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Cariporide Prodrugs: Targeting Brain Cancer Cells through Sodium-Proton Exchange Inhibition

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More than 200,000 people in the United States are diagnosed with a primary or metastatic brain tumor annually. The life expectancy for these individuals is approximately 9-12 months from the time of diagnosis. This poor prognosis is due to the ineffectiveness of existing therapies (i.e., chemotherapy and radiotherapy) against brain cancer, where the primary problem is the inability to differentiate cancer cells from healthy brain cells.

Relative to healthy brain tissue, the heightened metabolism of cancer cells increases their reliance on the ion transport proteins NHE (sodium-proton exchanger) and NCX (sodium-calcium exchanger). Inhibition of these proteins disrupts the intricate pH and ion balances within cancer cells to a much greater extent than in normal cells, and this leads to cancer cell death. In contrast, healthy brain cells are less affected by this targeted approach because they are far less reliant on NHE and NCX due to their normal (and lower) metabolic activity. Consequently, NHE and NCX are excellent molecular targets for a new, selective brain cancer therapy. Although potent NHE/NCX inhibitors are available, a fundamental impediment to the field is the delivery of these compounds to poorly vascularized tissues.

As part of our target-specific approach to treating brain cancer, we have synthesized analogs of cariporide, a potent (e.g., nanomolar IC50 activity) NHE inhibitor, to address the drug delivery challenge. The preparation and biological activities of our cariporide analogs will be discussed.