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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-( $\beta$ -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  $\alpha$  anomer as a minor product.

Tiazofurin (2- $\beta$ -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.<sup>1,2</sup> 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<sup>3</sup> and the ribose moiety<sup>4</sup> is indispensible for its biological activity.

We were interested in two types of novel tiazofurin analogues. One was 2benzylthiazole-4-carboxamide 4, tiazofurin with ribose moiety replaced by a group known to bind to a hydrophobic area on some enzymes.<sup>5</sup> The other was  $5-(\beta-D-$ 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<sub>3</sub>/MeOH 10M in ampule,  $120^{\circ}$ C, 48 h; iv, BSA, CH<sub>3</sub>CN, reflux, 12h, then AcBz<sub>3</sub>R, TMSTf reflux; v, Et<sub>3</sub>N/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.<sup>6</sup> 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.<sup>7</sup>

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.<sup>8,9</sup> Therefore, we employed the condensation of the silylated aminothiazole 5 with 1-0-acetyl-2,3,5-tri-0-benzoyl- $\beta$ -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<sub>3</sub>/MeOH at room temperature resulted in the cleavage of the glycosidic bond. The removal was accomplished by the treatment of 6 with Et<sub>3</sub>N/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  $5-(\beta$ -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<sub>3</sub>/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<sub>3</sub>N/MeOH afforded the desired thiazofurin analogue 10 (colorless solid, 70%).

From <sup>13</sup>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.<sup>10</sup> In addition, deprotected compounds 7 and 10 had deuterium exchangeable signals of 5'-hydroxyls in their <sup>1</sup>H 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<sup>11</sup> in the deuterium exchanged spectra. The compounds exhibiting the small  $J_{1',2'}$  values (3.7-4.3 Hz) were identified as  $\alpha$ , while those showing large  $J_{1',2'}$  value (9.3) as  $\beta$ . In the target carboxamide derivative 10 the  $\beta$  anomer prevailed ( $\beta:\alpha = 3:2$ ).

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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