Synthesis of Potential Glycosylated Anticancer Compounds

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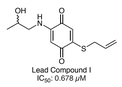
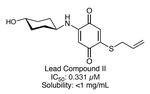
Introduction

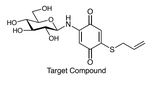
Project I: Based on research published in European Journal of Medicinal Chemistry where different benzoquinone derivatives were synthesized and tested in terms of anticancer activity.[1]

- *S*-allyl substituent was determined to be optimal
- Some amino substituents containing hydroxyl groups were potent, but had low solubility in water

Will using a glycosylamino substituent improve the solubility and ADMET properties of the compound while retaining the potency?


Lead Compound I
IC_{50}: 0.678 μM


Lead Compound II
IC_{50}: 0.331 μM
Solubility: <1 mg/mL

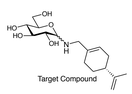

Target Compound

Project II: Based on research published in the Journal of Medicinal Chemistry where perillylglycosides were shown to have improved antiproliferative activity.[2]

- Perillyl alcohol is a plant metabolite shown to be a possible anticancer agent

Will perillylglycosylamines be more effective as anticancer agents than perillyl alcohol?


Perillyl Alcohol


Target Compound

Connection: Adding a glycosylamino substituent to a possible cancer drug to influence the compound's pharmacological or ADMET properties.

- ADMET refers to the Absorption, Distribution, Metabolism, Excretion and Toxicity of a compound

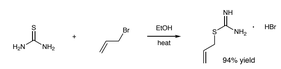
Methods: Organic Synthesis

Methods include the following generalized steps:

1. Setting up a reaction: combining reagents, adding catalysts and/or solvent
2. Monitoring the Reaction
   - TLC, NMR, Mass Spectrometry
3. Purification: isolating the desired product from the mixture
   - Extraction, evaporation under reduced pressure to remove solvent, filtration, flash chromatography, etc.

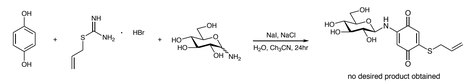
Project I: Synthesis of glucosylamine benzoquinone derivative

Synthesis of *S*-allylisothiuoronium bromide:

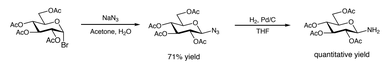


Synthesis of glucosylamine:

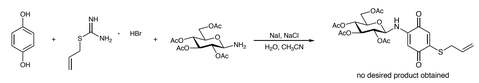
Synthesis of glucosylamine benzoquinone derivative:



Synthesis and reduction of peracetylated glucosyl azide[3]:



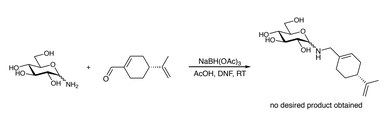
Synthesis of protected glucosylamine benzyoquinone derivative:



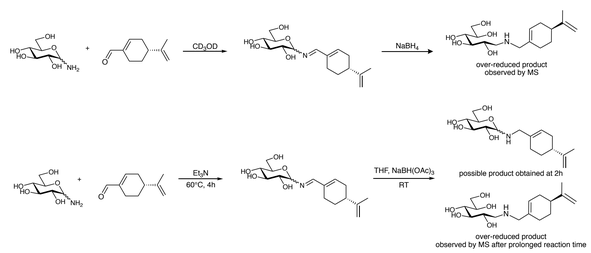
Project II: Synthesis of perillylglucosylamine

Synthesis of glucosylamine:

Synthesis of perillylglucosylamine via Reductive Amination:

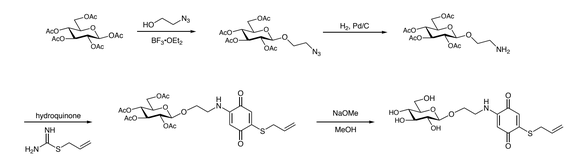


Indirect synthesis of perillylglucosylamine via reductive amination:



Future directions

Project I: Synthesis of benzoquinone derivative containing a carbohydrate with a more reactive amine



Project II: Indirect synthesis of perillylglucosylamine via reductive amination with a shortened reaction time

Both: Synthesize analogues with varying glycosylamines

Future Testing: Both compounds were originally tested against multiple cell lines, but showed promising results against PC3

- PC3 is a prostate cancer cell line

Acknowledgements

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References

1. Zhao, Y.; Lu, Y.; Li, R.; He, J.; Zhang, H.; Wang, X.; Ge, Z.; Li, R. *Eur. J. Med. Chem.* **2018,** *149*, 1-9
2. Nandurkar, N. S.; Zhang, J.; Qing, Y.; Ponomareva, L. V.; She, Q. B.; Thorson, J. S. *J. Med. Chem.* **2014,** *57*, 7478-7484
3. Ibatullin, F. M.; Shabalin, K. A. *Synth. Commun.* **2000**, *30*, 2819-2823