

SYNTHESIS OF A NOVEL SERIES OF 3- CARBORANYL ETHYLENEOXIDE DERIVATIVES OF THYMIDINE AND THEIR EVALUATION AS SUBSTRATES FOR HUMAN THYMIDINE KINASE 1

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Abstract

Boron neutron capture therapy (BNCT) is a chemo-radio therapeutic technique for the treatment of cancer. For successful BNCT, a minimum of 20-30mg of boron-10 per g of tumor tissue is required. The boron-10 loaded tumors are irradiated with low energy (thermal) neutrons, which converts non-radioactive boron-10 to cytotoxic alpha-particles and lithium nuclei capable of destroying tumor cells. Boronated thymidine analogs are good candidates for BNCT because of their potential metabolic pathways. Elevated levels of cytosolic thymidine kinase 1 (TK1) are present in proliferating tumor cells, which may convert boronated thymidines to the corresponding 5'-monophosphates, thereby entrapping them intracellularly. In phosphoryl transfer assays with recombinant TK1, phosphorylation rates for carboranyl thymidines were measured up to 75 % with respect to thymidine depending upon the type of modifications. Among thymidine analogs modified at the 3'-and N-3 positions with carboranyl groups, only the latter showed good TK1 substrate activities. Also, the degree of aqueous solubility of the N-3 modified thymidines improved the relative phosphorylation rates. Synthesis of a novel series of N-3 substituted carboranyl thymidines with additional hydrophilic moieties and the results of their phosphoryl transfer assay evaluation with recombinant TK1 will be presented.