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Synthesis and characterization of cobalt complex of 5-Amino-2-(4-thiazolyl)-1H-benzimidazole

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ABSTRACT:

There are vast number of pharmacologically active heterocyclic compounds known, many of which are in regular chemical use. Among these N and S containing heterocycles are of great importance. 5-Aminothiabendazole, known for its synthetic utility and broad spectrum of pharmacological activity, is one among such heterocyclic compounds. Several of its derivatives showed pharmacological activity. These are used as therapeutic agents and are thus interesting for the synthesis of biologically active compounds. The benzimidazole framework and many of its derivative exhibit variety of biological action. They are used as antibacterial, antiviral, anticancer and antifungal agents. 5-Aminothiabendazole is a well known Anthelmintic agent which is non-toxic to humans. It has also application as a fungicide in agriculture. Because of a structural similarity to chelating agents, such as 2, 2'-bipyridine and 1-10 phenanthroline, we were promoted to design and synthesize metal complexes of it.

KEY WORDS: 5-Aminothiabendazole, Cobalt complexes of 5-Aminothiabendazole, Anthelmintic agent, heterocyclic compounds, Cobalt complexes

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INTRODUCTION:

Sulfur and/or nitrogen heterocycles have acquired a great importance among the heterocycles, as these possess pharmaceutical activities and pest management potency. These widely occur in the nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cells. The utility of thiazoles in curative treatment has been firmly established. They exhibit anti-bacterial, anti-hypertensive, anti-anginal, anti-arrhythmic, anti-histaminic, narcotic antagonist, etc. activities[1]. Thiazole nucleus is found in many antibiotics and vitamins in one or another form.

The benzimidazole compounds have been proved to be the most important group of fungicides with systemic activity and are well known for their pronounced ability to control a large number of fungal diseases. Benomyl, thiabendazole and thiophanate methyl are main examples of this fungicide class. 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].

The 2-(4-thiazolyl)-1H-benzimidazoles are structurally analogous to benzimidazoles, well known as an anthelmintic agent and systemic fungicide. Its fungicidal properties and systemic properties in plants have already been reported as a fungicide with protective and curative action. It is used to control of *Aspergillus*, *Botrytis*, *Ceratocystis*, *Cercospora*, *Colletotrichum*, *Corticium*, *Diaporthe*, *Diplodia*, *Fusarium*,

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Gibberella, Gloeosporium, Oospora, Penicillium, Phoma, Rhizoctonia, Sclerotinia, Septoria, Thielaviopsis, Verticillium spp., etc.[3] in asparagus, avocados, bananas, barley, beans, cabbage, celery, chicory, cherries, citrus, cotton, some cucurbits, flax, mangoes, mushrooms, oats, onions, ornamentals, pawpaws, pome fruit, potatoes, rice, soybeans, strawberries, sugar beet, sweet potatoes, tobacco, tomatoes, turf, vines and wheat. Also used for control of storage diseases of fruits and vegetables and for control of Dutch elm disease. It is commonly used as an anthelmintic in human and veterinary medicine too [4]. Again thiabendazole has significant anthelmintic activity for gastrointestinal parasites in sheep, goats, cattle, horses, swine, dogs, and poultry. This compound is well-tolerated and does not stain the skin, hair or wool of animals. It may be given orally for therapeutic use or in feed or mineral supplements for the prophylactic control of parasites in domestic animals.

Benzimidazole and thiazole analogues have found applications in medicine and agriculture[5]. Therefore development of a simple, fast and flexible method to generate libraries of such compounds was desirable. The structural modification or derivatization and bioassay are highly essential to establish structure-activity relationships in order to exploit the molecules having better potency and efficacy. In continuation of our work on synthesis of biologically active compound using polymer-supported reactions, we report herein a simple, rapid and safer method for the preparation of N-alkyl and N-acyl derivatives of 2-(4-thiazolyl)-1H-benzimidazole. Easy separation of products with higher yield and purity by simple work-up, and speed are crucial features of the method. The metal complexes of thiabendazole structure, antimicrobial activity and photodynamic effects has been done[6]. Synthesis, X-ray crystal structures and biomimetic and anticancer activities of novel copper thiabendazole is done.[7]

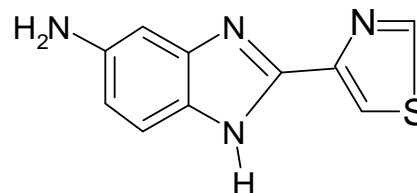
EXPERIMENTAL WORK

5-Aminothiabendazole acts as both acid and base, thus it is possible to make compounds which are neutral, cationic or anionic in nature, as well as report biological activity of metal complexes. The potential N,N'-donor chelating agent are quite rare. In present paper we report synthesis and characterization of derivatives of 5-Aminothiabendazole, and differentiate fungitoxic activity with those of nitrothiabendazole.

Since ,literature survey indicate that not much work had been done with 5-Aminothiabendazole the author has undertaken this consideration in present work because of structural similarity to chelating agents such as 2,2' bipyridine and 1,10 phenanthroline. We were promoted to synthesize metal

complexes, and in this case 5-Aminothiabendazole is selected as ligand that could form complexes with the metals such as Cu, Ni, Co, Zn. Herein we report the synthesis of these metal complexes and their biological activity.

Physicochemical properties like melting point, TLC and IR data were collected. The structure of ligand is –



Thiabendazole - 5-Amino 2-(4-thiazolyl) 1H benzimidazole (TBZ)

Molecular formula - $C_{10}H_8N_4S$.

Molecular weight - 216gm.

Nitrogen heterocycles have acquired an immense importance among the heterocycles, possessing pharmaceutical activities and widely occur in the nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cells. The utility of thiazoles in curative treatment has been firmly established. They exhibit anti-bacterial, anti-hypertensive, anti-anginal, anti-arrhythmic, anti-histaminic, narcotic antagonist, etc. activities. Thiazole nucleus is found in many antibiotics and vitamins in one or another form.

Benzimidazole and many of its derivatives exhibit a variety of biological actions, including antibacterial, antiviral, anticancer and antifungal activity [7]. Benomyl, thiabendazole and thiophnate methyl are main examples of this fungicide class. Because of their systematic activity, they can help to control some diseases after infection.

MATERIALS AND METHODS

Thiabendazole (supplied by_Vijay Chemicals ,Pune), Cobalt Chloride,Cobalt nitrate,zinc dust, methanol, formic acid / ammonium formate, chloroform, super saturated solution of NaCl, Other chemicals(supplied by Kishor Agencies,Jalgaon)

1. Thiabendazole To 5-Nitrothiabendazole

CHEMICALS:- Thiabendazole, conc. H_2SO_4 , conc. HNO_3 , sodium bicarbonate ($NaHCO_3$)

PROCEDURE:-

Take 2.1gm (5gm) of thiabendazole in dry beaker as a starting compound and add drop wise ice Cold 2.3(11.5ml) of Warm it

at 45-50° C for 10 min (for dissolving thiabendazole).

Nitrating mixture : On the other hand take ice cold 1.5 ml conc.H₂SO₄ add it drop wise to 10.2 ml of conc. HNO₃ keep the temp below - 4° C.

In ice bath take 1.5 ml nitrating mixture add it to beaker containing mix of thiabendazole and conc.H₂SO₄ keep the temp below - 4° C with constant stirring. After complete addition keep the reaction mixture aside for 45 min (i.e. at R.T.25° C).After 45 min warm the reaction mixture at 85-90° C for 90 min (1 ½ Hr).After 90 min (1 ½ Hr) allow the reaction mixture come the temp at room temperature. When the temp come at RT then add crushed ice with constant stirring very faint yellowish white precipitate is form add more amount of cold water in it. Decant the supernatant liquid through filter paper. Repeat the procedure till the acid become completely removes (when we give washing to the ppt the ppt becomes spongy increase in size with change in color very faint yellow to faint yellow).To test whether the acid is completely remove or not kept the blue litmus paper at the bottom of the funnel in the contact with flowing filtrate. If there is no change then acid is completely remove .OR

Add the sodium bicarbonate to the reaction (after adding ice) mixture until the effervescences of CO₂ is completely stops due to addition of sodium bicarbonate basicity of the precipitate is increases to remove basicity decant the reaction mixture add dist water to the precipitate repeat the procedure till the precipitate becomes neutral. Test it by holding the red litmus paper near the mouth of the funnel in to the running filtrate. Yellow precipitate is obtained. **(This procedure taking much more less time and less amount of distilled water)**

Remove the precipitate on filter paper allow it to dry it completely recrystallize it and take MP of it.

MELTING POINT: literature[8]:- 208-210° C.

Observe:- 212° C.

2. 5-Nitrothiabendazole To 5-Aminothiabendazole

PROCEDURE:-

Take 1.2 gm (4.8gm) of nitro thiabendazole in completely dry beaker add 0.4 gm (1.6gm) of Zn dust in it make it homogenous mixture by using glass rod.

After making homogenous mixture then add 5 ml (20ml) of methanol (as a solvent) stir it continuously till the mix dissolve in methanol.

Then add slowly 2.5 ml (10.0ml) of formic acid stir it vigorously. (when we add formic acid there is possibility of forming sticky residue continuously stirring may dissolve the sticky residue)filter the solution (here filtrate is important for us) take the filtrate in dry beaker warm it on the water bath till the complete organic solvent(i.e. methanol) completely evaporate out .(when viscous bubbles are come from solution).After completion of removing of methanol allow to cool the solution at RT (when solutions temperature is come down then dark brown crystal are form with viscous liquid)

Add few drops of ether or chloroform in it stir it well.Add supersaturated solution of NaCl (i.e. hot solution of saturated NaCl to remove the formic acid completely sticky residue is form when decant the solution and wash the sticky residue residue is slowly converted to the powdered residue)

Filtered the precipitate. Monitor the reaction through TLC and Melting point.[8]

- Melting point :- 1) Literature M.P.:- 233° C.
2) Observe M.P. :- 234° C.

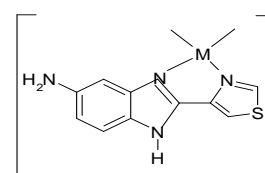
3. Synthesis of Metal Complexes of substituted 5-Amino 2-(4'-thiazolyl)-1H-benzimidazole based ligands



Where, M = Co

X = one of several monovalent anion

Synthesis of metal complexes of a 5-Amino thiabendazole with Co.



Synthesis- Metal- Co nitrates

1) Synthesis of 1:1 molar complexes

This compound was prepared by dissolving 1gm of 5-Amino TBZ in 40 ml of a boiling ethanol containing .0.27ml of 12N HCL and adding 1.47 gm of a corresponding metal nitrate in ~25 ml of ethanol the mix. Was refluxed for ~2 hrs. On a

steam bath. The comp. was separated by centrifugation and washed in the centrifuge tube with ethanol; the complexes of a Co are Yellowish coloured ppt.

2) Synthesis of 1:2 molar complexes

In case of Co it was prepared by dissolving 2.0 gm of 5-Amino TBZ and 1.44 gm of Co (NO₃)₂ 6H₂O in a 100ml hot water containing 0.85 ml 12N HCl. The solution was warmed on a steam bath for ~2 hrs.. The solution was filtered hot; filtrate allowed to cool and evaporate to dryness at a R.T, the dry crude Co TBZ (NO₃)₂ is obtained. It may be recrystallized by using ethanol. Same procedure for the metal complex Co-chloride also.

3) Synthesis of 1:3 molar complexes

In a case of Co 1:3 molar complex the compound prepared by dissolving 3 gm of 5-Amino TBZ in a 100 ml hot water containing 0.85 ml 12N HCl and when solution was complete add 1.44 gm of Co(NO₃)₂ 2 ml of 6N HCl was added and solution heated on steam bath for a 0.25hr. The solution was filtered hot and filtrate evaporated to dryness, at room temperature. Same procedure for the Co-chloride also.

5. Characterization

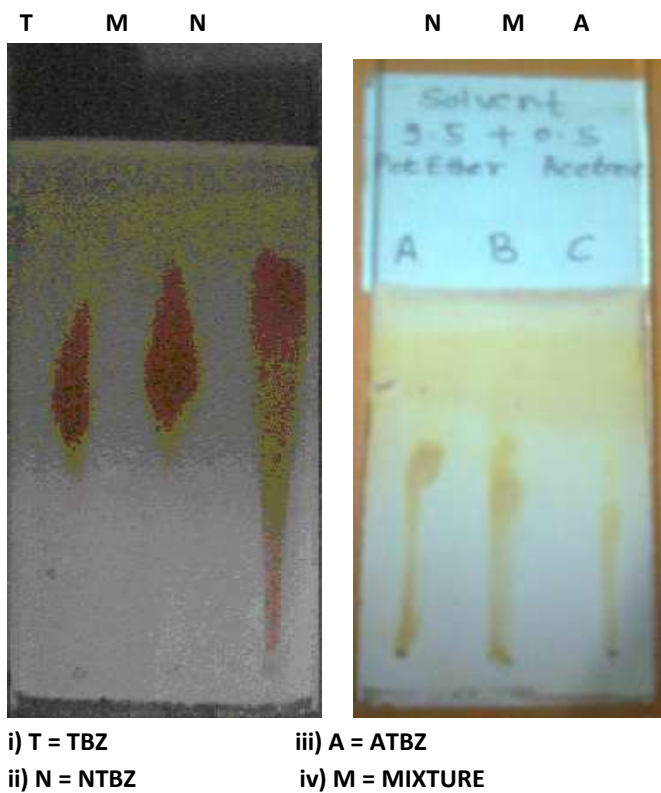


Figure 1: TLC of thiabendazole and its derivatives

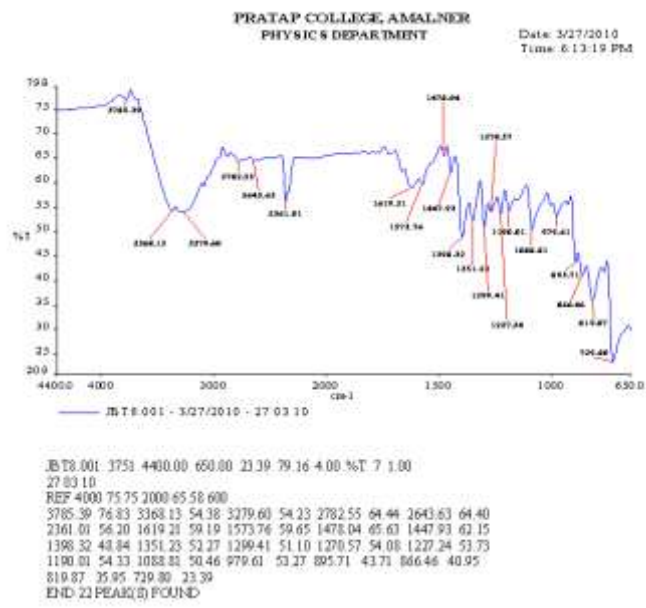


Figure 2: I.R. spectrum of Thiabendazole

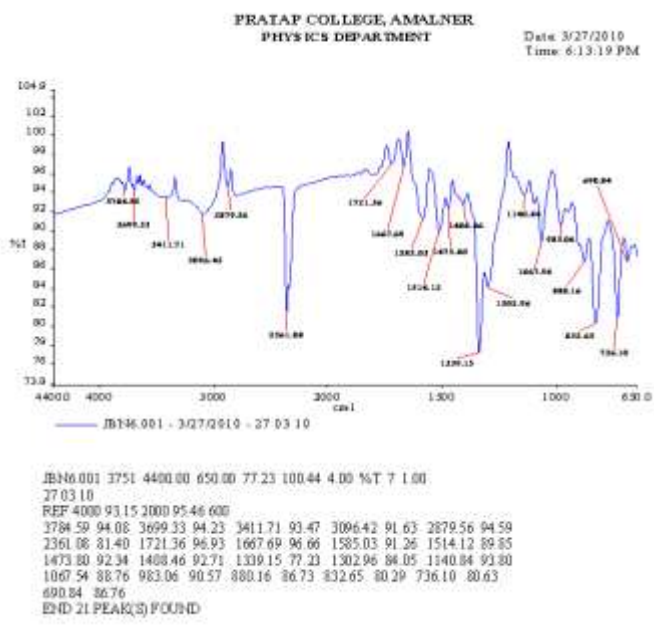
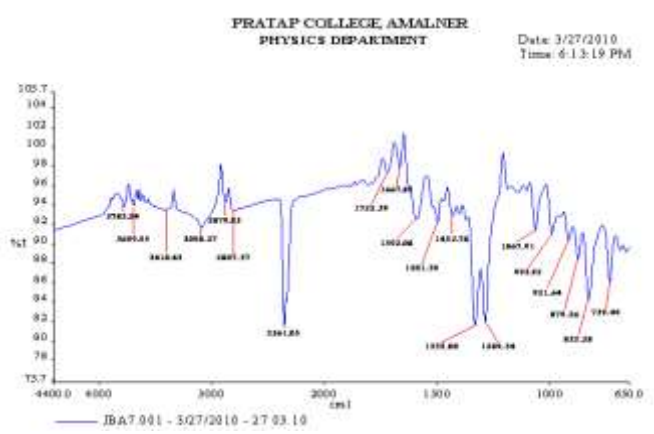


Figure 3: I.R. spectrum of 5-Nitrothiabendazole



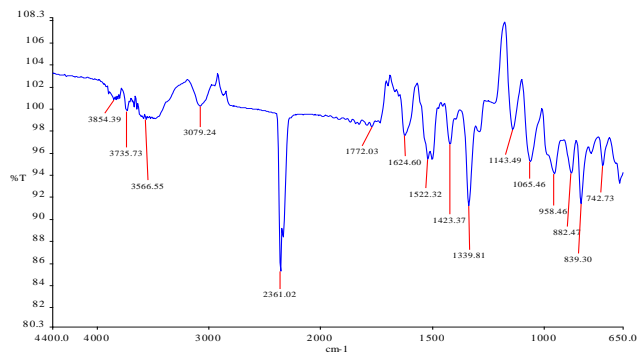
JBA7.001 3751 4400.00 650.00 81.40 101.46 4.00 %T 7 1.00
 27 03 10
 REF 4000 92.89 2000 95.56 600
 3785.24 93.30 3699.53 93.94 3410.43 93.46 3098.27 91.72 2879.83 94.31
 2807.37 93.40 2361.05 81.40 1722.39 97.36 1667.82 97.89 1592.08 92.61
 1501.39 92.07 1432.78 92.81 1333.00 81.51 1289.24 81.97 1067.91 91.37
 995.92 90.95 921.64 90.26 879.26 88.42 832.28 84.18 739.40 85.96

END 20 PEAK(S) FOUND

Figure 4: I.R. spectrum of 5-Aminothiabendazole

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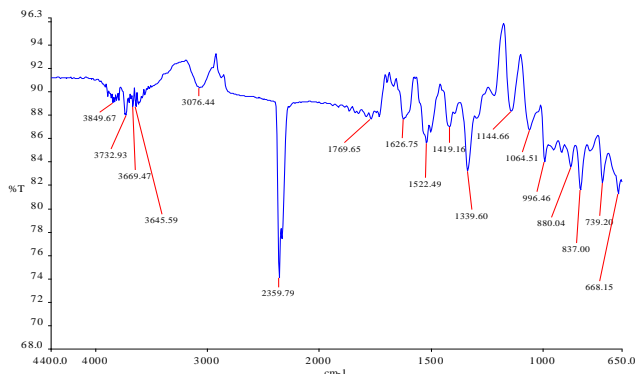


Figure 7: 1:1 Molar cobalt complex chloride

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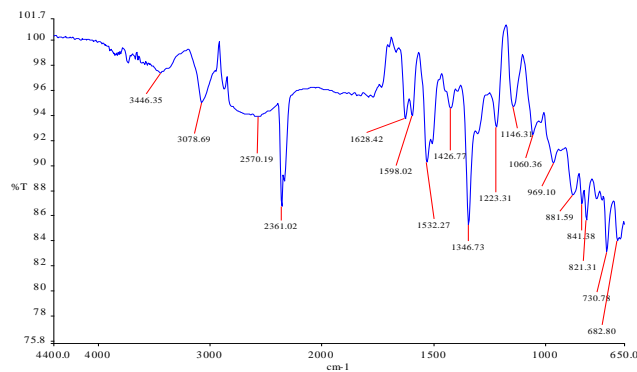


Figure 5: I.R. spectrum of 1:2 molar cobalt complex nitrite

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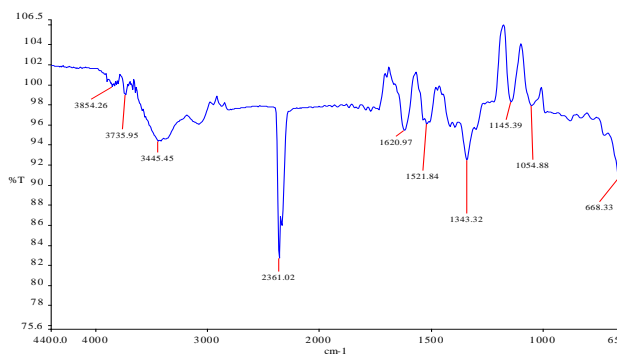


Figure 8: 1:3 Molar cobalt complex nitrate

Table : 1 IR spectral data

Sr. No.	IR freq. Range cm-1	Group
1.	600-680	C=C
2.	685-696	CH ₂ -NH-CH ₂
3.	739-789	NH ₂
4.	819-954	S-CH=CH ₂
5.	980-1088	RCH=CH ₂
6.	1144-1599	-NO ₂ and Ar NH ₂
7.	1600-1772	S-CH=CH ₂
8.	2360-2362	Presence of N atom in aromatic ring.
9.	2643-2877	RCH=CH ₂
10.	3075-3100	C-H stretching
11.	3279-3411	N-H stretching
12.	3589-3853	NH ₂ -C stretching

Figure 6: I.R. spectrum of 1:2 Molar cobalt complex nitrite

6. BIO-ASSAY

Bioassay is important and crucial in a evolution of bioactivity of compound and helpful to establish structure activity relationship (SAR) in a present work all derivative have been differentiate with Thiabendazole for antimicrobial potency such antimicrobial activity againsts different bacteria *Bacillus subtilis*, *Staphylococcus aureus*, *pseudomonas aerogenish*, *proteus vulgaris* , *Escerchia coli*. [09]

5-Amino Thiabendazole found most potent against fungi. The structural modification of a TBZ was found to be successfully effective to confer and increase pest management potency. In a present case

Parent compound reflected very good antifungal potency .comparatively less action was observed in its derivative in contrast to this parent was found to be totally inactive against bacteria but all of its derivative showed very good antibacterial efficiency.

Technique

To each petriplate 20 ml of sterilized medium was added after agar, had set ,10% of inoculam was added to each pertiplate and spread thoroughly by rotatory motion of the plate. Sterilized whatmann no.1 filter paper disc (6 mm) diameter were thoroughly moistened with the solution of a compound . then this disc are placed into the plates. Plates are incubated for 36 °C .A clear zone of inhibition was observed around paper disc demonstrate relative susceptibility of a bacteria to the synthesized derivative .the bacterial potency is proportional to diameter (in mm) of the zone inhibition the expt, were performed in duplicate average measured zone of inhibition was considered.[10]



Figure 9 : Zone of inhibition of 5-amino-thiabendazole and its cobalt complexes

Conclusion:- From the above data it clearly indicate that most of 5-amino-thiabendazole complexes found most potent against used bacterial species

Table :2 MICROBIAL ASSAY

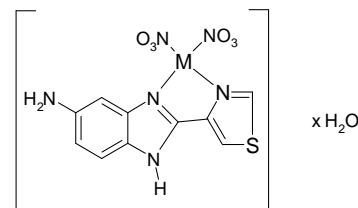
Complex	<i>Bacillus Subtilis</i> Zone of inhibition in mm	<i>Staphylococcus aureus</i> Zone of inhibition in mm	<i>Proteus Vulgaris</i> Zone of inhibition in mm	<i>Pseudomonas auregenish</i> Zone of inhibition in mm
5-Amino-Thiabendazole For 1,3,5 ppm	08	10	07	08
Co[5-NH ₂ TBZ](NO ₃) ₂ XH ₂ O	11	15	08	09
Co[5-NH ₂ TBZ] ₂ (NO ₃) ₂ XH ₂ O	23	16	11	22
Co[5-NH ₂ TBZ] ₃ (NO ₃) ₂ XH ₂ O	10	14	15	21
Co[5-NH ₂ TBZ]Cl ₂ XH ₂ O	13	12	09	08
Co[5-NH ₂ TBZ] ₂ Cl ₂ XH ₂ O	22	17	12	11
Co[5-NH ₂ TBZ] ₃ Cl ₂ XH ₂ O	12	14	16	23

7. RESULTS AND DISCUSSION

5-Aminothiabendazole is most potent antifungal agent. In an effort to extend this class of novel drug .We have been studying metal complexes containing benzimidazole based ligand. Benzimidazole and many of it's derivatives antibacterial, antiviral, anticancer and antifungal activity . Well known anthelmentic agent which are non toxic to human.

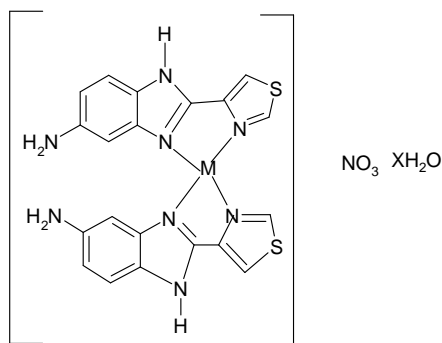
The metal free neutral TBZH is a very poor inhibitor of growth of pathogen .When a ligand is found to cationic & anionic state .Both are moderate anti-condida agent .

In this case it generate the complex similar to chelating agent 2,2' bipyridine and 1-10 phenanthroline.



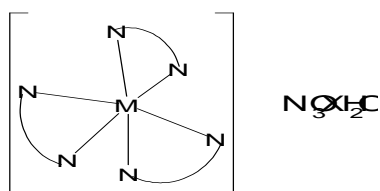
Where M is Co.

Figure: 10 Structure of 1:1 COMPLEX- NITRATE



Where M is Co.

Figure:11 Structure of 1:2 COMPLEX NITRATE



Where M is Co.

Figure:12 Structure of 1:3 COMPLEXES NITRATE

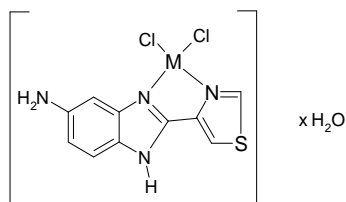


Figure :13 Structure of 1:1 COMPLEXES CHLORIDE

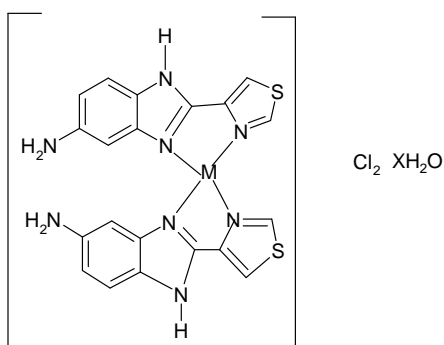


Figure:14 Structure of 1:2 COMPLEXES CHLORIDE

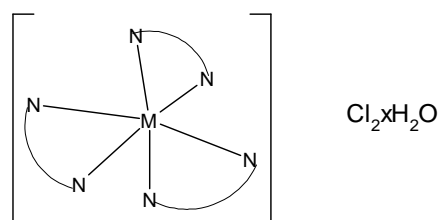


Figure:15 Structure of 1:3 COMPLEXES CHLORIDE

Table:2 Results

Complex	Practical	Colour	Reaction time
	Yield In gm		
$[\text{Co}(5\text{-NH}_2 \text{ TBZ})(\text{NO}_3)_2] \cdot x\text{H}_2\text{O}$	0.96	Reddish brown	~2
$[\text{Co}(5\text{-NH}_2 \text{ TBZ})_2](\text{NO}_3)_2 \cdot x\text{H}_2\text{O}$	1.69	Yellow with pink shade	~2
$[\text{Co}(5\text{-NH}_2 \text{ TBZ})_3](\text{NO}_3)_2 \cdot x\text{H}_2\text{O}$	1.44	yellow	~0.25
$[\text{Co}(5\text{-NH}_2 \text{ TBZ})\text{Cl}_2] \cdot x\text{H}_2\text{O}$	1.10	Reddish brown	~2
$[\text{Co}(5\text{-NH}_2 \text{ TBZ})_2]\text{Cl}_2 \cdot x\text{H}_2\text{O}$	1.89	Pinkish	~2
$[\text{Co}(5\text{-NH}_2 \text{ TBZ})_3]\text{Cl}_2 \cdot x\text{H}_2\text{O}$	1.57	Faint yellow	~0.25

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