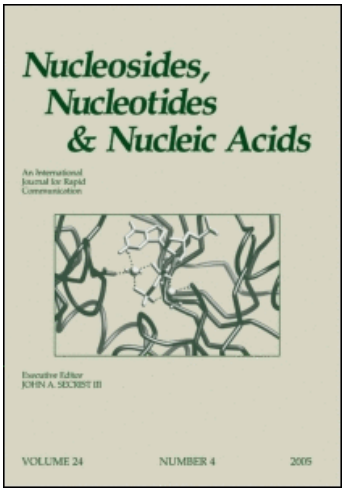

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Structure-Activity Relationships of Tiazofurin Analogs: Synthesis and Computational Studies of 4'-Thio Derivatives of Thiophenfurin and Furanfurin

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STRUCTURE-ACTIVITY RELATIONSHIPS OF TIAZOFURIN ANALOGS: SYNTHESIS AND COMPUTATIONAL STUDIES OF 4'-THIO DERIVATIVES OF THIOPHENFURIN AND FURANFURIN

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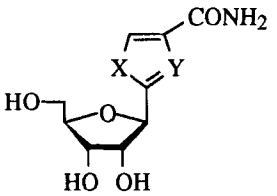
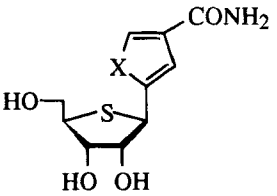
ABSTRACT: The synthesis and computational studies of 5-(4-thio-β-D-ribofuranosyl)-furan-3-carboxamide (furanthiofurin) and 5-(4-thio-β-D-ribofuranosyl)thiophene-3-carboxamide (thiophenthiofurin) are reported.

Thiophenfurin (5-β-D-ribofuranosylthiophene-3-carboxamide) and furanfurin (5-β-D-ribofuranosylfuran-3-carboxamide) are two analogs of tiazofurin, a C-glycosylthiazole nucleoside endowed with oncolytic efficacy. While thiophenfurin was found active as antitumor agent both *in vitro* and *in vivo*, furanfurin proved to be inactive.[1,2] In sensitive cells, thiophenfurin is metabolized to nicotinamide adenine dinucleotide (NAD) analog (TFAD) which is a strong inhibitor of inosine monophosphate dehydrogenase (IMPDH),[2,3] the enzyme which catalyzes the NAD-dependent conversion of inosine 5'-monophosphate (IMP) to guanosine 5'-monophosphate (GMP). Thus, resulting decrease in GTP and dGTP biosynthesis produces inhibition of tumor cell proliferation observed in model systems.



Tiazofurin (X = S, Y = N)
Thiophenfurin (X = S, Y = CH)
Furanfurin (X = O, Y = CH)



Furanthiofurin (X = O)
Thiophenthiofurin (X = S)

We found that the inactivity of furanfurin as antitumor agent was due both to its poor ability to be converted to furan-3-carboxamide adenine dinucleotide (FFAD) in target cells and to the poor affinity of this metabolite for IMPDH.[2,3]

Crystallographic and *ab initio* computational studies showed that in thiophenfurin, as in tiazofurin, an actractive electrostatic interaction between a positively charged thiophene sulfur and negatively charged furanose oxygen stabilizes the conformation in which these heteroatoms are adjacent (*cis*). On the contrary, in furanfurin the repulsive interaction between negatively charged furan and furanose oxygens destabilizes the conformers in which such atoms are *cis*.[3] In order to get further information about the structure-activity relationships of this type of antitumor C-nucleosides, we investigated furanfurin and thiophenfurin analogs in which the furanose ring oxygen O1' was replaced by sulfur atom (furanthiofurin, and thiophenthiofurin, respectively).

The synthesis of furanthiofurin and thiophenthiofurin was carried out by direct C-glycosylation of ethyl furan-3-carboxylate (**3**) and ethyl thiophen-3-carboxylate (**4**) with 1,2,3,5-tetra-*O*-acetyl-4-thio-D-ribofuranose (**5**) which in turn was synthesized starting from benzyl-2,3,5-tri-*O*-benzyl-1,4-dithio-D-ribofuranoside[4] as reported by Tiwari *et al.*[5]. The reaction of **3** or **4** with **5** in 1,2-dichloroethane in the presence of $SnCl_4$ gave a mixture of 2- and 5-glycosylated regioisomers as a mixture of α and β anomers which were separated by chromatography. The β-5-glycosylated isomers were deacetylated with methanolic ammonia and converted into furanthiofurin and thiophenthiofurin by reaction with 30% ammonium hydroxide.

Conformational studies on furanthiofurin and thiophenthiofurin were carried out by *ab initio* computations as previously reported.[1] Results indicate that the sulfur of thio-ribofuranose in both compounds has a reduced positive charge relative to that seen on the thiazole or thiophene sulfurs. This is a consequence of the less-delocalized environment of the saturated thiophene heterocycle. As a result, interactions between the thioribofuranose sulfur and furan oxygen (furanthiofurin) or thiophene sulfur (thiophenthiofurin) are reduced. Energy profiles for both compounds show significantly smaller barriers to rotation about the C-glycosidic bond (~2 Kcal/mol) than those calculated for tiazo- and thiophenfurin, suggesting that the thioribofuranose compounds are less constrained. Interestingly, thiophenthiofurin shows a broad local energy minimum centered about the *cis* conformer, qualitatively similar to the minima seen in tiazo- and thiophenfurin. However, furanthiofurin shows an energy maximum at this putatively favored conformation. Biological testing will examine the significance, if any, of these findings.

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REFERENCES

1. Franchetti, P.; Cappellacci, L.; Grifantini, M.; Barzi, A.; Nocentini, G.; Yang, H.; O'Connor, A.; Jayaram, H. N.; Carrell, C.; Goldstein, B. M. *J. Med. Chem.* **1995**, *38*, 3829-3837.
2. Franchetti, P.; Cappellacci, L.; Grifantini, M. *Il Farmaco* **1996**, *51*, 457-469, and references therein.
3. Franchetti, P.;. Cappellacci, L.; Perlini, P.; Jayaram, H. N.; Butler, A.; Schneider, B. P.; Collart, F. R.; Huberman, E.; Grifantini M. *J. Med. Chem.* **1998**, *41*, 1702-1707.
4. Leydier, C.; Bellon, L.; Barascut J.-L.; Deydier, J.; Maury, G.; Pelicano, H.; El Alaoui, M. A.; Imbach, J.-L. *Nucleosides Nucleotides* **1994**, *13*, 2035-2050.
5. Tiwari, K. N.; Secrist, J. A. III; Montgomery, J. A. *Nucleosides Nucleotides* **1994**, *13*, 1819-1828.