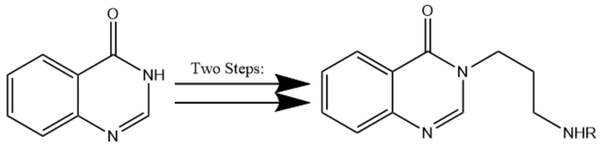
Synthesis of Novel *N3*-alkylamino 4-hydroxyquinazolinones

Alyssa Majurin, Samuel Corioso; Dr. Kelly Kim
Division of Sciences and Mathematics| University of Washington Tacoma

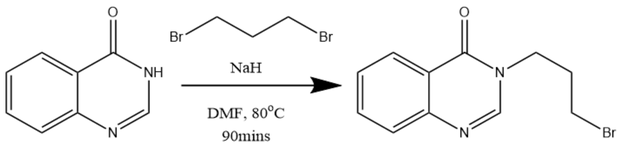
INTRODUCTION

- The quinazolinone scaffold is a privileged structure, which can have potentially bioactive properties such as antibacterial or antifungal activity.
- To explore the therapeutic potential of quinazolinone-containing compounds, our objective was to optimize the synthesis of a diverse array of quinazolinone derivatives to be contributed for further study.
- Our team focused on the diversification of the *N3* position on our starting material quinazolinone, starting with alkylation using a bromoalkene followed by a primary amine to access *N3* – alkylamino quinazolinones

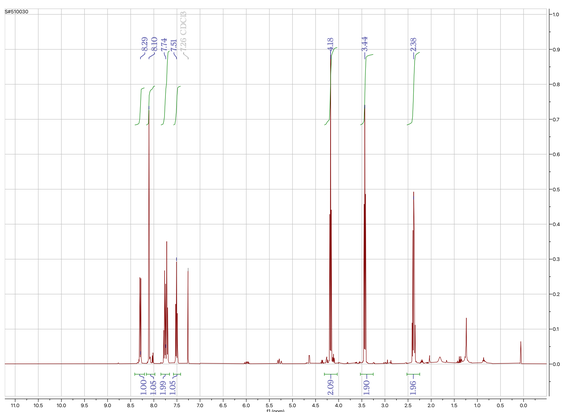


METHODS & RESULTS

Step 1: *N3*-alkylation of 4-hydroxyquinazoline

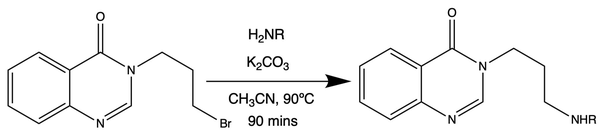


- Synthesized a *N3*-bromoalkyl quinazolinone intermediate through nucleophilic substitution of 1,3-dibromopropane
- Starting material quinazolinone was deprotonated with sodium hydride in solution of dimethylformamide and stirred in a reflux setup with 1,3-dibromopropane at 80°C under nitrogen atmosphere for 90mins
- Product purified by column chromatography
- 60% yield



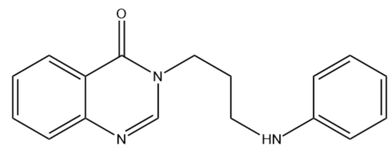
^{1}H-NMR ($CDCl_3$, 400 MHz) for the 3N-bromoalkane quinazolinone intermediate used as starting material for our final products.

Step 2: Amination of *N3*-alkylated quinazolinone

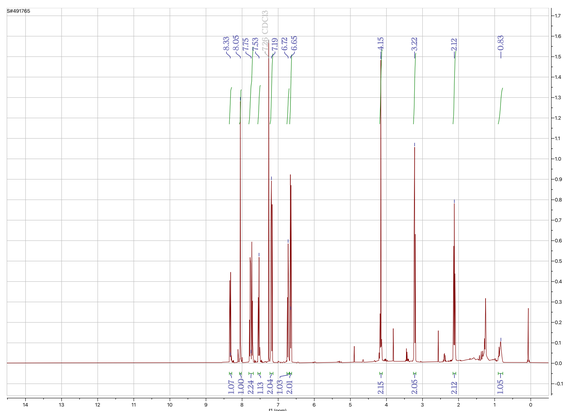


- Synthesized a 3*N*-alkylamino quinazolinone as a final product
- H_2NR reagent was deprotonated by potassium carbonate in solution of acetonitrile with intermediate 3N-bromoalkane quinazolinone in a reflux setup under nitrogen atmosphere at 90°C for 90mins
- Acetonitrile was evaporated from the reaction mixture and the final product was purified by column chromatography
- Both crude and purified product samples were collected for structure determination using ^{1}H-NMR

Amination Product #1: Aniline Substitution

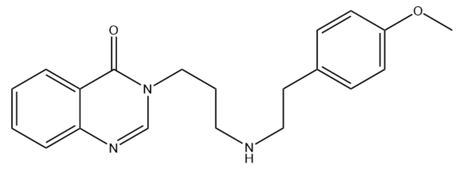


- 12% yield
- Reaction did not reach completion
- TLC results revealed that the crude product mixture had much leftover starting material and aniline
- The product of aniline substitution may have been produced at a higher yield with increased reaction time.



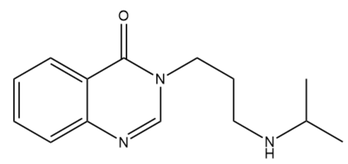
^{1}H-NMR ($CDCl_3$, 400 MHz) for our expected product following aniline substitution.

Amination Product #2: 4-Methoxyphenethylamine Substitution

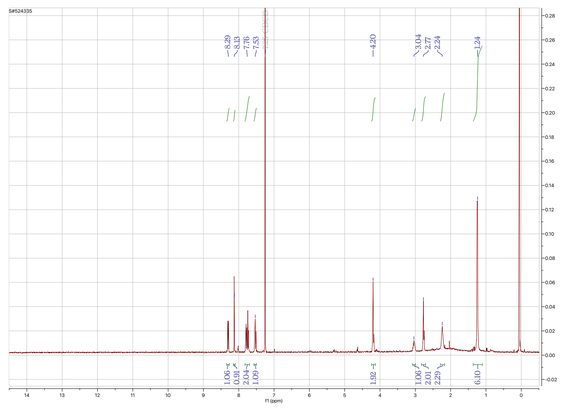


- Percent yield not available, intended product not formed
- Reaction did not reach completion, left mostly unreacted starting material
- ^{1}H-NMR results not available due to no purified sample matching expected product values
- It is possible that the electron-rich structure of 4-methoxyphethylamine may have prevented this reaction from occurring.

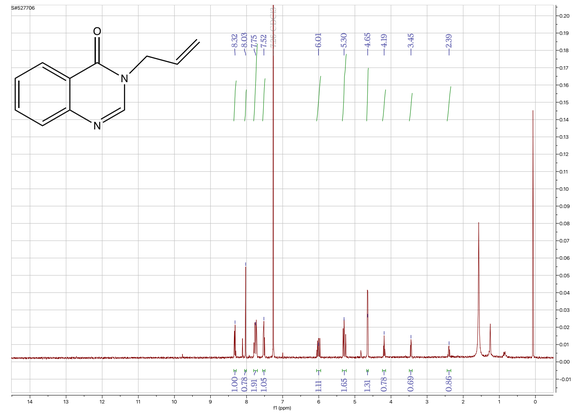
Amination Product #3: Isopropylamine Substitution



- Percent yield not determined (purified product not isolated)
- Reaction did not proceed to completion- TLC showed two products formed
- Based on analysis of crude ^{1}H-NMR, the major structure was the desired substitution product
- Compound purified and isolated from column was an elimination side product- different purification method is necessary



^{1}H-NMR ($CDCl_3$, 400 MHz) spectrum of crude product following substitution using isopropyl amine.



^{1}H-NMR ($CDCl_3$, 400 MHz) for the isolated elimination side product isolated from reaction with isopropylamine

CONCLUSIONS

- Identified conditions for reliably synthesizing *N3*-bromoalkyl quinazolinones.
- Further investigation required for optimization of alkylamino quinazolinone synthesis
- Steric and electronic properties impact the outcome of substitution reactions of 4-quinazolinones

ACKNOWLEDGEMENTS

- We would like to thank Dr. Kelly Kim for her mentorship and guidance in designing and carrying out the experiments.
- We would also like to thank the University of Puget Sound for providing access to their NMR spectrometer for experimental analysis.

REFERENCES

Liu J-F, Wilson CJ, Ye P, Sprague K, Sargent K, Si Y, Beletsky G, Yohannes D, Ng S-C. 2006. Privileged structure-based quinazolinone natural product-templated libraries: Identification of novel tubulin polymerization inhibitors. Bioorganic & Medicinal Chemistry Letters. 16(3):686–690. doi:10.1016/j.bmcl.2005.10.022.

Pitta E, Balabon O, Rogacki MK, Gómez J, Cunningham F, Joosens J, Augustyns K, Van Der Veken P, Bates R. 2017. Differential characterization using readily accessible NMR experiments of novel N- and O-alkylated quinolin-4-ol, 1,5-naphthyridin-4-ol and quinazolin-4-ol derivatives with antimycobacterial activity. European Journal of Medicinal Chemistry. 125:890–901. doi:10.1016/j.ejmech.2016.10.014.

Špulák M, Novák Z, Palát K, Kuneš J, Pourová J, Pour M. 2013. The unambiguous synthesis and NMR assignment of 4-alkoxy and 3-alkylquinazolines. Tetrahedron. 69(6):1705–1711. doi:10.1016/j.tet.2012.12.031.

Wang X, Chai J, Kong X, Jin F, Chen M, Yang C, Xue W. 2021. Expedient discovery for novel antifungal leads: 1,3,4-Oxadiazole derivatives bearing a quinazolin-4(3H)-one fragment. Bioorganic & Medicinal Chemistry. 45:116330. doi:10.1016/j.bmc.2021.116330.

Wang L, Dai F, Zhu J, Dong K, Wang Y, Chen T. 2011. Synthesis and Antibacterial Activities of Pleuromutilin Derivatives with Thiazole-5-Carboxamide and Thioether Moiety. Journal of Chemical Research. 35(5):313–316. doi:10.3184/174751911X13057375208346.