Towards Rosin Materials for Environmental and Pharmaceutical Applications

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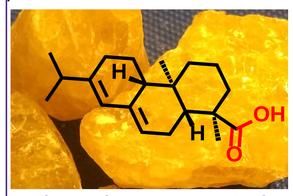
Introduction

Industrial environments are prevalent in many countries, and as a result, around the globe. However, there are issues that arise from the establishment of these many factories, especially those involved with pharmaceutical production, one serious concern pertaining to water contamination due to the presence of heavy metals (Hg, Pb, Ni, etc). Research has been performed to remove these heavy metals from being released into the environment, but there is still a need for an environmentally friendly ligand for removal; one solution uses biorenewable, biodegradable, and environmentally conscious materials capable of binding to the heavy metals and extracting them from various mediums. Other concerns targeted at the pharmaceutical industry consist of poor water dissolution and solubility of many drugs. One way to address this issue is through the prodrug strategy to eliminate disadvantages of solid state active pharmaceutical ingredients (APIs).

The chemical modifications of *Imidazole heterocycle* can lead to *imidazole-2-thione* or *imidazolium salts.* These salts form ligands that in turn, form complexes with heavy metals.



The main component of rosin: *abietic acid*

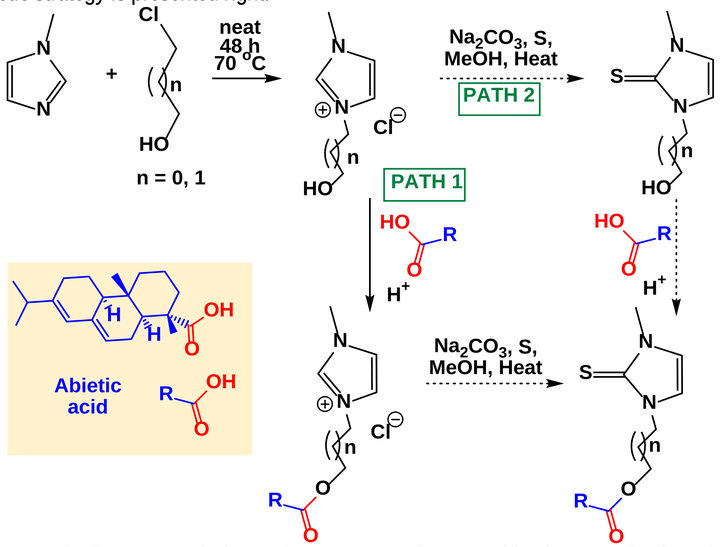
Rosin, a biodegradable, bioavailable material used as a binding agent in pharmaceutical tablets. It is comprised of *abietic acid* (left). This compound contains a carboxylic acid functional group (red) that can undergo an esterification reaction with compounds containing an alcohol functional group. This would permit one to incorporate the imidazole moiety into rosin based materials (such as beads, films, fibers) leading to the synthesis of biodegradable rosin based ligands for removal of heavy metal materials and for controlled release in APIs to promote long term stability.

Objective

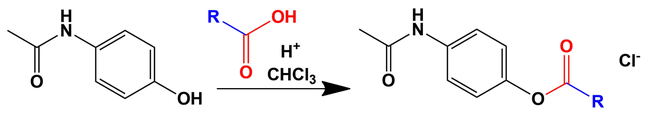
Here we present our efforts towards developing functionalized rosin esters as bio-renewable, biodegradable ligands for removal of heavy metals from the environment, and as potential prodrug delivery systems.

Synthetic Strategy

The research presented here focuses on the synthesis of new rosin ligands that contain in their structures the imidazole moiety needed for the removal of heavy metals. The proposed synthetic strategy is presented right.



The method presented here focuses on the esterification synthesis of APIs (acetaminophen) with abietic acid to improve water solubility and overall release of the drug. The proposed strategy is pictured below.

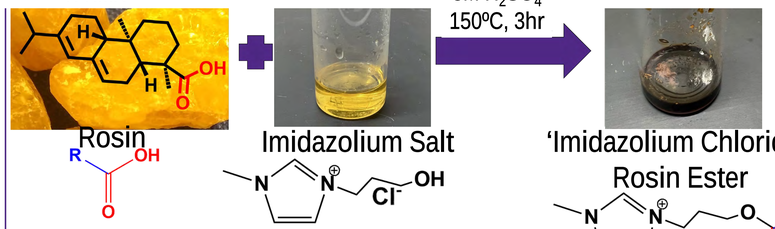


Experimental Results

Synthesis of Rosin Ester

The synthesis of the rosin ester was achieved in two steps:

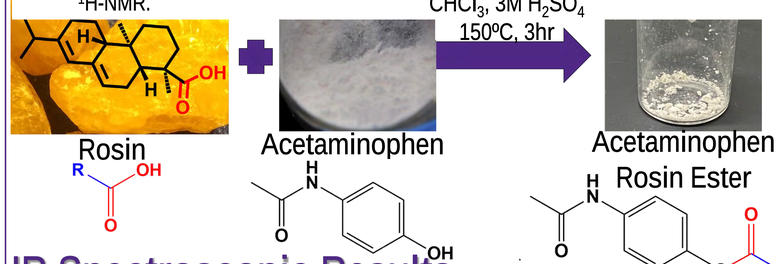
- *Step 1*: A mixture of a 1:1.1 molar ratio of N-methylimidazole and 3-chloropropanol was stirred for 48 hours at 60 ℃ to form the corresponding imidazolium salt.
- *Step 2*: A mixture of 1:1 molar ratio of the imidazolium salt from Step 1 and rosin was stirred for 3 hr at 150 ℃ in the presence of 3M H_2SO_4 to form the rosin based esters.
- Purity of synthesized compounds and completion of the reaction was determined by ^{1}H-NMR.



Synthesis of Acetaminophen Ester

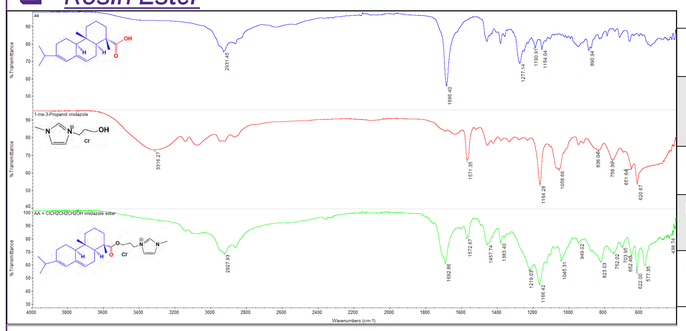
The synthesis of the acetaminophen ester was achieved in two steps:

- *Step 1*: A mixture of a 1:1 molar ratio acetaminophen and abietic acid was dissolved in 5mL of $CHCl_3$ with 3M H_2SO_4 at 100ºC and underwent esterification
- Purity of synthesized compounds and completion of the reaction was determined by ^{1}H-NMR.



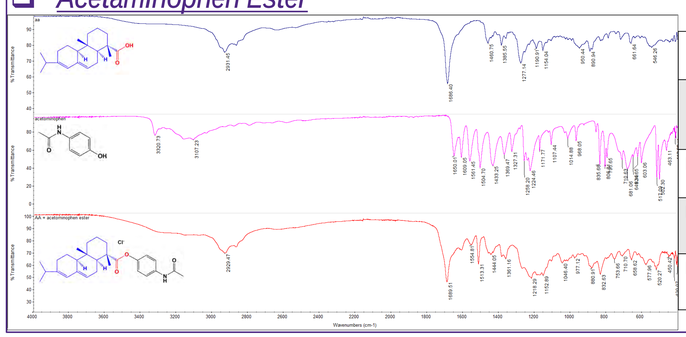
IR Spectroscopic Results

Rosin Ester



Peak Value (product)	Identity
Absence of 1385	Loss of O-H bend
Presence of 1692	Formed C=O
Presence of 1219	Formed C-C-O
Presence of 1045	Formed O-C-C

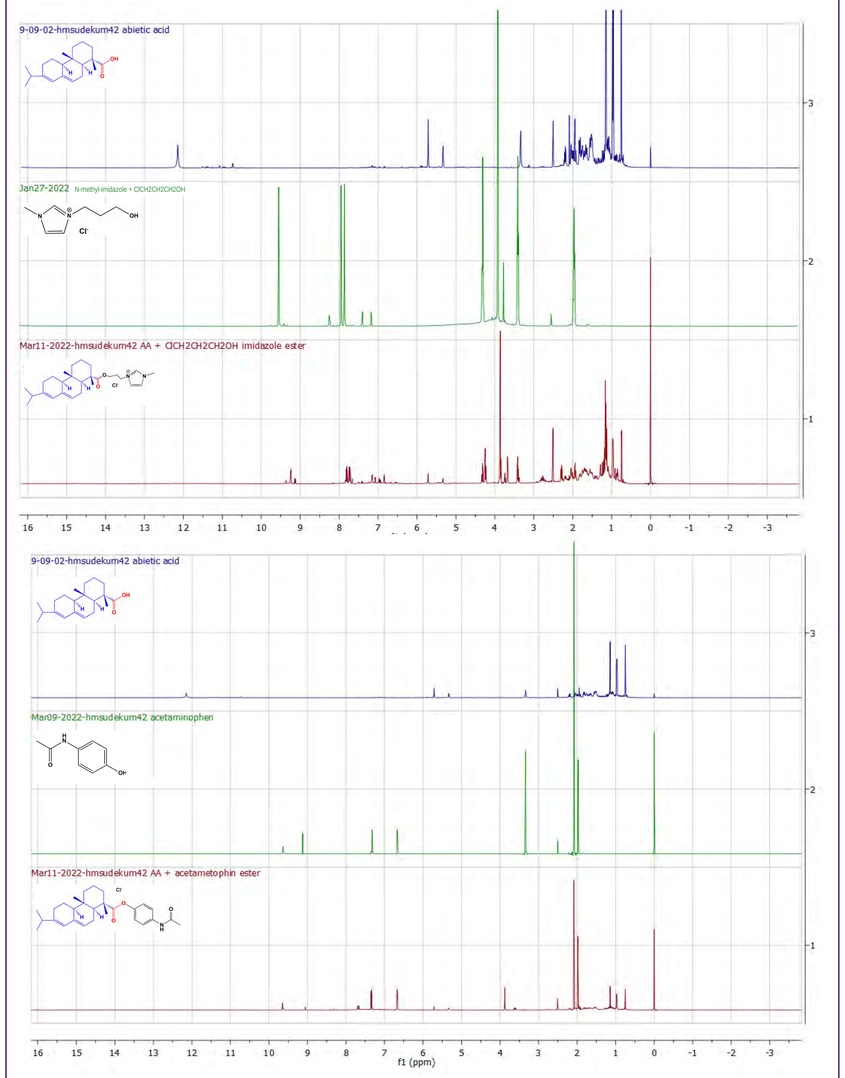
Acetaminophen Ester



Peak Value (product)	Identity
Absence of 1385	Loss of O-H bend
Presence of 1688	Formed C=O
Presence of 1218	Formed C-C-O
Presence of 1046	Formed O-C-C

^{1}H-NMR Characterization

All ^{1}H-NMR were recorded at room temperature, using dmso-d6 as the solvent and on a 500 MHz Bruker NMR Instrument,.



The disappearance of the acidic peak from rosin (~12.3 ppm) along with an up field shift of the three acidic hydrogens from the imidazolium salt indicates the formation of the ester. The esterification reaction required high temperatures to push the reaction to completion.

Future work

The reaction times and temperatures of this reaction will be optimized and the coordination chemistry of the obtained compound will be investigated. Moreover, the conversion of the obtained ester to the corresponding thione along with synthesizing the imidazole-2-thione rosin ester by following Path 2 from the "Synthetic Strategy" section and the ability to form beads, films, etc., from the synthesized rosin esters will also be investigated.

Acknowledgment

H.S. and O.A.C. would also like to acknowledge the NSF MRI 1531870 grant used to acquire the University's NMR spectrometer (Bruker 500 MHz).