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RESEARCH ARTICLE

In-Vitro Studies on Alpha Amylase and Alpha Glucosidase Inhibitory Activities of Synthesized Novel Sn(IV) Complexes of Schiff Base Ligand

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Abstract

Objectives: The current study is concerned with creatingSn(IV) complex with a novel synthesize schiff base ligand2,3-dimethyl-N'-(2-oxo-2,3-dihydro-1H-indol-3-yl)benzhydrazide and were investigated for the Inhibition of alpha-amylase and alpha-glucosidase enzyme. **Methods:** Ligand was synthesized by using isatin and 2,3-dimethylbenzoic acid hydrazide. n-Bu_3SnCl and n-Bu_2SnCl_2 were used for the synthesis of metal complexes. The structures of the ligand and metal complexes were confirmed by spectroscopic analysis i.e. 1H-NMR, IR and MS. **Findings:** A clinical disease known as diabetes mellitus is defined by hyperglycemia, in which a greater than normal amount of glucose circulates in the blood plasma. Inhibitors of alpha amylase and alpha glucosidaseare used to better manage hyperglycemia in type 2 diabetes mellitus. Synthesized metal complexes were investigated for the Inhibition of alpha-amylase and alpha-glucosidase enzyme. In the alpha amylase inhibition assay, L-1 (118.88±11.14), MC-1 (76.90±9.55), and MC-2 (73.28±8.31) all displayed 50% alpha amylase inhibition activity. The IC_{50} values for [L-1], [MC-1], and [MC-2] in the alpha glucosidase inhibition experiment were 128.86±10.27, 76.90±9.55, and 73.28±8.31 g/ml, respectively. Observed data revealed that MC-2 have higher inhibition activity. **Novelty:** Anti-hyperglycemia activity was investigated by using newly synthesized metal complexes.

Keywords: Schiff Base; Sn(IV); Hyperglycemia; Alpha Amylase; Alpha Glucosidase

1 Introduction

Metal complexes gain tremendous consideration in medicinal chemistry because of their marked and enormous biological properties [1]. They are used as anticancer [2], antimicrobial [3,4], antiviral [5], antiparasitic [6], antimalarial [7], antifungi [8] agents. Significance of "coordination chemistry is escalating constantly with the synthesis of organic ligand/s containing" assorted donor groups [9]. Saroya and co-researchers

synthesized Diorganotin(IV) complexes with Schiff base ligands and found that ONO donor atoms served as the tridentate conduit. Synthesized complexes were tested for anti-bacterial and anti-fungal efficacy and reveal that phenyl-substituted complexes showing superior activity. Additionally, the complexes were tested for their anticancer activity, and one of the synthesized complexes exhibited the most potent effect against the A549 cell line, comparable to the standard drug paclitaxel [10]. Additionally, Saroya et al. synthesized organotin complexes of Schiff bases and exhibited pentacoordinated geometry. The complexes showed enhanced antimicrobial and antioxidant activity compared to the ligands. Ligands with electron-withdrawing groups demonstrated higher antimicrobial activity, while electron-donating groups increased antioxidant activity [11]. Organometallic complexes offer multipurpose framwork for drug designing. Synthesized metal complexes with different types of ligands tested for their cytotoxic activity and found highly cytotoxic against human tumor cell lines [12]. In addition to the exploration of organometallic complexes, Agarwal et al. focused on the recent advancements in the anticancer potentials of first-row transition metal complexes. Their study reviewed the progress made in utilizing transition metal complexes for cancer treatment [13]. Deswal and co-researchers explored the synthesis, spectral characterization, antimicrobial, anticancer, and molecular docking studies of transition metal complexes of triazole-based bioactive ligands and found that some of the complexes showed significant anticancer activity against the three tested cancer cell lines i.e. HCT-116, DU145, and A549. The docking results correlate very well with the IC_{50} data and enabled the importance of interactions for depicting the binding energies of the potent compounds [14]. Further, copper(II) and tin(IV) complexes along with hydrazones demonstrate considerable pharmacology activity [15].

A chronic endocrine condition called diabetes mellitus alters how carbohydrates, proteins, fats, electrolytes, and water are metabolised. It comprises a class of metabolic illnesses known as hyperglycemia, in which blood sugar levels are raised due to either insufficient insulin production by the pancreas or ineffective insulin action on the cells [16]. Decrease postprandial hyperglycemia as a result is a therapeutic strategy for the management of diabetes [17]. This can be accomplished by inhibiting enzymes that hydrolyze carbohydrates, such as alpha amylase and alpha glucosidase [18]. Alpha amylase and alpha glucosidase are crucial enzymes in the breakdown of carbohydrates. Long chain carbohydrates are broken down by alpha amylase, while starch and disaccharides are converted to glucose by alpha glucosidase. They assist in intestinal absorption and act as the primary digestive enzymes. Deswal and colleagues synthesised compounds of Co, Ni, Cu, and Zn with the ligand to find possible drugs for the treatment of diabetes. Theoretical calculations and in vitro assays against α-amylase and α-glucosidase demonstrated promising results, with one of the complexes as a good inhibitor of α-amylase and another complex as a strong inhibitor of α-glucosidase. Molecular docking experiments and molecular dynamics simulations supported the observed interactions and stability of the complexes [19]. In 2022, Ajaza et al., examined the impact of synthesized Zn(II) complex on diabetes mellitus-2. Antidiabetic activities of the synthesized compounds were also evaluated by performing in vitro α-amylase and α-glucosidase inhibition studies and zinc(II) complexes were also found to be effective against α-amylase only. Similarly a series of silver(I) complexes of 2,4-dihydroxybenzaldehyde–amino acid Schiff bases were tested by Zheng & Ma in 2015 for α-glucosidase inhibition. Obtained results indicate that all the silver complexes possessed strong inhibitory activity. Sn(IV) metal complexes are not investigated for the anti-hyperglycemia activity in prior studies, despite the fact that several metal complexes have been tested for their anti-hyperglycemia activity. The discovery of lead drugs for the treatment of diabetes may focus on alpha amylase and glucosidase inhibitors [20].

2 Methodology

Melting points were determined in soft glass capillaries in an electrothermal melting point apparatus. The IR spectra were recorded on FTIR SHIMADZU 8400S spectrometer with KBr pellets. The 1H-NMR spectrum were recorded in $CDCl_3$andDMSO-d6 at 400 MHz on a Brucker NMR instrument, using TMS as internal standard. FAB mass spectra were recorded on JEOL SX 102 /DA-6000 mass spectrometer using Argon /Xenon as FAB gas.

2.1 Synthesis of 2,3-dimethyl-N'-(2-oxo-2,3-dihydro-1H-indol-3-yl benzhydrazide"(HL)

2.1.1 Step-1: Preparation of 2,3-dimethylbenzoic acid hydrazide precursor

2,3-dimethylbenzoic acid methyl ester (0.01 mole, 1.64 g) was refluxed with methanol solution of hydrazine hydrate 80% (0.25 mole) for 3 hours [21]. The resulting reaction mixture was filtered and washed with distilled water. Obtained solid product was purified with C_2H_5OH and dried in vacuum. Analysis:m.p.124-126^{0}C; Yield: 79%; IR (cm^{-1}, KBr): 3225 (-NH), 3035(Ar., -C-H), 1630 (C=O), 1545 (C=C).MS (EI) m/z: 164, 149, 133, 118, 105 etc. Molecular formula calculated as $C_9H_{12}N_2O$.

2.1.2 Step-2: Preparation of "2,3-dimethyl-N'-(2-oxo-2,3-dihydro-1H-indol-3-yl benzhydrazide"(HL)

0.01 mole of isatin (1.47 g) and 0.01 mole of 2,3-dimethylbenzoic acid hydrazide were taken in 20 ml ethanol solvent. This mixture was refluxed for 4 hrs [22]. The solid product obtained was separated by filtration and washed with cold water and then dried in vacuum. Analysis: Shiny light orange color, crystalline solid; m.p. 284-286^{0}C; Yield 82%; IR (cm^{-1}, KBr): 3275 (-NH), 3065(Ar., -C-H), 1724 (C=O, isatin), 1686 (C=O, amido) 1540 (C=N). ^{1}H NMR (δppm, DMSO-d6): 12.30 (s, 1H, -NH, isatin), 10.80 (s, 1H, -NH), 6.98-7.11 (m, 7H, Ar-H), 2.49 (s, 3H, -CH_3), 2.31 (s, 3H, -CH_3).MS (EI) m/z: 293, 278, 202, 174, 145 etc. Molecular formula calculated as $C_{17}H_{15}N_3O_2$.

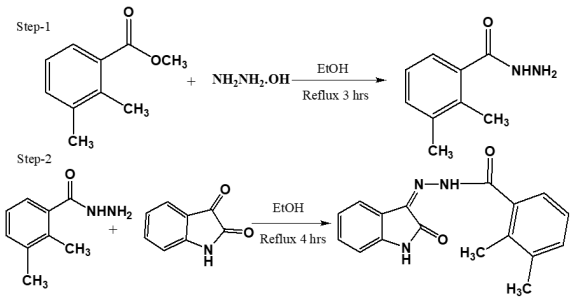

Fig 1. Synthesis of 2,3-dimethyl-N'-(2-oxo-2,3-dihydro-1H-indol-3-yl) benzohydrazide

2.3 Synthesis of Sn(IV complexes with Ligand (HL)

In the methanolic solution of ligand 2,3-dimethyl-N'-(2-oxo-2,3-dihydro-1H-indol-3-yl)benzhydrazide(6.55 mmol), equimolar Na metal (2.0 mmol) was added with constant stirring. The light yellow colour sodium salt was formed. This salt solution was refluxed under anhydrous condition for 01 hour. This methanolic solution of sodium salt of ligand was added to the anhydrous benzene solution of R_nSnCl_{4-n} (6.55 mmol of n-Bu_3SnCl / n-Bu_2SnCl_2) in 1:1 ratio. The ensuing solution was further refluxed for 06 hours under anhydrous atmosphere. The color of reaction mixture becomes more intense. NaCI produced during reaction was filtrated and concentrated in vacuum, which gave brown to dark brown solid. This solid was purified by re-crystallization with a mixture of dichloromethane and n-hexane under vacuum [23]. Yield 89%.

All these synthesized metal complexes found to be hygroscopic in nature & insoluble in organic solvents apart from DMF & DMSO. Their physical and analytical data are given in Tables 1, 2 and 3.

Table 1. Analytical and Physical data of Ligand and its Organotin(IV) complexes

S. No.	Compound	Emp. Formula	Color	M.P. (OC)	Mol. Wt.
1	HL	$C_{17}H_{15}N_3O_2$	Light Orange	284-286	293.32
2	n-Bu_3Sn(L)	$C_{29}H_{41}N_3O_2Sn$	Pale Brown	>300	582.37
3	n-Bu_2Sn(L)Cl	$C_{25}H_{32}ClN_3O_2Sn$	Brown	>300	560.71

Table 2. Important IR spectral data (cm^{-1}, KBr) of ligand and its corresponding organotin(IV) complexes

S. No.	Compounds	*ν*(NH)	*ν*(C=N)	*ν*(C=O)	*ν* (Sn-C)	*ν* (Sn- N)	*ν* (Sn-O)
1	HL	3275	1540	1686 1724	-	-	-
2	n-Bu_3Sn(L)	-	1530	-	620	430	548
3	n-Bu_2Sn(L)Cl	-	1525	-	632	428	545

Table 3. ^{1}H NMR spectral data of the ligand and its corresponding organotin(IV) complexes

S.No.	Compounds	Chemical Shift (δ ppm)		
		-NH	Aromatic	Sn-Bu
1	HL	12.30 (s, 1H) 10.80 (s, 1H)	6.98-7.11 (m, 7H)	-
2	n-Bu_3Sn(L)	12.45 (s, 1H)	6.82-7.73 (m, 7H)	0.73-1.48 (m, 27H)
3	n-Bu_2Sn(L)Cl	12.45 (s, 1H)	6.93-7.85 (m, 7H)	0.96-1.45 (m, 18H)

2.3 Antidiabetic activity

In-vitro antidiabetic activity by using alpha-amylase and alpha-glucosidase inhibition.

2.3.1 Inhibition of alpha-amylase enzyme

A starch solution (0.1% w/v) was obtained by stirring 0.1g of potato starch in 100 ml of 16 mM of sodium acetate buffer. The enzyme solution was prepared by mixing 27.5 mg of alpha-amylase in 100 ml of distilled water. The colorimetric reagent is prepared by mixing sodium potassium tartarate solution and 3, 5 di nitro salicylic acid solution 96 mM. Both control and plant extracts were added with starch solution and left to react with alpha- amylase solution under alkaline conditions at 25°C. The reaction was measured over 3 minutes. The generation of maltose was quantified by the reduction of 3, 5 dinitro salicylic acid to 3-amino-5-nitro salicylic acid. This reaction is detectable at 540 nm [24].

2.3.2 Inhibition of alpha-glucosidase enzyme

The inhibitory activity was determined by incubating a solution of starch substrate (2% w/v maltose or sucrose) 1 ml with 0.2 M Tris buffer pH 8.0 and various concentration of plant extract for 5 min at 37°C. The reaction was initiated by adding 1 ml of alpha-glucosidase enzyme (1U/ml) to it followed by incubation for 40 min at 35°C. Then the reaction was terminated by the addition of 2 ml of 6N HCl. Then the intensity of the colour was measured at 540nm [24].

Table 4. The percent inhibition of alpha amylase by Ligand (HL) [L-1] andSn(IV) metal complex i.e. n-Bu_3Sn(L) [MC-1] & n-Bu_2Sn(L)Cl [MC-2]at varying concentrations

Concentration (μg/ml)	% Inhibition by L-1	IC_{50} (μg/ml) (L-1)	% Inhibition by MC-1	IC_{50} (μg/ml) (MC-1)	% Inhibition by MC-2	IC_{50} (μg/ml) (MC-2)
20	8		32		34	
40	28		40		42	
60	32	118.88±11.14	18	70.58±9.66	21	67.58±7.11
80	36		52		55	
100	40		60		60	

Table 5. The percent inhibition of alpha glucosidase by Ligand (HL) [L-1] andSn(IV) metal complex i.e. n-Bu_3Sn(L) [MC-1] & n-Bu_2Sn(L)Cl [MC-2]at varying concentrations

Concentration (μg/ml)	% Inhibition by L-1	IC_{50} (μg/ml) (L-1)	% Inhibition by MC-1	IC_{50} (μg/ml) (MC-1)	% Inhibition by MC-2	IC_{50} (μg/ml) (MC-2)
20	8.5		29		31	
40	25		37.5		39	
60	29	128.86±10.27	47.6	76.90±9.55	50.3	73.28±8.31
80	33		48.5		55.6	
100	39		59.2		62	

3 Results and Discussion

3.1 Characterization of ligand 2,3-dimethyl-N'-(2-oxo-2,3-dihydro-1H-indol-3-yl benzhydrazide (HL)

The mass spectrum of this ligand showed a molecular ion peak at m/z 293 [M+] with other important peak at 278, 202, 174,145 etc. The molecular formula was determined as $C_{17}H_{15}N_3O_2$ with the help of ^{1}H NMR & elemental investigation.IR spectrum (cm^{-1}, KBr) of compound/ligand confirmed the presence of –NH group by showing absorption at 3275 cm^{-1}. The presence of carbonyl group was established by the absorption at 1724 and 1686 cm^{-1}. The absorption at 1540 indicated the presence of >C=N group.The ^{1}HNMR spectrum (δ ppm, DMSO-d6) showed sharp two singlets at 12.30 (s, 1H, -NH isatin) and 10.80 (s, 1H, -NHCO) which indicated the presence of –NH groups. Two another singlets were observed at 2.49 (s, 3H, -CH_3) and at 2.31 (s, 3H, -CH_3) for three protons each were ascertained to two methyl groups (-CH_3) at position C3'and C4'. A multiplet peak was observed between δ 6.98-7.11 (m, 7H, Ar-H) for remaining seven aromatic hydrogen.

The identity of the title compound/ligand was further confirmed by comparing the spectral data with reported values [25]. On the basis of above observation and discussion this compound/ligand was identified as 2,3-dimethyl-N'-(2 -oxo-2,3-dihydro-1H-indol-3-yl)benzhydrazide.

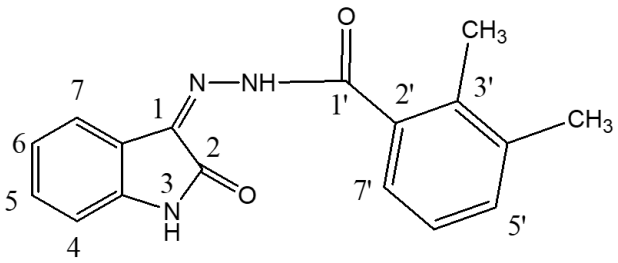

Fig 2. 2,3-dimethyl-N'-(2-oxo-2,3-dihydro-1H-indol-3-yl) benzhydrazide

3.2 Characterization of Sn(IV) complexes

These IR vibrations of all complexes have been compared with spectrum of free ligands and their derivatives. The -NH and C=O absorption bands ofamido group which appeared at 3275 cm^{-1} and 1686 cm^{-1} in the spectrum of free ligand, were not detect in spectrum of complexes. The emergence of a new band in IR spectrum of these complexes at 428&430 and 545 &548 cm^{-1} region, assigned to ν(Sn-N), ν(Sn−O) also support the coordination of N and O to the tin metal ion respectively [26].The new υ(C=N) mode observed at 1530 cm^{-1} in spectra of hydrazones undergoes little shifts in spectrum of the complexes recommend that N atom of the ligand moiety affixed to the indole ring also coordinating to metal ion in complexes formation. The above IR spectral data is indicated that, all the above mentioned complexes Sn, the ligand appeared to bind with metal via N and O in tridentate fashion.

The expected ^{1}HNMR spectral (δppm, DMSO-d6) information of ligand and their metal complexes are depicted. The signal appeared at δ 10.80 (s, 1H, -NHCO) due to –NH proton in free ligand spectrum, was absent in spectra of all these complexes, suggested that deportation was take place during the complexation and ligand attached to the Sn in neutral form. The other protons of ligand moiety like aromatic protons was appeared as a multiplate in the region δ 6.82-8.10 ppm in spectrum of complexes and almost same as ligand. Based on these observed chemical shift difference, it is assumed that coordination number of Sn in this complex is six [27].

3.3 Anti-hyperglycemia Activity

The results of this study's investigation into the inhibitory activity of Ligand (HL) [L-1] and Sn(IV) metal complex, specifically n-Bu_3Sn(L) [MC-1] & n-Bu_2Sn(L)Cl [MC-2], on alpha amylase and alpha glucosidase are displayed in Tables 4 and 5. L-1 (118.88±11.14), MC-1 (76.90±9.55), and MC-2 (73.28±8.31) all demonstrated 50% alpha amylase inhibition activity in the alpha amylase inhibition assay. L-1 had the least inhibitory action, followed by MC-1 and MC-2 who all shown good anti-alpha amylase activity. All of the substances increased their % inhibitory activity against alpha glucosidase in a dose-dependent manner. In the alpha glucosidase inhibition assay, [L-1], [MC-1], and [MC-2] had IC_{50} values of 128.86±10.27, 76.90±9.55, and 73.28±8.31 g/ml, respectively. Alpha glucosidase enzyme inhibition was more pronounced in MC-2.

4 Conclusion

The synthesized complex was characterized using various physico and spectrochemical techniques. The coordination sites are confirmed by using 1H-NMR and FT-IR. Based on these observed chemical shift difference, it is assumed that coordination number of Sn(IV) in this complex is six. Because of their distinctive properties and uncommon reactivity, schiff base complexes can be used as a building block to create complex compounds with potential uses across a wide range of industries. L-1 (118.88±11.14), MC-1 (76.90±9.55), and MC-2 (73.28±8.31) all showed 50% alpha amylase inhibition activity in the alpha amylase inhibition assay, while their respective IC_{50} values for [L-1], [MC-1], and [MC-2] in the alpha glucosidase inhibition experiment were 128.86±10.27, 76.90±9.55, and 73.28±8.31 g/ml. The study's conclusions suggested that MC-2 might be helpful in the treatment of postprandial hyperglycemia. When compared to alpha amylase, Sn(IV) metal complexes caused a slightly less potent alpha glucosidase enzyme inhibition.These unusual and novel characteristics open up a whole new field of study for the investigation of their potential biological, analytical, and therapeutic uses.

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