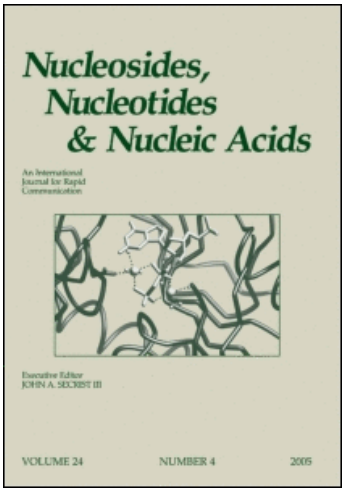

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis and Cytotoxic Activity of Selenophenfurin, a New Inhibitor of IMP Dehydrogenase

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To cite this Article Cappellacci, L. , Franchetti, P. , Sheikha, G. Abu , Jayaram, H. N. , Gurudutt, V. V. , Sint, T. , Schneider, B. P. , Goldstein, B. M. , Perra, G. , Poma, S. , La Colla, P. and Grifantini, M.(1997) 'Synthesis and Cytotoxic Activity of Selenophenfurin, a New Inhibitor of IMP Dehydrogenase', Nucleosides, Nucleotides and Nucleic Acids, 16: 7, 1045 — 1048
To link to this Article: DOI: 10.1080/07328319708006129
URL: http://dx.doi.org/10.1080/07328319708006129

NUCLEOSIDES & NUCLEOTIDES, 16(7–9), 1045–1048 (1997)

SYNTHESIS AND CYTOTOXIC ACTIVITY OF SELENOPHENFURIN, A NEW INHIBITOR OF IMP DEHYDROGENASE

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ABSTRACT: The synthesis of 5-β-D-ribofuranosylselenophene-3-carboxamide (selenophenfurin) is reported. Selenophenfurin was found active as cytotoxic agent and as inosine monophosphate dehydrogenase inhibitor.

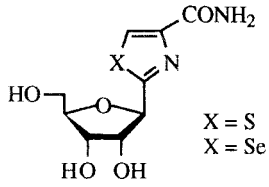
Selenazofurin (2-β-D-ribofuranosylselenazole-4-carboxamide, NSC 340847, SR) the selenium analog of tiazofurin (NSC 286193, TR), is a widely studied agent with a diverse array of biological effects. These include effective antitumor and antiviral activity, as well as efficacy as a maturation-inducing agent.[1a-d] Selenazofurin is 5- to 10-fold more potent than tiazofurin in several antitumor screens and in biochemical studies.[1d,2a,b] Both the antiproliferative and maturation-inducing effects of these nucleosides appear to be due to inhibition of inosine monophosphate dehydrogenase (IMPDH), which induces the shutdown of guanine nucleotide synthesis.[3] In sensitive cells, tiazo- and selenazofurin are converted to the cofactor nicotinamide adenine dinucleotide (NAD) analogs TAD and SAD, respectively, which are excellent inhibitors of IMPDH as well as of other dehydrogenases.[3]

Crystal structures of tiazo- and selenazofurin demonstrated a close intramolecular contact between the thiazole S or selenazole Se heteroatoms and the furanose ring oxygen O1'.[4] These close contacts have been attributed to an attractive electrostatic interaction between the positively charged sulfur or selenium and the lone-pair of electrons on the furanose oxygen, as confirmed by molecular orbital calculations.[5] This interaction would be expected to constrain rotation about the C-glycosidic bond in the active anabolites TAD and SAD, influencing the binding of these dinucleotide inhibitors to the target enzyme.

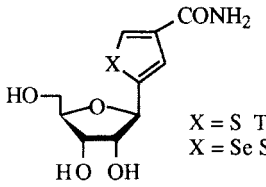
Recently we synthesized thiophenfurin (5-β-D-ribofuranosylthiophene-3-carboxamide, TPF) a C-nucleoside isoster of tiazofurin, in which the thiazole ring is replaced by the thiophene one.[6] Thiophenfurin was found to be active as an antitumor agent both *in vitro* and *in vivo* similarly to the parent compound, and to be an inhibitor of IMPDH. These studies supported the hypothesis that the presence of S in the heterocycle in position 2 with

respect to the glycosidic bond is essential for cytotoxicity and IMPDH inhibition, while the N atom of the tiazole ring of tiazofurin is not.

This finding prompted us to synthesize selenophenfurin (5-β-D-ribofuranosyl-selenophene-3-carboxamide, SPF, **1**), the selenophene analog of selenazofurin, and to study its biological activity.



X = S Tiazofurin
X = Se Selenazofurin



X = S Thiophenfurin
X = Se Selenophenfurin

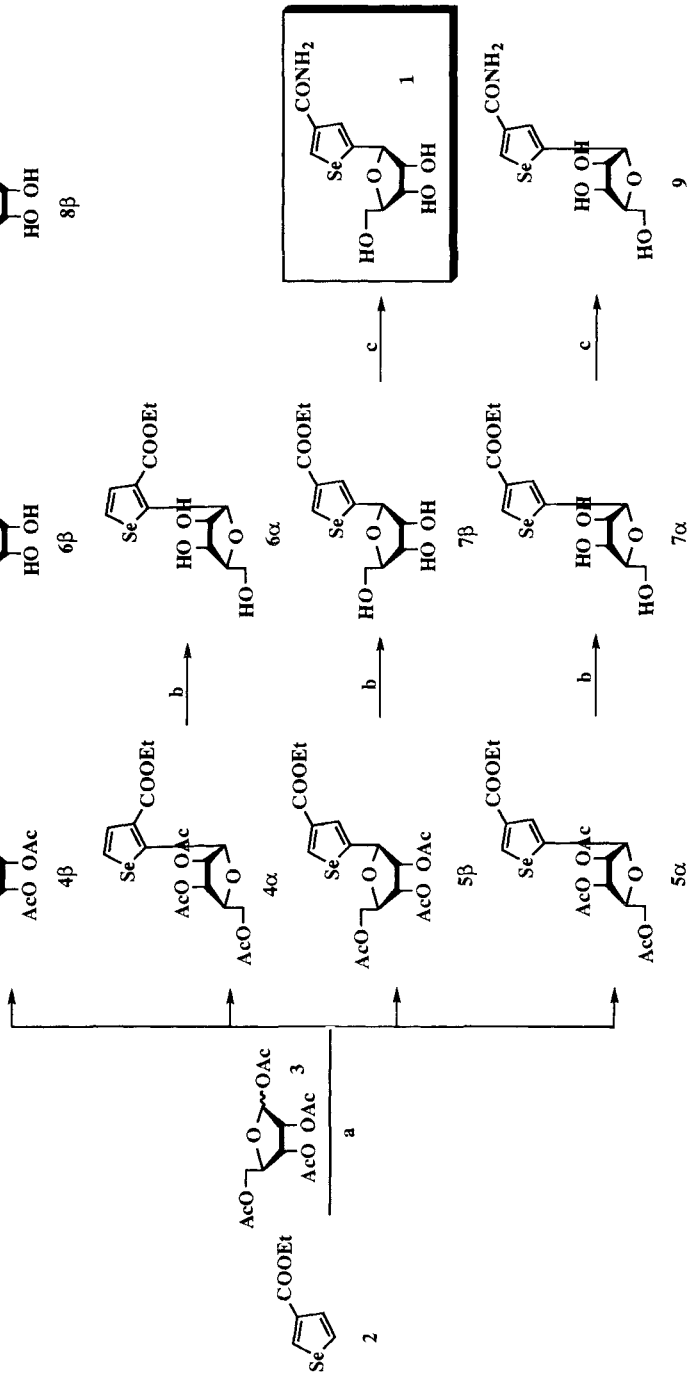
The synthesis of selenophenfurin (**1**) was carried out as outlined in Scheme 1, by direct C-glycosylation of ethyl selenophen-3-carboxylate (**2**) under Friedel-Crafts conditions as described for thiophenfurin.[6] Reaction of **2** with tetra-*O*-acetyl-β-D-ribofuranose (**3**) in 1,2-dichloroethane in the presence of $SnCl_4$ gave 2-, and 5-glycosylated regioisomers as mixture of α-, and β-anomers (**4β**, **4α**, **5β**, and **5α**, 42%). The mixture of the anomers **4β** and **4α**, and isomer **5β** was separated from **5α** by column chromatography. Treatment of **4β**, **4α**, and **5β** with a catalytic amount of sodium ethoxide in ethanol gave the corresponding deblocked ethyl esters **6β**, **6α**, and **7β**. In a similar way, starting from **5α** the ester **7α** was obtained. The glycosylation position and the anomeric configuration of ethyl esters **6β**, **6α**, **7β**, and **7α** were determined by ^{1}H-NMR, ^{13}C-NMR, proton-proton nuclear Overhauser effect (N.O.E.) difference spectroscopy, and by crystallographic data as previously reported for their sulfur analogs.[6] Treatment of **7β** with ammonium hydroxide gave selenophenfurin (**1**). In a similar way, ethyl esters **6β** and **7α** were converted into the amides **8β** and **9**.

BIOLOGICAL EVALUATION

Cytotoxicity studies.

Selenophenfurin (**1**) was tested *in vitro* against a panel of tumor cell lines, mostly derived from leukemias, lymphomas, and solid tumors (CCRF-SB, human acute B-lymphoblastic cells; CCRF-CEM and MOLT-4, human acute T-lymphoblastic leukemias; L1210, murine lymphocytic leukemia; K562, human myelogenous leukemia; Raji, human Burkitt lymphoma; CHO-K1, Chinese hamster ovary; HT-29, human colon adenocarcinoma; HeLa, human cervix carcinoma; ACHN, human renal adenocarcinoma; 5637, human bladder carcinoma). Selenazofurin, tiazofurin, and thiophenfurin were used as reference drugs. Tumor growth inhibition was evaluated by the MTT assay.[7]

Selenophenfurin proved to be a good antitumor agent with a potency comparable to that of selenazofurin, and was more cytotoxic than tiazofurin and thiophenfurin to all cell lines derived from leukemias and lymphomas with IC_{50}s values ranging from 0.3 to 0.9 μM. In general, human carcinoma cells showed greater susceptibility to the action of selenophenfurin than to that of selenazofurin, thiophenfurin, and in particular than to that



Reagents: (a) $SnCl_4/ClCH_2CH_2Cl$; (b) EtONa, EtOH; (c) 30% NH_4OH.

SCHEME 1

of tiazofurin. Of the four compounds, selenophenfurin was more cytotoxic to HT-29, HeLa, ACHN, and 5637 cells (IC_{50}s ranging from 1 to 10 μM).

The inactivity of the SPF's α-anomer **9**, and of the 2-glycosylated isomer **8β**, emphasizes the importance of the anomeric configuration, and of the glycosylation position for the cytotoxicity of this type of antitumor agent.

Effects of selenophenfurin on IMPDH activity.

Selenophenfurin and its parent compounds, selenazofurin, thiophenfurin, and tiazofurin were tested also for inhibitory properties against IMPDH of human myelogenous leukemia K562 cells in culture as previously reported.[6] The IMP dehydrogenase activity was potently inhibited by the action of selenophenfurin (76 % inhibition) with a potency similar to that of selenazofurin (80 %) and greater than that of thiophenfurin and tiazofurin.

In conclusion, this research shows that selenophenfurin is a C-nucleoside endowed with remarkable cytotoxicity against a variety of tumor cell lines in culture. Its potent activity in human leukemic cells and in solid tumors suggests that this agent might be useful against tumors in man. The finding that replacement of the nitrogen atom by the CH group in the selenazole ring of selenazofurin does not affect the biological activity confirms that, as found in the case of the sulfur analog tiazofurin, the nitrogen atom in the heterocycle is not essential for the activity.

Acknowledgements. *This investigation was supported by grants from Ministry of Health I.S.S. AIDS Project 1995, and CNR, Italy.*

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