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Discovery of Potential SARS-CoV-2N Protein Inhibitors by Docking-Based Virtual Screening

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Abstract: ***The SARS-CoV-2 is a highly infectious, novel strain of the corona virus family that is responsible for the 2020 Covid-19 pandemic. Members of the family Corona viridae have been known to cause a broad spectrum of animal and human diseases but they did not garner much interest owing to the mild nature of the respiratory disorders. But post 2003, the emergence of SARS-CoV, the more recent MERS-CoV and undoubtedly the outbreak of SARS-CoV-2 has established significant cause for the family to be considered a threat to public health. In this study, we attempted to discover potential drug candidates against a specific constituent protein, the nucleocapsid (N) protein, of SARS-CoV-2. The target protein was virtually screened in multiple stages against a library of ligands compiled from the ZINC database, and the selected potential drug candidates were further filtered based on their ADMET profiles.***

Keywords: SARS-CoV-2, Nucleocapsid Protein, Virtual Screening

1. Introduction

SARS-CoV-2 is a positive-sense, single-stranded RNA virus that is contagious in humans, and can be considered the successor of SARS-CoV, which was responsible for the 2002-2004 SARS outbreak. Like other members of the corona virus family, SARS-CoV-2 has conserved structural proteins: the trimeric spike glycoprotein S, small envelope protein E, matrix protein M and nucleocapsid protein N. These proteins have served as the primary targets for the development of potential drugs against this highly infectious and deadly virus but due to the high frequency of mutations (especially in S) as well as the sudden nature of the outbreak, it is proving difficult to synthesize anti-SARS-CoV-2 pharmaceuticals.

The nucleocapsid protein N interacts with the viral genome and forms aribonucleo protein core and it is known that this core has major roles in the subsequent synthesis of viral RNA, the transcription of genomic RNA and the translation of viral proteins. Due to the role it plays in the life cycle of the virus, it thus has the potential to be a very effective target for possible drug candidates that inhibit the N protein-RNA interactions.

As indicated above, coronavirus N protein has a multifunctional RNA-binding protein**,** which is considered to be an interesting pharmacological target that merits further attention due to its critical function in viral RNA transcription and replication. Two highly conserved domains, namely, an N-terminal RNA-binding domain and a C-terminal dimerization domain is present in this major CoV protein, together with a disordered central Ser/Arg-rich linker. As obtained from previous studies it has been revealed that the N-terminal domain is responsible for RNA binding, the C-terminal for oligomerization, and the Ser/Arg-rich linker for primary phosphorylation. The crystal structure of SARS-CoV-2 nucleocapsid N-terminal domain has been solved, showing an overall similarity with the same domain from other corona viruses, although the surface electrostatic potential showed a specific distribution. Significant stimulation for the drug discovery of ligands focused on this appealing target will be paved by these structural findings to block corona virus replication and transcription. The success in the development of compounds that interfere with N proteins of other corona viruses, such as the recent discovery of stabilizers of the protein–protein interaction of MERS-CoV N protein, reinforces the potential of the N protein as druggable target for SARS-CoV-2 infection. So quite arguably, the N protein is highly immunogenic and is now being looked up as a potential vaccine target and for the development of COVID-19 diagnostic methods**. [1]**

About SARS-CoV-2

The Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV-2) belongs to the enveloped positive-sense RNA viruses. A sample isolation from pneumonia patients who were some of the workers in the Wuhan seafood market found that strains of SARS-CoV-2 had a length of 29.9kb (F. Wu et al., 2020) [**16]** Structurally, SARS-CoV-2 has four main structural proteins including spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M) glycoprotein, and nucleocapsid (N) protein, and also several accessory proteins (Jiang et al., 2020) [**12]**.

2. Materials & Methods

Structure retrieval and analysis of binding sites of SARS-CoV-2N Protein

The crystal structure of the RNA-binding domain of nucleocapsid phosphoprotein of SARS-CoV-2 (monoclinic crystal form) was retrieved from the RCSB PDB Portal – PDB ID 6WKP. The structure obtained had 4 chains forming a homo-tetramer structure, represented by 1sequence-uniqueentityof173aminoacids. SWISS-PDB DeepView (Guex & Peitsch, 1997) [**9]** software was used to predict any missing or incomplete residues in the structure, followed by ligand binding site prediction and conservation analysis by PrankWeb (P2Rank) server (Jendele et al., 2019) [**11]** PrankWeb provides an interface to P2Rank, which is a

template-free machine learning method based on the prediction of local chemical neighbourhood ligand ability centred on points placed on a solvent-accessible protein surface. The predicted ligand sites and residues were cross-referenced with ligand interaction data from RCSBPDB.

Virtual screening using RPBSMTi Open Screen webserver

In recent years, as the computational approach to drug design has gained momentum, researchers have designed several robust docking software with highly efficient algorithms capable of depicting binding interactions with high accuracy. AutoDock Vina (Trott & Olson, 2009) [**15]**is one such popular and widely used free, open source docking software. These programs all require offline installation and even though are they are efficient in their own right, they significantly increase the time required to screen a large library of compounds against a single target due to the iron e-ligand-one-run methodology. To overcome this obstacle, we have used the MTi Open Screen online virtual screening server available through the RPBS Web Portal. The MTi Open Screen server searches for ligands within an incorporated database with user-specified molecular properties for filtering compounds and docks them one by one against the query protein, utilizing AutoDock Vina's algorithm (number of binding modes 10 and exhaustiveness 8). The list of active site residues was provided as per the predictions obtained from PrankWeb server, following which the server automatically calculated the grid dimensions and centre. The scoring function used by the server is based on the empirical scoring function used by Vina that approximates the binding affinity in kcal/mol. The server (MTiOpenScreen) provides 5 incorporated drug-like chemical libraries, out of which we selected Drug-lib, which is a collection of purchasable and approved drugs. This library was built on a protocol that includes the use of FAF-Drugs 4 physico-chemical and toxicophore filtering, visual inspection to remove compounds not suitable for docking and assessment of their purchase ability according to the ZINC15 database. The "drugs" subset of ChEMBL, the "approved" subset of Drug Bank (5.0.10), the Drug Central online compendium and the "approved" Super Drug 2 database (2.0) were the starting points for construction of the Drug-lib library and currently consists of 7173 stereo isomers corresponding to 4574 single isomer drugs. MTi Open Screen also provides the user with the option of using additional filters that can be applied onto the selected library, where we selected "lead-like", so that the small molecules in the library would satisfy Lipinski's rules (Lipinski, 2004) [**13]**. A set of ~1500 compounds was obtained as output. Amongst all the 1500 predicted compounds, the top 90 (3 sets of 30 each) were selected by each member for further analysis on the basis of better molecular interactions and better MTiOpen Screen binding scores.

Subsequent virtual screening using PyRx

The 3D structures of the top 30 compounds selected from the MTiOpenScreen results were obtained from the ZINC15 database using their respective ZINC IDs. OpenBabel (Boyle et al., 2011) [3] was used to prepare and compile the 30 compounds into a single ligand library. PyRx software (Dallakyan & Olson, 2014) [6] was used to virtually screen the newly prepared library against the N protein to further filter the results and obtain potential drug candidates with the best binding scores. PyRx utilizes AutoDock Vina's algorithm to perform the screening and the parameters can be manually set. To set the grid dimensions and centre, first the active site residues were selected and highlighted on the N protein molecule. Once the active site residues were clearly marked, a generalized grid was generated and manually positioned over the binding pockets with the active site residues already highlighted. The exhaustiveness was set to 8 in the Vina wizard tab and the screening was initiated, after both the molecule and the ligand library were adequately prepared through in-built PyRx modules. The top 3 compounds with the highest binding affinity scores were selected for further analysis.

Druggability and toxicity analysis

The top three compounds were subjected to absorption, distribution, metabolism, excretion and toxicity (ADMET) studies. pkCSM online server (Pires et al., 2015) [**14]** and SWISS-ADME (Daina et al., 2017) [**5]** were used to screen the compounds for drug-likeness and toxicity and LAZAR server (Maunz et. al., 2013) was used to predict the carcinogenicity of the compounds.

Analysis of binding poses and ligand interactions

PyMOL (PyMOL Molecular Graphics System, Version 2.3.4 Schrödinger, LLC) was used to visualize the binding interactions of the highest scoring ligands initially. To generate 2D images of the ligand interactions, as well as view the binding interactions at a higher level of manoeuvrability, BIOVIA Discovery Studio (Dassault Systèmes BIOVIA, Discovery Studiov 20.1.0.19295, San Diego: Dassault Systèmes, 2020) was used.

Hardware

All the *in-silico* analysis protocols have been carried out using freely licensed software and online servers. For any offline simulation studies, an MSI GV62VR 7RF laptop with an i77700HQ 2.8 GHz processor, 1TB HDD & 128 GB SSD, 16GB DDR5 RAM and Nvidia GTX10606 GB VRAM was used.

3. Results

From the first set of thirty compounds selected from the MTi Open Screen results, R428 (ZINC000051951668) and Mk3207 (ZINC000103760984) showed the best binding scores (-10.5kcal/ mol and-10.3kcal/ mol respectively) for both predicted binding pockets of the SARS-CoV-2N protein. The ADMET analysis of these two compounds showed them have a moderate volume of distribution and to be in violation of Lipinski's rules by a small margin, perhaps not enough to completely renounce the possibility of their efficacy as potential drug candidates. It also demonstrated that either the compounds are not mutagenic or toxic (according to the Ames Test parameter of pkCSM) but have the potential to be hepatotoxic. The 2D interaction maps of both the compounds are shown (Figures 1-2).

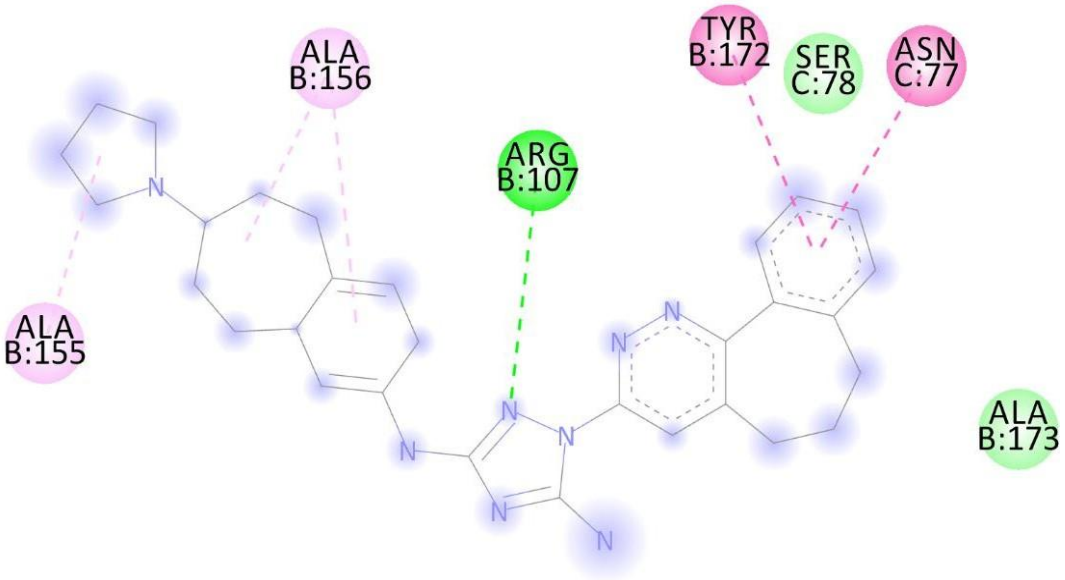

Figure 1 (a): R428 Ligand Interactions (the active site residues interacting with the ligands are shown, with the corresponding chain and residue number mentioned)

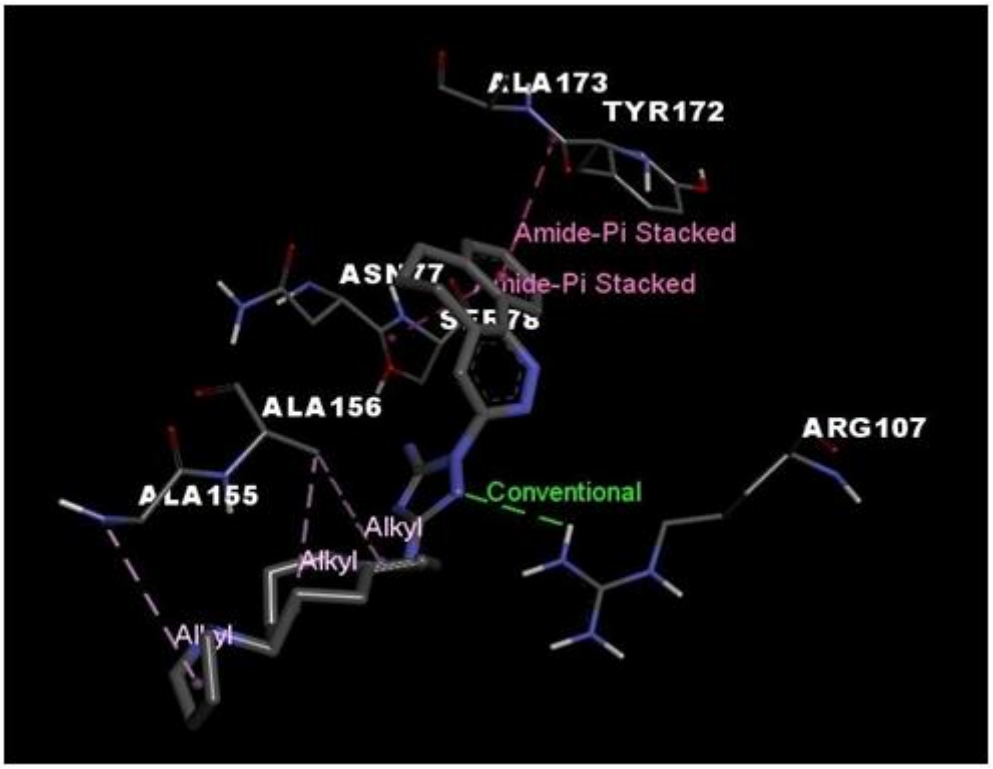

Figure 1 (b): R428 receptor-ligand interactions with labeled residues and nature of interaction

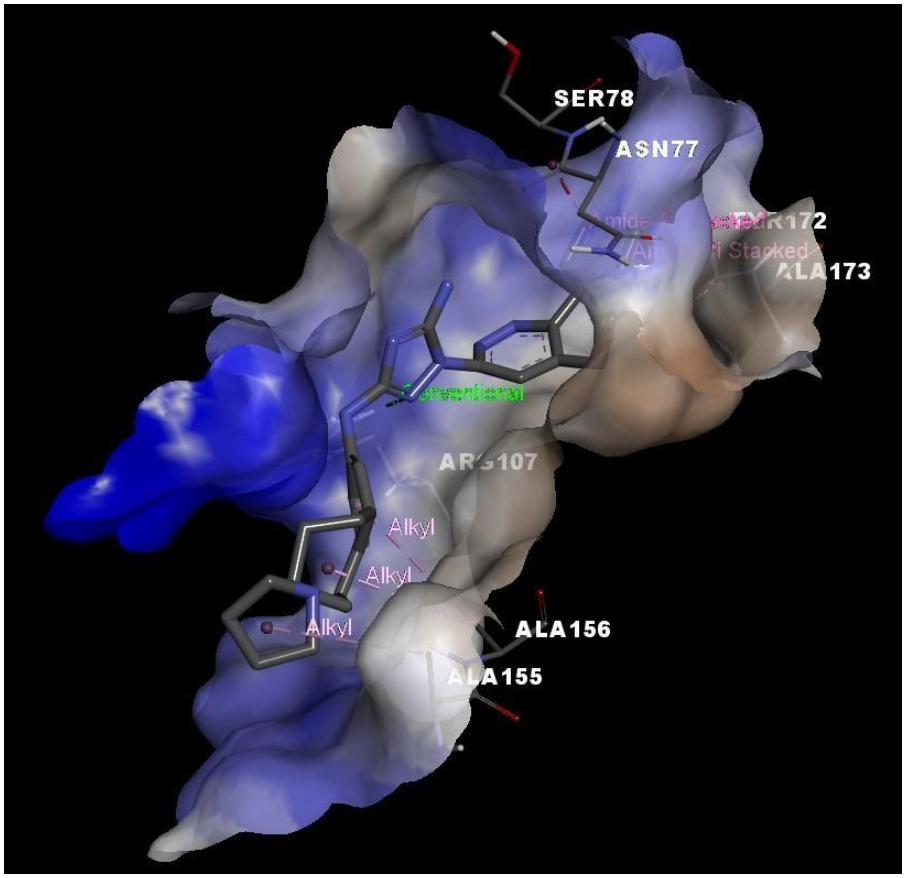

Figure 1 (c): R428 receptor-ligand interactions with labelled residues and nature of interaction, showing binding pocket

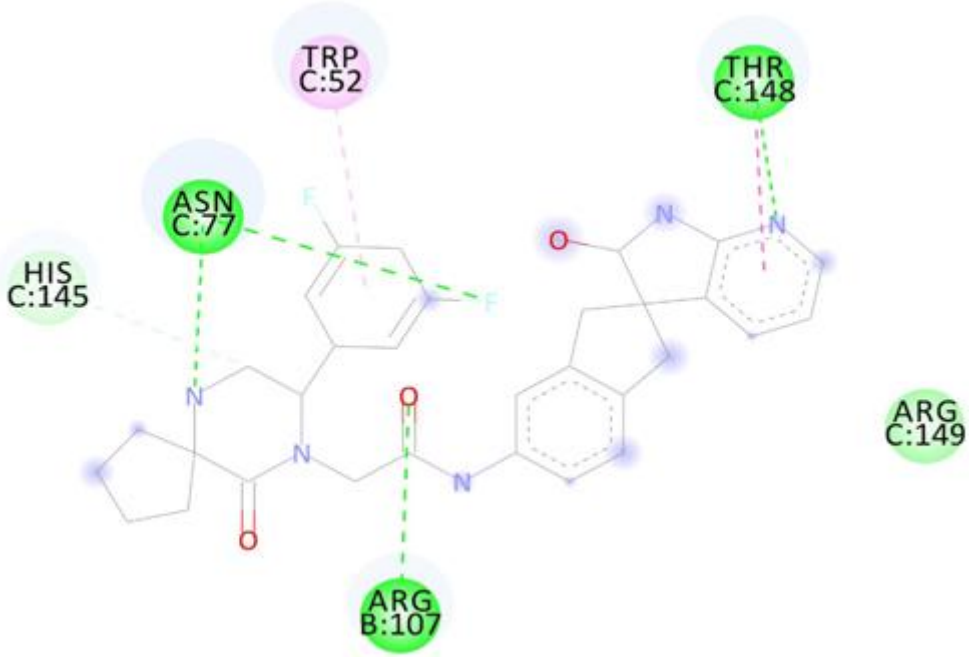

Figure 2 (a): Mk3207 ligand interactions (the active site residues interacting with the ligands are shown, with the corresponding chain and residue number mentioned)

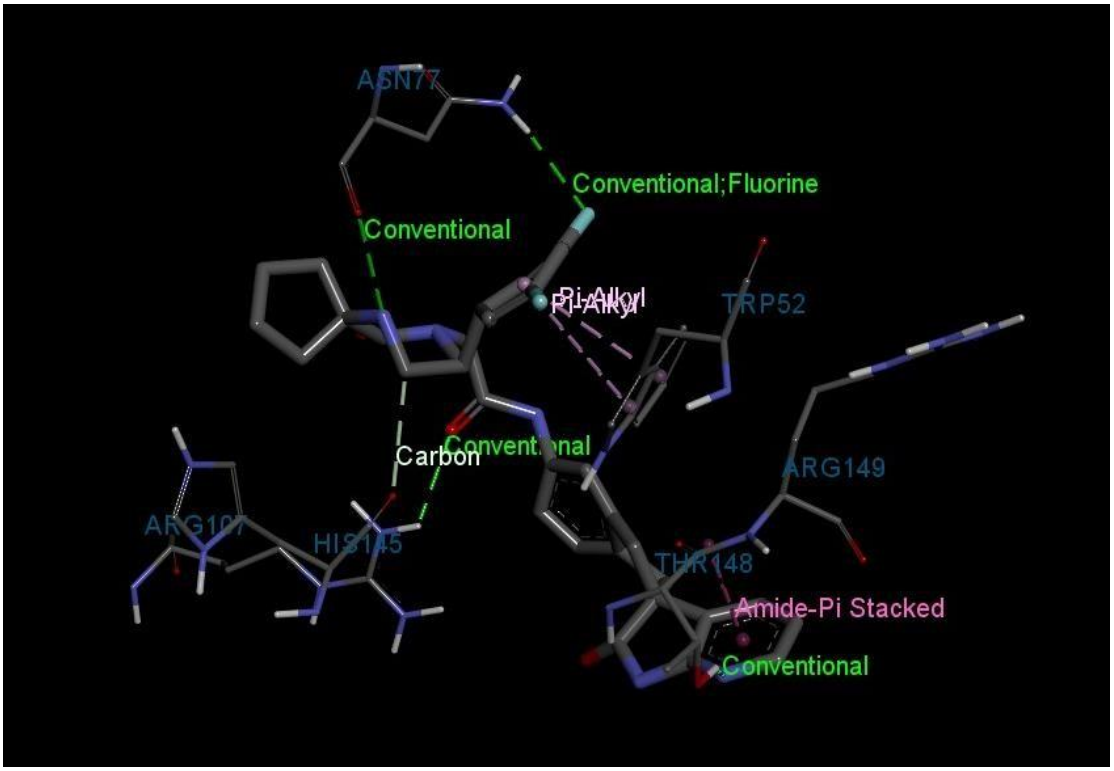

Figure 2 (b): Mk3207 receptor-ligand interactions, with labeled target residues and nature of interaction

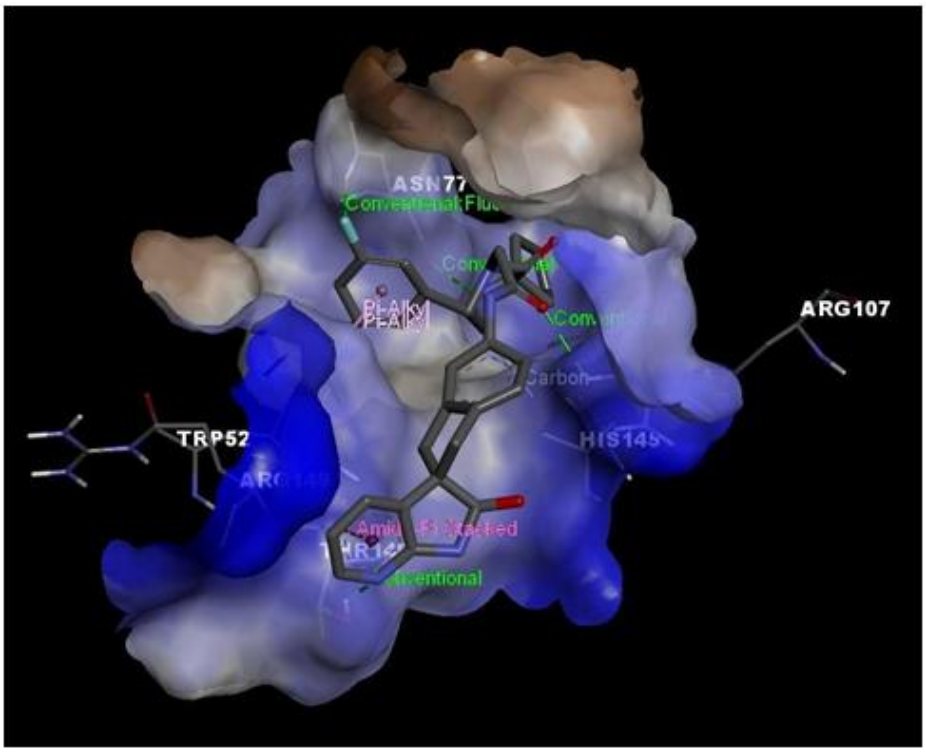

Figure 2 (c): Mk3207 receptor-ligand interactions with labelled target residues and nature of interaction, showing the binding pocket

Table 1: ADMET Properties of Ligands of Set I.

Ligand	VDss (logL/kg)	BBB Permeability	Intestinal Absorption (Human)	Caco2 Permeability (logPappin 10-6cm/s)	RatLD50 (mol/kg)	AMES Toxicity
R428	0.913	-1.031	100%	1.533	3.147	No
Mk2307	0.719	-0.795	94.673%	1.533	2.701	No
DHEC	1.529	-0.755	77.1%	0.904	2.861	No
Metergotamine	0.975	-0.496	72.588%	1.029	3.461	No
Elbasvir	0.123	-2.089	74.024%	0.299	2.482	No

It is clear from the ADMET parameters mentioned above that both of the ligands have poor blood-brain barrier permeability (log BB<-0.1 is considered to be extremely poor) but show exceptionally well absorption characteristics. Most of the candidates show a good Caco2 permeability and intestinal absorption score, without extremely high levels of toxicity.

Despite a remarkably strong binding affinity, R428 binding interactions are limited to just 1 conventional hydrogen bond at Arg A107, the others being van der Waals interactions and alkylorpi-amide interactions with residues that are not explicitly part of our predicted binding sites (Ala A155, Ala A156, Tyr B172, Ala B173, Asn C77 and Ser C78). Mk3207 binds with 3 conventional hydrogen bonds at Arg A107 (like R428), Thr C148 and Asn C77 (a site of interaction for R428 as well, if not the same type). ThrC148 participates in an amide-pi stacked interaction in addition to the hydrogen bond. The other residues of the target protein involved in the binding interactions include His C145, forming a carbon-hydrogen bond, Trp C52 involved in a pi-alkyl interaction and Arg C149 participating in a conventional van der Waals interaction.

Out of a list of the top 5 ligands with highest binding affinity, the first 2 are mentioned above. The other 3 are dihydroergocristine (ZINC000003995616), metergotamine (ZINC000072266819) and elbasvir (ZINC000150588351). They have shown a binding affinity of-9.7 kcal/mol,-9.6 kcal/mol and -9.6 kcal/mol respectively.

Of these 3, elbasvir is an approved antiviral drug that has been used to treat chronic hepatitis C caused by HCV. From comparing the ligand-interaction map of elbasvir given in Fig. 3 with the maps of the top 2 ligands mentioned earlier, it is evidently visible that elbasvir is involved in a greater variety of interactions than both R428 and Mk3207. Apart from the 2 standard hydrogen bonds at Ala B55 and Ala B155, it forms 4 carbon-hydrogen bonds at Ala B55, AsnC77, ILEC146 and LeuB159. O the interactions involve pi-pi stacked interactions at TrpC52, pi-alkyl interactions at Ala B155, Ala B156 and pi-sigma interaction at Thr B54. A point to note here would be that a majority of these residues involved in the interaction of elbasvir and our target protein are part of the predicted binding sites.

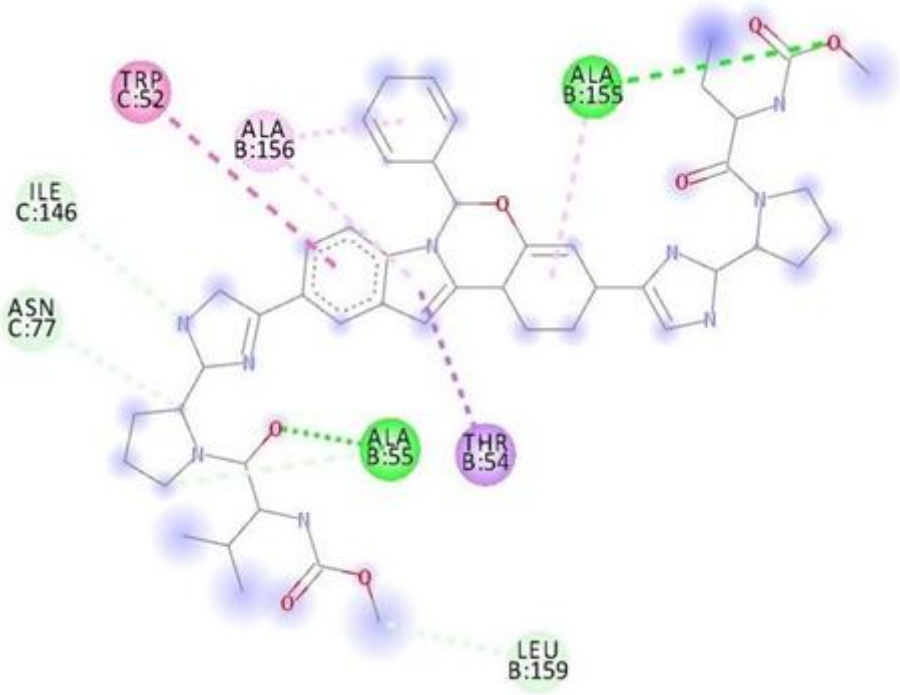

Figure 3 (a): Elbasvir ligand interactions (the active site residues interacting with the ligands are shown, with the corresponding chain and residue number mentioned)

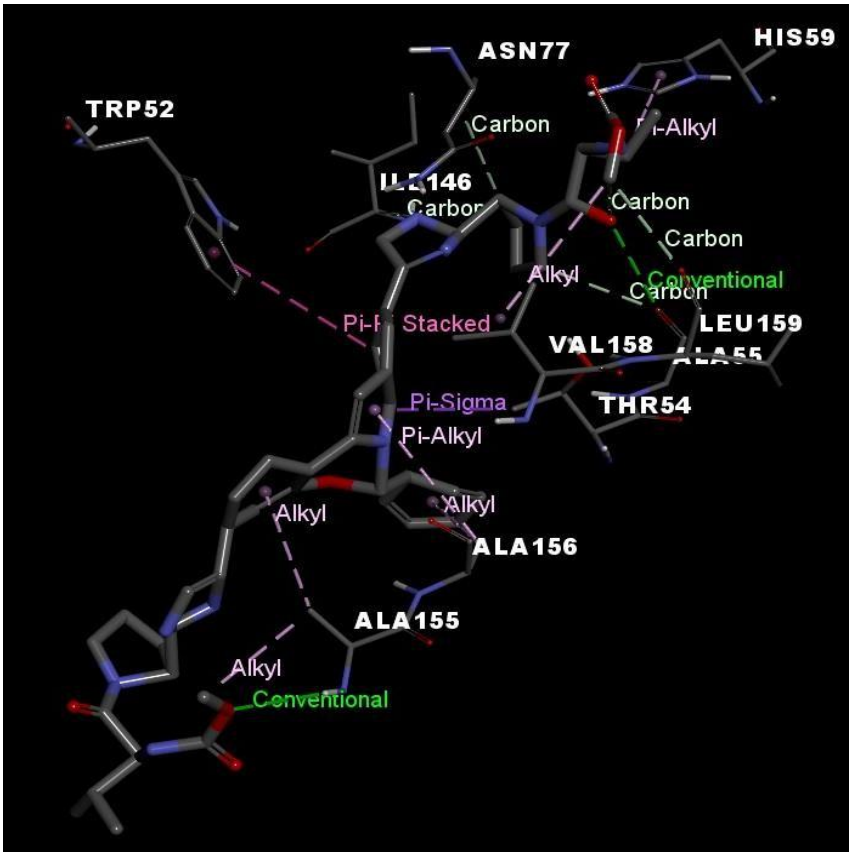

Figure 3 (b): Elbasvir receptor-ligand interactions, with labelled target residues and nature of interaction

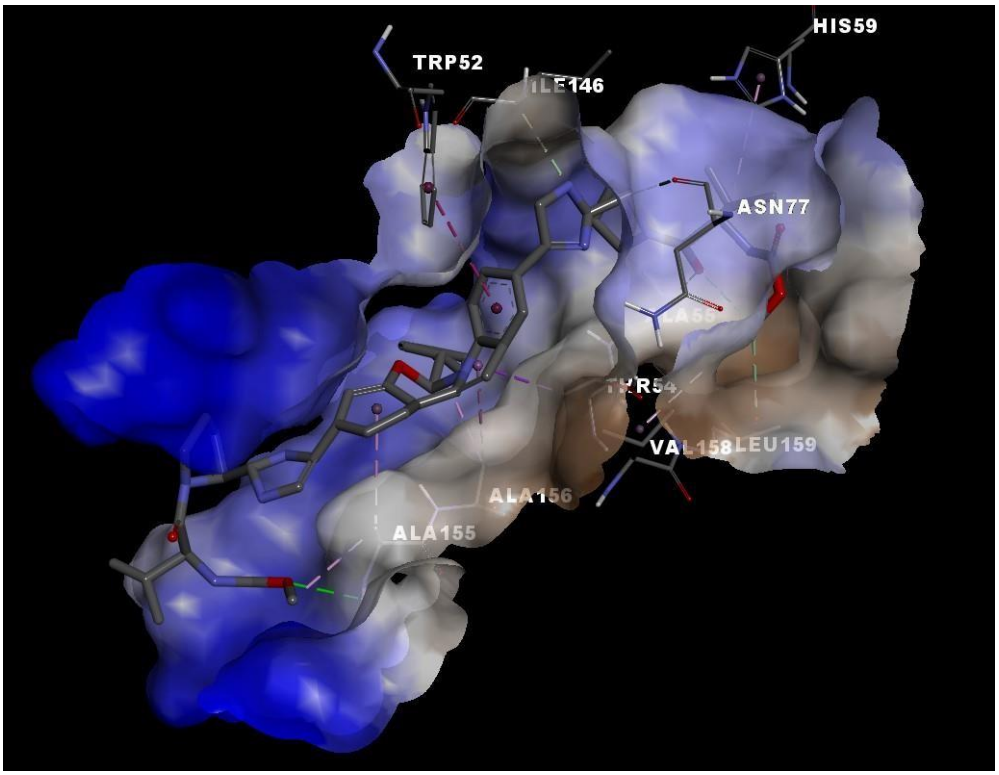

Figure 3 (b): Elbasvir receptor-ligand interactions, with labelled target residues and nature of interaction, showing binding pocket.

From the second set of MTi Open Screen results (*Ligands 31-62*) top 5 results of PyRx screening were selected.

Among those 5 compounds, 4 compounds, Netoglitazone (PubChemCID204109), Liafensine (PubChemCID58212050), Tixadil (PubChemCID178145), Mavatrep (PubChemCID17751090) were found to be carcinogenic even in small doses. Lycorine (PubChem CID72378) which is an indolizidine alkaloid was also found to be toxic.

Among the top 5 results of PyRx screening of the third set of

compounds, Zoliflodacin (PubChemCID76685216), Pf-00446687 (PubChemCID11328898), Capripramine (PubChemCID2580), Etoposide Phosphate (PubChemCID6918092) and Xaliproden (PubChem CID 128919) were obtained. Among them, Xaliproden turned out carcinogenic as it failed AMES toxicity test.

Table 2: ADMET Properties of Ligands of Set III

Ligand	Blood-brain barrier	Intestinal absorption (Humans)	CaCO2 permeability (logPappin10-6cm/s)	Toxicity (LD50) (mol/kg)	Carcinogenicity (AMESToxicity)
Zoliflodacin	0.10	81.19	0.56	2.99	Not Carcinogenic
Carpipramine	0.84	97.37	1.128	2.77	Not Carcinogenic
Xaliproden	0.85	89.92	1.077	2.71	Carcinogenic
Pf-00446687	0.66	92.14	1.346	2.66	Not Carcinogenic
Montelukast	0.55	93.59	0.028	2.65	Not Carcinogenic
Etoposide Phosphate	0.005	91.3	0.255	2.95	Not Carcinogenic

Whereas Carpipramine and Etoposide Phosphate and Zoliflodacin didn't show any toxicity/carcinogenicity other than being hepatotoxic to a controllable level.

Zoliflodacin and Carpipramine inspite of having the best binding affinities (-10.7kcal/mol and-9.9kcal/mol respectively) they don't bind to our desired active residues extensively, as is evident from their 2D Ligand interaction maps prepared with the help of BIOVIA Discovery Studio Visualizer.

For Carpipramine the only bonded residues were Threonine B54and TryptophanC52. Same is the case with Zoliflodacin as well, with the binding residues being AsparagineC75, AlanineB55 and ThreonineB57, none of which are our active residues except Asparagine C75.

Other than the top 5 or top 10 PyRx results we chose to test the toxicity of the first 20compounds of which one, namely Montelukast (*PubChem CID 5281040*), was shown to bind perfectly to most of our desired active residues (obtained from PrankWeb) of our homotetramer protein. The residues were Threonine B54, TryptophanC52, AsparagineC75, Asparagine C77, SerineC 78, Isoleucine C146, Isoleucine C 157 and Valine B 158.

Montelukast passed the other toxicity tests, namely AMES (for carcinogenicity) as well as the OralRat Acute Toxicity (LD50) test as already mentioned in the table.

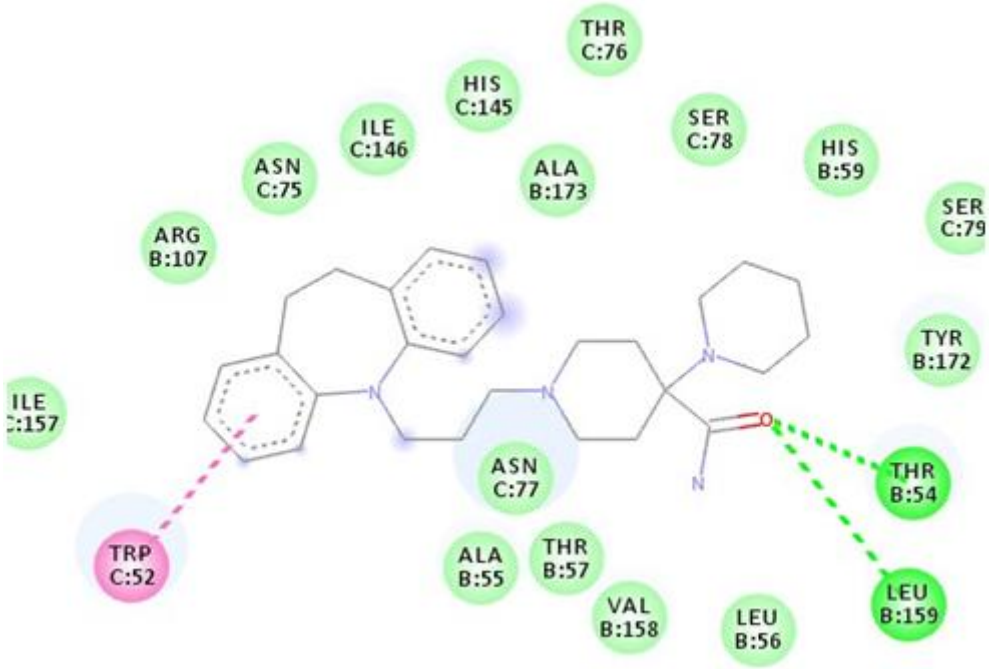

Figure 4: 2D interaction map of Carpipramine (PubChem CID 2580) with its best energy conformation uff_E=586.34 obtained from PyRx

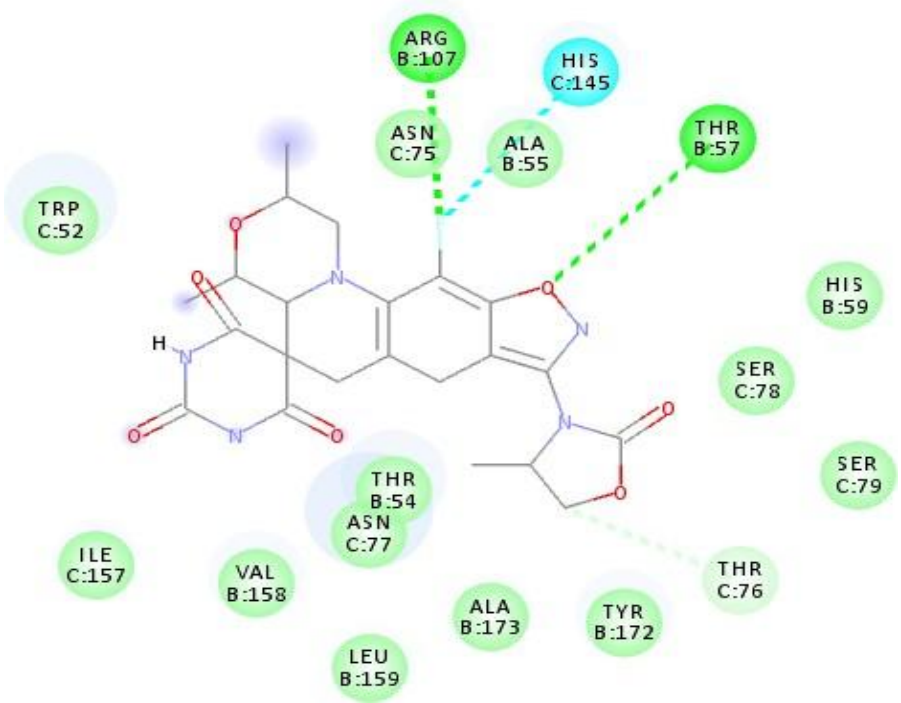

Figure 5: 2D interaction map of Zoliflodacin (PubChemCID76685216) with its best energy conformation uff_E=856.57 obtained from PyRx

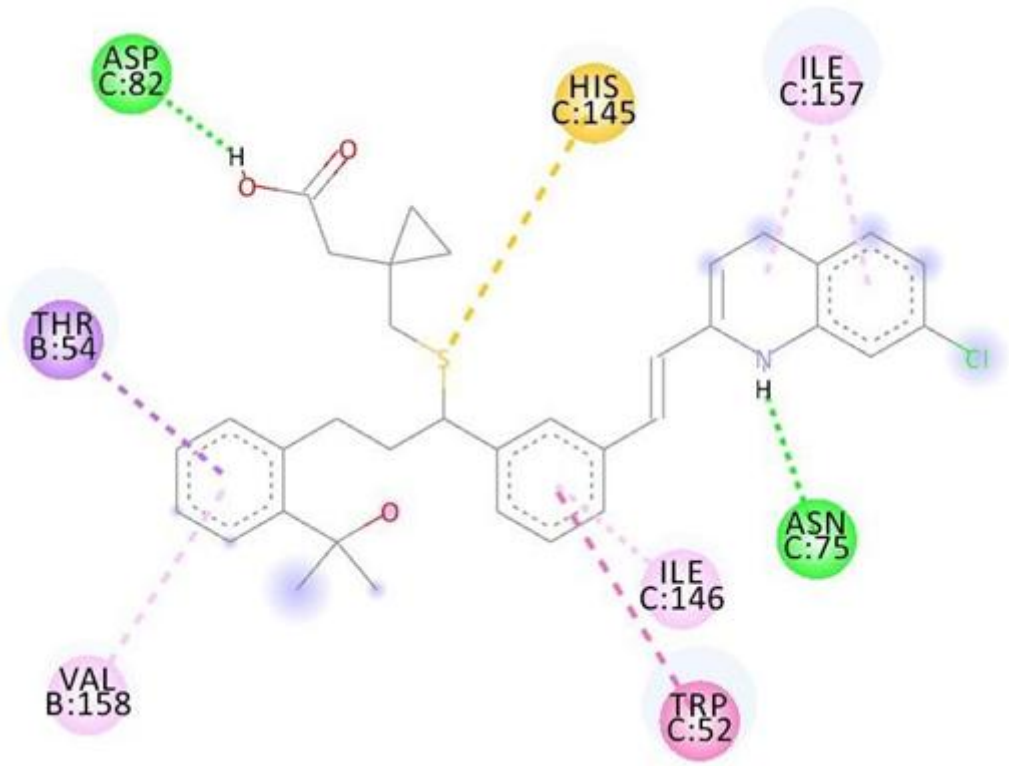

Figure 6 (a): 2D Interaction map of Montelukast (PubChem CID 5281040) with its best energy conformation uff_E=1732.46 obtained from PyRx

(*Types of Bond Interactions chart)*

As we can already note the difference in case of Montelukast, where we can find different interactions other than the Conventional Hydrogen Bond or the Van der Waals' interaction. Here we can note the Pi-sigma

interaction with Threonine B 54, Pi-Pi T-shaped interaction with Tryptophan C 52, Alkyl or Pi-Alkyl interactions with Isoleucine C 146 or Isoleucine C157 respectively, giving rise to an overall binding affinity of-8.7 kcal/mol which is quite a stubborn figure as far as its credibility is concerned.

We also have worked out the 3D interaction map for the same conformer (uff_E=1732.46) keeping in mind every possible source of interaction of our ligand and our target protein. As we can see from the results, for Montelukast there are some violations for Lipinski's rule, as far as its molecular weight and other related descriptors are concerned, but other than that, it's quite a formidable drug satisfying our other necessary parameters as mentioned.

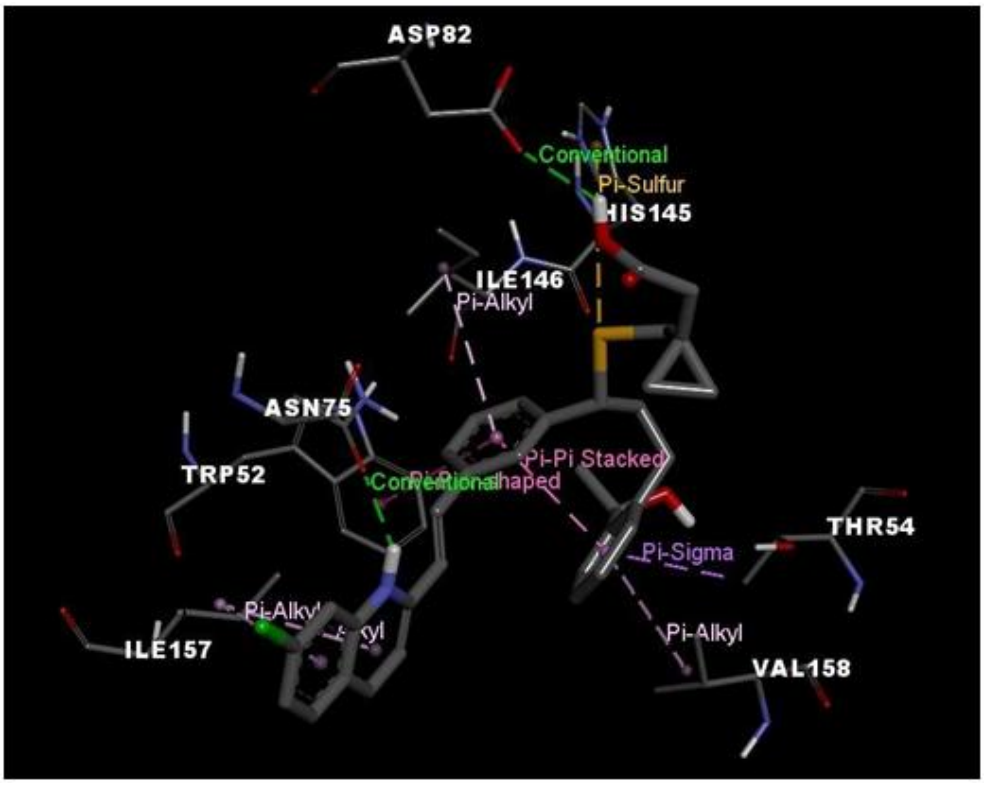

Figure 6 (b): 3D mapping of Montelukast (PubChemCID5281040) binding to the active site residues

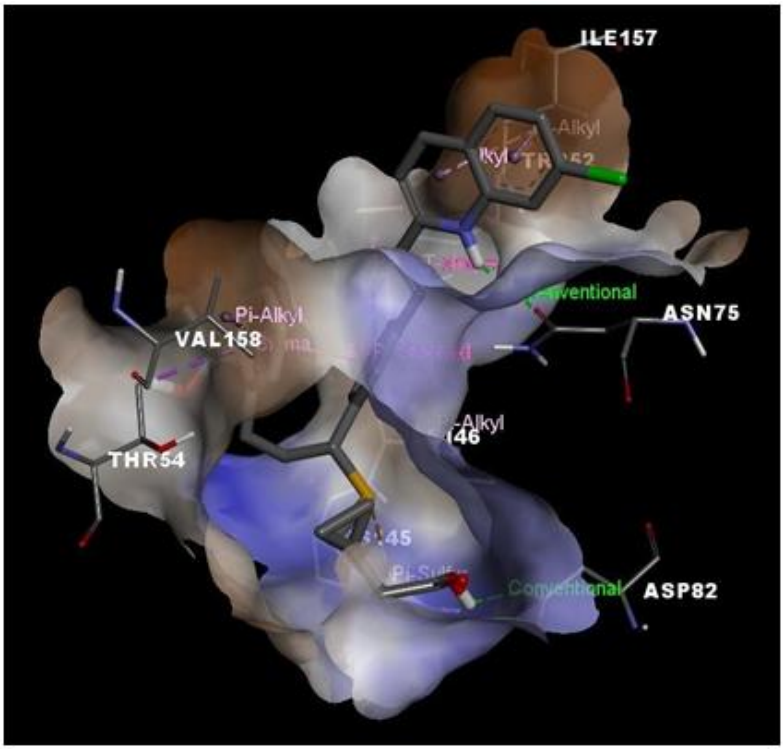

Figure 6 (b): 3D mapping of Montelukast (PubChemCID 5281040) binding to the active site residues, with labels and the binding pocket shown

4. Discussion & Future Prospects

Though not directly involved in antiviral activities, R428, with the strongest binding capacity in this study, is a tentative drug that is being investigated for therapeutic activity against a variety of cancers (non-small cell lung cancer (Felip et al., 2019) [**7]** metastatic breast cancer and adeno carcinomas, to name a few) in a formulation known as bemcentinib. Similarly, Mk3207 has been investigated for treatment against migraines as a calcitonin gene-related peptide (CGRP) antagonist (Hewitt et al., 2011) [**10]**. Metergotamine, anotherofthetop5ligandsof set 1 in the study, has also been studied as a potential anti-migraine agent, along with other molecules. Dihydroergocristine is part of the "ergoloid" mixture of products, with non-competitive antagonistic activity against serotonin receptors and partial agonist / antagonist activity against dopaminergic and adrenergic receptors; DHEC is a drug that increases cerebral blood flow and the oxygen consumption of the brain (Coppi, 1992) [4].

As mentioned earlier, elbasvir is a known antiviral agent that is used in combination therapy for chronic hepatitis C, caused by hepatitis C virus (HCV). It has shown a robust binding affinity for the predicted binding site of our target protein, if not the highest. Moreover, elbasvir has also shown stable and preferential binding interactions with RNA-dependent RNA polymerase, papain-like protease and helicase of SARS-CoV-2 (Balasubramaniam & Reis, 2020) [2]; our study has added another molecule to that list.

It is evident that the compounds we shortlisted from the third set, after screening by PyRx and ADMET tests and after subsequent analysis by PyMOL and BIOVIA, of them Montelukast (ZINC000003831151 & PubChemCID5281040) has cleared the credibility tests on almost all query parameters. It may serve as a possible drug candidate which binds to the active residues of the RNA binding domain of SARS-CoV2 Nucleocapsid protein as found out in our research. On the other hand, if we do a bit of groundwork, we can find that Montelukast is used commercially for preventing breathing difficulties, chest tightness and even dry coughs for asthma. The most important cause of COVID-19 related deaths is respiratory failure, which is progressive and unresponsive to treatment. ARDS (Acute Respiratory Distress Syndrome), which frequently occurs in these patients, is an acute inflammatory lung injury, a clinical condition that is not well understood due to its complex pathogenesis, and is a result of wide spread alveolar injury caused by intense inflammation. Montelukast is a potent cysteinylleukotriene (cysLT) receptor antagonist with anti-inflammatory effects and has been proven to significantly suppress oxidative stress (Fidan & Aydoğdu, 2020) [**8]**. It is thereby thought that Montelukast may have a limiting effect on the progression of the COVID-19 infection.

5. Conclusion

We can infer that these ligands have the potential to be therapeutically relevant when it comes to drug development and the fact that they have displayed such high scores in the docking study performed here goes to show that perhaps with some repurposing, these molecules could be transformed or formulated into drugs or drug mixtures (for example, Elbasviris generally used with Grazoprevir, a mixture that might aid in its predicted action against SARS-CoV-2) that might help in the fight against Covid-19 in the long run. Similar is the case for Montelukast, which our research has shown to be a worthy selection and can be effective individually or in combination with some other drugs. With further clinical trials, this can prove quite effective in preventing COVID-19 infections.

Acknowledgements

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The contributions of the respected authors are as follows:

- Designed Research/ Study: Dr. Nandan Kumar Jana
- Performed Research/ Study: Debarshee Sengupta & Arghyadip Bose
- Collection & Analyzation of Data: Debarshee Sengupta, ArghyadipBose and Tilottama Dasgupta

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