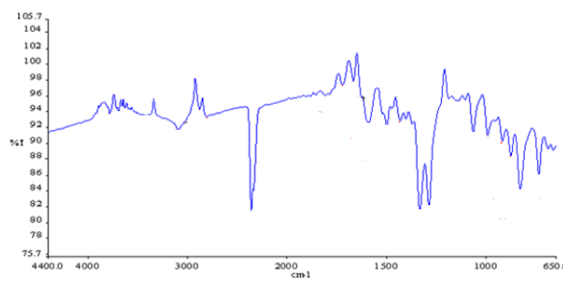
(Calcd) found ESI-MS m/z, ion M$^+$: $C_{10}H_8N_4S$ 216.58 (216.07), $C_{10}H_8N_4SNiCl_2$ 345.25 (345.84), $C_{15}H_{13}N_5SNiCl$ 389.92 (389.49), $C_{16}H_{15}N_5SNiCl$ 403.60 (403.51), $C_{16}H_{15}N_5SNiCl$ 403.35 (403.51), $C_{16}H_{15}N_5SNiCl$ 403.87 (403.51).

Analytical data (calculated):

1. L: % C 55.02 (55.54), % H 3.27 (3.73),% N 25.12 (25.91),% S 14.18 (14.83)
2. Ni-L.Cl_2: % Ni 16.22 (16.97), %Cl 20.11 (20.50), %C 34.08 (34.73), %H 2.93 (2.33), %N 16.84 (16.20), %S 9.77 (9.27).
3. Ni.L.Cl.Py: % Ni 15.84 (15.07), %C 46.91 (46.25), %H 2.93 (3.36), %N 18.60 (17.98), %S 8.97 (8.23).
4. Ni.L.Cl.α-Pico: % Ni 14.07 (14.54), %C 47.82 (47.62), %H 3.08 (3.75), %N 17.88 (17.36), %S 7.22 (7.95).
5. Ni.L.Cl. β-Pico: % Ni 14.20 (14.54), %C 47.14 (47.62), %H 3.10 (3.75), %N 17.92 (17.36), %S 7.15 (7.95).
6. Ni.L.Cl.γ-Pico: % Ni 14.22 (14.54), %C 47.84 (47.62), %H 3.15 (3.75), %N 17.84 (17.36), %S 7.28 (7.95).

IR SPECTRAL DATA in cm^{-1}

1. L: ν(C=N) 1728ν(N=C-S) 1670
2. Ni.L.Cl_2: ν(C=N),1650, ν(N=C-S) 1555
3. Ni.L.Cl.py.ν(C=N) 1642,ν (N=C-S) 1540, ν(M-N) base 265,Bands due to heterocyclic base 1440.
4. Ni.L.Cl.α-pico.:ν(C=N)1640ν(N=C-S) 1535,ν(M-N) base 260, Bands due to heterocyclic base 1445.
5. Ni.L.Cl.β-pico: ν(C=N) 1648, ν (N=C-S) 1530, ν (M-N) base 262, Bands due to heterocyclic base 1447.
6. Ni.L.Cl.γ-pico: ν(C=N) 1648, ν (N=C-S) 1540, ν (M-N) base 270, Bands due to heterocyclic base 1450.



IR spectrum of L

TGA analysis data:

The TGA curves of complexes were recorded between the temperatures 30 °C to 800 °C

1. Ni.L.Cl_2: First step, 200 °C, Mass loss 26.63 % second step, 350 °C, Mass loss, 38.49 % Third Step 600 °C, Mass loss, 62.81 % Fourth Step, Residue 778 °C, % of NiO, 16.22 (16.97).
2. Ni.L.Cl.py: First step, 210 °C, Mass loss 23.65 % second step,375 °C, Mass loss, 24.19, Third Step 675°C, Mass loss, 55.89 % , Fourth Step, Residue 780 °C, % of NiO, 15.78 (15.07).
3. Ni.L.Cl.α-pico. : First step, 220 °C, Mass loss 22.83 % second step 380 °C, Mass loss, 33.00 % , Third Step 680°C, Mass loss, 53.85 % , Fourth Step, Residue 780 °C, % of NiO, 14.08 (14.54).
4. Ni.L.Cl.β-pico : First step, 230 °C, Mass loss 21.83 % second step 370 °C, Mass loss, 32.00 % , Third Step 670°C, Mass loss, 52.85 % , Fourth Step, Residue 800 °C, % of NiO, 14.12 (14.54).
5. Ni.L.Cl.γ-pico: First step, 225 °C, Mass loss 22.55 % second step 385 °C, Mass loss, 33.50 % , Third Step 682°C, Mass loss, 52.85 % , Fourth Step, Residue 779 °C, % of NiO, 14.18 (14.54).

Biological activity (Well diffusion method)

Table.2 % Activity index of L, Ni (II) complexes and standard

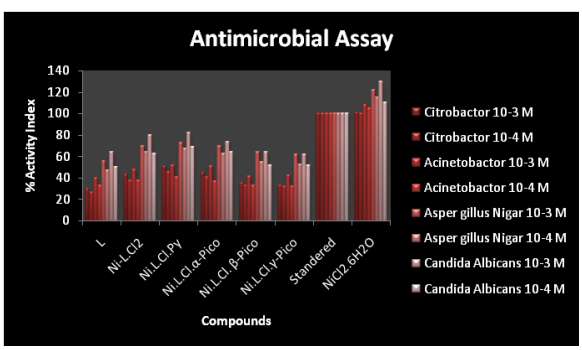
Compound % Activity Index	Citrobactor		Acinetobactor		Asper gillus Nigar		Candida Albicans	
	10^{-3} M	10^{-4} M	10^{-3} M	10^{-4} M	10^{-3} M	10^{-4} M	10^{-3} M	10^{-4} M
L	30.41	27.00	40.32	33.30	55.60	47.36	64.71	50.00
Ni-L.Cl,	43.12	37.91	48.38	37.69	70.19	64.19	80.30	63.00
Ni.L.Cl.Py	51.05	45.50	52.00	40.72	73.21	67.17	82.35	69.10
Ni.L.Cl.α-Pico	45.08	40.68	51.51	37.39	69.80	62.90	74.10	64.12
Ni.L.Cl. β-Pico	35.26	33.32	42.16	33.40	64.60	54.90	64.45	52.01
Ni.L.Cl.γ-Pico	33.20	32.13	42.18	32.43	62.14	52.64	62.43	52.00
Standard	100	100	100	100	100	100	100	100
$NiCl_2.6H_2O$	101.25	100.37	108.30	105.20	122.30	115.02	130.28	110.30

(Standard -Cefodoxine, Fluconazole)

% activity index was calculated by the formula

$$\% \text{ Activity Index} = \frac{\text{Zone of inhibition of test compound}}{\text{Zone of inhibition of standard (diameter)}} x100$$

Fig 1 Bar Graph % Activity Index



Result and discussion:

Elemental analysis, % yield, magnetic moment, molar conductance and other physical properties are presented in Table I. Elemental analysis data showed 1:1 ratio of metal ion, ligand for complex and 1:1:1 ratio of metal ion, ligand and heterocyclic base for all adducts. The compounds are insoluble in polar and non polar solvents and soluble in DMF in which conductivity measurements were made. The conductivity data indicate all compounds are non electrolyte [8]. The room temperature magnetic susceptibility of the complexes showed that complexes are diamagnetic. Mass spectral data confirmed the structure of ligand and complexes as indicated by molecular ion peak (M + 1) corresponding to their molecular weights.

The position of IR bands is useful to detect the bonding sites of all ligand molecules interacted with the metal. The coordination of nitrogen shifted ν(C = N),ν (N=C-S) to lower wave numbers. The band shifted from 1728-1670 cm^{-1} in uncomplexed compound to about 1500-1700 cm^{-1} in the spectra of complexes. The coordination of N atom of heterocyclic base is confirmed by ν (Ni-N) band in 260-270 cm^{-1} range. The bands of coordinated heterocyclic bases have also been observed in IR spectra of all complexes.

The TGA data of complexes indicated that the decomposition proceeded in four steps. In between temperature 30-115 ˚C, hydration of water molecules was lost. There is no change up to~200 ˚C after that there is break in the curves due to evaporation of part of molecule of organic ligand. The remaining ligand is removed from the coordination sphere in the temperature range 600-700°C. Finally the metal oxides were formed above 700°C. The decomposition was completed at ~780 °C. It has been found that Ni (II) complex was stable up to 200 °C and decomposition started above this temperature was completed in the temperature range 300-380°C. The second steps are in the range of 350-385°C. The third steps are in the range of 600-700°C. The solid residue is of Ni-O [9]. Thus complexes prepared with different metals decomposed in four steps. The organic part of the complex is removed above 200 °C. It is evaluated that the coordination of metal ion to ligand is responsible for the thermal stabilities of metal complexes [10].It is found that the thermal stability of all complexes is nearly same.

The results of antibacterial and antifungal studies are given in Table 2. The antimicrobial assay was carried out by the well diffusion method. The activity was determined by measuring the diameter of the inhibition zone in mm. Biological activity was measured in two different molar concentrations, 10^{-3}M and 10^{-4} M to study the effect of dilution. The chelate Ni.L.Cl.py showed maximum activity against bacterial and fungal species than free ligand and other complexes. The 5-aminothiabendazole was found less active than its complex..This difference might be due to chelation which reduces the polarity of the central metal atom because of the partial sharing of its positive charge with donor groups and possible π-electron delocalization within the whole chelating ring. Due to this, the lipophilic nature of the central metal atom increases, which facilitates the permeation of the complexes through the lipid layer of the cell membrane [11].Thus in complexes, coordination number increases which in turn increases microbial activity.Acinetobactor and Citrobactor are gram –ve bacterial species. In gram negative bacteria the outer membrane is thin and they possess outer membrane. It might not be easy for the complexes to diffuse inside the bacterial cell. A very good inhibitory activity was also found by the yeast Candida albicans [12]. The metal chloride salts were more effective than complexes. This shows that free metal ions are more effective than one bound in complexes. But use of metal ion solution for bacterial diseases is toxic, so it can be used in coordinated form with ligand. The general sequence of % activity index can be represented as -

Metal salt > Standard > Complexes > Ligand.

The % activity index is found higher in 10^{-3}M concentration than10^{-4} M. This indicates % activity index decreases on dilution.

REFERENCES

1. Foye W.O, Thomas L.L, David A and Williams B I. Principles of Medicinal Chemistry, Waverly Pvt. Ltd., New Delhi, Fourth Edition 1995. | 2. Kadam S S, Mahadik K R and Bothara K G. Principles of Medicinal Chemistry, Vol-I and II, 1997. | 3. Swearingen K., West D.X. , Trans. Met. Chem. 26 2001 252. | 4. Wood J.M., in: Sigel H. (Ed.), Microbial Strategies in Resistance to Metal Ion Toxicity, Metal Ions in Biology, Marcel Dekker, New York, 1984. | 5. Canadas M., Lopez-Torres E., Martinez-Arias A., Antonia Mendiola M., Tersa Sevilla M, Polyhedron, 12 2000 2060. | 6. Ali M.A., Mirza A.H., Nazimuddin M., Rahman H., Butcher R.J., Polyhedron, 2431 2001 | 7. Mathew M., Palenik G.J., Clark G.R., J. Inorg. Chem, 12 1973 346. | 8. Geary W.J., Coord. Chem. Rev, 1971, 7, 81. | 9. Sekerci M., Yakuphanoglu F., J. Therm. Anal. Cal, 75 2004 189. | 10. Mohamed G.G., Nour-El Dien FA, El-Gamel E.A., J. Therm. Anal. Cal 67 2002 135. | 11. Shrivastava R.S., Inorg. Chimica Acta, .I 56 1981 65. | 12.Mitic D,Milenkovic M. Milosavljevic S, Godevac D, Miodragovic Z, Andelkovic K,Miodragovic D. 44, 2009 1537. |