Piperidine nucleosides and nucleotides

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ABSTRACT

A novel series of racemic piperidin-3-yl and piperidin-4-yl derivatives of nucleobases and their phosphonate derivatives were prepared.

![Chemical structure](image)

**Fig. 1** B=nucleobase, X=CH$_3$, CH$_2$CH$_3$, CH$_2$CO, CO, SO

INTRODUCTION

Sugar-modified nucleosides belong to important group of antimetabolites which exhibit variety of biological properties. Piperidine nucleosides represent nucleosides analogues where sugar moiety is replaced with piperidine ring.

RESULTS AND DISCUSSION

Synthesis started from commercially available (RS)-3- or 4-hydroxypiperidine. First step in the synthesis of piperidine nucleosides consisted in the introduction of nitrogen protecting group (Boc, Tr), followed by nucleobase attachment.

Three general strategies for nucleobase introduction were investigated: **A**, Mitsunobu nucleosidation; **B**, Alkylation of nucleobase by mesyl derivative and **C**, Nucleobase assembly starting from appropriate amino derivative. Final nucleosides were obtained after deprotection of tert-butoxycarbonyl or trityl group.

![Chemical structure](image)

**Scheme 1.**

Piperidine analogues of nucleosides were then transformed into five diverse phosphonate analogues of nucleotides: phosphonomethyl (reaction with diisopropylphosphite and formaldehyde), phosphonoethyl (reaction with diisopropylvinylphosphate), phosphonoformate (reaction with diisopropyl phenyl phosphonoformate), phosphonothioformate (reaction with diisopropyl phosphonoacetic acid). Isopropyl groups were then removed by treatment with trimethylsilylboron.

![Chemical structure](image)

**Scheme 2.** X=CH$_3$, CH$_2$CH$_3$, CH$_2$CO, CO, SO

CONCLUSION

Piperidine nucleoside and nucleotide analogues were prepared. Pyrimidine nucleobase build-up procedure seems to be the most promising strategy for synthesis of piperidine nucleosides. The comparison of synthetic methods and reaction conditions (e.g. the influence of piperidine nitrogen protecting groups), with respect to the yield of nucleosidation reaction, as well as the biological activity of prepared compounds will be discussed.

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