

Nucleosides, Nucleotides and Nucleic Acids

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ISONUCLEOSIDES INCORPORATING UNIVERSAL BASES

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ABSTRACT

Enantiomeric isodideoxynucleosides of the (*S,S*) and (*R,R*) families with the universal base, imidazole-4-carboxamide as the nucleobase, were synthesized as biological mimics of anti-HIV active D- and L-related isodideo-xyadenosines. *In vitro* anti-HIV evaluation in CEM cells of these target compounds showed that they were inactive. Further antiviral studies are in progress.

The concept of a universal base that can base-pair all four natural bases found in nucleosides has been the subject of a number of recent studies (1–4). Irregular base-pairing occurs in nature and has been of importance in the understanding of the interpretation of the genetic code by tRNA molecules. Abnormal base-pairing also occurs in DNA. It was reported by Ohtsuka *et al.* (4) that 2'-deoxyinosine (dI) could behave as a universal nucleoside and participate in base-pairing with all four natural deoxynucleosides. Its binding to cytosine and thymine occurs *via* normal Watson-Crick base-pairing, but its binding to adenine occurs *via* Hoogsteen base-pairing. However, dI shows a distinct preference for base-pairing with deoxycytidine (dC). The compound, 1-(2-deoxy- β -D-ribofuranosyl) imidazole-4-carboxamide (dICAR – shown below, Fig. 1), has been reported by Sala *et al.* (2) and Johnson *et al.* (1) to behave also as a universal nucleoside but exhibiting a preference for behaving as a dA mimic.

For a number of years, we have investigated the chemistry and biology of isomeric nucleosides or isonucleosides (5–7). Of the many isodideoxynucleosides

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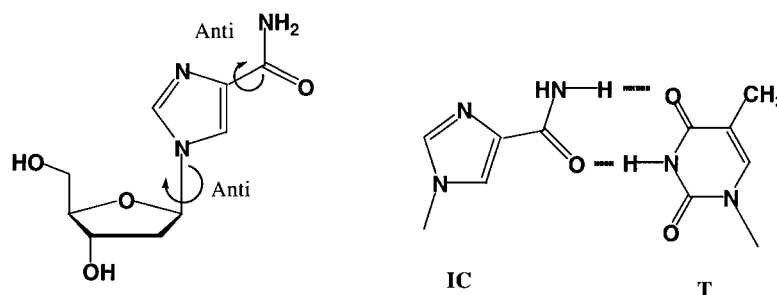
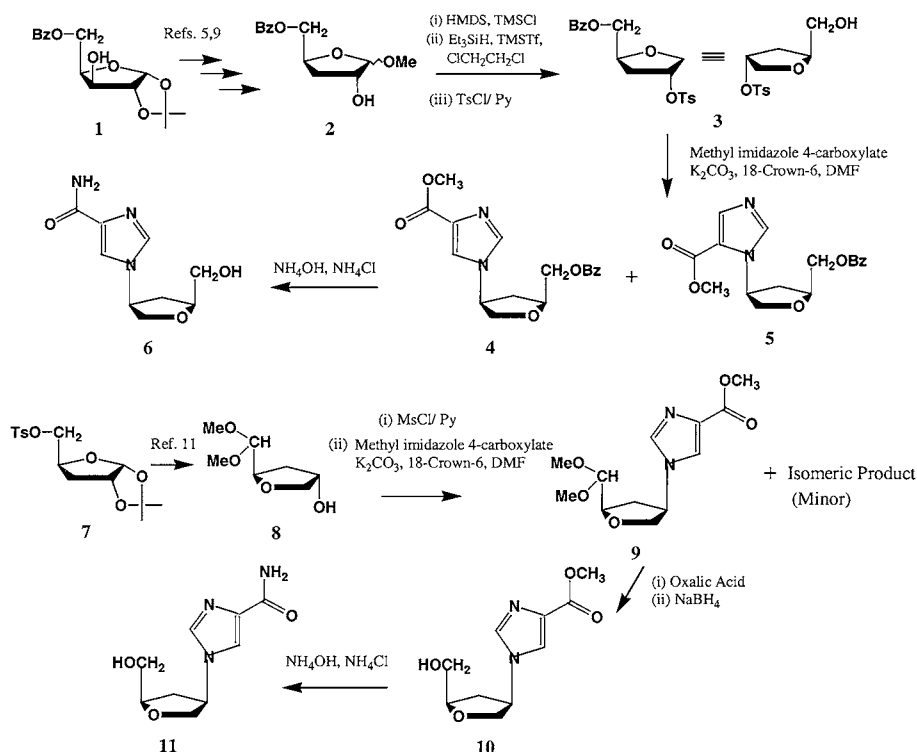


Figure 1.

synthesized in our research group, the most anti-HIV active member is (*S,S*)-isodideoxyadenosine which, as its triphosphate, inhibits HIV reverse transcriptase at the low nM level (6,7). It appears that potent anti-HIV activity of these isonucleosides is confined to compounds with the nucleobase, adenine. Substitution of other natural nucleic acid bases in place of adenine results in loss of antiviral activity (7,8). The question of whether the universal nucleobase, imidazole-4-carboxamide, capable of mimicking adenine could be substituted for adenine in these isonucleosides has not been investigated. This paper reports our results on the synthesis (Scheme 1) and anti-HIV activity studies of isonucleosides



Scheme 1.



of both the D- and L-related families that contain the base, imidazole-4-carboxamide.

The key carbohydrate intermediate for the synthesis of the L-related target compound, **6**, was tosylate **3**, which was prepared from **1** in several known steps including two deoxygenations (Scheme 1) (9). Coupling of **3** with methylimidazole-4-carboxylate in the presence of K_2CO_3 and 18-crown-6 gave **4** (32%) and its 3-substituted isomer **5** (24%) which were separated chromatographically and identified by 1H and ^{13}C NMR data. Interestingly, the Mitsunobu coupling reaction of the alcohol precursor of **3** with methylimidazole-4-carboxylate gave only low yields of the coupling products. Compound **4** was converted to the target molecule **6** (*S,S*-isomer) in 80% yield by treatment with NH_4Cl/NH_4OH (10). The enantiomeric target molecule **11** was synthesized by a related route with compound **8** as the key intermediate. Intermediate **8** was prepared from the rearrangement of **7** with $MeOH/HCl$ (11). A summary of the main steps involved in the synthesis of **11** is shown in Scheme 1. These two D- and L-related target compounds were screened for antiviral activity against HIV-1 in CEM-SS cells and were found to be inactive. Further evaluations against other viruses are in progress.

ACKNOWLEDGMENTS

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- Data for compound **6**: 1H NMR (CD_3OD): δ 1.92 (1H, m), 2.55 (1H, m), 3.58 (1H, m), 3.74 (1H, m), 3.95 (3H, m), 4.91 (1H, m), 7.78 (2H); ^{13}C NMR (CD_3OD):



δ 36.6, 59.4, 63.9, 74.6, 81.4, 122.0, 137.3, 138.2, 167.3; λ_{\max} 235 nm, FAB HRMS: calc. for $(M + H)^+$ 212.1011, found 212.1031. ^1H NMR data clearly differentiated between product **6** and its regioisomer as the chemical shift of the hydrogen on the carbon bearing the base was at δ 4.91 for **6** and at δ 5.69 for its regioisomer. Further confirmation of structure and stereochemistry for **6** and **11** came from NOESY experiments.

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