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Antimicrobial and anticancer activities of organoiron melamine dendrimers capped with piperazine moieties

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ABSTRACT

Three generations of a biologically active class of melamine dendrimers containing arene-cyclopentadienyliron cations were synthesized using the divergent method. These dendrimers were decorated with chloro-, hydroxyl-, or piperazine moieties. Cyclic voltammetric studies showed that dendrimers with chloro- or hydroxyl- terminal group exhibit reversible redox activity while dendrimers with piperazine moieties showed two distinct irreversible reductive waves. Organoiron dendrimers were thermally stable with the first degradation step at 200 °C associated with the decomplexation of the iron moieties. All dendrimers were evaluated against Gram-positive bacteria [Methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus warneri* and vancomycin-resistant *Enterococcus faecium* (VRE)], and showed significant activities against bacterial strains but were found to be less active in the case of chloro- terminal group. Second generation dendrimer **8** capped with piperazine exhibited inhibitory activity against Gram-positive bacteria generally comparable to that of reference vancomycin and rifampicin. Also, all dendrimers were screened against MCF-7 and HTB-26 breast cancer cell lines and dendrimer **8** exhibited significant inhibitory activity against MCF-7 compared with dendrimers in lower generations.

1. Introduction

Dendrimers are highly branched, three-dimensional, symmetrical molecules, and distinguished as members of the polymer family. The structure of a given dendrimer can be divided into three main parts: the core, the interior, and the periphery [1]. The core determines the three-dimensional shape of the dendrimer (i.e., spherical, ellipsoid, or cylindrical scaffolds), the interior affects the host–guest properties, and the periphery can be polymerized or modified with various functional groups [2]. As the diameter of a dendrimer increases, both the core composition and the number and/or the type of interior branches impact the overall morphology, while the number of surface groups increases significantly for each generation which causes steric overcrowding at the dendrimer surface [1]. Therefore, dendrimers at primary generations are usually flexible, while

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dendrimers at higher generations are dense and have 3D shapes because a dendrimer's generation number influences the rigidity of the aggregate structure [1].

Dendrimers differ from oligomers and linear polymers through their branching pattern, symmetry, and peripheral groups [3]. Dendrimers contain terminal reactive groups which allow for regulated molecular weight building, controlled branching and versatility in the design of the terminal groups [3]. Dendrimers are produced following either a convergent or divergent methodology, with each method having its own benefits [1]. The earliest syntheses of dendrimers were established by Tomalia et al. [3], Newkome et al. [4], and Astruc et al. [5] Astruc-type organometallic dendrimers are synthesized by divergent methods. The reactive side of the monomer is added to the polyfunctional core, while the opposite side of the monomer consists of unreactive or protected functional groups [1].

Dendrimers containing transition metals where the metal atoms are in the core [6,7], in the periphery [8,9] or in each generation [10,11] have been reported. Consecutive organometallic reactions used to synthesize dendrimers are limited due to the low stability of organometallic complexes in comparison to organic compounds [6]. The incorporation of transition-metal sandwich complexes in dendritic molecules results in many unique properties [5,7] due to the characteristics of the delocalized π-cyclic ring ligands [8–11]. Furthermore, dendrimers possessing redox-active organometallic units linked together in close vicinity promote an electronic connection between the metal sites in the dendritic structure. This allows for the design of new multi-metallic dendrimers with electron mobility and consequently attractive electrical, redox, optical, and magnetic properties [7]. Due to the rich redox properties of these complexes, such dendrimers have applications as stoichiometric redox reagents, redox catalysts, electron-transfer-chain catalysts, redox sensors, electrochemical references, and anticancer drugs [10–14]. Organometallic dendrimers with outer η^6-aryl-η^5-cyclopentadienyliron(II) moieties have been previously characterized [5,11,15]. η^6-Dichlorobenzene-η^5-cyclopentadienyliron(II) was successfully used to synthesize different classes of linear [16,17], star [18–21], and hyper branched macromolecules [22]. Since dendrimers are designated to incorporate terminal end-group functionality, this tunable property has utility in various biomedical applications [23].

Dendrimers based on the melamine core were previously reported as a mechanism for drug delivery [24], to increase the solubility of some cancer drugs, for example, methotrexate and 6-mercaptopurine [25,26], and to reduce the known hepatotoxicity associated with these drugs [25,27–30]. Historically, substituted amine moieties, particularly piperazine derivatives, have been evaluated for antifungal, antibacterial, and anticancer activities and recently labeled as chemotherapeutic agents for multiple diseases [24]. A number of candidate drugs contain piperazine moieties that interact with a wide range of biochemical targets across all therapeutic areas [31,32], including antianginals, antidepressants, antihistamines, antipsychotics, and urologicals [33–35].

In our present work, several novel organoiron melamine dendrimers capped with chloro, hydroxyl- and piperazine terminal end-groups were synthesized. The dendrimeric structure was confirmed by spectroscopic and elemental analyses, which were also used to differentiate between the three generations of dendrimers as well as terminal end groups of the same generation. Determination of the morphology of dried residues of the dendrimers was also performed using SEM and TEM. In addition, the electrochemical behaviours, thermal stabilities, and associated biological activities of these complexes were characterized.

2. Experimental

2.1. Materials

All chemicals and reagents were obtained from Sigma-Aldrich and were used without any further purification. All solvents were dried and stored over 3 Å molecular sieves before being used. The synthesis of the bimetallic organoiron complex followed previously reported procedures [36,37].

2.2. Instrumentation

A Bruker Avance NMR spectrometer (^{1}H, 300 MHz and ^{13}C, 75 MHz) was used to characterize all synthesized complexes in DMSO-d_6 or Acetone-d_6 with the chemical signals referenced to solvent residual signal in ppm. Attenuated total reflection Fourier transform IR (ATR-FTIR) absorption spectroscopic measurements were acquired on a Bruker Alpha FTIR spectrometer Alpha-P. Cyclic voltammetric experiments were carried out on a Princeton Applied Research/EG&G Model 263 potentiostat/galvanostat using glassy carbon working electrode, Pt counter electrode, and Ag reference electrode. The experiments, which were carried out at a scan rate between 0.1 and 1.5 V s^{-1} and at a temperature between 25 °C and −25 °C under nitrogen atmosphere in degassed propylene carbonate solvent and tetrabutylammonium hexafluorophosphate as supporting electrolyte, were externally referenced to a DMF solution of ferrocene. The scanning electron micrographs (SEM) of the complexes were obtained on a Hitachi TM3000 SEM. The transmission electron microscope (TEM) Hitachi Bio TEM 7500 was operated at 80 kV. Images were captured with a side mounted digital camera AMT XR40, purchased from Advance Microscopy Techniques, Danvers, MA, USA. Grids used in the experiment were 200 mesh copper grids carbon coated acquired from SPI Supplies Canada, London Ont. Elemental analyses were performed on CE-440 Elemental Analyser, Exeter