



Abstract

The quinolinone core is embedded in many biologically active products that have significant properties like conferring anti-cancer benefits. However, methods for synthesizing selectively 7-substituted quinolinones are limited and often require harsh conditions, such as the use of palladium catalysts or concentrated sulfuric acid (e.g. H₂SO₄), which can limit substrate scope and prevent cyclization for some compounds, to the desired quinolinone product. This study explores the use of boron trifluoride etherate (BF₃OEt₂) as a milder Lewis acid alternative for the cyclization of a 7-methoxy anilide intermediate in a two-step acylation–cyclization synthetic route. Reaction conditions, including Lewis acid equivalents, reaction time, temperature, and solvents, were systematically screened to evaluate their impact on product formation and improving yields. BF₃OEt₂ was found to promote cyclization to the desired quinolinone product, although yields remained limited under the conditions tested. Among the solvents examined, 1,4-dioxane produced the highest observed yields, indicating that solvent choice plays an important role in reaction efficiency. Overall, this work demonstrates that BF₃OEt₂ is a viable alternative to strong Brønsted acids and provides insight into conditions that may improve the synthesis of 7-substituted quinolinones under milder conditions. Future work could explore additional ethereal solvents to further optimize the BF₃OEt₂-catalyzed cyclization, improve yields and purity, and extend this method to other substrates, including the previously studied 7-cyano anilide.

Background & Knowledge Gap

Quinolinones are biologically important heterocyclic compounds commonly used as scaffolds in drug design.

- embedded in biologically active molecules such as natural products and enzyme inhibitors
- support functionalization at multiple positions on the ring system.
- confer biological benefits like anti-malarial, anti-tumor and anti-cancer

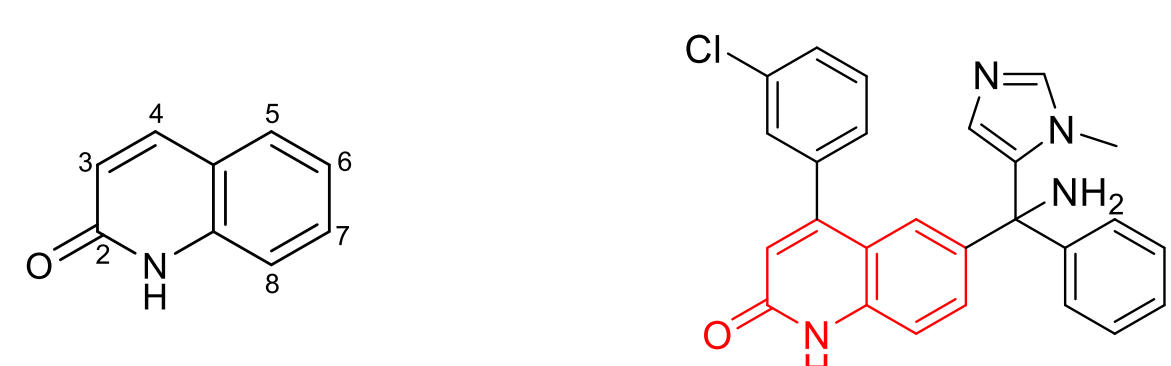


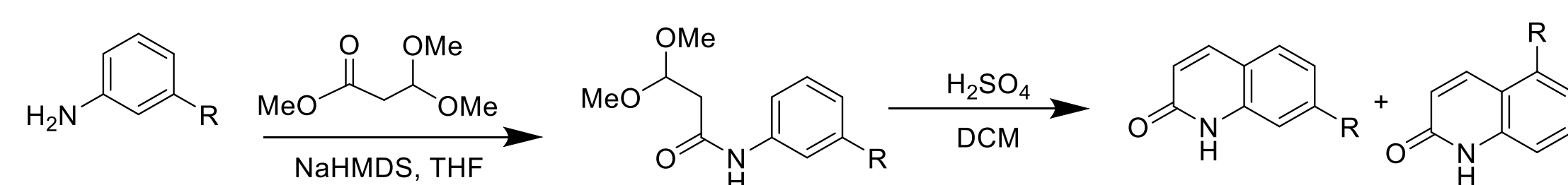
Figure 1: quinolinone core (left), anti-cancer drug Tipifarnib (right)

- Selective 7-position substitution is difficult to achieve
- 7-substituted quinolinones remain underrepresented in literature
- Limits access to biologically relevant derivatives
- Motivates development of improved synthetic methods

Rationale for Lewis Acid catalyst

Existing methods require harsh conditions;

- use of strong acids, metal catalysts etc.



Scheme 1: Martin lab synthesis (adapted from Zaugg et al)

Lewis acids offer a milder alternative for promoting cyclization reactions

- Avoid harsh acidic conditions (e.g., strong Brønsted acids)
- Improve functional group tolerance and substrate scope
- There is potential to improve selectivity and access to 7-substituted derivatives

To address these limitations, this study investigates BF₃OEt₂ acid-mediated cyclization as a strategy for synthesizing 7-substituted quinolinones under milder conditions.

Research Aims

Goal;

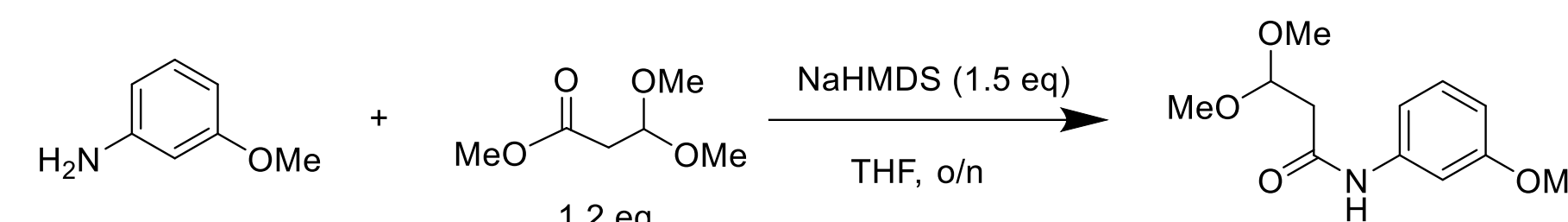
The long-term goal of this research is to develop a predictable and efficient synthetic route to 7-substituted quinolinones using a Lewis acid–promoted approach.

Preliminary work was begun with the Lewis acid; BF₃OEt₂. Reaction conditions were screened to identify effective and reproducible systems.

Specific Aims

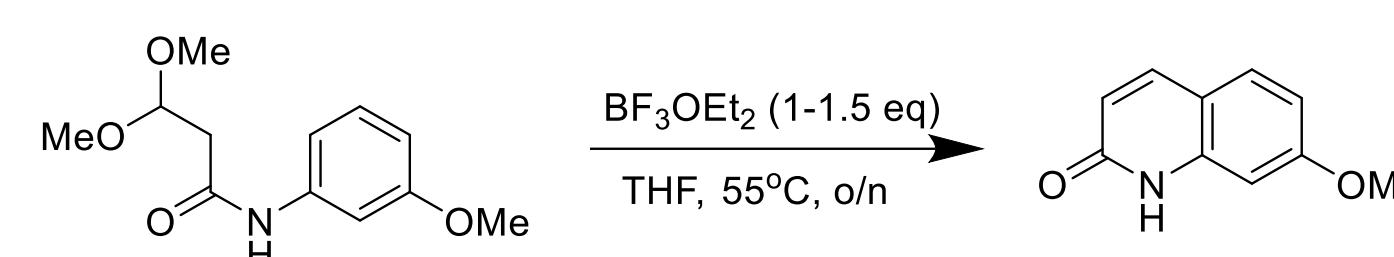
Aim 1: *Synthesis of 7-methoxy-anilide intermediate to be used as starting material.*

- acylation to form intermediate



Aim 2: *Evaluate the efficacy of BF₃OEt₂ in promoting the regioselective cyclization of anilide intermediates to 7-substituted quinolinones.*

- varying reaction conditions towards optimization of this route



Results

The reaction conditions for the cyclization reaction (Aim 2) were changed according to the table below

	Reaction screens	% yield
Equivalents of BF ₃ OEt ₂	1 equiv	16%
	1.5 equiv	11%
Time course	4 hours	10-13%
	room temp	0%
Temperature	55°C	22%
	65°C	0%
Solvents	THF	21%
	toluene	4%
	DMF	trace
	1,4- dioxane	30%

- From previous work, yields were consistently 25%
- Reaction yields remained modest under the conditions tested
- 1,4-dioxane shows promising results (ethereal solvent)

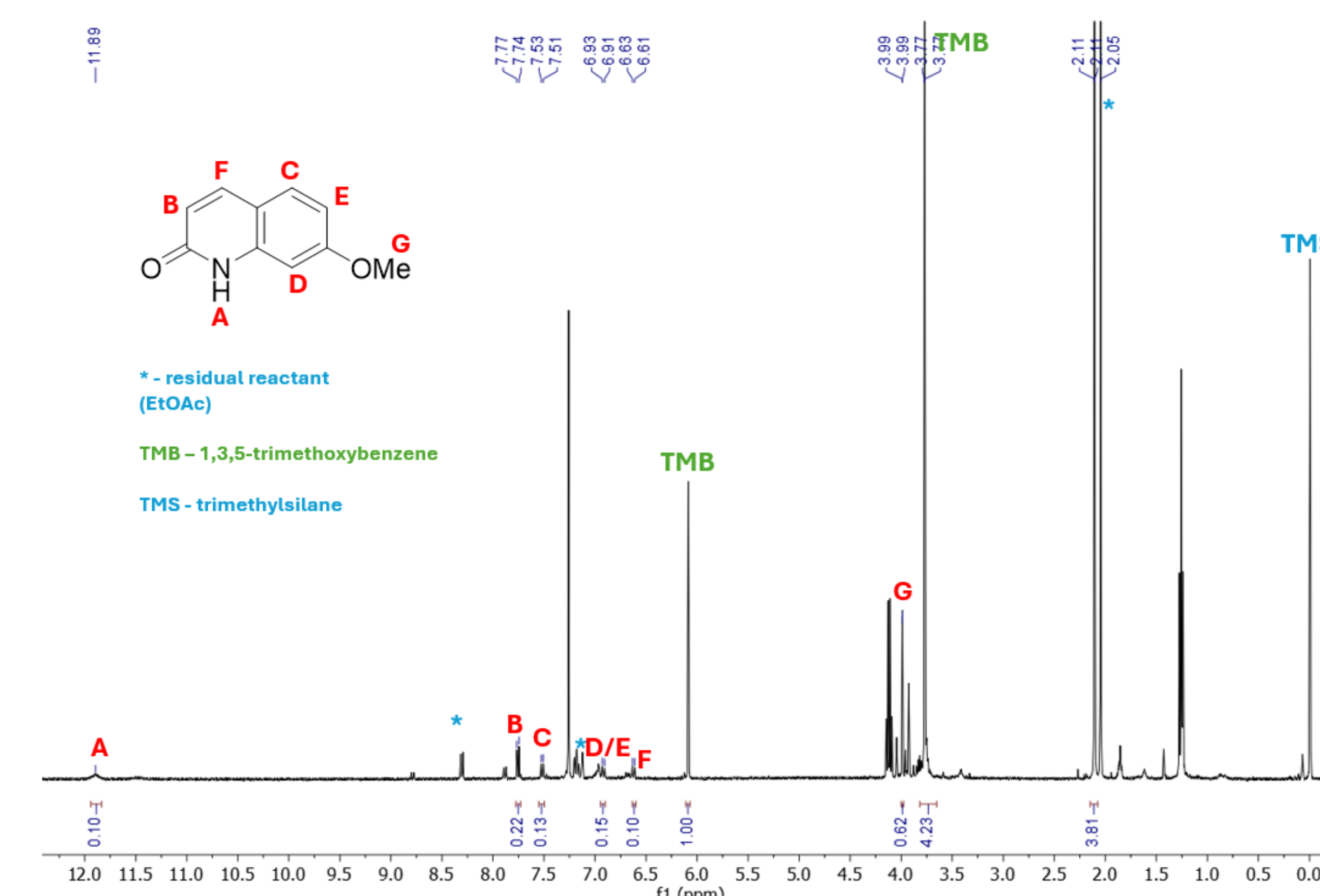


Figure 2: NMR spectra of crude methoxy quinolinone product

- NMR confirms presence of desired quinolinone product
- Impurities from residual solvent from reaction workup
- Some diagnostic peaks present for regioisomeric product; 5-substituted quinolinone

Future Directions

To build directly on this work, the next steps for a future study could include:

- Extend BF₃·OEt₂ conditions to 7-cyano anilide (substrate scope)
- Evaluate higher- temperature conditions in 1,4-dioxane (> 80 ° C)
- Screen additional ether-based solvents (Et₂O, MTBE, Bu₂O) to evaluate effects on reaction efficiency

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