

This article was downloaded by:

On: 26 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

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

Galina A. Korshunova^a; Eugene Y. Krynetski^{ab}; Manana T. Mtchedlidze^c; Denis V. Agapkin^c; William E. Evans^b; Natalia F. Krynetskaia^c

^a Belozersky Institute, ^b St. Jude Children's Hospital, Memphis, USA ^c Chemistry Department, MSU, Moscow, Russia

To cite this Article Korshunova, Galina A. , Krynetski, Eugene Y. , Mtchedlidze, Manana T. , Agapkin, Denis V. , Evans, William E. and Krynetskaia, Natalia F.(1999) 'Synthesis of Modified Thiopurine Nucleosides for Structural Characterization of Human Thiopurine S-Methyltransferase', *Nucleosides, Nucleotides and Nucleic Acids*, 18: 6, 1747 – 1748

To link to this Article: DOI: 10.1080/07328319908044839

URL: <http://dx.doi.org/10.1080/07328319908044839>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

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

Galina A.Korshunova^{1*}, Eugene Y.Krynetski^{1,3}, Manana T.Mtchedlidze², Denis V.
Agapkin², William E.Evans³, Natalia F.Krynetskaia²

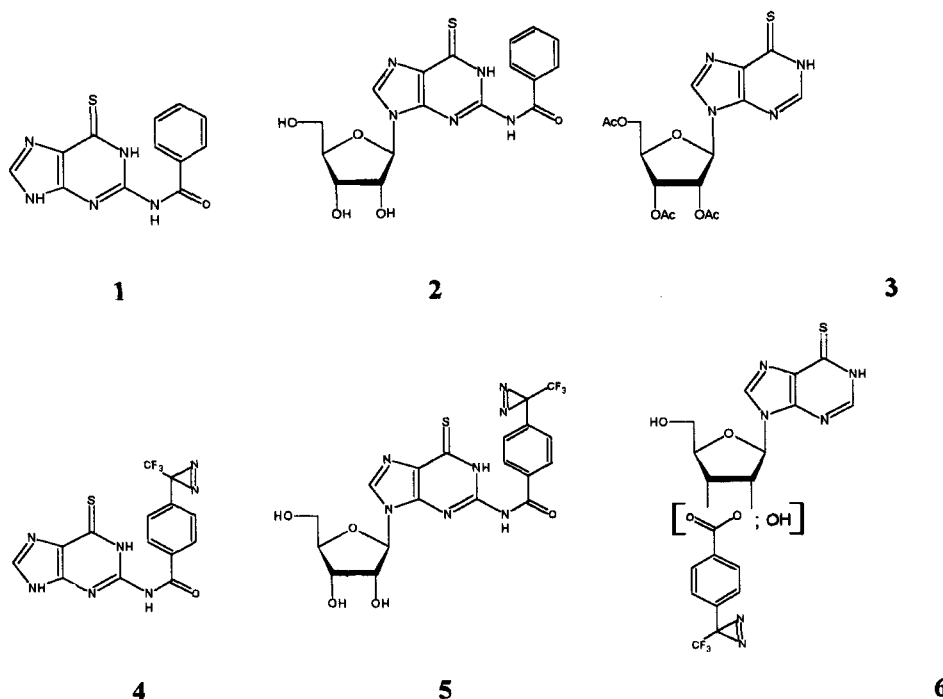
¹Belozersky Institute and ²Chemistry Department, MSU, Moscow, Russia and
³St.Jude Children's Hospital, Memphis, USA

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 reaction¹. The thiopurine moiety in these molecules provides a potential site for photocrosslinking experiments². 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 conditions³.

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



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

This investigation was partly supported by the NIH grants R37 CA36401, R01 CA78224, Cancer Center Support Grant CA21765, and by the American Lebanese Syrian Associated Charities (ALSAC).

REFERENCES

1. Krynetski, E.Y.; Krynetskaia, N.F.; Yanishevski, Y.; Evans, W.E. *Mol. Pharmacology* **1995**, *47*, 1141-1147.
2. Favre, A. in *Bioorganic Photochemistry: Photochemistry and Nucleic Acids* (Morrison, H., ed.) John Wiley & Sons, New York **1990**, 379-425.
3. Bayley, H. *Photogenerated Reagents in Biochemistry and Molecular Biology* **1983**, Oxford: Elsevier, Amsterdam/New York.