



## Noval 3d Series transition metal Complexes with Schiff base AEBTC (2-Thiophenecarboxaldehyde and 2-Amino-6-Ethoxybenzothiazole): Synthesis, Characterization, and Biological Importance

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### ABSTRACT

Schiff base derived from  $C_4H_3SCHO$  (TC) and  $C_9H_{10}N_2OS$  (AEB) chemical compounds, and characterized by using techniques like elemental analyses, Infrared,  $^1H$  NMR, mass, SEM, XRD, and thermo gravimetric analysis (TGA), IR studies reveal that (AEBTC) tridentately coordinates towards ions (transition metals) with NNS ligational sites on trizole N, azomethine N, thiophene S. The magnetic moment suggests octahedral geometries for the complexes. The TGA shows that the loss of water occurs first in the dehydration of hydrated complexes, followed by anions and ligand molecules. The antibacterial and antifungal activity were also evaluated, for ligand and the results were compared to those of the metal complexes for each against Gram-positive and Gram-negative bacteria and fungi like *A. niger* and *C. albicans*.

**Key words:** Schiff base, Thermal analysis, Metal complexes and Biological importance.

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### INTRODUCTION

Benzothiazoles and its derivatives are biologically active compounds. Various terrestrial or marine natural substances that have beneficial biological effects include the benzothiazole ring [1]. Due to its anticancer [2], antiviral [3], and antibacterial [4] properties, benzothiazole derivatives have grown in importance and attention. In these classes of heterocycles the positions 2 and 6 are critical for antibacterial action against both strains, according to structure activity relationship (SAR) studies [5]. A wide range of therapeutically intriguing medicines with anti-inflammatory [6], anticonvulsant [7], antidiabetic [8], antipsychotic, neuroprotective [9] and diuretic [10] properties include the benzothiazole nucleus. Schiff base ligands containing transition metal complexes are very effective as catalytic agents for both heterogeneous and homogeneous reactions. These activity of these complexes vary according to the coordination positions of ligands, & central metal ions. On analyzing stimulating action of the metal complexes the activity varies according to structure and kind of Schiff base ligands present in Schiff base complexes. Recently, Schiff bases have appeared in heterocyclic Schiff bases complexes. These compounds have also been utilised in the perfumery, cosmetics, and as oxygen absorbents [11]. Potential locations for biochemically active substances linked to proton transfer equilibria and intermolecular hydrogen bonding are provided by Schiff base molecules. The biological reactions essential to life processes utilize the transition metals. They bind to the proteins in large number of ways characteristically coordinate through the O- or N-terminal, hence are key for the function &

conformation of organic macromolecules [12]. Due to tremendous variety, versatility, and complexation with a metallo-element that Schiff base structures contribute to the stability and usefulness of the molecules containing  $-NH_2$  groups [13]. Schiff bases have intriguing antipyretic, antibacterial & DNA cleavage properties [14–17]. Their accretion, storage and passage in living systems can be demonstrated due to the presence certain metal ions in the human blood specifically in plasma [18]. Because of their structural diversity and ease of preparation, this type of ligands are formed with less effort & produce complexes with most of the metal ions [19–20]. These complexes are amongst the best stereo chemical models in core group and transition metal coordination chemistry.

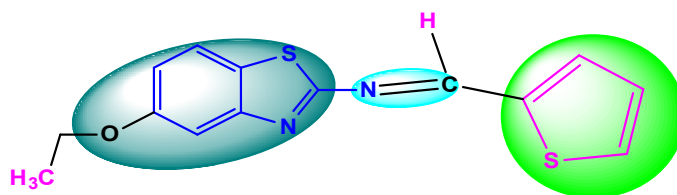
## MATERIAL AND METHODS

### Materials and reagents

All the chemicals used were of GR/AR grade. A pure sample of 2-thiophene-carboxaldehyde and 2-amino-6-ethoxybenzothiazole was obtained from Sigma Aldrich Ltd. The metal salt of  $NiCl_2$  and  $CuCl_2$  and  $ZnCl_2$  were from Hi-media Pharmaceuticals Ltd. Solvents used were ethanol, acetone, and DMF.

### Ligand Preparation (AEBTC Schiff base)

The appropriate amount of 2-amino-6-ethoxybenzothiazole (0.1 mol, 1.94 g) and 2-thiophenecarboxaldehyde (0.1 mol, 1.12 g) were mixed in equimolar proportions in a 100 ml diluted solution of ethanol and distilled water with a ratio of 60:40 in a round bottom flask. The reaction mixture was refluxed for 3 hours at 65–75°C. After refluxing, the reaction mixture is transferred to an evaporating cup and evaporated to 1/3 of its original volume. The evaporation cup was left on the water bath for one day until yellow crystals appeared. The product was separated from 100% ethanol using filtering and crystallisation. The crystallized solid is dried over  $CaCl_2$  in a desiccator and weighed. The melting point was also recorded. The yellow ship major is obtained with a yield of 61%.

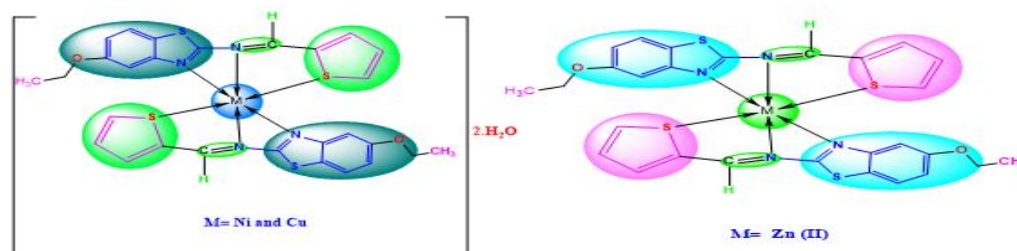


**5-ethoxy-N-(thiophen-2-ylmethylene)benzo[d]thiazol-2-amine**

**Fig 1.** Showing Schiff base (AEBTC)

### Preparation of metal complexes

0.02M sol. of AEBTC (0.577g) and 0.01M solutions of metal salts, like  $NiCl_2 \cdot 6H_2O$  (0.119g),  $ZnCl_2$  (0.068g) and  $CuCl_2 \cdot 2H_2O$  (0.085g) were prepared separately in pure ethanol and mixed in a round-bottomed flask. The resulting solutions were refluxed for 2 hours and kept for 3 days. The crystals obtained were then washed with the same solvent, dried over vacuum and weighed. Melting points were recorded. Yield obtained is 69–82%.



**Fig.2-3:** Synthesized 3d transition metal complexes  $ML_2$  type

## Biological activities

### Antibacterial Activity

$10^{-6}$  -  $10^{-7}$  spores/ml bacterial suspension (spore suspension) of (selected) tested organisms were added immediately before it solidifies to sterilized agar medium, then pour the mixture into sterile Petri dishes (diameter of 9 Cm) the allowed to stand until it harden or solidify. 3 holes were drilled in each plate with sterile cork borer (SCR) 6 cm in diameter, then compound (100  $\mu$ g/ml) dissolved in DMF poured in the well. Then incubation occurs at 37°C for 48 hours, and zone of inhibition were measured.

### Antifungal Activity

Sabouraud Dextrose Agar (for mushrooms) petri plates were prepared under aseptic conditions by using agar. 0.1 ml of the test organism is streaked onto an agar plate. By using sterilized drill a 5mm wide holes was drilled in the agar plate. A sample of Schiff's base, metal complex, standard drug and suitable control solvent are added individually to each well and the solution is allowed to diffuse into the agar medium. All plates containing mushrooms were incubated at 28°C for 48 hours. The inhibition zone around the well is measured in millimeters. The sample inhibition zones are compared with standards and the results are tabulated.

### Antioxidant Activity

DPPH(diphenylpicrylhydrazine) test. This method is based on the reduction of a colored solution of DPPH (1,1-diphenyl-2picrylhydrazyl) in the presence of the drug under test. DPPH solution (0.004% w/v) was prepared in 95% methanol. Various concentrations of Schiff base and its derivative complexes of 20 µg/ml, 40 µg/ml, 60 µg/ml, 80 µg/ml and 100 µg/ml were prepared in methanol. 0.5 ml of freshly prepared DPPH solution was added to each tube and allowed to react in the dark for 10 minutes. The absorbance was measured at 517 nm using a spectrophotometer.

## RESULTS AND DISCUSSION

In accordance with the instructions in the experiments section, Schiff base was synthesized, crystallised, dried, and submitted to an elemental analysis. The results of elemental analyses (C, H, N, S) with molecular formula are presented in Table 1.

Ligand/ Complexes	Color	M.Pt. (°C)	Mol. Wt.	Elemental analysis found (calcd.) %				
				C	H	N	S	Metals
AEBTC C <sub>14</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> S <sub>2</sub>	Yellow	102	(288.39)	58.78 (58.33)	3.79 (4.16)	10.03 (9.71)	21.76 (22.20)	---
[Ni(AEBTC) <sub>2</sub> ].2H <sub>2</sub> O C <sub>28</sub> H <sub>26</sub> N <sub>4</sub> O <sub>4</sub> S <sub>4</sub> Ni	Olive Drab	235	(669.49)	49.87 (50.23)	3.59 (3.88)	8.58 (8.37)	19.43 (19.13)	8.96 (8.77)
[Zn(AEBTC) <sub>2</sub> ] C <sub>28</sub> H <sub>22</sub> N <sub>4</sub> O <sub>2</sub> S <sub>4</sub> Zn	Light Grey	205	(640.16)	52.74 (52.55)	3.89 (3.44)	9.01 (8.75)	19.7 (20.01)	9.85 (10.22)
[Cu(AEBTC) <sub>2</sub> ].2H <sub>2</sub> O C <sub>28</sub> H <sub>26</sub> N <sub>4</sub> O <sub>4</sub> S <sub>4</sub> Cu	Dim Grey	>250	(674.34)	50.24 (49.86)	4.07 (3.85)	7.97 (8.31)	19.61 (18.99)	9.02 (9.42)

**Table-1** Analytical and Physio-chemical data of Schiff base ligand and its metal complexes

### IR spectra and mode of bonding

The IR studies confirm the tridentate nature of the AEBTC and coordinate to the metal via azomethine N, thiazole N and the thiophene S atoms [21]. The strong peak at 1656 cm<sup>-1</sup> in AEBTC is due to azomethine (-HC=N) group. the downward shift of about 17-41 cm<sup>-1</sup> of the peak in case complexes of AEBTC demonstrates the attachment along azomethine N [22]. The well-defined bands at 1594 cm<sup>-1</sup> in case of ligand is due to ν<sub>C=N</sub> thiazole ring [23]. The clear shift of this bands from 1594 cm<sup>-1</sup> to 1539-1578 cm<sup>-1</sup> in the complexes support the bonding via thiazole N atom of AEBTC to the metal ion [24]. The bands at 833 cm<sup>-1</sup> in case of ligand is due to ν<sub>C-S-C</sub> thiophene ring [25]. The shift of this band from 833 to 808-844 cm<sup>-1</sup> in the metal complexes support the coordination via thiophene S atom to the metal ion [26]. The aromatic ring exhibits the bands in the region 1506-1534 cm<sup>-1</sup> in AEBTC and complexes as well are attributed to ν<sub>C=C</sub> [27]. The presence of lattice water in case of Cu(II) and Ni(II) complexes is revealed by broad band in the region 3349-3432 cm<sup>-1</sup> [28]. TGA further clarifies the above observations. Novel bands in the region 623-688 cm<sup>-1</sup> and 425-472 cm<sup>-1</sup> for AEBTC metal complexes are attributed to ν<sub>M-N</sub> and ν<sub>M-S</sub> modes respectively [29-30]. So concluding the above observations it is obvious that AEBTC Schiff base binds to the metal(II) ions of Cu, Ni and Zn through thiophene S, azomethine N and thiophene S.

Ligand/Complexes	ν <sub>H2O</sub>	ν <sub>(HC=N)</sub>	ν <sub>(HC=N) Thiazole</sub>	ν <sub>(C=C) Aromatic</sub>	ν <sub>(C-S)Thiazole</sub>	ν <sub>(C-S-C)</sub>	ν <sub>M-N</sub>	ν <sub>M-S</sub>
AEBTC	...	1656	1594	1531	1318	833	...	...
[Ni(AEBTC) <sub>2</sub> ].2H <sub>2</sub> O	3432	1635	1539	1514	1313	808	634	425
[Zn(AEBTC) <sub>2</sub> ]	...	1623	1578	1521	1314	844	688	430
[Cu(AEBTC) <sub>2</sub> ].2H <sub>2</sub> O	3349	1617	1570	1534	1310	820	638	444

**Table 2:** IR spectral values

### <sup>1</sup>H NMR spectra

The Proton-<sup>1</sup>H NMR results (spectra) of AEBTC ligand shows that the band positioned at 7.28 ppm is because of proton in thiophene ring of ligand and showed upfield shifted to 7.75 ppm due to the ligation of Sulphur atom of the thiophene part to central ion. [31]. The AEBTC ligand shows a signal in the range of

7.26–6.71 ppm due to the aromatic proton [32] (Ar-H). This is due to the different environment around these protons. The azomethine [33] proton which appears at 7.26 ppm in the ligand shows an upward shift of 0.21 ppm and appears at 7.47 ppm in the complex, indicating azomethine-N coordination to the metal ion [34]. Signals in the range of 7.20–6.71 ppm appear as doublets and the multiplet shifts to 7.44–6.31 ppm for aromatic protons in the complexes. The wide singlet and multiplet ranges from 1.13 to 3.95 ppm are due to aliphatic protons [35].

#### Electronic spectra and magnetic susceptibility

Magnetic moment ( $\mu$ ) value of the Ni(II) complexes are (2.85 to 3.70 B.M). The derived complexes of Ni(II) showed bands at 10476–142768  $\text{cm}^{-1}$ , 15685–19458  $\text{cm}^{-1}$ , 21437–25500  $\text{cm}^{-1}$  with allowed transitions  $3A_{2g}(F) \rightarrow 3T_{1g}(p)$ ,  $3A_{2g}(F) \rightarrow 3T_{1g}(F)$ , and  $3A_{2g}(F) \rightarrow 3T_{2g}(F)$  respectively [36], illustrating the octahedral A band that the Zn(II) complex displays between 28360 and 31846  $\text{cm}^{-1}$  shows the transfer transition in synthesized ligand. As a result, electrostatic forces, size factors, and covalent bond forces alone influence the stereochemistry of Zn(II) complexes. Based on the additional information supplied, an octahedral geometry was proposed for them [38]. Magnetic moment values for the Cu(II) complex range from 1.97 to 2.86 B.M. [39]. the Cu(II) complexes shows the values of electronic spectra at 10167–11364  $\text{cm}^{-1}$  and 18532–19642  $\text{cm}^{-1}$  and the resolved transitions are as  $2B_{1g} \rightarrow 2A_{1g}$  and  $2B_{1g} \rightarrow 2B_{2g}$  [40–41].

#### Thermal analysis (TGA)

The thermal decomposition graph for the Ni(II) complex displays a three-step decay. The temperature range from 80–88°C marks the first step with a reduction of mass by 5.35 % (calcd. 5.2 %), is attributed for the mass equivalent to two molecules of lattice water. The second step of the decomposition from 425–755°C, with a mass equal to the organic moiety disintegration (coordinated & uncoordinated part of the ligand). The final residue corresponded to stable Ni(II) oxide 11.2 % (calcd. 11.0 %). The TGA graph for complex (Zn(II)) displays the decomposition from 295–880 °C, with a mass about 85% is in agreement with the organic moieties (coordinated and non-coordinated portion of ligand). Lastly Stable Zn(II) oxide 16% (calcd. 14.09 %) is left as a final residue. The TGA curve for Cu(II) complex also follows the same pattern of disintegration. The primary stage of decomposition involves the removal of two lattice H<sub>2</sub>O molecules accounting for the reduction of mass of 5.4% (calcd. 5.2%) at 85–91°C. In the second stage, decomposition occurs at temperature of 290–798°C indicating the loss of the organic moieties [42], whereas, in the last stage, stable state was observed above 798°C indicating the presence of metal oxide which is thermally stable. The residual weight percentage metal oxide (CuO) is 11.05 % which agrees well with the theoretical value 11.7% [43].

#### Mass Spectrum

The base peak of the ligand (C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>OS<sub>2</sub>) obtained at (m/z) 288.2 (I) is the said peak that corresponds to the molecular weight of Schiff base (L)<sup>+</sup>. Other fragmentations of Schiff base at 254 (II), 195.9 and 124.8 (m/z) is due to loss of (SH<sub>2</sub>)<sup>+</sup>, (C<sub>2</sub>H<sub>3</sub>S)<sup>+</sup>, (C<sub>2</sub>H<sub>3</sub>N<sub>2</sub>O)<sup>+</sup> from (III). The spectrum of [Cu(C<sub>28</sub>H<sub>26</sub>N<sub>4</sub>O<sub>4</sub>S<sub>4</sub>)] showed peak at m/z 674.2 (I) is because of [Cu(L).2.2H<sub>2</sub>O]<sup>+</sup>, indicating a dimeric nature and the molecular weight of (674) is confirmed. and the proposed formula for the complex. In addition to this peak, the complex exhibited fragment ion peaks with significant intensities at m/z values 611.7, 532.3, 437.3, 402.2, 286.9 and 168.1, indicating a fragmentation pattern. The observed peak at m/z 611.7 (II) is due to the loss of (C<sub>4</sub>H<sub>7</sub>O<sub>2</sub>)<sup>+</sup> from (I), at 532.3 (III) to the loss of (CH<sub>3</sub>S<sub>2</sub>)<sup>+</sup> from (II) and at m/z 437.3 (IV) due to the loss of (C<sub>4</sub>H<sub>3</sub>N<sub>2</sub>O)<sup>+</sup>. of (III), the high-intensity peak at 402.2 (V) is due to the loss of (C<sub>4</sub>H<sub>8</sub>N<sub>3</sub>O<sub>2</sub>)<sup>+</sup> from (III). Ion peak at 402.2 (V) is due to loss of (C<sub>4</sub>H<sub>8</sub>N<sub>3</sub>O<sub>2</sub>)<sup>+</sup> from (III). Another peak at 286.9 (VI) is due to the loss of (C<sub>3</sub>H<sub>3</sub>NCu)<sup>+</sup> from (V). the peak of 168.1 (VIII) is due to loss of (C<sub>4</sub>H<sub>5</sub>S<sub>2</sub>)<sup>+</sup> from (VI). The intensity values of different peaks provides the information of stability of different fragments [44–45].

#### X-Ray Diffraction Studies

Powdered XRD of derived metal complexes from their Schiff bases are entirely different. All the reflections in the complexes are new ones and the patterns are also new ones and fairly strong which signifies that there is a complete conversion of all reactants into products [46–47]. It is clear from the diffractogram patterns and respective d and 2 $\theta$  values, that in all the cases, new complexes/ compounds have been formed. Also, the sharp peak in the diffractogram of all complexes showed the crystalline nature of synthesized metal complexes [48].

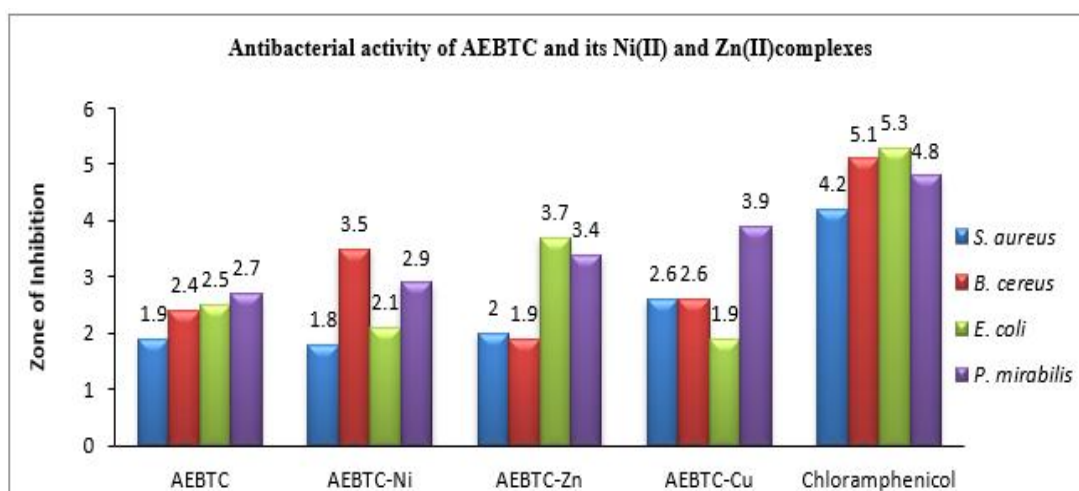
#### Antibacterial Activity

Antagonistic activity of (to be tested) compounds against various Gram+ve and Gram-ve infectivity was observed (Table 3). The synthesized complexes revealed potential antibacterial activity in comparison with the ligands and lower than that of standard chloramphenicol. Based on the inhibition zone created against the tested microbe or bacteria it is observed, Schiff base metal complexes of AEBTC shows enhanced antibacterial activity comparable to its ligand, in case of *P. mirabilis* with 2.7 mm inhibition

(zone). Likewise, other compounds show enhanced activities for the bacteria in this series. In case of Zn metal complexes shows enhanced antibacterial activity with 3.7 mm and 3.4 mm while Cu shows 1.9 mm and 3.9 zone of inhibition in case of *E. coli* and *P. mirabilis*[51, 52]. In case AEBTC with 1.9 mm and 2.4 mm of inhibition in *S. aureus* and *B. cereus* [53, 54]. In this case metals show little enhanced activities but in some cases its show less activities then their ligand.

Compounds	Gram Positive Bacteria		Gram Negative Bacteria	
	<i>S. aureus</i>	<i>B. cereus</i>	<i>E. coli</i>	<i>P. mirabilis</i>
AEBTC	1.9	2.4	2.5	2.7
AEBTC-Ni	1.8	3.5	2.1	2.9
AEBTC-Zn	2.0	1.9	3.7	3.4
AEBTC-Cu	2.6	2.6	1.9	3.9
Chloramphenicol	4.2	5.1	5.3	4.8

**Table-3:** Zone of inhibition for AEBTC and its derived metal complexes



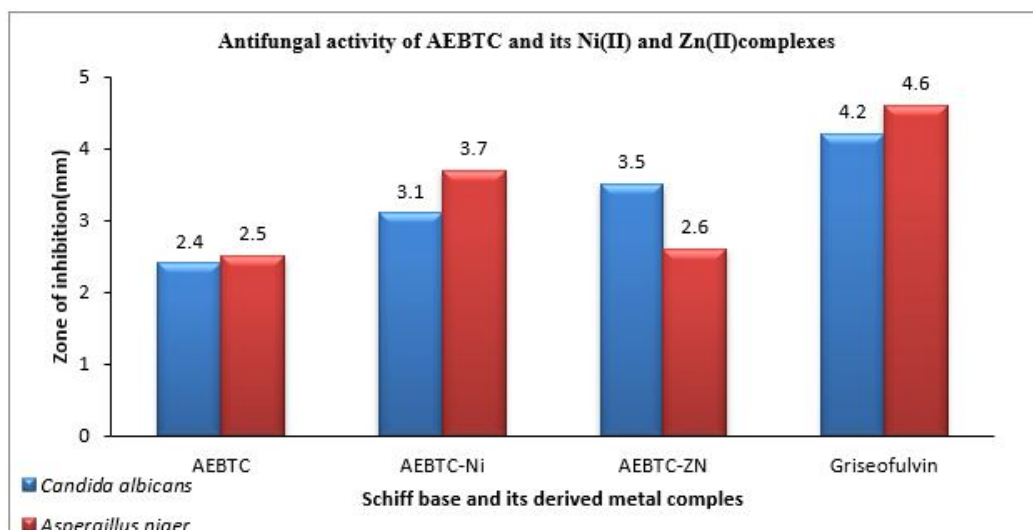
**Graph 1:** graph showing antibacterial activity of AEBTC and its derived metal complexes

**Antifungal Activity**

A varied antifungal activity was shown by complexes of both the synthesized ligands (ABS and AEBTC) against *A. niger* ranging between 2.9 mm to 3.7 mm. V and Co complexes of both the Schiff bases ABS and AEBTC were found to be potential against *A. niger* with 2.5 mm and 3.7 mm zone of inhibition and other compounds showed moderate action against *A. niger* while as, effective antifungal activity was shown against *C. albicans*, by the vanadium complexes of both ligands (Schiff base) with 2.4 mm and 3.5 mm zone of inhibition, whereas all other compounds showed good antifungal activity [55-57]. Thus, it can be concluded that complexation increases the biological activity.

Compounds	<i>Candida albicans</i>	<i>Aspergillusniger</i>
AEBTC	2.4	2.5
AEBTC-Ni	3.1	3.7
AEBTC-ZN	3.5	2.6
Griseofulvin	4.2	4.6

**Table4:** Zone of inhibition for AEBTC and its derived metal complexes (mm)



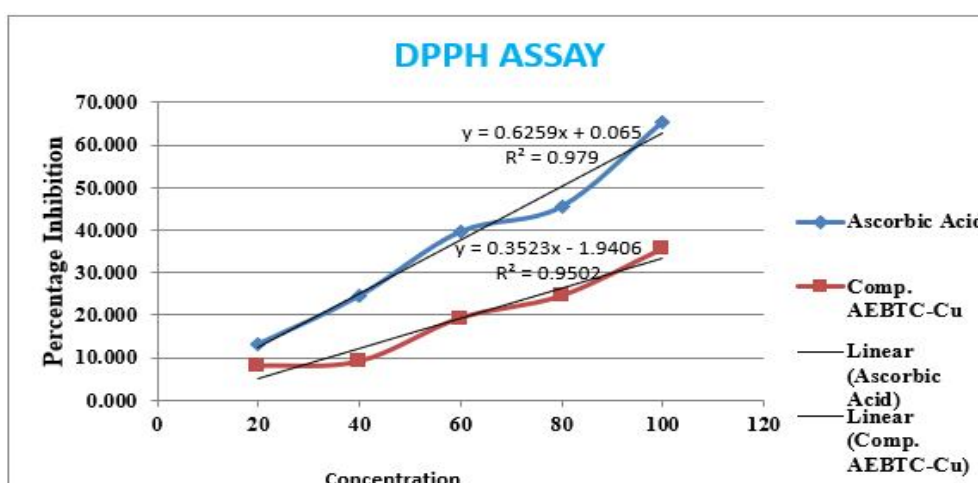
**Graph 2:** Bar graph showing antifungal activity of AEBTC and its metal complexes

**Antioxidant Activities**

*In vitro* free radical scavenging activity of different concentrations DPPH radicals i-e 20 40, 60, 80 and 100 (µg/ml's) was determined. Being stable radical, it is neutralized by molecules which donate H atoms. The absorbance at 517nm reveals the scavenging effect of DPPH radicals [58-59]. The tested compounds with electron donor groups (N, S) can act as radical scavengers and are able to resist oxidative challenges. It can be seen from the table that derived complexes revealed highest scavenging potential against DPPH, while the complexes derived from Schiff bases with Ni(II) and Zn(II) ions revealed moderate scavenging effect against DPPH.

S. No.	Concentration µg/ml	Ascorbic Acid	AEBTC-Cu
1	20	13.204±0.0012	7.938±0.0011
2	40	24.512±0.0015	9.004±0.004
3	60	39.590±0.0010	19.171±0.0015
4	80	45.463±0.0018	24.408±0.0010
5	100	65.315±0.0021	35.466±0.003

**Table 5:** Percent inhibition data of DPPH of free radical scavenging assay by Standard Ascorbic Acid and AEBTC-Cu complex Values are expressed as Mean±SD



**Graph 3:** Line graph showing antioxidant activity of AEBTC-Cu complex

**CONCLUSION**

The newly synthesized Schiff bases showed tridentate nature via thiazole N, thiophene S, and azomethine N towards central metal atoms. Spectroscopic studies shows that the metal complexes exhibit octahedral geometries (structures) with two lattice H<sub>2</sub>O molecules outside the coordination sphere of Ni

and Cu derived complexes. Well-defined crystalline properties of synthesized metal complexes are observed by powdered-XRD and Scanning Electron Microscopy analysis. The synthesized complex exhibits a higher biological activity.

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