Passerini Multicomponent Reactions with Plant-Derived Phenolic Acids for the Synthesis of Poly(ester-amide)s.

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Abstract

This research presents a sustainable and modular strategy for the synthesis of poly(ester-amide)s (PEAs) via the Passerini multicomponent reaction, employing plant-derived phenolic acids as renewable monomeric building blocks. Phenolic acids, biosynthesised via the shikimic acid pathway, offer an attractive platform due to their structural simplicity, abundance of functional groups, and derivatisation potential. To enable their use in Passerini polymerisation, these monofunctional acids were chemically modified into bifunctional diacids via esterification with adipoyl chloride.

Initial investigations into cyclic anhydrides revealed key challenges, including poor reactivity, low yields, and significant purification difficulties, primarily due to the phenolic hydroxyl group being a poor nucleophile under the reaction conditions. Adipoyl chloride proved more effective and led to the formation of symmetrical biphenolic diacid monomers bearing two free carboxylic acid groups, suitable for polymerisation, although purification remained challenging.

The effect of the solvent environment on Passerini reactivity was systematically studied. Ethyl acetate (EtOAc) was identified as the optimal solvent, achieving the highest yields and product selectivity. In contrast, hydrogen bond-donating solvents such as HFIP and TFE, although previously reported to accelerate multicomponent reactions, caused significant degradation of the isocyanide reagent under the tested conditions. Solvent-dependent reaction kinetics, solubility limitations, and monomer reactivity were key parameters influencing the overall efficiency.

Advanced techniques such as sonication and preparative HPLC were employed to overcome solubility and purification challenges. Sonication significantly accelerated reaction kinetics, while HPLC enabled the isolation of disubstituted Passerini products that were otherwise inseparable via standard chromatography.

Although the polymerisation was not achieved in this study, the successful synthesis and characterisation of diacid monomers laid the foundation for future development of bio-based PEAs. This work contributes to broader aims of green chemistry and circular material design by harnessing agricultural biomass into high-value macromolecular materials. Future research will focus on completing polymerisation, optimising material properties, and evaluating environmental performance.

Abbreviations

°C	Degrees in Celsius
^{1}H NMR	Proton Nuclear Magnetic Resonance
^{13}C NMR	Carbon 13 Nuclear Magnetic Resonance
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
EtOAc	Ethyl Acetate
ESI	Electrospray Ionisation
HFIP	1,1,1,3,3,3- Hexafluoroisopropanol
HPLC	High-Performance Liquid Chromatography
LC-MS	Liquid Chromatography-Mass Spectrometry
LCP	Liquid Crystalline Polymer
MAOS	Microwave-Assisted Organic Synthesis
MeCN	Acetonitrile
MeOH	Methanol
MCR	Multicomponent Reaction
NMR	Nuclear Magnetic Resonance
P-3CR	Passerini Three-Component Reaction
P-4CR	Passerini Four-Component Reaction
PDA	Photodiode Array Detector
PEA	Poly(ester-amide)
ppm	Parts Per Million (NMR)
Rf	Retention Factor
TFE	Trifluoroethanol
TfOH	Triflic Acid
TLC	Thin-Layer Chromatography
% v/v	Volume per Volume Percentage

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1 Introduction

The development of sustainable materials has gained increasing importance over the last few decades due to the depletion of fossil fuel resources, environmental concerns, and the broader push toward circular economies. As the demand for environmentally friendly alternatives grows, the design of functional polymers from renewable feedstocks has emerged as a promising strategy[1]. This research explores a novel route to synthesise bio-based poly(ester-amide)s by transforming phenolic acids into a bifunctional monomer for Passerini polymerisation.

The agricultural sector is increasingly adopting innovative strategies to improve value chains and generate income in a manner aligned with circular economy principles. A key area of focus is the development of sustainable, bio-based alternatives to petrochemical-derived materials. While the petrochemical industry has historically supplied essential building blocks for fine chemicals, pharmaceuticals, and advanced materials, its reliance on non-renewable resources has prompted the search for green alternatives. However, growing concerns about environmental degradation and the finite nature of fossil resources has accelerated the need for renewable and more sustainable substitutes[2, 3].

In response to this challenge, the European Union-funded Circular Cultivation and Chemistry Project was established to exploit the chemical potential of regional biomass[4]. This initiative combines eco-friendly cultivation techniques with advanced biorefinery and chemical synthesis methodologies. Uniquely, this project prioritises low-molecular weight metabolites, as opposed to traditional processes that rely on large-scale biomass components such as lignin and cellulose [5]. By refining cultivation practices, this project aims to increase the yield and availability of target biomolecules in regional crops in Limburg, including species such as nettles, blueberries, grapes and asparagus. By converting residual biomass into high-value chemicals, this work supports the development of next-generation materials.

Within this framework, phenolic acids emerged as promising molecular building blocks, offering a unique combination of structural simplicity, high functional group density, and derivatisation potential. These compounds have been successfully extracted from local plant sources by the research group, validating their accessibility and practical utility. Unlike bulkier biomass-derived polymers such as cellulose or lignin, phenolic acids can be more readily purified, chemically modified, and tailored for specific reactions. Their smaller size, well-defined structures, and compatibility with mild reaction conditions make them ideal candidates for precision functional materials and sustainable strategies.

These compounds, derived biosynthetically through the shikimic acid pathway from amino acids such as phenylalanine or tyrosine, feature aromatic rings substituted with hydroxyl and carboxyl groups [6, 7]. Structurally, phenolic acids are classified into hydroxybenzoic acids and hydroxycinnamic acids (see *Figure 1).* The position and number of hydroxyl groups across these frameworks, as well as the presence and absence of an unsaturated double bond in the side chain, afford diverse physicochemical properties and reactivity profiles. This structural variation enhances their potential for selective derivatisation and functionalisation, making them excellent candidates for advanced material synthesis.

1

Cinnamic acid derivatives
R_1= H p-coumaric acid
R_1= OMe p-ferulic acid

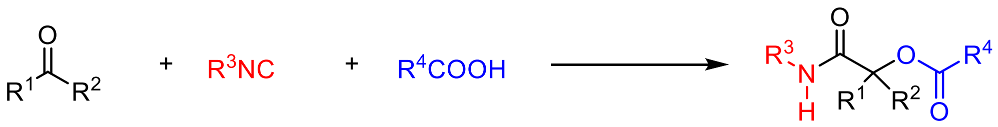
2

Benzoic acid derivatives
R_1= OH m-hydroxybenzoic acid
R_2= OH p-hydroxybenzoic acid

Figure 1: Representative Structures of hydroxycinnamic and hydroxybenzoic acid.

This intrinsic reactivity makes phenolic acids particularly well-suited to multicomponent reactions (MCRs), notably the Passerini reaction. First reported in 1921 by Mario Passerini, this isocyanide-based MCR allows for the one pot synthesis of α-acyloxy carboxamides via a carboxylic acid, an aldehyde or ketone, and an isocyanide in a single step (see *Scheme 1)* [8]. The reaction is appealing due to its operational simplicity, atom economy, and compatibility with a broad range of functional groups [9, 10]. The unique amphiphilic reactivity of isocyanides, acting both as nucleophiles and electrophiles, enhances the versatility of the process, enabling access to diverse molecular architectures[11].

While the traditional Passerini reaction has primarily been employed in small molecule synthesis, its adaptation to polymer chemistry requires careful consideration of monomer design and reactivity. Phenolic acids inherently possess a single carboxylic acid group and a phenolic hydroxyl group, rendering them monofunctional for step-growth polymerisation. To enable their use as bifunctional monomers, the phenolic hydroxyl must be converted into an additional carboxylic acid group. This modification yields a diacid structure that can participate in successive Passerini multicomponent reactions, enabling the formation of linear polymers through atom-economical, multicomponent step-growth polymerisation without byproduct elimination. Various cyclic anhydrides offer potential routes for modifying phenolic acids to generate bifunctional diacid monomers. Their differing reactivity profiles and structural flexibility provide opportunities to tailor polymer precursors for efficient multicomponent step-growth polymerisation. One such transformation can be efficiently accomplished through acylation with succinic anhydride, resulting in the formation of succinate-substituted phenolic derivatives [12].



3 4 5 6

Scheme 1: General Scheme of Passerini Multicomponent Reaction.

Succinic anhydride is well-documented, biodegradable, commercially available acylating agent, that introduces carboxylic acid groups under mild reaction conditions. Importantly, as highlighted in work by Liu et al., succinylation improves the hydrophilicity and reactivity of phenolic substrates, enhancing their compatibility for biomedical and material applications[13]. These attributes further justify the choice of succinic anhydride in developing functionalised phenolic monomers for Passerini-based polymerisation. Although prior studies involved simpler phenols, they demonstrated the viability of succinic modification and support its application to more complex phenolic acids [14, 15].

Once the diacid is synthesised, it becomes a suitable monomer for Passerini-based polymerisation. The use of this reaction in polymer chemistry has been demonstrated in prior work. For example, Deng et al. synthesised sequence-regulated poly(ester-amide)s (PEAs) using diacids, monoaldehydes, and diisocyanides [16]. Similarly, Zhang et al. employed electron-deficient ketones to access PEAs with tertiary ester linkages [17]. Synthetic approaches generally follow A+B+C strategy or AB+C method, where the carbonyl components are introduced as monofunctional reagent. In another study, Bai et al. synthesised bio-based poly(carbonate esters) with pendant amide groups using vanillin-derived bis(4-formyl-2-methoxyphenyl)carbonate (BFMC), further reacting with dicarboxylic acid chlorides and diisocyanates [18]. These studies demonstrate the feasibility of integrating renewable building blocks into the Passerini reaction to access functional, high performance polymeric materials.

In addition to monomer design, reaction conditions play a key role in optimising Passerini chemistry. Recent work, within the group has shown that strong hydrogen bond-donating (HBD) solvent such as using 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as co-solvent can modulate reaction rates and intermediate stability [19, 20]. However, these effects are complex and substrate dependent, and need to be explored in the context of phenolic substrates.

Once polymerised, the properties of the resulting PEAs can be systematically tuned by altering monomer composition and reaction conditions [21]. The modularity of the Passerini reaction allows tuning of polymer properties through variation of the monomer building blocks. Incorporation of aromatic phenolic acids imparts rigidity and thermal stability, while different aldehyde groups can influence crystallinity and side-chain functionality[22]. Additionally, the use of succinate linkers introduced via succinic anhydride modification can increase polymer chain flexibility and degradation behaviours, providing an opportunity to tailor both mechanical and environmental performance [13]. The resulting poly(ester-amide)s may exhibit features consistent with Liquid Crystalline Polymers (LCP)s (see *Figure 2).* The modularity of monomer design enables tuning of backbone rigidity and mesogenic character which are structural units that promote anisotropic molecular alignment, suggesting the potential for application in the development of bio-based LCPs [23].

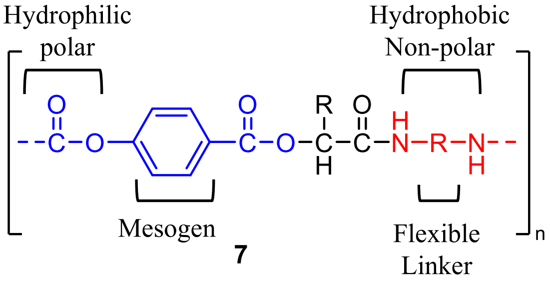


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Figure 2: Schematic structure of Poly(ester-amide) Liquid Crystalline Polymer.

This thesis therefore expands the role of the Passerini reaction beyond small-molecule synthesis into a platform for generating bio-based functional polymers. Using structurally modified phenolic acids as bifunctional monomers, the reaction incorporates diacids, diisocyanides, and aldehydes to yield PEAs under mild catalyst-free conditions. In contrast to conventional methods requiring high temperatures or metal catalysts, this route is operationally simple and environmentally benign [24]. It also benefits from the scalability and modularity inherent to MCRs, supporting the creation of diverse materials from biomass-derived inputs.

Despite progress in bio-based polymer research, most current approaches rely on macromolecular biomass such as cellulose or lignin, which often require harsh chemical or enzymatic treatments to break down into usable monomers. These complex structures not only demand energy-intensive processing but also provide limited functional group diversity, restricting their versatility in precision polymer synthesis. For example, cellulose requires derivatisation through harsh activation methods such as acid hydrolysis or chlorination, which can reduce functional group accessibility and complicate downstream modification[25]. In contrast, low-molecular-weight phenolics provide precise control over reactivity and substitution patterns, yet they remain underexplored. While Passerini reactions have been applied to petrochemical monomers, their potential in building renewable poly(ester-amide)s from plant-derived inputs remains largely untapped.

Moreover, the use of acylating agents to transform phenolic acids into bifunctional monomers for Passerini multicomponent step-growth polymerisation has not yet been explored. Understanding how solvent systems like HFIP affect reactivity with these substrates is equally important, particularly considering the conflicting roles of solubility, acidity, and reactivity.

This research addressed these knowledge gaps by developing and optimising a reaction pathway that combines phenolic acid modification, solvent-driven Passerini kinetics, and monomer scope expansion. The result is a new, modular platform for the sustainable synthesis of high-performance polymers from renewable resources.

1.1 Research Aims and Objectives

To directly address these gaps, this research aims to develop a scalable and sustainable synthetic strategy for producing bio-based poly(ester-amide)s using functionalised phenolic acids. This leads to the central research question: Can bio-based phenolic acids, via the Passerini multicomponent reaction, yield functional poly(ester-amide)s?

To address this, the project will focus on:

1. Synthesis of α-acyloxy carboxamides using phenolic acids
2. Optimisation of monomer synthesis conditions
3. Functionalisation of phenolic acids with acylating agents to form bi-functional diacid monomers
4. Synthesis of poly(ester-amide)s *via* Passerini polymerisation

1.2 Thesis Structure

The remainder of this thesis is structured as follows:

- Chapter 2 provides the results and discussion, including retrosynthesis analysis, characterisation of intermediates and optimisation of reaction conditions.
- Chapter 3 presents the conclusions drawn from this research and discusses their implications
- Chapter 4 presents potential future directions.
- Chapter 5 discusses societal impact
- Chapter 6 presents the experimental methods and synthetic procedures
- Supporting data is included in the references and appendix

2 Results and Discussion

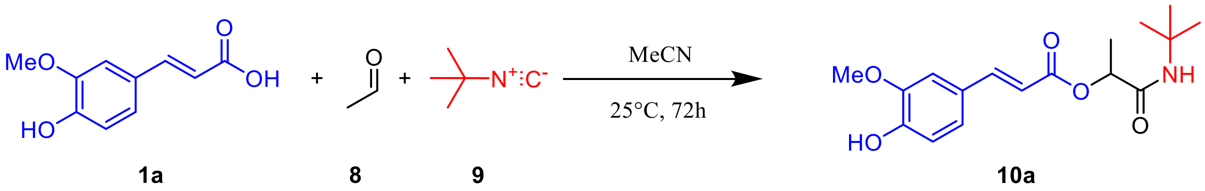
2.1 Synthesis of Mono-Isocyanide Passerini Products

2.1.1 Proof-of-Concept Study with Phenolic Acids

To evaluate the feasibility of using phenolic acids in the Passerini multicomponent reaction, a set of mono-Passerini reactions were conducted as a proof-of-concept study. These initial reactions served two purposes: to determine whether phenolic acids are viable substrates for the Passerini mechanism and to optimise the reaction conditions before transitioning to more complex polymerisation studies. The general procedure used was adapted from Zhang et al. [17].

2.1.2 Substrate Selection and Solubility Challenges

The first substrate tested was *p*-ferulic acid. The initial attempt was performed in dichloromethane (DCM), but poor solubility of ferulic acid under these conditions resulted in limited conversion and a heterogenous reaction mixture. In response, the solvent was changed to acetonitrile (MeCN), which improved the solubility of ferulic acid and led to the formation of the desired mono-Passerini product compound 10a in moderate yields (see *Scheme 2)*. Encouraged by this outcome, the study proceeded to evaluate two additional phenolic acids; *p*-coumaric acid and *m*-hydroxybenzoic acid, which were selected due to their structural diversity, biomass availability, and differing solubility properties.

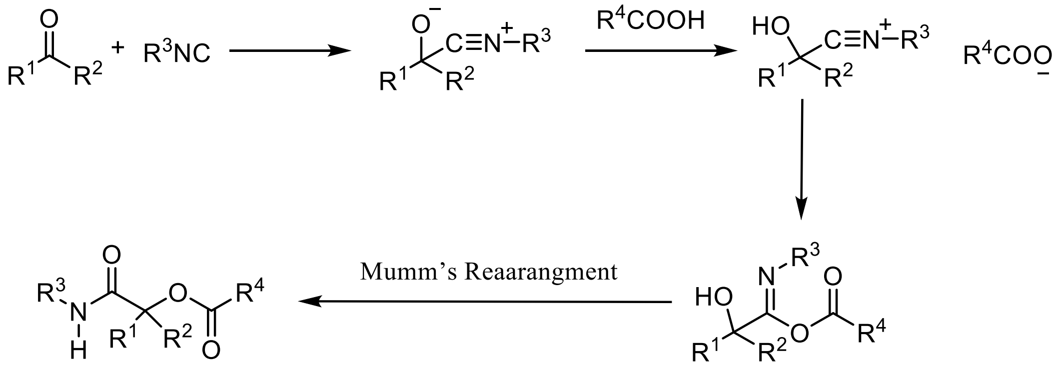


Scheme 2: p-Ferulic Acid Mono-isocyanide Reaction of Compound 10a.

The isocyanide and aldehyde reagent were carefully selected based on reactivity, compatibility with phenolic substrates, and prior success in previous multicomponent systems. Acetaldehyde and tert-butyl isocyanide were chosen as they have been known to work within the group. Acetaldehyde is the most electrophilic aldehyde as methyl is only slightly electron donating, so the carbonyl carbon is highly electron deficient and there is no steric hindrance, making it more reactive towards a nucleophile. Tert-butyl isocyanide was selected due to its optimal balance between reactivity, stability and ease of purification.

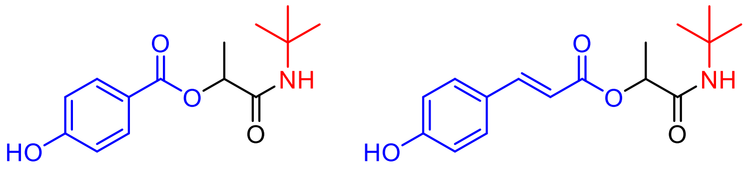
2.1.3 Reaction Mechanism and Product Characterisation

The Passerini reaction proceeded through nucleophilic attack by an isocyanide on an aldehyde to form a nitrilium intermediate. The carboxylic acid on the phenolic acid reacts with the intermediate to form imidate, which is converted into the α-acyloxy carboxamide via acyl rearrangement known as Mumm's rearrangement (see *Scheme 3*) [26].



Scheme 3: Reaction Mechanism of Passerini Reaction.

The corresponding reactions yielded the mono-Passerini products: Compound 10b from *p*-coumaric acid, compound 10a from *p*-ferulic acid, and compound 11 from *m*-hydroxybenzoic acid (see *Scheme 4*).



11 **10b**

Scheme 4: p-Coumaric and p-Hydroxybenzoic Acid Mono-isocyanide Reaction of Compounds 11 and 10b.

All three compounds were successfully synthesised and isolated in moderate yields ranging from 33% to 53%. Structural confirmation was achieved via NMR spectroscopy, with characteristic signal including a singlet peak around δ1.7ppm and the methylene and methyl groups of the α-acyloxy carboxamide moiety appeared as a quartet and doublet respectively at δ3.3 and 1.9ppm.

2.1.4 Impact of Solubility and Concentration

Upon scale-up, *m*-hydroxybenzoic acid was the only substrate that demonstrated complete solubility in MeCN. In contrast, both *p*-coumaric and *p*-ferulic acids remained only partially soluble, leading to heterogeneous mixtures [27-29]. The high solubility of *m*-hydroxybenzoic acid is attributed to its compact structure, higher polarity, and lack of extended conjugated side chain. The lower pKa of the phenolic hydroxyl in *m*-hydroxybenzoic acid ~9.1 compared to that of *p*-coumaric acid and ferulic acid ~9.5 enhances its hydrogen-bond donor strength [30, 31]. This subtle difference in acidity facilitates better solvation and interaction with polar solvents such as MeCN, thereby improving dissolution. Meanwhile, the conjugated side chains and methoxy group in *p*-coumaric and *p*-ferulic acid introduce hydrophobicity and encourage π-π stacking or intermolecular hydrogen bonding, limiting solvation [32].

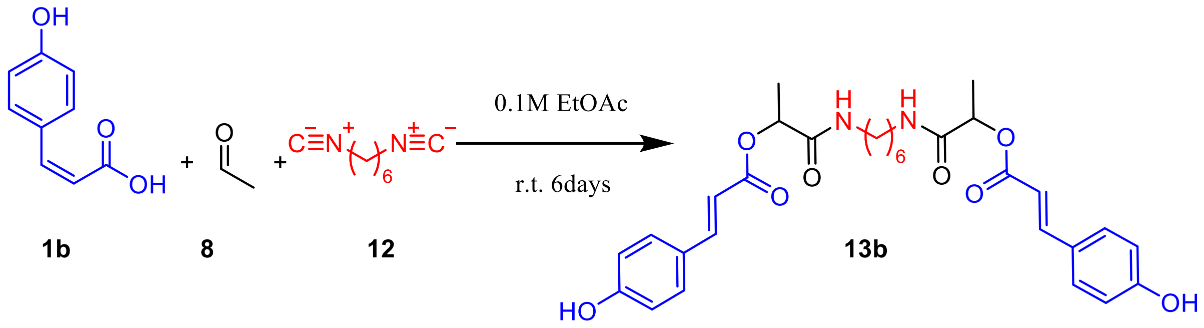
The low reaction molarity 0.1 M contributed to the moderate yields but was a necessary compromise due to solubility constraints. However, multicomponent reactions generally benefit from higher concentrations [33, 34]. These reactions rely on the simultaneous interaction of three different reactants: the carbonyl compound, phenolic acid and the isocyanide. Previous studies have shown that at lower concentrations, the frequency of effective molecular collisions between these components decreases significantly, which in turn slows down the overall reaction rate. Even modest dilutions can result in a dramatic reduction in reaction efficiency. Moreover, the slower reaction rate at low molarity and the solubility issue of the phenolic acids lead to a decrease in yield compared to traditional Passerini reactions.

These trials confirm the compatibility of phenolic acids with Passerini chemistry and highlight key factors affecting performance, namely solubility, solvent choice and reaction concentration. Future optimisation, particularly through the use of hydrogen bond-donating solvents, may enhance substrate dissolution and facilitate higher yields in bio-based multicomponent reactions.

2.2 Synthesis of Diisocyanide Passerini Products

2.2.1 Synthesis of Diisocyanide Monomer

Having demonstrated the feasibility of phenolic acids in mono-isocyanide Passerini reactions, the study next focused on extending this methodology to diisocyanide-based systems for potential monomer synthesis. To enable the formation of the diisocyanide Passerini products and facilitate step-growth polymerisation, the bifunctional isocyanide monomer 1,6-diisocyanhexane was synthesised through a two-step protocol, following the method reported by Goldeman et al. [35]. The synthesis began with the conversion of commercially available hexane-1,6-diamine to N,N'-(hexane-1,6-diyl)diformamide, which was dehydrated using phosphorus oxychloride ($POCl_3$) in the presence of a base to yield the target 1,6-diisocyanhexane. The product was obtained in high yield (89%) and characterised by its distinctive ^{1}H NMR signals corresponding to the isocyanide methylene unit. It flexible alkyl chain and symmetrical terminal isocyanide groups made it an ideal candidate to test dual Passerini reactivity and its compatibility with phenolic acid-based substrates. This method applies the Passerini reaction at both termini of the diisocyanide, with two equivalents of aldehyde and phenolic acid engaging in tandem (see *Scheme 5*).



Scheme 5: p-Coumaric Acid Di-isocyanide Reaction of Compound 13b.

2.2.2 Initial Trial Reaction and Solvent Screening

The initial reaction was conducted with *p*-coumaric acid and acetaldehyde in MeCN, based on its prior solvent moderate success in mono-Passerini study. Although it had not been fully optimised for the di-isocyanide system and solubility issues quickly emerged. As a result a comprehensive solvent screening was conducted to identify optimal conditions.

To assess the impact of solvent environment on reaction rate and product yield, six solvents: ethyl acetate (EtOAc), acetonitrile (MeCN), dichloromethane (DCM), methanol (MeOH), trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) were selected to represent a broad spectrum of chemical environments. The reaction was evaluated at two concentrations (0.1 M and 0.2 M), keeping the substrate stoichiometry constant with 3:3:1 for the aldehyde: phenolic acid: diisocyanide. The results in *Table 1*, revealed solvent-dependent variations in conversion, with several distinctive mechanistic implications.

Table 1: Solvent Screening Conditions and Yields.

Substrate	**Equivalents**	**Solvent**	**Concentration [M]**	**Time (h)**	**Yield %**
p-coumaric	3:3:1	TFE	0.1	48	0.16
p-coumaric	3:3:1	MeOH	0.1	48	0.41
p-coumaric	3:3:1	HFIP	0.1	48	0.73
p-coumaric	3:3:1	DCM	0.1	48	2.07
p-coumaric	3:3:1	EtOAc	0.1	48	41.55
p-coumaric	3:3:1	MeCN	0.1	48	9.93
p-coumaric	3:3:1	TFE	0.2	48	0.28
p-coumaric	3:3:1	MeOH	0.2	48	2.45
p-coumaric	3:3:1	HFIP	0.2	48	1.07
p-coumaric	3:3:1	DCM	0.2	48	16.68
p-coumaric	3:3:1	EtOAc	0.2	48	69.81
p-coumaric	3:3:1	MeCN	0.2	48	20.08

The results highlighted a consistent trend: aprotic solvents such as EtOAc and MeCN produced significantly higher yields than protic solvents like MeOH, TFE and HFIP [11, 36]. EtOAc gave the highest conversions, while MeOH and TFE yielded the lowest.

Notably, methanol was the only solvent in which complete solubility of all the components was obtained. However, despite complete solubility, only trace amounts of product were found. In protic solvents, extensive hydrogen bonding with the carboxylic acid can interfere with its reactivity, reducing its availability for nucleophilic attack. Additionally, methanol can stabilise the aldehyde through hydrogen bonding, reducing its electrophilicity and hindering formation of the carbon-carbon bond. The mechanistic behaviour has been extensively reported in prior studies[9, 37]. While solubility is often considered a prerequisite for successful reactions, it does not guarantee a high yield.

Although TFE and HFIP exhibit strong hydrogen bond-properties, they did not result in high product yields. This suggests that while fluorinated alcohols like TFE and HFIP can create a more acidic reaction environment, their impact on stabilising the nitrilium intermediate may not be sufficient in this case, possibly due to solubility limitation or over-stabilisation of the reactants.

Moreover, a noticeable orange discoloration was observed upon the additions of TFE and HFIP to the reaction mixture, which was not present in other solvents. This change in colour is an indication of potential isocyanide decomposition and/or the degradation of the product also. Both TFE and HFIP are highly fluorinated alcohols that create strongly acidic environments. Although such conditions can sometimes accelerate Passerini reactions by stabilising the nitrilium ion, they may also promote degradation pathways for sensitive isocyanide moieties. It is likely that the acidic nature of these solvents destabilised the isocyanide, leading to hydrolysis and discolouration. Isocyanides are known for their chemical sensitivity, particularly under strongly protic and acidic conditions. HFIP, due to its high polarity, strong hydrogen-bond donating ability an mildly acidic character pKa ~ 9.3, can engage in hydrogen bonding or even protonation of the isocyanide functional group. These interactions can activate the isocyanide toward hydrolysis, especially in the presence of trace amount of water, resulting in the degradation to formamides or other by-products [38, 39]. This aligns with previous reports highlighting the susceptibility of isocyanides to decompose under highly acidic or protic conditions[19, 40].

DCM gave moderate conversions, likely due to limited polarity that hampers solubility of phenolic acids. However, DCM remains a commonly used solvent in Passerini chemistry, as it provides a non-interfering environment for nucleophilic and electrophilic interactions.

EtOAc emerged as the most effective solvent, affording the highest yield, due to its moderate polarity (polarity index~4.4) and lack of hydrogen bonding. Its moderate polarity and aprotic nature allowed for the phenolic acid to partially dissolve and facilitated the formation of reactive intermediates. MeCN also performed relatively well, particularly at higher concentrations, though still below EtOAc. The lower yield may be due to limited solubility of less polar or bulky reagents. DCM, while less polar yielded moderate conversions due to partial solubility limitations for phenolic acids.

Overall, this data is in line with reports suggesting EtOAc and other medium polarity solvents ideal for Passerini type chemistry, providing sufficient solubility, reactivity and intermediate stability [17, 34].

2.2.3 Reaction Progression and Isolation

Subsequent reactions in EtOAc demonstrated more pronounced solubility issues upon scale up, due to phenolic acids amphiphilic nature and aggregation in organic media [32, 41]. *m*-hydroxybenzoic acid had improved solubility and reactivity due to its compact, polar structure and lack of bulky conjugated chains.

LC-MS analysis revealed numerous side products and incomplete conversions with significant mono-substituted adducts. Additionally, unproductive pathways were observed where the aldehyde reacted with the isocyanide but failed to engage the second phenolic acid, further contributing to challenges in achieving full di-substituted under suboptimal conditions.

Traditional silica gel chromatography was insufficient to separate the mono- and di-products due to their similar polarity and functional group profiles. Despite testing various eluents; EtOAc:heptane, MeOH:DCM, and even toluene modified system, adequate resolution was not achieved[42]. Acetic acid was added to suppress phenolic tailing, but without significant improvement.

Ultimately the di-product was only successfully isolated using preparative HPLC. This can be attributed to the significantly higher resolution and selectivity offered by reversed phase HPLC. Compared to normal-phase columns that rely on polar interactions, the C18 stationary phase used in HPLC separates compounds based on hydrophobicity, which is particularly effective in this case where there is a complex molecule containing polar functional groups and non-polar regions with alkyl chains and aromatics[43]. UV and MS detection enabled accurate fraction collection, albeit in modest yields.

The formation of the di-Passerini products was confirmed by purified ^{1}H and ^{13}C NMR. In all cases, new signals emerged in the ^{1}H NMR spectra following the reaction. A characteristic quartet around 4.9-5.0ppm, corresponding to the α-proton adjacent to the ester oxygen, and a doublet near 1.2-1.3ppm from the methyl group, confirmed the formations of the α-acyloxy carboxamide unit. Signals in the aliphatic region ~3.0ppm were consistent with the hexamethylene, while aromatic regions 7.9-6.7ppm supported the incorporation of the phenolic acid core. In the ^{13}C NMR, a new resonance between 170-166ppm supported the presence of two ester and two amide carbonyls, providing additional evidence of successful di-substitution.

Despite successful reaction progress and NMR confirmation of the di-Passerini product, the isolated yields remained low. Yield losses likely occurred during workup and HPLC purification, partly due to partial solubility of the di-product in EtOAc and sample loss during fractionation.

2.2.4 Further Optimisation via Temperature, Sonication, and Microwave Heating

Further experiments were carried out to investigate the increase of temperature on the rate of reaction. The reaction was heated to 40 °C. However, the overall results highlighted that at higher temperatures led to lower yields. This suggests that the Passerini reaction proceeds more efficiently at room temperature rather than elevated temperatures. This is due to the isocyanide or product degradation due to sensitivity of these compounds[10].

Further optimisation of the reaction was explored. To reduce the long reaction times of over 48 hours under ambient conditions and poor solubility, sonication and microwave heating were investigated on a 0.1 M reaction mixture the results can be seen in *Table 2*.

Previous work has been done on Passerini reaction using sonication where the yield has been increasing due to the increase in the rate of the reaction [44]. Ultrasound in general and specifically in MCR is often used due to its advantages such as increasing the reaction efficacy while decreasing waste by-products, short reaction times, cleaner reactions, easier experimental procedures and low energy requirements. Ultrasound operate via acoustic cavitation, which forms, expands and collapses gaseous and vaporous cavities in an ultrasound irradiated liquid. The mechanical effect of cavitation destroys those attractive forces of the molecules in the liquid phase and accelerates reaction rates by facilitating mass transfer in the microenvironment. Therefore, it was hypothesised the sonication could accelerate the reaction and increase the yield. Furthermore, the sonication would help break up particles and enhance the dissolution of the poorly soluble phenolic acid.

Table 2. Sonication and Microwave Reactor Conditions and Yields.

Substrate	**Equivalents**	**Solvent**	**Concentration [M]**	**Rxn Conditions**	**°C**	**Time (h)**	**Yield %**
p-coumaric	3:3:1	MeCN	0.1	Sonication	40	3	No product
p-coumaric	3:3:1	MeCN	0.1	Sonication	40	6	6.28
p-coumaric	3:3:1	EtOAc	0.1	Sonication	40	3	8.80
p-coumaric	3:3:1	EtOAc	0.1	Sonication	40	6	67.05
p-coumaric	3:3:1	EtOAc	0.1	Microwave Reactor	60	3	20
p-coumaric	3:3:1	EtOAc	0.1	Microwave Reactor	60	6	2.96

Sonication in EtOAc increase the yield from 8.8% after 1 hour to 67% after 6 hours. This confirms that ultrasound effectively solubilises and mobilises both phenolic acid and isocyanide, promoting more frequent productive collisions.

Other publications looked at microwave assisted organic synthesis (MAOS) [45]. Similar to sonication it has been shown to increase the rate of MCR reaction with significant improvements in reaction times and yields These reactions rely on dielectric heating, polar molecules couple with oscillating electromagnetic field, producing rapid volumetric heating and transient superheating of reaction microdomains. These conditions can lower activation barriers and shorten induction periods. However, in this case the microwave reactor did not obtain yields higher than 20% and a decrease in yield was obtained when the reaction was stirred for 6 hours. Indications that thermal degradation of the sensitive isocyanide may have happened. One of the previous studies also carried out the reaction in solvent free conditions.

2.2.5 Co-solvent Studies with HFIP

Building on the previous solvent optimisation, co-solvent studies were conducted to further explore the role of hydrogen bond-donating environments in this Passerini reaction. To investigate the effect of HFIP as a co-solvent, time-course studies were performed using 3 eq of HFIP in 0.1 M of EtOAc originally and increased to 20v/v%. EtOAc was selected due to the highest yield in the previous study [46].

As shown in *Table 3*, using 3 equivalents of HFIP resulted in slow but progressive conversion over time. After 1 hour there was only trace amounts of product formed and there is a gradual increase to 3.34% after 4 hours, 9.8% after 5 hours and reaching 17.78% after 14 hours. This gradual increase of yield suggests that there is a positive but limited influence of HFIP under these conditions. The low yields and slow initial rate imply that 3 equivalents of HFIP is not sufficient to have a positive impact on the reaction rate. HFIP which is known to enhance the Passerini reaction by acting as a strong hydrogen bond donor, stabilising the nitrilium ion intermediate, and acidifying the reaction environment, can accelerate imine formation and help Mumm's rearrangement[19, 46]. The small quantity used was insufficient to significantly impact the rate.

Table 3: 3 eq HFIP Conditions and Yields.

Substrate	**Equivalents**	**Concentration [M]**	**Time (h)**	**Yield %**
p-coumaric	3:3:3:1	0.1	1	Traces
p-coumaric	3:3:3:1	0.1	2	1.6
p-coumaric	3:3:3:1	0.1	3	2.19
p-coumaric	3:3:3:1	0.1	4	3.34
p-coumaric	3:3:3:1	0.1	5	9.8
p-coumaric	3:3:3:1	0.2	14	17.78

Given the modest effect of the 3 eq HFIP condition, a follow-up study was conducted using 20 v/v % HFIP to amplify solvent effect and getter stabilise intermediates.

Table 4: 20 v/v % HFIP Conditions and Yields.

Substrate	**HFIP**	**EtOAc**	**Time (h)**	**Yield %**
p-coumaric	200μL	800μL	1	0.20
p-coumaric	200μL	800μL	2	0.29
p-coumaric	200μL	800μL	3	0.35
p-coumaric	200μL	800μL	4	0.37
p-coumaric	200μL	800μL	5	0.47
p-coumaric	200μL	800μL	6	0.49
p-coumaric	200μL	800μL	14	0.51
p-coumaric	200μL	800μL	48	7.21

However, as seen in *Table 4* the use of 20 v/v % HFIP did not result in improved yields. The product was only formed in trace amounts, with the yield increasing marginally from 0.2% in 1 hour up to 7.21% after 2 days. Notably the reaction exhibited signs of discolouration, turning orange shortly after the addition of HFIP, suggesting instability of the isocyanide or product and formation of side products[10, 40]. As previously discussed, HFIPs can stabilise nitrilium intermediates, its acidic and protic nature also promotes degradation pathways [38].

While previous studies have been found to accelerate the Passerini reaction under specific conditions, its concentration and the nature of the monomers play critical roles. The Passerini reaction with phenolic acids gives relatively low yields compared to other Passerini reactions over extended reaction times, suggesting that the rate of the reaction is inherently slow under these conditions in EtOAc. This slow conversion likely increases the susceptibility of the isocyanide degradation over time. This is why the HFIP is more effective in higher concentrations when the rate of the reaction is much faster. This would also explain why there are higher yields in the 3 eq study due to the less acidic environment for isocyanide degradation.

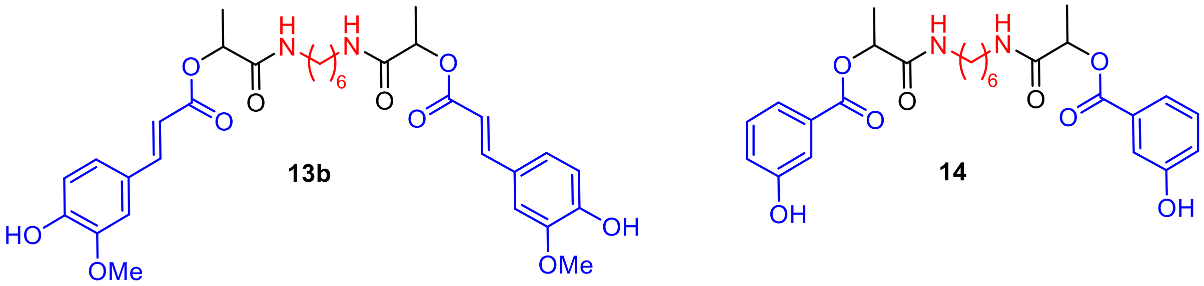
In addition to the solvent environment, the relatively low concentration of the reaction mixture 0.1 M may also have contributed to the observed slow reaction rates and enhanced susceptibility of the isocyanide to degradation. At lower concentration, the reaction kinetics are slowed down due to the lower number of effective collisions. This allows the isocyanide to be more susceptible to degradation. This highlights the importance of ensuring balanced kinetics, where the rate of product formation proceeds faster than any competing or destructive processes.

The predominance of the mono-substituted alkoxy carboxamide that can be seen in the LC-MS in these HFIP reactions can be also an explanation of why the yields are low. The strong hydrogen-bond donor may have accelerated the first isocyanide addition but stabilises the resulting nitrilium/carboxylate intermediates and only forming the mono-product. Furthermore, the hydrogen bonds may protonate the remaining isocyanide terminus, preventing the second attack.

In contrast, the same reaction performed in EtOAc 0.2 M, 48h reached 69% yield, illustrating the benefit of an aprotic, less acidic environment. Under identical conditions, pure HFIP yielding just ~1%, while 20 v/v % HFIP and 3 eq HFIP in EtOAC produced intermediate results, better then HFIP alone but still consistently lower to EtOAc. This confirms that excess acidity form HFIP limits the efficiency of the system rather than enhancing it.

2.2.6 Substrate Scope Expansion

The scope was further expanded beyond *p*-coumaric acid to include *p*-ferulic acid and *m*-hydroxybenzoic acid, confirming the reaction’s broader applicability with structurally diverse phenolic acids (see *Scheme 6*). Likewise, the reactivity of the aldehyde was investigated to see if it had an influence on the yield of the Passerini reaction. Tert-butyl aldehyde and benzyl aldehyde were selected as they have distinct electronic and steric properties which have a direct influence on reaction kinetics. Tert-butyl aldehyde had trace amount of product presence in the LCMS. Tert-butyl aldehyde is less reactive than acetaldehyde due to the presence of the bulky tert-butyl group, it is also electron-donating via inductive effects, making the carbonyl less electrophilic. Due to the steric hinderance it was expected that there were lower yields of the product. Benzyl aldehyde had no product formation. The benzene ring has a resonance effect that can stabilise the partial charge on the carbonyl which reduces the electrophilicity, it is less reactive compared to formaldehyde and concludes why there was no formation of product.



Scheme 6: p-Ferulic and m-Hydroxybenzoic Acid Di-isocyanide Reaction of Compound 13b and 14.

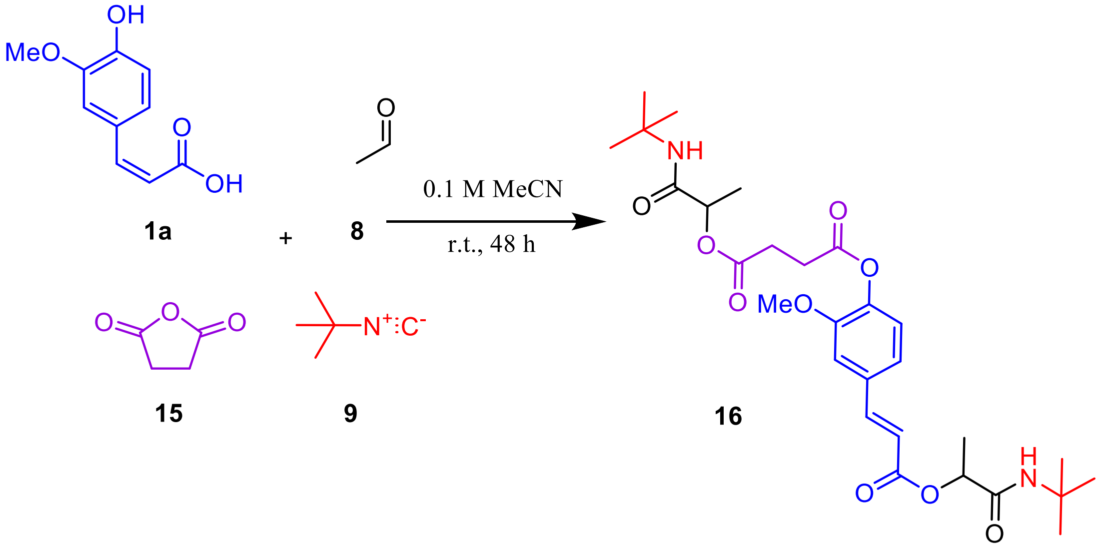
This research demonstrated the successful formation of di-Passerini adducts from phenolic acids and diisocyanide monomers, with EtOAc emerging as the optimal solvent. However, solubility limitations, side reactions, and poor yields form certain aldehydes and co-solvent systems, highlighted key challenges. Strategies such as sonication significantly improved yields, while HFIP, despite literature precedent, proved detrimental at higher concentrations. The findings establish a foundation for further optimisation and future development of bio-based step-growth polymerisation platforms.

2.3 Passerini Polymerisation

2.3.1 One-Pot Functionalisation and Polymerisation

The initial approach to developing a bio-based polymer platform was to employ the Passerini four-component reaction P-4CR for step growth polymerisation[37]. As a preliminary step, a proof-of-concept reaction was performed using mono-functional phenolic acid to synthesise α-acyloxy carboxamides. Following the initial evaluation, the plan was to optimise the system for polymerisation by systematically varying key parameters, including solvent, monomer structure, reaction time, and temperature.

The procedure was adapted from a paper by Salah Ayoup et al [47]. The initial reaction was carried out using acetaldehyde, tert-butyl isocyanide, ferulic acid and succinic anhydride in a one pot synthesis. Here the Passerini reaction would occur on the carboxylic acid moiety. In addition, in the phenolic alcohol, the hydroxyl oxygen serves as nucleophile and attack the succinic anhydride at the carbonyl and open the five membered ring to form the second carboxylic functionality (see *Scheme 7*). Once the carboxylic acid is formed, it can undergo the Passerini reaction to form compound 16.



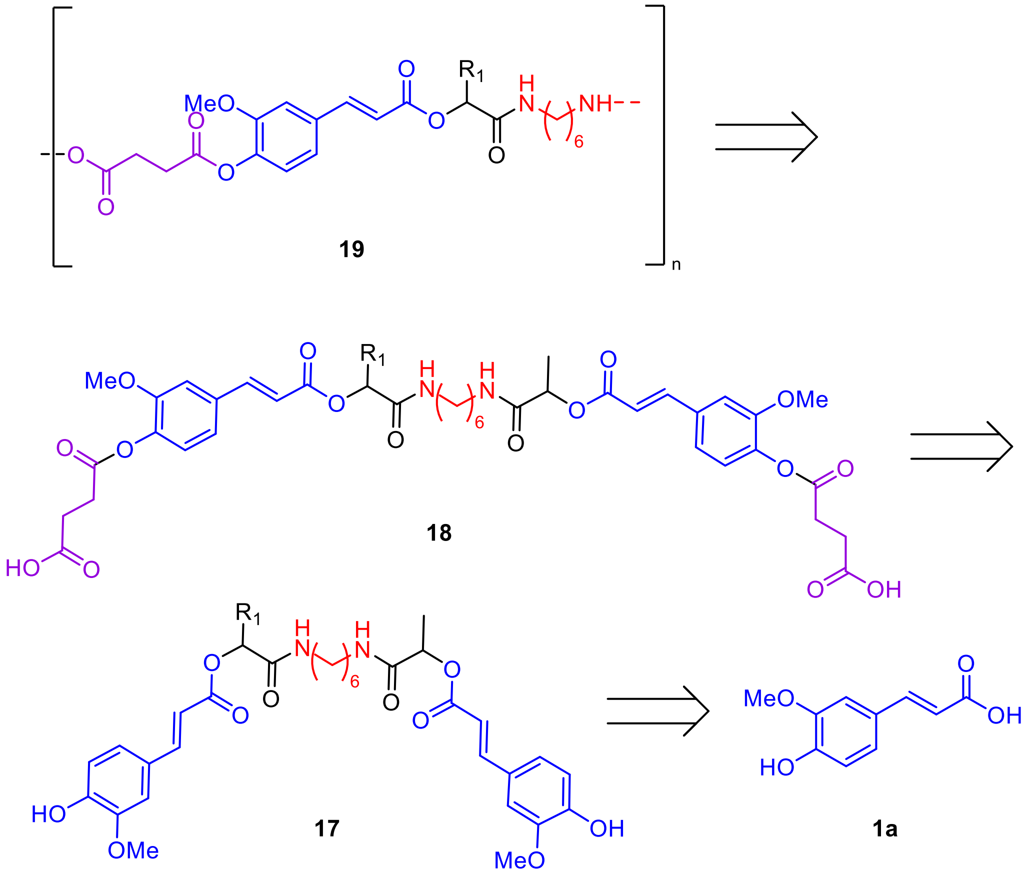
Scheme 7: Proposed Four component reaction.

However, this reaction was unsuccessful. The LC-MS revealed the Passerini reaction occurred only on the native carboxylic acid moiety and there was no addition of the succinic anhydride to the phenolic alcohol. The reason this reaction may not have been successful can be due to the pH of the reaction. Literature reports, including Banfi et al. confirm that the Passerini reaction is favoured under acidic conditions[11]. These conditions protonate the carbonyl oxygen of the aldehyde therefore, making it more electrophilic and allowing the isocyanide to attack. However, in the case of the addition of the succinic anhydride, it undergoes a nucleophilic acyl substitution: the alcohol needs to be deprotonated first, the oxygen becomes a nucleophile and attacks one of the carbonyl groups on the succinic anhydride. The 5-membered ring opens, and a tetrahedral intermediate, which then collapses and forms monoester succinic anhydride[14, 48, 49].

So, in the case of this reaction the optimal conditions are basic. This reaction was not carried out under basic conditions. This likely contributed to the reaction's failure under these conditions. Without the presence of the base, the phenolic OH likely remained neutral and unreactive, resulting in no formation of the monoester intermediate. This created a conflicting set of conditions, where acidity would favour the Passerini reaction, but basicity was required to activate the phenol for esterification with succinic anhydride. Due to this conflict in optimal conditions, the succinic anhydride reaction was carried out separately to the Passerini reaction to see if the reaction worked. Literature such as Wang et al. also reports issues with competing reactivity and steric hindrance when attempting esterification of multifunctional systems. This limitation required the separation of esterification and polymerisation into a sequential protocol [50].

2.3.2 Sequential Functionalisation

The second strategy involved reversing the order of functionalisation. Instead of attempting simultaneous esterification and Passerini chemistry in a single pot, the idea was to first synthesise the di-isocyanide product, then selectively introduce succinate units through esterification at the phenolic hydroxyl groups. This order of reactivity was chosen based on the hypotheses that the presence of free carboxylic acid groups was interfering with the succinic anhydride esterification, likely through competitive deprotonation, hydrogen bonding, or local steric/ electronic effects. By first consuming the carboxylic acid groups in the Passerini reaction, it was expected that the phenolic hydroxyls would be more accessible for subsequent coupling with succinic anhydride under basic conditions. The proposed polymerisation was revised and a new retrosynthesis approach was devised (see Scheme 8).



Scheme 8: New Proposed Retrosynthesis of Passerini polymer from p-Ferulic Acid. .

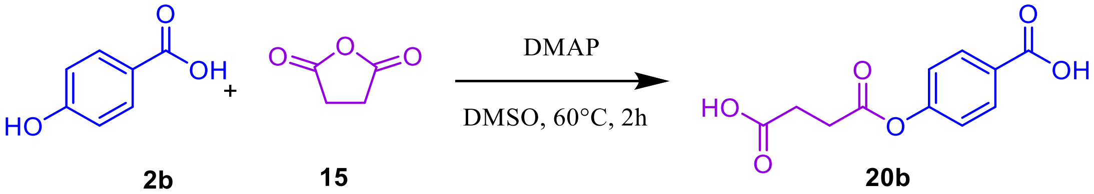
While the initial Passerini step to form the di-substituted intermediate was successful, the final succinate esterification step was hindered by solubility limitations. The di-product was only soluble in highly polar solvents such as MeOH and DMSO, and remained insoluble in standard organic solvents, complicating both the polymerisation step and analytical characterisation

2.3.3 Pre-Functionalised Diacid Monomers

While the di-Passerini adducts were successfully formed, their limited yields, solubility, and purification issues highlighted the need for a more robust polymerisation strategy. This focus therefore shifted toward the design of pre-functionalised monomers suitable for efficient Passerini-based step-growth polymerisation. The third strategy, centred on first synthesising the diacid monomer and subsequently subjecting it to Passerini polymerisation, emerged as a more modular and potentially effective route toward constructing bio-based polymers. A key requirement is the formation of functionalised diacid monomers. Succinic anhydride was originally selected as a bifunctional linker, capable of introducing carboxylic acid termini through esterification. However, coupling it with phenolic acids posed significant challenges, both in terms of selectivity and reactivity. This modification was critical to enable further transformation via Passerini polymerisation.

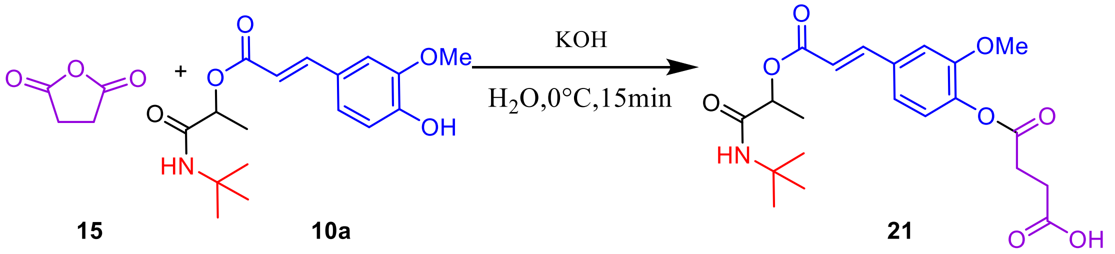
2.3.4 Succinic Anhydride Coupling with Phenolic Acids

Initial attempts to directly couple succinic anhydride to phenolic acids under Passerini reaction conditions were unsuccessful. Even when the reaction was carried out separately, using 99% succinic anhydride the reaction was unsuccessful. Several variations of this coupling reaction were explored using bases such a potassium hydroxide (KOH) and catalytic amount of 4-dimethylaminopyridine (DMAP) (see *Scheme 9) [51]*. It was hypothesised that the presence of the carboxylic acid group was interfering with the desired acylation of the phenolic hydroxyl, potentially due to competitive reactivity or steric hinderance.



Scheme 9: Proposed Synthesis of Compound 20b from m-Hydroxybenzoic Acid using DMAP.

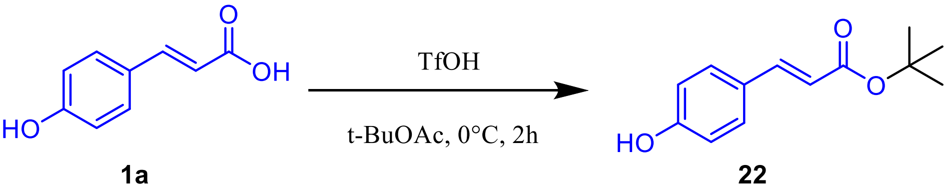
The lack of reactivity was attributed to interference by the carboxylic acid moiety present in the phenolic acids. Its significantly lower pKa of ~4.5 compared to the phenolic hydroxyl of ~9-10 leads to preferential deprotonation under basic conditions, forming a carboxylate anion. This anion can engage in intermolecular interactions of hydrogen bonding that supress nucleophilicity at the phenolic site. While both the phenol and carboxylic acid possess lone pairs, the carbonyl oxygen of the acid is a poor nucleophile due to resonance delocalisation and lower electron density. Therefore, even when deprotonated, the carboxylate is unlikely to attack the succinic anhydride. Instead, it likely interferes sterically or electronically, destabilising the transition state needed for efficient acylation of the phenolic OH.



Scheme 10: Synthesis of Compound 21 via Succinic Anhydride Coupling with p-Ferulic acid.

To investigate this further, succinic anhydride was reacted with the mono-Passerini product **10a** in which the carboxylic acid functionality had already undergone Passerini transformation, leaving a free phenolic hydroxyl group (see *Scheme 10*). LC-MS analysis indicated the formation of a small amount of the desired succinate adduct at the phenolic hydroxyl. However, a significant portion of the starting material remained unreacted, and only trace amount of the product were detected. These results suggest that the presence of a free carboxylic acid significantly affects the reactivity of phenolic hydroxyl groups towards succinic anhydride, potentially by altering the local chemical environment or through intramolecular interactions that hinder nucleophilic attack.

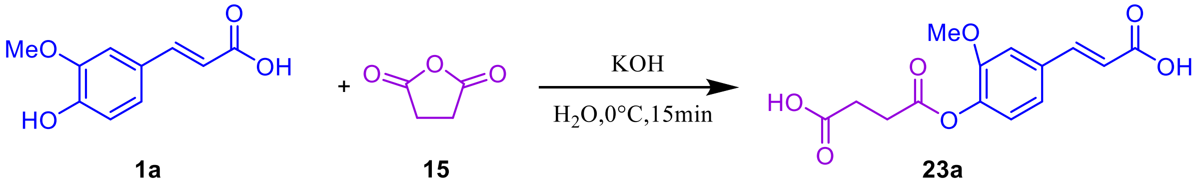
To address this, an alternative stepwise strategy was proposed (see *Scheme 8)*, wherein the carboxylic acid reacted in the Passerini reaction to form the di-Passerini product no free carboxylic acid would be present and the succinic anhydride would react under basic conditions leading to the formation of an adduct that could undergo a secondary Passerini reaction. One the di-product was successfully isolated; solubility presented a significant challenge. The product exhibited limited solubility in most organic solvents and was only soluble in MeOH and DMSO.



Scheme 11: Selective Protection of Phenolic Hydroxyl Group in p-Coumaric acid.

To overcome this, a protecting group strategy was explored to selectively block the carboxylic acid and facilitate acylation of the phenolic hydroxyl (see *Scheme 11)*. *p*-Coumaric acid was treated with TfOH at 0°C in a mixture of tert-butyl acetate and dichloromethane, this method was adapted form a paper by Ogasa et al. but in this case triflic acid was used instead of bis(trifluoromethanesulfonyl)imide [52]. Triflic acid was selected as the protecting group for the phenolic hydroxyl group due to its stability under basic conditions, which was essential for the subsequent succinic anhydride coupling step. The triflate ester can be easily cleaved under acidic conditions, ensuring that its remains intact during the coupling of with succinic anhydride, which requires basic conditions using KOH for esterification. This strategic choice allows for selective cleavage of the protecting group at the appropriate stage of the reaction, allowing for efficient synthesis Upon work-up, LC-MS and crude NMR confirmed that the reaction was only partially selective, yielding a mixture of products, 51% of which is the protection of the phenolic hydroxyl alone, and the other additional carboxylic acid protection. The mono-protected compound was successfully isolated and purified and confirmed by NMR. However, when this selectively protected compound was subsequently subjected to succinic anhydride coupling conditions, no reaction occurred, and no succinate-functionalised product was detected by LC-MS. This result suggests that the presence of a free carboxylic acid alone does not ensure acylation, and addition electronic or steric effects may still inhibit reactivity toward succinic anhydride.

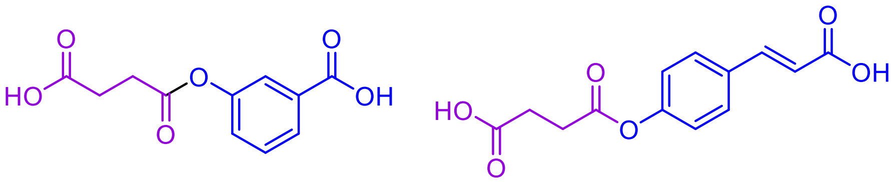
In the original paper reported in literature, which employed *p*-hydroxybenzoic acid, the reaction was performed using *m*-hydroxybenzoic acid and 97% pure succinic anhydride (see *Scheme 12)* [53]. LC-MS analysis of the crude product revealed a minor ion at m/z 239, consistent with the expected monoester. However, this compound exhibited poor signal intensity and expected $[M+H]^+$ or $[M-H]^-$ ions were not dominant peaks in the spectrum. Instead, m/z values of 261 and 499 were most prominent, suggesting the formation of sodium adducts.



Scheme 12: Synthesis of Compound 23a via Coupling of m-Hydroxybenzoic Acid with Succinic Anhydride using KOH.

The difficulty in ionisation can be attributed to structural physiochemical factors. Firstly, the presence of the two carboxylic acid groups, these functionalities are only weakly acidic and do not ionise readily under standard electrospray ionisation (ESI) conditions. Moreover, the product lacks basic groups or other readily ionisable functionalities that would typically promote efficient detection in LC-MS.

Similarly, reaction with *p*-coumaric and *p*-ferulic acid showed minor signals in LCMS indicating limited product formation. No clean NMR spectra were collected due to low conversion and challenges in isolating the product (see *Scheme 13*).



20a **23b**

Scheme 13: Synthesis of Compounds 20a and 23b via Coupling of Phenolic acids with Succinic Anhydride using KOH.

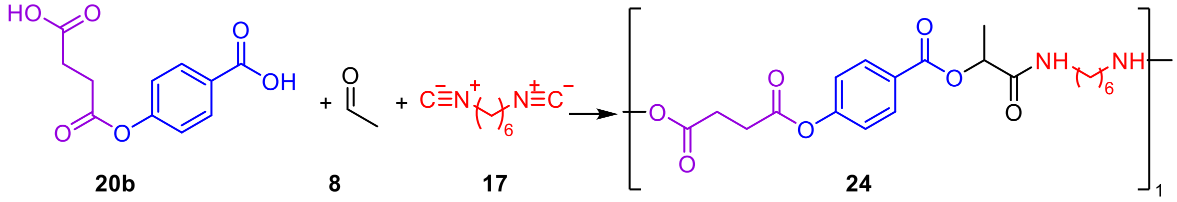
These difficulties isolating the product derived from the phenolic acids. Despite successful formation of the compound from crude LCMS, it could not be effectively separated from unreacted starting material using standard chromatographic techniques. Despite differences in the structural and polarity between these compounds they could not be isolated. This difficulty stems from the two compound's high polarity, which is due to the presence of multiple polar functional groups[50]. The 3-hydroxbenzoic acid contains phenolic acid and carboxylic acid, while the product contains two carboxylic acid groups and an ester linkage, all capable of hydrogen bonding and strong interactions with the silica. These features result in very low Rf values, causing the compound to either strongly absorb to the silica or elute extremely slowly, leading to co-elution.

Although TLC on normal-phase silica had initially indicated a reasonable separation between the product and starting material, this did not translate effectively to automated flash chromatography using normal phase column the starting material and product co-eluted. This discrepancy is likely due to differences in scale and dynamics, on TLC, smaller sample amount and slower development can enhance the resolution, while on the autocolumn, sample overloading and more rapid elution can reduce separation efficiency.

Prep-HPLC was used as this had previously separated product based on their hydrophobicity. However, during this process, a new complication arose, partial transesterification of the product was seen in the NMR preformed after the isolation. This may have occurred due to the use of methanol as the solvent to dissolve the product. Under acidic or silica supported conditions, the carboxylic acid groups within the product can react with alcohol solvents to form methyl or ethyl esters[51]. The incident highlighted the sensitivity of ester containing carboxylic acid derivatives.

To mitigate this cold crystallisation was explored. The crude product was first dissolved in hot ethyl acetate to create a saturated solution. Once fully dissolved, heptane was gradually added to the solution to reduce the overall polarity and induce selective crystallisation of the desired product. The mixture was allowed to cool slowly to room temperature before being placed in the fridge to encourage crystallisation. This method was chosen to help prevent transesterification of the product. Although this approach did not yield a crystalline solid under the initial conditions tested, it remains a promising strategy for isolating polar, hydrogen-bonding compounds with the succinate adduct. This method may be used if it is further optimised with the solvent ratios, cooling rates and seeding techniques.

If successfully functionalised, the resulting diacid would present two carboxylic acid groups positioned to undergo step-growth Passerini polymerisation which would enable the formation of PEAs (see *Scheme 14*).

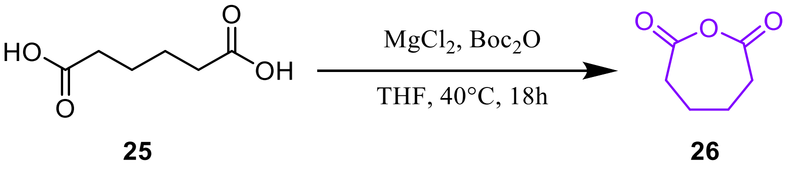


Scheme 14:Proposed Passerini Polymerisation of Functionalised p-Hydroxybenzoic Acid via Succinic Anhydride derived Diacid Monomer.

2.3.5 Adipic Anhydride Coupling with Phenolic Acids

However, the formation of the succinic anhydride adducts onto the phenolic acid remained low-yielding and challenging to isolate. A previous study by Jiang et al. reported that even after 3 days of reflux, the reaction between *p*-hydroxybenzoic acid and succinic anhydride yielding only 10%, despite structural similarity [12, 13]. Their conditions were slightly different using pyridine as the base which is weaker base than KOH. Better conversion was achieved using adipic anhydride to derivatise the phenolic OH. This enhanced reactivity may be attributed to the greater ring strain and lower stability of the resulting seven-membered cyclic anhydride, which likely increase its electrophilicity.

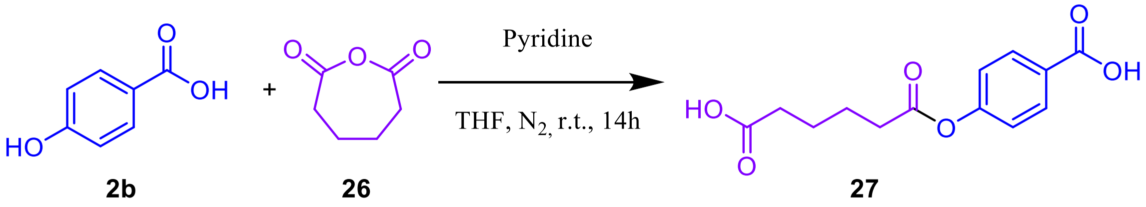
Building on this observation and despite extensive attempts to activate phenolic acids using succinic anhydride, yields and product isolation remained challenging, primary due to poor reactivity and purification difficulties. This limitation necessitated a shift in strategy. Adipic anhydride emerged as a promising alternative, offering improved electrophilicity and reactivity. This pivot proved crucial in establishing a more reliable route to functionalised diacid monomers suitable for subsequent Passerini polymerisation.



Scheme 15: Synthesis of Adipic Anhydride Compound 26.

To explore this alternative strategy, adipic anhydride was synthesised for adipic acid using a method adapted from Robert et al. (see *Scheme 15*) [54]. This method is an efficient, high yielding sustainable route to cyclic anhydride from bio renewable and inexpensive dicarboxylic acids. Cyclic anhydrides were synthesised from dicarboxylic acids using a catalyst prepared in situ from $MgCl_2$ and dialkyl dicarbonates. Unlike succinic anhydride, which forms a relatively stable five-membered ring, adipic anhydride is less stable due to its larger, seven-membered cyclic structure. This increase ring strain was expected to promote esterification under mild conditions, offering a new potential synthesis of a diacid monomer.

In addition to improved reactivity, the used of adipic anhydride introduces a longer aliphatic spacer in the resulting ester linkage, increasing the number of methylene units in the bifunctional linker. This structural change could influence the flexibility and spacing between the repeating units in the resulting polymer, potentially altering its physical properties and reactivity.



Scheme 16: Proposed Synthesis Compound 27 via Coupling of p-Hydroxybenzoic Acid and Adipic Anhydride.

Initial attempts to functionalise phenolic acids using adipic anhydride under basic conditions were unsuccessful, despite the increased electrophilicity of adipic anhydride relative to succinic anhydride (see *Scheme 16*). The failure of this reaction was attributed to the presence of residual moisture in the reaction medium , which may have led to the hydrolysis of adipic anhydride and subsequent reformation of adipic acid. The depletion of the reactive anhydride significantly supressed the esterification. Although the inherently low nucleophilicity of the phenolic hydroxyl group may have contributed to the limited reactivity. In phenolic systems such as *p*-hydroxybenzoic acid, the lone pair of electrons on the hydroxyl oxygen is delocalised into the aromatic ring through resonance, significantly reducing its ability to participate in nucleophilic attack. Furthermore, the presence of a carboxylic acid group on the ring exerts an additional electron-withdrawing inductive effect, further decreasing the electron density on the phenolic oxygen and exacerbating its poor reactivity toward acylation agents such as adipic anhydride. These observations suggest that to achieve successful acylation using adipic anhydride, the reaction must be conducted under strictly anhydrous conditions to prevent hydrolysis.

2.3.6 Selective Protection of Carboxylic Acids via Benzyl Ester Formation

To overcome these limitations, a protecting group strategy was employed to selectively mask the carboxylic acid functionality and improve the nucleophilic accessibility of the phenol. The method was adapted from Guo et al. [55]. Benzyl bromide was selected as the protecting agent due to its compatibility with mild reaction conditions and the ease with which the benzyl ester can be removed by hydrogenolysis[56]. Sodium bicarbonate was selected as the base to selectively deprotonate the carboxylic acid without affecting the phenolic hydroxyl, enabling clean and selective ester formation. Benzyl protection was favoured over the alternative strategies such as triflate. This selective protections prevented competitive deprotonation and intramolecular interactions involving the carboxyl group, thereby enabling esterification to proceed at the phenolic site. With the carboxylic acid group protected, the phenolic hydroxyl could undergo clean esterification with adipoyl chloride. This would enable the formation of a bifunctional monomer bearing both terminal carboxylic acids and internal ester linkage. While this protection proved effective, subsequent experiments revealed the direct esterification of phenolic acids.

2.3.7 Synthesis of Biphenolic Diesters via Adipoyl Chloride Coupling

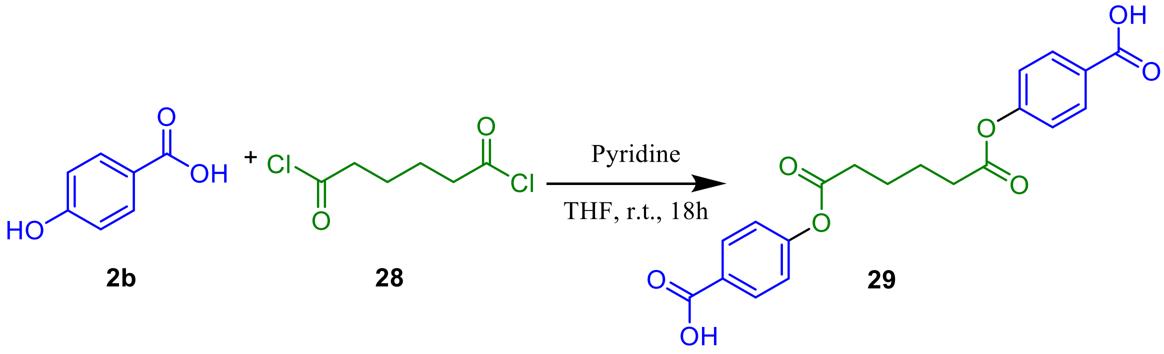
To achieve efficient diester formation at phenolic hydroxyls, adipoyl chloride was selected in place of cyclic anhydride. While cyclic anhydride are commonly employed for esterification, they are generally less reactive under mild conditions and prone to hydrolysis in aqueous or partially polar systems. In contrast, acid chlorides are significantly more electrophilic and can undergo nucleophilic acyl substitution readily with phenolic in the presence of mild base. The phenolic oxygen attacks the electrophilic carbonyl carbon of adipoyl chloride, forming a tetrahedral intermediate that collapses to release chloride ion and form and ester bond.

The use of adipoyl chloride enabled clean and efficient coupling with two equivalents of the benzyl protected phenolic acid, forming symmetrical biphenolic diester. This method was adapted from the work using adipoyl chloride to esterify the phenolic alcohol on cardol and also recent work by Jelley et al., who successfully used adipoyl chloride to esterify the phenolic hydroxyl groups of quercetin, a flavonoid derived from grape waster, to product antimicrobial polymeric materials from renewable feedstocks [57, 58].

During method development, a literature report by Prudencio et al. using salicylic acid (*o*-hydroxybenzoic acid) without carboxylic acid protection demonstrated a remarkably high yield of 92% for the esterification with anhydride under mild conditions [59]. This prompted an analogous reaction using *p*-hydroxybenzoic acid (see *Scheme 17*). In this case, product formation was observed, although with difficulties in purification. Crude NMR and LC-MS analysis confirmed the formation of the expected ester product. The LC-MS also revealed a peak at m/z 266, suggesting the presence of a monoester side product. The species is likely to be a partial esterification, where one hydroxyl group reacts with adipoyl chloride, while the second acyl chloride undergoes hydrolysis and is transformed back into the carboxylic acid.

Thie highlight the importance of maintaining strictly anhydrous conditions throughout the reaction to minimise hydrolysis.

The difference in reactivity is likely due to regioelectronic effects. In salicylic, the ortho-positioning of the hydroxyl group allows for intramolecular hydrogen bonding with the adjacent carboxyl group, enhancing the nucleophilicity of the phenol and possibly stabilising the transition state. In *p*-hydroxybenzoic acid, the hydroxyl is para to the carboxylic acid, which lacks stabilisation. Moreover, the electron withdrawing carboxyl group, when para to the hydroxyl, further depletes electron density via resonance, decreasing nucleophilicity and hence reactivity. These positional and electronic differences can have an effect of the reactivity of the reaction.



Scheme 17: Synthesis of Compound 27 via p-Hydroxybenzoic Acid and Adipoyl Chloride.

These effects become even more pronounced in *p*-coumaric acid and *p*-ferulic acid, where conjugated side chains and, in the case of ferulic acid, a methoxy substituent, further influence reactivity. The methoxy group is an electron-donating substituent, which should in principle increase the nucleophilicity of the phenolic hydroxyl through resonance. However, this theoretical enhancement may be effect by increased steric hindrance and reduced solubility. These factors can limit the accessibility of the phenolic OH for nucleophilic attack on the acylating agent.

The esterification proceeded successfully without the need to protect the carboxylic acid, yielding a bifunctional monomer bearing two free -COOH groups and two internal ester linkages connected via phenolic cores. Crude ^{1}H and LC-MS analysis confirmed the formation of the desired product, consistent with the successful ester formation. However, despite clear evidence of product formation, isolation remained challenging due to co-elution with unreacted starting materials and strong interactions with the purification media.

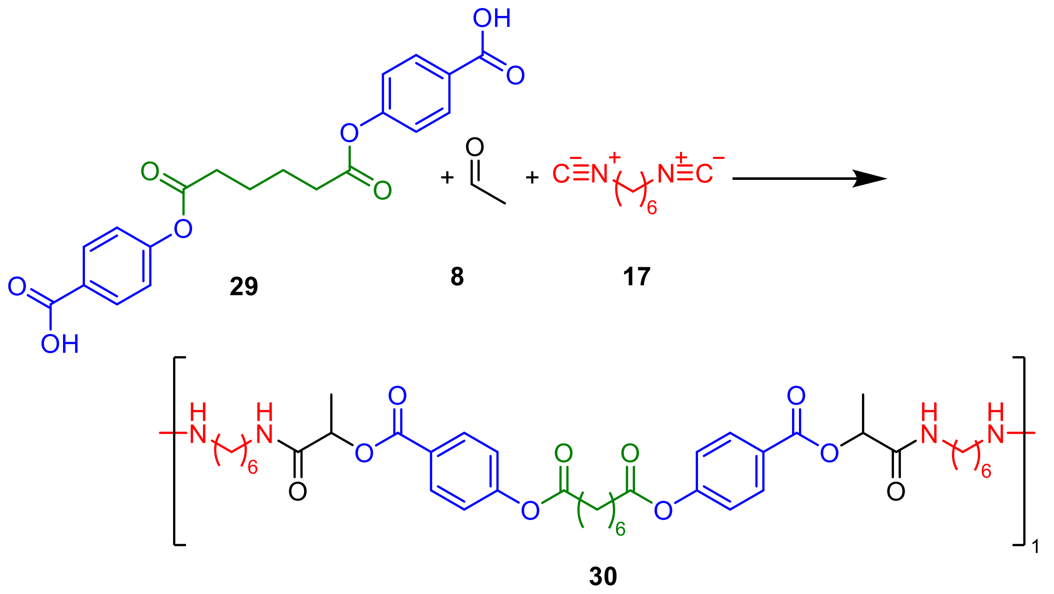
Notably, this reaction appears more promising than analogous attempts with cyclic anhydride, which yielded complex mixtures and lower conversions. In contrast, the adipoyl chloride approach produces fewer impurities and higher yields of product, making it more efficient and a cleaner route. This bi-phenolic scaffold provides a modular and highly functionalised platform with dual reactive sites suitable for multicomponent step-growth polymerisation, expanding the scope of accessible bio-based polymer architectures.

Moreover, this approach is particularly attractive because it eliminates the need for protecting group strategies, simplifying the synthesis workflow. The ability to directly esterify phenolic acids without carboxylic acid protection reduces the number of steps and avoids the use of additional reagents or harsh deprotection conditions. While isolation remains a challenge, efforts are underway to optimise purification using cold crystallisation techniques, which may provide a scalable and solvent-efficient route to obtain the product in high purity. If successful, this would offer a more practical and environmentally friendly pathway for the synthesis of functionalised diacid monomers from renewable feedstocks.

Crucially, the feasibility of the Passerini reaction with phenolic acid derivatives has already been demonstrated in both mono and diisocyanide systems described earlier in this study, confirming that this monomer design is chemically compatible with multicomponent polymerisation strategies.

2.3.8 Proposed Diacid Passerini Polymerisation

Following successful synthesis and isolation of the adipoyl chloride derived diacid monomer, a pathway toward Passerini polymerisation was designed but not experimentally completed within the scope of this study. The method involves combining the bifunctional diacid, 1,6-diisocyanhexane and acetaldehyde [60, 61]. The reaction would be carried out under optimised conditions in EtOAc at 0.2 M concentration, based on pervious solvent screening. The bifunctional nature of both the diacid and diisocyanide enabled a step-growth polymerisation via a repeated Passerini reaction mechanism., leading to the formation of poly(ester-amide)s, The proposed procedure was adapted from Lv et al. [22]. It relies on the bifunctionality of both the isocyanide and the diacid to drive liner polymer formation (see *Scheme 18*). While full polymerisation and characterisation were not performed, this synthetic design lay the groundwork for future development of sustainable bio-based polymers from phenolic acid derivatives.



Scheme 18: Proposed Passerini Polymerisation of Functionalised p-Hydroxybenzoic Acid via Adipoyl Chloride derived Diacid Monomer.

3 Conclusion

This research demonstrated the compatibility of phenolic acids with Passerini multicomponent reactions and explored multiple strategies to develop functionalised monomers suitable for multicomponent step-growth polymerisation. Initial mono-Passerini reactions confirmed that biomass-derived phenolic acids, such as *p*-coumaric, *p*-ferulic, and *m* and *p*-hydroxybenzoic acid, can react effectively under optimised conditions. However, limitations in solubility and reaction concentrations were shown to significantly impact yields and downstream transformations.

Further investigation into diisocyanide systems identified ethyl acetate as the most suitable solvent for di-Passerini adduct formation, while alternative conditions such as microwave heating and HFIP co-solvents yielded lower conversions. One of the major challenges was the limited solubility and difficult purification of intermediate and final products, which hindered scale-up and broader application.

Attempts to directly couple phenolic acids with cyclic anhydrides to produce diacid monomers proved inefficient due to poor reactivity and purification issues. The limitation prompted a shift toward adipoyl chloride as a coupling agent, which enabled the successful synthesis of biphenolic diesters. This generated bifunctional monomers bearing two carboxylic groups and internal ester linkages. This modular structure offers a promising platform for bio-based polymer development.

Although full polymerisation was not completed within this work, the groundwork was laid for Passerini step-growth polymerisation of the synthesised diacid monomers, the primary barrier was not chemical incompatibility, but purification and solubility. The results highlighted the importance of monomer design, solvent selection, and functional group reactivity in developing sustainable polymerisation systems.

Overall this study supports the broader mission of the Circular Cultivation and Chemistry Project by valorising agricultural biomass into high-value functional materials. Future studies will focus on completing polymer synthesis, optimising reaction parameters, and evaluating material properties such as thermal stability, mechanical strength, and environmental impact.

4 Future Research and Outlook

This study has demonstrated that phenolic acids are compatible with Passerini multicomponent chemistry, and can be transformed into bifunctional diacid monomers via adipoyl chloride esterification. While polymerisation was not carried out in this work, the successful synthesis of these monomers opens a promising route to bio-based poly(ester-amide)s. The proposed Passerini polymerisation thus remains the key objective for future research.

Once the polymer is synthesised it would be subsequently analysed using gel permeation chromatography (GPC). To discover the a number-average molecular weight (Mn) and polydispersity index (PDI) of the polymer, indicating molecular weight distribution. These findings would confirm successful polymer formation via multicomponent reaction and demonstrate the feasibility of using phenolic-derived diacids in polymerisations.

Additionally, the use of structurally alternative diacid chlorides presents a valuable direction for tuning polymer properties similar to the strategy demonstrated by Jelley et al [58]. Modifications to the linker structure, such as chain length, introducing aromatic units or unsaturation, or adding functional side groups, would influence, mechanical strength, thermal behaviour. Similarly, adjusting other monomer components, including para-substituted phenolic acids, linear aldehydes, or rigid diisocyanides, may enhance polymer regularity and mesogenic characteristic typical of LCPs and broaden the scope of the polymerisation. These structural modification provide valuable tools for fine-tuning material performance in terms of mechanical strength and crystallinity.

To fully characterise and evaluate these materials, thermal and mechanical analyses, including differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and tensile testing, should be carried out. These techniques will provide insight into thermal transitions, stability, and processability, and help establish clear structure property relationships.

Finally, as sustainability remains a core motivation behind bio-based materials, future efforts should also examine the environmental footprint of these poly(ester-amide)s. Investigations into the biodegradability, recyclability, and lifecycle analysis would provide critical data to evaluate their real-world applicability and alignment with circular materials design.

5 Innovation and Societal Impact

This research supports the objectives of the EU funded Circular Cultivation and Chemistry Project, which promotes the valorisation of regional biomass through eco-cultivation and advanced chemical synthesis. By focusing on these metabolites this work transitions away from petrochemical dependence and shifts toward bio-based material innovation.

The development of phenolic acids into diacid monomers for Passerini polymerisation not only demonstrates modular, green chemistry but also provides a scalable strategy to produce bio-based PEAs under mild, atom-economic conditions. These methods not only highlight synthetic innovation but the polymers offer potential in high performance applications, with tuneable properties for fields such as LCPs.

Beyond its scientific contributions, this work promotes circular value chains by integrating local agriculture with material innovation. By coupling agricultural waste valorisation with material design, the research promotes regional sustainability, resource efficiency, and alignment with broader EU goals in climate neutrality, bioeconomy development, and sustainable manufacturing.

6 Experimental

6.1 General Information

Commercially available reagents and solvents were purchased from Sigma-Aldrich, Fischer Scientific, Strem Chemicals, TCI chemicals, Activate Scientific, or Fluorochem and were used as purchased unless stated otherwise. Solvents were purchased from VWR Chemicals or Sigma-Aldrich and used without purification, unless mentioned otherwise.

Thin layer chromatography (TLC) was performed using plates from Merck (SiO_2,Kieselegl 60 F_{254} neutral, on aluminium with fluorescence indicator) and compounds were visualised by UV detections (254nm) and $KMnO_4$ stain. Liquid Chromatography- Mass Spectrometry (LC-MS) analysis was performed on a Shimadzu Nexera 2 UHPLC system equipped with Shimadzu LC-30AD pump, an SPD-M30A photodiode array detector and LCMS-2020 single quadrupole detector. The system was run on MilliQ water and LC-MS grade acetonitrile modified with 0.1% formic acid. A Water XSelect CSH C_{18} column (3.0mm x 75mm with particle size 3.5µm) was used operating at 30°C. The method was set up with a gradient of 5% acetonitrile with water for 2 min, an increase to 95% acetonitrile over 12 min, 1 min at 95% followed by flushing back to 5% acetonitrile.

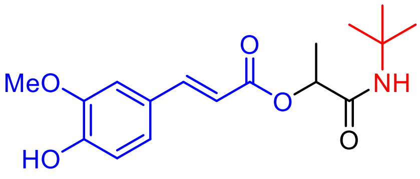
Flash column chromatography was performed by employing silica (200-300 mesh) as stationary phase and *n*-heptane/ ethyl acetate.

Preparative-scale purification was performed using a Shimadzu preparative HPLC system, consisting of a CBM-40 systems controller, LC-20AP preparative pump, FCV-200AL quaternary vale, SPD-M40 photodiode array detector, LCMS-2050 mass detector, LC-40D make-up pump, LH-40 fraction collector, and FCV-20AH2 valve unit. Separation was carried out using Shim-pack Scepter $C1_{18-120}$ column, (5µm, 20 x 150mm) with an optimised gradient elution for each compound (MeCN/MilliQ water with 0.1% TFA) at a flow rate of 20mL/min. Fraction collection was triggered by the PDA and/or MS signal detection.

NMR spectra were recorded on JEOL 400JJYH working on a frequency of 400MHz. Chemical shifts (δ) are given in ppm and coupling constants (J) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet) , q (quartet), and m (multiplet) or combinations thereof. NMR data was processed with Mestrenova version 12.

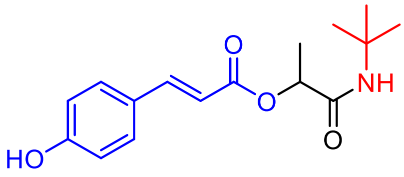
6.2 General Procedure for Mono-isocyanide Passerini reaction

Phenolic acid (4 mmol, 1 eq) was dissolved in 0.1 M MeCN. tert-butyl isocyanide (452.4 µL, 4 mmol, 1 eq) and acetaldehyde (225.9 µL, 1 eq) were added to the reaction and stirred at room temperature for 72 hours. The crude product was concentrated *in vacuo* and purified by column chromatography using a suitable gradient.



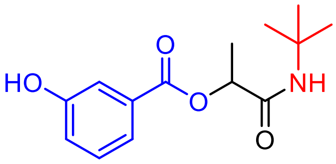
10a

Compound 10a 1-(tert-butylamino)-1-oxopropan-2-yl (E)-3-(4-hydroxy-3-methoxyphenyl)acrylate. Prepared from *p-ferulic acid* (776.72 mg, 4 mmol, 1 eq) according to the general procedure and isolated as a white solid. **Yield** 424 mg, (1.32 mmol, 33%). **^{1}H NMR** (400 MHz, DMSO-*D_6*) δ 10.20 (s, 1H), 8.12 – 8.04 (m, 2H), 7.85 (d, *J* = 2.0 Hz, 1H), 7.64 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.03 (d, *J* = 15.9 Hz, 1H), 4.34 (s, 3H), 1.87 (d, *J* = 6.8 Hz, 3H), 1.78 (s, 9H).



10b

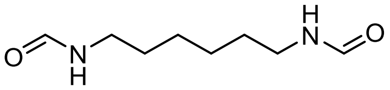
Compound 10b 1-(tert-butylamino)-1-oxopropan-2-yl (E)-3-(4-hydroxyphenyl)acrylate. Prepared from *p-coumaric acid* (656.6 mg, 4 mmol, 1 eq) according to the general procedure and isolated as a white solid. **Yield** 436.5mg, 1.5mmol, 37.5%. ^{1}H NMR (400 MHz, DMSO-*D_6*) δ 7.62 – 7.38 (m, 3H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.42 (d, *J* = 15.9 Hz, 1H), 4.94 (q, *J* = 6.8 Hz, 1H), 1.33 (d, *J* = 7.0 Hz, 3H), 1.25 (s, 9H). ^{13}C NMR (101 MHz, DMSO-*D_6*) δ 174.3, 170.0, 166.4, 160.4, 145.5, 130.9, 125.6, 116.3, 114.5, 70.2, 67.9, 50.6, 50.2, 40.6, 40.4, 40.2, 39.9, 39.8, 39.6, 39.4, 28.9, 21.6, 18.4.



11

Compound 11 1-(tert-butylamino)-1-oxopropan-2-yl 4-hydroxybenzoate. Prepared from *m-hydroxybenzoic acid* (552 mg, 4 mmol, 1 eq) according to general procedure and isolated as a white solid. **Yield** 465mg, 1.75 mmol, 43%. ^{1}H NMR (400 MHz, DMSO-D_6) δ 7.64 (s, 1H), 7.44 – 7.26 (m, 3H), 7.03 (d, J = 9.3 Hz, 1H), 5.04 (q, J = 6.8 Hz, 1H), 1.40 (d, J = 6.8 Hz, 3H), 1.25 (s, 9H).

6.3 N,N'-(hexane-1,6-diyl)diformamide



31

Hexane-1,6- diamine (1.97 g, 17 mmol, 1 eq) was dissolved in *ethyl formate* (34.74 mL, 425 mmol, 25 eq) acting both as the reagent and solvent. The reaction was heated at reflux in 100mL rbf in 70°C overnight. The solution was concentrated *in vacuo*. The product was obtained as a white powder. **Yield** 2.9 g, (17 mmol, 98%).

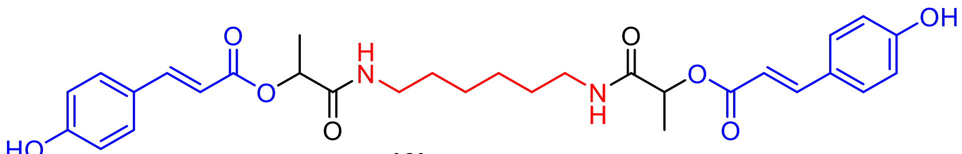
6.4 1,6-diisocyanohexane

17

N,N'-(hexane-1,6-diyl)diformamide (2.9 g, 17 mmol, 1 eq) and *triethylamine* (29.29 mL, 210 mmol, 12 eq) were dissolved in 85mL of DCM and cooled in an ice bath to 0°C. $POCl_3$ (4.84 mL, 51 mmol, 3 eq) was added dropwise. The reaction was stirred at 0°C for an hour and moved to room temperature for another two hours. The reaction mixture was cooled in an ice bath and was quenched with saturated K_2CO_3 for 15 minutes. The product was extracted with DCM, where the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo.* The product was purified via chromatography Cyclohexane:EtOAc 50:50 and the product obtained was a dark orange viscous oil. **Yield** 2.6 g, (15.1 mmol, 89%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.39 (s, 4H), 1.67 (s, 4H), 1.45 (s, 4H). Data was confirmed with literature [21].

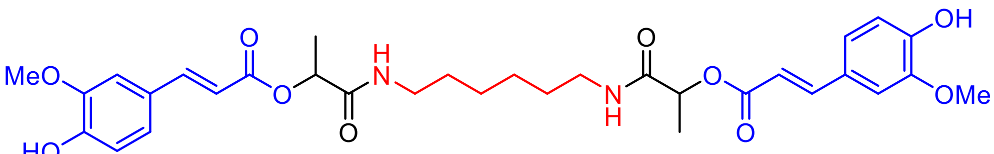
6.5 General Procedure for Diisocyanide Passerini Reaction

A solution of 1,6-diisocyanohexane (0.1 mmol, 1 eq) and the corresponding phenolic acid (0.3 mmol, 3 eq) was prepared in the appropriate solvent and concentration. Acetaldehyde (0.3 mmol, 3 eq) was added, and the reaction mixture was stirred at room temperature for a specific period.



13b

Compound 18b (hexane-1,6-diylbis(azanediyl))bis(1-oxopropane-1,2-diyl) (2E,2'E)-bis(3-(4-hydroxy-3-methoxyphenyl)acrylate). Prepared from *p-coumaric acid* (582.54 mg, 3 mmol, 3 eq) and *1,6-diisocyanohexane* (138.3 mg, 1 mmol, 1 eq) was added to a round-bottom flask (rbf) with 10mL EtOAc. The reaction was stirred at ambient temperature for 6 days. Excess EtOAc was added to dissolve the starting material, and the solution was centrifuged to collect the precipitate. The product was subsequently isolated by prep-HPLC with 45-55% gradient for 16mins 100-100dn. A very fine white powder was isolated. **Yield** 150 mg, (0.24 mmol, 24%). **^{1}H NMR** (400 MHz, DMSO-D_6) δ 9.59 (s, 2H), 7.95 (s, 2H), 7.53 (d, *J* = 15.9 Hz, 2H), 7.29 (s, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 6.76 (d, *J* = 8.1 Hz, 2H), 6.48 (d, *J* = 15.9 Hz, 2H), 4.96 (q, *J* = 6.8 Hz, 2H), 3.78 (s, 6H), 3.01 (q, *J* = 6.2 Hz, 4H), 2.46 (s, 3H), 1.35 – 1.19 (m, 14H).**^{13}C NMR** (101 MHz, DMSO-D_6) δ 170.4, 166.4, 149.9, 148.4, 145.9, 126.10 123.7, 116.0, 114.81, 111.6, 70.1, 56.2, 38.7, 29.5, 26.4, 18.4.



13a

Compound 18a (hexane-1,6-diylbis(azanediyl))bis(1-oxopropane-1,2-diyl)(2E,2'E)-bis(3-(4- hydroxyphenyl)acrylate). *p-ferulic acid* (492 mg, 3 mmol, 3 eq) under identical conditions to 14b. **Yield** 114mg, (0.2 mmol, 20%). **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.03 (s, 2H), 7.96 (t, *J* = 5.7 Hz, 2H), 7.60 – 7.50 (m, 6H), 6.82 – 6.74 (m, 2H), 6.42 (d, *J* = 16.0 Hz, 2H), 4.97 (q, *J* = 6.8 Hz, 2H), 3.03 (q, *J* = 6.6 Hz, 3H), 1.28 (d, *J* = 51.4 Hz, 14H).**^{13}C NMR** (101 MHz, DMSO-D_6) δ 170.4, 166.3, 160.4, 145.6, 130.8, 125.5, 116.3, 114.5, 70.1, 38.7, 29.5, 26.4, 18.4.

14

Compound 19 (hexane-1,6-diylbis(azanediyl))bis(1-oxopropane-1,2-diyl) bis(4-hydroxybenzoate). *m-Hydroxybenzoic acid* (414 mg, 3 mmol, 3 eq) under the same conditions as 14b. A clear viscous liquid was obtained. **Yield** 60 mg, (0.12 mmol, 12%). **^{1}H NMR** (400 MHz, DMSO-*D*$_6$) δ 10.04 (s, 2H), 7.98 (t, *J* = 5.7 Hz, 2H), 7.69 – 7.41 (m, 6H), 6.80 (d, *J* = 8.7 Hz, 4H), 6.43 (d, *J* = 16.0 Hz, 2H), 4.99 (q, *J* = 6.9 Hz, 2H), 3.04 (q, *J* = 6.5 Hz, 4H), 1.43 – 1.15 (m, 14H).**^{13}C NMR** (101 MHz, DMSO-*D*$_6$) δ 170.2, 165.5, 157.9, 131.2, 130.2, 120.6, 116.3, 83.5, 70.9, 38.8, 29.4, 26.4.

6.6 Kinetic Studies of Different Solvents in Diisocyanide Reaction

A kinetic study was conducted by comparing the LC-MS yield of the reaction when using different solvents see *Table 5.* The reaction conversion was monitored via LC-MS based on the peak area of compound 14b. Following the general procedure for diisocyanide reaction with trans-4-hydroxy-3-methoxycinnamic acid (49.2 mg, 0.3 mmol, 3 eq), 1,6-diisocyanohexane (13.8 mg, 0.1 mmol, 1 eq) and acetaldehyde (16.9 µL, 0.3 mmol, 3 eq). The reaction was stirred at room temperature for 48 hours. For each sample 1 mL of MeOH was added to ensure complete dissolution and homogeneity. Then 50 µL was taken from this homogenous mixture and 950 µL of MeOH was added and the solution was filtered through 0.2µm PTFE filter.

Table 5: Reaction Table for Solvent Screening.

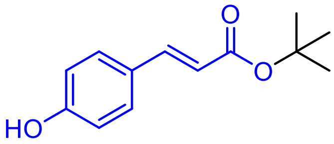
Substrate	Equivalents	Solvent	Concentration [M]	Time (h)
p-coumaric	3:3:1	TFE	0.1	48
p-coumaric	3:3:1	MeOH	0.1	48
p-coumaric	3:3:1	HFIP	0.1	48
p-coumaric	3:3:1	DCM	0.1	48
p-coumaric	3:3:1	EtOAc	0.1	48
p-coumaric	3:3:1	MeCN	0.1	48
p-coumaric	3:3:1	TFE	0.2	48
p-coumaric	3:3:1	MeOH	0.2	48
p-coumaric	3:3:1	HFIP	0.2	48
p-coumaric	3:3:1	DCM	0.2	48
p-coumaric	3:3:1	EtOAc	0.2	48
p-coumaric	3:3:1	MeCN	0.2	48

6.7 Kinetic Studies of HFIP 20v/v%

The kinetic study was conducted by comparing the LC-MS yield of the reaction following the general procedure for diisocyanide reaction with trans-4-hydroxy-3-methoxycinnamic acid

(49.2 mg, 0.3 mmol, 3 eq) and HFIP 20v/v%. The reaction conversion was monitored via LC-MS based on the peak area of compound 14b at 1,2,3,4,5,6,12 and 48 hours. For each sample 1 mL of MeOH was added to ensure complete dissolution and homogeneity. Then 50µL was taken from this homogenous mixture and 950µL of MeOH was added and the solution was filtered through 0.2µm PTFE filter. Other studies were done using 3 eq of HFIP in 0.1 M of EtOAc over the same number of hours.

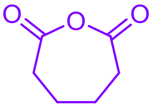
6.8 Protection of Phenolic Hydroxyl Group Using Triflic Acid



22

A suspension of *p-coumaric acid* (1 g, 6mmol, 1 eq) in 6 mL of t-*BuOAc* was cooled to 0°C and solution of *trifluromethanesulfonic acid TfOH* in 8 mL of chloroform was added. The mixture was stirred for 2 hours. The reaction was quenched by the slow addition to a stirred solution of saturated $NaHCO_3$ at 0°C. The aqueous layer. was extracted with CH_2Cl_2 (3x500 mL) and the combined organic layers were dried with Na_2SO_4, filtered and concentrated in *vacuo.* The product was isolated 80:20 Heptane:EtOAc. **Yield** 680 mg (3.1 mmol , 51%). 1H NMR (400 MHz, DMSO-D6) δ 7.63 – 7.22 (m, 3H), 6.77 (d, J = 8.7 Hz, 2H), 6.26 (d, J = 15.9 Hz, 1H), 1.46 (s, 9H).

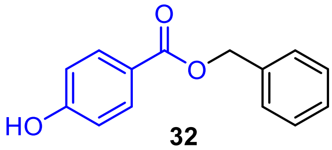
6.9 Adipic Anhydride Synthesis



26

MgCl₂ (20 mg, 0.2 mmol, 1 eq), *adipic acid* (1.46g, 10 mmol, 50 eq), *di-tert-butyl decarbonate* (2.2g, 10 mmol, 50 eq) in 10 ml of THF stirred in a round-bottom flask at 40°C in air. the reaction was left overnight, the conversion was checked by NMR spectroscopy, which indicated select conversion. The reaction was stirred for another 3 days. Yield 1.13g (8.8 mmol, 88%). 1H NMR (400 MHz, $CDCl_3$) δ 2.30 (d, J = 4.5 Hz, 2H), 1.64 (d, J = 16.5 Hz, 2H).

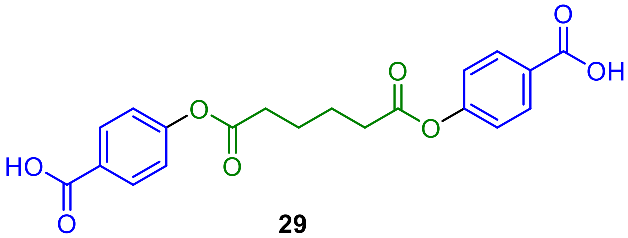
6.10 Benzyl Protection of Phenolic Carboxylic Acids



32

p-Hydroxybenzoic acid (1.38 g, 10 mmol, 1 eq) and *sodium bicarbonate* (1.68 g, 20 mmol, 2 eq) were suspended in 30 mL of a 1:1 mixture of water and acetone. The suspension was cooled in an ice bath 0 °C, and *benzyl bromide* (1.72 mL, 14.5 mmol, 1.45 eq) was added dropwise with stirring. The reaction mixture was allowed to warm to room temperature and stirred for 24 hours. After completion, the acetone was removed under reduced pressure, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography using a gradient of EtOAc:heptane (30:70 → 60:40) to afford the benzyl-protected compound as a white solid.

6.11 Synthesis of Diester-Functionalised Phenolic Acids via Adipoyl Chloride



29

p-Hydroxybenzoic acid (1.52 g, 11 mmol, 2 eq) was dissolved in dry tetrahydrofuran (40 mL) and *pyridine* (0.89 mL, 11 mmol, 2 eq) under nitrogen atmosphere at room temperature. *Adipoyl chloride* (0.95 mL, 5.5 mmol, 1 eq), dissolved in 10 mL of dry THF, was added dropwise over 5 minutes with stirring. The reaction mixture was stirred for 2 hours at room temperature, resulting in a pale suspension. Upon completion, the reaction was poured into 300 mL of deionised water and acidified to pH ~2 with concentrated hydrochloric acid. The resulting off-white precipitate was collected by vacuum filtration, washed with cold water (3 × 50 mL), and dried under vacuum overnight at room temperature to afford the diester-functionalised product. Crude NMR: 1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 15.2 Hz, 4H), 7.10 (d, J = 8.7 Hz, 4H), 2.58 (d, J = 19.5 Hz, 4H), 1.82 (d, 4H).

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I would also like to thank the PhD students in the lab for their assistance, collaboration, and for creating a friendly and stimulating working environment. I am grateful to my fellow student for their ongoing support and helpful contributions during my time here.

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9 Appendix

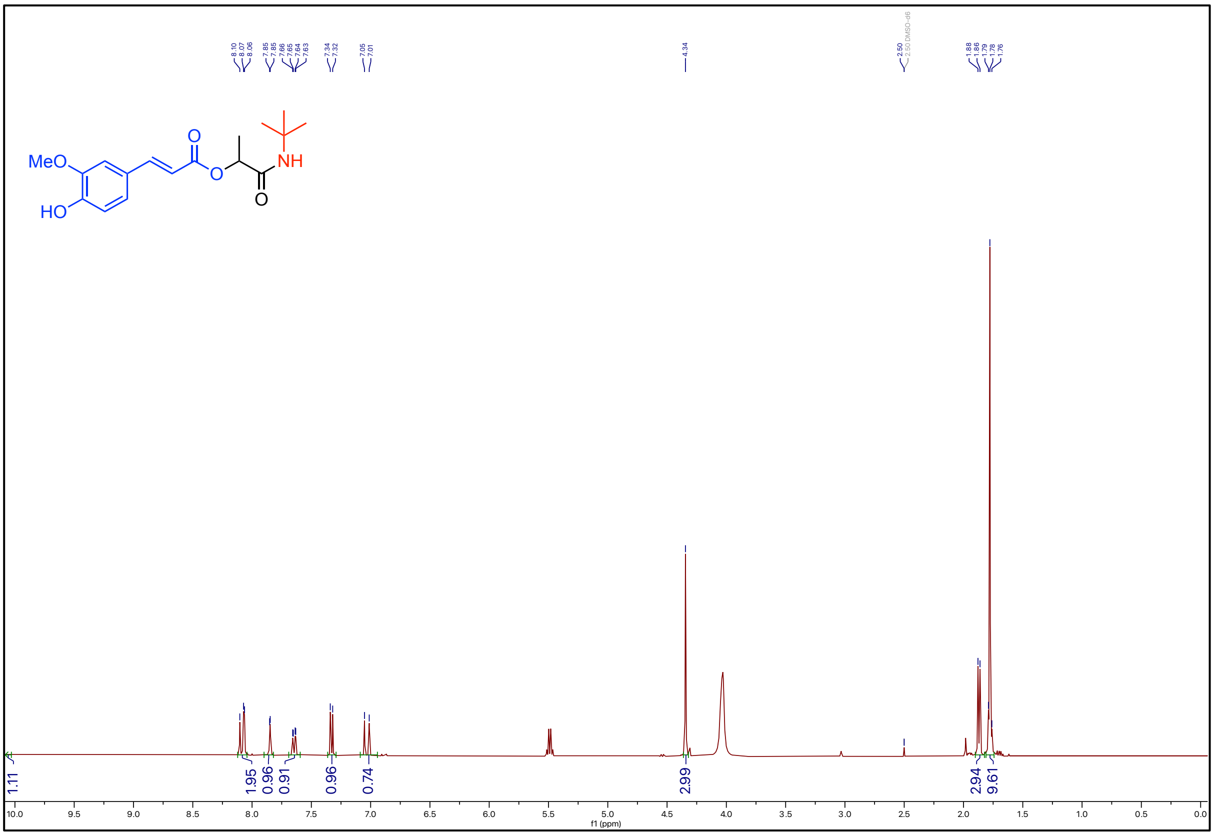

Figure 3: Proton NMR of Compound 10a.

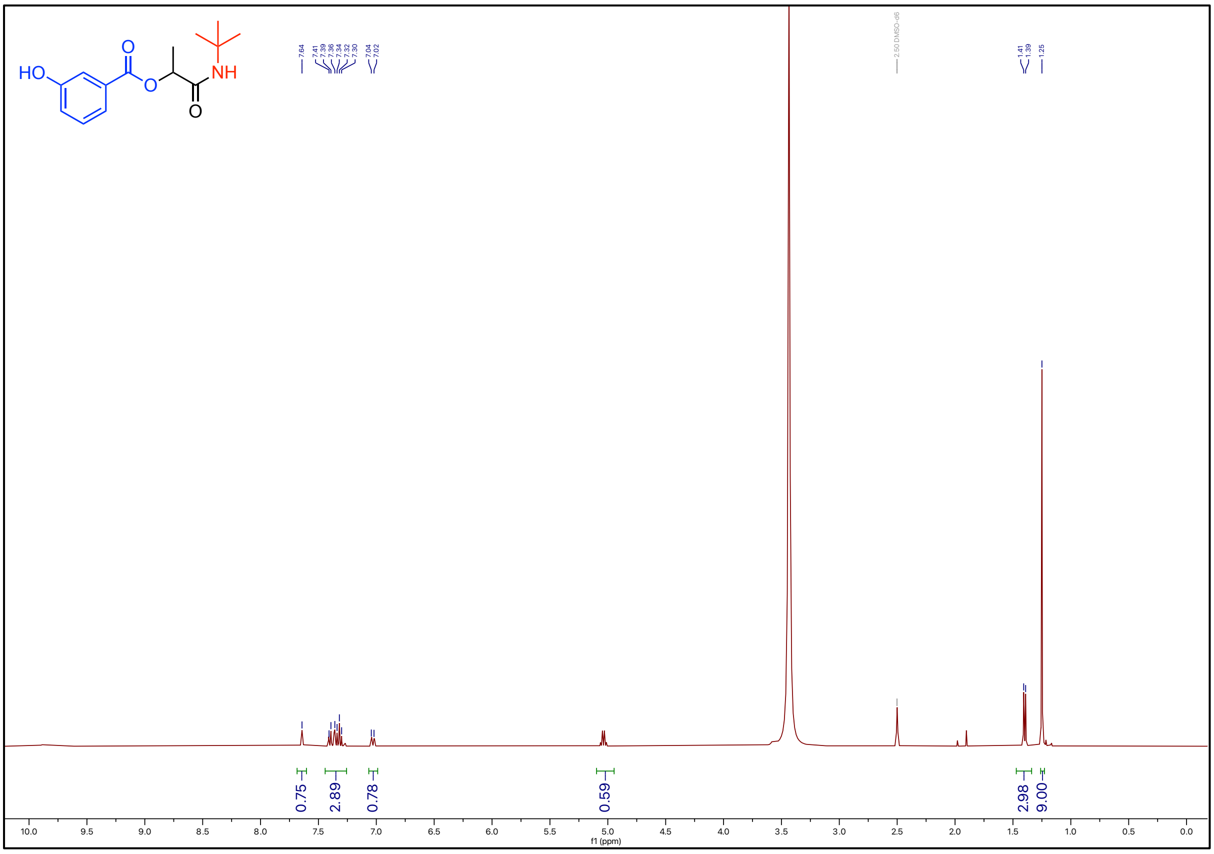

Figure 4: Proton NMR of Compound 11.

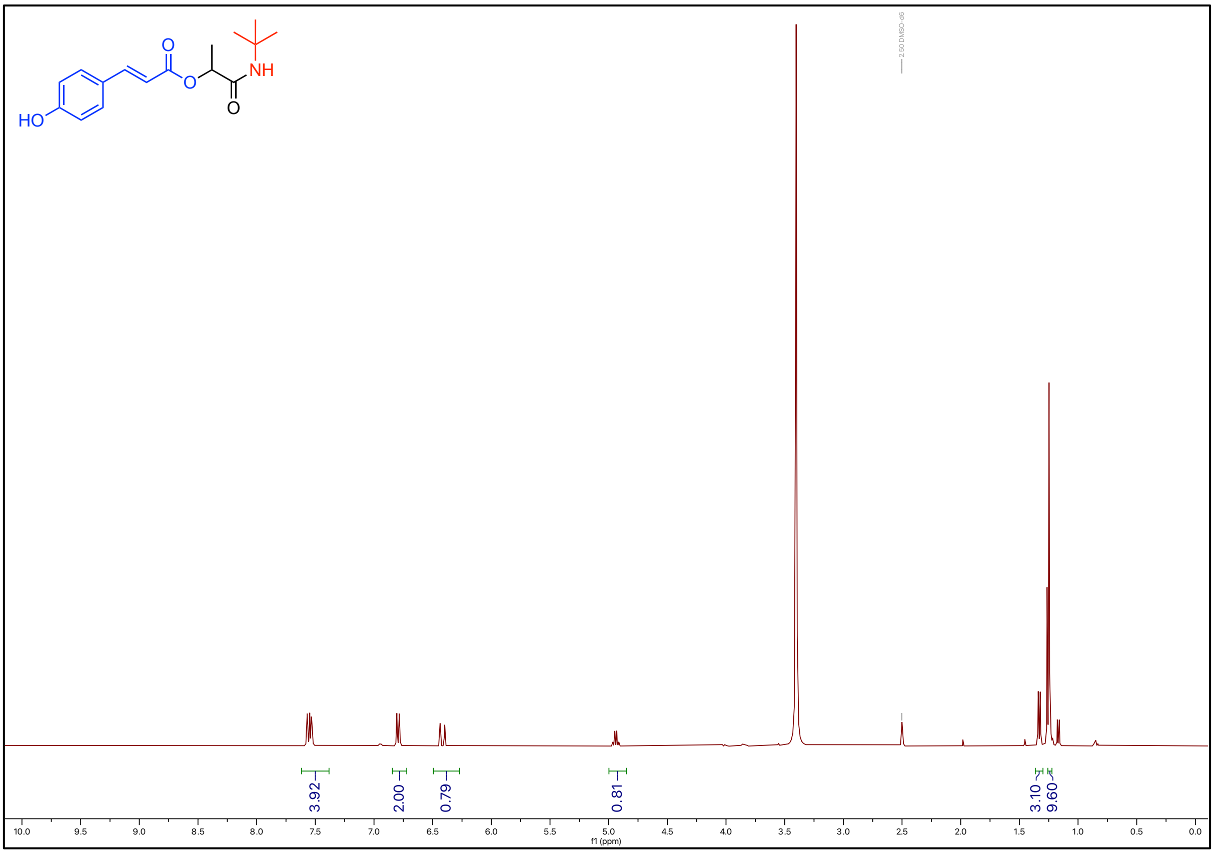

Figure 5: Proton NMR of Compound 10b.

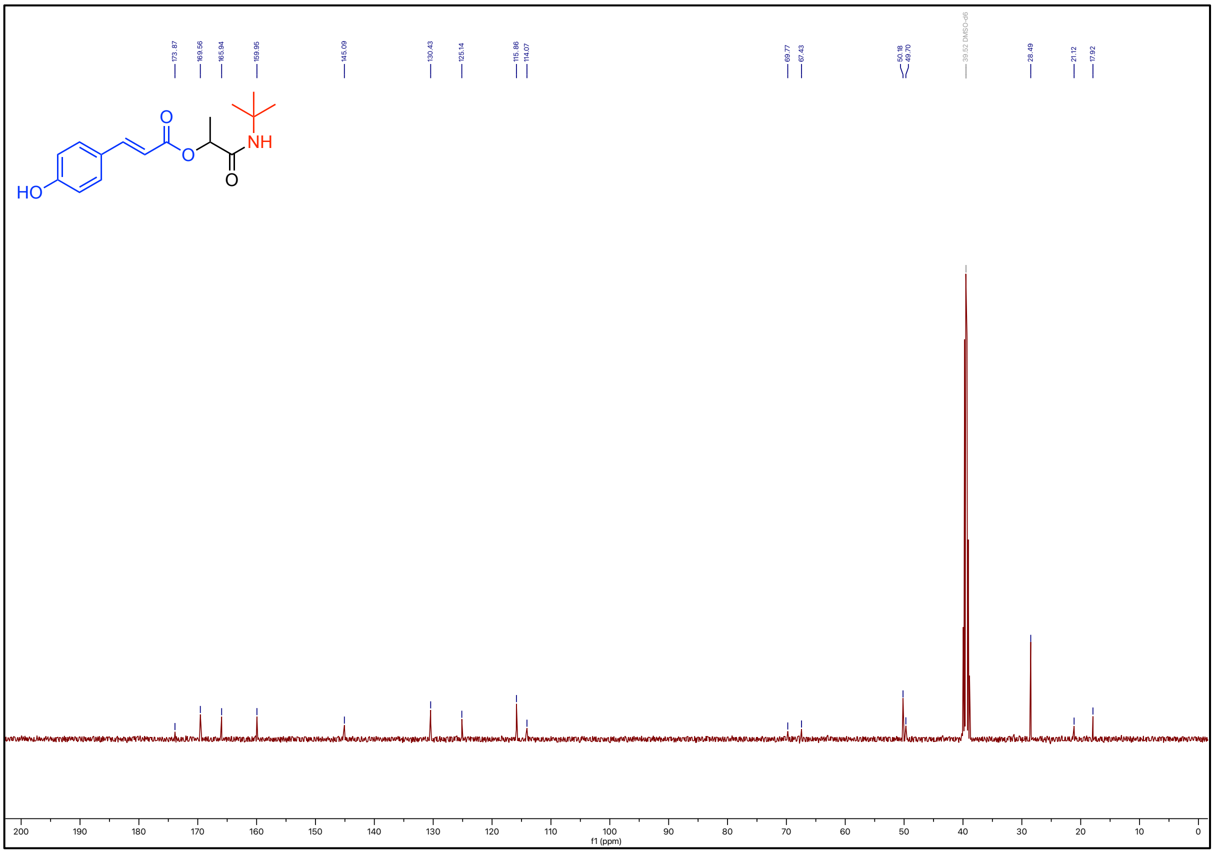

Figure 6: Carbon NMR of Compound 10b.

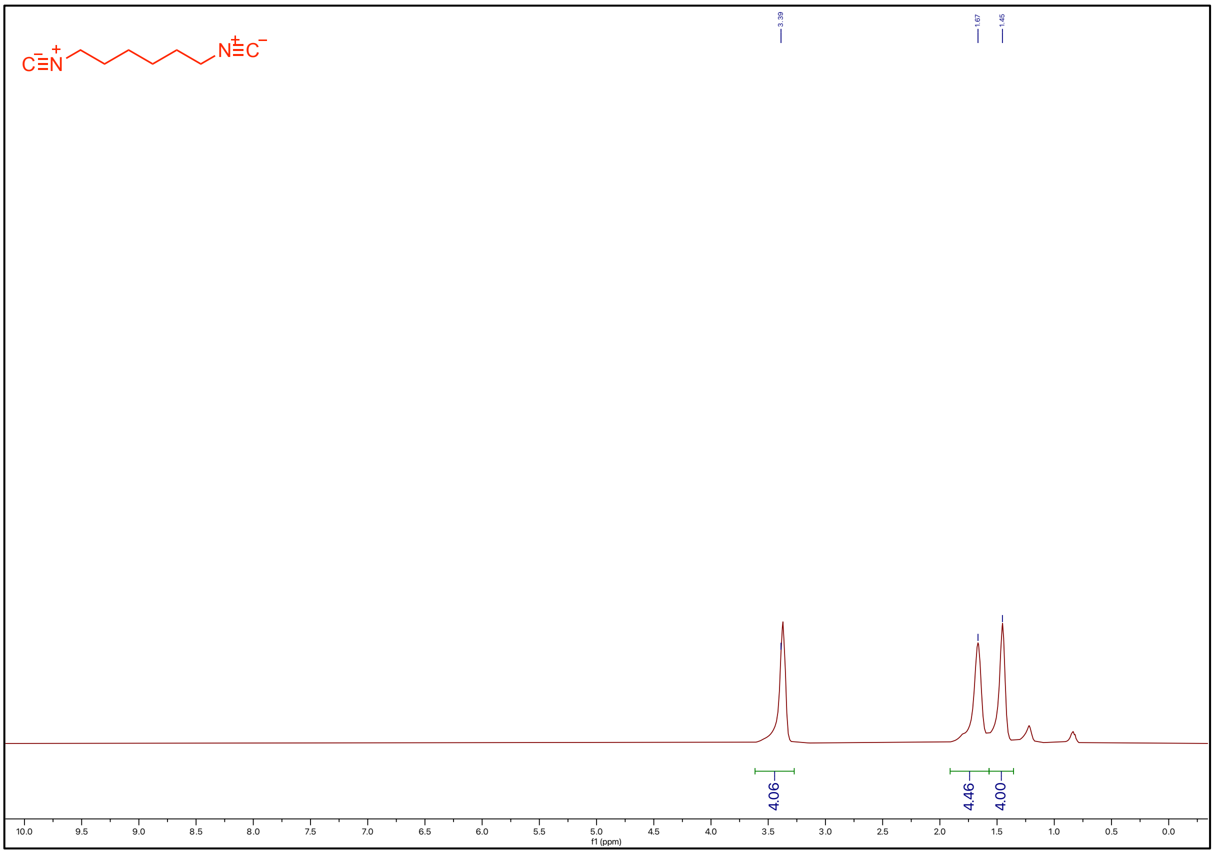

Figure 7: Proton NMR of Compound 17.

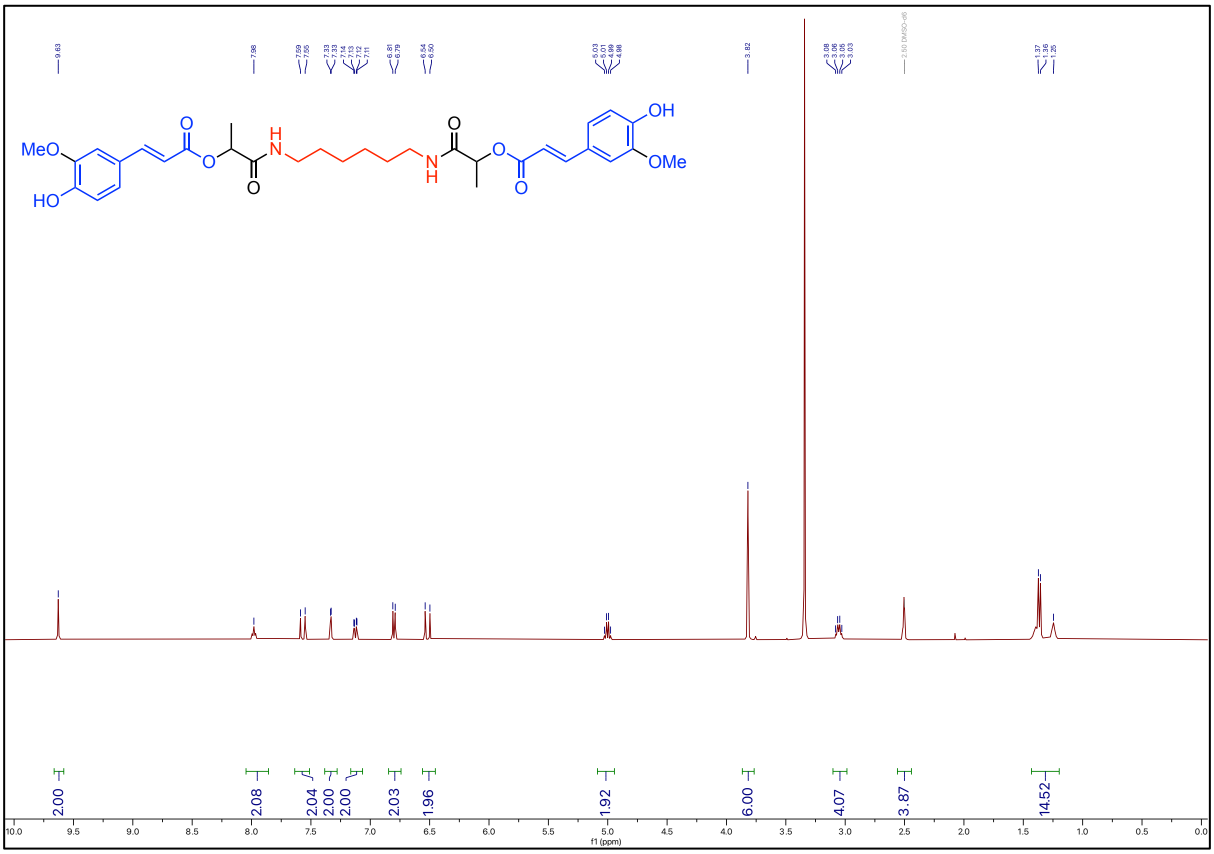

Figure 8:Proton NMR of Compound 13a.

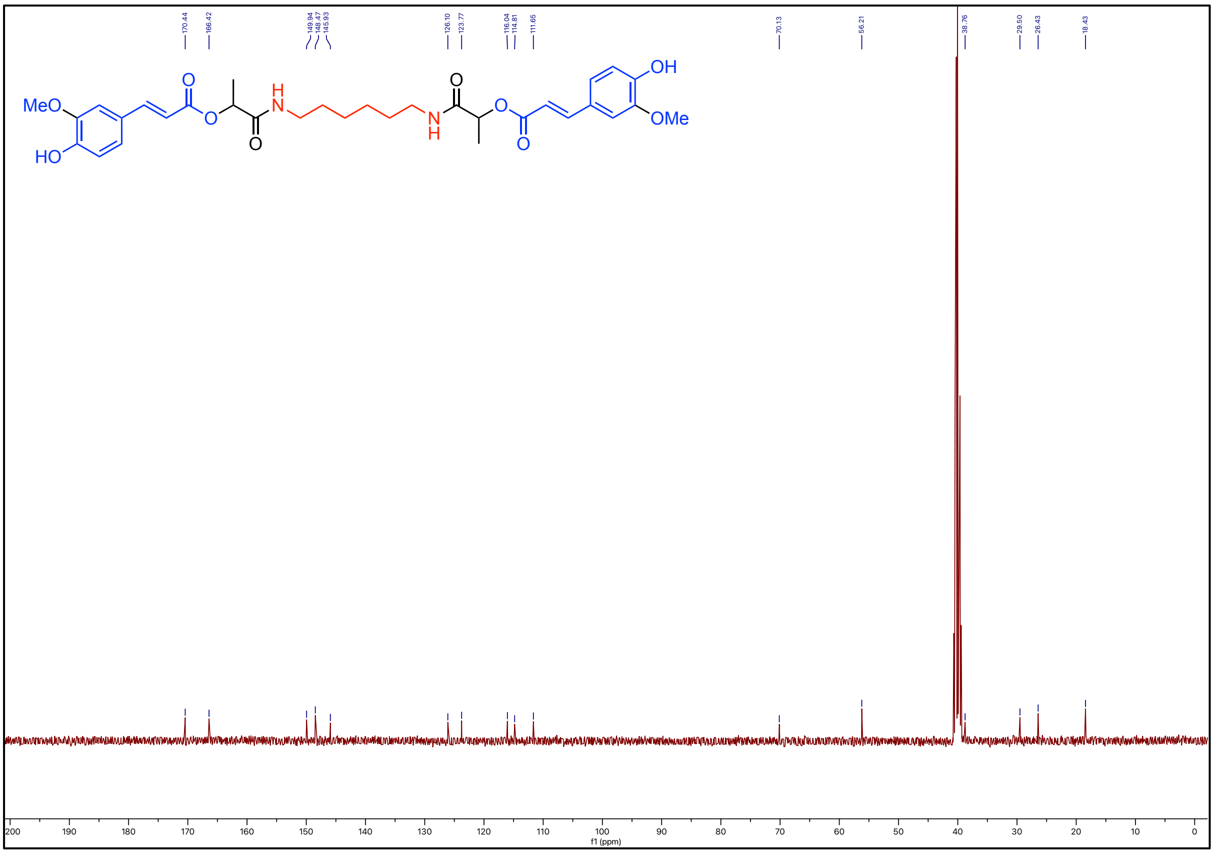

Figure 9:Carbon NMR of Compound 13a.

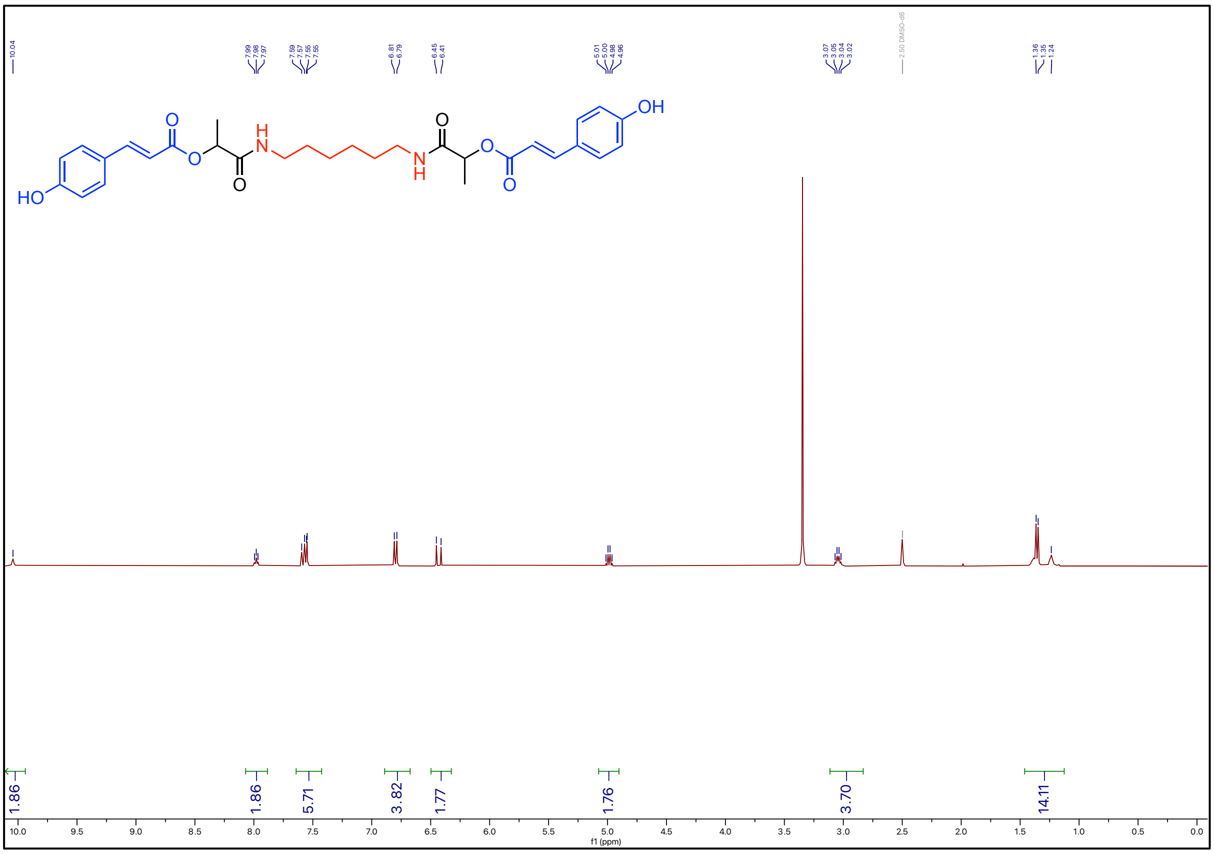

Figure 10: Proton NMR of Compound 13b.

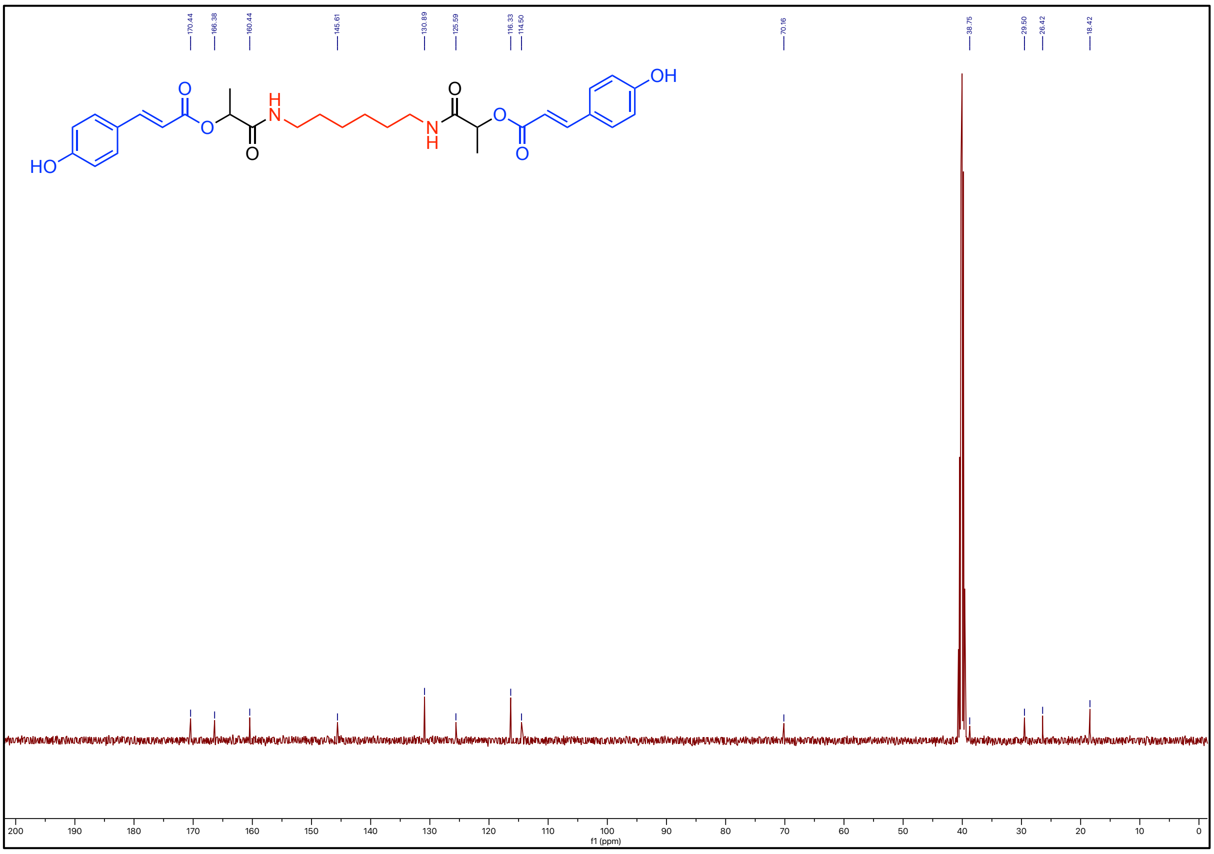

Figure 11: Carbon NMR of Compound 13b.

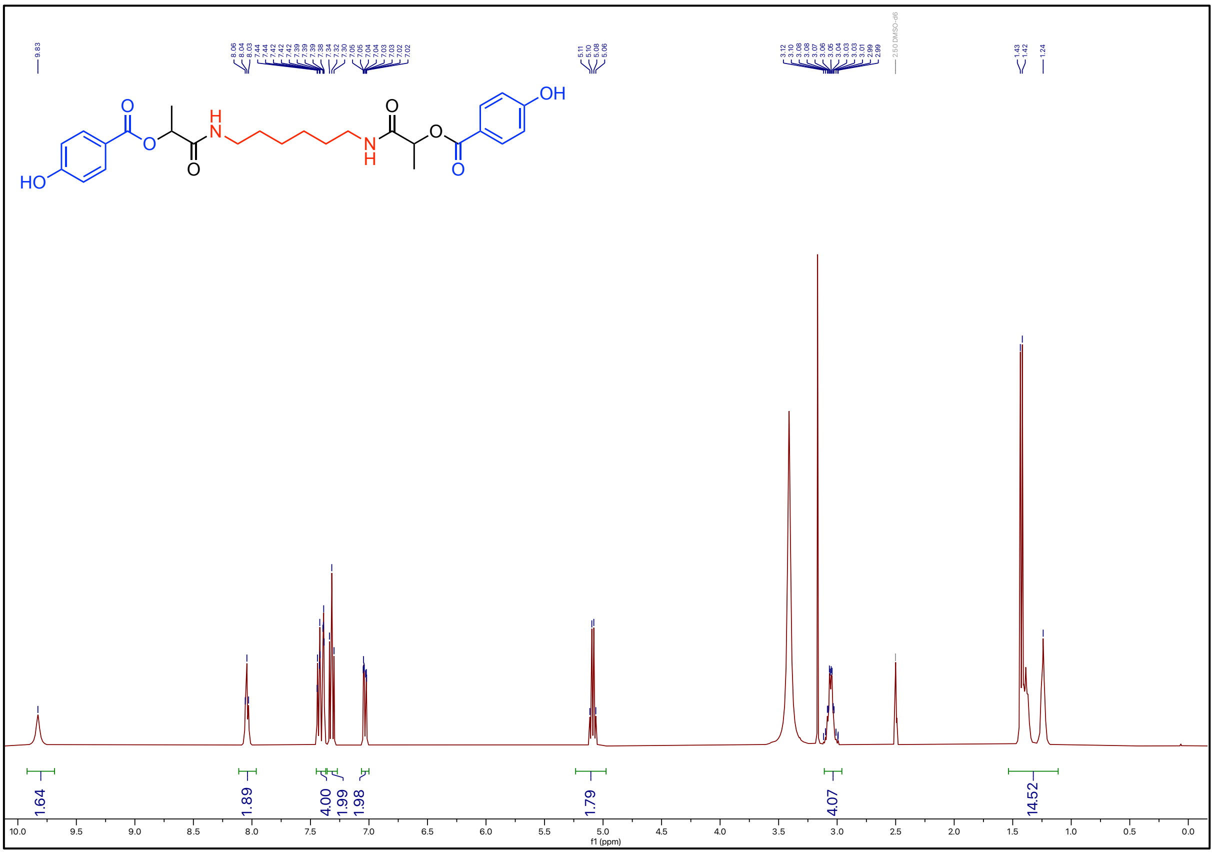

Figure 12: Proton NMR of Compound 14.

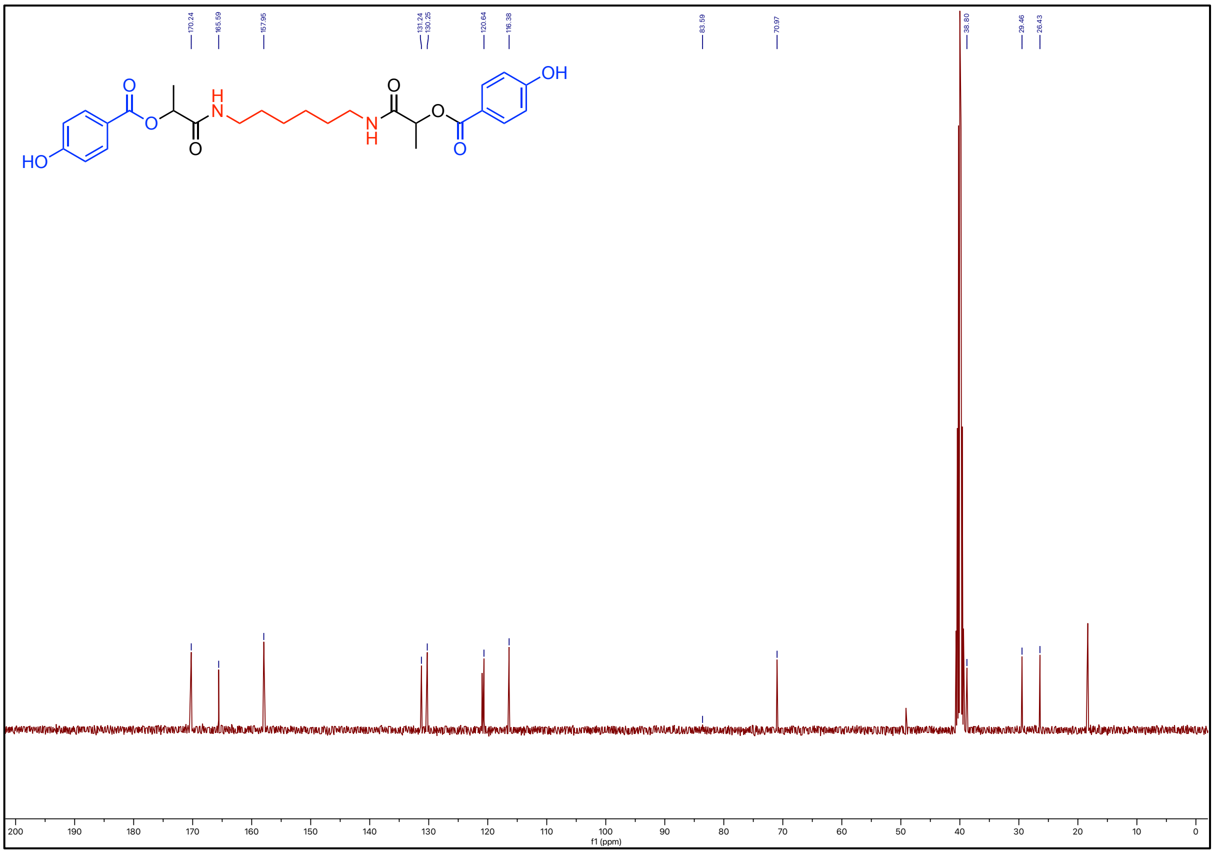

Figure 13: Carbon NMR of Compound 14.

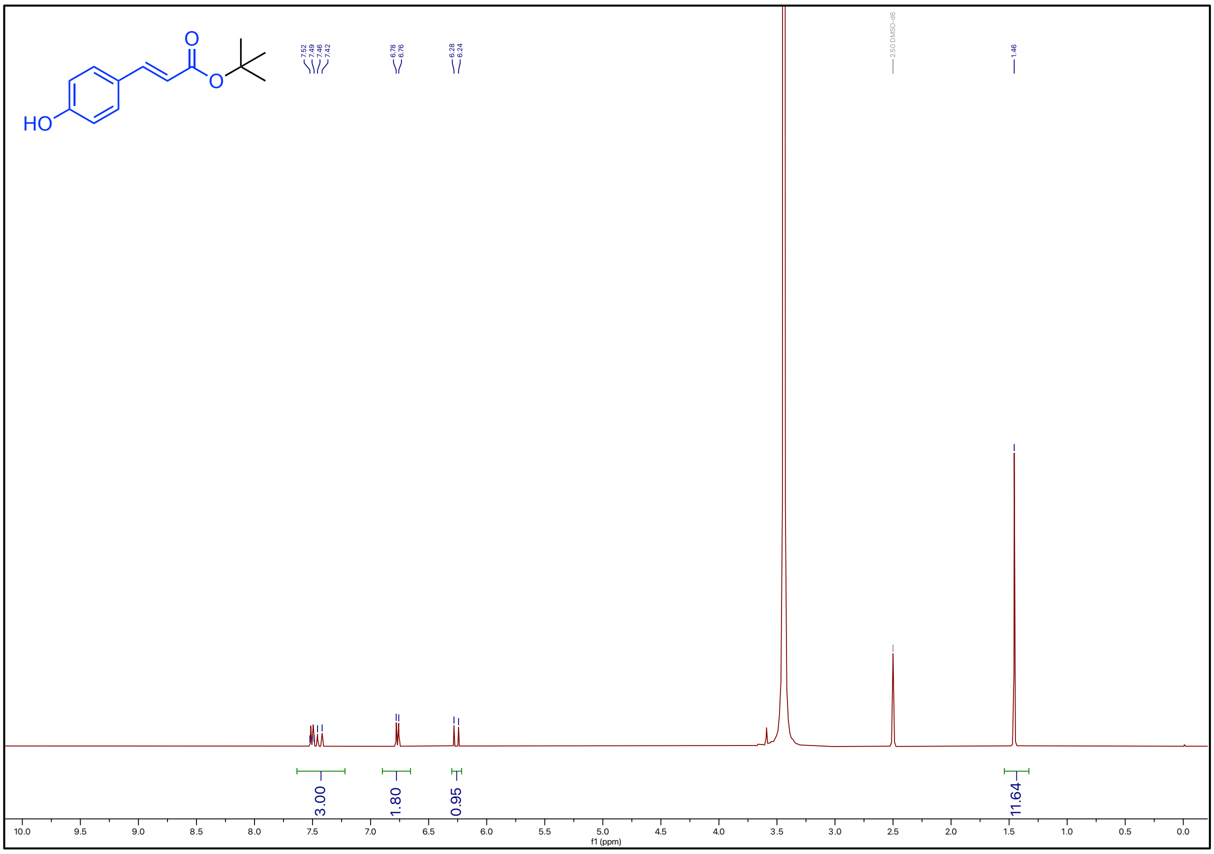

Figure 14: Proton NMR of Compound 22.

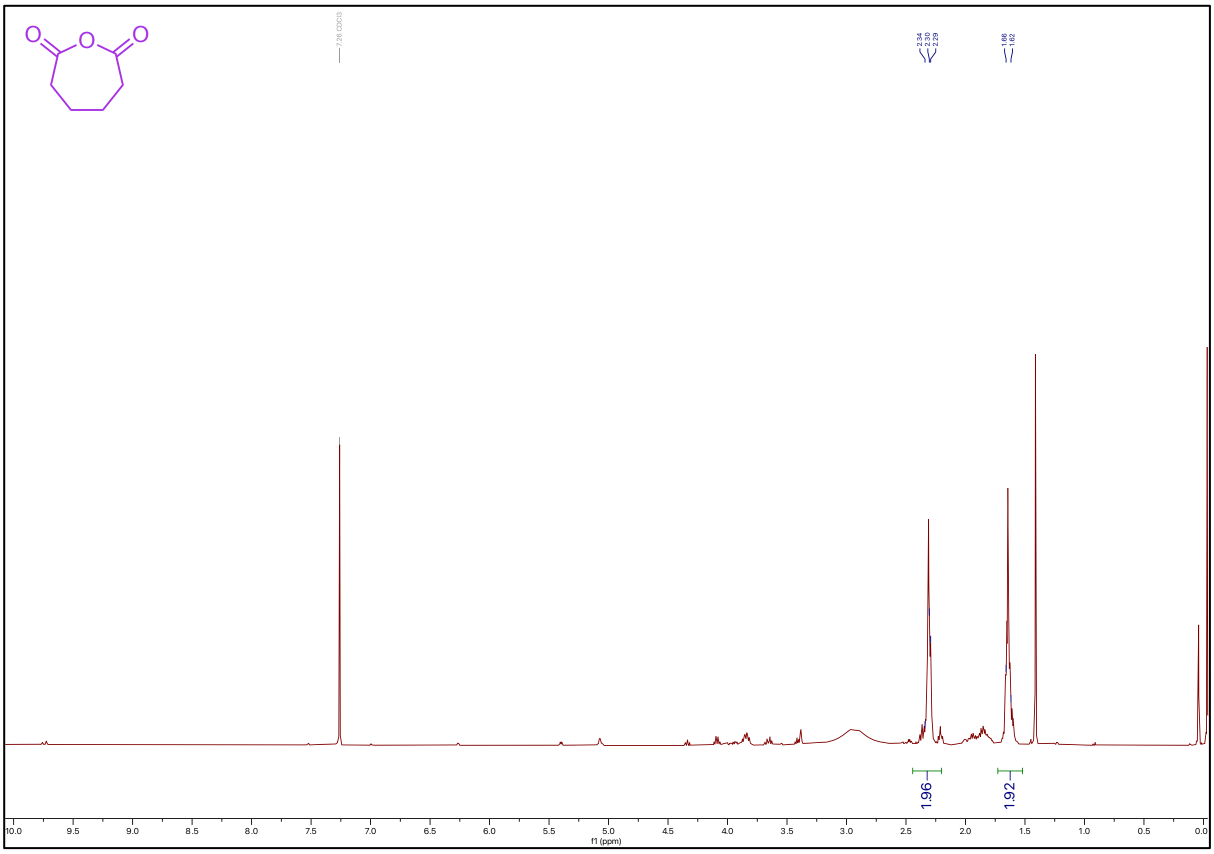

Figure 15: Proton NMR of Compound 26.

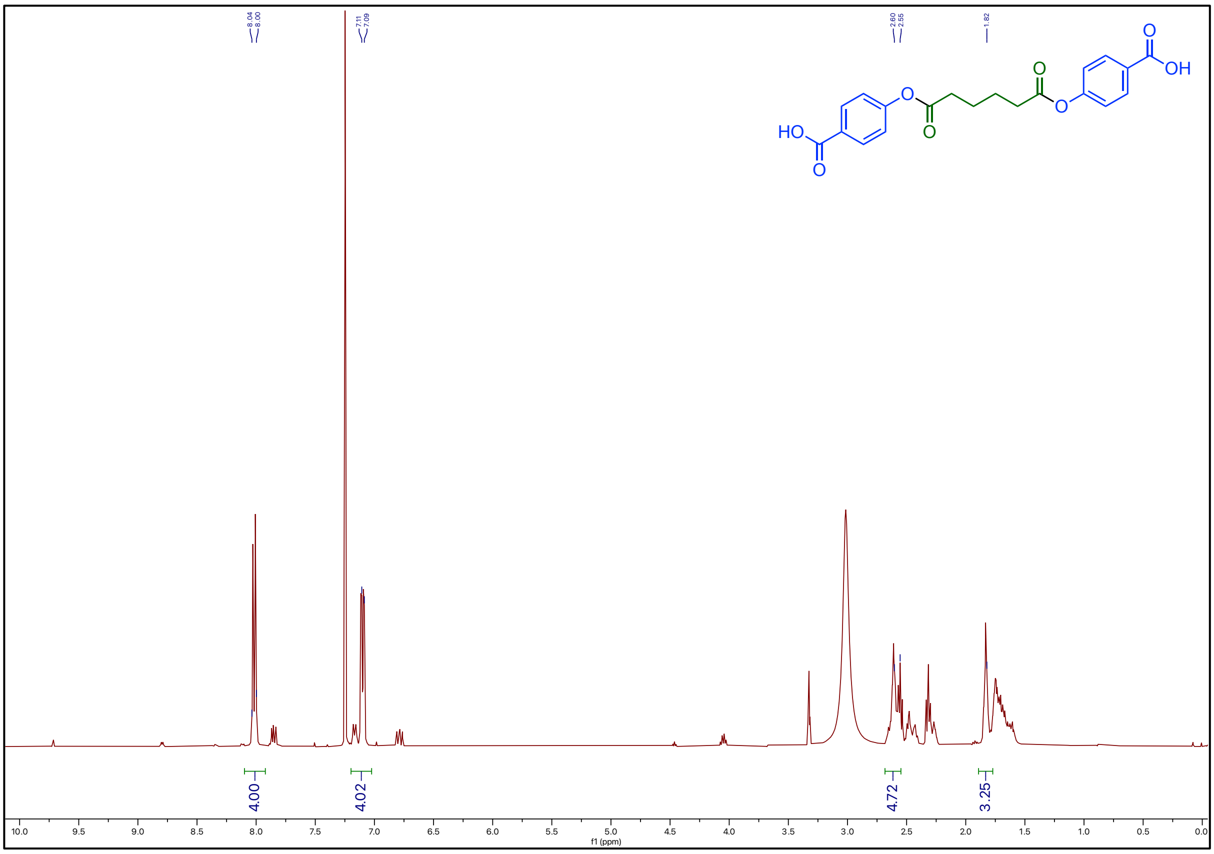

Figure 16: Crude Proton NMR of Compound 29.