# Rimantadine: A potential drug for COVID-19

Richard Njunge[1]

[1]Kabarak University

May 5, 2020



**Abstract**

Background and purpose: Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome- Coronavirus 2 (SARS-CoV2) is a highly contagious disease that has infected more than 200,000 patients and led to more than 10000 deaths in 166 countries in less than four months. New medications are needed to combat this disease. Since the process of discovery, development and approval of new drugs is long, old drugs can be repurposed for treatment of COVID-19. Oseltamivir is used for management of COVID-19 and Influenza A. Rimantadine is an alternative drug to oseltamivir for management of influenza A. Therefore, it is possible that rimantadine can be used for management of COVID-19 as an alternative to oseltamivir. The purpose of the study is to verify the potential of rimantadine as a drug for COVID-19 Methods: The SARS-CoV2 nucleocapsid was downloaded from the Protein databank and the chemical structure of rimantadine downloaded from Pubchem. Molecular docking of the nucleocapsid as the receptor and rimantadine as the ligand was done using avogadro and chimera software. Prediction of pharmacokinetic properties was done using SWISSADME website while the toxicity properties predicted using the ProTox server. Results: The interactions between rimantadine and the SARS-CoV2 nucleocapsid involved conventional hydrogen bonding with threonine & asparagine; attractive charge interaction with aspartate and Pi-alkyl interaction with tryptophan. Rimantadine has high gastrointestinal activity, very few drug-drug interactions and is relatively safe. Conclusion: Rimantadine binds to the SARS-CoV2 nucleocapsid and can thus be used for management of COVID-19.
Keywords: Rimantadine, COVID-19, SARS-CoV2, Oseltamivir

## Introduction

Coronavirus disease 2019 (COVID -19), a highly infectious condition caused by Severe Acute Respiratory Syndrome- Coronavirus 2 (SARS-CoV2), was initially reported in Wuhan, China in December 2019 (Wu *et al.* , 2020)(Zhu *et al.* , 2020)(Wang *et al.* , 2020). It was declared a pandemic by the World Health Organisation (WHO) on 11$^{\text{th}}$ March 2020 (Hageman, 2020). Based on an interactive web-tool created by Centre for Systems Science and Engineering at John Hopkins University, the number of confirmed cases as at 21$^{\text{st}}$ March 2020 was 287, 239. The total deaths stood at 11, 921 (Dong, Du and Gardner, 2020). Within less than four months, COVID-19 had already infected patients in 167 countries (Dong, Du and Gardner, 2020). New drugs are needed to curb the COVID-19 pandemic due to lack of specific antivirals for COVID-19 (Lu, 2020). However, due to the long process of drug discovery, approved drugs for other conditions can be tested for efficacy against COVID-19 (Lu, 2020).

SARS-CoV2 is a beta-coronavirus whose major structural genes are transcribed and translated to form a small membrane protein, spike protein, the nucleocapsid protein and a membrane glycoprotein (Velavan and Meyer, 2020). These proteins are potential targets for drugs to be used in management of COVID-19. The nucleocapsid protein of SARS-CoV2 binds viral RNA genome and thus affects replication and transcription. It can be targeted for development of potential drugs (Chen *et al.* , 2020).

Rimantadine (α –methyl-1- adamantane methylamine hydrochloride), a relatively safe antiviral, is effective for prevention and treatment of influenza A infections especially when neuraminidase inhibitors like oseltamivir are contraindicated (Alves Galvão, Rocha Crispino Santos and Alves da Cunha, 2014). Rimantadine inhibits

the M2 protein of influenza A and thus inhibits the uncoating of the nucleocapsid of the virus (Intharathep *et al.* , 2008) (Wang, Wei and Chou, 2009). It is a cheaper alternative to oseltamivir in management of influenza A (Smith and Roberts, 2002)(Lynd, Goeree and O'Brien, 2005). Oseltamivir has also been used for management of COVID-19 (Velavan and Meyer, 2020)(Lai*et al.* , 2020; Lee *et al.* , 2020). Therefore, since rimantadine has been used as an alternative for oseltamivir in management of influenza A infection, then it is plausible that it might also be used as an alternative in management of COVID-19.

**Methods**

In-silico drug analysis was done.

The 2-D structure of rimantadine was downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/*)* . It was converted to the 3-D structure by Avogadro software (Hanwell *et al.* , 2012). By using the Avogadro software, the 3-D structure was then optimised to the most stable conformation by using MMFF94s as the force field. The 3-D stable structure of rimantadine was saved. With the help of Chimera software, hydrogen atoms and charge were added to the stable conformation of rimantadine (Yang *et al.* , 2012).

The Protein Databank (PDB) (https://www.rcsb.org/*)* was used to access the RNA binding domain of nucleocapsid of SARS-CoV2 (PDB ID: 6VYO). This nucleocapsid was downloaded and residues removed by the Chimera software (Yang *et al.* , 2012). Surface - binding analysis was carried out between rimantadine and the nucleocapsid of SARS-CoV2 using AutoDock vina feature in the Chimera software. The receptor-ligand interactions were observed using Discovery Studio software.

For comparison purposes, the Influenza A M2 protein (PDB ID: 6BKK) was downloaded from PDB and residues removed. The binding properties between rimantadine and the M2 protein of influenza A were assessed using the AutoDock vina feature in Chimera software.

The pharmacokinetic profile of rimantadine was predicted using SWISSADME online tool (http://www.swissadme.ch/) (Daina, Michielin and Zoete, 2017). This online tool assists in predicting and evaluating drug-likeness, pharmacokinetic properties and medicinal chemistry likeness. The canonical SMILES of rimantadine were inserted on the SWISSADME website and the potential absorption, distribution, metabolism and excretion properties predicted.

The toxicity profile of rimantadine was predicted using the ProTox server: http://tox.charite.de/protox_-II/ (Banerjee *et al.* , 2018). Canonical SMILES of rimantadine were inserted in the ProTox server and the toxicity profile of the compound was predicted. ProTox server predicts oral toxicity, organ toxicity especially hepatotoxicity, toxicological endpoints (carcinogenicity, mutagenicity, immunotoxicity and cytotoxicity), toxicological pathways (nuclear receptor signaling pathways – 7 models and stress response pathways – 5 models) and 15 toxicity targets based on Novartis in vitro safety panels.

**Results**

Rimantadine binds to the nucleocapsid of SARS-CoV2 as shown in Figure 1. The highest binding energy for the rimantadine-SARS-CoV2 nucleocapsid complex was -7.5 which was slightly more optimal compared to the highest binding energy for rimantadine-influenza A M2 protein complex which was -7.3.

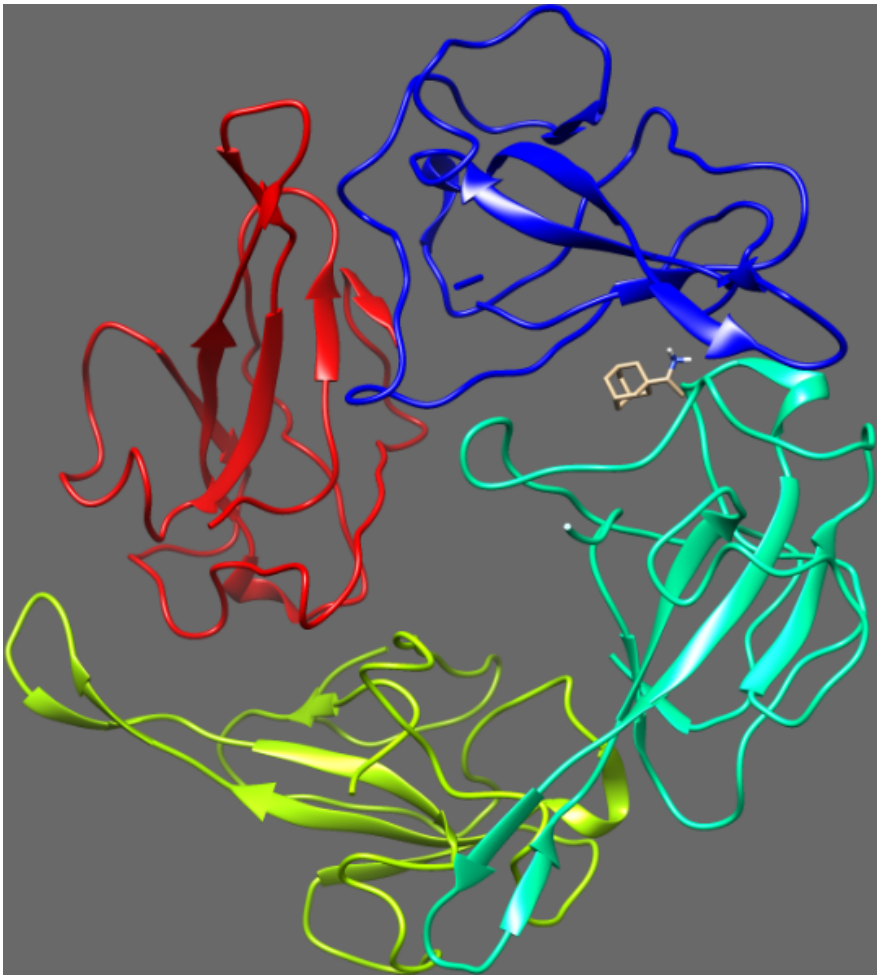

Figure 1: Receptor binding of Rimantadine on Nucleocapsid SARS-CoV2

The interactions between rimantadine and the SARS-CoV2 nucleocapsid involved conventional hydrogen bonding with threonine at position 57 in chain A, asparagine at position 77 in chain B; attractive charge interaction with aspartate at position 82 in chain B and Pi-alkyl interaction with tryptophan at position 52 in chain B. These interactions are demonstrated in Figure 2.

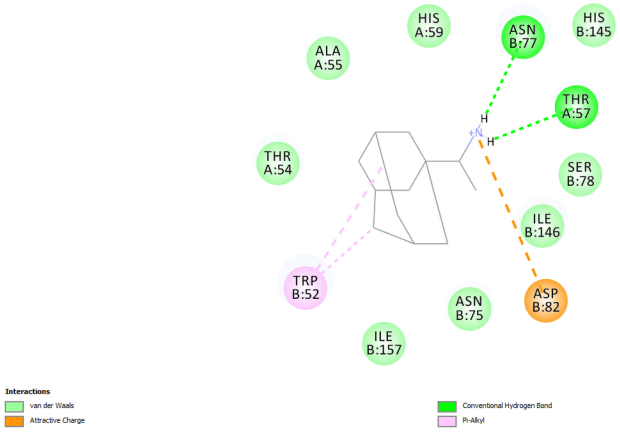


Figure 2: Interactions of Rimantadine and Nucleocapsid of SARS-CoV2

In silico pharmacokinetic analysis indicated that rimantadine had high gastrointestinal absorption, crosses the blood brain barrier, is not an inhibitor of either cytochrome P450 isoform 1A2,2C9,2C19, 2D6 or 3A4. The bioavailability score was 0.55 indicating absorption rate of approximately 55%. Rimantadine complies to Lipinski, Ghose, Veber and Egain rules on druglikeness.

Toxicity prediction resulted in median lethal dose (LD50) of 157mg/kg thereby classifying it in toxicity class 3 (LD50 between 50 and 300). Rimantadine had no effect on hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity and cytotoxicity. In terms of toxicity targets, the effects are as shown in Table 1.

**Table 1: Effect of Rimantadine on Toxicity Targets**

| | Toxicity target | Effect |
|---|---|---|
| | Aryl hydrocarbon Receptor | No effect |
| | Androgen Receptor | No effect |
| | Androgen Receptor – Ligand Binding Domain | No effect |
| | Aromatase | No effect |
| | Estrogen Receptor alpha | No effect |
| | Estrogen Receptor – Ligand Binding Domain | No effect |
| | Peroxisome Proliferator Activated Receptor Gamma | No effect |
| | Nuclear factor (erythroid derived 2) like 2/ antioxidant responsive element | No effect |
| | Heat shock factor response element | No effect |
| | Mitochondrial membrane potential | No effect |
| | Phosphoprotein p53 | No effect |
| | ATPase family AAA domain containing protein 5 | No effect |
| | Opioid receptor mu | Probable binding |

## Discussion

This data indicates that rimantadine has a higher affinity for SARS-CoV2 nucleocapsid compared to influenza A M2 protein based on a more negative binding energy. Rimantadine normally binds to the Influenza M2 protein and ensures that the closed conformation of the M2 protein pore is stable. One of the ways it ensures stability of the pore is by interacting with the amino acid tryptophan at position 41 which forms part of the gate of the M2 protein pore (Schnell and Chou, 2008). Interestingly, rimantadine interacts with tryptophan at position 52 of the nucleocapsid of SARS-CoV2 as shown in Figure 2. Serine (a hydroxyl-containing amino acid) at position 31 of the influenza A M2 protein interacts with the charged hydrogen bonds of the amine group of rimantadine (Intharathep *et al.* , 2008). The interactions between hydrogen bonds of the amine group of rimantadine and nucleocapsid of SARS-CoV2 involve threonine (a hydroxyl-containing amino acid) at position 57 and asparagine at position 77. These interactions indicate the potential binding of rimantadine to nucleocapsid of SARS-CoV2 and thus its potential use in management of COVID-19.

Prediction of rimantadine pharmacokinetics revealed that it has high gastrointestinal absorption which is in agreement with a human study done by Capparelli (Capparelli *et al.* , 1988). Rimantadine crosses the blood brain barrier and this would explain the central nervous system side effects reported by Tominack in 1988, Guay in 1994 and Galvao in 2014 (Tominack *et al.* , 1988) (Guay, 1994) (Alves Galvão, Rocha Crispino Santos and Alves da Cunha, 2014). Predicted bioavailability of rimantadine was 55%. A study done by Wills reported that following administration of a 100mg single dose of rimantadine, the bioavailability of the tablet formulation was higher than that of the syrup formulation but bioavailability for both formulations was still high (Wills *et al.* , 1987). Therefore, rimantadine can be administered either as a tablet or a syrup. Rimantadine does not inhibit cytochrome P450 isoforms CYP 1A2,2C9,2C19, 2D6 or 3A4. Lack of inhibition of cytochrome P450 demonstrates less or minimal effect on metabolism of other drugs and hence reduced effect on the pharmacodynamics of these drugs. This indicates that the drug has minimal drug-drug interactions.

Toxicity prediction revealed that rimantadine is a relatively non-toxic drug with a median lethal dose of 157mg/kg. According to Wills (1987), Tominack (1988), Guay (1994) and Galvao (2014), rimantadine is well tolerated and has few side effects which involve the gastrointestinal system and the central nervous system (Wills *et al.* , 1987; Tominack *et al.* , 1988; Guay, 1994; Alves Galvão, Rocha Crispino Santos and Alves da Cunha, 2014). Rimantadine probably binds to the opioid mu receptor and thus can mediate analgesia (Vaught, Rothman and Westfall, 1982). Another study demonstrated that rimantadine inhibits NMDA receptors and can thus also be used for parkinsonism while yet another reported that it has trypanocidal properties (Singer *et al.* , 2005; Torres *et al.* , 2012).

## Conclusion

Rimantadine has a high affinity for the SARS-CoV2 nucleocapsid and thus can be used for management of COVID-19.

## Recommendations

In vitro and in vivo studies need to be done to ascertain the efficacy of rimantadine against SARS-CoV2.

## Competing interests

None.

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