Visible Light Mediated Sustainable Transformation of α, β-Unsaturated Lactones

M.Sc. Thesis

by

Arindam Bhatta

Roll no. 2303131005

Department of Chemistry

Indian Institute of Technology Indore

MAY 2025

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CANDIDATE'S DECLARATION

I hereby certify that the work being presented in the thesis entitled "**Visible Light Mediated Sustainable Transformation of α, β Unsaturated Lactones",** in the partial fulfilment of the requirements for the award of the degree of **Master of Science** and submitted to the **Department of Chemistry, Indian Institute of Technology Indore**, is an authentic record of my work carried out during the period July 2024 to May 2025 under the supervision of **Dr. Debayan Sarkar** (Associate Professor) Department of Chemistry, Indian Institute of Technology Indore. I have not submitted the matter presented in this thesis for the award of any other degree of this or any other institute.

Arindam Bhatta
(22/05/2025)

Signature of the student with the date

(Arindam Bhatta)

This is to certify that the above statement by the candidate is correct to the best of my knowledge.

Debayan Sarkar
23/05/2025

Signature of the Supervisor with the date

(Dr. Debayan Sarkar)

Prefatory Notes

Nuclear Magnetic Resonance Spectra

^{1}H and ^{13}C NMR spectra were recorded on a Bruker (500MHz, and 125 MHz, respectively). Chemical shifts are reported in delta (δ, chemical shift relative to deuterochloroform (7.26 ppm) for ^{1}H NMR & 77.0 for ^{13}C NMR). Data for ^{1}H reported as follows: Chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity is recorded: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets.

Chromatography

Chromatography was performed using (100 - 200 mesh) silica gel & neutral active aluminium oxide. Analytical TLC was performed with 0.25 mm coated commercial silica gel plates (E. Merck, DC-Kiesel gel 60 F254) and visualized with UV light, iodine, and vanillin stain. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker (500 MHz and 125 MHz, respectively).

General

All reactions were carried out under oven-dried glassware. All solvents were dried over appropriate desiccant before use. All other reagents were purchased from TCI chemicals, Sigma-Aldrich, and BLDpharm and used without further purification. Na_2SO_4 was dried in an oven & utilized for drying the crude reaction mixture before chromatography.

ACKNOWLEDGEMENT

The research described in this report, entitled **"Visible Light Mediated Sustainable Transformation of α, β-Unsaturated Lactones",** was carried out in the Department of Chemistry, Indian Institute of Technology Indore, during the period of my research from July 2024 onwards under the supervision of Dr. Debayan Sarkar.

Firstly, I would like to express my Gratitude and special thanks to my supervisor, **Dr. Debayan Sarkar**, for his sincere guidance, supervision, and advice from the very first day of my research life, as well as for giving me all the valuable experiences throughout my research work. Above all, he encouraged and supported my success and failure throughout my research career.

This journey at IIT Indore has been a memorable time in my life. I extend my heartfelt thanks to all the Department of Chemistry, IIT Indore faculty members.

Special thanks to Ph.D. mentor Niladri Sekhar Roy, lab mates and seniors Shantanu Samanta, Barnali Roy, Argha Dey, Subarna Roy, Bhabani Sankar Lenka, Priya Ranjan Sahoo, Rama Kant Mishra, Sangita Bishi, and Dhrutiman Rout for their kind cooperation and helpful nature throughout my research.

During this journey, many people helped and encouraged me in various ways. I express my heartiest thanks to my friends. Thanks to all those colleagues whose names have been left unwillingly.

I dedicate this work to them to honor their love and kind support during this research period.

Arindam Bhatta

Roll No. 2303131005

Dedicated to my Parents and loved ones

ABSTRACT

Numerous methods are already available in the literature for synthesizing lactones. Techniques like Shiina macro lactonization, nucleophilic abstraction, and Yamaguchi esterification are particularly effective. In some cases, lactones such as γ-nonalactone, γ-octalactone, γ-undecalactone, and γ-decalactone can even be synthesized in a single step. Nowadays, visible light and photoredox catalysis have become a sustainable tool in organic chemistry, offering versatile and sustainable ways to form Carbon-Heteroatom bonds. Heterocyclic structures are commonly established in natural products, pharmaceuticals, and agrochemicals due to their wide range of biological activity, and a pharmacophoric lead molecule is present in the structural scaffolds. Light-mediated cyclization reactions—such as ring-opening and closure, electrocyclization, or intramolecular hydrogen abstraction—take advantage of the unique properties of photoexcited molecules.

These reactions often produce cyclic compounds with high stereoselectivity. we initially attempted cyclization with aliphatic molecules, but found UV absorption below 280 nm, which is outside the effective range for organic photocatalysts. To encounter this problem, we increased the conjugation using aromatic molecules, which have extended π-conjugation, making the reaction more feasible with visible light-mediated sustainable transformations. As we were unsuccessful in the synthetic attempts to make unsaturated lactones from aliphatic cores, we shifted to our previously reported lab protocol, which was reported in 2022. In our earlier article, we effectively synthesized coumarins from naphthols and phenols using a photosensitizer-free visible light-mediated method. We successfully synthesized β-substituted lactones from a ketone source using a similar strategy. Currently, we successfully synthesize β-substituted lactones from simpler ketones and have successfully synthesized various diversifications associated with the strategy.

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ACRONYMS

$CDCl_3$	Chloroform-d
$CHCl_3$	Chloroform
THF	Tetrahydrofuran
DCM	Dichloromethane
DMSO	Dimethyl sulfoxide
EWG	Electron-withdrawing group
Cs_2CO_3	Cesium Carbonate
K_2CO_3	Potassium carbonate
EtOH	Ethanol
RFTA	Riboflavin Tetraacetate
MeOH	Methanol
EDG	Electron-donating group
MeCN	Acetonitrile
Na_2SO_4	Sodium sulphate
PCC	Pyridinium Chlorochromate
NMR	Nuclear magnetic resonance
NH_4Cl	Ammonium chloride
LED	Light Emitting Diode
PPh_3	Triphenylphosphine
EtOAc	Ethyl Acetate
DMF	Dimethyl Formamide
Et_2O	Diethyl Ether
TLC	Thin layer chromatography
UV	Ultra-violet
UV-Vis	Ultra-violet and visible
X	Halide
NaOH	Sodium Hydroxide
KOH	Potassium Hydroxide
$^{13}C\{H\}$	Proton decoupled ^{13}C NMR

ABBREVIATIONS

˚C	Degree Celsius
h	hour
Hz	Hertz
M	Molar
mL	Millilitre
mg	Milligrams
MHz	megahertz
mmol	millimole
ppm	Parts per million

1. Introduction:

1.1. General Introduction:

Lactones are cyclic organic esters derived from hydroxycarboxylic acids, often produced by interacting a halogen atom or hydroxyl group with a carboxylic acid group inside the same molecule. These result from the intramolecular esterification of corresponding hydroxycarboxylic acids. It has a ring of two or more carbon atoms and a single oxygen atom. Lactones with three or four-membered rings exhibit considerable reactivity, rendering their isolation very challenging. Many natural chemicals and physiologically active intermediates have lactone motifs, which provide a crucial structural scaffold for many pharmacological agents currently on the market[1].

Their antibacterial properties have been used in traditional medicine for ages. Novel lactone compounds are now being documented in the literature. Certain structures have significant antibacterial potential, while other compounds are used to design and synthesize future pharmaceuticals[1,2] (**Figure 1**).

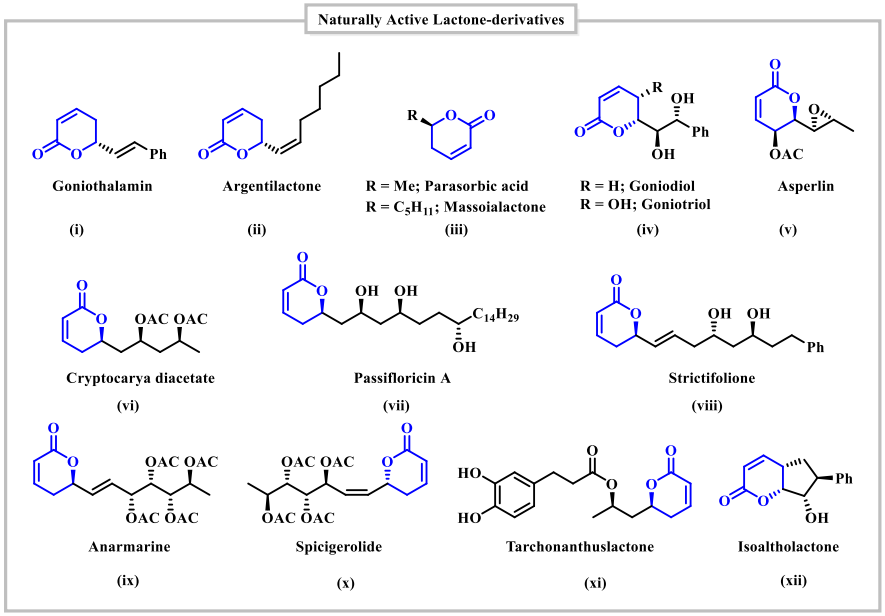


Figure 1. Different types of naturally available lactones

Numerous techniques used for ester synthesis apply to lactone synthesis—techniques including Shiina macro-lactonization, nucleophilic abstraction, and Yamaguchi esterification. A one-step procedure may synthesize lactones such as γ-nonalactone, γ-octalactone, γ-undecalactone, and γ-decalactone. Visible light and photoredox catalysis have emerged as potent and enduring tools for organic synthesis, highlighting the significance of various approaches for chemical bond formation[3]. Heterocyclic moieties are present in natural products, physiologically active compounds, pharmaceuticals, and agrochemicals.

Light-induced cyclization reactions can occur through various mechanisms, including photochemical ring-opening and closure, electrocyclization, and intramolecular hydrogen abstraction. Because the excited states produced by light absorption have special electrical and spatial characteristics, resulting in specific cyclic products[4].

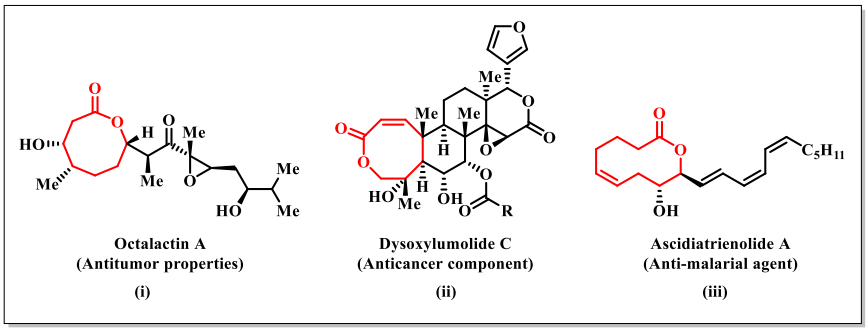


Figure 2. Different types of naturally available Macrocyclic Lactones

Lactones have significant biological activity, and some of the Big Billion market selling drugs, such as Warfarin, are widely available (**Figure 3**). In this light of hope, our trials towards the synthesis of 5,6-dihydro-2H-pyran-2-one (**Scheme 1**) and (Z)-5,6,7,8-tetrahydro-2H-oxocin-2-one moieties or macrocyclic lactones may lead to future pipeline drugs for the pharmaceutical Companies or Novel significant lead molecules for the betterment of human health and agrochemical, phytochemical industries, etc. On this vision, we tried various attempts to synthesize (Z)-5,6,7,8-tetrahydro-2H-oxocin-2-one moieties or macrocyclic lactones[5] (**Scheme 2**).

First identified by Tonka beans in 1820, coumarins are a family of metabolites with a broad range of biological actions, for example, anti-inflammatory, anti-cancer, anti-diabetic, anti-HIV, antioxidant, and vasodilator qualities[6]. In medicinal applications, the type of substituents on the pyrone and phenyl rings is essential. Due to its primary interaction with target protein binding, the fused electrophilic lactone moiety is necessary for biological activity. Agrochemicals, food and cosmetics, optical industries, aroma enhancers, and solar energy accumulators are just a few of the businesses that use coumarins.

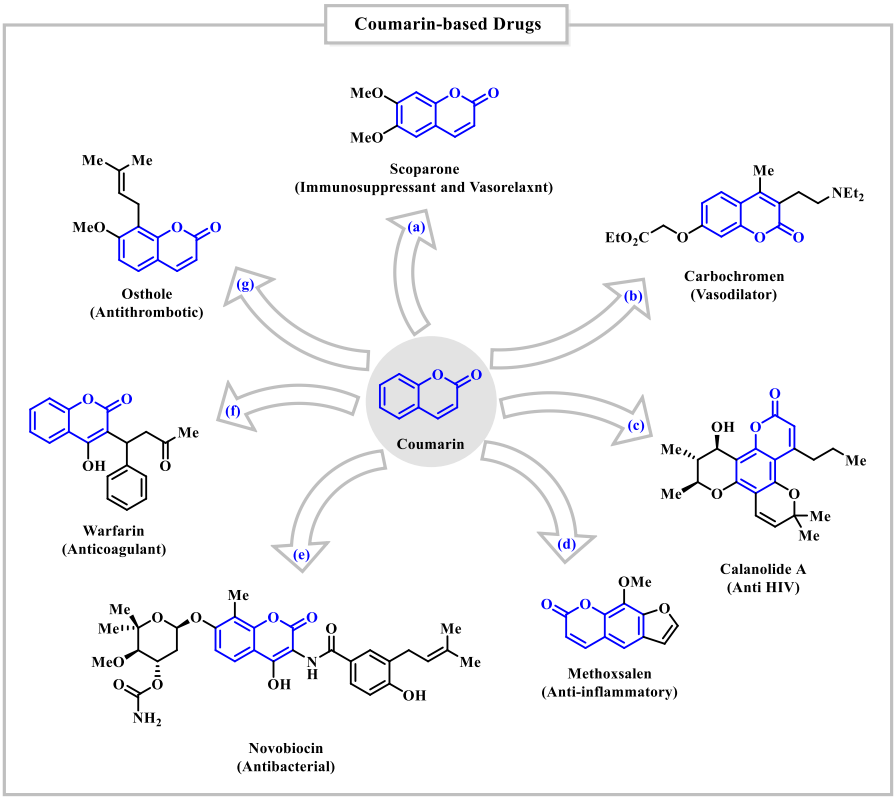


Figure 3. Structure of Some Coumarin-Based Drugs

Two strategies for synthesizing functionalized coumarins are conventional reactions like Pechmann, Knoevenagel, Perkin, Witting, and Reformatsky, which are multistep, time-consuming, and require acids and bases[7].

Light-induced cyclization reactions can proceed through various mechanisms, according to the type of starting material and the reaction conditions. Some common mechanisms include photochemical ring-

opening and closure, electrocyclization, and intramolecular hydrogen abstraction, among others. Furthermore, light-induced cyclization reactions often exhibit high stereoselectivity, resulting in the formation of specific cyclic products[8]. This selectivity arises from the unique electronic and spatial properties of the excited states generated by light absorption. By carefully designing the molecular structure and the reaction conditions, researchers can control the directionality and geometry of the cyclization process, leading to the desired product with high efficiency[9].

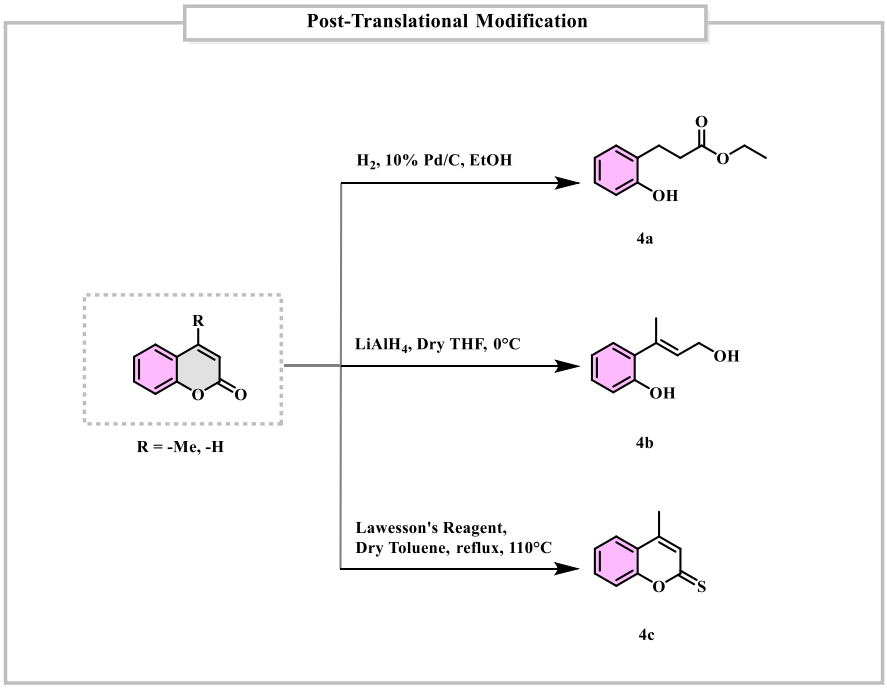


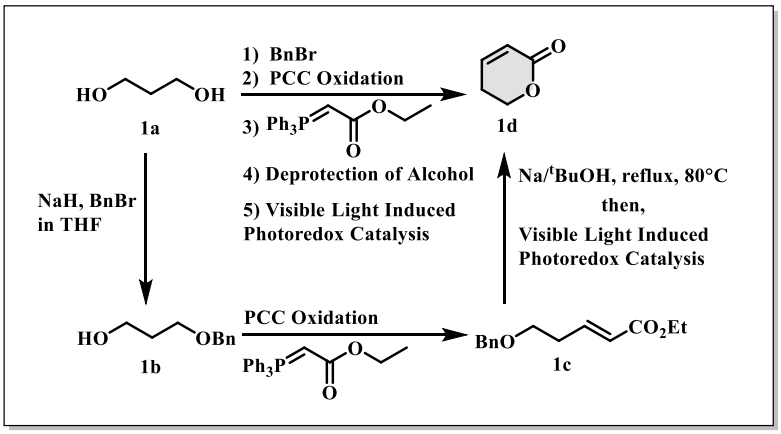
Figure 4. Post-Translational Modifications

1.2. Why Visible Light Catalysis?

Compared to other energy sources, visible light is abundant and environmentally favourable. Photocatalysis uses this energy source to perform chemical transformations, lowering dependency on non-renewable resources and generating less waste[10]. Visible light photocatalysis frequently functions at mild reaction conditions, such as room temperature and atmospheric pressure, which can reduce energy consumption and the formation of undesirable byproducts. Photocatalysis provides fine control over reaction pathways and selectivity, enabling the production of complex compounds with great

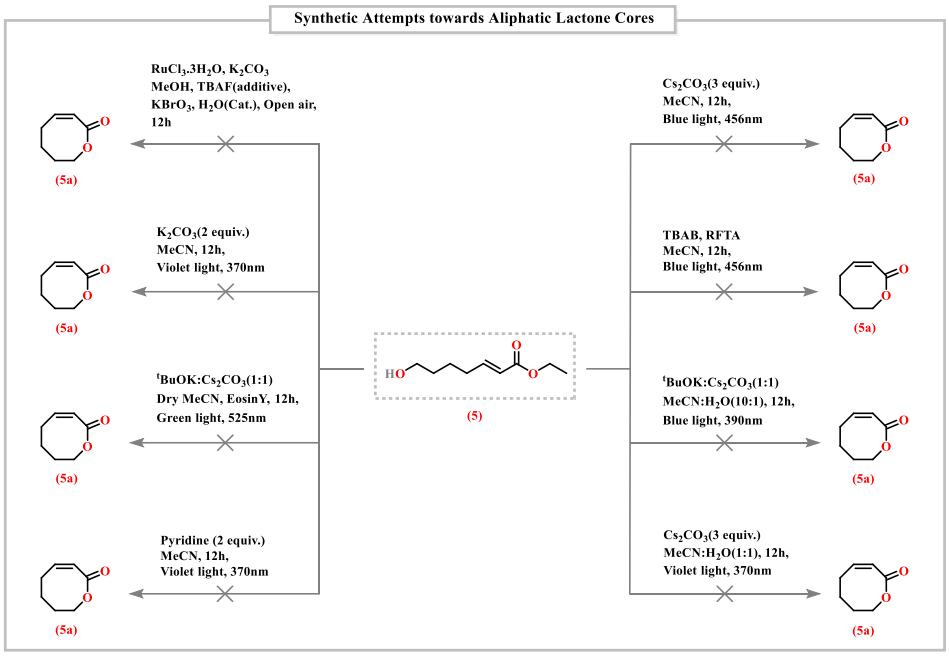
efficiency and specificity. This selectivity is very useful in the production of medicines and specialty compounds[11]. It is compatible with a wide range of functional groups, activating normally inert substrates and promoting the synthesis of complex compounds that would be difficult to get using traditional methods. Photocatalytic reactions frequently occur with high atom economy, which means that most of the starting material is integrated into the final product[12]. This efficiency decreases waste while improving the overall sustainability of chemical operations. It supports chemical changes, such as C-C and C-X bond formation, hydrogenation, oxidation, and rearrangements[13]. This adaptability makes it an invaluable resource for synthetic chemists in academia and industry. It has applications in drug discovery and development, allowing to produce new drug candidates and the modification of existing compounds to improve their pharmacological properties. Overall, visible light catalysis provides a sustainable, efficient, and adaptable approach to chemical synthesis, with applications ranging from medicines to materials research and beyond. Its value grows as researchers investigate new photocatalytic processes and broaden the range of its uses.

2. Results and Discussion:



Scheme 1. Synthetic Attempts Towards the Synthesis of 5,6-dihydro-2H-pyran-2-one

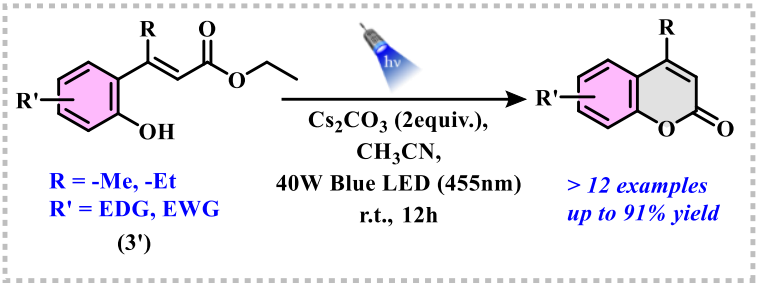
Initial attempts at cyclization with aliphatic molecules showed UV absorption below 300 nm, outside the effective range for organic photocatalysts (**Scheme 2)**. To address this, we increased the conjugation by using aromatic molecules, which have extended π-conjugation that shifts absorption into the 300–500 nm range, making the reaction more compatible with visible light-mediated sustainable transformation.



Scheme 2. Synthetic Attempts towards the Synthesis of (Z)-5,6,7,8 tetrahydro-2H-oxocin-2-one

We were unsuccessful in the synthetic attempts to make unsaturated lactones from aliphatic cores, so we shifted our previously reported lab protocol in 2022[14]. In our earlier article, we effectively synthesized coumarins from naphthols and phenols using a photosensitizer-free visible light-mediated method. We successfully synthesized β-substituted lactones from a ketone source using a similar strategy. Currently, we successfully synthesize β-substituted lactones from simpler ketones. In the next phase, we have diversified our synthesis to include complicated β-substituted lactones (**Figure 4)**.

Condition Optimization:



Scheme 3: Formation of β-substituted Coumarins by photoredox catalysis

Base Optimization				
Entry	**Solvent/ (κ)**	**Base (equiv.)**	**T°C/h**	**Isolated yield (%)**
1	MeCN/ (37.5)	Cs_2CO_3/1.5	25/16	84
2	MeCN/ (37.5)	Cs_2CO_3/2	25/13	91
3	MeCN/ (37.5)	Cs_2CO_3/3	25/14	87
4	MeCN/ (37.5)	K_2CO_3/2	25/16	81
5	MeCN/ (37.5)	Li_2CO_3/2	25/16	76
6	MeCN/ (37.5)	Na_2CO_3/2	25/16	74
7	MeCN/ (37.5)	Pyridine/2	25/16	63
8	MeCN/ (37.5)	DBU/2.5	25/16	58

Table 1. Optimization of base

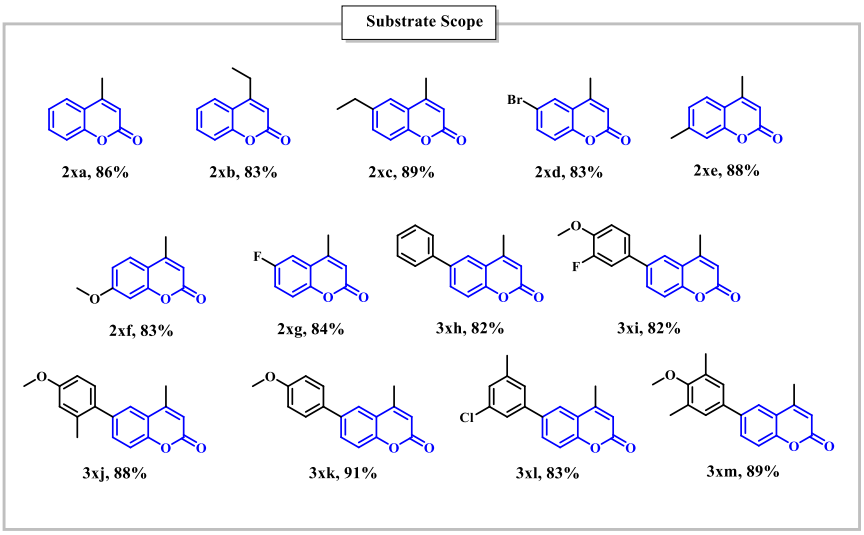
Solvent Optimization				
Entry	**Solvent/ (κ)**	**Base (equiv.)**	**T°C/h**	**Isolated yield (%)**
1	DCM/ (8.9)	Cs_2CO_3/2	25/14	78
2	Water/ (80)	Cs_2CO_3/2	25/15	56
3	DMSO/ (46.6)	Cs_2CO_3/2	25/14	51
4	Acetone/ (20.7)	Cs_2CO_3/2	25/14	63
5	Toluene/ (2.4)	Cs_2CO_3/2	25/16	28
6	1,4-Dioxane/ (2.2)	Cs_2CO_3/2	25/16	35
7	Ethanol/ (24.5)	Cs_2CO_3/2	25/16	83
8	MeCN/ (37.5)	Cs_2CO_3/2	25/13	91

Table 2. Optimization of solvent

Catalyst Optimization					
Entry	**Solvent/ (κ)**	**Base (equiv.)**	**T°C/(h)**	**Catalyst**	**Isolated yield (%)**
1	MeCN/ (37.5)	Cs_2CO_3/2	25/(14)	RFTA	92
2	MeCN/ (37.5)	Cs_2CO_3/2	25/(14)	EosinY	83
3	MeCN/ (37.5)	Cs_2CO_3/2	25/(14)	Rose Bengal	79
4	MeCN/ (37.5)	Cs_2CO_3/2	25/(14)	Eosin Blue	81
5	MeCN/ (37.5)	Cs_2CO_3/2	25/(15)	TXT	85
6	MeCN/ (37.5)	Cs_2CO_3/2	25/(15)	4CzIPN	84
7	MeCN/ (37.5)	Cs_2CO_3/2	25/(13)	ND	91

Table 3. Optimization of photosensitizer

Substrate Scopes for Scheme 3:



2.1. Experimental Procedure for Scheme 1:

Synthesis of Compound 1b

The compound was synthesized according to the reported procedure[15]: NaH (60% in oil, 300 mg, 12.5 mmol, 0.9 equiv.) was poured into a solution of 1,3-propanediol (**1a)** (1 mL, 13.9 mmol, 1 equiv.) in THF (10 mL) at 0 °C. At this temperature, the reaction

mixture was agitated for one hour. BnBr (benzyl bromide) (1.65 mL, 13.9 mmol ,1 equiv.). Overnight, the reaction mixture was stirred and progressively brought to room temperature. The reaction was quenched with saturated aqueous NH_4Cl. After it was finished, the phases were separated, EtOAc was used to extract the organic phase. The mixed organic layer was concentrated after being cleaned with brine and dried on Na_2SO_4. Column chromatography was used to purify the residue, producing mono-benzyl ether (**1b)** as a colourless oil.

Synthesis of Compound 1c

The compound was synthesized with the reported procedure as follows[16]: To a solution of alcohol (**1b)** (250 mg, 1.5 mmol, 1 equiv.) in freshly dried DCM was added a suspension of PCC (486 mg, 2.25 mmol) in DCM at 0°C. The reaction mixture was stirred at room temperature overnight. The reaction was diluted with diethyl ether (50 mL). It was further passed through a small Celite pad (with DCM rinsing). The solvent was removed under reduced pressure at room temperature. The product was used without purification for the next step.

To a solution of ethyl 2-(triphenyl-λ^5-phosphaneylidene)acetate (780 mg, 2.23 mmol, 1.5 equiv.) in benzene (10 ml), the aldehyde was added under reflux, and the mixture was heated for 4h. The solvent was evaporated under reduced pressure, and the product was purified by column chromatography to afford the pure ester (**1c)** as a liquid.

2.2. Experimental Procedure for Scheme 2:

At first, the Wittig salt (4.43g, 1.5 equiv.) was dissolved in dry DCM at room temperature. After dissolving the Wittig salt, we added the 5-hydroxypentanal (0.94 mL) dissolved in dry DCM via a syringe. The reaction mixture was left to stir for the next 16 hours under a N_2 atmosphere. Finally, the organic layer was collected in DCM, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting compound (ethyl-(E)-7-hydroxyhept-2-enoate) (**5)** was purified by column chromatography to obtain the starting material for the synthesis of (Z)-5,6,7,8-tetrahydro-2H-oxocin-2-one (**5a**).

2.3. General Procedure 1. Experimental Procedure for Scheme 3:

In a glass vial, substituted ethyl (E)-3-(2-hydroxyphenyl) but-2-enoate was dissolved in MeCN, followed by activated Cs_2CO_3 (2 equiv.). Following the septum closure of the glass vial, the reaction vial was irradiated with a 40W, 455 nm LED under stirring at room temperature. LED is visible through the bottom glass (0.5 cm to LED). The reaction mixture was concentrated at reduced pressure and subjected to column chromatography (silica gel).

2.4. Plausible Mechanism:

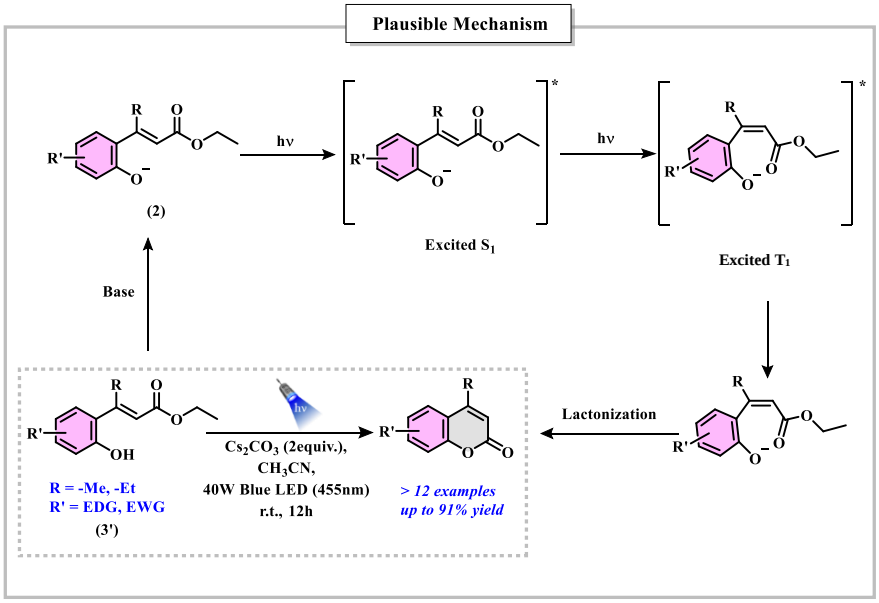
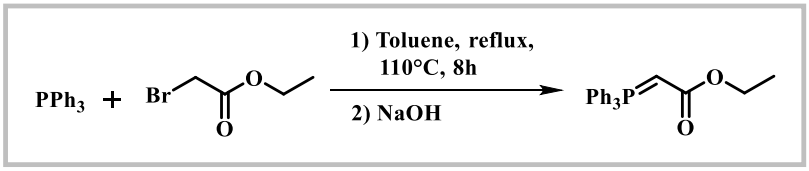


Figure 5: Plausible Mechanism for Scheme 3

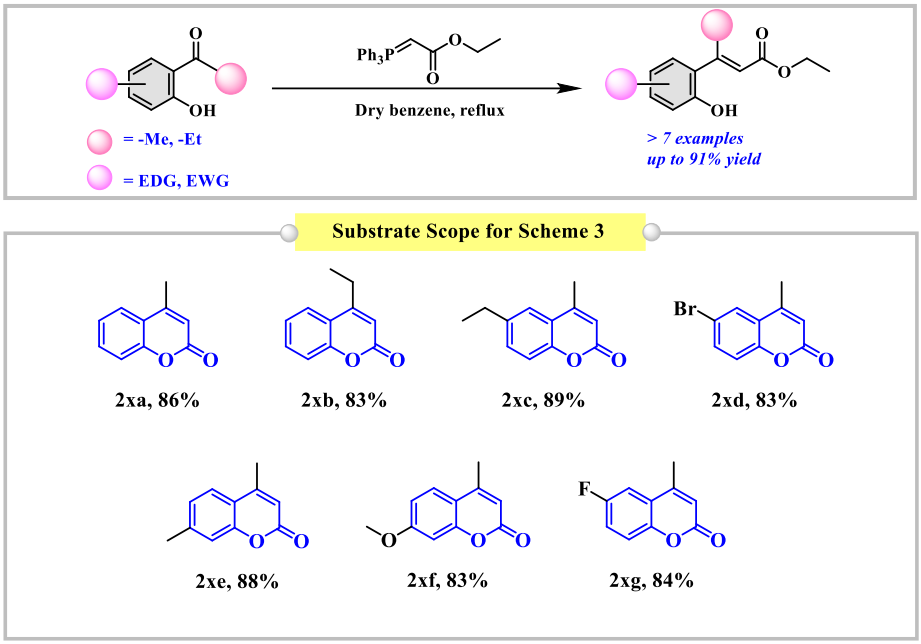
2.5. General Procedure 2. Synthesis of phosphonium salts:



The salt was synthesized following the reported procedure with 84% yield[17]. Triphenylphosphine (47.11g, 1.5 equiv.) was taken in a 250 mL two-neck RB flask. It was dissolved with toluene as a solvent. Ethyl 2-bromoacetate (20g, 13.24 mL) was added dropwise into the mixture. The reaction is set in reflux conditions at 110°C for

overnight. After 8 hours, the reaction mixture was filtered with toluene and hexane through a sintered funnel. The salt was dissolved in water and toluene, and the mixture was transferred to a separatory funnel, with an aqueous solution of NaOH and Phenolphthalein as an indicator.

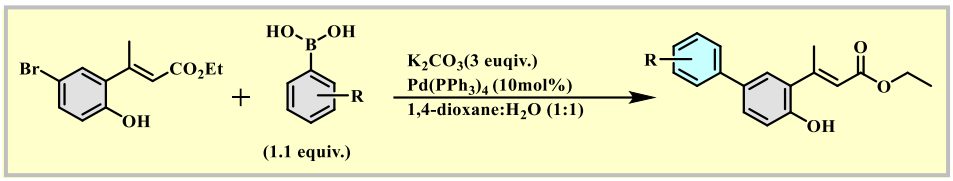
2.6. General Procedure 3. General experimental procedure for Wittig reaction:

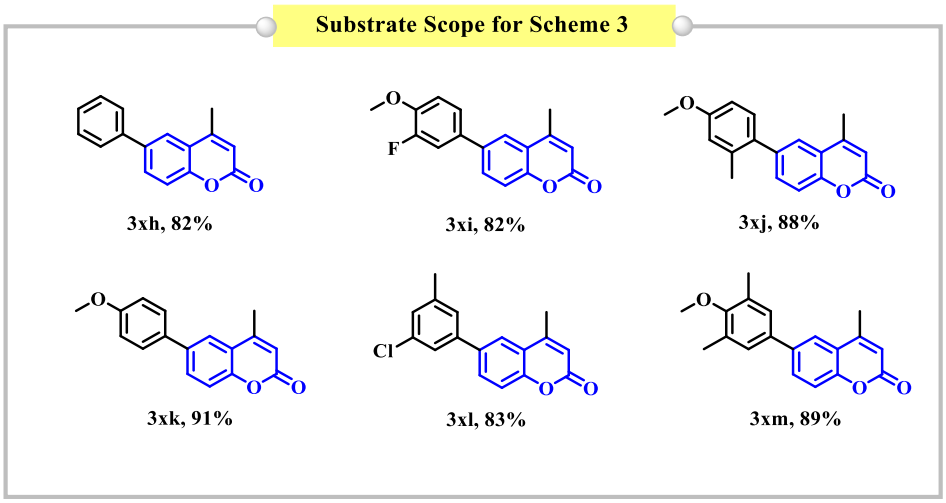


Previously synthesized Wittig salt (1.2 equiv.) was dissolved in dry benzene at room temperature. After dissolving the Wittig salt, the substituted 1-(2-hydroxyphenyl) ethan-1-one was dissolved in dry benzene via a syringe. The reaction mixture was left to stir for 8-10 hours under a N_2 atmosphere. After refluxing for 8-10 h, the reaction mixture was concentrated at reduced pressure. Column chromatography was performed to obtain the desired product on 100-200 mesh silica gel (Hexane/EtOAc). After that, the products are used directly as substrate (**3'**) for Scheme 3 to obtain our final products (**2xa to 2xg**).

We further performed a palladium-catalysed Suzuki coupling between ethyl (E)-3-(5-bromo-2-hydroxyphenyl)but-2-enoate and a series of structurally diverse phenyl boronic acids to expand our substrate scope.

2.7. General Procedure 4. Experimental Procedure for Suzuki coupling:





To a 50 mL sealed tube were added (1.0 equiv.) ethyl (E)-3-(5-bromo-2-hydroxyphenyl)but-2-enoate (1 equiv.), substituted phenylboronic acid (2.2 mmol, 1.1 equiv.), K_2CO_3 (3 equiv.), $Pd(PPh_3)_4$ (10 mol%), H_2O (2.5 mL), and 1,4-dioxane (2.5 mL). The mixture was stirred for 12 h at 100 °C. After completion of the reaction, the reaction was quenched with water and ethyl acetate. It was further passed through a small Celite pad (with ethyl acetate rinsing), and the resulting mixture was extracted with ethyl acetate (3 × 10 mL). The organic phases were combined and dried with anhydrous Na_2SO_4. After filtration, the solution was concentrated in vacuo. Column chromatography was performed to obtain the desired products on 100-200 mesh silica gel (Hexane/EtOAc). After that, the products are used directly as substrate (**3'**) for Scheme 3 to obtain our final products (**3xh to 3xm**).

2.8. Post Modification translations:

Synthesis of Compound 4a

The compound 4-methyl-2H-chromen-2-one (**2xa**) (200 mg, 1.369 mmol) was solubilized in dry (5 mL) Ethanol, and 10% Pd/C (10 mol%) was added to it. The resulting mixture was subjected to a 1 atm H_2 atmosphere and stirred for 12 hours. After completion, the reaction mixture was filtered and concentrated under reduced pressure. The crude product was purified using column chromatography on silica gel (petroleum ether/EtOAc) to afford the desired product (**4a)** as a colourless liquid.

Synthesis of Compound 4b

Add a solution of 4-methyl-2H-chromen-2-one (**2xa**) (200 mg, 1.369 mmol) in freshly dried (5 mL) THF dropwise to a suspension of $LiAlH_4$ (62.3 mg, 1.64 mmol) in THF (5 mL) at 0°C. Allow the resulting mixture to warm to room temperature. Stir the resulting mixture for 1 hour. The reaction was quenched with Saturated aqueous NH_4Cl after it was finished. After the phases were separated, EtOAc was used to extract the organic phase. The mixed organic layer was concentrated after being cleaned with brine and dried on Na_2SO_4. Column chromatography was used to purify the residue, the desired compound (**4b)** as a colourless liquid.

Synthesis of Compound 4c

It was done with the reported procedure as follows[18]: The compound 4-methyl-2H-chromen-2-one (**2xa**) (200 mg, 1.369 mmol) was solubilized in dry (5 mL) Toluene and then it was mixed with Lawesson's Reagent (332.23 mg, 0.821 mmol) in toluene (5 mL) and refluxed for 3h at 110°C. The crude was then evaporated under reduced pressure and purified by column chromatography to obtain the desired product (**4c**) of a yellow solid.

3. References:

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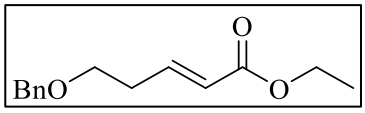
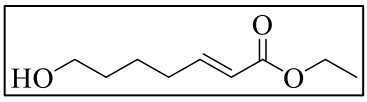
Supporting Information:

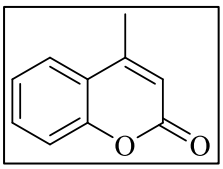
Following the procedure of scheme 1 (compound **1b**), employing **1a** as starting material, the desired product, 3-phenoxypropan-1-ol **(1b)**, was synthesized. **Isolated yield:** 63% (colourless oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.43 – 7.24 (m, 3H), 4.55 (s, 1H), 3.79 (t, *J* = 5.8 Hz, 1H), 3.68 (t, *J* = 5.9 Hz, 1H), 1.88 (q, *J* = 5.8 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 138.13, 128.48, 127.74, 127.69, 127.67, 73.26, 69.23, 61.66, 32.17.



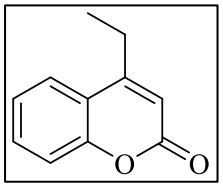
Following the procedure of scheme 1 (compound **1c**), employing **1b** as starting material, the desired product, ethyl (E)-5-(benzyloxy)pent-2-enoate **(1c)**, was synthesized. **Isolated yield:** 72% (colourless liquid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.31 – 7.16 (m, 5H), 6.90 (dt, *J* = 15.7, 6.9 Hz, 1H), 5.85 – 5.77 (m, 1H), 4.43 (s, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.49 (t, *J* = 6.5 Hz, 2H), 2.42 (q, *J* = 6.6 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 166.43, 145.59, 138.13, 128.43, 127.69, 122.96, 73.06, 68.30, 60.21, 32.65, 14.29.



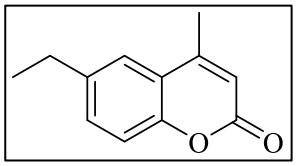
Following the procedure of scheme 2 (compound 5), employing 5-hydroxypentanal as starting material, the desired product, ethyl-(E)-7-hydroxyhept-2-enoate **(5)**, was synthesized and found as a diastereomeric pair. **Isolated yield:** 83% (colourless liquid). **^{1}H NMR** for E-isomer (major product) (500 MHz, $CDCl_3$) δ (ppm) 7.31 – 7.16 (m, 5H), 6.90 (dt, J = 15.7, 6.9 Hz, 1H), 5.85 – 5.77 (m, 1H), 4.43 (s, 2H), 4.10 (q, J = 7.1 Hz, 2H), 3.49 (t, J = 6.5 Hz, 2H), 2.42 (q, J = 6.6 Hz, 2H), 1.20 (t, J = 7.1 Hz, 3H). **^{13}C NMR** for E-isomer (major product) (126 MHz, $CDCl_3$) δ (ppm) 166.43, 145.59, 138.13, 128.43, 127.69, 122.96, 73.06, 68.30, 60.21, 32.65, 14.29.



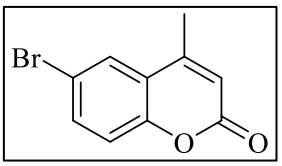
Following the general procedure 1 (**Scheme 3**), the desired product, 4-methyl-2H-chromen-2-one **(2xa)**, was synthesized. **Isolated yield:** 86% (white solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.55 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.30 – 7.21 (m, 2H), 6.24 (s, 1H), 2.38 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 160.83, 153.56, 152.35, 131.78, 124.56, 124.22, 120.01, 117.14, 115.17, 18.66.



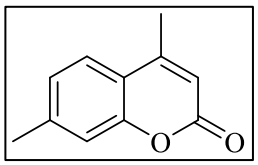
Following the general procedure 1 (**Scheme 3**), the desired product, 4-ethyl-2H-chromen-2-one **(2xb)**, was synthesised. **Isolated yield:** 83% (white solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.53 (dt, *J* = 7.3, 1.9 Hz, 1H), 7.45 – 7.33 (m, 1H), 7.19 (dd, *J* = 11.0, 9.1, 3.7, 1.5 Hz, 2H), 6.17 (dd, *J* = 3.5, 1.8 Hz, 1H), 2.71 (q, *J* = 7.5 Hz, 2H), 1.23 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 161.08, 157.41, 153.52, 131.55, 124.19, 124.13, 119.24, 117.13, 117.11, 112.88, 112.87, 24.56, 11.99.



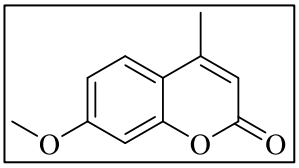
Following the general procedure 1 (**Scheme 3**), the desired product, 6-ethyl-4-methyl-2H-chromen-2-one **(2xc)**, was synthesized. **Isolated yield:** 89% (grey solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.37 – 7.07 (m, 3H), 6.19 (s, 1H), 2.64 (q, *J* = 7.6 Hz, 2H), 2.36 (s, 3H), 1.20 (t, *J* = 7.6 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 161.06, 152.43, 151.76, 140.28, 131.60, 123.29, 119.71, 116.89, 114.96, 28.42, 18.68, 15.79.



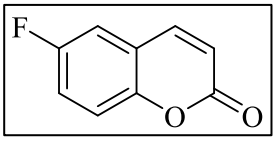
Following the general procedure 1 (**Scheme 3**), the desired product, 6-bromo-4-methyl-2H-chromen-2-one **(2xd)**, was synthesized. **Isolated yield:** 83% (white solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.72 (d, *J* = 2.3 Hz, 1H), 7.62 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 1H), 6.33 (s, 1H), 2.43 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 160.03, 152.44, 151.17, 134.55, 127.28, 121.64, 118.84, 117.01, 116.11, 18.62.



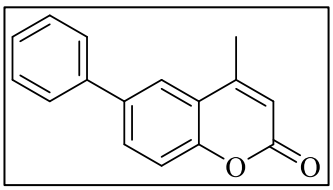
Following the general procedure 1 (**Scheme 3**), the desired product, 4,7-methyl-2H-chromen-2-one **(2xe)**, was synthesized. **Isolated yield:** 88% (white solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.47 (d, *J* = 8.0 Hz, 1H), 7.14 – 7.07 (m, 2H), 6.21 (d, *J* = 1.4 Hz, 1H), 2.44 (s, 3H), 2.41 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 161.15, 153.61, 152.44, 142.94, 125.37, 124.28, 117.60, 117.22, 114.02, 21.61, 18.62.



Following the general procedure 1 (**Scheme 3**), the desired product, 7-methoxy-4-methyl-2H-chromen-2-one **(2xf)**, was synthesized. **Isolated yield:** 83% (light green solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.04 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.96 (s, 1H), 6.24 (s, 1H), 3.80 (s, 3H), 2.36 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 161.00, 155.97, 151.97, 147.93, 120.46, 118.67, 118.02, 115.54, 107.67, 55.88, 18.74.

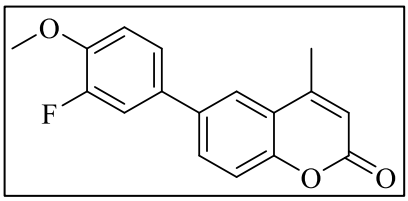


Following the general procedure 1 (**Scheme 3**), the desired product, 6-fluoro-4-methyl-2H-chromen-2-one **(2xg)**, was synthesized. **Isolated yield:** 84% (white solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.29 – 7.22 (m, 1H), 7.21 – 7.15 (m, 2H), 6.28 (s, 1H), 2.35 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 160.38, 159.76, 151.42, 151.40, 149.68, 149.67, 119.18, 118.99, 118.63, 118.56, 116.11, 110.42, 110.23, 18.65.

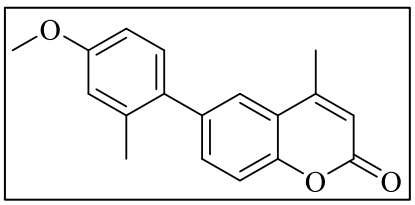


Following the general procedure 1 (**Scheme 3**), the desired product, 4-methyl-6-phenyl-2H-chromen-2-one **(3xh)**, was synthesized. **Isolated yield:** 82% (white solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.70 – 7.64 (m, 2H), 7.54 – 7.48 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.32 (dd, *J* = 8.0, 5.9 Hz, 2H), 6.26 (s, 1H), 2.42 (s, 3H). **^{13}C NMR** (126 MHz,

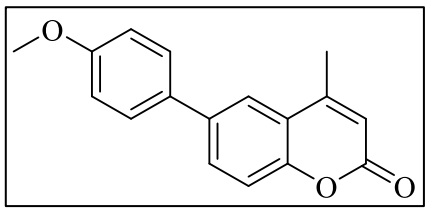
$CDCl_3$) δ (ppm) 160.71, 152.95, 152.36, 139.84, 137.67, 130.76, 129.05, 127.78, 127.17, 122.95, 120.18, 117.48, 115.47, 18.76.



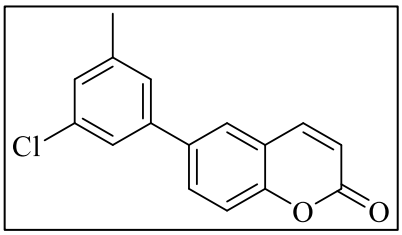
Following the general procedure 1 (**Scheme 3**), the desired product, 6-(3-fluoro-4-methoxyphenyl)-4-methyl-2H-chromen-2-one **(3xi)**, was synthesized. **Isolated yield:** 82% (white solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.35 – 7.25 (m, 2H), 6.85 – 6.60 (m, 2H), 6.27 (s, 1H), 3.79 (s, 3H), 2.40 (s, 3H) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.75, 152.67, 152.37, 132.31, 132.29, 130.92, 130.88, 124.72, 124.70, 119.97, 117.18, 115.39, 110.61, 102.31, 102.10, 55.72, 18.72.



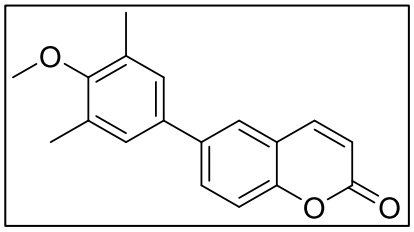
Following the general procedure 1 (**Scheme 3**), the desired product, 7-methoxy-4-methyl-2H-chromen-2-one **(3xj)**, was synthesized. **Isolated yield:** 88% (brown solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.45 – 7.35 (m, 2H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.08 (d, *J* = 8.3 Hz, 1H), 6.78 – 6.70 (m, 2H), 6.24 (s, 1H), 3.76 (s, 3H), 2.36 (s, 3H), 2.18 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 160.87, 159.20, 152.44, 152.34, 137.91, 136.80, 132.99, 132.98, 130.88, 125.14, 119.71, 116.69, 115.92, 115.30, 111.38, 55.33, 20.76, 18.71.



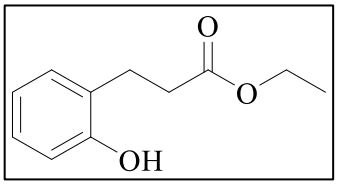
Following the general procedure 1 (**Scheme 3**), the desired product, 6-(4-methoxyphenyl)-4-methyl-2H-chromen-2-one **(3xk)**, was synthesized. **Isolated yield:** 91% (white solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.62 (d, *J* = 7.6 Hz, 2H), 7.47 – 7.41 (m, 2H), 7.33 – 7.27 (m, 1H), 6.97 – 6.90 (m, 2H), 6.25 (d, *J* = 1.6 Hz, 1H), 3.79 (s, 3H), 2.42 (d, *J* = 1.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 160.80, 159.52, 152.55, 152.40, 137.32, 132.33, 130.41, 128.22, 122.37, 120.14, 117.40, 115.40, 114.47, 55.43, 18.76.



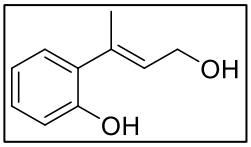
Following the general procedure 1 (**Scheme 3**), the desired product, 6-(3-chloro-methylphenyl)-4-methyl-2H-chromen-2-one **(3xl)**, was synthesized. **Isolated yield:** 83% (white solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.63 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.29 (d, *J* = 2.0 Hz, 1H), 7.13 (s, 1H), 6.28 (s, 1H), 2.44 (s, 3H), 2.35 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 160.57, 153.21, 152.22, 141.43, 140.52, 136.41, 134.66, 130.66, 128.40, 126.21, 124.39, 122.96, 120.25, 117.60, 115.64, 21.35, 18.80.



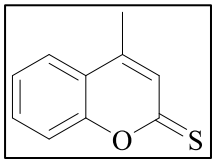
Following the general procedure 1 (**Scheme 3**), the desired product, 6 (4-methoxy-3,5-dimethylphenyl)-4-methyl-2H-chromen-2-one **(3xm)**, was synthesized. **Isolated yield:** 89% (light grey solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.65 – 7.58 (m, 2H), 7.33 – 7.27 (m, 1H), 7.15 (s, 2H), 6.26 (d, *J* = 1.6 Hz, 1H), 3.70 (s, 3H), 2.43 (s, *J* = 1.2 Hz, 3H), 2.30 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 160.81, 156.96, 152.69, 152.43, 137.48, 135.39, 131.55, 130.65, 127.60, 122.65, 120.08, 117.33, 115.38, 59.85, 18.81, 16.29.



Following the above-mentioned procedure of compound **4a, 2xa** as starting material, the desired product (**4a**) was synthesized. **Isolated yield:** 68%. ^{1}H **NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.29 (s, 1H), 7.04 – 6.90 (m, 2H), 6.85 – 6.63 (m, 2H), 4.02 (q, *J* = 7.1 Hz, 2H), 2.80 (t, *J* = 6.9 Hz, 2H), 2.58 (t, *J* = 6.9 Hz, 2H), 1.11 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 175.49, 154.37, 130.50, 127.91, 127.29, 120.66, 116.70, 61.22, 35.02, 25.10, 14.12.



Following the above-mentioned procedure of compound **4b, 2xa** as starting material, the desired product (**4b**) was synthesized. **Isolated yield:** 76% (colourless liquid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm) 7.09 – 6.87 (m, 2H), 6.80 (t, *J* = 8.3 Hz, 2H), 5.76 (t, *J* = 7.4 Hz, 1H), 3.81 (d, *J* = 7.5 Hz, 2H), 1.93 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 151.93, 137.19, 129.17, 128.70, 127.62, 127.19, 120.59, 116.18, 60.30, 25.27.



Following the above-mentioned procedure of compound **4a, 2xa** as starting material, the desired product (**4a**) was synthesized. **Isolated yield:** 72% (yellow solid). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.9 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.11 (s, 1H), 2.31 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm) 197.49, 156.15, 144.19, 132.10, 129.06, 125.36, 124.52, 121.47, 117.03, 18.04.

Spectral Data:

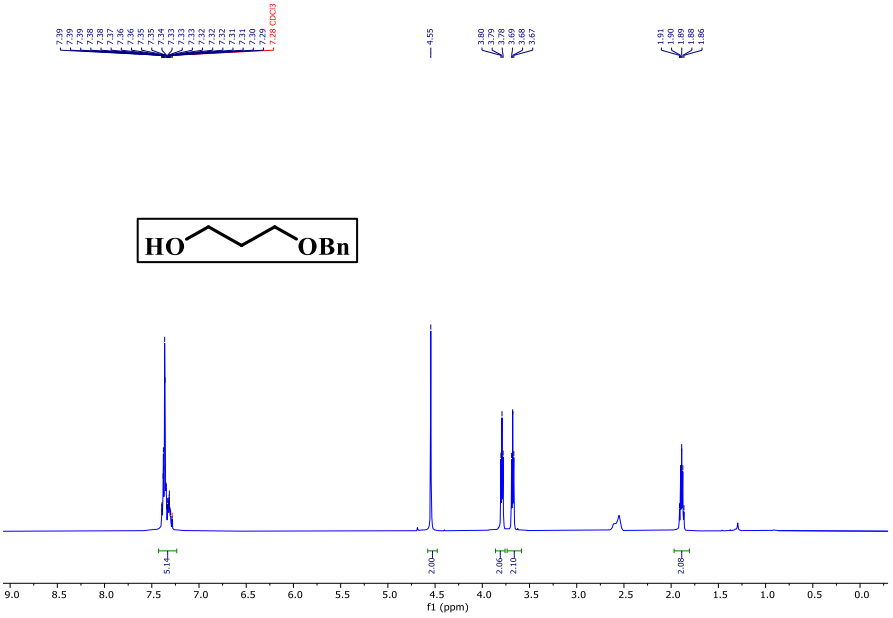


Figure 6. ^{1}H NMR spectrum of **1b** in $CDCl_3$

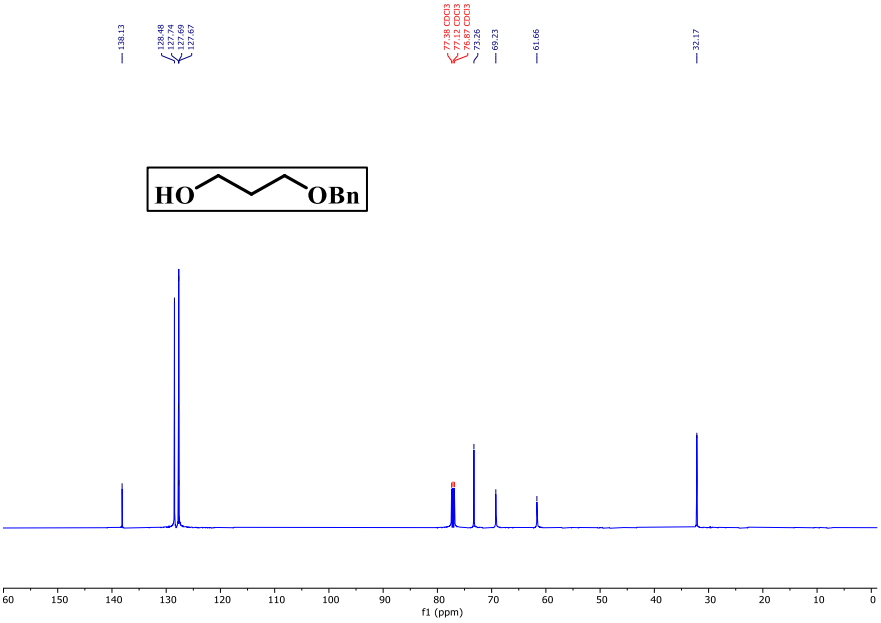


Figure 7. ^{13}C NMR spectrum of **1b** in $CDCl_3$

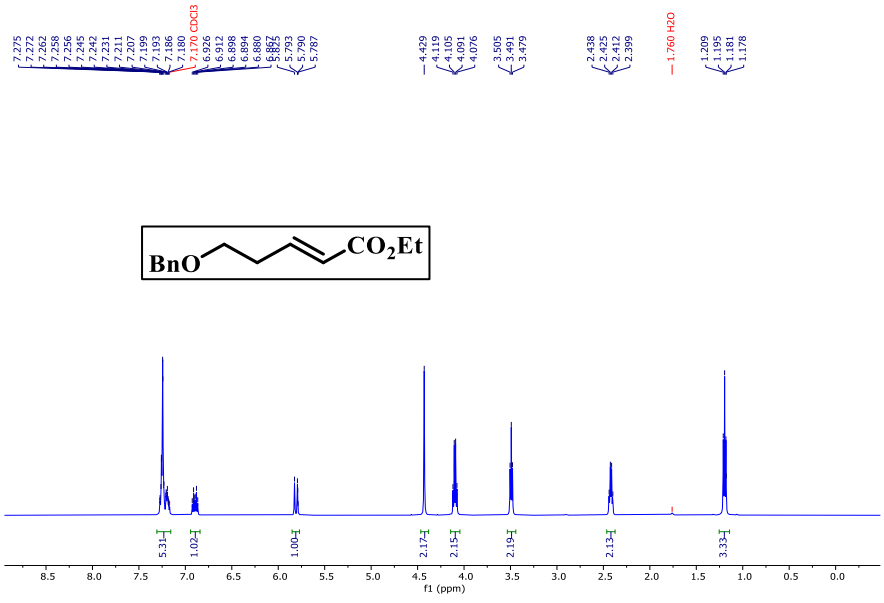


Figure 8. ^{1}H NMR spectrum of **1c** in $CDCl_3$

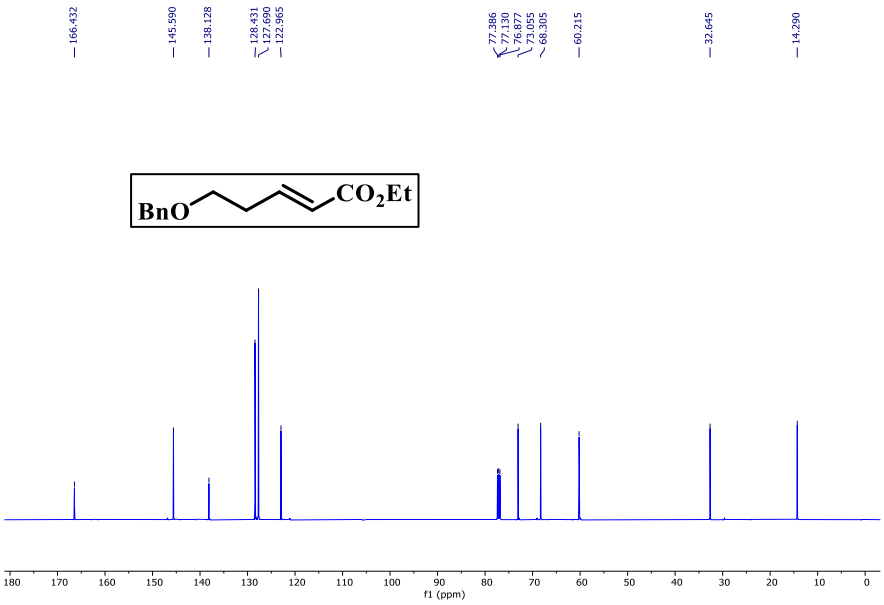


Figure 9. ^{13}C NMR spectrum of **1c** in $CDCl_3$

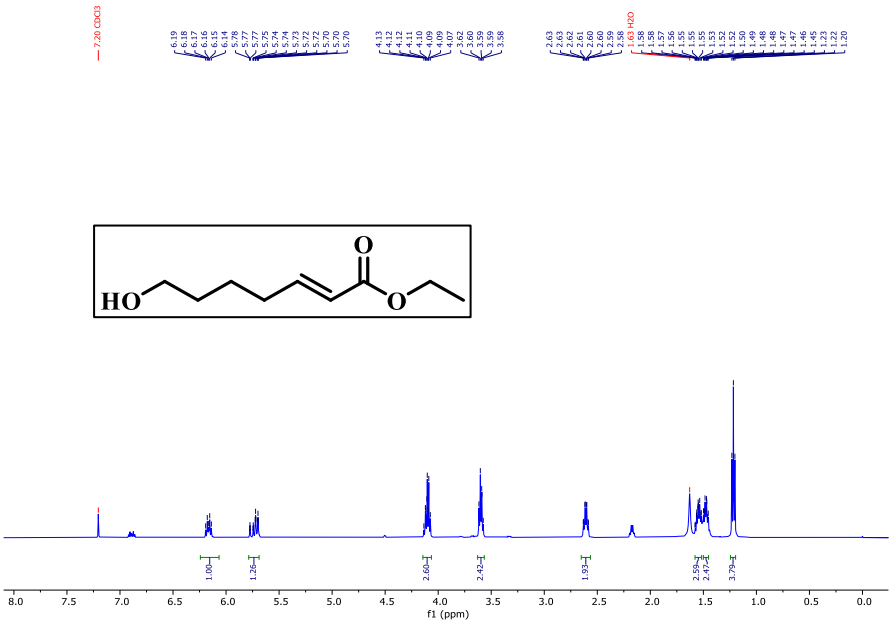


Figure 10. ^{1}H NMR spectrum of Compound **5** in $CDCl_3$

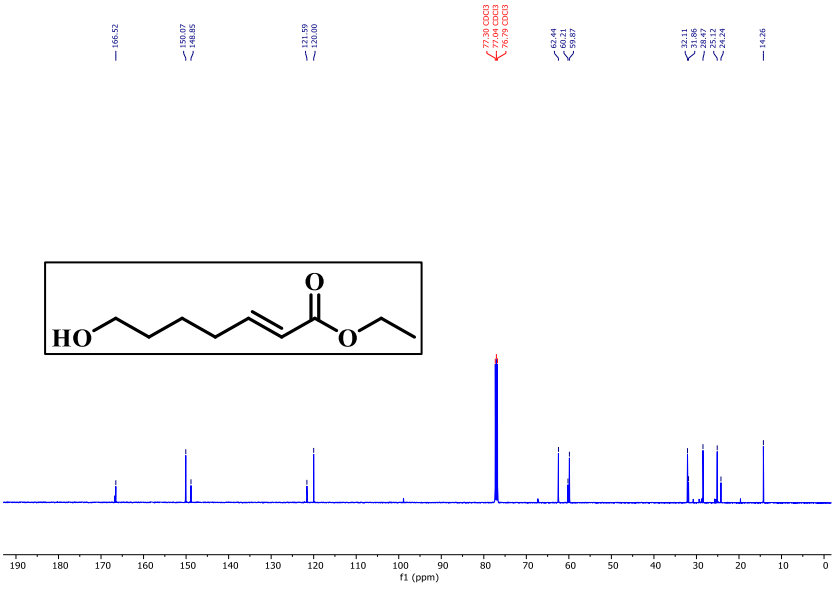


Figure 11. ^{13}C NMR spectrum of Compound **5** in $CDCl_3$

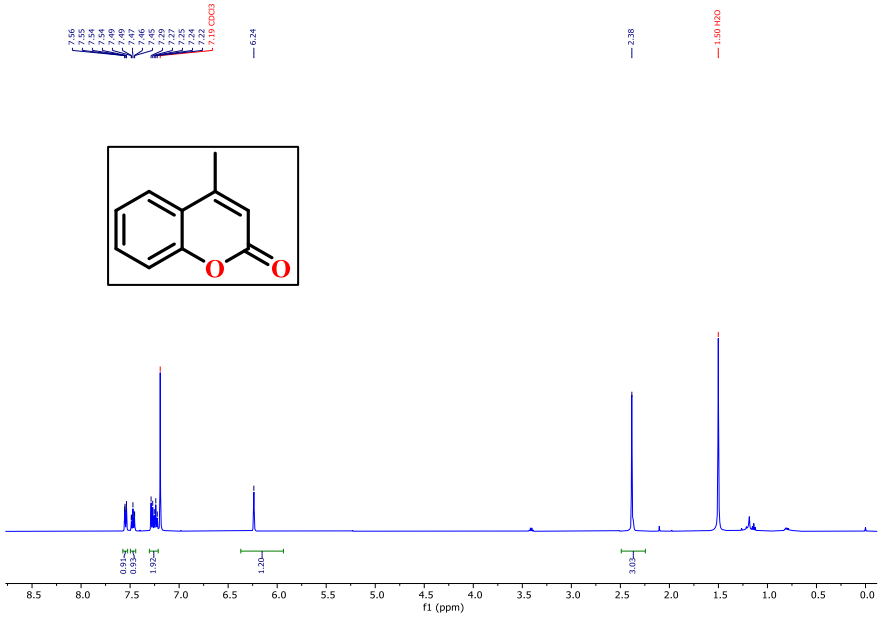


Figure 12: ^{1}H NMR spectrum of **2xa** in $CDCl_3$

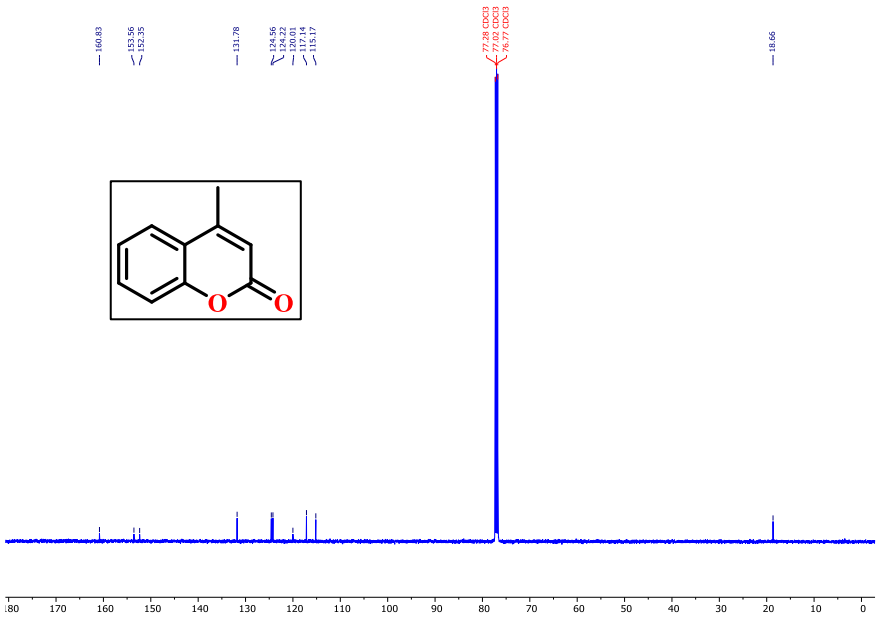


Figure 13: ^{13}C NMR spectrum of **2xa** in $CDCl_3$

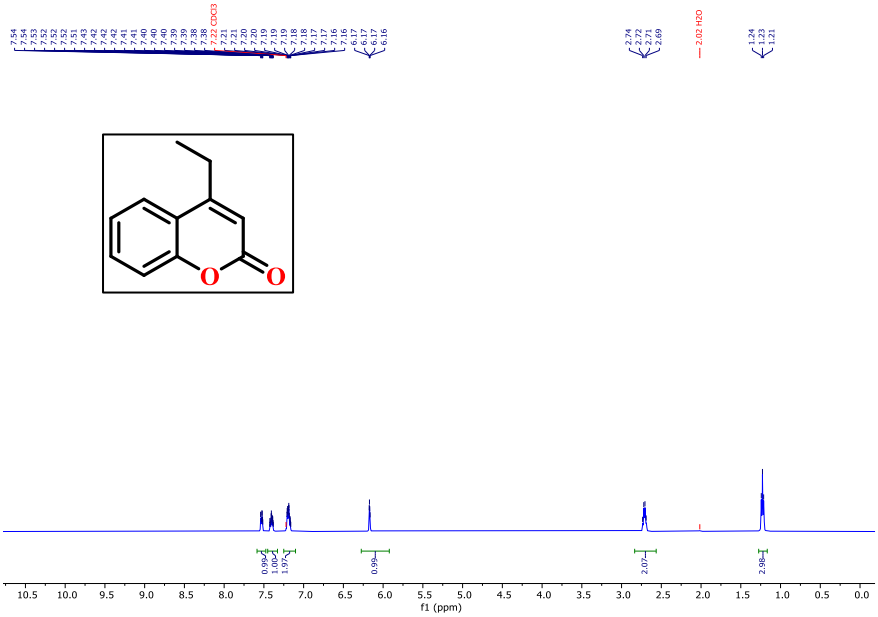


Figure 14: ^{1}H NMR spectrum of **2xb** in $CDCl_3$

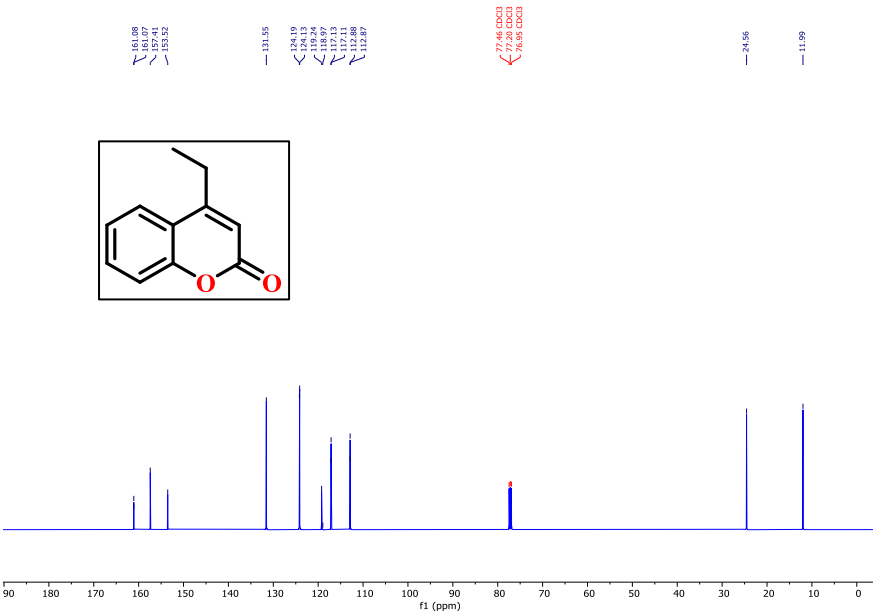


Figure 15: ^{13}C NMR spectrum of **2xb** in $CDCl_3$

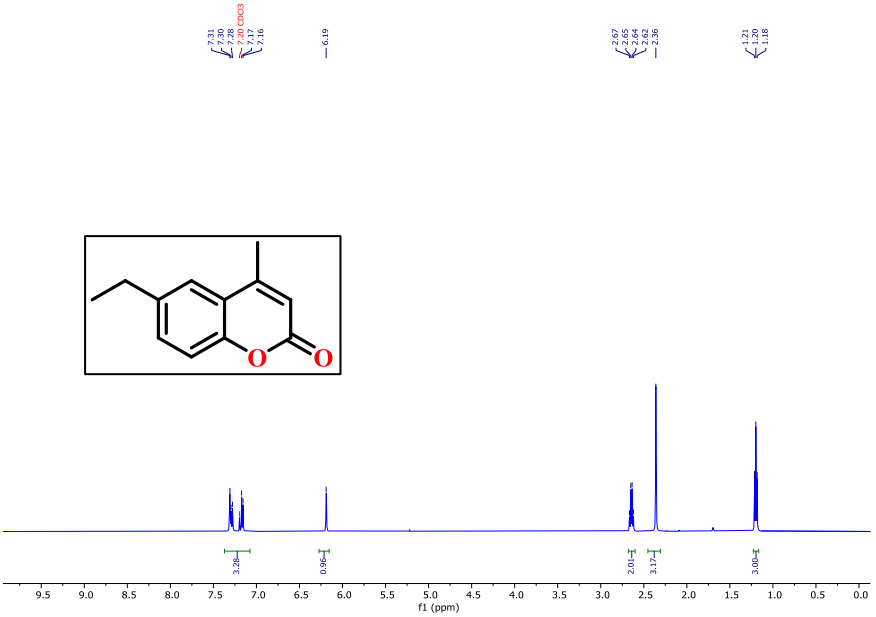


Figure 16: ^{1}H NMR spectrum of **2xc** in $CDCl_3$

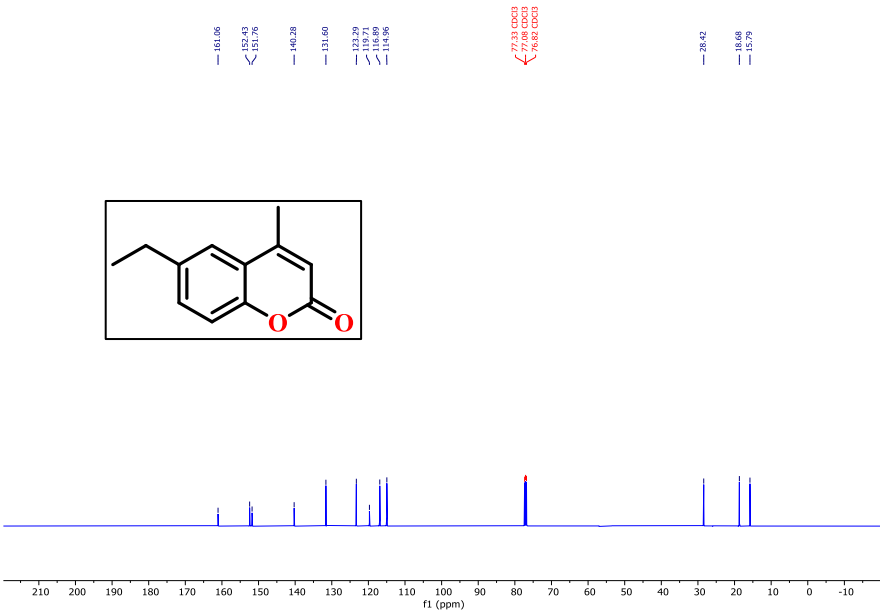


Figure 17: ^{13}C NMR spectrum of **2xc** in $CDCl_3$

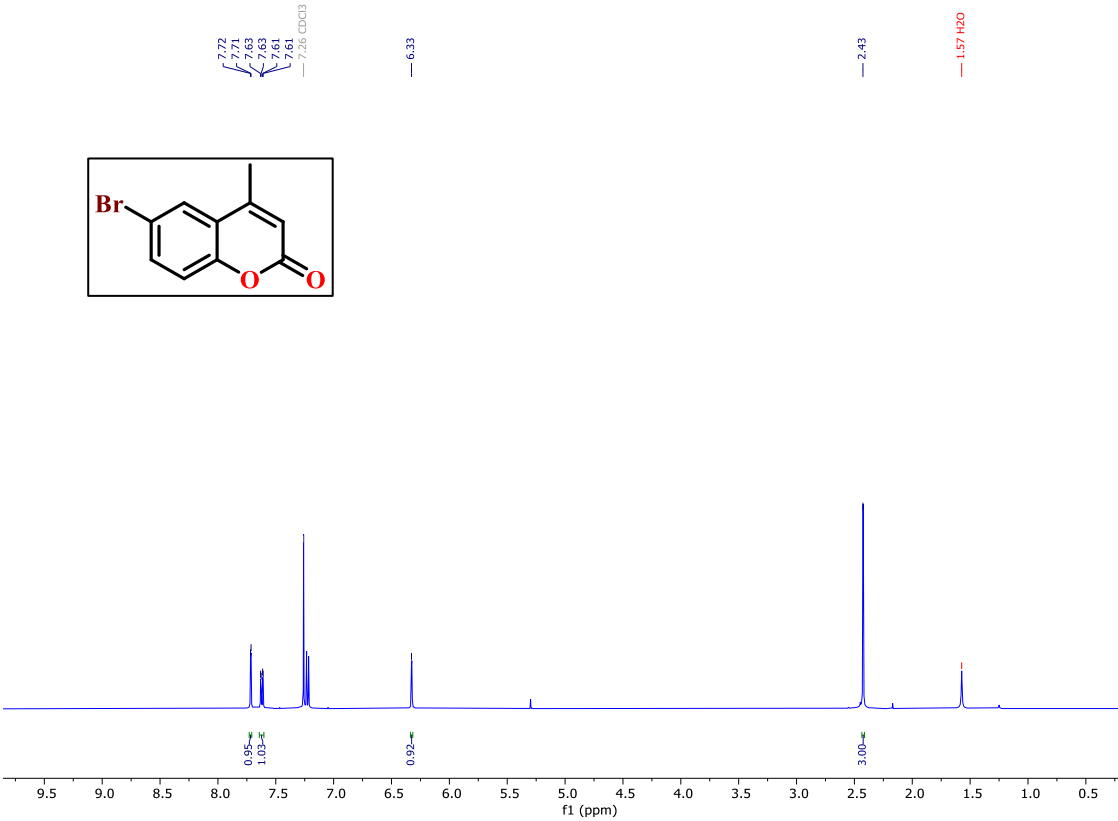


Figure 18: ^{1}H NMR spectrum of **2xd** in $CDCl_3$

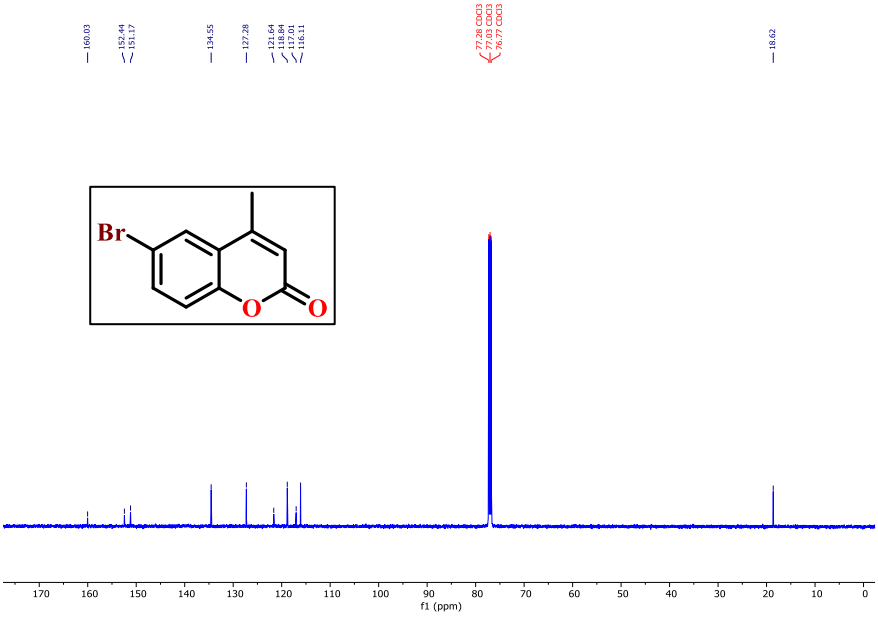


Figure 19: ^{13}C NMR spectrum of **2xd** in $CDCl_3$

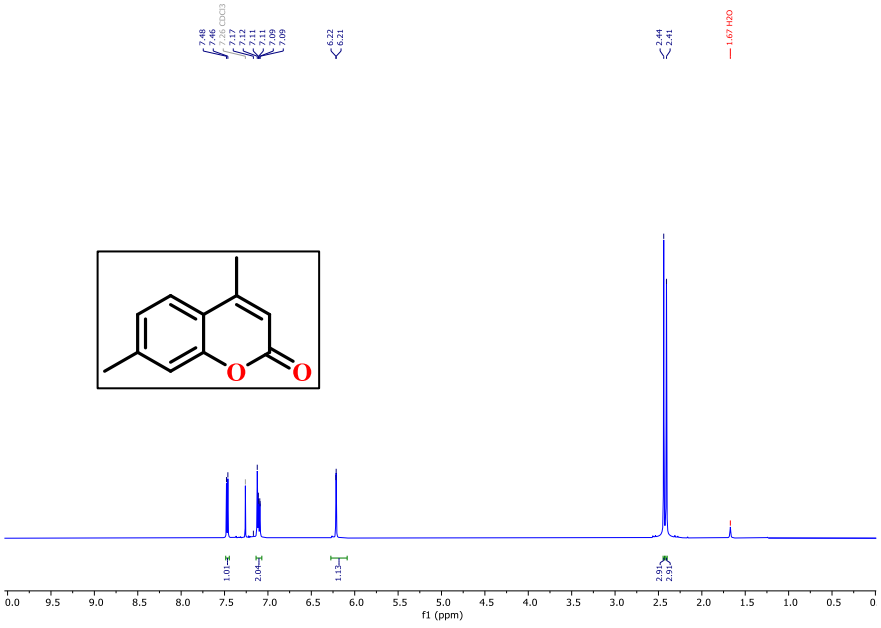


Figure 20: ^{1}H NMR spectrum of **2xe** in $CDCl_3$

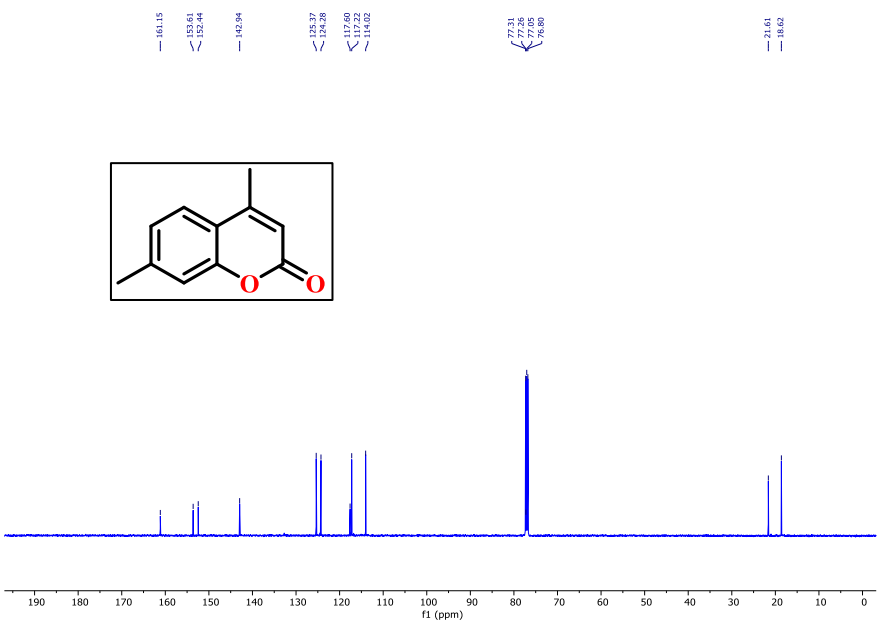


Figure 21: ^{13}C NMR spectrum of **2xe** in $CDCl_3$

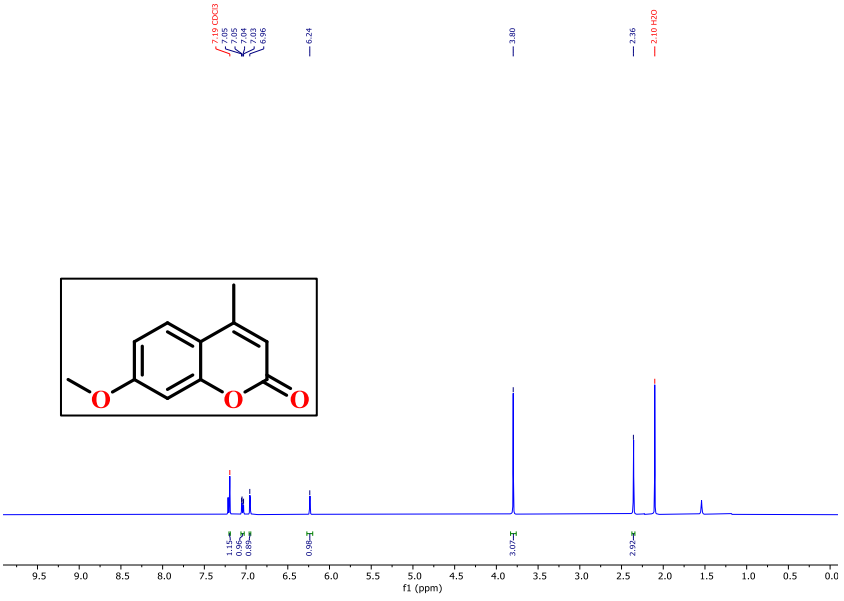


Figure 22: ^{1}H NMR spectrum of **2xf** in $CDCl_3$

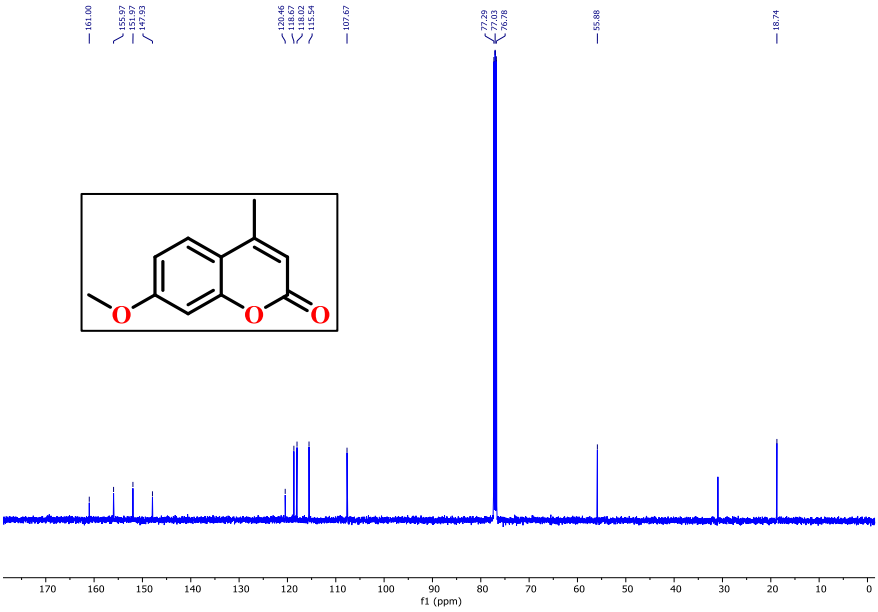


Figure 23: ^{13}C NMR spectrum of **2xf** in $CDCl_3$

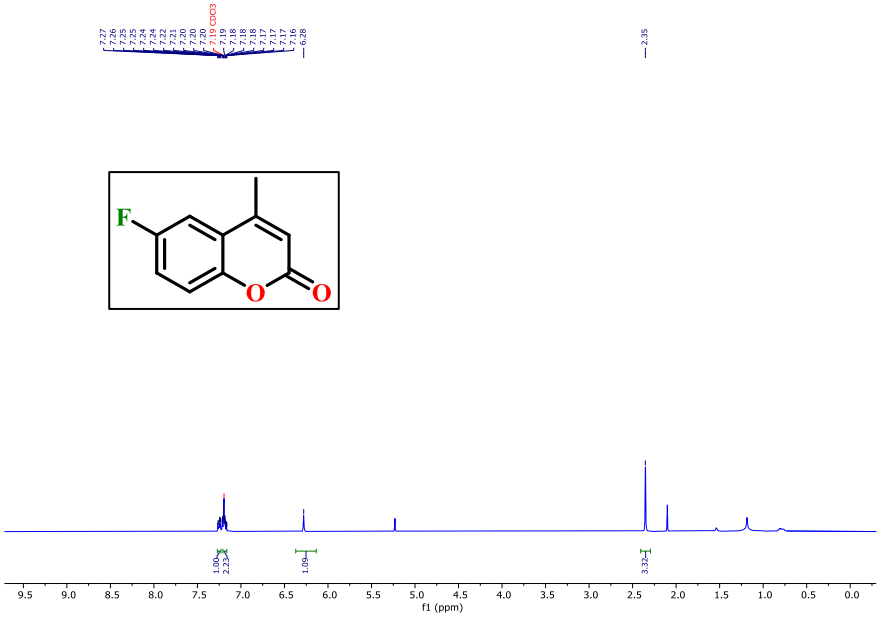


Figure 24: ^{1}H NMR spectrum of **2xg** in $CDCl_3$

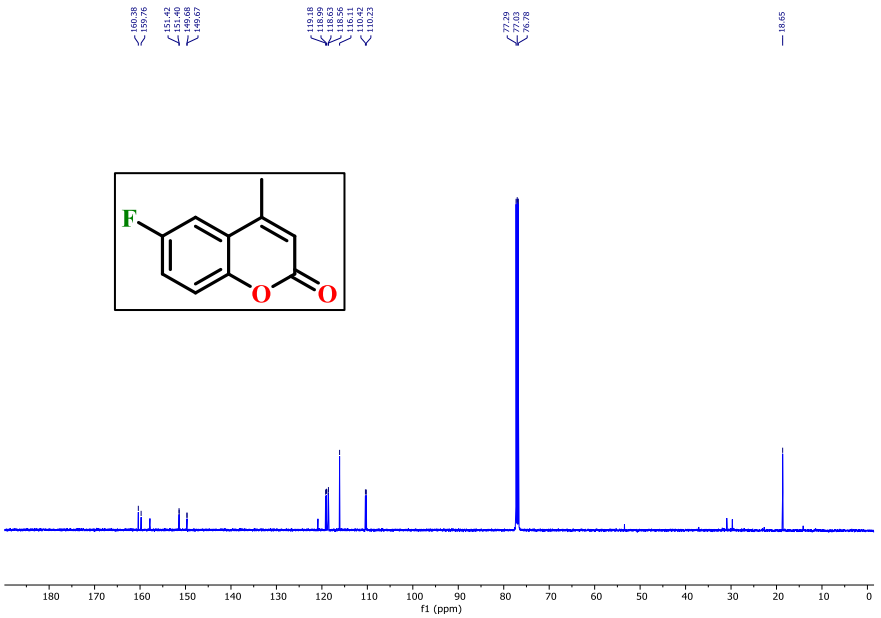


Figure 25: ^{13}C NMR spectrum of **2xg** in $CDCl_3$

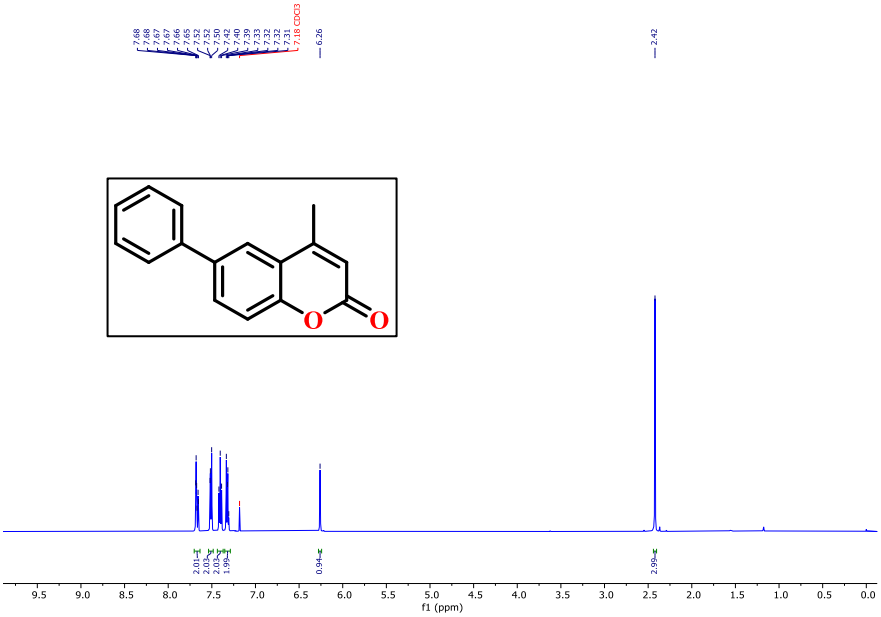


Figure 26: ^{1}H NMR spectrum of **3xh** in $CDCl_3$

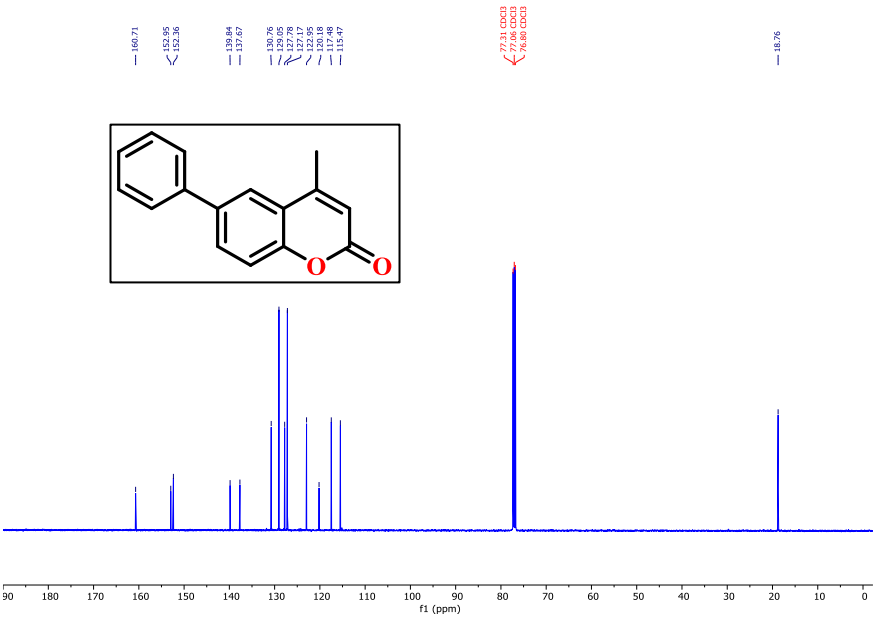


Figure 27: ^{13}C NMR spectrum of **3xh** in $CDCl_3$

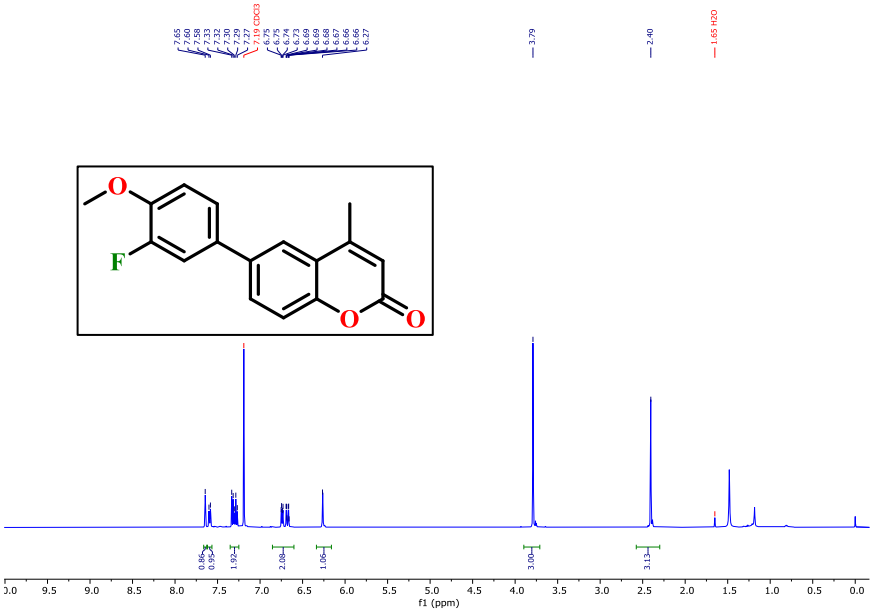


Figure 28: ^{1}H NMR spectrum of **3xi** in $CDCl_3$

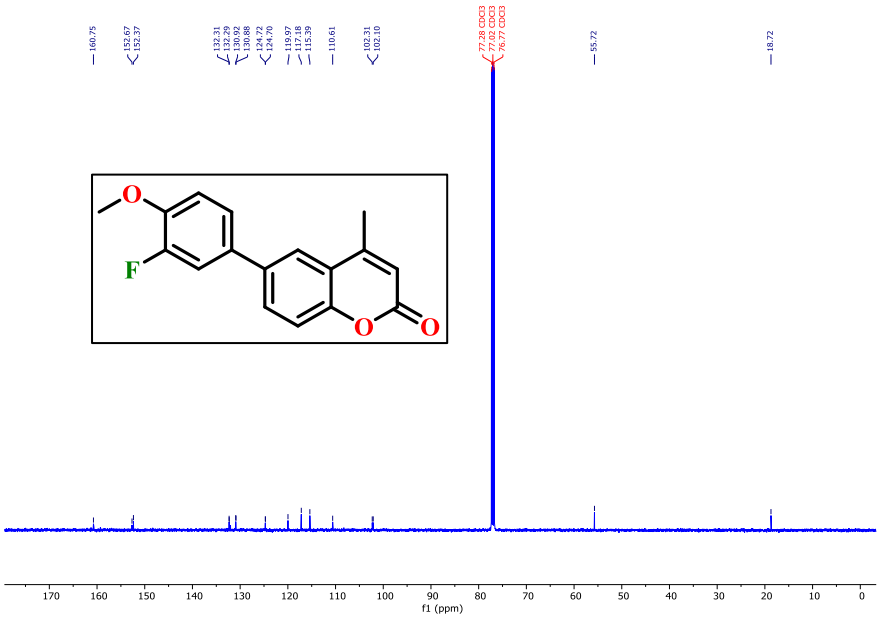


Figure 29: ^{13}C NMR spectrum of **3xi** in $CDCl_3$

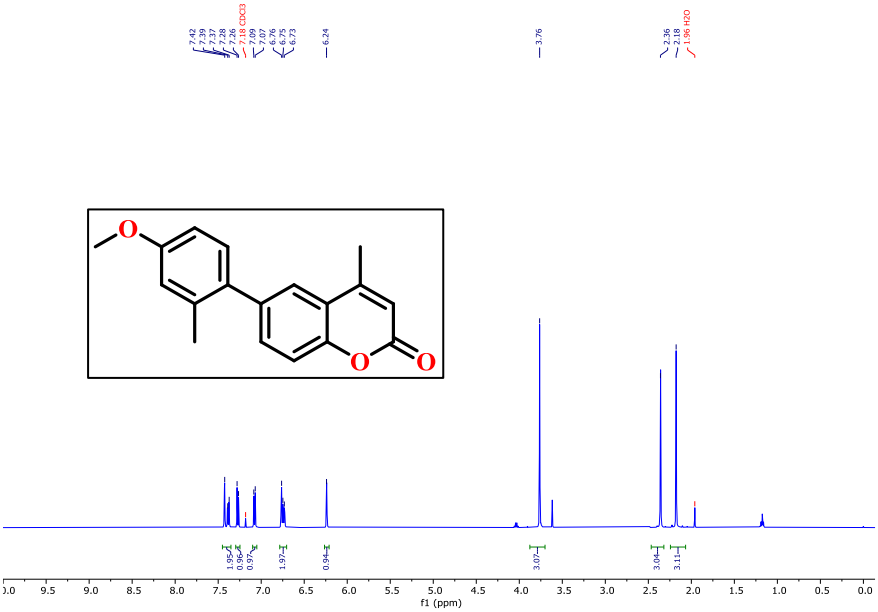


Figure 30: ^{1}H NMR spectrum of **3xj** in $CDCl_3$

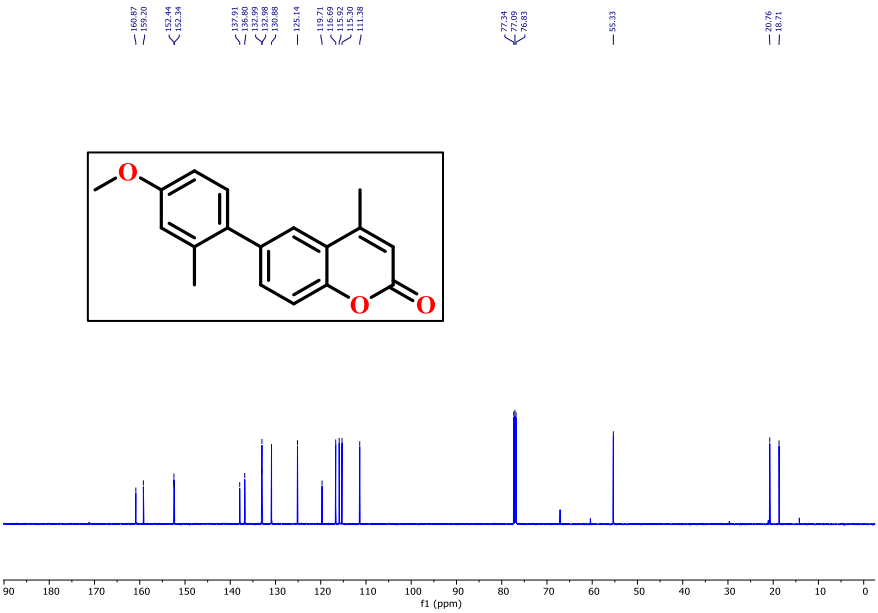


Figure 31: ^{13}C NMR spectrum of **3xj** in $CDCl_3$

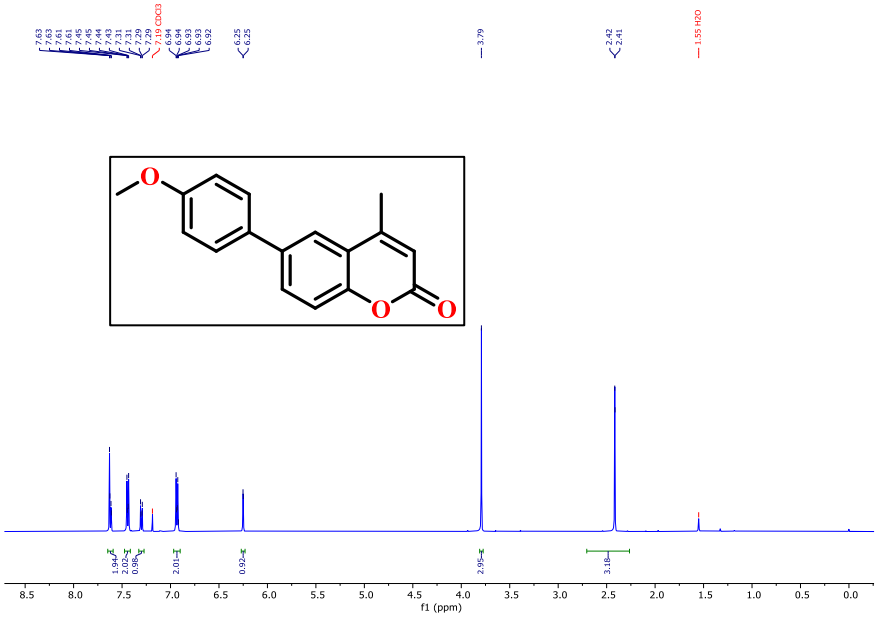


Figure 32: ^{1}H NMR spectrum of **3xk** in $CDCl_3$

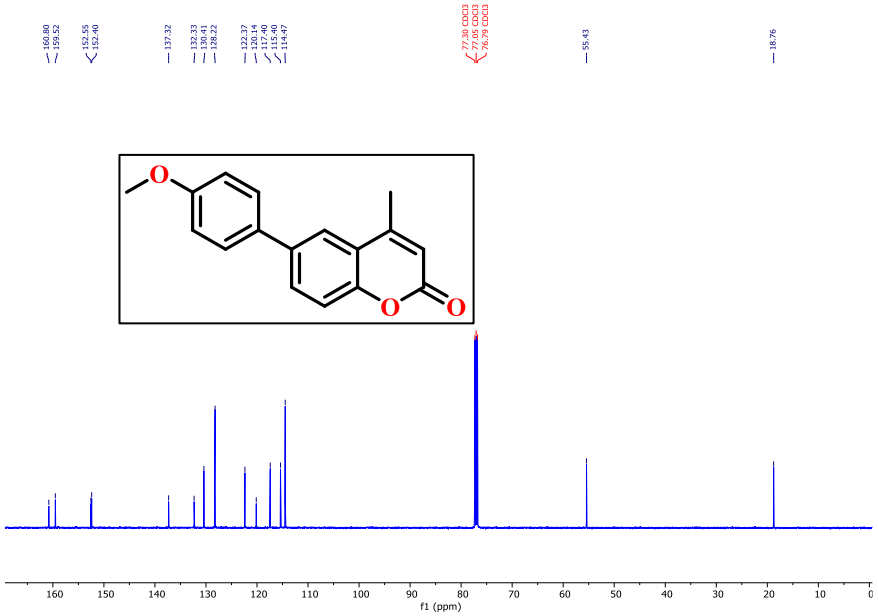


Figure 33: ^{13}C NMR spectrum of **3xk** in $CDCl_3$

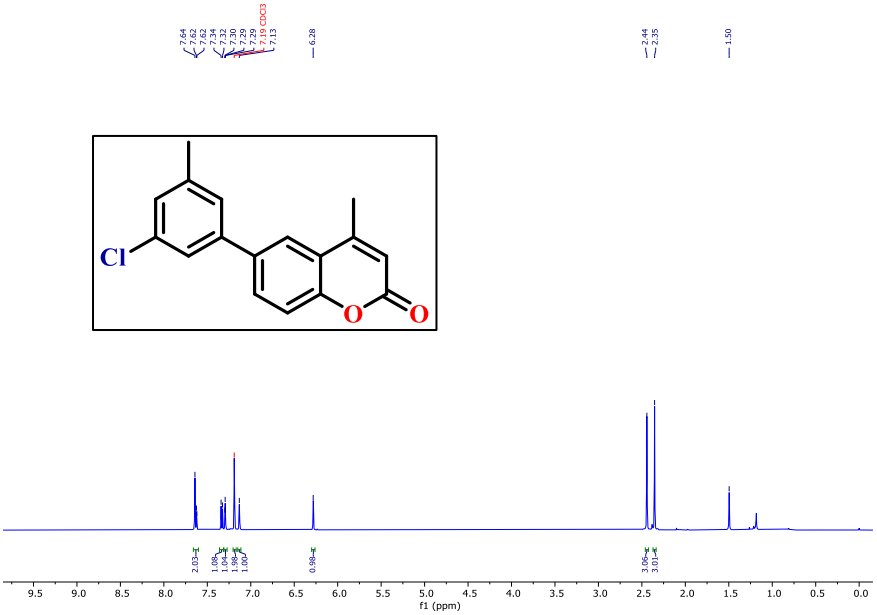


Figure 34: ^{1}H NMR spectrum of **3xl** in $CDCl_3$

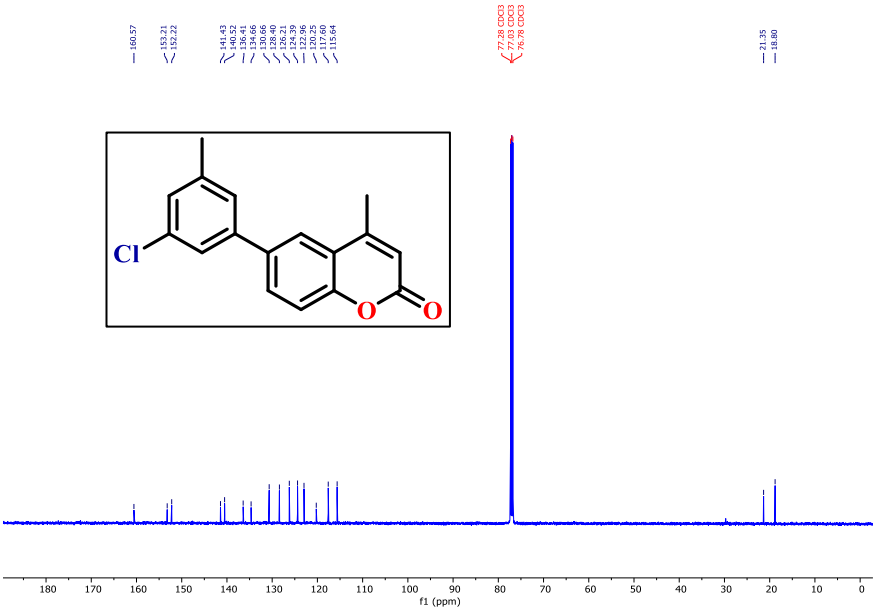


Figure 35: ^{13}C NMR spectrum of **3xl** in $CDCl_3$

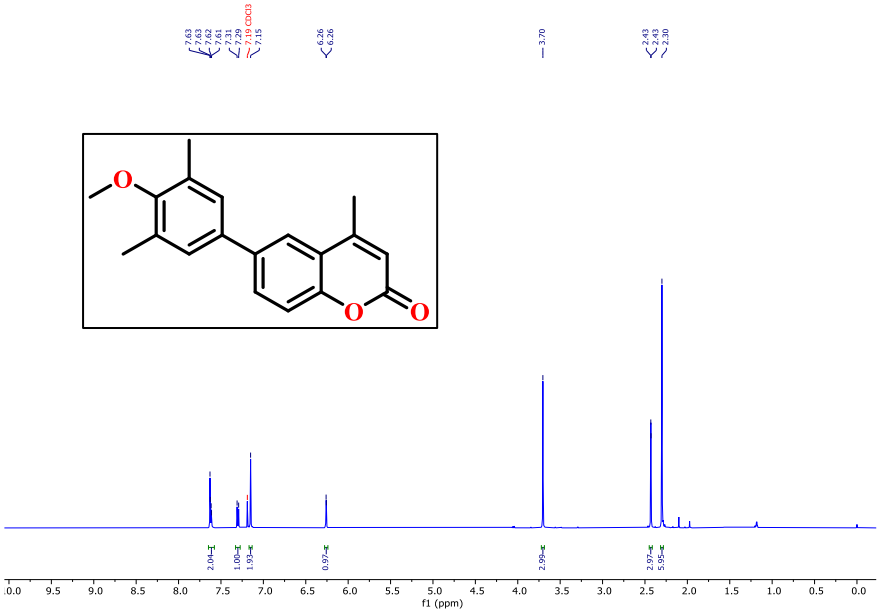


Figure 36: ^{1}H NMR spectrum of **3xm** in $CDCl_3$

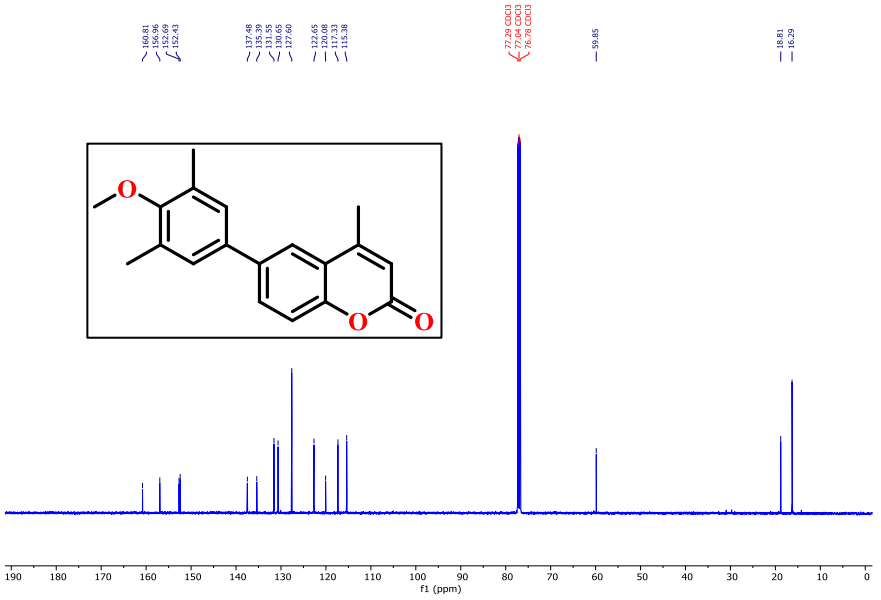


Figure 37: ^{13}C NMR spectrum of **3xm** in $CDCl_3$

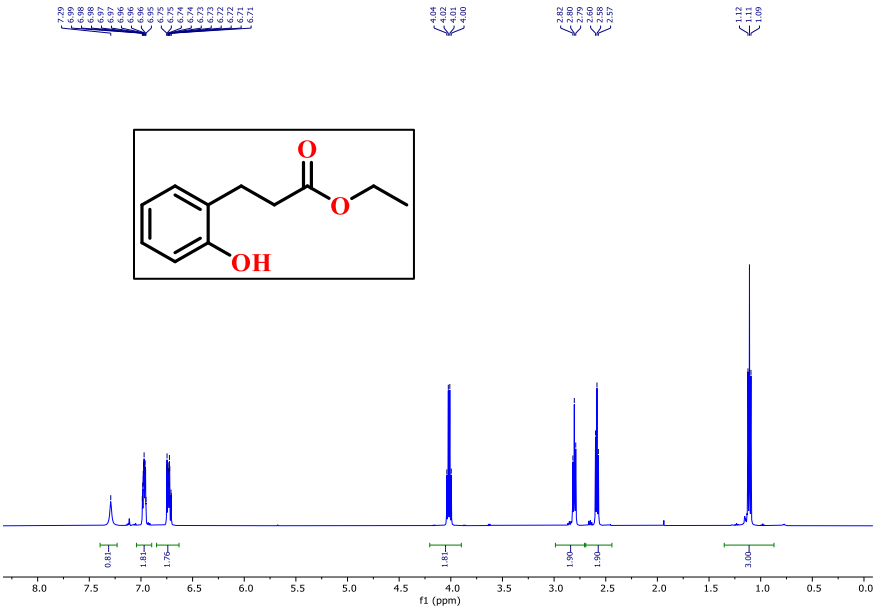


Figure 38: ^{1}H NMR spectrum of **4a** in $CDCl_3$

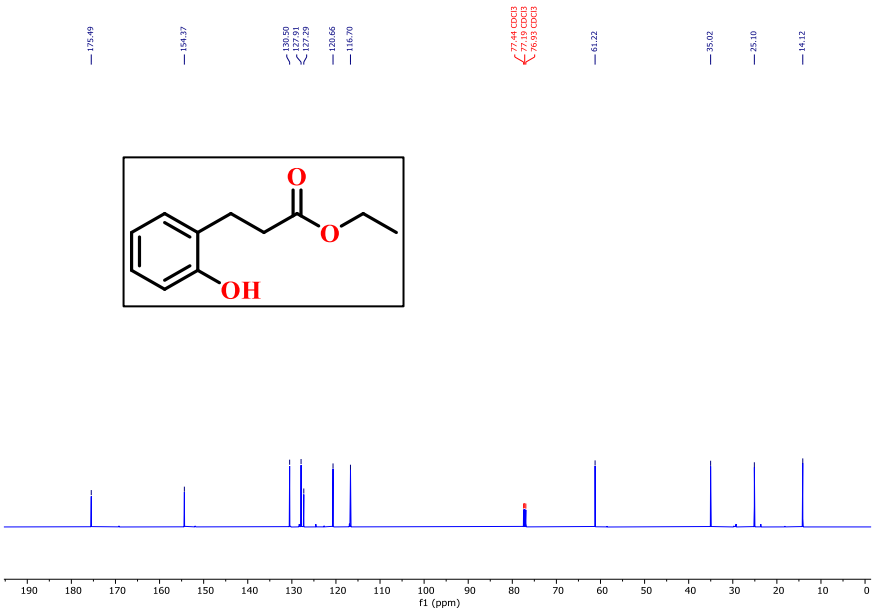


Figure 39: ^{13}C NMR spectrum of **4a** in $CDCl_3$

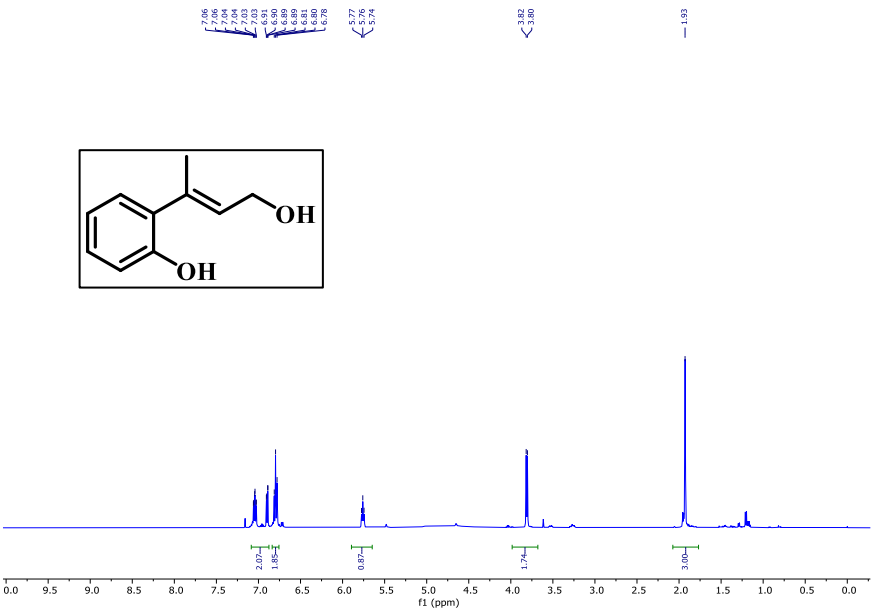


Figure 40: ^{1}H NMR spectrum of **4b** in $CDCl_3$

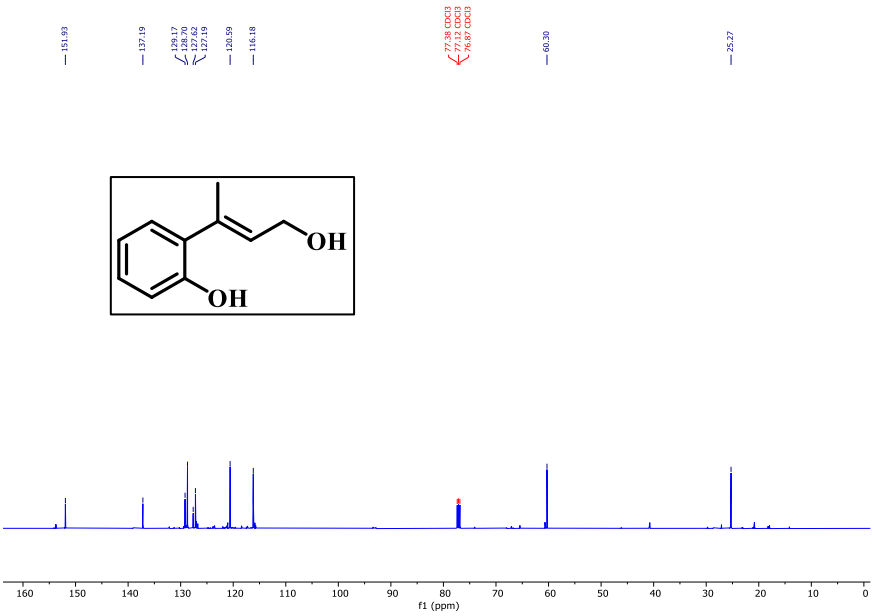


Figure 41: ^{13}C NMR spectrum of **4b** in $CDCl_3$

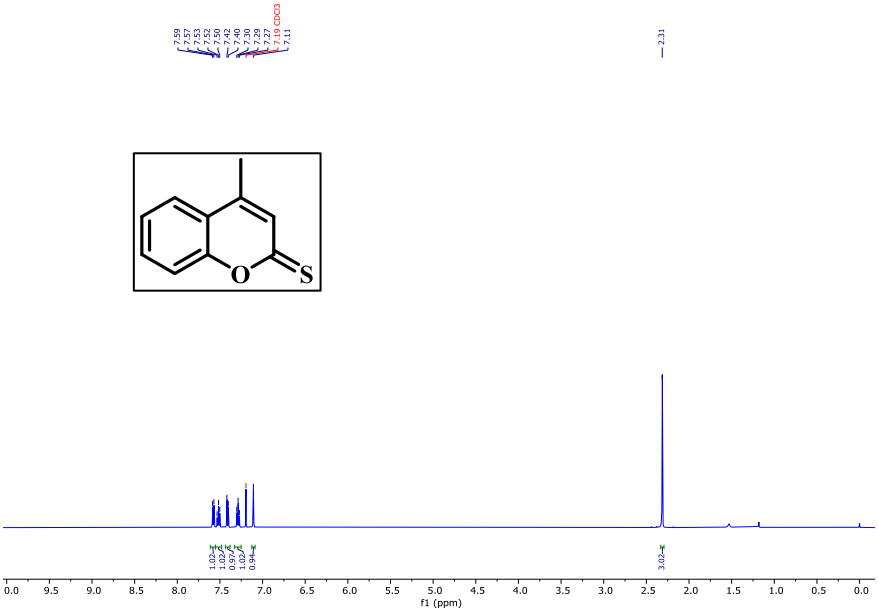


Figure 42: ^{1}H NMR spectrum of **4c** in $CDCl_3$

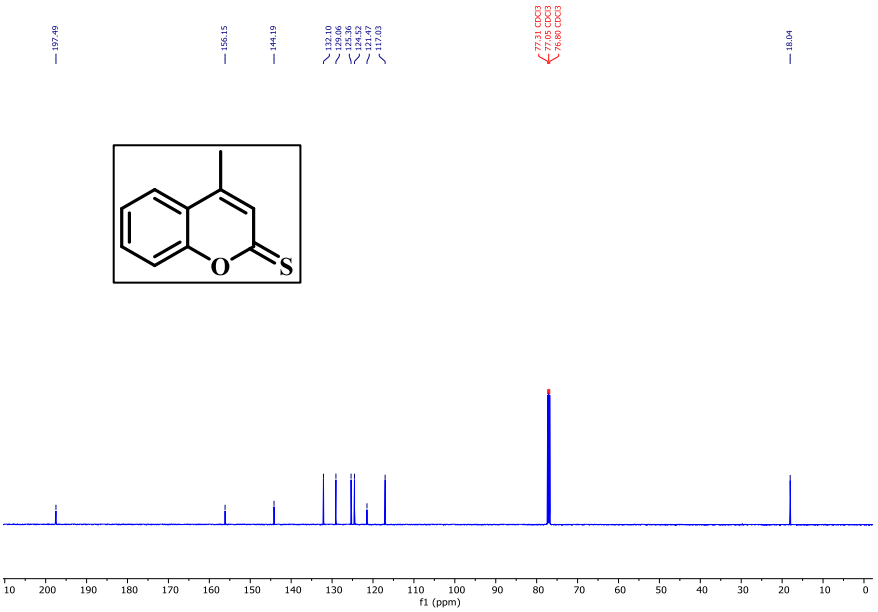


Figure 43: ^{13}C NMR spectrum of **4c** in $CDCl_3$