Alternatives to Remdesivir: Drug repurposing for inhibition of SARSCoV2 RNA dependent RNA polymerase

Kumar Sharp (ksharp0016@gmail.com)
Government Medical College and Hospital, Jalgaon https://orcid.org/0000-0002-5034-8326

Research Article

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Abstract

Even after more than a year of the beginning of COVID-19 pandemic, a specific treatment for the disease has not been discovered. Vaccination programmes are being rolled out as the fastest pace possible but achievement of herd immunity will take time.[1] Many drugs like favipiravir, remdesivir and tocilizumab are being used for the treatment of this disease but reports published by the World Health Organization and the New England Journal of Medicine shows that they do not produce any significant clinical results. In this study, by molecular docking a large set of drugs has been used to replace remdesivir in RdRp protein so that they can produce the same action and therefore provide suitable alternatives for clinical trials and emergency use. The drugs identified in the study are saquinavir, cefoperazone, gliquidone, nelfinavir, 5-methyltetrahyrofolate among various others.

Introduction

Even after more than a year of the beginning of COVID-19 pandemic, a specific treatment for the disease has not been discovered. Vaccination programmes are being rolled out as the fastest pace possible but achievement of herd immunity will take time.[1] Many drugs like favipiravir, remdesivir and tocilizumab are being used for the treatment of this disease but reports published by the World Health Organization and the New England Journal of Medicine shows that they do not produce any significant clinical results. [2][3] The need for a specific treatment against COVID-19 is paramount. Drugs are chemical compounds which bind upon a specific protein to produce its effects. They can thus bind on other proteins too and can therefore provide repurposed alternative treatments. Remdesivir works by inhibiting the action of RNA dependent RNA polymerase RdRp of SARS-CoV2 which is necessary for viral RNA replication.[4] In this study, by molecular docking a large set of drugs has been used to replace remdesivir in RdRp protein so that they can produce the same action and therefore provide suitable alternatives for clinical trials and emergency use.

Methodology

The general frame work of this study is based on one of my previous study with Dr. Shubhangi Dange [5]. It is depicted in the flowchart below: (please see figure 1)

Step 1: Obtaining three-dimensional structures of receptor and ligands from the databases

The three-dimensional structure of the receptor i.e. the RNA dependent RNA polymerase docked with remdesivir was obtained from the Protein Data Bank [6] (PDB id: 7BV2). Ligand structures were obtained from Zinc15 database [7]. For this study, filters like “in-vivo” and “world” filters were used to choose the ligands. Repurposing an already approved drug is faster than creating any new novel compound. Therefore the “world” approved filter was used to sort only those compounds which have been approved

by a competent authority in any part of the world and not just the United States Food and Drug Administration.

Step 2: Determining active site amino acid residues in the receptor

W. Yin et al. stated in their study [8] that “The complex structure reveals that the partial double-stranded RNA template is inserted into the central channel of the RdRp where Remdesivir is covalently incorporated into the primer strand at the first replicated base pair and terminates chain elongation.” To find suitable alternatives to remdesivir, we would have to produce the same interactions that it produces with the other suitable compounds. Such type of attempt in-silico would have either produced unsatisfactory results or results which would prove to be useless in-vivo. Therefore, I figured out an alternate way to inhibit the action of RdRp. If we can inhibit the binding of the template RNA strand to RdRp then there would no production of the primer strand by replication. Even if it would occur, remdesivir could bind to it can further weaken or inhibit the process. So, the amino acids targeted in this study were those which bound to these RNA strands according to W. Yin et al. These amino acids are listed with their positions as follows:

1. Y915
2. Y595
3. F594
4. S592
5. G590
6. A580
7. D684
8. A558
9. G683
10. G559
11. S682
12. K500
13. N534
14. S501
15. Q541
16. N507
17. L854
18. I847
19. R858

20. S861
21. D865
22. R836
23. A840
24. Q815
25. C813
26. S814
27. D761
28. S759
29. D760

Step 3: Preparation of receptor and ligand for docking

The receptor i.e. the RdRp protein was first processed in Drug Discovery studio [9] by removal of heterogenous atoms, water molecules, prime and template RNA strands and remdesivir. This gave us the clean RdRp molecule. Using PyRx docking software [10], it was converted automatically into an Autodock macromolecule. Around 750 drug molecules were loaded into PyRx using Open Babel plugin [11] which were then converted into Autodock ligands by minimization of their energies, addition of hydrogen atoms and addition of partial charges.

Step 4: Docking of ligands to the receptor within restricted search space of target amino acids

Using Autodock Vina [12], ligands were docked into the restricted search space containing the target amino acids in step 2. The search parameters set were as follows:

center_x = 81.0674935587

center_y = 90.6082924987

center_z = 112.717699441

size_x = 27.5120174204

size_y = 40.1660106465

size_z = 39.5156154165

The docking was conducted with maximum exhaustiveness of 4 modes. The study was conducted on a Windows 10 64-bit operating system which took about 8 hours to complete.

Step 5: Sorting of result on basis of binding affinity, interactions, inclusion and exclusion criteria.

The results obtained were filtered to include only the best mode of each ligand which had RMSD value of 0. They were then sorted from the highest to lowest order of binding affinity. The names of the ligands were derived from the Zinc15 database.

Step 6: Final potential drug candidates obtained.

Literature search about any possible association of these drugs to COVID-19 was done. Top 20 drugs were chosen and were included in this study.

Results

The final 20 drugs obtained from the study are displayed below in decreasing order of binding affinity.

Ligand	Binding Affinity (kcal/mol)	Name (as per Zinc15 database)
rdrp_7bv2_clean_ZINC000003914596	-8.6	Saquinavir
rdrp_7bv2_clean_ZINC000003830431	-8.6	Cefoperazone
rdrp_7bv2_clean_ZINC000001482077	-8.6	Gliquidone
rdrp_7bv2_clean_ZINC000003831231	-8.5	Novobiocin
rdrp_7bv2_clean_ZINC000003927822	-8.3	Lurasidone
rdrp_7bv2_clean_ZINC000000537877	-8.3	Ketanserin
rdrp_7bv2_clean_ZINC000001481956	-8.1	Paliperidone
rdrp_7bv2_clean_ZINC000001530886	-8	Telmisartan
rdrp_7bv2_clean_ZINC000000538337	-7.9	Sertindole
rdrp_7bv2_clean_ZINC000001542113	-7.9	Vilazodone
rdrp_7bv2_clean_ZINC000003914813	-7.8	Tudca
rdrp_7bv2_clean_ZINC000001542146	-7.7	Pranlukast
rdrp_7bv2_clean_ZINC000003872994	-7.7	Nizoral
rdrp_7bv2_clean_ZINC000001543181	-7.7	Ibutamoren
rdrp_7bv2_clean_ZINC000003833846	-7.6	Nelfinavir
rdrp_7bv2_clean_ZINC000001489478	-7.6	Sitagliptin
rdrp_7bv2_clean_ZINC000001481831	-7.5	Sitaxentan
rdrp_7bv2_clean_ZINC000002005305	-7.5	5-methyltetrahydrofolate
rdrp_7bv2_clean_ZINC000000586239	-7.5	Levocabastin
rdrp_7bv2_clean_ZINC000001481815	-7.5	Deferasirox/exjade

The drug interactions of all the molecules were studied in Drug Discover studio and the number of interactions which matched our target amino acids were noted.

Discussion

Saquinavir has been found to have inhibitory action on SARS-CoV2 spike glycoprotein and 3CL main protease [13]. Cefoperazone was included in the study because of its widespread use and availability as well as the high number of target amino acids it interacted with. However, no study linking it directly to inhibition of SARS-CoV2 was found. Gliquidone was found to have inhibitory effect on 3CL main protease as well as RdRp [14] [15]. Novobiocin was identified as an inhibitor of heat shock protein 90 which

allowed virus to control infected cells [16]. Lurasidone was found as the inhibitor of 3CL main protease in an in-silico study [17]. Ketanserin is being studied as aa potential additive drug to improve V/Q mismatch in COVID-19 [18]. No study linking paliperidone to SARS-CoV2 inhibition was found but it was included in the study due to the number of interactions as well as binding affinity. Telmisartan was found to demonstrate anti-inflammatory effect and improved morbidity in hospitalized patients infected with SARS-CoV2 [19]. Sertindole had inhibitory effect on main protease [20]. No study linking vilazodone to SARS-CoV2 inhibition was found but it was included in the study due to the number of interactions as well as binding affinity. Tudca/ ursodeoxycholic acid proven safety profiles that can reduce inflammation and prevent cell death to reduce morbidity and mortality in COVID-19 [21]. Pranlukast can improve COVID-19 prognosis [22] [23]. No study linking nizoral/ketoconazole to SARS-CoV2 inhibition was found but can reduce host vulnerability to COVID-19 [24]. Ibutamoren had inhibitory effect on main protease [25]. Nelfinavir has been found to inhibit replication of SARS-CoV2 invitro [26]. Sitagliptin administration was associated with reduced mortality in patients with type 2 diabetes and COVID-19 [27]. Sitaxentan, an endothelin receptor blocker, can improve prognosis of COVID-19 [28]. 5-methyltetrahydrofolate is a potential treatment for pulmonary hypertension associated with COVID-19 pneumonia [29]. Levocabastin can be used against SARS-CoV2 spike proteins as a nasal spray [30]. Deferasirox can be used as an iron chelator to reduce or hamper virus survival [31].

Conclusion

The drugs obtained above have also been identified in other in-silico studies as potential inhibitors of SARS-CoV2 by different mechanisms. They must be tried in-vitro because of the limitations of in-silico docking [32]. Alternatives and/or additives to remdesivir are important to help us come out of this crisis as soon as possible. These drugs can be expected to work on various proteins or mechanisms at the same time and provide quicker recovery of the patient.

Declarations

Source of funding: Nil

Ethical approval: Not required

Conflict of interest: The author hereby declares no conflict of interests.

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Figures

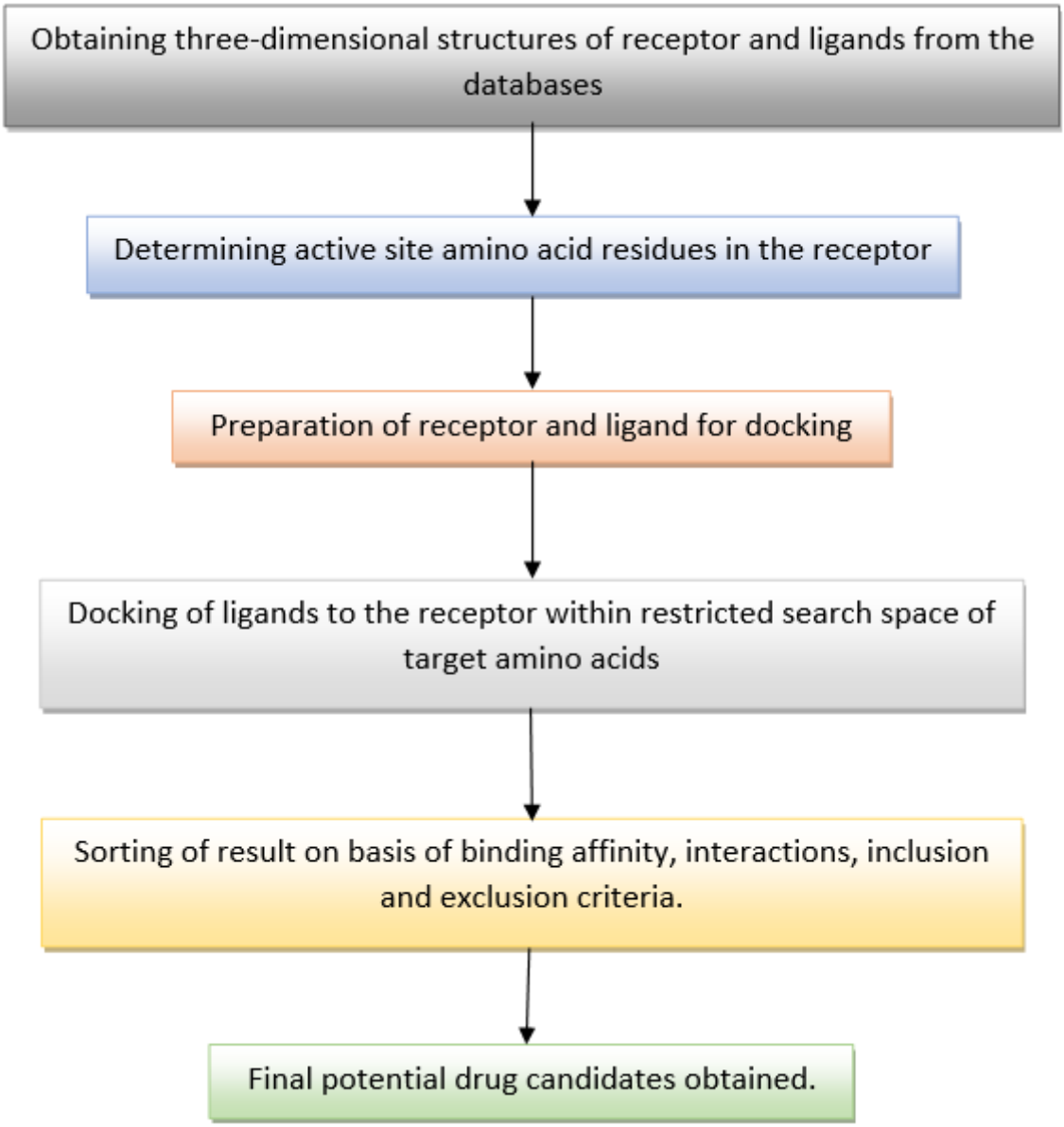

Figure 1

General summary of the study methodology followed.

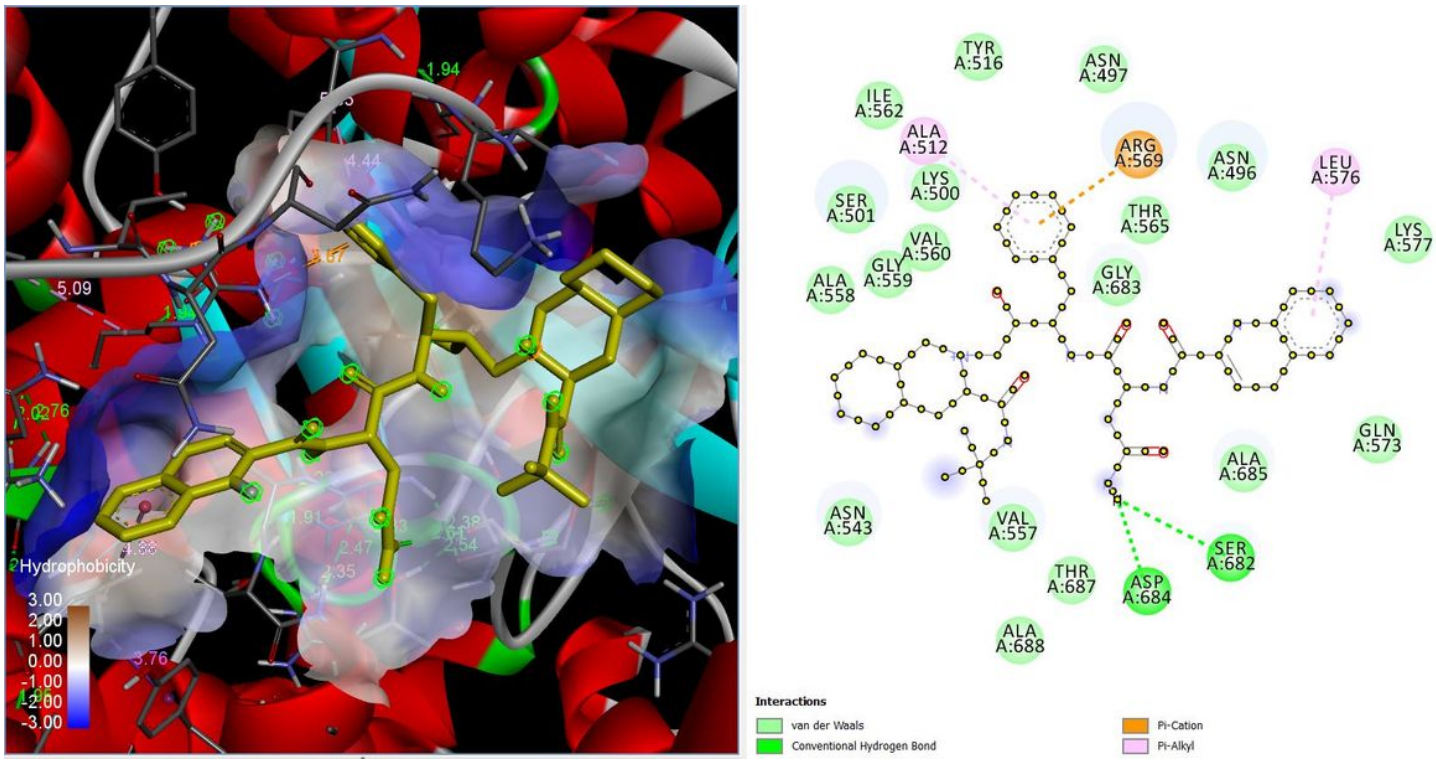

Figure 2

Saquinavir in its docking space in RdRp visualized using Drug Discover Studio. 7 target amino acids were interacted by it.

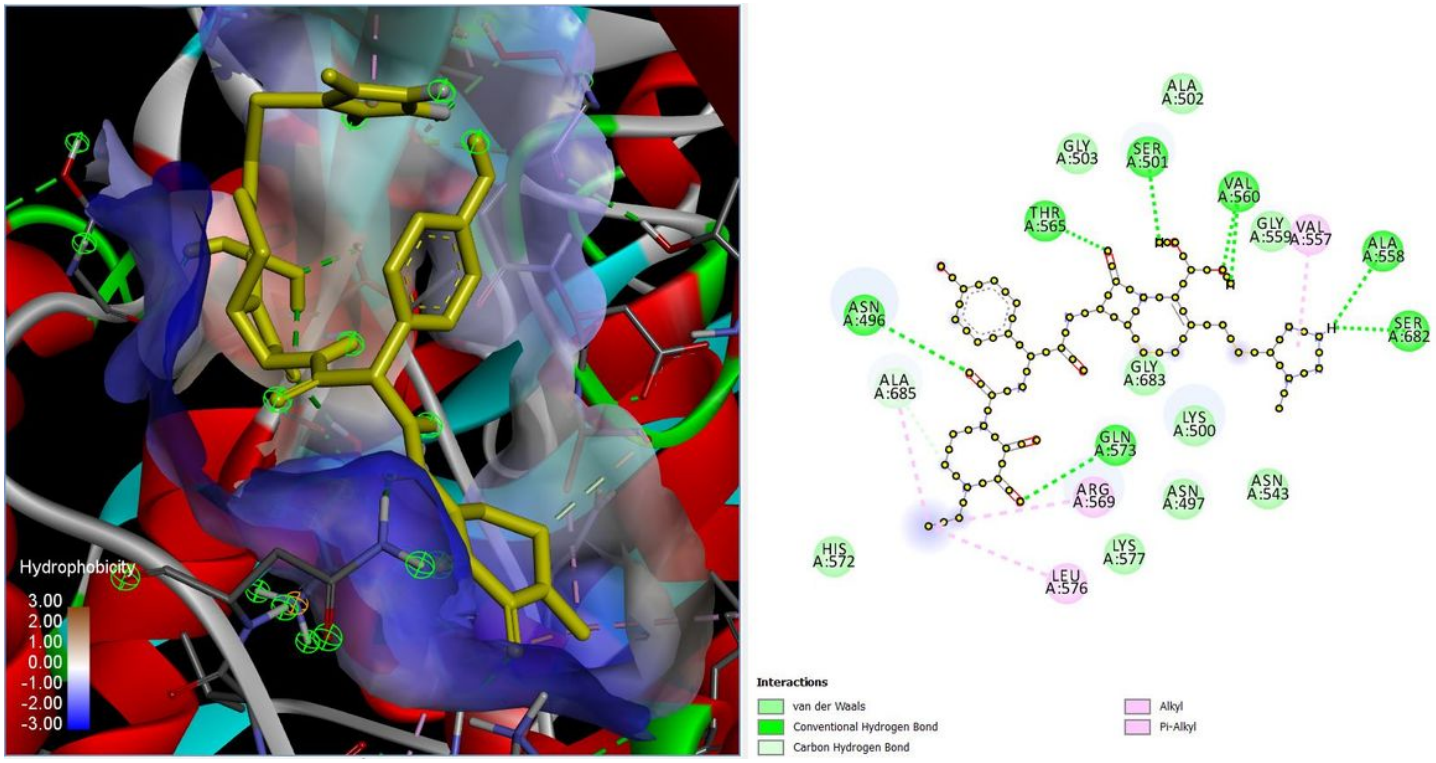

Figure 3

Cefoperazone in its docking space in RdRp visualized using Drug Discover Studio. 6 target amino acids were interacted by it.

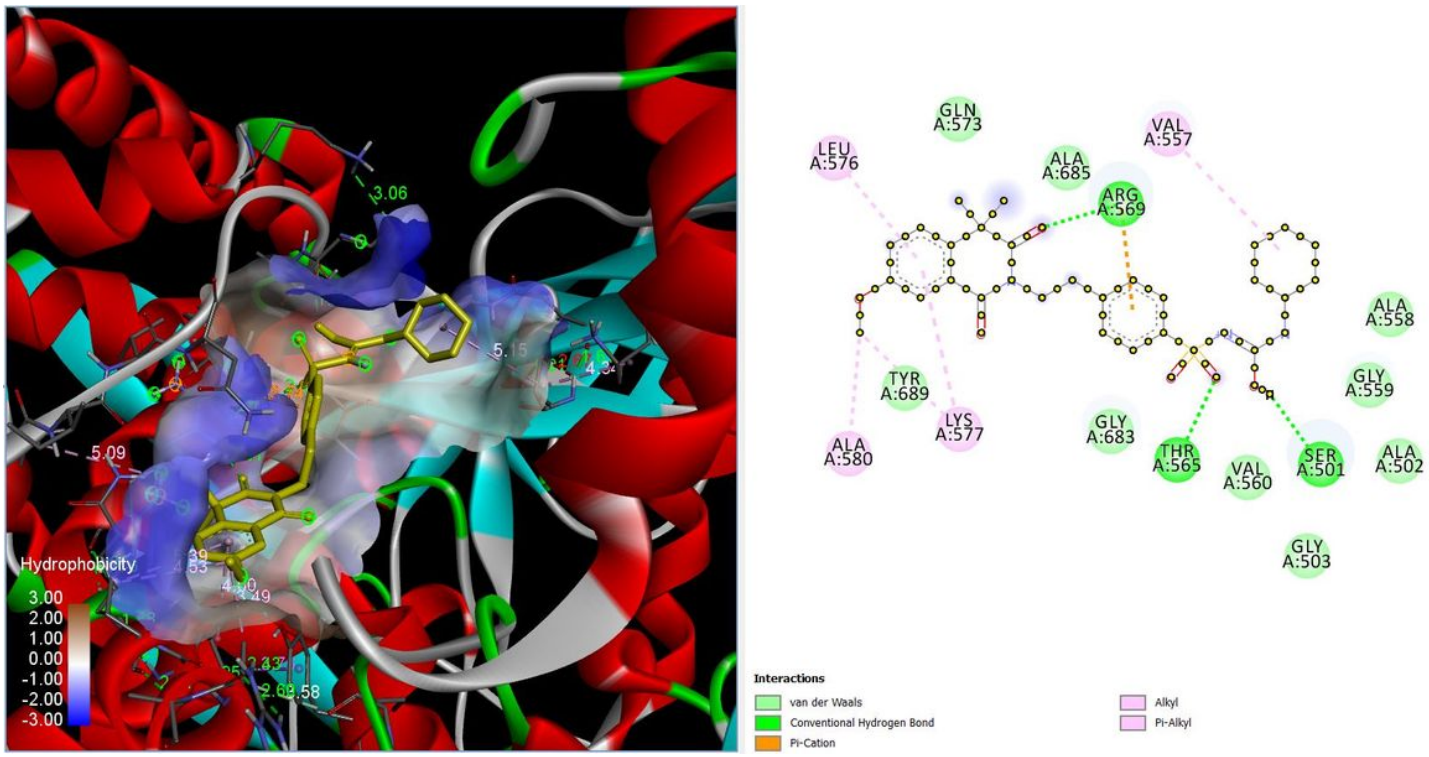

Figure 4

Gliquidone in its docking space in RdRp visualized using Drug Discover Studio. 5 target amino acids were interacted by it.

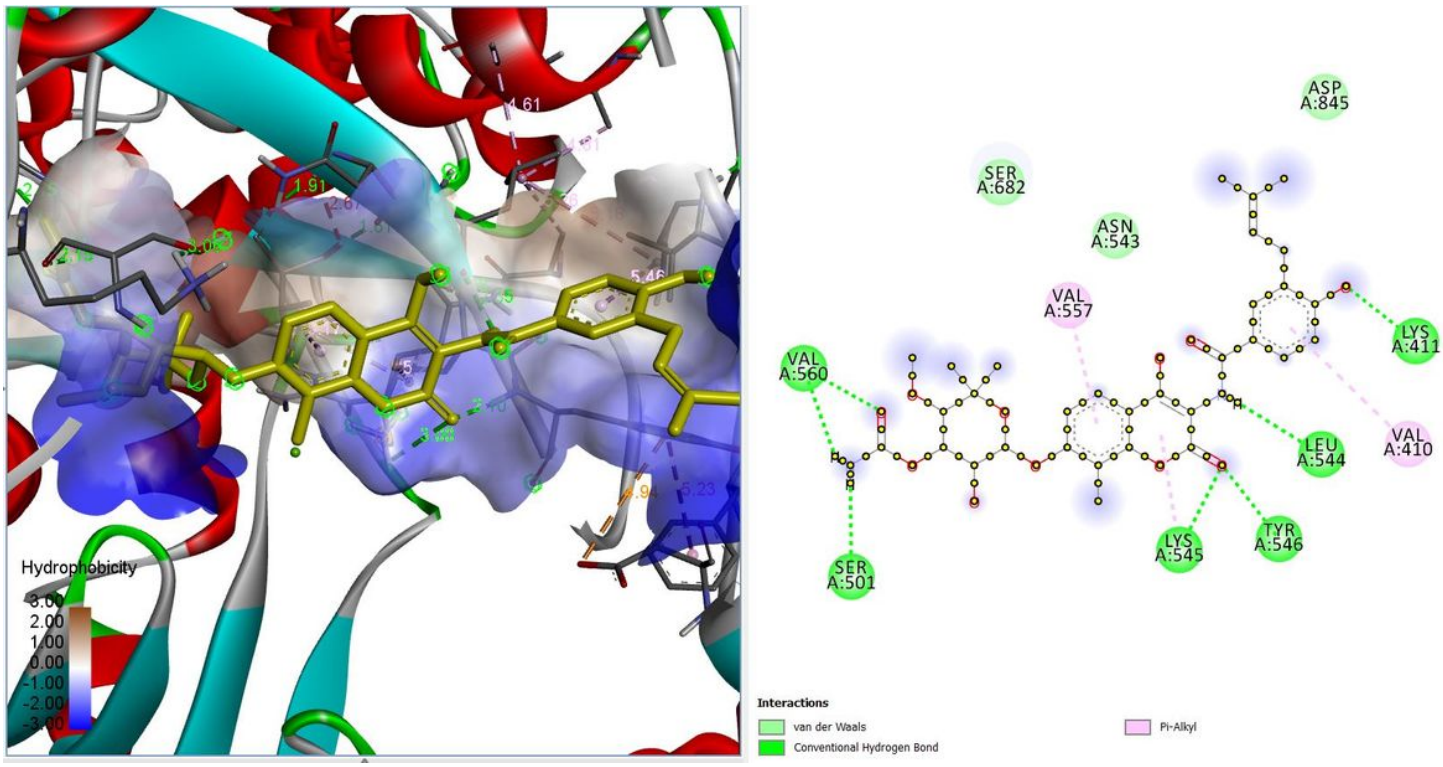

Figure 5

Novobiocin in its docking space in RdRp visualized using Drug Discover Studio. 2 target amino acids were interacted by it.

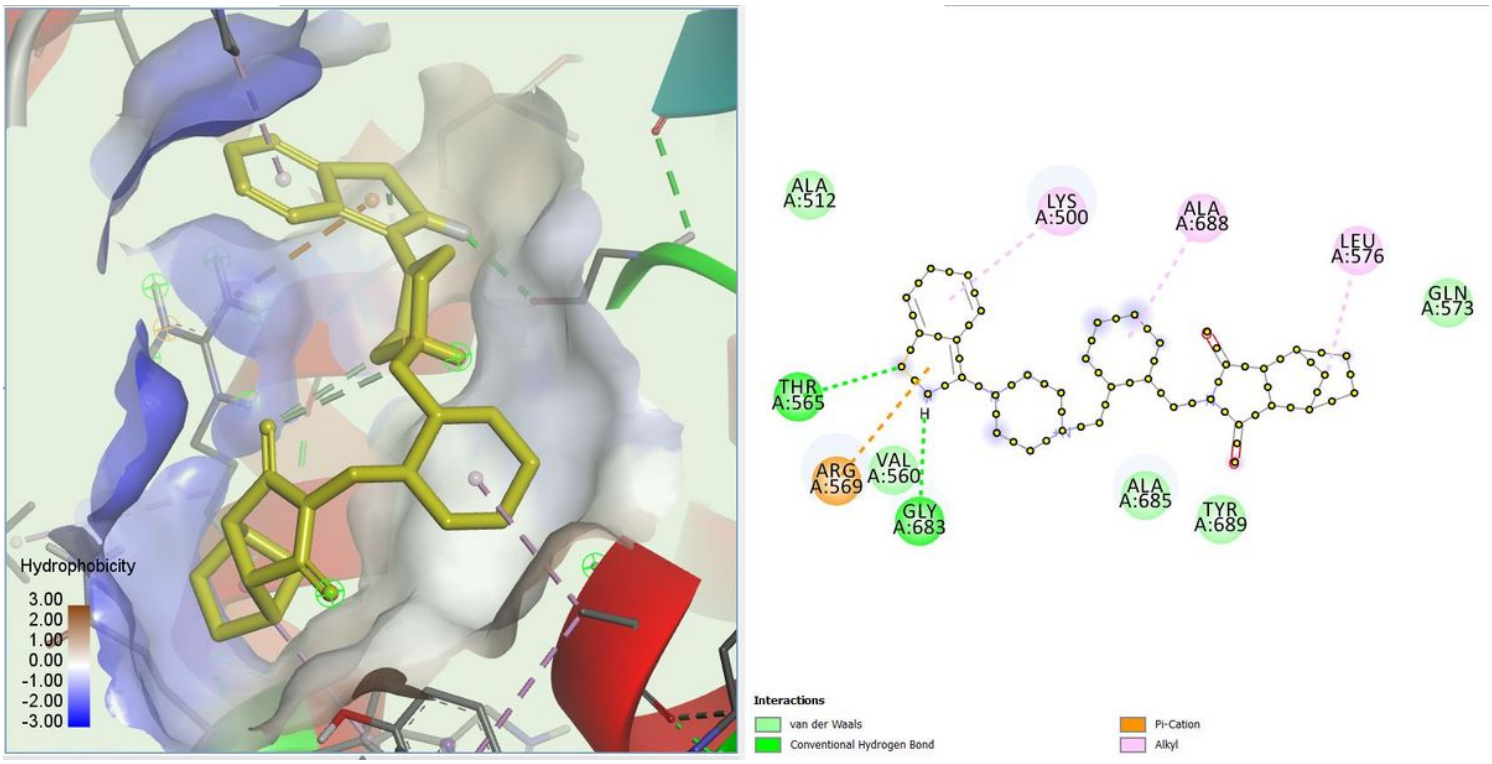

Figure 6

Lurasidone in its docking space in RdRp visualized using Drug Discover Studio. 2 target amino acids were interacted by it.

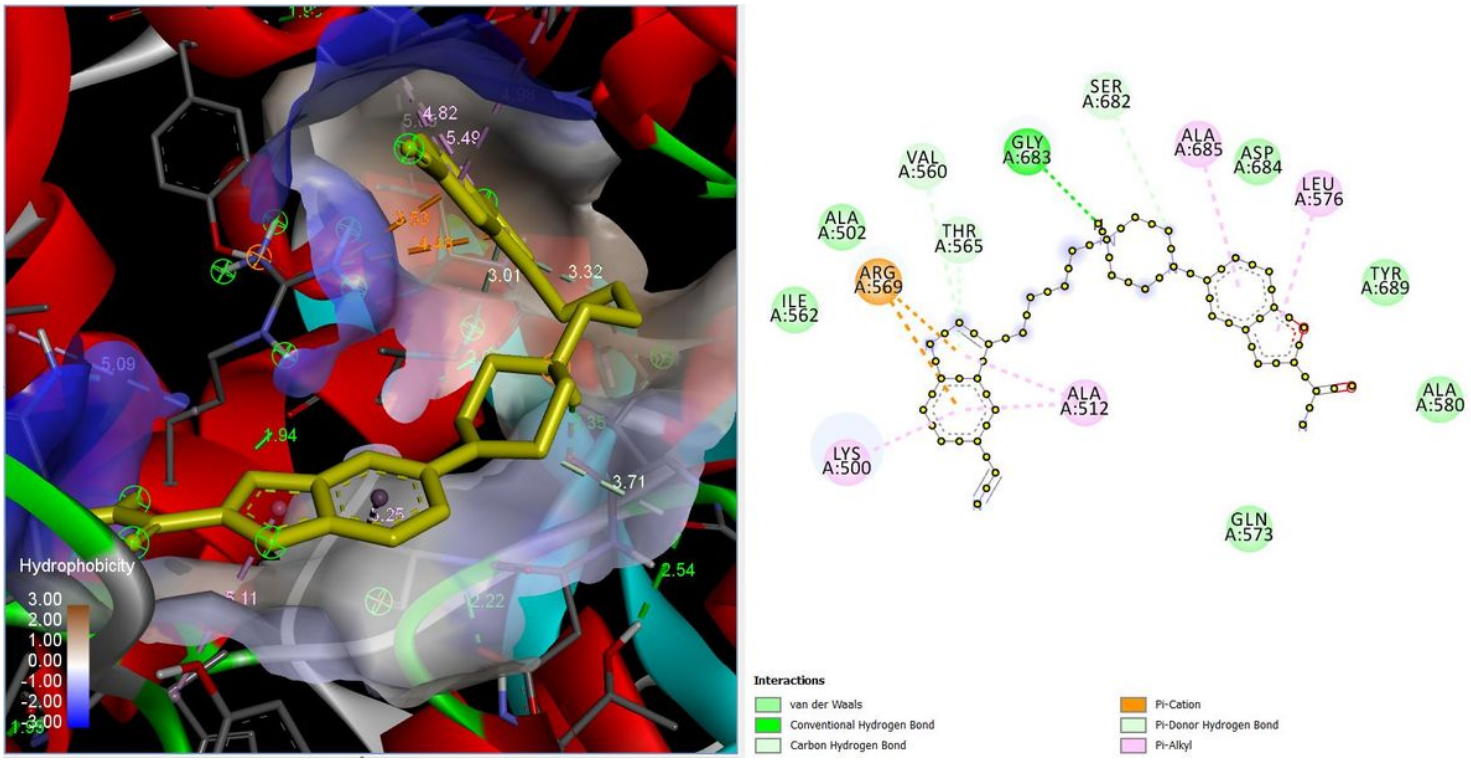

Figure 7

Ketanserin in its docking space in RdRp visualized using Drug Discover Studio. 0 target amino acids were interacted by it.

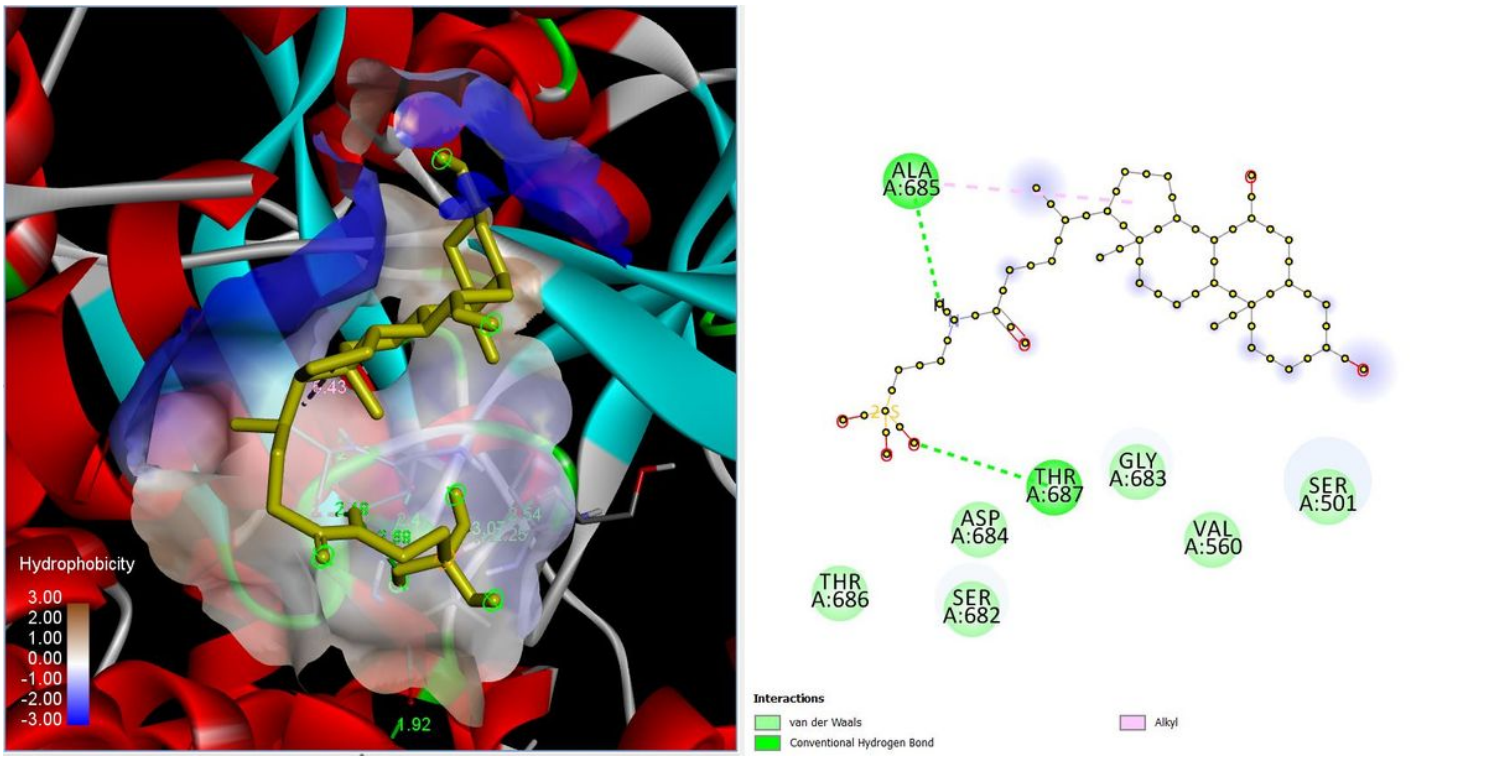

Figure 8

Palperidone in its docking space in RdRp visualized using Drug Discover Studio. 4 target amino acids were interacted by it.

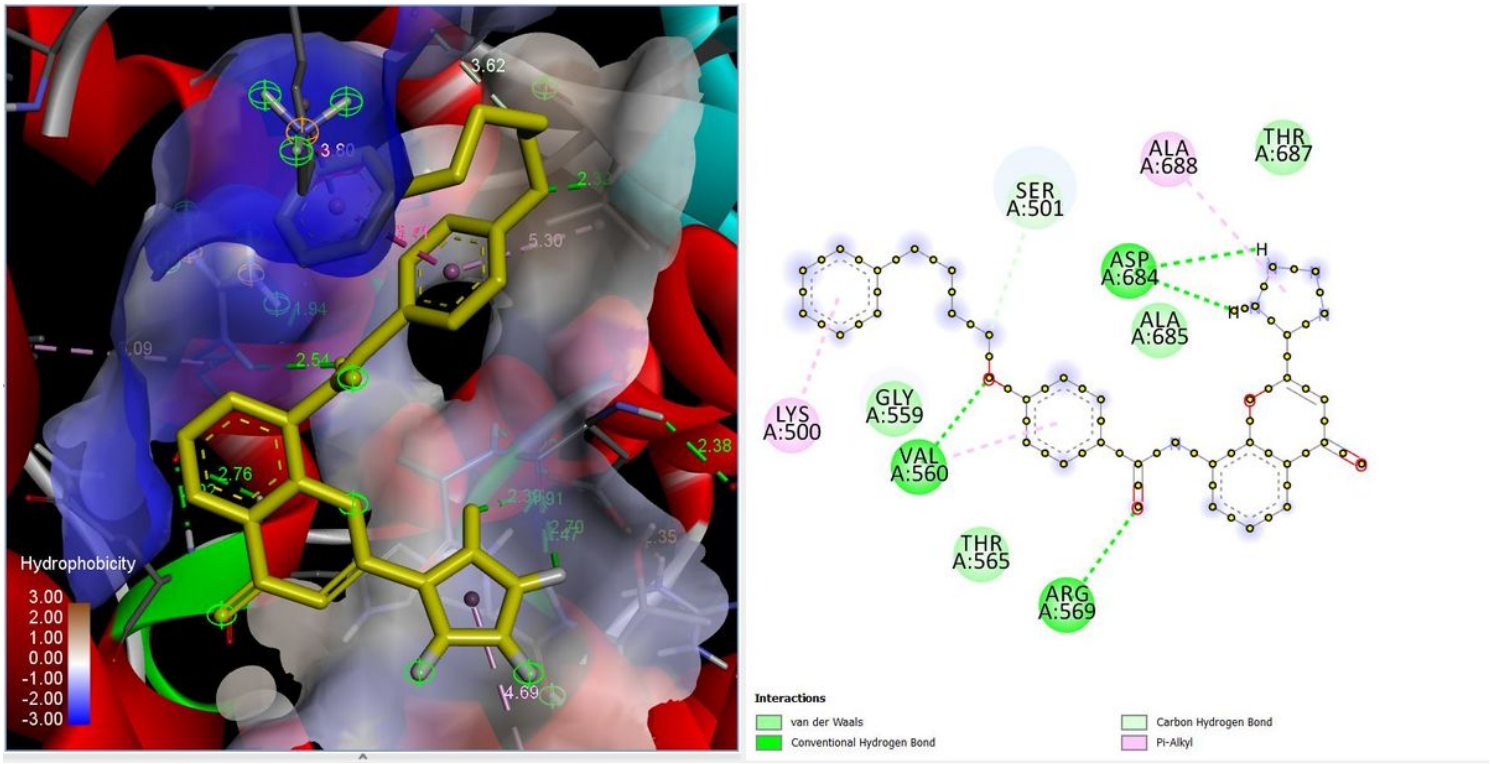

Figure 9

Telmisartan in its docking space in RdRp visualized using Drug Discover Studio. 3 target amino acids were interacted by it.

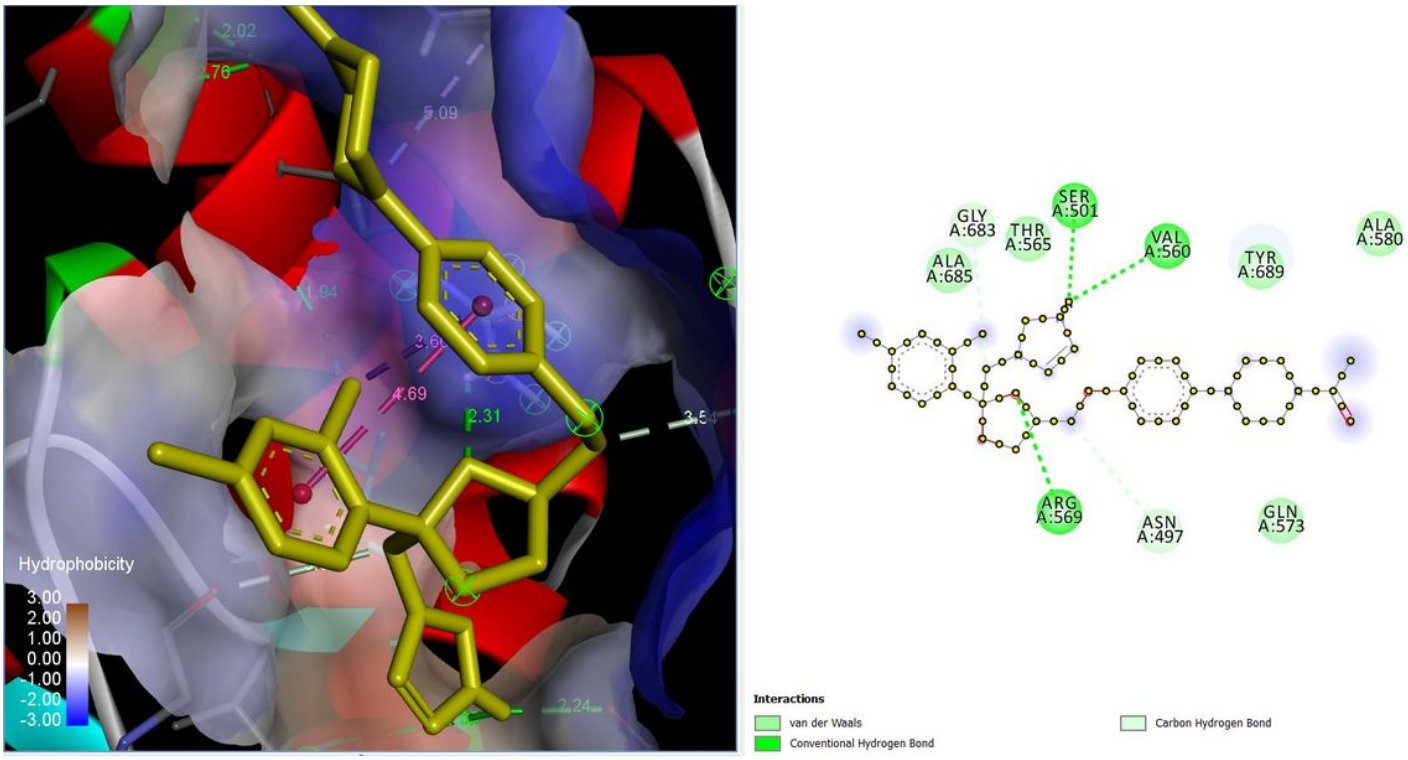

Figure 10

Sertindole in its docking space in RdRp visualized using Drug Discover Studio. 6 target amino acids were interacted by it.

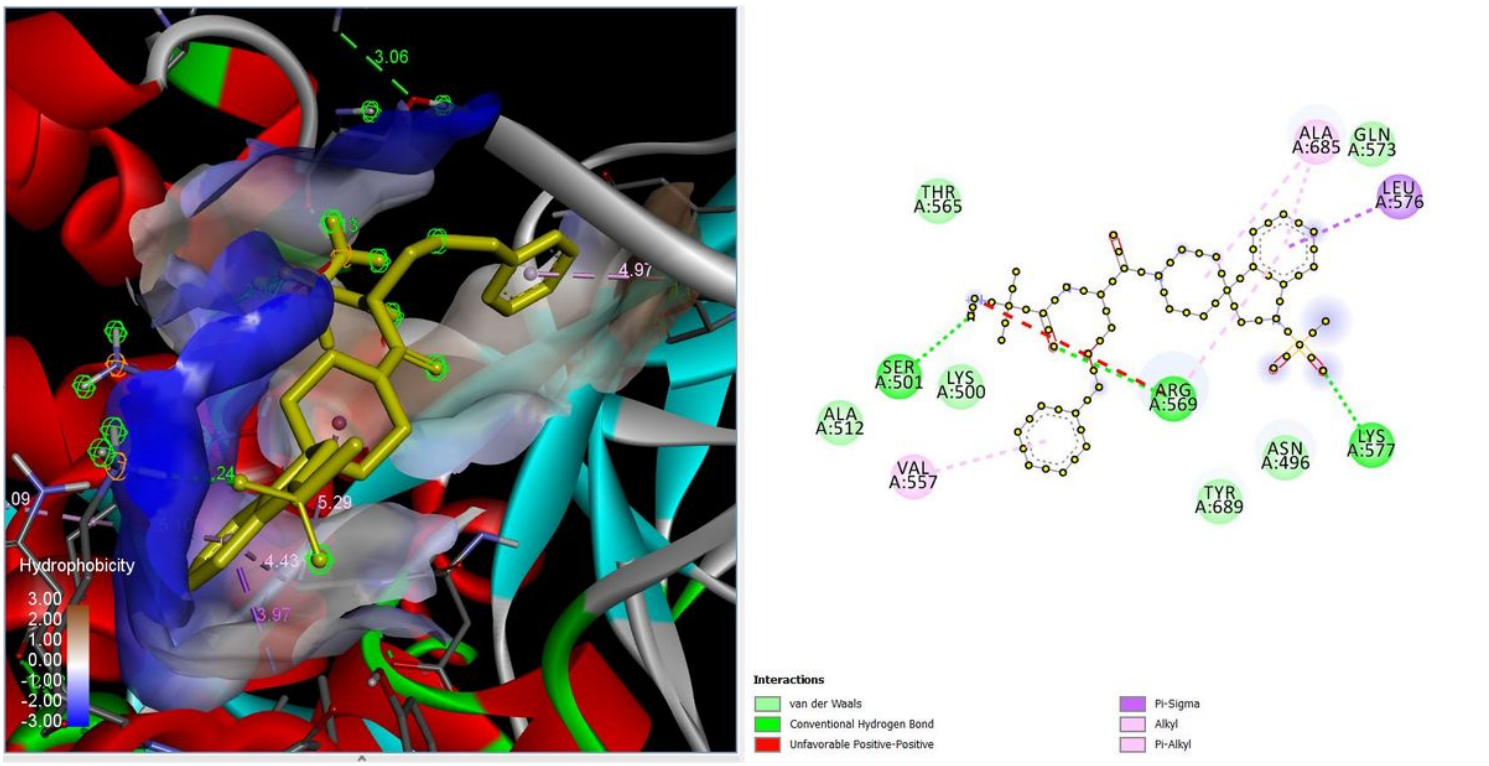

Figure 11

Vilazodone in its docking space in RdRp visualized using Drug Discover Studio. 5 target amino acids were interacted by it.

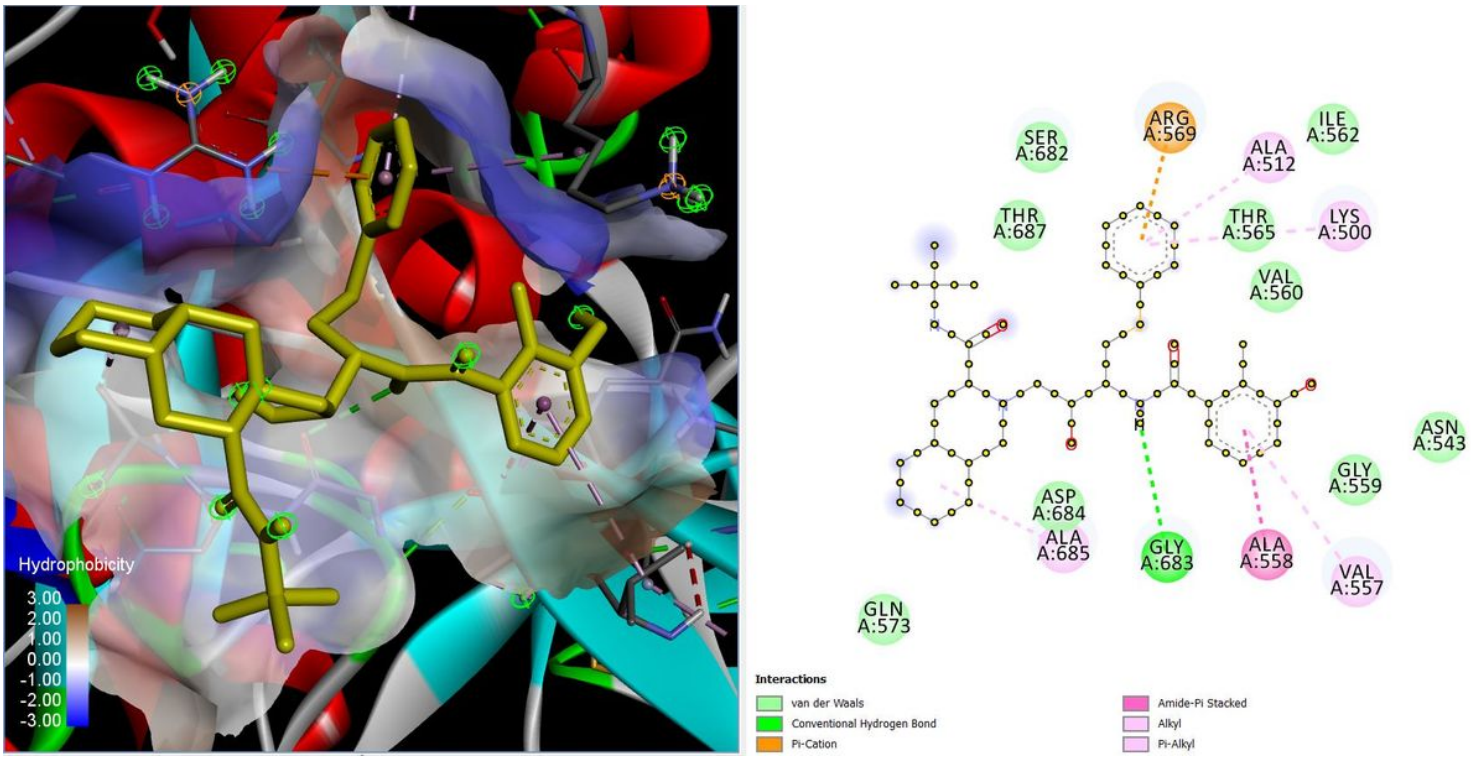

Figure 12

Tudca in its docking space in RdRp visualized using Drug Discover Studio. 4 target amino acids were interacted by it.

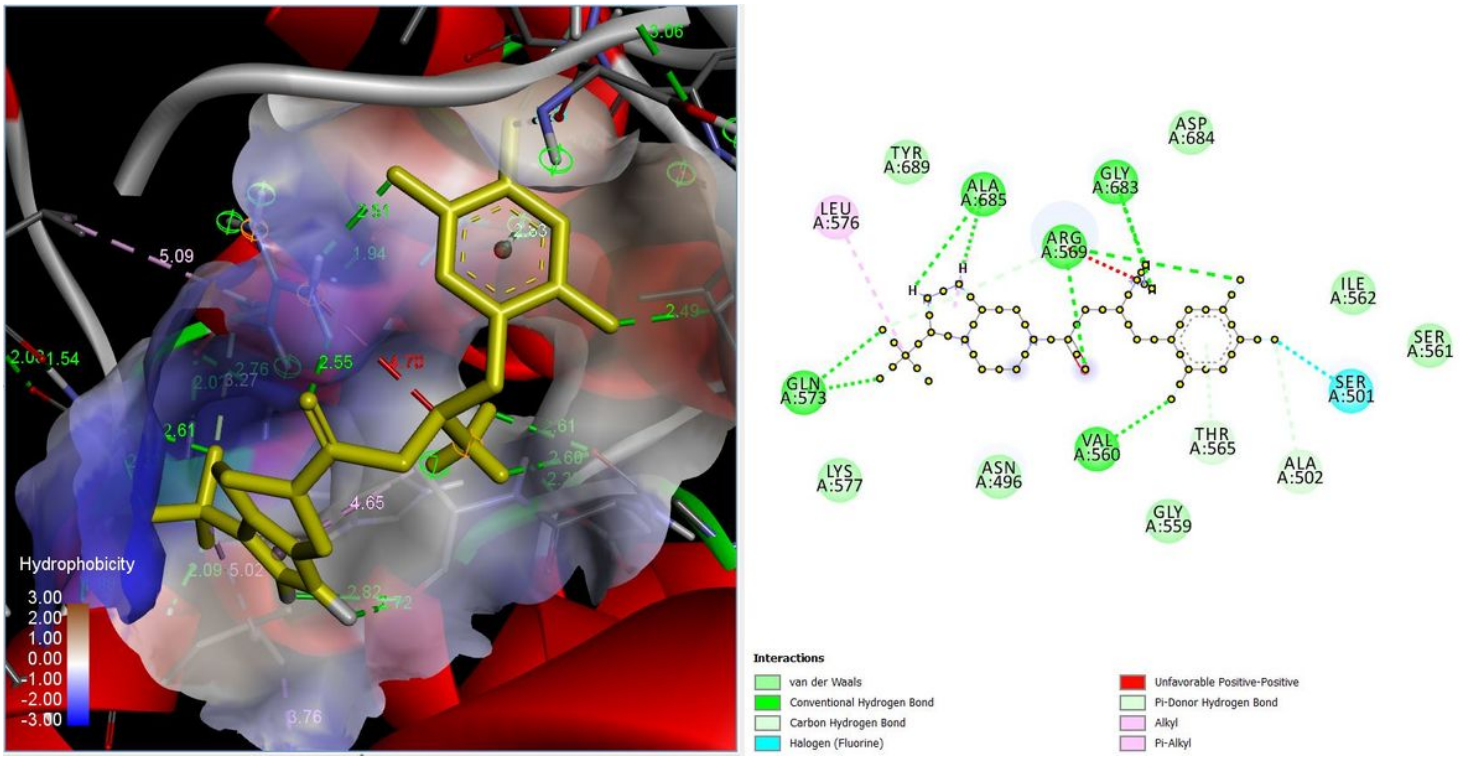

Figure 13

Pranlukast in its docking space in RdRp visualized using Drug Discover Studio. 4 target amino acids were interacted by it.

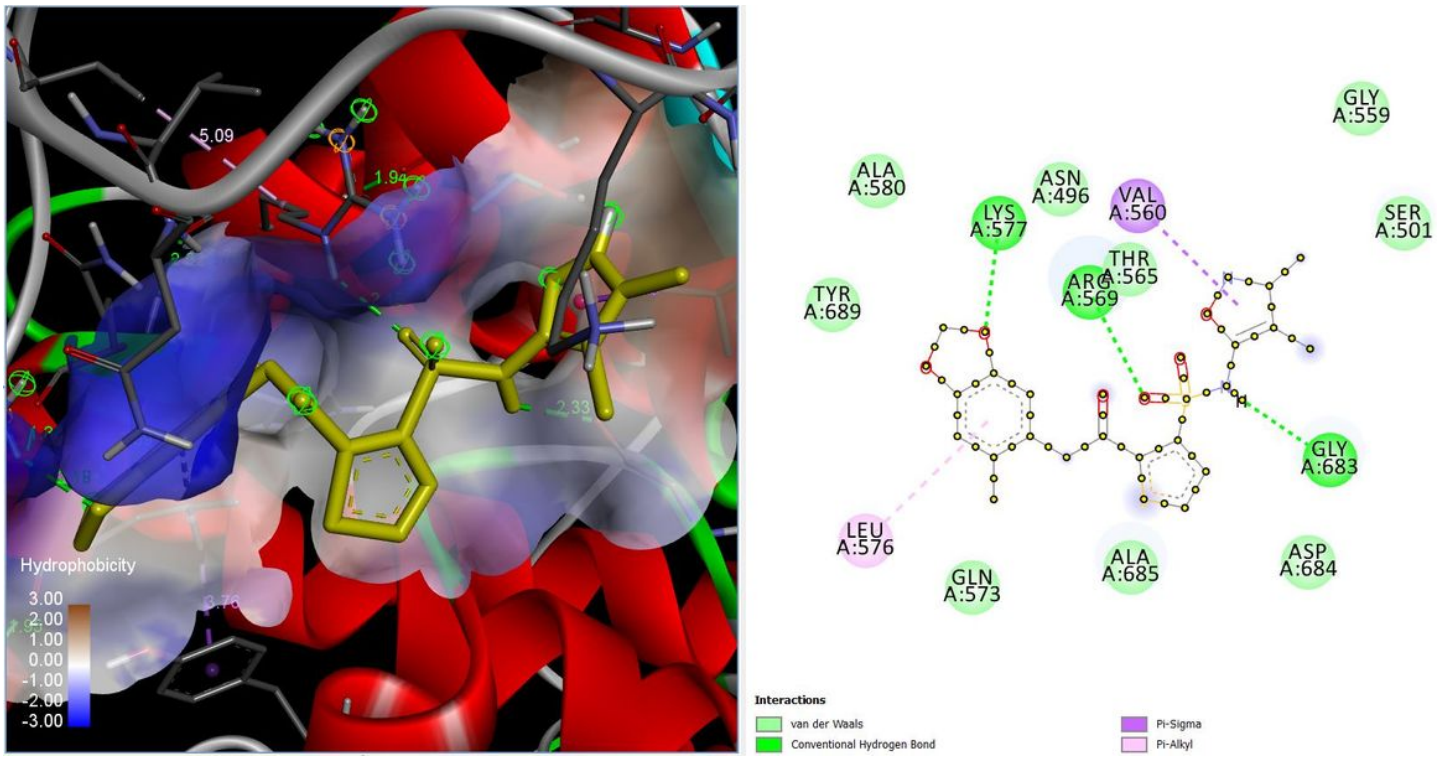

Figure 14

Nizoral in its docking space in RdRp visualized using Drug Discover Studio. 3 target amino acids were interacted by it.

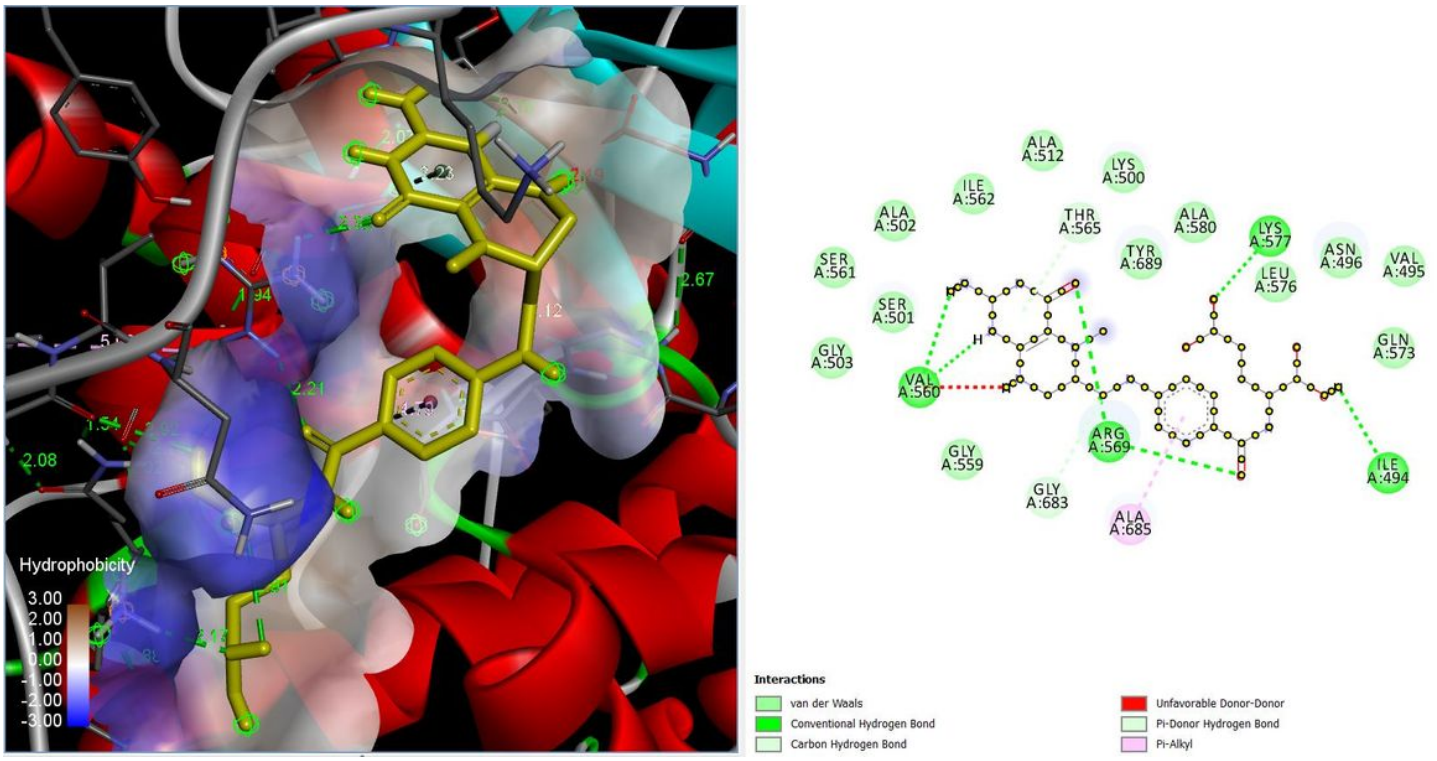

Figure 15

Ibutamoren in its docking space in RdRp visualized using Drug Discover Studio. 2 target amino acids were interacted by it.

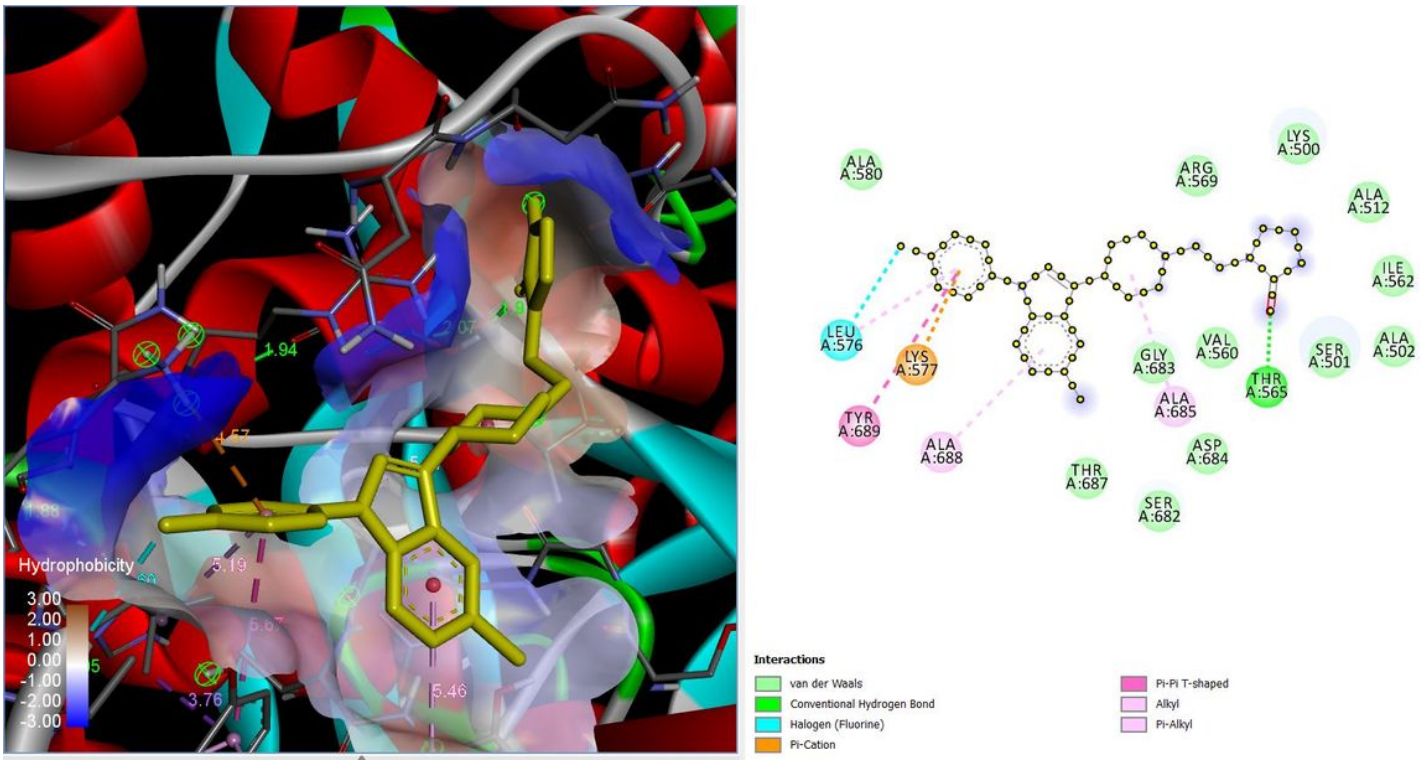

Figure 16

Nelfinavir in its docking space in RdRp visualized using Drug Discover Studio. 6 target amino acids were interacted by it.

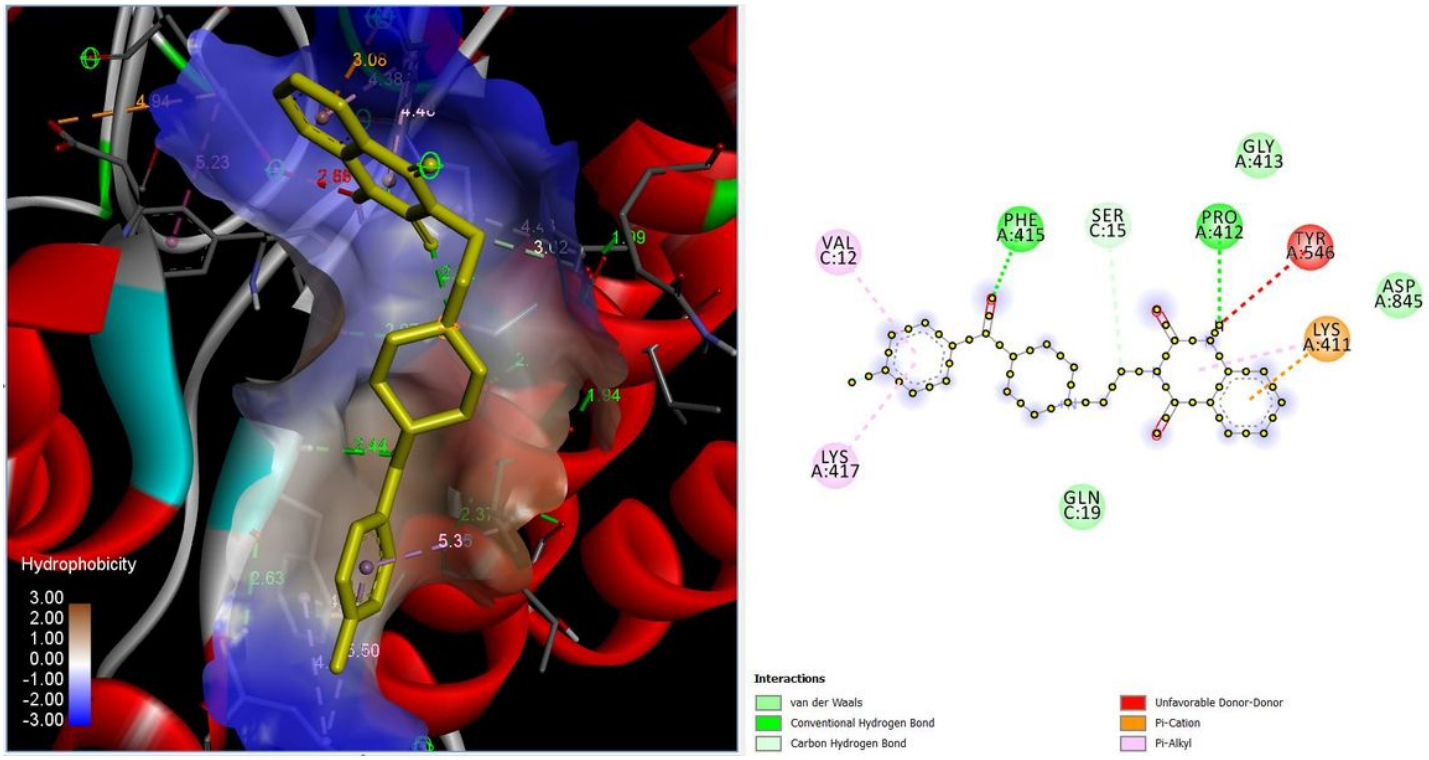

Figure 17

Sitagliptin in its docking space in RdRp visualized using Drug Discover Studio. 4 target amino acids were interacted by it.

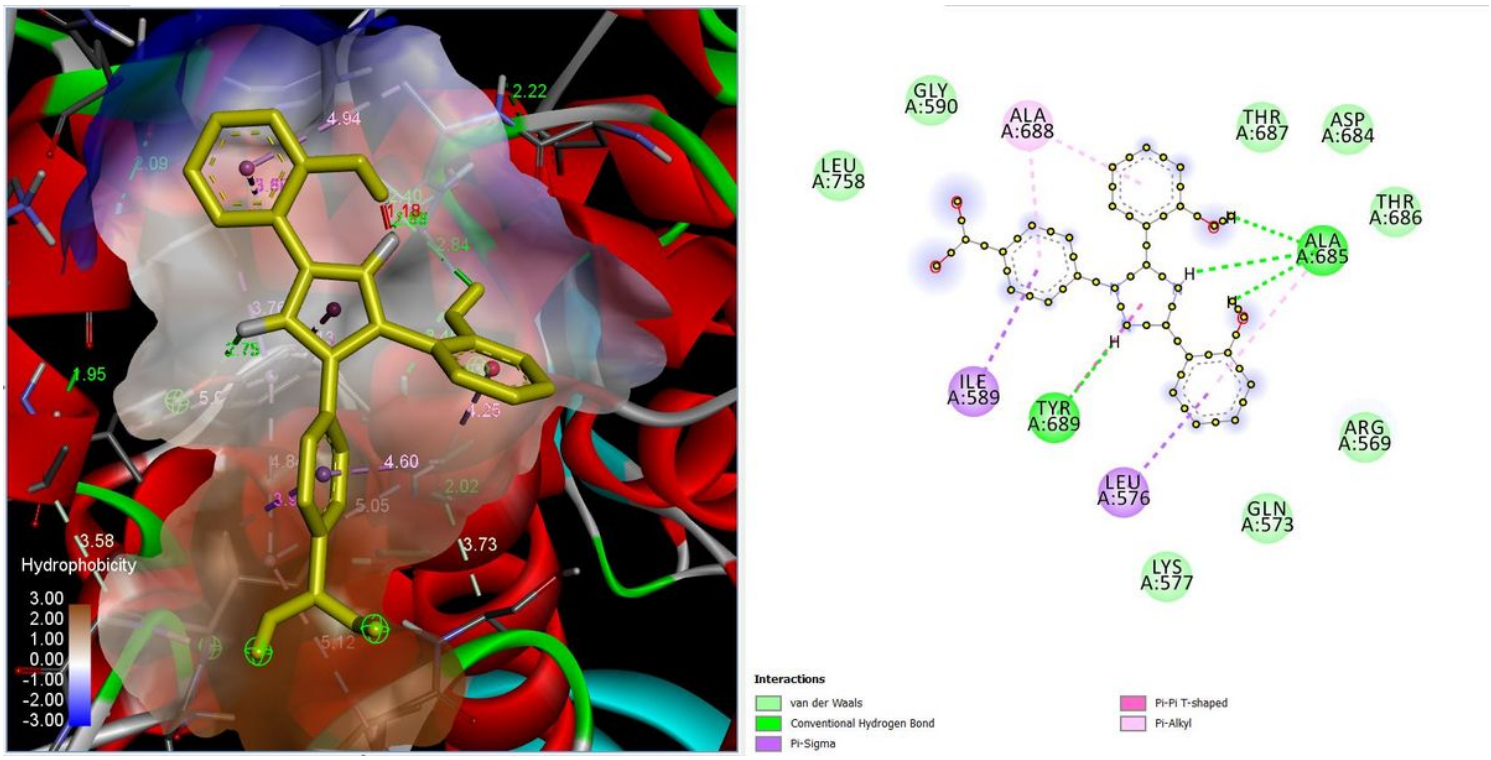

Figure 18

Sitaxentan in its docking space in RdRp visualized using Drug Discover Studio. 5 target amino acids were interacted by it.

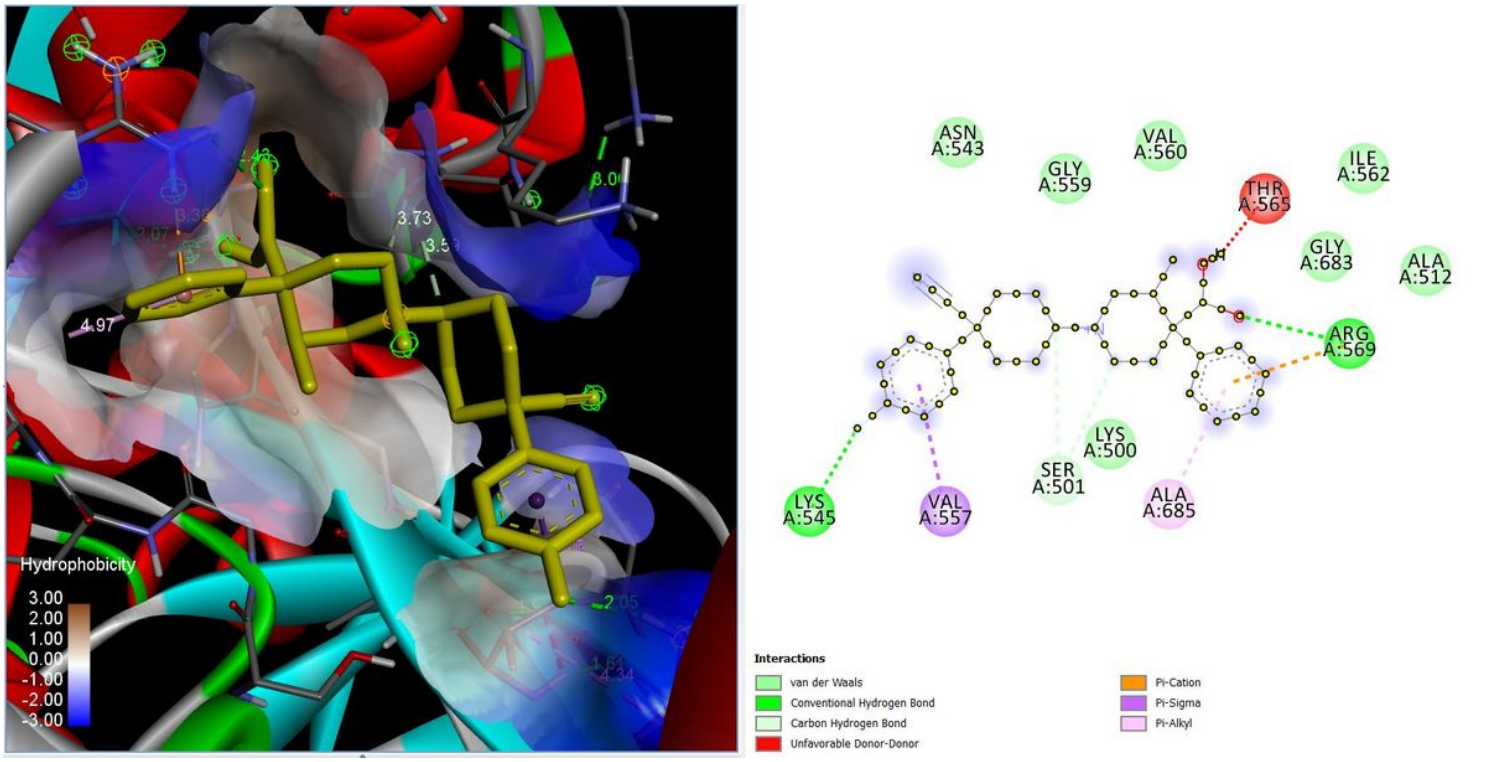

Figure 19

5-methyltetrahydrofolate in its docking space in RdRp visualized using Drug Discover Studio. 5 target amino acids were interacted by it.

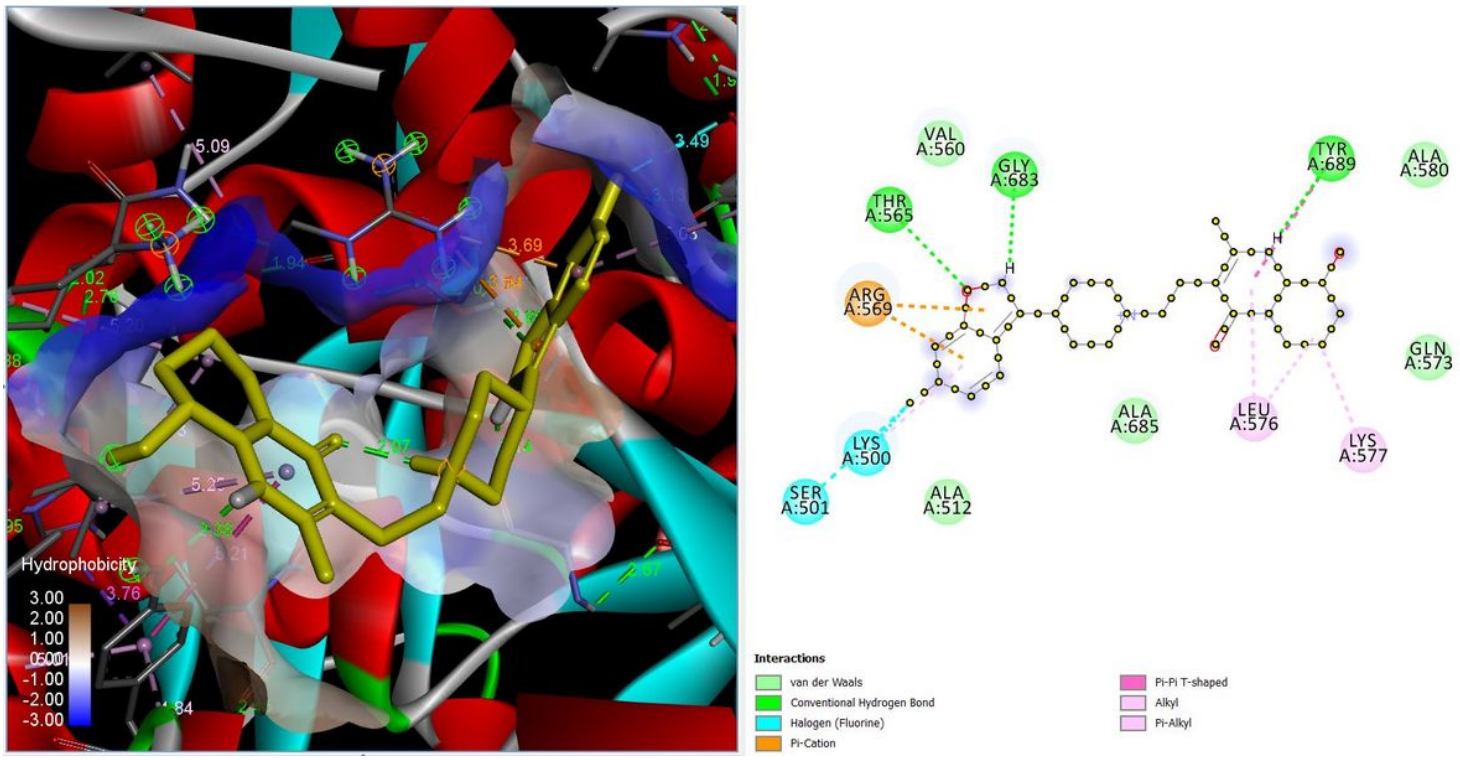

Figure 20

Levocabastin in its docking space in RdRp visualized using Drug Discover Studio. 3 target amino acids were interacted by it.

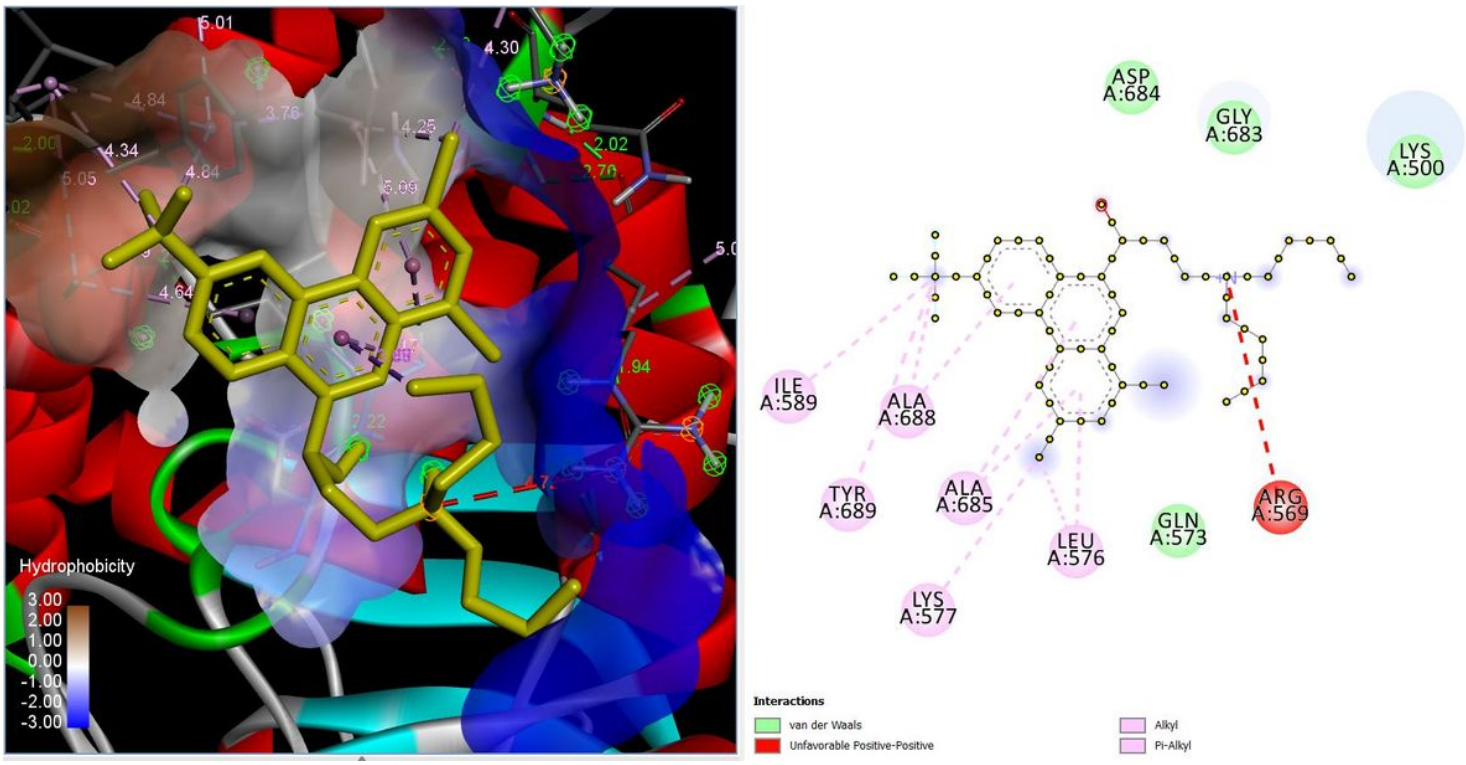

Figure 21

Deferasirox in its docking space in RdRp visualized using Drug Discover Studio. 2 target amino acids were interacted by it.