Synthesis, Enzyme Inhibition, and in Silico Studies of Amino Acid Schiff Bases

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ABSTRACT: *In this research, novel complexes of Zn(II) were produced using amino acid Schiff bases. First, new Schiff bases were synthesized from the reaction of 3-methoxy-2-hydroxybenzaldehyde (o-vanillin) and amino acid methyl esters (isoleucine, phenylalanine, methionine). The synthesis of new complexes was carried out by the response of these Schiff bases and $Zn(OAc)_2.2H_2O$. The structures of the synthesized complexes were elucidated using elemental analysis, FT-IR, NMR, UV-vis spectroscopy, and thermal analysis techniques. In this research, we synthesized new Zn(II) complexes with amino acid Schiff bases labeled as 1a-1c. We then examined their impact on specific metabolic enzymes, namely acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). The results showed that the molecules exhibited potent inhibitory activities against all targets compared to the standard inhibitor as indicated by IC50 values. Ki values of the compounds for AChE and BChE enzymes were obtained in the range of 78.04±8.66-111.24±12.61 and 24.31±3.98-85.18±7.05 µM, respectively. Molecular docking calculations were performed to investigate the biological activities of the metal complexes. The Protein Ligand Interaction Profiler (PLIP) was used to study the chemical interactions of metal complexes with enzymes.*

KEYWORDS: *Amino acid Schiff base; Zn(II) complexes; Bioactivity; Docking; PLIP.*

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INTRODUCTION

Due to their distinctive structures, Schiff bases and their metal complexes, produced via the condensation reaction of amino acids with aldehydes or ketones, are extensively used in a variety of industries. The paint business, the food industry, catalysis, fungicides, agrochemistry, and biological activities all use amino acid Schiff base complexes. It has been established that the imine group in these compounds is essential for their biological function. They are particularly significant in the world of medicine due to their biological applications, which include anticancer, antifungal, antiviral, and antibacterial properties. Additionally, transition metal complexes of Schiff bases are crucial for a number of enzyme functions [1,2].

Amino acid Schiff base zinc complexes constitute an important research area as potential agents for treating neurodegenerative diseases such as Alzheimer's disease (AD). Alzheimer's disease (AD) is one of the fastest-moving chronic neurodegenerative conditions, leading to symptoms like memory loss, cognitive impairment, disorientation, and behavioral problems. It is related to the insufficiency of cholinergic functioning in the cortex and basal forebrain [3]. Hence, in the end, it restricts cholinergic neurotransmission, which impairs learning and memory in Alzheimer's patients. Inhibiting the activity of cholinesterase is an effective and clinically superior treatment for AD, according to a review of the literature. This can activate the function of cholinergic neurotransmission. According to research, cholinergic transmission is actively targeted by acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes, which hydrolyze the neurotransmitter acetylcholine [4,5]. Acetylcholinesterase and certain of its subunits are found in cholinergic neurons, muscles, and the brain. It is a membrane-bound enzyme that is frequently seen in the G4 form. It is similar to the enzymes found in mammalian brains. However, the amount of this enzyme rises together with the number of deteriorating neurons. Furthermore, this enzyme regulates a variety of physiological processes by converting acetylcholine neurotransmitters in cholinergic synapses [6]. The butyrylcholinesterase enzyme, which is also present in the liver, lungs, stomach, serum, and kidneys, is expressed by neuroglia. It gives the ester-containing molecule catalytic activity. In hydrolyzing acetylcholine, BChE performs similarly to AChE, despite the fact that its level is constant and occasionally even rises [7,8].

Recent studies have shown that it has become very difficult to design and synthesize new and effective drugs. This situation has led researchers to new methods. The most important of these is the complexes formed by these molecules with metal atoms [9,10]. Studies have shown that these metal complexes are more effective and active than ligand molecules. In this study, the biological activities of metal complexes against AChE (pdb ID: 4M0E) [11] and BChE (pdb ID: 5NN0) [12] enzymes were evaluated. The chemical interactions of the metal complex with the highest activity by the Protein-Ligand Interaction Profiler (PLIP) method [13] will be examined in detail.

The literature has looked into a few biological functions of Schiff bases and metal complexes. According to research on the bioactive potentials of triazoles and vanadium metal, functional groups in substances like azomethine-N and other heteroatoms (N, O, and S) are to blame for boosting bactericidal and fungicidal actions [14,15]. Another study looked into the biological actions of metal-based sulfanilamides, their production, and their spectrum characterisation. Data on the metal complexes' antibacterial and antifungal activities revealed that they had more biological activity than non-chelated ligands against one or more bacterial and/or fungal strains. The locations that may have been responsible for the augmentation of antibacterial and antifungal activity were most likely the oxygen in furanyl, the sulphur in thioenyl, the nitrogen in azomethine, and isatin [16]. Metallic isatin compounds were assessed for their in vitro antimicrobial efficacy against specific fungal and bacterial strains. The outcomes of the antibacterial and antifungal tests demonstrated that the metal chelates exhibited greater biological activity when compared to their uncomplexed ligands [17].

This study represents a crucial stride in the creation and advancement of novel medications aimed at addressing neurodegenerative conditions, including Alzheimer's disease. Understanding the effects of amino acid Schiff base zinc complexes on the activities of AChE and BChE enzymes will provide valuable information in drug design and development process. Understanding the chemical interactions that affect the enzyme activities of these complexes may help to develop more effective and selective treatment methods [18]. Furthermore, this research marks a significant advancement in comprehending the impact of metal complexes on biological systems and in devising fresh approaches to drug exploration. Consequently, the investigation

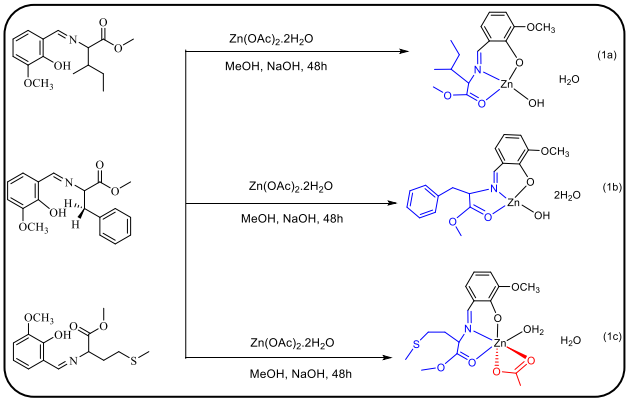


Fig. 1: The synthetic procedures for producing complexes of Zn(II) with amino acid Schiff bases encompass several stages.

of the effects of zinc complexes with amino acid Schiff bases on AChE and BChE enzymes is of paramount importance for forthcoming investigations in the realm of drug development and the management of neurodegenerative disorders [19].

In this research, we synthesized Zn(II) complexes using Schiff base ligands as a foundation. The structures of these complexes were analyzed through various methods, including 1H-NMR, 13C-NMR, FT-IR, UV-Visible spectroscopy, thermal analysis, and elemental analysis. Subsequently, we conducted in silico studies to assess their properties and examined their effects on bioactivity.

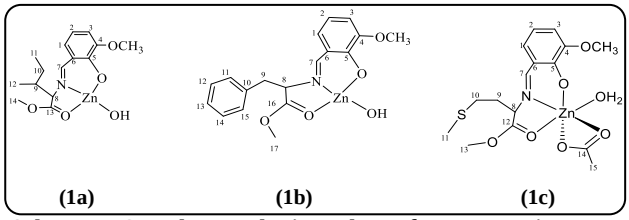
EXPERIMENTAL SECTION

Instrumentation and chemical products

UV area spectra were obtained in methanol using a spectrophotometer, specifically the Perkin-Elmer Lambda-35 UV spectrophotometer. FT-IR spectra spanning the range of 4000-400 cm^{-1} were collected using a Jasco FT/IR 340 FT-IR spectrometer. NMR spectra were recorded at a frequency of 600 MHz and a magnetic field strength of 14.1 Tesla, employing an Agilent Premium Compact NMR instrument. Thermal analysis results were generated using a HITACHI STA7300 TG/DTA thermal analyzer. Elemental analysis findings were documented using a Costech ECS 4010 elemental analyzer. The chemicals used in the study were of the utmost purity and were sourced from reputable suppliers, including Merck, Alfa Aesar, and Sigma Aldrich.

General procedure for synthesising the amino acid Schiff base

In the study, isoleucine methyl ester hydrochloride (1.0 g, 5.51 mmol), o-vanillin (0.56 g, 3.68 mmol) and triethylamine base (0.37 g, 3.68 mmol) in chloroform ($CHCl_3$) were first



Scheme 1: Complex numbering scheme for NMR assignment.

stirred under reflux for 24 h at the boiling temperature of the solvent. The reaction was continuously monitored by TLC (1THF:3Hexane) control. The product was then extracted with $CHCl_3$ and water, dried with $MgSO_4$ and the solvent removed in the evaporator. A yellow substance was obtained. Other Schiff bases were synthesized using the same method.

General procedure for synthesising amino acid Schiff base-Zn(II) complexes (1a-1c)

A clear solution of amino acid Schiff base (0.13 g, 0.41 mmol) and NaOH (0.02 g, 0.50 mmol) in methanol was prepared, and $Zn(OAc)_2{\cdot}2H_2O$ (0.05 g, 0.23 mmol) was introduced to the mixture. The reaction was then refluxed for 48 hours at its boiling point with continuous stirring. Subsequently, the solvent was evaporated, and the progress of the reaction was monitored using TLC. The reaction was concluded when it was observed that the Schiff base had been completely consumed. The remaining solvent was removed using an evaporator. The resulting solid was further purified by washing with acetonitrile and ether, resulting in the formation of a yellow solid. (Fig. 1).

1a: FT-IR (U_{max}/ cm^{-1}): 2964, 2935, 2875 (alif. C-H), 1636 (C=O), 1593 (C=N), 1455 (arom. C=C). H^1 NMR (600 MHz, DMSO-d_6) δ 8.23 (s, 1H, ***H***$_7$), 6.80 (d, 1H, *J*=7,78 Hz, ***H***$_1$), 6.77 (br, 1H, ***H***$_3$), 6.35 (t, 1H, ***H***$_2$), 3.69 (s, 3H, -OC***H***$_3$) 3.54 (d, 1H, J=6.30 Hz, ***H***$_8$), 3.36 (s, 3H, ***H***$_{14}$), 1.83-1.48 (m, 2H, ***H***$_9$), 1.13-1.04 (m, 1H, ***H***$_{10}$), 0.88 (t, 3H, *J* = 6.97 Hz, ***H***$_{11}$), 0.83 (d, 3H, *J* = 6.08 Hz, ***H***$_{12}$). C^{13}(150MHz, DMSO-d_6) δ (ppm): 168.17 (C13), 167.98 (C7), 152.04 (C5), 149.38 (C4), 126.54 (C1), 118.13 (C6), 113.78 (C2), 111.30 (C3), 72.48 (C8), 55.57 (Ar-OCH3), 52.17 (C14), 40.80 (C9), 25.30 (C10), 15.23 (C12), 11.70 (C11). $C_{15}H_{25}NO_7Zn$: C, 45.41; H, 6.35; N, 3.53; Found: C, 44.98; H, 6.11; N, 3.08.

1b: FT-IR (U_{max}/ cm^{-1}): 2933, 2846 (alif. C-H), 1622 (C=O), 1599 (C=N), 1446 (arom. C=C). H^1 NMR (600 MHz, DMSO-d_6) δ 7.40 (s, 1H, ***H***$_7$), 7.21-7.17 (m, 3H, ***H***$_{12}$, ***H***$_{13}$ and ***H***$_{14}$), 7.10-7.09 (m, 2H, ***H***$_{11}$ and ***H***$_{15}$), 6.73 (br, 1H, ***H***$_1$), 6.26 (br, 2H, ***H***$_2$ and ***H***$_3$), 3.75 (d, 1H, J=10.28

Hz, $\boldsymbol{H}_8$), 3.67 (s, 3H, Ar-OC$\boldsymbol{H}_3$), 3.37 (s, 3H, $\boldsymbol{H}_{17}$), 3.24 (d, 1H, J=12.13 Hz, $\boldsymbol{H}_9$), 2.03 (s, 1H, -O$\boldsymbol{H}$). C^{13}(150MHz, DMSO-d_6) δ (ppm): 175.31 (C16), 167.79 (C7), 152.48 (C5), 149.31 (C4), 138.40 (C10), 130.55 (C11,15), 128.73 (C12,14), 126.86 (C13), 126.61 (C1), 118.40 (C6), 113.93 (C2), 111.87 (C3), 70.87 (C8), 56.05 (Ar-OCH3), 49.24 (C17), 41.64 (C9). $C_{18}H_{23}NO_7Zn$: C, 50.19; H, 5.38; N, 3.25; Found: C, 50.80; H, 5.12; N, 3.41.

1c: FT-IR (U_{max}/ cm^{-1}): 2915, 2834 (alif. C-H), 1628 (C=O), 1602 (C=N), 1471 (arom. C=C). H^1 NMR (600 MHz, DMSO-d_6) δ 8.19 (s, 1H, $\boldsymbol{H}_7$), 6.77-6.74 (m, 2H, $\boldsymbol{H}_1$ ve $\boldsymbol{H}_3$), 6.31 (t, 1H, J=7.77 Hz, $\boldsymbol{H}_2$), 3.72 (s, 3H, Ar-OC$\boldsymbol{H}_3$), 3.63 (t, 1H, J=6.48 Hz, $\boldsymbol{H}_8$), 3.40 (s, 3H, $\boldsymbol{H}_{13}$), 2.55-2.42 (m, 2H, $\boldsymbol{H}_{10}$), 2.04-1.97 (m, 2H, $\boldsymbol{H}_9$), 2.01 (s, 3H, $\boldsymbol{H}_{11}$). 1.73 (s, 3H, $\boldsymbol{H}_{15}$). C^{13}(150MHz, DMSO-d_6) δ (ppm): 175.25 (C14), 174.90 (C12), 166.77 (C7), 160.85 (C5), 151.14 (C4), 126.06 (C1), 117.77 (C6), 111.81 (C2), 110.83 (C3), 69.32 (C8), 64.92 (Ar-OCH3), 55.11 (C13), 34.60 (C10), 29.34 (C9), 24.16 (C15), 14.48 (C11). $C_{16}H_{25}NO_8SZn$: C, 42.07; H, 5.52; N, 3.07; Found: C, 42.46; H, 5.68; N, 3.32.

Bioactivity assays

The impact of novel complexes comprising amino acid Schiff base-Zn(II) (1a-1c) on the inhibition of AChE and BChE activity was examined using the Ellman method. AChE/BChE and DTNB (Product No. D8130-1G, Sigma-Aldrich) were utilized to measure enzyme activity. The sample solution was prepared by dissolving it in 100 µL of 1 M Tris/HCl buffer (pH 8.0) in a 10 mL solution at varying concentrations. Subsequently, 50 µL of this solution was incubated with an AChE/BChE solution (5.32 X 103 EU) for 10 minutes at 25°C. Following incubation, 50 µL of DTNB (0.5 mM) was added. Then, 50 mL of AChE/BChE (10 mM, Product no. 01480-1G, Sigma-Aldrich) were introduced to initiate the reaction. The enzymatic hydrolysis of both substrates was assessed by monitoring the spectrophotometric generation of the yellow 5-thio-2-nitrobenzoate anion resulting from the interaction between DTNB and thiocholine at a wavelength of 412 nm [20,21]. To investigate the influence of novel amino acid Schiff base-Zn(II) complexes (1a-1c) on AChE, varying quantities of each compound were added to the reaction mixture, and the AChE/BChE activity was subsequently evaluated. IC50 values were determined by plotting activity (%) against the compounds.

Molecular docking

The biological activities of the investigated metal complexes have been extensively examined using the molecular docking approach [22]. to make it possible to make assumptions about a substance's biological effects before it is empirically tested. The biological effects of metal complexes on diverse targets, including the AChE [23] and BChE [24] enzymes, were compared in this study. The comparison method was conducted using the Hex 8.0.0 software [25] application. Grid dimension (0.6), FFT mode (3 D), correlation type (shape only), twist range (360), ligand range (180), receptor range (180), and distance range (40) are some other crucial calculation factors. The interaction between proteins and metal complexes was also investigated using the Protein-Ligand Interaction Profiler (PLIP) service.

1. Results and Discussion

Amino acid Schiff base-Zn(II) complexes: 1H-NMR and 13C-NMR comments

Based on the chemical shift values of the peaks in the ^{1}H-NMR and ^{13}C-NMR spectra of the complexes in DMSO-d_6, the structure of the complex (1a-1c) was tried to be confirmed. When the NMR spectra of Zn(II) complexes are examined, peaks belonging to -CH=N proton are observed in the range of δ=7.40-8.23 ppm. The aromatic ring protons in the complexes resonated in the range of δ=6.26-7.21 ppm. It is observed that the aliphatic –CH proton adjacent to the imine group resonates at δ=3.54-3.75 ppm. The singlet peak of O-CH_3 protons appears at δ=3.36-3.40 ppm. Benzylic –CH_2 protons of compound 1b were observed in the range of δ=2.83 ppm, and two –CH_2 protons of 1c were observed in the range of δ=2.55-2.42 and δ=2.04-1.97 ppm, respectively. The aliphatic –CH proton of 1a compound is seen as multiple peaks at δ=1.13-1.04 ppm, –CH_2 protons at δ=1.53-1.48 ppm, and methyl groups at δ= 0.83–0.88 ppm. When the ^{13}C-NMR spectra of the Zn(II) complexes (1a-1c) were examined, it was observed that the carbon atoms of the imine group resonated in the range of δ=166.77-167.98 ppm. In the 1c complex, two carbons belonging to the acetate group showed chemical shift values of δ=175.25 ppm and δ=24.16 ppm, respectively.

Amino acid Schiff base-Zn(II) complexes: elemental analysis comments

By using elemental analysis, the complexes C, H, and N contents were identified. Analysis results show that all complexes have 1:1 metal/ligand ratios; In addition,

Table 1: Spectral data in the UV-Visible of the synthesized complexes

Complexes	Wavelength (nm)			
1a	205	237	278	376
1b	206	232	278	376
1c	205	235	279	374

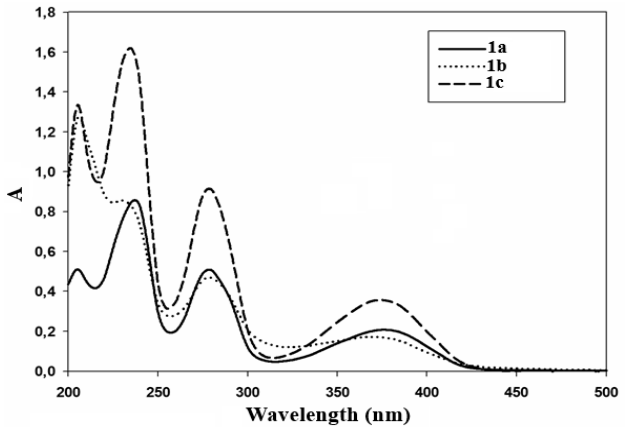


Fig. 2: UV-visible spectra of amino acid Schiff base-Zn(II) complexes

in order to provide charge balance, it was revealed that acetate ion in some complexes and water and hydroxyl ligands in some complexes are included in the structure.

FT-IR spectrum comments of amino acid Schiff base-Zn(II) complexes

FT-IR spectra of Zn(II) complexes were obtained in the range of 4000-400 cm^{-1}. In the spectra, the peaks belonging to the determining groups in the compounds were determined and the expected structures were tried to be confirmed. C=O stretching vibrations of the complexes were observed in the range of 1622-1636 cm^{-1} and C=N stretching vibrations were observed in the range of 1593-1602 cm^{-1}. In addition, the other groups in the structures of the complexes exhibited stretching vibrations at the expected wave numbers.

UV-Vis spectrum comments of amino acid Schiff base-Zn(II) complexes

When the UV-vis spectra of the complexes were examined, bands were observed in four different regions (Fig. 2). Transitions below 300 nm are $\pi \rightarrow \pi^*$ transitions originating from aromatic ring. The $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ electronic transitions of the C=N chromophore (Table 1) [19,20] are located in the band above 300 nm.

Table 2: Amino acid Schiff base-Zn(II) complexes thermal analysis data

Compound	Step	Temperature range (°C)	$DTG_{max.}$ (°C)	Mass loss %	Total mass loss %
1a	1	30–151	67	4.56	H_2O
	2	151–633	296	46.16	
	3	633–1005	800	33.44	84.16
1b	1	30–183	44	7.30	$2H_2O$
	2	183–682	322	56.20	
	3	682–1170	975	21.19	84.69
1c	1	30–126	101	3.89	H_2O
	2	126–209	183	4.11	H_2O
	3	209–571	266	37.95	
	4	571–998	808	40.03	85.98

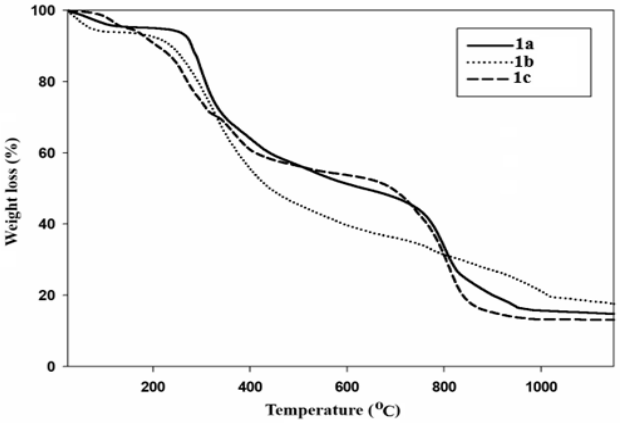


Fig. 3: TG curves of amino acid Schiff base-Zn(II) complexes

Comments on the Thermal Analysis of Amino Acid Schiff Base-Zn(II) Complexes

Compounds were recorded simultaneously in a ceramic crucible under an inert nitrogen atmosphere using 5-10 mg of sample at a heating rate of 10 °C/min (Fig. 3). Compounds decompose in three and four steps and were found to exhibit similar thermal analysis curves. While water was removed in the first step, it was observed that all metal-bound ligands were removed from the structure and Zn remained in the other steps (Table 2).

Enzyme results

The inhibitory activity against AChE exhibited by each of the newly synthesized amino acid Schiff base-Zn(II) complexes (1a-1c) was significantly greater than that of Tacrine, a frequently employed AChE inhibitor (TAC).

Table 3: The AChE and BChE enzymes are inhibited by new amino acid Schiff base-Zn(II) complexes (1a–1c).

Compounds	IC_{50} (µM)				Ki (µM)	
	AChE	r^2	BChE	r^2	AChE	BChE
1a	121.07	0.9321	34.30	0.9774	111.24±12.61	33.41±5.46
1b	104.41	0.9584	29.75	0.9818	88.45±9.54	24.31±3.98
1c	83.81	0.9848	95.98	0.9271		85.18±7.05
Tacrine	144.61	0.9782	94.37	0.9610	125.67±13.06	92.06±9.74

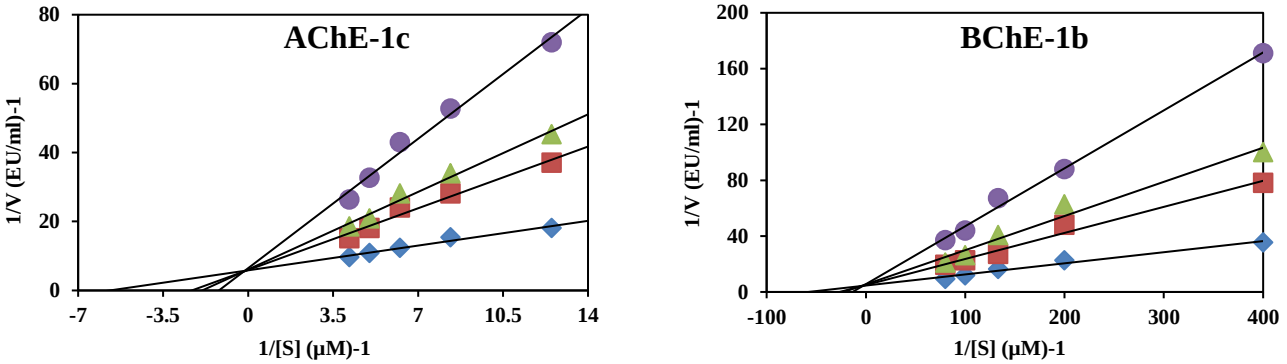


Fig. 4: Linwear burk graphs of the best inhibitors for AChE and BChE enzymes

Indeed, K_i values of synthesized compounds and standard compounds are summarized in Table 3. These inhibited AChE effectively, with K_i values in the range of 78.04±8.66 to 111.24±12.61 µM. However, all these compounds were found to inhibit very similarly. The most active compounds 1c and 1b showed K_i values of 78.04±8.66 and 88.45±9.54 µM, respectively. IC_{50} values of TAC as positive control and most active compounds were in the following order: 1c (83.81 µM, r^2: 0.9848) < 1b (104.41 µM, r^2: 0.9584) < 1a (121.07 µM, r^2: 0.9321) < TAC (144.61 nM, r^2: 0.9782). Furthermore, concerning BChE, all the novel amino acid Schiff base-Zn(II) complexes (1a-1c) demonstrated markedly superior inhibitory activity against BChE when compared to tacrine (TAC). For BChE, compounds 1b and 1a are the most active compounds for BChE with the K_i values 24.31±3.98 and 33.41±5.46 µM. IC_{50} values of TAC as positive control and the most active compounds in the following order: 1b (29.75 µM, r^2: 0.9818) < 1a (34.30 µM, r^2: 0.9774) < TAC (94.37 µM, r^2: 0.9610) < 1c (95.98 µM, r^2: 0.9271). Although the two enzymes' structures are very similar, there have been some changes in the size of their active site gorges, which most likely influence how both ChEs function. Thus far, anticholinesterase medications including rivastigmine, donepezil, eserine, tacrine, and galantamine have been the most commonly recommended formulations for treating AD. For a very long period, the AChE enzyme was the major target during AD treatment. BChE inhibition is also recommended as a wise therapeutic strategy toward limiting AD development because BChE activity is significantly increased in AD patients and is connected with A deposits [26, 27].

Molecular docking

It is widely recognized that metal complexes exhibit greater activity compared to their ligand counterparts. The enhanced biological activity of metal complexes can be attributed to the presence of metal atoms within these compounds. Chemical interactions between metal complexes and enzyme proteins have a significant impact on their activities. Notably, an increase in chemical interactions between metal complexes and proteins correlates with an increase in their biological activities [28]. Numerous chemical interactions contribute to the heightened activity of metal complexes, including hydrogen bonds, polar and hydrophobic interactions, as well as halogen bonding, among others [29-36]. The interactions of metal complexes with enzyme proteins are visually represented in Figs. 5 and 6.

In the molecular docking method, numerous parameters are computed based on the interactions between metal complexes and enzyme proteins [37-39]. Among these

Table 4: E total energy values of metal complexes

Metal complexes	AChE	BChE
1	-145.85	-256.67
2	-141.99	-280.26
3	-175.58	-291.03
Tacrine	-53.19	-202.58

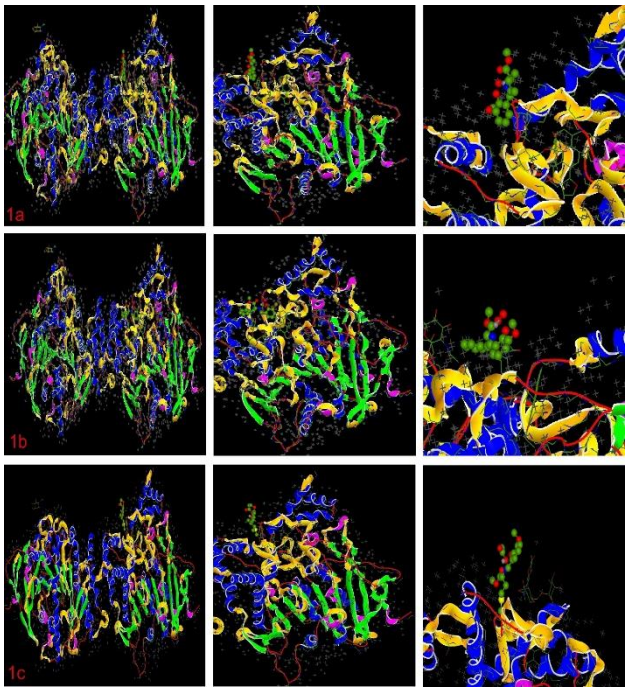


Fig. 5: Interaction between metal complex 1c and AChE

parameters, one of the most widely recognized for comparing biological activity is the E total energy value [40]. The molecule with the most negative E total energy value typically exhibits the highest biological activity. The primary factor influencing the E total energy of molecules is their interaction with proteins. As the interaction between molecules and proteins intensifies, the numerical value of E total energy decreases [39,40], resulting in an increase in the molecule's biological activity. The calculated numerical values of E total energy are provided in Table 4.

The tacrine molecule was used as a standard in the experimental enzyme study, and this molecule was again studied as a standard in the theoretical study [41-44]. The synthesized metal complexes have higher biological properties compared to this standard molecule [45-47].

After molecular docking calculations, Protein-Ligand Interaction Profiler (PLIP) analysis [13] was performed to examine the interactions between molecules and proteins in detail. All interactions that occur between molecules and proteins with this analysis are visualized in Tables 5-7. The interactions obtained from the Protein-Ligand Interaction Profiler (PLIP) analysis of the metal complex with the best activity are given in the analysis relative Figs. 7 and 8.

Table 5: Hydrophobic interactions of metal complexes

Index	Residue	AA	Distance	Ligand atom	Protein atom
Metal complex 1c with AChE					
1	230A	PRO	3.44	5775	2148
2	233A	VAL	2.76	5758	2177
3	396A	TYR	2.84	5791	3746
4	522A	TRP	3.89	5791	5056
5	526A	PHE	3.01	5795	5098
6	527A	PRO	3.58	5793	5108
Metal complex 1c with BChE					
1	344A	PRO	3.26	11654	3172
2	344A	PRO	3.62	11656	3173
3	361A	ALA	3.63	11656	3335

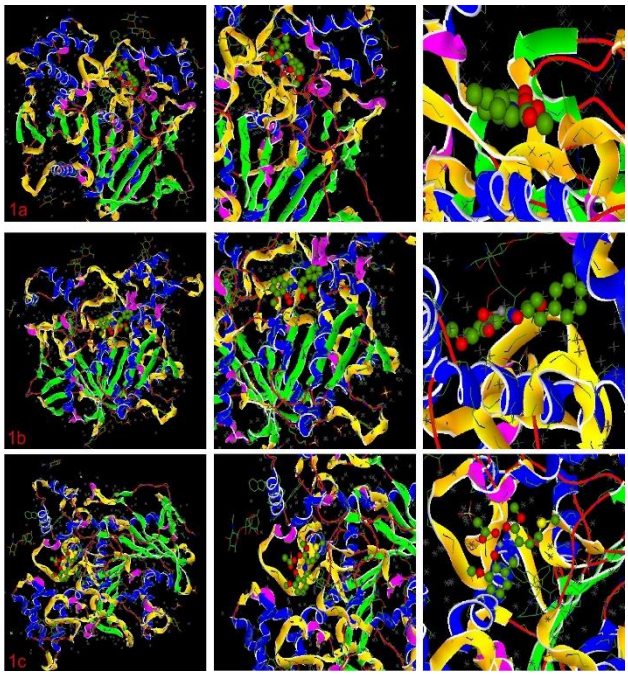


Fig. 6: Interaction between metal complex 1c and BChE

CONCLUSIONS

In this study, Zn(II) complexes based on Schiff base ligands have been prepared. 13C-NMR, FT-IR, UV-Visible, 1H-NMR, thermal and elemental analyses were used to characterize the structure of the complexes. The results of the analysis were found to be in agreement with the literature findings. Cholinesterase inhibitors are the

Table 6: Hydrogen interactions of metal complexes

Index	Residue	AA	Dist H-A	Dist D-A	Donor angle	Protein Donor?	Side chain	Donor atom	Acceptor atom
Metal complex 1c with AChE									
1	304A	ASP	3.62	4.08	112.05	X	√	5785 [O_3]	2856 [O_2]
Metal complex 1c with BChE									
1	292A	GLU	2.75	3.11	103.97	X	√	11630 [O_2]	2690 [O_2]

Table 7: Water bridge of metal complexes

Index	Residue	AA	Dist A-W	Dist D-W	Donor angle	Water angle	Protein donor?	Donor atom	Acceptor atom	Water atom
Metal complex 1c with AChE										
1	228A	ASN	2.89	3.79	134.61	92.83	√	2134 [Nam]	5778 [O.CO_2]	5447
2	233A	VAL	3.65	2.77	148.35	73.84	√	2173 [Nam]	5764 [O_3]	5580
3	522A	TRP	2.66	3.52	149.54	85.36	X	5779 [O.CO_2]	5049 [O_2]	5516

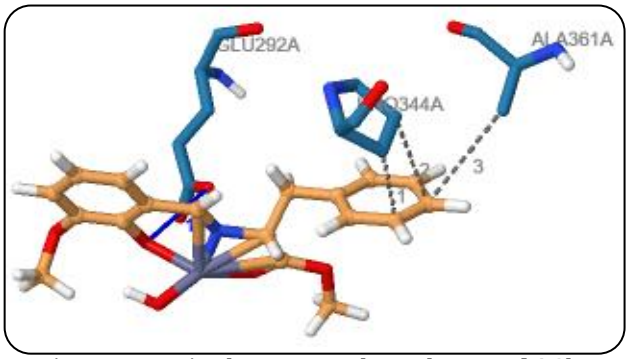


Fig. 7: Interaction between metal complex 1c and AChE

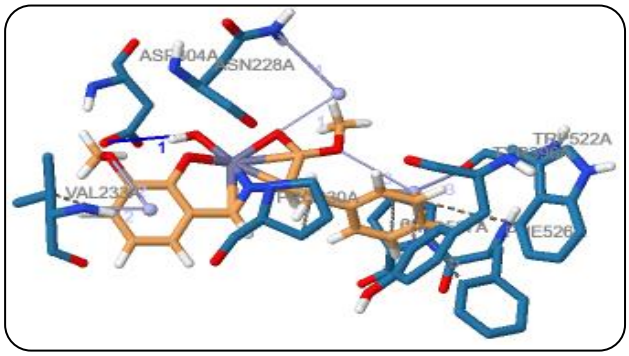


Fig. 8. Interaction between metal complex 1c and BChE

first-line medications in the clinical treatment of AD, although they cannot stop the disease progression and have little effect on advanced AD. Instead, they have been shown to significantly improve cognitive functioning. To battle AD, it is crucial to create new cholinesterase inhibitors, particularly those that are multi-targeted and can inhibit cholinesterase while also reducing amyloid plaque, mobilizing neurons, confronting oxidation, battling neuroinflammation, and/or other effects. In this study, compounds 1c and 1b were found to be good inhibitors for AChE; also, strong inhibitors of 1b and 1a were accepted for BChE, they may be used for anti - Alzheimer drug designs.

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