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Molecular docking analysis of FDA approved drugs with the glycoprotein from Junin and Machupo viruses

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Abstract:
Arenaviruses, Junin and Machupo are pathogenic viruses in regions of South America including Argentina and Bolivia causing haemorrhagic fever among humans. They have been transmitted to humans through mouse causing chronic illness with high mortality. Therefore, it is of interest to acquittance the molecular docking analysis data of FDA approved drugs with the glycoprotein from Junin and Machupo viruses for consideration in drug discovery. Thus, we report the optimal binding features of MK-3207 and Dihydro ergotamine with the protein target for further validation and consideration.

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Keywords: Drug design, ligands, Junin virus, Machupo virus, glycoprotein

Background:

Junin and Machupo human pathogenic New World Arenaviruses belongs to *Mammareavirus* genus of *Arenaviridae* family and were isolated in 1958 from regions of Argentina and Bolivia**[1 and 2]**. Junin virus was transmitted to humans from natural occurring reservoirs mainly *Calomys musculin* and Machupo virus from *Calomys callosus* **[3 & 4]**. Symptoms such as frailty, anorectic, pain and fever persuade by incubation of 7-14 days followed by further neurological, constitutional, cardiovascular and gastrointestinal signs **[5 and 6]**.

The genome of Arenaviruses possessing negative sense single-stranded RNA encompasses two segments pertaining Small (S) RNA segment (3.4 kb) and Large (L) segment (7.2 kb) **[7].** Small segment encodes for envelope glycoprotein precursor (GPC) and the nucleoprotein (NP), whereas large segment encodes for matrix protein (Z) and viral RNA-dependent RNA polymerase (L) **[7].** The glycoprotein precursor further degraded into N-terminal GP1; having binding capacity with host receptor and the transmembrane GP2, indulge in viral fusion by signal peptidases and subtilisin kexin isozyme-1or site-1 protease (SKI-1/S1P) **[7,8 and 4]**. Junin and Machupo viruses share a common receptor hTfR1 (human transferring receptor1) **[9]**.Apart from pervasion of studies for identification of therapeutic facilities for prevention and cure of both viruses, no drug out of date being administered **[10]**. Computational drug designing approaches are used to predict and evaluate drugs for various endemic (other diseases too) diseases **[11, 12]**. It has reduced the time span of effective and precise drug development. Considerable progress has been made in the areas of drug development pertaining to viral pathogenesis **[13]**. However, high mutability rates and variable genome dynamics of viruses have been the major obstacles in effective drug design against the detrimental pathogens **[14]**. With the increase in prevailing threat of Junin and Machupo viruses, there is a rising demand to design drugs for them **[15]**. Ribavirin (1-D ribofuranosyl.1.2.4. triazole-3-carboxamide) is the only anti-arenaviral drug currently available against Junin virus while it fails to increase the survival benefits among patients and also display many side effects including anaemia and febrile syndrome **[10]**. Scarcity of effective drugs against the menacing Arenaviruses is another domain of viral genomics that needs to be catered **[15, 12]**. Therefore, it is of interest to document the molecular docking analysis data of FDA approved drugs with the glycoprotein from Junin and Machupo viruses for consideration in drug discovery.

Materials and Methods:

Retrieval and pre-processing of protein structures:

GP1 subunit of glycoprotein binds to the human receptor transferrin receptor 1 (TfR1) and causes infection among humans **[9]**. So, highly resolved X-ray diffraction crystal structure of Glycoprotein (GP1) of Junin **[9] (Table1 and Figure1)** and Machupo virus **[9] (Table1 and Figure2)** was retrieved as target from Protein Data Bank (PDB) database. Further refinement of both structures was performed by removal of water molecules, addition of polar hydrogen and Kollaman charges in AutoDock tools **[16]**. Also, grid box was defined for GP1 of Junin and Machupo viruses within their active site which was concluded using CASTp (Computer Atlas of Surface Topography of Proteins) server **[17]**.

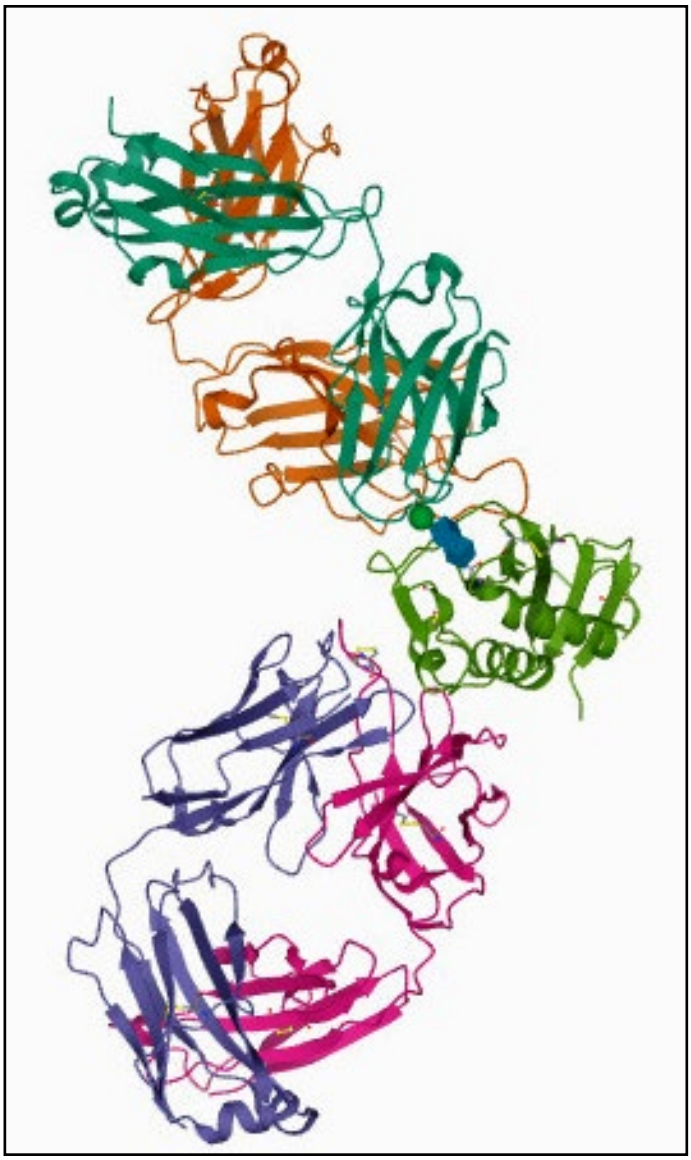

Figure 1: PDB structure of target protein of Junin virus (5W1K).

Retrieval of ligand structures:

Further ligand compounds were retrieved from ZINC15 database **[18]** by downloading 2115 FDA-approved drugs and 3754 investigational drugs in mol2 format. In addition, compounds prevailing mol2 structures were converted to PDBQT format structures by using Open Babel tool **[19]** and

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further PRODRG server **[20]** was used for energy minimization of the structures.

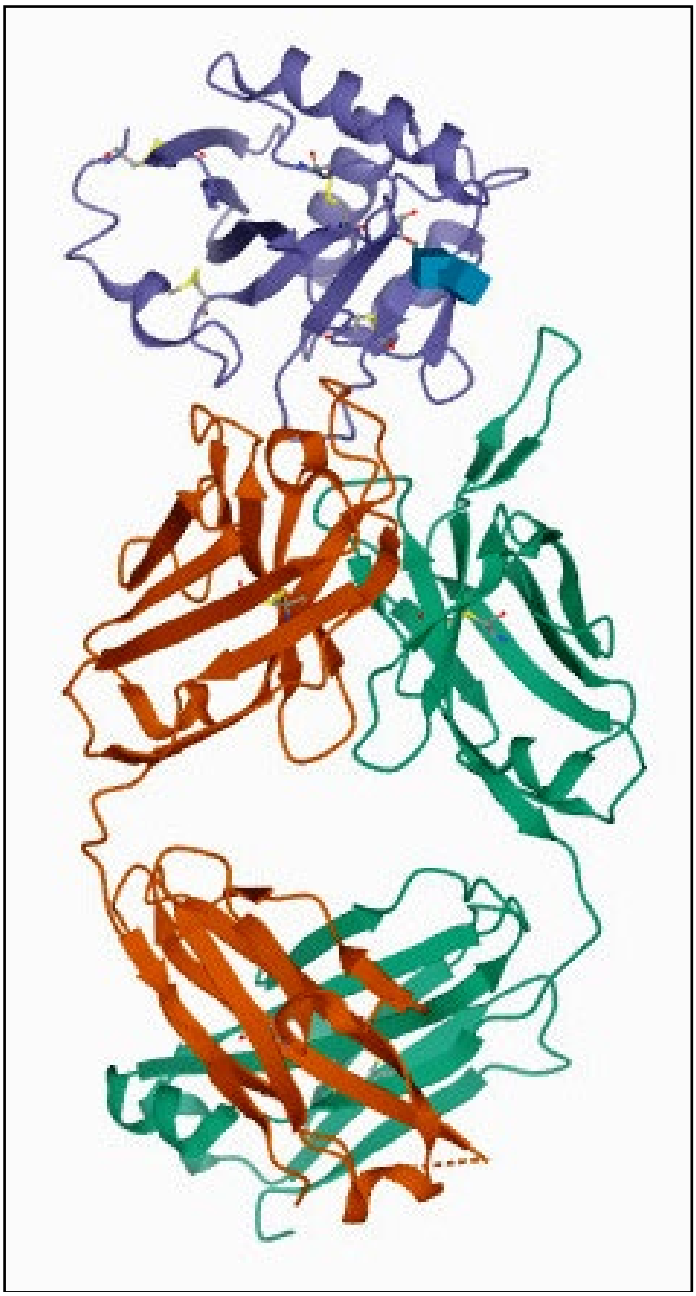

Figure 2: PDB structure of target protein of Macupo virus (5W1M)

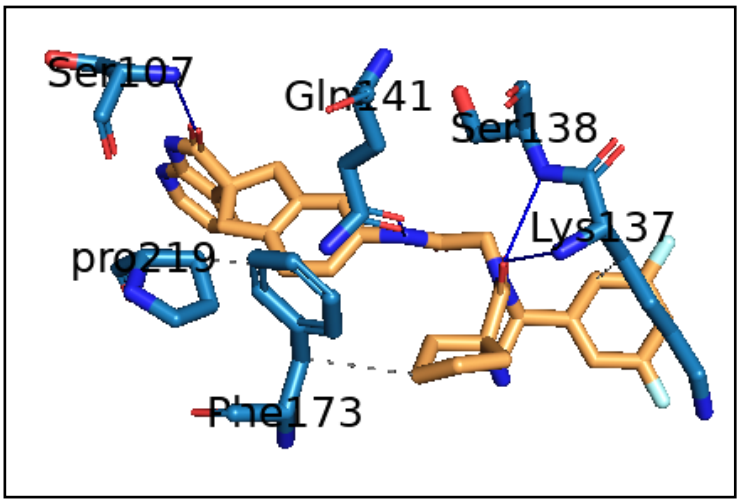

Figure 3: Mode of interaction of ligand MK-3207 with target protein GP1 of Junin virus. Hydrophobic interactions and Hydrogen bonds are shown in dashed and blue lines.

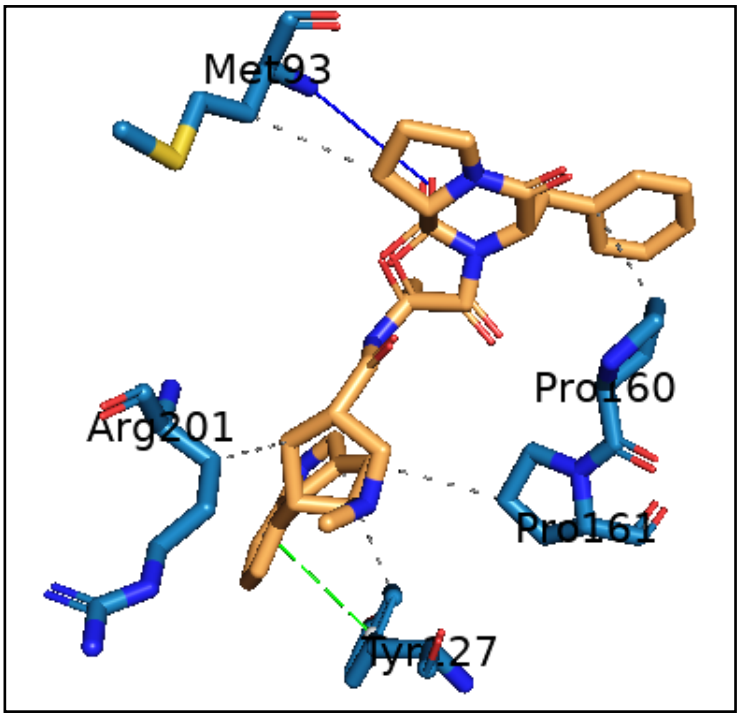

Figure 4: Mode of interaction of ligand Dihydroergotamine with target protein GP1 of Machupo virus. Hydrophobic interactions, Hydrogen bonds and π-stacking shown as grey dashed, blue and green dashed lines

Molecular Docking:

Screening of downloaded structures of ligands (.PDBQT format) was performed by computing docked score of each ligand within active site of GP1 target protein from Junin and Machupo viruses separately in AutoDock vina software **[21]**. Best scored ligands were selected for further analysis **[12]**. Furthermore, interactions between ligand and target was

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investigated by using Pymol and PLIP (protein-ligand interactor profiler) **[22]** tools.

Drug Likeliness and potential toxicity prediction:
Drug Likeliness **[23, 24]** based on physiochemical properties of best selected ligands were computed using SwissADME **[25]** and pkCSM servers **[26]**. The Pan-Assay Interference Structures (PAINS) analysis **[27]** was also performed in SwissADME server for each selected ligand. The toxicity parameters like mutagenicity, carcinogenecity and cytotoxicity of the selected ligands was estimated using the ProTox-II web-server **[28]** and further validation was performed with the vNN-ADMET server **[29]**.

Table 1: Showing PDB structure data of target proteins

PDBID	Chains	Resolution
5W1K	E,J,P,R	3.99 Angstrom
5W1M	E,J,K,L	3.91 Angstrom

Table 2: Showing results of best scored ligands (FDA approved library) for Junin virus

#	ZINC ID	Name	Binding energy score (kcal/mol)	Interacting residues
1	ZINC169289767	Trypan Blue	-9.4	Lys102P,Thr170P,Pro219P,Pro219P,Trp222P;Asn105P*,Lys137P*,Ser138P*,Gln141P*,Arg167P*,Thr168P*,Thr170P*,Thr220P*,Leu228P*;Lys102P^,Lys137P^
2	ZINC27990463	Lomitapide	-8.6	Pro120R,Leu163R,Asn178R,Thr182R,Leu212R;Asn178R*,Ser180R*,Asn185R*
3	ZINC000011679756	Eltrombopag	-8.4	Pro160R,Leu163R,Asn178R,Thr182R,Leu212R;Pro161R*,Leu163R*,Asn178R*,Ser180R*,Asn185R*
4	ZINC1612996	Irinotecan	-8.1	Ala106R,Gln141R,Arg167R,Thr170R,Pro219R;Lys137R*,Ser138R*,Gln141R*
5	ZINC3978005	Dihydroergotamine	-8.1	Lys137J,Phe173J,Pro219J; Gln141J*

Showing binding energy score of best ligands after screening from FDA-approved drug library for target protein of Junín virus. R, J is chains of target protein structure. Hydrophobic interactions shown in italics, Hydrogen bonds are marked with * and salt bridges marked with ^.

Table 3: Showing properties of best selected ligands (FDA approved drugs) for Junin virus

ZINC ID	Molecular weight	Log P	Number of hydrogen bond donor	Number of hydrogen bond acceptor
ZINC169289767	872.88	4.01	8	18
ZINC27990463	693.72	7.79	2	9
ZINC000011679756	**442.47**	**3.74**	**3**	**6**
ZINC1612996	*586.68*	*3.73*	*1*	*8*
ZINC3978005	*583.68*	*2.15*	*3*	*6*

Physiochemical properties of above selected ligands are mentioned and ligand following Lipinski's rule of five is highlighted. LogP is logarithm of partition coefficient. Ligands showing minor variations in Lipinski's Rule of five (Molecular weight>500) has been italicised.

Table 4: Showing toxicity of selected ligands (FDA approved drugs) for Junin virus

ZINC ID	Mutagenecity	Cytotoxicity	Carcinogenecity	PAINS alert
ZINC169289767	**Yes**	**No**	**Yes**	**0**
ZINC27990463	No	No	No	0
ZINC000011679756	*No*	*No*	*No*	*1*
ZINC1612996	**No**	**No**	**Yes**	**0**
ZINC3978005	No	No	No	0

Ligands showing toxicity are highlighted. PAINS-Pan-assay-interference structure and ligand showing PAINS alert is italicised.

Table 5: Showing results from best ligand results (investigational drug library) for Junin virus

#	ZINCID	Name	Binding Energy score	Interactions
1	ZINC000003975327	Telomestatin	-9.1	Ser138J*
2	ZINC000012358610	Phthalocyanine	-9.7	Ala116R,Pro120R,Ile125R,Pro160R,Pro161R,Leu163R,Leu214R;Asn178R*,Asn185R*
3	ZINC000043203371	MK-3207	-8.6	Lys137J,Phe173J,Pro219J;Ser107J*,Lys137J*,Ser138J*,Gln141J*
4	ZINC000003922429	Adozelesin	-8.8	Lys137R,Arg167R,Phe173R,Pro219R;Lys102R*,Gln141R*

5	ZINC000095561192	Unii-I6KF9AF7F7	-8.8	Lys137P,Gln141P,Phe173P,Pro219P,Trp222P;Asn105P*,Ser107P*,Gln141P*

Best ligands after screening from investigational drug library with their binding energy score with target protein Junin virus are shown. R, J and P are chains of target protein structure. Hydrophobic interactions shown in italics, Hydrogen bonds are marked with *.

Table 6: Showing properties of best ligands (investigational drug library) for Junin virus

ZINCID	Molecular weight	Number of hydrogen acceptors	Number of hydrogen donors	LogP
ZINC000003975327	582.5	15	0	2.21
ZINC000012358610	*518.57*	*2*	*6*	*5.88*
ZINC000043203371	557.59	7	3	3.32
ZINC000003922429	*502.52*	*4*	*3*	*3.82*
ZINC000095561192	680.77	6	2	6.63

Physiochemical properties of above selected ligands are mentioned. Ligand following Lipinski's rule of five with minor variation (Molecular Weight>500) has been italicised. LogP is logarithm of partition coefficient.

Table 7: Showing toxicity of best ligands (investigational drug library) for Junin virus

ZINCID	Mutagenecity	Carcinogenecity	Cytotoxicity	PAINS alert
ZINC000003975327	No	No	No	0
ZINC000012358610	**Yes**	**No**	**No**	**0**
ZINC000043203371	No	No	No	0
ZINC000003922429	**No**	**Yes**	**No**	**0**
ZINC000095561192	No	No	No	0

Ligands showing toxicity are highlighted. PAINS-Pan-assay-interference structure

Table 8: Showing results of best hit ligands (from FDA approved drug library) for Machupo virus

S. No	ZINCID	Name	Binding energy score **(kcal/mol)**	Interactions
1	ZINC000052955754	Ergotamine	-10.7	Leu91Q,Tyr127R,Pro160R;Met158R*,Cys237Q*;**Tyr127R**
2	ZINC000003978005	Dihydroergotamine	-11	Met93Q,Tyr127R,Pro160R,Pro161R,Arg201Q;Met93Q*;**Tyr127R**
3	ZINC000066166864	Alectinib	-10	Leu91Q,Tyr127R,Pro160R,Arg201Q;**Tyr127R**
4	ZINC000003914596	Saquinavir	-10	Leu88Q,Tyr127R,Pro160R,Pro161R,Arg201Q;Pro89Q*,Leu91Q*,Met93Q*,Lys120R*,Leu157R*,Met158R*,Arg201Q*,Gly202Q*
5	ZINC000100013130	Midostaurin	-11.1	Leu88Q,Met93Q,Tyr127R,Pro161R;**Trp147Q**

Binding energy of best selected ligands by screening of FDA-approved drug library for Machupo virus is shown. Hydrophobic interactions shown in italics, Hydrogen bonds are marked with *and π-stacking are highlighted in bold.

Table 9: Showing properties of best selected ligands (from FDA-approved drugs) for Machupo virus

ZINCID	Molecularweight	Log P	Number of hydrogen **donor**	Number of hydrogen acceptor
ZINC000052955754	*581.66*	*2.26*	*3*	*6*
ZINC000003978005	*583.68*	*2.15*	*3*	*6*
ZINC000066166864	**482.62**	**4.33**	**1**	**4**
ZINC000003914596	670.84	2.87	5	*7*
ZINC000100013130	*570.64*	*4.11*	*1*	*4*

Physiochemical properties of above selected ligands are mentioned. Ligand following Lipinski's rule of five has been highlighted. Ligands showing minor variations in Lipinski's ruke of five (Molecular weight>500) have been italicised. LogP is logarithm of partition coefficient.

Table 10: Showing toxicity of best selected ligands (from FDA approved drug library) for Machupo virus

ZINCID	PAINS alert	Mutagenecity	Cytotoxicity	Carcinogenecity
ZINC000052955754	**0**	**No**	**No**	**Yes**
ZINC000003978005	0	No	No	No
ZINC000066166864	0	No	No	No
ZINC000003914596	0	No	No	No
ZINC000100013130	**0**	**No**	**Yes**	**No**

Ligands showing toxicity are highlighted. PAINS-Pan-assay-interference structure

Table 11: Showing results from screening of investigational drug library for Machupo virus

S. No	ZINCID	Name	Binding energy score (kcal/mol)	Interactions
1	ZINC000012358610	Phthalocyanine	-11.4	Leu88Q,Tyr127R,Pro160R,Leu199Q,Arg201Q;Lys120R*
2	ZINC000095608296	Unii-G9Z22EU5FK	-10.6	Lys120R,Tyr127R,Trp147Q,Pro160R,Pro161R,Leu163R,Asp184R,Ala185R,Phe200Q;Leu91Q*,Lys120R*,Ser125R*,Asn178R*;Leu199Q&
3	ZINC000043203371	MK-3207	-10.4	Leu88Q,leu91Q,Tyr127R,Phe200Q,Arg201Q;Ser125R*,Tyr127R*,Met158R*;Leu91Q&
4	ZINC000100341584	Setrobuvir	-10.2	Met93Q,Tyr127R,Pro161R,Phe200Q,Arg201Q;Leu91Q*,Lys120R*,Ser125R*
5	ZINC000059749972	Radotinib	-10.2	Met93Q,Met158R,Pro160R,Val187R,Phe200Q;Lys191R*

5 Best ligands after screening of investigational drug library with their binding energy score with target protein GP1 of Machupo virus are shown. Q, R is the chains of target protein structure. Hydrophobic interactions shown in italics, hydrogen bonds are marked with *and halogen interactions are marked with &.

Table 12: Showing properties of best ligands (from investigational drug library) for Machupo virus

ZINCID	Molecular weight	Number of hydrogen acceptors	Number of hydrogen donors	LogP
ZINC000012358610	*518.57*	*2*	*6*	*5.88*
ZINC000095608296	771.87	9	0	5.15
ZINC000043203371	*557.59*	*7*	*3*	*3.32*
ZINC000100341584	*560.62*	*8*	*3*	*2.3*
ZINC000059749972	*530.05*	*9*	*2*	*4*

Physiochemical properties of above selected ligands are mentioned. Ligands showing minor variations in Lipinski's rule of Five (Molecular weight>500) have been italicised. LogP is logarithm of partition coefficient.

Table 13: Showing toxicity of best selected ligands (from investigational drug library) for Machupo virus

ZINCID	PAINS alert	Mutagenecity	Cytotoxicity	Carcinogenecity
ZINC000012358610	**0**	**Yes**	**No**	**No**
ZINC000095608296	0	No	No	No
ZINC000043203371	0	No	No	No
ZINC000100341584	0	No	No	No
ZINC000059749972	**0**	**No**	**No**	**Yes**

Ligands showing toxicity are highlighted. PAINS-Pan-assay-interference structure

Table 14: Summarizing the results

PDBID (Target structure)	Best Ligand	Binding energy **Kcal/mol**	Molecular weight	LogP	Interactions
5W1K (Junin virus)	MK-3207 (ZINC000043203371)	-8.6	*557.59*	*3.32*	Lys137J,Phe173J,Pro219J;Ser107J*,Lys137J*,Ser138J*,Gln141J*
5W1M (Machupo virus)	Dihydroergotamine (ZINC000003978005)	-11	*583.68*	*2.15*	Met93Q,Tyr127R,Pro160R,Pro161R,Arg201Q;Met93Q*;**Tyr127R**

MK-3207 and Dihydroergotamine selected as potent drugs for Junin and Machupo virus and can be considered for further studies.

Results & Discussion:

Molecular docking of all ligands was performed separately within active site of target structure of Junin virus (5W1K) **(Figure 1)** and Machupo virus (5W1M) **(Figure 2)**. Active site of 5W1K (Junin virus) target structure was selected by defining grid box dimensions as centre_X=-37.414, centre_Y=-0.048, centre_Z=-85.385; size_x=126, size_y=126, size_z=126 and similarly active site of 5W1M (Machupo virus) target structure was selected by defining grid dimensions as center_X=75.663, center_Y=222.274, center_Z=221.976; size_x=126, size_y=104, size_z=126 in AutoDock Vina software. Binding energy score of each ligand was computed with both target structures separately showing best scored ligands from FDA approved drugs library **(Table 2, 8)** and from investigational drug library **(Table 5, 11)**. Interactions of ligand with target structures were visualized in Pymol visualization tool **[30]** as shown in **Figure 3 and 4**. Physiochemical properties based on Lipinski's Rule of Five **[31]** which includes the following criteria that Molecular weight must be less than 500, Number of hydrogen-bond donors less than 5, Number of hydrogen bond acceptors less than 10 and Log P value must be less than 5 were computed for best scored ligands. These properties help in evaluation of drug-likeliness of ligand structures **[32]**.

Analysis of best hit ligands from FDA-approved drug library **(Table 2) [33]** and from investigational-drug library **(Table 5)** for Junin virus showed that only compound ZINC000011679756 with docking score of -8.4kcal/mol **(Table 3)** follow the Lipinski's rule of five **(Table 3 and 6)**.However, ligands showing mild variations in physiochemical properties **(Table 3 and 6)** yet can also be considered as modifications in physiochemical properties is also one of the techniques to increase the bioavailability of drug **[34, 35]**. Further, *in silico* evaluation of toxic parameters **[36, 34]** was also performed on best selected ligands and compounds active for toxic parameters were not considered further **(Table 4 and 7)**. One of the other parameter Pan-assay interference structures (PAINS), that include fluorescence of small molecules, redox reactivity and covalent modifications of target protein was also evaluated. Only one ligand compound ZINC000011679756 was predicted to possess PAINS value 1 **(Table 4 and 7)** and was not considered further. Thorough analysis of interaction, physiochemical properties and toxicity predicts ligand with Zinc ID ZINC000043203371 (MK-3207) **[37]** and docking score -8.6kcal/mol **[38]** as safe and best candidate for further studies against GP1 protein of Junin virus(Table5,6 and7).This predicts MK-3207 as potent inhibitor for Glycoprotein of Junin virus**(Table 14) [39]**. Similarly, extensive analysis of physiochemical properties of best docked ligands for Machupo virus was also done which predicts only compound ZINC000066166864 with docking score of -10kcal/mol **(Table 8)** has drug-likeliness according to Lipinski's rule of Five **(Table 9)**. Other ligands showing mild variations in physiochemical properties **(Table 9 and 12)** can also be considered as potent drugs. Ligands showing violations in more than 2 rules are considered to be of low solubility or permeability and cannot be preceded further **[40, 41]**. Toxicity parameters was also analysed to eradicate toxic compounds **(Table 10 and 13)**. Thorough

analysis of physiochemical properties and toxicity predicts ZINC000003978005 (Dihydroergotamine) **[42]** with docking score -11kcal/mol as safe and best candidate for further *in vitro and in vivo studies* to predict it as potent drug for GP1 protein of Machupo virus **(Table 14)**.

Conclusion:

We report MK-3207 and Dihydroergotamine with optimal binding features as potent inhibitors of glycoprotein in Junin and Machupo viruses and can be considered further for validation.

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