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PEGylated dendritic diaminocyclohexyl-platinum (II) conjugates as pH-responsive drug delivery vehicles with enhanced tumor accumulation and antitumor efficacy

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ABSTRACT

Environmentally responsive peptide dendrimers loaded with drugs are suitable candidates for cancer therapy. In this study, we report the preparation and characterization of mPEGylated peptide dendrimer-linked diaminocyclohexyl platinum (II) (dendrimer-DACHPt) conjugates as pH-responsive drug delivery vehicles for tumor suppression in mice. The DACHPt has a molecular structure, is and activity closely related to oxaliplatin and was linked to dendrimer via *N,O*-chelate coordination. The products were pH-responsive and released drug significantly faster in acidic environments (pH 5.0) than pH 7.4. Consequently, the conjugates suppressed tumor growth better than clinical oxaliplatin® without inducing toxicity in an SKOV-3 human ovarian cancer xenograft. Through the systemic delivery of conjugates, 25-fold higher tumor platinum uptake at 36 h post-injection was seen observed due to the enhanced permeability and retention (EPR) effect thereby remarkably enhancing the therapeutic indexes of this small-molecule drug. Thus, the mPEGylated peptide dendrimer-linked DACH-platinum conjugates are novel potential drug delivery systems with implications in future ovarian cancer therapy.

1. Introduction

Platinum-based cancer chemotherapy has been utilized for over 40 years and is still widely used today for testicular and ovarian cancer therapy [1]. However, even the third-generation platinum drug oxaliplatin has serous neurotoxicity [2]. This neurotoxicity is coupled with rapid inactivation from coordination to plasma proteins and limits the dose of oxaliplatin and therapeutic indexes in clinical applications [3]. Drug delivery vehicles loading platinum including liposomes, polymers, micelles and dendrimers [4–8], direct drug to the solid tumor via the enhanced permeability and retention (EPR) effect [9,10] increasing the accumulation in tumor tissues to improve anticancer efficacy and decrease side effects [11–14]. Physical encapsulation and chemical bonding are commonly and widely applied to load drugs into nanoscale vehicles. Due to low lipophilicity of platinum drugs, encapsulation formulation, especially liposomes, lead to rapid leakage of the drugs in the bloodstream and limit the bioavailability of the drugs in the tumor [15,16]. An alternative is to link platinum species to the macromolecular carriers via an environmentally sensitive bond [17].

Oxaliplatin is the best selling platinum therapeutic and has been approved worldwide for clinical use even supplanting carboplatin and cisplatin. Thus, many researchers focused on developing new platinum drug carriers utilize oxaliplatin to prepare active complex [18–20]. One successful method links the active platinum agent dichloro(1,2-diaminocyclohexane) platinum(II) (DACHPt) that is closely related to oxaliplatin to water-soluble materials via coordination chemistry. This strategy has been reported in a [*N*-(2-hydroxypropyl)methacrylamide] (HPMA) copolymer studies [21–24]. The *N,O*-chelate prepared by reacting the DACHPt$(OH_2)_2^{2+}$ with the carboxyl groups of the polymers was stable in physiological pH, but could be released at intracellular pH (pH = 5.0). This allowed the vehicle to liberate drug to the tumor cells after systemic circulation [25]. However, these linear polymers without branching architecture can be more easily eliminated by renal excretion due to their easy deformation and passage through the pores of the renal filtration membrane [26,27]. Thus, linear copolymers with high molecular weights (200–300 kDa) were used to increase blood circulation time [28]. However, biomedical applications via intravenous administration would be limited by the non-degradable backbone structure.

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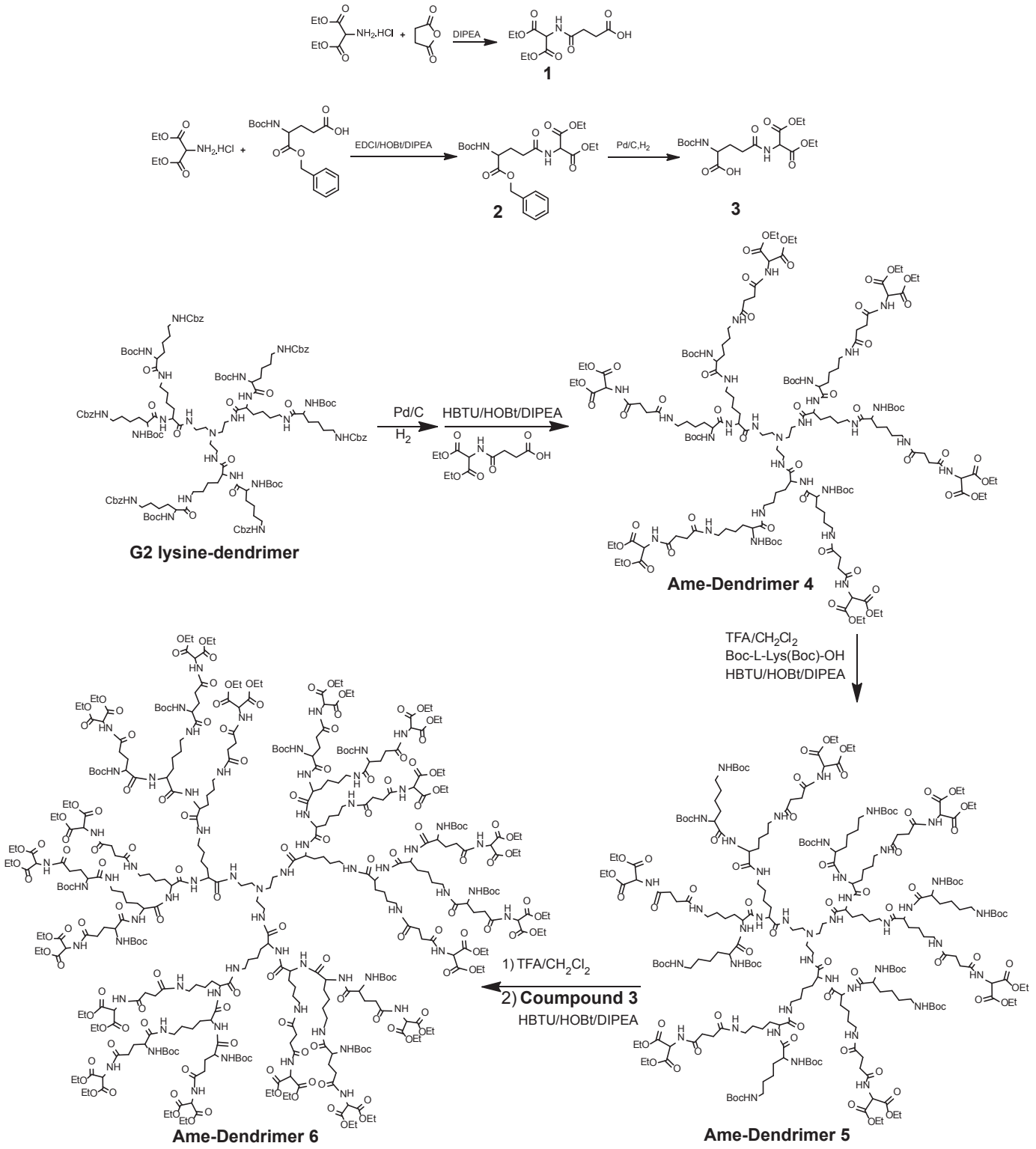
Peptide dendrimers are highly branched and symmetrical molecules which form a star-like structure, and the dendritic scaffold has similar properties to protein and is degradable. Such unique branched topologies and biodegradability allow peptide dendrimers with lower molecular weights (>~40 kDa) to remain in the blood much longer than linear polymers and have good safety profiles [29]. In addition, for all kinds of dendrimers, the multivalency is particularly useful to affix multiple copies of ligands to the terminal ends. This gives dendrimers the ability to add drugs as well as modified moieties like PEG (poly(ethylene glycol)) chains to the periphery [30]. PEGylation increases the molecular weight [31] and minimizes the toxicity of high generation products (>5 generation) [32]. Dendrimers with highly branched structures and PEGylation, therefore, have drastically increased blood circulation



Scheme 1. The synthesis route of the succinate-Ama-diEt compound (1), Boc-Glu(OH)-Ama-diEt compound (3) and functional dendrimers (Ame-dendrimer 4–6).