X-ray Sensitive Micellar Transporters for Controlled Drug Release Assisted by MRI

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Introduction

Current cancer treatments face significant limitations due to the lack of precise drug targeting and the systemic side effects caused by conventional therapies. This project proposes a novel drug delivery system based on self-assembled micelles, activated by ionizing radiation (IR) and monitored using Magnetic Resonance Imaging (MRI), enabling precise control of drug release.

The core of this approach lies in a "radioswitch" molecule introduced by Guesdon[1], that combines an azobenzene photoswitch with an IR-sensitive gadolinium (Gd) chelate. This mechanism facilitates controlled drug release in response to specific stimuli, providing a promising platform for targeted cancer therapy.

This work focuses on the synthesis and characterization of a radioswitch molecule, detailing the stepwise procedures and intermediate validations using NMR spectroscopy, as well as the evaluation of micelle formation through Dynamic Light Scattering (DLS).

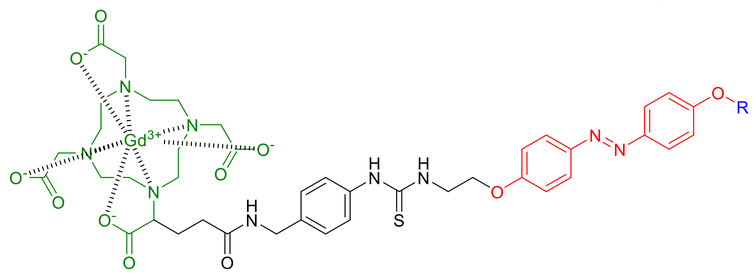
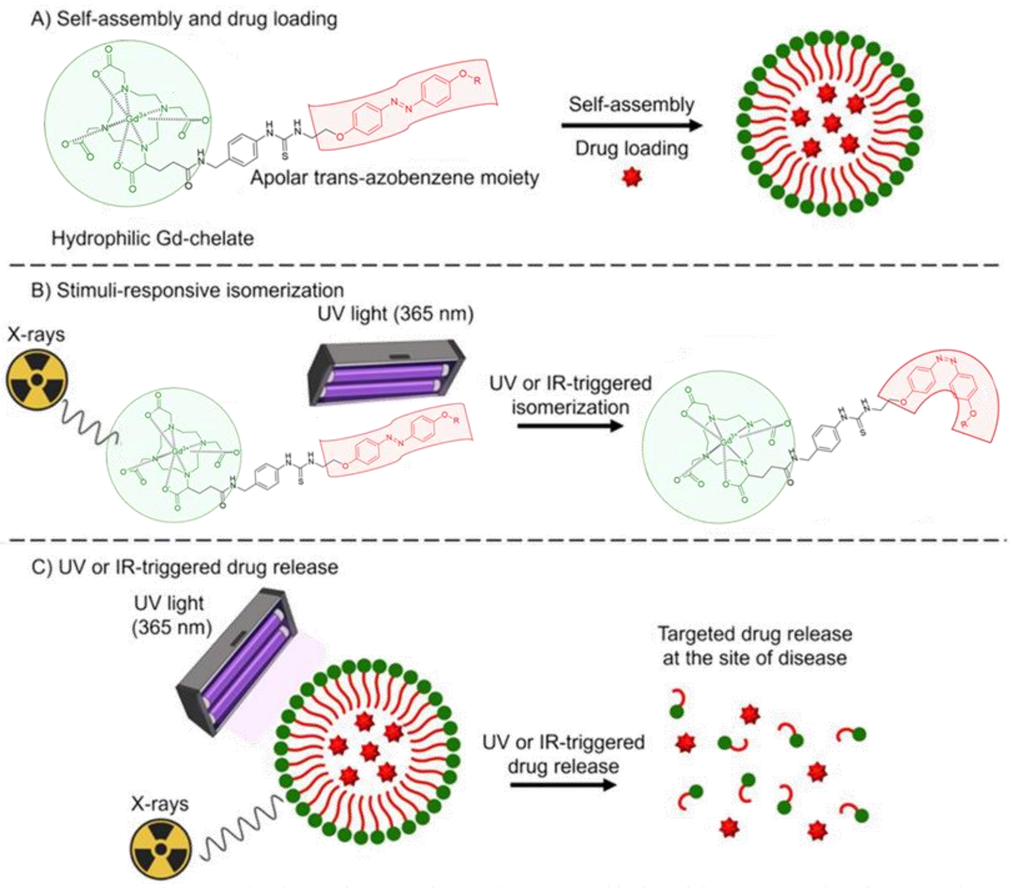


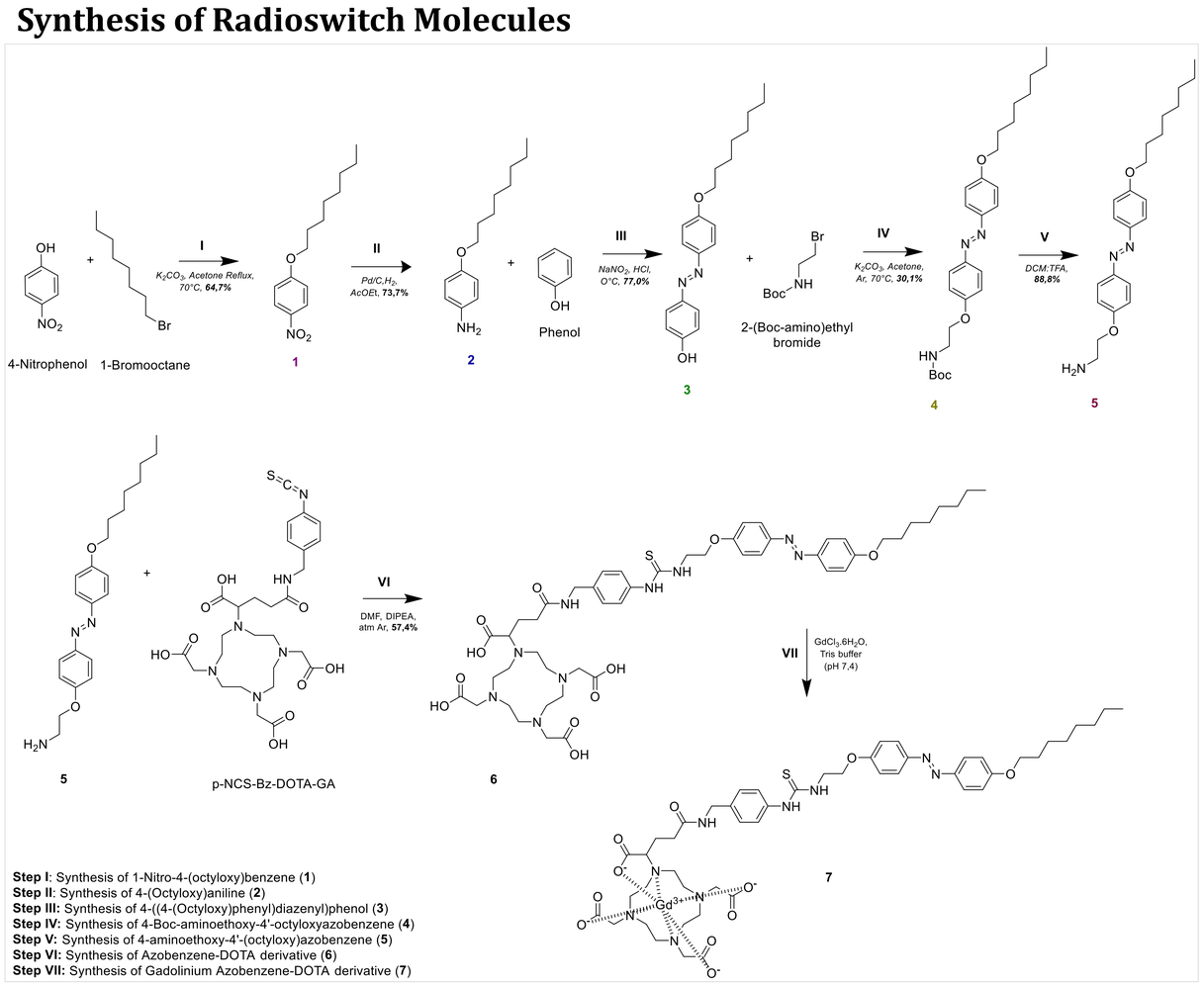
Illustration of the amphiphilic molecule containing (i) an IR-sensitive Gd chelate (green), (ii) an azobenzene photoswitch (red) and (iii) variable hydrophobic chains **R** (blue).



General strategy for the development of UV and IR-triggerable drug delivery systems based on the radioswitch structure, illustrating micelle self-assembly (A), stimuli-responsive isomerization (B), and drug release upon activation (C).

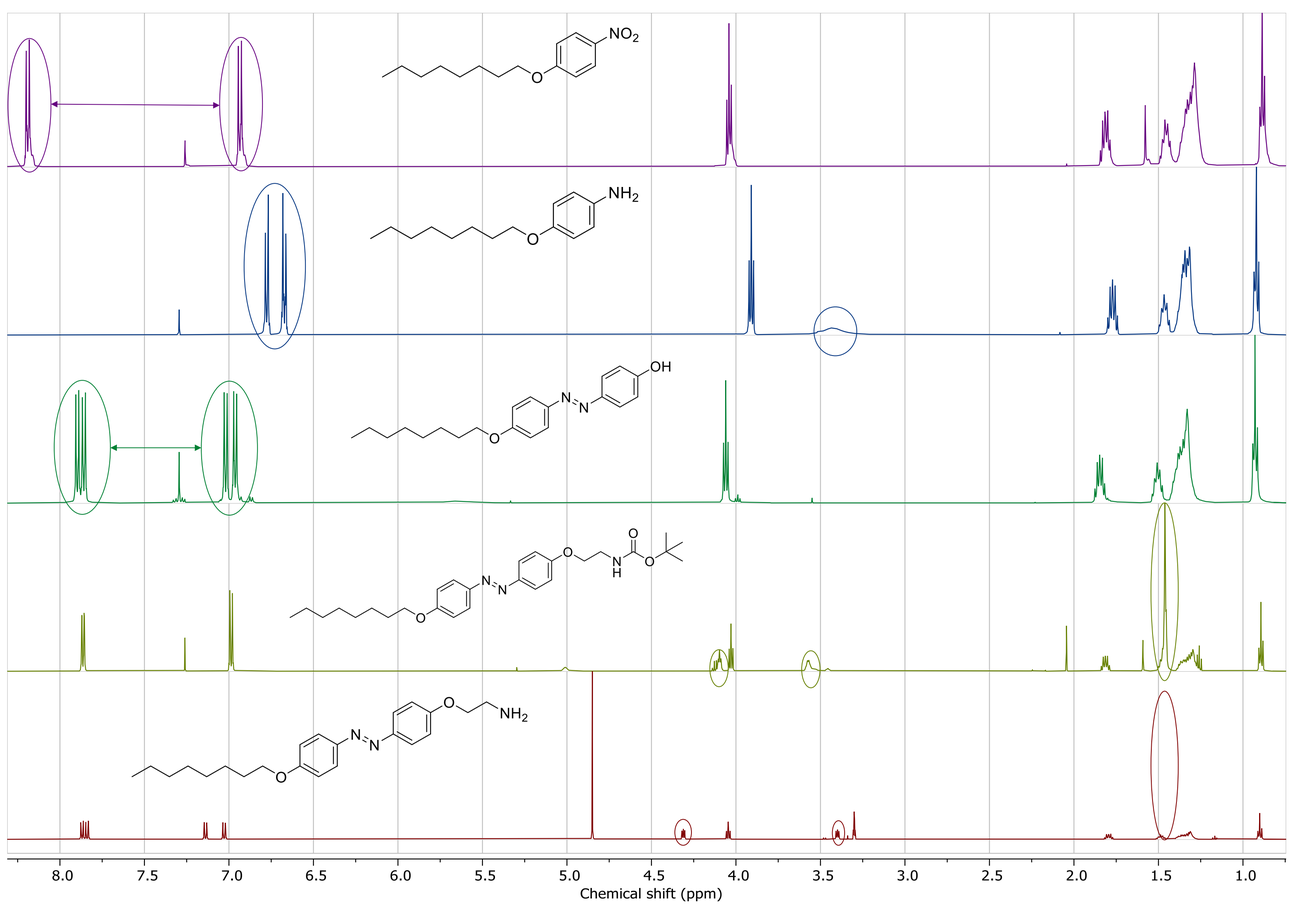
Results

Synthesis of Radioswitch Molecules



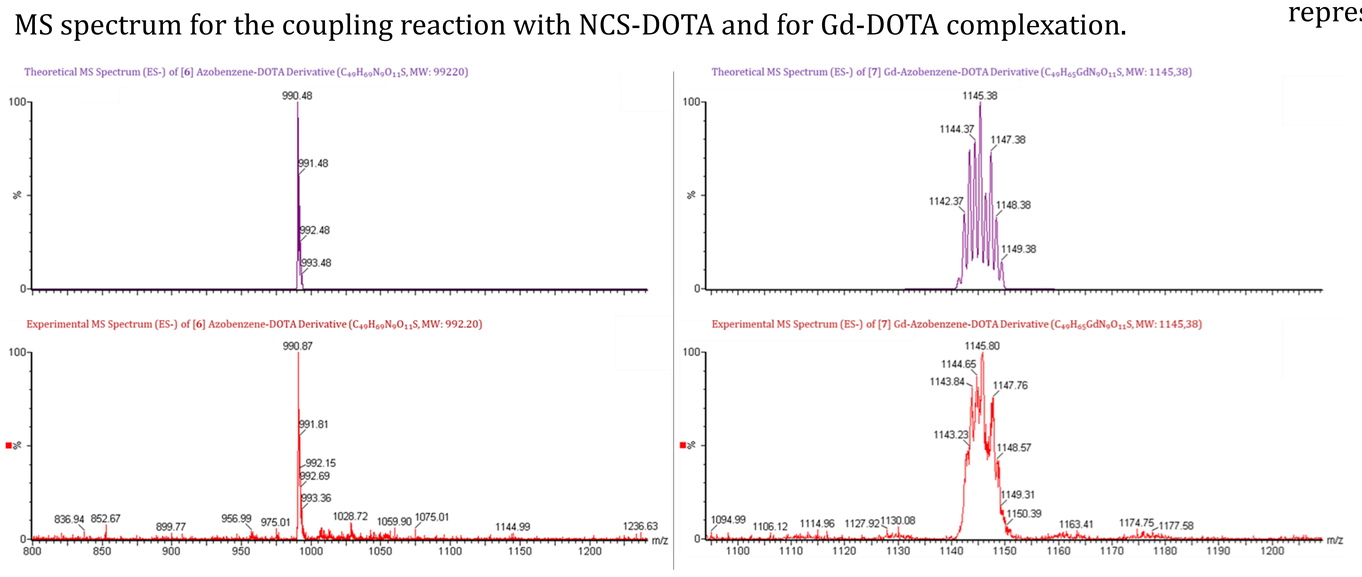
Step I: Synthesis of 1-Nitro-4-(octyloxy)benzene (**1**)
Step II: Synthesis of 4-(Octyloxy)aniline (**2**)
Step III: Synthesis of 4-((4-(Octyloxy)phenyl)diazenyl)phenol (**3**)
Step IV: Synthesis of 4-Boc-aminoethoxy-4'-octyloxyazobenzene (**4**)
Step V: Synthesis of 4-aminoethoxy-4'-(octyloxy)azobenzene (**5**)
Step VI: Synthesis of Azobenzene-DOTA derivative (**6**)
Step VII: Synthesis of Gadolinium Azobenzene-DOTA derivative (**7**)

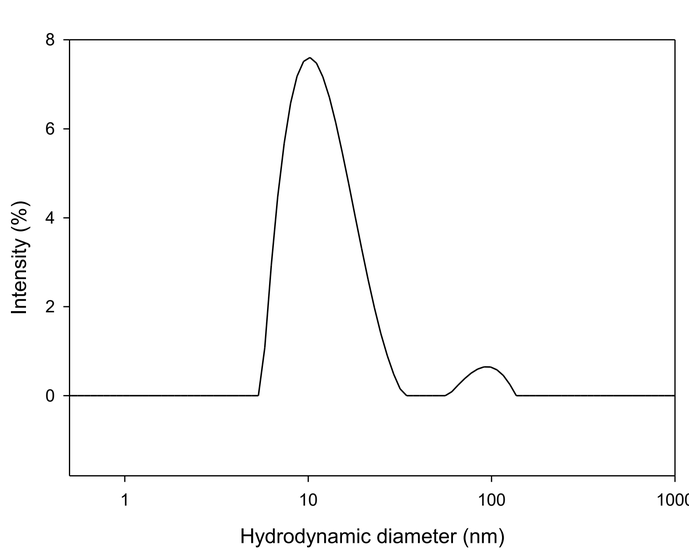
^{1}H-NMR spectra of intermediates compounds.



Dynamic Light Scattering (DLS) analysis of the radioswitch micelles in PBS at 25° C. The primary peak corresponds to micelles with a hydrodynamic diameter of **11.9 ± 1.6 nm**, representing 95.61% of the intensity.

MS spectrum for the coupling reaction with NCS-DOTA and for Gd-DOTA complexation.





Conclusion

The successful synthesis and characterization of radioswitch molecules highlight their potential as dual-function agents for drug delivery and imaging. Each intermediate and final product were validated using ^{1}H-NMR and Mass Spectrometry (MS), ensuring the structural integrity of the final products. Additionally, DLS analyses confirmed the formation of uniform micelles with favorable stability and size properties, paving the way for their application in targeted cancer therapy.

References: 1- A. Guesdon-Vennerie, P. Couvreur, F. Ali et al. Nat Commun, 2022, 13, 4102.
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