UNIVERSITY of WASHINGTON TACOMA

Progress toward the Synthesis of Novel 3*N*-Alkylamino Quinazolinones

Katrina Nguyen and Dr. Kelly Kim

Introduction

Quinazolinones are compounds with versatile binding properties and have been discovered to possess medicinally beneficial biological activities such as antibacterial, anticarcinogen, antiviral, and antifungal properties (Wang et al. 2021).

Project Aim: Based on the medicinal properties of quinazolinone-containing molecules, we aim to synthesize *N*-alkylated quinazolinones for further study and explore the efficiency of quinazolinone alkylation reactions.

Hypothesis: Alkylation using dihalide reagents with longer carbon linker lengths will proceed with higher yield due to reduced steric hindrance.

Approach: We sought to attach amine chemical groups to quinazolinones using two reactions featuring a dihalide N-alkylation and a primary amine substitution (**Figure 1**). The conditions of our reactions varied with carbon linker length reagent length to test the hypothesis.

Methods

- Starting materials were stirred in solvent and heated to reflux for 2 hours under nitrogen gas.
- Alkylation of quinazolinones was achieved using a base and an alkyl halide or dihalide reagent.
- Silica gel TLC plates were spotted with starting material, crude product, and a mix of both to determine if the reaction went to completion using UV light visualization.
- The crude product was isolated using liquid-liquid extraction and vacuum filtration, and then purified by column chromatography.
- Column chromatography fractions were collected and spotted on silica gel TLC plates and visualized using UV light.
- Fractions containing compounds were collected and evaporated using the rotary evaporator.
- ^{1}H NMR samples of the fractions were made using chloroform-D and analyzed to obtain NMR spectra.

Project Overview

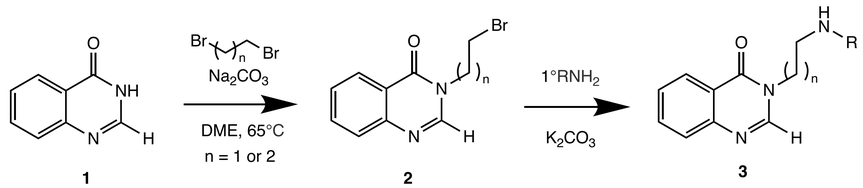


Figure 1. Dihalide *N*-alkylation of quinazolinones and subsequent alkylation of *N*-alkylated quinazolinones with alkyl amines.

Results

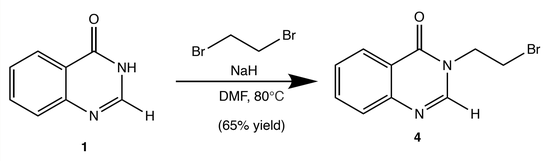
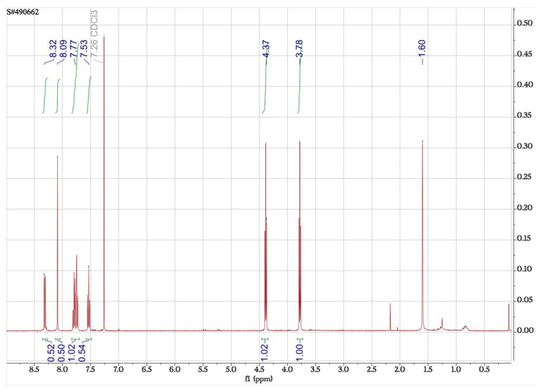


Figure 2. *N*-alkylation of quinazolinone **1** with 1,2-dibromoethane and ^{1}H NMR of product **4** ($CDCl_3$, 400 MHz)



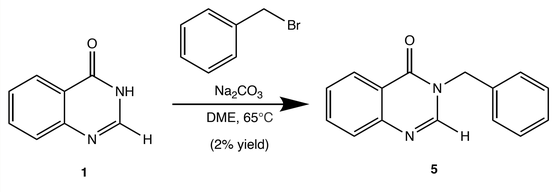
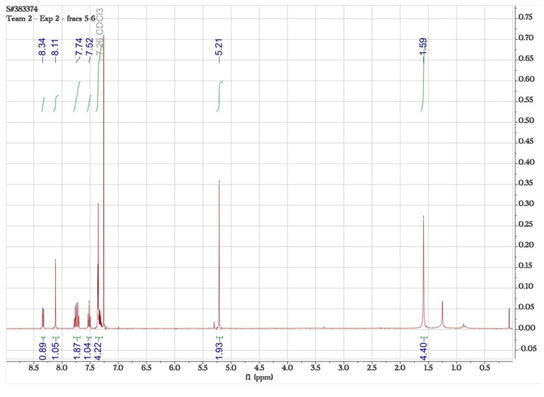


Figure 3. *N*-alkylation of quinazolinone **1** with benzyl bromide and ^{1}H NMR of product **5** ($CDCl_3$, 400 MHz)



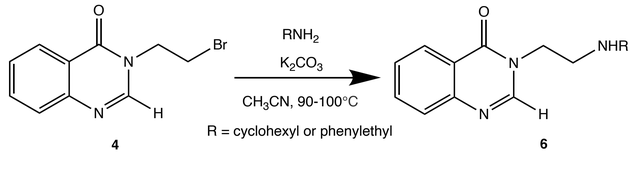


Figure 4. Second alkylation of *N*-alkylated quinazolinone **4** with primary amine. Complex mixture formed.

Conclusions

We successfully performed *N*-alkylation of quinazolinones using dihalide reagents of varying carbon linker lengths (**Figure 2**)**.** However, as seen with the benzyl bromide reaction, *N*-alkylation reactions of quinazolinones with short carbon linked dihalides result in low yield, decreasing the efficiency of the alkylation (**Figure 3**).

We were unable to successfully perform a second alkylation of *N*-alkylated quinazolinones with primary alkyl amines such as cyclohexylamine or phenylethylamine (**Figure 4**)**.** An elimination reaction may have occurred rather than the targeted substitution reaction. Reaction conditions were not varied for the second alkylation reactions due to time constraints; however, differing reaction conditions such as stronger nucleophiles and different solvent systems could possibly result in the targeted substitution reaction.

The data obtained supports the hypothesis but more research is required for verification. This subproject was incomplete since the target 3*N*-alkyl amino quinazolinones were not obtained.

Future Work

Further experimentation should be carried out with different reaction conditions to perform subsequent *N*-alkylations to attach chemical groups to obtain the target *N*3-alkylamino quinazolinones.

- varying electrophile strength
- temperature
- base identity/strength
- solvent identity

Exploration with substitution of different chemical groups onto quinazolinones should also be considered to further explore the medicinal possibilities of quinazolinones.

References

Liu et al. 2006. Privileged structure-based quinazolinone natural product-templated libraries: Identification of novel tubulin polymerization inhibitors. Bioorganic & Medicinal Chemistry Letters. 16(3):686–690. doi:https://doi.org/10.1016/j.bmcl.2005.10.022.

Špulák et al. 2013. The unambiguous synthesis and NMR assignment of 4-alkoxy and 3-alkylquinazolines. Tetrahedron. 69(6):1705–1711. doi:https://doi.org/10.1016/j.tet.2012.12.031.

Wang et al. 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:https://doi.org/10.1016/j.bmc.2021.116330. [accessed 2024 Feb 14]. https://www.sciencedirect.com/science/article/abs/pii/S0968089621003382?via%3Dihub.

Zhang et al. 2009. Synthesis and antibacterial activities of pleuromutilin derivatives. Chinese Chemical Letters. 20(1):29–31. doi:https://doi.org/10.1016/j.cclet.2008.09.009.

Special Thanks to

Dr. Kelly Kim for meticulously directing the project.

Jessica Lowry and all other undergraduate researchers who have contributed to this body of data.

The University of Washington Tacoma science department for making an amazing environment in which to research, work, and learn.

University of Puget Sound for providing data analysis equipment.