SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL STUDIES OF METAL COMPLEXES OF AN ORAL HYPOGLYCEMIC SULFONYLUREA DRUG, GLIBENCLAMIDE.

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ABSTRACT*: A series complexes of hypoglycemic sulphonylurea drug, glibenclamide 1-[[2-(5-chloro-o-anisamide)-ethyle]phenyl]sulphonyl]-3-cyclohexylurea with VO(IV), Mn(II), and Ag(I) have been synthesized. Characterization of these complexes was carried out on the basis of different spectroscopic and analytical techniques. These complexes were tested for their hypoglycemic activity in alloxan diabetic rabbits. VO(IV) complex have shown remarkable hypoglycemic activity compared to Mn(II), and Ag(I) complexes and the parent drug ligand itself. These complexes were also tested for their antibacterial activity and minimum inhibitory concentration (MIC) determination.*

Keywords: Glibenclamide, Diabetes, Hypoglycemic activity, Antibacterial activity,

The Role of metal elements in biological and biochemical systems have been increasingly recognized.[1,2]. Metals play a basic role in one third of the enzyme systems[3] Some antidiabetic potential metals such as chromium, zinc, vanadium, copper, selenium, *etc*., reduces blood sugar level (Hypoglycemic activity)

Vanadium "an Insulin-Mimetic"; with some synthetic compounds shows DNA-binding, antitumor and antidiabetic properties due to their influence in tyrosine phosphorylation via the insulin receptor [4]. Vanadate and vanadyl, two oxidized forms of the trace mineral vanadium, appear to have an insulin like action.They stimulates hexose transport in rat adipocytes and glucose oxidation (glycemic effect) in experimental animals. [5-8].

Manganese containing compounds protect the cells from oxidative damage in diabetic nephropathy and inhibit cytotoxicity in ß-cell [9-10]. Silver nanoparticles are beneficial against delayed wound healing in diabetic patients and protect them from many secondary infections. These nanoparticles cause an early wound healing with minimal scars [11].Silver possesses antibacterial, antiviral, antifungal and anti-inflammatory action.[12-14].Complexes of Amino acid derivatives with silver (I) exhibited effective antimicrobial activities against Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and yeasts (*Candida albicans* and *Saccharomyces cerevisiae*) [15]

Sulfonylurea class of compounds has the ability to reduce blood sugar levels without affecting glucose tolerance and have been used effectively as oral antidiabetic drugs for non-insulin dependent diabetes mellitus (NIDDM) which are effective even at lower dose due to their enhanced absorption through β-cell membrane in the liver. Moreover hundreds of (arylsulfony1) ureas have been prepared and their hypoglycemic activity is monitored [16-17]. Two generations of sulphonylureas have been differentiated according to substitution pattern. The second generation sulphonylureas have much greater intrinsic activity due to both pancreatic and extrapancreatic effects, whereas biguanides have predominantly extrapancreatic actions [18]. Investigation of metal complexes of sulfonylurea plays an important role in researching the cooperation between the metal ions and the ligand and exploring the mechanism of the molecular biology [19-20]. Metal complexes of first generation hypoglycemic sulphonylureas have been investigated [21] But complexes of second generation sulphonylureas have rarely been reported in literature. However some studies on the coordination chemistry as well as the way of action and drug transmission of sulphonylureas with some other metal ions have been done [22,23]. Extensive investigation of the later complexes is the focus of our research due to their pharmacological importance. Based on the extensive use, hypoglycemic action of sulfonylurea drugs and importance of metal based drugs in biomedical processes, we report the results of our studies regarding synthesis and pharmacology of complexes of Glibenclamide with some antidiabetic potential metals.

MATERIAL AND METHODS

General procedures: All chemicals and reagent used in experimental work were of analytical grade. Pure glibenclamide drug was imported from E. Merck Co Germany. In order to induce diabetes in experimental animals, alloxan was obtained from Sigma-Aldrich Co., U.S.A.

IR spectra (in KBr) were recorded on a Shimadzu FTIR 4200 infrared spectrophotometer. Mass Spectra of the compounds were carried out at MAT-312; ^{1}H- and ^{13}C-NMR (in DMSO-d_6) spectra were taken on NMR spectrometer, Bruker model 14.1T. This spectrometer operates at 600 MHz frequency. Elemental analysis was done on CHNS analyser Exeter Analytical CE-440. Atomic absorption spectrophotometer model AA-680 was used for metal analyses. This was fitted with ASA Arsenic analyzer and Graphite Furnace Atomizer GFA-4B. Melting and decomposition points of complexes were recorded Mel-Temp MP-D apparatus. Sealed capillary method was used for this purpose. Absorption spectra were recorded on Perkin-Elmer Lambda 20 spectrometer. Measurement of magnetic moments of complexes was carried out on Chyo Balance model MSB-10 [24].

Hypoglycemic activity of ligand and complexes was checked by administration of these compounds orally to alloxan diabetic rabbits (~1.75-2 kg body weight). Blood glucose

level was monitored after regular intervals and data was analyzed by using computer programme Microsoft Excel.

MIC(Minimum inhibitory concentrations) for different concentrations of compounds as well as blank solvent (DMSO/water) was determined against different gram positive and gram negative strains grown on MacConkey agar and blood agar, respectively [25] In order to account for solvent inhibitory action, test organisms were sub-cultured and re-identified by screening methods using a loopful of growth from a single colony and were inoculated in 10 mL of Mueller-Hinton broth, maintaining the concentration to human body. Antibacterial activity of metal complexes was tested against different strains of gram +ve and gram –ve bacteria. Only one concentration (100 mg/cm^3) of complexes was used in this study. Further their activity was compared with streptomycin sulphate taken as standard antibiotic drug [26] Results obtained from MIC were also involved in this study.

SYNTHESIS OF METAL COMPLEXES OF GLIBENCLAMIDE

Vanadyl(IV)-Glibenclamide Complex (III) :

A mixture of Glibenclamide (**I,II**),8 mmol, (3.95 g) and KOH,8 mmol, (0.448 g), dissolved in ethanol (50 mL) by stirring with reflux. To the boiling ligand solution was added dropwise an aqueous solution of hydrated vanadyl (IV) sulphate, 4 mmol (1.01g). Instantly, a green product appeared which was further refluxed for two hours to complete the reaction. Resulting volume of the mixture was reduced to about 35ml at room temperature and kept it in the freezer overnight. The final product was washed using ethanol, acetone and ether respectively. The product was then dried under vacuum at room temperature. Yield: 74 %. mp 148-150^{0}C (dec.). *m/z* 1167= (1203-2H_2O). IR: (KBr, cm^{-1}) (s, NH, str.)3370, (C=O, str.)1741, (C–N, str.) 1526, (SO_2, asym, sym str.)1337,1160, (M–O)704, (M–N str) 485. UV (λmax DMSO/H_2O, nm), (ε x 10^3): 0.31(20202), 0.21 (12077). μ_{eff} **(B.M)** 2.33. *Anal.* Calcd for [$VO(C_{23}H_{28}ClN_3O_5S)_2.(OH_2)$]. $SO_4.H_2O$: (%) M, 4.23C, 45.92; H, 5.03; N, 6.99; S, 8.0;; Found: M, 4.23 C, 45.90; H, 5.00; N, 6.95; S, 8.05;.

Managanese (II)-Glibenclamide Complex (IV):

Glibenclamide ligand 1.97g (4 mmol) and 0.224g (4 mmol) of KOH were dissolved in 50 mL of absolute alcohol by refluxing with stirring. To the hot ligand solution, 0.986 (4 mmol) of powdered manganese(II) acetate was added. In order to complete the reaction the above solution was refluxed for two hours and allowed to stand at room temperature for some time. The brown product settled down. It was separated by filtration and washed with dimethyl ether and acetone and dried under vacuum at room temperature. Yield: 80 %. mp 150-152^{0}C (dec.). *m/z* 706.1=(724.1–H_2O). IR (KBr, cm^{-1}) (s, NH) 3365 (C=O) 1638, (C–N)1558, (SO_2) 1340, 1158. UV (λmax DMSO/H_2O, nm), (ε x 10^3): 3.22 (32898), 3.27 (34722): 3.80 (33800). μ_{eff} **(B.M)** = 4.49 *Anal.* Calcd for K[$Mn(C_{23}H_{28}ClN_3O_5S)(OAc)_2$].$H_2O$: (%) C, 44.78; H, 5.01; N, 5.8; S, 4.43; M, 7.59; Found: C, 44.83; H, 5.0; N, 5.69; S, 4.40; M, 7.89.

Silver(I)-Glibenclamide Complex (V):

Ligand (GBA) 4.94g (10 mmol) and 0.56g (10 mmol) of KOH were dissolved in 50 mL of absolute alcohol in a flask by refluxing with stirring for 15 minutes. To the hot ligand solution, 0.848g (5 mmol) silver nitrate dissolved in 30 mL of ethanol water (4:1) was dropwise added at room temperature. The solution was stirred for 1 hour at room temperature, colourless complex precipitated out. It was filtered and then washed with acetone and ethanol and dried at 70^{o}C. Yield: 86 %. mp 210^{0}C - 215^{0}C (dec.). *m/z* 1132.9= (1168.9–2H_2O). IR (KBr, cm^{-1}) (s, NH) 3370, (C=O)1696, (C–N)1523, (SO_2, unsym, sym str.)1311, 1150, (M–N) 483. UV (λmax DMSO/H_2O, nm), (ε x 10^3): 2.67 (43859), 3.20 (47619), 8.31 (33557). δ_H (DMSO-d_6): (m, 11H)1.0 -1.7,(t, *J*2.3*Hz*,-CH_2-Ar)2.9,(b, αH) 3.4,(q, -^{c}N-CH_2-)3.5, (s, CH_3)3.8, (b, ^{a}N-H) 6.3, (d, *J* 7.3 *Hz* H-7) 7.1, (d, *J* 6.8 *Hz*, 3H) 7.5, (s, H-5)7.6, (d, *J* 6.8 *Hz*, 2H) 7.8, 8.3 (bs, ^{c}N-H). δ_C (DMSO-d_6); (C-1)124.63, (C-2)157.83, (C-3)114.17, (C-4) 128.44, (C-5) 142.37, (C-6)129.71, (C-7) 157.69, (C-8) 40.52, (C-9) 34.68, (C-10)124.63, (C-11) 127.03, (C-13) 128.44, (C-14) 163.62, (C-15) 48.45, (C-16) 33.01, (C-17) 24.6, (C-18) 25.38; *Anal.* Calcd for K[$Ag(C_{23}H_{27}ClN_3O_5S)_2$].2$H_2O$; (%) C, 47.26; H, 5.0; N, 7.19; S, 5.49; M, 9.23; Found: C, 47.30; H, 4.97; N, 7.10; S, 5.45; M, 9.31.

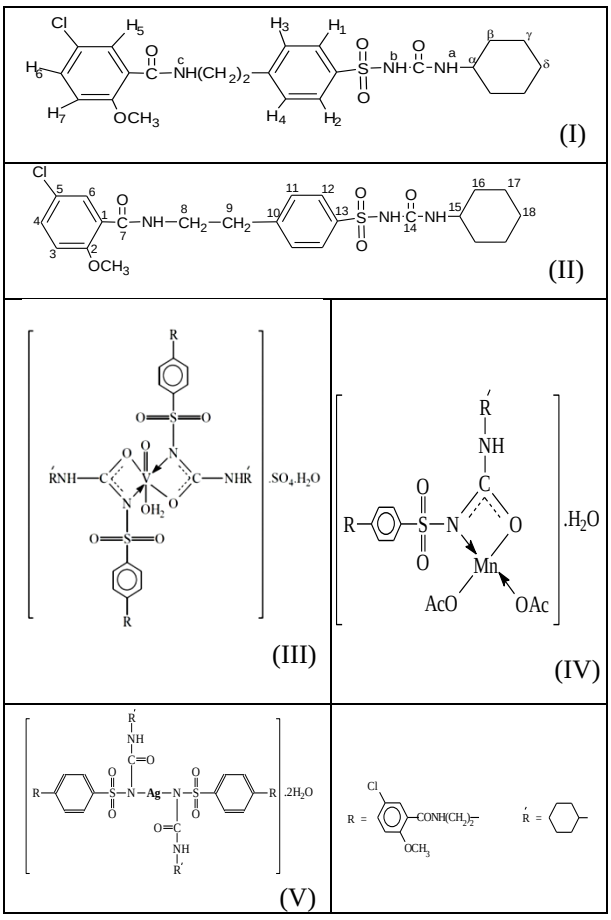
RESULTS AND DISCUSSION

Structural Studies:

Complexes of VO (IV), Mn(II) and Ag(I) with the ligand have been synthesized by reacting appropriate molar ratio (ligand : metal) in ethanol solution which have been characterize by IR, ^{1}H-NMR and ^{13}C-NMR. Elemental analyses (C, H, N, and metal) and magnetic susceptibility measurements. Absorption spectra of ligands consist of various high energy charge transfer bands in UV region, 33000-45000 cm^{-1}. Absorption spectra of GBA consist of high energy bands at 3344 cm^{-1}, 36630 cm^{-1} and 48859 cm^{-1}which are indicative of formation of complexes of these ligand.

The major characteristic of the ^{1}H-NMR spectra of the ligand is the position of N^b–H proton of –SO_2NHCO– group. When a metal ion coordinates through this nitrogen then the signal due to N^b–H proton was disappeared. This observation is in accordance with the result obtaine from the IR spectral data that nitrogen atom of –SO_2NHCO– moiety is involved in coordination with metals. In the ^{13}C-NMR spectrum, the two most downfield resonances in the spectra of glibenclamide are due to carbonyl carbons (C-7 and C-14) which gave signals at δ 155.68 ppm and δ 163.65 ppm in GBA respectively. The carbonyl signal (C-14) is shifted upfield positions on coordination with metals.

Heterocyclic ring carbons C-5 being a quaternary carbon, resonates at δ150.52 ppm. The upfield or in some cases downfield shift of this signals in the spectra of complexes of



these ligands, reveals that carbonyl group of $-SO_2NHCO-$ moiety in the ligand is involved in coordination with metals. This observation is also in accordance with results obtained from IR spectral data that carbonyl group (C=O) is involved in coordination and thus also supports the monodentate and bidentate mode of coordination of SUs ligands.

The comparison of IR spectral data of the drug exhibits characteristic bands due to vibrational and coordination modes. The N–H stretch of $-SO_2NHCO-$ group present in the spectra of free ligands (3210-3326 cm^{-1}) disappeared on coordination with metal ions through deprotonated nitrogen atom.

Vanadyl(IV)-Glibenclamide Complex

Elemental analysis of VO(IV)-glibenclamide complex fits into the formula $[VO(C_{23}H_{27}ClN_3O_5S)_2(OH_2)].SO_4$ which indicated a six coordinated, octahedral environment around the VO^{2+} ion, provided the ligand bound to metal in a bidentate fashion. A comparison of IR spectral data of complex with GBA ligand reveals that the N–H stretching band of $-SO_2NHCO-$ group present in the free ligand (3325 cm^{-1}) has disappeared in the spectra of complex, since nitrogen atom is deprotonated and is replaced by metal on coordination. The carbonyl C=O stretching band of $-SO_2NHCO-$ group observed for the free ligand at 1709 cm^{-1} is shifted upon coordination to 1741 cm^{-1}. The C–N stretch in resulting $-SO_2NCO-$ moiety in ligand (1519 cm^{-1}) is observed in this complex at 1526 cm^{-1}. The bands due to stretching frequencies $\nu_{asy}(SO_2)$and $\nu_{sym}(SO_2)$ were observed in the free ligand at 1330 cm^{-1} and 1157 cm^{-1} and in the complex at 1337 cm^{-1} and 1160 cm^{-1}. Thus almost no change in band position in the spectra of ligand and complex was observed. This observation suggests that coordination of metal with ligand does not occur through sulphonyl oxygen. The new bands because of M–O and M–N stretching mode appears for VO(IV)-GBA complex at 740 cm^{-1} and 483 cm^{-1}. The characteristic M=O stretching band for VO(IV) complex appears at 1001 cm^{-1}. It may be inferred here that ligand GBA coordinated to metal via nitrogen atom and oxygen atom of carbonyl group in $-SO_2NCO-$ moiety. So, four positions around the VO(IV) group are occupied by the ligand and remaining one coordination site is satisfied by a water molecule (**III**). This suggests an octahedral geometry around vanadium in VO(IV)-GBA complex. This was further confirmed by its absorption spectrum.

Effective magnetic moment (μ_{eff}) for this complex was found to be 2.23 B.M., corresponding to presence of one unpaired electron in this complex and further confirm octahedral geometry for the complex.

Manganese(II)-Glibenclamide Complexes

The elemental analysis of Mn(II) glibenclamide complexes fits well into formulae $K[Mn(C_{23}H_{27}ClN_3O_5S)(OAc)_2].H_2O$, indicating a four-coordinated environment along the metals and ligand is bonded in a bidentate fashon.

IR spectra of Mn(II)-GBA complex showed that band due to N–H frequency at 3325 cm^{-1} in the ligand has disappeared. It is because the N–H proton in $-SO_2NHCO-$group is exchanged with metal ion on coordination. The C–N stretch of resulting moiety ($-SO_2NCO-$) in free ligand (1519 cm^{-1}) is shifted to 1526 cm^{-1}. Carbonyl C=O stretching (1709 cm^{-1}) in ligand is shifted to 1638 cm^{-1} in the complex. $\nu_{asy}(SO_2)$ and $\nu_{sym}(SO_2)$ for Mn(II) complex shifted to 1340 cm^{-1} and 1158 cm^{-1} compared to ligand (GBA) at 1330 cm^{-1} and 1157 cm^{-1}. These shifts are negligible indicating no involvement of these groups in coordination. The band due to M–O stretching has been observed at 676 cm^{-1} while M–N stretching at 482 cm^{-1} for Mn(II) complex. So, IR spectral observations indicates that ligand is bound to metal in bidentate mode via nitrogen atom and oxygen atoms of $-SO_2NCO-$ group. From these observations it is proposed that Mn(II) form four coordinated complexes with ligand GBA. The remaining two coordination sites of tetrahedron in Mn(II) complex are satisfied by two acetate ions. Absorption spectra of Mn(II)-GBA complex in DMSO exhibited high intensity bands at 32894 cm^{-1}, 33800 cm^{-1} and 34640 cm^{-1} due to charge transfer transitions which are ligand bands and clearly show the formation of this complex.

Silver(I)-Glibenclamide Complex

The elemental analysis of Ag(I)-GBA complex fits well into formula K $[Ag(C_{23}H_{27}ClN_3O_5S)_2].2H_2O$. The coordination number of Ag(I) is one, hence, a linear geometry is expected for this complex, provided the ligand coordinated in a monodentate fashion.

In IR spectrum of this complex, stretching band due N–H group (3325 cm^{-1}) in the ligand has completely disappeared on coordination with metal. The C–N stretching of the resulting moiety ($-SO_2NCO-$) in

the ligand (1519 cm^{-1}) is, therefore, shifted to 1523 cm^{-1}. Carbonyl (C=O) stretching in ligand (1709 cm^{-1}) is slightly shifted (1696 cm^{-1}) in the complex which suggests a monodentate mode of coordination for Ag(I)-GBA complex. $\nu_{asy}(SO_2)$ and $\nu_{sym}(SO_2)$ for ligand (1330 and 1157 cm^{-1}) shifted to a very small extent in the complex (1317 and 1150 cm^{-1}) indicating no involvement of this group in coordination. Further, M–N stretching band have been observed at 483 cm^{-1}.

Absorption spectral data of the complex show high intensity bands at 33557 cm^{-1}, 43859 cm^{-1} and 47619 cm^{-1} which indicates the involvement of ligand and thus complex. On the basis of these observations the expected structures of the complex is linear one.

^1H NMR spectrum of this complex indicates a downfield signal of N^b–H proton in the ligand at 10.2 ppm has not appear in the spectrum of this complex upon coordination with metal. IR spectral data is further supported by ^1H NMR spectral data that $-SO_2NHCO-$ proton is exchanged with metal on coordination. A signal due to N^a–H proton in ligand at 6.3 ppm has broadened. It is because the cyclohexyl ring proton (H^α) coupled with N^a–H proton.

On the basis of spectral evidence it is inferred that Ag(I) is coordinated to ligand through nitrogen atom of the $-SO_2NHCO-$ group. So, a monodentate mode of coordination for ligand (GBA) is suggested in this case. The proposed structure for this compound is therefore linear **(V)**.

PHARMACOLOGICAL STUDIES

Hypoglycemic Activity: Complexes of Glibenclamide with VO(IV), Mn(II), and Ag(I) and ligand (GBA) itself were checked for their hypoglycemic action. The results of hypoglycemic activity of these compounds can be seen in Fig. 1. Hypoglycemic activity of calculated amounts of complexes and drug (GBA) was determined by oral administration of these compounds in various groups of rabbits. These rabbits were made diabetic with alloxan. The rabbits were monitored continuously to check the change in their blood glucose level (BGL) from the time of administration (0 hour) to eight (8) hours with a regular interval of one hour. Hypoglycemic activity of VO(IV)-GBA complexes have been shown to be significant as compared to original drug and control groups. Different curves obtained on plotting change in (BGL) with respect to time are shown in Fig. 1. The results obtained clearly indicates that hypoglycemic activity of VO(IV) complex has been enhanced significantly as compared to not only standard drug (glibenclamide) but also to Ag(I)-GBA and Mn(II)-GBA complexes. However, Ag(I)-GBA and Mn(II)-GBA complexes have retained their hypoglycemic activity without any significant variation with respect to parent drug.

Oral administration of standard drug and its complexes to induced diabetic rabbits causes a variation in BGL. After two (2) hours of administration the blood glucose level (BGL) of standard drug (GBA) treated animals was 424.46 ±8.47 whereas Ag(I)-GBA comlex treated group was 429.40± 7.33 and Mn(II)-GBA complex was 435.60 ±7.99. whereas the group treated with VO(IV)-GBA complex was 425.40 ±22.17. The results depicted in fig.1 illustrates that in the all groups

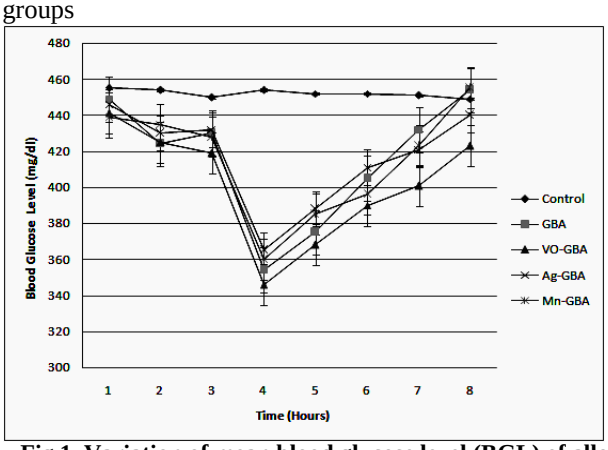


Fig.1. Variation of mean blood glucose level (BGL) of alloxan diabetic rabbits as a function of time, after oral administration of GBA and its VO(IV), Mn(II), and Ag(I) Complexes.

of experimental animals (Mn(II)-GBA, Ag(II)-GBA complex and drug loaded) the lowering of BGL almost remain same upto 2 hours (3-4%). However the decrease in blood glucose level in VO(II)GBA was observed to be not significant i.e., 425.40 ±22.17 as compared to the parent drug as well as other complexes which might be due to slow release of the compound from the synthesized metal complex. But after four hour time duration a significant decrease of blood glucose level was observed in the animal group treated with VO(IV)-GBA complex 346.80 ± 21.25 and reaches the level even lower than the parent drug itself (354.80 ±10.27) BGL remained considerably lower than the control group 454.20 ±5.97. After eight hours parent drug ligand and its complexes with Ag(I) and Mn(II) are exhausted and their hypoglycemic activity become compatible to the standard drug. For GBA it become 454.20 ±8.11 for Ag(II)-GBA 440.40 ± 5.93 and for Mn(II)-GBA 455.60 ±7.99, but VO(II)GBA complex remained active and continue to show hypoglycemic activity further more.

From the results, it was extracted that the VO(IV)GBA complex remained active and had eligibility to lower the BGL for more duration even after the end of eight hour experimental time and kept the glucose level lower than the parent drug i.e; 423.20 ± 18.71.This indicates that that the VO(IV)-GBA complexes shows more hypoglycemic action. It continue to keep the BGL lower than the parent drug GBA even after the expiry of the experimental time. The results are in consistent with the findings that vanadium is "an Insulin-Mimetic"; and have a role as anti-diabetics potential element. It is therefore infered that the VO-GBA complex is more active antidiabetic agent than the other two complexes under study.

Minimum Inhibitory Concentration (MIC)

Metal complexes of glibenclamide (GBA) with VO(IV), Mn(II), and Ag(I) were tested for the determination of their Minimum Inhibitory Concentration (MIC). A number of Gram Positive bacterial strains as *Staphylococcus coagulase, Staphylococcus aureus, and Streptococcus* and Gram Negative bacterial strain *as Escheria coli, Pseudomonas (C), Enterobacter faecalis, Enterobacter cloacae, Proteus*

mirabilis, Klebsiella pneumonia and *Salmonella sensitive* (Table 1). MIC of blank solvent was also determined in order to monitor the inhibitory effect of the solvent on these bacteria.

All complexes [VO (IV)-GBA, Ag (I) GBA, and Mn(II) GBA] have shown very weak or no inhibitory effect against all strains of gram-ive and +ive bacteria with MIC value 1280 μg/cm^3.All complexes have shown no activity against *E. coli(C).* VO (IV) complex also remained quite inactive against *Ent. Faccalis* and *Staph. Aureus E. Coli and Proteus mirabilis* bacteria whereas Ag(I) complex showed inactivity against *Klebsiella pneumoniae* in addition to *E. Coli and Proteus mirabilis.* However, the Mn(II) complex showed very weak inhibitory effect against all strain except *E. Coli (C).* MIC data of the metal complexes is reported in Table 1.

Antibacterial Activity:

Antibacterial activity of all metal complexes was examined for different strains of gram +ve and gram –ve bacteria. Only one concentration of these complexes i.e; 100 μg/cm^3 was used to compare their activity with streptomycin sulphate, a standard antibiotic. The results revealed that these complexes have not shown any activity against the studied organism upto 100 μg/cm^3 concentration (Table-2). The results obtained are consistent with previously conducted studies. According to which in the metal complexes of organic ligands, the type of ligand, nature of central metal atom its mode of coordination exert effect on the antibacterial activities of the complexes [27-28]

CONCLUSION:

Complexes of VO(IV), Mn(II), and Ag(I) with Glibenclamide drug ligand were successfully synthesized. Spectral and other analytical studies correlate with the proposed structures. VO(IV) Glibenclamide complex has shown enhanced hypoglycemic activity and keep the BGL lower compared to the parent drug ligand (GBA) even after the end of the experimental time. It can be used as an effective and desirable metal based drug having no toxicity. The Mn (II)-GBA and Ag(I)-GBA complexes have not shown enhanced hypoglycemic activity compared to the ligand (GBA) All metal complexes have shown a very weak inhibitory action and no antibacterial activity against the studied organism. A comprehensive investigation can find out whether the synthesized complexes are safe to use as Metal Based Antidiabetic Drugs for non-insulin dependent diabetes mellitus (NIDDM).

Table-1:Data of Minimum Inhibitory Concentration of Metal Complexes against Different Bacteria (MIC μg/cm^3).

Compound	Gram-Negative Bacteria										Gram-Positive Bacteria		
	1	2	3	4	5	6	7	8	9	10	11	12	13
VO-GBA	1280	–	1280	1280	–	1280	–	–	1280	1280	-	1280	1280
Mn-GBA	1280	–	1280	1280	1280	1280	1280	1280	1280	1280	1280	1280	1280
Ag-GBA	1280	–	1280	1280	–	1280	1280	–	–	1280	1280	1280	1280

*1.Pseudomonas (C)*2.E. coli (C) *3.Salmonella typhi (R)¶4.Pseudomonas5.E. coli 6.Ent. cloacae 7.Ent. Faccalis*
*8.Proteus mirabilis 9.Klebsiella pneumoniae 10.Salmonella sensitive 11.Staph. aureus 12.Staph. coagulase 13.Streptococcu**
* = mutant gene of the bacteria ¶ = resistant gene of the bacteria

Table- 2:Data of Antibacterial Activity of Metal Complexes against Gram Positive and Gram Negative Bacteria.

Compound	Zone of Inhibition of Organisms						
	Gram Negative bacteria			*Gram Positive bacteria*			
	E. coli	*B. bron-chiseptica*	*S. cerevisiae*	*Staph. aureus*	*B. subtilis*	*M. luteus*	*M. flavus*
Ag-GBA	–ve	–ve	–ve	–ve	–ve	–ve	–ve
Mn-GBA	–ve	–ve	–ve	–ve	–ve	–ve	–ve
VO-GBA	–ve	–ve	–ve	–ve	–ve	–ve	–ve
Streptomycin Sulphate Standard	22.0 mm	20.0 mm	18.0 mm	25.0 mm	27.0 mm	20.0 mm	18.0 mm

–ive *= No activity ,* ***Standard Drug*** *= Streptomycin in Sulphate,* ***Concentration*** *=100 μg/cm3* ***Solvent*** *= DMSO*

REFERENCES

[1] Anastassopoulou, J, Collery, P, Etienne, J-C, Theophanides, T (1992) Metal Ions in Biology and Medicine. John Libbey Eurotext, Paris, London

[2] H.Preuss, *J.Am.Coll. Nutr,* **16** 392 (1998)

[3] J. J. R. F. D. Silva and R. J. P. Williams, The Biological Chemistry of the Elements, 1991, Clarendon Press: Oxford.

[4] Gielen M, Tiekink E.R.T, *Metallotherapeutic Drugs and Metal-Based Diagnostic Agents. The Use of Metals in Medicine.* John Wiley & Sons, Hoboken, 584 (2005)

[5] Strout HV, Vicario PP, Saperstein R, et al: The insulin-mimetic effect of vanadate is not correlated with insulin receptor tyrosine kinaseactivity nor phosphorylation in mouse diaphragm in vivo. Endocrinology **124**:1918-1924, (1989)

[6] Shechter Y, Karlish SJD: Insulin-like stimulation of glucose oxidation in rat adipocytes by vanadyl (IV) ions. Nature **284**:556-558, (1980)

[7] Boden G, Chen X, Ruiz J, van Rossum G, Turco S, *Metabolism **9*** 1130 **(**1996)

[8] Crans, D. C, Trujillo A. M, Pharazyn P. S, Cohen, M. D, Coord. *Chem. Rev,* 255 2178 (2011)

[9] Möllsten A, Marklund S. L, Wessman M, Svensson M, Forsblom C, Parkkonen M, Brismar K.; Groop P. H.; Dahlquist G.; *Diabetes **56,*** 265 **(2007)**

[10] Olcott A. P.; Tocco G.; Tian J.; Zekzer D.; Fukuto J.; Ignarro L.; Kaufman D. L.; *Diabetes **53*** 2574 (2004)

[11] Digest Journal of Nanomaterials and Biostructures Vol. 3, No.2, June **2008,** 49 – 54

[12] Wright JB, Lam K, Hanson D, Burrell RE, *Am. J. Inf. Cont,* 27, 344(**1999)**

[13] Grier N, *Silver and its compounds*. In: Block SS, editor. Disinfection, Sterilization and Preservation, 3rd ed. Philadelphia, PA: Lea & Febiger, **1983**.

[14] Demling RH, DeSanti L, *Effects of silver on wound management. Wounds*, 13, **4** (2001).

[15] Noriko Chikaraishi Kasuga, Rie Oshikawa, Yoshitaka Sakai , and Kenji Nomiya, *Inorg. Chem*. ***51*** (3); 1640–1647 (2012)

[16] Muhammad Tawkir, A. A Iqbal, *Asian J Pharma Clin. Res*, (5) suppl **4** 129-137 (2012)

[17] Muller G, Hartz D, Punter J, Okonomopulos R, Kramer W, *Biochim. Biophys. Acta, 1191* 267 (1994)

[18] Lebovitz H.E, In *Therapy for Diabetes Mellitus and Related Disorders.* Lebovitz H.E. Ed.; American Diabetes Association, Alexandria, VA, 112 (1991)

[19] Hiromu Sakura, Yutaka Yoshikawa and Hiroyuki Yasui, *Chem. Sci.Rev*, **37** 2383-2392 (2008)

[20] Boyd A E, Agullar Bryan L, Nelson D.A, *Am. J. Med*, **20** 89 (1990)

[21] Shruti S, Sarwade, W.H, Jadhav and B.C Khade, *J. Chem. Bio and Phy.Sci*, **4** (2) 978-982 (2014)

[22] Hassan R. H. Ali, Gamal A, Saleh Samiha A. Hussein and Ahmad I. Hassan, *Der Pharma Chemica*, **5** (6); 156-163 (2013)

[23] Hatzidimtriou A. G.; Kessissoglou D. P, Manoussakis G. E, Kourounakis P. N, Economidis G, *J. Inorg. Biochem, 39,* 263, **(**1990)

[24] Figgis B.N, Lewis J, *In Progress in Inorganic Chemistry* Vol. 6, Lippard S.J. Ed.; Interscience Publications: New York, 37 **(1964)**

[25] Farmer J. J. III, Davis B. R, Hickman-Brenner F. W, McWhorter A, Huntley-Carter G. P, Asbury M. A, Riddle C, Wathen-Grady H. G, Elias C, Fanning G. R, *J. Clin. Microbiol. **21***, 46. (1985)

[26] Nannini E.C. Murray B.E. In *Principles and Practice of Clinical Bacteriology.* Gillespie S.H. Hawkey P.M. Eds.; John Wiley & Sons, Sussex; 59 **(2006)**

[27] Alena Pahentu, Falicia Julea, Tudor Rasu, Victor Purcarea, *J.Cell. Mol. Med*, **19**(4); 865-878 (2015)

[28] Liberta A.E, West D X, *Biometals* **5** 121-126 (1992)