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Search for biologically active azapurine analogs of nucleotides

Work was performed in:

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Analogues of nucleosides have been clinically used for over 50 years and constitute the significant group of compounds in the treatment of viral infections and cancer diseases.

Studies on the synthesis and evaluation of biological activity of nucleos(t)ide analogs led to the conclusion that modifications of the lead structure can occur within the nucleobase moiety, sugar ring, and modification of both these units at the same time is also possible.

The aim of my work was the synthesis and evaluation of biological activity of functionalized acyclic purine analogs of nucleotides in which the nucleobase and the sugar moiety were modified at the same time.

In the first part of my project a series of new diethyl 2- (7-oxo-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl)alkylphosphonates (analogs of 8-azahipoxanthin) was obtained via cyclization of respective diethyl (5-amino-4-carbamoyl-1,2,3-triazol-1-yl)alkylphosphonates with triethyl orthoformate. Diethyl (5-amino-4-carbamoyl-1,2,3-triazol-1-yl)alkylphosphonates were obtained via the cycloaddition reaction of diethyl ω-azidoalkylphosphonate with 2-cyanoacetamide. Derivatives of diethyl (5-amino-4-carbamoyl-1,2,3-triazol-1-yl)alkylphosphonates and diethyl 2-(7-oxo-1,2,3-triazolo[4,5-*d*] pyrimidin-3-yl)alkylphosphonates were evaluated for their antiviral activity against a wide range of DNA and RNA viruses and cytostatic activity toward the selected tumor cell lines.

None of the tested compounds showed inhibitory activity against any of the tested viruses at the concentrations up to 100 μM or affected the morphology as well as or the viability of cells (MDCK and CRFK) at the concentrations up to 100 μM.

The lack of the biological activity prompted me to synthesize new derivatives of acyclic analogs of nucleotides, namely triazolo[4,5-*b*]pyridine (1-deaza-8-azapurine), imidazo[4,5-*b*]pyridine (1-deazapurine) and imidazo[4,5-*b*]pyridin-2(3*H*)-one (1-deazapurin-8-one) derivatives. All these compounds were obtained from the corresponding diethyl 2-(3-aminopyridin-2-yl)aminoalkyl phosphonates by nucleophilic substitution in the 2-chloro-3-nitropyridine ring with the appropriate diethyl ω-aminoalkylphosphonates followed by reduction of the nitro group in diethyl 2-(3-nitropyridin-2-yl)aminoalkyl phosphonates.

In the last step diethyl (1,2,3-triazolo[4,5-*b*]pyridin-3-yl)alkylphosphonates, diethyl (imidazo[4,5-*b*]pyridin-3-yl)alkylphosphonates and diethyl (2-oxo-1*H*-imidazo[4,5-*b*] pyridin-3-yl)alkylphosphonates were converted to the corresponding phosphonic acids. The phosphonates as well as their phosphonic acids obtained in this part of the project were sent

for evaluation of their antiviral and anticancer activities. Analyses of the structure-activity relationship will be possible in case the synthesized compounds are biologically active. I am going to determine the influence of carbon chain length as well as its functionalization via incorporation of additional hydroxyl group or oxygen atom.