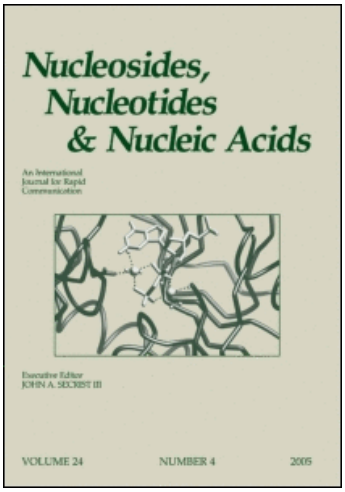

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SYNTHESIS OF MODIFIED NUCLEOSIDE 5'-TRIPHOSPHATES FOR *IN VITRO* SELECTION OF CATALYTIC NUCLEIC ACIDS [1]

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SYNTHESIS OF MODIFIED NUCLEOSIDE 5′-TRIPHOSPHATES FOR *IN VITRO* SELECTION OF CATALYTIC NUCLEIC ACIDS (1)

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ABSTRACT

2′-Modified pyrimidine nucleoside 5′-triphosphates comprising amino, imidazole and carboxylate functionality attached to the 5-position of the base were synthesized. Two different phosphorylation methods were used to optimize the yields of these highly modified triphosphates.

Recently, much attention has been focused on the development of functionalized nucleotides suitable for in vitro selection with the hope of increasing nucleic acids potential for binding and catalysis (2–4). For RNA in vitro selections, modifications should be at the nucleotide level so that they can be incorporated simply and efficiently using RNA polymerase, without problematic side reactions associated with synthetic post-transciptional modification.

When designing monomeric nucleoside triphosphates for selection of therapeutic catalytic RNAs one has to take into account nuclease stability of such molecules in biological sera. A common approach to increase RNA stability is to replace the sugar 2′-OH group with groups like 2′-fluoro, 2′-*O*-methyl or 2′-amino. Fortunately such 2′-modified pyrimidine 5′-triphosphates are shown to be substrates for RNA polymerases (3,5). On the other hand it was shown that variety of substituents at pyrimidine 5-position is well tolerated by T7 RNA polymerase

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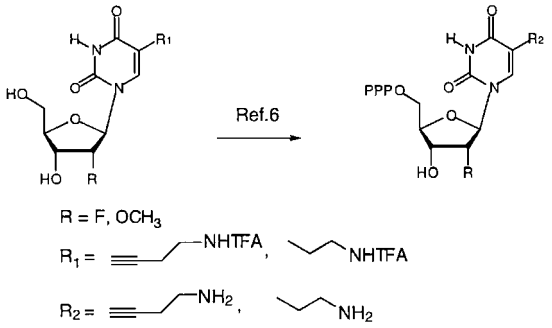

Figure 1.

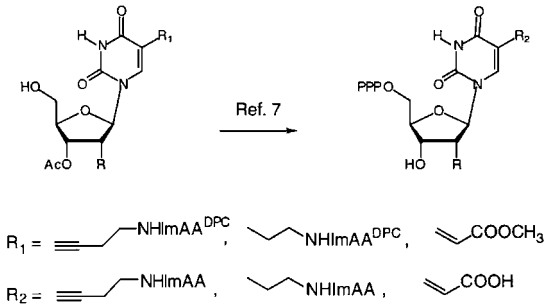

Figure 2.

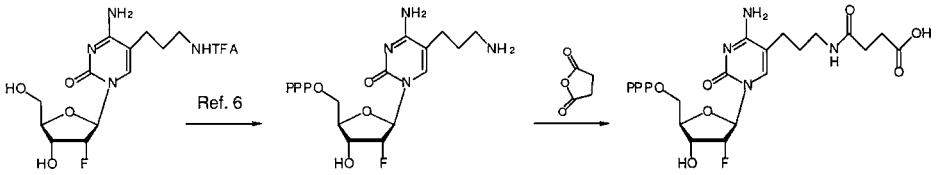

Figure 3.

(2), most likely because the natural hydrogen-bonding pattern of these nucleotides is preserved. We have chosen 2′-fluoro and 2′-*O*-methyl pyrimidine nucleosides as starting materials for attachment of different functionalities to the 5-position of the base. Both rigid (alkynyl) and flexible (alkyl) spacers are used. The choice of imidazole, amino and carboxylate pendant groups is based on their ability to act as general acids, general bases, nucleophiles and metal ligands, all of which can improve the catalytic effectiveness of selected nucleic acids.

5-Functionalized pyrimidine nucleosides were prepared using Pd-catalyzed coupling of 5-iodo nucleosides with *N*-protected propargylamine or methyl acrylate. Imidazole group was introduced through the peptide coupling of *N*-diphenylcarbamoyl protected 4-imidazoleacetic acid ($ImAA^{DPC}$) to the 5-[3-aminoalkyl-(alkynyl)] nucleosides.

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5-[3-Aminoalkyl(alkynyl)] nucleosides were successfully phosphorylated using the 'one pot, two steps' procedure (6), while 5-(4-imidazoleacetyl) nucleosides could be prepared in good yields by Ludwig-Eckstein's procedure (7).

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