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Gadolinium chelate with DO3A conjugated 2-(diphenylphosphoryl)-ethyldiphenylphosphonium cation as potential tumor-selective MRI contrast agent

Prashant Chandrasekharan [a], Cai-Xian Yong [a], Zihan Poh [a], Tao He [b], Zhengjie He [c], Shuang Liu [c], Edward G. Robins [a], Kai-Hsiang Chuang [a,**], Chang-Tong Yang [a,*]

[a] Laboratory of Molecular Imaging, Singapore Bioimaging Consortium, Agency for Science, Technology and Research (A*STAR), 11 Biopolis Way, #02-02 Helios, Singapore 138667, Singapore
[b] Institute of Chemical Engineering and Sciences, 1 Pesek Road, Jurong Island, Singapore 627833, Singapore
[c] School of Health Sciences, Purdue University, 550 Stadium Mall Drive, West Lafayette, IN, USA

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ABSTRACT

A series of organic cations, such as triphenylphosphonium (TPP), 2-(diphenylphosphoryl)-ethyl-diphenylphosphonium (TPEP), represent molecular probes for imaging tumors. These organic cations have been labeled with ^{64}Cu radioisotope for imaging tumors by positron emission tomograghy (PET). Among these organic cation ligands, TPEP was selected for extensive evaluation using magnetic resonance imaging (MRI) based on its higher tumor uptake and better Tumor/Background (T/B) ratios. This report presents the development of a new Gd(III) chelate [Gd(DO3A-xy-TPEP)]$^+$ as a cationic MRI contrast agent. The contrast agent was synthesized and characterized in vitro and in vivo. In vitro cell viability showed low cytotoxicity at low [Gd] concentrations. Cell uptake experiment shows that the [Gd(DO3A-xy-TPEP)]$^+$ has high affinity for tumor cells. The in vitro T_1 relaxivity measured at 9.4 T is about 50% higher than those of contrast agents in clinical use: Gd-DTPA (Magnevist) and Gd-DOTA (Dotarem). In vivo imaging studies in tumor-bearing mice at 7.0 T demonstrated significant signal enhancement at the site of the tumors. [Gd(DO3A-xy-TPEP)]$^+$ is a promising tumor-targeting MRI contrast agent for diagnostic imaging.

1. Introduction

Triphenylphosphonium (TPP) cations are rapidly taken up by mitochondria was first reported by Liberman because of their hydrophobicity and positive charge [1]. TPP cations are the one of most widely studied delocalized lipophilic cations used to targeting the mitochondria of tumor cells. These cations are under preclinical investigation for their potential application in targeting drugs to the mitochondria of tumor cells [2]. The mitochondrial transmembrane potential in carcinoma cells is significantly higher than that in normal epithelial cells ($\Psi\Delta m$ = 60 mV) [3–6]. Cationic molecules with appropriate structural features can therefore be driven electrophoretically through membranes by the negative mitochondrial transmembrane potential and accumulate inside the energized mitochondria in tumor cells [7–9]. These structure–activity relationship studies showed the TPP moiety is essential for anti-tumor activity.

Radiolabeled cations of quaternary phosphonium and arsonium complexes have been investigated as tumor selective radiotracers. Lipophilic cations such as 4-([^{18}F]-fluorobenzyl)-TPP ([^{18}F]BzTPP) and [^{3}H]-tetraphenylphosphonium ([^{3}H]-TPP) have been assessed as positron emission tomography radiotracers for tumor imaging [10–12]. Lipophilic, cationic radiotracers such as [^{18}F]BzTPP are highly sensitive to alterations in cellular membrane potential. This characteristic of [^{18}F]BzTPP could be useful for the diagnostic imaging of disease associated with mitochondria dysfunction and apoptosis [10]. [^{3}H]-TPP was reported to have a better tumor uptake than ^{99m}Tc-Sestamibi, the US Food and Drug Administration (FDA) approved radiotracer for myocardial perfusion imaging by single photon emission computed tomography (SPECT). But its tumor selectivity is very poor with the tumor/heart ratio being far below 1.0 and it exhibited minimal accumulation in adjuvant inflammatory tissues [11,12]. The high accumulation in heart and kidney and

* Corresponding author. Tel.: +65 64788727; fax: +65 64789957.
** Corresponding author. Tel.: +65 64788764; fax: +65 64789957.
E-mail addresses: chuang_kai_hsiang@sbic.a-star.edu.sg (K.-H. Chuang), yang_changtong@sbic.a-star.edu.sg (C.-T. Yang).

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