ScienSage

Journal of Advanced Scientific Research

Available online through http://www.sciensage.info

ISSN
0976-9595
Research Article

THEORETICAL DENGUE TARGET VITAMIN B6 BASED ZN(II) AND V (IV) MIXED-LIGAND COMPLEXES

K. N. Gita*[1], V. Chandrasekaran[2], P. Akilan[2]

[1]*Department of Chemistry, Government Arts College for Women, Salem, Tamil Nadu, India*

[2]*Department of Chemistry, Government Arts College (Autonomous), Salem, Tamil Nadu, India*

**Corresponding author: gitakn27@gmail.com*

ABSTRACT

The Schiff base transition metal complexes, Zn(II) and V(IV) (1-2) were synthesized using pyridoxal based ligand by refluxing with corresponding metal salts. The synthesized ligand and metal complexes were characterized by using various spectral methods like IR, UV-Vis and mass spectrometry. The synthesized metal complexes were docked with human DNA (PDB I.D: 1BNA) and dengue protein virus (PDB ID: 2VBC) using auto dock software tools version 1.5.6 and pymol. The binding of the ligand and biomolecule in grid point value of x × y × z directions of 90 × 90 × 90 and a grid space group value of 0.380 Å. The binding energy values of the metal complexes were respectively -8.1 and -6.2 kcal mol^{-1} towards B-DNA, while the binding energy values of the metal complexes were found to be -8.8 and -8.9 $kcalmol^{-1}$, respectively towards NS3 protease-helicase.

Keywords: Vitamin B6, Schiff base, Molecular docking, Zn(II) and V (IV) Mixed-ligand Complexes.

1. INTRODUCTION

Dengue is an intense viral contamination with possible deadly complications. Dengue fever was first referred as “water poison” related with flying bugs in a Chinese clinical reference book in 992 from the Jin Dynasty (265-420 AD). “Dengue” is derived from the Swahili phrase Ka-dingapepo, meaning “cramp-like seizure” [1-3]. The principal clinically perceived dengue pandemics happened almost simultaneously in Asia, Africa, and North America during the 1780s. The primary clinical case report dates from 1789 of 1780 plague in Philadelphia is by Benjamin Rush, who coined the expression "break bone fever" on account of the side effects of myalgia and arthralgia [4-7]. The term dengue fever came into general utilization simply after 1828. Dengue infections (DV) have a place with family Flaviviridae and there are four serotypes of the infection such as DV-1, DV-2, DV-3 and DV-4. DV is a positive-abandoned epitomized RNA virus and is made out of three basic protein qualities, which encode the nucleocapsid or center (C) protein, a film related (M) protein, a wrapped (E) glycoprotein and seven non-basic (NS) proteins [8, 9]. Each of the four serotypes can cause the full range of illness from a subclinical infuction to a gentle self-restricting infection, the dengue fever (DF) and a serious sickness that might be deadly, the dengue haemorrhagic fever/dengue stun condition (DHF/DSS) [10]. Determination of dengue infection contamination is regularly done by showing of hostile to DV IgM antibodies or by NS-1 antigen in patients' serum relying on day of sickness utilizing ELISA units (arranged by National Institute of Virology, Pune) and business packs [11]. Herewith we present a grown-up instance of conceivable post-dengue GBS in Sri Lanka and this case calls for uncommon consideration on the grounds that the dengue contamination stays a genuine general medical issue in numerous nations and the real rate of neurological complexities isn't very much revealed [12]. In this paper work we have synthesised zinc and vanadium based drug towards dengue. In this paper, we have synthesized biological important vitamin B6 backbone Schiff base (L) was synthesized and Zn(II), V(IV) metal complexes. The metal complexes were characterized by IR, UV-Vis and Mass spectrometry. The synthesized complexes were very vigorous in nature towards DNA and dengue virus protein binding.

2. EXPERIMENTAL

All the chemicals used in the synthesis were either of AR grade or chemically pure grade. Pyridoxal, ethanolamine, metal salts were purchased from Sigma Aldrich. Solvents were purchased from Merck and used as the same purity.

2.1. Synthesis of Schiff base (L1)

Schiff base (L1) was synthesized by the condensation reaction between pyridoxal hydrochloride (1mmol) and ethanolamine (1mmol). Both reactant was dissolved in methanol solvent and refluxed for 3 hrs. A yellow solution of Schiff base was formed. The reaction mixture was further used for the metal complex synthesis.

2.2. General procedure

Metal complexes were synthesized by template method. The methanolic solution of L1 (1mmol) was treated with metal salts (Zn perchlorate and V sulphate) (1mmol) which was dissolved in 5mL of methanol. Into the reaction mixture, 4, 4'-di-tert-butyl-2, 2'-bipyridine (1mmol) was added drop wise and refluxed the solution for 5hrs. Colored insoluble solid mass were appearing within one hour. The solid mass was filtered and washed with 5 ml cold methanol (zinc complex pale yellow and vanadium yellow color solid). The solutions kept into the deepfreeze for 5 days. A crystalline particle appeared. Crystals were washed with cold methanol and diethyl ether solution and carried out for further analysis.

2.3. Zinc (II) L1 metal complexes

Zinc perchlorate (1mmol), 4, 4'-di-tert- butyl-2, 2'-bipyridine (1mmol) and L1 (1 mmol), Refluxing time 1h, Colour of the complex-pale yellow, Yield (74%).

Chemical Formula: $C_{28}H_{37}ClN_4O_7Zn$ Elemental Analysis: C, 52.34; H, 5.80; Cl, 5.52; N, 8.72; O, 17.43; Zn, 10.18%. IR (KBr pellets) υ cm^{-1}:2980 (υ C-H), 1619 (υ C=N), 539 (υ Zn-N). Mass spectra: 645.38m/z base peak (M+3).

2.4. Vanadium (IV) L1 metal complexes:

Vanadylsulphate (1mmol), 4,4-di-tert-butyl-2,2-bipyridine (1mmol) and L1 (2.32g, 10mmol), Refluxing time 1h, Colour of the complex -yellow, Yield (85%).

Chemical Formula: $C_{30}H_{43}N_4O_4SV$. Elemental Analysis: C, 59.39; H, 7.14; N, 9.23; O, 10.55; S, 5.29; V, 8.40%. IR (KBr pellets) υ cm^{-1}:2982 (υ C-H), 1622 (υ C=N),560 (υ V-N). Mass spectra: 619.39m/z base peak (M+3).

3. RESULTS AND DISCUSSION

Synthesis and structural characterization of newly synthesized ligands and twelve metal complexes was done using various spectral analyses such as UV-Vis, FT-IR, Mass. The docking studies were carried out towards dengue protein and DNA biomolecule.

Using template method, the Metal complexes were synthesized. The methanolic solution of L1 with metal salts leads to the complex synthesis. The reactions were monitored by TLC plates. The basic information of the compounds was noted in the table.1. The complexes were characterized through physical, analytical and spectral methods (Scheme 1).

3.1. IR spectrum

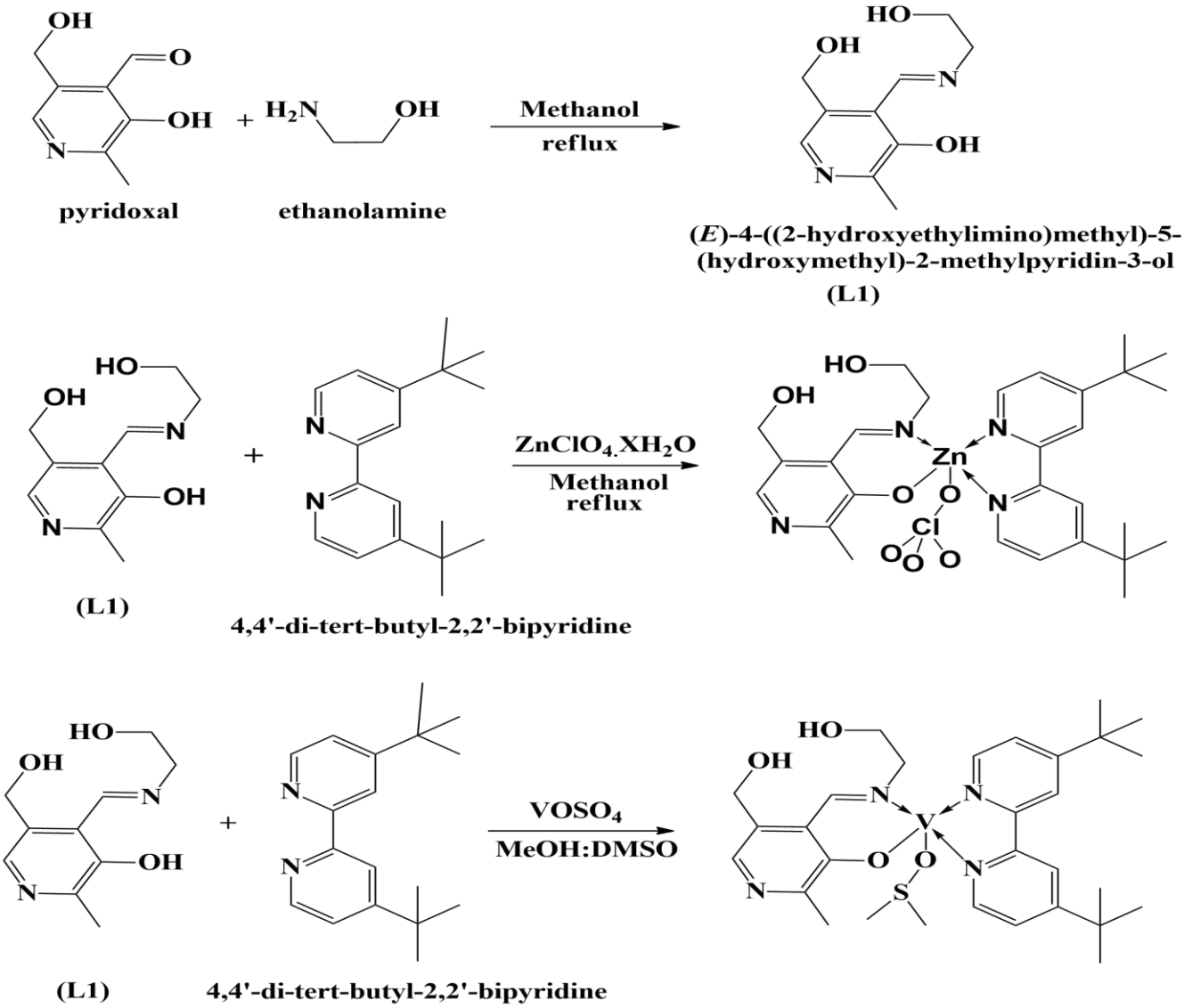
The IR spectra of the metal complexes were compared with the general frequency values and showed in table 2 and the corresponding IR spectra were produced in fig 1. FT-IR is one of the best tools to determine the nature of the functional group present and the formation of new complex from the reactant molecule. From spectral data bank (STBS) FT-IR peak of the pyridoxal shows the aldehyde CH=O stretching peak is in the range 1644cm^{-1}. For the synthesis of the new metal complexes the peak at the range of 1644cm^{-1} was disappeared and new peak was formed in the range of1619 and 1622 cm^{-1} for 1-2 complexes which represents the azomethine (-C=N-) group to confirm the formation of the Schiff base ligand. The new metal-ligand (N) peaks were formed in the range of 539 and 560 cm^{-1} in the range. The co-ligand peak also appeared in the range of 2800-2950cm^{-1} (-CH3) which confirms the co-ligand molecule also participate the coordination with the metal ions. The peak 3448-3138 cm^{-1} is due to OH group of the pyridoxal ligand.

3.2. Electronic spectra

The electronic absorption spectrum (UV-Vis) data of metal complexes 1-2 were reported in the table 3 and the corresponding spectrum images were shown in the Fig.2. The electronic absorption spectra was taken using DMSO solvent. The spectrums were taken in the range of 200-800 nm.

Table 1: Physical and analytical data of 1-4

Molecular formula of the Compound	Formula weight (a.m.u)	Colour	Elemental composition			
			%C	%H	%N	%M
$C_{28}H_{37}N_4O_7ClZn$[1]	642.41	Pale yellow	52.34	5.80	8.72	10.18
$C_{30}H_{43}N_4O_4SV$ [2]	616.28	Yellow	59.39	7.14	9.23	8.40



Scheme 1: Systematic representation of L and 1-2

Table 2: FT-IR data of L1 and complexes 1-2

Sample	ν C-H (cm^{-1})	ν C=N (cm^{-1})	ν CHO (cm^{-1})	ν M-N (cm^{-1})
L1	2985	-	1644	-
Complex 1	2980	1619	-	539
Complex 2	2982	1622	-	560

Table 3: UV data for complexes 1-2

Compound	λ_{max} (nm)	Assignment
$C_{28}H_{37}N_4O7Cl$ Zn[1]	248	π- π*
	325	n- π*
	419	n- π*
$C_{30}H_{43}N_4O_4SV$ [2]	217	π- π*
	287	n- π*
	359	LMCT
	450	$^3A_{1g} \rightarrow {}^1B_{2g}$
	572	$^1A_{1g} \rightarrow {}^1B_{1g}$

The zinc complex [1] shows the electronic spectra in the range of 248, 325 and 419 nm having the electronic transition of π- π* and n- π* respectively. The electronic spectra results suggest a five coordinated zinc (II) metal complex and having square pyramidal geometry. Vanadium Complex [2] having +4 oxidation state of the vanadium metal ion and also the spectra of 217, 287, 359, 450 and 572. The absorption bands represents the n- π*, LMCT, $^3A_{1g} \rightarrow {}^1B_{2g}$ and $^1A_{1g} \rightarrow {}^1B_{1g}$. The ligand metal (d-d) charge transfer represents the square pyramidal geometry structure.

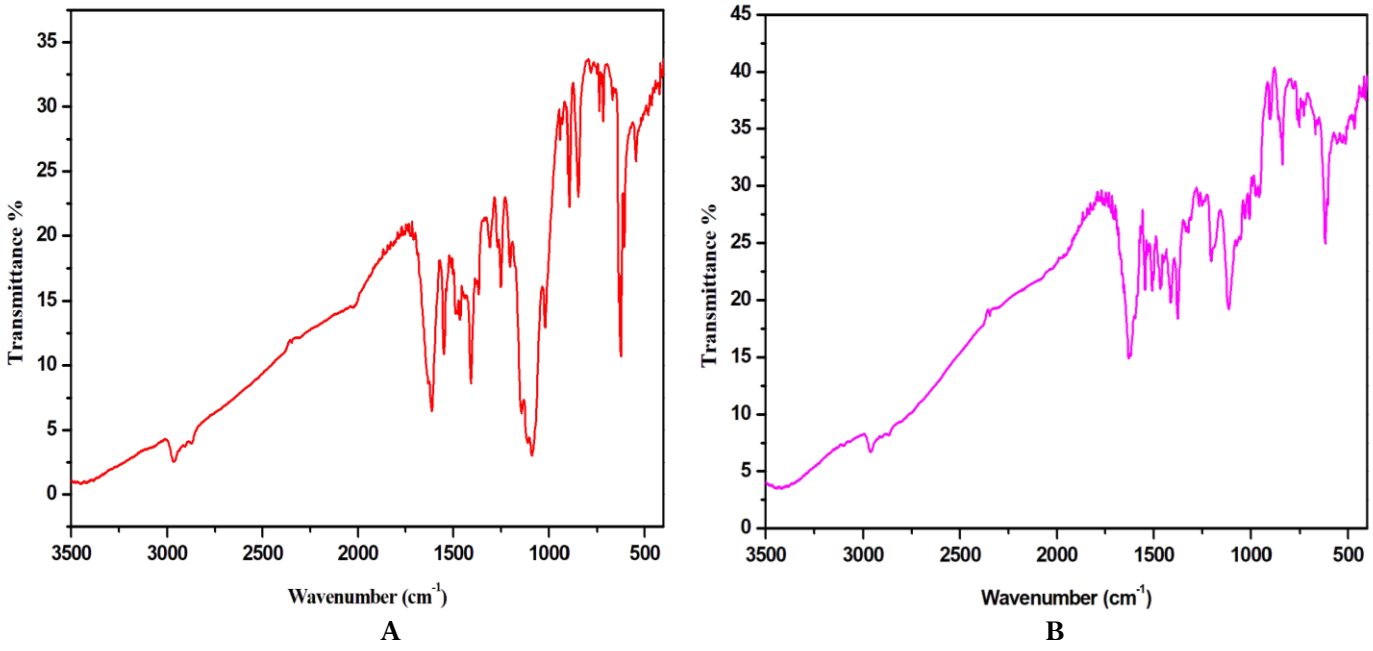


Fig. 1: IR spectrum of complexes 1-2

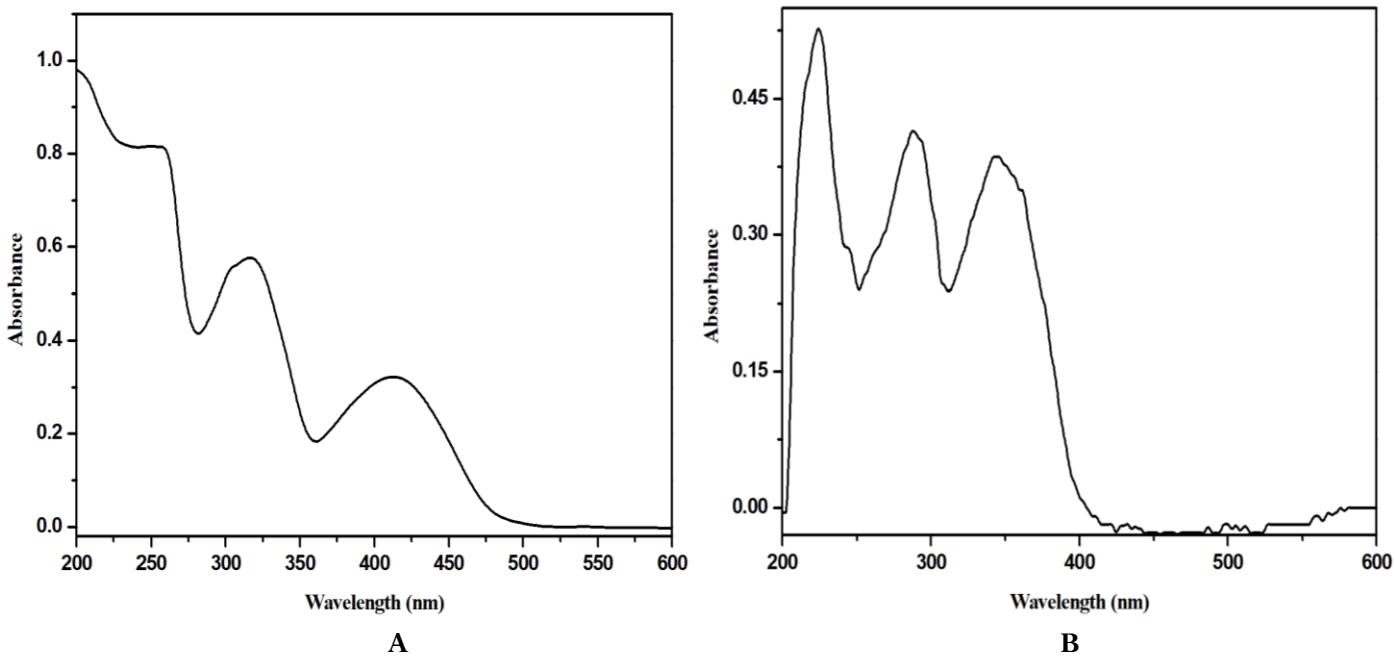


Fig. 2: UV-Vis spectrum of complexes 1-2

3.3. Mass spectrum

The LC-MS mass spectra of the metal complexes were recorded in the range of 200-800 m/z. The mass spectra details were shown in the table 4 and the mass spectra were placed in fig.3.

The mass spectra values shows M+3 fragment ions which supports the expected geometry. The total mass of 1-2 respectively 642.41 and 616.28.The total mass from the spectra respectively 645.38 and 619.39 which denotes the M+3 molecular fragment ions.The mass spectra values shows M+3 fragment ions which supports the expected geometry.

Table 4: Mass data of complexes 1-2

Sample	Chemical Formula	Molecular weight	Mass from spectra
Complex 1	$C_{28}H_{37}N_4O_7ClZn$	642.41	645.38
Complex 2	$C_{30}H_{43}N_4O_4SV$	616.28	619.39

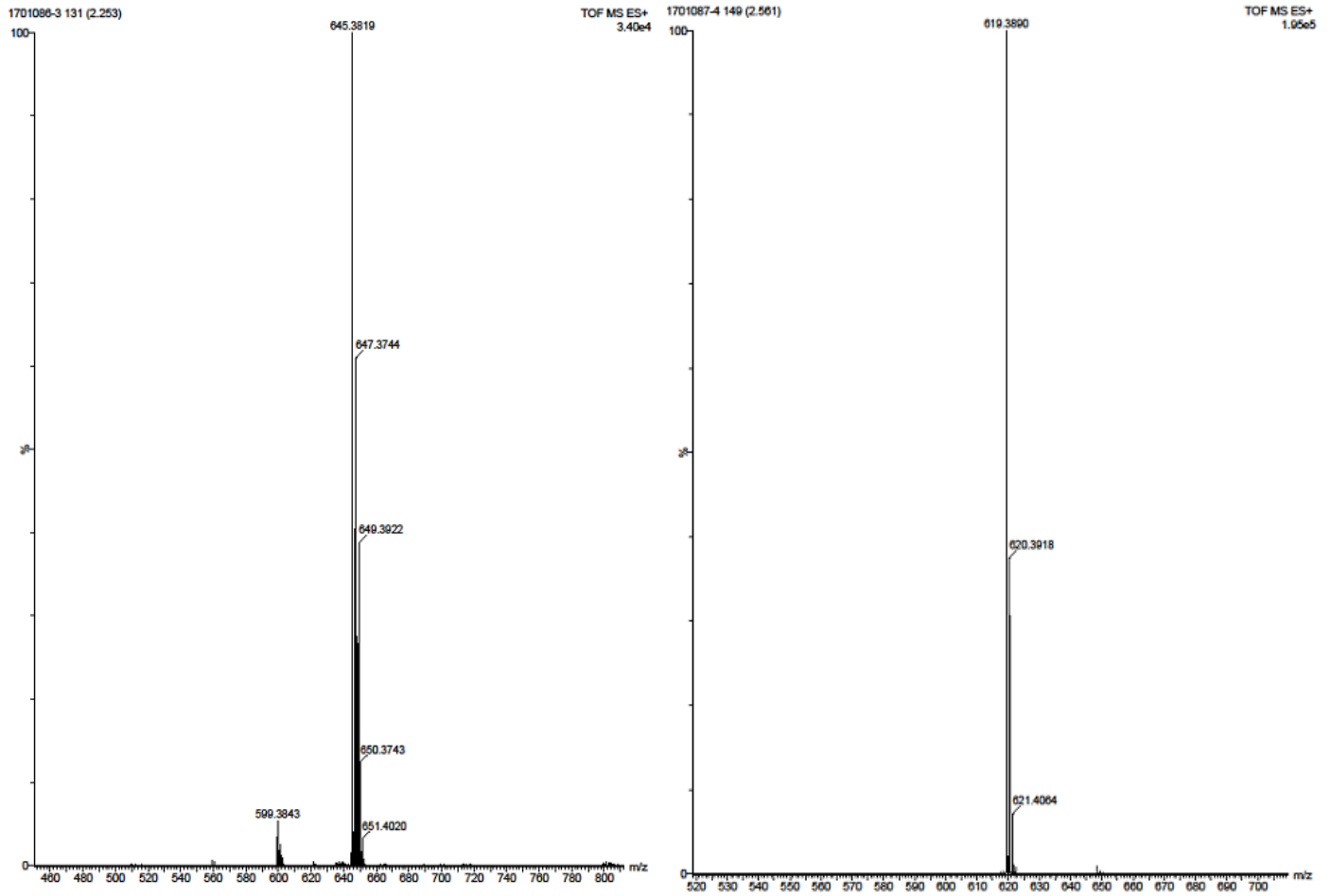


Fig. 3: LC-MS spectrum of complexes 1-2

3.4. Docking studies with BDNA

Molecular docking study is one of the best tools to understand the drug-biomolecular interaction. This study can help to improve the already available drugs potential and also helps to synthesis novel drugs for the suitable biomolecular target area. The synthesised metal complexes were used to dock with the DNA hexamer unit d(CGATCG)2 bi-functional enzyme B-DNA (PDB ID: 1BNA).

All the synthesized complexes exhibits intercalation mode of binding towards the targeted DNA molecule by considering the binding mode and the binding affinity. There will be nine possible confirmers which the molecule attack nine different position towards the

DNA. The complexes interact DG4, DG16, DT7, DC21, DC24 and DT8 nucleotide of the DNA molecule. From the docking results, complex 1 having great interaction and having great binding energy value. For the complex 1 the compound majorly interact the DNA molecule by using oxygen atom through Pi-Pi stacked interactions with the base pair. The binding modes of the synthesised complexes with DNA were shown in fig. 4. The binding interactions of drug-DNA were noted in table 5.

Table 5: Molecular docking results of complexes1-2 with DNA biomolecule

Complex	Acceptor group	Donor group	Binding energy (kcal mol−1)	Distance (Å)
1	O15	DA5	-8.1	2.28
	O15	DA6		2.17
	O7	DT19		2.37
	O37	DA6		2.77
2	C10	DG4	-6.2	4.21
	C10	DA5		4.92
	C13	DA17		3.38
	C28	DG16		5.19

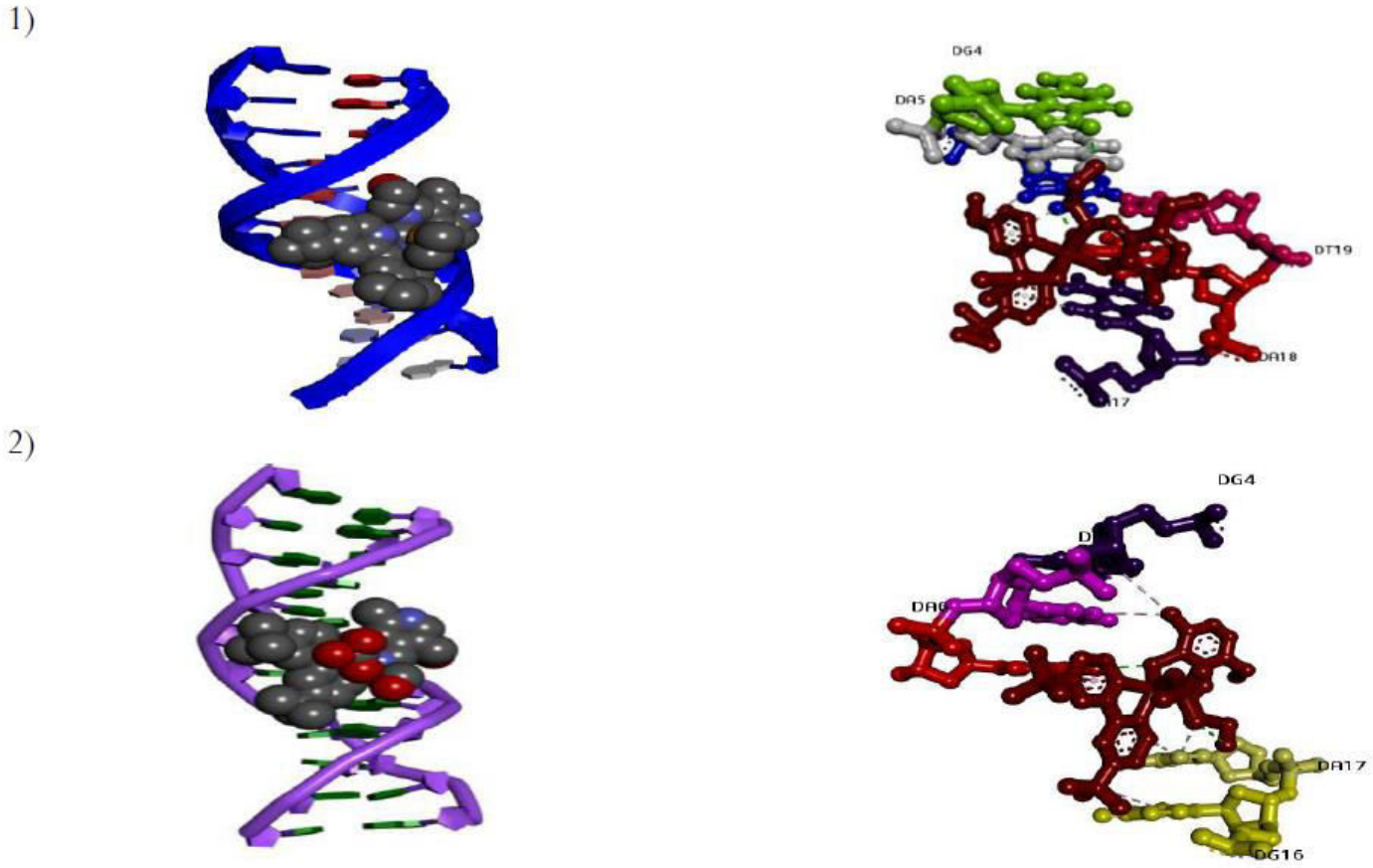


Fig. 4: DNA docking studies of complexes 1-2

3.5. Docking with BSA protein

The synthesized metal complexes were interact with the dengue protein NS3 protease-helicase (PDB ID: 2VBC) biomolecule. There are two side chains were present in the target receptor. Using docking study we can analyse the binding energy, binding mode and the binding interaction of the drug-protein. There are nine possible confirmers are available.

The best mode of binding is selected and shown in the fig. 5. Several amino acid residues were involved in the binding study. The amino acid residues ALA602, ALA606, PRO543, ARG599, ASP409, ARG387,

ASP409, LEU429, HIS487, ARG599, PRO543, ASP290, ARG599, ALA606, HIS487, ASP409, THR289, ALA452, SER453, LYS430, ARG599, LEU443, PRO291, HIS487, ASP409, HIS487, PRO431, PRO543, ALA406, CYS292, PRO291, ALA606, LEU429, HIS487, ALA602, ALA606, PRO543, ASP409 and HIS487. The amino acid residues interacted by the drugs atom by using pi-alkyl, pi-pi stacked, H-bonding and van der waals weak interactions. The interaction values and the mode were noted in the table 6. Complex 2 having the best binding interaction towards the dengue virus protein.

Table 6: Molecular docking results of complexes1-2 with NS3 protease

Complex	Acceptor group	Donor group	Binding energy (kcal mol−1)	Distance (Å)
1	C6-11	CYS292	-8.8	5.71
	C6-11	PRO291		4.76
	C15	ALA606		4.20
	Cl27	LEU429		4.76
	Cl22	HIS487		4.62
2	C15	ALA602	-8.9	3.89
	C16-21	ALA606		5.21
	C16-21	PRO543		4.57
	C6-11	ASP409		4.00
	C6-11	HIS487		4.38

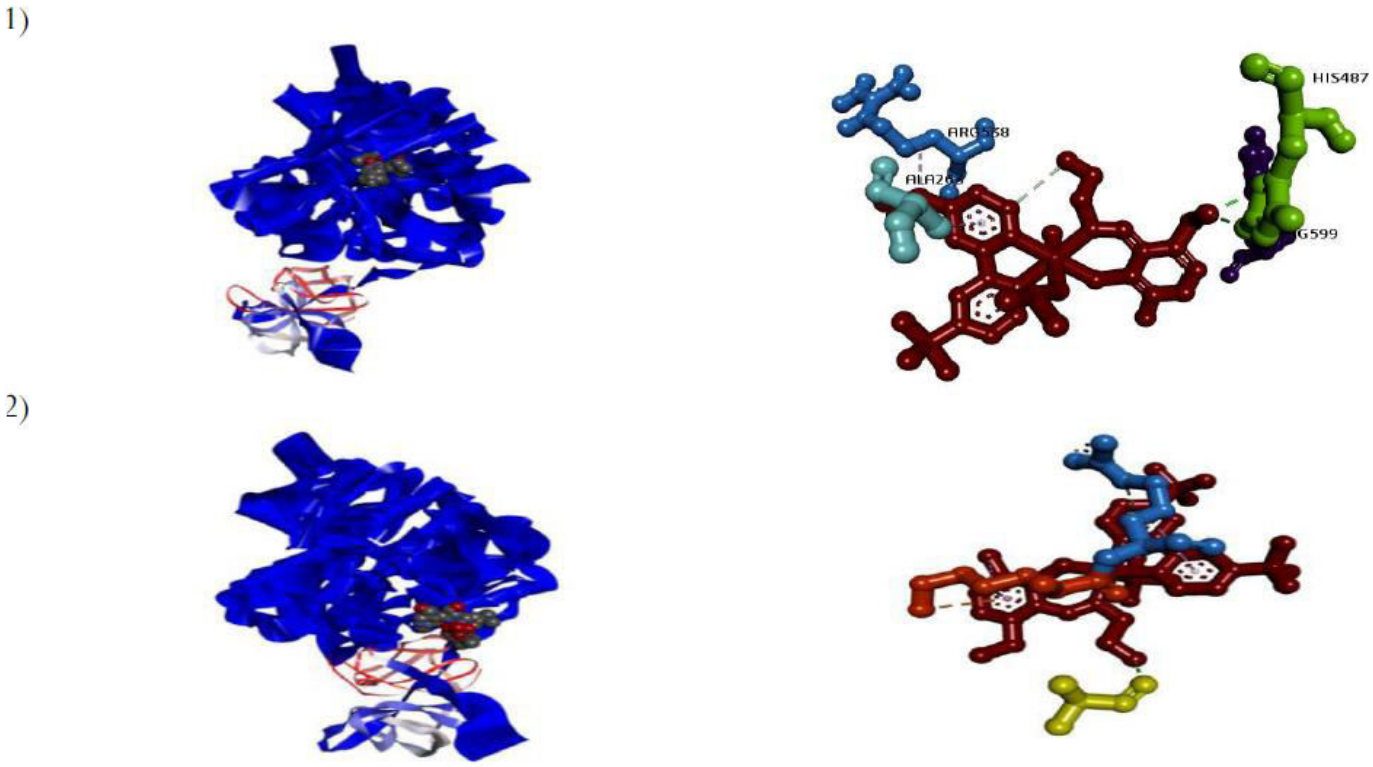


Fig. 5: Molecular docking study of complexes 1-2 with BSA protein

4. CONCLUSION

A novel Schiff base ligand (L) was synthesized using pyridoxal and ethanolamine. The metal complexes Zn(II) and V(IV) were synthesized using template synthesis method. The synthesized Schiff baseligand and its metal complexes were characterized by using IR, UV-Vis and Mass spectrometry. The synthesized complexes were docked with B-DNA (PDB ID: 1BNA) anddengue NS3 protease-helicase. The complex 1 having the greater binding energy towards both B-DNA andcomplex 2 forNS3 protease-helicase.

Conflict of Interest

None declared

5. REFERENCES

1. Whitehorn J, Farrar J. *Dengue bulletin*, 2010; **95(6)**:161-173.
2. Dengue: Guidelines for diagnosis, treatment, 7 prevention, and control in sub-Saharan Africa and other countries in South America. Geneva: World Health Organization; 2009. WHO. 10
3. Kimura R, Hotta S. *NippomIgaku.,* 1944; **3379**:629-633.
4. Sabin AB, Schlesinger MC, *Science*, 1945; **101(13)**:640-642.
5. Sarkar JK, Chatterjee SN, Chakravarty SK. *Indian J. Med. Res.,* 1964; **52**:651-659.
6. Chatterjee SN, Chakravarti SK, Mitra AC, Sarkar JK. *J. Indian Med. Asso.*, 1965; **45**:314-316.
7. Carey DE, Myers RM, Reuben R. *The Ame. J. Trop. Med. and Hygiene*, 1966; **15**:580-587.
8. Rigau-Perez JG, Clark GG, Gubler DJ, Reiter P, Sanders EJ. *Lancet*, 1998; **971**:24.
9. Kabra SK, Verma IC, Arora NK, Jain Y, Kalra V. *Bull World Health Organ.*, 1992; **70(1)**:105-108.
10. Bhattacharjee N, Mukherjee KK, Chakra-varti SK, Mukherjee MK. *J. Communicable Diseases*., 1993; **25(1)**:10-40.
11. Cherian T, Ponnuraj E, Kuruvilla T, Kiruba-karan C, John TJ, Raghupathy P. *Indian J Med Res.* 1994; **100**:51-56.
12. Dar L, Broor S, Sengupta S, Xess I, Seth P. *Emerg Infect Dis.,* 1999; **5(4)**:589-590.