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The Development of Gold Nanoparticle-cored Dendrimers as a Multifunctional Drug Delivery System for Chemotherapy

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INTRODUCTION

Chemotherapy is administered in a manner that is not tumor-specific, and the drugs are generally distributed throughout the body. When these drugs become active in parts of the body other than the tumor, they are highly toxic and cause severe side effects like hair loss, kidney damage and infection. Gold nanoparticles have the potential to improve the transport and effectiveness of chemotherapeutic agents, as their size aids in targeting tumors through the enhanced permeability and retention effect. The nanoparticles can also be designed for multiple functions by decorating them with tree-like molecules called dendrons and terminating the dendrons with different chemotherapeutic drugs, imaging dyes, and targeting agents. The dendrons can then be combined around a central gold nanoparticle to form a multifunctional dendrimer.

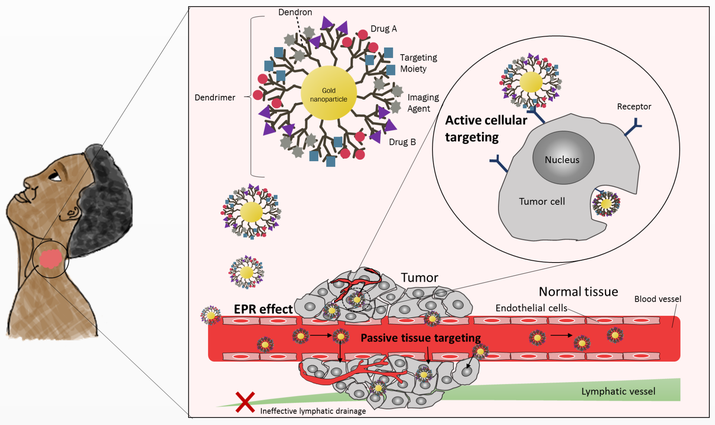


Figure 1. The dendrimers passively target tumor tissue through the EPR effect and, once inside the tumor they actively target cancer cells.

In this project, dendrons were synthesized and terminated with the chemotherapeutic agent cisplatin. All intermediates were characterized using ^{1}H NMR spectroscopy (for the dendron) or mass spectrometry (for the cisplatin derivatives). The final product was characterized by NMR and ICP-MS.

SYNTHETIC STRATEGY

Second-generation poly(propyleneimine) dendrons were synthesized and attached to a tetraethylene glycol (TEG) spacer terminated with thioctic acid. The thioctic acid molecule contains a cyclic disulfide group that will infer strong attachment onto the gold core. Once the spacers and dendrons were coupled, the dendron was grown to third-generation (8 branches) and its termini were modified so that the cisplatin drug molecules could be attached through a cleavable bond (acyl hydrazone) to allow for specific release into cancer cells.

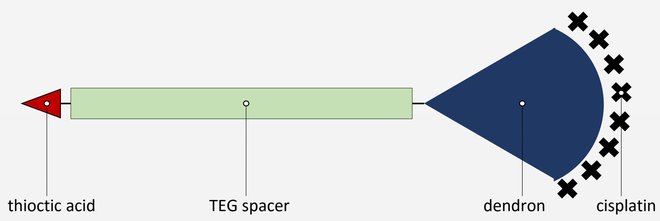
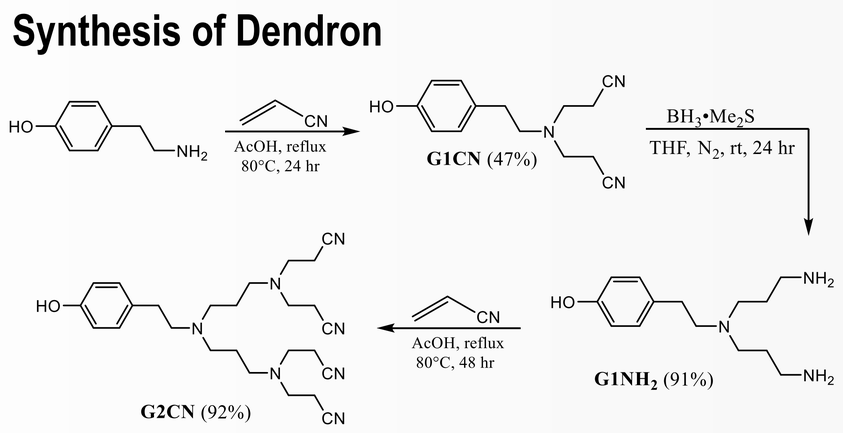


Figure 2. Generic structure of a completed dendron

Synthesis of Dendron



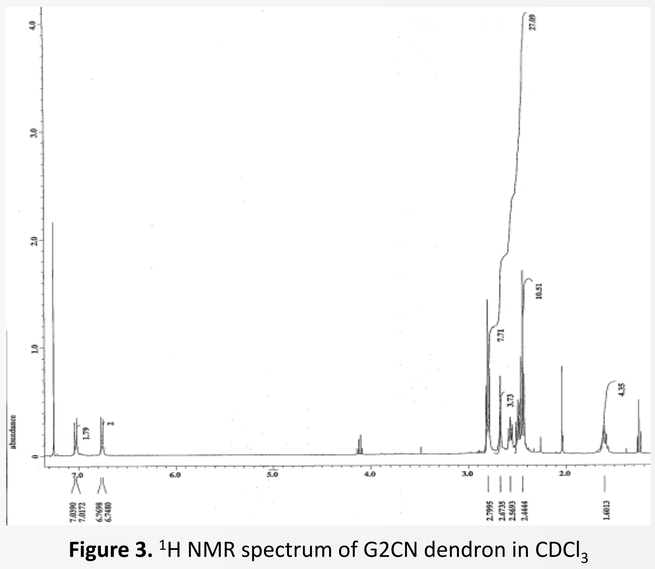
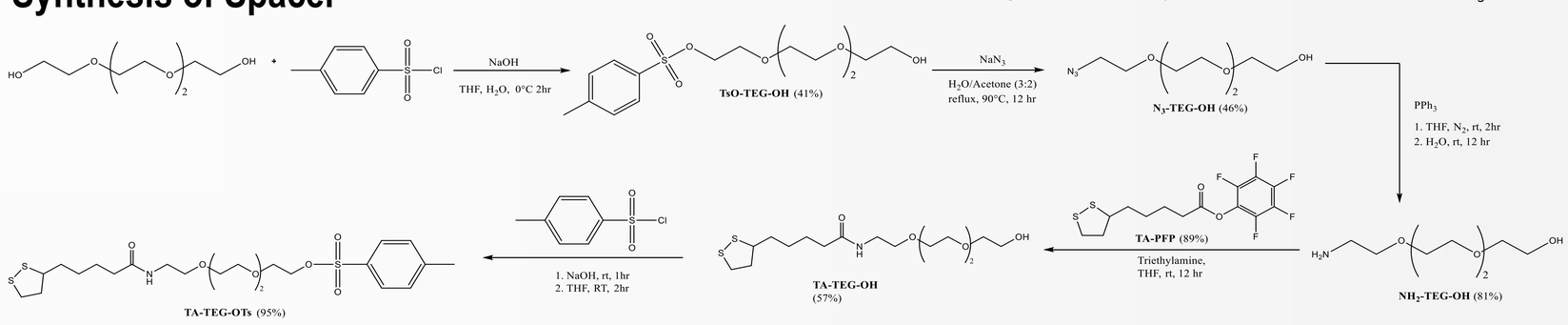
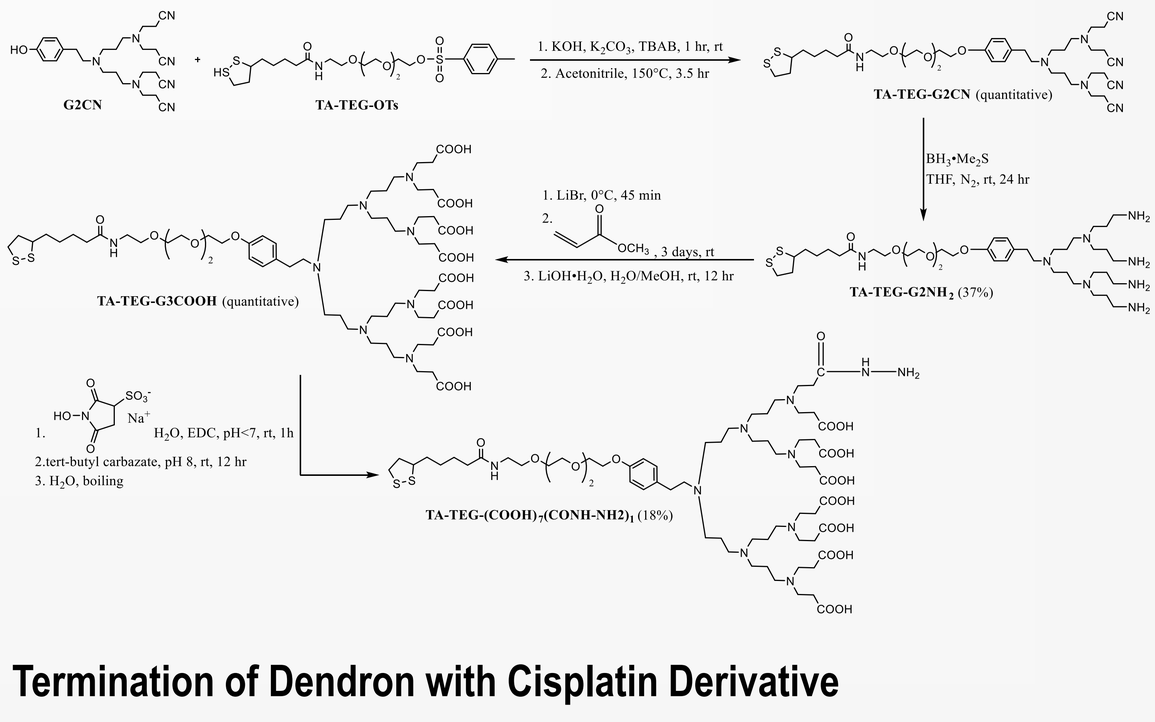


Figure 3. ^{1}H NMR spectrum of G2CN dendron in $CDCl_3$

Synthesis of Spacer



Coupling of Spacer and Dendron & Growth to Third Generation



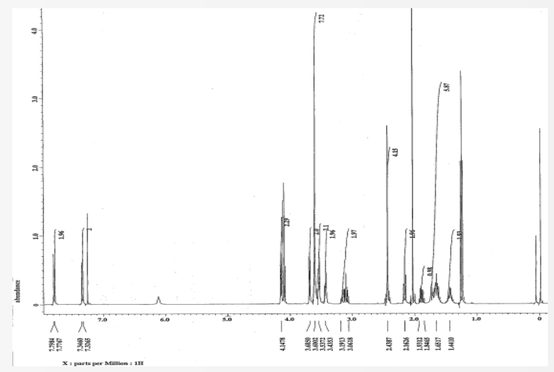


Figure 4. ^{1}H NMR spectrum of TA-TEG-OTs spacer in $CDCl_3$

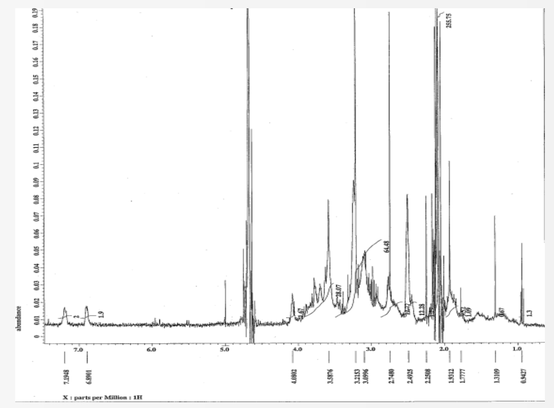
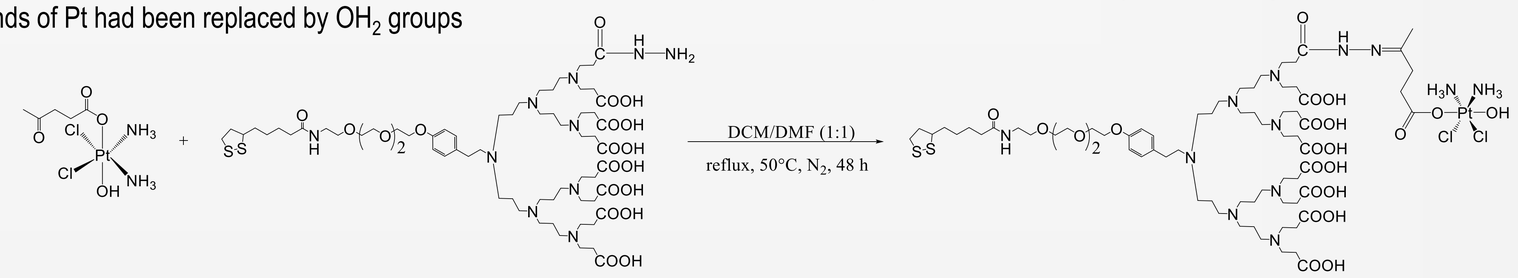


Figure 5. ^{1}H NMR spectrum of TA-TEG-G3NHNH$_2$ in D_2O

Termination of Dendron with Cisplatin Derivative

- NMR showed some broadening of some peaks, suggesting the presence of Pt on the dendron.
- ICP-MS showed the dendron to Pt ratio to be 2.45, meaning that for every 10 dendrons, 4 of them reacted with the cisplatin.
- ESI also confirmed the incorporation of one Pt into the dendron with a peak at 1556 (expected peak at 1591), and showing that the Cl ligands of Pt had been replaced by OH_2 groups



CONCLUSION

The dendrons were successfully synthesized and attached to TEG spacers. However, only one of the eight branches were modified with tert-butyl carbazate, thus the drug was only attached to that branch. Characterization of the final product by ICP-MS and mass spectrometry showed incorporation of Pt into the dendron branches.

FUTURE AIMS

- Optimize synthetic methods and improve the reaction yields
- Attach the completed dendrons to gold nanoparticle cores

ACKNOWLEGEMENTS

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