In Silico Analysis of Ferrocenyl-analogues as the Potential Drugs Against Aggressive UK-based Strain of SARS-CoV-2 Virus

MAYNAK PAL

NIT Manipur: National Institute of Technology Manipur

ABHISHEK PANWAR

NIT Manipur: National Institute of Technology Manipur

SHARMILA WAHENGAM

NIT Manipur: National Institute of Technology Manipur

DULAL Musib

NIT Manipur: National Institute of Technology Manipur

Mithun Roy (✉ mithunroy.iisc@gmail.com)

NIT Manipur: National Institute of Technology Manipur

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Abstract

The current global pandemic created by the SARS-CoV-2 virus is still at large due to the evolution of the virus in several mutant variant. One of such variants is (VUI 202012/01: Variant Under Investigation, 2020, December, variant 01). Due to the higher transmissibility of the virus and the less effectiveness of the vaccines against the mutant variant, it is becoming a looming threat for the global population. In our current work we have selected some antiviral and anticancer ferrocene derivatives and explored their ability to inhibit the mutant spike protein in silico. Spike protein is the root cause of the higher transmissibility of the virus. So by inhibiting the spike protein we can inhibit the viral pathogenesis. Among our selected compounds, derivative 1 exhibited very good inhibition parameters with binding energy of -10.22 kcal/mol. It also exhibited good inhibition of cytokine proteins like NF- κ B and IL-6 proteins. In several cases the covid affected patients are subjected to severe cytokine storm which in term leads to the alveolar edema and death. So by inhibiting the spike protein and cytokine proteins, derivative 1 can act as dual targeting drug that inhibits the mutant variant pathogenesis as well as cytokine inhibitor and decrease the mortality rate.

Highlights

- In-silico SAR based exploration of ferrocene based anticancer agents as potential inhibitors of major viral proteins of SARS-CoV-2 virus.
- Ferroquine, Ferrocifen and several other compounds exhibited very high binding energy towards the major viral proteins.
- Complex 1 also inhibited human Ca²⁺-channel efficiently inhibiting the cytokine related inflammatory signaling cascades.

Introduction

The pandemic (COVID-19) caused by the SARS-CoV-2 virus, has resulted in an unprecedented and noble global health crisis of the century, and infected almost 243 million individuals with 4.9 million mortalities since November 2019.¹ An effective cure for COVID-19 is still an elusive goal, although the vaccination is the emerging trends to prevent the COVID-19 infection.² Repurposing of antiviral drugs is the WHO recommended strategy to treat COVID-19 patients.³⁻⁵ The mutated SARS-CoV-2 (VUI 202012/01: Variant Under Investigation, 2020, December, variant 01) has emerged as the new potential threat South-East England and gradually spread all over the world again. 1 The severity of the new strain of SARS-CoV-2 virus are: (i) the mutations have proved to be more aggressive and resistant towards the current repurposed drugs, (ii) the vaccines which are developed by different pharmaceutical companies are reported to work against the new variants, but the sample size taken is small and the long-term effect on patients are yet to be analyzed.⁶ Moreover, Wang et al. reported that the vaccines produce only one third of antibodies that can neutralize the mutant variant.⁷ Therefore, it is of utmost importance to find a sustainable drug to work against the mutant variant VUI 202012/01.

The mutant variant is consisted of 23 mutations that includes 13 non-synonymous, 6 synonymous mutations and four amino acid deletion. The mutations have occurred in the vital structural spike (S) and nucleocapsid (N) protein with genetic protein ORF8. The mutations reported in S proteins are Δ H69, Δ V70, Δ Y144, N501Y, A570D, P681H, T716I, S982A, D1118H respectively.⁸ Most of the mutations are subjected to positioned in the S2 subunit of the S protein, but the N501Y mutation is pivotal as it is located in the Receptor Binding Domain (RBD) of S protein.⁹ In the cases of other variants which are reported, have the N501Y mutation in common. The mutated stains are reported to have more transmissibility (56%), causing more deaths. Molecular docking of the receptor binding domain of the S-protein of mutant SARS-CoV-2 and ACE2 receptor revealed significant number of intramolecular interactions in RBD of S protein, due to the mutation and resulted in extra stabilization (Δ G, - 0.42 kcal/mol) of the virus-ACE2 receptor assembly. This results from the conversion of ASN183 residue to TYR183 residue. This might attribute to the greater transmit ability of the VUI 202012/01 strain of SARS-CoV-2 as well as the drug resistance. The N501Y mutation, located in the Receptor Binding Domain (RBD) of S-protein of VUI 202012/01 strain of SARS-CoV-2 could be the reason of drug resistance and aggressiveness, and become pivotal to consider for drug development against the mutated SARS-CoV-2 variant.¹⁰

Transition metal complexes with wide range of oxidation states, extended coordination number and geometry, ligand-dependent variable formal charge, redox properties, tunable thermodynamic and kinetic properties in biological system have emerged as the potential and alternative candidates for diagnostics, medicinal including antiviral applications. In silico and in vitro studies have revealed sustainable utility of transition metal complexes against SARS-CoV-2 virus by inhibiting the key viral proteins.¹¹⁻¹⁵ Previous in-silico molecular docking revealed that ferrocene derivatives exhibit high potential to act as inhibitor of SARS-CoV-2 spike protein.¹⁴⁻¹⁵ Ferrocene derivatives are also emerged as potential antiviral and anticarcinogenic agents in the last few decades. This has prompted us to select several ferrocene-based derivatives for in silico studies against the spike protein of mutant SARS-CoV-2. We have selected antiviral and anticancer drug Ferroquine, Ferrocifen and several other active ferrocene-based derivatives to study their virustatic potential against the VUI 202012/01 strain of SARS-CoV-2 virus (Scheme 1).¹⁶⁻²¹

Several reports also revealed that the mortality rate of COVID-19 patients related to the acute respiratory distress is primarily attributed for the aggressive immune-response. The IL-6 and NF- κ B proteins are responsible for the immune response and cytokine storms that attributes to the severe inflammatory response in the patients. The NF- κ B is a cluster of complex immunoproteins that activates cytokine storm in the COVID-19 patients. It also causes inflammatory cells infiltration and diffuse pulmonary alveolar injury in the SARS-CoV-2 affected patients. Similarly, IL-6 protein also is the key mediator for the activation of cytokine storm in the SARS-CoV-2 patients.²²⁻²³ Therefore, targeting such immunoregulatory proteins could be an attractive strategy in preventing acute respiratory distress in virus-infected patents. The remarkable virustatic potential of the ferrocenyl derivative 1 the mutant variant VUI 202012/01 prompted us to explore its immunoregulatory potentials. Hence, by inhibiting the viral spike protein of mutant variant VUI 202012/01 and IL-6, NF- κ B protein, derivative 1 can act as multitargeting agent for the treatment of mutant SARS-CoV-2.

Experimental

Methods

We have selected auranofin and several ferrocene-based complexes for molecular docking with the spike protein of UK variant SARS-CoV-2. The crystal structures of the protein structure were obtained from the Protein Data Bank (PDB) (PDB ID: 7A97) database as .pdb format. The mutant model was obtained by online server mutabind. The proteins were prepared by deleting the water molecules and auxiliary ligand and followed by the addition of polar hydrogens and the addition of Gasteiger charges just before the molecular docking studies. The structure of cytokine proteins IL-6, and NF- κ B were obtained from the protein data bank with PDB id 1IL6, 1NFK, respectively. These proteins also were prepared for molecular docking as per the previously mentioned procedure. The geometry optimized structures of the complexes were used for molecular docking. The geometry optimization was performed using the LAN2DZ basis set in Gaussian 09 software. Prior to any further studies, the ADME analysis of the compounds were carried out to get a conclusive idea of their pharmacokinetics and understanding about their acceptability as drugs using SwissADME webserver.²¹ Molecular docking is performed using Autodock 4 software.²² The binding sites were identified for each protein and the molecular docking grid was prepared accordingly (Table S1). The molecular docking was performed considering the pH media 7 and the docking parameters were set to long (250000000) along with keeping other parameters as default. The output file is saved in Lamarckian GA format. The output files contain the binding parameters. The docked poses were analysed for interactions with the proteins using Discovery Studio 9 software.

Results And Discussion

Ferroquine is an FDA-approved antimalarial drug and it is currently explored for antitumor, anti-HIV effects. Phase III clinical trial revealed that Ferroquine exhibited better efficiency than chloroquine or hydroxychloroquine as antimalarial agent. Molecular docking studies previously revealed inhibitory effect on the RNA-dependent RNA polymerase (RdRp) with binding energy of -6.19 kcal/mol and inhibitory constant 28.88 μ M. The results stimulated us to explore ferroquine (1) as the potential repurposed drug against the mutant (VUI 202012/01) strain of SARS-CoV-2 virus. Here in, we were interested in understanding the binding efficacy of ferroquine (1) to the receptor binding domain of S-protein of the mutant strain of SARS-CoV-2 virus. Ferroquine contains total polar surface area (TPSA) of 27.30 Å². It also contains five rotatable bonds with two hydrogen bond donor and three hydrogen bond acceptor atoms. Hence ferroquine can form several noncovalent bonds with the proteins. The ADME analysis revealed that ferroquine had a consensus Log Po/w of 2.36 and it was moderately soluble in water. It also had high gastrointestinal absorption and blood brain barrier permeability with an additional property to inhibit CYP3A4 protein. The ADME analysis also predicted ferroquine to be used as an oral or intravenous drug. The drug-likeness analysis revealed zero violations in terms of Lipinsky, Ghose, Veber, Egan, Muegge analysis suggest the acceptability of ferroquine as a drug. Molecular docking of ferrocene is carried out into the ACE2 with S-protein mutant stain (VUI 202012/01). The molecular docking studies revealed significant binding efficacy of ferroquine (1) towards the ACE2 with S-protein mutant stain (VUI

202012/01) of SARS-CoV-2 virus with the binding energy of -7.1 Kcal/mol and inhibition constant of 6.3 μ M (Figure S1, Table S1). Ferroquine mainly inhibits in binding of the S-protein of the virus to the ACE2-receptor protein of the host alveolar cells. The noncovalent interactions are as follows-

- (i) Two hydrogen bonds with the TYR59, GLN100 residues of protein.
- (ii) One electrostatic interaction with Cl atom of ferroquine and the protein.
- (iii) One hydrophobic π - π interaction with the PHE56 residue.
- (iv) One hydrophobic π -alkyl interaction with the THR97 residue.
- (v) Two hydrophobic alkyl-alkyl interactions with the ALA60, PRO95 residues.

Ferroquine complexes can interact with the ACE2 via the electrostatic interactions along with their structural rigidity and charge separation providing an excellent scope for electrostatic interactions and stacking interaction. It is quite probable that the mutation N501Y indirectly affect the binding of ferroquine to the ACE2 protein. Previously in the non-mutated protein due to the ASN183 interaction with the ACE2 site the binding of ferroquine gets prohibited, but upon mutation those interactions were vanished and as a result ferroquine binds with RBD by the formation of intramolecular bonds. Thus, the site becomes available for ferroquine and exhibiting the higher binding energy.

Another ferrocene-based drug is ferrocifen. It is known for its antitumor activity. Ferrocifen contains total polar surface area (TPSA) of 12.47 Å². It also contains nine rotatable bonds with two hydrogen bond acceptor atoms. Hence ferrocifen can form several noncovalent bonds with the proteins. The ADME analysis revealed that ferroquine had a consensus Log Po/w of 5.11 and it was weakly soluble in water. It also had low gastrointestinal absorption and blood brain barrier permeability with an additional property to inhibit CYP3A4 protein. This indicates the application of ferrocifen as an intramuscular drug. The drug likeness analysis reveals a couple of violations in terms Lipinsky, Ghose, Veber, Egan, Muegge analysis. These was mainly because of the low solubility of the derivative in water. By using it as an intramuscular drug this was issue can be accounted for. It also attains zero PAINS alert and it was likely to be used as an intramuscular drug. To study the structure activity relationship of ferrocene-based drugs we performed docking studies of ferrocifen in mutant variant. In the mutant variant it exhibited the binding energy of -7.4 kcal/mol with inhibition constant of 2.36 μ M (Figure S2, Table S1). The noncovalent interactions are as follows-

- (i) Two hydrogen bonds with the TYR91, SER94 residues of protein.
- (ii) One electrostatic interaction with Fe atom of ferrocifen and the GLU166 residue of protein.
- (iii) One hydrophobic π - lone pair interaction with the ARG90 residue.
- (iv) One hydrophobic π -alkyl interaction with the PHE58 residue.

(v) Two hydrophobic alkyl-alkyl interactions with the ALA60, PRO95 residues.

Therefore, ferrocifen can be used as potential drug for mutant variant and it has main mode of action by interacting with the ACE2 protein, inhibiting S protein accessibility towards ACE2 receptors.

In our previous work on in silico studies of metal-based complexes on inhibition of spike and RdRp protein of SARS-CoV-2, we observed that ferroquine derivative 1, showed maximum inhibition power towards the spike and RdRp protein of SARS-CoV-2. After seeing the larger contribution of ferrocene-based drugs to inhibit the SARS-CoV-2 mutant in silico data, we are prompted to perform molecular docking of the derivative 1. Derivative 1 contains total polar surface area (TPSA) of 167.11 Å². It also contains nine rotatable bonds with two hydrogen bond acceptor atoms. Hence derivative 1 can form several noncovalent bonds with the proteins. The ADME analysis revealed that ferroquine had a consensus Log Po/w of 5.44 and it was poorly soluble in water. It also had low gastrointestinal absorption and blood brain barrier permeability with an additional property to inhibit CYP3A4 protein. This indicates the application of derivative 1 as an intramuscular drug. Therefore, the derivative could be an intramuscularly administered drug. The drug likeness analysis reveals two violations in terms Lipinsky, Ghose, Veber, Egan, Muegge analysis due to its larger size and poor aqueous solubility. Due to high polar surface area, high flexibility and a good amount of hydrogen bond donors and acceptors, derivative 1 can exhibit a very high binding affinity towards the spike protein of mutant SARS-CoV-2. The docking study reveals that the derivative binds with the mutant stain of S protein with binding energy of -10.22 kcal/mol with inhibition constant of 0.324 µM (Figure 1, Table S1), depicting it as a potential drug to inhibit the mutant stain by interacting with the protein. The noncovalent interactions are as follows-

(i) Three hydrogen bonds with the TYR449, TYR489 residues of protein.

(ii) One electrostatic interaction with Fe atom of derivative 1 and the ASP87 residue of protein.

(iii) Two hydrophobic π - π interactions with the PHE456, TYR171 residue.

(iv) One hydrophobic π -alkyl interactions with the TYR131, PHE100 residues.

The binding energy and inhibition constant for mutant protein are far more superior than conventional repurposed drugs and its organic derivative. This suggest as the derivative to be more potent to inhibit the virus for further in-vitro and in-vivo studies.

Derivative 2 is also a ferrocene derivative that exhibit very good antiviral and antitumor properties. It contains contains total polar surface area (TPSA) of 123.93 Å². It also contains six rotatable bonds with four hydrogen bond donor atoms. Hence derivative 1 can form several noncovalent bonds with the proteins. The ADME analysis revealed that ferroquine had a consensus Log Po/w of 1.91 and it is highly soluble in water. It also had low gastrointestinal absorption and blood brain barrier permeability with an additional property to inhibit CYP3A4 protein. The drug likeness analysis reveals no violations in terms Lipinsky, Ghose, Veber, Egan, Muegge analysis due to its larger size and poor aqueous solubility. Due to high polar surface area, high flexibility and a good amount of hydrogen bond donors and acceptors,

derivative 2 can exhibit a very high binding affinity towards the spike protein of mutant SARS-CoV-2. The derivative 2 exhibits binding energy of -7.93 kcal/mol with inhibition constant of 1.53 μ M (Figure S3, Table S1). The noncovalent bonds that contribute to the binding energy are as follows-

(i) Five hydrogen bonds with the ARG346, ASN450, LYS31, PHE347 and TYR451 residues of protein.

Five hydrogen bonds suggest the strong interaction between derivative 2 and spike protein. Hence derivative 2 has the potential to act as inhibitor of mutant spike protein of SARS-CoV-2.

Derivative 3 is also a ferrocene derivative with anticancer and antiviral properties. It is consisted of nine rotatable bonds with a total polar surface area (TPSA) of 126.81 $\text{\AA}^2$. It also contains three hydrogen bond acceptor atoms and 1 hydrogen bond donor atom. The ADME analysis reveals, Derivative 3 had a consensus Log Po/w of 2.24 and it was moderately soluble in water. It also had high gastrointestinal absorption and blood brain barrier permeability with an additional property to inhibit CYP3A4 protein. Hence derivative 3 can be used as oral, intervenous, intermuscular drug. The drug likeness analysis reveals no violations in terms Lipinsky, Ghose, Veber, Egan, Muegge analysis and all the data suggests the acceptability of derivative 3 as a drug. The docking study reveals that the derivative binds with the mutant stain of S protein with binding energy of -8.21 Kcal/mol with inhibition constant of 0.965 μ M (Figure S4, Table S1), depicting it as a potential drug to inhibit the mutant stain by interacting with the protein. The noncovalent interactions are as follows-

(i) One hydrogen bond with the PHE356 residues of protein.

(ii) One hydrophobic π - lone pair interactions with the ASP355 residue.

(iii) One hydrophobic π -alkyl interactions with the TYR449 residue.

The derivative 3 exhibited better binding energies than several reported repurposed organic drugs the strong hydrogen bond and π - lone pair interaction attribute to the potential activity of derivative 3 against mutant SARS-CoV-2 spike protein.

Among the selected ferrocenyl derivatives, the compound derivative 1 exhibited the highest potential to inhibit the mutant spike protein of SARS-CoV-2 with binding energy of -10.22 kcal/mol. This result prompted for further investigation of inhibition activity of derivative 1 against the NF- κ B and IL-6 proteins for reducing the cytokine storm and inflammatory effects observed in SARS-CoV-2 patients.

The ARDS is also associated with inflammatory responses occurred in the COVID-19 patients. This phenomenon is the result of cytokine storm. The cytokine storm is regulated mainly by the immune response proteins like NF- κ B and IL-6. Hence by inhibition of these proteins a drug can also act as anti-inflammatory agents for SARS-CoV-2 patients.

The best docked pose of ferrocenyl derivative 1 exhibited binding energy of -8.28 kcal/mol and the inhibition constant of 0.856 μ M (Figure S5, Table S1). The significant interactions responsible for the

binding energy are as follows-

- (i) Five hydrogen bonds with the HIS140, TYR55, LYS143, LYS144 residues of protein.
- (ii) Two hydrophobic alkyl-alkyl interactions with the CYS57, LYS182 residues.
- (iii) One electrostatic interaction with the HIS140 residue.
- (iv) Three hydrophobic π -alkyl interactions with TYR55, LYS143, LEU187 residues.
- (v) Two hydrophobic π - σ interaction with CYS57, LYS152 residues.

The strong electrostatic interaction with the protein and the Fe center as well as the hydrogen bonding interactions attribute to the high binding parameters. The outbreak of SARS-CoV-2 mutant variant VUI 202012/01 has caused many cases of infections and mortality all across the globe since 2021. Reports also mentioned the fewer effectiveness of the vaccines against the mutations. Hence the development of a potent drug for the mutation is becoming more emergence. Also, reports suggest the inflammatory response in the COVID-19 patients is also a major cause of mortality. Herein we investigated the inhibitory activity of antiviral and antitumor ferrocenyl derivatives against the mutant spike protein as well as inflammatory modulators like human IL-6 and NF- κ B cytokine proteins via in silico studies. Derivative 1 exhibited remarkable binding energy for inhibiting mutant spike protein with binding energy -10.22 kcal/mol and it significantly inhibited the modulator proteins with binding energies -8.28 and -9.07 kcal/mol respectively against NF- κ B and IL6 proteins. Overall, the in silico studies revealed the ferrocenyl derivatives as potent inhibitors of mutant spike protein and among them, derivative 1 can strongly inhibit the mutant spike protein as well as inflammatory proteins. Hence it can inhibit the SARS-CoV-2 viral replication process as well as modulate inflammatory signalling proteins in ARDS patients. These aspects represent derivative 1 as an effective therapeutic alternative for SARS-CoV-2 mutant variant VUI 202012/01 treatment.

Derivative 1 also strongly inhibit the IL6 protein with binding energy of -9.07 kcal/mol and inhibition constant of 0.222 μ M (Figure 2, Table S1). The noncovalent interactions which attributes to the binding energy are as follows-

- (i) Three hydrogen bonds with the GLN28, ARG24 residues of protein.
- (ii) One hydrophobic alkyl-alkyl interaction with the VAL121 residue.
- (iii) One electrostatic interaction with the HIS140 residue.
- (iv) Two hydrophobic π -alkyl interactions with ALA114, TYR31 residues.
- (v) One hydrophobic π - σ interaction with ALA114 residue.

Conclusions

Hence ferrocenyl derivative 1 can strongly bind to the human IL-6 and NF- κ B cytokine proteins and they can act as potential inflammatory modulators for the COVID-19 patients with ARDS and derivative 1 can exhibit dual effect for decreasing mortality rate in SARS-CoV-2 patients with mutant variant VUI 202012/01.

Declarations

AUTHOR CONTRIBUTIONS

Maynak Pal: Conceptualization, Data curation, Formal Analysis, Methodology, Dulal Musib: Data curation, Formal Analysis, Methodology, Mithun Roy: Conceptualization, Supervision, Funding acquisition, Investigation, Project administration, Resources, Validation, Visualization, writing – original draft, Writing – review & editing.

ASSOCIATED CONTENT

Electronic supplementary information (ESI)

Details on all the supplementary dock pose figures

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Scheme

Scheme 1 is available in the Supplemental Files section

Figures

Figure 1

(a) The dock-pose showing the binding of derivative 1 to the ACE2 receptor-bound S-protein of the newly mutated UK-based strain of SARS-CoV-2. (b) Schematic representation exhibiting the detail molecular interactions between derivative 1 and ACE2 receptor-bound S-protein of the newly mutated UK-based strain of SARS-CoV-2.

Figure 2

(a) The dock-pose showing the binding of derivative 1 to the human IL-6 protein. (b) Schematic representation exhibiting the detail molecular interactions between derivative 1 and human IL-6 protein.

Supplementary Files

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