# In Silico screening of Organo-selenium compounds for anti-viral activity against SARS-CoV2

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**Abstract**

Since the outbreak of the COVID-19 pandemic, researchers have been investigating several low molecular weight compounds, from both natural and synthetic origins, to design antiviral drugs against SARS-CoV-2. Recent work with selenium has demonstrated that its deficiency in human body leads to increased viral pathogenesis. Ebselen, a gold standard organoselenium compound, has shown promising anti-SARS-CoV-2 activity under *in-vitro* studies. With this background, the present study aimed to evaluate different organoselenium compounds and their sulfur analogues using a molecular docking approach to inhibit proteins that play a significant role in SARS-CoV-2 transmission. The organoselenium compounds used in the study are mostly synthesized *in-house,* including simple selenium containing amino acids and their derivatives, ebselen and their derivatives, selenopyridines and their derivatives. For the study, two viral protein Spike (S) Glycoprotein (PDB code: 6VXX) and Main Protease (3CLpro) (PDB code: 6LU7) of SARS-CoV-2 were used. The compounds were evaluated by comparing the docking scores calculated using AutoDock Vina as a docking engine. For comparison, standard drugs like Remdesivir and hydroxychloroquine (HOCQ) were used. The results showed that among all the molecules screened, the organoselenium compounds mostly showed stronger binding with the proteins as compared to their sulfur analogue, except oxidized glutathione. Additionally, ebselendiselenide (EbSeSeEb) and nicotinamide diselenide (NictSeSeNict) showed better inhibition to both the viral proteins as compared to Remdesivir and HOCQ. Thus, the present investigation highlights the influence of structure and substitution of organoselenium compound on their binding with the SARS-CoV-2 proteins and proposes NictSeSeNict as a candidate molecule for evaluating antiviral activity against SARS-CoV-2 using preclinical biological models.

## Introduction

Corona viruses (CoV) are a family of viruses containing positive strand ribonucleic acid (RNA) as a genetic material. In the past, these viruses have been reported for causing outbreaks of fetal pneumonia-like respiratory diseases in humans. The examples of such outbreaks are Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) during 2003 and 2012 respectively. Recently, in December 2019, several unidentified cases of pneumonia were reported from Wuhan, China. The molecular analysis of the bronchiolar lavage fluid (BAL) of these patients indicated the presence of a virus with RNA genome having more than 80% similarity with SARS-CoV. Accordingly, this virus was named as SARS-CoV-2 by International Virus Classification Commission on February 11, 2020. In a very short period of time, this virus has spread to several countries and as of today, there are nearly 24.3 million confirmed cases of SARS-CoV-2 infections worldwide and more than 8,28,000 deaths. In view of the increasing infections, the World Health Organization (WHO) named the SARS-CoV2 induced pathology as COVID-19 and declared this outbreak a pandemic on March 12, 2020. Currently, there is no specific treatment available for COVID-19 and therefore the outbreak poses huge threat to humans [1].

With regard to developing a therapeutic drug against COVID-19, the best strategy is to identify an already approved drug with some other indication for the efficacy against COVID-19. The advantages of using known drugs are that their dosages, route of administration, metabolic characteristics, potential efficacy and side effects are well characterized. This process is called drug repurposing and is the fastest way of drug development against new diseases. Indeed, several active clinical trials are in progress globally to evaluate several of food and drug administration (FDA) approved drugs for their efficacy against COVID-19. These include antiviral drugs, IL-6 antagonist and hydrocholoroquine (HOCQ) among others. Although these treatment strategies have shown considerable success in the clinical setting, none of these have been approved by FDA as a standard treatment protocol for COVID-19. This warrants the need for the development of vaccine and/or new specific drugs against COVID-19 [1,2].

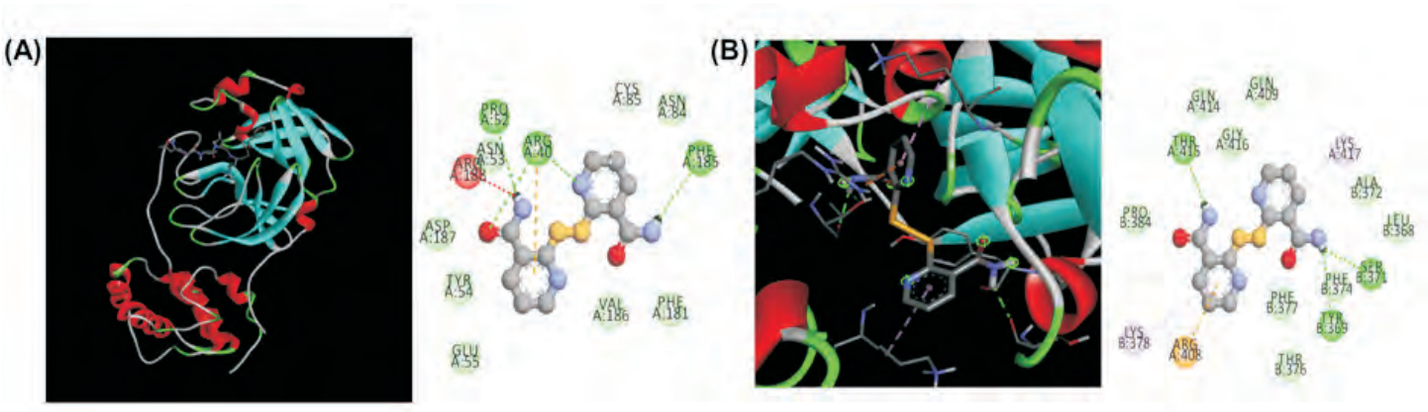
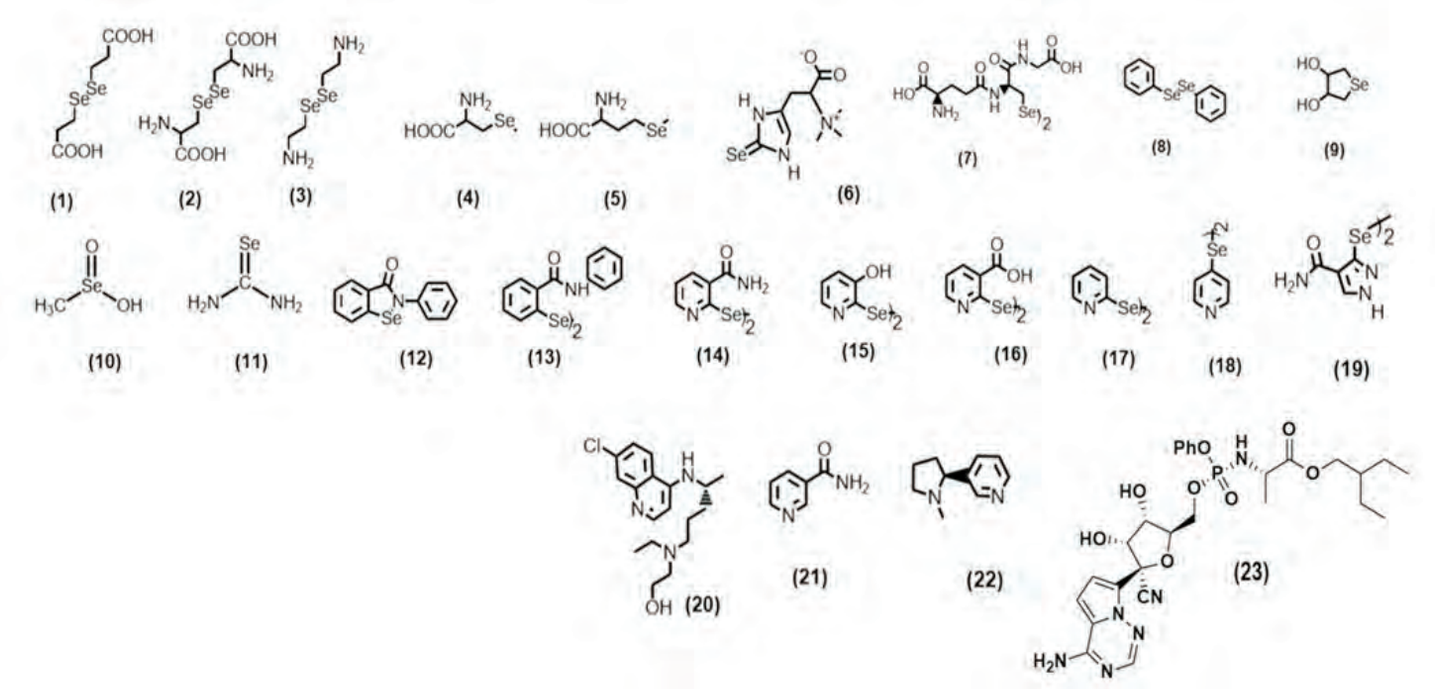



**Fig. 1: (A) Low energy binding conformation of NictSeSeNict with $M^{pro}$ of SARS-CoV2 (B) Low energy binding conformation of NictSeSeNict with spike protein of SARS-CoV2**

With the evolving knowledge of the pathophysiology of COVID-19, it has emerged that drugs targeting viral processing (entry and its replication within host cells) as well as the associated inflammatory responses could be the potential candidate drug molecules against COVID-19. Extensive research over the years has established that selenium- a micronutrient for humans- plays a very important role in maintaining the immune functions of body and in turn develops resistance against viral infections. Further, it is also known from the available literature that selenium deficiency enhances the probability of viral infection as well severity of viral diseases [3, 4]. Selenium boosts the immunity of host cells against viral infections by inducing the levels of selenoproteins with antioxidant activities like glutathione peroxidase (GPx) and thioredoxin reductase (TrxR) and altering the cellular redox state with the help of these proteins. In recent times, several of synthetic organoselenium compounds have been reported for various pharmacological activities, including anti-inflammatory and antiviral activities. Indeed, a recent publication in the popular journal *Nature* supports this hypothesis and has revealed that organoselenium compounds like ebselen could be potent inhibitor of viral proteins involved in replication of SARS-CoV2 within host cells [5]. Our group had been working on the similar research area with an objective to develop organoselenium compound based drugs for lung pathology. In this context, we have identified a compound called 3'-3' diselenodipropionic acid (DSePA) for its efficacy in preventing the radiation-induced pneumonia or inflammatory response in the lungs [6]. Additionally, the molecule also gains significance, as it is orally administrable. The lethal dose ($LD_{50}$) of DSePA is considerably higher than the known orgnoselenium compounds like selenomethionine and methyl selenocysteine that are available in market as health supplements. With this background, it was felt that it would be worth investigating DSePA and other related organodiselenides for possible interaction with viral proteins to act as inhibitors. In order to address this hypothesis, we used recently reported structures of spike (S) protein and 3 chymotrypsin-like protease ($3CL^{pro}$) or main protease ($M^{pro}$) involved in the entry and replication respectively of SARS-CoV2 within host cells for docking with the organoselenium compounds. The results were compared with standard antiviral drug like Remsdesivir and other standards like HOCQ reported in literature for potential activity against SARS-CoV2.

**Experimental method**

The structures of the different ligands (shown in scheme 1) for docking were prepared and the energies were minimized on Gamess, and saved as Mol2 file. All the protein structures were retrieved from protein data bank (www.rcsb.org). The molecular docking was performed on AutoDock Vina. In brief, the protein structures were freed from ligands and water molecules manually from the pdb files. The polar hydrogens and Kollman charges were added and the protein structures were saved in pdbqt format. Binding site for docking was defined by choosing amino acid residues present in the given domains expressed as grid region-according to the values reported in the literature [7]. The grid values of the different proteins are given below: SARS-CoV-2 spike: (center_x = 190.45, center_y = 197.88, center_z = 260.72, size_x = 61.32, size_y = 41.03, size_z = 43.79), SARS-CoV-2 main protease: (center_x = 16.69, center_y = 27.23, center_z = 68.46, size_x = 36.65, size_y = 42.12, size_z = 50.40). The scoring function and the binding energy of the ligands were ranked according to the RMDS by the building program in Autodock.




***Scheme 1:*** Structure of organoselenium compounds screened for docking. In case of selenium compounds, their corresponding sulfur compounds and urea were also docked[Structure refers to 1. Diselenodipropanoic acid (DSePA), 2. Selenocystine (CysSeSeCys), 3. Selenocystamine (DSePAmine), 4. Methyl selenocysteine (MeSeCys), 5. Selenomethionine (SeM), 6. Selenoneine (SeHis), 7. Selenolutathioneoxi (GSeSeG), 8. Diphenyl diselenide (PhSeSePh), 9. Dihydroxyl selenolane (DHS), 10. Methane selenenic acid (MSeA), 11. Selenourea (SeU)*, 12. Ebselen (EbSe), 13. Ebselendiselenide (EbSeSeEb), 14. Nicotinamide diselenide (NictSeSeNict), 15. Pyridinoldiselenide (HOPySeSePyOH), 16. Nicotinic acid diselenide (CarPySeSePyCar), 17. 2-pyridine diselenide (2-PySeSePy), 18. 4-pyridine diselenide (4-PySeSePy), 19. Pyrazole amide diselenide (PyzSeSePyz), 20. Hydroxylchloroquine (HOCQ), 21. Nicotinamide, 22. Nicotine and 23. Remdesivir)

## Results and Discussion

The genome of SARS-CoV2 encodes for structural proteins like spike (S) protein, envelope (E) protein, membrane (M) protein, nucleocapsid (N) protein and non-structural protein like replicase polyprotein. The structural proteins are involved in the formation of viral coat and the packaging of the RNA genome. The polyproteins undergo proteolytic cleavage to release proteins involved in viral replication and transcription by viral proteases $3CL^{pro}$ or $M^{pro}$, which by itself is released from polyproteins through autolytic cleavage. The S protein present in viral coat interacts with surface receptors like angiotensin-converting enzyme 2 (ACE2) to facilitate its entry in host cells (like lung epithelium). The functional importance of S and $M^{pro}$ in establishing SARS-CoV2 infection along with the absence of a closely related homologue of these proteins in humans, proposes them as an attractive target for the design of anti-viral drugs [8-11]. The molecular docking study of the above viral proteins with organoselenium compounds (Scheme 1) with varying functional groups have revealed a strong interaction with binding affinity ranging from approximately -3.0 kcal/mol to -9.0 kcal/mol. The binding energy of all the compounds with S and $M^{pro}$ of SARS-CoV2 are listed in Table 1. The results of the docking studies with the individual proteins are discussed under following sections:

### Interaction of organoselenium with S protein

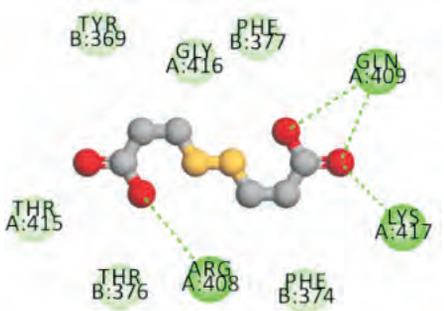
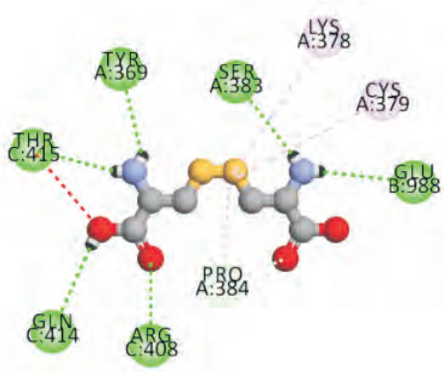
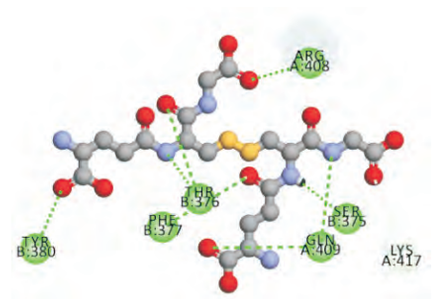
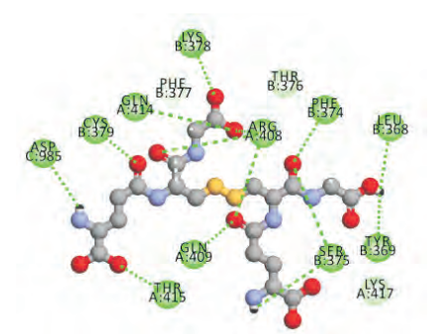
The S protein, a homotrimeric glycoprotein, interacts with host receptor, ACE2, via the receptor-binding domain (RBD). The RBD is known to exist in at least two primary conformational states called the up (receptor-accessible) and down (receptor-inaccessible) states. When the RBD is in the up state, the S protein is more "open" to facilitate the binding of ACE2. Studies have suggested that the down, receptor-inaccessible state, is more stable. This implies that low molecular weight molecules capable of binding RBD could stabilize the RBD in the down state, preventing the virus from interacting with ACE2; and thus limiting the COVID-19 infection [12]. Accordingly, for the present study, the down state form of the protein was used for docking (PDB code: 6VXX). The RBD region in S protein lies in the range from residues 331 to 524, while the most active amino acid residues are from 415 to 505 [13-16]. The binding energies of the organoselenium compound and their sulfur analogue with the S glycoprotein in terms of Vina scoring function are given in (Table 1). Docking results revealed that out of 19 selected organoselenium compounds,

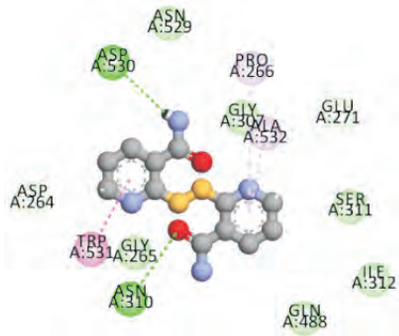
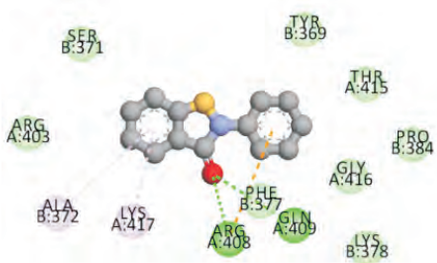
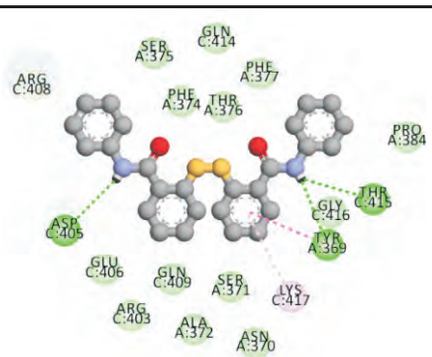
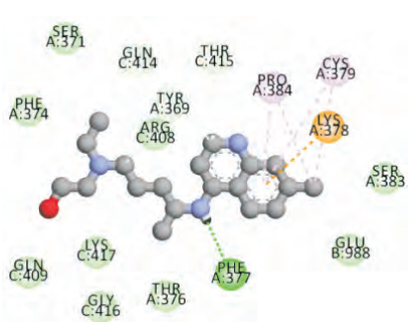
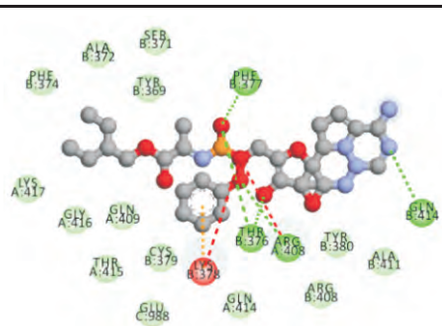
**Table 1:** Binding energy of the organoselenium compounds, their sulfur analogues and reference molecules (Nictotine*, Nictotinamide* and Remdesivir*) with SARS-CoV2 proteins.

| Sr. Nos | Compounds | Binding Energy (kcal/mol) | | | |
|---|---|---|---|---|---|
| | | 6VXX (S) | | 6LU7 ($M^{pro}$) | |
| | | Se | S | Se | S |
| 1 | DSePA | -4.5 | -4.1 | -4.5 | -3.9 |
| 2 | CysSeSeCys | -5.5 | -5.2 | -4.7 | -4.3 |
| 3 | DSePAmine | -3.6 | -3.5 | -3.3 | -3.1 |
| 4 | MeSeCys | -4.2 | -4.5 | -4 | -4.1 |
| 5 | SeM | -4 | -4 | -3.4 | -3.9 |
| 6 | Se-His | -5.7 | -5.8 | -4.7 | -4.7 |
| 7 | GSeSeG | -6.6 | -7.3 | -5.1 | -5.5 |
| 8 | PhSeSePh | -5.8 | -5.2 | -5.2 | -5 |
| 9 | DHS | -4 | -4 | -3.8 | -3.8 |
| 10 | MSeA | -3.8 | -3 | -3.1 | -3.1 |
| 11 | SeU | -3.1 | -3.6 | -3.2 | -3.3 |
| 12 | EbSe | -6.3 | -6.3 | -5.4 | -5.4 |
| 13 | EbSeSeEb | -9.4 | 8 | -7 | -6.2 |
| 14 | NictSeSeNict | -8.1 | -7.4 | -6.6 | -5.7 |
| 15 | HOPySeSePyOH | -6.8 | -6 | -5.8 | -5 |
| 16 | CarPySeSePyCar | -7.1 | -6.4 | -5.8 | -5.2 |
| 17 | 2-PySeSePy | -6.1 | -5.6 | -5.1 | -4.8 |
| 18 | 4-PySeSePy | -5.3 | -5.4 | -4.5 | -4.2 |
| 19 | PyzSeSePyz | -8 | -7.5 | -6.2 | -5.5 |
| 20 | Nicotinamide* | -5 | | -4.3 | |
| 21 | Nicotine* | -5.2 | | -4.2 | |
| 22 | HOCQ* | -6.3 | | -4.9 | |
| 23 | Remdesivir* | -8.2 | | -3.2 | |

the aliphatic selenium compounds showed lower binding as compared to the aromatic derivatives. In this series of compounds, only EbSeSeEb and NictSeSeNict showed higher binding interaction compared to the standard molecule, HOCQ and Remdesivir. The carboxylate group in DSePA, an aliphatic diselenide, is involved in conventional hydrogen bonding with Arg408, Gln 409 and Lys 417, while the aliphatic and diselenide moiety are involved in Van der Waals interaction with the amino acid residue (Table 2). Further in CysSeSeCys, where an amino group is added as compared to DSePA, along with the hydrogen bonding (Tyr369, Ser383, Thr415, Gln414, Arg408, Pro384, Ser383), alkyl interaction of Lys375 and Cys379 with the diselenide bond is observed. The amino group of CysSeSeCys is found to be involved in hydrogen bonding with Thr415, an amino acid involved in the receptor binding domain of S protein. This results in an increase in the binding energy of CysSeSeCys as compared to DSePA (Interaction as depicted in Table 2). On increasing the peptide bond as seen in GSeSeG and GSSG, the number of conventional bonds increase, which is reflected in the increase in the binding energy of these compounds with the S-protein. Also, the number of interactions observed is more in case of GSSG as compared to GSeSeG, which may be attributed to the size of the molecule to fit in the binding site. This results in the higher binding energy of GSSG. The aromatic organoselenium compounds showed higher binding energy compared to the similar molecular weight aliphatic analogues (for eg DSePA). This is attributed to the induction of pi-alkyl interaction along with the conventional hydrogen bonding interaction. Further, comparing the binding energy of aromatic compounds with different functional group such as carboxylate (CarPySeSePyCar), hydroxy (HOPySeSePyOH) and amide (NictSeSeNict), indicated that the compounds with amide functional group showed higher binding with the

**Table 2:** The amino acid residues involved in binding of organoselenium compounds with viral S protein (PDB Code: 6VXX). 🟢🟢🟣🟠🔴 represent hydrogen bonding, Van der Waals binding, pi-alkyl interaction, pi-cation attraction interaction and repulsive interaction.

| | | 2D Interaction |
|---|---|---|
| 1. | DSePA<br>Binding Energy = -4.5kcal/mol |  |
| 2. | CysSeSeCys<br>Binding Energy = -5.5kcal/mol |  |
| 3 | GSeSeG<br>Binding Energy = - 6.6kcal/mol |  |
| 4 | GSSG<br>Binding Energy = - 7.3 kcal/mol |  |

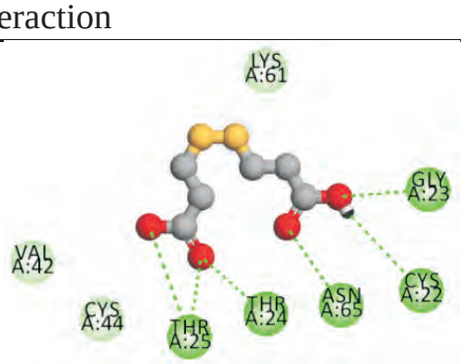
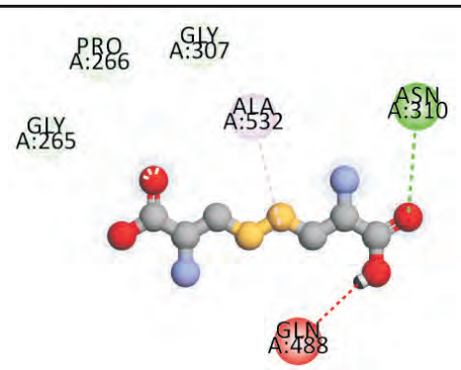
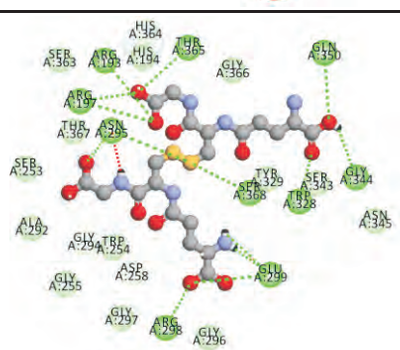
| | | |
|---|---|---|
| 5 | NictSeSeNict<br>Binding Energy= -8.1kcal/mol |  |
| 6 | Ebselen<br>Binding Energy = -6.3 kcal/mol |  |
| 7 | Ebselendiselenide<br>Binding Energy = -9.4 kcal/mol |  |
| 8 | HOCQ<br>Binding energy = -6.3 kcal/mol |  |
| 9 | Remdesivir<br>Binding energy = -8.2 kcal/mol |  |

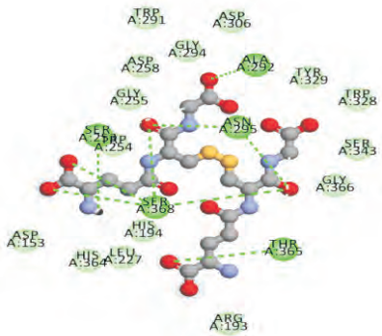
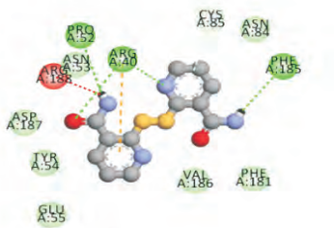
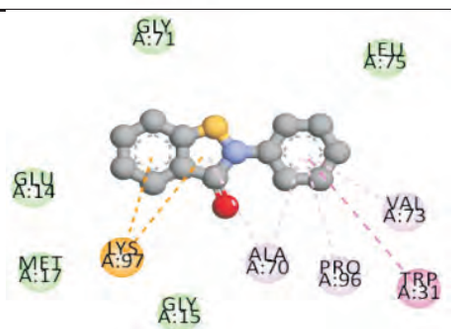
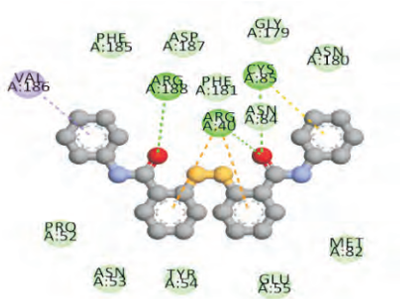
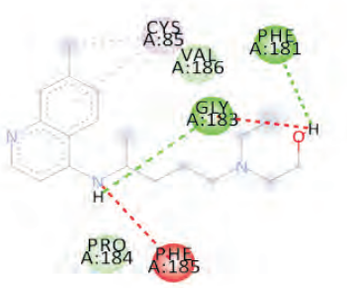
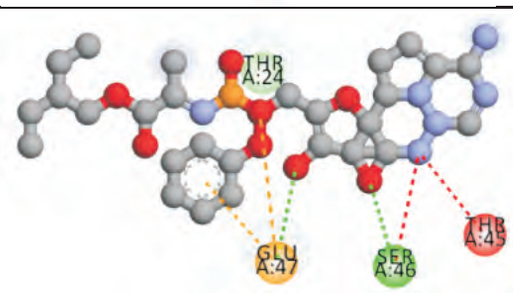
protein. The increase in binding energy may be attributed to the presence of hydrogen bond between -NH atom of amide and Thr415 of the protein. The amino acid, Thr415, is involved in the receptor binding domain of the S-protein. Similarly, the influence of heterocyclic diselenide can be compared from the values obtained for EbSeSeEb, PyzSeSePyz and NictSeSeNict. The presence of the N-hetrocyclic ring is found to influence the binding of the compound slightly away from the Thr415 residue where as the simple aromatic ring as seen in ebselen and its diselenide binds to Thr415, thus increasing the binding with the S-protein. Further, the plain ligand without selenium moiety was also docked to evaluate the influence of selenium atom in the binding. It was observed that the binding energy of the nictotiamide ligand was lesser compared to the diselenide form. The binding energy of 2,2'-dipyrdine diselenide was higher than the nicotinamide ligand. Higher binding values may be due to the presence of two aromatic rings in the molecule. The docking of the selone (the monoselenide form) form of NictSeSeNict showed similar value to nicotinamide ligand. The dipyrdine with amide group at the ortho position may itself be showing good affinity for S-protein. However, this molecule is not easy to synthesize and is also expected to be instable. On the contrary, the diselenide bond may act as a bridge to form the dinicotinamide moiety to get the desired activity.

### Interaction of organoselenium with $M^{pro}$ protein

$M^{pro}$ protein is a homodimer comprising of three domains viz., domain I (residue 8-101), domain II (residue 102-184) and domain III (residue 201-203) and a long loop (residues 201–303). The catalytic region is formed by the dyad His41-Cys145 that is highly conserved among the coronavirus proteases. This probable binding site for substrates is located in a cleft region between domains I and II, which is similar to that observed in the trypsin-like serine proteases. Table 3 shows the nature of

**Table 3:** The amino acid residues involved in binding of the organoselenium compounds and the viral $M^{pro}$ protein (PDB Code: 6LU7). represent hydrogen bonding, Van der Waals binding, pi-alkyl interaction, pi-cation attraction interaction and repulsive interaction.

| | | 2D Interaction |
|---|---|---|
| 1 | DSePA<br>Binding energy: -4.5 kcal/mol |  |
| 2 | CysSeSeCys<br>Binding energy = -4.7 kcal/mol |  |
| 3 | GSeSeG<br>Binding energy = -5.1 kcal/mol |  |

| | | |
|---|---|---|
| 4 | GSSG<br>Binding energy = -5.5 kcal/mol |  |
| 5 | NictSeSeNict<br>Binding Energy: -6.6 kcal/mol |  |
| 6 | Ebselen<br>Binding Energy: -5.4 kcal/mol |  |
| 7 | Ebselendiselenide<br>Binding Energy: -7.0 kcal/mol |  |
| 8 | HCQ<br>Binding Energy: -4.9 kcal/mol |  |
| 9 | Remdesivir<br>Binding Energy: -3.2 kcal/mol |  |

the binding interactions of some of the in-house synthesized organoselenium compounds like DSePA and NictSeSeNict along with the standard compounds like CysSeSeCys, ebselen, HOCQ and Remdesivir with SARS-CoV-2 main protease. The binding energy of DSePA is found to be lower than the other organoselenium compounds but it is still higher than the standard molecules, HOCQ and Remdesivir. The carboxylate group of DSePA is involved in the hydrogen bonding with Gly23, Cys22, Asn45, Thr24, Thr25, while the aliphatic alkyl diselenide chain is involved in Van der Waals interaction. However, it binds only in the domain I and is slightly away from the active site. In CySeSeCys, the amino acid residue Asp48, Ile43, Lys61, Cys44, Cys22 and Thr25 are involved in hydrogen bonding with the amino and carboxylate group of the diselenide. There is an unfavorable binding with Thr24 and the carboxylate group. Like DSePA, CysSeSeCys also binds with the amino acid in the extreme right side of domain I, these factors may be responsible for the low binding of CysSeSeCys with Mpro. As seen from the interaction in Table 3, docking of Mpro with GSeSeG, which has more number of amide bonds, exhibited higher binding energy. In case of GSSG, along with the conventional hydrogen bonding, an additional pi-alkyl interaction exists with Cys845, which is at the interface between domain I and II. This may be responsible for the higher binding energy of GSSG as compared to GSeSeG. The binding of PhSeSePh is also higher compared to similar molecular weight aliphatic compound DSePA. The lower binding energy of the aliphatic compound may be due to the wobbling of the alkyl chain, which is otherwise rigid in case of aromatic compound. Similarly, Ebselen shows binding with the amino acids present in the domain I but slightly towards the end of domain I. Hence its binding energy is also low. In case of NictSeSeNict and EbSeSeEb, it can be seen that these compounds effectively bind at the interface and near the catalytic site. The amide functional group in these molecules are involved in hydrogen bonding with polar amino residues, but the presence of aromatic ring increases the interaction between the selenium compounds and the protease by induction of hydrophobic and pi-alkyl interactions. Additionally, the binding energy of the selenium compounds is found to be higher as compared with their analogous sulfur compounds. This is attributed to the higher contribution of the Van der Waals interaction in selenium compounds, which arises due to its higher polarizability.

### *Conclusions & Future Directions*

*The present investigation revealed that organoselenium compounds exhibited higher binding affinity to the SARS-CoV2 proteins and can be suitable candidate molecules for designing an antiviral drug. Among the library of 22 organoselenium compounds studied in the present work, NictSeSeNict and EbSeSeEb showed the highest affinity for two viral proteins, namely S and $M^{pro}$. The molecular examination of the binding interaction of structurally related compounds with varying functional groups indicated that aromatic ring coupled with amide group plays an important role in establishing the interaction of organoselenium compound with the viral proteins. These results are only preliminary and our future studies will be focused to evaluate the most potent compound like NictSeSeNict by using recombinant viral proteins and active viruses. Additionally, DSePA, reported for its anti-inflammatory activity in lungs also exhibited a moderate interaction with the viral proteins, and therefore may also be effective in suppressing or delaying the pneumonia associated with COVID19. However, this hypothesis needs to be rigorously tested using preclinical models.*

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