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Investigation of Monocarbon Carboranes as Pendant Groups for Labeling Small Molecules with Astatine-211

The dianionic boron cage molecule *closo*-decaborate(2-) is being used as a pendant group to label monoclonal antibodies with the alpha-emitting radionuclide, astatine-211 (211At). While this works very well for antibody labeling, it appears that application of the same moiety for labeling small molecules can significantly alter blood clearance of biomolecule conjugates. As an example, in a murine model an 211At-labeled biotin derivative used in a cancer pretargeting approach clears the blood so rapidly that it fails to reach the antibody-streptavidin conjugate bound with tumor cells. Our hypothesis is that the dianionic nature of the astatinated pendant group facilitates rapid excretion of the biotin conjugate. Therefore we are investigating the use of another boron cage moiety, a monocarbon carborane, *closo*-1-carba-nonadecaborate(1-) {referred to as *closo*-1-CB9H10} as an alternative 211At-labeling moiety.

Two *closo*-CB9H10(1-) derivatives, 1-carboxyl-1-CB9H9, **1**, and 1-*p*-benzoate-1-CB9H9, **2**, were prepared following literature reports (Chem. Commun. 328-329,2004 & Dalton Trans. 3552-3561, 2004). Tetrafluorophenyl esters of the carboxylates in **1** & **2** were prepared and were reacted with an amine in a biotin-sarcosine derivative to provide biotin derivatives that contain the two anionic *closo*-CB9H9(1-) moieties. Electrophilic astatination reactions of the derivatives containing *closo*-CB9H9(1-) were found to be low yielding, even at elevated temperatures. To facilitate the astatination reactions, 10-substituted phenyl iodonium salts of **1** & **2**, compounds **3** & **4**, were prepared and astatination of those derivatives were evaluated using [211At]sodium astatide. While astatination occurred (up to 50%), it was noted that a new less lipophilic product was formed in the reaction, particularly at elevated temperatures. The labeling reactions of 1-*p*-benzoate-10-phenyl-iodonium-*closo*-CB9H8, **4**, had fewer side products than **3**, so that reagent was selected for our subsequent studies. Reactions conducted under the same conditions, but without 211At present, provided an opportunity to isolate and characterize the reaction side product. NMR and mass spectral data supported characterization of the compound as the 10-hydroxyl-1-*p*-benzoate-*closo*-CB9H8, **5**. Compound **5** is readily prepared from **4**. Electrophilic astatination of **5** provided a single compound in ~80% radiochemical yield, making it an attractive pendant group for small molecule labeling of 211At.

Astatination studies are continuing with compounds **2**, **4** and **5** to optimize the radiochemical yields, as are astatinations of biotin derivatives containing these moieties. Tissue biodistribution studies are planned to determine the in vivo stability of the 211At-labeled compounds. It should be noted that the use of the phenyliodonium intermediate allows introduction of 211At under nucleophilic non-oxidizing conditions, so this labeling method can be used for 211At-labeling of compounds that are sensitive to oxidizing (electrophilic) conditions.

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