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Chemistry of Virus and Antiviral Drug Development of Viral Diseases with Chemical Perspective taking COVID-19 Virus as Special Case

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Abstract: ***Viruses are mainly composed of proteins and nucleic acids. The constituents or the building blocks of protein are the amino acids, and most of the common amino acid are found in viruses. Now interestingly analysis of viral proteins have shown that viral proteins are not protamines or histones but rather ordinary in composition, in some cases viral proteins have been found to be quite acidic in character. The reactive groups of viruses appear to be essentially the same as those of proteins i. e amino, phenolic, indole, guanidino, sulphhydryl, carboxyl and aliphatic hydroxyl. Usually nucliec acids are regarded as very reactive compounds because of their primary phosphate group, however in viruses they are chemically inert. Enzymes are also found in viruses with other constituent of virus like nucleoprotein, lipids, polysaccharide, copper, biotin and flavin. Mostly viruses consist of three components the genetic material, some protein and a lipid layer. In the case of SARS - Cov - 2 virus responsible for the COVID - 19 disease the genetic material is 30, 000 repeat units RNA whilst others act as spikes to anchor human cell and the lipid layer acts toprotect the whole assembly. The strategies for combating viral diseases are prevention (vaccine) and treatment (antiviral drugs and antibody development). Treatment via antiviral drugs and knowing its chemical perspective would be our main concern in this article. Antiviral drug development be it for HIV AIDS or COVID - 19 virus can be considered a successful stories but currently only 90 drugs have been approved to treat viral infections despite of over 200 human viruses being known and nearly half of this quantity target HIV, and therefore creating shortage of antiviral drug for other known human viruses. Antiviral drug development for various human virus species may prove to be a breakthrough in biochemical sciences.***

Keywords: Protamines, nucleoprotein, SARS - Cov - 2 (Severe Acute Respiratory Syndrome), pandemic, breakthrough

1. Chemical Approach of Antiviral Drugs and Targets

Antiviral drug developments are steered by building upon existing successful strategies. Now will review key antiviral targets that have led to clinically approved antiviral, against herpes, HIV, HCV and influenza viruses and how these successful strategies can be applied to SAR - Cov - 2 drug discovery

Most approved antiviral drugs targets a viral enzyme that plays an essential role in virus replication. Viral polymerase; DNA or RNA is highly successful drug targets. Polymerase inhibitors can be divided into two broad classes:

1) Nucleos (t) ide analogues
2) Non nucleos (t) ide allosteric inhibitor

Allosteric inhibitor binds to the polymerase but not at the catalytic active sites, causing conformational changes that impair polymerase function.

2. Examples of Some Antivirals

1) Doravirine: - HIV non nucleoside reverse transcriptase inhibitor (NNRTIs) The most recent one to obtain FDA approval being Doravirinenucles (t) ide analogue inhibitor are chemically synthesized purine and pyridine derivative with chemical alterations in base or sugar components that abrogate the growing nucleotide chain during replication.

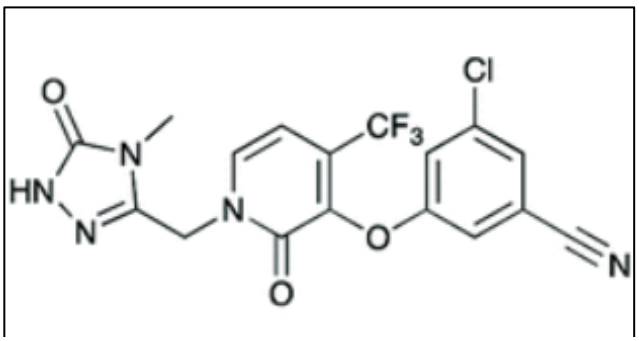


Figure 1: Doravirine

2) AZT (Azidothymidine): The first anti HIV reverse transcriptase inhibitor (NRTI) is a thymidine analogue that contains an azide group in place of the usual nucleoside OH group to which subsequent nucleoside cannot bind.

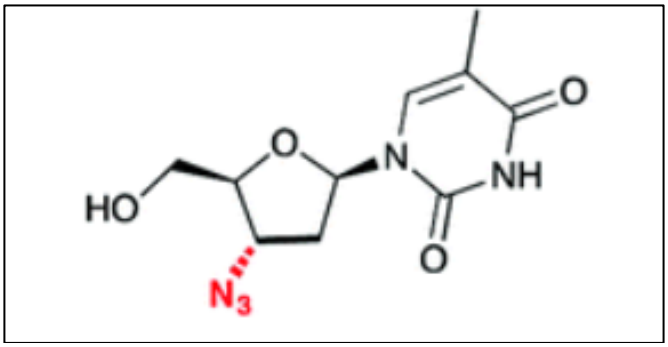


Figure 2: Azidothymidine

AZT/ Retrovir/Zidovidine

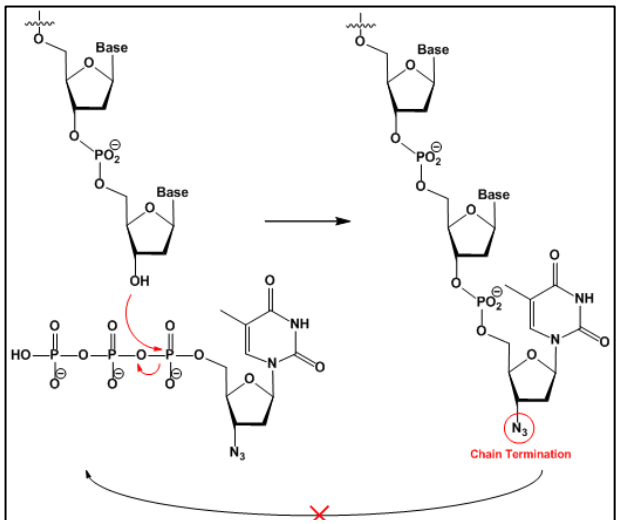
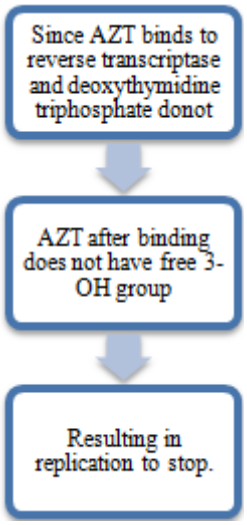


Figure 3: Enzyme inhibition by AZT



3) **Acyclovir**: - An acyclic guanosine analogue used to treat Herpes simplex virus infection has high selectivity due to specific phosphorylation by HSV encoded thymidine kinase confining activity to virus infected cells.

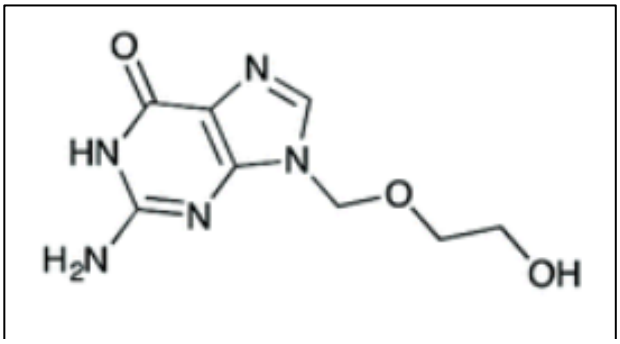


Figure 4: Acyclovir

Development of an effective antiviral drug is typically followed by expansion of the successful strategy with numerous chemical variations providing improvement in parameters including affinity pharmacology, toxicity and drug resistence profile. Expansion of the successful structure to other viruses beyond the initial clinical target is also possible, especially for polymerase inhibitors because all RNA viruses encode an RNA dependent RNA polymerase (RdRp). Drugs targetingRdRps may have the capacity for activity against different viruses for which antiviral drugs are not currently available. Such broadly acting antiviral is,

4) **Ribavirin**: - Another example of broadly acting antiviral, guanosine nucleoside analogue inhibitor. Ribavirine is often used with other antiviral agents and is clinically approved against HCV but is also used unlicensed against some viral hemorrhagic fevers.

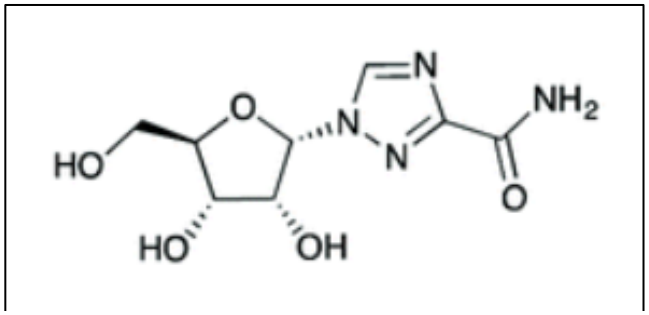


Figure 5: Ribavirin

5) **Remdisivir**: - A monophosphhate prodrug of a 1'cynodenosine nucleoside analogue has in - vitro, in - vivo activity against multiple RNA virus families including filoviruses (EBOV) and corona viruses (SARS - CoV - 1, SAR - CoV - 2, MERS - CoV) and has recently been granted FDA emergency use authorization for COVID - 19 treatment. Since coronaviruses are tricky simply the mimics won't work, because these virus have another protein that acts as an editor, monitering the polymerase's work, recognizing the decoy and cutting it out there comes Remdisivir it is also a nucleotide mimic but it is a special one, once incorporated into a piece of new viral genome (which is in case of corona virus made of RNA) it doesn't stop the strand's growth right away instead the polymerase keeps adding normal nucleotides but after its added a few, the drug bends the RNA strand so badly that the polymerase can't keep building by then since the corona virus editor protein no longer works the normal nucleotides added after Remdisivir seem to get in the way and the polymerase is stuck.

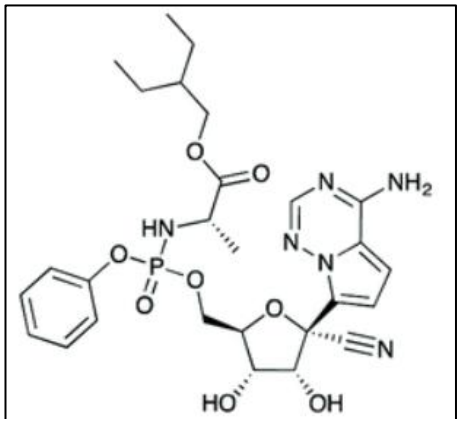


Figure 6: Remdisivir

6) Favipiravir: - Also in this category is Favipiravir, a prodrug that is ultimately converted into its ribofuranosyl 5' triphosphate metabolite (Favipiravir RTP) incorporated as a pseudopurine by the viral RdRp. It is clinically approved in Japan for treating influenza. It is also broadly active in in - vivo state against other RNA viruses including SARS - CoV - 1 and MERS - CoV. Favipiravir is incorporated at high rates resulting in lethal mutagenesis of SARS - CoV - 2 viral RNA during replication in - vitro and the compound is currently in clinical trials for treating COVID - 19.

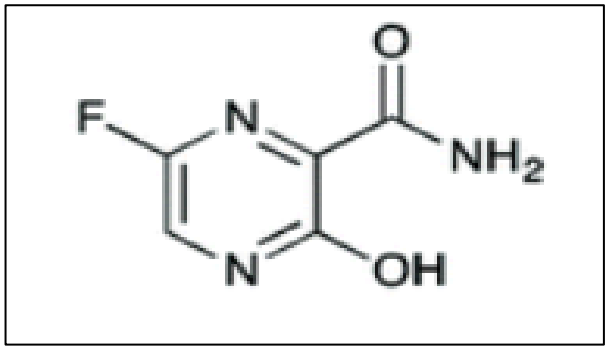


Figure 7: Favipiravir

Protease inhibitors are another major class of approved antiviral drug developed primarily to treat HIV and then HCV infections. All approved HIV protease inhibitor are designed with a peptidomimetichydroxyethylenescafford, example - Saquinavir. Exception being Tipranavir which has a coumarinscafford.

7) Saquinavir

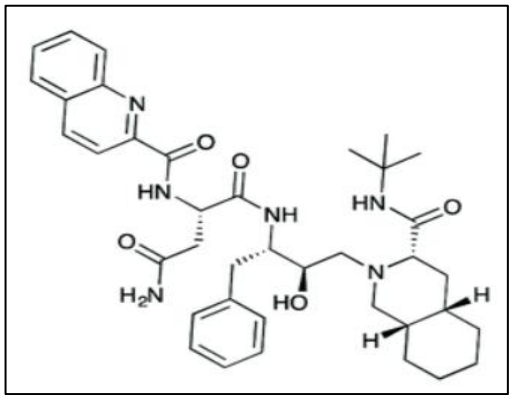


Figure 8: Saquinavir

8) Tipranavir

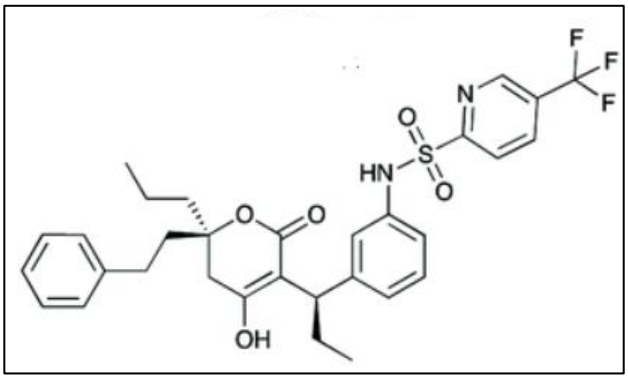


Figure 9: Tipranavir

Structural point of view and medicinal plant anticovid drug discovery for SARS - CoV - 2

Recent pandemic of corona virus disease 2019 has increased the curiosity among scientist and people to know more about this notorious virus causing enormous amounts of death and raising global health concerns with post COVID problems. To know more about this virus the basic question which arises is about its structure so it has been found that the viral 3 - chymotrypsin like cystein protease ($3CL^{Pro}$) enzyme controls corona virus replication and it is essential for its life cycle $3CL^{Pro}$ is a proven drug discovery target in the case of severe acute respiratory syndrome corona virus (SARS - CoV) and middle east respiratory syndromecorona virus (MERS - CoV). Recent studies on genome sequence of SARS - CoV - 1 and SARS - CoV - 2 have shown that they are very similar to each other. Therefore the analysis of the $3CL^{Pro}$ sequence constructed in 3D homology model when screened against a medicinal plant library containing potential antiviral phytochemicals (medicinal compounds) revealed that the top nine might serve as potential anti SARS - CoV - 2 molecules for optimization in future and drug development process to combat.

Analysis of Physiochemical parameters revealed that the SARS - Cov - 2 $3CL^{Pro}$ polypeptide is 306 amino acids long with a molecular weight of 33, 796.64 Da and GRAVY score (Grand average of hydropathicity index - GRAVY, is used to represent the hydrophobicity value of a peptide. +ve GRAVY indicates hydrophobic, - ve GRAVY indicates hydrophillic) comes out to be - 0.019 categorizing the protein as a stable, hydrophillic molecule capable of establishing hydrogen bonds.

Mutational analysis has depicted none of the mutation affects the overall structure of SARS - Cov - 2 which can fully superimpose on ther SARS - CoV $3CL^{Pro}$ structure, it is also revealed that SARS - CoV - 2 has a Cys - His (Cystein - Histidine) catalytic dyad consistent with that of SARS - CoV $3CL^{Pro}$, TGEV $3CL^{Pro}$ and HCOV $3CL^{Pro}$, thus the SARS - CoV - 2 receptor binding pocket conformation resembles that of the SARS - CoV $3CL^{Pro}$ binding pocket and raises the possibility that inhibitor intended for SARS - CoV $3CL^{Pro}$ may also inhibit the activity of SARS - CoV - 2 $3CL^{Pro}$. To test this (R) - N - (4 - tert - butyl) phenyl) - N - (2 - tert - butylamino) - 2 - oxo - 1 - pyridin - 3 - yl) ethylfuran - 2 - carboxamine), a potential non covalent inhibitor called as

ML188 of SARS - CoV $3CL^{Pro}$ was docked with the SARS - CoV - 2 homology model, also docked (R) - N - (4 - tert - butyl) phenyl) - N - (2 - tert - butylamino) - 2 - oxo - 1 - pyridin - 3 - yl) ethylfuran - 2 - carboxamine) ML188 with SARS - CoV $3CL^{Pro}$ structure as a reference and it was observed that ML188 bound strongly to the receptor binding site of SARS - CoV $3CL^{Pro.}$ The inhibitor targets the Cys - His catalytic dyad along with other residue and the docking score (S= - 12.27) was relatively high however, surprisingly ML188 did not show significant binding to the catalytic dyad of SARS - Cov - 2 and the docking score S= - 8.31 was considerable lower. These results indicated that the mutations indentified may disrupt important hydrogen bonds and alter the receptor binding sites affecting its ability to bind with the SARS - CoV inhibitor. Therefore it is essential to discover novel compounds that may inhibit SARS - CoV - 2 $3CL^{Pro}$ and serve as potential anti - covid - 19 drug compound.

On further analysis later it was found that nine novel non - toxic, drug able natural compounds have been identified that are predicted to bind with the receptor binding sites and catalytic dyad of SARS - Cov - 2 $3CL^{Pro}$. Among these screened phytochemicals 5, 7, 3', 4' - tetrahydroxy - 2' - (3, 3 - dimethylallyl) isoflavone is an isoflavone extracted from Psorothamnus arborescence that exhibits highest binding affinity (- 29.57 kcal/mole) and docking score S= - 16.35 and formed strong hydrogen bonds with the catalytic dyad residue Cys - 145 and His - 41 as well as significant interaction with the receptor binding residue Thr24, Thr25, Thr26, Cys44, Thr45, Ser46, Met49, Asn142, Gly143, His164, Glu166 and Gln189. It is also revealed that 5, 7, 3', 4' - tetrahydroxy - 2' - (3, 3 - dimethylallyl) isoflavone has been successfully used as antileishmanial agent. These result suggested that natural products identified may prove more useful candidates for COVID - 19 Drug therapy. Other possible phytochemicals might prove to be more useful in combating COVID - 19 are: -

1. 5, 7, 3', 4' - tetrahydroxy - 2' - (3, 3 - dimethylallyl) isoflavone

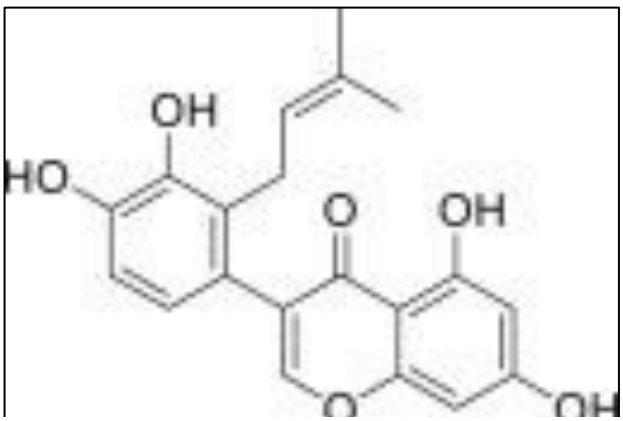


Figure 10: 5, 7, 3', 4' - tetrahydroxy - 2' - (3, 3 - dimethylallyl) isoflavone

2. Myricitrin

Plant name: - Myricacerifera

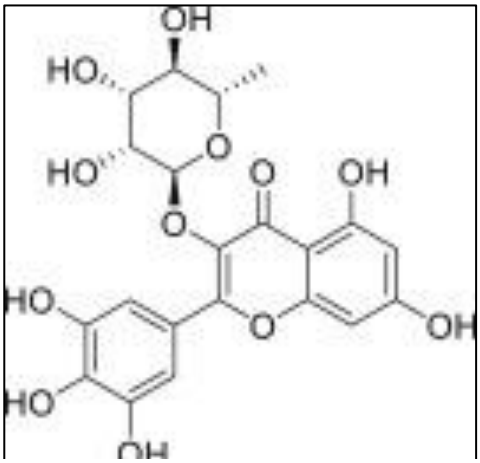


Figure 11: Myricitrin

3. Methyl rosamarinate

Plant name: - Hyptisatrorubens Poit.

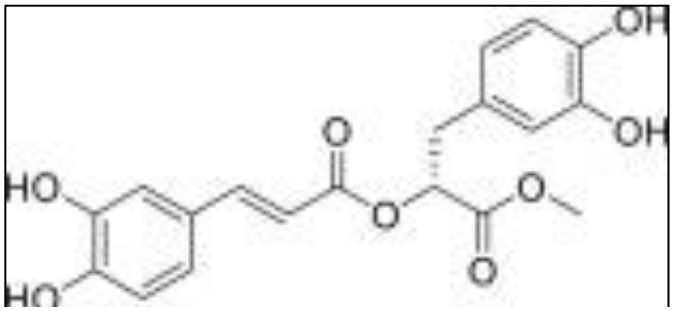


Figure 12: Methyl rosamarinate

Challenges Faced by Antiviral Drug Discovery

Antiviral drug discovery and development is a lengthy economically expensive this becomes even more complex considering the high attrition rate of compound during preclinical research. To add more to the complexity only 3 out of 10 drugs that make it to recover their capital investment, furthermore within the context of antiviral drug discovery efforts have been targeted to those viruses that are economically important in developed countries. Apart from these the number of antiviral are comparatively less in comparison to antibacterial or antifungal because most importantly viruses are much notorious, trickier agents than bacteria or fungus, also bacteria are whole living cells with the metabolic pathways they need for survivals so they offer plenty of targets for attack, in contrast viral pathogens live inside our own cells and depends on our proteins for most of their needs so they offer no such easy targets.

Furthermore most biggest challenge is to ensure that the drugs don't hurt the human host as well for example in the case of nucleotide mimics like acyclovir question that arises is that wouldn't there be a risk that they would get into cells DNA as well as virus's? Answer to that is that patients swallow the drug acyclovir in its inactive form and it is mainly activated by a viral protein.

Another challenge faced by antiviral drug development is that viruses can make tiny changes to their genes and proteins that leave them unharmed by the drug this called

viral resistance to the drug. Resistance is huge issue in antiviral drug discovery that is in the case of COVID - 19 virus it mutates and creates various variants of SARS - CoV - 2 namely α, β, γ, δ etc are the result of these mutations.

Antiviral drug discovery are faced by numerous challenges but in the end all the hardwork and risks pays off by preventing another upcoming pandemic.

3. Conclusion

The antiviral drug development is as tricky as the viruses, the viruses comes with a lot of complexities from their structure to their mutation properties making a whole new variant and resistance to the antiviral drug sometimes which makes the drug discovery even more difficult which also contribute to the declining ratio of antiviral drug to the viral species known. After the COVID - 19 pandemic it is quite clear that we need to combat the problems regarding antiviral drug discovery to prevent another pandemic to come in future. Even after more than a year since the COVID - 19 pandemic hit us there are no totally reliable antiviral developed. The second wave of COVID - 19 took lives in India beyond count since the mid march till may almost every individual in the country knew the importance of antiviral one of which is known by everyone that is Remdisivir (broadly acting antiviral), it recovered many people affected by SARS - CoV - 2 but the post COVID problems came with it. Even WHO stated - "no evidence that Remdisivir improves survival and other outcomes" and removed the drug from the recommended medicine list for COVID. This shows that even our best shots are not that effective and reliable which makes antiviral drug development more crucial and to be worked on. Most importantly the antiviral drug discovery should also focus on their side effects and post treatment problems, since many patients recovered from the COVID seem to develop different side effects and post treatment problems being hair loss, gastric problems, weight loss being the most common side effects differing person to person. This creates more need to explore the natural antiviral drug development i. e. from the phytochemicals medicinal plant compounds like 5, 7, 3', 4' - tetrahydroxy - 2' - (3, 3 - dimethylallyl) isoflavone have shown to be a good candidate in antiviral drug development for SARS - CoV - 2. Thus it is essential to discover other novel compounds for human viral species known that could possibly give rise to another pandemic possible. Such phytochemical compounds might serve as the breakthrough in the antiviral drug development with minimized side effects. Learning from the past year antiviral drug development with minimum side effect has become a necessity to prevent another pandemic as 'Prevention is better than cure'.

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