Synthesis of novel-6.8-disubstituted-chromone-2-carboxylic acid derivatives and their biological evaluation as potential antimalarial agents

by

MABASA NYIKO SAMUEL

14001601

Dissertation for the Master of Science Degree in the **field of Chemistry**

Faculty of Science, Engineering and Agriculture

Department of Chemistry

University of Venda

Thohoyandou, Limpopo

South Africa

Student: N.S Mabasa

Supervisor: Prof I.D.I Ramaite

Co-supervisor: Dr N.T Tavengwa

Declaration

I, Mabasa Nyiko Samuel, hereby affirm that the dissertation I am submitting for the University of Venda's Master of Science in Chemistry degree has never been submitted before for a degree from this or any other University. In terms of design and execution, it is my own work, and all citations used in this text have been acknowledged.

Signature:  **Date:** 09 March 2023

Plagiarism declaration

I, Mabasa Nyiko Samuel, hereby affirm the following:

- I understand and agree that plagiarism is unacceptable. Plagiarism is a serious academic offense for which the university may impose severe penalties. Plagiarism is a use of another person's ideas or published work as one's own.
- I affirm that I am the author of this thesis and I have properly acknowledged the contributions of others. For this degree, the work has never before been submitted to the University of Venda or another institution.
- I have not permitted and will not permit anyone to duplicate my own work with the goal of misrepresenting it as their own.

Signature:  Date: 16 August 2023

Abstract

Malaria is a mosquito vector-borne disease caused by a female anopheles mosquito belonging to a *plasmodium genus*, affecting more than 500 million people per annum. There are five *plasmodium genus* responsible for causing malaria, but four of them are responsible for causing human malaria. The most common one to cause malaria in Africa is *P.Falciparum*. The most commonly used drugs for malaria are quinine derivatives and artemisinin derivatives which are both derived from traditional plants. Malaria parasites have become resistance to almost all the currently used drugs.

In this project different synthetic approaches were used to prepare novel chromone derivatives. This study was focused on the synthesis of various 6.8-substituted-chromone-2-carboxylic acids **(41)** derivatives from the corresponding 5-substituted-2-hydroxyacetophenones **(38)**. The first step included the introduction of iodine on the 5-subsituted-2-hydroxyacetophenones **(38)** to give 5-substituted-3-iodo-2-hydroxyacetophenones **(39A-D)**. The same step was repeated but with bromine to give 5-substituted-3-bromo-2-hydroxyacetophenones **(39E-H)**. The 3.5-disubstituted-2-hydroxyacetophenones **(39A-H)** underwent condensation with diethyl oxalate and sodium ethoxide to form ethyl-6.8-disubstituted-chromone-2-carboxylates **(40A-H)**, which was converted to the corresponding 6.8-disubstituted-carboxylic acids (**41A-H)**. Attempted conversion of the acids to the corresponding carboxamides **43** *via* the carbonyl chloride intermediates **(42A-D)** was unsuccessful.

The percentage yield of synthesized 3.5-disubstituted-hydroxyacetophenones **(39A-H)** ranged between 46-82 %, whilst those of ethyl-6.8-disubstituted-chromone-2-carboxylates **(40A-H)** intermediates ranged between 44-95 %. The yields of synthesized 6.8-disubstituted-chromone-2-carboxylic acids **(41A-H)** ranged between 48-98 % while the corresponding acids chlorides **(42A-D)** ranged between 44-60 %. Our attempted synthesis of 6.8-disubstituted-chromone-2-carboxamides **(43)** was unsuccessful.

Compounds (**39-43)** were purified by recrystallization and characterized using NMR and FTIR spectroscopic techniques.

Keywords: *chromones, synthesis, malaria, bioactivity, drug resistance.*

Acknowledgement

Firstly, I want to express my gratitude to the Almighty God for giving me the courage and wisdom I needed to finish my dissertation.

I would like to express profound gratitude and sincere thanks to my supervisor Prof I.D.I Ramaite for his guidance, facilitation, oversight and concrete effective help through-out this project. Your contribution cannot be overstated because your advice made what look almost impossible at the beginning very much possible at the end.

I would also like to thank my co-supervisor Dr N.T Tavengwa for his contribution throughout this research. I would like to extend my gratitude for the funding he gave me and the research reagents that were purchased from his research funds. Your contribution didn't go unnoticed.

I would also like to thank Dr Maluta for the funding he provided during my extension period.

I would like to express my gratitude to the University of Venda's Chemistry department.

I would like to extend my gratitude to my lab mates, Malusela Thisundiwi, Tshifaro Bongani and Nyembe Sihle.

Lastly but not least I would like to send special thanks to our lab technician, Mr F.B Mutshaeni and our NMR facilitator, Mr P Pandelani.

Dedication:

This research is dedicated to my mother **(Mabasa Ntovhedzeni Caroline),** she is my pillar of strength and my number one motivator. Her prayers and words always motivated me to go on even when things were not promising. Her unwavering support and encouragement brought me this far and I say thank you once again.

I would also like to dedicate this study to the following people:

Mabasa Phathutshedzo Magnificent (Brother)

Mabasa Mukondeleli Solly (Brother)

Ramuya Orisedza (Brother)

Ramuhashi Shumani Samuel (Uncle)

Ramuhashi Rodgers Fhatuwani (Uncle)

Ramuhashi Azwimbavhi Dorren (Aunt)

List of Abbreviations

^{13}C NMR	Carbon Nuclear magnetic resonance
^{1}H NMR	Proton Nuclear magnetic resonance
AcOH	Acetic Acid
$CDCl_3$	Deuterochloroform
CH_3CN	Acetonitrile
CH_2Cl_2	Dichloromethane
CH_3	Methyl
CH_3O	Methoxy
DCM	Dichloromethane
DMF	N,N DimethylFormamide
DMSO	Dimethyl Sulphoxide
EtOAc	Ethyl Acetate
EtOH	Ethanol
FTIR	Fourie Transform Infrared
H_2SO_4	Sulphiric Acid
HCl	Hydrochloric Acid
Hz	Hertz
J	Coupling Constant
MHz	Megahertz
NaOEt	Sodium Ethoxide
NBS	N-Bromosuccinimide

NIS	**N-Iodosuccinimide**
$NaSO_4$	**Sodium Sulphate**
OH	**Hydroxyl**
ppm	**Parts Per Million**
rt	**Room Temperature**
TLC	**Thin Layer Chromatography**
WHO	**World Health Organization**

List of Tables

List of Figures

List of Schemes

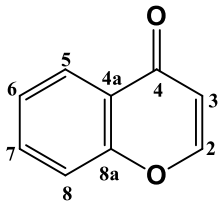
List of Appendixes

Table of Contents

CHAPTER 1

1.1 General description of chromones

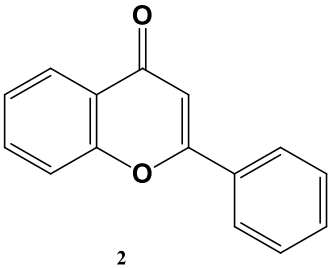
Chromone **(1)** is a heterocyclic compound that contains oxygen and it belongs to a significant class of pharmacologically active compounds. The word chromone is derived from the Greek word chroma (which means colour), this shows that many chromone derivatives show different colours. Due to its use in numerous biologically active compounds, the rigid bicyclic fragment has been designated as a favoured structure in drug discovery.[1] Some derivatives of these scaffolds have been widely used as building blocks in organic synthesis and plays a significant role in medicinal chemistry. The physical, chemical and biological properties of both natural and synthetic derivatives are primarily influenced by the structural diversity in terms of the type, number and location of substituents connected to the main core of chromone. Moreover, the chromone moiety is a modern active pharmacophore used in numerous therapeutic applications in pharmaceuticals.[2]



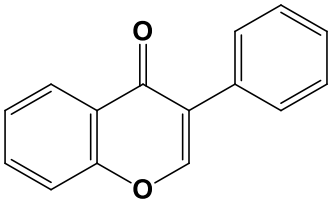
1

Figure 1: General structure and numbering of chromones

Several compounds found in plants especially flavones **(2)** and isoflavones **(3)**, have the chromone system (benzo-pyrone). The possibility of manufacturing these compounds' analogs with the goal of developing new, highly effective products for agriculture and medicine is defined by the high and diverse biological activity of these substances. For instance, it is well known that some synthetic analogs with an azole or azine ring in place of a furan or pyran ring are much more active, however in some cases this substitution changes the products' pharmacological profile.[3]



2



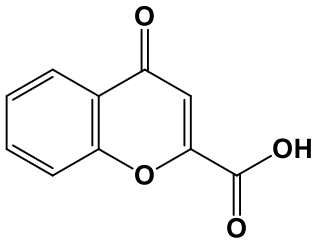
3

Figure 2: Flavonoids derivatives

The color and flavor of many fruits and vegetables are greatly influenced by flavonoids, which are found widely in plants. Other derivatives of chromone include chromone carboxylic acids and chromone carbaldehyde. Flavones (2-phenyl-4H-1-benzopyr-4-one) and isoflavones, which differ in position of the phenyl group, are both derivatives of the chromone. They are a key subclass of the naturally occurring substance known as flavonoids.[4]

1.2 Physical properties of chromone-2-carboxylic acids

The parent component of chromone-2-carboxylic acids **(4),** which is crystalline and has a high melting point, melts and decomposes with the emission of carbon dioxide. This explains the difference in melting point mentioned in the literature. Chromone-2-carboxylic acid has colors different than white due to various substituents present in the benzene ring. For instance, 5-hydroxy gives both the acid and ethyl a yellow color.[5]



4

Most of the alkyl, hydroxyl, alkoxyl, nitro, and or acyl group containing chromone-2-carboxylic acids (esters) and their derivatives are colorless while 5-hydroxy-chromone-2-carboxylic acid and its ethyl esters are bright yellow. Colored compounds may also results from a heterocyclic fused to the chromone. Chromone-2-carboxylic acid is slightly soluble in water but insoluble in ether

and light petroleum. It crystallizes from ethanol. Many of monosubstituted acids and esters are crystalized with ethanol or methanol.[5]

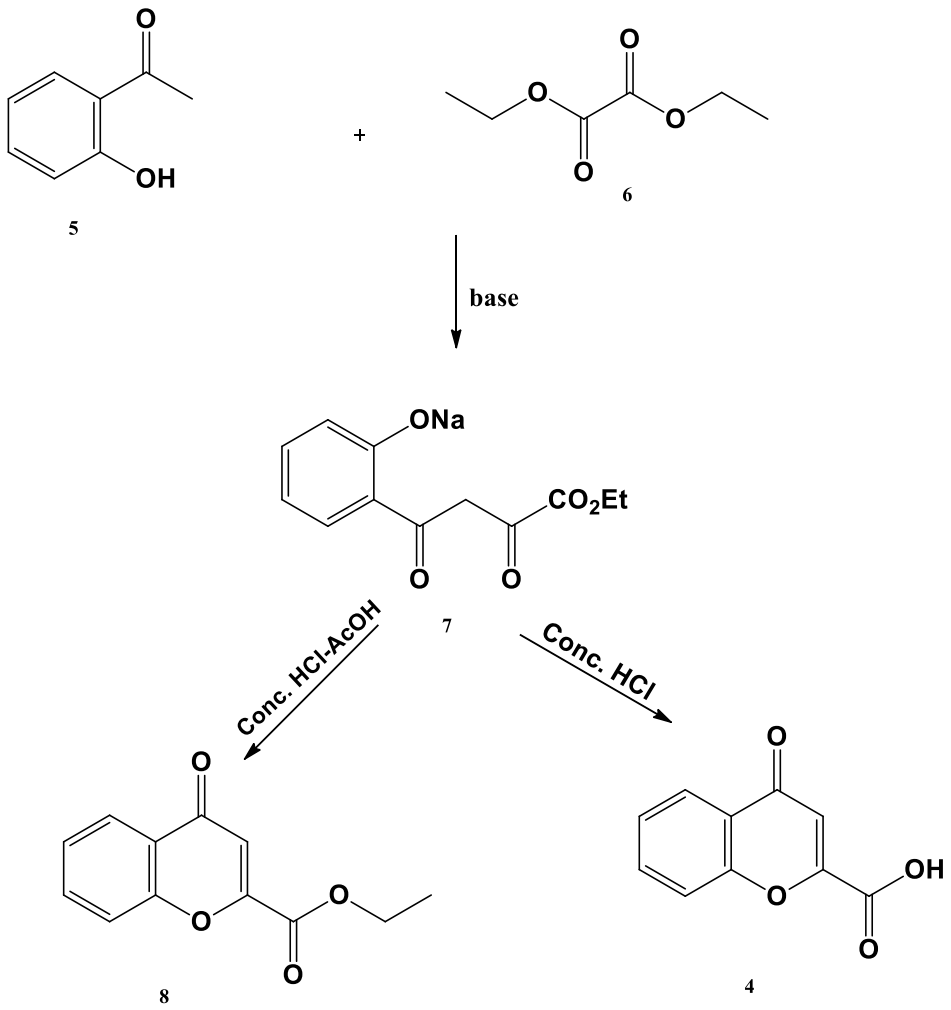
1.3 Synthesis of chromone-2-carboxylic acids

Chromone-2-carboxylic acids and their analogues can be synthesized in variety of ways. Methods of synthesizing chromone-2-carboxylic acids (or esters) may be divided into two main types: those in which the C-2 substituent is present at the cyclization stage (the direct synthesis) and those in which the substituent is formed from another group after the formation of the pyrone ring (the indirect synthesis).[6]

Between the direct and indirect synthesis, the one that is commonly used is the direct synthesis. Below is the summary of some of the methods by which a chromone-2-carboxylic acid or ester are synthesized directly from benzenoid precursors.

1.3.1 Kostanecki's method

In this process, 2-hydroxyacetophenones **(5)** and ethyl oxalate **(6)** are combined through a Claisen condensation in the presence of strong base such as sodium or sodium hydride to produce the brightly colored ethyl-3-(2-hydroxybenzoyl)-2-oxopropanoate **(7).** When electro-withdrawing substituents like a nitro group or two bromine atoms are present or when utilizing 2-hydroxyacetophenones, an excess of the base is normally used.[7]



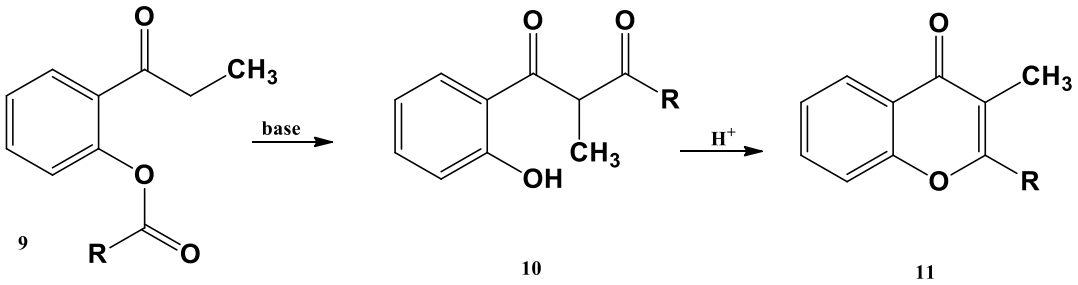
Scheme 1: Kostanecki's synthesis of chromone-2-carboxylic acid

Chromone-2-carboxylic acid (**4)** is synthesized by cyclization of the oxopropanoate **(7)** with either concentrated HCl or concentrated HCl-ethanol mixture, while ethyl-chromone-2-carboxylate (**8)** is synthesized when concentrated hydrochloric acid and acetic acid mixture is used.[7]

1.3.2 Baker-Venkataraman Rearrangement

In chromones synthesis, the Baker-Venkataraman rearrangement is frequently used. The 2-acetophenones **(9)** react chemically with the base to produce 1.3-diketones **(10).** An ester is created by benzolating the 2-hydroxyacetophenones. Enolate synthesis and acyl transfer are the first steps

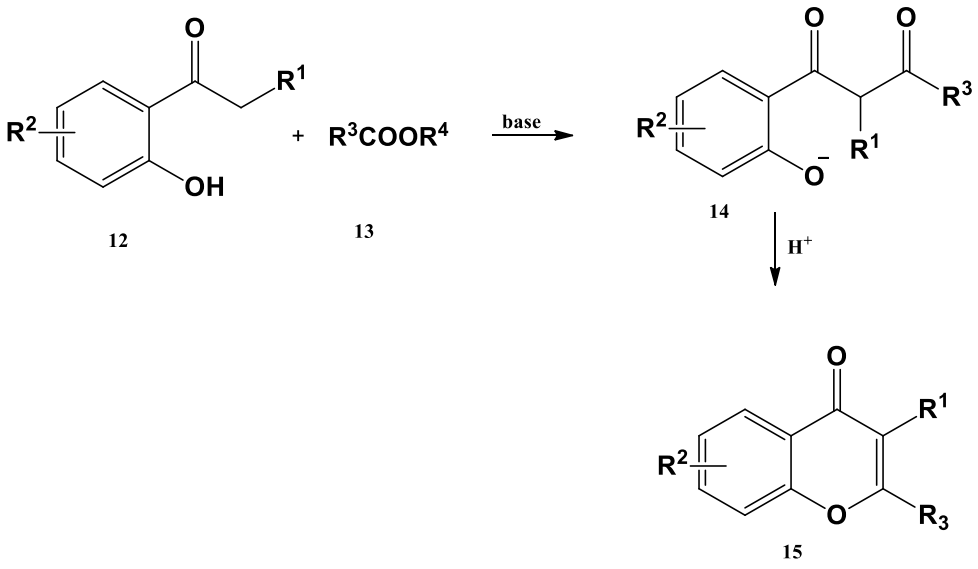
in this rearrangement reaction. Treatment with acid following the base-catalyzed rearrangement typically results in the chromone **(11)**.[8]



Scheme 2: Baker-Venkataraman rearrangement

1.3.3 Claisen condensation

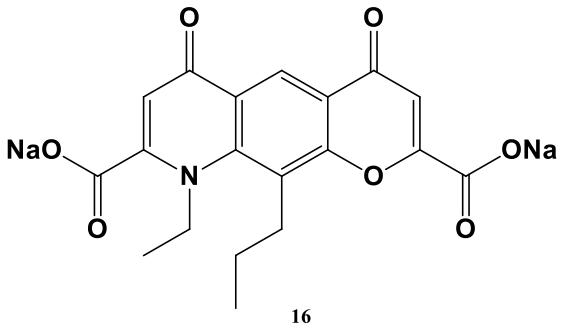
In the presence of strong base, the claisen condensation of an o-hydroxyaryl ketone **(12)** and a carboxylic ester **(13)** produces the dioxophenol intermediate **(14)**, which is subsquently heated in an acidic medium to yield the chromone **(15).**[6]



Scheme 3: Claisen condensation with a carboxylic ester

1.4 Challenges with chromones as a privileged scaffold in drug discovery

Future medicinal chemistry may benefit from study of the biological activity of chromone derivatives, especially when utilized in transdisciplinary fields. Although there are some obstacles that could deter further research into the chromone core, these include the infrequent existence of negative side effects associated with its administration, leading to a restricted use in many countries and a further discontinuation of its production and commercialization (e.g Nedocromil sodium **(16)**). The major obstacle still facing both research teams and pharmaceutical corporations is high expenses and complicated laws related to the discovery, development and commercialization of new pharmaceuticals. Although having effective synthetic processes, chromone-type chemicals have a negative influence on the environment since they require high temperatures and the addition of inorganic acids and bases.[9]



16

Novel processes utilizing microwave irradiation or solid-supported catalysts still need to be scaled up for industrial output. Because of this, there is a surge in the need for novel, adaptable, and long lasting synthetic processes for synthesizing chromones, as well as for methods that are more efficient for its isolation and purification, structural characterization and assessment of it biological qualities. Green synthetic principles must be investigated for the industrial applicability, which increases the demand for new green synthetic techniques. The next challenge is cytotoxicity and the negative effects of chromones. It has put certain limitations on how it can be manufactured and used in medicine.[10]

1.5 Chromone as privileged structure

Chromone is a favored structure used in drug development programs since it serves as the framework for many bioactive compounds' pharmacophores. The chromone scaffold is functionalized to produce exceptional derivatives, such as those with a reactive carbonyl group (such as carboxylic acid), which are adaptable synthons due to their capacity to take part in a wide range of chemical processes. [11] Chromones are typically categorized as mast cell stabilizers since it is thought that their main mechanism of action involves preventing the release of inflammatory mediators from mast cells. They are widely recognized to demonstrate cytotoxicity when applied to cancer cell lines that are MDR (Multi-drug resistant). Chromones have recently become important synthons for incorporating into a variety of chemical frameworks.[12]

Several types of biological activities are determined by the chromone scaffold substitution pattern. Several biological actions can be found in chromone derivatives. Chromone has been acknowledged as a privileged structure for the creation and development of novel drugs. The chromone scaffold's substitution pattern dictates various biological activity of various kinds. Due to its beneficial actions and low toxicity, the chromone scaffold is regarded as an appealing material for the creation of novel medications.[13]

Chromone is taken as a single molecule that can connect with many receptor types.[14] Chromones are phenolic substances that are present in human diet and are naturally occurring. Many chromone derivatives have been found thus far, both naturally occurring and synthesized. They should be a staple of a healthy diet because they not only provide nutrition advantages but also protection against a number of illnesses.[15]

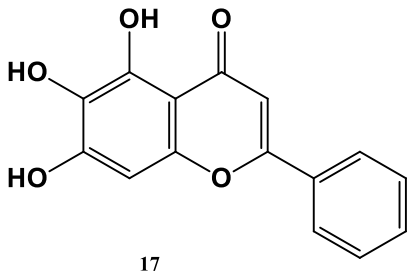
A good optimization process can result from the usage of privileged structures in drug development, which has been shown to be an effective technique for synthesizing novel hits and leads., chromone is acknowledged as a preferred structure and a valuable template for the design of new compounds with potential therapeutic relevance, notably in the realm of neurological, inflammatory, and infectious diseases as well as diabetes and cancer. Recent research has focused on the importance of the chromone scaffold in medicinal chemistry.[16]

The synthesis of a large variety of compounds with various pharmacological characteristics is made possible by the good template that chromones provide for structural modifications. They are crucial in medicinal chemistry and might be regarded as a favored structure for drug development due to their synthetic accessibility and structural variety.[17]

Moreover, chromones have been tested against additional pertinent biological targets and/or employed as a technique to validate new targets, namely their (patho) physiological function and potential for the creation of fresh treatment modalities. To hasten the discovery of new medicines, it is essential to create pharmacologically effective molecules based on reliable scaffolds, such as the chromone core, as well as new and enhanced drug-like libraries.[18]

1.6 Biological activities of chromones

It has been observed that chromones with heterocyclic substituents at position 2 and 3 have anti-allergic, muscle relaxing and anti-microbial properties.[19] Chromones and its derivatives are organic substances that are found in the plant kingdom, for instance, Baicalein **(17)** was employed in traditional Chinese medicine as a diuretic and anti-allergic medication. Several synthetic and natural chromone derivatives have been shown to have a significant biological properties, including anticancer, antihepatotoxic, antioxidant and anti-inflammatory, estrogenic and antibacterial effects.[20]

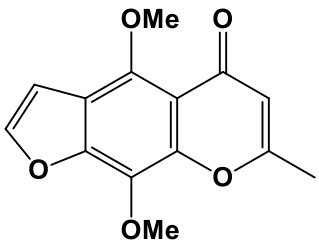


17

These applications have encouraged ongoing research into synthesis of novel molecules in this area and have already resulted in the release of a few medications.[21]One of the rarest class of natural chromones is 2-methylchromone.[22]

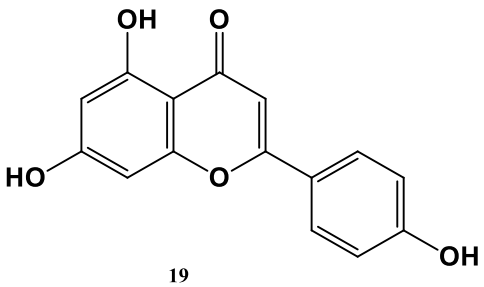
Chromones, particularly carboxamides, are crucial in the quest for novel effective anticancer medicines. Many chromone carboxamides have been identified as effective and targeted cytotoxic substances.[23]

Many chromone compounds are well-known for their pharmacological attributes even though there aren't many examples of them that has been or are used as medicines today.[24] Khellin **(18)** has been used as diuretic to relieve renal colic, as a smooth muscle relaxant and in the treatment of vitiligo, a pigmentation disorder.[25, 26]

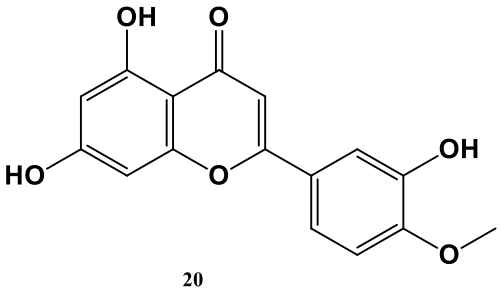


18

Chromones and their analogs are significant pharmacophores and privileged structural elements in medicinal chemistry that have been used in a variety of clinically effective medications. According to the most recent and relevant studies, chromone derivatives have wide range of pharmacological activities that fall into the following categories: Antimicrobial agents (apigenin) **(19),** anti-diabetic agents (diosmetin) **(20),** anti-oxidant agents (chrysin) **(21)** , anti-inflammatory (nobiletin) **(22),** Anti-malarial agents (luteolin**) (23).** [24]



19



20

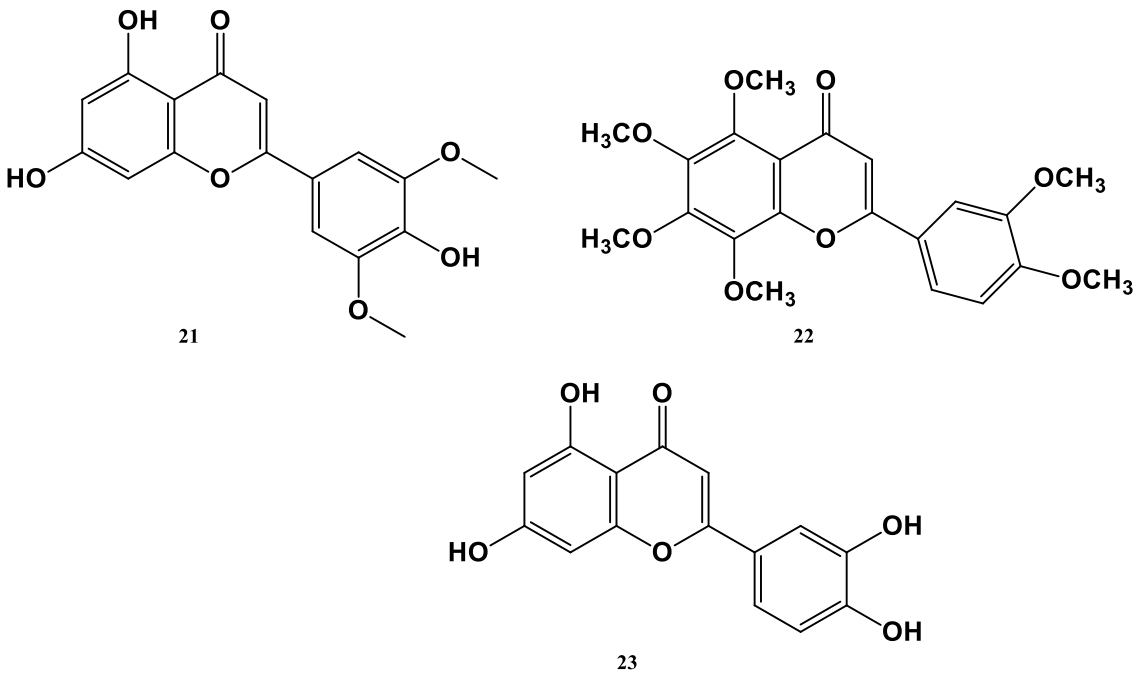


Figure 3: Recently used drugs derived from chromones

Several chromone derivatives have also shown to have kinase inhibitory properties, bind to benzodiazepine receptors, and be effective cystic fibrosis treatments.[27] Despite the fact that chromones have a variety of biological functions, this study primarily focuses on their application as antimalarial agents.

1.7 Background of malaria

Malaria is an infection that causes a greatest amount of morbidity and mortality worldwide, with mycobacterium tuberculosis being the single most significant infectious agent. Malaria has been there for many years.[28]

An estimated 219 million cases of malaria were reported globally in 2017, an increase from the 217 million cases reported in 2016. The number may be higher, but some cases may not be documented because of inadequate facilities. In 2017, malaria-related deaths were almost 435 000. The most vulnerable groups to be affected by malaria are children under the age of five, pregnant women and people who suffer from HIV/AIDS.[29] More than 600 thousand people die from malaria

each year worlwide. Malaria has had and continues to have the biggest negative effects on people's health and ability to support their families.[30]

History has shown that South Africa (SA) has historically been spared from much of the destruction brought on by malaria than the rest of Africa due to its geographic location at the southernmost extent of the disease's dispersion. It is evident that malaria does not respect national borders, and regional participation will be necessary for its effective eradication in South Africa. A malaria risk area is home to about 10 percent of South Africa's total population. Places that have most malaria endemic in SA are Limpopo, KZN and Mpumalanga. The majority of malaria cases among them are found in Limpopo, particularly in the Vhembe district. The majority of malaria transmission takes place from September to May, with a peak in March.[31]

1.8 Causes of malaria

A parasite species from the *genus Plasmodium* is what causes malaria. The parasite *genus plasmodium* contains more than 250 different species. Only five of them are capable of spreading the disease, but among these five, only four of them *P. Falcipurum, P. ovale, P. Vivax, and P. Malariae* can do so in humans. Malaria in monkeys is brought on by the last one, *P. knowlesi.* There are, however, a very small number of cases where *P. knowlesi* has proven to transmit malaria to people. *P. Falciparum,* which causes the most severe form of the disease and accounts for over 90 % of deaths from malaria, is the most common malaria species in the world, particularly in Africa. The second most prevalent species, *P. Vivax* is primarily found in Asia and South America and is capable of spreading the relapsing form of malaria.[32]

The female mosquitoes of the genus *Anopheles* carry the malaria parasite and bite people to transmit it to them. Malaria can also be spread through blood transfusions and sharing syringes in drug addicts, in addition to mosquito bites.[33]

1.9 Types of malaria

The three forms of malaria can be distinguished by their traits and symptoms. Typically, they are categorized as asymptomatic, simple or severe. Any kinds of malarial plasmodium can produce asymptomatic malaria. This type of malaria is the most challenging to diagnose because the patient has circulating parasites but no symptoms. All plasmodium species can also results in simple malaria. Typically, this type of malaria develops symptoms 7-10 days after the first mosquito bite. The last kind of malaria known as severe malaria, is typically brought on by contamination with *P. falciparum*, however, there are few cases were *P. vivax or P. knowlesi* caused severe malaria.[34]. Malaria is a true hematological illness that affects practically all blood components.[35]

1.10 Signs and symptoms

The most typical malarial symptoms are feverishness, weakness, nausea, hallucination, headache and vomiting. There have been few occurrences of severe malaria where patients manifested symptoms like insanity, paralysis, organ failure, hypoglycemia and occasionally death. Pregnant women who contract malaria are at risk of miscarriage, early delivery, low birth weight or fatal outcomes.[36]

1.11 Life cycle of *P. falciparum*

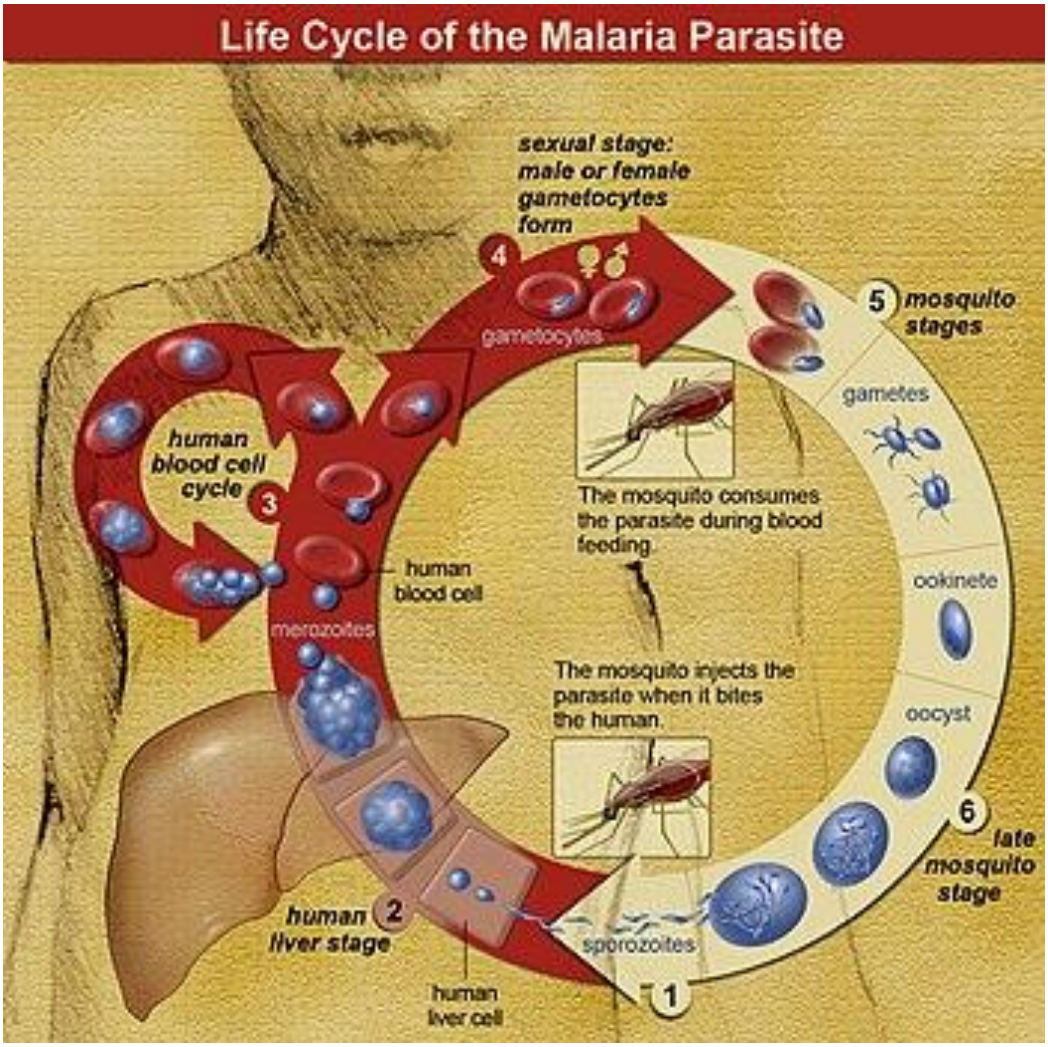


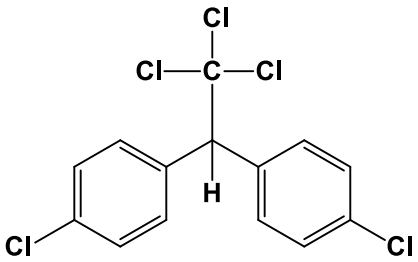
Figure 4: Showing life cycle of *Plasmodium falciparum*[37]

Humans and female Anopheles mosquitoes serve as hosts for the complex life cycle of the malaria parasite. With the bite of a contaminated anopheles, malaria parasites are transferred from the mosquito to humans. Several asexual reproductions of the parasite take place inside the human host. Malaria gametocytes are returned to the mosquito host when a different female mosquito feeds on the blood of the infected person. These immature gametes then mature, fuse to form zygotes, and undergo sexual recombination and meiosis. The haploid cells that result then reproduce asexually and form sporozoites, which move to the salivary glands to complete the life cycle, as shown in **figure 4.**[38]

1.12 Malaria control and elimination

Malaria is not only a serious threat to human life, but it is also incredibly challenging to control. It is nearly impossible to eradicate malaria because of the unusual nature of infection, which consists of both a parasite and the mosquito host of the parasite. Currently, a variety of strategies are used to control malaria, including the use of insecticide-treated bed nets, indoor mosquito spraying, the elimination of mosquito breeding grounds, preventive antimalarial drugs and prompt diagnosis and treatment of malarial infections to shorten the time the disease can spread among people.[39]

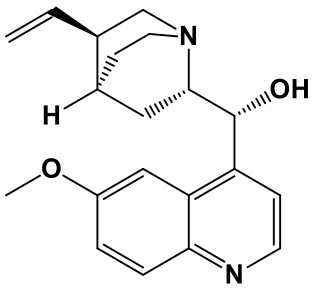
Vaccination programs are viewed as additional malaria prevention strategies. Use of insecticides like Dichlorodiphenyltrichloroethane (DDT) (24) is one of the malaria control strategies.[32]



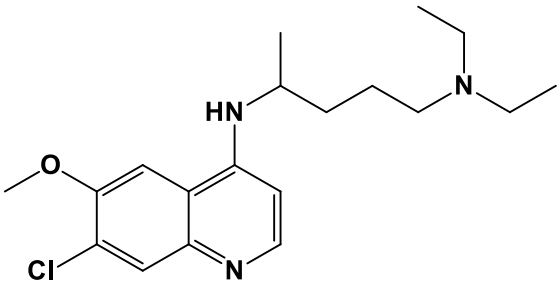
24

1.13 Treatment of malaria

Until more potent synthetic antimalarials became accessible, Quinine (**25)** was the backbone of malaria treatment. Chloroquine **(26)** is the most significant of these medications and was widely utilized, especially starting in the 1940s.[40]

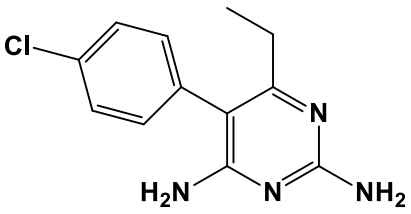


25

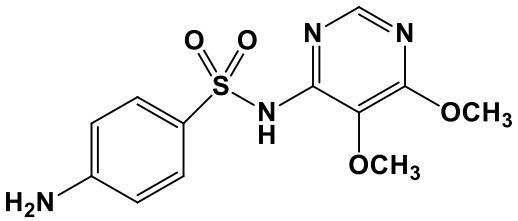


26

While being still commonly used in Africa, chloroquine's effectiveness is waning and it can no longer be depended upon in cases of severe malaria. In some regions of East and South Africa, Pyrimethamine **(27)** and Sulphadoxine **(28)** have now taken the place of Chloroquine as the first line of treatment. Fansidar is the brand name for a combination medication that contains Sulphadoxine and Pyrimethamine.[41]

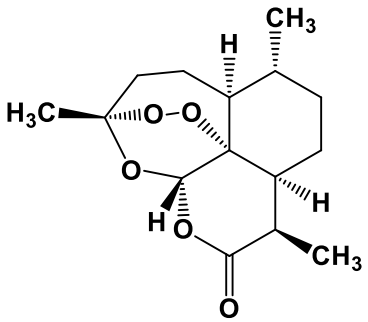


27

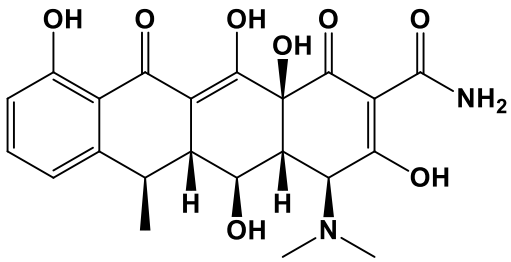


28

Although the majority of most the antimalarial medications currently on the market have been in use for many years, the emergence and spread of drug resistance has now restricted their usage.[42] Many traditional medical systems use a variety of herbs and herbal substances to treat malaria. The Chinese traditional system has employed the leaves of Artemisia annua or sweet wormwood shrub, which contains the active component artemisinin **(29)** to cure malaria. The most recent and powerful antimalarial medications are artemisinin and its variants. Some medications influence the parasite's ability to produce proteins.[43]

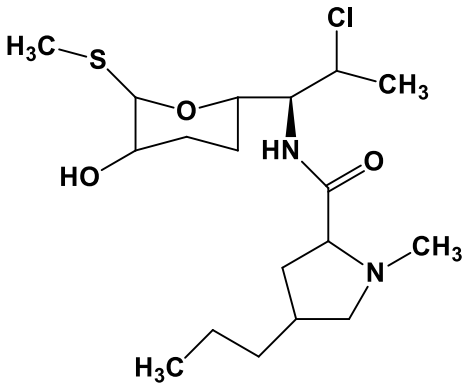


29

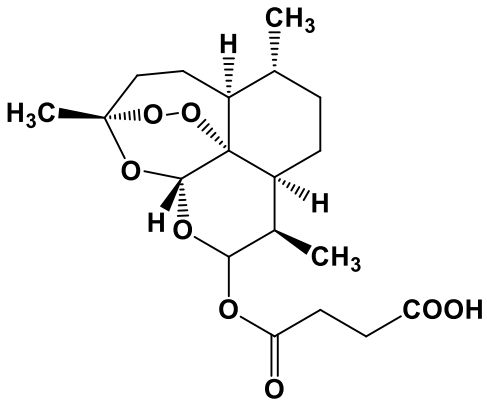


30

The preferred method of treatment for *P. Falciparum* malaria is now artemisinin-combination therapies (ACTs), which contain an artemisinin derivative.[44] With the aim of stopping the spread of antimalarials drug hostility to the most commonly used medications, the WHO advises treating malaria using a combination of two or more medications. Quinine must be taken with medications like doxycycline **(30)** and Clindamycin **(31).**

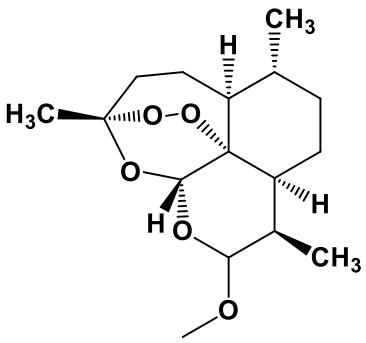


31

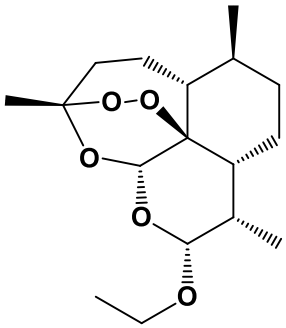


32

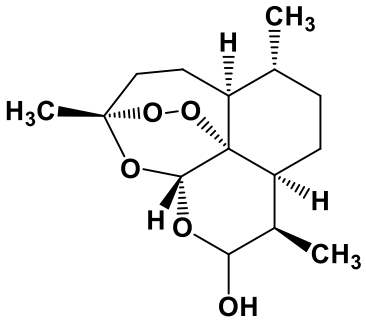
The artemisinins derivatives: artesunate (AS) (**32)**, artemether (ARM) (**33)**, arteether (AE) (**34)** and dihydroartemisinin (DHA) (**35)** are also be used as monotherapy.[45, 46]



33

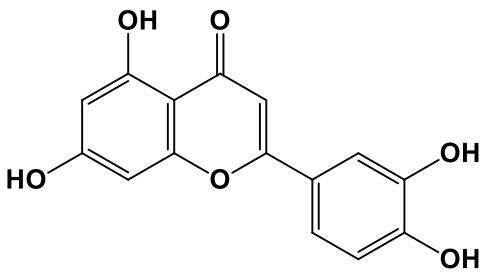


34

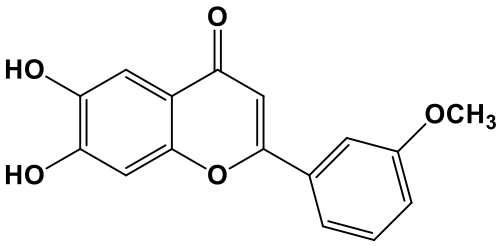


35

The literature showed that some of the chromone derivatives such as Luteolin **(23),** 6, 7-dihydroxy-2-(3-methoxyphenyl) chromones (**36)** and 7, 8-dihydroxy-3(4-nitrobenzoyl)-2(4-nitrophenyl) chromones (**37)** have exhibited an antimalarial activity.[47]

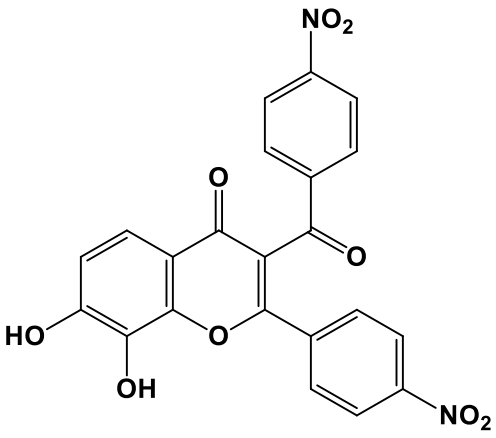


23



36

Antimalarial medications are synthesized with the intention of targeting various stages of the plasmodium life cycle in order to stop malaria from developing into a severe form in a human host.[48]



37

1.14 Antimalarial drug resistance

Chloroquine is a classical antimalarial drug. Resistance to Chloroquine slowly increased with frequent use. Quinine once more played a crucial role in the fight against Chloroquine resistance, especially in the treatment of severe form of malaria.[49] Despite the existence of numerous efficient anti-malarial drugs, misdiagnosis, ineffective dosing, poor drug quality absorption and resistance development are the main causes of malaria treatment failure. There are just a few clinically effective antimalarial medicines, such as Chloroquine, Amodiaquine, Sulphadoxine and Pyrimethamine, but their main issue is drug resistance.[46]

Artemisinin and its derivatives were introduced due to drug resistance in the majority of commonly used medications. Up until parasites developed a resistance to artemisinin, this appeared to be working. The WHO suggested quinine derivatives along with artemisinin derivatives as part of an artemisinin combination therapy to combat artemisinin resistance. Lately, incidences of multi-drug resistance where AXTs are no longer effective have been observed. A rise in multidrug resistant forms of malaria has made treatment increasingly challenging.[50] Because the parasite has developed a resistance to almost all antimalarial medications, malaria has grown to be a significant problem.[51]

CHAPTER 2

2.1 Problem statement

Malaria still poses a public unhealthiness due to hostility to the available medications, therefore, there is a need for ongoing research into innovative antimalarials. The design of antimalarials using computational approaches, synthesis, and biological assesment of produced molecules is a more effective approach.

The spread of hostility of *Plasmodium falciparum* to frequently used antimalarial medicines has developed an emergency need to create novel antimalarial treatments, preferably drugs that are economical to developing countries where malaria is prevailing. Drug resistance is a result of a number of factors, including subpar drug quality, interactions with other pharmaceuticals, inaccurate diagnoses and inappropriate dosages.

2.2 Motivation of study

There are many chromone derivatives which are known for their pharmacological properties but few of them have been tested and successfully used as therapeutic agents. Chromone offers wide opportunity for new research endeavours in both synthetic and medicinal chemistry. They are very useful as bioactive agents, and some are used as medicines. There has been some malaria drugs which include the chromone structure such as luteolin and 6.7-dihydroxy-2-(3-methoxyphenyl) chromone which has been synthesized. These compounds showed good potential to be used as antimalarial agents. Chromone has the prospective to be explored as lead compounds for antimalarial drugs.[47, 50]

This investigation is part of an ongoing research programme in heterocyclic chemistry in search for novel compounds.

CHAPTER 3

Aim and Objective(s)

Aim:

- To synthesize novel-6.8-disubstituted-chromones-2-carboxylic acids derivatives and their evaluation as potential antimalarial agents.

Objectives:

- To synthesize 5-substituted-3-iodo-2-hydroxyacetophenones.
- To synthesize ethyl-6-substituted-8-iodo-chromone-2-carboxylates derivatives.
- To synthesize 6-substituted-8-iodo-chromone-2-carboxylic acids derivatives.
- To synthesize 6-substituted-8-iodo-chromone-2-carbonyl chlorides intermediates.
- To synthesize novel 6.8-disubstituted-chromone-2-carboxamides derivatives.
- Use of various spectroscopy techniques to characterize synthesized compounds.
- Biological screening of target molecules for antimalarial agents.

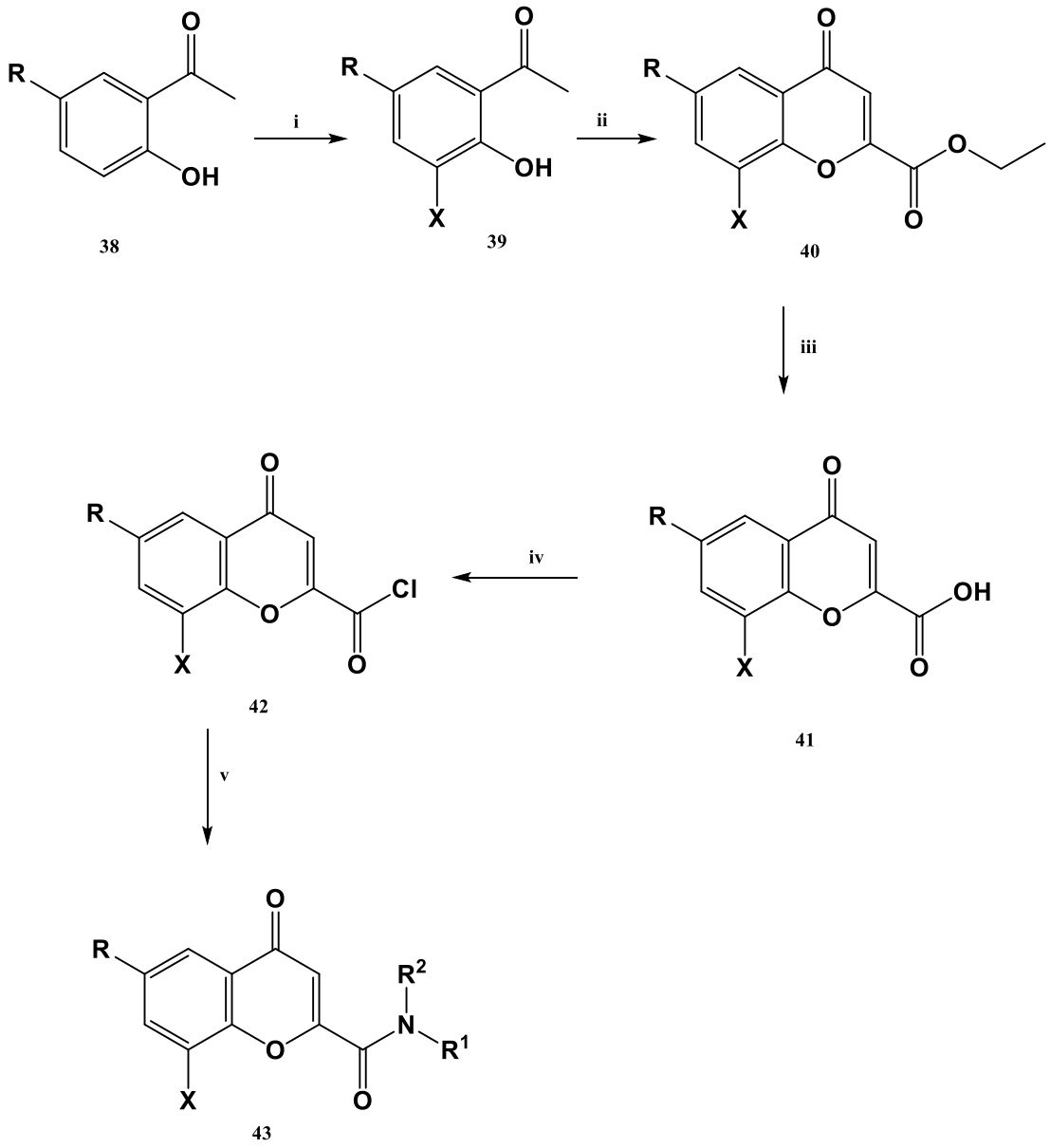
CHAPTER 4

4. Results and discussion

4.1 Research methodology

In this study, a number of chromones were synthesized starting from 5-substituted-2-hydroxacetophenones (**38)**. 5-substituted-2-hydroxyacetophenones (**38)** were brominated and iodinated at position 3 using NBS and NIS respectively in acetic acid to give 3.5-disubstituted-2-hydroxyacetophenones (**39)** as outlined in **scheme 4**. The 6.8-disubstituted-ethyl-chromone-2-carboxylates (**40)** were prepared by condensing 3.5-disubstituted-2-hydroxyacetophenones with diethyl oxalate in the presence of ethanolic solution (sodium ethoxide generated *in situ* by reacting dry ethanol with sodium metal).[55] The 6.8-disubstituted-ethyl-chromone-2-carboxylates were converted to the corresponding 6.8-disubstituted-chromone-2-carboxlic acids (**41)** by reacting them in hydrochloric acid and acetic acid. The 6.8-disubstituted chromone-2-carboxylic acids **(41)** were converted to 6.8-disusbstituted-carbonyl chloride acids (**42A-D)** and then to the respective 6.8-disubstituted chromone-2-carboxamides (**43)**.

All synthesized compounds were characterized by ^{1}H and ^{13}C NMR, and FT-IR spectroscopies.



Where R = H, Br, NO_2, F, Cl, OCH_3 R^1R^2 = O $(CH_2CH_2)_2NH$, $(CH_2)_5NH$, $(CH_3)_2NH$

X= H, Br, I

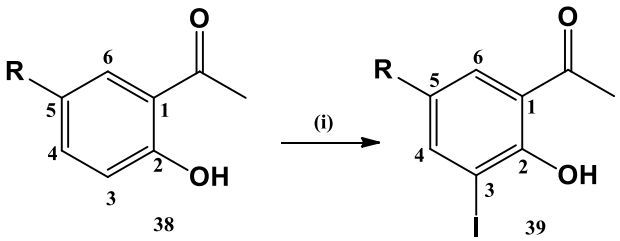
Reagents: (i) NIS, AcOH, (ii) NaOEt, EtOH, $(CO_2Et)_2$ (iii) AcOH: HCl (2:1),

(iv) $SOCl_2$, DMF (v) Pyridine, Amines

Scheme 4: Proposed Synthetic Scheme

4.2 Synthesis of 5-substituted-3-iodo-2-hydroxyacetophenones (39A-D)

N-iodosuccinimide was used to treat 5-substituted-2-hydroxyacetophenonesin acetic acid, resulting in a solution that was refluxed for two hours. Ice-cold water was then used to quench it, followed by filtration to afford the resulting 5-substituted-3-iodo-2-hydroxyacetophenons (**39A-D)** in moderate to excellent yields of 46-82 %. The reaction scheme is shown in **scheme 5**. Iodination of 2-hydroxyacetophenones and 5-methoxy-2-hydroxyacetophenones were unsuccessful as shown by the NMR. Attempts to increase reaction time and temperature didn't yield good results.

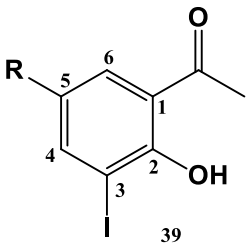


R= Br, NO_2, Cl, F

Reagents: (i) NIS, AcOH, Reflux, 2hr

Scheme 5: Synthesis of 5-subsituted-3-iodo-2-hydroxyacetophenone derivatives (**39A-D)**

All of the 3-iodo-5-substituted-2-hydroxyacetophenone derivatives' **(39A-39D)** structures were confirmed using NMR, IR spectroscopy and melting point information. However, two of the compounds didn't have literature melting points hence we assumed they are novel compounds. **Table 1** provides a summary of the melting points and the percentage yields of the synthesized 5-substituted-3-iodo-2-hydroxyacetophenones **(39A-D)**.



39

R= Br, NO_2, Cl, F

Table 1: Synthesized 5-Substituted-3-iodo-2-hydroxyacetophenones (**39)**

Compounds 39	**R**	Percentage Yields (%)	Lit. Melting Point (^oC)[53]	Melting point (^oC)
A	Br	82	89	112.7-114.8
B	Cl	60	105	101.6-103.8
C	F	46	-	90.4-98.2
D	NO_2	70	-	132.1-136.4

Spectroscopic techniques such as 1D NMR (^1H, ^{13}C, DEPT) and FTIR were used to characterize all synthesized compounds. Physical characteristics such as melting points were also used.

After taking into account the chemical shifts and coupling constants seen in the proton NMR spectra, the protons were assigned to the compounds (**39A-39D)**.

^1H NMR spectra of 5-substituted-3-iodo-2-hydroxyacetophenones (**39A-D**) showed three peak signals, except for compound (**39A)** which showed 4 peak signals including the OH peak . The OH peak for compound (**39A)** appeared at 12.98 ppm**.** Compounds (**39A-D)** resonate a singlet peak from the methyl group in the aliphatic region ranging between 2.50 - 2.53 ppm. In the aromatic region there are two peak signals resonating from proton 4 and proton 6. There is a doublet from proton at position 4 ranging between 7.86- 8.44 ppm and another doublet from proton 6 ranging from 7.98- 8.31 ppm.

The spectroscopic data obtained from carbon NMR and DEPT 135 was used to verify compounds (**39A-D).** From these compounds we found five quaternary carbons. The first quaternary carbon is at around 204.9-205.52 ppm and correlate to the carbonyl carbon. Four of the remaining quaternary carbons are coming from the aromatic region. We have C-1 and C-2 resonating at around 119.20-121.10 ppm and 155.31-162.92 ppm respectively. C-3 is where our reaction was happening and the peak ranges between 87.56-88.73 ppm which matches the 88-89 ppm from the literature. The last quaternary carbon is C-5, where a carbon is bonded to the functional groups Br, NO_2, Cl and F. These peaks are influenced by the electronegativity of the functional groups attached to it. The higher the electronegativity the more the chemical shift was shifted to the low field of the spectrum. Ranging from C-5 attached to: Br, Cl, NO_2, and F appearing at 111.33 ppm, 124.00 ppm, 142.08 ppm and 157.34 ppm respectively. The remaining two carbon peaks are C-4, appearing at around 117.03-146.85 ppm and C-6 appearing at 122.73-134.26 ppm. **Table 2** shows the observed carbon peaks of the synthesized 5-substituted-3-iodo-2-hydroxyacetophenones**.**

Amongst these compounds is 5-fluoro-3-iodo-2-hydroxyacetophenones which are unique. They exhibit an H-F coupling and C-F coupling. Instead of showing two doublets at the aromatic region they show two doublets of doublets due to H-F coupling. Each proton and each carbon appear to be coupled.

The FT-IR spectroscopy was used to confirm the presence of functional groups in the chemical structures of 5-substituted-3-iodo-2-hydroxyacetophenones such as, C=O peak at 1682 cm^{-1} and C-H at around 3000 cm^{-1}.

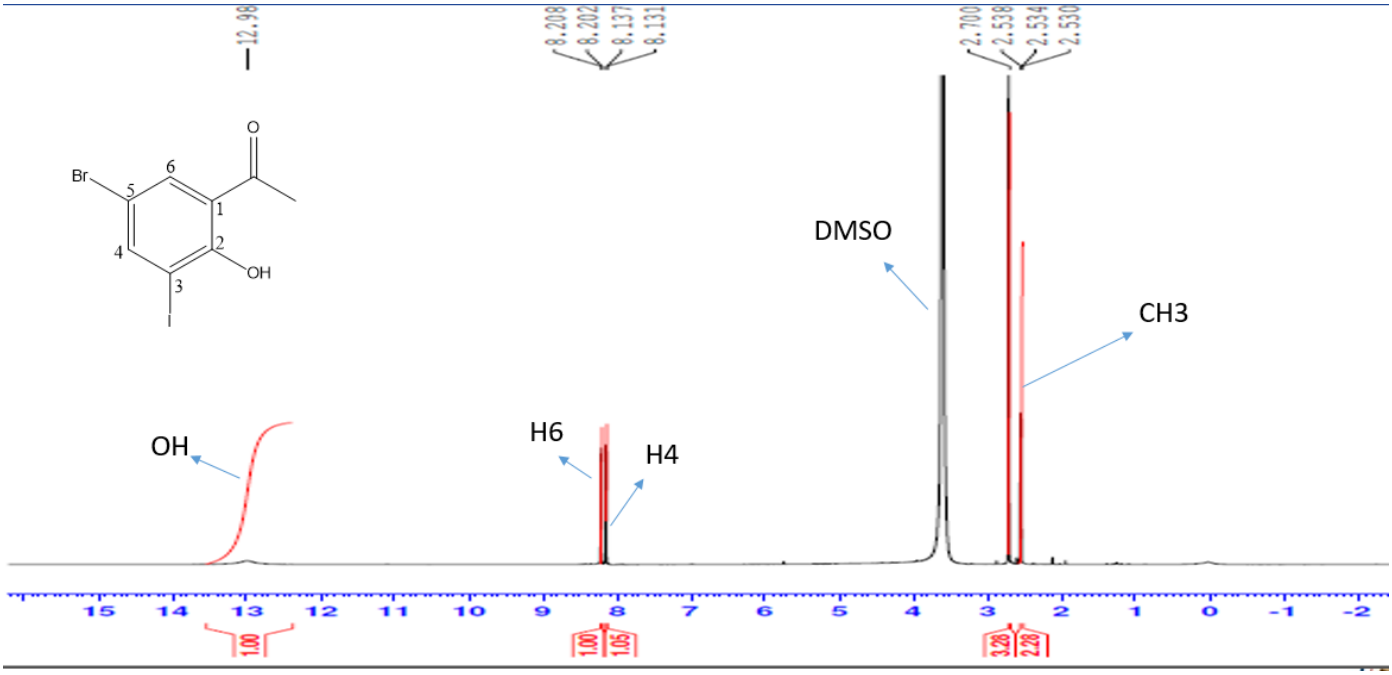


Figure 5: ^{1}H NMR spectrum of 5-bromo-3-iodo-2-hydroxyacetophenones **(39A)**

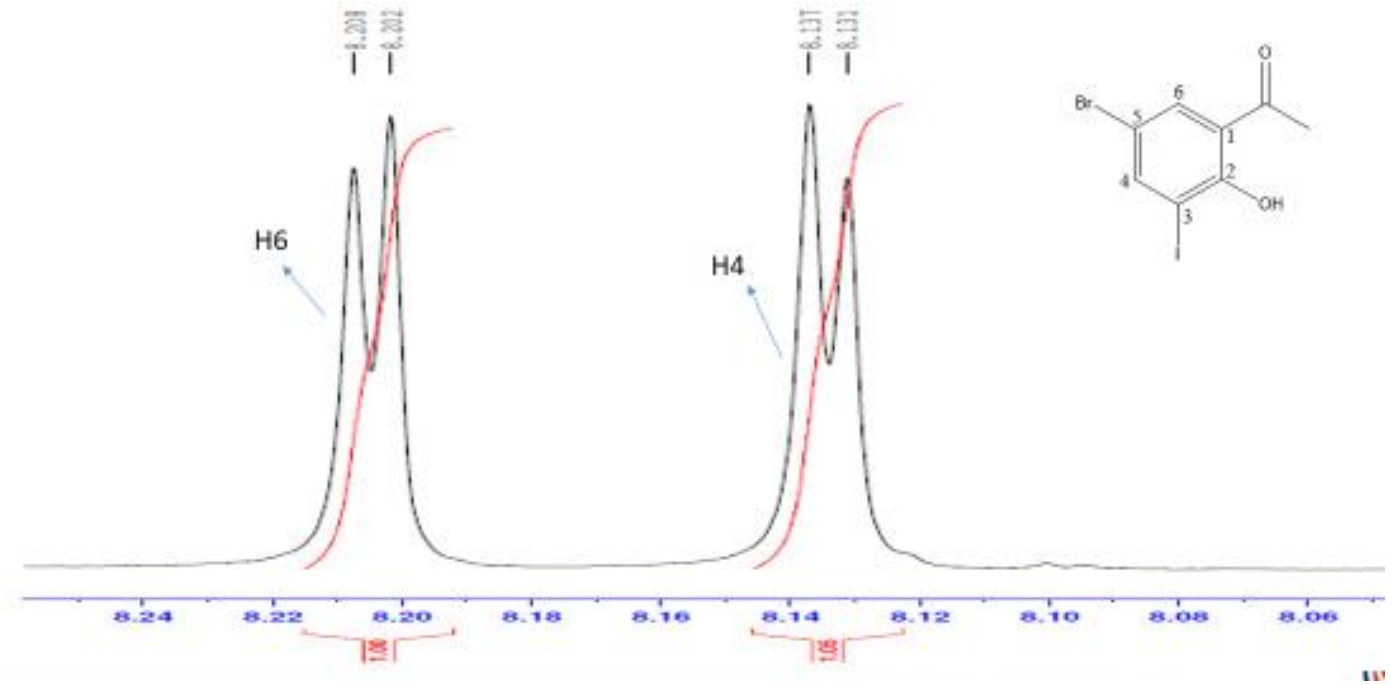


Figure 6: Expansion of ^{1}H NMR spectrum of 3-iodo-5-bromo-2-hydroxyacetophenones **(39A)** in DMSO-d_6

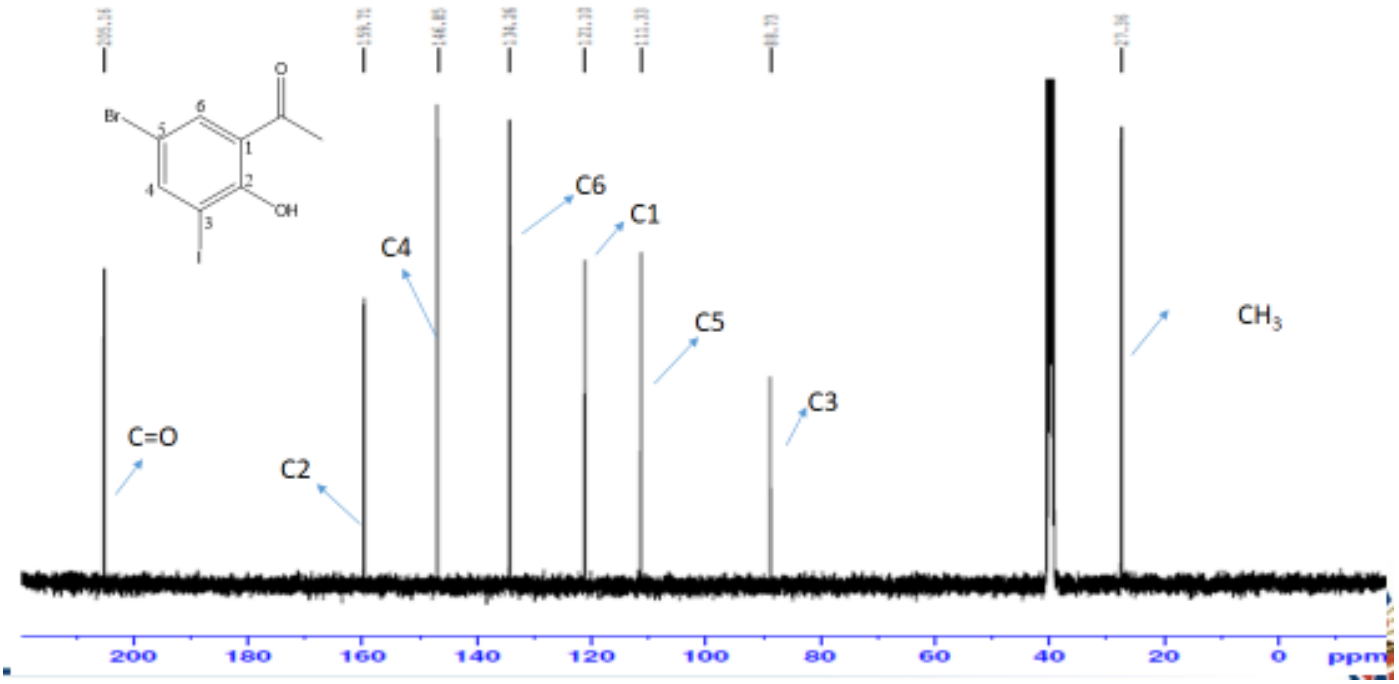


Figure 7: ^{13}C NMR of 5-bromo-3-iodo-2-hydroxyacetophenones **(39A)** in DMSO-d_6

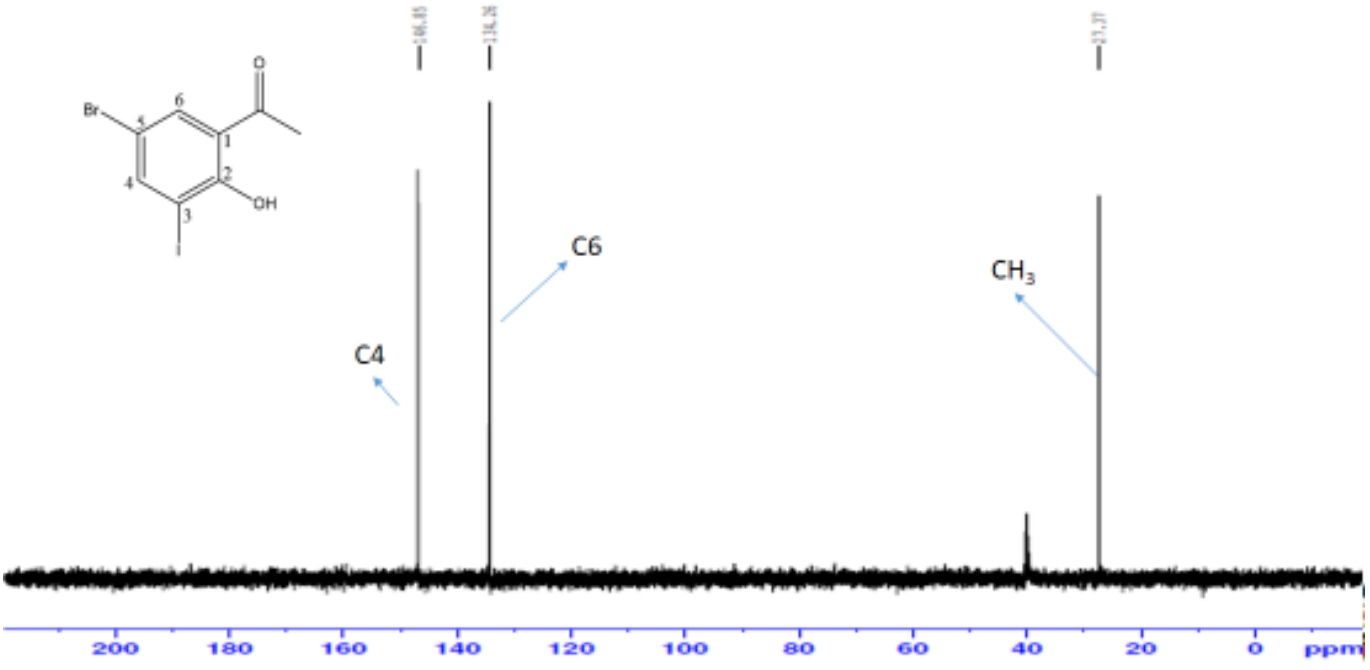


Figure 8: DEPT 135 of 5-bromo-3-iodo-2-hydroxyacetophenones **39A** in DMSO-d_6

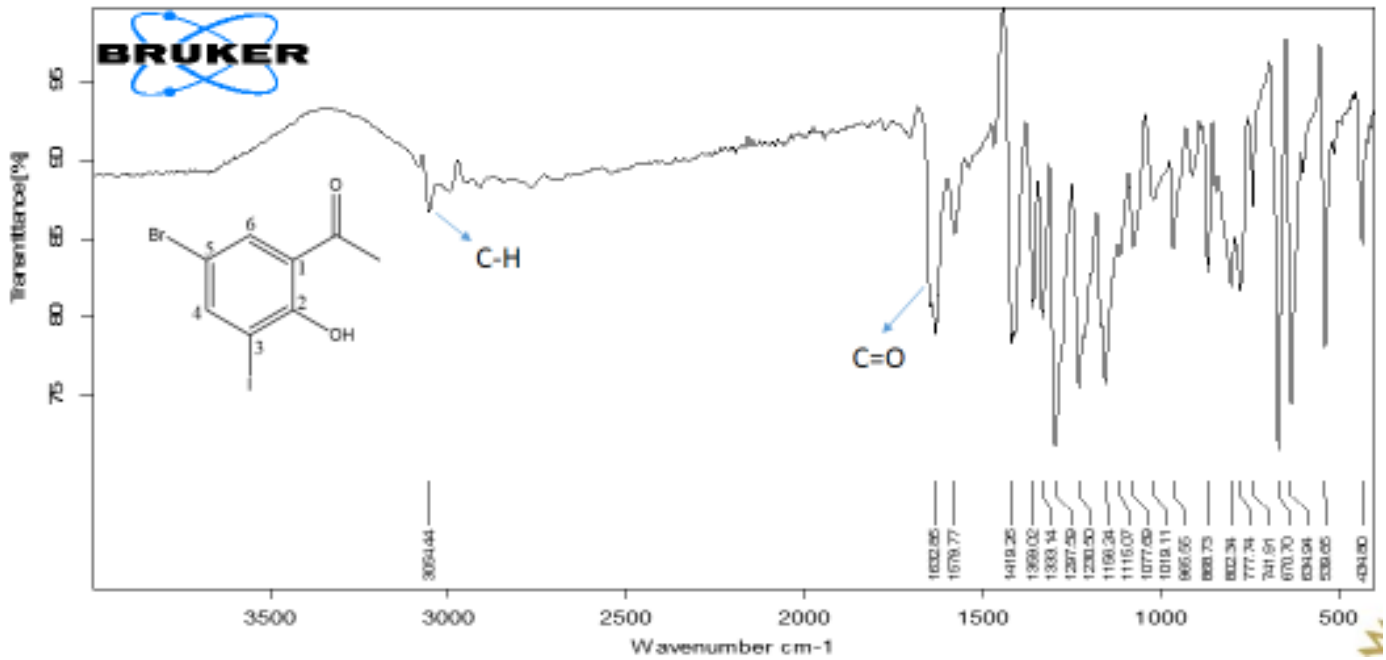
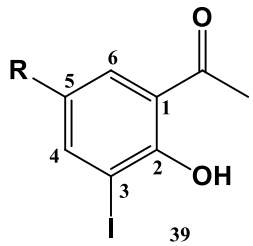


Figure 9: FTIR spectrum of 5-bromo-3-iodo-2- hydroxyacetophenone **(39A)**



39

R= Br, NO_2, Cl, F

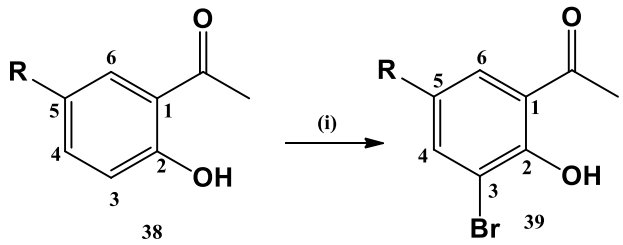
Table 2: ^{13}C NMR chemical shift values (ppm) of compound (**39)** in $CDCl_3$ and DMSO-d_6

Carbons	**Br**	**Cl**	**F**	**NO_2**
C-1	121.10	120.37	119.20	120.21
C-2	159.71	159.42	155.31	162.92
C-3	88.73	88.42	87.36	88.32
C-4	146.85	144.35	117.03	140.21
C-5	111.33	124.00	157.32	142.08
C-6	134.26	132.42	132.31	122.73
C=O	205.16	205.17	204.91	205.21
CH_3	27.36	27.44	27.46	27.71

4.3 Synthesis of 5-substituted-3-bromo-2-hydroxyacetophenones (39E-H)

The same procedure was repeated but instead of using N-iodosuccinimide, N-bromosuccinimide was used.

N-bromosuccinimide was used to treat 5-substituted-2-hydroxyacetophenones in acetic acid, resulting in a solution that was refluxed for two hours. Ice-cold water was then used to quench it. Filtration was used to collect the precipitates, and the resulting 5-substituted-3-bromo-2-hydroxyacetophenones (**39E-H)** were obtained**.** The synthesis of 5-substituted-3-bromo-2-hydroxyacetophenones were archived with good yields of 56-78 %. Bromination of 2 –hydroxyacetophenone and 5-methoxy-2-hydroxyacetophenones were unsuccessful as shown by NMR and TLC. Bromination of 2-hydroxyacetophenones and 5-methoxy-2-hydroxyacetophenones were unsuccessful as shown by the NMR. Attempts to increase reaction time and temperature didn't yield good results.The reaction scheme is outlined in **scheme 6**.

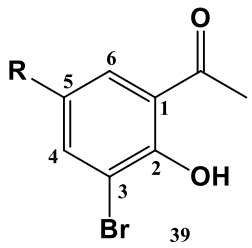


R= Br, NO_2, Cl, F

Reagents: (i) NBS, AcOH, Reflux, 2hr

Scheme 6: Synthesis of 5-subsituted-3-bromo-2-hydroxyacetophenone derivatives (**39E-H)**

All of the 3-bromo-5-substituted-2-hydroxyacetophenone derivatives' **(39E-39H)** structures were verified using NMR, IR spectroscopy and melting point information. **Table 3** provides a summary of the melting points and percentage yields of the synthesized 3-bromo-5-substituted-2-hydroxyacetophenones **(39E-39H)**.



39

R= Br, NO_2, Cl, F

Table 3: Synthesized 5-Substituted-3-bromo-2-hydroxyacetophenones (**39)**.

Compounds 39	**R**	Percentage Yields (%)	Lit. Melting Point (^oC)[54]	Melting point (^oC)
E	Br	78	108-111	98.7-102.3
F	Cl	68	100-103	86.2-94.1
G	F	62	94-97	91.7-94.1
H	NO_2	56	129-132	130.8-133.3

Spectroscopic techniques such as NMR (^1H, ^{13}C, DEPT) and FTIR were used to characterize all these synthesized compounds. Physical characteristics such as melting points were also used.

After taking into consideration the chemical shifts and coupling constants seen in the proton NMR spectra, the protons were assigned to the compounds **(39E-H)**.

^1H NMR spectra of 5-substituted-3-bromo-2-hydroxyacetophenones (**39E-F**) showed four peak signals. Compound (**39F)** and **(39H)** showed 3 peak signals without the OH peak. The OH peak for compound (**39E) a**nd (**39G)** appeared at 12.75 ppm and 12.66 ppm respectively. The singlet peak form the methyl group in the aliphatic region for compounds (**39E-H)** appeared around 2.66-2.80 ppm. In the aromatic region there are two peak signals resonating

from proton 4 and proton 6. There was a doublet from proton at position 4 ranging between 7.44-8.73 ppm and another doublet from proton 6 ranging from 7.55-8.66 ppm.

The spectroscopic data obtained from carbon NMR and DEPT 135 was used to confirm compounds (**39E-H).** From these compounds we found five quaternary carbons. The first quaternary carbon was at around 203.33-205.07 ppm and correlate to the carbonyl carbon. Four of the remaining quaternary carbons were coming from the aromatic region. We have C-1 and C-2 resonating at around 119.25-123.96 ppm and 152.85-162.95 ppm respectively. C-3 was where our reaction was happening and the peak ranges between 110.67-112.89 ppm which matches the 113 ppm from the literature. The last quaternary carbon is C-5, where a carbon is bonded to the functional groups Br, NO_2, Cl and F. The electronegativity of the functional groups connected to it has an impact on these peaks. The chemical shift was more strongly shifted to the low field of the spectrum with increasing electronegativity. Ranging from C-5 attached to: Br, Cl, NO_2, and F appearing at 112.55 ppm, 125.11 ppm, 139.67 ppm and 155.54 ppm respectively. The last two carbon peaks were C-4, appearing at around 127.39-141.05 ppm and C-6 appearing at 115.03-133.67 ppm. **Table 4** shows the observed carbon peaks of all the 5-substituted-3-bromo-2-hydroxyacetophenones **(39E-H)**.

Amongst these compounds is 5-fluoro-3-bromo-2-hydroxyacetophenone which is unique. They exhibit an H-F coupling and C-F coupling. Instead of showing two doublets at the aromatic region they show two doublets of doublets due to H-F coupling.

The existence of functional groups, such as C=O peak at 1600 cm^{-1} and the C-H peak at about 2900 cm^{-1}, and O-H Peak at around 3500 cm^{-1} in the chemical structures of 5-substituted-3-bromo-2-hydroxyacetophenones was confirmed using FT-IR spectroscopy

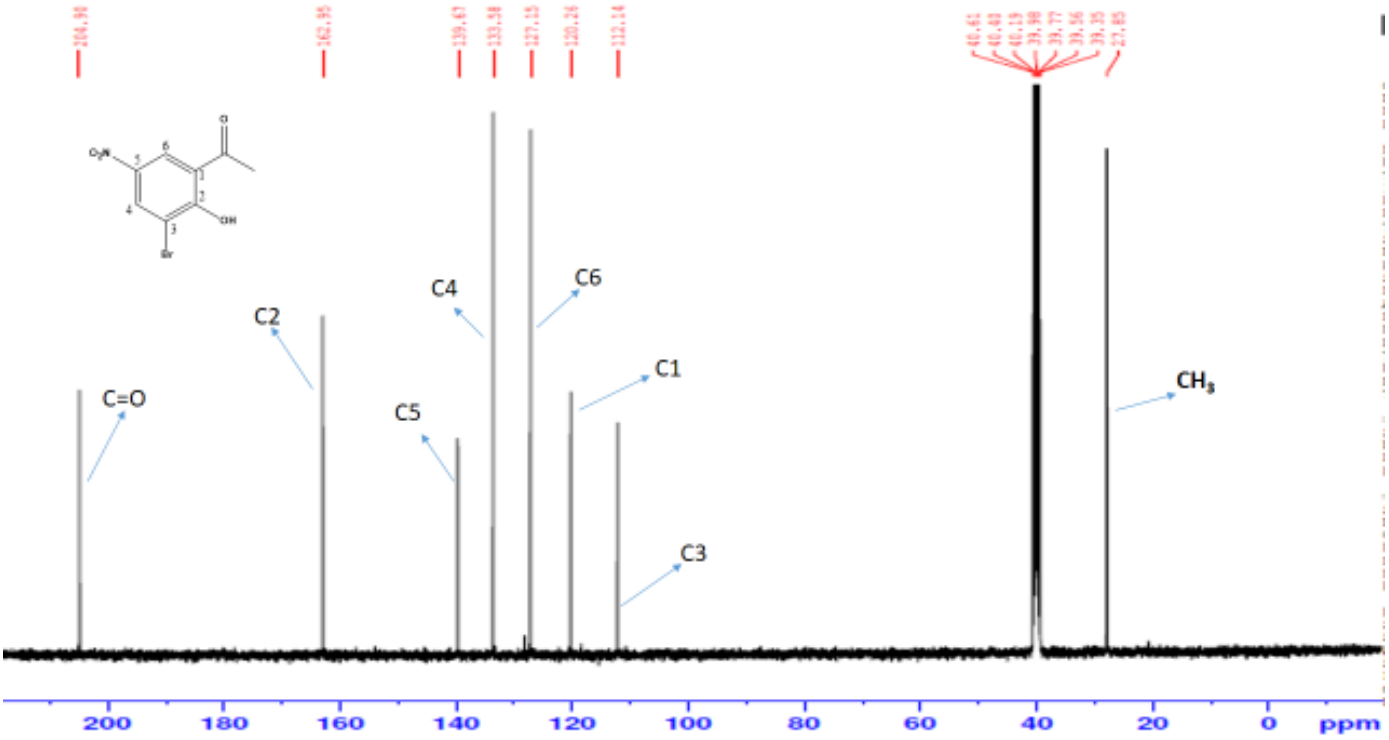


Figure 10: ^{13}C NMR of 5-nitro-3-bromo-2-hydroxyacetophenone **(39H)** in DMSO-d_6

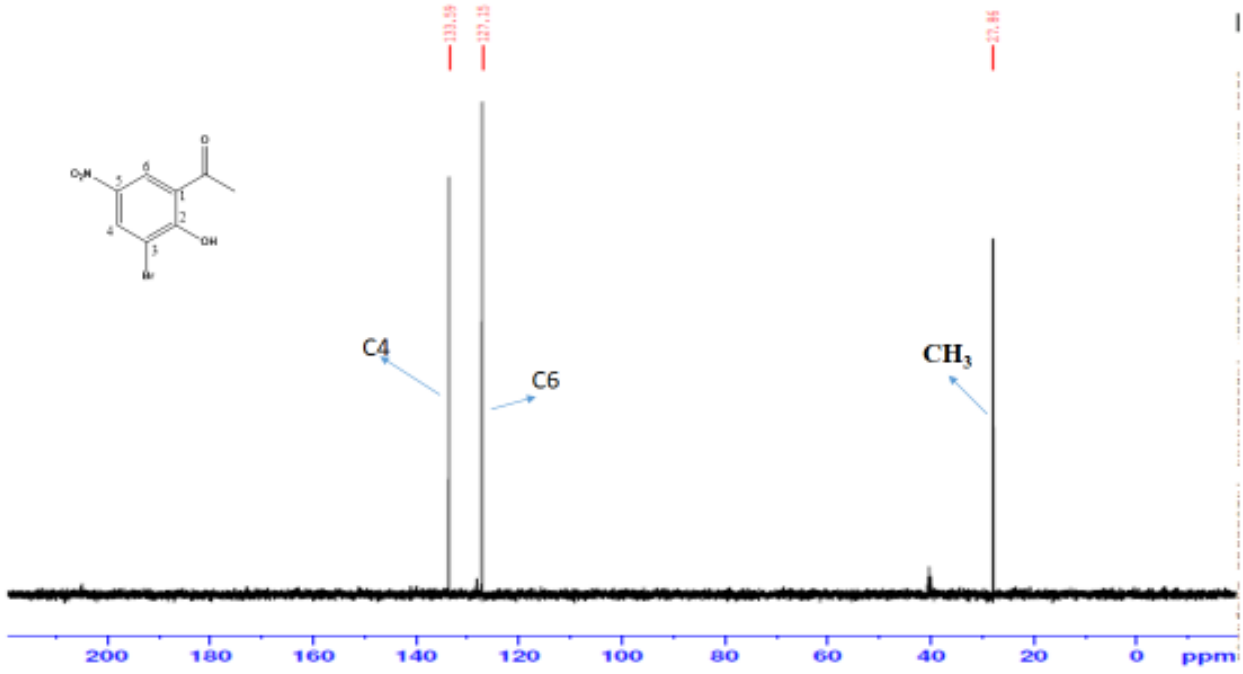


Figure 11: DEPT 135 of 5-nitro-3-bromo-2-hydroxyacetophenones **(39H)** in DMSO-d_6

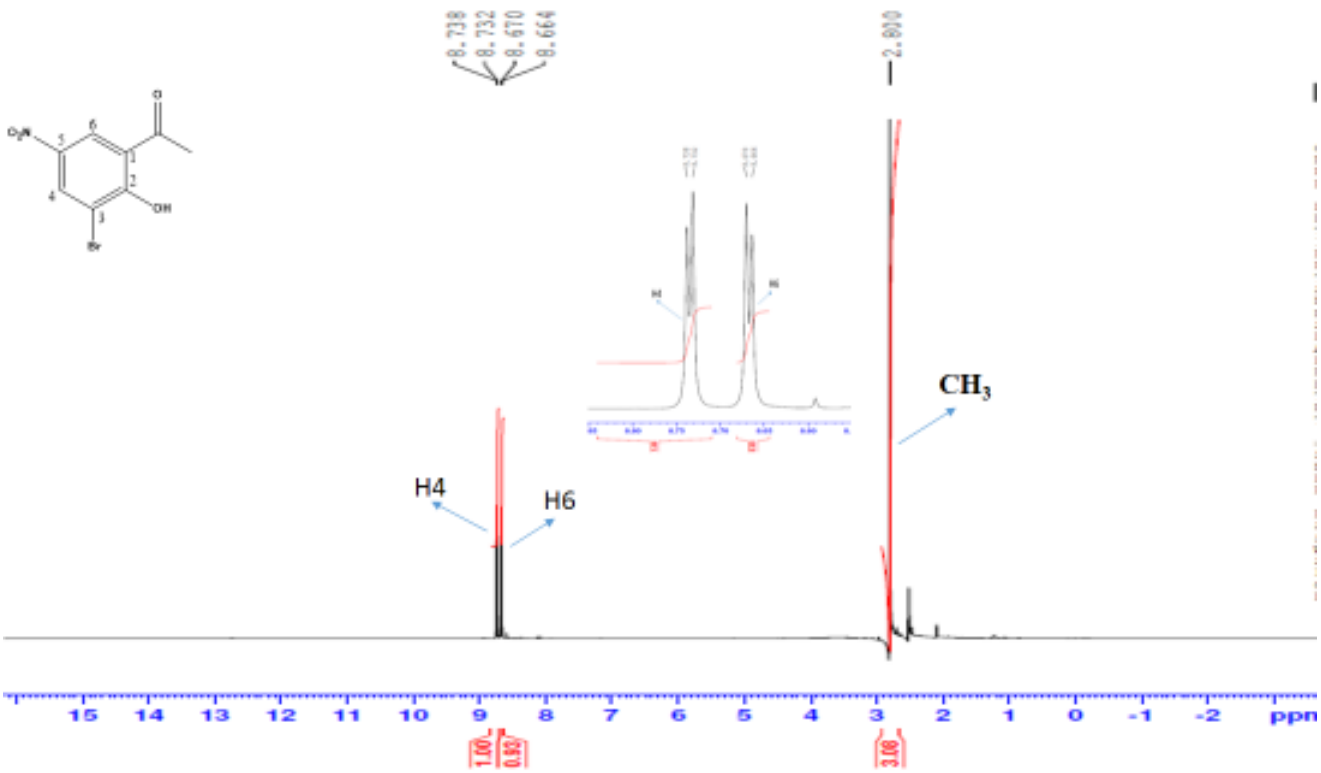


Figure 12: ^{1}H NMR of 5-nitro-3-iodo-2-hydroxyacetophenones **(39H)** in DMSO-d_6

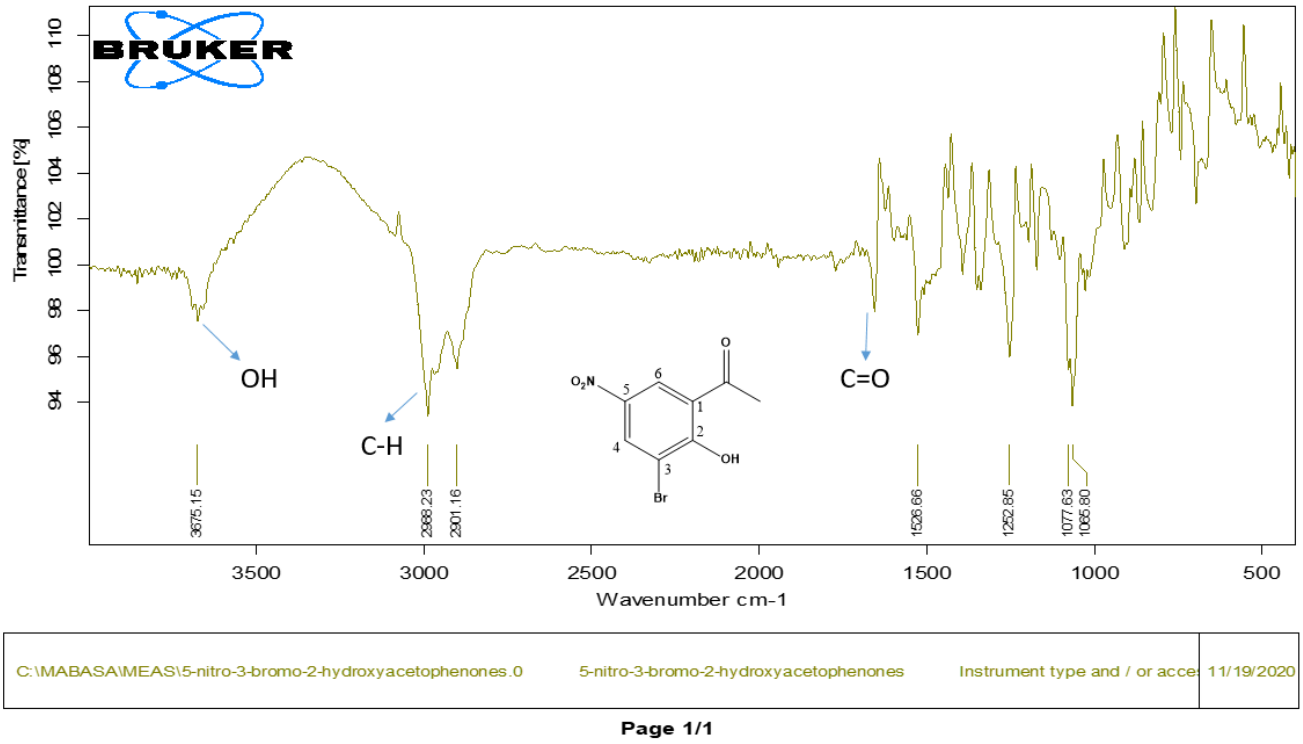
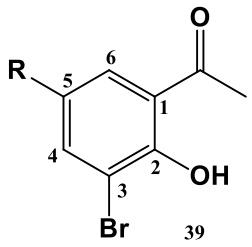


Figure 13: FTIR of 5-nitro-3-iodo-2-hydroxyacetophenones **(39H)**



R= Br, NO_2, Cl, F

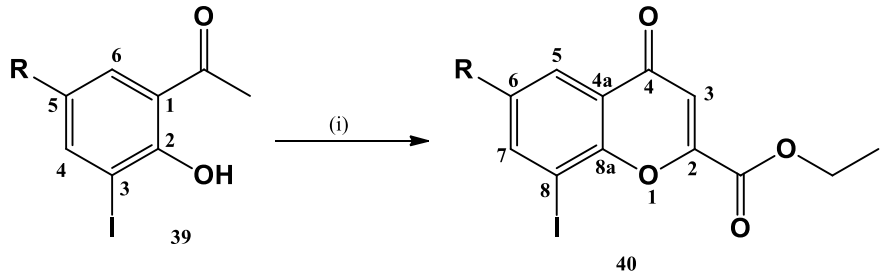
Table 4: ^{13}C NMR chemical shift values (ppm) of compound (**39)** in $CDCl_3$ **(39E-39G)** and DMSO-d_6 **(39H)**

Carbons	**Br**	**Cl**	**F**	**NO_2**
C-1	122.27	123.96	119.25	120.26
C-2	157.24	156.59	152.85	162.95

C-3	110.67	112.89	112.38	112.43
C-4	141.05	136.61	127.39	133.58
C-5	112.55	125.11	155.54	139.67
C-6	133.67	128.2	115.03	127.25
C=O	205.07	203.61	203.33	204.90
CH_3	27.79	26.71	26.78	27.85

4.4 Synthesis of ethyl-6-substituted-8-iodo-chromone-2-carboxylates (40A-D)

In this reaction, 5-substituted-3-iodo-2-hydroxyacetophenones were condensed with diethyl oxalate in the present of ethanolic solution (which was generated insitu by reacting sodium metal with absolute ethanol under inert environment). The reaction was refluxed until it formed a slurry. After allowing it to cool, diethyl ether was added and the filtrates was removed by vacuum suction. The yellow slurry was added to 2M HCl and then extracted 3 times by diethyl ether. The organic layers were combined and then dried using anhydrou sodium sulphate. The sulphate was filtered and organic parts were condensed under reduced pressure to give ethyl-6-substituted-8-iodo-chromone-2-carboxylates (**40A-40D).** The reaction scheme is outlined in **scheme 7**.

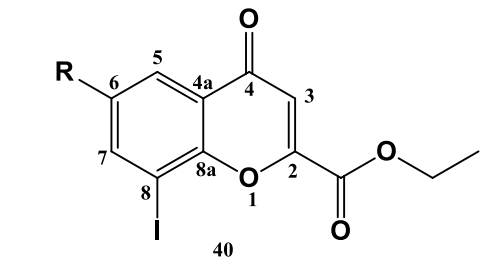


R= Br, F, Cl, NO_2

Reagent: (i) NaOEt-EtOH, Diethyl oxalate, reflux, 1hr

Scheme 7: Synthesis of ethyl 6-subsituted-8-iodo-chromone-2-carboxylates (**40A-40D)**

The ethyl-6-substituted-8-iodo-chromone-2-carboxylates were fully characterized by NMR and FTIR spectrums and their physical properties. The afforded yield was good to excellent (52-95 %). The melting points of these compounds are not reported in literature. The melting points and percentage yield of the synthesized ethyl-6-substituted-8-iodo-chromone-2-carboxylate **(40A-40D)** derivatives are reported in **table 5.**



40

R= Br, F, Cl, NO_2

Table 5: Synthesized ethyl-6-substituted-8-iodo-chromone-2-carboxylates (**40)**

Compounds 40	**R**	**Percentage yield (%)**	**Melting point (^{0}C)**
A	**Br**	95	198.9-214.8
B	**F**	52	157.7-163.5
C	**Cl**	70	133.2-142.1
D	**NO_2**	60	139.1-144.1

The synthesized compounds were fully characterized by 1D NMR (^{1}H, ^{13}C, DEPT), FTIR spectrum. Physical characteristics such as melting points were also used.

The assignment of the protons for compounds (**40A-D)** were done after considering the chemical shifts and coupling constants observed in the ^{1}H NMR spectra.

^{1}H NMR spectra of 6-substituted-8-iodo-chromone-2-carboxylates (**40A-D**) were characterized by five peak signals. Two of these signals were from the aliphatic region. We had a triplet from a methyl protons at around 1.37-1.38 ppm and a quartet at around 4.42

ppm which corresponds to CH_2 protons. From the aromatic region we have a singlet at 6.97-719 ppm. The remaining two peaks are doublet from protons at position 5 resonating at 7.86-8.20 ppm and another doublet from protons at position 7 resonating at 8.05-8.42 ppm. For compound containing fluorine, the doublets appear as doublets of doublets because of the H-F coupling.

Spectroscopic data obtained from ^{13}C NMR and DEPT 135 experiments were used to confirm the presence of 12 carbon peaks. From these peaks, we observe 7 quaternary carbons, from which two of these were carbonyl carbons from the pyrone ring and COOEt resonating at 176.21-176.98 ppm and 159.19-161.43 ppm respectively. The remaining five quaternary carbons were in the aromatic region which are C-2, C-4a, C-6, C-8 and C-8a resonating at 152.79-159.93 ppm, 124.21-125.64 ppm, 120.07-144.28 ppm, 86.37-88.72 ppm and 152.52-154.99 ppm respectively. We also observed three C-H peaks in the aromatic region resulting from C-3, C-5 and C-7 resonating at 113.70-114.43 ppm, 109.01-128.73 ppm and 143.31-146.51 ppm respectively. The last two peaks were from the aliphatic region from the CH_2 and CH_3. The CH_2 peak appeared at 63.28-63.34 ppm while that of the CH_3 appeared at 14.02-14.31 ppm. **Table 6** summarize the obtained carbon peaks for all the 6-substituted-8-iodo-chromone-2-carboxylates derivatives **(40A-D)** synthesized.

FTIR spectroscopy was used to confirm the presence of the functional groups in the chemical structures of 6-substituted-8-iodo-chromone-2-carboxylates derivatives **(40A-D).** The FT-IR revealed an aromatic group C-H between 2900-3100 cm^{-1} and C=C stretch at around 1600 cm^{-1} and a carbonyl around 1700 cm^{-1}.

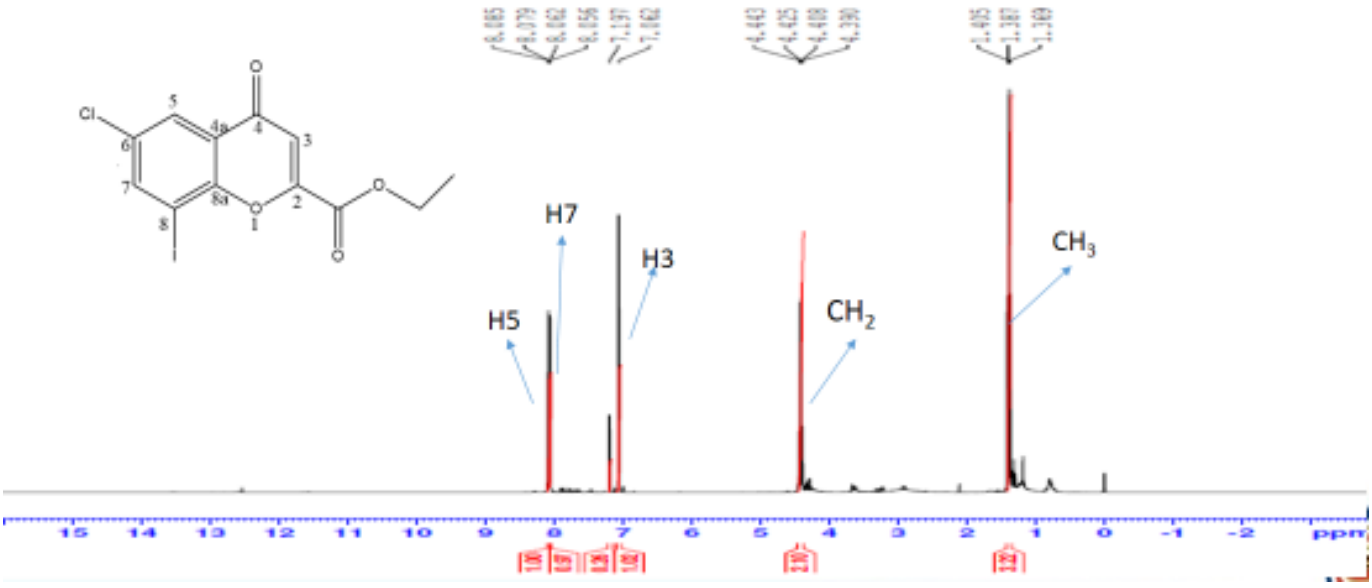


Figure 14: ^{1}H NMR of ethyl-6-chloro-8-iodo-chromone-2-carboxylates **(40C)** in DMSO-d_6

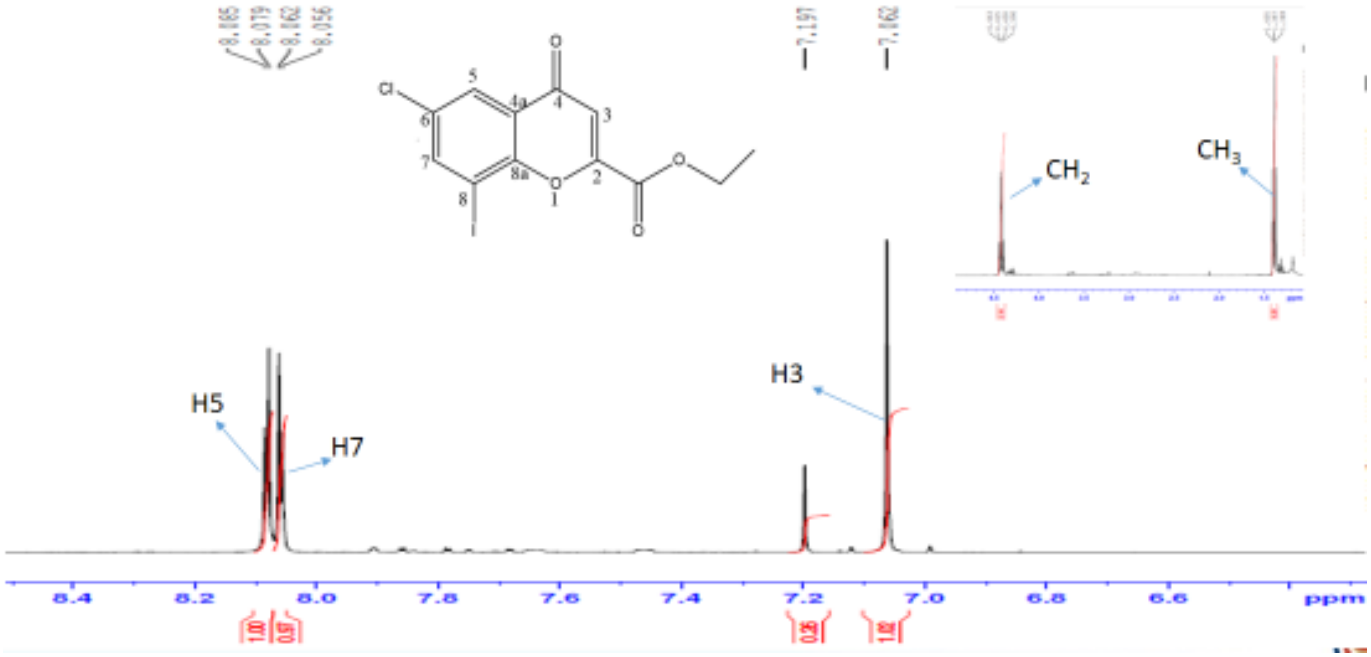


Figure 15: Expansion of ^{1}H NMR of ethyl-6-chloro-8-iodo-chromone-2-carboxylates **(40C)** in DMSO-d_6

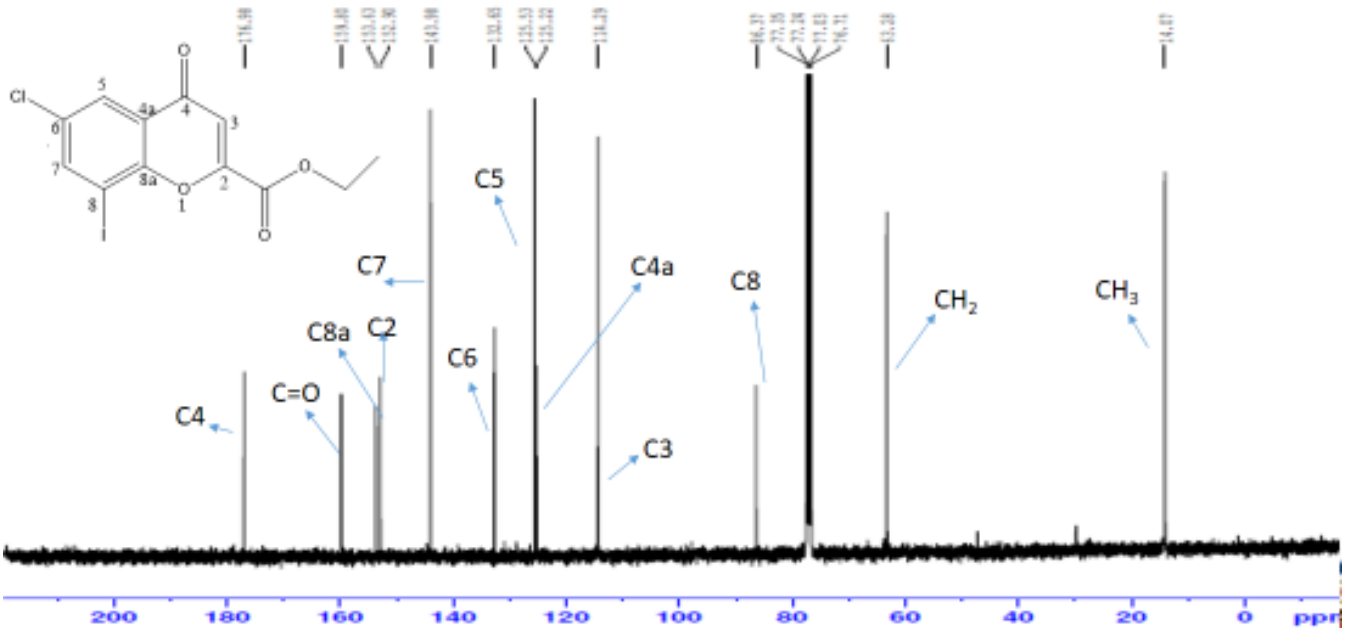


Figure 16: ^{13}C NMR of ethyl-6-chloro-8-iodo-chromone-2-carboxylates **(40C)** in DMSO-d_6

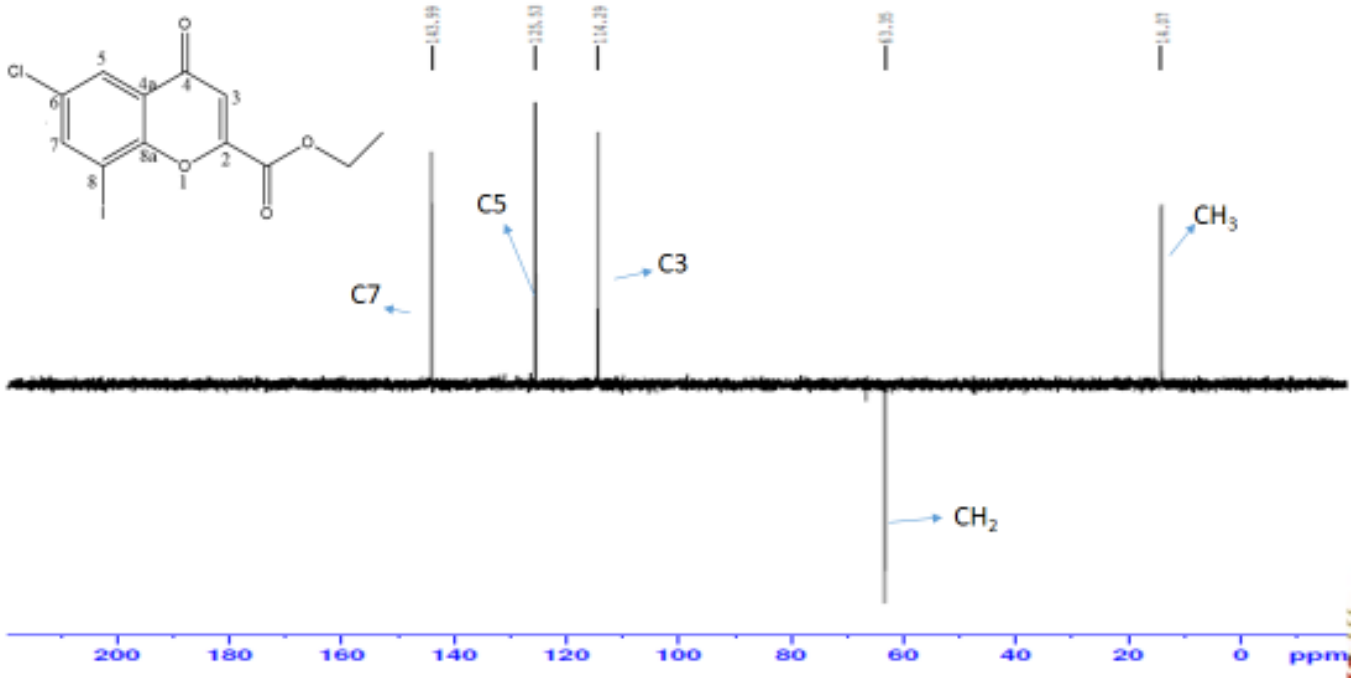


Figure 17: DEPT 135 of ^{13}C NMR of ethyl-6-chloro-8-iodo-chromone-2-carboxylates **(40C)** in DMSO-d_6

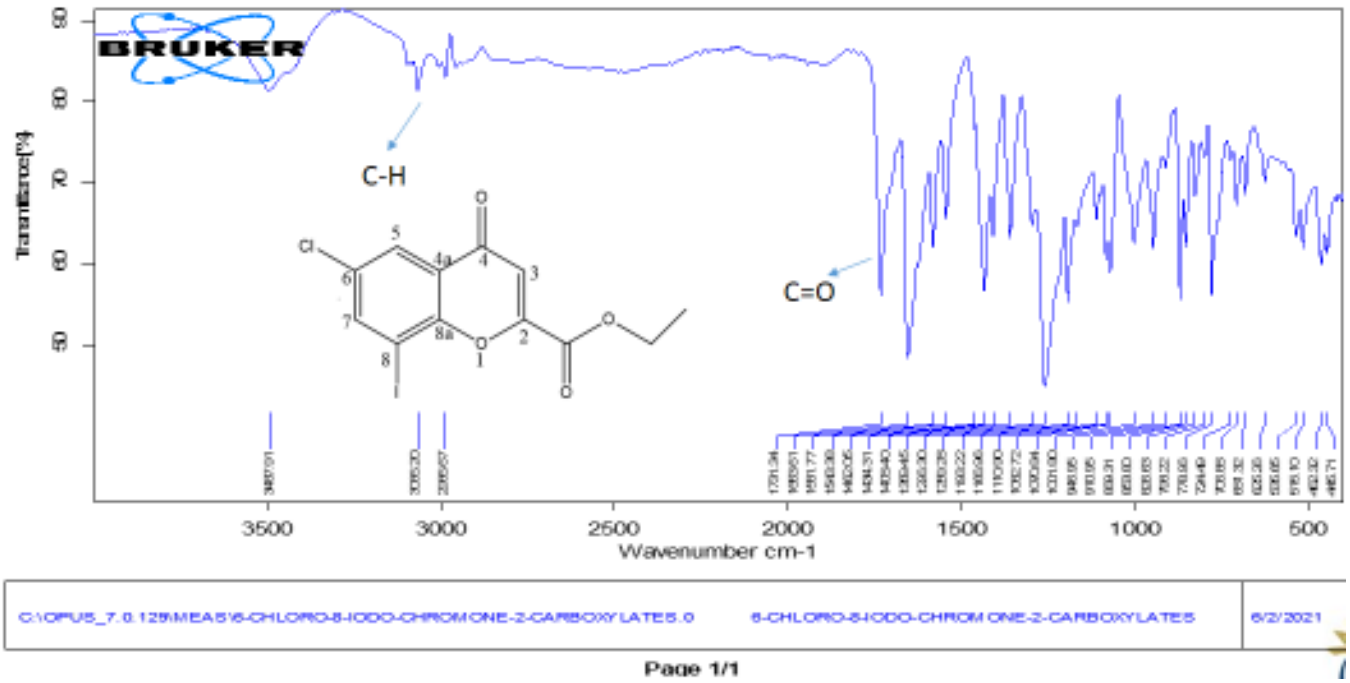
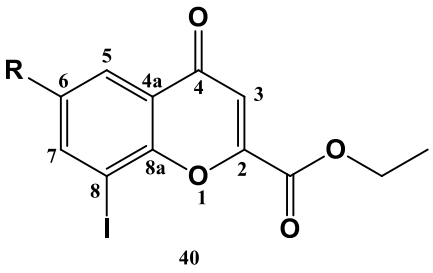


Figure 18: FTIR of ethyl-6-chloro-8-iodo-chromone-2-carboxylate **(40C)**



40

R= Br, F, Cl, NO_2

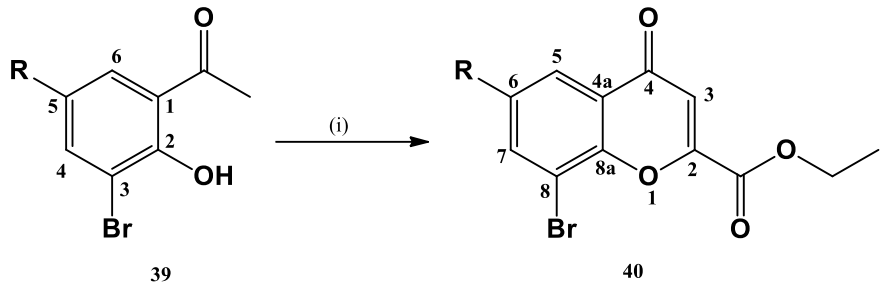
Table 6: ^{13}C NMR chemical shift values (ppm) of compounds **(40A-40D)** in DMSO-d_6

Carbons	**Br**	**F**	**Cl**	**NO_2**
C-2	159.79	159.12	152.90	159.93
C-3	114.43	113.93	114.29	113.70

C-4	176.68	176.21	176.98	176.76
C-4a	125.64	124.21	125.22	125.19
C-5	128.73	109.01	125.53	124.55
C-6	120.07	144.28	132.65	131.53
C-7	146.51	143.31	143.98	143.80
C-8	86.37	88.35	88.37	88.72
C-8a	152.52	154.21	153.68	154.99
COOEt	159.19	160.21	161.43	161.43
CH_2	63.30	63.31	63.34	63.34
CH_3	14.04	14.05	14.02	14.31

4.5 Synthesis of ethyl-8-bromo-6-substituted-chromone-2-carboxylates (40E-H)

The same procedure used to synthesize compounds (**40A-40D)** was followed. 5-substituted-3-bromo-2-hydroxyacetophenones were condensed with diethyl oxalate in the presence of ethanolic solution. The reaction was refluxed until it formed a slurry. After allowing it to cool, diethyl ether was added and the filtrates was removed by vacuum suction. The yellow slurry was added to 2M HCl and then extracted 3 times by diethyl ether. The organic layers were combined and then dried by sodium sulphate. The sulphate was filtered and organic parts were condensed under reduced pressure to give ethyl-6-substituted-8-bromo-chromone-2-carboxylates (**40E-40H).** The reaction scheme is outlined in **scheme 8**.



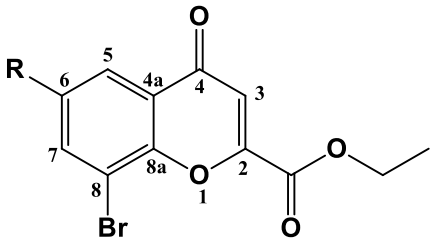
39 40

R= Br, F, Cl, NO_2

Reagent: (i) NaOEt-EtOH, Diethyl oxalate, reflux, 1hr

Scheme 8: Synthesis of ethyl 6-subsituted-8-bromo-chromone-2-carboxylates (**40E-40H)**

The ethyl-6-substituted-8-bromo-chromone-2-carboxylates **(40E-40H)** were fully characterized by NMR and FTIR spectrums and their physical properties. The obtained yield was moderate to good (44 -79 %). The melting points and percentage yield of the synthesized ethyl-6-substituted-8-bromo-chromone-2-carboxylate derivatives are reported in **table 7**.



40

R= Br, F, Cl, NO_2

Table 7: Synthesized ethyl-6-substituted-8-bromo-chromone-2-carboxylates (**40)**

Compounds 40	**R**	**Percentage yield (%)**	**Melting point (^{0}C)**
E	**Br**	72	108.3-112.1
F	**F**	44	165.1-174.9

G	**Cl**	53	109.2-113.4
H	**NO_2**	79	123.5-130.1

The compounds were fully characterized by 1D NMR (^1H, ^{13}C, DEPT), FTIR spectrum and their physical properties (melting points and color).

The assignment of the protons for compounds (**40E-H)** were done after considering the chemical shifts and coupling constants observed in the ^1H NMR spectra.

^1H NMR spectra of 6-substituted-8-bromo-chromone-2-carboxylates (**40E-H**) were characterized by five peak signals. Two of these signals were from the aliphatic region. We had a triplet from a methyl protons at around 1.36-1.38 ppm and a quartet at around 4.38-4.47 ppm which corresponds to CH_2 protons. From the aromatic region we had a singlet at 6.98-7.05 ppm. The remaining two peaks were doublet from protons at position 5 resonating at 7.30- 8.32 ppm and another doublet from protons at position 7 resonating at 7.74-8.59 ppm. For compound containing fluorine, the doublets appear as doublets of doublets because of the H-F coupling as shown in **figure 19.**

Spectroscopic data obtained from ^{13}C NMR and DEPT 135 experiments were used to confirm the presence of 12 carbon peaks. From these peaks, we observe 7 quaternary carbons, from which two of these were carbonyl carbons from the pyrone ring and COOEt resonating at 176.97-177.42 ppm and 159.21- 160.40 ppm respectively. The remaining five quaternary carbons were in the aromatic region which were C-2, C-4a, C-6, C-8 and C-8a resonating at 153.20-159.86 ppm, 123.41-126.44 ppm, 121.21-149.42 ppm, 113.42-113.98 ppm and 157.28-159.21 ppm respectively. We also observed three C-H peaks in the aromatic region resulting from C-3, C-5 and C-7 resonating at 113.29-113.79 ppm, 110.38-128.21 ppm and 126.21-145.13 ppm respectively. The last two peaks were from the aliphatic region from the CH_2 and CH_3. The CH_2 peak appeared at 63.12-63.62 ppm while that of the CH_3 appeared at 14.03-14.28 ppm. **Table 8** summarize the observed chemical shifts of carbons for all the 6-substituted-8-bromo-chromone-2-carboxylates derivatives **(40E-H)** synthesized.

FTIR spectroscopy was used to confirm the presence of the functional groups in the chemical structures of 6-substituted-8-bromo-chromone-2-carboxylate derivatives **(40E-H).** The FT-IR spectra revealed an aromatic group C-H between 2900-3100 cm^{-1} and C=C stretch at around 1600 cm^{-1} and a carbonyl around 1700 cm^{-1}.

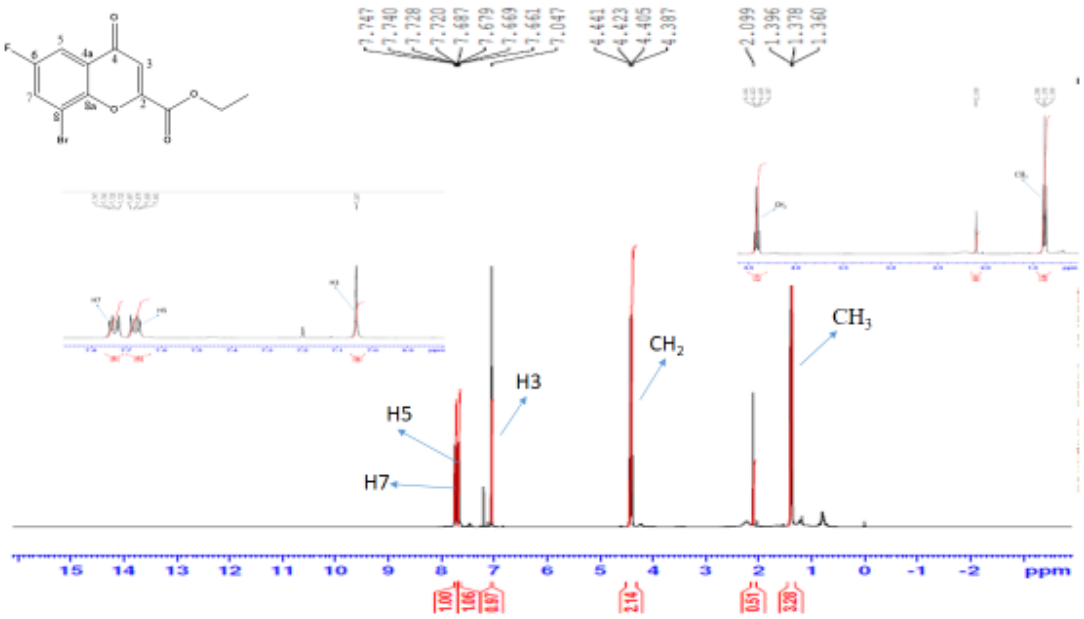


Figure 19: ^{1}H NMR of 6-fluoro-8-bromo-chromone-2-carboxylates **(40F)** in DMSO-d_6

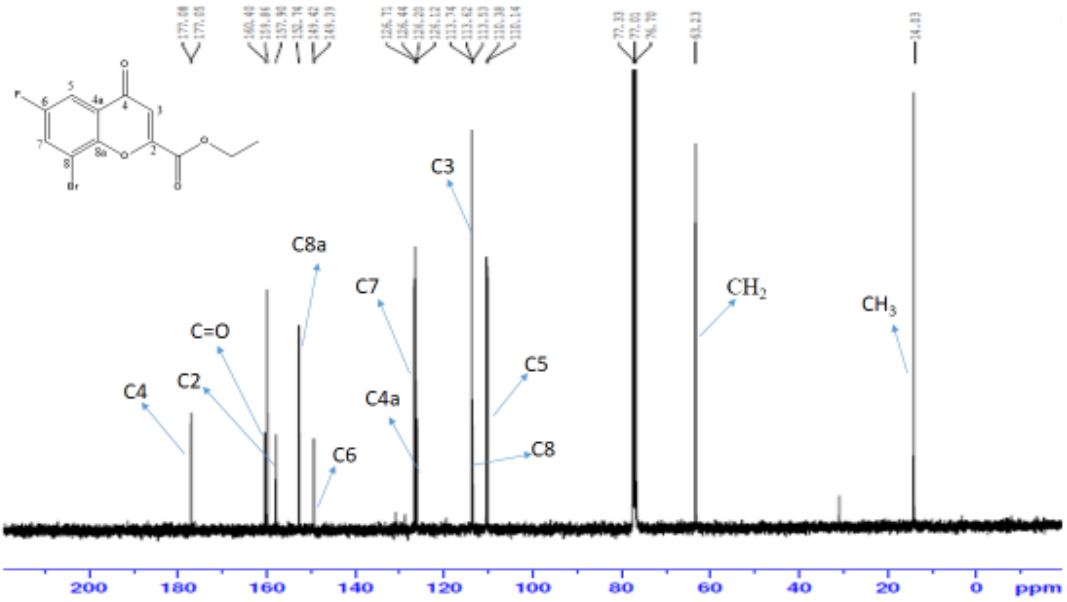


Figure 20: ^{13}C NMR of 6-fluoro-8-bromo-chromone-2-carboxylates (**40F)** in DMSO-d_6

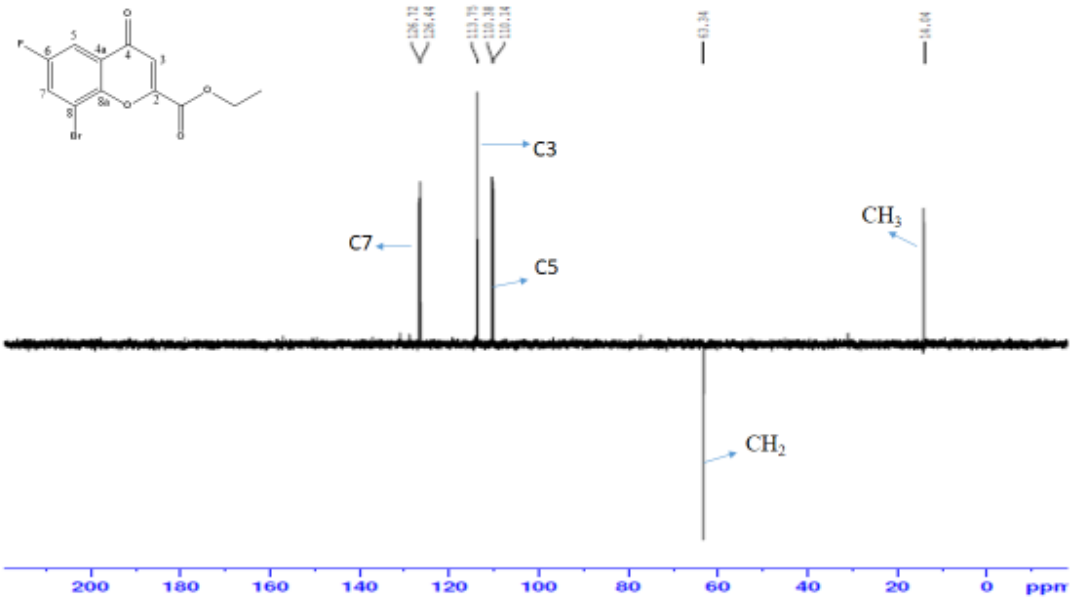
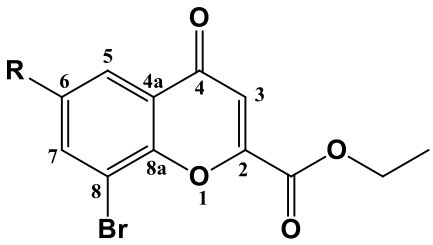


Figure 21: DEPT 135 of ^{13}C NMR of 6-fluoro-8-bromo-chromone-2-carboxylates **(40F)** in DMSO-d_6



40

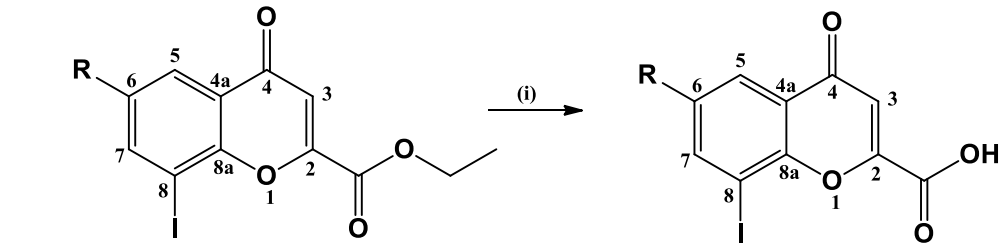
R= Br, F, Cl, NO_2

Table 8: ^{13}C NMR chemical shift values (ppm) of compounds **(40E-40H)** in DMSO-d_6

Carbons	**Br**	**F**	**Cl**	**NO_2**
C-2	159.21	159.86	153.91	153.20
C-3	113.29	113.75	113.82	113.79
C-4	177.23	177.08	177.42	176.97
C-4a	125.41	126.44	125.42	125.69
C-5	128.20	110.38	125.98	128.21
C-6	125.60	149.42	121.21	128.42
C-7	126.21	126.72	131.28	145.13
C-8	113.58	113.62	113.42	113.98
C-8a	159.12	157.90	158.26	157.28
C=O	160.36	160.40	159.79	159.21
CH_2	63.12	63.23	63.21	63.62
CH_3	14.28	14.03	14.09	14.21

4.6 Synthesis of 6-susbstituted-8-iodo-chromone-2-carboxylic acids (41A-D)

Ethyl-6-substituted-8-iodo-chromone-2-carboxylates **(40A-D)** were dissolved in a mixture of acetic acid and concentrated hydrochloric acid (The ratio of AcOH to HCl was always kept in 2:1). These reactions were allowed to reflux for 2 hours. After stopping the reaction and cooling, water was added to form 6-substituted-8-iodo-chromone-2-carboxylic acids (**41A-D)**. The synthesis of 6-substituted-8-iodo-chromone-2-carboxylic acids were achieved with moderate to excellent yields of 48-90 %. The reaction scheme is outlined in **scheme 9**.



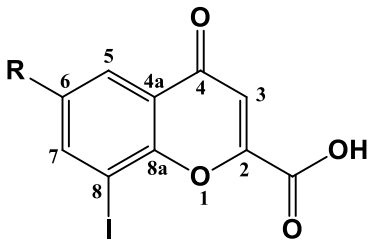
40 41

R= Br, F, Cl, NO_2

Reagent: (i) AcOH-HCl (2:1), reflux, 2 hr.

Scheme 9: Synthesis of 6-subsituted-8-iodo-chromone-2-carboxylic acids (**41A-41D)**

The 6-subsituted-8-iodo-chromone-2-carboxylic acids were fully characterized by NMR and FTIR spectrums and their physical properties. The afforded yield was moderate to excellent (48-90 %). The melting points and percentage yield of the synthesized 6-substituted-8-iodo-chromone-2-carboxylic acids derivatives are reported in **table 9**.



41

R= Br, F, Cl, NO_2

Table 9: Synthesized 8-iodo-6-substituted-chromone-2-carboxylic acids (**41)**

Compounds 41	**R**	**Percentage yield (%)**	**Melting point (^{0}C)**
A	**Br**	90	294.5-297.5
B	**F**	48	232.4-239.1
C	**Cl**	75	293.5-297.6
D	**NO_2**	57	260.2-263.1

The synthesized compounds were fully characterized by 1D NMR (^{1}H, ^{13}C, DEPT) and FTIR spectrum. Physical characteristics such as melting points were also used.

After taking into account the chemical shifts and coupling constants seen in the proton NMR spectra, the protons were assigned to the compounds (**41A-D)**.

^{1}H NMR spectra of 6-substiututed-8-iodo-chromone-2-carboxylic acids (**41A-D)** were characterized by four peak signals. This shows that indeed our reaction did form since the CH_3 and CH_2 were no longer visible. Three of these compounds showed an OH Peak at around 5.36- 6.20 ppm. Compound (**41B)** didn't show an OH Peak. In the aromatic region, the compounds were characterized by a singlet peak at around 7.03-7.18 ppm, which corresponded to the proton at position 3. There were two doublets resonating from proton at position 5 and proton at position 7. The doublet from proton 5 ranged between 7.96-8.82

ppm while that of proton 7 resonated between 8.15 and 9.05 ppm. For compound **(41B)**, there were some uniqueness in the proton NMR spectrum because of the H-F coupling. When the bonding electron was drawn to the fluorine, other protons were left exposed to one another. This caused proton 5 and 7 to appear as doublet of doublet instead of doublets.

The existence of 10 carbon peaks was confirmed using spectroscopic data obtained from ^{13}C NMR and DEPT 135 was used to confirm compounds (**41A-D).** These compounds exhibited 7 quaternary carbons and three C-H carbons. Amongst these seven quaternary carbons, two of them were carbonyl carbons. The first one resonated in 176.54-177.13 ppm and corresponded to the carbonyl in the pyrone ring while the second one was from COOH and appeared between 161.34-162.70 ppm. The remaining quaternary carbons at the aromatic region were C-2, C-4a, C-6, C-8 and C-8a and resonate at 158.65-161.88 ppm, 124.07-125.67 ppm, 119.14-154.39 ppm, 87.85-88.49 ppm and 152.15-154.64 ppm respectively. The C-H aromatic carbons were C-3, C-5 and C7 and appeared at 112.69-113.86 ppm, 110.01-127.64 ppm and 132.68-146.13 ppm respectively. The observed carbon peaks for all the synthesized 6-substituted-8-iodo-chromone-2-carboxylic acids **(41A- D)** are listed in **Table 10**.

FT-IR spectroscopy was used to confirm the presence of functional groups in the chemical structures of 6-substituted-chromone-2-carboxylic acids **(41A-D)**. FT-IR spectra revealed an aromatic (C-H) group at 3000 cm^{-1} and C=C stretch at 1670 cm^{-1} as indicated in **figure 25**.

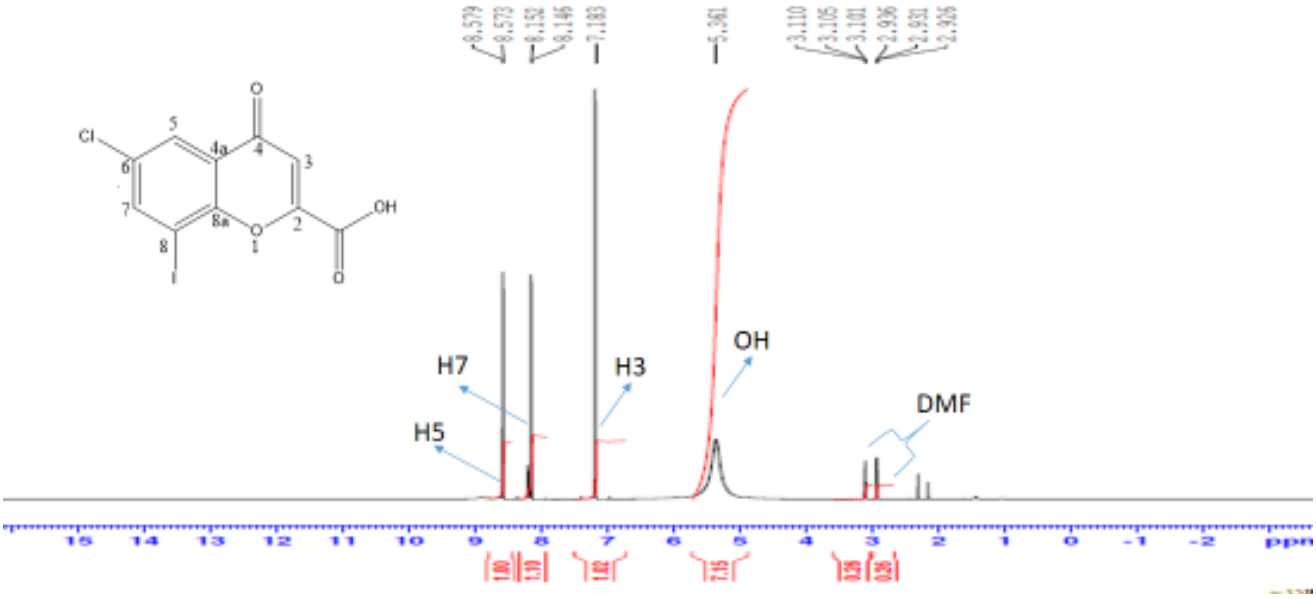


Figure 22: ^{1}H NMR of 6-chloro-8-iodo-chromone-2-carbpxylic acids **(41C)** in DMF-d_7

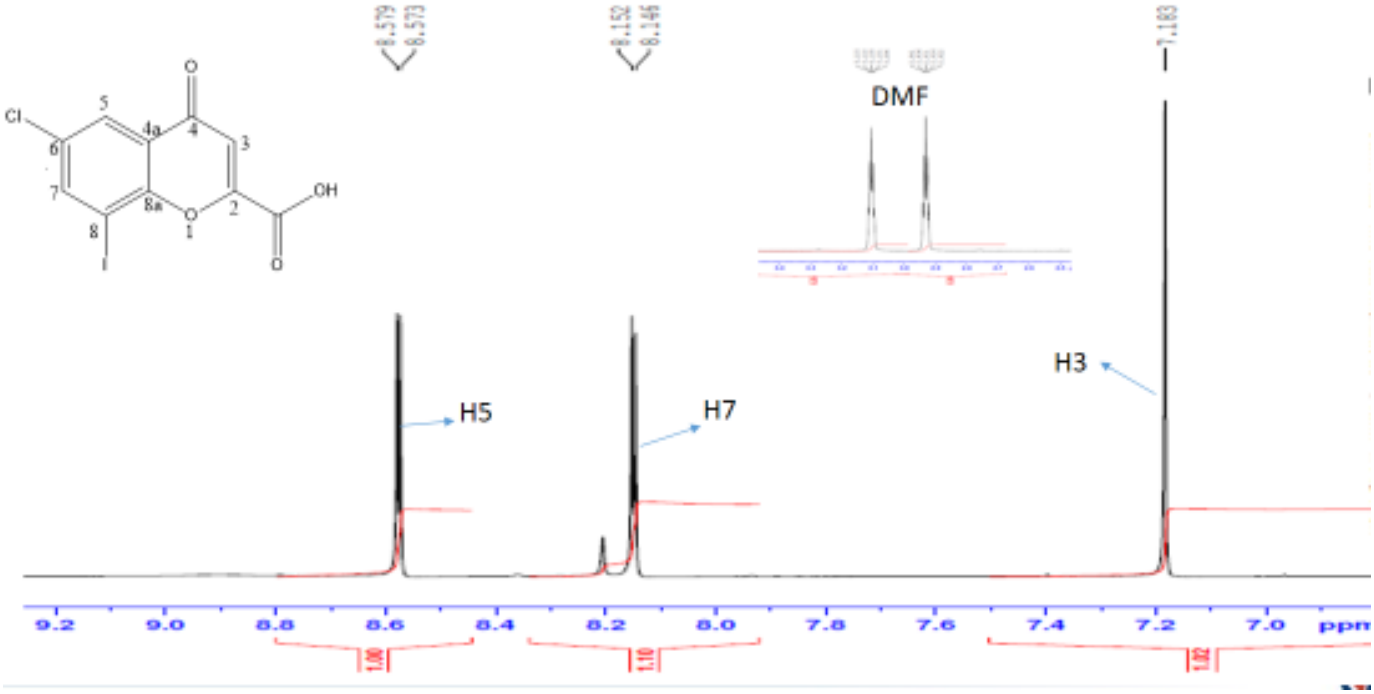


Figure 23**:** Expansion of ^{1}H NMR of 6-chloro-8-iodo-chromone-2-carboxylic acids (**41C)** in DMF-d_7

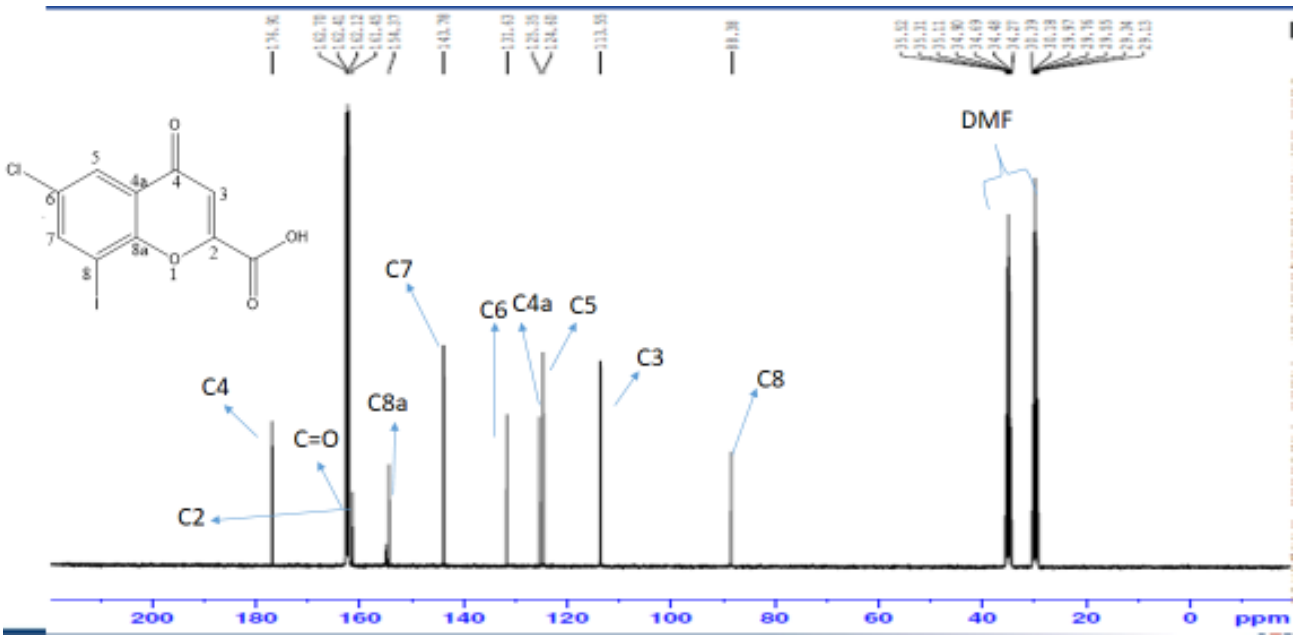


Figure 24: ^{13}C NMR of 6-chloro-8-iodo-chromone-2-carboxylic acid **41C** in DMF-d_7

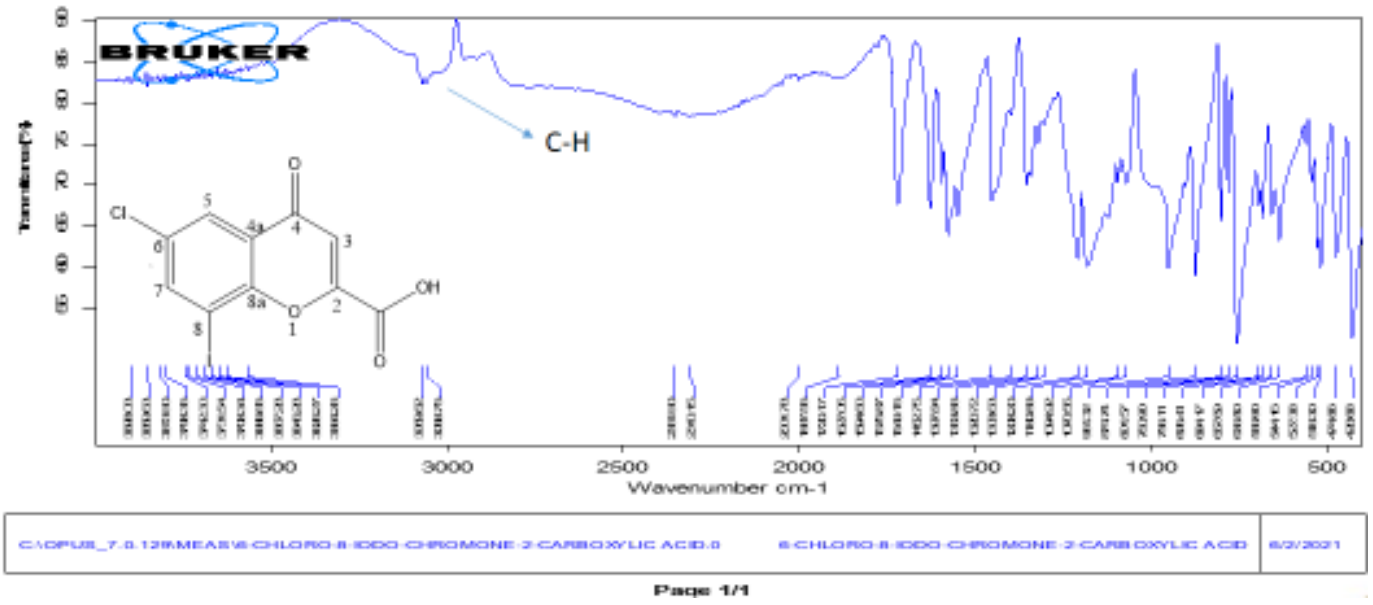
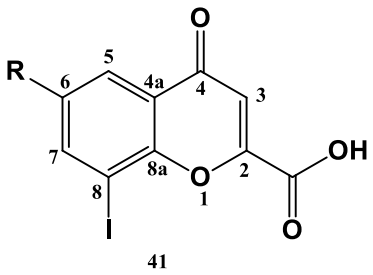


Figure 25: FTIR of 6-chloro-8-iodo-chromone-2-carboxylic acid (**41C)**



41

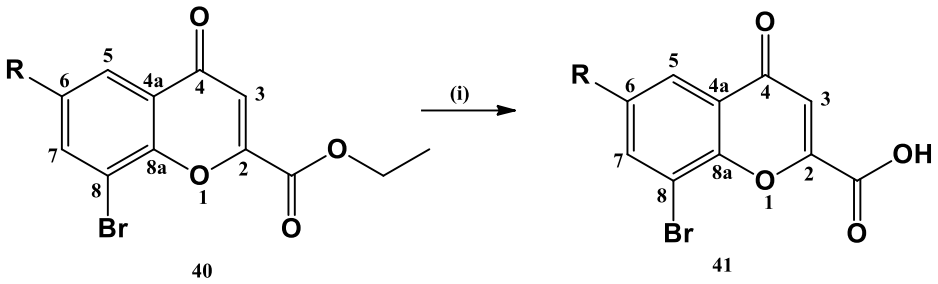
R= Br, F, Cl, NO_2

Table 10: ^{13}C NMR chemical shift values (ppm) of compounds **(41A-41D)** in DMF-d_7

Carbons	**Br**	**F**	**Cl**	**NO_2**
C-2	161.88	160.55	161.45	158.65
C-3	113.67	112,69	113.05	113.86
C-4	176.54	177.13	176.91	176.91
C-4a	125.67	125.25	125.35	124.07
C-5	127.64	110.01	124.60	120.93
C-6	119.14	154.39	131.63	145.14
C-7	146.13	132.68	143.78	138.10
C-8	88.49	87.85	88.38	88.12
C-8a	154.33	152.15	154.37	154.64
COOH	162.46	161.34	162.70	162.46

4.7 Synthesis of 6-susbstituted-8-bromo-chromone-2-carboxylic acids (41E-H)

The same procedure employed for compounds (**41A-41D)** was repeated. Ethyl-6-substituted-8-bromo-chromone-2-carboxylates were dissolved in a mixture of acetic acid and concentrated hydrochloric acid. These reactions were allowed to reflux for 2 hours. After stopping the reaction and cooling, water was added to form 6-substituted-8-bromo-chromone-2-carboxylic acids (**41E-H)**. The synthesis of 6-substituted-8-bromo-chromone-2-carboxylic acids was achieved with moderate to excellent yields of 49-98 %. The reaction scheme is outlined in **scheme 10**.



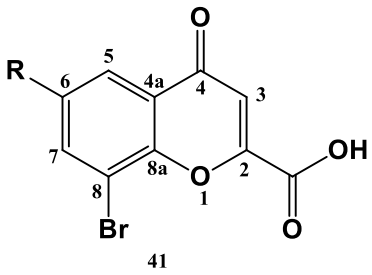
40 41

R= Br, F, Cl, NO_2

Reagent: (i) AcOH-HCl (2:1), reflux, 2 hr.

Scheme 10: Synthesis of 6-subsituted-8-bromo-chromone-2-carboxylic acids (**41E-H)**

The 6-subsituted-8-bromo-chromone-2-carboxylic acids were fully characterized by NMR and FTIR spectrums and their physical properties. The afforded yield was moderate to excellent (49-98 %). The melting points and percentage yield of the synthesized 6-substituted-8-bromo-chromone-2-carboxylic acids derivatives are reported in **table 11**.



41

R= Br, F, Cl, NO_2

Table 11: Synthesized 6-substituted-8-bromo-chromone-2-carboxylic acids **41**

Compounds 41	**R**	**Percentage yield (%)**	**Melting point (^{0}C)**
E	**Br**	98	256.8-260.5
F	**F**	49	259.4-261.9
G	**Cl**	78	91.6-93.5
H	**NO_2**	73	215.6-221.1

Spectroscopic techniques such as FTIR and NMR (1D) were used to characterize all these synthesized compounds. Physical characteristics such as melting points were also used

After taking into account the chemical shifts and coupling constants seen in the proton NMR spectra, the protons were assigned to the (**41E-H)**.

^{1}H NMR spectra of 6-substiututed-8-bromo-chromone-2-carboxylic acids (**41E-H)** were characterized by four peak signals. This shows that indeed our reaction did form since the CH_3 and CH_2 are no longer visible. The OH peak signal appeared around 5.56-6.02 ppm. In the aromatic region, the compounds were characterized by a singlet peak at around 6.78-7.13 ppm, which corresponds to the proton at position 3. The remaining proton peaks were two doublets appearing at position 5 and position 7 in the aromatic region. The doublet from

proton 5 ranged between 7.78-8.77 ppm while that of proton 7 resonated between 7.74 and 8.97 ppm. Compound (**41F)** exhibited some uniqueness in the proton NMR spectrum because of the H-F coupling. Protons appeared to be coupled due to H-F coupling.

The existence of 10 carbon peaks was confirmed using spectroscopic data obtained from ^{13}C NMR and DEPT 135 was used to confirm compounds (**41E-H).** These compounds exhibited 7 quaternary carbons and three C-H carbons. Amongst these seven quaternary carbons, two of them were carbonyl carbons. The first one resonated in 176.18-176.85 ppm and corresponded to the carbonyl in the pyrone ring while the second one was from COOH and appeared between 161.28-162.48 ppm. The remaining quaternary carbons at the aromatic region were C-2, C-4a, C-6, C-8 and C-8a and resonated at 154.00-157.79 ppm, 125.02-126.47 ppm, 118.57-144.84 ppm, 113.32-113.73 ppm and 151.30-154.56 ppm respectively. The C-H aromatic carbons were C-3, C-5 and C7 and appeared at 112.94-114.03 ppm, 109.71-127.04 ppm and 126.76-140.13 ppm respectively. The observed chemical shifts of carbons for all 6-substituted-8-bromo-chromone-2-carboxylic acids **(41E- 41H)** synthesized are listed in **Table 13**.

The existence of functional groups in the chemical structures of 6-substituted-8-bromo-chromone-2-carboxylic acids **(41A-D)** was confirmed using FT-IR spectroscopy. An aromatic (C-H) group at 2900-3000 cm^{-1} and C=C stretch at 1670-1700 cm^{-1} were determined by FT-IR spectroscopy**.**

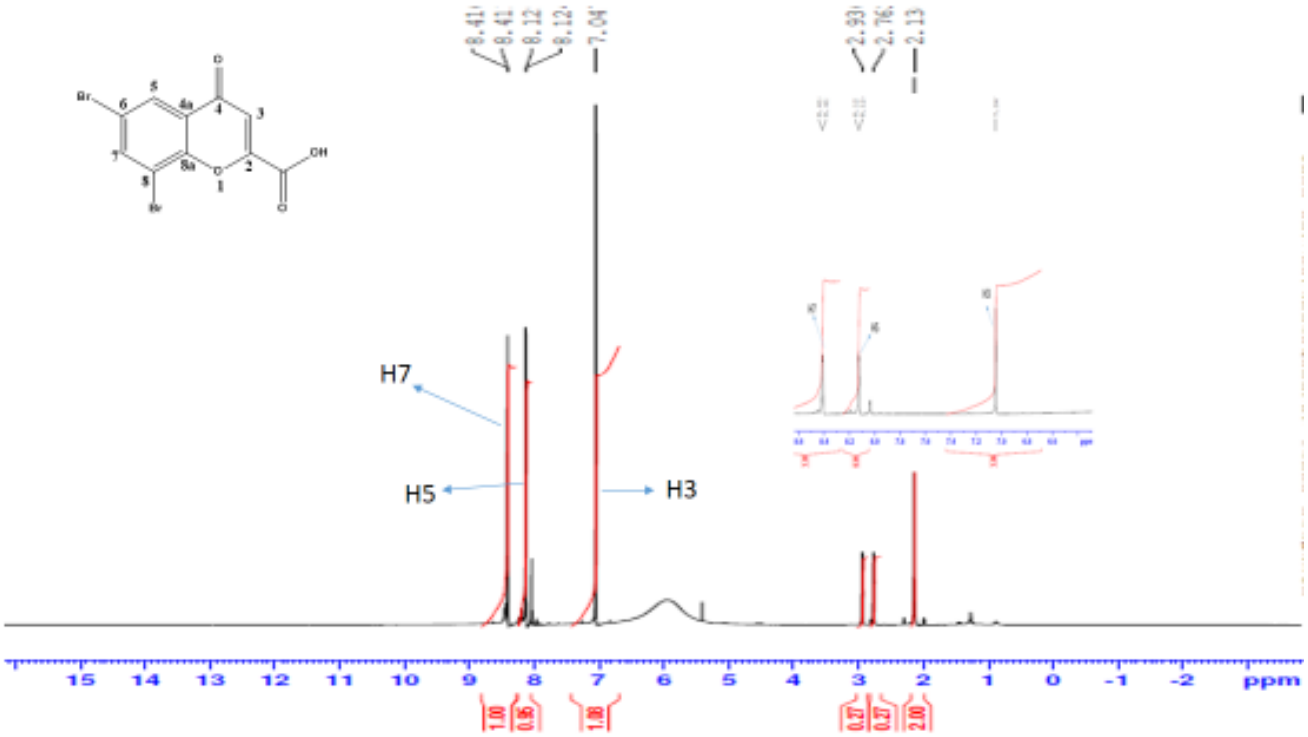


Figure 26: ^{1}H NMR of 6.8-dibromo-chromone-2-carboxylic acids (**41E)** in DMF-d_7

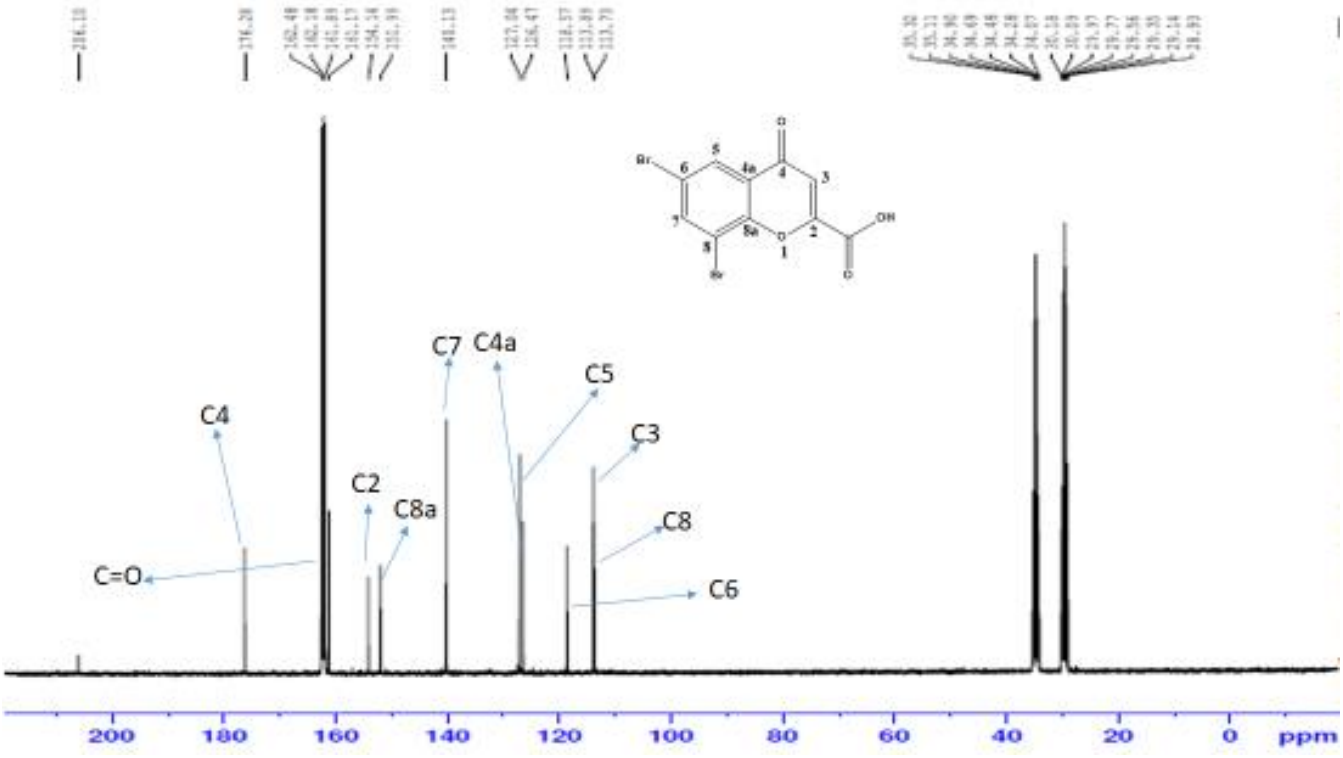


Figure 27: ^{13}C NMR of 6.8-dibromo-chromone-2-carboxylic acids **(41E)** in DMF-d_7

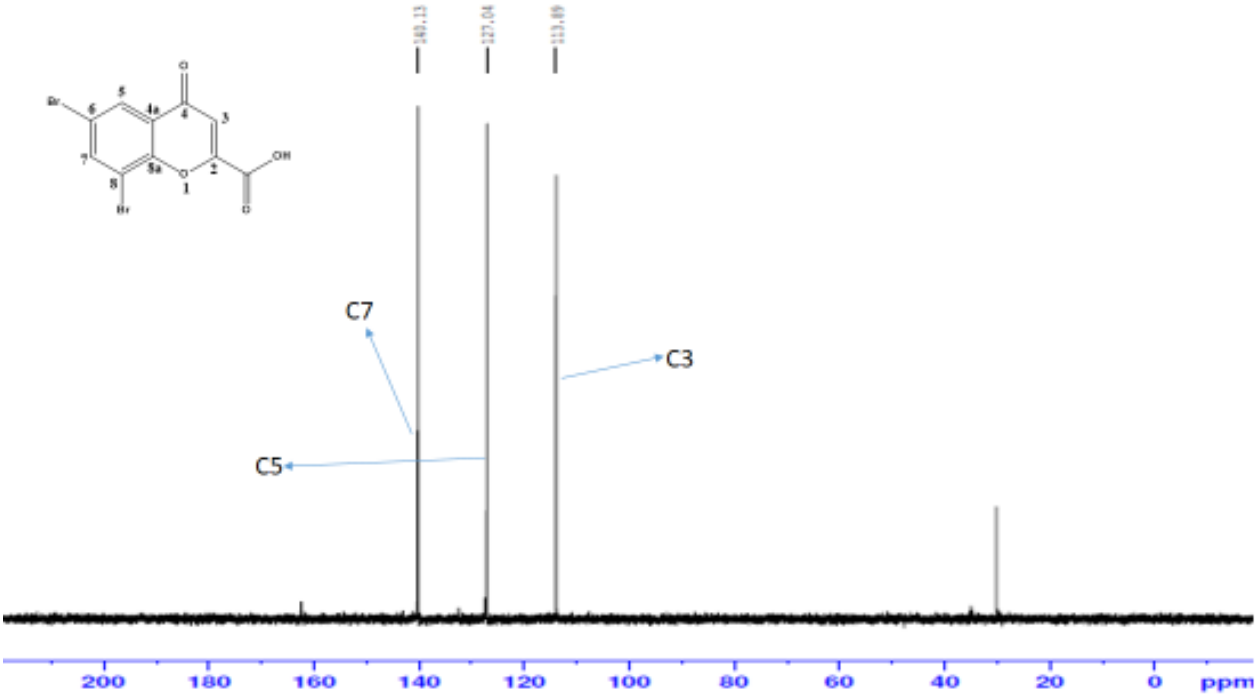
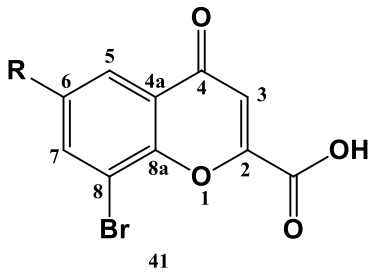


Figure 28: DEPT 135 of ^{13}C NMR of 6.8-dibromo-chromone-2-carboxylic acids **(41E)** in DMF-d_7



41

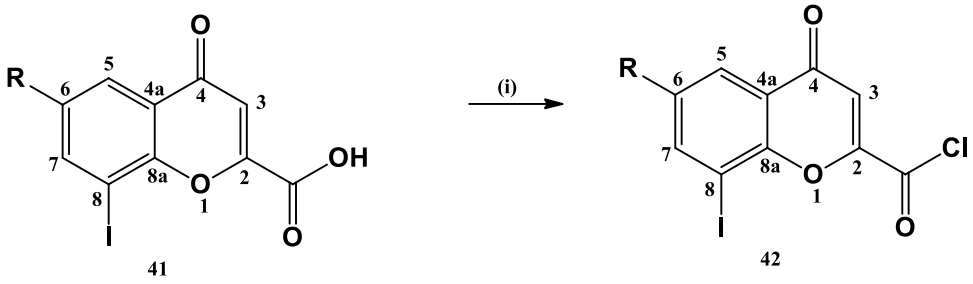
R= Br, F, Cl, NO_2

Table 13: ^{13}C NMR chemical shift values (ppm) of compounds **(41E-41H)** in DMF-d_7

Carbons	**Br**	**F**	**Cl**	**NO_2**
C-2	154.17	157.79	154.00	156.14
C-3	113.89	112.94	113.47	114.03
C-4	176.38	176.85	176.18	176.68
C-4a	126.47	126.13	125.80	125.02
C-5	127.04	109.71	123.62	120.24
C-6	118.57	134.27	130.13	144.84
C-7	140.13	126.76	138.13	132.05
C-8	113.73	113.45	113.32	113.69
C-8a	151.99	154.27	151.30	154.56
COOH	162.48	161.28	162.27	162.18

4.8 Synthesis of 6-substituted-8-iodo-chromone-2-carbonyl chlorides (42A-D)

In this reaction a 6.8-disubstituted-crhomone-2-carboxylic acids were dissolve in dry N,N-dimethylformamide and 1.2-dichloroethane. Thionyl chloride was added and the resulting mixture was refluxed under inert conditions (nitrogen gas or calcium chloride tube) for 2 hours. The reaction was allowed to cool to room temperature. The solvent was removed under reduced pressure and another 1.2-dichloroethane was added and removed under vacuum to afford 6-substituted-8-iodo-chromone-2-carbonyl chloride **(42A-D).** The synthesis of 6-substituted-8-iodo-chromone-2-carbonyl chlorides were achieved in moderate yields of 44-60 %. The reaction scheme is outlined in **scheme 11**.



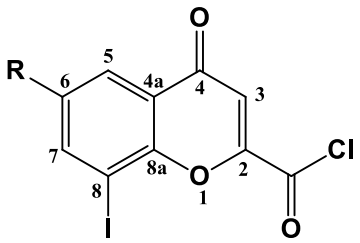
41 42

R= Br, F, Cl, NO_2

Reagent: (i) $SOCl_2$, DMF, reflux, 1 hr.

Scheme 11: Synthesis of 6-subsituted-8-iodo-chromone-2-carbonyl chloride (**42A-D)**

The 6-subsituted-8-iodo-chromone-2-carbonyl chlorides were fully characterized by NMR and FTIR spectrums and their physical properties. The afforded yields were moderate (44-60 %). The melting points and percentage yield of the synthesized 6-substituted-8-iodo-chromone-2-carbonyl chlorides derivatives are reported in **table 14**.



42

R= Br, F, Cl, NO_2

Table 14: Synthesized 6-substituted-8-iodo-chromone-2-carbonyl chlorides (**42)**

Compounds 42	**R**	**Percentage yield (%)**	**Melting point (^{0}C)**
A	**Br**	60	241.5-247,3
B	**F**	44	-
C	**Cl**	53	241.7-258.8
D	**NO_2**	47	-

Spectroscopic techniques such as FTIR and NMR (1D) were used to characterize all these synthesized compounds. Physical characteristics such as melting points were also used.

After taking into account the chemical shifts and coupling constants seen in the proton NMR spectra, the protons were assigned to the compounds (**42A-D)**.

Proton NMR spectra of 6-substituted-8-iodo-chromone-2-carbonyl chlorides (**42A-D)** were characterized by three peak signals. These three peaks were all in the aromatic region and the first one was a singlet resonating from proton at position 3. This peak appeared at 6.98-7-08 ppm. The last two peaks were two doublets resonating from protons at position 5 and position 7. These peaks appeared at 7.81-8.52 ppm and 7.79-8.78 ppm respectively.

The existence of 10 carbon peaks were confirmed using spectroscopic data from ^{13}C NMR and DEPT 135 studies. These compounds exhibited 7 quaternary carbons and three C-H

carbons. Amongst these seven quaternary carbons, two of them were carbonyl carbons. The first one resonated in 176.56-177.06 ppm and corresponded to the carbonyl in the pyrone ring while the second one is from COCl and appears between 161.13-162.30 ppm. The remaining quaternary carbons at the aromatic region were C-2, C-4a, C-6, C-8 and C-8a and resonate at 154.34-156.88 ppm, 124.43-125.21 ppm, 119,03-154.03 ppm, 88.12-88.85 ppm and 152.01-154.50 ppm respectively. The C-H aromatic carbons were C-3, C-5 and C-7 and appeared at 112.60-113.82 ppm, 109.80-128.21 ppm and 132.58-145.98 ppm respectively. The observed carbon peaks for all produced 6-substituted-8-iodo-chromone-2-carbonyl chlorides **(42A-42D)** are listed in **Table 15**.

FT-IR spectroscopy was used to confirm the presence of functional groups in the chemical structures of 6-substituted-8-iodo-chromone-2-carbony chlorides **(42A-D)**. FT-IR spectra revealed an aromatic (C-H) group at 2900-3000 cm^{-1} and C=C stretch at 1670-1700cm^{-1}.

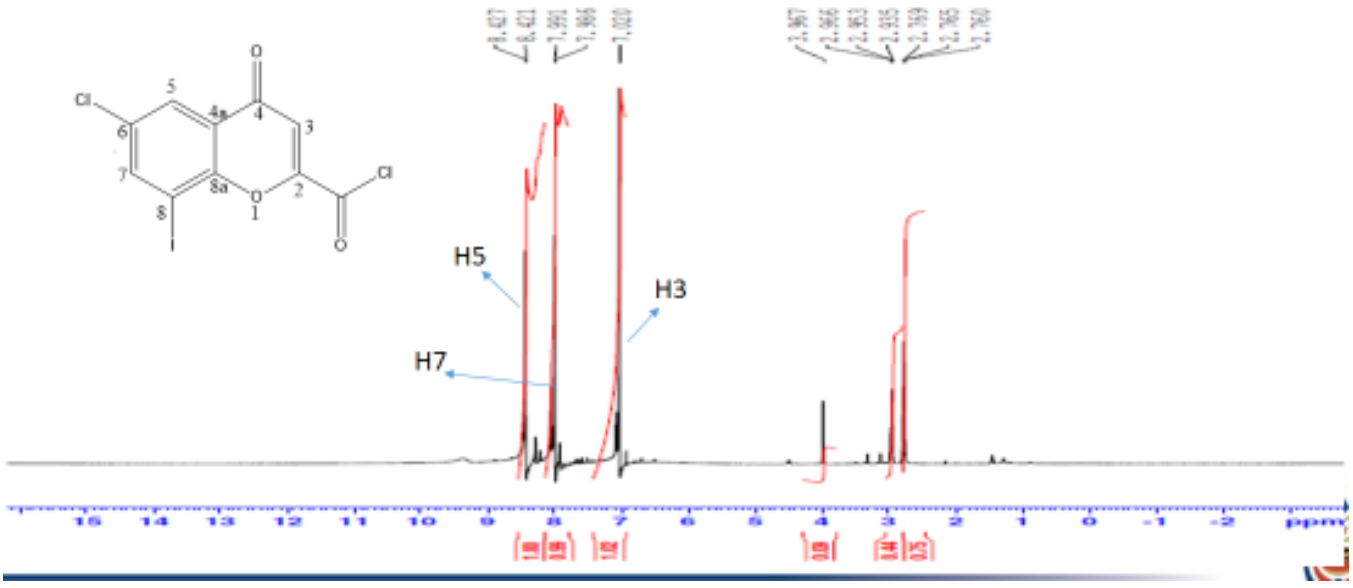


Figure 29: ^{1}H NMR of 6-chloro-8-iodo-chromone-2-carbonyl chloride (**42C)** in DMF-d_7

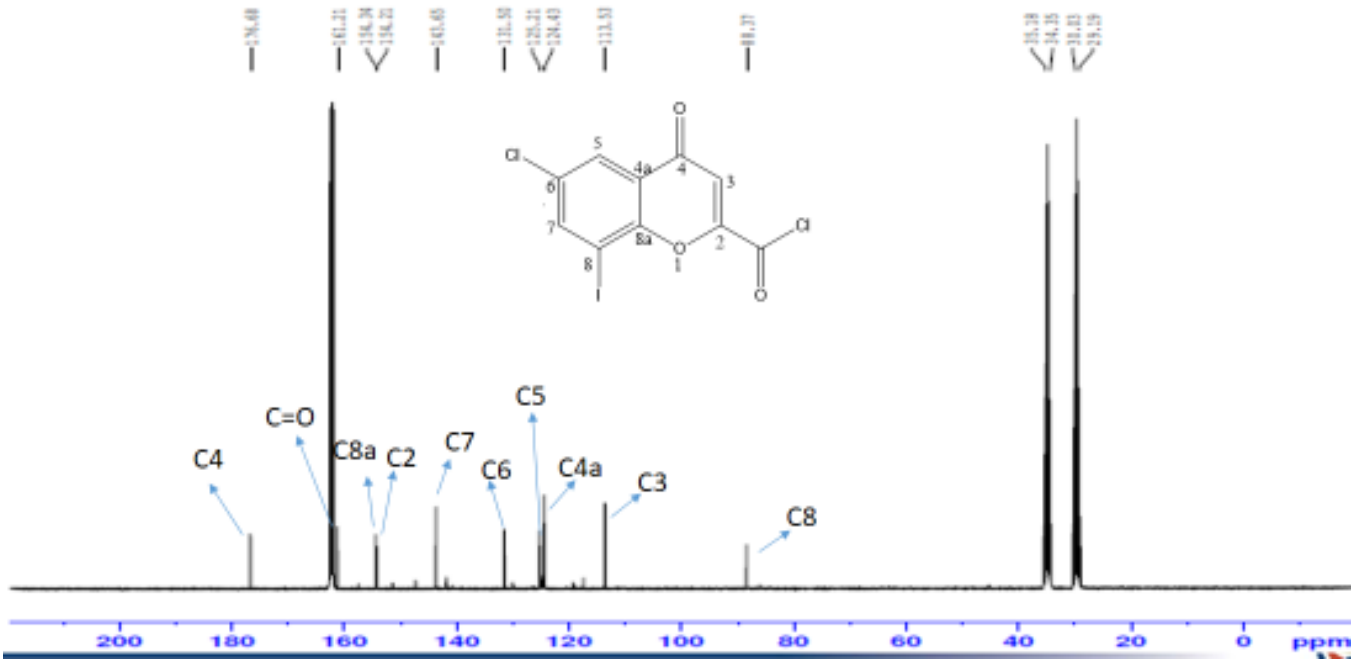


Figure 30: ^{13}C NMR of 6-chloro-8-iodo-chromone-2-carbonyl chloride **(42C)** in DMF-d_7

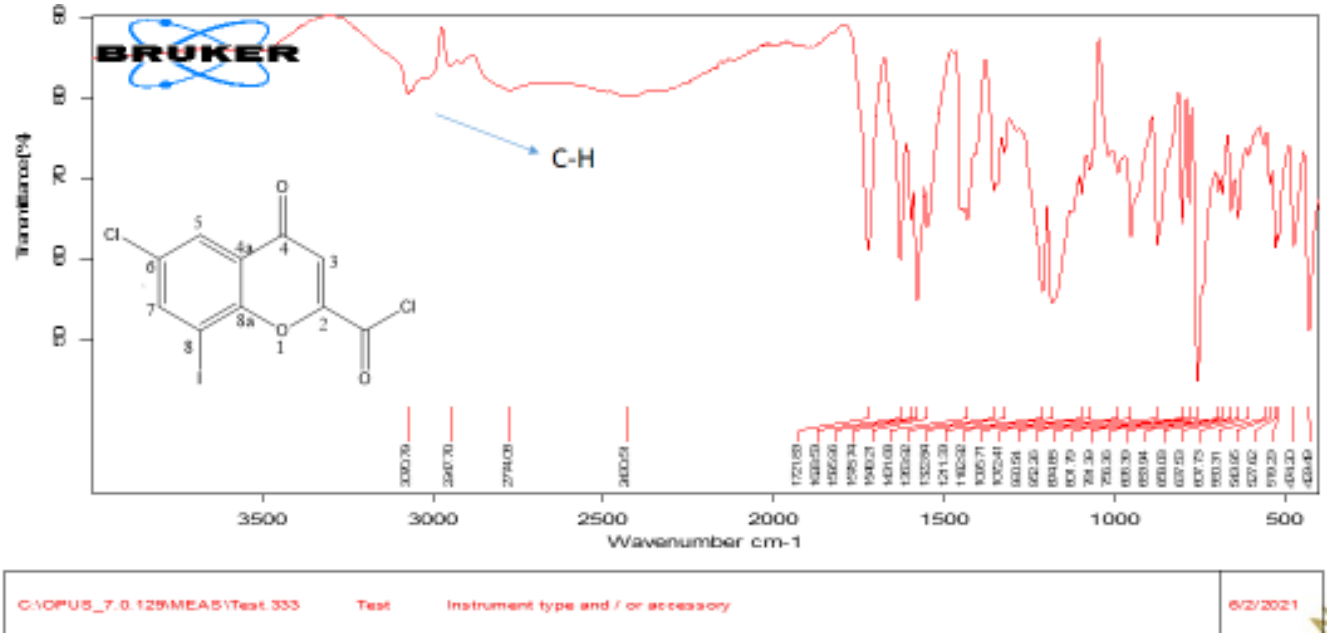
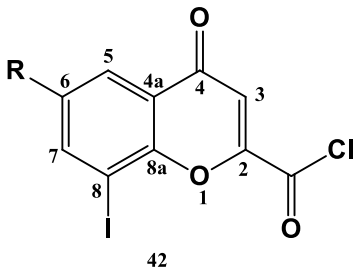


Figure 31: FTIR of 6-chloro-8-iodo-chromone-2-carbonyl chlorides **(42C)**



42

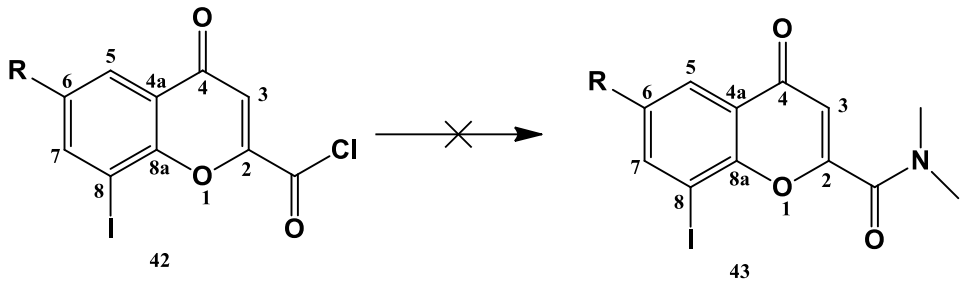
R= Br, F, Cl, NO_2

Table 15: ^{13}C NMR chemical shift values (ppm) of compounds **(42A-D)** in DMF-d_7

Carbons	**Br**	**F**	**Cl**	**NO_2**
C-2	154.65	156.88	154.34	156.55
C-3	113.58	112.60	113.53	113.82
C-4	176.56	177.06	176.68	176.83
C-4a	124.82	125.21	124.43	125.15
C-5	128.21	109.80	125.21	120.58
C-6	119.03	154.03	131.50	144.95
C-7	145.98	132.58	143.65	137.98
C-8	88.12	88.49	88.37	88.85
C-8a	154.50	154.28	154.21	152.01
COCl	162.30	161.13	161.21	161.24

4.9 Attempted synthesis of 6.8-disubsituted-chromone-2-carboxamides (43)

For these reactions, 6.8-disubstituted-chromone-2-carbonyl chlorides was poured into dry pyridine and cooled in ice for 30 minutes. A mixture of dimethylammonium chloride and pyridine was added dropwise. The reaction mixture was stirred in ice bath for 3 hours and then 21 hours in room temperature. The resulting mixture was poured in 2M HCl, cooled in ice for 30 minutes and extracted 4 times with ethyl acetate. It was then washed with 5% $NaHCO_3$ and saturated aqueous NaCl. The extract was dried with sodium sulphate and condensed under reduced pressure. With the aid of ethanol, the resultant solid was recrystallized. The 6.8-substituted-chromone-2-carboxamides (**43)** were intended to be produced by this reaction, however, NMR spectra showed a complex mixture which was difficult to separate. The proposed reaction is illustrated by **scheme 12**.



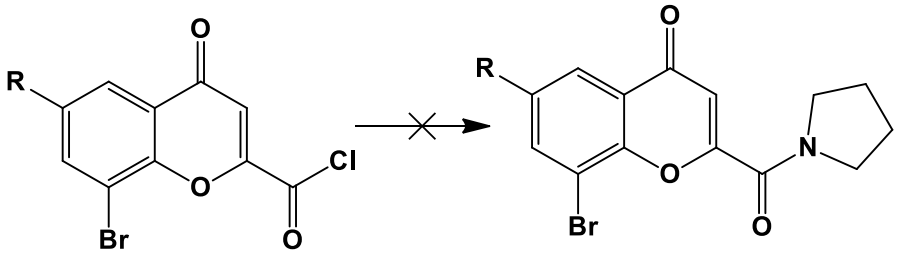
R= Br, F, Cl, NO_2

Reagent: (i) Pyridine, $(CH_3)_2NH$, ice bath (3 hr.). rt (23hr.)

Scheme 12: Attempted synthesis of 6-subsituted-8-iodo-chromone-2-carboxamides **43**

The attempted synthesized compounds for these kind of reactions are 6-fluoro-8-iodo-N,N-dimethyl-chromone-2-carboxamides and 8-bromo-8-iodo-N,N-dimethy-chromone-2-carboxamides . The spectrums of these compounds are illustrated in the appendix section**.**

Again we tried to use different amine were we replaced dimethyl ammonium with pyrrolidine as illustrated in the **scheme 13**.



42 43

R= H, Br, Cl

Reagent: (i) Pyridine, Pyrrolidine, ice bath (3 hr.). rt (23hr.)

Scheme 13: Attempted synthesis of 6.8-dibromo-2-(pyrollidine-1-carbonyl)-4H-chromen-4-one **43**

The parent chemical 2-(pyrrolidine-1-carbonyl)-4H-chromen-4-one was the subject of the first effort for this class of compounds, and it was successful but required careful purification. We then attempted to synthesize 6.8-dibromo-(pyrrolidine-carbonyl)-4H-chromone which is also shown in the appendix. This reaction didn't work as shown by the NMR. The TLC shows that the reaction reacted to completion. However, we have too many peaks in the spectrum.

CHAPTER 5

5.1 CONCLUSION

Due to the wide spectrum of biological activity the chromone scaffold has, derivatives of 6.8-disubstituted-chromone-2-carboxylic acids has been studied. The brominating of 5-substituted-2-hydroxyacetophenones **(39E-H)** at position 3 was successfully synthesized with moderate to good yields of 56-78 %. Also the iodinating of 5-substituted-2-hydroxyacetophenones **(39A-D)** at position 3 was achieved with good yields of 46-82 %. The 6.8-disubstituted-chromone-2-carboxylates **(40A-D** and **40E-H)** intermediates were successfully synthesized with good to excellent yields of 44-95 %. The 6.8-disubstituted-chromone-2-carboxylic acids (**41A-D** and **41E-H**) were successfully synthesized with good to excellent yields of 48-98 %. Synthesis of 6.8-disusbtituted-chromone-2-carbonyl chlorides **42A-D** achieved satisfactorily with average yields of 44-60 %. Most compounds were purified by recrystallizing and characterized by available physical data, NMR and FTIR spectroscopic methods.

Several attempts to synthesize 6.8-disubstituted-chromone-2-carboxamides were unsuccessful as shown by the NMR.

5.2 FUTURE WORK

- Synthesize 6,8-disubstituted-chromone-2-carboxamides.
- CHN and mass spectrum analysis of all synthesized 6.8-disubstituted-chromone-2-carboxylic acid derivatives.
- Biological evaluation of 6.8-disubstituted-chromone-2-carboxylic acids.

CHAPTER 6

6.1 General conditions

The only suppliers of the chemicals and solvents utilized were from Merck and Sigma Aldrich. Since every reagent was analytically pure, no additional purification was necessary. All reactions were conducted in oven-dried glassware, and TLC was used to monitor progress of reactions. UV light (λ = 254-365 nm) was used for TLC. The purification of synthesized compounds involved recrystallization.

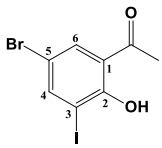
Bruker 400 MHz Spectrometer was used to record 1D spectrum. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded using either $CDCl_3$, DMSO-d_6 or DMF-d_7 as sample solvents and TMS as internal standard. The chemical shifts were expressed in parts per million (ppm). The splitting patterns were represented as follows: s for singlet, d for doublet, t for triplet, q for quartet, bs for broad singlet and m for multiplet. The coupling constants (J-values) were reported in hertz (Hz).

Perkin-Elmer 1420 spectrophotometer was used to determine the FT-IR spectra and the results were given in wave number (cm^{-1}). Open capillary tubes were used to determine the melting points using BUCHI Melting point B-540 equipment, and the results were uncorrected.

6.2 Synthesis

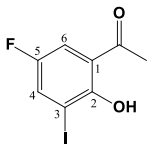
General synthesis of 5-substituted-3-iodo—2-hydroxyacetophenones (39A-D)

A stirred solution of 5-substituted-2-hydroxyacetophenones (1 equiv.) and N-iodosuccinimide (1 equiv.) in acetic acid (100 mL) was refluxed for 2h and then quenched with ice cold water. The resulting precipitate was filtered and recrystallized from ethanol to afford compounds (**39)** as a solid.[52] Compounds (**39A-D)** were prepared in this fashion



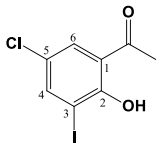
5-Bromo-3-iodo-2-hydroxyacetophenones (39A)

Brown solid (5.62 g, 82 %) mp. 112.7-114.8 ^{0}C (Lit.[53] 89 ^{0}C), IR ν_{max}/cm^{-1}= 3054.44 (C-H), 1579.77 (C=O) ^{1}H NMR (400 MHz, DMSO-d_6) δ_H= 12.98 (s, 1H, OH), 8.13 (d, 1H, J= 2 Hz, 4-H), 8.20 (d, 1H, J= 2.4 Hz, 6-H), 2.53 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c= 205.16 (C=O), 159.71 (C-2), 146.85 (C-4), 134.26 (C-6), 121.10 (C-1), 111.33 (C-5), 88.73 (C-3), 27.36 (CH_3).



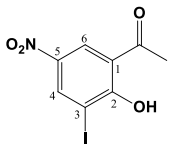
5-Fluoro-3-iodo-2-hydroxtacetophenones (39C)

Yellow solid (1.87 g, 46 %) mp. 90.4-98.2 ^{0}C, IR ν_{max}/cm^{-1}= 3073.80 (C-H), 1641.24 (C=O) , 793.90 (C-I) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H= 7.86 (dd, 1H, J= 5.2 Hz, 3.2 Hz, 4-H), 7.98 (dd, 1H, J= 4.8 Hz, 2.8 Hz, 6-H), 2.51 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_c= 205.21 (C=O), 155.31 (C-2), 117.03 (C-4), 132.31 (C-6), 119.20 (C-1), 157.32 (C-5), 87.36 (C-3), 27.46 (CH_3).



5-Chloro-3-iodo-2-hydroxyacetophenones (39B)

Brown solid (3.62 g, 60 %) mp. 101.6-103.8 ^{0}C (Lit.[53] 105 ^{0}C), IR ν_{max}/cm^{-1}= 2921.12 (C-H), 1637.86 (C=O) ^{1}H NMR (400 MHz, $CDCl_3$) δ_H= 8.02 (d, 1H, J= 2.4 Hz, 4-H), 8.09 (d, 1H, J= 2.4 Hz, 6-H), 2.50 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_c= 205.17 (C=O), 159.42 (C-2), 144.35 (C-4), 132.42 (C-6), 120.37 (C-1), 124.00 (C-5), 88.42 (C-3), 27.44 (CH_3).

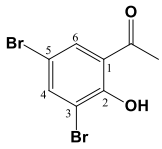


5-Nitro-3-iodo-2-hydroxyacetophenones (39D)

yellow solid (2.74 g, 70 %) mp. 132-136 ^{0}C , IR ν_{max}/cm^{-1}= 2988.23 (C-H), 1526.66 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H= 8.44 (d, 1H, J= 2.4 Hz, 4-H), 8.31 (d, 1H, J= 2.8 Hz, 6-H), 2.50 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_c= 205.21 (C=O), 162.92 (C-2), 140.21 (C-4), 122.73 (C-6), 120.21 (C-1), 142.08 (C-5), 88.32 (C-3), 27.71 (CH_3).

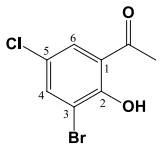
General synthesis of 5-substituted-3-bromo-2-hydroxyacetophenones (39E-H)

A stirred solution of 5-substituted-2-hydroxyacetophenones (1 equiv) and N-bromosuccinimide (1 equiv.) in acetic acid (100 mL) was refluxed for 2h and then quenched with ice cold water. The resulting precipitate was filtered and recrystallized from ethanol to afford compounds (**39)** as a solid.[52] Compounds (**39E-H)** were prepared in this fashion



3.5-Dibromo-2-hydroxtacetophenones (39E)

White solid (6.49 g, 78 %) mp. 98.7-102.3 ^{0}C (Lit.[54] 108-111 ^{0}C), IR ν_{max}/cm^{-1}= 2969.37 (C-H), 1650.80 (C=O), 3530.25 (O-H); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H= 12.75 (s, 1H, OH), 8.09 (d, 1H, J= 2 Hz, 4-H), 8.13 (d, 1H, J= 2.4 Hz, 6-H), 2.7 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_c= 205.07 (C=O), 157.24 (C-2), 141.05 (C-4), 133.67 (C-6), 122.27 (C-1), 112.55 (C-5), 110.67 (C-3), 27.79 (CH_3).

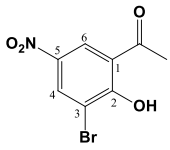


5-Chloro-3-bromo-2-hydroxyacetophenones (39F)

Brown solid (1.76 g, 68 %) mp. 86.2-94.1 ^{0}C (Lit.[54] 100-103 ^{0}C), ^{1}H NMR (400 MHz, $CDCl_3$) δ_H= 12.21 (s, 1H, OH), 7.40 (d, 1H, J= 2.4 Hz, 4-H), 7.79 (d, 1H, J= 2.4 Hz, 6-H), 2.68 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_c= 203.61 (C=O), 156.59 (C-2), 136.61 (C-4), 128.21 (C-6), 123.96 (C-1), 125.11 (C-5), 112.89 (C-3), 26.71 (CH_3).

5-Fluoro-3-bromo-2-hydroxyacetophenones (39G)

Light brown solid (3.25 g, 62 %) mp. 91.7-94.1 ^{0}C (Lit.[54] 94-97 ^{0}C), ^{1}H NMR (400 MHz, $CDCl_3$) δ_H= 7.44 (dd, 1H, J= 5.2 Hz, 3.2 Hz, 4-H), 7.56 (dd, 1H, J= 2.8 Hz, 4.8 Hz, 6-H), 2.66 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_c= 203.33 (C=O), 152.85 (C-2), 127.39 (C-4), 115.03 (C-6), 119.25 (C-1), 155.54 (C-5), 112.38(C-3), 27.78 (CH_3).

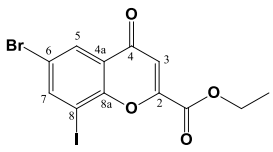


5-Nitro-3-bromo-2-hydroxyacetophenones (39H)

White solid (2.18 g, 56 %) mp. 130.8-133.3 ^{0}C (Lit.[54] 129-132 ^{0}C), IR ν_{max}/cm^{-1}= 2999.32 (C-H), 1526.66(C=O), 3675.15 (O-H); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H= 8.73 (d, 1H, J= 2.4 Hz, 4-H), 8.66 (d, 1H, J= 2.8 Hz, 6-H), 2.80 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c= 204.90 (C=O), 162.95 (C-2), 133.58 (C-4), 127.25 (C-6), 120.26 (C-1), 1139.67 (C-5), 112.40 (C-3), 27.85 (CH_3) .

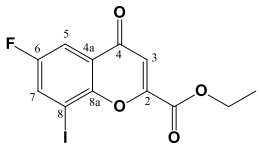
General synthesis of Ethyl-6-substituted-8-iodo-chromone-2-carboxylates (40A-D)

Sodium ethoxide (NaOEt) was generated *insitu* by adding sodium metal (1.60 g, 69.5 mmol) to absolute ethanol (100 mL) under inert conditions. A warm solution of 3-iodo-5-substituted-2-hydroxyacetophenones **(39A-D)** (1 equiv.) and diethyl oxalate (5.55 equiv.) was added to into NaOEt. The resulting yellow mixture was boiled gently under reflux for 1h (until it formed a slurry). The reaction mixture was allowed to cool to room temperature and poured into diethyl ether (73 mL). After standing for 30 minutes, the yellow sodium salt was filtered off (using vacuum suction), washed with Et_2O and dissolved in 2M HCl (Until it becomes acidic, checked using PH indicator). The mixture was extracted with Et_2O (3X 60 mL). The ethereal solutions were combined dried over $MgSO_4$ and evaporated to give compounds (**40)** as solids.[55] Compounds (**40A-D)** were prepared in this fashion



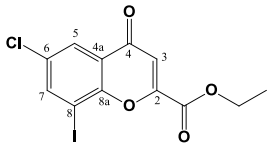
Ethyl-6-bromo-8-iodo-chromone-2-carboxylates (40A)

Light brown solid (3.15 g, 95 %) m.p 198.9-214.8^{0}C ; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_H= 7.06 (s, 1H, 3-H), 8.20 (d, 1H, J= 2.1 Hz, 5-H), 8.23 (d, 1H, J= 2.4 Hz, 7-H), 4.42 (q, 2H, J=7.1 Hz, CH_2), 1.37 (t, 3H, J= 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ_c= 176.68 (C-4), 159.19 (COOEt), 159.79 (C-2), 152.52 (C-8a), 146.51 (C-7) 128.73 (C-5). 125.64 (C-4a), 120.07 (C-6) 114.43 (C-3), 86.37 (C-8), 63.30 (CH_2), 14.04 (CH_3).



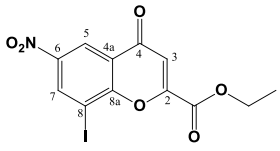
Ethyl-6-fluoro-8-iodo-chromone-2-carboxylates (40B)

Dark brown solid (1.80 g, 52 %) m.p 157.7-163.5 ^{0}C, ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_H= 7.18 (s, 1H, 3-H), 7.86 (dd, 1H, J= 4.7, 3.3 Hz, 5-H), 8.42 (dd, 1H, J= 5.2 Hz, 2.8 Hz, 7-H), 4.42 (q, 2H, J=6.8 Hz, CH_2), 1.38 (t, 3H, J= 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ_c= 176.21 (C-4), 160.21 (COOEt), 159.12 (C-2), 154.21 (C-8a), 143.31 (C-7) 109.01 (C-5). 124.21 (C-4a), 144.28 (C-6) 113.93 (C-3), 86.35 (C-8), 63.31 (CH_2), 14.05 (CH_3).



Ethyl-6-chloro-8-iodo-chromone-2-carboxylates (40C)

Brown solid (3.21 g, 70 %) m.p 133.2-142.1 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_H= 7.19 (s, 1H, 3-H), 8.08 (d, 1H, J= 2.3 Hz, 5-H), 8.05 (d, 1H, J= 2.4 Hz, 7-H), 4.42 (q, 2H, J=7.1 Hz, CH_2), 1.38 (t, 3H, J= 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ_c= 176.98 (C-4), 159.80 (COOEt), 152.90 (C-2), 153.68 (C-8a), 143.98 (C-7) 125.53 (C-5). 125.22 (C-4a), 132.65 (C-6) 114.29 (C-3), 86.87 (C-8), 63.28 (CH_2), 14.02 (CH_3).

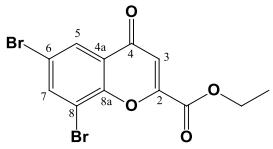


Ethyl-6-nitro-8-iodo-chromone-2-carboxylates (40D)

Cream white solid (2.03 g, 60 %) m.p 139.1-144.1 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H= 6.97 (s, 1H, 3-H), 7.91 (d, 1H, J= 2.1 Hz, 5-H), 8.38 (d, 1H, J= 2.3 Hz, 7-H), 4.42 (q, 2H, J=7.1 Hz, CH_2), 1.38 (t, 3H, J= 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c= 176.76 (C-4), 161.43 (COOEt), 159.93 (C-2), 154.99 (C-8a), 143.80 (C-7) 124.55 (C-5). 125.19 (C-4a), 131.53 (C-6) 113.70 (C-3), 88.72 (C-8), 63.34(CH_2), 14.31 (CH_3).

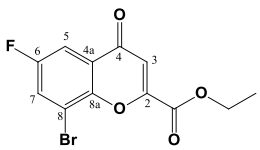
General synthesis of Ethyl-6-substituted-8-bromo-chromone-2-carboxylates (40E-H)

Sodium ethoxide (NaOEt) was generated insitu by adding sodium metal (1.60 g, 69.5 mmol) to absolute ethanol (100 mL) under inert conditions. A warm solution of 3-bromo-5-substituted-2-hydroxyacetophenones **(39E-H)** (1 equiv.) and diethyl oxalate (5.55 equiv.) was added to into NaOEt. The resulting yellow mixture was boiled gently under reflux for 1h (until it forms a slurry). The reaction mixture was allowed to cool to room temperature and poured into diethyl ether (73 mL). After standing for 30 minutes, the yellow sodium salt was filtered off (using vacuum suction), washed with Et_2O and dissolved in 2M HCl (Until it becomes acidic, checked using PH indicator). The mixture was extracted with Et_2O (3X 60 mL). The ethereal solutions were combined dried over $MgSO_4$ and evaporated to give compounds (**40)** as solids.[55] Compounds (**40E-H)** were prepared in this fashion



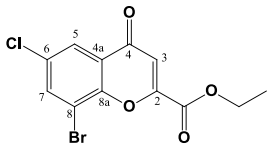
Ethyl-6.8-dibromo-chromone-2-carboxylates (40E)

Light brown solid (4.71 g, 72 %) m.p 108.3-112.1 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H= 6.98 (s, 1H, 3-H), 8.20 (d, 1H, J= 2.4 Hz, 5-H), 8.59 (d, 1H, J= 2Hz, 7-H), 4.47 (q, 2H, J=6.8 Hz, CH_2), 1.38 (t, 3H, J= 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c= 177.23 (C-4), 160.31 (COOEt), 159.21 (C-2), 159.12(C-8a), 126.21 (C-7) 128.20 (C-5). 123.41 (C-4a), 125.60 (C-6) 113.29 (C-3), 113.58 (C-8), 63.12(CH_2), 14.28 (CH_3).



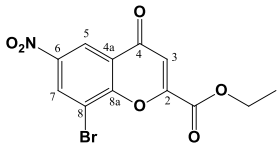
Ethyl-6-fluoro-8-bromo-chromone-2-carboxylates (40F)

Dark brown solid (3.9 g, 44 %) m.p 165.1-174.9 ^{0}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ_H= 7.05 (s, 1H, 3-H), 7.66 (dd, 1H, J= 4.7, 3.3 Hz, 5-H), 7.74 (dd, 1H, J= 5.2 Hz, 2.8 Hz, 7-H), 4.42 (q, 2H, J=6.8 Hz, CH_2), 1.37 (t, 3H, J= 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c= 177.08 (C-4), 160.40 (COOEt), 159.86 (C-2), 157.90 (C-8a), 126.72 (C-7) 110.38 (C-5). 126.44 (C-4a), 149.42 (C-6) 113.75 (C-3), 113.62 (C-8), 63.23 (CH_2), 14.03 (CH_3).



Ethyl-8-bromo-chloro-chromone-2-carboxylates (40G)

Yellow solid (1.54 g, 53 %) m.p 109.2-113.4 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H= 7.02 (s, 1H, 3-H), 8.32 (d, 1H, J= 2.4 Hz, 5-H), 7.92 (d, 1H, J= 2.3 Hz, 7-H), 4.38 (q, 2H, J=7.4 Hz, CH_2), 1.36 (t, 3H, J= 7.1 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c= 177.42 (C-4), 159.79 (COOEt), 153.91 (C-2), 158.26 (C-8a), 131.28 (C-7) 125.98 (C-5). 125.42 (C-4a), 131.21 (C-6) 113.82 (C-3), 113.42 (C-8), 63.21 (CH_2), 14.09 (CH_3).



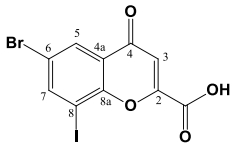
Ethyl-6-nitro-8-bromo-chromone-2-carboxylates (40H)

White solid (1.98 g, 79 %) m.p 123.5-130.1 ^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H= 6.97 (s, 1H, 3-H), 7.30 (d, 1H, J= 2.2 Hz, 5-H), 8.89 (d, 1H, J= 2.4 Hz, 7-H), 4.43 (q, 2H, J=7.1 Hz, CH_2), 1.38 (t, 3H, J= 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c= 176.97 (C-4), 159.21 (COOEt), 153.20 (C-2), 157.28 (C-8a), 145.13 (C-7), 128.21 (C-5). 125.69 (C-4a), 128.42 (C-6) 113.79 (C-3), 113.98 (C-8), 63.62 (CH_2), 14.21 (CH_3).

General synthesis of 6-substituted-8-iodo-chromone-2-carboxylic acids (41A-D)

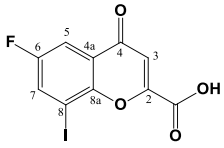
Ethyl-6-substituted-8-iodo-chromone-2-carboxylates (**40A-D)** was added to a mixture of Acetic acid (30 mL) and Hydrochloric acid (15 mL), (Note that the ratio of AcOH: HCl was always kept to 2:1). The mixture was allowed to reflux for 2 hours. After allowing the

reaction to cool, water (50 mL) was added. The precipitate was filtered to afford compounds (**41)** as solids.[56] Compounds (**41A-41D)** were prepared in this fashion



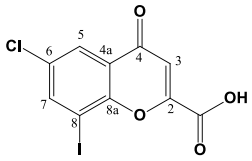
6.8-Dibromo-chromone-2-carboxylic acids (41A)

Light brown solid (1.42 g, 90 %) m.p 294.5-297.5 ^{0}C; ^{1}H NMR (400 MHz, DMF-d$_7$) δ_H= 5.77 (s, 1H, O-H), 7.03 (s, 1H, 3-H), 8.13 (d, 1H, J= 2.4 Hz, 5-H), 8.53 (d, 1H, J= 2.4 Hz, 7-H); ^{13}C NMR (100 MHz, DMF-d$_7$) δ_c= 176.54 (C-4), 162.46 (COOH), 161.88 (C-2), 154.33 (C-8a), 146.13 (C-7), 127.64 (C-5). 125.67 (C-4a), 119.14 (C-6), 113.67 (C-3), 88.49 (C-8).



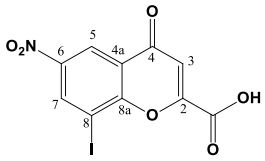
6-Fluoro-8-iodo-chromone-2-carboylic acids (41B)

Brown solid (1.09 g, 48 %) m.p 232.4-239.1 ^{0}C; ^{1}H NMR (400 MHz, DMF-d$_7$) δ_H= 7.19 (s, 1H, 3-H), 7.96 (dd, 1H, J= 5.2 Hz, 2.6 Hz, 5-H), 8.41 (dd, 1H, J= 3.2 Hz, 4.8 Hz 7-H); ^{13}C NMR (100 MHz, DMF-d$_7$) δ_c= 176.54 (C-4), 162.46 (COOH), 161.88 (C-2), 154.33 (C-8a), 146.13 (C-7), 127.64 (C-5). 125.67 (C-4a), 119.14 (C-6),113.67 (C-3), 88.49 (C-8).



6-Chloro-8-iodo-chromone-2-carboxylic acids (41C)

White solid (1.26 g, 75 %) m.p 293.5-297.6 ^{0}C; ^{1}H NMR (400 MHz, DMF-d$_7$) δ_H= 5.36 (s, 1H, O-H), 7.18 (s, 1H, 3-H), 8.56 (d, 1H, J= 2.2 Hz, 5-H), 8.15 (d, 1H, J= 2 Hz, 7-H); ^{13}C NMR (100 MHz, DMF-d$_7$) δ_c= 176.91 (C-4), 162.70 (COOH), 161.45 (C-2), 154.37 (C-8a), 143.78 (C-7), 124.60 (C-5). 125.35 (C-4a), 131.63 (C-6), 113.05 (C-3), 88.38 (C-8).

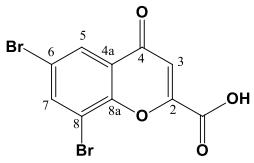


6-Nitro-8-iodo-chromone-2-carboxylic acids (41D)

Cream white (1.22 g, 57 %) m.p 260.2-263.1 ^{0}C; ^{1}H NMR (400 MHz, DMF-d_7) δ_H= 6.20 (s, 1H, O-H), 7.11 (s, 1H, 3-H), 8.82 (d, 1H, J= 1.9 Hz, 5-H), 9.05 (d, 1H, J= 1.9 Hz, 7-H); ^{13}C NMR (100 MHz, DMF-d_7) δ_c= 176.91 (C-4), 162.46 (COOH), 158.65 (C-2), 154.64 (C-8a), 138.10 (C-7), 120.93 (C-5). 124.07 (C-4a), 145.14 (C-6), 113.86 (C-3), 88.12 (C-8).

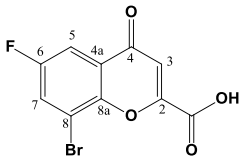
General synthesis of 6-substituted-8-bromo-chromone-2-carboxylic acids (41E-H)

Ethyl-6-substituted-8-bromo-chromone-2-carboxylates **(40E-H)** was added to a mixture of Acetic acid (30 ml) and Hydrochloric acid (15 mL), (Note that the ratio of AcOH: HCl is always kept to 2:1). The mixture was allowed to reflux for 2 hours. After allowing the reaction to cool, water (50 mL) was added. The precipitate was filtered to afford compounds (**41)** as solids.[56] Compounds (**41E-H)** were prepared in this fashion



6.8-Dibromo-chromone-2-carboxylic acids (41E)

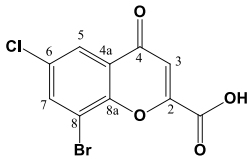
White solid (1.13 g, 98 %) m.p 256.8-260.5 ^{0}C; ^{1}H NMR (400 MHz, DMF-d_7) δ_H= 6.02 (s, 1H, O-H), 7.04(s, 1H, 3-H), 8.12 (d, 1H, J= 2.4 Hz, 5-H), 8.41 (d, 1H, J= 2.4 Hz, 7-H); ^{13}C NMR (100 MHz, DMF-d_7) δ_c= 176.38 (C-4), 162.48 (COOH), 154.17 (C-2), 151.99 (C-8a), 140.13 (C-7), 127.04 (C-5). 126.47 (C-4a), 118.57 (C-6), 113.39 (C-3), 113.73 (C-8).



6-Fluoro-8-bromo-chromone-2-carboxylic acids (41F)

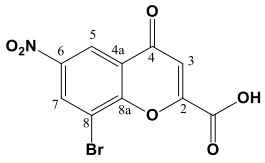
White solid (1.01 g, 49 %) m.p 259.4-261.9 ^{0}C; ^{1}H NMR (400 MHz, DMF-d_7) δ_H= 5.58 (s, 1H, O-H), 7.02 (s, 1H, 3-H), 7.78 (dd, 1H, J= 5.2 Hz, 2.6 Hz, 5-H), 8.25 (dd, 1H, J= 3.2 Hz, 4.8 Hz 7-H); ^{13}C NMR (100 MHz, DMF-d_7) δ_c= 176.85 (C-4), 161.28 (COOH), 157.79 (C-

2), 154.27 (C-8a), 126.76 (C-7), 109.71 (C-5). 126.13 (C-4a), 134.27 (C-6), 112.94 (C-3), 113.45 (C-8).



6-Chloro-8-bromo-chromone-2-carboxylic acids (41G)

Cream White solid (0.98 g, 78 %) m.p 91.6-93.5 ^{0}C; ^{1}H NMR (400 MHz, DMF-d_7) δ_H= 5.56 (s, 1H, O-H), 6.78 (s, 1H, 3-H), 8.05 (d, 1H, J= 2.4 Hz, 5-H), 7.74 (d, 1H, J= 2.2 Hz, 7-H); ^{13}C NMR (100 MHz, DMF-d_7) δ_c= 176.18 (C-4), 162.27 (COOH), 154.00 (C-2), 151.30 (C-8a), 138.13 (C-7), 123.62 (C-5), 125.80 (C-4a), 130.89 (C-6), 113.47 (C-3), 113.32 (C-8).



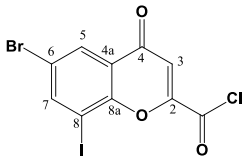
6-Nitro-8-bromo-chromone-2-carboxylic acids (41H)

Cream white solid (1.32 g, 73 %) m.p 215.6-221.1 ^{0}C; ^{1}H NMR (400 MHz, DMF-d_7) δ_H= 5.99 (s, 1H, O-H), 7.13(s, 1H, 3-H), 8.77 (d, 1H, J= 1.9 Hz, 5-H), 8.97 (d, 1H, J= 2 Hz, 7-H); ^{13}C NMR (100 MHz, DMF-d_7) δ_c= 176.68 (C-4), 162.18 (COOH), 156.14 (C-2), 154.56 (C-8a), 132.05 (C-7), 120.24 (C-5). 125.02 (C-4a), 144.84 (C-6), 114.03 (C-3), 113.69 (C-8).

General synthesis of 6-substituted-8-iodo-chromone-2-carbonyl chlorides (42A-D)

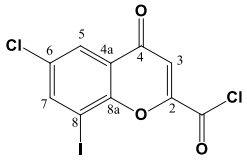
Thionyl chloride (0.7 mL, 10.6 mmol) was added to a suspension of 6-substituted-chromone-2-carboxylic acid (8 mmol) in dry 1.2-dichloroethane (12 mL) and dry N,N-dimethylformamide (0.16 mL, 1.2 mmol). The resulting mixture was heated under reflux for 2 hours under inert conditions (nitrogen gas and calcium chloride tubes were used). The reaction was allowed to cool to room temperature. The solvent was removed under vacuum. The vacuum pressure was broken and dry 1.2-dichloroethane (15 mL) was added and

removed under vacuum to afford compounds (**42**).[57] Compounds (**42A-D)** were prepared in this fashion.



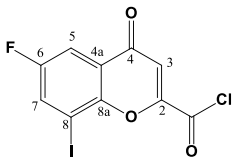
6-Bromo-8-iodo-chromone-2-carbonyl chlorides (42A)

Red solid (1.07 g, 60 %) m.p 241.5-247.3 ^{0}C, ^{1}H NMR (400 MHz, DMF-d$_7$) δ_H= 6.98 (s, 1H, 3-H), 7.92 (d, 1H, J= 2.4 Hz, 5-H), 8.28 (d, 1H, J= 2.4 Hz, 7-H); ^{13}C NMR (100 MHz, DMF-d$_7$) δ_c= 176.56 (C-4), 162.30 (COCl), 154.65 (C-2), 154.50 (C-8a), 145.98 (C-7), 128.21 (C-5). 124.82 (C-4a), 119.03 (C-6), 113.58 (C-3), 88.12 (C-8).



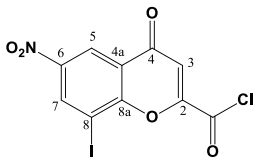
6-Chloro-8-iodo-chromone-2-carbonyl chlorides (42C)

Dark brown solid (0.28 g, 53 %) m.p 241.7-258.8 ^{0}C; ^{1}H NMR (400 MHz, DMF-d$_7$) δ_H= 7.02 (s, 1H, 3-H), 8.42 (d, 1H, J= 2 Hz, 5-H), 7.88 (d, 1H, J= 2.4 Hz, 7-H); ^{13}C NMR (100 MHz, DMF-d$_7$) δ_c= 176.68 (C-4), 161.21 (COCl), 154.34 (C-2), 154.21 (C-8a), 143.65 (C-7), 125.21 (C-5), 124.43 (C-4a), 131.50 (C-6), 113.53 (C-3), 88.37 (C-8).



6-Fluoro-8-iodo-chromone-2-carbonyl chlorides (42B)

Brown liquid (1.12 g, 44 %) ^{1}H NMR (400 MHz, DMF-d$_7$) δ_H= 7.08 (s, 1H, 3-H), 7.81 (dd, 1H, J= 5.2 Hz, 2.4 Hz, 5-H), 8.22 (dd, 1H, J= 3.1 Hz, 4.7 Hz 7-H); ^{13}C NMR (100 MHz, DMF-d$_7$) δ_c= 177.06 (C-4), 161.21 (COCl), 154.34 (C-2), 154.21 (C-8a), 143.65 (C-7), 125.21 (C-5). 124.43 (C-4a), 131.50 (C-6), 113.53 (C-3), 88.37 (C-8).



6-Nitro-8-iodo-chromone-2-carbonyl chlorides (42D)

Dark brown liquid (0.53 g, 47 %) ^{1}H NMR (400 MHz, DMF-d$_7$) δ_H= 7.01 (s, 1H, 3-H), 8.52 (d, 1H, J= 2 Hz, 5-H), 8.73 (d, 1H, J= 2.2 Hz, 7-H); ^{13}C NMR (100 MHz, DMF-d$_7$) δ_c= 176..83 (C-4), 161.24 (COCl), 156.55 (C-2), 152.01 (C-8a), 137.98 (C-7), 120.58 (C-5). 124.82 (C-4a), 144.95 (C-6), 113.82 (C-3), 188.85 (C-8).

CHAPTER 7

References

1. M.M. Rathore and S.B. Bante, *International Journal of Trend in Scientific Research and Development (IJTSRD)* ,2017, **1**, 2456-6470.
2. M.M Clementina, L.M Vera and M.S Silva. *Molecules* ,2017, **22**, 1665.
3. O. A. Lozinskii1, T.V. Shokol1 and V. P. Khilya1. *Chemistry of Heterocyclic Compounds*, 2011, **47**, 9.
4. S. Hong and P.L. Pedersen. *Microbiology and molecular biology reviews*, 2008, **72**, 590–641.
5. G.P Ellis and G. Barker. *Chemistry of heterocyclic compounds*, 1977, **31**, 78.
6. G.P Ellis and G. Barker. *Chemistry of heterocyclic compounds*, 1973, **31**, 67-76.
7. J.J. Li, C. Limberakis, E.J. Corey, Eds.; Wiley & Sons: Hoboken, NJ. *Kostanecki– Robinson Reaction*. In *Name Reactions in Heterocyclic Chemistry*, 2005, **2**, 521– 535.
8. S.T. James and A. Dana. *Mechanism and Application of Baker– Venkataraman O C Acyl Migration Reactions*, 2014, **47**. 141-158.
9. C.F.M Silva, V.F Batista, C.A.G Pinto and A.S.M Silva, *Expert opinion on drug discovery*, 2018. **13**, 795-798.

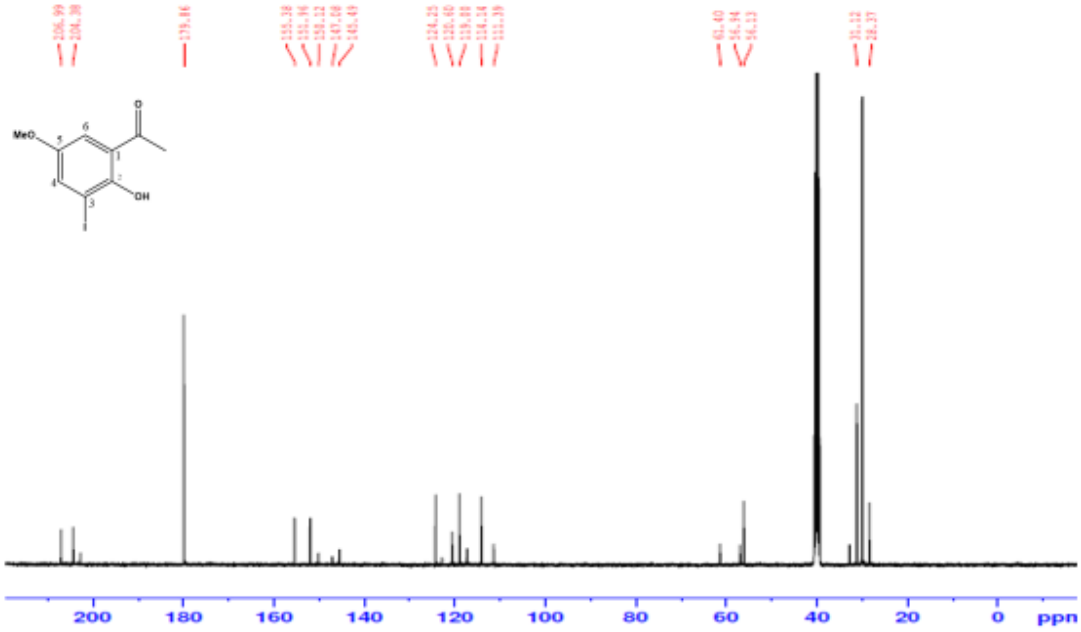
10. V.M Patil, N Masand, V. Masand and S Verma, *Chemical Biology & Drug design*, 2021, **00**, 1-11.
11. F. Cagide, C. Oliveira, J. Reis and F. Borges, *Optimizing the synthetic route of chromone-2-carboxylic Acids. Molecules*,2019, **24**, 4214.
12. S.k. Sharma, S Kumar, k Chand, A Kathuria, A Gupta and R Jain, *Current medicional chemistry*, 2011,**18**, 3825-3852.
13. D A. Horton, G. T Bourne, and M. L. Smythe, *chem rev.*, 2003, **103**, 893-930.
14. N.A Mohsin, M Irfan and S Hassan, *Pharmaceutical Chemistry Journal*, 2020, **54**, 1.
15. R.B. Semwal, D.K. Semwal and S. Combrinck, *Phytochem Rev*, 2020, **19**, 761-785.
16. J. Reis, A. Gaspar, N. Milhazes and F. Borges, *Journal of Medicinal Chemistry*, 2017, **60**, 7941-7957.
17. A. Gaspar, M.J. Matos, J. Garrid, E. Uriarte and F. Borges, *Chromone: A valid scaffold in medicinal chemistry. Chem. Rev.*, 2014, **114**, 4960-4992.
18. Vanguru *et al, Asian J Pharm Clin Res*, 2018, **11**, 9-16.
19. R.K. Dubey, P. Dixit amd S. Arya. *International journal of innovative research science, engineering and technology*, 2014, **3**, 1.
20. S, Khadem and R.J. Marles, Chromone and Flavonoids Alkaloids, 2012, **17**, 196-206.
21. M.A. Ibrahim, T.E. Ali, Y.A. Alnamer, and Y.A. Gabr, *Synthesis and chemical reactivity of 2-methylchromones (ARKIVOC)*, 2010, **1**, 98-135.
22. F. Bousejra-ElGarah, B. Lajoie, J.P Souchard, G. Baziard, J. Bouajila, S. El Hage, *Med. Chem. Res.*, 2016, **25**, 2547–2556.
23. S. Bhatnagar, S. Sahi, P. Kacker and A. Goel. *Bioorganic & medicinal chemistry letters*, 2010, **20**, 4945-50.
24. R.S. Keri et al. *European Journal of Medicinal Chemistry*, 2014, **78**, 340-374.
25. A.H. Tawfik, E.F. Ewies and W.S. El-Hamouly, international journal of research in pharmacy and chemistry (IJRPC) ,2014, **4**, 1046-1085.
26. M. Maleck, F.C dos Santos, M.T. Serdeiro, A.E. Guimarães, B. Ferreira and K. Gunaydin. *Journal of Natural Pharmaceuticals*, 2013, **4**, 1.
27. Pankaj S. Chaudhari et al .International Journal of ChemTech Research, 2017, **10** ,126-134.

28. M. N. Hamid, A. M. ABdalla, K. M. Ahmad, *prevelance of malaria in Fezzan region*, 2018, **13** , 1-3.
29. World malaria report. Geneva: World Health Organization, 2018.
30. J. M. Riveron, C. S. Wondji, B. D. Menze and M. Tchouakui, *towards malaria elimination-a leap forward*, 2018, **7**, 151-164.
31. R. Maharaj, N. Morris, I. Seocharan, P. Kruger, D. Moonasar, A. Mabuza, T*he feasibility of malaria elimination in Sa. Malaria journal*, 2012, **11**, 423-424.
32. A. T. Amadi, I. M. Ezeonu and O. N. Akoma, *MRJI*, 2019, **27**, 1-16.
33. A. P. Hall, *The treatment of malaria,British Medical Journal*, 1976, **1**, 323-328.
34. M.A. Phillips, J.N. Burrows, C. Manyando, W.C. Van Voorhis and T.N.C. Wells, *Nature Reviews Diseases Primers*, 2017, **3**, 1-11.
35. B. Prajapati, P. K. Praveen and R. Sujatha, *International Journal of Medical Science and Innovative Research (IJMSIR)*, 2018, **3**, 321-324.
36. C. Okangba, *Scientific Journal of Pure and Applied Sciences*, 2016, **5**, 339-350.
37. H. Chang, E. L. Moss, D. J. Park, S. K. Volkman, D. L. Hartl, *Malaria life cycle intensifies both natural selection and random genetic drift*, 2013, **110** , 20129-20134.
38. K. Y. Fong and D. W, Wright, *Future Med. Chem.*, 2013, **5** , 1437-1450.
39. S. Hossain, Dr S.Garg, *International Journal of Science and Research (IJSR)*, 2019, **8** , 1-8.
40. J. Chan, A. O. Talisuna, A. Erhart, A. Yeka, J. K. Tibenderana and P. J. Rosenthal, *Malaria Journal*, 2011, **10** , 32-34.
41. I. P. Subhash and C. Parija, *British Medical Bulletin*, 1998, **54**, 703-715.
42. A. ALam, M. Goyal, M.S. Igbal, C. Pal, S. Dey, S. Bindu, P. Maity and U. Bandyopadhyay, *Expert Rev. Clin. Pharmacol.* , 2009, **2**, 469-489.
43. U. Farooq, R. C. Mahajan, *Drug resistance in malaria*, 2004, **41**, 45-53.
44. C. X. Liu, *Chinese Herbal Medicines*, 2017, **9**, 101-114.
45. J. Talapko, I. Škrlec, T. Alebić, M. Jukić and A. Včev, *Malaria: The Past and the Present Microorganisms* 2019, **7**, 179-183.
46. A. R. Shabaraya, A.S. Parulkar, K. K. Kamath and D. Shripathy, *A novel approach of Artesunate pellets for treatment of malaria, 2018, **10**, 442-446.*
47. R. S. Keri et al. *European Journal of Medicinal Chemistry*, 2014, **78**, 340-374.

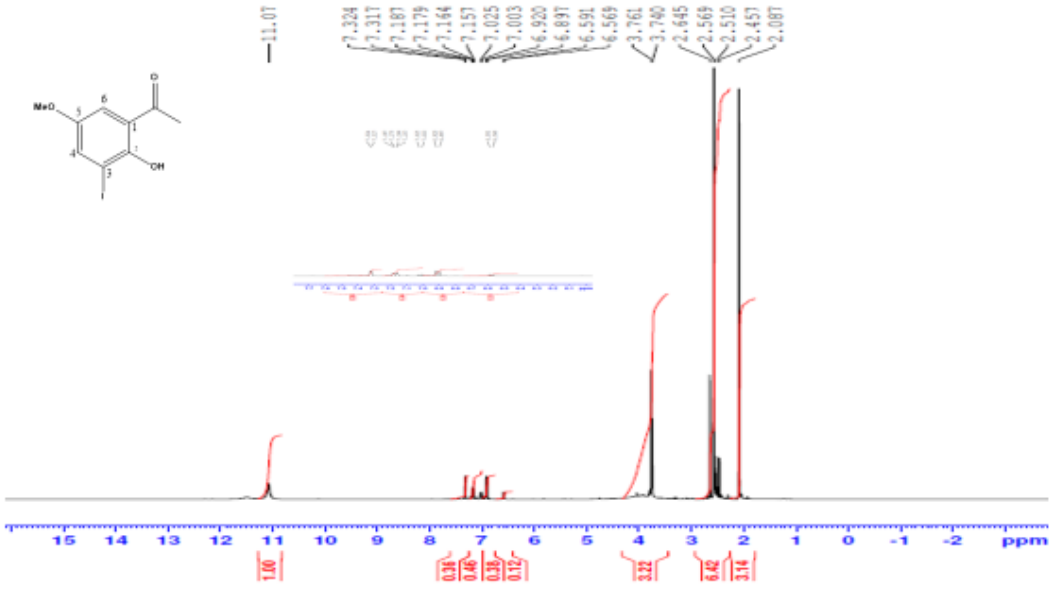
48. M. O. Raji & C. O. Bewaji, *African Scientist*, 2012, **13**, 205-224.
49. V. Wiwanitkit, *Journal of Nephropharmacology*, 2016, **5**, 11-12.
50. P. Lerdsirisuk, M. Maicheen, *Bioorganic Chemistry*, 2014, **57**, 142–147.
51. J. Aneja , D. Goya and B. Choudhary, *Psychosis consequent to antimalarial drug use in a young child. J Family Med Prim Care*, 2019, **8**, 1781-1783.
52. M.J Mphahlele, M.M Maluleka, A. Aro, L.J McGaw & Y.S Choong, *Journal of enzeme inhibition and medicinal chemistry*, 2018, **33**, 1518-1528.
53. S.V Khansole, S.S Mokle, M.A Sayyed, Y. Vibhute, *J Chinese Chem Soc*, 2008, **55**, 871-4.
54. E. Verner, B.A. Katz, J.R. Spencer, D. Allen, J. Hataye, W. Hruzewicz, H.C. Hui, A. Kolesnikov, Y. Li, C. Luong, A. Martelli, K. Radika, R. Rai, M. She, W. Shrader, P.A. Sprengeler, S. Trapp, J. Wang, W.B. Young, R.L. Mackman, *Journal of Medicinal Chemistry*, 2001, **44**, 2753-2771.
55. T. Walenzyk, C. Corola, H. Buchholz, B. Konig, *Tetrahedron*, 2005, **61**, 7366-77.
56. J.K Lynch, J.C Freeman, A.S Judd , R. Lyengar, G. Zhao, *Journal of medicinal chemistry*, 2006, **49**(22), 6569-6584.
57. Y. Guan, J.W Attard, A.E Mattson, chemisty-*A European journal*, 2020, **26**, 1742-1747.

Appendix

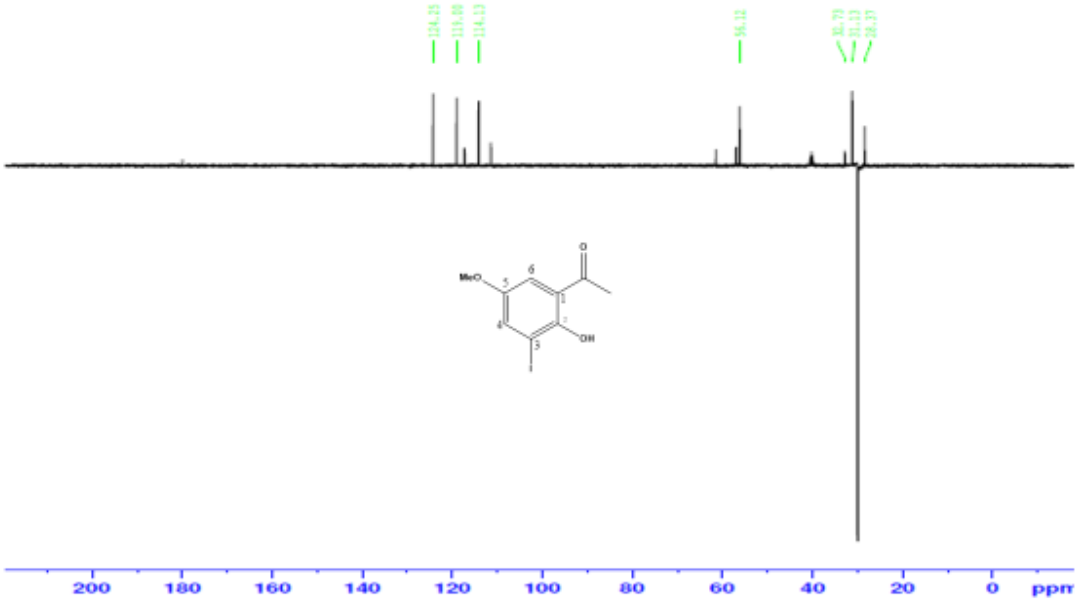
The following spectrums are those which shows compounds that did not work



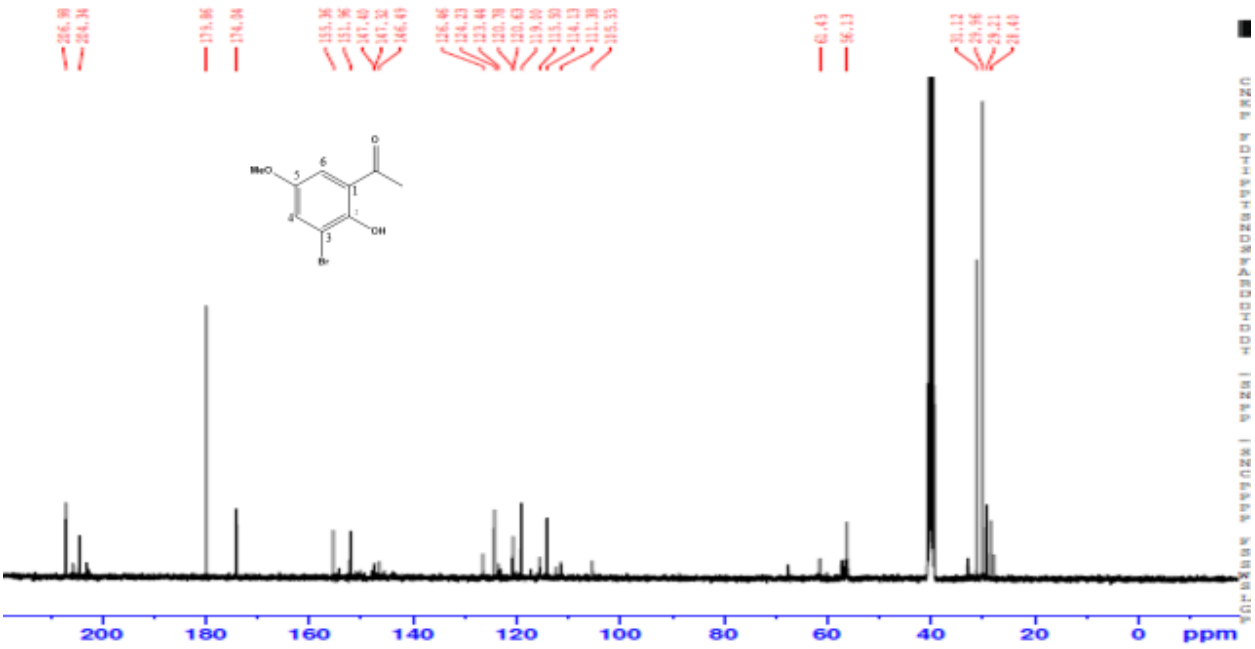
Appendix 1: ^{13}C NMR of 5-methoxy-3-iodo-2-hydroxyacetophenones (**39)** in $CDCl_3$



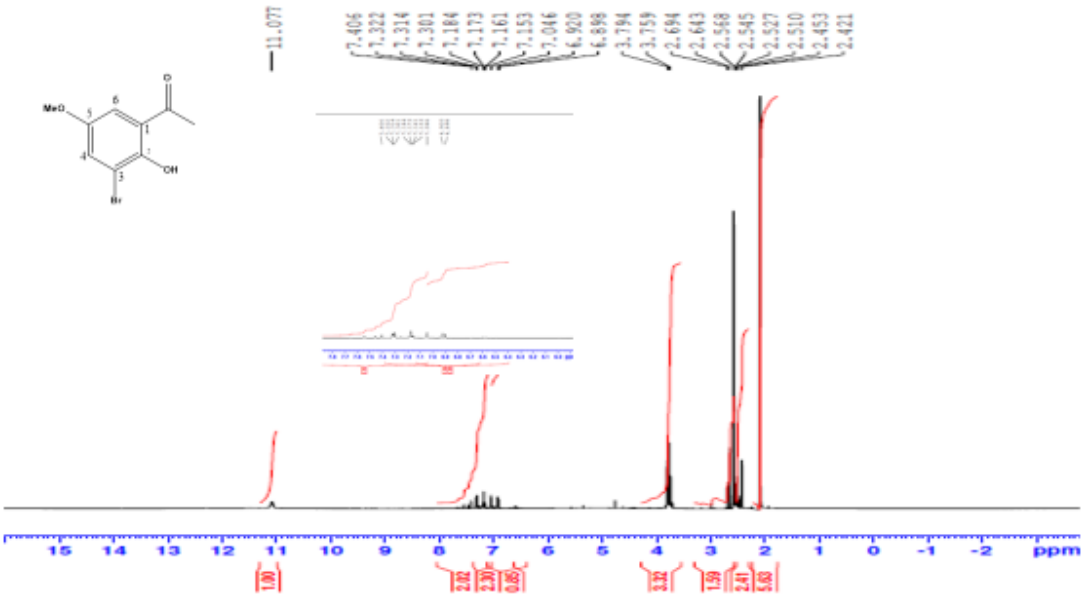
Appendix 2: ^{1}H NMR of 5-methoxy-3-iodo-2-hydroxyacetophenones (**39)** in $CDCl_3$



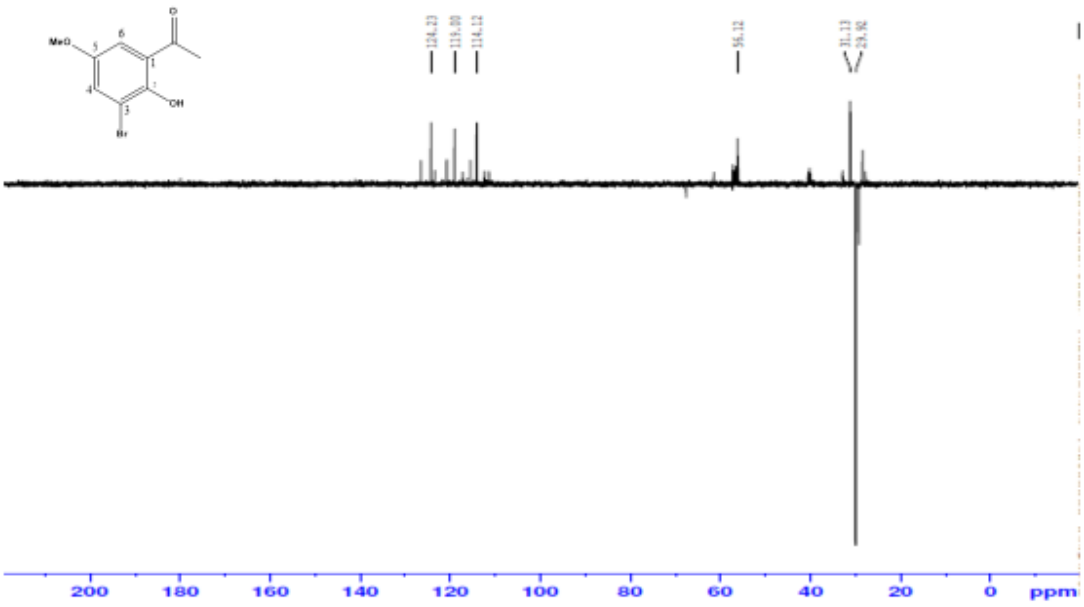
Appendix 3: DEPT 135 of 5-methoxy-3-iodo-2-hydroxyacetophenones (**39)** in $CDCl_3$



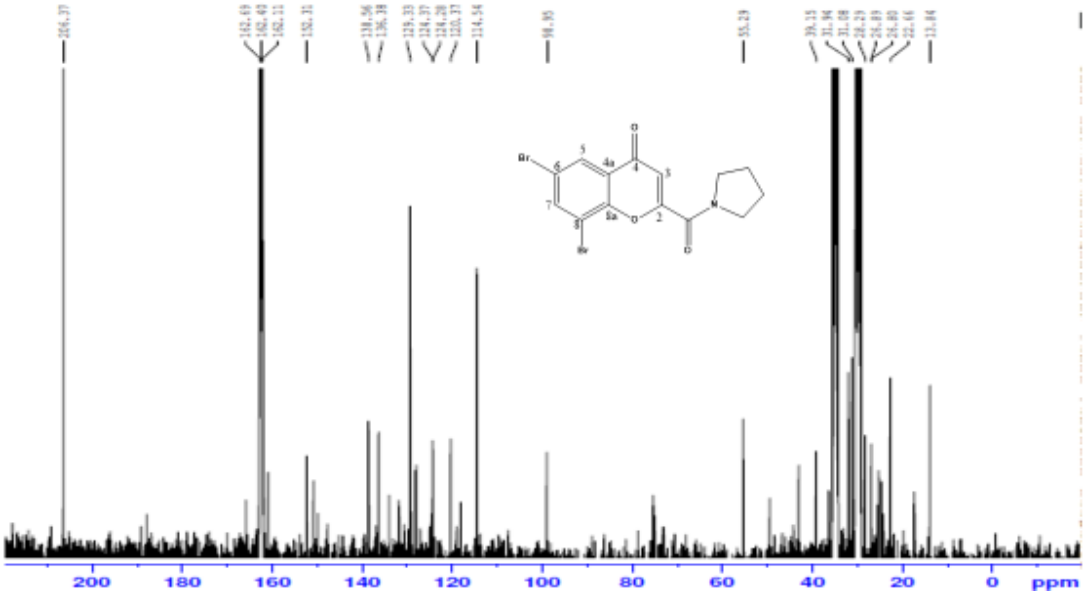
Appendix 4: ^{13}C NMR of 5-methoxy-3-bromo-2-hydroxyacetophenones (**39)**



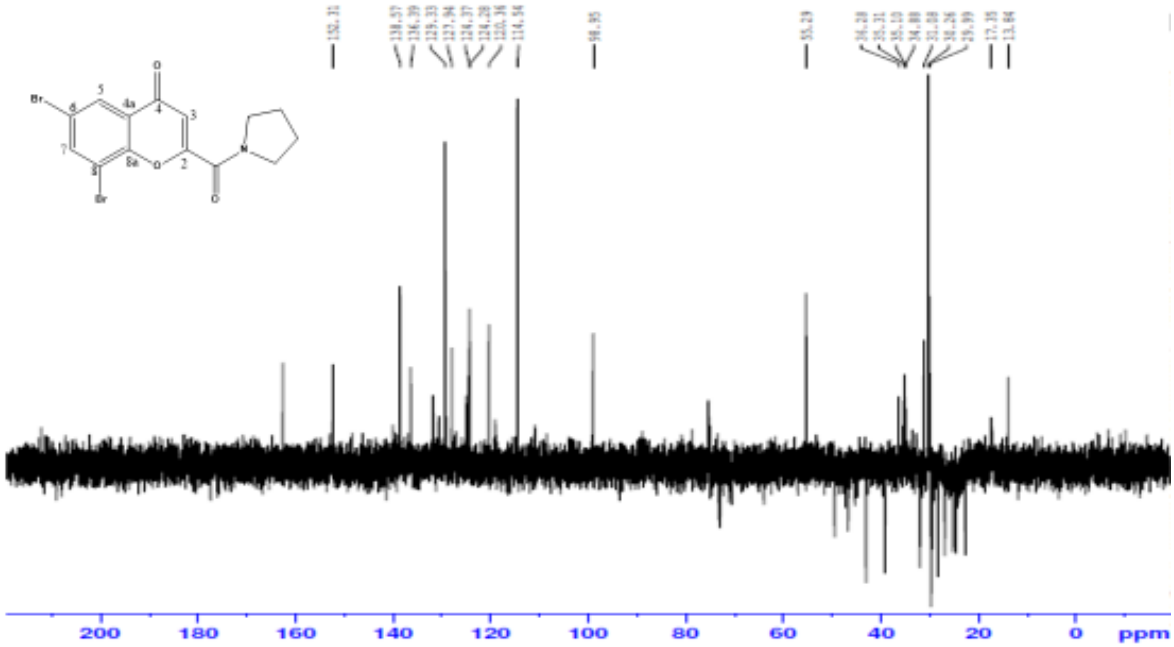
Appendix 5: ^{1}H NMR of 5-methoxy-3-bromo-2-hydroxyacetophenones (**39)** in $CDCl_3$



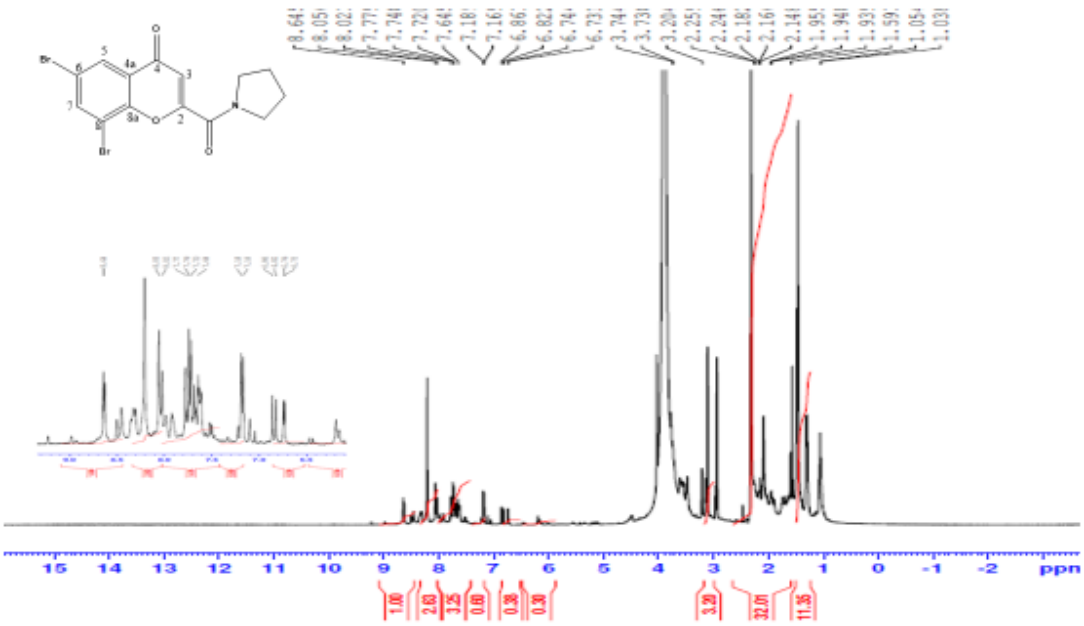
Appendix 6: DEPT 135 of 5-methoxy-3-bromo-2-hydroxyacetophenones (**39)** in $CDCl_3$



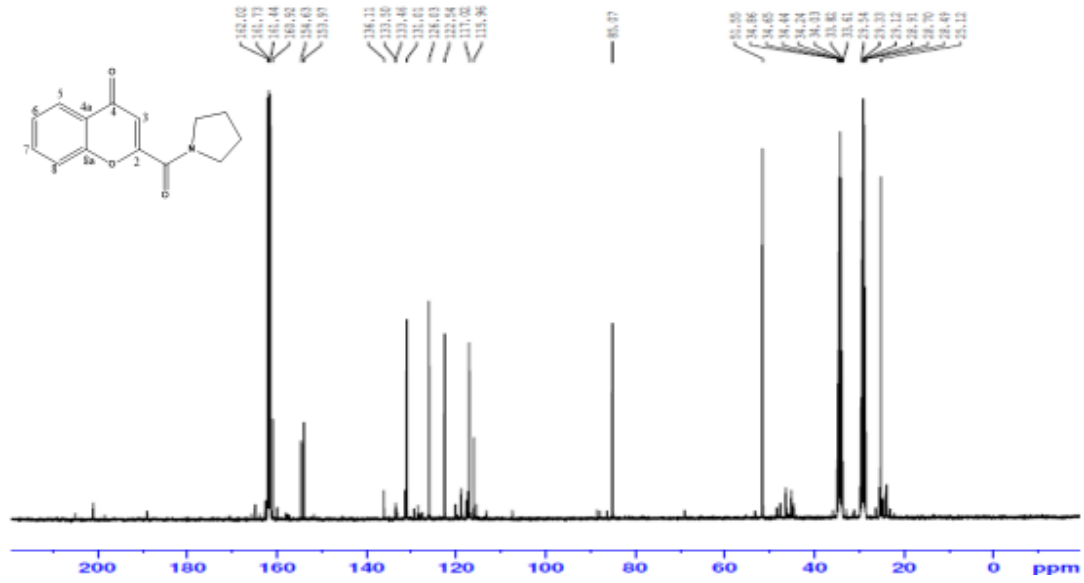
Appendix 7: ^{13}C NMR of 6.8-dibromo- 2-(pyrrolidine-1-carbonyl)-4H-chromen-4-one **(43)** in DMF-d-$_7$



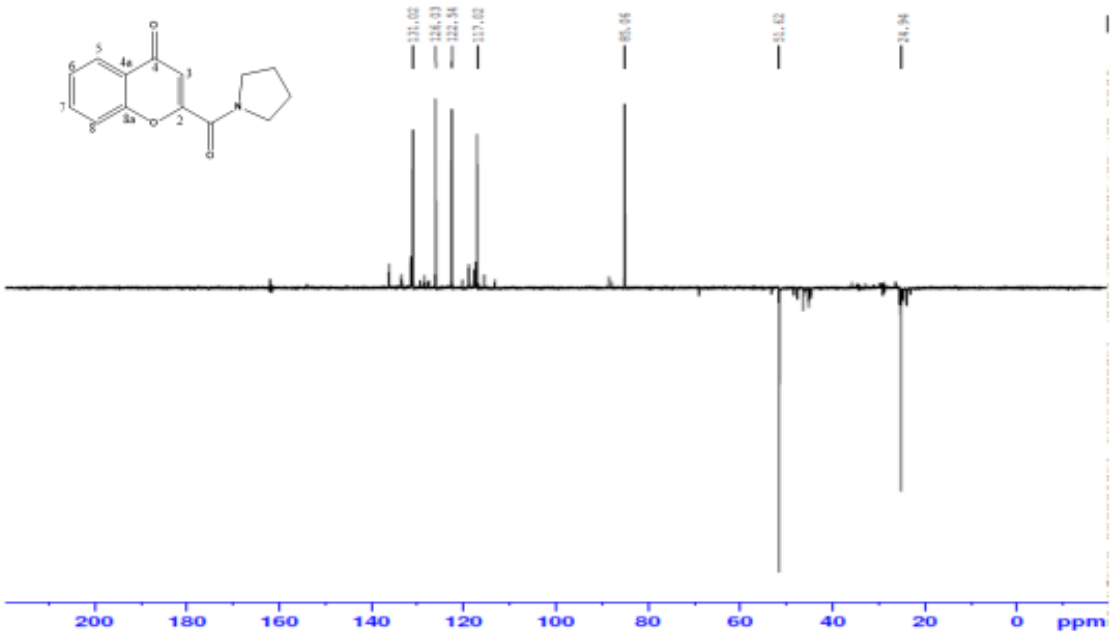
Appendix 8: DEPT 135 of 6.8-dibromo- 2-(pyrrolidine-1-carbonyl)-4H-chromen-4-one **(43)** in DMF-d_7



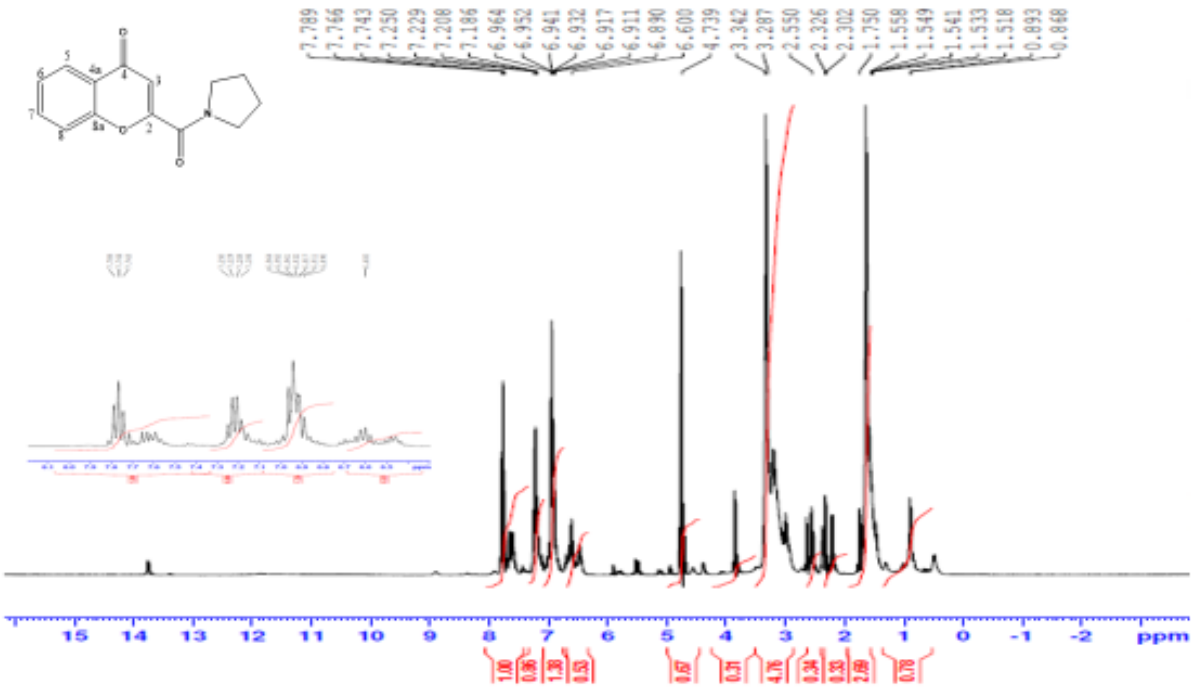
Appendix 9: ^{1}H NMR of 6.8-dibromo- 2-(pyrrolidine-1-carbonyl)-4H-chromen-4-one **(43)** in DMF-d_7



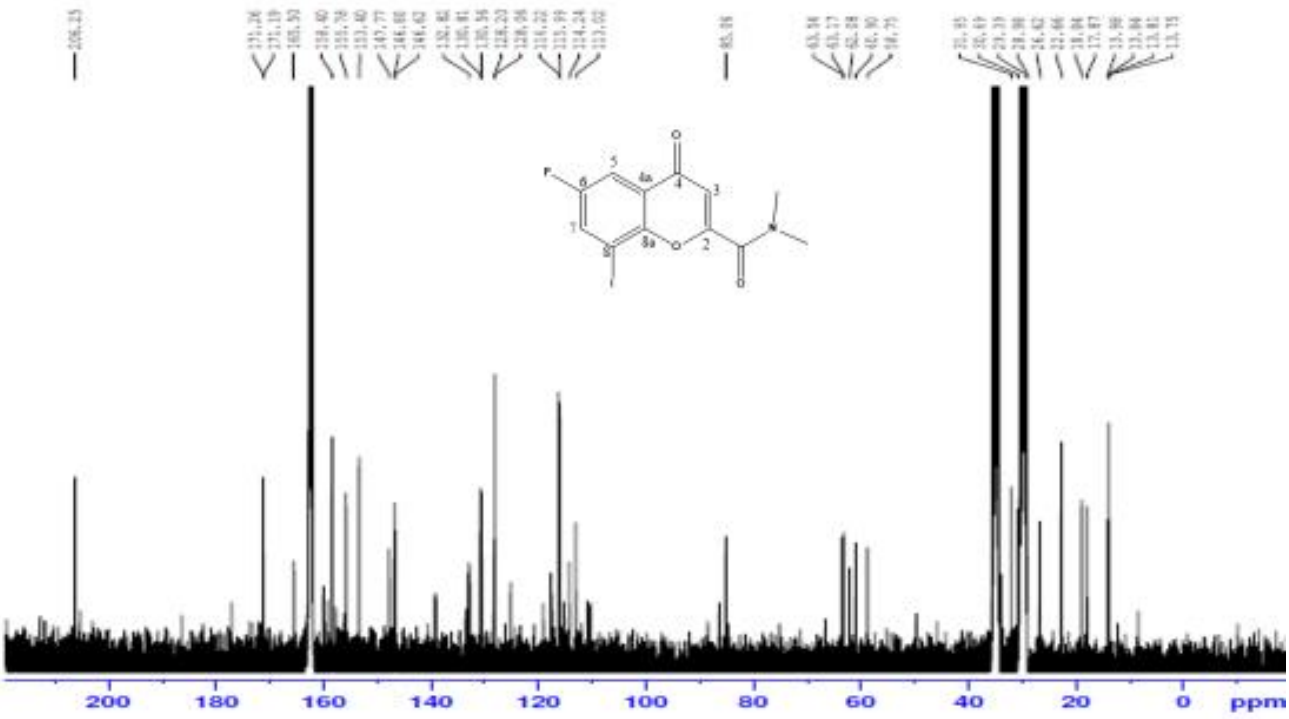
Appendix 10: ^{13}C NMR of 2-(pyrrolidine-1-carbonyl)-4H-chromen-4-one **(43)** in DMF-d_7



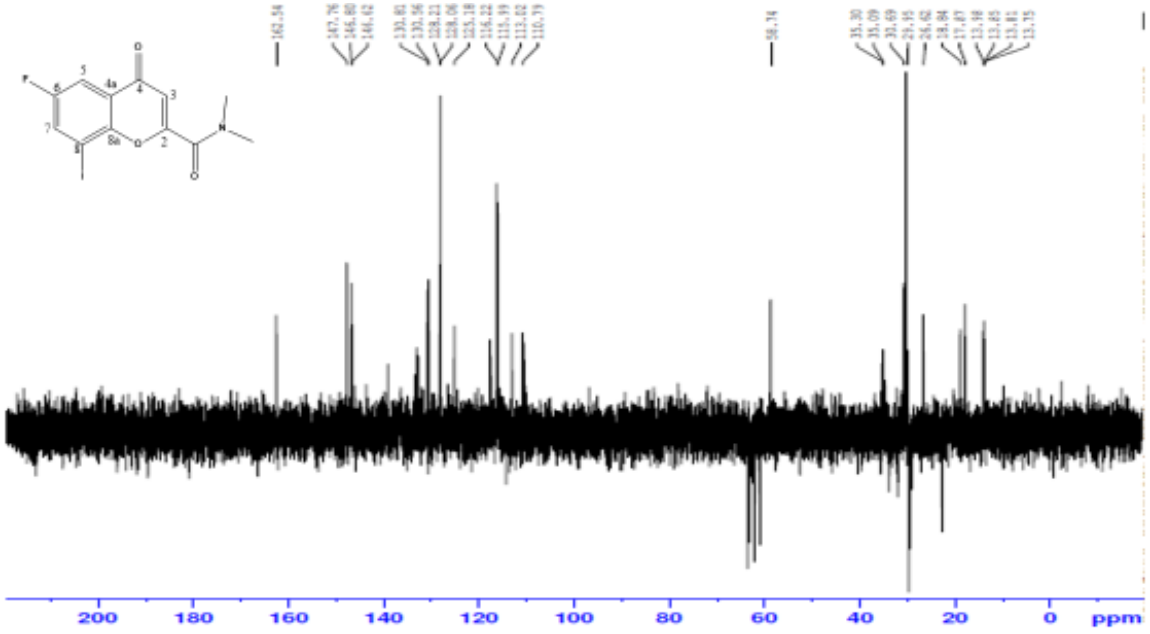
Appendix 11: DEPT 135 of 2-(pyrrolidine-1-carbonyl)-4H-chromen-4-one **(43)** in DMF-d_7



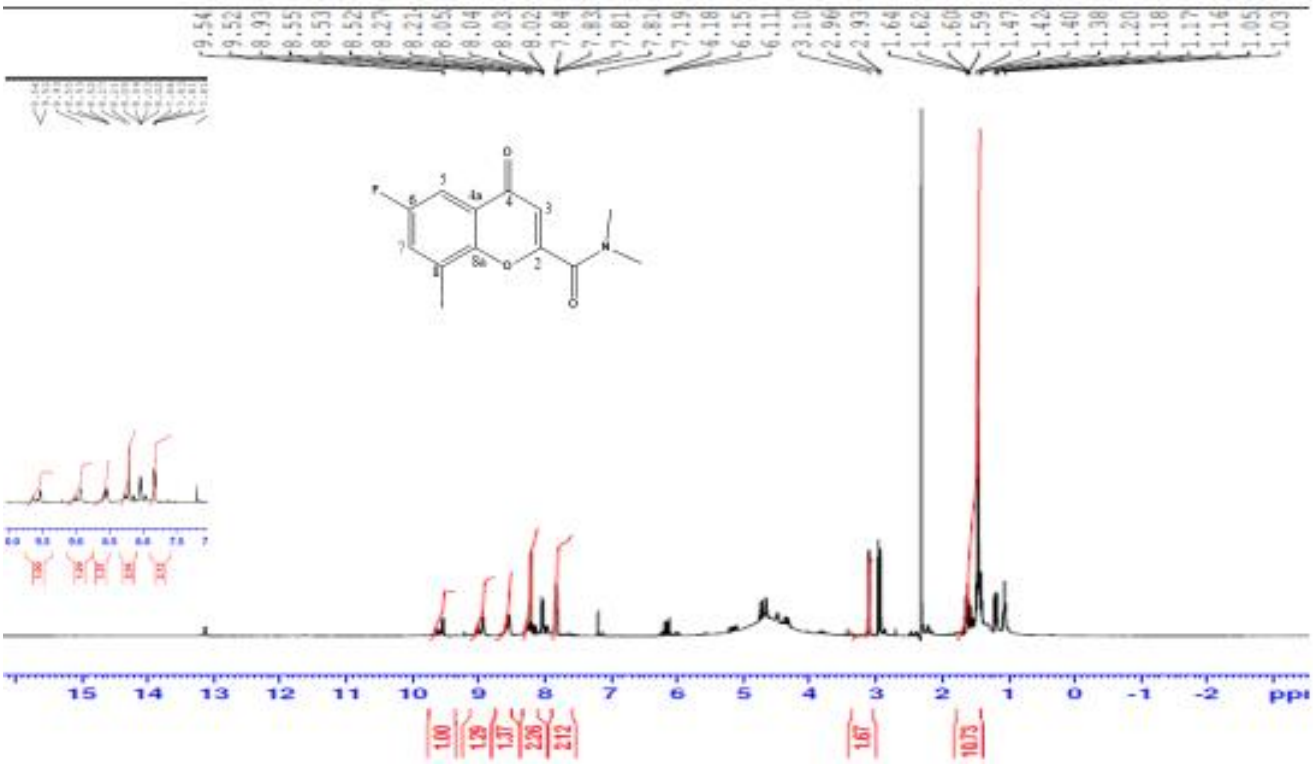
Appendix 12: ^{1}H NMR of 2-(pyrrolidine-1-carbonyl)-4H-chromen-4-one **(43)** in DMF-d_7



Appendix 13: ^{13}C NMR of 6-fluoro-8-iodo-N,N-dimethyl chromone-2-carboxamides **(43)** in DMF-d_7



Appendix 14: DEPT 135 of 6-fluoro-8-iodo-N,N-dimethyl chromone-2-carboxamides **(43)** in DMF-d_7



Appendix 15: ^{1}H NMR of 6-fluoro-8-iodo-N,N-dimethyl chromone-2-carboxamides **(43)** in DMF-d_7

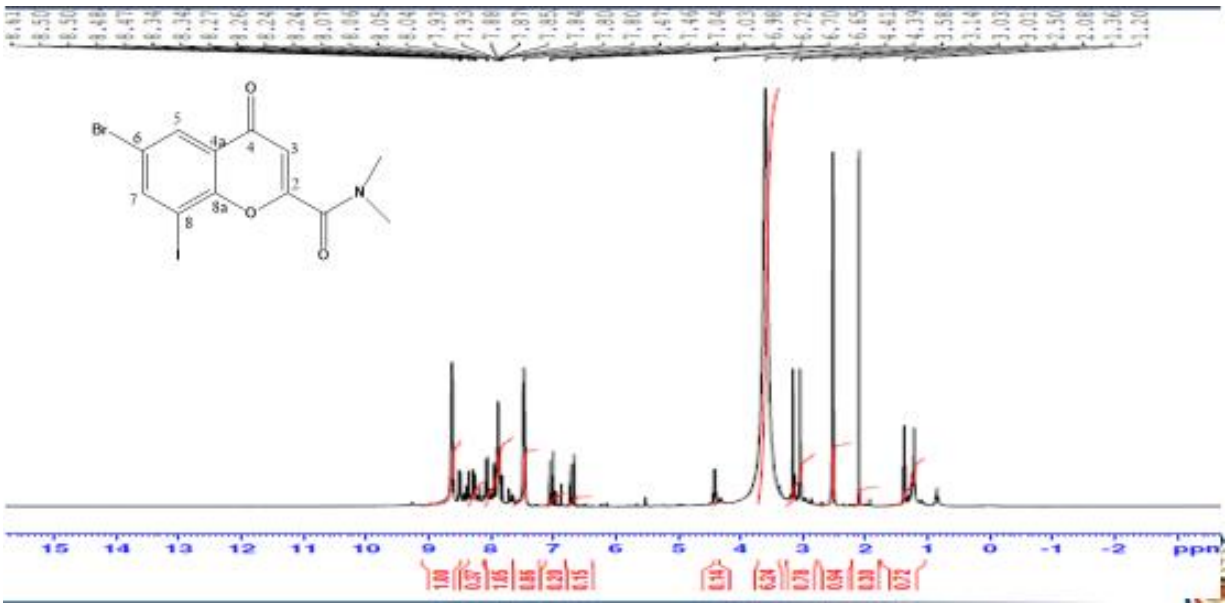


Figure 16: ^{1}H NMR of 6-bromo-8-iodo-N,N-dimethyl-chromone-2-carboxamides **(43)** in DMF-d_7

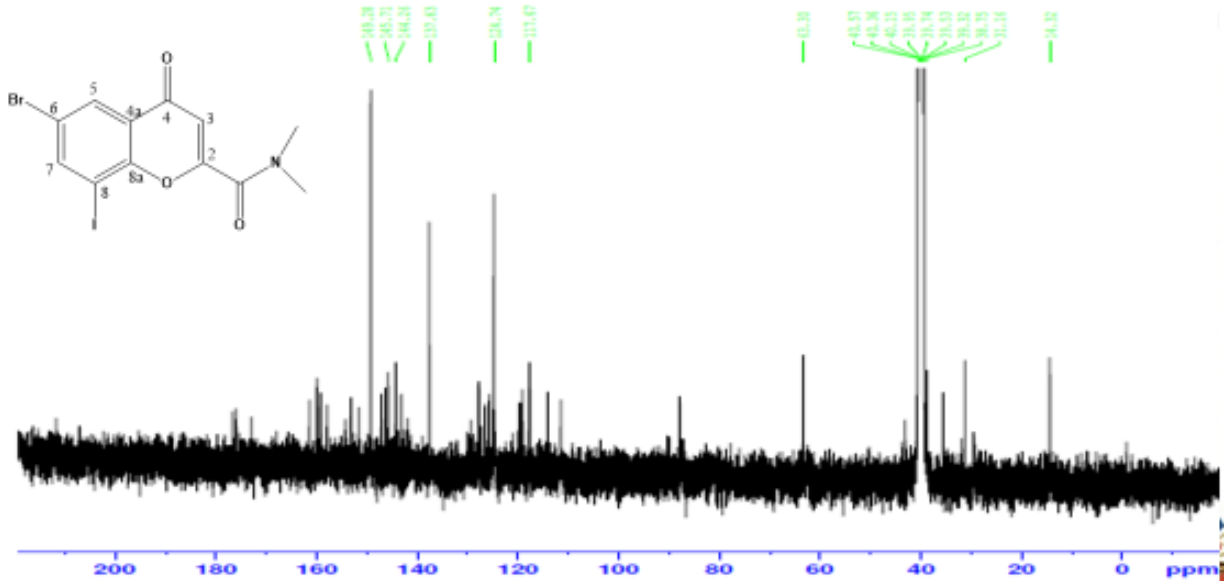


Figure 17: ^{13} C NMR of 6-bromo-8-iodo-N,N-dimethyl-chromone-2-carboxamides **(43)** in DMF-d_7

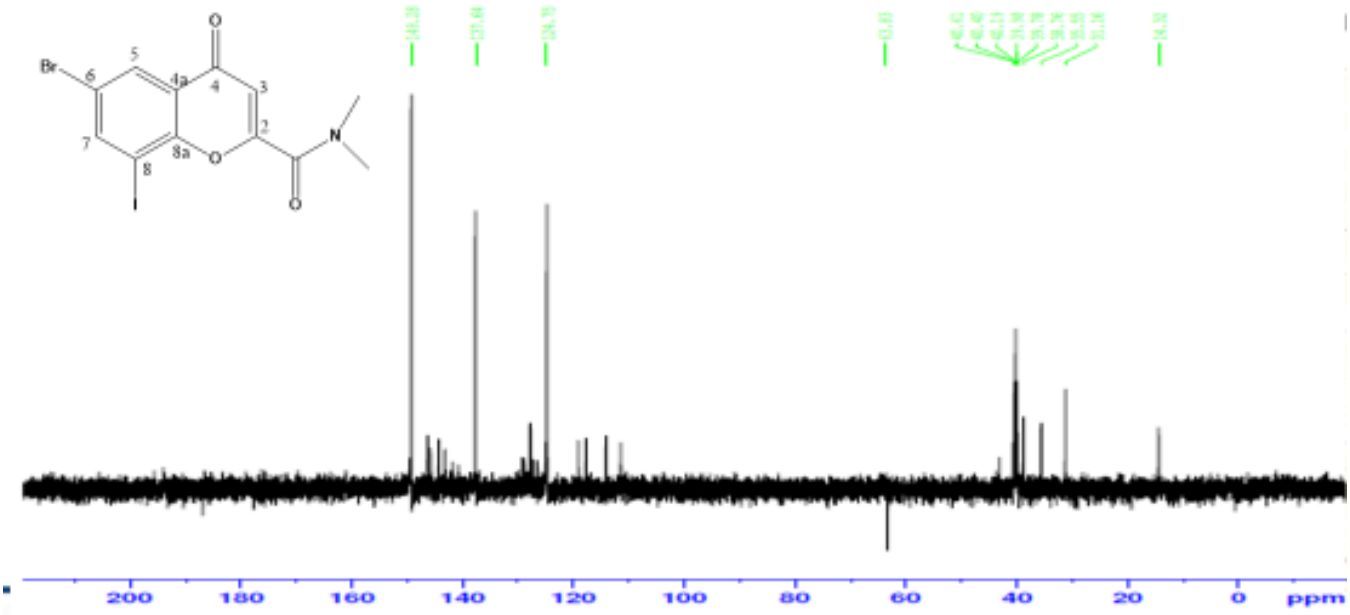


Figure 18: DEPT 135 of ^{13}C NMR of 6-bromo-8-iodo-N,N-dimethyl-chromone-2-carboxamides **(43)** in DMF-d_7