SYNTHESIS OF UNUSUAL BENZIMIDAZOLE NUCLEOSIDES

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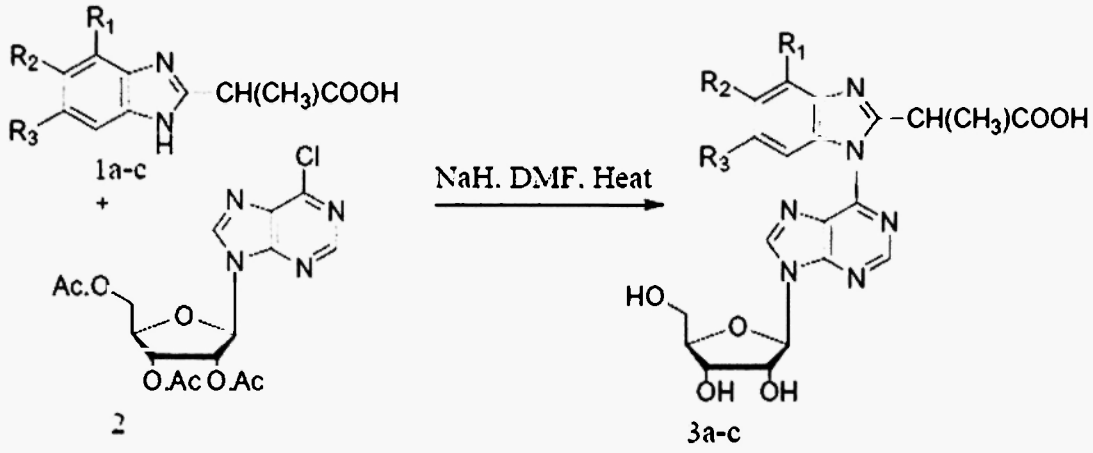
Abstract: Synthesis of some unusual benzimidazole nucleoside analogues viz.2-{1-[9-(3,4-Dihydroxy-5-hydroxymethyl-tetrahydro-furan-2-yl)-9H-purin-6-yl]1Hbenzimidazol-2-yl}-propionic acid (**3a**), 2-{5-Bromo-1-[9-(3,4-dihydroxy-5-hydroxymethyl-tetrahydrofuran-2-yl)-9*H*purin-6-yl]-6-nitro-1*H* benzo-imidazol-2-yl}-propionic acid **(3b)** and 2-{5-Bromo-1-[9-(3,4-dihydroxy-5-hydroxymethyl-tetrahydrofuran-2-yl)-9*H*-purin-6-yl]-4-nitro-1*H*-benzoimidazol-2-yl}-propionic acid(**3c)** have been reported.

Introduction

Synthetic nucleosides[1-16] possessing interesting pharmaceutical and biochemical properties such as antiviral, antitumor, antisense agents, antigene agents, antibiotic, antileukemic, immunosuppressive agent, kinase inhibitors and adenosine receptor antagonists have been prepared and characterized. Besides these biological applications, such molecules also form Langmuir-Blodgett films, liposomes, vesicles and can modify the transport characteristics through lipid membranes. We are encouraged by the work of Weisz et al.[17-18] and Seley et al.[19-21] These research workers have synthesized unique nucleosides for investigating enzyme-coenzyme as well as nucleic acid – protein interactions.

Design and synthesis[22-25] of such nucleoside molecules has been attempted in view of better biological activity as drugs. The synthesis of such innovative nucleosides has been reported for better understanding of exploring fundamental aspects of nucleic acid structure, function and stability and this can be also helpful to investigate enzyme binding site parameters. Similarity also lies in the fact that the synthesized nucleoside analogue and Ibuprofen, both cotain –CH(CH3)COOH moiety in their structure. Ibuprofen is a well known analgesic, antipyretic and anti-inflammatory drug in the world. Allopurinol like other units may also be incorporated in such molecules for combined drug activity. Novel synthetic analogues have been characterized with the help of required physicochemical techniques such as ^{1}H-NMR,^{13} C-NMR, mass spectroscopy, elemental analyses and chromatography.

Biological activities of these molecules are under investigation. Synthesis of some other nucleosideanalogues is presently under progress and the results of these efforts for drugs as well as other biological activities will be published as they become available. These compounds can be better candidate molecules to investigate nucleic acid related biological problems.



1a. 3a : R1=H. R2=H. R3=H
1b. 3b : R1=H. R2=Br. R3=NO2
1c. 3c : R1=NO2. R2=Br. R3=H

Scheme 1. Preparation of unusual nucleosides

Experimental

The **1H** and **13C NMR** spectra of the three compounds were measured at 300 MHz and 100 MHz respectively using Bruker (Avance) NMR instrument in DMSO-*d6*, and the chemical shifts(δ ppm) referenced to **TMS** as internal standard. Microanalysis was carried on a Carlo Erba 1108 instrument. Mass Spectra was taken on Jeol SX 102 spectrometer. All the chemicals used were of AR grade (Sigma, BDH, & E. Merck).

Synthetic Procedure:

The compound **1a25-27**was prepared on reacting o-phenylenediamine with 2-bromopropionic acid and subsequent conversion of Br-CN-COOH group. A solution of Br2 (130uL) in water (30 mL) was added drop wise to a suspension of **1a** (2.5 mmol) in a solution of KOAc (1g) in H2O (20mL). The resulting white suspension was stirred at 230C overnight and then was extracted with CH2C12. The combined organic layers were washed with satd. aq. NaCl and dried (MgSO4).Evaporation under reduced pressure afforded 5(6)- Bromo benzimidazoles derivatives. A solution of bromo derivative (1.5 mmol) in 1ml of 98% H2SO4 at 00 C was treated drop wise with a solution of 0.1mL on concentrated HNO3 in 1ml of 98% H2SO4.The reaction mixture was stirred at 0-50 C for 2 h, and then it was poured into an ice-water mixture. After usual work up, the crude product mixture was purified by column chromatography (7-9 % CH3OH -CH2C12) to afford 5-Bromo-6-nitro and 5-Bromo-4-nitro benzimidazole derivative **1b-c** in 70-80% yield. Compound **1a-c**(1 mmol) was dissolved in dry DMF (10mL), Sodium hydride (2 mmol) was added with stirring at 70C for 1.5 hr, cooled, a solution of 6-Chloropurineribosideacetate **2** (1 mmol) in dry acetone (5mL) was added, the reaction mixture was stirred for 5-6 hr, then evaporated under reduced pressure, deprotected and

purified on silica gel column chromatography (9:1 CHCl3- MeOH) to afford the product **3a-c** in 65-72% yield. The selected physico-chemical analysis supported their structures.

2-{1-[9-(3,4-Dihydroxy-5-hydroxymethyl-tetrahydro-furan-2-yl)-9H-purin-6-yl]-1H-benzimidazol-2-yl}-propionic acid (3a) : Yield 69%; 1H-NMR (300 MHz, DMSO-*d6*): δ7.62 (d, 1H, *J* 8.2 Hz, H-4), 7.19 (d, 1H, *J* 8.2 Hz, H-6), 3.77 (s, 1H, CH), 1.44 (s, 3H, CH3), 8.98 (s,1H, H-2), 8.66 (s, 1H, H-8), 5.96 (s, 1H, H-1′), 5.51-5.14 (m, 3H, OH-2′ ,OH-3′, OH-5′), 4.36-4.05 (m,3H, H-2′, H-3′ & H- 4′), 3.68-3.59 (m, 2H, H-5′, H-5″).13C-NMR (100 MHz, DMSO-*d6*): δ 175.61(-COOH), 153.2,151.40 (C-2), 147.84, 146.02,146.14,144.76, 141.48, 137.88, 121.86 (C-5, C-6), 116.26 (C-4, C-7), 88.02(C-1'), 71.26 (C-2' , C-4'), 71.11(C-3'), 62.22(C-5'), 37.78(-CH), 15.98 (-CH3).HRMS [M+H]+ : calcd: 441.4265. found: 441.4263. Anal. Calcd for C20H20O6N6 : C,54.55; H, 4.55; N, 9.09. Found : C, 54.51; H, 4.52; N, 19.11.

2-{5-Bromo-1-[9-(3,4-dihydroxy-5-hydroxymethyl-tetrahydro-furan-2-yl)-9*H*purin-6-yl]-6-nitro-1*H*benzoimidazol-2-yl}-propionic acid (3b) : Yield 65%; 1H-NMR (300MHz, DMSO-*d6*): δ 8.29 (s, 1H,H-4), 8.01(s, 1H, H-7), 3.72 (s, 1H, CH), 1.39 (s, 3H, CH3), 8.97 (s, 1H, H-2), 8.62 (s, 1H, H-8), 6.01(s, 1H, H-1′), 5.56-5.16 (m, 3H, OH-2′,OH-3′, OH-5′), 4.34-4.09 (m, 3H, H-2′, H-3′ & H- 4′), 3.66-3.58(m, 2H, H-5′,H-5″).13C-NMR (100 MHz, DMSO-*d6*): δ 176.88(-COOH), 153.52,150.96,147.84(C-8), 146.06 (C-6), 146.10,144.66, 141.48(C-2), 137.74(C-8), 128.38(C-5), 119.58(C-4), 112.57(C-5), 112.66(C-7), 88.21(C-1'), 71.96 (C-2' , C-4'), 71.18(C-3'), 62.32(C-5'), 37.98(-CH), 16.02(-CH3). 17.2. HRMS [M+H]+ : 563/565. Anal. Calcd for C20H18O8N7Br : C, 42.62 ; H, 3.19 ; N, 17.40 . Found :C, 42.56; H, 3.18; N, 17.38.

2-{5-Bromo-1-[9-(3,4-dihydroxy-5-hydroxymethyl-tetrahydro-furan-2-yl)-9*H*purin-6-yl]-4-nitro-1*H*benzoimidazol-2-yl}-propionic acid (3c) : Yield 72%, 1H-NMR (300 MHz,DMSO-*d6*): δ 7.80 (d, 1H,*J* 8.4 Hz, H-6), 7.61(d, 1H, *J* 8.4 Hz, H-7), 3.74 (s, 1H, CH), 1.40 (s, 3H, CH3), 8.94 (s, 1H, H-2), 8.60 (s, 1H, H-8), 6.00 (s, 1H, H-1′), 5.51- 5.14 (m, 3H, OH-2′ ,OH-3′, OH-5′), 4.36-4.05 (m, 3H, H-2′, H-3′& H- 4′), 3.68-3.59 (m, 2H, H-5′, H-5″). 13C -NMR (100 MHz, DMSO-*d6*): δ 176.48(-COOH), 154.29,151.86(C-2),147.64(C-8), 146.00,146.08,144.18, 141.48, 138.56 (C-4), 127.02 (C-6), 123.68 (C-7), 112.56(C-5), 88.18 (C-1'), 71.92 (C-2' , C-4'), 71.16(C-3'), 62.26(C-5'), 37.87(-CH), 16.04 (-CH3).HRMS [M+H]+ : 563/565. Anal. Calcd for C20H18O8N7Br : C,42.62 ; H, 3.19 ; N, 17.40 . Found : C, 42.57; H, 3.18; N, 17.36.

In conclusion, we have designed an innovative structure for unnatural benzimidazole nucleoside analogues which can possess chemotherapeutic and biochemical properties. A series of such compounds are under preparation for their biological activities.

Acknowledgement

VSY thanks Council of Science and Technology, U. P. for the award of Major Research Project (CST/Biotech/RS4/D- 3464 dated March 30, 2007).

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Received on 9 March 2008