# Chapter 5
# Rational Drug Design and Docking of the RNA Dependent RNA Polymerase Domain of NCoV


It is an urgent requirement of 2020 to develop a drug which can successfully treat the patients of COVID19 and gift them a healthy life back. The development of drugs against COVID is the need of the hour for the scientific community. However Drug development is a long term process requiring drug discovery, testing and validation and cannot be a suitable choice for the current situation. Thus instead of laying a complete focus on discovery of medication it is necessary to repurpose the available and validated drugs which were used previously against other similar virus infections. This chapter focuses on Drug repurposing and selection of suitable drug candidates which have been used previously for other similar infections and validated.

The drugs that were used in the treatment of MERS, SARS, and INFLUENZA etc. can be tried with the COVID19 victims based on their function and similarity to the NCoV. The major proteins of the virus which can be targeted in the disease are the structural proteins including Spike or S protein, Membrane or M protein, Nucleocapsid or N protein, Envelope or E protein etc. as well as the nonstructural proteins including all the NSPs from 1 to 16 and ORFs etc.

Extensive data mining works has revealed the use of ORF1ab and the Structural proteins in the treatment of MERS. Thus the same can be used in the COVID 19 therapy for the current relaxation from the virus. Some of the Drugs that can be repurposed and used for COVID19 treatment include ribavirin, glycyrrhizin and IFN-$\alpha$.



A. Kumar et al., *Novel Coronavirus 2019*,
SpringerBriefs in Forensic and Medical Bioinformatics,
https://doi.org/10.1007/978-981-15-7918-9_5

## 5.1 Selection Criteria for Chemicals

One of the important points to be considered in the treatment or the drug development for COVID 19 is time constraint. Currently Drug repurposing [1] is the best option that can be considered for the development of drugs in the treatment of the COVID victims.

In view of the above comparative analysis between MERS CoV and Novel Corona Virus 2019 which revealed a close genetic relation, all the medications that were successful in treating MERS can be used in the therapy of COVID with the molecular mechanism studied. All the drugs and their structures are obtained from two important public databases which are PUBCHEM [2] and CHEBI [3].

A **Selection of Chemicals**

1. **Remdesivir:**

This is an active inhibitor for the RNA dependent RNA polymerase enzyme which was already tested and proved to be effective against MERS [4] (https://www.jbc.org/content/early/2020/02/24/jbc.AC120.013056).

One of the study by Elfiky et al. [5] on MERS therapy stated that Guanosine derivatives are good inhibitors for virus polymerases (https://www.tandfonline.com/doi/full/10.1080/07391102.2020.1758789) and can be used in treating MERS which was validated by in silico docking studies. Thus these derivatives along with the proposed other drugs can be tested for COVID therapy. The compounds tested in the study were as follows:

2. Guanosine triphosphate (GTP)
3. Uridine triphosphate (UTP),
4. IDX-184 (GTP derivative),
5. Sofosbuvir (UTP derivative)
6. Ribavirin (wide acting antiviral drug)

B. **Collection of chemicals and their properties from Databases**:
The data has been retrieved from two data bases CHEBI and PUBCHEM

1. **Remdesivir [6] (CHEBI: 145994)**
   Formula: C27H35N6O8P
   Molecular Mass: 602.6
   Log P: 1.9
   H bond donor: 4
   H bond acceptor: 13
2. **Guanosine triphosphate [7] (GTP) (CHEBI:16690)**
   Formula: C10H18N5O20P5
   Molecular Mass: 683.14
   Log P: −5.7
   H bond donor: 8
   H bond acceptors: 16

3. **Uridine triphosphate [8] (UTP) (CHEBI:15713)**
   Formula: C9H15N2O15P3
   Molecular Mass: 484.14
   Log P: −5.8
   H bond donor: 7
   H bond acceptor: 15
4. **IDX-184 [9]**
   Formula: C25H35N6O9PS
   Molecular Mass: 626.6
   Log P: −1.3
   H bond donor: 6
   H bond acceptor: 13
5. **Sofosbuvir [10] (UTP derivative) CHEBI:85083**
   Formula: C22H29FN3O9P
   Molecular Mass: 529.4
   Log P: 1
   H bond donor: 3
   H bond acceptor: 11
6. **Ribavirin [11] (CHEBI:63580)**
   Formula: C8H12N4O5
   Molecular Mass: 244.2
   Log P: −1.8
   H bond donor: 4
   H bond acceptor: 7.

## 5.2 Docking of the Chemicals in HEX

The docking association of the above six ligands with RNA-dependent RNA polymerase domain was studied on HEX [12] and illustrated as follows:

1. **1DX-184** (Fig. 5.1).
2. **Guanosine Triphosphate** (Fig. 5.2).
3. **Uridintriphosphate** (Fig. 5.3).
4. **Sofosbuvir** (Fig. 5.4).
5. **Ribavirin** (Fig. 5.5).
6. **Remdesivir** (Fig. 5.6).

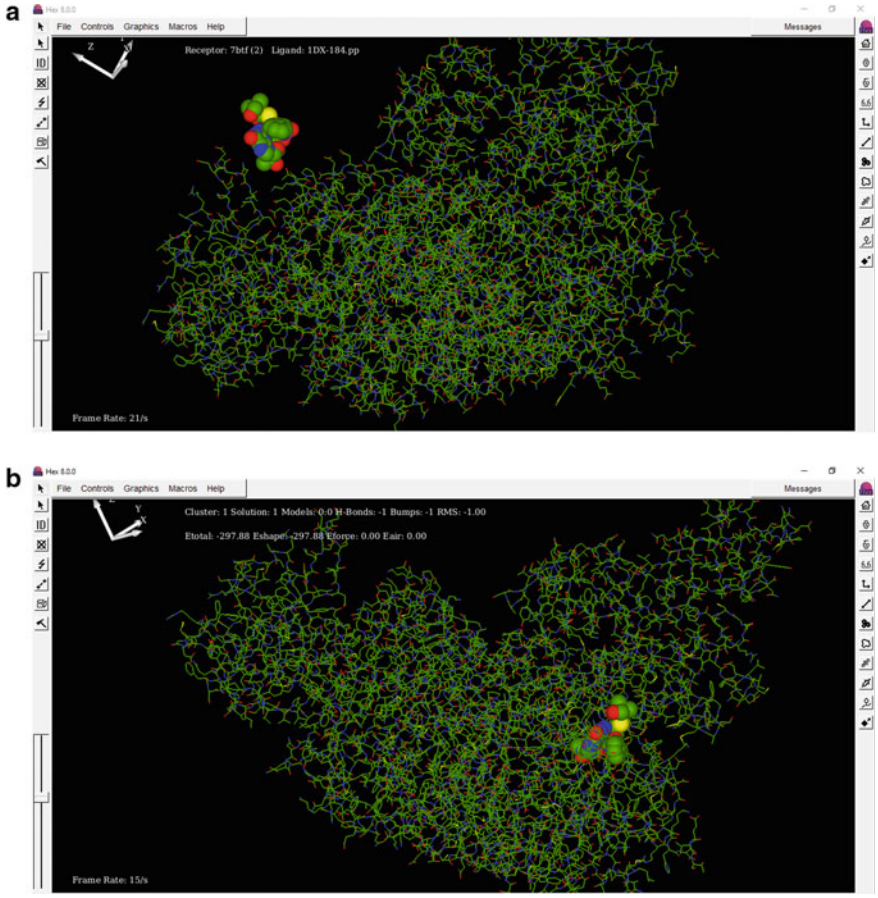


**Fig. 5.1** **a** and **b** Different poses of 1DX-184 and RNA-dependent RNA polymerase docking at energy −297.88

## 5.3 Docking Results Summarized

| S. No. | Ligand | HEX docking energy |
|---|---|---|
| 1 | Remdesivir | −276.31 |
| 2 | Guanosine triphosphate | −253.83 |
| 3 | Uridine triphosphate | −204.54 |
| 4 | IDX-184 | −297.88 |
| 5 | Sofosbuvir | −235.87 |
| 6 | Ribavirin | −162.23 |

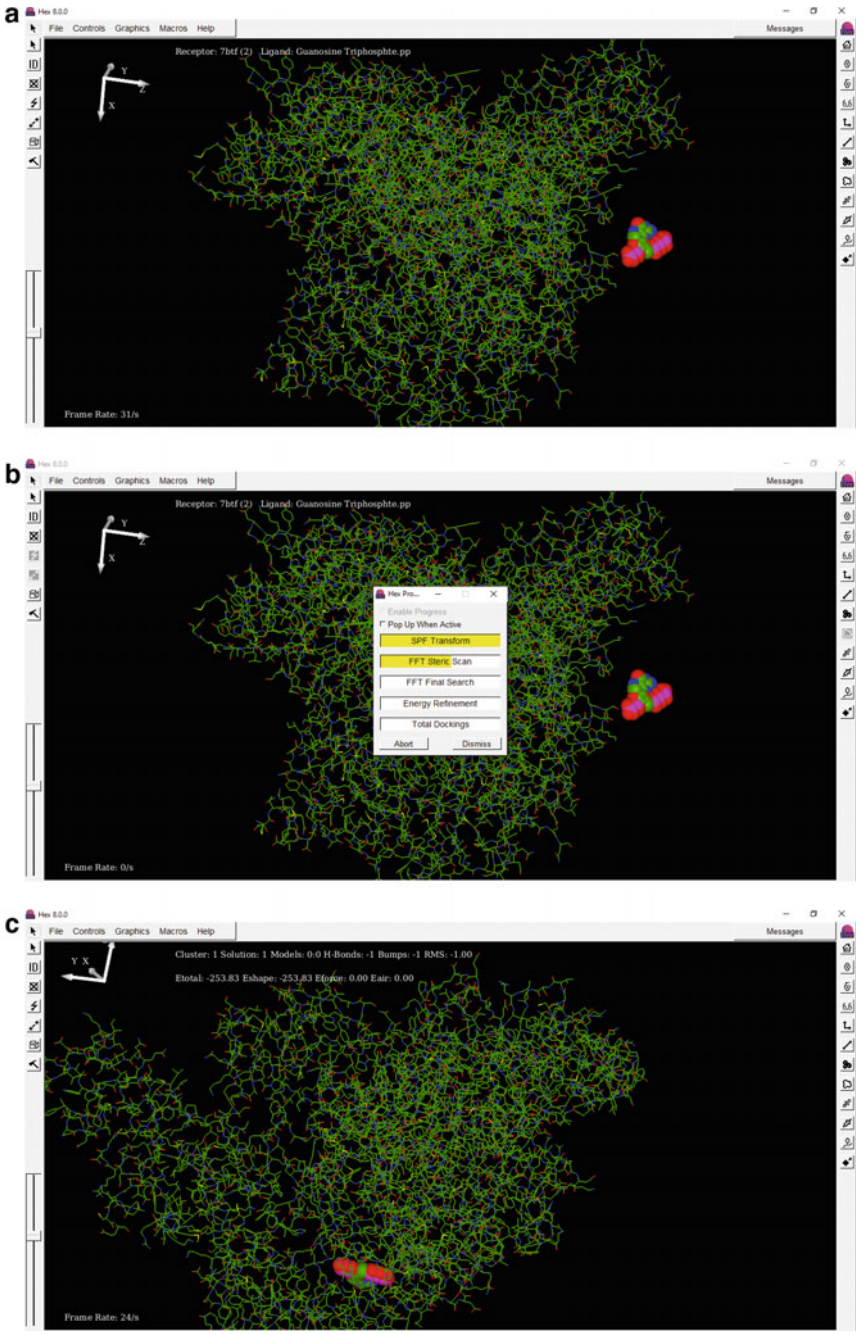


**Fig. 5.2** **a**, **b** and **c** Different poses of Guanosine Triphosphate and RNA-dependent RNA polymerase docking at energy −253.83

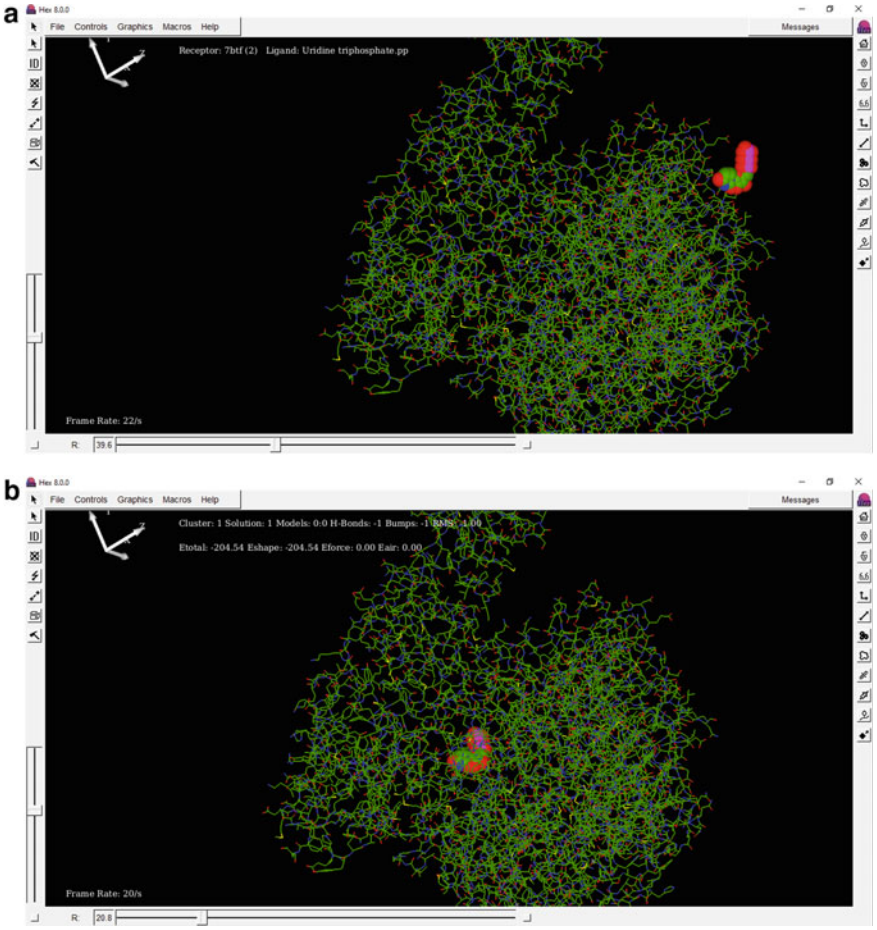


**Fig. 5.3** **a** and **b** Different poses of Uridintriphosphate and RNA-dependent RNA polymerase docking at energy −204.54

The docking was performed between the selected ligands and the PDB structure 7btf corresponding to the RNA dependent RNA polymerase domain of ORF1AB protein. All the docking energies are energetically favorable and closer except Ribavirin. This indicates that the ligands Remdesivir, IDX-184 and Guanosine triphosphate etc can be used as efficient drugs.

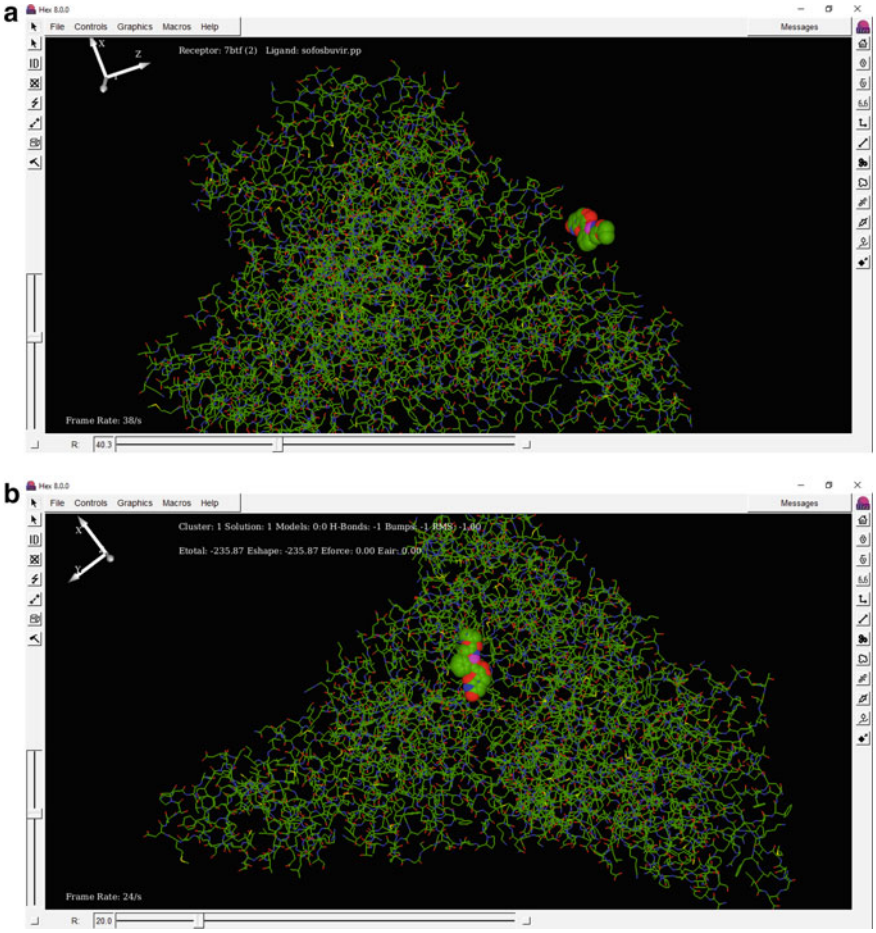


**Fig. 5.4** **a** and **b** Different poses of Sofosbuvir and RNA-dependent RNA polymerase docking at energy −235.87

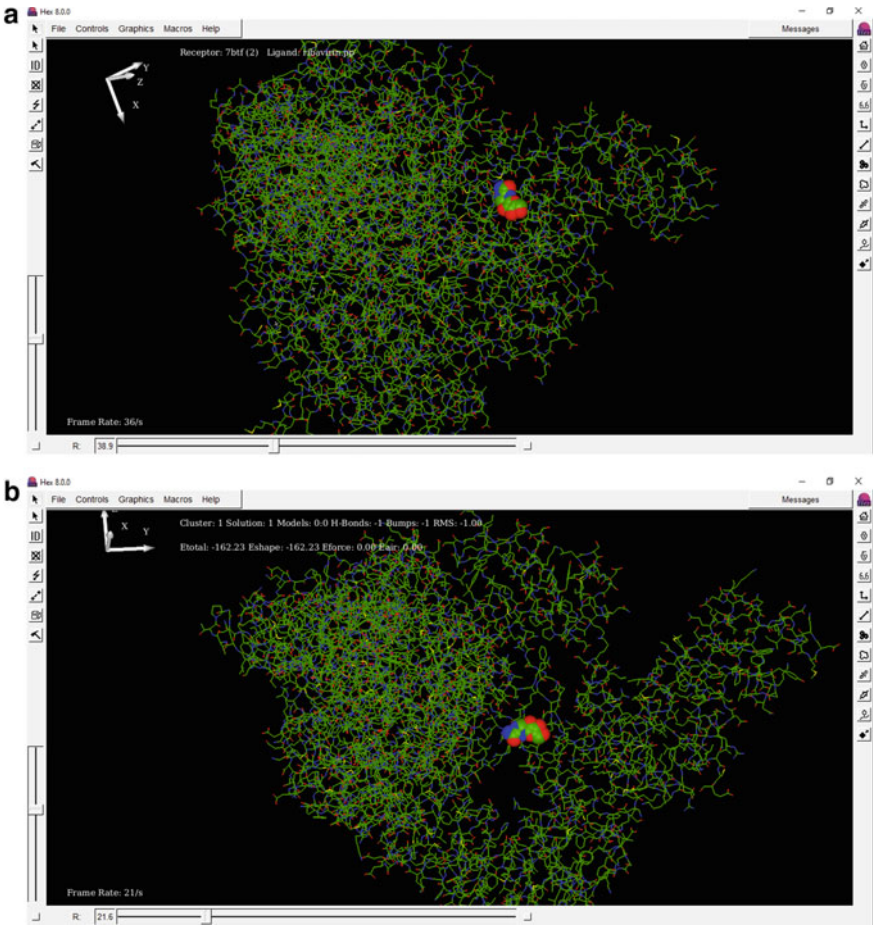


**Fig. 5.5** **a** and **b** Different poses of Ribavirin and RNA-dependent RNA polymerase docking at energy −162.23

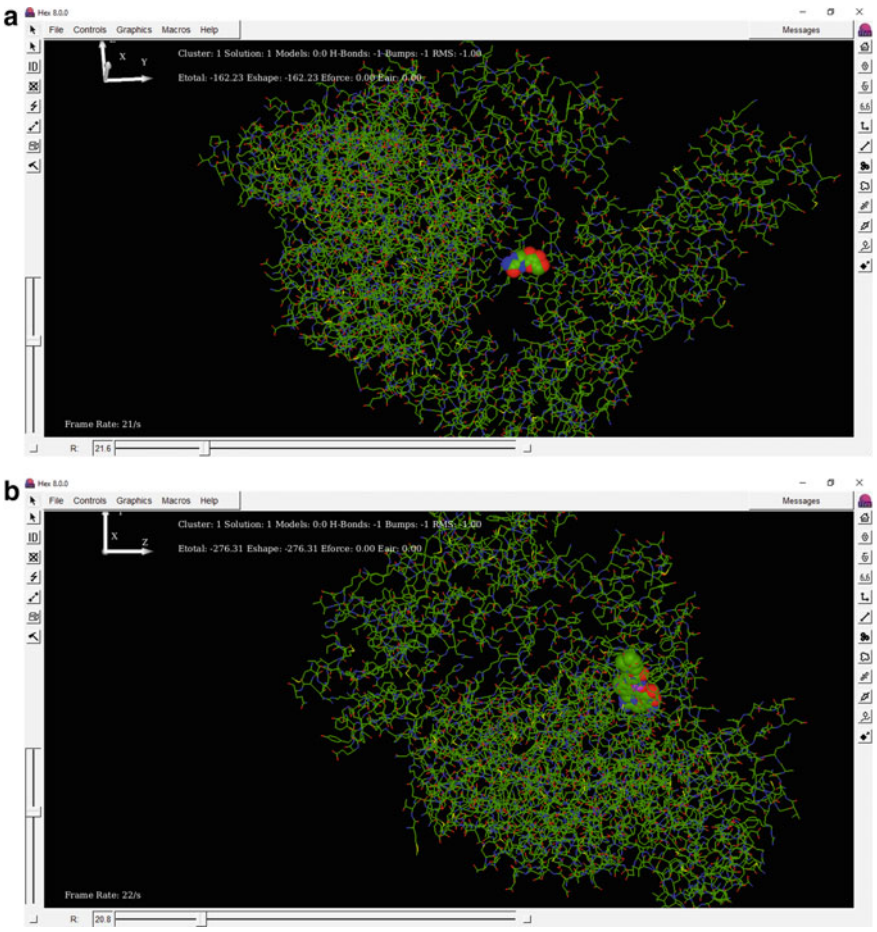


**Fig. 5.6** **a** and **b** Different poses of Remdesivir and RNA-dependent RNA polymerase docking at energy −276.31

## References

1. Serafin MB et al (2020) Drug repositioning is an alternative for the treatment of coronavirus COVID-19. Int J Antimicrob Agents Jun 2020; 55(6):105969. https://doi.org/10.1016/j.ijantimicag.2020.105969 Epub 2020 Apr 9
2. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, Li Q, Shoemaker BA, Thiessen PA, Yu B, Zaslavsky L, Zhang J, Bolton EE (2019) PubChem 2019 update: improved access to chemical data. Nucleic Acids Res 47(D1):D1102–D1109. https://doi.org/10.1093/nar/gky1033
3. Hastings J, de Matos P, Dekker A et al (2013) The ChEBI reference database and ontology for biologically relevant chemistry: enhancements for 2013. Nucleic Acids Res 41(Database issue):D456–D463. https://doi.org/10.1093/nar/gks1146
4. Gordon CJ et al (2020) The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. JBC Papers in Press.

Published on February 24, 2020 as Manuscript AC120.013056
5. Elfiky AA et al (2020) Novel guanosine derivatives against MERS CoV polymerase: an in silico perspective. J Biomol Struct Dyn 27
6. Wang M, Cao R, Zhang L et al (2020) Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 30:269–271
7. Amayed P, Carlier MF, Pantaloni D (2000) Stathmin slows down guanosine diphosphate dissociation from tubulin in a phosphorylation-controlled fashion. Biochemistry 39(40):12295–12302
8. Knobloch B et al (2011) Stability and structure of mixed-ligand metal ion complexes that contain $Ni^{2+}$, $Cu^{2+}$, or $Zn^{2+}$, and Histamine, as well as adenosine 5'-triphosphate (ATP4-) or uridine 5'-triphosphate (UTP(4-): an intricate network of equilibria. Chemistry 17(19):5393–5403. https://doi.org/10.1002/chem.201001931 Epub 2011 Apr 4
9. https://chem.nlm.nih.gov/chemidplus/sid/1207451953
10. https://pubchem.ncbi.nlm.nih.gov/compound/Sofosbuvir#section=Literature
11. https://www.drugbank.ca/drugs/DB00811
12. Assignment DF, Argos P (1995) Knowledge-based protein secondary structure, Proteins: Struct Funct Genet 23:566–579. ftp://ftp.ebi.ac.uk/pub/software/unix/stride