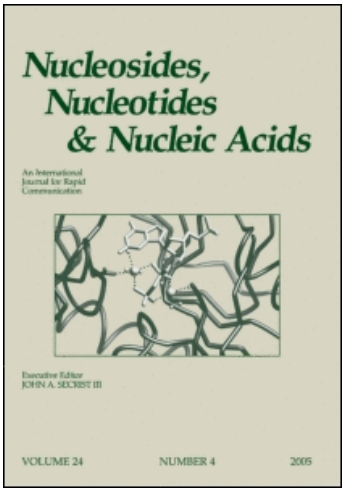

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A NEW SYNTHETIC METHODOLOGY FOR TIAZOFURIN

Kanda S. Ramasamy[a]; Johnson Y. N. Lau[a]
[a] ICN Pharmaceuticals, Inc., Costa Mesa, California, U.S.A.

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A NEW SYNTHETIC METHODOLOGY FOR TIAZOFURIN

Kanda S. Ramasamy* and Johnson Y. N. Lau

ICN Pharmaceuticals, Inc., 3300 Hyland Avenue, Costa Mesa, California 92626

ABSTRACT

A new synthesis of tiazofurin is described from 2,3-*O*-isopropylidene-5-*O*-benzoyl-β-D-ribofuranosyl cyanide.

Tiazofurin (1) [1, 2-(β-D-ribofuranosyl)thiazole-4-carboxamide)] attracted considerable attention because of its significant activity against both human lymphoid (2), and lung tumor cell lines (3), and murine-implanted human ovarian cancers (4). The biological effects also include its efficacy in the treatment of acute myeloid leukemia (5). In addition, recent studies of tiazofurin have generated even more interest as a possible treatment for patients with chronic myeloid leukemia (CML) in blast crisis (6). Tiazofurin shows activity by inhibition of inosine monophosphate dehydrogenase (IMPDH), by forming the corresponding NAD-like tiazofurin adenine dinucleotide (TAD), which induces the shutdown of guanine nucleotide synthesis (7).

Several methods are known in the literature (8–14) for the synthesis of tiazofurin. But, most of them suffer from low yield, give a mixture of products (**2** & **3**) and utilize hydrogen sulfide gas, which is environmentally unsafe on large-scale production. The biological importance of tiazofurin and the problems associated with the reported methods encouraged us to discover a new synthetic methodology for the preparation of tiazofurin. In this communication, we describe a new method for the synthesis of tiazofurin, which eliminates the use of H_2S gas and the by-products.

*Corresponding author.

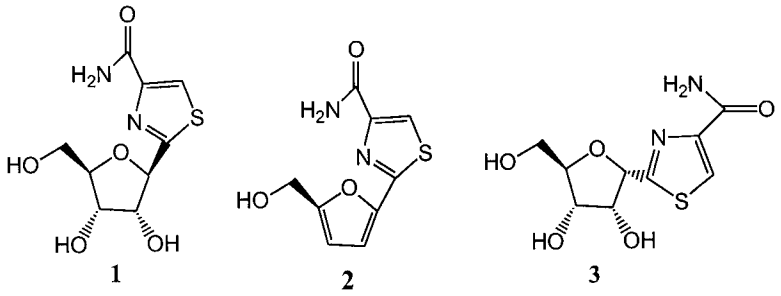
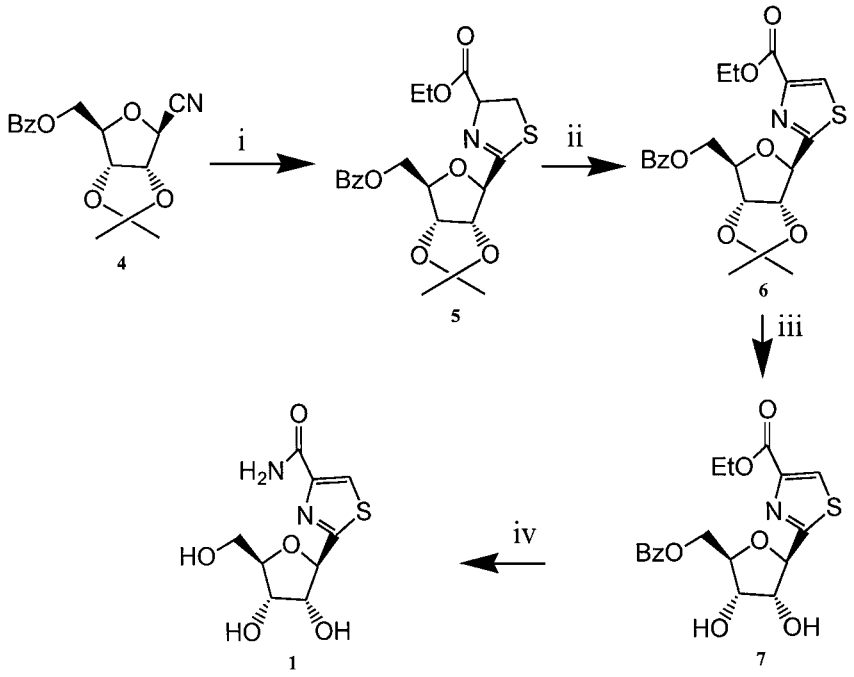


Figure 1.

The synthetic route for tiazofurin is shown in Scheme 1. We elected to use the known 1-cyano-2,3-*O*-isopropylidene-5-*O*-benzoyl-β-D-ribofuranose (**4**) (15) as our starting material. Reaction of **4** with cysteine ethyl ester hydrochloride in the presence of triethylamine at room temperature gave readily thiazoline intermediate **5** in 90% yield. ^{1}H NMR spectrum of **5** showed the presence of a thiazoline methylene group at δ3.61 and a methine proton at δ5.08 which are characteristic of Δ^2-thiazolines (16). Oxidation of **5** with activated MnO_2 (17) in benzene afforded a clean product **6**. Observation of the NMR spectrum of **6** indicated the absence of the methylene and the methine protons of the thiazoline ring and the presence of a vinyl



Scheme 1. Reagents and conditions: i) Cysteine ethyl ester HCl/TEA; ii) MnO_2/Benzene; iii) 90%TFA; iv) NH_3/MeOH.

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proton, which accounted for the dehydrogenation of **5**. Exposure of **6** to 90% TFA for 1 h at room temperature gave ethyl 2-(5′-*O*-benzoyl-β-D-ribofuranosyl)thiazole-4-carboxylate (**7**) in 98% yield. Finally, treatment of **7** with methanolic ammonia at room temperature for 12 h afforded tiazofurin in 90% yield.

There are several merits to the present method. First, it avoided the use of toxic mercuric salt and hydrogen sulfide, which are environmentally unsafe. Secondly, the formation of the side products **2** and **3** were eliminated, and the yield of tiazofurin is substantially improved over previous methods. Third, the present method does not require column chromatographic purification, thereby reducing the cost of production of the drug. Fourth, the same methodology could be used to construct other five membered C-nucleosides by replacing sulfur in **1** with heteroatoms such as oxygen, selenium or nitrogen. The synthesis of other such C-nucleosides are in progress and their results will be reported elsewhere.

In summary, we have developed a safe, convenient and higher yielding new methodology for the synthesis of the important antitumor agent tiazofurin.

REFERENCES

1. Tiazofurin is the generic name approved by the United States Adopted Name Council.
2. Earle, M. F.; Glazer, R. I. *Cancer Res.* **1983**, *43*, 133.
3. Carnex, D. N.; Abluwalia, G. S.; Jayaram, H. N.; Cooney, D. A.; Johns, D. G. *J. Clin. Invest.* **1985**, *75*, 175.
4. Micha, J. P.; Kucera, P. R.; Preve, C. N.; Rettenmaier, M. A.; Stratton, J. A.; DiSaia, P. J. *Gynecol. Oncol.* **1985**, *21*, 351.
5. Tricot, G. T.; Jayaram, H. N.; Nichols, C. R.; Pennington, K.; Lapis, E.; Weber, G.; Hoffman, R. *Cancer Res.* **1997**, *47*, 4988.
6. Weber, G. *United States Patent* 5, 405,837 (1995).
7. Olah, E.; Natusmeda, Y.; Ikegami, T.; Kote, Z.; Horanyi, M.; Szelenye, J.; Paulik, E.; Kremmer, T.; Hollan, S. R.; Sugar, J.; Weber, G. *Proc. Natl. Acad. Sci. USA.* **1988**, *85*, 6533.
8. Srivastava, P. C.; Pickering, M. V.; Allen, L. B.; Streeter, D. G.; Campbell, M. T.; Witkowski, J. T.; Sidwell, R. W.; Robins, R. K. *J. Med. Chem.* **1977**, *20*, 256.
9. Fuertes, M.; Garcia-Lopez, T.; Garcia-Munoz, G.; Stud, M. *J. Org. Chem.* **1976**, *41*, 4074.
10. Hennen, W. J.; Hinshaw, B. C.; Riely, T. A.; Wood, S. G.; Robins, R. K. *J. Org. Chem.* **1985**, *50*, 1741.
11. Bimwala, R. M.; Vogel, P. *Helv. Chim. Acta* **1989**, *72*, 1825.
12. Humber, D. C.; Mulholland, K. R.; Stoodley, R. J. *J. Chem. Soc. Perkin Trans. 1* **1990**, 283.
13. Parsons, J. L.; Vizine, D.; Summer, M.; Marathe, S.; Dubicki, H. *United States Patent* 4,451,648 (1984).
14. Ramasamy, K. S.; Averett, D. *Nucleosides & Nucleotides* **1999**, *18*, 2425.
15. Cook, P. D.; McNamara, D. J. *J. Heterocycl. Chem.* **1986**, *23*, 155.
16. Minster, D. K.; Jordis, U.; Evans, D. L.; Hecht, S. M. *J. Org. Chem.* **1978**, *43*, 1624.
17. Ishihara, H.; Shimura, K. *FEBS Lett.* **1988**, *226*, 319.

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