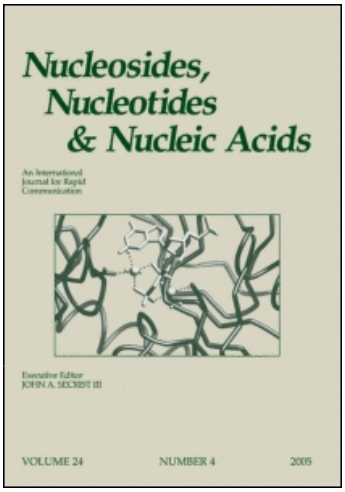

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Synthesis of Modified Thiopurine Nucleosides for Structural Characterization of Human Thiopurine S-Methyltransferase

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SYNTHESIS OF MODIFIED THIOPURINE NUCLEOSIDES FOR STRUCTURAL CHARACTERIZATION OF HUMAN THIOPURINE S-METHYLTRANSFERASE

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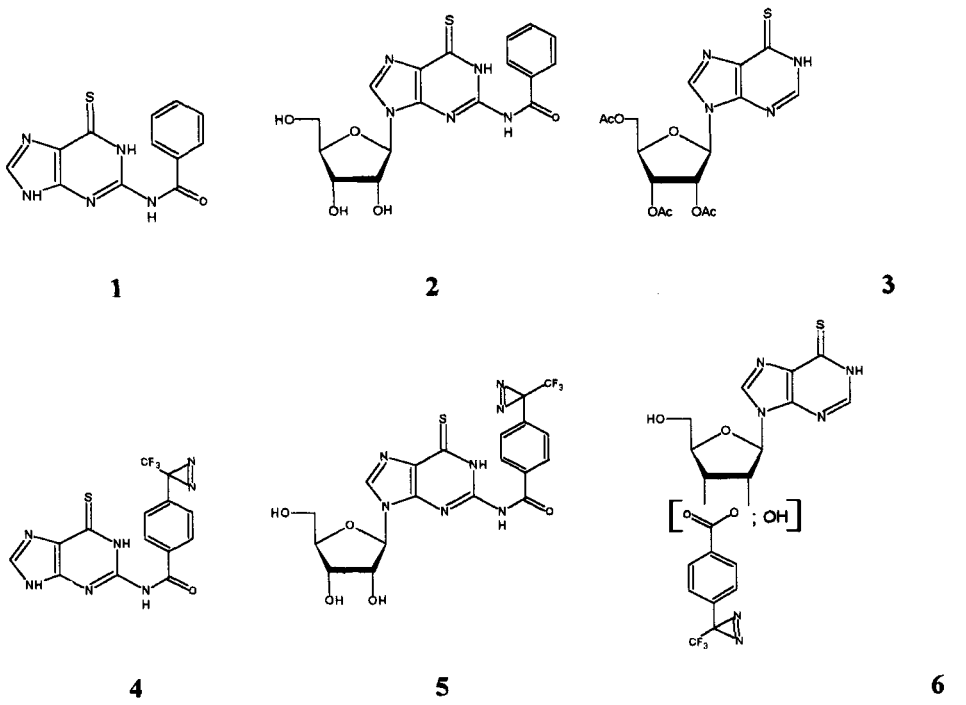
ABSTRACT: Synthesis of a number of photoactive thiopurine-containing nucleosides was described. S-methylation of the synthesized compounds in the course of the reaction catalyzed by recombinant human thiopurine S-methyltransferase was studied by UV-spectroscopy.

Thiopurine S-methyltransferase (TPMT) plays an important role in metabolism of widely used anticancer and immunosuppressive drugs mercaptopurine, thioguanine and azathioprine. It was demonstrated that thiopurine nucleosides and nucleotides are substrates for TPMT and can be methylated in the course of the TPMT-catalyzed reaction[1]. The thiopurine moiety in these molecules provides a potential site for photocrosslinking experiments[2]. Aryl(trifluoromethyl)diazirine (ATFMD) derivatives of thiopurine nucleosides can be also useful as they are highly reactive when irradiated with near-UV light, and the crosslink products are reasonably stable under various conditions[3].

We report the synthesis and substrate properties of a number of thiopurine nucleoside derivatives that can be used for photocrosslinking technique. Two sets of photoactive thiopurine analogues were synthesized, differing in the structure of the photoactive group as shown in Figure 1. The first set includes acyl derivatives of thiopurine or thiopurine nucleosides (**1-3**). The second set (**4-6**) contains ATFMD moiety introduced into either the exocyclic amino group or into the sugar residue. Compounds

Fig. 1



1 2 3

4 5 6

were purified by silica gel column chromatography, and their structures were confirmed by UV-spectroscopy.

The synthesized compounds were shown to be substrates for the recombinant human TPMT.

Acknowledgments

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