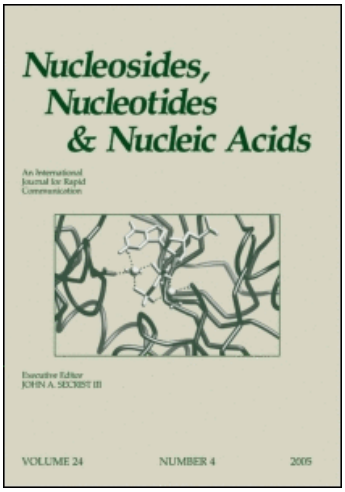

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NOVEL ANALOGUES OF TIAZOFURIN BY LAWESSON REAGENT EFFECTED CYCLIZATION

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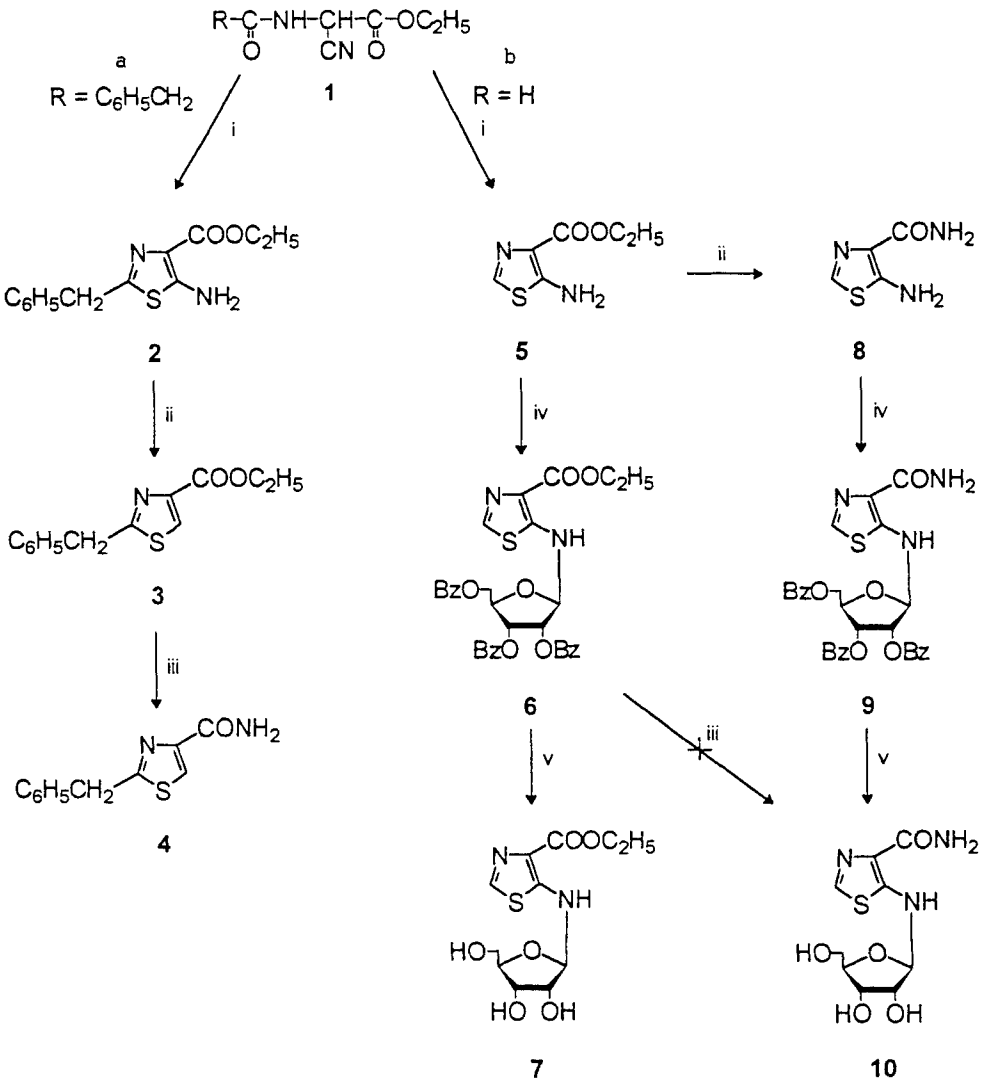
ABSTRACT: 2-Benzylthiazole-4-carboxamide **4** and 5-(β-D-ribofuranosylamino) thiazole-4-carboxamide **10** were synthesized from phenylacetylamino- and formylamino cyanoacetic acid esters **1a** and **1b**, respectively. The ribosylation reaction leading to **10** gave rise also to its α anomer as a minor product.

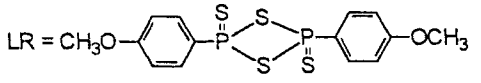
Tiazofurin (2-β-D-ribofuranosylthiazole-4-carboxamide) is a potent antitumor and antiviral agent. The compound acts *via* the inhibition of inosine monophosphate dehydrogenase (IMP DH) forming the corresponding NAD-like tiazofurin adenine dinucleotide after phosphorylation at the 5'-hydroxyl group.[1,2] The previous alterations in its structure, which aimed at the enhancement of its selectivity and understanding of the mechanism of action, led to a conclusion that the presence of thiazole-4-carboxamide unit[3] and the ribose moiety[4] is indispensible for its biological activity.

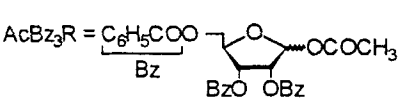
We were interested in two types of novel tiazofurin analogues. One was 2-benzylthiazole-4-carboxamide **4**, tiazofurin with ribose moiety replaced by a group known to bind to a hydrophobic area on some enzymes.[5] The other was 5-(β-D-ribofuranosylamino)thiazole-4-carboxamide **10**, a glycosylamine carrying in different arrangement two crucial structural units mentioned above.

The synthetic route we used is shown in the scheme.



Reagents and conditions : i, LR, benzene, reflux; ii, n-pentyl nitrite, THF, anh, reflux; iii, NH_3/MeOH 10M in ampule, 120°C, 48 h; iv, BSA, CH_3CN, reflux, 12h, then $AcBz_3R$, TMSTf reflux; v, Et_3N/MeOH 1:10 v/v, room temperature.





The starting aminothiazoles **2** and **5** were prepared from the appropriate acylaminocyanoesters **1** subjected to Lawesson Reagent (LR) in refluxing benzene according to the cyclization reaction we reported earlier.[6] Compound **2** (mp 156-157°C, 30% yield) was then deaminated with n-pentyl nitrite in refluxing anhydrous tetrahydrofuran to give **3** (mp 77-78°C, 57%). The aminolysis of **3** performed with 10 M methanolic ammonia at 120°C provided the target 2-benzylthiazole-4-carboxamide **4** (mp 195-196°C, 90%) identical in all respects with the compound isolated upon photochemical degradation of cephalosporins.[7]

The synthesis of N-arylglycosylamines by coupling amines to reducing sugars in organic solvents has been found to afford the pyranose isomers rather than the furanose isomers.[8,9] Therefore, we employed the condensation of the silylated aminothiazole **5** with 1-0-acetyl-2,3,5-tri-0-benzoyl-β-D-ribofuranose in refluxing acetonitrile in the presence of trimethylsilyl triflate (TMSTf, 0.27 eq). Thus, the protected 5-(ribofuranosylamino)thiazole-4-carboxylic acid ethyl ester **6** was formed (colorless oil, 52%). An attempt to remove the benzoyl groups with 10 M NH_3/MeOH at room temperature resulted in the cleavage of the glycosidic bond. The removal was accomplished by the treatment of **6** with Et_3N/MeOH (1:10, v/v) at room temperature for 72 h to afford **7** (colorless solid, 79%).

Due to the instability of the N-exoamino glycosydic bond in concentrated methanolic ammonia it was impossible to convert compound **6** directly into the final 5-(β-D-ribofuranosylamino)thiazole-4-carboxamide **10**. This goal was reached by performing the aminolysis of the 4-substituent at the stage of aglycone. Thus, **5** treated with 10 M NH_3/MeOH at 120°C provided **8** (mp 136°C, 85%) which was reacted with peracylated sugar under the conditions identical to that applied for ribosylation of ester precursor **5** to give protected **9** (sticky crystals, 44%). The removal of the benzoyl groups with Et_3N/MeOH afforded the desired thiazofurin analogue **10** (colorless solid, 70%).

From ^{13}C NMR data the ribosylated compounds **6**, **7**, **9** and **10** were identified as furanosides because of the appearance of their C-4' signals at the range 79.1 - 80.5 ppm showing the proximity of ether oxygen.[10] In addition, deprotected compounds **7** and **10** had deuterium exchangeable signals of 5'-hydroxyls in their ^1H NMR spectra.

The NMR data indicated that compounds **6, 7, 9** and **10** were mixtures of anomers. Anomeric configurations for the major and minor components of deprotected compounds were assigned on the basis of H-1' coupling constants[11] in the deuterium exchanged spectra. The compounds exhibiting the small $J_{1',2'}$ values (3.7-4.3 Hz) were identified as α, while those showing large $J_{1',2'}$ value (9.3) as β. In the target carboxamide derivative **10** the β anomer prevailed (β:α = 3:2).

The N-exoamino glycosylic bond of 5-(ribofuranosylamino)thiazoles **7** and **10** was found to be stable at pH 3, 7 and 10.

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