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Design, Synthesis and Evaluation of 2-Deoxy-2-iodovinyl-branched Carbohydrates as Potential Brain Imaging Agents

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DESIGN, SYNTHESIS AND EVALUATION OF 2-DEOXY-2-IODOVINYL-BRANCHED CARBOHYDRATES AS POTENTIAL BRAIN IMAGING AGENTS

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Glucose is the primary energy souce of the brain and is also an important metabolic substrate for the normoxic heart. A number of glucose analogues labeled with the positron emitting radionuclides, carbon-11 and fluorine-18, have been utilized noninvasively to determine regional cerebral glucose metabolism in humans. Clinical studies using the glucose analogue, 2-[^{18}F]-fluoro-2-deoxy-D-glucose (2-FDG) have shown that the metabolic rate for glucose utilization in the brain varies in patients with pathological disorders (1,2,3). In patients with Alzheimers' disease (4,5), Parkinsons' disease (6), and dementia (5,7), 2-FDG shows a characteristic distribution of reduced glucose metabolism in the parietal region of the brain. However, because carbon-11 ($t_{1/2}$ = 20 min) and fluorine-18 ($t_{1/2}$ = 110 min) are short-lived radioisotopes and because only a few regions have clinical institutions with in-house cyclotrons and positron tomographic devices, only a small patient population can utilize these revolutionary diagnostic techniques available from these agents. Radioiodinated glucose analogues are better candidates for widespread clinical use because of the attractive radionuclidic properties of iodine-123, a single photon emitter (159 keV) with a 13.3 h half-life.

Radioiodinated carbohydrates such as 2-deoxy-2-iodo-D-glucose (8) and 3-deoxy-3-iodo-D-glucose (9) undergo facile chemical or in vivo deiodination which precludes their use as radiotracers of glucose metabolism in tissues. To overcome the problems resulting from in vivo deiodination, we explored the concept of stabilizing radioiodide on a model carbohydrate, (E)-C-3-iodovinyl-D-allose (10) as an iodovinyl moiety. This agent did not exhibit brain specificity but showed low in vivo deiodination which demonstrated for the first time that radioiodide can be stabilized on a carbohydrate. The goal of this study was to develop a deoxy-branched carbohydrate with radioiodide stabilized as a vinyliodide with the objective of achieving high brain uptake.

The synthetic approach for the preparation of the deoxy iodovinyl-branched carbohydrate involved the scission of a 2,3 anhydro sugar with a Grignard reagent. Methyl 2,3-anhydro-4,6-O-benzylidene-β-D-allopyranoside (1) was treated with ethynyl magnesium chloride to afford methyl 4,6-O-benzylidene-2-deoxy-2-ethynyl-β-D-altropyranoside (2) (Scheme I). Hydrostannylation of 2 with tri-n-butyltin hydride $(n\text{-}Bu)_3SnH$ gave the key intermediate, methyl 4,6-O-benzylidene 2-deoxy-2-(E)-(tributyltin)ethylene-β-D-altropyranoside (3). Iodide was introduced into the geminal position of the ethylene moiety by iododestannylation of the tin intermediate 3. Treatment of 3 with sodium iodide and N-chlorosuccinimide gave methyl 4,6-O-benzylidene 2-deoxy-2-(E)-iodovinyl-β-D-altropyranoside (4). Hydrolysis of 4 with 40% CH_3SO_3H gave 2-deoxy-2-(E)-iodovinyl-D-altrose (6), whereas hydrolysis with 20% CF_3COOH followed by treatment with pyridine-acetic anhydride gave methyl 2-deoxy-2-E-iodovinyl-2,4,6-O-triacetyl-β-D-altropyranoside (7). Tissue distribution studies of ^{125}I-labeled 7 (Table 1) and 6 were performed in rats. Iodine-125 7 showed good brain uptake, 1.65% dose/gm at 5 min, and 55% retention of radioactivity in the brain, 0.89% dose/gm at 30 min. In addition, the agent showed low in vivo deiodination which resulted in low thyroid uptake, 33% dose/gm at 60 min.

The high brain uptake of methyl 2-deoxy-2-E-iodovinyl-2,4,6-O-triacetyl β-D-altropyranoside (7) is most likely due to passive diffusion since 7 is not a substrate for the carrier system required for active sugar transport across the blood/brain barrier. Nevertheless, the delivery to the brain of a radioiodinated sugar with radioiodide stabilized as an iodovinyl moiety has been

successfully demonstrated with the synthesis of this model agent. A series of iodovinyl deoxy sugars with active D-gluco and D-manno configurations are presently being prepared for biological evaluation.

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Scheme I. Synthesis of 2-Deoxy-2-iodovinyl Altrose Derivatives

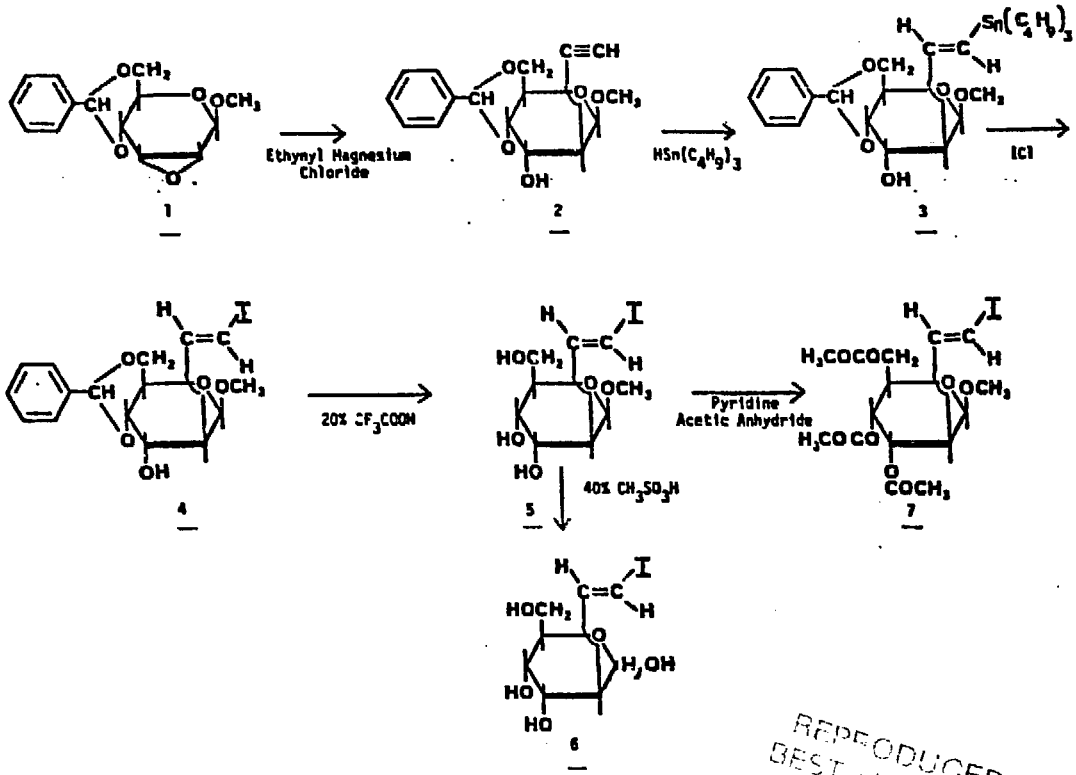

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Table 1. Distribution of Radioactivity in Tissues of Fischer 344 Rats Following Intravenous Administration of Methyl-2-deoxy-2-(E)-iodovinyl-2;4,6-O-triacetyl-β-D-altropyranoside (7)

	Mean % injected dose/g (range) at the following times after injection			
Tissue	5 min	15 min	30 min	60 min
Brain	1.65 (1.56-1.73)	1.19 (1.10-1.32)	0.89 (0.75-1.05)	0.72 (0.71-0.75)
Blood	1.05 (1.00-1.10)	0.93 (0.89-0.96)	0.80 (0.74-0.89)	0.65 (0.64-0.68)
Heart	1.14 (1.09-1.16)	1.07 (1.01-1.17)	0.87 (0.81-0.94)	0.68 (0.64-0.73)
Kidneys	1.55 (1.50-1.59)	1.57 (1.49-1.63)	1.68 (1.52-1.84)	1.57 (1.41-1.74)
Lungs	1.19 (1.09-1.33)	1.03 (0.97-1.11)	0.83 (0.74-0.92)	0.66 (0.66-0.67)
Liver	1.39 (1.34-1.42)	1.37 (1.33-1.39)	1.23 (1.12-1.42)	1.05 (0.97-1.10)
Thyroid	20.64 (20.06-21.27)	18.91 (17.53-20.53)	25.70 (22.95-30.15)	33.49 (27.79-43.47)