# SYNTHESIS OF NOVEL 6,8-DISUBSTITUTED-CHROMONE-3-CARBOXAMIDES AND THEIR EVALUATION AS POTENTIAL ANTI-TUBERCULOSIS AGENTS

BY

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# ABSTRACT

This project focusses on the synthesis of novel 6,8-disubstituted-chromone-3-carboxamides and their evaluation as potential anti-tuberculosis agents.

In this study, four 3-iodo-5-substituted-2-hydroxyacetophenones **(58A-D)** and three 3-bromo-5-substituted-2-hydroxyacetophenones **(63A-C)** were successfully synthesized from 5-substituted-2-hydroxyacetophenones **(57A-D).** The Vilsmeier-Haack reaction was used to synthesize the 8-iodo-6-substituted-chromone-3-carbaldehydes and 8-bromo-6-substituted-chromone-3-carbaldehydes from the 3-iodo/bromo-5-substituted-2-hydroxyacetophenones. These compounds were treated with sodium chlorite and sulfamic acid to afford corresponding chromone-3-carboxylic acids**.**

Recrystallization with either ethanol or methanol was used to purify the synthesized compounds. All compounds were synthesized in good to excellent yields. The yields of the 3-iodo-5-substituted-2-hydroxyacetophenones **(58A-D)** ranged from 55 - 75 %, the 3-bromo-5-substituted-2-hydroxyacetophenones **(63A-C)** were synthesized with yields from 66 - 87 %, the percentage yields are significantly different probably because different methods were used. The yields of the 8-iodo-6-substituted-chromone-3-carbadehydes **(59A-D)** ranged from 78 – 90 %, the 8-bromo-6-substituted-chromone-3-carbaldehydes **(64A-C)** with yields from 85 - 87 %, 8-bromo-6-substuted-chromone-3-carboxylic acids from 47 – 52 %, and chromone-3-carboxylic acid afforded a yield of 57 %.

$^{1}$H NMR, $^{13}$C NMR and FTIR spectroscopic techniques were used to characterize synthesized compounds and also confirmed by melting points for compounds reported in literature.

**Keywords:** *Synthesis, chromones, chromone-3-carboxamides, biological activities, anti-tuberculosis*

## Acknowledgements

To my lovely God, I would like to thank him for giving me strength and courage to complete this project. It is only through His grace that this project was accomplish.

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## Declaration

I, MALUSELA THISUNDIWI, hereby declare that the dissertation titled "Synthesis of novel 6,8-disubstituted-chromone-3-carboxamides and their evaluation as potential anti-tuberculosis agents" submitted by me at University of Venda for master's degree was not submitted for any degree at this institution or any other, that it is my work, and that all references used have been acknowledged.

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I, **Malusela Thisundiwi**, hereby declare the following:

- Plagiarism is wrong, and I am aware of it, plagiarism is the practice of representing another person thoughts or work as one's own, and it is an academic infraction that could result in serious consequences from the university.
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## List of Abbreviations

| | |
|---|---|
| $^{13}C$ NMR | Carbon-13 nuclear magnetic resonance |
| $^{1}H$ NMR | Proton nuclear magnetic resonance |
| AIDS | Acquired Immunodeficiency Syndrome |
| $B(OH)_2$ | Boronic acid |
| $CDCl_3$ | Deuterochloroform |
| DMSO-$d_6$ | Dimethyl sulfoxide-$d_6$ |
| d | Doublet |
| dd | Doublet of doublets |
| DCM | Dichloromethane |
| DMF | Dimethylformamide |
| EMB | Ethambutol |
| $Et_3N$ | Triethylamine |
| FTIR | Fourier Transform Infrared Spectroscopy |
| Hz | Hertz |
| HIV | Human Immunodeficiency Virus |
| $H_2NSO_3H$ | Sulfamic acid |
| INH | Isoniazid |
| MHz | Megahertz |
| MDR-TB | Multi-drug resistant Tuberculosis |
| MeOH | Methanol |
| Mtb | Mycobacterium tuberculosis |
| $NaClO_2$ | Sodium chlorite |
| NBS | *N*-Bromosuccinimide |
| NIS | N- Iodosuccinimide |
| NMR | Nuclear Magnetic Resonance |
| ppm | Parts per million |
| $POCl_3$ | Phosphorus oxychloride |
| Pd | Palladium |
| PZA | Pyrazinamide |
| RIF | Rifampicin |
| s | Singlet |
| SAR | Structure-activity relationship |

| | |
|---|---|
| **$SOCl_2$** | **Thionyl chloride** |
| **TB** | **Tuberculosis** |
| **TLC** | **Thin-layer chromatography** |
| **t** | **Triplet** |
| **XDR-TB** | **Extensively-drug resistant tuberculosis** |
| **WHO** | **World Health Organization** |

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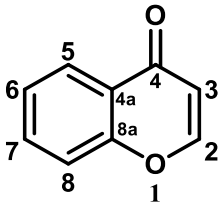
# CHAPTER 1 INTRODUCTION

Heterocyclic compounds are among the most important compounds in medicinal chemistry and one of the most complex branches of chemistry.[1] They have made significant contributions to the industrial and physiological significance of synthetic methodologies and their theoretical implications.[2] Synthetic heterocyclic chemistry has not only played an important role in various aspects of human life improvement, but their application is also found in diverse fields such as agriculture, medicine, polymers, and various industries.[3]

The main objective of the research is on the synthesis of chromones, and their related compounds are not only to develop more diverse and complex compounds with large variety of biological activities and also investigate their SAR, but also to develop various fluorescence probes because of their interesting photophysical and photochemical properties.[4]

## 1.1 Chromones

Chromone (**1)** consists of a substituted keto group on the pyran ring and a benzopyran ring structure fused together.[5] The chromone substructure is found in the chemical structure of flavonoids, a class of naturally occurring compounds that are currently of interest because of their biological activity and classified as prevailed structure for the development of novel pharmacologically interesting compounds in drug discovery.[6]




**1**

**Figure 1**: The structure of chromone

The chromone structure is a key component of many flavonoids (Figure 2), such as flavones (**2)**, flavanols **(3)** and isoflavones **(4).**[7] Several chromone derivatives have been used for the treatment of cystic fibrosis because they can be used to inhibit kinase (protein kinase inhibitor) and be attached to benzodiazepine receptors .[8.]

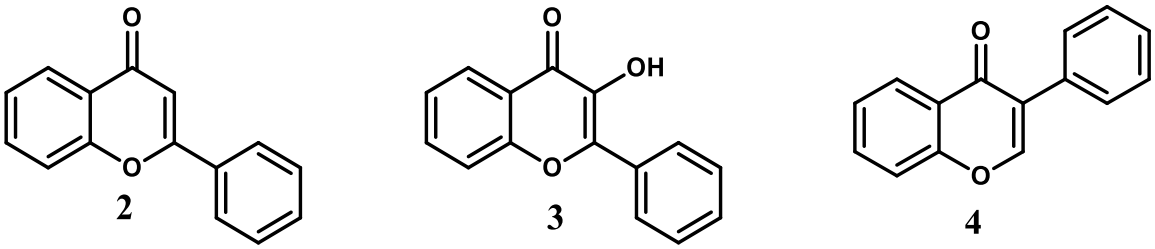



**Figure 2**: Examples of phenylsubstituted chromones

Some chromone derivatives, both natural and synthetic, have already been marketed as lead compounds in various therapeutic treatments such as nedocromil and cromoglycate.[9] Chromones that are present in nature are flavones and isoflavones, which are the 2- and 3-aryl substituted derivatives. Chromones, such as 3-methylchromones **(5)** and 2-styrylchromones **(6),** have been found in the plant kingdom (Figure 3). [10.]

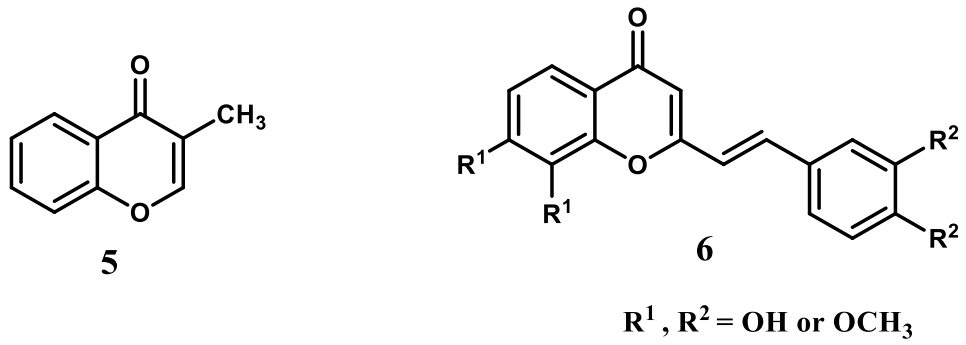



**Figure 3**: Some examples of chromones

## 1.2 Structure and spectroscopic properties of chromones

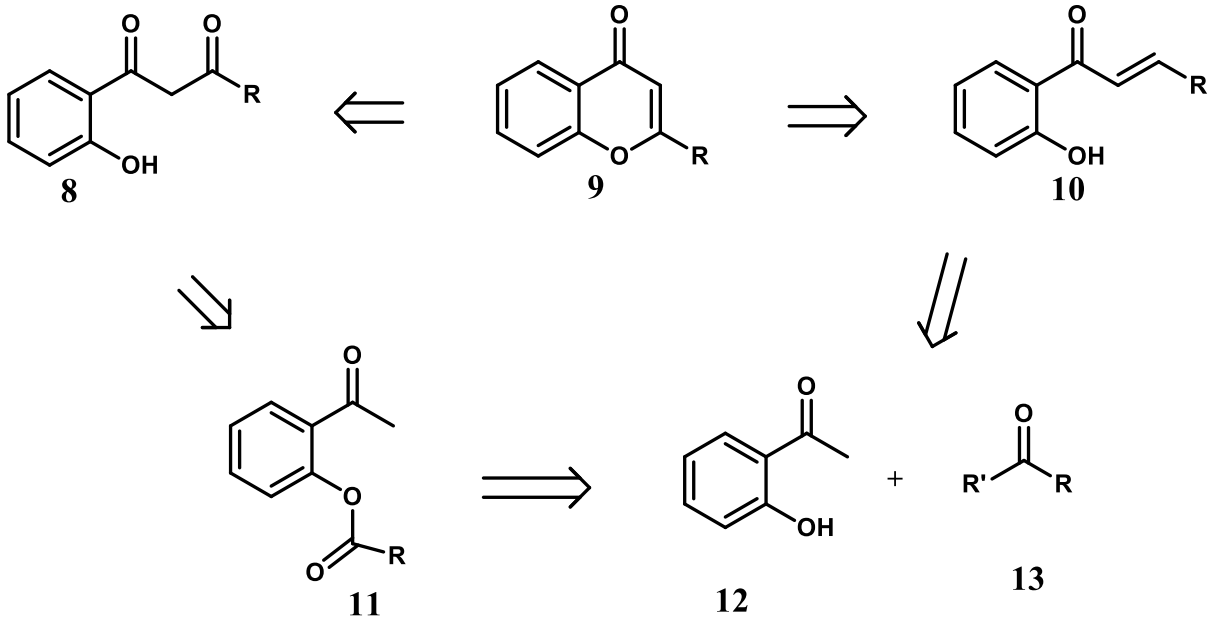
The structure of chromone **(1)** is isomeric with coumarin **(7)**; the difference between the two structures (Figure 4) is the position of the carbonyl group. Chromone has a carbonyl at position C-4 and in the coumarin it appears on position C-2.[11] The chromone IR carbonyl (C=O) stretching frequency is at max 1660 cm-1, but it is much lower than of the coumarin which has the carbonyl stretching of $\nu_{max}$ 1710 $cm^{-1}$. [12]

**Figure 4**: Isomeric structures of chromone

## 1.3 Synthesis of chromones

Various synthetic methods for the chromones have been developed over many years and include: Claisen condensation,[15] Baker-Venkataraman rearrangement,[16] Kostanecki-Robinson, [17] Simonis reaction, [19] and Gammill's protocol[18] among many other methods. Most chromone synthetic methods use various 2-hydroxyacetophenones as starting materials.[13]

The general retrosynthetic strategy to show the disconnection approach to chromones is shown in Scheme 1.[14]

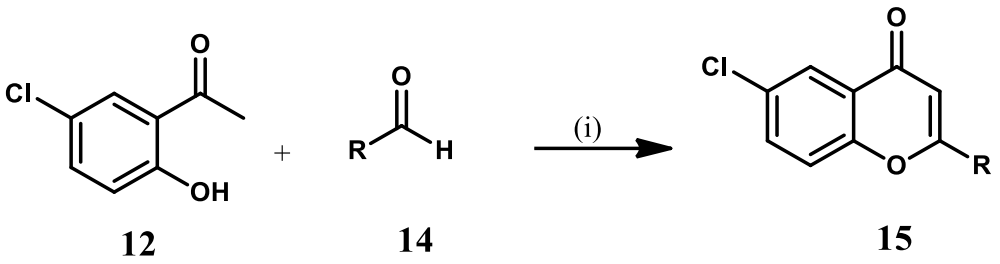



**R=H, Ph, alkyl**
**R'=H, Cl**

**Scheme 1**: Retrosynthetic strategy for chromones

### 1.3.1 Claisen condensation reaction

In this reaction (Scheme 2), a substituted-2-hydroxyacetophenone (e.g., 5-chloro-2-hydroxyacetophenone **12**) reacts with aliphatic aldehydes **(14)** to form a chromone **(15).**[15.]




12 14 15

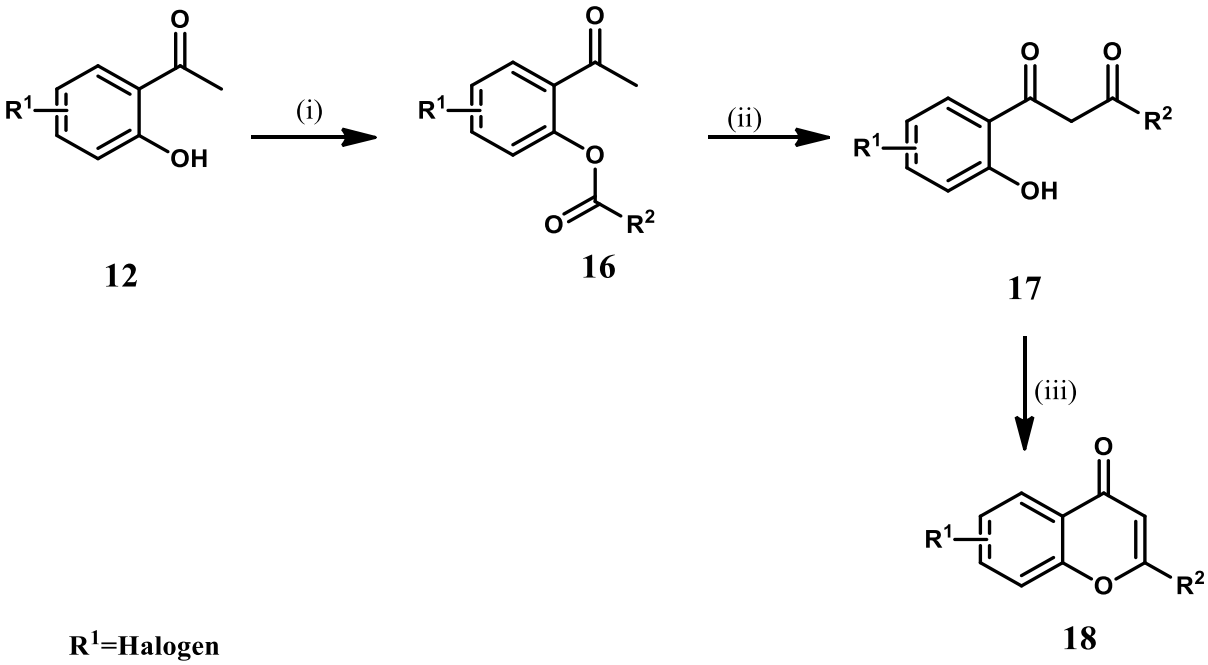
**R= Alkyl**

*Reagents*: (i) DIPA, EtOH

**Scheme 2**: Claisen condensation reaction

### 1.3.2 Baker-Venkataraman rearrangement

Various aromatic carboxylic acids and $POCl_3$ were used to prepare an ester intermediate **(16)** from substituted-2-hydroxyacetophenone **(12)** (Scheme 3), followed by treating ester **(16)** with KOH in dry pyridine to form 1.3 diones **(17).** Cyclization of 1.3 diones **(17)** under reflux using ethanoic acid to afford 2-substituted chromone **(18).**[16.]




12 16 17 18

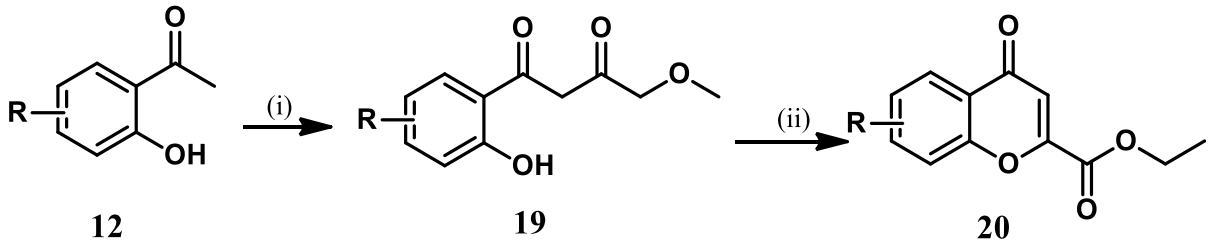
**$R^1$=Halogen**
**$R^2$=Alkyl, phenyl, benzyl**

*Reagents*: (i) RCOOH, $POCl_3$, (ii) KOH, piperidine, (iii) $CH_3COOH$, reflux

**Scheme 3**: Baker-Venkataraman rearrangement reaction

### 1.3.3 Kostanecki-Robinson reaction

The Kostanecki-Robinson reaction (Scheme 4) is a synthetic method for chromones that involves the condensation of substituted 2-hydroxyacetophenones **(12)** with a particular ester diethyl oxalate and treated with NaOEt in EtOH, followed by cyclization of 1,3-dioxophenoxy intermediate **(19)** under acidic conditions to form compound **(20)** analogues**.** Compounds (**20)** may be hydrolysed to form the corresponding chromone-2-carboxylic acids.[17]




**12** **19** **20**

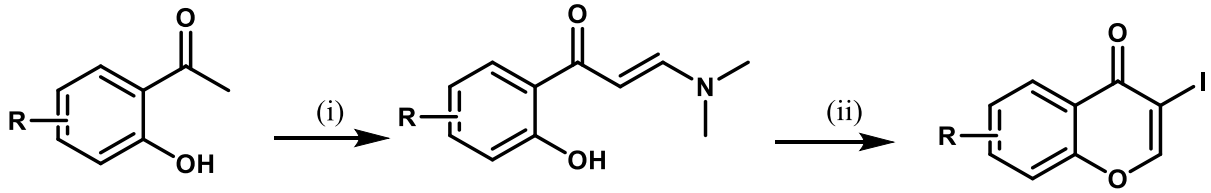
**R= Halogens, Alkyl**

*Reagents*: (i) Diethyl oxalate, NaOEt, EtOH, (ii) $H_2SO_4$

**Scheme 4**: Kostanecki-Robinson reaction

### 1.3.4 Gammill's Protocol

In this synthesis (Scheme 5), compound **(21)** was formed by condensation of substituted-2-hydroxyacetophenones **(12)** with DMF-DMA. Cyclization of compound **(21)** to form 3-halochromones **(22)**, which acts as precursor for isoflavones synthesis**.**[18.]




**12** **21** **22**

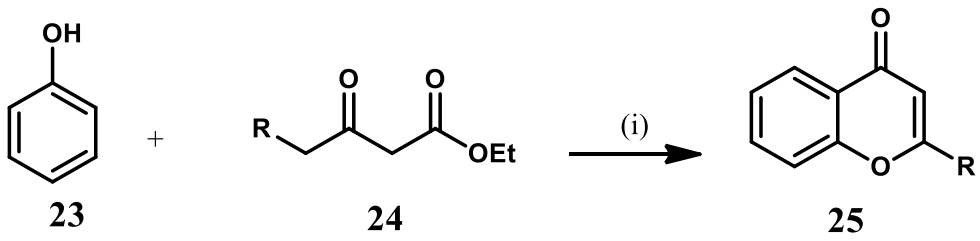
**R= Halogen, Alkyl, Aryl**

*Reagents*: (i) DMF-DMA, (ii) $I_2$, $CHCl_3$

**Scheme 5**: Gammill's protocol

### 1.3.5 Simonis Reaction

The Simonis synthesis of chromones (Scheme 6) involves phenols **(23)** and β-keto ester (**24)** in the presence of condensing reagents such as phosphorus pentoxide or phosphoric acid to generate a chromone (**25).**[19.]




**23** **24** **25**

**R= alkyl**

*Reagents*: (i) $P_2O_5$

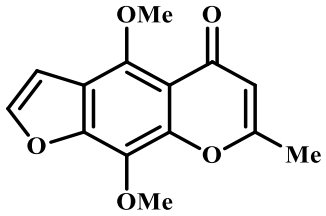
**Scheme 6**: Simonis reaction

## 1.4 Biological activities of chromones

Heterocyclic compounds have significant impact in the development of novel bioactive scaffolds. These compounds that contain oxygen with benzoannelated pyrone ring are some of the important compounds that belong to the flavonoid family.[20] The wide variety of bioactivities due to the chromone moiety has resulted in significant research focused on these compounds and subsequent evaluation of their biological activities to be targeted in medicinal applications .[21.]

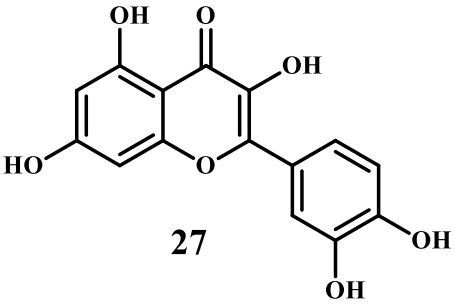
### 1.4.1 Biological activities of plant-based chromones

The first chromone isolated from the seed of the plant *Ammi visnaga* and utilized in clinical practice in pure form was khellin **(26).**[22] This plant grows worldwide, the eastern Mediterranean, and decoctions of its seeds have been used for centuries as a muscle relaxant, particularly for ureteric colic disorders.[23] This plant is also used in herbal medicine for different purposes such as kidney diseases and asthma.[24] Their side effects include liver dysfunction and allergic reactions. Khellin is used for the treatment of vitiligo.[25]



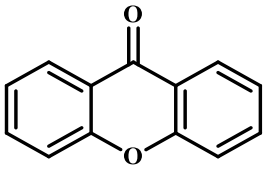

**26**

Quercetin **(27)** is one of the flavanols; most abundant bioflavonoids belong to the genus *Eriocaulon*, extracted from *Scutellaria baicalensis*, with the activity due to the presence of several hydroxyl groups.[26] It is a naturally occurring compound, that prevents the development of bacterial growth on the plant embryo.[27,28.]



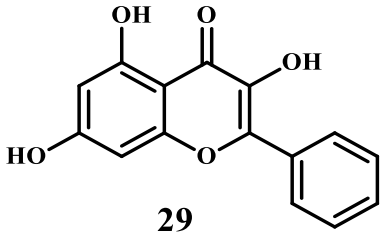

**27**

Xanthones **(28)** belong to naturally occurring heterocyclic compounds which contains oxygens and are characterized by a wide range of functional groups and have diverse pharmacological properties.[29] Their pharmacological activities are inhibitors of monoamine oxygenase enzymes, acting as anti-inflammatory, antioxidant, anti-ulcer agents, as bronchodilators in asthma treatment and other diseases.[30]




**28**

Galangin **(29)** is a naturally occurring compound that is abundant in *Alpinia officinarum and Helichrysum aureonitens* and in the rhizome of *Alpinia galanga*. Galangin has been shown to have in vitro antibacterial and antiviral activity. These compounds also inhibit the growth of breast tumour cells in vitro.[31]




29

### 1.4.2 Biological activities of synthesized chromones

Chromone derivatives are privileged compounds structures in medicinal chemistry, they have been recommended in several clinical drugs to be used.[32] The most applicable and current studies shows that chromones have various range of pharmacological applications such as anti-cancer agents, anti-HIV agents, anti-oxidants, anti-tuberculosis agents, and many others.[33]

#### *1.4.2.1 Anti-tuberculosis agents*

In this research project, novel 6,8-disubstituted chromone-3-carboxamide derivatives will be synthesized and evaluated as potential anti-tuberculosis agents.

*Mycobacterium tuberculosis*, which causes the infectious disease tuberculosis, spreads through the air, and typically affects the lungs.[34] Two million people die as results of this widespread heath problem annually.[35]

Various literature confirms that TB is amongst the highest leading cause of death worldwide and it is more lethal than HIV/AIDS.[36] Estimation by WHO was that TB presently affects one-third of people worldwide, with almost 10 % acquiring active TB during their lifetime. Every second, a new person becomes infected with tuberculosis, and every 15 minutes, another person dies from the disease. [37]

TB is a global health threat that affects everyone. In the past five years, Asia had the highest number of new tuberculosis cases with 62 %, followed by Africa with 25 %. India and China alone estimated 35 % of TB cases worldwide and developing countries account for 95 % of all TB cases.[38]

According to the WHO, there were 10.0 million new cases of tuberculosis in 2018, 1.2 million deaths from TB infection, and approximately 0.25 million people with HIV died because if TB.[39] Furthermore, estimated number of 0.5 million new cases of rifampicin-resistant tuberculosis, with 78% being multi-drug resistant tuberculosis.[40]

### *1.4.2.2 Types of tuberculosis*

The two types of tuberculosis are Active and Latent tuberculosis.

Latent tuberculosis is a condition in which you have tuberculosis, but the bacteria remain dormant in your body and cause no symptoms. Although latent tuberculosis is not contagious, it has the potential to become active.[41]

Active tuberculosis is a condition in which tuberculosis bacteria multiply in your body and the immune system fails to prevent the spread of the bacteria causing illness and the development of tuberculosis symptoms. Tuberculosis disease become extremely contagious once the lungs are infected with active tuberculosis. Active tuberculosis has four types which include pulmonary tuberculosis, extrapulmonary tuberculosis, MDR TB, and XDR TB.[42] When tuberculosis affects the lungs, it is known as pulmonary tuberculosis. Extrapulmonary tuberculosis infection can affect any organ in the body, but most commonly affects the lymphatic system, the genitourinary system, the bones, and the joints.[43] When tuberculosis is resistant to first-line drugs, it is said to be multi-drug resistant (INH and RIF). Extensively-drug resistant tuberculosis is defined as resistance to multi-drug resistant tuberculosis plus a fluoroquinolone, as well as at least one injectable second-line drug such as bedaquiline, levofloxacin, delamanid, linezoid and moxifloxacin. Drug resistance is difficult to treat and necessitates individualized care.[44]

### *1.4.2.3 Causes of tuberculosis*

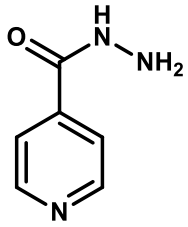
Tuberculosis is caused by a group of bacterial species which are closely related and is *mycobacterium tuberculosis* complex. The *Mycobacterium* tuberculosis complex consists of seven different strains, three of which are found in humans (*M. tuberculosis*, *M. africanum, and M. canetti*) and four of which are found in animals (*M. bovis, M. carprae, M. macroti, and M. pinnipedii*).[45] *M. bovis* is the leading cases of TB in cattle that occasionally affects other species of mammals. Human become infected by *Mycobacterium bovis* usually via milk, milk products or meat from infected animals.[46] *M. macrotia* typically causes disease voles, wood mice, and shrews, although it was also detected in a limited number of other mammalian species.[47] *M. caprae* was first isolated from goats in Spain but has been found in other animals such as cattle, pigs, red deer, and wild boars.[48]

### *1.4.2.4 Signs and Symptoms of tuberculosis*

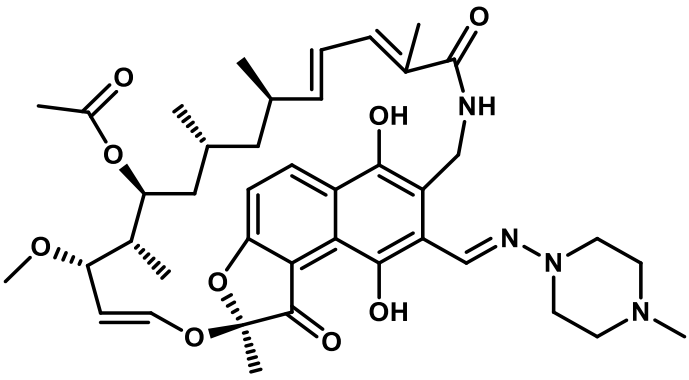
Many active tuberculosis symptoms are the direct result of extensive tissue damage caused by the bacteria in the lungs.[49] A bad dry cough that lasts for more than three weeks is a sign of active tuberculosis that may result in one coughing blood sputum. Other symptoms such as night sweat, fever, unexplained weight loss when the body attempts to fight with infection, loss of appetite, chills, chest pain or pain breathing and fatigue.[50]

### *1.4.2.5 Treatment of tuberculosis*

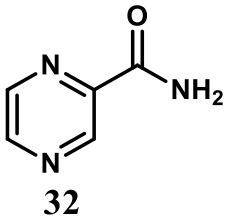
Isoniazid (**30**), rifampicin (**31**), pyrazinamide (**32**), and ethambutol (**33**) are the current first-line anti-tuberculosis medications that are recommended for use in a six-month regimen for new tuberculosis patients.[51] Treatments for tuberculosis are divided into two phases; the intensive phase, which lasts for the first two months, is when all four first-line medications are administered. The last four months are referred to as the continuation phase, and only rifampicin **(31)** and isoniazid **(30)** are used during this phase.[52]



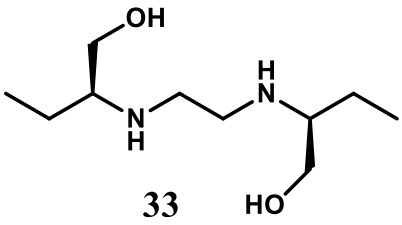

**30**
Isoniazid




**31**
Rifampicin




**32**
Pyrazinamide

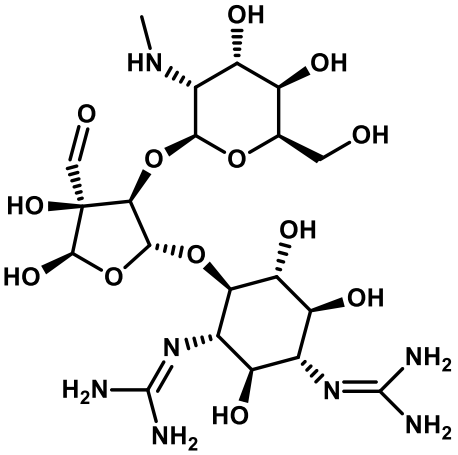



**33**
Ethambutol

The second-line drugs that are used for the treatment of *Mycobacterium tuberculosis* are classified as aminoglycoside, polypeptides, fluoroquinolones, and alternative anti-tuberculosis drugs.[53] The synthetic region mostly possessing a bacteriostatic activity, including the

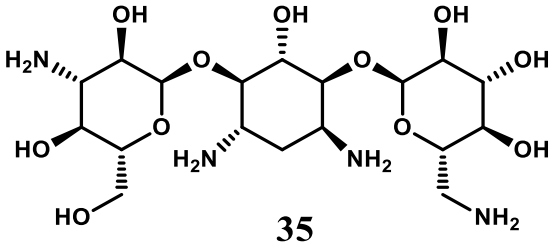
derivatives such as oxazolidinones, isoxazolidinones, thionamides, *para*-aminosalicylic acid and thioacetazone.[54]

Anti-tuberculosis aminoglycosides are based on spectrum of antibiotics isolated from *Streptomyces*.[55] The structure consists of a basic aglycon moiety, a mono or disaccharides attached by glycoside bonds. Streptomycin **(34)** is the second line anti-TB drug and the first antituberculosis agent to be discoved. [56] It is an aminocyclitol glycoside-based antibiotic which was isolated from the soil bacterium *Streptomyces griseus*. Kanamycin **(35)** and amikacin **(36)** are used for the treatment of rifampicin- and isoniazid-resistant *Mycobacterium tuberculosis*.[57]



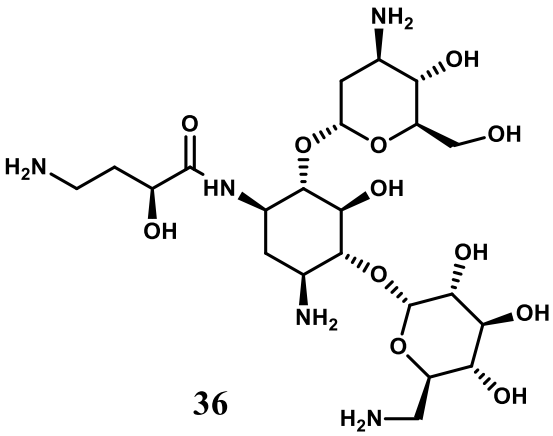

34

Streptomycin




35

Kanamycin

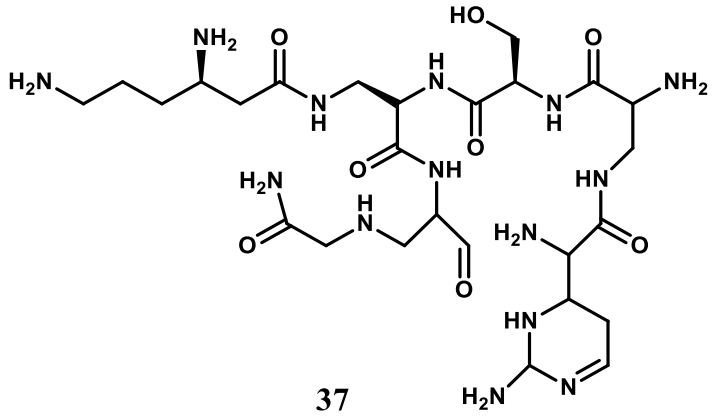



36

Amikacin

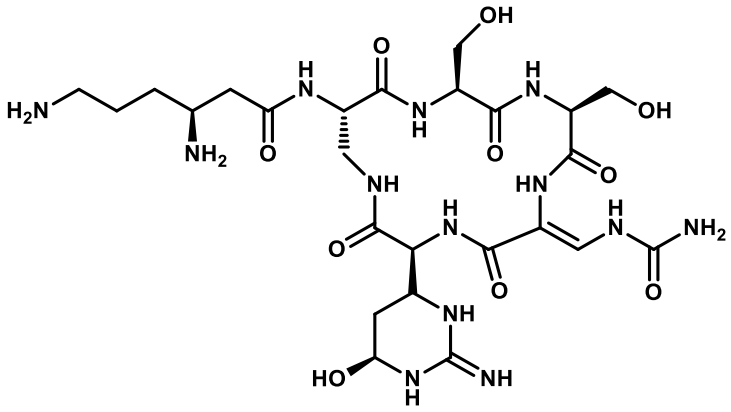
Capreomycin **(37)** and viomycin **(38)** are polypeptides for the treatment of tuberculosis, are also called tuberactinomycin are cyclic basic polypeptides antibiotics isolated from

*Streptomyces* species like aminoglycoside that inhibit protein synthesis and possess bacteriostatic activity.[58]



**37**

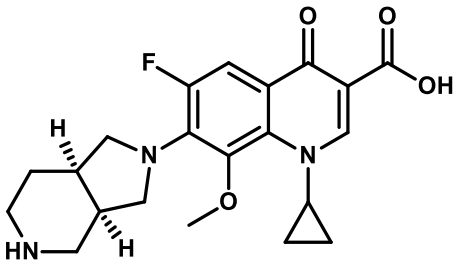
Capreomycin



**38**

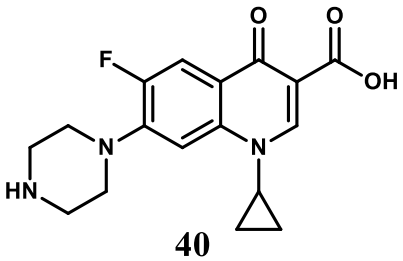
Viomycin

Fluoroquinolones is a class of nalidixic acid derivatives that contains fluorine and were introduced some 20 years ago.[59] They have become important drugs for the treatment of tuberculosis.[60] In order to prevent or reduce drug resistance, they have been recommended as a second-line treatment for tuberculosis in combination with other drugs. The anti-TB activity of moxifloxacin (**39**), ciprofloxin (**40**), and levofloxacin (**41**) have been shown to have a high efficacy against *Mycobacterium tuberculosis*. Ciprofloxacin has been found to be more effective than the other drugs in treating *Mycobacterium tuberculosis*.[61]



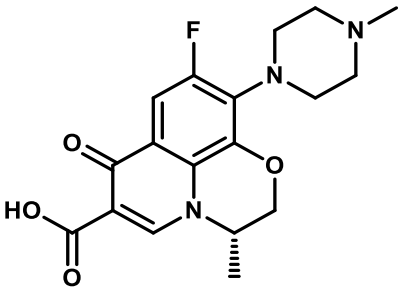

**39**

Moxifloxacin




**40**

Ciprofloxin




**41**

Levofloxacin

### *1.4.2.6 Drug resistance of tuberculosis*

There are two ways that drug-resistant TB might result, namely primary resistance and secondary resistance. When a person is first exposed to and infected with a resistant bacterium, primary resistance develops. The secondary resistance develops during TB treatment, either as a result of the patient receiving an insufficient regimen or failing to be following the recommended treatment plan, regimen as directed, or other conditions.[62.]

Drug-resistant tuberculosis is no more contagious and like to drug-resistant TB, it spreads by contact. Drug resistance or prolonged infectiousness, however, it could encourage increased transfer and subsequent drug resistance development.[63] The germs that produce MDR TB are resistant to the most efficient anti-TB drugs, such as INH and RIF. These drugs are examined first-line therapy and are used to treat patients with TB. XDR TB is comparatively rare type of drug-resistant tuberculosis. XDR TB is ineffective to INH and RIF, and any fluoroquinolone and a minimum one of three injectable second-line remedy (amikacin, kanamycin, or capreomycin). While first- and second-line drugs are ineffective against XDR TB, patients only have access to more harmful, more expensive, and much less effective therapeutic options.[64]

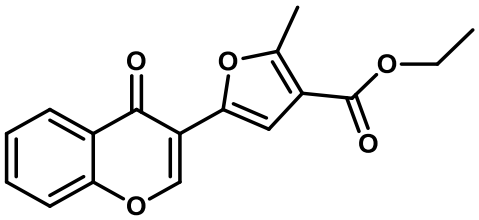
### *1.4.2.7 Elimination and control of tuberculosis*

Tuberculosis remains poorly controlled in many resources-limited settings while elimination is hard to achieve elsewhere in the world. Some of the measures to control TB, whenever you cough cover your mouth, as soon as you cough, or sneeze wash your hands.[65]The WHO have introduced various approaches to eliminate or reduce the burden of TB on the population. [66]

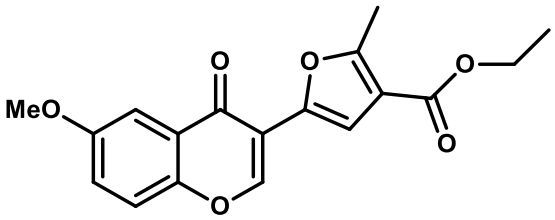
### 1.4.3 Chromones as potential candidates

The most applicable and current studies shows that chromones various pharmacological activities, including as anti-tuberculosis agents amongst others.[67]

Literature review showed that some of the chromones such as 3-(3-ethoxycarbonyl-2-methylfuran-5-yl)-chromones **(42)** and 6-methoxy-3-(3-ethoxycarbonyl-2-methylfuran-5-yl)-chromones **(43)** have exhibited an anti-tuberculosis activity.[68]

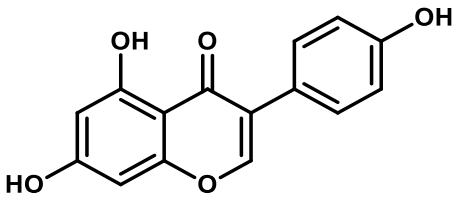



**42**

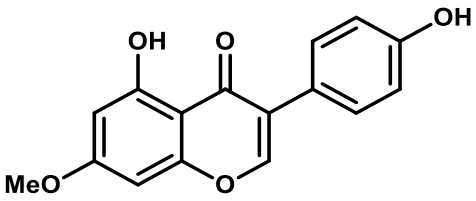



**43**

Genistein **(44)** and prunetin **(45)** have been used as medicine against asthma, coughs, and tuberculosis and they are also very effective against mycobacterium tuberculosis.[69]




**44**

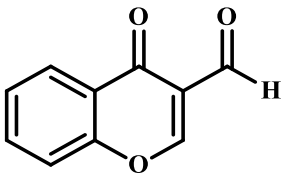



**45**

## 1.5 Chromone-3-carbaldehyde

Chromone-3-carbaldehydes **(46)** are a class of chromone derivatives distinguished by the aldehyde group at C-3 position being modified by the insertion of an aldehyde functional

group.[58] Chromone-3-carbaldehydes show significant biological activities such as anti-HIV and anti-malarial.[70] These compounds served as components that make up the synthesis of many heterocyclic compounds with medicinal applications.[71]



**46**

### 1.5.1 Properties of Chromone-3-carbaldehydes

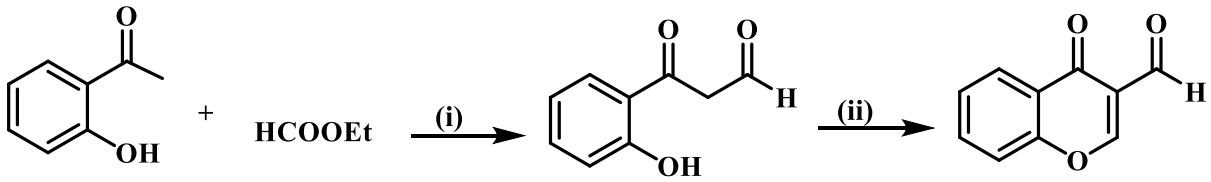
Given that there are three electron-deficient sites at C-2, the carbon of the aldehyde group (HC=O), and the carbon of the carbonyl group C-4, chromone-3-carbaldehydes are highly reactive compounds. Chromone-3-carbaldehyde can behave as both a dienophile and a Michael acceptor or a heterodiene, and fused heterocycles can be produced immediately through reaction of 3-(2-hydroxy-phenyl)-3-oxopropanal with bifunctional nucleophiles.[72]

### 1.5.2 Synthesis of Chromone-3-carbaldehydes

Chromone-3-carbaldehydes have previously been synthesized in low to good yields (40 -60 %) by reacting 2-formyl-2-hydroxyacetophenones with ethyl orthoformate and acetic anhydride. In contrast, the synthesis of chromone-3-carbaldehydes from 2,2-difluoro-4-methylnaphtho-1,2,3-dioxaborin compounds has also been reported in very good yields (82 -90 %).[73.]

#### *1.5.2.1 Claisen Condensation*

Eiden and Haverland synthesized chromone-3-carbaldehyde using the condensation (Scheme 7) of 2-hydroxyacetophenone **(47)** and ethyl orthoformate **(48)** to form 3-(2-hydroxy-phenyl)-3-oxopropanal **(49),** which is subsequently subjected to treatment with ethyl orthoformate to afford chromone-3-carbaldehyde **(46).**[74.]



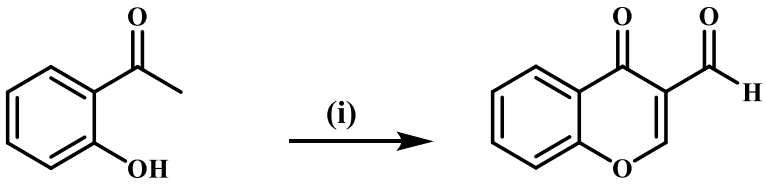

**47** **48** **49** **46**

*Reagents*: (i) Na; (ii) $HC(OEt)_3$, $Ac_2O$.

**Scheme 7**: Claisen condensation reaction

### *1.5.2.2 Vilsmeier-Haack Reaction*

Aldehydes, C-2, and C-4 carbons in the carbonyl group are examples of electron-deficient locations that are available, chromone-3-carbaldehyde derivatives are the commonly used synthons in heterocyclic synthesis with various biological activities; a good biological activity and simple synthesis by Vilsmeier-Haack formylation in good yields.[75] The Vilsmeier-Haack reaction (Scheme 8) is the best route for the synthesis of chromone-3-carbaldehydes. This synthesis of Vilsmeier-Haack reaction involves condensation of 2-hydroxyacetophenones with $POCl_3$ and DMF.[76]



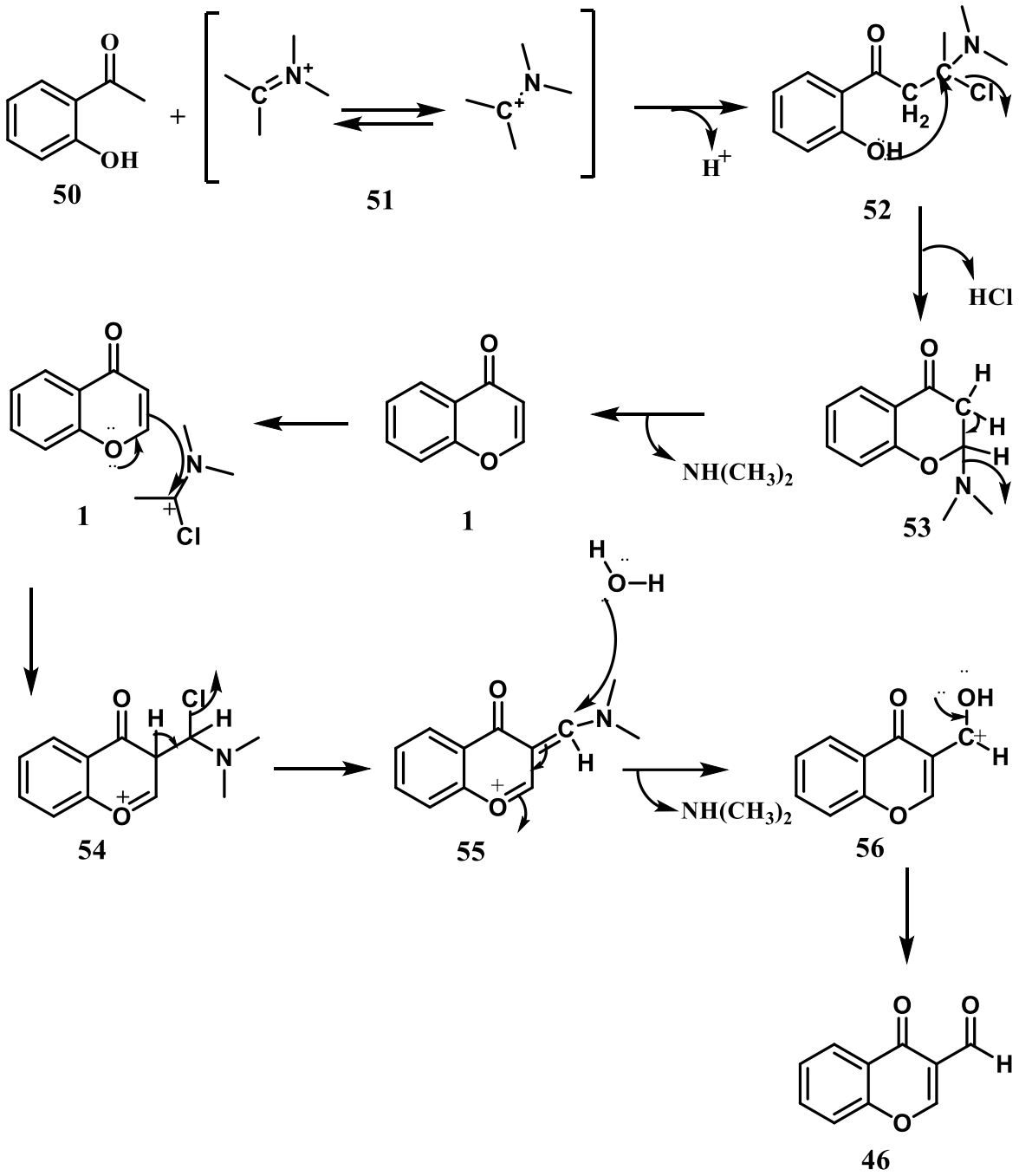

**50** **46**

*Reagents:* (i) $POCl_3$, DMF.

**Scheme 8**: Vilsmeier-Haack reaction

### 1.5.3 Mechanism of synthesis of chromone-3-carbaldehydes

In the synthesis of chromone-3-carbaldehydes, the mixture of DMF and $POCl_3$ produces a chloroiminium ion, a carbon electrophile (Scheme 9). The functional group in DMF reacts with $POCl_3$ except for the production of the strong phosphorus-oxygen bond, which removes the amide oxygen and replaces it with chlorine atom. The iminium cation then reacts with the acetophenone enolate, which is produced by protonation of the carbonyl oxygen. This results in the formation of a chromen-4-one, which reacts with another iminium cation to form a cationic intermediate. Following hydrolysis and proton transfer, a formyl group is added to position 3 of the chromone ring, yielding chromone-3-carbaldehyde.[77]




**Scheme 9**: Mechanism of chromone-3-carbaldehyde synthesis from 2-hydroxyacetophenone.

# CHAPTER 2 PROBLEM STATEMENT

TB is still a serious global health issue and one of the deadliest human pathogens with millions of new infections annually. [78]

According to the WHO annual TB report for 2021, 10 million new TB cases were reported, and 1.5 million people died from the disease. [79]

Mycobacterium tuberculosis, which causes TB, may be treated with isoniazid, rifampicin, pyrazinamide, and ethambutol. Unfortunately, as the ubiquity of MDR TB and XDR TB rises, these drugs are becoming less effective; thus, it is of high demand for the production of novel, active, and fast-acting tuberculosis treatments that are effective against both active and latent infection with minimal toxicity.[80]

The use of heterocyclic compounds, both natural and synthetic, is frequently used in the development of new drugs. Heterocyclic compounds, including flavones, isoflavones, chromones, coumarins, chromans, and others are crucial for developing new pharmacological entities with potential for therapeutic applications.[81]

There is an urgent need for the design and development of innovative chemical entities with promising anti-tuberculosis against TB given the severe global effects of this disease.[69] Chromone structures such as 3-(3-ethoxycarbonyl-2-methylfuran-5-yl)-chromones **(42),** genistein **(44),** and prunetin **(45)** have been synthesized and have shown good activity against anti-tuberculosis agents. Literature has thus confirmed that indeed chromones have potential to be investigated as lead compounds for novel anti-tuberculosis drug development.[82]

# CHAPTER 3 AIM AND OBJECTIVES

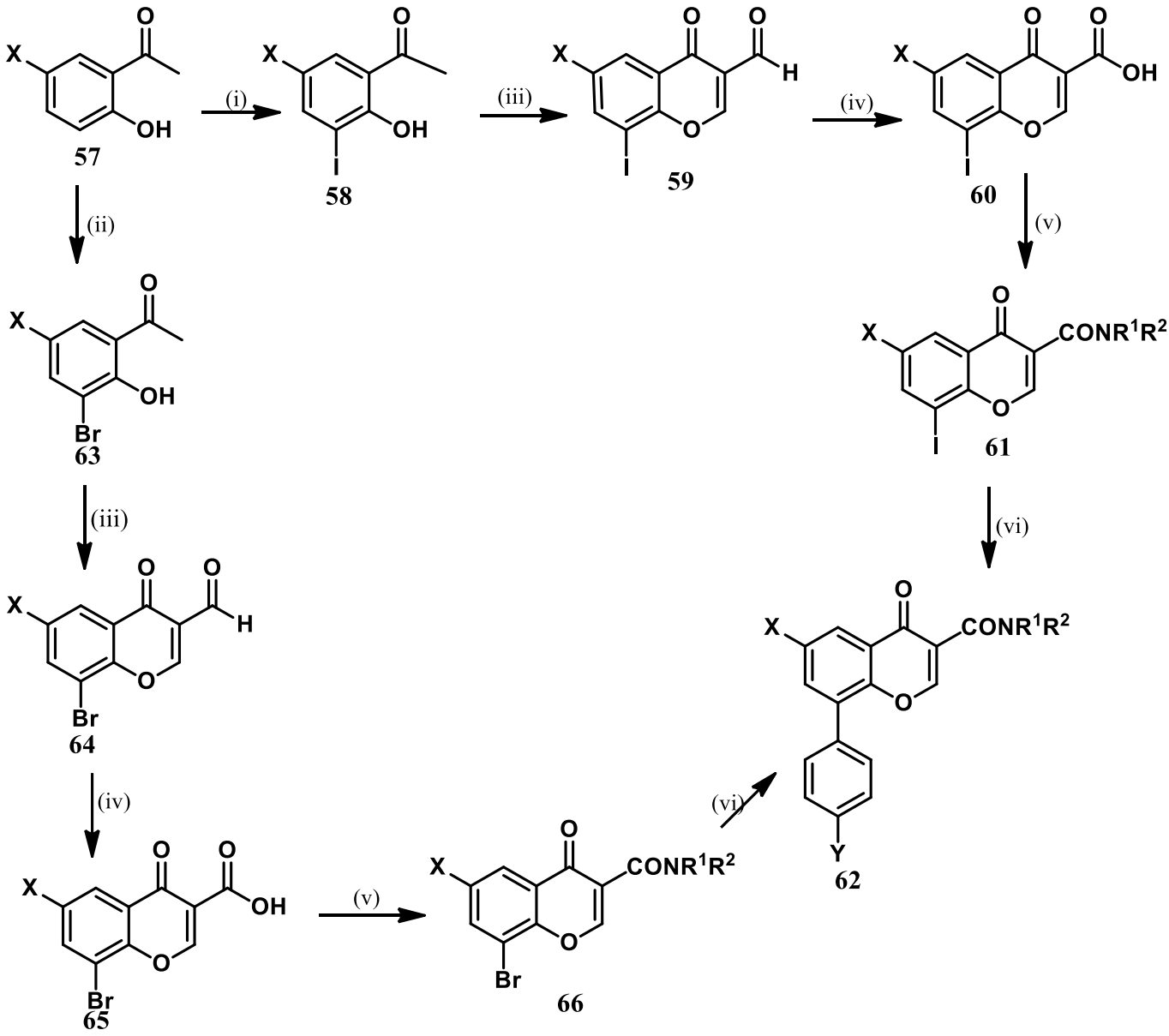
The main aim of the research project was to synthesize novel 6,8-disubstituted chromone-3-carboxamide derivatives and their evaluation as potential anti-tuberculosis agents.

The study had the following objectives:

- To synthesize 3-iodo-5-substituted 2-hydroxyacetophenones.
- To synthesize 8-iodo-6-substituted chromone-3-carbaldehydes.
- To synthesize 8-iodo-6-substituted chromone-3-carboxylic acids.
- To synthesize novel 6,8-disubsituted chromone-3-carboxamide derivatives.
- Suzuki cross coupling at position 8 of 6,8-disubstituted chromone-3-carboxamide derivatives
- To characterize the synthesized compounds using $^{1}H$ and $^{13}C$ NMR, FTIR and MS spectroscopic techniques.
- Biological screening of target compounds as potential anti-tuberculosis agents.

# CHAPTER 4 RESULTS AND DISCUSSION

In this project, novel 6,8-disubstituted chromone-3-carboxamide derivatives were synthesized as potential anti-tuberculosis agents. The proposed synthetic methodology is presented in Scheme 10. The first step involved the iodination of 5-substituted 2-hydroxyacetophenones **(57),** which were treated with NIS-AcOH to form 3-iodo-5-substituted 2-hydroxyacetophenones **(58)** and the bromination of 5-substituted-2-hydroxyacetophenones **(57)** in the presence of NBS-MeOH to form 3-bromo-5-substituted 2-hydroxyacetophenones **(63).** The 8-iodo-6-substituted chromone-3-carbaldehydes **(59)** and 8-bromo-6-substituted chromone-3-carbaldehyde derivatives **(64)** were synthesized by condensing the corresponding 3-iodo-5-substituted- 2-hydroxyacetophenenes **(58)** and the corresponding 3-bromo-5-substituted 2-hydroxyacetophenones (**63)** with DMF-$POCl_3$. The conversion of 8-iodo-6-substituted chromone-3-carbaldehydes **(59)** and 8-bromo-6-substituted chromone-3-carbaldehydes **(64)** to 8-iodo-6-substituted chromone-3-carboxylic acids **(60)** and the corresponding to 8-bromo-6-substituted chromone-3-carboxylic acids **(65)** was achieved by using sodium chlorite and sulfamic acid. These acids were then converted to 8-iodo-6-substituted chromone-3-carboxamides **(66)** and 8-bromo-6-substituted chromone-3-carboxamide derivatives **(61)** via acid chloride synthesized by treatment with thionyl chloride and triethylamine in dichloromethane. The 6,8-disubstituted chromone-3-carboxamide derivatives **66** and **61** were subjected to Suzuki cross coupling reaction at position 8 with phenylboronic acids, palladium catalyst and a base to form 8-phenyl-6-substituted chromone-3-carboxamides derivatives **(62).** The target compounds will be tested for biological activities to determine if they could be employed as anti-tuberculosis drugs. All synthesized compounds were characterized by $^{1}H$ and $^{13}C$ NMR and FTIR spectroscopic techniques.




*Where* X = H, Br, $NO_2$, F, Cl, $OCH_3$ $R^1R^2 = O(CH_2CH_2)_2NH$, $(CH_3)_2NH$

Y= H, Br, I

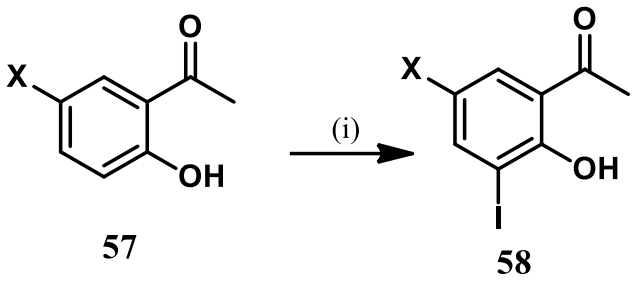
*Reagents and conditions* (i) NIS, AcOH, (ii) NBS, MeOH (iii) DMF- $POCl_3$, (iv) $NaClO_2$, Sulfamic acid, (v) $SOCl_2$, $Et_3N$, DCM, (vi) $C_6H_7BO_2$, Pd catalyst.

**Scheme 10**: Proposed Synthetic Scheme

## 4.1 Iodination of 5-substituted 2-hydroxyacetophenones (58A-D)

The reactions were conducted for the iodination of 5-substituted 2-hydroxyacetophenones **(57A-D)** to form 3-iodo-5-substituted 2-hydroxyacetophenones

(Scheme 11) by dissolving and stirring the mixture of 5-substituted 2-hydroxyacetophenone **(57A-D)** and *N*-iodosuccinimide in acetic acid. After that, the solution was heated under reflux for two hours and quenched with ice water, filtered, and recrystallized with ethanol to afford the product of interest. The 5-substituted-2-hydroxyacetophenones reactions were successful except for the 5-methoxy-2-hydroxyacetophenone.




**57** **58**

***Where X* = Br, I, Cl, F.**

*Reagents*: NIS, AcOH, reflux, 2h

**Scheme 11:** Iodination of 5-substituted 2-hydroxyacetophenones **(57A-D).**

**Iodination of 5-bromo-2-hydroxyacetophenone 58A)**

The 5-bromo-2-hydroxy-3-iodoacetophenone **(58A)** was synthesized by stirring the mixture of 5-bromo-2-hydroxyacetophenone **(57A)** and *N*-iodosuccinimide in acetic acid. After that, the solution was refluxed for 2 hours, then poured into ice water. The resulting precipitate were filtered, dried, and recrystallised by ethanol to obtain 5-bromo-2-hydroxy-3-iodoacetophenone **(58A)**. The synthesized compounds were characterized by using proton and carbon NMR and FTIR spectroscopic techniques as shown in Figures **5**, **6**, and **7**, respectively. All compounds synthesized are shown in Table **1**, with good yields of the average percentage of 60 % and the meting points correspond to the literature reported values.

The $^{1}$H NMR spectra of 5-bromo-2-hydroxy-3-iodoacetophenone **(58A)** reveals four peaks as expected (Figure 5). The two peaks which account for two doublets on the aromatic region corresponding to two protons at benzene ring, the first doublet resonates at 8.19 ppm and corresponds to 4-H proton and the other doublet which resonate at 8.12 ppm accounting for 6-H proton. The singlet peak downfield resonates at 12.96 ppm and was assigned as OH proton and another singlet resonate at 2.69 ppm which corresponds to $CH_3$ protons. The $^{1}$H NMR spectrum confirmed the formation of 5-bromo-2-hydroxy-3-iodoacetophenone **(58A).** These

peaks have also been observed in 3-iodo-5-substituted 2-hydroxyacetophenones**(58A-D)** synthesized.

The $^{13}C$ NMR spectrum (Figure 6, Table 2)) shows eight peaks as was expected from the structure. The carbon at around 205.19 ppm which is the carbonyl carbon (C=O). The carbon at around 159.72 ppm which assigned for C-2, carbon at around 146.86 ppm for C-4, carbon at 134.28 ppm corresponding to C-6, carbon at around 121.07 ppm which account for C-5 and carbon at around 111.36 ppm corresponding to C-1. The $^{13}C$ NMR spectra shows the carbon that shows the formation of iodine at position 3 and was around 88.83 ppm accounting for C-3. The carbon signal at 27.42 ppm correspond to $CH_3$ carbon. The $^{13}C$ NMR spectrum has thus confirmed the formation of 5-bromo-2-hydroxy-3-iodoacetophenone since all peaks have been accounted for. All peaks have also been accounted for the 3-iodo-5-substituted 2-hydroxyacetophenones **(58B-D)** synthesized.

The IR spectrum shows a wavelength at around 3057.44 $cm^{-1}$ for an OH group, a band at 1634.72 $cm^{-1}$ for a carbonyl group (C=O), and a band at 650.62 $cm^{-1}$ for carbon with halogen (C-I) as shown in Figure 7. The same bands were also observed with 3-iodo-5-substituted 2-hydroxyacetophenones **(58B-D).** However, the ($^{1}H$ and $^{13}C$) NMR and FTIR spectroscopic results show that 5-methoxy-2-hydroxy-3-iodoacetophenone **(58E)** was not successfully synthesized as expected, although different conditions in terms of time and methods have been attempted.

**Table 1: Iodination of 5-substituted-2-hydroxyacetophenones (58A-D)**

| Compound 58 | X | Yields (g) | % Yields | Melting points (°C) | Lit. Melting points (°C) |
|---|---|---|---|---|---|
| **A** | **Br** | **1.63** | **76** | **96.4-98.3** | **105** [83] |
| **B** | **Cl** | **0.96** | **58** | **88.5-90.5** | **89** [83] |
| **C** | **F** | **1.53** | **55** | **101.4-105.5** | **-** |
| **D** | **I** | **2.42** | **66** | **125.8-127.6** | **125-127** [84] |

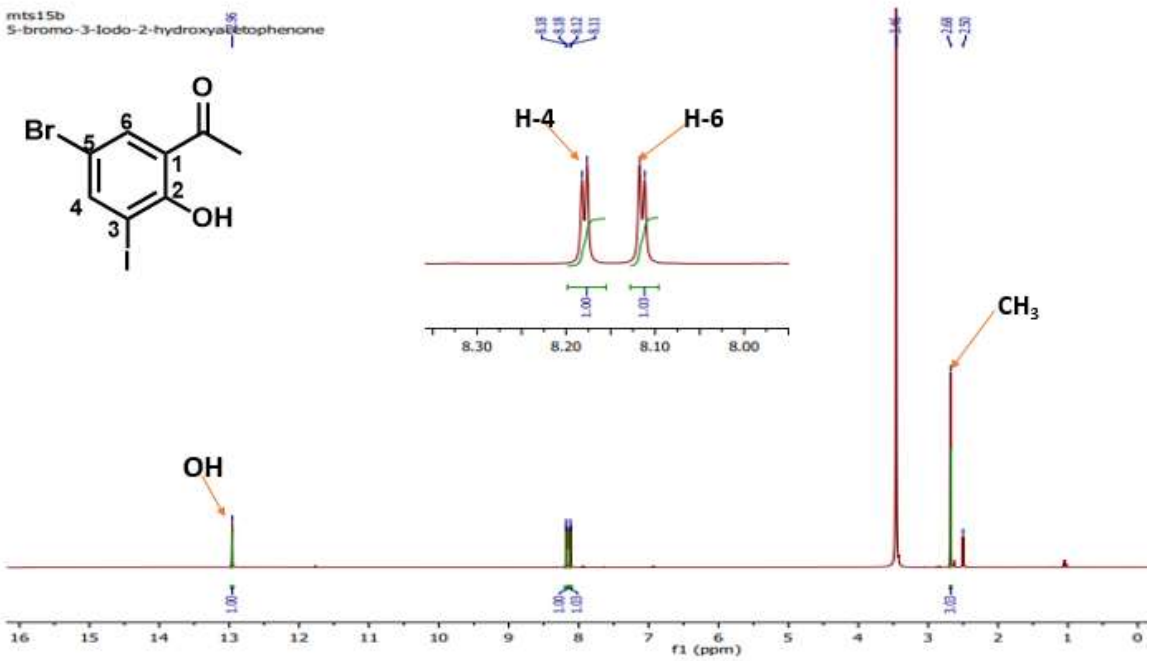



**Figure 5**: 400 MHz $^{1}$H NMR spectrum of 5-bromo-2-hydroxy-3-iodoacetophenone **(58A)** in DMSO-$d_6$

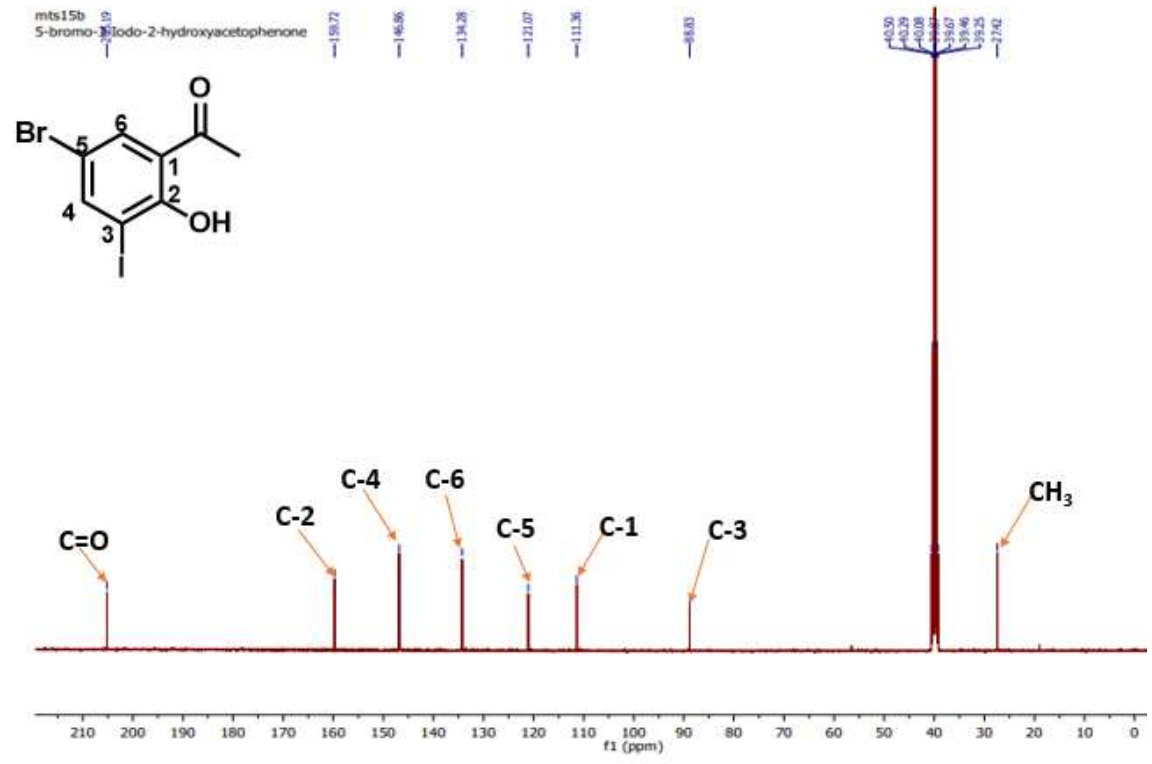



**Figure 6**: 100 MHz $^{13}$ C NMR spectrum of 5-bromo-2-hydroxy-3-iodoacetophenone **(58A)** in DMSO-$d_6$

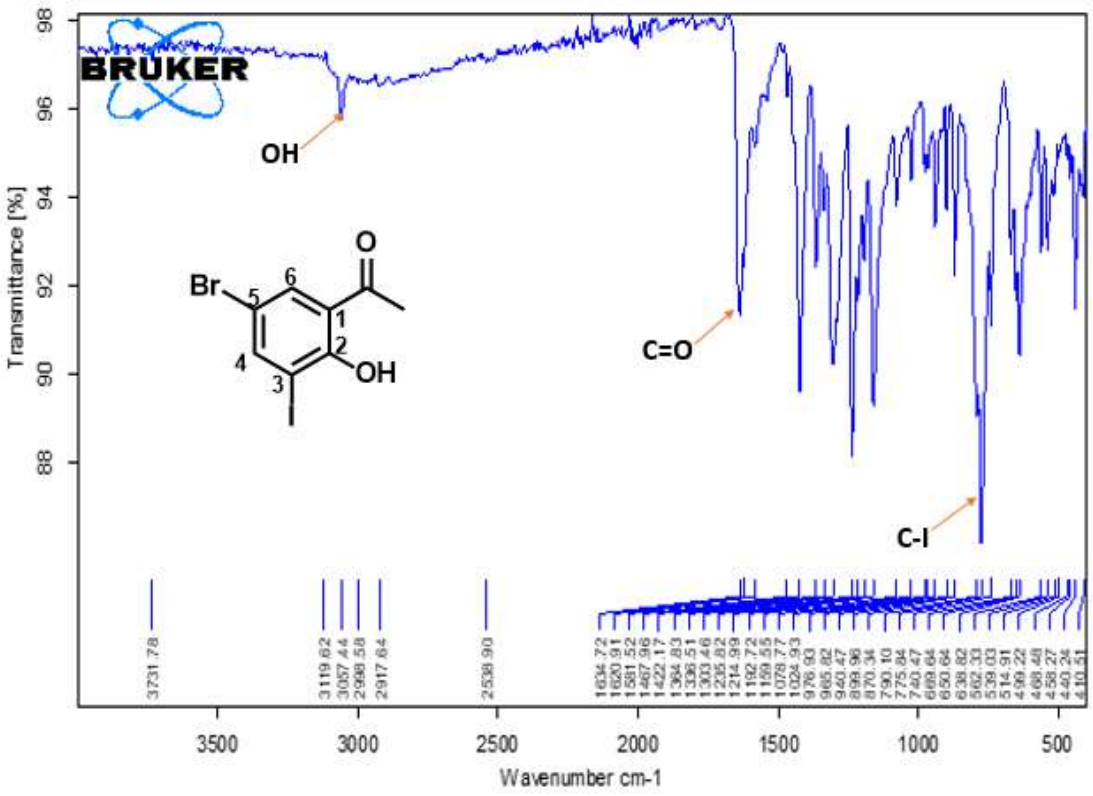
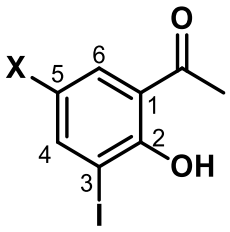



**Figure 7**: FTIR spectrum of 5-bromo-2-hydroxy-3-iodoacetophenone **(58A)**




**58**

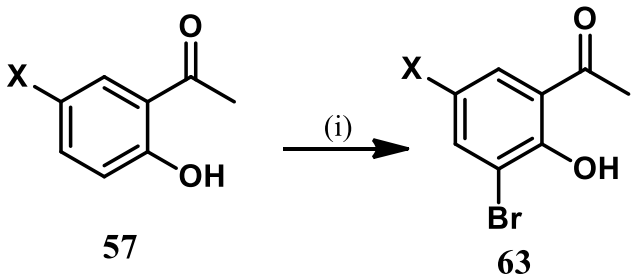
**Table 2: 100 MHz $^{13}$C NMR chemical shift values (ppm) of 3-iodo-5-substituted-2-hydroxyacetophenones (58A, B, C, and D) in DMSO-*d*$_6$**

| **Carbons** | **58A**<br>**X=Br** | **58B**<br>**X=Cl** | **58C**<br>**X=F** | **58D**<br>**X=I** |
|---|---|---|---|---|
| C=O | 205.19 | 205.22 | 205.17 | 205.14 |
| C-1 | 111.36 | 120.36 | 117.84 | 121.89 |

| | | | | |
|---|---|---|---|---|
| C-2 | 159.72 | 159.39 | 157.17 | 160.14 |
| C-3 | 88.83 | 88.37 | 87.26 | 82.69 |
| C-4 | 146.86 | 144,43 | 153.47 | 152.14 |
| C-5 | 121.07 | 124.05 | 119.19 | 89.28 |
| C-6 | 134.28 | 131.43 | 133.00 | 140.06 |
| $CH_3$ | 27.42 | 27.42 | 27.38 | 27.43 |

## 4.2 Bromination of 5-substituted 2-hydroxyacetophenones (63A-C)

The synthesis involves the bromination of 5-substituted-2-hydroxyacetophenones **(57A-C).** The reactions (Scheme 12, Table 3) were conducted for the bromination of 5-substituted 2-hydroxyacetophenones **(57A-C)** to form 3-bromo-5-substituted 2-hydroxyacetophenones (**63A-C**) by dissolving 5-substituted 2-hydroxyacetophenones **(57A-C)** and *N*-bromosuccinimide in methanol. The mixture was then stirred at room temperature for 3 hours before being quenched with water, filtered, and dried to afford the expected products. All reactions conducted were successful except for the bromination of 5-methoxy-2-hydroxyacetophenone **(63D**) although different conditions and methods were attempted. The synthesized compounds were characterized and confirmed using proton and carbon NMR and FTIR spectroscopic techniques.




**57** **63**

Where **X: Br, Cl, F.**

*Reagents*: NBS, MeOH, rt, 3h

**Scheme 12:** Bromination of 5-substituted-2-hydroxyacetophenones **(57A-C).**

3,5-Dibromo-2-hydroxyacetophenone **(63A)** was synthesized by dissolving 5-bromo-2-hydroxyacetopnenone **(57A)** and *N*-bromosuccinimide in methanol. The mixture was then stirred at room temperature for 3 hours, quenched with water, filtered, and dried to yield 3,5-dibromo-2-hydroxyacetophenone **(63A).** The synthesized compound was characterized by

proton and carbon NMR and FTIR as shown in figure **8**, **9**, and **10.** Table **2** below shows good yields with the average percentage of 71 % and the melting points corresponds to the literature reported.

In the $^{1}H$ NMR spectra of 3,5-dibromo-2-hydroxyacetophenone **(63A),** four peaks were observed (Figure 8); the two protons account for two doublets at aromatic region corresponding two protons on the benzene ring. The first doublet at 7.79 ppm account for 4-H and the other doublet at 7.75 ppm assigned for 6-H. The singlet observed downfield at 12.80 ppm which has the characteristic of OH proton and the other singlet at 2.59 ppm which correspond to $CH_3$ protons. The $^{1}H$ NMR spectrum data confirm the formation of 3,5-dibromo-2-hydroxyacetophenone **(63A).** These peaks have also been observed on the other 3-bromo-5-substituted 2-hydroxyacetphenones **(63B-C)** which have been synthesized.

The $^{13}C$ NMR spectra (Figure 9, Table 4) shows all peaks as were accounted for. The first peak observed was carbonyl carbon (C=O) at 203.34 ppm, carbon at 158.11 ppm assigned for C-2 with the OH group, carbon at 141.5 ppm which assigned for C-4, carbon at 132.20 ppm which correspond to C-6, and carbon at 121.14 ppm which correspond to C-1 carbon. The attachment of bromine at position 3 of $^{13}C$ NMR spectrum confirmed that the reaction did take place. The results demonstrate that the carbon at 113.20 ppm which correspond to C-3 is in agreement with the literature data. The carbon at 110.39 ppm which was assigned for C-5 and carbon at 26.77 ppm correspond to $CH_3$ carbon. The $^{13}C$ NMR spectrum data thus confirm the formation of 3,5-dibromo-2-hydroxyacetophenone. The peaks observed on the synthesized compounds have also been observed on other synthesized 3-bromo-5-substituted 2-hydroxyacetophenones **(63B-C).**

The IR spectra (Figure 10) shows a wavelength at around 3005.50 $cm^{-1}$ for the OH group, a band at around 1634.25 $cm^{-1}$ for the carbonyl group (C=O), and a band at 682.65 $cm^{-1}$ for (C-I) carbon with halogen as shown in Figure 3. The same bands were also observed with other 3-iodo-5-substituted 2-hydroxyacetophenones **(63B-C).** The NMR and FTIR spectroscopic results could not confirm the successful synthesis of 3-bromo-5-methoxy-2-hydroxyacetophenone **(63D).**

**Table 3: Bromination of 5-substituted 2-hydroxyacetophenones (63A-C)**

| Compound 63 | X | Yields (g) | % Yields | Melting points (°C) | Lit. Melting points (°C) |
|---|---|---|---|---|---|
| A | Br | 2.68 | 86 | 103.4 -105.2 | 105-107 [85] |

| | | | | | |
|---|---|---|---|---|---|
| **B** | **Cl** | **1.54** | **68** | **109.3 -111.5** | **112** [85] |
| **C** | **F** | **1.85** | **66** | **95.8 -99.4** | **97** [86] |

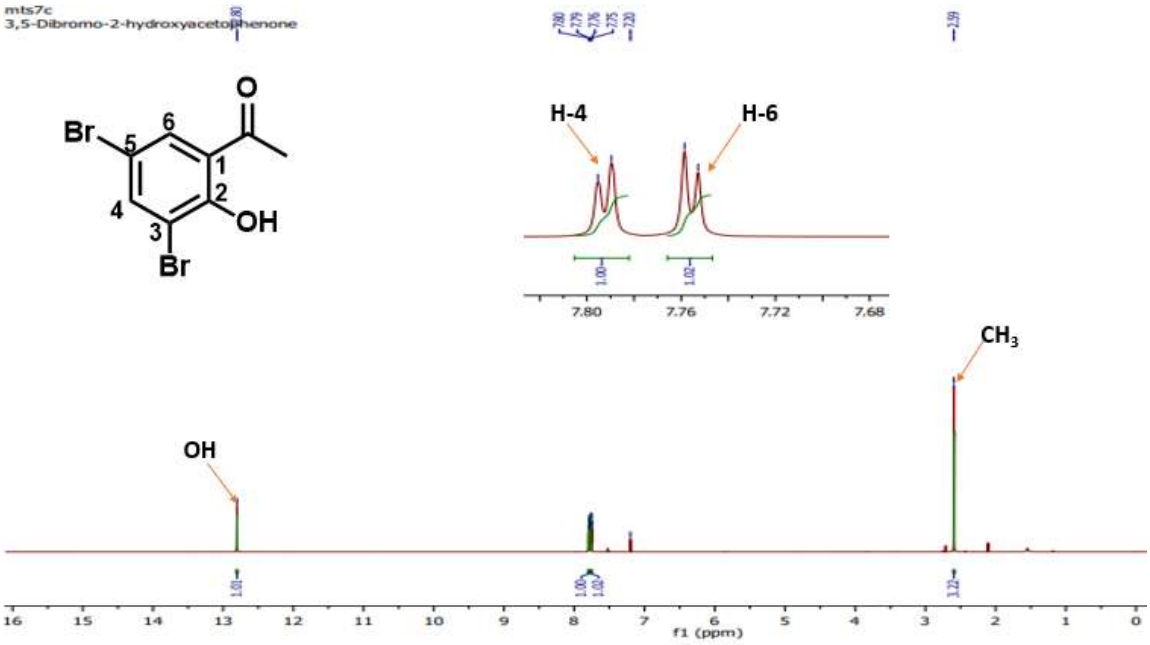



**Figure 8**: 400 MHz $^{1}$H NMR spectrum of 3,5-dibromo-2-hydroxyacetophenone (**63A)** in $CDCl_3$

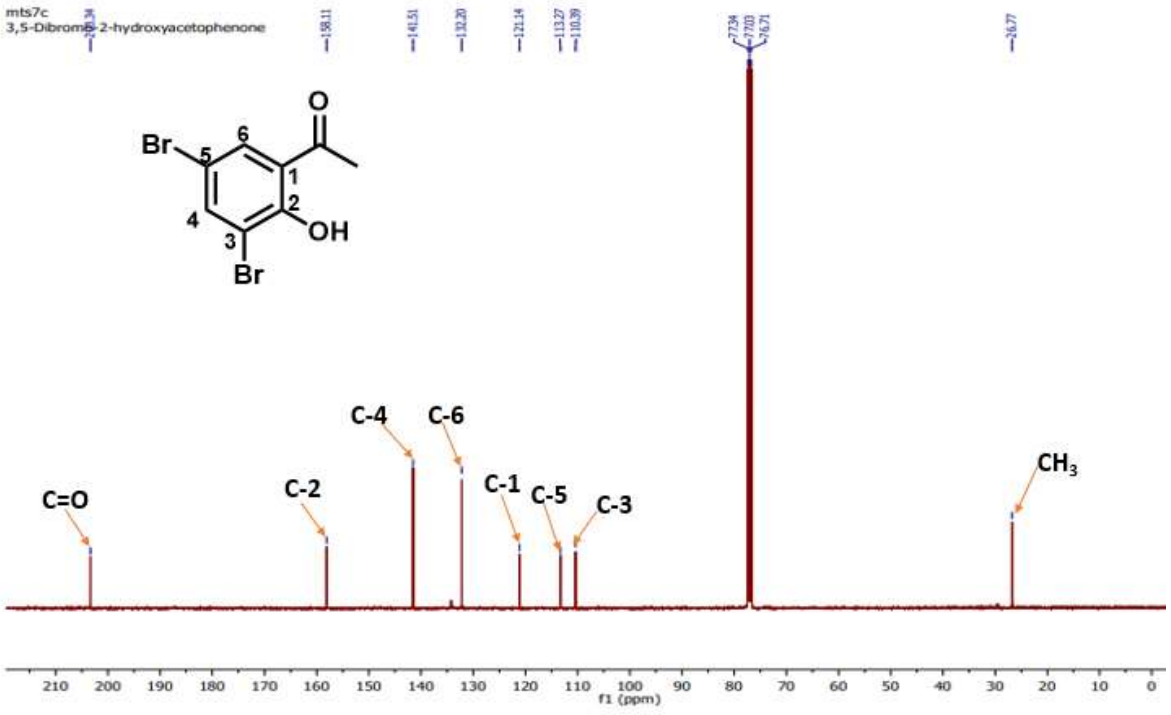



**Figure 9**: 100 MHz $^{13}C$ NMR spectrum of 3,5-dibomo-2-hydroxyacetophenone **(63A)** in $CDCl_3$

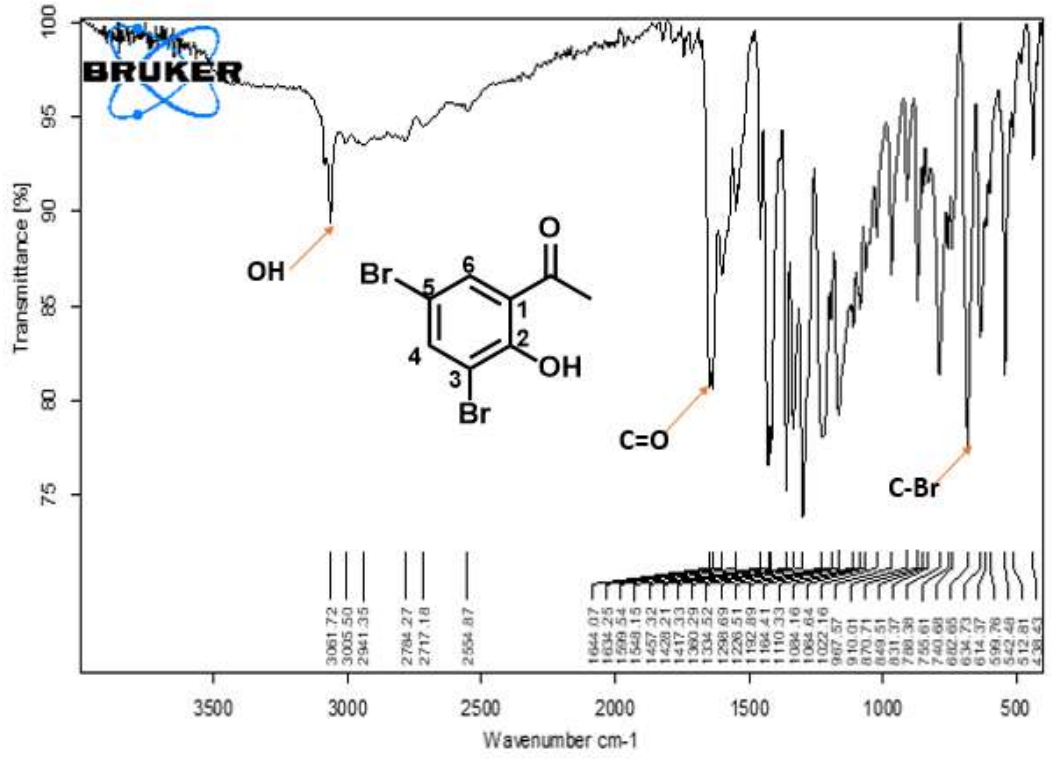
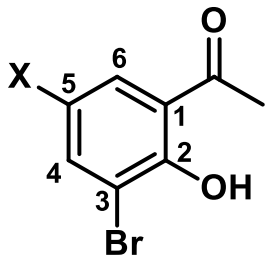



**Figure 10**: FTIR spectrum of 3,5-dibromo-2-hydroxyacetophenone **(63A)**



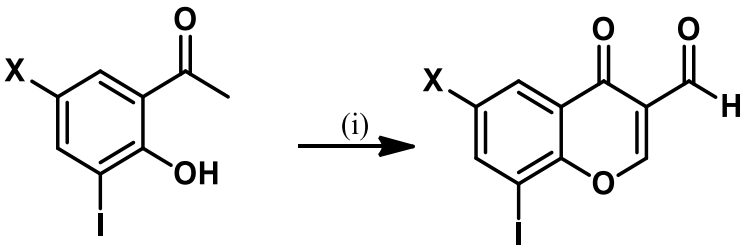

63

**Table 4: 100 MHz $^{13}C$ NMR chemical shift values (ppm) of 3-bromo-5-substituted 2-hydroxyacetophenones (63A, B, and C) in $CDCl_3$**

| **Carbons** | **63A**<br>**X=Br** | **63B**<br>**X=Cl** | **63C**<br>**X=F** |
|---|---|---|---|
| C=O | 203.34 | 203.42 | 203.40 |
| C-1 | 121.14 | 123.83 | 119.24 |
| C-2 | 158.11 | 157.67 | 155.56 |
| C-3 | 110.39 | 112.91 | 112.30 |
| C-4 | 141.51 | 138.93 | 152.85 |
| C-5 | 113.27 | 120.45 | 115.30 |
| C-6 | 132.20 | 129.21 | 127.19 |
| $CH_3$ | 26.77 | 26.77 | 26.79 |

## 4.3 Synthesis of 8-iodo-6-substituted chromone-3-carbaldehydes (59A-D)

A series of 6,8-disubstituted chromone-3-carbaldehydes **(59A-D)** were prepared using the Vilsmeier-Haack reaction (Scheme 13, Table 5). The 3-iodo-5-substituted 2-hydroxyacetophenones **(58A)** were treated with $POCl_3$ in anhydrous DMF at 0 °C for 0.5 h in ice cold water. After cooling to room temperature, the solution was stirred for 12 hours, then quenched on ice cold water, to form solid crystals that was collected through filtration, then dried and recrystallized from ethanol to obtain 8-iodo-6-substituted chromone-3-carbaldehydes **(59A-D).**




58 59

Where X=Br, F, Cl, I

*Reagents and conditions*: DMF, $POCl_3$, $H_2O$, 0-25˚C,12h

**Scheme 13:** Synthesis of 8-iodo-6-substituted chromone-3-carbaldehydes **(59A-D)**

**The synthesis of 6-bromo-8-iodochromone-3-carbaldehyde (59A)**

The reaction was conducted by mixing 5-bromo-2-hydroxy-3-iodoacetophenone **(58A)** were treated with $POCl_3$ in anhydrous DMF at 0 °C for 0.5 h in ice cold water. After cooling to room temperature, the solution was stirred for 12 hours, then quenched on ice cold water, to form solid crystals that was collected through filtration, then dried and recrystallized from ethanol to obtain 8-iodo-6-bromochromone-3-carbaldehydes **(59A).** The synthesized compounds were characterized by proton and carbon NMR and FTIR spectroscopic techniques as shown in Figure **11**, **12**, and **13** below. Table **3** below, shows good yields from 86- 90 % and their melting points.

The $^{1}$H NMR spectrum (Figure 11) of 6-bromo-8-iodochromone-3-carbaldehyde **(59A)** shows four proton peaks. Two singlets which correspond to the formyl proton and methine proton. The formation of those two singlets also confirms that the structure formed, the carbaldehyde proton (CHO) at 10.27 ppm and methine proton (C-2) at 8,54 ppm. The presence of two doublets was also observed at the aromatic region, first doublet at 8.32 ppm which assigned for H-7 proton and another doublet at 8.24 ppm was assigned for H-5 proton. The $^{1}$H NMR spectroscopy data confirmed the formation of 6-bromo-8-iodo-chromone-3-carbaldehyde **(59A).**

From the $^{13}$C NMR spectrum (Figure 12, Table 6) ten carbon peaks observed as was expected. The first three peaks from the spectra confirm the formation of carbaldehyde, peak at 187.71 ppm corresponds to the aldehyde carbon, the pyrone carbon at around 174.42 ppm which corresponds to C-4, and carbon at 160.74 ppm for C-2. Carbon at 154.34 ppm corresponding to C-8a, Carbon at 146.62 ppm which was assigned for C-7, carbon at 129.11 ppm for C-5,

carbon at 126.91 ppm which correspond to C-4a. The carbon at around 120.90 ppm correspond to C-3, carbon at 120.07 ppm which correspond to C-6, and lastly carbon at 86.55 ppm for C-8 carbon. The $^{13}C$ NMR spectra confirm the formation of 6-bromo-8-substituted-chromone-3-carbaldehyde **(59A).** These peaks have also been observed with other 8-iodo-6-substituted chromone-3-carbaldehydes **(59D)** synthesized.

The 6-bromo-8-iodochromone-3-carbaldehyde **(59A)** was also confirmed by IR spectroscopy (Figure 13). The carbonyl stretches (C=O) of the pyrone ring that corresponds to C-4 was detected at 1668.42 $cm^{-1}$, and the other carbonyl stretch was detected at 1695. 35 $cm^{-1}$ corresponding to aldehyde (HC=O)

**Table 5: Synthesis of 8-iodo-6-substituted chromone-3-carbaldehydes (59A-D)**

| Compound 59 | X | Yield (g) | % Yield | Melting points (°C) | Lit. Melting points (°C) |
|---|---|---|---|---|---|
| **A** | **Br** | **1.72** | **90** | **137.8-141.6** | **-** |
| **B** | **Cl** | **0.47** | **78** | **154.8-162.4** | **-** |
| **C** | **F** | **1.24** | **86** | **186.7-191.2** | **-** |
| **D** | **I** | **1.20** | **88** | **156.4-161.2** | **-** |

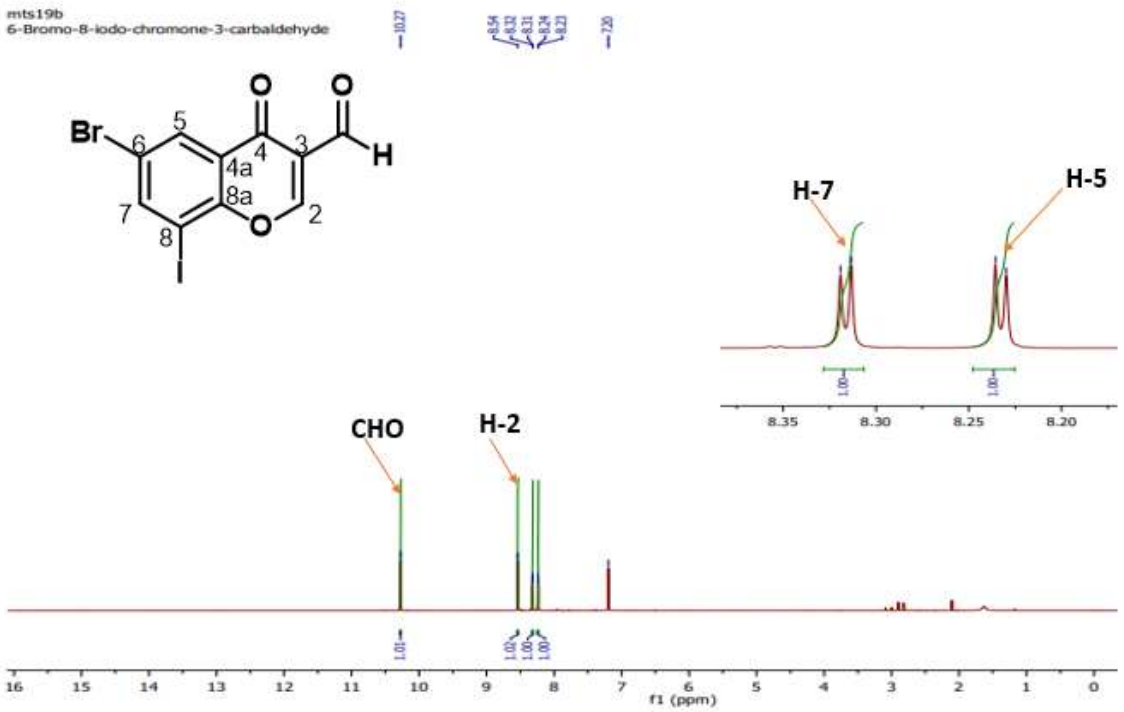


**Figure 11**: 400 MHz $^{1}H$ NMR spectra of 6-bromo-8-iodochromone-3-carbaldehyde **(59A)** in $CDCl_3$

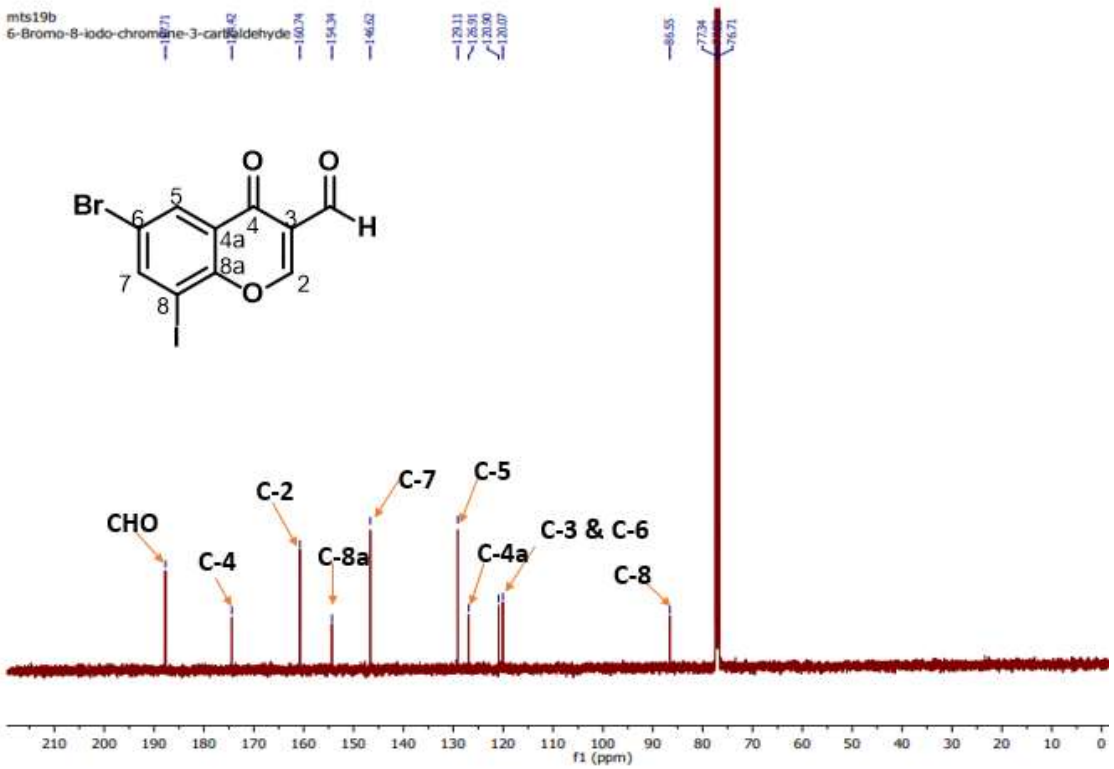



**Figure 12**: 100 MHz $^{13}C$ NMR spectra of 6-bromo-8-iodochromone-3-carbaldehyde **(59A)** in $CDCl_3$

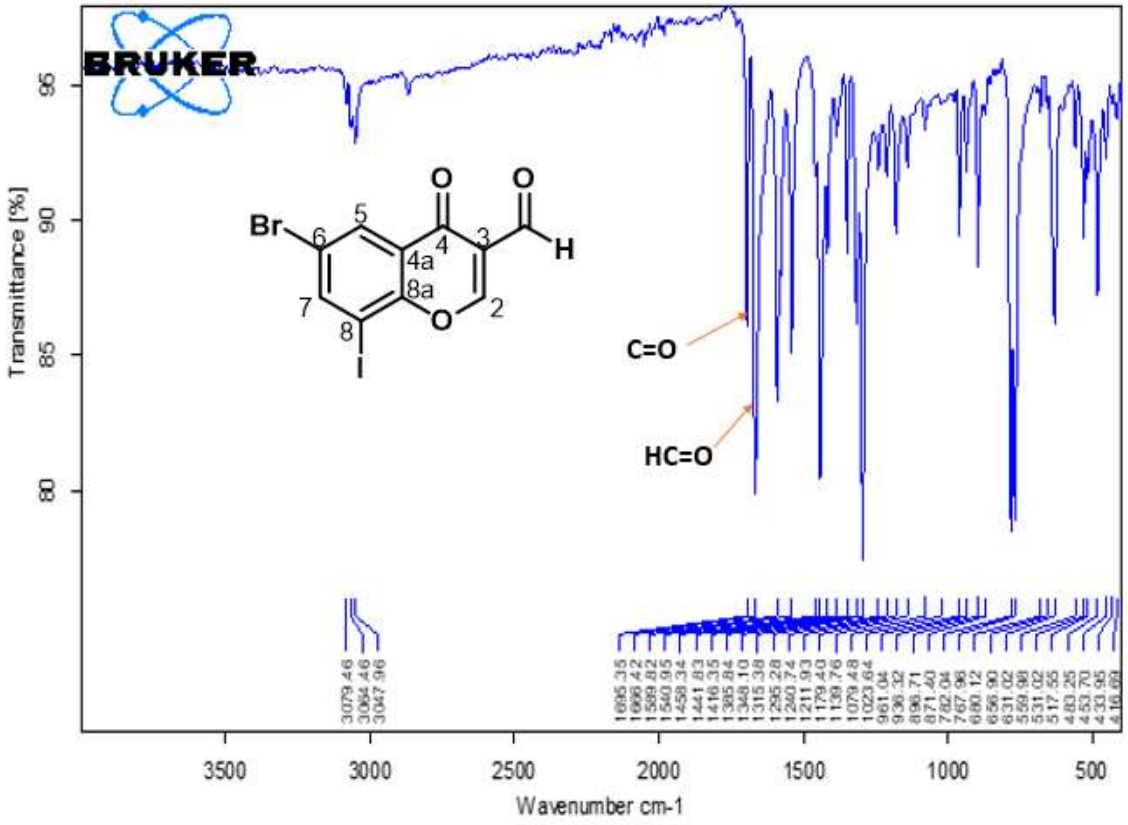
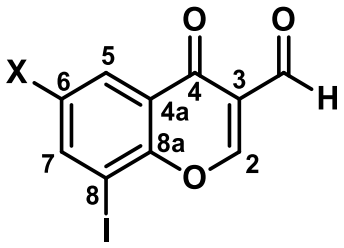



**Figure 13**: FTIR spectrum of 6-bromo-8-iodochromone-3-carbaldehyde **(59A)**




**59**

**Table 6: 100 MHz $^{13}$C NMR chemical shift values(ppm) of 8-iodo-6-substituted chromone-3-carbaldehydes (59A, B, C, and D) in $CDCl_3$ and DMSO-$d_6$**

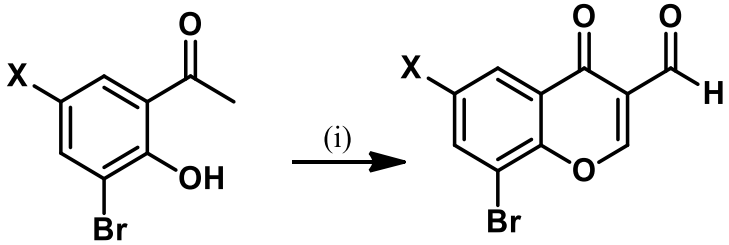
| **Carbons** | **59A X=Br** | **59B X=Cl** | **59C X=F** | **59D X=I** |
|---|---|---|---|---|
| CHO | 187.71 | 188.36 | 187.74 | 188.42 |
| C-2 | 160.74 | 164.50 | 160.77 | 164.44 |
| C-3 | 120.90 | 124.88 | 119.31 | 120.44 |
| C-4 | 174.42 | 174.15 | 174.85 | 173.93 |
| C-4a | 126.91 | 126.45 | 126.76 | 127.15 |
| C-5 | 129.11 | 132.17 | 132.72 | 134.09 |
| C-6 | 120.07 | 120.14 | 111.90 | 93.27 |
| C-7 | 146.42 | 143.64 | 151.97 | 151.38 |
| C-8 | 86.55 | 89.93 | 86.02 | 90.21 |
| C-8a | 154.34 | 154.22 | 158.51 | 155.04 |

## 4.4 Synthesis of 8-bromo-6-chloro-chromone-3-carbaldehyde (64A)

The reaction (Scheme 14) was carried out by mixing 3-bromo-5-chloro-2-hydroxyacetophenone **(63A)** were treated with $POCl_3$ in anhydrous DMF at 0 °C for 0.5 h in ice cold water. After cooling to room temperature, the solution was stirred for 12 hours, then quenched on ice cold water, to form solid crystals that was collected through filtration, then dried and recrystallized from ethanol to obtain 8-bromo-6-chlorochromone-3-carbaldehydes **(64A).** The compound was characterized by proton and carbon NMR and FTIR spectroscopic as shown in figure **14, 15,** and **16** below. Table **7** shows good percentage yields with the average of 87 % and their melting points.

The $^1$H NMR spectrum (Figure 14) of 8-bromo-6-chlorochromone-3-carbaldehyde **(64A)** shows four proton peaks. Two singlets were observed which corresponds to the formyl proton and methine proton. The formation of those two singlets also confirms that indeed reaction was successful. The first singlet shows the signal at 10.27 ppm and confirms the formation of the aldehyde proton, the other singlet for methine proton at around 8.52 ppm corresponds to C-2. The two doublets, both observed at the aromatic region of a benzene ring. The first doublet at 8.13 ppm assigned for H-7 proton and another doublet at 7.88 ppm assigned for H-5 proton.

The same protons peaks also observed on the other 8-bromo-6-substituted-chromone-3-carbaldehyde derivatives **(64B-C)** synthesized.




**63** **64**

Where X=Br, F, Cl

*Reagents and conditions*: DMF, $POCl_3$, $H_2O$, 0-25˚C,12h

**Scheme 14**: Synthesis of 8-bromo-6-substututedchromone-3-carbaldehydes **(64A-C)**

**Table 7: Synthesis of 8-bromo-6-substituted chromone-3-carbaldehydes (64A-C)**

| Compound 64 | X | Yields (g) | %Yields | Melting points (°C) | Lit. Melting points (°C) |
|---|---|---|---|---|---|
| **A** | **Cl** | **1.24** | **87** | **164.5-168.2** | **-** |
| **B** | **Br** | **1.06** | **86** | **175.5-178.2** | **174-176** [87] |
| **C** | **F** | **1.21** | **85** | **126.2-132.6** | **-** |

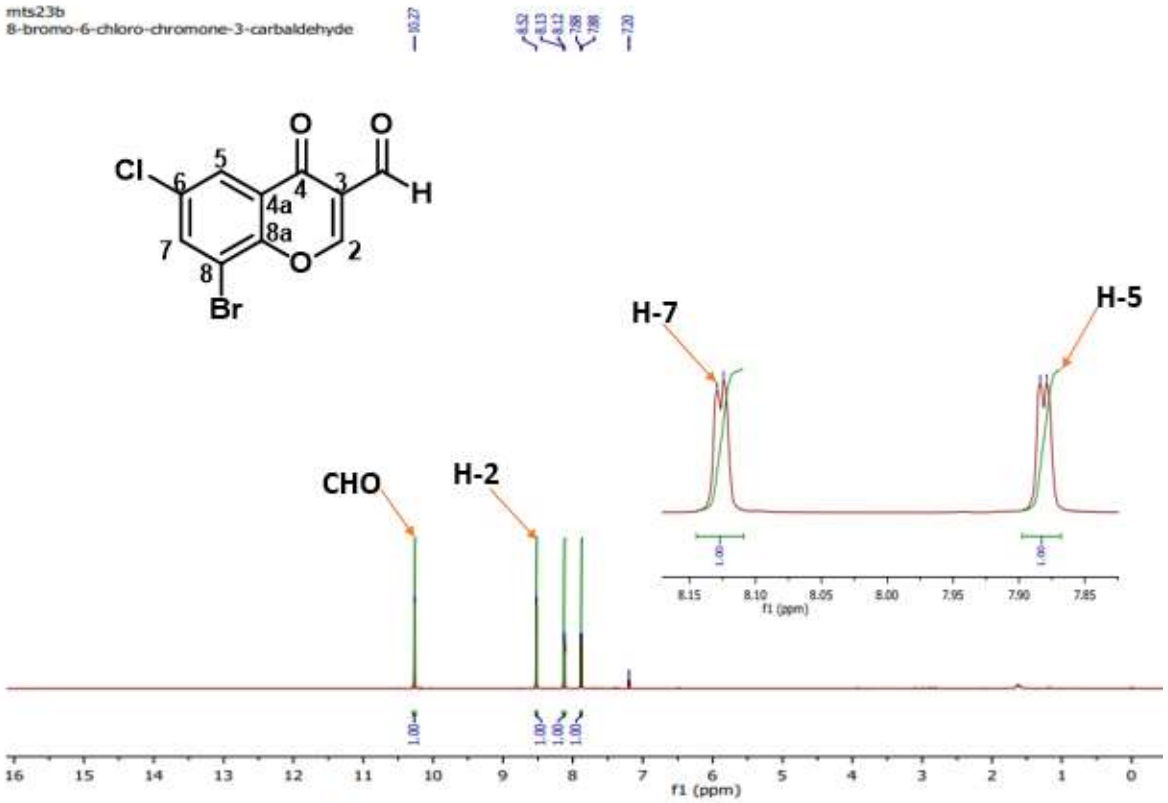



**Figure 14**:400 MHz $^{1}H$ NMR spectrum of 8-bromo-6-chlorochromone-3-carbaldehyde **(64A)** in $CDCl_3$

In the $^{13}C$ NMR spectrum (Figure 15, Table 8), ten peaks were observed. The first peaks from the spectra confirm the formation of carbaldehyde. The aldehyde carbon at 187.57 ppm assigned for CHO, the pyrone carbon at 174.26 ppm correspond to C-4, and the carbon at 160.52 ppm corresponds to C-2. The carbon at 151.88 ppm corresponds to C-8a, carbon at 137.97 ppm which corresponds to C-7, carbon at 132.98 ppm which corresponds to C-6, carbon at 129.17 ppm correspond to C-5, carbon at 124.96 ppm which correspond to C-4a, carbon at 120.18 ppm assigned for C-3, and the last carbon at 113.31 ppm which correspond to C-8. The $^{13}C$ NMR spectra confirm the formation of 8-bromo-6-chlorochromone-3-carbaldehyde. The same peaks have also been observed with other 8-bromo-6-substituted chromone-3-carbaldehyde derivatives **(64B-D)** synthesized.

The 8-bromo-6-chlorochromone-3-carbaldehyde **(64A)** was also further confirmed by FTIR spectroscopy (Figure 16). The carbonyl vibration stretches on the pyrone ring which corresponds to C-4 was observed at wavenumber 1670.84 $cm^{-1}$ and the other carbonyl band observed corresponds to aldehyde group (HC=O) at wavenumber 1694.84 $cm^{-1}$.

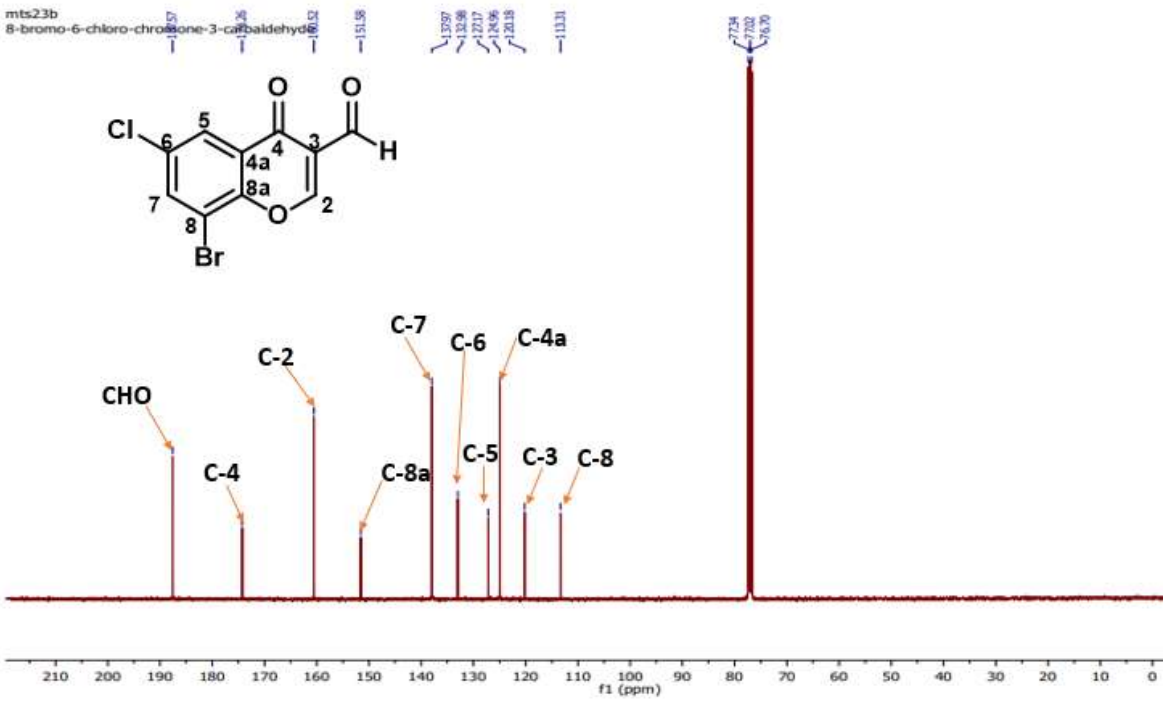



**Figure 15**: 100 MHz $^{13}C$ NMR spectrum of 8-bromo-6-chromone-3-carbaldehyde **(64A)** in $CDCl_3$

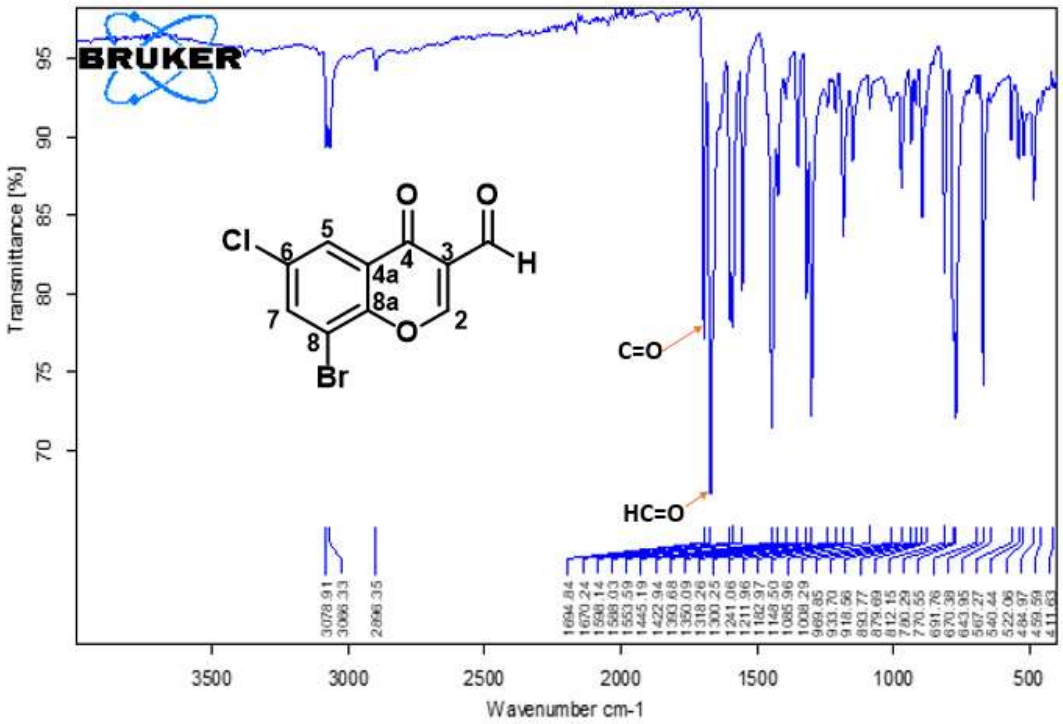
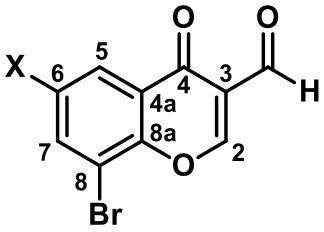



**Figure 16**: FTIR spectrum of 8-bromo-6-chlorochromone-3-carbaldehyde **(64A).**



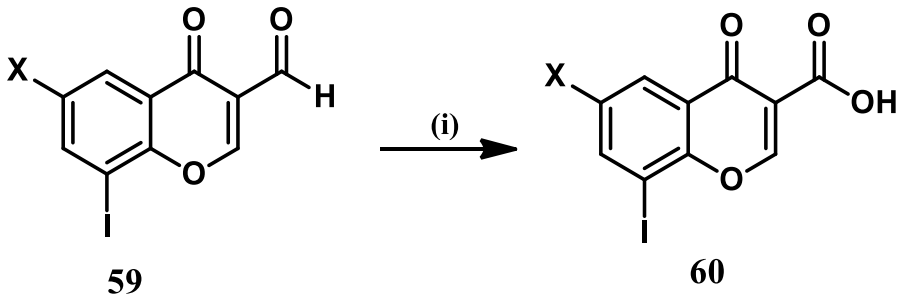

64

**Table 8: 100 MHz $^{13}$C NMR chemical shift values (ppm) of 8-bromo-6-substituted-chromone-3-carbaldehydes (64A, B, and C) in $CDCl_3$ and DMSO-$d_6$**

| **Carbons** | **64A**<br>**X=Cl** | **64B**<br>**X=Br** | **64C**<br>**X=F** |
|---|---|---|---|
| CHO | 187.57 | 188.37 | 187.75 |
| C-2 | 160.52 | 164.38 | 160.63 |
| C-3 | 120.18 | 119.62 | 113.43 |
| C-4 | 174.26 | 173.82 | 174.64 |
| C-4a | 124.96 | 120.55 | 119.53 |
| C-5 | 129.17 | 127.54 | 126.73 |
| C-6 | 132.98 | 127.73 | 127.43 |
| C-7 | 137.97 | 140.38 | 149.67 |
| C-8 | 113.31 | 113.93 | 111.00 |
| C-8a | 151.88 | 152.10 | 158.26 |

## 4.5 Synthesis of 8-iodo-6-substituted chromone-3-carboxylic acids

The synthesis of 8-iodo-6-substituted chromone-3-carboxylic acid **(60A-D)** derivatives (Scheme 15) was achieved by mixing 6,8-disubstituted chromone-3-carbaldehyde **(59A-D)** and sulfamic acid in dichloromethane stirred at 0 °C. Sodium chlorite in water was poured drop wise in an ice water bath at 0 °C. After cooling to room temperature, the solution was stirred for 3 hours, and water was added after the completion reaction. The resultant mixture was extracted with DCM, dried with anhydrous $MgSO_4$, and DCM was removed by a rotary evaporator to afford 8-iodo-6-substituted chromone-3-carboxylic acids **(60A-D).**[92.]




**59** **60**

Where X=H, Br, Cl, F, I

*Reagents and conditions*: $H_3NSO_3$, $NaClO_2$, $H_2O$, DCM, 0˚C,3h

**Scheme 15**: Synthesis of 8-iodo-6-substituted chromone-3-carboxylic acid **(60A)**

The chromone-3 carboxylic acids **(60A)** were characterized by $^{1}H$ and $^{13}C$ NMR, and FTIR spectroscopies as shown in Figures **17, 18,** and **19**. The chromone-3-carboxylic acid shows good percentage yield of around 57.48 % and the melting points corresponds to the literature melting points.[88]

The $^{1}H$ NMR spectra chromone-3-carboxylic acid **(60A)** shows six proton peaks. The OH peak couldn't be detected downfield probably due to hydrogen deuterium exchange. . The peak at 9.08 ppm which correspond to the H-2. The aromatic peaks were observed as four peaks. Two doublets account for the first doublet at 8.14 ppm corresponding to H-5 proton and another doublet at 7.76 ppm corresponding to 8-H proton. The first triplet at 7.92 ppm which corresponds to H-7 proton and the second triplet at 7.61 ppm corresponds to the H-6 proton.

In the $^{13}C$ NMR spectra, ten peaks were observed. The double peaks from the spectra confirm the carboxylic acid peak together with the C-2 peak at 164.47 and 164.41 ppm. The carbon at 176.79 ppm assigned for C-4, the carbon at 156.32 ppm corresponds to C-8a, and the carbon at 136.19 ppm corresponds to C-7. The carbon at 127.46 ppm corresponds to C-6, carbon at 126.03 ppm corresponds to C-5, carbon at 123.92 ppm corresponds to C-4a, carbon at 119.44 ppm corresponds to C-8. The last carbon at 114.94 ppm which corresponds to the C-3 carbon.

The chromone-3-carboxylic acid **(60A)** was also further confirmed by FTIR spectroscopy. The FTIR spectroscopy show the OH band at wavenumber 3066.91 $cm^{-1}$.

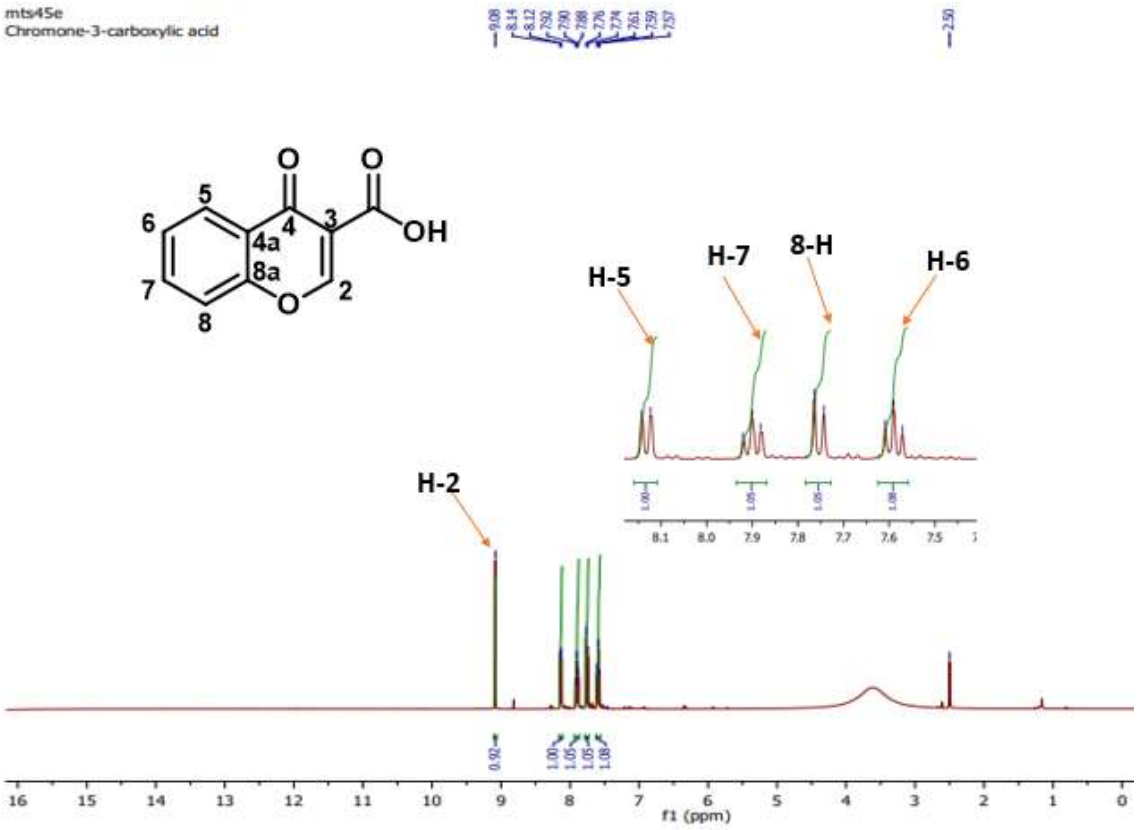



**Figure 17**: $^{1}$H NMR spectrum of chromone-3-caboxylic acid **(60A).**

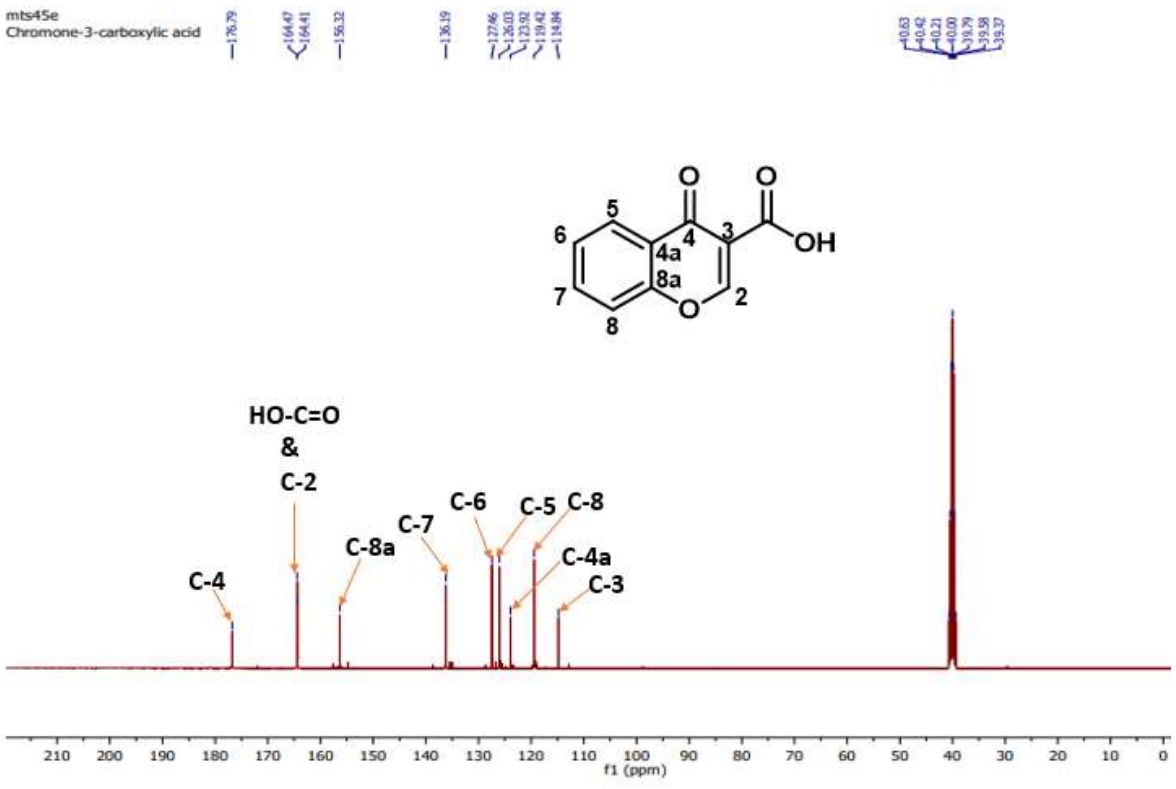



**Figure 18**: $^{13}$C NMR spectrum of chromone-3-carboxylic acid **(60).**

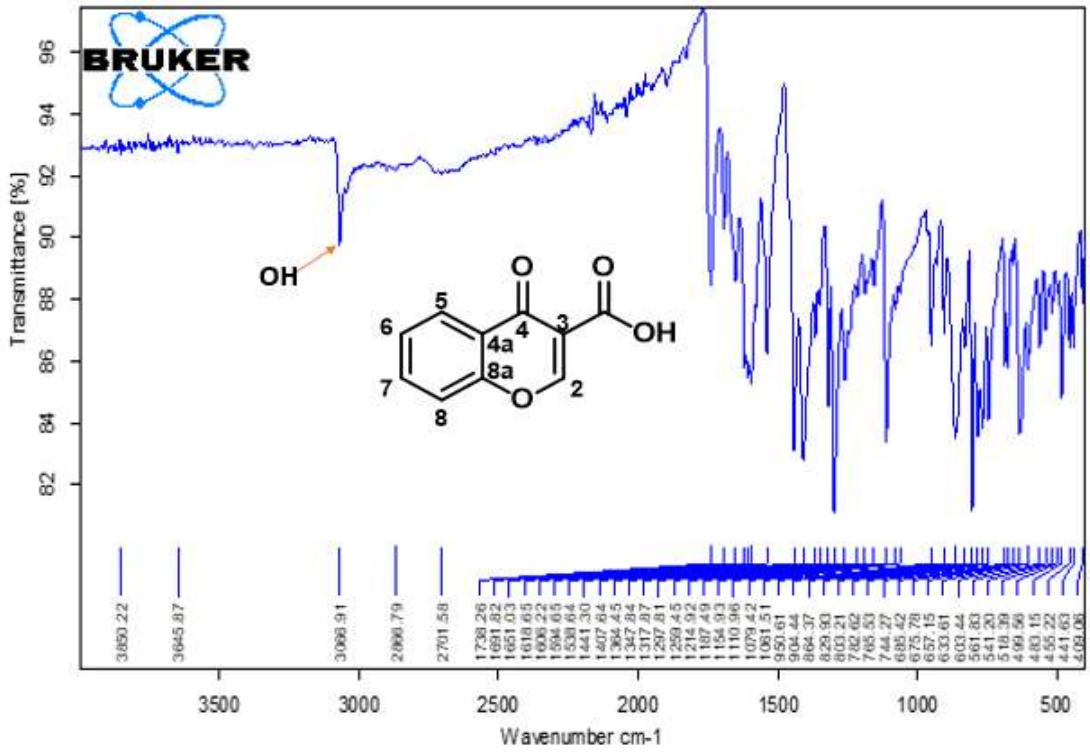
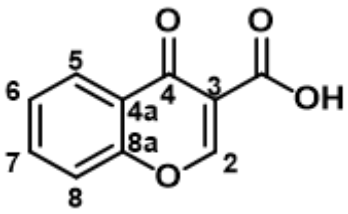


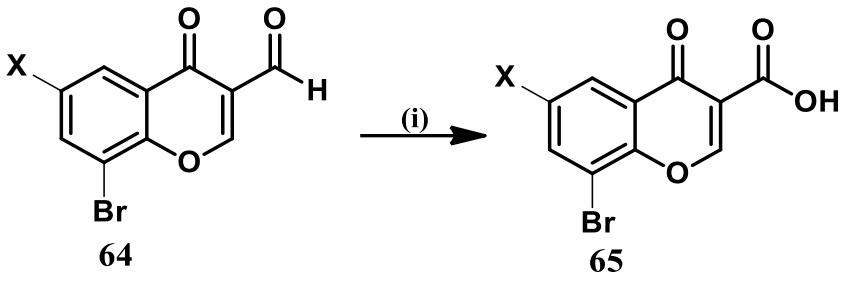

**Figure 19**: FTIR spectrum of chromone-3-carboxylic acid **(60A)**




**60A**

## 4.6 Synthesis of 8-bromo-6-substituted chromone-3-carboxylic acids

The 8-bromo-6-substituted chromone-3-carboxylic acids **(65A-B)** were synthesized by treatment of 8-bromo-6-substituted chromone-3-carbaldehydes **(64A-B)** with sulfamic acid and sodium chlorite in dichloromethane at 0˚C as shown in scheme **16.** . After cooling to room temperature, the solution was stirred for 24 hours, then quenched with water, and extracted with DCM. The combined organic layers that separated from aqueous layers were dried over $MgSO_4$ and evaporated using a rotary evaporator. The isolated solid compounds were recrystallized to afford 8-bromo-6-substituted chromone-3-carboxylic acids **(65A-B).**




64 65

Where X= Br

*Reagents and conditions*: $H_3NSO_3$, $NaClO_2$, $H_2O$, DCM, 0˚C,3h

**Scheme 16**: Synthesis of 8-bromo-6-substituted chromone-3-carboxylic acids **(65A-B)**

**Table 9: Synthesis of 8-bromo-6-substituted-chromone-3-carboxylic acids**

| **Compound 65** | **X** | **Yields (g)** | **% Yield** | **Melting points (°C)** | **Lit. melting points (°C)** |
|---|---|---|---|---|---|
| **A** | **Br** | **0.62** | **52** | **205.4-207.2** | **-** |
| **B** | **Cl** | **0.57** | **47** | **224.6-226.9** | **-** |

The 6,8-dibromochromone-3-carboxylic acid **(65A)** was characterized by proton and carbon NMR, FTIR Spectroscopic techniques as shown in Figures **20**, **21**, and **22**. The percentage yield of 6,8-dibromo-chromone-3-carboxylic acid ranged from 47-52 %

Four peaks were expected in the $^{1}$H NMR spectrum of 6,8-dibromochromone-3-carboxylic acid **(65A),** but the spectrum only shows three peaks. The OH peak couldn't detect downfield probably due to hydrogen deuterium exchange. In the spectra below two doublets were observed with the first doublet at 8.27 ppm corresponding to the H-7 proton, and the second doublet resonates at 7.98 ppm corresponding to the H-5 proton. The singlet at 6.14 ppm correspond to the H-2 proton.

The $^{13}$C NMR spectrum (Table 10) showed ten peaks as expected. The carbonyl carbon peak at 179.44 ppm which corresponds to C-4, peak at 152.83 ppm which shows the carbonyl carbon of carboxylic acid and C-2. The carbon at 146.60 ppm which corresponds to the C8a. The carbon at 130.02 ppm for C-7, carbon at 119.52 ppm which corresponds with C-5, carbon at 114.98 ppm which corresponds to C-4a. The carbon at 113.60 ppm correspond to C-6, carbon

at 99.33 ppm which corresponds to C-3, lastly the carbon at 83.39 ppm which resonating at C-8 respectively.

The 6,8-disubstituted chromone-3-carboxylic acid **(65A)** was also further confirmed by FTIR spectroscopy. The FTIR spectroscopy show the OH band at wavenumber 33342.91 $cm^{1}$.

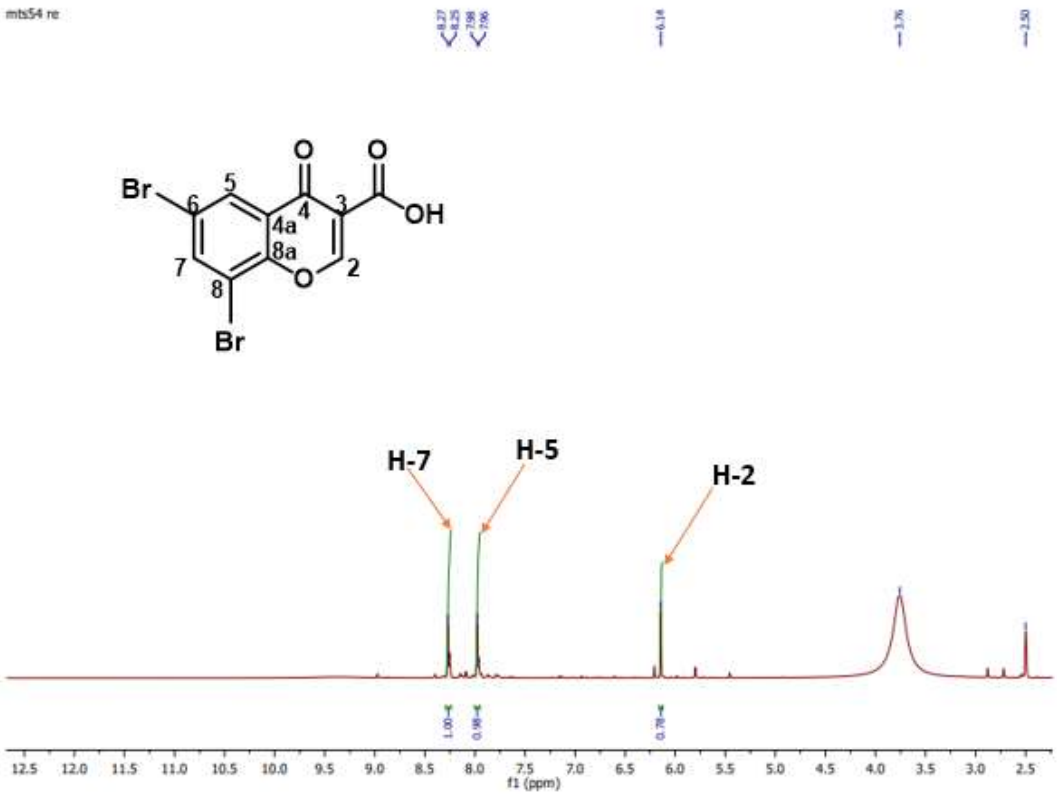



**Figure 20**: $^{1}$H NMR spectrum of 6,8-dibromochromone-3-caboxylic acid **(65A).**

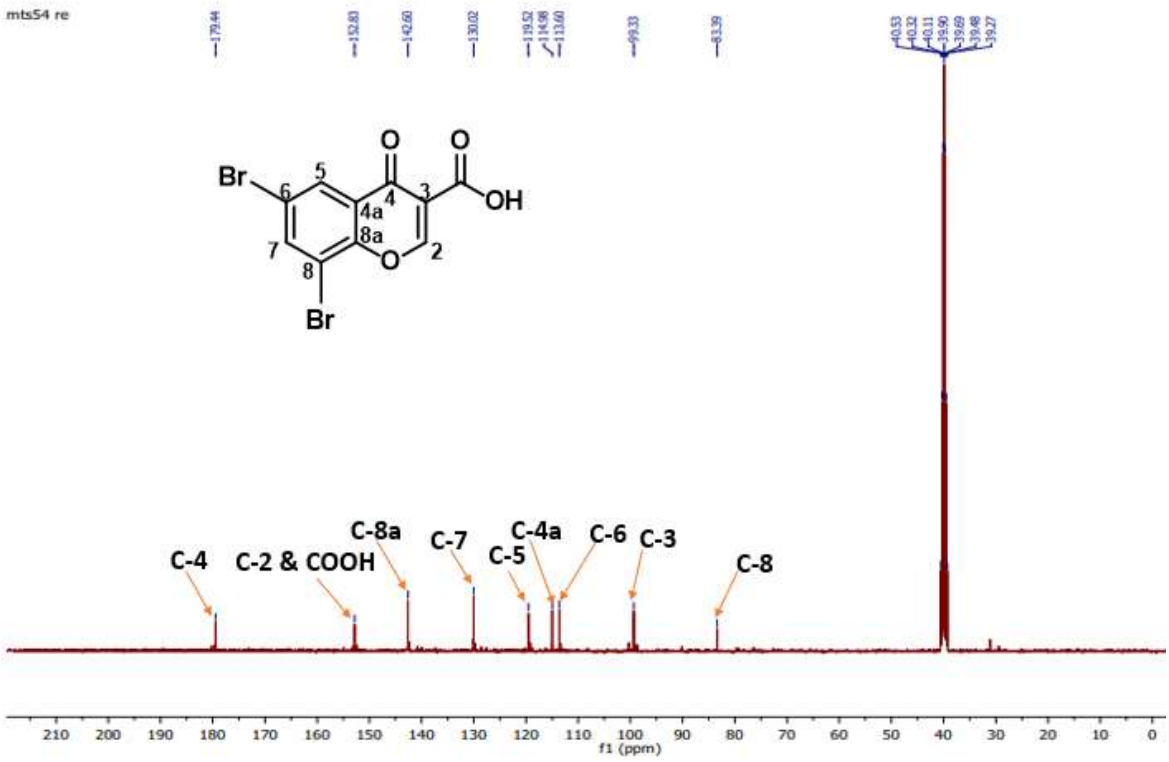



**Figure 21**: $^{13}$C NMR spectrum of 6,8-dibromochromone-3-carboxylic acid **(65A).**

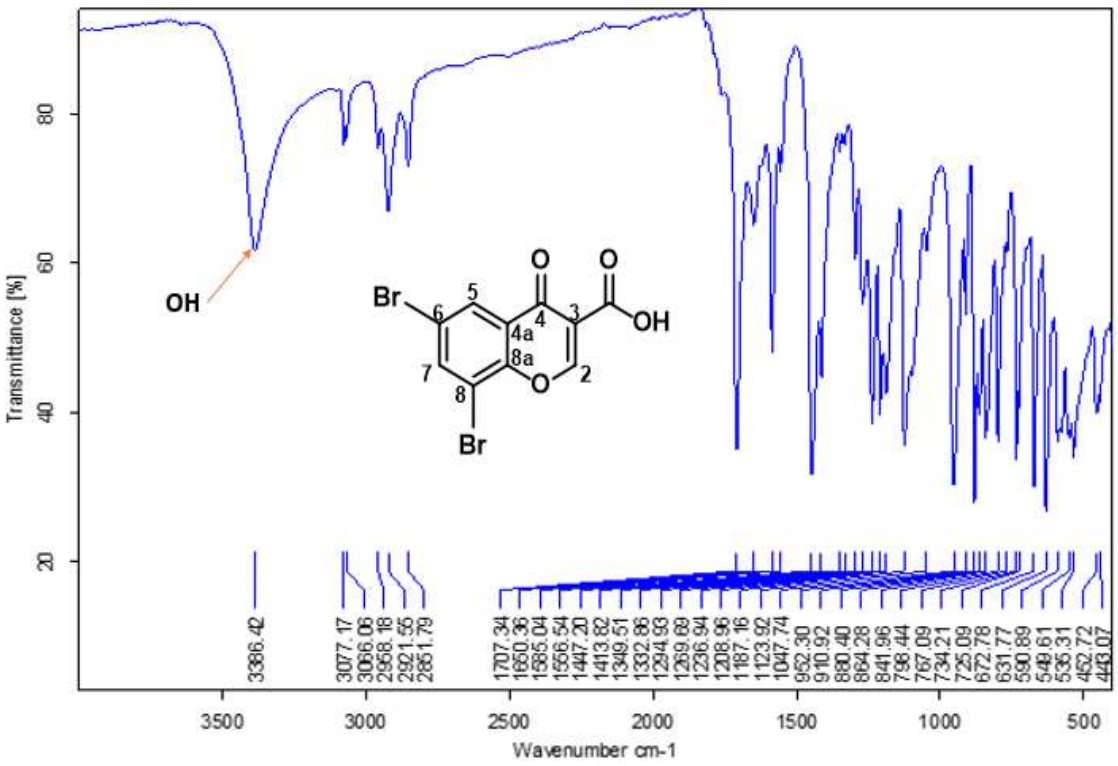
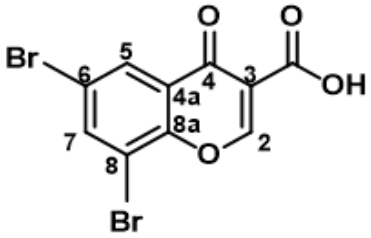



**Figure 22**: FTIR spectrum of 6,8-dibromochromone-3-carboxylic acid **(65A)**




**65A**

**Table 10: 100 MHz $^{13}$C NMR chemical shift values (ppm) of 8-bromo-6-substituted chromone-3-carboxylic acids (65A-B) in DMSO-$d_6$**

| **Carbons** | **65A**<br>**X=Br** | **65B**<br>**X=Cl** |
|---|---|---|
| C2 | 152.83 | 152.51 |
| C3 | 99.33 | 99.38 |
| C4 | 179.44 | 179.95 |
| C4a | 114.98 | 119.09 |
| C5 | 119.52 | 127.10 |
| C6 | 113.60 | 113.36 |
| C7 | 130.02 | 127.77 |
| C8 | 83.39 | 83.49 |
| C8a | 142.60 | 140.12 |
| COOH | 152.83 | 152.51 |

# CHAPTER 5 CONCLUSION

The iodination of 5-substituted-2-hydroxyacetophenones **(57)** at position 3 was successful and the yields obtained were good to excellent yields of 55 - 75 %. The bromination of 5-substituted-2-hydroxyacetophenones was also successful, with moderate to excellent yields of 66-86 %. The 3-iodo-5-substituted 2-hydroxyacetophones **(58A-D)** were further treated with $POCl_3$ and DMF using the Vilsmeier-Haack reaction to synthesize 8-iodo-6-substituted chromone-3-carbaldehydes **(59A-D)** with excellent yields of 78 - 90 %. All synthesized compounds are novel compounds and the 3-bromo-5-substituted 2-hydroxyacetophenones **(63A-C)** were used successfully to convert them to 8-bromo-6-substituted chromone-3-carbaldehydes **(64A-C)** with excellent yields of 85 - 87 % as well.

The oxidation of the 6,8-disustituted chromone-3-carbaldehydes **(60A-D)** in the presence of $NaClO_2$ and $H_3NSO_3$ was not very successful although various modification on the method were attempted, except for the chromone-3-carboxylic acid **(60A)** with a moderate yield of 57 % and the 8-dibromo-6-substituted chromone-3-carboxylic acids **(65A-B)** with moderate yields of 47 - 52 %. Attempts to use Jone`s reagent for the oxidation of chromone-3-carbaldehydes was also not successful. All Synthesized compounds were characterized using ($^{1}H$ and $^{13}C$) NMR and IR spectroscopic techniques.

Although challenges were encountered with the methods used to oxidize carboxylic acid derivatives, some 6,8-disubstituted-chromone-3-carboxylic acids were successfully synthesized. The final target compounds couldn't be synthesized; however, four 8-iodo-6-substituted-chromone-3-carbaldehydes **(59A-D)**, three 8-bromo-6-substituted-chromone-3-carbaldenydes **(64A-C)**, one chromone-3-carboxylic acid **(60A),** and two 8-bromo-6-substituted-chromone-3- carboxylic acids **(65A-B)** successfully synthesized will be send for screening as potential anti-tuberculosis agents.

## 5.1 Future work

- Reinvestigate other methods of synthesizing chromone-3-carboxylic acids.
- Convert carboxylic acids to chromone-3-carboxamides.
- Suzuki metal coupling reaction of 6,8-disubstituted chromone-3-carboxamides.
- Biological screening of 6,8-disubstituted-chromone-3-carboxamide derivatives as potential anti-tuberculosis agents.

# CHAPTER 6 EXPERIMENTAL

## 6.1 General

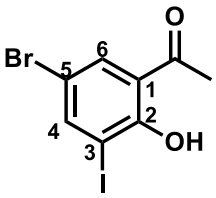
Reagents and solvents used for the project were purchased from Sigma Aldrich / Merck / other local chemical suppliers and were used without further purification, unless indicated.

The $^{1}H$ NMR (400 MHz) and $^{13}C$ NMR (100 MHz) spectra were characterized on a Bruker 400 MHz spectrometer using DMSO-$d_6$ and $CDCl_3$as the solvents. Chemical shift values of $^{1}H$ NMR and $^{13}C$ NMR were reported in ppm. For NMR signals, the following multiplicity abbreviations were used: s for singlet, d for doublet, dd for doublet of doublet, t for triplet, q for quartet, m for multiplet, and coupling constants, J in hertz (Hz) unit. $^{1}H$ chemical shifts of solvents $CDCl_3$ ($\delta$ = 7.26 ppm), DMSO-$d_6$ ($\delta$ = 2.5 ppm), residual water in DMSO-$d_6$ ($\delta$ = 3.44 ppm). $^{13}C$ chemical shifts of solvents $CDCl_3$ ($\delta$ = 77.16 ppm), DMSO-$d_6$ ($\delta$ = 39.52 ppm).

All reactions were synthesized using oven dried round bottom flasks and reaction were monitored by thin-layer chromatographic plates and visualized under UV light ($\lambda$=254-365 nm). The melting points were measured with a capillary tube using a Buchi melting point B-540 instrument. IR spectra in wavelength absorption ($cm^{-1}$) was determined using Perkin-Elmer 1420.

## 6.2 Iodination of 5-substituted-2-hydroxyacetophenones [89] (58A-D)

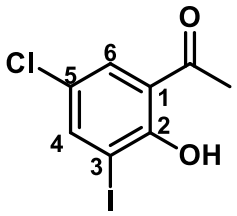
***5-Bromo-2-hydxoxy-3-iodoacetophenone (58A)***




5-Bromo-2-hydroxyacetophenone **(57A)** (1.00 g, 4.65 mmol) in acetic acid (50 ml) treated with *N*-iodosuccinimide (1.05 g, 4.66 mmol). The mixture was then stirred under reflux for 2 hours. The reaction mixture was stopped after the disappearance of 5-bromo-2-hydroxyacetophenone **(57A)**, monitored by TLC. The resulting mixture was quenched with ice water and resulting precipitate was collected through filtration, dried and recrystalised from ethanol to obtain 5-bromo-2-hydroxy-3-iodoacetophenone **(58A)** as brown solid (1.63 g, 63 %), m.p. 96.4-98.3 °C (lit.,[83] 105 °C ); IR $\nu_{max}/cm^{-1}$ 2938,53 (OH), 1620.91 (C=O), 552.30 (C-I); $\delta_H$ (400 MHz,

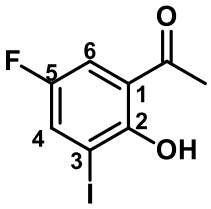
DMSO) 12.96 (1H, s, OH), 8.18 (1H, d, J =2.2 Hz, 4-H), 8.12 (1H, d, J = 2.2 Hz, 6-H), 2.68 (3H, s, $CH_3$); $\delta_C$ (100 MHz, DMSO) 203.14 (C=O), 160.28 (C-2), 144.24 (C-4), 139.3 (C-6), 123.88 (C-5), 120.75 (C-1), 81.42 (C-3), 28.82 ($CH_3$).

***5-Chloro-2-hydroxy-3-iodoacetophenone (58B)***




The same experimental procedure used for synthesis of 5-bromo-2-hydroxy-3-iodoacetophenone **(58A)** was followed using 5-chloro-2-hydroxyacetophenone **(57B)** (1.00 g, 5.86 mmol) in acetic acid (50 ml) treated with N-iodosuccinimide (1.32 g, 5.86 mmol). The mixture was then stirred under reflux for 2 hours. The reaction mixture was stopped after the disappearance of 5-chloro-2-hydroxyacetophenone **(57B)**, monitored with thin layer chromatography. The resulting mixture was quenched with ice water and precipitates formed were filtered, dried and recrystalised from ethanol to obtain 5-chloro-2-hydroxy-3-iodoacetophenone **(58B)** as brown solid (0.96 g, 58 %), m.p. 88.8-90.5 °C (lit., [83] 89 °C ); IR $\nu_{max}/cm^{-1}$ 3066.22 (OH), 1642.79 (C=O), 544.83 (C-I); $\delta_H$ (400 MHz, DMSO) 12.94 (1H, s, OH), 8.09 (1H, d, J =2.2 Hz, 4-H), 8.03 (1H, d, J = 2.2 Hz, 6-H), 2.68 (3H, s, $CH_3$); $\delta_C$ (100 MHz, DMSO) 205.22 (C=O), 159.39 (C-2), 144.37 (C-4), 131.43 (C-6), 124.05 (C-5), 120.36 (C-1), 88.37 (C-3), 27.42 ($CH_3$).

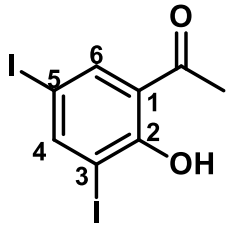
***5-Fluoro-2-hydroxy-3-iodoacetophenone (58C)***




Th same experimental procedure used for the synthesis of 5-bromo-2-hydroxy-3-iodoacetophenone **(58A)** was followed using 5-fluoro-2-hydroxyacetophenone **(57C)** (1.00 g, 6.50 mmol) in acetic acid (50 ml) was treated with N-iodosuccinimide (1.46 g, 6.50 mmol). The resulting mixture was stirred for 2 hours under reflux. The reaction was stopped after the

disappearance of 5-fluoro-2-hydroxyacetophenone **(57C),** monitored by thin layer chromatography. The resulting mixture was quenched with ice water and precipitates formed were filtered, dried and recrystalised from ethanol to obtain 5-fluoro-2-hydroxy-3-iodoacetophenone **(58C)** as brown solid (1.53 g, 55 %), m.p. 101.4-104.5 °C; IR $\nu_{max}/cm^{-1}$ 3075.45 (OH), 1642.55 (C=O), 544.83 (C-I); $\delta_H$ (400 MHz, DMSO) 12.74 (1H, s, OH), 8.00 (1H, d, J =2.2 Hz ,4-H), 7.88 (1H, d, J = 2.2 Hz, 6-H), 2.66 (3H, s, $CH_3$); $\delta_C$ (100 MHz, DMSO) 205.17 (C=O), 157.17 (C-2), 153.47 (C-4), 133.00 (C-6), 119.19 (C-5), 117.84 (C-1), 87.26 (C-3), 27.38 ($CH_3$).

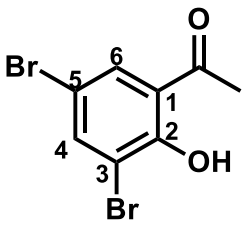
***3,5-Diiodo-2-hydroxyacetophenone (58D)***




Th same experimental procedure for the synthesis of 5-bromo-2-hydroxy-3-iodoacetophenone **(58A)** was followed using a solution 2-Hydroxyacetophenone **(57D)** (2.26 g, 16.60 mmol) in acetic acid (50 ml) was treated with *N*-iodosuccinimide (7.47 g, 33.20 mmol). The mixture was then stirred under reflux for 2 hours. The reaction mixture was stopped after the disappearance of 2-hydroxyacetophenone **(57D)**, monitored with thin layer chromatography. The resulting mixture was quenched with ice water and precipitates formed were filtered, dried and recrystalised from ethanol to obtain 3,5-diiodo-2-hydroxyacetophenone **(58D)** as brown solid (2.42 g, 66 %), m.p. 124.8-126.6 °C (lit.,[84] 125-127 °C ); IR $\nu_{max}/cm^{-1}$3075.12 (OH), 1631.33 (C=O), 539.19 (C-I); $\delta_H$ (400 MHz, DMSO) 12.97 (1H, s, OH), 8.28 (1H, d, J =2.2 Hz , 4-H), 8.20 (1H, d, J = 2.2 Hz, 6-H), 2.67 (3H, s, $CH_3$); $\delta_C$ (100 MHz, DMSO) 205.14 (C=O), 160.14 (C-2), 152.14 (C-4), 140.06 (C-6), 121.89 (C-1), 89.28 (C-5), 82.69 (C-3), 27.45 ($CH_3$).

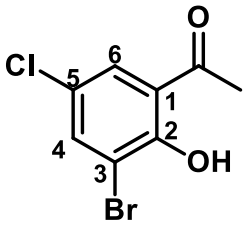
## 6.3. Bromination of 5-substituted-2-hydroxyacetophenones[90] (63A-C)

***3.5-Dibromo-2-hydroxyacetophenone (63A)***



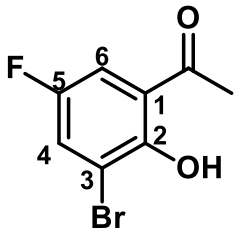

5-Bromo-2-hydroxyacetophenone **(57A)** (2.00 g, 9.30 mmol) in MeOH (50 ml) was treated with NBS (1.66 g, 9.33 mmol). The mixture was stirred for 3 hours at room temperature, then water (40 ml) was added. The resultant pale-yellow solid formed filtrered, washed with water and the product was allowed dry to obtain 3,5-dibromo-2-hydroxyacetophenone **(63A)** as yellow solid (2.68 g, 86 %), m.p. 103.4-105.2 °C (lit.,[85] 105-107 °C ); IR $\nu_{max}/cm^{-1}$ 3006,50 (OH), 1644.07 (C=O), 599.76 (C-Br); $\delta_H$ (400 MHz, $CDCl_3$) 12.80 (1H, s, OH), 7.80 (1H, d, J =2.2 Hz, 4-H), 7.76 (1H, d, J = 2.2 Hz, 6-H), 2.59 (3H, s, $CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 203.34 (C=O), 158.11 (C-2), 141.51 (C-4), 132.20 (C-6), 121.14 (C-1), 113.27 (C-5), 110.39 (C-3), 26.77 ($CH_3$).

***3-Bromo-5-chloro-2-hydroxyacetophenone (63B)***




The same experimental procedure used for 3,5-dibromo-2-hydroxyacetophenone **(63A)** was followed, where 5-chloro-2-hydroxyacetophenone **(57B)** (1.50 g, 8.79 mmol) in MeOH (50 ml) was treated with NBS (1.57 g, 8.82 mmol). The mixture after stirring for 3 hours at room temperature, the water (40 ml) was added. The resultant pale-yellow solid formed filtered, washed with water and the product was allowed dry to obtain 3-bromo-5-chloro-2-hydroxyacetophenone **(63B)** as yellow solid (1.54 g, 68 %), m.p. 109.3-111.5 °C (lit.,[85] 112 °C ); IR $\nu_{max}/cm^{-1}$3066.16 (OH), 1691.15 (C=O), 546.71(C-Br); $\delta_H$ (400 MHz, $CDCl_3$) 12.78 (1H, s, OH), 7.66 (1H, d, J =2.2 Hz, 4-H), 7.62 (1H, d, J = 2.2 Hz, 6-H), 2.59 (3H, s, $CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 203.42 (C=O), 157.67 (C-2), 138.93 (C-4), 129.21 (C-6), 123.83 (C-1), 120.45 (C-5), 112.91 (C-3), 26.77 ($CH_3$).

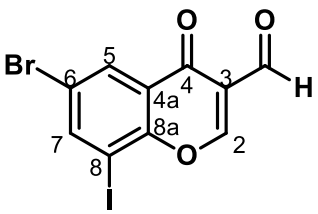
***3-Bromo-5-fluoro-2-hydroxyacetophenone (63C)***




The same experimental procedure used for 3,5-dibromo-2-hydroxyacetophenone **(63A)** was followed, where 5-fluoro-2-hydroxyacetophenone **(57C)** (1.85 g, 12.00 mmol) in MeOH (50 ml) was treated with NBS (2.14 g, 12.02 mmol). The mixture after stirered for 3 hours at room temperature, water (40 ml) was added. The resultant brown solid that was formed was filtrered and washed with water and the product was allowed to dry to obtain 3-bromo-5-fluoro-2-hydroxyacetophenone **(63C)** as brown solid (1.54 g, 68 %) , m.p. 99-99 °C (lit.,[86] 97 °C ); IR $\nu_{max}/cm^{-1}$3056.08 (OH), 1640.68 (C=O), 560.82(C-Br); $\delta_H$ (400 MHz, $CDCl_3$) 12.61 (1H, s, OH), 7.49 (1H, d, J =2.2 Hz, 4-H), 7.37 (1H, d, J = 2.2 Hz, 6-H), 2.58 (3H, s, $CH_3$); $\delta_C$ (100 MHz, $CDCl_3$) 203.40 (C=O), 155.56 (C-2), 152.85 (C-4), 127.19 (C-6), 119.24 (C-1), 115.30 (C-5), 112.30 (C-3), 26.79 ($CH_3$).

## 6.4 Synthesis of 8-iodo-6-substituted-chromone-3-carbaldehydes[91] (59A-D)

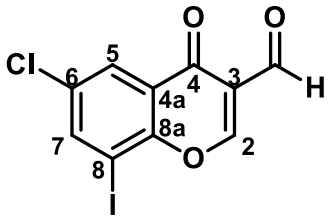
***6-Bromo-8-iodochromone-3-carbaldehyde (59A)***




5-Bromo-2-hydroxy-3-iodoacetophenone **(58A)** (1.00 g, 2.93 mmol) in anhydrous DMF (15.00 ml) was cooled at 0˚C. $POCl_3$ (2.00 ml) was added drop wise with dropping funnel. The colour change of the solution was observed from brown to dark brown. The resulting mixture was then stirred at room temperature for 12 hours while monitoring with TLC [ethyl acetate–petroleum ether (50:50)] to completion and quenched with ice water. Precipitates formed were filtered, washed with water, dried, and recrystalised from ethanol to obtain 6-bromo-8-

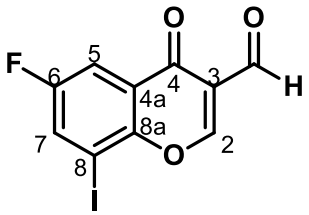
iodochromone-3-carbaldehyde **(59A)** as light brown solid (1.72 g, 90 %) , m.p. 137.8-141.6 °C ; IR $\nu_{max}/cm^{-1}$1666.42 (C=O), 1695.35 (HC=O); $\delta_H$ (400 MHz, $CDCl_3$) 10.27 (1H, s, CHO), 8.54 (1H, s, 2-H), 8.32 (1H, d, J = 2.8 Hz, 7-H), 8.24 (1H, d, J=2.8 $H_Z$, 5-H); $\delta_C$ (100 MHz, $CDCl_3$) 187.71 (HC=O), 174.42 (C-4), 160.74 (C-2), 154.34 (C-8a), 146.62 (C-7), 129.11 (C-5), 126.91 (C-4a), 120.90 (C-3), 120.06 (C-6), 86.55 (C-8).

***6-Chloro-8-iodochromone-3-carbaldehyde (59B)***




The 5-chloro-2-hydroxy-3-iodoacetophenone (**58B)** (1.00 g, 3.37 mmol) in anhydrous DMF (15.00 ml) was cooled at 0 ˚C. $POCl_3$ (2.00 ml) was added drop wise wit dropping funnel. The colour change of the solution was observed from brown to dark brown. The mixture was then stirred at room temperature for 12 hours while monitoring by TLC [ethyl acetate–petroleum ether (50:50)] to completion and the resulting mixture quenched with ice water. Precipitates formed were filtered, washed with water, dried, and recrystallized from ethanol to obtain 6-chloro-8-iodochromone-3-carbaldehyde (**59B)** as light brown solid (0.91 g, 78 %), m.p. 154.8-162.4°C ; IR $\nu_{max}/cm^{-1}$1660.54 (C=O), 1691.19 (HC=O); $\delta_H$ (400 MHz, DMSO) 10.05 (1H, s, CHO), 9.01 (1H, s, 2-H), 8.37 (1H, d, J = 2.8 Hz, 7-H), 7.97 (1H, d, J=2.8 $H_Z$, 5-H); $\delta_C$ (100 MHz, DMSO) 188.36 (HC=O), 174.15 (C-4), 164.50 (C-2), 154.22 (C-8a), 143.64 (C-7), 132.17 (C-5), 126.45 (C-4a), 124.88 (C-3), 120.14 (C-6), 89.93 (C-8).

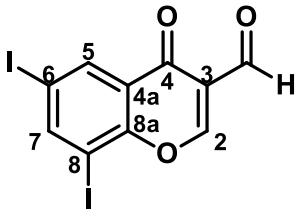
***6-Fluoro-8-iodo-chromone-3-carbaldehyde (59C)***




The 5-fluoro-2-hydroxy-3-iodoacetophenone **(58C)** (1.00 g, 3.57 mmol) in anhydrous DMF (15.00 ml) was cooled at 0˚C. $POCl_3$ (2.00 ml) was added drop wise using dropping funnel. The colour change of the solution was observed from brown to dark brown. The mixture was then stirred at room temperature for 12 hours while monitoring by TLC [ethyl acetate–petroleum ether (50:50)] to completion, and the resulting mixture quenched with ice water.

Precipitates were filtered, washed with water, dried, and recrystallized from ethanol to obtain 6-fluoro-8-iodochromone-3-carbaldehyde **(59C)** as brown solid (1.24 g, 86 %) , m.p. 186.7-191.2 °C; IR $\nu_{max}/cm^{-1}$1660.68 (C=O), 1693.04 (HC=O); $\delta_H$ (400 MHz, $CDCl_3$) 10.27 (1H, s, CHO), 8.54 (1H, s, 2-H), 7.88(1H, d, J = 2.8 Hz, 7-H), 7.66 (1H, d, J=2.8 $H_Z$, 5-H); $\delta_C$ (100 MHz, $CDCl_3$) 187.74 (HC=O), 174.85 (C-4), 160.77 (C-2), 158.51 (C-8a), 151.97 (C-7), 132.72 (C-5), 126.76 (C-4a), 119.31 (C-3), 111,90 (C-6), 86.02 (C-8).

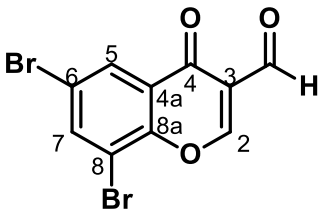
***6,8-Diiodochromone-3-carbaldehyde (59D)***




The 3,5-diiodo-2-hydroxyacetophenone **(58D)** (1.00 g, 2.58 mmol) in anhydrous DMF (15.00 ml) was cooled at 0˚C $POCl_3$ (2.00 ml) was added drop wise using dropping funnel. The colour change of the solution was observed from brown to dark brown. The mixture was then stirred at room temperature for 12 hours while monitoring by TLC [ethyl acetate–petroleum ether (50:50)] to completion and the resulting mixture quenched with ice water. Precipitates was filtrered, washed with water, dried, and recrystallized from ethanol to obtain 6,8-diiodochromone-3-carbaldehyde (**59D)** as brown solid (1.20 g, 88 %) , m.p. 152.8-158.2 °C; IR $\nu_{max}/cm^{-1}$1659.60 (C=O), 1693.14 (HC=O); $\delta_H$ (400 MHz, $CDCl_3$) 10.04 (1H, s, CHO), 9.00 (1H, s, 2-H), 8.58 (1H, d, J = 2.8 Hz, 7-H), 8.25 (1H, d, J=2.8 $H_Z$, 5-H); $\delta_C$ (100 MHz, $CDCl_3$) 188.42 (HC=O), 173.93 (C-4), 164.44 (C-2), 155.04 (C-8a), 151.97 (C-7), 134.09 (C-5), 127.15 (C-4a), 120.44 (C-3), 93.27 (C-6), 90.21 (C-8).

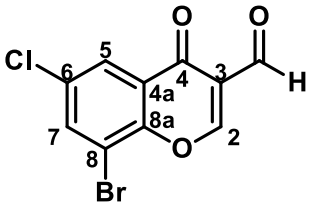
## 6.5 Synthesis of 8-bromo-6-substituted-chromone-3-carbaldehydes[91] (64A-C)

***6,8-Dibromochromone-3-carbaldehyde (64A)***




The 3,5-dibromo-2-hydroxyacetophenone **(63A)** (1.00 g, 3.40 mmol) in anhydrous DMF (15.00 ml) was cooled at 0˚C. $POCl_3$ (2.00 ml) was added drop wise using dropping funnel. The colour change of the solution was observed from yellow to orange. The mixture was then stirred at room temperature for 12 hours while monitoring by TLC [ethyl acetate–petroleum ether (50:50)] to completion and the resulting mixture quenched ice water. Precipitates formed filtered, washed with water, dried, and recrystallized from ethanol to obtain 6,8-dibromochromone-3-carbaldehyde **(64A)** as creamy white solid (1.06 g, 86 %) , m.p. 175.5-178.2 °C (lit.,[87] 174-176 °C ); IR $\nu_{max}/cm^{-1}$1667.70 (C=O), 1694.34 (HC=O); $\delta_H$ (400 MHz, DMSO) 10.06 (1H, s, CHO), 9.04 (1H, s, 2-H), 8.46 (1H, d, J = 2.8 Hz, 7-H), 8.18 (1H, d, J=2.8 Hz, 5-H); $\delta_C$ (100 MHz, DMSO) 188.37 (HC=O), 173.82 (C-4), 164.38 (C-2), 152.10 (C-8a), 140.38 (C-7), 127.73 (C-6), 127.54 (C-5), 120.55 (C-4a), 119.62 (C-3), 113.93 (C-8).

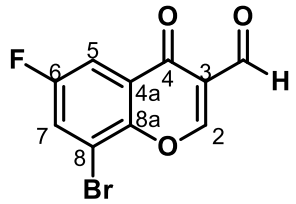
***8-Bromo-6-chlorochromone-3-carbaldehyde (64B)***




The 3-bromo-5-chloro-2-hydroxyacetophenone **(63B)** (1.00 g, 4.00 mmol) in anhydrous DMF (15.00 ml) was cooled at 0˚C. $POCl_3$ (2.00 ml) was added drop wise using dropping funnel. The colour change of the solution was observed from yellow to orange. The mixture was then stirred at room temperature for 12 while monitoring by TLC [ethyl acetate–petroleum ether (50:50)] to completion, and the resulting mixture was quenched with ice water. Precipitates formed filtered, washed with water, dried, and recrystallized from ethanol to obtain 8-bromo-6-chlorochromone-3-carbaldehyde **(64B)** as creamy white solid (1.24 g, 87 %) , m.p. 164.5-168.2 °C; IR $\nu_{max}/cm^{-1}$1670.24 (C=O), 1694.84 (HC=O); $\delta_H$ (400 MHz, DMSO) 10.27 (1H, s, CHO), 8.52 (1H, s, 2-H), 8.13 (1H, d, J = 2.8 Hz, 7-H), 8.88 (1H, d, J=2.8 Hz, 5-H); $\delta_C$ (100

MHz, DMSO) 187.57 (HC=O), 174.26 (C-4), 160.52 (C-2), 151.58 (C-8a), 137.97 (C-7), 132.98 (C-6), 127.17 (C-5), 124.96 (C-4a), 120.18 (C-3), 113.93 (C-8).

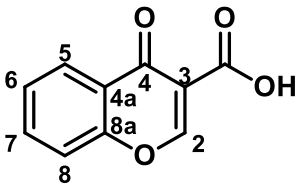
***8-Bromo-6-fluorochromone-3-carbaldehyde (64C)***




The 3-bromo-5-fluoro-2-hydroxyacetophenone **(63C)** (1.00 g, 4.30 mmol) in anhydrous DMF (15.00 ml) was cooled at 0 ˚C. $POCl_3$ (2.00 ml) was added drop wise using dropping funnel. The colour change of the solution was observed from yellow to orange. The mixture was then stirred at room temperature for 12 hours while monitoring by TLC [ethyl acetate–petroleum ether (50:50)] to completion and the resulting mixture was then quenched with ice water. Precipitates formed filtrered, washed with water, dried, and recrystallized from ethanol to obtain 8-bromo-6-fluoro-chromone-3-carbaldehyde **(64C)** as cream white solid (1.21 g, 85 %) , m.p. 126-133 °C; IR $\nu_{max}/cm^{-1}$1658.70 (C=O), 1695.51 (HC=O); $\delta_H$ (400 MHz, DMSO) 10.28 (1H, s, CHO), 8.54 (1H, s, 2-H), 7.86 (1H, d, J = 2.8 Hz, 7-H), 7.69 (1H, d, J=2.8 $H_Z$, 5-H); $\delta_C$ (100 MHz, DMSO) 187.75 (HC=O), 174.64 (C-4), 160.63 (C-2), 158.26 (C-8a), 149.67 (C-7), 127.43 (C-6), 126.73 (C-5), 119.53 (C-4a), 113.43(C-3), 111.00 (C-8).

## 6.6 Synthesis of 8-iodo-6-substituted-chromone-3-carboxylic acid[92]

***Chromone-3-carboxylic acid (60A)***

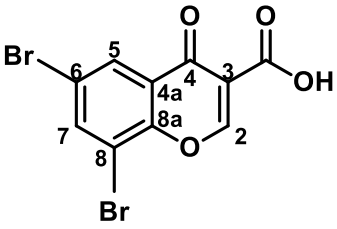



Chromone-3-carbaldehyde (1.00 g, 5.74 mmol) and sulfamic acid (2.23 g, 22.97 mmol) were mixed in DCM (15 ml) in an ice bath. Sodium chlorite (1.56 g, 17.23 mmol) in water (5 ml) at 0 ˚C was added dropwise in the mixture. The resultant mixture was stirred at room temperature for 3 hours to completion, monitored by TLC. Distilled water (25 ml) was added to the mixture and then extracted with DCM (3 x 25 ml). Organic layers were separated from aqueous layer,

using separating funnel, and dried with $MgSO_4$. The DCM solvent was evaporated with rotary vapor. The yellow residue obtained was recrystallized from methanol to obtain chromone-3-carboxylic acid **(60A)** as yellow solid (1.07 g, 57 %) , m.p. 201.4-204.6 °C (lit.,[93] 204-205 °C ); IR $\nu_{max}/cm^{-1}$3066.91 (OH); 1695.51 $\delta_H$ (400 MHz, DMSO) 9.08 (1H, s, 2-H), 8.14 (1H, d, J=8.8Hz, 5-H), 7.92 (1H, t, J = 8.8 Hz, 7-H), 7.61 (1H, d, J=8.8 $H_Z$, 8-H);7.76 (1H, t, J=8.8Hz, 6-H); $\delta_C$ (100 MHz, DMSO) 176,79 (C-4), 164.47 (COOH), 164,41 (C-2), 156.32 (C-8a), 136,19 (C-7), 127.46 (C-6), 126.03 (C-5), 123.92 (C-4a), 119,42(C-8), 114 (C-3).

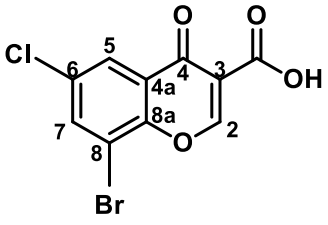
## 6.8. Synthesis of 8-bromo-6-substituted chromone-3-carboxylic acids[92]

***6,8-Dibromochromone-3-carboxylic acid (65A)***




The 6,8-dibromochromone-3-carbaldehyde **(64A)** (1.00 g, 3.95 mmol) and sulfamic acid (1.92 g, 19.77 mmol) was mixed in DCM (15 ml) in an ice bath. Sodium chlorite (1.43 g, 15.81 mmol) in water (5 ml) at 0˚C was added dropwise in the mixture. The resultant mixture stirred at room temperature for 24 hours to completion, monitored by TLC. Distilled water (25 ml) and then extracted with DCM (3 x 25 ml). Organic layers were separated from aqueous layer using separating funnel and dried with $MgSO_4$. The DCM solvent was evaporated with rotary vapour. The yellow residue obtained was recrystallized from methanol to give 6,8-dibromochromone-3-carboxylic acid **(65A)** as yellow solid (0,62 g, 53 %) , m.p. 205.4-207.2 °C; IR $\nu_{max}/cm^{-1}$ 3336.42 (OH); $\delta_H$ (400 MHz, DMSO) 6.14 (1H, s, 2-H), 8.27 (1H, d, J=8.8Hz, 7-H), 7.98 (1H, d, J=8.8 $H_Z$, 5-H); $\delta_C$ (100 MHz, DMSO) 179,44 (C-4), 152.83 (COOH), 152.83 (C-2), 142.60 (C-8a), 130.02 (C-7), 113.60 (C-6), 119.52 (C-5), 114.98 (C-4a), 83.39 (C-8), 99.33 (C-3).

***8-Bromo-6-chlorochromone-3-carboxylic acid (65B)***



The 8-bromo-6-chloro-chromone-3-carbaldehyde **(64B)** (1.00 g, 3.48 mmol) and sulfamic acid (1.68 g, 17.30 mmol) was mixed in DCM (15 ml) in an ice bath. Sodium chlorite (1.25 g, 13.82 mmol) in water (5 ml) at 0˚C was added dropwise in the mixture. The resultant mixture was stirred at room temperature for 24 to completion, monitored by TLC. Distilled water (25 ml) and then extracted with DCM (3 x 25 ml). Organic layers were separated from aqueous layer, using separating funnel, and dried with $MgSO_4$. The DCM solvent was evaporated by rotary vapour. The resulting yellow residue obtained was recrystallized from methanol to give 8-bromo-6-chlorochromone-3-carboxylic acid **(65B)** as yellow solid (0,62 g, 53 %), m.p. 205.4-207.2 °C; IR $\nu_{max}/cm^{-1}$ 3016.42 (OH); $\delta_H$ (400 MHz, DMSO) 6.16 (1H, s, 2-H), 8.19 (1H, d, J=8.6 Hz, 7-H), 7.87 (1H, d, J=8.6 $H_Z$, 5-H); $\delta_C$ (100 MHz, DMSO) 179.95 (C-4), 152.51 (COOH), 152.51 (C-2), 140.12(C-8a), 127.77 (C-7), 113.36 (C-6), 127.10 (C-5), 119.09 (C-4a), 83.49 (C-8), 99.38 (C-3).

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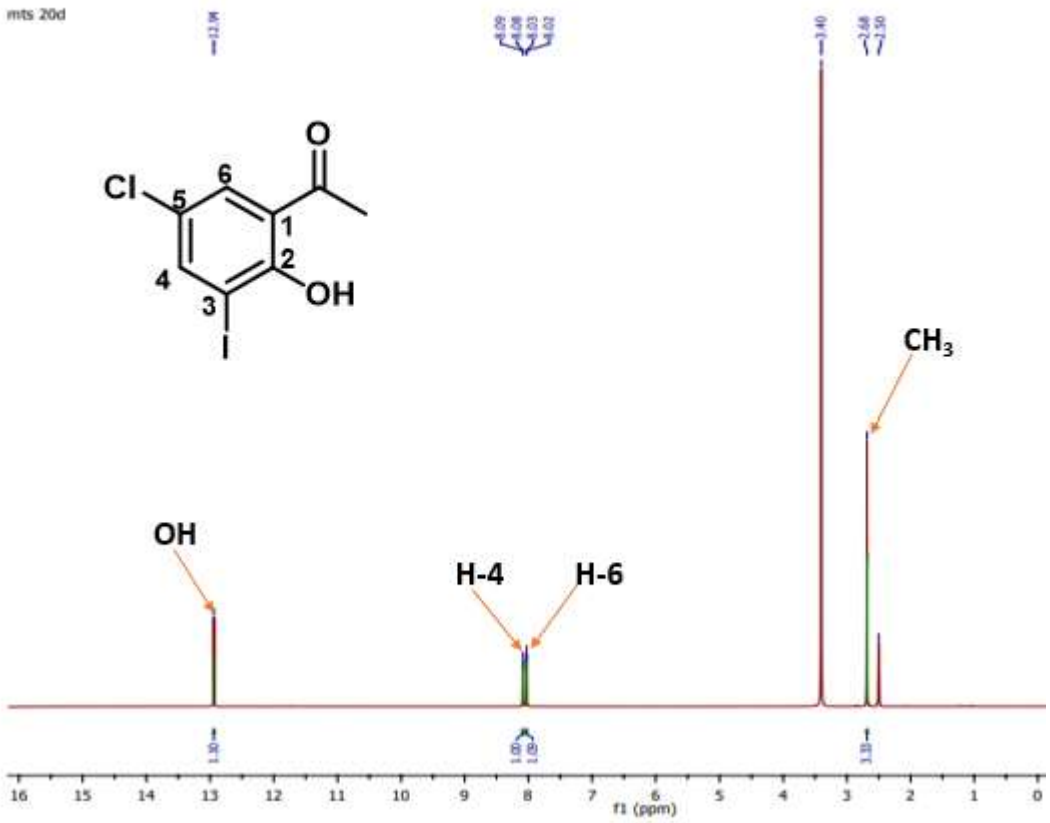
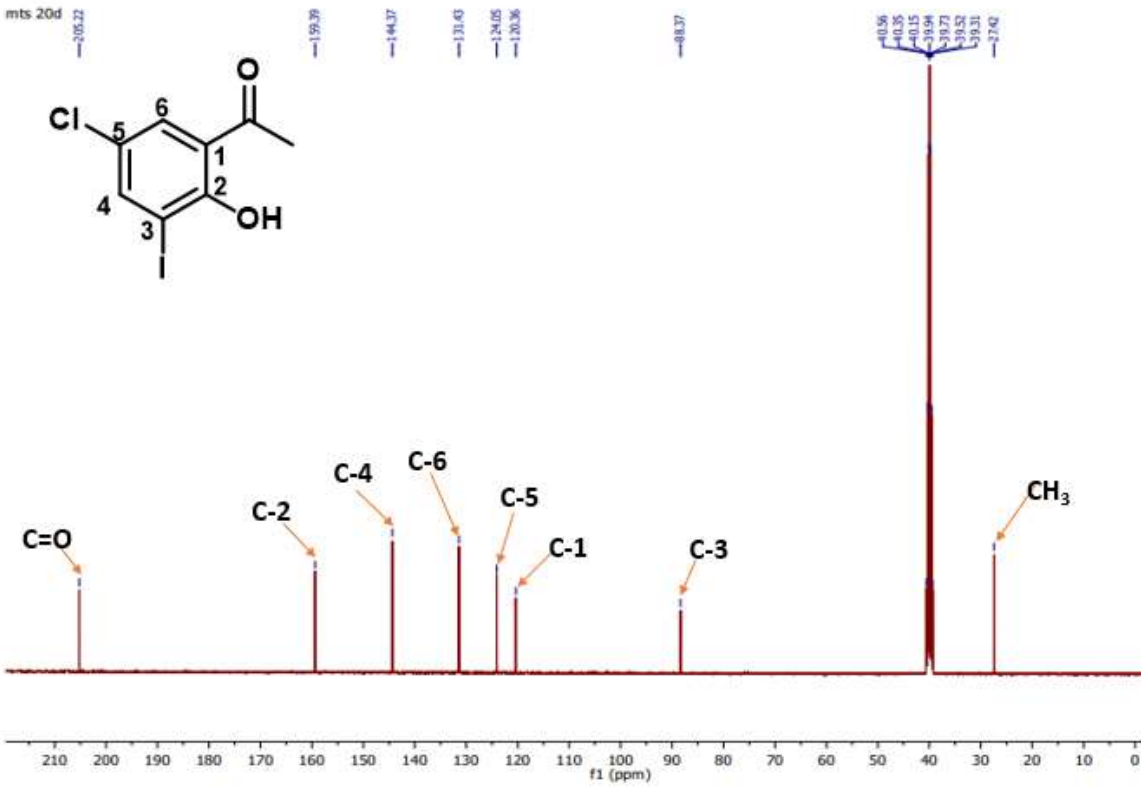
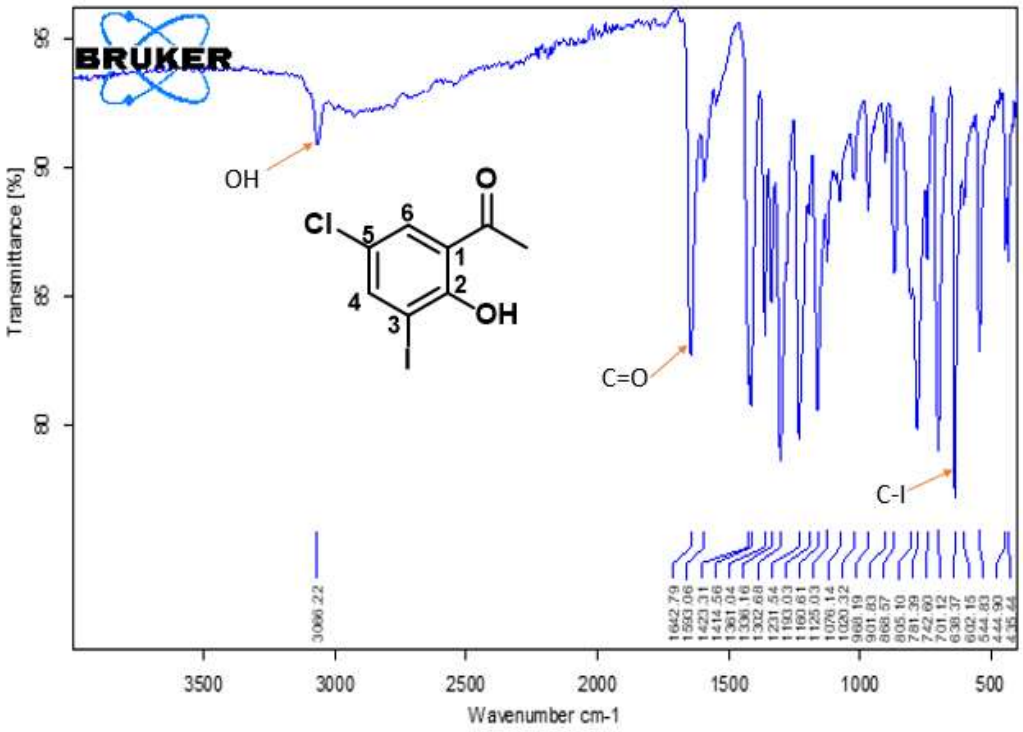
# Appendixes



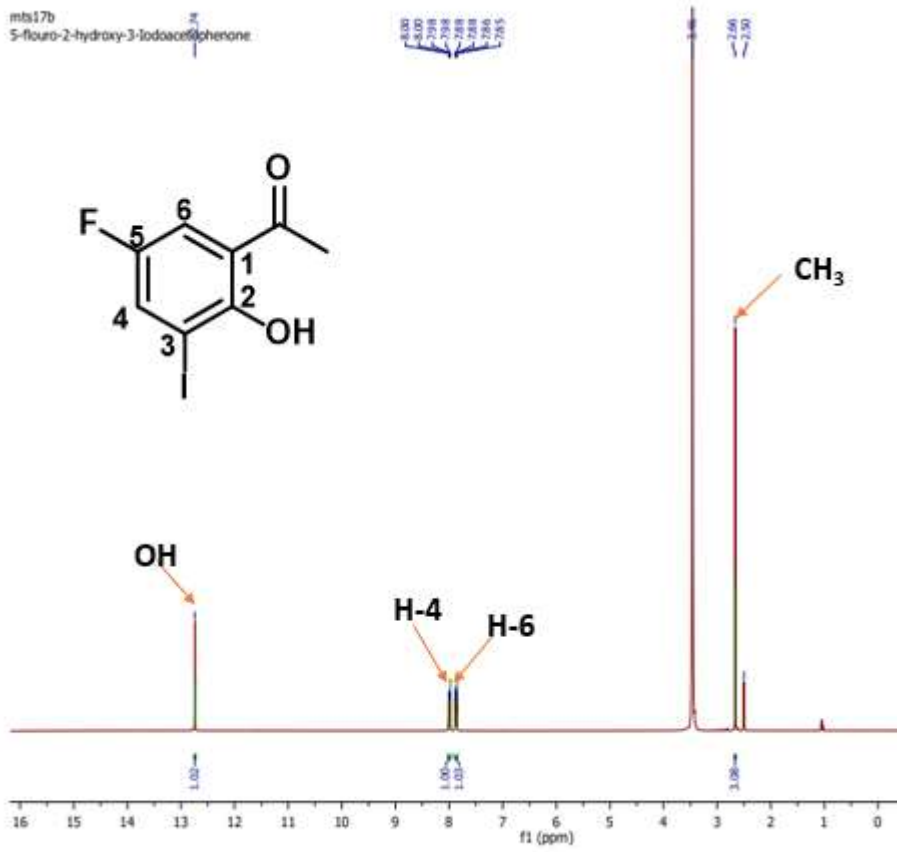

**Appendix 1**: $^{1}$H NMR spectrum of 5-chloro-2-hydroxy-3-iodoacetophenone **(58B)**



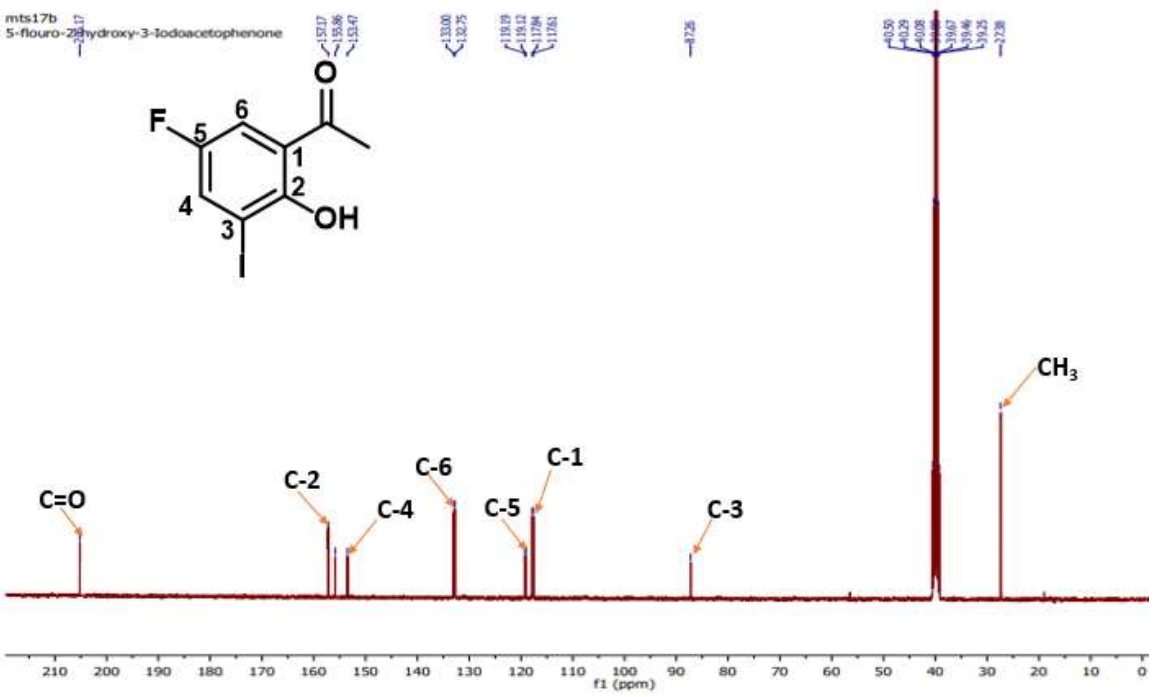

**Appendix 2:** $^{13}C$ NMR spectrum of 5-chloro-2-hydroxy-3-iodoacetophenone **(58B)**



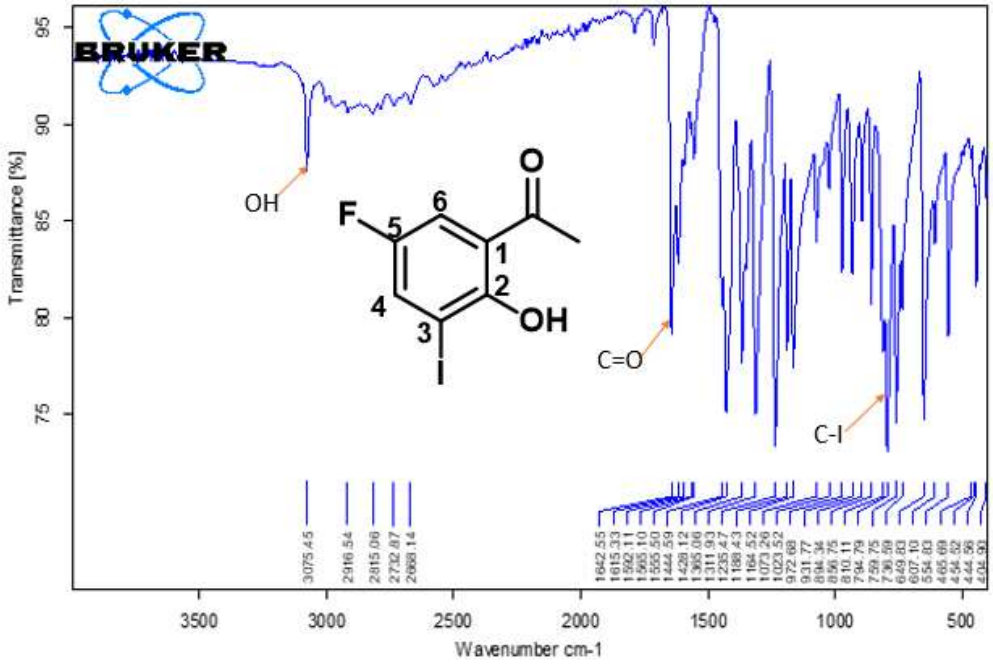

**Appendix 3:** IR spectrum of 5-chloro-2-hydroxy-3-iodoacetophenone **(58B)**



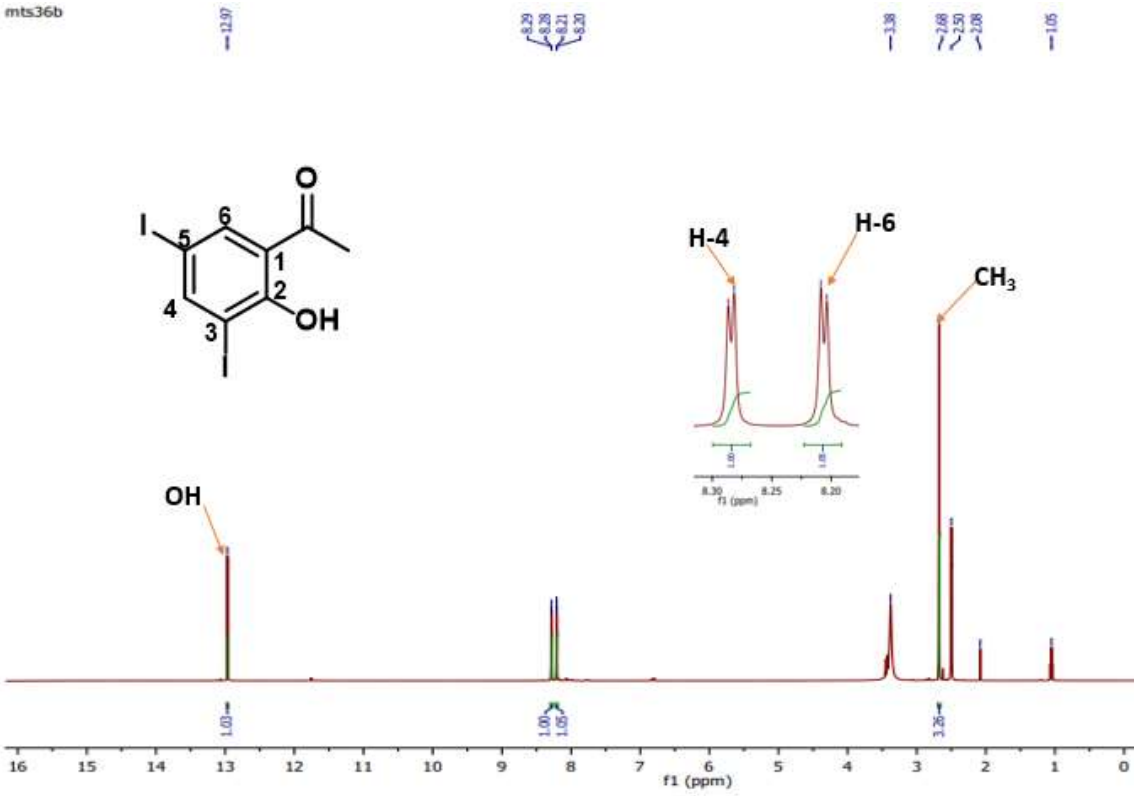

**Appendix 4:** $^{1}$H NMR spectrum of 5-fluoro-2-hydroxy-3-iodoacetophenone **(58C)**



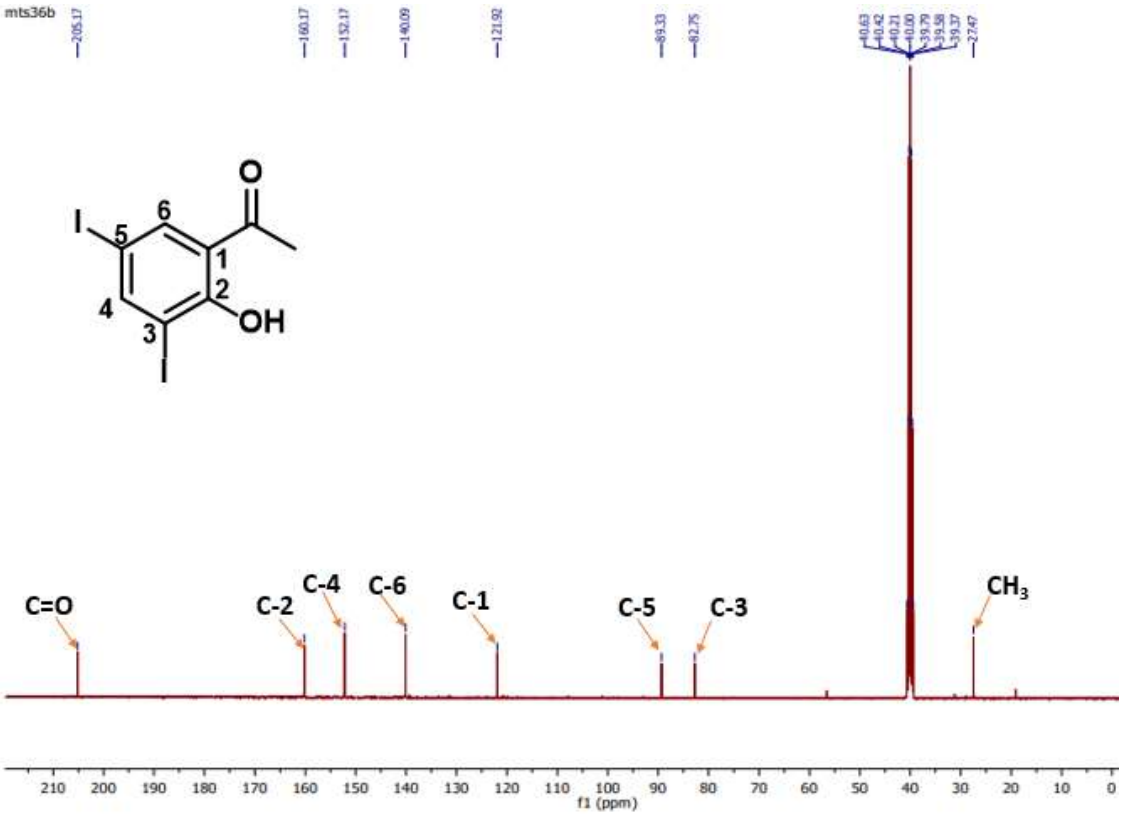

**Appendix 5:** $^{13}C$ NMR spectrum of 5-fluoro-2-hydroxy-3-iodoacetophenone **(58C)**



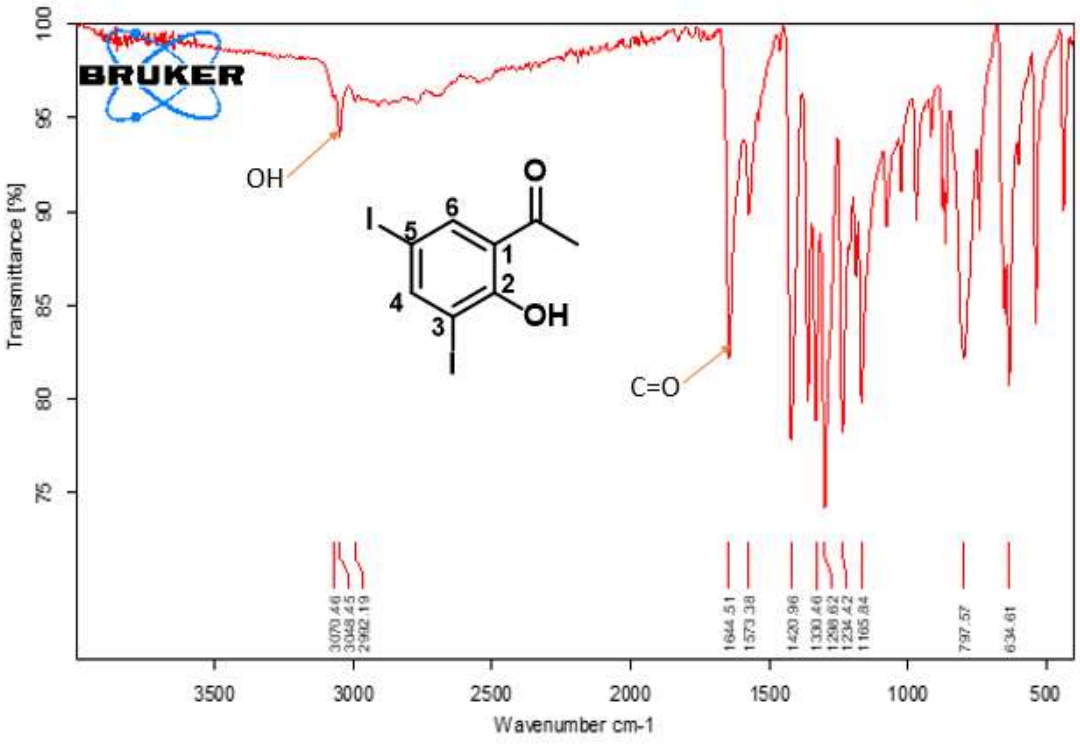

**Appendix 6**: IR spectrum of 5-fluoro-2-hydroxy-3-iodoacetophenone **(58C)**



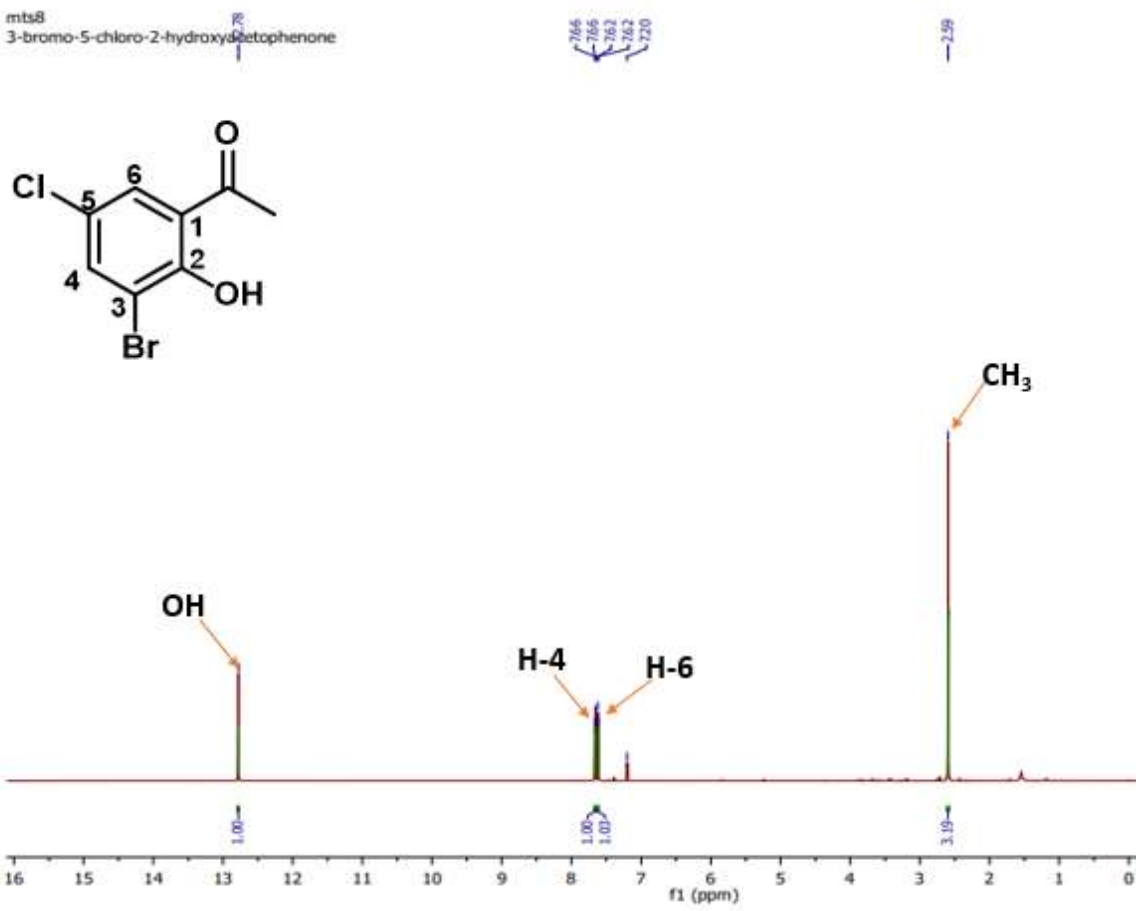

**Appendix 7:** $^{1}$H NMR spectrum of 3,5-diiodo-2-hydroxyacetophenone **(58D)**



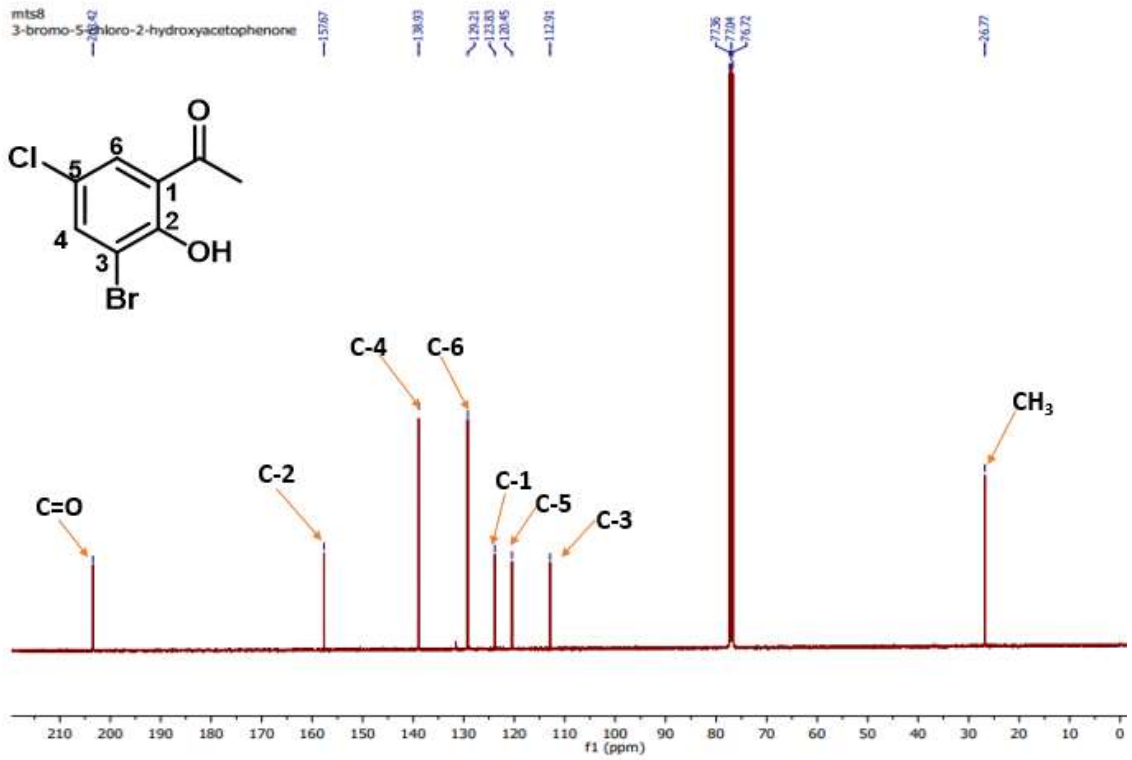

**Appendix 8:** $^{13}$C NMR spectrum of 3,5-diiodo-2-hydroxyacetophenone **(58D).**



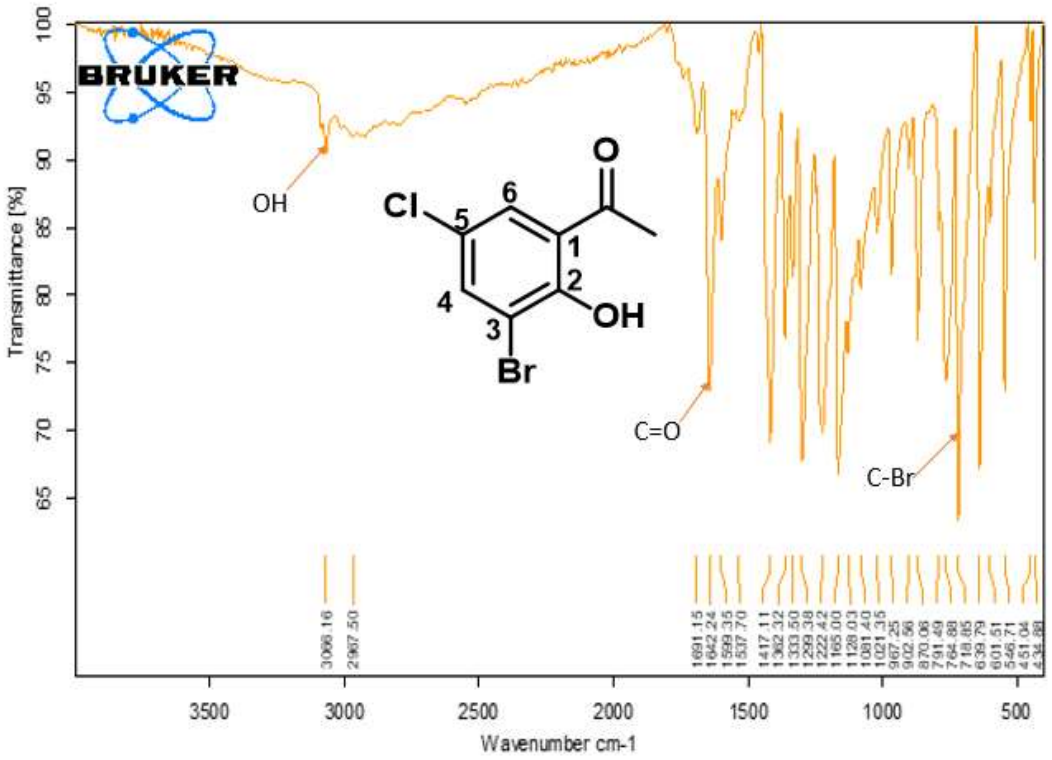

**Appendix 9:** IR spectrum of 3,5-diiodo-2-hydroxyacetophenone **(58D).**



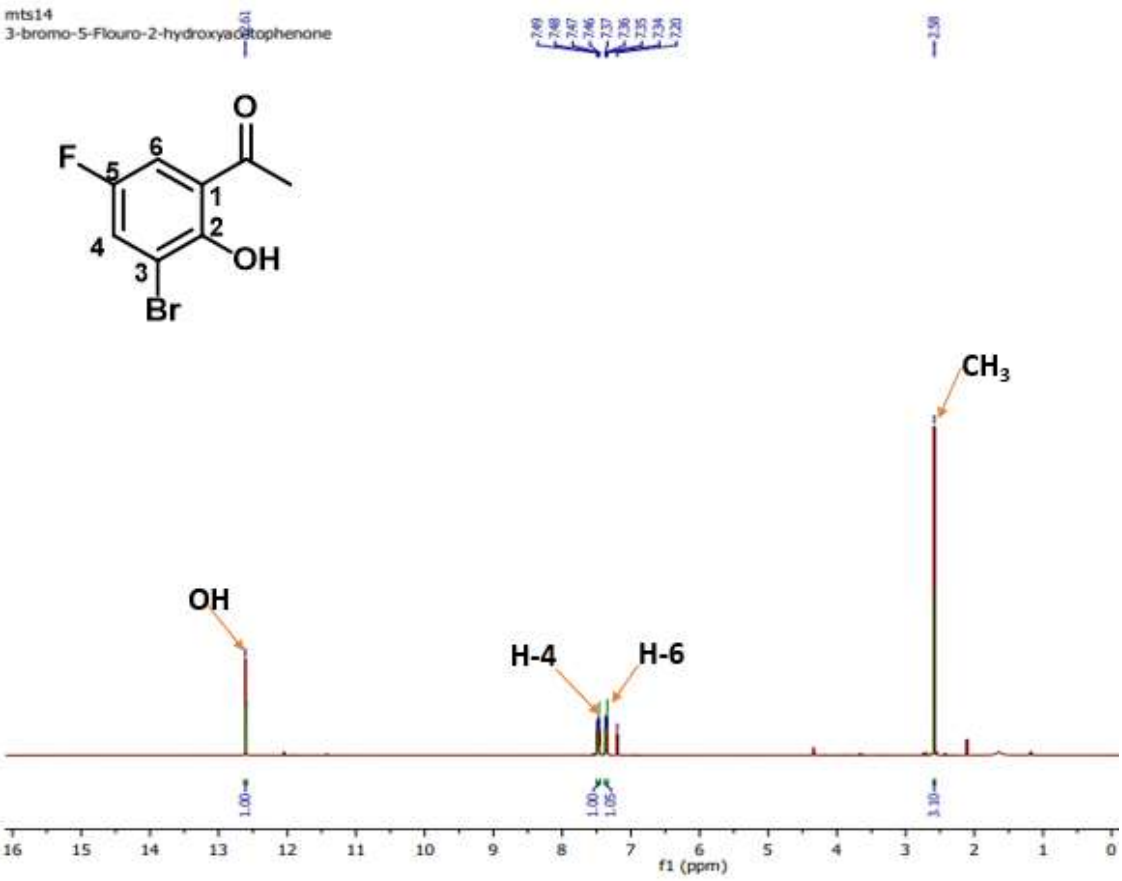

**Appendix 10:** $^{1}$H NMR spectrum of 3-bromo-5-chloro-2-hydroxyacetophenone **(63B)**



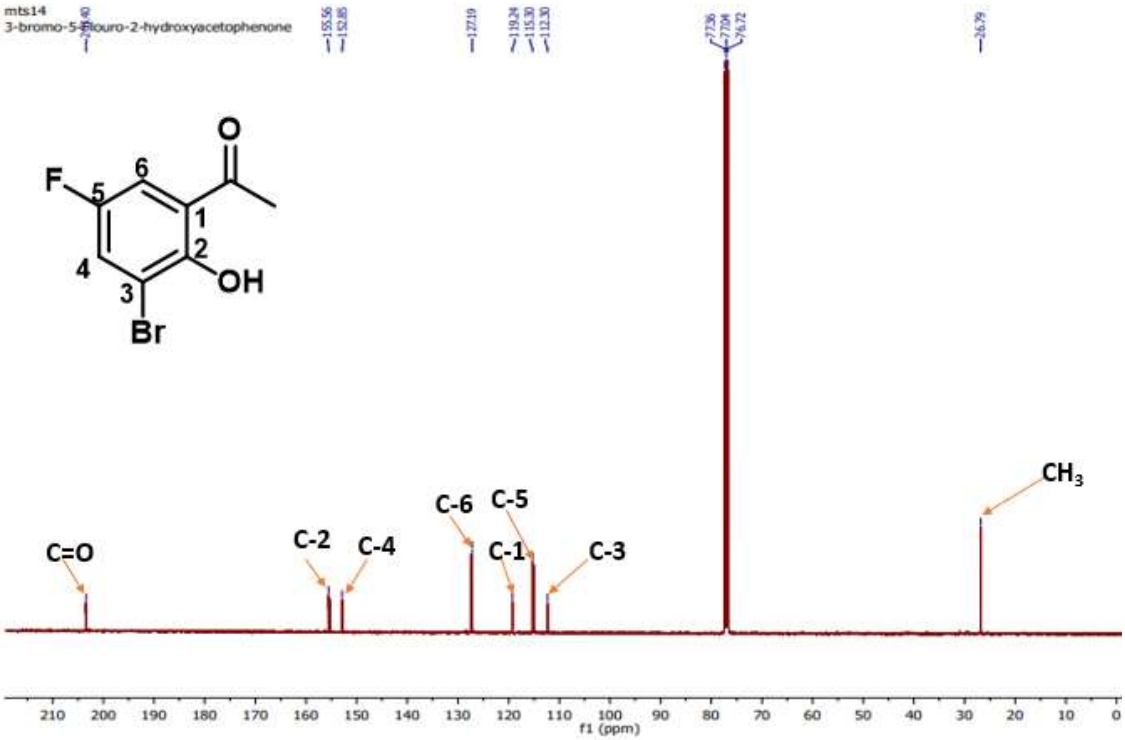

**Appendix 11:** $^{13}C$ MNR spectrum of 3-bromo-5-chloro-2-hydroxyacetophenone **(63B).**



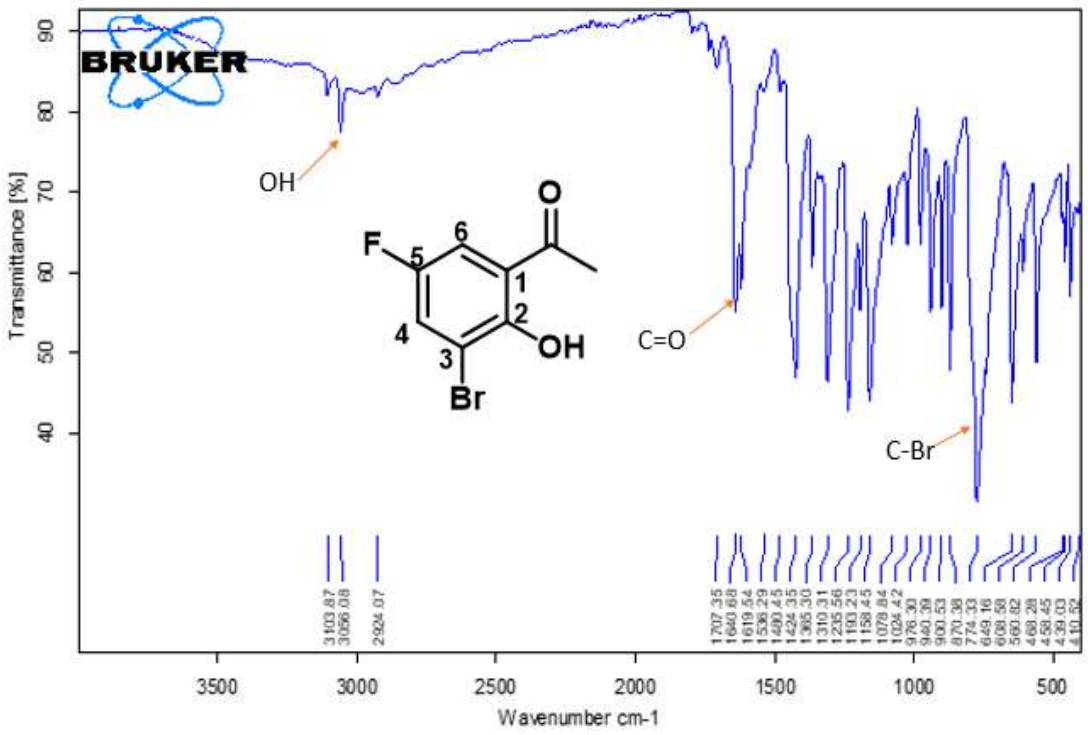

Appendix 12: IR spectrum 3-bromo-5-chloro-2-hydroxyacetophenone **(63B).**



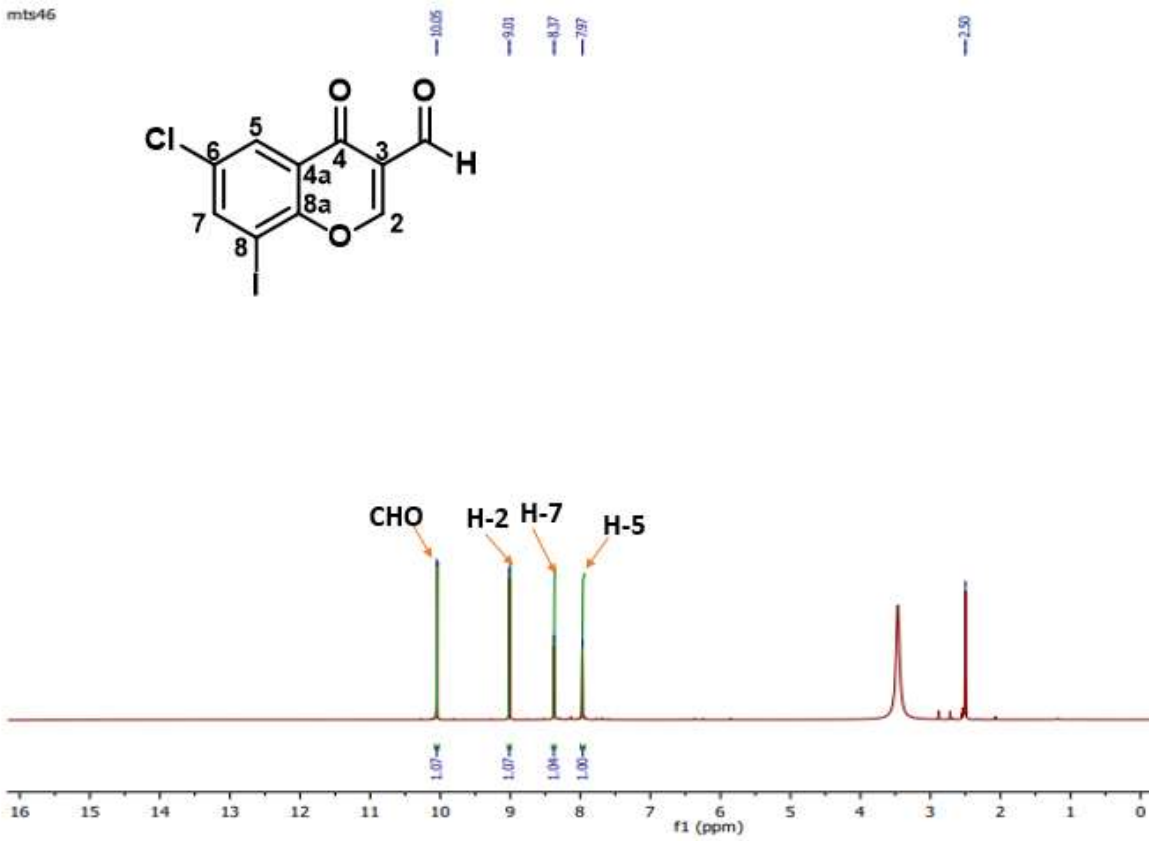

**Appendix 13:** $^{1}$H NMR spectrum of 3-bromo-5-fluoro-2-hydroxyacetophenone **(63C).**



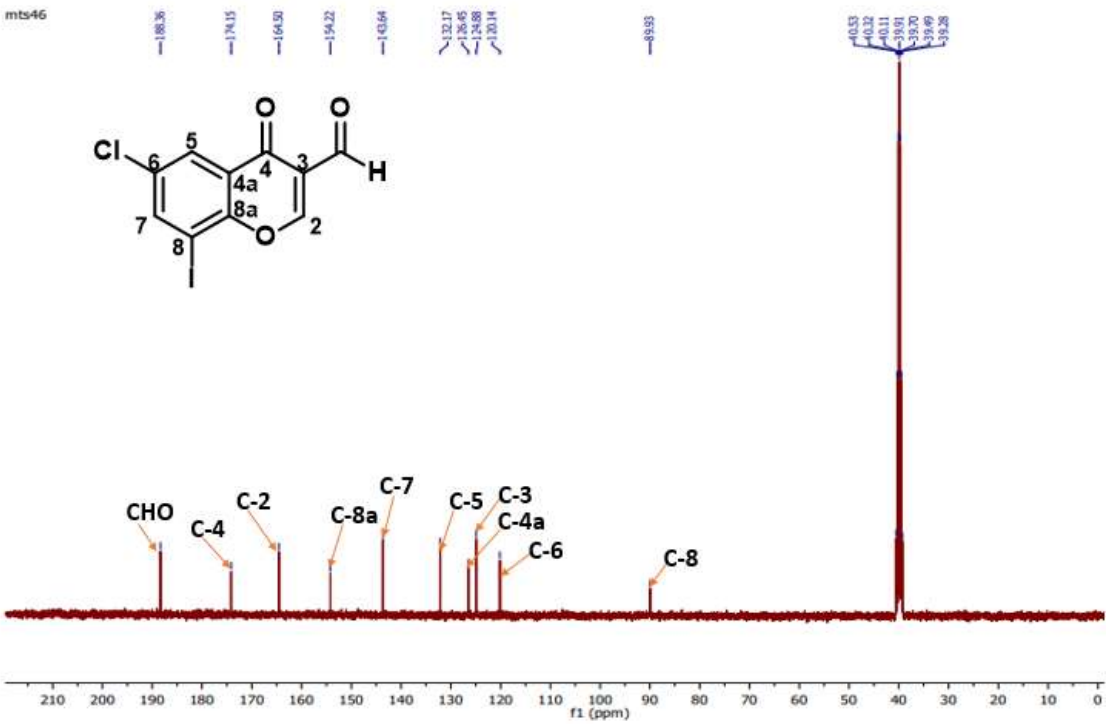

**Appendix 14:** $^{13}C$ NMR spectrum of 3-bromo-5-fluoro-2-hydroxyacetophenone **(63C).**



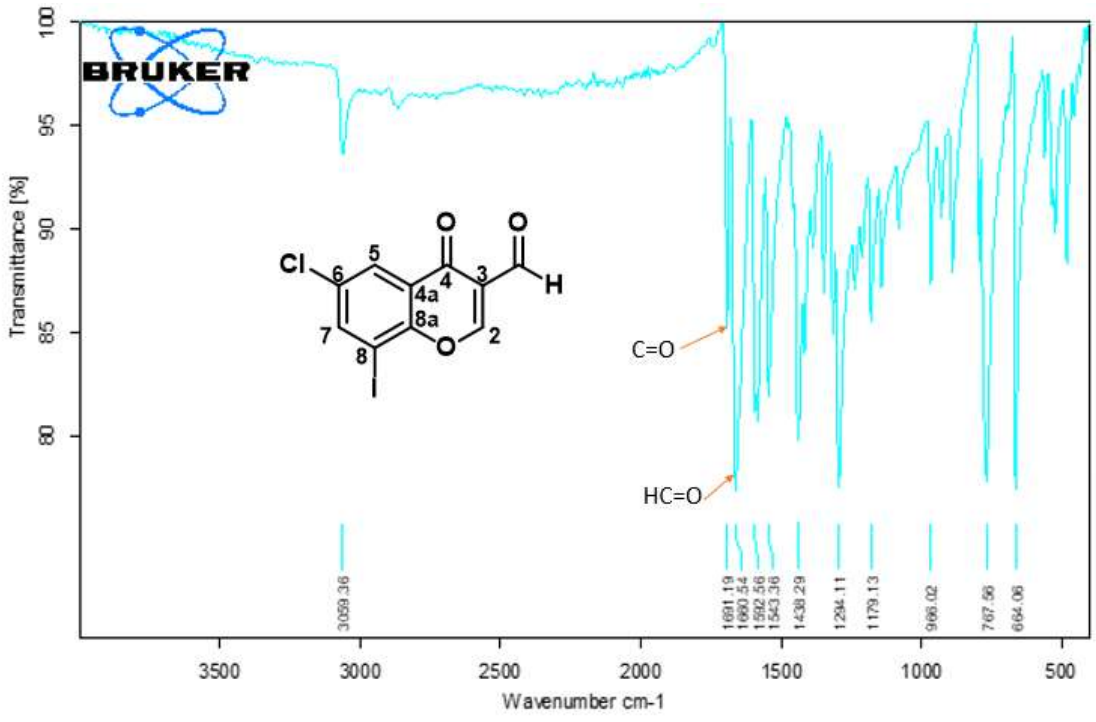
**Appendix 15:** IR spectrum of 3-bromo-5-fluoro-2-hydroxyacetophenone **(63C).**



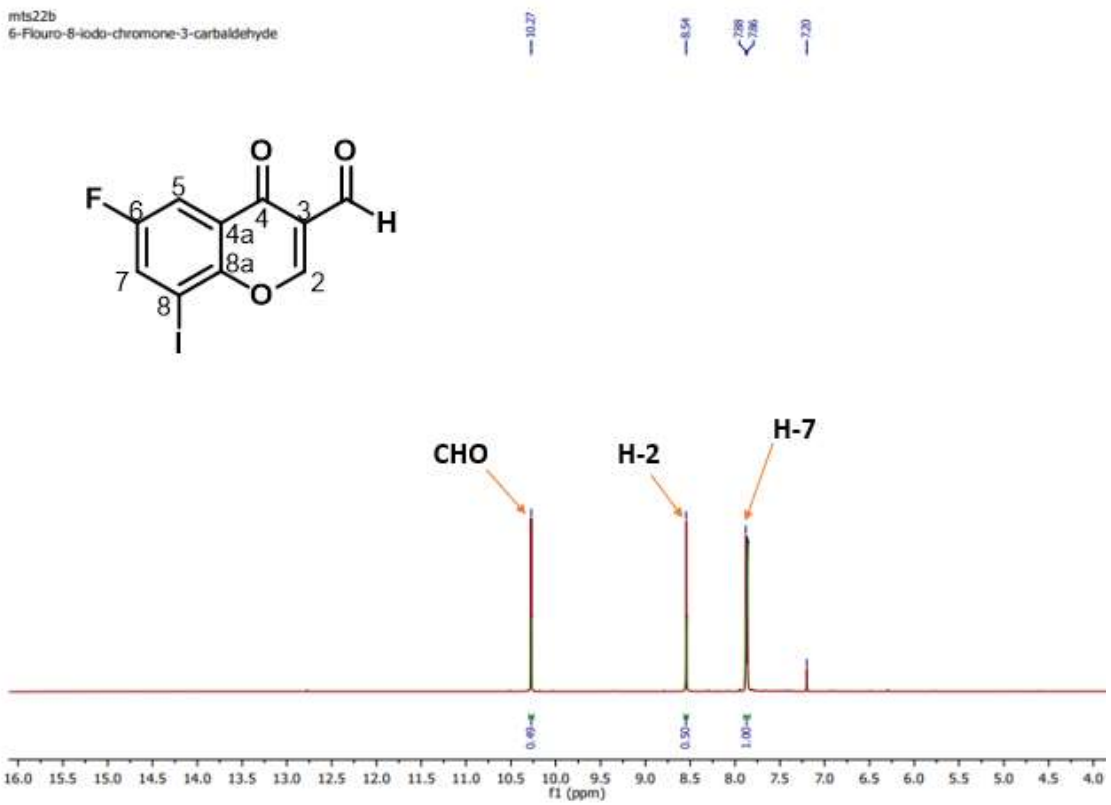

**Appendix 16:** $^{1}$H NMR spectrum of 6-chloro-8-iodochromone-3-carbaldehyde **(59B).**



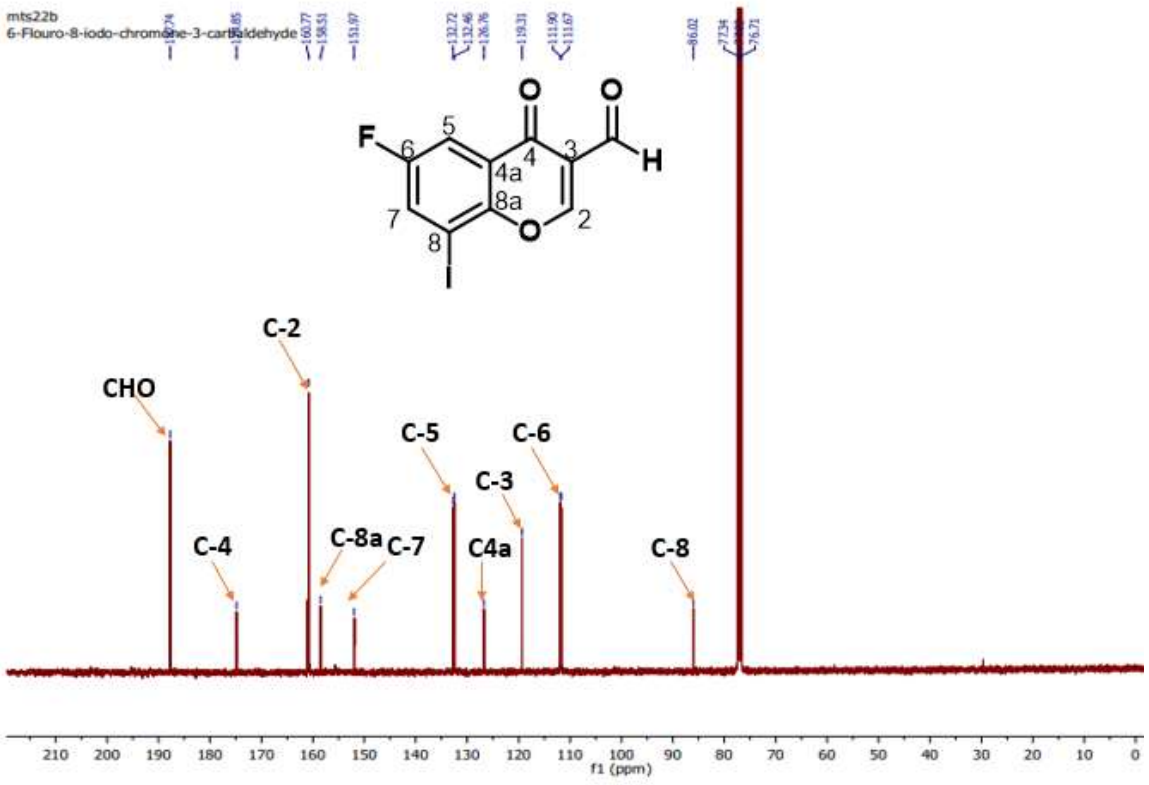

**Appendix 17:** $^{13}C$ NMR spectrum of 6-chloro-8-iodochromone-3-carbaldehyde **(59B).**



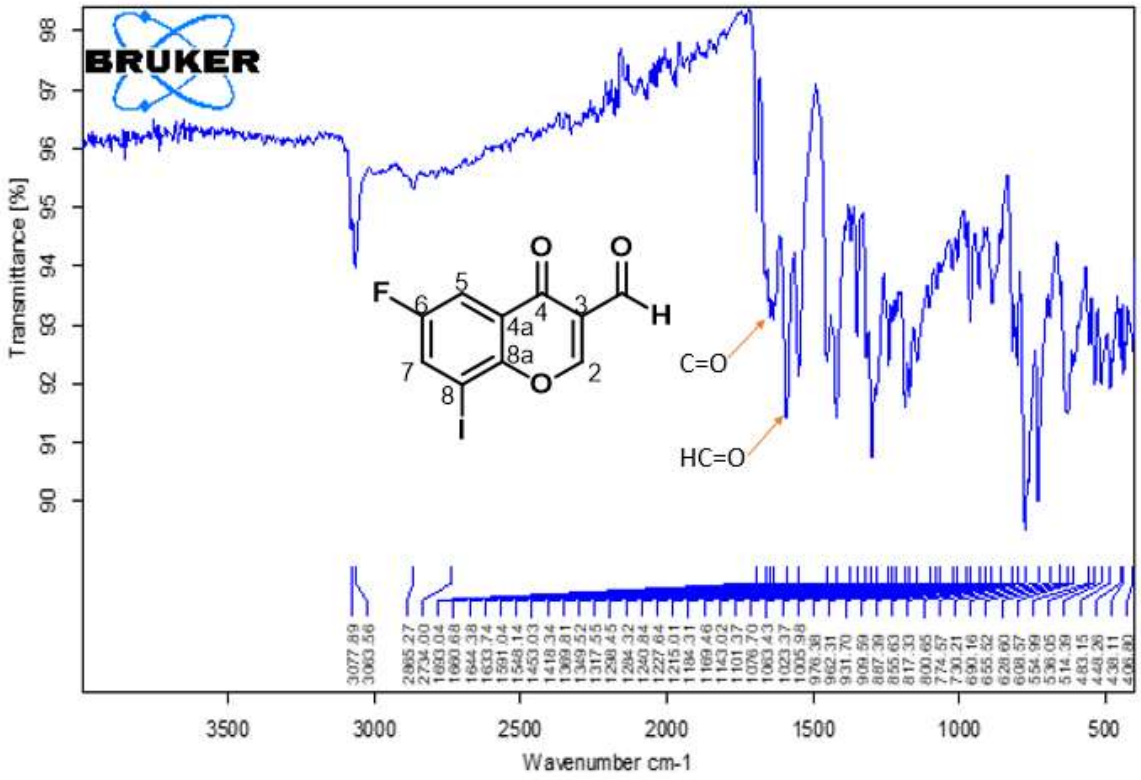

**Appendix 18:** IR spectrum of 6-chloro-8-iodochromone-3-carbaldehyde **(59B).**



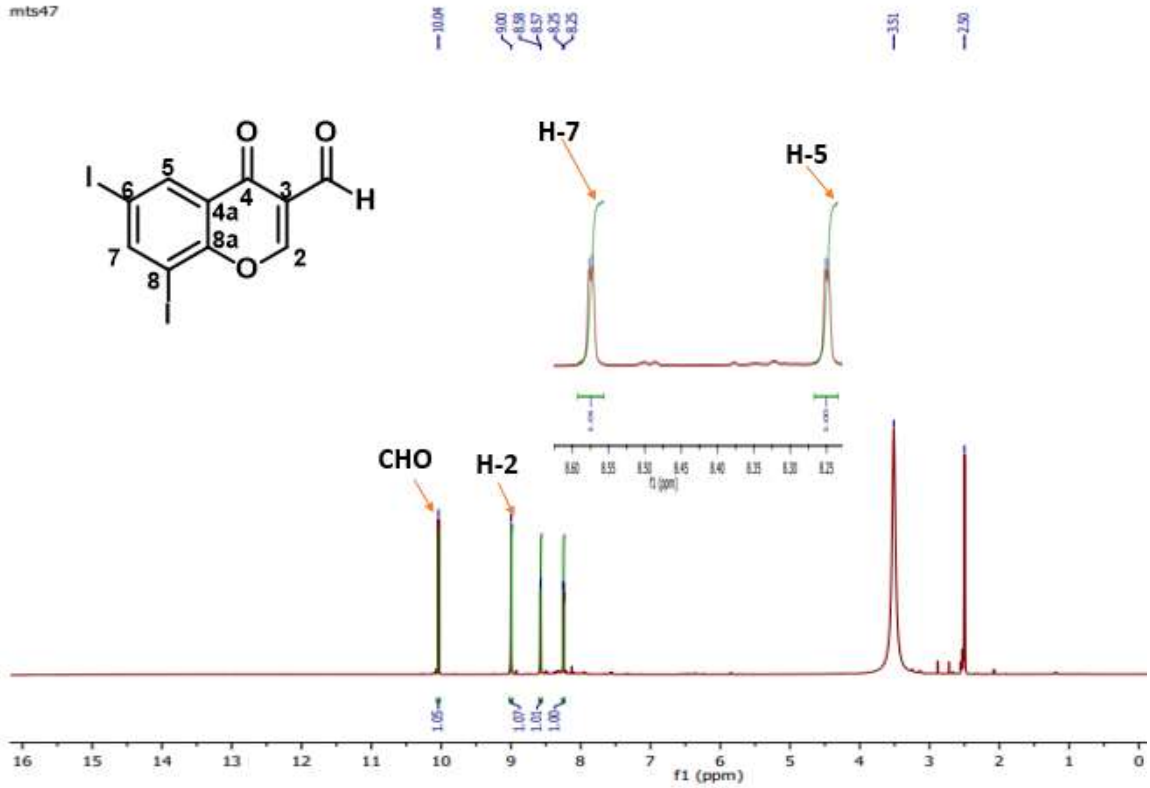

**Appendix 19:** $^{1}$H NMR spectrum of 6-fluoro-8-iodochromone-3-carbaldehyde **(59C).**



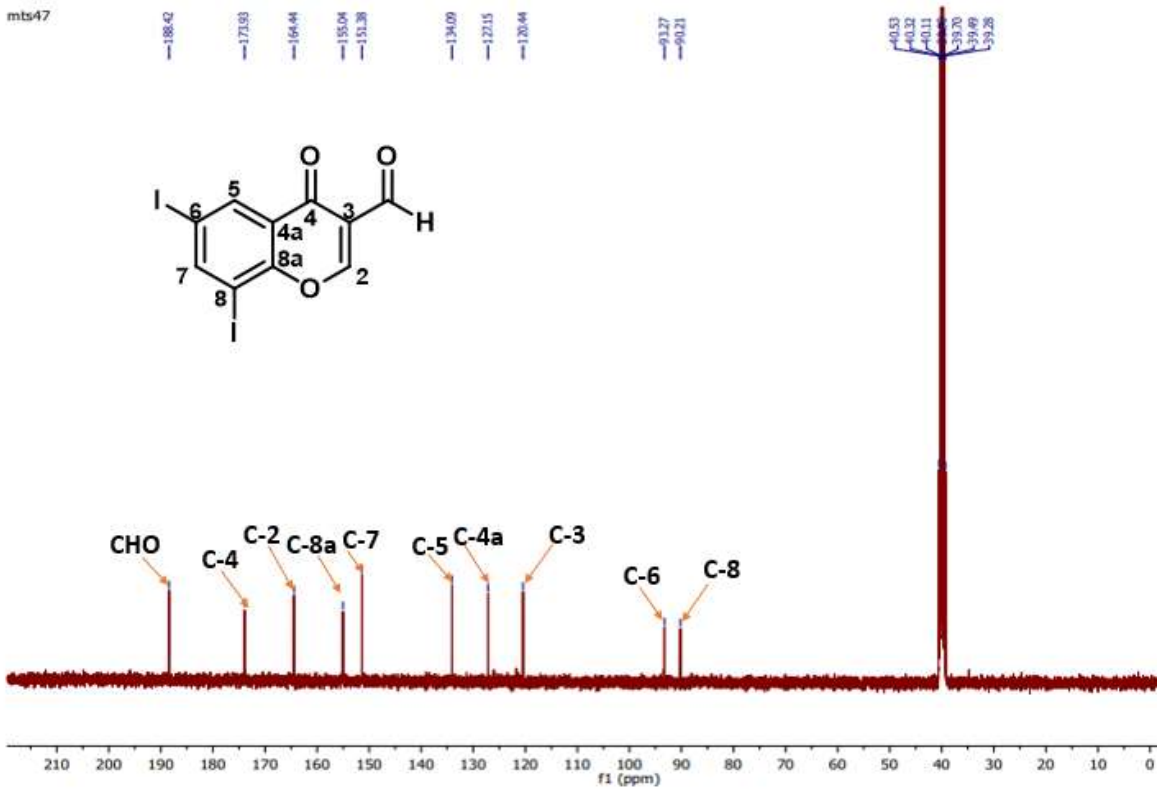

**Appendix 20:** $^{13}$C NMR spectrum of 6-fluoro-8-iodochromone-3-carbaldehyde **(59C).**



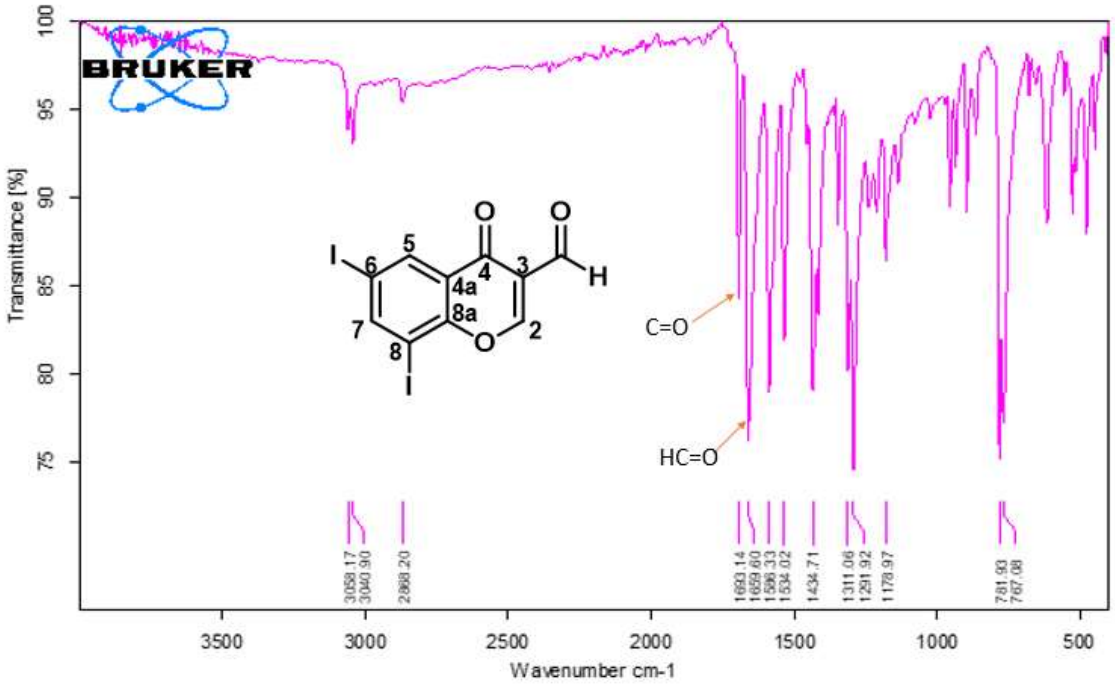

**Appendix 21:** IR spectrum of 6-fluoro-8-iodochromone-3-carbaldehyde **(59C).**



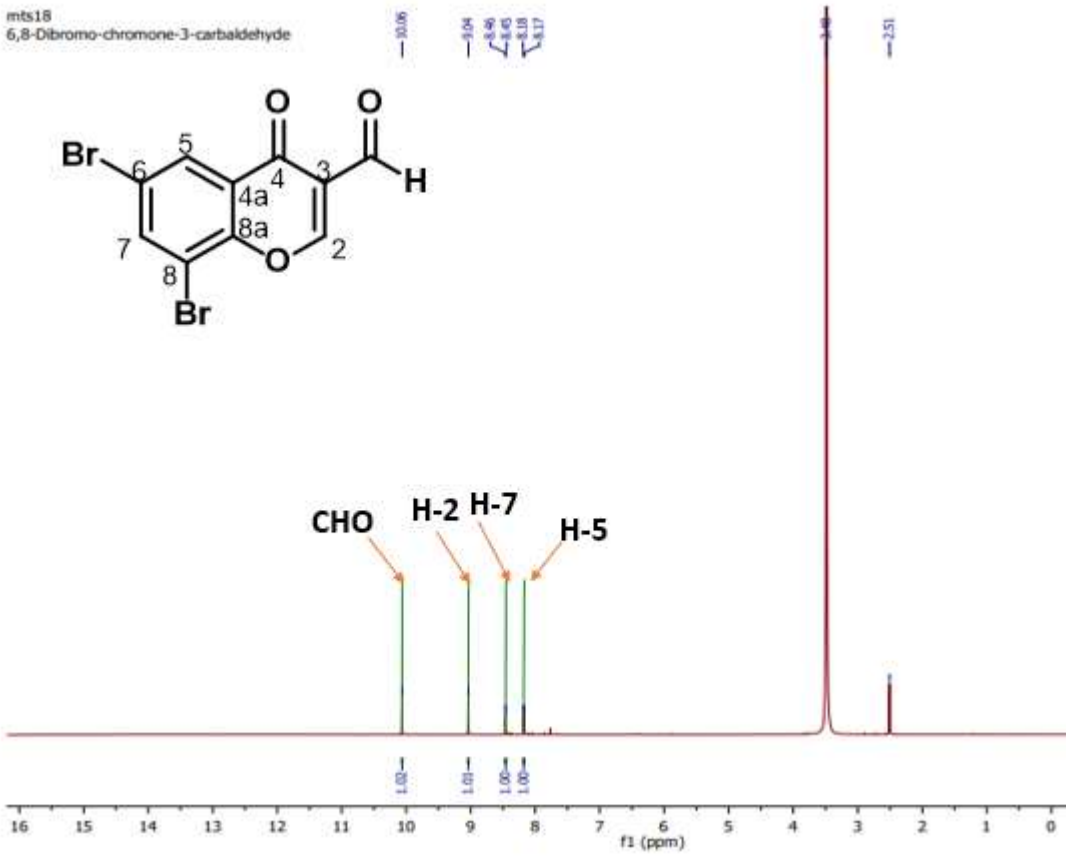

**Appendix 22:** $^{1}$H NMR spectrum of 6,8-diiodochromone-3-carbaldehyde **(59D).**



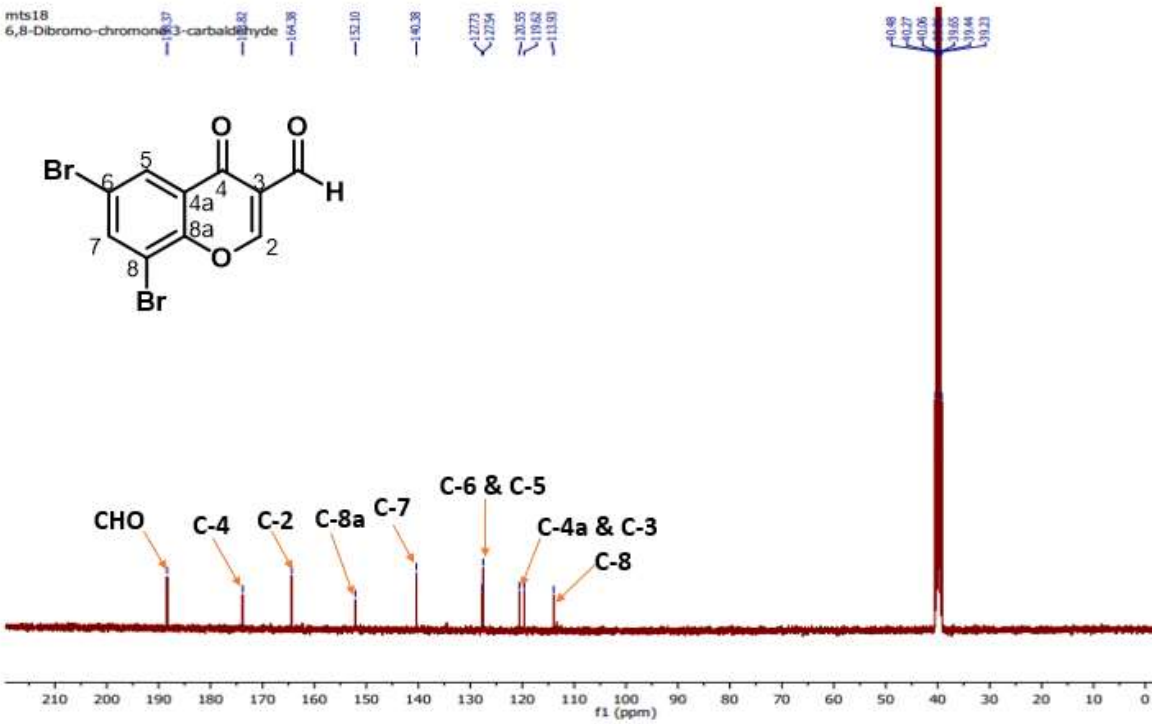

**Appendix 23:** $^{13}C$ NMR spectrum of 6,8-diiodochromone-3-carbaldehyde **(59D).**



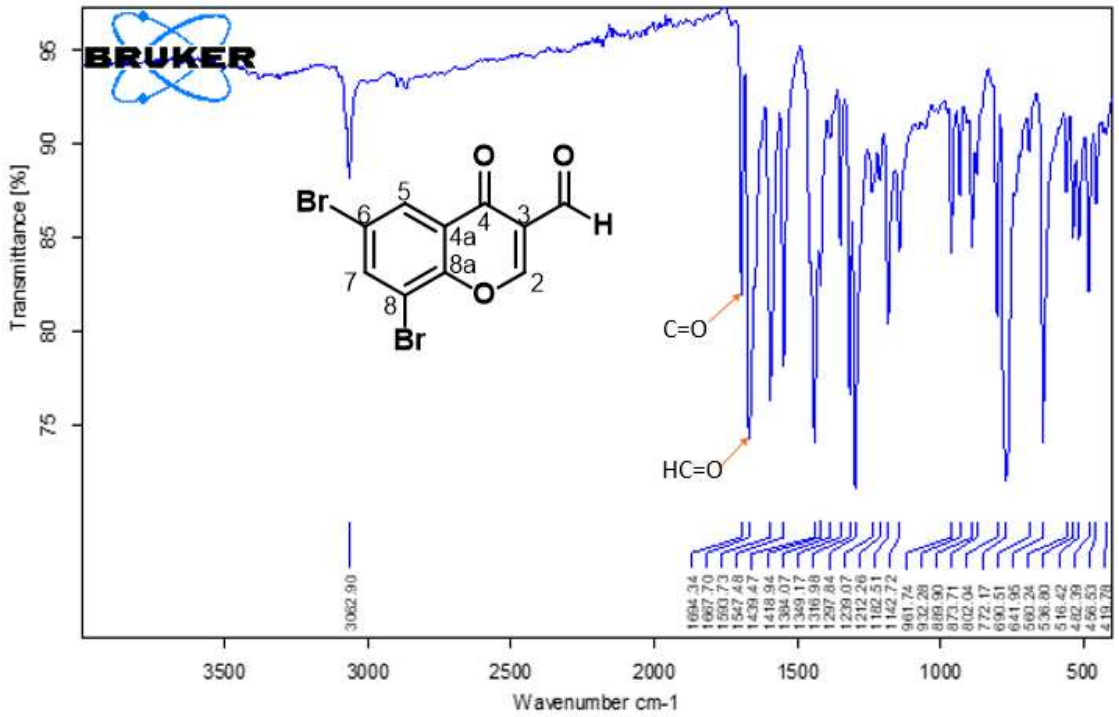

**Appendix 24:** IR spectrum of 6,8-diiodochromone-3-carbaldehyde **(59D)**



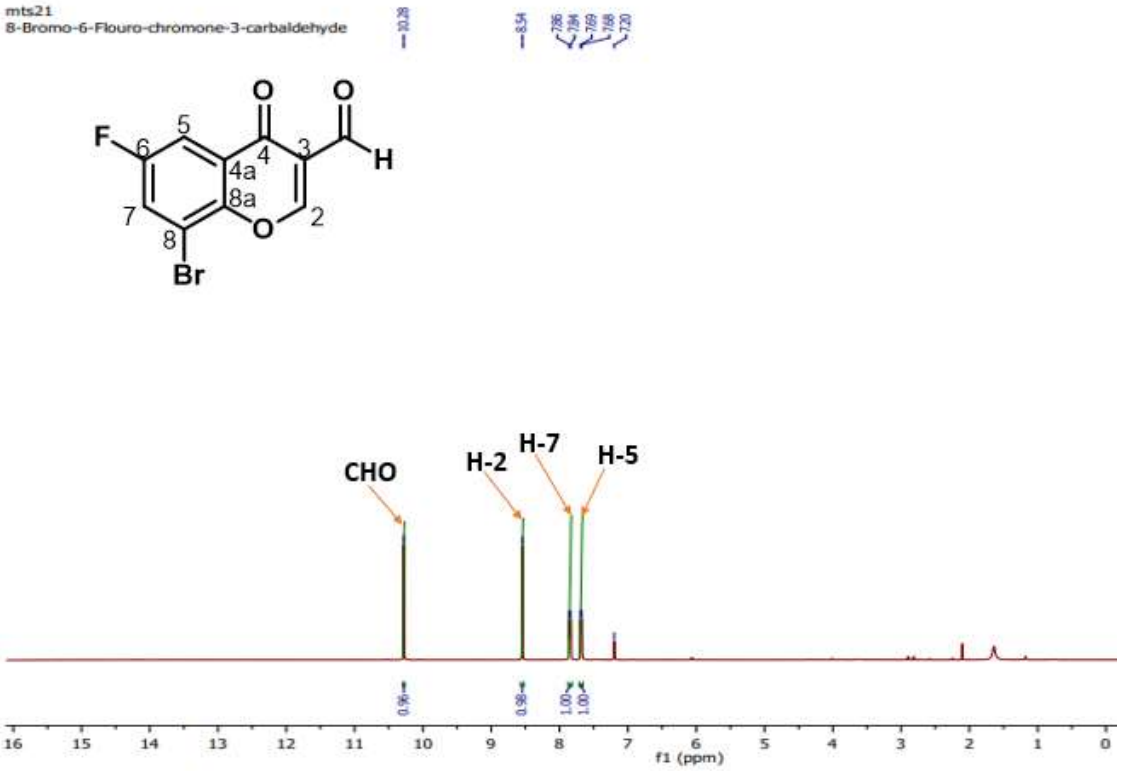

**Appendix 25:** $^{1}H$ NMR spectrum of 6,8-dibromochromone-3-carbaldehyde **(64B).**



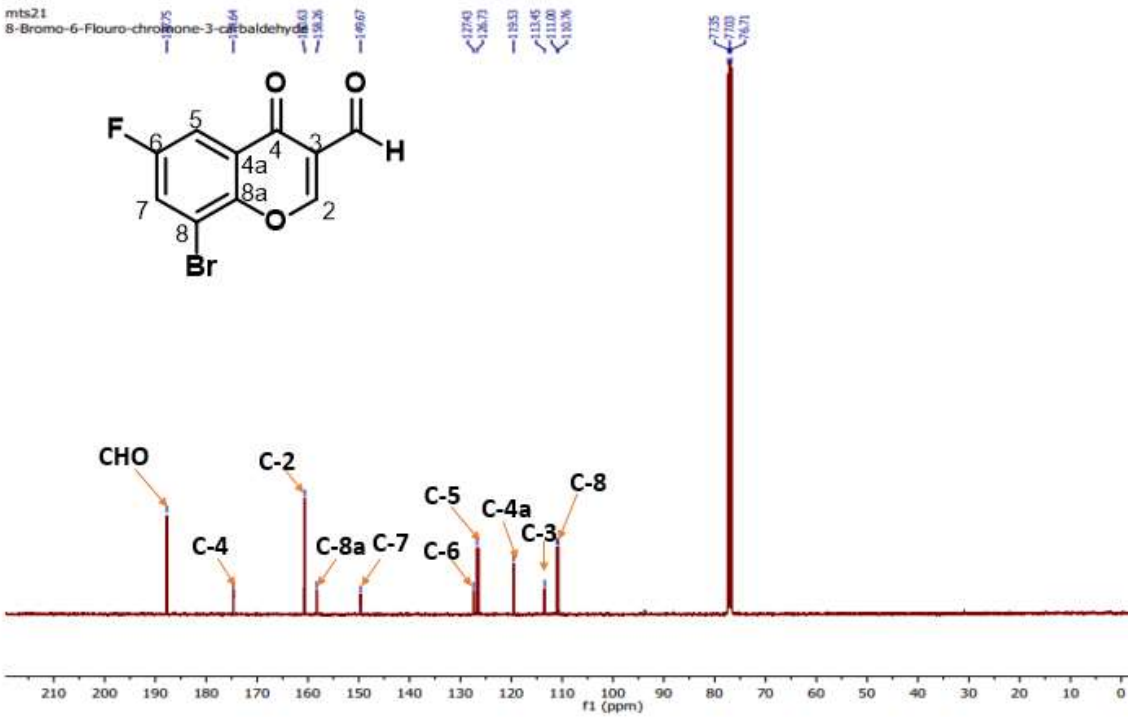

**Appendix 26:** $^{13}C$ NMR spectrum of 6,8-dibromochromone-3-carbaldehyde **(64B).**



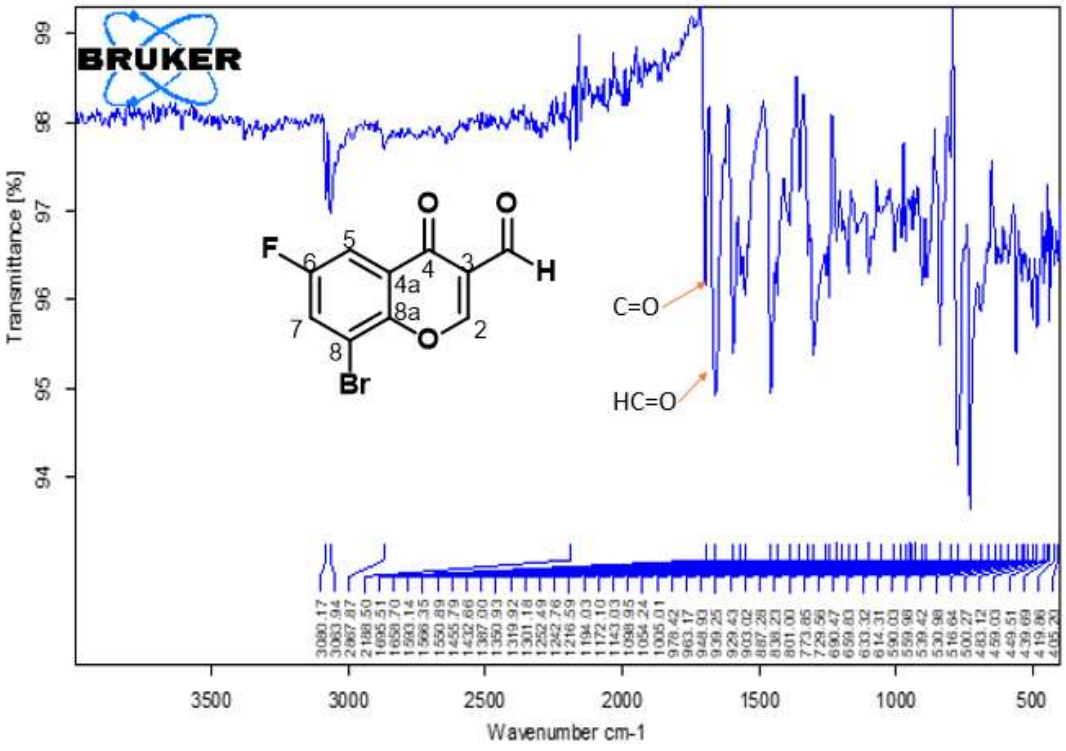

**Appendix 27:** IR spectrum of 6,8-dibromochromone-3-carbaldehyde **(64B).**



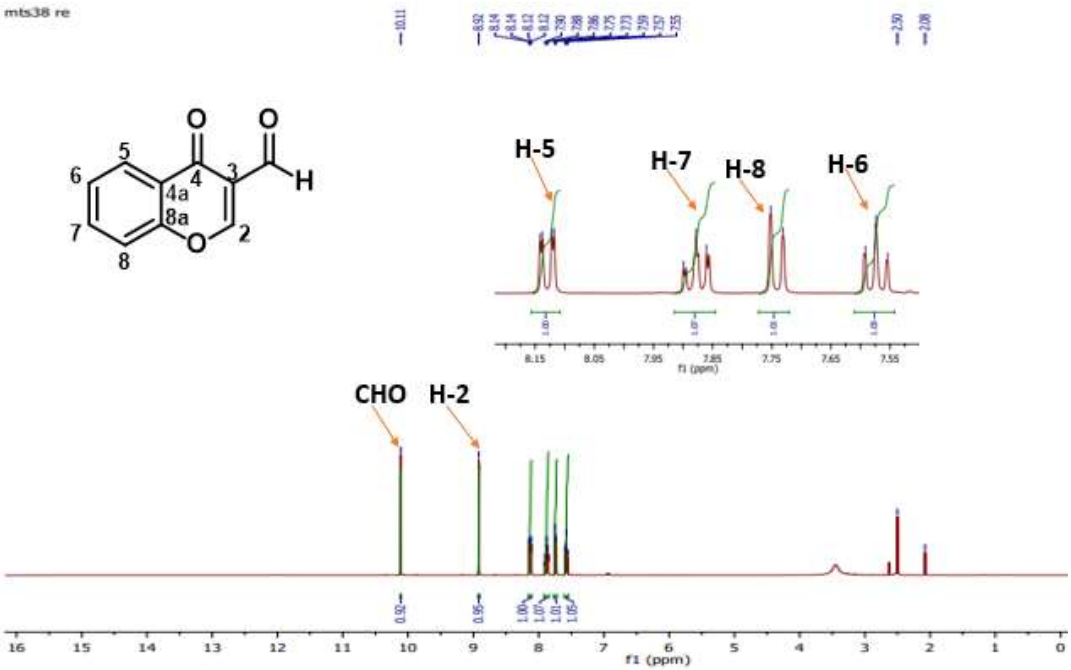

**Appendix 28:** $^{1}$H NMR spectrum of 8-bromo-6-fluorochromone-3-carbaldehyde **(64C).**



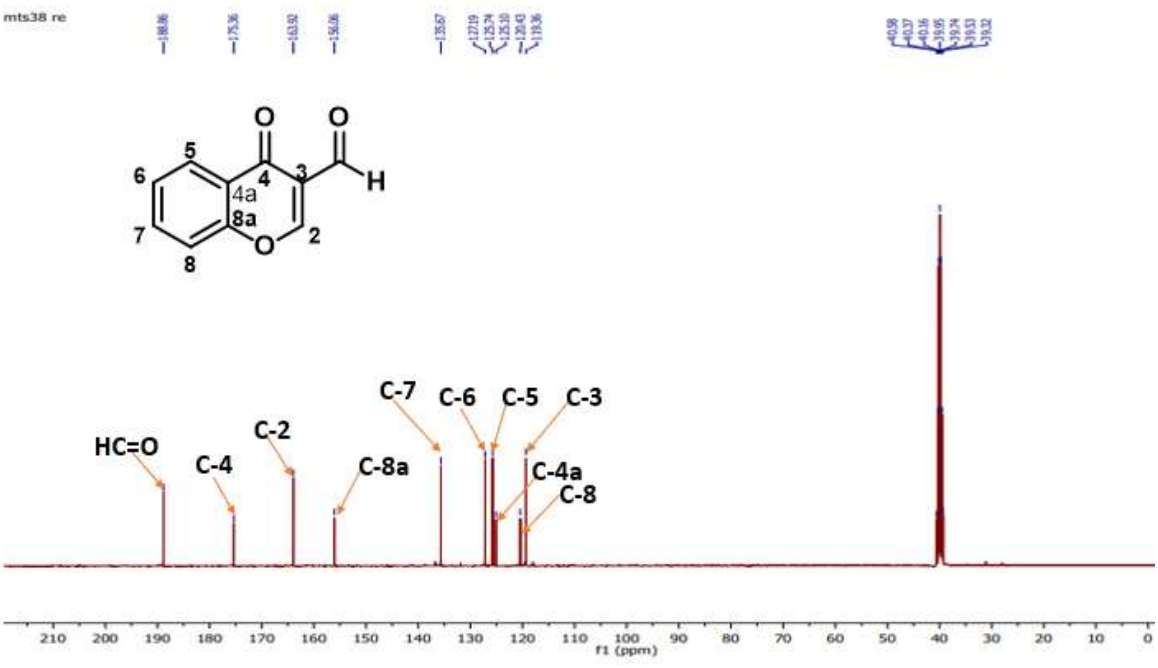

**Appendix 29:** $^{13}C$ NMR spectrum of 8-bromo-6-fluorochromone-3-carbaldehyde **(64C)**



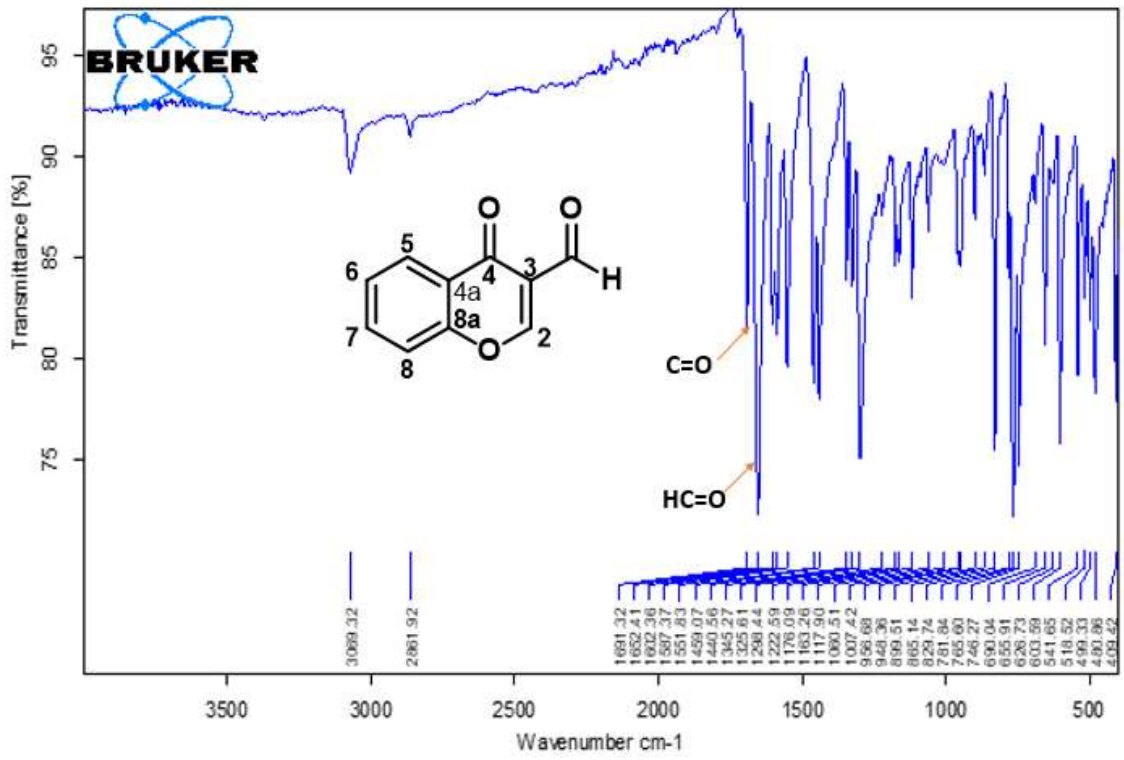

**Appendix 30:** IR spectrum of 8-bromo-6-fluorochromone-3-carbaldehyde **(64C)**



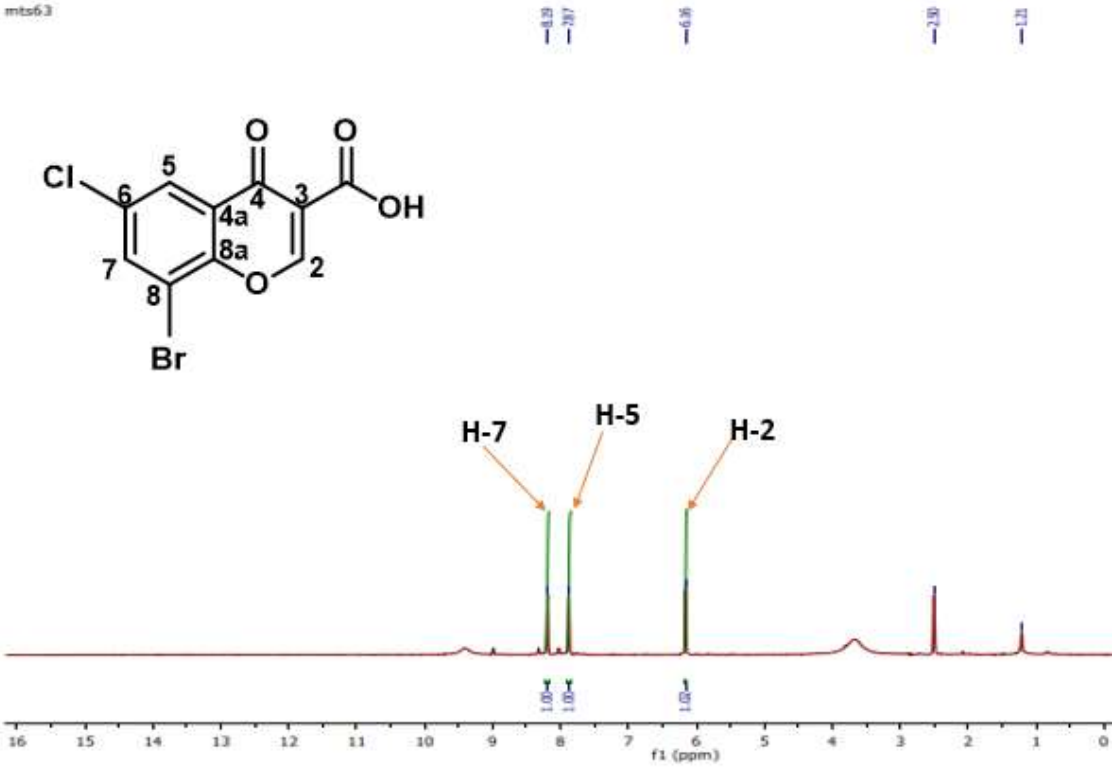

**Appendix 31:** $^{1}$H NMR spectrum of chromone-3-carbaldehyde **(59E).**



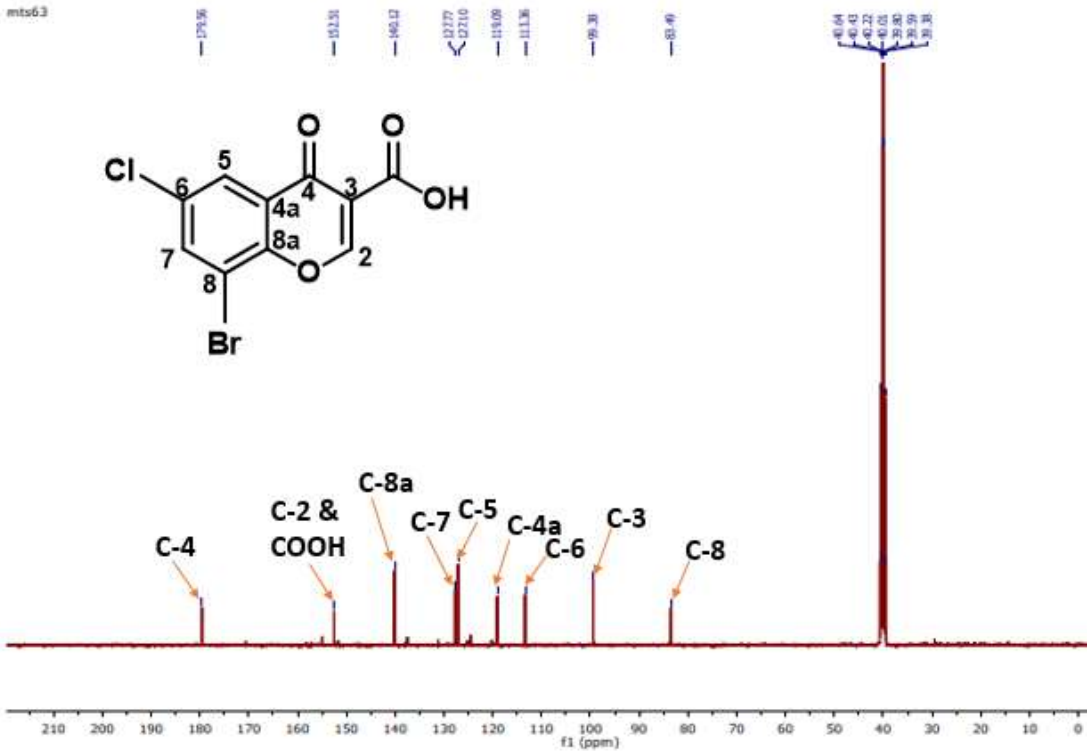

**Appendix 32:** $^{13}$C NMR spectrum of chromone-3-carbaldehyde **(59E).**




**Appendix 33:** IR spectrum of chromone-3-carbaldehyde **(59E).**




**Appendix 34:** $^{1}$H NMR spectrum of 8-bromo-6-chlorochromone-3-carboxylic acid (**65B).**




**Appendix 35:** $^{13}$C NMR spectrum of 8-bromo-6-chlorochromone-3-carboxylic acid (**65B).**