A Proposal of the Structure of Modified Nucleosides Expected to be Highly Anti-Viral Active and Lowly Toxic.

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ABSTRACT

The structure of modified nucleosides expected to be highly anti-viral active and lowly toxic is proposed.

INTRODUCTION

Development of highly potent and lowly toxic antiviral drugs, especially for Flu-virus, is urgently required. Our study on the development of highly anti-HIV active and lowly toxic 2'-deoxy-4'-C-ethynyl-2-fluoroadenosine(4'Ed2FA) and Merck's study on highly anti-HCV active and lowly toxic 7-fluoro-2'-C-methyltubercidine(2'M7FT) showed that human DNA and RNA polymerases are much more sophisticated than viral polymerases and do not accept the nucleosides modified at two or more positions of physiologic nucleosides as their substrates but viral polymerases do accept them. On the basis of these findings, the structure of modified nucleosides expected to be highly anti-viral active and lowly toxic is proposed.

1. To be active (to be the chain-terminator of enzymatic DNA and RNA polymerization), the modified nucleosides should have deactivated 3'-OH.
2. To be highly anti-viral active and prevent the emergence of resistant virus variants, the modified nucleosides should have the structure alike to those of physiologic nucleosides as like as possible.
3. To be lowly toxic, the modified nucleosides should have the structures modified at two or more positions of physiologic nucleosides so that human DNA and RNA polymerases do not accept them as their substrates.

As an example of the development, the way how we reached to 4'Ed2FA will be presented in detail.

CONCLUSION

It is expected that modified nucleosides highly anti-viral active, especially against Flu-virus which uses RNA dependent RNA polymerase for its replication, and lowly toxic could be developed based on this proposal.

REFERENCES

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