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Identification of Potential Inhibitor for Nucleoprotein of Lassa Virus: A Combination of Virtual Screening, ADMET Studies and Pharmacophore Modeling

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Abstract

Lassa fever is an acute viral zoonotic illness caused by Lassa virus, a member of the *Arenaviridae* family and responsible for a severe hemorrhagic fever characterized by fewer, sour throat, muscle pain, nausea. In this work, we performed virtual screening against Nucleoprotein with entire 45 analogs compounds from Zinc Database using Auto Dock 4.2 software. These complexes were ranked according to their docking score, using methodology that was shown to achieve maximum accuracy. Finally we got six potent compounds with the best Auto dock docking Score. These six compounds were analyzed through Python Molecular Viewer for their interaction studies. From the docking result it was observed that ZINC79045769, ZINC04900951, ZINC21986245, ZINC75626110 have the lowest docking energy and thus have potential to inhibit the activity of nucleoprotein of Lassa virus. A 2-D pharmacophore was generated for these analogs using LigandScout to confirm it. A shared feature pharmacophore was also constructed that shows four common features (one hydrogen bond Donar, Two hydrogen bond Acceptor and one ionizable area) help compounds to interact with this enzyme.

INTRODUCTION

Lassa fever is an acute viral zoonotic illness caused by Lassa virus, a member of the *Arenaviridae* family and responsible for a severe hemorrhagic fever characterized by fever, sour throat, muscle pain, nausea [1]. Lassa fever was first described in Sierra Leone in the 1950s but the virus responsible for the disease was not identified until 1969 when two missionary nurses died in Nigeria, West Africa, and the cause of their illness was found to be Lassa virus, named after the town in Nigeria (Lassa in the Yedseram River valley) where the first cases were isolated [2,3]. There are an estimated 300,000 to 500,000 cases of Lassa fever each year [4,5] with a mortality rate if 15-20% for hospitalized patient. Mortality rate become high as 50% during epidemic and 90% in third month pregnancy for the expectant mother and the featus both [6-8]. Since then, a number of outbreaks of Lassa virus infection were reported in various parts of Nigeria including Jos, Zonkwua, Onitsha, Owerri, Abo Mbaise, Lafiya and Epkoma [9-12]. Epidemics of Lassa fever were also documented in other West African countries including Liberia, Sierra Leone, Guinea, Mali and Senegal [2,10,13]. A few cases of the importation of Lassa virus into other parts of the world for example by travelers were documented.

Morphologically, Lassa virus consists of enveloped particles that vary in diameter from approximately 60 to more than 300 nm, with mean particle size of 92 nm. The virus is approximately spherical, enveloped particles that rang in diameter from 50 to 300 nm [14,15]. Lassa virus having ambisense genomic organization (two viral gene separated by an intergenic region), negative sense, bisegmented, ssRNA genome S (small ~3.4 kb) & L (large ~7.2 kb) segments [16,17]. The small segment encodes the 75 KDa glycoprotein precursors (GPC) and the 63KDa nucleoprotein (NP). After part translation modification GPC cleaved in to GP1 and GP2. The large segment of RNA encodes the 11KDa Z protein, which binds zinc and as Matrix protein and the 200KDa L protein,

which is act as matrix protein. Replication and transcription of the genome occurs in the cytoplasmic of an infected cell and both take place within Rib nucleoprotein complex [18,19].

Lassa virus is transmitted to human being from the rodent reservoir *Mastomys natalensis*, by direct content with infected tissue, food contaminated with excreta. Mostomys natalensis, is a common rodent in village houses, there for primary human infection are common. Lassa fever may also spread through person to person contact. Lassa virus transition occurs when a health person comes in to contact with virus in the blood, secretion, tissue or excretion of any infected individual. The virus cannot be transmitting through skin to skin contact without exchange of body fluid. Lassa virus enters the cell via the alpha-dystroglucan receptor [20]. Furthermore, ribavirin should be made available in hospitals and health centres in the endemic areas particularly in rural communities. This would help to control the disease.

The aim of this study to design the drug for Lassa virus. Structure based drug designing is an *in silico* technique which is very helpful in biological target identification, modeling of target protein virtual screening of potent drug compound and molecular docking studies to find out the best lead like compound. In the drug designing portion, we select the three inhibitors (Nucleozin, Naproxen and Ribavirin) and their analogs to predict the potential Nucleoprotein Inhibitors for Lassa virus using virtual screening, ADMET is screening and pharmacophore modeling. Nucleoprotein (NP) is a main drug targeted protein has distinct N- and C- terminal domains connected by a flexible linker. The Lassa virus nucleoprotein (NP) is a multifunctional protein that plays an essential role in many aspects of the viral life cycle, including RNA encapsidation, viral replication and transcription, recruitment of ribonucleoprotein complexes to viral budding sites, and inhibition of the host cell interferon response [21,22]. Nucleozin and Naproxen both are the nucleoprotein inhibitor while Ribavirin is used for the treatment of the infection of Lassa virus on clinical level.

MATERIAL AND METHODS

Structure retrieval and processing

For the docking analysis crystal structure of nucleoprotein was downloaded from database protein data bank (www.resb.org/pdb) with PDBID 3MWP A. The model contains solvent molecules along with hetero groups like its inhibitors and few of the calcium ions. Solvent and hetero groups were also removed using SPDBV Select and Build utilities. The crystal structure of nucleoprotein was further optimizing by energy minimization by Gromos96, implemented in Swiss PDB viewer software. This tool is form the molecular dynamic of the entire bonded and non banded atom with the model structure [23,24].

Active site Analysis

The active sites were revealed by Q site finder. It is a energy based method for the prediction of protein ligand binding site it uses the interaction energy between the protein and simple vander walls probe to locate energetically favorable binding site [25]. Energetically favorable probe sit were clustered according to their spatial proximity and cluster war ranked according to the sum of interaction energy.

Ligand Selection

The CID files of the ligands were downloaded from PubChem database. These files converted into PDB format by using Open Bable software [26]. Their energy minimization was carried out with the GROMOS96, implemented in Swiss-PDB viewer software [24]. GROMOS96 performs the molecular dynamics of all the bonded and non-bonded atoms with the model structure and obtain the minimum potential energy.

Zinc database screening

Zinc database contains over 13 million commercially available compounds in ready to dock and 3D format for structure based virtual screening. Zinc database is updated regularly and may be downloaded and used free of cost [27]. A total of 49 (17 Nucleozin + 16 Naproxen + 16 Ribavirin analogs) compounds were screened by using structure based searching method. These compounds were converted into PDB format from SDF by using Open Bable [26]. Their energy minimization was carried out with the GROMOS96, implemented in Swiss-PDB viewer software.

Virtual screening

Virtual screening is a key tool in structural molecular biology and computer added drug designing. In this docking studies are performed to product the predominant binding models of legend with a protein of know 3D structured. Molecular docking between selected compound and nucleoprotein crystal structure was done using Autodock 4.2 [28]. This program used a simulated annealing approach for explore the conformation space between the ligand and target protein. The energy evaluation process is done by using grid-based molecular affinity potential, the docking was performed on the basis of Lamarckian Genetic Algorithm. The energy grid was built within a box of dimension 68, 88, 78 for nucleoprotein with a spacing of 0.375 Å.

ADMET analysis

The compounds with good pharmacological and druggist property are very important to structure based drug designing. Pharmacological studies of lead molecule include absorption, distribution, metabolism, excretion and toxicity (ADMET) properties. These ADMET properties of the lead compounds were predicted by computational tools. Here, all 15 compounds identified were tested for their drug-likeliness, ADME profile and toxicity analysis by Pre-ADMET web tool. The ADMET includes the extent and rate of absorption, distribution, metabolism, excretion and toxicity. Absorption check the process of a substance entering the blood circulation, distribution explains the dispersion or dissemination of substances throughout the fluids and tissues of the body, metabolism or biotransformation is the irreversible transformation of parent compounds into daughter metabolites and excretion explains the process of removal of the substances from the body. Pre-ADMET use to predict drug likeness of compounds and check heterogeneous human epithelial colorectal adenocarcinoma cell lines (Caco2-cell) and Madin-Darby Canine Kidney (MDCK) cell models for oral drug absorption and skin permeability prediction, and human intestinal absorption

model for drug absorption prediction. Similarly, the programme uses plasma protein binding models and blood brain barrier penetration (BBB) to predict the distribution. Pre-ADMET can predict the toxicity based on the mutagenicity of Ames test parameters and rodent carcinogenicity assays of mouse and rat [29].

Pharmacophore generation

Pharmacophore modeling is one of the most powerful computational method to categorize & identify key features from a large group of molecules and a 3D-pharmacophore is a set of interactions (functionalities or chemical features) aligned in three-dimensional space. Subsequently, pharmacophore model representing ligand-receptor binding derived from each of these small molecules and its neighboring amino acids. The pharmacophore models will provide a new insight to design new compounds that can inhibit the function of the target and will be useful in drug designing strategies [30]. Six compounds were taken on the basis of higher binding energy and best ADMET studies for pharmacophore modeling. Ligand scout (http://www.inteligand.com/ligandscout/) was used to develop pharmacophore model of selected compound. Different types of chemical feature and volume constraints for each selected compound were examined using feature directory from LigandScout software. By consolidating all the available features, six common features were used to generate pharmacophore model: Hydrogen bond donar, Hydrogen bond accepter, hydrophobic centroids, aromatic rings, cations, and anions.

RESULTS AND DISCUSSION

Active site analysis

Q-site finder detected the fallowing putative functional site residue for the targeted nucleoprotein protein MET54, ARG59, ASN71, VAL74, ASN75, LYS110, VAL113, ILE114, THR116, GLU117, ARG118, LEU120, SER121, ILE144, TRP164, ALA169, GLU170, LEU172, ASN173, ASN174, GLN175, PHE176, GLY177, THR178, MET179, LEU182. In this nucleoprotein protein the binding site cavity volume was 1166 cubic angstroms and it also showed that the coordinates the binding site box around predicted site had minimum cords 48, -63, -32 and maximum cords 73, -29, -7.

Virtual screening result

Docking studies was carried out using Autodock software to predict the interaction behavior of ligand with protein and residue involve in this interaction. The entire 52 compound were docked with the 3D crystal structure of Nucleoprotein. The docking results are shown in the Table 1 for Nucleozin and their analogs and Table 2 for Naproxen and their analogs and Table 3 for Ribavirin and their analogs. After the docking analysis of nucleoprotein with the selected compounds, sixteen compounds are screened out for the further analysis. After the ADME result of all sixteen compounds we select six compounds Nucleozin (-10.67), ZINC79045769 (-11.7), ZINC04900951 (-11.57), Naproxen (-11.73), ZINC21986245 (-12.32) and ZINC75626110 (-11.91) as potent inhibitor.

ADMET analysis

ADMET profiles determine drug like activity of the ligand molecules based on Lipinski rule of 5, rate of absorption, distribution, metabolism, and excretion and toxicity based on Ames test and rodent carcinogenicity assay. Increasing clinical failures of new drugs call for a more effective use of ADMET technologies. Drug-likeliness and ADME profile prediction of selected compounds using by Pre-ADMET tool shown in Table 4 and Table 5 respectively. The main rules used to test the drug likeliness were Lipinski's Rule, Lead like Rule, CMC-like rule,

Table 1: Docking results of Nucleozin analogs with Nucleoprotein.

ZINC_ID	xLogP	Polar Desolvation	H Donors	H Acceptors	Molecular Weight	Rotatable Bonds	Docking Energy	Build H Bond
Nucleozin	**3.9**	**-11.34**	**0**	**6**	**426.852**	**3**	**-10.67**	**3**
ZINC08781115	3.37	-11.83	0	8	426.86	4	-9.94	2
ZINC22064357	3.70	-11.9	0	8	440.887	4	-8.90	1
ZINC22064361	3.70	-12.68	0	8	461.305	4	-7.94	2
ZINC08855058	**4.00**	**-12.26**	**0**	**8**	**400.822**	**4**	**-12.02**	**3**
ZINC04974049	3.48	-16.33	2	8	426.86	7	-8.09	2
ZINC16677244	3.34	-13.31	0	8	475.332	4	-9.66	1
ZINC20076590	4.33	-12.51	0	8	475.332	4	-9.05	1
ZINC20076587	4.33	-14.11	0	8	396.878	4	-9.76	0
ZINC79045769	**2.48**	**-11.15**	**2**	**6**	**435.267**	**3**	**-11.72**	**3**
ZINC22064878	4.12	-17.52	2	8	381.863	7	-9.32	2
ZINC06912077	**3.43**	**-10.69**	**0**	**5**	**426.86**	**3**	**-10.75**	**2**
ZINC08454078	3.37	-12.45	0	8	461.305	4	-8.59	2
ZINC22064955	3.97	-13.62	0	8	392.415	4	-10.05	1
ZINC04900951	**2.76**	**-17.99**	**0**	**8**	**461.305**	**4**	**-11.57**	**3**
ZINC08435355	4.02	-14.59	0	8	461.305	4	-10	2
ZINC08435353	3.39	-14.44	0	8	426.86	4	-8.56	1
ZINC04565291	3.46	-15.53	2	8	400.822	7	-9.73	0

Table 2: Docking results of Naproxen analogs with Nucleoprotein.

ZINC_ID	xLogP	Polar Desolvation	H Donors	H Acceptors	Molecular Weight	Rotatable Bonds	Docking Energy	Build H Bond
Naproxen	**3.3**	**-47.28**	**1**	**3**	**230.259**	**3**	**-11.73**	**2**
ZINC00105216	3.38	-47.82	0	3	229.255	3	-8.43	1
ZINC00113439	3.38	-48.58	0	3	229.255	3	-7.22	1
ZINC01843439	3.55	-50.37	0	3	243.282	3	-10.56	1
ZINC71610607	3.35	-49.05	0	3	229.255	3	-11.01	0
ZINC06030355	3.35	-49.67	0	3	229.255	3	-9.67	1
ZINC02014886	2.58	-49.03	0	3	215.228	3	-8.98	1
ZINC06030370	2.88	-47.85	0	3	229.255	3	-9.32	0
ZINC06037142	2.88	-49.51	0	3	229.255	3	-9.45	1
ZINC06037131	**2.84**	**-49.29**	**1**	**3**	**215.228**	**2**	**-12.03**	**2**
ZINC02570852	**2.84**	**-47.00**	**3**	**3**	**215.228**	**2**	**-11.53**	**2**
ZINC75626106	2.84	-47.32	1	3	215.228	2	-9.31	1
ZINC75626110	**2.84**	**-48.93**	**1**	**3**	**215.228**	**2**	**-11.91**	**2**
ZINC77303118	3.28	-49.01	0	3	243.282	3	-8.33	0
ZINC77303121	3.28	-49.23	0	3	243.282	3	-7.43	1
ZINC21986247	3.35	-9.15	3	0	244.29	4	-8.37	1
ZINC21986245	**3.35**	**-9.15**	**3**	**0**	**244.29**	**4**	**-12.32**	**2**

Table 3: Docking results of Ribavirin analogs with Nucleoprotein.

ZINC_ID	xLogP	Polar Desolvation	H Donors	H Acceptors	Molecular Weight	Rotatable Bonds	Docking Energy	Build H Bond
Ribavirin	**-1.8**	**-18.73**	**4**	**7**	**244.204**	**3**	**-10.67**	**3**
ZINC00896749	-2.77	-16.15	5	9	244.207	3	-10.91	3
ZINC21981355	-2.77	-21.78	5	9	244.207	3	-8.87	2
ZINC06603353	-2.77	-21.52	5	9	244.207	3	-9.55	2
ZINC21981353	**-2.77**	**-24.81**	**5**	**9**	**244.207**	**3**	**-11.98**	**4**
ZINC01035331	-2.77	-17.41	5	9	244.207	3	-9.12	2
ZINC01091444	-2.77	-18.93	5	9	244.207	3	-8.82	2
ZINC03831418	-2.77	-16.84	5	9	244.207	3	-10.45	3
ZINC03831419	-2.77	-17.96	5	9	244.207	3	-9.34	3
ZINC03831420	**-2.77**	**-15.05**	**5**	**9**	**244.207**	**3**	**-12.34**	**5**
ZINC03831421	**-2.77**	**-21.51**	**5**	**9**	**244.207**	**3**	**-12.87**	**4**
ZINC04245717	-2.77	-19.79	5	9	244.207	3	-9.98	4
ZINC28463692	-2.77	-20.4	5	9	244.207	3	-8.76	1
ZINC05291792	-2.07	-27.38	4	10	286.244	5	-7.23	3
ZINC05291810	-2.07	-22.06	4	10	286.244	5	-8.93	2
ZINC05291808	-2.07	-24.15	4	10	286.244	5	-10.65	2
ZINC05291797	**-2.07**	**-21.81**	**4**	**10**	**286.244**	**5**	**-12.90**	**3**

MDDR-like rule and WDI-like rule and ADME profile (caco-2, MDCK, BBB, HIA, plasma protein binding and skin permeability data) analysis. Some compounds are Non-qualified and failure in some rules. Toxicity prediction is the final step of ADMET analysis of selected lead compounds. In this toxicity prediction study, we have found that the predicted toxicities of selected compounds were suitable for further studies (Table 6). ZINC79045769 and ZINC04900951 analogs of Nucleozin and ZINC21986245 and ZINC75626110 analogs of Naproxen showed better drug likeness, pharmacokinetics and toxicity properties. Hence, these lead compounds were identified as the best ligands for pharmacophore modeling.

Pharmacophore generation

After virtual screening and ADMET studies we select four best compounds for the pharmacophore generation. Pharmacophore

Table 4: Drug-likeliness prediction of selected compounds using Pre-ADMET tool. The main rules used to test the drug likeliness were Lipinski's Rule, Lead like Rule, CMC-like rule, MDDR-like rule and WDI-like rule.

Compound	Lipinski's Rule	Lead like Rule	CMC-like rule	MDDR-like rule	WDI-like rule
Nucleozin	Suitable	Violated	Qualified	Mid-structure	In 90% cutoff
ZINC08855058	Suitable	Violated	Qualified	Mid-structure	In 90% cutoff
ZINC79045769	Suitable	Violated	Qualified	Mid-structure	In 90% cutoff
ZINC04900951	Suitable	Violated	Qualified	Mid-structure	In 90% cutoff
ZINC06912077	Suitable	Violated	Qualified	Mid-structure	In 90% cutoff
Naproxen	Suitable	Suitable	Qualified	Mid-structure	In 90% cutoff
ZINC21986245	Suitable	Violated	Qualified	Mid-structure	In 90% cutoff
ZINC06037131	Suitable	Suitable	Failed	Mid-structure	In 90% cutoff
ZINC75626110	Suitable	Suitable	Non-qualified	Mid-structure	Failed
ZINC02570852	Suitable	Suitable	Failed	Mid-structure	Failed
Ribavirin	Suitable	Violated	Qualified	Mid-structure	In 90% cutoff
ZINC05291797	Suitable	Violated	Qualified	Mid-structure	Failed
ZINC03831420	Suitable	Violated	Non-qualified	Mid-structure	In 90% cutoff
ZINC03831421	Suitable	Violated	Non-qualified	Mid-structure	In 90% cutoff
ZINC21981353	Suitable	Violated	Non-qualified	Mid-structure	In 90% cutoff

Table 5: ADME prediction of compounds using Pre-ADMET tool.

Compound	Human Intestinal Absorption	Caco2 Cell Permeability	MDCK Cell Permeability	Plasma protein biding	Blood Brain Barrier Penetration
Nucleozin	99.522063	20.1692	0.0755843	98.999182	0.298094
ZINC08855058	99.136228	17.9378	0.0564337	98.480451	0.294334
ZINC79045769	96.663744	22.9271	0.198448	88.368975	0.0462123
ZINC04900951	98.832066	7.79045	0.586648	91.185904	0.212613
ZINC06912077	97.485649	41.3096	0.151602	91.387010	0.10315
Naproxen	98.089935	14.7189	185.873	93.954170	0.042197
ZINC21986245	98.697048	29.7656	105.055	90.868524	0.0915844
ZINC06037131	95.674448	4.84276	109.044	86.393242	0.903749
ZINC75626110	95.674448	21.122	109.044	87.118936	0.903749
ZINC02570852	95.674448	4.84276	109.044	86.393242	0.903749
Ribavirin	21.502254	1.36443	2.22093	7.329473	0.150118
ZINC05291797	23.068541	3.34818	0.900147	8.068397	0.011005
ZINC03831420	21.502254	1.36443	2.22093	7.329473	0.150118
ZINC03831421	21.502254	1.36443	2.22093	7.329473	0.150118
ZINC21981353	21.502254	1.36443	2.22595	7.329473	0.150118

Table 6: Toxicity prediction of selected compounds by Pre-ADMET tool.

Compound	AMES Test							Carcinogenicity	
	TA100 +s9	TA100 -s9	TA1535 +s9	TA1535 -s9	TA98 +s9	TA98 -s9	Result	Mouse	Rat
Nucleozin	+	-	+	-	-	+	**M**	-	-
ZINC08855058	+	-	+	-	-	-	M	-	+
ZINC79045769	+	+	+	-	+	-	**M**	-	-
ZINC04900951	+	+	-	-	-	+	**M**	-	-
ZINC06912077	+	-	+	-	-	-	M	-	+

Naproxen	+	-	-	-	+	+	**M**	-	-
ZINC21986245	-	-	-	-	+	+	**M**	-	-
ZINC06037131	+	-	-	-	+	+	M	-	+
ZINC75626110	+	-	-	-	+	+	**M**	-	-
ZINC02570852	+	-	-	-	+	+	M	-	+
Ribavirin	-	-	+	-	+	-	M	-	+
ZINC05291797	-	-	+	-	+	-	M	-	+
ZINC03831420	-	-	+	-	+	-	M	-	+
ZINC03831421	-	-	+	-	+	-	M	-	+
ZINC21981353	-	-	+	-	+	-	M	-	+

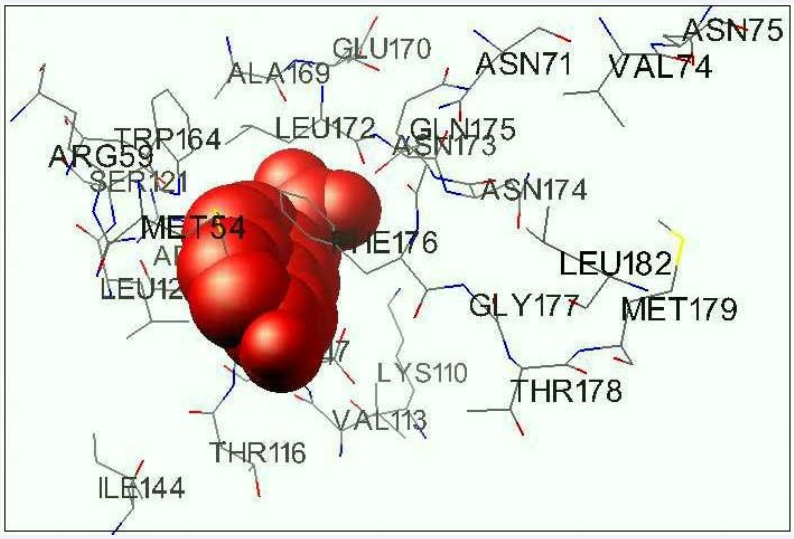

Figure 1 Predicted pocket (red color) of Nucleoprotein and involved amino acid.

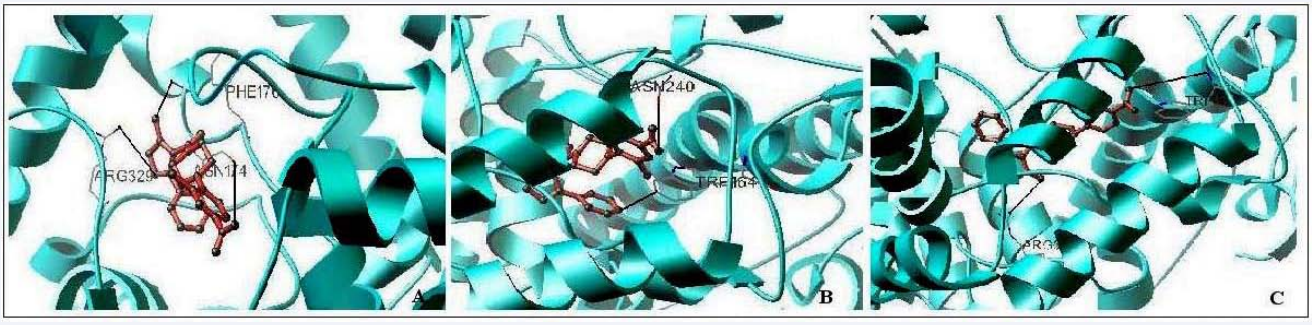

Figure 2 Docking conformation of: a) Nucleozin b) ZINC79045769 c) ZINC04900951 analyzed by Python Molecular Viewer (docked ligand shown by balls and sticks while hydrogen bonds shown by black sticks.

model generation was done for all six compounds by using Ligand scout which are shown in (Figures 1-4) Shared featured pharmacophore of Nucleozin with analogs and Naproxen with analogs were generated by aligning pharmacophores and molecules using reference points as shown in (Figure 5).

CONCLUSION

The Nucleoprotein of Lassa Virus is the drug targeting proteins for the drug discovery fighting with the current pandemic. Crystal structure of nucleoprotein was downloaded from database protein data bank (www.resb.org/pdb) with PDBID 3MWP A. All Fifty two compounds screened from ZINC database were docked with crystal structure of Nucleoprotein. After docking four compounds ZINC79045769, ZINC04900951, ZINC21986245, ZINC75626110 were predicted as potent candidate drugs for Lassa Virus. Yet pharmacological studies have to confirm it.

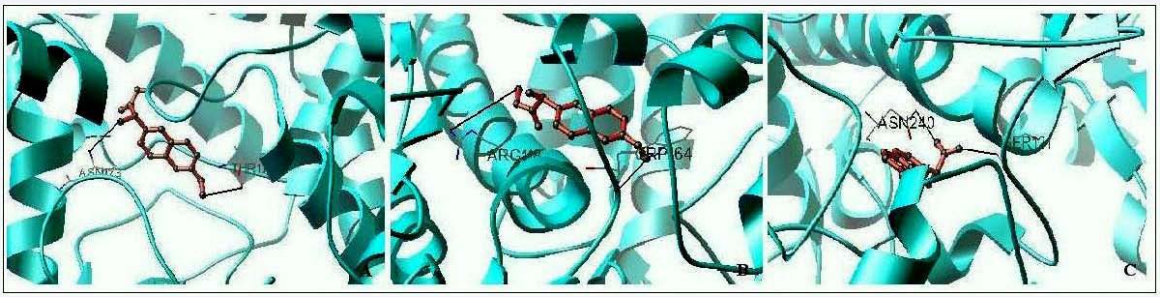

Figure 3 Docking conformation of: a) Naproxen b) ZINC21986245 c) ZINC75626110 analyzed by Python Molecular Viewer (docked ligand shown by balls and sticks while hydrogen bonds shown by black sticks.

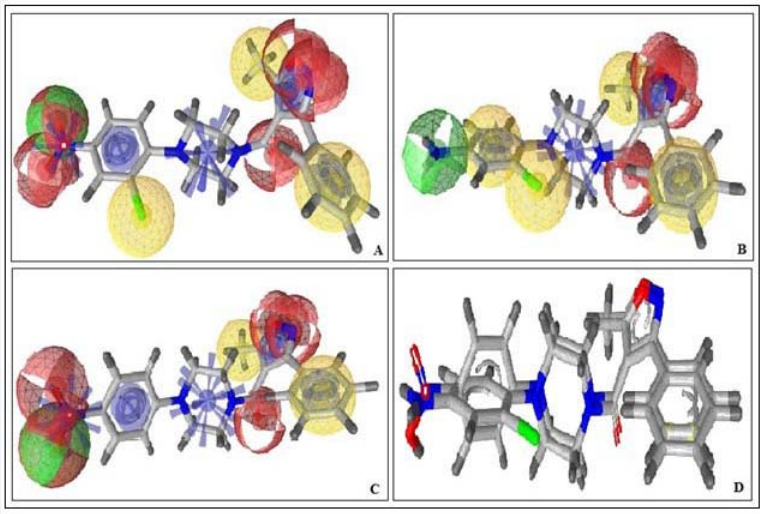

Figure 4 3-D Pharmacophore model of a) Nucleozin b) ZINC79045769 c) ZINC04900951 d) overlapped model of ZINC79045769 and ZINC04900951 generated by LigandScout (hydrogen bond Donor: green sphere, hydrogen bonds Acceptor: Red sphere and ionizable area: Blue asterisk and Aromatic rings).

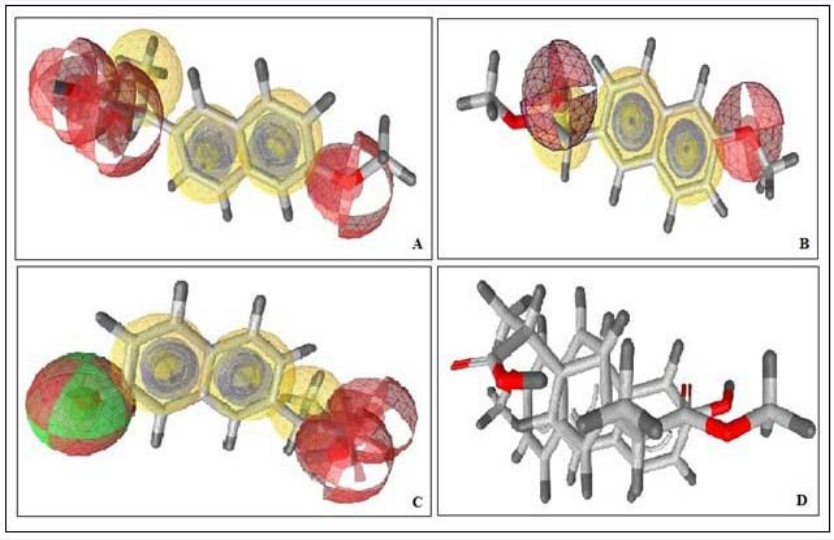

Figure 5 3-D Pharmacophore model of a) Naproxen b) ZINC21986245 c) ZINC75626110 d) overlapped model of ZINC21986245 and ZINC75626110 generated by Ligand Scout (hydrogen bond Donor: green sphere, hydrogen bonds Acceptor: Red sphere and ionizable area: Blue asterisk and Aromatic rings).

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