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# Carbohydrates and platform molecules as polar building blocks for the design of bio-based surfactants

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**Les glucides & molécules plateformes  
comme briques polaires pour la  
conception de tensioactifs biosourcés**

**Carbohydrates & platform molecules as  
polar building blocks for the design of  
biobased surfactants**

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## List of Abbreviations

<b>BHMF</b>	Bishydroxymethylfuran
<b>BHMTHF</b>	Bishydroxymethyltetrahydrofuran
<b><math>\alpha</math>-CAG</b>	Cholesteryl 6- <i>O</i> -tetradecanoyl- $\alpha$ -D-glucopyranoside
<b>CMC</b>	Critical micelle concentration
<b>CPD</b>	1,3-Cyclopentanediol
<b>DA</b>	Diels-Alder
<b>DABCO</b>	1,4-Diazabicyclo[2.2.2]octane
<b>DBU</b>	1,8-Diazabicyclo[5.4.0]undec-7-ene
<b>DFE</b>	2,5-Diformylfuran
<b>DFT</b>	Density Functional Theory
<b>DIPEA</b>	<i>N, N</i> -Diisopropylethylamine
<b>DMAP</b>	4-(Dimethylamino)pyridine
<b>DMF</b>	Dimethylformamide
<b>DSC</b>	Differential scanning calorimetry
<b>FA</b>	Furfuryl alcohol
<b>FAES</b>	Ethoxylate-based fatty alkyl ether sulfates
<b>GA</b>	Glyoxylic acid
<b>GMF</b>	$\alpha$ -D-Glucosyloxymethylfurfural
<b>HCPO</b>	3-Hydroxymethylcyclopentanol
<b>HLB</b>	Hydrophilic-Lipophilic Balance
<b>HMF</b>	5-Hydroxymethylfurfural
<b>3-HQD</b>	3-Hydroxyquinuclidine
<b>LAS</b>	Linear alkylbenzene sulfonates
<b>2-MeTHF</b>	2-Methyl tetrahydrofuran
<b>MVK</b>	Methyl vinyl ketone
<b>OFSs</b>	Oleo-furan sulfonates
<b>PTS</b>	Proton transfer step
<b>RDS</b>	Rate-determining step
<b>SAXS</b>	Small Angle X-ray Scattering
<b>SDBS</b>	Sodium dodecyl benzene sulfonate
<b>TFAA</b>	Trifluoroacetic anhydride
<b>THFA</b>	Tetrahydrofurfuryl alcohol



<b>TLC</b>	Thin-Layer Chromatography
<b>TMG</b>	Tetramethylguanidine
<b>XRD</b>	X-Ray Diffraction

**Abstract & Résumé**

**Contents**

**General Introduction**



## Abstract

The use of biomass as renewable resource in strategies for the production of novel biobased chemicals has gained more and more attention in recent years. It is particularly important for the sector of amphiphilic compounds, which play important roles in our daily life in the field of fine chemicals (such as surfactants) and in biology (such as glycolipids). Biobased platform molecules, such as furanic compounds and other small polar molecules, are potential raw materials for the production of biobased amphiphiles. 5-Hydroxymethylfurfural (HMF) and analogous furanic compounds which are prepared directly from carbohydrates, offer interesting alternatives owing to their availability and diversified reactive functions. However, the use of biobased furanic aldehydes for the design of novel amphiphiles is still in its infancy. Likewise, glyoxylic acid, an interesting cheap C2 building block, has rarely been utilized as a polar moiety in the production of biobased amphiphiles even though it bears a hydrophilic carboxylic acid group.

The main purpose of this thesis is to investigate the use of these two types of biobased aldehydes, furanic ones and glyoxylic acid, in an original strategy for designing amphiphilic systems based on their combination with non-polar acrylic partners through the Morita-Baylis-Hillman (MBH) reaction.

The Morita-Baylis-Hillman (MBH) reaction is a well-known atom economical C-C bond forming reaction between electrophiles (mainly aldehydes) and activated alkenes (such as acrylates, acrylonitrile, acrylamides etc.). However, the MBH reaction of furanic platform molecules, such as HMF, GMF and furfural, is still limited. Our group has focused on this topic and useful results have been obtained previously by Dr. Jianeng TAN and Dr. Lianjie WANG in our lab.

For the scope of activated alkenes, acrylamides are generally regarded as low reactive substrates in MBH reactions, especially secondary *N*-alkyl acrylamides. I focused on these rarely reported substrates to expand the scope of the MBH reaction and the application of this strategy to the design and synthesis of novel biobased surfactants. A complete methodological investigation on the MBH reaction of secondary *N*-alkyl acrylamides has been conducted and a series of MBH adducts were synthesized under

mild conditions. HMF and GMF were also included in the aldehyde scope of this work. Thus amphiphilic MBH adducts possessing an amide bond were prepared from HMF and GMF.

The promoter/solvent couple 3-HQD/2-MeTHF:H<sub>2</sub>O (v/v=1/1) was found efficient for the MBH reaction of *N*-butylacrylamide and provided more eco-friendly conditions than the dioxane containing systems previously reported. These optimum conditions were then applied to a range of secondary *N*-alkyl acrylamides with longer chain length and aromatic aldehydes giving novel MBH adducts in moderate to good yields. A series of novel biobased amphiphiles was thus obtained by the use of this strategy.

The physicochemical properties were examined in the frame of a collaboration with the CISCO team of the UCCS lab in Lille led by Prof Véronique Nardello-Rataj. This characterization showed the higher hydrophilicity of the HMF-amide surfactants compared to the ester ones, which is caused by the introduction of the nitrogen atom and its higher capacity to be involved in hydrogen bonds.

Next, the MBH reaction of glyoxylic acid, virtually unreported in literature, was investigated. A complete study of the MBH reaction of glyoxylic acid (GA) with alkyl acrylates or acrylamides was thus performed. Eco-friendly and mild conditions and easy protocols were developed, giving high yields of MBH adducts with acrylates and fair yields with acrylamides. Once the optimized conditions established, the methodology was developed for the first time toward the synthesis of amphiphiles.

The promoter/solvent couple DABCO/EtOH was found effective for the reaction of GA with acrylates whereas the 3-HQD/2-MeTHF:H<sub>2</sub>O (v/v=1/1) system was found preferable for the case of secondary *N*-alkyl acrylamides. Under these appropriate conditions, the strategy was applied to a wide range of acrylates and acrylamides giving novel MBH adducts in moderate to good yields. This is the first systematic and complete report on the use of GA in MBH reactions. Applied to longer chain and even fatty acrylates and *N*-alkyl acrylamides, amphiphilic MBH adducts were formed. The properties of the GA-MBH adducts were also characterized in Lille. The first results indicate their good ability to reduce surface tension at low concentrations, suggesting promising utilizations as surfactants.

In this one-step strategy towards new products, GA is used directly from its cheap commercially available aqueous solution. Furthermore, the mildness of the reaction conditions (aqueous or biobased solvents, no high temperature), the atom economical character of the reaction and the easy protocol are additional advantages.

Overall, the application of this MBH route to renewable biobased feedstock such as furanic aldehydes and glyoxylic acid offers a very original and attractive access to new biobased surfactants.

A parallel project, also related to amphiphilic compounds made from biomolecular building blocks, concerns glyco steroids. Such compounds are analogous to glycolipids which play important roles in biology, notably in biological membranes. They were here studied for understanding their thermotropic behavior, in the frame of a continuing collaboration on liquid crystalline glycolipids with Prof. John W. Goodby at the University of York. A family of “Janus” cellobiose based glyco steroids were synthesized and characterized. In detail, the composition of this series of glyco steroids are: a disaccharidic head group and a steroid unit linked via a methylene linker, and bearing a lateral fatty chain of varying length. The condensed phases generated from the self-assembly of the products as a function of temperature were characterized by differential scanning calorimetry, thermal polarized light microscopy, and small angle X-ray scattering. Here in this thesis, the scope of disaccharidic products has been extended for completing a series prepared by previous PhDs (Dr. Rui Xu and Dr. Zonglong Yang) in our lab. This work finalized the preparation of a family of products which are now under evaluation in the hands of our colleagues in York.

The two sub topics studied in this thesis, first the MBH strategy applied to biobased aldehydes toward surfactants, and second, the thermotropic behavior of glycolipid analogs, though appearing different, concern the same global matter. They both relate to innovation in structural design of amphiphiles made from naturally occurring building blocks. Both contribute to a better understanding of their interfacial or self-assembling properties and illustrate the importance of amphiphilicity in molecular architectures.

**Key words:**

5-Hydroxymethylfurfural (HMF), glyoxylic acid, secondary *N*-alkyl acrylamide, Morita-Baylis-Hillman reaction, surfactants, glyco steroids, liquid crystals.

## Résumé

L'utilisation de la biomasse comme ressource renouvelable dans les stratégies de production de nouveaux produits chimiques biosourcés a attiré de plus en plus d'attention ces dernières années. C'est particulièrement important pour le secteur des composés amphiphiles, qui jouent un rôle important dans notre vie quotidienne dans le domaine de la chimie fine (comme les tensioactifs) et de la biologie (comme les glycolipides). Les molécules plateformes biosourcées, telles que les composés furaniques et autres petites molécules polaires, sont des matières premières potentielles pour la production d'amphiphiles biosourcés. Le 5-hydroxyméthylfurfural (HMF) et les composés furaniques analogues qui sont préparés directement à partir de glucides, offrent des alternatives intéressantes de par leur disponibilité et leurs fonctionnalités diversifiées. Cependant, l'utilisation d'aldéhydes furaniques biosourcés pour la conception de nouveaux amphiphiles est très peu exploitée. De même, l'acide glyoxylique, un bloc de construction C2 bon marché et intéressant, a rarement été utilisé comme fraction polaire dans la production d'amphiphiles biosourcés, malgré la présence d'un groupe acide carboxylique hydrophile.

L'objectif principal de cette thèse est d'étudier l'utilisation de ces deux types d'aldéhydes biosourcés, HMF, furfural et dérivés, d'une part, et l'acide glyoxylique, dans une stratégie originale de conception de systèmes amphiphiles basée sur leur association avec des partenaires acryliques non polaires à travers la réaction de Morita-Baylis-Hillman (MBH).

La réaction de Morita-Baylis-Hillman (MBH) est une réaction bien documentée, permettant la formation de liaison C-C entre des électrophiles (principalement les aldéhydes) et des alcènes activés (tels que les acrylates, l'acrylonitrile, les acrylamides, etc.). Cependant, la réaction MBH de molécules plateformes furaniques, telles que le HMF, le GMF et le furfural, est encore limitée. Notre groupe s'est intéressé à l'étude de ce sujet et des résultats utiles pour son développement ont été obtenus précédemment par Dr. Jianeng TAN et Dr. Lianjie WANG dans notre laboratoire.



En ce qui concerne les alcènes activés, les acrylamides sont généralement considérés comme des substrats peu réactifs dans les réactions de type MBH, en particulier les *N*-alkyl acrylamides secondaires.

Je me suis intéressé à ces substrats pour élargir la portée de la réaction MBH et l'application de cette stratégie à la conception et à la synthèse de nouveaux tensioactifs biosourcés. Une étude méthodologique variée sur la réaction MBH des *N*-alkyl acrylamides secondaires a été menée et une série d'adduits MBH ont été synthétisés dans différentes conditions. Le HMF et le GMF ont été inclus parmi les nombreux aldéhydes étudiés dans ce travail. Ainsi, des adduits amphiphiles de MBH possédant une liaison amide ont été préparés à partir de ces derniers.

Le couple promoteur/solvant 3-HQD/2-MeTHF:H<sub>2</sub>O (v/v=1/1) s'est avéré efficace pour la réaction MBH du *N*-butyl acrylamide et a permis l'utilisation des conditions plus respectueuses de l'environnement en comparaison avec les systèmes contenant du dioxane précédemment rapportés. Ces conditions optimales ont ensuite été appliquées à une variété de *N*-alkylacrylamides secondaires à chaîne plus longue et d'aldéhydes aromatiques donnant de nouveaux adduits MBH avec des rendements modérés à bons. Une série de nouveaux amphiphiles biosourcés a ainsi été obtenue par l'utilisation de cette stratégie.

Les propriétés physico-chimiques des nouveaux amphiphiles ont été examinées dans le cadre d'une collaboration avec l'équipe CISCO du laboratoire UCCS de Lille dirigée par le Pr Véronique Nardello-Rataj. Cette caractérisation a montré l'hydrophilie plus élevée des tensioactifs HMF-amide par rapport aux esters, qui est causée par l'introduction de l'atome d'azote et sa plus grande capacité à être impliqué dans les liaisons hydrogène.

Ensuite, la réaction MBH de l'acide glyoxylique, rarement rapportée dans la littérature, a été étudiée. Une étude complète de cette réaction avec des acrylates d'alkyle ou des acrylamides a ainsi été réalisée. Des conditions respectueuses de l'environnement et douces et des protocoles simples ont été développés, donnant des rendements en adduits MBH, élevés avec des acrylates et moyens avec des acrylamides. Une fois les conditions optimisées, la méthodologie a été développée et appliquée pour la première fois à la synthèse d'amphiphiles.

Le couple promoteur/solvant DABCO/EtOH s'est montré efficace pour la réaction de GA avec les acrylates alors que le système 3-HQD/2-MeTHF:H<sub>2</sub>O (v/v=1/1) s'est avéré plus favorable pour le cas des *N*-alkyl secondaires acrylamides. Dans ces conditions appropriées, la stratégie a été appliquée à une large gamme d'acrylates et d'acrylamides donnant de nouveaux adduits MBH avec des rendements modérés à bons. Il s'agit du premier rapport systématique et complet sur l'utilisation de GA dans les réactions MBH. Appliqués à des acrylates à chaîne plus longue et même gras et à des *N*-alkyl acrylamides, des adduits amphiphiles de MBH se sont formés. Les propriétés des adduits GA-MBH ont également été caractérisées à Lille. Les premiers résultats indiquent leur bonne capacité à réduire la tension superficielle à de faibles concentrations, suggérant des utilisations prometteuses en tant que tensioactifs.

Dans cette stratégie en une étape vers de nouveaux produits, GA est utilisé directement à partir de sa solution aqueuse bon marché disponible dans le commerce. De plus, la douceur des conditions de réaction (solvants aqueux ou biosourcés, pas de haute température), le caractère économe en atomes de la réaction et la simplicité du protocole sont des avantages supplémentaires.

Globalement, l'application de cette voie de MBH à des matières premières biosourcées renouvelables, tels que les aldéhydes furaniques et l'acide glyoxylique offre un accès original et attractif à de nouveaux tensioactifs biosourcés.

Un projet parallèle, également lié aux composés amphiphiles fabriqués à partir de blocs de construction biosourcés, concerne les glycostéroïdes. De tels composés sont analogues aux glycolipides qui jouent des rôles importants en biologie, notamment dans les membranes biologiques. Ils ont été ici étudiés pour comprendre leur comportement thermotrope, dans le cadre d'une collaboration de longue date sur les glycolipides cristallins liquides avec le professeur John W. Goodby de l'Université de York. Une famille de glycostéroïdes à base de cellobiose « Janus » a été synthétisée et caractérisée. Dans le détail, la composition de cette série de glycostéroïdes est la suivante : un groupe de tête disaccharidique et une unité stéroïdienne liés via un lien méthylène, et portant une chaîne grasse latérale de longueur variable. Les phases condensées générées par l'auto-assemblage des produits en fonction de la température ont été caractérisées par calorimétrie à balayage différentiel, microscopie à lumière

polarisée thermique et diffusion des rayons X aux petits angles. Ici, dans cette thèse, la portée des produits disaccharidiques a été étendue pour compléter une série préparée par des docteurs précédents (Dr Rui Xu et Dr Zonglong Yang) dans notre laboratoire. Ce travail a finalisé la préparation d'une famille de produits qui sont actuellement en cours d'évaluation entre les mains de nos collègues de York.

Les deux sous-thèmes étudiés dans cette thèse, d'une part la stratégie MBH appliquée aux aldéhydes biosourcés vis-à-vis des tensioactifs, et d'autre part, le comportement thermotrope des analogues glycolipidiques, bien qu'apparaissant différents, concernent la même problématique globale. Ils sont tous deux liés à l'innovation dans la conception structurelle d'amphiphiles fabriqués à partir de blocs de construction naturels. Tous deux contribuent à une meilleure compréhension de leurs propriétés d'interface ou d'auto-assemblage et illustrent l'importance de l'amphiphilie dans les architectures moléculaires.

**Mots clés:**

5-Hydroxyméthylfurfural (HMF), acide glyoxylique, N-alkylacrylamide secondaire, réaction de Morita-Baylis-Hillman, tensioactifs, glycostéroïdes, cristaux liquides.

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## General Introduction

Among chemicals, the family of amphiphilic molecules are commonly encountered and very specific in their properties. They play important roles in many fields, both in industries and in everyday and personal life. Their peculiar amphiphilic structures give them the capacity to lower the superficial and interfacial tension in multiphase systems, making numerous processes possible. Many amphiphilic compounds are also referred to as surfactants---surface active agents. The consumption of surfactants is remarkably large due to their utilization in a wide range of applications as detergents, emulsifiers, wetting agents etc. The market demand for surfactants, already high due to the need in industries and everyday life, keeps increasing with the developing world economy. However, surfactants are mainly manufactured from fossil resources, which are limited and unrenewable. The application of renewable feedstocks is one of the important principles of green chemistry and this principle has been widely applied to many manufactured products. Likewise, developing technologies to produce surfactants from renewable resources is a tendency in research and innovation strategies. Besides amphiphiles derived from carbohydrates, other biobased building blocks also can be envisaged for serving as the polar part of biobased amphiphiles. This is notably the case of platform molecules such as HMF and its analogues, or other smaller molecules carrying polar functions, such as glyoxylic acid. This is the main purpose of this thesis, which focuses on the design, synthesis and evaluation of the properties of novel families of biobased amphiphiles. We have combined biobased aldehydes as key substrates, in particular furanic aldehydes, and glyoxylic acid, with non-polar acrylates or acrylamides in a strategy relying on the Morita-Baylis-Hillman (MBH) reaction. In a separate, parallel project dealing also with amphiphiles made from biomolecular building blocks, a series of amphiphilic systems composed of a sugar, a steroid and an alkyl chain were synthesized and studied.

The first chapter of this thesis is a bibliographic introduction which includes general information on surfactants, focusing then on biobased surfactants, followed by a more detailed overview on furanic surfactants. General information on glyoxylic acid chemistry and the Morita-Baylis-Hillman (MBH) reaction are also given.

The second chapter reports our study on the MBH routes towards biobased surfactants. After a short introduction of the backgrounds and aims, it describes first the results of our methodological study of the use of secondary-*N*-alkyl acrylamides in MBH reactions. Then it shows the application of this strategy to the synthesis of a set of amide bond containing biobased surfactants from HMF and GMF when the fatty chains substituted secondary-*N*-alkyl acrylamides are used. It is followed next by the section reporting the methodological investigation of the MBH reaction of glyoxylic acid, an easily available and biobased C2-molecule rarely used in MBH chemistry, and its application to the design of a second series of original biobased surfactants. For both novel families of surfactants described in these two chapters, the characterizations of their physicochemical properties have been performed by the team of Prof. Véronique Nardello-Rataj and Dr. Jesús Fermin Ontiveros of the CISCO team of the UCCS research unit in Lille. These two sections emphasize the design and synthesis of biobased surfactants using the MBH reaction for connecting aldehydic platform molecules to non-polar building blocks.

The chapter 3 reports our investigations on another family of surfactants built from natural polar and non-polar moieties, namely a carbohydrate, a steroid and a fatty chain, showing liquid crystalline properties. The series of glycosteroidic compounds is based on a cellobiose disaccharide as the polar moiety. The investigation of the liquid crystalline properties of this series of compounds was performed at the University of York in by Prof. John. W. Goodby and Dr. Stephen J. Cowling and colleagues.

After a General Conclusion, all experimental procedures and data are gathered in one Experimental Section, followed by the full list of references.

Besides illustrating the interest of the use of biomolecular or biobased buiding blocks in the design of novel families of surfactants, this thesis also highlights the importance of amphiphilicity in chemical architectures, demonstrating that understanding the physicochemical behavior of amphiphiles and their structure-property relationships cover phenomena with very diverse applications and interests.

# **Chapter I**

## **Bibliography**

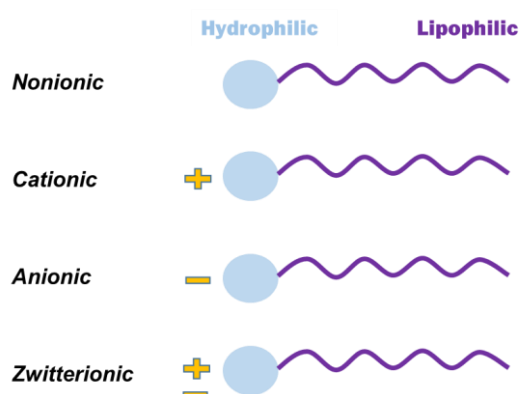




# Chapter I Bibliography

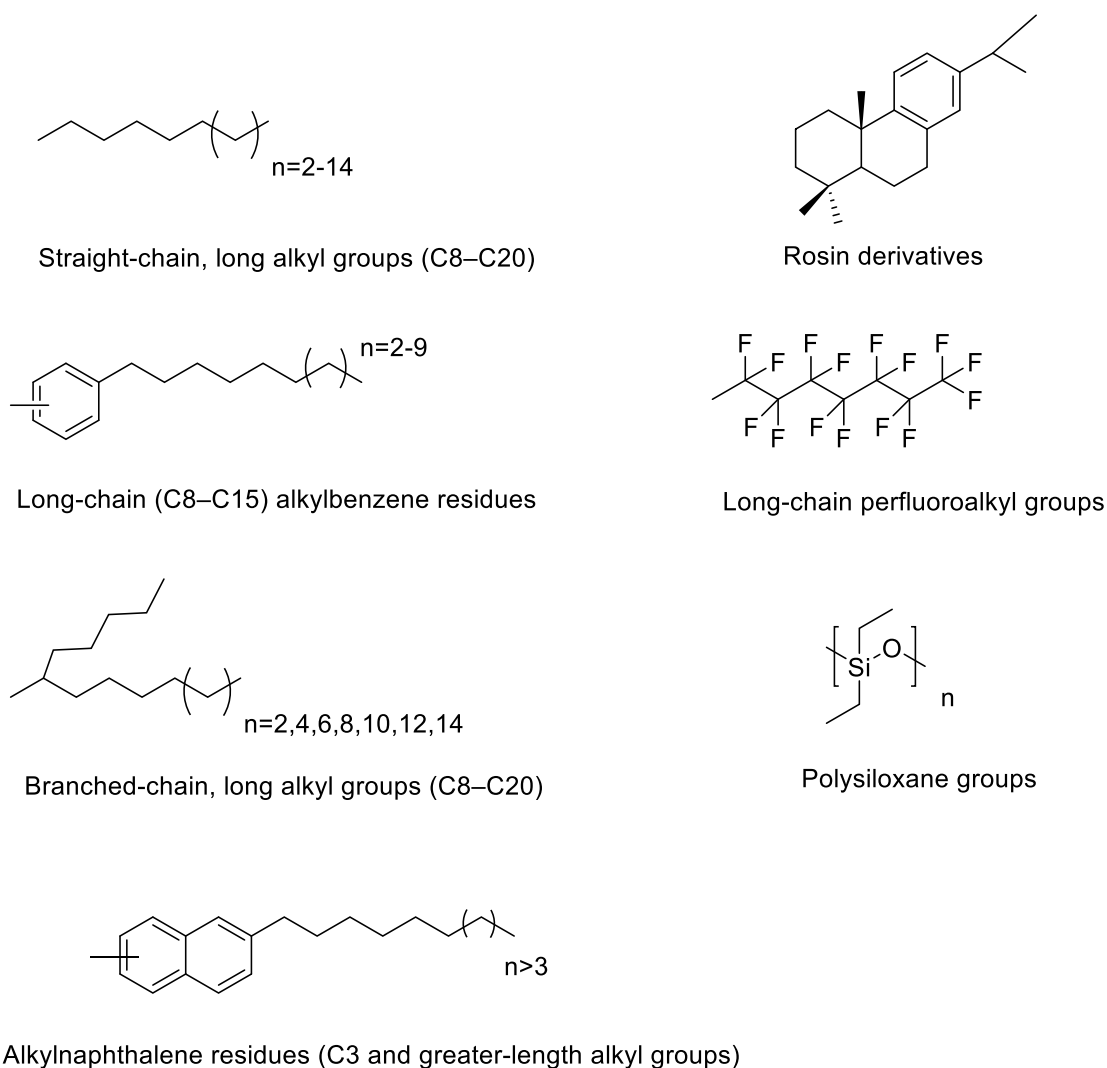
## 1.1 General introduction on surfactants

Surfactants, active chemicals reducing the surface tension between two immiscible phases (air-liquid, liquid-liquid and solid-liquid), are widely used in several areas of our daily lives, for example, as detergents for washing activities, emulsifiers for food industry and foaming agents for construction and manufacturing industries, etc. The surface free energy reducing capacity owes generally to the amphiphilic architecture of surfactants, consisting of a hydrophilic head and a lipophilic tail. The polar moiety interacts with water or other hydrophilic phases while the unpolar part attracts oil, air or other hydrophobic media and surfaces. The hydrophilic group can be an ionic or a highly polar group. Depending on the nature of the hydrophilic group, surfactants are classified as nonionic, cationic, anionic, or zwitterionic ones (Figure 1). Some compounds referred to as amphoteric can be either one or the other among ionic types depending on pH.



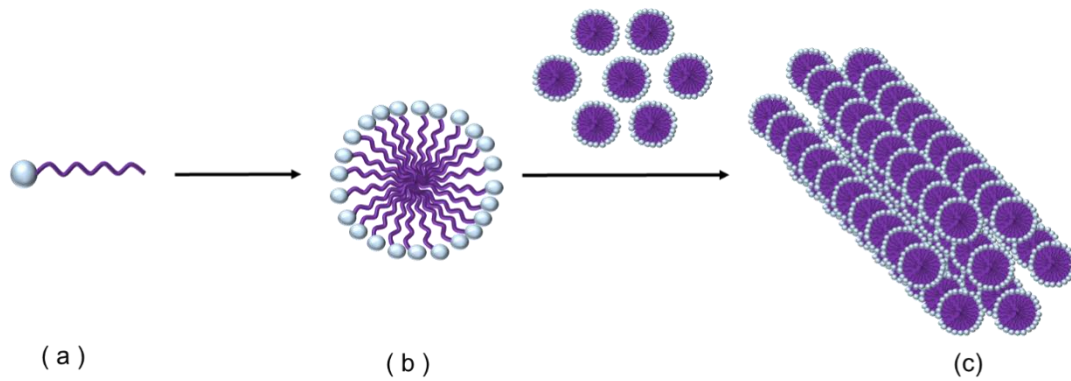
**Figure 1.** Classification of surfactants based on charge types of polar head.

The hydrophobic group diversity is usually less pronounced than for the hydrophilic one. In most systems, the hydrophobic character relies on a hydrocarbon residue such as straight-chain long alkyl groups ( $C_8$ – $C_{20}$ ), branched-chain long alkyl groups ( $C_8$ – $C_{20}$ ) or long-chain ( $C_8$ – $C_{15}$ ) alkylbenzene residues. Less commonly, alkylnaphthalene residues ( $C_3$  and greater-length alkyl groups), rosin derivatives, long-chain perfluoroalkyl groups and polysiloxane groups can also be used (Figure 2).<sup>[1]</sup>



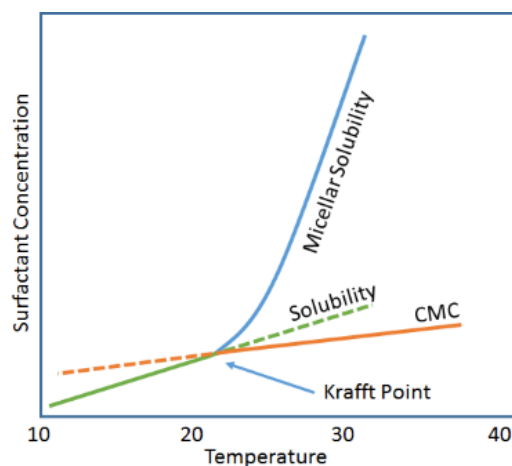
**Figure 2.** Examples of hydrophobic groups for surfactants.<sup>[1]</sup>

The self-assembling ability is the key behavior leading to the observed properties of surfactants. In general, a single surfactant molecule, also called “unimer”, self-assemble into aggregates, named micelles, under a specific concentration in solution. At low concentration, the compounds behave as a unimer, a fully soluble isolated molecule. Upon increasing the concentration, when the first micelle is formed, the critical micelle concentration (CMC) is reached. Then, above this concentration, more micelles are generated while the concentration of free surfactant unimers remains constant. With the increase of the micelles concentration, larger patterns such as surfactant liquid crystals (lyotropic) can form (Figure 3). The structures of surfactant liquid crystals mainly inherit from that of the micelles, which themselves inherit from the self-assembling behaviors of the initial surfactants.<sup>[1, 2]</sup>



**Figure 3.** (a) Surfactant molecule, (b) Surfactant micelle, (c) Lyotropic surfactant liquid crystalline aggregate

The formation of micelles is deeply influenced by temperature, in relation with the dependence of the solubility of surfactants unimers on the temperature. In many cases, the solubility of unimers increases with temperature, therefore the ability to form micelles will also decrease. At a certain temperature, when CMC is reached, the first micelle will be obtained. This temperature is named the Krafft temperature. The Krafft point is the intersection of two curves: critical micelle concentration and maximum solubility of surfactants unimers (Figure 4).<sup>[3, 4]</sup> However, there are also some examples for which the relationship between solubility and temperature is more complex, such as polyethoxylated systems, in which the polarity relies on the hydration shell, and which can lose some of their level of hydration at higher temperatures.



**Figure 4.** Krafft point or Krafft temperature <sup>[5]</sup>

Usually, surfactants with longer hydrophobic tails exhibit a higher Krafft point whereas branched hydrophobic tail give a lower one. The relationship between the structure and physicochemical properties of surfactants is thus a complex combination of parameters, including the type of polar and non-polar moieties, the overall shape of molecules and their solubility profiles. The design of novel high performance surfactants relies also on modifications of their chemical structures by introducing new scaffolds and development of alternative strategies for connecting polar and unpolar parts into surfactant molecules.

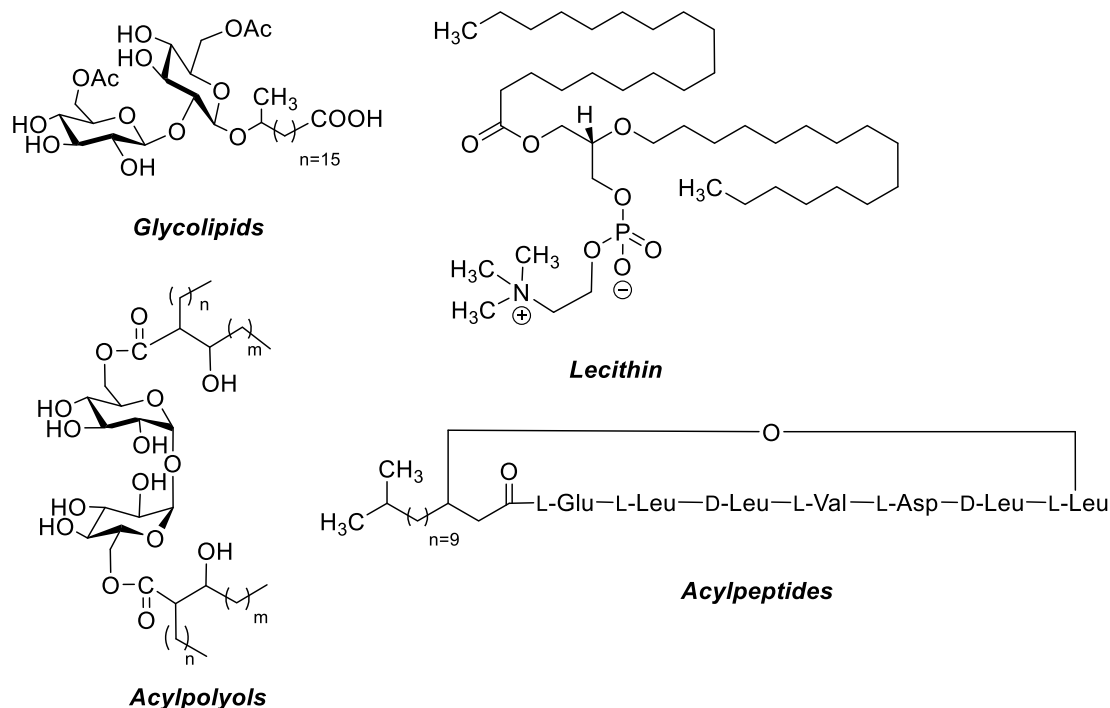
Apart from the classification on the type of polar moiety, surfactants can also be classified based on various principles: natural or synthetic, and petro-based or bio-based. Some common natural surfactants, such as phospholipids, play important roles in biological transport process of nature. Of course, the vast majority of surfactants are synthetic products designed for various purposes and their manufacture has developed significantly in the past decades. But as we know, most of them are produced from unrenewable, fossil based resources and still only a minority from renewable raw materials.

Surfactants are major industrial products with millions of metric tons produced annually throughout the world. Nowadays, more than 15 million tons of surfactants are prepared and utilized yearly, causing environmental problems connected to difficult biodegradability, eutrophication, etc. Among directions for improving their environmental impact, there has been intense interest in recent years in using renewable, readily biodegradable resources for both the hydrophilic and hydrophobic groups of commercial surfactants in order to provide them with a more favorable environmental (“green”) character. Related researches were notably focused on the use of natural fats and of naturally occurring carbohydrates and amino acids (from proteins) as resources for constituting the hydrophobic and hydrophilic groups, respectively. In terms of environment protection, notably global climate change, the utilization of renewable feedstock is also potential, even though the benefit from them is not always huge, as the overall carbon footprint is a sum of several contributions, not only the type of resources, the more utilization of renewable resources will still indeed reduce the CO<sub>2</sub> emission. Patel et al. estimated that oleochemicals may lead to greater CO<sub>2</sub> savings when used for surfactants production rather than in the

production of biodiesel.<sup>[6]</sup> They also estimated that the total CO<sub>2</sub> emissions associated with surfactant production and use could be reduced by as much as 37% if renewable surfactants were to entirely replace petrochemical surfactants in the EU.<sup>[7]</sup> Therefore, the development of the strategies to produce green surfactants from renewable feedstock is no doubt a tendency in the future and an effective method to make the production of surfactants get rid of the dependence on fossil resources. Indeed, the field of biobased surfactants has kept increasing in the recent years, in terms of production and of market.

## 1.2 Biobased surfactants

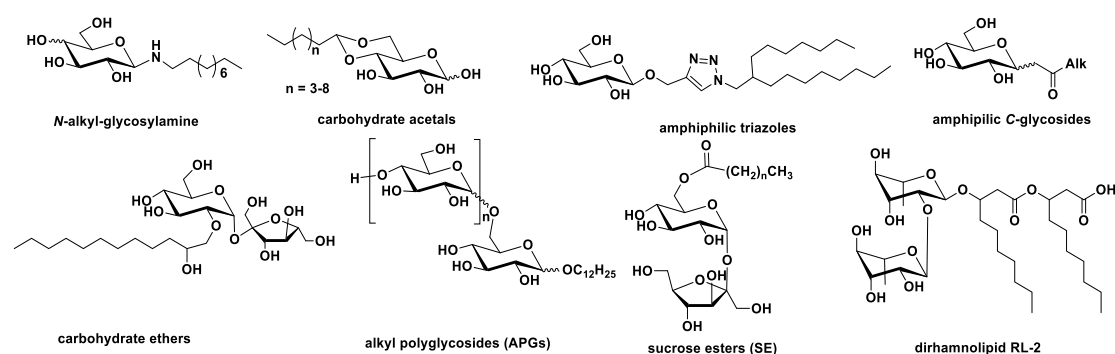
Biobased surfactants are synthetic molecules, different from naturally occurring surfactants referred to as “biosurfactants”, which result from biosynthetic processes. Lecithin is the most typical biosurfactant, and it can be extracted from soybean or egg yolk.<sup>[8]</sup> Another family of biosurfactants are ones from fermentation processes, which can be obtained in high yield while avoiding the large cost of a chemical synthesis work-up.<sup>[9]</sup> The representative biosurfactants from fermentation routes include acylpolyols, glycolipids and acylpeptides.



**Figure 5.** Examples of natural biosurfactants.<sup>[11]</sup>

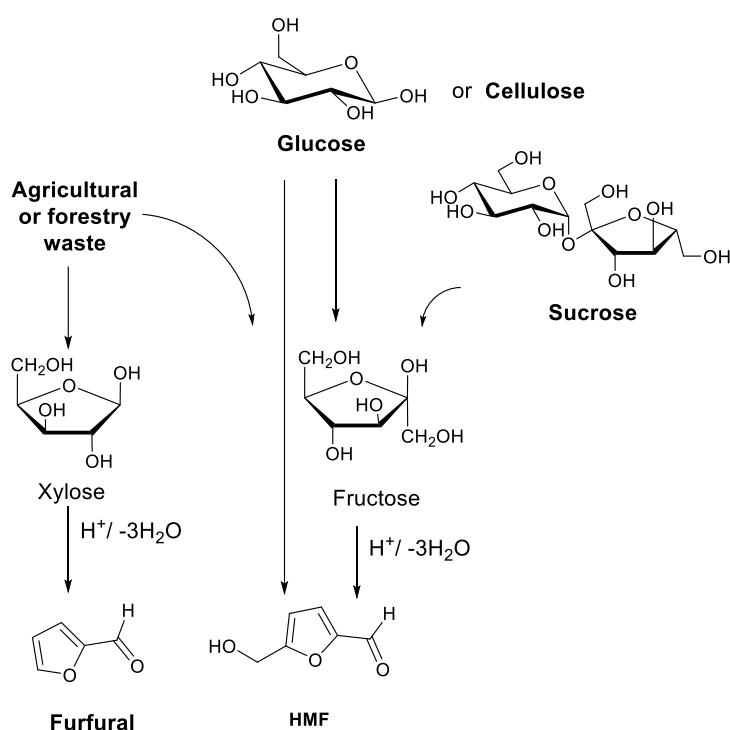
Acylpolyols are important constituents of the bacterial cell wall, and are mainly hydroxy fatty acids esters of disaccharides produced by microorganisms such as actinomycetes, for instance, *Mycobacterium*, *Corynebacterium* and *Brevibacterium*.<sup>[10]</sup> Glycolipids are generally the glycosides of hydroxy fatty acids with sugars and the most typical ones are sophorolipids and rhamnolipids, which are produced via *Candida* and by *Pseudomonas* separately. Acylpeptides are usually cyclic esters of hydroxyl acid and short chain peptide. The most widely known example is achieved under the treatment of *Bacillus subtilis*, which has been a commercial biosurfactant (Figure 5).<sup>[11]</sup>

A more general concept of biobased surfactants also includes the synthetic surfactants prepared synthetically from renewable feedstocks, or biobased intermediates molecules as hydrophilic parts or lipophilic parts. In terms of the resources of polar head, polyhydroxylated molecules are the main choices occupy almost half of the whole scale.<sup>[12]</sup> Indeed, the abundant hydroxy-rich carbohydrates have become the most attractive resources for constituting the polar moiety of surfactants and have been investigated a lot, thanks to their very large availability and wide structural scope. For carbohydrates-based surfactants, Wang and Queneau<sup>[13]</sup> classified the major families of them based on the various connector between the two parts of surfactant molecules, including acetals (glycosides and non-glycosides acetals), esters, ethers, nitrogen-containing compounds, C-glycoside and furanic derivatives. As is shown in their chapter in the Wiley Green Chemistry and Engineering Encyclopedia, most of the carbohydrate-based surfactants (Figure 6) utilize directly natural carbohydrates molecules as the hydrophilic moiety, owing to their high intrinsic polarity.<sup>[14]</sup>



**Figure 6.** Typical examples of carbohydrate-based surfactants<sup>[13]</sup>

Apart from native carbohydrates, some of their derived platform molecules possessing hydrophilic function groups, obtained via oxidation, reduction and dehydration, can also serve as building blocks for the design of novel surfactants. In particular, furanic aldehydes are interesting systems among all carbohydrate derived platform molecules, being available from several resources. For example, the dehydration of monosaccharides can lead to furfural or 5-(hydroxymethyl)furfural (HMF) depending if it is a C-5 carbohydrate or a C-6 one (Figure 7). These two furanic compounds are both emphasized in the list of the US Department of Energy's "Top 10" high-valued chemicals from biorefinery carbohydrates.<sup>[15]</sup>

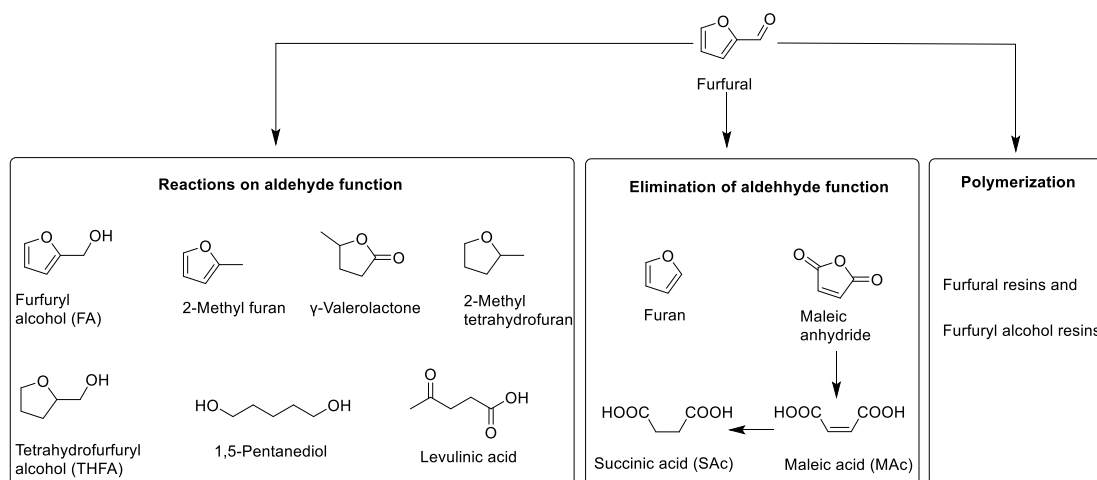


**Figure 7.** Carbohydrate-based platform molecules from dehydration of saccharides.

Both furfural and HMF have been studied a lot in the field of their catalytic preparation from biomass and their application in fine chemistry. Furfural can be prepared from xylose using several catalysts, such as acidic zirconia, titanate, niobate, silica-supported heteropolyacid and niobium silicate catalysts <sup>[16-19]</sup>, with variable levels of conversions and selectivities. Improvements were reported using a hierarchical (micro-meso) sulfonated silicon which exhibited a good performance, giving a 91% conversion and 82% selectivity to furfural.<sup>[20]</sup> A recent study revealed



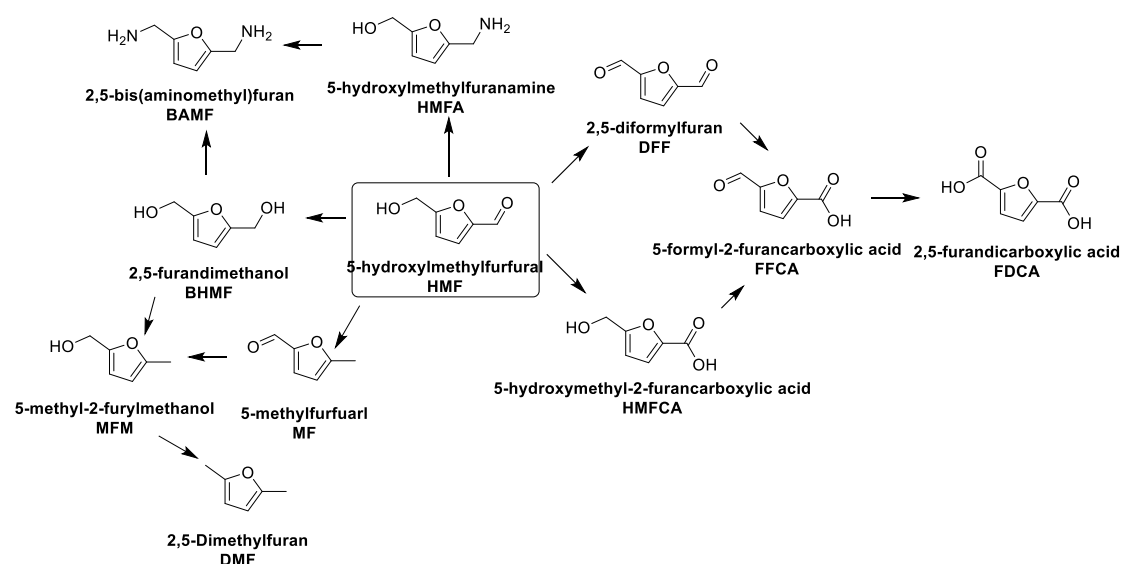
the beneficial effect of choline chloride as additive, via the involvement of an intermediate choline xyloside exhibiting better tendency to dehydrate than the native xylose.<sup>[21]</sup> López Granados *et al.*<sup>[22, 23]</sup> have reviewed the downstream uses of furfural in fine chemistry. They distinguished families of furfural derived chemicals and fuels from three different routes: reactions on the aldehyde function, elimination of the aldehyde function and polymerization of furfural. The main one is the family of products arising from reactions on the aldehyde function, including hydrogenation, amination, oxidation, acetalisation and condensation reactions, giving several chemicals, such as furfuryl alcohol (FA), levulinic acid,  $\gamma$ -valerolactone, tetrahydrofurfuryl alcohol (THFA), 1,5-pentanediol, 2-methyl furan, 2-methyl tetrahydrofuran (2-MeTHF), cyclopentanone, furfurylamine furoic acid and their derivatives. The chemicals from the elimination of the aldehyde function of furfural mainly refer to furan and its derivatives via decarbonylation, and maleic acid and succinic acid via oxidation. The chemicals from polymerization of furfural are FA derived resins, which are commercial products. (Figure 8)



**Figure 8** .Examples of fine chemicals from furfural.

HMF also attracts extensive attention and plays an increasingly important role in fine chemistry with the rising requirements for developing novel chemicals in the “green chemistry” context, a concept summarized as 12 principles by Paul Anastas and John Warner in 1998.<sup>[24]</sup> The most reactive substrates for the acid catalyzed dehydration to HMF is fructose. However, attempts to reach HMF from other more common C6 sugars, such as glucose, or polysaccharides, such as cellulose, are developing now,

though most of them still suffer from lower efficiency. Moreover, the instability of HMF under the acidic conditions required for promoting its formation also limit the selectivity of the processes.<sup>[25]</sup> In the recent years, several studies have been conducted to use biphasic solvent to isolate HMF timely or to design more effective catalytic systems to promote the conversion of cheaper biomass to HMF via more efficient and safe pathways (green solvents and mild conditions etc.). The development of the application of HMF in fine chemistry is nowadays widely investigated. Fan *et al.* <sup>[26]</sup> and Shen *et al.* <sup>[25]</sup> summarized the utilization of HMF in the construction of novel organic scaffolds and classified the relevant reactions from the different reactive parts of HMF: aldehyde group, hydroxymethyl group and furan ring, including work on multi components and multi-step synthesis involving HMF (Figure 9). Recently, an extensive review on the manufacture and utilization of HMF was published by Hou *et al.* <sup>[27]</sup> and the developments of HMF chemistry was summarized critically. The recent perspective by Bielski and Gryniewicz <sup>[28]</sup> also gave an overview on the various fine chemicals from HMF and particularly introduced the chiral furans in this strategy.



**Figure 9.** Examples of fine chemicals from HMF.<sup>[25]</sup>

Despite of the importance of the surfactant sector in the chemical industry, the application of these carbohydrate-based platform molecules in the design of biobased surfactants is still a limited area. It is however developing rapidly, and we focus in the next section on the furan routes towards surfactants, with original design from the viewpoints of the different raw materials and of innovative synthetic strategies and structures.

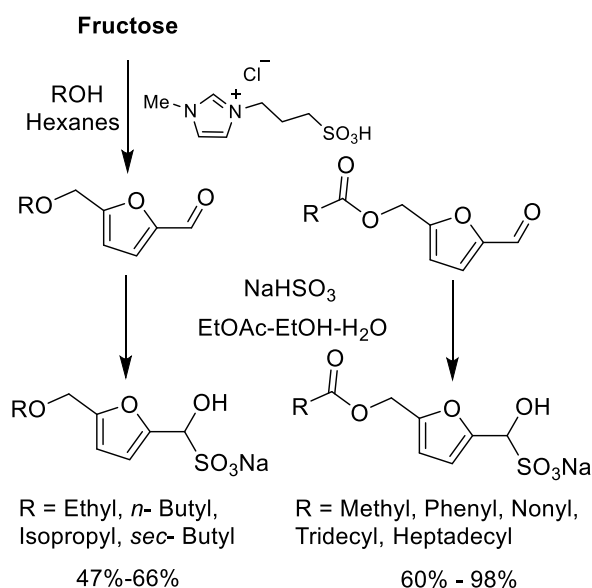
## 1.3 Furanic surfactants

*This section is the basis of a review recently published in ChemSusChem in 2022* <sup>[29]</sup>, and the schemes in this sections are also taken from this review.

### 1.3.1 HMF based amphiphiles

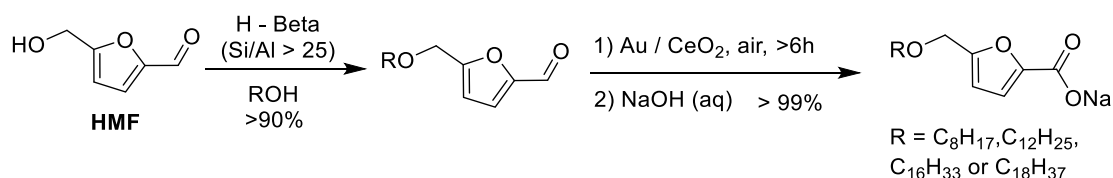
Several strategies have been reported for designing amphiphilic compounds starting from HMF. Both the CH<sub>2</sub>OH moiety and the aldehyde can be envisaged as precursors of the future polar or non-polar appendages of the target product. They are classified herein, first with compounds relying on a fatty ether or ester, then compounds exhibiting an acetal function, before finishing with designs based on a carbon-carbon bond connection.

The etherification of the CH<sub>2</sub>OH group of HMF by reaction with a fatty alcohol has been used as initial step in several sequences. Kraus *et al.* reported in 2013 the preparation of sulfonated HMF ethers by simple treatment with sodium bisulfite based on an efficient initial one-pot conversion of fructose using a task-specific ionic liquid (Scheme 1).<sup>[30, 31]</sup> The direct sulfonation of the aldehyde group appears a simple and effective pathway to graft a highly hydrophilic moiety on the HMF fatty ethers. Such products can be considered as alternatives to linear alkylbenzene sulfonates (LAS) which are the most commonly used sulfonates surfactants,<sup>[32]</sup> but characterized by harsh synthesis conditions and their fossil origin. HMF fatty esters can also undergo the same sequence. Most of these sulfonates exhibited high solubility in H<sub>2</sub>O at room temperature, while the longer chain esters required to heat up to 80 °C for reaching the Krafft temperatures. Though, the poor stability under basic conditions of these systems limits their possible usages to only acidic or neutral formulations.



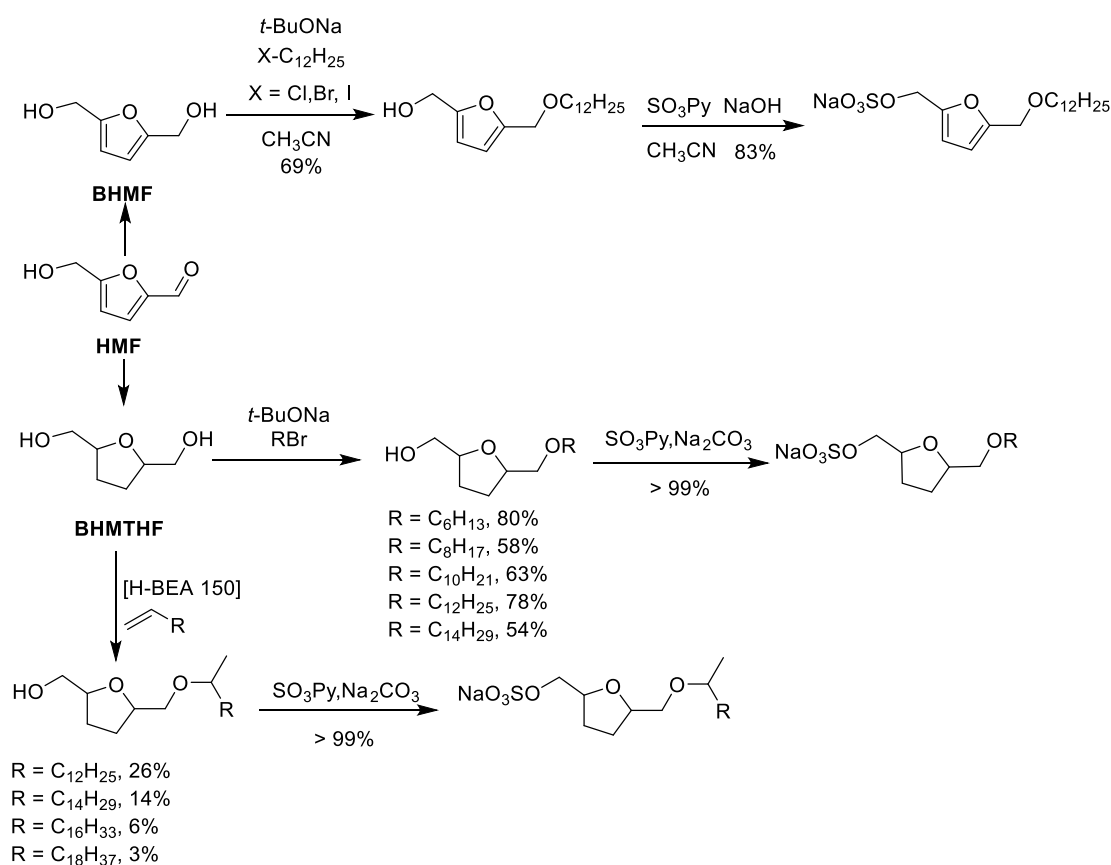
**Scheme 1.** Amphiphilic sulfonated HMF ethers and esters. <sup>[30, 31]</sup>

In 2014, Climent, Corma and colleagues reported another family of biobased anionic surfactants, namely 5-alkoxymethyl furoic acid salts, prepared from HMF ethers through a strategy consisting of two catalytic steps (Scheme 2).<sup>[33]</sup> For the initial HMF etherification, the use of a H-Beta zeolite (Si/Al > 25) led to a high selectivity towards the desired alkoxymethyl furfurals, while limiting the self-etherification of HMF to its dimer, and the formation of dialkylacetals, due to the self-organization ability of the intermediate. Subsequently, the polar part is provided by the oxidation of the aldehyde group to a carboxylate salt under the catalysis of Au/CeO<sub>2</sub>, a catalyst reported for the oxidation of HMF to FDCA in which the 5-hydroxymethylfuran carboxylic acid is the primary intermediate.<sup>[34]</sup> The properties of these 5-alkoxymethyl furoic acid sodium salts were characterized and showed surface tension reducing ability, comparable to the commercial surfactant sodium dodecyl benzene sulfonate (SDBS).



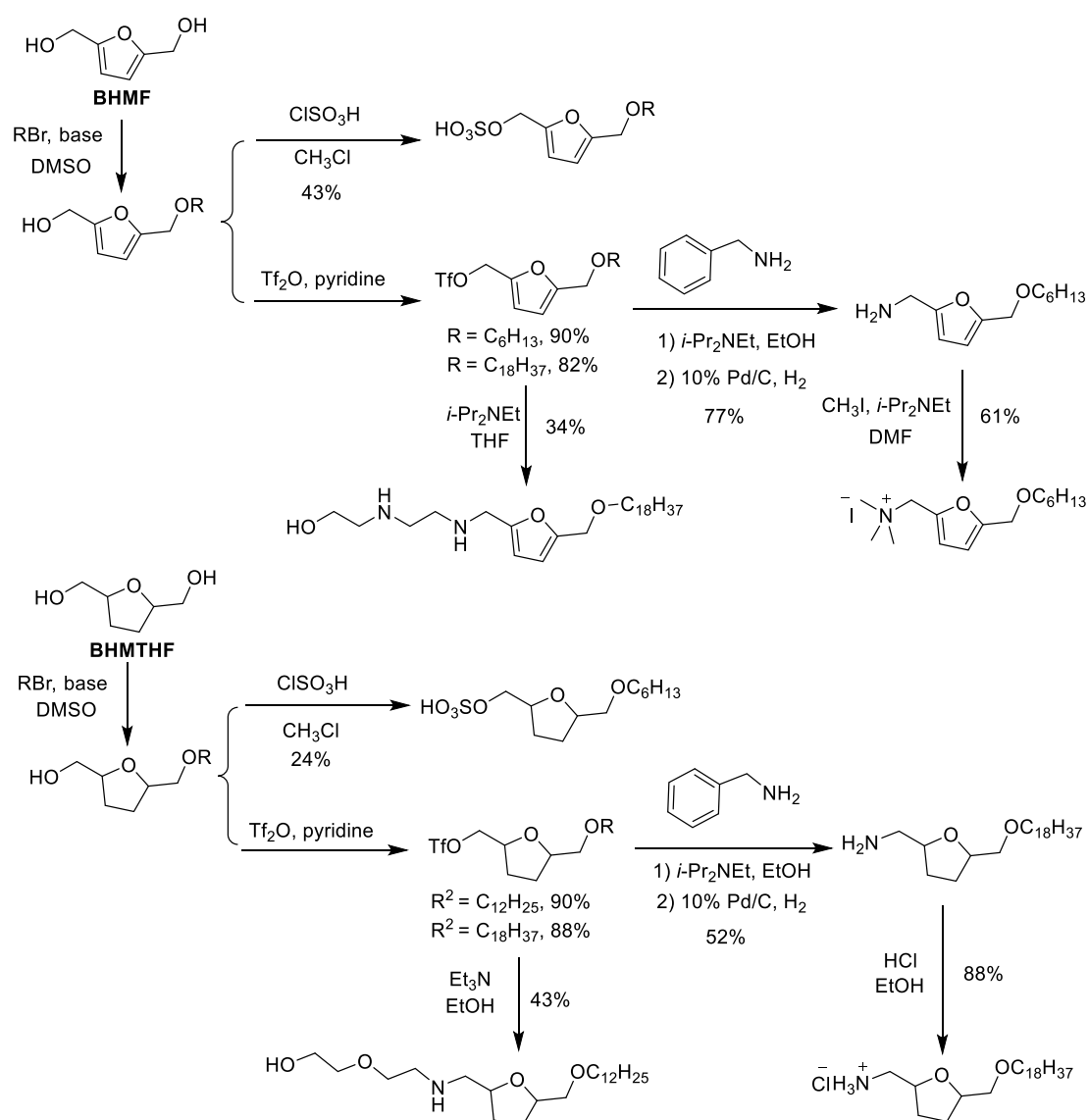
**Scheme 2.** Oxidation of HMF fatty ethers to amphiphilic carboxylates <sup>[33]</sup>

The hydrophilic part can also arise from the sulfatation of hydroxyl groups. This has been applied in sequences starting from bishydroxymethylfuran (BHMF) and bishydroxymethyltetrahydrofuran (BHMTHF), both easily obtained from HMF.<sup>[35-40]</sup> First, a selective etherification on only one of the two hydroxyl group must be performed, either by Williamson reaction with a haloalkane using sodium tert-butoxide as the base, or by addition on olefins promoted by an acidic zeolite catalyst.<sup>[41-44]</sup> The hydrophilic part is then provided by sulfatation with the SO<sub>3</sub>·Py-complex (Scheme 3). In terms of properties, the BHMTHF derived surfactants with C12, C14 and C16 fatty chains exhibited a comparable surface tension reduction ability to that of the commercial surfactants linear alkylbenzene sulfonates (LAS) and ethoxylate-based fatty alkyl ether sulfates, however at a lower CMC.<sup>[45]</sup>



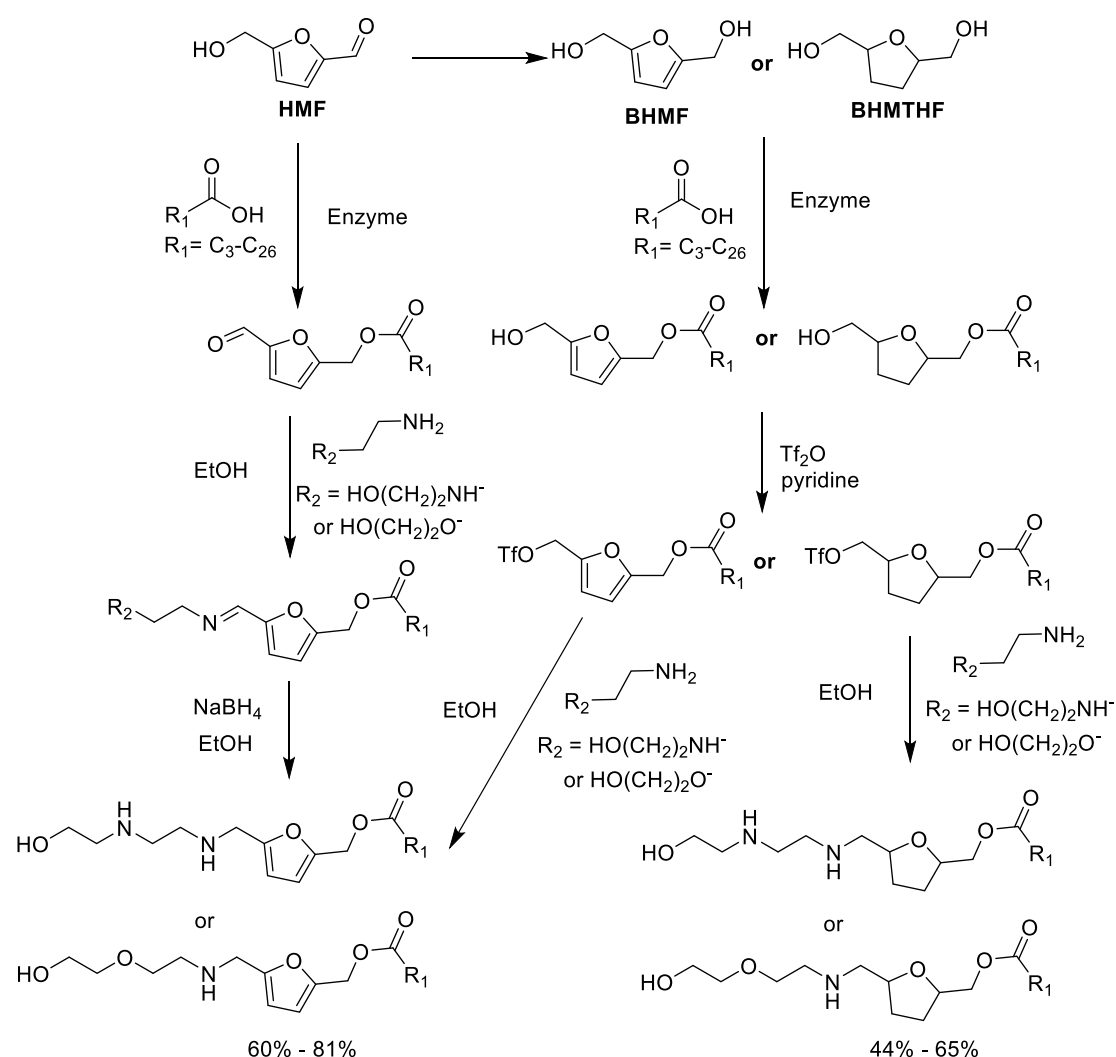
**Scheme 3.** Synthesis of BHMF-based and BHMTHF-based ether-sulfate surfactants <sup>[45]</sup>

Other amphiphilic fatty ethers based on the BHMf, BHMTHF or tetrahydrofurfurylamine backbones have been reported by Stensrud in a 2015 patent (Scheme 4). Cationic, anionic and nonionic amphiphiles were prepared by grafting either ammonium ions, sulfates, and hydroxyethylaminoethylamino or hydroxyethoxyethylamino polar moieties, respectively. Sulfates were obtained directly from the HMF-ethers, while furfurylamine derivatives were prepared by substitution of an intermediate triflate.<sup>[46]</sup>



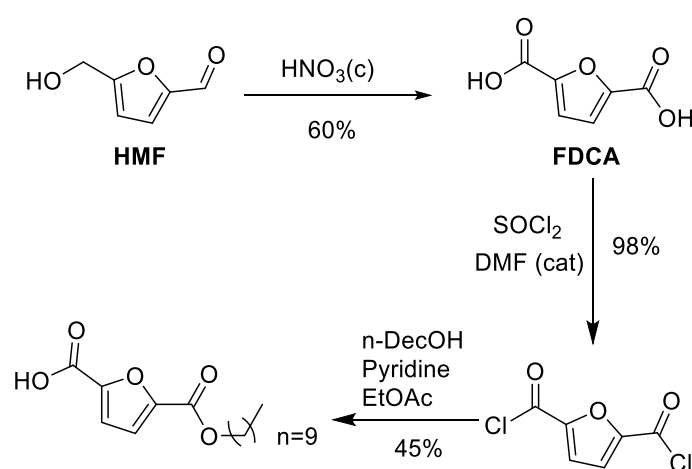
**Scheme 4.** Anionic, non-ionic and cationic amphiphiles from HMF ethers <sup>[46]</sup>

A similar strategy from the same group was applied to a series of fatty ester of HMF, BHMF, or BHMTF. An initial enzymatic esterification step using a lipase provided selectively monoesters when two hydroxyl groups were present in the substrate. From HMF, the polar hydroxyethylaminoethylamino or hydroxyethyloxyethylamino moieties were introduced through the formation of an imine from the aldehyde group, followed by reduction using sodium borohydride, while the BHMF or BHMTF derived systems require the displacement of a triflate by the corresponding amine (Scheme 5).<sup>[47]</sup>



**Scheme 5.** Non-ionic surfactants from HMF fatty esters <sup>[47]</sup>

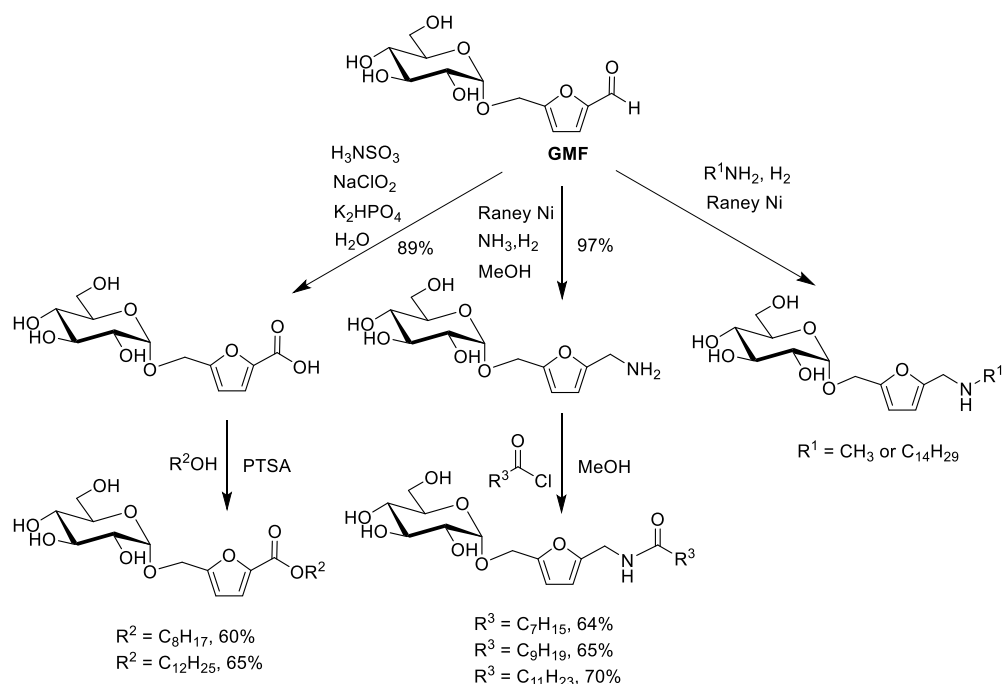
Apart from the examples in Scheme 1 and 5<sup>[31, 47]</sup>, a couple more examples of amphiphilic systems derived from HMF esters have been described. One starts from furandicarboxylic acid (FDCA). The simple hemiester of this diacid with decanol was found by Estrine *et al.* to be a useful additive in a preparation of APGs from decanol and D-glucose (Scheme 6). This monoester of FDCA exhibits an amphiphilic structure, in which the carboxylic acid function group is the hydrophilic part. When added to polyglycosides, the mixture exhibits a reduced wetting time and satisfactory biodegradation based on the EU norm (monosodium form, 68 % after 28 d).<sup>[48]</sup>



**Scheme 6.** Amphiphilic FDCA hemiesters<sup>[48]</sup>

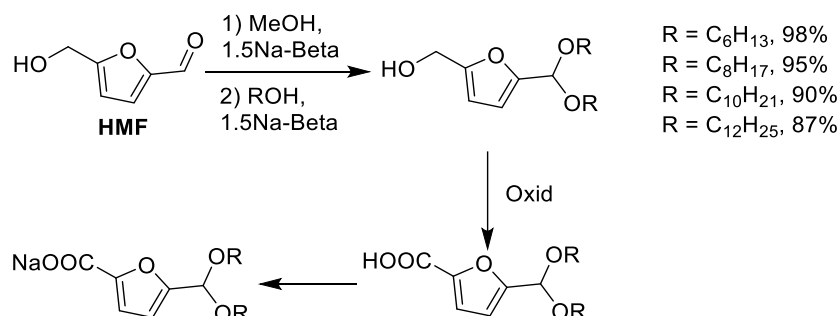
The glucosylated analogue of HMF,  $\alpha$ -D-glucosyloxymethylfurfural (GMF, obtained by dehydration of the disaccharide isomaltulose, glucosyl-6-O-fructose)<sup>[49-51]</sup>, was used to design amphiphilic systems in which the glucose moiety brings the polar, non-ionic, part. Reaction of GMF derived carboxylic acid with fatty alcohols to fatty esters, or GMF-furfurylamine with fatty acids to amides, introduced the non-polar part. Alternatively, a reductive amination sequence led to amphiphilic secondary amines. The mesomorphic behavior of some of these products confirmed their ability to exist at the state of liquid crystal (Scheme 7).<sup>[49, 52]</sup>





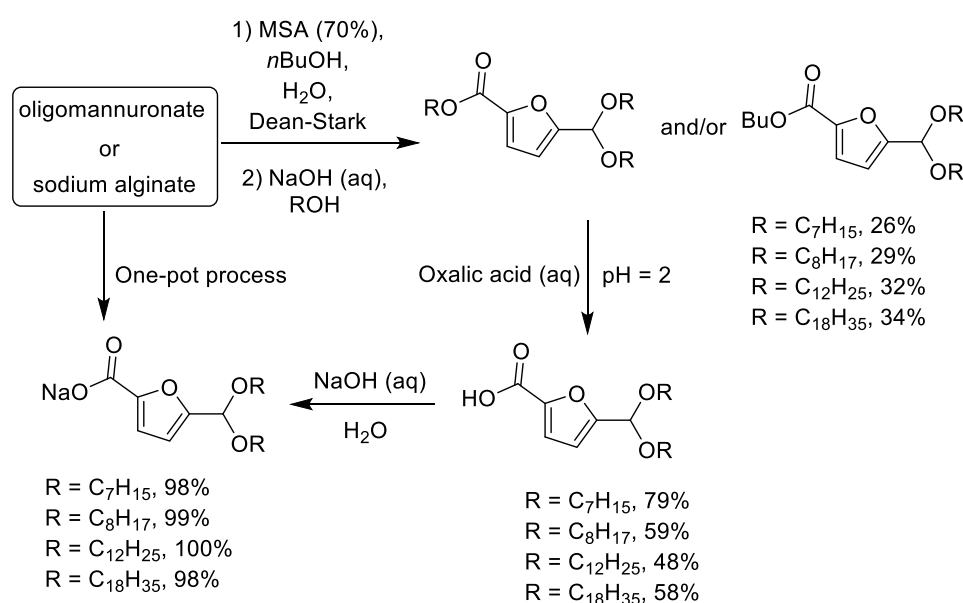
**Scheme 7.** Amphiphiles from GMF via esterification, amination and amidation [49, 52]

The acetal linkage can also be found in a few examples of HMF-derived amphiphiles. This confers to the products increased sensitivity to acidic conditions. A straightforward route reported by Climent *et al.* is an acetalization-oxidation sequence (Scheme 8). Using Na-exchanged Beta zeolites for the generation of the dimethyl acetal and its transacetalization with a fatty alcohol, higher selectivity and shorter reaction time was observed, while avoiding the unexpected etherification of the  $CH_2OH$  group. Further oxidation to the carboxylic acid and saponification of this latter provided the polar part of the surfactant.<sup>[53]</sup>



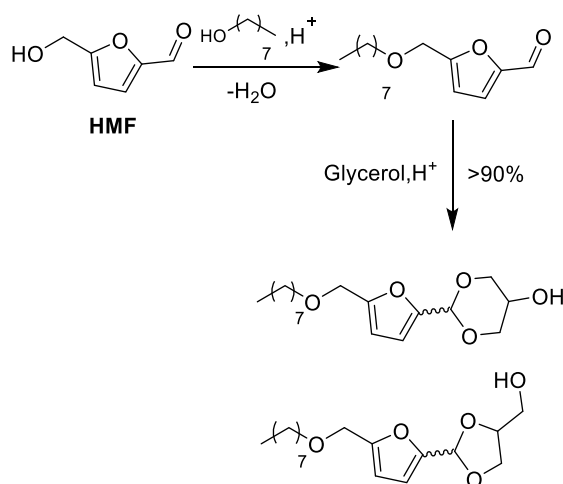
**Scheme 8.** HMF acetals of fatty alcohol [53]

A very recent alternative sequence towards similar acetal-carboxylates has been reported by Benvegna *et al.* who developed the direct conversion of oligo-alginates or alginate into butyl 5-(dibutoxymethyl)-2-furoate. This latter can be then transesterified and/or transacetalized with long chain alcohols. Saponification of the intermediate esters led to the target acetals-carboxylates. (Scheme 9) These surfactants were found to reduce the water surface tension down to  $25 \text{ mN m}^{-1}$ , and exhibited high foaming ability. In addition to the satisfactory eco-design, these compounds were readily biodegradable (96 % biodegradation after 28 d) and found non-toxic for the aquatic organisms.<sup>[54]</sup>



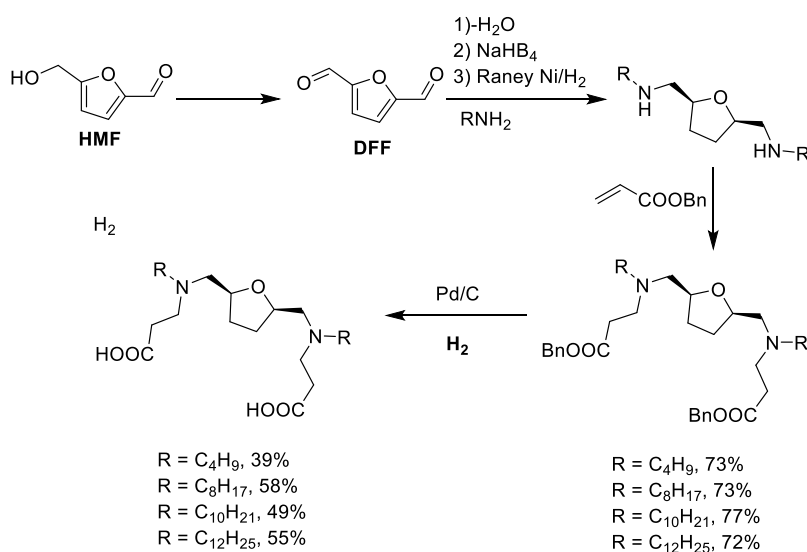
**Scheme 9.** Synthesis of non-ecotoxic anionic furanic surfactants from alginate oligo- or polysaccharides <sup>[54]</sup>

A last example of acetal, developed by Corma and co-workers developed from HMF fatty ethers, relies on the acetalization of the aldehyde group with glycerol, thus targeting non-ionic systems (Scheme 10). The order of the two steps could be changed while leading to the same molecules, thanks to the specificity of each acidic catalyst. Two different compounds can be formed due to the presence of three reacting hydroxyl groups in glycerol.<sup>[55]</sup> These compounds exhibited Hydrophilic Lipophilic Balance (HLB) values ranging from 4.9 to 6.6, which are consistent with applications as humectants or emulsifiers. Their stability in water was excellent, with no change over 50 hours, as well as their thermal stability with no degradation before 200 °C.



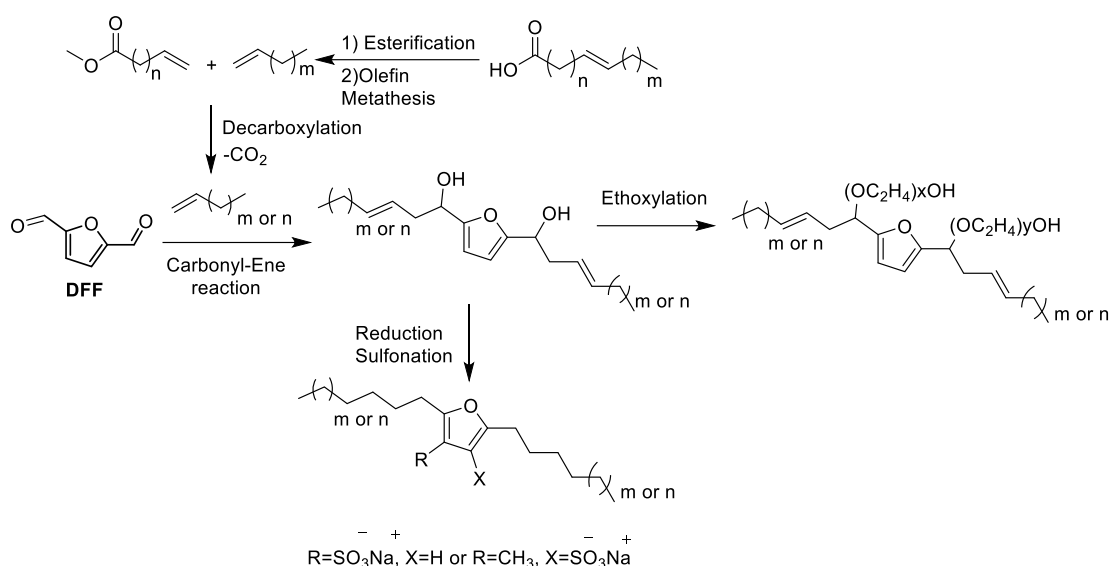
**Scheme 10.** Non-ionic glycerol acetals from HMF ethers <sup>[55]</sup>

HMF can be oxidized to the bis aldehydic product 2, 5-diformylfuran (DFF). A series of gemini surfactants were synthesized from DFF by Hoffmann's group.<sup>[56]</sup> Condensation of DFF with alkyl amines, followed by the reduction to secondary amines with NaHB<sub>4</sub> and further reduction of the furan moiety led to tetrahydrofuran secondary amines. These bis-amines were carboxyethylated in two steps, firstly with a Michael addition on benzyl acrylate, followed by catalytic hydrogenation to the final amphoteric bis-aminocarboxylates (Scheme 11). These surfactants exhibited remarkable ability to reduce water surface tension (down to 30 mN.m<sup>-1</sup>) at an extremely low CMC (ca.1.5 μmol.L<sup>-1</sup>). Being amphoteric, a strong influence of pH on the properties was observed. In addition to the physicochemical properties, the compounds behaved as antifungal agents against *Fusarium graminearum*.



**Scheme 11.** Synthesis of gemini surfactants from DFF <sup>[56]</sup>

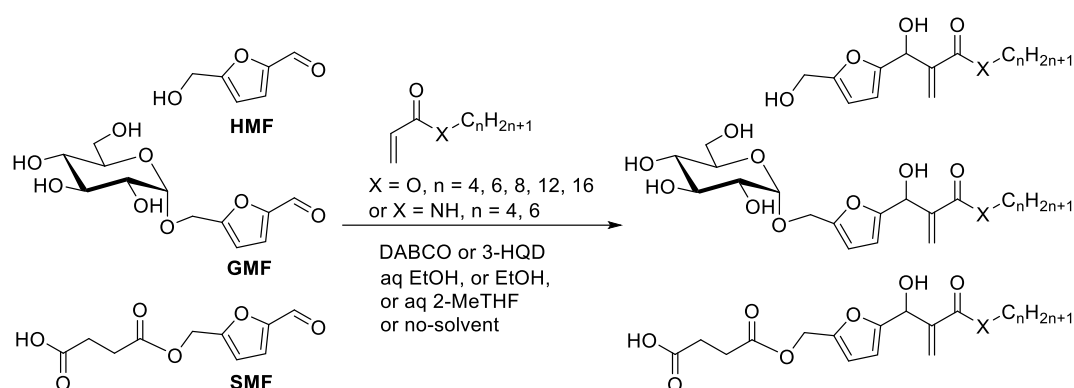
After all the above examples all relying on carbon-heteroatom chemistry, a handful of carbon-carbon bond formation strategies should be also mentioned. One example is a sequence using the carbonyl-ene reaction of an unsaturated fatty acid as the key step, reported in a recent patent by Krumm *et al.* This process starts from unsaturated fatty acids which are esterified to their methyl esters, then subjected to an olefin metathesis reaction generating two new unsaturated olefins, among one is a carboxylic ester which can be decarboxylated. The resulting mixture of two fatty unsaturated olefins can then undergo a carbonyl-ene reaction with DFF. After hydrogenation, a sulfonation or ethoxylation step introduces the polarity in the targeted amphiphiles (Scheme 12).<sup>[57]</sup>



**Scheme 12.** Synthesis of oleo-furan surfactants from DFF with unsaturated fatty acid. <sup>[57]</sup>

Queneau and colleagues have investigated the application of the atom economical Morita-Baylis-Hillman (MBH) C-C bond formation reaction to furanic aldehydes.<sup>[58, 59]</sup> The strategy was further applied to HMF, its glucosylated analogue GMF<sup>[49-51]</sup> and succinic hemiester (SMF, prepared by reaction with succinic anhydride)<sup>[60]</sup> were used as aldehydes, and fatty acrylates or acrylamides as activated alkenes. Thus, a new family of biobased amphiphilic derivatives, prepared in clean aqueous or biobased solvents and under mild conditions, was thus designed (Scheme 13).<sup>[61]</sup> GMF derivatives exhibited lower CMC values than the corresponding alkyl  $\beta$ -D-glucopyranoside. Hydrogenation of the acrylic linkage led to less hydrophilic

behavior, as seen by PIT-slope values, an interesting method for comparing surfactants behavior.<sup>[62, 63]</sup> HMF short chain amphiphilic acrylamides were more hydrophilic than the corresponding acrylic esters. The C<sub>12</sub> GMF compounds were found to stabilize O/W emulsions, while the more lipophilic C<sub>16</sub>-SMF adduct under the acidic form could be used to formulate W/O emulsions.

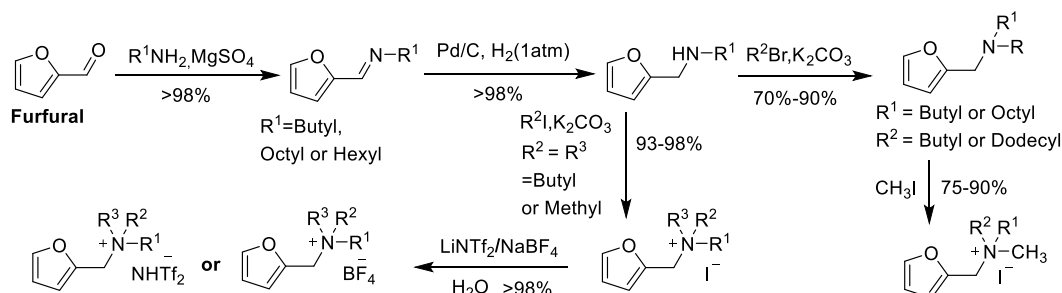


**Scheme 13.** The Morita-Baylis-Hillman route to furanic surfactants <sup>[61]</sup>

### 1.3.2 Furfural based amphiphiles

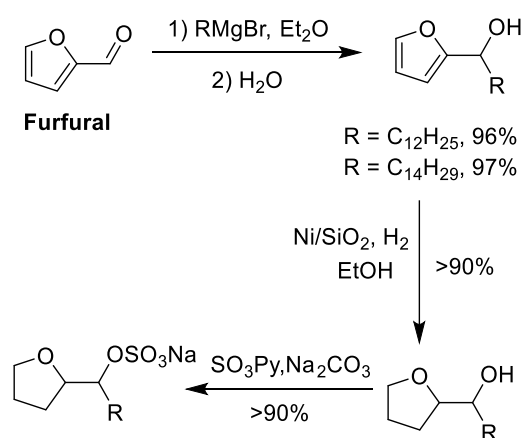
Several quaternary ammonium salts were synthesized from furfural by Paola Galletti and co-workers.<sup>[64]</sup> Solvent-free condensation of furfural with amines (butylamine, octylamine or hexylamine) under the catalysis of MgSO<sub>4</sub> generated the corresponding imines. Subsequent catalytic hydrogenation led to the alkyl substituted furfural-based amines, which could be further substituted to the tertiary amines with bromoalkanes then quaternized to the ammonium iodide using iodomethane. Alternatively, the secondary amines could be directly treated by iodoalkanes, leading to the quaternary ammonium iodides. Further anion exchange allowed to vary the counteranion, for example as bis(trifluoromethane)sulfonimides and tetrafluoroborates (Scheme 14). The solubility of these quaternary ammonium salts was investigated showing high solubility in polar solvents with variations depending on the alkyl chain length and on the counter anion. Their chemical stability was good investigated under basic, neutral and weak acidic conditions, whereas quick decomposition was observed in strong acidic media. The compounds were found thermally stable until 165 °C or higher. NTf<sub>2</sub> salts showing higher thermal stability, low melting point and low viscosity can

be envisaged for use as ionic liquid solvents. The acute ecotoxicity of the furanic salts was comparable to that of tetrabutylammonium iodide and benzyltributylammonium iodide, suggesting possible uses as alternative biocides.



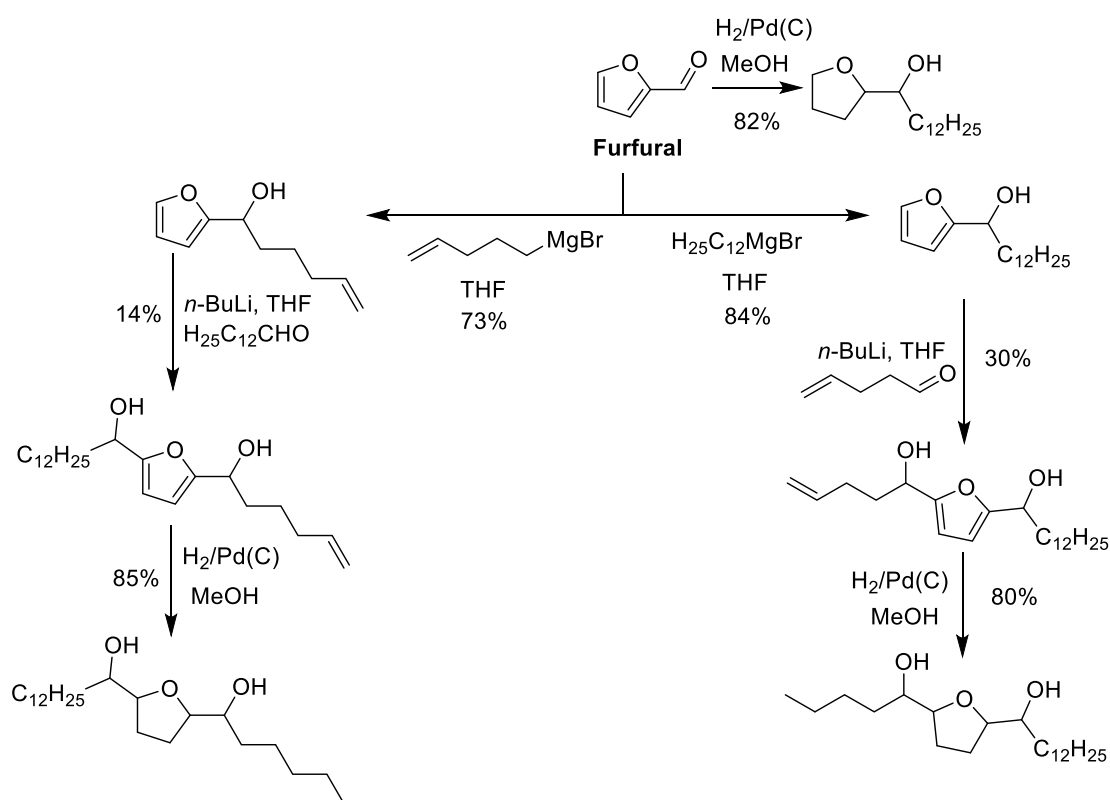
**Scheme 14.** Synthesis of quaternary ammonium salts from furfural <sup>[64]</sup>

Grignard reactions targeting the aldehyde group of furfural have been used as a key step towards amphiphilic furans. This has been well illustrated by the Palkovits' group who reported anionic surfactants prepared by this route. <sup>[45]</sup> The alkylated molecules they obtained could be fully hydrogenated using Ni/SiO<sub>2</sub> as catalyst, and the subsequent sulfation of the hydroxyl group with SO<sub>3</sub>·Py-complex and neutralization with Na<sub>2</sub>CO<sub>3</sub> (Scheme 15), led to the target amphiphilic compounds. The CMC and interfacial tension between water and isopropyl myristate at pH 8.5 of the C12 (0.24 g L<sup>-1</sup>, 3.5 mN m<sup>-1</sup>) and C14 (0.01 g L<sup>-1</sup>, 2.9 mN m<sup>-1</sup>) compounds was compared to linear alkylbenzene sulfonates (LAS, 0.08 g L<sup>-1</sup>, 0.9 mN m<sup>-1</sup>) and ethoxylate-based fatty alkyl ether sulfates (FAES, 0.05 g L<sup>-1</sup>, 3.9 mN m<sup>-1</sup>).



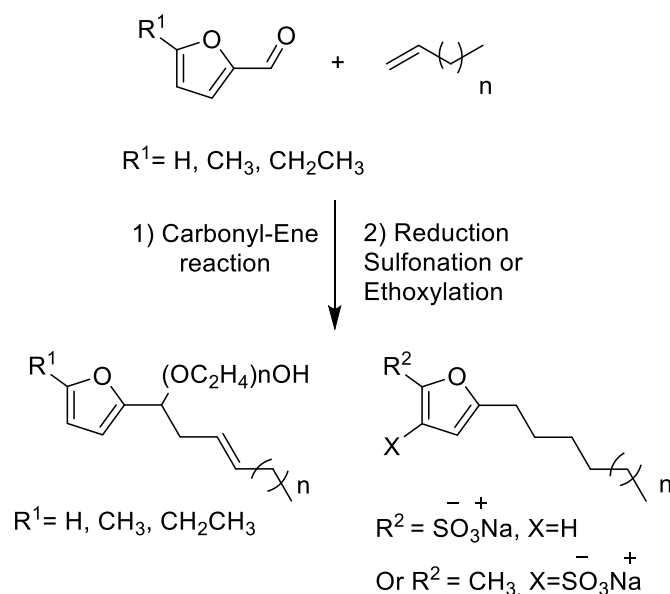
**Scheme 15.** Synthesis of amphiphilic alkylated furfural sulfates <sup>[45]</sup>

Earlier, two families of such 2,5-dialkylfurans and 2,5-dialkyltetrahydrofurans were reported by Krauss *et al.* for being used as antibacterial agents. The reaction of furfural with dodecylmagnesium bromide generated an alcohol, which could be lithiated with *n*-BuLi then added onto pent-4-enal to give a 2,5-disubstituted furan. Systems bearing either one hydroxy group and one alkyl chain, or two hydroxy groups and two alkyl chains, could thus be obtained, while subsequent hydrogenation provided additional tetrahydrofuryl derivatives in the series (Scheme 16).<sup>[65]</sup> Alternatively, Grignard reaction of furfural with pent-4-enylmagnesium bromide, lithiation with *n*-BuLi followed by reaction with dodecylaldehyde led to other disubstituted furans, and tetrahydrofurans after hydrogenation (Scheme 16).<sup>[65]</sup> While no expected antibacterial activity was observed, the compounds exhibited significant cytotoxicity against HL 60 cell line.



**Scheme 16.** Synthesis of 2,5-dialkylfurans and tetrahydrofurans from furfural<sup>[65]</sup>

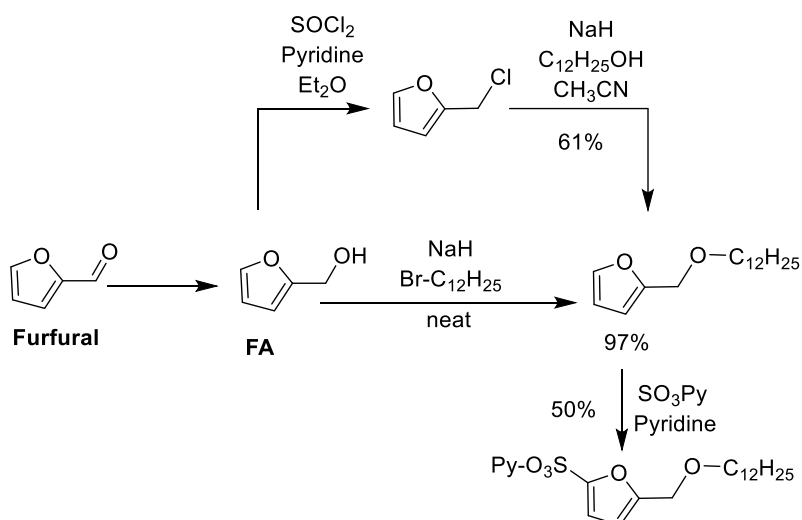
The patent of Krumm *et al.* [57] also included the preparation of furfural based surfactants from furfural and alkyl furfurals with the olefins, which were generated from the unsaturated fatty acid esterification and olefin metathesis, via carbonyl-ene reaction. The hydrophilic moiety could also be introduced via a process comprising reduction and sulfonation process, or a process of ethoxylation (Scheme 17).



**Scheme 17.** Synthesis of oleo-furan surfactants from furfural with unsaturated fatty acid. [57]

Furfuryl alcohol (FA), easily obtained from furfural by reduction, could also serve as intermediate towards amphiphiles. In their work targeting different families of amphiphilic products from furfural and furan, Palkovits and coworkers extended the scope of possible products using FA as substrate in an alkylation/sulfonation sequence (Scheme 18).<sup>[45]</sup> Alkylated FA were prepared by Williamson etherification of alkyl bromides or iodides, however competitive E2-elimination gave side n-olefin in variable extent depending on the haloalkane and the solvent. Alkyl iodide and solvent-free condition led to the higher selectivity for this process. The alternative two-step sequence involving the furfurylation of dodecanol by furfuryl chloride suffered from degradation during the distillation process. The sulfonation on the furan moiety of the furfurylether with  $\text{SO}_3\cdot\text{Py}$ -complex was found to occur with concomitant ether cleavage, thus producing dodecylsulfate as side product.





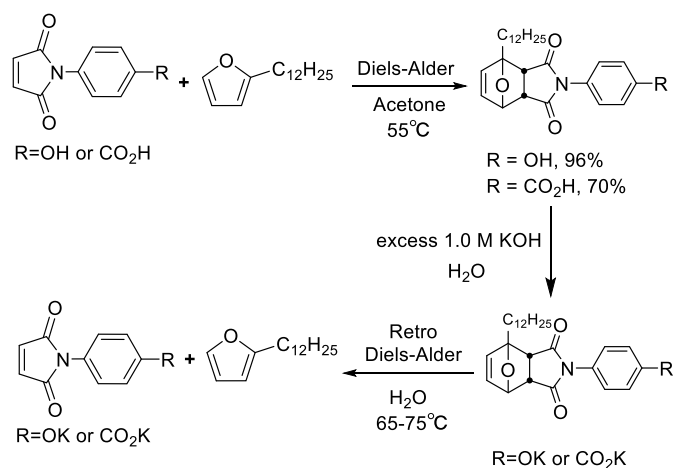
**Scheme 18.** Synthesis of surfactant furfuryl alcohol ethers sulfonates <sup>[45]</sup>

### 1.3.3 Furan based amphiphiles

Furan can be prepared by decarbonylation of furfural.<sup>[66-68]</sup> It can therefore be considered as a pertinent biobased platform among furanic scaffolds, as well as 2-alkylfurans which can be obtained from various precursors, including furan itself, or furfural as exemplified in the previous section.

Furans or alkylfurans, thanks to their dienic nature, can undergo Diels Alder cycloadditions (DA), a reaction showing two interesting characters, firstly to be an atom economical reaction, and secondly to be reversible at higher temperature. This offers a possibility to design thermally cleavable products. This has been exploited to reach surfactants in a study reported in 2005 by Blake A. Simmons and collaborators. As depicted in Scheme 19, the Diels-Alder reaction of dodecylfuran with maleimides was utilized as a key step to synthesize two series of amphiphiles. The non-polar character is present in the alkylated furanic substrate, while the polar one is an anionic group, either a potassium phenolate or a potassium carboxylate, provided as substituents on the maleimide dienophile. The adducts resulting from the DA reaction were found to exhibit interesting surfactants properties, with CMC values in the mM range and good ability to form micelles as demonstrated by small-angle neutron scattering experiments. As expected from their design, they exhibited the interesting property to be thermally cleavable, with reversion of the reaction when exposed to

temperatures above 50°C leading to smaller and non-amphiphilic degradation products. Such a behavior can be useful for example in sol gel syntheses of mesoporous materials in which the surfactant must be removed finally.<sup>[69]</sup>

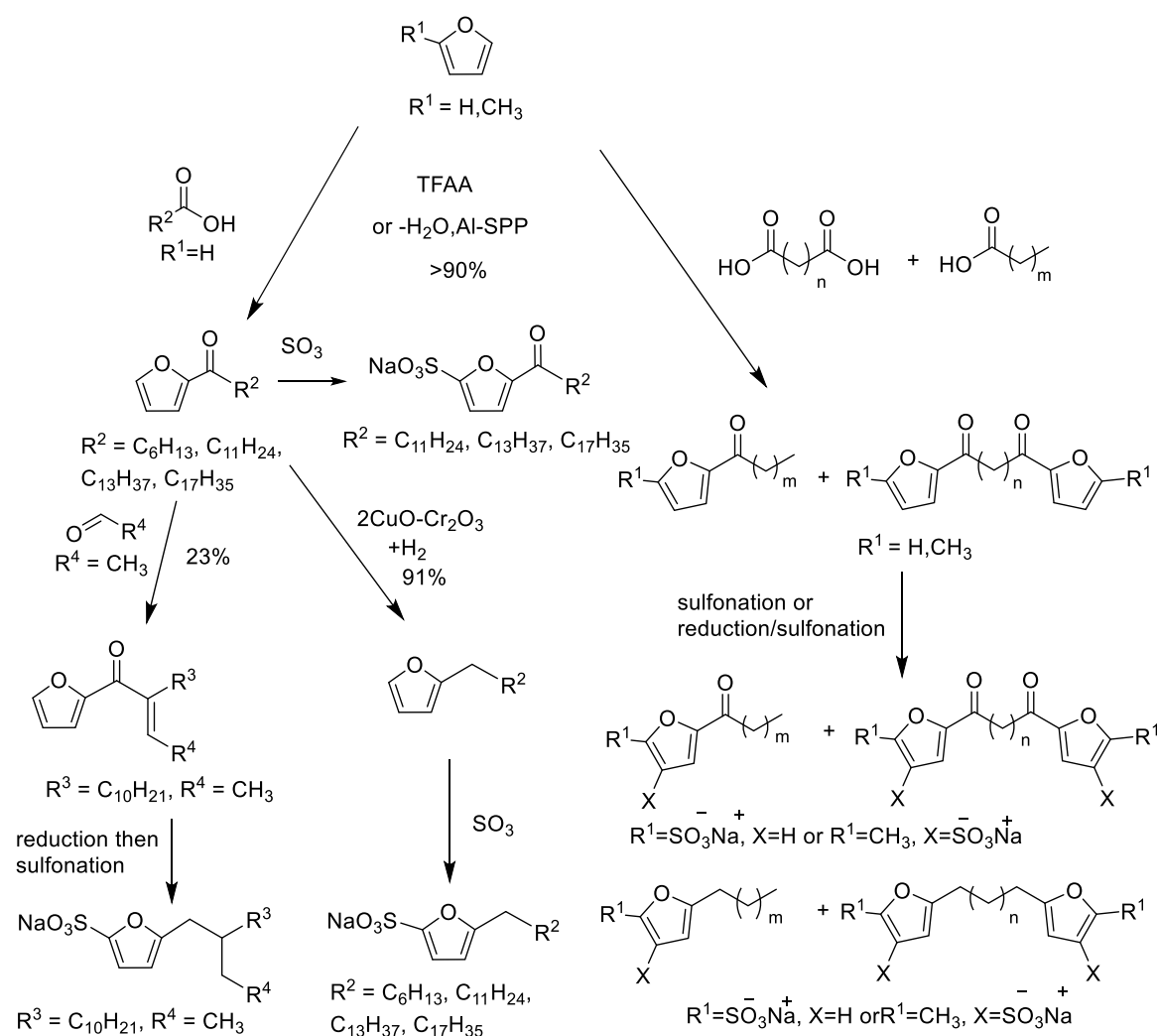


**Scheme 19.** Synthesis of thermally cleavable surfactants from alkyl furans by DA reaction <sup>[69]</sup>

More recently, Dauenhauer and colleagues reported the design of 2,5-disubstituted furanic amphiphiles starting from furan itself. The strategy relies on grafting a non-polar moiety through a Friedel-Crafts acylation reaction of a fatty acyl chain onto the furan  $\alpha$  position, and on a late sulfonation at the  $\alpha'$  position providing the polar group.<sup>[70]</sup> The name of “oleofurans” gives a clear indication of the biomass origin of these compounds.

The Friedel-Crafts acylation step could be performed with long chain alkyl anhydrides using heterogeneous catalysts, such as Al-SPP, however one equivalent of fatty acid is also formed in this sequence. A more atom-economical route was preferred, using directly the fatty acids in presence of trifluoroacetic anhydride (TFAA) or the H-ZSM-5 zeolite.<sup>[71]</sup> The ketone of the intermediate acylfuran could be reduced selectively in presence of copper chromite, retaining the complete furan structure, leading the alkyl analogs. The scope of oleofurans was extended further to branched systems through an intermediate aldol condensation of the furanic ketones with acetaldehyde (Scheme 20). A mixture of fatty carboxylic acids or diacids arising from an olefin metathesis-alkene oxidation sequence could also be used in the Friedel-Craft acylation step of furan (or methyl furan) leading to additional alkylfurans including symmetrical bis furanic systems.<sup>[57]</sup> An alternative clean and

atom economical route to the acylfurans using the cross-ketonization reaction of 2-furoic acid and lauric acid under heterogeneous catalysis only giving H<sub>2</sub>O and CO<sub>2</sub> as side products was also recently proposed by Vlachos *et al.*<sup>[72]</sup> Other approaches towards long chain alkylfurans lubricants reported recently by the Vlachos' group<sup>[73-75]</sup>, relying either on the coupling of alkylfurans with fatty aldehydes or ketones leading to di-furanic products, or on the conjugate addition of alkyl furans onto unsaturated aldehydes, might be also considered for extending the scope of possible amphiphilic targets.



**Scheme 20.** Furan acylation to renewable oleo-furansulfonate <sup>[57,70]</sup>

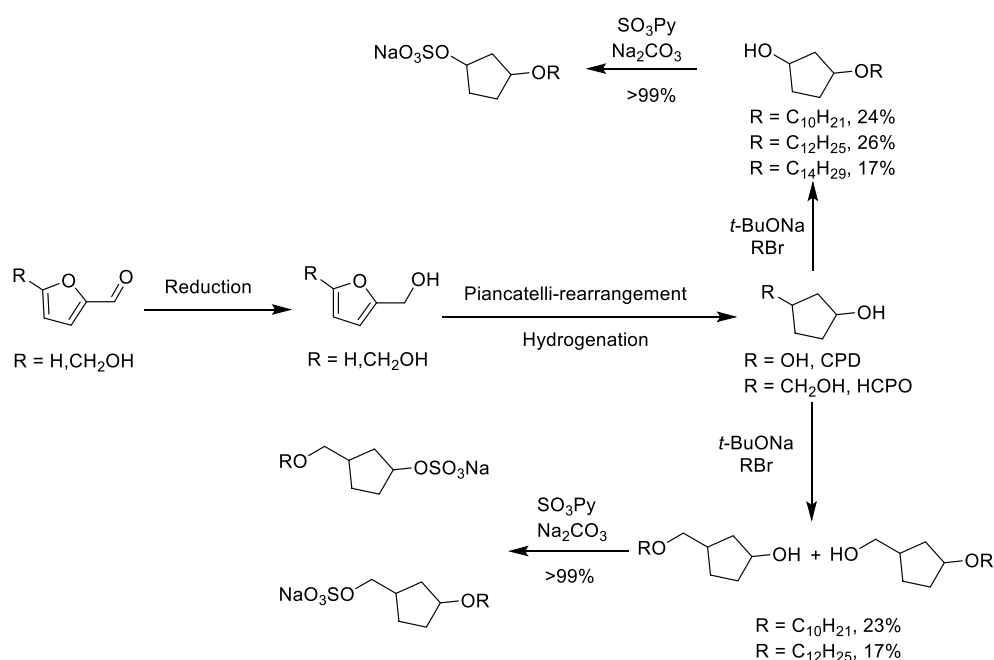
The remnant  $\alpha$  carbon of the acyl or alkyl furans could be sulfonated through two strategies: one is sulfur trioxide sulfonation and the other is sulfur trioxide-pyridine complex sulfonation (Scheme 20). These oleo-furan sulfonates (OFSs) surfactants exhibit same performance as LAS in terms of interfacial properties however at lower

concentrations (CMC) and Krafft temperatures ( $T_k$ ) due to a favorable effect of the furan moiety on the solubility, consistent with better detergency ability. Faster wetting capacity and same foaming behavior were found as compared to LAS. Interestingly, the OFS surfactants exhibited improved stability in hard water, suggesting applications in which the utilization of additional chelating agents can be avoided.

### 1.3.4 Alternative Structural Scope of Furanic Amphiphiles

#### 1.3.4.1 Amphiphiles via the Piancatelli cyclopentanol platform

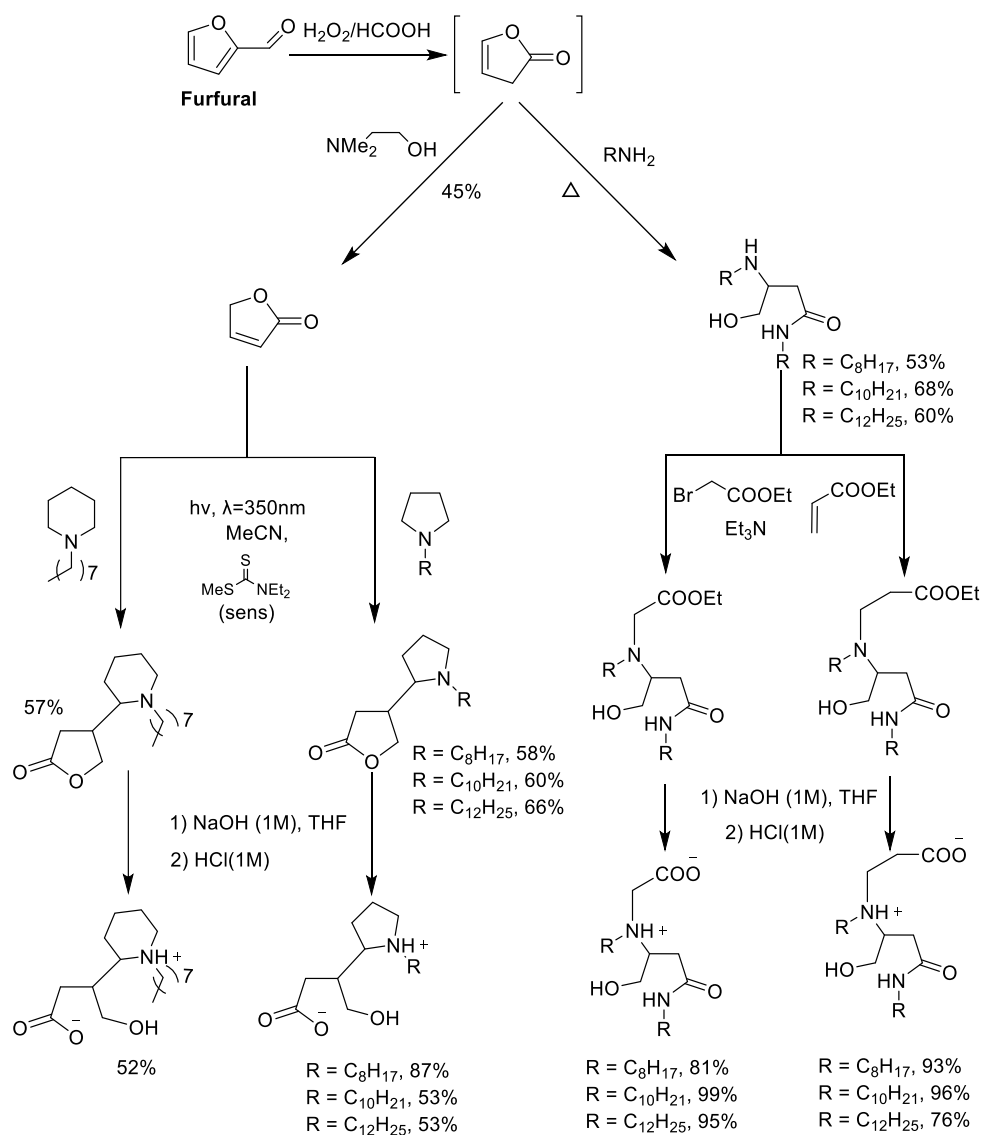
The Piancatelli rearrangement is a way to transform furfuryl alcohols to cyclopentenones.<sup>[76]</sup> Therefore, when applied to HMF or furfural, biobased 5-membered carbocyclic diols, such as 3-(hydroxymethyl)cyclopentanol (HCPO), and 1,3-cyclopentanediol (CPD) can be reached from a hydrogenation/Piancatelli rearrangement/hydrogenation sequence, respectively.<sup>[77, 78]</sup> New surfactants derived from these diols have been prepared by selective Williamson monoetherification of one of the hydroxyl groups, followed by sulfatation of the remaining one (Scheme 21). Physicochemical evaluation in this series (CMC, interfacial tension) compared to LAS and FAES showed interesting values for the C10 product ( $0.13 \text{ g L}^{-1}$ ,  $3.5 \text{ mN m}^{-1}$ ).<sup>[45]</sup>



**Scheme 21.** Synthesis of HCPO-based and CPD-based surfactants <sup>[45]</sup>

### 1.3.4.2 Amphiphiles via the 2[5H]-furanone platform

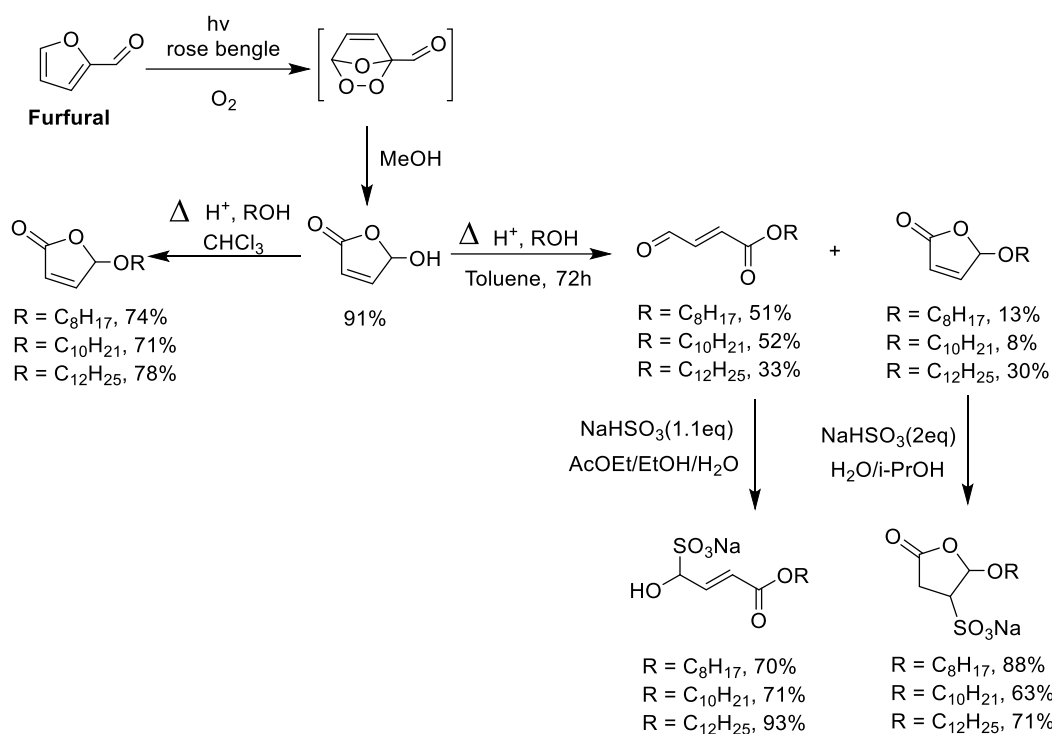
The Hoffmann group has exploited two different 2[5H]-furanone platforms obtained from furfural by oxidation of furfural, for designing amphiphilic compounds. 2[5H]-Furanone was generated from the oxidation of furfural by H<sub>2</sub>O<sub>2</sub> / formic acid, followed by isomerization in presence of *N,N*-dimethylethanolamine. Radical addition of cyclic tertiary amines carrying long fatty chains under photochemical induction by catalytic amounts of 4,4'-dimethoxybenzophenone as sensitizers, led to the Michael adducts, which could then be transformed to the amphiphilic ammonium/carboxylates by lactone opening and amine protonation (Scheme 22).<sup>[79]</sup>



**Scheme 22.** Synthesis of surfactants from 2[5H]-furanone.<sup>[79,80]</sup>

The same 2[5H]-furanone could also react with two equivalent fatty amines in concomitant Michael addition and amide transformation of the lactone, grafting simultaneously to two hydrophobic chains. Selective carboxymethylation or carboxyethylation of the secondary amine either by reaction with ethyl bromoacetate or methyl acrylate, respectively, followed by saponification to the carboxylate and protonation to the ammonium, led to a second family of amphiphilic ammonium/carboxylates (Scheme 22).<sup>[80]</sup> Interesting surfactant properties for the cyclic systems were observed at pH 10, where the anionic form is favored. The acyclic ones exhibited lower CMC than the conventional single-alkyl chain surfactants (carboxylate, sulfate or sulfonate) and similar to other Gemini surfactants. Water surface tensions as low as 30 mN m<sup>-1</sup>, was measured, suggesting potential application as wetting agents, especially under the basic conditions (pH=10). The acyclic systems could be classified as potentially biodegradable under the E.U. directive standard<sup>[81]</sup> with 30 %~40 % degradation after 28 days.<sup>[80]</sup>

A photooxygenation reaction of furfural gives access to an hemiacetalic type of 2[5H]-furanone platform, namely 5-hydroxy-2[5H]-furanone. Its acetalization with fatty alcohols under azeotropic distillation generated the corresponding 5-alkoxy-2[5H]-furanones. Prolonged reaction time led to the transesterification of the lactone group to the corresponding fatty esters, while the remaining enol rearranged into an  $\alpha,\beta$ -unsaturated aldehyde. The furanone acetal and the linear  $\alpha,\beta$ -unsaturated aldehyde could both be sulfonated with NaHSO<sub>3</sub> to provide a polar part, achieving the surfactant design, among which the cyclic systems exhibited chemical stability consistent with potential uses as surfactants (Scheme 23). For the furanone sulfonates, the higher lipophilicity of the furan moiety led to lower CMC as compared to alkylsulfate and alkylsulfonate surfactants with same fatty chain length, while similar to that of LAS surfactants. The furanone surfactants were classified as biodegradable (70 % after 28 d), which is better than LAS (26 %~50 % after 28 d).<sup>[82]</sup>



**Scheme 23.** Synthesis of alkoxyfuranones based surfactants [82]

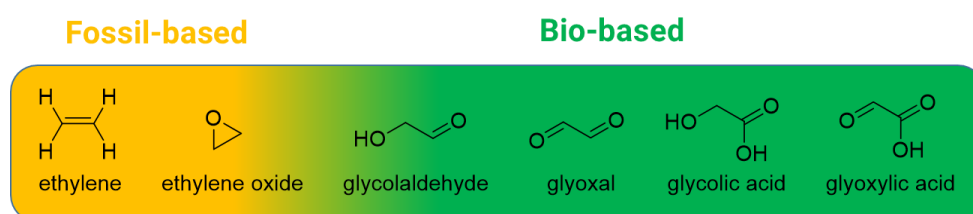
## 1.4 Glyoxylic acid (GA)--- a promising biobased platform molecule

### 1.4.1 C2 biobased chemistry

Several C2 compounds are applied as starting materials in the chemical industry for the production of various fine chemicals, fuels and polymers. Typical C2 building blocks are for example ethylene and ethylene oxide, which have been used as feedstock in plastic and fuel industries for a long time (Figure 10). However, most C2 compounds are mainly produced from fossil resources presently, and finding more sustainable routes to the C2 chemistry can contribute to the global effort towards lower dependence of chemistry on fossil feedstocks. Actually, biobased ethylene exists, being obtained by dehydration of bioethanol. Ethylene oxide can therefore also be found as biobased when biobased ethylene is used for its manufacture. However, bioethanol fermentation is unfortunately accompanied by the formation of significant amounts of CO<sub>2</sub>. On this purpose, alternative biobased platform molecules can be

envisaged for being utilized as alternative feedstock to conventional fossil-based C2 molecules. Recent studies include glycolaldehyde, which is a promising C2 biobased platform compound to replace ethylene oxide in the production of many commercial chemicals. Ethylene glycol is a typical secondary feedstock prepared from glycolaldehyde, and it is a pertinent raw material to produce some polymers. Glyoxal and glycolic acid, another two C2 platform molecules also available from glycolaldehyde via oxidation, have also emerged, notably for applications to the production of recyclable plastic. The amination of glycolaldehyde has also been reported as an alternative eco-friendly route for the production of ethylamine chemicals.<sup>[83]</sup> Ethylene glycol is also a biobased C2 platform molecule which can be obtained from cellulose under the action of a tungsten carbide catalyst promoted by nickel.<sup>[84]</sup>

The development of C2 platform molecules can address a wide scope of processes in the basic chemical industries, and the use of more biobased C2 alternatives will lead the whole chemical industries to more economic and more eco-friendly direction.



**Figure 10.** Typical C2 platform molecules.

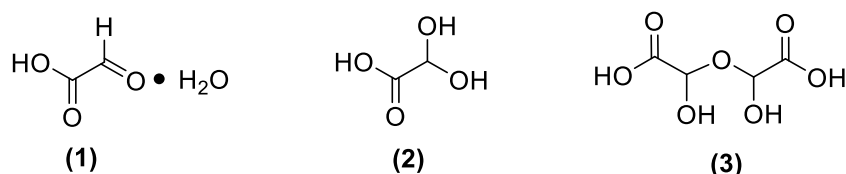
The smallest  $\alpha$ -hydroxy acid, glyoxylic acid, is another very interesting C2 building block. As a part of this thesis concerns its use in an innovative strategy towards surfactants, let us first make a focus on its occurrence and uses in the next section.

#### 1.4.2 Glyoxylic acid (GA): generalities

Glyoxylic acid (GA), also called oxoacetic- or glyoxalic acid, and found by H. Debus in 1856 <sup>[85]</sup>, is an essential aldo-acid found in plants and the metabolic cycle of



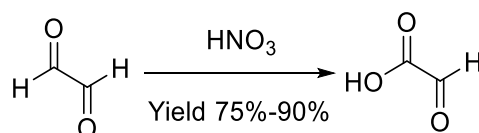
animals. Generally, the commercial form of glyoxylic acid is a 50 wt % aqueous solution of the acid and its density is  $1.34 \text{ g cm}^{-3}$  at  $25 \text{ }^\circ\text{C}$ . GA can crystallize as the glyoxylic acid monohydrate (1) under a controlled specific concentration, in a structure established by Perkin in 1868.<sup>[86]</sup> Based on the NMR spectra ( $^1\text{H}$  and  $^{13}\text{C}$  data), GA exists in aqueous solution in the state of a dihydroxy acetic acid (2), along with a small quantity of the linear dimer (3) (Figure 11).<sup>[87]</sup>



**Figure 11.** Forms of glyoxylic acid: (1) monohydrate, (2) dihydroxy acetic acid, and (3) linear dimer.<sup>[87]</sup>

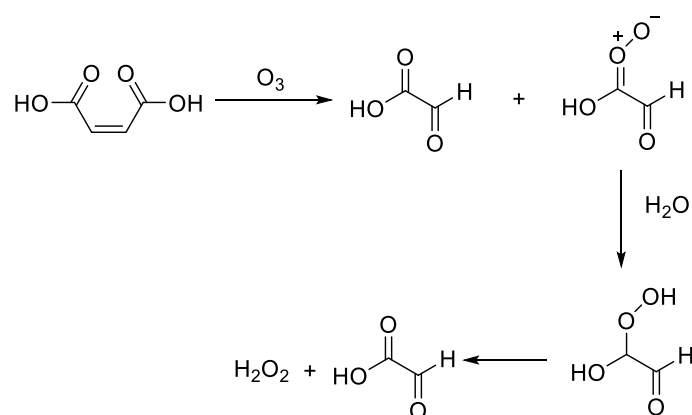
### 1.4.3 Preparation of glyoxylic acid

Several technologies have been developed to prepare GA from various substrates, such as glyoxal, maleic acid, glycolic acid, oxalic acid, tartaric acid, ethylene glycol, silver dichloroacetate and ethanol, etc. However, the modest yield and selectivity of most of these procedures prevented them to be transferred from lab level to the industrial scale. Among these starting materials, only aqueous glyoxal and maleic acid are feedstocks actually used for the production of GA in industry. Through the oxidation of glyoxal in aqueous solution with 65 % nitric acid (Scheme 24)<sup>[88, 89]</sup>, 75 %-90 % yield of GA can be obtained. The difficulties reported for this process are keeping a constant temperature and the complicated isolation of GA from its mixture with side products (mainly oxalic acid) and residual nitric acid.



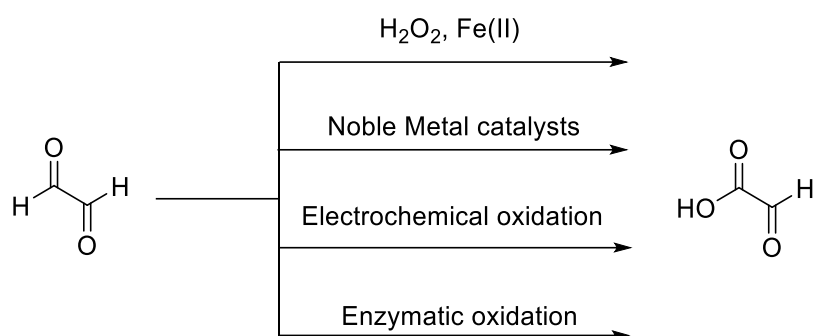
**Scheme 24.** Preparation of glyoxylic acid from glyoxal <sup>[88, 89]</sup>

The ozonolysis of maleic acid<sup>[90]</sup> (or its anhydride) is another common route to produce GA in industry, owing to the high GA yield and a high purity above 97%, even though it necessitates the utilization of ozone, which is toxic and harmful to human respiratory organs. The mechanism of this process was also investigated and is depicted in Scheme 25.<sup>[91-93]</sup>



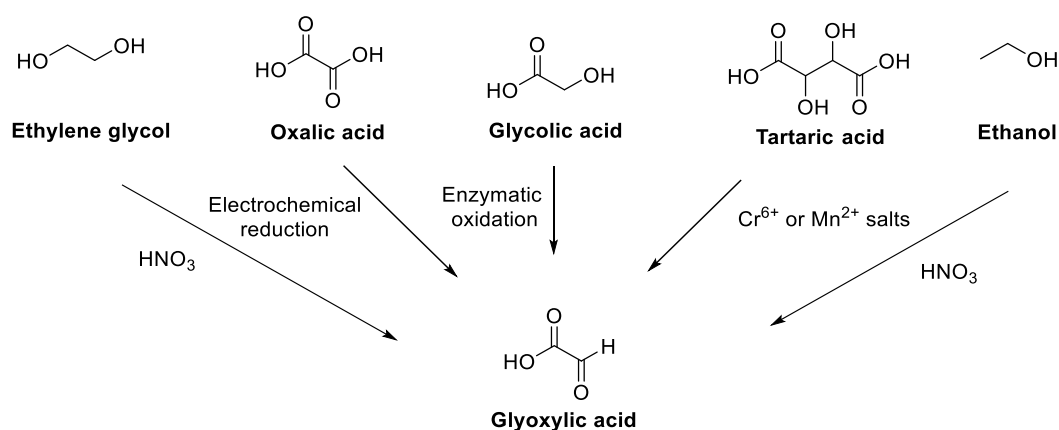
**Scheme 25.** Mechanism of the proposed by Pope *et al.*<sup>[91]</sup>

Besides the processes used in the industrial production of glyoxylic acid, more strategies, still at the fundamental stage, have been developed. For homogeneous oxidation of glyoxal, Fenton's reagent [a mixture of H<sub>2</sub>O<sub>2</sub> with iron (II) salts] was used as oxidant instead of nitric acid and gave ~70% yield of GA.<sup>[94]</sup> For the heterogeneous oxidation of glyoxal, several noble metal catalysts was applied, including Pt-, Ru-, Rh-, Pd-, and Ir based monometallic catalysts, Pd—Au bimetallic catalysts and some trimetallic catalytic systems have been studied in recent years.<sup>[95-99]</sup> But these heterogeneous catalysts are hardly applied in industry production due to three main reasons: moderate yields, low selectivities, complex processes to prepare the catalysts and remove catalysts after reaction.<sup>[87]</sup> Besides, the oxidation of glyoxal towards GA also could be realized via electrochemical routes with a platinum anode<sup>[100, 101]</sup> and enzymes promotion, such as glycolate oxidase.<sup>[102-106]</sup> But these two methods face the same drawbacks like low yield and selectivity, along with a necessity of expensive equipment due to the required temperature and pressure conditions. (Scheme 26)



**Scheme 26.** Other routes for the oxidation from glyoxal to glyoxylic acid

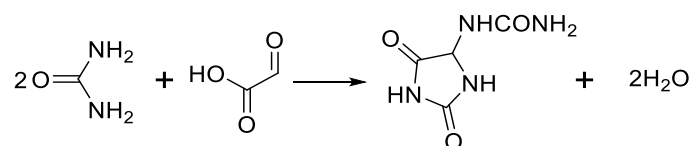
Other routes towards GA include the oxidation of glycolic acid either enzymatically by action of glycolate oxidase<sup>[107, 108]</sup> or chemically under the catalysis of strong base, the oxidation of ethylene glycol and ethanol by nitric acid, and the electrochemical transformation of oxalic acid (a side product during preparation of GA from glyoxal).<sup>[109]</sup> This latter method is limited by the problem of the passivation of the lead electrodes. The preparation of GA by oxidation of tartaric acid with  $\text{Cr}^{6+}$  or  $\text{Mn}^{2+}$  salts was also reported,<sup>[110]</sup> but the utilization suffers from a complicated synthesis procedure of catalyst. Some older publications describe the production of GA by heating silver dibromoacetate in water,<sup>[111]</sup> however this method is rarely applied due to low yields and the use of expensive chemicals ( Scheme 27).



**Scheme 27.** Preparation of glyoxylic acid from other feedstocks

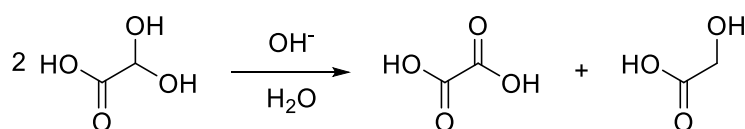
#### 1.4.4 Applications of glyoxylic acid

Glyoxylic acid possesses the characteristic properties of two kinds of compounds, due to the presence of both an aldehyde and a carboxylic acid functions, therefore giving a wide scope of usages. For instance, because both aldehyde and hemiacetal react easily with nucleophiles, some heterocyclic compounds could be produced through coupling polynucleophiles with GA. An example is the formation of allantoin, which could be obtained from the reaction of GA with urea under acidic catalysis (Scheme 28).<sup>[112]</sup>

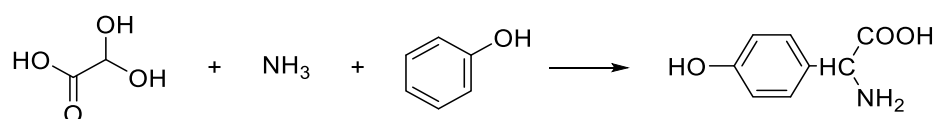


**Scheme 28.** Preparation of allantoin from glyoxylic acid <sup>[112]</sup>

GA is able to undergo Cannizzaro reaction, Mannich reaction and amidoalkylation reactions. It could be thus transformed into glycolic acid and oxalic acid under simple heating (Scheme 29). Oxidation of GA by nitric acid also produces oxalic acid. Reacting with phenol and ethylenediamine in alkaline medium, glyoxylic acid leads to the sodium salt of *N,N'*-ethylenebis[2-(2-hydroxyphenyl) glycine]. By reaction with phenol and ammonia, GA can lead to 4-hydroxyphenylglycine (Scheme 30), an intermediate for the production of the semisynthetic penicillin amoxicillin. <sup>[112]</sup>

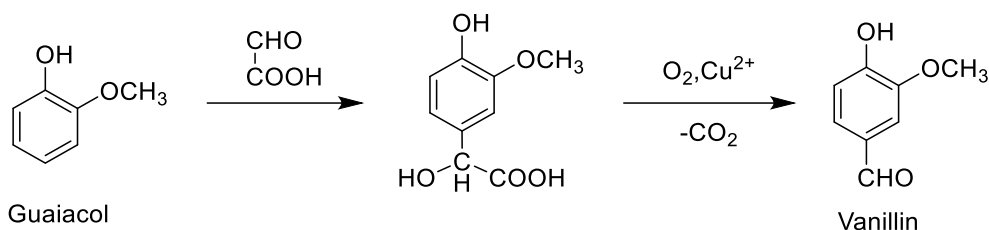


**Scheme 29.** Cannizzaro reaction of glyoxylic acid <sup>[112]</sup>



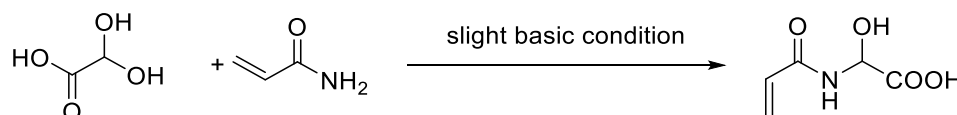
**Scheme 30.** Preparation of 4-hydroxyphenylglycine from glyoxylic acid <sup>[112]</sup>

The reaction of GA with phenols is used in several industrial syntheses of benzaldehydes. For example, the guaiacol could be converted into vanillin by oxidative decarboxylation of the corresponding mandelic acid (Scheme 31). <sup>[112]</sup>



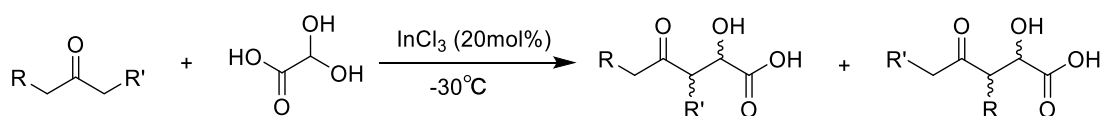
**Scheme 31.** Application of glyoxylic acid on production of vanillin <sup>[112]</sup>

Under slightly basic condition, GA can react with amide, for example acrylamide, to produce acrylamidoglycolic acid as a copolymerizable cross-linking agent, applied extensively in the polymer industry (Scheme 32). <sup>[112]</sup>



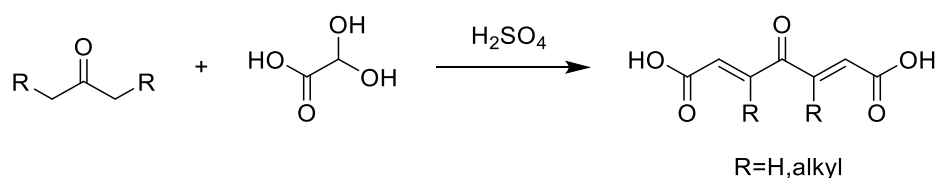
**Scheme 32.** Preparation of acrylamidoglycolic acid (AGA) from glyoxylic acid <sup>[112]</sup>

The aldol reaction is one of the most powerful tools for the construction of carbon-carbon bond. Glyoxylic acid also can undergo an aldol reaction with ketones (Scheme 33), catalyzed by acid or base, in aqueous phase. Many studies have been reported in this field, as its application to GA can generate a variety of  $\alpha$ -hydroxy acids, which are molecules of interest in biology. However, this reaction often suffers from poor yields and low regioselectivity due to harsh reaction conditions. Furthermore, side-reactions such as self-condensation of the ketone or/and dimerization of the aldehyde usually occur along with the aldol reaction. Since, more efforts have been made to accelerate this aldol reaction and improve regioselectivity. <sup>[113]</sup>



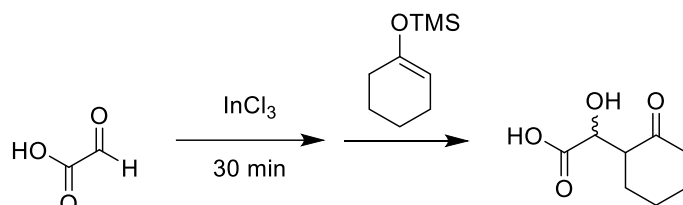
**Scheme 33.** Aldol reaction of glyoxylic acid with ketones <sup>[113]</sup>

Amarasekara *et al.* proposed a new route to prepare 4-oxo-2,5-heptdienedioic acids, which are polymerizable compounds, through the aldol reaction of GA and two equivalent ketones (Scheme 34). By using a stepwise heating method and increasing the catalyst loading, they improved the yield of 4-oxo-2,5-heptdienedioic acid from 45% up to 88%.<sup>[114]</sup>



**Scheme 34.** Acid catalyzed condensation of glyoxylic acid with ketones <sup>[114]</sup>

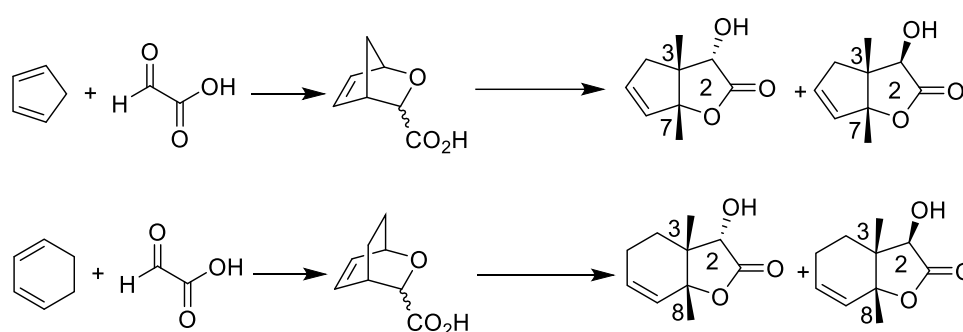
Glyoxylic acid monohydrate also was used in the Mukaiyama aldol reaction by Teck-Peng Loh *et al.* GA monohydrate was reacted with trimethylsilyloxycyclohexene and 1-phenyl-1-trimethylsilyloxyethylene separately in the presence of  $\text{InCl}_3$  (20 mol%),  $\text{H}_2\text{O}$ , 15h, leading to the desired adducts in yields up to 80% (Scheme 35). They mentioned that the order of addition of the reagents, catalyst and solvent influences the yield in this process.<sup>[115]</sup>



**Scheme 35.** Catalytic  $\text{InCl}_3$  (20%)-Promoted Mukaiyama Aldol Reaction <sup>[115]</sup>

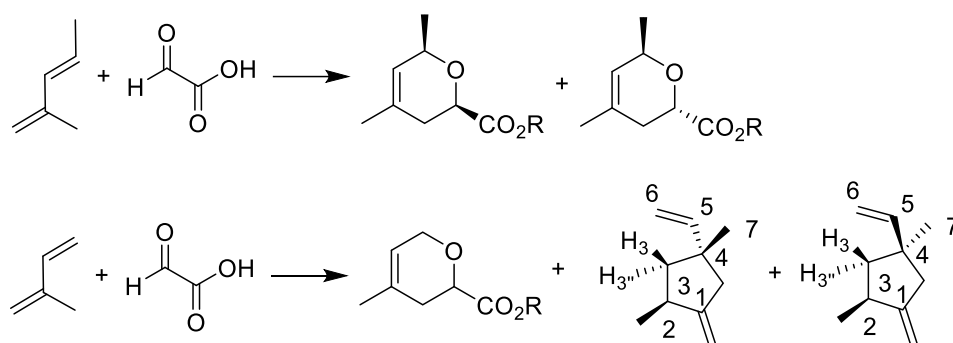
Hetero Diels-Alder reaction of GA has been systemically investigated. While anhydrous glyoxylic esters were normally used, a different strategies using the glyoxylic acid monohydrate are aqueous solution of glyoxylic acid was also used in this reaction. In 1991, Lubineau *et al.* firstly investigated the aqueous cycloaddition of cyclic dienes with GA (Scheme 36). In detail, they used the commercial aqueous solution of glyoxylic acid to react with cyclopentadiene and cyclohexadiene respectively. In these two cases, the reaction gave the corresponding  $\alpha$ -hydroxy- $\gamma$ -lactones as a mixture of epimers in excellent yields. Through the

NOESY experiments, the structure of  $\alpha$ -hydroxy- $\gamma$ -lactones was confirmed and they supposed that  $\gamma$ -lactones might generate from the rearrangement of the endo and exo cycloadducts. They also investigated the effect of pH on this reaction, and a lower pH was proved to make the hetero Diels-Alder reaction more efficient. The reaction of butyl glyoxylate with cyclopentadiene in neat conditions or in toluene was also carried out for comparison, but in this case, only dimerization of the diene occurred instead of hetero Diels-Alder reaction. Therefore, water as the solvent was proved to dramatically change the outcome of the reaction by enabling a faster hetero Diels-Alder reaction than the dimerization of cyclopentadiene.<sup>[116]</sup>



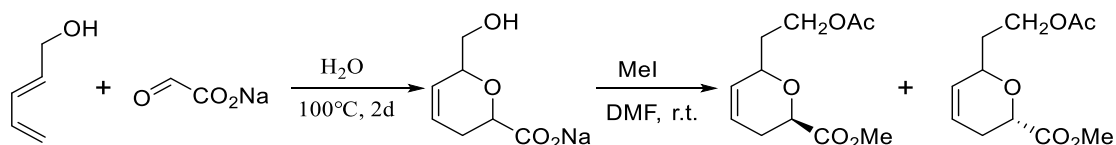
**Scheme 36.** Cycloaddition of cyclopentadiene (or cyclohexadiene) with an aqueous solution of glyoxylic acid <sup>[116]</sup>

In 1994, in order to explore the application of commercially available aqueous solution of some small molecules. Lubineau et al. continued to study the reaction of these aqueous solution of glyoxylic acid, pyruvaldehyde and glyoxal with cyclic and non-cyclic dienes.<sup>[117]</sup> In this work, they proved that the aqueous solution of glyoxylic acid, pyruvaldehyde and glyoxal can react with non-cyclic dienes (2-methylpentadiene or 2-methylbutadiene) to get excellent yields of adducts as a mixture of epimers. (Scheme 37) They observed that the  $\alpha$ -hydroxy- $\gamma$ -lactones could generate from the ene compound rather than the rearrangement of the endo and exo cycloadducts. Activated ketones such as pyruvic acid were also tested in the aqueous hetero Diels-Alder reaction with 2-methylpentadiene under the same condition in water and the corresponding cycloadducts were produced as a mixture of epimers. When the reaction was conducted in neat and toluene solution, the same yield of cycloadducts was obtained but with a reverse selectivity of epimers. This reversal of selectivity have been proved to be the result of thermodynamic control in water and kinetic control in toluene.



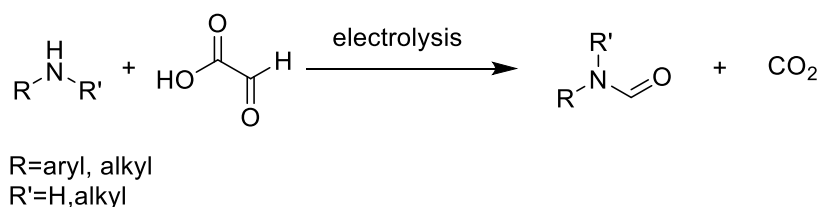
**Scheme 37.** Cycloaddition of non-cyclic dienes with an aqueous solution of glyoxylic acid <sup>[117]</sup>

In 1995, Queneau *et al.* proposed a route to prepare the activated 2-ulosonic esters through the combination of the aqueous hetero Diels-Alder (DA) cycloaddition of commercially available sodium glyoxylate, followed by a radical dibromination achieving the anomeric functionality elaboration (Scheme 38).<sup>[118]</sup>



**Scheme 38.** Preparation of the 2-ulosonic esters precursors from sodium glyoxylate <sup>[118]</sup>

GA has also been widely used as a formylation reagent, alternative to formaldehyde. For example, Huang *et al.* reported an *N*-alkylation sequence based on the decarboxylation of GA via electrochemical routes (Scheme 39). Indicating a new pathway to prepare formamides under mild conditions and only with CO<sub>2</sub> as side product.<sup>[119]</sup>



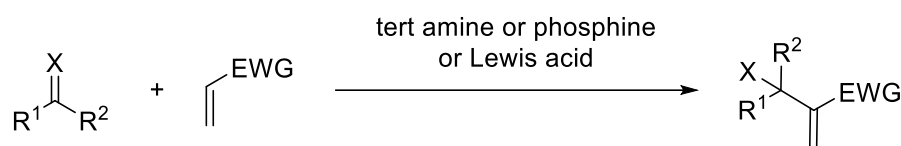
**Scheme 39.** Decarboxylative *N*-formylation of amines with glyoxylic acid via electrolysis <sup>[119]</sup>



## 1.5 The Morita-Baylis-Hillman reaction

### 1.5.1 Introduction and mechanism

The Morita-Baylis-Hillman (MBH) reaction is a famous C-C bond forming reaction, connecting an activated alkene with an electrophilic carbonyl compound under the promotion of a nucleophilic promoter. It is widely used for the construction of novel chemical architectures. (Scheme 40) This reaction exhibits several advantages, such as its atom economy, the wide scope of substrates which can be used, and the mild reaction conditions.<sup>[120, 121]</sup> It was first reported by Morita in 1968<sup>[122]</sup>, using phosphines as nucleophilic promoters. Baylis and Hillman reported the overall same reaction catalyzed with tertiary amines (DABCO) in 1972.<sup>[123]</sup>



R<sup>1</sup>= alkyl, aryl, heteroaryl

R<sup>2</sup>= H, alkyl, COOR

X= O, NCO<sub>2</sub>R, NTs, NSO<sub>2</sub>Ar, NP(=O)R<sub>2</sub>

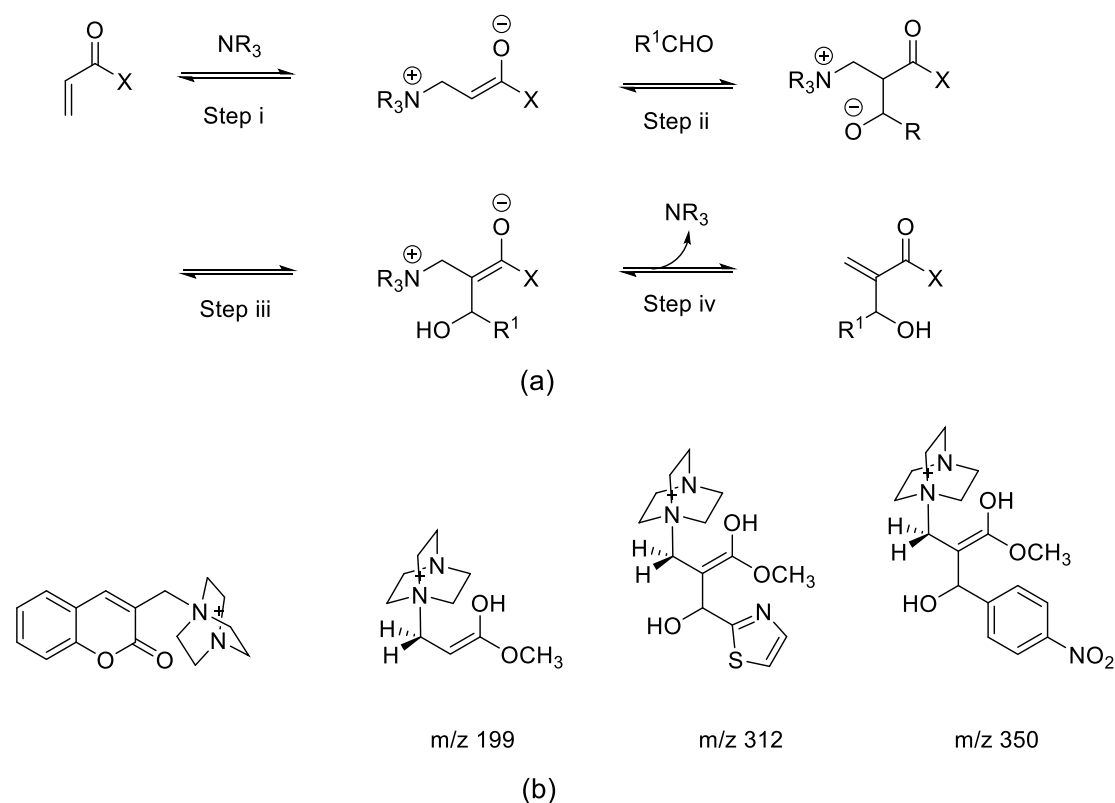
EWG= COR, CHO, CN, CO<sub>2</sub>R, PO(OEt)<sub>2</sub>, SO<sub>2</sub>Ph, SO<sub>3</sub>Ph, SPh

**Scheme 40.** Morita-Baylis-Hillman reaction

Despite its advantages, there was a long period of neglect before the use of this reaction started to flourish and its scope expanded. Among representative examples of its synthetic usefulness, Drewes *et al.* developed a five-step route for the total synthesis of integerrineic acid in 1982, including the  $\beta$ -hydroxy-ester generated from MBH reaction of ethyl acrylate with acetaldehyde.<sup>[124]</sup> Hoffmann *et al.* also reported convenient ways to prepare mikanecic acid with MBH adduct of tert-butyl acrylate and acetaldehyde.<sup>[125, 126]</sup> Perlmutter applied MBH reaction on the easier synthesis of 2-methylidene-3-aminopropanoates,<sup>[127]</sup> and Basavaiah produced a family of  $\alpha$ -methylene- $\beta$ -hydroxyalkanones via the MBH reaction of methyl vinyl ketone with various aldehydes.<sup>[128]</sup>

The widely accepted mechanism of MBH reaction were firstly proposed by Hoffmann *et al.* in their work towards mikanecic acid in 1983 [Scheme 41(a)], and was further confirmed by Isaacs *et al.*<sup>[129]</sup> This mechanism includes four key steps: firstly, a

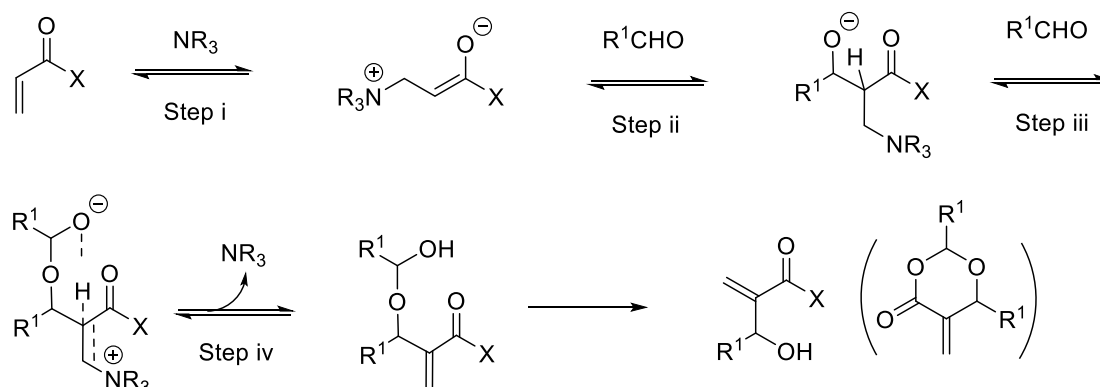
Michael addition of the promoter (a nucleophilic organocatalyst such as an amine or a phosphine) onto an activated alkenes, producing a first enolate, secondly the addition of this first enolate to the electrophilic partner (generally an aldehyde) leading to a the zwitterionic intermediate , thirdly an intramolecular proton transfer of the zwitterionic intermediate producing a second enolate, and finally the formation of the final adduct driven by the release of the promoter. According to the reaction kinetics study of Isaacs, the rate-determining step (RDS) is regarded as the step ii, based on a weak kinetic isotopic effect at the  $\alpha$ -position of the activated alkene. Furthermore, the isolation of intermediates by Drewes *et al.* [130] and Eberlin *et al.* [131] strongly supported this mechanism. [Scheme 41(b)]



**Scheme 41.** (a) Mechanism proposed by Hoffmann and (b) the isolated intermediates by Drewes and Eberlin *et al.* [130,131]

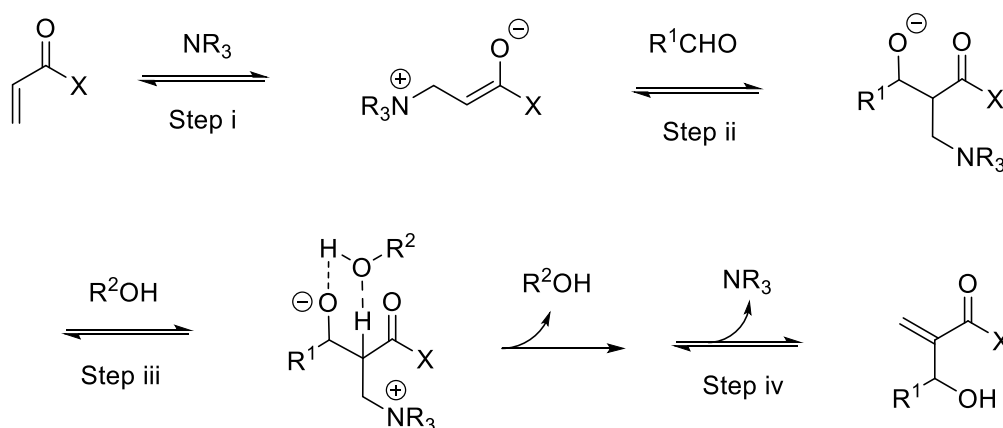
Refined mechanisms were later proposed for this reaction. Notably, McQuade and co-workers<sup>[132]</sup> established that the RDS of the MBH reaction was the proton transfer step (PTS), rather than the aldolization step, based on two main reasons (Scheme 42). One is the PTS is a second order rate law with respect to the electrophile and first order in amine promoter and activated alkene. The other reason is the significant

kinetic isotopic effect on the  $\alpha$ -position of activated alkenes which was observed. Thus a new mechanism indicating that the assistance of a second molecule of aldehyde towards the RDS was proposed, in which the intermediate enolate builds a hemiacetalate which can assist the proton transfer through a six-membered ring process. Kaye *et al.*<sup>[133]</sup> also performed a kinetic and mechanistic investigation by  $^1\text{H}$  NMR, demonstrating the rate-determining role of the PTS and explaining the significant effect of the aldehyde substituent and the alkyl substituent on the stability of the dipolar intermediate.



**Scheme 42.** Mechanism proposed by McQuade and co-workers.<sup>[132]</sup>

Also supporting that the proton shift step was a key rate determining step, Aggarwal and co-workers<sup>[134]</sup> demonstrated the catalytic influence of the MBH products themselves, which might play a role like proton donor as the protic solvent to promote this reaction (Scheme 43).



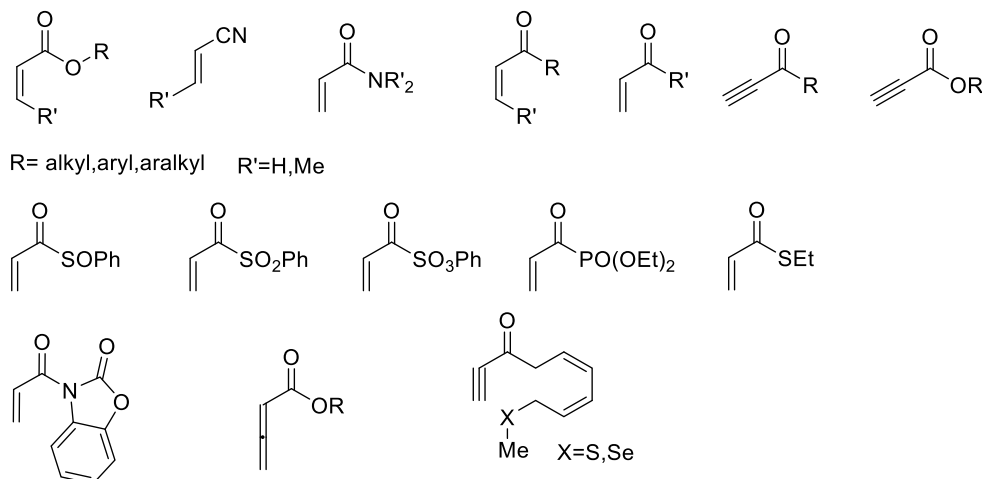
**Scheme 43.** Mechanism proposed by Aggarwal and co-workers.<sup>[134]</sup>

As a proof, Elberlin *et al.*<sup>[135]</sup> isolated the intermediate and characterized its structure, thus demonstrating that the mechanism is strongly dependent on the proton shift step. Moreover, Singleton and co-workers<sup>[136]</sup> showed the influence of the temperature, indicating that the proton shift is the RDS at 25°C while replaced by the aldolization at a lower temperature. Calculations have also been utilized to aid explaining the exact mechanism and predict the MBH reactions, while still a processing area.<sup>[136, 137]</sup>

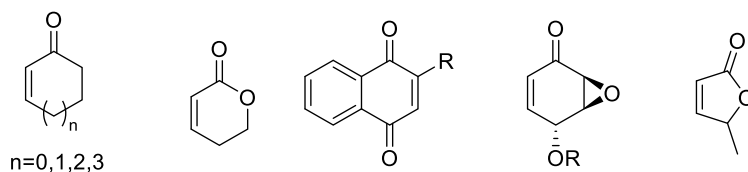
### 1.5.2 Scope of substrates-alkenes and electrophiles

The structural scope for the application of the MBH reaction concerns both substrates, activated alkenes and electrophiles. With respect to the reaction conditions, a third important element is the nucleophilic promoters. The scopes of these three partners have expanded significantly in recent decades, and this has been reviewed extensively. In terms of the activated alkenes, acrylates, acrylonitrile, acrylamides, alkyl vinyl ketones, vinyl sulfoxide, vinyl sulfones, vinyl sulfonates, vinyl phosphonates, allenic esters, dienophile, and ethynyl ketone are concerned. (Figure 12)<sup>[125, 128, 138-154]</sup> Cyclic alkenes can also react, such as dihydropyranone, alkyl naphthalenedione, oxabicyclo heptane and methyl furanone.<sup>[155-160]</sup>

#### Acyclic activated alkenes:

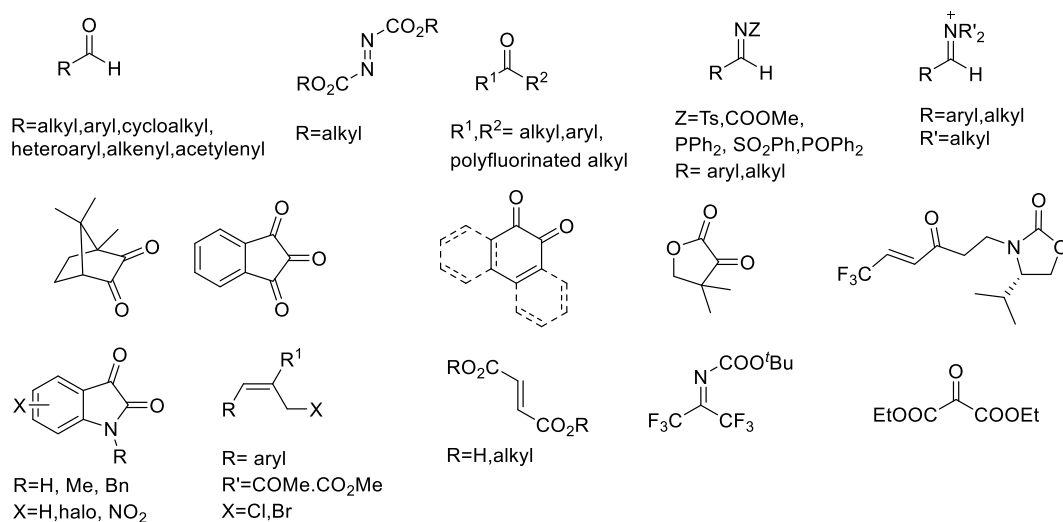


#### Cyclic activated alkenes:



**Figure 12.** Scope of the activated alkenes for MBH reaction

In terms of the electrophilic partner, various alkyl, aryl, cycloalkyl, heteroaryl, alkenyl, and acetylenyl aldehydes are commonly utilized in this strategy.<sup>[161, 162]</sup> Furthermore, other reactive families of electrophiles include  $\alpha$ -keto esters, aldimine derives, di- and fluoro- ketones and activated alkenes.<sup>[163-172]</sup> (Figure 13)



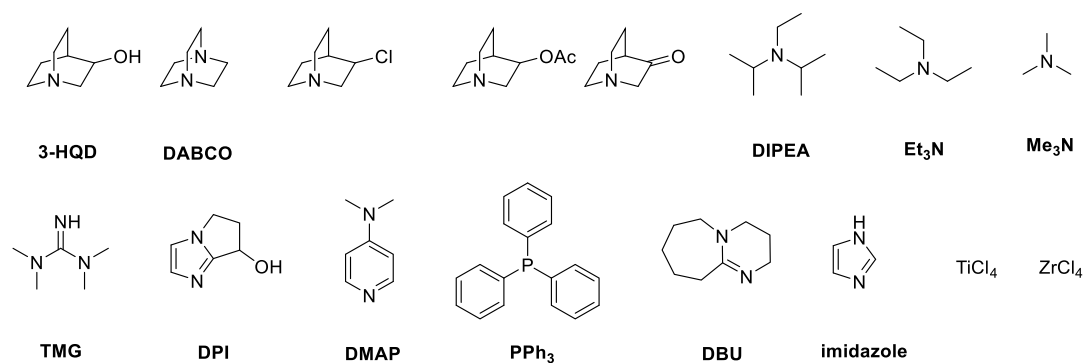
**Figure 13.** Scope of the electrophiles for MBH reaction

### 1.5.3 Acceleration of the MBH reaction

Although the MBH reaction is extremely general in terms of substrate scope, its rate is remarkably slow in most cases, thus limiting its practical applicability. Many studies have thus concerned strategies aiming at accelerating the reaction, either targeting the efficiency of the promoter, or looking for improved reaction conditions in terms of reaction medium.

#### 1.5.3.1 Acceleration via promoters and catalytic systems

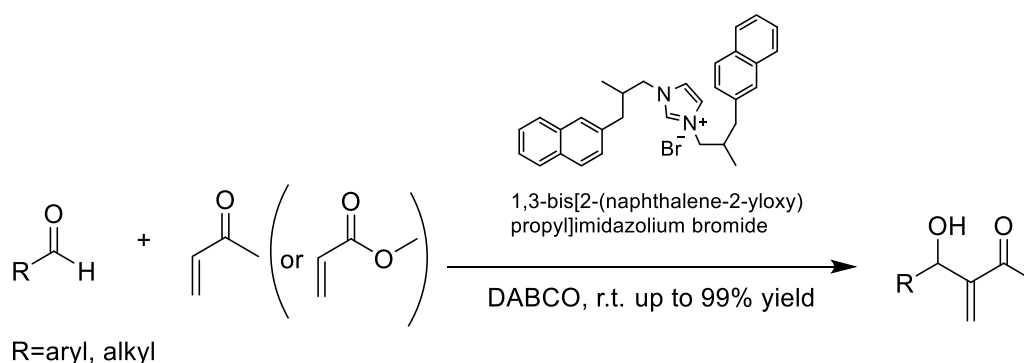
As mentioned above, a third important element for MBH reaction is the nucleophilic promoters, whose scope is also need to extend. An effective method to accelerate MBH reaction is also exploring more efficient promoters. According to the unique effect of the tertiary amines or phosphines catalysts on MBH reaction. Several analogous compounds were investigated and included in the scope of MBH promoters (Figure 14).



**Figure 14.** Different promoters for MBH reaction

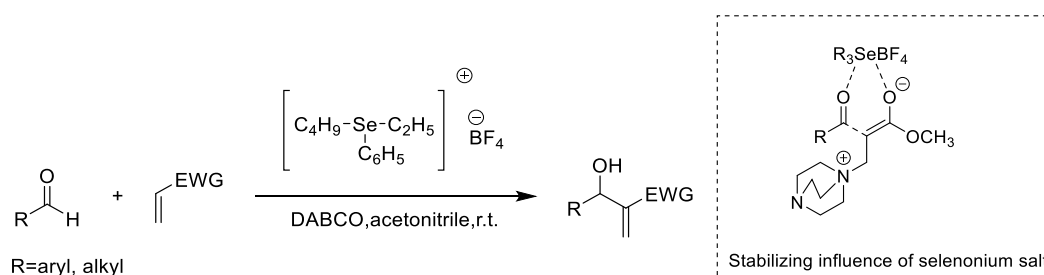
Besides the conventional tertiary amines or phosphines catalysts for MBH reaction, several more efficient promoters have also been developed to accelerate this reaction, such as ionic liquid, Lewis acid catalysts and some multi-component catalytic systems.

Ionic liquid could be used as promoter, co-promoter or solvent in MBH reaction. In 2006, Tsai and co-workers<sup>[173]</sup> reported a highly efficient ionic liquid co-catalyst, di-naphthalene imidazolium salt, which could be used along with DABCO in the MBH reaction of aryl aldehydes with methyl vinyl ketone (MVK) or methyl acrylate. This hydrophilic ionic liquid co-promoter realized high yield MBH reaction in a short time and could be recycled for several runs, which is a more sustainable and efficient system for MBH reaction (Scheme 44).



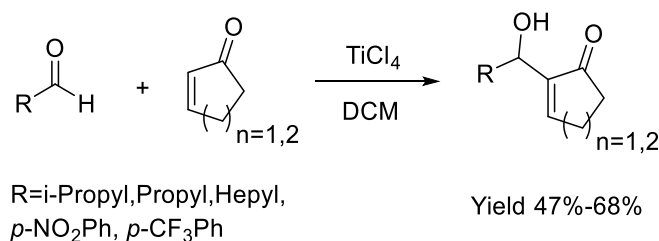
**Scheme 44:** MBH reactions under the co-catalysis of ionic liquid and DABCO by Tsai *et al.*<sup>[173]</sup>

Eder *et al.* also prepared a series of Se-containing ionic liquid additives, which were proved to promote the DABCO catalyzed MBH reaction efficiently (Scheme 45).<sup>[174]</sup> Related researches about the use of ionic liquid as solvent in MBH reaction will be introduced in following section.



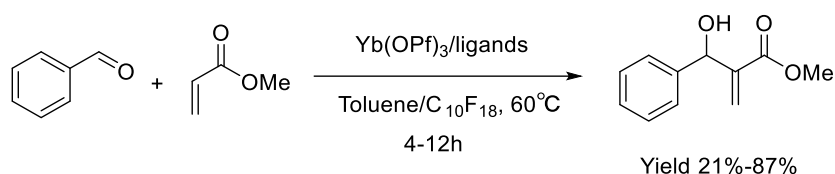
**Scheme 45:** MBH reactions under the co-catalysis of ionic liquid and DABCO by Eder *et al.* <sup>[174]</sup>

Some Lewis acid based catalysts were also proved a favorable choice. In 2000, Li *et al.* <sup>[150]</sup> reported the MBH reaction of cycloketones catalyzed by  $\text{TiCl}_4$  at the absence of Lewis bases. They proposed that the released  $\text{Cl}^-$  ion played a similar role as the Lewis base in the conjugate addition to aid the formation of the enolate intermediate, enabling the reaction even if no basic catalyst is present (Scheme 46).

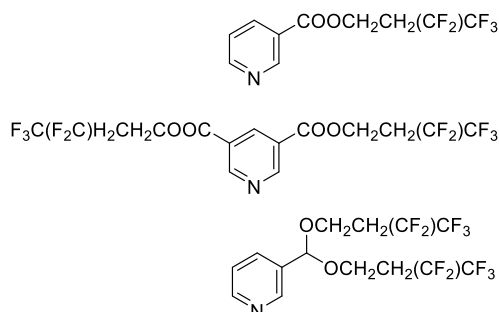


**Scheme 46:** MBH reactions catalyzed by  $\text{TiCl}_4$  <sup>[150]</sup>

A highly active and recyclable catalytic system involving ytterbium perfluorooctanesulfonate  $[\text{Yb}(\text{OPf})_3]$  /perfluoroalkylated-pyridine was reported by Yi *et al.* <sup>[175]</sup>, to promote the reaction of benzaldehyde and methyl acrylate in a fluoruous biphasic solvent. They suggested that a suitable amount of ligand connects with  $\text{Yb}(\text{OPf})_3$  to form a complex, which serves as a Lewis acid and helps the reactive metal center to associate with electrophiles (Scheme 47).

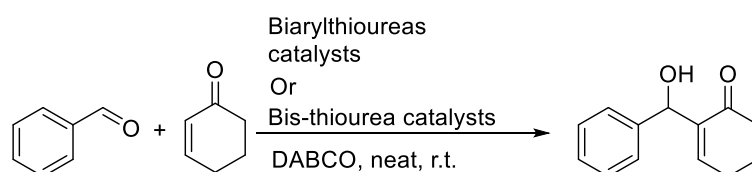
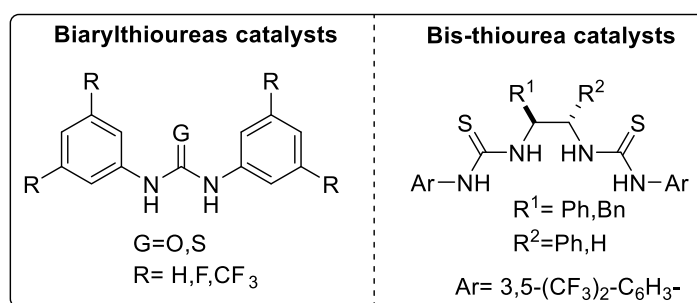
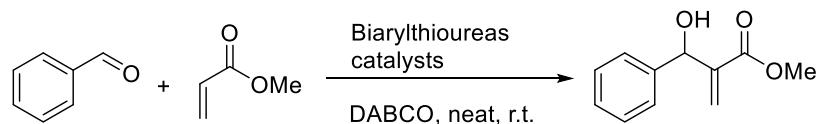


ligands:



**Scheme 47:** MBH reactions catalyzed by catalytic system of [Yb(OPf)<sub>3</sub>]/perfluoroalkylated-pyridine [175]

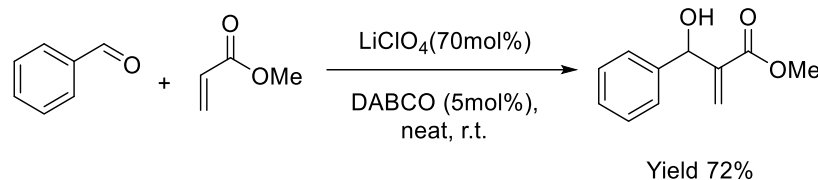
Connon's group [176] and Nagasawa's group [177] both reported the synergistic catalytic systems of DABCO and achiral biarylthioureas, which could enhance the reaction rate significantly thanks to the occurring carbonyl activation promoted by hydrogen bonding. Moreover, in Nagasawa's work, the new bis-thiourea-type catalysts were also designed and synthesized to realize an enantioselective MBH reaction. (Scheme 48)



**Scheme 48:** MBH reactions catalyzed by catalytic systems of DABCO with biarylthioureas or bis-thiourea catalysts [176,177]

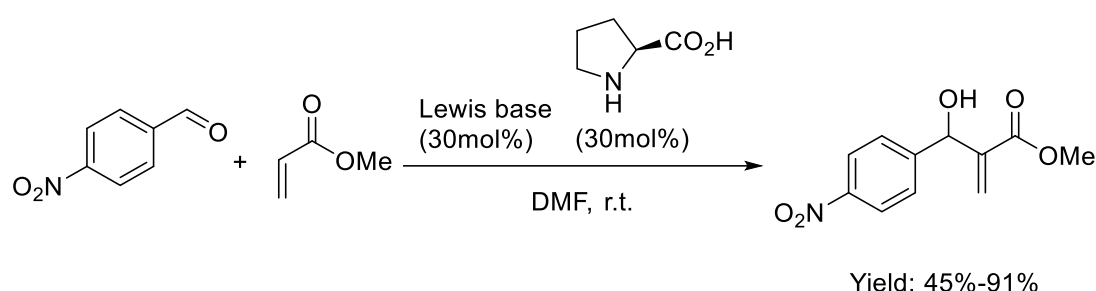


Kobayashi and co-workers reported the co-catalytic influence of DABCO and small amount of LiClO<sub>4</sub> (Scheme 49), demonstrating the increasing of reaction rate owing to better stabilization of enolate intermediate by the presence of the Li<sup>+</sup>.<sup>[178]</sup>



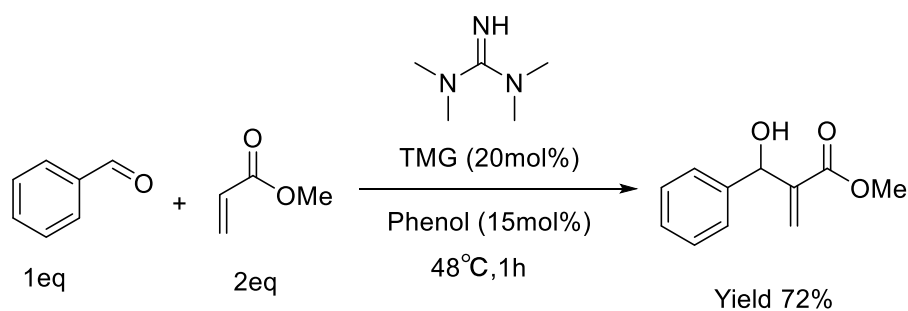
**Scheme 49:** MBH reactions catalyzed by catalytic systems of DABCO with LiClO<sub>4</sub><sup>[178]</sup>

Shi *et al.* investigated the cooperative catalytic effects of L-proline with two weak Lewis bases, imidazole and triethylamine, respectively, in MBH reactions of aldehydes with methyl acrylate (Scheme 50). Increasing the efficiency of normally inert bases in promoting the asymmetric MBH reaction.<sup>[179]</sup>



**Scheme 50:** MBH reactions catalyzed by L-proline with weak Lewis bases<sup>[179]</sup>

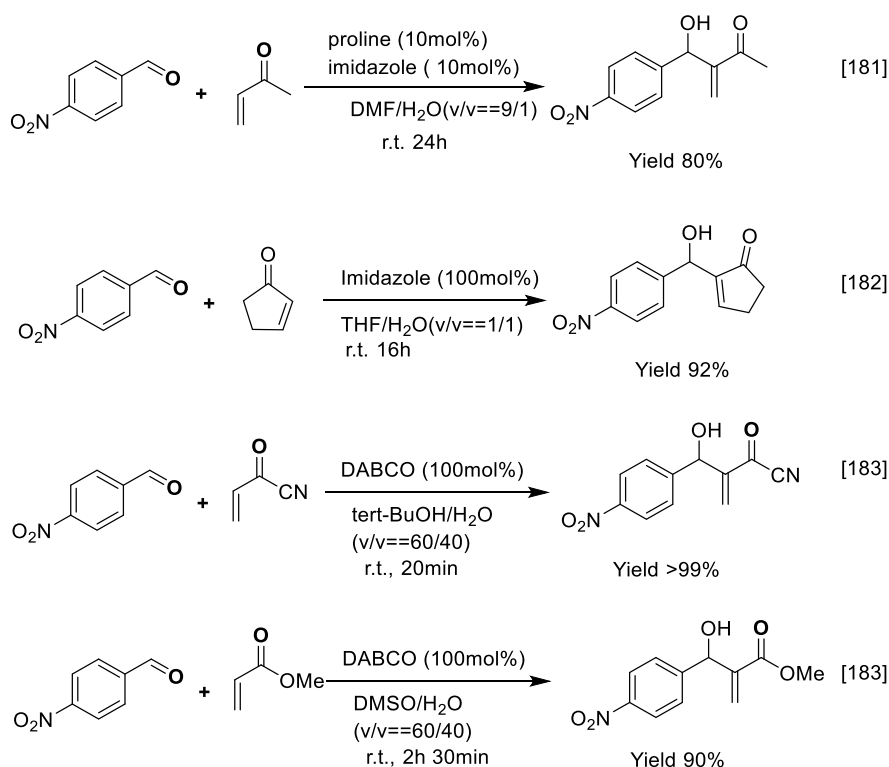
Tetramethylguanidine (TMG) was investigated as the promoter for MBH reaction by Leadbeater *et al.*<sup>[180]</sup> (Scheme 51), leading to a faster reaction rate, which could be further improved via the addition of phenol as the co-promoter when the ratio of aldehyde to acrylate is 1:2 due to the protonation of phenol to TMG.



**Scheme 51:** MBH reactions catalyzed by Tetramethylguanidine (TMG)<sup>[180]</sup>

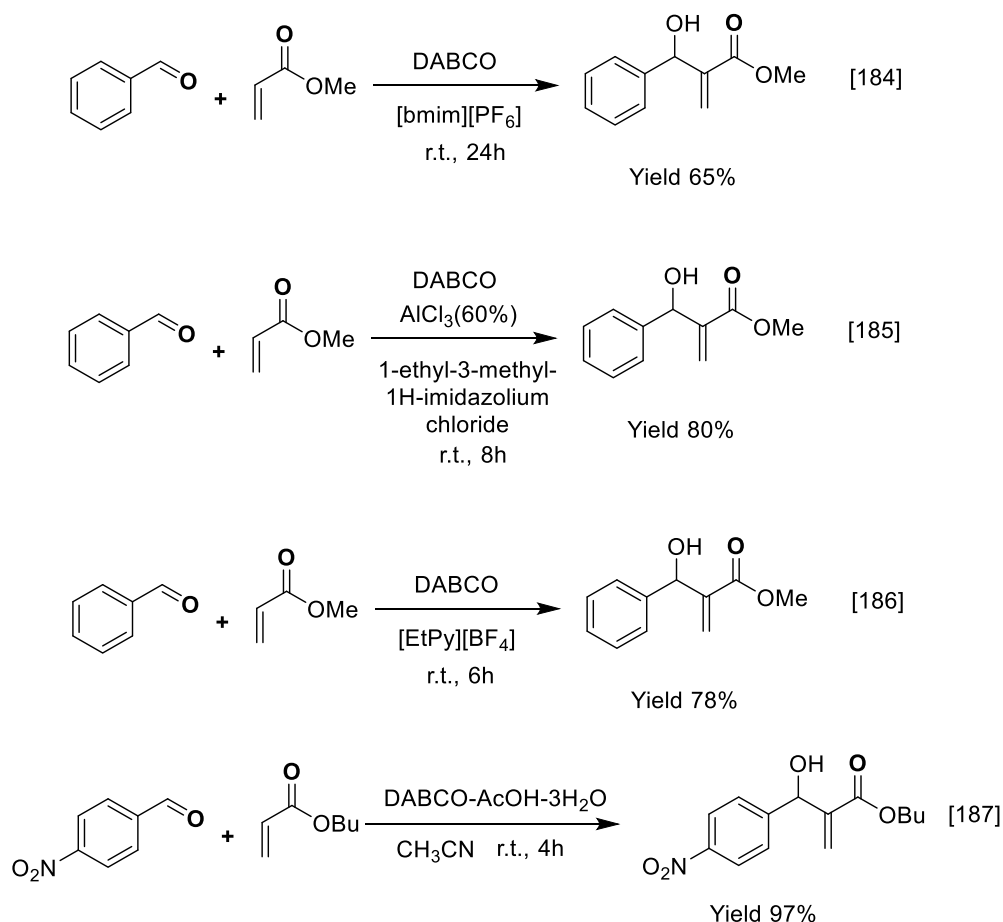
### 1.5.3.2 Alternative solvents used in MBH reactions

Solvent is also an important factor to accelerate the rate of MBH reaction, especially the utilization of H<sub>2</sub>O, ionic liquid and some other unconventional solvents. As discussed in the mechanism section, the use of aqueous media for accelerating the MBH reaction has caught much attention. Tomkinson *et al.* reported the significant influence of small amount of water on the acceleration of MBH reaction of methyl vinyl ketone (MVK) with various electrophiles in a mixture with organic solvent, such as DMF and THF. But pure water gave a lower yield of MBH adducts, only about 10 %.<sup>[181]</sup> Cheng and co-workers reported the MBH reaction of cyclopent-2-enone in aqueous solution catalyzed by imidazole, showing that a side aldol addition also occurred in this process.<sup>[182]</sup> In the work of de Souza *et al.* in 2008, tert-butanol/water (v/v=60/40) mixture solvent was found as an efficient system for the MBH reaction of acrylonitrile and the reaction time was shortened to 20 min from 6h to achieve a high yield over 90%. DMSO/water (v/v=60/40) was also found to give similarly good yield of MBH adducts from acrylates in a shorter time compared with using pure DMSO, especially for the reaction of less reactive aldehyde (Scheme 52).<sup>[183]</sup>



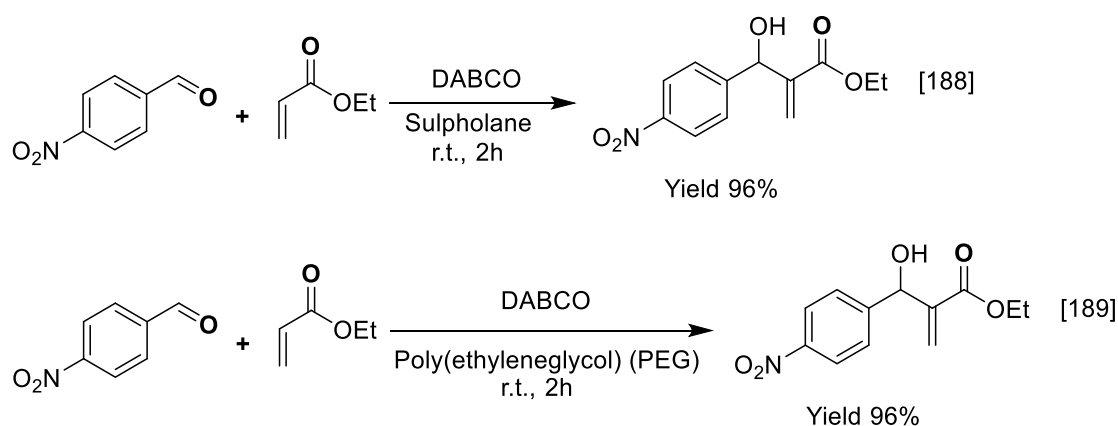
**Scheme 52:** MBH reactions in aqueous solvents.

Ionic liquids not only play the role as catalyst (like in examples discussed in the previous section), but also a good choice as solvent in MBH reaction. In 2001, Afonso and Santos<sup>[184]</sup> reported a faster MBH reaction in 1-n-butyl-3-methylimidazolium hexafluorophosphates ([bmim][PF<sub>6</sub>], a reusable ionic liquid solvent, with a rate 33.6 times higher compared to the same reaction in acetonitrile. Chloroaluminate ionic liquids were also used as a recyclable solvent to accelerate the DABCO-promoted MBH reaction, designing a more convenient procedure.<sup>[185]</sup> A non-imidazolium-based ionic liquid, [EtPy][BF<sub>4</sub>], was proposed as a new solvent for MBH reactions, exhibiting significantly faster reactions and higher yields. Furthermore, the recyclability of the ionic liquid was demonstrated.<sup>[186]</sup> A recoverable protic-ionic-liquids (PILs) catalytic system, DABCO–AcOH–H<sub>2</sub>O, was designed by Zou *et al.*<sup>[187]</sup> to accelerate MBH reaction of aldehydes with acrylates or acrylonitrile, achieving a comparable result as using traditional DABCO and exhibiting good recyclability and wide range of substrates scopes. (Scheme 53)



**Scheme 53:** MBH reactions in ionic liquid solvents.

Some unconventional organic solvents can also influence the rate of MBH reactions. Krishna *et al.*<sup>[188]</sup> reported that sulpholane could lead to comparable MBH adducts yields from various substrates in shorter time, even for the low reactive acrylamide. Chandrasekhar *et al.*<sup>[189]</sup> applied poly(ethyleneglycol) (PEG) as a alternative solvent giving high yields in less than 5 hours. Furthermore, DABCO could be recycled without any obvious decrease of MBH adducts yields compared with the first cycle. They suggested that the effect was due to the stabilization of the enolate intermediate caused by more and stronger hydrogen bonds. (Scheme 54)

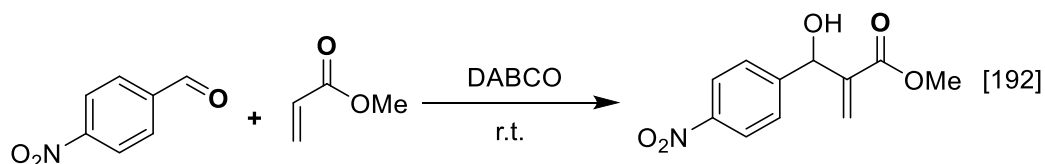


**Scheme 54:** MBH reactions in some other solvents.

### 1.5.3.3 Acceleration via other methods

Some physical methods also could cause an increased speed of MBH reaction. For instance, high pressure, ultrasound and microwave. Isaacs and co-workers found the acceleration influence of higher pressure for MBH reaction of acetone with acrylonitrile.<sup>[144]</sup> The same results were confirmed again by Jenner *et al.*<sup>[190]</sup> when they investigated the pressure and water activation in MBH reaction specifically, and this effect were more obvious in solvent-free systems.

As a conventional method to improve the rate of reactions, ultrasonication was also applied to a MBH reaction to solve the slow rate problem. (Scheme 55) As expected, this method indeed promote MBH reaction rates acceleration owing to the introduction of extra energy, demonstrated by Coelho *et al.*<sup>[191, 192]</sup> in the case of the reaction of various aldehydes with MVK. The reaction rate could be increased about 4 times compared to the same reaction without ultrasound radiation.



Condition 1: Without ultrasound, 72h, yield 45%

Condition 2: With ultrasound, 16h, yield 88%

**Scheme 55:** MBH reactions accelerated by ultrasound.

Another method for providing extra energy assistance is the use of microwave irradiation, which was successfully applied in the MBH reaction of aldehydes with acrylates by Bhat *et al.*<sup>[193]</sup>. This might be due to the enhanced temperature, however the complex mechanism and the numerous steps and intermediates prevent to clearly understand the cause of the beneficial effect.

Coelho and co-workers investigated the synergic influence of various promoters and additives to obtain carbohydrate-based MBH adducts more efficiently. An ionic liquid was selected as a model catalyst and investigated in combination with ultrasound or temperature. Their results showed an obvious improvement of MBH reaction yield or rate using the ionic liquid at low temperature. The phenomenon was attributed to the lamellar structure of ionic liquid at 0°C.<sup>[194]</sup>



Condition 1: Ultrasound, r.t. [bmimPF6], yield 25%

Condition 2: Ultrasound, 0°C, yield 30%

Condition 3: Ultrasound, 0°C, [bmimPF6], yield 92%

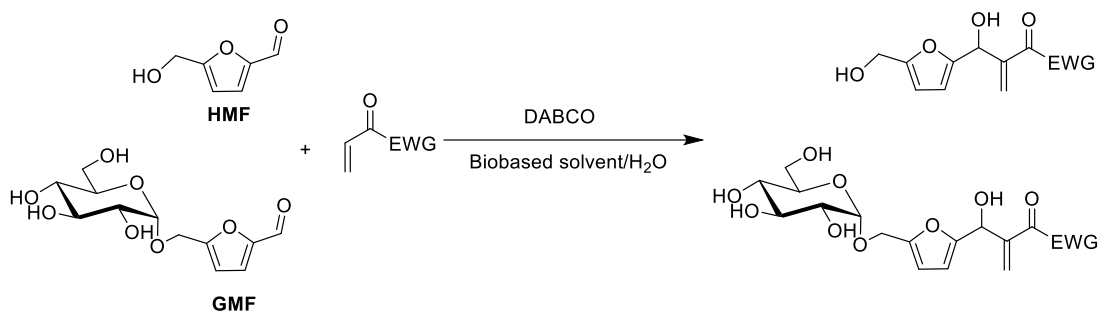
Condition 3: Stirring, 0°C, [bmimPF6], yield 95%

**Scheme 56:** MBH reactions accelerated by synergic activated methods.

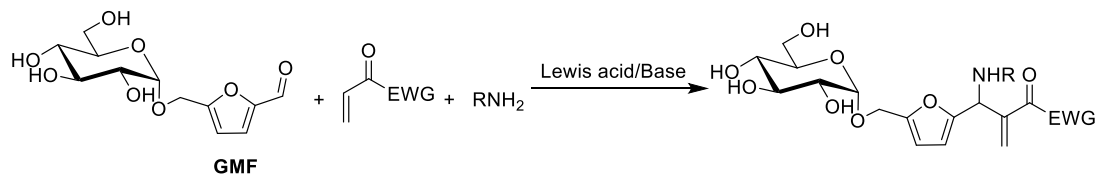
### 1.5.4 MBH reaction of furanic aldehydes (Related work in our group)

For several years, our group has investigated the MBH reaction of furfural, HMF and GMF ( $\alpha$ -lucosyloxymethylfurfural) aiming at expanding the utilization of these furanic platforms in biobased chemistry. Dr. Jianeng TAN investigated the MBH reaction of GMF with acrylates and found that some biobased solvents, such as dimethylmisosorbide (DMI), tetrahydrofuryl alcohol (THFA) and others, and their mixtures with water, were efficient for this process. He also extended his study to the multicomponent aza-MBH reaction of GMF.<sup>[195]</sup>

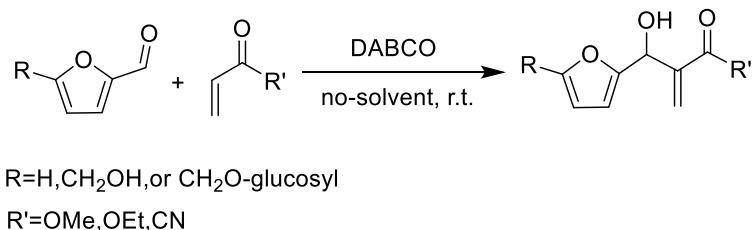
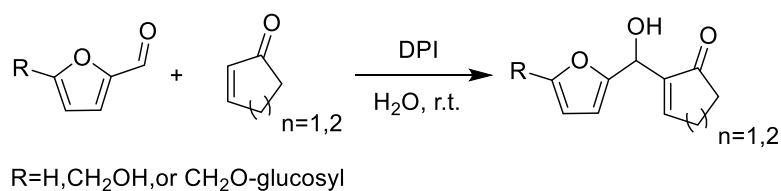
#### Morita-Baylis-Hillman reaction:



#### Aza-Morita-Baylis-Hillman reaction:



**Scheme 57:** MBH reactions of HMF and GMF in Dr. Jianeng TAN's thesis <sup>[195]</sup>

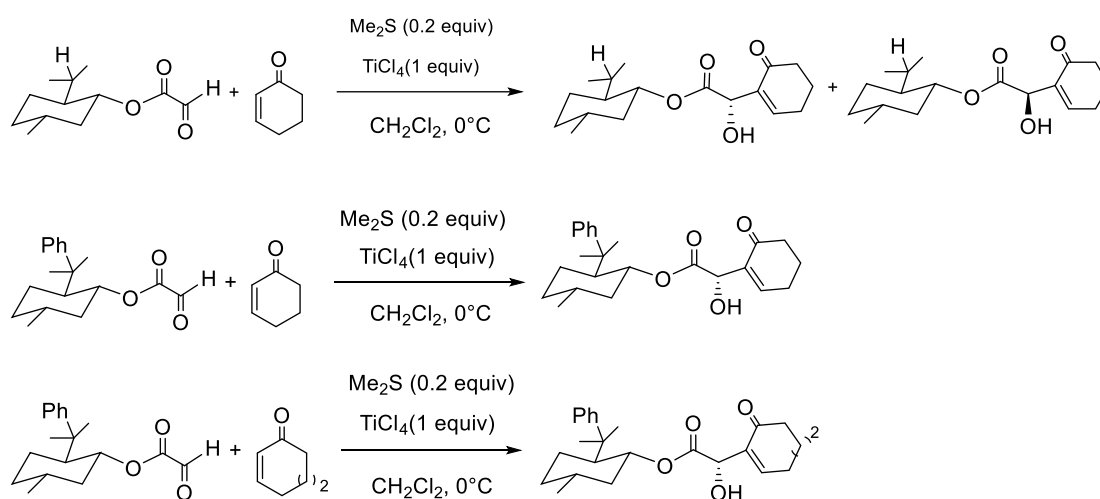


**Scheme 58:** MBH reactions of HMF and GMF in Dr. Lianjie WANG's Thesis <sup>[196]</sup>

In Dr. Lianjie WANG's work, the MBH reaction of furanic aldehydes was extended to react with cycloalkenones in aqueous media and same reaction with acrylates were promoted under solvent-free conditions.<sup>[196]</sup> Collaborating with Prof. Véronique RATAJ and Dr. Jesús Fermin ONTIVEROS of the CISCO lab of UCCS laboratory in Lille, a series of biobased furanic surfactants were also synthesized and characterized based on their work.<sup>[61]</sup>

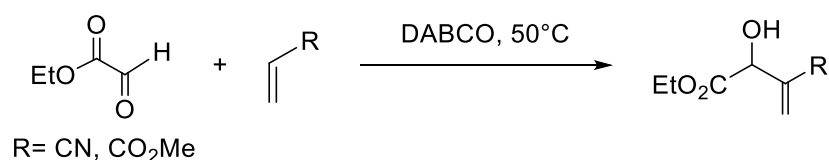
### 1.5.5 MBH reaction of alkyl glyoxylates and glyoxylic acid

The literature on MBH concerns nearly exclusively alkylglyoxylates. In 2001, Bauer *et al.* reported the asymmetric MBH reaction of chiral glyoxylates with cyclic  $\alpha$ ,  $\beta$ -unsaturated ketones under the catalysis of methyl sulfide catalysts. The best results were obtained using (-)-8-phenylmenthyl glyoxylate as substrates (76-78% of yield). Meantime, only single diastereoisomer was produced, thus the diastereoisomeric excess of the reaction can be described as >95%. While menthyl glyoxylate was used instead will cause a mixture of two diastereoisomers with a low diastereoisomeric excess, only 8.7%.<sup>[197]</sup>



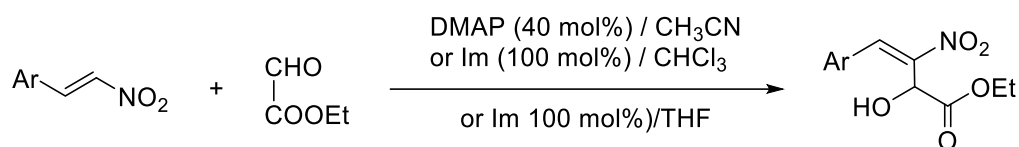
**Scheme 59:** MBH reactions of chiral glyoxylates <sup>[197]</sup>

Fikentscher *et al* reported the MBH reaction of ethyl glyoxylate coupling with acrylonitrile or acrylate esters under the catalysis of tertiary amine catalysts, such as DABCO, in aqueous media at pH  $\geq 6$ . They obtained a yield of 79% when the reaction with carry out with methyl acrylate, DABCO as the catalyst at 50°C.<sup>[198]</sup>



**Scheme 60.** MBH reactions of ethyl glyoxylate <sup>[198]</sup>

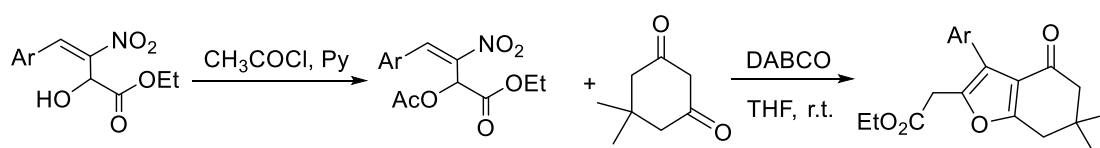
Heteroaromatic nitroalkenes as 4-methoxy- $\alpha$ -nitrostyrene were used to react with ethyl glyoxylate by Namboothiri *et al*. Two reaction systems, DMAP (40 mol %)/CH<sub>3</sub>CN and imidazole (100 mol%)/CHCl<sub>3</sub>, both exhibit good performance on this reaction.<sup>[199, 200]</sup>



Ar= aromatic nucleus

**Scheme 61:** MBH reactions between nitroalkenes and ethyl glyoxylate <sup>[199, 200]</sup>

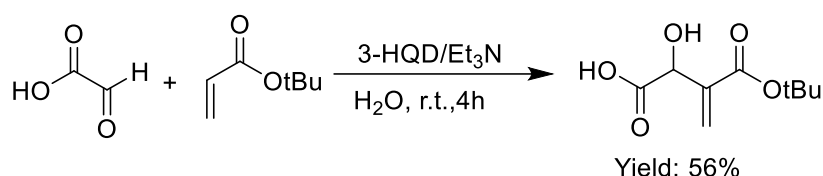
The same team further synthesized furans and pyrans from the MBH product above in good to excellent yields. After an acetate protection step on the hydroxyl group, an addition of the MBH adducts with a ketone occurred under the presence such as DABCO, giving furans or pyrans in THF. They found that the product could be achieved with a good yield 75-94% in a short time.<sup>[201]</sup>



**Scheme 62.** Synthesis of fused furans via addition of dimedone to MBH acetates <sup>[201]</sup>



Besides these examples on GA esters, glyoxylic acid itself, either under the form of its 50wt% GA aqueous solution or as the monohydrate, has been nearly never used in MBH reaction directly, based on the idea that the absence of aldehyde function in GA aqueous solution disfavors any reaction which would involve the aldehyde group. Indeed, there is only one example, actually one line of a table in one paper focusing on other aspects of the MBH reaction, which concerns the reaction of aqueous GA.<sup>[202]</sup>



**Scheme 63.** MBH reaction of GA monohydrate with tert-butylacrylate <sup>[202]</sup>

## 1.6 Inspiration for this thesis

In this bibliographic section, we have emphasized the interest and importance of biobased chemistry, notably that of furanic platforms, and the wide scope of the use of the MBH reaction. The research project sustaining this thesis has been built on these two aspects, first on developing further the use of the reaction using some normally less popular alkenes, namely secondary-*N*-alkyl acrylamides. Secondly, being virtually unexplored, the use of the cheap and readily available commercial GA aqueous solution in MBH reactions has been investigated.

By combining hydrophilic and hydrophobic building blocks, both the furanic aldehydes and glyoxylic acid MBH reactions have been then applied to an innovative design strategy of novel amphiphilic molecules. The physicochemical properties of these new compounds have been evaluated allowing to propose this new strategy as an original new family of biobased surfactants.

# **Chapter II**

## **MBH routes towards biobased surfactants**



## Chapter II MBH routes towards biobased surfactants

### 2.1 Backgrounds and aims

Our project aims at developing innovative strategies connecting biobased polar and non-polar moieties for designing original amphiphilic molecules. The goal is to widen the scope of potential novel products with surfactant properties exhibiting significant level of renewable carbon content. We want to do so by also addressing the cleanness and mildness of the reaction conditions. Ultimately, such novel biobased surfactants would give more choice of more eco-friendly routes for industries and may benefit to the general objective of a better and cleaner chemistry.

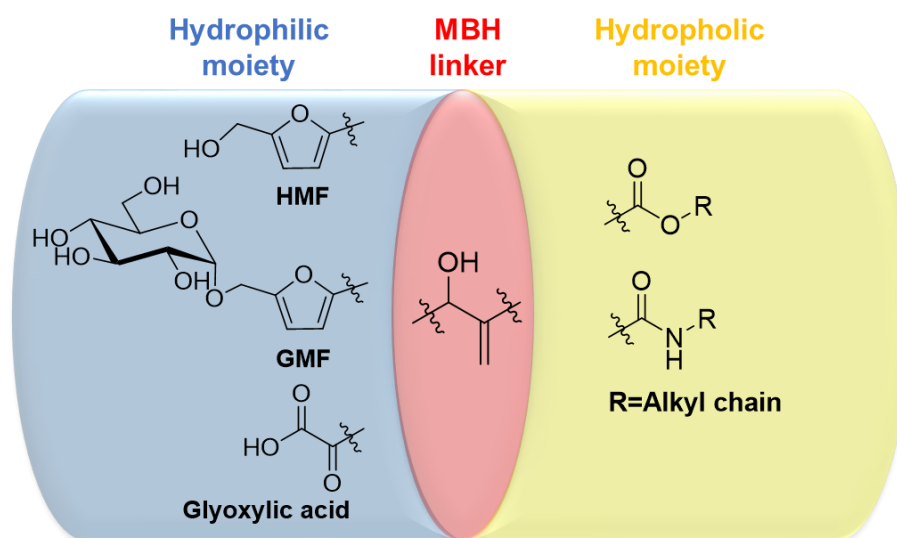
The route that we have chosen is to extend the use of the Morita-Baylis Hillman (MBH) reaction to biobased aldehydes and hydrophobic acrylates and acrylamides. This reaction offers several advantages such as atom-economy, scope and mildness which fit with the general aims of our work. With respect to the type of biobased aldehydes, we have targeted two types, first the furanic aldehydes derived from carbohydrate dehydration, which is the purpose of the present chapter, and second, the C2 building block glyoxylic acid (GA).

The furanic platform molecules have been only recently considered for serving as building blocks towards amphiphiles, and is now developing rapidly, concomitantly with the increasing availability of these platforms on the industrial scale. For this, we have extended the investigation of the MBH reaction of several furanic aldehydes to various long chain alkyl acrylamides.

On the glyoxylic acid side, nearly nothing has been reported on its use in MBH reactions, and absolutely nothing has ever been reported in the field of surfactant design.

For both these two kinds of aldehydes, our work has included the careful structural characterization of the products, the detailed study of the influence of the reaction conditions with respect to the nature of the MBH promoter, solvent system, temperature, stoichiometry, concentration, reaction time, and structural scope. Having a collection of compounds in these two series of new amphiphiles, their

physicochemical properties have been evaluated in the frame of a collaboration with the colleagues of the Catalyse et Chimie Moléculaire, Colloïdes Catalyse Oxydation (CISCO) team of UCCS at the University of Lille, led by Prof Véronique Nardello-Rataj.



**Figure 15:** Design of the amphiphiles from biobased platform molecules via MBH reaction

Overall this work has completed the synthesis and evaluation of two families of new biobased surfactants. The first one is prepared from HMF and some of its analogues, such as GMF, as polar part through an MBH reaction with secondary *N*-alkyl acrylamides. The second one unveils a totally novel design using glyoxylic acid (GA) as hydrophilic head, by application of the MBH reaction of GA with acrylates and acrylamides (Figure 15).

## 2.2 MBH reaction of secondary *N*-alkyl acrylamides

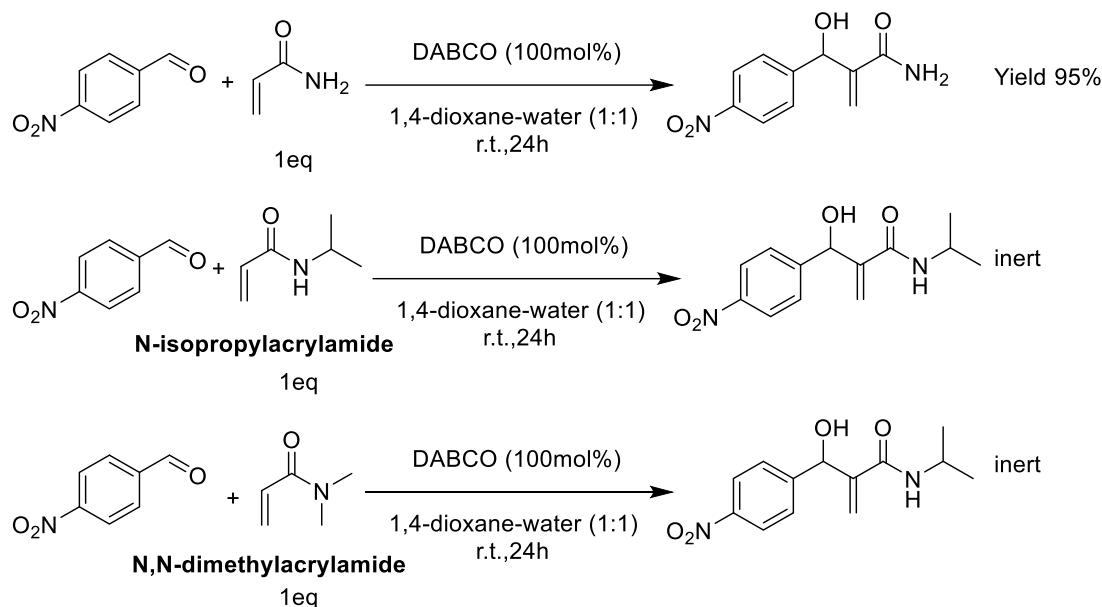
*This section is the basis of an article published in C.R. Chimie in 2021*<sup>[203]</sup>

### 2.2.1 Introduction

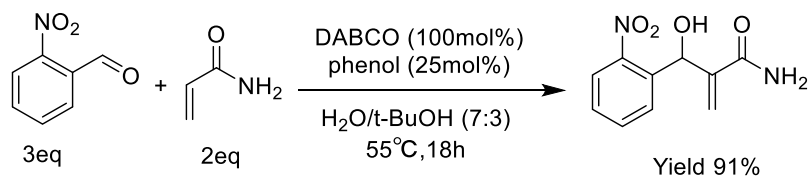
The MBH reaction exhibits many advantages: in addition to its favorable atom economy and its ability to run under mild conditions, already mentioned, a high level of structures and functionalities in the products results from its versatility in terms of scope of starting aldehydes and alkenes.<sup>[204]</sup> However, among reported alkenes, *N*-substituted acrylamides are rarely used, being reported either as inert or poorly

reactive due to a weaker electron withdrawing ability compared to acrylates or nitriles for example. Furthermore, the presence of a relatively labile proton on the nitrogen atom of the secondary amide group enables a competitive acido-basic reaction when a basic tertiary amine is used as promoter.

**Work of Yu *et al***



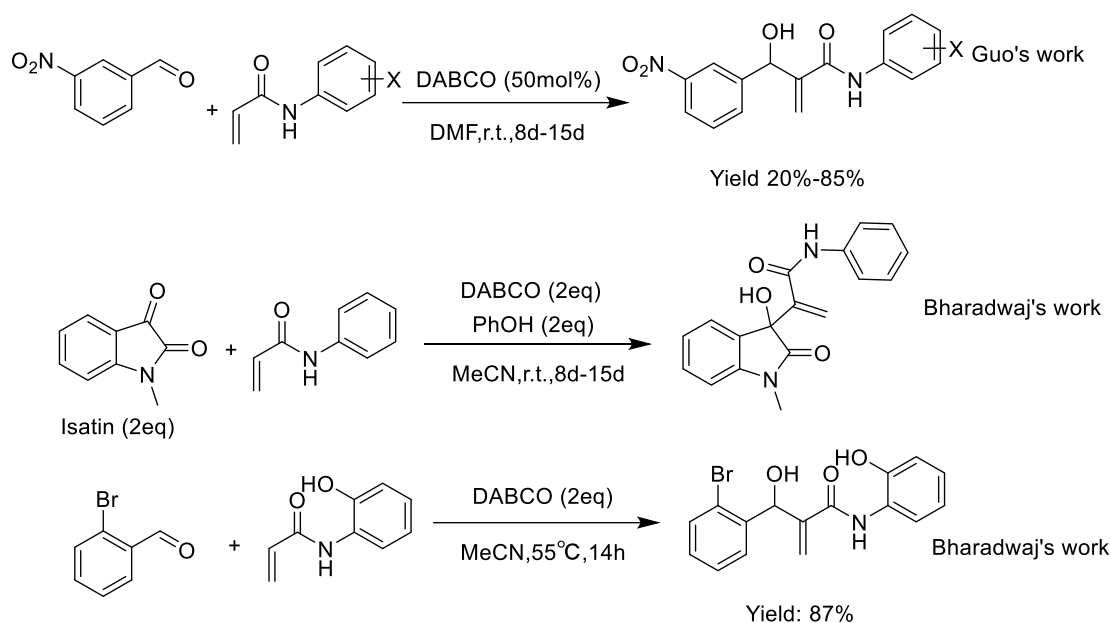
**Work of Faltin *et al***



**Scheme 64:** Reported MBH reaction of acrylamides <sup>[205,206]</sup>

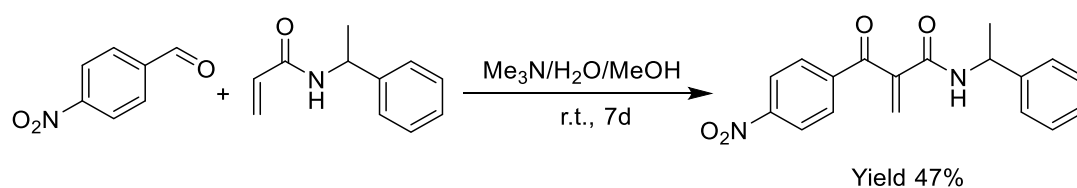
Concerning unsubstituted acrylamides, up to now, only a few examples of MBH reactions have been reported. Yu *et al.* reported in 2002 the reaction of acrylamide with aromatic aldehydes in dioxane-water. In this paper, the authors mentioned that *N*-isopropylacrylamide and *N,N*-dimethylacrylamide were both inert under the same conditions.<sup>[205]</sup> In 2004, Faltin's work dealt also with acrylamide MBH reactions but did not include any substituted ones in the scope.<sup>[206]</sup> (Scheme 64)

Among *N*-mono-substituted acrylamides, only *N*-aryl ones have been studied, with Guo's work on MBH reactions of  $\alpha$ -substituted *N*-aryl acrylamides mentioning also lower reactivity for acrylamide or *N*-alkyl acrylamides,<sup>[207]</sup> and Bharadwaj's studies on MBH reactions of isatin derivatives with *N*-phenylacrylamide.<sup>[208]</sup> A higher reactive acrylamide, *N*-(2-hydroxyphenyl)acrylamide, which was activated by intramolecular hydrogen bond, was also designed by Bharadwaj and applied to react with a wider scope of aldehydes, including some low reactive ones.<sup>[209]</sup> (Scheme 65)



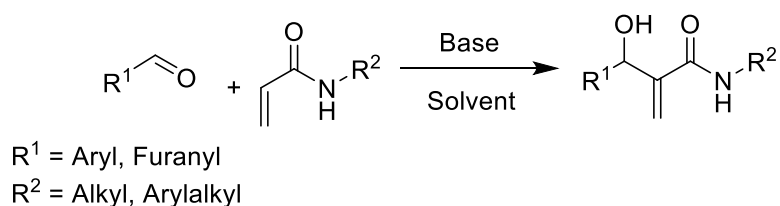
**Scheme 65:** MBH reaction of *N*-aryl acrylamides <sup>[207,208]</sup>

Only one example of MBH reaction using a secondary *N*-alkyl acrylamide was reported by Tang *et al.* (Scheme 66), but the focus of this work was more on the comparison between ester or amide chiral auxiliaries in asymmetric MBH reactions than on the structural scope.<sup>[210]</sup>



**Scheme 66:** MBH reaction of secondary *N*-alkyl acrylamides in Tang's work. <sup>[210]</sup>

Despite the availability of *N*-alkyl acrylamides, and the usefulness of amide containing products in the fields of fine chemicals and polymer chemistry (high stability, strong inter- or intramolecular interactions) <sup>[211, 212]</sup>, very limited knowledge on the use of secondary *N*-alkyl acrylamides in MBH reactions is given in literature, apart from saying they are poorly reactive. We have thus investigated in more details this reaction aiming at finding appropriate reaction conditions, in particular with respect to the promoter/solvent best matching couple. In order to be able to relate our work to previous methodological studies on MBH reactions reported in literature, we first used 4-nitrobenzaldehyde as reference aldehyde. The work has then addressed the structural scope with different secondary *N*-alkyl acrylamides and different aromatic aldehydes, notably the furanic ones, in the context of our project dedicated to the use of biobased aldehydes (Scheme 67).



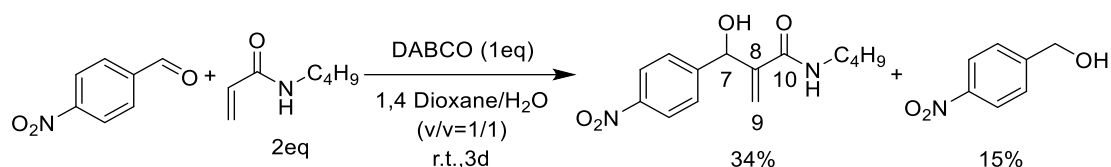
**Scheme 67:** MBH reaction of secondary *N*-alkyl acrylamides in this chapter

## 2.2.2 Reaction of 4-nitrobenzaldehyde with *N*-butylacrylamide

### 2.2.2.1 Procedure, isolation and proof of structure of the products

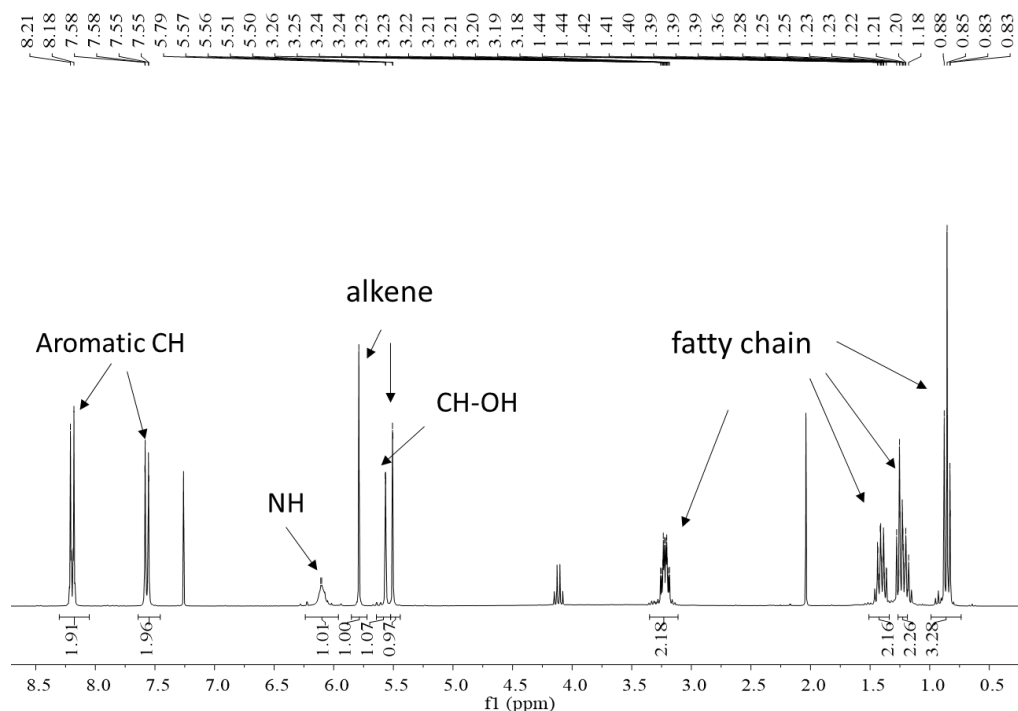
As a starting point, we performed the MBH reaction of 4-nitrobenzaldehyde with *N*-butyl acrylamide using DABCO as promoter and 1,4-dioxane/H<sub>2</sub>O (v/v=1/1) as solvent, which are conditions proved efficient for unsubstituted acrylamide reported by Hu's team.<sup>[205]</sup> The reaction was rather slow, and TLC showed the appearance of several new spots. A more polar new product with a chromatographic behavior consistent with expected MBH hydroxyl acrylamide was observed. Once the starting aldehyde was almost completely consumed, the basic promoter was removed by filtration through a short pad of silica, then the solvent was evaporated and the residue was purified via silica gel column chromatography, giving a pure product in 34% yield. 4-Nitrobenzyl alcohol was also obtained as a side product in 15% yield.



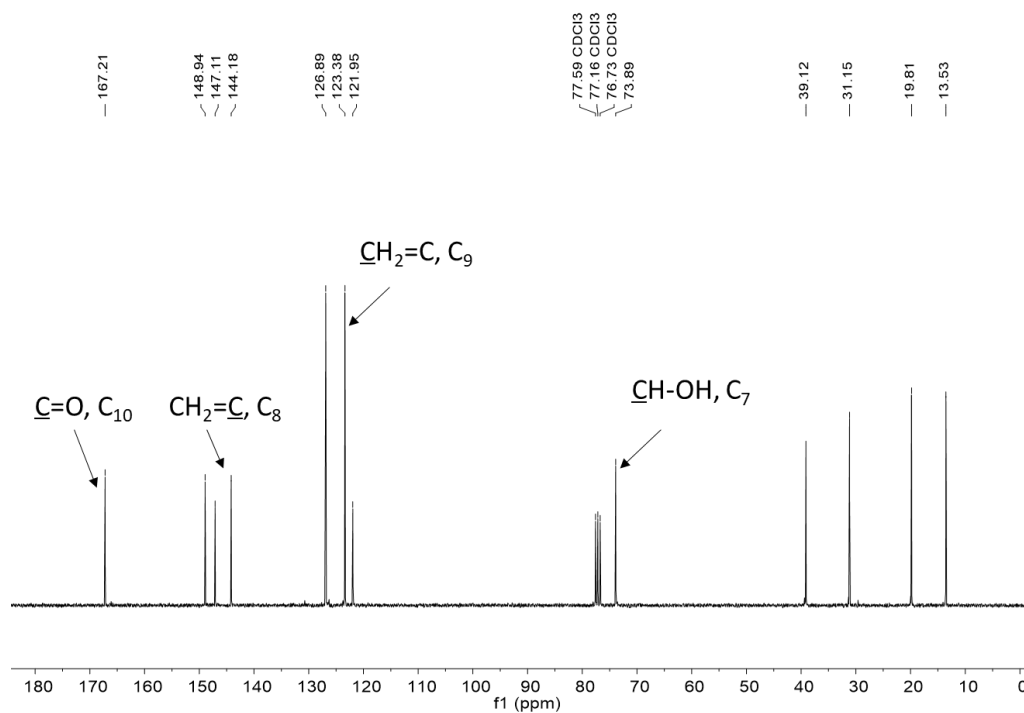


**Scheme 68.** MBH reaction of 4-nitrobenzaldehyde with *N*-butyl acrylamide

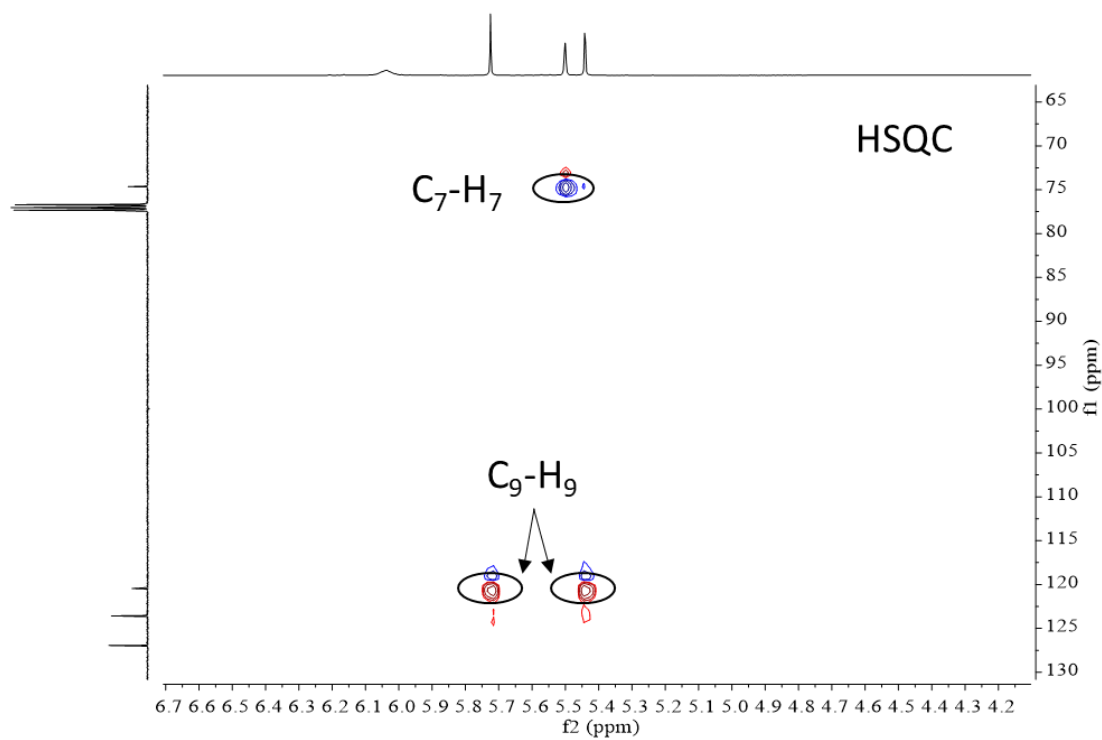
The right structure of the expected MBH adduct was identified by NMR and HR mass spectra and compared with the analogous products obtained in previous works of our lab<sup>[59, 213]</sup>. The signal corresponding to the proton of  $\text{CH-OH}$  ( $\text{H}_7$ ) could be found at the typical  $\delta$  5.56 ppm position in the  $^1\text{H}$ NMR spectrum (Figure 16) and the typical carbon signal for  $\text{C}_7$  could also be found at  $\delta$  73.89 ppm in the  $^{13}\text{C}$ NMR spectrum (Figure 17). And these two signals are related each other, as is shown in HSQC spectrum (Figure 18a). Meantime, the alkene protons ( $\text{CH}_2=\text{C}$ ,  $\text{H}_9$ ) could be found at  $\delta$  5.70 ppm and  $\delta$  5.50 ppm and responded to the carbon signal at  $\delta$  121.95 ppm ( $\text{C}_9$ ) in HSQC. Indicating the formation of the new C-C bond via MBH reaction. HMBC spectrum (Figure 18b) proved the interaction of the proton of the new position ( $\text{CH-OH}$ ,  $\text{H}_7$ ) with the carbons of the nearby alkene ( $\text{CH}_2=\text{C}$ ,  $\text{C}_8$  &  $\text{C}_9$ ) at  $\delta$  144.18 ppm ( $\text{C}_8$ ) and  $\delta$  121.95 ppm ( $\text{C}_9$ ) respectively, and carbonyl groups ( $\text{C}=\text{O}$ ,  $\text{C}_{10}$ ) at  $\delta$  167.21 ppm ( $\text{C}_{10}$ ).



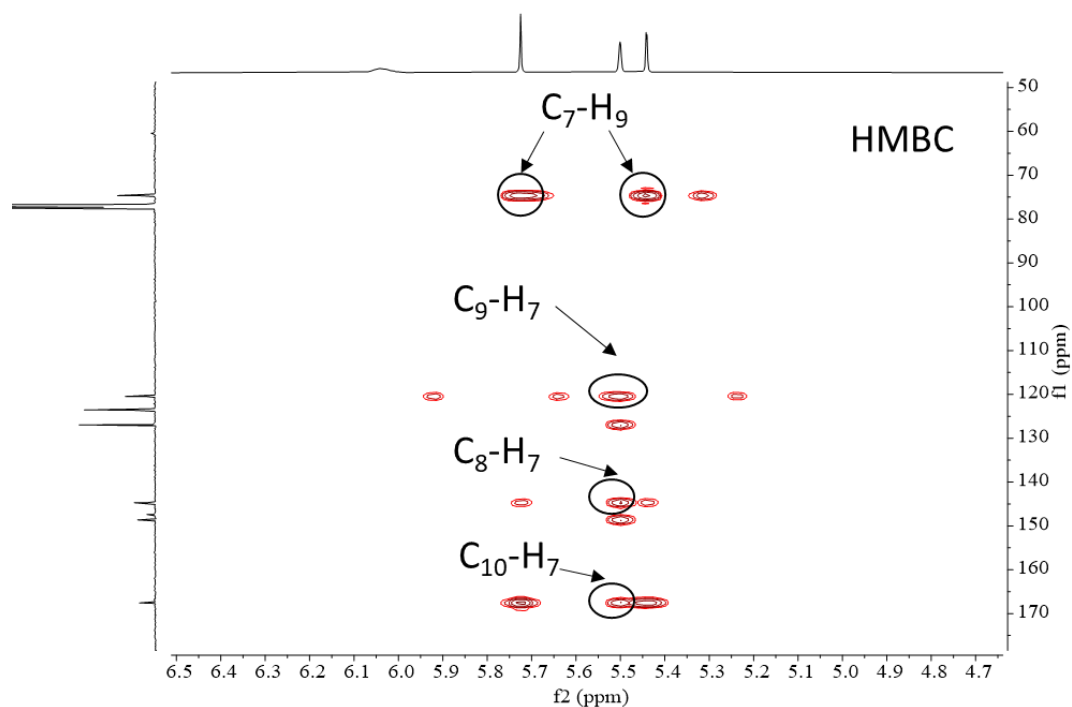
**Figure 16.**  $^1\text{H}$  NMR spectrum of MBH adduct from 4-nitrobenzaldehyde and *N*-butyl acrylamide



**Figure 17.**  $^{13}\text{C}$  NMR spectrum of MBH adduct from 4-nitrobenzaldehyde and *N*-butyl acrylamide

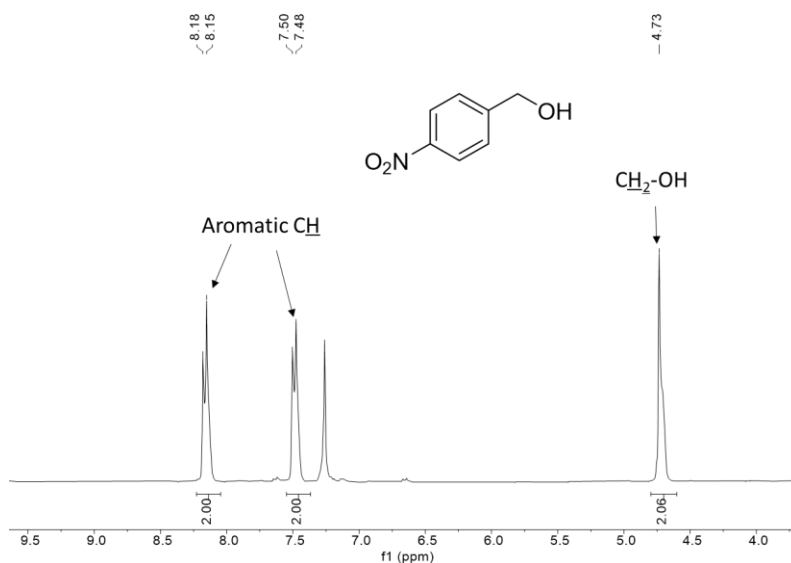


**Figure 18a.** HSQC spectrum of MBH adduct from 4-nitrobenzaldehyde and *N*-butyl acrylamide



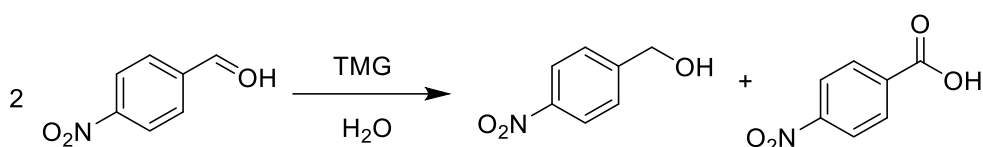
**Figure 18b.** HMBC spectrum of MBH adduct from 4-nitrobenzaldehyde and *N*-butyl acrylamide

As mentioned above, the 4-Nitrobenzyl alcohol was obtained in certain amount. Its structure was easily identified by NMR spectrum (Figure 19) and comparison with the data in literature<sup>[214]</sup>, showing the signal corresponding to the proton of aromatic cycle at the typical  $\delta$  7.50 ppm and  $\delta$  8.15 ppm position and the signal corresponding to the two protons of  $\text{CH}_2\text{-OH}$ . Along with the confirmation of the molecular mass via mass spectroscopy.



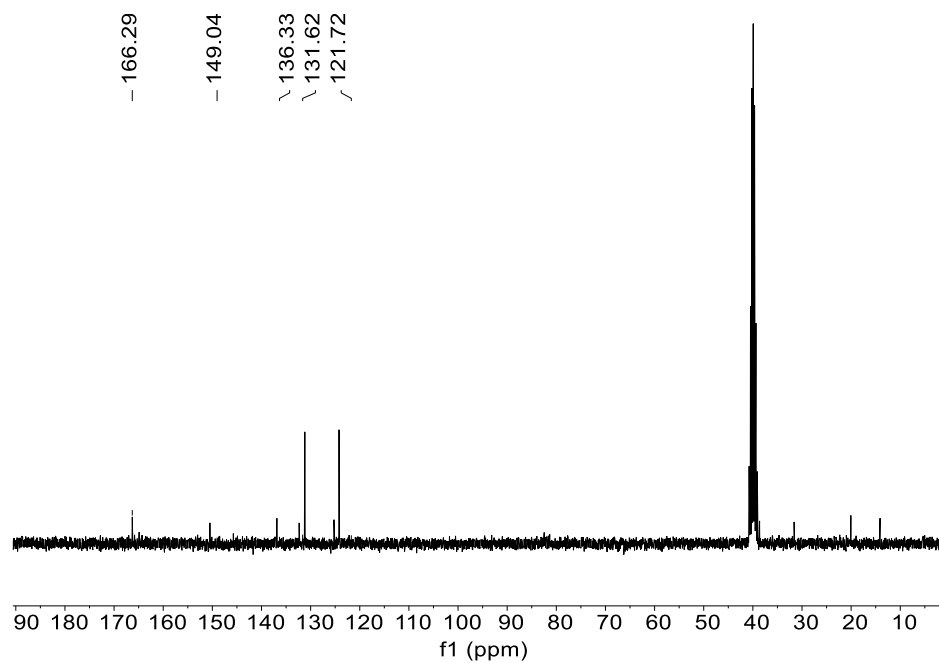
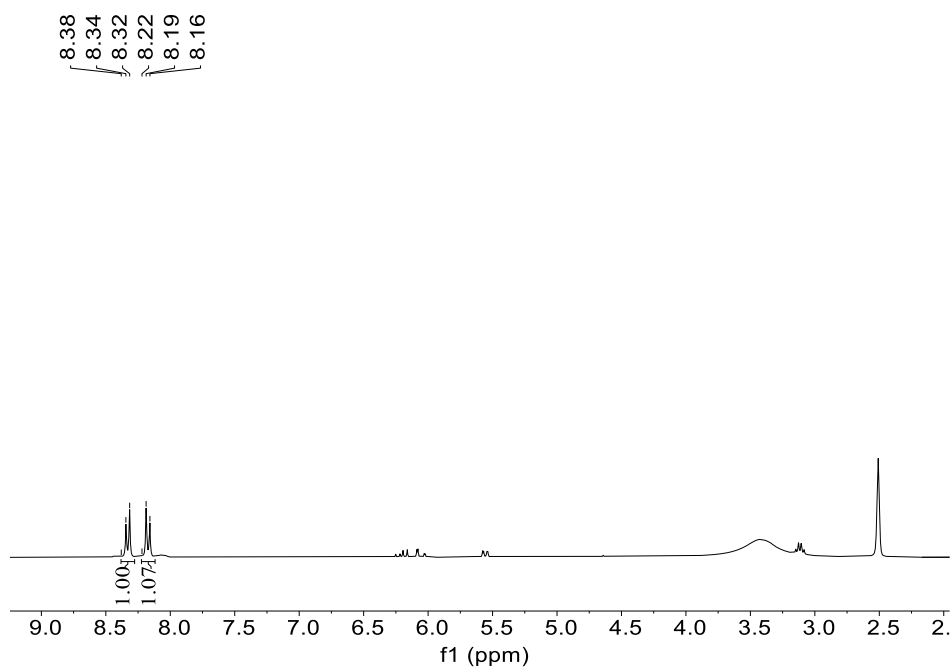
**Figure 19.**  $^1\text{H}$  NMR spectrum of 4-Nitrobenzyl alcohol

The formation of side products was thus investigated, showing the presence of 4-nitrobenzyl alcohol, possibly arising from the base-mediated Cannizzaro reaction of the aldehyde. Basavaiah *et al.* reported that organobases can indeed promote the Cannizzaro reaction (Scheme 69).<sup>[214]</sup>



**Scheme 69.** Tetramethylguanidine (TMG) promoted Cannizzaro reaction

However, if the Cannizzaro reaction occurs, this means that not only 4-Nitrobenzyl alcohol but also the 4-nitrobenzoic acid is formed. We therefore went back to looking for the presence of the acid. Considering the protocol for the purification after reaction, we noticed that the generated acid may have been transformed into the corresponding salt after the extraction step. Meantime, also taking the isolation for the 4-Nitrobenzoic acid mention in Basavaiah's work into account, the aqueous layer obtained from the extraction of the final mixture from the MBH reaction of 4-nitrobenzaldehyde with *N*-butyl acrylamide was acidified with HCL (1M) and extracted with ethyl acetate again to retrieve the other Cannizzaro product, 4-nitrobenzoic acid. The obtained compound was characterized by NMR spectroscopy (see the spectra in Figure 20). The signal corresponding to the aromatic protons could be found at  $\delta$  8.16-8.22ppm and  $\delta$  8.32-8.38ppm in <sup>1</sup>H NMR and the relevant signal at  $\delta$  166.29 corresponding to the carbon of COOH in <sup>13</sup>C NMR. The right molecular mass via HR-MS spectrum could also confirm that the obtained compound is the expected 4-Nitrobenzoic acid. The isolated yield (14%) of the acid obtained after the evaporation of the solvent was consistent with the alcohol yield.



**Figure 20.**  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra of obtained 4-Nitrobenzoic acid

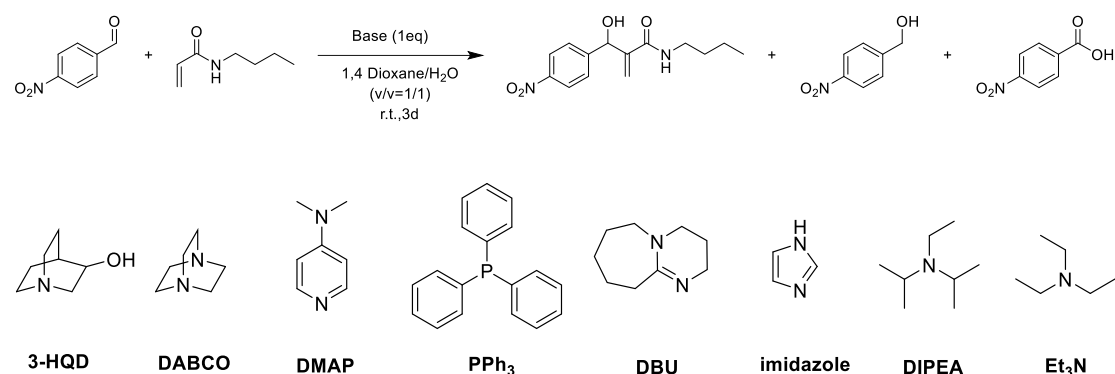
Overall, having observed the formation of both the alcohol and acid, we had a complete proof of the competition between the desired MBH pathway and the undesired Cannizzaro reaction. The influence of several reaction parameters on this competition was then investigated and the results are described in the following sections.

In order to easily investigate the influence of reaction parameters on the outcome of the reaction, a method based on the calculation of the NMR yield was introduced by addition of an internal standard, 1,2,4,5-tetramethylbenzene. The obtained crude mixture was analyzed by  $^1\text{H}$ NMR using 1, 2, 4, 5-tetramethylbenzene as internal standard and deuterated chloroform ( $\text{CDCl}_3$ ) as solvent allowing the measurement of the NMR yield. NMR and/or isolated yields in MBH and Cannizzaro products allow to determine a “selectivity” value, measured as  $\text{MBH} / (\text{Alcohol} + \text{Acid})$ , giving an image of the preference of the aldehyde toward one or the other pathway.

#### **2.2.2.2 Influence of the promoter**

Searching for optimal promoter, the reaction of 4-nitrobenzaldehyde with *N*-butyl acrylamide was performed using various nucleophilic promoters and the results are summarized in Table 1.

Among all tested promoters, only 3-hydroxyquinuclidine (3-HQD) and 1,4-diazabicyclo[2.2.2]octane (DABCO) promoted the generation of the corresponding MBH adduct, in 52 and 34% yields respectively, although the conversion of the starting aldehyde was nearly complete. The results can be analyzed in terms of selectivity between the MBH and the Cannizzaro pathway, showing significant differences among all tested promoters, either giving only Cannizzaro products like DBU or DMAP, or half and half, like DABCO, or more MBH like 3-HQD.

**Table 1.** Promoter screening for the MBH reaction of secondary *N*-alkyl acrylamide <sup>a</sup>

Promoter	NMR yield (MBH)	NMR yield (alcohol)	Yield (acid)	Conversion (aldehyde)	Selectivity (MBH)/Cannizzaro <sup>b</sup>
3-HQD	52%	18%	21%	97%	1.3
DABCO	34%	15%	14%	70%	1.2
DBU	-	47%	45%	95%	No MBH
DMAP	-	35%	30%	93%	No MBH
Et <sub>3</sub> N	-	-	-	6%	-
DIPEA	-	-	-	28%	-
PPh <sub>3</sub>	-	-	-	45%	-
imidazole	-	-	-	3%	-

<sup>a</sup> Reaction conditions: 4-nitrobenzaldehyde 0.5mmol, *N*-butylacrylamide 1mmol, promoter, 0.5mmol, 1,4-dioxane/ H<sub>2</sub>O (v/v=1/1) 250μL, r.t, 3d. <sup>b</sup> The value is calculated as follow: the yield of MBH/(yield of alcohol +yield of acid). If this ratio is more than 1, means the MBH reaction is preferable, on the contrary, Cannizzaro reaction is preferable. This value in the following tables are the same definition.

### 2.2.2.3 Influence of solvent, stoichiometry and concentration

As for the solvent issue, we focused on the use of protic media knowing their beneficial effect by stabilization of the zwitterionic intermediate. In the case of unsubstituted acrylamide, both the nitrogen and oxygen atoms can be involved in hydrogen bonds.<sup>[117, 183, 202, 215-219]</sup> Several solvent systems were thus tested for the 3-HQD promoted reaction of 4-nitrobenzaldehyde with *N*-butyl acrylamide (Table 2).

**Table 2.** Solvent screening <sup>a</sup>

Solvent	NMR yield (MBH)	NMR yield (alcohol)	Yield (acid)	Conversion (aldehyde)	Selectivity (MBH)/Cannizzaro)
Solvent free	15%	-	-	29%	No Cannizzaro
H <sub>2</sub> O	40%	24%	20%	94%	0.9
DMF/H <sub>2</sub> O (v/v=1/1)	38%	6%	8%	55%	2.7
MeCN/H <sub>2</sub> O (v/v=1/1)	41%	13%	16%	96%	1.4
Isopropanol/H <sub>2</sub> O (v/v=1/1)	43%	17%	15%	95%	1.3
EtOH/H <sub>2</sub> O (v/v=1/1)	50%	21%	25%	98%	1.1
1,4-dioxane/H <sub>2</sub> O (v/v=1/1)	52%	18%	21%	97%	1.3
2-MeTHF/H <sub>2</sub> O (v/v=1/1)	62%	13%	10%	92%	2.7
2-MeTHF/H <sub>2</sub> O (v/v=1/9)	48%	13%	11%	97%	2.0
2-MeTHF:H <sub>2</sub> O (v/v=3/7)	52%	12%	15%	95%	1.9
2-MeTHF:H <sub>2</sub> O (v/v=7/3)	43%	7%	11%	70%	2.4
2-MeTHF:H <sub>2</sub> O (v/v=9/1)	31%	4%	6%	63%	3.1
2-MeTHF	24%	-	-	53%	No Cannizzaro

<sup>a</sup>Reaction conditions: 0.5mmol 4-nitrobenzaldehyde, 1mmol *N*-butylacrylamide, 0.5mmol 3-HQD, 250μL solvent, r.t, 3d.

Purely organic solvent conditions, either solvent free or pure 2-MeTHF, gave low yields of MBH adducts, 15% and 24% respectively, though without any formation of Cannizzaro products. With a 40% yield in MBH adducts and concomitant extensive Cannizzaro reaction (44%), pure water is found to accelerate both pathways. Looking for the most appropriate balance between organic and aqueous conditions, mixtures of water with various solvents were used. Aqueous 1,4-dioxane, popular for MBH reactions, was included in the list, however, dioxane being a category 3 CMR (carcinogenic, mutagenic and reprotoxic) substance and regarded as HAP (hazardous airborne pollutant) in US,<sup>[220]</sup> the more efficient and eco-friendly alternative solvent 2-MeTHF,<sup>[220, 221]</sup> available from furfural was also investigated. Interestingly, a better MBH yield was found for the reaction in 1:1 water-2-MeTHF as compared to 1:1 water-dioxane (62 % vs 52 %). Among all tested systems, 2-MeTHF/H<sub>2</sub>O (v/v=1/1) appears the optimal ratio in terms of yield and selectivity towards the MBH vs the Cannizzaro reactions. Comparing the influence of the ratio of water-2-MeTHF mixtures, it is confirmed that presence of water is indispensable for reasonable



aldehyde conversion, even though formation of Cannizzaro products cannot be avoided, with an optimum for the 1/1 (v/v) ratio. A three days reaction time was required to get the best results, however extending it further led to only modest improvements.

**Table 3.** Influence of stoichiometry and concentration <sup>a</sup>

3-HQD (eq)	N-Butyl acrylamide (eq)	Concentration [CHO]	NMR yield <sup>b</sup> (MBH)	NMR yield <sup>b</sup> (alcohol)	Yield <sup>b</sup> (acid)	Conversion (aldehyde)	Selectivity (MBH)/Cannizzaro)
<b>0.5</b>	2	2M	47%	20%	17%	94%	1.3
<b>1</b>	2	2M	62%	13%	10%	92%	2.7
<b>1.5</b>	2	2M	58%	9%	11%	98%	2.9
1	<b>1</b>	2M	41%	13%	15%	88%	1.5
1	<b>2</b>	2M	62%	13%	10%	92%	2.7
1	<b>3</b>	2M	62%	12%	10%	98%	2.8
1	2	<b>0.5M</b>	38%	24%	26%	87%	0.8
1	2	<b>1M</b>	60%	15%	12%	94%	2.2
1	2	<b>4M</b>	58%	10%	15%	98%	2.3

<sup>a</sup>Reaction conditions: 0.5mmol 4-nitrobenzaldehyde, r.t., 3d

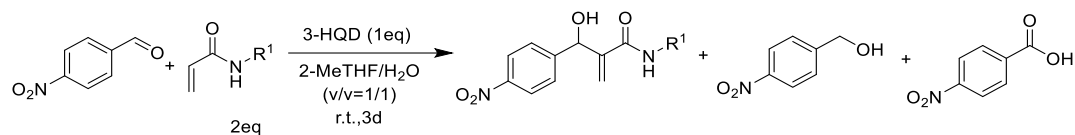
The influence of the stoichiometry and concentration were also investigated (Table 3). Using less than 1 equivalent of 3-HQD led to significant decrease of the yield, reducing the MBH pathway while favoring the Cannizzaro one, although adding more than one equivalent was of no benefit. Regarding the quantity of *N*-butylacrylamide, 2 equivalents were required for pushing the MBH pathway vs the Cannizzaro one and observing acceptable reaction rate, though adding more than 2 was not useful either. Regarding the concentration of the whole reaction mixture, varying from 0.5 M to 4 M led to significant improvement up to 2 M (38% at 0.5 M, 60% at 1 M, 62% at 2 M, 58% at 4 M).

### 2.2.3 Scope of secondary *N*-alkyl acrylamides

Having chosen a favorable set of conditions based on the above experiments, the scope of the reaction could be addressed. First, a series of secondary *N*-alkyl acrylamides was used, with variation in the alkyl chain length and the branching on the first carbon atom of the chain, while keeping 4-nitrobenzaldehyde as the aldehyde (Table 4).

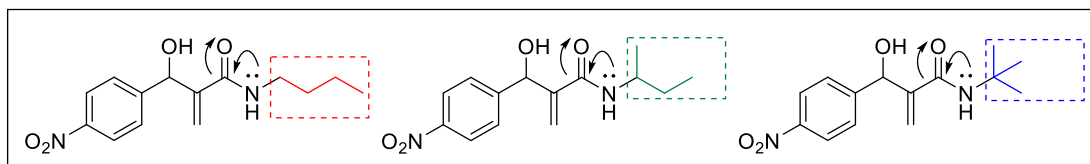
All examples with no branching on the first carbon atom gave rather similar results, with moderate to fair yields in MBH products and quite the same distribution among possible products, either MBH or Cannizzaro. A closer look allows to see that longer chain gave lower yields in MBH, and lower selectivity for MBH vs Cannizzaro. This can be ascribed to a bulkiness issue or to a solubility issue, but performing the reaction in solvent mixtures with richer organic content did not change significantly the yield. Benzylic amides such as *N*-benzyl or 4-OMe-benzyl acrylamides gave good results. Regarding the branched systems, a consistent decrease of the yield in MBH adducts was observed upon bulkiness and branching of the alkyl chain of the starting *N*-alkyl amides.

Comparing the butyl acrylamides, either *n*-butyl, *sec*-butyl or *tert*-butyl, leads to obvious decrease of the MBH product, in 60 %, 35 % and 16% yield respectively, with concomitant increase of the Cannizzaro products. Consistently with Yu *et al.* remark on the role of the delocalization of the lone pair on the nitrogen atom of the amide group as the main reason for the lower reactivity of alkyl acrylamides as substrates in MBH reactions,<sup>[205]</sup> we found in the present work that increasing the inductive effect from *n*-butyl, to *sec*-butyl and *tert*-butyl intensifies this loss of reactivity. Increasing the electron-donating ability of the nitrogen atom might increase the enolate form in the amide-enol tautomeric equilibrium, possibly limiting the alkene Michael reactivity required for the MBH pathway, and possibly increasing the basicity of the medium favoring the Cannizzaro reaction.

**Table 4.** Scope of *N*-alkyl acrylamides <sup>a</sup>

R <sup>1</sup>	Yield <sup>b</sup> (MBH adduct)	Yield <sup>b</sup> (alcohol)	Yield <sup>b</sup> (acid)	Conversion (aldehyde)	Selectivity (MBH)/Cannizzaro)
	60%	11%	10%	92%	2.9
	47%	18%	20%	96%	1.2
	43%	22%	19%	87%	1.0
	35%	32%	30%	98%	0.6
	50%	22%	20%	98%	1.2
	43%	27%	23%	95%	0.9
	16%	34%	35%	90%	0.2
	40%	26%	24%	92%	0.8
	59%	10%	12%	99%	2.7
	65%	15%	17%	99%	2.0
	45%	10%	9%	98%	2.4
	70%	5%	6%	98%	6.4
H	55%	-	-	96%	No Cannizzaro

<sup>a</sup> Reaction conditions: 1mmol 4-nitrobenzaldehyde, 2mmol acrylamide, 1mmol 3-HQD, 500μL 2-MeTHF/H<sub>2</sub>O (v/v=1/1), r.t, 3d. <sup>b</sup> Isolated yield.



**Scheme 70.** Inductive effect of *n*-butyl, to *sec*-butyl and *tert*-butyl on N atom.

As a matter of comparison, the same conditions were applied to *N*-phenylacrylamide, which gave a 70% yield with high selectivity towards the MBH pathway, and unsubstituted acrylamide gave a much faster reaction without formation of Cannizzaro products. Overall, the comparison in the series highlights a significant difference among all secondary *N*-alkyl acrylamides with those for which MBH reaction is preferred, being less bulky and less branched, and those for which the MBH pathway is disfavored as compared to the Cannizzaro reaction, consistently with branching at the first carbon atom of the alkyl chain.

#### 2.2.4 Scope of aldehydes

The scope was then developed with respect to various aromatic aldehydes, while keeping *N*-butylacrylamide as the activated alkene partner (Table 5). Nitro benzaldehydes (2-, 3- and 4-nitrobenzaldehyde) are readily transformed to their MBH adducts with 55-60% yields. Logically, the meta-substituted one is less reactive and lower conversion is found over the same reaction time. The renowned highly electrophilic 2-pyridinecarboxaldehyde gave logically the best yield in the study (79%), whereas unactivated benzaldehydes (benzaldehyde, 4-chlorobenzaldehyde or 2-methoxy-benzaldehyde) are virtually unreactive in the reaction. Cannizzaro products are found only for the four highly activated aldehydes, consistently with Bassaviahs remarks.<sup>[214]</sup> As for furanic aldehydes, 5-(hydroxymethyl)-2-furaldehyde (HMF) gave a 56% yield of MBH adducts without any generation of Cannizzaro products, albeit with a slightly lower conversion rate. This is thus a different behavior compared to the ready conversion of HMF to bishydroxymethylfuran and the furancarboxyaldehyde arising under NaOH catalysis or in ionic liquids.<sup>[222, 223]</sup>

**Table 5.** Scope of aldehydes <sup>a</sup>

R <sup>2</sup>	Yield <sup>c</sup> (MBH)	Yield <sup>c</sup> (alcohol)	Yield <sup>c</sup> (acid)	Conversion (aldehyde)	Selectivity (MBH)/Cannizzaro)
	60%	11%	10%	92%	2.7
	61%	13%	10%	93%	2.7
	55%	8%	8%	73%	3.4
	79%	8%	6%	94%	5.6
	4% <sup>b</sup>	-	-	6%	No Cannizzaro
	10% <sup>b</sup>	-	-	15%	No Cannizzaro
	-	-	-	4%	-
	56%	-	-	78%	No Cannizzaro
	44%	-	-	66%	No Cannizzaro
	46%	-	-	67%	No Cannizzaro
	42%	-	-	60%	No Cannizzaro

<sup>a</sup> Reaction conditions: 1mmol aldehyde, 2mmol *N*-butylacrylamide, 1mmol 3-HQD, 500μL 2-MeTHF:H<sub>2</sub>O=1:1, r.t, 3d. <sup>b</sup> NMR yield, 1,2,4,5-Tetramethylbenzene (1mmol) as internal standard.

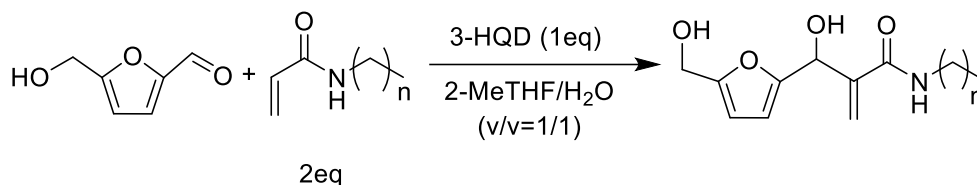
<sup>c</sup> Isolated yield

The yields of the MBH adduct from furfural and 5-( $\alpha$ -D-glucosyloxymethyl)furfural (GMF) were both slightly lower than HMF, with 46% and 44% respectively. In order to assay the influence of the hydroxyl group on the reactivity of 5-HMF in this reaction, 5-methoxymethylfurfural was used and led a 42% isolated yield, similar to that of GMF or furfural. The presence of the OH is therefore an activating factor making HMF nearly as reactive as 4-nitrobenzaldehyde, anyway much more reactive than benzaldehyde with respect to the MBH reaction. This observation can be useful for extending the uses of biobased aldehydes as platform molecules in the design of fine chemicals.<sup>[22, 224-226]</sup>

### 2.2.5 Synthesis of amphiphilic amides from HMF and GMF

After the work by Dr. Lianjie WANG who applied the strategy to HMF or GMF with various long fatty chain acrylates, we completed the scope of biobased surfactants by synthesizing a family of new amphiphilic molecules by the MBH strategy of secondary *N*-alkyl acrylamides.

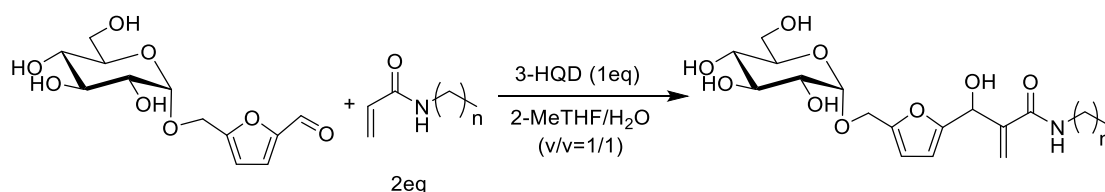
As is shown in Table 6 and 7, a series of long chain alkyl acrylamides were used in the MBH reaction with HMF and GMF respectively. The reactions of HMF gave moderate to good yields of MBH adducts in a range of 40 %~60 % under the optimized condition developed in the section above. But GMF only gave 24%~41% yield of MBH adduct. The reduction of the yield of the MBH adducts with the increase of the alkyl chain length may be attributed to the lower solubility of the acrylamide with a longer fatty chain. Although increasing the temperature solved the solubility problem, it caused the degradation of HMF and GMF, therefore not improving the MBH adduct yield.

**Table 6.** MBH adducts of various secondary *N*-alkylacrylamides with HMF

Entry	MBH adducts from HMF	Yield <sup>c</sup>
1 <sup>a</sup>		53%
2 <sup>a</sup>		60%
3 <sup>a</sup>		54%
4 <sup>a</sup>		45%
5 <sup>b</sup>		43%
6 <sup>b</sup>		42%
7 <sup>b</sup>		57%

<sup>a</sup>Reaction conditions: 2mmol HMF, 4mmol Alkyl acrylamide, 2mmol 3-HQD, 2-MeTHF/ H<sub>2</sub>O (v/v=1/1) 1ml, r.t, 3d. <sup>b</sup>Reaction conditions: 0.5mmol HMF, 1mmol Alkyl acrylamide, 0.5mmol 3-HQD, 2-MeTHF: H<sub>2</sub>O=1:1 250μl, 80°C, overnight (~16h). <sup>c</sup> Isolated yield.

**Table 7.** MBH adducts of various secondary *N*-alkylacrylamides with GMF



Entry	MBH adducts from GMF	Yield <sup>c</sup>
1 <sup>a</sup>		44%
2 <sup>a</sup>		31%
3 <sup>b</sup>		24%
4 <sup>b</sup>		35%

<sup>a</sup>Reaction conditions: 2mmol GMF, 4mmol Alkyl acrylamide, 2mmol 3-HQD, 2-MeTHF/ H<sub>2</sub>O (v/v=1/1) 1ml, r.t, 3d. <sup>b</sup>Reaction conditions: 0.5mmol GMF, 1mmol Alkyl acrylamide, 0.5mmol 3-HQD, 2-MeTHF/ H<sub>2</sub>O (v/v=1/1) 250μl, 80°C, overnight (~16h). <sup>c</sup> Isolated yield.

As lower yields of the MBH adducts were found in the case of GMF, the conditions were further optimized, especially solvent, temperature and reaction time issues. *N*-butyl acrylamide was used as the model acrylamide in this process and the related results are shown in Table 8.



**Table 8.** Optimization of the MBH reaction of secondary *N*-alkyl acrylamides with GMF<sup>a</sup>

Catalyst (eq)	Temp (°C) Time (h)	Solvent, [GMF]	NMR yield (MBH)	Remaining aldehyde
3-HQD (2eq)	40°C,3d	1,4-dioxane/H <sub>2</sub> O (v/v=1/1), 1M	42%	8%
DABCO (2eq)	40°C,40h	H <sub>2</sub> O, 1M	38% (36% <sup>c</sup> )	10%
DABCO (2eq)	r.t.3d	THFA/H <sub>2</sub> O (v/v=1/1), 1M	17%	35%
DABCO (1eq)	r.t. 3d	Isopropylidenglycerol, 1M	-	70%
3-HQD (1eq)	r.t. 3d	Isopropylidenglycerol, 1M	-	65%
DABCO (1eq)	r.t. 3d	EtOH, 1M	-	69%
3-HQD (1eq)	r.t. 3d	EtOH, 1M	15%	48%
DABCO (1eq)	r.t. 3d	isopropanol/H <sub>2</sub> O (v/v=1/1), 1M	15%	51%
3-HQD (1eq)	r.t. 3d	isopropanol/H <sub>2</sub> O (v/v=1/1), 1M	35% (32% <sup>c</sup> )	25%
3-HQD (1eq) <sup>b</sup>	r.t. 24h	2-MeTHF/H <sub>2</sub> O (v/v=1/1), 0.5M	-	78%
3-HQD (1eq) <sup>b</sup>	r.t. 24h	2-MeTHF/EtOH (v/v=1/1), 0.5M	-	75%
3-HQD (1eq) <sup>b</sup>	r.t. 24h	2-MeTHF/isopropanol (v/v=1/1), 0.5M	-	68%

<sup>a</sup>Reaction conditions: 0.5mmol GMF, 1mmol *N*-butylacrylamide. <sup>b</sup>*N*-tetradecylacrylamide 1mmol.

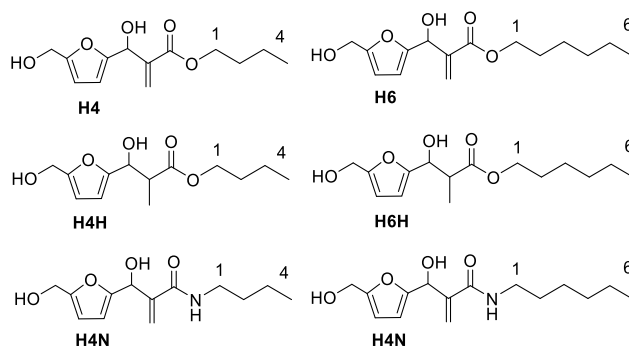
<sup>c</sup>Isolated yield

Earlier work showed that the reaction of GMF with acrylates in pure water, some biobased solvent, such as ethanol, isopropylidenglycerol isopropanol and tetrahydrofurfuryl alcohol (THFA) or the mixture of these organic solvent with water gave fair to good yield of MBH adducts.<sup>[59]</sup> We thus studied the use of these solvents in our work with acrylamides. Isopropanol/H<sub>2</sub>O (v/v=1/1) gave an acceptable yield of 32% when 3-HQD was used as promoter and this value decreased to 15% when the promoter was replaced by DABCO. Using ethanol as solvent, only the reaction with 3-HQD could give 15% yield of MBH adducts. But isopropylidenglycerol is a totally ineffective solvent for this reaction. THFA/H<sub>2</sub>O (v/v=1/1) media gave 17% yield of MBH adducts from GMF even though more promoter (2 equivalents) was used. Pure water and 1,4-dioxane/H<sub>2</sub>O (v/v=1/1), reported solvents for the MBH reaction of acrylamide, seemed effective with 38% and 42% yield of MBH adducts, respectively, similar to the yield obtained in 2-MeTHF/H<sub>2</sub>O (v/v=1/1), but both are under higher temperature (40°C) and with larger catalyst quantities. In all these cases, the conversion of GMF was much higher than the yield of MBH adducts, especially

under heating, indicating significantly more degradation. Ethanol and isopropanol were found to be efficient solvents, even for the ones with longer chain. Attempts to perform the reaction of *N*-tetradecyl acrylamide was carried out in 2-MeTHF/ H<sub>2</sub>O (v/v=1/1), 2-MeTHF/ EtOH(v/v=1/1) and 2-MeTHF/isopropanol (v/v=1/1) respectively, hoping that 2-MeTHF would help full dissolution of the hydrophobic fatty chain parts, were unsuccessful. Considering all the results for the MBH reaction of GMF with long chain acrylamides, the condition with promoter / solvent couple 3-HQD / 2-MeTHF/H<sub>2</sub>O (v/v=1/1), higher temperature but in a shorter time, for example, 16h is more efficient for the reaction, as shown in Table 7 (Entry 3 and 4).

### 2.2.6 Physicochemical properties of MBH adducts from HMF

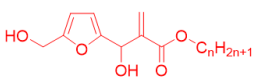
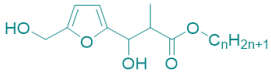
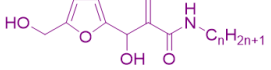
The evaluation of the properties of surfactants was handled by Dr. JF Ontiveros and Prof. V Rataj in Lille. The results shown in this section concerns the first collection of MBH adducts sent to Lille, mainly containing acrylates, and including a couple of the newly synthesized acrylamides (Figure 21). This collection was composed of compounds obtained from HMF (H4 and H6) and the compounds with eventual further hydrogenation of the acrylic double bond (H4H and H6H), prepared by Dr.Lianjie Wang as a previous part of my project during his thesis in the Lyon Laboratory. All structural parameters were thus possible to analyze, comparing the hydrophilic moiety (CH<sub>2</sub>OH, glucosyl, succinyl; the chain length, the saturation level). Two amides, H4N and H6N, were present in this collection, arising from the MBH reaction of HMF with butyl and hexyl acrylamide, ready to be compared to the corresponding H4, H6, H4H and H6H. With all these compounds in hands, a first information on the influence of all structural features could be consistently assessed.



**Figure 21.** MBH adducts from HMF for property evaluation

The HMF-based surfactants have been first investigated with respect to their ability to reduce the water surface tension at  $10^{-4}$  M ( $\gamma$  at  $10^{-4}$  M), which is shown in Table 9. Stjerndahl and Holmberg<sup>[227]</sup> have compared linear amides, esters, carbonates and ethers with the same alkyl chain and 4 ethylene oxide units and the amide surfactant present the higher CMC and also the higher cloud point. However, in terms of the surface tension reducing ability, the amide surfactants H4N and H6N were virtually ineffective, showing almost the same value as that of pure water.

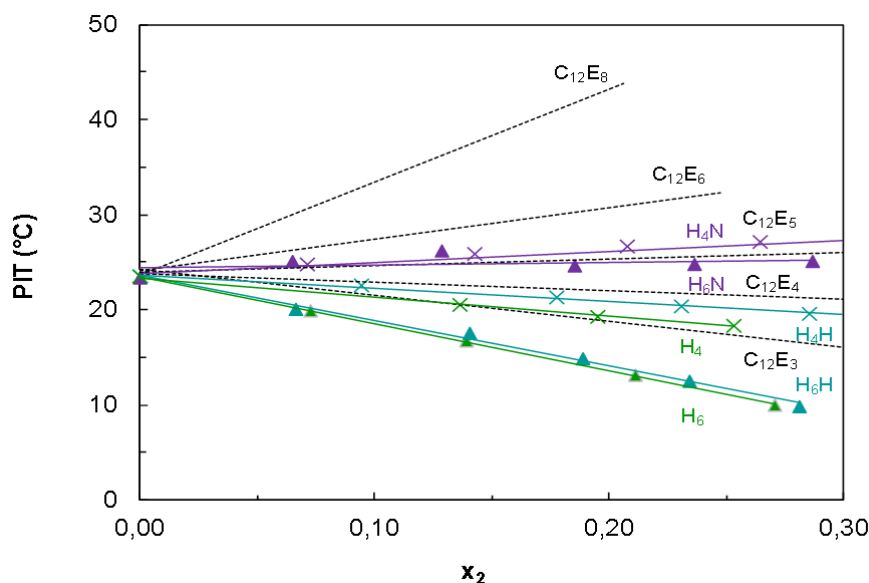
**Table 9.** Visual aspect of 0.1 wt.% solutions and surface tension at  $10^{-4}$  M ( $\gamma_{10^{-4} \text{ M}}$ ) of HMF derived surfactants.

Structure	Abbreviation	$T_{0.1\text{wt.}\%}$ (°C)	$\gamma_{1 \cdot 10^{-4} \text{ M}}$ (mN/m)	Visual aspect		
				25°C	45°C	75°C
	H4	> 75	56.9	Not soluble	Not soluble	Not soluble
	H6	> 75	61.3	Not soluble	Not soluble	Not soluble
	H4H	50	62.4	Not soluble	Not soluble	Soluble
	H6H	60	58.6	Not soluble	Not soluble	Soluble
	H4N	35	71.2	Not soluble	Soluble	Soluble
	H6N	40	70.1	Not soluble	Soluble	Soluble

Due to their low solubility in water, the visual aspect was studied with solutions at 0.1 wt. % instead of 1 wt. % as for the common determination of the Krafft or Cloud points as to have comparative values for the whole family. Acrylates H4 and H6 exhibit a very poor solubility, and were even not entirely soluble in the studied interval of temperatures, while the hydrogenation of the double bond significantly improves the water-solubility of the esters H4H and H6H. Interestingly, the presence of the amide group in H4N and H6N leads to the most soluble compounds within the HMF series thanks to their higher capacity of making hydrogen bonding (accept and donate) with water molecules.

The Hydrophilic Lipophilic Balance (HLB) value of the compounds was determined using the PIT-slope method<sup>[62, 63]</sup> which is based on the perturbation of the phase inversion temperature (PIT) of the reference 3%  $\text{C}_{10}\text{E}_4/n$ -octane/0.01M  $\text{NaCl}_{(\text{aq})}$  system at  $f_w = 0.5$  through addition of the

surfactant. The PIT is determined by conductivity monitoring and linearly changes as a function of the added surfactant. Consequently, the behavior of each surfactant can be quantified by the value of the slope,  $dPIT/dC$  (mass concentration) or  $dPIT/dx_2$  (molar fraction). Positive values indicate a more hydrophilic surfactant than  $C_{10}E_4$  while negative values indicate a more lipophilic behavior when using temperature as a formulation variable.



**Figure 22.** Phase Inversion Temperature (PIT) vs. molar fraction  $x_2$  for the system 3%  $C_{10}E_4/S_2/Octane/10^{-2}M NaCl$  at  $f_w = 0.5$ .  $S_2 = H_4N$  ( $\times$ );  $H_6N$  ( $\blacktriangle$ );  $H_4$  ( $\times$ );  $H_6$  ( $\blacktriangle$ );  $H_4H$  ( $\times$ );  $H_6H$  ( $\blacktriangle$ ). Lines indicate linear fitting leading to  $dPIT/dx_2$ . Black dotted lines indicate the PIT-slope for several  $C_{12}E_j$  surfactants.

In the Figure 22, the values of  $H_i$ ,  $H_iH$  and  $H_iN$  series ( $i$  means the chain length of the HMF derived MBH adducts), were shown in purple, green and blue respectively, along with some results for typical polyethoxylated surfactants in black. The linearity slope of the PIT with the molar fraction diminishes as the following order:  $H_iN > H_iH \approx H_i$ , responding to the solubility order in aqueous phase. Moreover, the reduction of the slope value also incorporate to the increase of alkyl chain length. The exact values of PIT-slope (mass  $dPIT/dC$  and molar fraction  $dPIT/dx_2$ ) of these surfactants were also summarized in Table 10. The amides  $H_iN$  are more hydrophilic than esters  $H_i$ , because both O and N are able to form hydrogen bond with water and their PIT-slope are higher.

**Table 10.** PIT-slope (mass dPIT/dC and molar fraction dPIT/dx<sub>2</sub>) of HMF derived surfactants.

Surfactant	dPIT/dC (°C/wt.%)	dPIT/dx <sub>2</sub> (°C)
H4	-6.7	-20.4
H6	-14.4	- 49.7
H4H	-4.0	-13.8
H6H	-13.4	- 47.6
H4N	3.4	11.7
H6N	0.2	1.3

Complementary data are still to be collected from evaluations of the remaining samples sent to Lille which include a larger series of HMF and GMF products involving the amide linkage, thus providing additional elements on the influence of the nitrogen atom on their properties in this new family of surfactants.

### 2.2.7 Conclusion

Secondary *N*-alkyl acrylamides can be used in Morita-Baylis-Hillman reactions despite their notorious lower electron withdrawing ability which caused their discarding from earlier studies. Competition between the desired MBH and the undesired Cannizzaro pathways must be addressed, in particular for highly activated aldehydes. A balance between the beneficial effect of the use of aqueous media on both reactions must be found. The promoter / solvent couple 3-HQD / 2-MeTHF/H<sub>2</sub>O (v/v=1/1) was found efficient and provided more eco-friendly conditions than dioxane containing systems. Overall, the reaction can be applied to a wide range of secondary *N*-alkyl acrylamides and aromatic aldehydes giving novel MBH adducts in moderate to good yields.

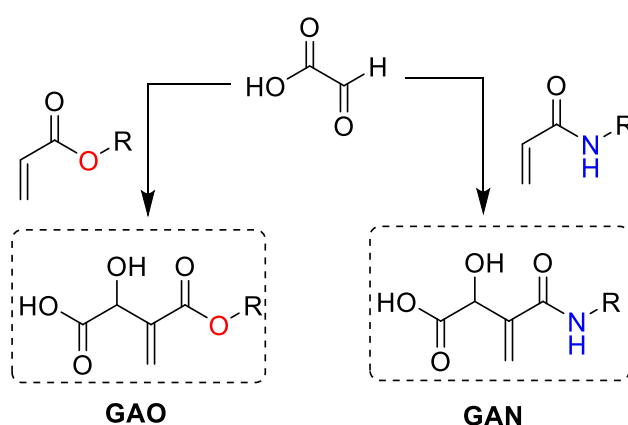
The branching at the first carbon atom of the alkyl chain appears essential, as any further inductive enrichment of the nitrogen amide is deleterious to the desired MBH reactivity. With respect to aldehydes, classical higher reactivity is found for nitrobenzaldehydes and 2-pyridinecarboxaldehyde while unactivated benzaldehydes are virtually unreactive. Interestingly, biobased aldehydes such as furfural and HMF are possible substrates for this reaction, with HMF appearing nearly as activated as 4-nitrobenzaldehyde. This extends further the possible uses of these platform molecules in the design of fine chemicals. For the HMF amphiphiles, the decreasing hydrophilic order is:  $\text{HiN} > \text{HiH} \approx \text{Hi}$ .

## 2.3 MBH reaction of glyoxylic acid towards biobased surfactants

### 2.3.1 Introduction

Continuing to expand the MBH strategy to prepare biobased surfactants, we then investigated the use of glyoxylic acid (GA) as the aldehydic substrate. As stressed in the bibliographic section 1.4.3, GA can be classified as a biobased platform molecules since it can be generated from other primary biomass-derived compounds such as glyoxal or ethylene glycol. However, GA has never been used as a possible building block toward surfactants, although its carboxylic acid group could serve as precursor of the hydrophilic anionic group. GA appears therefore an ideal substrate in the MBH strategy toward surfactants, possessing both the necessary aldehyde group as reactive function and the carboxylic group as polar moiety precursor.

Surprisingly, the MBH reaction of GA has been nearly never studied. To the best of our knowledge, the only work concerning MBH reaction of GA is a simple mention in a table with no indication in the experimental in a paper from Aggarwal and collaborators focusing on the use of aqueous media for MBH reaction of acrylates with carbonyl compounds.<sup>[202]</sup> Facing this lack of information, we have undertaken a full investigation of the MBH reaction of GA with various alkyl acrylates and secondary *N*-alkyl acrylamides as activated alkenes, which are hydrophobic alkenes, to define the best conditions for reaching amphiphilic adducts.



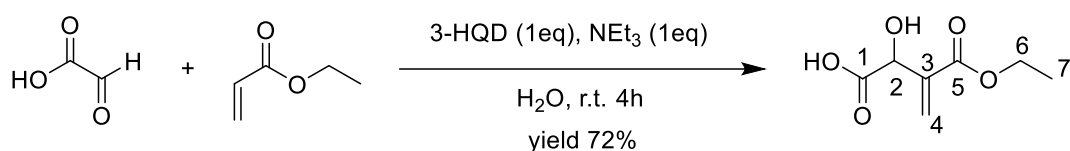
**Figure 23.** Design of glyoxylic acid derived surfactants via MBH reaction

A series of amphiphilic adducts arising from MBH reaction of GA with acrylates (**GAO** series) and acrylamides (**GAN** series) respectively was thus prepared (Figure 23) and their physicochemical properties were evaluated.

### 2.3.2 MBH reaction of GA with alkyl acrylates

#### 2.3.2.1 Characterization of the GA MBH adducts

The MBH reaction of glyoxylic acid aqueous solution (50 wt %) with ethyl acrylate was first performed using 1 equivalent of 3-HQD and 1 equivalent of NEt<sub>3</sub> as promoters, at room temperature in pure water as solvent, like reported by Aggarwal and co-workers <sup>[202]</sup> (Scheme 71).



**Scheme 71.** MBH reaction of GA with ethyl acrylate under the condition of Aggarwal *et al.* <sup>[202]</sup>

After 4h, the reaction mixture was acidified with HCl aqueous solution (1M) and extracted by ethyl acetate to produce an organic solution containing the mixture of a new product and the remaining acrylate. Dehydration over Na<sub>2</sub>SO<sub>4</sub> and concentration led to a crude residue which was purified by silica gel column chromatography (EtOAc:AcOH = 95:5). The final glyoxylic acid MBH adduct could be isolated with 80% yield and was further characterized via NMR and HR-MS spectroscopy. As shown in Figure 24 and 25, the typical signal for the proton of CH-OH of the MBH adduct could be found at  $\delta$  4.91 ppm (H<sub>2</sub>), along with the <sup>13</sup>C signal at  $\delta$  70.53 ppm (C<sub>2</sub>), indicating the formation of the C-C bond connection from the MBH reaction. The HMBC spectrum (Figure 26b) of the product also displayed the patterns indicating the correlation of H<sub>4</sub> of CH<sub>2</sub>=C with C<sub>2</sub>, and of H<sub>2</sub> (of CH-OH) with each of C<sub>1</sub>, C<sub>3</sub>, C<sub>4</sub> and C<sub>5</sub>, confirming further the structure.



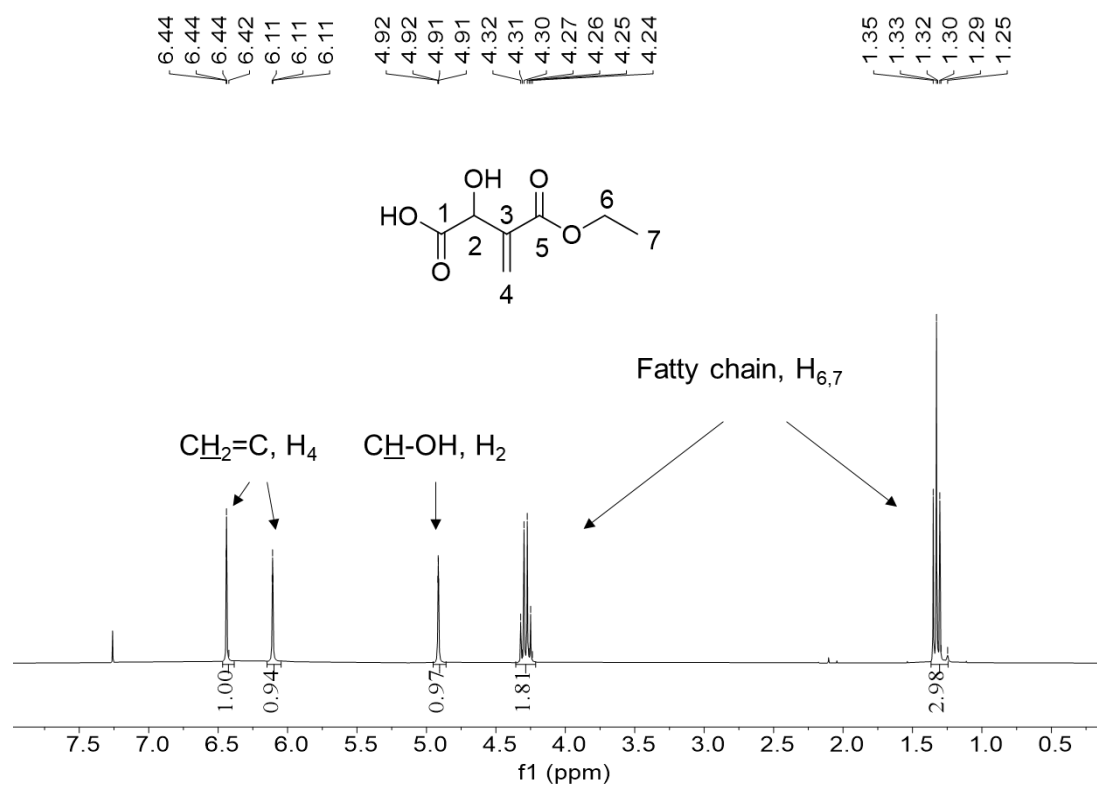


Figure 24. <sup>1</sup>H NMR spectrum of the MBH adduct of GA with ethyl acrylate

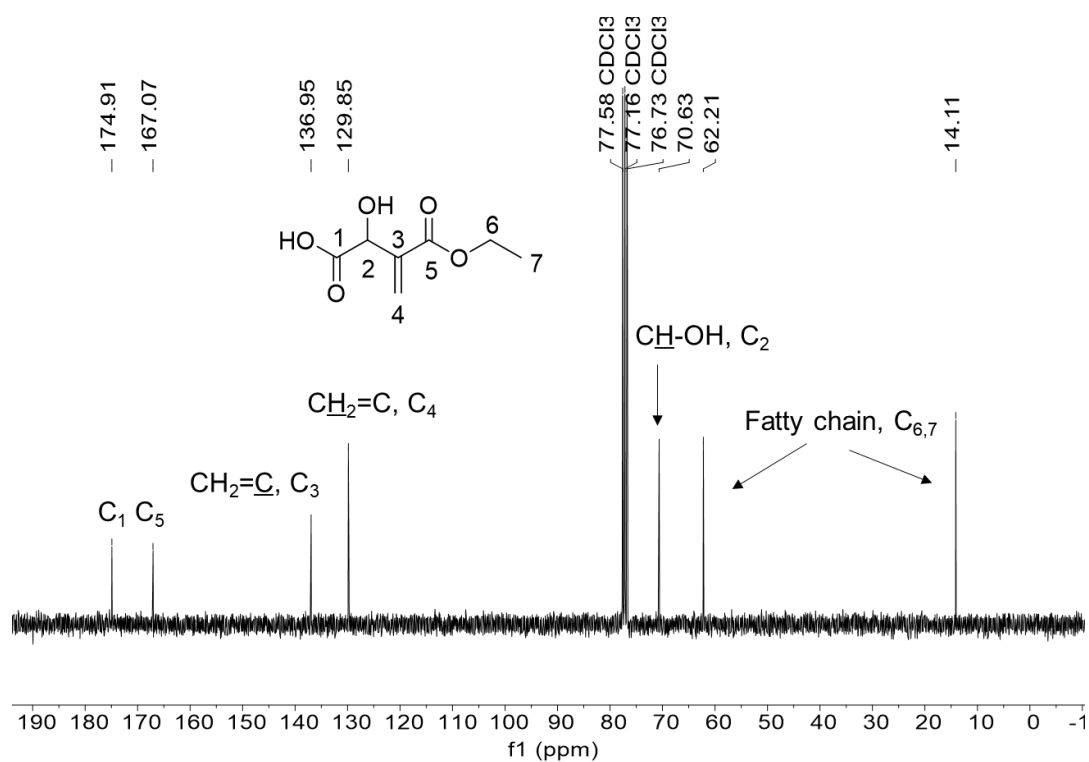
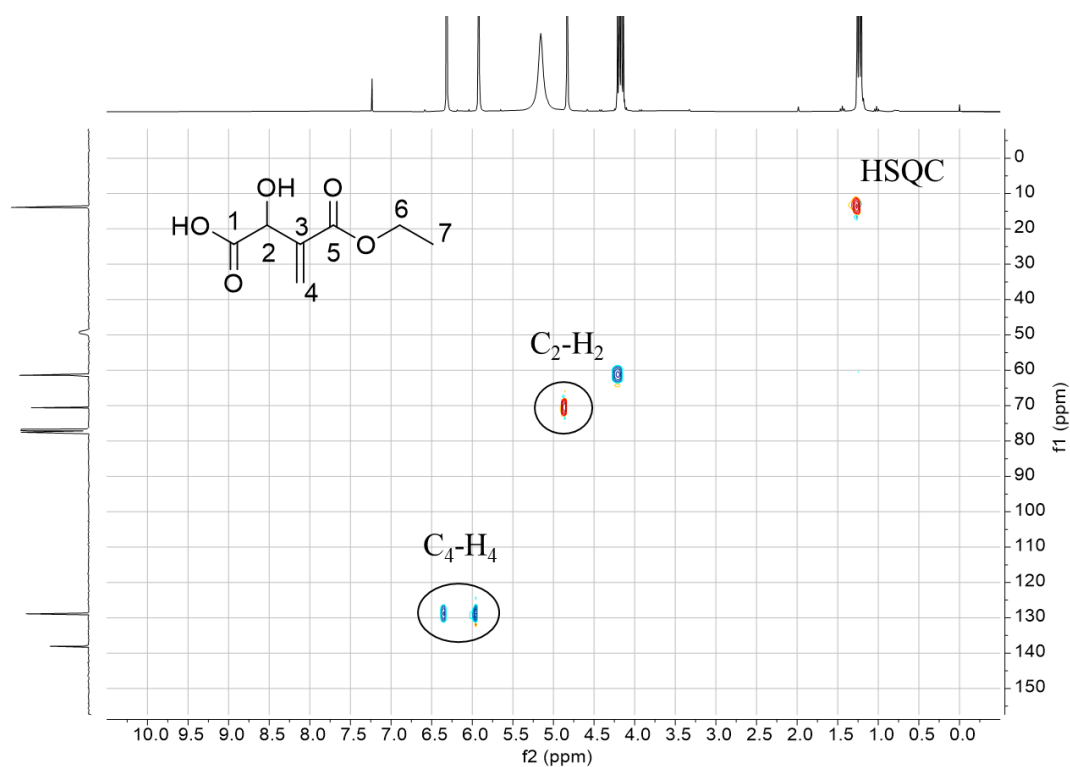
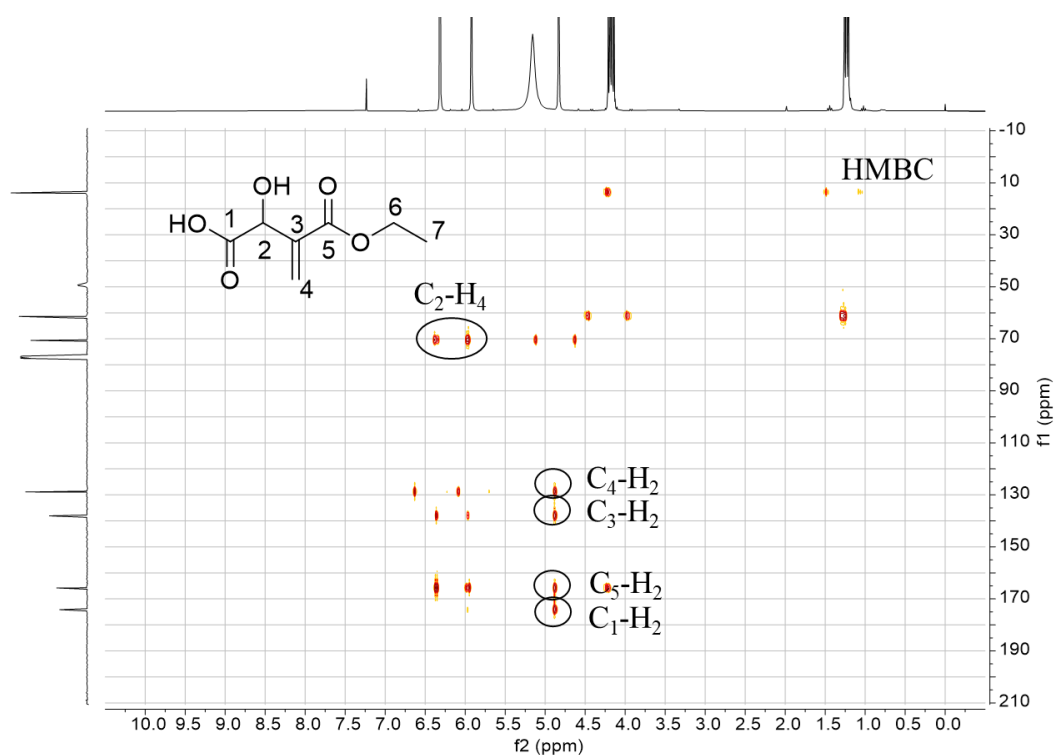


Figure 25. <sup>13</sup>C NMR spectrum of the MBH adduct of GA with ethyl acrylate



**Figure 26a.** HSQC spectrum of MBH adduct of GA with ethyl acrylate



**Figure 26b.** HMBC spectrum of MBH adduct of GA with ethyl acrylate

### 2.3.2.2 Initial optimization and extension to long chain acrylates

After the first experiments using ethyl acrylate and the synergistic catalytic system (1eq 3-HQD + 1eq Et<sub>3</sub>N) or the alternative equimolar DABCO /Et<sub>3</sub>N mixture, in water or ethanol, giving good yields (Table 11), we turned to longer chain systems able to provide enough lipophilicity to the non-polar tail, with the aim to prepare amphiphilic molecules. However, Table 11 also shows that when dodecyl acrylate is used instead of ethyl acrylate as activated alkene, the same conditions did not provide the corresponding MBH adducts. Simply changing the solvent to ethanol, or using longer reaction time (24h) was not successful either. A complete methodological investigation of the reaction of glyoxylic acid with alkyl acrylates, including long chain ones was thus necessary.

**Table 11.** Preliminary Study of the MBH reaction of glyoxylic acid with alkyl acrylates

Alkyl acrylate	Solvent	Promoter	Reaction time	Yield <sup>a</sup> (MBH adduct)
Ethyl acrylate	H <sub>2</sub> O	1eq 3-HQD+1eq Et <sub>3</sub> N	4h	80%
Ethyl acrylate	H <sub>2</sub> O	1eq DABCO+1eq Et <sub>3</sub> N	4h	78%
Ethyl acrylate	Ethanol	1eq DABCO+1eq Et <sub>3</sub> N	4h	77%
Dodecyl acrylate	H <sub>2</sub> O	1eq DABCO+1eq Et <sub>3</sub> N	4h	-
Dodecyl acrylate	H <sub>2</sub> O	1eq 3-HQD+1eq Et <sub>3</sub> N	4h	-
Dodecyl acrylate	Ethanol	1eq DABCO+1eq Et <sub>3</sub> N	4h	-
Dodecyl acrylate	Ethanol	1eq DABCO+1eq Et <sub>3</sub> N	24h	-

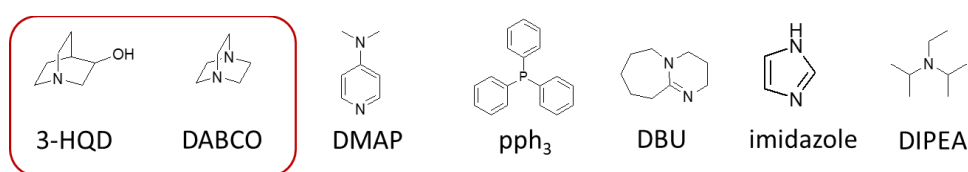
*Reaction conditions:* 1mmol glyoxylic acid (50wt% aqueous solution), 2mmol Alkyl acrylate, 1ml solvent, r.t. <sup>a</sup>. Isolated yield.

### 2.3.2.3 Promoter screening

The reported condition by Aggarwal *et al.* for the MBH reaction of GA with tert butyl acrylate being unsuccessful with long chain acrylates, alternative catalytic systems were investigated, using dodecyl acrylate as model fatty substrate. The yields of MBH adducts were evaluated by NMR using 1,2,4,5-tetramethylbenzene as internal

standard and the results are shown in the Table 12. Two equivalents of DABCO or 3-HQD both exhibited good performance on promoting this reaction, with 58% and 78% yield of corresponding MBH adducts, respectively. Other tested nucleophilic promoters did not give any desired MBH adduct in reasonable time. Thus, DABCO and 3-HQD were both used as promoter for further optimization of conditions by studying the influence of stoichiometry, concentration and reaction time.

**Table 12.** The influence of various promoters on the MBH reaction of GA with acrylates



Entry	Base	NMR yield (MBH)
1	DABCO	58%
2	3-HQD	78%
3	p <sub>ph</sub> <sub>3</sub>	-
4	DBU	-
5	DMAP	-
6	Imidazole	-
7	DIPEA	-

*Reaction conditions:* 0.5mmol glyoxylic acid (50 wt% aqueous solution), 1mmol Dodecyl acrylate, 1mmol promoter, 500μL EtOH, r.t, 3d.

#### 2.3.2.4 Optimization of conditions using DABCO as promoter

The DABCO catalyzed MBH reaction of GA with dodecyl acrylate was investigated and the results are shown in Table 13. Firstly, the influence of the quantity of promoter was studied. No reaction was observed when less than 1 equivalent of DABCO was used. This is due to the neutralization with the carboxylic acid group of GA, leading to the protonation of DABCO nucleophilic nitrogen atom, thus losing

any ability to intervene in the MBH pathway. The yield of MBH adduct raised sharply to 37% using 1.5 equivalent of DABCO, and this value kept rising with more addition of promoter, up to 66% when using 2.5 equivalent DABCO. Adding more DABCO was ineffective.

**Table 13.** Optimization of conditions using DABCO as promoter <sup>a</sup>

Entry	DABCO (eq)	Dodecyl acrylate (eq)	Concentration [GA ]	Time	NMR yield (MBH)
<b>1</b>	<b>0.5</b>	2	1M	72h	-
	<b>1</b>	2	1M	72h	-
	<b>1.5</b>	2	1M	72h	37%
	<b>2</b>	2	1M	72h	58%
	<b>2.5</b>	2	1M	72h	66%
<b>2</b>	2	<b>1</b>	1M	72h	34%
	2	<b>1.5</b>	1M	72h	32%
	2	<b>2</b>	1M	72h	60%
	2	<b>2.5</b>	1M	72h	66%
	2	<b>3</b>	1M	72h	74%
<b>3</b>	2	2	<b>0.5M</b>	72h	28%
	2	2	<b>1M</b>	72h	58%
	2	2	<b>2M</b>	72h	80%
	2	2	<b>4M</b>	72h	95%( 90% <sup>c</sup> )
	2	2	<b>8M</b>	72h	95%
	2	2 <sup>b</sup>	<b>4M</b>	72h	87% <sup>c</sup>
<b>4</b>	2	2	4M	<b>6h</b>	66%
	2	2	4M	<b>16h</b>	76%
	2	2	4M	<b>24h</b>	85%
	2	2	4M	<b>30h</b>	90%
	2	2	4M	<b>40h</b>	88%
	2	2	4M	<b>48h</b>	90%
	2	2	4M	<b>72h</b>	91%

<sup>a</sup>Reaction conditions: 0.5mmol glyoxylic acid (50 wt% aqueous solution), Dodecyl acrylate, EtOH, r.t.

<sup>b</sup> 1mmol Decyl acrylate(C10). <sup>c</sup>Isolated yield.

The influence of the quantity of alkyl acrylates was then studied. It showed an obvious increase of yield in MBH adducts from ~30% to ~60% when the quantity of acrylate increased from 1.5 to 2 equivalents. The yield kept increasing with more addition of acrylate, though in smaller extent.

The study of the influence of the concentration was conducted by reducing the amount of solvent while keeping all quantities of substrates and promoter as before. The results show the significant yield increase at higher concentration, even reaching a 95% NMR yield at 4M. This latter result was confirmed by a 90% isolated yield obtained after further purification over silica gel column chromatography. The same set of conditions was also applied to the reaction with decyl acrylate, which gave an 87% yield of corresponding MBH adduct.

As for the influence of reaction time, the NMR yield of MBH adduct could reach to 85% after 24h, longer reaction time will a little higher yield up to 90% but no more. Therefore, the optimum concentration and reaction time for this reaction could be concluded as [4M] and 24h.

#### **2.3.2.5 Optimization of conditions using 3-HQD as promoter**

Similar investigations were then conducted for the reaction using 3-HQD as promoter. Like for DABCO, the study of the influence of the quantity of 3-HQD showed the necessity to add more than one equivalent, as the first equivalent is immediately neutralized by the carboxylic acid group of GA. Checking the influence of concentration was carried out at a range from [0.5 M] to [8 M], with no significant change as the yield of MBH adduct reached already 76% at [0.5 M]. It is thus observed that unlike the case of the DABCO promoted reaction, concentration here has no significant influence. However, the reaction is significantly faster using 3-HQD, as seen by a much higher yield of MBH adduct, 76 % at [0.5 M], compared to 28 % yield using DABCO at the same concentration. As for the reaction time, a 72 % yield of MBH adduct could be reached in 6h, which is close to the 66 % yield obtained with DABCO after the same reaction time but at a higher concentration.

**Table 14.** Optimization of conditions using 3-HQD as promoter

Entry	3-HQD (eq)	Concentration [GA]	Time	NMRyield (MBH)
1	1	1M	72h	-
	2	1M	72h	78%
	3	1M	72h	79%
	4	1M	72h	78%
2	2	<b>0.5M</b>	72h	76%
	2	<b>1M</b>	72h	78%
	2	<b>2M</b>	72h	74%
	2	<b>4M</b>	72h	72%
	2	<b>8M</b>	72h	72%
3	2	1M	<b>6h</b>	72%
	2	1M	<b>16h</b>	76%
	2	1M	<b>24h</b>	76%
	2	1M	<b>30h</b>	76%
	2	1M	<b>40h</b>	82%
	2	1M	<b>48h</b>	80%
	2	1M	<b>72h</b>	78%

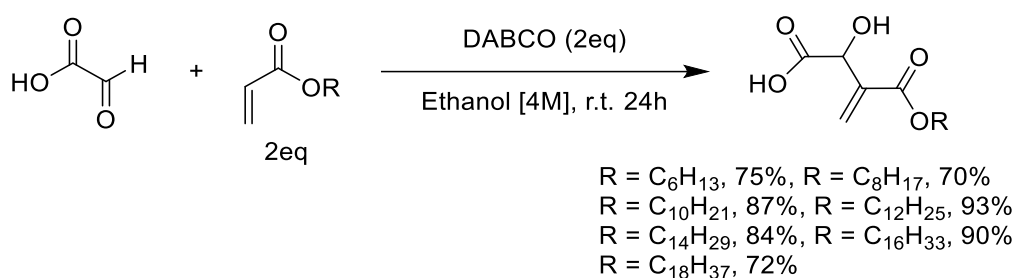
*Reaction conditions:* 0.5mmol glyoxylic acid (50 wt% aqueous solution), Dodecyl acrylate, EtOH, r.t.

The yield increased up to 82 % when the reaction was expanded to 40h, while decreased a little to 78 % upon a longer reaction time 72 h. Overall, similar influence of reaction time on the yield of MBH adduct is found whatever 3-HQD or DABCO is used as promoter.

### 2.3.2.6 Amphiphilic esters from GA via MBH reaction

In the work described above, the MBH reaction of GA with acrylates has been investigated with respect to parameters including concentration, stoichiometry and reaction time using two efficient promoters: DABCO and 3-HQD respectively. Though the 3-HQD reaction is faster, the highest yields were found when DABCO was used. The final optimum conditions for this reaction are thus chosen as follows: 2 equivalent of acrylates, 2equivalent of DABCO as promoter, ethanol as solvent with a concentration of [4 M], at room temperature for 24 h. This set of conditions was next applied to alkyl acrylates with various fatty chains (from C6 to C18) and gave the corresponding MBH adducts in moderate to good yield.

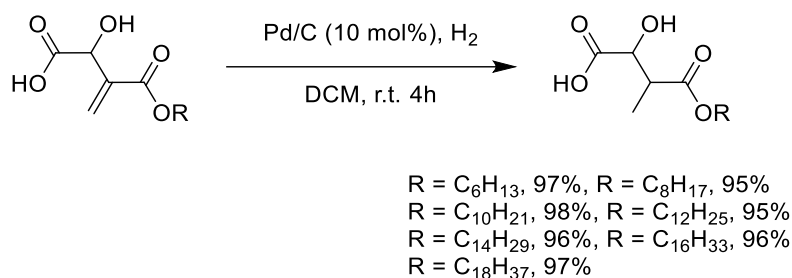
The MBH adducts GAO<sub>n</sub> series (n=6, 8, 10, 12, 14, 16 and 18) could be synthesized under the following conditions: glyoxylic acid (50wt% in water) (1.1ml, 10mmol), 2 equivalent alkyl acrylates, 2 equivalent of DABCO as promoter in 2.5ml Ethanol at room temperature (Scheme 72). The reaction mixture was washed with HCl (1M) and water to remove DABCO and the final products were isolated via column chromatography of silica gel (EtOAc: AcOH=100:0→95:5 as eluent). The purity of desired products were confirmed via NMR and HR MS spectra.



**Scheme 72.** MBH reaction of GA with alkyl acrylates

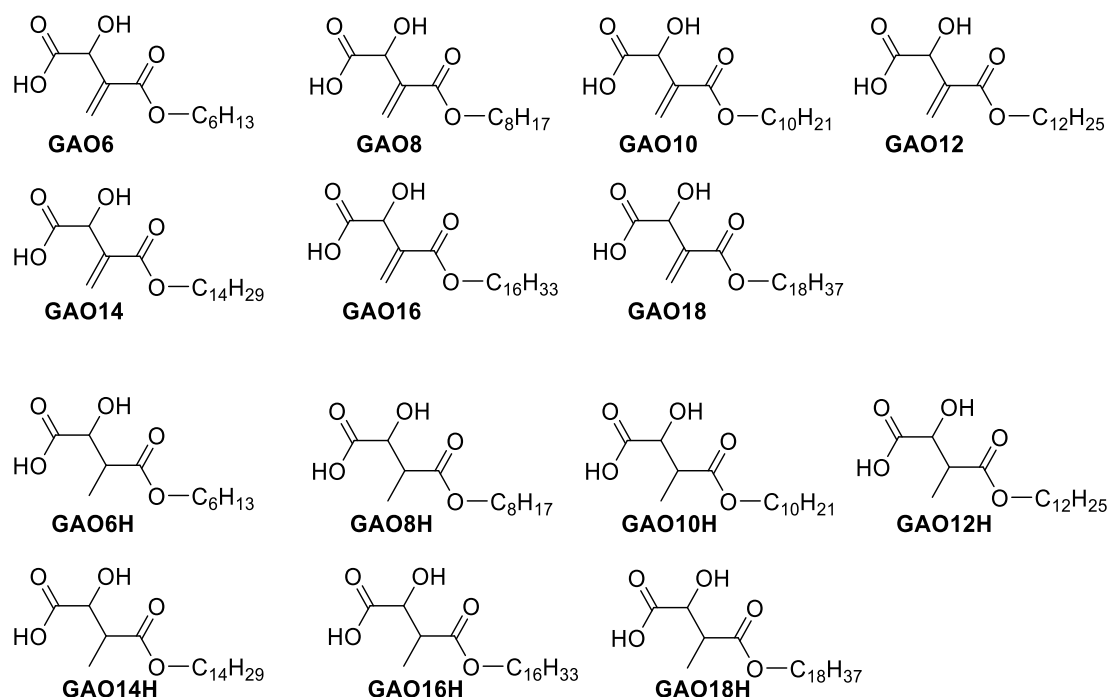
The presence of unsaturated bonds might lead difficulties in applications of these compounds as surfactants due to their potential reactivity as a Michael acceptors. Thus the family was extended to saturated systems obtained by hydrogenation catalyzed by palladium catalysts. The conditions developed by Dr. Lianjie WANG for his work to hydrogenate the MBH adducts of SMF [Pd/C (10 mol%), DCM, 2h, r.t.] have been applied to the hydrogenation of GA derived amphiphiles (Scheme 73). However, as remaining unhydrogenated MBH adducts were observed, the reaction time was expanded to 4h for full hydrogenation. After filtration of the Pd catalysts over celite, evaporation of the solvent under vacuum and purification through column chromatography (EtOAc: AcOH=100:0→95:5 as eluent), the desired product could be obtained and the purity and structure were fully characterized with NMR and HR MS spectroscopy.





**Scheme 73.** Hydrogenation of the MBH adducts from GA with acrylates

The synthesized products have been summarized in Figure 27: the MBH adduct of glyoxylic acid with hexyl-acrylate (GAO6), octyl acrylate (GAO8), decyl acrylate (GAO10), dodecyl acrylate (GAO12), tetradecyl acrylate (GAO14), hexadecyl acrylate (GAO16) and octadecyl acrylate (GAO18). And the selectively hydrogenated products GAO6H, GAO8H, GAO10H, GAO12H, GAO14H, GAO16H and GAO18H.



**Figure 27.** Amphipathic molecules from MBH reaction of GA and further hydrogenation.

### 2.3.3 MBH reaction of GA with alkyl acrylamides

The success of the MBH reaction of glyoxylic acid with alkyl acrylates encouraged us to expand our study to alkyl acrylamides targeting amide-bond containing surfactants. A methodological investigation was thus undertaken, benefiting from our earlier results on the reactivity of acrylates in MBH reaction with GA, as well as on the reactivity of secondary *N*-alkyl acrylamides in MBH reaction with various aldehydes developed in the section 2.2. The influence of the promoter, solvent system and concentration were studied using *N*-butyl acrylamide, before applying the best conditions to a scope of variously *N*-substituted acrylamides, and the results are shown in Table 15.

DABCO and 3-HQD as promoters exhibited both good performance of in the reaction, although with significantly lower yields (40% NMR) as compared to acrylates. Regarding the solvent, the use of H<sub>2</sub>O gave a higher yield of MBH adduct than 2-MeTHF/H<sub>2</sub>O (v/v=1). The addition of water to EtOH and MeOH was also beneficial of the MBH reaction. Changing the concentration had no significant effect on the yield of desired adducts unlike what was observed for the reaction of GA with acrylates. Extending the reaction time from 6 h to 40 h led to a yield increase from 8% to 54% of MBH adducts, however longer reaction time did not improve the yield. These studies allowed to propose the optimized set of the conditions as: 2 equivalents of 3-HQD as promoter, water as solvent, room temperature and 48 h for the MBH reaction of GA with secondary *N*-butyl acrylamide.

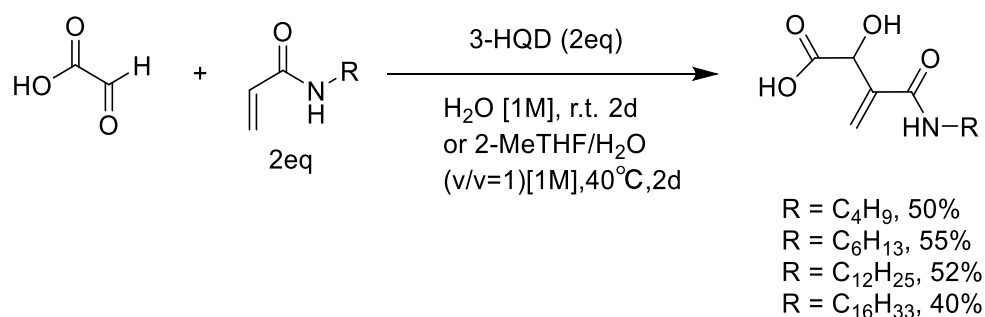
**Table 15.** Optimization of conditions using DABCO as promoter for the *N*-butyl acrylamide reaction with GA<sup>a</sup>

Entry	Promoter	Solvent	Concentration [GA]	Time	NMR yield (MBH)
1	DABCO	2-MeTHF/H <sub>2</sub> O (v/v=1)	2M	72h	26%
	3-HQD	2-MeTHF/H <sub>2</sub> O (v/v=1)	2M	72h	40%
	DBU	2-MeTHF/H <sub>2</sub> O (v/v=1)	2M	72h	-
	DMAP	2-MeTHF/H <sub>2</sub> O (v/v=1)	2M	72h	-
	Et <sub>3</sub> N	2-MeTHF/H <sub>2</sub> O (v/v=1)	2M	72h	-

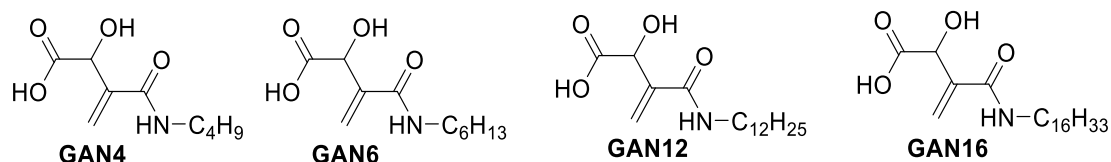
	3-HQD	<b>H<sub>2</sub>O</b>	2M	72h	52%
	3-HQD	<b>2-MeTHF/H<sub>2</sub>O (v/v=1)</b>	2M	72h	40%
<b>2</b>	3-HQD	<b>EtOH /H<sub>2</sub>O (v/v=1)</b>	2M	72h	20%
	3-HQD	<b>MeOH /H<sub>2</sub>O (v/v=1)</b>	2M	72h	12%
	3-HQD	<b>EtOH</b>	2M	72h	-
	3-HQD	<b>MeOH</b>	2M	72h	-
	3-HQD	H <sub>2</sub> O	<b>1M</b>	72h	52%
<b>3</b>	3-HQD	H <sub>2</sub> O	<b>2M</b>	72h	52%
	3-HQD	H <sub>2</sub> O	<b>4M</b>	72h	48%
	3-HQD	H <sub>2</sub> O	2M	<b>6h</b>	8%
	3-HQD	H <sub>2</sub> O	2M	<b>16h</b>	20%
	3-HQD	H <sub>2</sub> O	2M	<b>24h</b>	28%
<b>4</b>	3-HQD	H <sub>2</sub> O	2M	<b>30h</b>	42%
	3-HQD	H <sub>2</sub> O	2M	<b>40h</b>	54%
	3-HQD	H <sub>2</sub> O	2M	<b>48h</b>	52%
	3-HQD	H <sub>2</sub> O	2M	<b>72h</b>	58%

*Reaction conditions:* 0.5mmol glyoxylic acid (50 wt% aqueous solution), 1mmol *N*-butylacrylamide, 1mmol promoter. 250 $\mu$ L solvent, r.t, 3d.

The *N*-hexylacrylamide MBH adduct of GA (GAN6) was synthesized under same condition as for the *N*-butyl acrylamide adduct (GAN4) (Scheme 74). However, longer chain substrates such as *N*-dodecyl acrylamide and *N*-hexadecyl acrylamide required a higher temperature (40°C) and the use of the mixed aqueous-organic solvent system 2-MeTHF/H<sub>2</sub>O (v/v=1), leading to the MBH adducts (GAN12 and GAN16) in 40 to 55 % yields (Figure 28).



**Scheme 74.** MBH reaction of GA with secondary *N*-alkyl acrylamides



**Figure 28.** Amphiphatic amide molecules from MBH reaction of GA

### 2.3.4 Properties of MBH adducts from GA

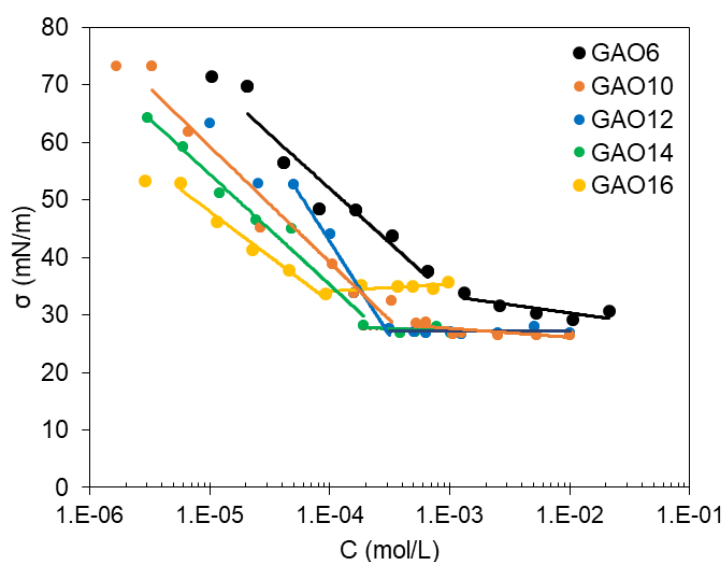
Firstly, the stability these new surfactants under various pH was investigated. This was studied using GAO10 as an example. GAO10 was dissolved in three different aqueous solutions, all of which kept stirring at room temperature for 3 days to check the stability. Solution 1: 0.5mmol GAO10 + 2.5ml (0.01M NaCl aqueous solution), which are the condition used for property evaluation; Solution 2: 0.5mmol GAO10 + 0.5mmol NaOH +2.5ml H<sub>2</sub>O; Solution 3: 0.5mmol GAO10 + 1 mmol NaOH +2.5ml H<sub>2</sub>O. After 3days, these three solutions were directly extracted with ethyl acetate, followed by dehydration over NaSO<sub>4</sub> and concentration under vacuum. The obtained product was checked by NMR in DMSO-D<sub>6</sub>. Only the third solution contained some C10 alcohol with a yield of 25.3%. Addition of HCL (1M) to the aqueous phases and extraction with EtOAc allowed to recover the remaining GAO10 compound. This set of experiments demonstrated that the surfactants are stable under neutral condition, but degradable under basic condition.

A preliminary evaluation of the surfactant properties has also been conducted by Dr. JF Ontiveros and Prof. V. Nardello-Rataj of the CISCO team of UCCS in the University of Lille on a part of the series of novel amphiphiles. Up to now, the tested samples are GAO6, GAO10, GAO12, GAO14 and GAO16. The parameters for the properties evaluation include critical micellar concentration (CMC), reflecting the surface tension reducing ability of compounds in aqueous solution and also the solubility in water, and the amphiphilicity determined by the PIT-slope values. The PIT-slope method was developed in the CISOCO lab <sup>[62, 63]</sup> to evaluate the “Hydrophlic Lipophilic Balance” (HLB) of the novel amphiphiles by comparison with conventional surfactants. This methods gives useful information of the utilization area of the new products.

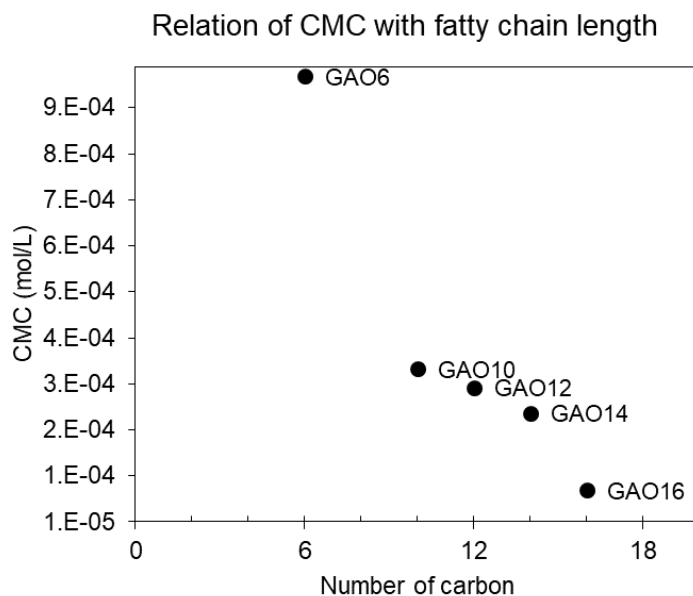
**Table 16.** CMC, surface tension at CMC, solubility and cloud point of GA derived surfactants.

Sample	CMC (mol/L)	$\sigma_{\text{CMC}}$ (mN/m)	pH ( $10^{-3}$ mol/L)	Solubility (mol/L)	Cloud Point ( $^{\circ}\text{C}$ )
GAO6	9.79E-04	33.25	3.9	2.00E-02	
GAO10	3.42E-04	28.38	3.7	1.00E-02	
GAO12	3.02E-04	27.01	4.3	5.00E-03	>55 $^{\circ}\text{C}$
GAO14	2.47E-04	27.69	5.0	1.00E-03	
GAO16	7.83E-05	33.97	5.6	1.00E-03	

As is shown in Table 16, the surface tensions of the new amphiphiles at CMC ( $\sigma_{\text{CMC}}$ ) are lower than the value for pure water, which is about 70 mN/m, indicating the good surface tension reducing ability of these samples. A reduction occurred for CMC values with the increase of the fatty chain length due to the higher lipophilicity of the compounds with longer chains, corresponding to the lower solubility in water (Figure 29 and 30). The high lipophilicity also lead a high cloud point > 55 $^{\circ}\text{C}$ . The pH value is positively correlated to the increase of fatty chain length from 3.9 (GAO6) to 5.6 (GAO16), but all in a range of weak acidic value.

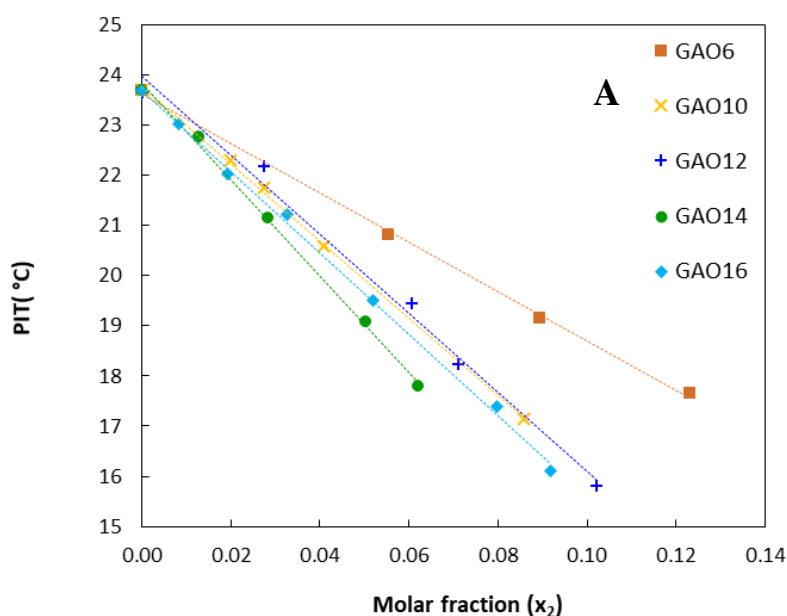


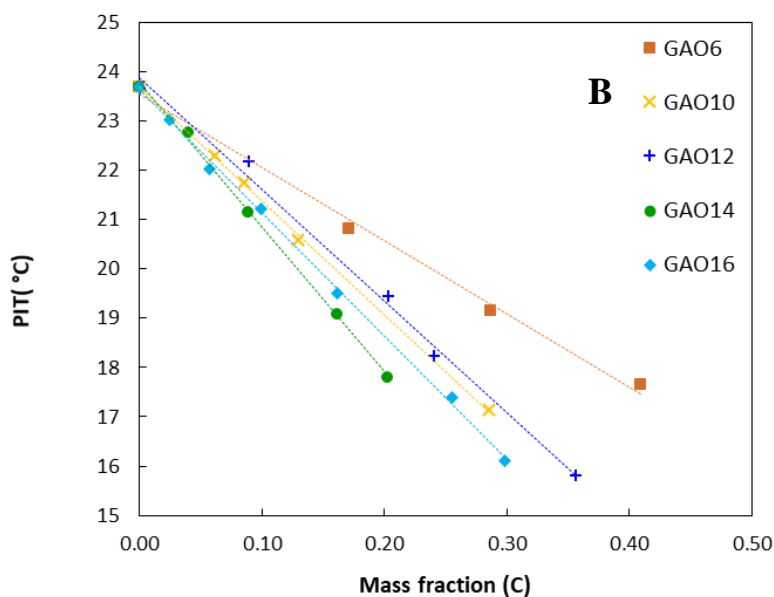
**Figure 29.** CMC of GAO series of surfactants.



**Figure 30.** The relation of CMC with chain length of GAO series of surfactants.

The HLB value of the samples were also investigated via PIT-slope method and the relation of Phase Inversion Temperature (PIT) with the molar fraction (Figure 31 A) and mass fraction (Figure 31B) in the system of 3% $C_{10}E_4/S_2/Octane/10^{-2}M NaCl$  at  $f_w = 0.5$ . ( $S_2$  refers to the surfactant we were evaluating) respectively. The slope of the fitting lines showed the increasing lipophilicity of the compounds with longer fatty chains. The comparison with the commercial surfactants will also be conducted.





**Figure 31.** Phase Inversion Temperature (PIT) vs. molar fraction  $x_2$  (A) or mass fraction C (B) for the system 3%  $C_{10}E_4/S_2/Octane/10^{-2}M NaCl$  at  $f_w = 0.5$ .  $S_2 = GAO6$  (■); GAO10 (×); GAO12 (+); GAO14 (●); GAO16 (◆). Lines indicate linear fitting leading to  $dPIT/dx_2$  or  $dPIT/dC$ .

The primary results of the already examined new compounds showed their good surface tension reducing ability and the higher lipophilicity with the increasing length of the alkyl chain. Further investigations on the full family of products, including hydrogenated ones and those derived from acrylamides are still in progress.

### 2.3.5 Conclusion

In this section, we proposed a new design of surfactant prepared from glyoxylic acid with acrylates and acrylamides via MBH reaction. Eco-friendly reaction conditions were developed, leading to the desired products in moderate to good yields. The structural variations include the O or N systems arising from acrylates or acrylamides, the alkyl chain length, and the presence of the double bond or not. The interfacial properties were examined by our colleagues in CISCO-UCCS lab in Lille. The preliminary results showed their potential application as surfactants. A more detailed prediction of their utilization will be defined after further characterization and study of the full family.

## **Chapter III**

# **Carbohydrate based amphiphiles: synthesis and properties of liquid crystalline glyco steroids**





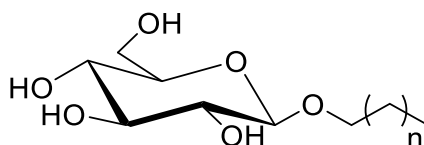
## Chapter III Carbohydrate based amphiphiles: synthesis and properties of liquid crystalline glycosteroids

*This section is related to a collaborative work between our lab and the team of Prof John W. Goodby at the University of York, UK, and will be included in a paper which is under preparation* <sup>[228]</sup>

cite :Fahima Ali-Rachedi, Nuno M. Xavier, Xiaoyang Yue, Mohammed Ahmar,, Stéphane Chambert, Xianbing Zeng, Richard J. Mandle, Stephen J. Cowling, Yves Queneau \* and John W. Goodby \*, in preparation.

### 3.1 Introduction

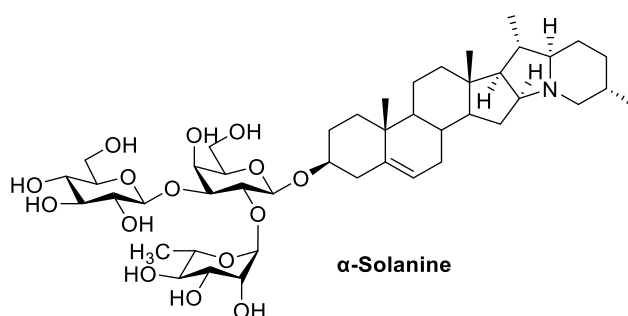
The physicochemical investigations of carbohydrate amphiphiles not only include the surfactants aspects but can also include their ability to behave as liquid crystals. This phenomenon, though not fully understood, was first observed by Emil Fischer and Burckhart Helferich <sup>[229]</sup> during their study on the melting behavior of *n*-hexadecyl  $\beta$ -D-glucopyranoside (Figure 32) which began to soften at 78°C, but melted finally as a clear fluid only when heated at about 145°C. <sup>[230]</sup> The reason for this “double melting” was related to a liquid crystalline behavior only in 1938 when Noller and Rockwell studied alkyl  $\beta$ -D-glucopyranosides. <sup>[231]</sup>



**Alkyl  $\beta$ -D-glucopyranoside**

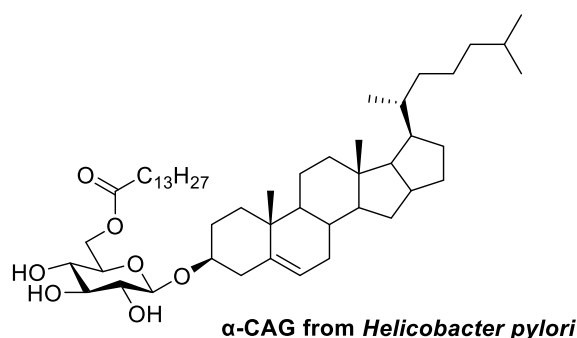
**Figure 32:** Structure of the alkyl  $\beta$ -D-glucopyranosides

Among natural amphiphilic carbohydrate compounds, solanine is one of the earliest one to be investigated for its liquid crystal behavior. Solanin is a common poison found in nightshade plants family (solanaceae). Its role is to protect the plants themselves from pests. Solanine (Figure 33) is a glycoesteroid with a dichotomous structure which has been found to form thermotropic liquid crystals.<sup>[232, 233]</sup>



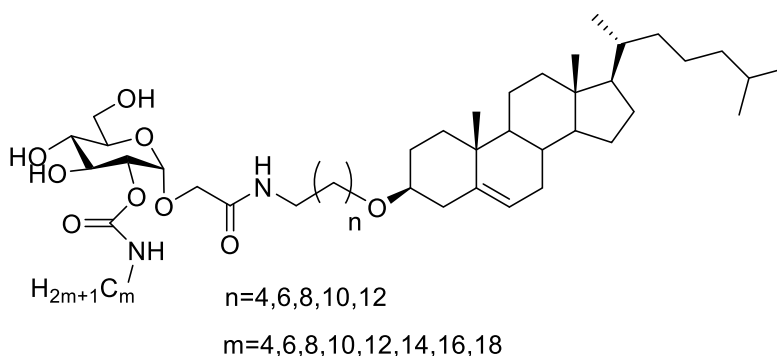
**Figure 33:** Structure of  $\alpha$ -solanine

Actually, glycoesteroids are a wide family of natural products like saponins found in many vegetals. Some are also found in bacteria, such as  $\alpha$ -CAG (Figure 34) present in the cell membrane of *Helicobacter pylori*, a bacterial species causing diseases of the digestive tract.<sup>[234]</sup>  $\alpha$ -CAG possesses a hydrophilic carbohydrate moiety, a hydrophobic steroid part and a fatty chain, leading a trichotomous structure, responsible for its thermotropic liquid crystal behavior. Recently, Dr. Zonglong Yang prepared a series of  $\alpha$ -CAG analogs with different chain length, anomeric configuration in glucose and galactose series and investigated their ability to form thermotropic mesophases in collaboration with Prof. John W. Goodby and Dr. Stephen J. Cowling in the University York, UK.<sup>[235]</sup>



**Figure 34:** Structure of  $\alpha$ -CAG from *Helicobacter pylori*

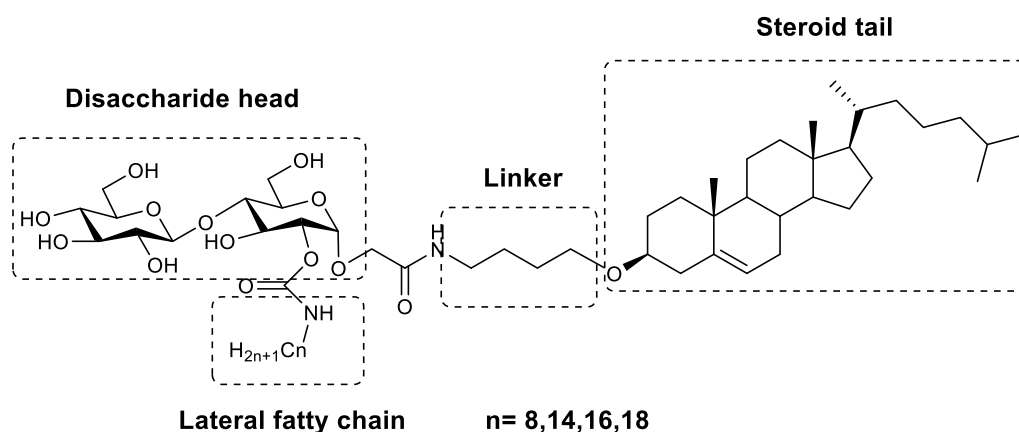
Generally, the introduction of a flexible spacer between the two inflexible fragments lowers the transition temperature of glyco steroid by increasing the flexibility, beneficial for achieving the self-assembling phenomenon even at room temperature. This was investigated further using another family of compounds exhibiting a trichotomous structure, comprising a glucose head and a steroidal parts linked by methylene spacers of various length, and a lateral hydrophobic side chain. In order to investigate the influence of each block on the thermotropic properties (within a collaborative project with Prof. John Goodby and Dr. Stephen J.Cowling in the University York, UK), a series of analogs were synthesized by Dr. Rui Xu in our lab (Figure 35). The melting behavior of this family of amphiphiles was investigated, showing the formation of several types of self-assembled architectures. A consistent change of the thermal stability of the mesophases (transition temperature) with respect to the fatty chain length was observed. [236]



**Figure 35:** Structure of glycolipids of Dr. Rui Xu's work

The work was then extended to disaccharidic systems (Figure 36). While most of the investigations had been achieved by Dr. Rui Xu, a few compounds had to be resynthesized for repeating some physicochemical assays. This additional synthetic task has been entrusted to me as a parallel project in my PhD work.

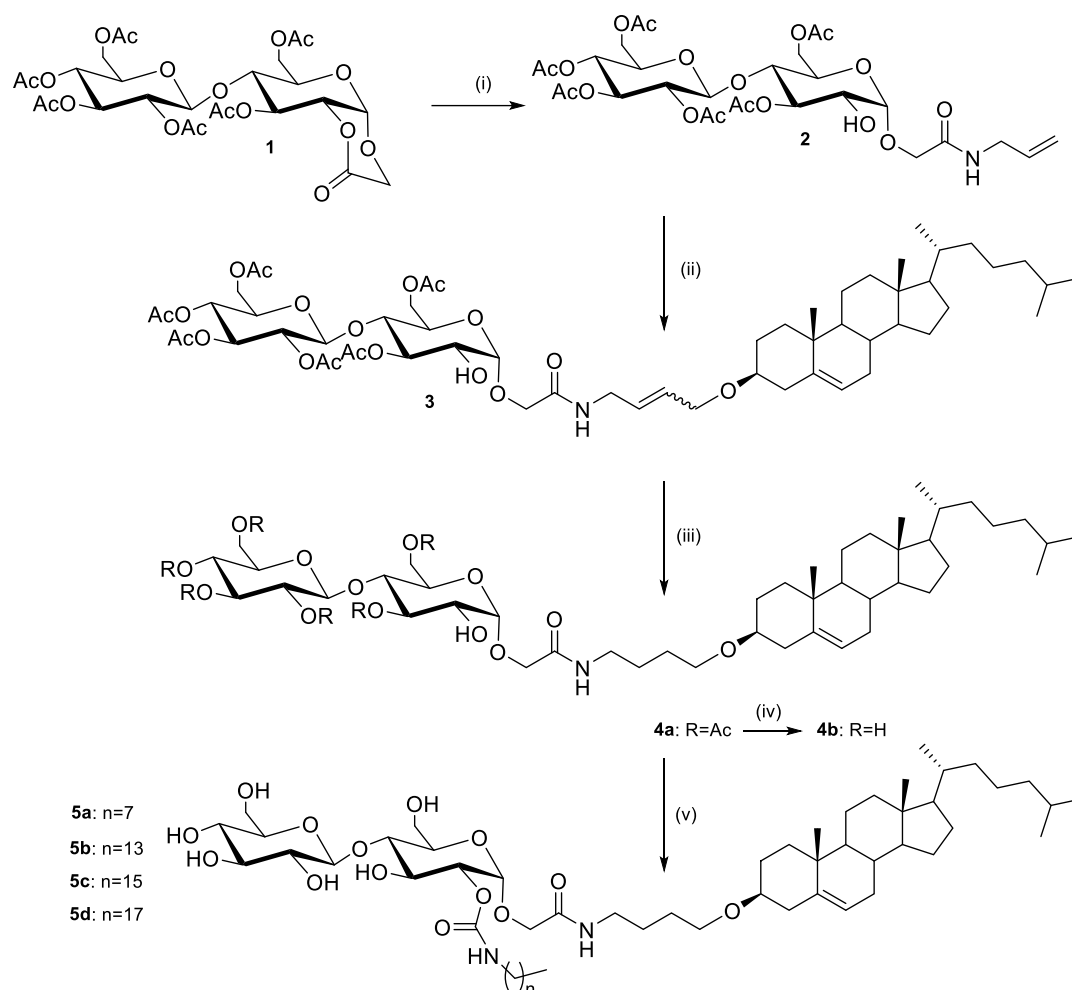
In this chapter, I describe first the synthetic aspects toward the glycoesters, for which I followed the procedures optimized by Dr. Rui Xu and Dr Fahima Ali-Rachedi. Then, I give a few elements on the physicochemical studies performed by the colleagues in York, and still ongoing, notably the mesomorphic properties of the resulting materials characterized by thermal optical microscopy, differential scanning calorimetry, and X-ray diffraction.



**Figure 36:** Structure of target disaccharidic glycoesters in this work

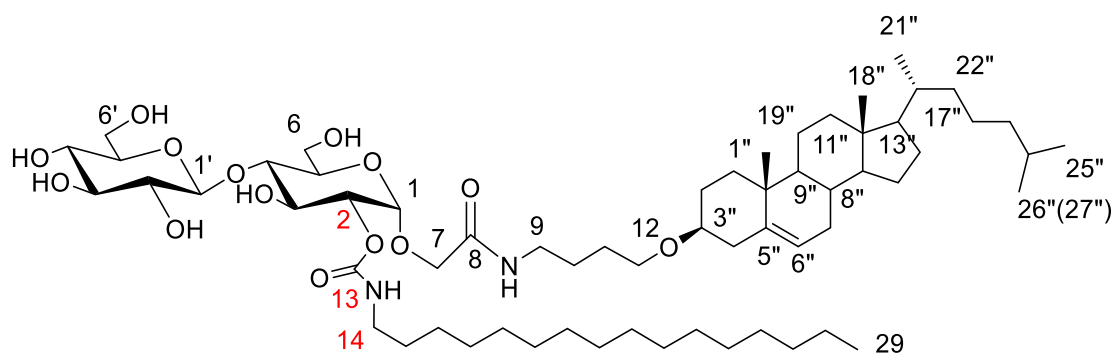
### 3.2 Synthesis and identification of the disaccharidic glycoesters

The series of disaccharidic glycoesters targeted for this study were synthesized as shown in Scheme 75 following a similar strategy as the one developed for the synthesis of the corresponding monosaccharidic structures <sup>[236, 237]</sup>. The starting point is the disaccharidic carbohydrate lactone 1 <sup>[238]</sup> prepared from the highly available disaccharide cellobiose, the disaccharidic glucosyl- $\beta$ -1,4-glucosyl repeating unit found in cellulose. Addition of allylamine to lactone 1 gave the allylamide 2 which was submitted to olefin cross-metathesis with allyl cholesteryl ether <sup>[239]</sup> as key connecting step leading the glycoester 3 having an unsaturated butenyl spacer between the carbohydrate and the steroid moieties. Selective hydrogenation of this butenyl spacer led to intermediate 4a. This latter could be either directly deacetylated to give the unprotected cellobiose adduct 4b, or, possessing a single hydroxyl function at position 2, transformed to urethanes 5a-d by reaction of OH-2 with alkyl isocyanates of different chain lengths and subsequent deprotection of the acetyl groups 5a-d.

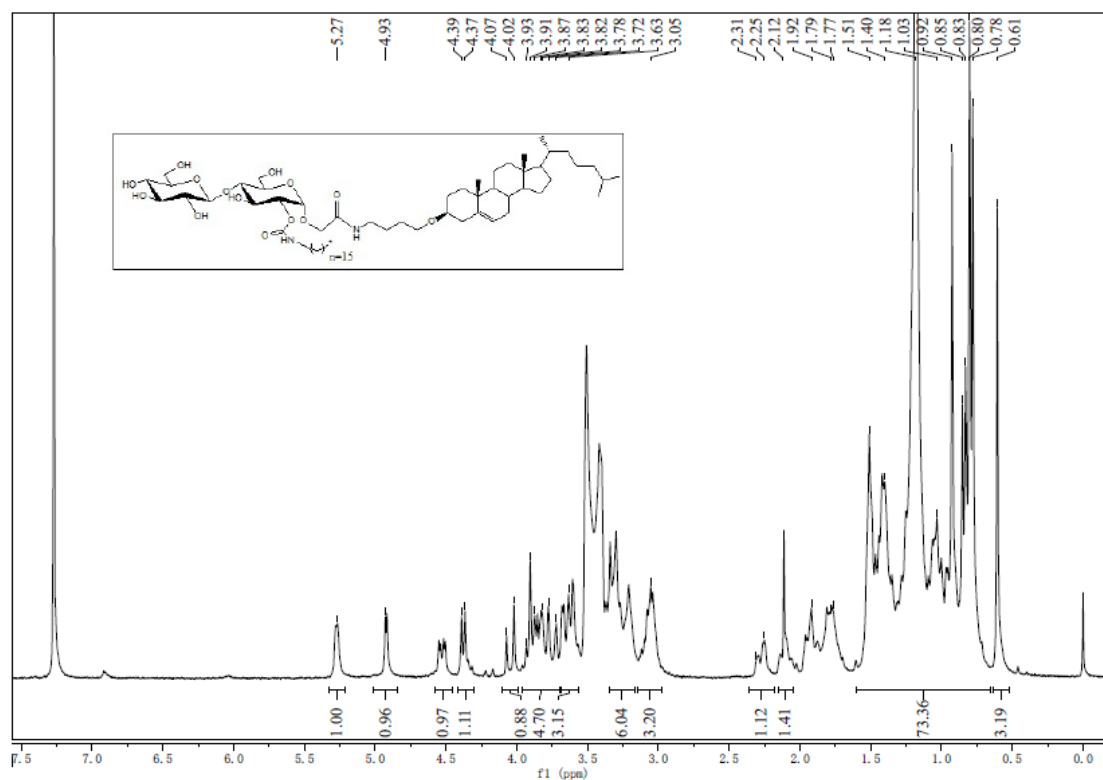


**Scheme 75:** Synthesis of the target disaccharidic glycoesters. Reagents and conditions: (i) allylamine,  $\text{CH}_2\text{Cl}_2$ , 24h, RT, 96%; (ii) Allyl cholesterol ether, 5% Grubbs-Hoveyda II,  $\text{CH}_2\text{Cl}_2$ , 24h, RT, 63%; (iii)  $\text{H}_2$ , Pd/C, THF, 1h, RT, 95%; (iv) MeOH/ $\text{NEt}_3$ / $\text{H}_2\text{O}$  (8/1/1, v/v), 3h, 40°C, 92%; (v) 1) alkyl isocyanate, DBU,  $\text{CH}_2\text{Cl}_2$ , 3 days, RT, 2) MeOH/ $\text{NEt}_3$ / $\text{H}_2\text{O}$  (8/1/1, v/v), 3h, 40°C, 50-65% from 4a.

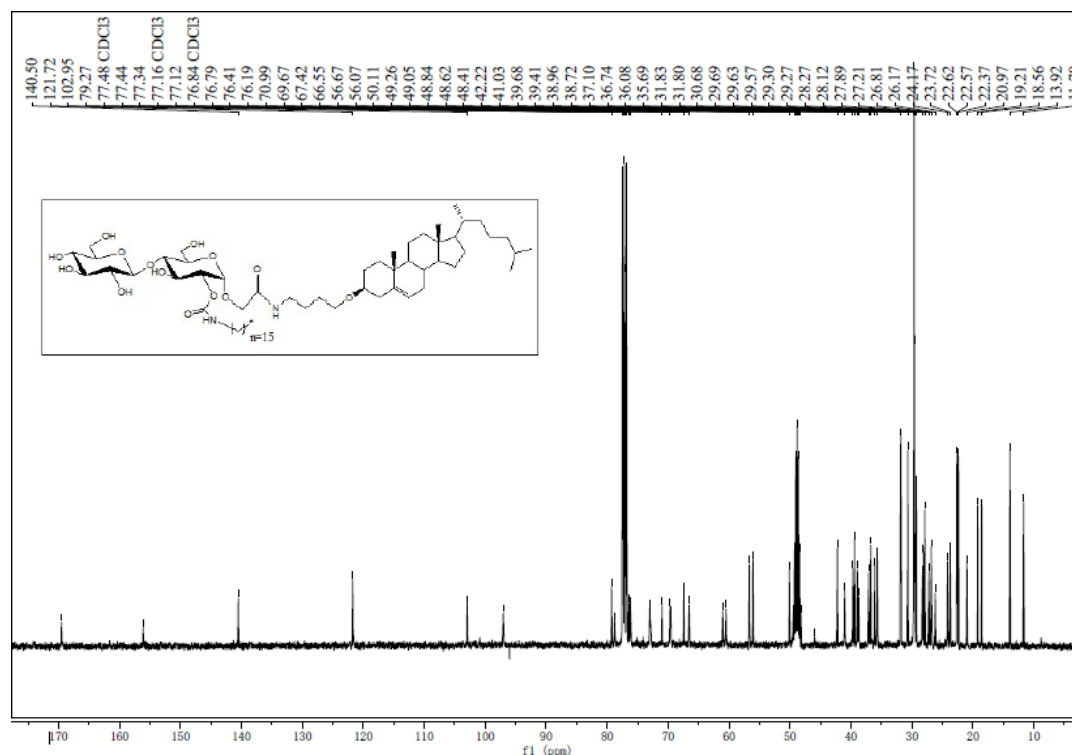
The structure of the target products was characterized using NMR and HR-MS spectroscopy. Here we use compound 5c ( $n=16$ ) (Figure 37) as an example for explaining how of the structure of products was confirmed. In the  $^1\text{H}$ NMR spectrum in Figure 38, the signal corresponding to the proton H-1 is found at  $\delta 4.92$  with a coupling constant value  $J=3.7$ , indicating an  $\alpha$ -glycosidic connection between the sugar part and methylene linker part. The signals corresponding to the other parts of the disaccharide and the steroid part are rather complex but are consistent with what is expected, notably when compared to the more simple monosaccharidic systems previously synthesized, which was further confirmed by HR-MS spectroscopy.



**Figure 37.** Structure of compound 5c



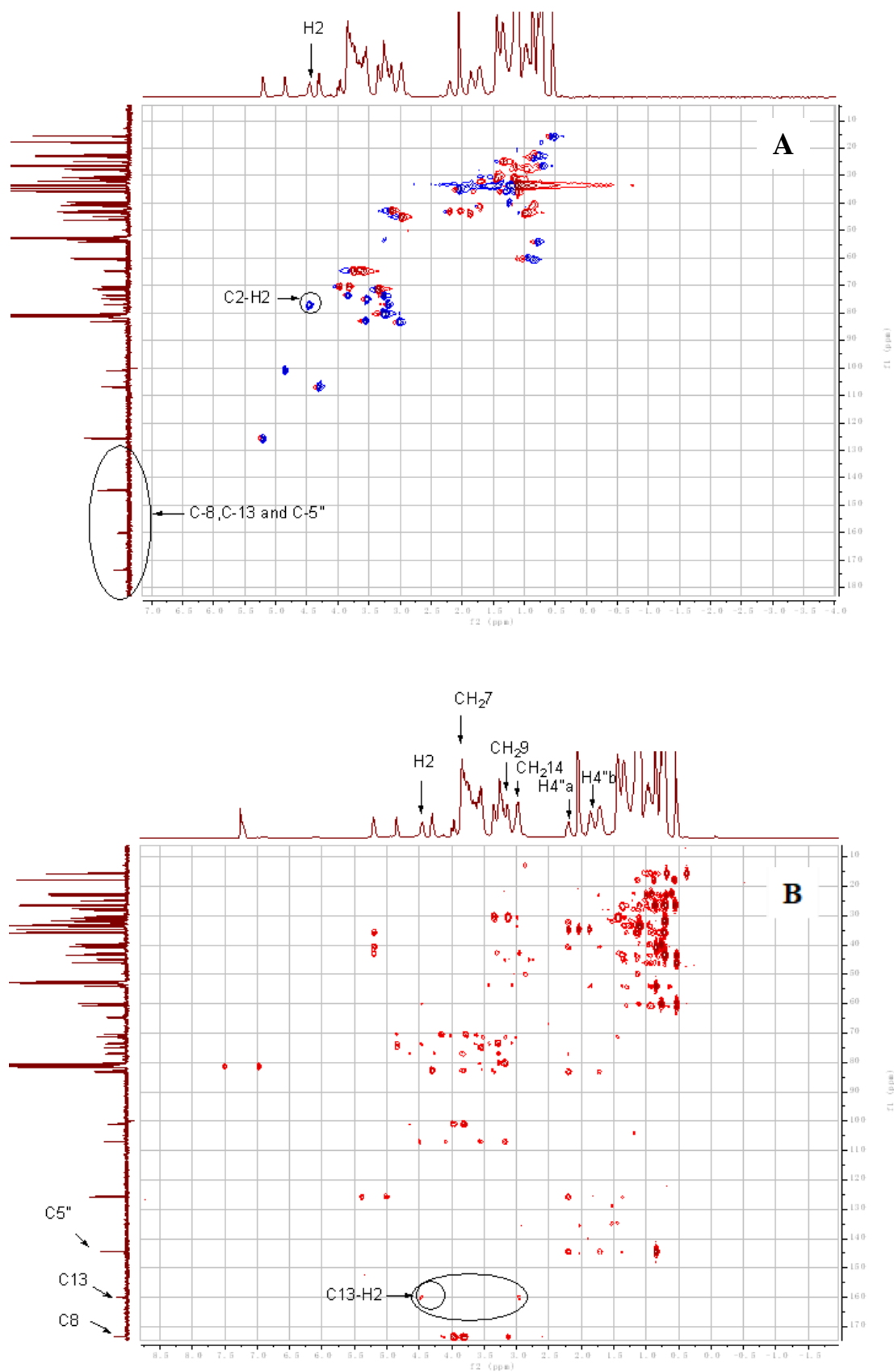
**Figure 38.**  $^1\text{H}$ NMR- spectrum of compound 5c



**Figure 39.**  $^{13}\text{C}$ NMR spectrum of compound **5c**

In the structure of the final compounds, the connection of the urethane chain at O-2 is ascertained by 2D NMR experiments. The HSQC and HMBC spectra of compound **5c** are shown in Figure 40 A and B. In the HSQC spectrum, the proton H2 could be identified at 4.52ppm which was correlated with the carbon C2 at  $\delta$ 73.02ppm. In the HMBC spectrum, both the protons of H2 and H14 were found to have interaction with the carbon atom signal at  $\delta$ 156.11 ppm, which is the signal of C13, the carbonyl group in the urethane group bearing the fatty chain. Therefore, we confirmed the connection position between the fatty chain and the sugar part.

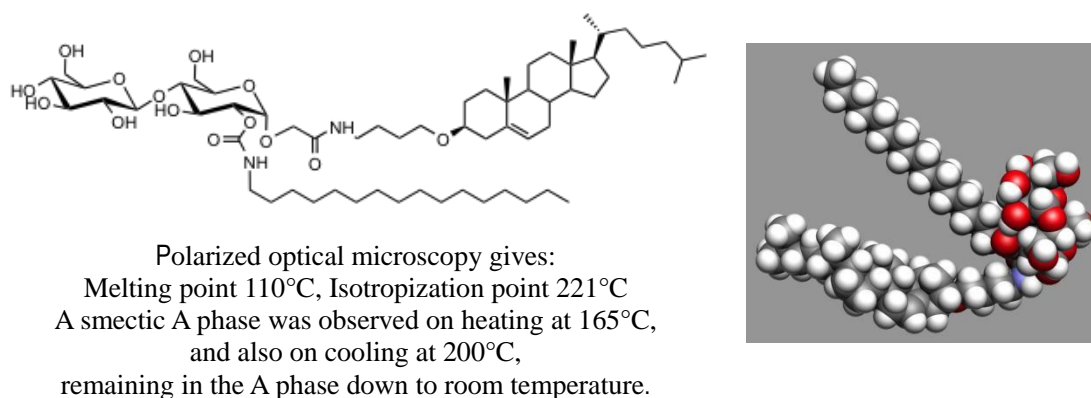




**Figure 40.** 2DNMR spectra of compound 5c: A. HSQC, B. HMBC

### 3.3 Some elements on the physicochemical properties

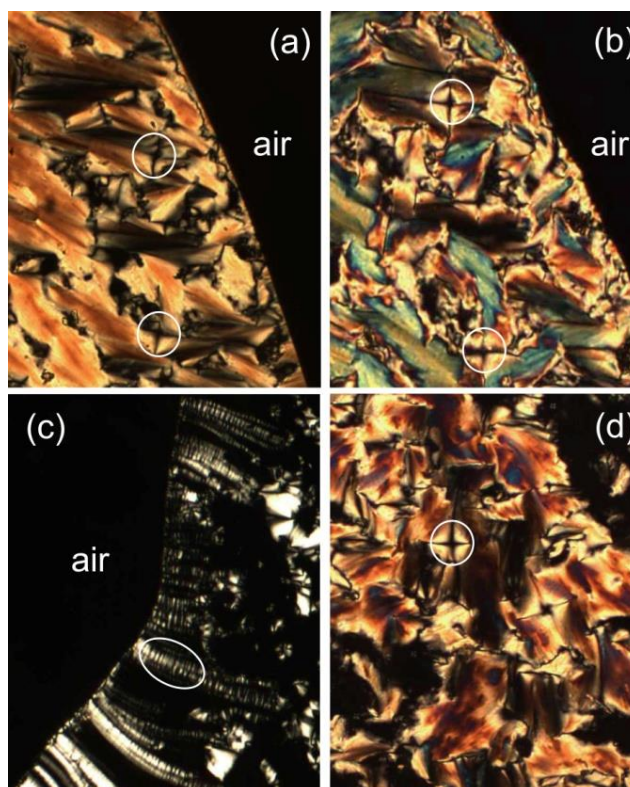
The experiments described in this section were handled by our colleagues of the Liquid Crystal group of the Materials Science Department at the University York and University Lyon 1. The initial investigation showed that the phase transitions are not reversible as predicted.<sup>[237]</sup> Moreover, for several homologues, the way how the mesophases rearrange is not reproducible on heating and cooling after the first transition to the liquid phase is achieved, although with chemical purity, as seen by significant changes in the polarized optical microscope and calorimetry characterization respectively. The transitions and phase types through X-ray diffraction (XRD) have obvious differences through microscopy. As a preliminary information on the ongoing studies, we can show some data concerning the hexadecyl substituted glycosteroidal amphiphile 5c. Figure 41 shows the structure and the minimized space filling architecture and shape of 5c determined by DFT calculations for a single molecule in a continuum, and its transitional phase behavior, checked with thermal microscopy. The amphiphile 5c began to melt to a smectic A phase at 110°C and further into an isotropic liquid at 221°C.



**Figure 41:** Structure and transition temperatures for glycosteroid 5c. The minimised geometries were optimised at the B3LYP/6-31G(d) level of DFT and ChemDraw 3D

The polarized light microscopy experiments showed that the first phase obtained at ~ 210°C is a lamellar phase, revealed by the existence of the focal-conic texture. The black crosses in the texture are also the proofs for the formation of a smectic A phase. Once cooling, the phase are more stable and remains no-change throughout the range of temperature at which the cube could form. It remains as down as room temperature and glassification occurred, as shown by the comparative textures in Figure 42 (a) at

170°C and Figure 42 (b) at room temperature. In addition, a homeotropic texture crossed with focal-conic strings was also found, as shown in Figure 42 (c). Such textures are typical for thermotropic and lyotropic phases of glyco- and phospho-lipids. After several hours at room temperature, the glassified liquid crystal phase retained its defect textures, as shown in Figure 42 (d), which clearly displayed the focal-conic and homeotropic domains.



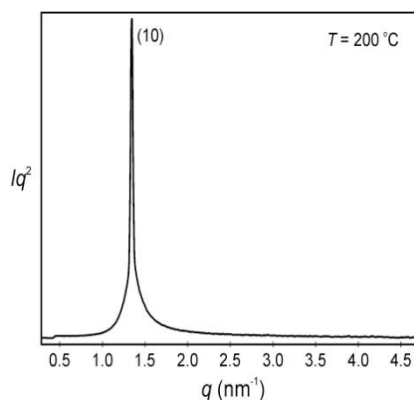
**Figure 42:** Defect textures (x100) formed by glyco-steroid **5c** under crossed polars in transmission optical microscopy. (a) The focal-conic texture (an ellipse and hyperbola are circled) obtained upon cooling at 171°C; (b) the same area, still exhibiting focal-conic defects (circled) at room temperature; (c) the homeotropic and focal-conic (oval ring) textures at the mesophase-air interface at 170°C; and (d) the glassified focal-conic (circled) texture at room temperature after a period of several hours.

The phase behaviour and mesophase structures were investigated through small angle X-ray scattering (SAXS) by the following procedure: first taking data at 10°C intervals on heating and at the extremes of the temperature ranges of the various phases, and then analyzing the data with respect to the mesophase structure. During the process from solid to a lamellar phase, a cubic phase was observed formed at 174 °C, with a lattice parameter of  $a_{\text{cub}} = 12.10$  nm decreasing to 11.73 nm at 190 °C.

For the next lamellar phase, the spacing of layer “*d*” was 4.67 nm. A phase transition to lamellar phase could occur at a temperature over 190°C for glyco steroid 5c. As shown in Figure 43 and Table 17, a unique signal (10) of SAXS results could be observed at 200°C. A spacing of  $d = 4.67$  nm was obtained, which corresponds to the phase transition.

**Table 17:** Experimental and calculated *d*-spacing of the observed SAXS reflection of the lamellar phase in glyco steroid 5c at 200°C.

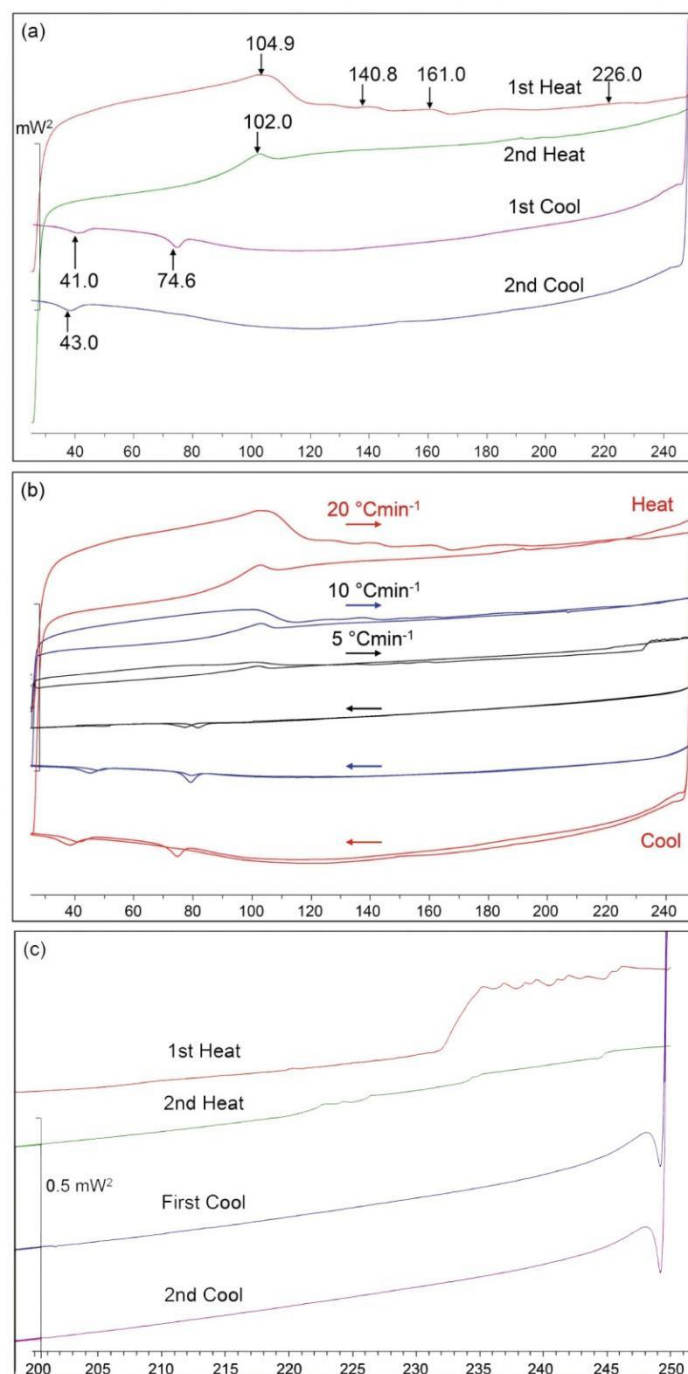
( <i>hk</i> )	<i>d</i> <sub>obs.</sub> – spacing (nm)	<i>d</i> <sub>cal.</sub> – spacing (nm)	intensity	Phase
(10)	4.67	4.67	100.0	$\pi$
$d = 4.67$ nm				



**Figure 43:** Powder diffraction pattern of the lamellar phase recorded at 200°C for glyco steroid 5c.

In order to confirm the reproducibility of the results above and the thermal stability of the materials in this section, the synthesis of glyco steroid 5c was repeated but the results from chemical and physical characterization were still same. Moreover, the X-ray diffraction studies performed on different instruments also showed similar patterns with sharp diffraction peaks, indicating that the two materials were identical, pure and stable even at high temperatures.

Differential scanning calorimetry (DSC) was also conducted to investigate the effect of the rate for heating and cooling on the phasic behaviors. While the thermograms appeared to be of poor quality, they however correlated with the materials prepared, i.e. transition temperatures, and observed thermal decomposition, which was very little. The first thermogram given in Figure 44 (a) shows first and second heating and cooling traces taken at rate of 20°C min<sup>-1</sup>.



**Figure 44:** Differential scanning calorimetric thermograms ( $\text{mW}^2/\text{°C}$ ) for the hexadecyl substituted (**6**,  $n = 16$ ) glycosteroidal bolaphile. (a) Shows first and second heating and cooling traces taken at rates of  $20\text{°Cmin}^{-1}$ ; (b) Shows scans taken at 20, 10 and  $5\text{°C min}^{-1}$  on the first and second heating and cooling cycles; and (c) Shows an expansion of figure 44(b) near to the clearing point for glycosteroid 5c.

The melting points for both heating are similar and thus reproducible, but the value of the enthalpy for the second cycle was smaller. The cooling cycles showed some differences in the recrystallisation processes: the first cooling cycle showed two

transition processes and two crystals could be formed, whereas for the second cooling only the lower temperature solid phase was observed. The temperature for the solidification was about 43°C, higher than room temperature, indicating the solid form of the material in the room temperature microscopy studies described above.

The second thermogram in Figure 44 (b) shows the scans taken with rates of 20, 10 and 5°C min<sup>-1</sup> on all the heating and cooling cycles respectively. These studies show that kinetic behavior could affect the phase transitions. The faster scan rates showing the reproducible behavior for the solidification process, whereas the slowest scan shows that the lower temperature solid form does not appear, and there is variation in the temperature of the first solidification process. The first heating scan at 5°C min<sup>-1</sup> differs from the faster scans because there is a step in the baseline at the clearing point transition. An expansion of this trace is shown in Figure 44 (c) and the baseline smoothly approaches the transition with fluctuations due to pan settling occurring in the liquid state once the transition was complete. Such fluctuations, and step in the baseline, do not occur for the other scan rates shown in Figure 44 (c). The cooling cycles, however, do not show any enthalpies associated with the liquid-to-liquid crystal phase transitions, indicating that the two phases have similar properties and structures.

Although the thermograms are not as clean as expected one for classical liquid crystal materials, the reproducibility of sample origin and the slight variations caused by kinetic processes suggest that the poor reversible baselines of cooling and heating cycles indicate the results are real and not affected by artefacts, and that the phase behaviors differ with temperatures.

### **3.4 Conclusion**

To summarize the work achieved until now, a family of glyco steroids was synthesized and the investigation of their melting behavior has resulted in evidences for the formation of mesophases. The studies of the physicochemical properties are close to completion in York, and their interpretation based on the whole series of compounds, discussing the concepts of liquid crystals vs soft-crystals is in progress.



# **General conclusions and perspectives**





## General conclusions and perspectives

In this thesis, two types of amphiphilic architectures in which the polar and non-polar parts come from renewable platform molecules or from biomolecules have been investigated. It involves the collaboration with two teams, one is the CISCO team of the UCCS lab in Lille led by Prof. Véronique Nardello-Rataj, and the other one is the team at the University of York led by Prof. John W. Goodby.

In a first part, we have investigated a novel family of surfactants arising from biobased furanic aldehydes such as HMF or GMF, or from the smaller C2 glyoxylic acid platform. We have proposed a new design relying on the connection of these aldehydes with activated alkenes via the atom economical Morita-Baylis-Hillman (MBH).

A first aspect has been the extension of the scope of the strategy to secondary *N*-alkyl acrylamides. Since such alkenes had nearly never been used in the MBH reaction, a complete methodological investigation was necessary.

The MBH reaction of secondary *N*-alkyl acrylamide could occur successfully using 1 equivalent of 3-HQD as promoter in 2-MeTHE/H<sub>2</sub>O (v/v=1/1) at room temperature. This optimal set of conditions could be applied to a wide scope of secondary *N*-alkyl acrylamides and aromatic aldehydes, giving new hydroxyamide-MBH adducts in fair to good yields. Our work demonstrated that the MBH reaction could be efficiently extended to secondary *N*-alkyl acrylamides, which were previously nearly unreported MBH substrates.

For the reaction of HMF and GMF as aldehydes with various substituted acrylamides, room temperature was fine for short chain alkyl acrylamides, whereas higher temperature up to 80°C could help to overcome the lower reactivity of long chain ones and achieve the desired MBH reactions. Among the biobased furanic surfactants, the HMF-amide ones showed a higher hydrophilicity over than ester ones as seen from PIT-slope values measured in Lille.

The second main purpose of our work on the MBH reaction in biobased chemistry has been about the utilization of glyoxylic acid as the aldehydic partner, and its application for designing new biobased surfactants for the first time.

Being never previously systematically studied, the reaction of glyoxylic acid with acrylates and acrylamides was fully investigated. Appropriate promoters / solvents couples were found to be effective. Using DABCO as promoter and EtOH as solvent allowed the reaction with acrylates, while 3-HQD as promoter and 2-MeTHF: H<sub>2</sub>O (v/v=1/1) as solvent was preferable for secondary *N*-alkyl acrylamides. Both systems were applied to synthesize two series of novel biobased surfactants in moderate to high yield from the commercial glyoxylic acid aqueous solution and various alkyl acrylates and secondary *N*-alkyl acrylamides. The preliminary evaluation of the physicochemical properties showed their good ability to lower surface tension, therefore to be promising surfactants.

It is important to stress that for both families, either arising from furanic aldehydes or glyoxylic acid, we have focused on finding mild and eco-friendly conditions. This is an additional advantage to that of the atom economy of the strategy and the biobased character of the substrates. The generality of the strategy can be extended to other applications, for example to other HMF derivatives to synthesize surfactants, or as potential monomers due to the presence of a polymerizable acrylic group in the MBH adducts.

In a second, shorter section, we have completed the synthesis of complex glycolipidic systems, dedicated to be studied with respect to their liquid crystalline properties. Here, the design is based on several biomolecular building blocks, a carbohydrate, a steroid and fatty chains. A series of “Janus” glycosteroids were prepared from cellobiose. Their condensed phases arising from their self-assembling ability during their melting is under investigation in York, with indication that these compounds are able to exhibit both liquid crystal and soft-solid phases properties.

Overall, this thesis provides several original results: one is the design of novel families of biobased amphiphiles, another is the demonstration that secondary *N*-alkyl acrylamides can be used as MBH substrates, a third one is the use of glyoxylic acid in MBH reactions. Two families of novel biobased surfactants were synthesized,

contributing to both the innovation in molecular design of surfactants, and the diversification of the use of platform molecules in fine chemistry.

Together with the final section on glycosteroidal glycolid analogs and their self-assembling properties, our results demonstrated the significant influence of amphiphilicity, a character which covers very diverse phenomena and applications in chemistry and biology.



# Experimental section



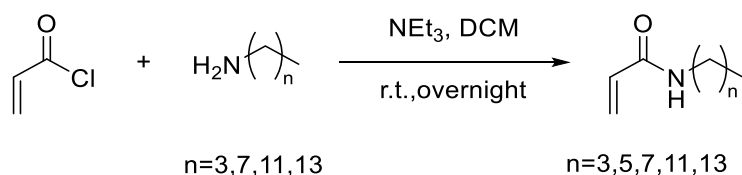
## Experimental section

### 1. General information

The reagents and solvents were purchased from Sigma-Aldrich, Alfa Aesar and TCI and utilized without any purification unless mentioned specifically. The solvents for the column chromatography were purchased from Carlo Erba company. The thin-layer chromatography (TLC) analysis was conducted on the aluminum-backed plates pre-coated 0.2mm silica gel 60. The flash chromatographies were performed using Merck Si 60 silica gel (40–63  $\mu\text{m}$ ).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker DRX-300 spectrometer ( $^1\text{H}$ : 300, 400 or 500 MHz;  $^{13}\text{C}$ : 75, 100 or 125 MHz). High-resolution mass spectra (HRMS) were recorded on Bruker MicroTOF-Q II XL spectrometer using ESI as ionization source. The procedure to investigate the physicochemical properties of surfactants follows the method in references.<sup>[61]</sup>

### 2. Synthesis of raw materials

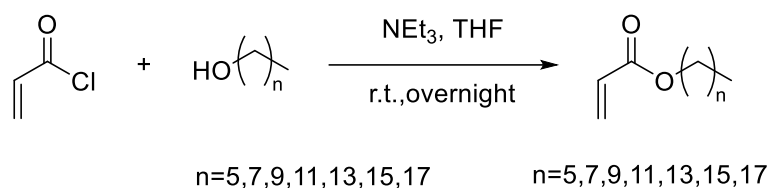
#### 2.1 Preparation of secondary *N*-alkyl acrylamides



Secondary *N*-alkyl acrylamides were prepared based on the methods on literature. In detail, *N*-alkyl acryl amine (12 mmol) and anhydrous triethylamine (12 mmol, 1.7 mL) were dissolved in anhydrous DCM (50 mL). Acryloyl chloride (10 mmol, 820  $\mu\text{L}$ ) was dripped slowly into the solution under  $0^\circ\text{C}$ . The reaction mixture was left to react overnight at room temperature. The solution was concentrated and dissolved again in ethyl acetate. The precipitate was removed by filtration and filtrate was concentrated. The obtained crude product was purified by column chromatography using mixture of EtOAc/Pentane (v/v=1/2) as eluent to yield the corresponding *N*-alkyl acrylamide.



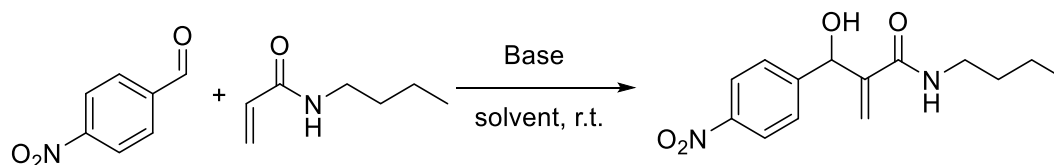
## 2.2 Preparation of alkyl acrylates



Alkyl acrylates were prepared based on the methods on literature. In detail, alkyl alcohol (10 mmol) and anhydrous triethylamine (10 mmol, 1.4 mL) were dissolved in anhydrous THF (50 mL). Acryloyl chloride (9 mmol, 730  $\mu$ L) was dripped slowly into the solution under 0°C. The reaction mixture was left to react overnight at room temperature. The precipitate was removed by filtration and filtrate was concentrated. The obtained crude product was purified by column chromatography using mixture of EtOAc/Pentane (v/v=5/95) as eluent to yield the corresponding alkyl acrylates.

## 3. Experimental section of the MBH reaction of secondary *N*-alkyl acrylamides

### 3.1 Optimization of MBH reaction of secondary *N*-alkyl acrylamides



4-Nitrobenzaldehyde (0.5mmol) and *N*-Butyl acrylamide (1mmol) were mixed in solvent and base (0.5mmol) was added into reaction system. NMR yields was calculated for these conditions screening reactions.

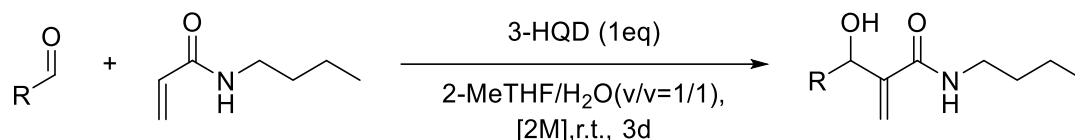
#### i). Calculation of NMR yield

The reaction mixture was transferred to a separating funnel with water and EtOAc, followed by the extraction with EtOAc (3  $\times$  30 mL). The organic layer consisted of MBH adduct, remaining 4-nitrobenzaldehyde and 4-nitrobenzyl alcohol. This organic layer was dried (over Na<sub>2</sub>SO<sub>4</sub>) and concentrated under vacuum and the obtained crude mixture was analyzed by <sup>1</sup>HNMR using 1, 2, 4, 5-tetramethylbenzene (1 equivalent) as internal standard and CDCl<sub>3</sub> was used as solvent to check NMR yield.

#### ii). Calculation of isolated yield

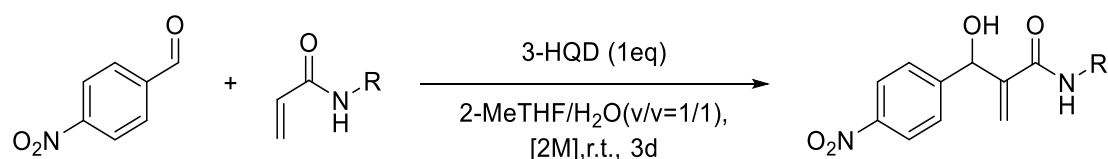
The reaction mixture was removed to a separating funnel with water and EtOAc , followed by the extraction with EtOAc (3 × 30 mL). The organic layer consisted of MBH adduct, remaining 4-nitrobenzaldehyde and 4-nitrobenzyl alcohol. This organic layer was dried (over Na<sub>2</sub>SO<sub>4</sub>) and concentrated under vacuum and the obtained crude mixture was purified by column chromatography using EtOAc/ Pentane (v/v=1/1) as eluent to obtain every isolated component separately. The aqueous layer was acidified with HCL (1 M), and extracted with EtOAc (3 × 30 mL). This organic layer was dried (over Na<sub>2</sub>SO<sub>4</sub>) and concentrated under vacuum to give 4-nitrobenzoic acid.

### 3.2 Procedure for the investigation of aldehyde scope



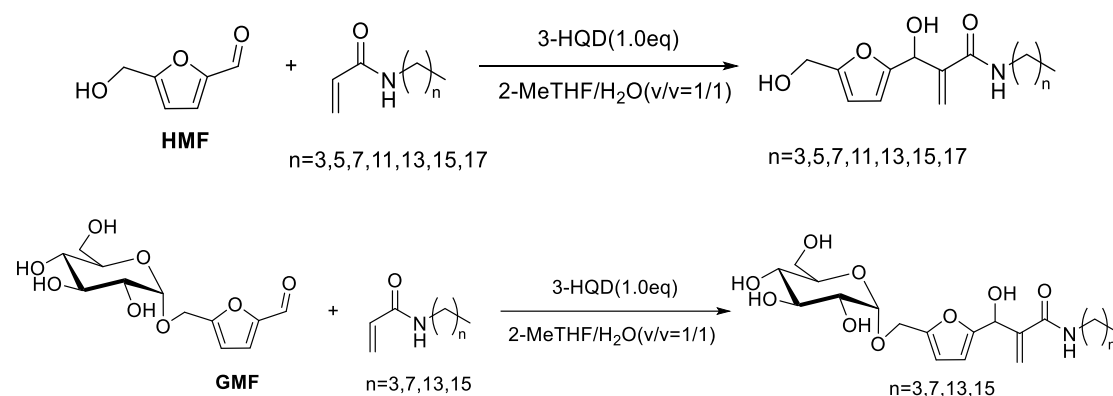
Aldehyde (1 mmol) and *N*-Butyl acrylamide (2 mmol) were mixed in 0.5 ml of 2-MeTHF/H<sub>2</sub>O (v/v=1/1) as solvent and 3-HQD (1 mmol) was added into reaction system. Treatment is followed the previous protocol for calculation of isolated yield in methodology section.

### 3.3 Procedure for the investigation of secondary *N*-alkyl acrylamide scope



4-Nitrobenzaldehyde (1mmol) and secondary *N*-alkyl acrylamide (2 mmol) were mixed in 0.5 ml of 2-MeTHF/H<sub>2</sub>O (v/v=1/1) as solvent and 3-HQD (1 mmol) was added into reaction system. Treatment is followed the previous protocol for calculation of isolated yield in methodology section.

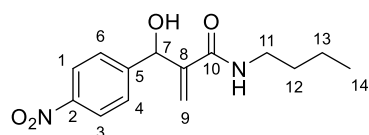
### 3.4 Procedure of MBH reaction of HMF or GMF with various secondary *N*-alkyl acrylamides



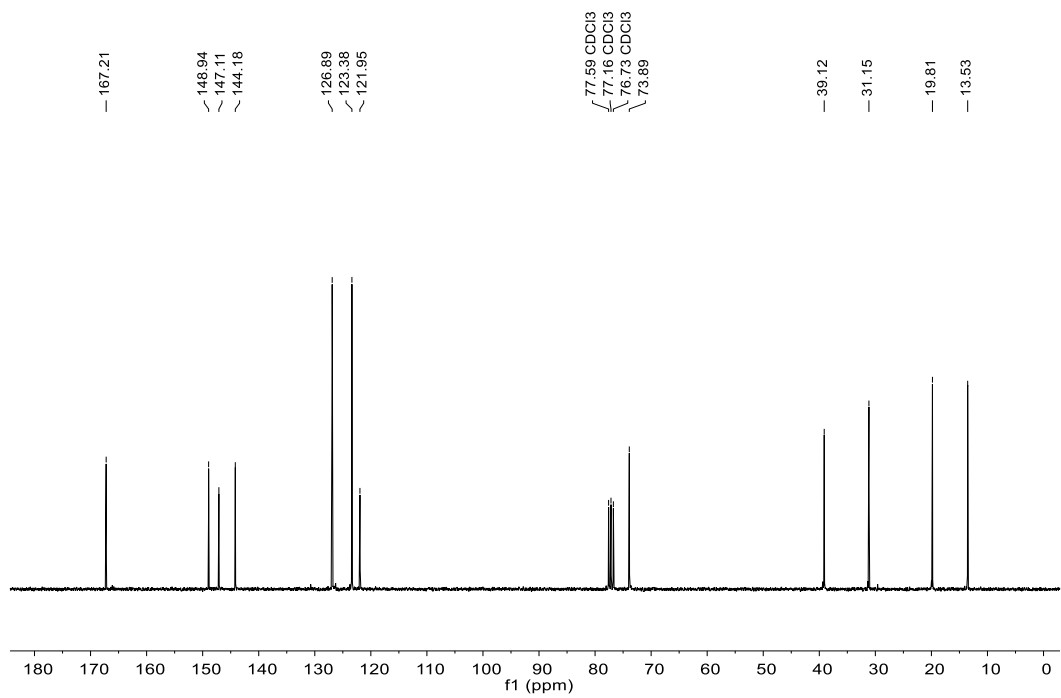
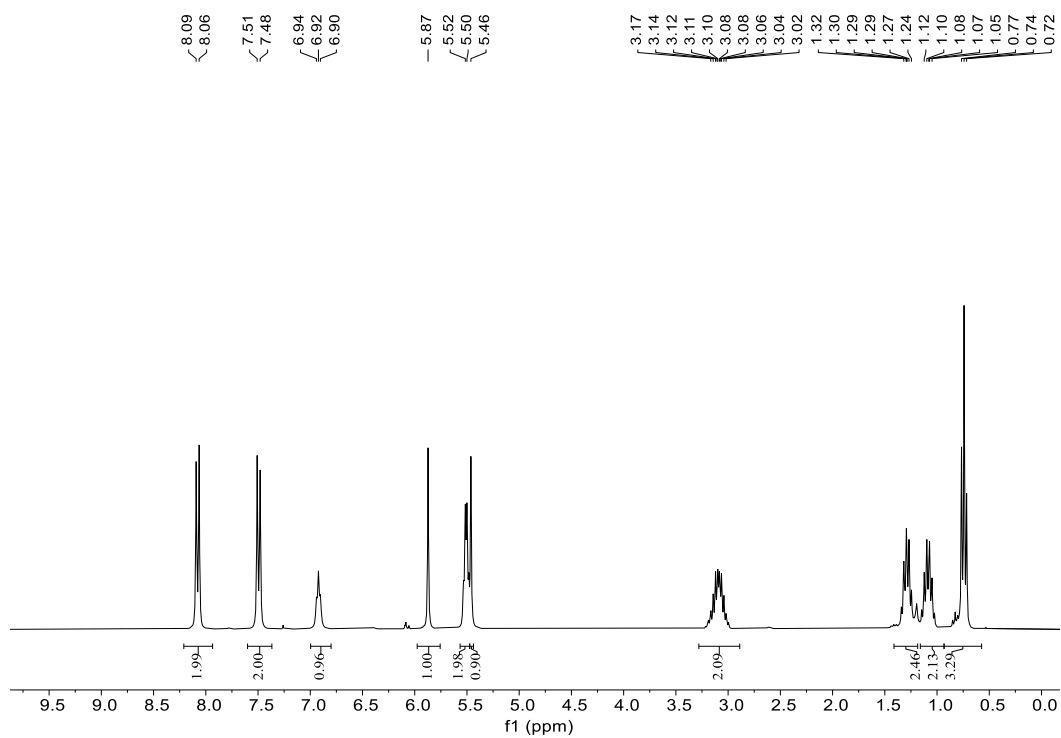
HMF/GMF (10mmol), 3-HQD (10mmol) were mixed in 5ml of 2-MeTHF/H<sub>2</sub>O (v/v=1/1) and the corresponding secondary *N*-alkyl acrylamide was added in reaction system under room temperature. After 3 days, the reaction mixture was added HCL (1M) and extracted with EtOAc (3 × 50 mL), the organic layer was washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. The obtained crude product was purified by flash column chromatography on silica gel with a eluent comprising EtOAc/ Pentane (v/v=1/1). (For the acrylamides n= 13,14,15,17, the reactions are realized at 80°C overnight.)

### 3.4 Characterization of MBH adducts

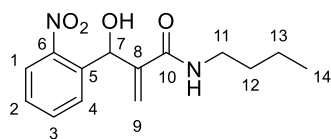
*N*-Butyl-2-[hydroxy(4-nitrophenyl)methyl]acrylamide (C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>)



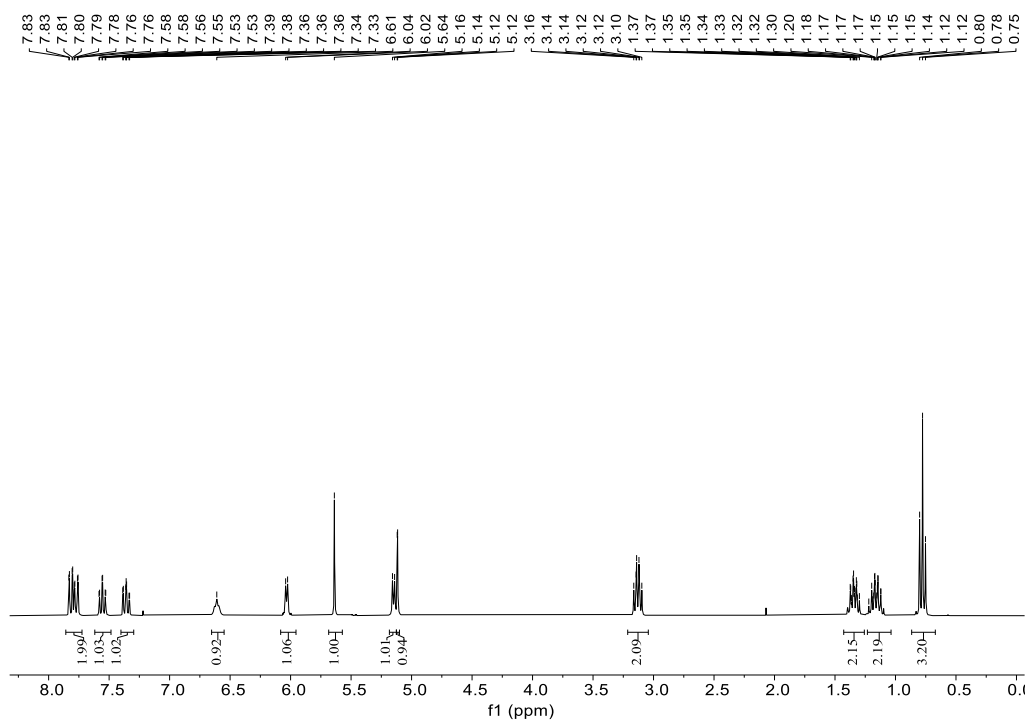
<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 8.08 (d, *J* = 8.7 Hz, 2H, H<sub>1</sub>, H<sub>3</sub>), 7.49 (d, *J* = 8.5 Hz, 2H, H<sub>4</sub>, H<sub>6</sub>), 6.92 (t, *J* = 5.7 Hz, 1H, NH), 5.87 (s, 1H, C=CH<sub>2</sub>), 5.51 (d, *J* = 4.6 Hz, 2H, CH-OH), 5.46 (s, 1H, C=CH<sub>2</sub>), 3.09 (dq, *J* = 10.5, 6.8 Hz, 2H, H<sub>11</sub>), 1.36 – 1.19 (m, 2H, H<sub>12</sub>), 1.18 – 0.99 (m, 2H, H<sub>13</sub>), 0.74 (t, *J* = 7.3 Hz, 3H, H<sub>14</sub>). <sup>13</sup>C NMR (75 MHz, Chloroform-*d*): δ 167.21 (C<sub>10</sub>), 148.94 (C<sub>5</sub>), 147.11 (C<sub>2</sub>), 144.18 (C<sub>8</sub>), 126.89 (C<sub>4</sub>, C<sub>6</sub>), 123.38 (C<sub>1</sub>, C<sub>3</sub>), 121.95 (C<sub>9</sub>), 73.89 (C<sub>7</sub>), 39.12 (C<sub>11</sub>), 31.15 (C<sub>12</sub>), 19.81 (C<sub>13</sub>), 13.53 (C<sub>14</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>NaO<sub>4</sub> 301.1159; Found 301.1165.

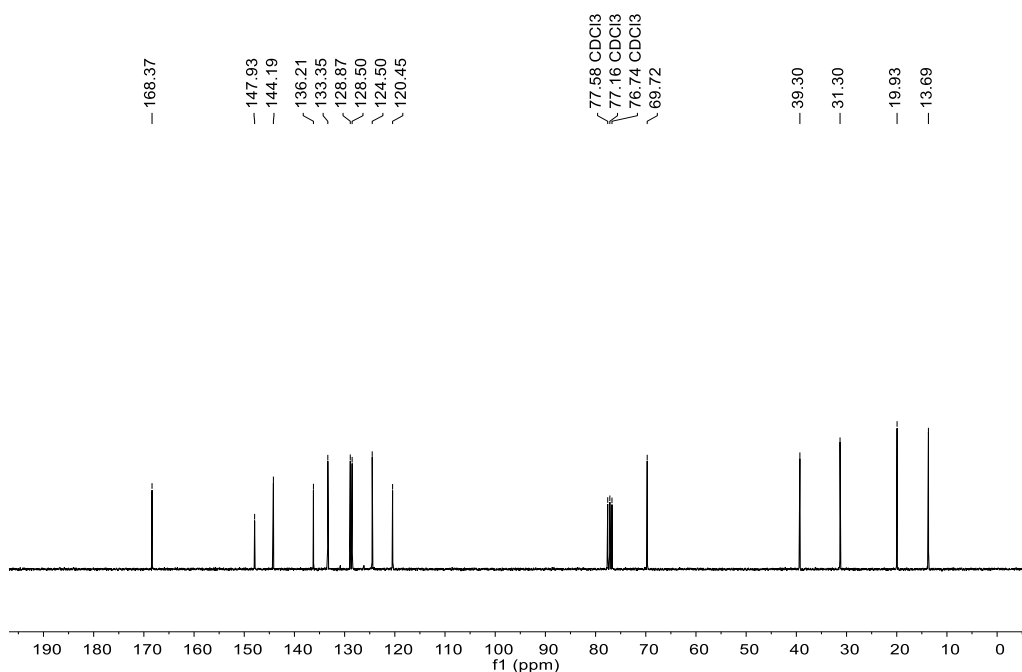


*N*-Butyl-2-[hydroxy(2-nitrophenyl)methyl]acrylamide (C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>)

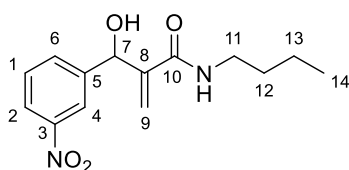


<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 7.79 (m, 2H, H<sub>1</sub>, H<sub>2</sub>), 7.56 (td, *J* = 7.6, 1.4 Hz, 1H, H<sub>3</sub>), 7.36 (m, 1H, H<sub>4</sub>), 6.61 (s, 1H, NH), 6.03 (d, *J* = 4.8 Hz, 1H, CH-OH), 5.64 (s, 1H C=CH<sub>2</sub>), 5.15 (d, *J* = 5.2 Hz, 1H, OH), 5.12 (d, *J* = 1.0 Hz, 1H C=CH<sub>2</sub>), 3.13 (td, *J* = 7.1, 5.8 Hz, 2H, H<sub>11</sub>), 1.44 – 1.28 (m, 2H, H<sub>12</sub>), 1.24 – 1.07 (m, 2H, H<sub>13</sub>), 0.78 (t, *J* = 7.3 Hz, 3H, H<sub>14</sub>). <sup>13</sup>C NMR (75 MHz, Chloroform-*d*): δ 168.37 (C<sub>10</sub>), 147.93 (C<sub>6</sub>), 144.19 (C<sub>8</sub>), 136.21 (C<sub>5</sub>), 133.35 (C<sub>3</sub>), 128.87 (C<sub>2</sub>), 128.50 (C<sub>4</sub>), 124.50 (C<sub>1</sub>), 120.45 (C<sub>9</sub>), 69.72 (C<sub>7</sub>), 39.30 (C<sub>11</sub>), 31.30 (C<sub>12</sub>), 19.93 (C<sub>13</sub>), 13.69 (C<sub>14</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>NaO<sub>4</sub> 301.1159; Found 301.1163.

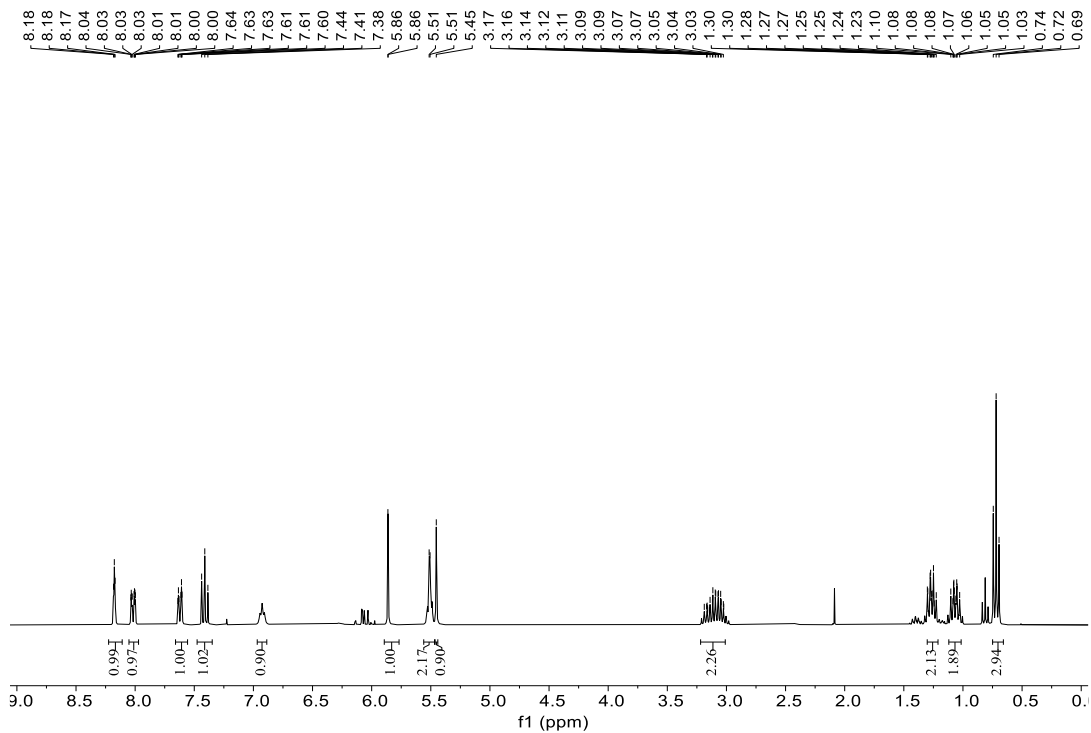




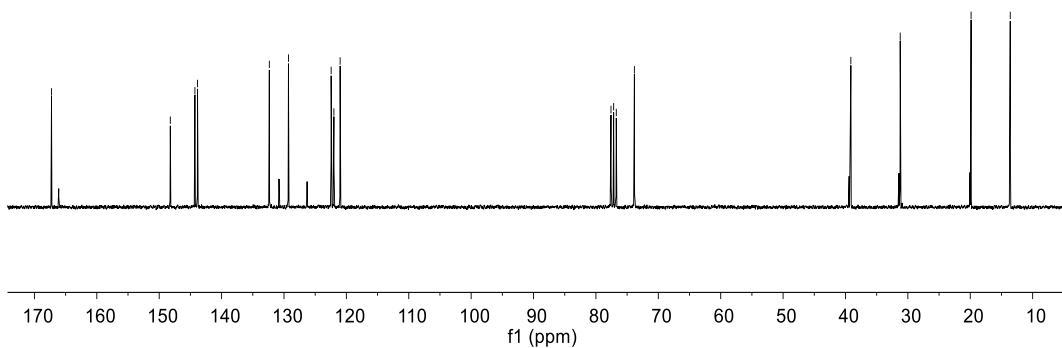
*N*-Butyl-2-[hydroxy(3-nitrophenyl)methyl]acrylamide (C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>)



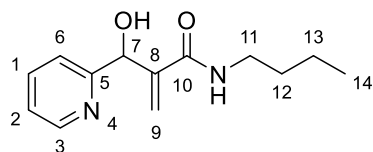
<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 8.18 (t, *J* = 2.0 Hz, 1H, H<sub>4</sub>), 8.02 (ddd, *J* = 8.2, 2.4, 1.1 Hz, 1H, H<sub>2</sub>), 7.62 (dt, *J* = 7.7, 1.4 Hz, 1H, H<sub>6</sub>), 7.41 (t, *J* = 7.9 Hz, 1H, H<sub>1</sub>), 6.93 (t, *J* = 5.8 Hz, 1H, NH), 5.90 – 5.82 (m, 1H, C=CH<sub>2</sub>, a), 5.51 (d, *J* = 2.3 Hz, 2H, CH-OH), 5.45 (s, 1H, C=CH<sub>2</sub>, b), 3.11 (dddd, *J* = 20.6, 13.6, 7.1, 5.7 Hz, 2H, H<sub>11</sub>), 1.36 – 1.20 (m, 2H, H<sub>12</sub>), 1.15 – 0.98 (m, 2H, H<sub>13</sub>), 0.72 (t, *J* = 7.3 Hz, 3H, H<sub>14</sub>). <sup>13</sup>C NMR (75 MHz, Chloroform-*d*): δ 167.26 (C<sub>10</sub>), 148.22 (C<sub>3</sub>), 144.28 (C<sub>8</sub>), 143.86 (C<sub>5</sub>), 132.35 (C<sub>6</sub>), 129.28 (C<sub>1</sub>), 122.44 (C<sub>4</sub>), 122.00 (C<sub>9</sub>), 121.00 (C<sub>2</sub>), 73.83 (C<sub>7</sub>), 39.14 (C<sub>11</sub>), 31.23 (C<sub>12</sub>), 19.87 (C<sub>13</sub>), 13.59 (C<sub>14</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>NaO<sub>4</sub> 301.1159; Found 301.1161.



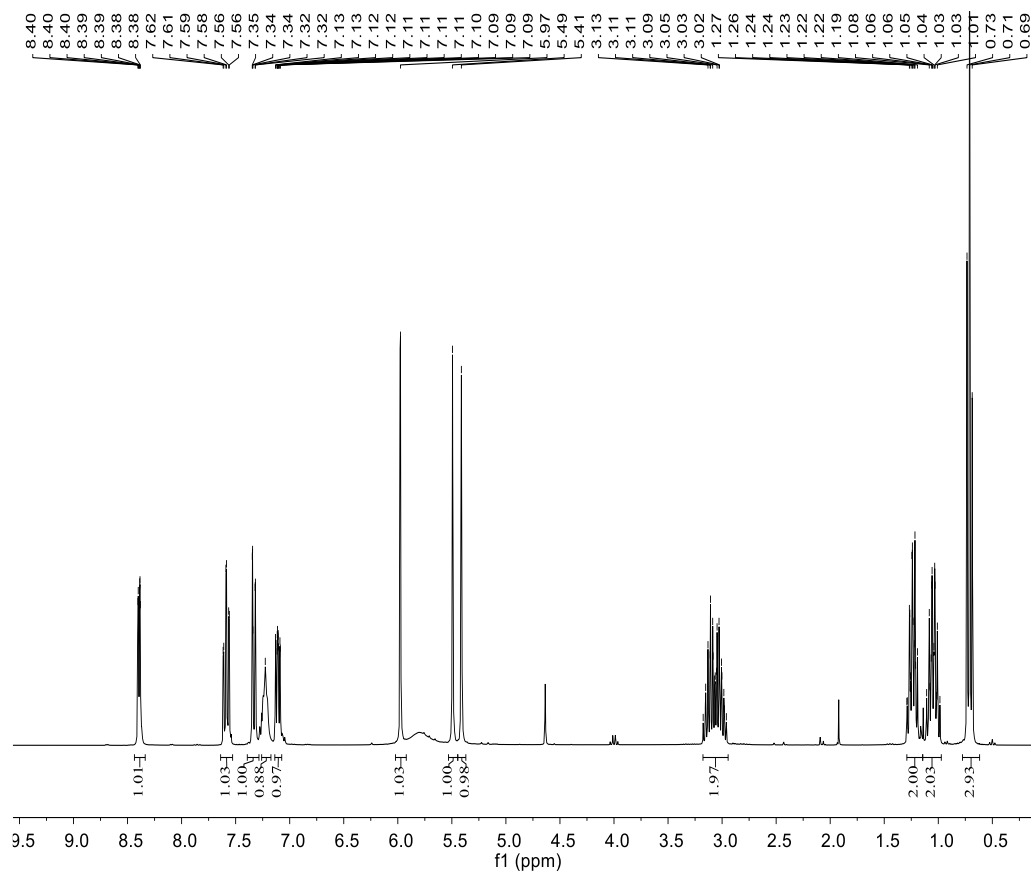
- 167.26
- 148.22
- 144.28
- 143.86
- 132.35
- 129.28
- 122.44
- 122.00
- 121.00
- 77.59 CDCl3
- 77.16 CDCl3
- 76.74 CDCl3
- 73.83
- 39.14
- 31.23
- 19.87
- 13.59



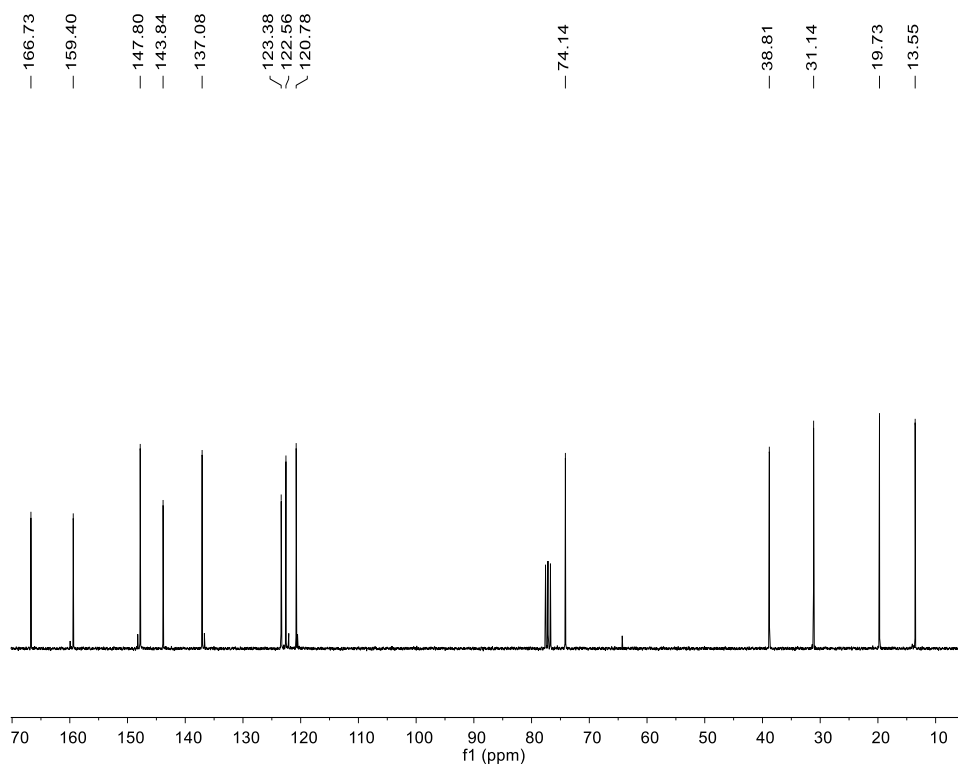
*N*-Butyl-2-[hydroxy(pyridin-2-yl)methyl]acrylamide (C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>)



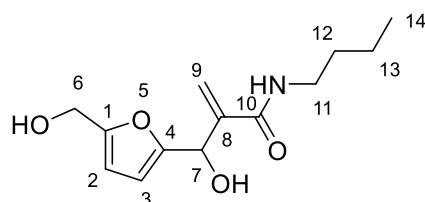
<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 8.41 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H, H<sub>3</sub>), 7.60 (td, *J* = 7.7, 1.7 Hz, 1H, H<sub>1</sub>), 7.35 (dq, *J* = 7.9, 1.0 Hz, 1H, H<sub>6</sub>), 7.25 (q, *J* = 5.3 Hz, 1H, NH), 7.12 (ddd, *J* = 7.5, 5.0, 1.2 Hz, 1H, H<sub>2</sub>), 5.99 (s, 1H, C=CH<sub>2</sub>), 5.51 (s, 1H, CH-OH), 5.43 (s, 1H, C=CH<sub>2</sub>), 3.22 – 2.95 (m, 2H, H<sub>11</sub>), 1.25 (dtd, *J* = 8.7, 7.0, 5.5 Hz, 2H, H<sub>12</sub>), 1.09 – 0.97 (m, 2H, H<sub>13</sub>), 0.73 (t, *J* = 7.2 Hz, 3H, H<sub>14</sub>): <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 166.73(C<sub>10</sub>), 159.40 (C<sub>5</sub>), 147.80 (C<sub>3</sub>), 143.84 (C<sub>8</sub>), 137.08 (C<sub>1</sub>), 123.38 (C<sub>9</sub>), 122.56 (C<sub>6</sub>), 120.78 (C<sub>2</sub>), 74.14 (C<sub>7</sub>), 38.81(C<sub>11</sub>), 31.14 (C<sub>12</sub>), 19.73(C<sub>13</sub>), 13.55(C<sub>14</sub>). HRMS (ESI) *m/z*: Calcd for [M+H]<sup>+</sup> C<sub>13</sub>H<sub>19</sub>N<sub>2</sub>O<sub>2</sub> 235.1441; Found 235.1440.



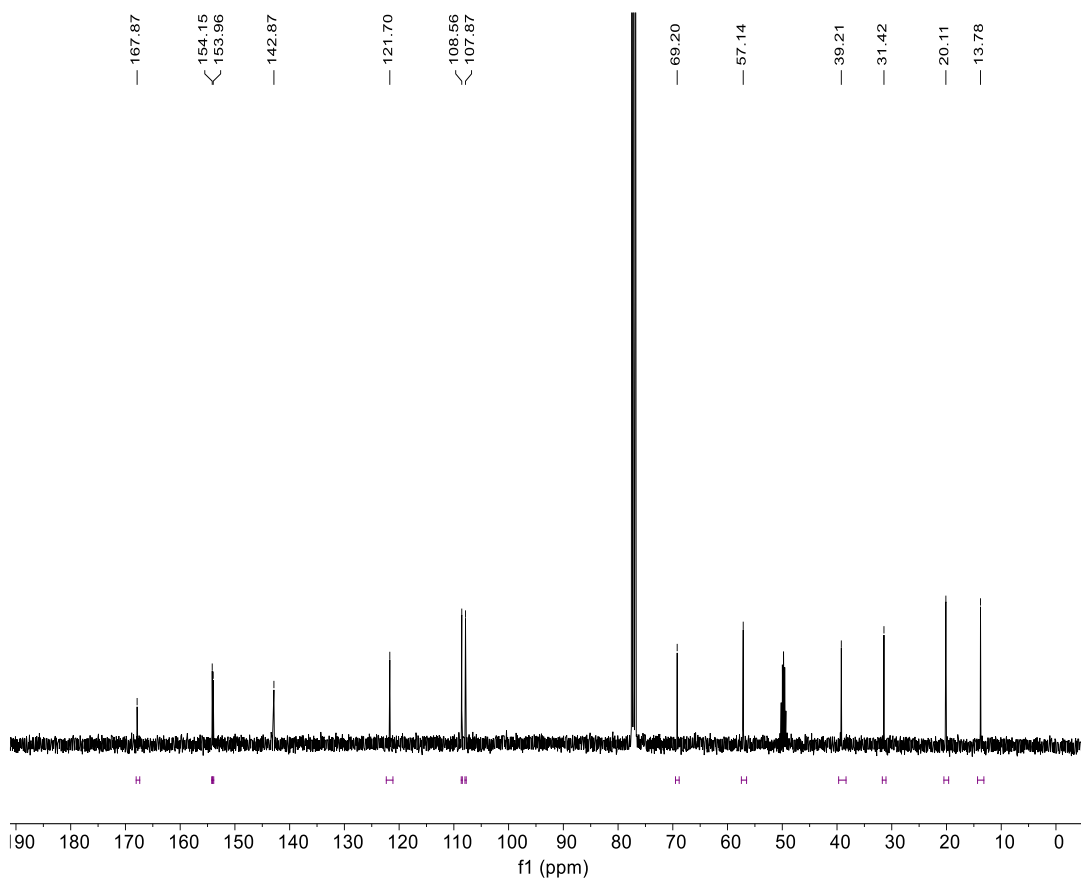
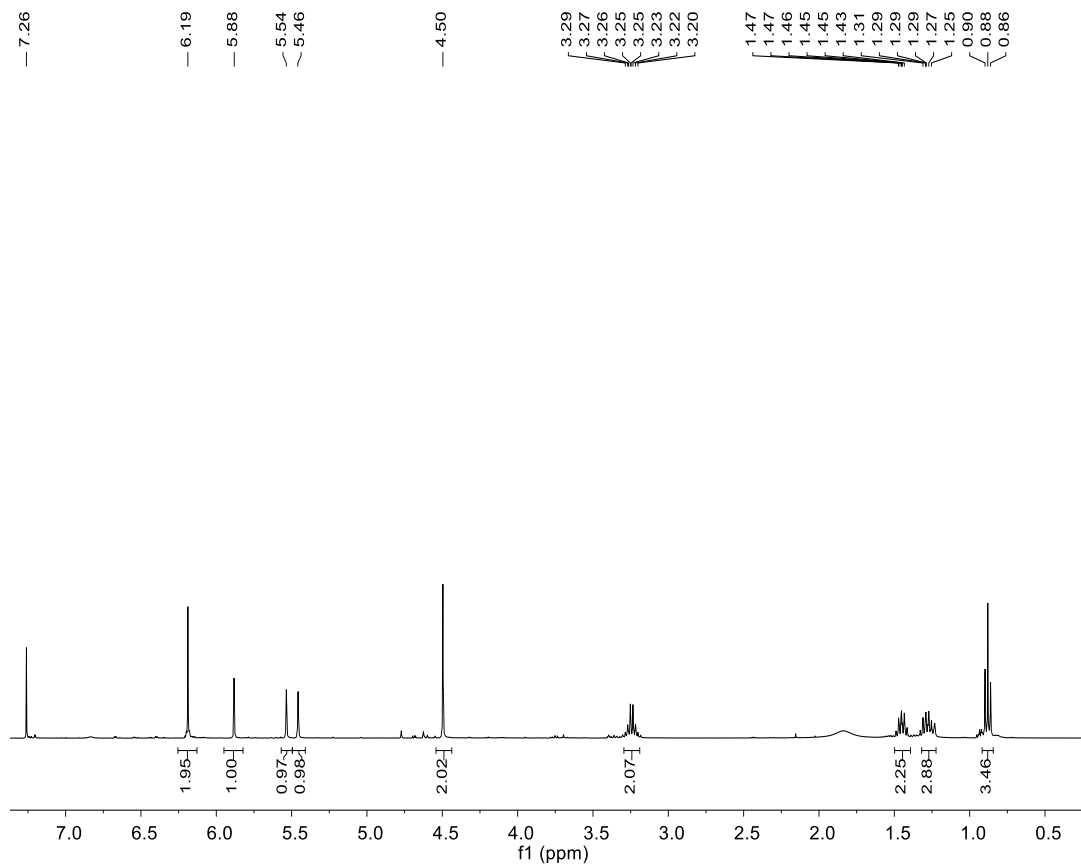




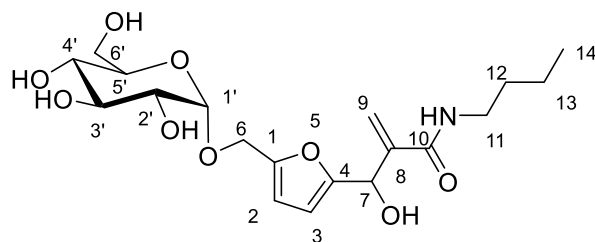
*N*-Butyl-2-{hydroxyl[5-(hydroxymethyl)furan-2-yl]methyl}acrylamide (C<sub>13</sub>H<sub>19</sub>NO<sub>4</sub>)



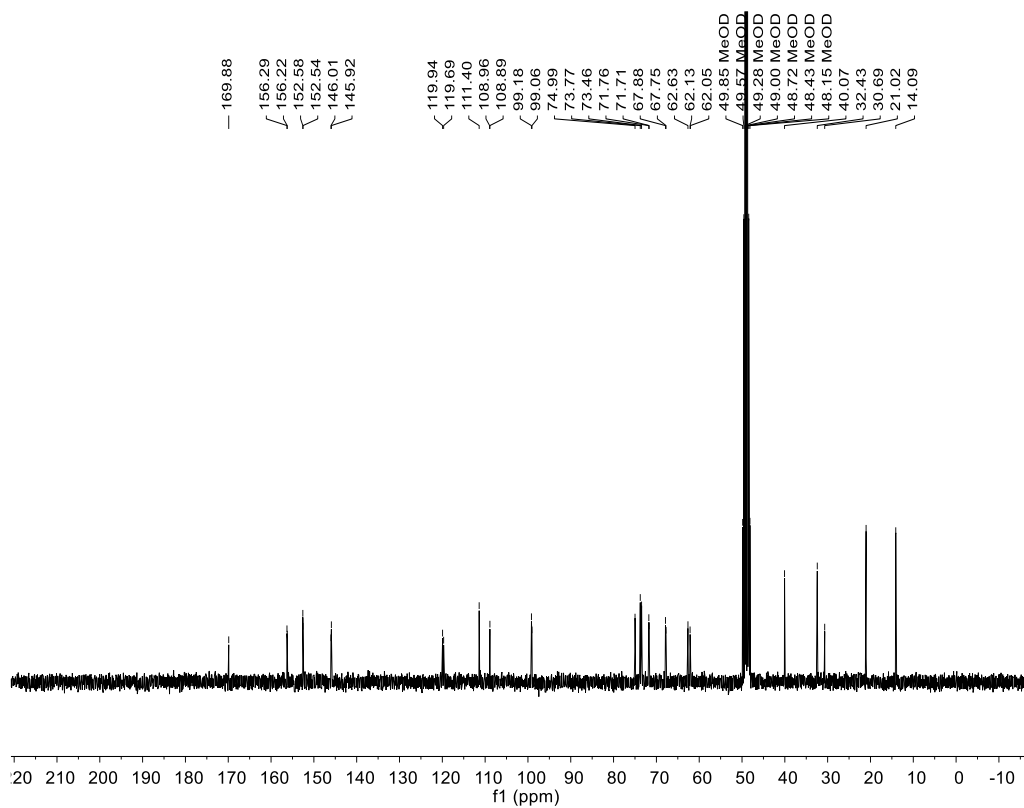
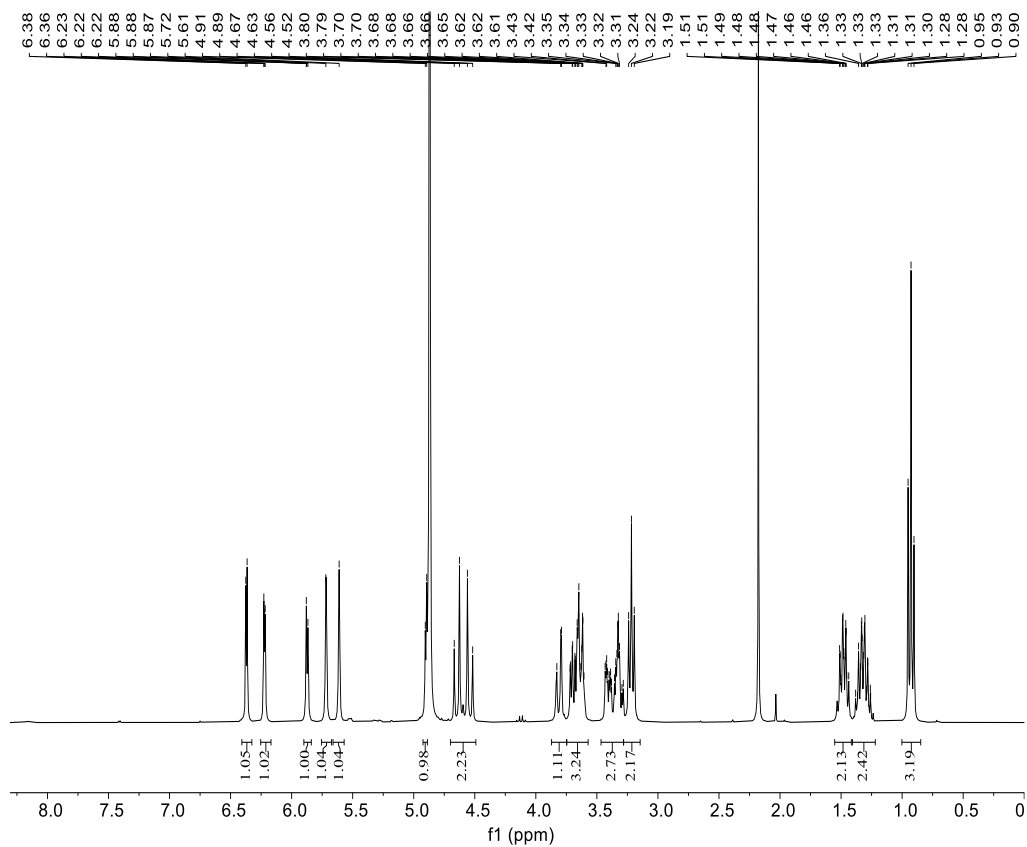
<sup>1</sup>H NMR (400 MHz, Chloroform-*d*): δ 6.19 (s, 2H, H<sub>2</sub>, H<sub>3</sub>), 5.88 (d, *J* = 0.7 Hz, 1H, C=CH<sub>2</sub>), 5.54 (d, *J* = 0.8 Hz, 1H, C=CH<sub>2</sub>), 5.46 (d, *J* = 0.9 Hz, 1H, CH-OH), 4.50 (s, 2H, H<sub>6</sub>), 3.33 – 3.15 (m, 2H, H<sub>11</sub>), 1.53 – 1.39 (m, 2H, H<sub>12</sub>), 1.34 – 1.21 (m, 2H, H<sub>13</sub>), 0.88 (t, *J* = 7.3 Hz, 3H, H<sub>14</sub>). <sup>13</sup>C NMR (101 MHz, Chloroform-*d*): δ 167.87 (C<sub>10</sub>), 154.15 (C<sub>1</sub>), 153.96 (C<sub>4</sub>), 142.87 (C<sub>8</sub>), 121.70 (C<sub>9</sub>), 108.56 (C<sub>3</sub>), 107.87 (C<sub>2</sub>), 69.20 (C<sub>7</sub>), 57.14 (C<sub>6</sub>), 39.21 (C<sub>11</sub>), 31.42 (C<sub>12</sub>), 20.11 (C<sub>13</sub>), 13.78 (C<sub>14</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>13</sub>H<sub>19</sub>NNaO<sub>4</sub> 276.1206; Found 276.1199.



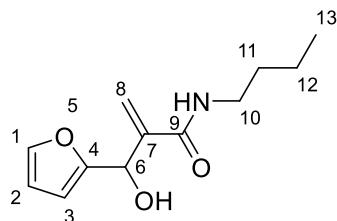
*N*-Butyl-2-{hydroxyl[5-( $\alpha$ -D-glucopyranosyloxymethyl)-furan-2-yl]methyl}acrylamide  
(C<sub>19</sub>H<sub>29</sub>NO<sub>9</sub>)



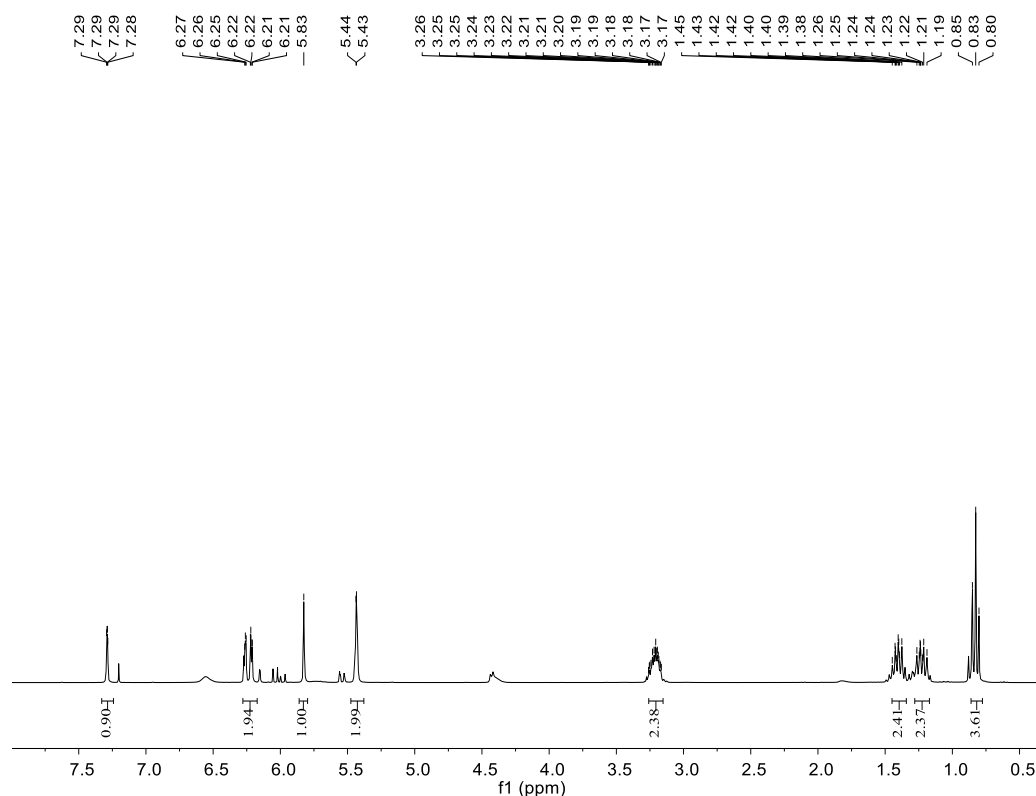
<sup>1</sup>H NMR (300 MHz, Methanol-*d*<sub>4</sub>):  $\delta$  6.37 (d,  $J$  = 3.2 Hz, 1H, H<sub>2</sub>), 6.22 (d,  $J$  = 3.2 Hz, 1H, H<sub>3</sub>), 5.87 (s, 1H, C=CH<sub>2</sub>), 5.72 (s, 1H, C=CH<sub>2</sub>), 5.61 (s, 1H, CH-OH),  $\delta$  4.90 (d,  $J$  = 3.6 Hz, 1H, H<sub>1'</sub>), 4.71 – 4.48 (m, 2H, H<sub>6</sub>), 3.86 – 3.75 (m, 1H, H<sub>6'</sub>), 3.75 – 3.55 (m, 3H, H<sub>6'</sub>, H<sub>3'</sub>, H<sub>5'</sub>), 3.48 – 3.26 (m, 2H, H<sub>4'</sub>, H<sub>2'</sub>), 3.22 (t,  $J$  = 6.9 Hz, 2H, H<sub>11</sub>), 1.57 – 1.40 (m, 2H, H<sub>12</sub>), 1.41 – 1.20 (m, 2H, H<sub>13</sub>), 0.93 (t,  $J$  = 7.3 Hz, 3H, H<sub>14</sub>). <sup>13</sup>C NMR (75 MHz, Methanol-*d*<sub>4</sub>):  $\delta$  169.88 (C<sub>10</sub>), 156.29, 156.22 (C<sub>4</sub>), 152.58, 152.54 (C<sub>1</sub>), 146.01, 145.92 (C<sub>8</sub>), 119.94, 119.69 (C<sub>9</sub>), 111.40 (C<sub>3</sub>), 108.96, 108.89 (C<sub>2</sub>), 99.18, 99.06 (C<sub>1'</sub>), 74.99 (C<sub>5'</sub>), 73.77 (C<sub>7</sub>), 73.46 (C<sub>3'</sub>), 71.76, 71.71 (C<sub>2'</sub>), 67.88, 67.75 (C<sub>4'</sub>), 62.63 (C<sub>6</sub>), 62.13, 62.05 (C<sub>6'</sub>), 40.07 (C<sub>11</sub>), 32.43 (C<sub>12</sub>), 21.02 (C<sub>13</sub>), 14.09 (C<sub>14</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>19</sub>H<sub>29</sub>NNaO<sub>9</sub> 438.1735; Found 438.1725.

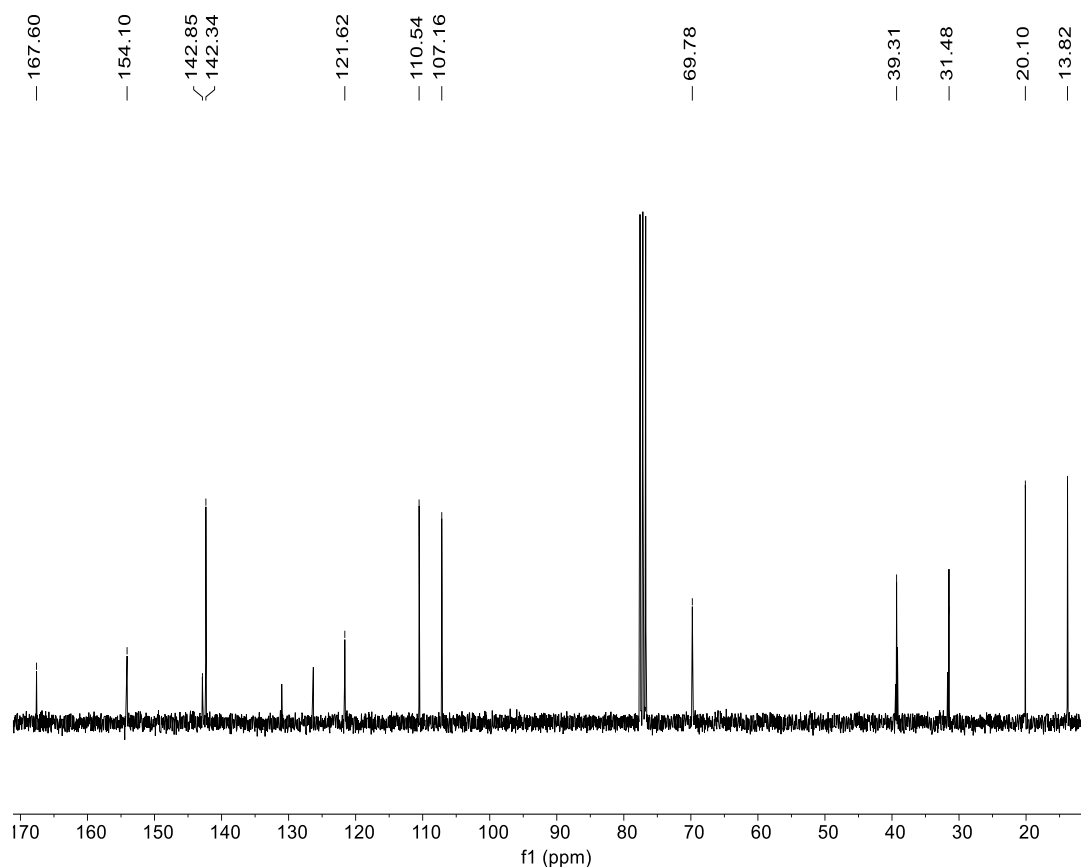


*N*-Butyl-2-[furan-2-yl(hydroxy)methyl]acrylamide (C<sub>12</sub>H<sub>17</sub>NO<sub>3</sub>)

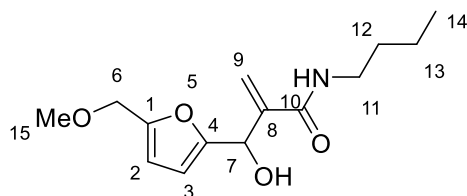


<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 7.29 (dd, *J* = 1.8, 0.9 Hz, 1H, H<sub>1</sub>), 6.26 (d, *J* = 1.8 Hz, 1H, H<sub>2</sub>), 6.22 (d, 1.8 Hz, 1H, H<sub>3</sub>), 5.83 (s, 1H, C=CH<sub>2</sub>), 5.46 – 5.39 (m, 2H, C=CH<sub>2</sub>, CH-OH), 3.21 (m, 2H, H<sub>10</sub>), 1.49 – 1.31 (m, 2H, H<sub>11</sub>), 1.27 – 1.17 (m, 2H, H<sub>12</sub>), 0.83 (t, *J* = 7.2 Hz, 3H, H<sub>13</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 167.60 (C<sub>9</sub>), 154.10 (C<sub>4</sub>), 142.85 (C<sub>7</sub>), 142.34 (C<sub>1</sub>), 121.62 (C<sub>8</sub>), 110.54 (C<sub>2</sub>), 107.16 (C<sub>3</sub>), 69.78 (C<sub>6</sub>), 39.31 (C<sub>10</sub>), 31.48 (C<sub>11</sub>), 20.10 (C<sub>12</sub>), 13.82 (C<sub>13</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>12</sub>H<sub>18</sub>NaO<sub>3</sub> 246.1101; Found 246.1101.

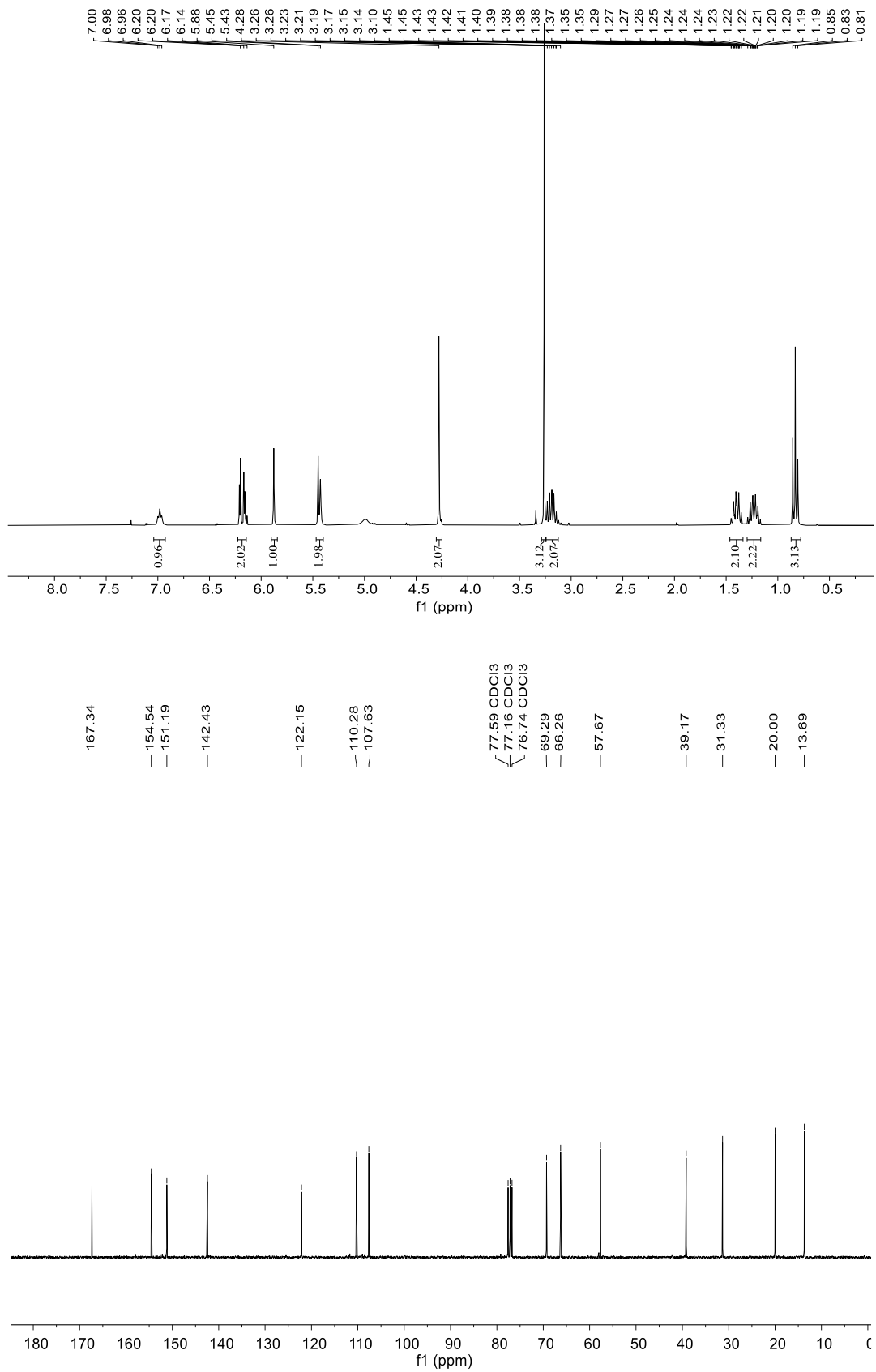




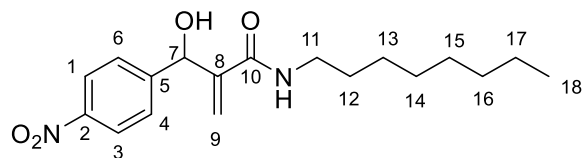
*N*-Butyl-2-{hydroxyl[5-(methoxymethyl)furan-2-yl]methyl}acrylamide (C<sub>14</sub>H<sub>21</sub>NO<sub>4</sub>)



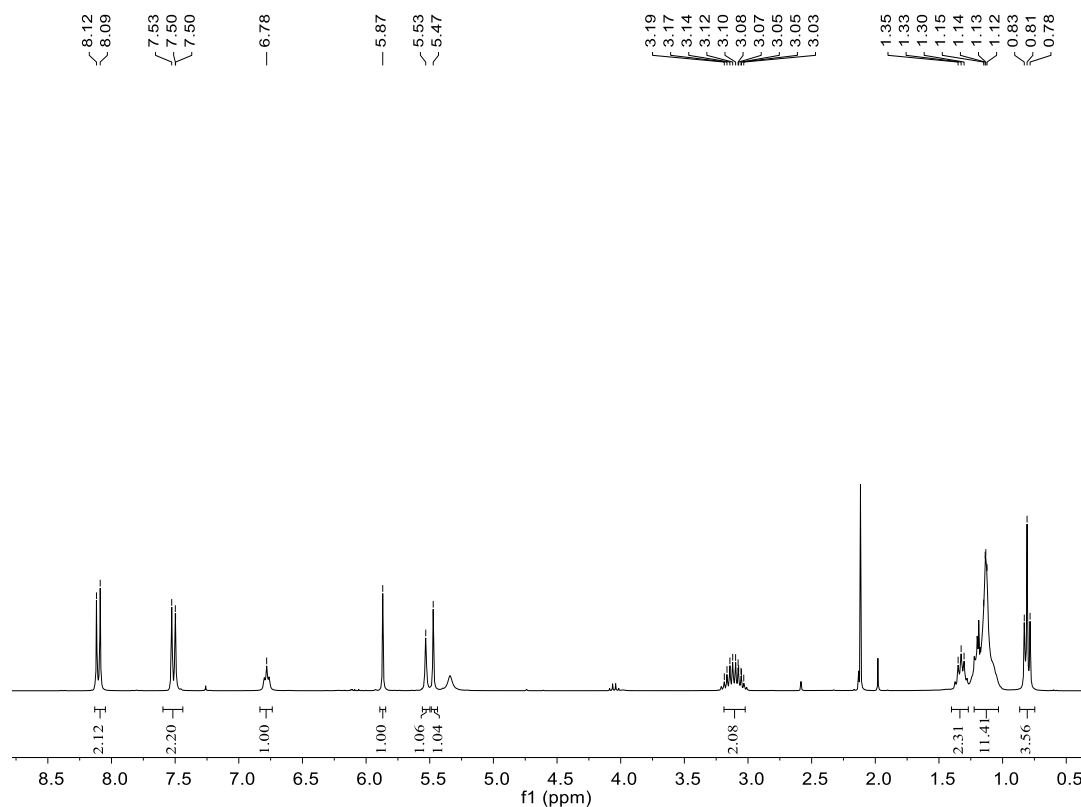
<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 6.98 (t, *J* = 5.8 Hz, 1H, NH), 6.18 (d, *J* = 9.4 Hz, 2H, H<sub>2</sub>,H<sub>3</sub>), 5.88 (s, 1H, C=CH<sub>2</sub>), 5.44 (m, 2H, C=CH<sub>2</sub>; CH-OH), 4.28 (s, 2H, H<sub>6</sub>), 3.26 (s, 3H, H<sub>15</sub>), 3.24 – 3.13 (m, 2H, H<sub>11</sub>), 1.47 – 1.33 (m, 2H, H<sub>12</sub>), 1.30 – 1.12 (m, 2H, H<sub>13</sub>), 0.83 (t, *J* = 7.3 Hz, 3H, H<sub>14</sub>). <sup>13</sup>C NMR (75 MHz, Chloroform-*d*): δ 167.34 (C<sub>10</sub>), 154.54 (C<sub>4</sub>), 151.19 (C<sub>1</sub>), 142.43 (C<sub>8</sub>), 122.15 (C<sub>9</sub>), 110.28 (C<sub>2</sub>), 107.63 (C<sub>2</sub>), 69.29 (C<sub>7</sub>), 66.26 (C<sub>6</sub>), 57.67 (C<sub>15</sub>), 39.17 (C<sub>11</sub>), 31.33 (C<sub>12</sub>), 20.00 (C<sub>13</sub>), 13.69 (C<sub>14</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>14</sub>H<sub>21</sub>NNaO<sub>4</sub> 290.1363; Found 290.1362.



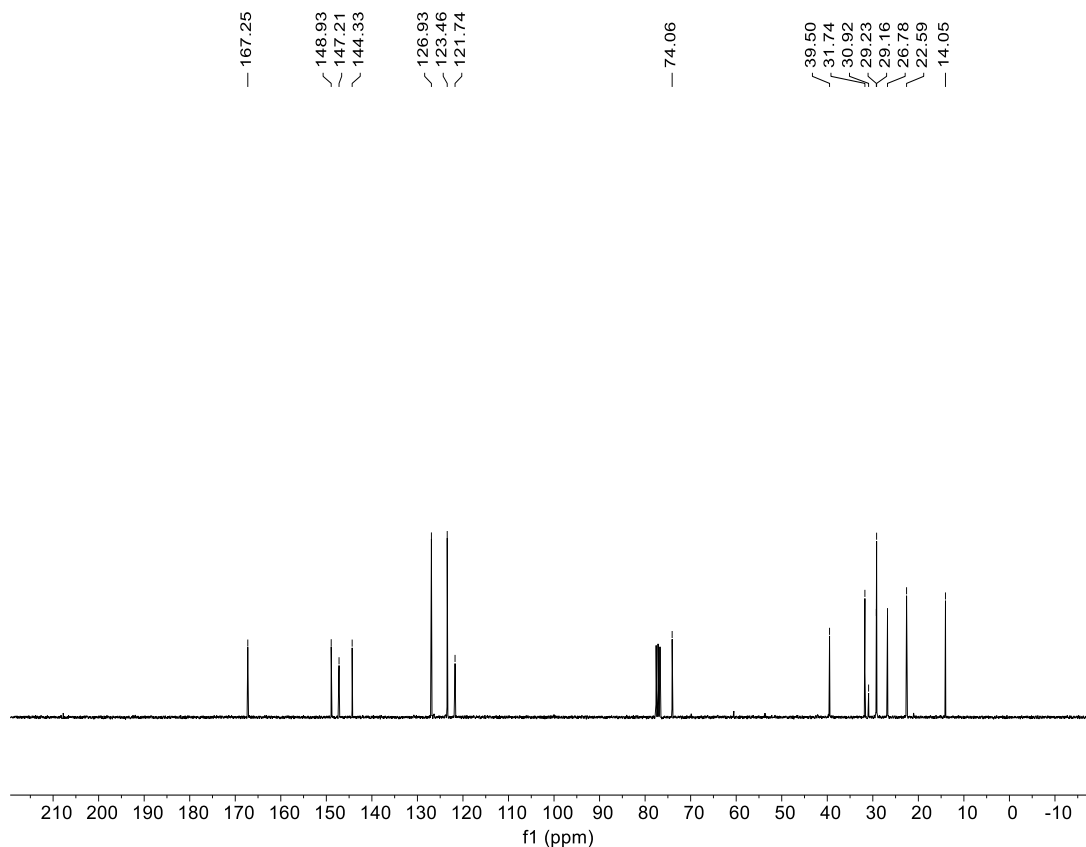
*N*-Octyl-2-[hydroxy(4-nitrophenyl)methyl]-acrylamide (C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>)



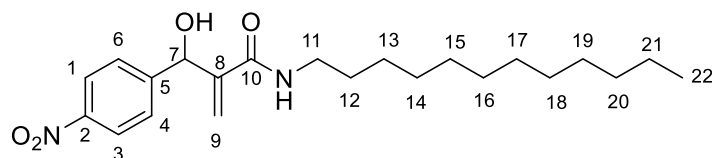
<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 8.10 (d, *J* = 8.8 Hz, 2H, H<sub>1</sub>, H<sub>3</sub>), 7.51 (d, *J* = 8.5 Hz, 2H, H<sub>4</sub>, H<sub>6</sub>), 6.78 (s, 1H, NH), 5.87 (s, 1H, C=CH<sub>2</sub>), 5.53 (s, 1H, C=CH<sub>2</sub>), 5.47 (s, 1H, CH-OH), 3.23 – 2.96 (m, 2H, H<sub>11</sub>), 1.39 – 1.26 (m, 2H, H<sub>12</sub>), 1.26 – 0.97 (m, 10H, H<sub>13-17</sub>), 0.81 (t, *J* = 6.8 Hz, 3H, H<sub>18</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 167.25 (C<sub>10</sub>), 148.93 (C<sub>5</sub>), 147.21(C<sub>2</sub>), 144.33(C<sub>8</sub>), 126.93 (C<sub>6</sub>, C<sub>4</sub>), 123.46 (C<sub>1</sub>, C<sub>3</sub>), 121.74 (C<sub>9</sub>), 74.06 (C<sub>7</sub>), 39.50 (C<sub>11</sub>), 31.74 (C<sub>16</sub>), 30.92 (C<sub>12</sub>), 29.23 (C<sub>14</sub>), 29.16 (C<sub>15</sub>), 26.78 (C<sub>13</sub>), 22.59 (C<sub>17</sub>), 14.05 (C<sub>18</sub>). HRMS (ESI) *m/z*: Calcd for [M+H]<sup>+</sup> C<sub>18</sub>H<sub>27</sub>N<sub>2</sub>O<sub>4</sub> 335.1965; Found 335.1962.



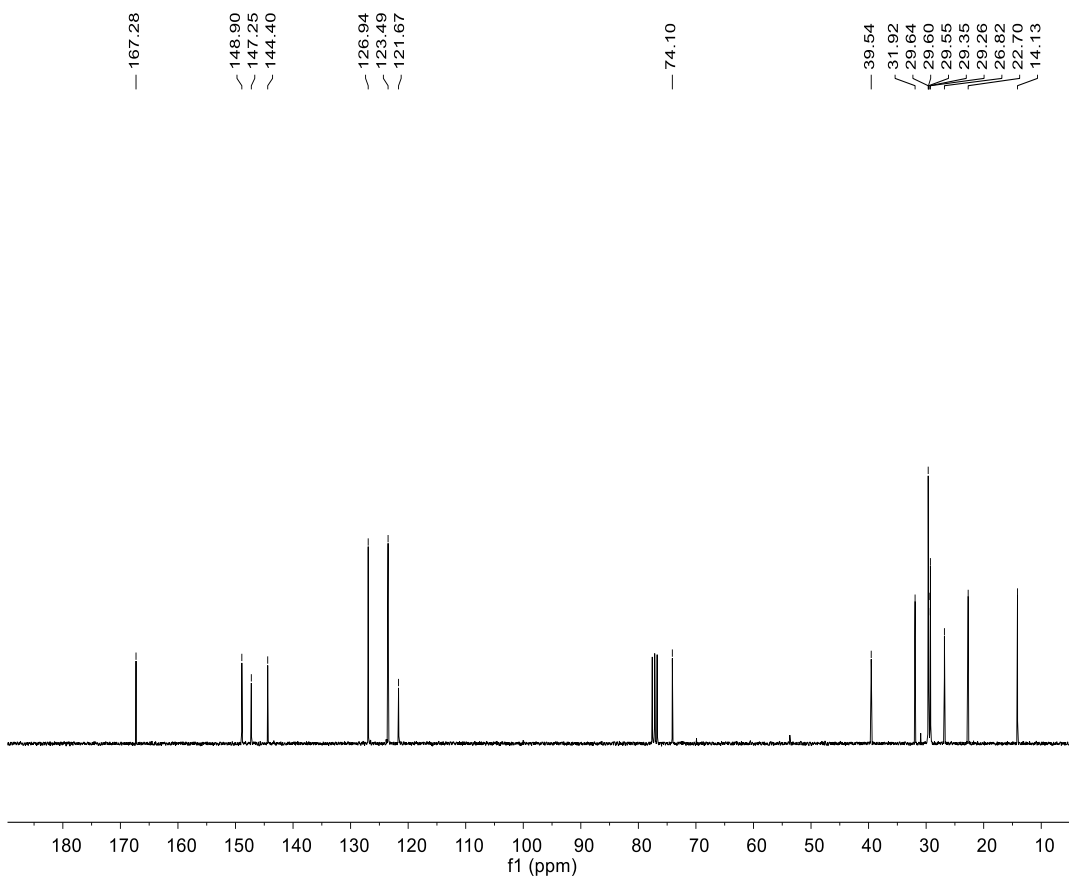
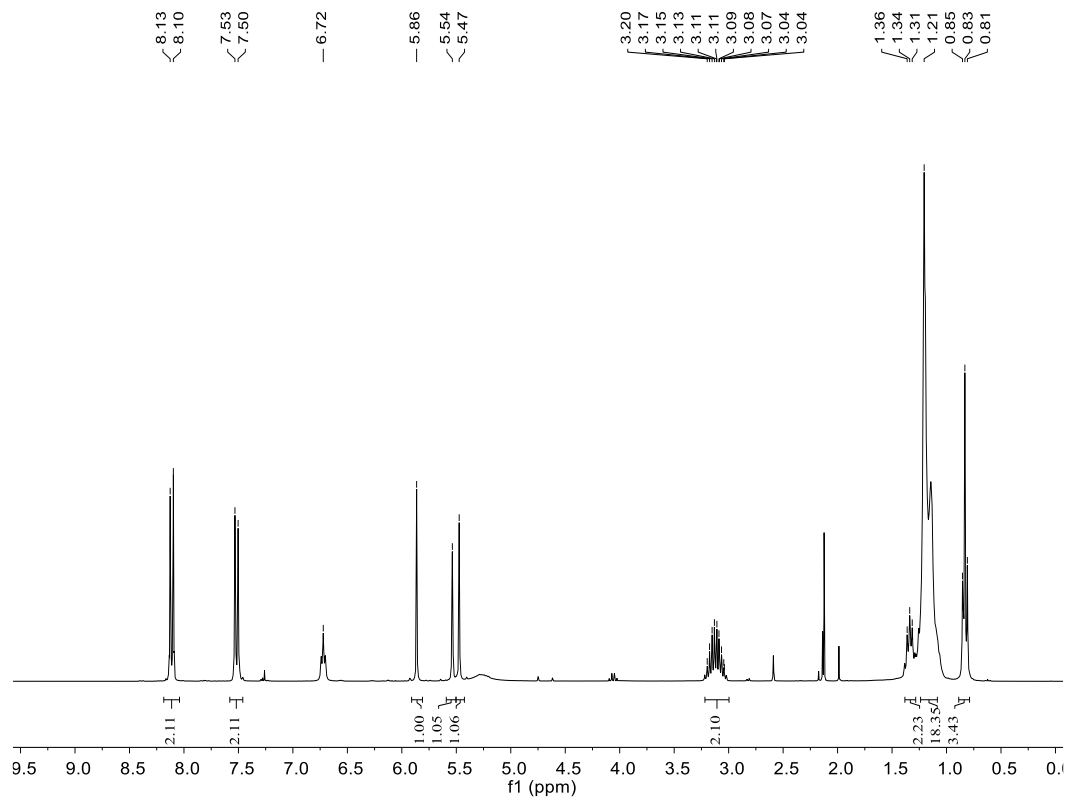




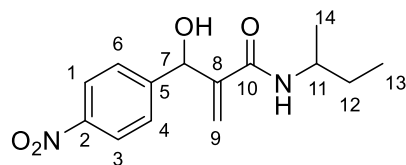
*N*-Dodecyl-2-[hydroxy(4-nitrophenyl)methyl]acrylamide (C<sub>22</sub>H<sub>34</sub>N<sub>2</sub>O<sub>4</sub>)



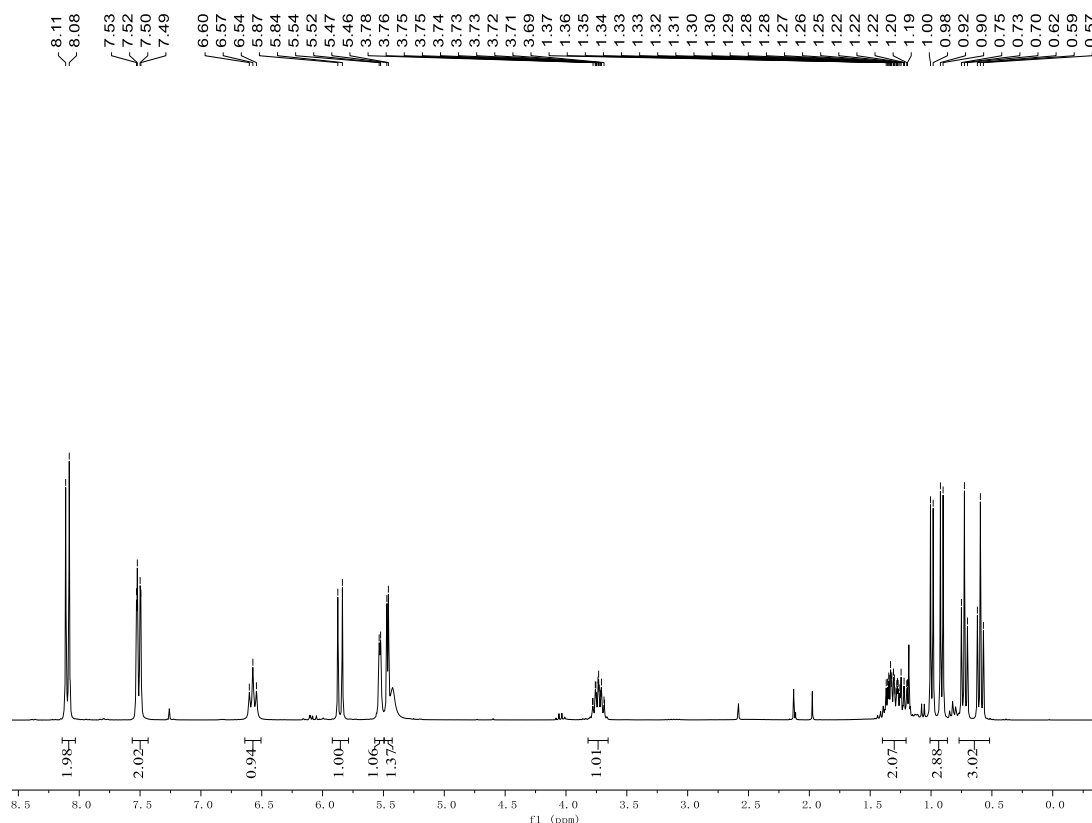
<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 8.11 (d, *J* = 8.8 Hz, 2H, H<sub>3</sub>), 7.52 (d, *J* = 8.7 Hz, 2H, H<sub>4</sub>, H<sub>6</sub>), 6.72 (s, 1H, NH), 5.86 (s, 1H, C=CH<sub>2</sub>), 5.54 (s, 1H, C=CH<sub>2</sub>), 5.47 (s, 1H, CH-OH), 3.27 – 2.97 (m, 2H, H<sub>11</sub>), 1.39 – 1.27 (m, 2H, H<sub>12</sub>), 1.21 (s, 18H, H<sub>13-21</sub>), 0.90 – 0.71 (t, 3H, H<sub>22</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 167.28, 148.90, 147.25, 144.40, 126.94, 123.49, 121.67, 74.10, 39.54, 31.92, 29.64, 29.60, 29.55, 29.35, 29.26, 26.82, 22.70, 14.13. HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>22</sub>H<sub>34</sub>N<sub>2</sub>NaO<sub>4</sub> 413.2411; Found 413.2408.

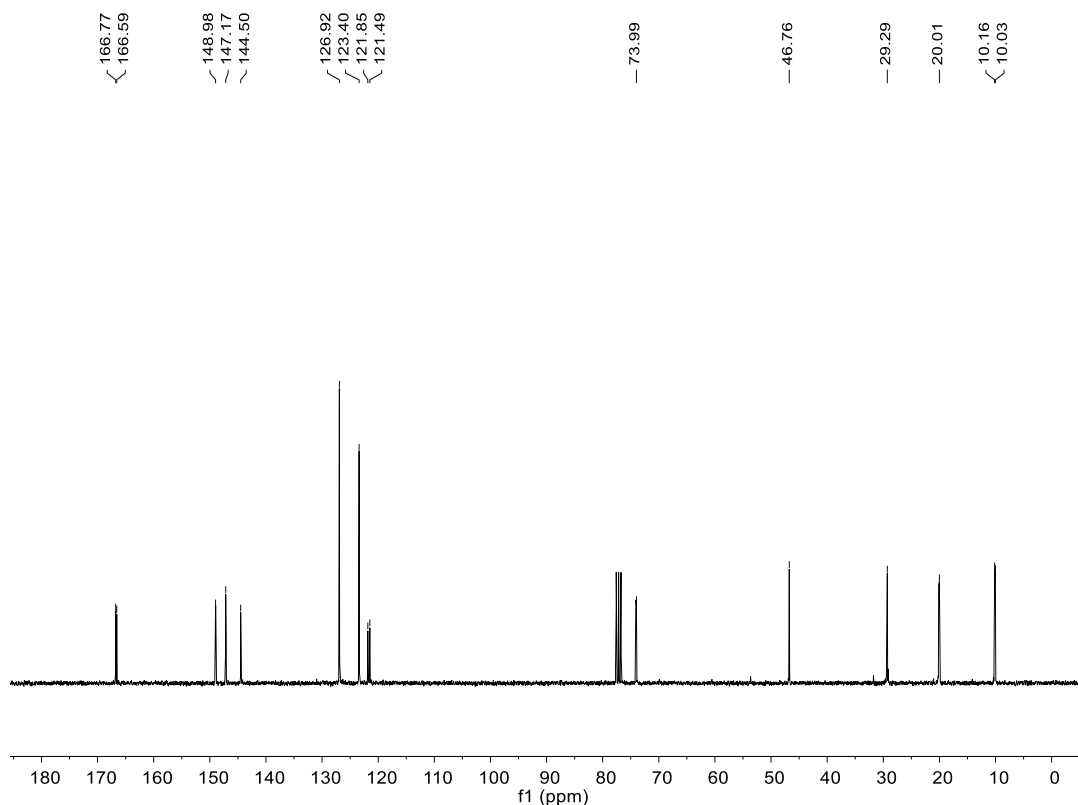


*N*-(*Sec*-butyl)-2-[hydroxy(4-nitrophenyl)methyl]acrylamide (C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>)

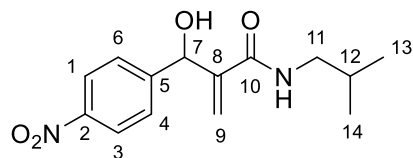


<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 8.10 (d, *J* = 8.8 Hz, 2H, H<sub>1</sub>,H<sub>3</sub>), 7.51 (dd, *J* = 8.8, 1.9 Hz, 2H, H<sub>4</sub>,H<sub>6</sub>), 6.57 (s, 1H,NH), 5.86 (d, *J* = 11.3 Hz, 1H, C=CH<sub>2</sub>, a), 5.53 (d, *J* = 3.6 Hz, 1H, C=CH<sub>2</sub>,b), 5.47 (d, *J* = 3.8 Hz, 1H, CH-OH), 3.81 – 3.66 (m, 1H, H<sub>11</sub>), 1.48 – 1.17 (m, 2H, H<sub>12</sub>), 0.95 (dd, *J* = 24.5, 6.6 Hz, 3H, H<sub>14</sub>), 0.66 (dt, *J* = 39.4, 7.4 Hz, 3H, H<sub>13</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 166.77, 166.59 (C<sub>10</sub>), 148.98 (C<sub>5</sub>), 147.17 (C<sub>2</sub>), 144.50 (C<sub>8</sub>), 126.92 (C<sub>6</sub>, C<sub>4</sub>), 123.40 (C<sub>1</sub>, C<sub>3</sub>), 121.85, 121.49 (C<sub>9</sub>), 73.99 (C<sub>7</sub>), 46.76 (C<sub>11</sub>), 29.29 (C<sub>12</sub>), 20.01(C<sub>14</sub>), 10.16, 10.03(C<sub>13</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>NaO<sub>4</sub> 301.1159; Found 301.1156.

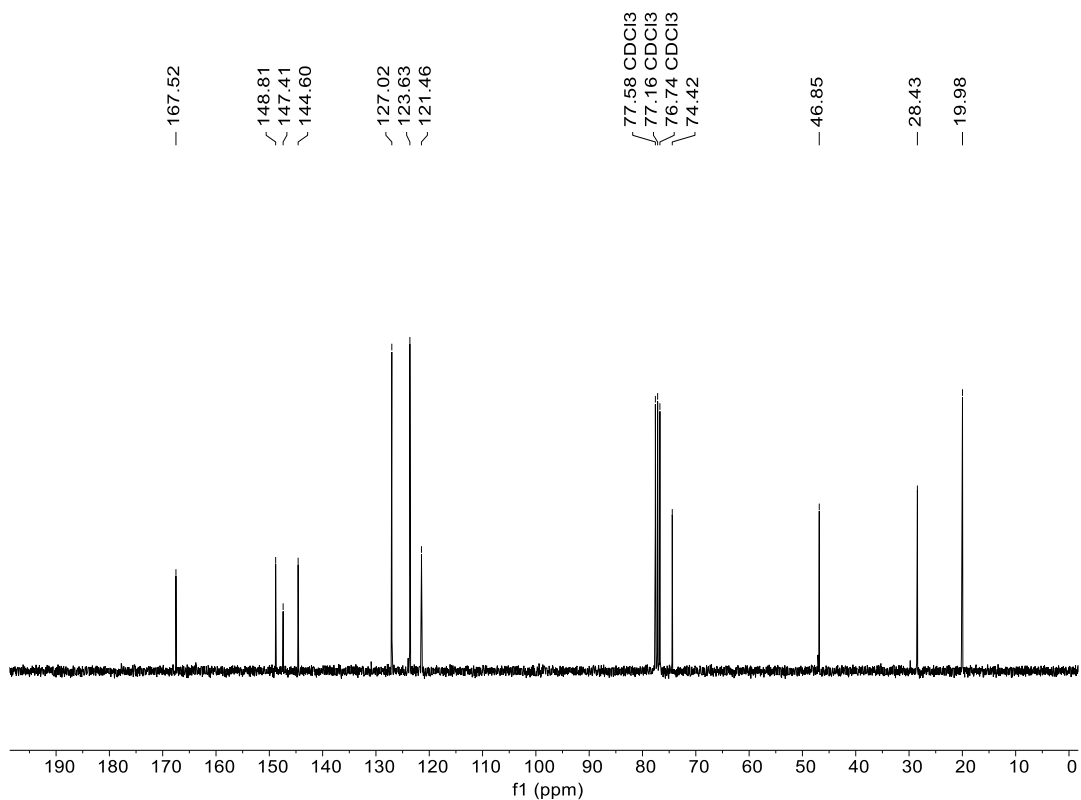
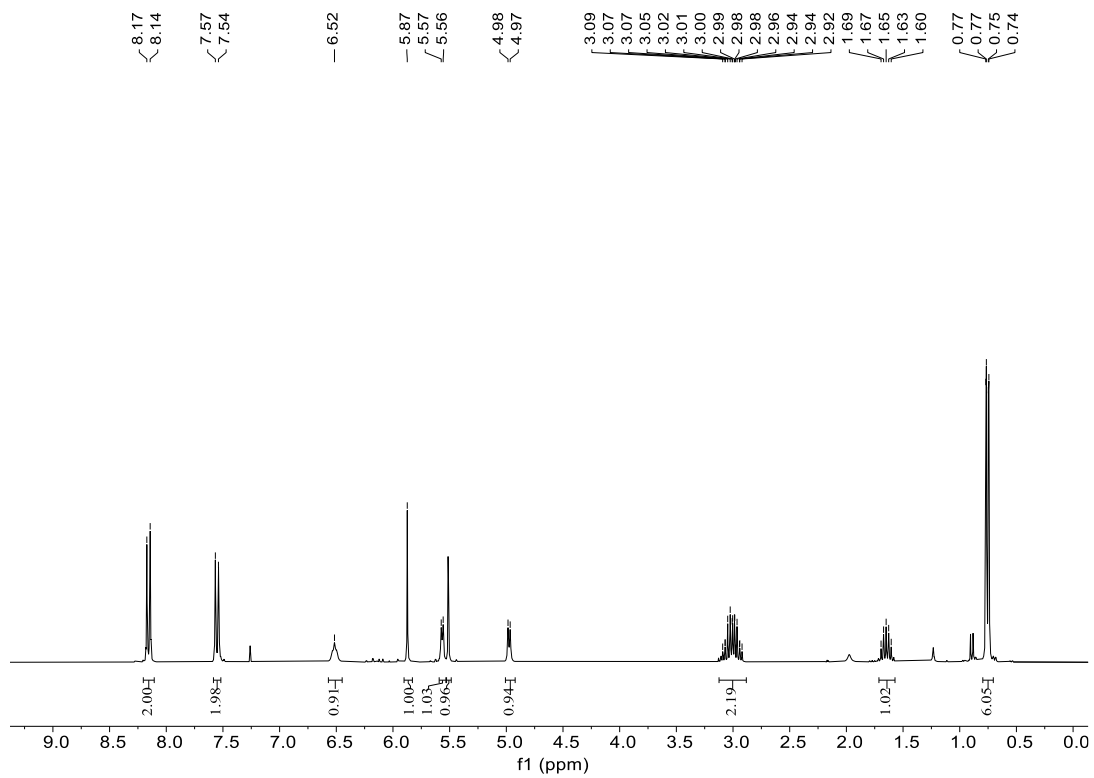




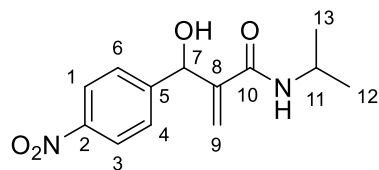
*N*-Isobutyl-2-[hydroxy(4-nitrophenyl)methyl]acrylamide (C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>)



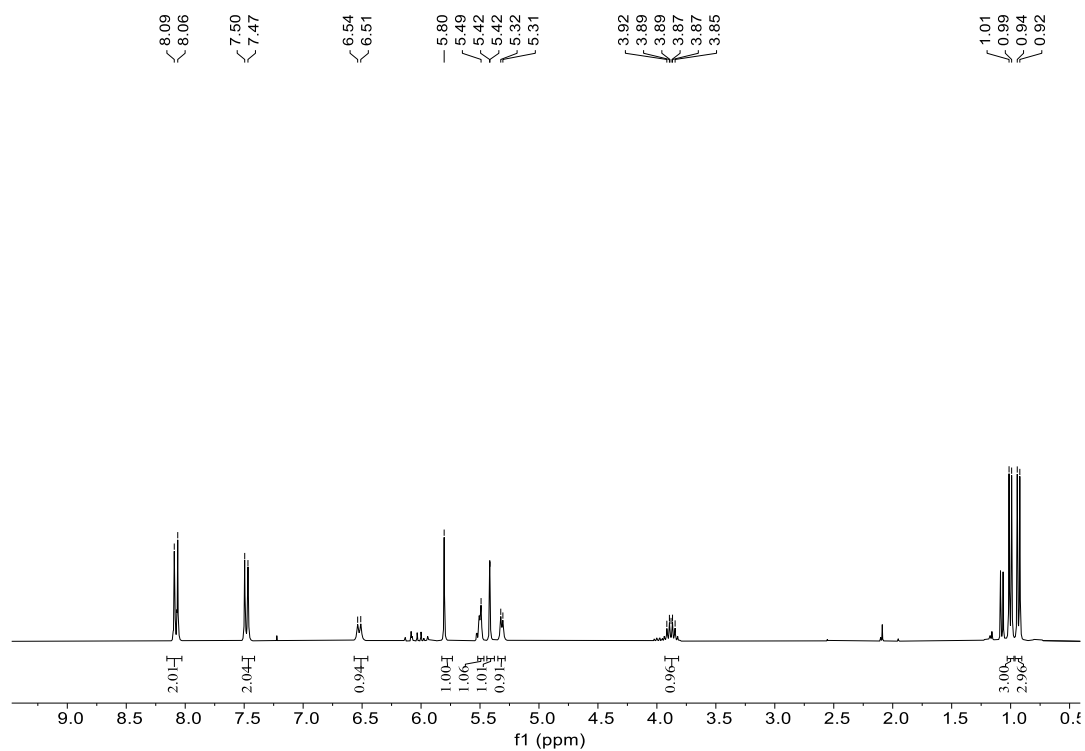
<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 8.16 (d, *J* = 8.8 Hz, 2H, H<sub>1</sub>, H<sub>3</sub>), 7.55 (d, *J* = 8.2 Hz, 2H, H<sub>4</sub>, H<sub>6</sub>), 6.52 (s, 1H, NH), 5.87 (s, 1H, C=CH<sub>2</sub>), 5.57 (s, 1H, C=CH<sub>2</sub>), 5.51 (s, 1H, CH-OH), 4.98 (s, 1H, CH-OH), 3.14 – 2.86 (m, 2H, H<sub>11</sub>), 1.72 – 1.58 (m, 1H, H<sub>12</sub>), 0.76 (dd, *J* = 6.7, 1.5 Hz, 6H, H<sub>13</sub>, H<sub>14</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 167.52 (C<sub>10</sub>), 148.81 (C<sub>5</sub>), 147.41 (C<sub>2</sub>), 144.60 (C<sub>8</sub>), 127.02 (C<sub>4</sub>, C<sub>6</sub>), 123.63 (C<sub>1</sub>, C<sub>3</sub>), 121.46 (C<sub>9</sub>), 74.42 (C<sub>7</sub>), 46.85 (C<sub>11</sub>), 28.43 (C<sub>12</sub>), 19.98 (C<sub>13</sub>, C<sub>14</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>NaO<sub>4</sub> 301.1159; Found 301.1160.

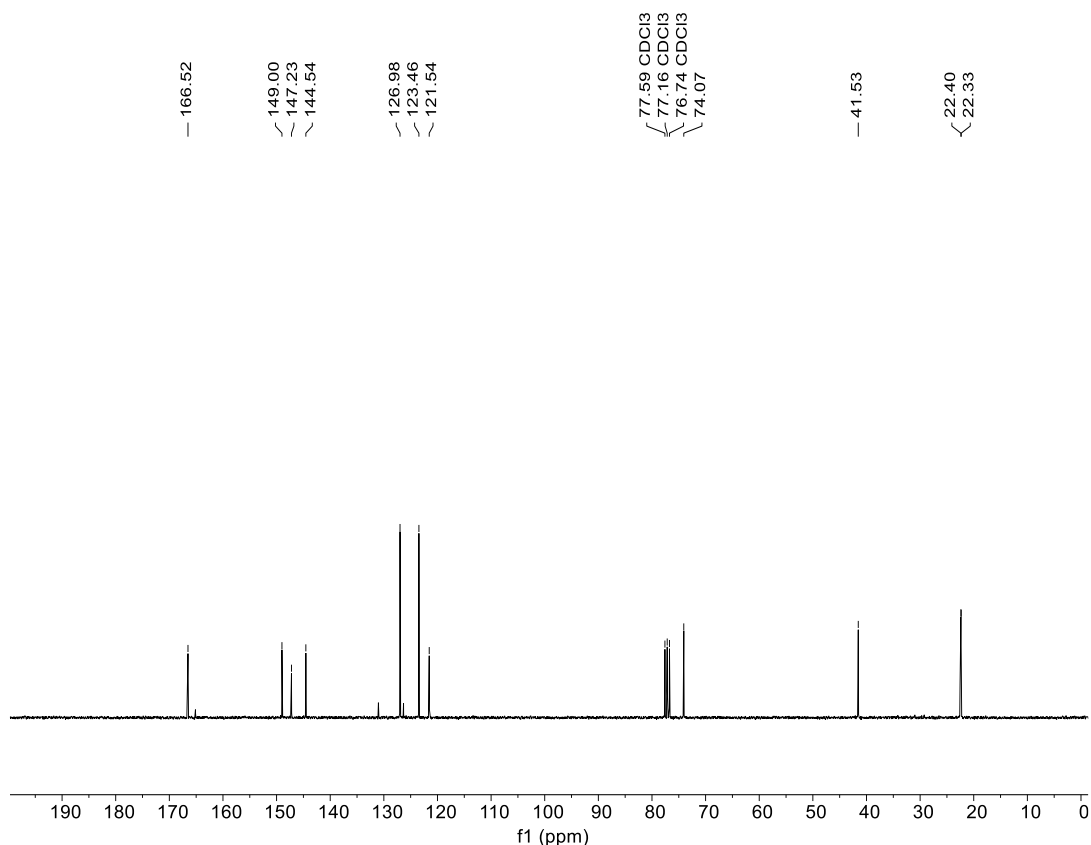


*N*-Isopropyl-2-[hydroxy(4-nitrophenyl)methyl]acrylamide (C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>)

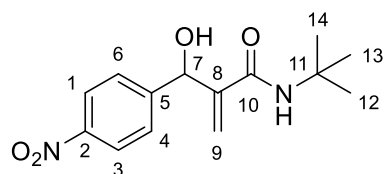


<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 8.08 (d, *J* = 8.8 Hz, 2H, H<sub>1</sub>, H<sub>3</sub>), 7.48 (d, *J* = 8.2 Hz, 2H, H<sub>4</sub>, H<sub>6</sub>), 6.52 (d, *J* = 7.9 Hz, 1H, NH), 5.80 (s, 1H, C=CH<sub>2</sub>), 5.49 (s, 1H, C=CH<sub>2</sub>), 5.42 (s, 1H, CH-OH), 5.32 (s, 1H, CH-OH), 3.88 (dt, *J* = 8.0, 6.6 Hz, 1H, H<sub>11</sub>), 1.00 (d, *J* = 6.6 Hz, 3H, H<sub>13</sub>), 0.93 (d, *J* = 6.5 Hz, 3H, H<sub>12</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 166.52 (C<sub>10</sub>), 149.00 (C<sub>5</sub>), 147.23 (C<sub>2</sub>), 144.54 (C<sub>8</sub>), 126.98 (C<sub>4</sub>, C<sub>6</sub>), 123.46 (C<sub>1</sub>, C<sub>3</sub>), 121.54 (C<sub>9</sub>), 74.07 (C<sub>7</sub>), 41.53 (C<sub>11</sub>), 22.40, 22.33 (C<sub>12</sub>, C<sub>13</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>NaO<sub>4</sub> 287.1002; Found 287.1002.

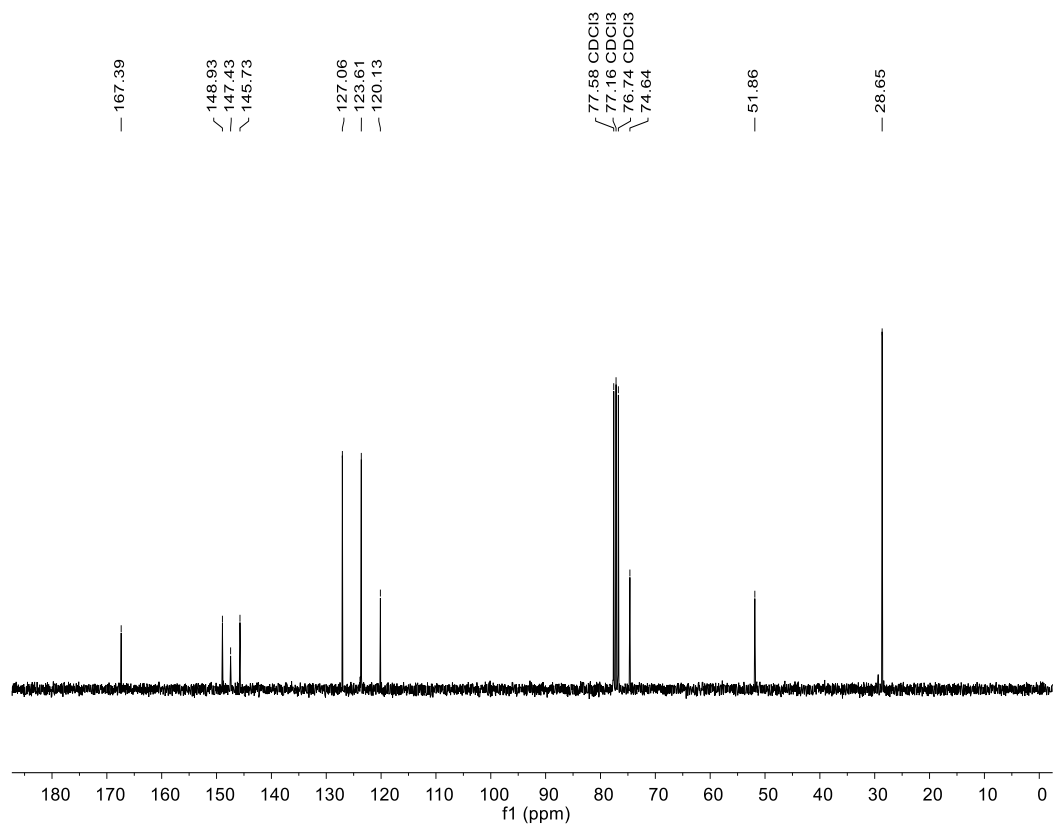
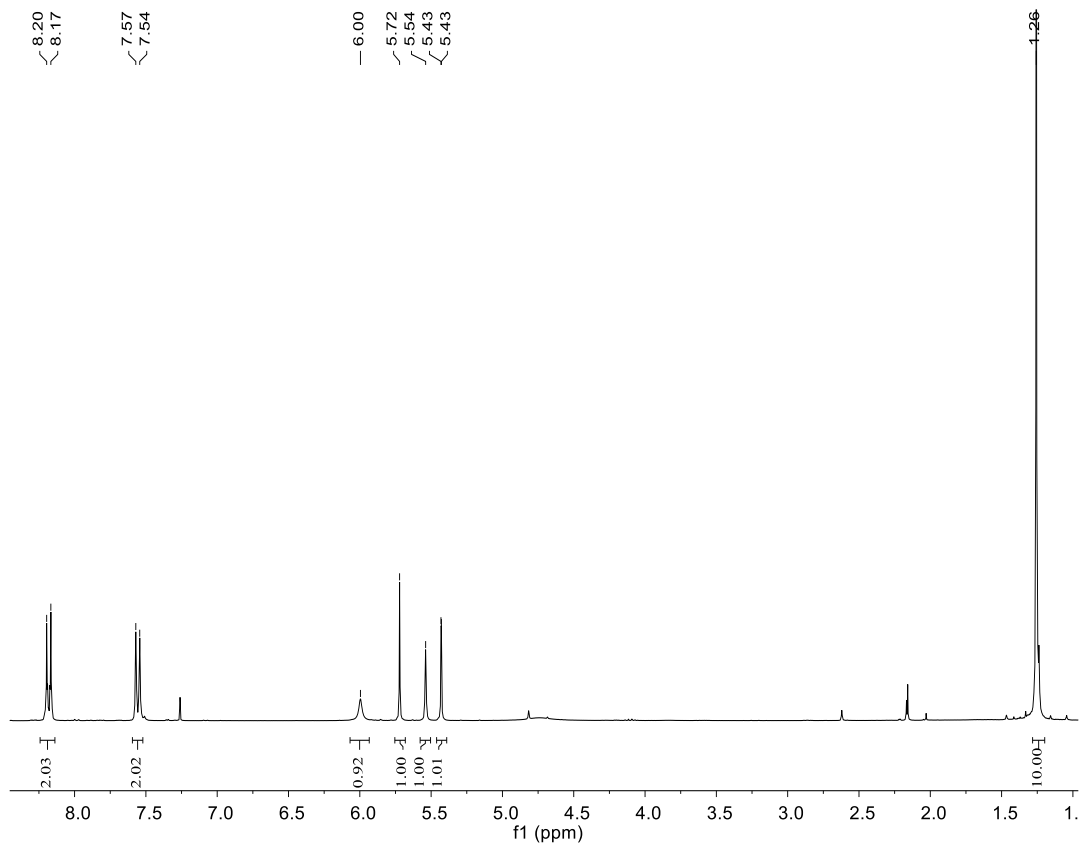




*N*-(*Tert*-butyl)-2-[hydroxy(4-nitrophenyl)methyl]acrylamide (C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>)

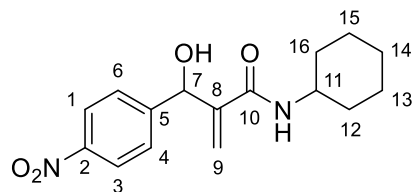


<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 8.18 (d, *J* = 8.8 Hz, 2H, H<sub>1</sub>,H<sub>3</sub>), 7.56 (d, *J* = 8.3 Hz, 2H, H<sub>4</sub>,H<sub>6</sub>), 6.00 (s, 1H, NH), 5.72 (s, 1H, C=CH<sub>2</sub>), 5.54 (s, 1H, C=CH<sub>2</sub>), 5.43 (d, *J* = 0.9 Hz, 1H, CH-OH), 1.26 (s, 9H, H<sub>12-14</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 167.35 (C<sub>10</sub>), 148.91 (C<sub>5</sub>), 147.40 (C<sub>2</sub>), 145.66 (C<sub>8</sub>), 127.04 (C<sub>4</sub>,C<sub>6</sub>), 123.59 (C<sub>1</sub>,C<sub>3</sub>), 120.27 (C<sub>9</sub>), 74.56 (C<sub>7</sub>), 51.83 (C<sub>11</sub>), 28.62 (C<sub>12-14</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>NaO<sub>4</sub> 301.1159; Found 301.1156.

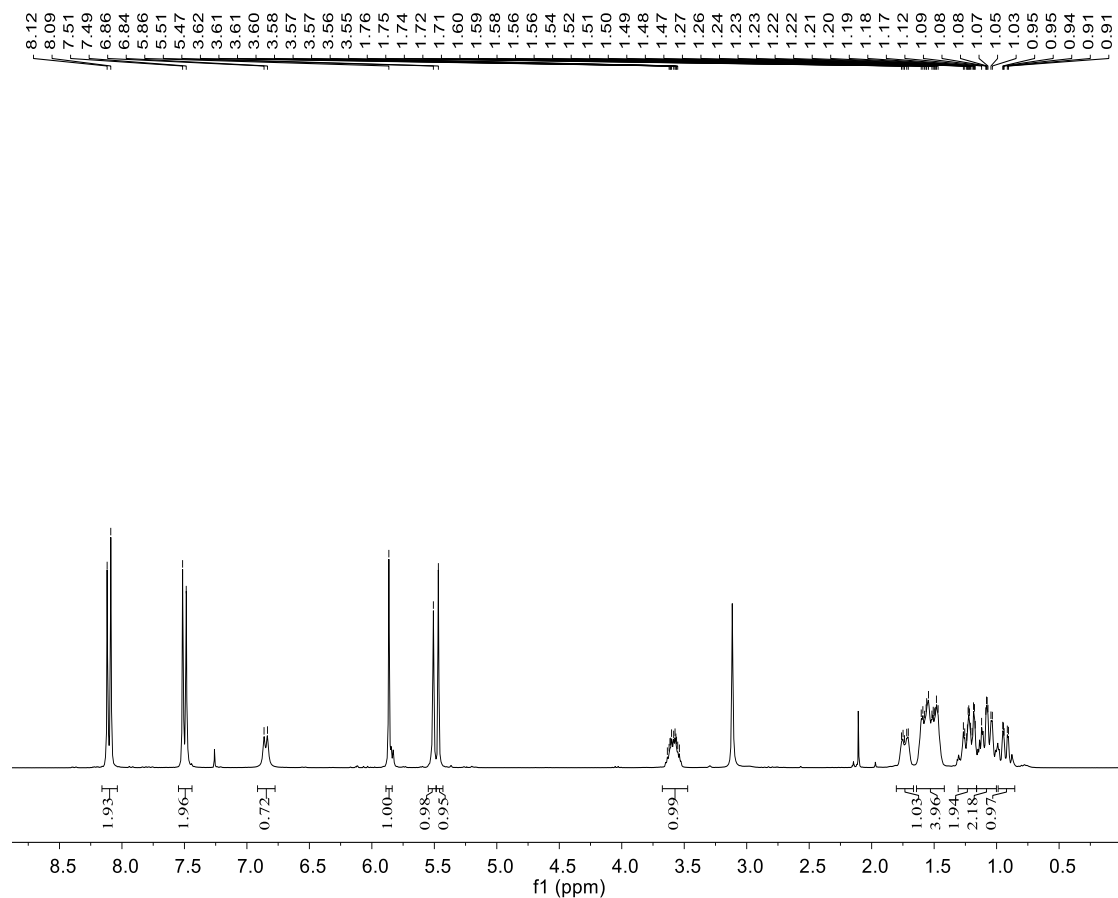


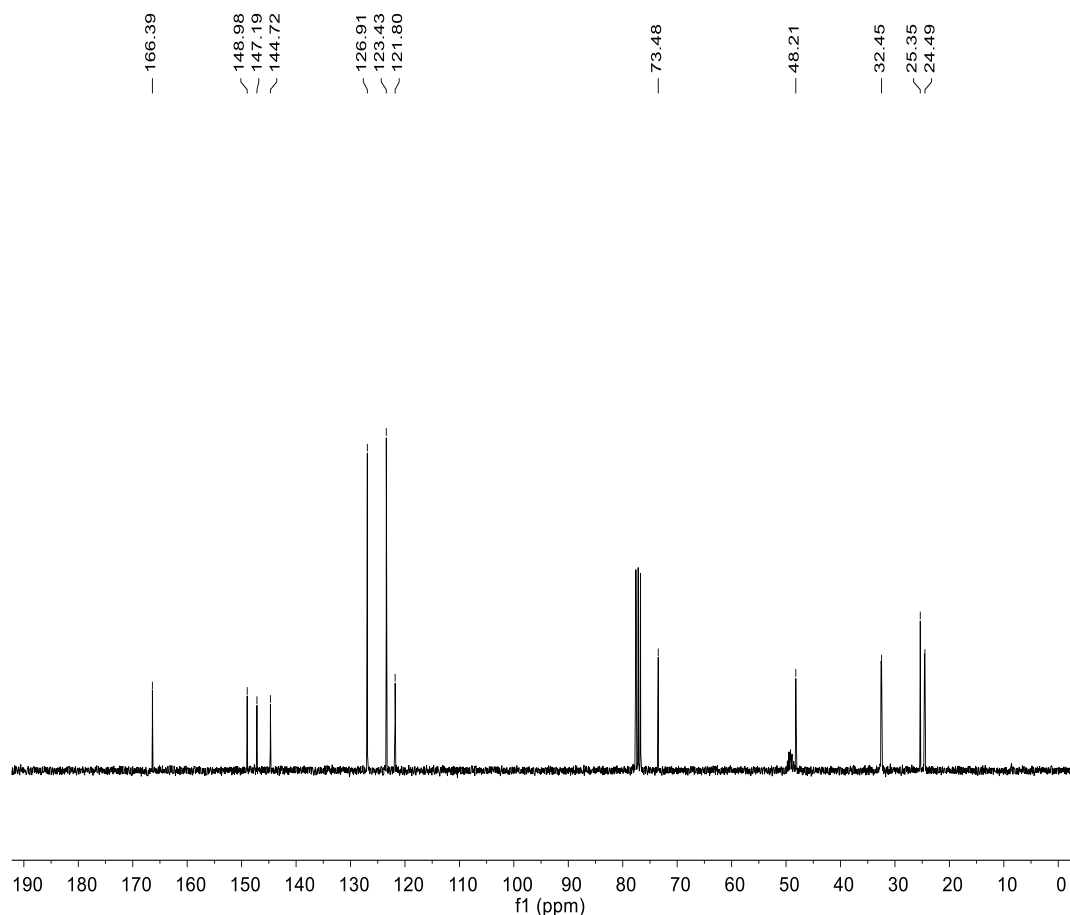


*N*-Cyclohexyl-2-[hydroxy(4-nitrophenyl)methyl]acrylamide (C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>)

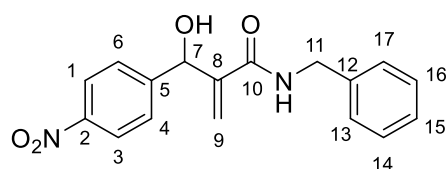


<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 8.10 (d, *J* = 8.8 Hz, 2H, H<sub>1</sub>, H<sub>3</sub>), 7.50 (d, *J* = 8.7 Hz, 2H, H<sub>4</sub>, H<sub>6</sub>), 6.85 (s, 1H, NH), 5.86 (s, 1H, C=CH<sub>2</sub>), 5.51 (s, 1H, C=CH<sub>2</sub>), 5.47 (s, 1H, CH-OH), 3.59 (dd, *J* = 9.7, 3.3 Hz, 1H, H<sub>11</sub>), 1.73 (dd, *J* = 12.6, 3.8 Hz, 1H, H<sub>12a</sub>), 1.67 – 1.41 (m, 4H, H<sub>12b</sub>, H<sub>16b</sub>, H<sub>14</sub>), 1.29 – 1.15 (m, 2H, H<sub>16a</sub>, H<sub>15a</sub>), 1.15 – 1.01 (m, 2H, H<sub>15a</sub>, H<sub>13a</sub>), 0.98 – 0.86 (m, 1H, H<sub>13b</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 166.39 (C<sub>10</sub>), 148.98 (C<sub>5</sub>), 147.19 (C<sub>2</sub>), 144.72 (C<sub>8</sub>), 126.91 (C<sub>6</sub>, C<sub>4</sub>), 123.43 (C<sub>1</sub>, C<sub>3</sub>), 121.80 (C<sub>9</sub>), 73.48 (C<sub>7</sub>), 48.21 (C<sub>11</sub>), 32.45 (C<sub>12</sub>, C<sub>16</sub>), 25.35 (C<sub>14</sub>), 24.49 (C<sub>12</sub>, C<sub>16</sub>). HRMS (ESI) *m/z*: Calcd for [M+H]<sup>+</sup> C<sub>16</sub>H<sub>21</sub>N<sub>2</sub>O<sub>4</sub> 305.1496; Found 305.1497.

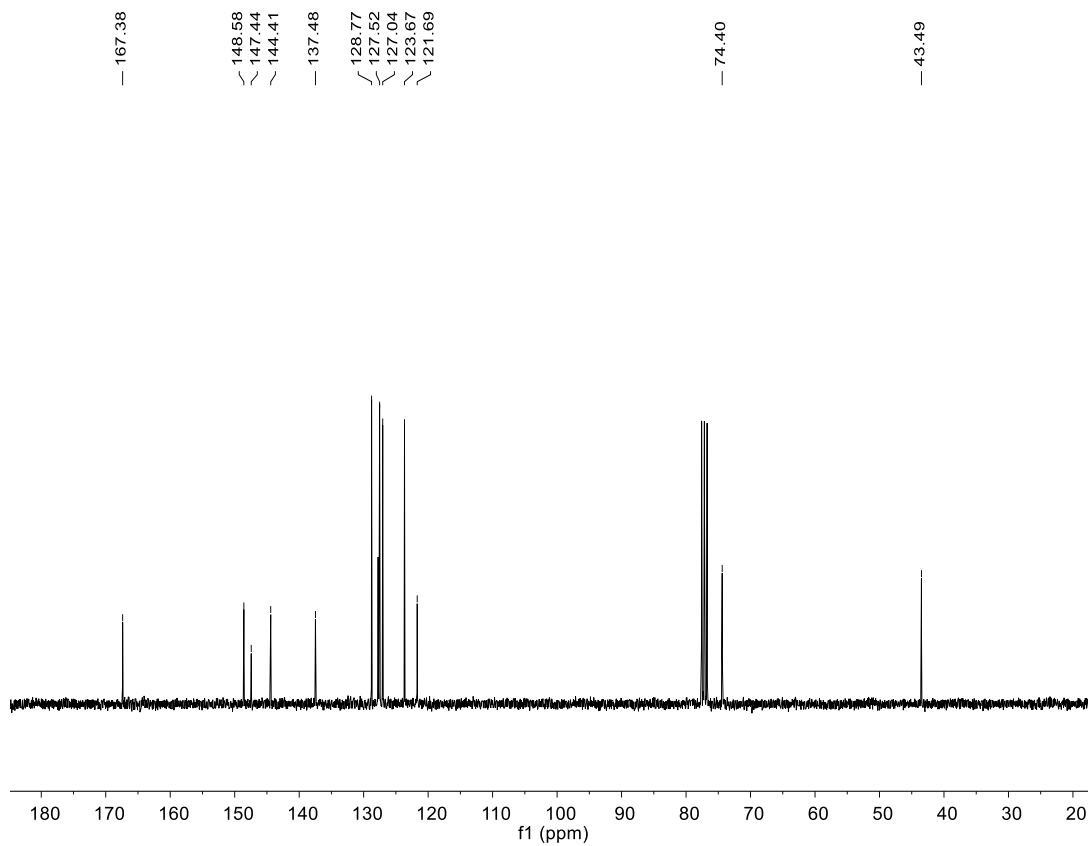
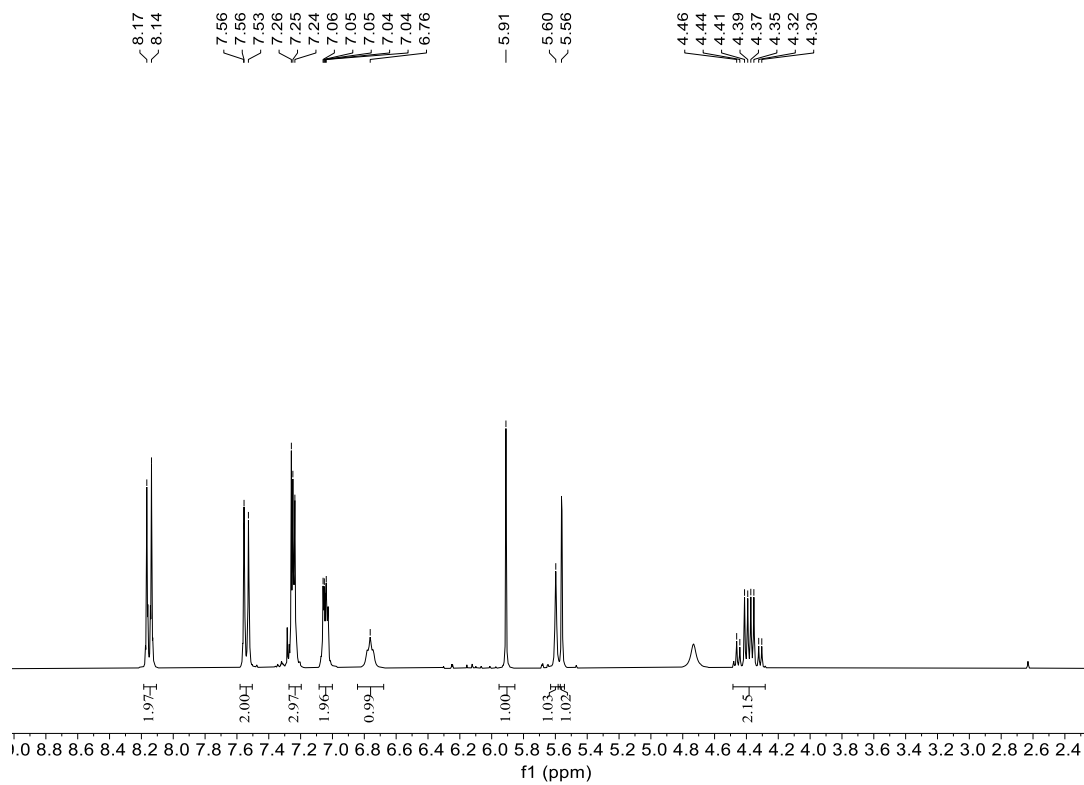




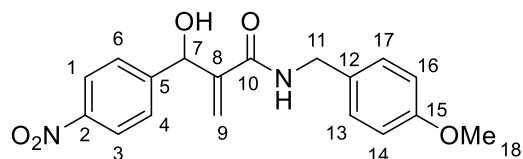
*N*-Benzyl-2-[hydroxy(4-nitrophenyl)methyl]acrylamide (C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>)



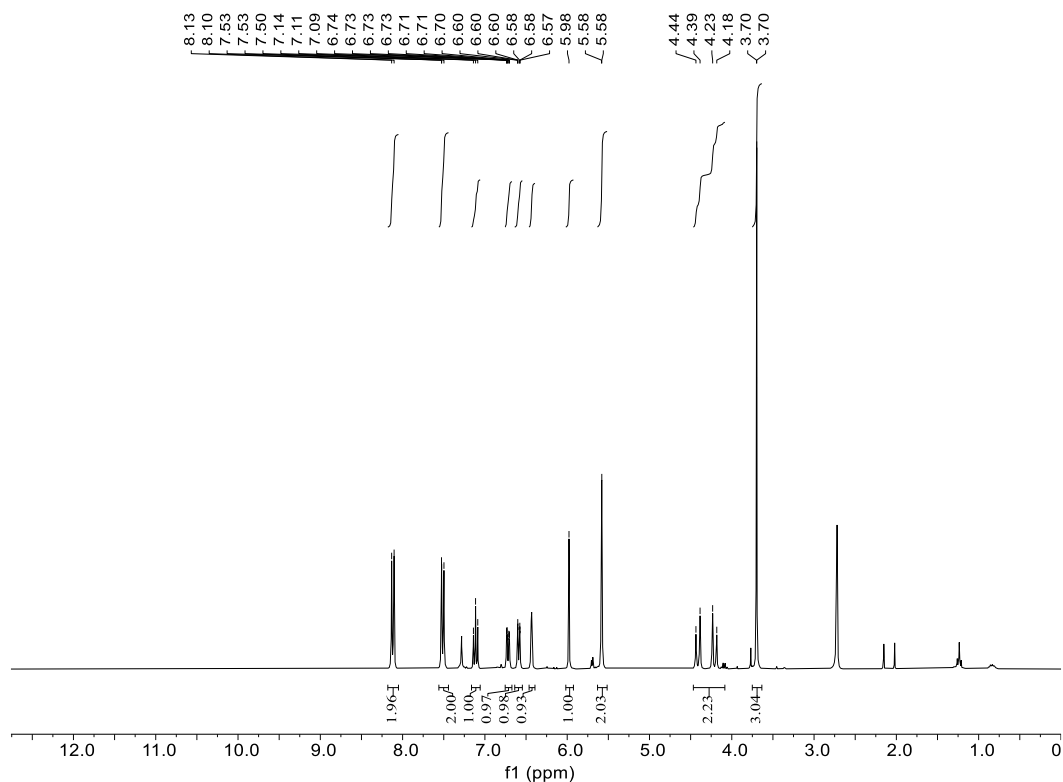
<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 8.15 (d, *J* = 8.3 Hz, 2H, H<sub>1</sub>, H<sub>3</sub>), 7.54 (d, *J* = 8.2 Hz, 2H, H<sub>4</sub>, H<sub>6</sub>), 7.27 – 7.22(m, 3H, H-Ar), 7.08 – 7.00 (m, 2H, H-Ar), 6.76 (s, 1H, NH), 5.91 (s, 1H, C=CH<sub>2</sub>), 5.60 (s, 1H, C=CH<sub>2</sub>), 5.56 (s, 1H, CH-OH), 4.47 – 4.24 (m, 2H, C<sub>11</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 167.38 (C<sub>10</sub>), 148.58 (C<sub>5</sub>), 147.44 (C<sub>2</sub>), 144.41 (C<sub>8</sub>), 137.48 (C<sub>12</sub>), 128.77 (C<sub>14</sub>, C<sub>16</sub>), 127.52 (C<sub>4</sub>, C<sub>6</sub>), 127.04 (C<sub>13</sub>, C<sub>15</sub>, C<sub>17</sub>), 123.67 (C<sub>1</sub>, C<sub>3</sub>), 121.69 (C<sub>9</sub>), 74.40 (C<sub>7</sub>), 43.49 (C<sub>11</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>NaO<sub>4</sub> 335.1002; Found 335.0997.

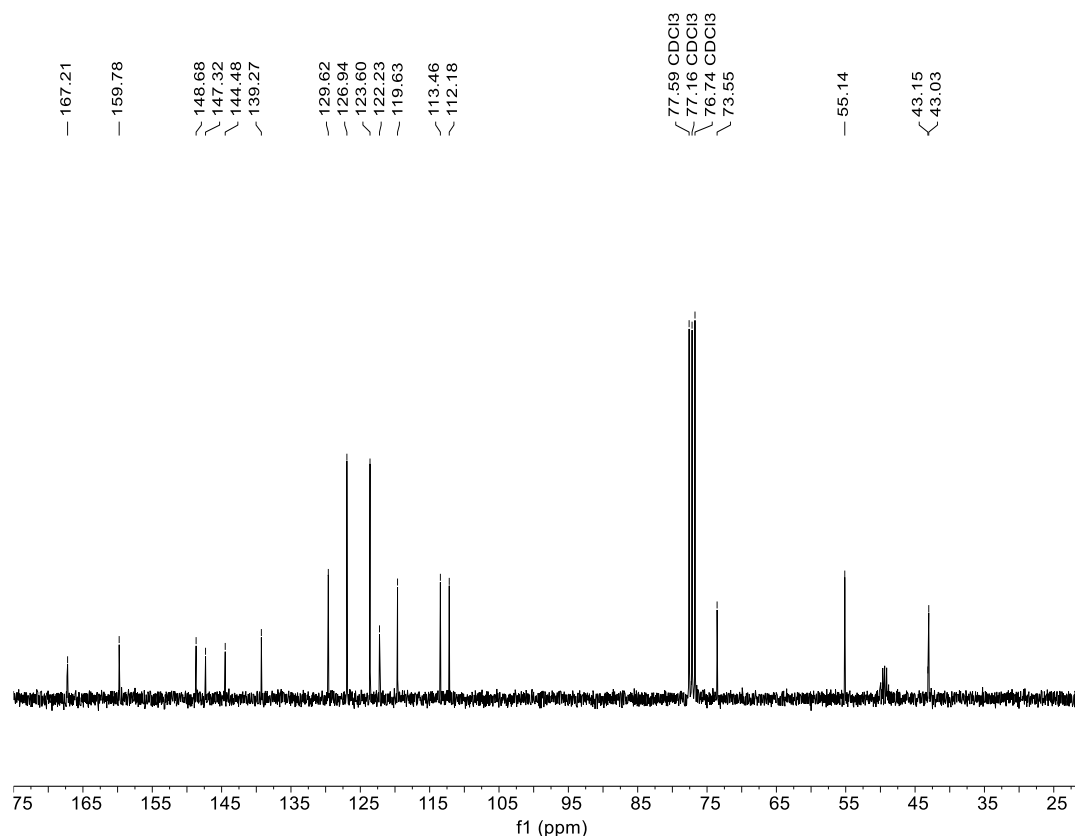


*N*-(4-Methoxybenzyl)-2-[hydroxy(4-nitrophenyl)methyl]acrylamide (C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>)

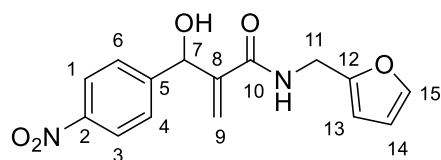


<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 8.12 (d, *J* = 9.0 Hz, 2H, H<sub>1</sub>,H<sub>3</sub>), 7.56 – 7.47 (d, *J* = 9.0 Hz, 2H, H<sub>4</sub>,H<sub>6</sub>), 7.11 (m, 1H, H-Ar), 6.77 – 6.67 (m, 1H, H-Ar), 6.63 – 6.55 (m, 1H, H-Ar), 6.46 – 6.40 (m, 1H, H-Ar), 5.98 (s, 1H, C=CH<sub>2</sub>), 5.61 – 5.55 (m, 2H, C=CH<sub>2</sub>, CH-OH), 4.50 – 4.15 (m, 2H, C<sub>11</sub>), 3.70 (d, *J* = 0.8 Hz, 3H, C<sub>18</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 167.21(C<sub>10</sub>), 159.78 (C<sub>15</sub>), 148.68 (C<sub>5</sub>), 147.32 (C<sub>2</sub>), 144.48 (C<sub>8</sub>), 139.27, 129.62 (C<sub>12</sub>, C<sub>13</sub>, C<sub>17</sub>), 126.94 (C<sub>4</sub>, C<sub>6</sub>), 123.60 (C<sub>1</sub>, C<sub>3</sub>), 122.23, 119.63(C<sub>9</sub>), 113.46 (C<sub>14</sub>), 112.18 (C<sub>16</sub>), 73.55 (C<sub>7</sub>), 55.14 (C<sub>18</sub>), 43.15, 43.03(C<sub>11</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>NaO<sub>5</sub> 365.1108; Found 365.1109.

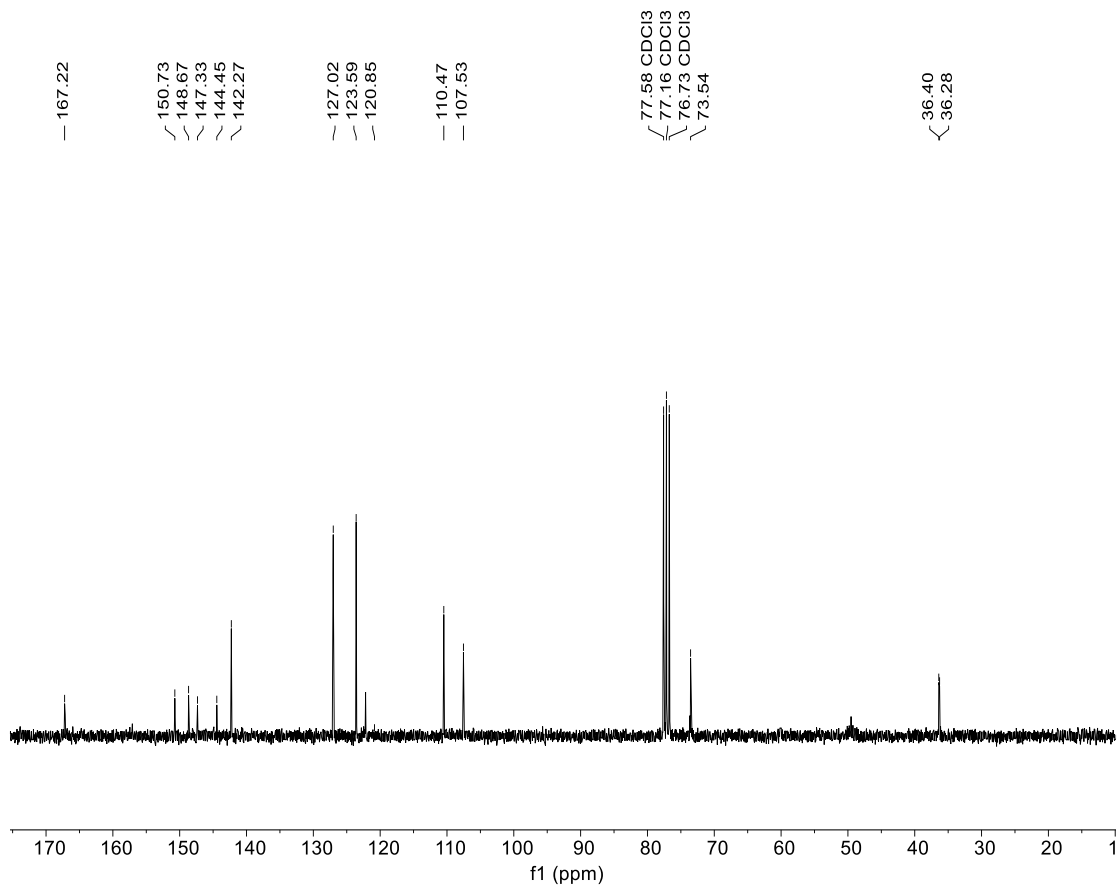
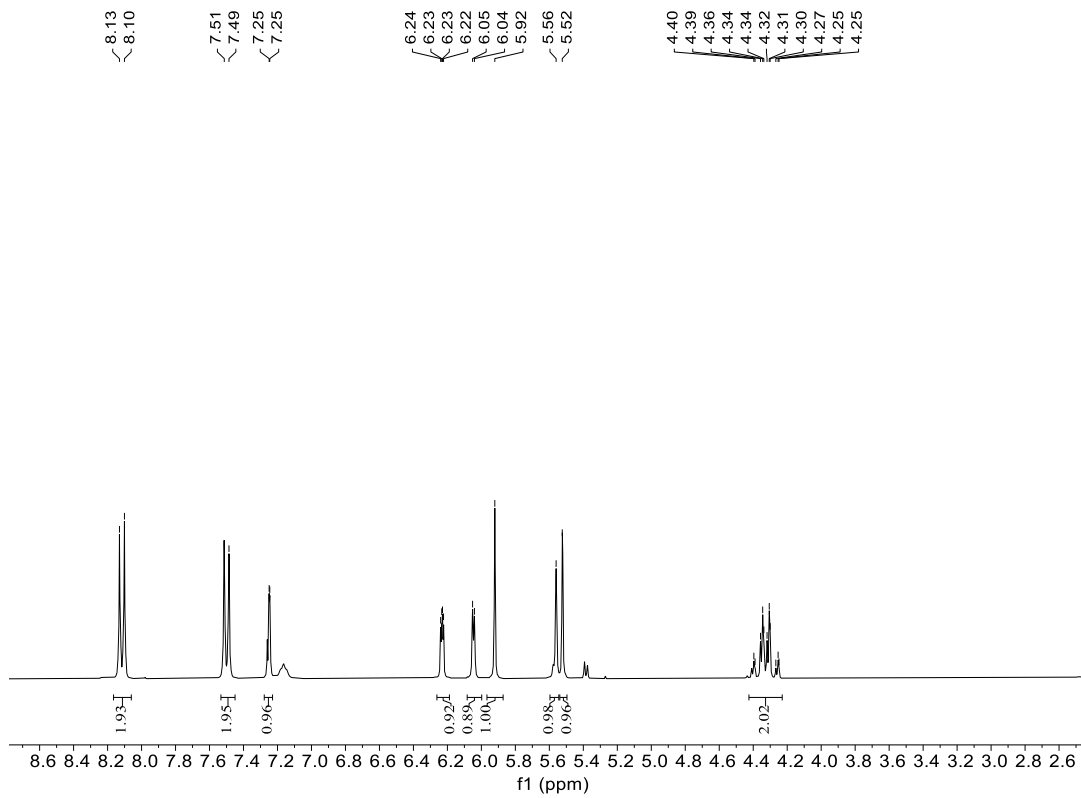




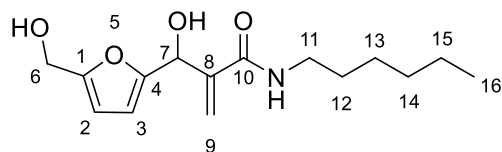
*N*-(Furan-2-ylmethyl)-2-[hydroxy(4-nitrophenyl)methyl]acrylamide (C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O<sub>5</sub>)



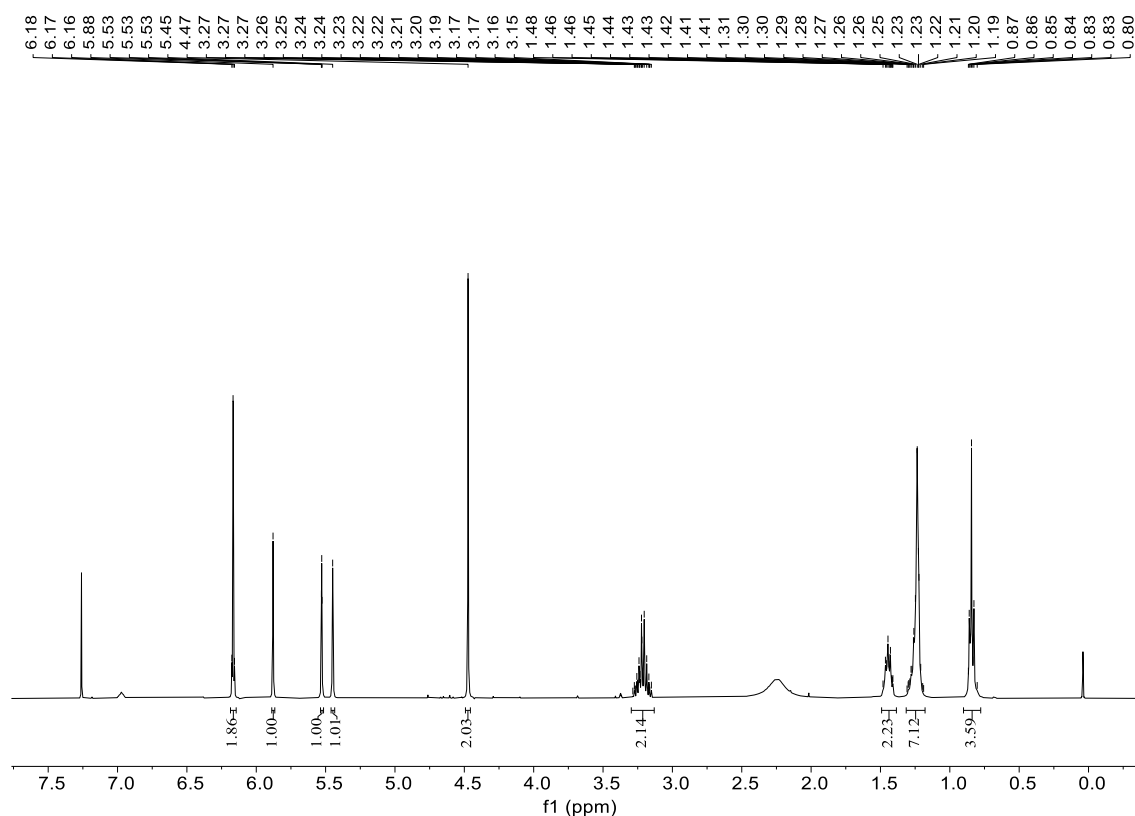
<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 8.12 (d, *J* = 8.8 Hz, 2H, H<sub>1</sub>,H<sub>3</sub>), 7.50 (d, *J* = 8.3 Hz, 2H, H<sub>4</sub>,H<sub>6</sub>), 7.25 (s, 1H, NH), 6.23 (dd, *J* = 3.2, 1.9 Hz, 1H, H<sub>13</sub>), 6.05 (d, *J* = 3.2 Hz, 1H, H<sub>14</sub>), 5.92 (s, 1H, C=CH<sub>2</sub>), 5.56 (s, 1H, C=CH<sub>2</sub>), 5.52 (s, 1H, CH-OH), 4.47 – 4.22 (m, 2H, C<sub>11</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 167.22 (C<sub>10</sub>), 150.73 (C<sub>5</sub>), 148.67 (C<sub>2</sub>), 147.33 (C<sub>12</sub>), 144.45 (C<sub>8</sub>), 142.27 (C<sub>15</sub>), 127.02 (C<sub>4</sub>, C<sub>6</sub>), 123.59 (C<sub>1</sub>, C<sub>3</sub>), 120.85 (C<sub>9</sub>), 110.47 (C<sub>13</sub>), 107.53 (C<sub>14</sub>), 73.54 (C<sub>7</sub>), 36.40, 36.28 (C<sub>11</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>NaO<sub>5</sub> 325.0795; Found 325.0790.

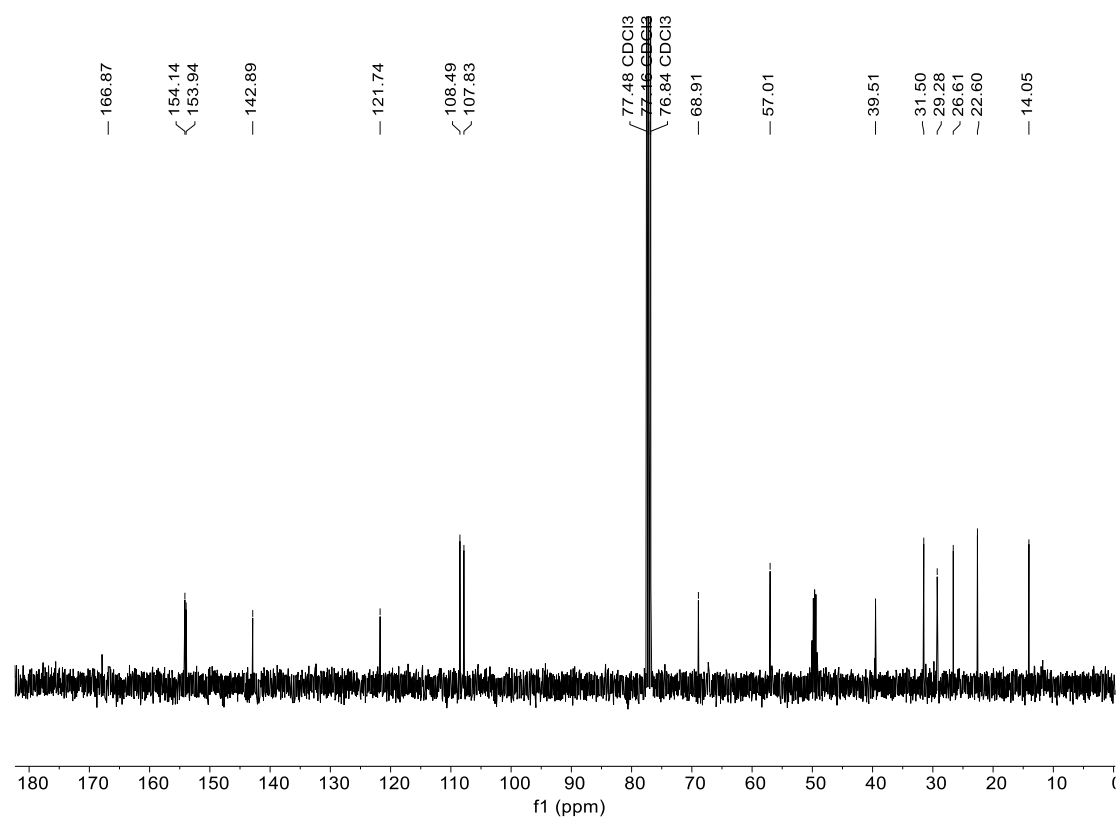


*N*-Hexyl-2-{hydroxyl[5-(hydroxymethyl)furan-2-yl]methyl}acrylamide (C<sub>15</sub>H<sub>23</sub>NO<sub>4</sub>)

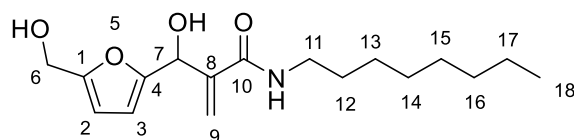


<sup>1</sup>H NMR (400 MHz, Chloroform-*d*): δ 6.17 (s, 2H, H<sub>2</sub>, H<sub>3</sub>), 5.88 (s, 1H, C=CH<sub>2</sub>), 5.53 (d, *J* = 0.9 Hz, 1H, C=CH<sub>2</sub>), 5.45 (s, 1H, CH-OH), 4.47 (s, 2H, H<sub>6</sub>), 3.31 – 3.13 (m, 2H, H<sub>11</sub>), 1.44 (td, *J* = 8.6, 7.9, 5.4 Hz, 2H, H<sub>12</sub>), 1.32 – 1.21 (m, 6H, H<sub>13-15</sub>), 0.88 – 0.80 (m, 3H, H<sub>16</sub>). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 166.87 (C<sub>10</sub>), 154.14 (C<sub>1</sub>), 153.94 (C<sub>4</sub>), 142.89 (C<sub>8</sub>), 121.74 (C<sub>9</sub>), 108.49 (C<sub>3</sub>), 107.83 (C<sub>2</sub>), 68.91 (C<sub>7</sub>), 57.01 (C<sub>6</sub>), 39.51 (C<sub>11</sub>), 31.50 (C<sub>14</sub>), 29.28 (C<sub>12</sub>), 26.61 (C<sub>13</sub>), 22.60 (C<sub>15</sub>), 14.05 (C<sub>16</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>15</sub>H<sub>23</sub>NNaO<sub>4</sub> 304.1519; Found 304.1511.



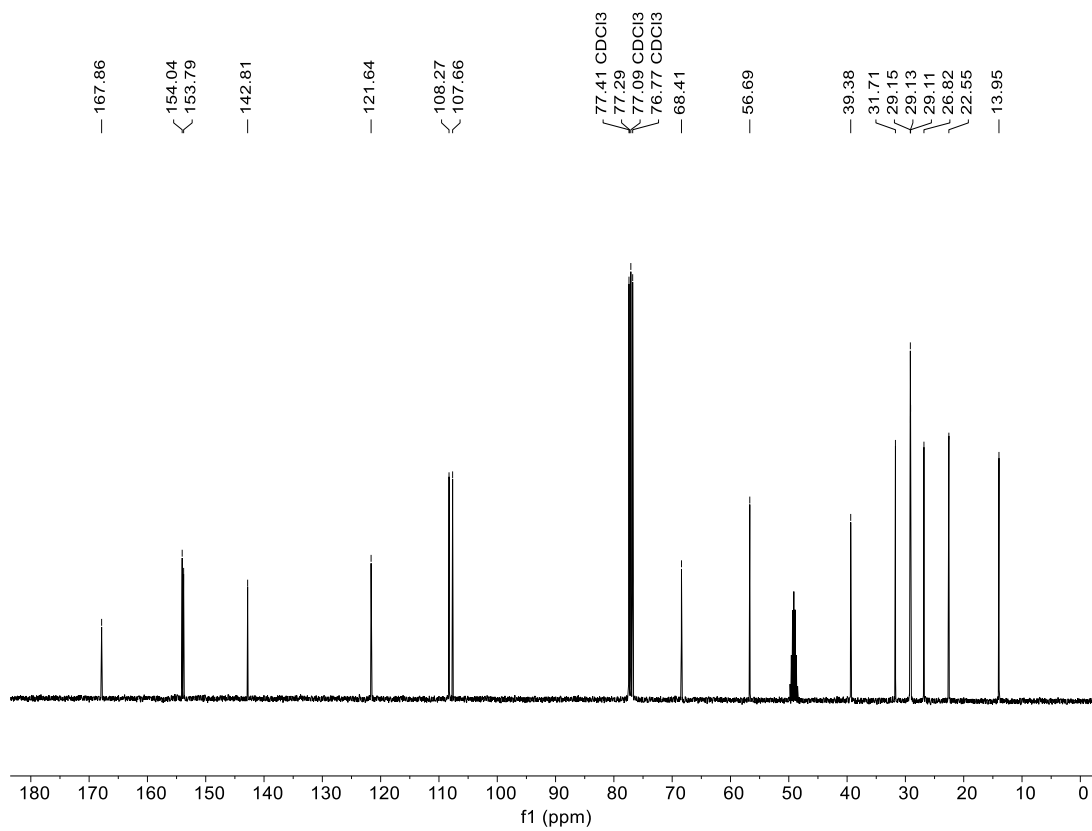
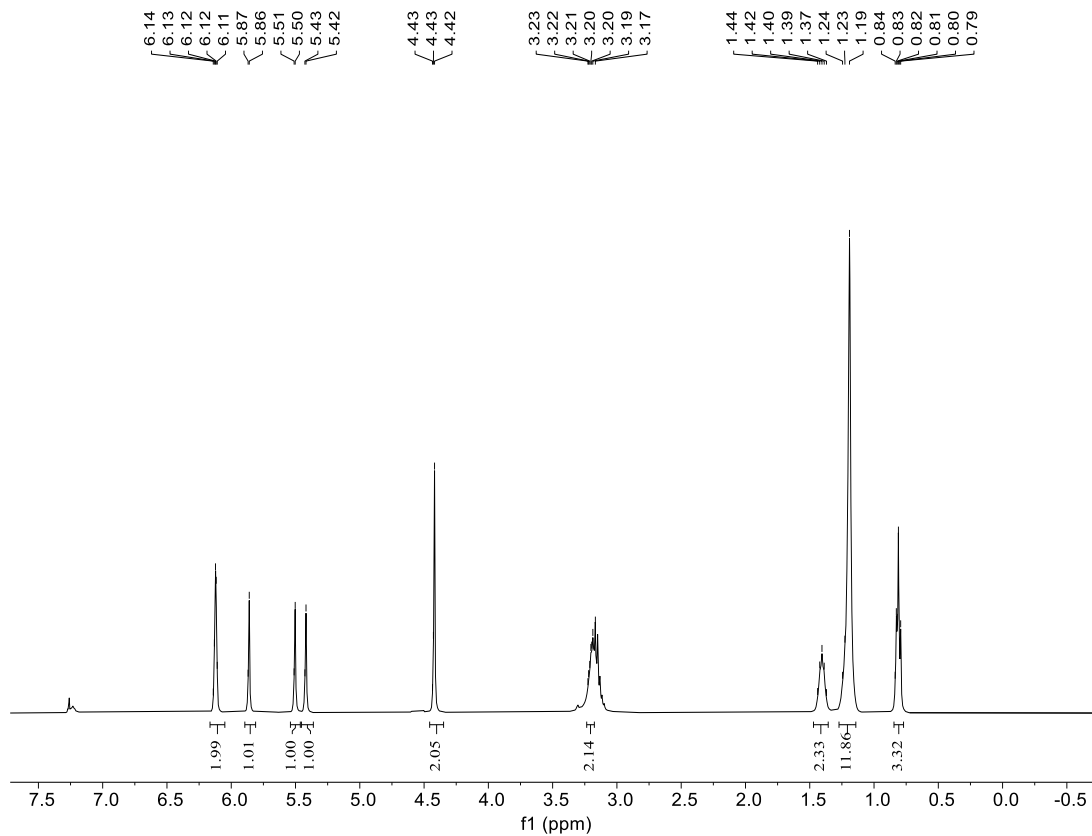


*N*-Octyl-2-[hydroxyl[5-(hydroxymethyl)furan-2-yl]methyl]acrylamide (C<sub>17</sub>H<sub>27</sub>NO<sub>4</sub>)

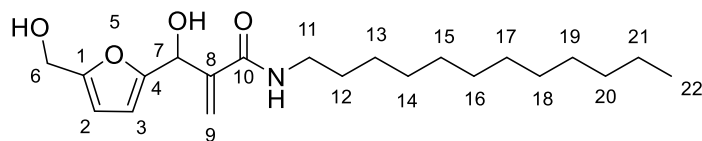


<sup>1</sup>H NMR (400 MHz, Chloroform-*d*): δ 6.14 (s, 2H, H<sub>2</sub>, H<sub>3</sub>), 5.89 (d, *J* = 3.5 Hz, 1H, C=CH<sub>2</sub>, a), 5.53 (d, *J* = 3.5 Hz, 1H, C=CH<sub>2</sub>, b), 5.45 (d, *J* = 3.4 Hz, 1H, CH-OH), 4.45 (d, *J* = 3.6 Hz, 2H, H<sub>6</sub>), 3.25 – 3.20 (m, 2H, H<sub>11</sub>), 1.43 (t, *J* = 6.9 Hz, 2H, H<sub>12</sub>), 1.21 (s, 11H, H<sub>13-17</sub>), 0.84 (td, *J* = 6.8, 3.4 Hz, 3H, H<sub>18</sub>). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 167.86 (C<sub>10</sub>), 154.04 (C<sub>1</sub>), 153.79 (C<sub>4</sub>), 142.81 (C<sub>8</sub>), 121.64 (C<sub>9</sub>), 108.27 (C<sub>3</sub>), 107.66 (C<sub>2</sub>), 68.41 (C<sub>7</sub>), 56.69 (C<sub>6</sub>), 39.38 (C<sub>11</sub>), 31.71 (C<sub>16</sub>), 29.15, 29.13, 29.11 (C<sub>12</sub>, C<sub>14</sub>, C<sub>15</sub>), 26.82 (C<sub>13</sub>), 22.55 (C<sub>17</sub>), 13.95 (C<sub>18</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>17</sub>H<sub>27</sub>NNaO<sub>4</sub> 332.1832; Found 332.1838.

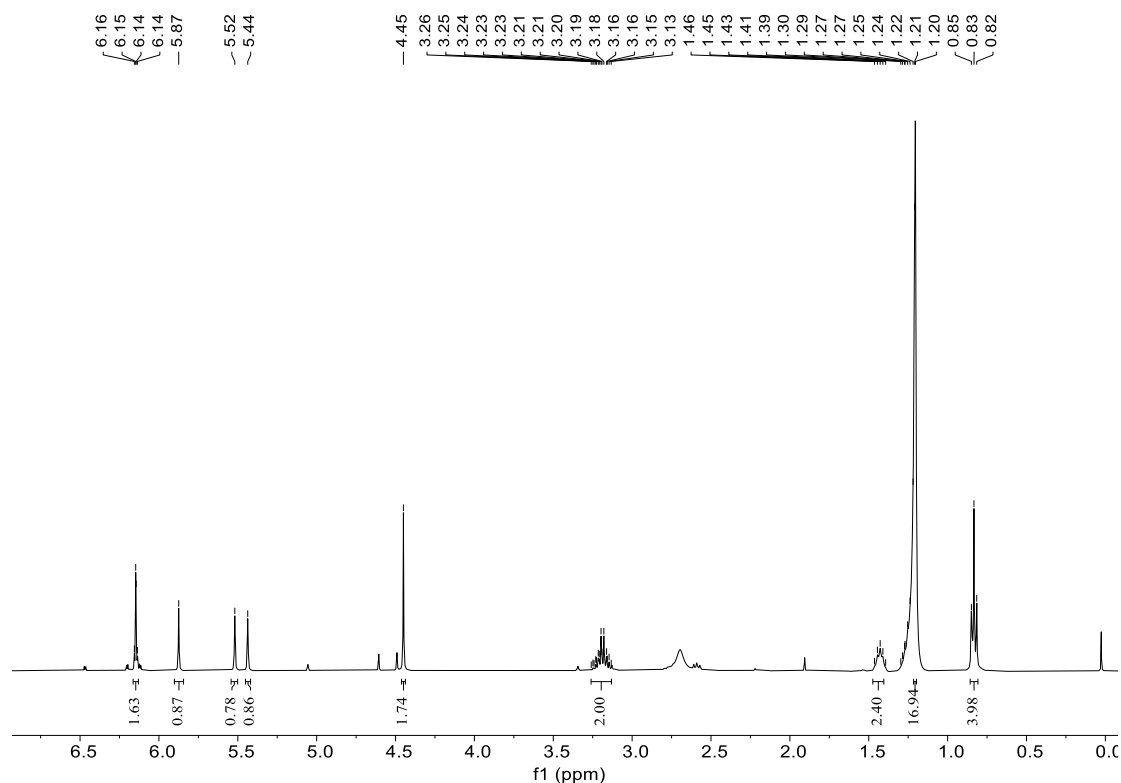


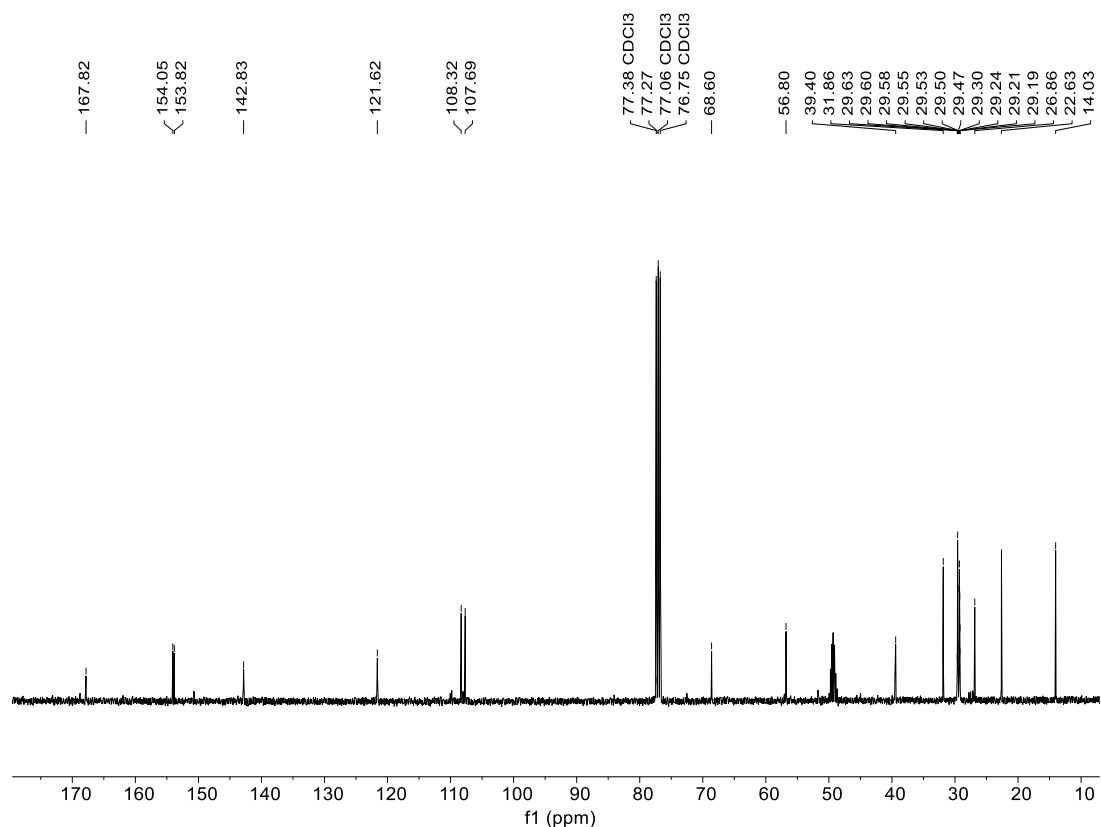


*N*-Dodecyl-2-{hydroxyl[5-(hydroxymethyl)furan-2-yl]methyl}acrylamide (C<sub>21</sub>H<sub>35</sub>NO<sub>4</sub>)

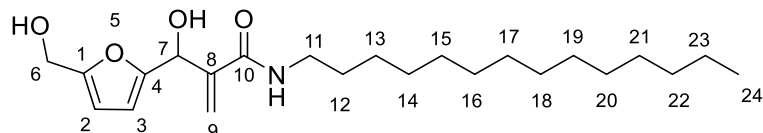


<sup>1</sup>H NMR (400 MHz, Chloroform-*d*): δ 6.16 – 6.13 (m, 2H, H<sub>2</sub>, H<sub>3</sub>), 5.87 (s, 1H, C=CH<sub>2</sub>), 5.52 (s, 1H, C=CH<sub>2</sub>), 5.44 (s, 1H, CH-OH), 4.45 (s, 2H, H<sub>6</sub>), 3.27 – 3.09 (m, 2H, H<sub>11</sub>), 1.47 – 1.39 (m, 2H, H<sub>12</sub>), 1.21 – 1.19 (m, 20H, H<sub>13-21</sub>), 0.83 (t, *J* = 6.7 Hz, 3H, H<sub>22</sub>). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 167.82 (C<sub>10</sub>), 154.05 (C<sub>1</sub>), 153.82 (C<sub>4</sub>), 142.83 (C<sub>8</sub>), 121.62 (C<sub>9</sub>), 108.32 (C<sub>3</sub>), 107.69 (C<sub>2</sub>), 68.60 (C<sub>7</sub>), 56.80 (C<sub>6</sub>), 39.40 (C<sub>11</sub>), 31.86 (C<sub>20</sub>), 29.63, 29.60, 29.58, 29.55, 29.53, 29.50, 29.47, 29.30, 29.24, 29.21, 29.19 (C<sub>12</sub>, C<sub>14-19</sub>), 26.86 (C<sub>13</sub>), 22.63 (C<sub>21</sub>), 14.03 (C<sub>22</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>21</sub>H<sub>35</sub>NNaO<sub>4</sub> 388.2458; Found 388.2450

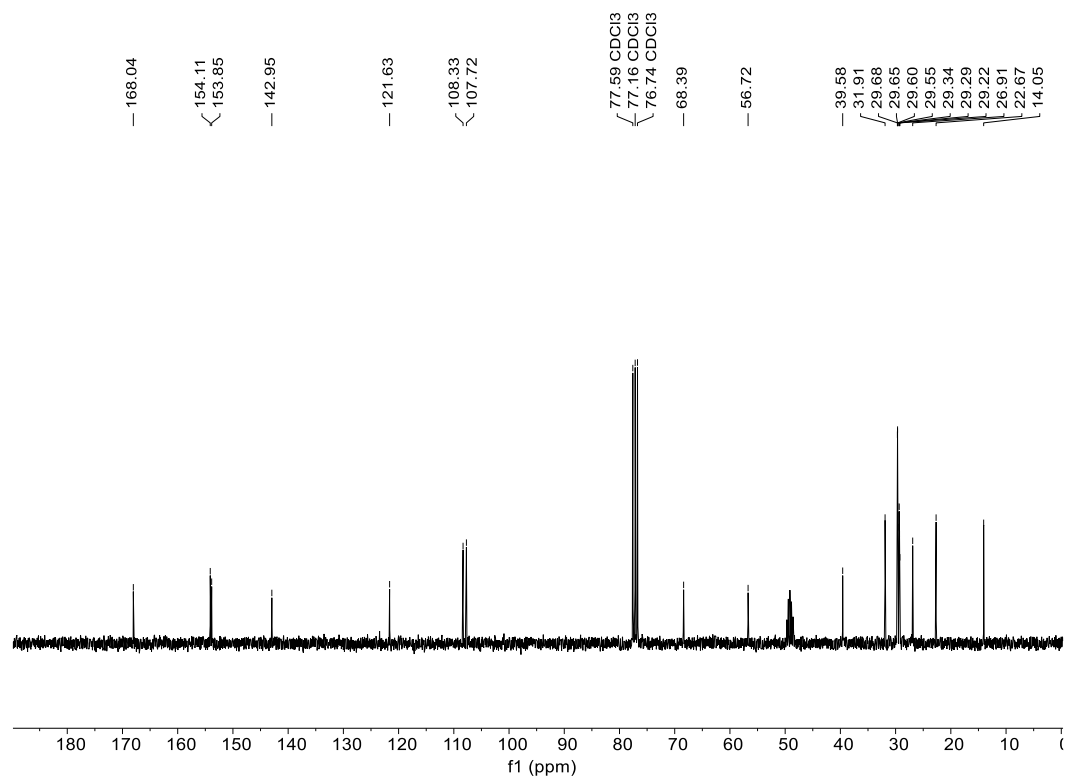
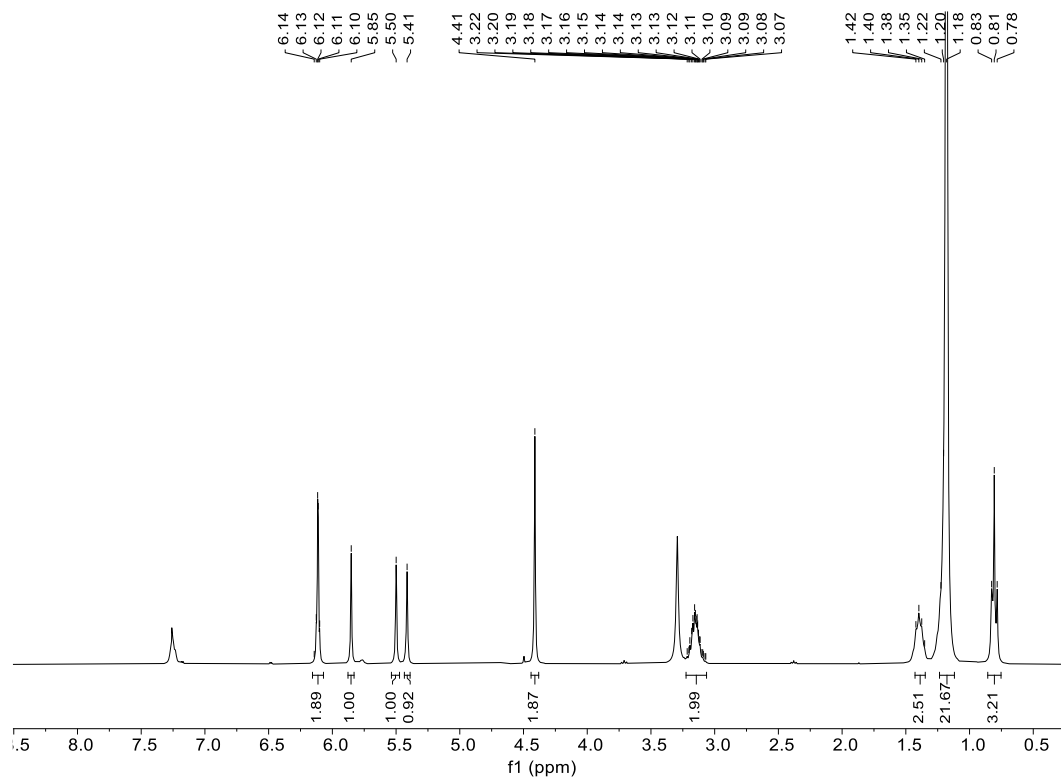




*N*-Tetradecyl-2-{hydroxyl[5-(hydroxymethyl)furan-2-yl]methyl}acrylamide  
(C<sub>23</sub>H<sub>39</sub>NO<sub>4</sub>)

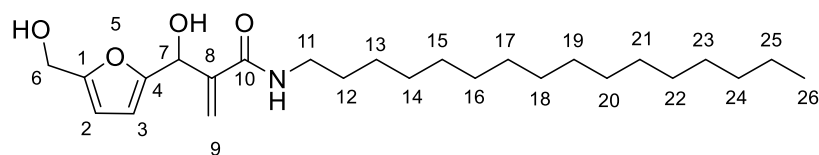


<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 6.12 (d, *J* = 2.3 Hz, 2H, H<sub>2</sub>, H<sub>3</sub>), 5.85 (s, 1H, C=CH<sub>2</sub>), 5.50 (s, 1H, C=CH<sub>2</sub>), 5.41 (s, 1H, CH-OH), 4.41 (s, 2H, H<sub>6</sub>), 3.14 (s, 2H, H<sub>11</sub>), 1.39 (q, *J* = 6.9 Hz, 2H, H<sub>12</sub>), 1.18 (s, 22H, H<sub>13-23</sub>), 0.86 – 0.75 (m, 3H, H<sub>24</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 168.04 (C<sub>10</sub>), 154.11(C<sub>1</sub>), 153.85(C<sub>4</sub>), 142.95 (C<sub>8</sub>), 121.63 (C<sub>9</sub>), 108.33 (C<sub>3</sub>), 107.72 (C<sub>2</sub>), 68.39 (C<sub>7</sub>), 56.72 (C<sub>6</sub>), 39.58 (C<sub>11</sub>), 31.91(C<sub>22</sub>), 29.68, 29.65, 29.60, 29.55, 29.34, 29.29, 29.22(C<sub>12</sub>, C<sub>14-21</sub>), 26.91(C<sub>13</sub>), 22.67 (C<sub>23</sub>), 14.05 (C<sub>24</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>23</sub>H<sub>39</sub>NNaO<sub>4</sub> 416.2771; Found 416.2773.

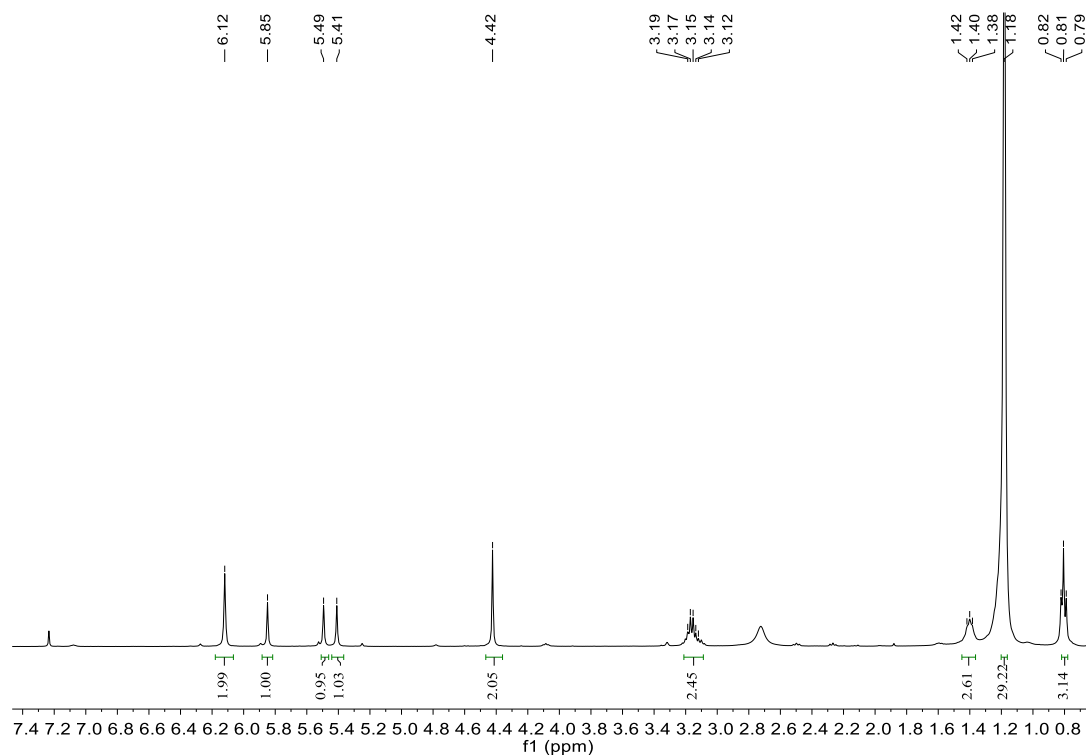


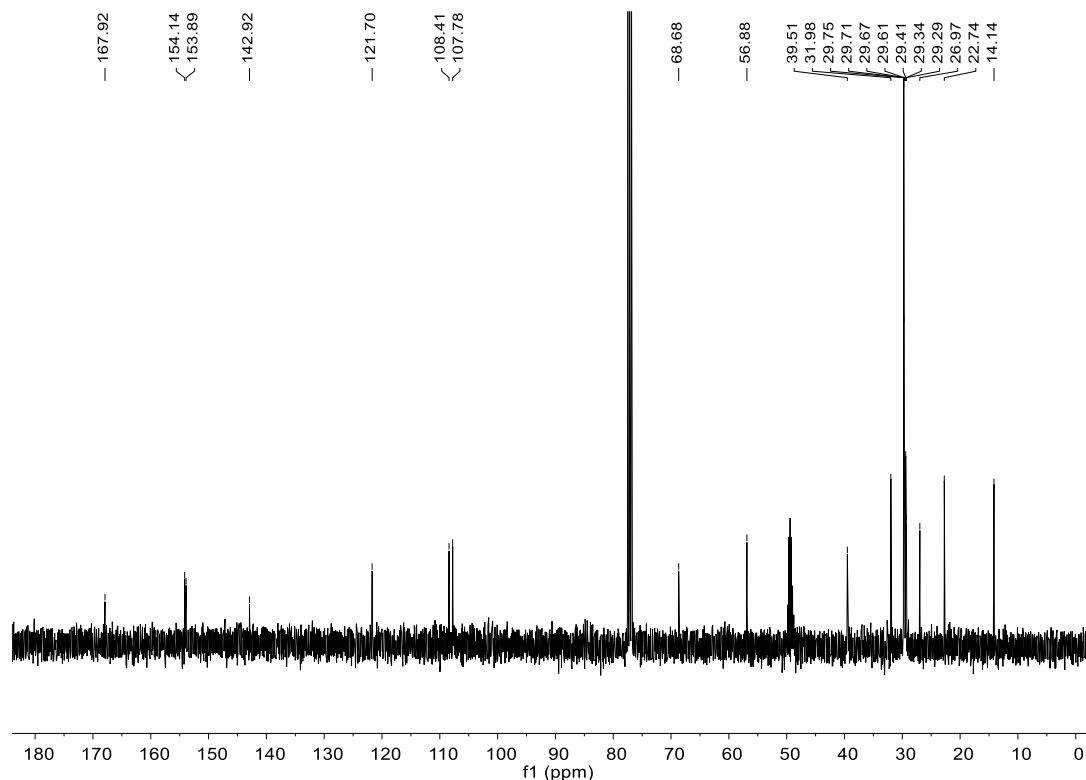
*N*-Hexadecyl-2-{hydroxyl[5-(hydroxymethyl)furan-2-yl]methyl}crylamide

(C<sub>25</sub>H<sub>43</sub>NO<sub>4</sub>)

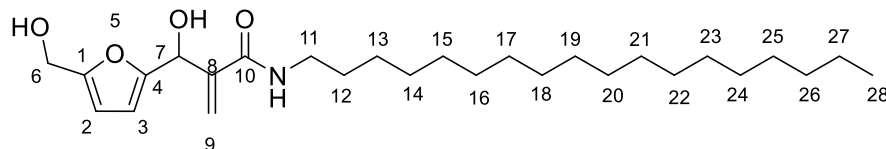


<sup>1</sup>H NMR (400 MHz, Chloroform-*d*): δ 6.12 (s, 2H, H<sub>2</sub>, H<sub>3</sub>), 5.85 (s, 1H, C=CH<sub>2</sub>), 5.49 (s, 1H, C=CH<sub>2</sub>), 5.41 (s, 1H, CH-OH), 4.42 (s, 2H, H<sub>6</sub>), 3.16 (q, *J* = 6.7 Hz, 2H, H<sub>11</sub>), 1.40 (t, *J* = 7.0 Hz, 2H, H<sub>12</sub>), 1.18 (s, 26H, H<sub>13-25</sub>), 0.81 (t, *J* = 6.6 Hz, 3H, H<sub>26</sub>). <sup>13</sup>C NMR (101 MHz, Chloroform-*d*): δ 167.92 (C<sub>10</sub>), 154.1 (C<sub>1</sub>), 153.89 (C<sub>4</sub>), 142.92 (C<sub>8</sub>), 121.70 (C<sub>9</sub>), 108.41 (C<sub>3</sub>), 107.78 (C<sub>2</sub>), 68.68 (C<sub>7</sub>), 56.88 (C<sub>6</sub>), 39.50 (C<sub>11</sub>), 31.98 (C<sub>24</sub>), 29.87 – 28.99 (m) (C<sub>12</sub>, C<sub>14-23</sub>), 26.97 (C<sub>13</sub>), 22.74 (C<sub>25</sub>), 14.14 (C<sub>26</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>25</sub>H<sub>43</sub>NNaO<sub>4</sub> 444.3084; Found 444.3078.

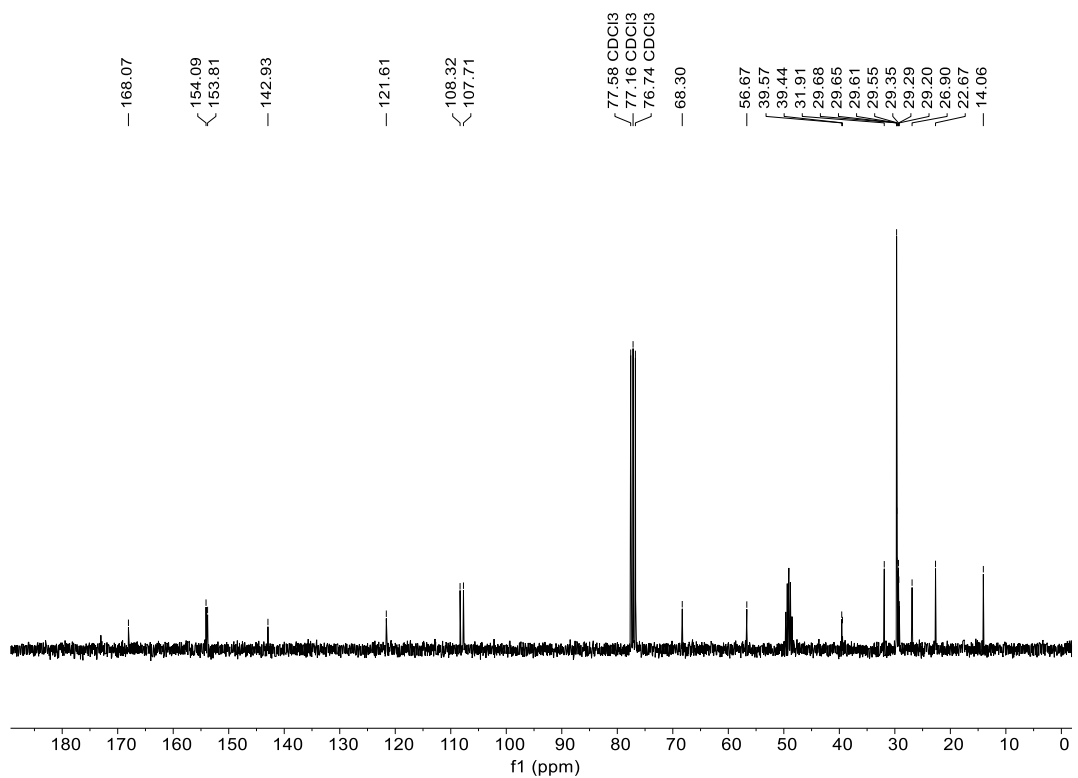
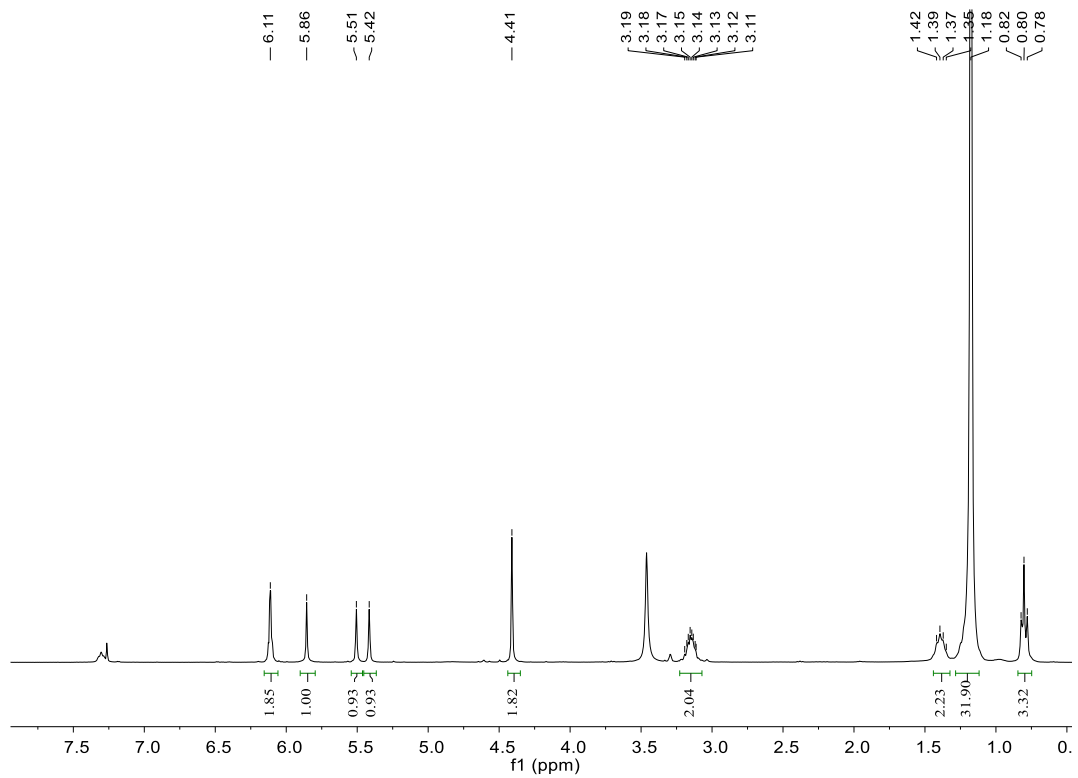




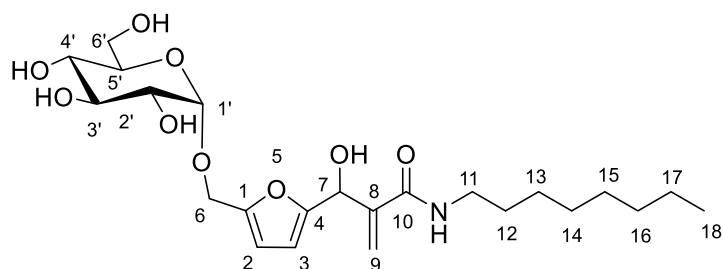
*N*-Octadecyl-2-{hydroxyl[5-(hydroxymethyl)furan-2-yl]methyl}acrylamide  
(C<sub>27</sub>H<sub>47</sub>NO<sub>4</sub>)



<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 6.11 (d, *J* = 1.9 Hz, 2H, H<sub>2</sub>, H<sub>3</sub>), 5.86 (s, 1H, C=CH<sub>2</sub>), 5.51 (s, 1H, C=CH<sub>2</sub>), 5.42 (s, 1H, CH-OH), 4.41 (s, 2H, H<sub>6</sub>), 3.15 (dt, *J* = 6.8, 3.1 Hz, 2H, H<sub>11</sub>), 1.38 (d, *J* = 7.0 Hz, 2H, H<sub>12</sub>), 1.18 (s, 30H, H<sub>13-27</sub>), 0.80 (t, *J* = 6.6 Hz, 3H, H<sub>28</sub>). <sup>13</sup>C NMR (76 MHz, Chloroform-*d*): δ 168.07 (C<sub>10</sub>), 154.09 (C<sub>1</sub>), 153.81 (C<sub>4</sub>), 142.93 (C<sub>8</sub>), 121.61 (C<sub>9</sub>), 108.32 (C<sub>3</sub>), 107.71 (C<sub>2</sub>), 68.30 (C<sub>7</sub>), 56.67 (C<sub>6</sub>), 39.57 (C<sub>11</sub>), 31.91 (C<sub>26</sub>), 30.01 – 28.81 (m) (C<sub>12</sub>, C<sub>14-25</sub>), 26.90 (C<sub>13</sub>), 22.67 (C<sub>27</sub>), 14.07 (C<sub>28</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>27</sub>H<sub>47</sub>NNaO<sub>4</sub> 472.3397; Found 472.3384.

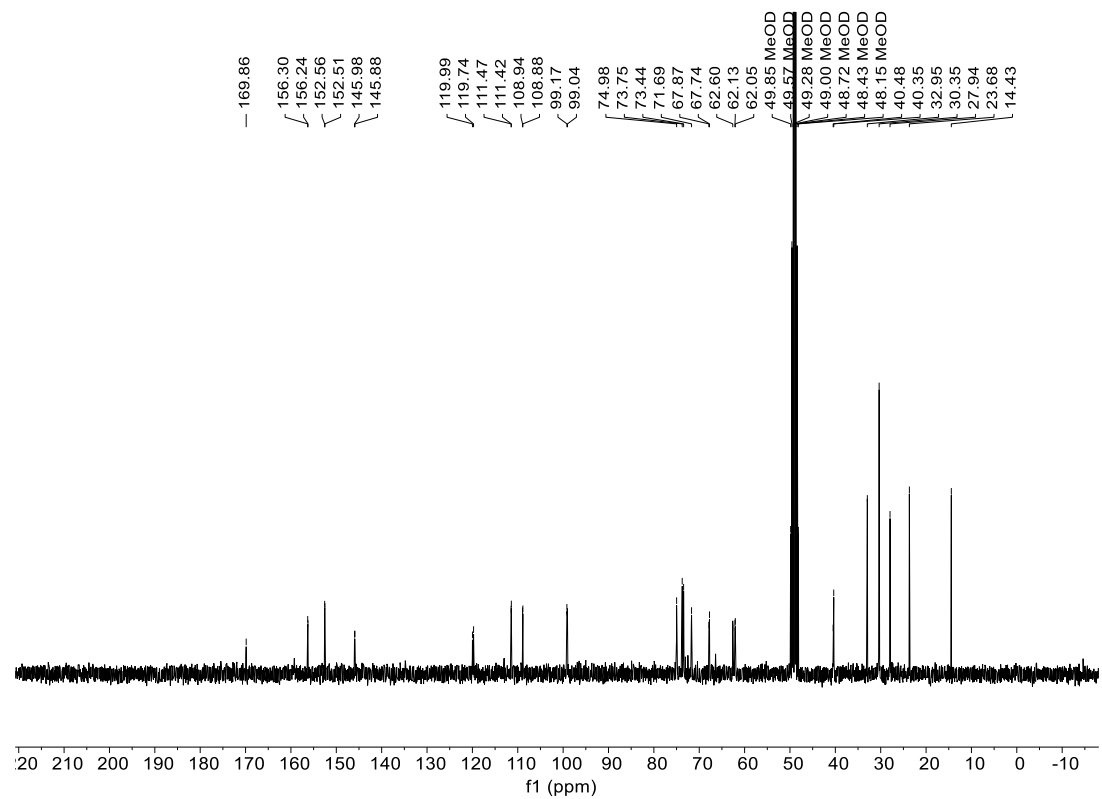
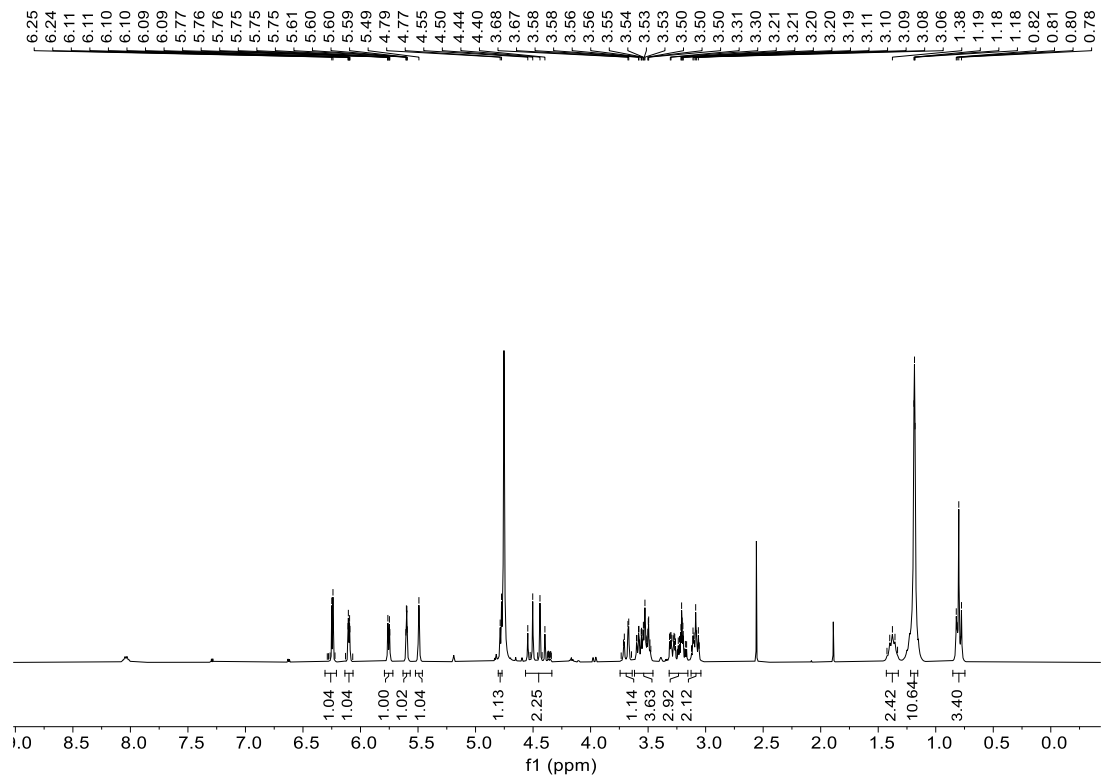


*N*-Octyl-2-{hydroxyl[5-( $\alpha$ -D-glucopyranosyloxymethyl)-furan-2-yl]methyl}acrylamide  
(C<sub>23</sub>H<sub>37</sub>NO<sub>9</sub>)

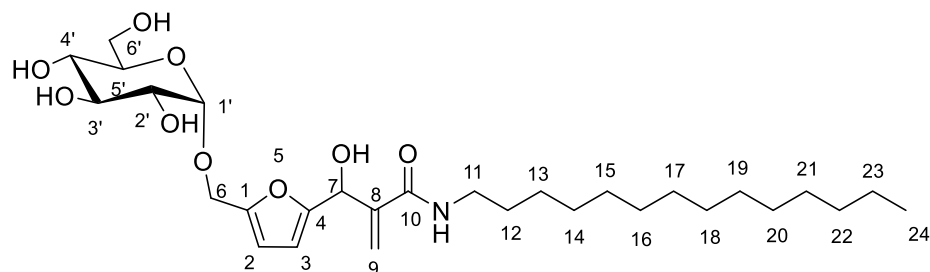


<sup>1</sup>H NMR (300 MHz, Methanol-*d*<sub>4</sub>):  $\delta$  6.24 (d,  $J$  = 3.2 Hz, 1H, H<sub>2</sub>), 6.10 (dt,  $J$  = 3.2, 0.9 Hz, 1H, H<sub>3</sub>), 5.75 (dd,  $J$  = 4.0, 1.0 Hz, 1H, C=CH<sub>2</sub>), 5.60 (q,  $J$  = 1.3 Hz, 1H, C=CH<sub>2</sub>), 5.49 (s, 1H, CH-OH), 4.78 (d,  $J$  = 3.5 Hz, 1H, H<sub>1'</sub>), 4.57 – 4.34 (m, 2H, H<sub>6</sub>), 3.69 (dd,  $J$  = 11.6, 2.2 Hz, 1H, H<sub>6'a</sub>), 3.62 – 3.46 (m, 3H, H<sub>6'b</sub>, H<sub>3'</sub>, H<sub>5'</sub>), 3.32 – 3.15 (m, 2H, H<sub>4'</sub>, H<sub>2'</sub>), 3.09 (td,  $J$  = 6.8, 4.3 Hz, 2H, H<sub>11</sub>), 1.38 (d,  $J$  = 7.0 Hz, 2H, H<sub>12</sub>), 1.22 – 1.16 (m, 10H, H<sub>13-17</sub>), 0.85 – 0.75 (m, 3H, H<sub>18</sub>). <sup>13</sup>C NMR (75 MHz, Methanol-*d*<sub>4</sub>):  $\delta$  169.86 (C<sub>10</sub>), 156.30, 156.24 (C<sub>4</sub>), 152.56, 152.51 (C<sub>1</sub>), 145.98, 145.88 (C<sub>8</sub>), 119.99, 119.74 (C<sub>9</sub>), 111.47, 111.42 (C<sub>3</sub>), 108.94, 108.88 (C<sub>2</sub>), 99.17, 99.04 (C<sub>1'</sub>), 74.98 (C<sub>5'</sub>), 73.75 (C<sub>7</sub>), 73.44 (C<sub>3'</sub>), 71.69 (C<sub>2'</sub>), 67.87, 67.74 (C<sub>4'</sub>), 62.60 (C<sub>6</sub>), 62.13, 62.05 (C<sub>6'</sub>), 40.48 (C<sub>11</sub>), 40.35 (C<sub>12</sub>), 32.95, 30.35, 27.94 (C<sub>13-16</sub>), 23.68 (C<sub>17</sub>), 14.43 (C<sub>18</sub>). HRMS (ESI)  $m/z$ : Calcd for [M+Na]<sup>+</sup> C<sub>23</sub>H<sub>37</sub>NNaO<sub>9</sub> 494.2361; Found 494.2361.

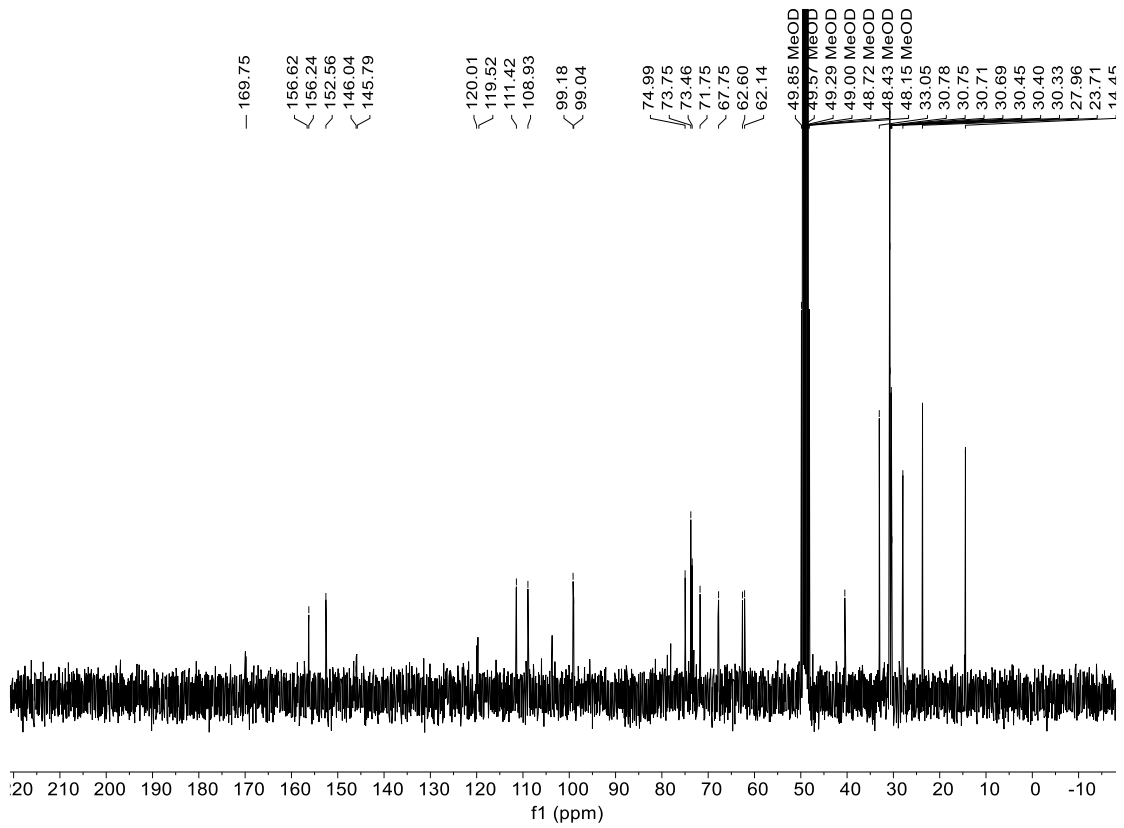
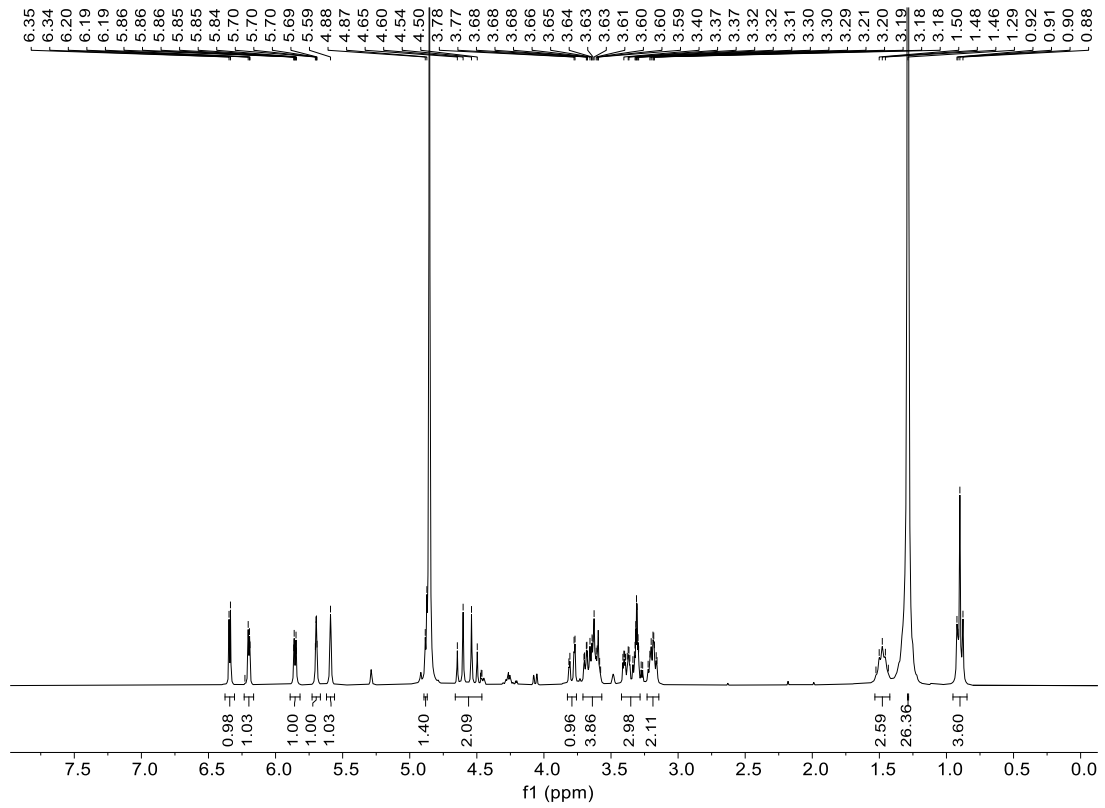




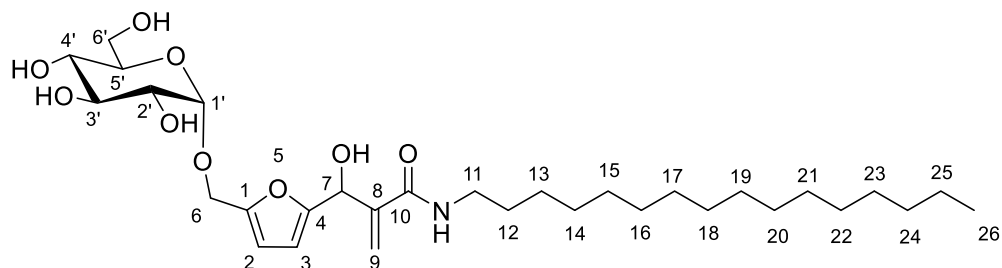
*N*-Tetradecyl-2-{hydroxyl[5-( $\alpha$ -D-glucopyranosyloxymethyl)-furan-2 yl]methyl} acrylamide (C<sub>29</sub>H<sub>49</sub>NO<sub>9</sub>)



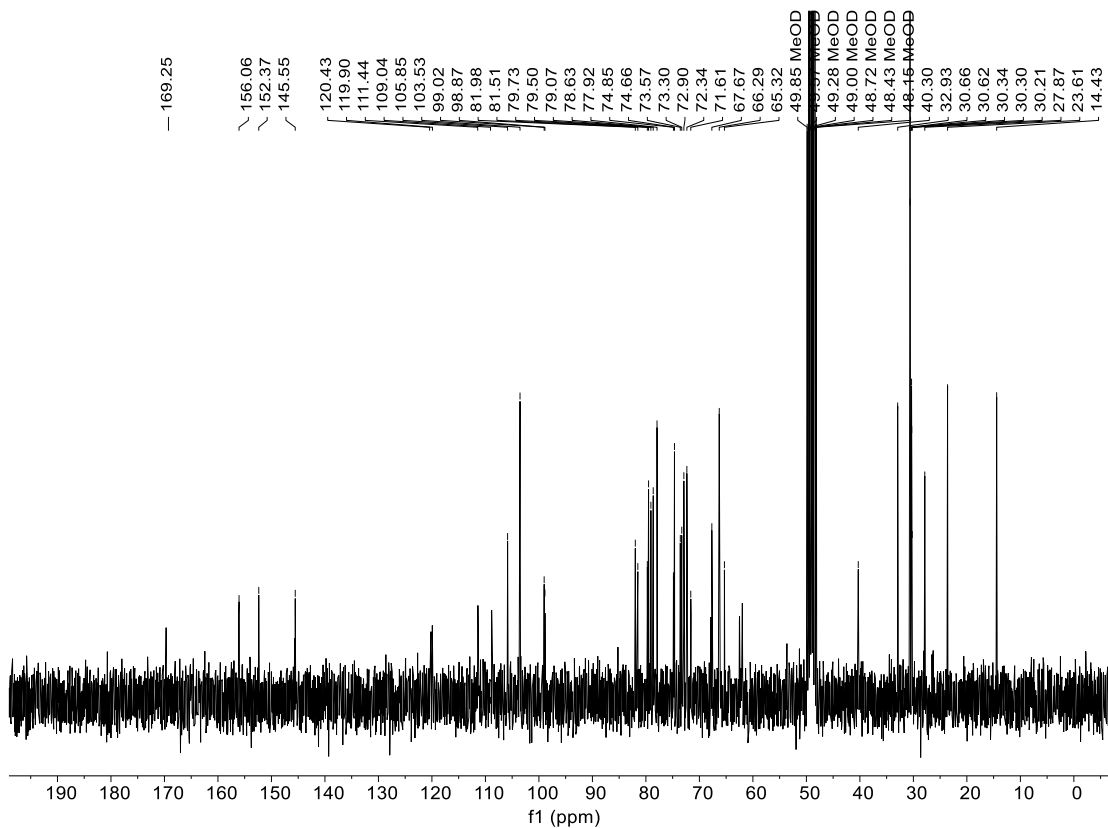
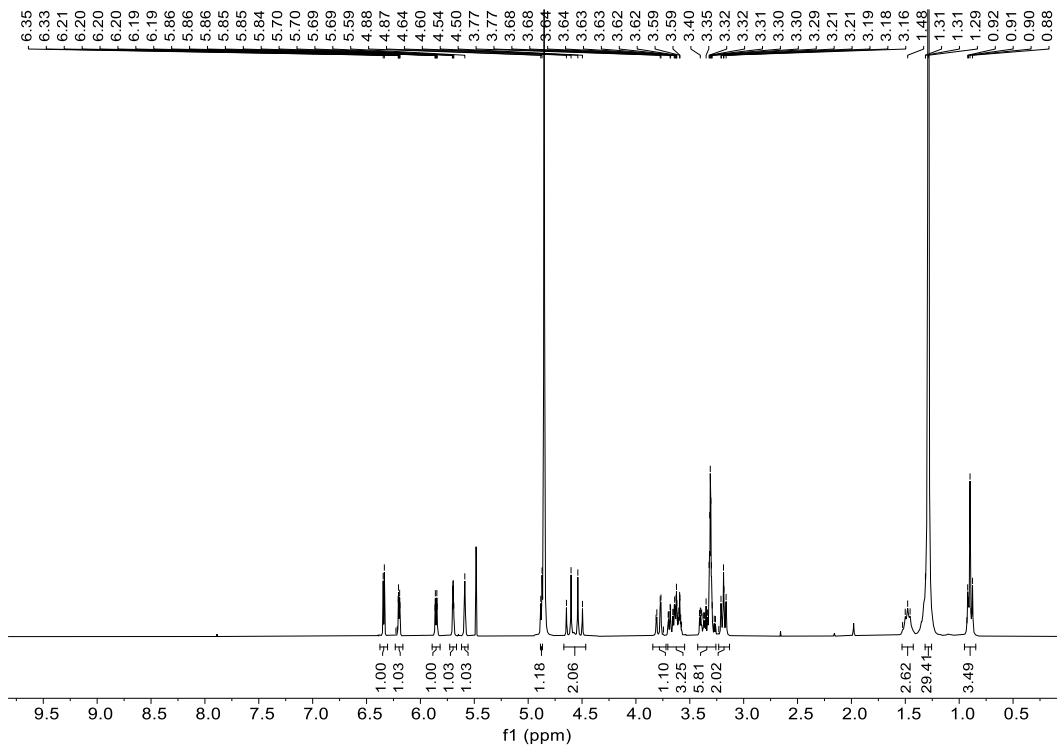
<sup>1</sup>H NMR (300 MHz, Methanol-*d*<sub>4</sub>):  $\delta$  6.34 (d,  $J$  = 3.2 Hz, 1H, H<sub>2</sub>), 6.20 (d,  $J$  = 3.0 Hz, 1H, H<sub>3</sub>), 5.86 (dd,  $J$  = 4.1, 1.0 Hz, 1H, C=CH<sub>2</sub>), 5.70 (q,  $J$  = 1.3 Hz, 1H, C=CH<sub>2</sub>), 5.59 (s, 1H, CH-OH), 4.88 (d,  $J$  = 3.6 Hz, 1H, H<sub>1'</sub>), 4.66 – 4.46 (m, 2H, H<sub>6</sub>), 3.79 (dd,  $J$  = 11.5, 2.1 Hz, 1H, H<sub>6'a</sub>), 3.71 – 3.57 (m, 3H, H<sub>6'b</sub>, H<sub>3</sub>, H<sub>5</sub>), 3.42 – 3.28 (m, 2H, H<sub>2'</sub>, H<sub>4'</sub>), 3.19 (qd,  $J$  = 6.3, 5.9, 2.9 Hz, 2H, H<sub>11</sub>), 1.48 (t,  $J$  = 6.9 Hz, 2H, H<sub>12</sub>), 1.29 (s, 22H, H<sub>13-23</sub>), 0.95 – 0.85 (m, 33H, H<sub>24</sub>). <sup>13</sup>C NMR (75 MHz, Methanol-*d*<sub>4</sub>):  $\delta$  169.75 (C<sub>10</sub>), 156.62, 156.24 (C<sub>4</sub>), 152.56 (C<sub>1</sub>), 146.04, 145.79 (C<sub>8</sub>), 120.01, 119.52 (C<sub>9</sub>), 111.42 (C<sub>3</sub>), 108.93 (C<sub>2</sub>), 99.18, 99.04 (C<sub>1'</sub>), 74.99 (C<sub>5'</sub>), 73.75, 73.46 (C<sub>3'</sub>), 71.75 (C<sub>2'</sub>), 67.75 (C<sub>4'</sub>), 62.60 (C<sub>6</sub>), 62.14 (C<sub>6'</sub>), 40.49 (C<sub>11</sub>), 33.05 (C<sub>12</sub>), 30.78, 30.75, 30.71, 30.69, 30.45, 30.40, 30.33, 27.96 (C<sub>13-22</sub>), 23.71 (C<sub>23</sub>), 14.45 (C<sub>24</sub>). HRMS (ESI)  $m/z$ : Calcd for [M+Na]<sup>+</sup> C<sub>29</sub>H<sub>49</sub>NNaO<sub>9</sub> 578.3300; Found 578.3299.



*N*-Hexadecyl-2-{hydroxyl[5-( $\alpha$ -D-glucopyranosyloxymethyl)-furan-2-yl]methyl} acrylamide (C<sub>31</sub>H<sub>53</sub>NO<sub>9</sub>)

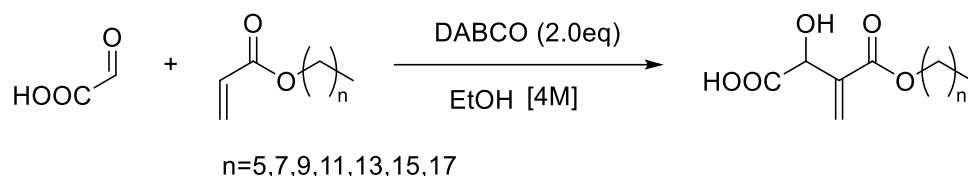


<sup>1</sup>H NMR (300 MHz, Methanol-*d*<sub>4</sub>):  $\delta$  6.34 (d,  $J = 3.2$  Hz, 1H, H<sub>2</sub>), 6.20 (dt,  $J = 3.2, 0.9$  Hz, 1H, H<sub>3</sub>), 5.85 (d,  $J = 1.0$  Hz, 1H, C=CH<sub>2</sub>), 5.70 (d,  $J = 1.3$  Hz, 1H, C=CH<sub>2</sub>), 5.59 (s, 1H, CH-OH, H<sub>7</sub>), 4.88 (d,  $J = 3.5$  Hz, 1H, H<sub>1'</sub>), 4.67 – 4.47 (m, 2H, H<sub>6</sub>), 3.79 (dd,  $J = 11.5, 2.2$  Hz, 1H, H<sub>6'a</sub>), 3.70 – 3.55 (m, 3H, C<sub>6'b</sub>, C<sub>3'</sub>, C<sub>5'</sub>), 3.43 – 3.26 (m, 3H, C<sub>4'</sub>, C<sub>2'</sub>), 3.19 (dd,  $J = 7.7, 6.5$  Hz, 2H, H<sub>11</sub>), 1.49 (q,  $J = 7.0$  Hz, 2H, H<sub>12</sub>), 1.29 (s, 26H, H<sub>13-25</sub>), 0.95 – 0.85 (m, 3H, H<sub>26</sub>). <sup>13</sup>C NMR (75 MHz, Methanol-*d*<sub>4</sub>):  $\delta$  169.25 (C<sub>10</sub>), 156.06 (C<sub>4</sub>), 152.37 (C<sub>1</sub>), 145.55 (C<sub>8</sub>), 120.43, 119.90 (C<sub>9</sub>), 111.44 (C<sub>3</sub>), 109.04 (C<sub>2</sub>), 105.85 (C<sub>1'</sub>), 103.53, 99.02, 98.87, 81.98, 81.51 (C<sub>5'</sub>), 79.73, 79.50 (C<sub>7</sub>), 79.07, 78.63, 77.92 (C<sub>3'</sub>), 74.85, 74.66 (C<sub>2'</sub>), 73.57, 73.30 (C<sub>4'</sub>), 72.90, 72.34, 71.61 (C<sub>6</sub>), 67.67, 66.29, 65.32 (C<sub>6'</sub>), 40.30 (C<sub>11</sub>), 32.93 (C<sub>24</sub>), 30.66 (C<sub>12</sub>), 30.62, 30.34, 30.30, 30.21 (C<sub>14-23</sub>), 27.87 (C<sub>13</sub>), 23.61 (C<sub>25</sub>), 14.43 (C<sub>26</sub>). HRMS (ESI)  $m/z$ : Calcd for [M+Na]<sup>+</sup> C<sub>31</sub>H<sub>53</sub>NNaO<sub>9</sub> 606.3613; Found 606.3606.



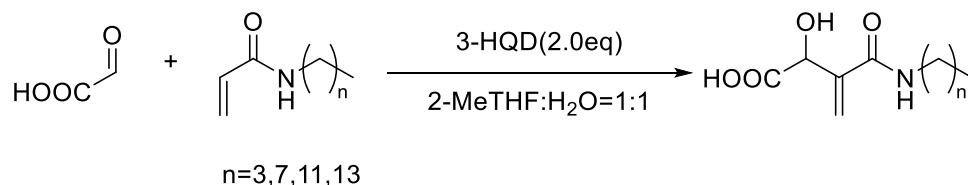
#### 4. Experimental section of the MBH reaction of glyoxylic acid towards novel surfactants

##### 4.1 Procedure for MBH reaction of glyoxylic acid with alkyl acrylates



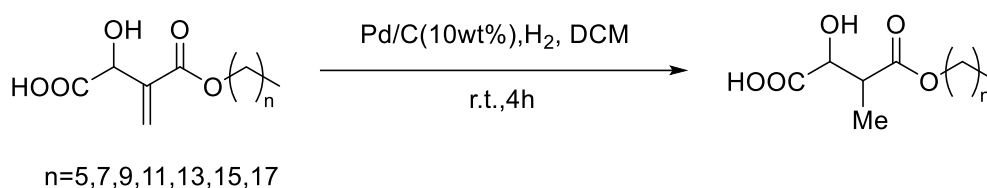
The corresponding alkyl acrylate (20 mmol) and DABCO (20 mmol) were added into 5ml of EtOH at room temperature. Glyoxylic acid (50wt% solution in water) (10 mmol) was added and the mixture was stirred for 24h. To the reaction mixture was added HCl (1 M) and extracted with EtOAc (3 × 50 mL). The organic layer was washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. The crude mixture was purified by flash column chromatography using Pentane/EtOAc (5/1 → 3/1 → 1/1) as eluent to achieve the desired products.

##### 4.2 Procedure for the MBH reaction of glyoxylic acid with alkyl acrylamides



The corresponding secondary *N*-alkyl acrylamide (20 mmol) and 3-HQD (20 mmol) were mixed in 10ml 2Me-THF: H<sub>2</sub>O (1:1) and Glyoxylic acid (50wt% solution in water) (10 mmol) was added in reaction system under 45°C. After 3days, to the reaction mixture was added HCL(1 M) and extracted with EtOAc (3 × 50 mL), the organic layer was washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>.The obtained crude product was purified by flash column chromatography using EtOAc/ Pentane (1/1 to 98/2) as eluent to obtain the expected products.

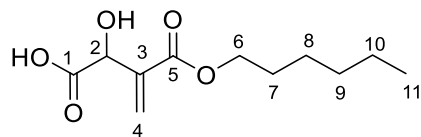
### 4.3 Procedure for the hydrogenation of MBH adducts of glyoxylic acid with alkyl acrylates



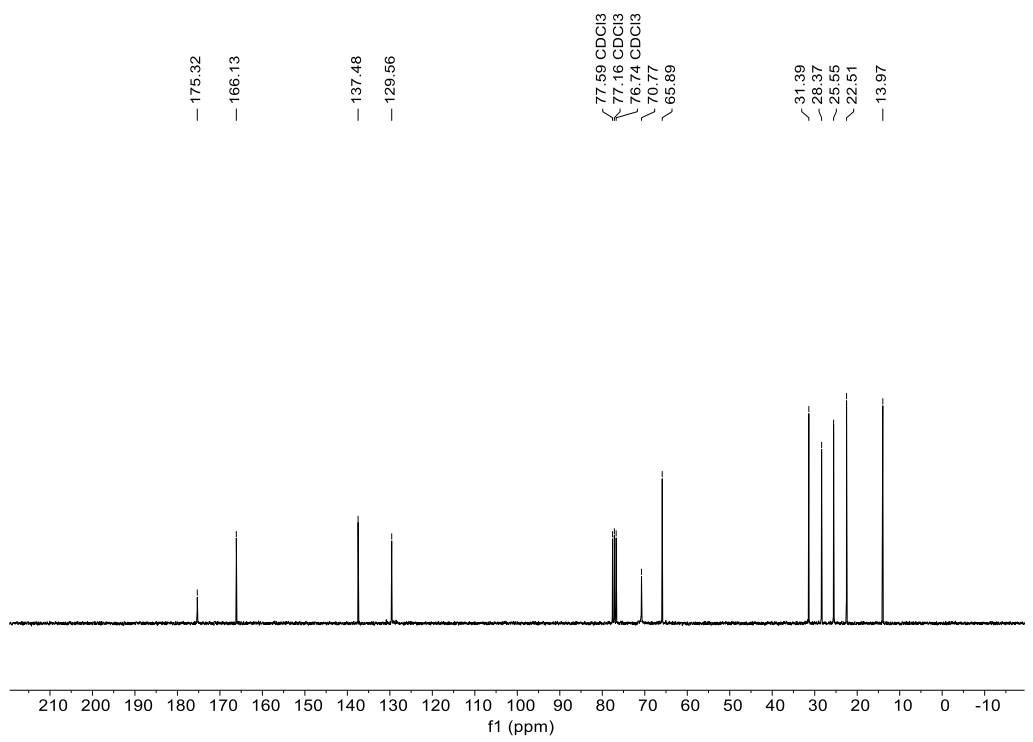
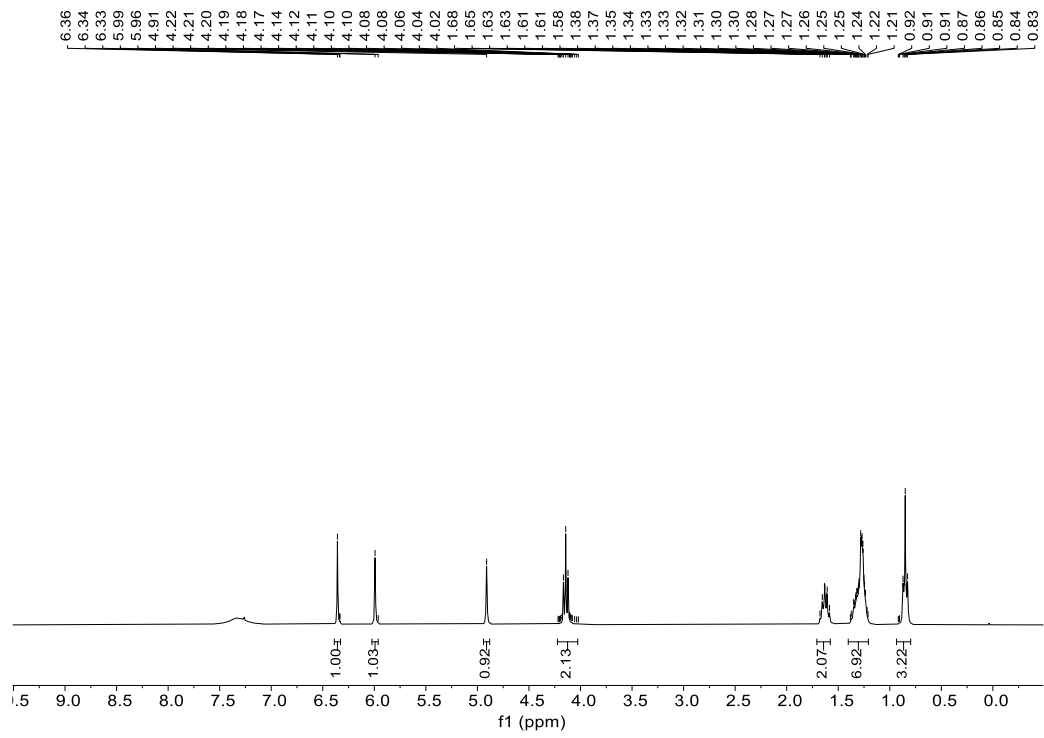
The MBH adducts from the reaction of GA with acrylate—GAOn (5 mmol), Pd/C (10 wt%) (0.5 mmol) were mixed in 20ml DCM. The flask was degassed three times under vacuum/Nitrogen, followed by occupied by H<sub>2</sub> (balloon) under 1 atmosphere. The solution kept stirring at room temperature for 4h, then the mixture was filtered through a pad of celite and the obtained filtrate was concentrated to give the hydrogenated products--GAOnH.

### 4.4 Characterization of products

*3-[(Hexyloxy)carbonyl]-2-hydroxybut-3-enoic acid (C<sub>11</sub>H<sub>18</sub>O<sub>5</sub>)*

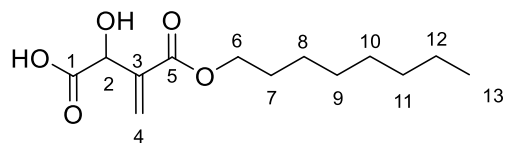


<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 6.36 (s, 1H, C=CH<sub>2</sub>), 5.99 (s, 1H, C=CH<sub>2</sub>), 4.91 (s, 1H, CH-OH), 4.14 (t, *J* = 6.7 Hz, 2H, H<sub>6</sub>), 1.71 – 1.58 (m, 2H, H<sub>7</sub>), 1.40 – 1.21 (m, 7H, H<sub>8-10</sub>), 0.93 – 0.80 (m, 3H, H<sub>11</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 175.32 (C<sub>1</sub>), 166.13 (C<sub>5</sub>), 137.48 (C<sub>3</sub>), 129.56 (C<sub>4</sub>), 70.77 (C<sub>2</sub>), 65.89 (C<sub>6</sub>), 31.39 (C<sub>9</sub>), 28.37 (C<sub>7</sub>), 25.55 (C<sub>8</sub>), 22.51 (C<sub>10</sub>), 13.97(C<sub>11</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>11</sub>H<sub>18</sub>NaO<sub>5</sub> 253.1046; Found 253.1037.

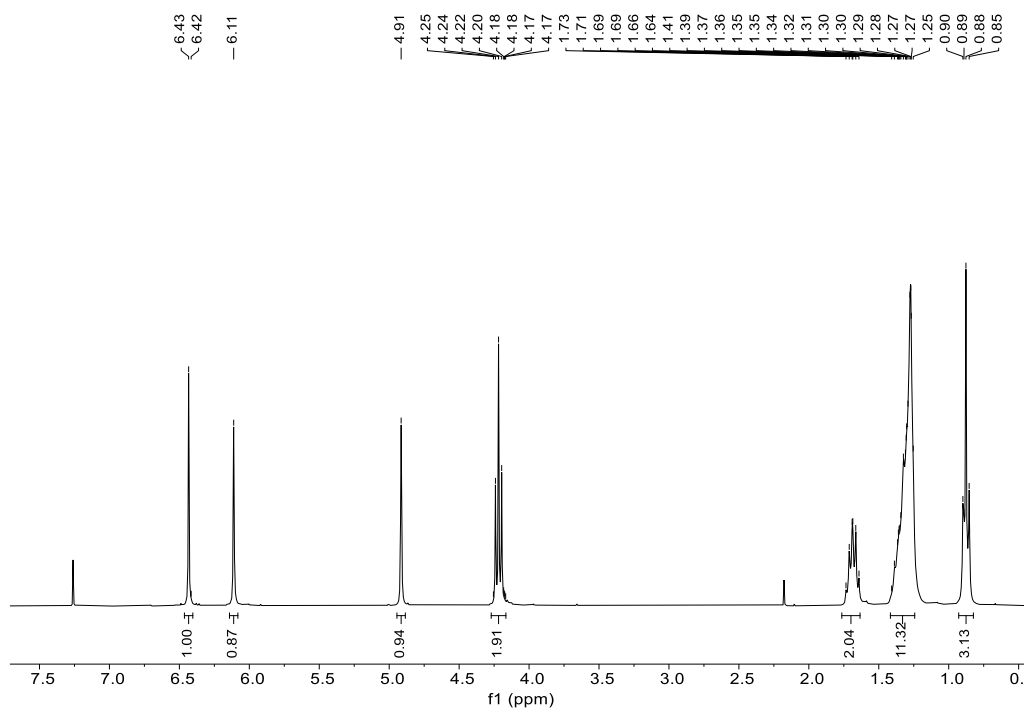


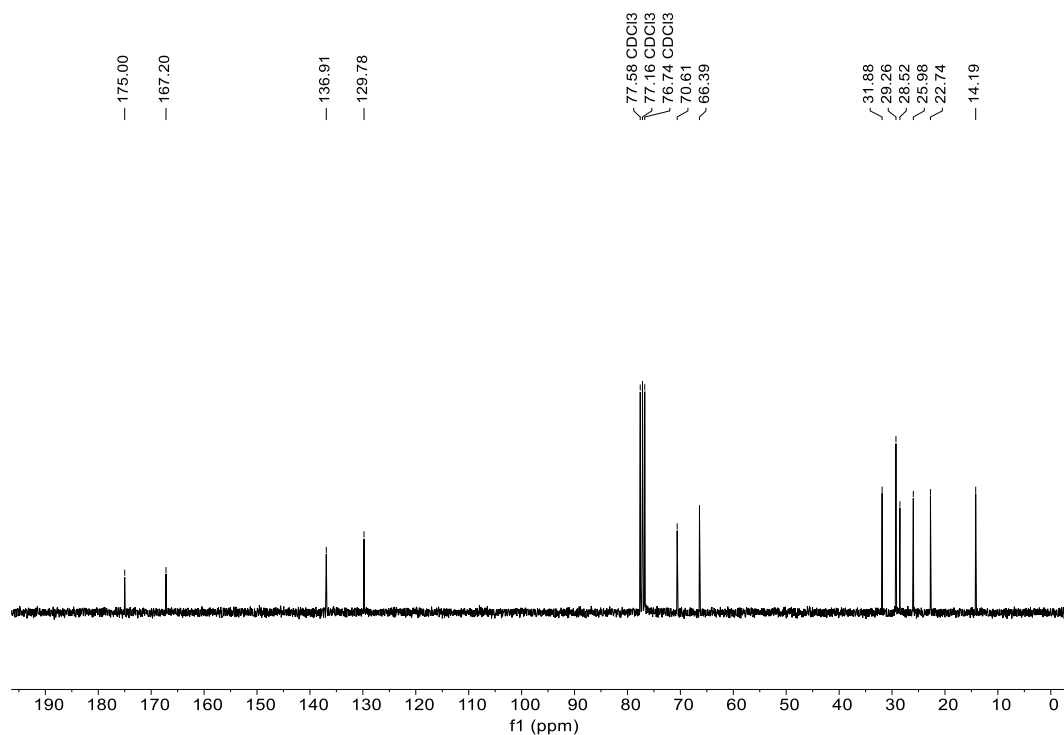


3-[(Octyloxy)carbonyl]-2-hydroxybut-3-enoic acid (C<sub>13</sub>H<sub>22</sub>O<sub>5</sub>)

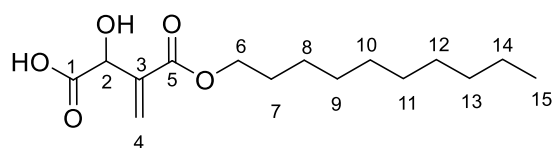


<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 6.43 (s, 1H, C=CH<sub>2</sub>), 6.11 (s, 1H, C=CH<sub>2</sub>), 4.91 (s, 1H, CH-OH), 4.22 (t, *J* = 6.7 Hz, 2H, H<sub>6</sub>), 1.76 – 1.63 (m, 2H, H<sub>7</sub>), 1.42 – 1.24 (m, 11H, H<sub>8-12</sub>), 0.93 – 0.82 (m, 3H, H<sub>13</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 175.00 (C<sub>1</sub>), 167.20 (C<sub>5</sub>), 136.91 (C<sub>3</sub>), 129.78 (C<sub>4</sub>), 70.61 (C<sub>2</sub>), 66.39 (C<sub>6</sub>), 31.88 (C<sub>11</sub>), 29.26 (C<sub>7,9</sub>), 28.52 (C<sub>10</sub>), 25.98 (C<sub>8</sub>), 22.74 (C<sub>12</sub>), 14.19 (C<sub>13</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>13</sub>H<sub>22</sub>NaO<sub>5</sub> 281.1359; Found 281.1357.

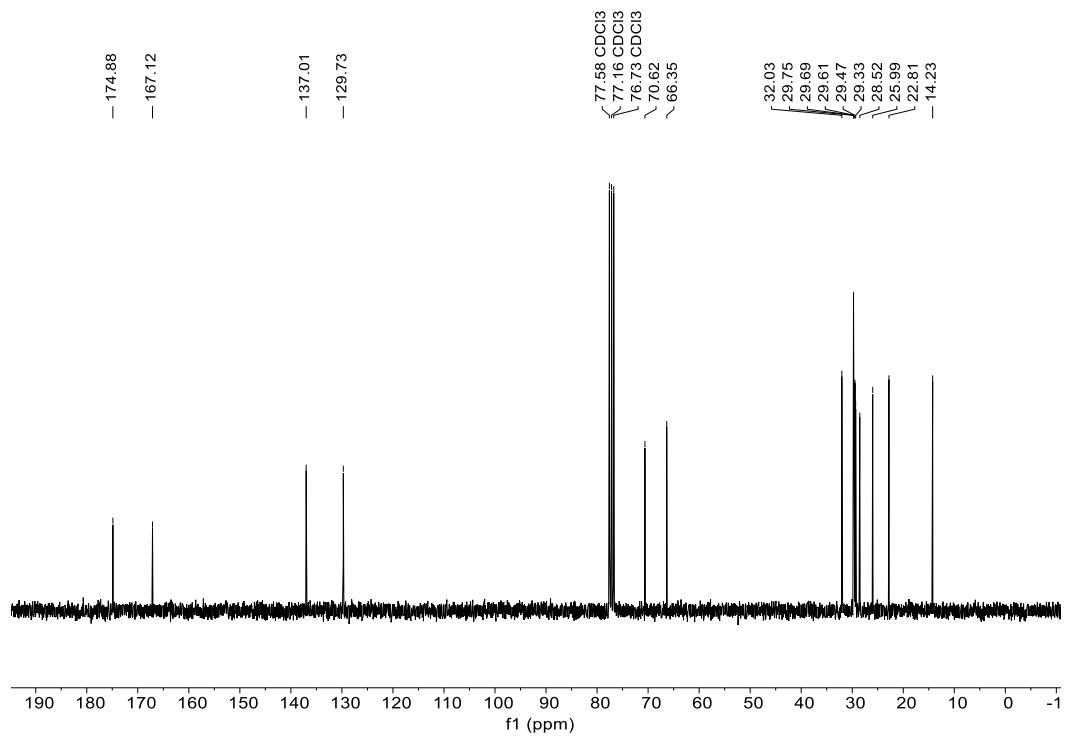
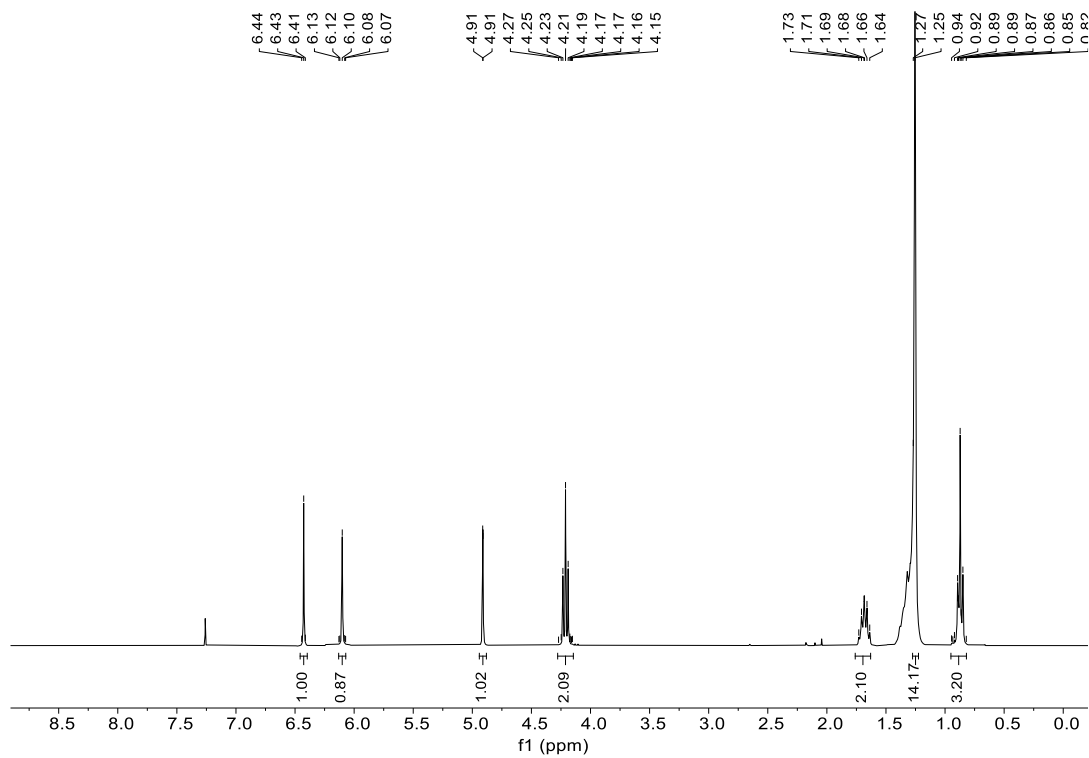




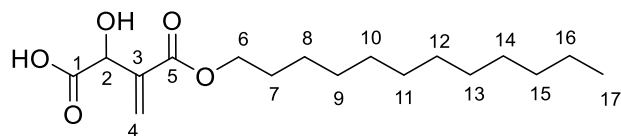
*3-[(Decyloxy)carbonyl]-2-hydroxybut-3-enoic acid (C<sub>15</sub>H<sub>26</sub>O<sub>5</sub>)*



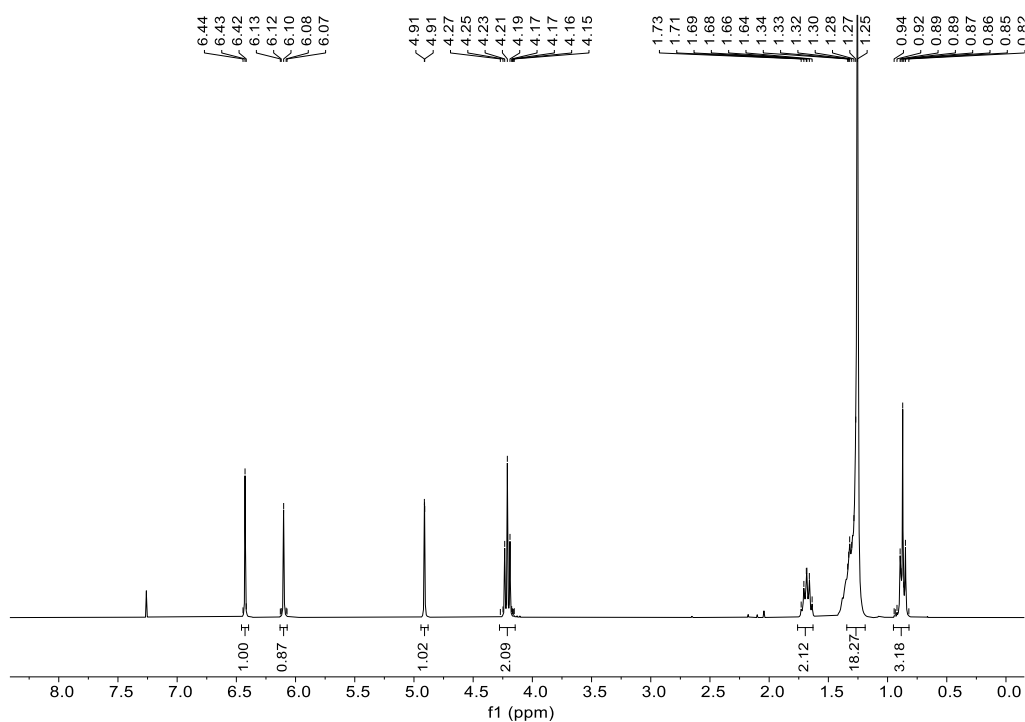
<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 6.43 (s, 1H, C=CH<sub>2</sub>), 6.10 (s, 1H, C=CH<sub>2</sub>), 4.91 (d, *J* = 0.8 Hz, 1H, CH-OH), 4.21 (t, *J* = 6.7 Hz, 2H, H<sub>6</sub>), 1.76 – 1.63 (m, 2H, H<sub>7</sub>), 1.26 (d, *J* = 4.3 Hz, 14H, H<sub>8-14</sub>), 0.95 – 0.82 (m, 3H, H<sub>15</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 174.88 (C<sub>1</sub>), 167.12 (C<sub>5</sub>), 137.01 (C<sub>3</sub>), 129.73 (C<sub>4</sub>), 70.62 (C<sub>2</sub>), 66.35 (C<sub>6</sub>), 32.03 (C<sub>13</sub>), 29.75, 29.69, 29.61, 29.47, 29.33, 28.52 (C<sub>7</sub>, C<sub>9-12</sub>), 25.99 (C<sub>8</sub>), 22.81 (C<sub>14</sub>), 14.23 (C<sub>15</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>15</sub>H<sub>26</sub>NaO<sub>5</sub> 309.1672; Found 309.1672.

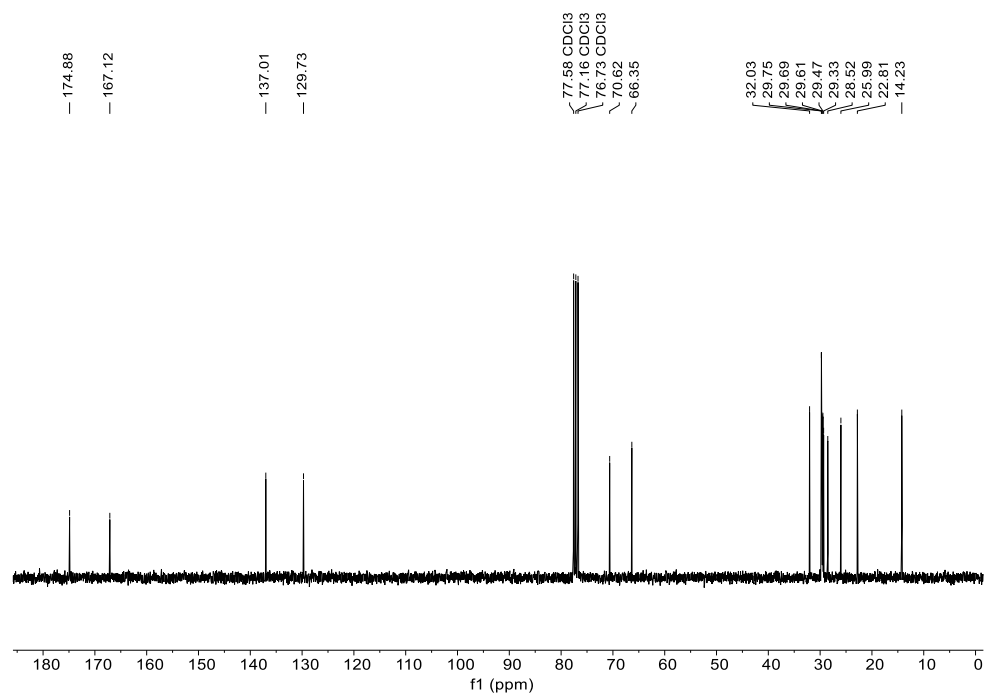


3-[(Dodecyloxy)carbonyl]-2-hydroxybut-3-enoic acid (C<sub>17</sub>H<sub>30</sub>O<sub>5</sub>)

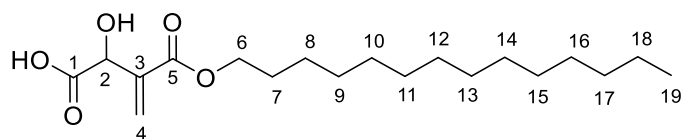


<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 6.43 (s, 1H, C=CH<sub>2</sub>), 6.10 (s, 1H, C=CH<sub>2</sub>), 4.91 (d, *J* = 0.8 Hz, 1H, CH-OH), 4.21 (t, *J* = 6.7 Hz, 2H, H<sub>6</sub>), 1.76 – 1.63 (m, 2H, H<sub>7</sub>), 1.34 – 1.19 (m, 18H, H<sub>8-16</sub>), 0.95 – 0.82 (m, 3H, H<sub>17</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 174.88 (C<sub>1</sub>), 167.12 (C<sub>5</sub>), 137.01 (C<sub>3</sub>), 129.73 (C<sub>4</sub>), 70.62 (C<sub>2</sub>), 66.35 (C<sub>6</sub>), 32.03 (C<sub>15</sub>), 29.75, 29.69, 29.61, 29.47, 29.33, 28.52 (C<sub>7</sub>, C<sub>9-14</sub>), 25.99 (C<sub>8</sub>), 22.81 (C<sub>16</sub>), 14.23 (C<sub>17</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>17</sub>H<sub>30</sub>NaO<sub>5</sub> 337.1985; Found 337.1988.

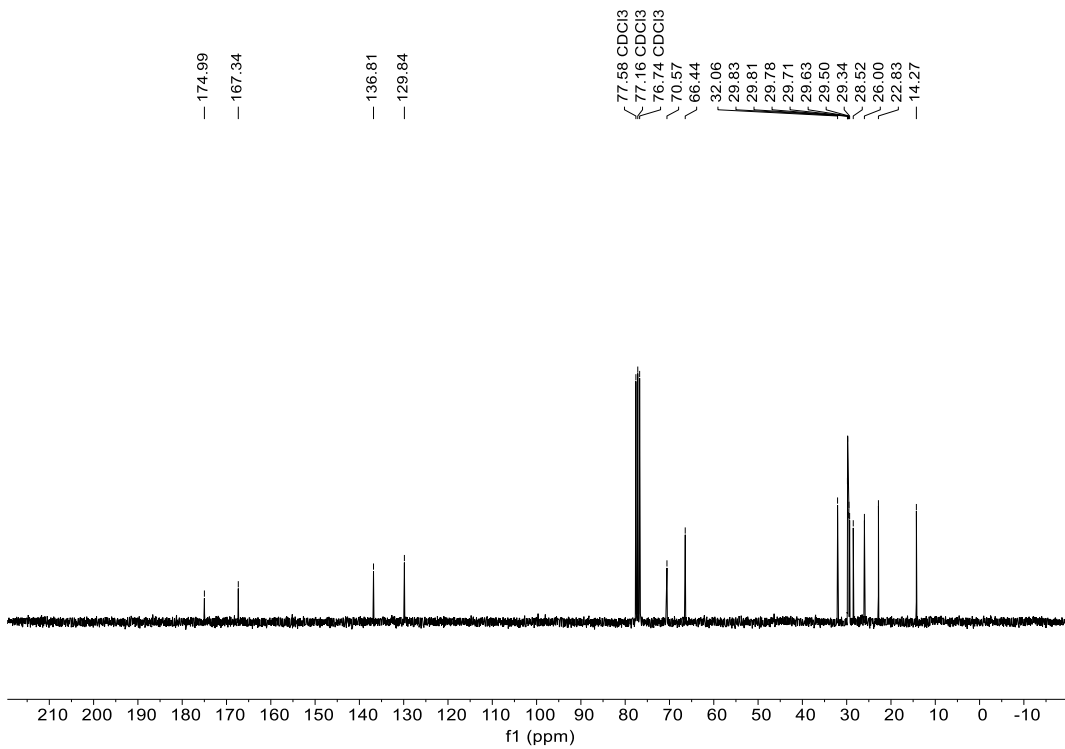
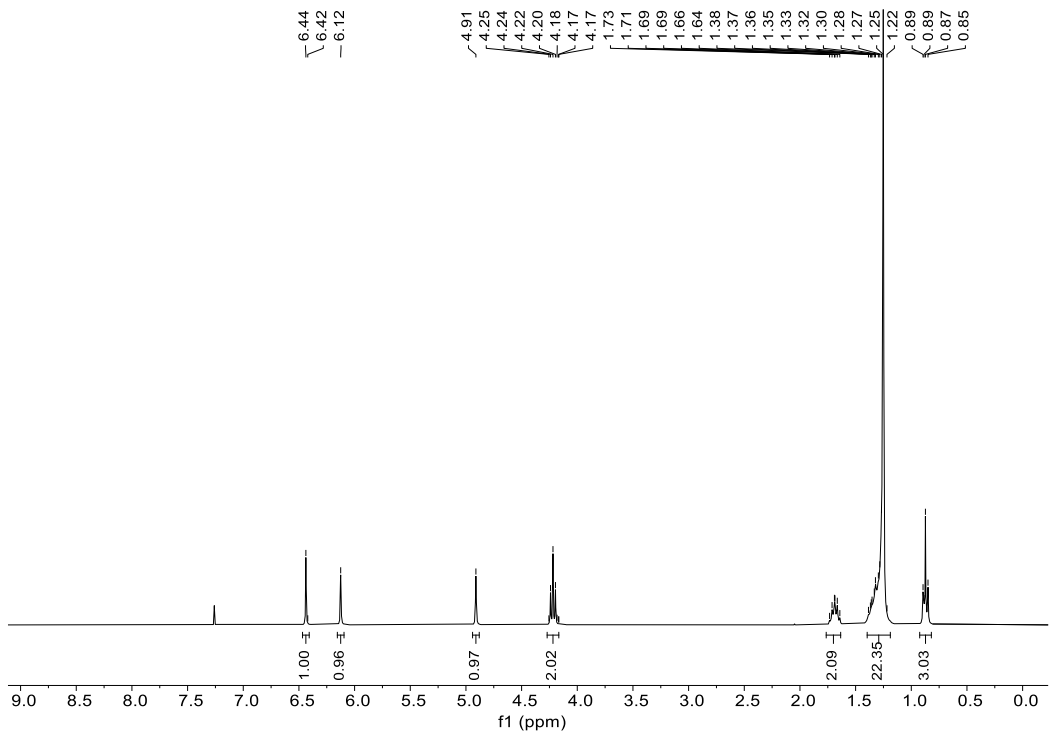




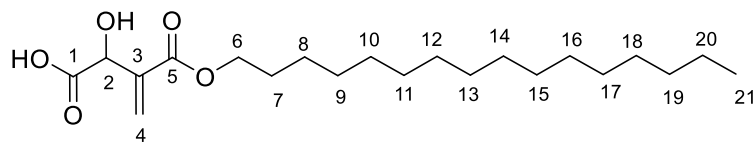
3-[(Tetradecyloxy)carbonyl]-2-hydroxybut-3-enoic acid (C<sub>19</sub>H<sub>34</sub>O<sub>5</sub>)



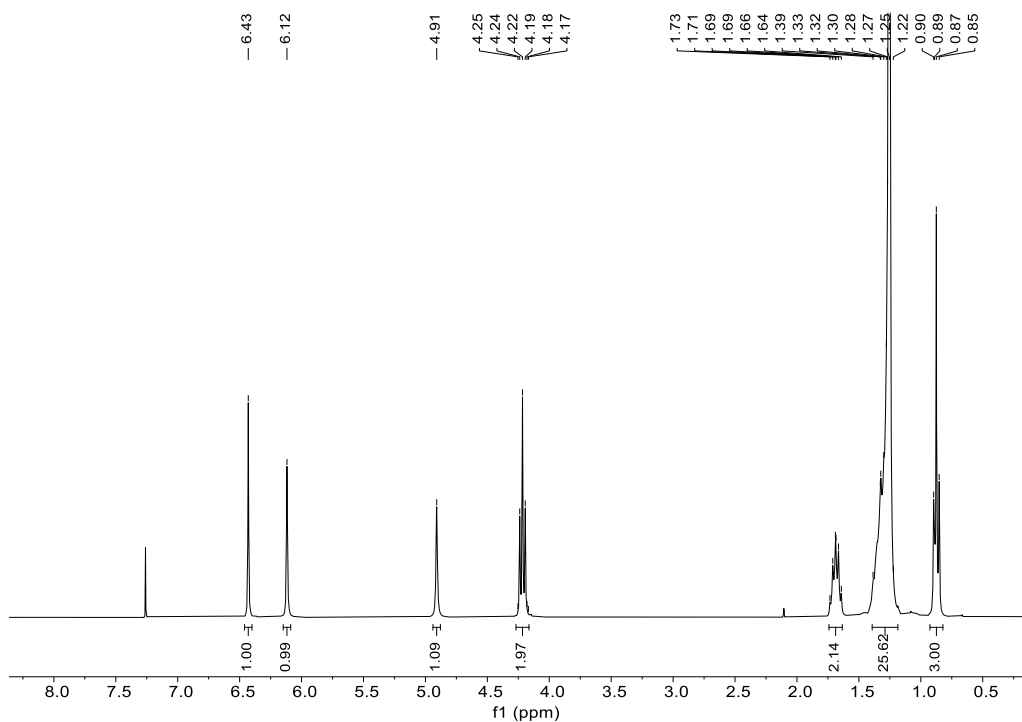
<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 6.44 (s, 1H, C=CH<sub>2</sub>), 6.12 (s, 1H, C=CH<sub>2</sub>), 4.91 (s, 1H, CH-OH), 4.22 (t, *J* = 6.7 Hz, 2H, H<sub>6</sub>), 1.76 – 1.63 (m, 2H, H<sub>7</sub>), 1.25 (s, 22H, H<sub>8-18</sub>), 0.92 – 0.82 (m, 3H, H<sub>19</sub>). <sup>13</sup>C NMR (76 MHz, CDCl<sub>3</sub>): δ 174.99 (C<sub>1</sub>), 167.34 (C<sub>5</sub>), 136.81 (C<sub>3</sub>), 129.84 (C<sub>4</sub>), 70.57 (C<sub>2</sub>), 66.44 (C<sub>6</sub>), 32.06 (C<sub>17</sub>), 29.83, 29.81, 29.78, 29.71, 29.63, 29.50, 29.34, 28.52 (C<sub>7</sub>, C<sub>9-16</sub>), 26.00 (C<sub>8</sub>), 22.83 (C<sub>18</sub>), 14.27 (C<sub>19</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>19</sub>H<sub>34</sub>NaO<sub>5</sub> 365.2298; Found 365.2294.

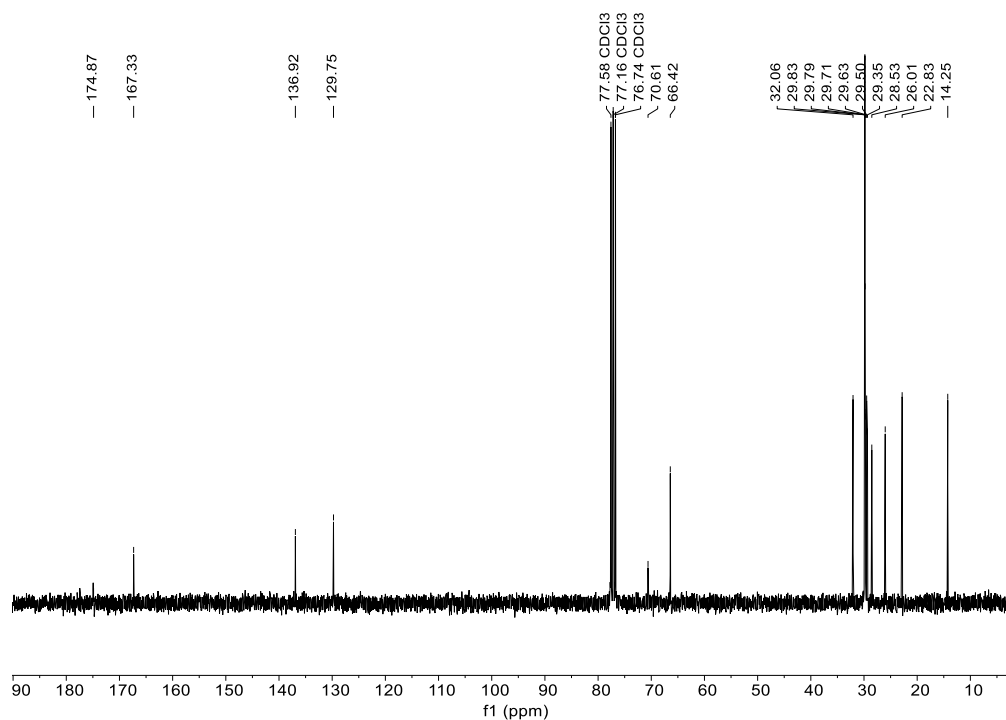


3-[(Hexadecyloxy)carbonyl]-2-hydroxybut-3-enoic acid (C<sub>21</sub>H<sub>38</sub>O<sub>5</sub>)

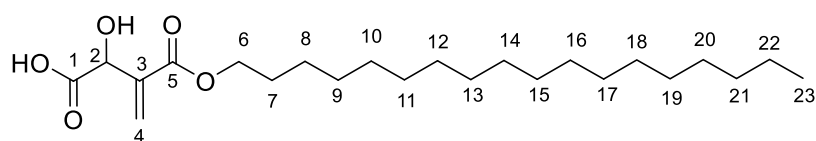


<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 6.43 (s, 1H, C=CH<sub>2</sub>), 6.12 (s, 1H, C=CH<sub>2</sub>), 4.91 (s, 1H, CH-OH), 4.22 (t, *J* = 6.7 Hz, 2H, H<sub>6</sub>), 1.74 – 1.63 (m, 2H, H<sub>7</sub>), 1.25 (s, 26H, H<sub>8-20</sub>), 0.93 – 0.82 (m, 3H, H<sub>21</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 174.87 (C<sub>1</sub>), 167.33 (C<sub>5</sub>), 136.92 (C<sub>3</sub>), 129.75 (C<sub>4</sub>), 70.61 (C<sub>2</sub>), 66.42 (C<sub>6</sub>), 32.06 (C<sub>19</sub>), 29.83, 29.79, 29.71, 29.63, 29.50, 29.35, 28.53 (C<sub>7</sub>, C<sub>9-18</sub>), 26.01 (C<sub>8</sub>), 22.83 (C<sub>20</sub>), 14.25 (C<sub>21</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>21</sub>H<sub>38</sub>NaO<sub>5</sub> 393.2611; Found 393.2604.



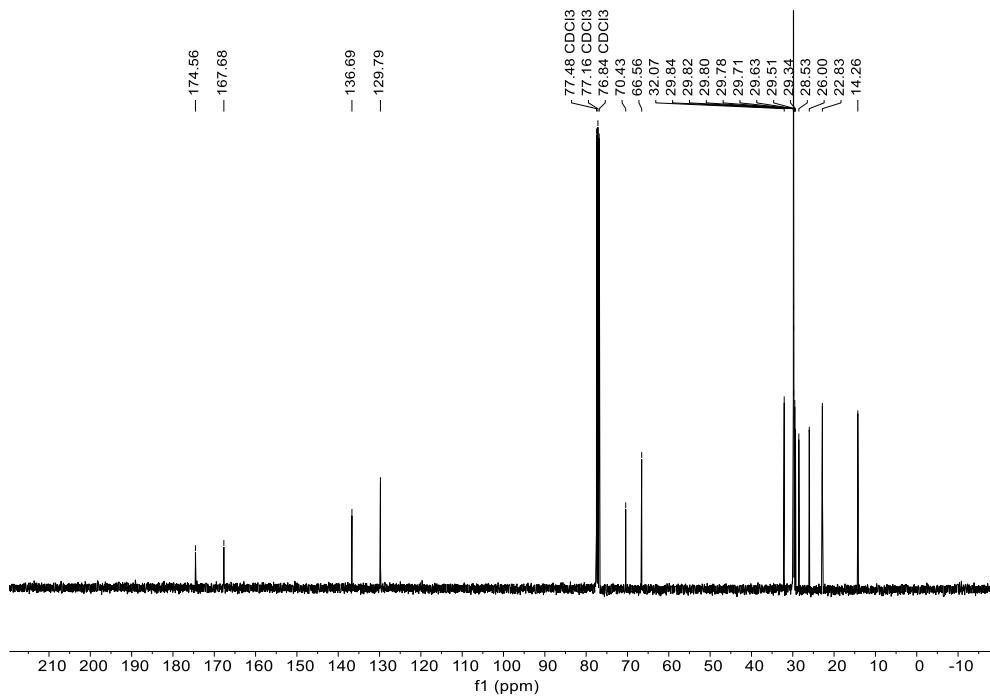
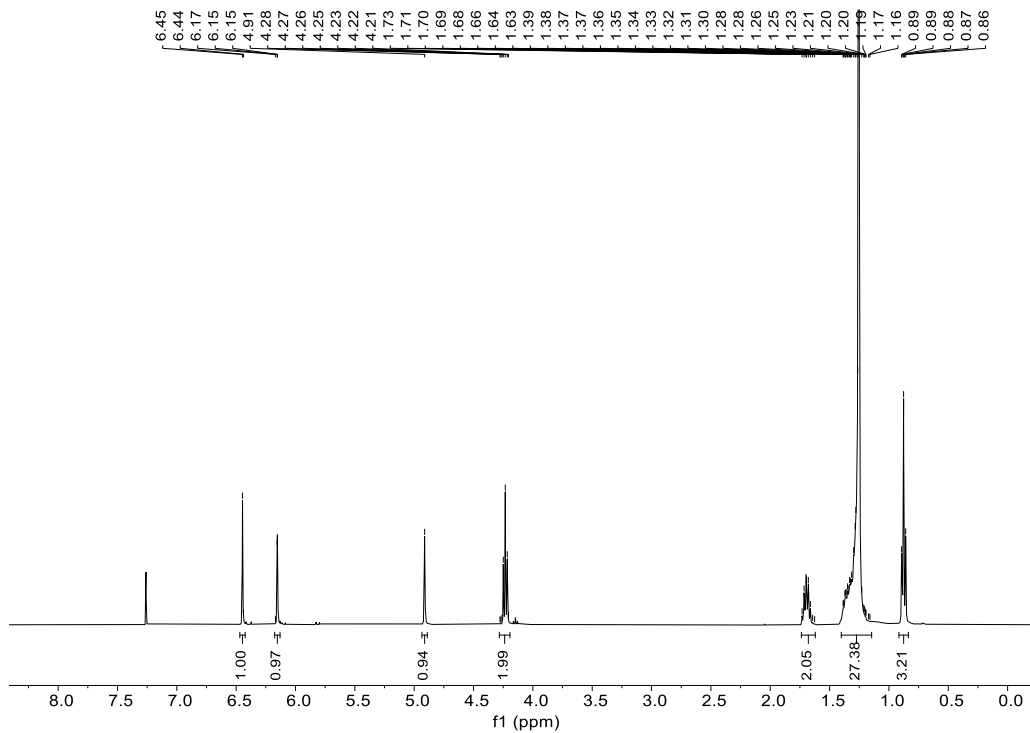


3-[(Octadecyloxy)carbonyl]-2-hydroxybut-3-enoic acid (C<sub>23</sub>H<sub>42</sub>O<sub>5</sub>)

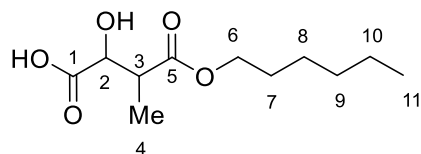


<sup>1</sup>H NMR (400 MHz, Chloroform-*d*): δ 6.45 (s, 1H, C=CH<sub>2</sub>), 6.15 (d, *J* = 1.2 Hz, 1H, C=CH<sub>2</sub>), 4.91 (s, 1H, CH-OH), 4.23 (t, *J* = 6.7 Hz, 2H, H<sub>6</sub>), 1.74 – 1.62 (m, 2H, H<sub>7</sub>), 1.25 (s, 30H, H<sub>8-22</sub>), 0.92 – 0.84 (m, 3H, H<sub>23</sub>). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 174.56 (C<sub>1</sub>), 167.68 (C<sub>5</sub>), 136.69 (C<sub>3</sub>), 129.79 (C<sub>4</sub>), 70.43 (C<sub>2</sub>), 66.56 (C<sub>6</sub>), 32.07 (C<sub>21</sub>), 29.84, 29.82, 29.80, 29.78, 29.71, 29.63, 29.51, 29.34, 28.53 (C<sub>7</sub>, C<sub>9-20</sub>), 26.00 (C<sub>8</sub>), 22.83 (C<sub>22</sub>), 14.26 (C<sub>23</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>23</sub>H<sub>42</sub>NaO<sub>5</sub> 421.2924; Found 421.2915.

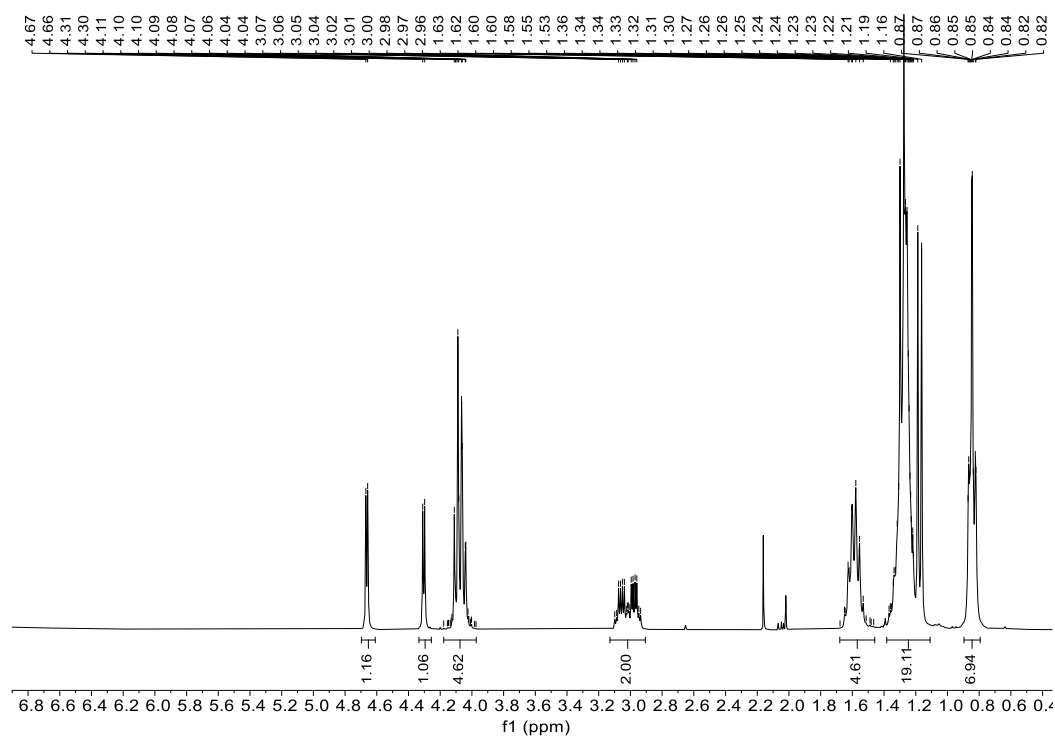


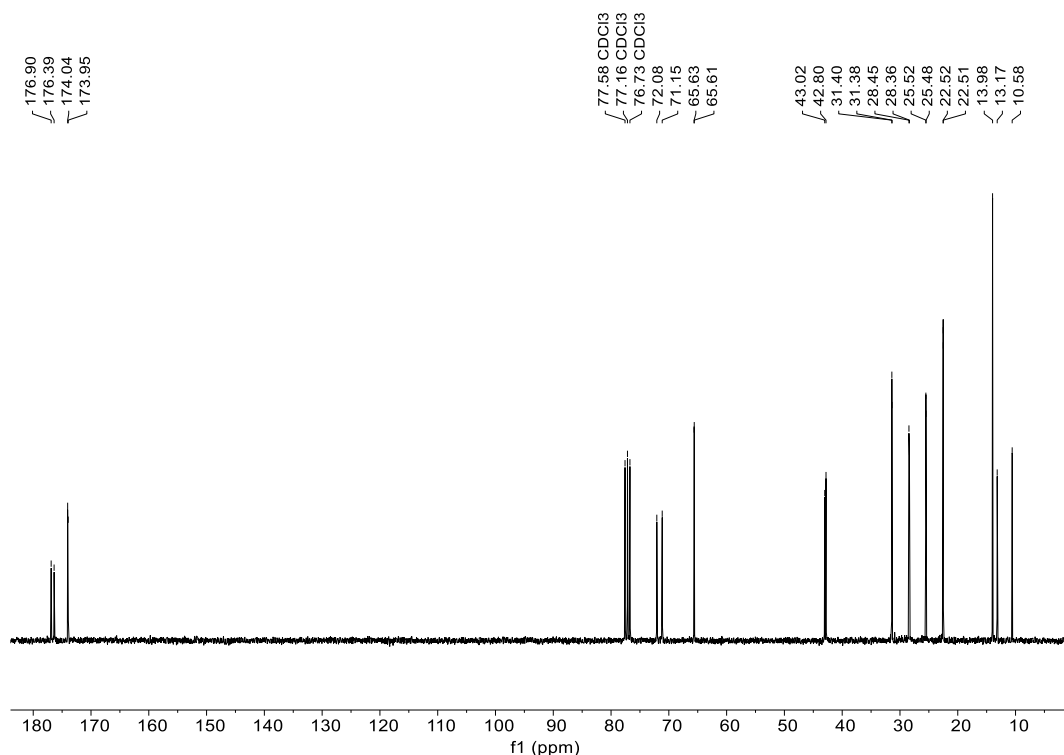


(syn+anti) 4-(Hexyloxy)-2-hydroxy-3-methyl-4-oxobutanoic acid (C<sub>11</sub>H<sub>20</sub>O<sub>5</sub>)

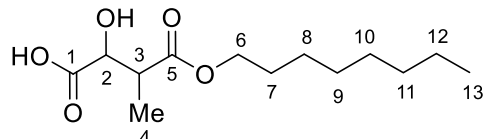


<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 4.66 (d, *J* = 3.4 Hz, 1H, H<sub>2</sub>, syn), 4.30 (d, *J* = 3.6 Hz, 1H, H<sub>2</sub>, anti), 4.07 (m, 4H, H<sub>6</sub>), 3.02 (m, 2H, H<sub>3</sub>, syn + anti), 1.68 – 1.46 (m, 4H, H<sub>7</sub>), 1.38 – 1.11 (m, 18H, H<sub>8-10</sub>, H<sub>4</sub>), 0.90 – 0.79 (m, 6H, H<sub>11</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 176.90, 176.39, 174.04, 173.95 (C<sub>1</sub>, C<sub>5</sub>), 72.08, 71.15 (C<sub>2</sub>), 65.63, 65.61 (C<sub>6</sub>), 43.02, 42.80 (C<sub>3</sub>), 31.40, 31.38 (C<sub>9</sub>), 28.45, 28.36 (C<sub>7</sub>), 25.52, 25.48 (C<sub>8</sub>), 22.52, 22.51 (C<sub>10</sub>), 13.98, 13.17 (C<sub>11</sub>), 10.58 (C<sub>4</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>11</sub>H<sub>20</sub>NaO<sub>5</sub> 255.1203; Found 255.1195.

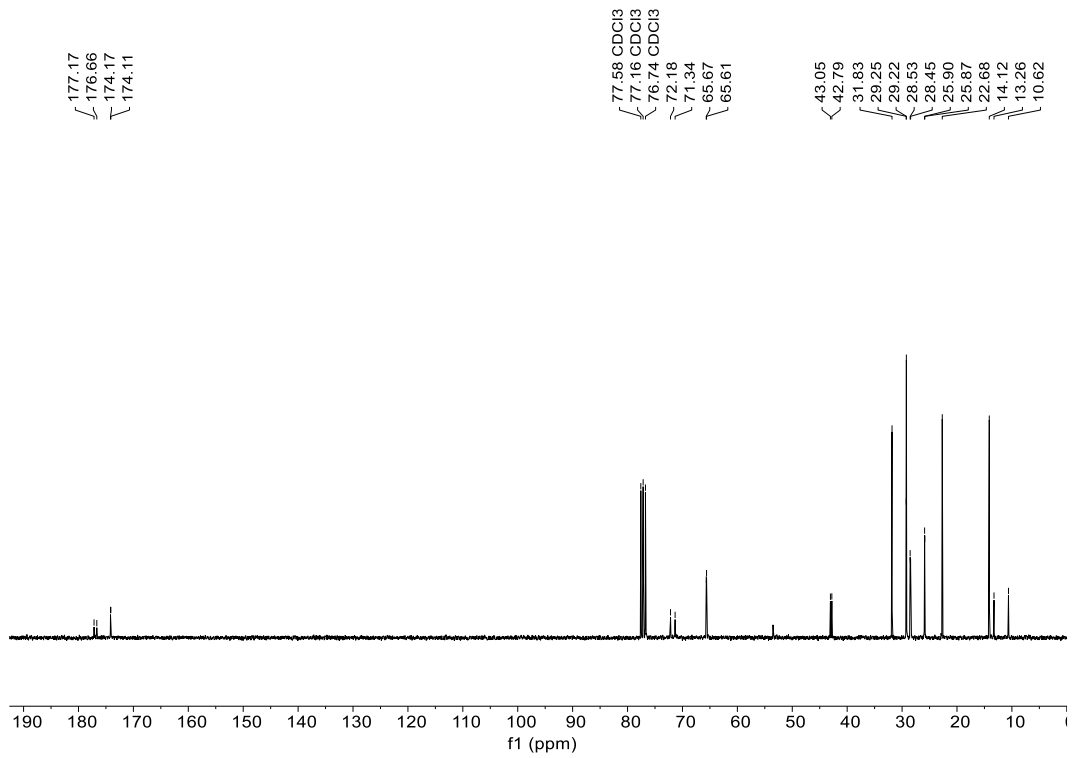
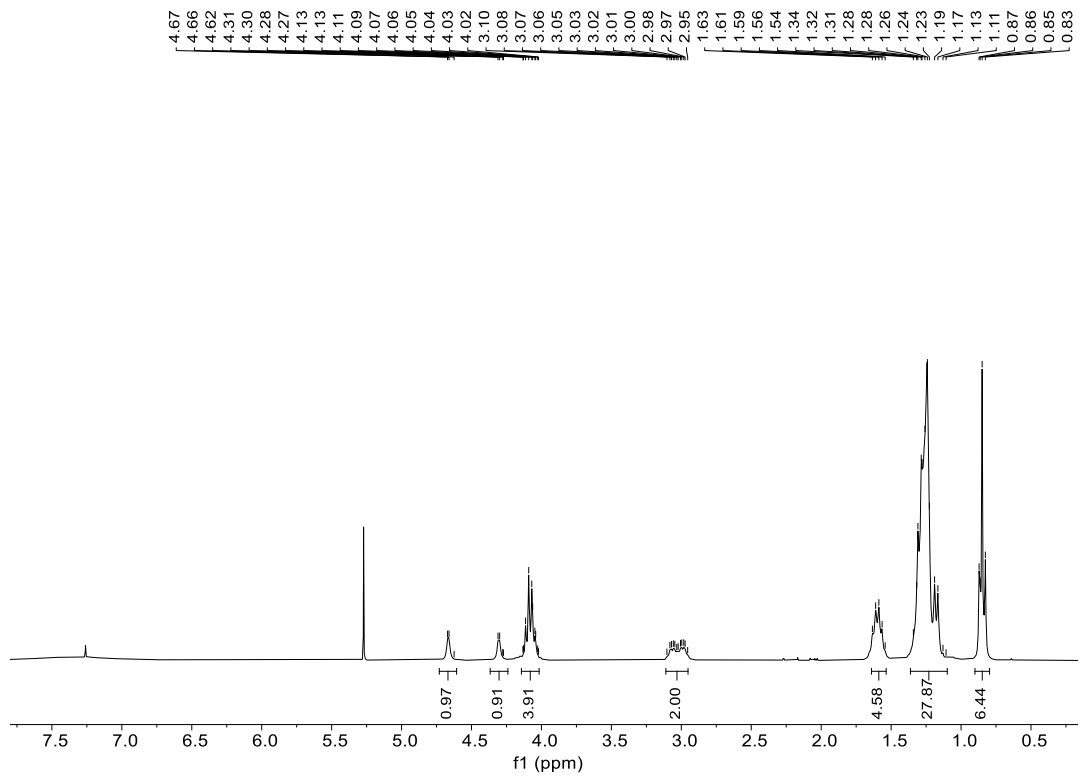




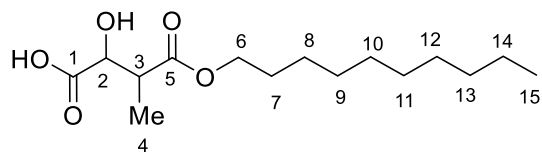
(syn+anti) 4-(Octyloxy)-2-hydroxy-3-methyl-4-oxobutanoic acid (C<sub>13</sub>H<sub>24</sub>O<sub>5</sub>)



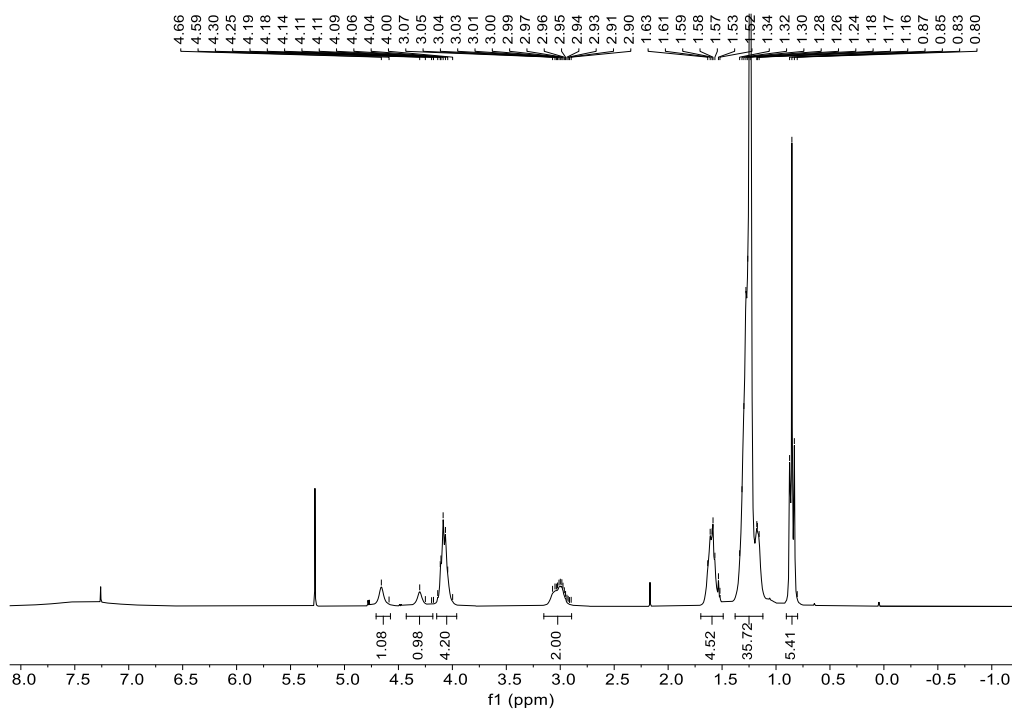
<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 4.67 (s<sub>br</sub>, 1H, H<sub>2</sub>, syn) and 4.30 (s<sub>br</sub>, 1H, H<sub>2</sub>, anti), 4.14 – 4.02 (m, 4H, H<sub>6</sub>), 3.02 (m, 2H, H<sub>3</sub>, syn + anti), 1.59 (p, *J* = 6.8 Hz, 4H, H<sub>7</sub>), 1.36 – 1.10 (m, 26H, H<sub>8-12</sub>, H<sub>4</sub>), 0.90 – 0.80 (m, 6H, H<sub>13</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 177.17, 176.66(C<sub>1</sub>), 174.17, 174.11(C<sub>5</sub>), 72.18, 71.34 (C<sub>2</sub>), 65.67, 65.61(C<sub>6</sub>), 43.05, 42.79 (C<sub>3</sub>), 31.83 (C<sub>11</sub>), 29.25, 29.22(C<sub>9, 10</sub>), 28.53, 28.45(C<sub>7</sub>), 25.90, 25.87(C<sub>8</sub>), 22.68 (C<sub>12</sub>), 14.12, 13.26(C<sub>13</sub>), 10.62 (C<sub>4</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>13</sub>H<sub>24</sub>NaO<sub>5</sub> 283.1516; Found 283.1514.

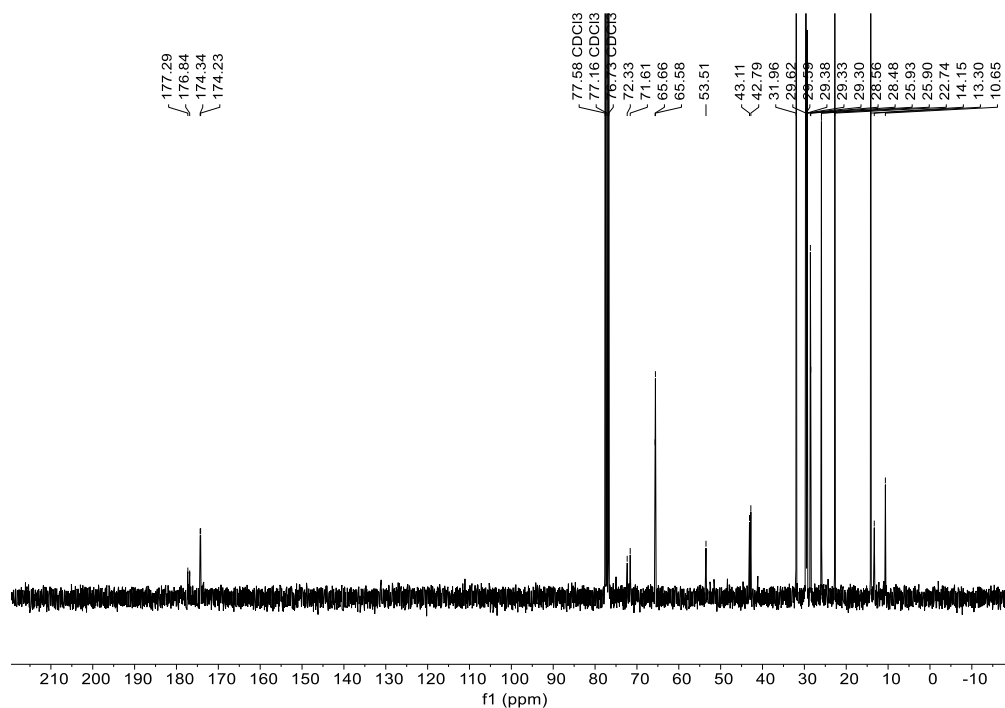


(syn+anti) 4-(Decyloxy)-2-hydroxy-3-methyl-4-oxobutanoic acid (C<sub>15</sub>H<sub>28</sub>O<sub>5</sub>)

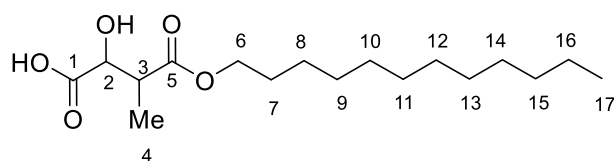


<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 4.66 (s<sub>br</sub>, 1H, H<sub>2</sub>, syn or anti,) and 4.30 (s<sub>br</sub>, 1H, H<sub>2</sub>, syn or anti), 4.09 (dt, *J* = 12.7, 6.6 Hz, 4H, H<sub>6</sub>), 3.15 – 2.89 (m, 2H, H<sub>3</sub>, syn+anti), 1.70 – 1.49 (m, 4H, H<sub>7</sub>), 1.26 (d, *J* = 11.8 Hz, 34H, H<sub>8-14</sub>, H<sub>4</sub>), 0.90 – 0.80 (m, 6H, H<sub>15</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 177.29, 176.84 (C<sub>1</sub>), 174.34, 174.23 (C<sub>5</sub>), 72.33, 71.61 (C<sub>2</sub>), 65.66, 65.58 (C<sub>6</sub>), 43.11, 42.79 (C<sub>3</sub>), 31.96 (C<sub>13</sub>), 29.62, 29.59, 29.38, 29.33, 29.30 (C<sub>9-12</sub>), 28.56, 28.48 (C<sub>7</sub>), 25.93, 25.90 (C<sub>8</sub>), 22.74 (C<sub>14</sub>), 14.15, 13.30 (C<sub>15</sub>), 10.65 (C<sub>4</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>15</sub>H<sub>28</sub>NaO<sub>5</sub> 311.1829; Found 311.1822.

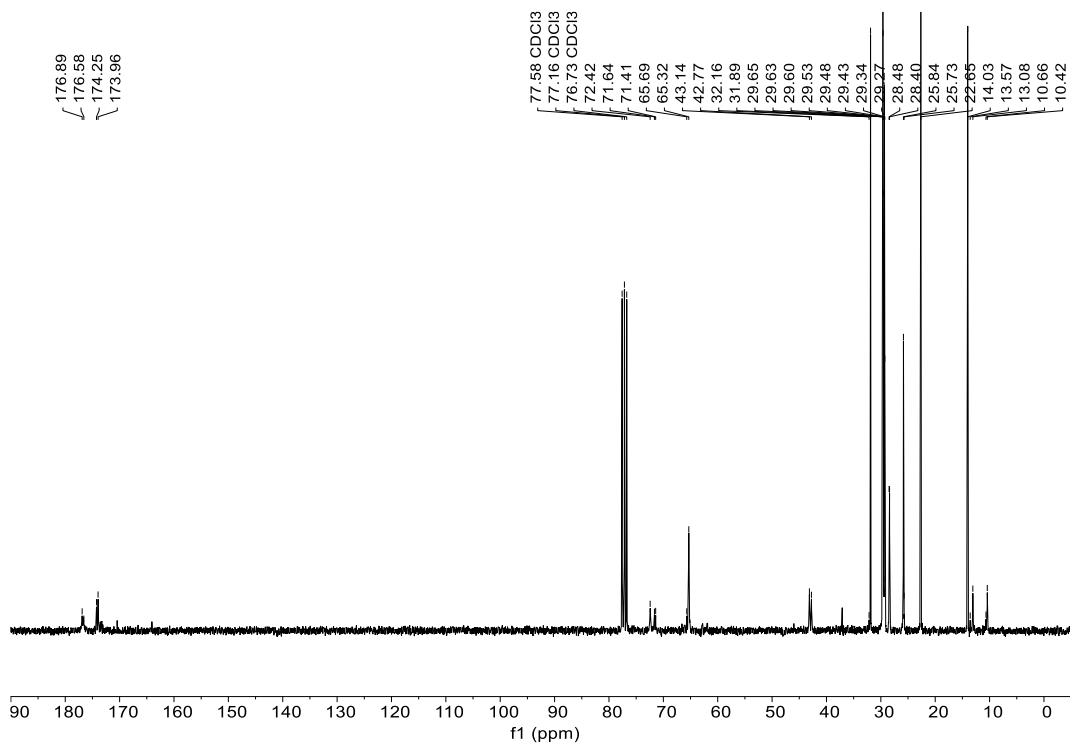
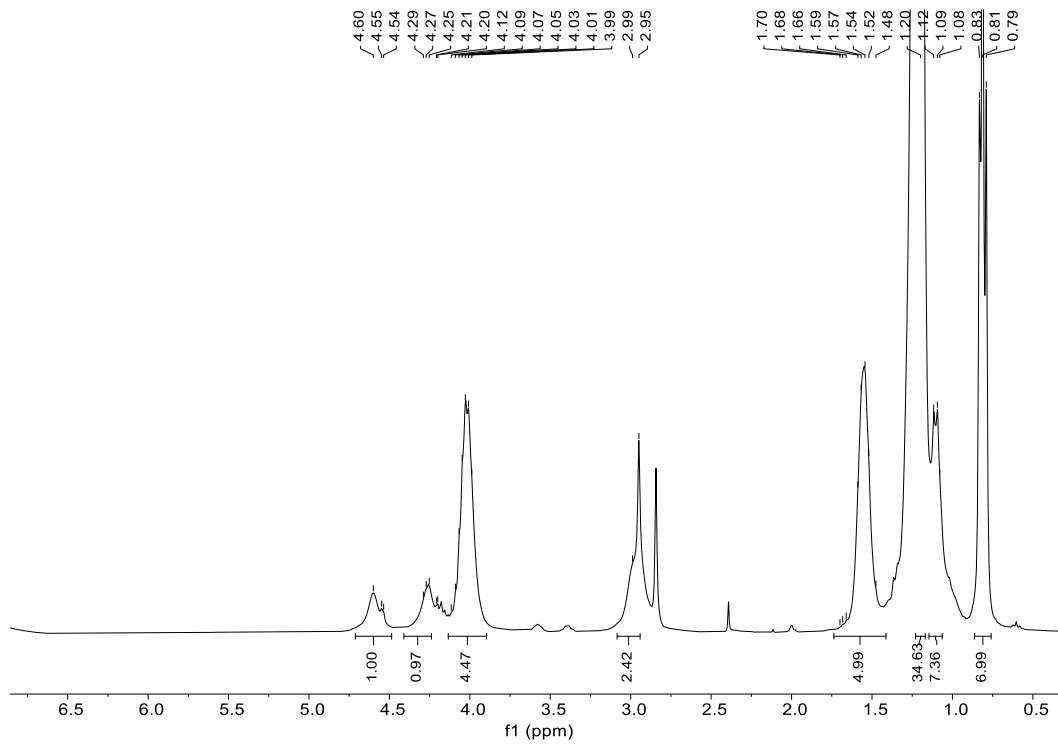




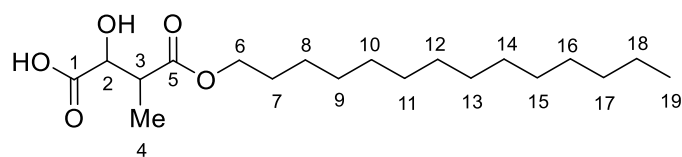
(syn+anti) 4-(Dodecyloxy)-2-hydroxy-3-methyl-4-oxobutanoic acid (C<sub>17</sub>H<sub>32</sub>O<sub>5</sub>)



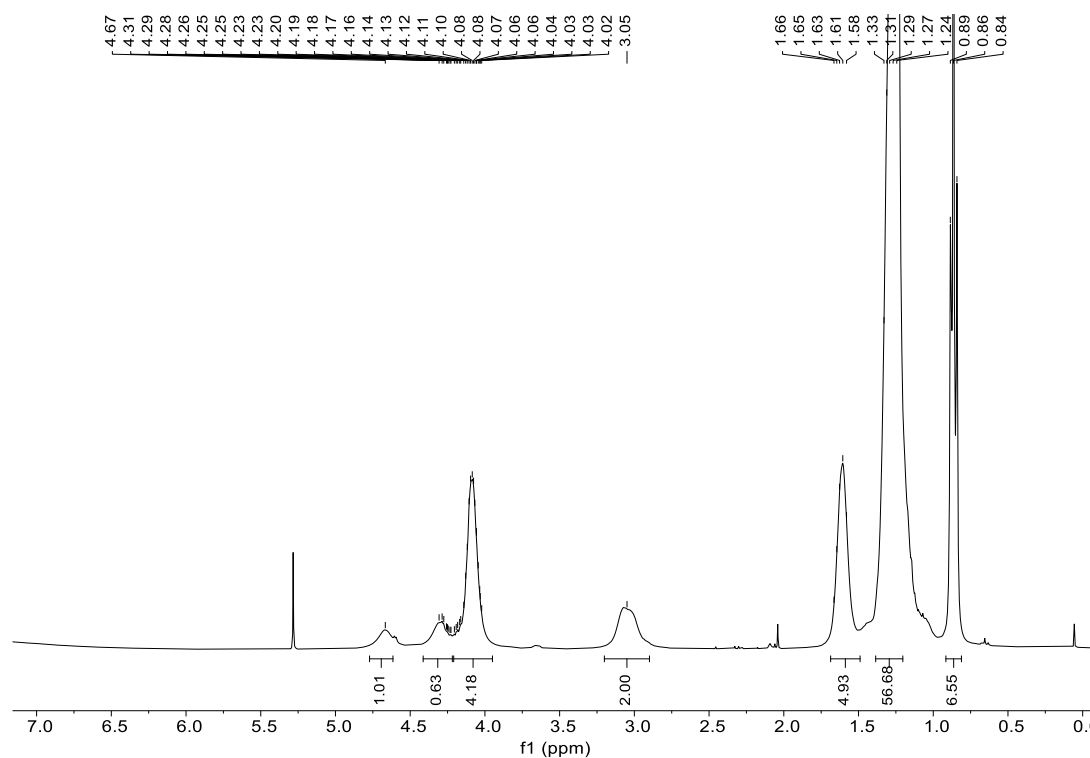
<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 4.57 (s<sub>br</sub>, 1H, H<sub>2</sub>, syn or anti), 4.39 (s<sub>br</sub>, 1H, H<sub>2</sub>, syn or anti), 4.03 (dt, *J* = 12.2, 6.0 Hz, 4H, H<sub>6</sub>), 2.97 (m, 2H, H<sub>3</sub>, syn+anti), 1.55 (q, *J* = 7.1, 6.6 Hz, 4H, H<sub>7</sub>), 1.20 (s, 36H, H<sub>8-16</sub>), 1.15 – 1.06 (m, 6H, H<sub>4</sub>), 0.86 – 0.76 (m, 6H, H<sub>17</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 176.89, 176.58 (C<sub>1</sub>), 174.25, 173.96 (C<sub>5</sub>), 72.42, 71.64, 71.41 (C<sub>2</sub>), 65.69, 65.32 (C<sub>6</sub>), 43.14, 42.77 (C<sub>3</sub>), 32.16, 31.89 (C<sub>15</sub>), 29.65, 29.63, 29.60, 29.53, 29.48, 29.43, 29.34, 29.27 (C<sub>9-14</sub>), 28.48, 28.40 (C<sub>7</sub>), 25.84, 25.73 (C<sub>8</sub>), 22.65 (C<sub>16</sub>), 14.03, 13.57, 13.08 (C<sub>17</sub>), 10.66, 10.42 (C<sub>4</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>17</sub>H<sub>32</sub>NaO<sub>5</sub> 339.2142; Found 339.2142.



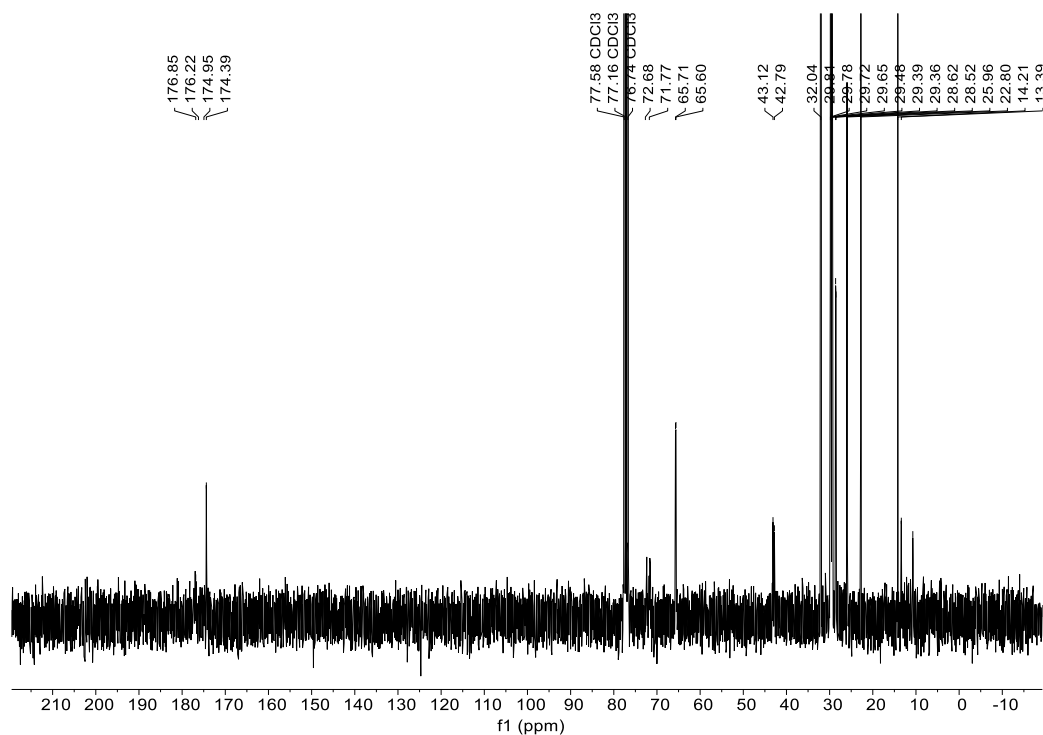
(syn+anti) 4-(Tetradecyloxy)-2-hydroxy-3-methyl-4-oxobutanoic acid (C<sub>19</sub>H<sub>36</sub>O<sub>5</sub>)



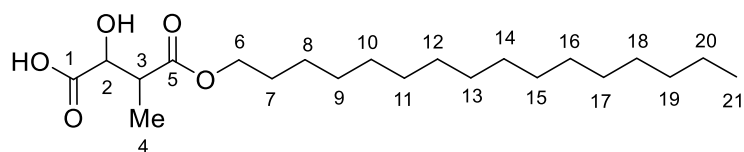
<sup>1</sup>H NMR (300 MHz, Chloroform-*d*) δ 4.67 (sbr, 1H, H<sub>2</sub>, syn or anti), 4.41 (sbr, 1H, H<sub>2</sub>, syn or anti), 4.21 – 3.95 (m, 4H, H<sub>6</sub>), 3.05 (s, 2H, H<sub>3</sub>), 1.69 – 1.49 (m, 4H, H<sub>7</sub>), 1.24 (s, 50H, H<sub>4</sub>, H<sub>8-18</sub>), 0.92 – 0.81 (m, 6H, H<sub>19</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 176.85, 176.22 (C<sub>1</sub>), 174.95, 174.39 (C<sub>5</sub>), 72.68, 71.77 (C<sub>2</sub>), 65.71, 65.60 (C<sub>6</sub>), 43.12, 42.79 (C<sub>3</sub>), 32.04 (C<sub>17</sub>), 29.81, 29.78, 29.72, 29.65, 29.48, 29.39, 29.36 (C<sub>9-17</sub>), 28.62, 28.52 (C<sub>7</sub>), 25.96 (C<sub>8</sub>), 22.80 (C<sub>18</sub>), 14.21, 13.39 (C<sub>19</sub>), 10.73 (C<sub>4</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>19</sub>H<sub>36</sub>NaO<sub>5</sub> 395.2455; Found 395.2456.



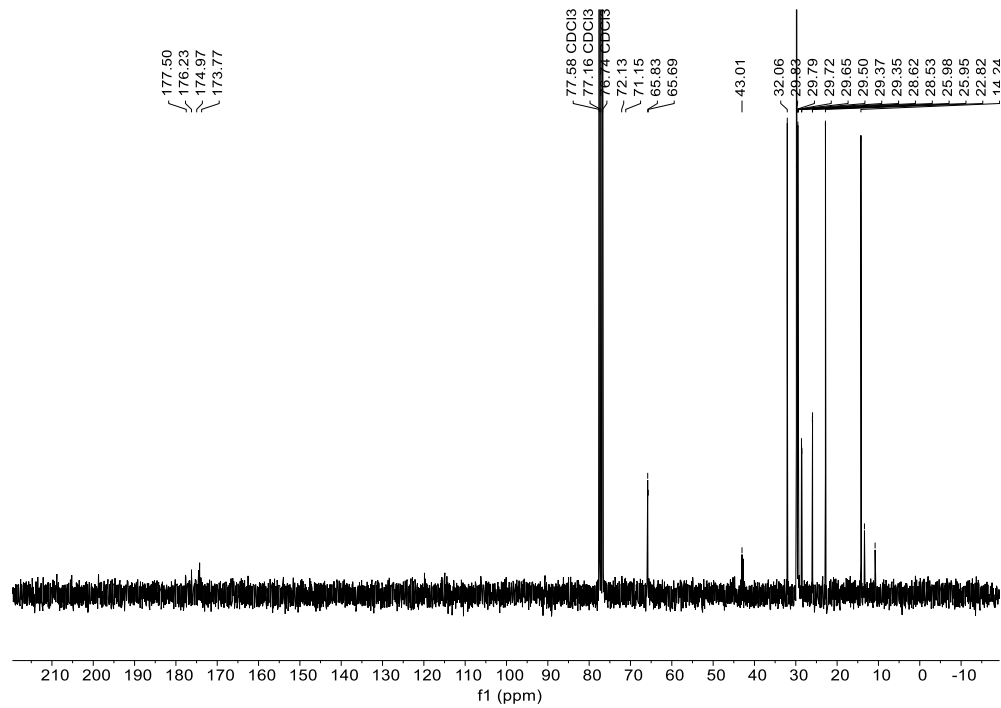
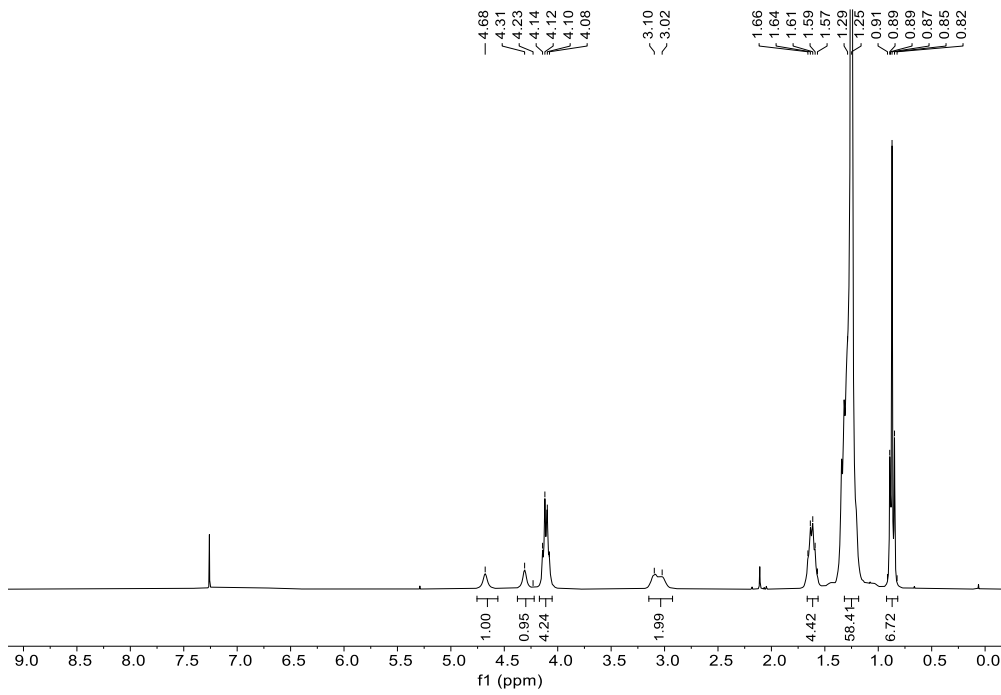




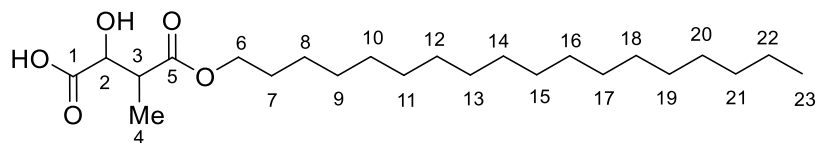
(syn+anti) 4-(Hexadecyloxy)-2-hydroxy-3-methyl-4-oxobutanoic acid (C<sub>21</sub>H<sub>40</sub>O<sub>5</sub>)



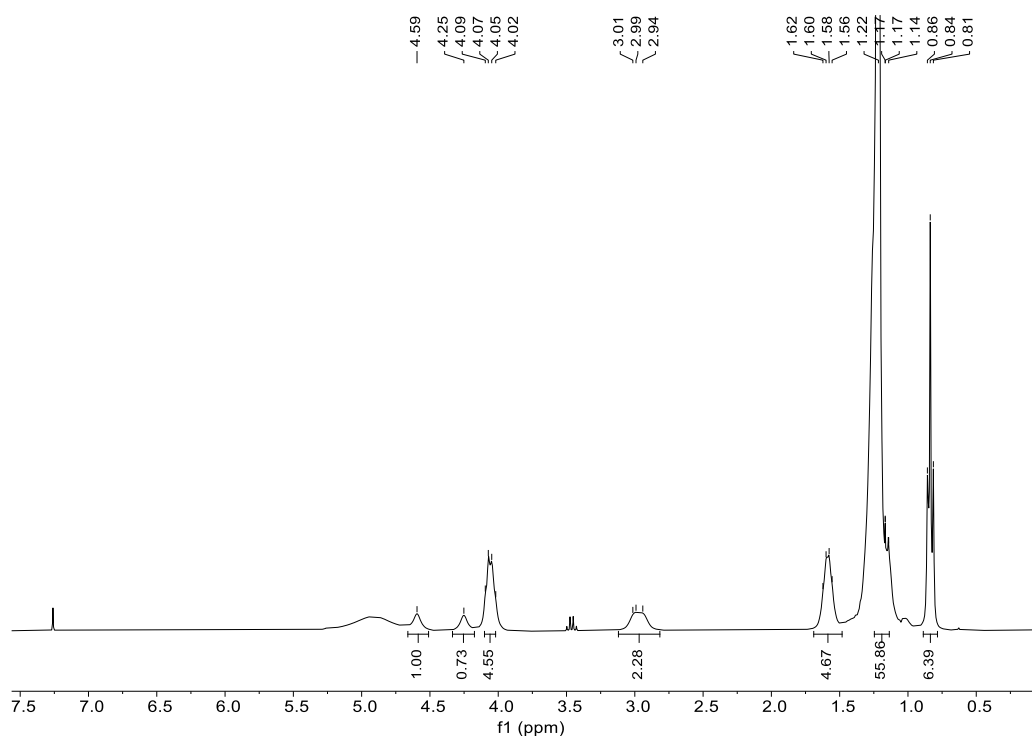
<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 4.68 (s<sub>br</sub>, 1H, H<sub>2</sub>, syn or anti), 4.31 (s<sub>br</sub>, 1H, H<sub>2</sub>, syn or anti), 4.11 (q, *J* = 6.3 Hz, 4H, H<sub>6</sub>), 3.06 (d, *J* = 22.0 Hz, 2H, H<sub>3</sub>, syn+anti), 1.61 (p, *J* = 6.7 Hz, 4H, H<sub>6</sub>), 1.25 (s, 58H, H<sub>4</sub>, H<sub>8-20</sub>), 0.92 – 0.82 (m, 6H, H<sub>21</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 177.50, 176.23 (C<sub>1</sub>), 174.97, 173.77 (C<sub>5</sub>), 72.13, 71.15 (C<sub>2</sub>), 65.83, 65.69 (C<sub>6</sub>), 43.01 (C<sub>3</sub>), 32.06 (C<sub>19</sub>), 29.83, 29.79, 29.72, 29.65, 29.50, 29.37, 29.35 (C<sub>9-18</sub>), 28.62, 28.53 (C<sub>7</sub>), 25.98, 25.95 (C<sub>8</sub>), 22.82 (C<sub>20</sub>), 14.24, 13.38 (C<sub>21</sub>), 10.81 (C<sub>4</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>21</sub>H<sub>40</sub>NaO<sub>5</sub> 395.2768; Found 395.2766.

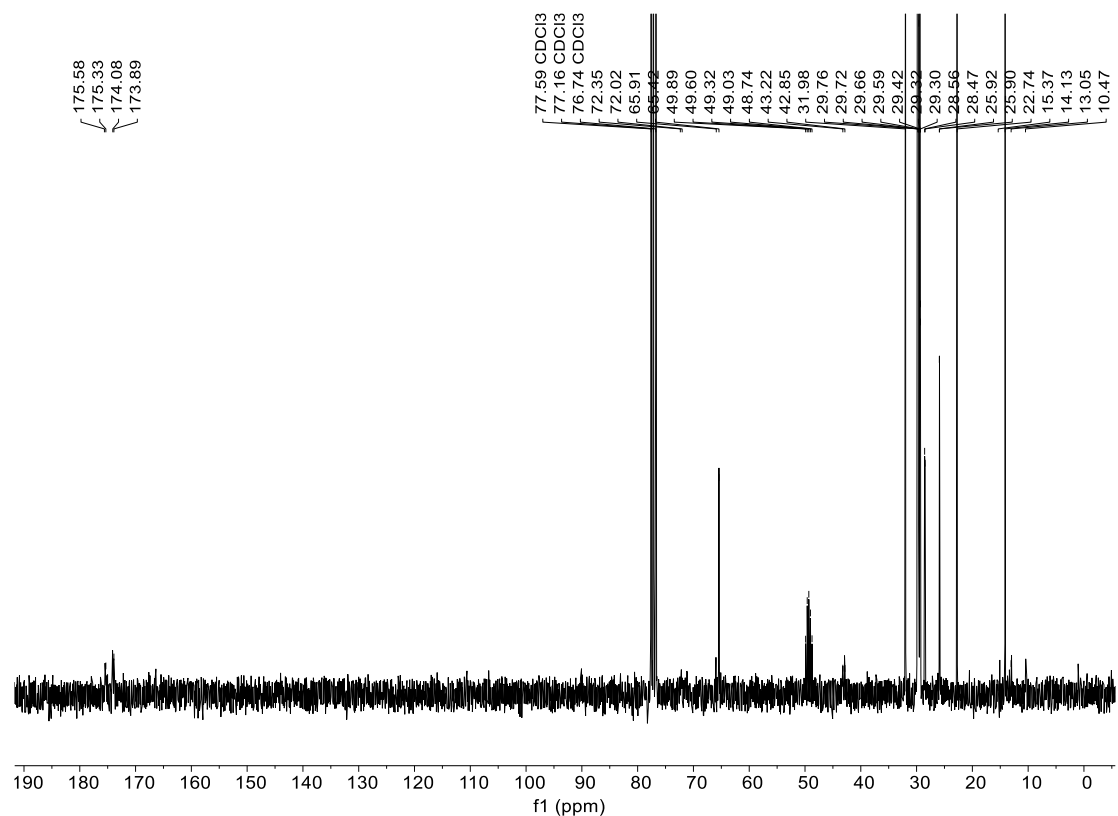


(syn+anti) 4-(Octadecyloxy)-2-hydroxy-3-methyl-4-oxobutanoic acid (C<sub>23</sub>H<sub>44</sub>O<sub>5</sub>)

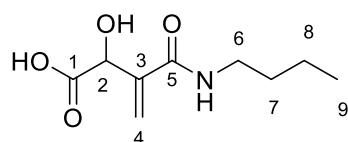


<sup>1</sup>H NMR (300 MHz, Chloroform-*d*) δ 4.59 (s<sub>br</sub>, 1H, H<sub>2</sub>, syn or anti), 4.25 (s<sub>br</sub>, 1H, H<sub>2</sub>, syn or anti), 4.06 (d, *J* = 7.5 Hz, 4H, H<sub>6</sub>), 3.12 – 2.82 (m, 2H, H<sub>3</sub>, syn+anti), 1.59 (q, *J* = 6.7 Hz, 4H, H<sub>7</sub>), 1.22 (s, 66H, H<sub>4</sub>, H<sub>8-22</sub>), 0.89 – 0.78 (m, 6H, H<sub>23</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 175.58, 175.33 (C<sub>1</sub>), 174.08, 173.89 (C<sub>5</sub>), 72.35, 72.02 (C<sub>2</sub>), 65.91, 65.42 (C<sub>6</sub>), 43.22, 42.85 (C<sub>3</sub>), 31.98 (C<sub>21</sub>), 29.76, 29.72, 29.66, 29.59, 29.42, 29.32, 29.30 (C<sub>9-20</sub>), 28.56, 28.47 (C<sub>7</sub>), 25.92, 25.90 (C<sub>8</sub>), 22.74 (C<sub>22</sub>), 15.37, 14.13, 13.05 (C<sub>23</sub>), 10.47 (C<sub>4</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>23</sub>H<sub>44</sub>NaO<sub>5</sub> 423.3081; Found 423.3082.

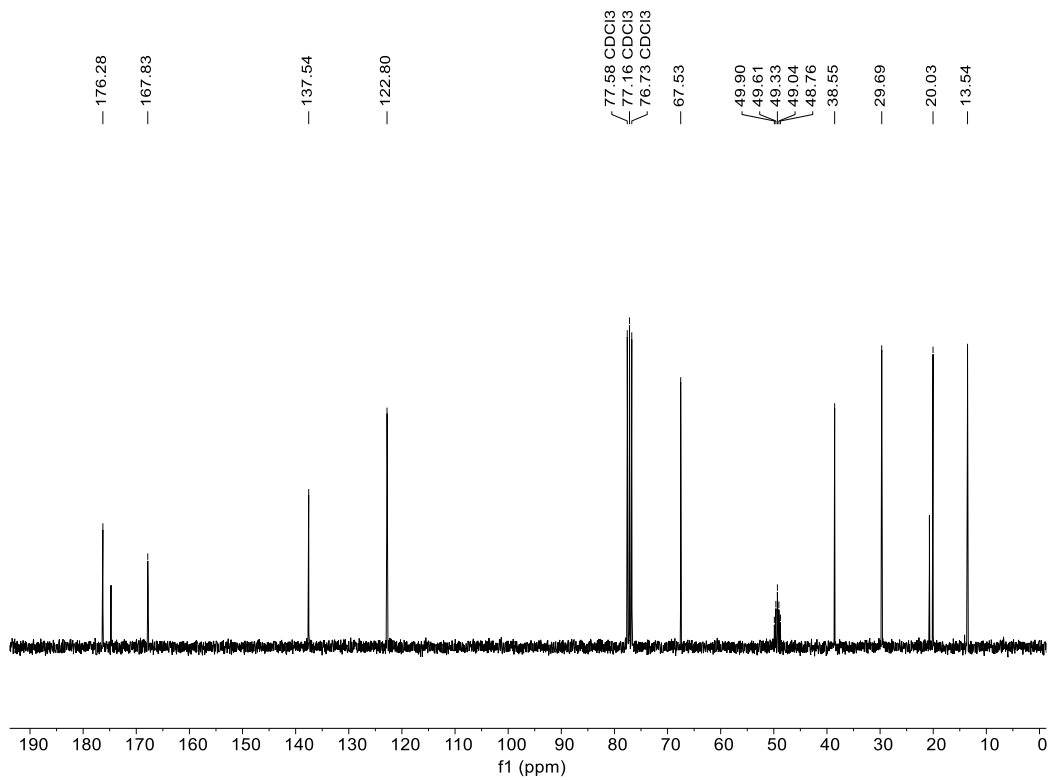
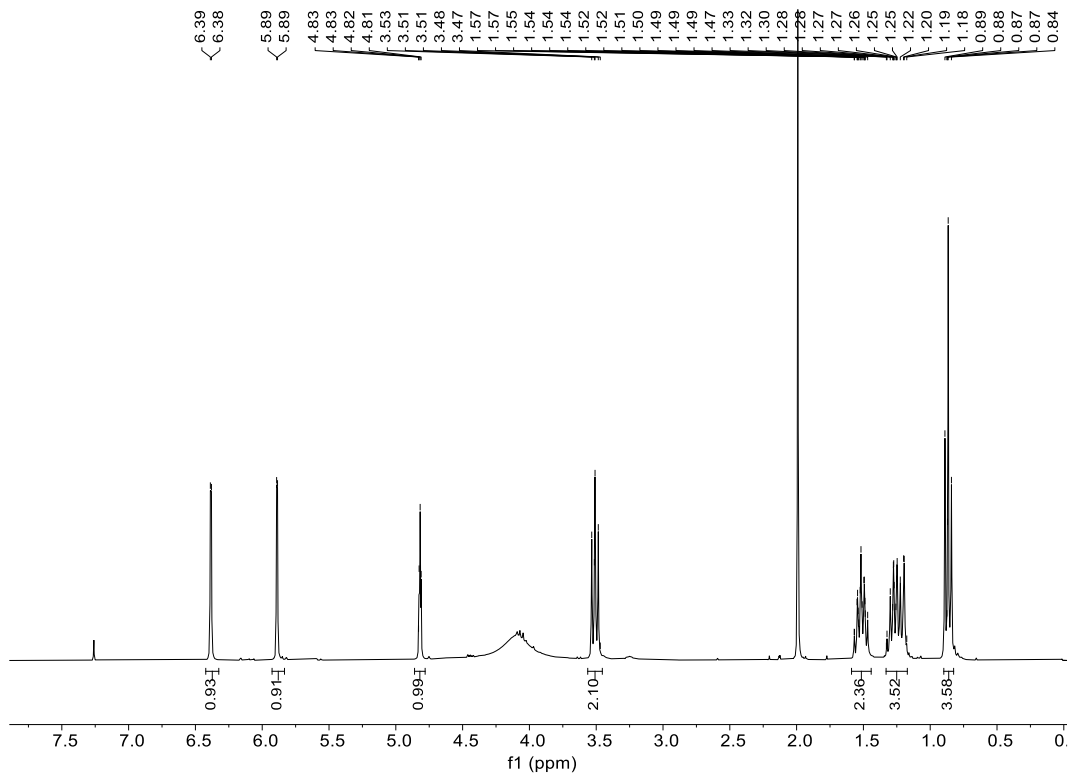




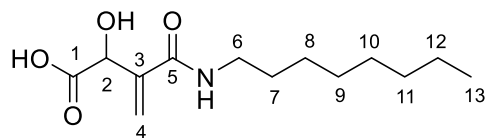
*3-(Butylcarbamoyl)-2-hydroxybut-3-enoic acid* (C<sub>9</sub>H<sub>15</sub>NO<sub>4</sub>)



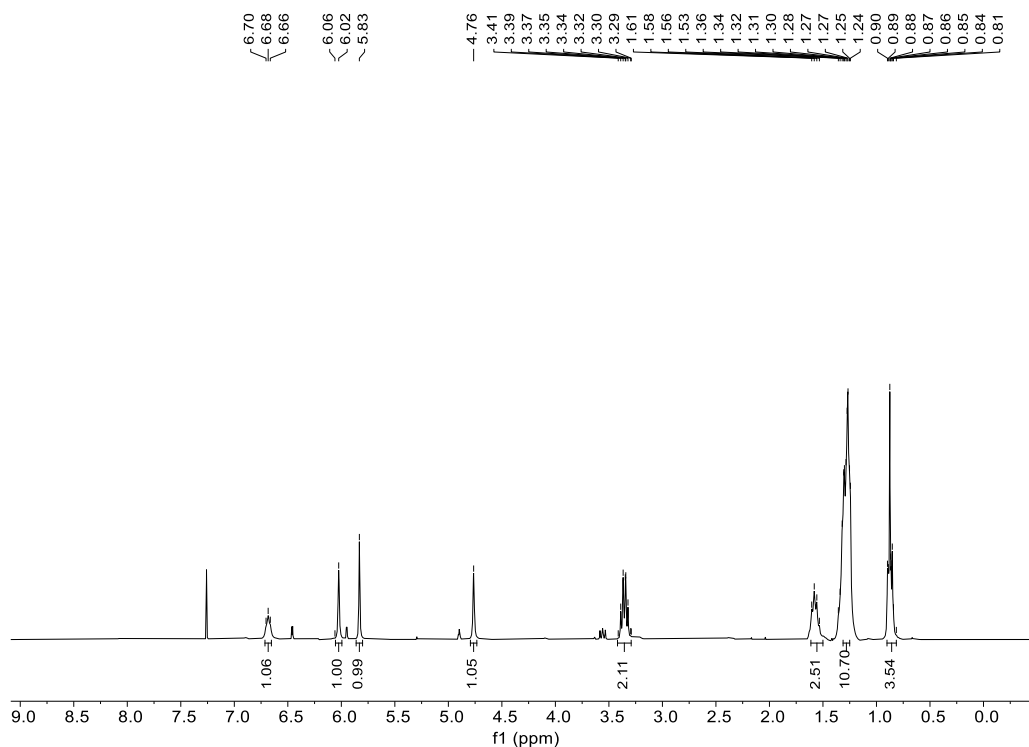
<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 6.38 (d, *J* = 2.4 Hz, 1H, C=CH<sub>2</sub>, a), 5.89 (d, *J* = 2.0 Hz, 1H, C=CH<sub>2</sub>, b), 4.82 (t, *J* = 2.3 Hz, 1H, CH-OH), 3.51 (dd, *J* = 8.1, 6.6 Hz, 2H, C<sub>6</sub>), 1.52 (tdd, *J* = 8.6, 7.5, 6.2 Hz, 2H, C<sub>7</sub>), 1.33 – 1.17 (m, 2H, C<sub>8</sub>), 0.87 (t, *J* = 7.3 Hz, 3H, C<sub>9</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 176.28 (C<sub>1</sub>), 167.83 (C<sub>5</sub>), 137.54 (C<sub>3</sub>), 122.80 (C<sub>4</sub>), 67.53 (C<sub>2</sub>), 38.55 (C<sub>6</sub>), 29.69 (C<sub>7</sub>), 20.03 (C<sub>8</sub>), 13.54 (C<sub>9</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>9</sub>H<sub>15</sub>NNaO<sub>4</sub> 224.0893; Found 224.0893.

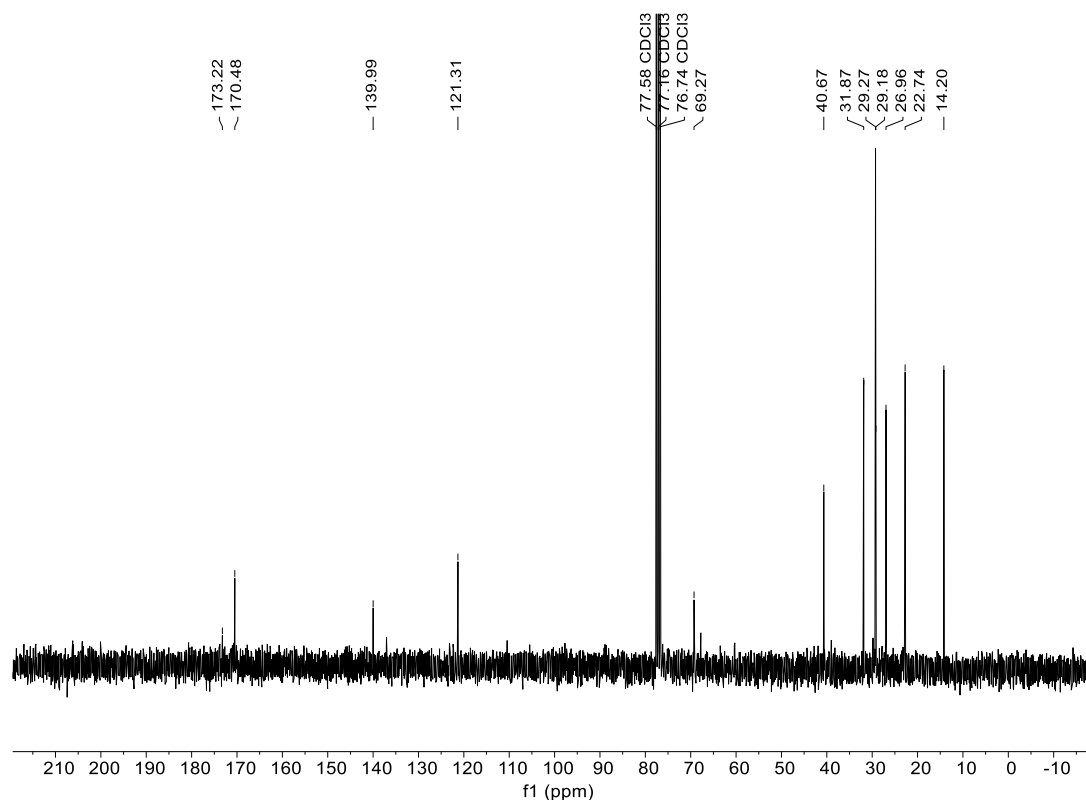


3-(Octylcarbamoyl)-2-hydroxybut-3-enoic acid (C<sub>13</sub>H<sub>23</sub>NO<sub>4</sub>)

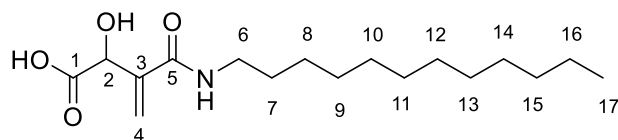


<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 6.67 (d, *J* = 6.0 Hz, 1H, NH), 6.02 (s, 1H, C=CH<sub>2</sub>, a), 5.83 (s, 1H, C=CH<sub>2</sub>, b), 4.76 (s, 1H, CH-OH), 3.42 – 3.29 (m, 2H, C<sub>6</sub>), 1.58 (t, *J* = 7.2 Hz, 2H, C<sub>7</sub>), 1.31 – 1.25 (m, 10H, C<sub>8-12</sub>), 0.90 – 0.81 (m, 3H, C<sub>13</sub>). <sup>13</sup>C NMR (76 MHz, CDCl<sub>3</sub>): δ 173.22 (C<sub>1</sub>), 170.48 (C<sub>5</sub>), 139.99 (C<sub>3</sub>), 121.31 (C<sub>4</sub>), 69.27 (C<sub>2</sub>), 40.67 (C<sub>6</sub>), 31.87 (C<sub>11</sub>), 29.27 (C<sub>7</sub>), 29.18 (C<sub>9</sub>), 26.96 (C<sub>8</sub>), 22.74 (C<sub>12</sub>), 14.20 (C<sub>13</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>9</sub>H<sub>15</sub>NNaO<sub>4</sub> 280.1627; Found 280.1628.

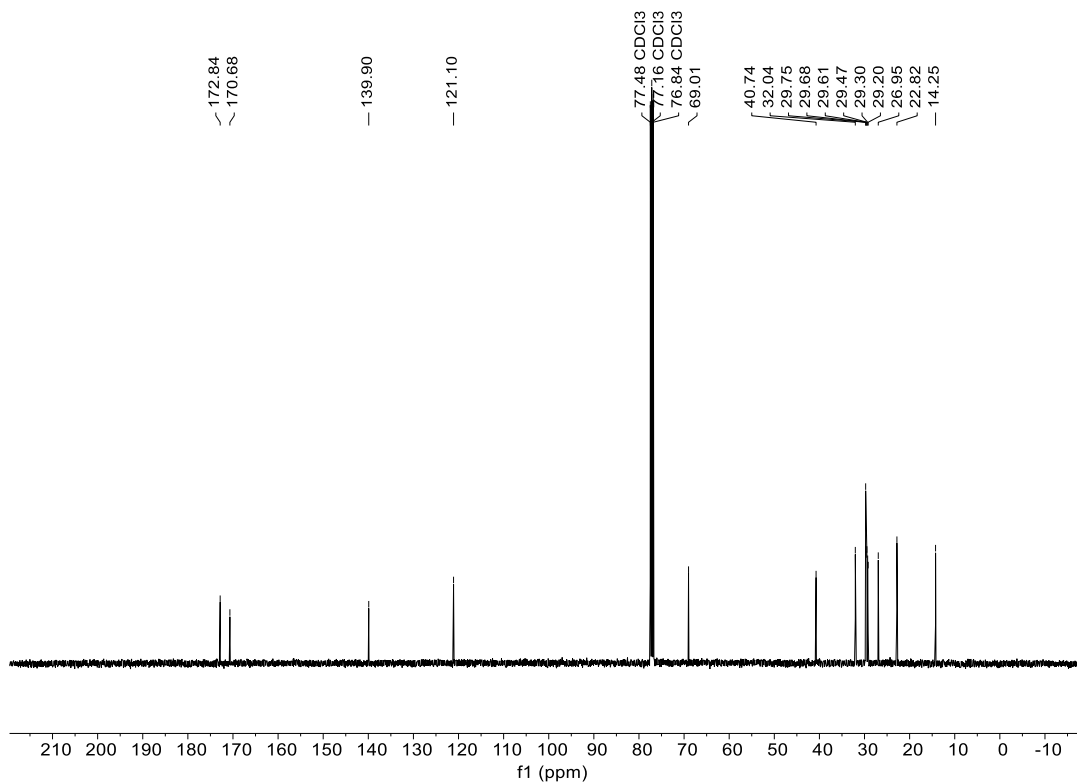
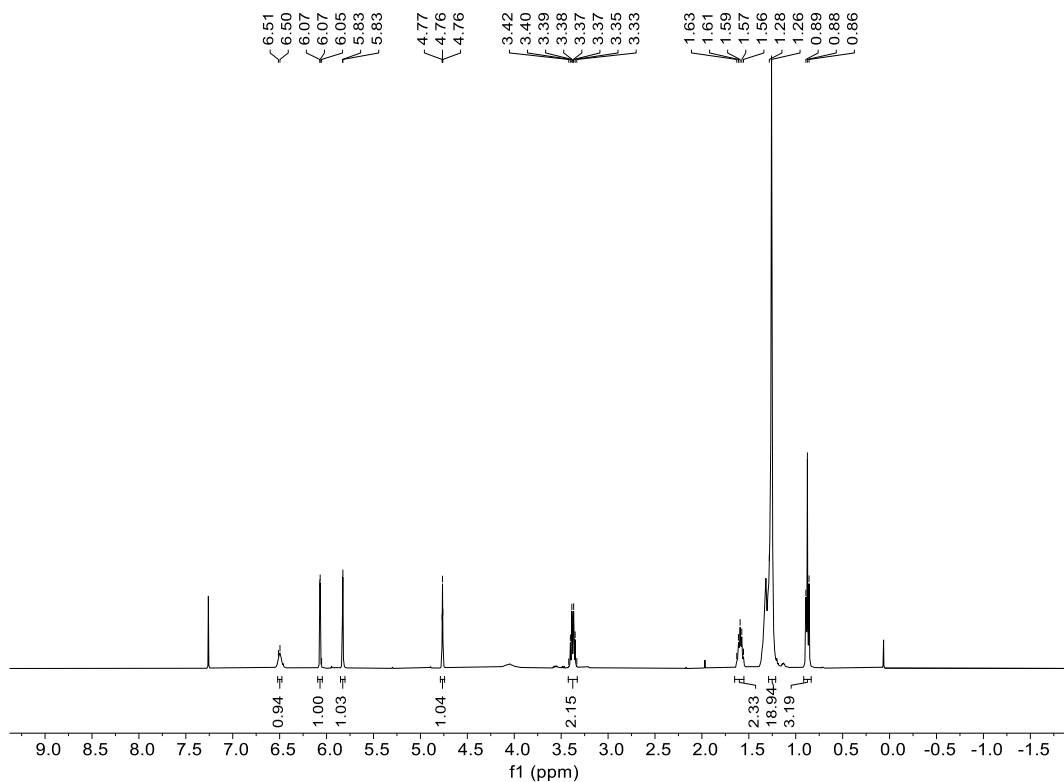




*3-(Dodecylcarbamoyl)-2-hydroxybut-3-enoic acid* (C<sub>17</sub>H<sub>31</sub>NO<sub>4</sub>)

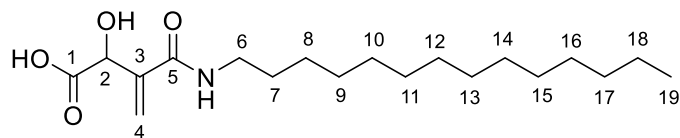


<sup>1</sup>H NMR (400 MHz, Chloroform-*d*): δ 6.50 (d, *J* = 6.6 Hz, 1H, NH), 6.07 (d, *J* = 1.6 Hz, 1H, C=CH<sub>2</sub>, a), 5.83 (d, *J* = 1.2 Hz, 1H, C=CH<sub>2</sub>, b), 4.76 (d, *J* = 1.4 Hz, 1H, CH-OH), 3.38 (dt, *J* = 7.9, 6.4 Hz, 2H, H<sub>6</sub>), 1.59 (p, *J* = 7.1 Hz, 2H, H<sub>7</sub>), 1.27 (d, *J* = 9.5 Hz, 18H, H<sub>8-16</sub>), 0.91 – 0.84 (m, 3H, H<sub>17</sub>). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 172.84 (C<sub>1</sub>), 170.68 (C<sub>5</sub>), 139.90 (C<sub>3</sub>), 121.10 (C<sub>4</sub>), 69.01 (C<sub>2</sub>), 40.74 (C<sub>6</sub>), 32.04 (C<sub>15</sub>), 29.75, 29.68, 29.61, 29.47, 29.30, 29.20 (C<sub>7</sub>, C<sub>9-14</sub>), 26.95 (C<sub>8</sub>), 22.82 (C<sub>16</sub>), 14.25 (C<sub>17</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>17</sub>H<sub>31</sub>NNaO<sub>4</sub> 336.2145; Found 336.2148.

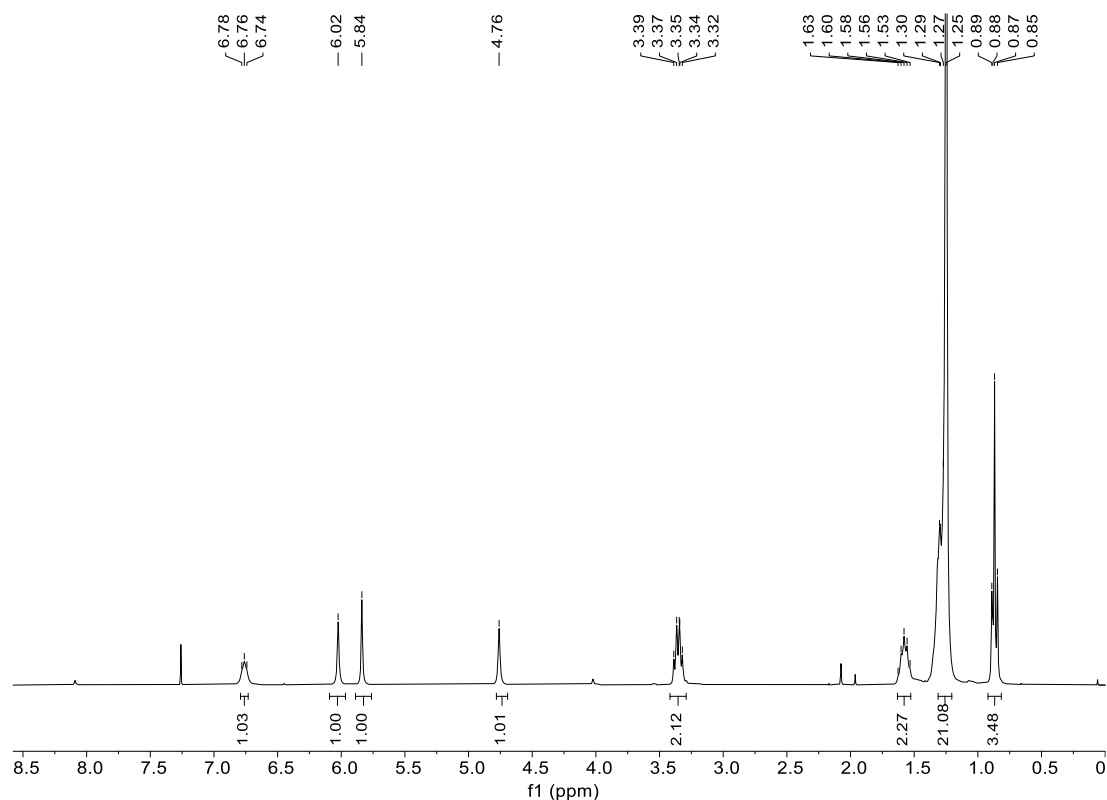


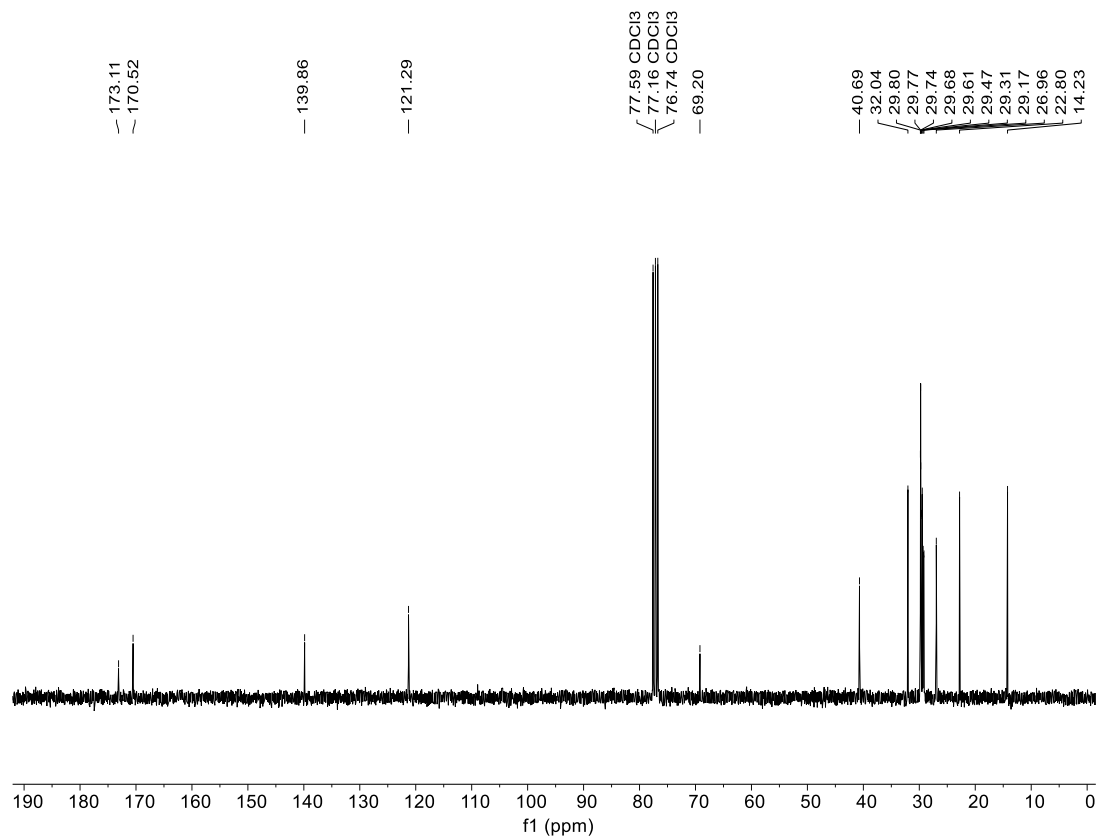


3-(Tetradecylcarbamoyl)-2-hydroxybut-3-enoic acid (C<sub>19</sub>H<sub>35</sub>NO<sub>4</sub>)



<sup>1</sup>H NMR (300 MHz, Chloroform-*d*): δ 6.75 (d, *J* = 6.0 Hz, NH), 6.02 (s, 1H, 1H, C=CH<sub>2</sub>, a), 5.84 (s, 1H, C=CH<sub>2</sub>, b), 4.76 (s, 1H, CH-OH), 3.36 (q, *J* = 7.0 Hz, 2H, H<sub>6</sub>), 1.57 (q, *J* = 7.1 Hz, 2H, H<sub>7</sub>), 1.25 (s, 22H, H<sub>8-18</sub>), 0.92 – 0.82 (m, 3H, H<sub>19</sub>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 173.11 (C<sub>1</sub>), 170.52 (C<sub>5</sub>), 139.86 (C<sub>3</sub>), 121.29 (C<sub>4</sub>), 69.20 (C<sub>2</sub>), 40.69 (C<sub>6</sub>), 32.04 (C<sub>17</sub>), 29.80, 29.77, 29.74, 29.68, 29.61, 29.47, 29.31, 29.17 (C<sub>7</sub>, C<sub>9-16</sub>), 26.96 (C<sub>8</sub>), 22.80 (C<sub>18</sub>), 14.23 (C<sub>19</sub>). HRMS (ESI) *m/z*: Calcd for [M+Na]<sup>+</sup> C<sub>19</sub>H<sub>35</sub>NNaO<sub>4</sub> 364.2458; Found 364.2440.







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## FOLIO ADMINISTRATIF

### THESE DE L'UNIVERSITE DE LYON OPEREE AU SEIN DE L'INSA LYON

NOM : YUE

DATE de SOUTENANCE : 30 Mars 2022

Prénoms : Xiaoyang

TITRE : Les glucides & molécules plateformes comme briques polaires pour la conception de tensioactifs biosourcés

NATURE : Doctorat

Numéro d'ordre : 2022LYSEI018

Ecole doctorale : ED de Chimie

Spécialité : Chimie

RESUME :

L'utilisation de la biomasse comme ressource renouvelable pour produire des tensioactifs est devenu un domaine important. L'objectif de cette thèse est d'étudier l'utilisation d'aldéhydes biosourcés furaniques dans une stratégie originale de conception de systèmes amphiphiles basée sur leur couplage par réaction de Morita-Baylis-Hillman (MBH) avec des partenaires acryliques non polaires, notamment des N-alkylacrylamides secondaires. Leurs propriétés physico-chimiques ont été examinées dans le cadre d'une collaboration avec le laboratoire UCCS de Lille dirigée par le Pr Véronique Nardello-Rataj.

La stratégie a été étendue ensuite à la réaction de l'acide glyoxylique avec les acrylates et acrylamides à longue chaîne conduisant à des amphiphiles. Il s'agit de la première étude systématique sur l'utilisation de l'acide glyoxylique dans les réactions MBH. Les propriétés des produits ont été caractérisées à Lille. Les premiers résultats indiquent leur bonne capacité à réduire la tension superficielle de l'eau à de faibles concentrations.

Dans cette stratégie en une étape et économe en atomes, l'acide glyoxylique est utilisé directement à partir de sa solution aqueuse commerciale et peu coûteuse, dans des conditions douces (solvants aqueux ou biosourcés, pas de haute température), et un protocole simple.

Un projet parallèle a concerné les glycostéroïdes et leur comportement thermotrope, dans le cadre d'une collaboration sur les cristaux liquides glycolipidiques avec le professeur John W. Goodby de l'Université de York. L'architecture de cette série de glycostéroïdes comporte une tête saccharidique, reliée à une unité stéroïdienne via un espaceur méthylène, et portant une chaîne grasse latérale de longueur variable. Ce travail a finalisé la préparation d'une famille de produits qui sont actuellement en cours d'évaluation entre les mains de nos collègues de York.

Les deux sous-thèmes étudiés dans cette thèse contribuent à une meilleure compréhension des propriétés d'interface ou d'auto-assemblage et illustrent l'importance de l'amphiphilie dans les architectures moléculaires.

MOTS-CLÉS : 5-Hydroxyméthylfurfural (HMF), acide glyoxylique, N-alkylacrylamide secondaire, réaction de Morita-Baylis-Hillman, tensioactifs, glycostéroïdes, cristaux liquides.

Laboratoire (s) de recherche : ICBMS

Directeur de thèse: QUENEAU Yves

Président de jury :

Composition du jury :

LUBIN-GERMAIN Nadège, Professeure des Universités, Université de Cergy-Pontoise, Rapporteur  
DRAYE Micheline, Professeure des Universités, Université Savoie Mont Blanc, Rapporteur  
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