Synthesis & Characterization of Potential Pharmaceutical Analogs of a GVSU Lead Compound: an investigation of antibiotic & anti-tumor activity

Nicole M. Horne, Dr. Laurie Witucki, Dr. William Schroeder, Dr. Roderick Morgan
Chemistry Department & Biology Department, Grand Valley State University; Allendale, MI

Abstract

In support of ongoing anti-microbial & anti-tumor research, analogs of a GVSU lead compound, a derivative of the known telomerase inhibitor BIBR1532, were synthesized. These compounds were submitted for biological analysis to determine pharmacological activity toward the discovery of either an antibiotic that can resist bacterial enzymatic degradation or a chemotherapeutic molecule that can destroy tumors cells without increasing toxicity. The anti-microbial interest in these compounds was based on the fact that they are non-penicillin based antibiotics and display a broad range of efficacy against targeted bacteria, including C-Diff & MRSA, with minimal toxicity. Although the compounds presented in this poster were not biologically active, the general interest in these molecules was based on the efficacy of the aforementioned antibiotics. The compounds displayed here were made via nucleophilic acyl substitution chemistry, where various substituted anthranilic acid molecules were coupled via a condensation reaction with either commercially available or synthetically made acid chlorides. Characterization of these compounds was accomplished by TLC, IR, & ^{1}H-NMR analysis.

Introduction

- **β-lactam antibiotics are chemotherapeutic agents, containing highly strained four-carbon lactam rings, along with a reactive amide group, within the ring.[1]**
- **Because of this reactive moiety, they are subject to degradation, as a result of antibacterial resistance.[2]**
- **The mechanism for β-lactams is that they target penicillin-binding proteins (PBPs), which catalyze peptidoglycan cross-linking.[3]**
- **β-lactamases are robust enzymes that undermine β-lactams, due to their ability to cause bacterial resistance.[2]**
- **Due to the degradative nature of these enzymes, innovative research is underway, developing novel non-penicillin based antibiotics with low toxicity, where the molecular structure is not impaired by the machinery of bacterial enzymatic resistance.**
- **The focus of this research, is the synthesis of compounds, where the newly formed aromatic amide is substituted with functional groups possesing the ability to inhibit the mechanisms of bacterial resistance to antibiotics.**

Synthetic Mechanism

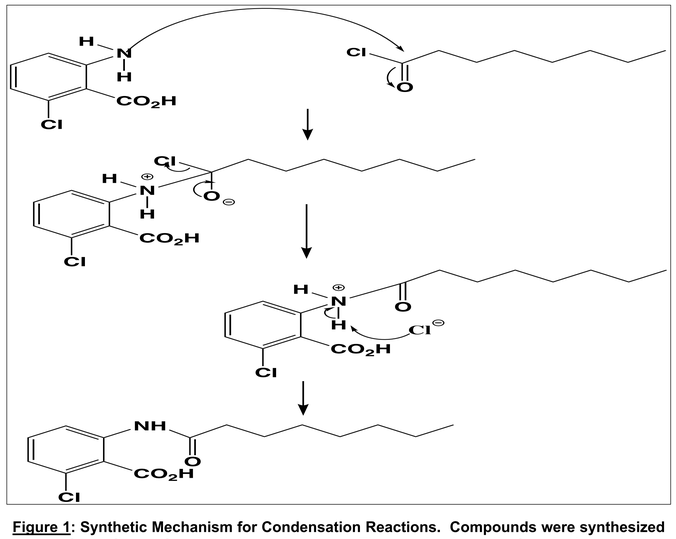
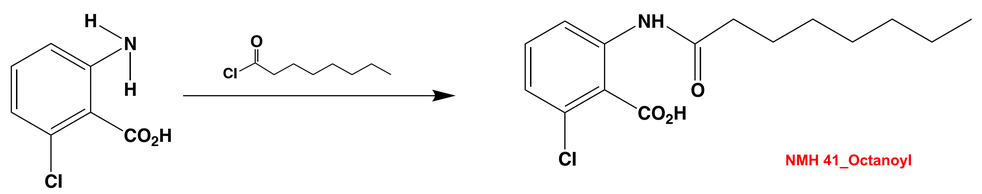
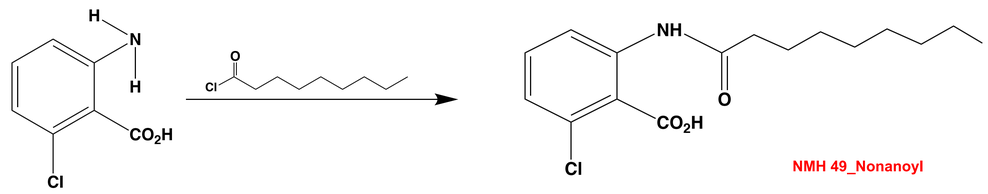
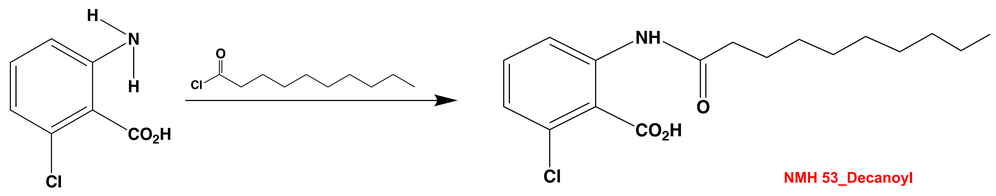


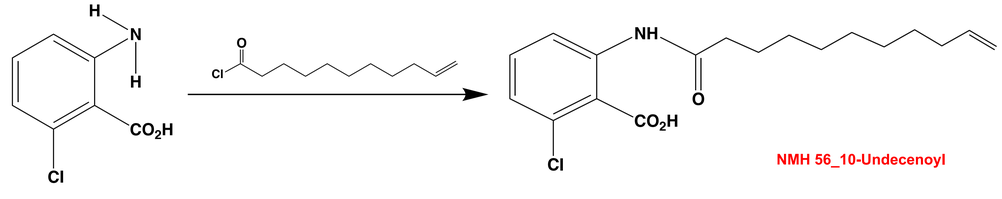
Figure 1: Synthetic Mechanism for Condensation Reactions. Compounds were synthesized via nucleophilic acyl substitution chemistry. The mechanism displayed above is the formation of NMH41_Octanoyl, as the acid chloride & the derivatized anthranilic acid compound(s) react to make the final aromatic amide product.

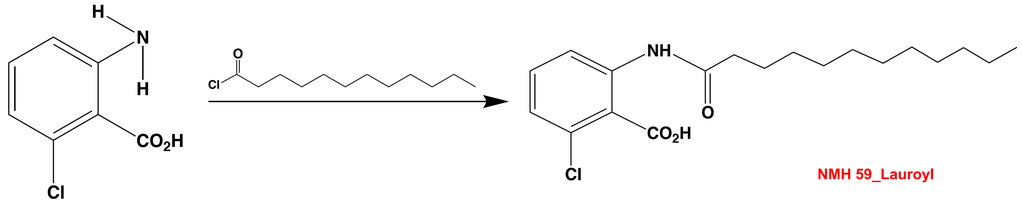
Compounds Synthesized



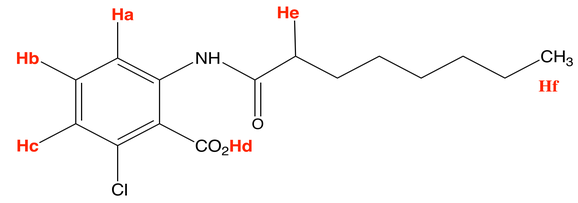






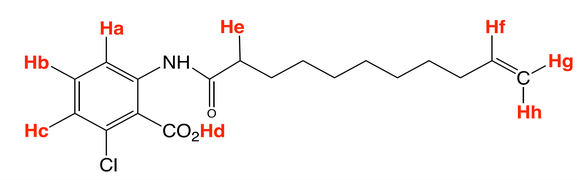


^{1}H-NMR, JEOL 400 MHz



Hydrogen Atom	Chemical Shift (ppm)	Integration	Splitting	J Value (Hz)
a	7.28	1	dd	1.4, 7.96
b	7.36	1	t	7.84
c	7.42	1	dd	1.36, 8.24
d	9.58	1	s	-
e	2.23	2	tt	7.36
f	0.82	3	tt	6.72

Figure 2: ^{1}H-NMR Data, JEOL 400 MHz, DMSO. The ^{1}H-NMR data above represents the chemical shift, integration, & splitting for the following molecules: NMH 41_Octanoyl, NMH 49_Nonanoyl, NMH 53_Decanoyl, & NMH 59_Lauroyl.



Hydrogen Atom	Chemical Shift (ppm)	Integration	Splitting	J Value (Hz)
a	7.27	1	dd	7.56
b	7.36	1	t	7.92
c	7.43	1	dd	8.36
d	9.58	1	s	-
e	2.24	2	tt	7.60
f = alkene	pending	1	pending	pending
g = alkene	pending	1	pending	pending
h = alkene	pending	1	pending	pending

Figure 3: ^{1}H-NMR Data, JEOL 400 MHz, DMSO. The ^{1}H-NMR data above represents the chemical shift, integration, & splitting for the following molecule: NMH 56_10-Undecenoyl. Hydrogens f, g, & h exhibited geminal splitting of cis/trans protons on an alkene.

Conclusion

Although the aforementioned compounds did not exhibit biological activity, upon submission to Dr. Roderick Morgan for testing, future work will investigate nucleophilic acyl substitution using various alkyl-substituted cinnamic acid groups.

Literature Cited

1. Fernandes, R., Amador, P., Prudencio, C. (2013) β–Lactams: chemical structure, mode of action and mechanisms of resistance. Reviews In Medical Microbiology. 24, 7-17.
2. Jacoby, G. (2009) AmpC β-Lactamases. Clinical Microbiology Reviews. 22, 161-182.
3. Livermore, D.M. (1995) β–Lactamases in Laboratory and Clinical Resistance. Clinical Microbiology Reviews. 8, 557-584.