SYNTHESIS AND EVALUATION OF HYDROXYL BENZOPHENONE DERIVED METAL COMPLEXES AS ANTIDIABETIC AGENTS

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ABSTRACT:

The M(II) complexes derived from hydroxyl benzophenone and o-phenylenediamine have been synthesised. All the compounds were characterized by elemental analysis, ^1H NMR, FT-IR, UV-visible, Mass spectroscopy, molar conductometry, magnetic susceptibility and thermal analysis study. The FT-IR spectral study reveals that the ligand behaves as a dibasic tetradentate ligand with N_2O_2 donor atoms sequence towards central metal ion. The physico-chemical study reveals octahedral geometry for the complexes. The results show the formation of 2:1(ligand: metal chloride) complexes with amine and screened for anti-diabetic activity.

INTRODUCTION:

During the past two decades, considerable attention has been paid to the chemistry of metal complexes containing nitrogen and other donor[1]. The tetradentate Schiff base complexes are well known to form stable complexes, where coordination takes place through the N_2O_2 donor set[2-4]. N, O- bidentate and N_2O_2 -tetradentate ligands (soft and hard donor) possess many, advantages such as facile approach, relative tolerance, readily adjusted ancillary ligands, and tunable steric and electronic coordination environments on the metal center[5]. This may be attributed to their potential application in many fields such as oxidation catalysis[6] and electrochemistry[7]. Transition metals are involved in many biological processes which are essential to life process. The metals can coordinate with O- or N-terminals from proteins in a variety of models and play a crucial role in the conformation and function of biological macromolecules[8, 9]. This paper reports the synthesis, characterization, thermal and

biological studies of metal(II) complexes derived from the reaction of hydroxyl benzophenone and o-phenylenediamine in alcohol.Diabetes mellitus (DM), which develops many secondary complications such as atherosclerosis, microangiopathy, renal dysfunction and failure, cardiac abnormality, diabetes retinopathy and ocular disorders, is classified as either insulin-dependent type 1 or non-insulin-dependent type 2, according to the definition of WHO. Although several types of insulin preparations for type 1 DM and those of synthetic drugs for type 2 DM have been developed and clinically used, they have several problems such as physical and mental pain due to daily insulin injections and defects involving side effects, respectively. Over thousands of years, people have produced many types of inorganic compounds, and the modern concept of chemotherapy was achieved by Ehrlich, who used an arsenic-containing compound to treat syphilis. In the 21^{st} century, a new class of pharmaceuticals should be introduced. For this reason, metallopharmaceutical compounds containing vanadium and zinc ions are expected to treat both types of DM, by making effective use of unique characteristics of the metals. Focusing on the preparations and coordination structures of the complexes and in vitro and in vivo evaluations as well as the possible mechanism. Since then, many metallopharmaceutics have been developed worldwide. This review will be helpful to researchers who are interested in the current states of anti-diabetic metal complexes.

CHEMISTRY

Materials and Methods:

All the chemicals used in the preparation of Schiff base and its metal complexes were of AR grade. A Perkin-Elmer CHN analyzer (model 2400) was used for C, H and N analyses.. The electronic absorption spectra of the complexes were recorded as dilute solutions on a Shimadzu 160A/240A UV-visible spectrophotometer. The ^{1}H NMR spectra were recorded using Bruker DRX 400 spectrometer at 400 MHz with TMS as the internal standard. Mass

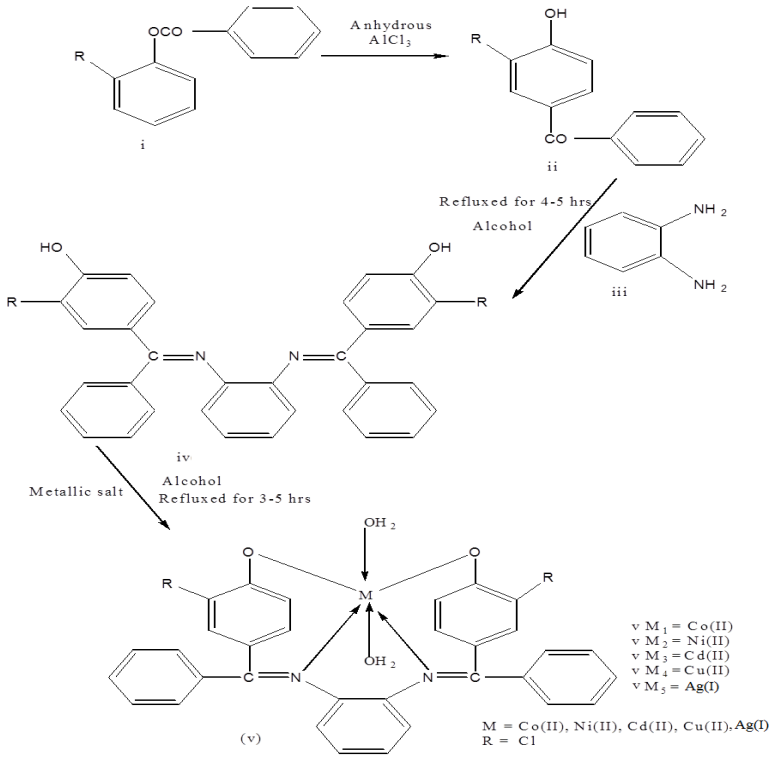
spectra were obtained with a VG70-70H spectrophotometer. The infrared spectra of the solid samples were recorded in the range 4000-500 cm^{-1} on a Perkin-Elmer 597/1650 spectrophotometer using KBr pellets.

METHODOLOGY:

A mixture of o-phenylenediamine (**iii**) and substituted hydroxybenzophenone (**ii**) in 1:2 molar ratio in methanol was refluxed with constant stirring. This condensation reaction was carried by using 3 drops of acetic acid for 5 hours. The formed water was removed from the reaction mixture by using sodium sulphate as dehydrating agent. After completion of the reaction, the mixture was reduced to half of its original volume and kept aside at room temperature. The white precipitate (**iv**) was formed on slow evaporation.

iv: Yield 85%; M.p. 167^{o}C; IR (Nujol): (C=N) 1665, (O-H) 3505 cm^{-1}, ^{1}H NMR (DMSO): δ 6.9-8.1 (m, 20H, Ar-H), 10.7 (bs, 2H, -OH $_{phenolic}$). MS: m/z 536Anal.Calcd.for $C_{32}H_{22}Cl_2N_2O_2$: C, 71.51; H, 4.13; N, 5.21. Found: C, 71.63; H, 4.22; N, 5.62%.

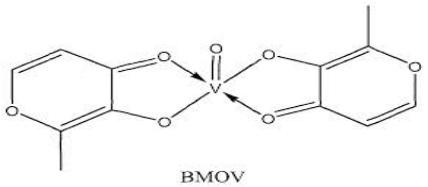
A solution of ligand (**iv**) and cobalt(II) chloride hexa hydrate in 1:1 molar ratio in ethanol was refluxed for 6 hours. The resulting solution was reduced to half of its volume and kept aside. On standing, the obtained solid product was filtered off and washed with water and ethanol.



RESULTS AND DISCUSSION

All the complexes vM_1-M_5 are colored, stable at room temperature, soluble in DMSO and melt with decomposition above 250°C. Therefore the ligands and their complexes were characterized on the basis of elemental analysis, ^{1}H NMR, IR, magnetic susceptibility measurement, electronic spectra data, melting point, partial elemental analyses and molar conductivities.Benzophenone derivatives showed inhibition for alpha glucosidase. The inhibition was measured by IC50 value calculation. The compound V-M5 showed maximum inhibition at a concentration of 6.4µg/ml

BIOLOGY:Antidiabetic Activity: Some of the reported antidiabetic metal complexes are



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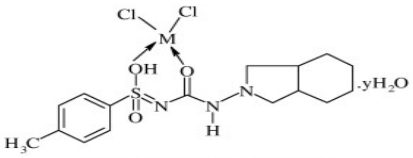
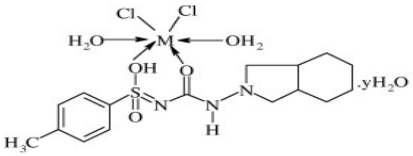
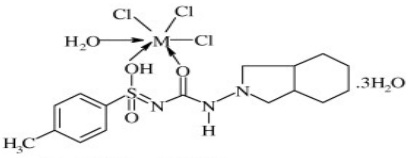


M = Mn(II) and Zn(II), y = 0-1



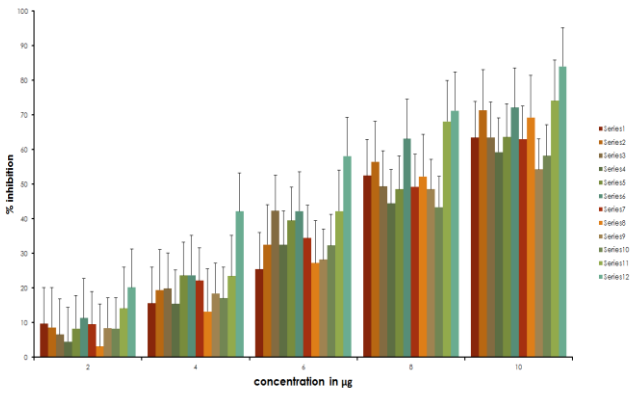
M = Co(II), Ni(II) and Cu(II), y = 0-2



M = Cr(III) and Fe(III)

The activity was performed using assay mixture of 5µl of enzyme alpha-glucosidase, 50µl of substrate p-nitrophenyl-alpha-D-glycopyranoside and 10µg concentrations of different inhibitors were taken in test tubes and they were incubated for 30mins at 30°c.Then, the volume was made upto 1ml using phosphate buffer(0.1M,pH7). A tube containing only the enzyme and substrate was used as the control. The absorbance was measured at 405nm. Inhibitory activity was calculated by,

Inhibition(%)=Absorbance of the control-Absorbance of the sample/ Absorbance of the control× 100



COMPOUNDS	IC50 value (µg/ml)
iv Ligand	7.7
V-M1 Co(II)	7.1
V-M2 Ni(II)	8
V-M3 Cd(II)	8.6
V-M4 Cu(II)	8.1
V-M5 Ag(I)	6.4

CONCLUSION

In conclusion, we have achieved efficient method for the preparations of Schiff bases and evaluated antidiabetic activity. Some of the compounds exhibit minimum inhibition and compound VM_5 prove to be important antidiabetic agent.

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