Discovery of Potential Compounds Against SARS-COV-2 Based on 3clpro/RdRp Dual-Target an in Silico Approach

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Research Article

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Abstract

Currently, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) lacks clinically specific drugs. In this study, the new coronavirus SARS-CoV-2 3-chymotrypsin-like protease (3CLpro) and RNA-dependent RNA polymerase (RdRp) were used as targets for virtual screening. After analysis of molecular docking and molecular dynamics simulation results, ZINC04259665, ZINC12659533 and ZINC70705490 have good docking scores, and they are stable in combination with 3CLpro/RdRp. The prediction of drug-like properties found that ZINC04259665 has good druggability and has the potential to further explore its anti-SARS-CoV-2.

1 Background

Coronavirus Disease 2019 (COVID-19) resulted from infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The COVID-19 outbreak was severe and caused a great loss to the global economy. Therefore, COVID-19 becomes an urgent public health problem, but there is currently no specific drugs for the treatment of COVID-19.

Finding suitable drug targets based on the mechanism of action of the virus has become a hot spot in the research of anti-SARS-CoV-2 drugs. The nonstructural proteins of coronaviruses play a very important role for processes such as virus replication and assembly, and similar protein structures are not contained in humans[1]. The 3-chymotrypsin-like protease (3CLpro) and the RNA dependent RNA polymerase (RdRp) are two pros with high sequence conservation among non structural proteins of coronaviruses and are not susceptible to viral variation. 3CLpro and RdRp are also contained in SRAS with MERS virus[2]. 3CLpro is a class of cysteine protein whose main role is to hydrolyze the polyproteins pp1a and pp1ab encoded during coronavirus replication to produce functional proteins, and inhibition of this enzyme can inhibit the viral polypeptide translation process[3].

RdRp is a key enzyme in viral RNA replication and functions in RNA synthesis from the 5' end to the 3' end depending on the template strand[4–6]. Inhibition of this enzyme may inhibit the viral replication process.

Therefore, targeting these two targets is expected to develop drugs that are not susceptible to the mutation of SARS-COV-2, and it will also have a certain effect on the coronavirus that may appear in the future.

As a complementary technology of high-throughput screening, virtual screening has the advantages of low cost, high speed and high hit rate, and is widely used in drug discovery[7]. In this study, we used virtual screening based on the crystal structure of SARS-COV-2 3CLpro in complex with an N3 inhibitor (PDB:6LU7) and the crystal structure of RNA dependent RNA polymerase in complex with cofactor (PDB:6M71), selected virtual targets, used rigid docking, screened the top scoring
compounds, and performed molecular dynamics simulation and ADME prediction. To provide relevant data for rational development of anti SARS-COV-2 drugs.

2 Materials And Methods

2.1 Molecular docking

2.1.1 Target selection and processing

Download the high-resolution crystal structure of SARS-COV-2 3CLpro and N3 inhibitor complex (PDB ID: 6LU7) and the crystal structure of RNA polymerase and cofactor complex (PDB ID: 6M71) from the PDB database (http://www.rcsb.org). Use the Structure preparation and Protonate 3D modules of the Molecular Operating Environment (MOE) 2015.10 software to modify the chemical bond sequence, add hydrogen atoms, and remove water molecules and heteroatoms in the crystal structure of the 6LU7 structure. The Amber 10:ETH force field is used to optimize the energy of the pre-processed protein, and a PDB format file (*.pdb) is generated.

2.1.2 Ligand optimization

The Shards database (120,000 natural small molecule compounds) in the ZINC database (ZINC, http://ZINC.docking.org/) was used as the candidate molecule for the screening of potential ligands for SARS-COV-2 3CLpro. The Molecule-Energy Minimize module in MOE is used to optimize the energy minimization of each compound molecule. Under the force field Amber 10:ETH, a batch file (*.mol2) is generated.

2.1.3 Determine the docking site

The center of the target binding site grid is specified by the active site residues. On the Site Finder interface of MOE, calculate and generate 10 possible binding sites for SARS-COV-2 3CLpro, as shown in Fig. 1. The binding site 2 has a larger cavity and is similar to the original ligand N3 inhibitor. The overlapping of the pockets indicates the consistency of the pair of interface pockets and the binding sites of the ligand, which can be used for the next docking analysis. The active binding site is defined by the virtual atom established in binding site 2. The binding pocket is composed of Thr25 Thr26 Leu27 His41 Cys44 Met49 Pro52 Tyr54 Phe140 Leu141 Asn142 Gly143 Ser144 Cys145 His163 His164 Met165 Glu166 Leu167 Pro168 Asp187 Arg188 Gln189 Thr190 Ala191 Gln192 amino acids (Fig. 2).

On the Site Finder interface of MOE, calculate and generate 5 possible binding sites for SARS-COV-2 RNA-dependent RNA polymerase and cofactor complexes, as shown in Fig. 3. The binding site 11 has a larger cavity and it is located in the center of the protein and can be used for the next step of docking analysis. The active binding site is defined by the virtual atom established in the binding site 11. The binding pocket is made up of Phe165 Pro169 Leu172 Thr246 Arg249 Ala250 Leu251 Thr252 Val315 Ser318 Thr319 Pro323 Phe326 Gly327 Tyr346 His347 Phe348 Arg349 Glu350 Thr394 Cys395 Phe460 SN Thr628 Pro628 Pro628 Ser664 Val675 Lys676 Pro677 Gly678 amino acids (Fig. 4).
2.1.4 Molecular docking

Use MOE’s Dock module for rigid docking, import the candidate ligand database into the MBD file, perform molecular docking for all candidate compounds, and select ASE for the scoring mode. The docking score of receptor-ligand docking integrates the ligand energy, receptor energy and the binding energy between the two. The greater the absolute value of the score, the stronger the receptor affinity and the stronger the binding between the two \(^8\).

First, the ligand database was docked with SARS-COV-2 3CLpro, and several candidate compounds with better scores were screened out. The selected candidate compounds were then docked with SARS-COV-2 RdRp, and finally, candidate compounds with good scores for the 3CLpro/RdRp dual targets were screened out.

2.2 Molecular dynamics simulation

In MOE.2015, first, perform 1000 steps of energy minimization for the protein and small molecule ligand complex at a temperature of 300 K, and then perform 100 ps NVT ensemble balance and 100 ps NPT ensemble balance on the optimized system. In this process, the position of the system is restricted, and finally, the temperature of the whole system is kept at 300 K for 50 ns kinetic simulation, the time interval is 2 fs, and the coordinate trajectory file is saved once every 50 ps. Extract 150 frames of kinetic trajectory files from 30–50 ns stable kinetic trajectories.

2.3 ADME prediction

The ligand molecular structural formula was submitted to the Swiss-ADME website (http://www.swissadme.ch/) for ADME prediction. Lipophilicity (iLOGP, XLOGP3, WLOGP, MLOGP, SILICOS-IT, Log P \(_{0/w}\)), water solubility (Log S (ESOL, Ali, SILICOS-IT)), drug likeness rules (Lipinski, Ghose, Veber, Egan and Muegge), medicinal chemistry properties, and synthetic accessibility were analyzed.

3 Results

3.1 Analysis of molecular docking results

3.1.1 6LU7 and ZINC database docking results

At present, some researchers believe that Lopinavir and Indinavir can be used as potential drugs to target SARS-COV-2 3CLpro\(^9\). After molecular docking, the scores of Lopinavir and Indinavir were -42.54 and -40.40 respectively. Therefore, using a docking score of less than -40.40 as the preliminary screening condition, 3207 compounds meeting the screening criteria were obtained. And taking the docking score less than the original ligand N3 inhibitor (docking score = -58.42) as further screening conditions, 9 compounds that met the screening criteria were obtained (Table 1 & Fig.5).
This binding pocket has a certain degree of openness, can accommodate small molecular compounds with larger molecular mass, and prefers hydrogen bond donor acceptors and aromatic functional groups. However, due to the slightly flattened shape of the middle section of the pocket, it is not suitable for compounds with larger molecules. Lopinavir and the 9 best-scoring compounds had more interactions with amino acid residues Cys145, Glu166, Thr26, and Gly143. Hydrogen bonding makes the receptor-ligand binding more stable. Therefore, ZINC79210210, ZINC13782937, ZINC01530668, ZINC85867434, ZINC85867035 and ZINC04510409, which have strong hydrogen bonding with the receptor, have a higher ligand exposure than the highest scored ZINC12371967, the overall score is improved due to hydrogen bonding.

**Table 1 Sites of Lopinavir, Indinavir and the 9 best scored compounds**

| Compounds  | Residue Receptor of 3CLpro | Docking Score |
|------------|---------------------------|---------------|
| 1          | ZINC12371967               | Met165         | -92.11         |
| 2          | ZINC79210210               | His163•Glu166•Gln192•Met165•His41•Thr26•Gly143 | -64.17         |
| 3          | ZINC13782937               | Thr26•His164•Met165 | -64.04         |
| 4          | ZINC01530668               | Gln189•Met49   | -62.92         |
| 5          | ZINC85867434               | Thr190•Gln189•Asp187•Gly143•Glu166•Cys145 | -62.21         |
| 6          | ZINC85867035               | Thr25•Leu141•Met49•Cys145•Gly143 | -61.56         |
| 7          | ZINC70712316               | Cys145         | -61.55         |
| 8          | ZINC04510409               | Cys143         | -60.72         |
| 9          | ZINC02147456               | Gln189•Thr25   | -58.47         |
| 10         | Lopinavir                  | Gln189•Glu166•Gly143 | -42.54         |
| 11         | Indinavir                  | /              | -40.40         |

### 3.1.2 The docking results of 6M71

Currently, some researchers believe that favipiravir can be used as a potential drug targeting SARS-CoV-2 RdRp[10]. After molecular docking, Favipiravir scores were -24.41. Therefore, using a docking score of less than -24.41 as the screening condition, 3 compounds with good scores for 3CLpro/RdRp were obtained. (Table 2).

The ligand-receptor interaction map of compound ZINC04259665 with 3CLpro is shown in Fig.6, one of the oxygen atoms has an interaction with amino acid residue Met165 at a distance of 3.67Å. The ligand-receptor action diagram of compound ZINC04259665 with RdRp is shown in Fig.7, the tetrazolium ring has hydrogen atom five membered ring interaction with Pro677.
The ligand-receptor action diagram of compound ZINC12659533 with 3CLpro is shown in Fig.8, the benzene ring has hydrogen atom benzene ring interaction with amino acid residue Thr25. The ligand-receptor interaction map of compound ZINC12659533 with RdRp is shown in Fig.9, which can fit the pocket well and has less exposure of the ligand.

The ligand-receptor interaction diagram of compound ZINC70705490 with 3CLpro is shown in Fig.10, in which one of the oxygen atoms has an interaction with amino acid residue His41, resulting in one hydrogen bond with a distance of 2.06Å. A diagram of the ligand receptor interaction with RdRp is shown in Fig.11, in which one of the oxygen atoms has an interaction with Leu251 to form a hydrogen bond with a distance of 2.50Å.

Favipiravir also interacts with Arg349 to produce a hydrogen bond with a distance of 2.05Å, in addition, it interacts with the amino acid residue Glu350.

In summary, the binding pockets of 3CLpro and RdRp have a certain degree of openness, can accommodate small molecular compounds with larger molecular mass, and prefer hydrogen bond donor acceptors and aromatic functional groups. Through the analysis of molecular docking results, it can be inferred that the binding sites Met165–Thr25–His41–Cys145–Met49 of 3CLpro and Arg349 of RdRp have good binding affinity.

### Table 2 Sites of Favipiravir and the 3 best scored compounds

| Compounds   | Residue Receptor of RdRp | Docking Score | Residue Receptor of 3CLpro | Docking Score |
|-------------|--------------------------|---------------|----------------------------|---------------|
| 12          | ZINC04259665             | Pro677        | -52.43                     | Met165        | -42.53         |
| 13          | ZINC12659533             | Tyr346-Arg349 | -51.72                     | Thr25         | -42.40         |
| 14          | ZINC70705490             | Leu251        | -53.73                     | His41-Cys145-Met49 | -42.19        |
| 15          | Favipiravir              | Arg349-Glu350 | -24.41                     | --            | --             |

### 3.2 Analysis of molecular dynamics simulation results

We used the ligand-protein complex in molecular docking as the initial structure, and performed 50 ns molecular dynamics studies on ZINC04259665, ZINC12659533 and ZINC70705490. In the process of molecular dynamics simulation, the system stabilized after 10 ns, and the trajectory overlap showed that the spatial position of the molecule did not change much. These results indicate that the molecular dynamics orbital has a good balance and the molecular docking complex in the system remains relatively stable (Fig.13,14).

#### 3.2.1 Molecular dynamics analysis of ZINC04259665
In molecular dynamics simulations for 3CLpro, ZINC04259665 was immobilized in a hydrophobic pocket consisting mainly of the following amino acid residues: His164, Gln189, Arg188, Met49 as well as Glu166. Obviously, this binding region is consistent with the hydrophobic site analyzed in molecular docking. On the other hand, the force between the molecules and amino acid Met165 was lost due to torsion, and a new hydrogen bonding force with amino acid Met49, Glu166 was generated to make the ligand more strongly bound in the corresponding site, which did not affect the binding site of the molecule as a whole (Fig. 15).

In molecular dynamics simulations targeting RdRp, ZINC04259665 was immobilized in a hydrophobic pocket consisting mainly of the following amino acid residues: Pro677, Phe396, Arg349, Thr246 as well as Ser664. Obviously, this binding region is consistent with the hydrophobic site analyzed in molecular docking. On the other hand, the force of ligand molecule binding in molecular dynamics is relatively similar to that in molecular docking revealed previously, and the important force of ZINC04259665 with amino acid Pro677 still exists, indicating the conservation of amino acid Pro677, which supports to some extent the conclusion obtained during docking. But the reason why the molecule has undergone torsion makes a hydrophobic force and a new hydrogen bonding force with amino acid Ser664, Arg349, which makes the ligand more strongly bound in the corresponding site, and this does not affect the binding site of the molecule as a whole (Fig. 16).

In summary, ZINC04259665 remained stable at the active site in the molecular dynamics study under aqueous environment, and the obtained results were also largely consistent with the molecular docking results.

3.2.2 Molecular dynamics analysis of ZINC12659533

In molecular dynamics simulations for 3CLpro, ZINC12659533 is anchored within a hydrophobic pocket consisting mainly of the following amino acid residues: Thr25, Glu166, Thr26, His164 as well as His41. Obviously, this binding region is consistent with the hydrophobic site analyzed in molecular docking. On the other hand, the force of the molecule with amino acid Thr25 was lost due to the torsion happened to the molecule, and a new hydrogen bond was generated with amino acid His41, making the ligand more strongly bound in the corresponding site, which did not affect the binding site of the molecule as a whole (Fig. 17).

In molecular dynamics simulations targeting RdRp, ZINC12659533 was immobilized in a hydrophobic pocket consisting mainly of the following amino acid residues: Pro323, Arg349, Ala250, Leu251 as well as Tyr346. Obviously, this binding region is consistent with the hydrophobic site analyzed in molecular docking. But the reason why the molecule has undergone torsion makes new force with the amino acids Pro323, Arg349, so that the ligand binds more forcefully into the corresponding site, which does not affect the overall binding site of the molecule.

In summary, ZINC12659533 remained stable at the active site in the molecular dynamics study under aqueous environment, and the obtained results were also largely consistent with the molecular docking results.
results (Fig. 18).

### 3.2.3 Molecular dynamics analysis of ZINC70705490

In molecular dynamics simulations against 3CLpro, ZINC70705490 is anchored in a hydrophobic pocket consisting mainly of the following amino acid residues: Met49, Met165, Thr190, Cys145 as well as His41. Obviously, this binding region is consistent with the hydrophobic site analyzed in molecular docking. On the other hand, the molecular forces with amino acids Cys145, His41 and Met49 were lost due to torsion, and new interaction forces with amino acids Gln189 and Gly143, including 2 hydrogen bonds, were generated to make the ligand more strongly bound in the corresponding site, which did not affect the binding site of the molecule as a whole (Fig. 19).

In molecular dynamics simulations for RdRp, ZINC70705490 was immobilized in a hydrophobic pocket consisting mainly of the following amino acid residues: Leu247, Thr246, Thr252, Pro677, Arg349 as well as Ser664. Obviously, this binding region is consistent with the hydrophobic site analyzed in molecular docking. However, the molecular forces with amino acid Leu251 were lost due to torsion, and new forces with amino acids Thr246, Arg249, Thr252, including 2 hydrogen bonds, were generated to make the ligand bind more strongly in the corresponding site, which did not affect the binding site of the molecule as a whole (Fig. 20).

### 3.3 ADME prediction

ADME prediction was performed using swiss-ADME for ZINC04259665, ZINC12659533 and ZINC70705490.

The physicochemical properties of ZINC70705490 were: number of heavy atoms 39, hydrogen bond acceptors 5, hydrogen bond donors 3, molar refractive index 143.68, and polar surface area (TPSA) of molecular topology 193.97 Å², lipophilicity iLOGP of molecule 2.36, XLOGP3 1.20, WLOGP 1.96, MLOGP 2.31, SILICOS-IT 3.96, and P0/W 2.09. The predicted water solubility properties were -3.15 for ESOL and 3.84e-01 mg/ml for genera soluble, -4.87 for Ali and 7.32e-03 mg/ml for genera moderately soluble, and -7.74 for SILICOS-IT and 9.94e-06 mg/ml for genera poorly soluble. The predicted pharmacokinetic data are high gastrointestinal absorption (GI), inability to permeate the blood-brain barrier, and as P-gp substrates, do not inhibit CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 cytochromes. The skin permeation kinetics (log Kp) was -8.76 cm/s, the drug like factor did not meet the Lipinski rule, did not meet the drug like scoring rule of Ghose, Veber, Egan, Muegge, etc., and the bioavailability score was 0.11. Medicinal chemistry parameters no PAINS warning, no brenk structure warning, alert to coumadine, the synthesis accessibility was 4.82 (Fig. 21).

The physicochemical properties of ZINC04259665 were 36 heavy atoms, 6 hydrogen bond acceptors, 3 hydrogen bond donors, molar refractive index 136.64, and molecular topological polar surface area (TPSA) 107.63 Å², the lipophilic iLOGP of the molecule was 3.61, XLOGP3 was 1.61, WLOGP was 0.04, MLOGP was -1.39, SILICOS-IT was 1.25, and P0/W was 1.02. The predicted water solubility properties
were -3.65 for ESOL and 1.09e−01 mg/ml for genera soluble and -3.48 for Ali and 1.62e−01 mg/ml for genera soluble and -6.06 for SILICOS-IT and 4.29e−04 mg/ml for genera slightly soluble. The predicted pharmacokinetic data were high gastrointestinal absorption (GI), inability to permeate the blood-brain barrier, non-P-gp substrates, and no inhibition of CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 cytochromes. The skin permeation kinetics (log \( K_p \)) was -8.15 cm/s, the drug-like factor conformed to the drug-like scoring rule of Lipinski, Veber, Egan, and Muegge, did not conform to the Ghose scoring rule, and the bioavailability score was 0.55. The pharmacochemical parameters had no PAINS warning, no brenk structure warning, and the synthesis accessibility rate was 5.07 (Fig. 22).

The physicochemical properties of ZINC12659533 were 34 heavy atoms, 4 hydrogen bond acceptors, 2 hydrogen bond donors, a molar refractive index of 141.10, and a molecular topology polar surface area (TPSA) of 75.63 Å², the lipophilicity of the molecule was 5.30 for iLOGP, 6.27 for XLOGP3, 6.01 for WLOGP, 3.54 for MLOGP, 7.56 for SILICOS-IT, and 5.74 for P₀/W. The predicted water solubility properties were -5.60 for ESOL and 1.18e−03 mg/ml for genus poorly soluble and -7.65 for Ali and 1.07e−05 mg/ml for genus poorly soluble and -8.72 for SILICOS-IT and 9.05e−07 mg/ml for genus poorly soluble. The predicted pharmacokinetic data were high gastrointestinal absorption (GI), inability to permeate the blood-brain barrier, use as P-gp substrates, and do not inhibit CYP1A2, CYP2C19, CYP2C9 cytochromes, and CYP2D6 and CYP3A4 cytochromes. The skin permeation kinetics (log \( K_p \)) was found to be -4.74. The pharmacochemical parameters had no PAINS warning, no brenk structure warning, and the synthesis accessibility rate was 4.34.

In summary, ZINC04259665 is a small molecule compound with good druggability. TPSA shows that the compound has good transmission properties. By investigating the lipophilicity of the drug compound, it can be known that the compound has better lipophilicity. The drug is predicted to be a water-soluble drug based on its water-soluble properties. The compound does not inhibit CYP1A2, CYP2C19, CYP2D6 cytochromes, and complies with the drug-like rules, indicating that the compound can be used as a drug in biological systems. According to medical chemistry parameters, the compound has no PAINS warning, indicating that it is a compound worthy of biochemical analysis. It is hoped that after post-modification and structural optimization, a lead compound with better activity against SARS-COV-2 is designed.

4 Conclusion

In this study, a virtual screening technique based on computer-aided drug design was performed on a library of 120000 natural small molecule compounds using the high rate crystal structures of SARS-COV-2 3CLpro in complex with N3 inhibitor and SARS-COV-2 RNA dependent RNA polymerase in complex with cofactor as acceptors. ZINC04259665, ZINC12659533 and ZINC70705490 showed strong binding to 3CLpro/RdRp docking scores. It can be speculated that the binding sites Met165, Thr25, His41, Cys145, Met49 of 3CLpro and Arg349 of RdRp have better binding affinity by molecular docking results analysis, which may provide a reference for new drug development. The results in the molecular dynamics simulation further indicated the reliability of the docking results. According to the prediction of drug-like
properties, ZINC04259665 is a small molecule compound with good druggability, and is a compound worthy of biochemical analysis and testing. It is hoped that after post-modification and structural optimization, a lead compound with better activity against the new coronavirus is designed.

Virtual screening at this stage is mostly based on existing drugs, but with little success. Given that SARS-COV-2 is highly infectious, mutates quickly, and the virus is not easily inactivated, there is an urgent need to efficiently develop new drugs and new vaccines. Virtual screening can speed up the discovery of new drugs, and natural small molecule compounds play a key role as precursors for new drug development. We hope that the results of this study can provide relevant data for the rational development of anti-SARS-COV-2 drugs in the future.

Declarations

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Conflicts of interest

No potential conflict of interest was reported by the authors.

Availability of data and material

(a) The article I have submitted to the journal for review is original, has been written by the stated authors, and has not been published elsewhere.

(b) The images I have submitted to the journal are all original and have not been published elsewhere.

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**Figures**
Figure 1
SARS-COV-2 3CLpro site prediction (green dummy-atom: sites 1–10)

Figure 2
Docking pocket of SARS-COV-2 3CLpro
Figure 3

SARS-COV-2 RdRp site prediction (green dummy-atom: sites 11-15)

Figure 4

Docking pocket of SARS-COV-2 RdRp
Figure 5

Schematic diagram of the receptor-ligand interaction of the 3 best scored compounds and the N3 inhibitor (the ligand is marked in green)
Figure 6

Schematic diagram of the receptor-ligand interaction of ZINC04259665 with 3CLpro (the ligand is marked in green)

Figure 7

Schematic diagram of the receptor-ligand interaction of ZINC04259665 with RdRp (the ligand is marked in green)
Figure 8

Schematic diagram of the receptor-ligand interaction of ZINC12659533 with 3CLpro (the ligand is marked in green)

Figure 9

Schematic diagram of the receptor-ligand interaction of ZINC12659533 with RdRp (the ligand is marked in green)
**Figure 10**

Schematic diagram of the receptor-ligand interaction of ZINC70705490 with 3CLpro (the ligand is marked in green)

![Figure 10](image1.png)

**Figure 11**

Schematic diagram of the receptor-ligand interaction of ZINC70705490 with RdRp (the ligand is marked in green)

![Figure 11](image2.png)
Figure 12

Schematic diagram of the receptor-ligand interaction of Fapiravir with RdRp (the ligand is marked in green)

Figure 13

ZINC04259665

ZINC12659533

ZINC70705490
Overlays of ZINC04259665, ZINC12659533, and ZINC70705490 with trajectories at 40ns (green), 45ns (purple), and 50ns (yellow) of the molecular dynamics simulation of 3CLpro.

**Figure 14**

Overlays of ZINC04259665, ZINC12659533, and ZINC70705490 with trajectories at 40ns (green), 45ns (purple), and 50ns (yellow) of the molecular dynamics simulation of RdRp.
Figure 15

molecular dynamics simulation binding site diagram of ZINC04259665 with 3CLpro

Figure 16
molecular dynamics simulation binding site diagram of ZINC04259665 with RdRp

Figure 17

molecular dynamics simulation binding site diagram of ZINC12659533 with 3CLpro
Figure 18

molecular dynamics simulation binding site diagram of ZINC12659533 with RdRp
Figure 19

molecular dynamics simulation binding site diagram of ZINC70705490 with 3CLpro
Figure 20

molecular dynamics simulation binding site diagram of ZINC70705490 with RdRp
Figure 21

ADME prediction of ZINC70705490
**Figure 22**

ADME prediction of ZINC04259665
Figure 23

ADME prediction of ZINC12659533