YILDIZ TECHNICAL UNIVERSITY
INSTITUTE OF SCIENCE

ULTRASOUND-ASSISTED SYNTHESIS OF NEW HETEROCYCLIC COMPOUNDS

BY
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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR
THE DEGREE OF MASTER OF SCIENCE
IN
ORGANIC CHEMISTRY

ADVISOR
PROF. DR. ZUHAL TURGUT

İSTANBUL, 2012

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Thesis prepared by Tamrat ZELEKE on 27/ 06/ 2012 at Yildiz Technical University, Institute of Science has been accepted as a master thesis at the Department of Chemistry by the following jury.

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ACKNOWLEDGEMENTS

Foremost, I would like to express my sincere gratitude to my advisor Prof. Dr. Zuhal TURGUT for the continuous support of my study and research, for her patience, motivation, enthusiasm, and immense knowledge. Her guidance helped me in all the time of research and writing of this thesis.

My sincere thanks also goes to Dr. Kadir TURHAN, S.Arda ÖZTÜRKCAN, and Mehmet ULUER for their helps in my research.

I would like to thank my classmates and labmates in Organic Chemistry Laboratory: Aslı ÖZKAN, Arş. Gör. Ömer Tahir GÜNKARA, Murat Emrah MAVİŞ and Aslı KÖPRÜCELİ, for different kinds of support and friendship.

I would like to thank the Government of Republic Turkey for giving me a full scholarship to study here.

Last but not the least, I would like to thank my family for supporting me all the time.

May, 2012

Tamrat Yimenu ZELEKE

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LIST OF SYMBOLS

δ	Chemical shift
Δ	Show location of double bond
J	Jeromatic constant

LIST OF ABRVIATIONS

FTIR	Fourier Transform Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance
TLC	Thin Layer Chromatography
GC/MS	Gas Chromatography- mass spectroscopy
UV	Ultraviolet
ATR	Attenuated Total Reflectance
TFA	Trifluoroacetic acid
TMGT	Tetramethylguanidinium triflouroacetate
DMF	Dimethylformamide
THF	TetrahydroFuran
PDT	Photodynamic Therapy
UAOS	Ultrasound-assisted Organic Rea
BcF	Benzo[*c*]fluorene
PDC	Pyridium dichromate
HMPA	Hexamethylphosphoramide
PWA	12 dodecatungstophosphoric acid
TryR	trypanothione Reductase
CQ	Chloroquine
CAN	Ceric ammonium nitrate
MCRS	Multi-component Reactions
h	Hour
PtsA	p-toluenesulfonic acid

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ABSTRACT

ULTRASOUND-ASSISTED SYNTHESIS OF NEW HETEROCYCLIC COMPOUNDS

Tamrat Yimenu ZELEKE

Chemistry Department

MSc. Thesis

Advisor: Prof. Dr. Zuhal TURGUT

Various new substituted naphthopyrane compounds were synthesized through a one-pot condensation of substituted benzaldehydes with β-naphthol and 1, 3-dione compounds in the presence of $Cu(OTf)_2$ using ultrasonic irradiation and conventional heating.

The structures of the obtained new compounds have been clarified by spectroscopic methods (FTIR, ^{1}H NMR, ^{13}C NMR, and GC-MS) after the purification processes.

Key words: Naphthopyrane, Xanthene, one-pot condensation, triflate, Ultrasonic-assisted reaction

YILDIZ TECHNICAL UNIVERSITY

GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

ÖZET

ULTRASOUND DESTEKLİ YENİ HETERO HALKALI BİLEŞİKLER SENTEZİ

Tamrat Yimenu ZELEKE

Kimya Anabilim Dalı

Yüksek Lisans Tezi

Tez Danışmanı: Prof. Dr. Zuhal TURGUT

Çeşitli yeni substitue naftopiran bileşikleri substitue benzaldehitler ile β-naftol ve 1, 3-dion bileşiklerinin tek-kap kondenzasyonu ile $Cu(OTf)_2$ varlığında ultrasound ve geleneksel ısıtma yöntemleri kullanılarak çeşitli yeni substitue naftopiran bileşikleri sentezlendi.

Saflaştırma işlemlerinden sonra elde edilen yeni bileşiklerin yapıları spektroskopik metodler ile (FTIR, ^{1}H NMR, ^{13}C NMR ve GC-MS) ile aydınlatılmıştır.

Anahtar Kelimeler: Naftopiran, Ksanten, Tek-Kap Kondenzasyonu, Triflat, Ultrsound Destekli reaksiyonu

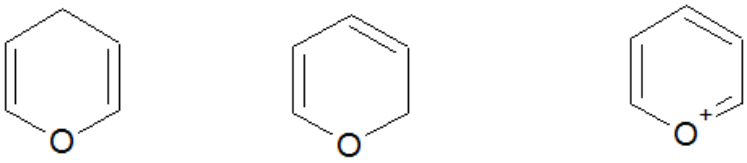
CHAPTER 1

INTRODUCTION

1.1 Literature Review

1.1.1 Pyran and Pyrylium Cation

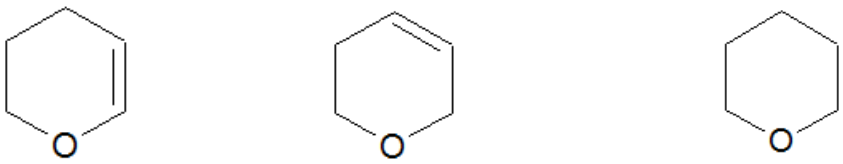
A Pyran, or oxine, is a six-membered heterocyclic compound, non-aromatic ring, consisting of five carbon atoms and one oxygen atom and containing two double bonds. The molecular formula is C_5H_6O. There are two isomers of pyran that differ by the location of the double bonds. A pyrylium cation is a conjugated six membered carbon ring system with one carbon atom replaced by a positively charged oxygen atom. It is, like benzene, an aromatic compound, yet it is reactive.



4*H*-pyran 2*H*-pyran pyrylium cation

Fig 1.1 Isomers of pyran

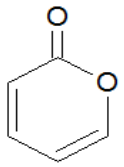
Reduction of one double bond from pyran gives two isomers of dihydropyran. Complete reduction of pyran results tetra hydropyran [1].



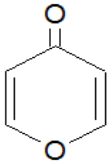
Δ^2- dihydropyran Δ^3-dihydropyran tetrahydropyran

Fig 1.2 Hydropyranes

Pyrones or pyranones are a class of cyclic chemical compounds containing an unsaturated six membered ring containing one oxygen atom and a ketone functional group. There are two isomers of denoted as 2-pyrone and 4-pyrone.



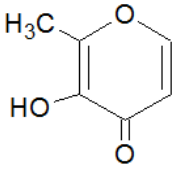
2-pyrone



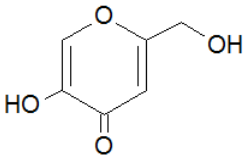
4- pyrone

Fig 1.3 Isomers of pyrones

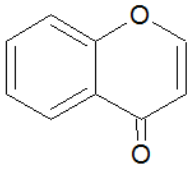
The 2-pyrone or α-pyrone structure is found in nature as part of the coumarin ring system. 4-pyrone or γ- pyrone is found in some natural chemical compound such as chromone, maltol, and kojic acid [2].



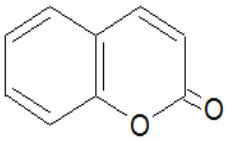
Maltol



Kojic acid



Chromone

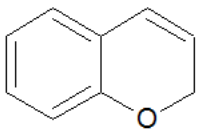


Coumarin

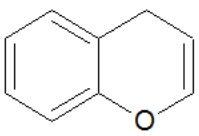
Fig 1.4 naturally existing pyrones

1.1.2 Benzopyran and Benzopyrylium Cation

Benzopyran is a polycyclic organic compound that results from the fusion of a benzene ring to a heterocyclic pyran ring. According to IUPAC nomenclature it is called chromene. There are two isomers of benzopyran that vary by the orientation of the fusion of the two rings compared to the oxygen, resulting in 1-benzopyran (chromene) and 2-benzopyran (isochromene). Each of them has also two structural isomers [3], [4].

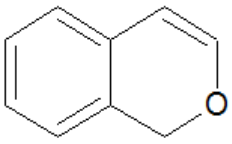


2*H*-chromene

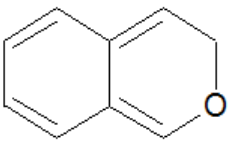


4*H*-chromene

Fig 1.5 Structural isomers of chromene

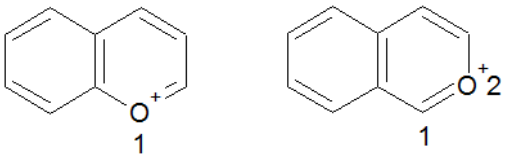


1*H*-isochromene



3*H*-isochromene

Fig1.6 Structural isomers of isochromene

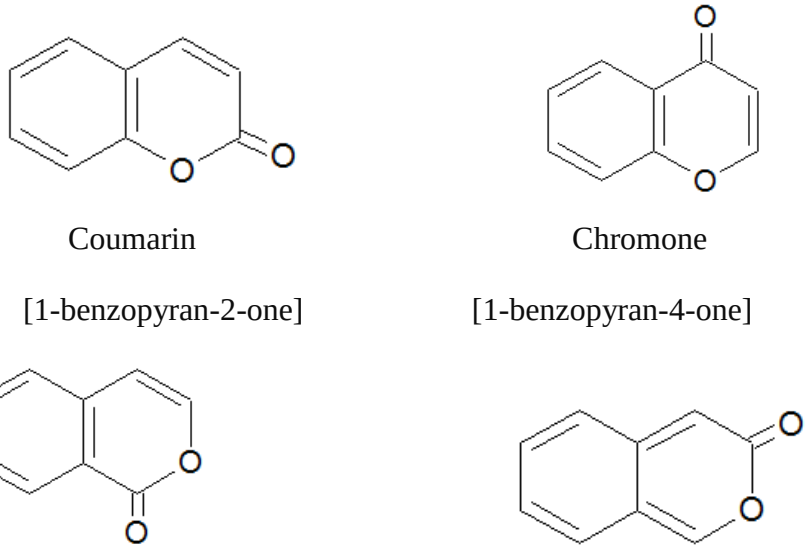


Chromylium cation (benzo[*b*]pyrylium) [1-benzopyrylium]

isochromylium cation (benzo[*c*]pyrylium) [2-benzopyrylium]

Fig 1.7 Benzopyrylium cation isomers

Benzopyrones or coumarin has a distinctive odor which has led people to use it as a food additive and ingredient in perfume since the late 1800s. It has been used as an aroma enhancer in pipe tobaccos and certain alcoholic drinks, although in general it is banned as a flavorant food additive due to concerns about a potential liver and kidney toxin. Coumarin has fungicidal properties as well as anti-HIV, anti-tumor, anti-hypertension, anti-arrhythmia, anti-inflammatory, anti-osteoporosis, antiseptic, and analgesic (pain relief). It is also used in the treatment of asthma. Coumarin has been used in the treatment of lymphedema. Some chemicals in the coumarin family (to be specific, the 4-hydroxycoumarins) have been used as anticoagulant drugs and/or as rodenticides, which work by the anticoagulant mechanism [4], [5], [6].



Coumarin [1-benzopyran-2-one]

Chromone [1-benzopyran-4-one]

Isocoumarin [1*H*-2-benzopyran-1-one]

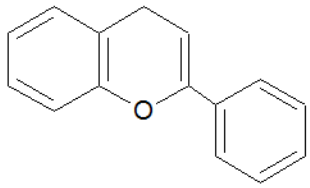
[2-benzopyran-3-one]

Fig 1.8 Isomers of Benzopyrones

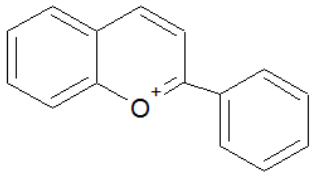
In recent years, coumarin derivatives have received significant attention owing to their diverse range of biological properties such as anti-viral, anticoagulant, antibacterial, antifungal, anti-HIV and antihistamine actions. Besides the wide biological applications of coumarin and its derivatives the chemical literature also embodies their some applications from the material view point such as cosmetics, optical brightening agents, dispersed fluorescent and laser dyes. In addition, some coumarins are of interest because of their toxicity, carcinogenity and photodynamic effects [7].

1.1.3 Flavonoids

Flavonoids are the most important plant pigments for flower coloration producing yellow or red/blue pigmentation in petals designed to attract pollinator animals. In higher plants, Flavonoids are involved in UV filtration, symbiotic nitrogen fixation and floral pigmentation.

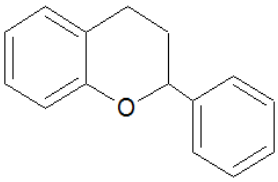


(2-phenyl -4*H*- chromene)

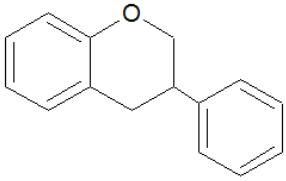


(2-phenyl-1–benzopyrylium)

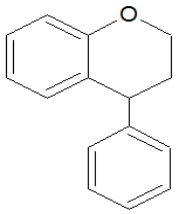
Fig 1.9 Flaven and Flavylium Cation



Flavan
(2-phenylchromane)



Isoflavan
(3-phenylchromane)



Neoflavan
(4-phenylchromane)

Fig 1.10 Isomers of flavan

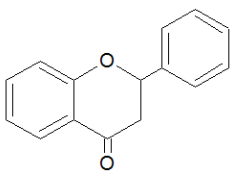
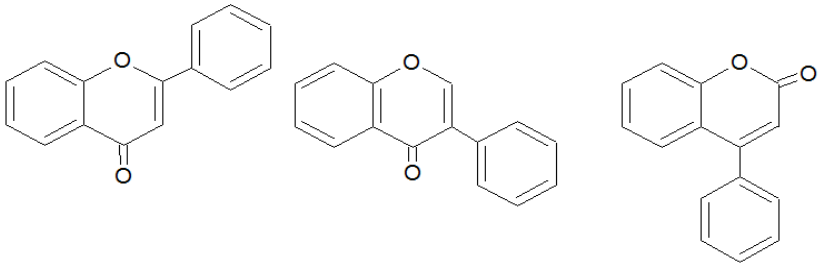


Fig 1.11 Flavanone (2, 3-dihydro-2-phenylchromen-4-one)

According to the IUPAC nomenclature, flavonoids are classified into flavonoids, isoflavonoids, and Neoflavonoids.



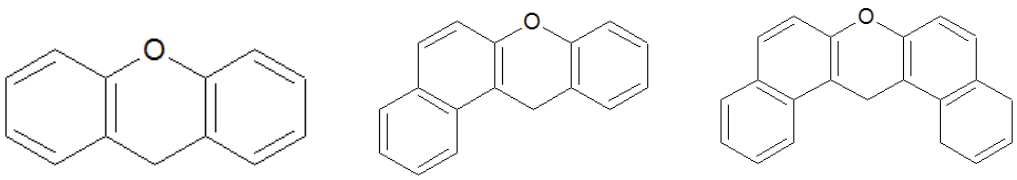
Flavone (2-phenylchromen-4-one) Isoflavon (3-phenylchromen-4-one) Neoflavone (4-phenylcoumarine)

Fig 1.12 Isomers of Flavoids

Over 4,000 flavonoids have been identified, many of which occur in fruits, vegetables and beverages (tea, coffee, beer, wine and fruit drinks). The flavonoids have aroused considerable interest recently because of their potential beneficial effects on human health. They have been reported to have antibacterial, antitoxin, and anti-fungal, antiviral, anti-tumor and antioxidant activities, anti-allergic and anti inflammatory. Antioxidants are compounds that protect cells against the damaging effects of reactive oxygen species, such as singlet oxygen, superoxide, peroxyl radicals, hydroxyl radicals and peroxynitrite. An imbalance between antioxidants and reactive oxygen species results in oxidative stress, leading to cellular damage [8], [9].

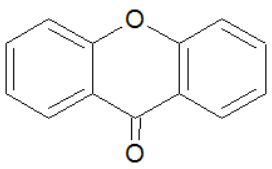
1.1.4 Xanthene and Benzoxanthene

Xanthene is a heterocyclic compound having three fused rings with one oxygen atom. It is heterocyclic compound having pyran nucleus. It molecular formula is $C_{13}H_{10}O$. It molar mass is 182.22 g/mol. It melting point is 101-102 °C. It boiling point is 310-312°C. It appearance is Yellow solid. It is soluble in diethyl ether [10].

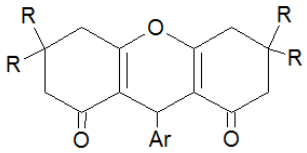


Xanthene Benzo[*a*]xanthene 14H-dibenzo[*a, j*]xanthene

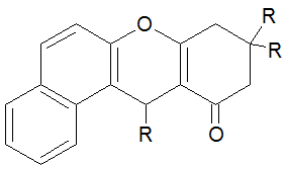
Fig 1.13 Xanthenes



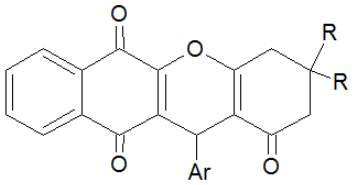
Xanthone



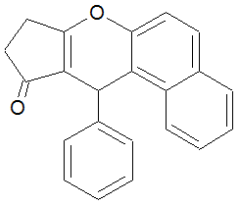
xanthenedione



tetrahydrobenzo[*a*]xanthene-11-one



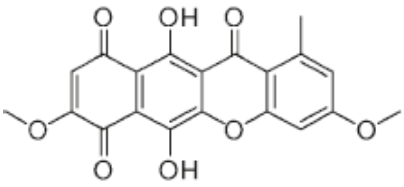
12-phenyl-3,4-dihydro-1*H*-benzo[*b*]xanthene-1,6,11(2*H*,12*H*)-trione



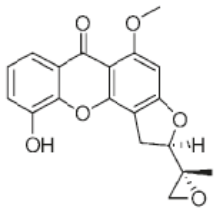
8,9-dihydrobenzo[*f*]penta[*b*]chrome10(11*H*)-one

Fig 1.14 Xanthene derivatives

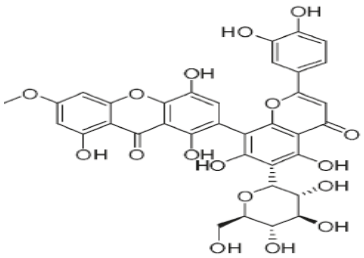
There are numerous natural products having xanthene nucleus that exhibit interesting biological activity. For example, the antitumor compound bikaverin, is a reddish pigment produced by different fungal species, most of them from the genus Fusarium, with antibiotic properties against certain protozoa and fungi. Mangeferin isolated from the mangosteen fruit, which anti-oxidant and an anti-viral agent. The anti-cancer compound psorospermin, a natural product isolated from roots and stem bark of the African plant Psorospermum febrifugum, is mechanistically related to the pluramycin family of antitumor and antibiotics. The anti-HIV compound swertifrancheside isolated from Swertia franchetiana [11].



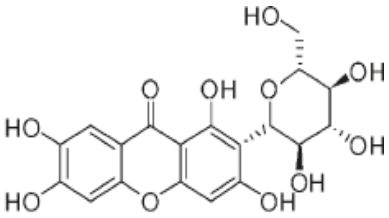
Bikaverin



Psorospermin



Swertifrancheside



Mangeferin

Fig 1.15 Biologically active xanthene derivatives

Heterocyclic compounds with naphthopyran as a structural unit have received considerable interest due to their wide range of interesting biological and therapeutic properties, such as antiviral, antibacterial, anti-inflammatory activities, as well as sensitizers in photodynamic therapy (PDT; a method of treating tumors by combined use of a photosensitizer and light). Such compounds are also utilized for antagonism of the paralyzing action of zoxazolamine. Because of their interesting spectroscopic properties, these compounds have also found applications to dyes, pH-sensitive fluorescent materials for visualization of biomolecules, and utility in laser technologies. As a result, the synthesis of various new xanthene derivatives as well as the development of more rapid, eco-friendly and efficient method to these heterocyclic is great importance [12].

Several methods have been reported for the synthesis of naphthopyran derivatives. In comparison with other routes, the one that employs one-pot reaction of β-naphthol, 1, 3-dicarbonyl compounds and aromatic aldehydes under various conditions has been believed to be the most efficient. One-pot reaction (multi-component method) has been became one of the most important aspects in Organic Chemistry. One-pot synthesis is subjecting successive chemical reactions in just one reactor. One-pot(multi-component reaction) offers a significant advantages over single linear step synthesis such as simple work-up, less time, less energy and less raw-material consuming. Since One-pot method avoids a lengthy separation process and purification of the intermediate chemical compounds, it would save time and resources while increasing chemical yield. Thus, MCRs (multi-component reactions) provide benefits both economically and environmentally [13].

1.1.5 Ultrasonic-assisted Organic Synthesis (UAOS)

Using of ultrasound as source of energy which can be used to enhance a wide range of chemical processes have been grouped under the general name sonochemistry. Ultrasound is defined as sound of a frequency beyond that to which the human ear can respond. Ultrasound is generally considered to lie between 20 kHz to beyond 100 MHz. Sonochemistry generally uses frequencies between 20 and 40 kHz. Because this is the range employed in common laboratory equipment. Alfred L. Loomis noticed the first chemical effects of ultrasound in 1927, but the field of sonochemistry lay fallow for

nearly 60 years. The renaissance of sonochemistry occurred in the 1980's, soon after the advent of inexpensive and reliable laboratory generators of high-intensity ultrasound [14].

As increasing environmental consciousness in chemical research and industry, the challenge for a sustainable environment calls for clean procedures. Ultrasonic-assisted organic synthesis (UAOS) as a green synthetic approach is a powerful techqinue that is being used to acelerate organic reactions. UAOS can be extremely efficient and it is applicable to a broad range of practical syntheses. The notable features of the ultrasound approach are enhanced reaction rates, formation of purer products in high yields, easier manipulation and considered a processing aid in terms of energy conservation and waste minimization which compared with traditional methods, this technique is more convenient taking green chemistry concepts into account. However, the use of ultrasound in heterocyclic system is not fully explored. Only a few reports are available in the literature about application of ultrasound in the synthesis of naphthopyran derivatives [15], [16], [17]. In order to expand the application of ultrasound in the synthesis of heterocyclic compound, we planned to develop a general, efficient and eco-friendly method for the synthesis of hydrobenzo[f]chromen-2-yl phenyl methanone.

1.1.6 Triflates

Trifluoromethanesulfonate, also known by the trivial name triflate, is a functional group with the formula $CF_3SO_3^-$. The triflate group is often represented by –OTf. The triflate anion, $CF_3SO_3^-$ is an extremely stable polyatomic ion, being the conjugate base of triflic acid (CF_3SO_3H), one of the strongest acids known. A triflate group is an excellent leaving group used in certain organic reactions.

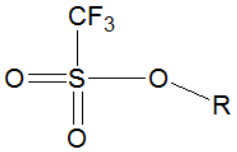


Fig 1.16 Triflate

The triflate anion owes its stability to resonance stabilization which causes the negative charge to be spread over the three oxygen atoms and the sulfur atom. An additional

stabilization is achieved by the trifluoromethyl group as a strong electron-withdrawing group.

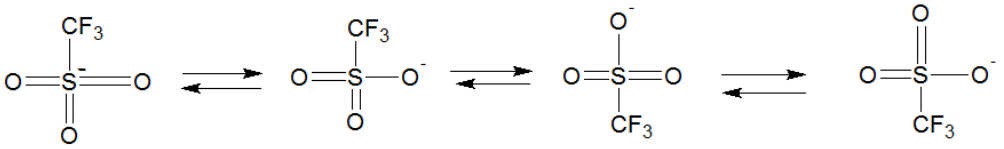


Fig 1.17 Triflate mesomeric stability

Metal Triflate salts are thermally very stable with melting points up to 350°C especially in water-free form. They can be obtained directly from triflic acid and the metal hydroxide or metal carbonate in water. Alternatively, they can be obtained from reacting metal chlorides with neat triflic acid or silver triflate, or from reacting barium triflate with metal sulfates in water.

$$MCl_n + n\ HOTf \rightarrow M(OTf)_n + n\ HCl$$

$$MCl_n + n\ AgOTf \rightarrow M(OTf)_n + n\ AgCl \downarrow$$

$$M(SO_4)_n + n\ Ba(OTf)_2 \rightarrow M(OTf)_{2n} + n\ BaSO_4 \downarrow$$

Lanthanide triflates of the type $Ln(OTf)_3$ (where Ln = La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu, Y) are used as Lewis acids in organic synthesis because of their stability compared to typical catalysts such as $AlCl_3$, BF_3, $SnCl_4$, etc. which are unstable in water. While most Lewis acids are decomposed or deactivated in the presence of water, lanthanide triflates are stable and works as Lewis acids in water solutions. A catalytic amount of $Ln(OTf)_3$ is enough to complete reactions in most cases [18].

The use of lanthanide triflates has given many advantages in organic synthesis. Lanthanide triflates are mild and selective catalysts, which have been used widely in C–C and C–X bond-forming reactions, including Friedel–Crafts, Baylis–Hilman, aromatic nitration, and Diels–Alder reactions. In contrast to classical Lewis acids, which often are required in stoichiometric quantities, lanthanide triflates readily promote a range of reactions in catalytic quantities [19].

Rare earth metal triflates, a new type of lewis acid were widely applied in organic synthesis as catalysts due to their low toxicity, high stability, ease of handling, water tolerance and recoverability from water. Furthermore, lanthanide triflates can be recovered and reused without the loss of activity. Thus, lanthanide triflates are

environmentally friendly catalyst [20]. $Yb(OTf)_3$, $Sr(OTf)_2$, $Zr(OTf)_3$, and proline triflates were used as Lewis acid to catalyze the synthesis of naphyhopyran derivatives [19], [20], [21], [22]. These reports showed that rare earth metal triflates are efficient catalysts for the synthesis of naphthopyran derivatives. Based on these reports we aimed to use $Cu(OTf)_2$ as a catalyst to synthesis new naphthopyran derivatives.

1.2 Aim of the work

Heterocyclic compounds with naphthopyran as a structural unit posses biological and therapeutical activities. They can act as antimicrobial, antitumor, antifugal, cytotoxic, antioxidant, anti-inflammatory, antiviral and sensitizers in photodynamic therapy. They can be also used as dye, pH-sensitive fluorescent materials for visualization of biomolecules, and in laser technologies. Due to these great properties, synthesis of many naphthopyran derivatives, especially with xanthene moiety have been reported. No reports are available at all on the synthesis of hydrobenzo[f]chromen-2-yl phenyl methanone. Thus, we aimed to develop a method to synthesize new naphthopyran derivatives by a one-pot condensation of various substitued aromatic aldehydes with β-naphthol and 1, 3-dicarbonyl compounds in the presence of cupper triflate as a catalyst under conventional heating or ultrasounic irradiation.

1.3 Hypothesis

Seven new naphthopyran derivatives which may show biological activities were synthesized at 80^0C in 2h under ultrasonic irradiation. The method is very important since it is envirnomental friedly.

CHAPTER 2

PREPARATION OF XANTHENE DERIVATIVES

2.1 Synthesis of Xanthene Derivatives

Chih-Wei Kuo and Jim-Min Fang have reported that benzaldehydes and acetophenones undergo the intramolecular phenyl–carbonyl coupling reactions, by mediation of samarium diiodide and hexamethylphosphoramide (HMPA), to afford the xanthenes containing carbonyl and hydroxyl substituents. By the mediation of $(CuOTf)_2$, C_6H_6 and Cs_2CO_3, 3-(dimethoxymethyl) phenol undergoes a coupling reaction with 2-bromobenzaldehyde to give 1a in 72% yield, after hydrolysis of the moiety of dimethyl acetal. Coupling of 3-(dimethoxymethyl) phenol with 2-bromoacetophenone, followed by hydrolysis, also afforded compound 1b in 83% yield (Fig 2.1).

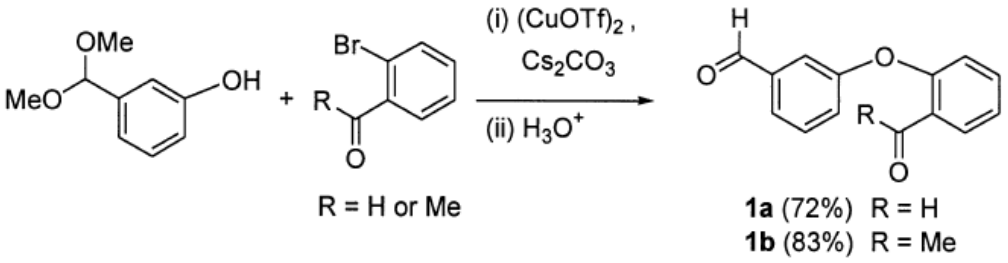


Fig 2.1 Preparation of diphenyl ether

The intramolecular phenyl–carbonyl coupling reaction is achieved by slow addition of a THF solution of 1a to the deep purple solution of SmI_2/ hexamethylphosphoramide (HMPA) in THF at 0^0C (Fig 2.2). After stirring at room temperature for 2h, the reaction mixture is treated with NH_4Cl solution and exposed to the air to furnish the final

oxidative step to regenerate the aromaticity, giving the xanthenecarbaldehyde 2a in 81% yield. Compound 2a decomposes gradually on standing (even in the refrigerator); it is thus converted to the stable xanthones 3a and 3b by oxidation with pyridinium dichromate (PDC) or $KMnO_4$.

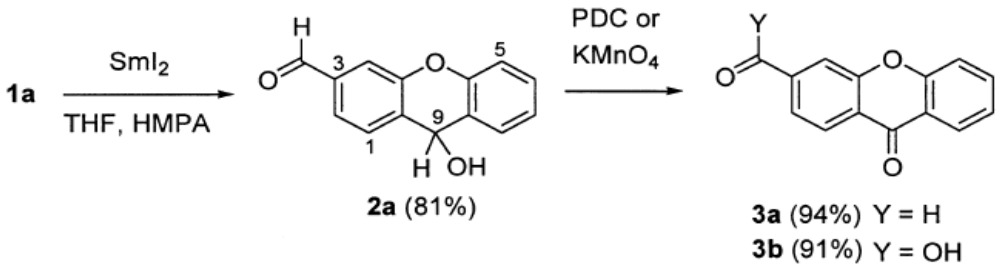


Fig 2.2 Phenyl-carbonyl coupling reactions

Under similar reaction conditions, the cyclization of 1b is less effective, giving a 38% yield of xanthenecarbaldehyde 2b, along with 12% recovery of 1b. The presumed Sm(III)-enolate intermediate B is trapped by alkylation with benzyl bromide to give 4 in a stereoselective manner. The intramolecular coupling reaction might proceed via transition state A, followed by alkylation of the intermediate B via the less hindered face, to give 4 [23].

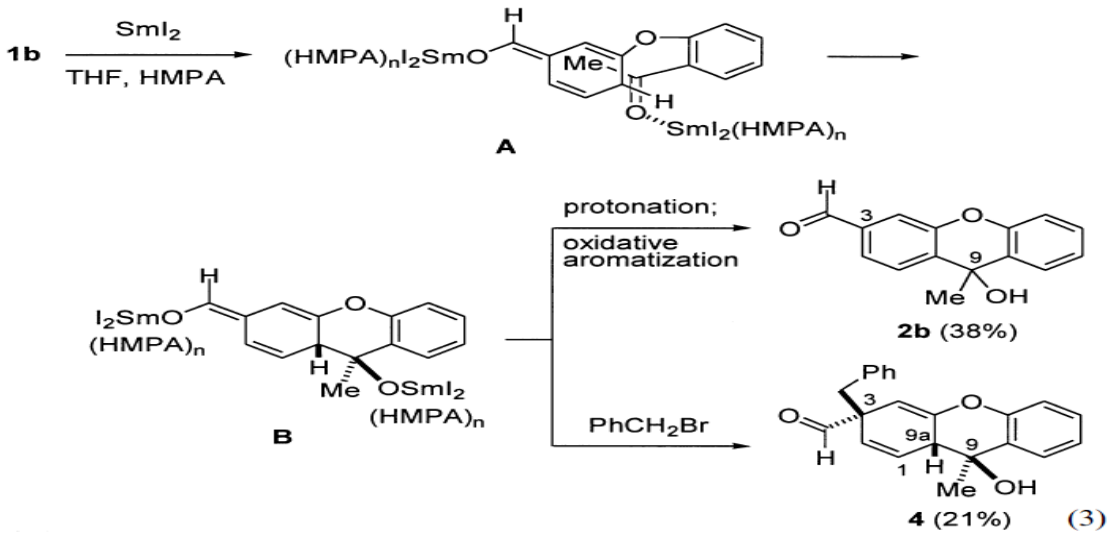


Fig 2.3 Intramolecular coupling reaction by 1b

Kentaro Okuma and coworkers have reported synthesis of xanthenes from the reaction of salicylaldehydes with benzyne prepared from *o*-trimethylsilyphenyl triflate and CsF (cesium fluoride) give xanthenes and xanthones [24].

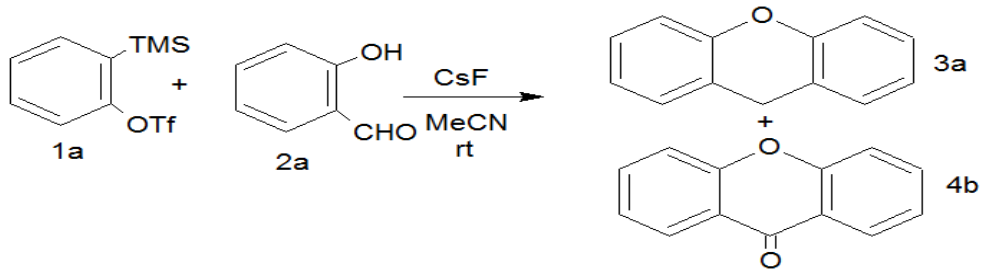


Fig 2.4 Reaction of salicylaldehydes with benzyne in the presence of CsF

When the reaction was carried out under basic conditions, 9-hydroxyxanthenes (xanthols) were obtained in good yields (R=H, 91%).

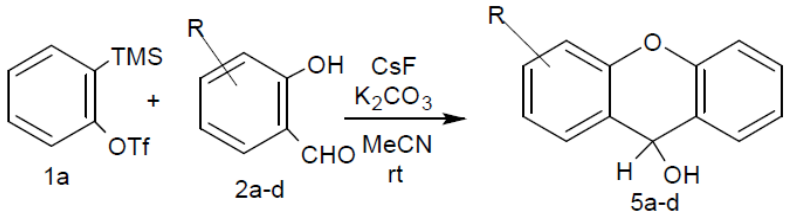


Fig 2.5 Reaction of salicylaldehydes with benzyne in the Presence of CsF in basic conditions.

Yanzhon Li and co-workers have reported the synthesis of xanthenes with various benzylating reagents and phenol in the presence of iron-catalysed microwave-promoted reactions. Benzyl acetates, benzyl bromides, and benzyl carbonates are suitable benzylating reagents [25].

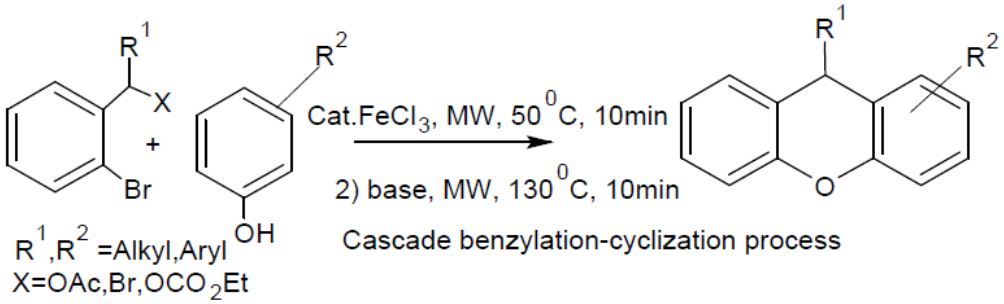


Fig 2.6 Cascade benzylation-cyclization process.

Xanthenedione is also synthsized achieved by the condensation of aldehydes with1, 3-cyclohexanediones in the presence of various catalysts (Scheme 2.2), such as $ZrO(OTf)_2$ [21], Fe_3O_4 nanoparticles [26], Montmorillonite K10 [27], TMGT/TFA [28], silica sulfuric acid [29], and $InCl_3$ [30].

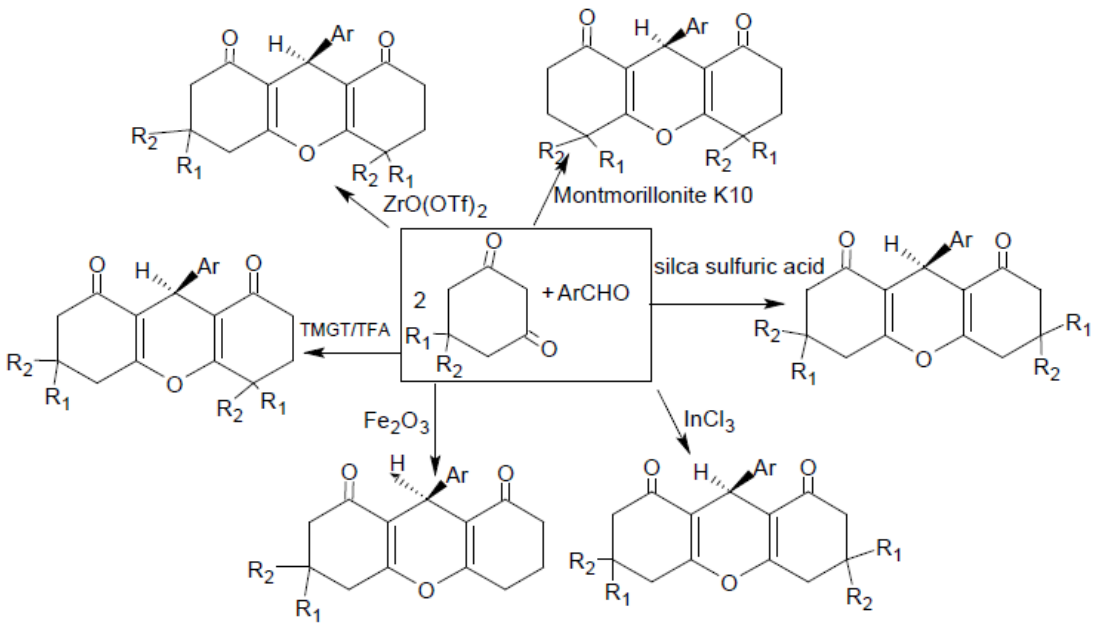


Fig 2.7 Preparation of xanthenedione by condensation of a wide range or aryl aldehydes and 1, 3-cyclohexanediones.

2.2 Synthesis of Benzoxanthene Derivatives

Ronand G.Harvey and co-worker have synthesized benzoxanthene while they were investigating for an alternative approach for the 7*H*-benzo[c]fluorine (BcF), a principal component of tar responsible for formation of the DNA adducts. Alklation of the enamine of cyclohexanone by 2-bromo methyl naphthalene gave 2-(2 naphthylmyethyl) cyclohexanone. Dehyderogenation of 2-(2-naphthylmyethyl) cyclohexanone over a 10% palladium-charcoal catalyst refluxing in trigylme at 240^{o}C gives 2-(2 naphthylmyethyl)phenol and converted to triflates by treatment with Triflouro methane sulfuric acid anhydride and 2,6-lutidine. The reaction of the corresponding triflate, LiCl, and DBU with bis(triphenylphosphine)palladium chloride (0.1equiva) in DMF at 145^{o}C

give white solid with mp 88-89^{o} C (scheme 2.3). The novel product was identified as 7H benzo[c]xanthene [31].

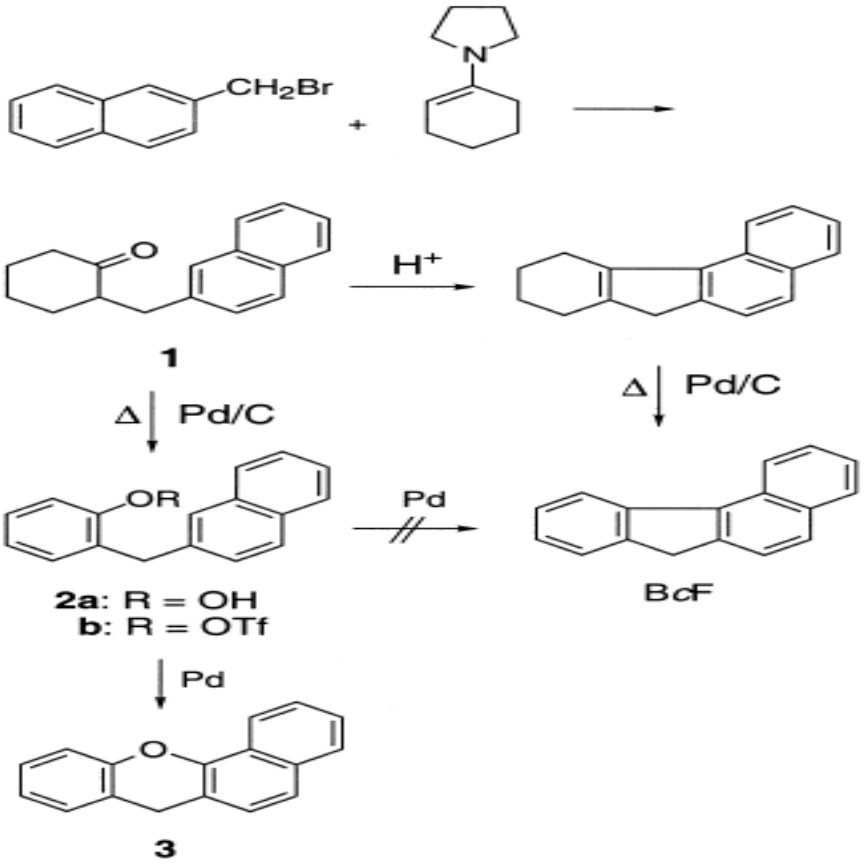


Fig 2.8 Synthesis of benzo[c]xanthene

The reaction between 2-Tetralone and 2-hydroxyarylaldehydes yields 12H-benzo[a]xanthenes under acidic conditions [32].

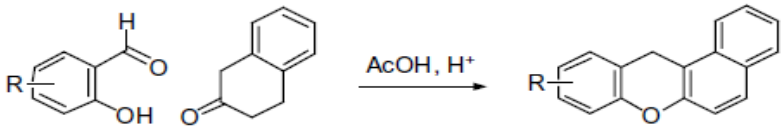


Fig 2.9 Reaction of 2-hydroxyaromatic aldehydes with 2-tetralone

The synthesis of 8, 9, 10,12-tetrahydrobenzo[a]xanthene-11-one has been developed by three component cyclocondensation of aldehydes, β-naphthol and cyclic 1,3-dicarbonyl compounds in the presence of various catalysts(scheme 2.4), such as proline triflate [22], Strontium triflate [20], Indium (III) chloride or phosphorous pentoxide [33], ceric ammonium nitrate (CAN) [34], and 12 dodecatungstophosphoric acid (PWA) [35].

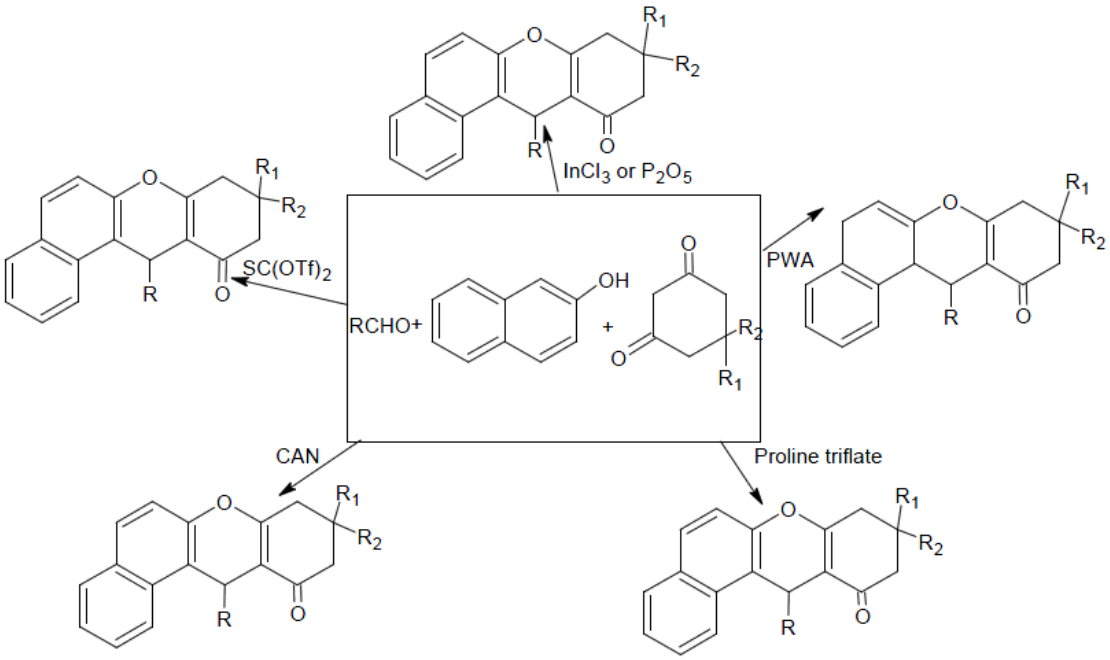


Fig 2.10 Preparation of 8, 9, 10, 12-tetrahydrobenzo[a]xanthene-11-one derivatives

Weike Su and coworkers have been able to synthesize benzo[c]xanthene from α-naphthanol [22].

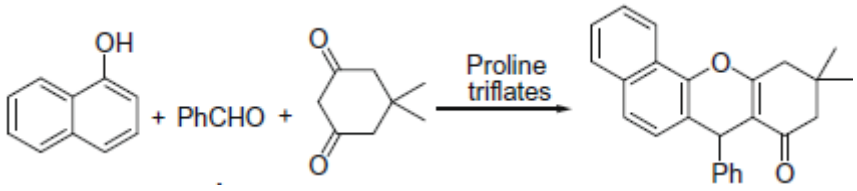


Fig 2.11 Reaction of α-naphthol, aldehyde, and 1, 3-dicarbonyl compounds catalyzed by proline triflates

2.3 Synthesis of Dibenzoxanthene Derivatives

14-aryl-14*H*-dibenzo[a.j]xanthenes and related products have been prepared by the reaction of β-naphthol with formamide, 2-naphthol-1-methanol, and carbon monoxide. Recently, the synthesis of dibenzoxanthene and its analogs have been achieved by the condensation of aldehydes with β-naphthol in the presence of various catalysts (scheme 2.6), such as such as AcOH–H_2SO_4, p-TSA, $MeSO_3I$ 16 ıic acid, ionic liquid, iodine, heteropolyacid, silica sulfuric acid, Amberlys ınuric chloride, LiBr, $CoPy_2Cl_2$, $Yb(OTf)_3$, $Sc[N(SO_2C_8F_{17})_2]_3$, $NaHSO_4$ and $Al(HSO_4)_3$ [36].

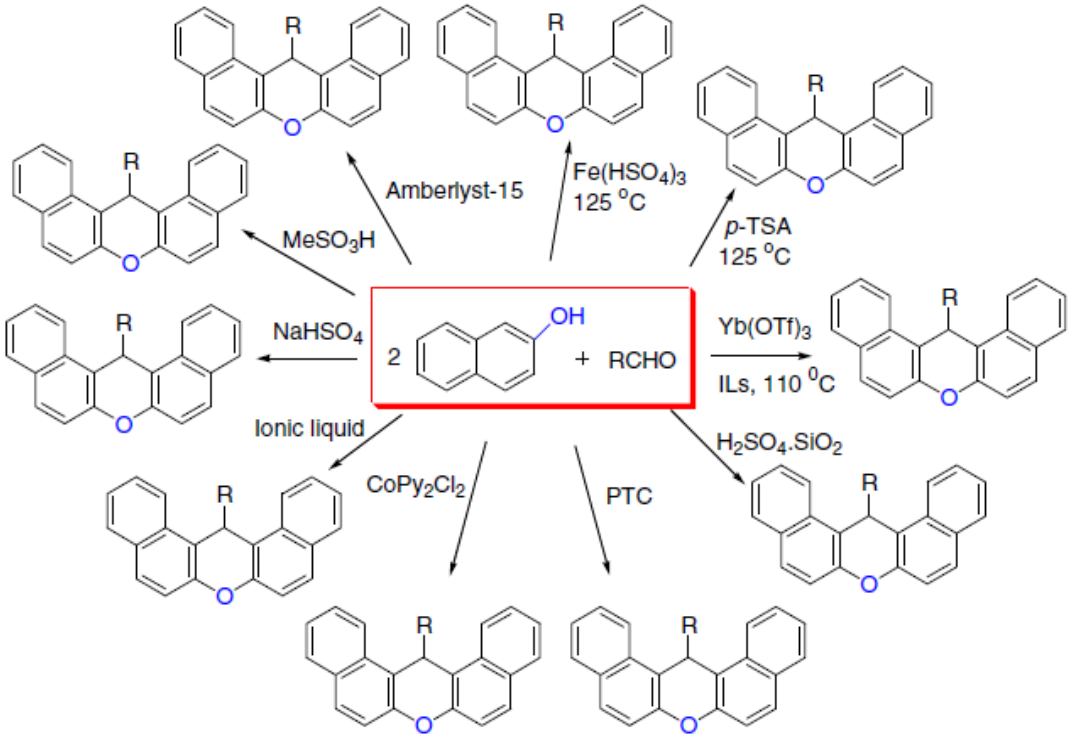


Fig 2.12 Preparation of 14-substituted-14H-dibenzo[*a,j]* xanthenes by condensation of 2-naphthol and aldehydes.

CHAPTER 3

USES OF XANTHENE DERIVATIVES

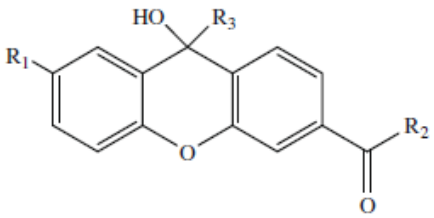
Xanthenes and benzoxanthenes are important biologically active heterocyclic compounds, which possess antiviral, antibacterial, anti-inflammatory, antiplasmodial, anticancer, antioxidant. These are also being utilized as antagonists for paralyzing action of zoxazolamine and in photodynamic therapy. In addition to this, they can be employed as dyes, intracellular pH indicators, molecular probes in chemical biology, and fluorescent materials for visualization of biomolecules, in laser technologies. Consequently, the development of novel methods for the synthesis of these heterocyclic compounds has been received considerable interest in both organic and medicinal fields [22], [36], [37].

3.1 Biological Activities of Xanthene Derivatives

3.1.1 Anticancer activity

Xanthones and xanthenes are tricyclic dibenzopyrans with diverse physicochemical and pharmacological properties. Xanthones are active against a variety of pathogens and show promise for use as antioxidants, antineoplastics, vasodilators, and anti inflammatories. In most cases, the mechanism of action is not known, greatly complicating the drug discovery process. Recently, Na and co-workers reported the synthesis of several xanthone- based analogs that are cytotoxic to cancer cells in vitro. There are a number of other studies have appeared that show substituted xanthones are cytotoxic to cancer cells. David M. Ferguson and co-workers also synthesized a series

of substituted xanthenes and screened for their activity against three well known cancer cell [prostate (DU-145), breast (MCF-7), and cervical (HeLa)].([N,N-diethyl]-9-hydroxy-9-(3-methoxyphenyl)-9H-xanthene-3-carboxamide) was found to inhibit cancer cell growth with IC_{50} values ranging from 36 to 50 μM across all three cancer cell lines [38].



R_1=H, R_2= Diethylamine, R_3= –Ph(3-OMe)

Fig 3.1 Cancer cell cytotoxic xanthene derivative

3.1.2 Trypanothione reductase inhibitors and chloroquine potentiating agents

Molecules based on the 9, 9-dimethylxanthene moiety have potential as TryR inhibitors and CQ potentiating agents and show both antimalarial and CQ potentiating activity. Parasitic protozoa Trypanosoma and Leishmania which are responsible for African sleeping sickness in humans (nagana in cattle), Chagas disease and leishmaniasis utilize the trypanothione/trypanothione reductase (TryR) system for the maintenance of an intracellular reducing environment. Effective inhibition of TryR should compromise the parasites ability to defend itself against reactive oxygen molecules like hydrogen peroxide and hydroxyl radicals, agents known to destroy DNA and cellular membranes. Xanthene derivatives (fig 3.2) have shown a potential as trypanothione reductase (TryR) inhibitors.

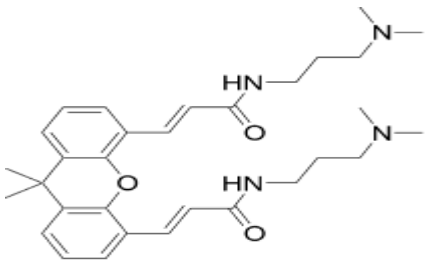
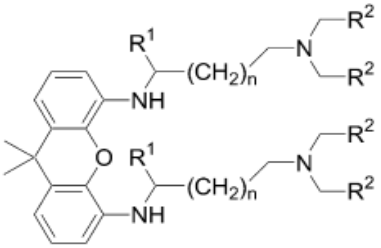
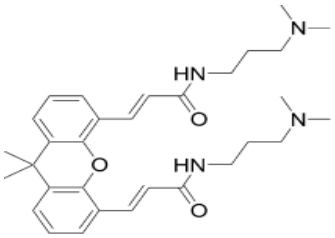


Fig 3.2 Trypanothione reductase (TryR) inhibitor

A number of xanthene derivatives increase CQ accumulation and potentiating effects in a resistant strain of Plasmodium falciparum and some of them also display strong intrinsic antimalarial activity. Plasmodium falciparum malaria continues to be a major health threat throughout the tropical world. While potential demand for antimalarial is high, drug resistance to Plasmodium falciparum is a major problem. Previous first line drugs such as chloroquine (CQ) have been rendered completely ineffective in most endemic areas. Since resistant malaria parasites accumulate less CQ compared to sensitive parasites, chemical agents which increase CQ accumulation in resistant parasites have potential as CQ resistance reversing agents. When co-administered with CQ, xanthene derivatives (fig 3.3a, b, &c) showed a 5–6 fold increase in CQ accumulation in a CQ resistant strain of Plasmodium falciparum. The combination of xanthene derivatives (fig 3.3a & c) with CQ showed resistance reversing or potentiating effects in a resistant strain of Plasmodium falciparum and completely reverse the resistance of cells to the cytotoxic action of CQ. Xanthene derivative sulfonamides [fig 3.3c (R=SO_2PhMe)] displayed strong antimalarial activity [39].





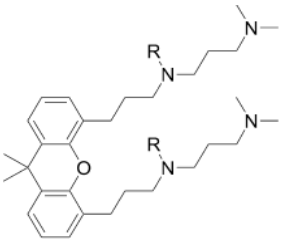


Fig 3.3a
R^1=Me, R^2=Me,n=2
R^1 =H,R^2=1,n=1

Fig 3.3b

Fig 3.3c
(R=SO_2PhMe, SO2 (2-Naphthalene)

Fig 3.3a, b, c Chloroquine potentiating agents

3.2 Uses as Dyestuff

Xanthene forms an important class of synthetic dyes which are widely used. Most of them present three acid–base groups: two phenolic sites and one carboxylic site. Because 0f xanthene dyes show strong antimicrobial activity under photo irradiation, they have potentially valuable applications in food, medicine and the environment. They are commonly used as dyestuffs in the food, cosmetics and textile industries. These

synthetic colorants form one of the most important classes of food additives, because they are easier to produce, are less expensive and have better coloring properties than natural colors from plant, animal and mineral sources. Such colorants undergo rigorous scrutiny concerning their toxicity before receiving approval for use. The use of these additives is strictly controlled in most countries. Among the dyes, phloxine B and erythrosine B are approved for use in the United States; erythrosine B in the EU; and rose bengal, phloxine B and erythrosine B in Japan [40]. Xanthene derivatives undergo rapid activation when exposed to light, leading to the formation of singlet oxygen and superoxide anions. Therefore, when insects ingest a photosensitizer and are then exposed to light their detoxifying systems become overwhelmed and they consequently die. Xanthene dyes represent a family of photosensitizers that have been extensively tested as photo insecticides to control fruit flies [41].

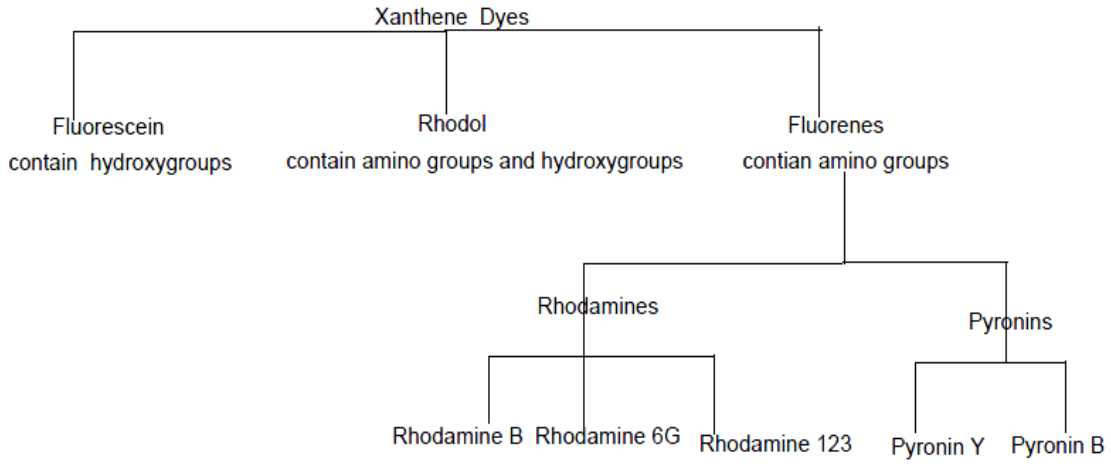


Fig 3.4 Xanthene dyes

3.2.1 Fluorescein derivatives

Fluorescein is one of the most widely used xanthene dyes due to its high light absorption and high fluorescence yield. It is employed as a fluorescent probe in medical investigations, in chemical analysis, and in industries. Some interesting fluorescein derivatives are well-known xanthenes such as eosin Y, erythrosin B, and rose bengal. These compounds are employed in cell analysis, in diagnosis and in industries as commercial dyes [42]. Fluorescein is a poor photosensitizer, but by replacing some of the hydrogen with halides, these compounds become efficient photosensitizers.

Photosensitizers generate reactive oxygen species such as singlet oxygen which oxidize biological molecules, including lipids, proteins and nucleic acids, that leading to bacterial cell death [40].

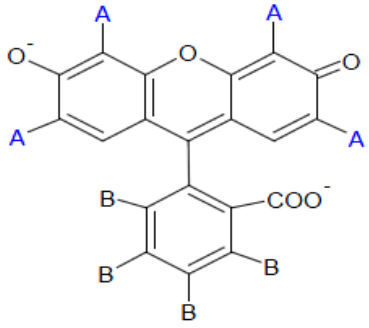
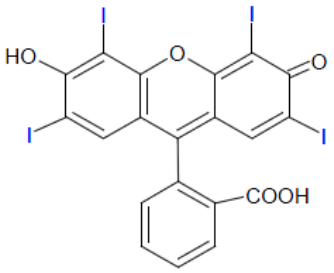
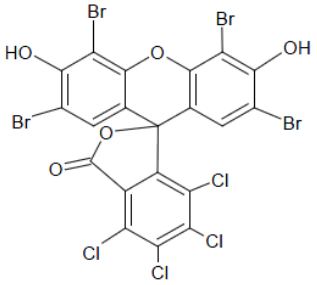


Fig 3.5 General Structure of Fluorescein

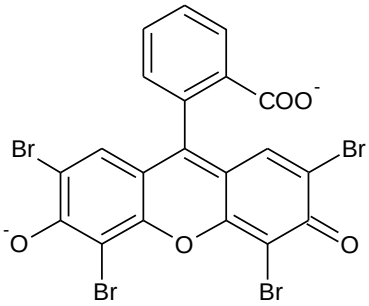
When A=H, B=H, Fluorescein, used in tracing underground currents in sea and rivers as well as a marker during accidents. When A=Br, B=H, it becomes eosin yellowish. Eosin is used to dye silk and wool. When A=I, B=H, it becomes erythrosin B which is used as a food additive and photo insecticide. When A=I, B= Cl, it becomes rose bangal which is used to diagnose liver and eye cancer. It also used as an insecticide. When A=Br, B=Cl, it becomes Phloxine B which is used as a colorant in food, drugs, cosmetics like lipsticks and photo insecticide. It is used in such products as biological stains, inks, and lacquers for coating and dyeing paper.



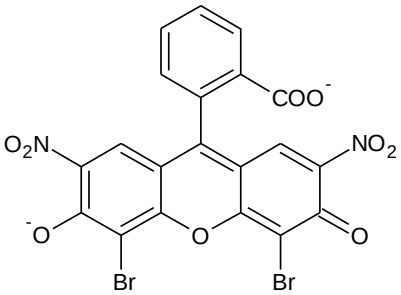
Erythrosin B



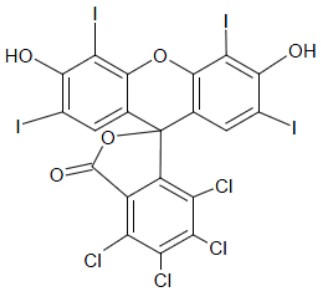
Phloxine B



Eosine Y



Eosine B

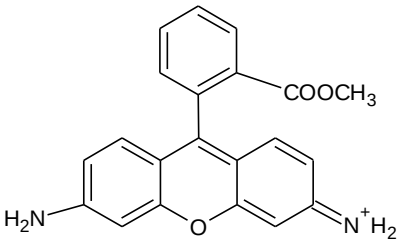


Rose Bengal

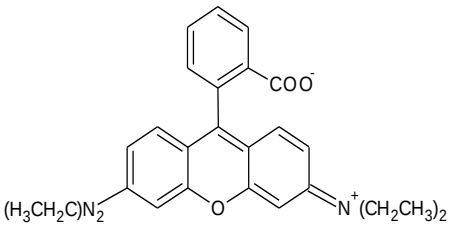
Fig 3.6 Fluorescein Derivatives

3.2.2 Rhodamines

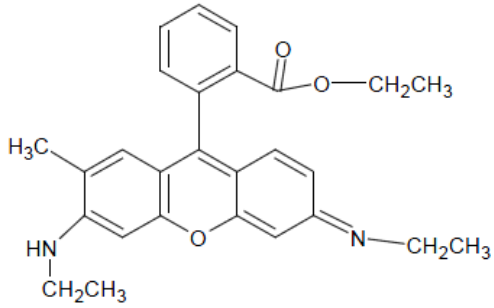
Rhodamine dyes are used extensively in biotechnology applications such as fluorescence microscopy, flow cytometry, fluorescence correlation spectroscopy. They also show antiviral and antimalarial activity. Rhodamines are used to dye papers. They are also used to dye silk, cotton and wool mordanted with tannin where brillant shade of fluorsence effects are required. These dyes are used in a wide range of applications, for example, as biological stains, sensitizers, fluorescent probes, tracing agents, and laser dyes. Rhodamine dyes are widely used for dyeing materials in the textile and plastics.



Rhodamine 123



Rhodamine B



Rhodamine 6G

Fig 3.7 Rhodamines

The first synthesis of rhodamine B was performed by Noelting and Dziewonski in 1905. Rhodamine B, 9-(2carboxyphenyl)-3, 6-bis(diethylamino)xanthylium chloride, fit into the class of xanthene dyes, which is extremely water-soluble. It is broadly applied as a fabric dye, a pigment in drug and cosmetic preparations. It is an analytical reagent for metals, dyeing reagent in the cell fluorescence, a tracing agent in water pollution studies and as a color marker in herbicide sprays, colored glass, dyeing silk, wool, jute, leather and cotton. They are often used as a tracer dye with in water to determine the rate and direction of flow and transport. Evidences have shown that rhodamine dyes have the potential cocarcinogenicity or carcinogenicity for animals and humans. Rhodamine B is dangerous if swallowed by human beings and animals, causes irritation to the skin, eyes and respiratory tract. The carcinogenicity, reproductive and developmental toxicity, neurotoxicity and chronic toxicity towards humans and animals have been experimentally proven. Therefore, RB has been widely prohibited as a food colorant in the world [43].

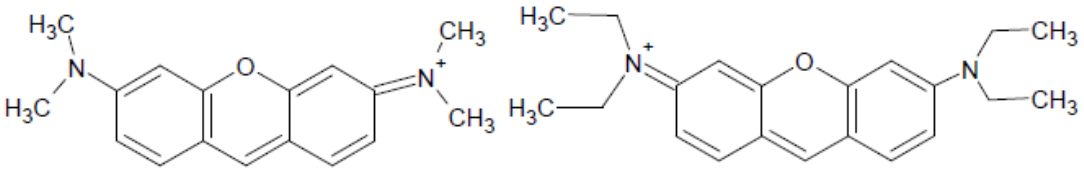
The ethyl ester of rhodamine B (rhodamine 6G) was used in one of the first laser dye and it is remains a commonly used laser dye. Rhodamine 6G with the chemical structure shown in Fig 3.7 is a derivative of the xanthene dyes, which is highly water soluble. It is among the oldest and most commonly used synthetic dyes that are used as a colorant in

textile and foodstuffs. Most of synthetic dyes are carcinogenic and others after transformation or degradation yield compounds such as aromatic amines, which may be carcinogenic or otherwise toxic [44].

Rhodamine 123 has been utilized for the location of mitochondria in the living cells. The first investigations on the potential use of rhodamine 123 for cancer chemotherapy were published in 1983. It was shown that in nonlethal doses, rhodamine 123 exhibited significant and measurable antitumor activity in mice. Further toxicity studies, however, demonstrated that the concentrations necessary to produce antitumor effects were also cytotoxic for normal fibroblasts. The role of rhodamine 123 strictly as a cancer chemotherapeutic agent appears to be limited. However, more promising is the potential of rhodamine 123 as a photo sensitizer of tumor cells. The first use in this regard, combined with the argon laser was reported in 1986. The effectiveness of permanent eradication in the animal model is remarkable [45].

3.2.3 Pyronins

Pyronin Y and pyronin B are very important biological strains, used with methyl green to selectively demonstrate RNA (red) in contrast to DNA (green) with the Unna-Pappenheim method. It is used to dye silk tannin-mordanted cotton a crimson red. It is used for detection of mercury, tin, and silver [46].



Pyronin Y pyronin B

Fig 3.8 Pyronins

CHAPTER 4

EXPERIMENTAL

4.1 Materials

Reagents

Reagents purchased from Merck were: benzaldehyde, 4-nitrobezaldehyde, 4-chlorobenzaldehyde, 4-methylbenzaldehyde, 3,5-dichlorobenzaldehyde, 2-naphthol, benzoylacetone, 1,3-diphenyl-1,3-propandione, $Cu(OTf)_2$, 1,2-dichloroetane, dichloromethane, and sea sand. All reagents were used as purchased from the manufactures.

Solvents

Dichloromethane and 1, 2-dichloroethane were used as delivered. Ethyl acetate (99.9% pure) and n-hexane (99% pure) were distilled again in the laboratory. Purification of product carried out by Column chromatography which was conducted on silica gel 60(70-230 mesh) purchased from Merck. TLC was carried out on aluminum sheets pre-coated with silica gel $60F_{254}$ purchased from Merck, and the spots were visualized with UV light (254/366 nm) using a Camag UV lamp.

4.2 Specific equipment

NMR (^{1}H ve ^{13}C) spectra were recorded on a Bruker Avance ıı 500 MHz at Yildiz Technical University Department of Biology Laboratory and INOVA 500MHz at Istanbul University Advanced Analysis Laboratory. Chloroform was used as a solvent.

FTIR spectra were recorded on a Philips PU 9714 ATR spectrophotometer using Perkin-Elmer Spectrum One program at of Yildiz Technical University Instrumental Analysis Laboratory.

GC/MS spectra were recorded on Agilent 6890N GC system-5973 IMSO Instrument at Yildiz Technical University Instrumental Analysis Laboratory.

In addition melting points of purified products were recorded on a Gallenkamp, a device which has a digital thermometer to determine the melting point with open capillary tubes.

Ultrasound-assisted reactions were performed in an ultrasound cleaner model MIN4 (Intersonik, Turkey) with a frequency of 25kHz, an ultrasound output power of 100W and heating at 200W.

4.3 General Procedure for Synthesis of hydrobenzo[f]chromen-2-yl phenyl methanone

4.3.1 Conventional heating method (method A)

To a mixture of β-naphthol (1.0 mmol), aldehyde (1.0 mmol), and 1, 3-dicarbonyl compounds (1.0 mmol) was added cupper triflate (0.1 mmol) in 1, 2-dichloroetane (2 mL). The reaction mixture was vigorously stirred with magnetic stirrer at 80^0C for a given time (table 4.1). The progress of the reaction was monitored by TLC. After completion of the reaction, mixture was diluted by 10 mL of ethyl acetate and water. Organic phase was separated and aqueous phase extracted with 10 mL ethyl acetate three times. The collected organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated, and the crude product was purified by column chromatography on silica gel with dichloromethane: n-hexane as eluents.

4.3.2 Ultrasound irradiation method (method B)

To a solution of $Cu(OTf)_2$ (0.1 mmol) in 2 mL of 1,2-dichloroetane was added the aldehyde (1 mmol), 2-naphthol (1.0 mmol) and 1,3-dione (1.0 mmol). The reaction mixture was sonicated at 80^0C in an Ultrasound Cleaner bath during the mentioned time. The flask was suspended at the center of the bath because the reaction flask was located in the maximum energy area in the cleaner. The progress of the reaction was

monitored by TLC. The aqueous phase was extracted with EtOAc (3 x 10 mL). The organic phases were combined and consecutively, dried over $MgSO_4$, and filtered. The solvents were removed under reduced pressure. The crude mixture was purified by column chromatography (dichloromethane: n-hexane).

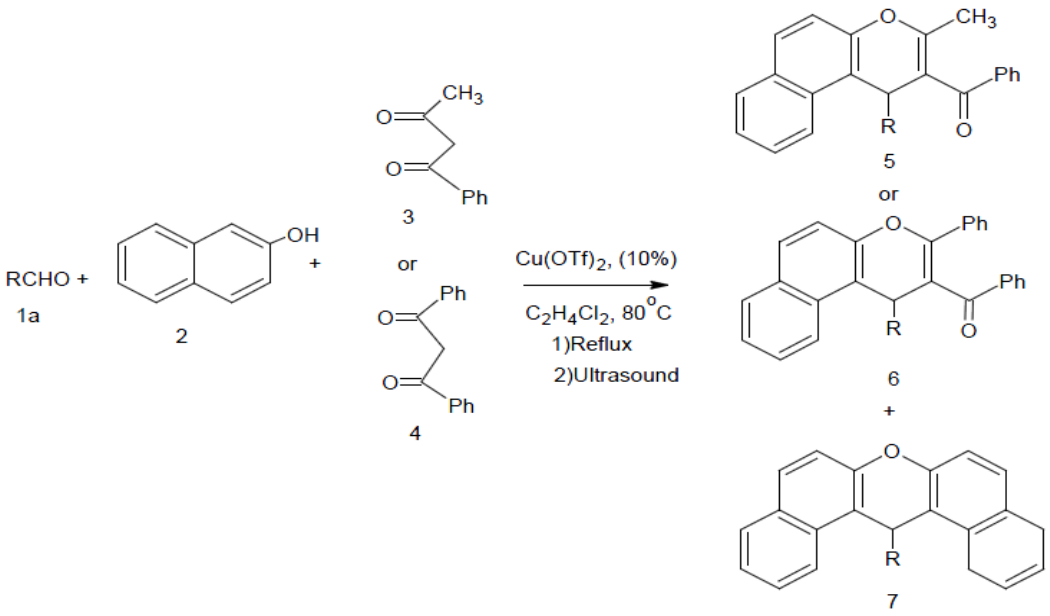


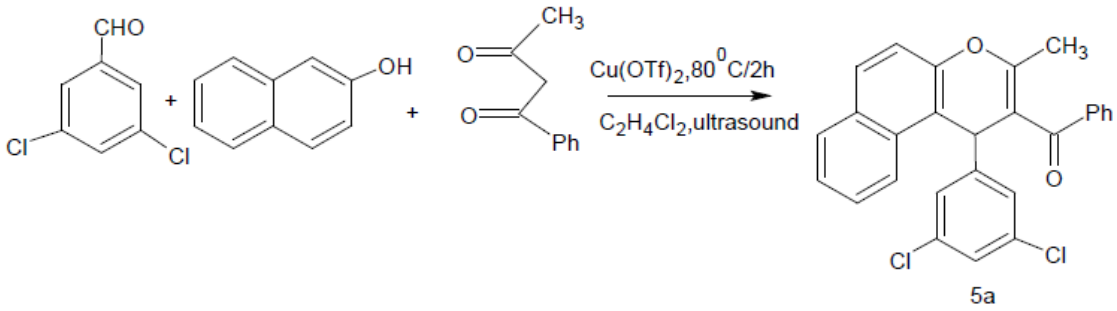
Fig 4.1 $Cu(OTf)_2$ catalyzed condensation of β- naphthol, aromatic aldehydes, and 1,3-dicarbonyl compounds.

Table 1 Synthesis of chromene in the presence of $Cu(OTf)_2$

Entry	R	Product	Condition	Time (h)	M.P(^{0}C)
1	3, 5-(Cl) C_6H_3	5a	MethodA/MethodB	5&2	249-250
2	p-(Cl) C_6H_4	5b	MethodA/MethodB	5&2	281-282
3	p-(NO_2) C_6H_4	5c	MethodA	5	317-318
4	C_6H_5	6a	MethodB	2	191
5	p-(Cl) C_6H_4	6b	MethodB	2	-
6	p-(CH_3) C_6H_4	6c	MethodB	2	171.5
7	3, 5-(Cl) C_6H_3	6d	MethodA/MethodB	5&2	174.5

4.3.1 Compound 5a ($C_{27}H_{18}Cl_2O_2$)

(1-(3, 5-dichlorophenyl)-3-methyl-1*H*-benzo[*f*]chromen-2-yl)(phenyl)methanone



5a

Fig 4.2 Preparation of compound 5a

Eluents mixture: 2 hexane/1 dichloromethane

White crystal, M.P: 249-250^{0}C

Analytical Data:

FTIR $\gamma_{max/cm}^{-1}$: 3058, 2921, 1730, 1619, 1592, 1514, 1468, 1403, 1241, 995, 807, 735.

^{1}H NMR (500MHz, $CDCl_3$): δ (ppm) 1.52 (3H, s, CH), 5.45 (1H, s, CH), 6.89-6.92 (2H, m, Ar-H), 7.27-7.31 (4H, m, Ar-H), 7.42-7.51 (2H, m, Ar-H), 7.59-7.63 (3H, m, Ar-H), 7.79-7.87 (3H, m, Ar-H).

^{13}C NMR (100MHz, $CDCl_3$): δ (ppm) 34.21, 40.10, 117.46, 118.09, 123.11, 124.55, 127.04, 128.40, 128.75, 129.11, 129.28, 130.88, 131.56, 132.68, 132.78, 142.22, 148.90.

M^+ (m/z) = 445

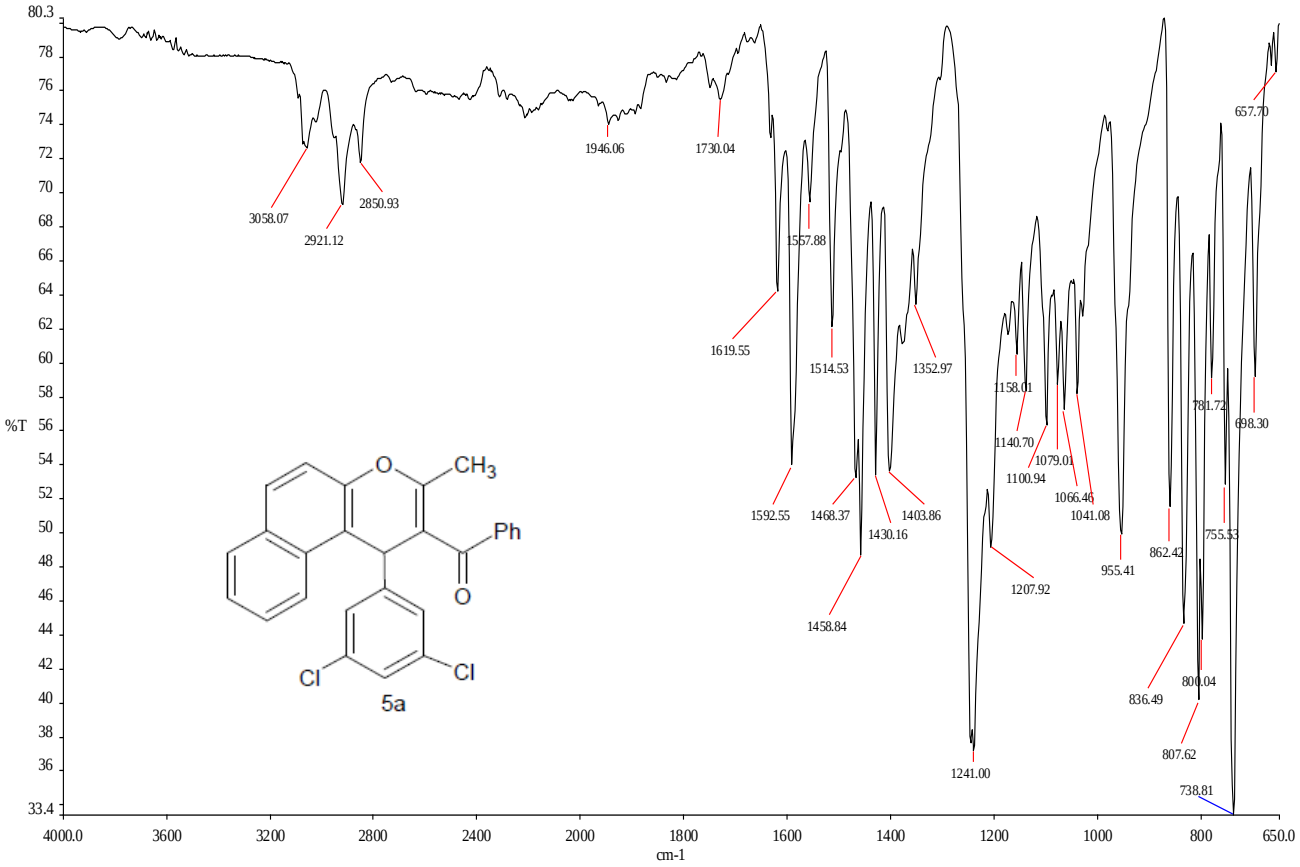


Fig 4.3 FTIR spectrum of compound 5a

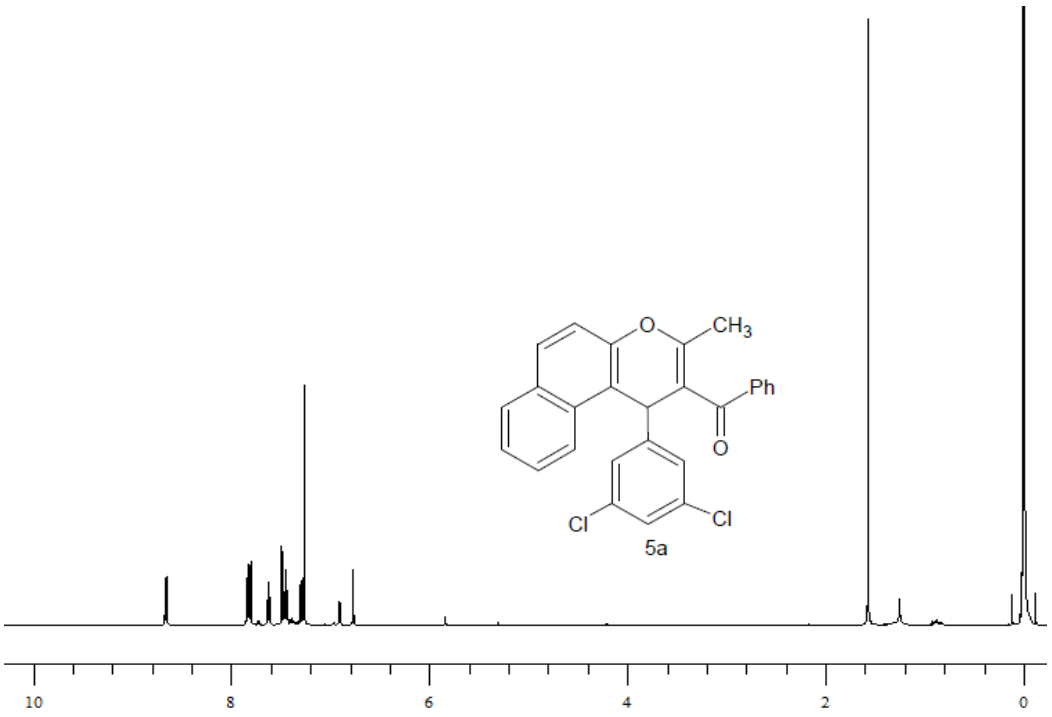


Fig 4.4 ^{1}H NMR spectrum of compound 5a

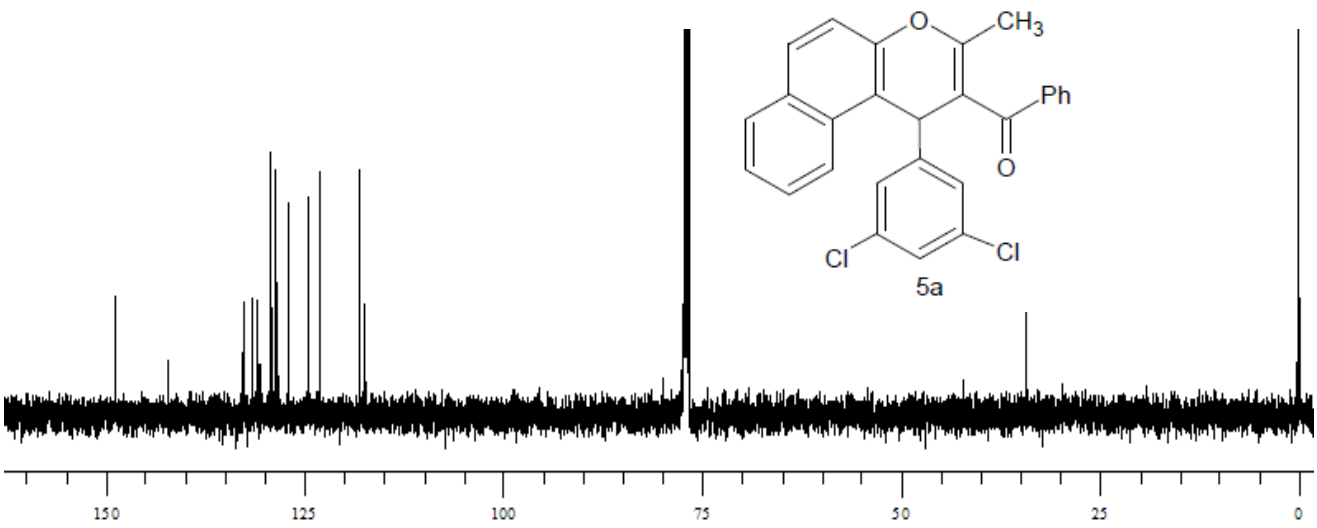


Fig 4.5 ^{13}C NMR spectrum of compound 5a

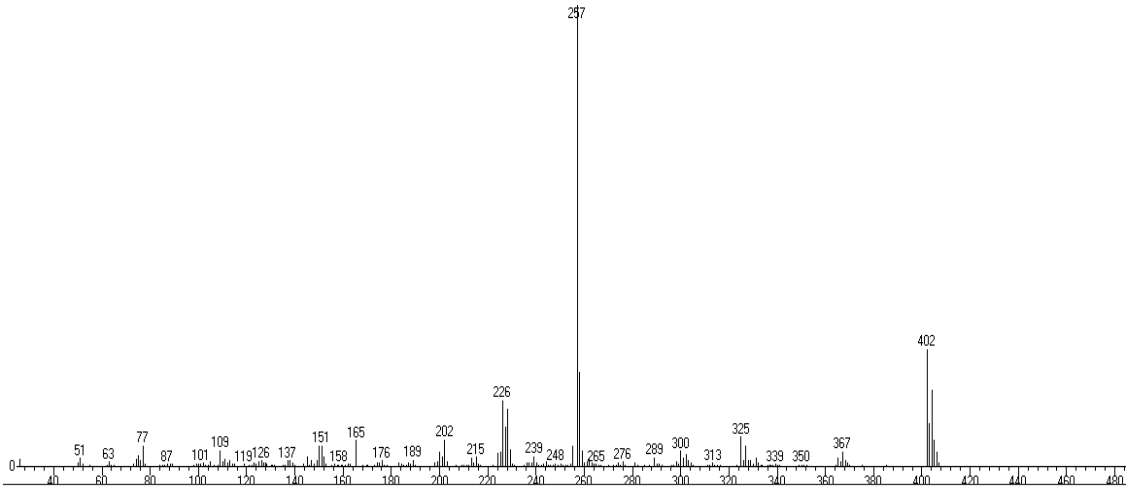


Fig 4.6 GC/MS spectrum of compound 5a

4.3.2 Compound 5b ($C_{27}H_{19}ClO_2$)

(1-(4-chlorophenyl)-3-methyl-1*H*-benzo[*f*]chromen-2-yl)(phenyl)methanone

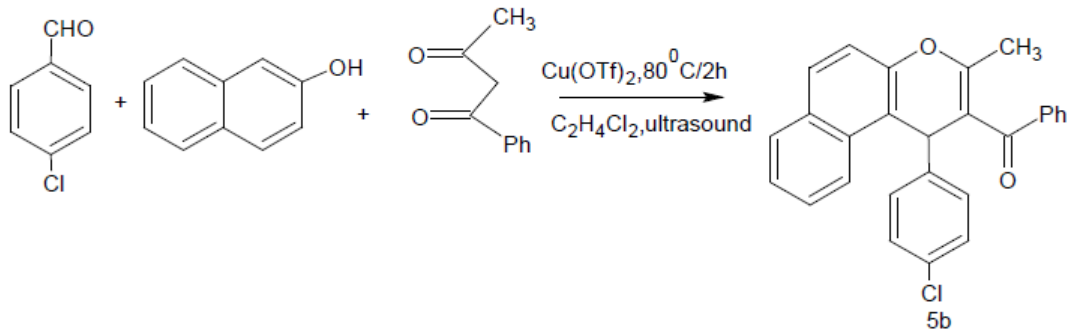


Fig 4.7 Preparation of compound 5b

Eluents mixture: 1hexane/ 1 dichloromethane

White crystal, melting point: 281-282^{0}C

Analytical Data:

FTIR $\gamma_{max/cm}^{-1}$: 3067, 2919, 1739, 1592, 1486, 1231, 1083, 806, 741.

^{1}H NMR (500MHz, $CDCl_3$): δ (ppm) 1.47 (3H, s, CH), 6.40 (1H, s, CH), 7.07-7.11(2H, d, *J* = 2.5Hz), 7.39-7.48 (5H, m, Ar-H), 7.54-7.60 (3H, m, Ar-H), 7.73-7.85 (4H, M, Ar-H), 8.28-8.31 (1H, d, *J* = 8.59Hz).

^{13}C NMR (100MHz, $CDCl_3$): δ (ppm) 37.34, 38.55, 116.71, 117.99, 122.37, 123.37, 124.34, 124.69, 126.65, 126.88, 127.35,128.35, 128.49, 128.61, 128.88, 128.96, 128.99, 129.06, 129.46, 131.01, 131.01, 131.21, 132.05, 143.43, 148.65.

M^+ (m/z) = 410

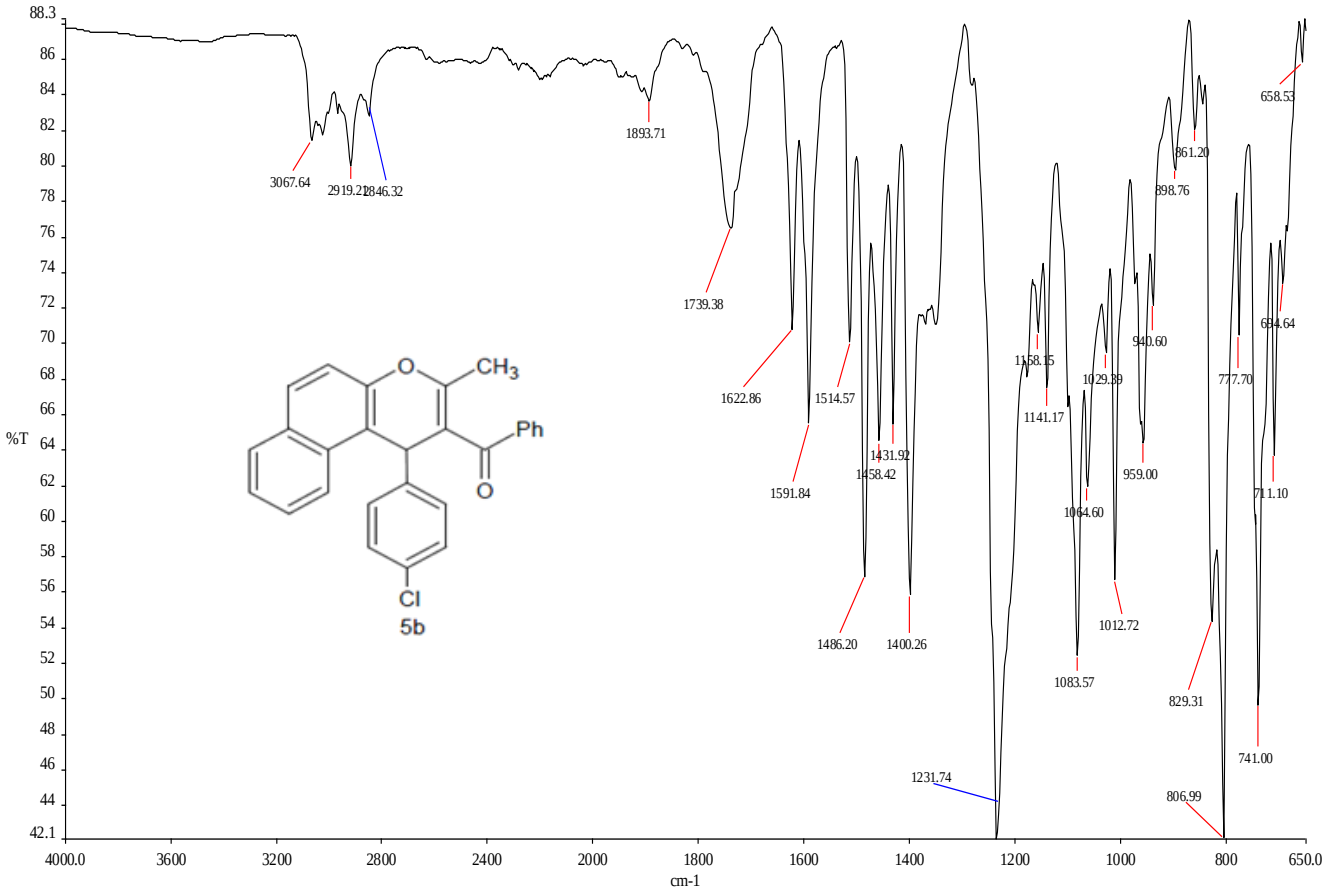


Fig 4.8 FTIR spectrum of compound 5b

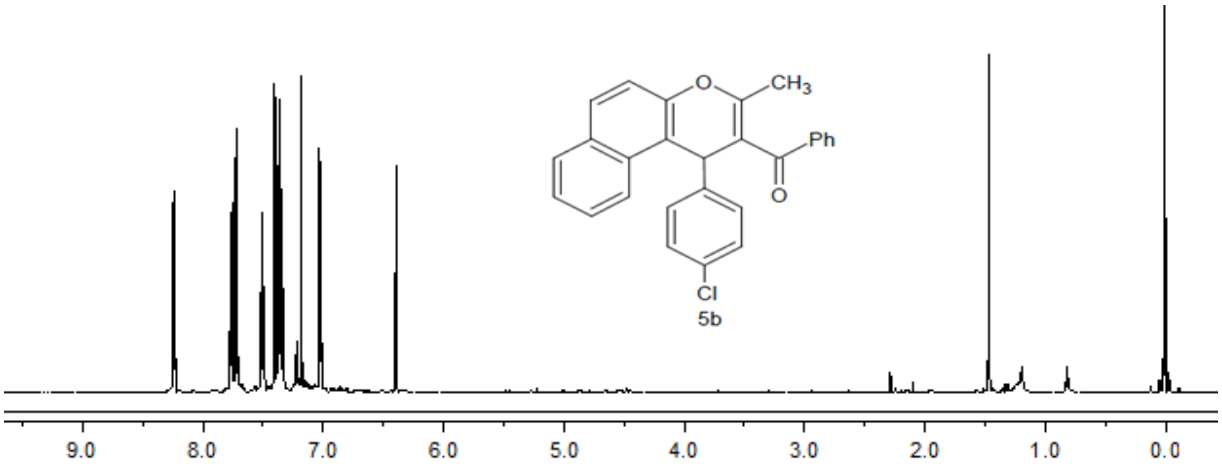


Fig 4.9 ^{1}H NMR Spectrum of compound 5b

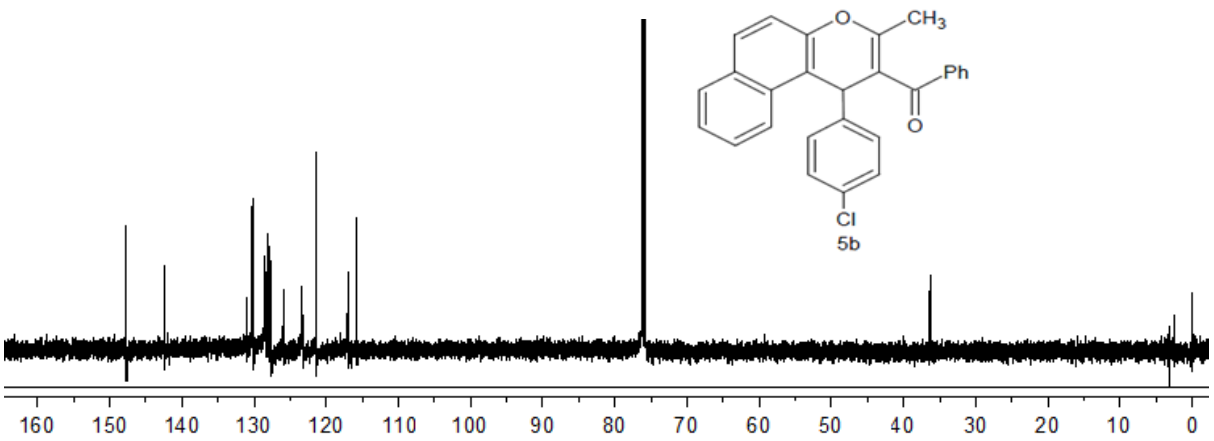


Fig 4.10 ^{13}C NMR Spectrum of compound 5b

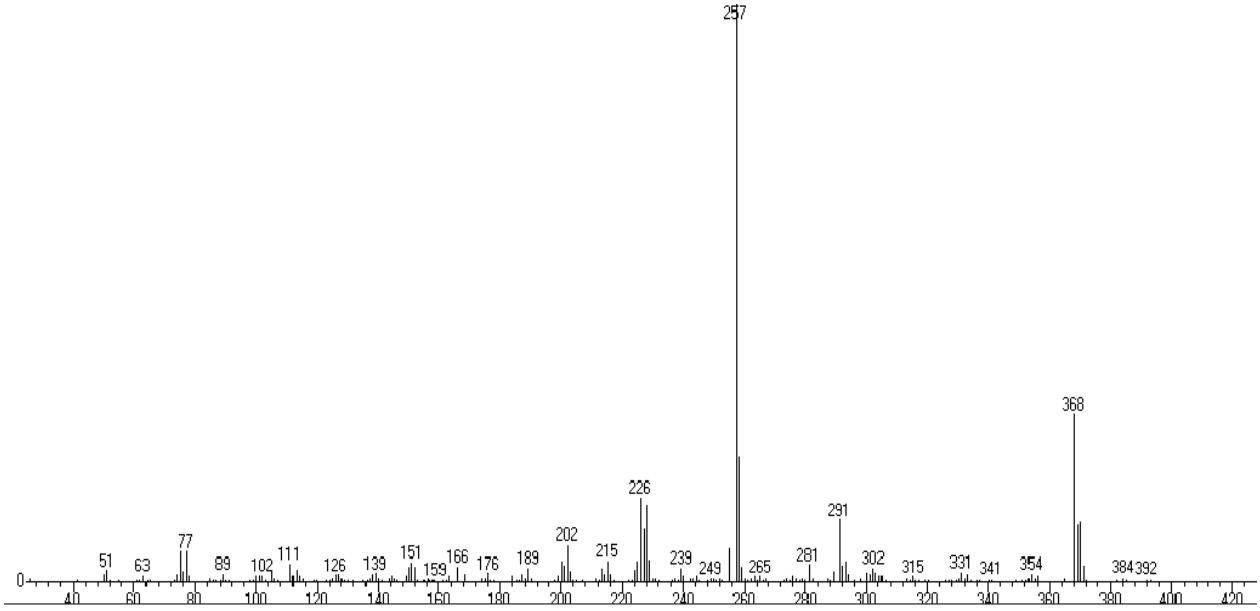


Fig 4.11 GC/MS Spectrum of compound 5b

4.3.3 Compound 5c ($C_{27}H_{19}NO_4$)

(3-methyl-1-(4-nitrophenyl)-1*H*-benzo[*f*]chromen-2-yl)(phenyl)methanone

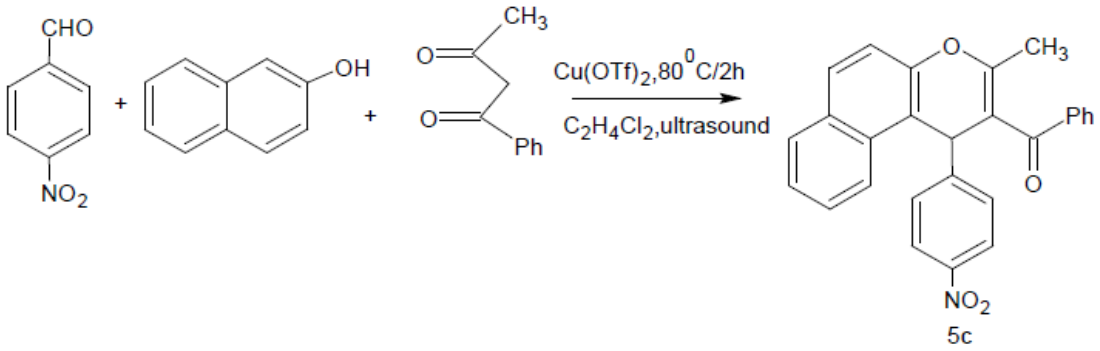


Fig 4.12 Preparation of compound 5c

Eluents mixture: 1 hexane/ 2 dichloromethane

Yellow crystal, melting point: 317.5-318.5^{0}C

Analytical Data:

FTIR $\gamma_{max/cm}^{-1}$: 3064, 2927, 1726, 1590, 1507, 1399, 1236, 1106, 825, 740.

^{1}H NMR (500MHz, $CDCl_3$): δ (ppm) 1.47 (3H, s, CH), 6.51 (1H, s, CH), 7.41-7.48 (3H, m, Ar-H), 7.50-7.52(2H, d, *J* = 8.90Hz), 7.58-7.62 (3H, m, Ar-H), 7.67-7.71 (2H, d, *J* = 8.80Hz), 7.82-7.88 (3H, m, Ar-H), 7.98-8.02 (2H, d, *J* = 8.80Hz).

^{3}C NMR (100MHz, $CDCl_3$): δ (ppm) 38.04, 43.56, 111.78, 114.72, 116.72, 117.04, 120.98, 122.83, 123.25, 123.77, 126.16, 127.35, 127.88, 128.04, 128.52, 128.56, 130.02, 130.04, 130.22, 132.41, 145.26, 146.68, 147.74, 148.57, 150.95, 152.34,189.71.

M^+ (m/z) = 421.

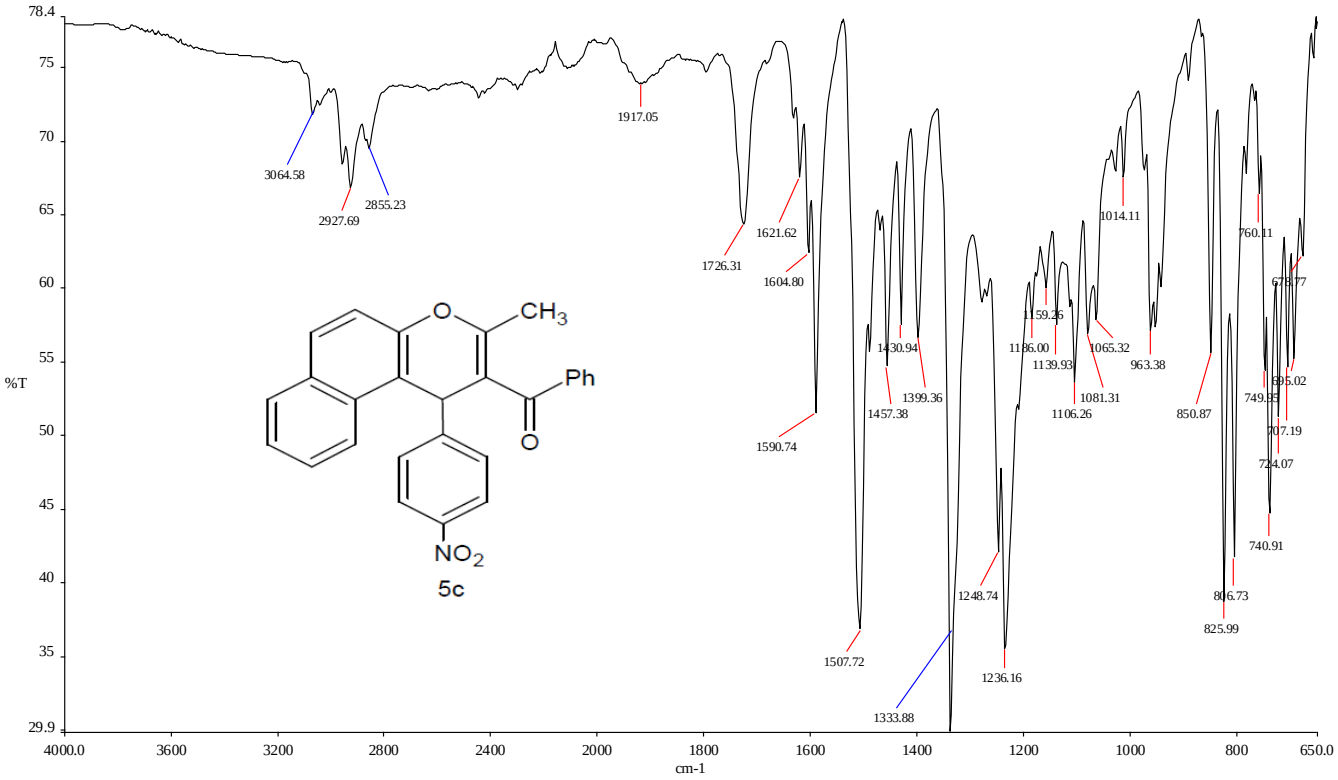


Fig 4.13 FTIR spectrum of compound 5c

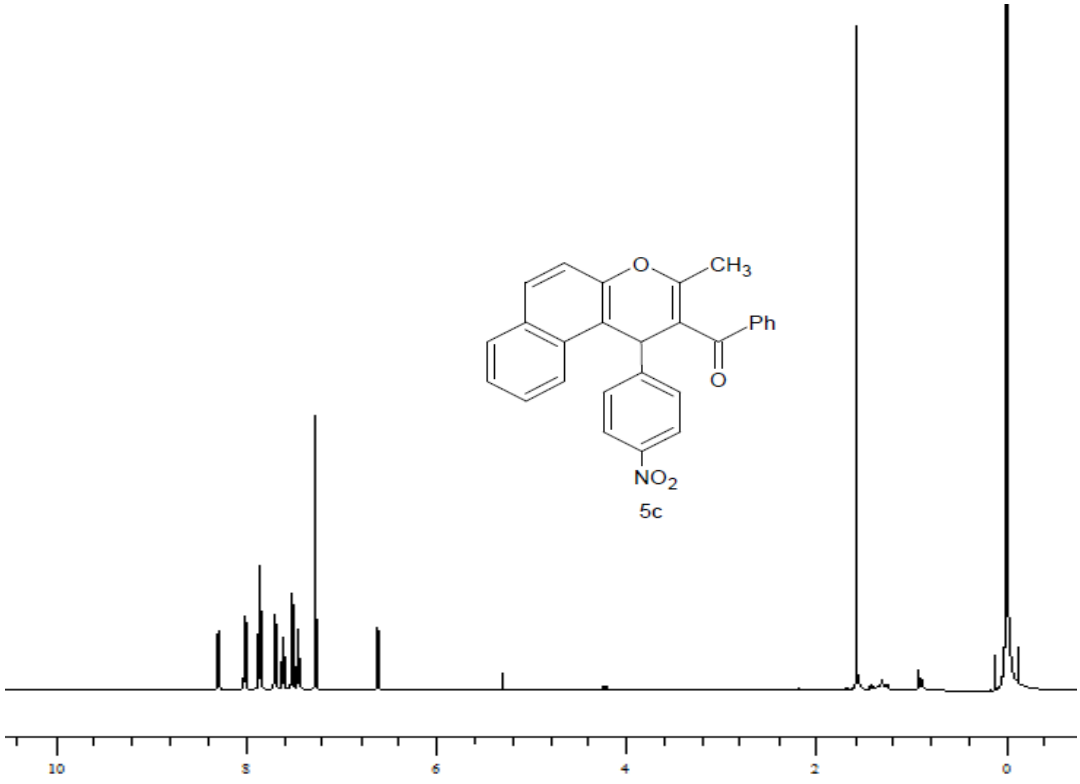


Fig 4.14 ^{1}H NMR spectrum of compound 5c

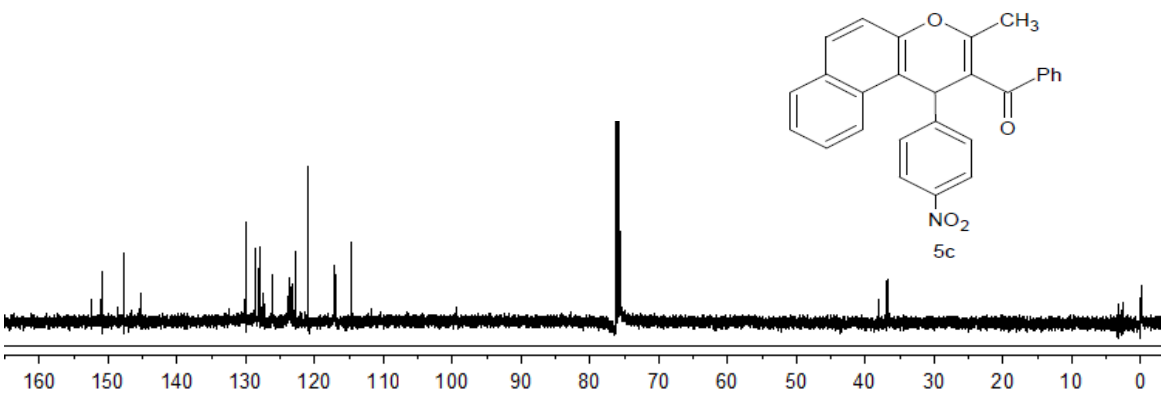


Fig 4.15 ^{13}C NMR spectrum of compound 5c

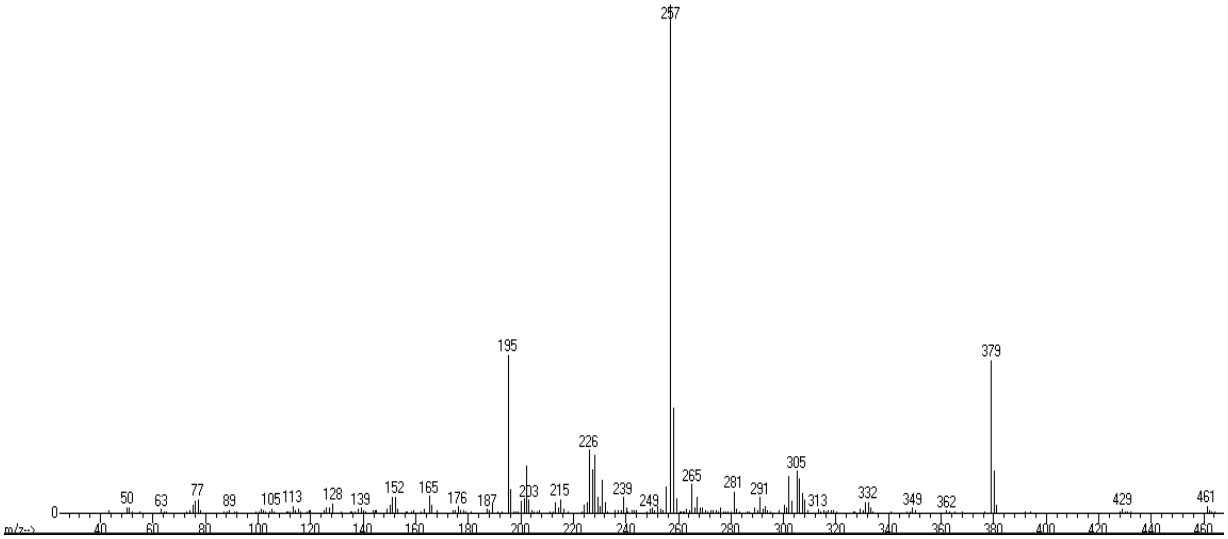


Fig 4.16 GC/MS spectrum of compound 5c

4.3.4 Compound 6a ($C_{32}H_{22}O_2$)

(1, 3-diphenyl-1*H*-benzo[*f*]chromen-2-yl)(phenyl)methanone

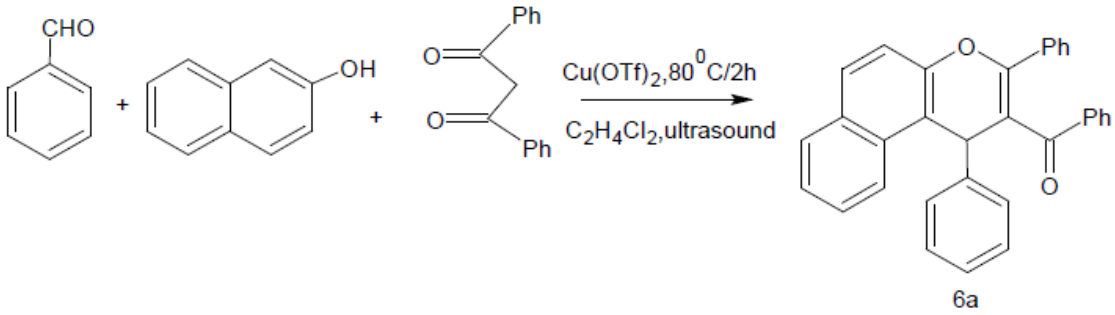


Fig 4.17 Preparation of compound 6a

Eluents mixture: 3 hexane/ 2 dichloromethane

White crystals, melting point: 191^0C

Analytical Data:

FTIR $\gamma_{max/cm}^{-1}$: 3055, 2874, 1664, 1596, 1445, 1330, 1224, 813, 728.

^{1}H NMR (500MHz, $CDCl_3$): δ (ppm) 5.82 (1H, s, CH), 6.90-6.97 (2H, m, Ar-H), 6.99-7.10 (4H, m, Ar-H), 7.12-7.15 (4H, m, Ar-H), 7.28-7.33 (4H, m, Ar-H), 7.33-7.39 (5H, m, Ar-H), 7.73-7.75 (1H, d, *J* = 8.3 Hz), 7.84-7.88 (1H, d, *J* = 8.30Hz).

^{3}C NMR (100MHz, $CDCl_3$): δ (ppm) 40.32, 114.40, 115.34, 116.33, 122.52, 123.64, 125.64, 125.94, 126.15, 126.62, 126.85, 127.05, 127.45, 127.61, 127.66, 127.97, 128.05, 128.18, 128.63, 130.17, 130.37, 130.72, 131.43, 132.79, 137.58, 143.53, 147.71, 153.25, 196.99.

M^+ (m/z) = 438

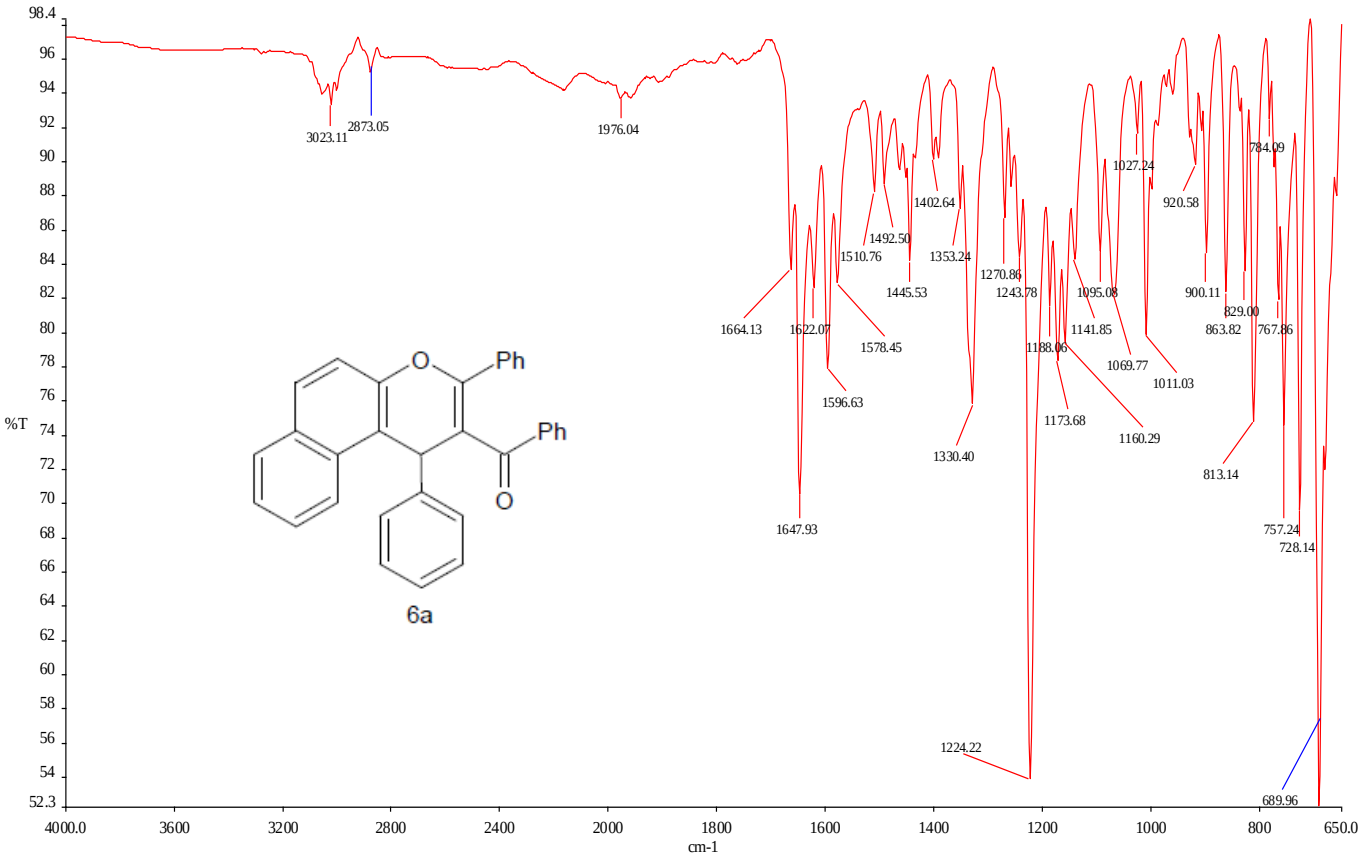


Fig 4.18 FTIR spectrum of 6a

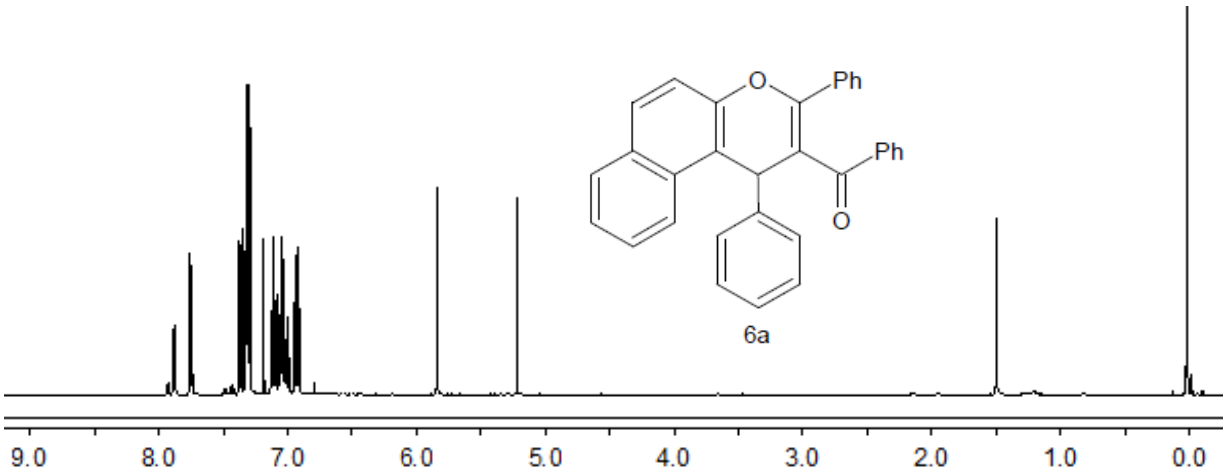


Fig 4.19 ^{1}H NMR spectrum of 6a

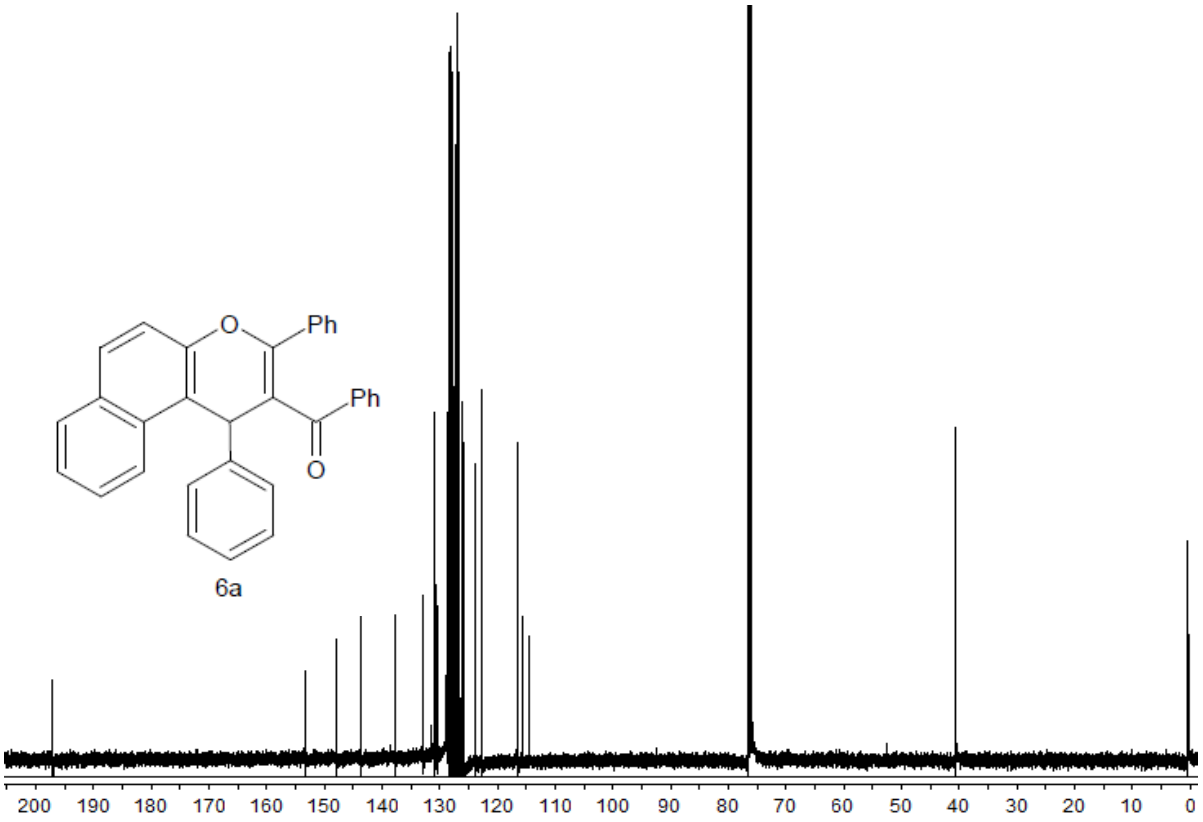


Fig 4.20 ^{13}C NMR spectrum of compound 6a

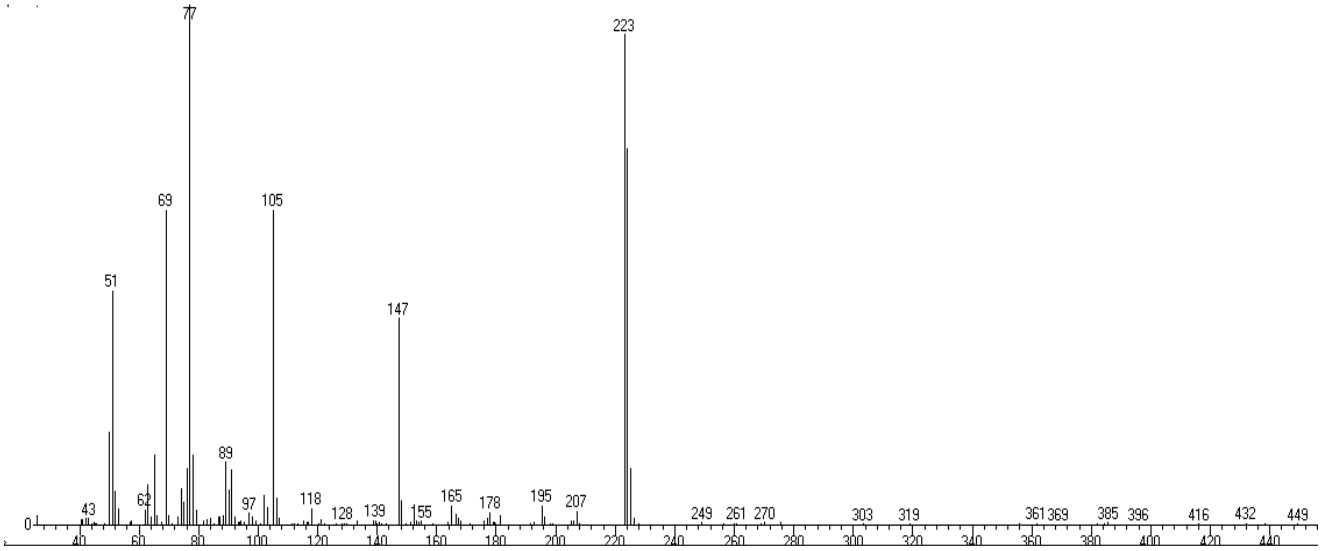


Fig 4.21 GC/MS spectrum of compound 6a

4.3.5 Compound 6b ($C_{32}H_{21}ClO_2$)

(1-(4-chlorophenyl)-3-phenyl-1*H*-benzo[*f*]chromen-2-yl)(phenyl)methanone

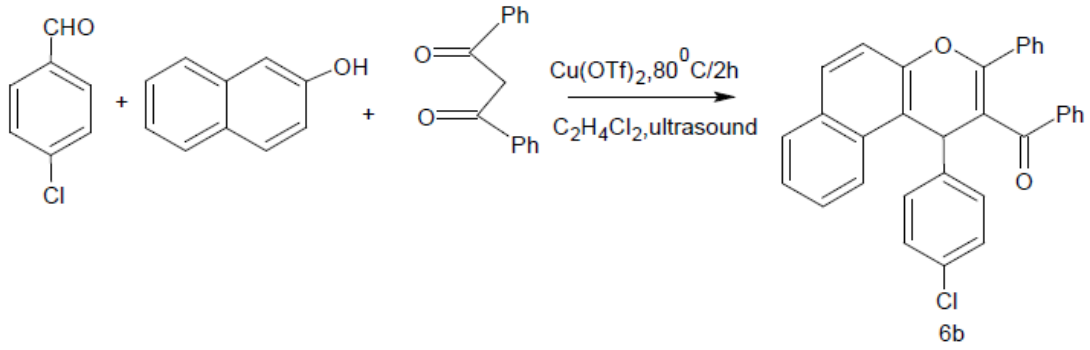


Fig 4.22 Preparation of compound 6b

Eluents mixture: 2 hexane/ 1 dichloromethane

White crystals, melting point:

Analytical Data:

FTIR $\gamma_{max/cm}^{-1}$: 3055, 2958, 1723, 1628, 1590, 1486, 1270, 1222, 1073, 729.

^{1}H NMR (500MHz, $CDCl_3$): δ (ppm) 5.80 (1H, s, CH), 6.98-7.04 (3H, m, Ar-H), 7.08-7.18 (6H, m, Ar-H), 7.23-7.26 (2H, d, *J* = 8. 45Hz), 7.31-7.51 (6H, m, Ar-H), 7.81-7.85 (2H, d, *J* = 8.75Hz), 7.87-7.91 (2H, d, *J* = 8.35Hz).

^{3}C NMR (100MHz, $CDCl_3$): δ (ppm) 40.52, 114.70, 116.09, 117.33, 123.25, 124.84, 127.11, 127.16, 127.75, 127.92, 128.22, 128.60, 128.68, 128.78, 129.05, 129.23, 129.45, 129.90, 130.94, 131.41, 131.85, 132.37, 132.46, 133.60, 135.51, 138.49, 143.22, 148.63, 155.43, 185.76.

M^+ (m/z) = 472

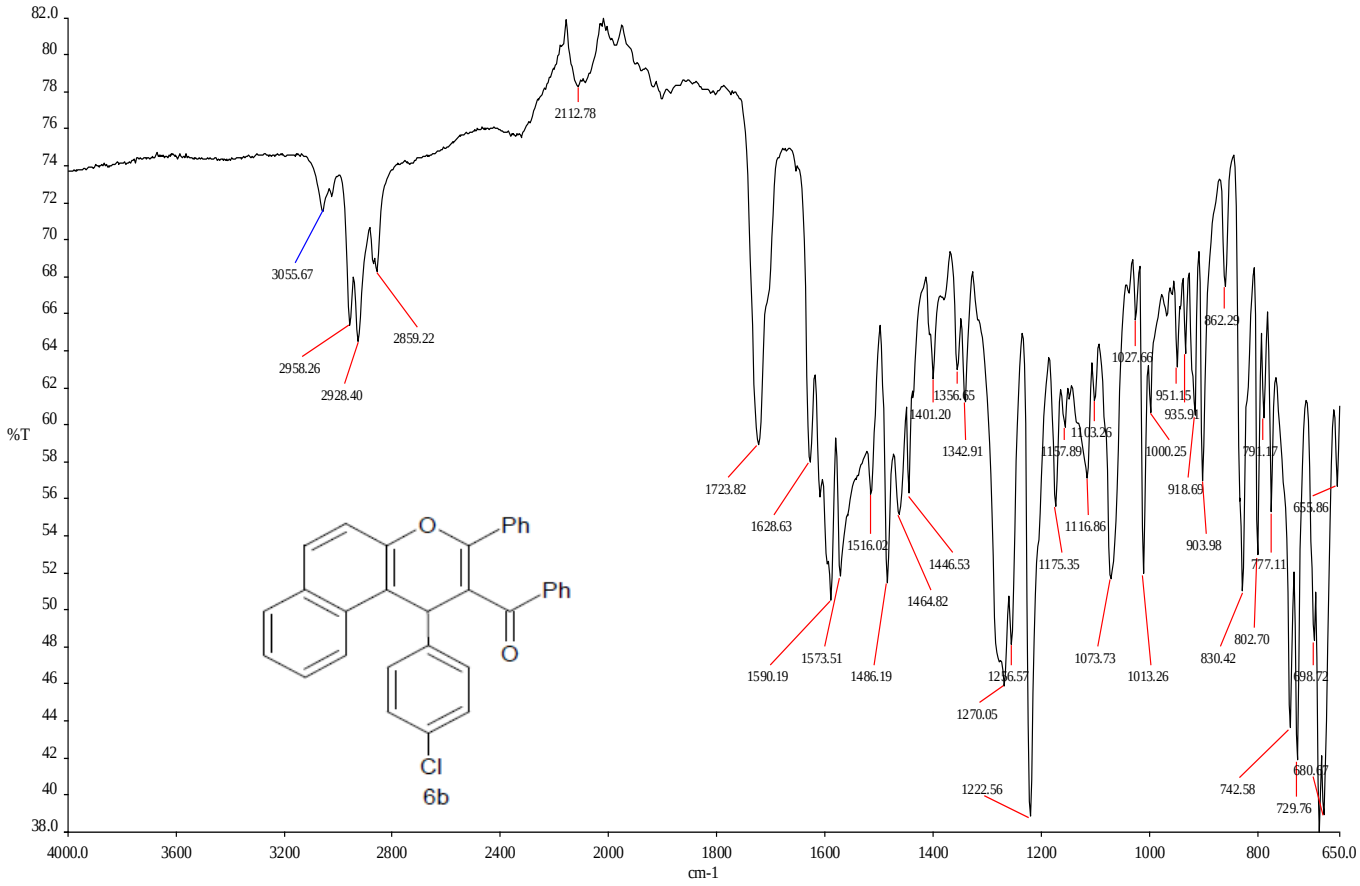


Fig 4.23 FTIR spectrum of compound 6b

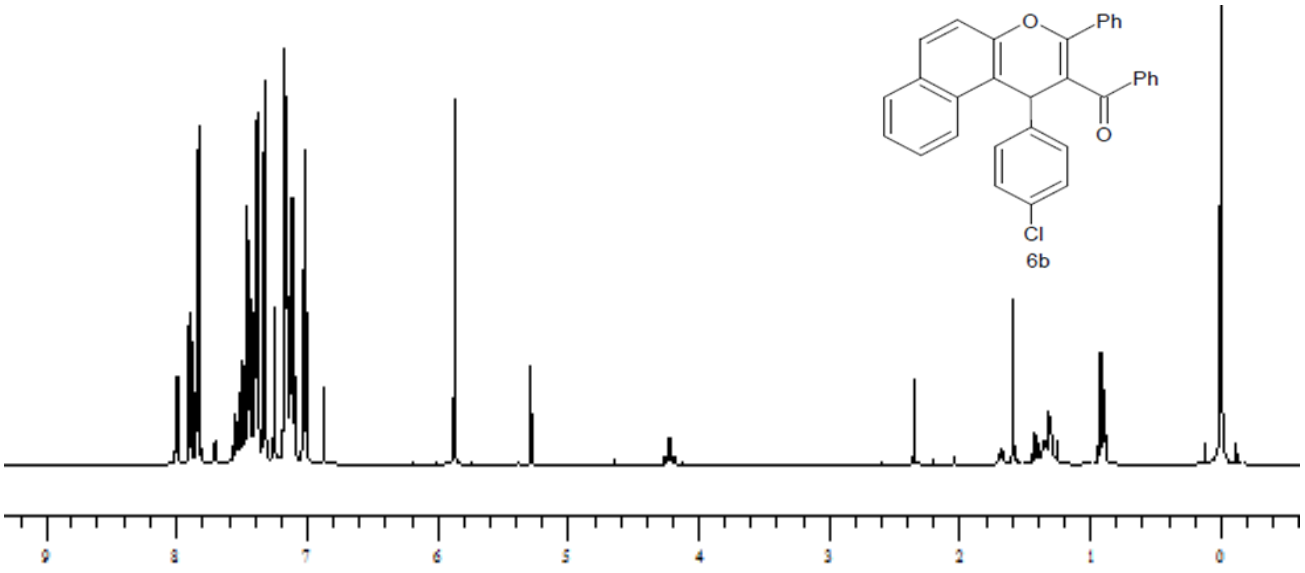


Fig 4.24 ^{1}H NMR spectrum of compound 6b

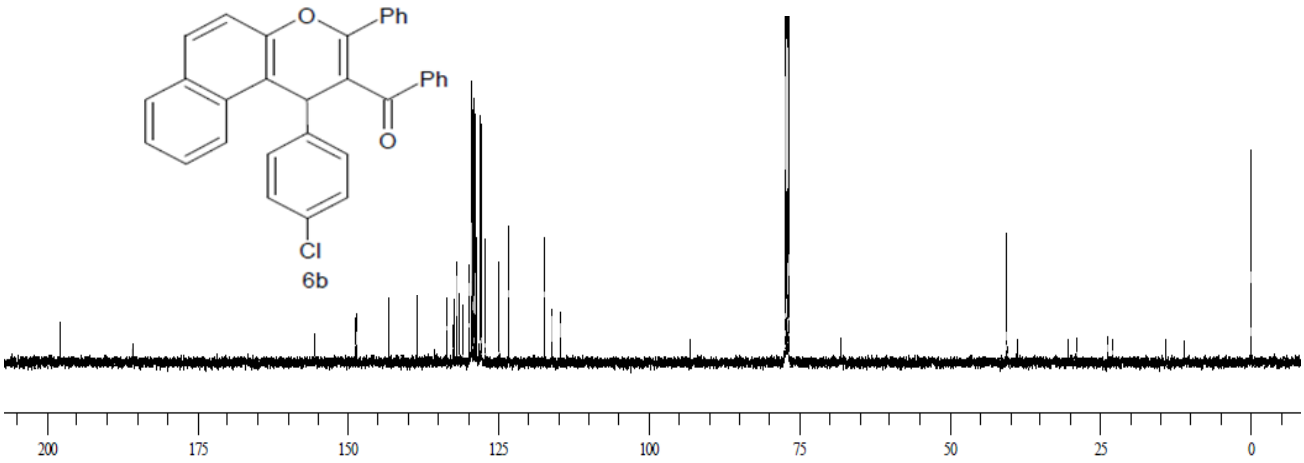


Fig 4.25 ^{13}C NMR spectrum of compound 6b

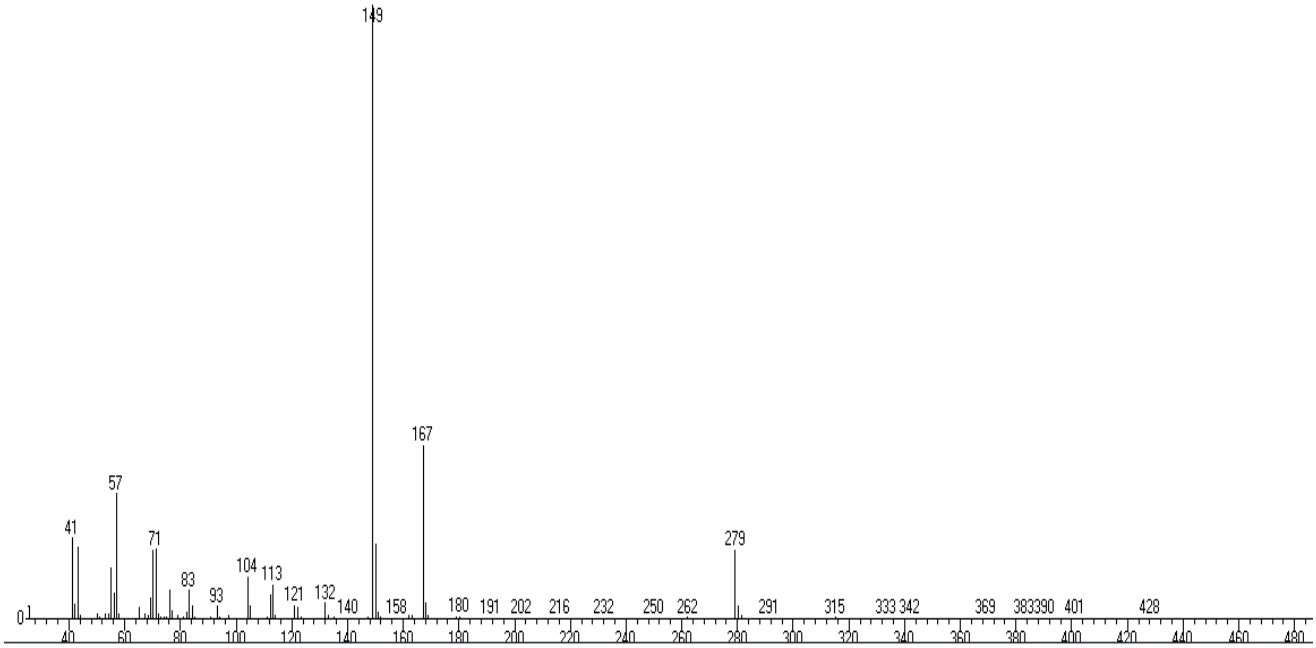


Fig 4.26 GC/MS spectrum of compound 6b

4.3.6 Compound 6c ($C_{32}H_{24}O_2$)

(1-(4-methylphenyl)-3-phenyl-1*H*-benzo[*f*]chromen-2-yl)(phenyl)methanone

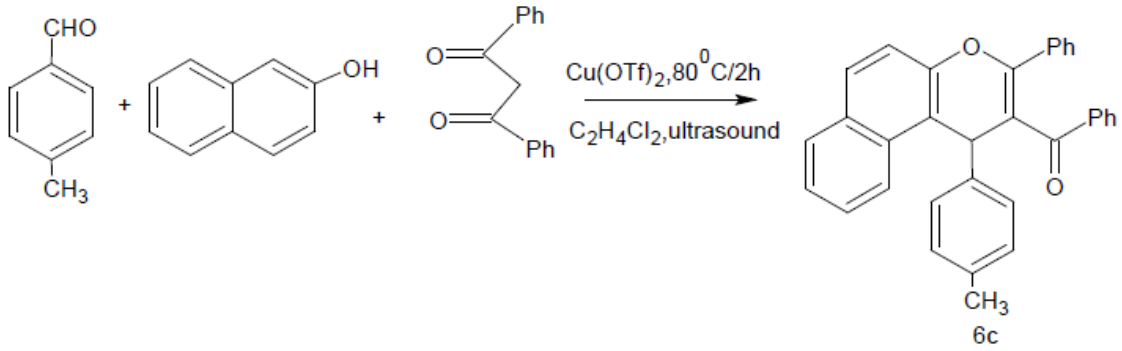


Fig 4.27 Preparation of compound 6c

Eluents mixture: 2 hexane/ 1 dichloromethane

White crystals, melting point: 171.5^0C

Analytical Data:

FTIR $\gamma_{max/cm}^{-1}$: 3022, 2940, 1738, 1631, 1589, 1508, 1343, 1222, 903, 803.

^{1}H NMR (500MHz, $CDCl_3$): δ (ppm) 2.11 (3H, s, CH), 5.81 (1H, s, CH), 6.89-6.95 (5H, m, Ar-H), 7.02-7.11 (4H, m, Ar-H), 7.15-7.20 (2H, m, Ar-H), 7.29-7.38 (5H, m, Ar-H), 7.71-7.74 (4H, m, Ar-H).

^{13}C NMR (100MHz, $CDCl_3$): δ (ppm) 19.97, 39.86, 114.51, 115.66, 116.33, 122.48, 123.61, 125.91, 126.15, 126.63, 26.83, 126.91, 127.44, 127.66, 127.84, 128.11, 128.23, 128.31, 128.61, 130.17, 130.37, 130.68, 132.84, 135.11, 137.62, 140.67, 147.61, 153.42, 196.92.

M^+ (m/z) = 452.

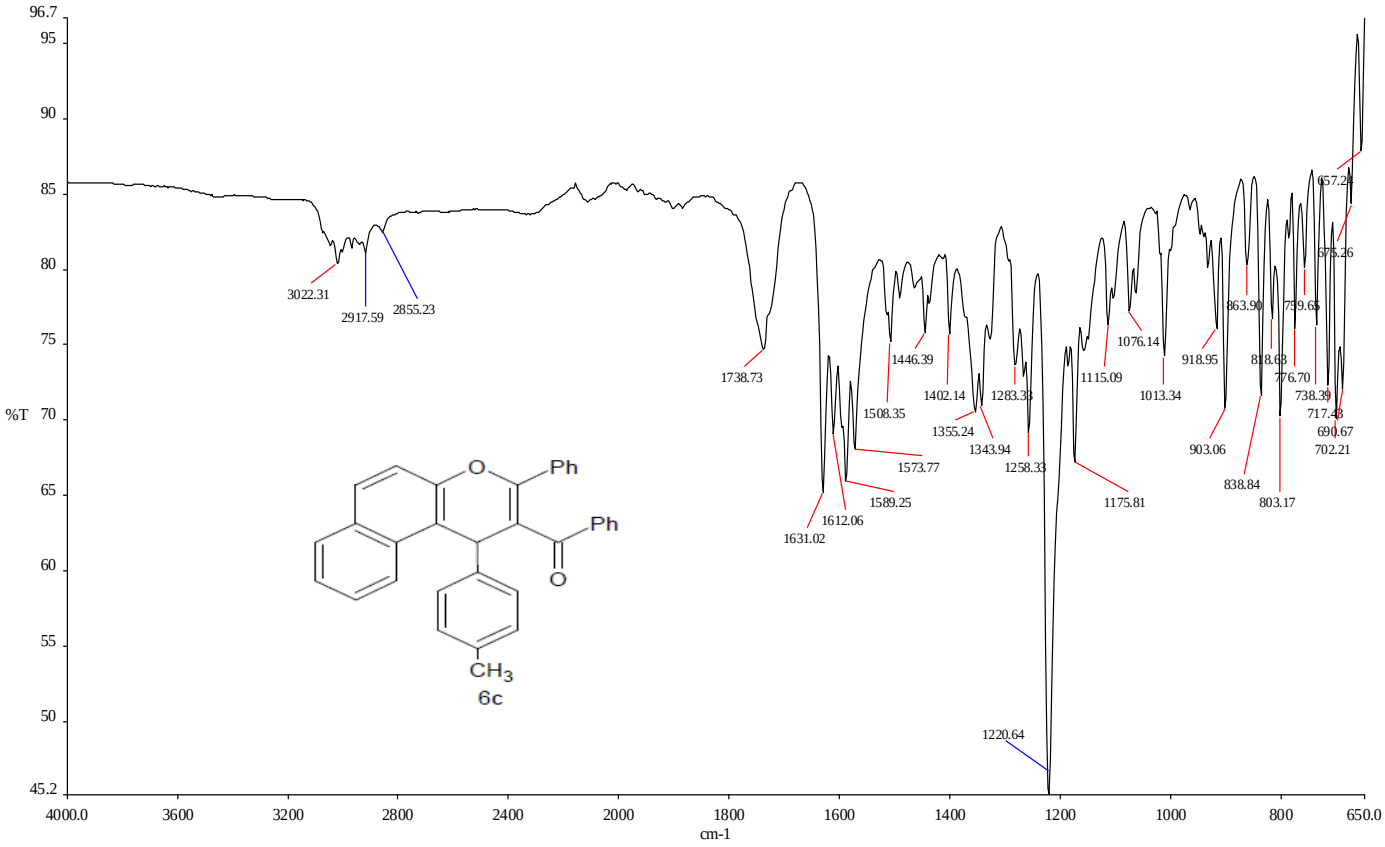


Fig 4.28 FTIR spectrum of compound 6c

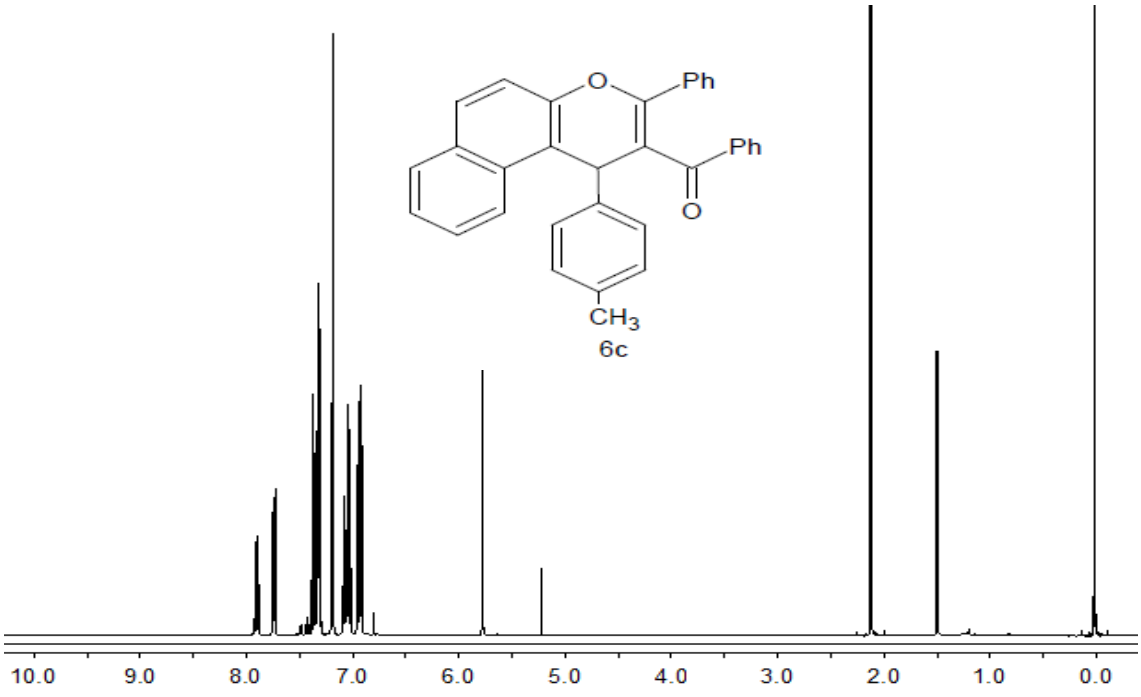


Fig 4.29 ^{1}H NMR spectrum of compound 6c

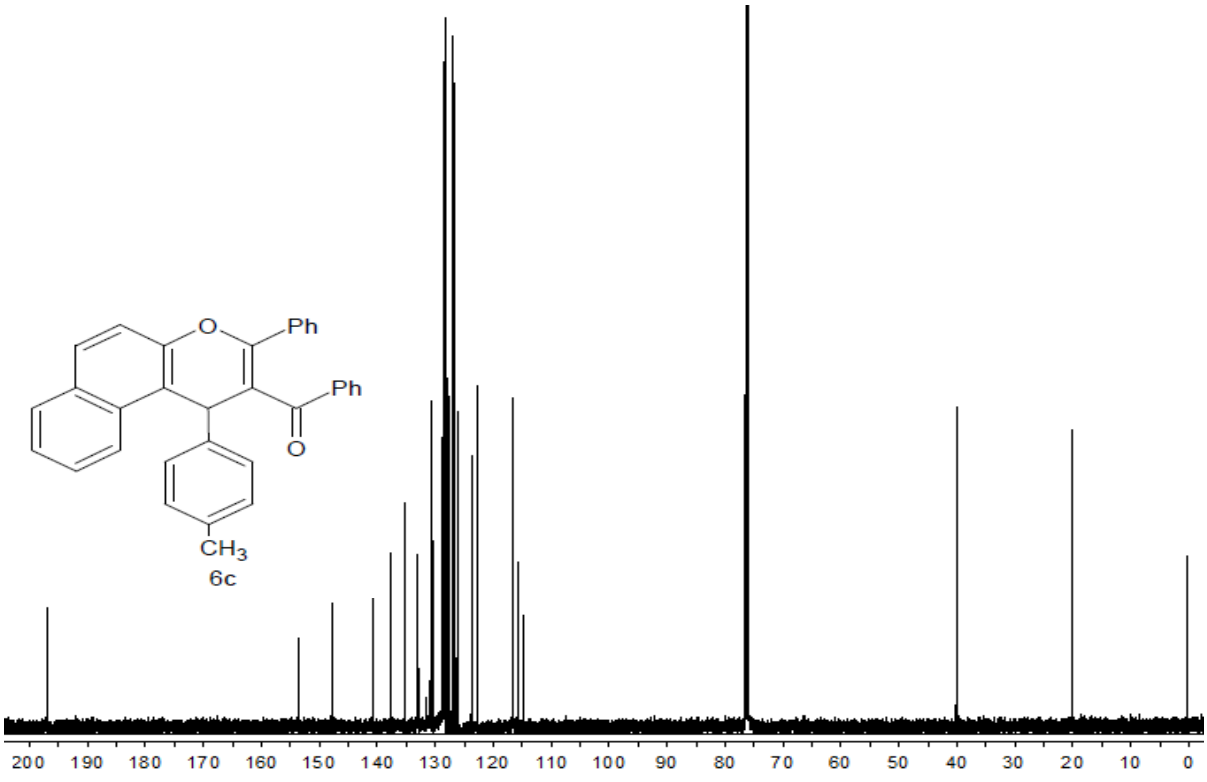


Fig 4.30 ^{13}C NMR spectrum of compound 6c

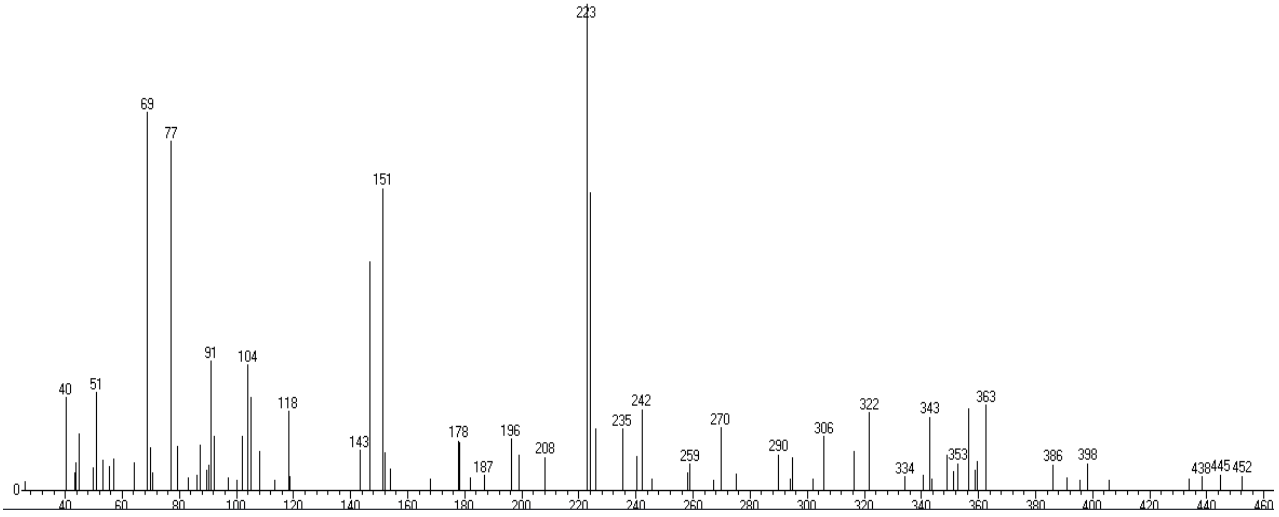


Fig 4.31 GC/MS spectrum of compound 6c

4.3.7 Compound 6d ($C_{32}H_{20}Cl_2O_2$)

(1-(3, 5-dichlorophenyl)-3-phenyl-1*H*- benzo[*f*]chromen-2-yl)(phenyl)methanone

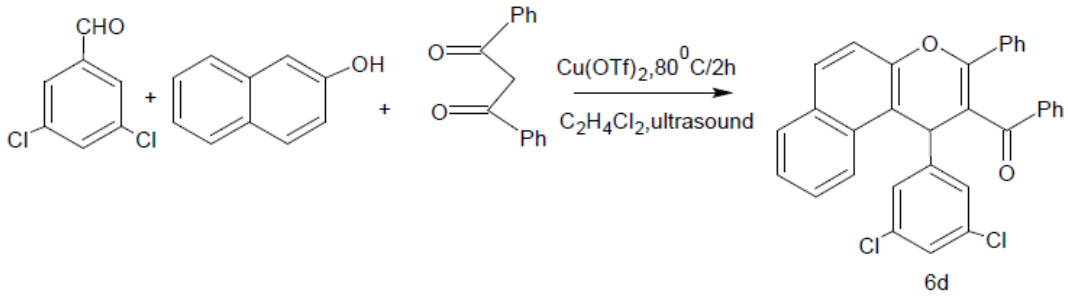


Fig 4.32 Preparation of compound 6d

Eluents mixture: 2hexane/ 1 dichloromethane

White crystals, melting point: 174.5^{0}C

Analytical Data:

FTIR $\gamma_{max/cm}^{-1}$: 3058, 2924, 1729, 1619, 1592, 1459, 1247, 959, 807.

^{1}H NMR (500MHz, $CDCl_3$): δ (ppm) 6.78 (1H, s, CH), 6.89-6.92 (2H, m, Ar-H), 7.23-7.32 (4H, m, Ar-H), 7.41-7.50 (5H, m, Ar-H), 7.61- 7.64 (3H, m, Ar-H), 7.78-7.87 (5H, m, Ar-H).

^{13}C NMR (100MHz, $CDCl_3$): δ (ppm) 34.21, 117.46, 118.09, 123.11, 124.55, 127.04, 128.40, 128.75, 129.11, 129.28, 130.56, 130.88, 131.56, 132.68, 132.78, 142.21, 148.90, 190.19.

M^+ (m/z) = 507

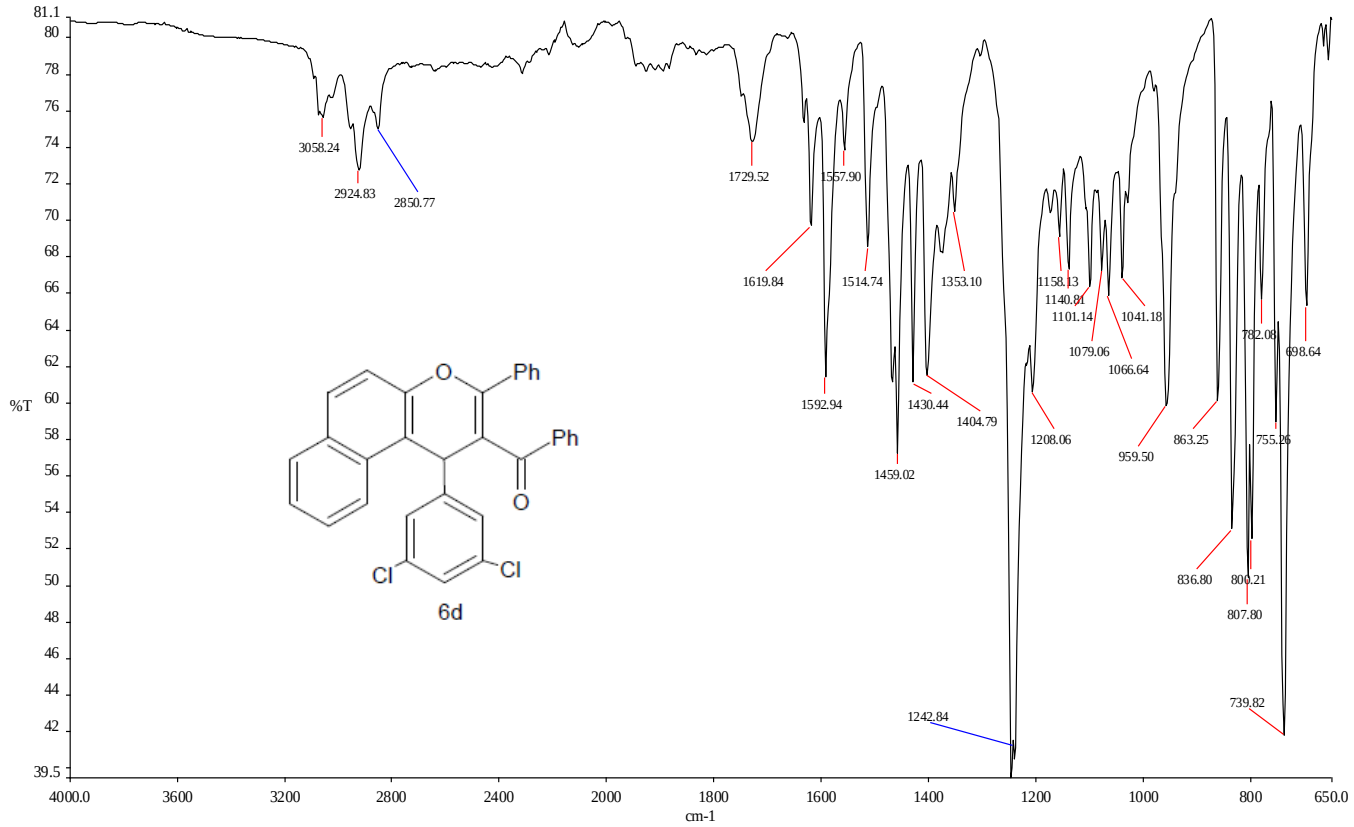


Fig 4.33 FTIR spectrum of compound 6d

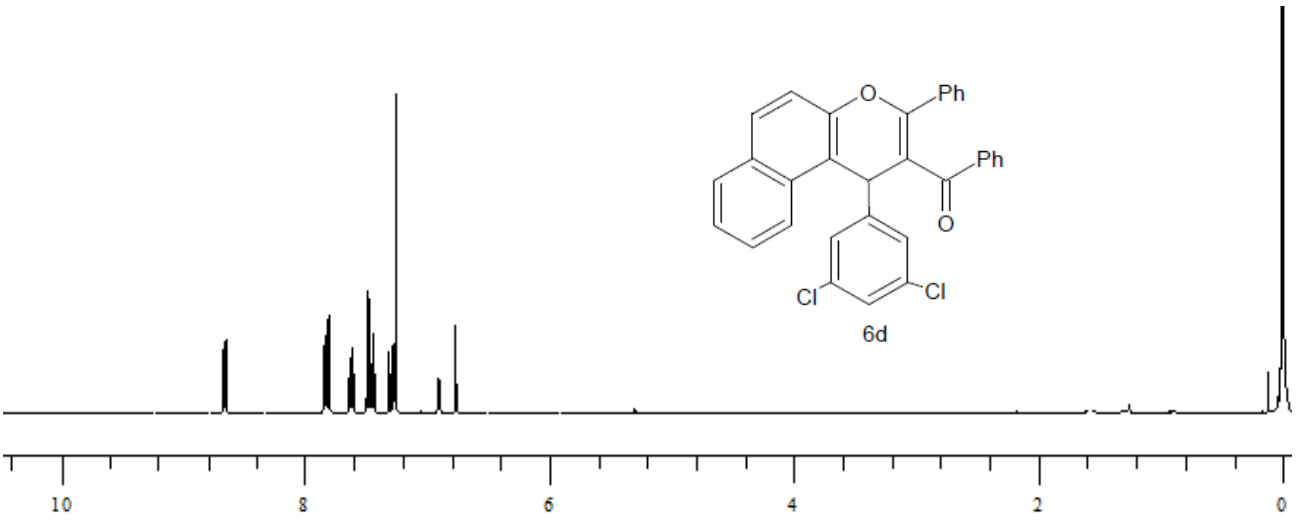


Fig 4.34 ^{1}H NMR spectrum of compound 6d

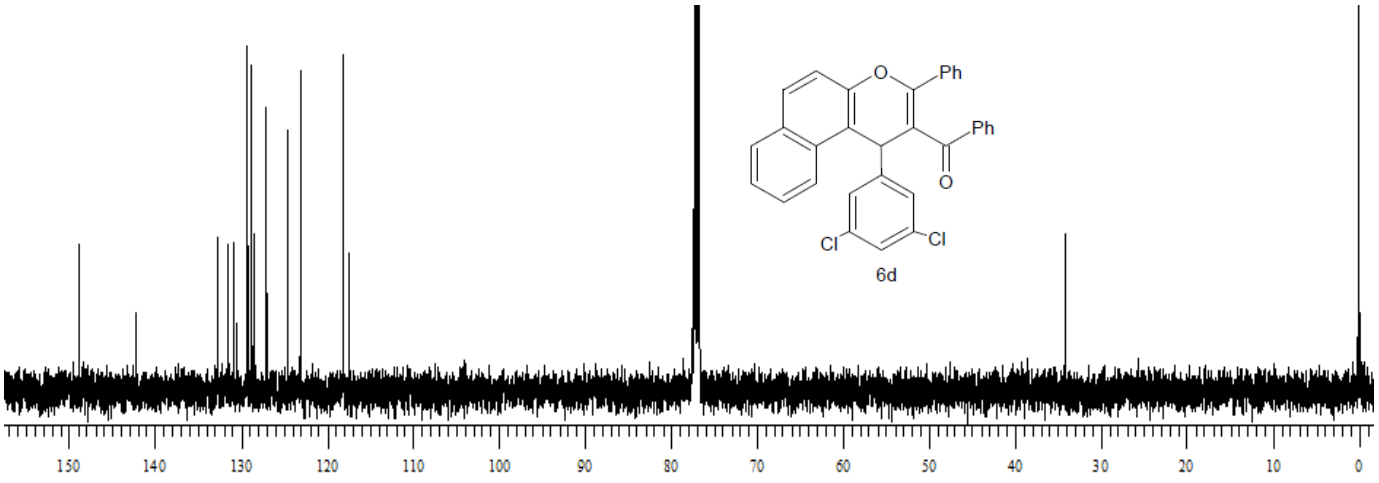


Fig 4.35 ^{13}C NMR spectrum of compound 6d

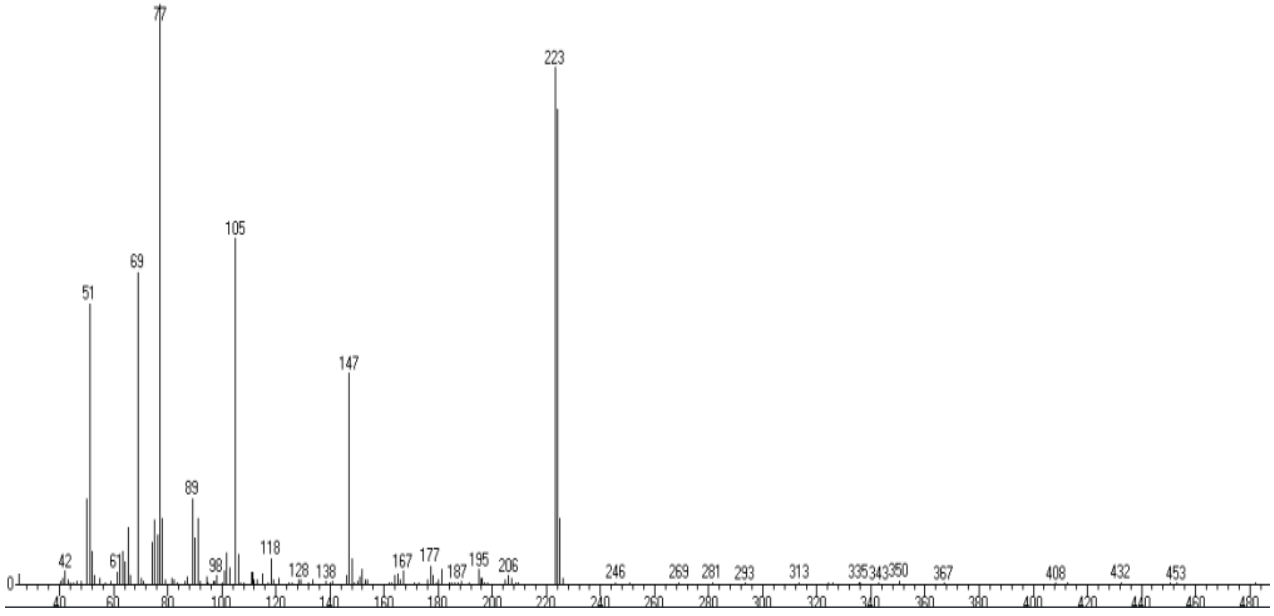


Fig 4.36 GC/MS spectrum of compound 6d

CHAPTER 5

DISCUSSION AND CONCLUSION

Various routes are available in literatures to synthesis naphthopyran derivatives including trapping of benzynes by phenols, phenyl–carbonyl coupling reactions of benzaldehydes and acetophenones, cyclization of polycyclic aryltriflate esters, annulation of arynes by salicylaldehydes, cyclo condensation between 2-hydroxy aromatic aldehydes and 2-teralone and a cascade benzylation-cyclization process. In addition, 14*H*-dibenzo[*a*,*j*]xanthenes and related products are prepared by the reaction of β-naphthol with formamide, 2-naphthol-1-methanol and carbon monoxide [47].

Recently, several improved procedures were reported including one-pot reaction of β -naphthol, 1, 3-dicarbonyl compounds and aldehydes under various conditions for the synthesis of benzoxanthenes and related compounds. One-pot reaction (multi-component method) has been became one of the most important aspects in Organic Chemistry. On other hand, Ultrasonic-assisted organic synthesis(UAOS) as a green synthetic approach is a powerful techqinue that is being used to acelerate organic reactions. Rare earth metal triflates, a new type of lewis acid were widely applied in organic synthesis as catalysts due to their low toxicity, high stability, ease of handling, water tolerance and recoverability from water.

In our initial research, the condensation reaction of β-naphthol, 1,3,-diones (benzoylacetone or 1, 3-diphenyl-1, 3-propandione) with substituted benzaldehyde was carried out in 1, 2-dichloroetane for 5h in reflux conditions in the presence of $Cu(OTf)_2$.

In order to show the effect of ultrasonic irradiation in these reactions, the synthesis of naphthopyran compounds were compared with the conventional heating ones. The experimental results show that the reaction times are shorter under ultrasound.

We obtained seven new compounds. In addition a by-product was characterized, 14-aryl-14*H*-dibenzo[*a*,*j*]xanthene (scheme 4.1). The results are shown in Table 4.1.

In all cases, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the products in moderate yields.

A tentative mechanism for the formation of derivatives 6 is prosed in scheme 5.1 by referring to the literature [20].

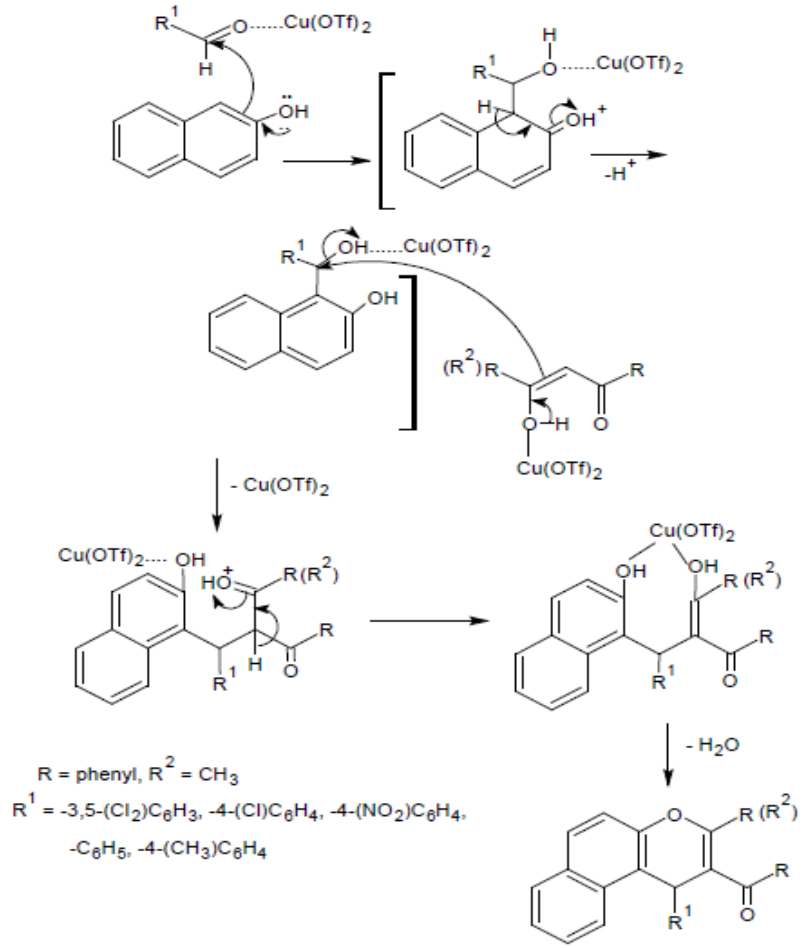
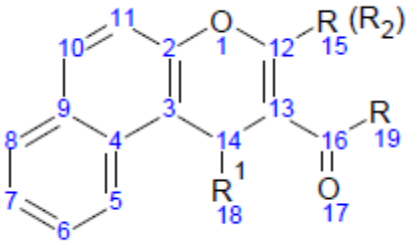


Fig 5.1 Proposed mechanism for the condensation reaction of aldehydes, 2-naphthol and 1, 3-diones.

The reaction may proceed via the ortho-quinone methides intermediate which was formed by the nucleophilic addition of 2-naphthol to aldehyde catalyzed with $Cu(OTf)_2$. Subsequent substitution of the oxygen atom, which was coordinated by cupper triflate, with 1, 3-dicarbonyl compounds. After one molecule of water eliminated, the product 5and 6 were obtained. The structures of the products have been clarified by FTIR, ^{1}H NMR, ^{13}C NMR and GC/MS spectral data.

The characteristic absorption bands of C=O (carbonyl) groups were observed at 1732-1729cm^{-1} in the FTIR spectra of the naphthopyran derivatives.



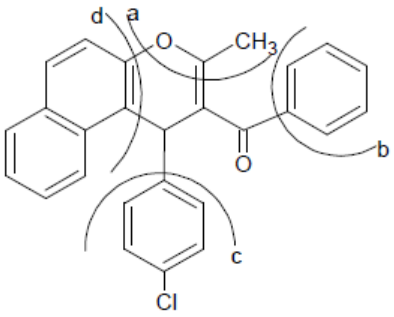
R = -phenyl,
R^1 = -3, 5-(Cl) C_6H_3, -p-(Cl) C_6H_4, -p-(NO_2) C_6H_4, -C_6H_5, -p-(CH_3) C_6H_4
R^2 = -CH_3, -phenyl

Fig 5.2 Naphthopyran

The ^{1}H and ^{13}C NMR spectra of (5 &6) proved that in $CDCl_3$ solution. All of the products exhibited a singlet in ^{1}H NMR spectra of δ= 5.80-6.78 ppm for H-14 on the ring of pyran and also a distinguishing peak at δ= 34.21-40.52 ppm for C-14 in their ^{13}C NMR spectra. The resonances of carbonyl groups (C-16) in the ^{13}C NMR spectra of compound 5 and 6 appeared at δ= 185.76-190.19 ppm.

The H-atoms of –CH_3 which belong to the compounds (5a-c) and 6c were observed in the ranges 1.47- 1.49 ppm and 2.11pm respectively. On the other hand, in all new compounds (5&6) signals belonging to aromatic protons vary between 6.89-7.91ppm.

The structures of the all compounds have also been confirmed by their GC-MS spectral data.



a=43, b=76, c=111, d=126

Fig 5.2 M/z of compound 5b

In summary, we have developed an efficient and mild method for the preparation of (1-substituted phenyl-3-methyl-1*H*-benzo[*f*]chromen-2-yl)(phenyl) methanones and (1-substituted phenyl-3-phenyl-1*H*-benzo[*f*]chromen-2-yl)(phenyl) methanones. This method is efficiently promoted by the $Cu(OTf)_2$. It is a recyclable catalyst.

In this study, we compared ultrasound method with conventional heating. The advantages of ultrasound method are short reaction times, simple work-up, and environmental friendly.

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Personal information

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Date of birth and place : 19/11/1984- Hossa'en

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Educational Background

level	**Area**	**School/University**	**Graduation year**
Master	Organic Chemistry	Yildiz Technical University	2012
Degree	Chemistry	Alemaya University	2006
High school	Natural Science	Wachamo High school	2002

Work Experience

Year	**Organization**	**Position**
2008-2009	Ministry of Education	Graduate assistant at Samara University
2006 -2008	Ministry of Education	High school teacher