Pyrrolidine analogues of nucleosides and nucleotides

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ABSTRACT
Among the structurally diverse nucleoside phosphonic acids, several compounds possessing strong antiviral properties have been found. Our effort in this area was focused to the synthesis of novel compounds – pyrrolidine-based nucleoside phosphonic acids and their derivatives.

INTRODUCTION
Many analogues of nucleosides as well as nucleoside phosphonic acids exhibit strong antiviral properties. Their mode of action consists in interaction with RNA or DNA polymerisation machinery.

Recently, we have described synthesis of two series of pyrrolidine nucleosides based on alkylation of nucleobases with appropriate mesyl derivative or via Mitsunobu alkylation.¹²

RESULTS AND DISCUSSION
A series of pyrrolidine nucleosides was prepared. Direct alkylation of nucleobases with mesyl derivative, Mitsunobu alkylation with hydroxy derivative or nucleobase assembly using amino derivative was examined. Free pyrrolidine nucleosides were subjected to the phosphorylation reaction on the pyrrolidine nitrogen atom. Thus phosphonomethyl, phosphonoethyl, phosphonooctyl, phosphonocarbonyl and phosphonothiocarbonyl moieties were introduced (Scheme 1).

Phosphonomethyl derivative was prepared by Manich type reaction of pyrrolidine nucleoside with dialkyl phosphite and formaldehyde. Phosphonoethyl derivative was prepared by Michaelis addition of pyrrolidine nucleoside to dialkyl vinylphosphonate. Phosphonocarbonyl derivative was prepared by the reaction of pyrrolidine nucleoside with dialkyl phenyl phosphonoformate. Condensation of dialkyl phosphonoacetic acid with pyrrolidine nucleoside, catalysed by EDC and DMAP, yielded the N-phosphonoacetyl derivative. And finally, methyl disopropylphosphonodithioformate afforded N-phosphonothiocarbonyl derivative when reacted with pyrrolidine nucleoside.

Chosen analogues of nucleotides were converted to their diphosphoryl derivatives (analogues of triphosphates) via morpholidate precursor (Scheme 2). Thus appropriate phosphonic acid was refluxed with morpholine in the presence of DCC. Obtained phosphonomorpholidate was treated with tri n-butylammonium salt of pyrophosphoric acid in DMSO. Final product was obtained after purification on Poros 50HQ column using a linear gradient of aqueous TEAB followed by final reverse phase HPLC purification.
Scheme 2

Prepared compounds were also evaluated for:

(i)  the ability to inhibit RNA polymerisation in *in vitro* transcription systems utilising RNA polymerase from *B. subtilis* and *E. coli*;

(ii) antibacterial properties.

CONCLUSION

A series of pyrrolidine analogues of nucleosides, nucleotides and nucleoside triphosphates was synthesized and evaluated for their potential antimicrobial activity.

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