



Copper (II) and Nickel (II) Mixed-ligand Complexes Containing 1,10-phenanthroline and their Biological Evaluation

K. N. Gita^{1*}, V. Chandrasekaran² and P. Akilan²

¹ Department of Chemistry, Government Arts College, Salem – 636 008 Tamil Nadu, INDIA

² Department of Chemistry, Government Arts College (Autonomous), Salem – 636 007 Tamil Nadu, INDIA

* Correspondance: E-mail: gitachem@gmail.com

(Received 06 Dec, 2017; Accepted 16 Dec, 2017; Published 21 Dec, 2017)

ABSTRACT: A novel water-soluble vitamin B12 backbone Schiff base ligand containing two mixed ligand transition metal complexes Cu(II) and Ni (II)) were synthesized by template method. The synthesized two mixed ligand metal Complexes were characterized by IR, Mass and elementary analysis. The synthesized compounds were docked with Dengue NS3 protease-helicase bi-functional enzyme (PDB ID: 2VBC) and B-DNA (PDB ID: 1BNA) using Auto Dock tools version 1.5.6 and auto dock vina docking programs and Discovery studio software. The binding of the ligand and receptor in grid point value of $x \times y \times z$ directions of $80 \times 80 \times 80$ and a grid space group value of 0.380 \AA . The binding energy values of the Ni(II) and Co(II) complexes respectively -7.4 and $-7.2 \text{ kcal mol}^{-1}$ towards NS3 protease-helicase. The binding energy values of the Ni(II) and Cu(II) complexes respectively -6.6 and $-6.5 \text{ kcal mol}^{-1}$ towards B-DNA. These results shown as the synthesized compounds act as an Anti-Dengue and show greater binding affinity towards B-DNA.

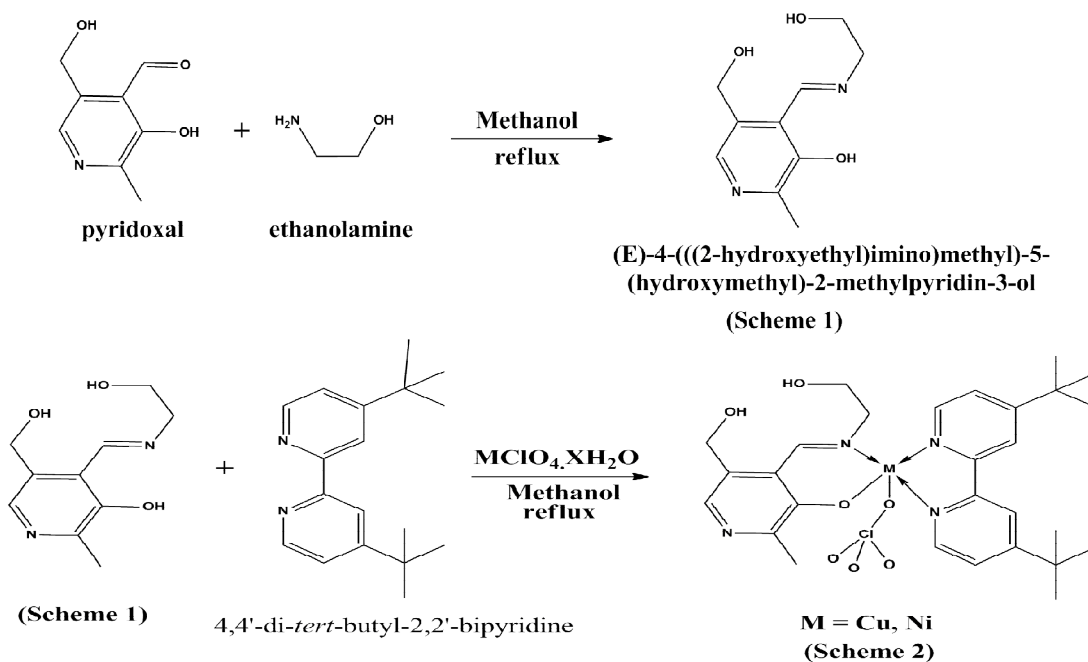
Keywords: Vitamin B12; Schiff base; binding energy; Ni(II) and Cu(II) complexes.

INTRODUCTION: The dengue virus (DENV) is one of the member of the flaviviridae family. DENV is the major reason of dengue fever. It is one of the important mosquito-borne pathogen which human suffering and cost, with a high rate of hospitalization and also considered to be a deadly disease.¹ DENV has four distinct serotypes (DENV-1–DENV-4).^{2,3} The fifth type of DENV is reported recently in Malaysia, Sarawak.⁴ DENV is not only the reason for dengue fever but also it will lead to dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Dengue infection is a serious problem and cause health issue in more than 100 countries, mainly in tropical and subtropical regions.⁵⁻⁸ Now, there is no licensed vaccine or antiviral drug available against dengue infection. It may lead to serious problem. So, there is a necessary to design a drug for DENV. Several research institutions have begun medicinal chemistry projects using rational approaches for DENV. Thus, the anti-dengue drug development efforts have been increased considerably in the world wide.⁹⁻¹⁶ Also, research on interactions between the transition metal complexes (particularly Cu(II) and Ni(II)) helps to give a knowledge about development of novel chemotherapeutics and medicinal chemistry¹⁷⁻¹⁹. Docking is one of the best tool to develop a drug with efficient one. In this paper water soluble vitamin B12 backbone Cu(II) and Ni(II) complexes were synthesized. The synthesized compounds were characterized by elemental analysis, FT-IR and mass. Then the synthe-

sized compounds were docked with Dengue NS3 protease-helicase bi-functional enzyme (PDB ID: 2VBC) and B-DNA (PDB ID: 1BNA).

MATERIALS AND METHODS: All the chemicals used in the present work were purchased from commercial sources and used the chemicals without further purification during the reaction. Pyridoxal hydrochloride, ethanolamine, Copper and Nickel perchlorate salts were bought from Sigma Aldrich, USA and used as received. Solvents were used in the present research were bought from Merck and commercial source and used without further purification.

Preparation of Copper (II) and Nickel (II) Schiff base metal complexes: Metal complexes were synthesized by template method. Pyridoxal hydrochloride (1mmol) and ethanolamine (1mmol) were stirred in a RB flask using 10ml methanol for 1 hr. A bright yellow solution of Schiff base obtained. From the Schiff base solution 4,4-di-tert-butyl-2,2-bipyridine (1mmol) were added. The solution was refluxed for 4 hrs. Then methanolic solution of Nickel perchlorate (1mmol) or Copper perchlorate (1mmol) were added and stirred in room temperature for 12hr. For copper complex a green colour and for nickel complex a red colour solution were obtained, kept the solution into deepfreeze for 5 days. A crystalline particle was appeared. Crystals were washed with cold methanol and diethyl ether solution (Schemes 1 & 2).



The metal complexes were confirmed by FT-IR (Figure 1; Table 1).

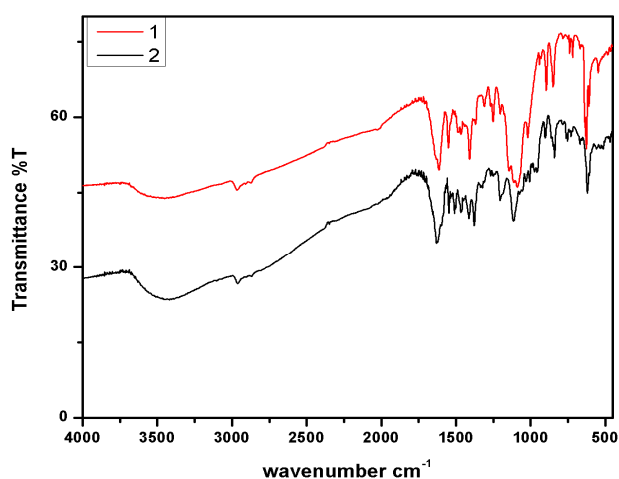


Figure 1: FT-IR spectrum for (1) Cu(II) and (2) Ni(II) complexes.

Table 1: FT-IR spectral values of Ni(II) and Cu(II) complexes.

Sample	ν C-H (cm ⁻¹)	ν C=N (cm ⁻¹)	ν CHO (cm ⁻¹)	ν M-N (cm ⁻¹)
Pyridoxal	2985	-	1644	-
1	2958	1625	-	508
2	2955	1617	-	521

Molecular docking study: Molecular docking is one of the powerful weapon for the design of ligand or metal complexes toward a specific biopolymer target. The synthesized compounds were docked with Dengue NS3 protease-helicase bi-functional enzyme (PDB ID: 2VBC) and B-DNA (PDB ID: 1BNA) using Auto Dock tools version 1.5.6 and auto dock vina

docking programs and Discovery studio software.²⁰ The protein structures were obtained from Protein Data Bank (<http://www.rcsb.org/pdb>). Metal complexes were converted into PDB format using Mercury and Discovery studio software.²¹ The protein and DNA molecules were selected as receptor and the metal complexes were selected as a ligand. In the binding mode was enclosed in a script box which having a much number of grid points in $x \times y \times z$ directions of $80 \times 80 \times 80$ and a grid spacing of 0.380 Å. Using Auto Dock Tools (ADT) version 1.5.4. The Docking studies were carry out and finalized by Auto Dock vina program.²² The output was export from discovery studio software.

RESULTS AND DISCUSSION:

Molecular docking with B-DNA: B-DNA was a selective targeting area for synthesizing the drug which efficient to bind with DNA and gave some useful observation. The newly synthesized water-soluble vitamin B12 backbone Copper(II) and Nickel(II) complexes having efficient binding values towards B-DNA. The binding was shown in fig.2 and the values were noted in Tables 2 and 4. From the docking with B-DNA there are nine different conformer form of metal complex were obtained. The lowest binding affinity value will give the highest binding mode. From the docking study B-DNA was considered to be a receptor and Cu(II) and Ni(II) complexes were ligands. The specified binding nature of the metal complex were shown in the Figure 2 and the binding residue detail were shown in Tables 3 and 5, the binding affinity of Cu(II) and Ni(II) complexes towards B-DNA with respectively -6.5 and -6.6 kcal mol⁻¹.

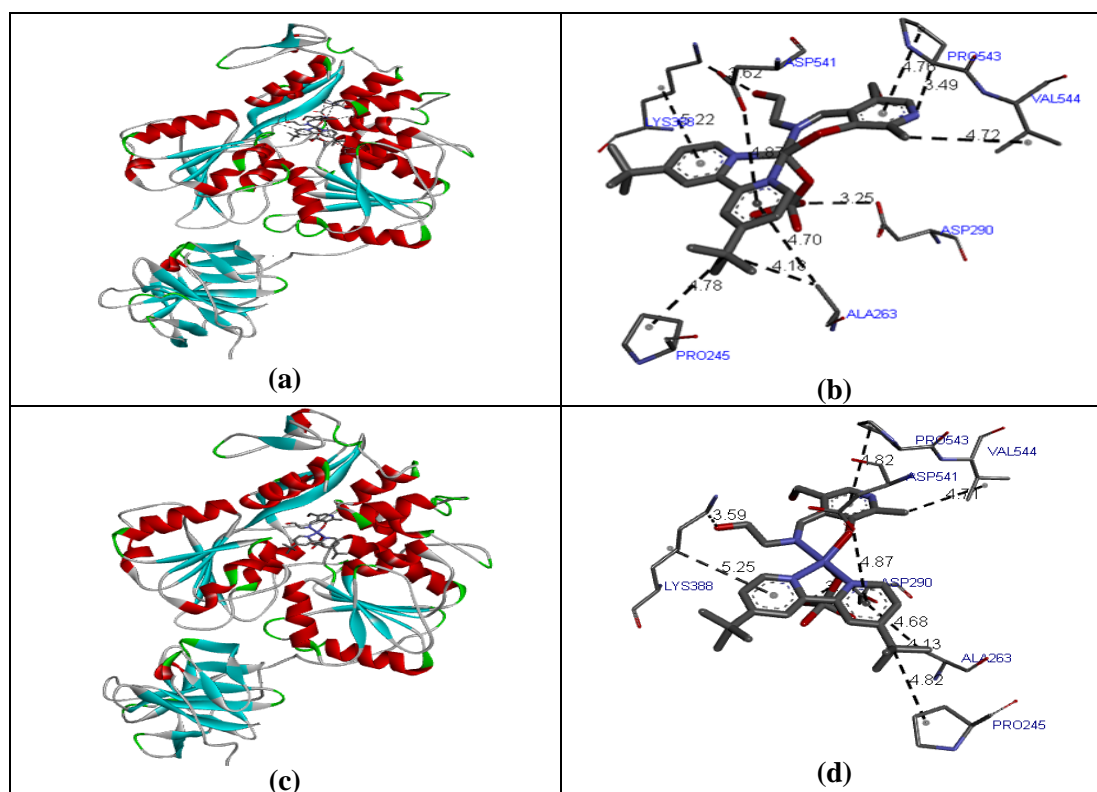


Figure 2: (a) and (c) respectively Cu(II), Ni(II) complexes bind with active site of NS3 protease-helicase, (b) and (d) respectively Cu(II), Ni(II) complexes bind with selective Amino acid residue of NS3 protease-helicase.

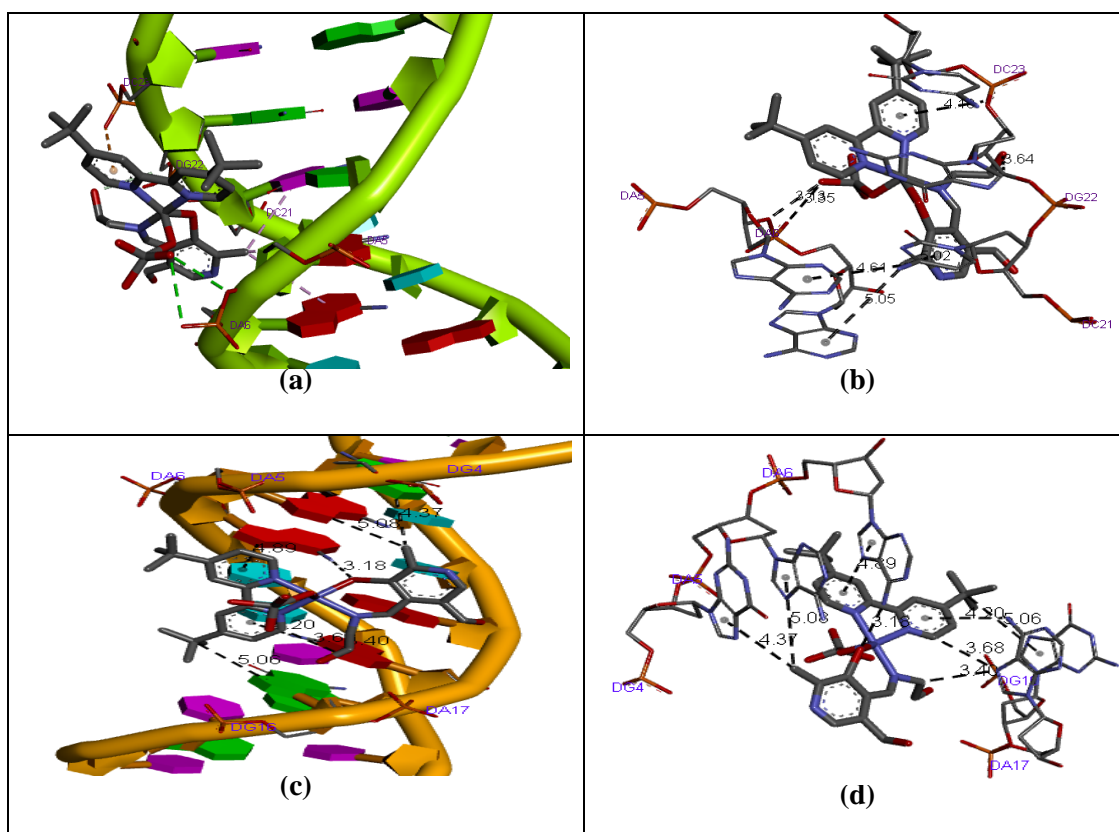


Figure 3: (a) and (c) respectively Cu(II), Ni(II) complexes bind with active site of human DNA, (b) and (d) respectively Cu(II), Ni(II) complexes bind with selective Nucleotide of human DNA Molecular docking with NS3 protease-helicase.

NS3 protease-helicase (dengue virus) is representing dengue protein. So, it was very valuable docking to understand the binding of the complexes towards the NS3 protease-helicase. NS3 protease-helicase is considered to be a receptor and the synthesized metal complexes were considered to be a ligand. The bind-

ing was shown in figure 3. The selected binding of complexes with amino acid residue is shown in figure 3 and the detailed binding nature with distance is noted in table 2-5. The binding affinity of Cu(II) and Ni(II) complexes towards NS3 protease-helicase with respectively -7.2 and -7.4 kcal mol⁻¹.

Table 2: Binding interactions of Ni(II) complex with human DNA and NS3 protease-helicase.

Mode	Affinity (kcal/mol)		Dist from best mode			
	B-DNA	NS3 protease-helicase	B-DNA		NS3 protease-helicase	
			rmsdl.b.	rmsdu.b.	rmsdl.b.	rmsdu.b.
1	-6.6	-7.4	0.000	0.000	0.000	0.000
2	-6.5	-7.3	11.841	17.560	11.573	17.663
3	-6.4	-7.3	15.281	12.804	11.948	18.354
4	-6.2	-7.1	15.377	11.901	12.727	17.825
5	-6.2	-6.9	11.954	12.321	11.733	17.947
6	-5.9	-6.8	14.640	10.225	12.315	17.338
7	-5.8	-6.5	17.369	13.712	16.385	11.726
8	-5.8	-6.1	12.349	19.610	10.661	14.252
9	-5.2	-5.9	15.571	2.245	2.817	9.072

Table 3: Ligand (Ni(II)complex) binds with different amino acid residues and nucleotide of receptors.

ligand	Receptor	Distance A°	Residue
Ni(II) complex	NS3 protease-helicase	3.27	ASP290-O39
		3.59	LYS388-O15
		4.13	ALA263-C29
		4.72	VAL544-C10
		4.82	PRO245-C29
	B-DNA	3.18	DA6-O7
		3.40	DA17-C13
		3.68	DA17-C16
		4.37	DG4-C10

Table 4: Binding interactions of Cu(II) complex with human DNA and NS3 protease-helicase.

Mode	Affinity (kcal/mol)		Dist from best mode			
	B-DNA	NS3 protease-helicase	B-DNA		NS3 protease-helicase	
			rmsdl.b.	rmsdu.b.	rmsdl.b.	rmsdu.b.
1	-6.5	-7.2	0	0	0	0
2	-6.4	-7.0	13.871	9.445	12.459	10.338
3	-6.3	-6.6	13.521	8.126	14.393	18.79
4	-6.2	-6.6	14.112	8.526	11.405	19.713
5	-5.9	-6.4	14.148	9.307	14.273	18.645
6	-5.7	-6.3	15.178	12.357	10.596	17.523
7	-5.6	-6.3	20.101	19.257	14.684	18.329
8	-5.6	-6.1	15.450	22.117	13.498	18.79
9	-5.6	-6.1	5.726	7.891	2.94	8.217

Table 5: ligand (Cu(II)complex) binds with different amino acid residues and nucleotide of receptors.

Ligand	Receptor	Distance A°	Residue
Cu(II) complex	NS3 protease-helicase	3.25	ASP290-O39
		3.49	PRO543-N2
		3.62	LYS388-O15
		4.18	ALA263-C29
		4.78	PRO245-C29
	B-DNA	3.13	DA6-O40
		3.35	DA6-O40
		3.64	DG22-C5
		4.10	DG23-C21

CONCLUSION: A new novel water-soluble vitamin B12 backbone Schiff base ligand and its Ni(II) and Co(II) complexes were synthesized by template method. The docking studies were carried out using synthesized metal complexes with B-DNA (PDB ID: 1BNA) and Dengue NS3 protease-helicase bifunctional enzyme (PDB ID: 2VBC) using Auto Dock tools1.5.4, Auto Dock vina and Discovery studio software. The binding energy values of the Ni(II) and Co(II) complexes respectively -7.4 and -7.2 kcal mol⁻¹ towards NS3 protease-helicase and binding towards B-DNA respectively -6.6 and -6.5 kcal mol⁻¹ which showed these types of compounds to be an Anti-Dengue agent.

ACKNOWLEDGEMENT: The author was thankful to Dr. S. Gnavel, Research and Project Centre for Chemical and Biological Science, Mettur, Salem.

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