



Synthesis of Poly-Phenolic Derivatives and Evaluation for Anti-Bacterial and Anti-Fungal Activity

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Introduction

The biological activities of curcumin and resveratrol, two common poly-phenolic compounds present in everyday ingredients, have been quite thoroughly explored, although the quality and quantity of said activities is limited. This project seeks to explore how modifications to various functional groups affect each compound's bioactivity. A library of derivatives are produced and tested for anti-bacterial and anti-fungal activity. Targets for modification on each compound were chosen to create a potentially more potent drug against target microorganisms. However, the importance of maintaining chemical stability of novel molecules also played a factor in their design.

Background

Curcumin

- Aliphatic alkylation of phenolic alcohols is proposed as a means disrupting cell membrane activity. While mono-alkylation is performed, di-alkylation creates a more symmetric molecule, and may yield better results. Alkylation is performed with butyl, octyl, and hexadecyl carbon chains to determine the influence of increasing lengths on activity.
- Cyclization of the 1,3-diketone functional groups is proposed to better stabilize the compound. Keto-enol tautomerization of this group commonly occurs at pH levels greater than 6.5 and reduces the compound's bioactivity¹. Pyrazole and oxazole derivatives are to be synthesized, and similarly alkylated at the phenolic alcohols and central carbon.

Resveratrol

- To maintain some form of symmetry, only two of the three phenolic alcohols of resveratrol are to be alkylated. While all three sites may be converted, current laboratory work and structure-activity relationships indicate a decrease in activity.
- In order to create the necessary resveratrol derivatives, a Wittig reaction must be performed with an aldehyde and phosphonium ylide. A protective group is required on the phenolic alcohol that remains unalkylated.

Results

- Many of the curcumin derivatives have been synthesized in acceptable yield. However, the resveratrol synthetic pathway forming compound **14** produced both *E*- and *Z*- isomers. Because the *Z*- isomer is biologically inactive, a separate pathway was researched, and produced solely the *E*- isomer.
- Current bioactivity tests have been performed only on curcumin, **2**, **5**, and **8** against *Escherichia coli* and *Staphylococcus aureus*. At concentrations of 10 µg/mL in water, each compound unexpectedly exhibited no measurable activity, counter to established reports². Solvent and concentration modifications are being studied to determine how more desirable results can be obtained.

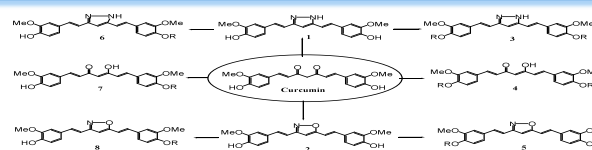
Conclusion

As the research process continues, the library of poly-phenolic derivatives will change based upon results of bioactivity tests. It should be noted that until appropriate concentration and solvent conditions are found that produce sufficient biological activity, tests will not be expanded past the use of *E. coli* and *S. aureus*.

References

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Methodology

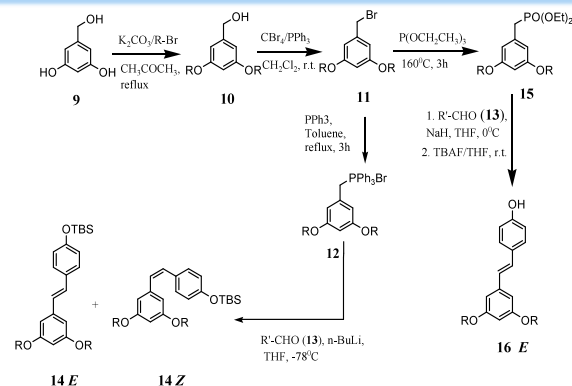


Synthesis of Compounds 1-2

Hydroxylamine hydrochloride/Hydrazine hydrate (1.1 equiv) and acetic acid (10 ml) was used for synthesis of **1** and **2** respectively.

Synthesis of Compounds 3-8

1-Bromobutane/ 1-bromooctane/ 1-bromohexadecane (2 equiv. for **3-5** and 1 equiv. for **6-8**) and K₂CO₃ (2 equiv. for **3-5** and 1 equiv for **6-8**) in dry acetone (10 mL) was used.



Synthesis of Compound 13

4-Hydroxybenzaldehyde was dissolved in CH₂Cl₂ and cooled to 0 °C. *tert*-Butyldimethylsilyl chloride (1.2 eq.) and imidazole (3 eq.) were added. The solution was allowed to warm to room temperature for 5 hr.

Chemistry

Compound **14** was isolated as mixture of *E*- and *Z*- isomers and could not be separated. A separate reaction scheme utilizing a different phosphonium reagent yielded exclusively compound **16**, the *E*- isomer.