"4-*N*-substituted 5-azacytosine derivatives - synthesis, structure and chemical properties"

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Abstract

Compounds inhibiting methylation of cytosine in DNA may play an important role in cancer therapy. Lack of the effective anti-cancer drugs causes the development of new DNMT1 methyltransferase inhibitors. Several have been identified so far. These mainly include cytidine derivatives, such as 5-azacytidine and 5-aza-2'-deoxycytidine. These compounds are characterized by high toxicity towards the cancer cells and, unfortunately, also to healthy ones. In addition, they are chemically unstable.

Earlier studies of research groups of Prof. Markiewicz and Prof. Barciszewski at the Institute of Bioorganic Chemistry of the Polish Academy of Sciences were focused on synthesis and recognition of the biological properties of numerous cytosine derivatives. In terms of biological properties, the most promising compounds were 4-N-furfurylcytosine and 4-N-furfuryl-5,6-dihydro-5-azacytosine. This fact became the inspiration for the attempt to obtain derivatives combining the features of these compounds (i.e. a nitrogen atom in the 5-position of the ring and a double bond between N-5 nitrogen and C-6 carbon atoms).

The main goal of this dissertation was the development and optimization of the conditions of the new synthetic route for N-substituted 5-azacytosine derivatives. Four such derivatives were obtained using a four-step synthesis. In addition, tests were performed to determine the stability of the obtained products towards hydrous and alkaline environment, including physiological conditions. Moreover the effect of the substituent at the N-1 position of the triazine ring on this feature was determined. Tests have also been carried out for analogous derivatives of 5-azacytosine (not bearing substituents at the N-4 position).

During the research, a possibility of application of chlorotrimethylsilane (TMSCl) (instead of previously used iodotrimethylsilane, generated *in situ*) in the demethylation reactions of compounds with different numbers of nitrogen atoms in the ring, i.e. the methoxy derivatives of s-triazine (3), pyrimidine (2), pyridine (1) and benzene (0) has been checked.

In order to broaden the spectrum of compounds, mono- and diamino-substituted 5-azacytosine derivatives were obtained up to a total of thirty-two such substances.

The structures of all obtained products were confirmed using nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS, HRMS). The obtained

compounds were transferred for the biological studies to determine their inhibition of DNMT1 constant values. These studies are still ongoing.