CHAPTER- 2

A Sustainable and Greener Approach for the Synthesis of 3-Functionalized Coumarins derivatives catalyzed by Beta cyclodextrin

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2.1 Introduction

Coumarin or 2H-chromen-2-one is an aromatic organic compound with formula $C_9H_6O_2$. Its molecule can be described as a benzene molecule with two adjacent hydrogen atoms replaced by an unsaturated lactone ring −(CH)=(CH)−(C=O) −O−, forming a second six-membered heterocycle that shares two carbons with the benzene ring. It belongs to the benzopyrone chemical class and considered as a lactone [1]**.** Coumarin is a colorless crystalline solid with a sweet odor resembling the scent of vanilla and a bitter taste [2]**.** Coumarins have important applications in fragrances, cosmetics, pharmaceuticals and food additives [3]. 3-Functionalized coumarin derivatives exhibit numerous significant in biological activities such as the reported moiety exhibits a variety of biological activities, including, immunomodulatory [4,6]**,** antimicrobial [7]**,** antifungal [8]**,** antitumor [9]**,** anti-inflammatory [10]**,** antiangiogenic [11]**,** antioxidant [12]**,** agrochemicals [13]**,** antibacterial [14]**,** skin diseases [15]. Coumarins are one of the most significant, thoroughly researched and easily accessible chemical compounds. Several natural products, like cephalosol, bergenin, and cytogenin include their derivatives. (**Figure 1.1**). Moreover, these derivatives have remarkable applications in material science, polymer and dye synthesis.

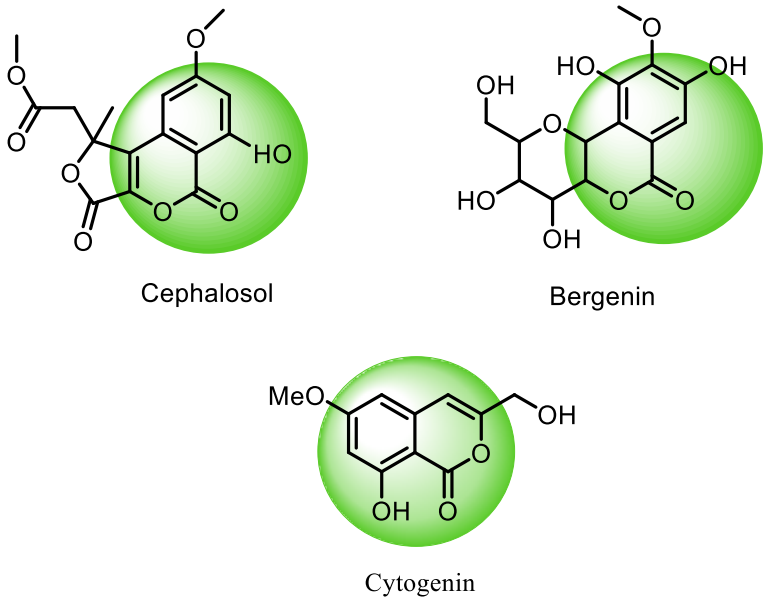


Figure 2.1 Coumarins moiety with biological and medicinal activity compounds

Coumarin was first isolated from tonka beans in 1820 by A. Vogel. Many methods are used to synthesize oxygen-containing heterocyclic molecules, including the Knoevenagel, von Pechmann, Wittig and Perkin reactions. Knoevenagel condensation is not only an alternative but also an efficient method for the synthesis of 3-substituted coumarins from salicylaldehyde with active methylene compounds such as malonate esters, Meldrum acid and ethyl cyanoacetate, etc. [16]. Synthesis of 3-substituted coumarins via Knoevenagel condensation was achieved using different metal and metal-free catalysts like natural clay [17], Mg-Al hydrotalcite [18], NaOH [19], piperidine [20], L-proline [21], mesoporous molecular sieve MCM-41 **[**22], ZrCl4 [23], p-toluene sulphonic acid [24], $MgFe_2O_4$ nanoparticles [25].

In addition, several modifications of the classical Pechmann procedure have also been reported, such as 2-methanesulfonic acid (MsOH**)** [26] MsOH on Al_2O_3 [27], p-TsOH [28], Ti (IV)-doped ZnO matrix [29], 3-methyl-1-sulfonic acid imidazolium hydrogen sulfate [30], FeF_3[31], Fe_3O4@SiO2-imidazolium nanoparticles [32], poly(4-vinylpyridine)-CuI [33], and glutamic acid [34] have been employed. In 2015, Sunita *et al*. reported an elegant [$Rh_2(OAc)_4$] catalytic system for the synthesis of coumarin derivatives using NaOAc as a base and HCO_{2H} as a reducing agent [35]. Boroujeni et al. reported ionic liquid-based catalyst [P_4VPy-BuSO_3H] Cl-X($AlCl_3$) possessing both Lewis and Brønsted acidic groups [36].1-Ethyl-3-(3-sulfopropyl)- benzimidazolium trifluoromethanesulfonate ([PSebim][OTf]) was also reported for the synthesis of bis coumarins [37-38]. Recently Siddharth R. Kamat, *et al*. have reported synthesis of 3- functionalized coumarins using various reactant in the presence β-CDs catalyst. But this method suffers from some drawbacks including high priced substrate and tedious reaction workup because water being used as solvent[38-**a**]. However, most of these methods have multiple drawbacks, including hazardous organic solvents, high catalyst costs, and prolonged reaction times. A family of cyclic oligosaccharides known as cyclodextrins is composed of a macrocyclic ring of glucose subunits connected by α (1-4) order with glycosidic linkages. CDs are produced by the hydrolysis of starch in the presence of an enzyme that is formed from biomass [39]**.** A cyclodextrin consists of six, seven, eight or more D-glucose units through 1,4-alpha linkages in such a way as to form a ring chain bracelet, each link of which is the pyranose hexagon in (**Figure.2.2)**. They are utilized in the food, pharmaceutical, medicine delivery, chemical, agricultural, and environmental

engineering industries. A- α-Cyclodextrin: 6 Glucose subunits, B- β-Cyclodextrin:7 Glucose units & C- γ-Cyclodextrin: 8Glucose subunits.

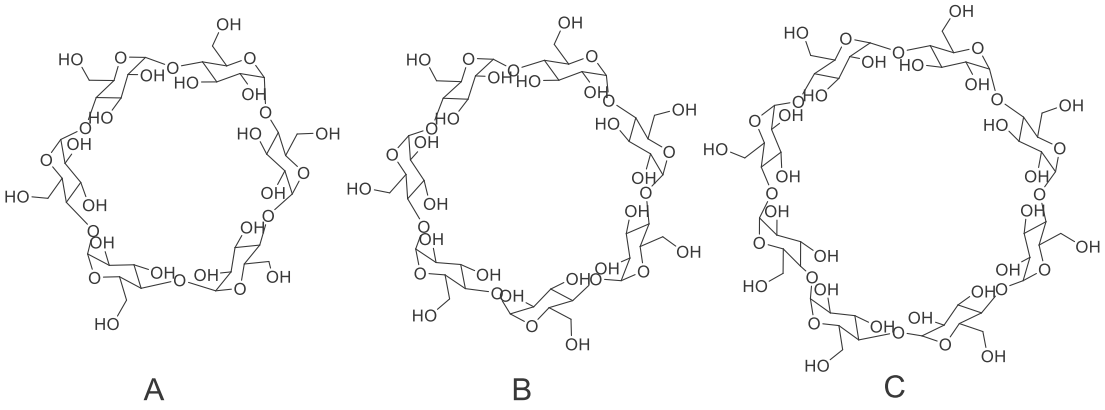
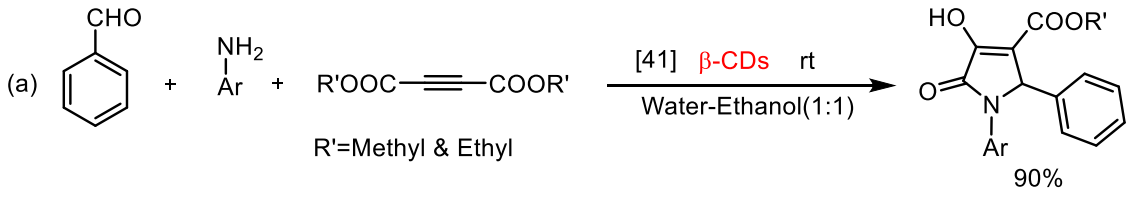
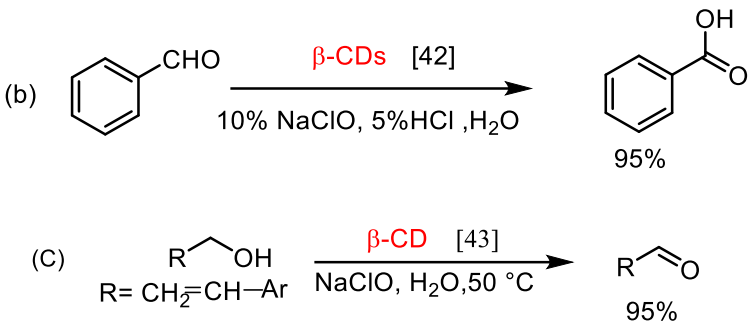


Figure 2.2 Cyclodextrin Derivatives.

β-Cyclodextrin is a cyclic oligosaccharide, as shown in (**Figure.2.3**), possessing a hydrophobic cavity, which binds the substrates selectively and catalyzes a number of organic transformations with high selectivity. In general, the reactivity profile of β-Cyclodextrin can be depicted by the reaction catalysis employing non-covalent supramolecular bonding with the reversible formation of host-guest complexes, as seen in enzymes [40]. The design of several significant organic transformations using cyclodextrin and its derivatives follows the similar mechanism and is summarized in various articles [41-46] and their schemes are shown in **scheme 2.1(a-c)**.





Scheme 2.1 Different organic transformation using β- Cyclodextrin.

Due to their wide-range uses in agrochemicals, pharmaceuticals and heterocyclic scaffolds, these are frequently chosen by researchers [47-49]. Furthermore, β- Cyclodextrin are readily available, and high stability and easy handling are the major advantages of using β-cyclodextrins as green catalysts. Therefore, in organic synthesis, an effective and straightforward method for synthesizing coumarins from simple, easily available, and cheap starting materials is still in high demand. So herein, we endeavor to report, for the first time, a simple and efficient method for the synthesis of 3-Functionalized coumarin derivatives using more easily available and economically favorable starting materials such as 2-hydroxybenzaldehyde and active methylene, catalyzed by beta-cyclodextrin as a green catalyst in the equimolar ratio of ethanol:water (1:1) **(Scheme 2.2).** A comparative study of the percentage of yields of synthesis of coumarin and its derivatives by different earlier reported methods with the present method is shown in (**Figure 2.4).** Accordingly, a model reaction for the coumarin synthesis carried by us is shown in **(scheme 2.2).**

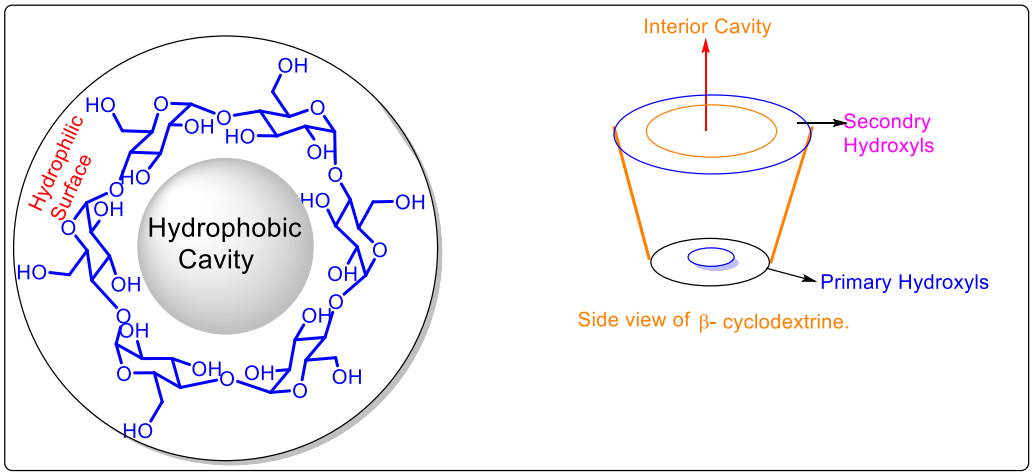


Figure 2.3 A schematic representation of β-cyclodextrin. The secondary-OH group face outward about the "upper" rim, and the primary CH_2OH group face outward about the "lower" rim. The cavity is lined with C-H's and glycosidic 'O' in three bonds lying one above another.

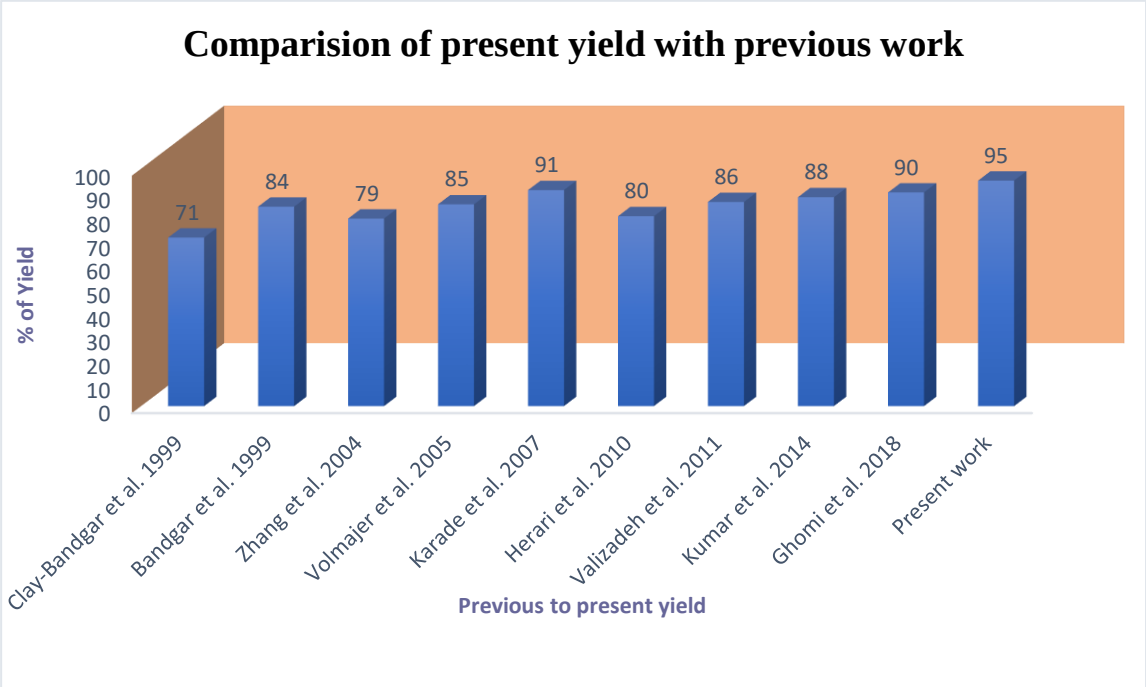
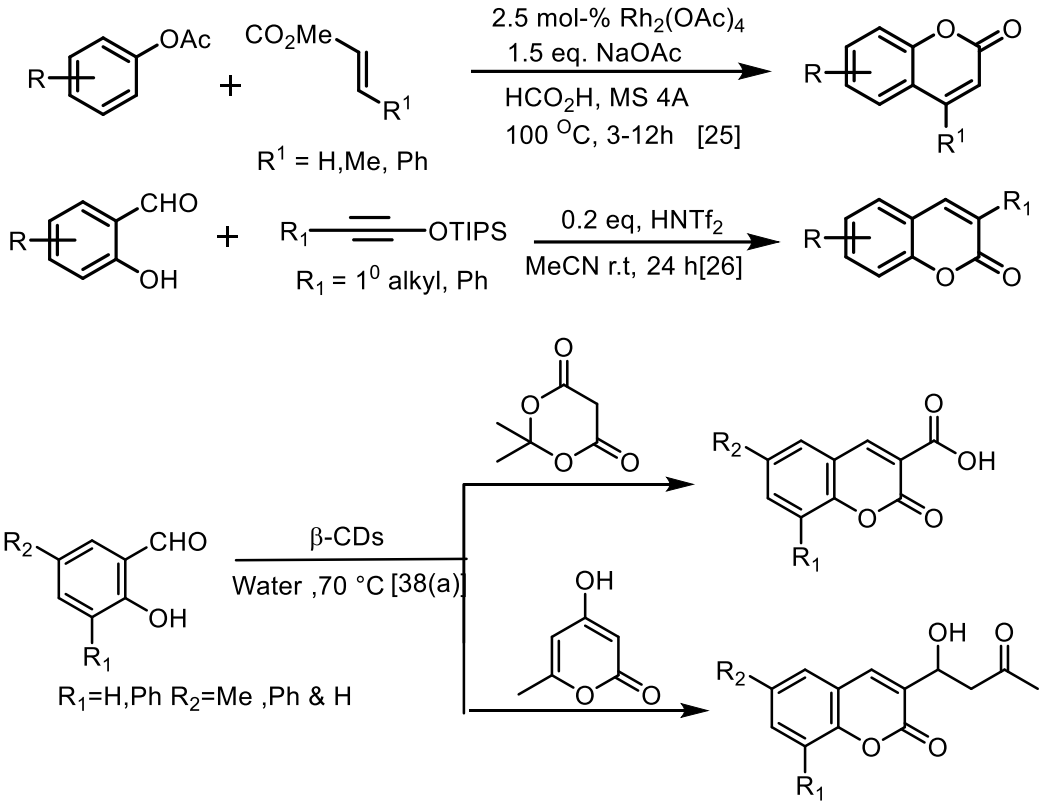
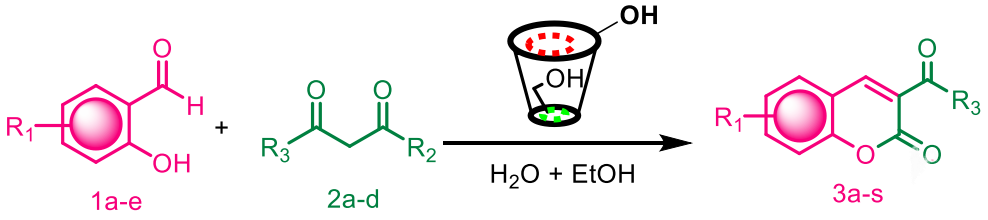


Figure: 2.4 Comparison of the % of yield for the synthesis of coumarin.

A- Previous work



B-Present work



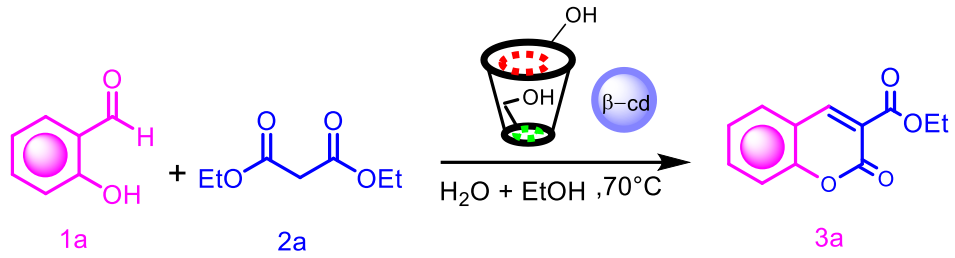
R_1 = H, Cl, Br, OMe, $N(C_2H_5)_2$

R_2 = OEt, OMe

R_3 = OEt, OMe, Me,OH

"Green Synthesis "Mild Reaction condition "Gram-Scale "Chromatography-Free

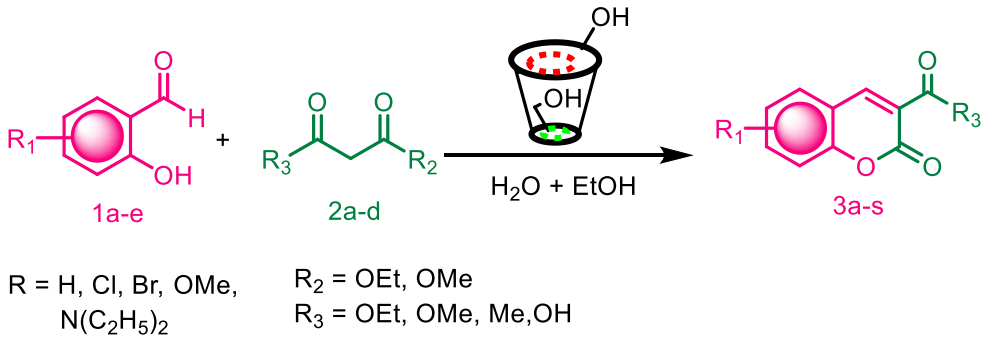
Scheme 2.2 Various previous and present methods for the synthesis of coumarin.



Scheme 2.3 Model reaction for the synthesis of coumarin.

2.2 Results and discussion

2.2.1 Optimization of Reaction Conditions: In the beginning, in order to optimize the reaction conditions for the synthesis of 3-functionalized coumarins employing the reactant, 2-hydroxybenzaldehyde, and ethyl malonate in the presence of β –cyclodextrin and aqueous ethanol: water **(1:1) (Scheme 2.4).**



Scheme 2.4 Synthesis of 3-functionalized coumarins derivatives in the presence of aqueous ethanol and β-cyclodextrin.

Our initial approach was to examine the impact of the catalyst on the reaction time and product yield. The reaction did not occur without the catalyst (**Table 2.1, entry 1**). Even after

a longer period of time, the yield of the desired product was very low when the reaction was conducted with AcOH present (**Table 2.1, entry 2**). The yields of the products were 35% and 40% when the reactions were conducted in the presence of PTSA (p-Toluenesulfonic acid) and [bimim]OH, respectively (**Table 2.1, entry 3-4)**. The effect of the well-known green catalyst β-cd is delightfully observed, resulting in excellent product yields for the reaction. The best results were achieved by optimizing with different forms of cyclodextrin (α and γ-cd), but the presence of β-cd yielded excellent yield is obtained results (as evidenced by (**Table 2.1**, **entry 5-7),** and accomplished in less time).

Table 2.1 Impact of catalyst on reaction time and yields for the synthesis of 3-functionalized coumarins.[a]

Entry	Catalyst (10 mol %)	Time (h)	Yield (%) [b]
1	No catalyst	5	-
2	AcOH	5	20
3	PTSA	5	35
4	[bmim]OH	5	40
5	α-cyclodextrin	5	48
6	γ-cyclodextrin	5	60
7	**β-cyclodextrin**	**2.5**	**95**

[a]**Reaction conditions:** 2-hydroxybenzaldehyde **(1.0 mmol**) and diethylmalonate **(1.0 mmol)** with β-cyclodextrin **(1.0 mmol)** in ethanol and water. [b] isolated yield of product.

Next, optimization is based on the different amounts of the catalyst. The synthesis of coumarins was then optimized through a series of reactions (**3a**). The quantity of catalysts present is crucial for the reaction to start. The product yields were **64%** whenever the resulting mixture was agitated with **5** mol% of catalyst (**Table 2.2, entry 1**). The product yield was outstanding when amount catalyst increased to **10** mol% **(Table 2.2, entry 2)**. The product yield did not rise even when the catalyst increased to **15** mol% **(Table 2.2, entry 3)**.

Table 2.2 Screening of the amount of catalyst for the synthesis of compound 3a.[a]

Entry	Amount of catalyst	Yield (%) [b]	Time (h)
1	5	64	2.5
2	**10**	**95**	**2.5**
3	15	95	2.5

[a]**Reaction conditions:** 2-hydroxybenzaldehyde (**1.0 mmol**) and diethylmalonate (**1.0 mmol**) with β-cyclodextrin (**1.0 mmol)** in ethanol and water. [b] **isolated yield** of product

Further, the model reaction was optimised for different parameters, including temperature, solvent, and time, which is crucial for the formation of the product (**3a**). Initially, the condensation of o-cresol and active methylene was carried out with a green catalyst (β-cd) in the presence of different non-polar solvents like toluene, benzene, and hexane to give no yield **(Table 2.3, entries 1-3)** and also polar solvents such as acetonitrile, dichloromethane, 1,4-dioxane, chloroform, ethanol and methanol **(Table 2.3, entries 4-10)** at refluxed temperature. The reaction proceeded smoothly in all the solvents tested in this study, and the desired product (**3a**) was obtained in **20-40%** yield. In order to improve the yield of the

products, a greener method was used where a mixture of water and ethanol (**1:1**) at room temperature (**25 °C**) was used. Even though no products were obtained (**Table 2.3, entry 11**). The yield of the product (**3a**) was found to increase as the temperature was raised from 50 °C to 70 °C **(Table 2.3, entry 12-15).** At **75 °C**, the reaction provided a **95%** yield **(Table 2.3, entry 16)** of the product. Any further increase in reaction temperature did not show a significant change in reaction time and yield of product **(Table 2.3, entries 17-18)**. It is important to mention that the reaction temperature affects the yield of the product for the hydrogen-bond interaction of H_2O: EtOH mixture with **β-cd**; appropriate activation energy is required, and in our reaction, that is achieved at **75 °C**. The model reaction of o-cresol and diethyl malonate was also investigated with different ratios of solvents such as water: ethanol **(1:2 and 2:1)** (**Table 2.3, entries 19-20)**, Further, we observed that any change in the solvent mixture did not improve the yield. Thus, we have optimised the model reaction conditions, implying the use of a solvent mixture of water and ethanol (**1:1**) at **75**°C using 1 mole β-cd as a green catalyst.

Table 2.3 Optimization of solvent, temperature and reaction time on the yield of 3a.[a]

Entry	Solvent	Catalyst	Temperature (°C)	Time (h)	Yield (%) [b]
1.	Toluene	β-Cyclodextrin	Reflux	5	NR
2.	Benzene	β-Cyclodextrin	Reflux	7	NR
3.	Hexane	β-Cyclodextrin	Reflux	6	NR

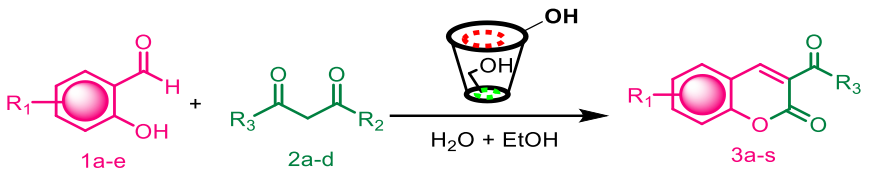
4.	Acetonitrile	β-Cyclodextrin	Reflux	5	NR
5.	DCM	β-Cyclodextrin	Reflux	6	NR
6.	1,4-dioxane	β-Cyclodextrin	Reflux	6	NR
7.	Water	β-Cyclodextrin	Reflux	7	20
8.	Ethanol	β-Cyclodextrin	Reflux	7	30
9.	Methanol	β-Cyclodextrin	Reflux	6	20
10.	Chloroform	β-Cyclodextrin	Reflux	4	20
11.	Water: Ethanol (1:1)	β-Cyclodextrin	rt	7	40
12	Water: Ethanol (1:1)	β-Cyclodextrin	50	5	45
13.	Water: Ethanol (1:1)	β-Cyclodextrin	60	5	55
14.	Water: Ethanol (1:1)	β-Cyclodextrin	65	4	60
15.	Water: Ethanol (1:1)	β-Cyclodextrin	70	4	70
16.	**Water : Ethanol (1:1)**	**β-Cyclodextrin**	**75**	**2.5**	**95**
17.	Water: Ethanol (1:1)	β-Cyclodextrin	100	2.5	95
18.	Water: Ethanol (1:1)	β-Cyclodextrin	80	2.5	95
19.	Water: Ethan0l (1:2)	β-Cyclodextrin	75	2.5	85
20.	Water: Ethanol (2:1)	β-Cyclodextrin	75	2.5	95

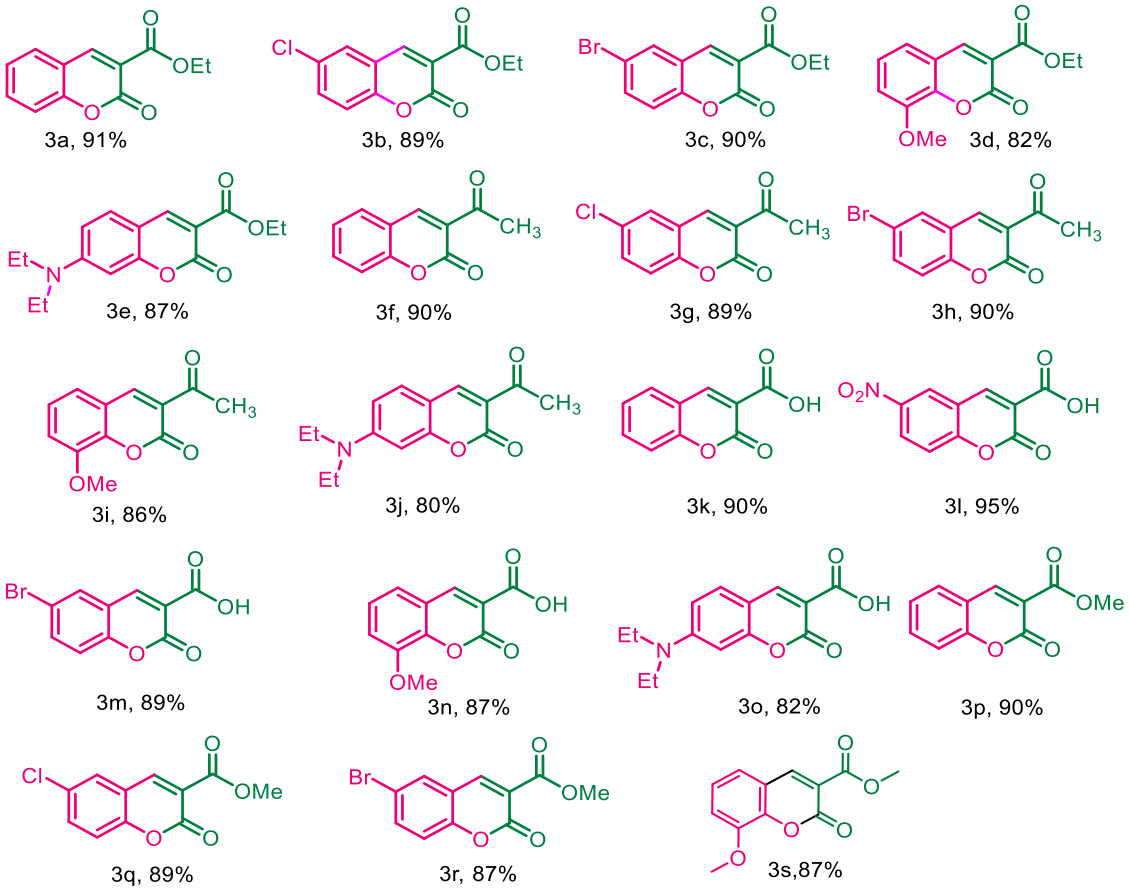
[a]**Reaction conditions:** 2-hydroxybenzaldehyde (1.0 mmol) and diethylmalonate (1.0 mmol) with β-cyclodextrin (1.0 mmol) in ethanol and water. [b]isolated yield of product.

For the present protocol, the multiple substrate scope was then optimized and listed in (**Table 2.4)**. We use a variety of active methylene groups with phenyl ring substitutions. The Phenyl group that has been substituted with both electron-withdrawing and electron-donating groups underwent a smooth conversion to produce the related yields 3a-r. ^{1}HNMR, ^{13}CNMR, and mass spectra are permitted to confirm the composition of all essential products.

2.2.2 Substrates scope for 3-functionalized coumarins derivatives

Table 2.4 Substrate Scope. [ab]

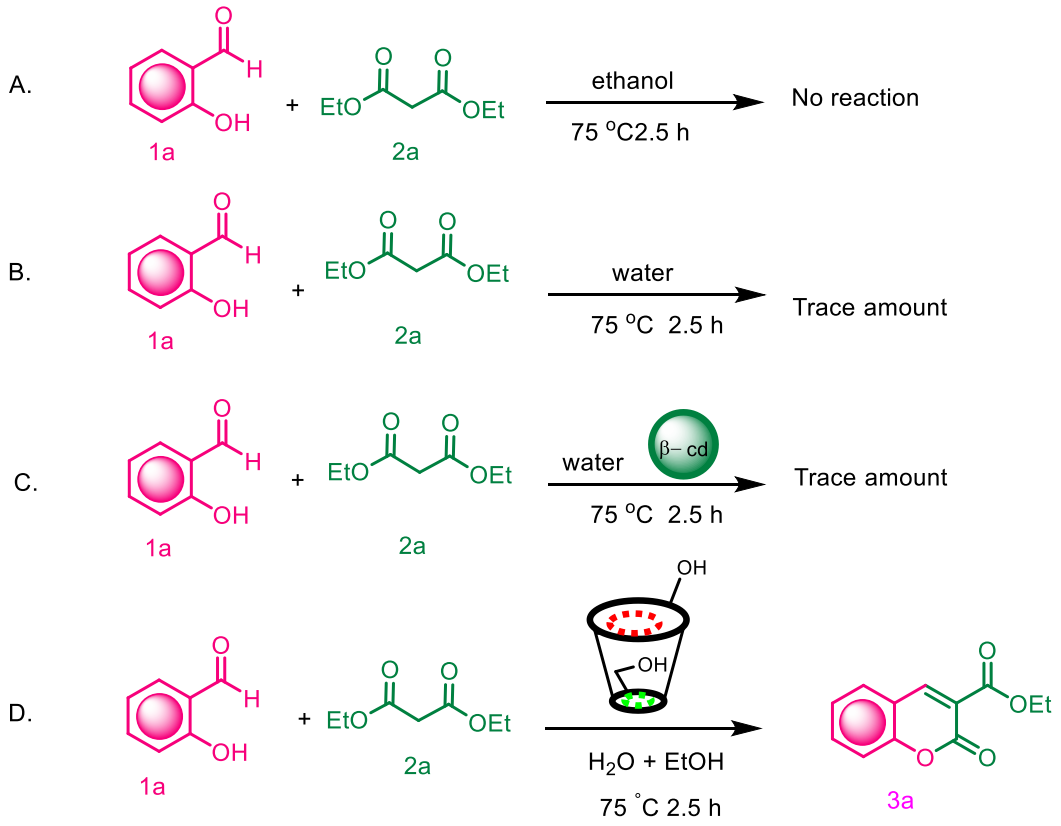




[a]**Reaction conditions:** 2-hydroxy benzaldehyde (1.0 mmol) and dimethylmalonate -cyclodextrin (1.0 mmol) in ethanol and water [b]isolated the yield of product.

2.3 Controlled Experiments and Mechanistic studies

To investigate the role of solvent (Water: Ethanol) and catalyst (β-cyclodextrin) in the present (**Scheme 2.5)**, the reaction of 2-hydroxybenzaldehyde (**1a**) with diethyl malonate (**2a**) was carried out at 75 °C in the absence of β-cyclodextrin and water (**Scheme 2.5 A)**, even after **2.5** hours this reaction did not yield the anticipated result.

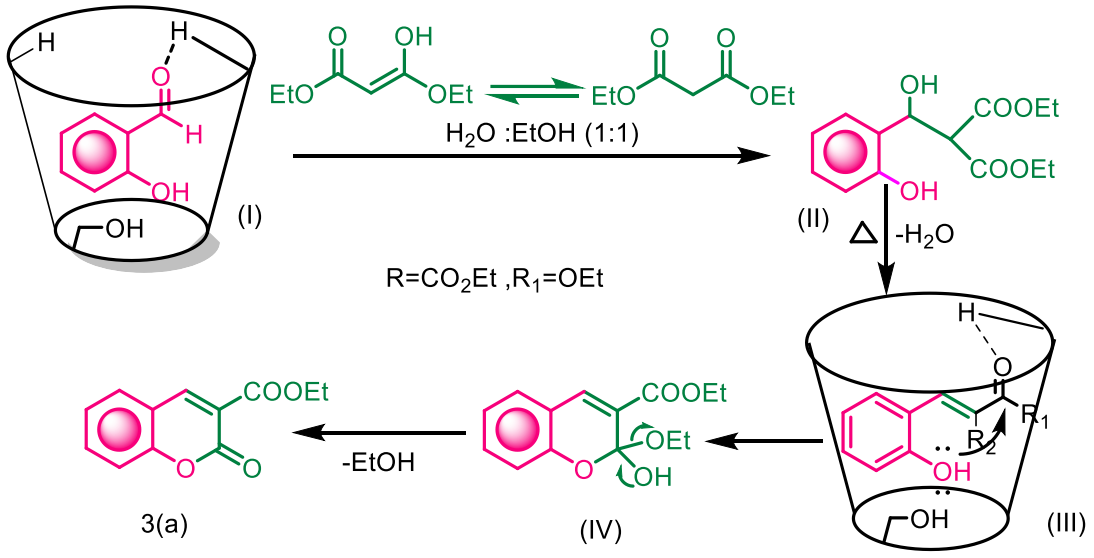


Scheme 2.5 Controlled experiments.

To further ensure that water did not facilitate the reaction, the reaction was carried out in the water and in the absence of beta-cyclodextrin, a trace amount of yield was obtained (**Scheme 2.5 B**), proving that water only did not participate in the Knoevenagel condensation.

However, the desired product was produced in a trace amount yield when the reaction was conducted with water in the presence of β-cyclodextrin (**Scheme 2.5 C**). Finally, the desired product was produced with good to excellent yield under standard reaction conditions (**Scheme 2.5 D**).

2.3.1 Plausible Reaction Mechanism



Scheme 2.6 A plausible mechanism for the synthesis of 3-functionalized coumarins derivatives.

A feasible process for synthesizing the targeted moiety is shown in (**Scheme 2.6)**. It is based on the findings of our experiments and literature review [50-56]. The β-cyclodextrin-catalysed organic transformation in aqueous media because the outer hydroxyl polar group of β-CD increases its solubility in water, and the inner lipophilic characteristic attracts the organic molecule in the cavity, which creates the reaction's microenvironment [54]. The functional group of substrates that has a propensity to form hydrogen bonds with the hydroxyl

group of cyclodextrin is activated, increasing the reactivity of the guest substrate and enabling effective transformation. Thus, the β-cyclodextrins activated the carbonyl group of 2-hydroxybenzaldehyde **(I)**. The activated molecule reacts with diethyl malonate to form an adduct **(II)** and, after dehydration, form a compound **(III) [55]**. The nucleophile of the hydroxyl group attacks the carbonyl group of esters to form an intermediate **(IV) [55]**. This intermediate **(IV)** is unstable and produces the expected product **(3a)** by removing the ethanol molecule.

2.3.2 Recovery of the catalyst:

After that, the reaction was finished, the matching solid product was separated by straightforward filtration, and the filtrate was used for the following cycle. The identical substrates and recycled β-cd were used in the process, and (**Figure-2.5).** Depicts all the outcomes. For the synthesis of compounds, the reusability of the catalyst was examined five times (including the new catalyst), and only a slight decrease in the yield of the desired result was seen.

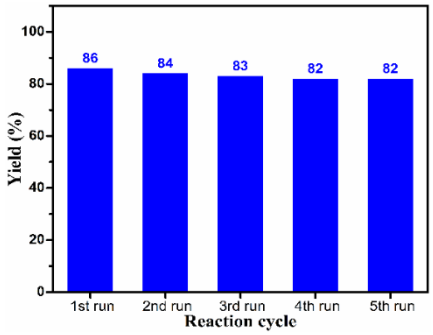


Figure 2.5 Reuse and recovery of β-cd

2.4 Gram-scale synthesis of 3-functionalized coumarin derivatives

To establish the potential synthetic application of this methodology the synthesis of 3-functionalized coumarin derivatives (**3a**) was carried out on gram scale with diethylmalonate (**1a**) (2.13 mL, 20 mmol) and 2-hydroxybenzldehyde (**2**) (1 g, 10 mmol) using β-Cyclodextrin (3 mmol). Under optimized reaction conditions it gave desired products (**3a**) in 91% yield.

2.5 Advantages of the present method: The present method is a straightforward, simple, eco-friendly and green approach for the synthesis 3-functionalized coumarins derivatives using a bio-degradable, eco-benign, green, supramolecular catalyst β-cyclodextrin, in water–ethanol medium. The main advantage of the reaction is that it's being carried out in absence of any additional metal catalyst or metal salt, and volatile organic solvent under mild reaction conditions, recovery of catalyst, no need for column chromatography. Metal free approach and easy isolation which boosts the benefits of the procedure. Further, the replacement of toxic and costly metal catalysts with an ecofriendly, bio-degradable, green and inexpensive organo-catalyst is the unique benefit of this synthetic procedure.

2.6 Experimental Section

2.6.1 General procedure for the synthesis of ethyl 2-oxo-2*H*-chromene-3-carboxylate (3a-3r) Firstly, 10 ml of distilled water in 50 ml round bottom flask was taken and add β-cyclodextrin **(1.0 mmol)** to heat at 75 ^{o}C for 15-20 minutes to form a clear solution (white

suspended solutions) and after 20 minutes, we have added 2ml of pure ethanol to form a solution of (β-cd) and aqueous ethanol then respective 2-hydroxybenzldehyde (**1.0 mmol**) and diethylmalonate (**1.0 mmol)** were added under stirring at 75 ºC. It was allowed to stir till the reaction was completed, as indicated on (TLC). After that, the corresponding solid product was isolated by simple filtration, and filtrate was utilized for the next cycle. The solid product was recrystallized from ethanol.

2.7 Analytical data

2.7.1 Analytical data of ethyl 2-oxo-2*H*-chromene-3-carboxylate derivatives.

Ethyl 2-oxo-2H-chromene-3-carboxylate (3a) Yield 198 mg (91%); white crystalline solid; m.p. 91-92 (Lit. 92 ˚C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.53 (s, 1H), 7.64 (dd, 2H), 7.63 (t, J = 8.6 Hz, 2H), 4.44 (q, J = 6.8 Hz, 2H), 1.43 (t, J = 6.8 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 163.06, 156.71, 155.1, 148.5, 134.3, 129.5, 124.8, 118.3, 117.8, 116.7, 61.9, 14.2. **HRMS** (ESI): Anal. Calc. For $C_{12}H_{10}O_4$ $[M+H]^+$ 218.0601; Obser.: 218.2159

Ethyl 6-bromo-2-oxo-*2H*-chromene-3-carboxylate (3b) Yield 266 mg (90%); white crystalline solid; m.p. 163-164 ˚C (Lit. 165-166˚C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.45 (s, 1H), 7.77 – 7.23 (m, 2H), 7.28-7.26 (d, J = 8.1 Hz, 1H), 4.46-4.42 (q, J = 6.8 Hz, 2H), 1.44-1.41 (t, J = 6.7 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 162.6, 156.6, 155.9, 153.9, 147.1, 136.9, 131.5, 119.5, 119.3, 118.6, 62.2, 14.2. **HRMS** (ESI): Anal. Calc. For $C_{12}H_9BrO_4$ $[M+H]^+$ 297.0922; Obser.: 295.9701.

Ethyl6-chloro-2-oxo-*2H*-chromene-3-carboxylate (3c) Yield 224 mg (90%); white crystalline solid; m.p. 175-177 ^{O}C (Lit. 172-174 $^{\circ}$C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.45 (s, 1H), 7.61-7.59 (d, J = 10.5 Hz, 2H), 7.34-7.28 (t, J = 12.3 Hz, 1H), 4.46-4.42 (q, J = 6.8 Hz, 2H), 1.44-1.41 (t, J = 6.9 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 162.6, 156.1, 153.5, 147.1, 134.1, 130.1, 128.4, 119.5, 118.9, 118.2, 62.2, 14.2. . **HRMS** (ESI): Anal. Calc. For $C_{12}H_9ClO_4$ $[M+H]^+$ 252.65001 Obser.: 252.0270.

Ethyl 8-methoxy-2-oxo-*2H*-chromene-3-carboxylate (3d) Yield 218 mg (88%); yellow crystalline substance; m.p. 88-92 °C (Lit. 88 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.57 (s, 1H), 7.18 (d, 1H), 7.30-7.28 (d, 1H), 7.21-7.20 (s, 1H), 4.00 (q, J = 7.1 Hz, 2H), 3.98 (s, 3H), 1.60 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 163.2, 157.2, 148.9, 146.1, 144.0, 125.8, 121.7, 117.5, 116.9, 63.1, 55.4, 13.3.48.17. **HRMS** (ESI): Anal. Calc. For $C_{13}H_{12}O_5$ $[M+H]^+$ 248.2301 Obser.: 248.0712.

Ethyl 7-(diethylamino)-2-oxo-*2H*-chromene-3-carboxylate (3e) Yield 251 mg (87%); yellowish solid; m.p. 77 ^{O}C (Lit. 76 $^{\circ}$C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.45 (s, 1H), 7.34-7.37 (d, J = 9.0 Hz, 1H), 6.64-6.48 (dd, 1H), 6.44-6.48 (d, J = 2.4 Hz, 1H), 3.93 (s, 2H), 3.49-3.44 (q, J = 7.1 Hz, 4H), 1.27-1.24 (t, J = 7.1 Hz, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 165.6, 158.5, 158.3, 152.9, 149.7, 131.1, 110.0, 109.6, 108.5, 107.7, 96.7, 52.3, 45.1, 12.4. **HRMS** (ESI): Anal. Calc. For $C_{16}H_{19}NO_4$ $[M+H]^+$ 289.3302 Obser.: 289.1302.

3-Acetyl-*2H*-chromen-2-one (3f) Yield 169 mg (90%); yellowish solid; m.p. 121-120 $^{\circ}$C (Lit. 123- 125 $^{\circ}$C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.53 (s, 1H), 7.69– 7.67 (m, 2H), 7.47–7.37 (m, 2H), 2.75 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 195.5, 159.2, 154.4,

155.3, 147.5, 134.4, 130.2, 125.0, 124.5, 118.2, 116.7, 30.5. **HRMS** (ESI): Anal. Calc. For $C_{11}H_8O_3$ $[M+H]^+$ 188.1800 Obser.: 188.0512.

3-Acetyl-6-bromo-*2H*-chromen-2-one (3g) Yield 239 mg (90%); white substance; m.p. 230-233 ^{O}C (Lit. 235-237 $^{\circ}$C); **^{1}H NMR** (500 MHz, DMSO) δ (ppm): 8.61 (s, 1H), 8.23-8.22 (s, 1H), 7.90-7.98 (d, J = 8.7 Hz, 1H), 7.46-7.44 (d, J = 8.8 Hz, 1H), 2.58 (s, 3H); **^{13}C NMR** (126 MHz, DMSO) δ (ppm): 195.4, 158.4, 154.0, 146.0, 137.0, 132.9, 125.8, 120.5, 118.8, 116.8, 30.4. . **HRMS** (ESI): Anal. Calc. For $C_{11}H_7B_rO_3$ $[M+H]^+$ 188.1800 Obser.: 188.0512.

3-Acetyl-6-chloro-*2H*-chromen-2-one (3h) Yield 197 mg (89%); yellow solid; m.p. 211-212 ^{O}C (Lit. 209- 211 $^{\circ}$C); **^{1}H NMR** (500 MHz, DMSO) δ (ppm): 8.58 (s, 1H), 8.07 (s, 1H), 7.76 (s, 1H), 7.51 (s, 1H), 2.55 (s, 3H); **^{13}C NMR** (126 MHz, DMSO) δ (ppm): 205.6, 164.6, 163.5, 148.5, 135.5, 129.4, 126.8, 120.1, 118.4, 114.0, 33.0.47.84. **HRMS** (ESI): Anal. Calc. For $C_{11}H_7ClO_3$ $[M+H]^+$ 222.6201 Obser.: 222.0110.

3-Acetyl-8-methoxy-*2H*-chromen-2-one (3i) Yield 187 mg (86%); yellow solid; m.p. 161-162 ^{O}C (Lit 163- 164 $^{\circ}$C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.50 (s, 1H), 7.30 – 7.20 (m, 3H), 4.01 (s, 3H), 2.75 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 195.6, 158.7, 147.7, 147.0, 145.0, 124.8, 124.6, 121.3, 118.8, 115.9, 56.3, 30.6.47.72. **HRMS** (ESI): Anal. Calc. For $C_{12}H_{10}O_4$ $[M+H]^+$ 218.0201 Obser.: 218.610.

3-Acetyl-7-(diethylamino)-*2H*-chromen-2-one (3j) Yield 207 mg (80%); yellow solid; m.p. 152-154 ^{O}C (Lit 151-152 $^{\circ}$C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.45 (s, 1H), 7.42-7.40 (d, J = 8.7 Hz, 1H), 6.64-6.62 (d, J = 8.8 Hz, 1H), 6.48-6.48 (s, 1H), 3.49-3.45 (dd, 4H), 2.69 (s, 3H), 1.27-1.24 (t, J = 6.8 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 195.7,

160.9, 158.7, 153.0, 147.8, 131.9, 116.1, 109.8, 108.1. 96.61, 45.1, 30.6, 12.4. **HRMS** (ESI): Anal. Calc. For $C_{15}H_{17}NO_3$ $[M+H]^+$ 259.0311 Obser.: 259.1202.

2-Oxo-*2H*-chromene-3-carboxylic acid (3k) Yield 171 mg (90%); yellow crystalline substance; m.p. 189-190 °C (Lit. 189-191 ^{O}C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 11.41 (s, 1H), 8.74 (s, 1H), 7.42-7.38 (dd, 2H), 7.16– 6.98 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 164.7, 159.8, 133.4, 132.5, 119.7, 117.3, 117.1. **HRMS** (ESI): Anal. Calc. For $C_{10}H_6O_4$ $[M+H]^+$ 190.0150 Obser.: 190.0032

6-Bromo-2-oxo-*2H*-chromene-3-carboxylic acid (3l) Yield 88%; Yellow powder; m.p. 293-294 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 7.93-7.91 (d, 1H), 7.73-7.71 (d, 2H), 7.50-7.46 (m, 3H), 7.36-7.33 (t, 2H), 7.27-7.25(t, 2H), 7.14-7.12 (t, 2H), 5.48 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ (ppm): 143.00, 138.34, 134.82, 133.99, 130.53, 130.36, 129.87, 127.46, 126.30, 126.03, 125.62, 122.85, 122.36, 110.50, 45.58. . **HRMS** (ESI): Anal. Calc. For $C_{10}H_5BrO_4$ $[M+H]^+$ 269.0510 Obser.: 267.9401.

6-Chloro-2-oxo-*2H*-chromene-3-carboxylic acid (3m) Yield 197 mg (88%); yellow solid; m.p. 122−123 °C (Lit. 121−124 °C); **^{1}H NMR** (500 MHz, DMSO) δ (ppm): 12.14 (s, 1H), 8.95 (s, 1H), 7.76 (s, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.01 (d, J = 8.6 Hz, 1H); **^{13}C NMR** (126 MHz, DMSO) δ (ppm): 159.6, 153.4, 146.6, 132.92, 126.7, 126.1, 116.5, 114.0. . **HRMS** (ESI): Anal. Calc. For $C_{10}H_5ClO_4$ $[M+H]^+$ 224.6012 Obser.: 233.9901.

8-Methoxy-2-oxo-*2H*-chromene-3-carboxylic acid (3n) Yellow solid; yield 191 mg (87%); m.p. 219-221 °C (Lit. 216- 217 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 11.55 (s, 1H), 8.68 (s, 1H), 7.01 (d, J = 7.2 Hz, 2H), 6.93 (t, J = 7.4 Hz, 1H), 3.94 (s, 3H); **^{13}C NMR** (126 MHz,

$CDCl_3$) δ (ppm): 165.9, 148.8, 147.4, 125.1, 118.5, 116.4, 114.2, 55.3. . **HRMS** (ESI): Anal. Calc. For $C_{11}H_8O_5$ $[M+H]^+$ 220.1812 Obser.: 220.0401.

7-(Diethylamino)-2-oxo-*2H*-chromene-3-carboxylic acid (3o) Yield 214 mg (82%); orange crystal m.p. 221-223 ^{O}C (Lit 223-224 ^{O}C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 11.82 (s, 1H), 8.44 (s, 1H),7.08 (d, J = 8.5 Hz, 1H), 6.24 (m, 1H), 6.21 (s, 1H), 3.38 (q, J = 6.6 Hz, 4H), 1.22 (t, J = 6.7 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 161.4, 160.9, 151.1, 133.2, 106.9, 103.8, 97.8, 44.5, 12.7. **HRMS** (ESI): Anal. Calc. For $C_{14}H_{15}NO_4$ $[M+H]^+$ 261.2810 Obser.: 261.1040.

Methyl 2-oxo-*2H*-chromene-3-carboxylate (3p) Yield: 183 mg (90%); white substance; m.p. 115-118 ^{O}C (Lit. 118-120 ^{O}C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.59 (s, 1H), 7.68 – 7.65 (m, 2H), 7.39-7.35 (dd, 2H), 3.98 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 163.7, 156.7, 155.2, 149.1, 134.4, 129.5, 124.9, 117.9, 117.8, 116.8, 52.9. **HRMS** (ESI): Anal. Calc. For $C_{11}H_8O_4$ $[M+H]^+$ 261.2810 Obser.: 261.1040.

Methyl 6-bromo-2-oxo-*2H*-chromene-3-carboxylate (3q) Yield; 250 mg (89%); white substance m.p. 184-185 ^{O}C (Lit. 185 -186 ^{O}C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.49 (s, 1H), 7.77-7.76 (dd, 2H), 7.28-7.27 (d, J = 8.7 Hz, 1H), 3.98 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 163.2, 155.9, 154.0, 147.5, 137.1, 131.1, 119.3, 119.1, 118.5, 117.4, 53.1. **HRMS** (ESI): Anal. Calc. For $C_{11}H_7BrO_4$ $[M+H]^+$ 283.0820 Obser.: 283.9540.

Methyl 6-chloro-2-oxo-*2H*-chromene-3-carboxylate (3r) Yield 207 mg (87%); white substance; m.p. 196-197 ^{O}C (Lit. 198-200 ^{O}C); **^{1}H NMR** (500 MHz, $CDCl_3$): δ (ppm): 8.44 (s, 1H), 7.74–7.71 (m, 2H), 7.23 (d, J = 8.7 Hz, 1H), 3.95 (s, 3H); **^{13}C NMR** (126 MHz,

$CDCl_3$) δ (ppm): 164.3, 155.0, 153.1, 146.6, 136.1, 132.7, 118.4, 118.2, 117.6, 116.5, 52.1. **HRMS** (ESI): Anal. Calc. For $C_{11}H_7ClO_4$ $[M+H]^+$ 238.6220 Obser.: 283.0001.

Methyl 8-methoxy-2-oxo-2*H*-chromene-3-carboxylate (3s) Yield 203 mg (87%); yellow solid; m.p. 124 –125 °C (Lit. 125– 127 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.56 (s, 1H), 7.30 – 7.28 (m, 1H), 7.30-7.28 (s, 1H), 7.21-7.19 (d, J = 7.6 Hz, 1H), 3.99 (s, 3H), 3.97 (s, 3H); **^{13}C NMR** (126 MHz, CDCl3) δ (ppm): 163.8, 156.1, 149.4, 147.1, 144.9, 124.7, 120.6, 118.4, 118.2, 115.93, 56.3, 52.9. **HRMS** (ESI): Anal. Calc. For $C_{12}H_{10}O_5$ $[M+H]^+$ 234.2021 Obser.: 234.0501

2.8 Some spectrum of Ethyl 2-oxo-2*H*-chromene-3-carboxylate derivatives of ^{1}H NMR, ^{13}C NMR and HRMS.

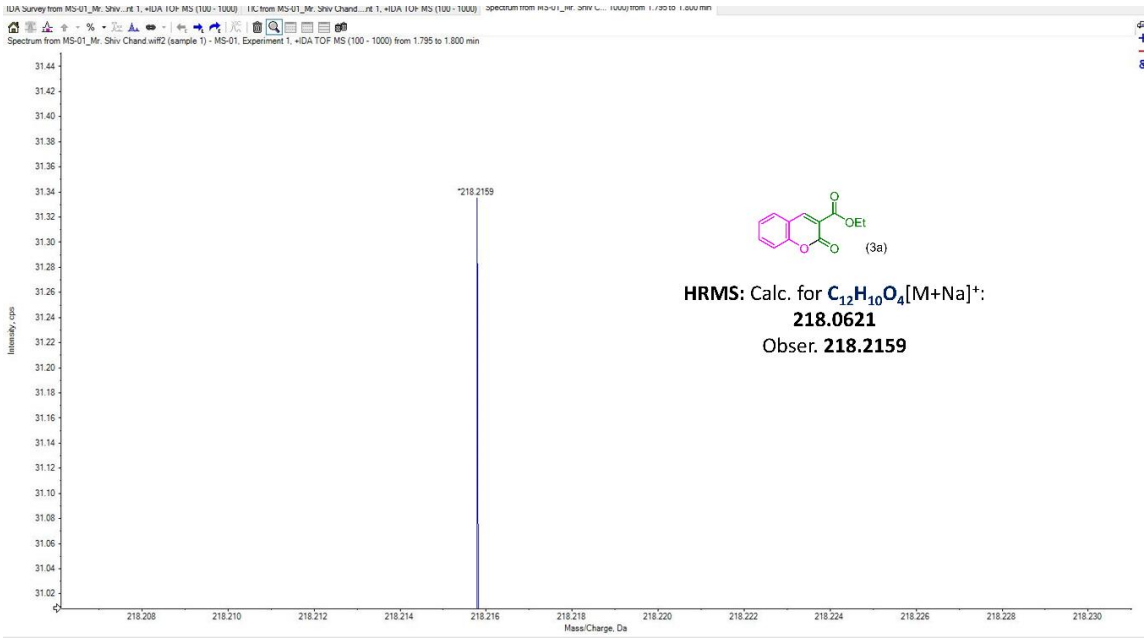


Figure 2.6 Mass spectra of Ethyl 2-oxo-2*H*-chromene-3-carboxylate (3a)

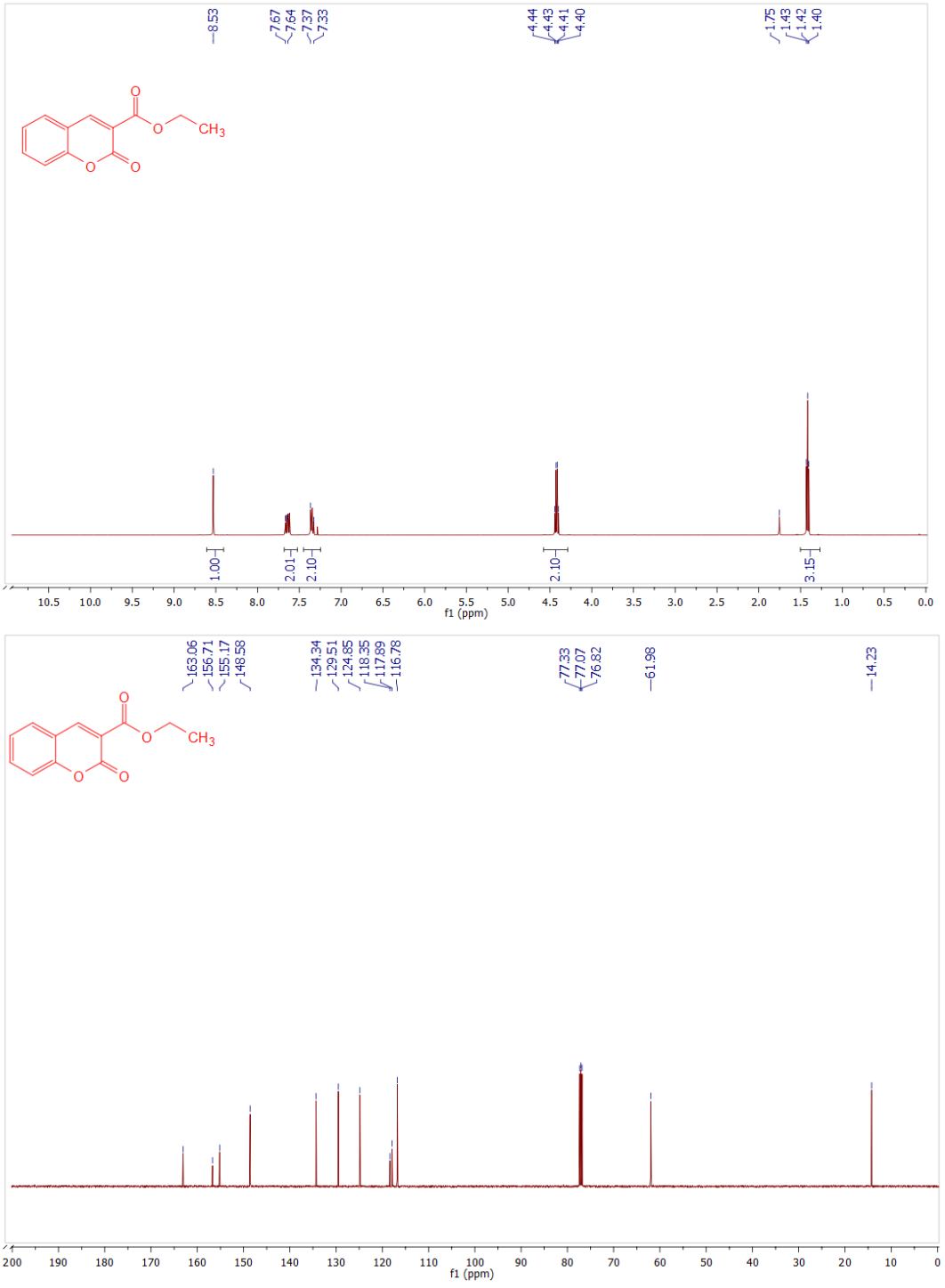


Figure 2.7: ^{1}H and ^{13}C NMR spectra of Ethyl 2-oxo-2H-chromene-3-carboxylate (3a).

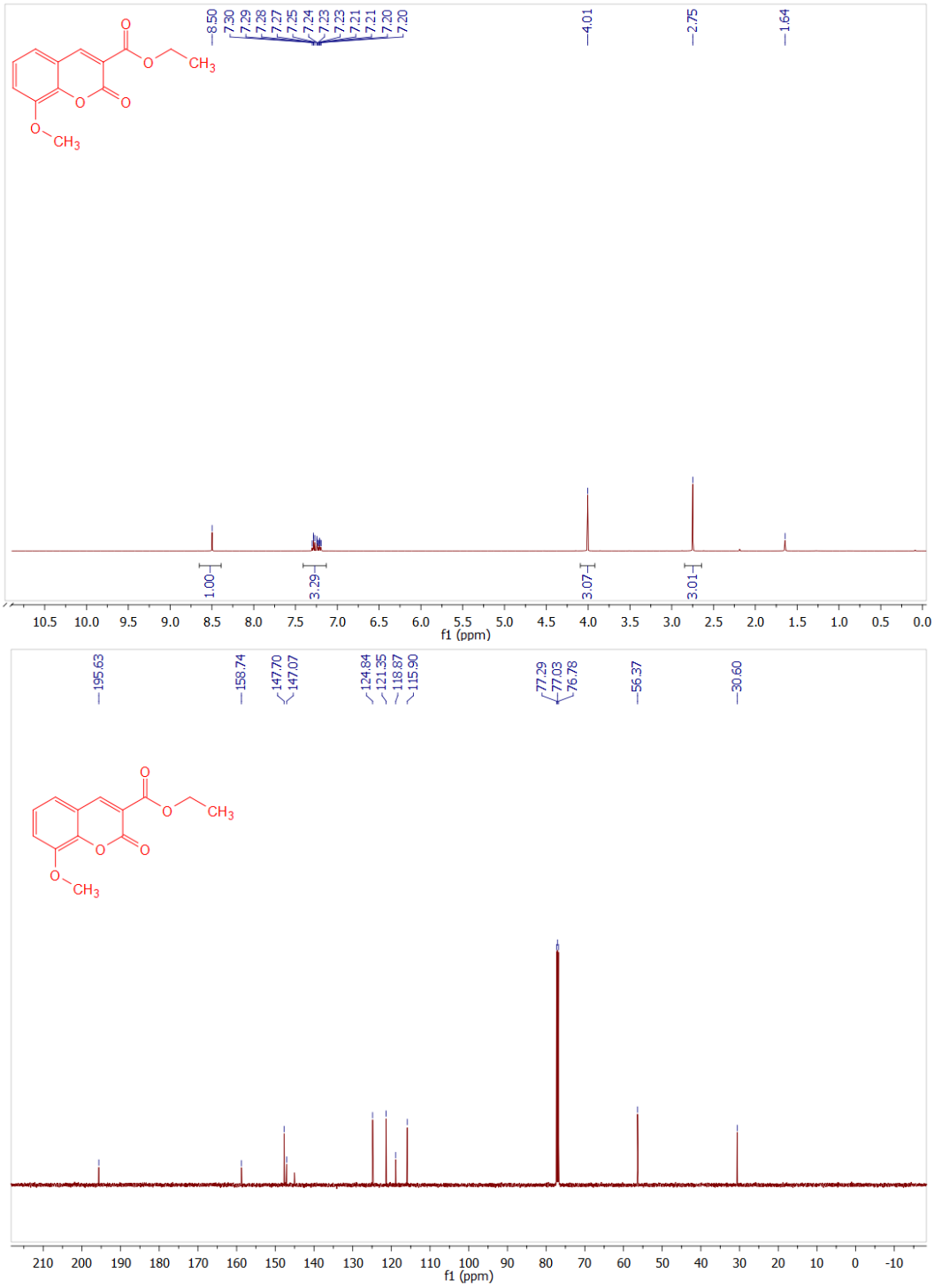


Figure 2.8: ^{1}H and ^{13}C NMR spectra of ethyl 8-methoxy-2-oxo-*2H*-chromene3carboxylate (3d).

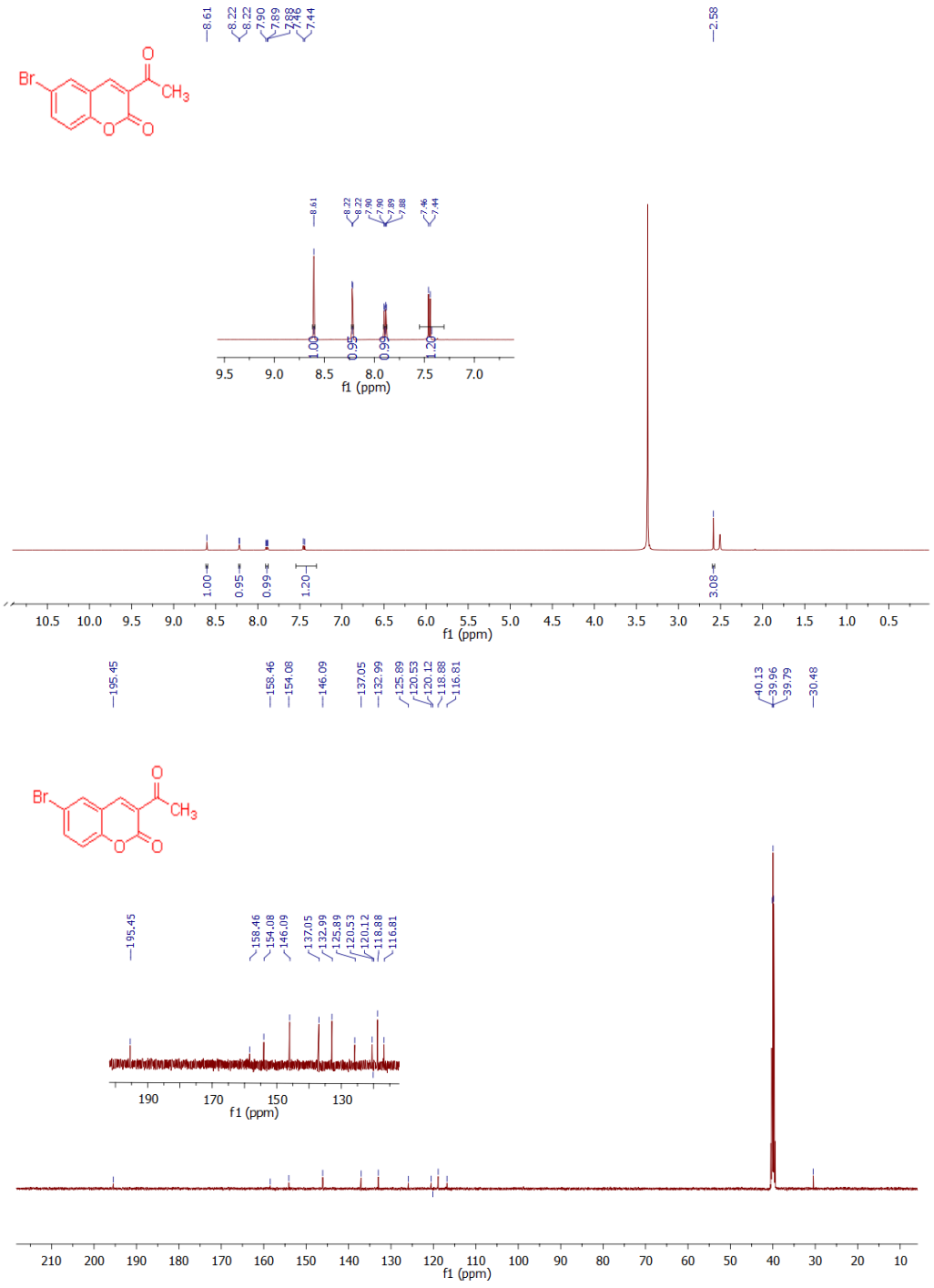


Figure 2.9: ^{1}H and ^{13}C NMR spectra of 3-acetyl-6-chloro-*2H*-chromen-2-one (3h).

Figure 2.10: ^{1}H and ^{13}C NMR spectra of ethyl 7-(diethylamino)-2-oxo-*2H*-chromene-3-carboxylate (3e).

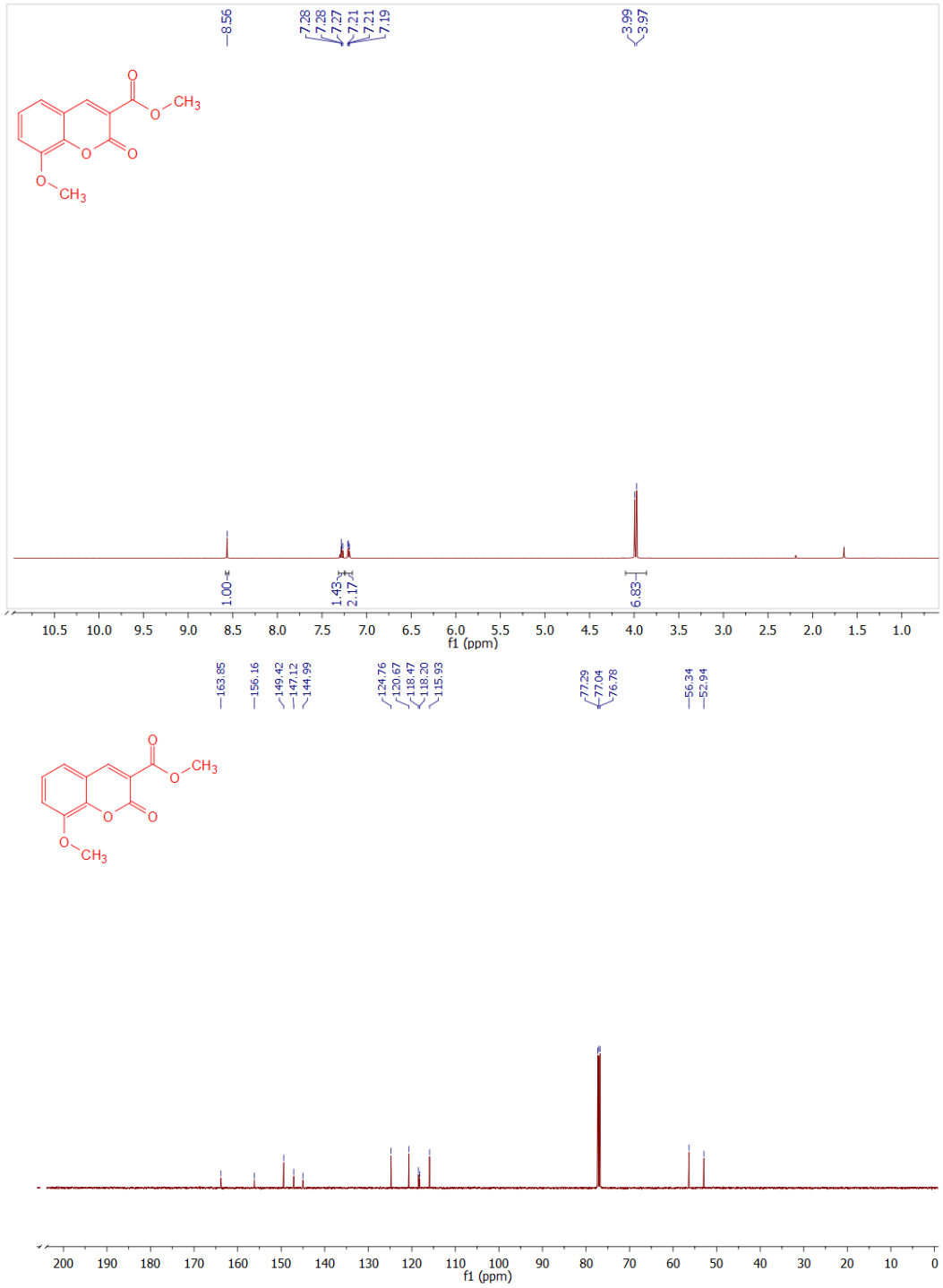


Figure 2.11: ^{1}H and ^{13}C NMR spectra of methyl 8-methoxy-2-oxo-2*H*-chromene-3carboxylate (3s).

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