The Study of 5-(Chloromethyl)furfural-Derived Nucleophiles

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(1) Miao, H.; Shevchenko, N.; Otsuki, AL.; Mascal, M. Diversification of the Renewable Furanic Platform via 5-(Chloromethyl)furfural-Based Carbon Nucleophiles. *ChemSusChem* **2021**, *14*, 303−305.

(2) Miao, H.; Ling, H.; Shevchenko, N.; Mascal, M. Generation of Organozinc Nucleophiles Based on the Biomass-Derived Platform Molecule 5-(Chloromethyl)furfural. *Organometallics* **2021**, *40*, *23*, 3952−3957.

(3) Miao, H.; Ling, H.; Wei, J.; Mascal, M. Furylogous Nucleophile Chemistry for the Preparation of Renewable Dyes. *ACS Sustainable Chem. Eng.* **2023**, *11*, *4*, 1502–1507.

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The Study of 5-(Chloromethyl)furfural-Derived Nucleophiles

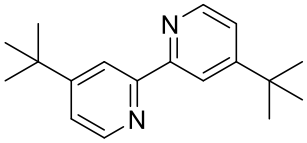
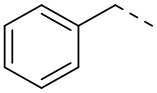
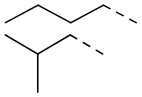
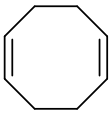
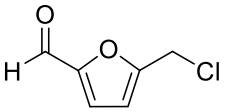
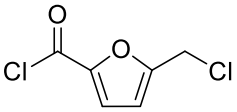
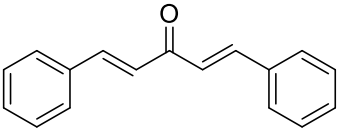
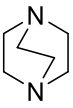
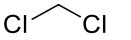
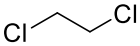
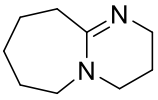
Abstract

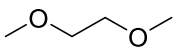
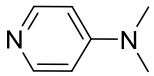
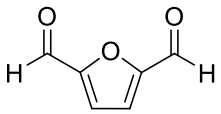
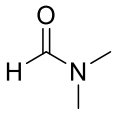
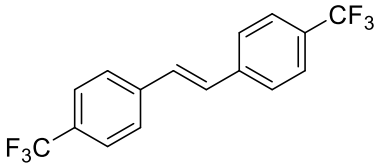
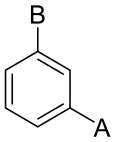
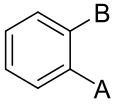
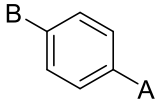
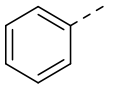
5-(Chloromethyl)furfural (CMF) is a versatile, biobased platform molecule that can be made in high yield directly from raw biomass. Although many studies have been dedicated to the applications of CMF, carbon nucleophilicity in CMF-derived molecules remains little explored. This work describes several strategies to prepare and utilize CMF-derived carbon nucleophiles based on the furylogous effect.

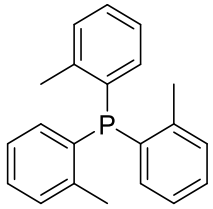
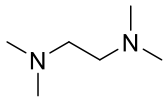
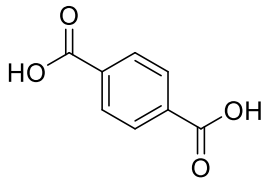
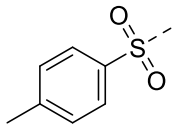
Biobased 5-(chloromethyl)furoate and 5-methylfuroate esters were directly deprotonated to function as furylogous enolates. The chloromethylfuroates can also participate in Reformatsky-type reactions, giving carbonyl addition products in high yields. This study was extended to furylogous malonate esters, which react well with aromatic aldehydes under Knoevenagel conditions. Biobased synthetic colorants were developed in moderate to excellent yields covering a spectrum from yellow to red.

Through the study and discussion of furylogous enolate chemistry, this work describes continuing efforts to develop practical tools in the synthetic repertoire for converting cellulosic biomass into useful organic molecules.

List of Abbreviations

Abbreviation	Chemical Name	Chemical Structure
Ac	acetyl	
aq.	aqueous	
Ar	aryl	
BBBPY	4,4′-di-*tert*-butyl-2,2′-dipyridyl	
Bn	benzyl	
br	broad	
n-Bu	*n*-butyl	
s-Bu	*sec*-butyl	
t-Bu	*tert*-butyl	
calcd.	calculated	
conc.	concentrated	
COD	1,5-cyclooctadiene	
CMF	5-(chloromethyl)furfural	
CMFCC	5-(chloromethyl)-2-furancarbonyl chloride	
δ	chemical shift in parts per million	
d	doublet	
dba	trans,trans-dibenzylideneacetone	
DABCO	1,4-diazabicyclo[2.2.2]octane	
DCM	dichloromethane	
DCE	1,2-dichloroethane	
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	

DME	1,2-dimethoxyethane	
DMAP	4-dimethylaminopyridine	
DMSO	dimethyl sulfoxide	
DFF	2,5-diformylfuran	
DMF	dimethylformamide	
E	electrophile	
EI	electron-impact	
ESI	electrospray ionization	
equiv	equivalents	
Et	ethyl	
FG	functional group	
^{F}stb	(*E*)-1,2-bis(4-(trifluoromethyl)phenyl)ethene	
GC	gas chromatography	
h	hour	
IR	infra-red	
J	coupling constant (NMR)	
M	molar concentration	
m	*meta*	
m	multiplet	
Me	methyl	
min	minute	
mmol	millimole	
MS	mass spectrometry	
NMR	nuclear magnetic resonance	
o	*ortho*	
p	*para*	
Ph	phenyl	

P(*o*-tol)$_3$	tris(2-methylphenyl)phosphane	
quant.	quantitative(ly)	
i-Pr	isopropyl	
q	quartet	
R	organic substituent	
rt	room temperature	
sat.	saturated	
s	singlet	
THF	tetrahydrofuran	
TLC	thin layer chromatography	
TMEDA	tetramethylethylenediamine	
TMS	trimethylsilyl	
TPA	terephthalic acid	
Ts	4-toluenesulfonyl	

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Chapter 1

Introduction

1.1 - Biomass-Derived Chemicals

Fast-depleting fossil fuel resources have been the center of conversation for a variety of sectors, including the environment, economy, and global policy, during recent decades. In 2015, the United Nations (UN) released its Sustainable Development Goals (SDGs), a comprehensive plan dedicated to identifying principles for responsible and equitable development that is considerate of people and ecosystems.[1] The SDGs establish a defined agenda to be accomplished by 2030 (Agenda 2030) which consists of 17 goals and 169 objectives that encourage economic progress, environmental preservation, social inclusion, and human well-being.[2,3] Timing is essential in the implementation of Agenda 2030. For example, China is committed to reaching the maximum of carbon dioxide emissions before 2030 and achieving carbon neutrality before 2060.[4] According to the Central Economic Work Conference, national strategic changes and institutional action plans are being pushed and implemented.[5] These significant challenges bring great opportunities. Given the shifting focus of national science policies, many national resources will likely be dedicated to the field of sustainability in the coming years.

The use of carbohydrates for chemical production is crucial to achieving carbon neutrality. In 2010, Bozell *et al.* noted "*the choice of appropriate products for addition to the biorefinery's portfolio is challenged by a lack of board-based conversion technology coupled with a plethora of potential targets"*.[6] The arsenal of synthetic organic chemistry has been expanded to include more accessible and versatile renewable platform molecules by chemists working in the field of green chemistry.

Biomass processing methods can be categorized into three types: pyrolysis, fermentation, and the chemical-catalytic method. Pyrolysis is a quick process but generally leads to complex mixtures (bio-oil or biogas), which require expensive and difficult upgrading to commercial products.[7] Fermentation is a slow process and typically focuses on market-ready target

compounds (e.g., hydrogen, methane, and alcohols). The chemical-catalytic method shows potential advantages over its competitors: it is a fast process often coupled with good chemoselectivity.[8,9]

A collection of biomass conversion products from the chemical-catalytic method is presented in Figure 1.1. These biorenewable chemicals established a pool of candidates for further systematic studies. More information can be found in a report edited by Werpy and Petersen.[10]

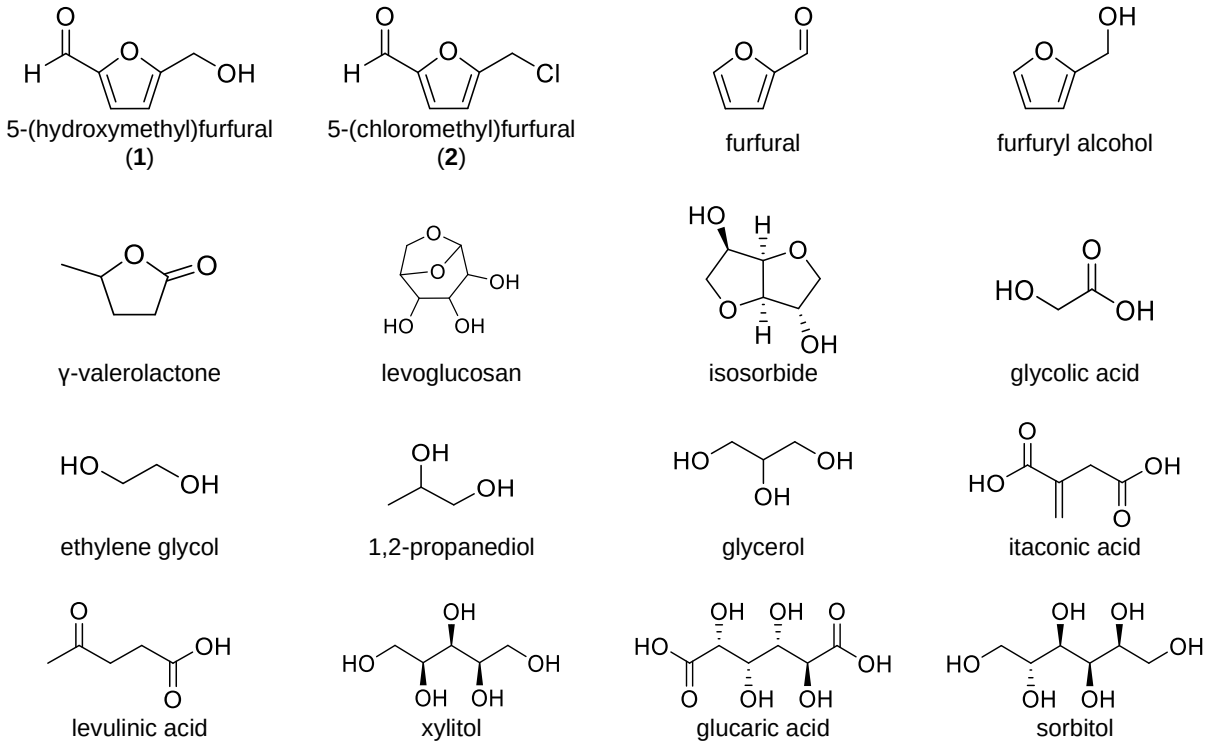


Figure 1.1 - Common platform molecules derived from carbohydrates via chemical catalysis.[11,12]

5-(Hydroxymethyl)furfural (HMF, **1**) was the iconic biomass-derived platform molecule for decades. HMF was first characterized as a product of the acidic processing of sugars in 1895,[13,14] and the definitive structural assignment was published in 1910.[15] Since then, academic focus on this platform molecule has generated numerous research articles.[16-24] However, the

commercialization of HMF stalled because of the difficulty in isolation, acid sensitivity, and the need for specific sugars as feedstocks for high-yield production.[25,26] These persistent obstacles in the industrial scale production of HMF **1** have shifted attention toward its chlorinated analog, 5-(chloromethyl)furfural (CMF, **2**).[26] CMF **2** has the advantage of being obtainable in high yields directly from any cellulosic biomass, and the hydrophobicity of CMF makes isolation from the medium of production facile.[27-29]

1.2 - Research Interests in 5-(Chloromethyl)furfural

CMF **2** is superior to HMF **1** not only in ease of derivation from raw biomass but also in synthetic versatility. CMF **2** has been used as a valuable precursor to a range of biofuels, various specialty chemicals, and renewable monomers, as shown in Figure 1.2.

The oxidation of HMF **1** or CMF **2** yields a promising monomer, 2,5-furandicarboxylic acid (FDCA). This transformation has gained much research attention because FDCA is a potential replacement for terephthalic acid (TPA), which has an expected market value of 110.66 billion USD by 2025.[30] The biorenewable replacement of TPA is highly desirable from an economic and environmental perspective. The use of FDCA as a substitute for TPA, together with biobased ethylene glycol, enables the preparation of entirely renewable polyesters, thus significantly reducing greenhouse gas emissions.[31] More details about CMF-derived commercial products can be found in recent reviews.[7,26]

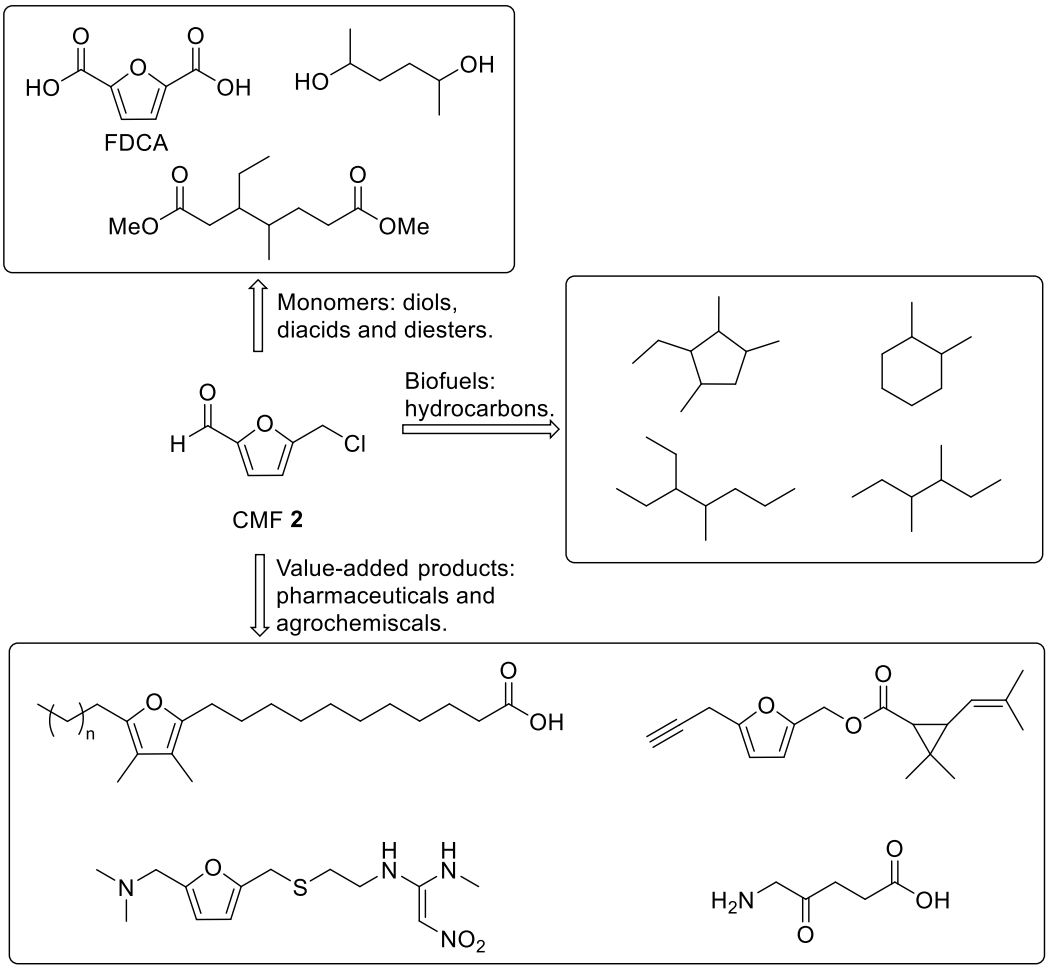


Figure 1.2 - Examples of CMF-derived products.

1.3 - Charge Affinities Present in HMF and CMF

Much continues to be made of the potential of HMF **1** to serve as a carbohydrate-derived platform molecule for the production of biobased chemicals, even though it is practically derivable only from the food sugar fructose.[25] CMF **2**, on the other hand, has attracted comparatively less attention and can be made in high yield directly from raw biomass.[26] Both HMF **1** and CMF **2** have been used in various synthetic contexts,[7,17] which are summarized in Figure 1.3. Most of the transformations involving CMF have made use of its native electrophilicity, which does not take

advantage of the full potential of this platform molecule. A description of how the chloromethyl group can be used to generate C-nucleophiles is given below.

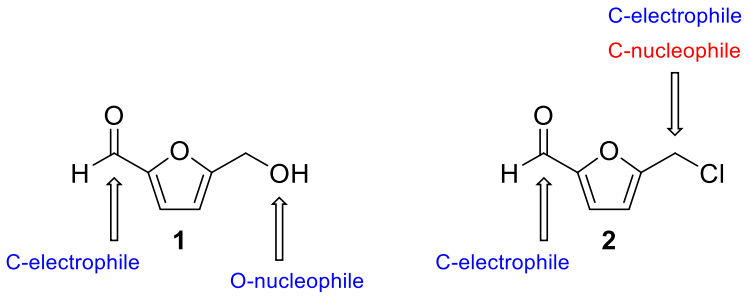
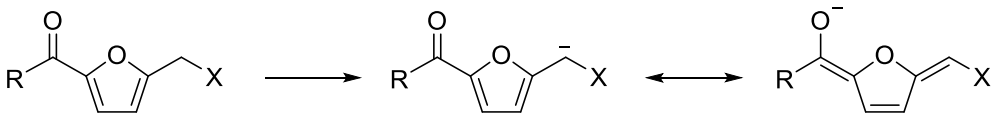


Figure 1.3 - Charge affinities in HMF (left) and CMF (right).

1.4 - Furylogy Effect on CMF Derivatives

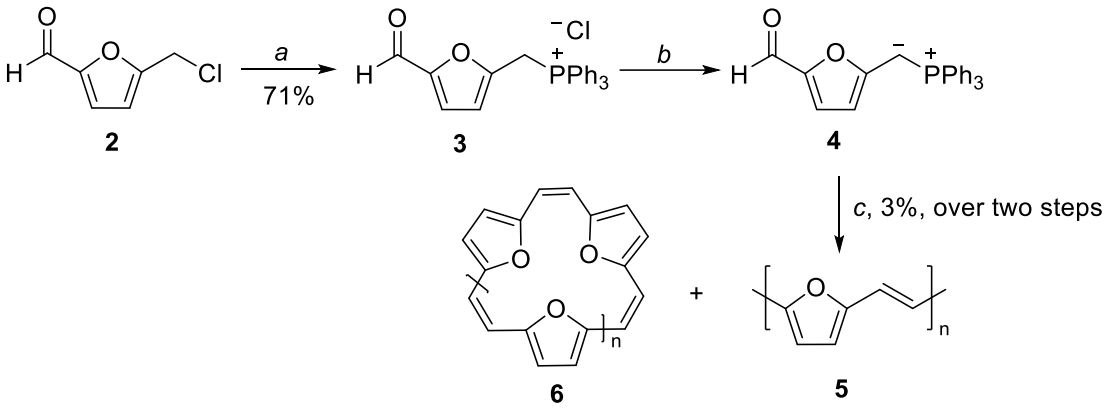
The delocalization of a negative charge through the furan ring into the carbonyl function, termed furylogy (*cf*. vinylogy), contributes to stabilization of the enolate generated at the methylene group. CMF **2** and its derivatives can form furylogous enolates due to the relatively weak aromaticity of the furan ring. Attempting this with CMF **2** itself is challenging due to the reactivity of the aldehyde, and in fact the approach has been used to prepare a CMF homopolymer.[32] The corresponding esters, however, possess sufficient stability to realize the kind of species represented in Scheme 1.1. The remaining sections in this chapter provide examples of furylogous enolates generated from CMF derivatives.



Scheme 1.1 - Concept of furylogous enolate generation from CMF derivatives (X = H, Cl; R = H, OR).

1.5 - CMF-Derived Ylides

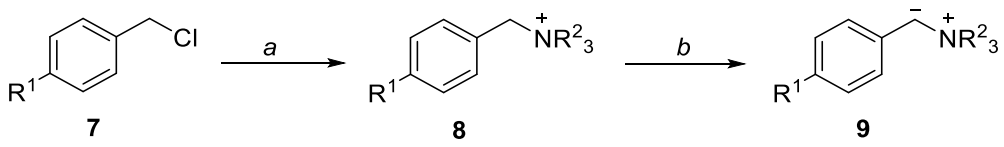
One way to prepare CMF-derived carbon nucleophiles was accomplished by forming its ylides. Elix reported a polycondensation reaction of CMF **2** via a phosphonium ylide intermediate.[33] In Elix's description, the reaction of CMF **2** with triphenylphosphine in benzene gave phosphonium salt **3**. Treatment of this phosphonium salt with lithium ethoxide resulted in the corresponding ylide **4** that underwent polymerization to give a mixture of poly(2,5-furanylvinylene) **5** and macrocycles **6** (Scheme 1.2). This approach however suffers from low yields, poor atom economy and is unsuitable for green chemistry.



Scheme 1.2 - Synthesis of polymers and macrocycles from CMF **2**. Reagents and conditions: *a*. PPh_3. *b*. LiOEt. *c*. Wittig reaction.

Kimachi and coworkers published a study of a Darzens-type epoxidation using ammonium ylides in 2005.[34] A series of 2,3-diaryl epoxides was synthesized from *para*-substituted benzylammonium chlorides and aromatic aldehydes. It was shown that substrates with electron-withdrawing groups on the *para* position afforded better yields than those with electron-releasing groups (Scheme 1.3).[35] This observation suggests that the ylides were stabilized by the delocalization of charge density over the conjugated system. Based on these findings, exploring

the possibility of using CMF-derived ammonium ylides in Darzens-type epoxidations was tempting.

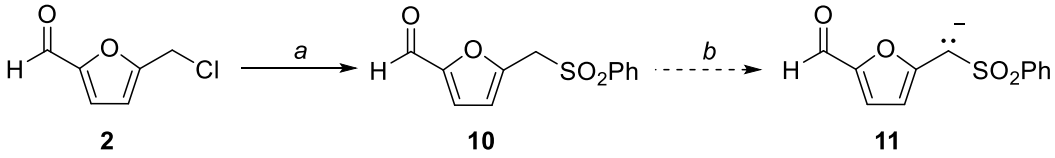


R^1= CH_3, CH_3O, CF_3, CN, *t*-BuOC(O), $Et_2NC(O)$.

Scheme 1.3 - Derivation of ammonium ylides from benzylic chlorides. Reagents and conditions: *a*. DABCO or Et_3N. *b*. KO*t*-Bu. In the literature procedure, these ammonium ylides were prepared *in situ* and were used without isolation.[35]

1.6 - CMF-Derived Alkylsulfone Anion

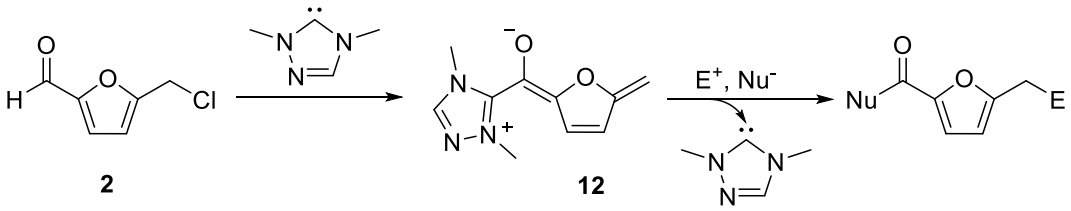
Alternatively, CMF-derived carbon nucleophiles can be prepared by replacing the chloride with anion-stabilizing sulfone groups. Szmant and Chundury reported the preparation of several novel derivatives of CMF **2**.[36] Substitution of the chloride in CMF **2** with a sulfone group leads to **10**, which could be deprotonated to give a CMF-derived alkysulfone anion **11** (Scheme 1.4). The disadvantage here is that it is restricted to the synthesis of furan-substituted sulfones.



Scheme 1.4 - Derivation of alkylsulfone anion **11** from CMF **2**. Reagents and conditions: *a*. $PhSO_2Na$, acetone. *b*. base.

1.7 - N-Heterocyclic Carbene Catalyzed Transformations of CMF

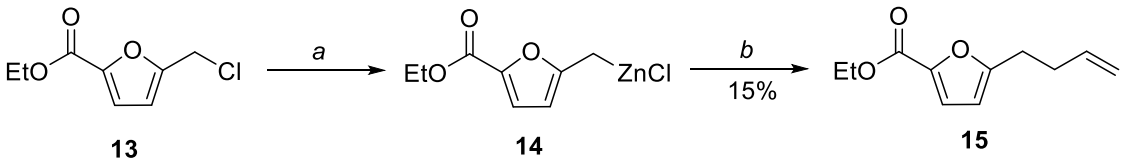
To achieve better atom economy in utilizing CMF-derived nucleophiles, the applications of carbene-catalysis in the transformations of CMF **2** were also explored. In a 2012 patent, the synthesis of 5-methylfuran-2-carboxylic acid esters was described by the reaction of CMF **2** with an alcohol in the presence of an N-heterocyclic carbene (NHC) catalyst.[37] Dai and coworkers further developed this NHC approach by extending the scope of NHCs and electrophiles.[38] However, the weak carbon nucleophilicity of species like **12** (Breslow intermediates) results in limited overall utility.



Scheme 1.5 - NHC-catalyzed transformations of CMF **2**.

1.8 - CMF-Derived Organozinc Reagents

Organozinc reagents are common synthetic tools that benefit from ample reactivity and high functional group tolerance.[39-41] Previously, Cho and Kim reported a cross-coupling reaction of an organozinc furoate ester **14** and allyl bromide (Scheme 1.6).[42] Despite the poor yield of **15**, the facile formation of intermediate **14** is encouraging. With further development, this type of CMF-derived organozinc nucleophile could serve as a practical tool in the synthetic repertory for converting cellulosic biomass into useful organic molecules.



13 14 15

Scheme 1.6 - The coupling reaction of **14** with allyl bromide. Reagents and conditions: *a*. Zn, THF, rt, 1 h. *b*. allyl bromide, 10 mol% CuI, 20 mol% LiCl, 0 °C to rt, 2 h, 15%.

These studies on the reactivity of methylene group in CMF inspired the development of novel strategies in biomass conversion, which is discussed in the subsequent chapters.

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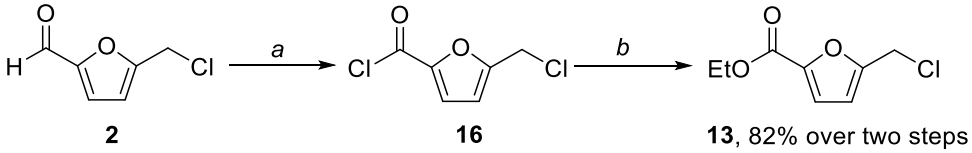
Chapter 2

Syntheses of Furoate Esters from CMF

2.1 - Synthesis of 5-(Chloromethyl)furan-2-carboxylates

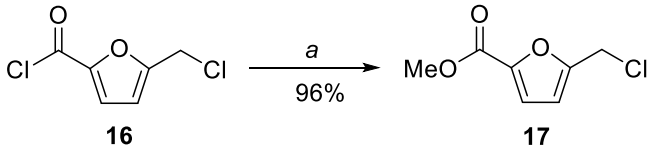
This section describes the synthesis of 5-(chloromethyl)furan-2-carboxylates. Methyl, ethyl, and *t*-butyl furoate esters were synthesized from CMF **2** to study how steric effects influence the reactivity of anions derived from CMF **2**.

The direct oxidation of CMF **2** to 5-(chloromethyl)furan-2-carbonyl chloride (CMFCC, **16**) is remarkably facile. *t*-BuOCl is made by mixing household bleach, *t*-butanol, and acetic acid, followed by phase separation. CMF **2** is added, and the resulting CMFCC **16** can be used directly without purification to make ethyl 5-(chloromethyl)furan-2-carboxylate **13** (Scheme 2.1).[1]



Scheme 2.1 - Synthesis of ethyl 5-(chloromethyl)furan-2-carboxylate **13**. Reagents and conditions: *a*. *t*-BuOCl, rt, 24 h. *b*. EtOH, 50 °C, 6 h, 82% over two steps.

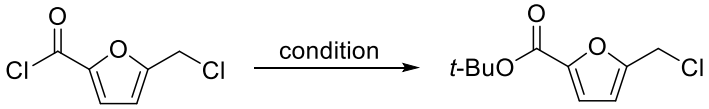
A small-scale (500 mg) synthesis of methyl 5-(chloromethyl)furan-2-carboxylate **17** was developed under mild conditions (Scheme 2.2). A stoichiometric amount of potassium carbonate was suspended in a solution of **16** in methanol and the reaction mixture was stirred for 2 h at room temperature. The crude mixture was purified by filtration through silica gel to give compound **17** in 96% yield.



Scheme 2.2 - Synthesis of methyl 5-(chloromethyl)furan-2-carboxylate **17**. Reagents and conditions: *a*. MeOH, K_2CO_3, rt, 2 h, 96%.

The less sterically hindered furoate esters, e.g., methyl ester and ethyl ester, were vulnerable to nucleophilic attack. Therefore, a *t*-butyl group was introduced to prevent nucleophilic attack on the carbonyl carbon. Table 2.1 shows conditions for synthesizing *tert*-butyl 5-(chloromethyl)furan-2-carboxylate **18**. Mixing CMFCC **16** with warm *t*-butanol did not lead to the formation of **18**. The addition of potassium *t*-butoxide also failed to give the desired product **18**. Finally, the synthesis of *t*-butyl analog **18** was achieved by the addition of DMAP as an acyl transfer catalyst.[2] This synthetic route produced **18** in a 70% yield.

Table 2.1 - Synthesis of *tert*-butyl 5-(chloromethyl)furan-2-carboxylate **18**.



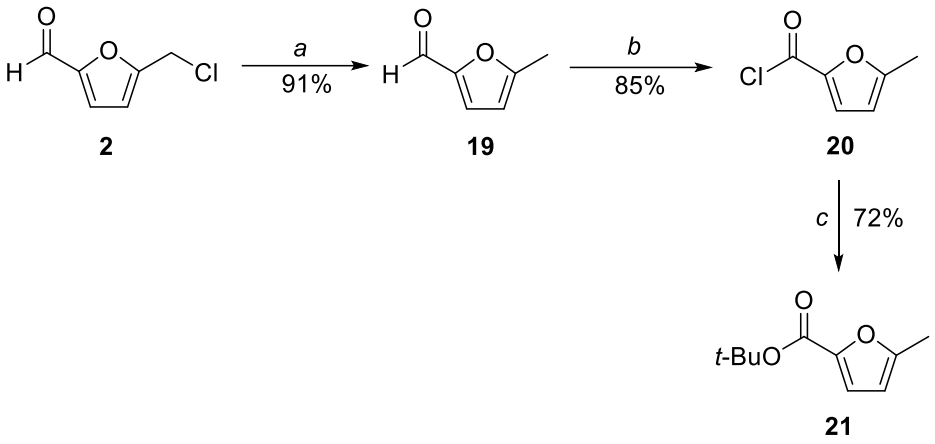
16 **18**

Entry	Reagent	Solvent	Additive	Temp./°C	Time/h	Yield/%*
1	*t*-BuOH	neat	-	50	12	0 (NR)
2	KO*t*-Bu	Dioxane	-	50	12	0 (NR)
3	*t*-BuOH	neat	DMAP	30	18	70

*Isolated yields. The experiments were monitored by ^{1}H and ^{13}C NMR spectroscopy.

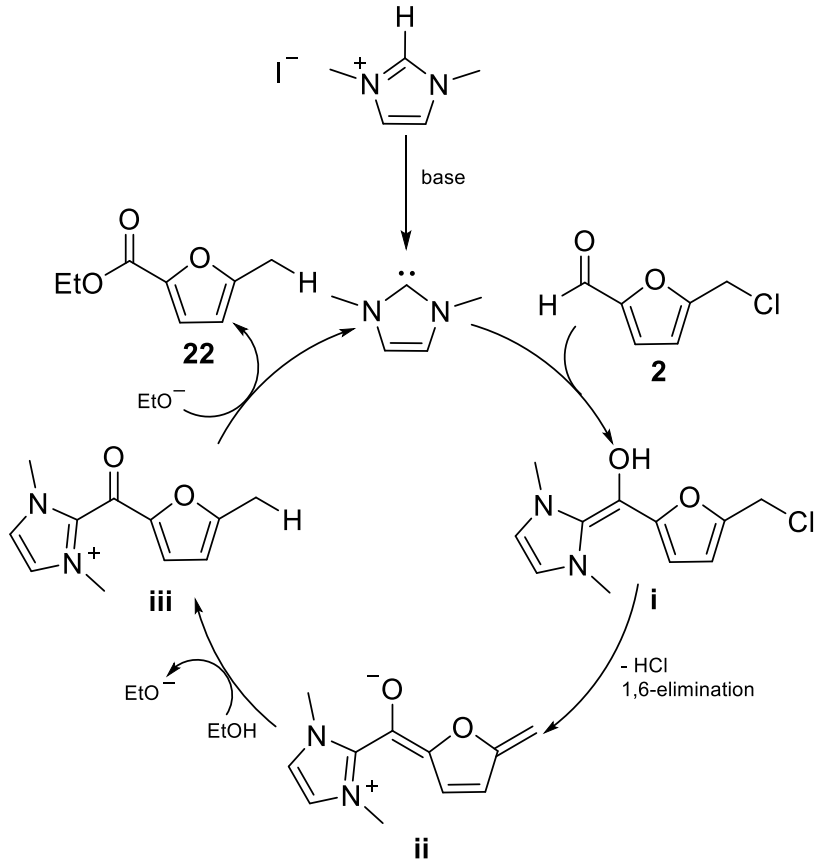
2.2 - Syntheses of 5-Methylfuran-2-carboxylates

The hydrodehalogenated analog **21** can be synthesized from CMF **2**. The hydrogenation of CMF **2** to 5-methylfurfural (5-MF, **19**) is achieved in high yield in a biphasic reaction.[3] After hydrogenation, compound **19** was subjected to a *t*-BuOCl + alcohol quench procedure to give compound **21**.



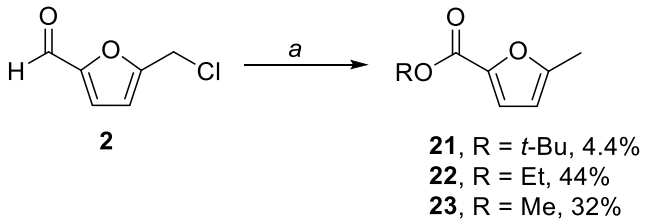
Scheme 2.3 - Synthesis of *tert*-butyl 5-methylfuran-2-carboxylate **21**. Reagents and conditions: *a*. H_2, Pd/C, toluene-water, 91%. *b*. *t*-BuOCl, 85%. *c*. *t*-BuOH, DMAP, 30 °C, 12 h, 72%.

N-Heterocyclic carbenes (NHCs) have been widely studied as effective organocatalysts in different chemical processes.[4-8] The carbene-catalyzed transformation of CMF **2** to 5-methylfuranoate esters has been patented.[9-11] A postulated mechanism for NHC-catalyzed CMF transformation is shown in Scheme 2.4. The imidazolium salt is deprotonated by DBU to give the corresponding carbene *in situ*. The addition of the NHC to CMF **2** generates Breslow intermediate **i**. The imidazolium trienolate intermediate **ii** is formed from the Breslow structure **i** by the 1,6-elimination of HCl under basic conditions. The trienolate **ii** is then quenched by ethanol and results in adduct **iii**. The subsequent substitution of the NHC moiety of **iii** with an ethoxy group yields the final product **22**.



Scheme 2.4 - A postulated mechanism for NHC-catalyzed transformations of CMF **2**.

We applied the conditions of Mikochik and Cahana in the synthesis of three CMF-derived furoates (Scheme 2.5).[10] The poor yield of *t*-butyl furoate **21** is attributed to the difficulty of replacing the NHC moiety with the bulky *t*-butoxide group in the final step. However, the isolated yields of ethyl analog **22** and methyl analog **23** did not exceed 50%.



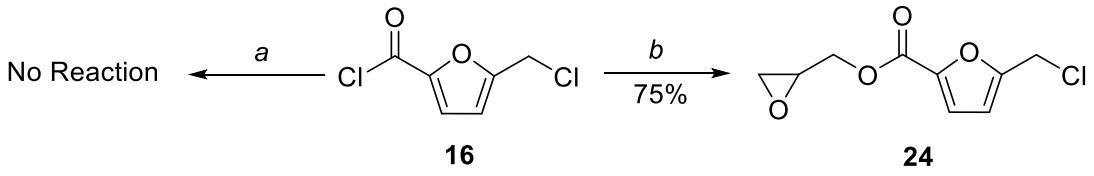
2

21, R = *t*-Bu, 4.4%
22, R = Et, 44%
23, R = Me, 32%

Scheme 2.5 - The NHC-catalyzed synthesis of 5-methylfuran-2-carboxylates. Reagents and conditions: *a*. 1,3-dimethylimidazolium iodide, DBU, ROH.

2.3 - Synthesis of Other Novel Furoate Esters

Beharaj and colleagues used triethylamine (TEA) as an acyl transfer catalyst for synthesizing glycidyl esters which were further polymerized into biodegradable adhesives.[12] Encouraged by their promising results, the synthesis of CMF-derived epoxide **24** was attempted. Glycidol was mixed with an excess of triethylamine in DCM at 0 °C before adding CMFCC **16**. This procedure gave compound **24** in 75% yield (Scheme 2.6). On the other hand, a different route to **24** using K_2CO_3 as the base was found to be ineffective (Scheme 2.6).

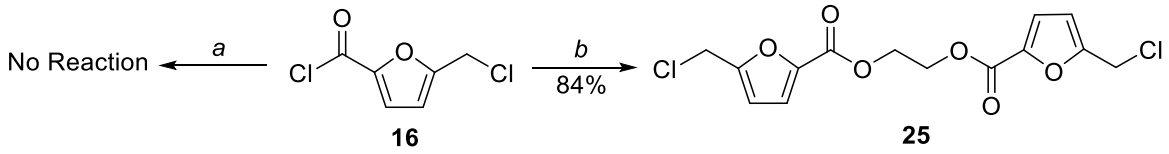


16 **24**

Scheme 2.6 - Synthesis of oxiran-2-ylmethyl 5-(chloromethyl)furan-2-carboxylate **24**. Reagents and conditions: *a*. glycidol, K_2CO_3, THF, rt, 2 h. *b*. glycidol, Et_3N, DCM, 0 °C to rt, 3.5 h, 75%.

Continuing the exploration of other novel furoate esters, we proposed the synthesis of compound **25**, which should possess similar reactivity to **13**. Moreover, considering its symmetrical nature, **25** is a biobased candidate for sustainable polymers.[13] The two-fold esterification shown in

Scheme 2.7 produced **25** in good yield. It is worth noting that substitution with ethylene glycol did not occur without using DMAP, even at elevated temperature.



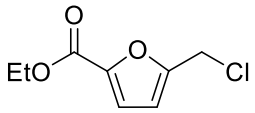
Scheme 2.7 - Synthesis of ethane-1,2-diyl bis(5-(chloromethyl)furan-2-carboxylate) **25**. Reagents and conditions: *a*. ethylene glycol, THF, 50 °C, 6 h. *b*. ethylene glycol, DMAP, 30 °C, 12 h, 84%.

2.4 - Conclusion

The *t*-BuOCl + alcohol quench procedure for preparing methyl and ethyl furoates proved a facile route to CMF-derived esters. Acyl transfer catalysts, such as Et_3N or DMAP, were found to be necessary for the preparations of the *t*-butyl (**21**) and other novel furoates (**24** and **25**). We also tested an NHC-catalyzed procedure for preparing methyl, ethyl, and *t*-butyl furoates (**21**, **22**, **23**). Unfortunately, the yields using this method were not satisfactory.

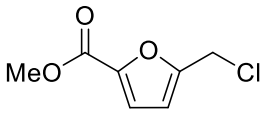
Further transformations of these biorenewable molecules will be discussed in the following chapters.

Experimental Procedures



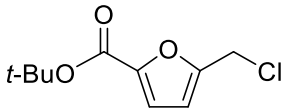
Ethyl 5-(chloromethyl)furan-2-carboxylate (**13**)

This compound was prepared according to previously published procedure.[1] The NMR spectra match those reported in the literature.



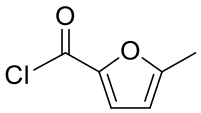
Methyl 5-(chloromethyl)furan-2-carboxylate (**17**)

CMFCC **16** (500 mg, 2.79 mmol, 1.0 equiv) and K_2CO_3 (500 mg, 3.62 mmol, 1.2 equiv) were added to anhydrous methanol (10 mL) in a 100 mL round-bottomed flask. The reaction mixture was stirred at rt for 1 h. The volatiles were evaporated under reduced pressure, and the residue was passed through a silica gel plug using DCM to give methyl 5-(chloromethyl)furan-2-carboxylate **17** as a light-yellow oil (0.47 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 3.2 Hz, 1H), 6.49 (d, *J* = 3.2 Hz, 1H), 4.59 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 154.3, 145.0, 119.0, 111.5, 52.2, 36.8; HRMS: (ESI$^+$) $C_7H_7ClO_3Na^+$ $[M + Na]^+$ *m/z* calcd. 196.9981, found 196.9984.



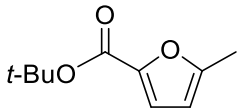
tert-Butyl 5-(chloromethyl)furan-2-carboxylate (**18**)

To a solution of CMFCC **16** (2.00 g, 11.2 mmol, 1.0 equiv) in *t*-BuOH (40 mL) was added DMAP (1.77 g, 14.5 mmol, 1.3 equiv). The reaction was stirred at 30 °C for 18 h. The mixture was diluted with water (250 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (DCM) to yield **18** as a pale yellow oil (1.68 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 3.4 Hz, 1H), 6.45 (d, *J* = 3.4 Hz, 1H), 4.59 (s, 2H), 1.57 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 153.7, 146.3, 117.9, 111.3, 82.4, 37.0, 28.4; HRMS: (ESI$^+$) $C_{10}H_{13}ClO_3Na^+$ $[M + Na]^+$ *m/z* calcd. 239.0451, found 239.0446.



5-Methylfuran-2-carbonyl chloride (**20**)

5-Methylfurfural **19** (3.16 g, 28.7 mmol) was dissolved in *t*-BuOCl (10 mL), and the solution was stirred at rt for 24 h. The solvent was removed under reduced pressure. The crude reaction mixture was purified by filtration through silica gel using DCM to give the product **20** as a yellow solid (3.53 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 3.6 Hz, 1H), 6.26 (d, *J* = 4.2 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9, 155.2, 144.7, 127.0, 110.4, 14.5; HRMS: (ESI$^+$) $C_6H_5ClO_2^+$ $[M]^+$ *m/z* calcd. 143.9978, found 143.9983.



***tert*-Butyl 5-methylfuran-2-carboxylate** (**21**)

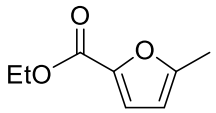
To a solution of **20** (1.00 g, 6.92 mmol, 1.0 equiv) in *t*-BuOH (20 mL) was added DMAP (1.10 g, 8.99 mmol, 1.3 equiv), and the reaction was stirred at 30 °C for 18 h. The mixture was diluted with water (250 mL) and then extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (DCM) to give product **21** as a pale yellow oil (0.902 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 3.3 Hz, 1H), 6.06 (dd, *J* = 3.3, 0.8 Hz 1H), 2.35 (s, 3H), 1.56 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 156.5, 144.4, 118.4, 108.1, 81.4, 28.3, 13.9; HRMS: (ESI$^+$) $C_{10}H_{14}O_3Na^+$ $[M + Na]^+$ *m/z* calcd. 205.0841, found 205.0833.

CMF (**2**) **to *tert*-butyl 5-methylfuran-2-carboxylate (21), ethyl 5-methylfuran-2-carboxylate** (**22**)**, and methyl 5-methylfuran-2-carboxylate** (**23**) **via an NHC procedure with 1,3-dimethylimidazonium iodide.**[10]

An oven-dried 100 mL round-bottomed flask was charged with a stir bar and 1,3-dimethylimidazonium iodide (0.155 g, 0.691 mmol, 0.10 equiv), and then sealed with a rubber septum. The flask was placed under an argon atmosphere by evacuating and backfilling (three cycles). Anhydrous THF (23 mL), an alcohol (*t*-butanol (13.1 mL), ethanol (8.1 mL), or methanol (5.6 mL)) and DBU (2.10 mL, 14.1 mmol, 2.0 equiv) were added to the flask. The mixture was stirred for 5 min at rt before adding CMF (1.00 g, 6.92 mmol, 1.0 equiv). The resulting mixture was stirred for an additional 3 h at rt. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with

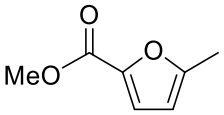
brine (3 × 50 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The crude reaction mixture was purified by flash chromatography on silica gel (15/85 EtOAc/hexanes) to give the products.

***tert*-Butyl 5-methylfuran-2-carboxylate** (**21**) was isolated as a pale green oil (44.4 mg, 4.4%). NMR data see above.



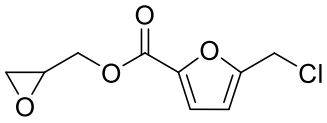
Ethyl 5-methylfuran-2-carboxylate (**22**)

The product was isolated as a pale green oil (471 mg, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 3.1 Hz, 1H), 6.11 (d, *J* = 2.6 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.38 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 157.2, 143.4, 119.4, 108.5, 60.9, 14.5, 14.1.



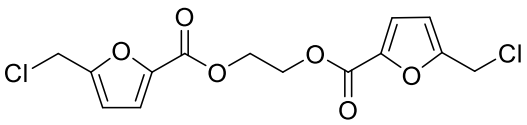
Methyl 5-methylfuran-2-carboxylate (**23**)

The product was isolated as a pale green oil (305 mg, 32%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.07 (d, *J* = 3.3 Hz, 1H), 6.09 (d, *J* = 3.3 Hz, 1H), 3.85 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.3, 157.3, 143.0, 119.6, 108.5, 51.8, 14.1.



Oxiran-2-ylmethyl 5-(chloromethyl)furan-2-carboxylate (**24**)

A round-bottomed flask was charged with glycidol (34 µL, 37 mg, 0.50 mmol, 1.0 equiv), TEA (140 µL, 101 mg, 1.00 mmol, 2.0 equiv), and DCM (9 mL). The mixture was cooled to 0 °C and a solution of CMFCC **16** (99.0 mg, 0.550 mmol, 1.1 equiv) in DCM (1 mL) was added. The reaction was stirred at 0 °C for 30 min and slowly warmed up to rt. After 3 h, the mixture was quenched with DI water (100 mL) and extracted with DCM (3 × 100 mL). The combined organic layer was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (40/60 EtOAc/hexanes) to yield **24** as a pale yellow oil (80.2 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 3.5 Hz, 1H), 6.50 (d, *J* = 3.4 Hz, 1H), 4.62 (dd, *J* = 12.2, 3.2 Hz, 1H), 4.59 (s, 2H), 4.14 (dd, *J* = 12.2, 6.3 Hz, 1H), 3.31 (dq, *J* = 6.2, 3.2 Hz, 1H), 2.88 (t, *J* = 4.5 Hz, 1H), 2.71 (dd, *J* = 4.7, 2.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 154.7, 144.4, 119.5, 111.6, 65.6, 49.4, 44.9, 36.7.



Ethane-1,2-diyl bis(5-(chloromethyl)furan-2-carboxylate) (**25**)

A 50 mL round-bottomed flask was charged with CMFCC **16** (376 mg, 2.10 mmol, 2.1 equiv), DMAP (269 mg, 2.20 mmol, 2.2 equiv), and THF (10 mL). Ethylene glycol (62.0 mg, 1.00 mmol, 1.0 equiv) was added and the solution was stirred at rt overnight. The reaction mixture was quenched with DI water (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic

layer was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (30/70 EtOAc/hexanes) to yield **25** as a pale green oil (292 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 3.5 Hz, 2H), 6.49 (d, *J* = 3.5 Hz, 2H), 4.61 (s, 4H), 4.59 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 154.7, 144.4, 119.5, 111.6, 62.7, 36.7.

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Chapter 3

Generation of CMF-Derived Nucleophiles by Deprotonation

3.1 - C-C Bond Formation with Furylogous Enolates

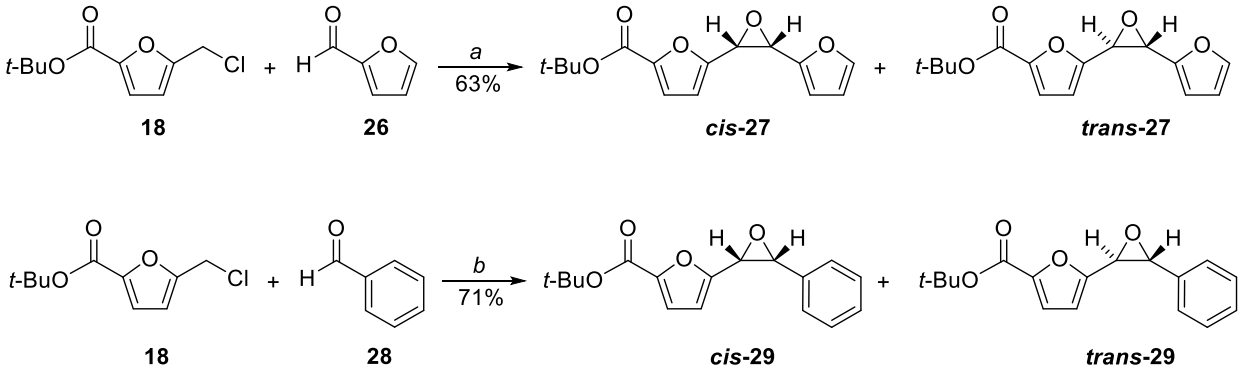
Since synthesis formally involves the generation of C-C bonds, the presence of a leaving group in CMF **2** has always been a significant advantage over HMF **1**, allowing the introduction of carbon nucleophiles by substitution,[1,2] as well as catalytic transition metal-mediated reactions.[3] It is further demonstrated here that the methylene group could be rendered C-nucleophilic via the generation of either a furylogous enolate or an organometallic function.

As discussed in Chapter 1, previous efforts to manipulate the chloromethyl group in CMF **2** for synthetic purposes included conversion to a phosphonium salt[4] or sulfone,[5] which enabled the generation of stabilized anions. The N-heterocyclic carbene catalyzed transformations of CMF **2** were also explored.[6,7]

Previous work suggested the application of furylogy to activate the methylene of CMF towards deprotonation was highly promising. These furylogous intermediates are of interest as biobased carbon nucleophiles in the context of sustainability. Therefore, this chapter begins with the direct deprotonation of the biobased furoates and will further explore furylogous enolate chemistry from different perspectives.

3.2 - Darzens-Type Epoxidations of *t*-Butyl 5-(Chloromethyl)furan-2-carboxylate

The lithium enolate derived from *t*-butyl furoate **18** underwent a Darzens-type reaction with aromatic aldehydes to form epoxides. Quenching with furfural **26** gave a mixture of stereoisomeric products ***cis*-27** and ***trans*-27** (Scheme 3.1). The reaction also works well with benzaldehyde **28**. Unfortunately, applying these conditions to the less hindered ethyl furoate **13** resulted in self-condensation. Therefore, the *t*-butyl group is necessary under the current conditions of the Darzen-type epoxidation.



Scheme 3.1 - Syntheses of epoxides **27** and **29**. Reagents and conditions: *a*. 1.2 equiv LDA, 1.3 equiv furfural, THF, –78 °C to rt, 1 h, 63%, isomer ratio 40:60. *b*. 1.2 equiv LDA, 1.3 equiv benzaldehyde, THF, –78 °C to rt, 1 h, 71%, *cis*/*trans* ratio 35:65.

The mixture of *cis*- and *trans*- isomers of *tert*-butyl 5-(3-phenyloxiran-2-yl)furan-2-carboxylate (***cis*-29** and ***trans*-29**) were separated by preparative TLC (80/20 DCM/hexanes) and structural assignments were made based on comparison of the vicinal H-H coupling of the epoxide fragment (J_{trans} = 1.9 Hz and J_{cis} = 4.0 Hz).[8] The relative ratio of *cis/trans* was calculated using the integral value of the epoxide ring signals (Figure 3.1, *cis*/*trans* = 35/65). The same method was applied to estimate the ratio of ***cis*-27** and ***trans*-27**. However, the minor difference between the *J* coupling constants did not allow a conclusive *cis/trans* ratio to be determined (Figure 3.2, isomer ratio = 40/60).

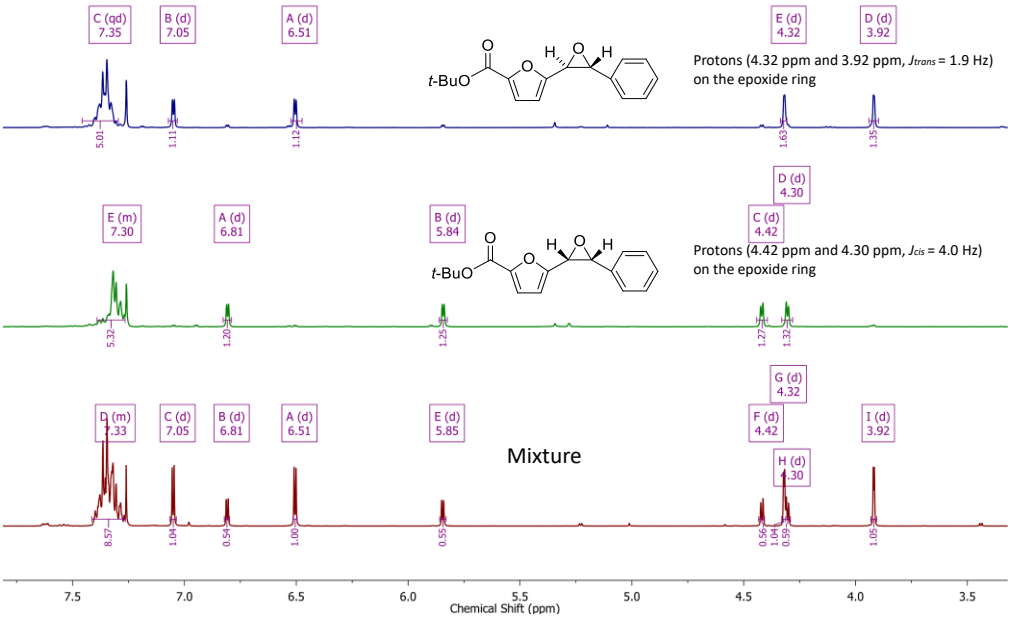


Figure 3.1 - ^{1}H NMR spectra of ***cis*-29**, ***trans*-29**, and the mixture thereof.

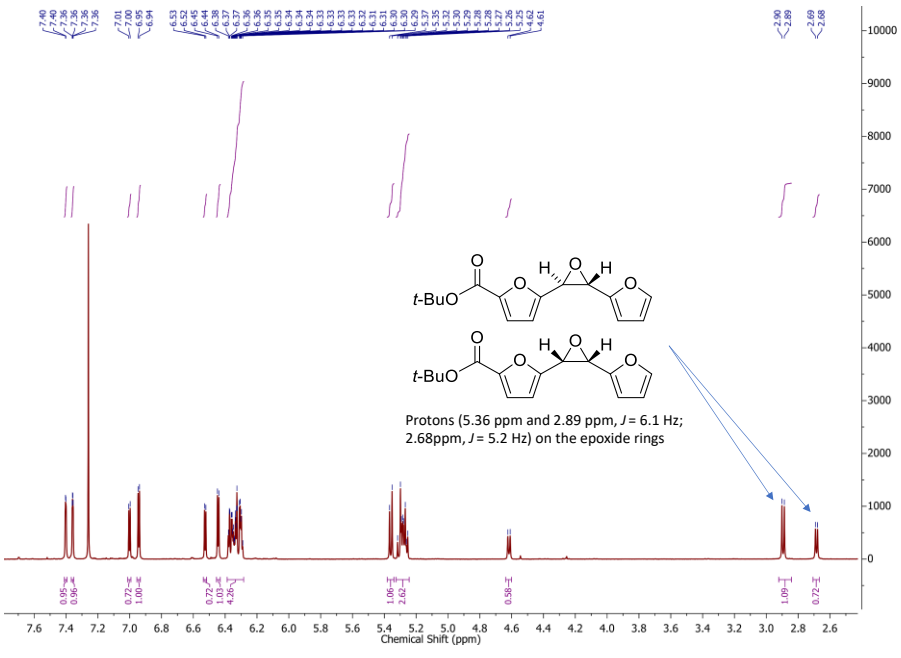
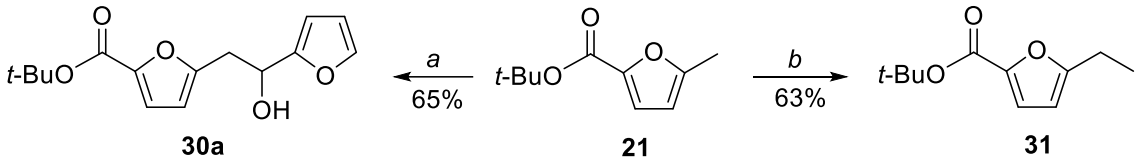


Figure 3.2 - ^{1}H NMR spectrum of the mixture of ***cis*-27** and ***trans*-27**.

3.3 - Methylation of *t*-Butyl 5-Methylfuran-2-carboxylate

Success with the Darzens reaction led us to consider whether simple 5-methylfuroate esters would similarly deprotonate. These can be prepared in a single step from CMF **2**.[6] Alternatively, we can apply the *t*-BuOCl + alcohol quench method to 5-methylfurfural (5-MF) **19** as shown in Scheme 2.3. 5-MF **19** can be prepared by hydrogenation of CMF **2** using the literature procedure in high yield.[9] Deprotonation of **21** with LDA and quenching with furfural installed a 2-(furan-2-yl)-2-hydroxyethyl group (**30a**), while homologation with methyl iodide gave 5-ethylfuroate ester **31**.



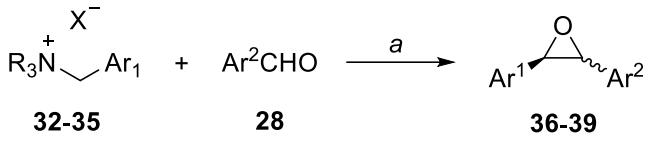
Scheme 3.2 - Generation of a carbon nucleophile of **21** by direct deprotonation. Reagents and conditions: *a*. 1.2 equiv LDA, furfural, THF, –78 °C to rt, 12 h, 65%. *b*. 1.2 equiv LDA, MeI, THF, –78 °C to rt, 12 h, 63%.

3.4 - CMF-Derived Ammonium Ylide Mediated Epoxidations

The direct generation of furylogous enolates from **18** and **21** required the use of LDA and the placement of a bulky *t*-butyl group. Compound **18** could not be deprotonated with weaker bases, such as KO*t*-Bu and LiHMDS. Deprotonation of the ethyl analog **13** with LDA resulted in self-condensation. Since the use of LDA is not very green, we then shifted the direction of work toward methods that involved no strong bases and would not require *t*-butyl blocking groups.

In 2005, Kimachi *et al.* pioneered the use of benzylic ammonium ylides for epoxidation.[10] The Aggarwal group improved the original yields using support from detailed computational studies.[11]

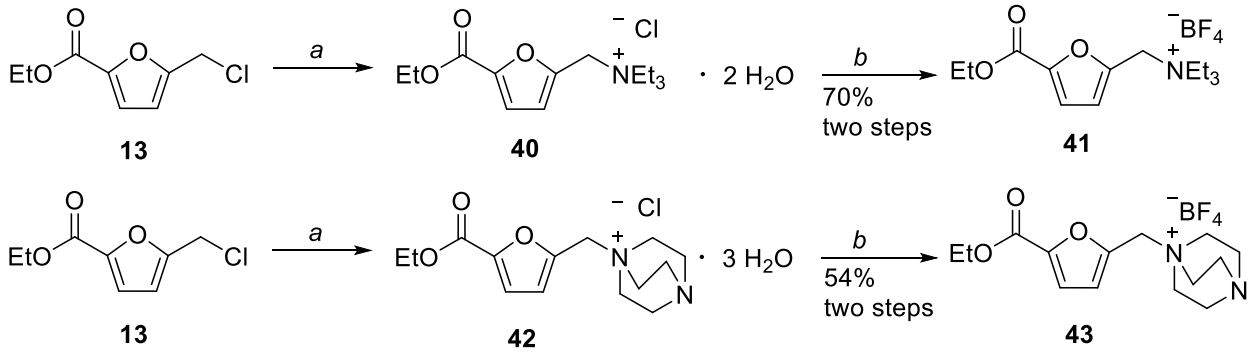
Recognizing that the amine leaving group plays an important role, the Waser group further optimized the ammonium ylide-mediated epoxidation reaction, shown in Scheme 3.3.[12]



Kimachi et al. (**2005**): Et_3N (**32**), 26% (**36**, $Ar^1 = Ar^2$ = Ph), *cis/trans* = 27/73
Aggarwal et al. (**2006**): DABCO (**33**), 42% (**37**, $Ar^1 = Ar^2$ = Ph), *cis/trans* = 30/70
quinuclidine (**34**), 41% (**38**, $Ar^1 = Ar^2$ = Ph), *cis/trans* = 8/92
Waser et al. (**2016**): Me_3N (**35**), 93% (**39**, $Ar^1 = Ar^2$ = Ph), *cis/trans* = 34/66

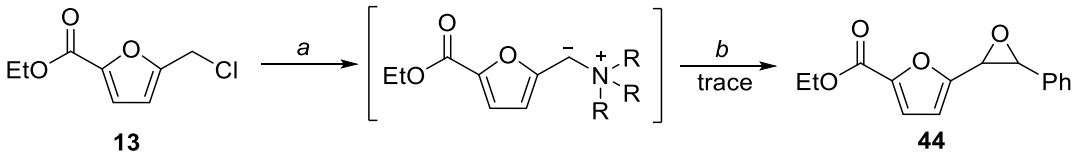
Scheme 3.3 - Summary of recent research on epoxidations via benzylic ammonium ylides. Reagents and conditions: *a*. KO*t*-Bu, THF.

Ammonium salts **40** and **42** were synthesized by substitution of the chloride in **13** with Et_3N and DABCO (Scheme 3.4) in moderate to good yields. However, the chloride salts **40** and **42** could only be isolated as hydrates, as shown by NMR spectra. Anhydrous ammonium salts **41** and **43** can be obtained by exchanging the counter anion from Cl^- to BF_4^-. The absence of bound water was confirmed by NMR spectroscopy (see Appendix).



Scheme 3.4 - Synthesis of CMF-derived ammonium salts **41** and **43**. Reagents and conditions: *a*. DABCO or Et_3N, THF, argon, reflux, 16 h. *b*. NH_4BF_4, MeOH, 1 h, over two steps: 70% (**41**), 54% (**43**).

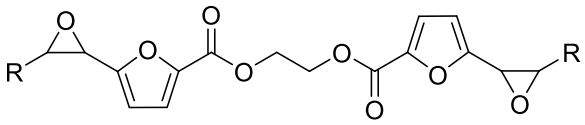
An anhydrous one-pot procedure was developed to prevent hydrate formation, which is critical for ylide generation (Scheme 3.5). The ammonium chloride salts were directly treated with KO*t*-Bu to produce the ammonium ylides *in situ*. Unfortunately, quenching these ylides with benzaldehyde afforded only a trace amount of isolated product **44**.



13 **44**

Scheme 3.5 - Synthesis of epoxide **44**. Reagents and conditions: *a*. DABCO or Et_3N, THF, argon, reflux, 16 h. *b*. KO*t*-Bu, benzaldehyde, rt, trace.

Although current methods for synthesizing novel furan epoxides via CMF-derived ammonium ylides are unsatisfactory, it is still worth investigating these Darzens-type products. Novel epoxides such as **45** (as shown in Figure 3.3) could expand the market of biorenewable polymers with integrated flame retardancy.[13] Currently, the majority of biobased epoxy resin research involves the use of epichlorohydrin[14,15], however, Darzens-type approaches could offer a greener alternative to existing methods.



45

Figure 3.3 - Proposed structure of novel epoxide **45**.

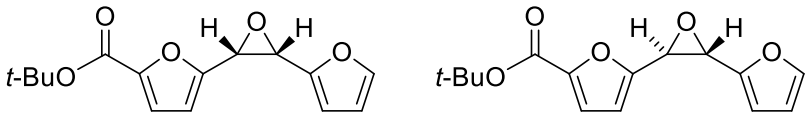
3.5 - Conclusion

Diversification of the synthetic utility of platform chemicals is the key to unlocking new markets for sustainable products. Up to now, the methylene group of CMF derivatives has seen limited engagement as a nucleophile. Here, the direct deprotonation of CMF derivatives **18** and **21** was described to give furylogous enolate systems. In the case of the chloromethylfuroate ester, the Darzens products represent a potentially new approach to preparing precursors to novel biobased epoxy resins. The deprotonated 5-MF **19** ester reacts like any other enolate, giving typical addition and substitution products. A synthetic route to novel furan epoxides was explored via CMF-derived ammonium ylide mediated epoxidations. Despite the successful synthesis of ammonium salts **40**-**43**, low yields of epoxides were observed on treatment with base and benzaldehyde.

Experimental Procedures

Darzens reactions

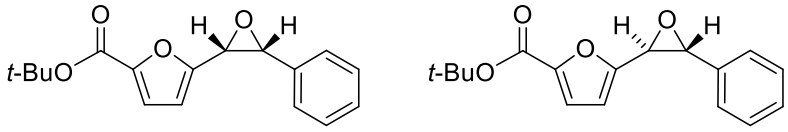
To a solution of diisopropylamine (0.180 mL, 1.30 mmol, 1.3 equiv) in THF (10 mL) at –78 °C was added a 2.59 M solution of *n*-BuLi in hexanes (0.460 mL, 1.20 mmol, 1.2 equiv) and the resulting LDA solution was stirred for 1 min at –78 °C. A solution of *tert*-butyl 5-(chloromethyl)furan-2-carboxylate **18** (217 mg, 1.00 mmol) in THF (1.0 mL) was added via cannula, and the mixture was stirred for 15 min at –78 °C. The electrophile (benzaldehyde **28**, 0.130 mL, 0.135 g, 1.27 mmol, 1.3 equiv) or furfural **26** (0.110 mL, 0.128 g, 1.33 mmol, 1.3 equiv) was added to the mixture at –78 °C. The reaction was stirred at –78 °C for 15 min, then 0 °C for 1 h. The mixture was quenched with water (50 mL) and then extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (50 mL) and dried over sodium sulfate. The solvents were removed under reduced pressure. The crude reaction mixture was purified by passing through a short silica gel plug (DCM) to yield stereoisomeric products ***cis*-27**, ***trans*-27**, ***cis*-29** and ***trans*-29**.



The mixture of *cis*- and *trans*-*tert*-Butyl 5-3-(furan-2-yl)oxiran-2-yl)furan-2-carboxylate (*cis*-27 and *trans*-27)

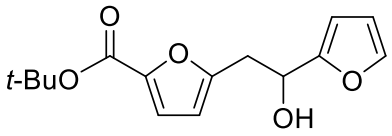
The mixture was a brown oil (173 mg, isomer ratio = 40/60, 63%). The proton signals at 5.36 ppm, 2.80 ppm and 2.68 ppm were tentatively assigned to the oxirane protons in ***cis*-27** and ***trans*-27**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.39 (m, 1H), 7.36 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.00 (d, *J* = 3.5 Hz, 0.7H), 6.94 (d, *J* = 3.5 Hz, 1H), 6.53 (d, *J* = 3.5 Hz, 0.7H), 6.44 (d, *J* = 3.5 Hz, 1H), 6.39 – 6.28 (m, 4H), 5.36 (d, *J* = 6.3 Hz, 1H), 5.33 – 5.24 (m, 2.7H), 4.62 (d, *J* = 6.0 Hz, 1H), 2.89 (d, *J*

= 6.1 Hz, 1H), 2.68 (d, *J* = 5.2 Hz, 0.7H), 1.57 (s, 6H), 1.56 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.94, 153.98, 152.56, 146.05, 145.89, 136.01, 133.79, 128.81, 128.78, 128.26, 128.14, 126.83, 125.73, 117.98, 117.57, 110.55, 110.22, 82.25, 82.06, 60.40, 59.72, 56.08, 53.97, 28.36, 28.33; HRMS: (ESI$^+$) $C_{15}H_{16}O_5Na^+$ [M + Na]$^+$ *m/z* calcd. 299.0895, found 299.0897.



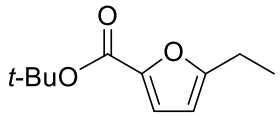
The mixture of *cis*- and *trans*-*tert*-butyl 5-(3-phenyloxiran-2-yl)furan-2-carboxylate (*cis*-29 and *trans*-29)

The mixture was a pale yellow oil (204 mg, *cis*/*trans* = 35:65, 71%). The proton signals at 4.42 ppm and 4.30 ppm were assigned to ***cis*-29**; the proton signals at 4.32 ppm and 3.92 ppm were assigned to ***trans*-29**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.26 (m, 9H), 7.05 (d, *J* = 3.5 Hz, 1H), 6.81 (d, *J* = 3.5 Hz, 0.54H), 6.51 (d, *J* = 3.5 Hz, 1H), 5.85 (d, *J* = 3.5 Hz, 0.55H), 4.42 (d, *J* = 4.0 Hz, 0.56H), 4.32 (d, *J* = 1.9 Hz, 1H), 4.30 (d, *J* = 4.0 Hz, 0.59H), 3.92 (d, *J* = 1.9 Hz, 1H), 1.58 (s, 9H), 1.53 (s, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.94, 153.98, 152.56, 146.05, 145.89, 136.01, 133.79, 128.81, 128.78, 128.26, 128.14, 126.83, 125.73, 117.98, 117.57, 110.55, 110.22, 82.25, 82.06, 60.40, 59.72, 56.08, 53.97, 28.36, 28.33; HRMS: (ESI$^+$) $C_{17}H_{18}O_4Na^+$ [M + Na]$^+$ *m/z* calcd. 309.1103, found 309.1096.



***tert*-Butyl 5-(2-(furan-2-yl)-2-hydroxyethyl)furan-2-carboxylate** (**30a**)

To diisopropylamine (0.180 mL, 1.30 mmol, 1.3 equiv) in THF (10 mL) at –78 °C was added a 2.59 M solution of *n*-BuLi in hexanes (0.460 mL, 1.20 mmol, 1.2 equiv) and the resulting LDA solution was stirred 1 min at –78 °C. A solution of *tert*-butyl 5-methylfuran-2-carboxylate **21** (182 mg, 1.00 mmol) in THF (1 mL) was added via cannula, and the mixture was stirred for 15 min at –78 °C. Furfural (0.110 mL, 0.128 g, 1.33 mmol, 1.3 equiv) was added, and the reaction was stirred for 15 min at –78 °C then at rt overnight. The mixture was quenched with saturated aqueous NH_4Cl (100 mL) and then extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (50 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (25/75 EtOAc/hexanes) to yield **30a** as a pale yellow oil (182 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 1.7, 0.7 Hz, 1H), 6.97 (d, *J* = 3.4 Hz, 1H), 6.33 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.27 (d, *J* = 3.2 Hz, 1H), 6.17 (d, *J* = 3.4 Hz, 1H), 5.09 (q, *J* = 6.6 Hz, 1H), 3.25 (d, *J* = 6.7 Hz, 2H), 2.23 (d, *J* = 4.5 Hz, 1H), 1.56 (s, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 156.0, 155.2, 145.1, 142.4, 118.2, 110.4, 109.8, 106.7, 81.8, 66.2, 35.0, 28.4; HRMS: (ESI$^+$) $C_{15}H_{18}O_5Na^+$ $[M + Na]^+$ *m/z* calcd. 301.1052, found 301.1055.



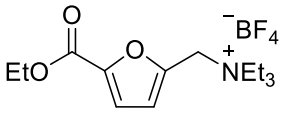
***tert*-Butyl 5-ethylfuran-2-carboxylate** (**31**)

To diisopropylamine (0.180 mL, 1.30 mmol, 1.3 equiv) in THF (10 mL) at –78 °C was added a 2.59 M solution of *n*-BuLi in hexanes (0.460 mL, 1.20 mmol, 1.2 equiv) and the resulting LDA solution was stirred 1 min at –78 °C. A solution of *tert*-butyl 5-methylfuran-2-carboxylate **21** (182 mg, 1.00 mmol, 1.0 equiv) in THF (1 mL) was added via cannula, and the mixture was stirred for 1 h at –78 °C. Iodomethane (0.310 mL, 5.00 mmol, 5.0 equiv) was added and the reaction was stirred for 15 min at –78 °C then at rt overnight. The mixture was quenched with saturated aqueous NH_4Cl (100 mL) and then extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (50 mL) and dried over sodium sulfate. The crude product was purified by passing through a short plug of silica gel (10/90 EtOAc/hexanes) to give a mixture of the product **31** and a small amount of **21** (total 135 mg). 1,4-Dioxane (2 µL) was added to a solution of the mixture of **31** and **21** (13.5 mg) in $CDCl_3$. The calculated yield of methylated product **31** was 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J* = 3.4 Hz, 1H), 6.10 (d, *J* = 3.3 Hz, 1H), 2.73 (q, *J* = 7.5 Hz, 2H), 1.58 (s, 9H), 1.28 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 158.6, 144.3, 118.3, 106.6, 81.5, 28.4, 21.8, 12.0; HRMS: (ESI$^+$) $C_{11}H_{16}O_3Na^+$ $[M + Na]^+$ *m/z* calcd. 219.0997, found 219.0989.

Preparation of ammonium salts 41 and 43

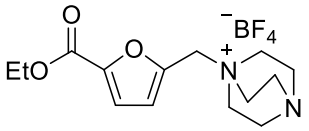
A 25 mL round-bottomed flask was attached to a condenser and was evacuated and backfilled with argon three times. Ethyl 5-methylfuran-2-carboxylate **13** (188 mg, 1.00 mmol, 1.0 equiv), tertiary amine (triethyl amine or DABCO, 1.5 equiv), and anhydrous THF (10 mL) were added to

the flask. The reaction mixture was refluxed for 16 h. The crude mixture was cooled to rt and concentrated. A minimum amount of chloroform was added to dissolve the crude mixture. Et_2O was added to the solution until a precipitate formed. The white crystalline solid was filtered and washed with Et_2O (50 mL) then dissolved in MeOH (10 mL). NH_4BF_4 (419 mg, 4.00 mmol, 4.0 equiv) was added to the solution and the mixture was stirred at rt for 1 h. The suspension was filtered and concentrated to yield the final product.



N-((5-(ethoxycarbonyl)furan-2-yl)methyl)-N,N-diethylethanaminium tetrafluoroborate (**41**)

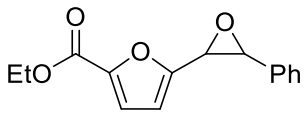
The product was isolated as a white solid (239 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 3.5 Hz, 1H), 7.00 (d, *J* = 3.5 Hz, 1H), 4.57 (s, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.33 (q, *J* = 7.2 Hz, 6H), 1.43 (t, *J* = 7.2 Hz, 9H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 147.1, 145.5, 118.7, 118.6, 61.7, 54.0, 53.2, 14.4, 7.8.



1-((5-(Ethoxycarbonyl)furan-2-yl)methyl)-1,4-diazabicyclo[2.2.2]octan-1-ium tetrafluoroborate (**43**)

The product was isolated as a white solid (190 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 3.5 Hz, 1H), 7.03 (d, *J* = 3.5 Hz, 1H), 4.65 (s, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.48 (t, *J* = 7.4 Hz,

6H), 3.25 – 3.16 (m, 6H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 147.3, 145.7, 119.7, 118.7, 61.7, 59.3, 52.8, 45.6, 14.4.



Ethyl 5-(3-phenyloxiran-2-yl)furan-2-carboxylate (**44**)

A 25 mL round-bottomed flask was attached to a condenser and was evacuated and backfilled with argon three times. Ethyl 5-methylfuran-2-carboxylate **13** (188 mg, 1.00 mmol, 1.0 equiv), DABCO (168 mg, 1.5 mmol, 1.5 equiv), and anhydrous THF (10 mL) were added to the flask. The mixture was refluxed for 16 h. The reaction was cooled to rt before adding benzaldehyde (0.110 mL, 1.10 mmol, 1.1 equiv). A suspension of potassium *tert*-butoxide (224 mg, 2.00 mmol, 2.0 equiv) in THF (5 mL) was added dropwise at 0 °C and the mixture was stirred at rt overnight. The reaction was quenched with DI water (100 mL), and the mixture was extracted with EtOAc (3 × 50 mL). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (DCM) to yield **44** as a yellow oil (trace, with impurities). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 5H), 7.16 (d, *J* = 3.5 Hz, 1H), 6.54 (d, *J* = 3.5 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 4.32 (d, *J* = 2.1 Hz, 1H), 3.94 (d, *J* = 2.1 Hz, 1H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 154.5, 145.0, 135.9, 128.9, 128.8, 125.7, 118.8, 110.7, 61.3, 60.5, 56.1, 14.5.

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Chapter 4

Generation of Organozinc Nucleophiles Based on CMF

4.1 - Novelty of the Generation of Organozinc Nucleophiles from CMF

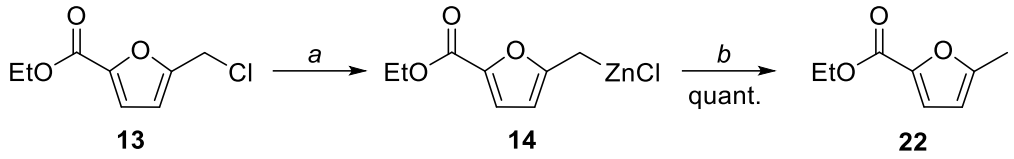
Organometallic reagents are classic alkyl anion synthons. Among these, the organozinc nucleophile stands out for showing good reactivity and yet high tolerance of functional groups.[1] Another advantage within the context of sustainability is that zinc is an earth-abundant metal.[2] Previously, Cho and Kim described the preparation of a zinc insertion product of a furoate ester for use in copper- and nickel-catalyzed coupling reactions, but product yields were at most 15% (Section 1.8).[3]

In Chapter 3, the applications of furylogous enolate chemistry to the extension of the six-carbon framework of CMF **2** to C7, C11, and C12 systems, were briefly discussed.[4] In this chapter, the production of organozinc nucleophiles from CMF-derived esters in terms of insertion kinetics, solvent and temperature effects, and electrophile scope, will be presented.

4.2 - Kinetic Study of the Insertion of Zn into Ethyl 5-(Chloromethyl)furan-2-carboxylate

The addition of finely divided zinc metal to an organic halide in an ether solvent is the most general method for producing an organozinc reagent. Here, ethyl 5-(chloromethyl)furan-2-carboxylate **13** was used as the model compound (Scheme 4.1). To achieve high reactivity, it is essential to remove the oxide layer covering the zinc surface before use. While common zinc activation protocols involve the use of either chlorotrimethylsilane or iodine,[5,6] it was found that the latter generally gives better reproducibility. The progress of the reaction was monitored by quenching with aqueous acid and observing the ratio of chloromethyl protons in **13** to methyl protons in **22** by ^{1}H NMR spectroscopy. The results are given in Figure 4.1. The study shows a modest acceleration of rate occurs between room temperature and 40 °C, but the little benefit is seen in

raising the temperature further. While insertion is ~80% complete after 3 h at 40 °C, full conversion is only reached after >12 h.



13 **14** **22**

Scheme 4.1 - Insertion of Zn into **13**. Reagents and conditions: *a.* Zn, I_2, THF. *b.* aq. NH_4Cl.

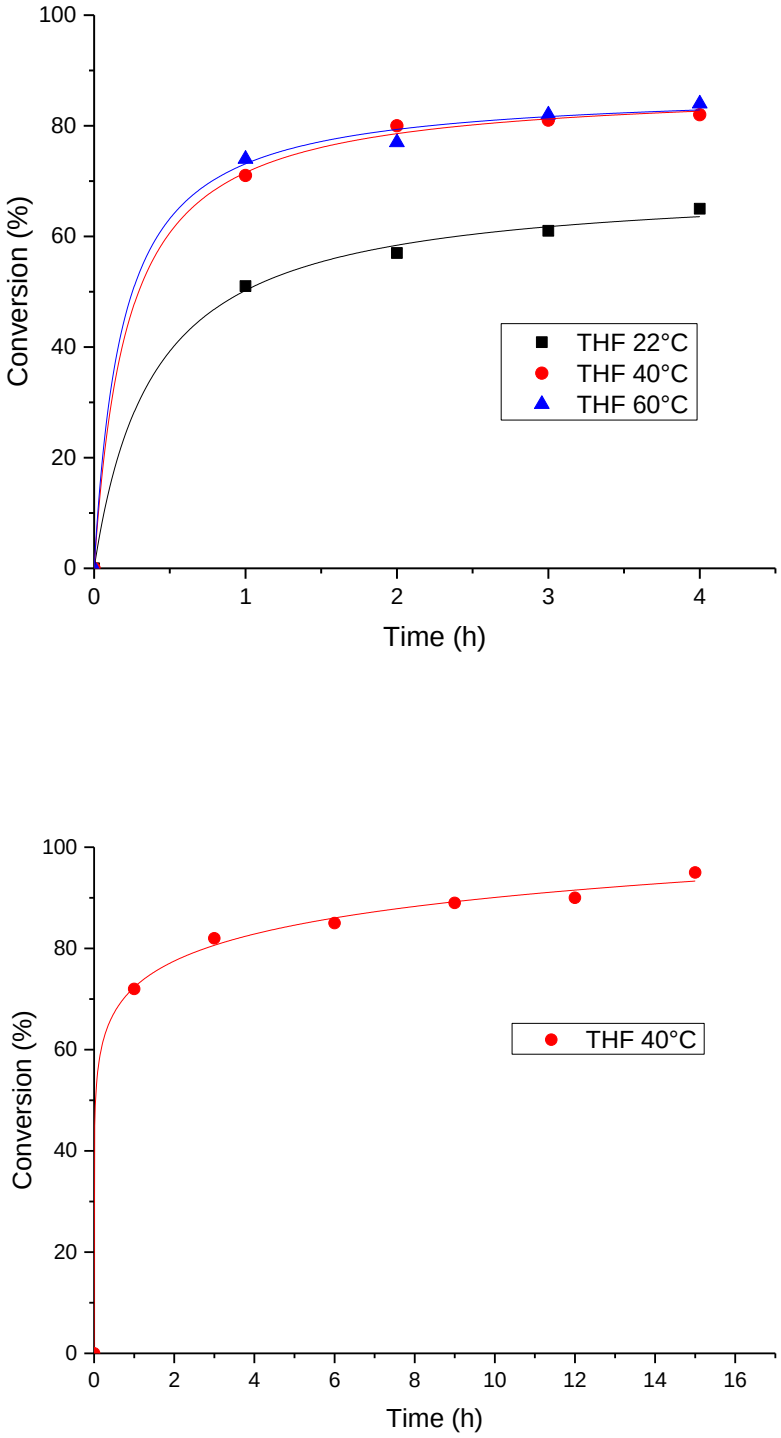


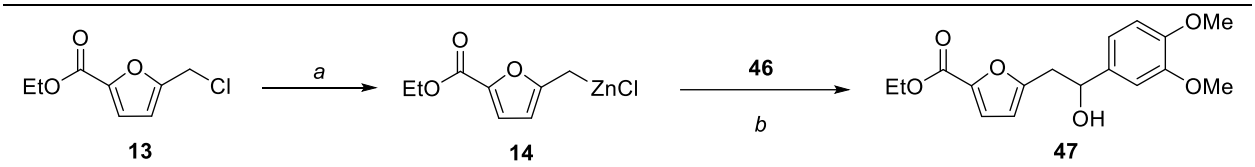
Figure 4.1 - Rate plots for the insertion of Zn into **13**. Conversion was measured by the integration of the methyl protons in **22** in the ^{1}H NMR against a dioxane internal standard.

4.3 - Optimization of the Reformatsky Reactions of Ethyl 5-(Chloromethyl)furan-2-carboxylate

Having established the optimal kinetics for the formation of **14**, we then turned to reaction optimization. The reference electrophile chosen was the vanillin derivative 3,4-dimethoxybenzaldehyde **46**, due to its low electrophilicity and therefore moderate reactivity. The organozinc reagent was prepared in the stated solvent and in the case an additive was used, it was injected after the completion of Zn insertion (24 h), followed by the electrophile. The reaction was observed to progress in all of the solvents tested except Cyrene (dihydrolevoglucosenone), with which the organozinc reagent reacted. Table 4.1 shows that the highest yields were in tetrahydrofuran (THF) and acetonitrile. The discrepancies in reactivity between the ether solvents are not easy to rationalize but are likely to involve differences in coordination to the metal.

A number of literature reports suggest that salts, Lewis acids, or amine additives can improve reactivity in Reformatsky reactions. For example, Knochel and co-workers reported that the presence of LiCl or $MgCl_2$ enhanced both the solubility and reactivity of organozinc reagents.[7] Fernández-Sánchez employed $AlMe_3$ and $BF_3{\cdot}OEt_2$ as promoters for Reformatsky reactions.[8] Rathke showed that trimethyl borate significantly improved the yield of room temperature Reformatsky reactions.[9] Finally, Mineno and co-workers found that amines enhanced the reactivity of Reformatsky reagents, where bidentate amines such as DABCO and TMEDA were seen to be particularly effective.[10] To our surprise, the inclusion of a selection of additives led only to decreased yields in all cases (Table 4.1, entries 7−15).

Table 4.1 - Organozinc reaction with 3,4-dimethoxybenzaldehyde **46** in different solvents and the presence of additives.



13 **14** **47**

Entry	Solvent	Additives/equiv	Yield[c]/%
1	THF	-	62
2	DME	-	46
3	dioxane	-	34
4	MeCN	-	61
5	DMF	-	18
6	Cyrene	-	0
7	THF	$AlCl_3$ (0.33)	Decomp.
8	THF	$B(OMe)_3$ (1.0)	44
9	THF	$MgCl_2$ (1.0)	49
10	THF	LiCl (1.0)	39
11	THF	$BF_3{\cdot}Et_2O$ (1.0)	34
12	THF	pyridine (2.0)	28
13	THF	DABCO (2.0)	9
14	THF	TMEDA (2.0)	4

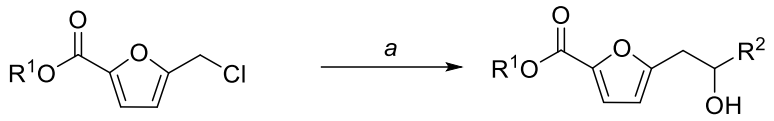
Reaction conditions: *a*. Zn (2.0 mmol, 2.0 equiv), iodine (0.20 mmol, 20 mol%), ethyl 5-(chloromethyl)furan-2-carboxylate **13** (1.0 mmol, 1.0 equiv), 3,4-dimethoxybenzaldehyde **46** (1.1 mmol, 1.1 equiv). *b*. additive (indicated equiv), solvent (4.0 mL), 40 °C, 48 h. *c*. Isolated yields of **47** from **13**.

4.4 - Steric Effects of CMF-Derived Organozinc Reagents

A comparison experiment was designed to evaluate the steric influence of different esters in the CMF-derived Reformatsky reaction. Organozinc compounds were prepared from methyl (**17**), ethyl (**13**), and *t*-butyl furoate (**18**) via direct insertion of Zn. The respective organozinc furoates were quenched with aldehydes to give Reformatsky adducts.

Treatment of different organozinc furoates with furfural **26** gave adducts with good yields, with the methyl analog performing the best (Table 4.2, entries 1 to 3). Interestingly, the steric influence was unnoticeable when the organozinc furoates were quenched with benzaldehyde **28** (Table 4.2, entries 4 to 6). Thus, it is clear that the steric congestion presented by the *t*-butyl blocking group has a minimal influence on the carbon nucleophilicity of the CMF-derived organozinc compound.

Table 4.2 - Synthesis of **30**.



13, **17**, and **18** — **30a-f**

Entry	R_1	R_2	Product	Yield/%
1	*t*-Bu	2-furyl	**30a**	88
2	Et	2-furyl	**30b**	88
3	Me	2-furyl	**30c**	92
4	*t*-Bu	Ph	**30d**	98
5	Et	Ph	**30e**	99
6	Me	Ph	**30f**	99

Reaction conditions: *a*. Zn (2.0 mmol, 2.0 equiv), iodine (0.20 mmol, 20 mol%), furoate (**13**, **17**, or **18**, 1.0 mmol, 1.0 equiv), aldehydes (1.1 mmol, 1.1 equiv), THF (4.0 mL), argon, 40 °C, 24 h.

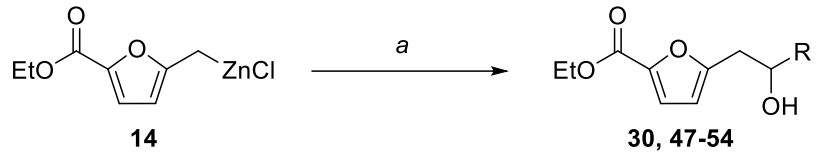
4.5 - Reformatsky Reactions of Ethyl 5-(Chloromethyl)furan-2-carboxylate

To investigate the scope of the reaction, reagent **14** was combined with a selection of biobased aldehydes (Table 4.3). As described above, **14** reacts with 3,4-dimethoxybenzaldehyde **46** to give product **47**. Since electrophilicity generally corresponds to the degree of electron donation into the C=O bond, 4-methoxybenzaldehyde, an electrophile of reactivity intermediate between that 3,4-dimethoxybenzaldehyde and benzaldehyde **28**, predictably gives an addition product **48** in a yield between those of **47** and **30e**. This tendency is also evident in furan electrophiles, *cf.* product **30b** versus **49**. The vinylogous aromatic aldehyde cinnamaldehyde, which was of interest ultimately for the generation of an extended conjugation path, gave addition product **50** in only moderate yield. Quenching **14** with methylated isatin (an α diketone) gave an orange product **51** in low yield.

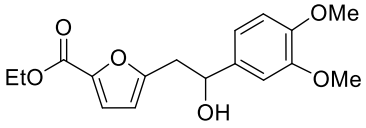
Aliphatic aldehydes also gave products in good yields, although longer reaction times were needed (48 h for **52**−**54** vs. 24 h for **30**, **47**−**51**). These electrophiles were explicitly chosen to install moieties of potential interest in natural product synthesis starting from biobased feedstocks.[11] Thus, the isobutyraldehyde addition product **52** could be used in an approach to

rosefuran **55**,[12] a valuable fragrance chemical, whereas both **53** and **54** incorporate structural elements of antioxidant furan fatty acids **56** (Figure 4.2).[13]

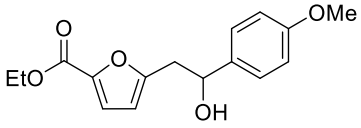
Table 4.3 - Reformatsky reactions of **14** with carbonyl compounds.



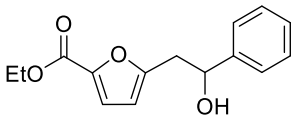
14 **30, 47-54**



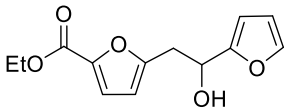
47 (62%)



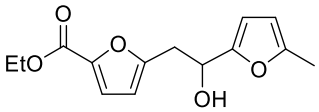
48 (70%)



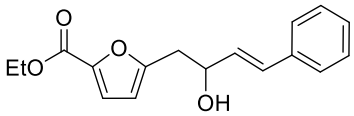
30e (99%)



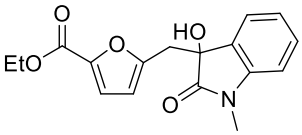
30b (88%)



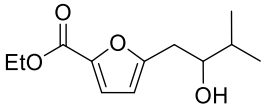
49 (78%)



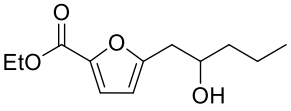
50 (36%)



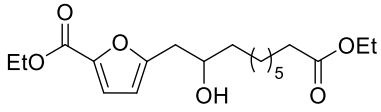
51 (30%)



52 (72%)

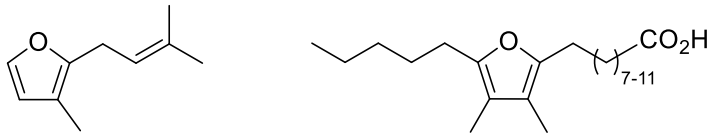


53 (76%)



54 (57%)

Reaction conditions: *a*. **14** (1.0 mmol, 1.0 equiv), electrophile (1.1 mmol, 1.1 equiv), THF (4.0 mL), 40 °C, 24-48 h. Isolated yields (by chromatography) are given.



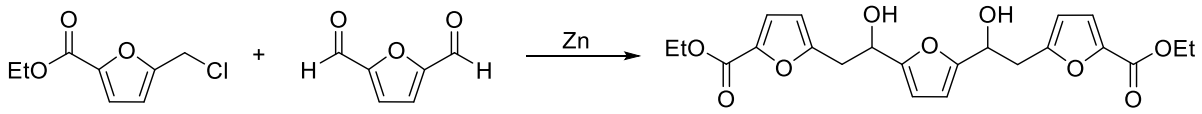
55 **56**

Figure 4.2 - Structures of the natural products rosefuran **55** and furan fatty acids **56**.

4.6 - Two-fold Reformatsky Reactions of Ethyl 5-(Chloromethyl)furan-2-carboxylate

Finally, consistent with the interest in producing biobased synthetic colorants, an extension of the electrophile scope was attempted to the biobased dialdehyde diformylfuran (DFF) **57**. Product **58** can be dehydrated to an extended chromophore, which will be the subject of the next section. Although the test reaction in Table 4.1 could be performed as a one-pot procedure (entry 2), zinc insertion failed completely in the presence of DFF **57** (Table 4.4, entries 1 and 2), which was assumed to involve a passivating effect of **57** on the metal. Thus, adding **57** to a preformed mixture of Zn and furoate ester **13** gave the best overall outcomes (Table 4.4, entries 4 and 5). This reaction performs slightly better in dioxane than in THF, which may have to do with the better solubility of **57** in dioxane. Although the remaining mass balance was mainly starting material, entries 5 and 6 indicate that a longer reaction time and a higher temperature are either ineffective or even deleterious to yield. Some investigators have described filtering the organozinc reagent before use.[14] However, use of the filtered nucleophile solution of **14** only led to incomplete reactions.

Table 4.4 - Two-fold organozinc addition to DFF **57**.



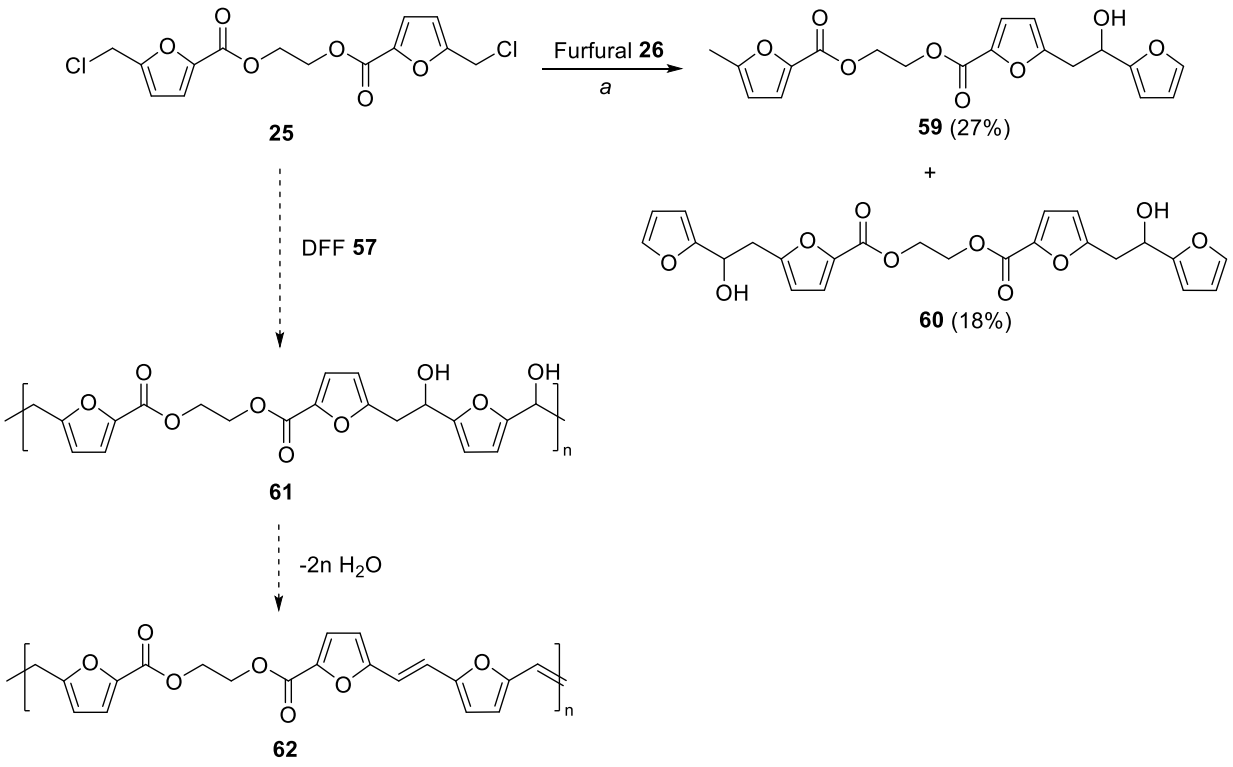
13 **57** **58**

Entry	Solvent	T/°C	Time/h	Yield/%
1	THF	40	one-pot[a]	0[b]
2	dioxane	40	one-pot[a]	0[b]
3	THF	40	1[c]	62
4	dioxane	40	1[c]	78
5	dioxane	40	4[c]	75
6	dioxane	40-80	1[c]	34

a. **13** and DFF **57** were added together into a Zn suspension. *b*. no zinc insertion was observed. *c*. DFF **57** was added into the mixture of **13** and Zn after the indicated time. The mixture was then stirred for an additional 24 h.

The successful synthesis of **58** led to speculation of how **25** would behave if subjected to a similar Reformastsky procedure (Scheme 4.2). The two-fold Reformatsky reaction of **25** with furfural **26** produced mono-adduct **59** and di-adduct **60** in low yields. The absence of the chloromethylene group in the crude mixture indicated the complete formation of the organozinc compound from **25**, which either reacted with furfural **26** or was quenched during the acidic workup.

Based on these observations, it is reasonable to propose the synthesis of sustainable polymer **61** from the polycondensation of **25** and **57** (Scheme 4.2). The resulting hydroxy groups on **61** could serve as handles for further modification. Alternatively, thermal or catalytic dehydration of **61** would produce polymer **62** with extended conjugation, thus changing its physical and chemical properties, i.e., tensile strength, hydrophilicity, and crystallinity.[15]



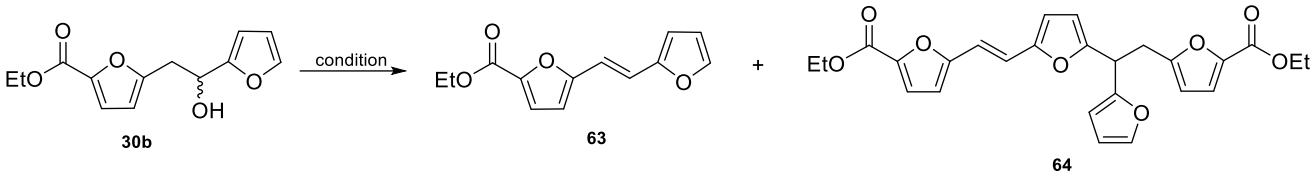
Scheme 4.2 - Two-fold Reformatsky reaction of **25** with furfural **26** and the proposed synthetic route to polymers **61** and **62**. Reagents and conditions: *a.* Zn, I_2, furfural **26**, THF, 40 °C, 24 h, **59** (27%), **60** (18%).

4.7 - Development of a Reformatsky-Dehydration Route to Biobased Chromophores

Given our strong interest in producing sustainable dyes, the opportunity to create extended conjugation was clearly present in the Reformatsky products. That said, various dehydration methods were tested on **30b** (Table 4.5), which was chosen as a model compound. Dehydration of **30b** did not proceed at rt (entries 1 and 2). The yield of the conjugated product **63** was only 25%, even after 48 h at 160 °C (entries 3 and 4). At 200 °C, only decomposition was observed (entry 5). An acid-catalyzed dehydration of **30b** using ion-exchange resin Amberlyst 15, and the conversion was enhanced significantly (entry 6). However, the amount of Amberlyst 15 was critical for obtaining good yields of **63** (entries 7 and 9). Interestingly, dehydration with Amberlyst 15 proceeded with excellent stereoselectivity; only the *trans* isomer was isolated. The dehydration

to produce **63** also gave a significant amount of dimeric self-alkylation product **64** (24%). Amberlite 120, an alternative ion-exchange resin, performed much worse in generating **63** compared to Amberlyst 15 (entry 10). Prolonged reaction time led to the decomposition of **63** and **64** (entry 8). Lewis acids also failed to accomplish this transformation (entries 11 to 13).

Table 4.5 - Dehydration of **30b**.



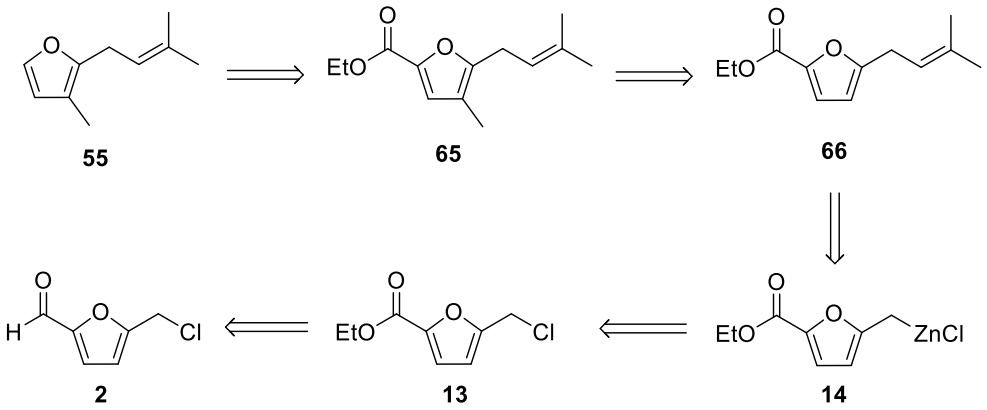
30b **63** **64**

Entry	Conditions	Conv./%[a]	**63**/%[b]	**64**/%[b]
1	DCM, rt, 3 Å MS, overnight	0 (NR)	0	0
2	DCM, rt, 3 Å MS, TFA, overnight	0 (NR)	0	0
3	Toluene, 3 Å MS, 160 °C (pressure vessel), 24 h	19	19	0
4	Toluene, 3 Å MS, 160 °C (pressure vessel), 48 h	25	25	0
5	Toluene, 200 °C (pressure vessel), 24 h	100 (dec.)	0	0
6	Toluene, 60 °C, 3 Å MS, Amberlyst 15 (100% w/w), 2 h	65	42	14
7	Toluene, 60 °C, 3 Å MS, Amberlyst 15 (100% w/w), 7 h	84	64	24
8	Toluene, 60 °C, 3 Å MS, Amberlyst 15 (100% w/w), 22 h	90	50	11
9	Toluene, 60 °C, 3 Å MS, Amberlyst 15 (200% w/w), 7 h	88	46	25
10	Toluene, 60 °C, 3 Å MS, Amberlite 120 (100% w/w), 7 h	43	0	0
11	Toluene, rt, Tf_2NH, 12 h	99	trace	10
12	Toluene, 60 °C, $AlPO_4$, $MgSO_4$, 4 h	0 (NR)	0	0
13	Toluene, -78 °C to rt, Tf_2O, DMAP, 12 h	91	5	5

a. The conversions were determined by the consumption of **30b**. *b*. Isolated yields.

4.8 - Attempted Syntheses of Rosefuran

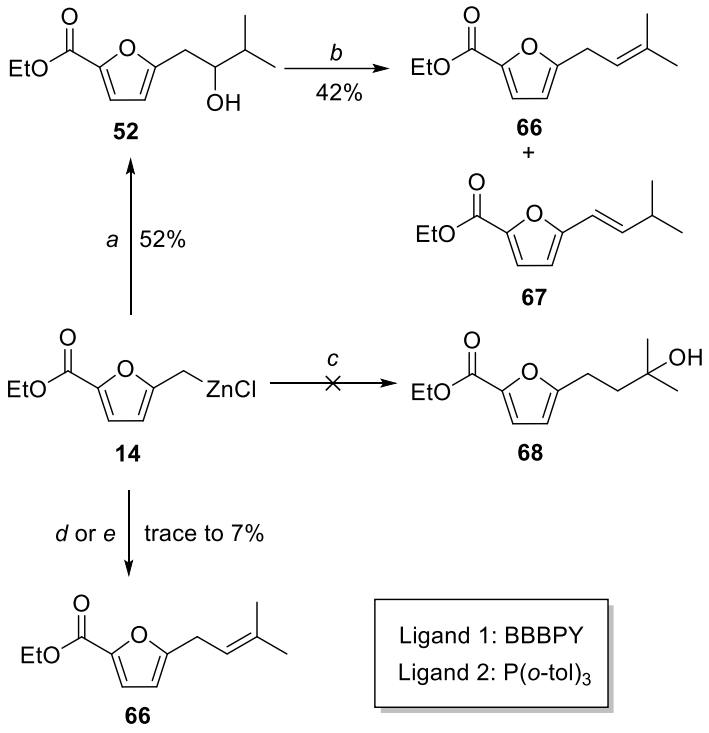
Retrosynthetically, rosefuran **55** can be achieved by the hydrolysis and decarboxylation of furoate ester **65**. A methyl group could be introduced by bromomethylation-hydrodebromination of intermediate **66**.[16] C-C Bond formation could be accomplished by the Reformatsky reaction of **14**. Alternatively, a different approach that utilizes a cross-coupling reaction can also transform **14** to **66** (Scheme 4.3).



Scheme 4.3 - Retrosynthetic analysis of rosefuran **55**.

To accomplish the transformation of **14** to **66**, three synthetic routes were explored (Scheme 4.4). The first synthetic route applied the Reformatsky reaction (*a* then *b* in Scheme 4.4). Quenching **14** with isobutyraldehyde gave **52** in moderate yield (Table 4.3). Acid-catalyzed dehydration with Amberlyst 15 failed to produce **66**. An alternative dehydration method using Tf_2O and DMAP gave a mixture of isomers **66** and **67**. In the second synthetic route (*c* in Scheme 4.4), an epoxide was proposed as the electrophilic component to produce tertiary alcohol **68** that circumvents the generation of a mixture of isomers. Compound **14** was treated with dimethyloxirane under the optimized Reformatsky conditions. Unfortunately, no reaction was observed.

A common application of organozinc derivatives is their use in transition metal-catalyzed cross-coupling reactions.[17-20] Therefore, an alternative route to **66** was proposed using a cross-coupling strategy (*d* or *e* in Scheme 4.4). The reaction between **14** and isocrotyl bromide was examined using two catalysts. The reaction treated with 5 mol% Pd_2dba_3 + 5 mol% P(*o*-tol)$_3$ produced small amounts of **66**. On the other hand, a parallel attempt using 5 mol% $Ni(COD)_2$ + 5 mol% BBBPY only generated trace amounts of **66**, as confirmed by GCMS. These poor yields were attributed to the unoptimized reaction conditions.



Scheme 4.4 - Attempted syntheses of **66**. Reagents and conditions: *a*. isobutyraldehyde, THF, argon, 40 °C, 24 h, 52%. *b*. Tf_2O, DMAP, 42% (**66** + **67**). *c*. dimethyloxirane, THF, argon, 40 °C, 24 h, NR. *d*. isocrotyl bromide, 5 mol % $Ni(COD)_2$, BBBPY, THF, rt, 12 h, trace. *e*, isocrotyl bromide, 5 mol % Pd_2dba_3, P(*o*-tol)$_3$, THF, rt, 12 h, 7%.

It is evident from these preliminary results that a transition-metal-catalyzed cross-coupling reaction could be a promising route to **66** after systematic optimization. The development and application of robust catalysts that permit manipulation without using Schlenk techniques or gloveboxes are advantageous for the large-scale production of biobased compounds. For example, the Cornella group recently reported an air-stable binary Ni(0)-olefin catalyst ($Ni(^{F}stb)_3$), which demonstrated excellent performance across a wide variety of nickel-catalyzed transformations.[21]

4.9 - Conclusion

The expansion of the synthetic scope of CMF **2** has been a central objective of efforts toward the further advancement of the integrated biorefinery, and the use of metals to diversify the chemistry of biomass-derived platforms is of extraordinary interest. While CMF itself is a classic electrophile, here the focus is on CMF-based carbon nucleophiles accessed by the insertion of zinc into the carbon−chlorine bond of a CMF-derived furoate ester such as **13**. The formation of the organometallic species **14** is complete within 12−24 h under mild conditions. This Reformatsky-like nucleophile reacts with a range of aldehydes in good to excellent yields. Applications toward the synthesis of renewable chemicals of industrial interest are demonstrated, and double addition to the biobased dialdehyde DFF **57** shows the potential of this method to generate extended, biobased chromophores. Dehydration using a heterogeneous catalyst was investigated for extending the conjugation path of these carbonyl addition products. Finally, the synthesis of rosefuran **55** was attempted. The dehydration of Reformatsky adduct **52** produced intermediate **66** as a mixture of isomers. Additionally, the cross-coupling reaction between **14** and isocrotyl bromide only yielded a small amount of **66**. Future work should focus on optimizing the cross-coupling reaction of CMF-derived organometallic compounds (e.g., **14**) with biobased electrophiles. These endeavors will expand the synthetic toolkit for biomass conversion.

Experimental Procedures

Pretreatment of Zn dust

Zn dust (2.0 g, <10 μm) and dilute HCl solution (1.0 M, 20 mL) were added to a 50 mL culture tube. The mixture was sonicated at rt for 15 min. After decanting the acid, the Zn was washed with DI water (50 mL), acetone (50 mL), and diethyl ether (50 mL) in this order. The solid was dried under vacuum.

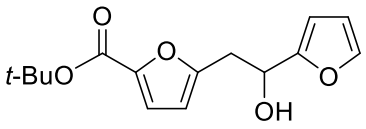
Kinetic study of Insertion of Zn into 13

Zinc dust (131 mg, 2.00 mmol, 2.0 equiv) was introduced into a round-bottomed flask along with iodine (50 mg, 0.20 mmol, 20 mol%). The flask was sealed with a rubber septum and three evacuation/argon refill cycles were performed. An argon balloon attached to a needle was inserted through the septum. Anhydrous THF (2.0 mL) was added and the resulting suspension was stirred for 15 min at rt. A solution of ethyl 5-(chloromethyl)furan-2-carboxylate **13** (188 mg, 1.00 mmol, 1.0 equiv) in THF (1.0 mL) was added and the reaction was stirred at the stated temperature. Aliquots of the mixture (0.10 mL) were sampled periodically and quenched into a saturated aq. NH_4Cl. These were extracted with EtOAc (3 × 1.0 mL) and the combined organic layers were concentrated. ^1H NMR spectra were used to quantify conversion to the organozinc compound against a 1,4-dioxane internal standard (2.0 μL).

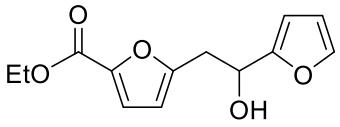
General procedure for the reaction of organozinc furoate esters with aldehydes

Zinc dust (131 mg, 2.00 mmol, 2.0 equiv) was introduced into a round-bottomed flask along with iodine (50 mg, 0.20 mmol, 20 mol%). The flask was sealed with a rubber septum and three

evacuation/argon refill cycles were performed. An argon balloon attached to a needle was inserted through the septum. Anhydrous THF (2.0 mL) was added and the resulting suspension was stirred for 15 min at rt. A solution of ethyl 5-(chloromethyl)furan-2-carboxylate **13** (188 mg, 1.00 mmol, 1.0 equiv) in THF (1.0 mL) was added, and the mixture was stirred at 40 °C for 24 h. A solution of the aldehyde (1.10 mmol, 1.1 equiv) in THF (1.0 mL) was added and the reaction was stirred at 40 °C for another 24-48 h, as indicated. The mixture was filtered through Celite, and the filtrate was quenched with saturated aq. NH4Cl and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (3 × 50 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the crude reaction mixture was purified by flash chromatography on silica gel (20:80 to 40:60 EtOAc/hexanes) to give the products.



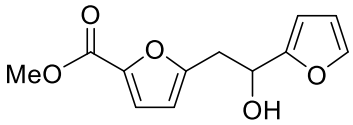
***tert*-Butyl 5-(2-(furan-2-yl)-2-hydroxyethyl)furan-2-carboxylate** (**30a**). See Chapter 3.



Ethyl 5-(2-(furan-2-yl)-2-hydroxyethyl)furan-2-carboxylate (**30b**)

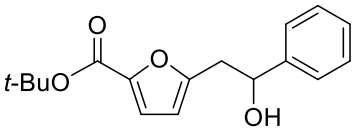
The product was a pale yellow oil (220 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.08 (d, *J* = 3.4 Hz, 1H), 6.33 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.26 (d, *J* = 3.2 Hz, 1H), 6.20 (d, *J* = 3.4 Hz, 1H), 5.09 (t, *J* = 6.2 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.26 (d, *J* = 6.7 Hz, 2H), 2.28

(s, 1H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 156.6, 155.1, 144.0, 142.4, 119.1, 110.4, 110.0, 106.8, 66.2, 61.0, 35.0, 14.5; HRMS: (ESI$^+$) $C_{13}H_{14}O_5Na^+$ [M + Na]$^+$ *m/z* calcd. 273.0739, found 273.0728.



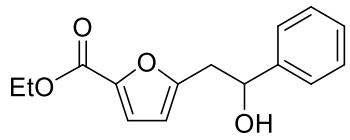
Methyl 5-(2-(furan-2-yl)-2-hydroxyethyl)furan-2-carboxylate (**30c**)

The product was a pale yellow oil (217 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.08 (d, *J* = 3.4 Hz, 1H), 6.32 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.25 (d, *J* = 3.2 Hz, 1H), 6.20 (d, *J* = 3.4 Hz, 1H), 5.08 (t, *J* = 6.7 Hz, 1H), 3.86 (s, 3H), 3.25 (d, *J* = 6.7 Hz, 2H), 2.41 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 156.8, 155.1, 143.6, 142.4, 119.4, 110.4, 110.0, 106.7, 66.1, 52.0, 35.0; HRMS: (ESI$^+$) $C_{12}H_{12}O_5Na^+$ [M + Na]$^+$ *m/z* calcd. 259.0583, found 259.0578.



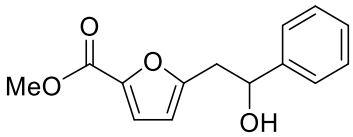
***tert*-Butyl 5-(2-hydroxy-2-phenylethyl)furan-2-carboxylate** (**30d**)

The product was a pale yellow oil (283 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 6.97 (d, *J* = 3.3 Hz, 1H), 6.15 (d, *J* = 3.4 Hz, 1H), 5.08 (t, *J* = 6.7 Hz, 1H), 3.16 – 3.04 (m, 2H), 2.30 (s, 1H), 1.57 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 156.8, 145.0, 143.3, 128.7, 128.0, 125.9, 118.2, 109.7, 81.8, 72.6, 38.6, 28.4; HRMS: (ESI$^+$) $C_{17}H_{20}O_4Na^+$ [M + Na]$^+$ *m/z* calcd. 311.1259, found 311.1259.



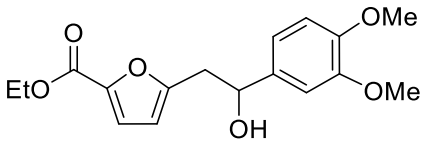
Ethyl 5-(2-hydroxy-2-phenylethyl)furan-2-carboxylate (**30e**)

The product was a pale-yellow oil (257 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 7.08 (d, *J* = 3.4 Hz, 1H), 6.18 (dt, *J* = 3.4, 0.7 Hz, 1H), 5.09 (ddd, *J* = 8.3, 5.1, 3.2 Hz, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.19 – 3.05 (m, 2H), 2.21 (d, *J* = 3.3 Hz, 1H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 157.3, 144.0, 143.3, 128.7, 128.1, 125.9, 119.1, 110.0, 72.6, 61.0, 38.6, 14.5; HRMS: (ESI$^+$) $C_{15}H_{16}O_4Na^+$ [M + Na]$^+$ *m/z* calcd. 283.0946, found 283.0937.



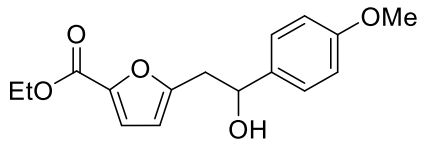
Methyl 5-(2-hydroxy-2-phenylethyl)furan-2-carboxylate (**30f**)

The product was a pale yellow oil (243 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 7.09 (d, *J* = 3.4 Hz, 1H), 6.18 (d, *J* = 3.4 Hz, 1H), 5.08 (t, *J* = 6.6 Hz, 1H), 3.87 (s, 3H), 3.19 – 3.05 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 157.5, 143.6, 143.2, 128.7, 128.1, 125.8, 119.4, 110.1, 72.6, 52.0, 38.5; HRMS: (ESI$^+$) $C_{14}H_{14}O_4Na^+$ [M + Na]$^+$ *m/z* calcd. 269.0790, found 269.0795.



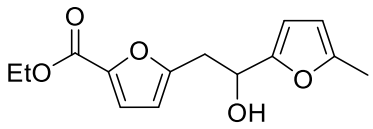
Ethyl 5-(2-(3,4-dimethoxyphenyl)-2-hydroxyethyl)furan-2-carboxylate (**47**)

The product was isolated as a yellow oil (199 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 3.4 Hz, 1H), 6.93 – 6.87 (m, 2H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.18 (d, *J* = 3.4 Hz, 1H), 5.07 – 5.01 (m, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 3.87 (s, 3H), 3.10 (qd, *J* = 15.1, 6.7 Hz, 2H), 2.21 – 2.14 (m, 1H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 157.4, 149.2, 148.8, 143.9, 135.9, 119.1, 118.1, 111.1, 110.0, 108.9, 72.4, 61.0, 56.1, 56.0, 38.6, 14.5; HRMS: (ESI^+) $C_{17}H_{24}NO_6^+$ $[M + NH_4]^+$ *m/z* calcd. 338.1604, found 338.1632.



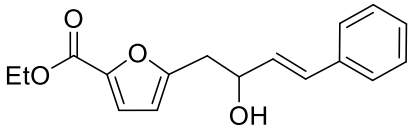
Ethyl 5-(2-hydroxy-2-(4-methoxyphenyl)ethyl)furan-2-carboxylate (**48**)

The product was isolated as a pale yellow oil (203 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 3.4 Hz, 1H), 6.90 – 6.85 (m, 2H), 6.17 (d, *J* = 3.4 Hz, 1H), 5.06 – 5.01 (m, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.10 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 159.0, 157.5, 143.9, 135.4, 127.1, 119.1, 114.1, 109.9, 72.2, 61.0, 55.4, 38.5, 14.5; HRMS: (ESI^+) $C_{16}H_{18}O_5Na^+$ $[M + Na]^+$ *m/z* calcd. 313.1052, found 313.1062.



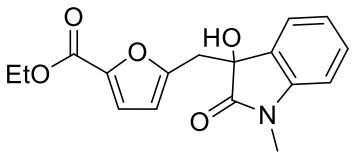
Ethyl 5-(2-hydroxy-2-(5-methylfuran-2-yl)ethyl)furan-2-carboxylate (**49**)

The product was isolated as a pale yellow oil (206 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 3.4 Hz, 1H), 6.20 (d, *J* = 3.4 Hz, 1H), 6.11 (d, *J* = 3.1 Hz, 1H), 5.89 – 5.87 (m, 1H), 5.00 (t, *J* = 6.8 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.22 (d, *J* = 6.8 Hz, 2H), 2.26 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 156.9, 153.3, 152.2, 143.8, 119.1, 109.9, 107.6, 106.2, 66.1, 60.9, 34.9, 14.5, 13.6; HRMS: (ESI$^+$) $C_{14}H_{16}O_5Na^+$ [M + Na]$^+$ *m/z* calcd. 287.0890, found 287.0888.



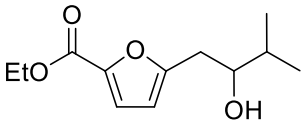
Ethyl (*E*)-5-(2-hydroxy-4-phenylbut-3-en-1-yl)furan-2-carboxylate (**50**)

The product was isolated as a pale yellow oil (103 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.22 (m, 5H), 7.11 (d, *J* = 3.4 Hz, 1H), 6.63 (d, *J* = 15.8 Hz, 1H), 6.31 – 6.21 (m, 2H), 4.69 (q, *J* = 6.4, 5.9 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.05 – 3.01 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 157.0, 144.0, 136.5, 131.3, 130.7, 128.7, 128.0, 126.7, 119.1, 110.0, 71.1, 61.0, 36.8, 14.5; HRMS: (ESI$^+$) $C_{17}H_{18}O_4Na^+$ [M + Na]$^+$ *m/z* calcd. 309.1103, found 309.1127.



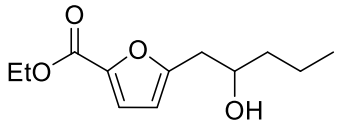
Ethyl 5-((3-hydroxy-1-methyl-2-oxoindolin-3-yl)methyl)furan-2-carboxylate (**51**)

The product was isolated as an orange solid (93.0 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.3 Hz, 1H), 7.07 – 6.99 (m, 2H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.18 (d, *J* = 3.2 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 1H), 3.42 (d, *J* = 14.8 Hz, 1H), 3.23 (d, *J* = 14.7 Hz, 1H), 3.14 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 158.7, 154.1, 144.0, 143.2, 130.1, 129.0, 124.5, 123.4, 118.9, 111.0, 108.6, 75.5, 60.9, 37.2, 26.4, 14.4; HRMS: (ESI^+) $C_{17}H_{18}NO_5^+$ $[M + H]^+$ *m/z* calcd. 316.1185, found 316.1213.



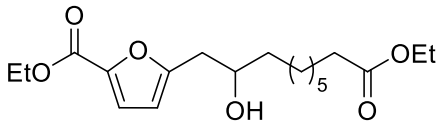
Ethyl 5-(2-hydroxy-3-methylbutyl)furan-2-carboxylate (**52**)

The product was isolated as a colorless oil (117 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 3.4 Hz, 1H), 6.24 (d, *J* = 3.4 Hz, 1H), 4.37 – 4.27 (m, 2H), 3.80 –3.71 (m, 1H), 2.89 (dd, *J* = 15.2, 3.4 Hz, 1H), 2.76 (dd, *J* = 15.2, 9.1 Hz, 1H), 1.83 (s, 1H), 1.76 – 1.66 (m, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 0.96 (dd, *J* = 6.8, 2.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 158.6, 143.8, 119.1, 109.5, 74.7, 60.9, 33.7, 33.5, 18.8, 17.3, 14.5; HRMS: (ESI^+) $C_{12}H_{19}O_4^+$ $[M + H]^+$ *m/z* calcd. 227.1283, found 227.1303.



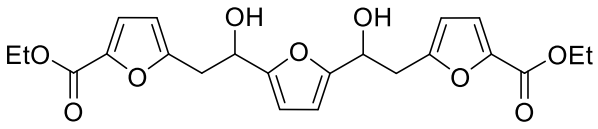
Ethyl 5-(2-hydroxypentyl)furan-2-carboxylate (**53**)

The product was isolated as a colorless oil (172 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 3.4 Hz, 1H), 6.24 (d, *J* = 3.4 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.99 (tq, *J* = 8.6, 4.6 Hz, 1H), 2.93 – 2.75 (m, 2H), 1.75 (d, *J* = 4.6 Hz, 1H), 1.52 – 1.44 (m, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 158.1, 143.9, 119.1, 109.7, 70.0, 60.9, 39.2, 36.7, 18.9, 14.5, 14.1; HRMS: (ESI$^+$) $C_{12}H_{18}O_4Na^+$ [M + Na]$^+$ *m/z* calcd. 249.1097, found 249.1099.



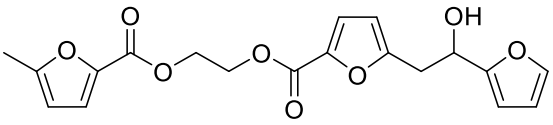
Ethyl 5-(10-ethoxy-2-hydroxy-10-oxodecyl)furan-2-carboxylate (**54**)

The product was isolated as a colorless oil (203 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 3.4 Hz, 1H), 6.24 (d, *J* = 3.4 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.96 (dt, *J* = 9.5, 4.9 Hz, 1H), 2.92 – 2.74 (m, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.55 (dt, *J* = 46.2, 6.6 Hz, 6H), 1.38 – 1.28 (m, 9H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 159.0, 158.0, 143.9, 119.1, 109.7, 70.2, 60.9, 60.3, 37.0, 36.7, 34.5, 29.4, 29.3, 29.2, 25.6, 25.0, 14.5, 14.4; HRMS: (ESI$^+$) $C_{19}H_{31}O_6^+$ [M + H]$^+$ *m/z* calcd. 355.2115, found 355.2111.

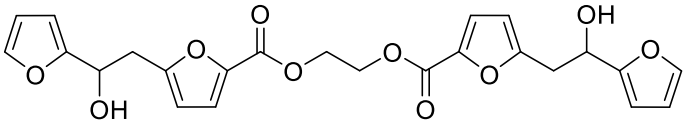


Diethyl 5,5'-(furan-2,5-diylbis(2-hydroxyethane-2,1-diyl))bis(furan-2-carboxylate) (**58**)

Zinc dust (131 mg, 2.00 mmol, 2.0 equiv) was introduced into a round-bottomed flask along with iodine (50 mg, 0.20 mmol, 20 mol%). The flask was sealed with a rubber septum and three evacuation/argon refill cycles were performed. An argon balloon attached to a needle was inserted through the septum. Anhydrous dioxane (2.0 mL) was added and the resulting suspension was stirred for 15 min at rt. A solution of ethyl 5-(chloromethyl)furan-2-carboxylate **13** (188 mg, 1.00 mmol, 2.5 equiv) in anhydrous dioxane (1.0 mL) was added and the mixture was stirred at 40 °C for 1 h. A solution of DFF **57** (49.6 mg, 0.400 mmol, 1.0 equiv) in dioxane (1.0 mL) was added, and the reaction was stirred at 40 °C for another 24 h. The mixture was filtered through Celite, and the filtrate was quenched with saturated aq. NH_4Cl and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (3 × 50 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The crude reaction mixture was purified by flash chromatography on silica gel (60/40 EtOAc/hexanes) to give the product diethyl 5,5'-(furan-2,5-diylbis(2-hydroxyethane-2,1-diyl))bis(furan-2-carboxylate) **58** (136 mg, 78%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 3.3 Hz, 2H), 6.19 (d, *J* = 3.3 Hz, 2H), 6.14 (d, *J* = 1.8 Hz, 2H), 5.02 (td, *J* = 6.6, 2.7 Hz, 2H), 4.31 (q, *J* = 7.1 Hz, 4H), 3.24 (d, *J* = 6.8 Hz, 4H), 3.03 (s, 2H), 1.34 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 156.7, 155.0, 143.8, 119.1, 110.0, 107.4, 66.1, 61.0, 35.0, 14.5; HRMS: (ESI^+) $C_{22}H_{24}O_9Na^+$ $[M + Na]^+$ *m/z* calcd. 455.1318, found 455.1307.



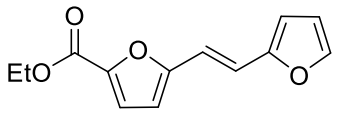
2-((5-(2-(Furan-2-yl)-2-hydroxyethyl)furan-2-carbonyl)oxy)ethyl 5-methylfuran-2-carboxylate (**59**) and



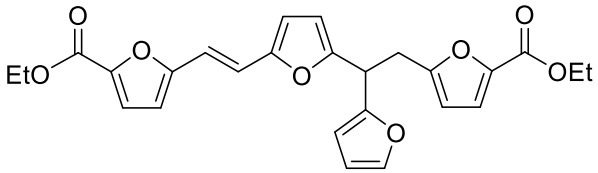
Ethane-1,2-diyl bis(5-(2-(furan-2-yl)-2-hydroxyethyl)furan-2-carboxylate) (**60**)

Zinc dust (131 mg, 2.00 mmol, 2.0 equiv) was introduced into a round-bottomed flask along with iodine (50 mg, 0.20 mmol, 20 mol%). The flask was sealed with a rubber septum and three evacuation/argon refill cycles were performed. An argon balloon attached to a needle was inserted through the septum. Anhydrous THF (2.0 mL) was added and the resulting suspension was stirred for 15 min at rt. A solution of **25** (173 mg, 0.500 mmol, 1.0 equiv) in THF (1.0 mL) was added and the mixture was stirred at 40 °C for 24 h. A solution of furfural (0.110 mL, 1.10 mmol, 1.1 equiv) in THF (1.0 mL) was added and the reaction was stirred at 40 °C for another 24 h. The mixture was filtered through Celite and the filtrate was quenched with saturated aq. NH_4Cl and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (3 × 50 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the crude reaction mixture was purified by flash chromatography on silica gel (30/70 to 40/60 EtOAc/hexanes) to give the product **59** as a green oil (49.6 mg, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.36 (m, 1H), 7.10 (d, *J* = 3.4 Hz, 2H), 6.31 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.24 (d, J = 3.2 Hz, 1H), 6.20 (d, *J* = 3.4 Hz, 1H), 6.12 – 6.10 (m, 1H), 5.08 (t, *J* = 6.6 Hz, 1H), 4.56 (s, 4H), 3.24 (d, *J* = 6.7 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 158.5, 157.8, 157.1, 155.1, 143.3, 142.7, 142.4, 120.2, 119.9, 110.4, 110.1, 108.7, 106.7, 66.1, 62.6, 62.4, 35.0, 14.1.

Product **60** was also isolated as a green oil (41.1 mg, 18%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.36 (m, 2H), 7.11 (d, *J* = 3.4 Hz, 2H), 6.31 (dd, *J* = 3.2, 1.8 Hz, 2H), 6.24 (d, *J* = 3.2 Hz, 2H), 6.20 (d, *J* = 3.4 Hz, 2H), 5.07 (t, *J* = 6.4 Hz, 2H), 4.56 (s, 4H), 3.24 (d, *J* = 6.7 Hz, 4H), 2.53 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 157.2, 155.1, 143.2, 142.4, 119.9, 110.4, 110.1, 106.7, 66.0, 62.4, 35.0.



Ethyl (*E*)-5-(2-(furan-2-yl)vinyl)furan-2-carboxylate (**63**) **and**

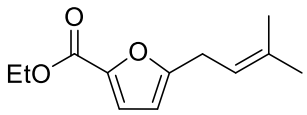


Ethyl (*E*)-5-(2-(5-(2-(5-(ethoxycarbonyl) furan-2-yl)-1-(furan-2-yl)ethyl)furan-2-yl)vinyl)furan-2-carboxylate (**64**)

A 25 mL round-bottomed flask was charged with **30b** (250 mg, 1.00 mmol, 1.0 equiv), Amberlyst 15 (100 mg), and PhMe (10 mL). The reaction mixture was stirred at 60 °C for 7 h. The mixture was cooled to rt and the solid was filtered. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography on silica gel (10/90 EtOAc/hexanes) to give the product **63** as a pale yellow oil (149 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.15 (d, *J* = 3.6 Hz, 1H), 7.05 (d, *J* = 16.1 Hz, 1H), 6.79 (d, *J* = 16.1 Hz, 1H), 6.42 (d, *J* = 3.4 Hz, 2H), 6.38 (d, *J* = 3.6 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101

MHz, $CDCl_3$) δ 158.9, 156.6, 152.4, 143.6, 143.1, 119.9, 118.7, 113.7, 112.1, 110.9, 110.1, 61.0, 14.5.

The byproduct **64** was isolated as a green oil (28 mg, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 1.9, 1.0 Hz, 1H), 7.15 (d, *J* = 3.7 Hz, 1H), 7.00 (d, *J* = 3.6 Hz, 1H), 6.96 (d, *J* = 16.1 Hz, 1H), 6.71 (d, *J* = 16.1 Hz, 1H), 6.38 (d, *J* = 3.7 Hz, 1H), 6.32 – 6.28 (m, 2H), 6.12 (d, *J* = 3.2 Hz, 1H), 6.09 (d, *J* = 3.3 Hz, 1H), 5.96 (d, *J* = 3.4 Hz, 1H), 4.58 (t, *J* = 7.7 Hz, 1H), 4.39 – 4.29 (m, 4H), 3.44 (d, *J* = 7.8 Hz, 2H), 1.40 – 1.36 (m, 3H), 1.36 – 1.32 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.91, 158.89, 157.43, 156.67, 154.57, 153.10, 151.69, 143.70, 143.61, 141.98, 119.98, 118.99, 118.57, 113.28, 111.81, 110.44, 109.97, 109.43, 109.25, 106.93, 61.00, 60.90, 38.28, 32.08, 14.51, 14.48; HRMS: (ESI$^+$) $C_{26}H_{24}O_8Na_+$ $[M + Na]^+$ *m/z* calcd. 487.1369, found 487.1362.



Ethyl 5-(3-methylbut-2-en-1-yl)furan-2-carboxylate (**66**)

Zinc dust (131 mg, 2.00 mmol, 2.0 equiv) was introduced into a round-bottomed flask along with iodine (50 mg, 0.20 mmol, 20 mol%). The flask was sealed with a rubber septum and three argon evacuation/refill cycles were performed. An argon balloon attached to a needle was inserted through the septum. Anhydrous THF (2.0 mL) was added and the resulting suspension was stirred for 15 min at rt. A solution of ethyl 5-(chloromethyl)furan-2-carboxylate **13** (188 mg, 1.00 mmol, 1.0 equiv) in THF (1.0 mL) was added and the mixture was stirred at 40 °C for 24 h. The resulting organozinc mixture was cooled to rt. Isocrotyl bromide (0.160 mL, 1.50 mmol, 1.5 equiv), Pd_2dba_3 (22.9 mg, 5 mol%), and P(*o*-Tol)$_3$ (15.2 mg, 5 mol%) were added at rt under argon. The reaction was stirred at rt overnight. The mixture was filtered through Celite and the filtrate was quenched

with saturated aq. NH_4Cl and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (3 × 50 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography on silica gel (10/90 EtOAc/hexanes) to give the product **66** as a green oil (14.0 mg, 7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 3.4 Hz, 1H), 6.11 – 6.06 (m, 1H), 5.35 – 5.28 (m, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.43 – 3.37 (m, 2H), 1.75 (s, 3H), 1.67 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4, 159.1, 143.4, 135.3, 119.2, 118.1, 107.6, 60.8, 27.5, 25.8, 18.0, 14.5.

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Chapter 5

Furylogous Nucleophile Chemistry for the Preparation of Renewable Dyes

5.1 - Introduction

Recently, the Mascal group described the concept of renewable, biobased synthetic dyes.[1] These compounds are differentiated from petrochemical dyes in that they are produced from non-fossil carbon sources, and from botanical dyes in that they are not agriculturally derived. Little in the way of explanation is needed to convey why the annual production of >1M tonnes of petrochemical dyes is ultimately undesirable, given the current environmental movement and the fact that, unlike other petrochemical products, dyes are never recycled. It might then be supposed that botanical dyes, simply by virtue of the fact that they are natural products, are a more sustainable choice. However, agriculture is resource-intensive (land, water, energy), and often involves the use of chemical fertilizers and pesticides. Natural dyes are also expensive, limited in color selection, require the use of mordants, and often show inferior performance.[2,3] It may be noted here that, as a reaction to these concerns, microbiologically-produced colorants are being introduced into the market.[4,5] However, similar issues involving cost, limited color range, and constraints in production volume would suggest this is not a comprehensive solution to the problem. Between these two extremes are synthetic dyes that are fully sourced from biomass-derived intermediates. While the stereotypical targets of green synthesis have been fuels and monomers, other high-volume products such as agrochemicals and detergents have started to receive attention.[6-9] There remains however a white space in the field of colorants, a million-tonne global industry that is dominated by polyaromatics derived from coal tar refining. In previous work in the Mascal group, a butenolide from biomass-derived levulinic acid was condensed with a derivative of CMF **2** to give chromophores that showed excellent performance as dyes.[1] CMF **2** is a highly versatile biobased platform chemical and disruptive innovation in the field of biorefinery research.[10,11] In this chapter, the concept of furylogy is further developed,[12] by which we have been able to expand the scope of colorant chemistry that stems from CMF.

5.2 - C-H Activation via the Furylogy Effect

Figure 5.1 shows the natural charge affinity of a 5-(chloromethyl)furoate ester, which can be derived from CMF by oxidation with a simple reagent mixture consisting of household bleach, acetic acid, and *tert*-butanol, followed by esterification with the relevant alcohol.[13] In Chapter 3, deprotonation of the furoate ester was observed to lead to Darzens-type reactivity, whereas the simple enolate of the dehalogenated furoate participated in classic carbon nucleophile reactions such as alkylation and addition to carbonyl compounds.[12] On the other hand, metalation of the halide led to Reformatsky-type reactivity with a range of aldehydes.[14]

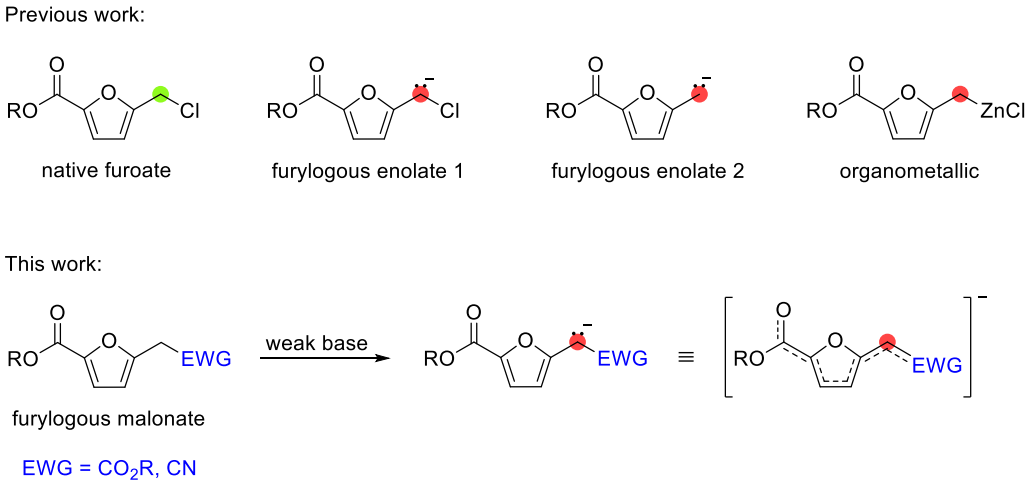
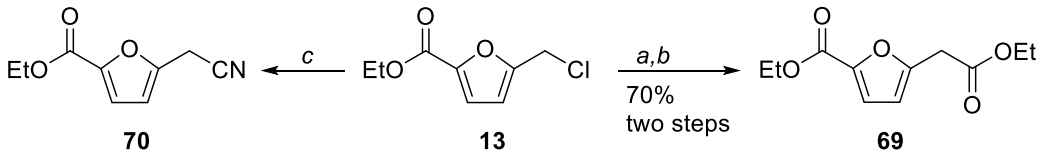


Figure 5.1 - Graphical relationship of this work to previous work. A green highlight over carbon denotes an electrophilic center, red highlights denote nucleophilic centers.

5.3 - Syntheses of a Furylogous Malonate Ester and its Cyanoacetate Analog

In recent work, the Mascal group has described the electrochemical fixation of the greenhouse gas carbon dioxide into ethyl 5-(chloromethyl)furan-2-carboxylate **13** to give, after esterification, ethyl 5-(carbethoxymethyl)furan-2-carboxylate **69**.[15] Likewise, **13** can undergo nucleophilic substitution with cyanide to give cyanoacetate ester **70** (Scheme 5.1). Analog **70** is included in

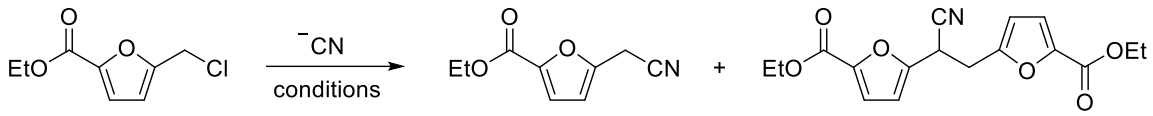
this study to further expand the spectrum of reactivity at the neighboring methylene group. Since HCN is produced industrially from methane and ammonia, the cyanide reagent could, like CO_2, also be sustainably derived, given the prevalence of biomethane production in anaerobic waste digesters.[16]



Scheme 5.1 - Syntheses of furylogous malonate ester **69** and cyanoacetate ester **70**. Reagents and conditions: *a*. –2.7 V (vs. Fc/Fc^+), Ag/Al, 2 F mol^{-1}, 75% (ref. 15); *b*. EtOH, H_2SO_4, 40 °C, 12 h, 93%; *c*. NaCN, see conditions in Table 5.1.

Although carboxylation of **13** was straightforward,[15] it was surprising to find that the cyanation of **13** was a remarkably capricious reaction, particularly given that an analogous substitution with azide anion was observed to proceed in >90% yield.[6] As shown in Table 5.1, the reaction performed poorly under classic S_N2 conditions in polar aprotic solvents DMF and DMSO. Therefore, phase transfer catalysts (PTCs) were used first in biphasic systems and finally as additives. Although some success was seen in ethyl acetate/water mixtures over long periods at elevated temperatures, it is found that halogenated hydrocarbons to perform better, most favorably in a single phase. Ultimately, the reaction in dichloromethane in the presence of tetrabutylammonium bromide gave an acceptable yield (entry 18), although some self-alkylation product **71** was also formed. While the addition of sodium iodide had an accelerating effect in the two-phase reaction (*cf.* entries 10 and 11), in the single phase it only served to degrade the mass balance. The inferior results in acetonitrile (entries 21 and 22) also serve to show how sensitive this reaction is.

Table 5.1 - Optimization of the cyanation of ethyl 5-(chloromethyl)furan-2-carboxylate **13**.



13 **70** **71**

Entry	Solvent(s)	PTC	Temp./°C	Time/h	**13**/%*	**70**/%*	**71**/%*
1	DMF		0	0.25	100	0	0
2	DMF		rt	6	16	38	0
3	DMF		rt	12	5	43	0
4	DMF		rt	24	trace	29	0
5	DMSO		rt	3	3	42	6
6	PhMe/H_2O	Bu_4NBr	rt	24	97	trace	0
7	Et_2O/H_2O	Bu_4NBr	rt	24	83	trace	0
8	EtOAc/H_2O	Bu_4NBr	rt	24	85	5	0
9	EtOAc/H_2O	Bu_4NBr	rt	48	80	10	0
10	EtOAc/H_2O	Bu_4NBr	40	24	56	30	1
11	EtOAc/H_2O	Bu_4NBr/NaI	40	24	3	52	13
12	EtOAc/H_2O	Bu_4NBr	60	24	25	38	1
13	DCM/H_2O	Et_4NBr	rt	24	90	0	0
14	DCM/H_2O	Bu_4NBr	rt	24	13	62	10
15	$CHCl_3$/H_2O	Bu_4NBr	rt	24	23	46	11
16	DCM/H_2O	Bu_4NBr	rt	48	3	61	12
17	DCM	Bu_4NBr	rt	12	15	60	11
18	DCM	Bu_4NBr	rt	24	2	71	12
19	DCM	Bu_4NBr/NaI	rt	24	9	43	10
20	DCM	$BnEt_3NBr$	rt	24	78	4	0
21	ACN	Bu_4NBr	rt	24	66	18	3
22	ACN	Bu_4NBr/NaI	rt	24	10	41	13

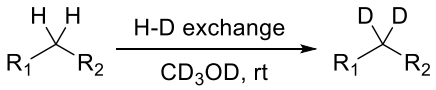
Reaction conditions: **13** (500 mg, 2.66 mmol), NaCN (143 mg, 2.93 mmol, 1.1 equiv used in the reactions without PTC, or 195 mg, 3.98 mmol, 1.5 equiv used in the reactions with PTC), indicated organic solvent (5.0 mL), H_2O (5.0 mL, where indicated), tetrabutylammonium bromide (86 mg, 0.27 mmol, 0.10 equiv) or tetraethylammonium bromide (56 mg, 0.27 mmol, 0.10 equiv) or benzyltriethylammonium bromide (73 mg, 0.27 mmol, 0.10 equiv) where indicated, 0 °C to 60 °C. *Isolated yields.

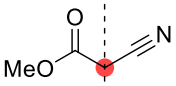
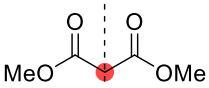
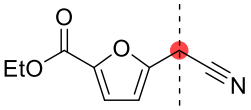
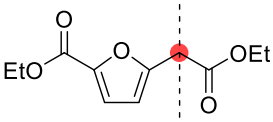
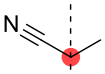
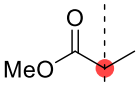
5.4 - Deuterium Exchange Experiment of a Furylogous Malonate Ester and its Cyanoacetate Analog

The acidity of the activated methylene position in **69** and **70** was assessed relative to the non-furylogous parent systems by hydrogen-deuterium exchange. These experiments were conducted in dilute methanol-d_4 solutions at room temperature. No catalyst was added. Methyl cyanoacetate, dimethyl malonate, propanenitrile, and methyl propanoate were chosen as benchmarks (Table 5.2). As expected, entries 1 and 2 involved fast deuteration kinetics. We were

pleased to see the cyanofuroate **70** exchange even more quickly than the parent cyanoacetic ester. The process in the diester analog **69** was however significantly slower, with exchange proceeding in a nonlinear fashion, and only reaching 43% after 16 days at room temperature. For completeness, these results were compared to the mono-activated analogs (entries 5 and 6 in Table 5.2), where essentially no evidence of exchange was seen, which supports the case for a furylogous effect. These experimental observations match a computational analysis which was also published in the paper.[17]

Table 5.2 - Hydrogen-deuterium exchange rates at the indicated carbons.

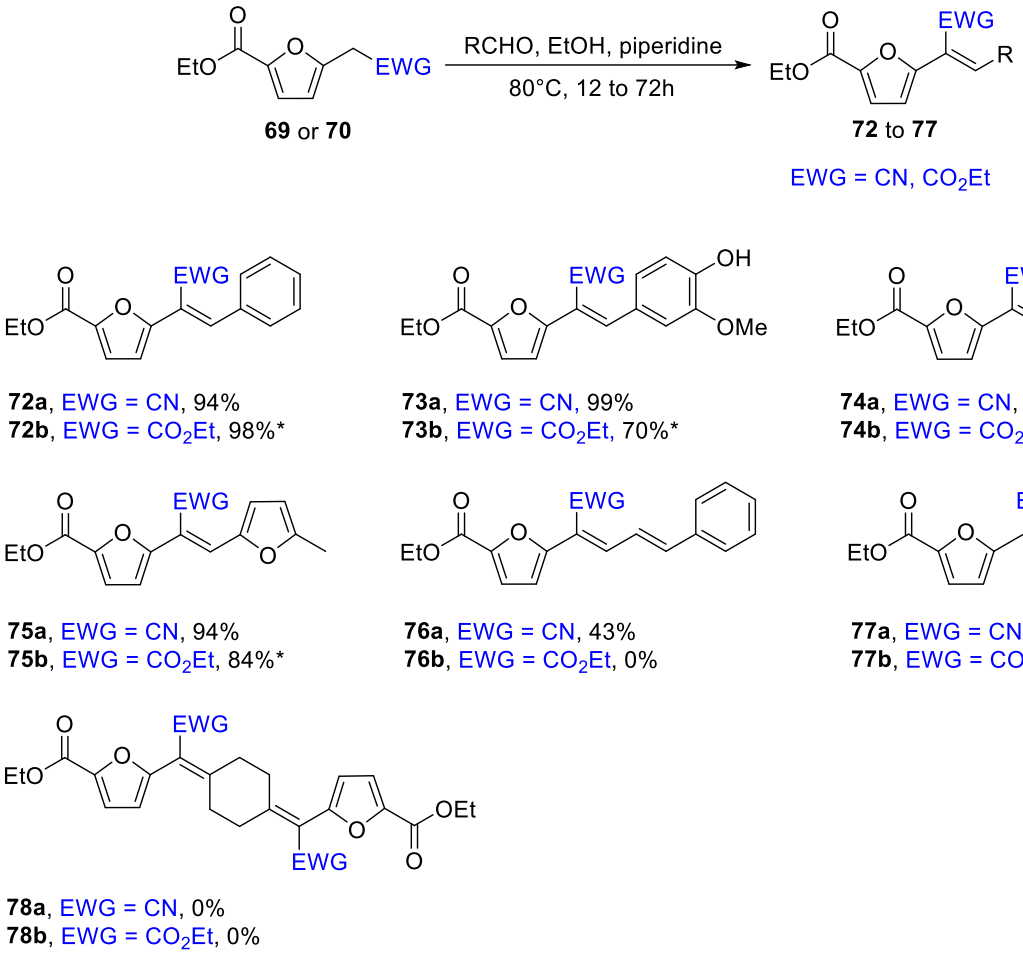


Entry	R_1	R_2	Time	Deuteration Rate/%
1			12 h 20 h 1 d	66 80 88
2			1 d 2 d	75 92
3		(**70**)	10 min	92
4		(**69**)	16 d	43
5			16 d	<1
6			16 d	<1

5.5 - Synthesis of CMF-Derived Chromophores via Knoevenagel Condensations

A classic reaction of activated methylene compounds is the Knoevenagel condensation. Given the enhanced acidity of **69** and **70** via the furylogy effect, it was proposed that these molecules would readily undergo this transformation with aldehydes to give products reminiscent of the strong chromophores obtained earlier from the reaction of levulinic acid-derived butenolides with furfurals.[1] Thus, a test reaction of both **69** and **70** with the benzaldehyde in the presence of piperidine gave the benzylidenes **72** in excellent yield. Moving on to biobased, auxochromic aldehydes, lignin-derived vanillin, though less reactive than benzaldehyde, gave the condensation product in essentially quantitative yield with **70**, while the reactivity with **69** was somewhat more moderate. In all cases, reaction times for **69** were longer than those for **70**. Nevertheless, both furfural and 5-methylfurfural gave excellent yields of products both with diester **69** and cyanoester **70**. An attempt to introduce another unsaturation into the conjugation path via cinnamaldehyde was largely unsuccessful, giving a poor yield of **76a** and no product at all with **69**. Knoevenagel condensations of **70** gave the *trans* stereoisomers as the sole products. However, mixtures of *cis* and *trans* isomers were obtained from the condensation reactions of **69** due to the steric influence of the ester group.

Condensations of these C-H activated compounds **69** and **70** were also probed with ketones. Compound **70** reacted with cyclohexanone to give **77a** in good yield. However, a two-fold condensation did not occur between **70** and 1,4-cyclohexanedione, which could have given an interesting chromophore after a subsequent oxidation step. Analogous attempts with diester **69** and these same ketones were unsuccessful due to the lower reactivity at the methylene group, attributed to weaker C-H activation by the ester group.



69 or **70**

72 to **77**

EWG = CN, CO_2Et

72a, EWG = CN, 94%
72b, EWG = CO_2Et, 98%*

73a, EWG = CN, 99%
73b, EWG = CO_2Et, 70%*

74a, EWG = CN, 98%
74b, EWG = CO_2Et, 91%*

75a, EWG = CN, 94%
75b, EWG = CO_2Et, 84%*

76a, EWG = CN, 43%
76b, EWG = CO_2Et, 0%

77a, EWG = CN, 85%
77b, EWG = CO_2Et, 0%

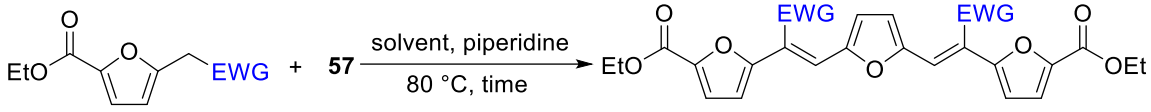
78a, EWG = CN, 0%
78b, EWG = CO_2Et, 0%

Scheme 5.2 - Knoevenagel condensations of furylogous malonate ester **69** and cyanoacetic ester **70** with carbonyl compounds. An asterisk denotes a mixture of stereoisomers.

5.6 - Synthesis of CMF-Derived Chromophores via Two-fold Knoevenagel Condensations

Another strategy for realizing a more extensive conjugation path and therefore stronger chromophores is to perform a two-fold Knoevenagel reaction on the CMF derivative 2,5-diformylfuran (DFF, **57**). The reaction proceeded in excellent yield either in ethanol or dioxane with **70** but more slowly and only in ethanol for **69**, again indicative of their difference in reactivity.

Table 5.3 - Two-fold Knoevenagel condensations of **69** and **70** with DFF **57**.



69 or **70**

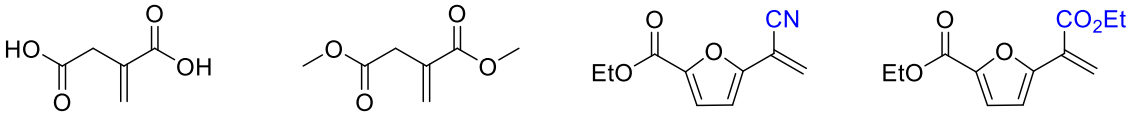
79a, EWG = CN
79b, EWG = CO_2Et

Entry	EWG	Solvent	Time/h	Yield/%
1	CN	dioxane	24	97
2	CN	EtOH	24	98
3	CO_2Et	dioxane	72	12*
4	CO_2Et	EtOH	72	93*

*These products were isolated as mixtures of isomers.

5.7 - Attempted Syntheses of CMF-Derived Itaconate Analogs

Polymers derived from itaconic acid (IA) have been extensively studied for the past 60 years.[18,19] The global itaconic market reached 98.4 million USD in 2021, and is estimated to reach 110.4 million USD by 2027 due to the increasing demand for biobased chemicals.[20] Currently, itaconic acid is industrially produced from the fermentation of *Aspergillus terreus*.[21] The production capacity, biorenewability, and synthetic versatility of itaconic acid have encouraged further exploration of the chemistry of itaconate polymers.[22,23] With success in synthesizing sustainable dyes, preparation of CMF-derived itaconate analogs from the same C-H activated compounds **69** and **70** was sought. This section describes the attempted syntheses of compounds **80a** and **80b** (Figure 5.2).



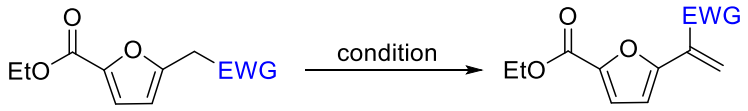
itaconic acid dimethyl itaconate **80a** **80b**

itaconate-like compounds

Figure 5.2 - Structures of itaconic acid, dimethyl itaconate, and proposed itaconate-like compounds **80a** and **80b**.

Attempts to synthesize **80a** and **80b** are summarized in Table 5.4. Despite the success of the previous Knoevenagel reactions, no desired products were observed from the attempted methylenation of **69** and **70** (Table 5.4, entry 1). Biphasic reactions with PTCs resulted in the decomposition of the starting materials (Table 5.4, entry 2). Bugarin and coworkers reported a diisopropylammonium trifluoroacetate (*i*-Pr_2NH:TFA) mediated method for the direct α-methylenation of carbonyl compounds.[24] However, the addition of this organocatalyst did not promote methylenation. Alternatively, dibromomethane has been used as a one-carbon source for α-methylenation.[25,26] Switching the reagent from CH_2O to CH_2Br_2 failed however to generate the target molecules **80a** and **80b**.

Table 5.4 - Methylenation of **69** and **70**.



69 or **70** — **80a**, EWG = CN; **80b**, EWG = CO_2Et

Entry	Reactant	Condition	Result*
1	Formaldehyde (aq. or gas)	EtOH, piperidine (cat.), rt-80 °C, 24 h	NR
2	Paraformaldehyde	PhMe, TBAB or $TBAHSO_4$, K_2CO_3, 80 °C, 24 h	Decomp.
3	Paraformaldehyde	THF, *i*-Pr_2NH:TFA (1:1.1 to 2:1), reflux, 2-18 h	Decomp.
4	Dibromomethane	Et_2NH, DCM, rt-40 °C, 0.5-3 d	Decomp.

***The experiments were monitored by ^1H and ^{13}C NMR spectroscopy.

5.8 - Conclusion

Synthetic dyes inaugurated the chemical industry and have had a multidimensional impact on economies, fashion, and various technologies, and the work here was motivated from the premise that this is a legacy that should not be simply discarded because of their unsustainable derivation. In this chapter, the potential of CMF to deliver renewable solutions for commercial markets was showcased in terms of industrially relevant synthetic colorants, in this case exploiting

Knoevenagel-type reactivity between a furylogous malonate **69** or a furylogous cyanoacetate **70** and biomass-derived aldehydes, with no metals, strong bases, or harsh conditions involved. The products have bright colors from the yellow to red region of the spectrum and were shown to demonstrate good color performance and colorfastness on selected fabrics.[17] The prospect of producing 100% renewable textiles, where both the synthetic fibers and dyes are biobased, is thus within reach.

To further explore the applications of Knoevenagel-type reactivity of **69** and **70**, the syntheses of two itaconate-like compounds **80a** and **80b** were proposed and investigated. The unsuccessful outcomes of these attempts suggest that the methylenation products of **69** and **70**, if they form at all, are unstable and decompose under the reaction conditions.

Experimental Procedures

Deuterium Exchange Experiment

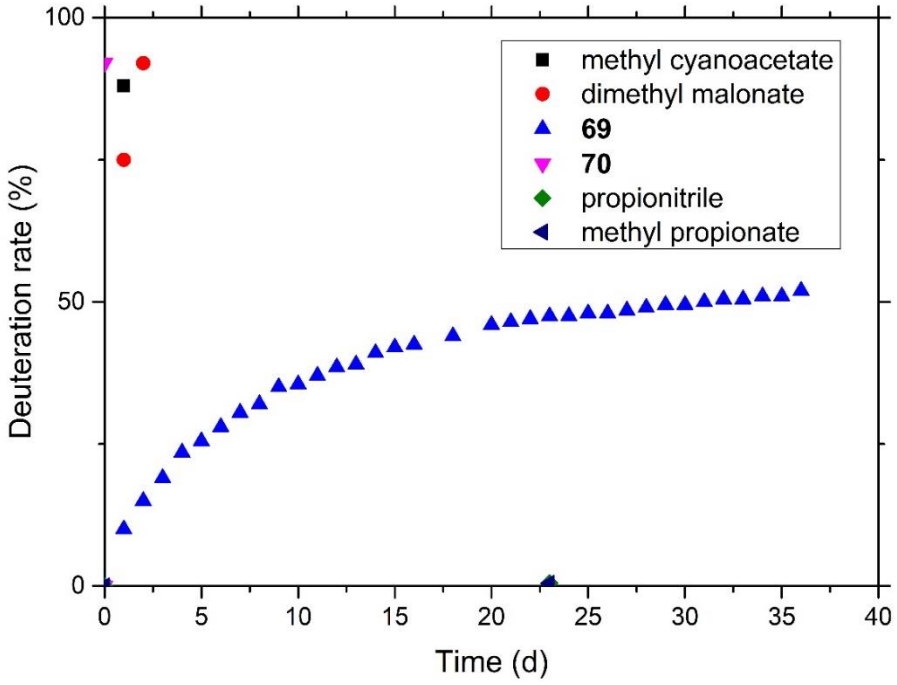
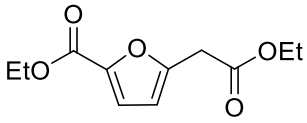


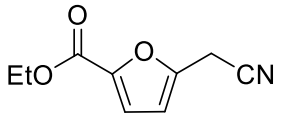
Figure 5.3 - Hydrogen-deuterium exchange of **69**, **70**, and other carbon acids in methanol-d_4

Samples were prepared by dissolving samples in methanol-d_4 (0.05 M) at room temperature. The deuteration rate was measured by the evolution of the ^{1}H NMR spectra (Figure 5.3). Compound **70** was 92% deuterated after 10 min, while dimethyl malonate required two days to reach a 92% deuteration rate. The D-H exchange process was slower for **69**. After 16 days, only 43% of the methylene group protons were exchanged, and after 23 days, only 47%. As references, propionitrile and methyl propionate showed no D-H exchange after 23 days.



Ethyl 5-(carbethoxymethyl)furan-2-carboxylate (**69**)

Ethyl (5-carboxymethyl)furan-2-carboxylate was prepared with a literature procedure.[15] Ethyl (5-carboxymethyl)furan-2-carboxylate (198 mg, 1.00 mmol, 1.0 equiv) was dissolved in ethanol (10 mL). One drop of conc. H_2SO_4 was added and the reaction mixture was stirred for 12 h at 40 °C. The reaction was cooled to rt. The solvent was evaporated and the crude product was chromatographed on silica gel (25/75 EtOAc/hexanes). Product **69** was isolated as a pale green oil (210 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 3.4 Hz, 1H), 6.38 (d, *J* = 3.4 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 2H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 158.8, 152.4, 144.3, 119.1, 110.6, 61.6, 61.0, 34.4, 14.5, 14.2; HRMS: (ESI$^+$) $C_{11}H_{15}O_5^+$ $[M + H]^+$ *m/z* calcd. 227.0920, found 227.0929; UV/Vis (acetonitrile): $\lambda_{max}(\varepsilon)$ = 258 nm (1.90×10^4 $M^{-1}cm^{-1}$).



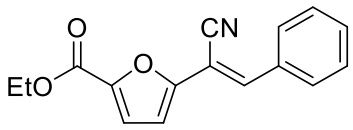
Ethyl 5-(cyanomethyl)furan-2-carboxylate (**70**)

To a 25 mL round-bottomed flask were added ethyl 5-(chloromethyl)furan-2-carboxylate **13** (500 mg, 2.66 mmol, 1.0 equiv), tetrabutylammonium bromide (86.0 mg, 0.270 mmol, 0.10 equiv), and DCM (5.0 mL). Powdered sodium cyanide (195 mg, 3.98 mmol, 1.5 equiv) was added and the resulting suspension was stirred for 24 h at rt. The reaction mixture was diluted with water (50 mL) and the aqueous layer was extracted with ethyl acetate (50 mL × 3). The combined organic

layer was dried over sodium sulfate and chromatographed on silica gel (25/75 EtOAc/hexanes). Ethyl 5-(cyanomethyl)furan-2-carboxylate (**70**) was isolated as a yellow solid (338 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 3.5 Hz, 1H), 6.50 (d, *J* = 3.5 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 147.4, 145.5, 118.8, 114.7, 110.8, 61.4, 18.1, 14.4; HRMS: (ESI$^+$) $C_9H_{10}NO_3^+$ $[M + H]^+$ *m/z* calcd. 180.0661, found 180.0660; UV/Vis (acetonitrile): λ_{max} (ε) = 252 nm (1.10×10^4 M^{-1} cm^{-1}).

General Procedure for Knoevenagel condensations

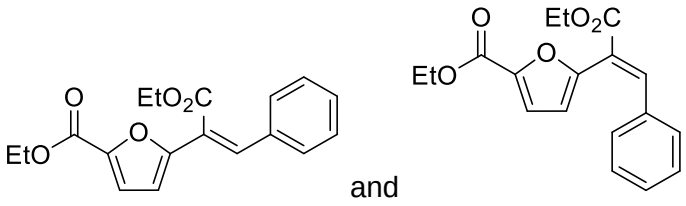
To a 25 mL round-bottomed flask were added furoate ester (**69** or **70**, 1.00 mmol), aldehyde or ketone (2.00 mmol, 2.0 equiv), the indicated solvent (10 mL), and piperidine (10 µL, 0.1 equiv). The reaction mixture was heated in an oil bath at 80 °C for 0.5 to 7 d, depending on the ester-reagent combination. The mixture was cooled to rt and then concentrated. The crude product was purified on silica gel by flash chromatography (10/90 to 25/75 EtOAc/hexanes).



Ethyl (*E*)-5-(1-cyano-2-phenylvinyl)furan-2-carboxylate (**72a**)

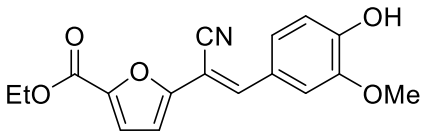
The product was isolated as a yellow solid (251 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.82 (s, 1H), 7.48 (dd, *J* = 5.0, 1.9 Hz, 3H), 7.23 (d, *J* = 3.6 Hz, 1H), 6.76 (d, *J* = 3.6 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 152.4, 145.4, 141.3, 133.0, 131.5, 129.7, 129.3, 119.7, 116.0, 111.4, 100.9, 61.5, 14.5;

HRMS: (ESI$^+$) $C_{16}H_{14}NO_3^+$ [M + H]$^+$ *m/z* calcd. 268.0974, found 268.0970; UV/Vis (acetonitrile): λ_{max} (ε) = 340 nm (4.20 × 10^4 M^{-1} cm^{-1}).



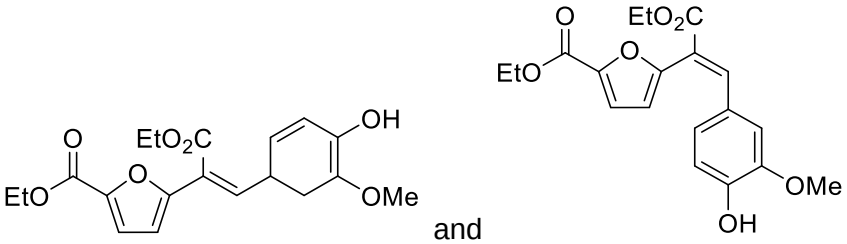
The mixture of ethyl (*Z*)-5-(3-ethoxy-3-oxo-1-phenylprop-1-en-2-yl)furan-2-carboxylate and ethyl (*E*)-5-(3-ethoxy-3-oxo-1-phenylprop-1-en-2-yl)furan-2-carboxylate (**72b**)

The mixture was isolated as a yellow oil (308 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 0.50H), 7.54 (s, 0.42H), 7.40 – 7.24 (m, 4.24H), 7.21 (d, *J* = 3.5 Hz, 0.53H), 7.18 (d, *J* = 3.6 Hz, 0.44H), 7.15 (s, 0.59H), 7.13 (d, *J* = 1.5 Hz, 0.46H), 6.51 (d, *J* = 3.6 Hz, 0.42H), 6.48 (d, *J* = 3.5 Hz, 0.51H), 4.41 – 4.25 (m, 4H), 1.39 (t, *J* = 7.1 Hz, 1.39H), 1.32 (td, *J* = 7.1, 2.2 Hz, 3.21H), 1.20 (t, *J* = 7.1 Hz, 1.33H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.07, 165.98, 158.79, 158.76, 154.04, 152.16, 145.32, 144.38, 144.35, 134.98, 134.08, 132.31, 130.26, 130.08, 129.02, 128.82, 128.56, 128.52, 124.00, 121.53, 119.69, 119.22, 113.17, 110.60, 61.86, 61.72, 61.20, 61.04, 14.49, 14.46, 14.36, 13.88; HRMS: (ESI$^+$) $C_{18}H_{18}O_5Na^+$ [M + Na]$^+$ *m/z* calcd. 337.1052, found 337.1057; UV/Vis (acetonitrile): λ_{max} (ε) = 375 nm (2.27 × 10^4 M^{-1} cm^{-1}).



Ethyl (*E*)-5-(1-cyano-2-(4-hydroxy-3-methoxyphenyl)vinyl)furan-2-carboxylate (**73a**)

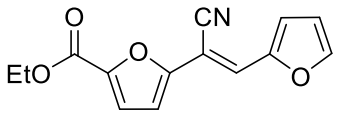
The product was isolated as a yellow solid (309 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.69 (d, *J* = 1.6 Hz, 1H), 7.37 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.21 (d, *J* = 3.6 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.68 (d, *J* = 3.6 Hz, 1H), 6.07 (s, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 3.98 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 152.9, 149.1, 146.9, 144.9, 141.4, 126.2, 125.7, 119.8, 116.7, 115.1, 110.5, 110.3, 97.6, 61.4, 56.2, 14.5; HRMS: (ESI$^+$) $C_{17}H_{16}NO_5^+$ [M + H]$^+$ *m/z* calcd. 314.1028, found 314.1029; UV/Vis (acetonitrile): λ_{max} (ε) = 379 nm (2.80 × 10^4 M^{-1} cm^{-1}).



The mixture of ethyl (*Z*)-5-(3-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-3-oxoprop-1-en-2-yl)furan-2-carboxylate and ethyl (*E*)-5-(3-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-3-oxoprop-1-en-2-yl)furan-2-carboxylate (**73b**)

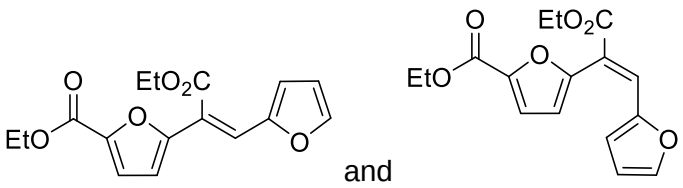
The mixture was isolated as a yellow-green oil (252 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 0.72H), 7.43 (s, 0.26H), 7.27 (s, 0.75H), 7.17 (d, *J* = 3.6 Hz, 0.23H), 6.98 – 6.87 (m, 0.75H), 6.84 – 6.82 (m, 1.33H), 6.52 (s, 0.69H), 6.51 (d, *J* = 3.5 Hz, 0.73H), 6.44 (d, *J* = 3.6 Hz, 0.23H), 5.85 (s, 0.67H), 5.79 (s, 0.22H), 4.41 – 4.24 (m, 4H), 3.90 (s, 0.71H), 3.67 (s, 2H), 1.33 (dtt, *J* =

21.3, 14.2, 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.47, 166.29, 158.81, 158.78, 154.46, 152.74, 148.13, 146.89, 146.46, 146.33, 146.02, 144.32, 144.05, 132.18, 127.20, 126.47, 126.24, 123.13, 121.92, 119.77, 119.44, 118.44, 114.64, 114.48, 112.97, 111.67, 111.39, 109.85, 61.84, 61.55, 61.15, 61.12, 56.04, 55.71, 14.51, 14.48, 14.40, 14.07; HRMS: (ESI$^+$) $C_{19}H_{21}O_7^+$ [M + H]$^+$ *m/z* calcd. 361.1287, found 361.1289; UV/Vis (acetonitrile): λ_{max} (ε) = 344 nm (4.38 × 10^4 M^{-1} cm^{-1}).



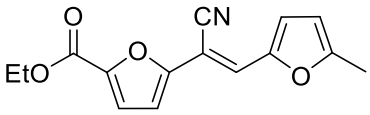
Ethyl (*E*)-5-(1-cyano-2-(furan-2-yl)vinyl)furan-2-carboxylate (**74a**)

The product was isolated as a yellow solid (252 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 1.6 Hz, 1H), 7.59 (s, 1H), 7.21 (d, *J* = 3.6 Hz, 1H), 7.11 (d, *J* = 3.6 Hz, 1H), 6.71 (d, *J* = 3.6 Hz, 1H), 6.59 (dd, *J* = 3.6, 1.8 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 158.4, 152.2, 149.7, 146.3, 145.2, 126.9, 119.9, 117.7, 115.7, 113.3, 111.1, 97.1, 61.4, 14.5; HRMS: (ESI$^+$) $C_{14}H_{12}NO_4^+$ [M + H]$^+$ *m/z* calcd. 258.0766, found 258.0767; UV/Vis (acetonitrile): λ_{max} (ε) = 368 nm (2.63 × 10^4 M^{-1} cm^{-1}).



The mixture of ethyl (*Z*)-5-(3-ethoxy-1-(furan-2-yl)-3-oxoprop-1-en-2-yl)furan-2-carboxylate and ethyl (*E*)-5-(3-ethoxy-1-(furan-2-yl)-3-oxoprop-1-en-2-yl)furan-2-carboxylate (**74b**)

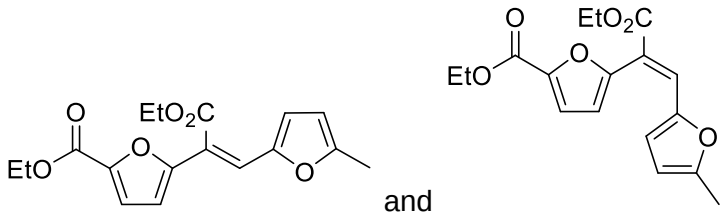
The mixture was isolated as an orange solid (277 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 0.52H), 7.53 (d, *J* = 1.4 Hz, 0.52H), 7.48 (d, *J* = 1.4 Hz, 0.40H), 7.29 (s, 0.41H), 7.23 (s, 0.40H), 7.18 (d, *J* = 3.6 Hz, 0.41H), 7.15 (d, *J* = 3.7 Hz, 0.56H), 6.80 (d, *J* = 3.6 Hz, 0.52H), 6.73 (d, *J* = 3.4 Hz, 0.42H), 6.51 (dd, *J* = 3.5, 1.6 Hz, 0.53H), 6.50 – 6.48 (m, 0.41H), 6.47 (d, *J* = 3.7 Hz, 0.41H), 4.39 (ddq, *J* = 30.8, 26.6, 7.1 Hz, 4H), 1.43 – 1.32 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.57, 165.94, 158.87, 158.69, 153.91, 152.36, 150.39, 145.80, 144.53, 144.19, 144.01, 129.67, 119.88, 119.84, 119.29, 117.99, 117.95, 116.18, 115.12, 113.53, 113.17, 112.51, 110.47, 61.86, 61.65, 61.14, 61.07, 14.48, 14.35, 14.29; HRMS: (ESI$^+$) $C_{16}H_{17}O_6^+$ $[M + H]^+$ *m/z* calcd. 305.1025, found 305.1031; UV/Vis (acetonitrile): λ_{max} (ε) = 344 nm (4.38×10^4 M^{-1} cm^{-1}).



Ethyl (*E*)-5-(1-cyano-2-(5-methylfuran-2-yl)vinyl)furan-2-carboxylate (**75a**)

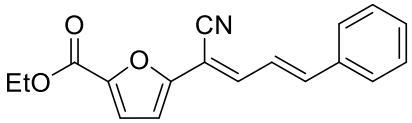
The product was isolated as a yellow solid (255 mg. 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.20 (d, *J* = 3.6 Hz, 1H), 7.03 – 6.99 (m, 1H), 6.68 – 6.64 (m, 1H), 6.23 – 6.20 (m, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.43 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 157.6, 152.7, 148.4, 144.8, 126.8, 120.0, 119.7, 116.0, 110.4, 110.2, 95.0, 61.4, 14.5, 14.3;

HRMS: (ESI$^+$) $C_{15}H_{14}NO_4^+$ [M + H]$^+$ *m/z* calcd. 272.0923, found 272.0923; UV/Vis (acetonitrile): λ_{max} (ε) = 381 nm (2.12 × 10^4 M^{-1} cm^{-1}).



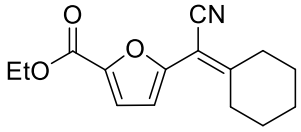
The mixture of ethyl (*Z*)-5-(3-ethoxy-1-(5-methylfuran-2-yl)-3-oxoprop-1-en-2-yl)furan-2-carboxylate and ethyl (*E*)-5-(3-ethoxy-1-(5-methylfuran-2-yl)-3-oxoprop-1-en-2-yl)furan-2-carboxylate (**75b**)

The mixture was isolated as an orange solid (268 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 0.54H), 7.26 (d, *J* = 3.7 Hz, 0.61H), 7.15 (d, *J* = 3.7 Hz, 0.73H), 7.04 (d, *J* = 3.5 Hz, 0.56H), 6.75 (d, *J* = 3.6 Hz, 0.56H), 6.63 (d, *J* = 3.3 Hz, 0.39H), 6.42 (d, *J* = 3.6 Hz, 0.39H), 6.11 (d, *J* = 3.4 Hz, 0.56H), 6.09 – 6.06 (m, 0.38H), 4.43 – 4.24 (m, 4H), 2.31 (s, 1.20H), 2.27 (s, 1.71H), 1.41 – 1.29 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.80, 166.16, 158.91, 158.72, 156.81, 155.21, 154.31, 152.81, 148.99, 143.88, 143.65, 129.75, 120.06, 119.92, 119.33, 118.29, 118.09, 117.00, 114.22, 113.16, 109.99, 109.90, 109.14, 61.73, 61.45, 61.05, 60.97, 14.47, 14.37, 14.20, 14.01; HRMS: (ESI$^+$) $C_{17}H_{19}O_6^+$ [M + H]$^+$ *m/z* calcd. 319.1182, found 319.1188 UV/Vis (acetonitrile): λ_{max} (ε) = 355 nm (1.00 × 10^4 M^{-1} cm^{-1}).



Ethyl 5-((1*E*,3*E*)-1-cyano-4-phenylbuta-1,3-dien-1-yl)furan-2-carboxylate (**76a**)

The product was isolated as a yellow solid (126 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 11.4 Hz, 1H), 7.58 – 7.53 (m, 2H), 7.43 – 7.32 (m, 3H), 7.28 (d, *J* = 15.4 Hz, 1H), 7.21 (d, *J* = 3.6 Hz, 1H), 7.12 (d, *J* = 15.4 Hz, 1H), 6.67 (d, *J* = 3.6 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 152.0, 145.3, 143.5, 141.8, 135.6, 130.2, 129.2, 128.0, 124.2, 119.8, 115.0, 111.2, 102.4, 61.4, 14.5; HRMS: (ESI$^+$) $C_{18}H_{16}NO_3^+$ $[M + H]^+$ *m/z* calcd. 294.1130, found 294.1129; UV/Vis (acetonitrile): λ_{max} (ε) = 375 nm (2.27×10^4 M^{-1} cm^{-1}).

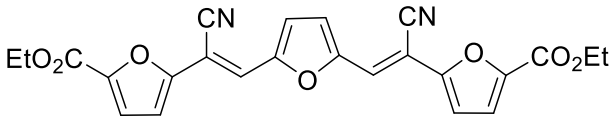


Ethyl 5-(cyano(cyclohexylidene)methyl)furan-2-carboxylate (**77a**)

The product was isolated as a yellow solid (221 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 3.6 Hz, 1H), 6.59 – 6.55 (m, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.72 (dt, *J* = 34.2, 6.1 Hz, 4H), 1.83 – 1.62 (m, 6H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 158.5, 151.3, 144.6, 118.9, 116.4, 112.5, 98.7, 61.3, 36.2, 32.1, 28.4, 28.0, 25.9, 14.4.

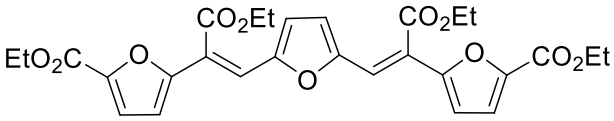
Two-fold Knoevenagel-Doebner condensation

To a 25 mL round-bottomed flask were added DFF (49.6 mg, 0.400 mmol, 1.0 equiv), furoate ester (1.00 mmol, 2.5 equiv), the indicated solvent (10.0 mL), and piperidine (10.0 µL). The reaction mixture was heated in an oil bath at 80 °C for 24 to 72 h. The reaction mixture was cooled to rt and the solvent was evaporated. Purification was as described in the General Procedure for Knoevenagel condensations.



Diethyl 5,5'-((1*E*,1'*E*)-furan-2,5-diylbis(1-cyanoethene-2,1-diyl))bis(furan-2-carboxylate) (**79a**)

The product was isolated as an orange solid (175 mg, 98%) by chromatography on silica gel (100% DCM to 100% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 2H), 7.39 (s, 2H), 7.24 (d, *J* = 3.7 Hz, 2H), 6.81 (d, *J* = 3.6 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 4H), 1.41 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 152.0, 151.7, 145.9, 125.2, 120.0, 119.2, 115.3, 112.7, 100.0, 61.6, 14.5; HRMS: (ESI$^+$) $C_{24}H_{19}N_2O_7^+$ $[M + H]^+$ *m/z* calcd. 447.1192, found 447.1192; UV/Vis (acetonitrile): λ_{max} (ε) = 452 nm (2.84×10^4 M^{-1} cm^{-1}).



The stereoisomeric mixture of diethyl 5,5'-((1*Z*,1'*Z*)-furan-2,5-diylbis(3-ethoxy-3-oxoprop-1-ene-1,2-diyl))bis(furan-2-carboxylates) (**79b**)

The mixture was isolated as an orange solid (201 mg, 93%) by chromatography on silica gel (25/75 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 0.47H), 7.62 (s, 0.56H), 7.50 (d, *J* = 3.9 Hz, 0.48H), 7.31 - 7.22 (m, 2.33H), 7.19 - 7.15 (m, 1.36H), 6.95 (d, *J* = 3.6 Hz, 0.48H), 6.91 (s, 0.36H), 6.87 (d, *J* = 3.6 Hz, 0.57H), 6.82 (d, *J* = 3.9 Hz, 0.50H), 6.56 (d, *J* = 3.6 Hz, 0.35H), 6.52 (d, *J* = 3.6 Hz, 0.49H), 4.48 – 4.28 (m, 8H), 1.44 - 1.32 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.22, 165.87, 165.60, 165.58, 158.80, 158.74, 158.62, 158.60, 153.70, 153.55, 152.57, 152.47, 152.25, 152.00, 151.93, 144.70, 144.49, 144.24, 144.16, 127.73, 127.38, 122.04, 120.98, 120.53, 120.05, 119.93, 119.88, 119.44, 119.32, 118.34, 118.32, 118.27, 117.78, 117.11, 116.60, 114.41, 114.39, 111.66, 111.61, 62.15, 62.12, 61.88, 61.82, 61.28, 61.24, 61.20, 14.49, 14.47, 14.45, 14.35, 14.33, 14.29; HRMS: (ESI$^+$) $C_{28}H_{29}O_{11}^+$ $[M + H]^+$ *m/z* calcd. 541.1710, found 541.1694; UV/Vis (acetonitrile): λ_{max} (ε) = 431 nm (2.27×10^4 M^{-1} cm^{-1}).

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Appendix

General Information and NMR Spectra

General Information

Chemicals were purchased from Sigma-Aldrich, TCI America, Spectrum Chemicals & Laboratory Products, Honeywell Research Chemicals, Acros Organics B.V.B.A., and Fisher Scientific. Argon (ultra-high purity grade, 99.999%) was purchased from Linde AG. All solvents and reagents were used as supplied.

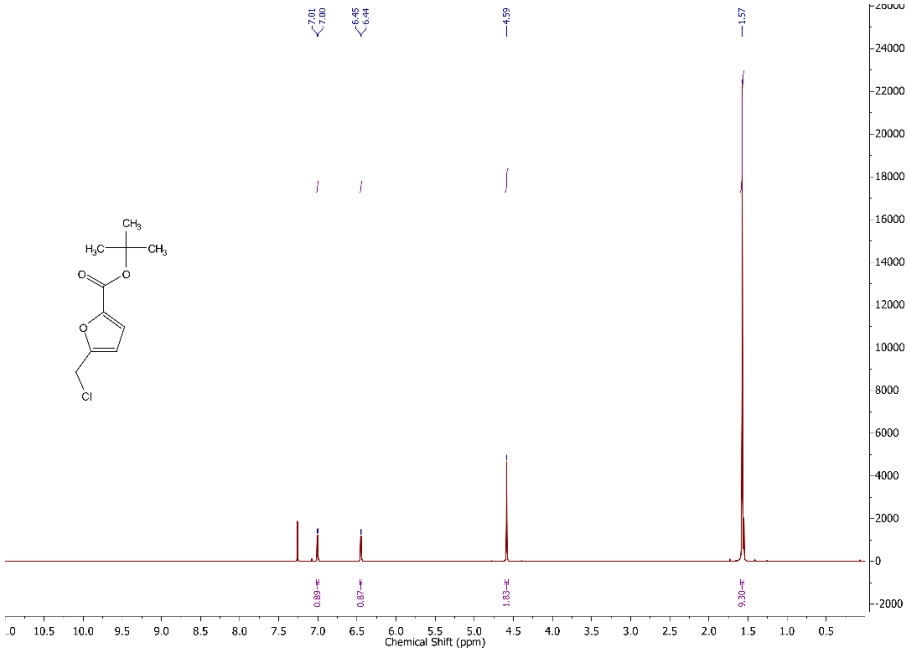
Glassware was oven dried at 150 °C for 2 h and allowed to cool under a stream of nitrogen before use. Reactions were heated using an oil bath and a stirrer-hotplate with an integrated thermocouple. Reactions were monitored using thin layer chromatography (TLC) on Sorbtech Silica XG TLC plates with fluorescent indicator. Plates were visualized using ultra-violet light (254 nm) and/or $KMnO_4$ solution as appropriate. Flash chromatography was performed using Sorbtech Silica Gel 60. Solvent mixtures given in the description of each reaction refer to v/v composition.

A Bruker Avance NEO 300 MHz spectrometer, a Bruker Nanobay 400 MHz spectrometer, or a Varian 600 MHz NMR spectrometer were used to record ^{1}H and ^{13}C spectra in the indicated deuterated solvent. All chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peaks as follows: $CDCl_3$ (δH = 7.26 ppm, δC = 77.16 ppm) or CD_3OD (δH = 3.31 ppm, δC = 49.00 ppm). Coupling constants (*J*) are averaged. The multiplicity of a ^{1}H NMR signal is designated by one of the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal. The ^{13}C NMR spectra are ^{1}H decoupled.

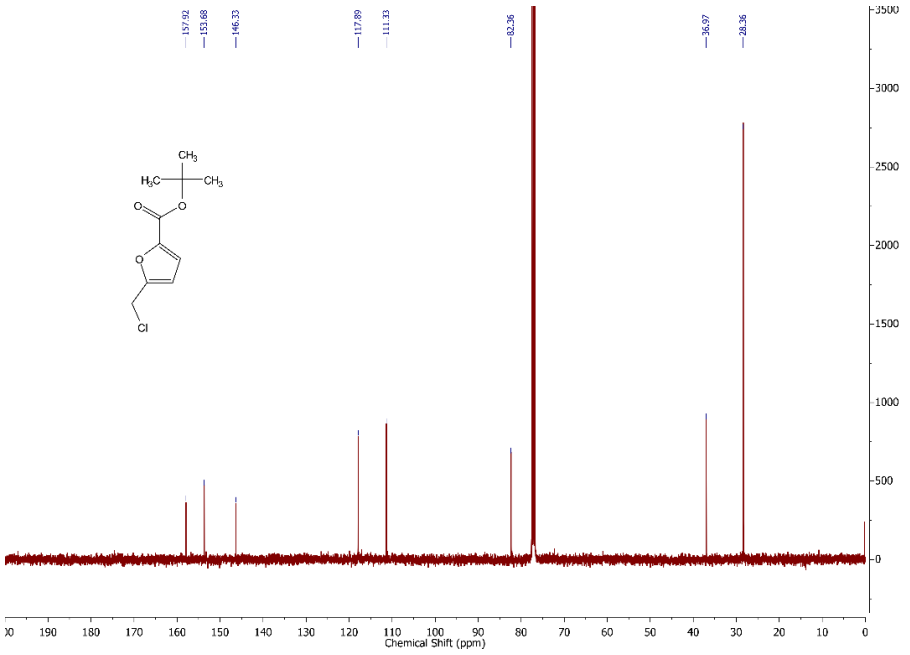
High-resolution mass spectra were recorded on a Thermo Fisher Hybrid LTQ-Orbitrap XL mass spectrometer. HRMS data were obtained by direct infusion and mass calibration was performed using Pierce ESI positive and negative calibration standard solution (Thermo Fisher Inc.). Molecular formula assignments were performed using the Molecular Formula Calculator published by the National High Magnetic Field Laboratory (https://nationalmaglab.org/). Either the $[M + Na]^+$, $[M + NH_4]^+$, and $[M + H]^+$ ions were observed.

UV-Vis data was recorded on Agilent 8453 spectrometer and all samples were measured in acetonitrile (HPLC grade).

NMR Spectra



^{1}H NMR spectrum of *tert*-butyl 5-(chloromethyl)furan-2-carboxylate **18** in $CDCl_3$



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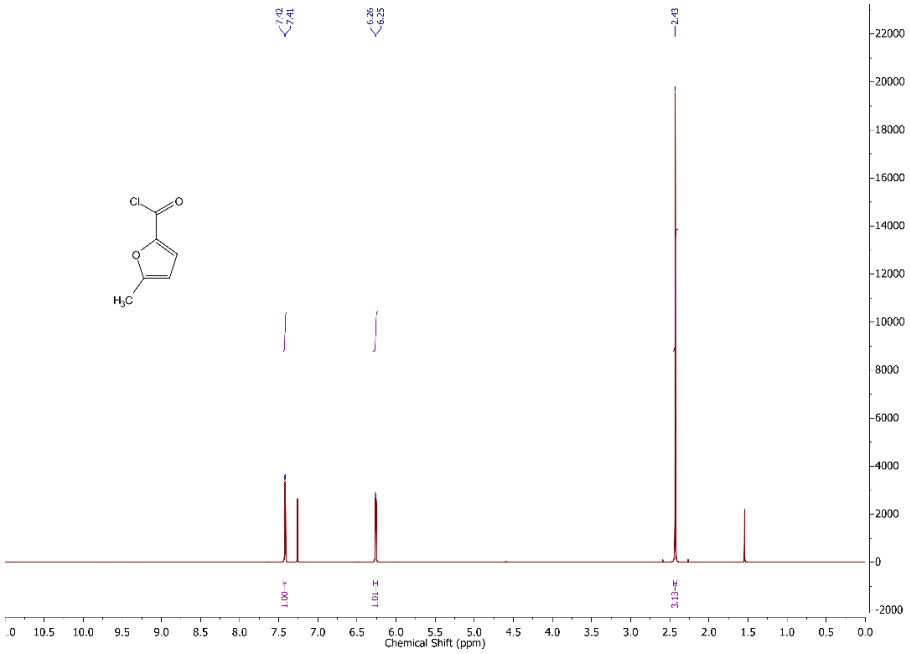

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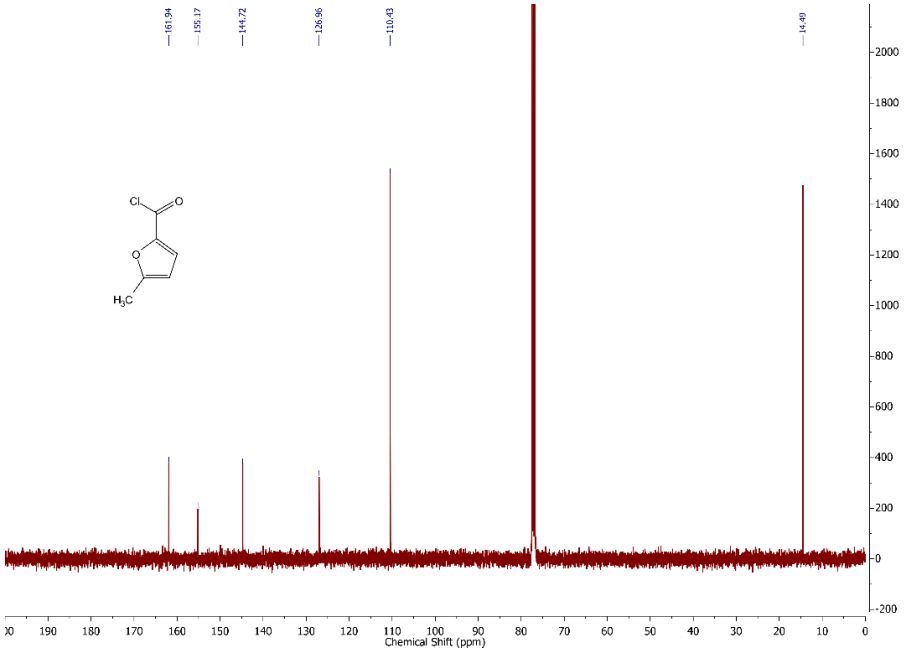

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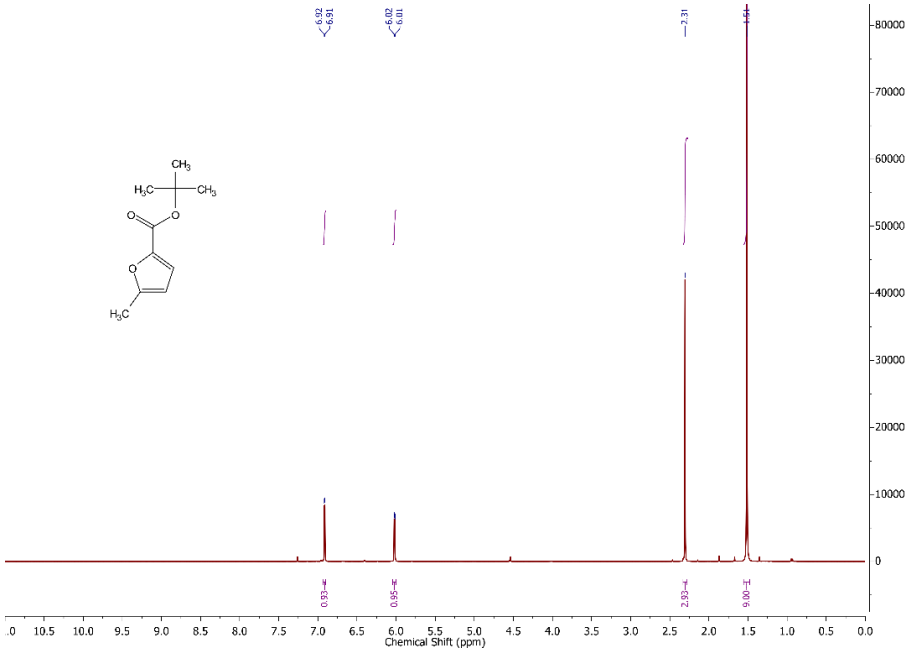

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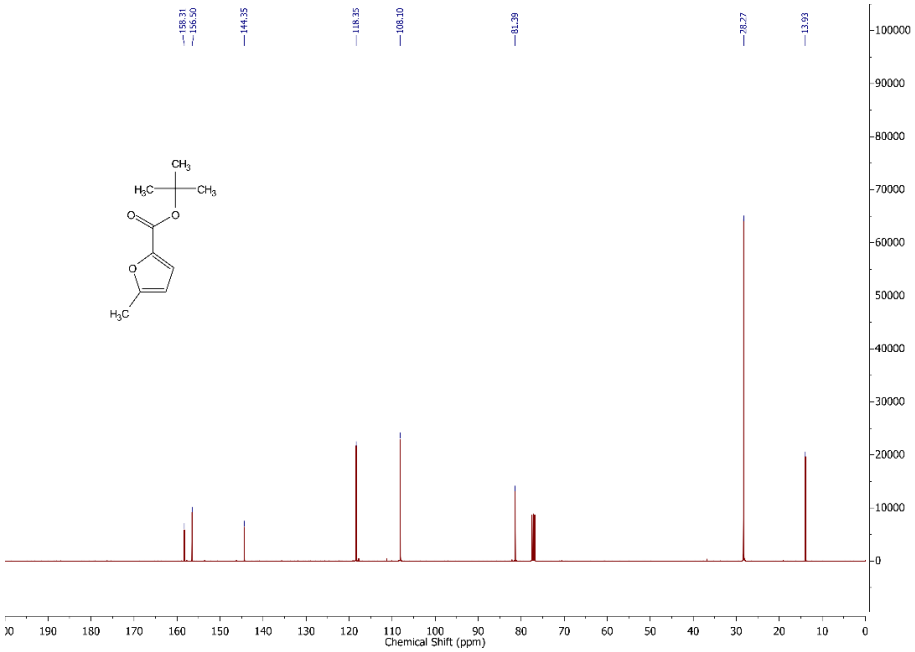

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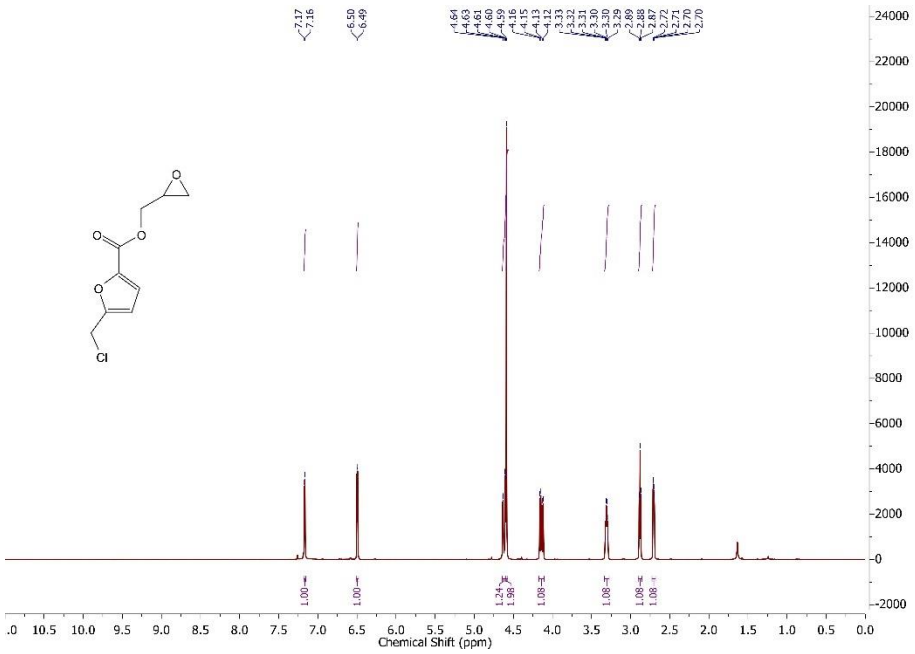
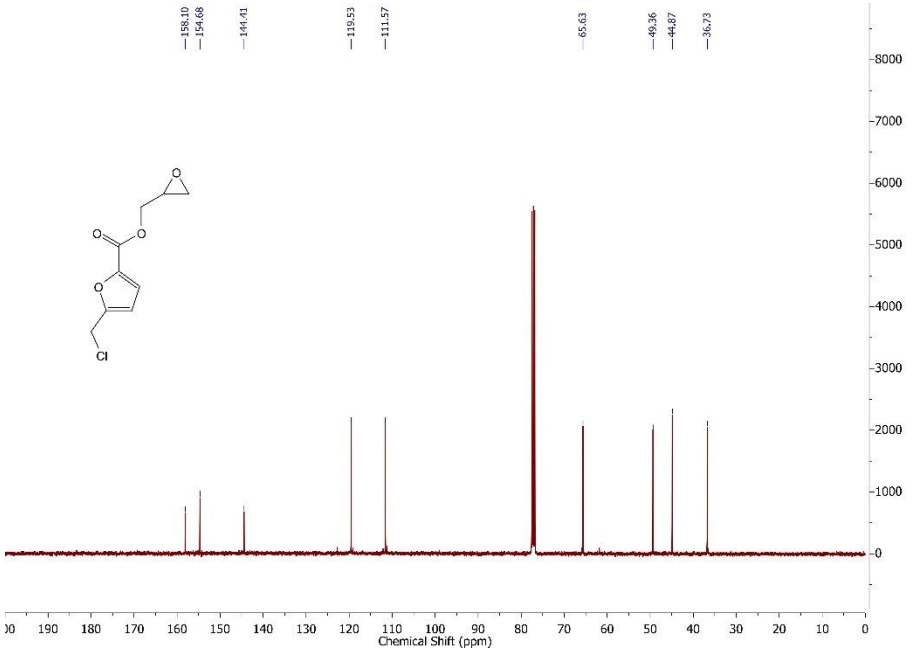


^{1}H NMR spectrum of oxiran-2-ylmethyl 5-(chloromethyl)furan-2-carboxylate **24** in $CDCl_3$



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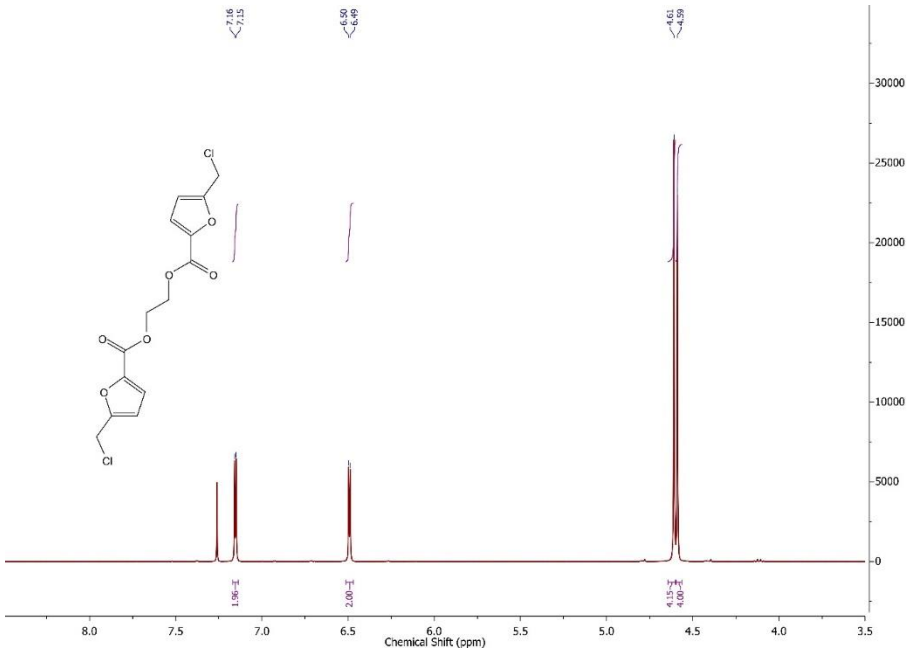

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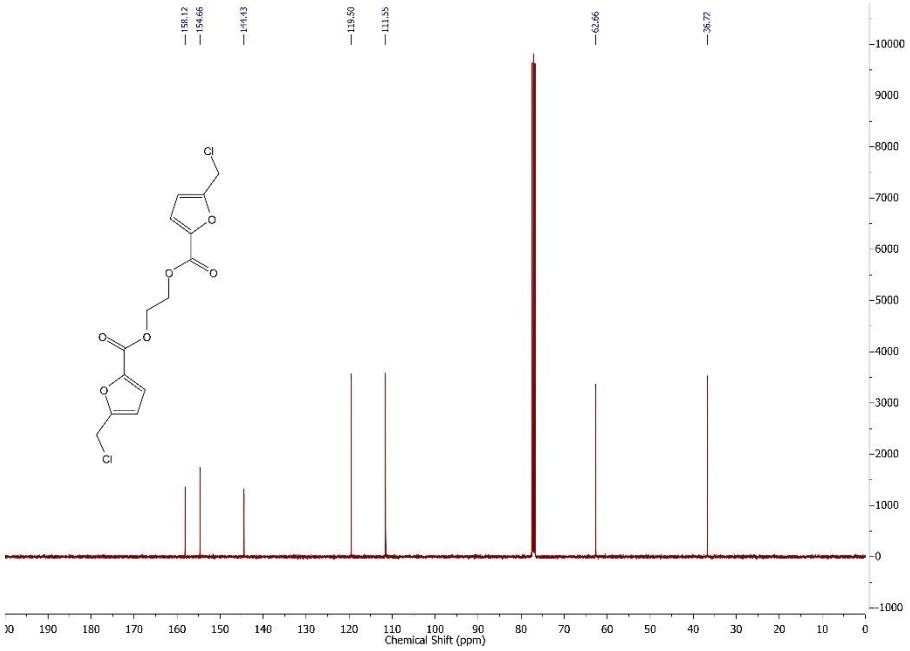

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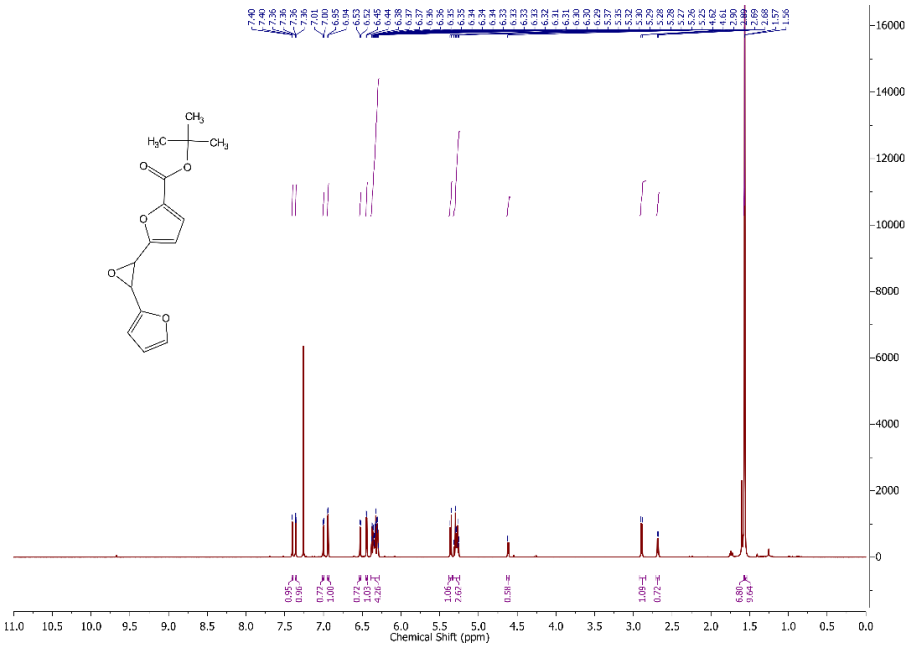

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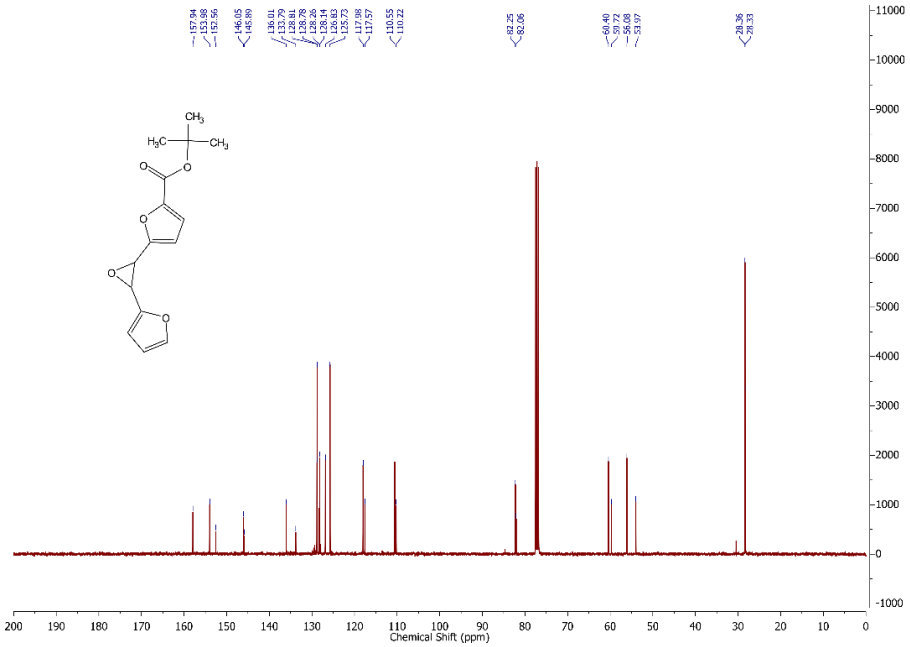

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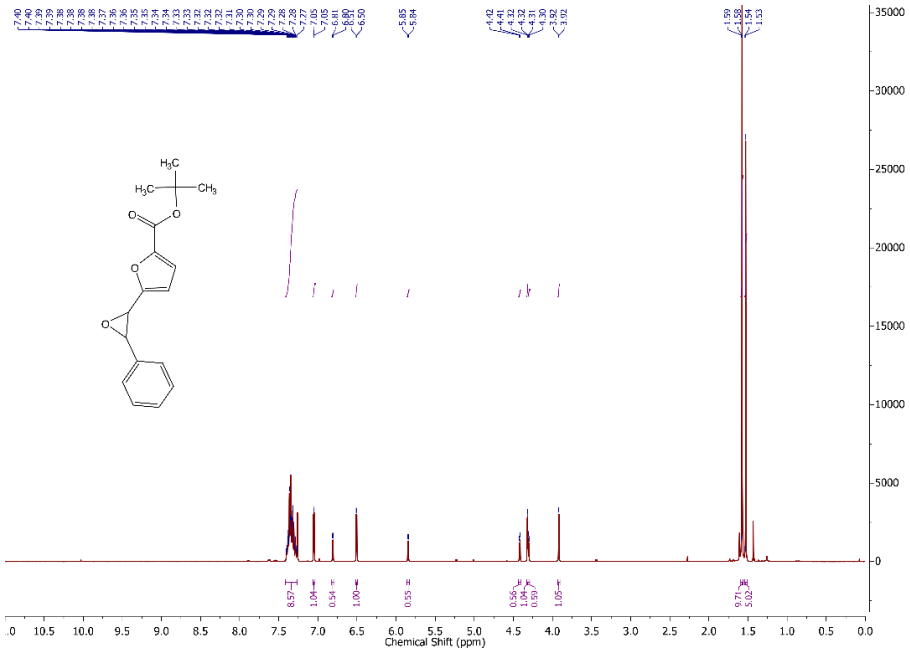

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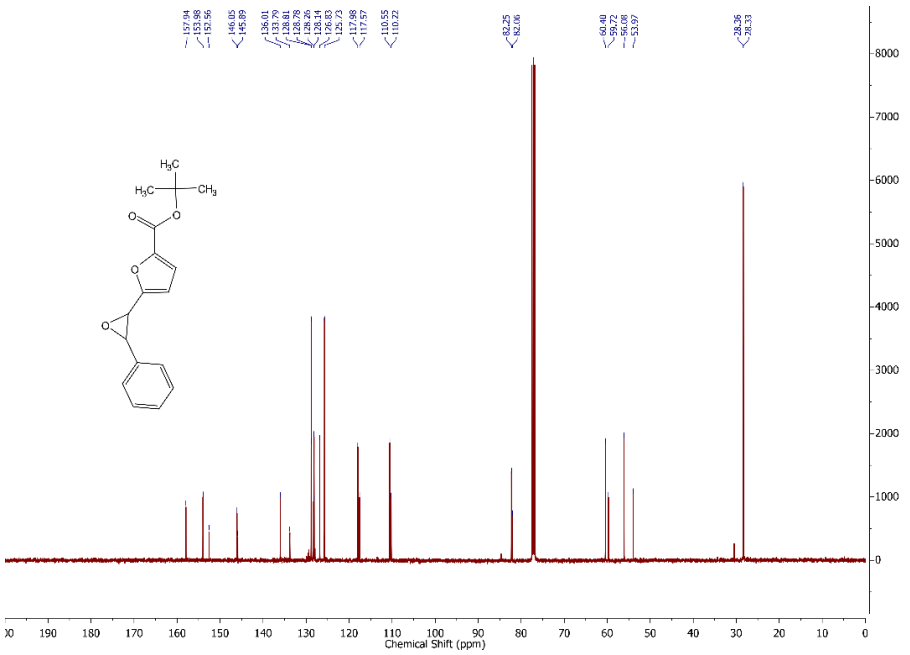

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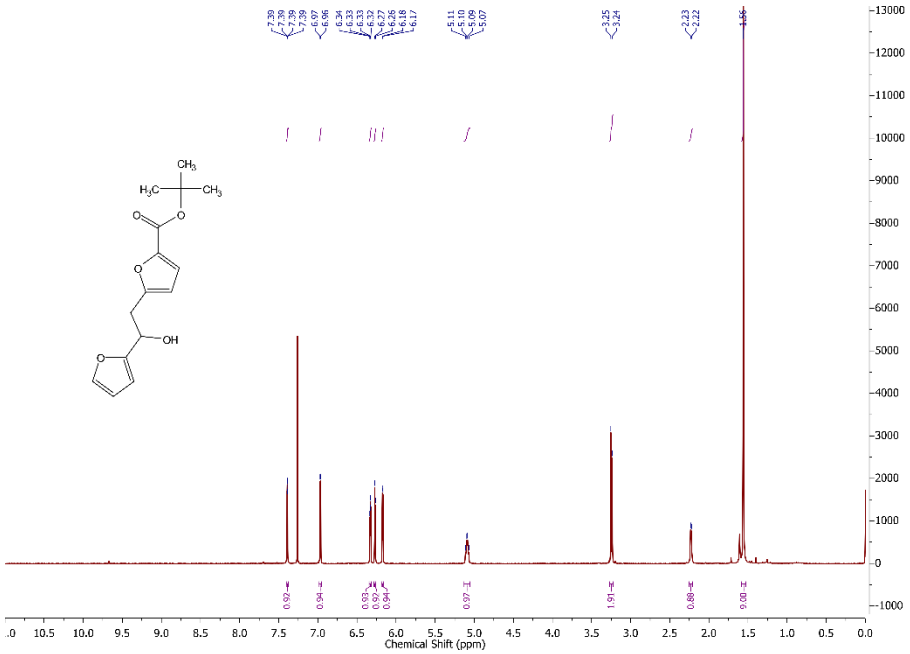

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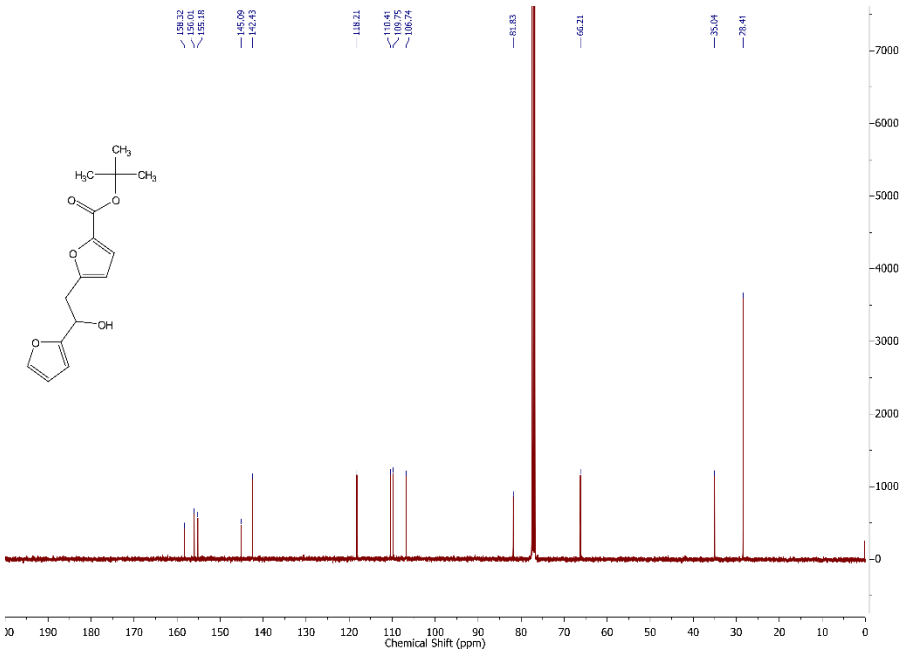

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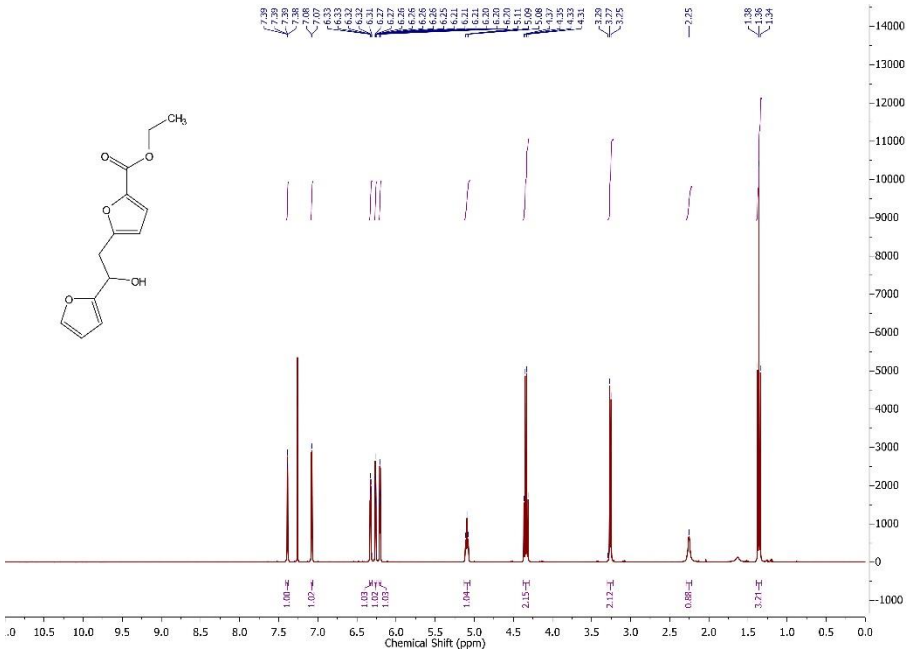

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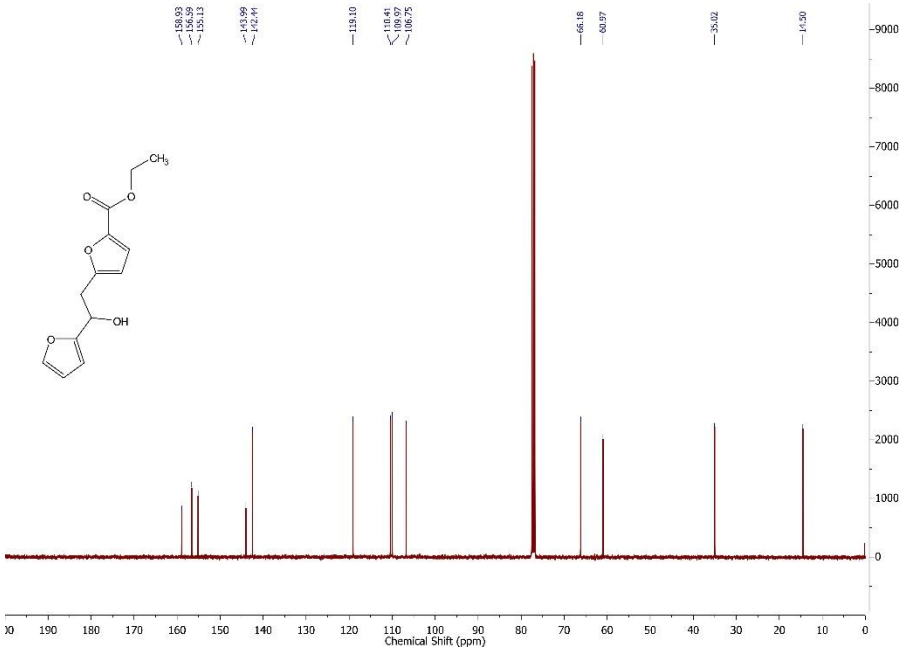

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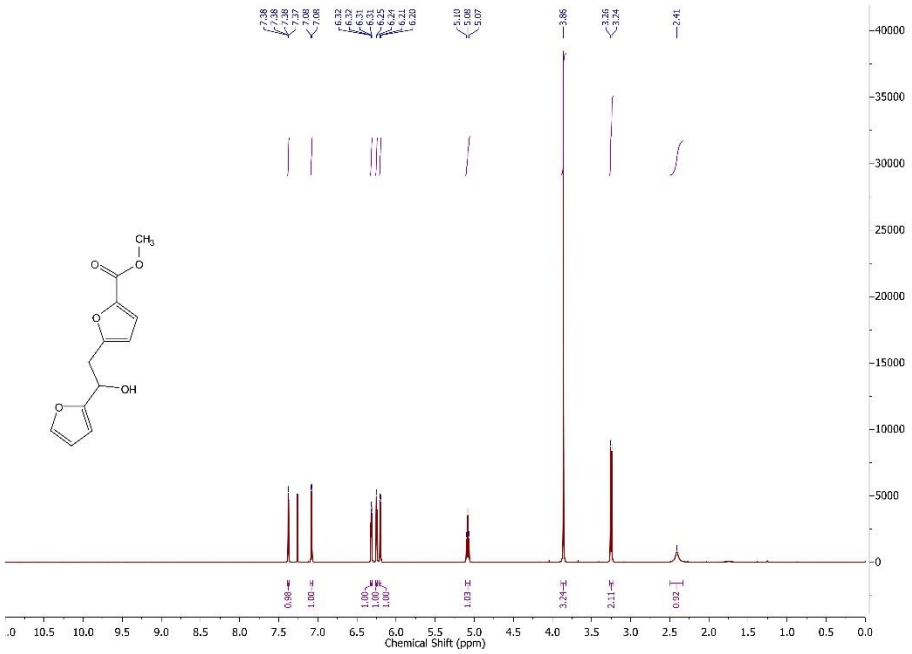

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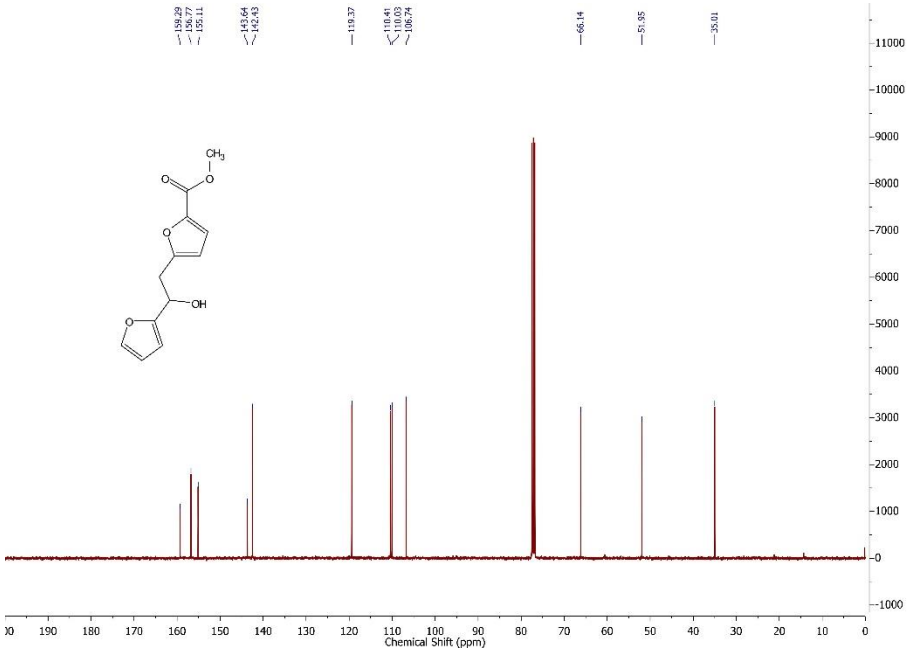

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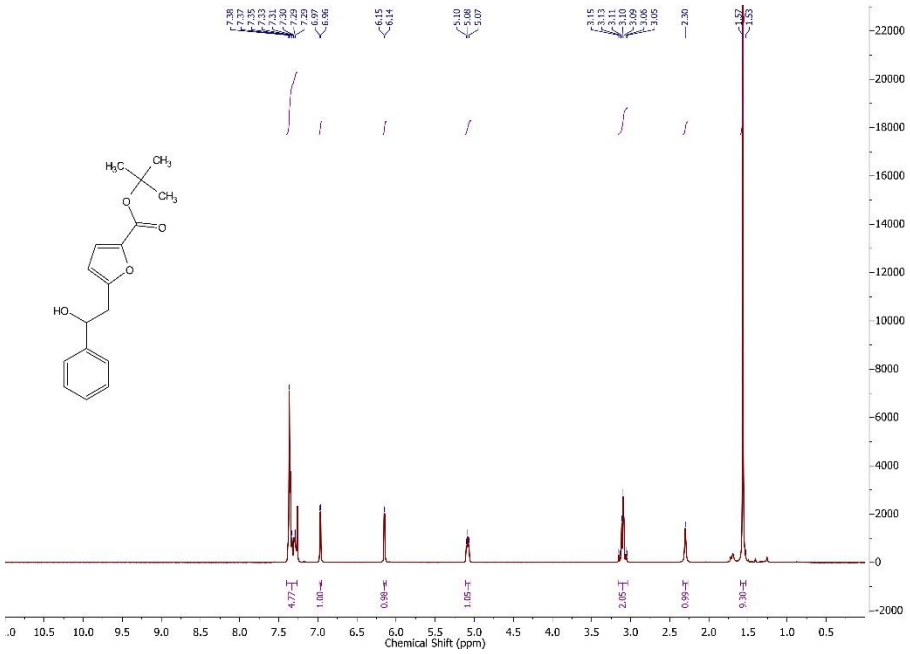

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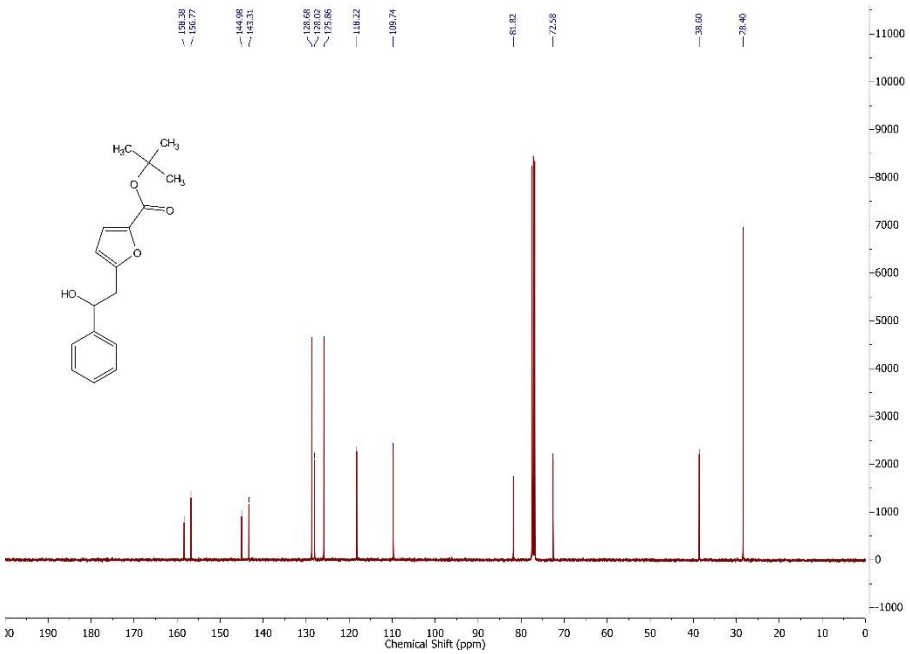

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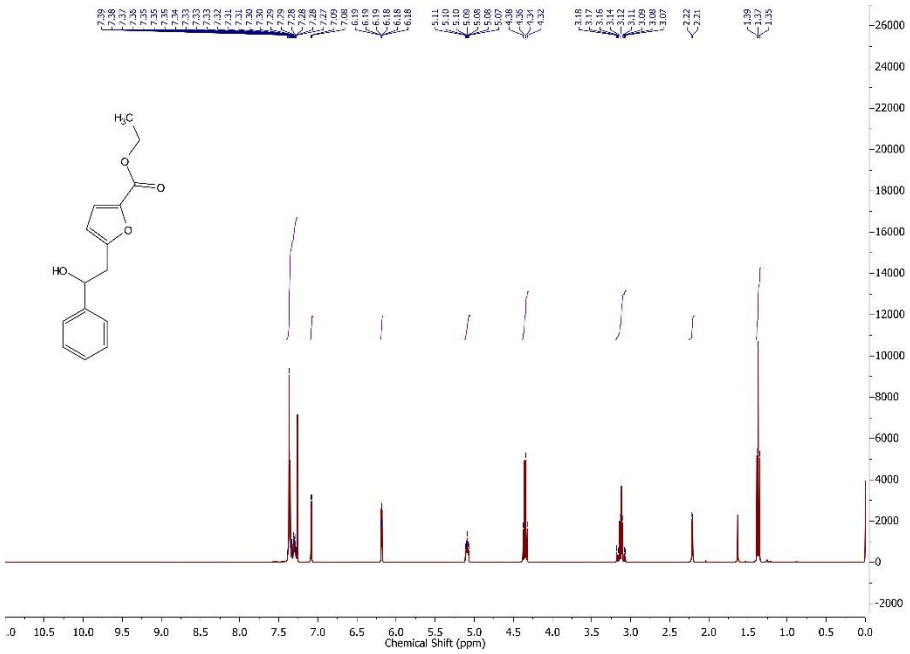

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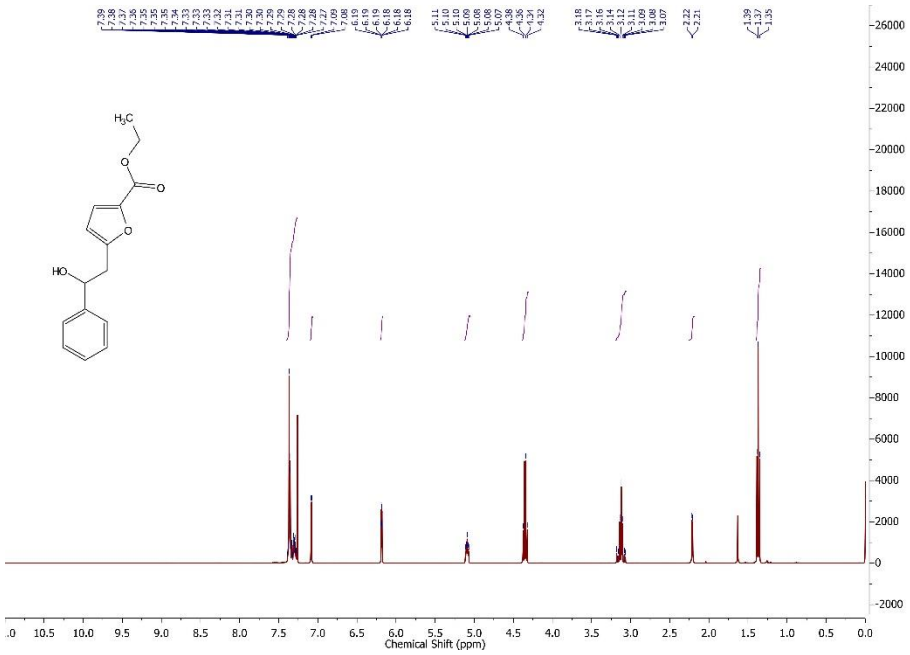

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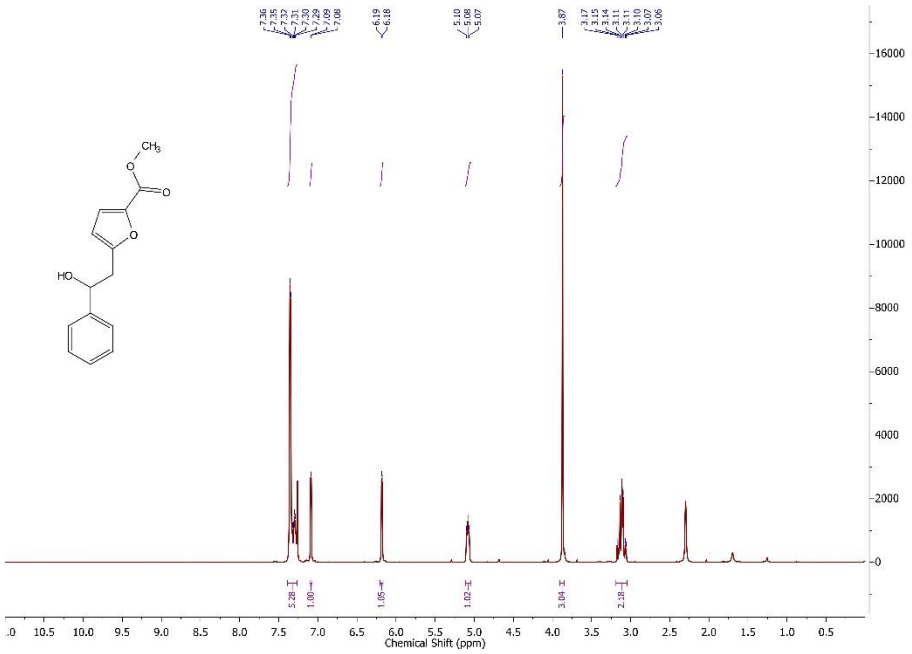

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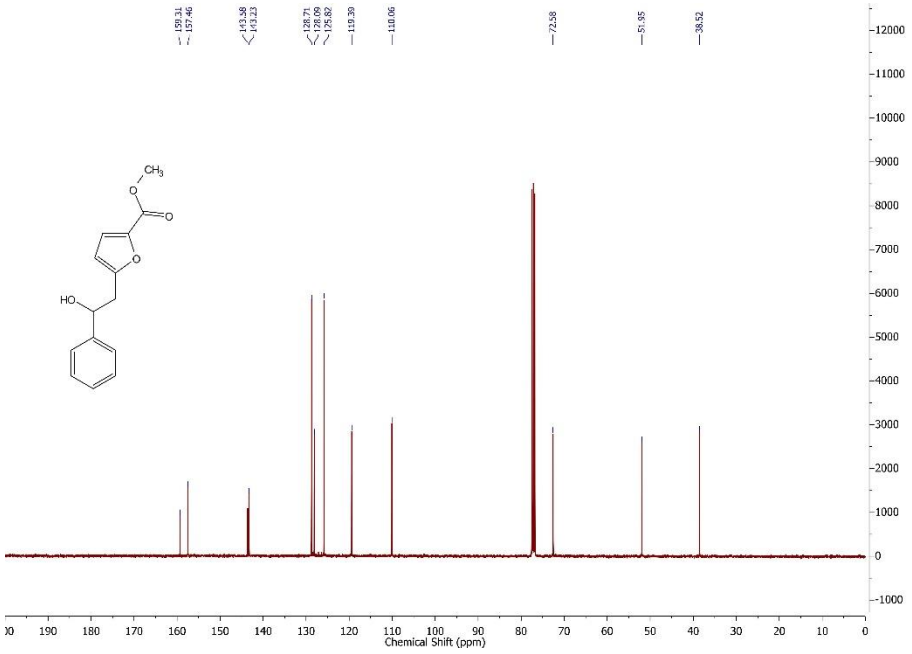

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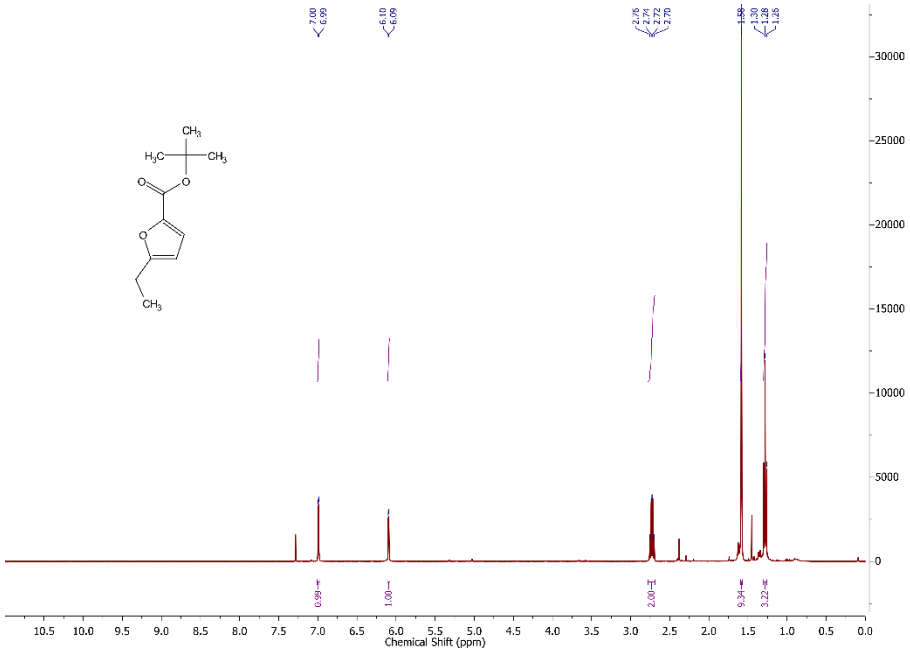

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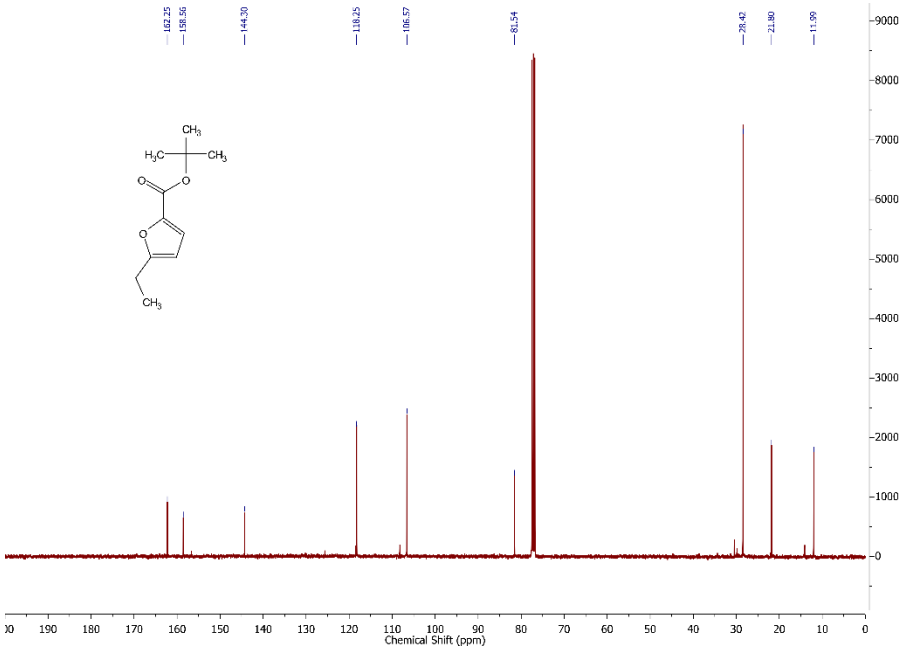

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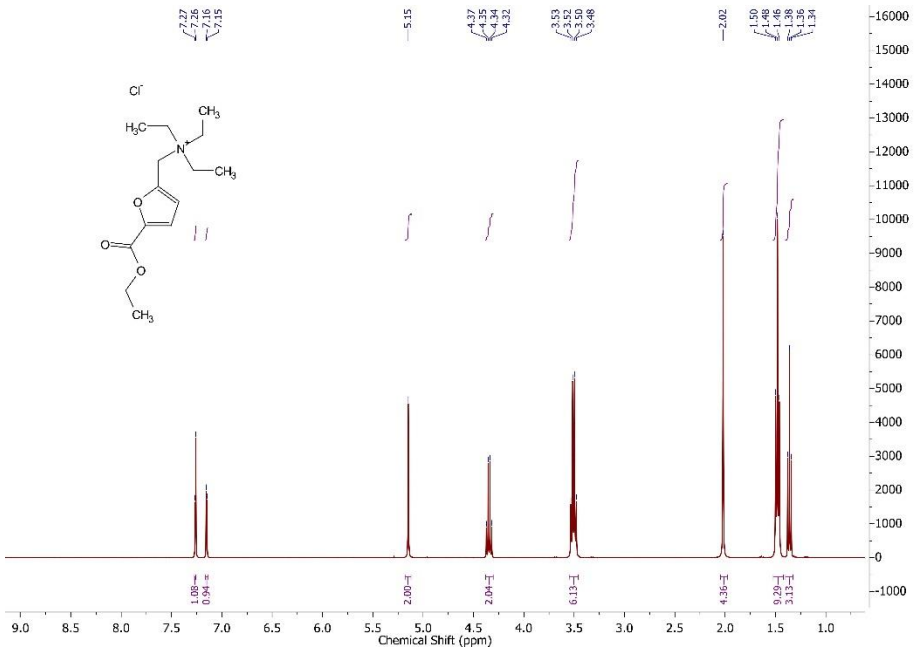
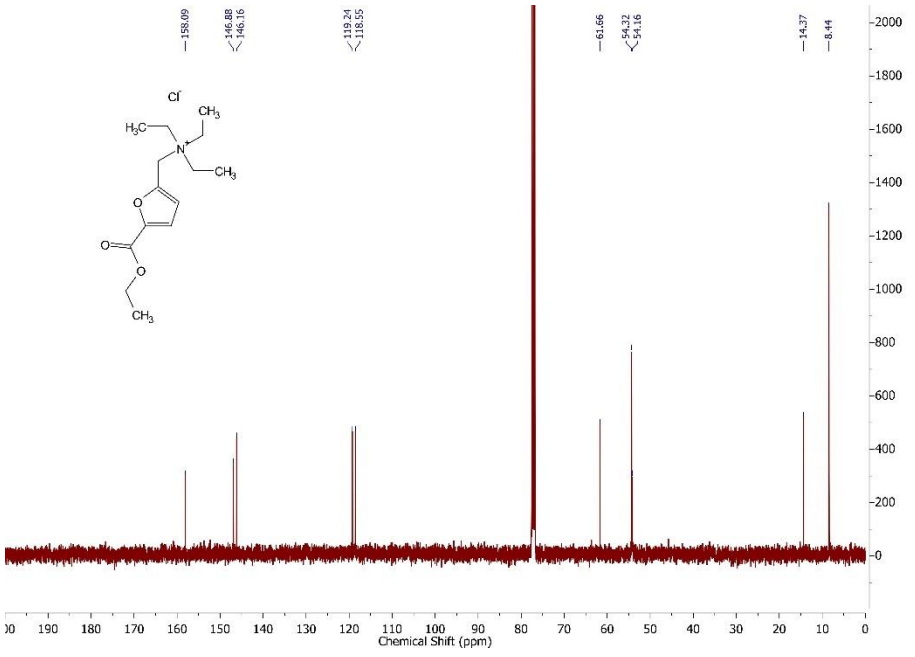


^{1}H NMR spectrum of N-((5-(ethoxycarbonyl)furan-2-yl)methyl)-N,N-diethylethanaminium chloride dihydrate **40** in $CDCl_3$



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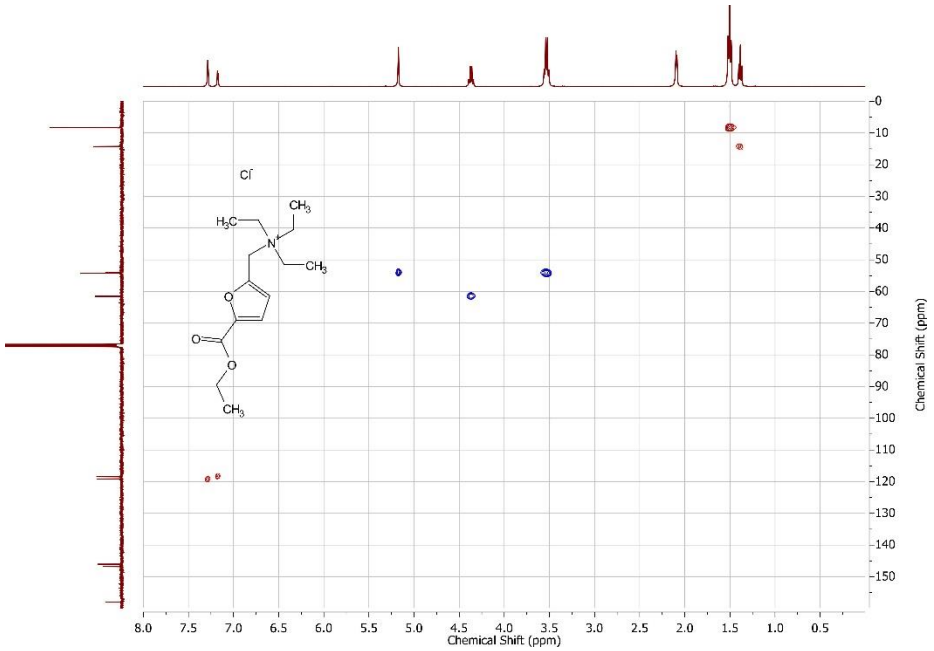

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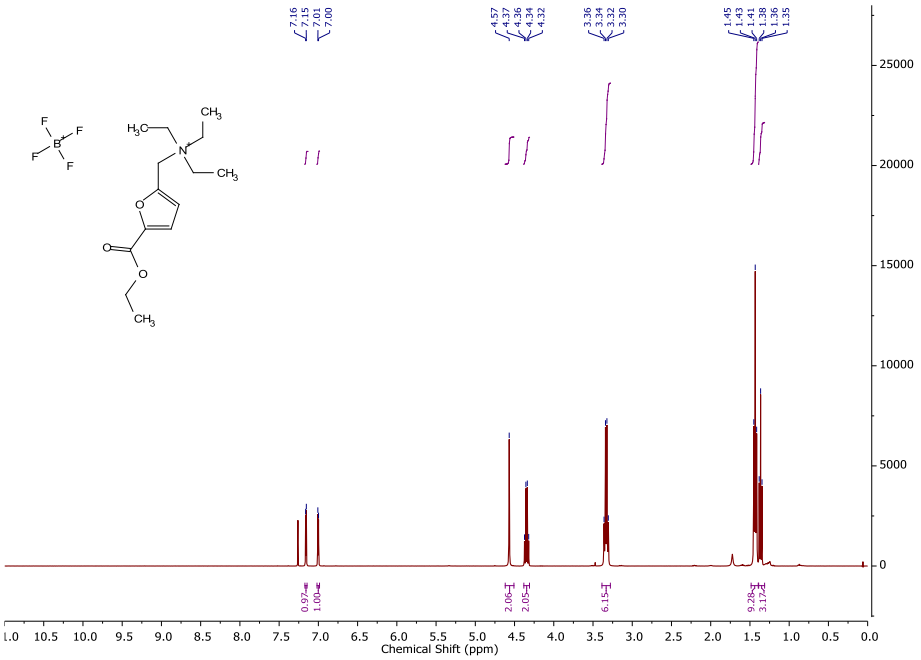

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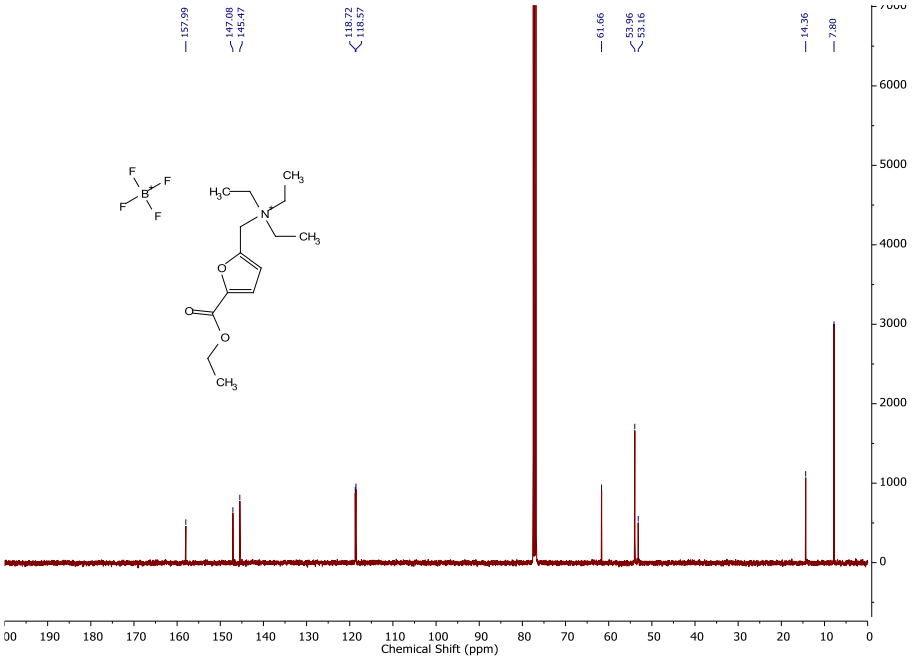
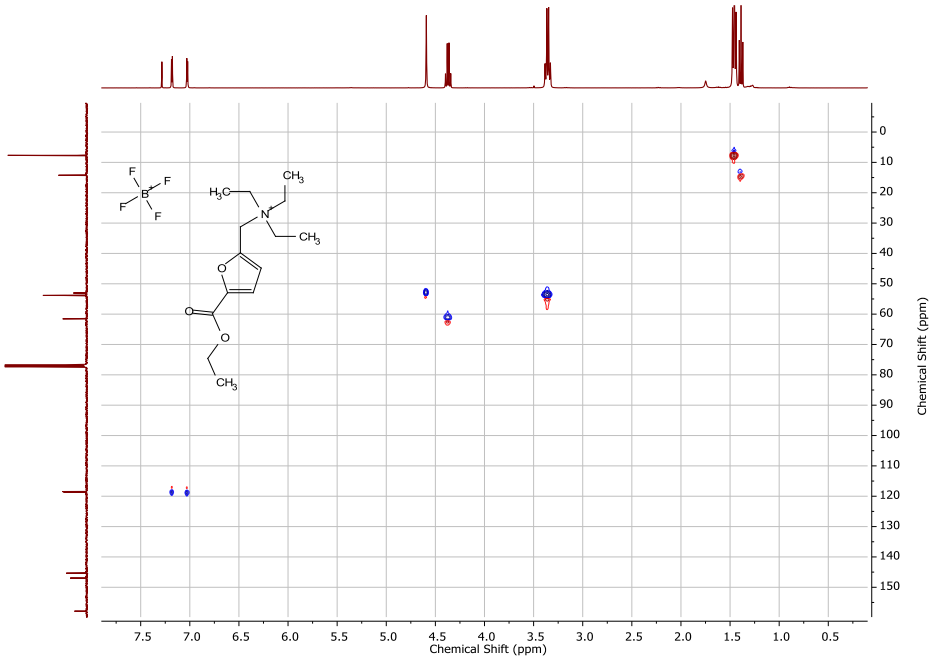
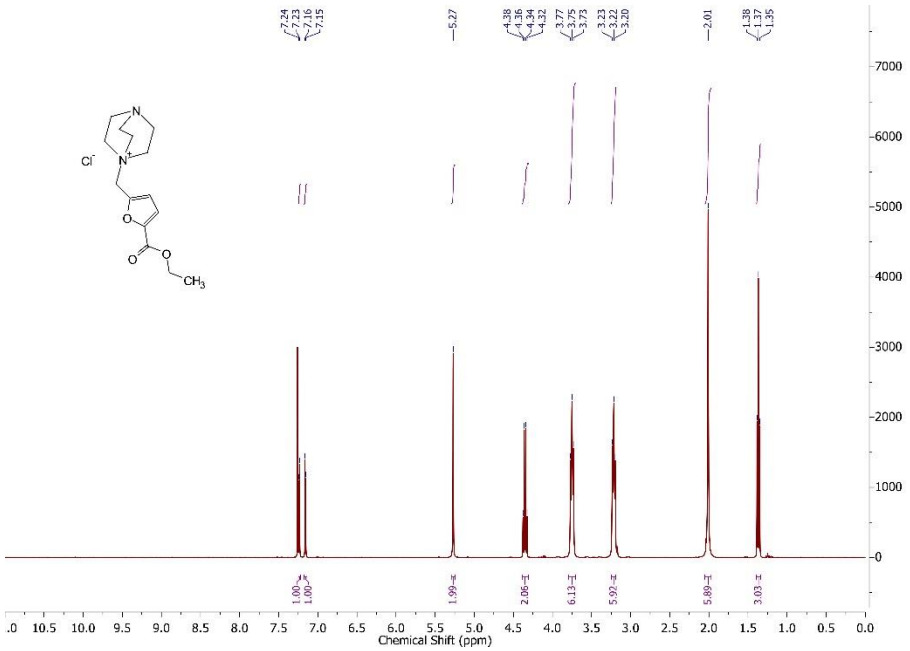


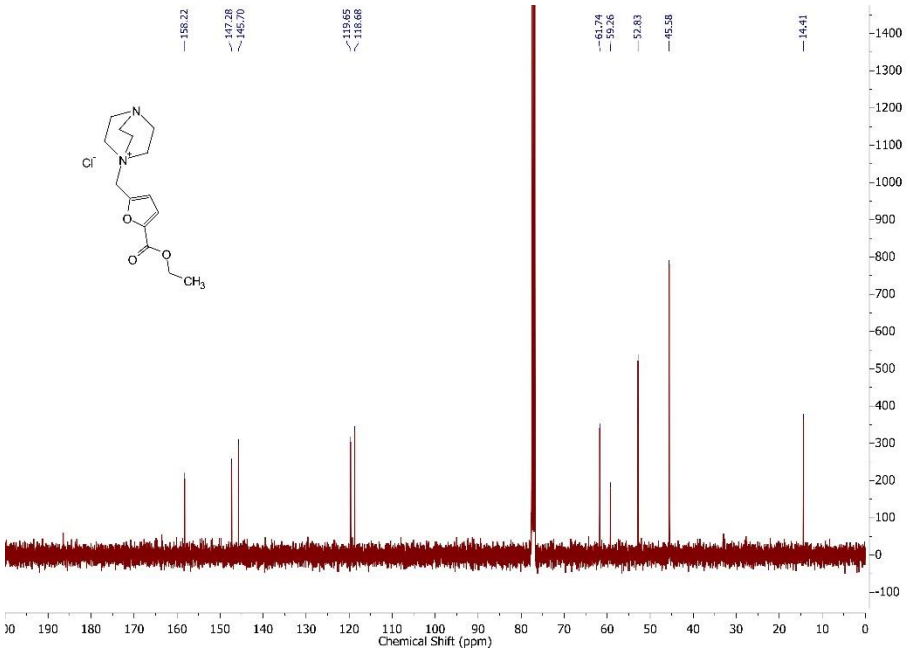
^{13}C NMR spectrum of N-((5-(ethoxycarbonyl)furan-2-yl)methyl)-N,N-diethylethanaminium tetrafluoroborate **41** in $CDCl_3$



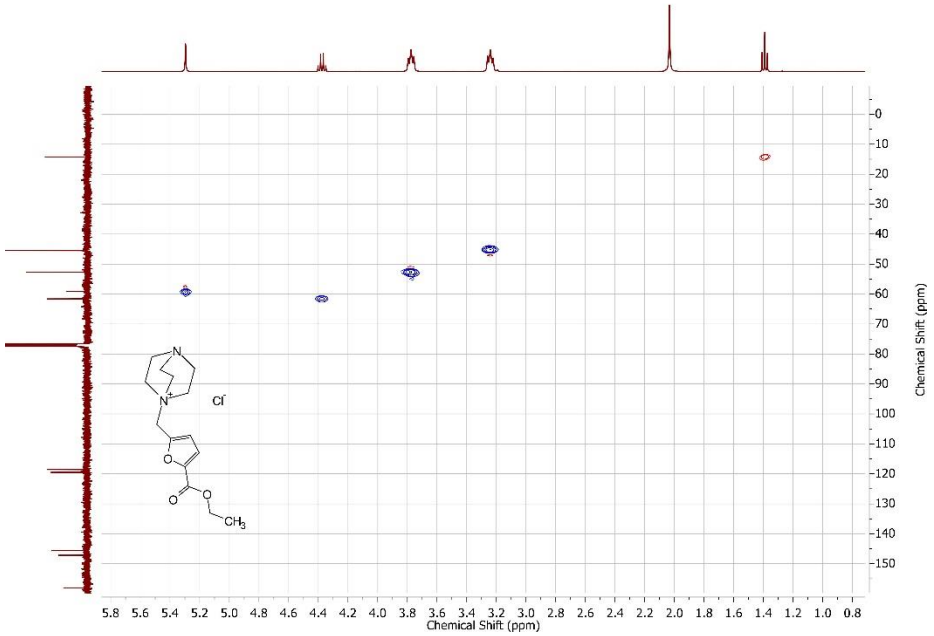
^{1}H-^{13}C HSQC NMR spectrum of N-((5-(ethoxycarbonyl)furan-2-yl)methyl)-N,N-diethylethanaminium tetrafluoroborate **41** in $CDCl_3$



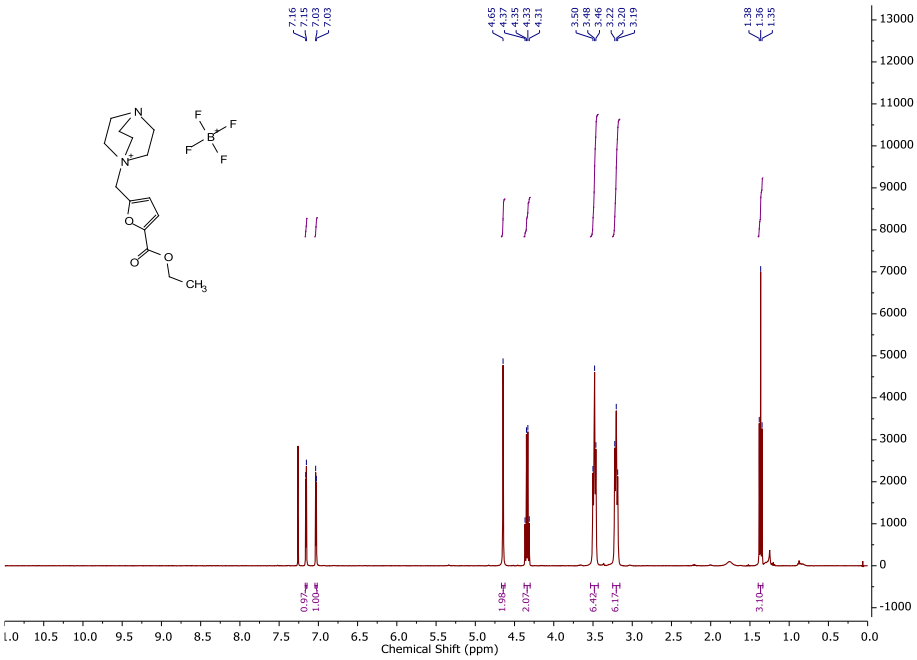
^{1}H NMR spectrum of 1-((5-(ethoxycarbonyl)furan-2-yl)methyl)-1,4-diazabicyclo[2.2.2]octan-1-ium chloride trihydrate **42** in $CDCl_3$



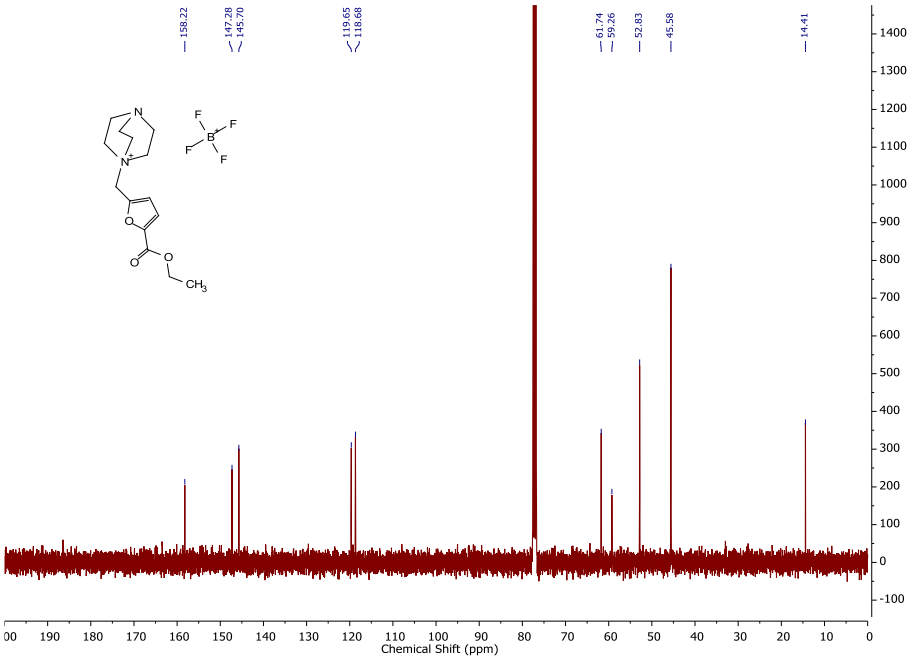
^{13}C NMR spectrum of 1-((5-(ethoxycarbonyl)furan-2-yl)methyl)-1,4-diazabicyclo[2.2.2]octan-1-ium chloride trihydrate **42** in $CDCl_3$



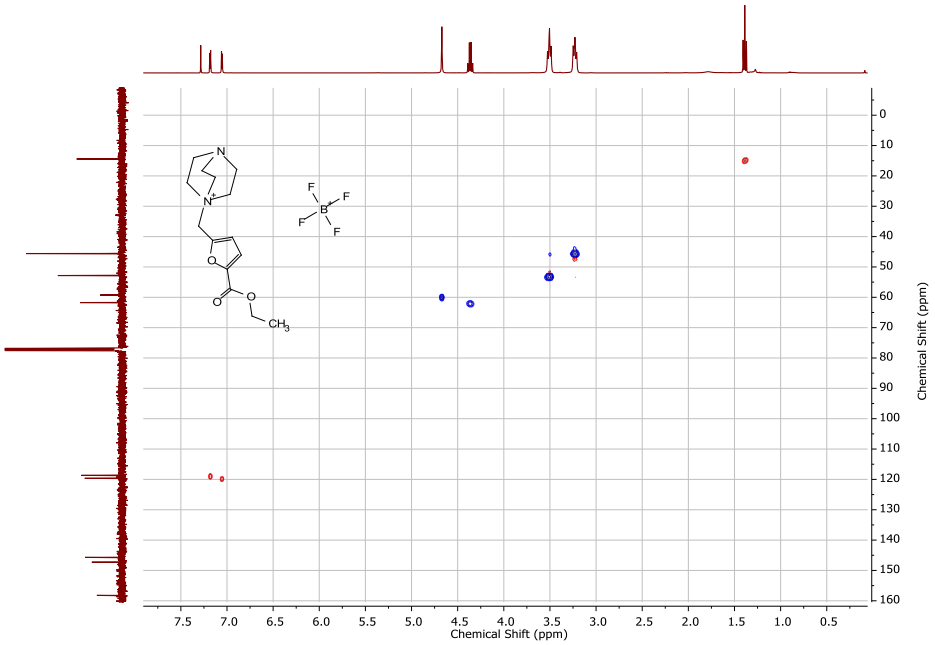
^{1}H-^{13}C HSQC NMR spectrum of 1-((5-(ethoxycarbonyl)furan-2-yl)methyl)-1,4-diazabicyclo[2.2.2]octan-1-ium chloride trihydrate **42** in $CDCl_3$



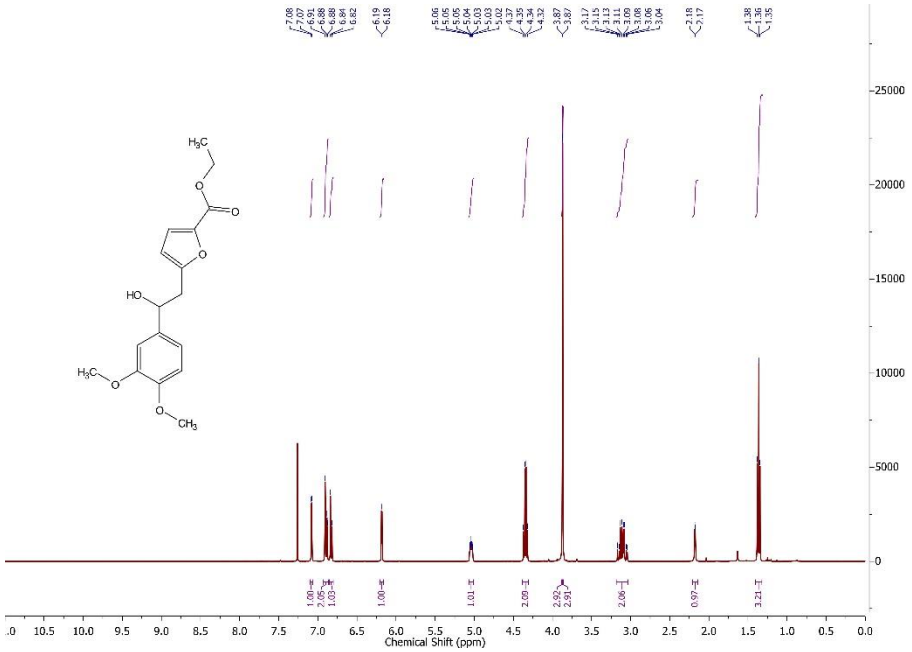
^{1}H NMR spectrum of 1-((5-(ethoxycarbonyl)furan-2-yl)methyl)-1,4-diazabicyclo[2.2.2]octan-1-ium tetrafluoroborate **43** in $CDCl_3$



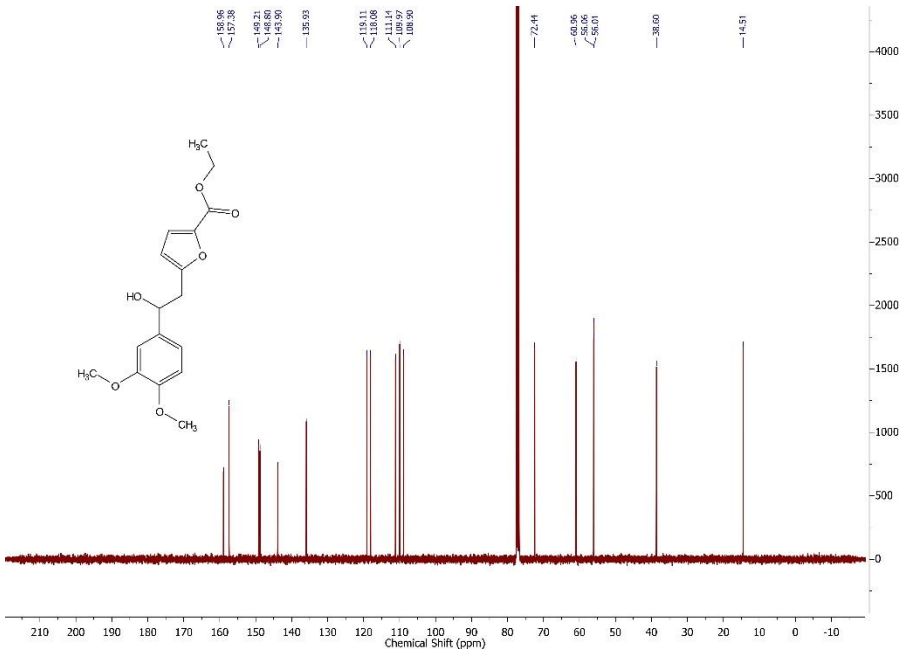
^{13}C NMR spectrum of 1-((5-(ethoxycarbonyl)furan-2-yl)methyl)-1,4-diazabicyclo[2.2.2]octan-1-ium tetrafluoroborate **43** in $CDCl_3$



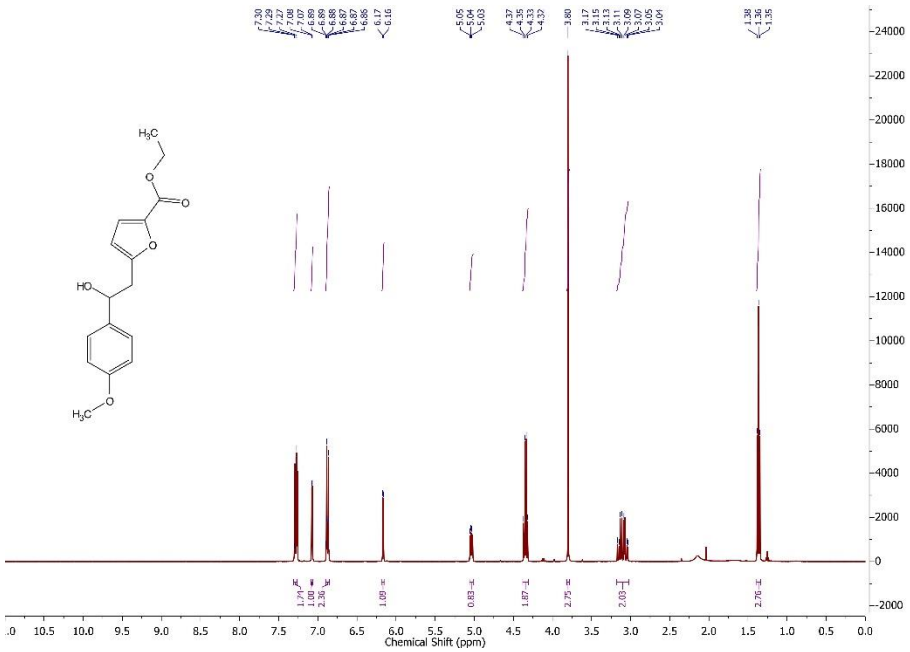
^{1}H-^{13}C HSQC NMR spectrum of 1-((5-(ethoxycarbonyl)furan-2-yl)methyl)-1,4-diazabicyclo[2.2.2]octan-1-ium tetrafluoroborate **43** in $CDCl_3$



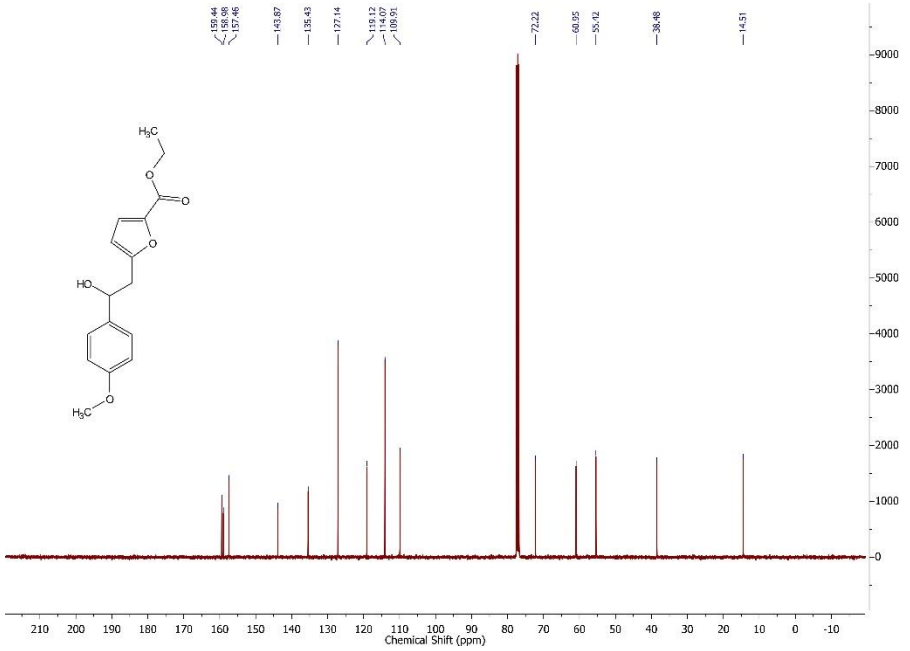
^{1}H NMR spectrum of ethyl 5-(2-(3,4-dimethoxyphenyl)-2-hydroxyethyl)furan-2-carboxylate **47** in $CDCl_3$



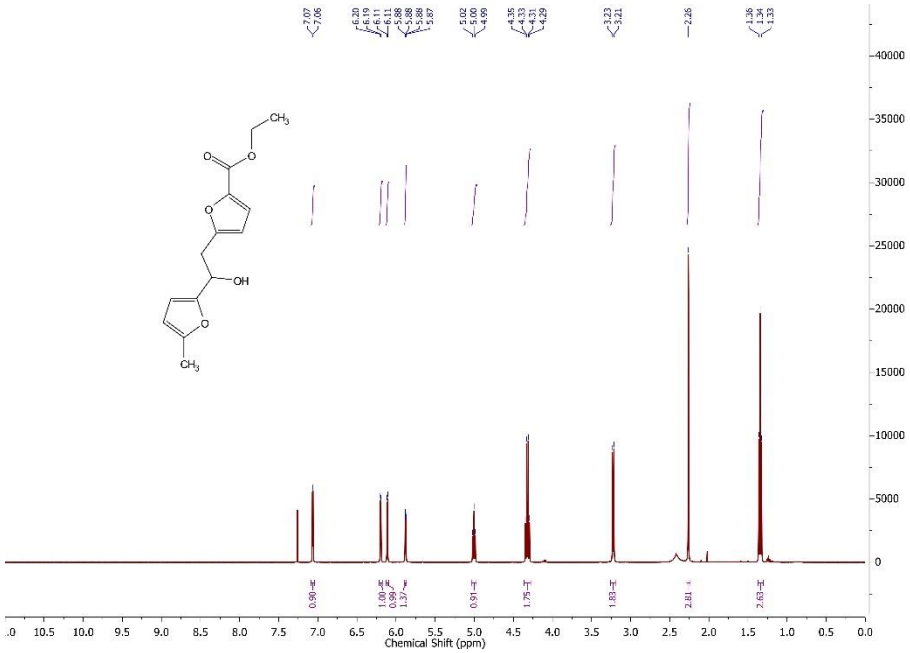
^{13}C NMR spectrum of ethyl 5-(2-(3,4-dimethoxyphenyl)-2-hydroxyethyl)furan-2-carboxylate **47** in $CDCl_3$



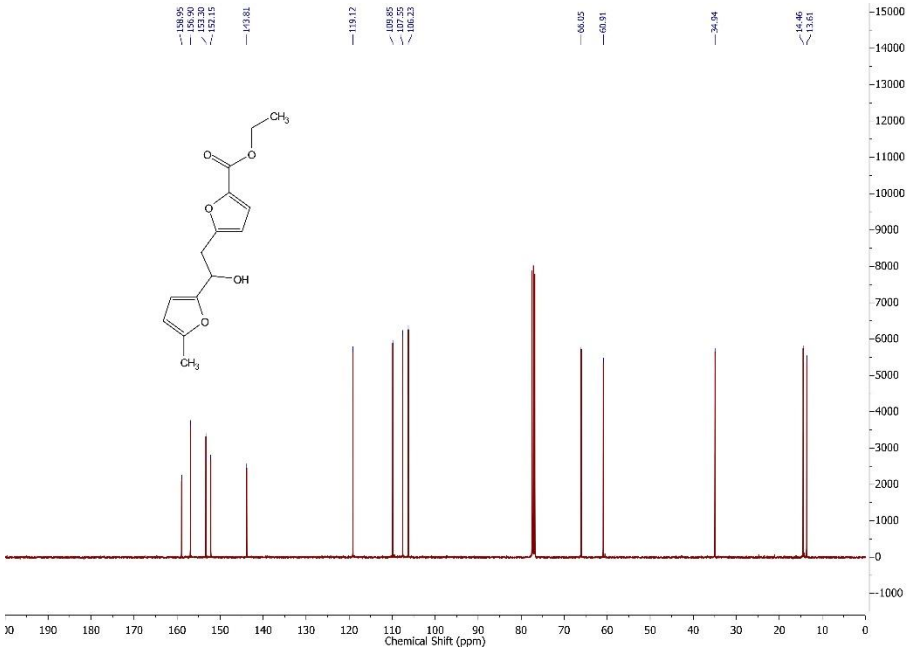
^{1}H NMR spectrum of ethyl 5-(2-hydroxy-2-(4-methoxyphenyl)ethyl)furan-2-carboxylate **48** in $CDCl_3$



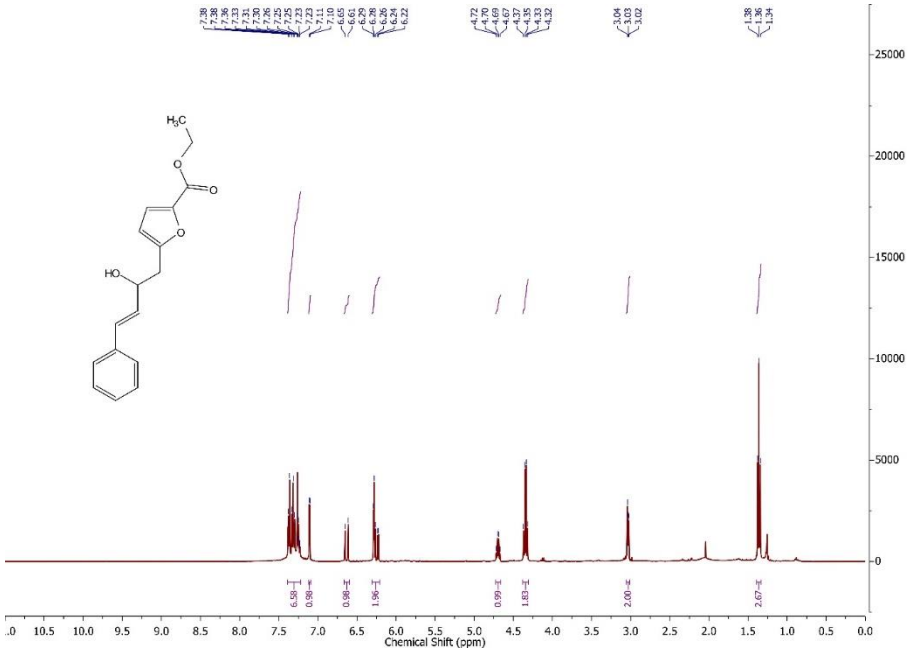
^{13}C NMR spectrum of ethyl 5-(2-hydroxy-2-(4-methoxyphenyl)ethyl)furan-2-carboxylate **48** in $CDCl_3$



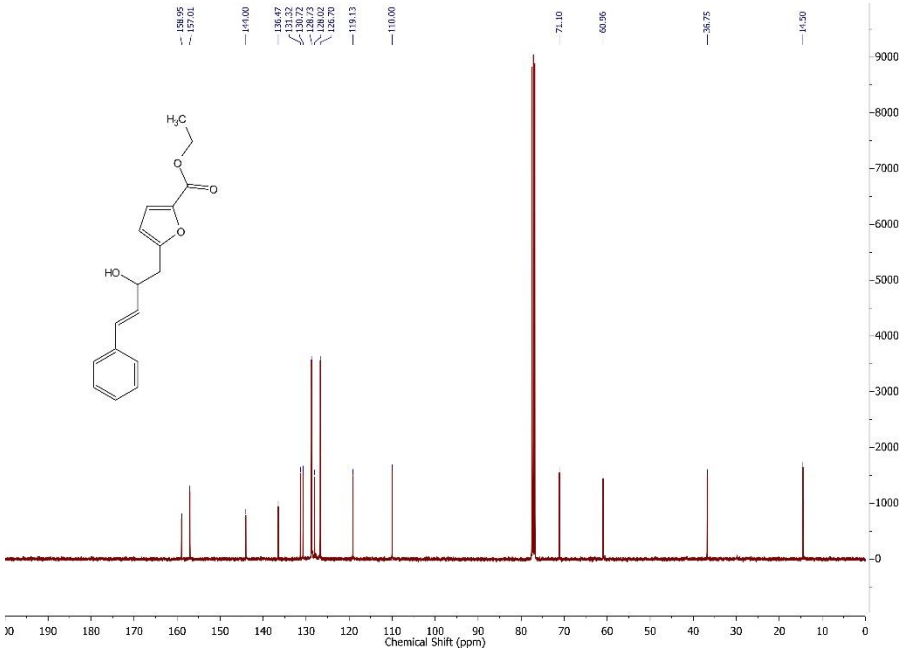
^{1}H NMR spectrum of ethyl 5-(2-hydroxy-2-(5-methylfuran-2-yl)ethyl)furan-2-carboxylate **49** in $CDCl_3$



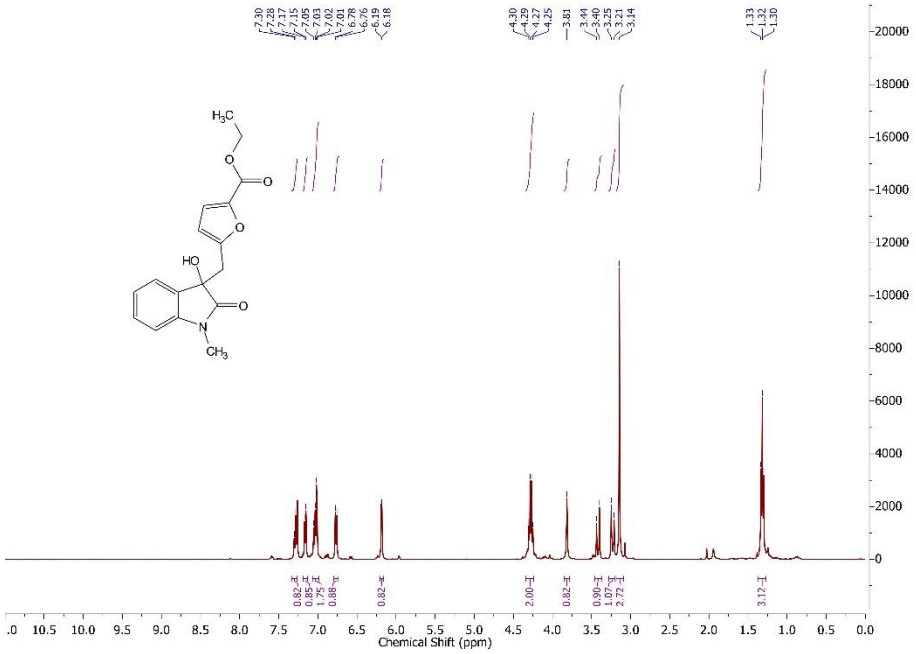
^{13}C NMR spectrum of ethyl 5-(2-hydroxy-2-(5-methylfuran-2-yl)ethyl)furan-2-carboxylate **49** in $CDCl_3$



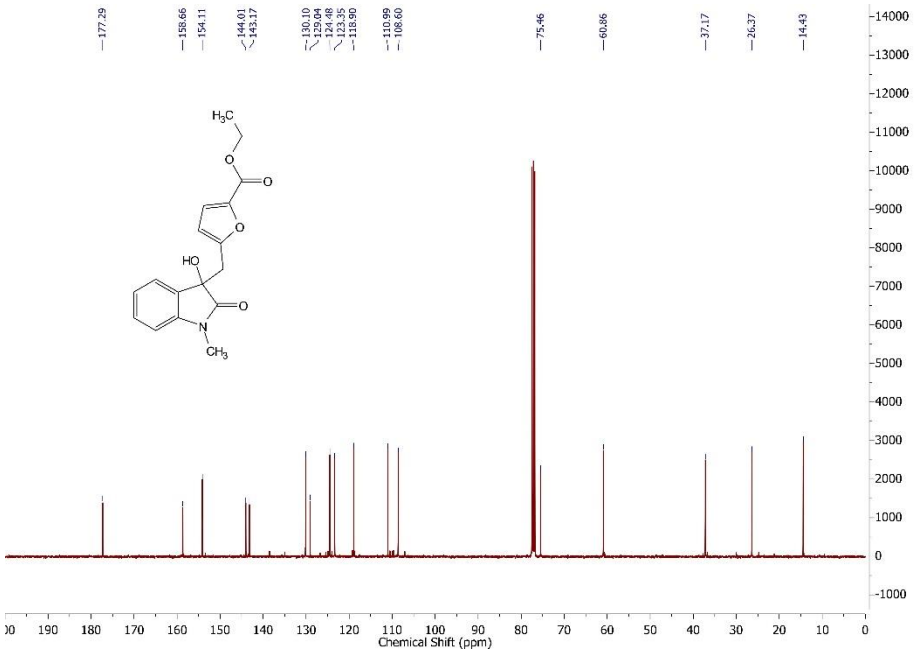
^{1}H NMR spectrum of ethyl (*E*)-5-(2-hydroxy-4-phenylbut-3-en-1-yl)furan-2-carboxylate **50** in $CDCl_3$



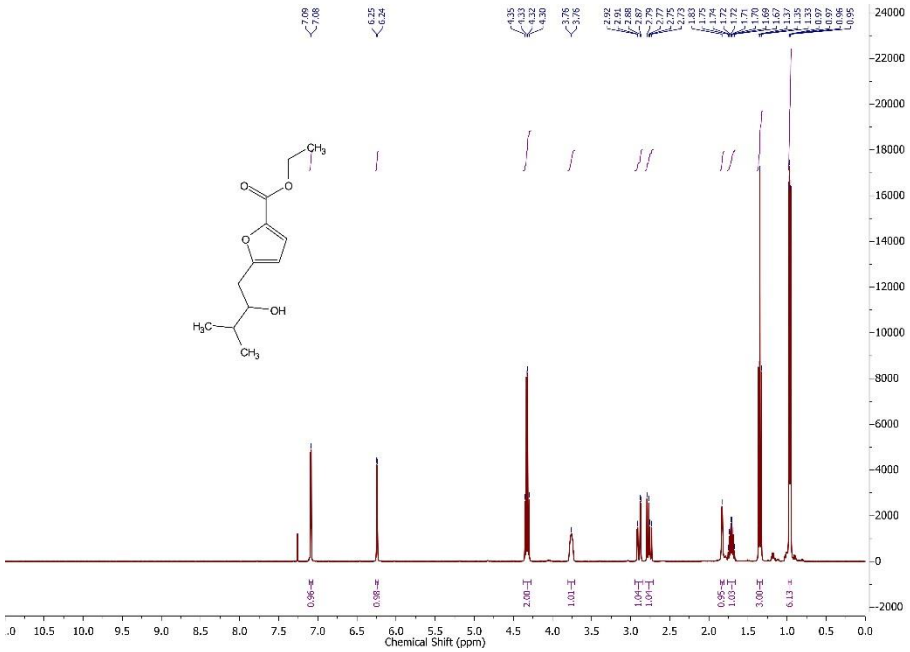
^{13}C NMR spectrum of ethyl (*E*)-5-(2-hydroxy-4-phenylbut-3-en-1-yl)furan-2-carboxylate **50** in $CDCl_3$



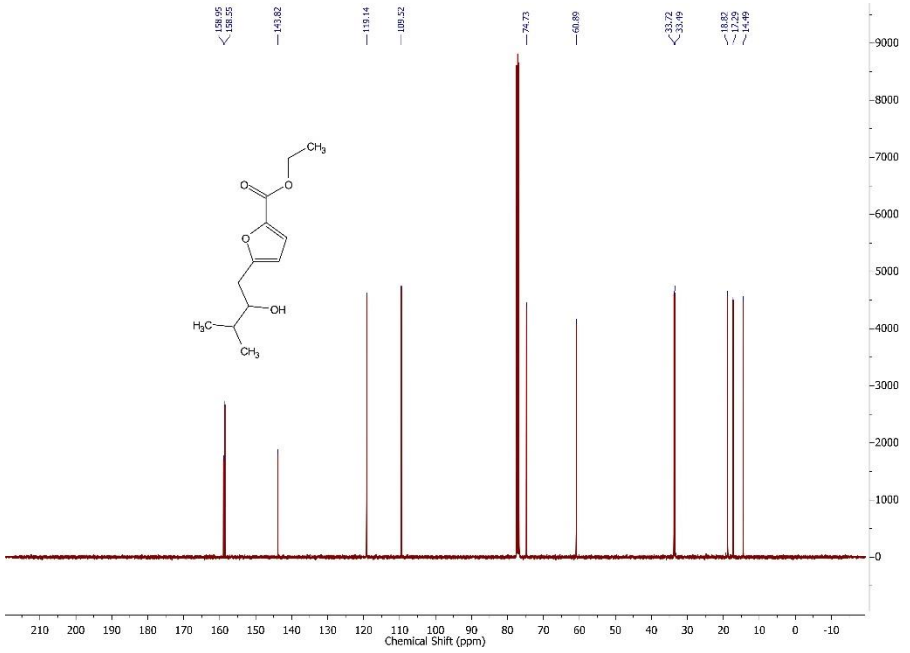
^{1}H NMR spectrum of ethyl 5-((3-hydroxy-1-methyl-2-oxoindolin-3-yl)methyl)furan-2-carboxylate **51** in $CDCl_3$



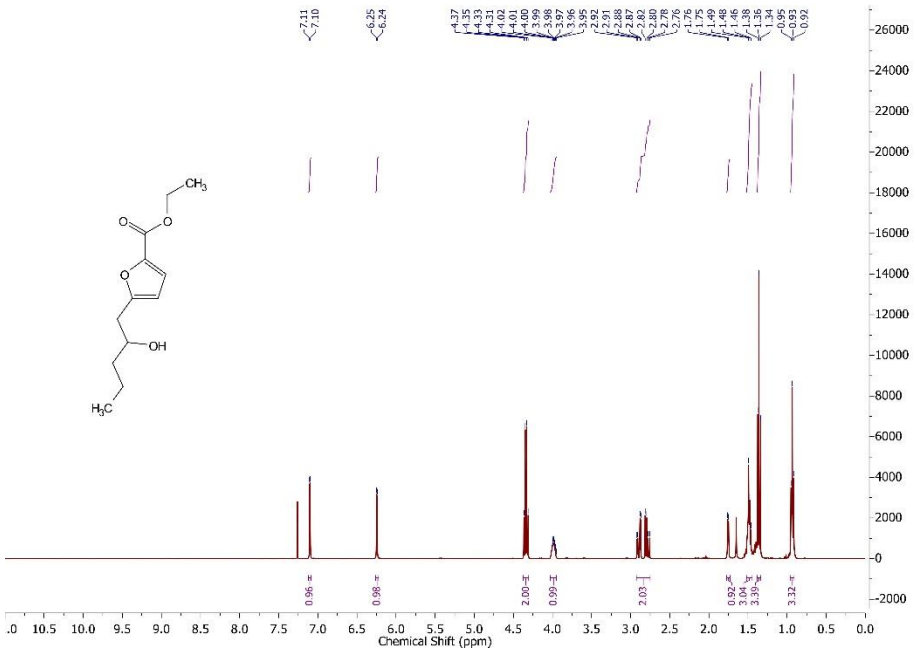
^{13}C NMR spectrum of ethyl 5-((3-hydroxy-1-methyl-2-oxoindolin-3-yl)methyl)furan-2-carboxylate **51** in $CDCl_3$



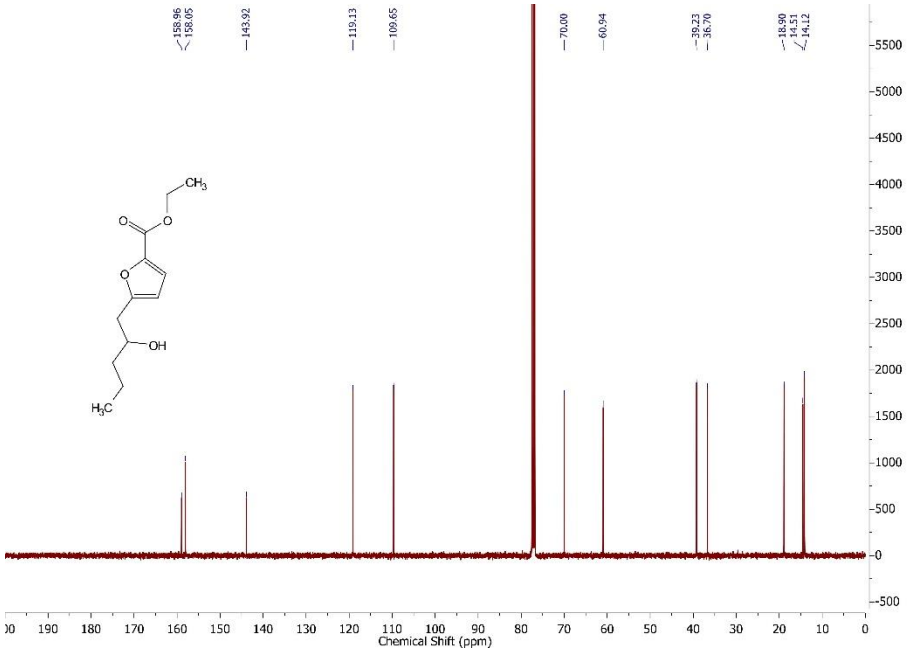
^{1}H NMR spectrum of ethyl 5-(2-hydroxy-3-methylbutyl)furan-2-carboxylate **52** in $CDCl_3$



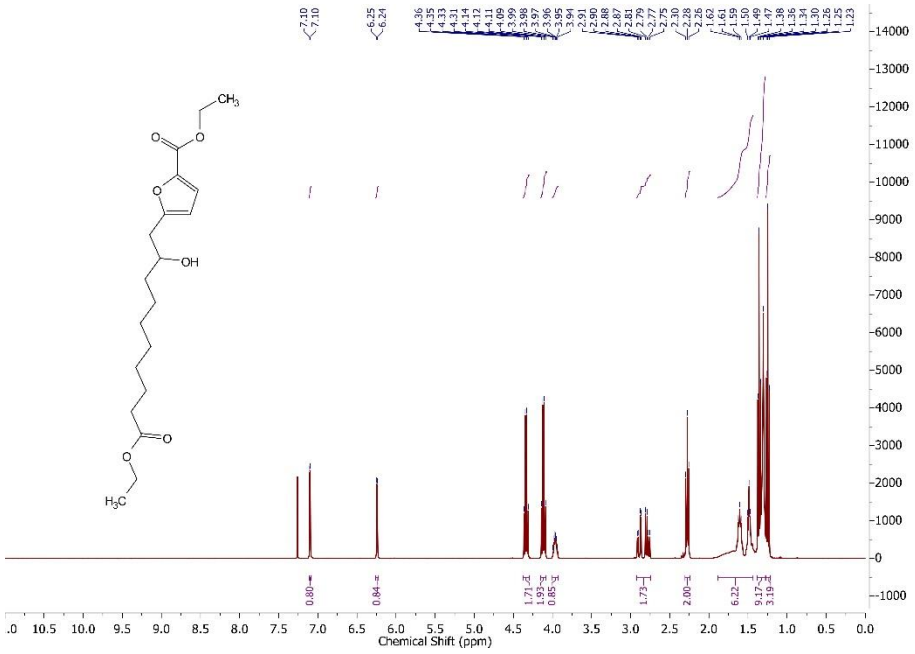
^{13}C NMR spectrum of ethyl 5-(2-hydroxy-3-methylbutyl)furan-2-carboxylate **52** in $CDCl_3$



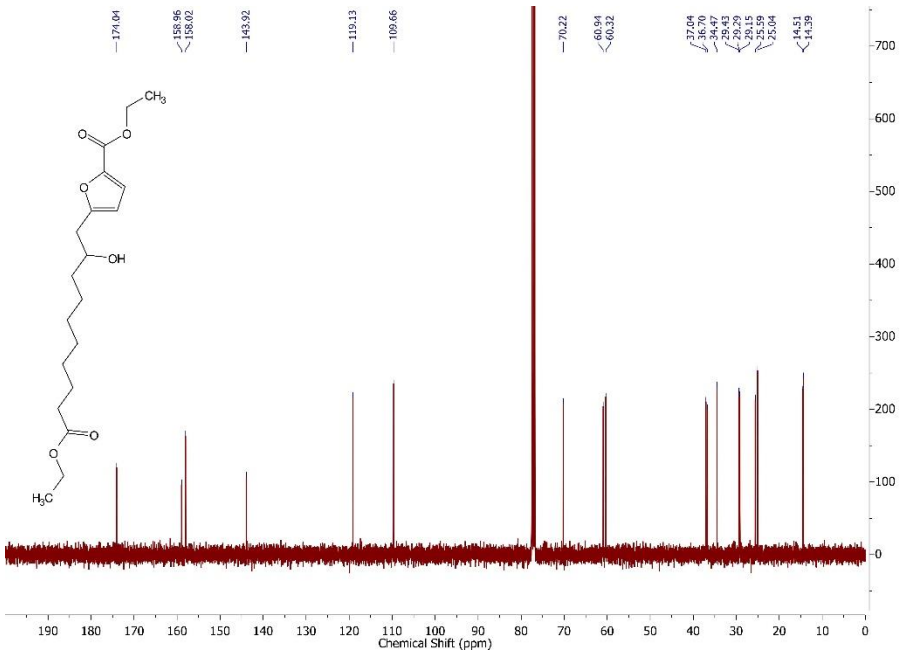
^{1}H NMR spectrum of ethyl 5-(2-hydroxypentyl)furan-2-carboxylate **53** in $CDCl_3$



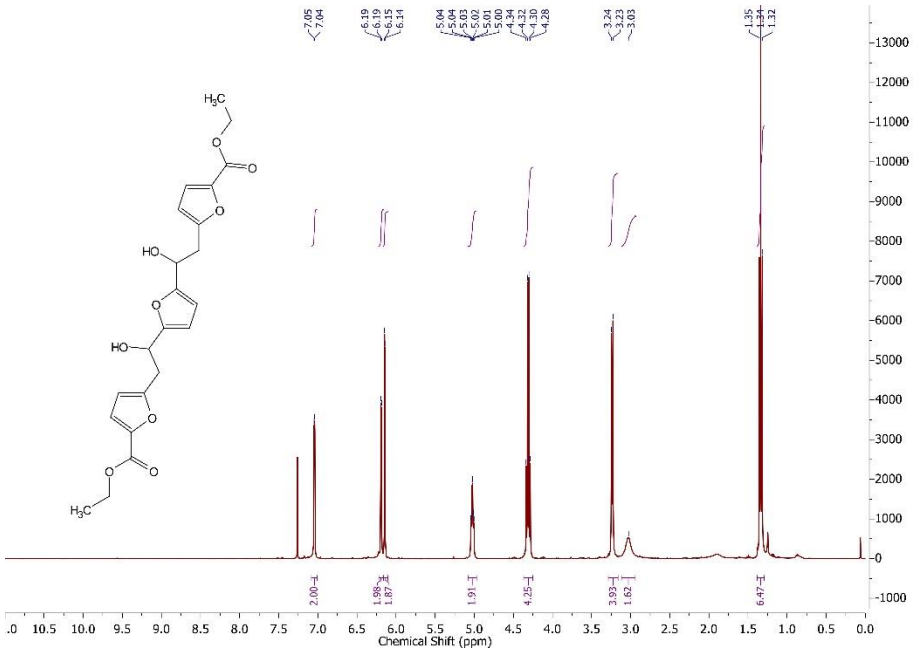
^{13}C NMR spectrum of ethyl 5-(2-hydroxypentyl)furan-2-carboxylate **53** in $CDCl_3$



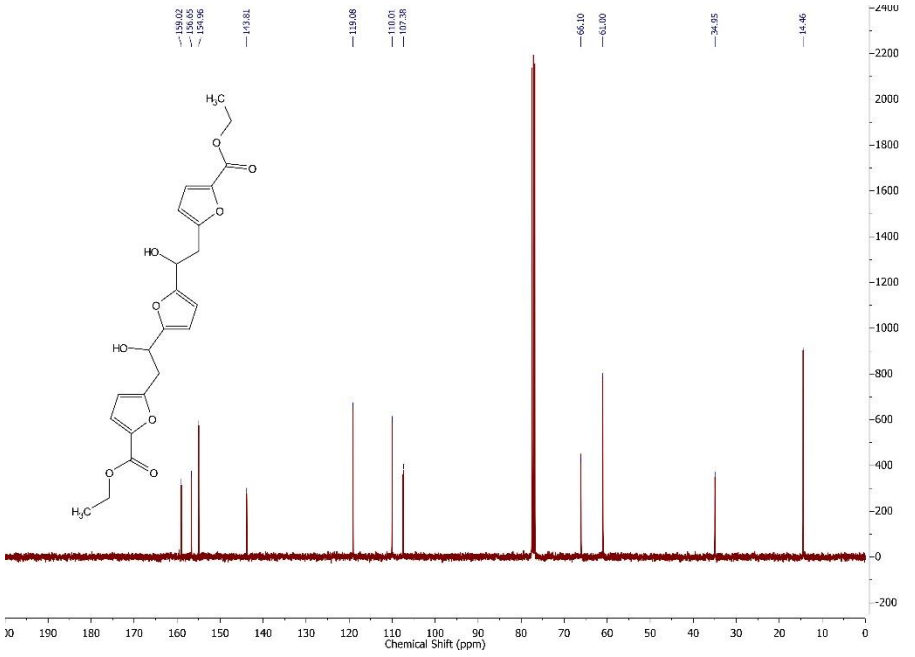
^{1}H NMR spectrum of ethyl 5-(10-ethoxy-2-hydroxy-10-oxodecyl)furan-2-carboxylate **54** in $CDCl_3$



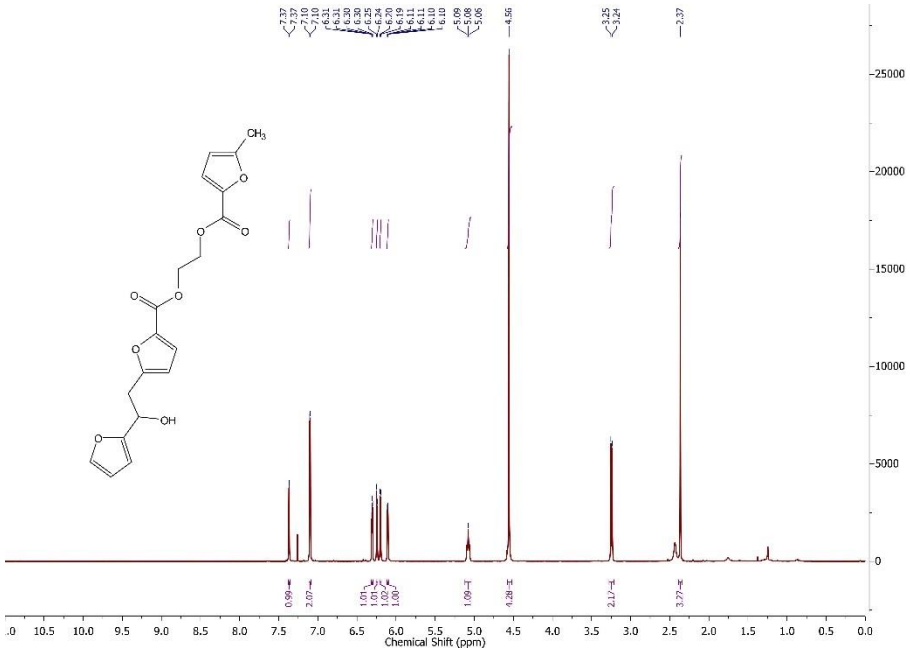
^{13}C NMR spectrum of ethyl 5-(10-ethoxy-2-hydroxy-10-oxodecyl)furan-2-carboxylate **54** in $CDCl_3$



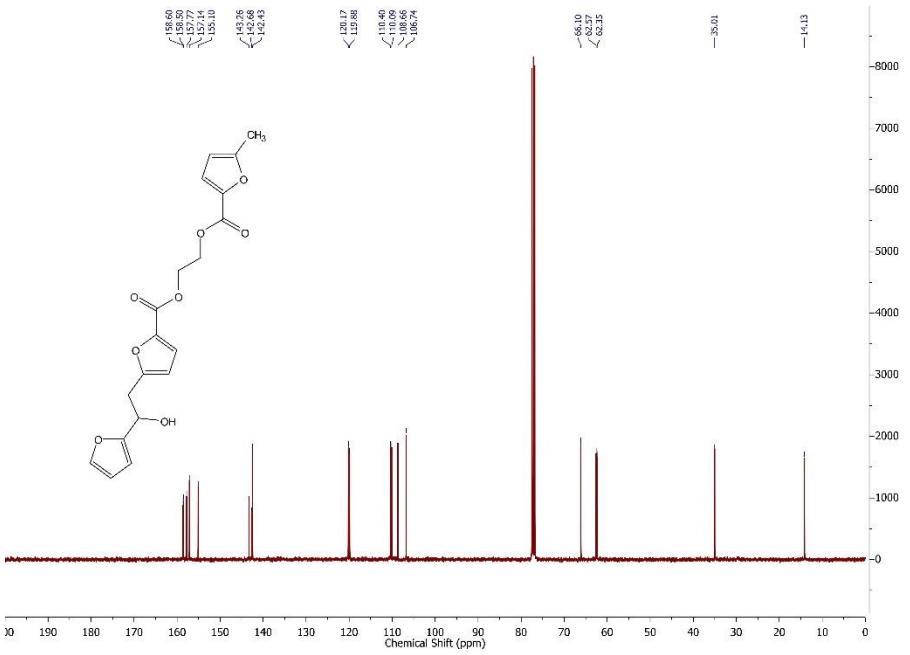
^{1}H NMR spectrum of diethyl 5,5'-(furan-2,5-diylbis(2-hydroxyethane-2,1-diyl))bis(furan-2-carboxylate) **58** in $CDCl_3$



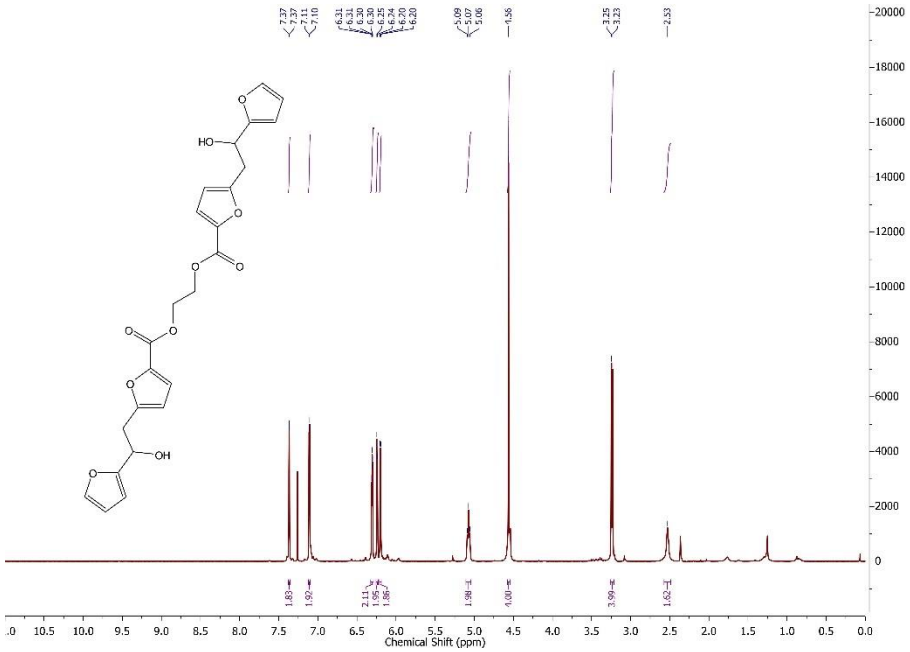
^{13}C NMR spectrum of diethyl 5,5'-(furan-2,5-diylbis(2-hydroxyethane-2,1-diyl))bis(furan-2-carboxylate) **58** in $CDCl_3$



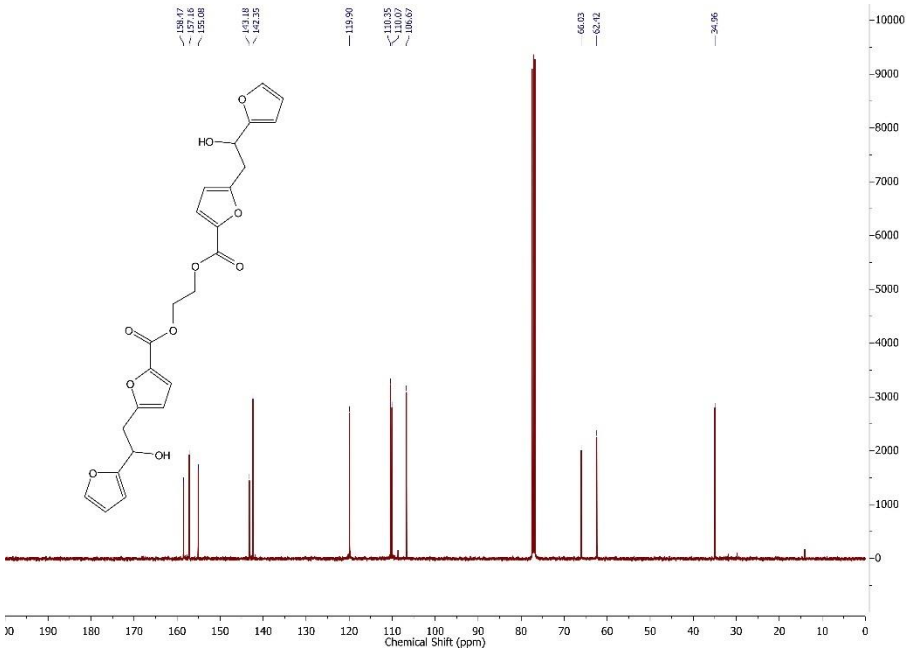
^{1}H NMR spectrum of 2-((5-(2-(furan-2-yl)-2-hydroxyethyl)furan-2-carbonyl)oxy)ethyl 5-methylfuran-2-carboxylate **59** in $CDCl_3$



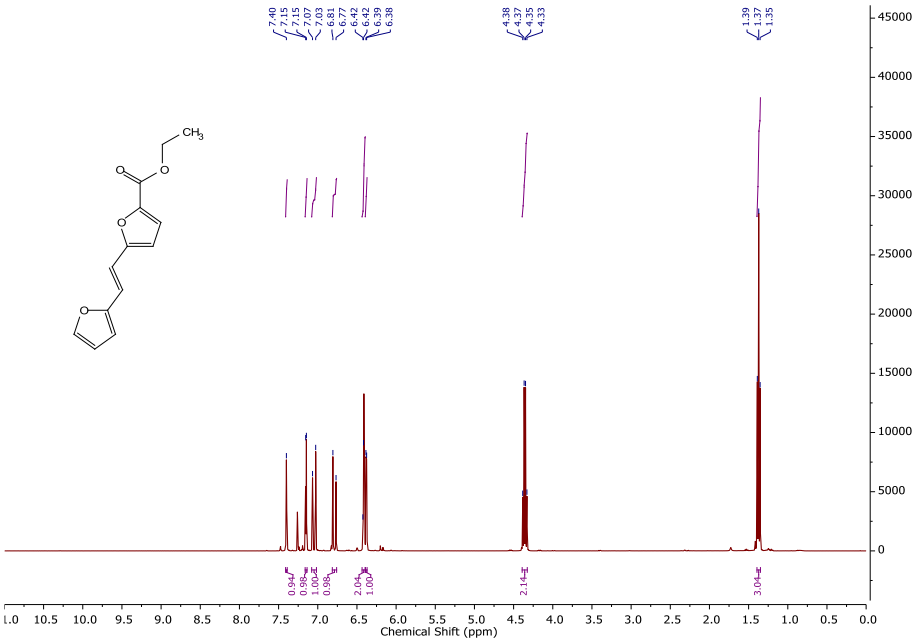
^{13}C NMR spectrum of 2-((5-(2-(furan-2-yl)-2-hydroxyethyl)furan-2-carbonyl)oxy)ethyl 5-methylfuran-2-carboxylate **59** in $CDCl_3$



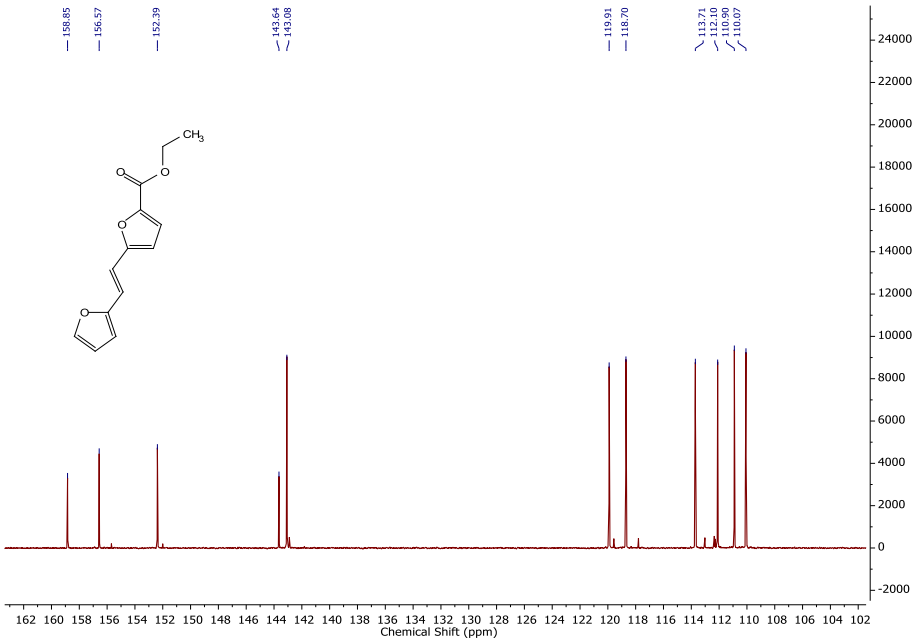
^{1}H NMR spectrum of ethane-1,2-diyl bis(5-(2-(furan-2-yl)-2-hydroxyethyl)furan-2-carboxylate) **60** in $CDCl_3$



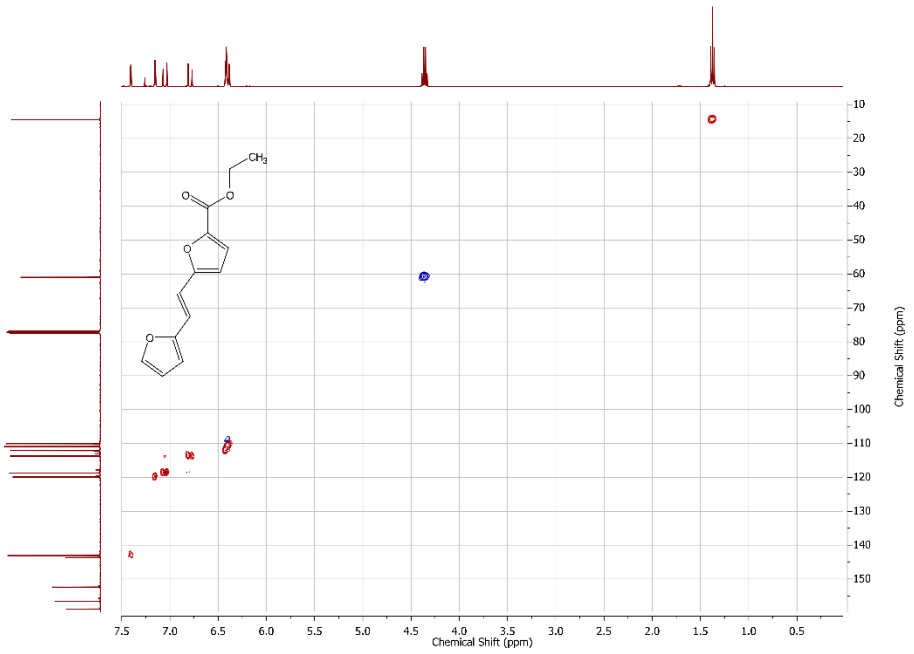
^{13}C NMR spectrum of ethane-1,2-diyl bis(5-(2-(furan-2-yl)-2-hydroxyethyl)furan-2-carboxylate) **60** in $CDCl_3$



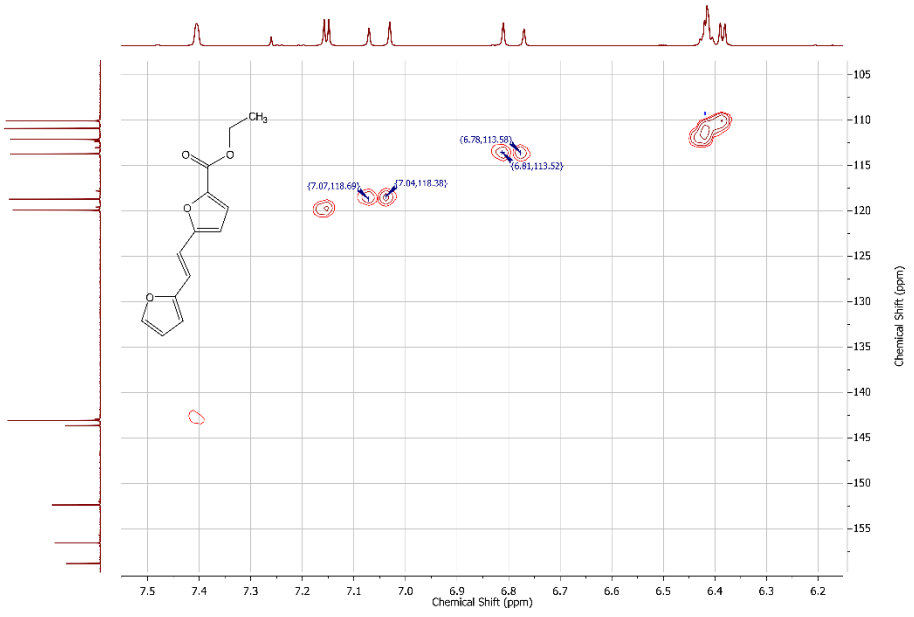
^{1}H NMR spectrum of ethyl (*E*)-5-(2-(furan-2-yl)vinyl)furan-2-carboxylate **63** in $CDCl_3$



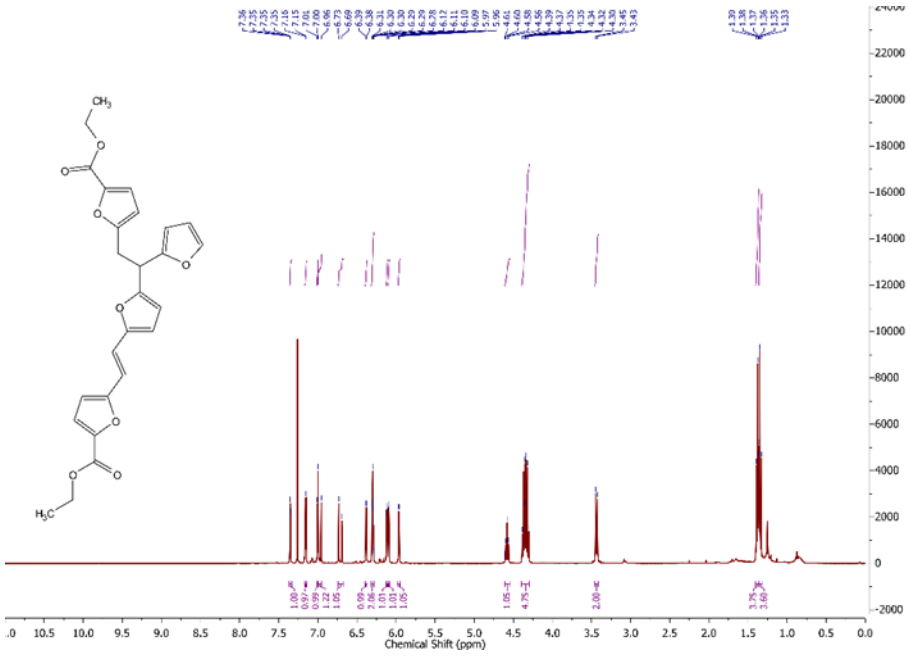
^{13}C NMR spectrum of ethyl (*E*)-5-(2-(furan-2-yl)vinyl)furan-2-carboxylate **63** in $CDCl_3$



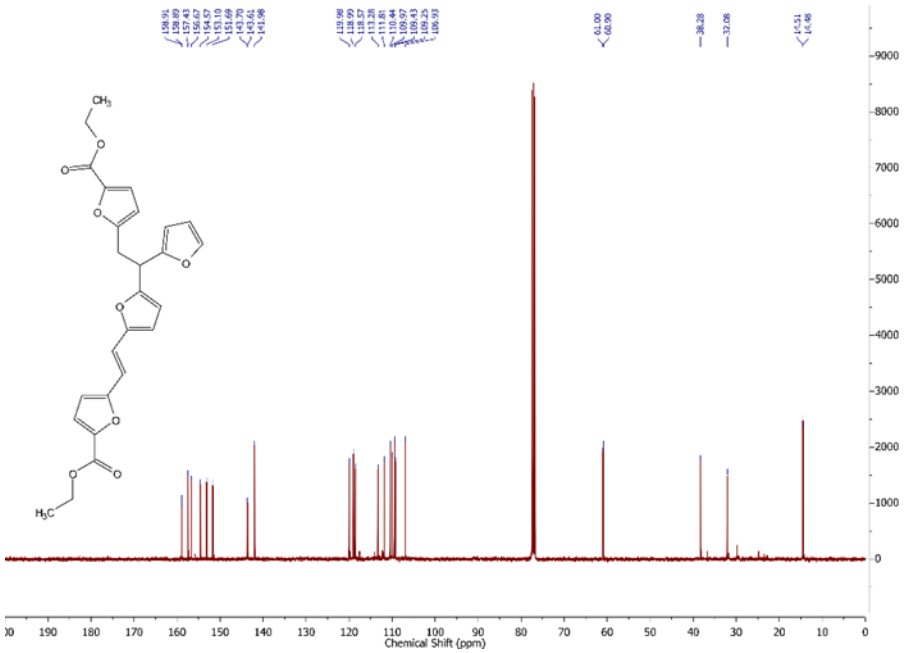
^{1}H-^{13}C HSQC NMR spectrum of ethyl (*E*)-5-(2-(furan-2-yl)vinyl)furan-2-carboxylate **63** in $CDCl_3$



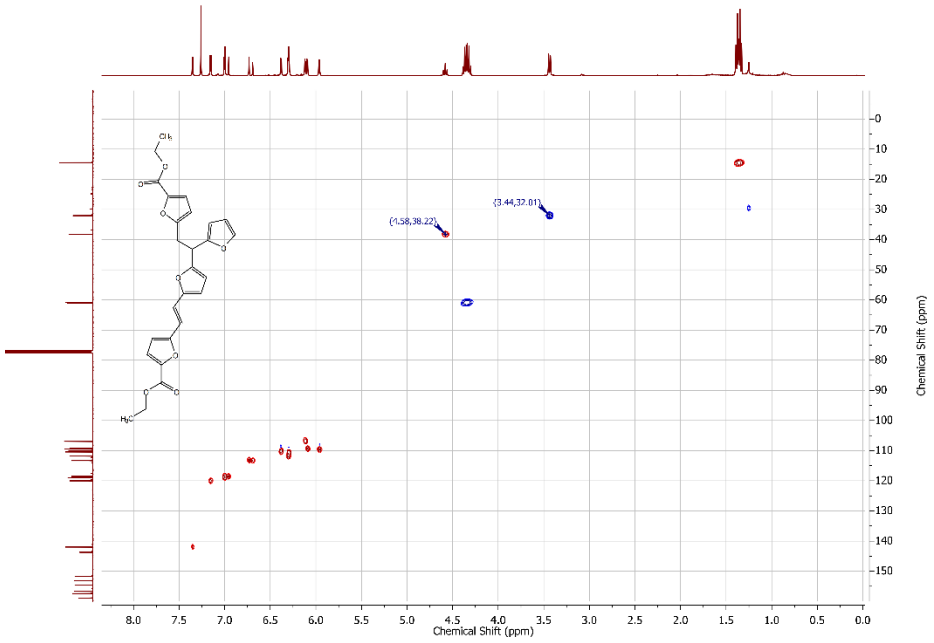
^{1}H-^{13}C HSQC NMR spectrum of ethyl (*E*)-5-(2-(furan-2-yl)vinyl)furan-2-carboxylate **63** in $CDCl_3$ (zoom in)



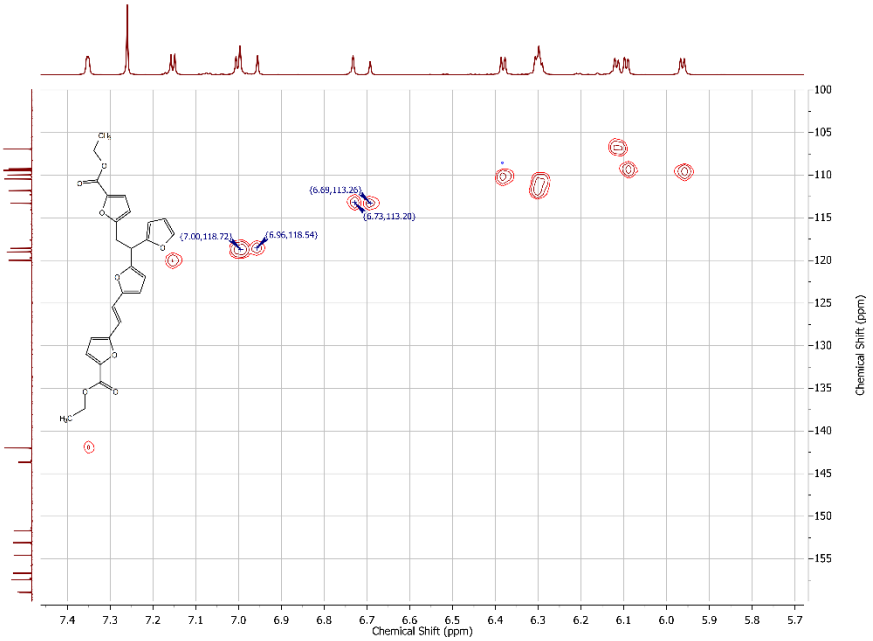
^{1}H NMR spectrum of ethyl (*E*)-5-(2-(5-(2-(5-(ethoxycarbonyl)furan-2-yl)-1-(furan-2-yl)ethyl)furan-2-yl)vinyl)furan-2-carboxylate **64** in $CDCl_3$



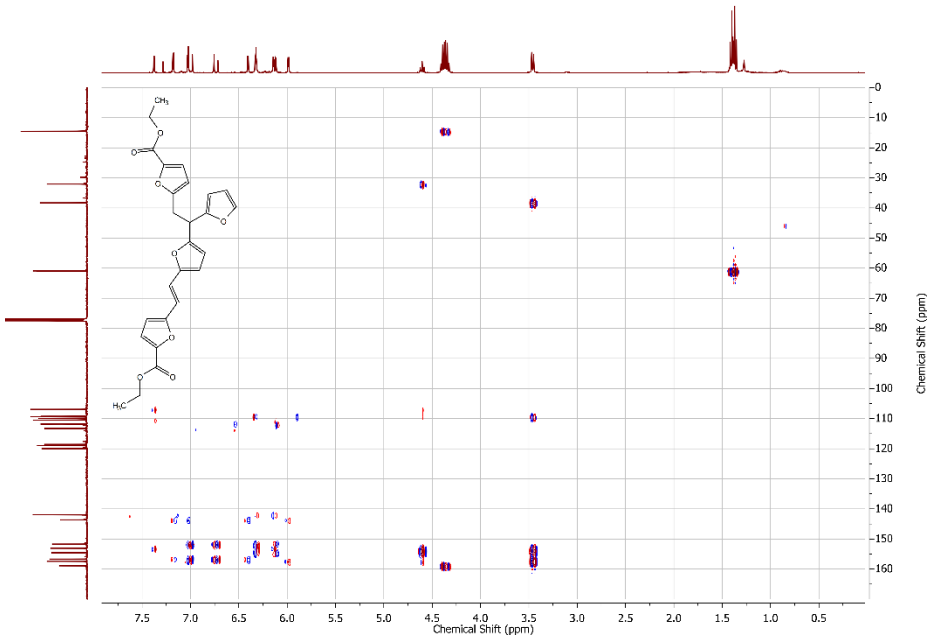
^{13}C NMR spectrum of ethyl (*E*)-5-(2-(5-(2-(5-(ethoxycarbonyl)furan-2-yl)-1-(furan-2-yl)ethyl)furan-2-yl)vinyl)furan-2-carboxylate **64** in $CDCl_3$



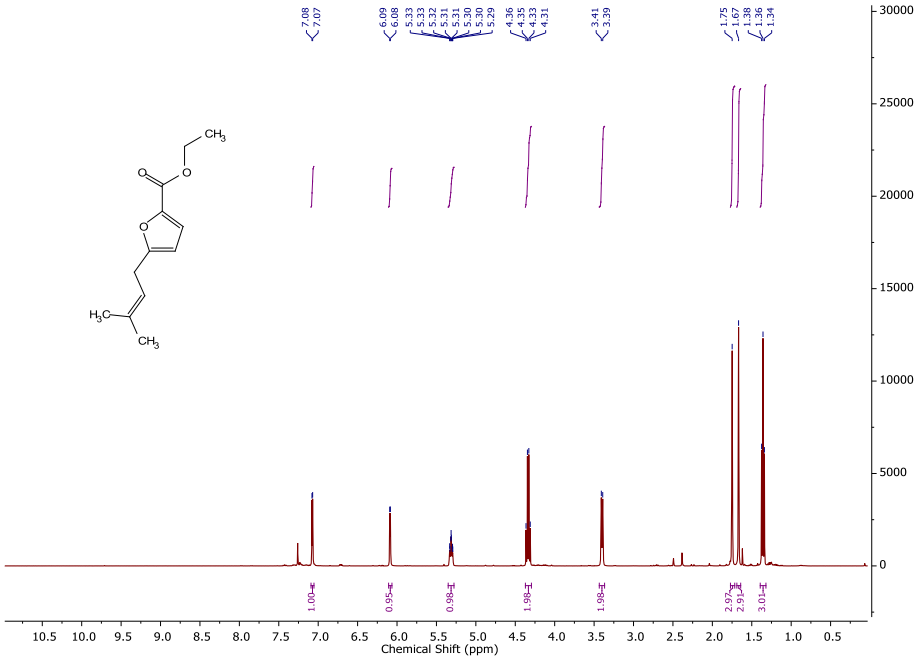
^{1}H-^{13}C HSQC NMR spectrum of ethyl (*E*)-5-(2-(5-(2-(5-(ethoxycarbonyl)furan-2-yl)-1-(furan-2-yl)ethyl)furan-2-yl)vinyl)furan-2-carboxylate **64** in $CDCl_3$



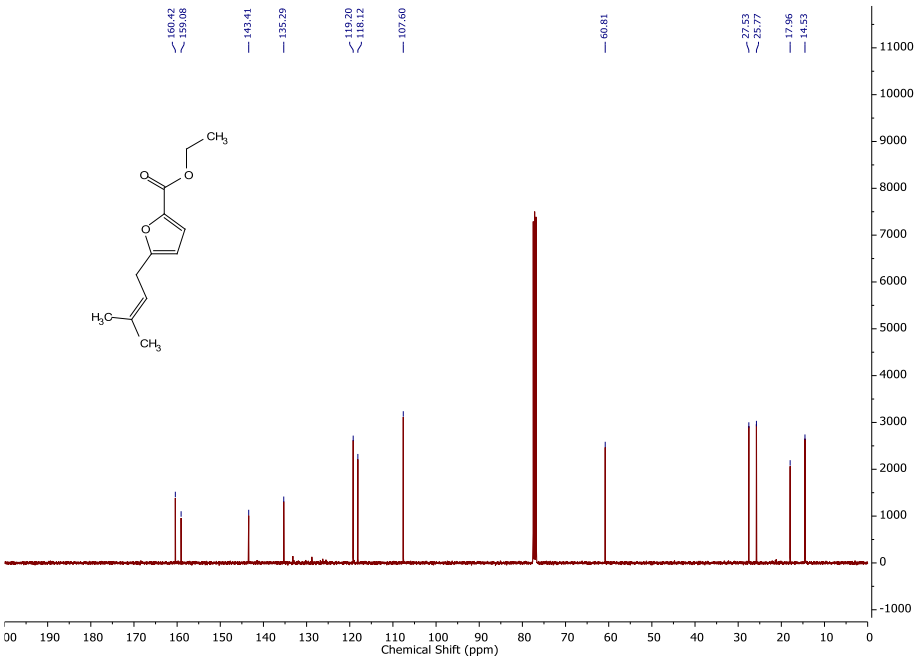
^{1}H-^{13}C HSQC NMR spectrum of ethyl (*E*)-5-(2-(5-(2-(5-(ethoxycarbonyl)furan-2-yl)-1-(furan-2-yl)ethyl)furan-2-yl)vinyl)furan-2-carboxylate **64** in $CDCl_3$ (zoom in)



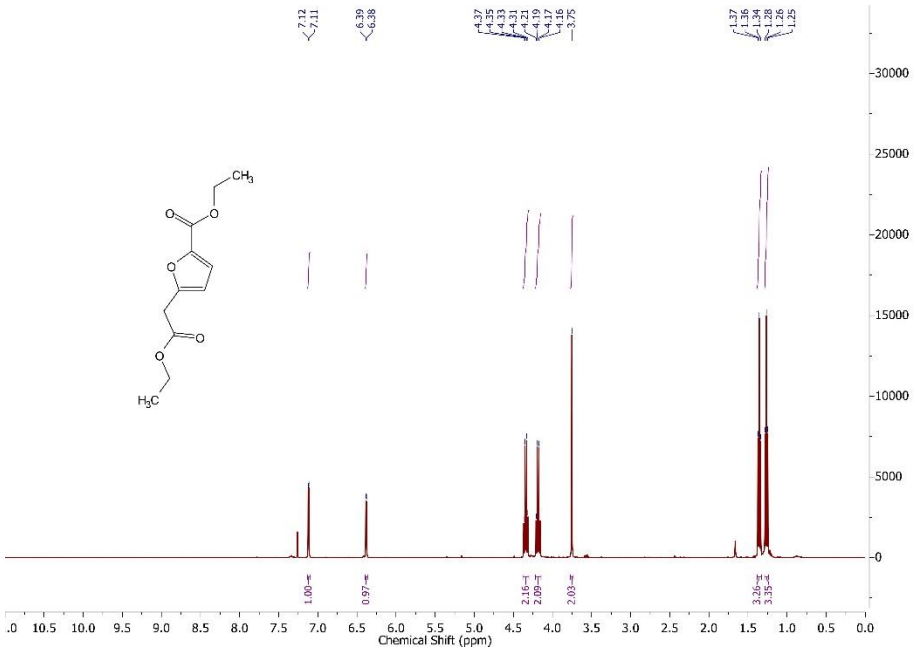
^{1}H-^{13}C HMBC NMR spectrum of ethyl (*E*)-5-(2-(5-(2-(5-(ethoxycarbonyl)furan-2-yl)-1-(furan-2-yl)ethyl)furan-2-yl)vinyl)furan-2-carboxylate **64** in $CDCl_3$



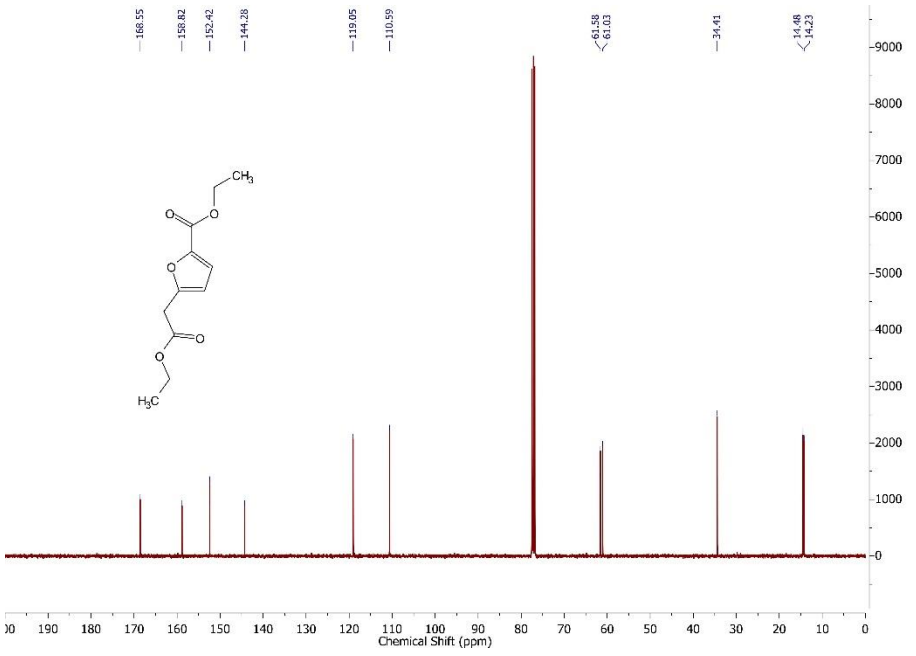
^{1}H NMR spectrum of ethyl 5-(3-methylbut-2-en-1-yl)furan-2-carboxylate **66** in $CDCl_3$



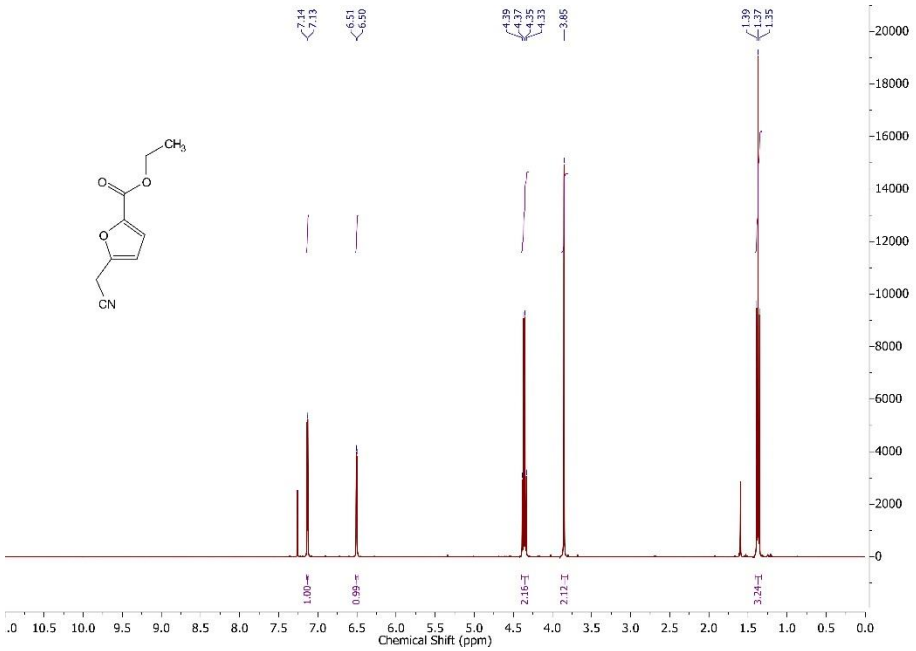
^{13}C NMR spectrum of ethyl 5-(3-methylbut-2-en-1-yl)furan-2-carboxylate **66** in $CDCl_3$



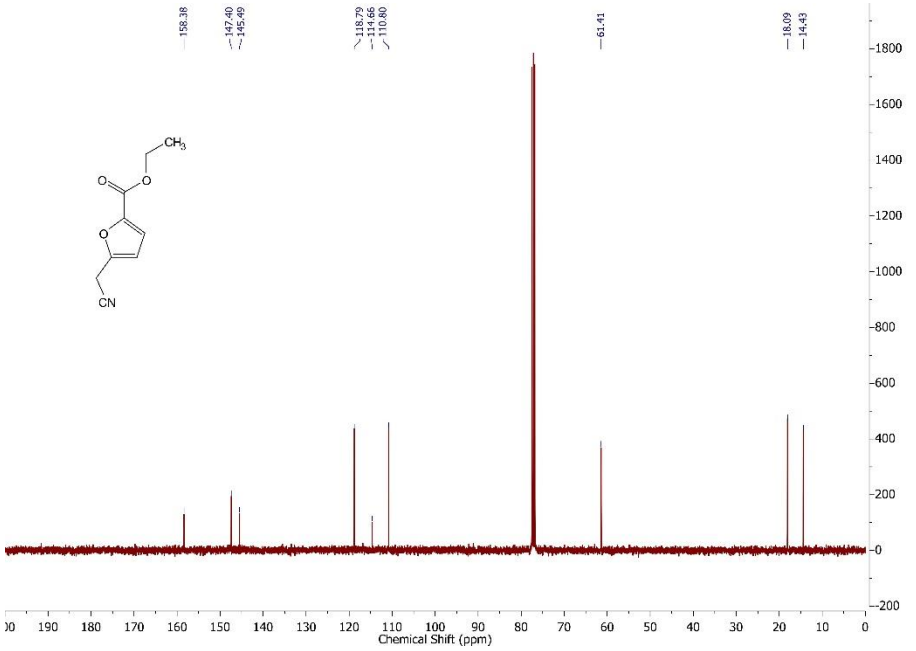
^{1}H NMR spectrum of ethyl 5-(carbethoxymethyl)furan-2-carboxylate **69** in $CDCl_3$.



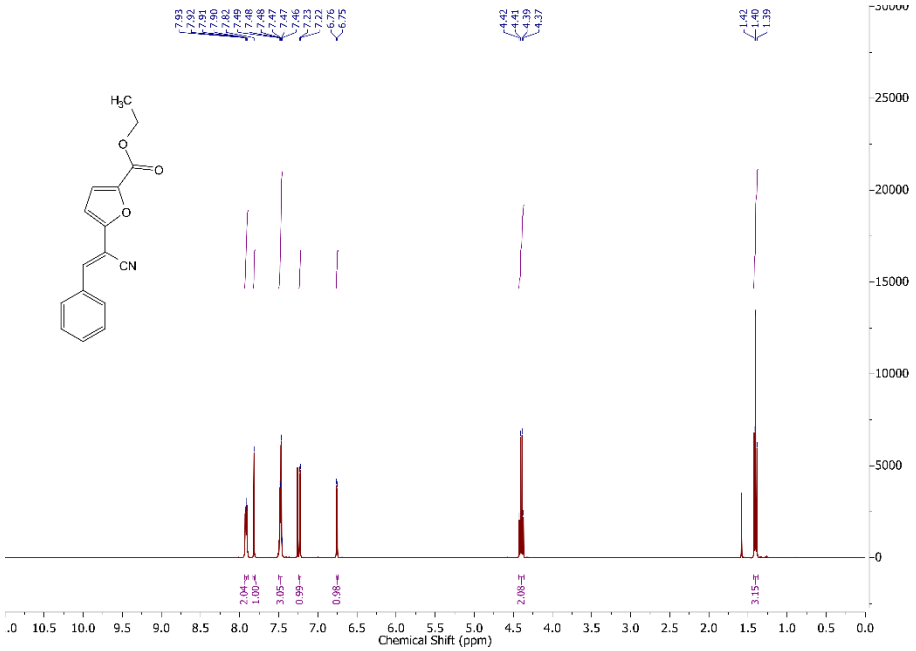
^{13}C NMR spectrum of ethyl 5-(carbethoxymethyl)furan-2-carboxylate **69** in $CDCl_3$.



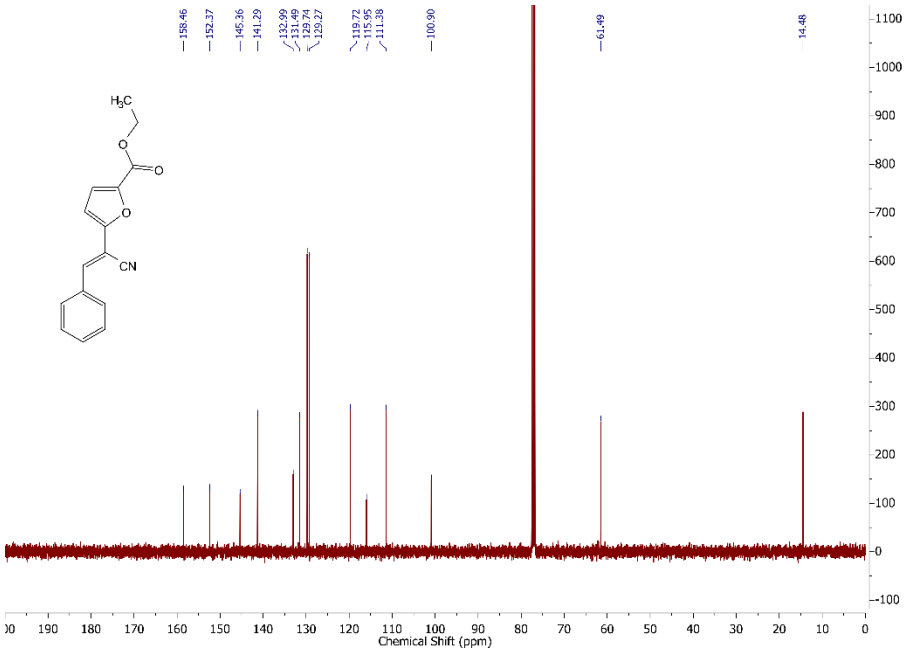
^{1}H NMR spectrum of ethyl 5-(cyanomethyl)furan-2-carboxylate **70** in $CDCl_3$.



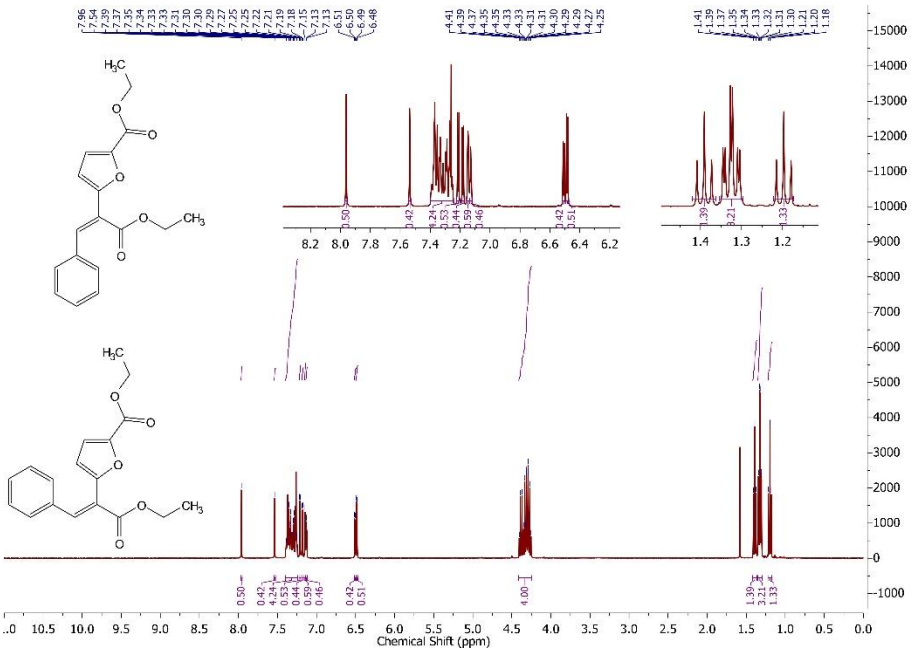
^{13}C NMR spectrum of ethyl 5-(cyanomethyl)furan-2-carboxylate **70** in $CDCl_3$.



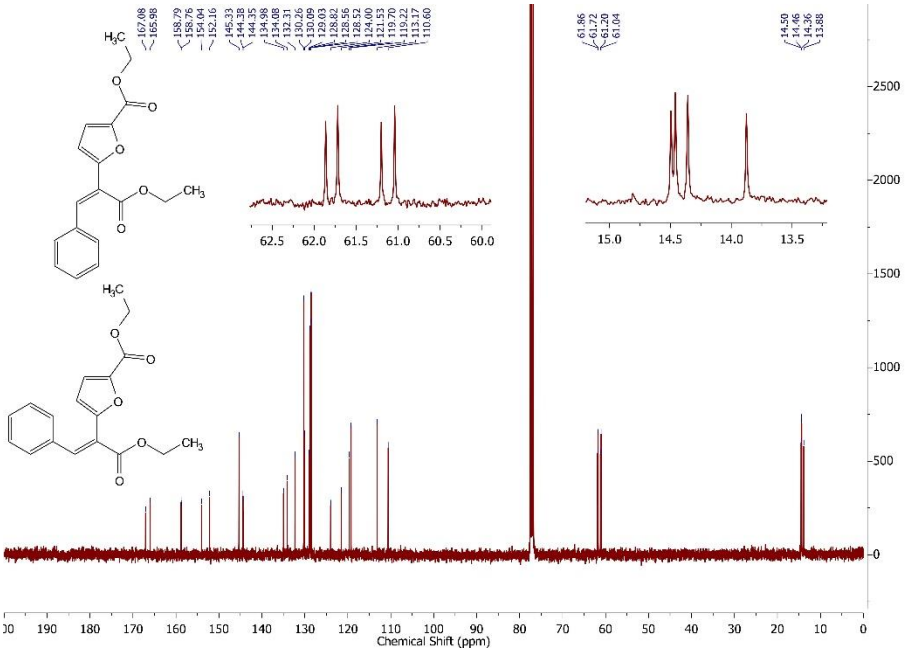
^{1}H NMR spectrum of ethyl (*E*)-5-(1-cyano-2-phenylvinyl)furan-2-carboxylate **72a** in $CDCl_3$.



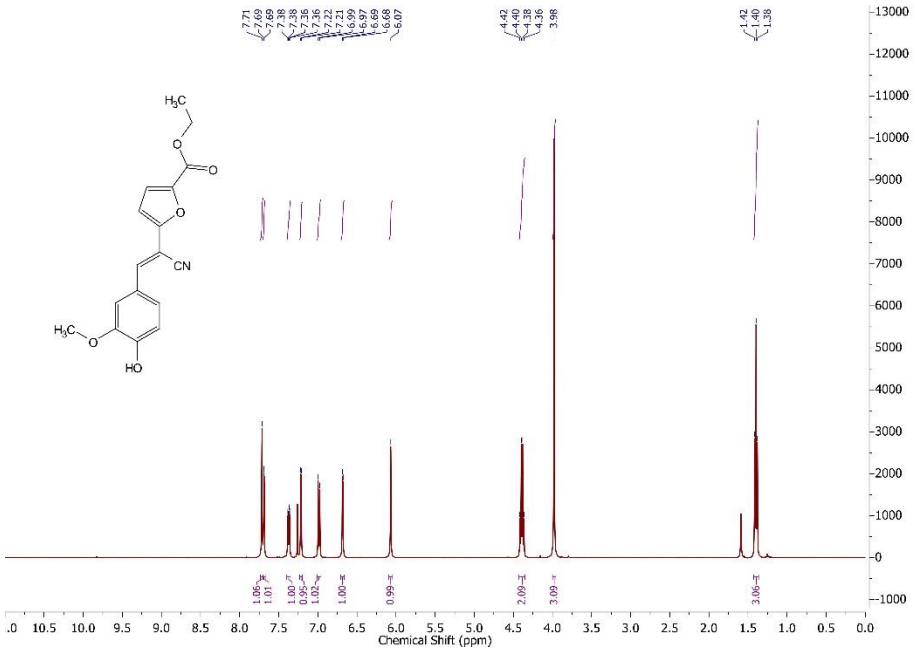
^{13}C NMR spectrum of ethyl (*E*)-5-(1-cyano-2-phenylvinyl)furan-2-carboxylate **72a** in $CDCl_3$.



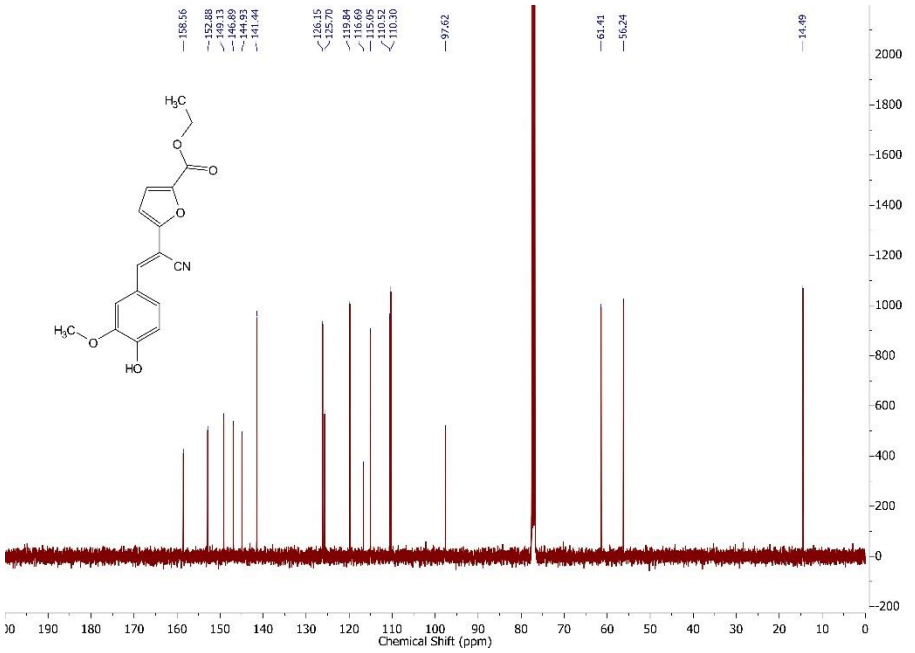
^{1}H NMR spectrum of the mixture of ethyl (*Z*)-5-(3-ethoxy-3-oxo-1-phenylprop-1-en-2-yl)furan-2-carboxylate and ethyl (*E*)-5-(3-ethoxy-3-oxo-1-phenylprop-1-en-2-yl)furan-2-carboxylate **72b** in $CDCl_3$.



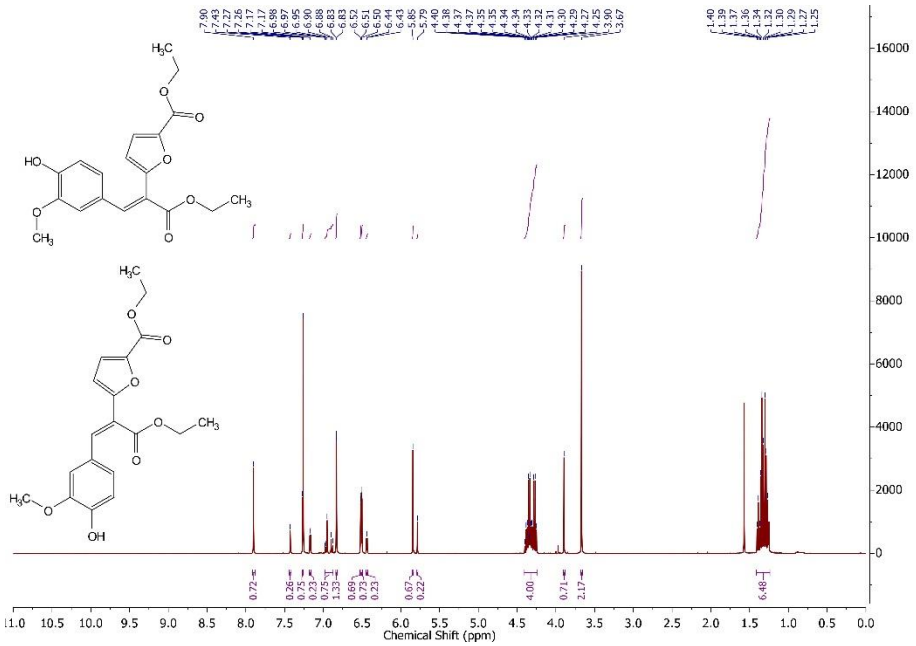
^{13}C NMR spectrum of the mixture of ethyl (*Z*)-5-(3-ethoxy-3-oxo-1-phenylprop-1-en-2-yl)furan-2-carboxylate and ethyl (*E*)-5-(3-ethoxy-3-oxo-1-phenylprop-1-en-2-yl)furan-2-carboxylate **72b** in $CDCl_3$.



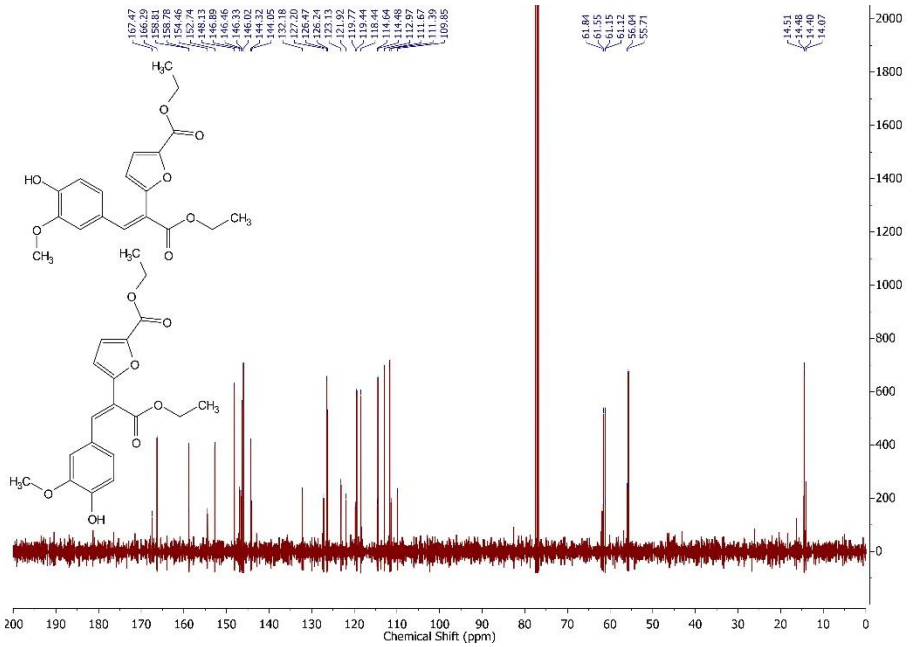
^{1}H NMR spectrum of ethyl (*E*)-5-(1-cyano-2-(4-hydroxy-3-methoxyphenyl)vinyl)furan-2-carboxylate **73a** in $CDCl_3$.



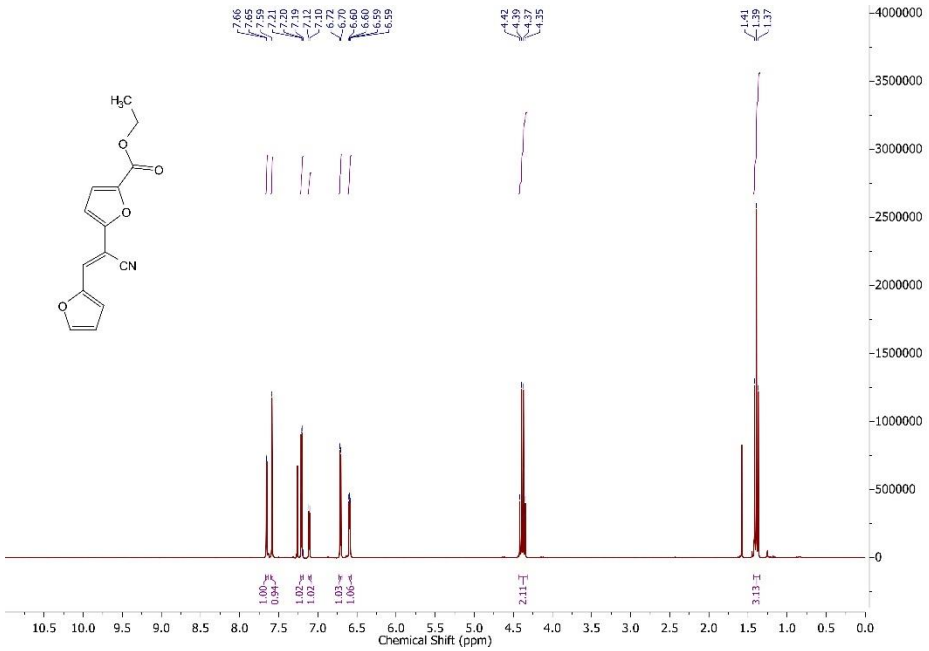
^{13}C NMR spectrum of ethyl (*E*)-5-(1-cyano-2-(4-hydroxy-3-methoxyphenyl)vinyl)furan-2-carboxylate **73a** in $CDCl_3$.



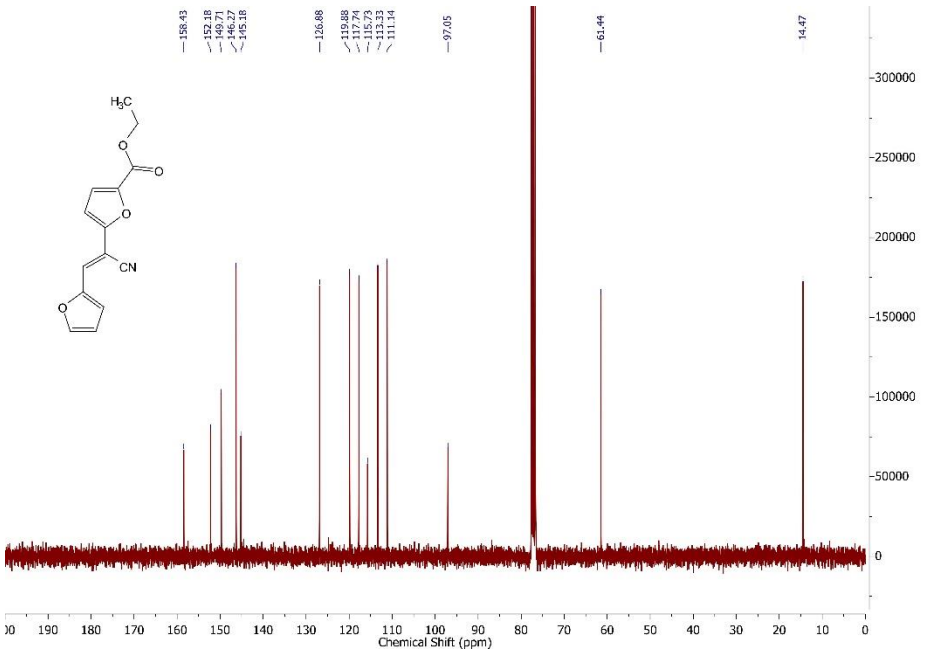
^{1}H NMR spectrum of the mixture of ethyl (*Z*)-5-(3-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-3-oxoprop-1-en-2-yl)furan-2-carboxylate and ethyl (*E*)-5-(3-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-3-oxoprop-1-en-2-yl)furan-2-carboxylate **73b** in $CDCl_3$.



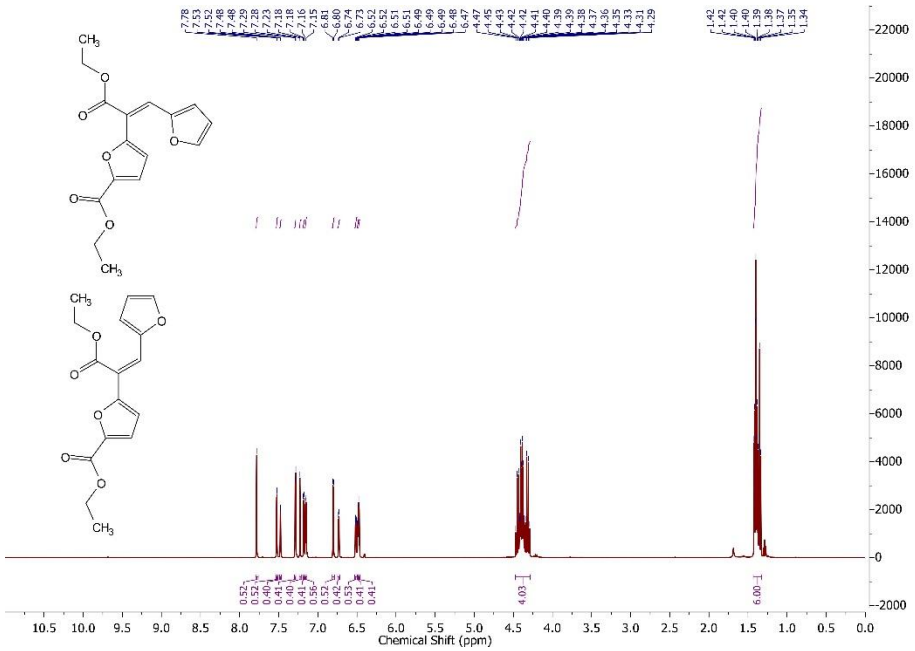
^{13}C NMR spectrum of the mixture of ethyl (*Z*)-5-(3-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-3-oxoprop-1-en-2-yl)furan-2-carboxylate and ethyl (*E*)-5-(3-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-3-oxoprop-1-en-2-yl)furan-2-carboxylate **73b** in $CDCl_3$.



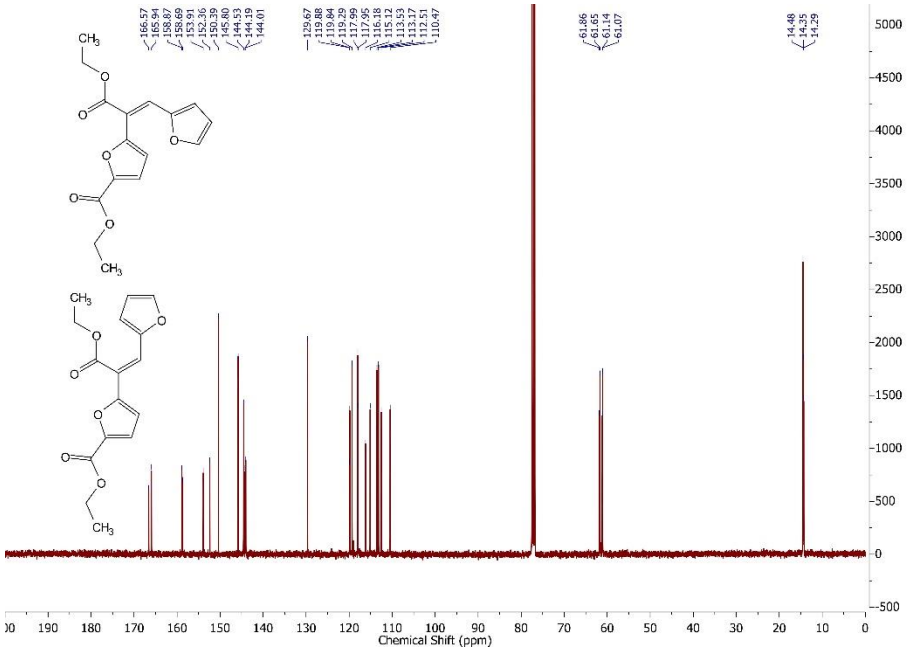
^{1}H NMR spectrum of ethyl (*E*)-5-(1-cyano-2-(furan-2-yl)vinyl)furan-2-carboxylate **74a** in $CDCl_3$.



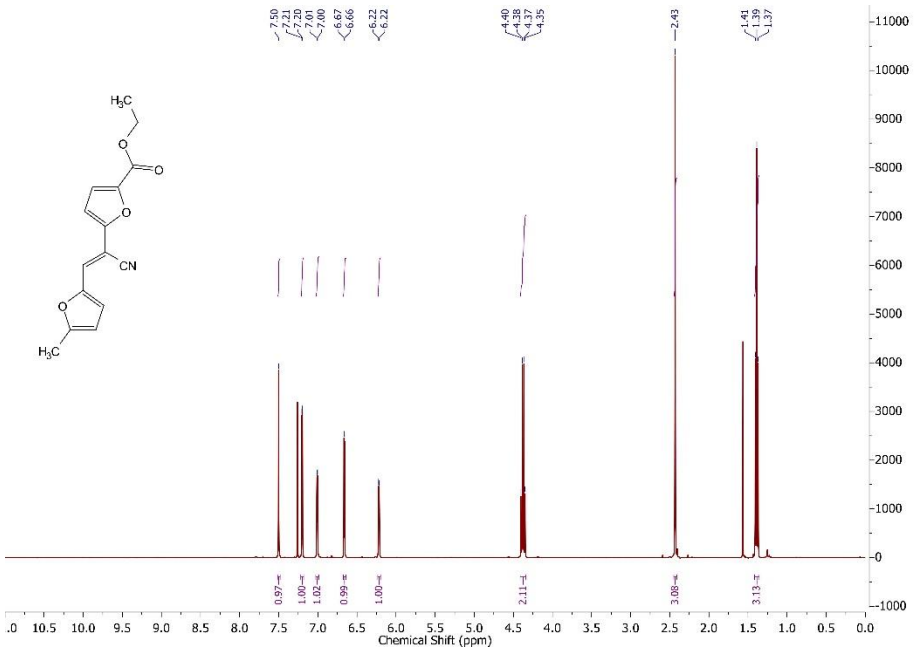
^{13}C NMR spectrum of ethyl (*E*)-5-(1-cyano-2-(furan-2-yl)vinyl)furan-2-carboxylate **74a** in $CDCl_3$.



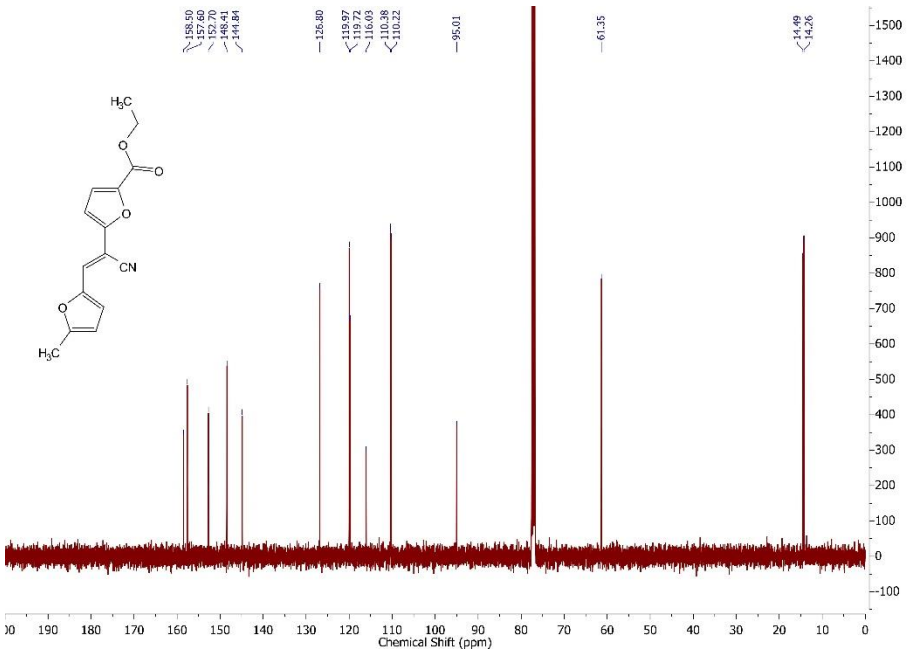
^{1}H NMR spectrum of the mixture of ethyl (*Z*)-5-(3-ethoxy-1-(furan-2-yl)-3-oxoprop-1-en-2-yl)furan-2-carboxylate and ethyl (*E*)-5-(3-ethoxy-1-(furan-2-yl)-3-oxoprop-1-en-2-yl)furan-2-carboxylate **74b** in $CDCl_3$.



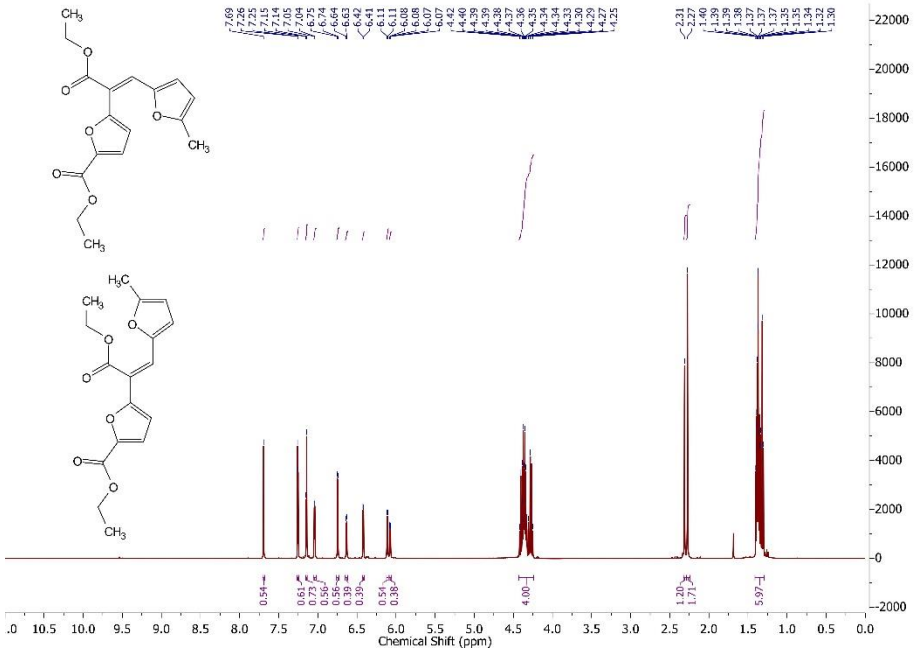
^{13}C NMR spectrum of the mixture of ethyl (*Z*)-5-(3-ethoxy-1-(furan-2-yl)-3-oxoprop-1-en-2-yl)furan-2-carboxylate and ethyl (*E*)-5-(3-ethoxy-1-(furan-2-yl)-3-oxoprop-1-en-2-yl)furan-2-carboxylate **74b** in $CDCl_3$.



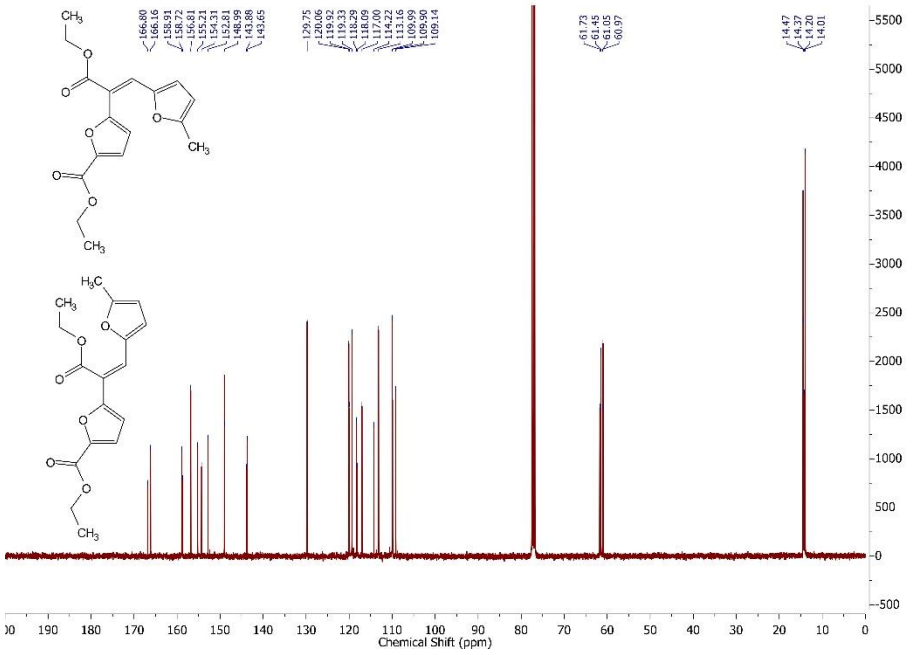
^{1}H NMR spectrum of ethyl (*E*)-5-(1-cyano-2-(5-methylfuran-2-yl)vinyl)furan-2-carboxylate **75a** in $CDCl_3$.



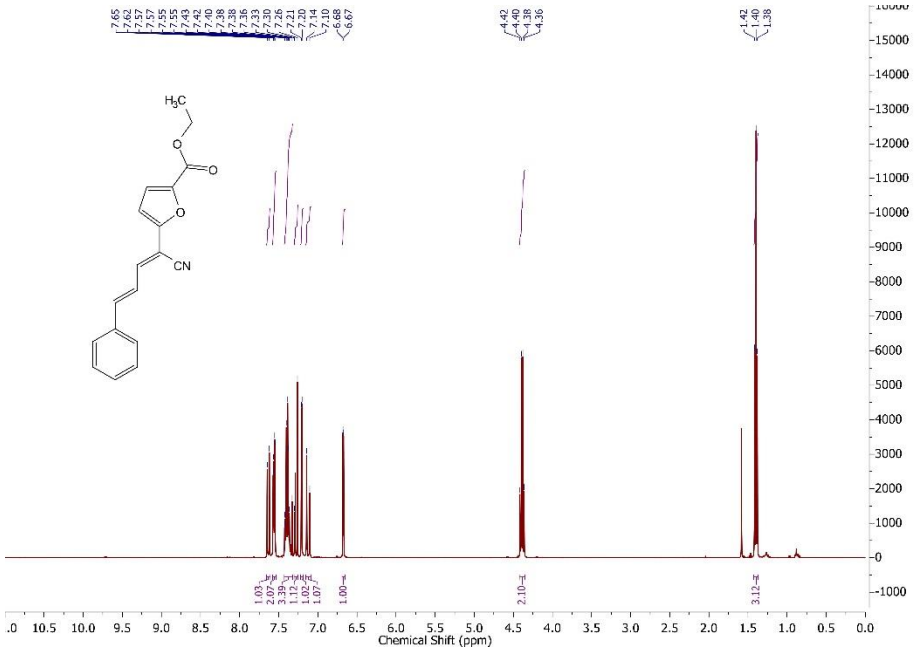
^{13}C NMR spectrum of ethyl (*E*)-5-(1-cyano-2-(5-methylfuran-2-yl)vinyl)furan-2-carboxylate **75a** in $CDCl_3$.



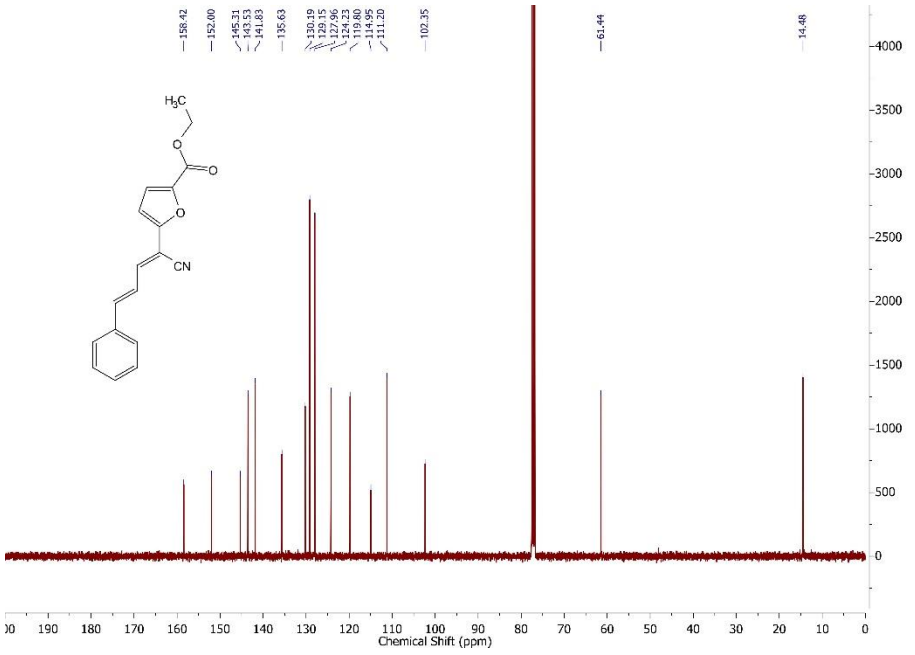
^{1}H NMR spectrum of the mixture of ethyl (*Z*)-5-(3-ethoxy-1-(5-methylfuran-2-yl)-3-oxoprop-1-en-2-yl)furan-2-carboxylate and ethyl (*E*)-5-(3-ethoxy-1-(5-methylfuran-2-yl)-3-oxoprop-1-en-2-yl)furan-2-carboxylate **75b** in $CDCl_3$.



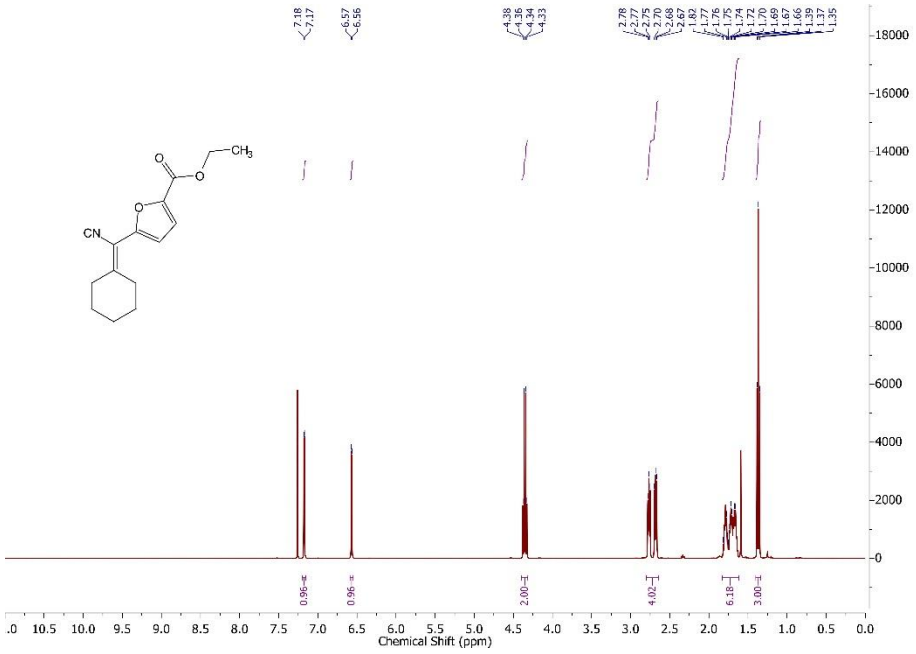
^{13}C NMR spectrum of the mixture of ethyl (*Z*)-5-(3-ethoxy-1-(5-methylfuran-2-yl)-3-oxoprop-1-en-2-yl)furan-2-carboxylate and ethyl (*E*)-5-(3-ethoxy-1-(5-methylfuran-2-yl)-3-oxoprop-1-en-2-yl)furan-2-carboxylate **75b** in $CDCl_3$.



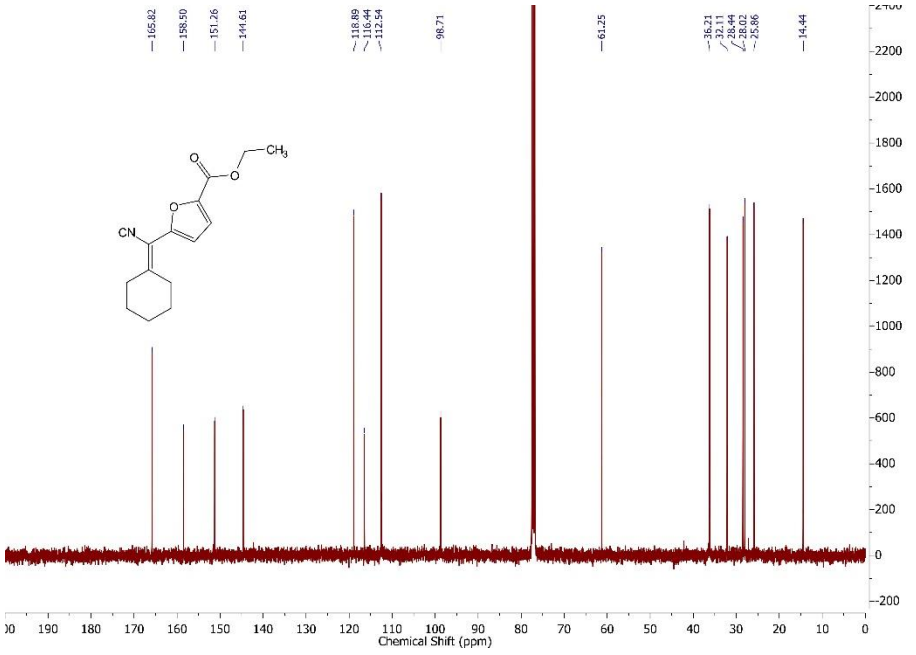
^{1}H NMR spectrum of ethyl 5-((1*E*,3*E*)-1-cyano-4-phenylbuta-1,3-dien-1-yl)furan-2-carboxylate **76a** in $CDCl_3$.



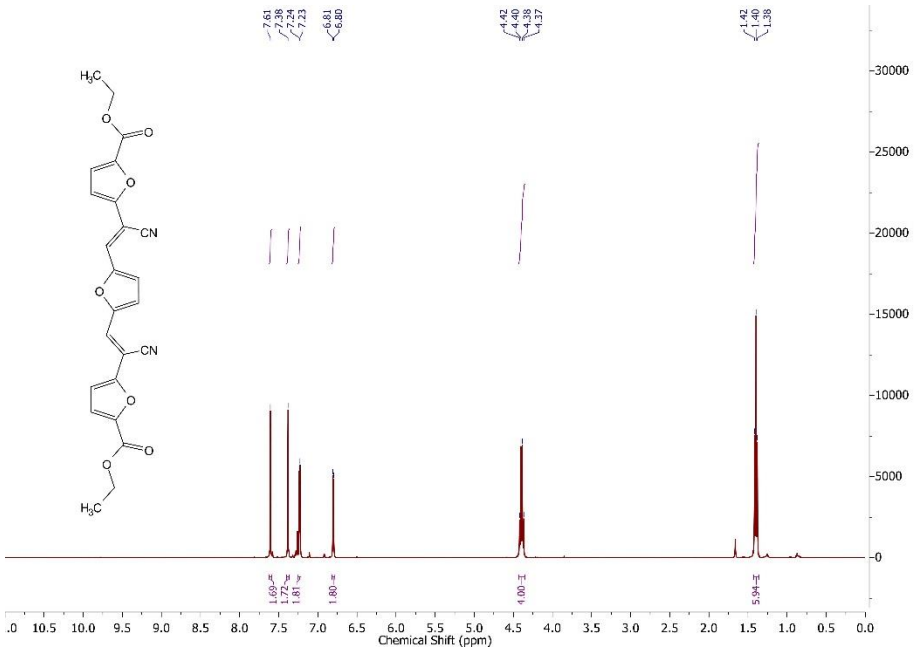
^{13}C NMR spectrum of ethyl 5-((1*E*,3*E*)-1-cyano-4-phenylbuta-1,3-dien-1-yl)furan-2-carboxylate **76a** in $CDCl_3$.



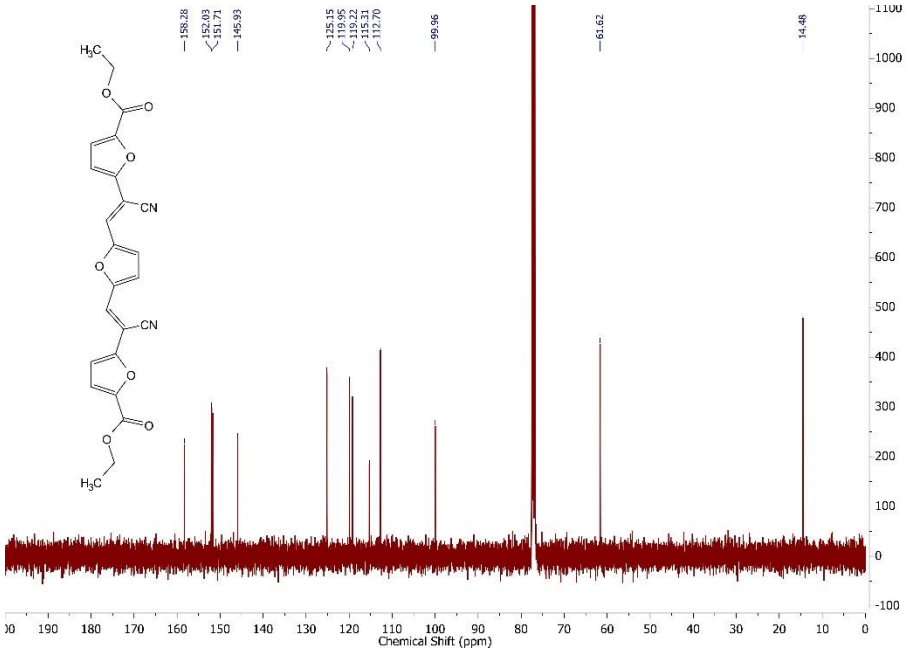
^{1}H NMR spectrum of ethyl 5-(cyano(cyclohexylidene)methyl)furan-2-carboxylate **77a** in $CDCl_3$.



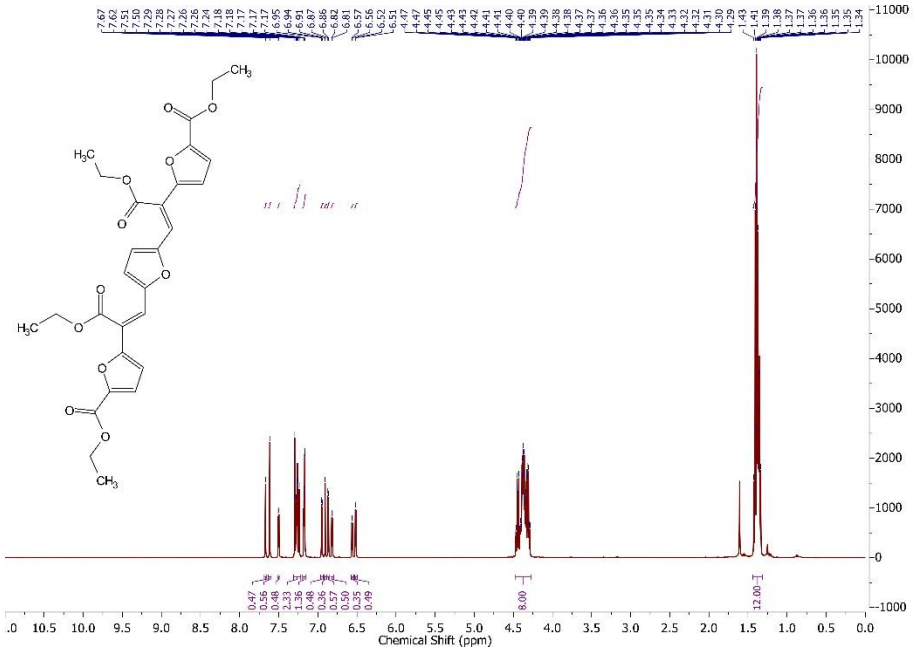
^{13}C NMR spectrum of ethyl 5-(cyano(cyclohexylidene)methyl)furan-2-carboxylate **77a** in $CDCl_3$.



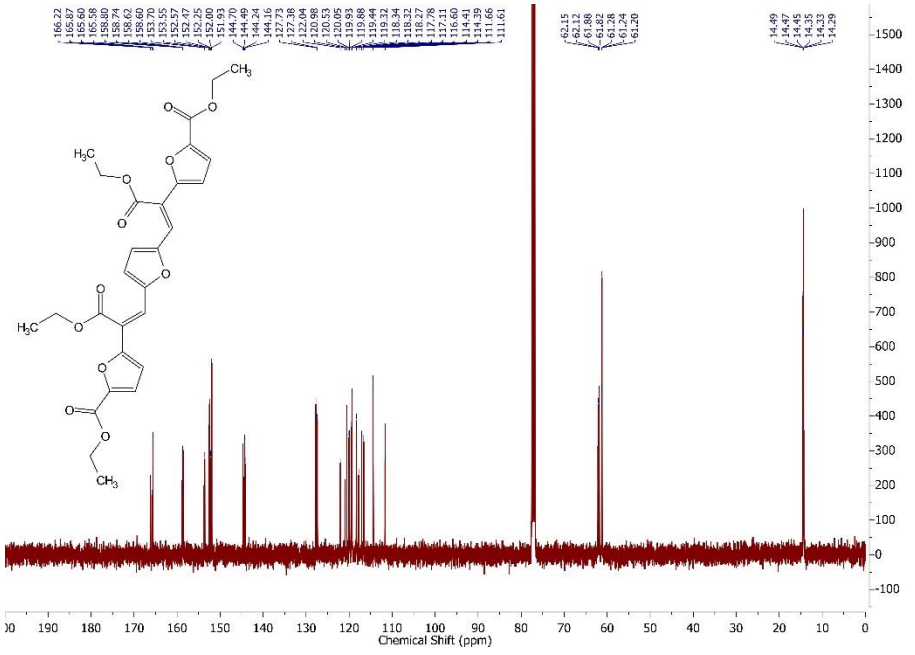
^{1}H NMR spectrum of diethyl 5,5'-((1*E*,1'*E*)-furan-2,5-diylbis(1-cyanoethene-2,1-diyl))bis(furan-2-carboxylate) **79a** in $CDCl_3$.



^{13}C NMR spectrum of diethyl 5,5'-((1*E*,1'*E*)-furan-2,5-diylbis(1-cyanoethene-2,1-diyl))bis(furan-2-carboxylate) **79a** in $CDCl_3$.



^{1}H NMR spectrum of the mixture of diethyl 5,5'-((1*Z*,1'*Z*)-furan-2,5-diylbis(3-ethoxy-3-oxoprop-1-ene-1,2-diyl))bis(furan-2-carboxylate) and stereoisomer **79b** in $CDCl_3$.



^{13}C NMR spectrum of mixture of diethyl 5,5'-((1*Z*,1'*Z*)-furan-2,5-diylbis(3-ethoxy-3-oxoprop-1-ene-1,2-diyl))bis(furan-2-carboxylate) and stereoisomer **79b** in $CDCl_3$.