

Synthesis of dihydropyranones from chromene aldehydes *via* an oxidative NHC-catalyzed kinetic resolution

Master's thesis in the Materials Chemistry programme

Mathias Westerlund

MASTER'S THESIS 2019

**Synthesis of dihydropyranones from chromene
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Gothenburg, Sweden 2019

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Cover: The NHC-catalyzed formation of dihydropyranones from a chromene aldehyde and a 1,3-dicarbonyl.

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Synthesis of dihydropyranones through aerial oxidative NHC-catalysis
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Abstract

In this work, the NHC-catalyzed Michael/lactonization reaction between different chromene aldehydes and 1,3-dicarbonyls has been investigated. It was discovered early on that the reaction proceeds *via* a kinetic resolution. The reaction conditions were investigated and it was determined that the optimum was achieved using 1 eq. of the chromene aldehyde in a 0.1 molar concentration of THF, 1 eq. of the dicarbonyl, 1 eq. of the Kharash oxidant, 0.5 eq. of sodium benzoate and 10 mol% of the NHC catalyst. Furthermore, the scope of the reaction was determined. The reaction worked successfully with both aromatic-substituted chromenes as well as alkyl-substituted chromenes at carbon 2. For the aromatic-substituted chromenes, only parasubstitution on the phenyl ring gave adequate results. The reaction also worked using cyclic dicarbonyls as well as when using chromene aldehydes with substitution on carbon 6, however in low enantioselectivities. The products were in most cases isolated as single diastereomers in yields of up to 34% and with ee-values of up to 97%.

Keywords: NHC-catalysis, dihydropyranone, Michael/lactonization, kinetic resolution, chromene, chiral HPLC, asymmetric synthesis.

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List of Abbreviations

Bz	Benzyl
CAM	Cerium ammonium molybdate
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCM	Dichloromethane
DKR	Dynamic kinetic resolution
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
ee	Enantiomeric excess
EtOAc	Ethyl acetate
er	Enantiomeric ratio
eq.	Equivalent
HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
IPA	Isopropyl alcohol
IUPAC	International Union of Pure and Applied Chemistry
KR	Kinetic resolution
LUMO	Lowest unoccupied molecular orbital
MS	Molecular sieves
NA	Not available
NHC	<i>N</i> -heterocyclic carbene
PE	Petroleum ethers
Ph	Phenyl
TAA	Tert-amyl alcohol

<i>t</i> -Bu	<i>Tert</i> -butyl
THF	Tetrahydrofuran
UV	Ultraviolet

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1

Introduction

1.1 Background

An element that most people likely will have heard of is carbon. Carbon is perhaps most commonly known as the single component in both graphite, as well as in diamonds. But carbon's role is much more vast than that. Carbon is essential for life to exist as we know it. All living things, whether it be humans, animals, or plants, rely on carbon-containing compounds to function. These carbon-containing compounds are more commonly called organic compounds, and fall under the scientific field of organic chemistry. Although organic chemistry originally was a field of chemistry limited to the study of compounds produced by living organisms, it has since been expanded to include substances made synthetically by humans. This includes pharmaceuticals, petrochemicals, cosmetics, and plastics, among many other types of substances [1].

Organic chemists making new types of compounds or improving the syntheses of existing compounds work within the field of organic synthesis. In order to achieve their desired product, a number of different transformations need to be performed. These transformations break the bonds between atoms in order to create new ones. However, simply forming these bonds is often not enough. Compounds exhibiting chirality are substances that in addition need the proper stereochemistry. The stereochemistry of a compound is determined by the arrangement of the atoms in space and may affect the compound's physical and chemical properties as well as its reactivity. This is represented in Figure 1.1 for the case of thalidomide which is a pharmaceutical product which intended use was that of a sedative.

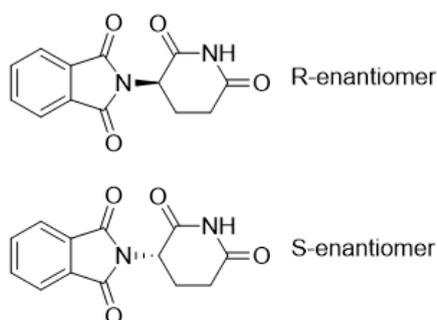


Figure 1.1: The two enantiomers of thalidomide

Achieving proper stereochemistry is of paramount importance in especially pharmaceutical products, since the wrong stereochemistry may reduce the efficiency of drugs, or in some cases, have more deleterious effects. This was the case for thalidomide in the 1960's. As mentioned, the intended use of the drug was that of a sedative, but it contained both of the enantiomers (mirror-images) of the compound where one of the enantiomers gave the desired sedative effect, while the other resulted in teratogenic effects for pregnant women [2].

A common way of achieving proper stereochemistry is with the use of chiral catalysts. A catalyst is a compound that increases the rate of a reaction without itself being consumed. If the catalyst in addition is chiral, it can induce stereospecific transformations by in some way favouring the desired product, or disfavoring the undesired product. Utilizing chiral catalysts in such a way is called asymmetric synthesis, and has been used for decades as a source for stereoselective synthesis [3].

In recent years, a special class of catalysis, *N*-heterocyclic carbene catalysis, has been used by the Sundén group, among others, to investigate the synthesis of dihydropyranones from cinnamaldehyde derivatives and 1,3-dicarbonyl compounds [4]. The reaction has been described as occurring through a Michael addition of the dicarbonyl to the aldehyde with a subsequent lactonization to form the final dihydropyranones in high yields and high enantiomeric excess (ee).

Dihydropyranones exhibiting the skeletal structure shown in Figure 1.2a are especially interesting due to their resemblance to other natural products such as bisaboscal A (Figure 1.2b), tetrahydrocannabinol (Figure 1.2c) and mulberrofuran K (Figure 1.2d). These natural products exhibit properties such as, antifungal [5], anti-nauseant [6], and anti-inflammatory [7] properties respectively. It would therefore be of great interest to find a simple and effective way of synthesizing these types of dihydropyranone structures. Furthermore, dihydropyranones are also important as reactants, giving access to compounds such as enamines [8], α -pyrones [9], γ -lactones [10], and substituted benzenoids [11] (Scheme 1.1).

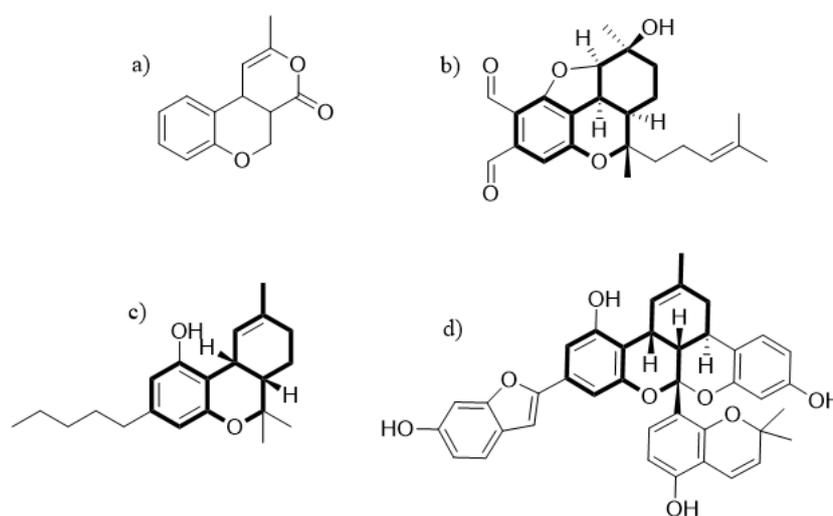
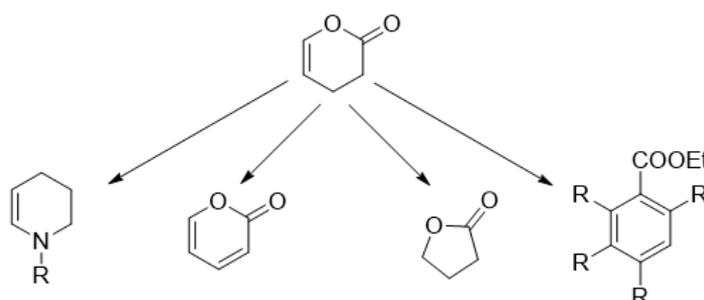


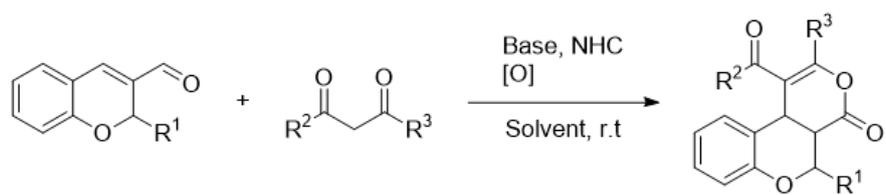
Figure 1.2: (a) Dihydropyranone with a 3-ring skeletal system, (b) bisabosqual A, (c) tetrahydrocannabinol (c) and (d) mulberrofuran K.



Scheme 1.1: Possible transformations of dihydropyranones into enamines, α -pyrones, γ -lactones and substituted benzenoids.

1.2 Aim of the study

The aim of the project was to investigate oxidative NHC-catalyzed synthesis of dihydropyranones in accordance to Scheme 1.2, and optimize the efficiency of the reaction in terms of yield and enantiomeric excess. The scope of the reaction was also investigated by performing the reaction with different 1,3-dicarbonyls as well as using derivatives of the aldehyde.



Scheme 1.2: Synthesis of a dihydropyranone with a 3-ring skeletal structure.

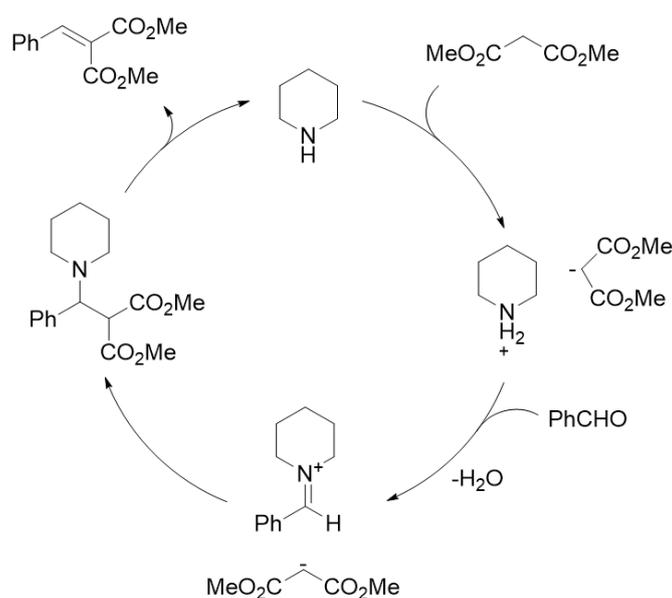
2

Theory

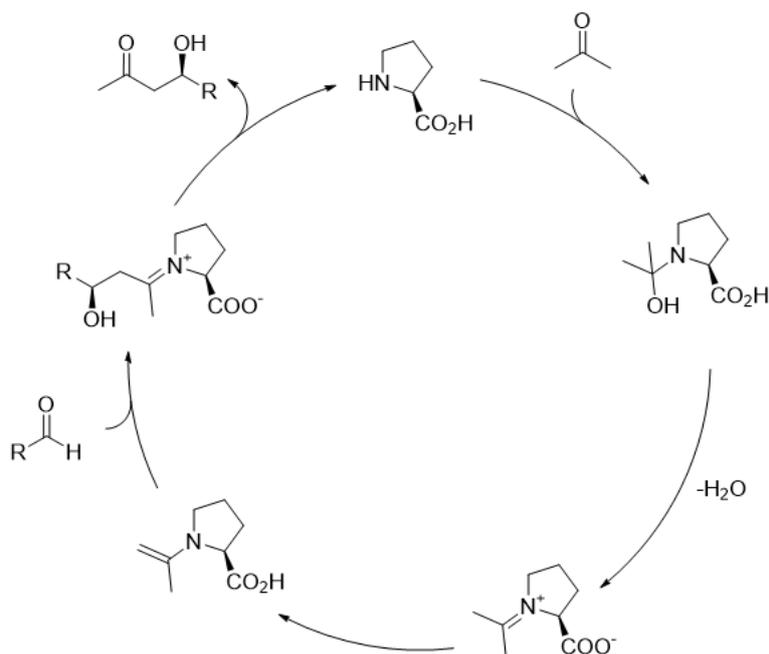
2.1 Organocatalysis

A commonly occurring phenomenon within chemistry is catalysis. Catalysts are compounds that participate in a reaction, but are not consumed, and serves the purpose of increasing the rate of the reaction. As a consequence, a catalyst may allow the reaction to be performed under milder conditions, reducing the energy needed for the reaction to proceed. There are several different types of catalysis, for example, a catalytic process may either be heterogeneous or homogeneous. For homogeneous catalysis, the phase of the catalyst is the same as the phase of the reactant, while for heterogeneous catalysis, the phases differ. Furthermore, catalytic processes may fall under more specific classes, such as transition-metal catalysis, enzymatic catalysis, or organocatalysis [3].

Organocatalysis is a type of catalysis that utilizes small organic molecules to achieve catalytic transformations. The term was coined in the twenty-first century, but the use of organocatalysis can be traced back as far as 1896 when Emil Knoevenagel used amines to catalyze the reaction between dicarbonyls and aldehydes (Scheme 2.1) [12]. Since then, the field of organocatalysis has grown to be a powerful tool to not only achieve a wide variety of transformations, but also for asymmetric catalysis. List and coworkers' use of enamine catalysis for an asymmetric aldol reaction (Scheme 2.2), is a very important example of such asymmetric organocatalysis [13].



Scheme 2.1: The organocatalytic cycle of the Knoevenagel condensation reaction with piperidine as catalyst.



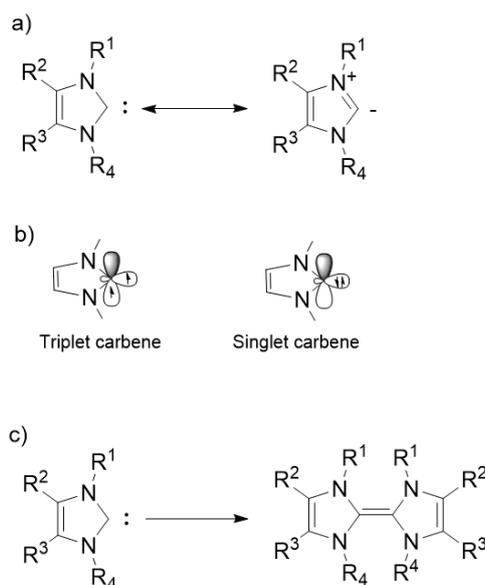
Scheme 2.2: The organocatalytic cycle of List's enamine catalysis using L-proline as a catalyst.

In addition to achieving many different transformations, organocatalysis has the benefit of working under mild conditions and avoids the use of metals, which is more common for classical catalysis. This is beneficial seen from a sustainability perspective since the catalytic reactions can often occur at room temperature.

Because no metals are used, organocatalysis also becomes cheaper, avoids the environmental damage caused by the mining industry, and removes the problem of metals leaching from the catalyst. However, organocatalysts often need a higher loading of the catalyst to achieve comparable conversions [14].

2.2 *N*-heterocyclic carbene catalysis

As stated, organocatalysis has in recent years gained a lot of traction. One type of catalysts of particular interest are *N*-heterocyclic carbenes (NHCs). NHCs are a class of catalysts that are characterized by the inclusion of a carbene in an *N*-heterocycle. Carbenes are a class of compounds containing a carbon atom which is both neutral and bivalent, and are in general very reactive. They can, however, in the case of NHCs, be stabilized by adjacent heteroatoms that allows for resonance *via* the ylide (Scheme 2.3a). This is due to the heteroatom decreasing the energy of the highest occupied molecular orbital (HOMO) while also increasing the energy of the lowest unoccupied molecular orbital (LUMO) and hence favoring the more stable singlet state over the triplet state (Scheme 2.3b). Nitrogen substituents also disfavor the dimerization of the carbenes (Scheme 2.3c) [15].



Scheme 2.3: (a) Resonance stabilization of the NHC *via* the ylide, (b) the triplet and singlet state of NHCs and (c) dimerization of an NHC catalyst (c).

The majority of the stable carbenes used are carbene derivatives of thiazolium, imidazolium and triazolium salts (Figure 2.1). There are of course also asymmetric variants of these types of catalysts, allowing for asymmetric synthesis [16].

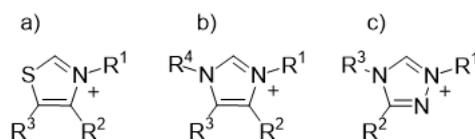
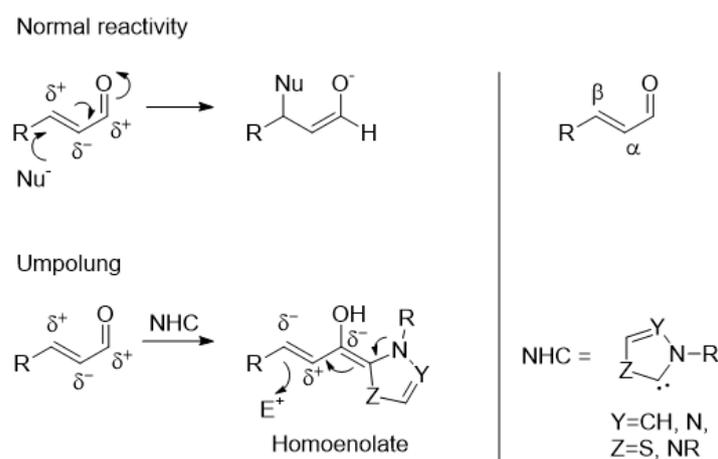


Figure 2.1: Structures of the common, stable azolium salts thiazolium (a), imidazolium (b), and triazolium (c).

A very useful property of the NHC-catalysts contributing to their interest is their ability to achieve umpolung. Umpolung essentially means reversal of reactivity, or reversal of polarity. By this action, a normally nucleophilic site may become electrophilic and vice versa [17]. For NHC-catalysis, umpolung is achieved mainly for aldehydes in order to reverse the reactivity at the β -position as well as at the carbonyl carbon into nucleophilic sites (Scheme 2.4) [14].



Scheme 2.4: Reversal of reactivity for α,β -unsaturated aldehydes using NHCs.

Despite reports of NHC-catalyzed benzoin reactions dating as far back as 1943, the use of NHC catalysis did not gain attention until the beginning of the 2000s when the groups of Bode, Rovis and Glorius used NHC-catalysis in order to use α -functionalized aldehydes as acylating agents [16]. Since then, a plethora of remarkable NHC-catalyzed transformations has been developed, such as forming complex thiochroman [18] and tetrahydroquinoline [19] structures (Figure 2.2).

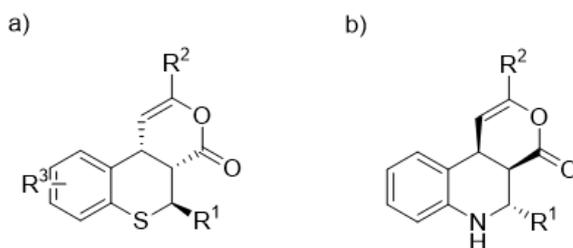
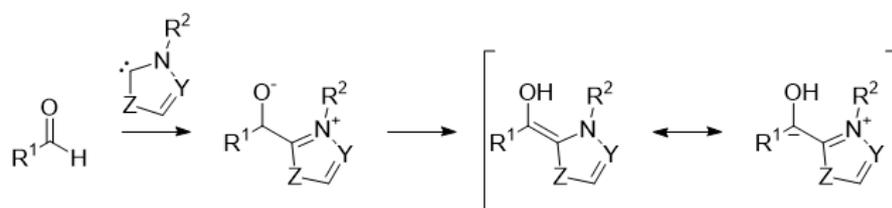


Figure 2.2: Previously synthesized dihydropyranones with (a) thiochroman and (b) tetrahydroquinoline structures.

2.2.1 Mechanisms of NHC catalysis

2.2.1.1 Generation of intermediates

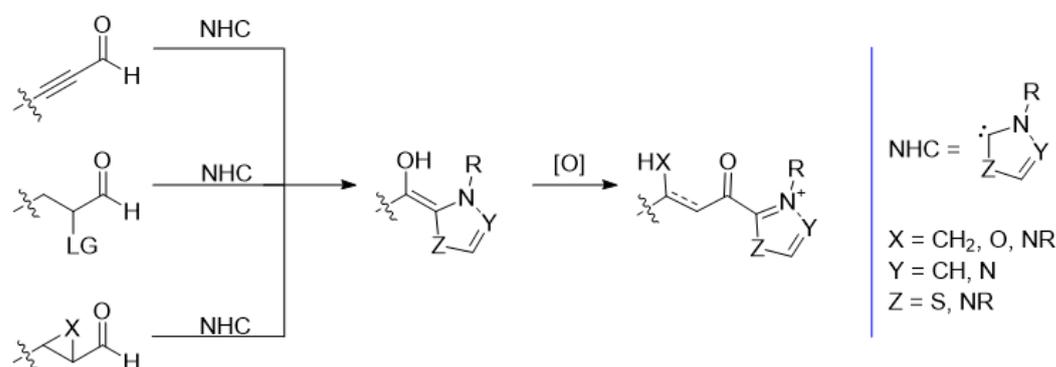
For most NHC catalyzed reactions, the so called Breslow intermediate is an important intermediate in the reaction mechanism. The intermediate was suggested in 1958 by Breslow and has been studied mainly for the Stetter reaction and the benzoin condensation [20]. The Breslow intermediate is obtained by nucleophilic addition of the NHC catalyst to an aldehyde to generate a tetrahedral intermediate followed by a proton transfer (Scheme 2.5)



Scheme 2.5: Generation of the Breslow intermediate.

Using NHC catalysis together with α,β -unsaturated aldehydes gives rise to a special kind of Breslow intermediate called the extended Breslow intermediate, or the homoenolate which can be seen in the umpolung reaction in Scheme 2.4. The mechanism for the generation of the homoenolate is very much similar to that of the Breslow intermediate.

The homoenolate may subsequently react further through an oxidation. This step very much depends on the type of compound that is used and may either be an internal oxidation or an external one. However, the intermediate formed from this oxidation, called an acyl azolium intermediate (Scheme 2.6), is similar for the different oxidations. For internal oxidation to occur, the aldehyde needs to be α -functionalized. This includes compounds such as α -haloaldehydes [21], ynals [22], epoxyaldehydes [23], cyclopropanes [24], aziridines [25], *etc.* These compounds may then form the acyl azolium through loss of leaving group, redox isomerization or ring opening respectively.



Scheme 2.6: Generation of the acyl azolium intermediate, where X signifies either a CH_2 -, O-, or NR-groups in the case of ring opening.

By obtaining the acyl azolium using an external oxidant, the requirement for an α -functionalized aldehyde is removed. The type of oxidants that can be used varies, with both inorganic and organic oxidants being feasible options. However, the most common is the Kharasch oxidant (3,3',5,5'-tetra-*tert*-butyldiphenoquinone), along with for example manganese dioxide, azobenzene and phenazine (Figure 2.3). From a green chemistry approach, external oxidants have poor atom economy, due to often having large molar masses in addition to being used in stoichiometric amounts. This generates a larger amount of waste, and thus, other alternatives are generally preferred [14].

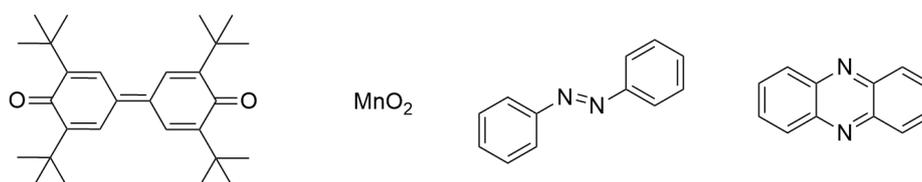


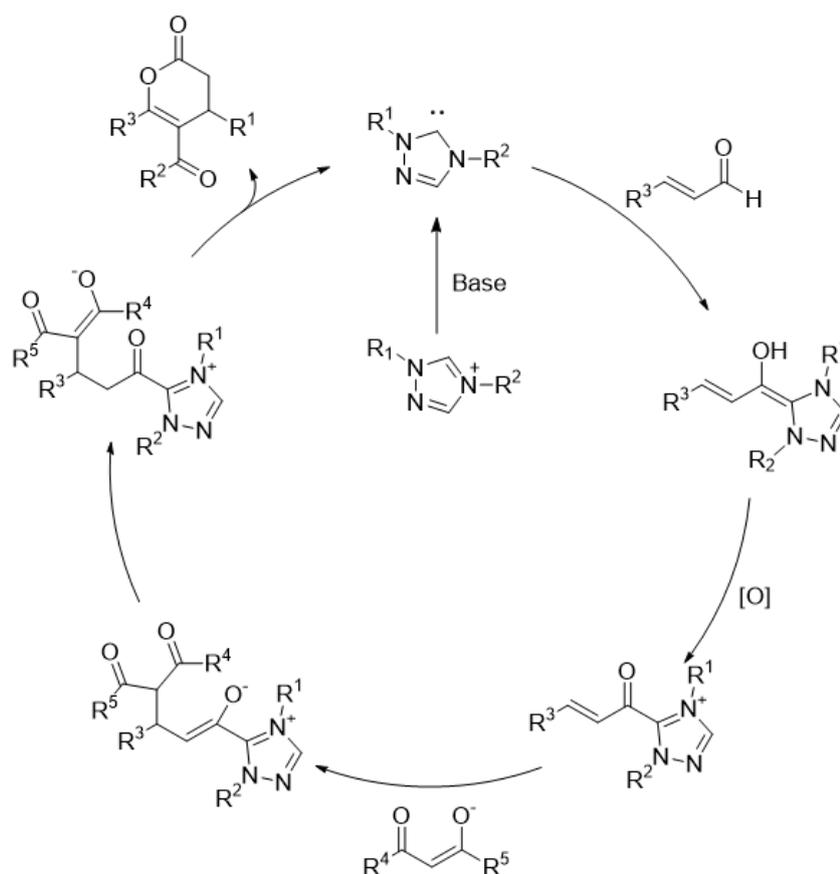
Figure 2.3: External oxidants used for NHC catalysis.

In addition to being applied in organic syntheses, the acyl azolium intermediate also has a biological significance. It was found in 2007 by Merski and Townsend that the formation of the acyl azolium with vitamin B1 is a key step in the biological synthesis of clavulanic acid, which is used in combination with antibiotics as a β -lactamase inhibitor [26].

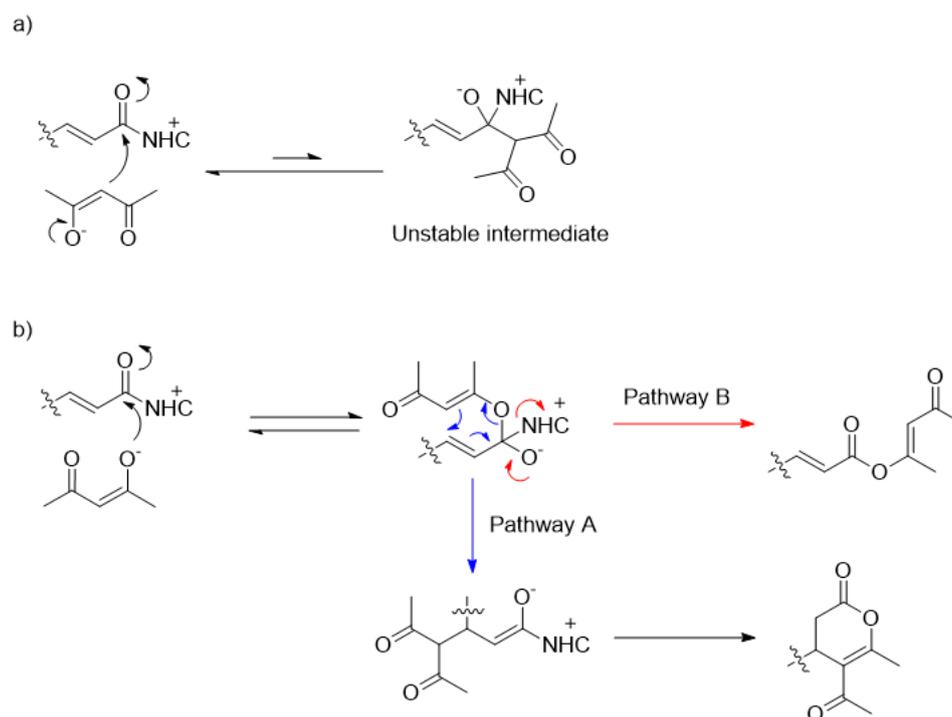
2.2.1.2 Formation of dihydropyranones

The synthesis of dihydropyranones has been studied for over two decades, and has been described as proceeding through a Michael addition/lactonization cascade reaction [27] (Scheme 2.7). Using an NHC-catalyst, this is achieved by first generating the Breslow intermediate from an α,β -unsaturated aldehyde followed by generation of the acyl azolium in accordance to section 2.2.1.1. The acyl azolium

species then readily reacts with an enolate at the 1,4-position (β -carbon) rather than the 1,2-position. This can be explained as being due to the formation of the thermodynamically unstable tetrahedral intermediate from the 1,2-attack of the enolate carbon (Scheme 2.8a). It can also be explained as being due to the soft-hard paradigm which states that soft nucleophiles (for example enolate carbons) will react with soft electrophiles (for example the β -carbon), while hard nucleophiles react with hard electrophiles. This would in addition also explain why there is no attack of the enolate oxygen (hard nucleophile) at the β -carbon. A subsequent hydrogen transfer then occurs, forming the enolate on the attached dicarbonyl. This makes a lactonization reaction possible, where the NHC can act as the leaving group to be regenerated. Following the soft-hard paradigm, an alternative mechanistic explanation would then be that the hard enolate oxygen reacts at the hard 1,2-position, with a subsequent Claisen rearrangement and lactonization to achieve the dihydropyranone structure (Scheme 2.8b, pathway A). This type of mechanism would also mean that the NHC catalyst instead can act as the leaving group, potentially resulting in the formation of an uncyclized ester (Scheme 2.8b, pathway B) [14].

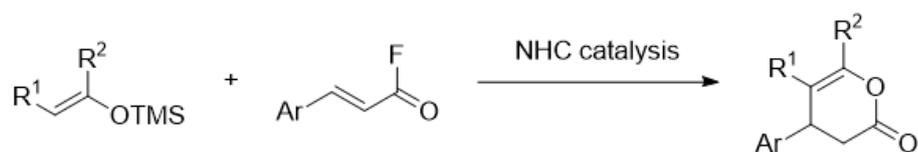


Scheme 2.7: The catalytic cycle of the NHC-catalyzed Michael addition/lactonization cascade reaction.



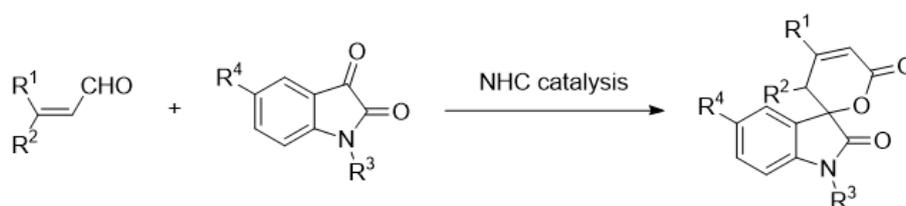
Scheme 2.8: 1,2-addition of the enolate carbon forming an unstable intermediate (a), and a 1,2-addition of the enolate oxygen to form the dihydropyranone and an uncyclized ester (b).

Various other strategies has been used in order to obtain dihydropyranones. Lupton et al. used acyl fluorides together with silyl enol ethers in order to generate dihydropyranones through NHC-catalysis. Generating the acyl azolium from the acyl fluoride would release the fluoride ion which desilylates the silyl enol ether, allowing it to attack the acyl azolium to generate the dihydropyranone (Scheme 2.9). The generated dihydropyranones were obtained in yields of up to 92% [28].



Scheme 2.9: Lupton and coworkers' synthesis of dihydropyranones from silyl enol ethers and acyl fluorides.

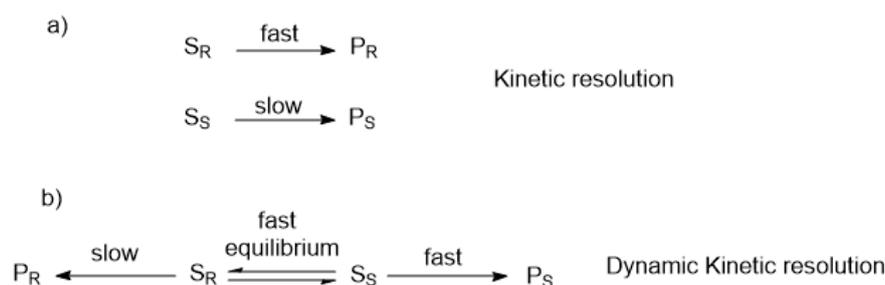
Another strategy used by Yao and coworkers was to use oxindoles to generate spirocyclic oxindole dihydropyranones (Scheme 2.10). The dihydropyranones were generated in yields up to 81%, but with poor enantioselectivities for their chiral entries [29].



Scheme 2.10: Yao and coworkers' synthesis of dihydropyranones from oxindoles.

2.3 Kinetic resolution

One of the very earliest methods of performing asymmetric synthesis has been the use of kinetic resolution (KR). IUPAC defines KR as "The achievement of partial or complete resolution by virtue of unequal rates of reaction of the enantiomers in a racemate with a chiral agent (reagent, catalyst, solvent, *etc.*)" [30]. This is represented in Scheme 2.11a, where S is the substrate, P is the product and the subscripts R and S are the different enantiomers [31].



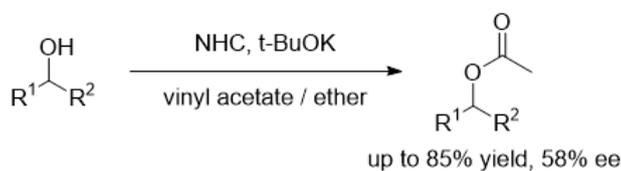
Scheme 2.11: Illustration of kinetic resolution (a) and dynamic resolution (b).

To characterize the efficiency of the kinetic resolution of a reaction, the *s*-value may be used (Equation 2.1).

$$s = \frac{\ln[(1 - C)(1 - ee)]}{\ln[(1 - C)(1 + ee)]} \quad (2.1)$$

The value takes into account both the conversion (*C*) and the *ee* of either the recovered substrate or the chiral product. A limitation to a kinetically resolved reaction is a maximum theoretical yield of 50% can only be achieved, due to only one enantiomer being able to form the product. Strategies to resolve this drawback has been made, and the most important of these is the use of dynamic kinetic resolution (DKR). This method introduces an equilibrium between the two enantiomers that persists throughout the reaction (Scheme 2.11b). For a DKR process to be more successful, this equilibrium rate should be faster than the rate of the reaction of the slow-reacting enantiomer.

KR has been under development for over one and a half decades [31] and has been widely used in industrial processes in order to obtain enantioenriched products from racemates using catalytic reactions [32]. Currently, KR may be achieved by using either enzyme catalysis, transition-metal catalysis, or organocatalysis. Within organocatalysis, NHCs has proven to be useful for KR processes, although they have limited applications. The first reported case of this was by Suzuki in 2004 which concerned enantioselective acylation of secondary alcohols using a chiral NHC catalyst (Scheme 2.12). With this method, ee-values of up to 58% were achieved. Although poor ee, the reaction was later improved by the work of Maruoka and co-workers to obtain ee-values of up to 96% [33]. Following the work of Suzuki and Maruoka, NHC-catalyzed KR processes have been on the rise with applications such as using aldehydes as acylating agents [34], selectively acylating cyclic diols [35], obtaining enantioenriched secondary amines from racemates [36], among other remarkable feats.



Scheme 2.12: Kinetic resolution of NHC-catalyzed acylation of alcohols.

2.4 Analysis methods

Herein, relevant methods of analysis used for the work will be presented.

2.4.1 High-performance liquid chromatography

High-performance liquid chromatography, or high-pressure liquid chromatography (HPLC) is a type of improved column chromatography that is used for separating compounds based on polarity. High pressure is used to push a sample together with a solvent - the mobile phase - through a column packed with a stationary phase. The two most common types of HPLC is normal-phase and reversed-phase HPLC. In normal-phase HPLC, the column stationary phase is composed of silica particles and a non-polar solvent is used as the mobile phase. In reversed-phase, the silica particles are modified in order to make the non-polar, and a polar mobile phase is instead used [37].

No matter what type of HPLC that is used, the principle behind the separation is the same. A more polar substance will adhere more strongly to the polar phase while non-polar substances will adhere more strongly to the non-polar phase. For example in reversed-phase HPLC, the more non-polar substance in the sample will spend more time adhered to the stationary phase, while the more polar substance will travel along the column with the mobile phase, causing a separation between

the substances. After the column, a detector, often a UV-detector, is connected that can show the retention times of the separated substances [37].

Another type of HPLC is chiral HPLC. This type utilizes a column with chiral substitutions on the stationary phase. This not only separates based on polarity, but also based on stereochemistry. This means that even enantiomers can be separated on the column. The enantiomeric excess can then be calculated as the difference in area between the peaks of the substances [37].

2.4.2 Nuclear magnetic resonance

Nuclear magnetic resonance (NMR) is a very powerful analytical technique for determining for example purity and molecular structure of a sample, as well as determining the yield of a reaction. The success behind the technique is based on the fact that some atomic nuclei possess spin that generates a magnetic field. By applying an external magnetic field, two spin states occur; one spin that is aligned with the external magnetic field, and one that is opposed to it. By then applying a radio frequency signal a transformation between the spin states can be induced. After the radio signal has been switched off, the spins relax back and release a measurable radio frequency signal. These signals depend on the environment of the different nuclei and from the signals, information about the sample can therefore be extracted. The most common atom nuclei to analyze are the ^1H and ^{13}C nuclei. [3]

2.4.3 Specific rotation measurement

One very important property of chiral molecules is their ability to rotate plane-polarized light. Two enantiomers of the same compound will rotate the light in opposite directions, and thus, one may determine which enantiomer is in a sample. The enantiomer that rotates the plane-polarized light to the right (positive rotation) is called the (+)-enantiomer while the one that rotates plane-polarized light to the left (negative rotation) is called the (-)-enantiomer. Since the absolute values of the rotation are the same for the two enantiomers, a racemic mixture will have a net rotation of 0° [3].

A polarimeter is a common type of equipment used to analyze whether the specific rotation of a sample is racemic or not. The polarimeter utilizes a monochromatic light source, commonly generated from a sodium lamp, together with a plane-polarizing filter. The sample is irradiated with the monochromatic light which then reaches a detector that can indicate to what extent the light has been rotated. The rotation is influenced by a number of different factors, such as temperature, concentration, path length, solvent, *etc.* Standard measurements are done at 20°C and ethanol or chloroform are commonly used solvents. The specific rotation can then be calculated from equation 2.2.

$$[\alpha]_D^{20} = \frac{\alpha}{cl} \quad (2.2)$$

$[\alpha]_D^{20}$ is the specific rotation at 20°C using the D-line of a sodium lamp (589 nm),

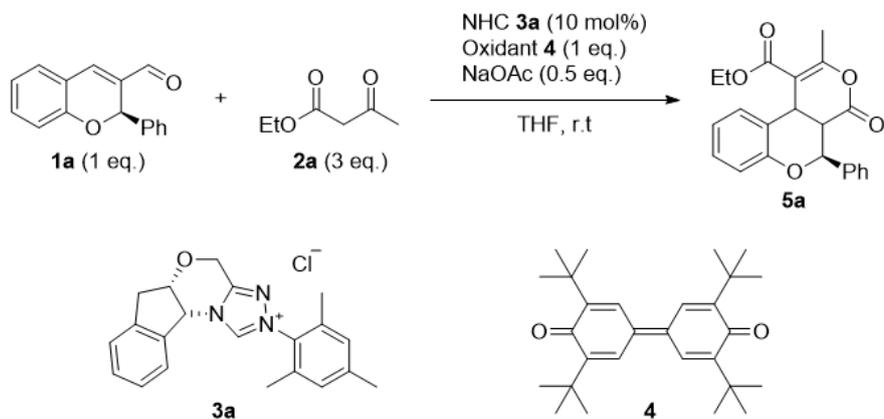
α is the observed optical rotation, c is the concentration in g/cm^3 , and l is the path length in dm [3].

3

Results and discussion

3.1 Formation of product racemate

Initially, the dihydropyranone **5a** was successfully synthesized by reacting **1a** (82% ee) with ethyl acetoacetate (**2a**), NHC catalyst **3a**, oxidant **4**, and sodium acetate in THF (Scheme 3.1). Given this promising result, attempts were made to acquire a racemate of a dihydropyranone product in order to identify the conditions for the HPLC as well as determining the retention times of the enantiomers in preparation for the optimization. Several different dicarbonyls and catalysts were screened in order to see if a product racemate could form, be purified, and be separated on the HPLC. The reaction conditions used for these tests were the same as those presented in Scheme 3.1, but using rac-**1a** rather than **1a**. The tested NHC catalysts are presented in Figure 3.1.



Scheme 3.1: First successful synthesis of a dihydropyranone

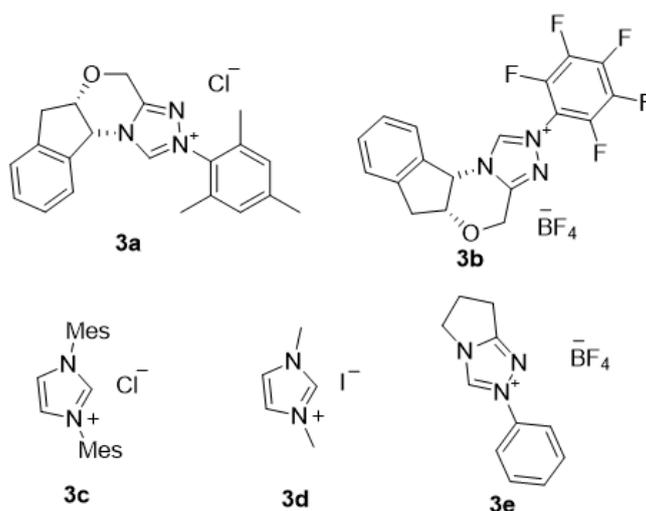


Figure 3.1: Different NHC-catalysts screened in order to obtain a racemic product mixture.

In addition to the target dihydropyranone products **5**, sideproducts **6** and **7** (Figure 3.2) were also observed in varying amounts. Rather than a Michael addition, **6** is formed through a Knoevenagel condensation, while **7** is formed from a 1,2-addition of the enolate oxygen to form an acyclic ester. The double bond of the chromene ring also seems to be able to isomerize between carbons *3-4* and *2-3*, as well as be reduced.

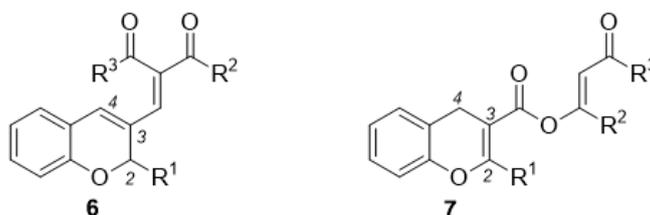
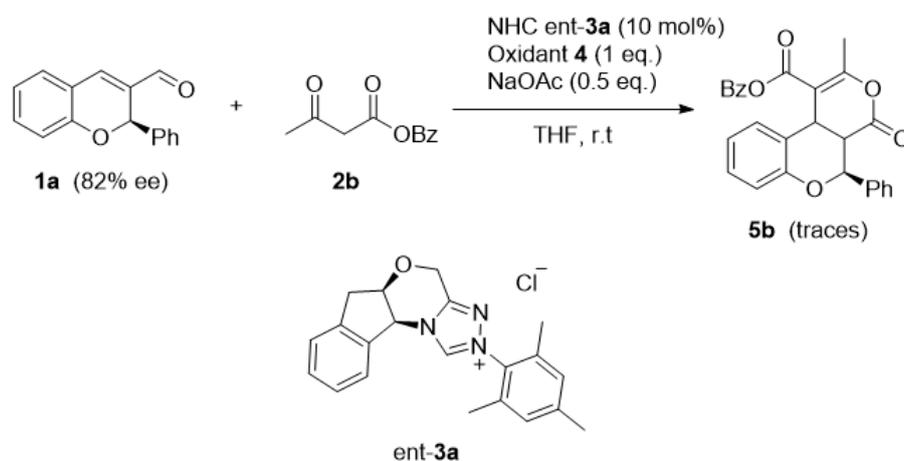


Figure 3.2: Sideproducts formed from the reaction presented in Scheme 1.2.

While several different dicarbonyls formed the target dihydropyranone products, the use of either ethyl acetoacetate or benzyl acetoacetate gave products **5a** and **5b** respectively that could more easily be purified using flash chromatography. These products were isolated in yields of 24% and 14% respectively. No other catalyst but **3a** gave any product desired product. Both **3c** and **3d** only resulted in **7** with incomplete consumption of the aldehyde, whereas **3b** and **3e** did not seem to react at all.

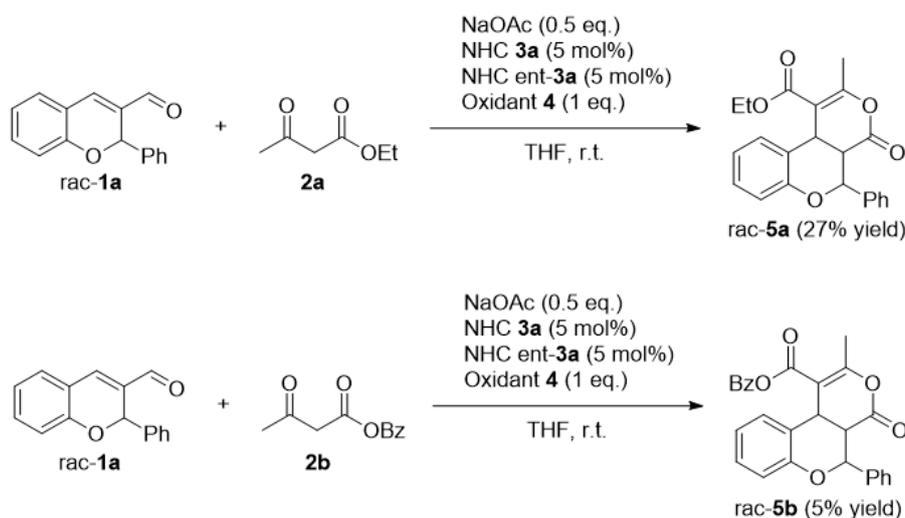
Both products **5a** and **5b** were analyzed on the chiral HPLC columns OJ, OD-H, AD, and AD-H with between 1-20% IPA in hexane. None of the HPLC runs gave any separation of a racemic product. At this point, it was suspected that the

reaction exhibited a kinetic resolution, such that the catalyst is selective enough to only convert one of the enantiomers into the desired product. Due to this suspicion, specific rotation measurements were made on two samples of **5b**; one synthesized from **1a** and one synthesized from rac-**1a**. The reason **5b** was analyzed instead of **5a** was because the polarimeter required as pure of a sample as possible, and the **5b** was able to be made much purer. The homochiral starting material had been analyzed on the AD-H HPLC column using 15% IPA in hexane and its ee was determined to be 82%. The product mixtures were each dissolved in 3 ml chloroform and the measurements were done with a sodium lamp at 20°C. Using equation 2.2, the specific rotation for the product obtained from rac-**1a** was calculated to be 102.6°, while the product obtained from **1a** was calculated to be 106.2°. This confirmed the suspicion that the product was in fact not racemic. As a further confirmation, a reaction using the homochiral aldehyde in a similar manner, but with ent-**3a**, rather than **3a**, was conducted in accordance to Scheme 3.2. It was believed that since the enantiomer of the homochiral aldehyde **1a** was converted to **5b** using catalyst **3a**, then catalyst ent-**3a** would convert little or no aldehyde into the product. This was indeed the case and **5a** was observed in trace amounts.



Scheme 3.2: Synthesis of dihydropyranone **5b** using catalyst ent-**3a**. Product was obtained in trace amounts.

New attempts were made to form a product racemate. Since the catalyst only reacted with one enantiomer, an equal mixture of both catalyst **3a**, and ent-**3a** were needed. Since both dicarbonyls **2a** and **2b** had formed the product adequately, both of these were tested according to Scheme 3.3. The products both separated on AD-H column using 10% IPA in hexane with retention times of 13.6 and 16.9 minutes for **5a**, and 19.2 and 21.4 minutes for **5b**.



Scheme 3.3: Synthesis of racemic product.

Following the revelation of the existence of a kinetic resolution, a small investigation regarding the resolution was made. By performing the reaction with 0.5 eq. of **4**, instead of the usual 1 eq., only half of the aldehyde starting material would react. It was hoped that the resolution takes place before the oxidation, meaning only the homoenolate of the enantiomer that forms the product will be oxidized into the acyl azolium species. This would theoretically mean that only half an equivalent of **4** would be needed to achieve the maximum 50% yield, while the unreacted aldehyde would be able to be isolated enantioenriched. After performing the reaction with 0.5 eq. **4** and the rac-**1a**, the unreacted aldehyde was isolated and analyzed on the AD-H column with 10% IPA in hexane. The er of the aldehyde was determined to be 54:46. Because of this, it was concluded that the resolution occurs after the oxidation, meaning 1 eq. of **4** will be needed for further experiments. The er of the aldehyde also revealed that one enantiomer reacts slightly faster than the other, since the aldehyde was not completely racemic. By comparing the chromatogram of the recovered aldehyde with the synthesized homochiral aldehyde, it was determined that it is in fact the enantiomer that forms the product that reacts slower. It was also made apparent that it is indeed the (*R*)-enantiomer of **1a** that reacts, to form the (*5R*)-enantiomer of the products, the structure of which is shown in Scheme 3.1.

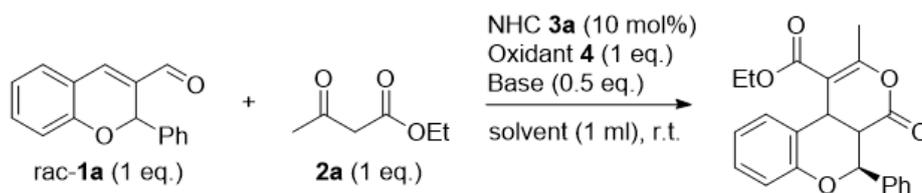
3.2 Optimization

Due to being synthesized in adequate yield, as well as being easier to purify than **5b**, product **5a** was used as a model compound for the optimization of the reaction. Because different NHC-catalysts were tested in previous experiments, these were not tested again, and catalyst **3a** was used for all subsequent experiments. Most reactions were left stirring over night, with reaction times of approximately 18 hours. Yields were calculated using ^1H NMR with DMF as an internal standard. The ee values were measured using HPLC, unless yields were

unsatisfactory, or HPLC measurements were deemed unnecessary. The reaction was also tested using 1 eq. of **2a**, rather than the previous 3 eq., and it was determined this was sufficient to achieve full conversion of the aldehyde. The following experiments were therefore performed using 1 eq. of the dicarbonyl. Other than that, the initial reaction for the optimization was the same as the model reaction described in section 3.1.

3.2.1 Screening of bases

The optimization initiated with a screening of bases. A total of 11 bases were tested, ranging from organic to inorganic bases (Table 3.1). Although NaOAc gave higher ee, sodium benzoate (NaOBz) was chosen as a more suitable base due to the much higher yield. KOAc also gave comparable values to that of sodium benzoate, but generated more of the Knoevenagel sideproduct **6a**. DABCO also formed the product in adequate yield, but with much lower ee. In general, inorganic bases worked better than organic bases.



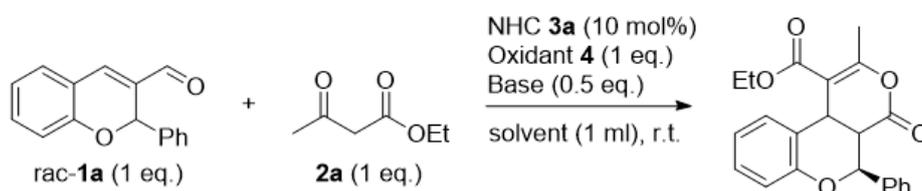
entry	NHC	base	solvent	Additional change	yield	ee
1	3a	NaOAc	THF	-	23%	96%
2	3a	KOAc	THF	-	39%	94%
3	3a	CsOAc	THF	-	19%	95%
4	3a	NaHCO ₃	THF	-	10%	NA
5	3a	Cs ₂ CO ₃	THF	-	24%	94%
6 ⁱ	3a	Na ₂ HPO ₄	THF	-	0%	NA
7	3a	DBU	THF	-	22%	85%
8	3a	DABCO	THF	-	35%	90%
9 ⁱ	3a	LiOAc*2H ₂ O	THF	-	4%	NA
10	3a	NaOBz	THF	-	39%	94%
11 ⁱ	3a	Na ₂ C ₂ O ₄	THF	-	0%	NA

ⁱ Uncomplete consumption of aldehyde

Table 3.1: Optimization table of tested bases.

3.2.2 Screening of solvents

Next, a total of 13 solvents/solvent mixtures were tested (Table 3.2). Neither toluene, DCM, DMSO, 1,4-dioxane, acetonitrile or isobutyl acetate gave any adequate yields. Apparently, the success of the reaction is highly dependent on the solvent, and the only solvent which gave comparable yield to THF was the very similar solvent 2-methyltetrahydrofuran. It is quite possible that this is due to the structure of THF which can readily coordinate itself to the ions in the solution, and by this action, increase the yield of the product. Although generated in lower yield, EtOAc gave slightly better ee. These solvents were therefore pooled in hopes of achieving the ee of ethyl acetate, but with higher yield. This was not the case, as the yield was less than for THF, and with the same ee. The optimization was therefore continued with THF.



entry	NHC	base	solvent	Additional change	yield	ee
12 ⁱ	3a	NaOBz	toluene	-	0%	NA
13 ⁱ	3a	NaOBz	DCM	-	5%	NA
14 ^{i,ii}	3a	NaOBz	DMSO	-	0%	NA
15	3a	NaOBz	EtOAc	-	31%	96%
16	3a	NaOBz	1,4-dioxane	-	8%	NA
17	3a	NaOBz	MTBE	-	24%	94%
18	3a	NaOBz	Et ₂ O	-	19%	31%
19 ^{i,ii}	3a	NaOBz	CH ₃ CN	-	3%	NA
20	3a	NaOBz	2-MeTHF	-	38%	93%
21	3a	NaOBz	Isobutyl acetate	-	7%	NA
22	3a	NaOBz	THF:TAA, 3:1	-	20%	94%
23	3a	NaOBz	THF:EtOAc, 3:1	-	34%	94%

ⁱ Uncomplete consumption of aldehyde

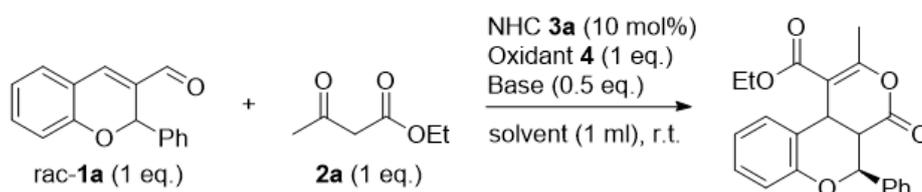
ⁱⁱ Low or no dissolution of **4**

Table 3.2: Optimization table of tested solvents and solvent mixtures.

3.2.3 Screening of additives

A number of different additives were added to monitor their effects (Table 3.3). Both ZnBr₂ and LiCl were tested together with DABCO in the hopes of achieving higher ee. This was however not the case as the reactions did not proceed at all. 4Å MS were added to remove any trace amounts of water that might interfere with

the reaction. This operation only gave a lower yield of the product. IPA was then added in hopes of forming the isopropyl ester from the enantiomer that did not yield the product and thus receiving two products from the reaction that could easily be separated. This was however not the case as the isopropyl ester was not observed. The Lewis acids $\text{Ti}(\text{OiPr})_4$ and LiCl were tested as these had been reported to achieve higher ee-values [38, 39]. However, both gave lower yields and ee-values. In fact, LiCl seems to almost have completely removed the enantioselectivity, achieving an ee of only 10%. Lastly, the effect of the sodium ions was tested by both increasing the concentration of sodium using NaBF_4 and removing the ions with 15-crown-5. The yields in both cases decreased while the ee of using the crown ether was comparable to not using it.



entry	NHC	base	solvent	Additional change	yield	ee
24 ⁱ	3a	DABCO	THF	1.5 eq. LiCl	0%	NA
25 ⁱ	3a	DABCO	THF	1.2 eq. ZnBr_2	0%	NA
26	3a	NaOBz	THF	4Å MS	16%	NA
27	3a	NaOBz	THF	0.5 eq. IPA	23%	NA
28	3a	NaOBz	THF	0.2 eq. $\text{Ti}(\text{OiPr})_4$	18%	91%
29	3a	NaOBz	THF	0.2 eq. LiCl	16%	10%
30 ⁱ	3a	NaOBz	THF	0.2 eq. NaBF_4	3%	NA
31	3a	NaOBz	THF	0.5 eq. 15-crown-5	27%	93%

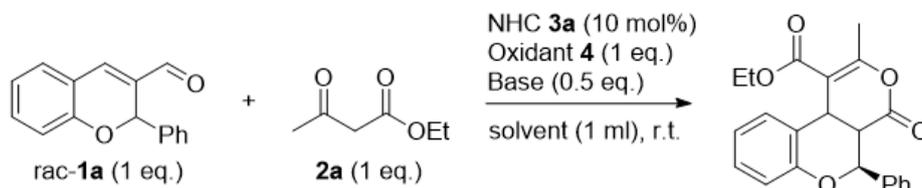
ⁱ Uncomplete consumption of aldehyde

Table 3.3: Optimization table of tested additives.

3.2.4 Screening of equivalents and miscellaneous

To conclude the optimization, different equivalents of the dicarbonyl, base and NHC were tested, as well as other changes (Table 3.4). Increasing the amount of dicarbonyl to 2 eq. severely decreased the yield, while the ee was unaffected. Either increasing the base to 1 eq. or decreasing to 0.25 eq. also negatively affected the yield, but left the ee the same. Similar effects were seen with 20 mol% and 5 mol% of NHC, although a slight increase in ee was observed with a higher catalyst loading. Performing the reaction at 0 °C decreased the kinetics of the reaction, achieving only 83% conversion of the aldehyde after 48 hours. Selectivity of the reaction was however improved, and the ee was increased from 94% to 97%. Different concentrations of the starting materials were also tested. Decreasing the

concentration worsened the yield and selectivity, while increasing it seemed to give no major difference. Lastly, KOAc and EtOAc were tried together, as both of these had given promising results in previous experiments. However, the yield was drastically decreased.



entry	NHC	base	solvent	Additional change	yield	ee
32	3a	NaOBz	THF	2 eq. 2a	15%	93%
33	3a	NaOBz	THF	0.25 eq. base	23%	NA
34	3a	NaOBz	THF	1 eq. base	24%	94%
35	3a	NaOBz	THF	20 mol% 3a	28%	95%
36	3a	NaOBz	THF	5 mol% 3a	12%	NA
37 ^{i,ii}	3a	NaOBz	THF	0°C	24%	97%
38	3a	NaOBz	THF	2 ml THF	25-32%	89%
39	3a	NaOBz	THF	0.5 ml THF	36%	94%
40 ⁱ	3a	KOAc	EtOAc	-	10%	NA

ⁱ Uncomplete consumption of aldehyde

ⁱⁱ Reaction time of 2 days

Table 3.4: Optimization table of miscellaneous tests.

3.3 Scope of reaction

After the optimization, the scope of the reaction was investigated. The reaction conditions used for the following reactions were the same as for the initial conditions of the optimization, but using 0.5 eq. of sodium benzoate, rather than sodium acetate. The scope was investigated by both changing the nucleophile, and using derivatives of the starting material **1**. Successful products are presented in Figure 3.3, together with ee-values and isolated yields. It is apparent that the reaction works with both aromatic R¹-substituents as well as with alkyl substituents at carbon 2 of the chromene ring. It should be noted that product **5f** was successfully synthesized, but was not purified due to time restrictions. In the case of aromatic substituents, parasubstitution of electron-withdrawing groups such as fluorine substitution work better than electron-donating groups, such as methoxy substitution. It should also be mentioned that the reaction was successful with a nitrogroup substituted in the para-position, but due to a complex reaction mixture and time restrictions, the product could not be isolated and is therefore

not included in this report. Attempts were also made to synthesize products with ortho-substitution of both nitro- and methoxy groups. However, none of these resulted in product formation, meaning there is probably a steric hindrance effect associated with the aromatic rings.

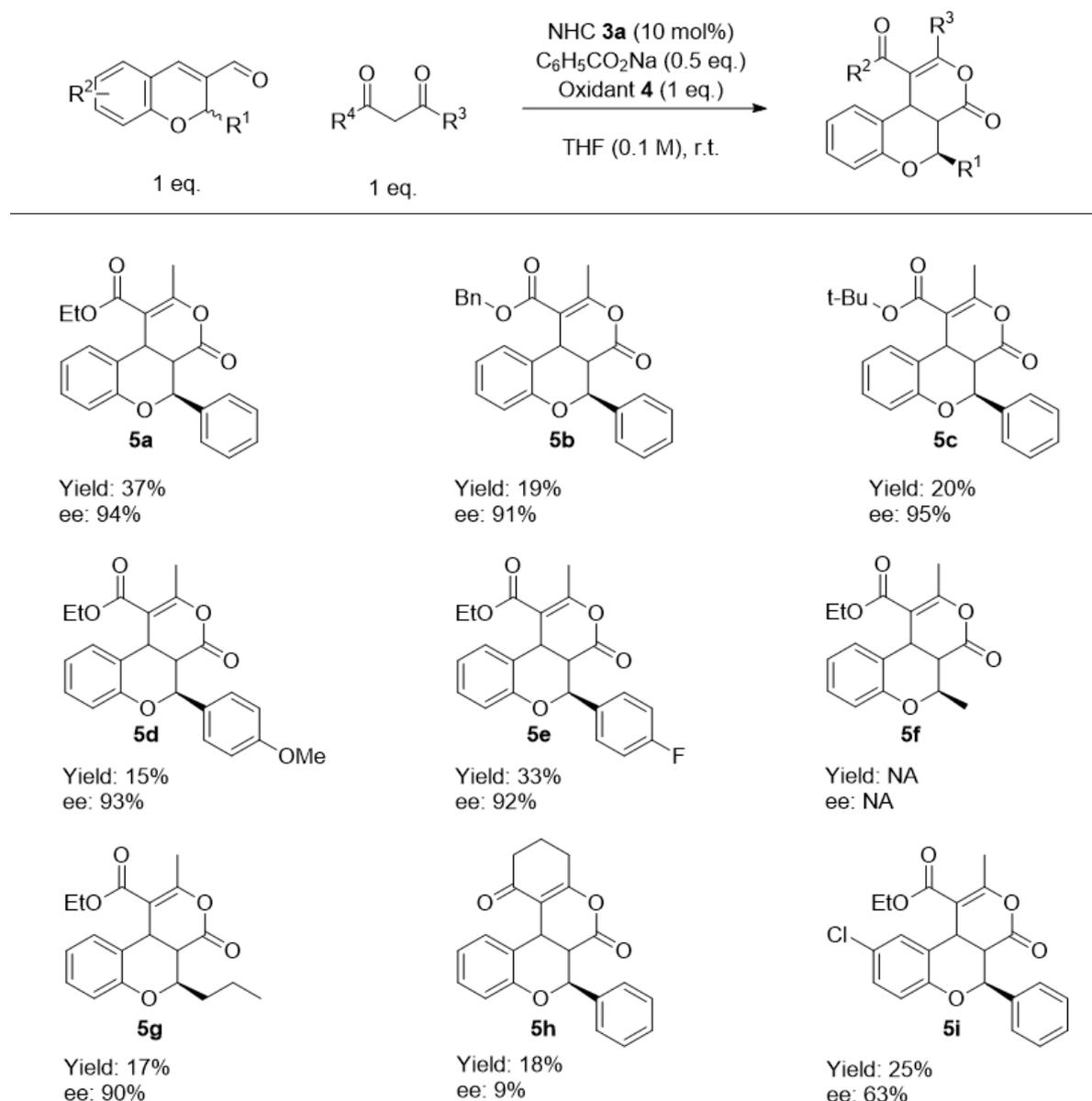
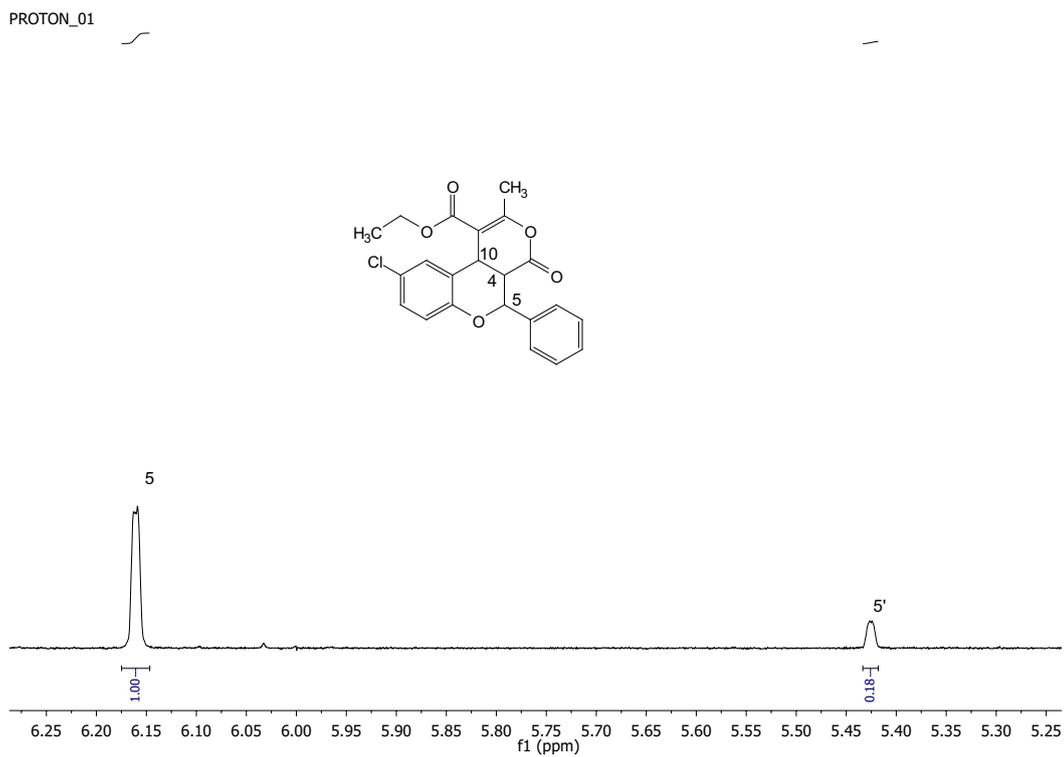
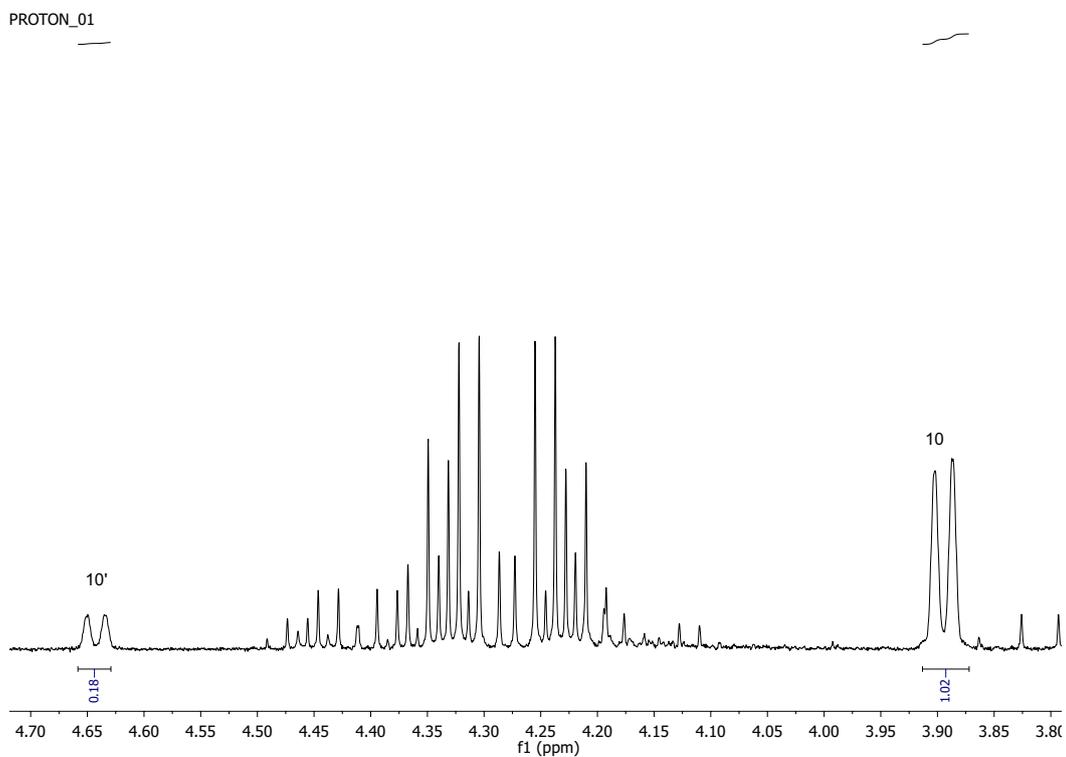


Figure 3.3: Scope of the dihydropyranone reaction. Yields refer to isolated yields.

In addition to the alkyl-substituted entries **5f** and **5g**, an attempt was made to create the dimethyl substituted dihydropyranone, in the hopes of achieving a product structure even closer to that of tetrahydrocannabinol (Figure 1.2c). However, this also did not result in product formation, most likely due to the addition of a second methyl group which acts as a steric hindrance.

The cyclic dicarbonyl 1,3-cyclohexanedione was also tested in order to add an additional ring to the skeletal structure. The reaction worked, and the product was able to be isolated. Surprisingly, however, the enantioselectivity of the reaction drastically dropped compared to the other entries, and an ee-value of just 9% was achieved. The reason for this is unclear, but similar results were obtained by Lupton and coworkers when they tried to form a dihydropyranone from an enol ester of 1,3-cyclohexanedione [28]. The Lupton group achieved a moderate ee-value of 50%, but only after changing the reaction conditions as well as the type of catalyst used.

Finally, a dihydropyranone with a chloro-substitution on carbon 6 of the chromene ring was synthesized (**5i**). It was believed that **5i** would form in better yield due to the chlorine being electron withdrawing, making the aldehydic carbonyl as well as the β -position more electron poor and therefore more reactive towards nucleophiles. Although the product was isolated in only the comparably moderate yield of 25%, another effect was discovered. The product seemingly formed two diastereomers, according to the ^1H NMR, as duplicates of all peaks were present with different shifts. Examples of such peaks are shown in figures 3.4-3.6. The reason for the decreased diastereoselectivity may be due to the chlorine making the chromene aldehyde more reactive, and as a consequence of that, makes the selectivity decrease. However, the exact reason why this product would form different diastereomers is not completely certain. It was also hypothesized that rather than diastereomers, rotamers were instead formed, where the chlorine atom and the ester group would hinder the product's rotation. ^1H NMR was therefore done in deuterated DMSO rather than deuterated chloroform. If the isomers were in fact rotamers, the solvent change would change the equilibrium between the isomers, giving a different integration ratio between them in the NMR. This was however not the case, and similar ratios were achieved using DMSO as with chloroform. This does therefore not support the hypothesis that the product exists as rotamers. No further investigations regarding the true nature of **5i** was thereafter done, due to time restrictions. Assuming the product existed as diastereomers, the dr was calculated from the crude product mixture to be 6.4:1.

Figure 3.4: Duplicate of signal for carbon 5 of **5i**Figure 3.5: Duplicate of signal for carbon 10 of **5i**

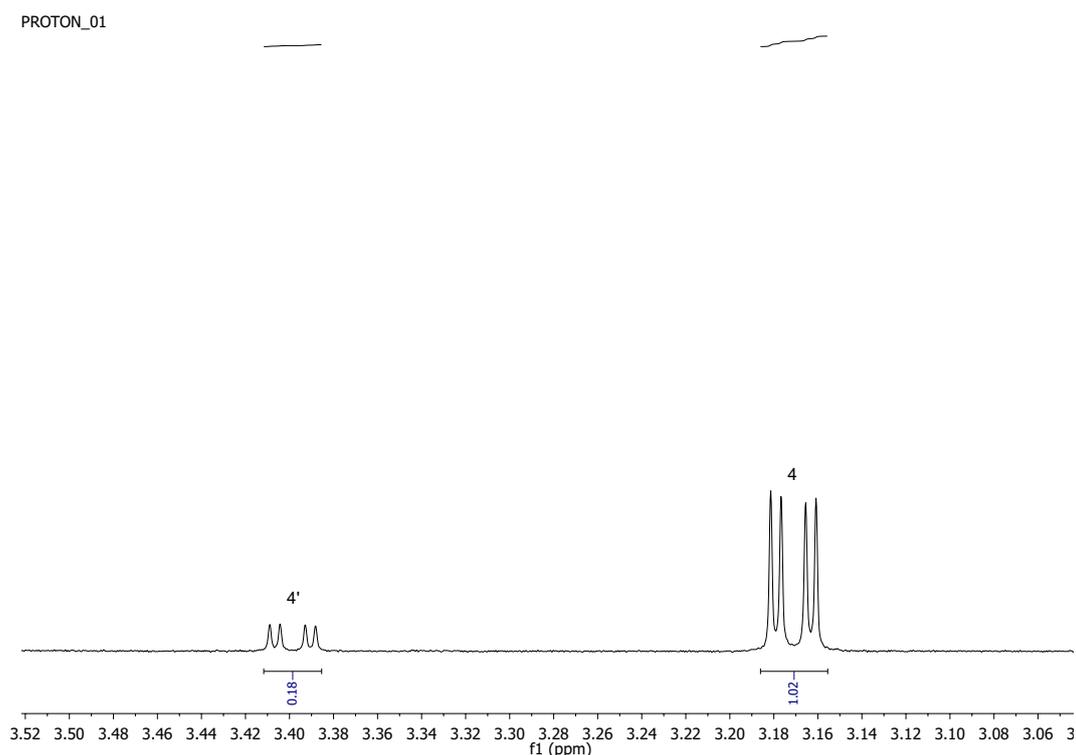


Figure 3.6: Duplicate of signal for carbon 4 of **5i**

The full list of products that were not observed at all or observed in trace amounts are presented in figure 3.7. It is worth noting however, that attempts to make **5k**, **5m**, **5o**, and **5q** were made during section 3.1 and were therefore not tested with the optimized conditions. One is still able to conclude that there seems to be some kind of steric hinderance effect with the type of dicarbonyl used. Replacing ethyl acetoacetate with for example ethyl benzoylacetate or ethyl pivaloylacetate in the hopes of forming **5n** or **5o** respectively, no reaction to form the respective dihydropyranone was observed. The aldehydes did however react to form sideproducts. In addition, there may also be rather strong electronic effect associated with the type of dicarbonyl used. Attempting to make **5p** from ethyl 4,4,4-trifluoroacetoacetate resulted in no consumption of the aldehyde. Whether the desired reaction is inhibited by the steric bulk of the CF₃-group, or by its strong electron withdrawing ability is undetermined. The side reactions, however, proceeded regardless of the bulkiness in previous attempts. This would mean that at least the side reactions are likely to be inhibited by electronic effects. It could be that the CF₃-group makes the deprotonated dicarbonyl much more stable, due to the lower pK_a, and thus making it unable to react. It could on the other hand also be due to the more electrophilic nature of the ketone which may cause the NHC catalyst to react with the CF₃-carbonyl instead of attacking the aldehyde.

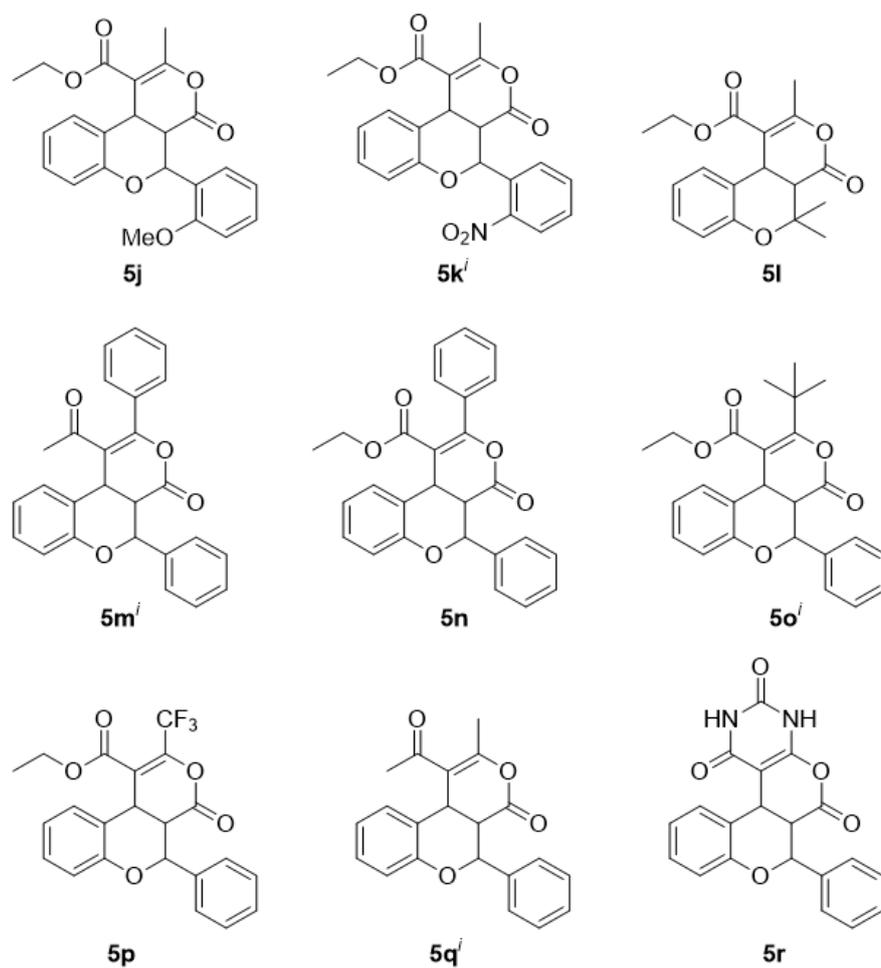


Figure 3.7: Products not observed or observed in trace amounts

ⁱAttempt to make product was made using the pre-optimized conditions described in section 3.1

4

Conclusion

In this report, the reaction to form dihydropyranones from chromene aldehydes and 1,3-dicarbonyls has been optimized and the scope has been investigated. The reaction proceeds through a kinetic resolution to form a homochiral product from racemic starting materials, in addition to in most cases only forming one diastereomer. Of the tested parameters, the optimal conditions were achieved at room temperature with sodium benzoate as a base, THF as a solvent and by performing the reaction under dry conditions. Investigation of the scope revealed that the reaction is successful for para-substitution on the phenyl ring with both activating as well as deactivating groups. Ortho-substitution did however inhibit the reaction, likely due to sterics. The reaction is also successful when exchanging the phenyl ring for an alkyl group. Enantioselectivities were also drastically dropped when using a cyclic dicarbonyl as well as when using a chromene with a chloro-substitution on carbon 6. The latter also seemed to form two different diastereomers, however the reason for this is still unknown.

For future studies, it would be interesting to further investigate the effect of substitution on the aromatic ring of the chromene structure, as only one such entry was presented here. It would also be of interest to test other cyclic 1,3-dicarbonyls to see if similar unsatisfactory ee-values are obtained as for the 1,3-cyclohexanedione, and in that case, how it could be improved. Finally, it would be of great interest to make the reaction more green by using electron transfer mediators and oxygen as a terminal oxidant, similar to earlier work of the Sundén group [4]. This would mean substoichiometric amounts of the oxidant can be used, and thus, less waste would be generated.

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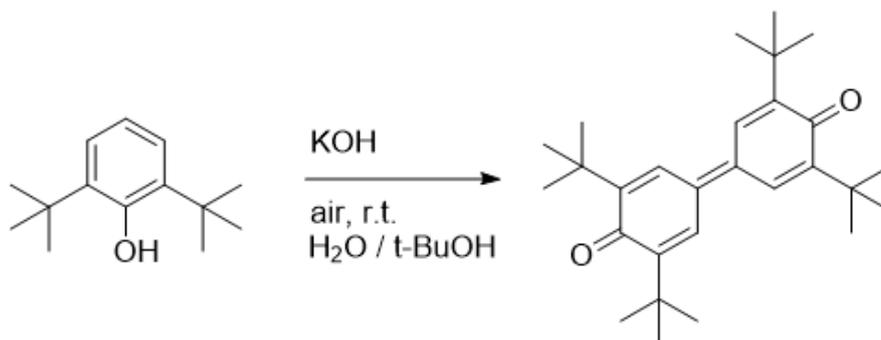
A

Appendix A - Experimental section

All commercial reagents were used as received. Anhydrous solvents were obtained by adding 4Å MS to an oven-dried round-bottom flask, capping it and then evacuating and refilling with nitrogen gas (5 times). Solvent was then added via syringe and once again evacuated and refilled with nitrogen gas (5 times). The solvents were stored for 24 hours before usage. Flash column chromatography was performed using the biotage Isolera™ Spektra One with either Biotage SNAP®-10 g or SNAP®-25 g KP-sil columns. Samples were loaded onto a samplet and left to dry under nitrogen gas for at least 40 minutes before performing flash chromatography. When THF was used as a solvent, this was first evaporated under reduced pressure before loading onto the samplet. TLC was performed using silica gel plates with UV-light (254 nm) and/or CAM-staining for visualization. ¹H NMR (400 MHz) and ¹³C NMR (101 MHz) data were obtained from a Varian 400, using deuterated chloroform (CDCl₃) as a solvent. The chemical shifts are reported as parts per million (ppm) and the coupling constants of the multiplicities are reported in Hertz (Hz). Multiplicities are assigned as followed: s = singlet, as = apparent singlet, d = doublet, t = triplet, q = quartet, dq = doublet of quartet, etc. The MestReNova software was used as an analysis tool. Chiral HPLC was done on a Varian 9012 with a Varian 9050 UV detector (254 nm) using the CHIRALPAK® columns AD-H and AD, as well as the CHIRALCEL® columns OJ and OD-H with a flow rate of 1 ml/min. Optical rotation measurements were done on a Perkin Elmer Polarimeter 341 LC with chloroform as a solvent and a 10 cm cell.

A.1 Synthesis of compounds

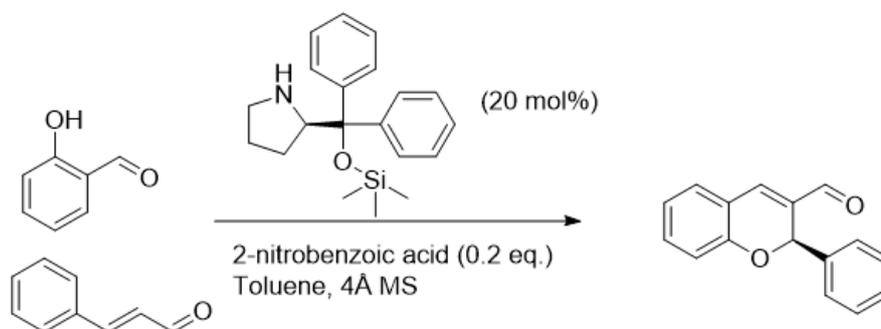
A.1.1 Procedure for the synthesis of 3,3',5,5'-tetra-*tert*-butyldiphenone (4) [40]



Scheme A.1: Synthesis of the Kharash oxidant 4.

To a 1000 ml round-bottom flask, KOH (20.1 g, 360 mmol) was added and dissolved in 30 ml of distilled water, followed by 250 ml of *t*-BuOH. Then, 2,6-di-*tert*-butylphenol (24.5 g, 119 mmol) was added to the round-bottom flask and stirred with air bubbling through the solution for 2 days. Solvent was added during this time as it evaporated. After the 2 days, the mixture was diluted with 250 ml of water and then filtrated. Recrystallization with IPA was performed and the product was then filtrated, washed with IPA and then dried under reduced pressure. The product was isolated as brown crystals in 80% yield.

A.1.2 Procedure for the synthesis of homochiral starting material (1a)

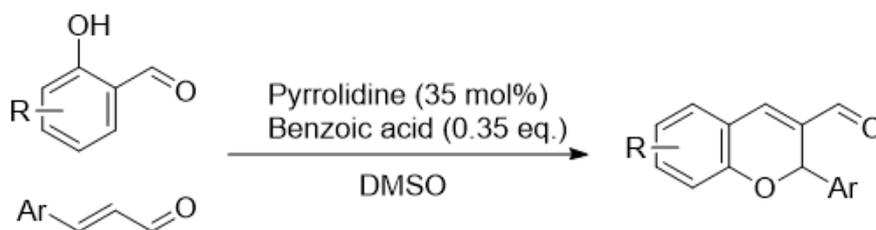


Scheme A.2: Synthesis of homochiral starting material 1a.

Procedure was done as described by Sundén et al. [41]. To an oven-dried microwave reaction vial was added a magnet, 2-nitrobenzoic acid (135 mg, 0.807

mmol), (S)-(-)- α,α -Diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (278 mg, 0.854 mmol) and 8 ml dry toluene. The vial was capped and via syringe was added *trans*-cinnamaldehyde (604 μ L, 634 mg), followed by salicylaldehyde (426 μ L, 488 mg). The solution was left stirring for 24 hours. The mixture was separated using flash chromatography using an eluent of 5 vol% EtOAc in PE ($R_f = 0.13$) and isolated as a yellow solid in 54% yield. Chiral HPLC was performed with an AD-H column with an eluent consisting of 15% IPA in hexane. The ee was determined to be 82%.

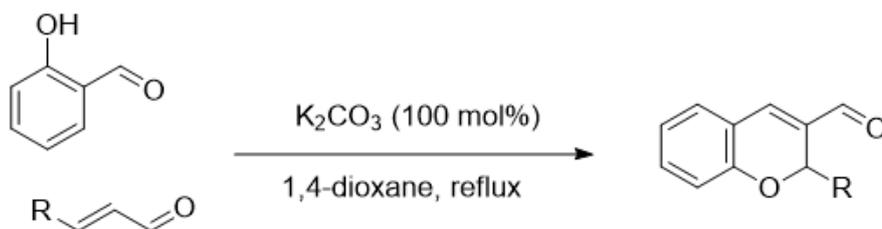
A.1.3 General procedure 1 for the synthesis of racemic starting materials



Scheme A.3: Synthesis of racemic starting material

Procedure was done as described by Sundén et al. [42]. To a round-bottom flask was added a magnet, 0.35 eq. benzoic acid, 35 mol% pyrrolidine, and DMSO (15 ml). While stirring, 1.5 eq. salicylaldehyde was added followed by 1 eq. of the appropriate *trans*-cinnamaldehyde (945 mg). The reaction was left over night and then diluted with 50 ml EtOAc and 100 ml water. The layers were separated and the water phase was washed with additional 50 ml EtOAc twice. The organic phase was collected and concentrated under reduced pressure followed by separation using flash chromatography.

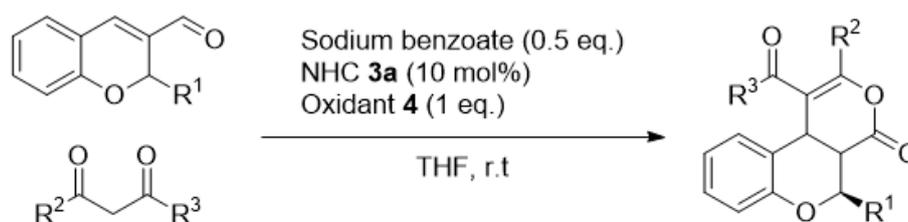
A.1.4 General procedure 2 for the synthesis of racemic starting materials



Scheme A.4: Synthesis of racemic starting materials

Procedure was done as described in patent US6596758 [43]. To an oven-dried microwave reaction vial was added a magnet and 100 mol% K_2CO_3 . The vial was capped and evacuated and refilled with N_2 (5 times). Dry 1,4-dioxane (5 ml) was added along with 1 eq. salicylaldehyde. The mixture was stirred at room temperature while 1.1 eq. of the appropriate enal was added. The mixture was placed in an oil bath (110 °C) and after 2.5-3.5 hours, the mixture was removed from the bath and left to cool over night. The mixture was then diluted with water (30 ml) and EtOAc (70 ml). The layers were separated and the organic phase was washed with additional water (2x30 ml). The organic phase was then washed with K_2CO_3 (pH = 11, 3x40 ml) and brine (30 ml). The organic phase was dried over $MgSO_4$ and then dried under reduced pressure.

A.1.5 General procedure for the synthesis of dihydropyranones



Scheme A.5: Synthesis of dihydropyranones

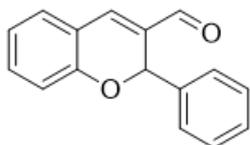
To an oven-dried microwave reaction vial was added a magnet, appropriate aldehyde **1** (0.10 mmol), 10 mol% NHC catalyst **3a**, 1 eq. of oxidant **4**, and 0.5 eq. sodium benzoate. The vial was capped and then evacuated and backfilled with N_2 3 times. 1 eq. of appropriate dicarbonyl was added in 1 ml of THF. The mixture was left on stirring over night. The mixture was then separated using flash chromatography.

B

Appendix B - Detailed analytical data

Herein are presented detailed analytical data of all of the synthesized starting materials, products, as well as the oxidant. All entries but **1c**, **1e**, **1f**, **5f** and **5g** were synthesized by me. These entries were instead synthesized by PhD student Anton Axelsson, and included for the sake of increasing the scope and to better understand the reaction.

2-phenyl-2*H*-chromene-3-carbaldehyde (**1a**) [44]



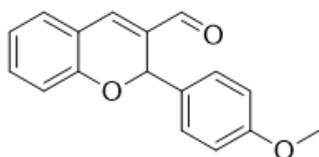
Prepared according to section A.1.3 for racemic version, and A.1.2 for homochiral version. Product was separated using flash chromatography with an eluent consisting of 5 vol% EtOAc in PE ($R_f = 0.13$). The product was isolated as a yellow solid in up to 54% yield.

HPLC conditions: CHIRALPAK® AD-H (15 vol% IPA in hexane). $t_R = 7.8$ min for the (R)-enantiomer (major) and 9.1 for the (S)-enantiomer (minor). er of homochiral version = 91:9 (R:S).

^1H NMR: (400 MHz, CDCl_3) δ 9.65 (s, 1H), 7.42 (s, 1H), 7.36-7.24 (m, 7H), 6.96-6.93 (m, 1H), 6.88-6.85 (m, 1H), 6.34 (s, 1H).

^{13}C NMR: (101 MHz, CDCl_3) δ 190.1, 154.8, 140.9, 139.1, 133.7, 129.5, 128.5, 126.8, 121.8, 120.0, 117.1, 74.2, 64.01, 25.3.

2-(4-methoxyphenyl)-2*H*-chromene-3-carbaldehyde (**1b**) [45]



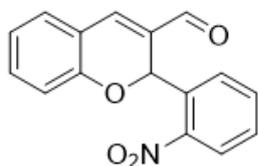
Prepared according to section A.1.3. Product was separated using flash chromatography with an eluent consisting of 5 vol% EtOAc in PE ($R_f = 0.07$). The product was isolated as a yellow solid in 46%

yield.

^1H NMR: (400 MHz, CDCl_3) δ 9.62 (s, 1H), 7.41 (s, 1H), 7.30–7.23 (m, 4H), 6.96–6.92 (m, 1H), 6.85–6.82 (m, 1H), 6.81–6.76 (m, 2H), 6.26 (s, 1H), 3.74 (s, 3H).

^{13}C NMR: (101 MHz, CDCl_3): δ 190.0, 159.9, 154.7, 140.6, 133.8, 133.6, 131.2, 129.3, 128.3, 121.7, 120.0, 117.2, 113.9, 74.0, 55.2.

2-(2-nitrophenyl)-2*H*-chromene-3-carbaldehyde (1c)

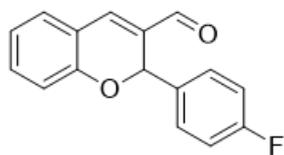


Prepared according to section A.1.3. Product was separated using flash chromatography with an eluent consisting of 25% EtOAc in PE (R_f = 0.18). The product was isolated as a red/orange solid in 49% yield.

^1H NMR: (400 MHz, CDCl_3) δ 9.68 (s, 1H), 7.87–7.83 (m, 1H), 7.57 (s, 1H), 7.46–7.40 (m, 2H), 7.29–7.26 (m, 2H), 7.26–7.24 (m, 1H), 7.08 (s, 1H), 6.98–6.94 (m, 1H), 6.81–6.78 (m, 1H).

^{13}C NMR: (101 MHz, CDCl_3): δ 189.3, 154.2, 142.2, 134.0, 132.5, 132.0, 131.9, 129.7, 129.3, 128.6, 124.8, 122.3, 119.6, 117.3, 69.2.

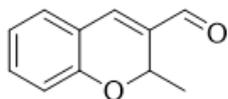
2-(4-fluorophenyl)-2*H*-chromene-3-carbaldehyde (1d) [46]



Prepared according to section A.1.3. Product was separated using flash chromatography with an eluent consisting of 5 vol% EtOAc in PE (R_f = 0.06). The product was isolated as a yellow solid in 48% yield.

^1H NMR: (400 MHz, CDCl_3) δ 9.64 (s, 1H), 7.43 (s, 1H), 7.35–7.25 (m, 4H), 6.99–6.93 (m, 3H), 6.87–6.84 (m, 1H), 6.30 (s, 1H).

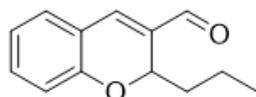
^{13}C NMR: (101 MHz, CDCl_3): δ 189.9, 162.81 (d, $J=247.3$ Hz), 154.6, 140.9, 134.9 (d, $J=3.3$ Hz), 133.8, 133.6, 129.4, 128.7 (d, $J=8.3$ Hz), 121.9, 119.8, 117.2, 115.5 (d, $J=21.7$ Hz), 73.5.

2-methyl-2H-chromene-3-carbaldehyde (1e) [47]

Prepared according to section A.1.4. Product was separated using flash chromatography with an eluent consisting of 5 vol% EtOAc in PE ($R_f = 0.19$). The product was isolated as a yellow oil in 58% yield.

^1H NMR: (400 MHz, CDCl_3) δ 9.53 (s, 1H), 7.32-7.27 (m, 1H), 7.22-7.18 (m, 2H), 6.96-6.92 (m, 1H), 6.88-6.86 (m, 1H), 5.41 (q, $J=6.6$ Hz, 1H), 1.35 (d, $J=6.7$ Hz, 3H).

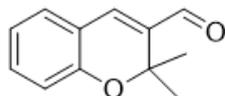
^{13}C NMR: (101 MHz, CDCl_3): δ 190.0, 154.4, 140.3, 136.1, 133.4, 129.2, 121.6, 119.9, 117.3, 69.8, 19.9.

2-propyl-2H-chromene-3-carbaldehyde (1f) [41]

Prepared according to section A.1.4. Product was separated using flash chromatography with an eluent consisting of 5 vol% EtOAc in PE ($R_f = 0.27$). The product was isolated as a yellow oil in 54% yield.

^1H NMR: (400 MHz, CDCl_3) δ 9.53 (s, 1H), 7.32-7.27 (m, 1H), 7.21-7.18 (m, 2H), 6.96-6.91 (m, 1H), 6.89-6.86 (m, 1H), 5.28 (dd, $J=9.4, 3.1$ Hz, 1H), 1.80-1.70 (m, 1H), 1.57-1.42 (m, 3H), 0.90 (t, $J=7.1$ Hz, 3H).

^{13}C NMR: (101 MHz, CDCl_3): δ 190.2, 154.6, 140.7, 135.5, 133.3, 129.2, 121.5, 120.4, 117.2, 73.1, 35.8, 18.3, 13.7.

2,2-dimethyl-2H-chromene-3-carbaldehyde (1g) [48]

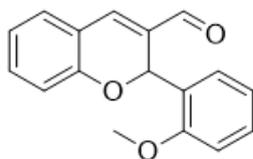
Prepared according to section A.1.4. Product was separated using flash chromatography with an eluent consisting of 5 vol% EtOAc in PE ($R_f = 0.21$). The product was isolated as a yellow oil in 17% yield.

^1H NMR: (400 MHz, CDCl_3) δ 9.45 (s, 1H), 7.31-7.26 (m, 1H), 7.18-7.15 (m, 1H), 7.09 (s, 1H), 6.92-6.88 (m, 1H), 6.83-6.80 (m, 1H), 1.62 (s, 6H).

^{13}C NMR: (101 MHz, CDCl_3): δ 190.4, 154.2, 142.5, 139.0, 133.5, 128.8, 121.2,

119.6, 116.8, 78.7, 26.6.

2-(2-methoxyphenyl)-2*H*-chromene-3-carbaldehyde (1h) [45]

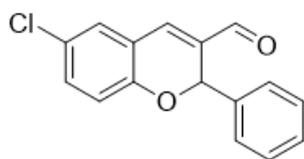


Prepared according to section A.1.3. Product was separated using flash chromatography with an eluent consisting of 5 vol% EtOAc in PE ($R_f = 0.11$). The product was isolated as a yellow solid in 53% yield.

^1H NMR: (400 MHz, CDCl_3) δ 9.58 (s, 1H), 7.50 (s, 1H), 7.28-7.21 (m, 3H), 7.13-7.10 (m, 1H), 6.94-6.90 (m, 2H), 6.85-6.74 (m, 3H), 3.89 (s, 3H)

^{13}C NMR: (101 MHz, CDCl_3): δ 189.7, 157.3, 154.8, 141.2, 133.4, 133.0, 130.4, 129.0, 128.3, 126.0, 121.4, 120.3, 120.0, 117.2, 111.3, 69.1, 55.8.

6-chloro-2-phenyl-2*H*-chromene-3-carbaldehyde (1i) [44]

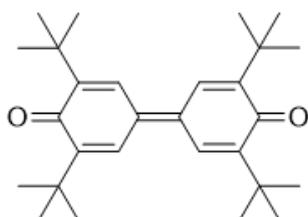


Prepared according to section A.1.3. Product was separated using flash chromatography with an eluent consisting of 5 vol% EtOAc in PE ($R_f = 0.18$). The product was isolated as a yellow solid in 64% yield.

^1H NMR: (400 MHz, CDCl_3) δ 9.64 (s, 1H), 7.36-7.26 (m, 6H), 7.24-7.19 (m, 2H), 6.82-6.80 (m, 1H), 6.34 (s, 1H).

^{13}C NMR: (101 MHz, CDCl_3): δ 189.8, 153.2, 139.2, 138.5, 134.5, 133.1, 128.9, 128.7, 128.5, 126.8, 126.5, 121.2, 118.6, 74.5

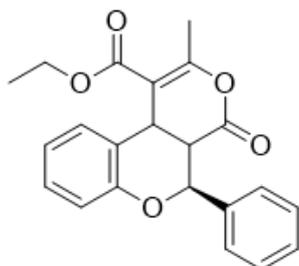
3,3',5,5'-tetra-*tert*-butyldiphenoquinone (4) [40]



Prepared according to section A.1.1.

^1H NMR: (400 MHz, CDCl_3) δ 7.69 (s, 4H), 1.35 (s, 36H).

^{13}C NMR: (101 MHz, CDCl_3): δ 186.5, 150.4, 136.1, 126.0, 36.0, 29.6.

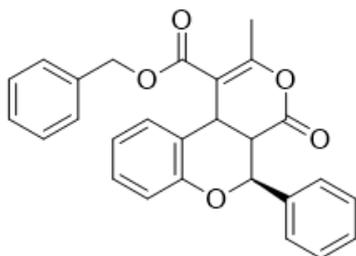
ethyl (5S)-2-methyl-4-oxo-5-phenyl-4a,10b-dihydro-4H,5H-pyrano[3,4-c]chromene-1-carboxylate (5a)

Prepared according to section A.1.5. Product was separated using flash chromatography with an eluent consisting of 70% PE and 30% of a 1:19 mixture of EtOAc:DCM. Product was isolated as a yellow oil in 20% yield.

HPLC conditions: CHIRALPAK® AD-H (10 vol% IPA in hexane), $t_R = 13.6$ (major), 16.9 min (minor), ee = 94%.

^1H NMR: (400 MHz, CDCl_3) δ 7.39–7.26 (m, 5H), 7.24–7.19 (m, 1H), 7.03–7.00 (m, 1H), 6.96–6.85 (m, 2H), 6.17 (as, 1H), 4.30 (dq, $J=10.9, 7.1$ Hz, 1H), 4.22 (dq, $J=10.9, 7.1$ Hz, 1H), 3.95 (d, $J=6.3$ Hz, 1H), 3.17 (dd, $J=6.3, 1.9$ Hz, 1H), 2.38 (s, 3H), 1.26 (t, $J=7.1$ Hz, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 166.5, 166.3, 161.3, 153.0, 139.8, 129.2, 128.9, 128.0, 127.6, 124.9, 121.0, 120.3, 117.0, 110.6, 73.3, 61.2, 42.5, 27.6, 19.0, 14.2

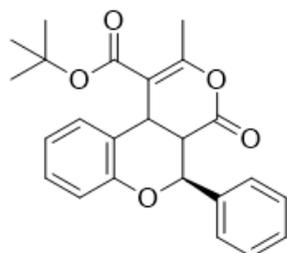
benzyl (5S)-2-methyl-4-oxo-5-phenyl-4a,10b-dihydro-4H,5H-pyrano[3,4-c]chromene-1-carboxylate (5b)

Prepared according to section A.1.5. Product was separated using flash chromatography with an eluent consisting of 35% PE and 65% DCM ($R_f = 0.14$). Product was isolated as a yellow oil in 19% yield.

HPLC conditions: CHIRALPAK® AD-H (10 vol% IPA in hexane), $t_R = 19.2$ (major), 21.4 min (minor), ee = 91%.

^1H NMR: (400 MHz, CDCl_3) δ 7.35–7.30 (m, 6H), 7.27–7.18 (m, 5H), 7.02–6.99 (m, 1H), 6.90–6.87 (m, 1H), 6.84–6.80 (m, 1H), 6.16 (as, 1H), 5.24 (s, 2H), 4.01 (d, $J=6.3$, 1H), 3.17 (dd, $J=6.3, 1.9$ Hz, 1H), 2.38 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 166.2, 166.1, 153.0, 139.8, 135.5, 129.3, 128.9, 128.6, 128.3, 128.0, 128.0, 127.7, 121.0, 120.0, 116.9, 110.4, 73.3, 66.8, 42.5, 27.6, 19.1

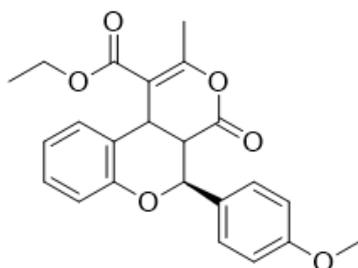
***tert*-butyl (5*S*)-2-methyl-4-oxo-5-phenyl-4a,10b-dihydro-4*H*,5*H*-pyrano[3,4-*c*]chromene-1-carboxylate (5c)**

Prepared according to section A.1.5. Product was separated using flash chromatography with an eluent consisting of 40% PE and 60% DCM ($R_f = 0.09$). Product was isolated as a yellow oil in 20% yield.

HPLC conditions: CHIRALPAK® AD-H (10 vol% IPA in hexane), $t_R = 7.0$ (major), 8.4 min (minor), ee = 95%.

^1H NMR: (400 MHz, CDCl_3) δ 7.37-7.26 (m, 4H), 7.25-7.18 (m, 2H), 7.02-6.99 (m, 1H), 6.94-6.85 (m, 2H), 6.15 (as, 1H), 3.94 (d, $J=6.6$ Hz 1H), 3.15 (dd, $J=6.4$, 1.9 Hz, 1H), 2.34 (s, 3H), 1.49 (s, 9H).

^{13}C NMR (101 MHz, CDCl_3): δ 166.5, 165.7, 160.0, 153.0, 139.9, 129.1, 128.8, 128.0, 127.6, 124.9, 121.0, 120.4, 116.9, 112.0, 82.0, 73.4, 42.4, 28.1, 27.6, 18.9

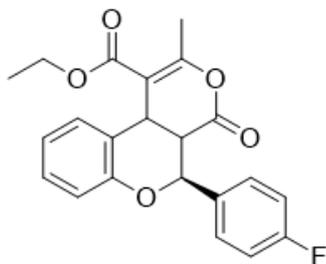
ethyl (5*S*)-5-(4-methoxyphenyl)-2-methyl-4-oxo-4a,10b-dihydro-4*H*,5*H*-pyrano[3,4-*c*]chromene-1-carboxylate (5d)

Prepared according to section A.1.5. Product was separated using flash chromatography with an eluent consisting of 40% PE and 60% DCM ($R_f = 0.18$). Product was isolated as a yellow oil in 15% yield.

HPLC conditions: CHIRALPAK® AD-H (10 vol% IPA in hexane), $t_R = 20.1$ (major), 23.5 min (minor), ee = 93%

^1H NMR: (400 MHz, CDCl_3) δ 7.23-7.15 (m, 3H), 7.01-6.98 (m, 1H), 6.96-6.93 (m, 1H), 6.89-6.84 (m, 3H), 6.11 (as, 1H), 4.31 (dq, $J=10.9$, 7.1 Hz, 1H), 4.23 (dq, $J=10.8$, 7.1 Hz, 1H), 3.98 (d, $J=6.7$ Hz, 1H), 3.79 (s, 3H), 3.13 (dd, $J=6.3$, 1.9 Hz, 1H), 2.38 (s, 3H), 1.29 (t, $J=7.1$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 166.5, 166.4, 161.3, 159.3, 153.0, 131.8, 129.2, 127.6, 126.1, 121.0, 120.3, 117.0, 114.3, 110.7, 73.1, 61.2, 55.3, 42.6, 27.6, 19.0, 14.2.

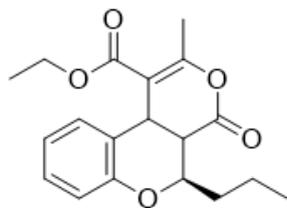
ethyl (5S)-5-(4-fluorophenyl)-2-methyl-4-oxo-4a,10b-dihydro-4H,5H-pyrano[3,4-c]chromene-1-carboxylate (5e)

Prepared according to section A.1.5. Product was separated using flash chromatography with an eluent consisting of 65% PE and 35% of a 1:19 mixture of EtOAc:DCM ($R_f = 0.14$). Product was isolated as a yellow oil in 33% yield.

HPLC conditions: CHIRALPAK® AD-H (15 vol% IPA in hexane), $t_R = 11.3$ (minor), 12.4 min (major), ee = 92%

^1H NMR: (400 MHz, CDCl_3) δ 7.27-7.18 (m, 3H), 7.07-6.98 (m, 3H), 6.96-6.92 (m, 1H), 6.96-6.86 (m, 1H), 6.14 (as, 1H), 4.31 (dq, $J=10.9, 7.1$ Hz, 1H), 4.24 (dq, $J=10.8, 7.1$ Hz, 1H), 3.93 (d, $J=6.5$ Hz, 1H), 3.14 (dd, $J=6.3, 1.9$ Hz, 1H), 2.39 (s, 3H), 1.29 (t, $J=6.1$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3): δ 166.4, 166.1, 162.3 (d, $J=246.8$ Hz), 161.4, 152.8, 135.5 (d, $J=3.2$ Hz), 129.3, 127.7, 126.7, (d, $J=8.3$ Hz), 121.2, 120.2, 117.0, 115.9 (d, $J=21.7$ Hz), 110.5, 72.9, 61.3, 42.6, 27.6, 19.0, 14.2.

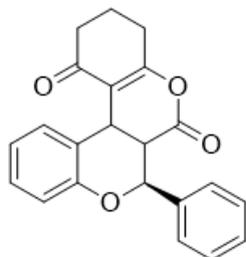
ethyl (5R)-2-methyl-4-oxo-5-propyl-4a,10b-dihydro-4H,5H-pyrano[3,4-c]chromene-1-carboxylate (5g)

Prepared according to section A.1.5. Product was separated using flash chromatography with an eluent consisting of 70% DCM in PE. Product was isolated as a yellow oil in 17% yield.

HPLC conditions: CHIRALPAK® AD-H (10 vol% IPA in hexane), $t_R = 5.74$ (major), 7.35 min (minor), ee = 90%.

^1H NMR: (400 MHz, CDCl_3) δ 7.15-7.10 (m, 1H), 6.97-6.94 (m, 1H), 6.85-6.81 (m, 2H), 4.98 (ddd, $J=9.3, 4.6, 1.9$ Hz, 1H), 4.40 (dq, $J=10.9, 7.1$ Hz, 1H), 4.34 (dq, $J=10.9, 7.1$ Hz, 1H), 4.31 (d, $J=6.8$ Hz, 1H), 2.85 (dd, $J=6.8, 1.9$ Hz, 1H), 2.38 (s, 3H), 1.89-1.79 (m, 1H), 1.65-1.43 (m, 3H), 1.38 (t, $J=7.1$ Hz, 3H), 0.98 (t, $J=7.2$ Hz, 3H)

^{13}C NMR (101 MHz, CDCl_3): δ 166.8, 166.5, 161.3, 152.2, 128.9, 127.6, 120.7, 120.0, 117.7, 110.3, 71.9, 61.3, 40.3, 34.9, 28.2, 19.2, 18.9, 14.3, 13.8

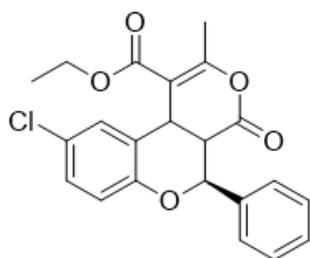
(7S)-7-phenyl-2,3,4,5,6a,12b-hexahydro-1H,6H-chromeno[3,4-c]chromene-1,6-dione (5h)

Prepared according to section A.1.5. After 18 hours, the solution was diluted with EtOAc (20 ml) and washed with water (2x40 ml) and once with brine (20 ml). Product was separated using flash chromatography with an eluent consisting of 60% PE and 30% of a 1:19 mixture of EtOAc:DCM ($R_f = 0.28$). Product was isolated as a yellow oil in 18% yield.

HPLC conditions: CHIRALPAK® AD-H (10 vol% IPA in hexane), $t_R = 23.9$ (major), 32.5 min (minor), ee = 9%

^1H NMR: (400 MHz, CDCl_3) δ 7.35-7.28 (m, 3H), 7.24-7.17 (m, 3H), 7.02-7.00 (m, 1H), 6.86-6.82 (m, 1H), 6.78-6.75 (m, 1H), 6.19 (as, 1H), 4.03 (d, $J=6.6$ Hz, 1H), 3.20 (dd, $J=6.8, 1.9$ Hz, 1H), 2.65-2.44 (m, 4H), 2.15-2.06 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3): δ 197.5, 167.3, 165.9, 152.7, 139.2, 129.1, 129.0, 128.0, 124.8, 121.2, 119.8, 118.0, 117.0, 73.1, 42.5, 36.7, 27.3, 25.4, 24.0, 20.5.

ethyl (5S)-9-chloro-2-methyl-4-oxo-5-phenyl-4a,10b-dihydro-4H,5H-pyrano[3,4-c]chromene-1-carboxylate (5i)

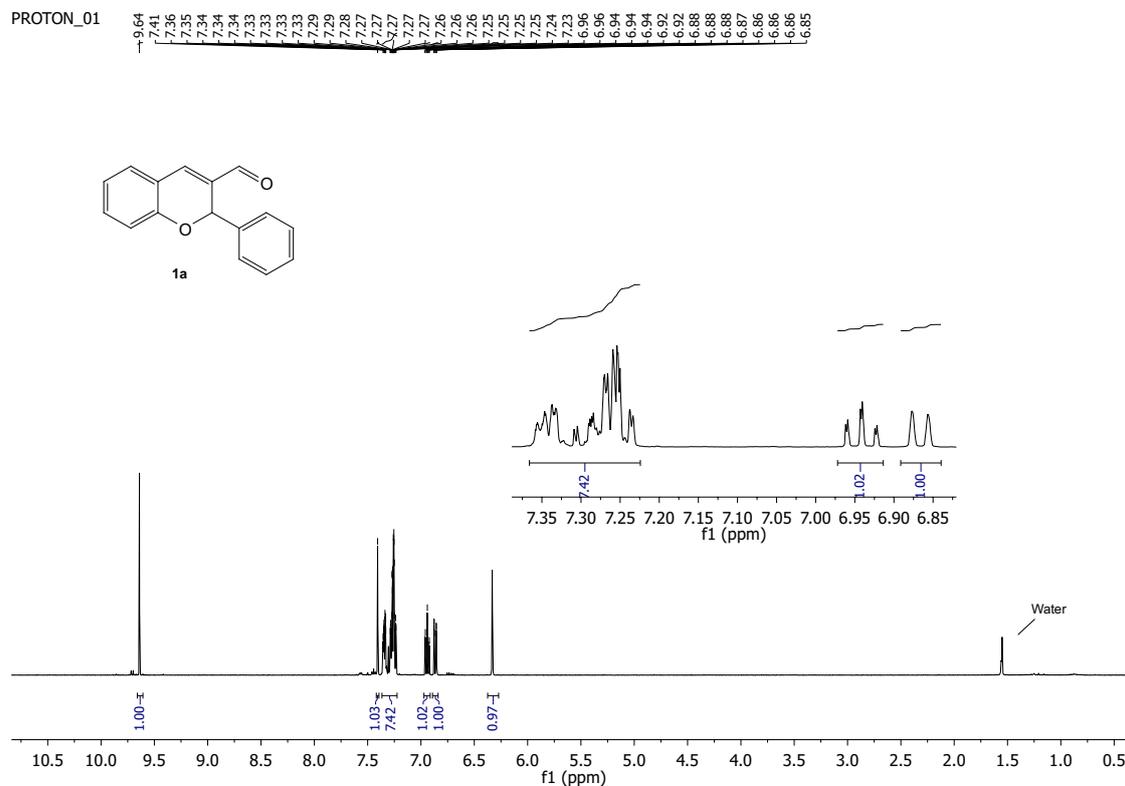
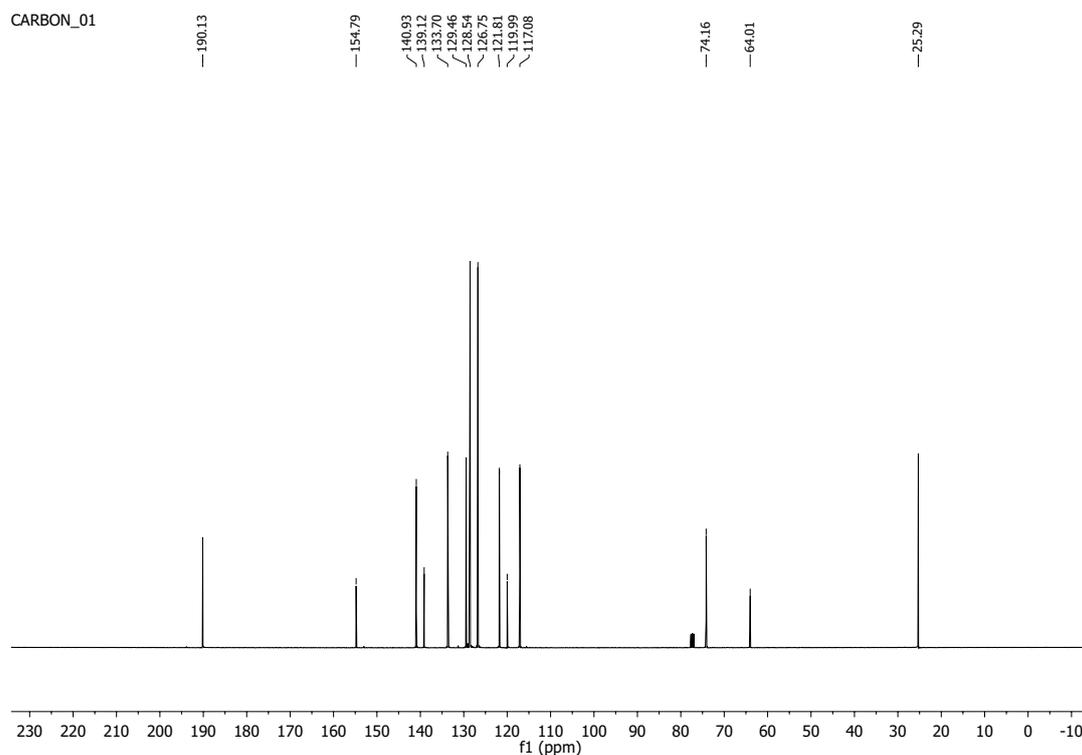
Prepared according to section A.1.5. After 18 hours, the solution was diluted with EtOAc (20 ml) and washed with water (2x40 ml) and once with brine (20 ml). Product was separated using flash chromatography with an eluent consisting of 70% PE and 30% of a 1:14 mixture of EtOAc:DCM ($R_f = 0.17$). Product was isolated as a yellow oil in 25% yield, and a dr of 6.4:1

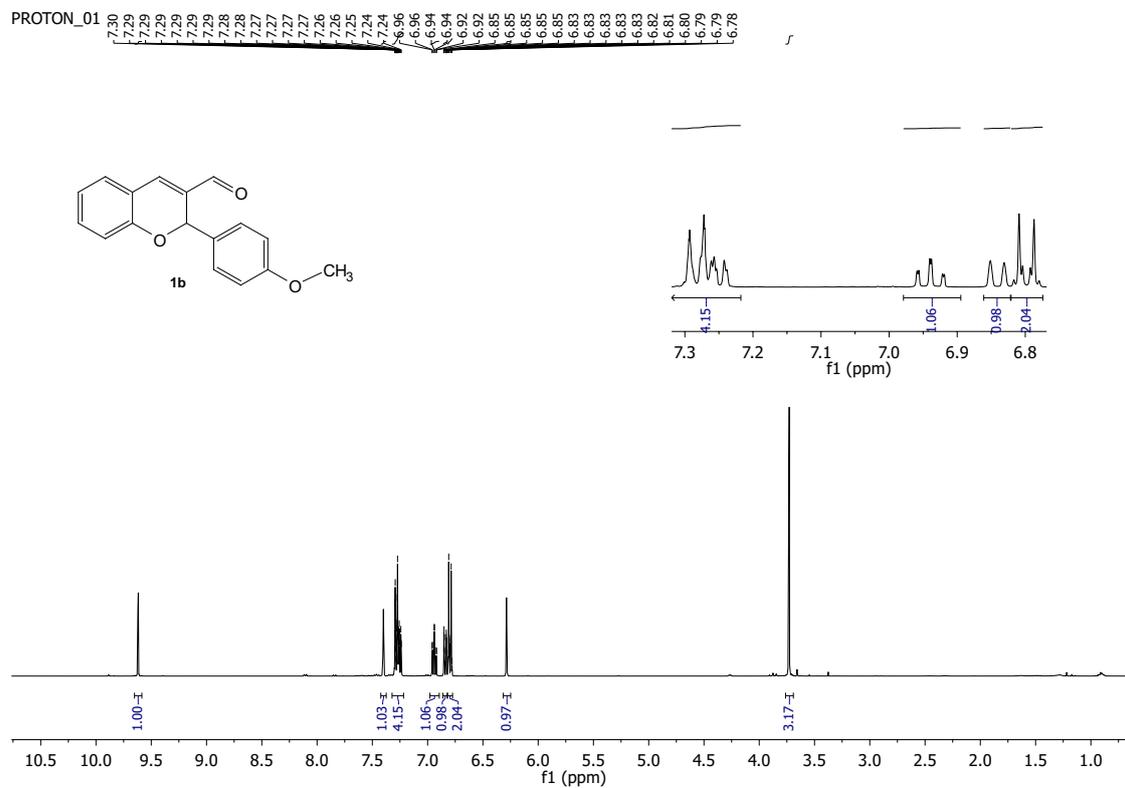
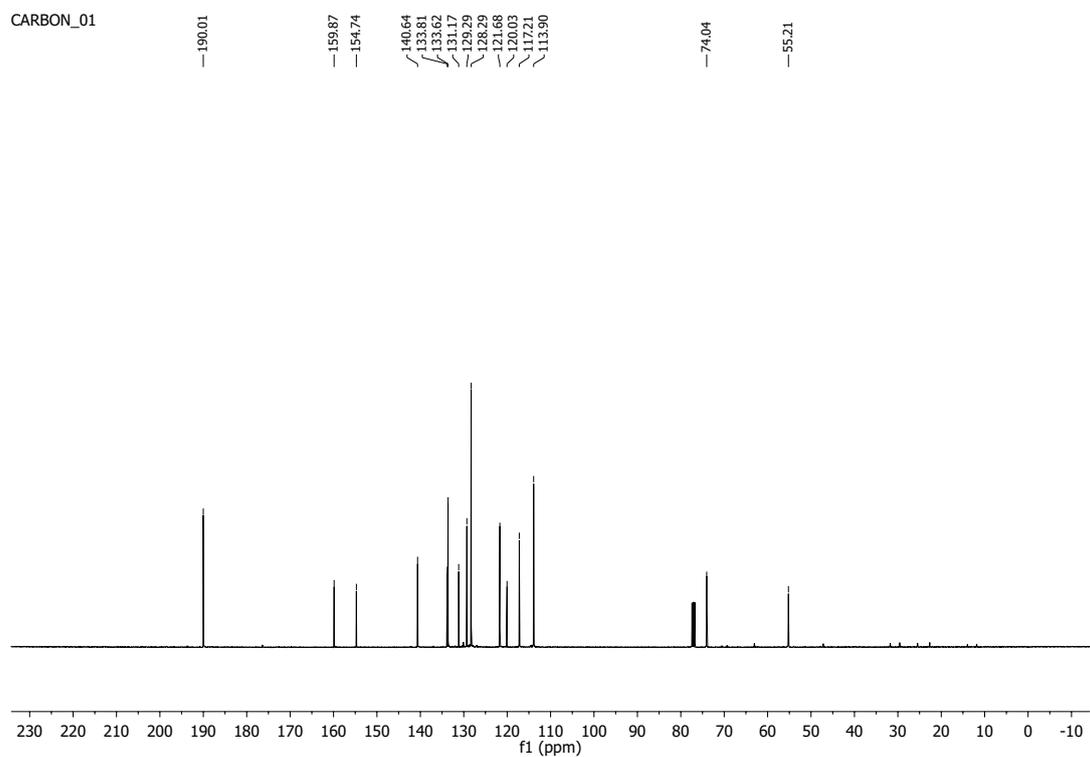
HPLC conditions: CHIRALPAK® AD-H (5 vol% IPA in hexane), $t_R = 11.5$ (major), 14.6 min (minor), ee = 63%

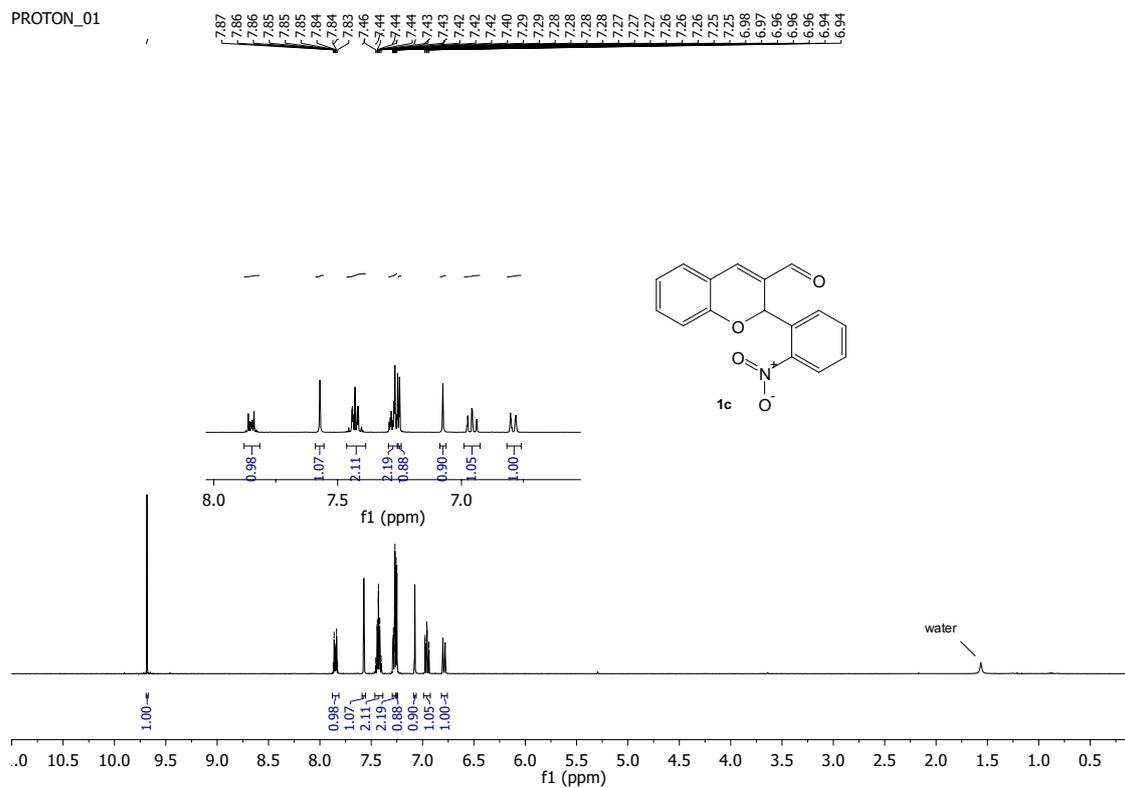
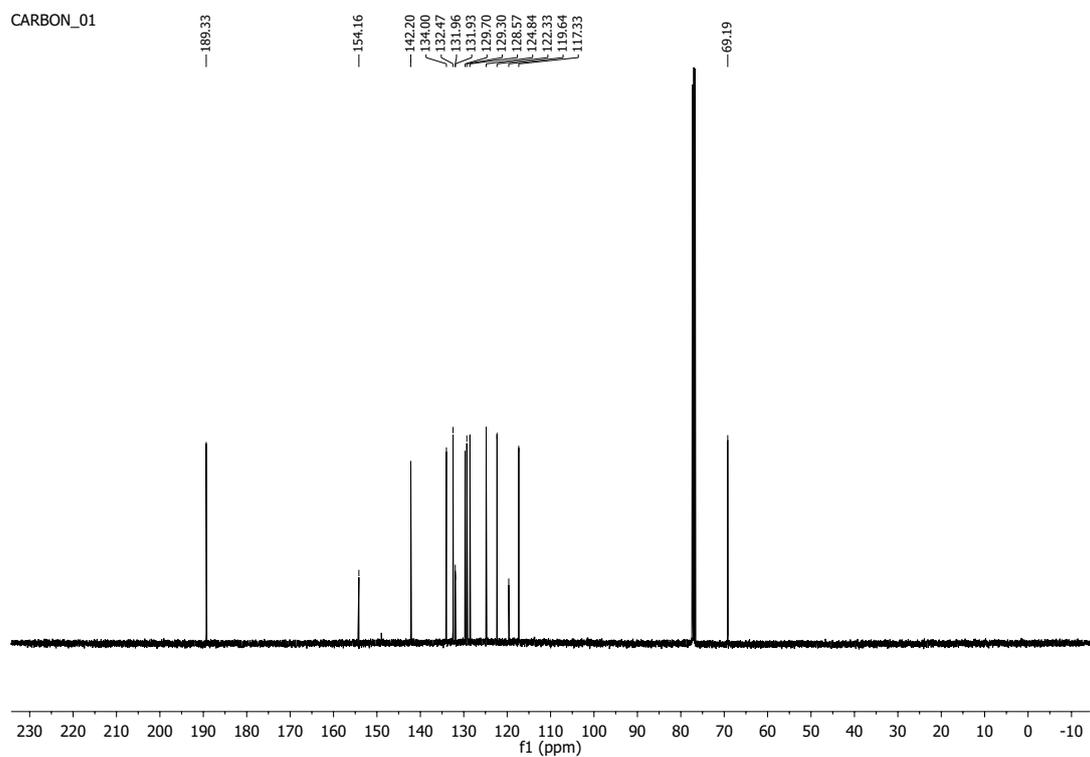
^1H NMR: (400 MHz, CDCl_3) δ 7.38-7.31 (m, 3H), 7.24-7.21 (m, 2H), 7.19-7.16 (m, 1H), 6.97-6.93 (m, 2H), 6.16 (as, 1H), 4.33 (dq, $J=10.9, 7.1$ Hz, 1H), 4.23 (dq, $J=10.9, 7.1$ Hz, 1H), 3.89 (d, $J=6.4$ Hz, 1H), 3.17 (dd, $J=6.3, 1.9$ Hz, 1H), 2.40 (s, 3H), 1.29 (t, $J=7.1$ Hz, 3H)

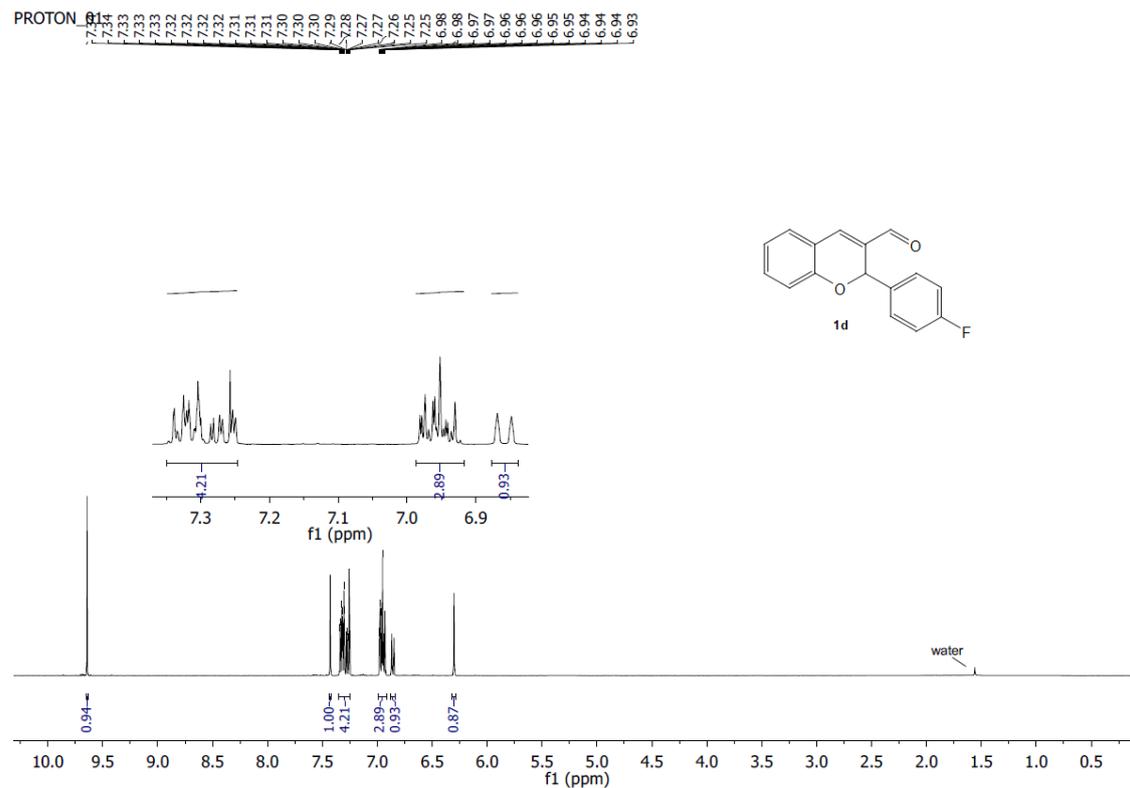
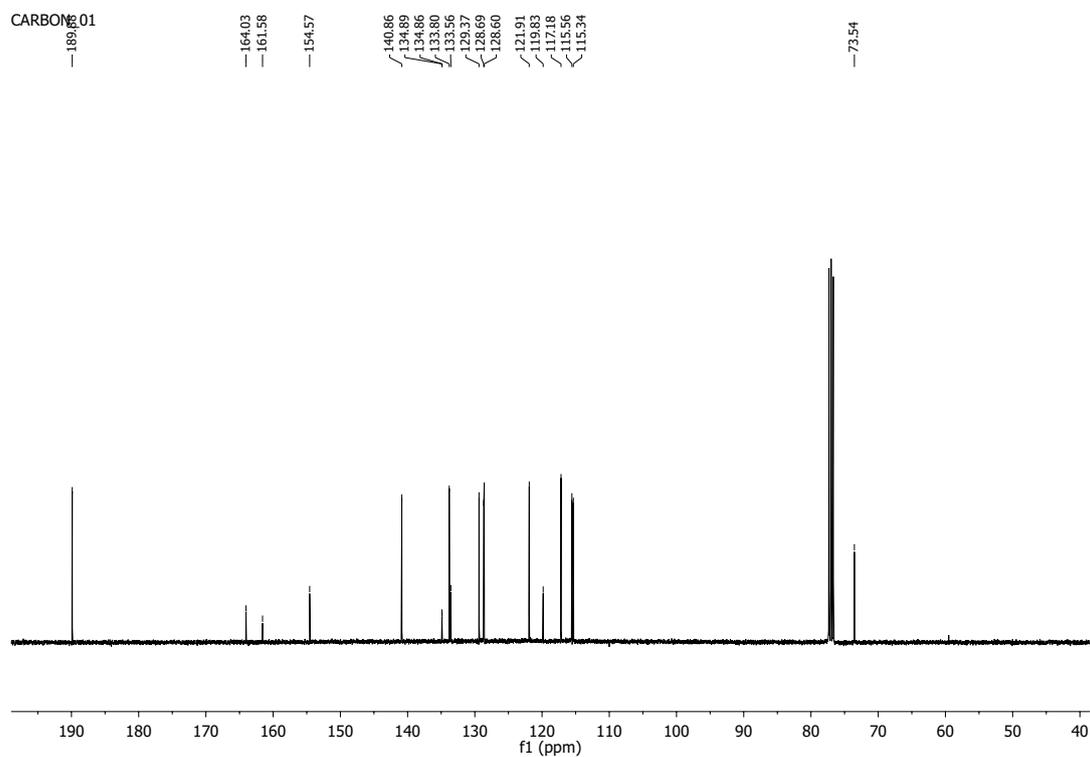
^{13}C NMR (101 MHz, CDCl_3): δ 166.2, 165.9, 161.9, 151.6, 139.3, 129.3, 129.0, 128.2,

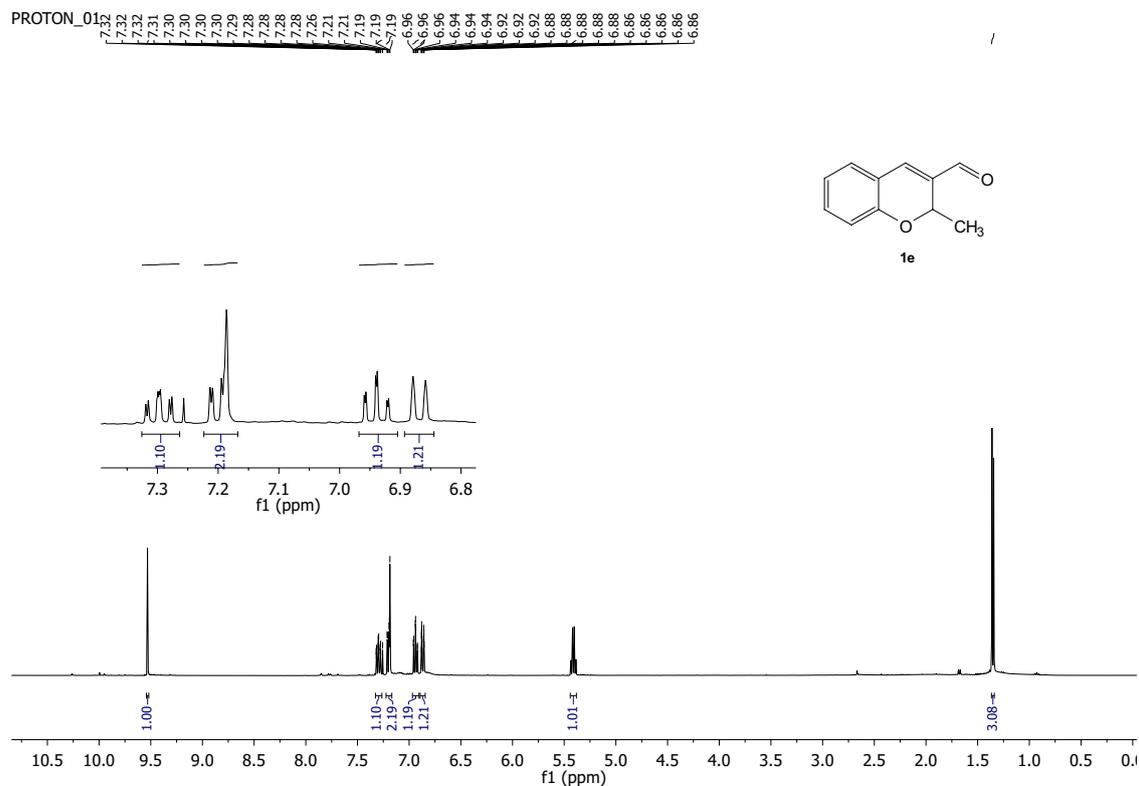
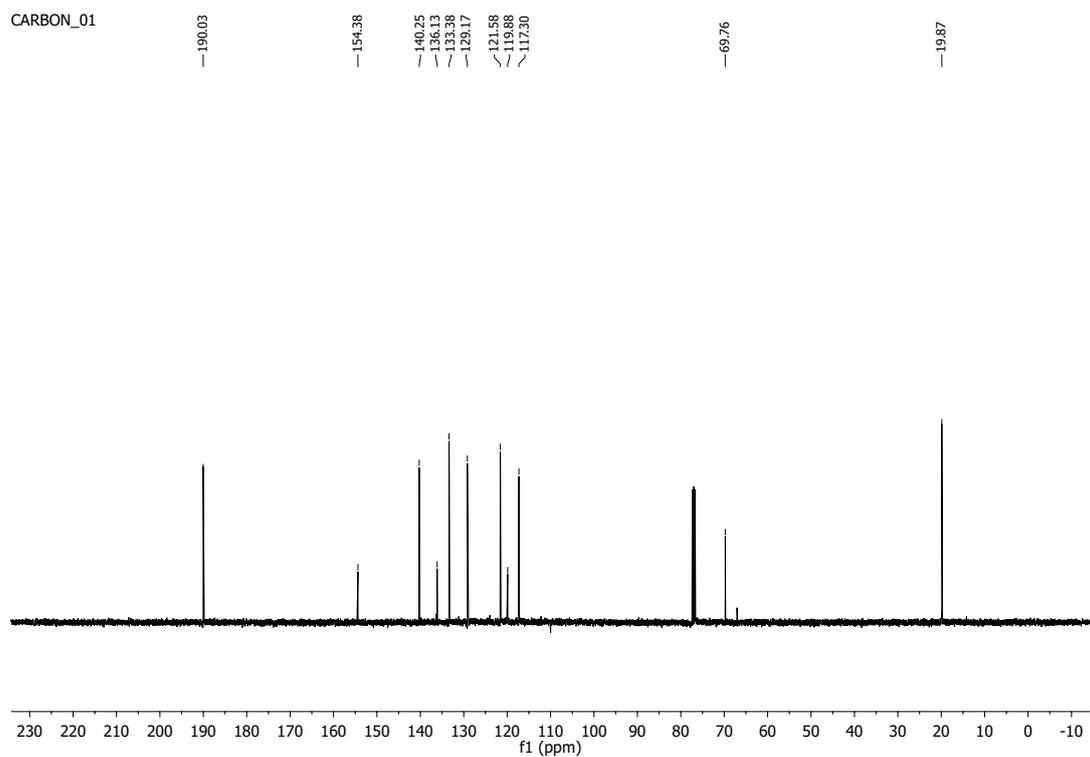
127.5, 125.9, 124.7, 121.8, 118.4, 110.1, 73.5, 61.4, 42.2, 27.7, 19.1, 14.2.

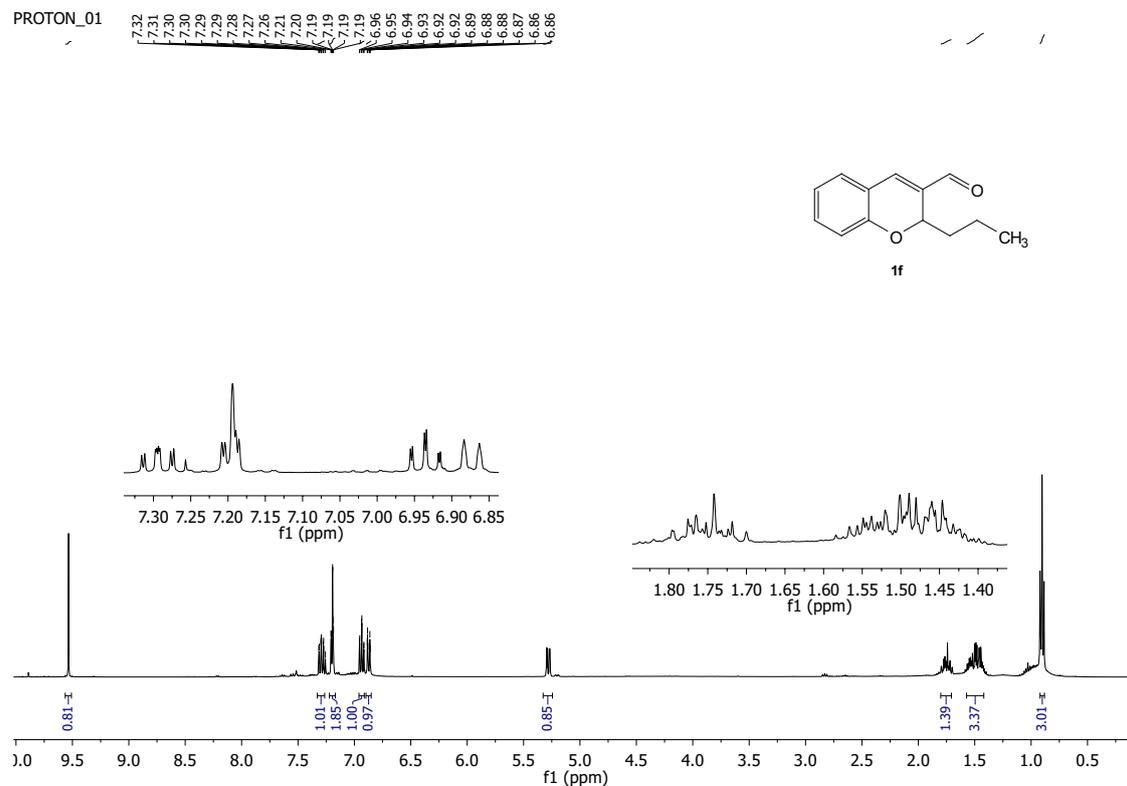
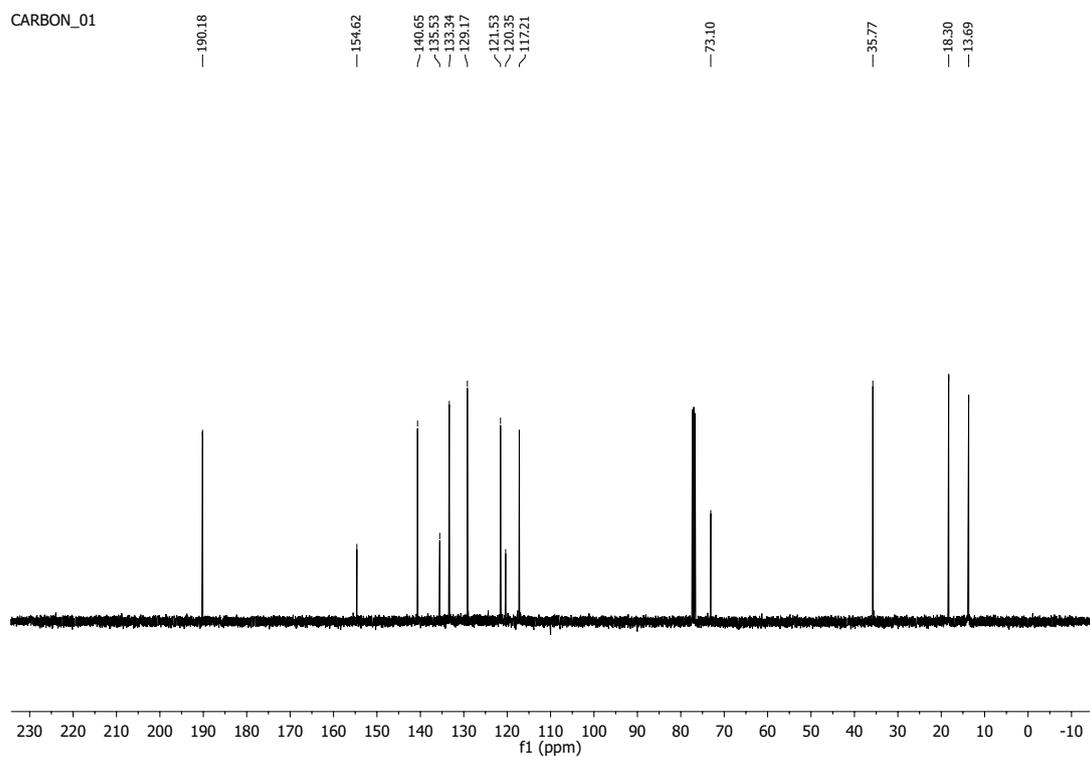
^1H NMR spectrum of Compound **1a** (400 MHz, CDCl_3) ^{13}C NMR spectrum of Compound **1a** (101 MHz, CDCl_3)

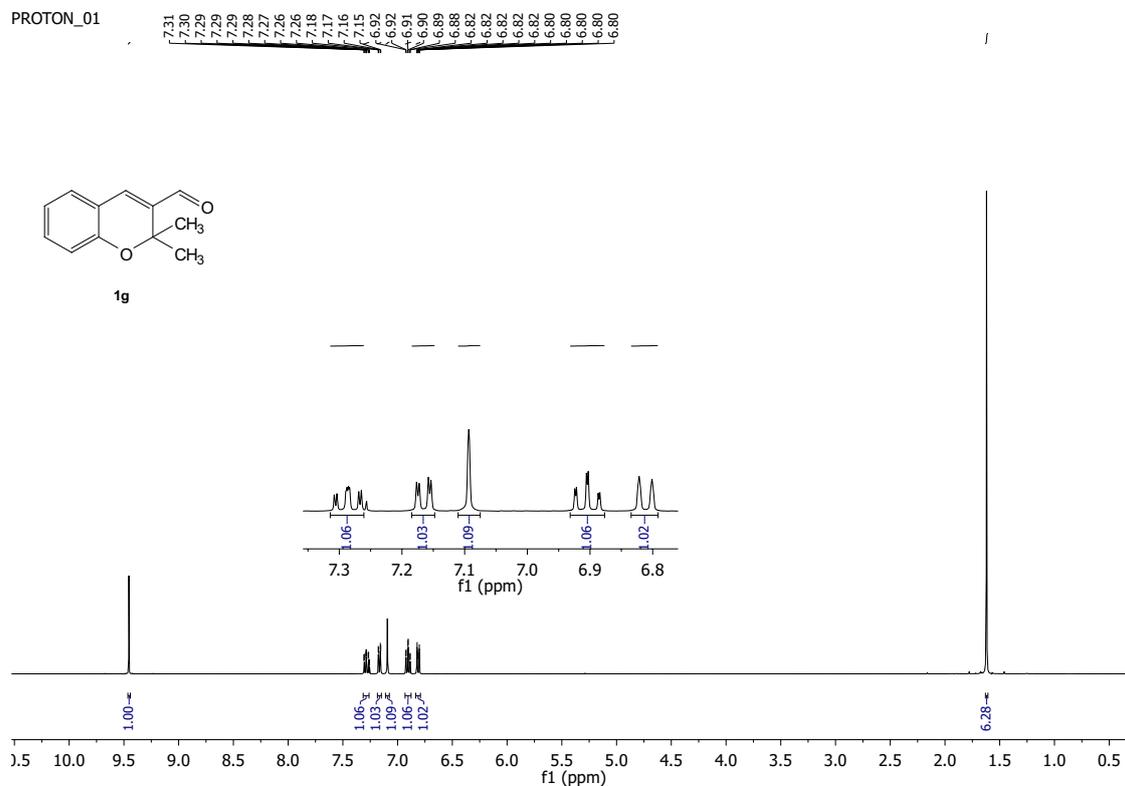
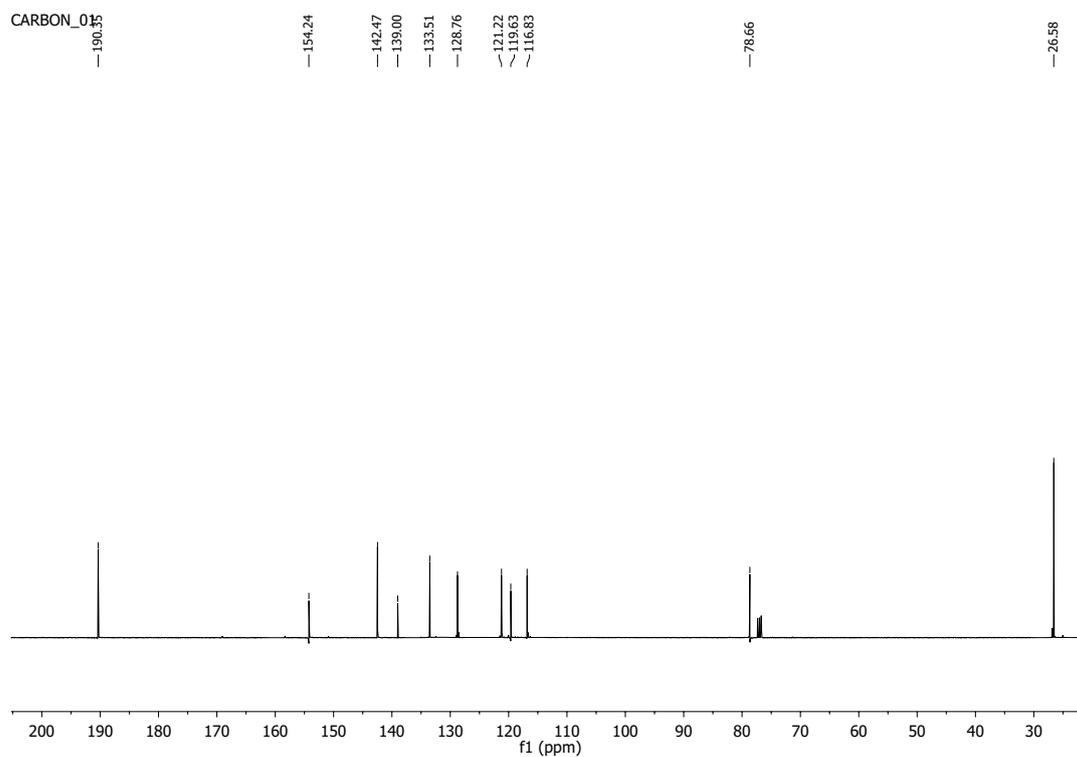
^1H NMR spectrum of Compound **1b** (400 MHz, CDCl_3) ^{13}C NMR spectrum of Compound **1b** (101 MHz, CDCl_3)

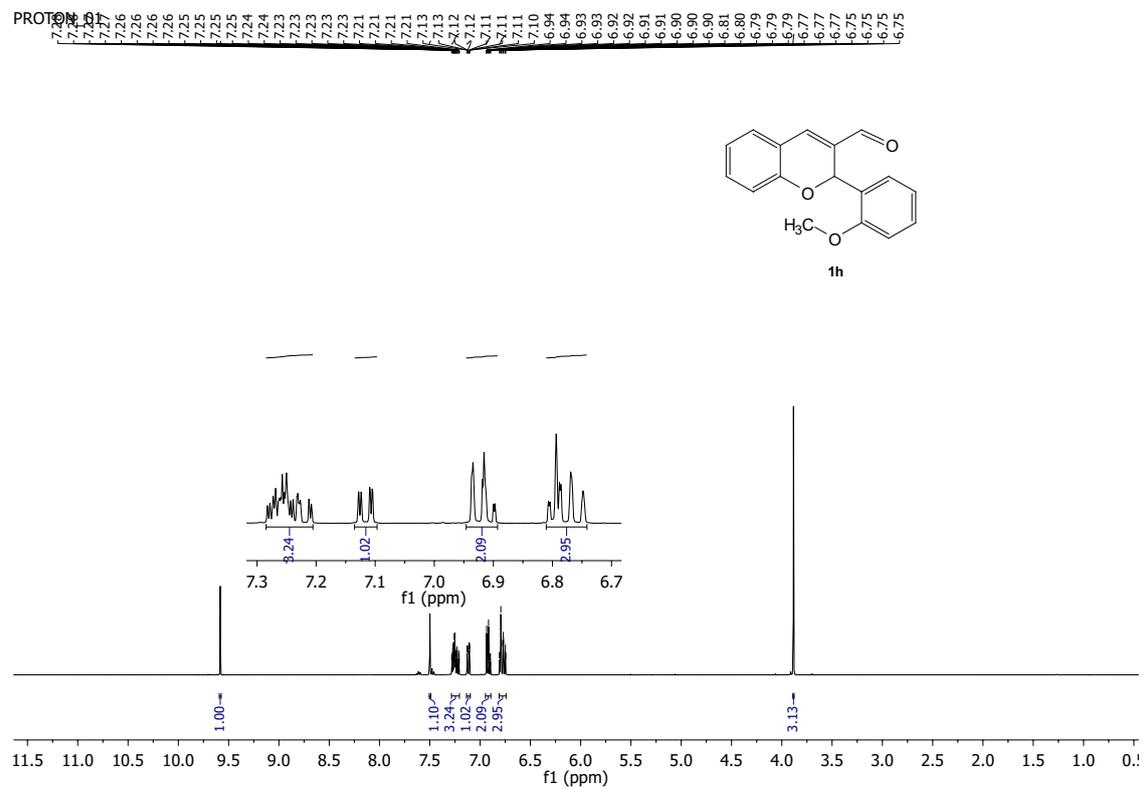
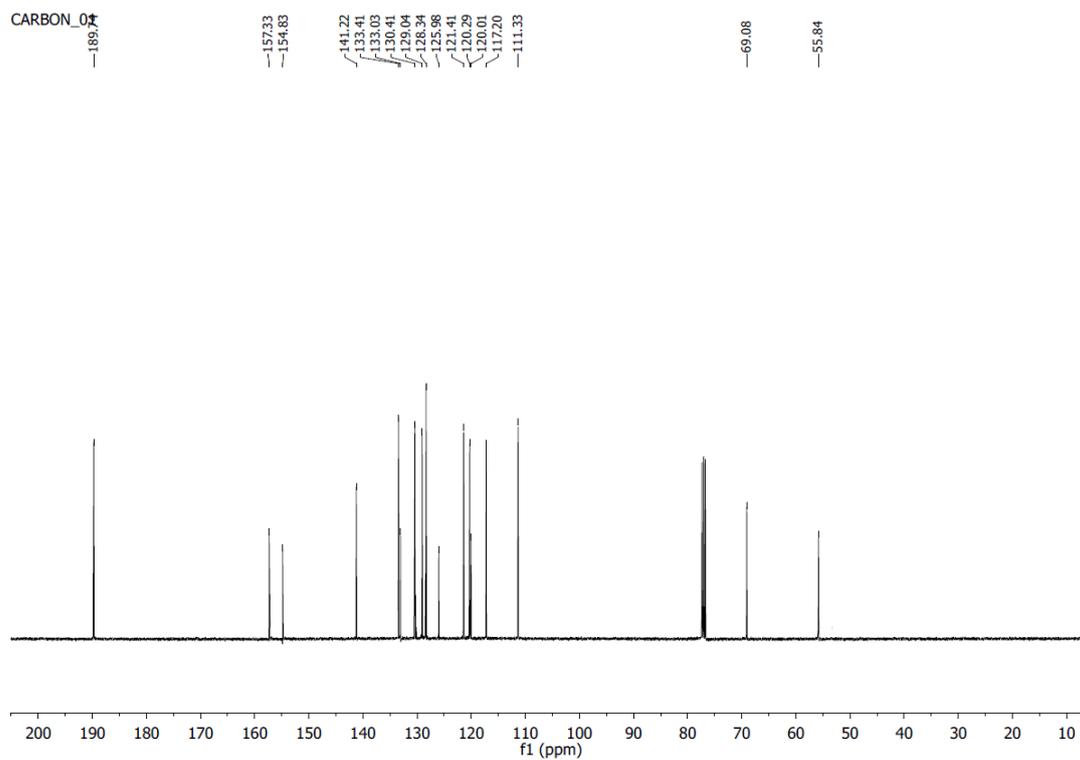
^1H NMR spectrum of Compound **1c** (400 MHz, CDCl_3) ^{13}C NMR spectrum of Compound **1c** (101 MHz, CDCl_3)

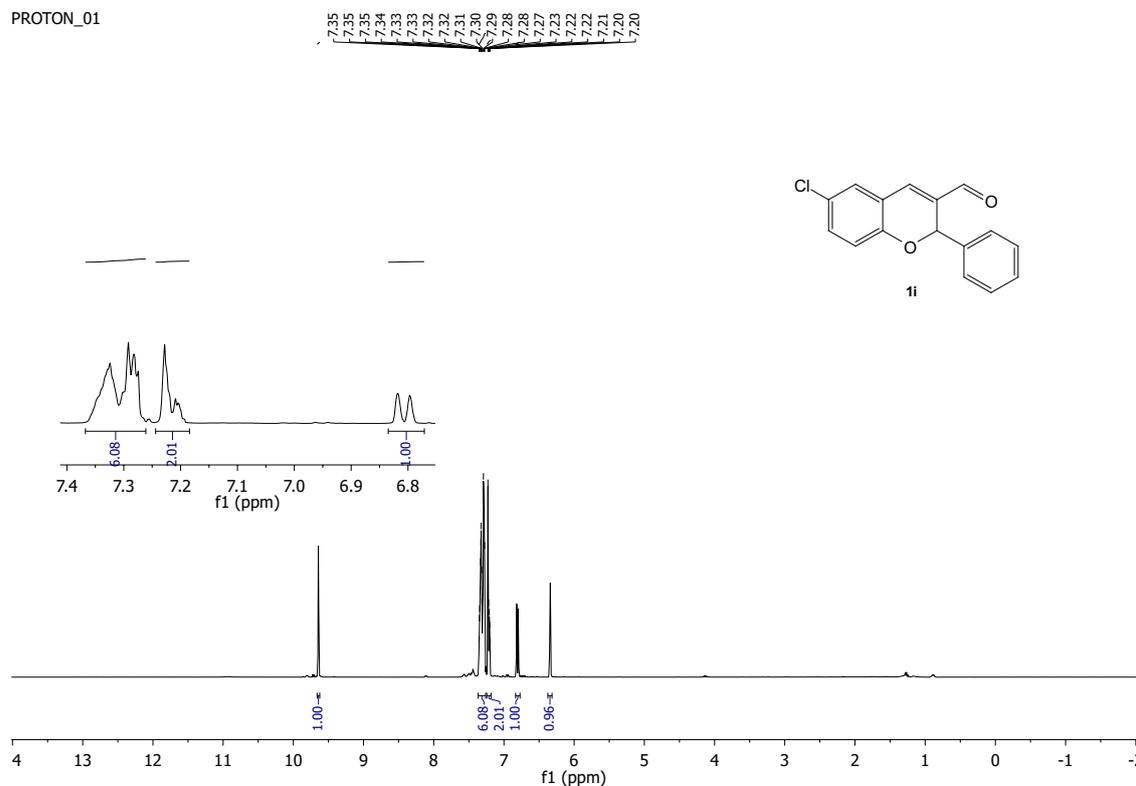
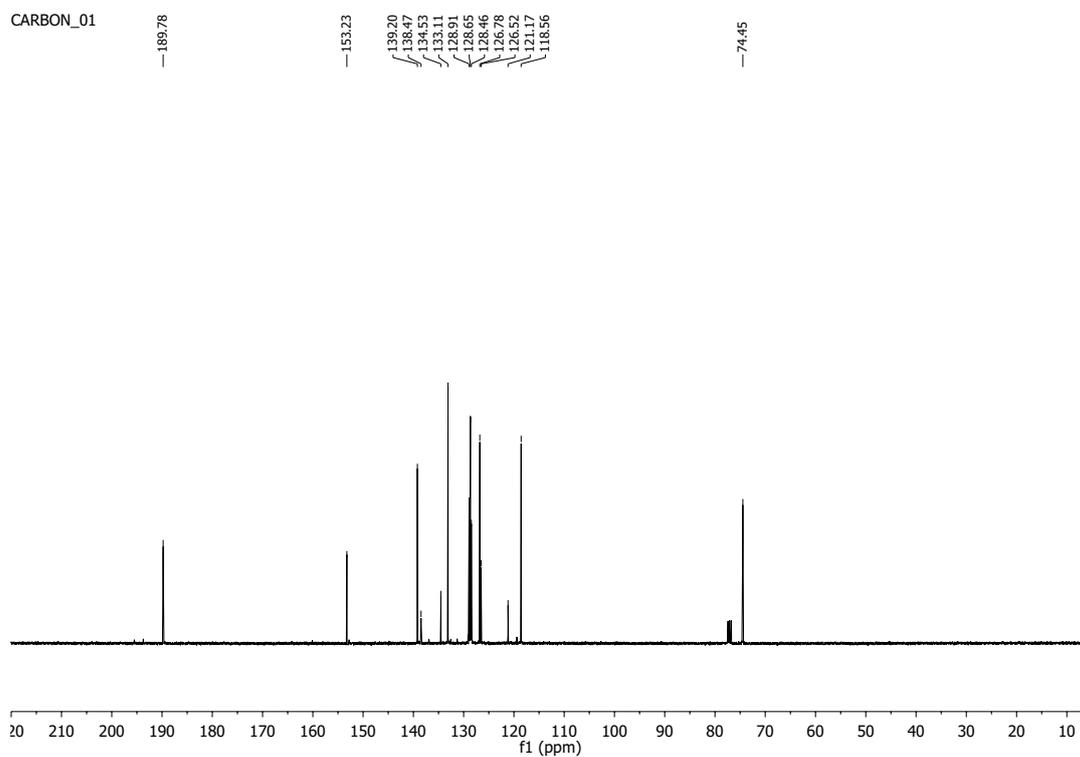
^1H NMR spectrum of Compound **1d** (400 MHz, CDCl_3) ^{13}C NMR spectrum of Compound **1d** (101 MHz, CDCl_3)

^1H NMR spectrum of Compound **1e** (400 MHz, CDCl_3) ^{13}C NMR spectrum of Compound **1e** (101 MHz, CDCl_3)

^1H NMR spectrum of Compound **1f** (400 MHz, CDCl_3) ^{13}C NMR spectrum of Compound **1f** (101 MHz, CDCl_3)

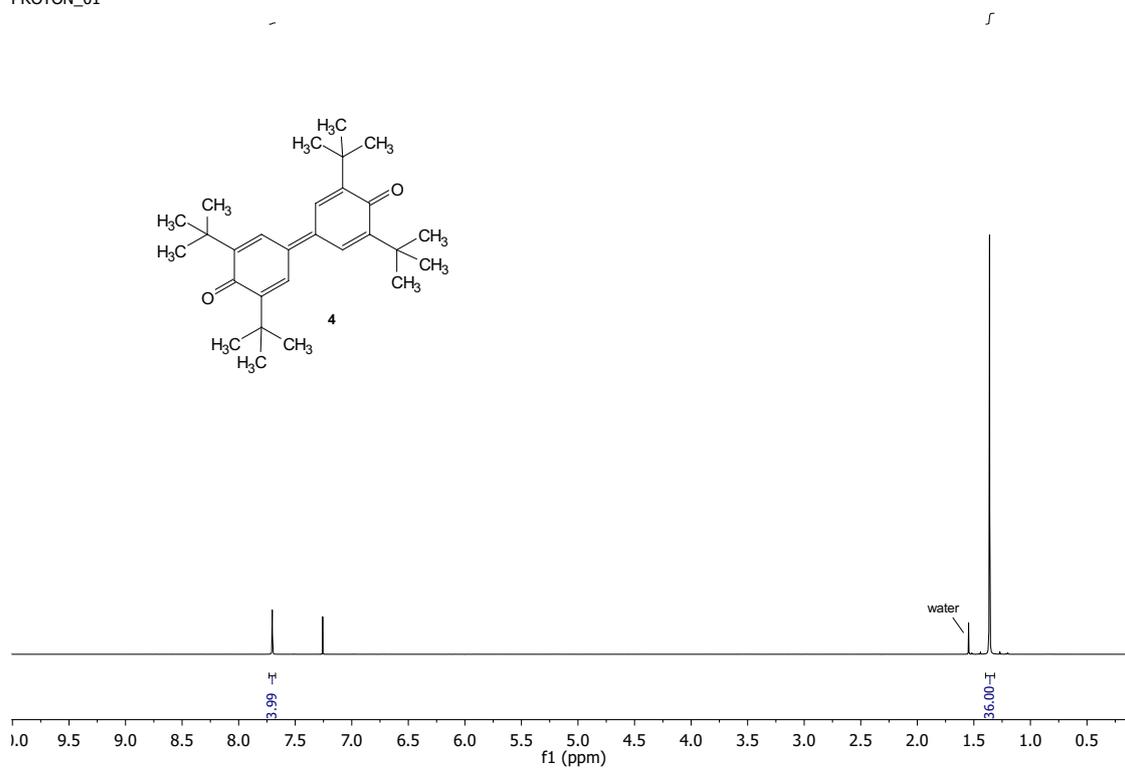
^1H NMR spectrum of Compound **1g** (400 MHz, CDCl_3) ^{13}C NMR spectrum of Compound **1g** (101 MHz, CDCl_3)

^1H NMR spectrum of Compound **1h** (400 MHz, CDCl_3) ^{13}C NMR spectrum of Compound **1h** (101 MHz, CDCl_3)

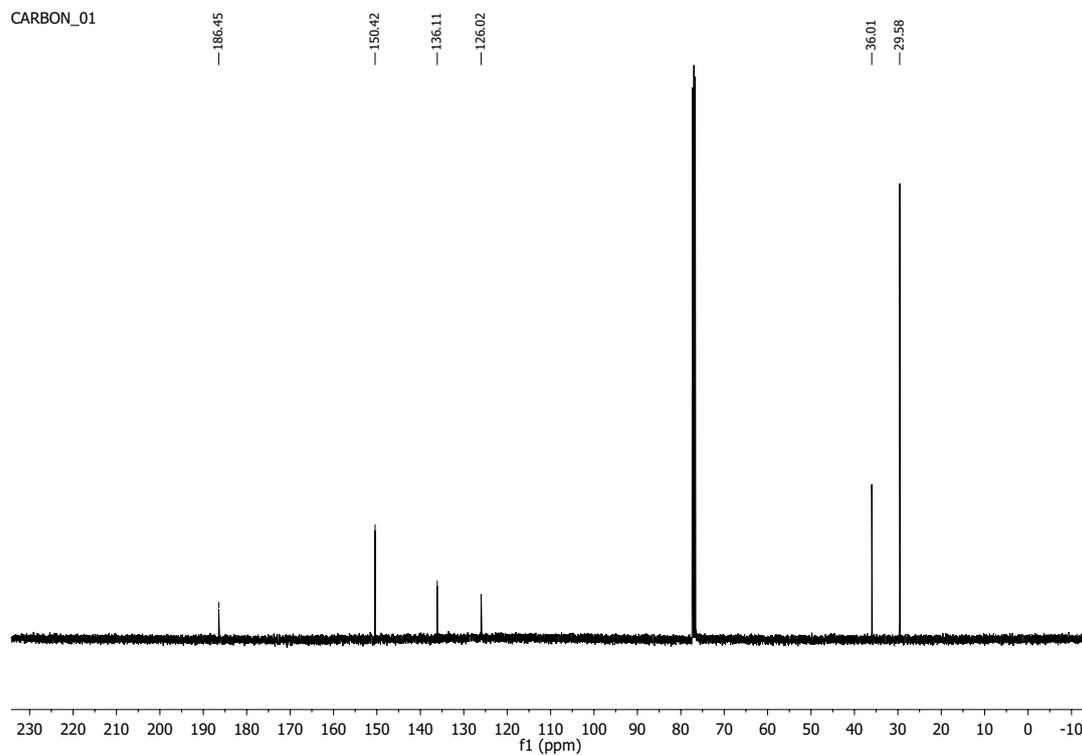
^1H NMR spectrum of Compound **1i** (400 MHz, CDCl_3) ^{13}C NMR spectrum of Compound **1i** (101 MHz, CDCl_3)

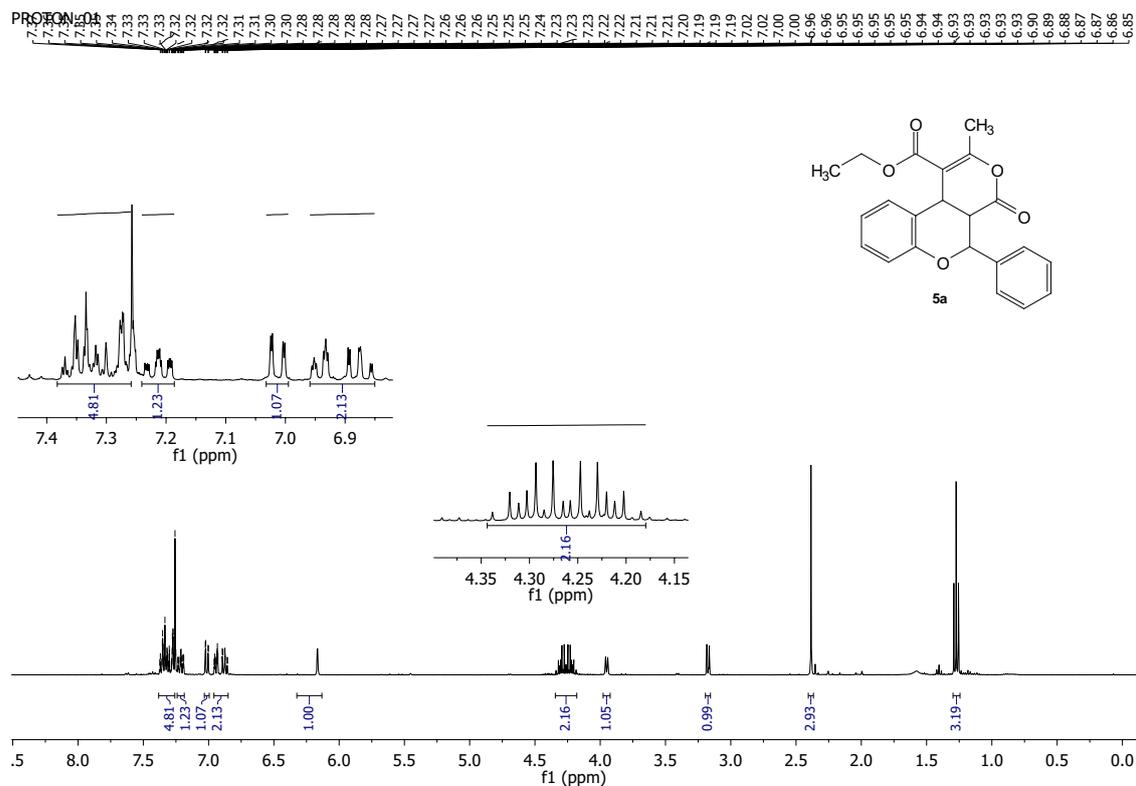
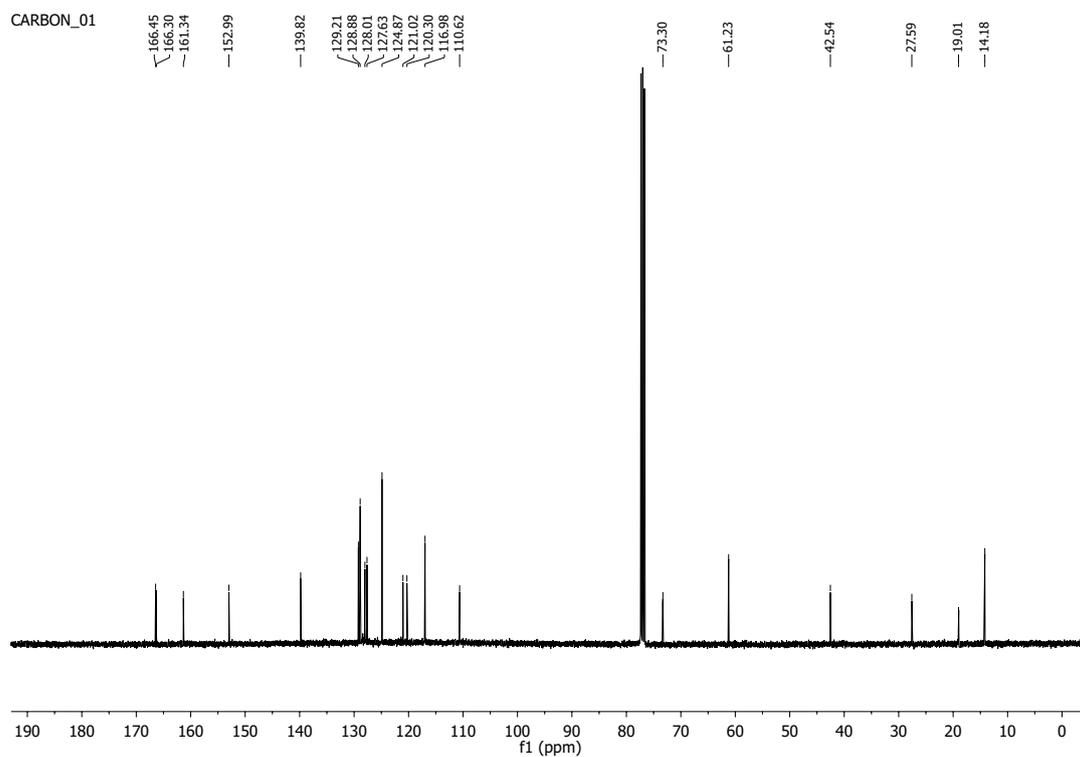
^1H NMR spectrum of Compound 4 (400 MHz, CDCl_3)

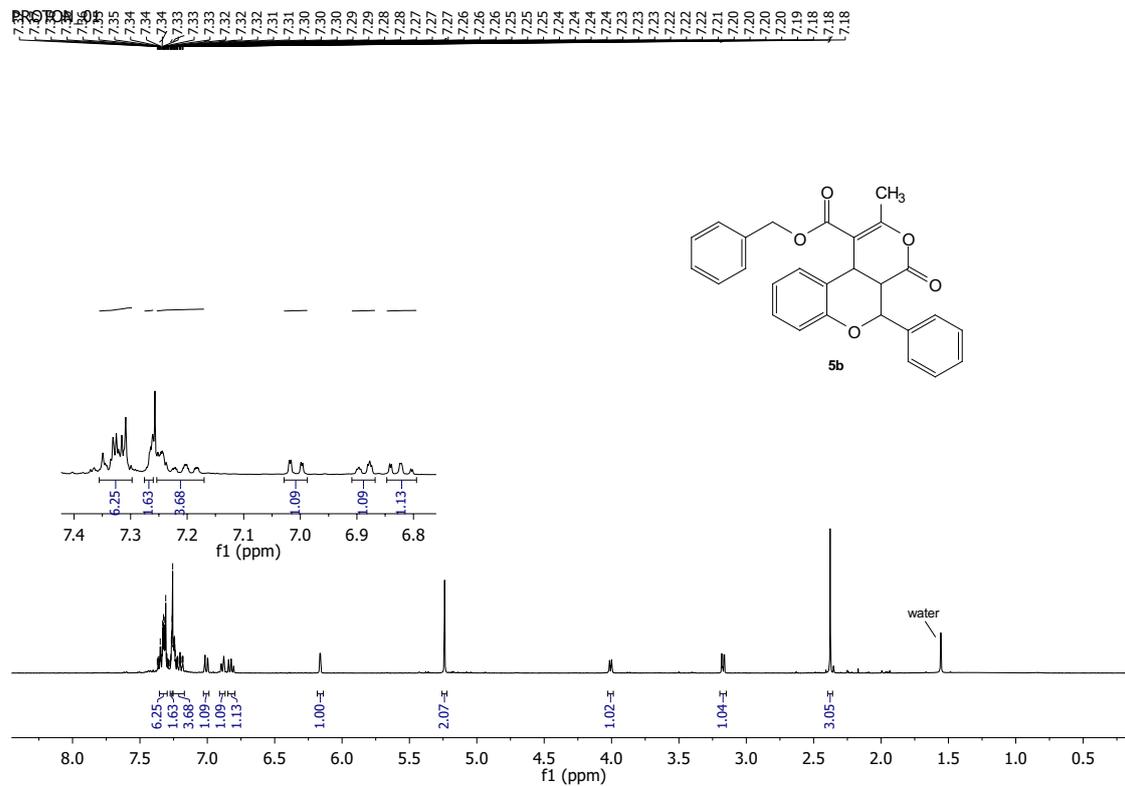
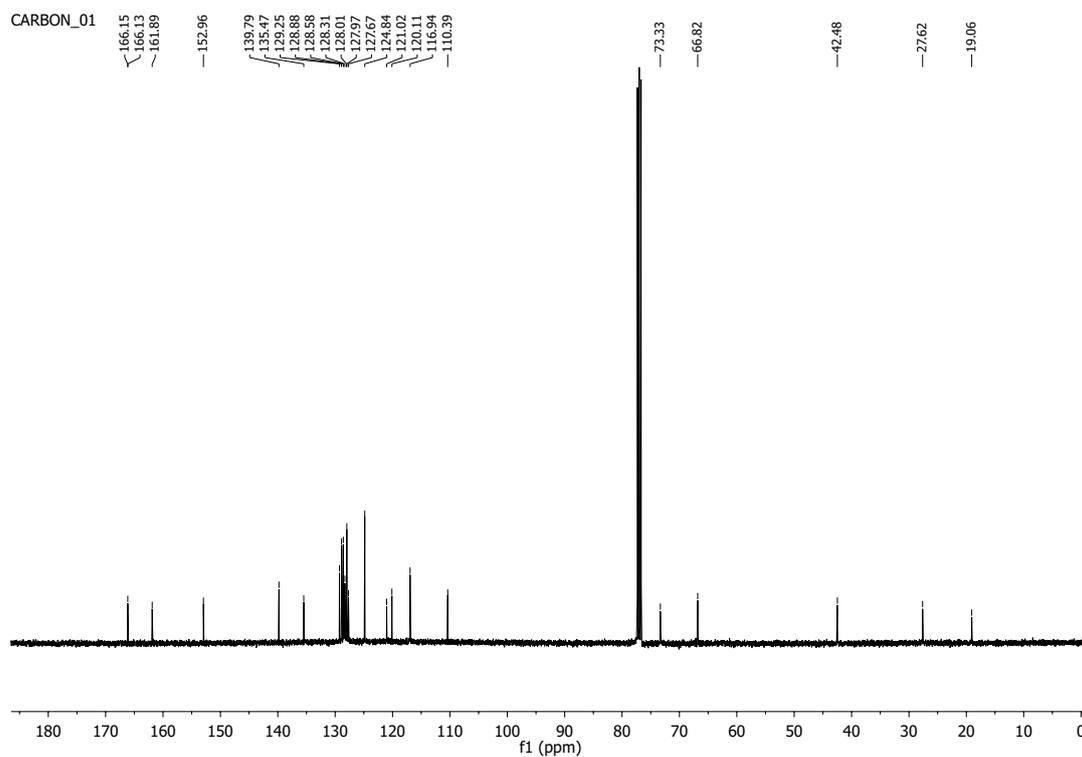
PROTON_01

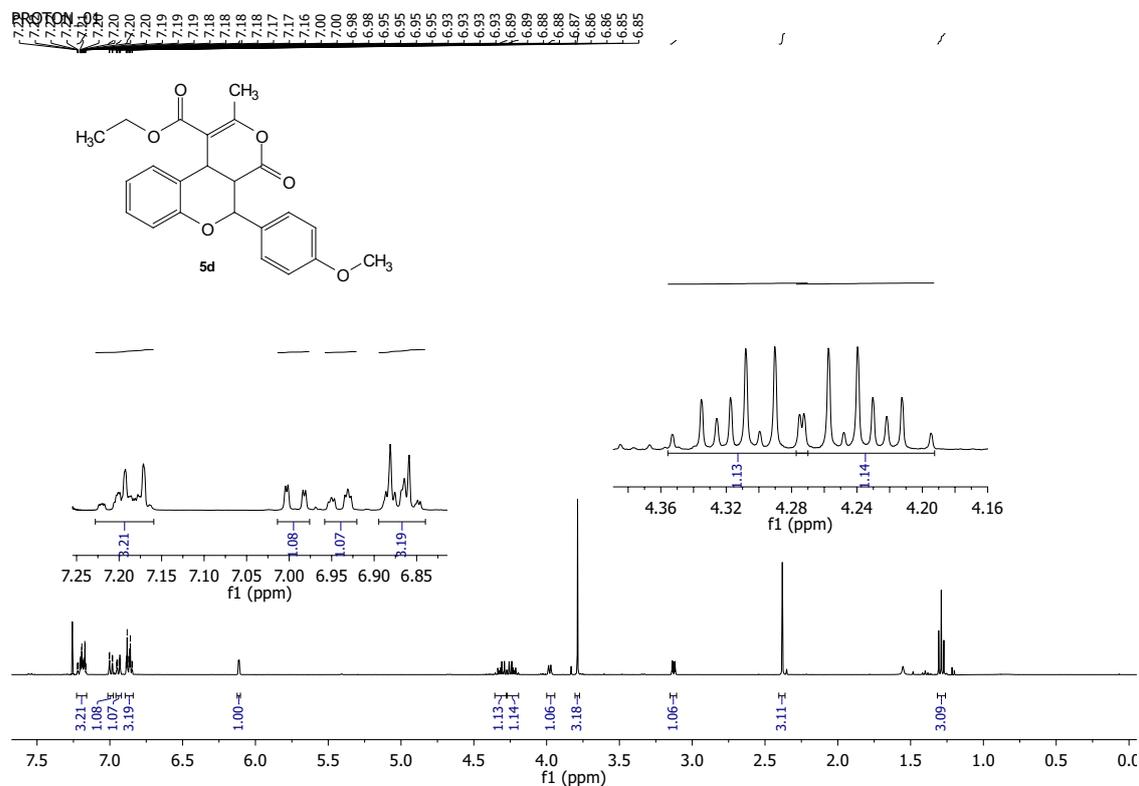
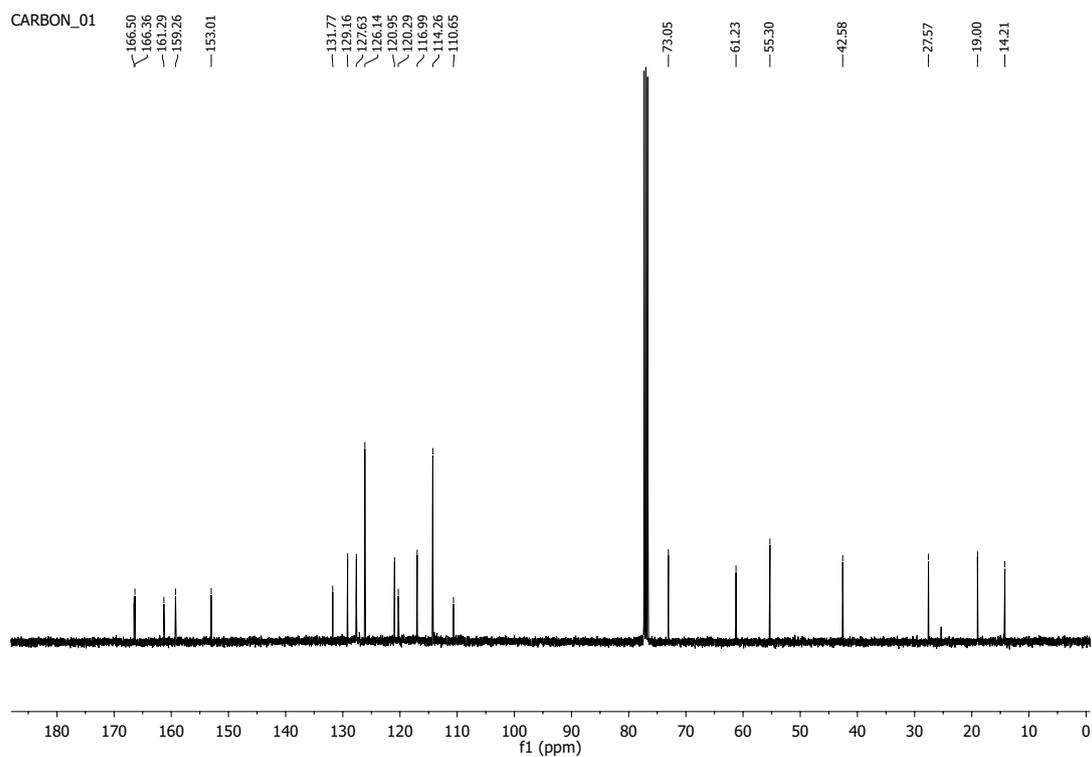
 ^{13}C NMR spectrum of Compound 4 (101 MHz, CDCl_3)

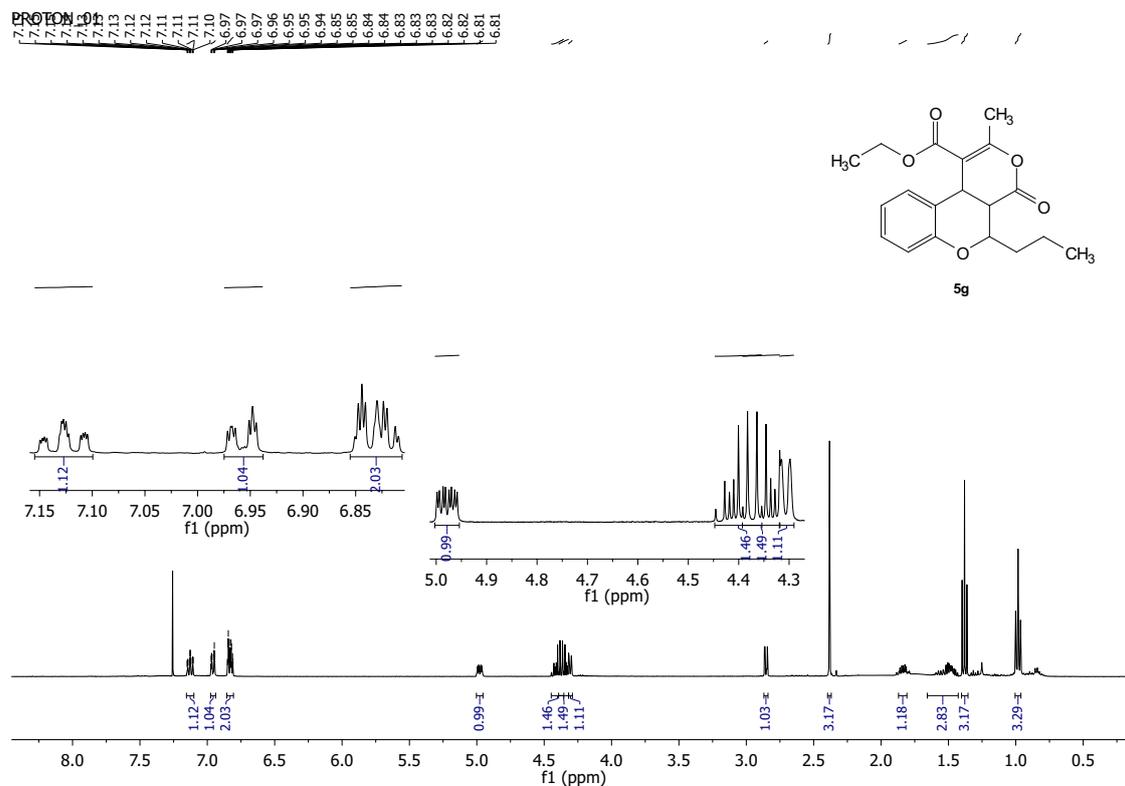
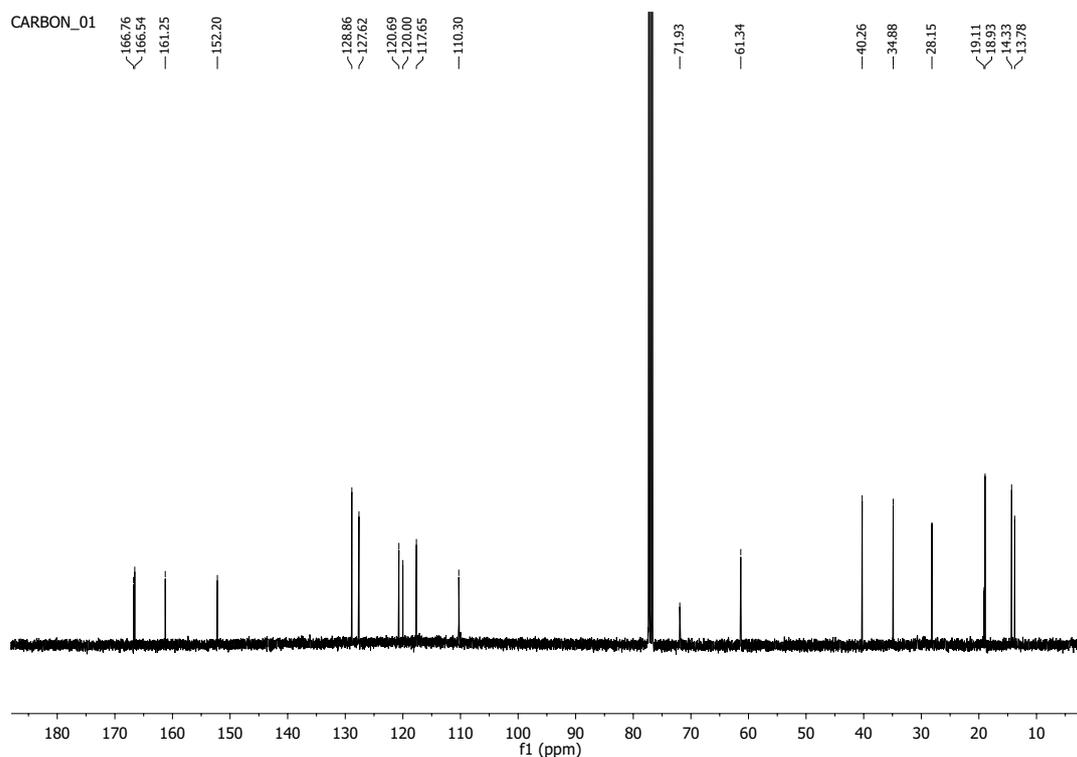
CARBON_01

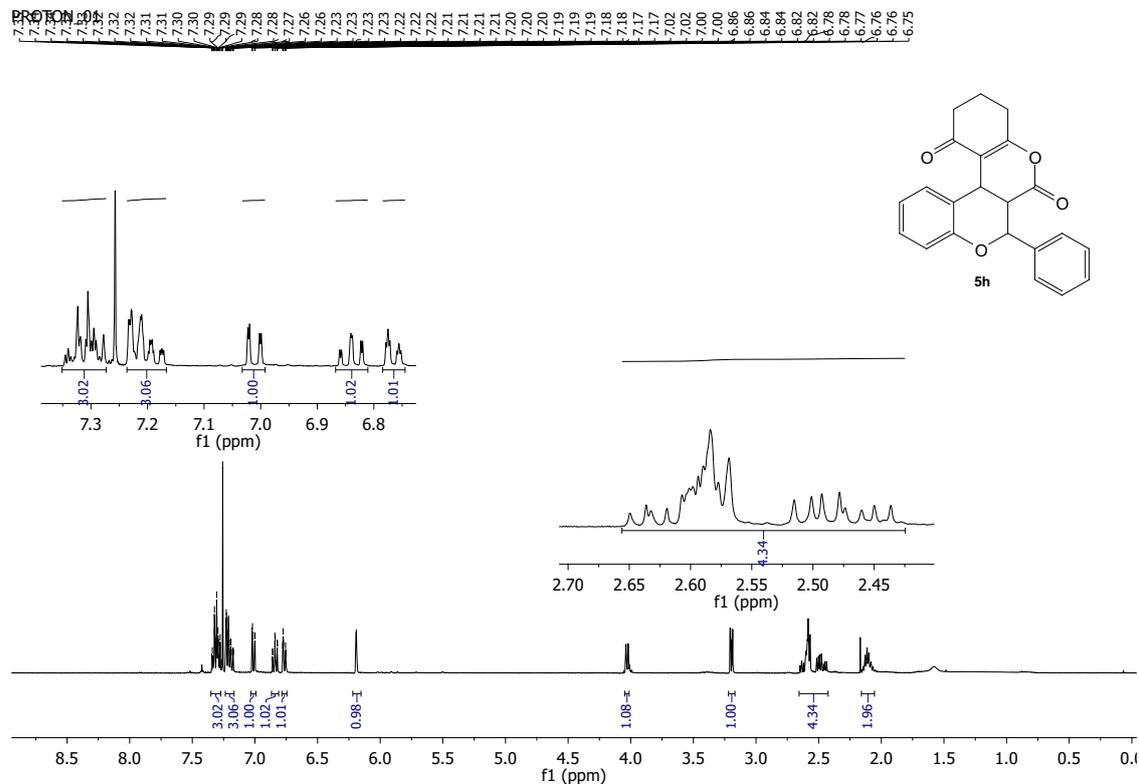
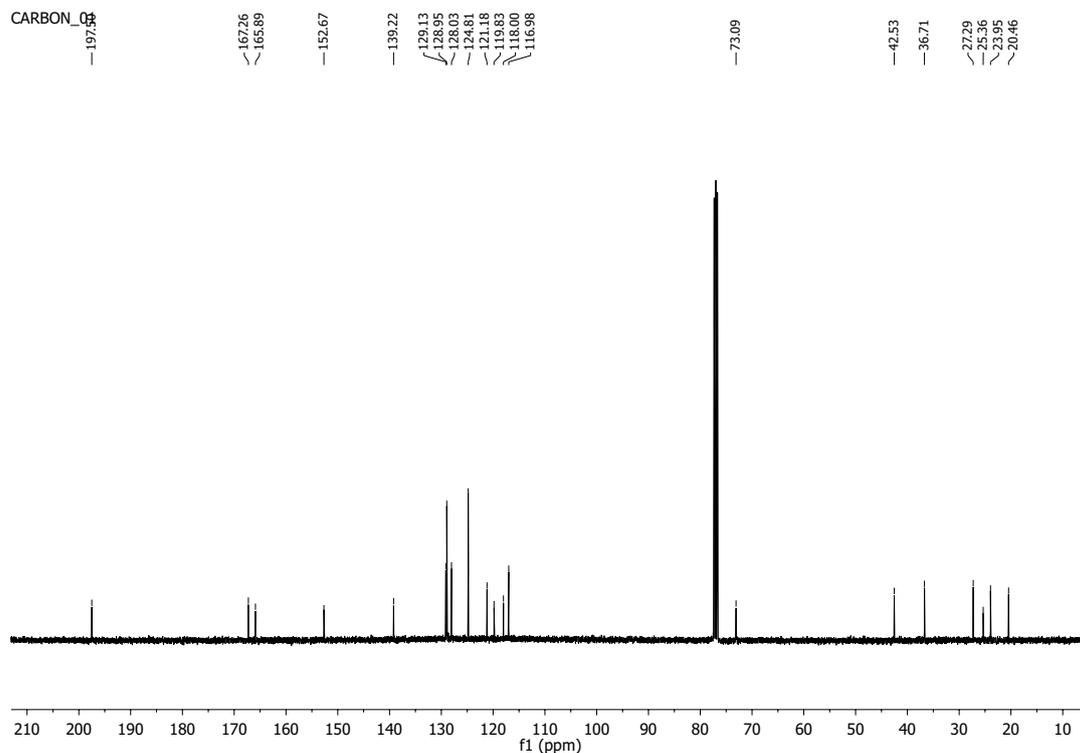


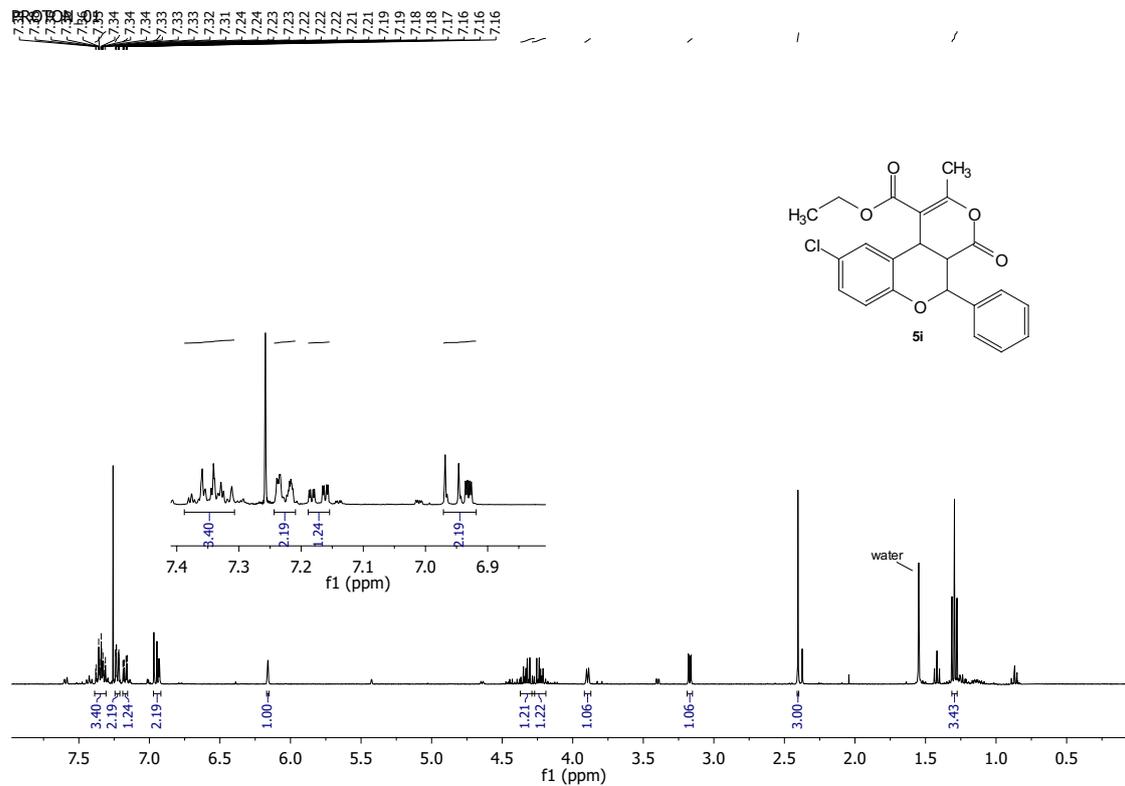
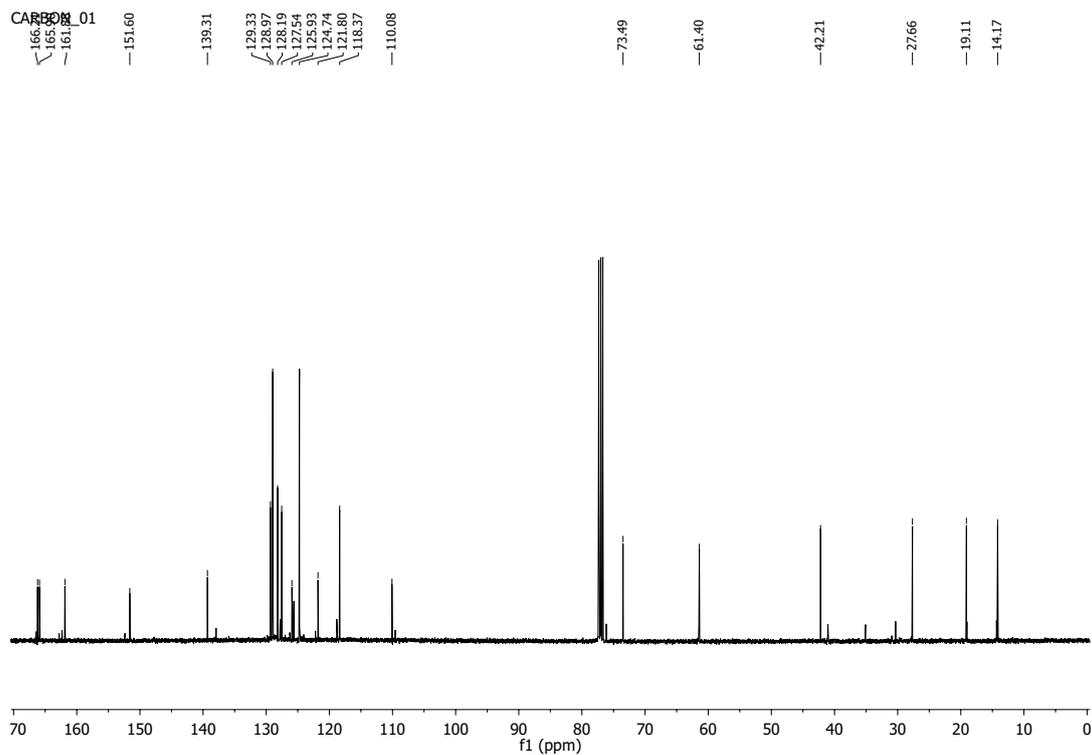
^1H NMR spectrum of Compound **5a** (400 MHz, CDCl_3) ^{13}C NMR spectrum of Compound **5a** (101 MHz, CDCl_3)

^1H NMR spectrum of Compound **5b** (400 MHz, CDCl_3) ^{13}C NMR spectrum of Compound **5b** (101 MHz, CDCl_3)

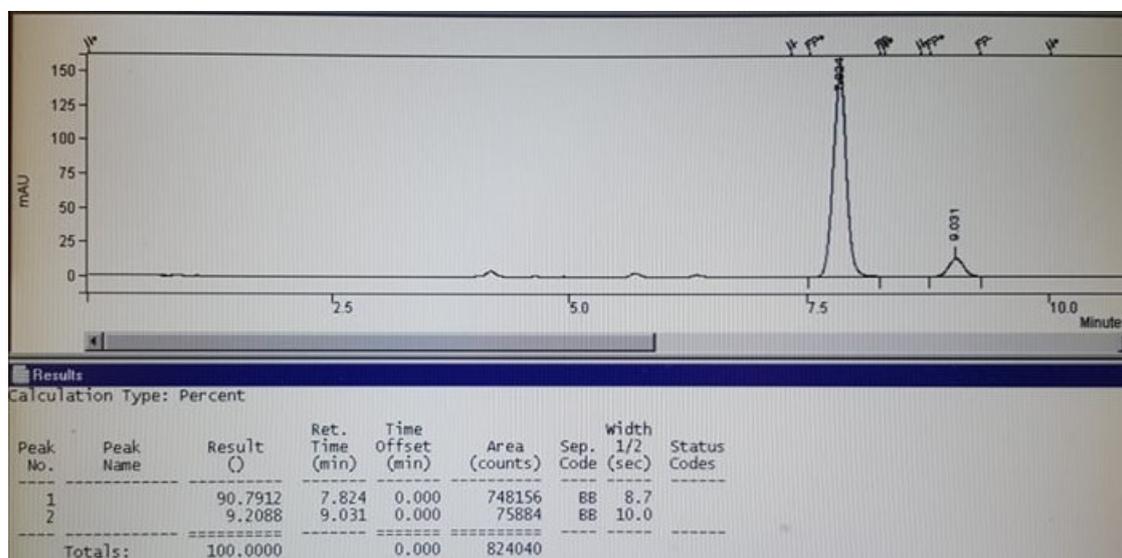
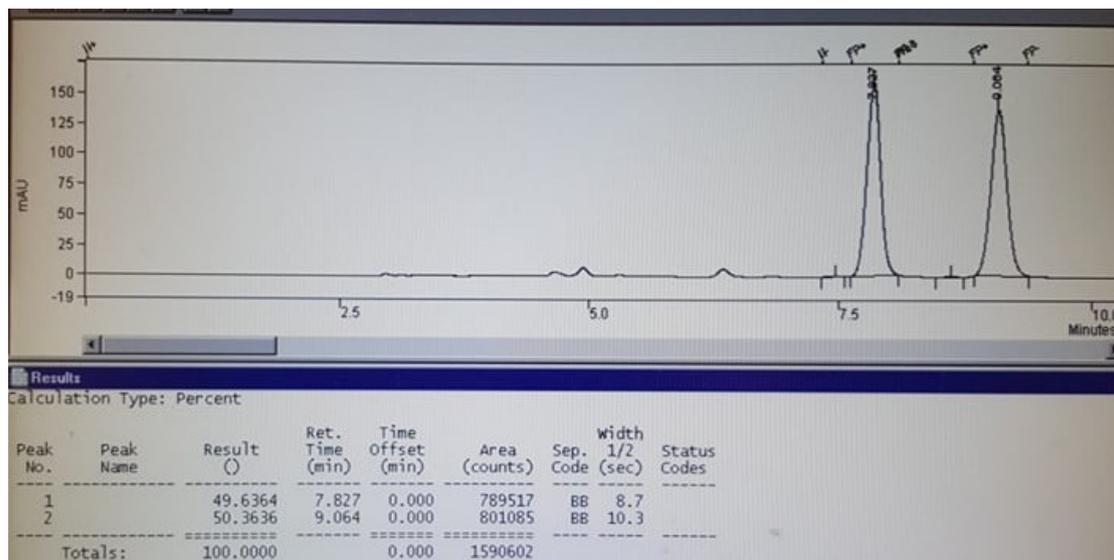
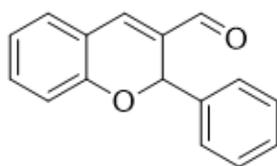
^1H NMR spectrum of Compound **5d** (400 MHz, CDCl_3) ^{13}C NMR spectrum of Compound **5d** (101 MHz, CDCl_3)

^1H NMR spectrum of Compound **5g** (400 MHz, CDCl_3) ^{13}C NMR spectrum of Compound **5g** (101 MHz, CDCl_3)

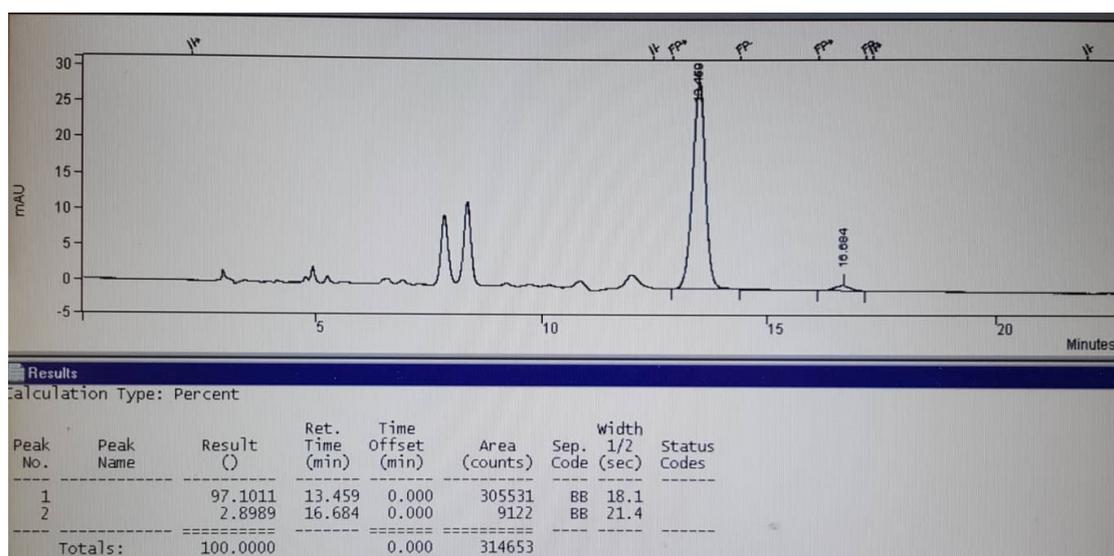
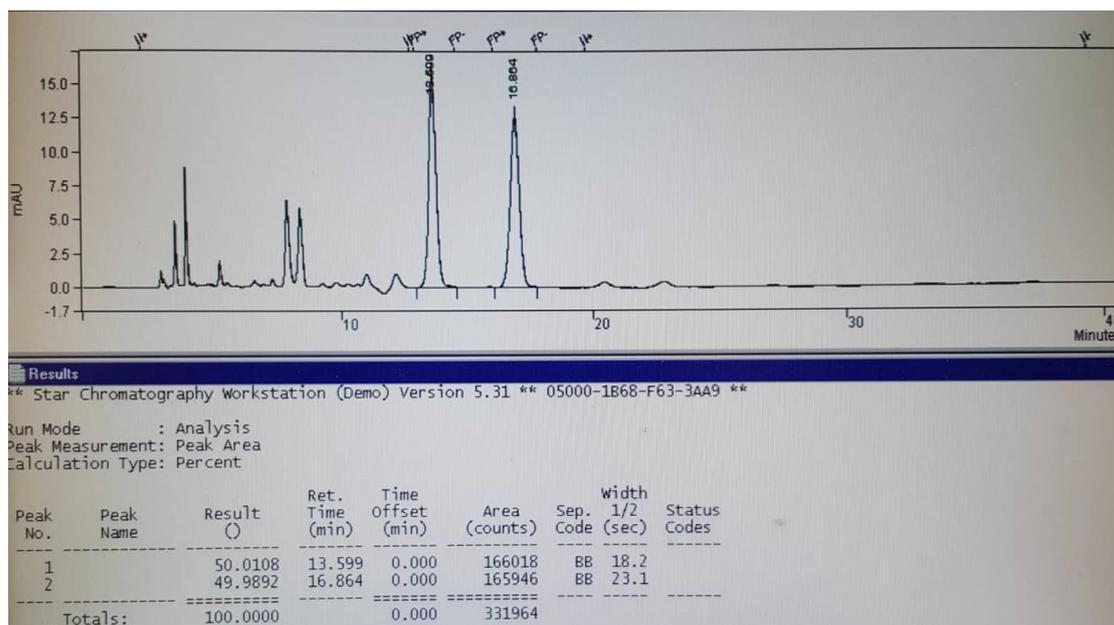
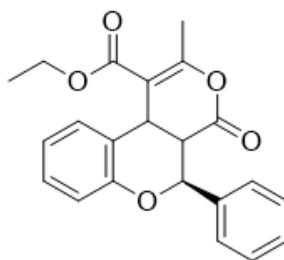
^1H NMR spectrum of Compound **5h** (400 MHz, CDCl_3) ^{13}C NMR spectrum of Compound **5h** (101 MHz, CDCl_3)

^1H NMR spectrum of Compound **5i** (400 MHz, CDCl_3) ^{13}C NMR spectrum of Compound **5i** (101 MHz, CDCl_3)

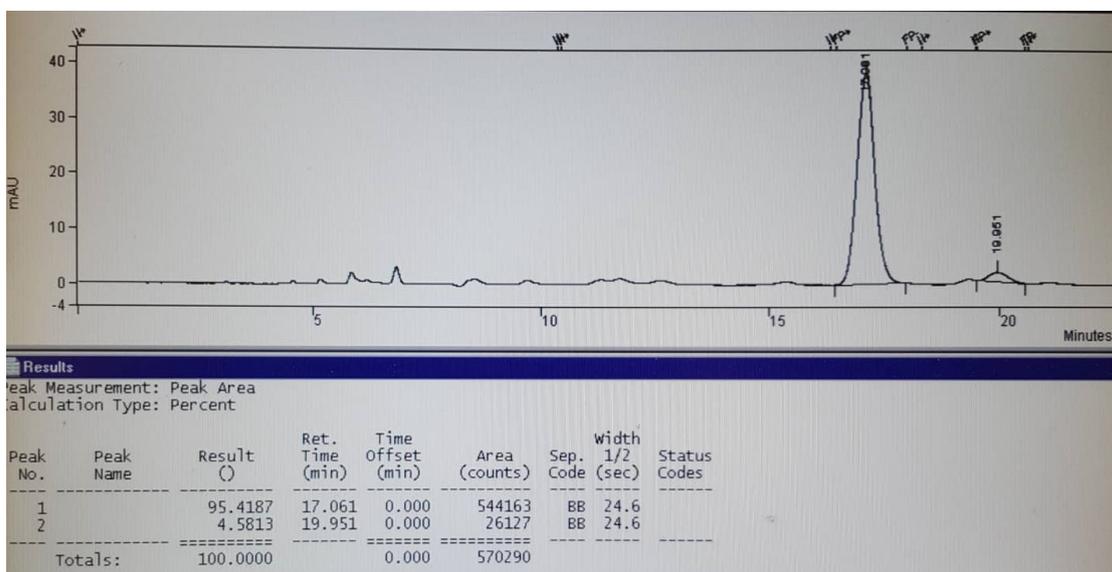
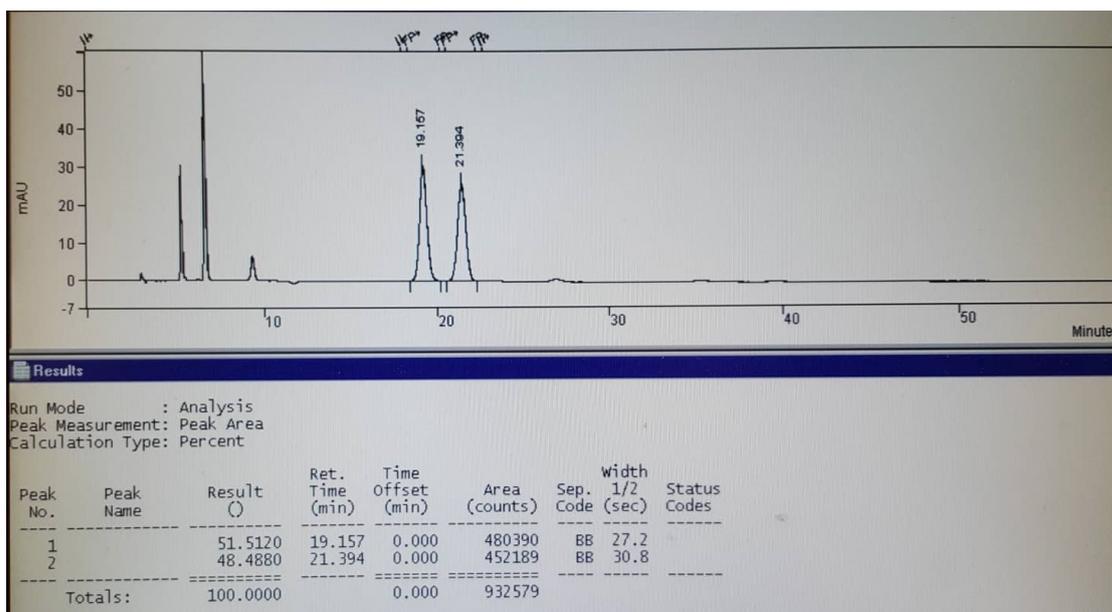
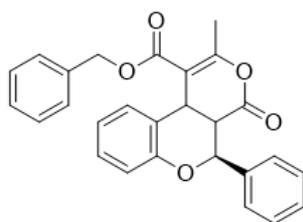
B. Appendix B - Detailed analytical data



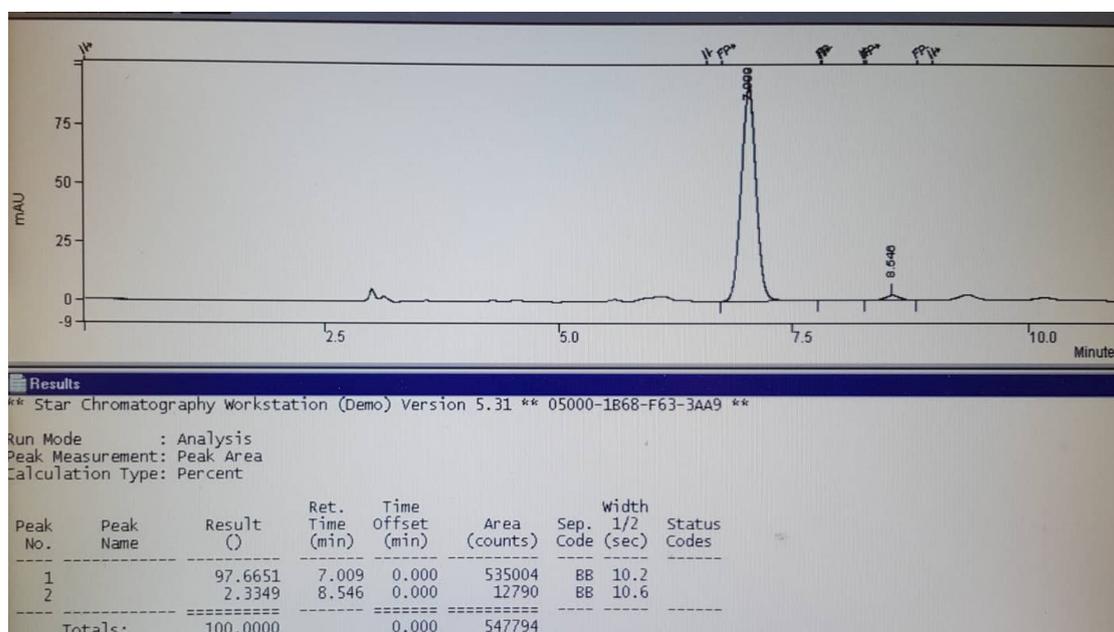
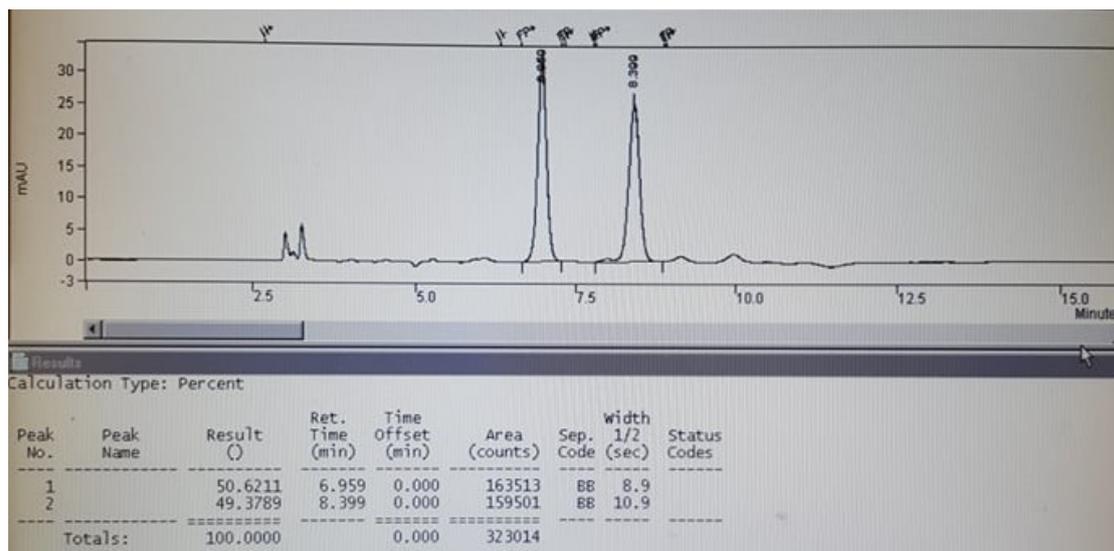
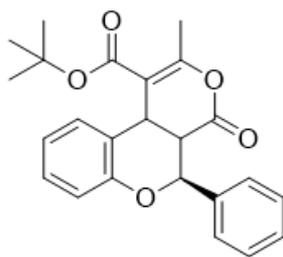
B. Appendix B - Detailed analytical data



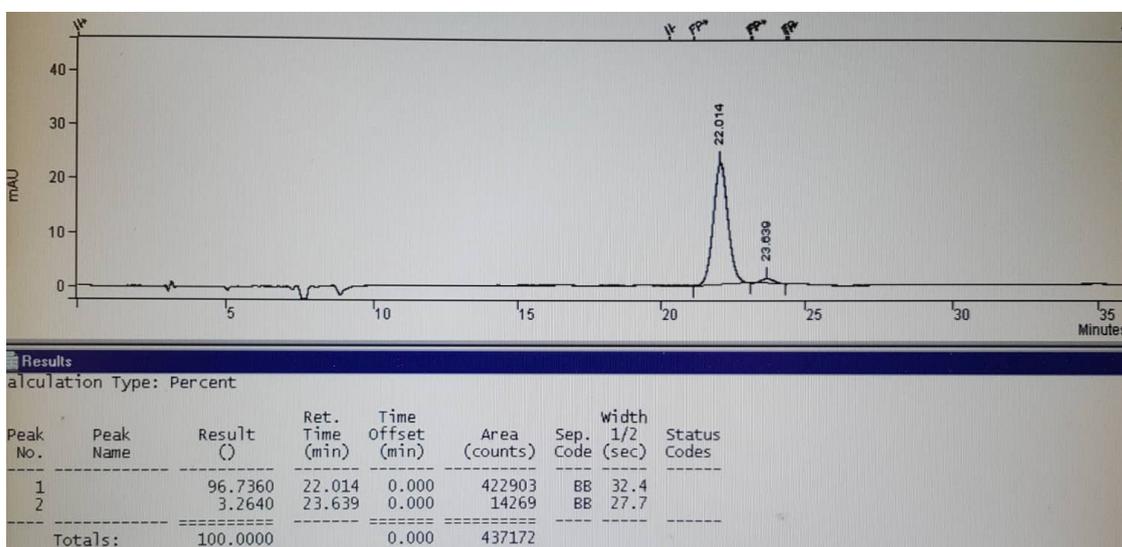
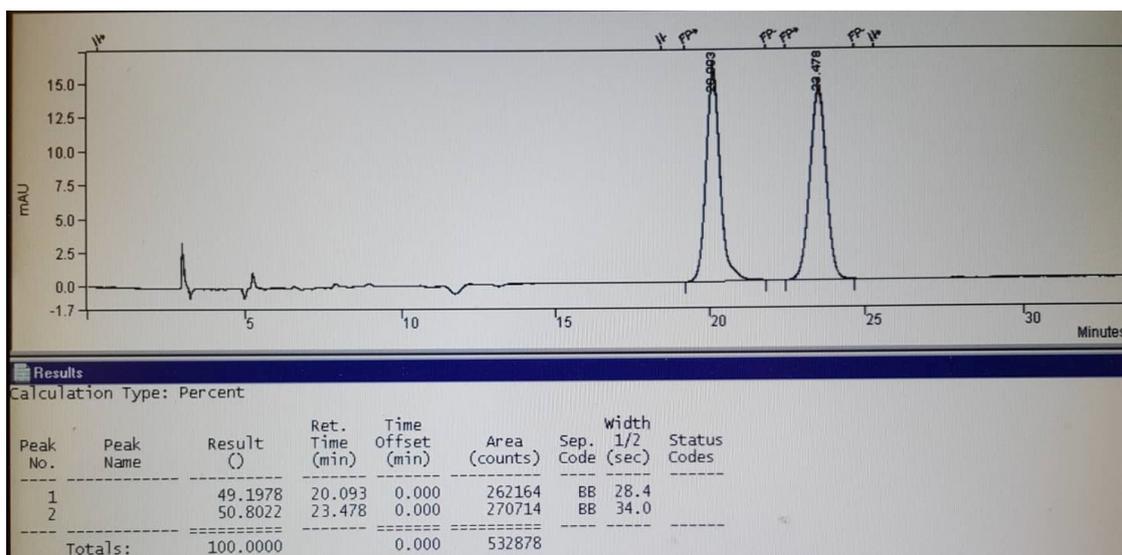
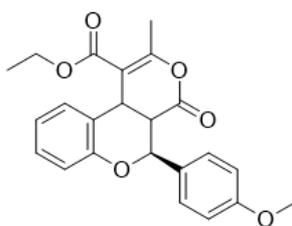
B. Appendix B - Detailed analytical data



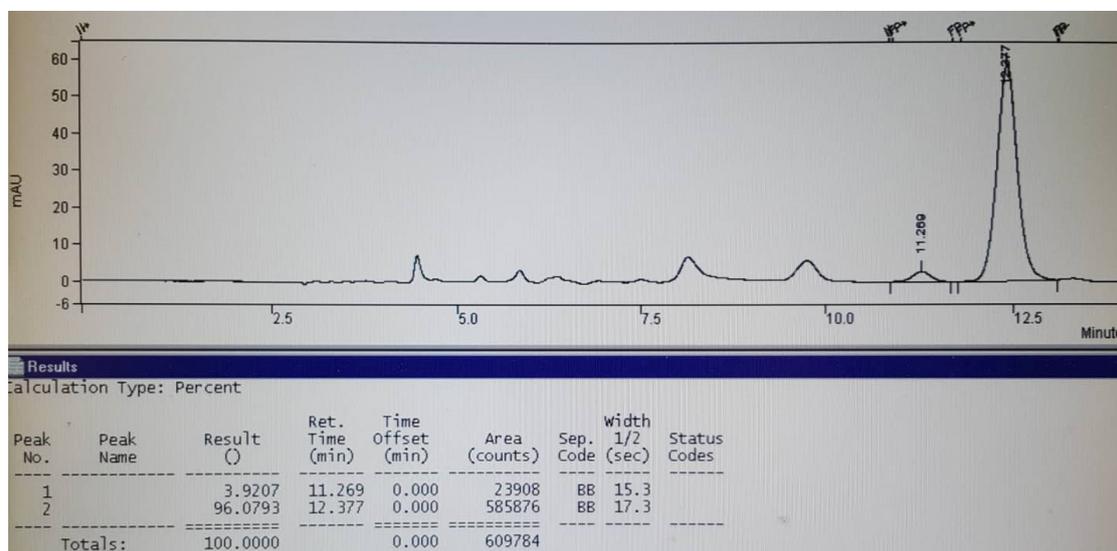
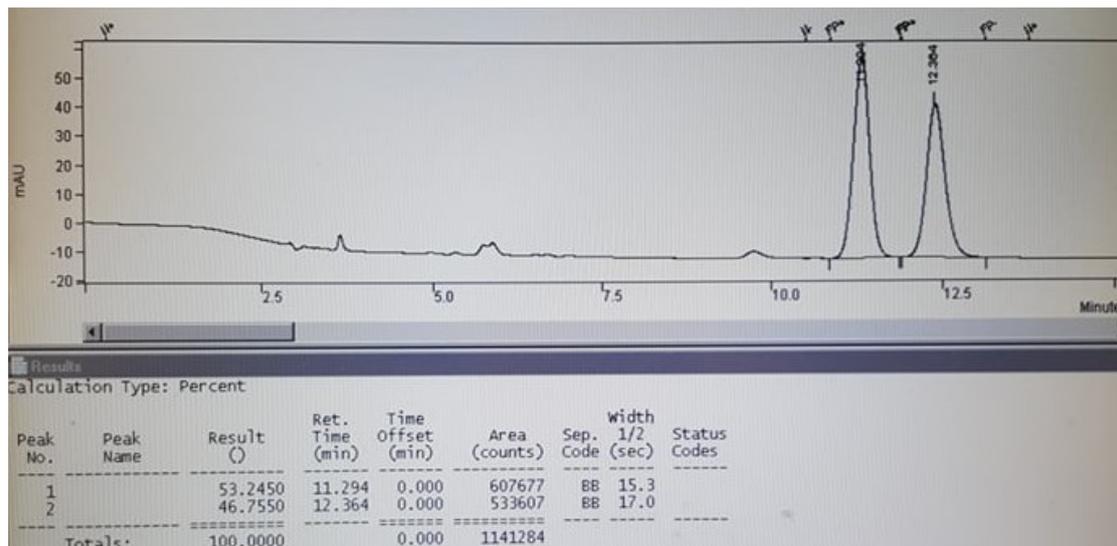
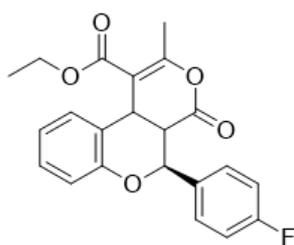
B. Appendix B - Detailed analytical data



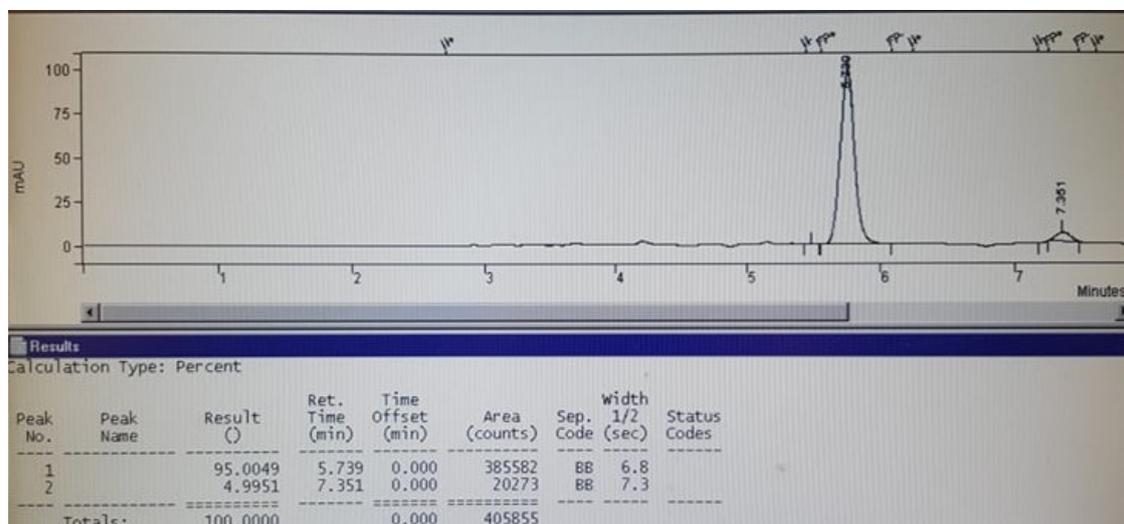
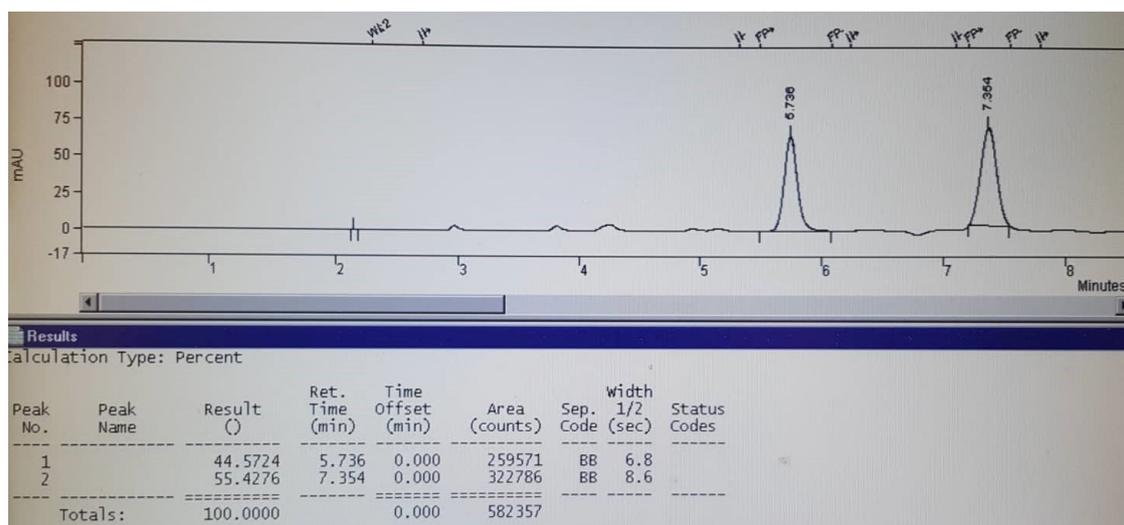
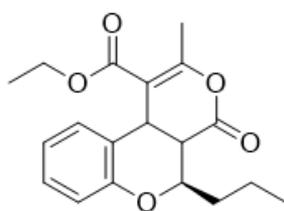
B. Appendix B - Detailed analytical data



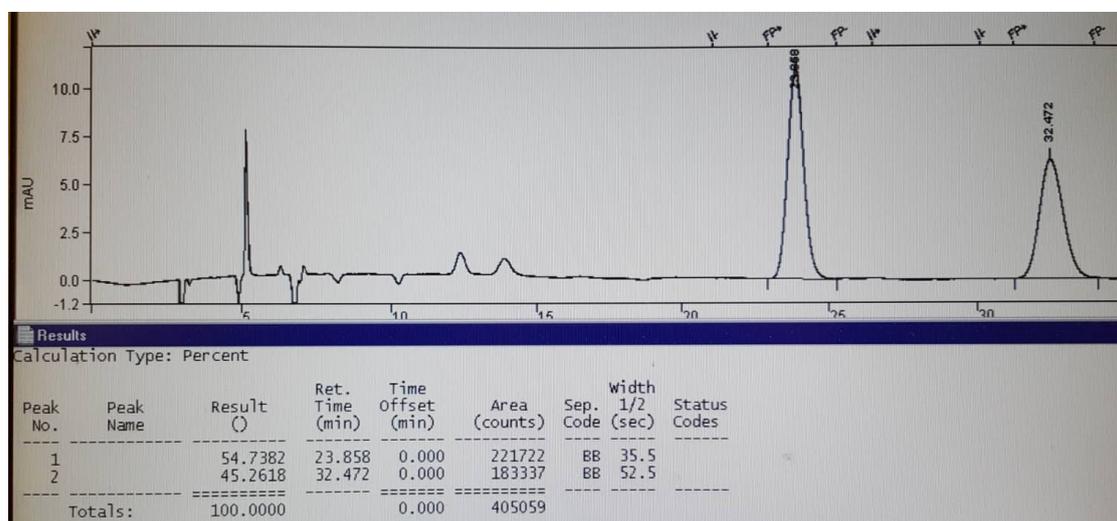
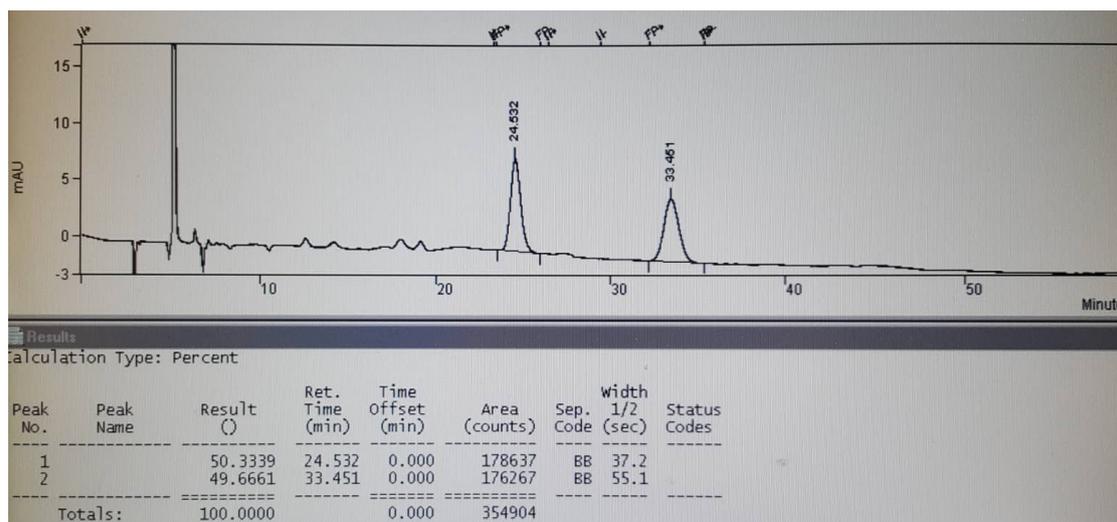
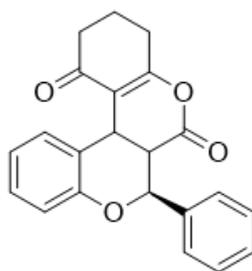
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