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METAL COMPLEXES OF RIBAVIRIN; SYNTHESIS, CHARACTERIZATION AND *IN-VITRO* BIOLOGICAL SCREENING

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ABSTRACT: Medicinal applications of metals and its compound were reported centuries ago but it gained huge appreciation after the discovery of anticancer activity of metal based drug cisplatin. After cisplatin discovery many medicinal synthetic chemist moved into the field of organometallics for combating diseases and investigating the excellent pharmaceutical potential of metal complexes, giving birth to modern medicinal organometallic chemistry. Derivatization of the already existing drugs is the emerging field of pharmaceutical and synthetic medicinal chemistry. Working on metal complexes of already approved drugs can substantially reduce the time and money spent in clinical development. Organotin(IV), Cu(II), Zn(II), Fe(III) and Sb(III) complexes of Ribavirin were synthesized keeping the same in mind. These complexes were characterized by elemental analysis, IR, 1H, and 13C NMR spectroscopic studies. The synthesized complexes and the parent drug were screened for *in-vitro* biological activities. Interestingly some of the synthesized metal complexes of ribavirin have shown impressive antibacterial and antifungal on the other hand ribavirin was found to be inactive.

INTRODUCTION: Ribavirin (1-[(2R, 3R, 4S, 5R)- 3, 4-dihydroxy- 5- (hydroxymethyl)oxolan- 2-yl]- 1H- 1, 2, 4-triazole-3-carboxamide) is available in the market as potential antiviral drug [1]. Ribavirin is clinically advised against Lassa fever virus [2], Congo hemorrhagic fever [3], Venezuelan hemorrhagic fever [4], Hantavirus and respiratory syncytial virus [5]. It is used in combination with interferon alpha for the treatment of hepatitis C and Human immune deficiency Virus (HIV) [6, 7].

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Recently their activities against severe acute respiratory syndrome (SARS) have been recognised [8]. Literature has also shown the use of ribavirin to cure rabies in combination with other drugs ketamine, midazolam and amantadine [9, 10]. It was first synthesized in 1970 and reported to have antiviral activity in 1972 [11]. It works by interference with duplication of the viral genetic material as it resembles building blocks of RNA molecule. Structurally it is a RNA nucleotide analogue having a natural sugar moiety ribose linked to a non-natural base resembling purines. Its mechanism of action is still not well understood. Ribavirin is unique in this regard as it is clinically active against viruses form different families with no sequence homology [12]. Derivatization of ribavirin can lead us to the development of novel antiviral and other drugs.

Metals and their compounds have been used throughout history to treat many kinds of illness including bacterial, fungal, viral, leishmanial infections and other disorders [13]. The field of organometallic medicinal chemistry gained its boom after the discovery of first metallic anticancer drug cisplatin when it became the field of choice for many synthetic medicinal chemists. Since the Bronze Age tin and its compounds were used in variety of fields including medicine. They have shown their potential as antitumor and antimicrobial agents and also been investigated for anti-trypanocidal activity [14]. Recently tin ethyl etiopurpurin were reported to be used for curing age related macular degeneration [15]. Zinc, copper and iron are essential trace minerals required for normal functioning of our body. The deficiency of the above three metals in the human body leads to abnormal growth, decreased immunity, and especially without iron life is difficult to imagine as it is responsible to transport oxygen to each and every cell of our body [16].

Many complexes of Zn, Cu and Fe have been synthesized with various marketed drug and other biologically active moieties and the incorporation of these metal to them have effectively enhanced their therapeutic potentials [17, 18]. The earliest recorded medicinal use of antimony was by ancient Egyptians who used it to treat fevers and skin irritations and during the twentieth century its compounds were used as first line therapy for the treatment of leishmaniasis [19]. Anticancer activities of antimony compounds have also been reported in literature [20]. Present work describes the synthesis, spectroscopic characterization of organotin, zinc, copper, iron and antimony complexes of ribavirin followed by their *in-vitro* antibacterial, antifungal activities.

EXPERIMENTAL:

MATERIALS AND METHODS: Reagents and all the other chemicals including metal salts were purchased from Sigma Aldrich and used as received. Ribavirin was a gift from a pharmaceutical industry. Quick fit glassware was used and melting points were recorded with Gallenkamp melting point apparatus. IR and NMR spectra were carried on Bruker FT-IR spectrophotometer and AV400RG spectrophotometer respectively. Elemental analysis was performed with LECO-183 CHN analyser. Synthesis, antibacterial and antifungal screening was done in Riphah Institute of Pharmaceutical Science Islamabad, Pakistan and spectroscopic characterization was performed at Institute of Pharmaceutical Sciences, Kings Collage London.

General Procedure for Synthesis of Organotin Metal Complexes (R1-R6): Di/tri organotin complexes of ribavirin were synthesized with the following scheme shown in **Fig. 1**.

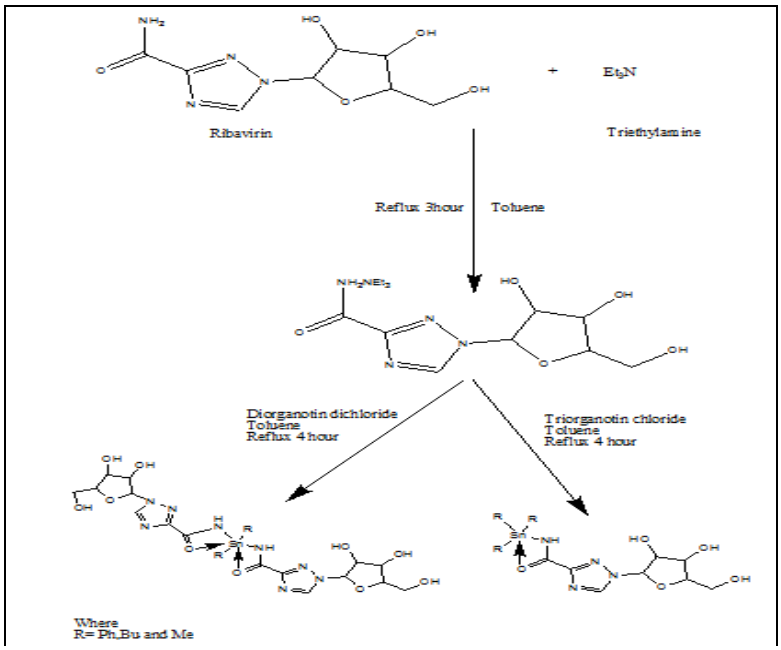

FIG. 1: SYNTHETIC SCHEME OF ORGANOTIN COMPLEXES OF RIBAVIRIN

Ribavirin (2M mol) was refluxed with triethylamine Et_3N (1M mol) with constant stirring in dry toluene for 3 h. After reflux the mixture was allowed to cool down to room temperature and triorganotin(IV) chloride (2M mol) or diorgano-tin(IV) chloride (1M mol) was added and the mixture was refluxed again with continuous stirring for 6 h. Then the by-product crystals of Et_3NHCl were filtered off and the organotin complexes in the filtrate were isolated with evaporation. The product was recrystallized from chloroform / pet. ether mixture [21, 22].

Synthesis of Zinc Complex (R-7): Ribavirin (2M mol) was dissolved in methanol 10 ml and Zinc chloride (2M mol) was also dissolved in methanol. The two solutions were mixed with constant stirring and heated to 60 °C for 1 h and then cooled to room temperature. After cooling the solution was filtered and by evaporation of the filtrate product was obtained washed with cold ethanol and recrystallized with chloroform and hexane mixture (1:1) [23].

Synthesis of Copper Complex (R-8): Ribavirin and Copper(II) acetate monohydrate (1mmol) were dissolved in methanol 15 - 20 ml separately and then mixed together. The pH of the solution was maintained to 7 with the addition of few drops of Et_3N. The reaction mixture was stirred at room temperature for 4 h and then refrigerated for overnight. Then the product was filtered and washed with cold methanol and dried in vacuum [24].

Synthesis of Iron Complex (R-9): Iron(III) chloride (1M mol) was added to a solution of ribavirin (1M mol) in methanol. The mixture was refluxes for 2 - 3 h on oil bath. After cooling the solution was filtered and the resulting precipitates were washed with methanol and dried in desiccator containing silica gel [25]. The synthesis of the complex is given in the **Fig. 2**.

Synthesis of Antimony Complexes (R10-R11): A solution of ribavirin (1M mol) in dry methanol 25ml was added slowly with constant stirring to a freshly prepared solution of antimony halide (1M mol) in 10 ml of dry methanol at room temperature. The reaction was refluxed for 5 - 6 h and then the resulting mixture was kept in darkness for about 8 h. The product was obtained in the form of precipitates after filtration. The precipitates were washed with cold ethanol and purified by recrystallization in ethanol/hexane mixture (1:1) [26]. The synthesis of the product is given in the **Fig. 2**.

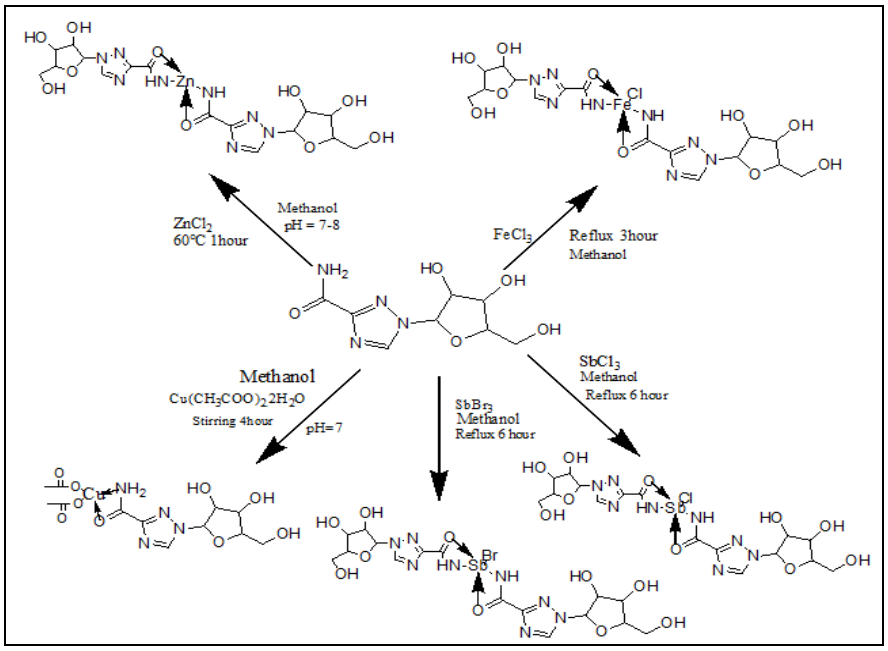

FIG. 2: SYNTHETIC SCHEME OF Cu (II), Zn (II), Fe (III) AND Sb (III) COMPLEXES OF RIBAVIRIN

Antibacterial Assay: *In vitro* antibacterial assay of the synthesized complexes and the parent drug were carried out against the available pathogenic strains of bacteria using agar well diffusion method [27, 28]. Nutrient agar (Merck) was used to perform the activities. The bacterial species consisted of a Gram-positive bacteria *Staphylococcus aureus* and a Gram-negative bacterium *Escherichia coli*.

Cefexime 20 µg/disc was used as a positive control and DMSO was used as a negative control. The antibacterial activity was calculated by measuring the zone of inhibition in mm. The experiment was performed three times and the mean values were considered.

Antifungal Assay: The parent drug ribavirin and the synthesized complexes were screened against six infectious strains of fungi namely *Aspergillus flavous, Aspergillus niger, Aspergillus fumigatus, Fusarium solani* and Mucor SP. Terbinafine was used as positive control and DMSO as negative control. Tube diffusion method [29, 30] was followed using sabouraud dextrose agar (Merck). Experiments were repeated in triplicate and mean of three readings was reported. Growth inhibition was calculated with reference to negative control using formula:

$$\% \text{ inhibition of fungal growth} = \frac{100 - \text{Linear growth in test}}{\text{Linear growth in control)}} \times 100$$

RESULTS AND DISCUSSION: The analytical data of the parent drug Ribavirin and the synthesized metal complexes are given below.

Ribavirin: White powder, melting point 174-176°C, FT-IR (4000-400cm^{-1}), ν(NH) 3245, ν(CH) 3058, 2954, ν (CH=N) 1623, ν(C−N) 1137, ν(C=O) 1655, ν(C−O) 1269 . ^{1}H NMR (DMSO$_{4-D6,}$ ppm), 3.31-3.5m; 5.61-5.63d; (−CH−OH), 5.8s (−NH$_2$), 7.77s(CH=N), 1.80 (−OH) ^{13}C NMR (DMSO$_4$−D6, ppm), 92.17 (C-1), 70.42 (C-2), 74.93 (C-3), 85.91 (C-4), 61.74 (C-5), 145.47 (C-6), 157.74 (C-7), 160.89 (C-8). Elemental Analysis for $C_8H_{12}N_4O_5$: calculated/ found C (39.35/39.49), H (4.95/5.07), N (22.94/22.75).

R-1 (Ribavirin-triphenyltin Complex): Yield 58 %, melting point 159 °C, FT-IR (4000-400 cm^{-1}), ν(CH) 3067, ν (CH=CH) 1479,… ν(Sn-N) 562, ν(Sn-O) 446. ^{1}H NMR (DMSO$_{4-D6,}$ ppm), 3.12-3.14m; 5.28-5.3d; (−CH−OH), 7.75s (−NH$_2$), 7.8s (CH=N), 1.78 (−OH), 7.25m; (C$_6$H$_5$−) ^{13}C NMR (DMSO$_4$−D6, ppm), 91.96 (C-1), 71.42 (C-2), 74.31 (C-3), 83.91 (C-4), 61.42 (C-5), 143.72 (C-6), 153.77 (C-7), 157.89 (C-8), 129.0 (C-9), 136.2 (C-10/14), 128.71 (C-11/13), 128.01 (C-12). Elemental Analysis for $C_{26}H_{26}N_4O_5$ Sn: calculated/found C (52.64/52.70), H (4.42/4.57), N (9.44/9.61).

R-2 (Ribavirin-diphenyltin Complex): Yield 60%, melting point 125 °C, FT-IR (4000-400 cm^{-1}), ν (CH=CH) 1478, ν(C−N) 1075, ν(C−O) 1250, ν(Sn-N) 522, ν(Sn-O) 472. ^{1}H NMR (DMSO$_{4-D6,}$ ppm), 3.21-3.23m; 5.53-5.55d; (−CH−OH), 7.62s (−NH), 7.66s(CH=N), 1.72 (−OH), 7.31-7.33m (C$_6$H$_5$−) ^{13}C NMR (DMSO$_4$−D6, ppm), 91.90 (C-1), 71.2 (C-2), 75.65 (C-3), 83.82 (C-4), 61.31 (C-5), 143.42 (C-6), 153.72 (C-7), 156.95 (C-8), 128.78 (C-9), 136.07 (C-10/14), 128.52(C-11/13), 128.18 (C-12). Elemental Analysis for $C_{28}H_{32}N_8O_{10}Sn$: calculated/ found C (44.29/44.37), H (4.25/4.12), N (14.76/14.65).

R-3 (Ribavirin-trimethyltin Complex): Yield 57%, melting point 137 °C. FT-IR (4000-400 cm^{-1}), ν(CH) 2853, ν(C−N) 1148, ν(C=O) 1710, ν(CH=N) 1640, ν(C−O) 1251, ν(Sn-N) 536, ν(Sn-O) 436. ^{1}H NMR (DMSO$_{4-D6,}$ ppm), 3.16-3.119 m; 5.44-5.46d; (−CH−OH), 7.78s (−NH$_2$), 7.83s (CH=N), 1.75 (−OH), 0.68s (CH$_3$−) ^{13}C NMR (DMSO$_4$−D6, ppm), 91.6 (C-1), 71.2 (C-2), 74.4 (C-3), 84.12 (C-4), 61.2 (C-5), 143.0 (C-6), 154.2 (C-7), 159.42 (C-8), 5.85 (C-9). Elemental Analysis for $C_{11}H_{20}N_4O_5Sn$: calculated/ found C (32.46/32.27), H (4.95/5.09), N (13.77/13.55).

R-4 (Ribavirin- Dimethyltin Complex): Yield 62%, melting point 111 °C. FT-IR (4000-400 cm^{-1}), ν(CH) 2920, ν (CH=N) 1656, ν(C−N) 1159, ν(C=O) 1733, ν(C−O) 1235 ν(Sn-O) 452. ^{1}H NMR (DMSO$_{4-D6,}$ ppm), 3.0-3.02 m; 5.3-5.33d; (−CH−OH), 7.55s (−NH$_2$), 7.6s(CH=N), 1.80 (−OH), 0.66s (CH$_3$−) ^{13}C NMR (DMSO$_4$−D6, ppm), 91.54 (C-1), 71.15 (C-2), 74.63 (C-3), 84.41 (C-4), 61.35 (C-5), 143.3 (C-6), 154.25 (C-7), 159.45 (C-8), 5.7 (C-9). Elemental Analysis for $C_{18}H_{28}N_8O_{10}Sn$: calculated/ found C (34.04/33.95), H (4.44/4.57), N (17.64/17.77).

R-5 (Ribavirin- Tributyltin Complex): Yield 65%, melting point 104 °C, FT-IR (4000-400 cm^{-1}), ν(CH) 2854, 2950, ν(CH=N) 1650, ν(C−N) 1089, ν(C=O) 1689, ν(C−O) 1230, ν(Sn-N) 540, ν(Sn-O) 430. ^{1}H NMR (DMSO$_{4-D6,}$ ppm), 3.08-3.10m; 5.40-5.42d; (−CH−OH), 7.85s (−NH$_2$), 7.9s (CH=N), 1.83 (−OH), 0.80 d (CH$_3$−), 1.35-1.37 m (−CH$_2$−) ^{13}C NMR (DMSO$_4$−D6, ppm), 91.7(C-1), 71.25

(C-2), 74.52 (C-3), 84.02 (C-4), 61.25 (C-5), 143.1 (C-6), 154.08 (C-7), 159.62 (C-8), 8.92 (C-9), 21.23 (C-10), 25.56 (C-11), 11.85 (C-12). Elemental Analysis for $C_{20}H_{38}N_4O_5Sn$: calculated/ found C (45.05/44.97), H (7.18/7.25) N (10.51/ 10.78).

R-6 (Ribavirin-dibutyltin Complex): Yield 54%, melting point 88 °C. FT-IR (4000-400 cm^{-1}) ν(CH) 2857, 2872, 2925, 2958, ν(CH=N) 1666, ν(C−N) 1157, ν(C=O) 1739, ν(C−O) 1247, ν(Sn-N) 558, ν(Sn-O) 480. ^{1}H NMR ($DMSO_{4-D6,}$ ppm), 3.12-3.14m; 5.36-5.38d; (−CH−OH), 7.81s (−NH_2), 7.85s (CH=N), 1.78 (−OH), 0.85d (CH_3−), 1.19-1.22m (−CH_2−). ^{13}C NMR ($DMSO_4$−D6, ppm), 91.5 (C-1), 71.3(C-2), 74.46 (C-3), 84.2 (C-4), 61.33 (C-5), 143.08 (C-6), 154.25 (C-7), 159.51 (C-8), 8.85 (C-9), 21.13(C-10), 25.36 (C-11), 11.78 (C-12). Elemental Analysis for $C_{24}H_{40}N_8O_{10}Sn$: calculated/ found C (40.07/40.21), H (5.60/5.51), N (15.58/15.49).

R-7 (Ribavirin-Zinc Complex): Yield 83%, melting point >300 °C. FT-IR (cm^{-1}), ν(CH) 3117, ν (CH=N) 1605, ν(C−N) 1171, ν(C=O) 1699, ν(C−O) 1295, ν(Zn-N) 543. ^{1}H NMR ($DMSO_{4-D6,}$ ppm), 2.97-3.0m; 5.2-5.23d; (−CH−OH), 7.4s (−NH_2), 7.45s(CH=N), 1.73 (−OH), ^{13}C NMR ($DMSO_4$−D6, ppm), 91.71 (C-1), 69.93 (C-2), 74.44 (C-3), 85.44 (C-4), 61.25 (C-5), 144.93 (C-6), 157.26 (C-7), 160.38 (C-8). Elemental Analysis for $C_{16}H_{22}N_8O_{10}Zn$: calculated / found C (34.83/ 34.73), H (4.02/3.91), N (20.31/20.45).

R-8 (Ribavirin-Copper Complex): Yield 70%, melting point 191 °C. FT-IR (4000-400 cm^{-1}) ν(CH) 3118, ν(CH=N) 1622, ν(C−N) 1138, ν(C=O) 1655, ν(C−O) 1285 ν(Cu-N) 550. ^{1}H NMR ($DMSO_{4-D6,}$ ppm), 3.18-3.2m; 5.1-5.12d; (−CH−OH), 7.54s (−NH_2), 7.6s (CH=N), 1.92 (−OH), 0.87 d (CH_3−). ^{13}C NMR ($DMSO_4$−D6, ppm), 91.7 (C-1), 69.92 (C-2), 74.44 (C-3), 85.44 (C-4), 61.25 (C-5), 144.93 (C-6), 157.22 (C-7), 160.35 (C-8), 25.45 (C-9), 164.02 (C-10). Elemental Analysis for $C_{12}H_{18}CuN_4O_9$: calculated/ found C (33.85/33.96), H (4.26/4.39), N (13.16/ 13.01).

R-9 (Ribavirin - Iron Complex): Yield 72%, melting point 114°C. FT-IR (cm^{-1}), ν(C−N) 1183, ν(C=O) 1671, ν(C−O) 1248, ν(Fe−N) 536. ^{1}H NMR ($DMSO_{4-D6,}$ ppm), 3.08-3.10m; 5.35-5.38d; (−CH−OH), 7.67s (−NH_2), 7.72s (CH=N), 1.87 (−OH). ^{13}C NMR ($DMSO_4$−D6, ppm), 92.15 (C-1), 70.3(C-2), 74.81 (C-3), 85.52 (C-4), 61.62 (C-5), 144.92 (C-6), 156.75 (C-7), 159.96 (C-8). Elemental Analysis for $C_{16}H_{22}ClFeN_8O_{10}$: calculated/found C (33.27/33.42), H (3.84/3.75), N (19.40/19.23).

R-10 (Ribavirin-Antimony Chloride Complex): Yield 80%, melting point 141 °C. FT-IR (4000-400cm^{-1}), ν(NH) 3449, ν(CH) 2954, ν(CH=N) 1623, ν(C−N) 1137, ν(C=O) 1655, ν(C−O) 1269, ν(Sb-N) 532. ^{1}H NMR ($DMSO_{4-D6,}$ ppm), 3.37-3.4m; 5.53-5.55d; (−CH−OH), 7.92s (−NH_2), 8.01 s(CH=N), 1.80 (−OH). ^{13}C NMR ($DMSO_4$−D6, ppm), 92.21 (C-1), 70.43 (C-2), 74.95 (C-3), 85.95 (C-4), 92.21 (C-5), 145.44 (C-6), 157.74 (C-7), 160.89 (C-8). Elemental Analysis for $C_{16}H_{22}Cl N_8O_{10}Sb$: calculated / found C (29.86/29.97), H (3.45/3.55), N (17.41/17.49).

R-11 (Ribavirin-Antimony Bromide Complex): Yield 78%, melting point 123 °C. FT-IR (4000-400 cm^{-1}), ν(CH) 3118, ν(CH=N) 1656, ν(C−N) 1137, ν(Sb-N) 533. ^{1}H NMR ($DMSO_{4-D6,}$ ppm), 3.43-3.45m; 5.3-5.33d; (−CH−OH), 7.9s (−NH_2), 7.96s (CH=N), 1.97 (−OH). ^{13}C NMR ($DMSO_4$−D6, ppm), 92.11 (C-1), 70.52 (C-2), 74.84 (C-3), 85.99 (C-4), 92.31 (C-5), 145.55 (C-6), 157.65 (C-7), 161.89 (C-8). Elemental Analysis for $C_{16}H_{22}Br N_8O_{10}Sb$: calculated/found C (27.93/27.66), H (3.22/3.35), N (16.29/16.17).

The synthesis of the metal complexes of Ribavirin was carried out by the reported procedure. The yields of the complexes were in appreciable amount. The reasonable difference in the melting point of the complexes and free drug as well as physical appearance supports the formation of the complexes. Calculated and found results of elemental analysis are well in balance with each other which further justifies the synthesis.

Inspection of infrared spectra revealed characteristic frequencies of the organic moiety of the complexes which allowed us to confirm their coordination modes. Frequency around 3300-3200 cm^{-1} may be attributed to *ν*(N-H) which is present in free drug but absent in metal complexes. For all the complexes coordination of metal was supported by shifting of ν(C-N) and ν(C-O) as compared to free drug in IR spectra.

All the complexes exhibited the appearance of metal-nitrogen ν(M-N) in the range of 450 - 560 cm^{-1}. The organotin complexes have also shown very week and wide bands assigned to ν(Sn-O) in the region of 400 - 490 cm^{-1} justifying the formation of Sn-O bond.

The structural elucidation of the complexes was done by ^{1}H and ^{13}C NMR spectra. In ^{1}H NMR of the complexes and the free drug ribavirin we have seen significant shift of the signals. Complexation of the ribavirin by metal ions resulted in downfield shifts of the ribose proton signals, this can be due to the lowering of negative charge on hydrogen atom. In ^{13}C NMR the difference in chemical shifts were quiet notable of the carbon atoms which are in close proximity to the complex centre, which is in favour of the complex formation. IR and NMR data indicates the successful synthesis of the complexes

TABLE 1: ANTIBACTERIAL ACTIVITY OF SYNTHESIZED COMPLEXES

S. no.	Samples	*S. aureus*	*E. coli*
1	R	0	0
2	R-1	10	8
3	R-2	7	8
4	R-3	0	10
5	R-4	13	12
6	R-5	11	13
7	R-6	0	11
8	R-7	15	14
9	R-8	6	0
10	R-9	15	14
11	R-10	15	16
12	R-11	0	8
13	Cefexime	21	22
14	DMSO	0	0

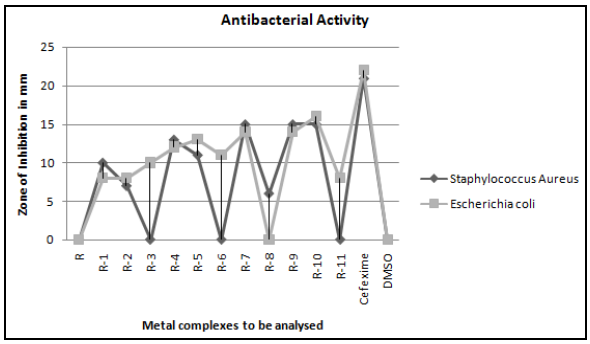

FIG. 3: GRAPH REPRESENTING ANTIBACTERIAL ACTIVITY

The biological activities of the metal complexes were tested against available strains of bacteria and fungi. The free drug ribavirin was also tested but showed virtually no activity in both the assays but the synthesized complexes showed impressive outcomes against the bacterial strains. Antifungal results of only organotin complexes were appreciable. The results of antibacterial and antifungal evaluation are given in **Table 1** and **Table 2**, with their graphical illustrations in **Fig. 3** and **Fig. 4** respectively.

TABLE 2: ANTIFUNGAL ACTIVITY OF SYNTHESIZED COMPLEXES

S. no.	Samples	*A. flavous*	*A. niger*	*F. solani*	*A. fumigatus*	Mucor SP
1	R	0	0	0	0	0
2	R-1	14	17	13	16	18
3	R-2	18	17	14	15	16
4	R-3	0	0	0	0	0
5	R-4	0	8	0	0	0
6	R-5	28	25	18	29	18
7	R-6	28	0	0	0	0
8	R-7	11	10	14	13	12
9	R-8	0	0	0	0	0
10	R-9	0	0	0	0	0
11	R-10	0	0	0	0	0
12	R-11	0	0	0	0	0
13	Terbinafine	28	32	34	30	32
14	DMSO	0	0	0	0	0

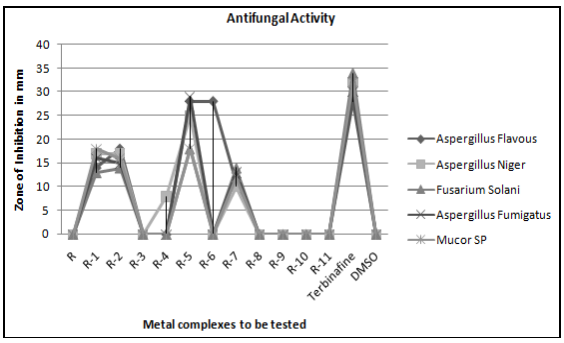

FIG. 4: GRAPH REPRESENTING ANTIFUNGAL ACTIVITY

CONCLUSION: The result shown in this experimental work gives impact that we were successful in synthesizing biologically active organotin, Zn (II), Cu (II), Fe (III), and Sb (III) complexes of ribavirin. The study revealed that the metal complexation has potentialize the biological effects of the free drug. Further studies to unveil other pharmacological aspects of the synthesized complexes are needed which are included in our future research plans.

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CONFLICTS OF INTEREST: Nil

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