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Synthesis And *In Vitro* Biological Evaluation Of Metal Complexes Of 2-Aminobenzothiazole

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Abstract:
Antibiotic resistance is a growing problem in today's healthcare which increase the demand of heterocyclic compounds. Heterocyclic compound bears different biological activity, like anti-cancer, anti-inflammatory, anti-oxidant, antibacterial, etc. therefor its demand increase in development of new compounds to overcome microbial resistance. The coordination chemistry of 2-aminobenzothiazole, which possesses potential coordinating sites including one exocyclic (NH_2) and two endocyclic (N and S), has received significant attention in recent decades. The interest has led to the discovery of various transition metal complexes exhibiting diverse structures. 2-amino benzothiazole and substituted aldehyde (2,4 dichlorbenzaldehyde ,4-benzyloxybenzaldehyde) used as a reactant in synthetic organic chemistry and also used for making Schiff base ligand for increase the potency of the final product. The reaction of the Schiff bases (SB_1 and SB_2) with the core metals like Cobalt chloride, manganese chloride, nickel chloride, and copper (II) has produced metal complexes (MC_{1-8}) of Schiff bases. In our study, we employed the DPPH assay and the agar diffusion method to assess the anti-oxidant and antimicrobial characteristics of the synthesized ligands and their metal complexes.

Keywords 2-aminobenzothiazole, Schiff base, metal complexes, spectral analysis, biological evaluation and antioxidant activity

Introduction

Microbial resistance arises as a direct consequence of the widespread use of antimicrobial medications across diverse sectors, including human medicine, veterinary practices, and agricultural applications. Microorganisms acquire resistance through diverse mechanisms, including obstructing access to the target, altering antibacterial targets through mutations, and directly modifying drug (Reygaert, 2018).Current research is primarily focused on exploring inorganic coordination compounds and their applications in the field of pharmaceuticals (Ceramella *et al.*,2022). This research direction is vital for the discovery and development of more efficient drugs to combat various diseases. An important aspect of this research involves the investigation of drug-metal complexes, which have shown promising potential in medicinal applications (Mahmood *et al.*, 2022).

Benzothiazole, because of their wide range of physiological functions, are highly crucial for drug development and co-ordination chemistry (Yadav *et al.*, 2023). Benzothiazole and its reported derivatives have been thoroughly investigated for potential biological activity. Benzothiazole derivatives, especially 2-aminobenzothiazoles, were studied in the 1950s for their potential muscle relaxant effects (Sharma *et al.*, 2012). Benzothiazole analogues have been discovered with pharmacological effects, including analgesic, antiviral, antioxidant, anti-inflammatory, antimicrobial, anticancer, and anticonvulsant properties. Transition metals are present in the majority of pharmaceutical agents (Kyhoiesh *et al.*, 2021) .The role of metals in therapeutic agents has grown, leading to the development of numerous valuable and interesting medications like bismuth for ulcers and cis-platin for cancer. The pharmacological activities of the Schiff base ligand are enhanced by the complexation of metal with imine group (Gopichand *et al.*, 2023b).

The coordination chemistry of 2-aminobenzothiazole, which possesses potential coordinating sites including one exocyclic (NH_2) and two endocyclic (N and S), has received significant attention in recent decades. The interest has led to the discovery of various transition metal complexes exhibiting diverse structures (Jiang *et al.*, 2021). In continuing our research, this study centres on synthesizing and characterizing metal complexes with core metals like Cobalt chloride (Bahsis *et al.*, 2020), manganese chloride, nickel chloride, and cupric acetate (Sunjuk *et al.*, 2022b) with Schiff base of 2-aminobenzothiazole. We then evaluated the antimicrobial activities and antioxidant activity of both the synthesized ligands and their metal complexes using the agar diffusion method and DPPH assay (Amin *et al.*, 2018).

Materials and Method

The starting material 2,4-chlorobenzaldehyde, 4-benzyloxybenzaldehyde, 2-aminobenzothiazole, and cobalt chloride, manganese chloride, nickel chloride, cupric acetate were bought from a range of suppliers, including CDH Pvt. Ltd, Loba Chemie Pvt. Ltd, Sigma-Aldrich and HiMedia Laboratories Pvt. Ltd. Chem Draw Ultra 12.0 was used to draw the

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synthetic scheme for the synthesized derivatives. . The development of the chemical reaction was monitored using Thin Layer Chromatography (TLC). Silica gel G was utilized to create the TLC plates acting as the stationary phase, while various mobile phases, including chloroform: toluene and ethyl acetate: n-hexane were used for the synthesized derivatives.

The Brucker software OPUS spectrophotometer was employed to capture the infrared (IR) spectra (in cm^{-1}). NMR data of the compounds are indicated by the presence of singlet (s), doublet (d), triplet (t), and multiplet (m) signals, representing number of protons in each compound. TMS was used as an internal standard while recording the ligands and metal complexes NMR spectra. Parts per million are used to express chemical changes in relation to TMS. Using the DPPH assay method, evaluate antioxidant activity of synthesised derivatives. The disc/well diffusion method was employed for the evaluation of the antimicrobial activity of all synthesized compounds on Muller-Hinton agar media and potato dextrose agar (PDA).

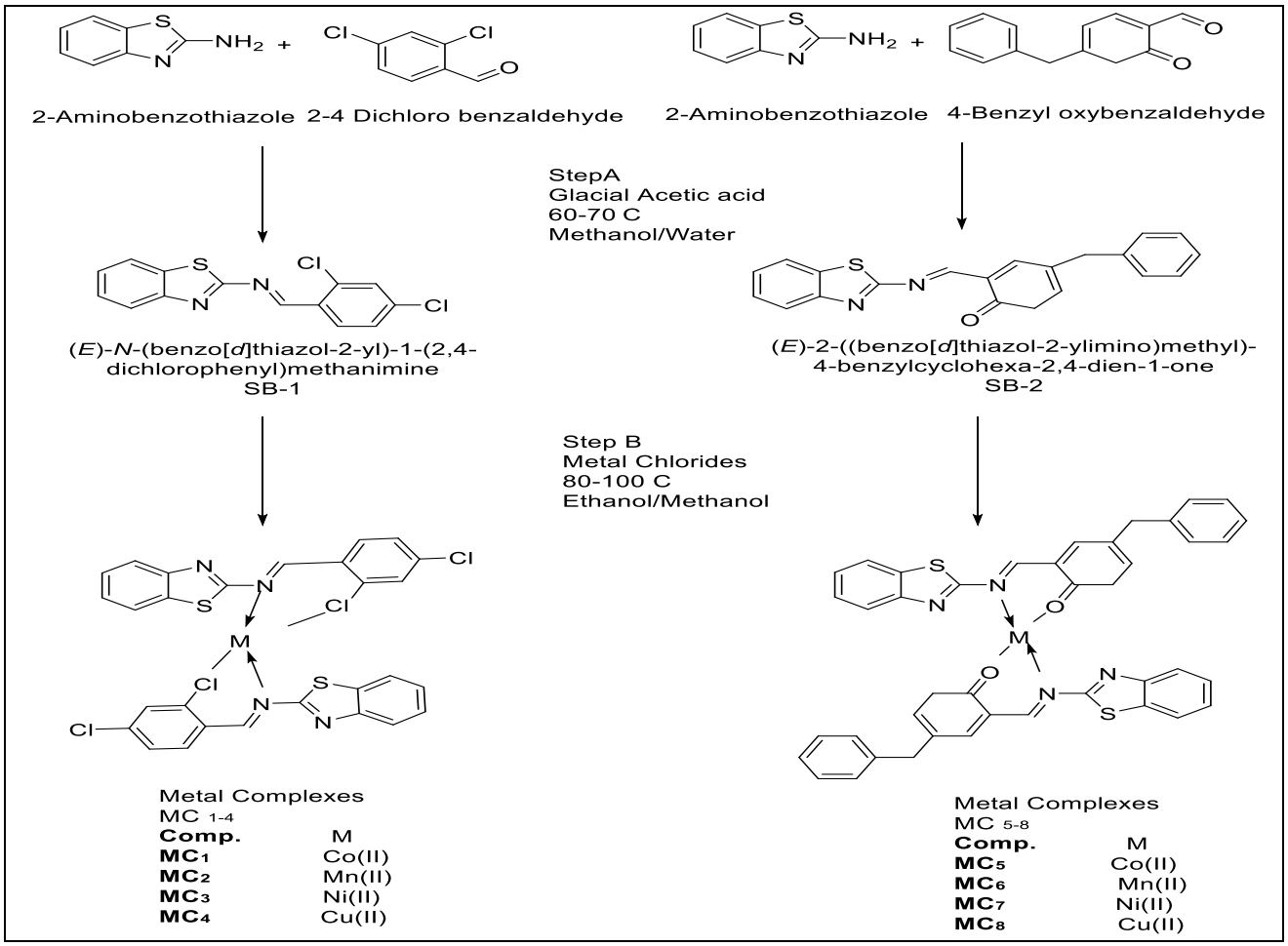
Synthetic Procedure for synthesis of 2-aminobenzothiazole derivatives:

Step a: Synthesis of Schiff base (SB_1-SB_2)

0.01 mol methanolic solution of 2-aminobenzothiazole and substituted aldehyde (2, 4-dichlro benzaldehyde and 4-benzyl oxybenzaldehyde) was added to a (RBF) round bottom flask with 2-3 drops of glacial acetic acid, as a catalyst. Further, resulting mixture were refluxed for a duration of 8-9 hours with continuously stirring. Then, TLC were used to verify that the reaction is complete & the final mixture was cooled in cold water. Then, the precipitate of Schiff base was separated, dried and recrystallized using methanol (Kanagavalli *et al.*, 2019).

Step b: Synthesis of Metal Complexes derivatives (MC_1-MC_8)

0.01mol methanolic solutions of Schiff base ligand and the metal chlorides (0.01 mol) [$CoCl_2$, $MnCl_2$, $NiCl_2$ and $CuCl_2$] were refluxed for 6-7 hour at molar ratio of 2:1 to formed the metal complexes. A portion of the solvent in the solution evaporated, using the TLC method, the reaction's completion was observed. Then, the resultant product is precipitate. After the precipitate was obtained, it was sequentially washed with cold ethanol, ice water, and then dried (Omaka 2018b, Sunjuk 2022)



Scheme 1: Synthesis of Schiff bases and metal complexes containing 2-aminobenzothiazole (SB_1-MC_{1-4} and SB_2-MC_{5-8})

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SB_1:- yellow powder, yield: 77.52%, m.p.-138-140 ^{0}C, chemical formula: - $C_{14}H_8Cl_2N_2S$, M.W:- 307.19, IR (selected vibrations, cm-^{1}:- [1518 .51 (C=C str.), 3116.72 (C-H str.) of Ar- ring], 3371.37(NH- str.), 1699.07 (N=C, str.), 698.74 (C-Cl); ^{1}H NMR ($CDCl_3$, 400 MHz), 7.83 – 7.98 (m, 2H of Ar-H), 7.33 – 7.56 (d, 2H of Ar-H), δ 8.97 (s, 1H of CH=N), 7.62-7.98 (3H, m of 1-benzene)

SB_2:- light yellow powder, yield: 81.97%, m.p.-106-108 ^{0}C, chemical formula: - $C_{21}H_8Cl_2N_2OS$, M.W:- 344.43, IR (selected vibrations, cm-^{1}:- [1510.42 (C=C str.), 2967.42(C-H str.) of Ar-ring], 3413.02(NH- str.), 1640.52(C=N str.), 1709.55 (C=O str.) ; ^{1}H NMR ($CDCl_3$, 400MHz), 8.19-7.52 (4H, m of Ar-H), 8.06 (1H, s of CH=N), 7.29-7.17 (3H, m of 1-benzene, 8.21 (1H, m of ethylene)

MC_1:- dark blue powder, yield: 72.54%, m.p.-122-124 ^{0}C, chemical formula:- $C_{28}H_{16}C_{l4}CoN_4S_2$, M.W:- 673.32, IR (selected vibrations, cm-^{1}:- [1533.23 (C=C str.), 3115.46 (C-H str.) of Ar -ring], 3451.73(N-H str.), 1694.98(C=N str.), 835.90 (C-Cl), 755.79 (M-N), 835.90(M-Cl); ^{1}H NMR ($CDCl_3$, 400 MHz), 7.48 – 7.98 (d, 2H of Ar-H), 7.85-8.02 (m, 2H of Ar-H), δ 9.76 (s, 1H of CH=N), 7.34-7.86 (3H, m of 1-benzene)

MC_2:- light yellow powder, yield: 56.52%, m.p.-138-140 ^{0}C, chemical formula: - $C_{28}H_{16}Cl_4MnN_4S_2$, M.W:- 699.39, IR (selected vibrations, cm-^{1}:- [1531.86(C=C str.), 2993.50 (C-H str.) of Ar- ring], 3668.76(N-H str.), 1672.38(C=N str.), 810.64(C-Cl), 759.03(M-N), 810.64(M-Cl) ; ^{1}H NMR ($CDCl_3$, 400 MHz), 7.92 – 8.07 (d, 2H of Ar-H), 7.47-7.52 (m, 2H of Ar-H), δ 9.80 (s, 1H of CH=N), 7.51-7.92 (3H, m of 1-benzene)

MC_3:- green powder, yield: 56.52%, m.p.-138-140 ^{0}C, chemical formula: - $C_{28}H_{16}Cl_4MnN_4S_2$, M.W:- 699.39, IR (selected vibrations, cm-^{1}:- [1531.86(C=C str.), 2993.50 (C-H str.) of Ar -ring], 3668.76(N-H str.), 1672.38(C=N str.), 810.64(C-Cl), 759.03(M-N), 810.64(M-Cl) ; ^{1}H NMR ($CDCl_3$, 400 MHz), 7.36-7.52(d, 2H of Ar-H), 7.99-8.04 (m, 2H of Ar-H), δ 9.80 (s, 1H of CH=N), 7.92-8.02 (3H, m of 1-benzene)

MC_4:- blue powder, yield: 61.72%, m.p.-140-142 ^{0}C, chemical formula: - $C_{28}H_{16}Cl_4CuN_4S_2$, M.W:- 677.93, IR (selected vibrations, cm-^{1}:- [1520.05(C=C str.), 3096.72 (C-H str.) of Ar- ring], 3204.04(N-H str.), 1691.07(C=N str.), 779.39 (C-Cl), 666.91(M-N), 779.39(M-Cl); ^{1}H NMR ($CDCl_3$, 400 MHz), 7.59 – 8.03 (d, 2H of Ar-H), 7.39-7.57 (m, 2H of Ar-H), δ 9.49 (s, 1H of CH=N), 7.59-7.97 (3H, m of 1-benzene)

MC_5:- green powder, yield: 79.66%, m.p.-118-120^{0}C, chemical formula: - $C_{44}H_{38}CoN_4O_2S_2$, M.W:- 777.56, IR (selected vibrations, cm-^{1}:- [1464.11(C=C str.), 3112.04 (C-H str.) of Ar- ring], 3562.36 (N-H str.), 1517.96 (C=N str.), 696.42 (M-O), 624.36(M-N); ^{1}H NMR ($CDCl_3$, 400 MHz),7.99-7.48(4H, m of Ar-H), 8.32 [(2H, s of $(CH=N)_2$], 7.62-7.98 (3H, m of 1-benzene, 5.37, (2H, s of 1-ethylene),3.35, (2H, s of CH_2)

MC_6:- light yellow powder, yield: 65.63%, m.p.-70-72^{0}C, chemical formula: - $C_{44}H_{38}MnN_4O_2S_2$, M.W:- 773.87, IR (selected vibrations, cm-^{1}:- [1656.32(C=C str.), 3114.51 (C-H str.) of Ar- ring], 3164.52(N-H str.), 1531.32 (C=N str.), 881.74(M-O), 752.97(M-N); ^{1}H NMR ($CDCl_3$, 400 MHz),7.47-7.85(4H, m of Ar-H), 7.50 [(2H, s of $(CH=N)_2$], 7.02-7.48 (3H, m of 1-benzene, 5.15 (2H, s of 1-ethylene),3.59 (2H, s of CH_2)

MC_7:- brown powder, yield: 69.49%, m.p.-118-120^{0}C, chemical formula: - $C_{44}H_{38}NiN_4O_2S_2$, M.W:- 777.67, IR (selected vibrations, cm-^{1}:- [1664.45(C=C str.), 2989.52 (C-H str.) of Ar- ring], 3110.51(N-H str.), 1515.28(C=N str.), 786.03(M-O), 669.29(M-N); ^{1}H NMR ($CDCl_3$, 400 MHz),7.27-7.15(4H, m of Ar-H), 9.88 [(2H, s of $(CH=N)_2$], 7.62-7.98 (3H, m of 1-benzene, 5.14, (2H, s of 1-ethylene), 3.43(2H, s of CH_2)

MC_8:- olive green powder, yield: 71.79%, m.p.-110-112^{0}C, chemical formula: - $C_{44}H_{38}CuN_4O_2S_2$, M.W:- 782.48, IR (selected vibrations, cm-^{1}:- [1675.55(C=C str.), 2983.45 (C-H str.) of Ar- ring], 3209.13N-H str.), 1518.90(C=N, str.), 786.03(M-O), 669.29(M-N); ^{1}H NMR ($CDCl_3$, 400 MHz),7.36-7.61(4H, m of Ar-H), 8.21 [(2H, s of $(CH=N)_2$], 7.84-7.97 (3H, m of 1-benzene, 5.38, (2H, s of 1-ethylene), 3.73(2H, s of CH_2)

Antimicrobial Evaluation:-

The disc diffusion method was used to assess the antimicrobial activity against all compounds on Muller Hinton agar media (HiMedia Ltd, Mumbai) for gram +ve and gram –ve bacteria & Potato dextrose agar (PDA) for fungal strain (Mishra *et al.,* 2019b). The synthesized derivatives were examined against common bacterial and fungal strains as antibacterial agents and antifungal agents (Ismail et al., 2020). To make petri plate 3.9 grams of Muller Hinton Agar and 3.9 grams of potato dextrose agar, was separately dissolved in 100 millilitre of distilled water. Subsequently, the medium were autoclaved for 30 minutes at 121°C to sterilize it (Khalil *et al.,* 2021). Through sub-culturing in nutrient agar media, the bacterial strains (*E. coli* and *B. subtilis)* & fungal strain *(A. clavatus*) were brought back to life (Al-Resayes et al., 2023).The culture of fungal was incubated for three to seven days at 28^0 C, while the bacterial cultures were kept at 37°C for twenty-four hours.[17] Dimethyl sulfoxide (DMSO) was used as the solvent to generate stock solutions of the synthesized compounds and standard medications (fluconazole and ampicillin) at concentration of 1000 µg/ml (Ahamed *et al.,* 2014) Then, analyze the plates for areas of the zone of inhibition surrounding each disc after incubation. These zones are easily identifiable as places where bacterial growth is suppressed. Using a calliper or ruler, measure the diameter of the zones of inhibition (Wang *et al.,* 2024).

Anti-oxidant activity;

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Free radicals are very reactive chemicals that can cause cellular damage and have a role in aging, chronic illnesses including cancer, and cardiovascular disorders, among other health issues. Antioxidants work by donating electrons to neutralize free radicals, thus preventing or reducing oxidative damage to cells and tissues (Gul *et al.,* 2020). They are essential for preserving the health of the body's cells and shielding it from oxidative stress. The antioxidant activity of a substance can be evaluated through DPPH assays, such as the (2, 2-diphenyl-1-picrylhydrazyl) (Khan *et al.,* 2013). These assays measure the capacity of a compound to eliminate free radicals or inhibit oxidative reactions in vitro (Kyhoiesh *et al.,* 2023). Upon reaction with hydrogen-donating species, DPPH forms hydrazine, resulting in a subsequent decrease in absorbance at 517 nm (Hasi *et al.,* 2016). Antioxidant agents extract hydrogen from DPPH, causing it to reduce, resulting in the transformation of its dark violet colour to yellow (Shah *et al.,* 2020). A DPPH solution of 3 µg/ml was prepared using methanol. For the blank reference, a mixture of DPPH and methanol (1:1) solutions was utilized. Various dilutions of the standard drug (ascorbic acid) with each synthesized compound were prepared using methanol, with concentrations ranging from 100 to25 µg/ml (Zheng *et al.,* 2020). In each concentration tube, one ml of DPPH solution was added. After complete mixing, the first reaction mixture was maintained at ambient temperature (25 °C) for over 32 minutes in a dark environment. Absorbance was recorded using UV at 517 nm. Lower values of DPPH free radical inhibitory concentration indicate higher free radical scavenging potential (Lemilemu *et al.,* 2021).

DPPH Scavenged (%) = $\frac{(A^{\circ}-A*)}{A^{\circ}} \times 100$

A^0 = absorbance of control

A* = absorbance of sample

Result and Discussion

All the metal complexes and Schiff base ligands are water insoluble and soluble in organic solvent like chloroform, methanol, ethanol, DMSO etc. They are highly coloured compounds and stable in normal conditions. FTIR spectra give important information on the functional groups found in compounds, including the type of azomethine linkage (C=N) found in metal complexes formed by synthetic Schiff base ligands. Strong absorption bands are seen in all of the metal compounds below those found in Schiff bases (SB_1 & SB_2), at 1699 cm^{-1} and 1640 cm^{-1}, respectively. These bands show that azomethine has attached itself to metal ions. Additional absorption bands in the 800 cm^{-1} to 450 cm^{-1} region were found in metal complexes. These bands were likely the result of heteroatoms (N, O, and S) forming coordinate bonds with core metal ions.

Antimicrobial activity

The biological evaluation showed that certain bacterial and fungal strains could be inhibited by ligands and their metal complexes. Of all the metal complexes, Compound MC_5 showed the greatest ability to suppress the *A. Clavatus* fungal strain, but Compounds $SB_1$and MC_8 showed only modest levels of inhibition. Regarding *E. coli* and *B. Subtilis* every metal complex shown efficacious outcomes but MC_5 and MC_4 show significant effect. According to the biological results, metal complexes were more bioactive than ligands. Metal complexes showed good to moderate efficacy against every strain that was assessed like *E. coli* and *B. subtilis* & fungal strain *(A. clavatus*). The data of antimicrobial activity were shown in ***Table 1***.

Table 1:-Anti-microbial activity of synthesized compound

Compounds	**Zone of Inhibition diameter (IZD = millimetre)**		
	Bacteria Strains		**Fungus Strain**
	Escherichia coli	***Bacillus subtilis***	***Aspergillus clavatus***
SB_1	16.4	14.9	17.8
SB_2	12.6	11.2	16.3
MC_1	17.4	13.6	16.8
MC_2	11.8	11.5	14.6
MC_3	15.9	13.1	12.4
MC_4	14.5	**17.8**	12.9
MC_5	**18.6**	16.4	**18.9**
MC_6	12.3	14.6	15.7
MC_7	15.4	15.4	16.4
MC_8	13.4	16.3	17.5
Ampicillin	25	22	-
Fluconazole	-	-	27

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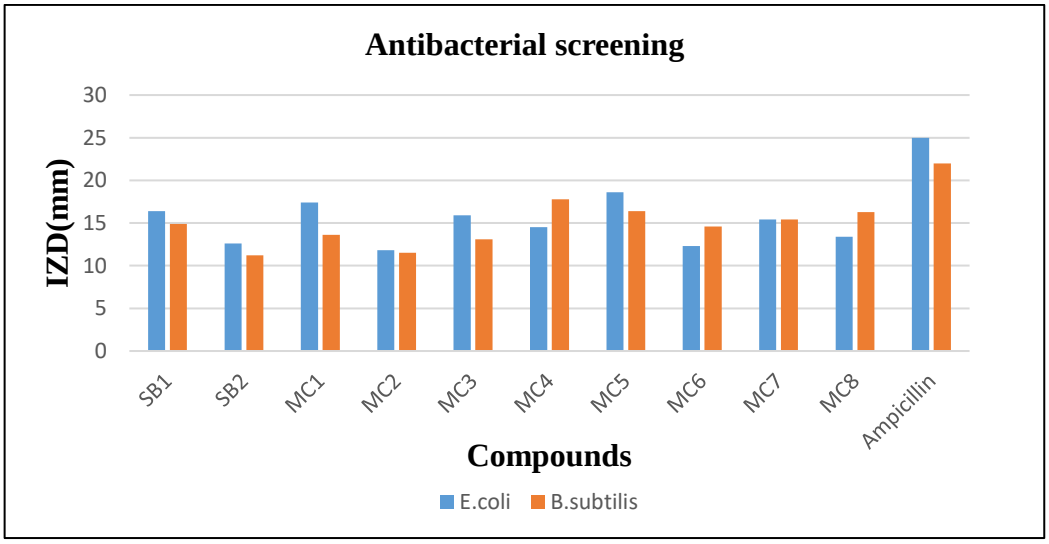

Figure 1:-Graphical representation of antibacterial activity

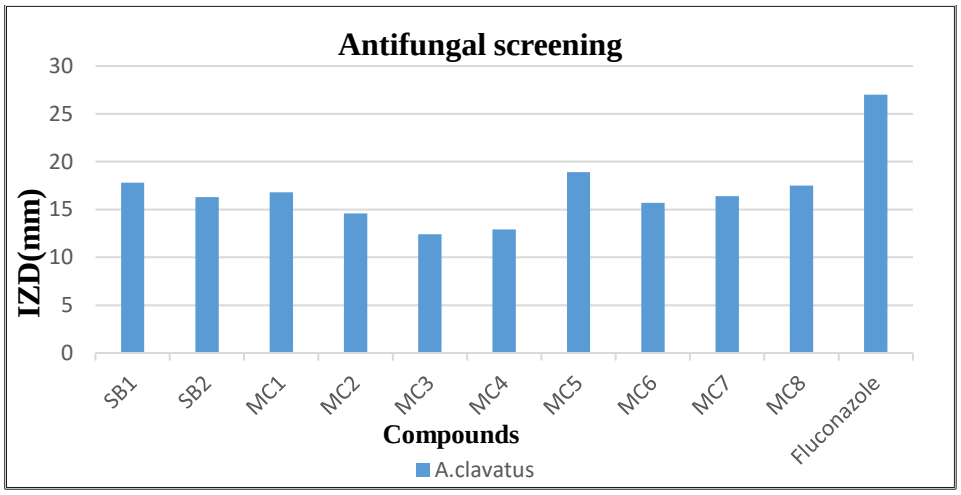

Figure 2:-Graphical representation of antifungal activity

Anti-oxidant activity

Antioxidant activity of a synthesized derivatives can be assessed using methods like DPPH, (2, 2-diphenyl -1-picrylhydrazyl). These assay analyze the ability of a compound to scavenge free radicals or inhibit oxidative reactions in vitro. The antioxidant assessment revealed that compounds SB_1 with value of IC_{50} (60.96 µg/ml) and MC_5 with value of IC_{50} (61.86 µg/ml) were had significant activity, when compared with standard (Ascorbic acid) (59.08 µg/ml). The data of antioxidant activity were shown in ***Table 2***.

Table 2:- Antioxidant estimation of the synthesized compounds (SB1-2&MC1-8)

Compounds	**(%) Percentage inhibition**				**IC_{50} *µg/ml***
	25 *µg/ml*	**50** *µg/ml*	**75** *µg/ml*	**100** *µg/ml*	
SB1	25.41	45.16	61.46	71.79	**60.96**
SB2	17.83	37.89	57.1	67.19	69.96
MC1	24.52	43.61	57.96	71.33	63.54
MC2	19.1	39.8	55.41	61.46	73.10
MC3	20.06	37.89	60.19	71.33	66.24
MC4	23.88	38.53	53.82	74.49	65.96
MC5	22.29	41.71	60.5	77.38	**61.86**
MC6	23.56	42.35	57.32	64.96	67.80
MC7	16.89	37.57	54.77	67.51	71.10
MC8	16.56	41.4	55.73	72.92	67.06
Ascorbic acid	20.56	45.86	64.79	79.48	**59.08**

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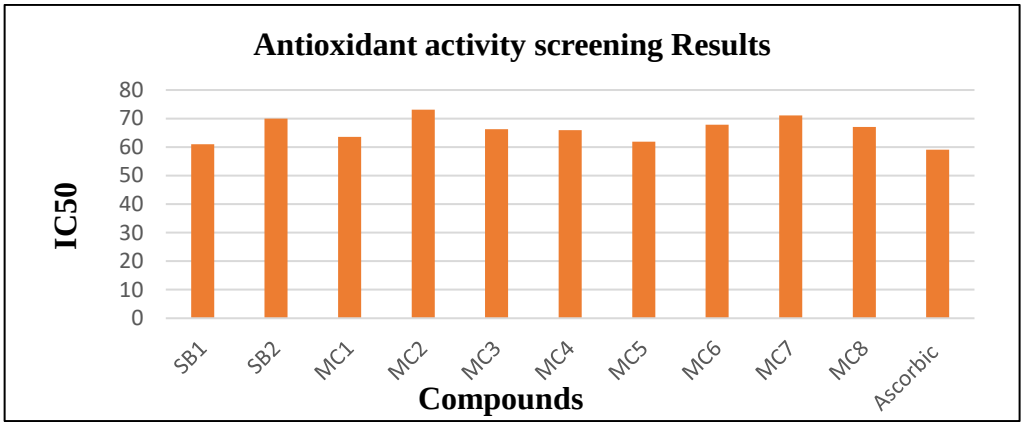

Figure 3:-Graphical representation of antioxidant activity

Conclusion

Metal complexes containing 2-aminobenzothiazole were created and analysed using various physical, chemical, and spectral techniques. These synthesized compounds showed potential as antibacterial and antifungal agents. Specifically, metal complexes MC_5 and MC_4 demonstrated significant antimicrobial activity. Additionally, the complex SB_1 & MC_5 displayed excellent antioxidant properties according to the DPPH assay method. In conclusion, the Schiff base and metal complexes could serve as promising starting points for the development of new antimicrobial and antioxidant agents, respectively.

Conflict of Interest

The author declares no conflict of interest, financial or otherwise.

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