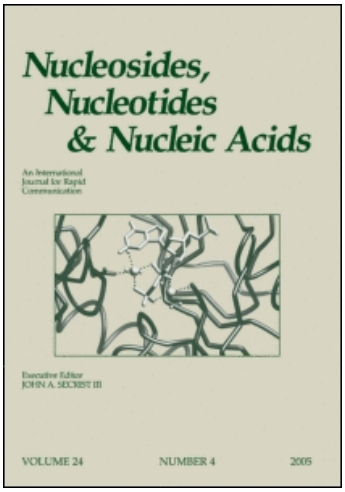

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SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW ENANTIOMERS OF 5-*o*-CARBORANYL PYRIMIDINE NUCLEOSIDES

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ABSTRACT: The synthesis of new enantiomers of 5-*o*-carboranyl pyrimidine nucleosides is described. Some of these agents should be considered for boron neutron capture therapy.

High-boron-content molecules are desirable for boron neutron capture therapy (BNCT) used for the treatment of gliomas, melanomas, and malignancies.[1] This therapeutic modality combines the utilization of boron-containing compounds targeted to the tumor cells and neutron irradiation as an initiator to produce micronuclear reactions within tumors.[2] Several carboranyl compounds have already been synthesized such as 5-*o*-carboranyl-2'-deoxyuridine (D-CDU)[3,4] and 5-*o*-carboranyl-1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-uracil (D-CFAU).[5] The encouraging results obtained with these compounds prompted us to develop the enantiomeric synthesis of new β-L- and D-5-*o*-carboranyl pyrimidine nucleosides (Figure 1) with potentially improved physicochemical and biological properties.

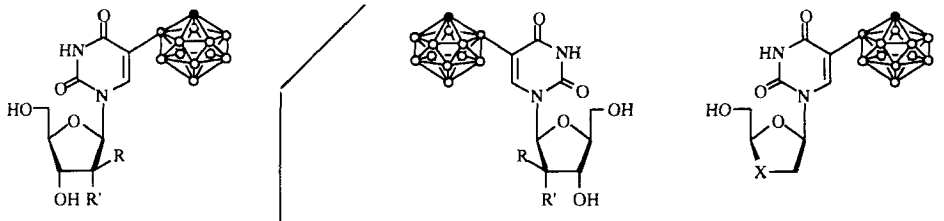

Figure 1. Structures of new 5-*o*-carboranyl pyrimidine nucleosides

5-*o*-Carboranyl derivatives were prepared either by glycosylation (compounds **7** and **8**) or directly from the parent β-D or β-L nucleoside (compounds **1-6**). Using the already described synthesis of compound **7**,[6] the dioxolane analogue **8** was synthesized by the same coupling

procedure with the protected dioxolane sugar.[7] L-Derivative intermediates were obtained from L-arabinose in good overall yield according to the procedure described by Holy.[8] Iodination was performed with *N*-iodosuccinimide or iodine, and the carbonylation step was conducted as reported for the preparation of 5-o-carboranyluracil (CU).[6]

Although compounds described were primarily developed for BNCT, they were also tested for cytotoxicity and antiviral activity in various normal and cancer cells. β-D-Ara-CU (**3**) and β-D-dioxolane-CU (**8**) were the most potent anti-HIV-1 analogues (EC_{50} = 0.19 and 0.58 μM, respectively). They were also found to be moderately toxic in CEM and PBM cells at much higher concentrations. Excluding 3'-modified carboranyl derivatives (**7** and **8**), L-enantiomers exhibited the lowest toxicity in rapidly dividing Vero cells. The relative toxicity was : β-D-CDU > β-D-ribo-CU > β-D-ara-CU ≥ β-L-ribo-CU > β-L-CDU > β-L-ara-CU. In addition, D- and L-enantiomers gave similar cytotoxicity profiles in PBM and CEM cells. Preliminary accumulation experiments of the carbonyl derivatives in CEM cells showed that D- and L-ribo-CU (**5** and **6**) were less susceptible to serum-binding than the other compounds. Taken together these results suggest that D-ribo-CU (**5**) and L-ribo-CU (**6**) are candidates for further biologial studies. However, D- or L-CDU (**1** and **2**) and CU should be considered since they accumulate to the greatest extent in cells.

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