

Does HCV RNA polymerase accept 2'-Deoxynucleosides as its substrates?

Hiroshi Ohrui

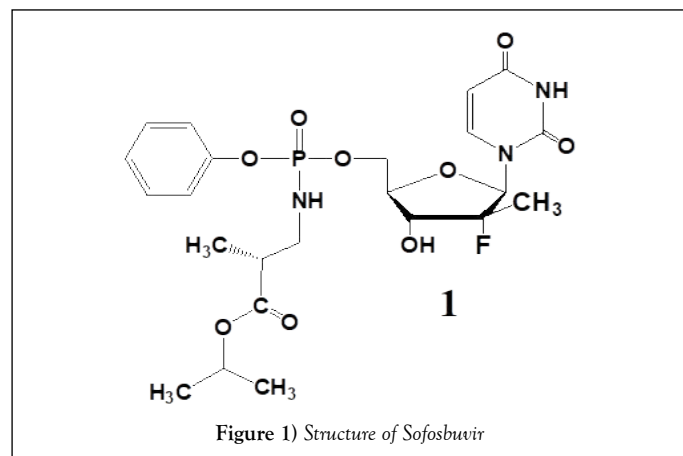
Ohruai H. Does HCV RNA Polymerase Accept 2'-Deoxynucleosides as Its Substrates? *J Pharm Toxicol.* 2018;1(2):23-24

Many emerging viral infectious diseases, for example, the spreads of MAIDS, Flu, HCV, HBV, West Nile Virus, SARS, and so on, are causing major threats to global public health. Therefore, the development of highly active and lowly toxic antiviral drugs is required. Modified nucleosides are expected to be excellent antiviral drugs. In order to develop excellent antiviral modified nucleosides, it is necessary to understand the structure-activity relationship of nucleoside drugs. This commentary describes questions about the substrate selectivity of HCV RNA polymerase and the role of the 2'-fluorine atom of Sofosbuvir. At first, I would like to describe my general idea for the development of antiviral modified nucleosides.

Mutative viruses adapt themselves to the environmental change by mutation. Mutation causes resistant viral mutants and makes the treatment of viral infectious disease very difficult. Therefore, the mutation has been taken for only the cause of the problems in the treatment of viral infectious disease. However, I think that the mutation is the heaven-sent opportunity for the development of antiviral modified nucleosides, for the following reasons.

Mutation is that viruses change their genes by taking not-programmed nucleosides into their genes ignoring the Watson-Crick A: T, G: C pairings. This indicates that the substrate selectivity of mutative viral nucleic acid polymerases is not strict. On the other hand, human beings do not mutate and do not accept the not-programmed nucleosides into their genes. This indicates that the substrate selectivity of human nucleic acid polymerases is very strict. Thus, the substrate selectivity is different between mutative viral nucleic acid polymerases and human nucleic acid polymerases. Therefore, by taking advantage of the difference of the substrate selectivity it is possible to develop the modified nucleosides which can be accepted by viral nucleic acid polymerases (active to viruses) but not by human nucleic acid polymerases (not toxic to human beings).

Sofosbuvir (1) (Figure 1) is really the winner in the treatment of HCV infection. [1] The structure of 1 has prompted me to think of two curious

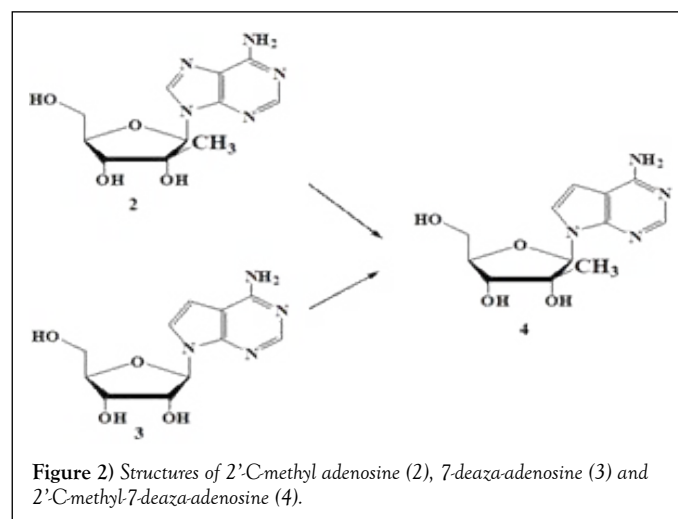


questions. One is "if HCV RNA polymerase accepts 2'-deoxynucleosides as substrate? Another is "if the fluorine atom of 1 plays the role of the 2'-hydroxyl group of ribonucleoside so that 1 could be accepted as a substrate by HCV RNA polymerase?"

1 is a very strong chain-terminator of HCV RNA polymerase, therefore highly active to HCV. On the other hand, 1 is not toxic to human beings, indicating that 1 is not the chain-terminator of human RNA polymerase, namely human RNA polymerases do not accept 1 [1]. These results may suggest that the 2'-fluorine atom of 1 plays the role of a hydroxyl group with HCV RNA polymerase but not with human RNA polymerase, or the 2'-fluorine atom does not play the role of a hydroxyl group with both HCV RNA polymerase and human RNA polymerase, but HCV RNA polymerase accepts 1 which is a 2'-deoxy nucleoside. It should be noted that 1 has 3'-OH which is a neopentyl type secondary alcohol [2]. The activity of 1 to viruses other than HCV is interesting. Further, since uracil is restricted to RNA, the biological activity of the analogues of 1 having nucleobases other than uracil is very interesting.

Eldrup AB reported that 2'-C-methyl-7-deaza adenosine (4) (Figure 2) a hybrid of very toxic 2'-C-methyl adenosine (2) and very toxic 7-deaza-adenosine (3), is highly anti-HCV active and not toxic [3]. This indicates that HCV RNA polymerase accepts 4 but human RNA polymerases do not accept 4, because human RNA polymerases do not recognize the two position modified nucleoside as their substrate similarly to the substrate selectivity of human DNA polymerases [2]. Thus, the substrate selectivity of HCV RNA polymerase is different from that of human RNA polymerases.

On the other hand, Smith DB reported that 4'-C-azido-cytidine (5) (Figure 3) is anti-HCV active. Further, they reported that 4'-C-azido-arabino-furanosyl



Yokohama University of Pharmacy, 601 Matanocho, Toysukaku, Yokohama 245-0066, Japan

Correspondence: Hiroshi Ohruai, Yokohama University of Pharmacy, 601 Matanocho, Toysukaku, Yokohama 245-0066, Japan. Telephone 203-459-4376, e-mail h.ohruai@hamayaku.ac.jp

Received: September 28, 2018, Accepted: October 03, 2018, Published: October 13, 2018



This open-access article is distributed under the terms of the Creative Commons Attribution Non-Commercial License (CC BY-NC) (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits reuse, distribution and reproduction of the article, provided that the original work is properly cited and the reuse is restricted to noncommercial purposes. For commercial reuse, contact reprints@pulsus.com

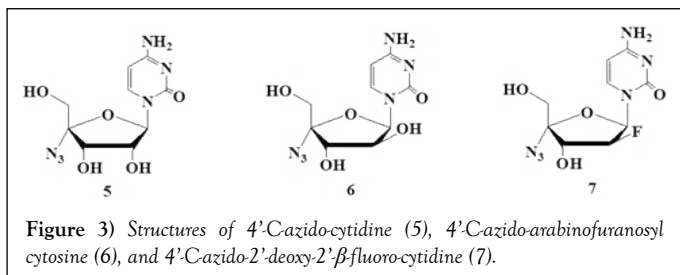


Figure 3) Structures of 4'-Azido-cytidine (5), 4'-Azido-arabinofuranosyl cytosine (6), and 4'-Azido-2'-deoxy-2'-β-fluoro-cytidine (7).

cytidine (6) and 4'-Azido-2'-deoxy-2'-β-fluoro-cytidine (7) are more active than 5 and low toxic, and 5, 6 and 7 are chain-terminators of HCV RNA polymerase [4,5]. Compound 6 and 7 are 2'-deoxynucleosides. Surprisingly, HCV-RNA-polymerase accepted these 2'-deoxynucleosides!

It has been reported that 4'-Cethynyl-2'-deoxycytidine (8) (Figure 4) and 4'-Cethynyl arabinofuranosyl cytosine (9) are highly anti-HIV active and highly toxic. [2] Therefore, I wonder about the anti-HIV activity and the toxicity of 6 and 7. It should be noted that all the chain-terminator nucleosides (1-9, except 3) have 3'-OH which is a neopentyl type secondary alcohol.

Thus, the different substrate selectivity between viral nucleic acid polymerases and human nucleic acid polymerases is very important factor for the development of antiviral modified nucleosides.

REFERENCES

1. Bhatia HK, Singh H, Grewal N, et al. Sofosbuvir: A novel treatment option for chronic hepatitis C infection. *J Pharmacol Pharmacother.* 2014;5:274-84.
2. Ohrui H. Development of modified nucleosides that have supremely high anti-HIV activity and low toxicity and prevent the emergence of resistant HIV mutants. *Proc Jpn Acad, Ser. B.* 2011;87:53-65.
3. Eldrup AB, Prhave M, Brooks J, et al. Structure-activity relationship of heterobase-modified 2'-C-methyl ribonucleosides as inhibitors of hepatitis C virus RNA replication. *J Med Chem.* 2004;47:5284-97.
4. Smith DB, Kalayanov G, Sund C, et al. The Design, Synthesis, and Antiviral Activity of 4'-Azidocytidine Analogues against Hepatitis C Virus Replication: The Discovery of 4'-Azidoarabinocytidine. *J Med Chem.* 2009;52:219-23.
5. Smith DB, Kalayanov G, Sund C, et al. The design, synthesis and antiviral activity of monofluoro and difluoro analogues of 4'-azidocytidine against hepatitis C virus replication: the discovery of 4'-azido-2'-deoxy-2'-fluorocytidine and 4'-azido-2'-deoxy-2',2'-difluoro-cytidine. *J Med Chem.* 2009;14:2971-8.

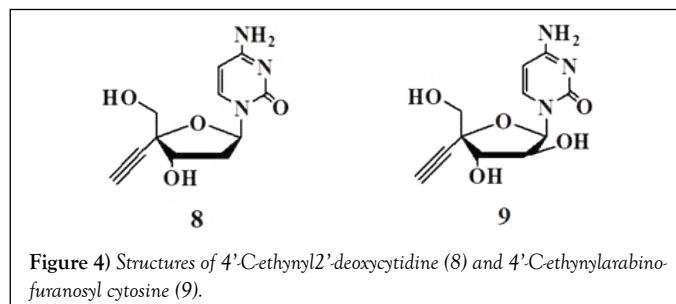


Figure 4) Structures of 4'-Cethynyl-2'-deoxycytidine (8) and 4'-Cethynylarabinofuranosyl cytosine (9).