A convenient synthesis of antiviral acyclic C-nucleosides incorporating 1,3,4-thiadiazine nucleus as a nucleobase

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Adducts 4a-d obtained by nucleophilic addition of sulphonylated dimethyl sulphoxide derivatives 2a,b to glucose thiosemicarbazones 3a,b undergo intramolecular cyclisation, involving methanesulphinyl leaving group, with 90% H₂SO₄ and Pummerer rearrangement with glacial acetic acid to yield acyclic C-nucleosides, 2-arylamino-6-(5-aryl-1,3,4-thiadiazol-2-ylthio)-5-(d-glucopyranosyl)-4H,5,6-dihydro-1,3,4-thiadiazines 6a-d and 2-arylamino-6-(5-aryl-1,3,4-thiadiazol-2-ylthio)-5-(d-glucopyranosyl)-6-methylthio-4H,5,6-dihydro-1,3,4-thiadiazines 7a-d, respectively.

The isolation of naturally occurring antiviral C-nucleosides like formycin, formycin B⁷⁻³, pyrazomycin, pyrazomycin B⁴⁻³, and the discovery of potent antiviral acyclic nucleosides like acyclovir⁸ and its analogues⁹⁻¹⁰ have led to significant progress in the development of useful antiviral agents. This has prompted the synthesis of various acyclic C-nucleosides⁹⁻¹². In continuation of our work on the synthesis of antiviral agents, particularly via heterocyclisation of nitrogen derivatives of sugars¹¹⁻¹³, we report in this paper a direct synthesis of hitherto unknown acyclic C-nucleosides 6a-d and 7a-d (Scheme 1). In the present study, 1,3,4-thiadiazine structure has been used as a nucleobase owing to its biological potential¹⁵⁻¹⁷.

The synthetic sequence leading to the formation of 6a-d and 7a-d is outlined in Scheme 1. The reaction of chloromethyl methyl sulphoxide and the sodium salt of 5-aryl-2-mercapto-1,3,4-thiadiazoles 1a,b in refluxing ethanol furnished 2a,b. Nucleophilic addition of sulphur-stabilised carbanions, generated by the action of sodium methoxide on 2a,b in methanol at room temperature, to C=N of glucose thiosemicarbazones 3a,b followed by quenching with dil. HCl afforded 4a-d in 65-76% yield. Adducts 4a-d underwent intramolecular cyclisation, involving the acid labile methanesulphinyl leaving group, on treatment with 90% H₂SO₄ at <0°C to furnish 6a-d in 62-73% yield. Adducts 4a-d on treatment with glacial acetic acid underwent Pummerer rearrangement to give 7a-d in 60-68% yield.

The structural assignments of the products were based on their elemental analyses, IR and ¹H NMR data. The spectral data of only representative compounds are reported in the Experimental Section. The IR spectra of compounds 4a-d exhibited a strong band around 1035 cm⁻¹ due to S=O function, whereas their successors 6a-d and 7a-d were devoid of this band. All the compounds 4, 6 and 7 revealed significant bands in the region 3305-3375 cm⁻¹ attributable to NH groups. The ¹H NMR spectra of compounds 4a-d exhibited a singlet in the range δ 2.57-2.59 due to MeSO protons, whereas compounds 6a-d and 7a-d were devoid of this signal. Similarly, compounds 7a-d revealed a singlet for MeO protons in the region δ 2.17-2.19 which was absent in case of compounds 6a-d. Compounds 4a-d and 6a-d exhibited a doublet in the range δ 3.70-4.16 and a multiplet in the region δ 4.93-5.28 attributable to SCH and NCH protons, respectively. The doublet was absent in the ¹H NMR spectra of 7a-d. In addition, all the compounds 4, 6 and 7 exhibited the expected ¹H NMR signals for glucopyranosyl, aryl and MeO protons present in them (cf. Experimental Section).

Antiviral Screening

The antiviral activity of compounds 4, 6 and 7 was evaluated in vitro against the viral species Chenopodium amaranticolor as reported in the literature¹⁹⁻²¹. Inoculations were made by leaf rubbing method. The compounds were applied as their suspensions in acetone-water (20:80 v/v) at 1000 ppm and 100 ppm concentrations. A standard antiviral agent, Virazone (1-β-D-ribofuransyl-1,2,4-triazole-3-carboxamide) was tested under similar conditions for comparison. The antiviral activity was recorded as percentage inhibition over control. The results are summarized in Table 1.
Amongst the tested compounds, the most active were 6c and 7c. Although compounds 4 have a preformed open-chain skeleton of 1,3,4-thiadiazine, these were found to be far less potent than their cyclized products 6 and 7 indicating that the presence of 1,3,4-thiadiazine nucleus plays a key role in the antiviral potential of these compounds. Likewise, compounds 6 were less active than their methythio analogues 7. It was however noteworthy that the introduction of a methoxy or chloro group into the aryl moiety of these compounds tends to augment their antiviral activity and that the introduction of a chloro group is more effective than that of a methoxy group.

Experimental Section

General. Melting points were determined in open capillaries and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 993 infrared spectrophotometer ($\nu_{\text{max}}$ in cm$^{-1}$) and $^1$H NMR spectra
were recorded on a Perkin-Elmer R-32 (90 MHz) spectrometer in DMSO-d₆ using TMS as internal reference (chemical shifts are expressed in δ, ppm and coupling constants, J in Hz).

The requisite compounds 1a,b were prepared according to the procedure already reported in the literature.¹⁸

4-Arylamino-6-(5-aryl-1,3,4-thiadiazol-2-ylthio)ethythiosemicarbazides 4a-d. To a solution of MeONa (0.01 mole) in MeOH (25 mL) was added 2 (0.01 mole), and after stirring the reaction mixture at room temperature for 45 min, thiosemicarbazone 3 (0.01 mole) was added. The reaction mixture was further stirred at room temperature for 1 hr followed by stirring at 50-60°C for 30-45 min, then it was quenched with H₂O (25 mL) and acidified with 5N HCl (2.2 mL) just to neutrality. The product thus precipitated was recrystallised twice from EtOH to obtain an analytical sample of 4.

4a: IR: 1030 (S=O), 3310 (NH), 1836 (NH), 3365, 3370 (NH). ¹H NMR: 1.85-3.02 (2H, m, 5'-H), 2.58 (3H, s, MeS), 3.72 (1H, d, J = 4, SCH), 3.75 (3H, s, OMe), 3.76-3.80 (1H, m, 1'-H), 4.05-4.13 (3H, m, 2', 3', 4'-H), 4.43 (SH, brs, 5xOH), 4.93-5.22 (1H, m, NCH), 7.24-7.72 (9H, m, ArH), 8.42-9.15 (3H, brs, NHNHSN). ¹³C NMR: 105, 120-21 (C, ArH), 110-11 (C, ArH), 115-17 (C, ArH), 118-51 (C, ArH), 120-21 (C, ArH), 135. ¹⁹F NMR: 105, 120-21 (C, ArH), 110-11 (C, ArH), 115-17 (C, ArH), 118-51 (C, ArH), 120-21 (C, ArH), 135.

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