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Research Article

Hydroxychloroquine as Potent Inhibitor of COVID -19 Main Protease: Grid Based Docking Approach

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Abstract

Objectives: Coronavirus (COVID-19) is an enveloped RNA virus that occurs in various forms in humans and wildlife. A total of six disease-causing species have been identified in humans. Viral infections play a vital role in human diseases, and recent outbreaks have developed globally in the form of novel corona. The SS-RNA virus from the enveloped coronavirus family caused SARS (Severe Acute Respiratory Syndrome), a life-threatening viral infection. In many countries around the world, the spread of infection is rapid. As of March 26, 2020, there were 462.684 confirmed cases globally, and 20.834 deaths were recorded. The World Health Organization (WHO) described COVID-19 as a pandemic on March 11, 2020. There are numerous drug trials going on with some positive results. However, since no vaccine is available, the best way to combat the virus is to use preventive methods.

Methods: In this study, an attempt was made to find the new COVID-19 main protease inhibitor with a molecular docking approach. A grid-based docking approach was chosen to find the binding using VLife MDS software. The 2D structure of the compounds was created and then converted into the 3D, and then, it was energetically minimized up to the RMS gradient of 0.01, using the Merck Molecular Force Field (MMFF). By using cavity determination option, the enzyme's cavities were determined. Cavity no.1 was selected for docking. The active site for docking was defined as all atoms within 5A˚ radius.

Results: Hydroxychloroquine is a slow-acting antirheumatic drug. The value of hydroxychloroquine is analogous to that reported for other disease-modifying anti-rheumatic drugs. The docking score obtained was -4.308880 and the number of receptor atoms was 77, while the number of ligand atoms was 20, which shows that hydroxychloroquine binds effectively with Covid-19 protease.

Conclusion: Hydroxychloroquine was taken as drug following Lipinski's rule of five, so it had a very good drug score and drug-likeness score as well. This study reveals that Hydroxychloroquine has good binding affinity with COVID-19 protease and thus can be used as prophylaxis and therapeutic treatment for corona patients.

Keywords: COVID-19, Hydroxychloroquine, Molecular Docking & Prevention measures

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A novel coronavirus (SARS-CoV) virus is the first major epidemic of the new millennium in many different countries of the world. The repeated emergence and outbreaks of CoVs indicate a public health threat. This suggests the possibility of animal-to-human and human-to-human transmission of newly emerging CoVs. The ongoing changes in ecology and climate make the future emergence of such infections more likely. The coronavirus COVID-19 is troubling 188 countries and territories around the world. According to the reported survey, there were 312002 total

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cases and 13071 deaths reported from coronavirus.[1] The treatment of coronavirus-associated SARS has been still developing and consequently is no consent on an optimal regimen. The predictable therapeutic interventions for SARS involve broad-spectrum antibiotics and supportive care, as well as antiviral agents and immune-modulation therapy.[2] This time, nearly a decade after SARS, another highly pathogenic CoV, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) appeared in the Middle Eastern countries.[3] Coronaviruses (CoVs) are the main group of viruses belonging to the order Nidovirales, which includes Coronaviridae, Arteriviridae, and Roniviridae families.[4] Coronavirus (Fig. 1) is an enveloped and single-stranded ribonucleic acid with 9-12 nm-long surface spikes. Various symptoms include fever, cough andshortness of breath.[5]

Mode of transmission[6]

The human-to-human transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is thought to occur mainly through respiratory droplets.

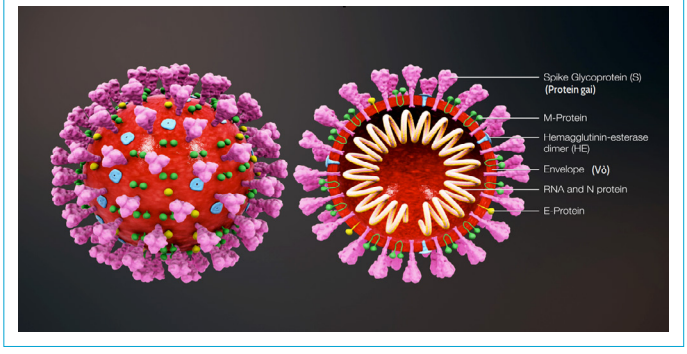

Figure 1. Structure of CoV.

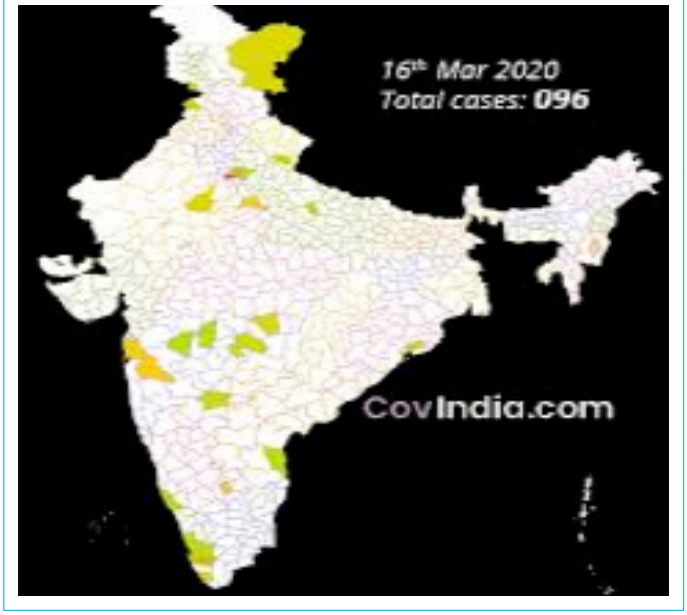

Figure 2. Spread of Corona in India.

Infection (Fig. 2) can also occur when people touch their eyes, nose, or mouth after touching an infected surface.

Co-morbidity associated with CO-V 19

A logical analysis of CoV cases suggests that diabetes and hypertension are equally ubiquitous in approximately 50% of the patients. % of cases have CHD and 16% have obesity. These conditions downregulate the synthesis of proinflammatory cytokines and damage the innate and humoral immune systems of the host.[7]

- For prevention of COVID-19[8]
- Wash your hands; Use a hand sanitizer that contains at least 60% alcohol
- keep away from touching your eyes, nose, and mouth with unwashed hands
- Avoid close contact
- Cover your mouth and nose
- Wear a facemask
- Clean AND disinfect frequently touched surfaces daily

Symptoms are mainly like influenza and include fever, malaise, myalgia, headache, diarrhea, and shivering (rigors). Although fever is the most frequently reported symptom, it is sometimes not found on initial measurement, especially in elderly and immunocompromised patients.[9]

Measures to prevent COVID-19

Social distancing measures should be implemented by Govt. of India for spreading the epidemic. This can help disrupt the chains of human-to-human transmission.

- Immediate isolation of suspected or confirmed symptomatic persons.
- Suspension of the mass gathering.
- Social distancing events at workplaces

Hydroxychloroquine (Fig. 3) is known as disease modifying drugs10. Hydroxychloroquine sulfate chemically known as 2-[[4-[(7-Chloro-4-quinolyl)amino]pentyl] ethylamino]

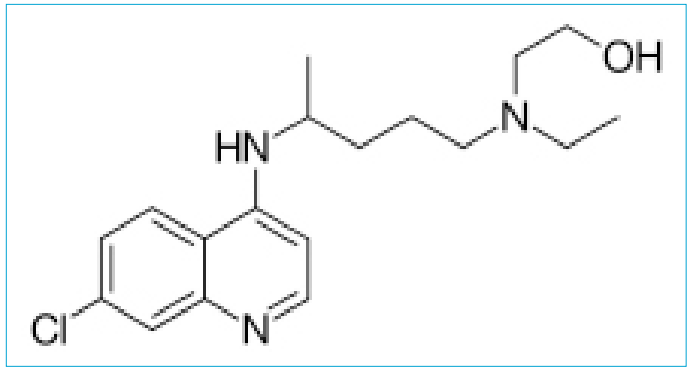

Figure 3. Hydroxychloroquine.

ethanol sulfate (1:1) having molecular weight 433.95 and molecular formula is $C_{18}H_{26}ClN_{3O}.H_2SO_4$. It is used in Malaria, Lupus Erythematosus & Rheumatoid Arthritis.[11]

Experimental Works:

In this research study, hydroxychloroquine binding affinity with Covid-19 main protease was accessed through Grid-Based Docking studies by using VLife MDS software. [12] Covid-19 main protease structure was downloaded from RCSB Protein Data Bank (PDB ID: 6LU7)[13] and saved in PDB file format. The structure was present in the complex with an inhibitor N3, therefore the ligand was first removed and then the protease structure was used for further docking studies. Hydroxychloroquine structure was drawn using Marvin JS (Chem Axon) at RCSB PDB and it was also saved in PDB file format. The structure of Hydroxychloroquine and Covid-19 main protease ise shown in figure 4 and figure 5.

Docking studies were performed by using the Biopredicta software tool, where grid-based docking was made by selecting Hydroxychloroquine as the ligand molecule and Covid-19 main protease as the receptor molecule. The cavity number was set as 1, the angle of rotation was set as 25.0 ,and then the docking score was calculated. After successful completion of the docking process, a docked

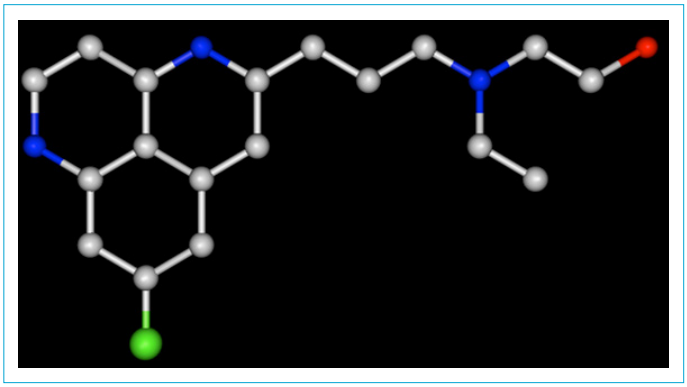

Figure 4. Hydroxychloroquine.

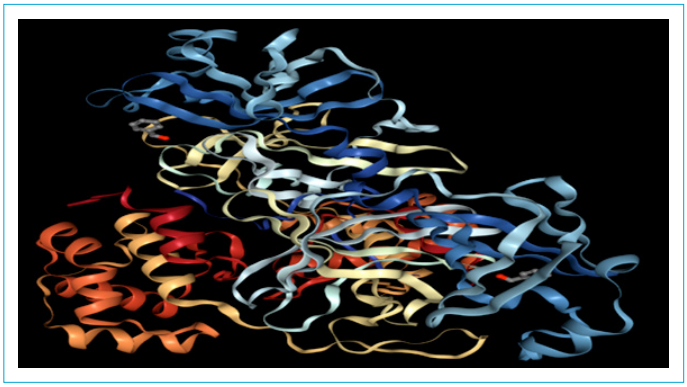

Figure 5. Crystal Structure of Covid 19 main protease.

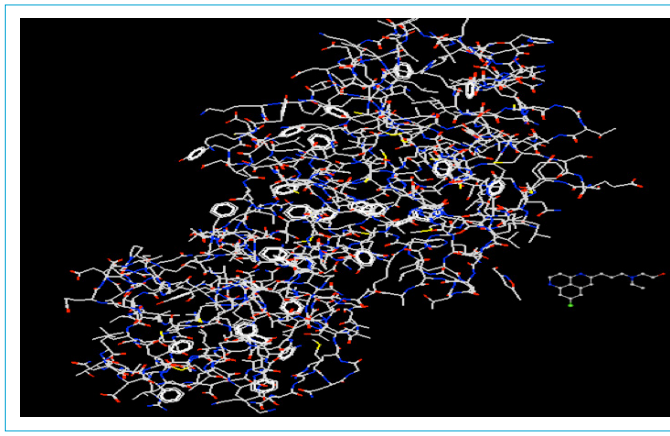

Figure 6. Structures of Covid 19 Protease and Hydroxychloroquine before docking.

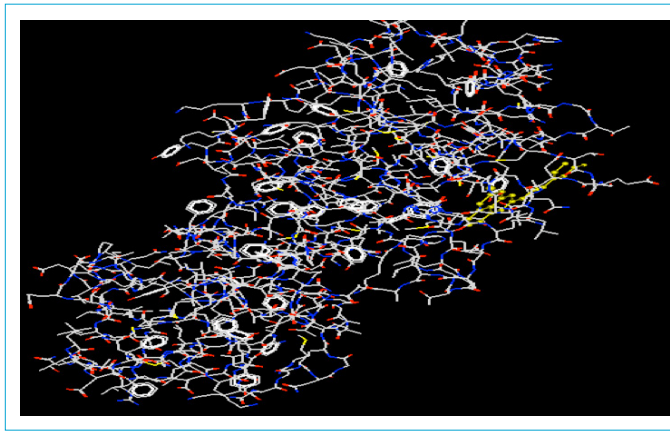

Figure 7. Docked Complex (Hydroxychloroquine is shown in golden colour ball and stick model).

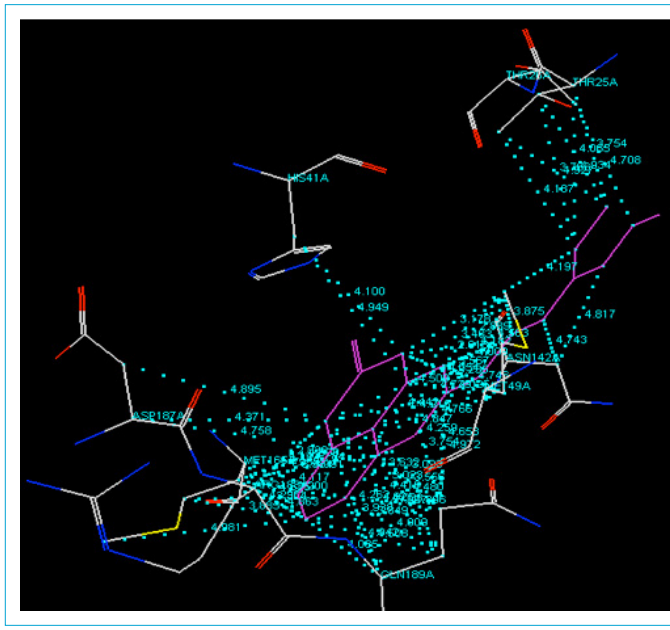

Figure 8. Hydrophobic Interaction.

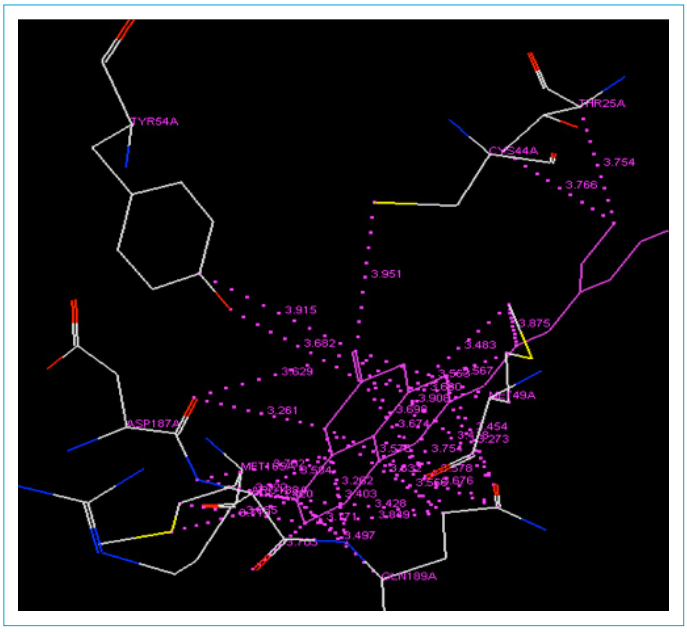

Figure 9. Van der Waals Interaction.

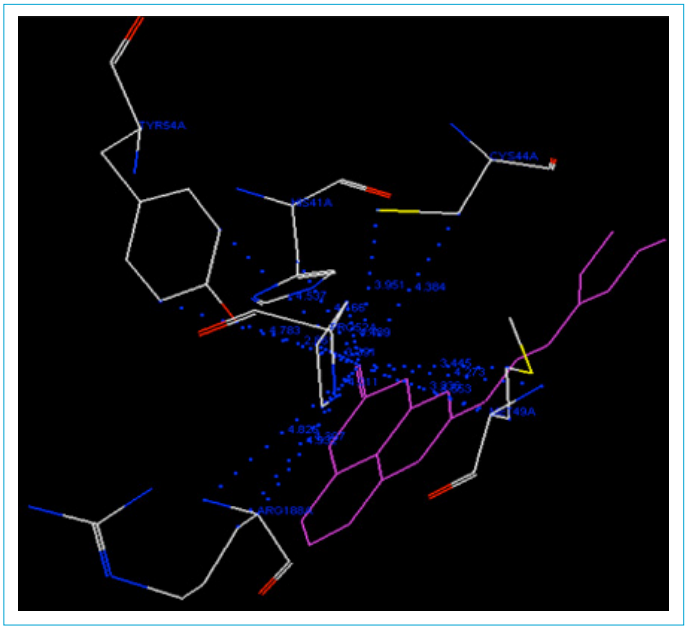

Figure 10. Charge Interaction.

complex was formed and then the interaction between the ligand and receptor molecule was detected.

Result and Discussion

The current docking studies revealed that Hydroxychloroquine has a good binding affinity for Covid-19 main protease (Figs. 6, 7). The resulting docking score was -4.308880 and the number of receptor atoms was 77, while the number of ligand atoms was 20, indicating that Hydroxychloroquine binds effectively with Covid-19 protease. The binding affinity was confirmed by hydrophobic, charged and Van der Waals

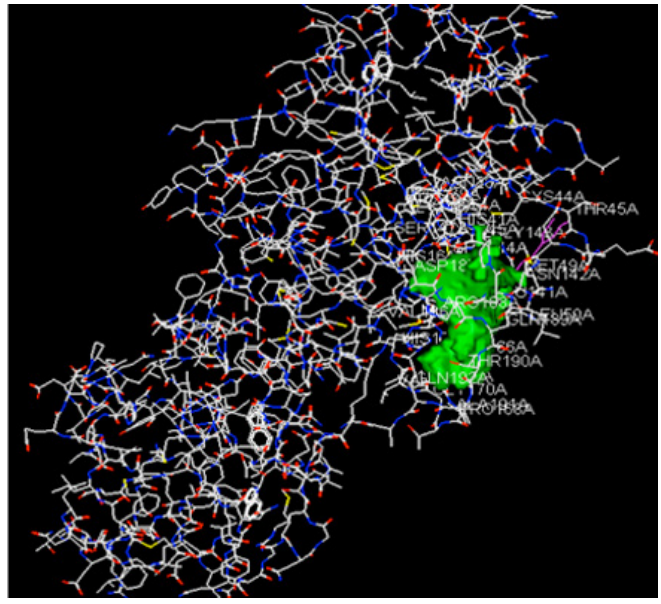

Figure 11. Cavity Surface with Ligand and Receptor Atoms.

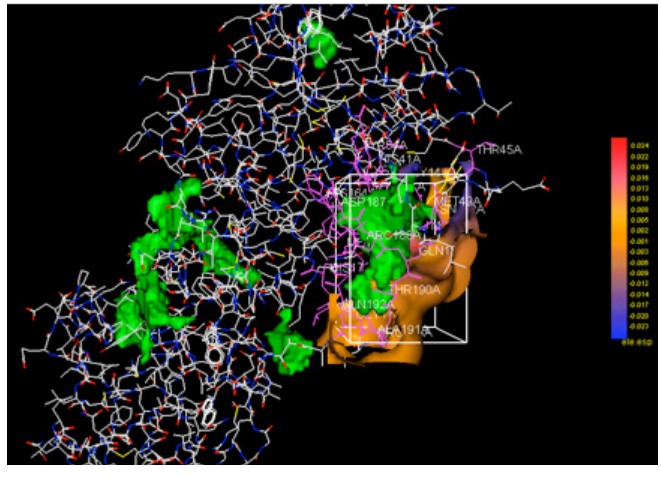

Figure 12. Cavity points Mapped properties and Grid Box.

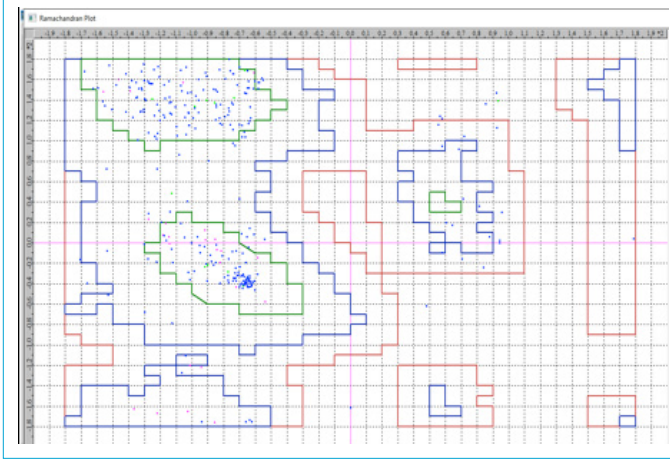

Figure 13. Ramachandran Plot for Ligand-Receptor Complex.

type of interaction between ligand and receptor molecules with a total of 123 interactions.. Amino acid residues actively involved in binding with ligand atoms were THR (Threonine), HIS (Histidine), MET (Methionine), ASN (Asparagine), ASP (Aspartic acid), ARG (Arginine), GLN (Glutamine), CYS (Cysteine), PRO (Proline), TYR (Tyrosine) and all of these showed different types of interactions. Detailed data on main interactions with residue atom, ligand atom and distance are shown in Table: 1 and Figure 8, Figure 9, Figure 10, Figure 11, Figure 12 and Figure 13 for various types of interactions.

Conclusion

The 2019-Novel coronavirus (nCoV) is the main source of disaster in the 21st century. However, the lack of specific drugs to prevent/treat an attack is a major need at this time. Drug discovery against the CoV is a challenging task owing to recurrent recombination events. Developing a a vaccine is another important issue. However, preventive measures need to be taken to spreading the SARs. From current molecular docking studies, it is concluded that hydroxychloroquine may act as a as a preventive drug for the treatment of SARS, as it acts as a potent inhibitor of the Covid-19 main protease and shows good binding affinity with the macromolecule with a very good docking score and various binding interactions. Prophylactic and therapeutic treatment can be done using Hydroxychloroquine to combat Covid-19 infections.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – J.K.M.; Design – H.S.; Supervision – J.K.M.; Materials – S.S.; Data collection &/or processing – J.K.M.; Analysis and/or interpretation – S.S.; Literature search – H.S.; Writing – S.S.; Critical review – J.K.M.

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14. RCSB Protein Data Bank. Available at: www.rcsb.org Accessed Sep 17, 2020.

Table 1. Interactions between Hydroxychloroquine and Covid-19 main protease

Residue Atom	Ligand Atom	Distance	Interaction Type
1 THR25A 197C	19C	4.934	HYDROPHOBIC_INTERACTION
2 THR25A 197C	20C	3.754	HYDROPHOBIC_INTERACTION
3 THR25A 200C	19C	4.927	HYDROPHOBIC_INTERACTION
4 THR25A 200C	20C	4.065	HYDROPHOBIC_INTERACTION
5 THR25A 202C	19C	4.187	HYDROPHOBIC_INTERACTION
6 THR25A 202C	20C	3.766	HYDROPHOBIC_INTERACTION
7 THR26A 209C	22C	4.708	HYDROPHOBIC_INTERACTION
8 HIS41A 330C	10C	4.949	HYDROPHOBIC_INTERACTION
9 HIS41A 330C	11C	4.100	HYDROPHOBIC_INTERACTION
10 MET49A 388C	3C	4.442	HYDROPHOBIC_INTERACTION
11 MET49A 388C	11C	4.054	HYDROPHOBIC_INTERACTION
12 MET49A 391C	3C	4.215	HYDROPHOBIC_INTERACTION
13 MET49A 391C	4C	4.847	HYDROPHOBIC_INTERACTION
14 MET49A 391C	9C	4.766	HYDROPHOBIC_INTERACTION
15 MET49A 391C	10C	4.025	HYDROPHOBIC_INTERACTION
16 MET49A 391C	11C	3.235	HYDROPHOBIC_INTERACTION
17 MET49A 391C	14C	4.746	HYDROPHOBIC_INTERACTION
18 MET49A 392C	3C	4.500	HYDROPHOBIC_INTERACTION
19 MET49A 392C	9C	4.729	HYDROPHOBIC_INTERACTION
20 MET49A 392C	10C	3.567	HYDROPHOBIC_INTERACTION
21 MET49A 392C	11C	2.618	HYDROPHOBIC_INTERACTION
22 MET49A 392C	14C	4.009	HYDROPHOBIC_INTERACTION
23 MET49A 394C	10C	3.483	HYDROPHOBIC_INTERACTION
24 MET49A 394C	11C	3.178	HYDROPHOBIC_INTERACTION
25 MET49A 394C	13C	4.182	HYDROPHOBIC_INTERACTION
26 MET49A 394C	14C	2.889	HYDROPHOBIC_INTERACTION
27 MET49A 394C	15C	4.563	HYDROPHOBIC_INTERACTION
28 MET49A 394C	16C	3.875	HYDROPHOBIC_INTERACTION
29 MET49A 394C	19C	4.197	HYDROPHOBIC_INTERACTION
30 ASN142A 1124C	17C	4.743	HYDROPHOBIC_INTERACTION
31 ASN142A 1124C	21C	4.817	HYDROPHOBIC_INTERACTION
32 MET165A 1297C	6C	4.625	HYDROPHOBIC_INTERACTION
33 MET165A 1297C	7C	4.117	HYDROPHOBIC_INTERACTION
34 MET165A 1297C	8C	4.784	HYDROPHOBIC_INTERACTION
35 MET165A 1300C	4C	4.959	HYDROPHOBIC_INTERACTION
36 MET165A 1300C	6C	3.304	HYDROPHOBIC_INTERACTION
37 MET165A 1300C	7C	3.200	HYDROPHOBIC_INTERACTION
38 MET165A 1300C	8C	4.091	HYDROPHOBIC_INTERACTION
39 MET165A 1300C	9C	4.890	HYDROPHOBIC_INTERACTION
40 MET165A 1301C	6C	3.885	HYDROPHOBIC_INTERACTION
41 MET165A 1301C	7C	4.296	HYDROPHOBIC_INTERACTION
42 MET165A 1303C	6C	4.981	HYDROPHOBIC_INTERACTION
43 ASP187A 1462C	3C	4.371	HYDROPHOBIC_INTERACTION
44 ASP187A 1462C	4C	4.758	HYDROPHOBIC_INTERACTION
45 ASP187A 1465C	3C	4.895	HYDROPHOBIC_INTERACTION
46 ARG188A 1470C	3C	2.830	HYDROPHOBIC_INTERACTION
47 ARG188A 1470C	4C	3.584	HYDROPHOBIC_INTERACTION
48 ARG188A 1470C	6C	4.863	HYDROPHOBIC_INTERACTION
49 ARG188A 1473C	3C	4.142	HYDROPHOBIC_INTERACTION
50 GLN189A 1481C	3C	4.262	HYDROPHOBIC_INTERACTION

Table 1. CONT.

Residue Atom	Ligand Atom	Distance	Interaction Type
51 GLN189A 1481C	4C	3.938	HYDROPHOBIC_INTERACTION
52 GLN189A 1481C	6C	4.085	HYDROPHOBIC_INTERACTION
53 GLN189A 1481C	7C	4.942	HYDROPHOBIC_INTERACTION
54 GLN189A 1481C	9C	4.821	HYDROPHOBIC_INTERACTION
55 GLN189A 1484C	3C	4.416	HYDROPHOBIC_INTERACTION
56 GLN189A 1484C	4C	4.036	HYDROPHOBIC_INTERACTION
57 GLN189A 1484C	6C	4.508	HYDROPHOBIC_INTERACTION
58 GLN189A 1484C	7C	4.909	HYDROPHOBIC_INTERACTION
59 GLN189A 1484C	8C	4.896	HYDROPHOBIC_INTERACTION
60 GLN189A 1484C	9C	4.480	HYDROPHOBIC_INTERACTION
61 GLN189A 1485C	3C	3.632	HYDROPHOBIC_INTERACTION
62 GLN189A 1485C	4C	3.023	HYDROPHOBIC_INTERACTION
63 GLN189A 1485C	6C	3.849	HYDROPHOBIC_INTERACTION
64 GLN189A 1485C	7C	3.907	HYDROPHOBIC_INTERACTION
65 GLN189A 1485C	8C	3.556	HYDROPHOBIC_INTERACTION
66 GLN189A 1485C	9C	3.096	HYDROPHOBIC_INTERACTION
67 GLN189A 1485C	10C	3.754	HYDROPHOBIC_INTERACTION
68 GLN189A 1485C	11C	4.259	HYDROPHOBIC_INTERACTION
69 GLN189A 1485C	13C	4.972	HYDROPHOBIC_INTERACTION
70 GLN189A 1485C	14C	4.653	HYDROPHOBIC_INTERACTION
71 HIS41A 330C	1Cl	4.166	CHARGE_INTERACTION
72 CYS44A 355C	1Cl	4.384	CHARGE_INTERACTION
73 CYS44A 356S	1Cl	3.951	CHARGE_INTERACTION
74 MET49A 387N	1Cl	4.273	CHARGE_INTERACTION
75 MET49A 388C	1Cl	3.236	CHARGE_INTERACTION
76 MET49A 391C	1Cl	3.553	CHARGE_INTERACTION
77 MET49A 392C	1Cl	3.445	CHARGE_INTERACTION
78 PRO52A 415C	1Cl	4.489	CHARGE_INTERACTION
79 PRO52A 416C	1Cl	3.391	CHARGE_INTERACTION
80 PRO52A 417C	1Cl	4.011	CHARGE_INTERACTION
81 TYR54A 434C	1Cl	4.537	CHARGE_INTERACTION
82 TYR54A 435C	1Cl	4.783	CHARGE_INTERACTION
83 TYR54A 437O	1Cl	2.861	CHARGE_INTERACTION
84 ARG188A 1469N	1Cl	4.826	CHARGE_INTERACTION
85 ARG188A 1470C	1Cl	4.307	CHARGE_INTERACTION
86 ARG188A 1473C	1Cl	4.932	CHARGE_INTERACTION
87 THR25A 197C	20C	3.754	VDW_INTERACTION
88 THR25A 202C	20C	3.766	VDW_INTERACTION
89 CYS44A 356S	1Cl	3.951	VDW_INTERACTION
90 MET49A 388C	2C	3.630	VDW_INTERACTION
91 MET49A 389C	1Cl	3.908	VDW_INTERACTION
92 MET49A 390O	1Cl	3.698	VDW_INTERACTION
93 MET49A 390O	2C	3.674	VDW_INTERACTION
94 MET49A 390O	3C	3.576	VDW_INTERACTION
95 MET49A 391C	1Cl	3.553	VDW_INTERACTION
96 MET49A 392C	10C	3.567	VDW_INTERACTION
97 MET49A 394C	10C	3.483	VDW_INTERACTION
98 MET49A 394C	16C	3.875	VDW_INTERACTION
99 TYR54A 436C	1Cl	3.915	VDW_INTERACTION
100 TYR54A 437O	2C	3.682	VDW_INTERACTION

Table 1. CONT.

Residue Atom	Ligand Atom	Distance	Interaction Type
101 MET165A 1301C	6C	3.885	VDW_INTERACTION
102 MET165A 1302S	5N	3.713	VDW_INTERACTION
103 ASP187A 1464O	1Cl	3.629	VDW_INTERACTION
104 ASP187A 1464O	3C	3.261	VDW_INTERACTION
105 ARG188A 1469N	4C	3.702	VDW_INTERACTION
106 ARG188A 1469N	5N	3.322	VDW_INTERACTION
107 ARG188A 1470C	4C	3.584	VDW_INTERACTION
108 ARG188A 1470C	5N	3.420	VDW_INTERACTION
109 ARG188A 1472O	6C	3.703	VDW_INTERACTION
110 GLN189A 1480N	3C	3.262	VDW_INTERACTION
111 GLN189A 1480N	4C	3.403	VDW_INTERACTION
112 GLN189A 1480N	5N	3.171	VDW_INTERACTION
113 GLN189A 1481C	5N	3.497	VDW_INTERACTION
114 GLN189A 1485C	3C	3.632	VDW_INTERACTION
115 GLN189A 1485C	5N	3.428	VDW_INTERACTION
116 GLN189A 1485C	6C	3.849	VDW_INTERACTION
117 GLN189A 1485C	8C	3.556	VDW_INTERACTION
118 GLN189A 1485C	10C	3.754	VDW_INTERACTION
119 GLN189A 1486C	8C	3.676	VDW_INTERACTION
120 GLN189A 1486C	9C	3.578	VDW_INTERACTION
121 GLN189A 1487O	10C	3.418	VDW_INTERACTION
122 GLN189A 1487O	13C	3.273	VDW_INTERACTION
123 GLN189A 1487O	14C	3.454	VDW_INTERACTION