Novel norbornane-based nucleoside and nucleotide analogues and their antiviral activities

*Milan Dejmek[1], Michal Šála[1], Hubert Hřebabecký[1], Graciela Andrei[2], Jan Balzarini[2], Lieve Naesens[2], Johan Neyts[2], Radim Nencka[1]**

[1]Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, v.v.i., Czech Republic

[2]Rega Institute for Medical Research, Minderbroedersstraat 10, BE-3000, Leuven, Belgium

nencka@uochb.cas.cz

esf european social fund in the czech republic · EUROPEAN UNION · MINISTRY OF EDUCATION, YOUTH AND SPORTS · OP Education for Competitiveness

INVESTMENTS IN EDUCATION DEVELOPMENT

INTRODUCTION

Nucleoside and nucleotide antiviral therapeutics have always exceeded all other classes of drugs used in the treatment of viral diseases. Various locked nucleosides were reported in the past and some of them brought a significant promise for the successful treatment of infections caused by diverse viral pathogens.[1]

Recently, we introduced norbornane as one of the possible bicyclic systems that could serve as a conformationally locked substitute of a natural furanose ring and we showed that several 9-norbornylpurines exert significant activity against Coxsackieviruses (*Picornaviridae*).[2,3]

RESULTS AND DISCUSION

In our current work, we have turned our attention to the conformationally locked norbornane-based derivatives of abacavir, a commercially successful anti-HIV agent, and prepared a number of derivatives with the pseudosugar locked in North, South and also East conformation in order to investigate their potential to serve as antiviral agents.

Table 1. Antiviral activities of prepared nucleosides

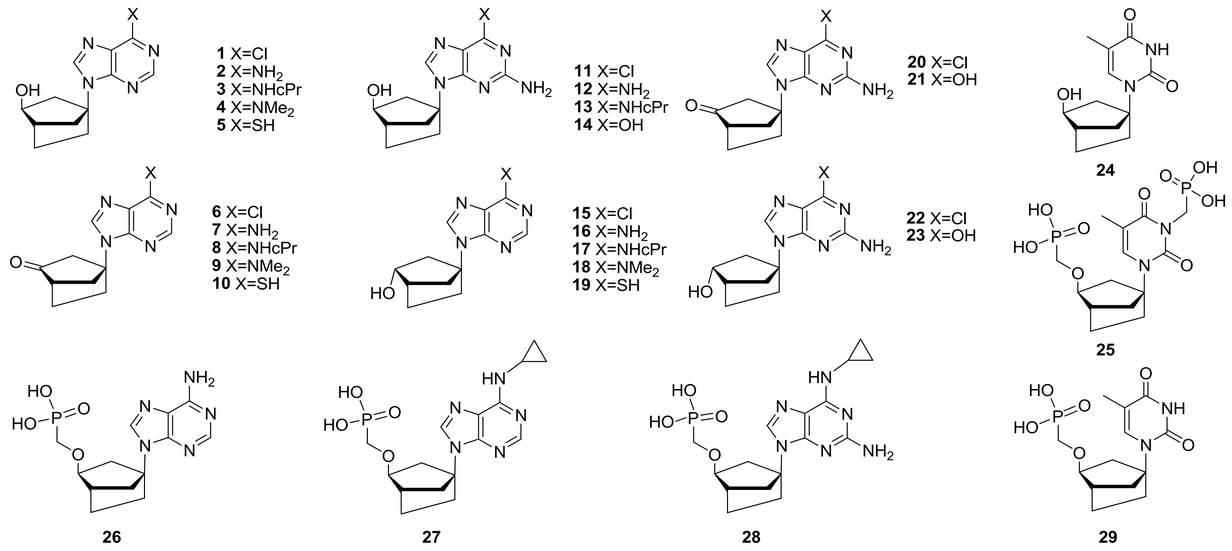
Compound	FHV EC_{50} ($\mu g.mL^{-1}$)	HIV 1 EC_{50} ($\mu g.mL^{-1}$)	HIV 2 EC_{50} ($\mu g.mL^{-1}$)	CVB3 EC_{50} ($\mu g.mL^{-1}$)	Toxicity CC_{50} ($\mu g.mL^{-1}$)
1	ND	ND	ND	8.7	>100[a]
2	14±3	>100	>100	>100	>100[b]
6	ND	ND	ND	7.6	>100[a]
7	7±2	>100	>100	>100	>100[b]
8	52±7	>20	>20	ND	>100[b]
11	>100	>20	≥20	13.6	100[a]
15	ND	ND	ND	22	ND[a]
16	51±1	>20	>20	>100	>100[b]
17	42±15	>100	>100	>100	>100[b]
20	ND	>100	>100	15.3	>100[a]
22	ND	>100	>100	9.8	>100[a]
30	ND	ND	ND	7.0	100[a]
31	15±2	26 ± 7.8	60 ± 17	>100	>100[b]
35	>20	>4	>4	8.9	>100[a]
44	ND	ND	ND	8.0	>100[a]
49	ND	>100	>100	9.3	>100[a]

[a]Cytotoxicity in VERO cells. [b]Cytotoxicity in CRFK cell cultures.

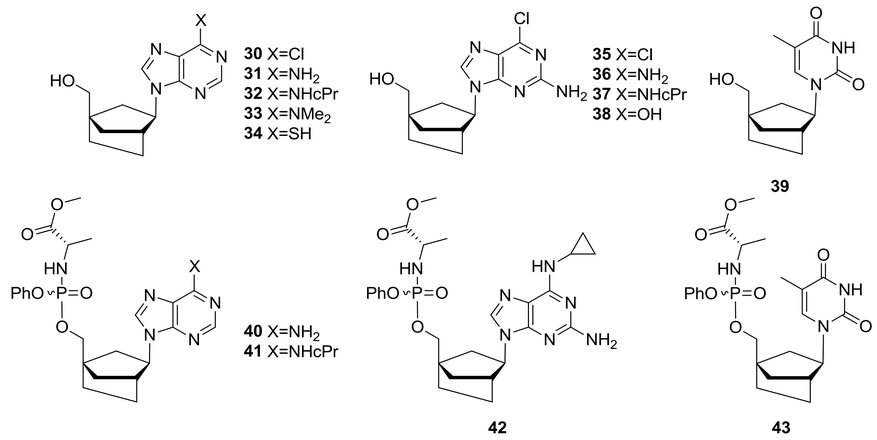
CONCLUSION

A number of the obtained nucleoside derivatives exerted significant activities against Feline herpes virus (FHV) or Coxsackievirus B3 (CVB3). Only one analogue locked in North conformation, the adenine derivative **31**, exerted modest activity against HIV. This compound inhibited also the replication of FHV and Influenza H1N1. Most of the prepared nucleotide derivatives exerted rather cytotoxic effect than desired antiviral activity.

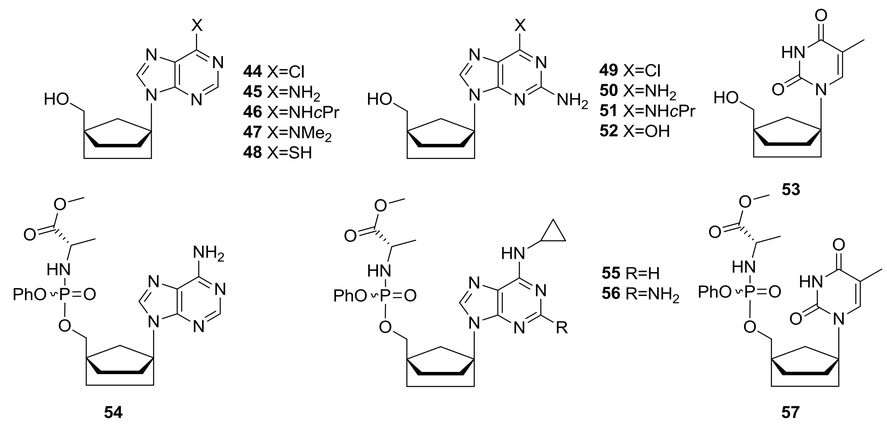
Nucleosides/tides in South conformation



Nucleosides/tides in North conformation



Nucleosides/tides in East conformation



REFERENCES

1. Marquez, V. E. *Modified Nucleosides: in Biochemistry, Biotechnology and Medicine.* Wiley-VCH: 2008; p 684.
2. Šála, M.; De Palma, A. M.; Hřebabecký, H. *et al. Bioorg. Med. Chem. Lett.* **2011**, *21*, 4271-4275.
3. Šála, M.; De Palma, A. M.; Hřebabecký, H. *et al. Bioorg. Med. Chem.* **2010,** *18*, 4374-4384.

ACKNOWLEDGEMENT

Authors are grateful to project CZ.1.07/2.2.00/28.0184 coming from European Social Fund. The study was supported by Gilead Sciences, Inc. (Foster City, CA, USA)and subvention for development of research organization (RVO: 61388963).