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# Synthesis and Preclinical Characterization of a Cationic Iodinated Imaging Contrast Agent (CA4+) and Its Use for Quantitative Computed Tomography of Ex Vivo Human Hip Cartilage

Rachel C. Stewart,[†,‡] Amit N. Patwa,[†] Hrvoje Lusic,[†] Jonathan D. Freedman,[†,‡] Michel Wathier,[§] Brian D. Snyder,[*,‡] Ali Guermazi,[*,∥] and Mark W. Grinstaff[*,†]

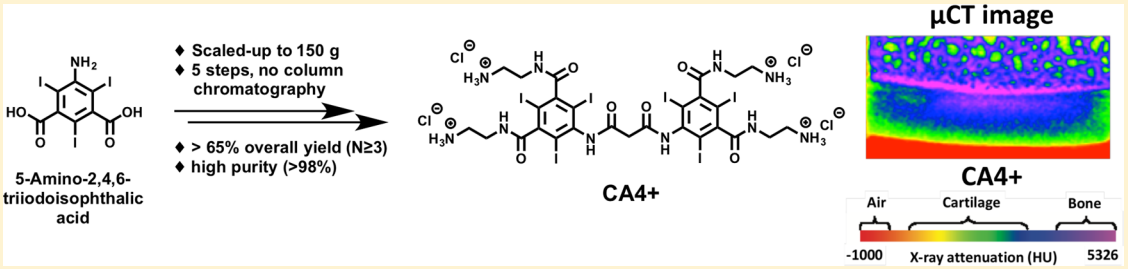
[†]Departments of Biomedical Engineering, Chemistry, and Medicine, Boston University, 590 Commonwealth Ave., Boston, Massachusetts 02215, United States

[‡]Center for Advanced Orthopaedic Studies, Beth Israel Deaconess Medical Center and Harvard Medical School, 1 Overland Street, RN 115, Boston, Massachusetts 02215, United States

[§]Ionic Pharmaceuticals, Boston, Massachusetts 02445, United States

[∥]Department of Radiology, Boston University School of Medicine, Boston, Massachusetts 02118, United States

Supporting Information




**ABSTRACT:** Contrast agents that go beyond qualitative visualization and enable quantitative assessments of functional tissue performance represent the next generation of clinically useful imaging tools. An optimized and efficient large-scale synthesis of a cationic iodinated contrast agent (CA4+) is described for imaging articular cartilage. Contrast-enhanced CT (CECT) using CA4+ reveals significantly greater agent uptake of CA4+ in articular cartilage compared to that of similar anionic or nonionic agents, and CA4+ uptake follows Donnan equilibrium theory. The CA4+ CECT attenuation obtained from imaging ex vivo human hip cartilage correlates with the glycosaminoglycan content, equilibrium modulus, and coefficient of friction, which are key indicators of cartilage functional performance and osteoarthritis stage. Finally, preliminary toxicity studies in a rat model show no adverse events, and a pharmacokinetics study documents a peak plasma concentration 30 min after dosing, with the agent no longer present in vivo at 96 h via excretion in the urine.

## INTRODUCTION

X-ray computed tomography (CT) is a well-established imaging modality that captures virtual slices of biological structures noninvasively and is commonly employed to diagnose disease and trauma, to guide interventional or therapeutic procedures, and to monitor the effectiveness of therapy. The quality of CT images for diagnostic purposes largely depends on differences in the X-ray attenuation of the tissue of interest relative to its surrounding environment, which is known as image contrast. CT provides the best contrast between neighboring tissues that have different densities and compositions. CT is less effective at distinguishing between contiguous soft tissues (for example, synovial fluid and articular cartilage), both of which are composed largely of water. When natural image contrast is insufficient for clear differentiation of tissues, imaging agents are employed to afford a temporary enhancement of the image quality.[1−9]

Several FDA approved contrast agents are iodinated water-soluble anionic or nonionic (Figure 1) small molecules (<2000 g/mol),[10] which are often used for imaging the vasculature. First-generation iodinated contrast agents possessed anionic polar groups to increase solubility, but ionic moieties are prone to interactions with cell membranes and other biological structures as well as possess intrinsically high osmolality.[11,12] In order to overcome these issues, second-generation contrast agents employed hydroxyl and amide functional groups, that readily hydrogen bond, to promote water solubility. Additionally, multiple iodinated aromatic rings are fused together in order to reduce osmolality while maintaining high administered iodine content. Though several contrast agents (ionic, nonionic, and one/two aromatic ring structures) are approved for clinical use and produced worldwide, new contrast agents with

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