SYNTHESIS OF NATURAL PRODUCTS-BASED ORGANIC ANTHRACENE SCAFFOLDS AND SOME OF THEIR ANTI-CANCER ACTIVITY

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BY

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I, **THECHANO MERRY**, hereby declare that the matter illustrated in this Thesis entitled **"SYNTHESIS OF NATURAL PRODUCTS-BASED ORGANIC ANTHRACENE SCAFFOLDS AND SOME OF THEIR ANTI-CANCER ACTIVITY"** submitted by me for the degree of Doctor of Philosophy in Chemistry is the result of investigations carried out by me in the Department of Chemistry, Nagaland University under the Supervision of **Dr. MADDELA PRABHAKAR**, Assistant Professor, Department of Chemistry, Nagaland University.

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******

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Thechano Merry

(THECHANO MERRY)

Ded icated

to

My brother Lt. Yanbemo Merry

My husband and

My Parents

Abbreviations

[3H] 8-OH-DPAT	[3H]-8-Hydroxy-2-(di-n-propylamino)tetralin
[3H] DAMGO	[3H]-[D-Ala^2, N-MePhe^4, Gly-ol]-enkephalin
[3H] FNZ	[3H]-Flunitrazepam
5-FU	Fluorouracil
A-549	Adenocarcinoma cell line
A549	Human Lung cancer cell line
AChE	Acetylcholinesterase
AcOH	Acetic acid
ADA	Adenosine Deaminase
ADP	Adenosine Diphosphate
AICAR	5-Aminoimidazole-4-carboxamide riboside
AIDS	Acquired Immunodeficiency
Al_2O_3	Aluminum oxide
AMPK	AMP-Activated Protein Kinase
ATCC	American Type Culture Collection
$Ba(OH)_2$	Barium hydroxide
BCRP	Breast Cancer Resistance Protein
C	Control growth
CA	Carbonic anhydrase
Ca9-22	Cellosaurus cell line
CHN	Carbon Hydrogen Nitrogen
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CS	Claisen–Schmidt
CYP17A1	17α-Hydroxylase/17,20-lyase
DBH	1,3-Dibromo-5,5-dimethylhydantoin
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane

DHCs	Dihydrochalcones
DMARDs	Disease Modifying Anti-rheumatic Drugs
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
ED_{50}	Effective dose 50
EGFR	Epidermal Growth Factor Receptor
EtOH	Ethanol
FAO	Fatty Acid Oxidation
FBS	Fetal Bovine Serum
$GABA_A$	Gamma-aminobutyric Acid
GI_{50}	50% Growth Inhibition
GTT	Glucose Tolerance Test
H37Rv	*Mycobacterium tuberculosis*
H37Rv	Mycobacterium tuberculosis strain
H4IIE	Rat hepatoma cell line
hCA I	Human carbonic anhydrase I
hCA II	Human carbonic anhydrase II
HCT-116	Human colon cancer cell line
HDAC2	Histone deacetylace 2
HeLa	Cervical cancer cell line
HepG2	Human liver carcinoma cell line
HGF	Hepatocyte Growth Factor
HIV	Human Immunodeficiency viruses
HMI: IMSS	*Entamoeba histolytica*
HOP-92	Non-small cell lung cancer
HPC	Hematopoietic Progenitor Cells
HPLC	High Performance Liquid Chromatography
HPLF	Human Peridontal Ligament Fibroblasts

HSC-2	Cellosaurus cell line
HSC-3	Cellosaurus cell line
HSC-4	Cellosaurus cell line
IC_{50}	Inhibitory Concentration
InhA	Inhibin alpha
IR	Infrared Radiation
K-562	Human immortalised myelogenous leukemia cell line
KDP	Potassium Dihydrogen Phosphate
KF	Potassium fluoride
Ki	Inhibitory Constant
KOH	Potassium hydroxide
L1210	Mouse lymphocytic leukemia cell line
LED	Light Emitting Diode
$LiNbO_3$	Lithium niobate
MCF-7	Breast cancer cell line
MDCK	Madin-Darby Canine Kidney
MeOH	Methanol
MFC	Maximum Fungicidal Concentrations
MgO	Magnesium oxide
MIAPACA	Human pancreatic cancer cell line
MIC	Minimum inhibitory concentration
mmol	Millimoles
MOM	Methoxy methyl ether
Mp	Melting point
MS	Mass spectroscopy
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
$NaNO_3$	Sodium nitrate
NaOH	Sodium hydroxide
NDPC	3-(Naphthalen-2-yl)-*N*,5-diphenyl-pyrazoline-1-carbothioamide

NF-$_K$B	Factor-kappa B
NLO	Non-linear optics
NMR	Nuclear Magnetic Resonance
NSAIDs	Non-steroidal anti-inflammatory drugs
OD	Optical Density
ODCB	1,2-Dichlorobenzene
ORTEP	Oak Ridge Thermal Ellipsoid Plot
OSCC	Oral Squamous Cancer Cell Carcinoma
PAHs	Polycyclic aromatic hydrocarbons
PC-3	Prostate cell line
Pf3D7	*Plasmodium falciparum* 3D7
Ph	Phenyl
Ppm	Parts per million
PTC	Phase Transfer Catalysis
QSAR	Quantitative Structure-activity Relationship
rt	Room temperature
SARs	Structure Activity Relationship studies
SGC-7901	Gastric cancer cell line
SHG	Second Harmonic Generation
SIHA	Cervical cancer cell line
SK-N-SH	Neuroblastoma cancer cell line
SR	Spontaneous Remission
SRB	Sulforhodamine B
SW 872	Human liposarcoma cells
T2DM	Type-2 diabetes mellitus
T47D	Breast cancer cell line
TB	Tuberculosis
TBAB	Tributylammoniumbromide
TEA	Triethylamine

THF	Tetrahydrofuran
Ti	Test growth
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TMV	Tobacco Mosaic Virus
Tz	Time zero
UO-87	Human primary glioblastoma cell line
UO-31	Renal cancer
UV	Ultra violet
VLPC	Visible Light Photoredox Catalysis
WHO	World Health Organization
μM	Micro Mole

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Chapter 1

Introduction

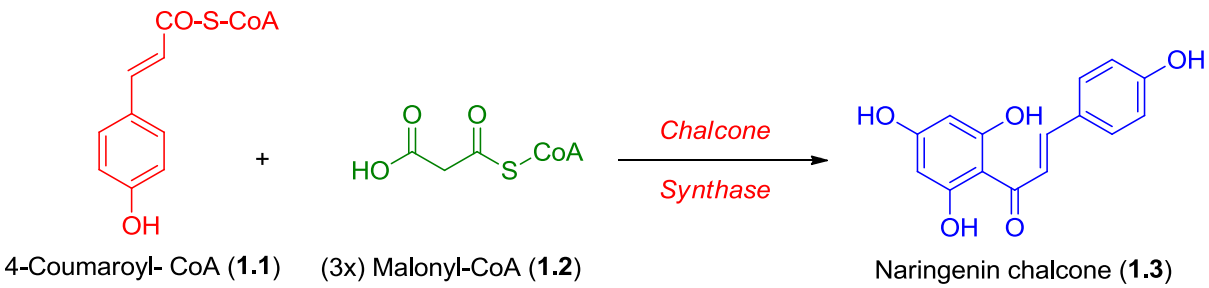
Abstract

In this chapter, the importance of the various natural and synthetic chalcones, pyrazoles, pyrazolines, heterocyclic compounds, anthracenes and their biological activities has been briefly discussed. The aim of the present investigation has been stated in the background of known chemistry of chalcones, pyrazoles, pyrazolines, heterocycles, anthracenes and their biological activities.

1.1 Historical Perspective & Chemistry of Chalcone

The chemistry of chalcones has generated rigorous scientific studies throughout the world. Special attention was given to its synthesis and its biodynamic activities. The name "Chalcones" was first given by Kostanecki and Tambor. These compounds are also known as benzalacetophenone or benzylideneacetophenone.[1] Chalcones and chalcone moieties are very common substructures in natural product chemistry and is one of the most abundant and ubiquitous groups of natural products.[2] Chalcones belong to the flavonoid family and are abundantly available in fruits like citruses and apples, etc., vegetables like tomatoes, shallots, bean sprouts, potatoes, etc., and various plants and spices like licorice as well as in tea and soy-based foodstuff and a number of them are polyhydroxylated in the aryl rings. Most of these have been used for centuries as traditional folk remedies especially in India and China.[3] They are flavonoid, isoflavonoids secondary metabolites precursors and are important pharmacophore[3] which can be synthesized from plants. The explanation for the formation and metabolic transformations of naturally occurring chalcones are shown by different biosynthetic pathways especially the shikimic acid and malonate pathways. *Chalcone synthase* and *Chalcone isomerase enzymes* have been found to play an important role in these pathways and are responsible for their biosynthesis and the biosynthetic transformations. A continuous and intense study on these pathways allows researchers to explain the formation of these chalcone molecules.[4] One of the synthesized form of chalcone in higher plants such as citrus fruit and several other plants is 4,2',4',6'-tetrahydroxychalcone (also called naringenin chalcone) (**1.3**), which is derived from biosynthesis of one molecule of 4-coumaril-CoA (**1.1**) and three molecules of malonyl-CoA (**1.2**) catalyzed by the enzyme *Chalcone synthase* (Scheme 1.1).[5] Naringenin chalcone (**1.3**) acts as a substrate in the flavonoid biosynthetic pathway and contributes significantly for further synthesis of flavonoids.[6] Another enzyme, called the

Chalcone isomerase "type I" produces the 5-hydroxyflavanone naringenin which is known to be found in many higher plants (except leguminous plants) and is the biosynthetic precursor of almost all flavonoids (flavones, isoflavones, flavonols, condensed tannins and anthocyanins).[7]



Scheme 1.1. Biosynthesis of naringenin chalcone in plants and citruses (condensation of three molecules of malonyl-CoA and one molecule of 4-coumaroyl-CoA catalyzed by *Chalcone synthase* resulting in the formation of naringenin chalcone). It is a substrate for further synthesis of flavonoids.

Chalcones are biochemically related compounds of restricted occurrence and the other naturally occurring related bioactive compounds are flavanones, flavanols, retrochalcones and dihydrochalcones (DHCs). Because of their restricted occurrence in nature, chalcones and other bioactive molecules are described as minor flavonoids. They are the customary constituents of human diet. Out of this compounds, flavanones and flavonols have saturated C-ring whereas chalcones, retrochalcones along with dihydrochalcones are unsaturated and have open structure and the carbon skeleton for these compounds are numbered in such a way that is different compared to other flavonoids (Figure 1.1).[1]

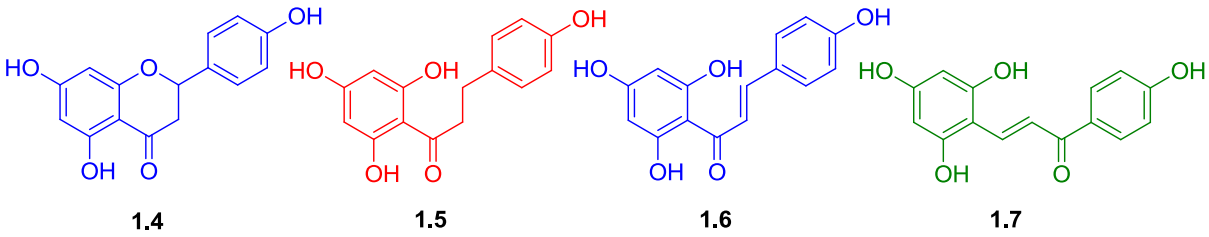


Figure 1.1. Structures of naturally occurring bioactive compounds: Naringenin (flavanone) **1.4**, Phloretin (dihydrochalcone) **1.5**, Isosalipurpurin (chalcone) **1.6**, Retrochalcone **1.7**.

Chalcone comes under an α,β-unsaturated ketone that forms the central core for a variety of important biological compounds. Chalcones exist in two isomeric forms, *cis*- and *trans*. The *trans*-isomer being the most thermodynamically stable (Figure 1.2).[8]

cis-Chalcone *trans*-Chalcone

Figure 1.2. Chemical structure of *cis*- and *trans*-chalcone.

Due to its diverse and remarkable pharmacological and biological activities, chalcone acts as mediator in the synthesis of beneficial therapeutic compounds. Special attention has been given to study chalcone and the development of new synthetic chalcone protocol due to its simple structure and its ample pharmacological and therapeutic values.[9]

1.2 Synthetic Importance of Chalcone

Although chalcones are known to be available naturally, many efficient and simple synthetic methods can be employed for the synthesis of chalcone in terms of yield and purity.[10] One of the most common classical method used for the preparation of chalcone is the Claisen–Schmidt (CS) condensation of an appropriate acetophenone and benzaldehyde derivatives or aryl ketone carried out in basic or acidic media under homogeneous conditions in the presence of a polar solvent (methanol or ethanol) in which formation of C–C bond takes place giving chalcone product.[11] Chalcone can also be prepared by an Aldol condensation between a benzaldehyde and an acetophenone in the presence of base.[12]

Of the many methods reported, till date Aldol condensation method and Claisen–Schmidt (CS) condensation methods occupy prominent positions for the synthesis of chalcone.[13] Due to their many potential biological activity and synthetic utility reported by many researchers, chalcones have attracted many pharmacologists and chemists to design and develop new synthetic methods for chalcone preparation. Reports shows the use of aqueous base like NaOH, KOH, $Ba(OH)_2$, etc.,[14] for the synthesis of chalcone and chalcone derivatives. Other reported base catalysts used for the synthesis of chalcones are magnesium t-butoxide,[15] potassium carbonate,[16] alumina,[17] MgO,[18] calcinated hydrotalcites,[19] natural phosphate/$NaNO_3$,[20] KF/natural phosphate[21] and piperidine.[22] Several researchers have also reported the synthesis of chalcone using different catalysts like zinc oxide,[23] organolithium,[24]

$KF–Al_2O_3$,[25] modified phosphates,[20a] zeolites and hydrotalcites.[19a] Many new eco-friendly methods developed and reported for the synthesis of chalcone and chalcone derivatives are ultrasonic radiations,[26] microwave assisted,[27] solvent free synthesis by grinding, etc.[28] Other non-classical methods reported for the synthesis of chalcone are Suzuki,[13] direct crossed-coupling,[29] Heck reaction,[30] Friedel–Crafts reaction[31] and Julia–Kocienski reaction[32] (Figure 1.3).

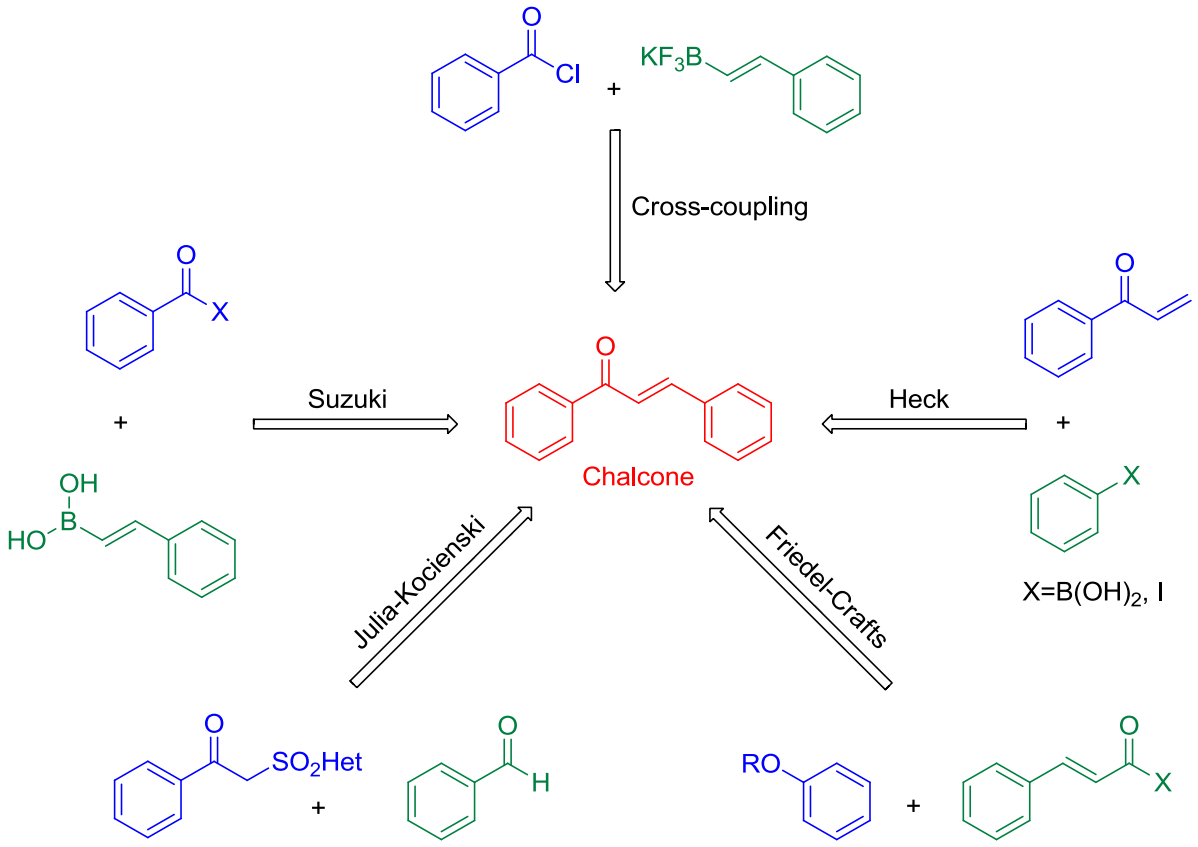


Figure 1.3. Synthesis of chalcone using well-known non-classical reaction methods.

1.3 Synthesis and Biological Importance of Chalcone

Extensive literature survey shows that many patents were reported by using plant extract rich in chalcone compounds having numerous biological activities, some of which are isoliquiritigenin (**1.8**), licochalcone A (**1.9**), xanthoangelol (**1.10**), isobavachalcone (**1.11**), xanthohumol (**1.12**), nardoaristolone A (**1.13**) and other naturally important chalcone derivatives some of which are briefly described below (Figure 1.4).

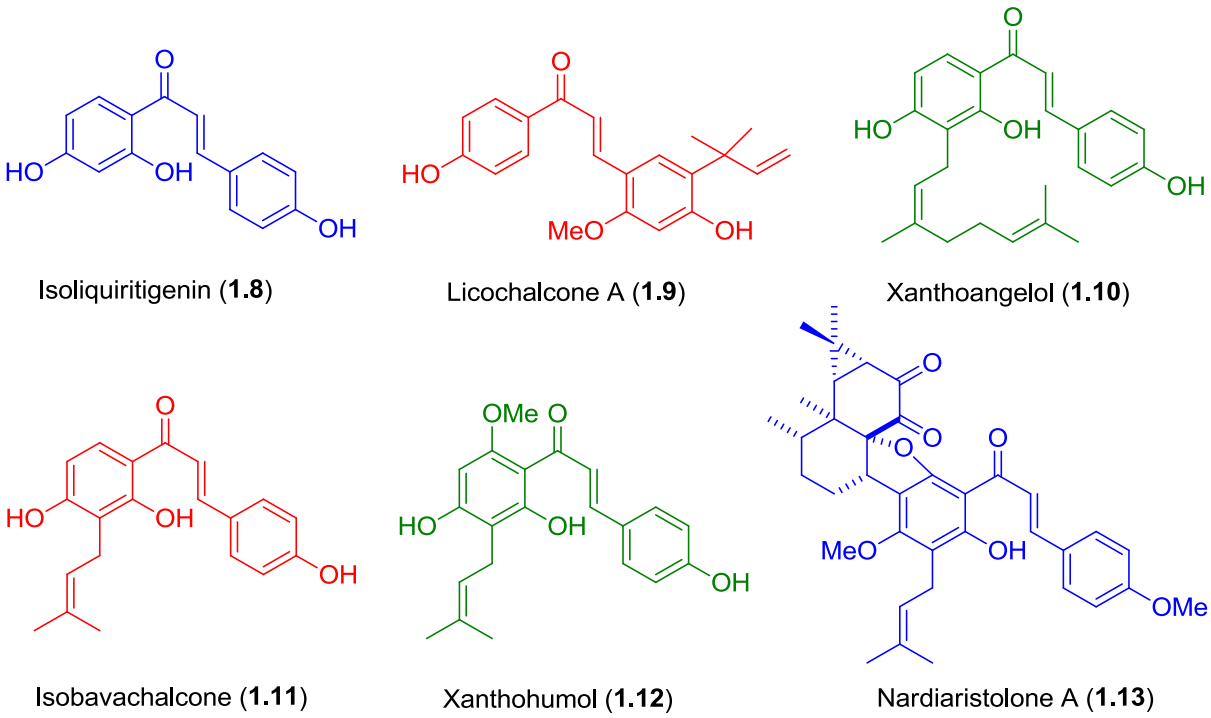


Figure 1.4. Chemical structures of chalcones found in natural product sources.

One of the simplest known natural chalcone is isoliquiritigenin (**1.8**) which is a component of the plant of the genus *Dalbergia*.[33] Some important biological activities of isoliquiritigenin reported by different authors are cardiovascular diseases; cosmetics for suppressing skin aging and wrinkles;[34] isoliquiritigenin from *Radix glycyrrhizae* extracts presented effects of anti-aging, skin whitening, irritation relieving, atopic dermatitis treatment and anti-acne;[34] activating $GABA_A$-benzodiazepine receptor;[35] hypnotic, sedative, anxiolytic, anticonvulsant effects and preparation of eye drops containing isoliquiritigenin;[36] preventing and/or treating cardio-cerebrovascular diseases.[37]

Different authors reported vegetable sources rich in licochalcone A and its activity as dermatological or hair-cosmetic preparations,[38] treatment of acne,[39] preparation of cosmetic toners and skin-whitening properties,[40] significant amount of licochalcone A was added to cosmetic compositions of essential oils, bath salts,[41] agents for preventing, improving or treating AMPK-related diseases (adenosine monophosphate-activated protein kinase), specifically disorders involving lipid metabolism[42] and treating influenza virus infection-correlated diseases.[43] Another important naturally occurring chalcone is xanthoangelol (also known as isoprenil-chalcone) and is a major constituent of *Angelica keiskei* extracts which is an antioxidant compound, used in the treatment of inflammatory diseases as well as on the lipid metabolism and also used as component of deodorants.[44] Another compound belonging to

isoprenil chalcones family is Isobavachalcone. Many authors reported the biological activities of this chalcone molecule, some of which are melanin formation inhibitors and skin-lightening agents;[45] in the therapeutic of nerve inflammatory diseases;[46] cholesterol absorption inhibitors;[47] application in prevention and control of plant diseases.[48] Xanthohumol are prenylated chalcone present in *Humulus lupulus* and has been used as cancer chemopreventive agent, as antioxidants, intranasal application in the form of a nasal spray for prophylactic and/or curative treatment of chronic inflammation of the nasal mucosa, particularly viral, allergic and/or vasomotor rhinitis;[49] it inhibits the activity of α-glucosidase; treating diabetes, AIDS or malignant tumor,[50] treating osteoporosis.[51] Finally, more complex chalcone nardoaristolones A and B are a class of terpenoid chalcones. Nardoaristolone A is used in the treatment of several types of skin and endometrium cancers;[52] in the preparation of a medicament for increasing the number of red blood cells;[53] as a medicament for promotion of small bowel peristalsis,[54] or as anti-tubercular drugs.[55] These are some of the biological and therapeutic activities of some of the most common naturally occurring chalcone compounds.

Having such diverse pharmacological activities, chalcones have attracted many pharmacologists/medicinal chemists to develop new synthetic methods to treat diseases. A perusal example of the existing literature review of chalcone associated with different activities are emphasized below.

1.3.1 Chalcone with Anti-cancer Activity

Cancer is reported to be the second most leading cause of human death after cardiovascular diseases in developed as well advance countries.[56] For more than three decades, extensive research is still going on in both the academia and industry for anti-cancer activity of chalcones.[57] However, only few reports described the detail mechanism of cytotoxicity or anti-proliferative activity of chalcone. Chalcone exhibits its cytotoxicity activity through multiple mechanisms which include cell cycle disruption, angiogenesis inhibition, tubulin polymerization inhibition, apoptosis induction and blockade of nuclear factor-kappa B (NF-$_{K}$B) signaling pathway.[58] Chemotherapy and radiotherapy are the most common methods for treating this disease but due to their high systemic toxicity, drug resistance and adverse side effects, this procedure limits the successful treatment options in most cases.[59] 4-Trihydroxy-5-geranyl chalcone, named as isoxanthoangelol isolated from the leaves of *Artocarpus communis* is reported to possess anti-cancer activity in SW 872 human liposarcoma cells.[60]

Breast cancer is one of the most common cancers in women because in these tumor cells, the estrogen receptors are over-expressed and therefore leads to excessive proliferation.[61]

In the recent years, scientists have developed steroidal molecules such as estradiol (**1.14**), 2-methoxyestradiol (**1.15**) and fulvestrant (**1.16**) (Figure 1.5).

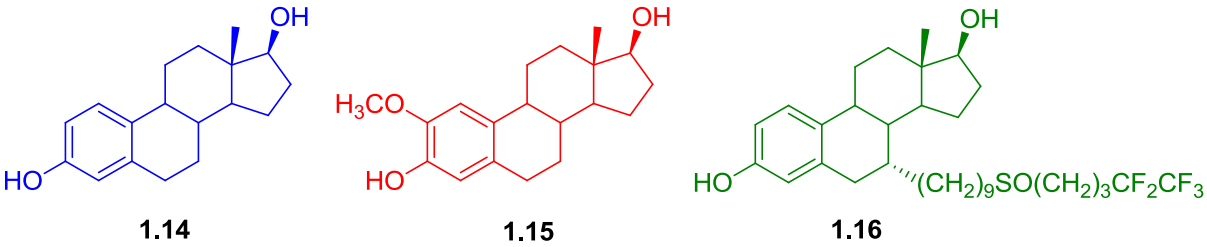


Figure 1.5. Structures of estradiol (**1.14**), 2-methoxyestradiol (**1.15**) and fulvestrant (**1.16**).

These steroids emerged as potent anti-cancer agents to fight against breast cancer.[62] However, many researchers are still targeting in designing simple and easier methods for preparation of non-steroidal drugs with potential anti-cancer activity. Some of the naturally occurring and synthetic chalcone derivatives reported as good anti-cancer agents against a variety of cancer cell lines have been described below.

In **2012**, Kapil Juvale *et al*. have reported the synthesis of chalcones and benzochalcones with different substituents (-OH, -OCH_3, -Cl) on ring A and B of the chalcone structure (Figure 1.6) and all the synthesized compounds were tested by Hoechst 33342 accumulation assay to determine their inhibitory activity in two different cell lines i.e., MCF-7 MX and MDCK cells expressing Breast Cancer Resistance Protein (BCRP). Screening showed that compounds with 3,4-dimethoxy substituents at ring B were found to be most active whereas compounds with 2- and 4-chloro substitution also showed a positive effect on BCRP inhibition.[63]

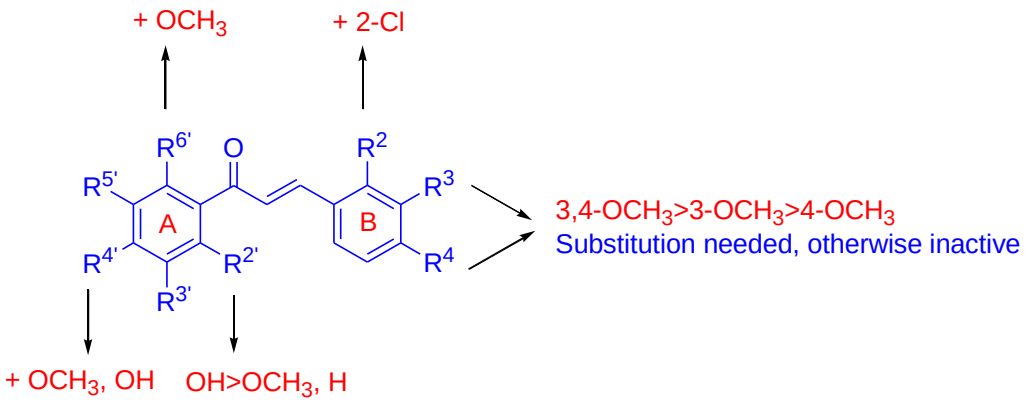
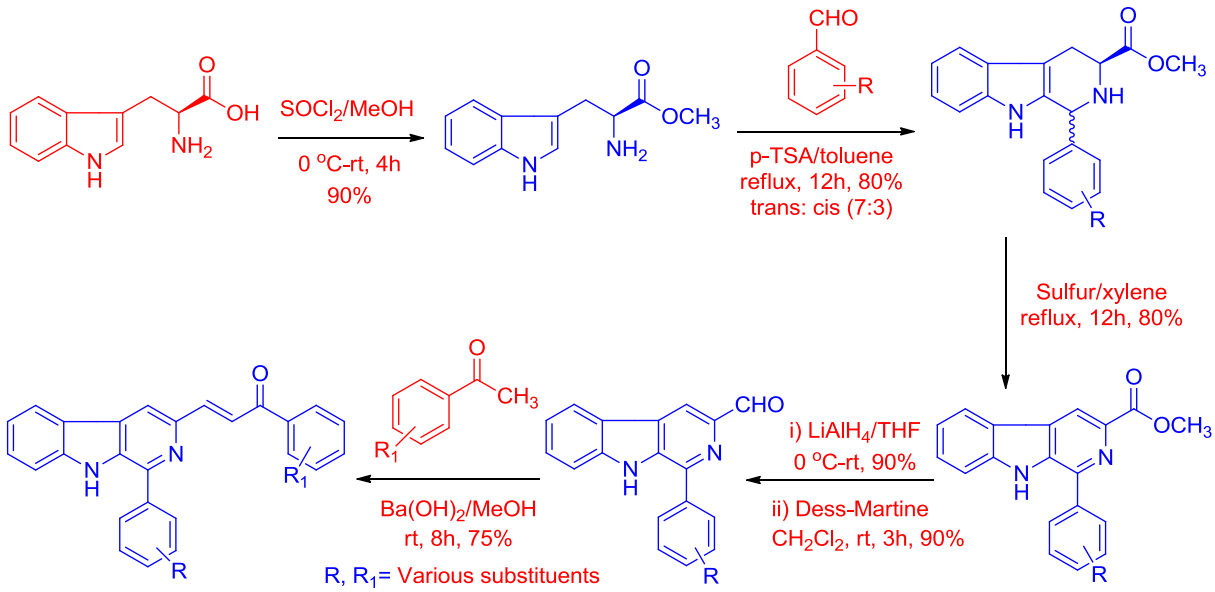


Figure 1.6. Chalcone scaffold with various functional groups on the phenyl rings for anti-cancer activity.

Nagula Shankaraiah and co-workers (**2015**) described the synthesis of a series of DNA-interactive β-carboline–chalcone conjugates. These compounds were evaluated for *in vitro* cytotoxicity (anti-cancer potential) and DNA-binding affinity. Screening showed that most of these hybrids show potent cytotoxic activities against adenocarcinoma cell line (A-549). It was observed that the Structure Activity Relationship studies (SARs) based on their cytotoxicity DNA-binding affinity screening that substitution of phenyl ring at C1-position of β-carboline with flouro and methoxy groups shows higher cytotoxicity and DNA-binding potential. Also, the substitution of nitro, amino, trimethoxy and hydroxyl on the chalcone part of the ring imparts considerable cytotoxicities (Scheme 1.2).[64]



Scheme 1.2. Synthesis of β-carboline-chalcone analogues.

Four natural chalcones bearing prenyl or geranyl groups, i.e., bavachalcone (**1.17**), xanthoangelol (**1.18**), isobavachalcone (**1.19**), and isoxanthoangelol (**1.20**) (Figure 1.7, Scheme 1.3 and 1.4) were synthesized by Hao-Meng Wang *et al.* in **2015** by regio-selective iodination and the Suzuki coupling reaction as key steps. The first total synthesis of isoxanthoangelol (**1.20**) was achieved in 5 steps in 36% overall yield. A series of diprenylated and digeranylated chalcone analogs were also synthesized. 16 chalcone derivatives were screened for anti-cancer activity against human tumor cell line K562 by MTT assay *in vitro* and the SAR test result showed that the 5'-prenylation (**1.17** and **1.18**) of the chalcones significantly enhanced their cytotoxic activity and also the 3'-geranyl mono-substituted chalcone xanthoangelol (**1.20**) showed good cytotoxic activity. Among them, bavachalcone (**1.17**) exhibited the most effective cytotoxic activity against K562 cell line.[65]

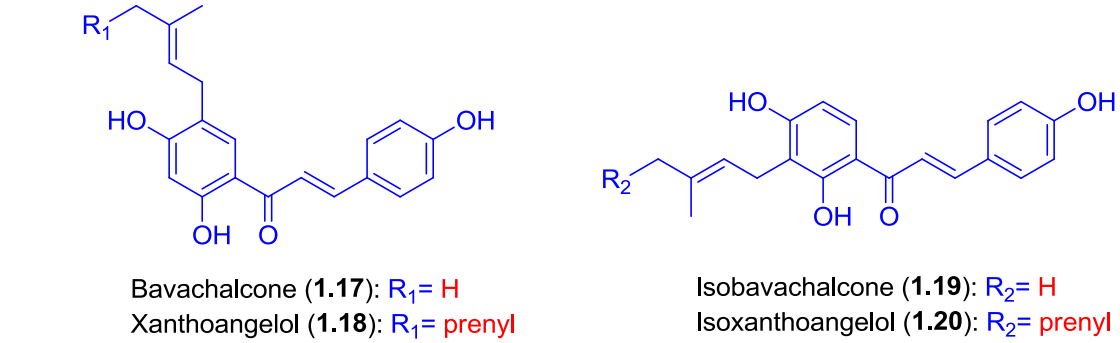
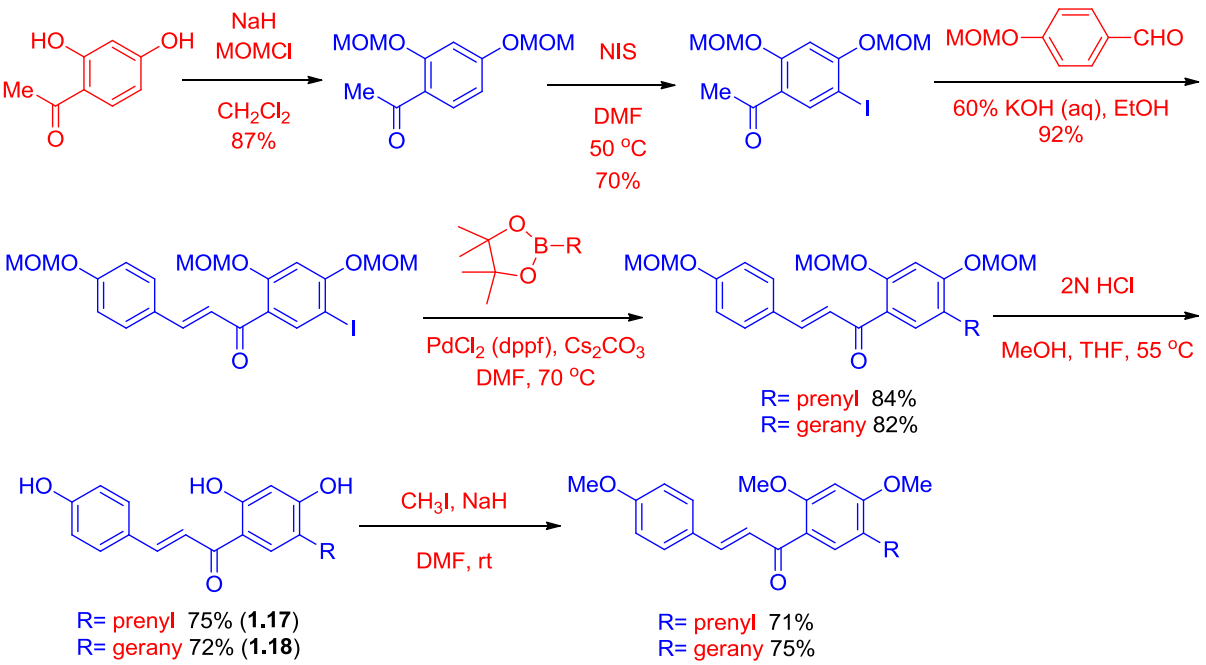
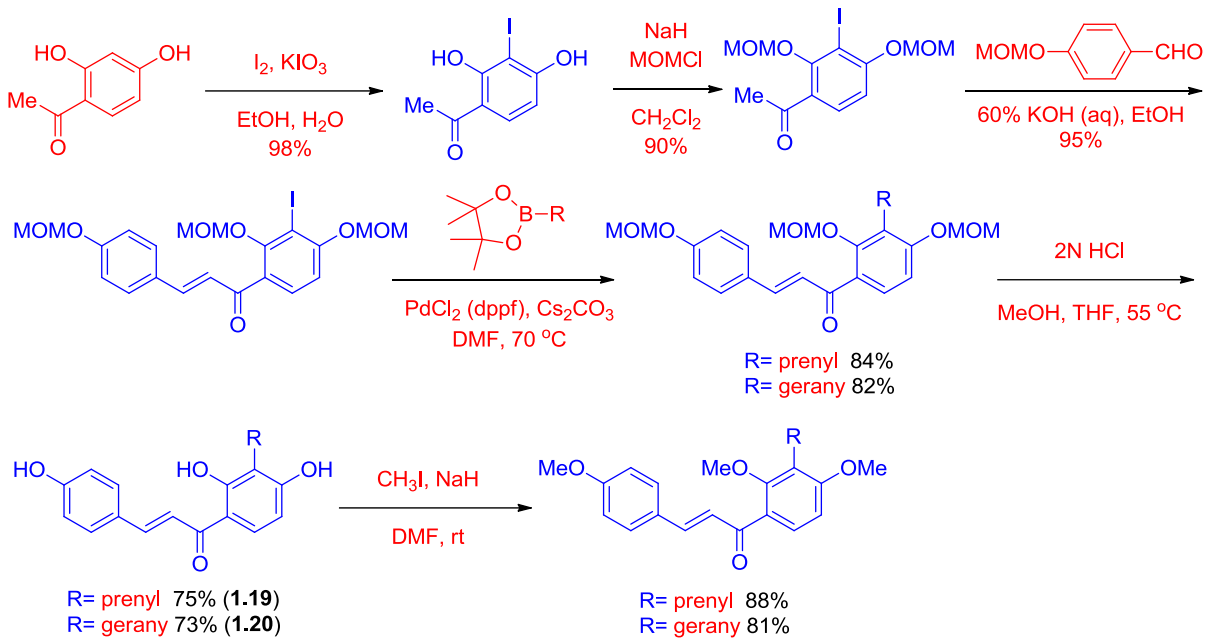


Figure 1.7. Total synthesis structures of natural product chalcones.

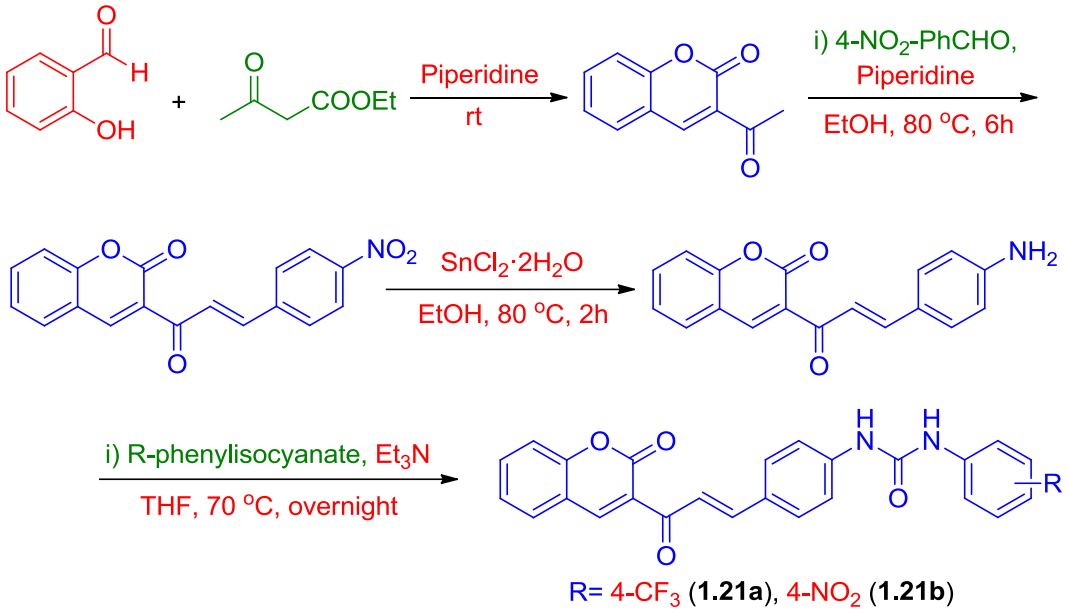


Scheme 1.3. Total synthesis of natural chalcones **1.17** and **1.18**.



Scheme 1.4. Total synthesis of natural chalcones **1.19** and **1.20**.

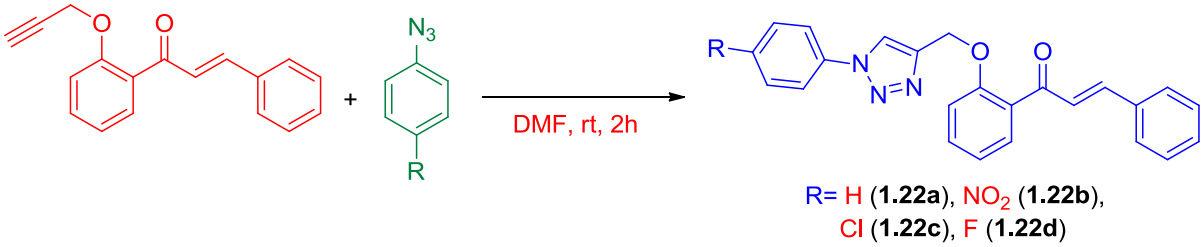
Belma Zengin Kurt *et al*. in **2020** reported the synthesis of coumarin derivatives bearing diversely substituted chalcone-urea moieties. These molecules were evaluated for their anti-proliferative activities against H4IIE and HepG2 cancer cell lines. Among the synthesized compounds, 1-(4-(3-oxo-3-(2-oxo-2H-chromen-3-yl)prop-1-en-1-yl)phenyl)-3-(4(trifluoromethyl)phenyl)urea (**1.21a**) was found to show better inhibition of H4IIE compared to standard sorafenib and 1-(4-nitrophenyl)-3-(4-(3-oxo-3-(2-oxo-2H-chromen-3-yl)prop-1-en-1-yl)phenyl)urea (**1.21b**) showed better inhibition against HepG2 than sorafenib (Scheme 1.5).[66]



Scheme 1.5. Synthesis of substituted coumaryl-chalcone urea derivatives.

1.3.2 Chalcone with Anti-microbial Activity

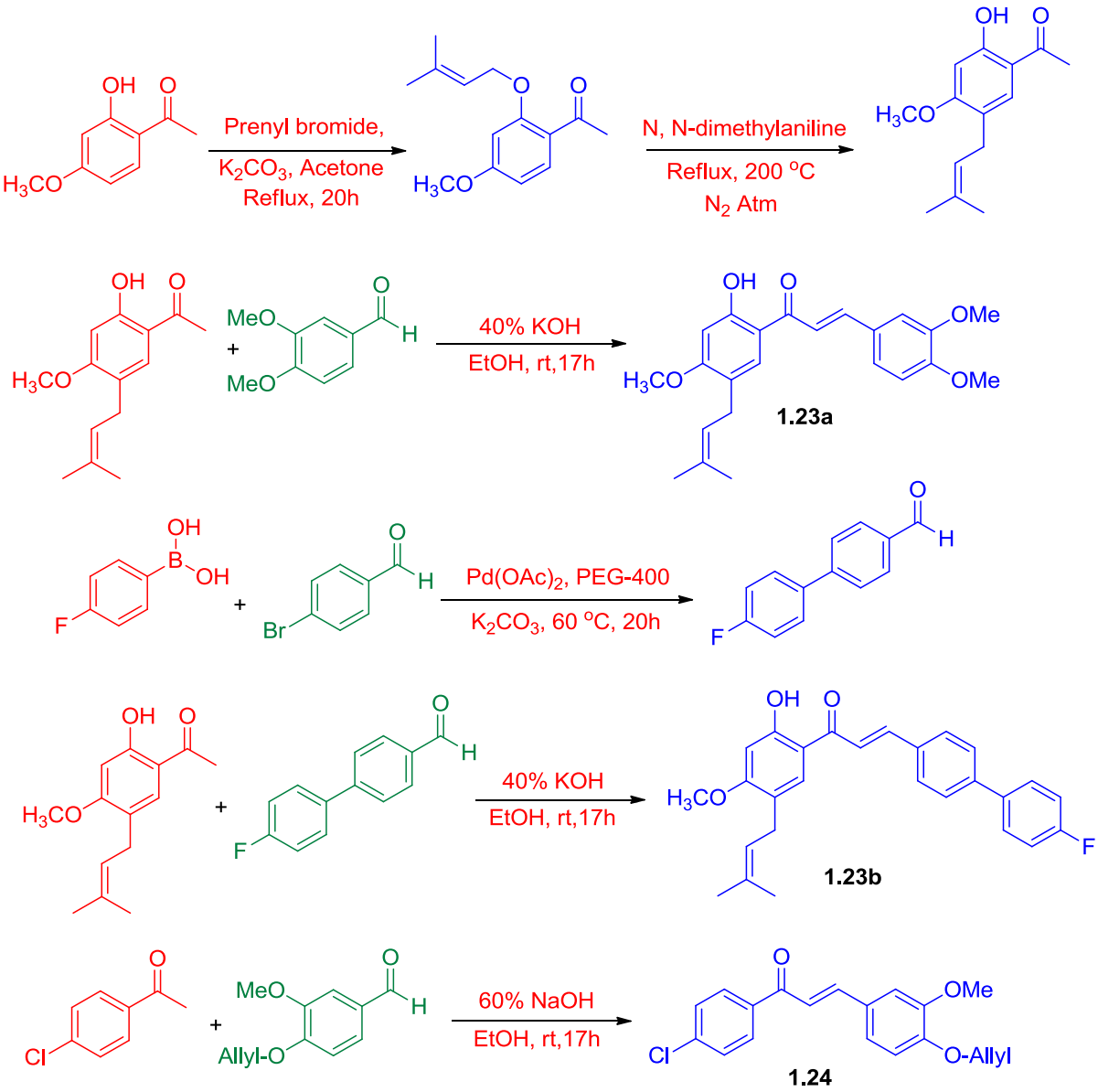
In **2016**, Ahmed Habeeb Radhi and Y. Hemasri synthesized 1,2,3-triazoyl chalcones (**1.22a-d**) (Scheme 1.6). These synthesized molecules were evaluated for their anti-cancer (breast cancer cell line) and antibacterial studies. Screening reports showed that these molecules do not show any anti-cancer activity confirmed with standard cisplatin but the results evaluated for antibacterial activity showed that in both Gram-positive and Gram-negative bacteria, where the compounds **1.22b** and **1.22c** showed more anti-bacterial activity at 150 µg concentration.[67]



Scheme 1.6. Synthesis of 1,2,3-triazoyl chalcones.

Prenylated and allylated chalcone analogues were synthesized by Jufrizal Syahri and co-workers in **2017** and were investigated for their antimalarial activity against chloroquine-sensitive *Plasmodium falciparum* 3D7 (Pf3D7) strain. Screening results showed that prenylated chalcone (*E*)-3-(3,4-dimethoxyphenyl)-1-(2-hydroxy-4-methoxy-5-

(prenyl)phenyl)-prop-2-en-1-one (**1.23a**) and allylated chalcone (*E*)-3-(4-(allyloxy)-3-methoxyphenyl)-1-(4-chlorophenyl)prop-2-en-1-one (**1.24**) showed the best IC_{50} values of 1.08 and 1.73 µg/mL respectively (1.37 and 2.33 µg/mL based on QSAR analysis) describing them as good antiplasmodial compounds (Scheme 1.7).[68]



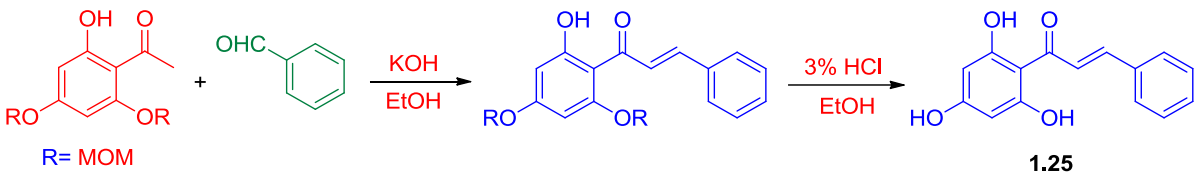
Scheme 1.7. Synthesis of prenylated and allylated chalcone derivatives.

1.3.3 Chalcone with Anti-diabetic Activity

Diabetes is another form of health issue faced by many countries. Diseases like cardiovascular diseases, peripheral vascular diseases, stroke, diabetic neuropathy, amputations, renal failure and blindness results in increasing disability, reducing life expectancy and enormous health costs are complications of this disease.[69] As reported by World Health

Organization (WHO), around 250 million people are currently living with diabetes and this number is expected to increase to 366 million by 2030.[70] Type-2 diabetes mellitus (T2DM) threatens human health and life, and the drug used for treatment (such as direct insulin administration and other oral drugs that promotes insulin secretion) have several side effects, especially for those patients with liver and renal functional disorders.[71] A compound called methyl hydroxychalcone found in cinnamon was reported to be insulin mimetic showing improvement in insulin response to diabetics. It was thus concluded that flavonoid is responsible for the insulin-like biological activity.[72] Treatment of diabetes and its prevention has become a challenging problem to human life therefore, the need of the hour is to develop new drug for controlling diabetes for improving life quality of human beings. Chalcone shows many biological activities, but despite of its many pharmacological and biological activities, reports on the activity of chalcone towards diabetes is scarce.[73] Following are chalcone analogues having anti-diabetic property.

In **2018**, Jooseok Shin and co-workers synthesized 2',4',6'-trihydroxychalcone derivatives and examined their potential anti-diabetic effects in a cell-culture system and a diabetic mouse model *in vivo* as well as *in vitro.* Some of the compounds showed increase of the fatty acid oxidation (FAO) without affecting the cell viability. Trihydroxychalcone derivatives, 2',4',6'-trihydroxychalcone (**1.25**) showed increased AMP-activated protein kinase (AMPK) phosphorylation rapidly at much lower concentrations as compared to 5-aminoimidazole-4-carboxamide riboside (AICAR), a well-known AMPK activator. The chalcone compound **1.25** exhibited potent anti-diabetic effects *in vivo* and is the first study to investigate the anti-diabetic effects of trihydroxychalcone compounds (Scheme 1.8).[74]



Scheme 1.8. Synthesis of 2',4',6'-trihydroxychalcone derivatives.

1.3.4 Other Applications of Chalcone

Chalcone, apart from its biological activities have been found to be useful in material science field such as non-linear optics (NLO).[75] Chalcone derivatives are reported as excellent blue light transmittance and good crystallizability materials for application in nonlinear optics.[76] Among many organic compounds reported for their second harmonic generation

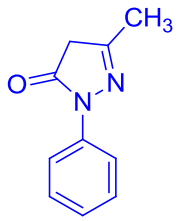
(SHG), chalcone and its derivatives are found to be excellent materials for optical communications and optical electronics.[77] Most commonly used non-linear optical inorganic crystals in the bulk form are ADP, KDP, ADA, $LiNbO_3$, etc. Several organic and molecular crystalline materials have also been identified as high-performance, second-order, optically non-linear crystals.[78] Extensive research is still going on for the development of such optical materials, optical limiting,[79] electrochemical sensing,[80] Langmuir films and photo-initiated polymerization.[81] Other applications of chalcone reported are, it is used as photo protectors in plastic,[82] solar creams,[83] food additives.[84] Besides their importance as starting material for many syntheses, chalcones are being explored as a new class of non-azo dyes,[85] fluorescent probes,[86] as photoresists and photographic emulsions.[87] For more than a decade, synthetic pesticides (fungicides, insecticides and bactericides) have been used for agricultural purposes for protecting crops but in an uncontrolled way. This led to emergence of weed agrochemical-resistant[88] leading to economic losses, potential health risks and environmental contamination.[89] For decades, chalcones are reported to have numerous pesticidal activities which led to the interest for researchers to study activity of chalcones in agricultural systems as well as plant production.[90]

1.4 Heterocyclic Compounds

Another group of molecules belonging to natural product family that shows biological activities are the heterocyclic compounds. The structural subunits i.e., their ring system are present in many natural products (vitamins, hormones, antibiotics, enzymes, nucleic acids, etc.) and are of great significance to life. It is abundantly found in nature. Synthetic members of this group also act as chemotherapeutic agents.[91] The syntheses of such molecules are of great importance because it has been reported that nitrogen containing heterocyclic compounds play an important role in medicinal chemistry. Pyrimidine, a six-membered heterocyclic compound contains nitrogen in the 1st and 3rd positions.[92] Pyrimidine derivatives occur in natural products like nucleic acids and vitamin B1. They are good anti-infectious agents, some of which are anti-tubercular,[93] anti-bacterial,[94] anti-oxidant,[94] anti-inflammatory,[95] HIV and anti-diabetic.[96] Quinoline is another heterocyclic molecule that shows good anti-infectious activity.[97] Pyrazole, also a well-known heterocyclic molecule where many synthetic methods and procedures have been developed to study their biological importance. Based on literature survey, historical perspective, chemistry and biological importance of pyrazole and pyrazolines have been discussed below.

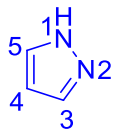
1.4.1 Historical Perspective & Chemistry of Pyrazole

Pyrazole have well-known history and its term was first given by Ludwig Knorr, a German chemist in 1883. Knorr first synthesized this compound by the reaction of ethyl acetoacetate with phenyl hydrazine which yielded 1-phenyl-3-methyl-5-pyrazolone (Figure 1.8).[98] Pyrazoles are five membered heterocyclic ring structures composed of three carbons and two nitrogens bound to each other, which are belonging to the azole class with two endocyclic double bonds which are basic in nature (Figure 1.9).[99]



1-Phenyl-3-methyl-5-pyrazolone

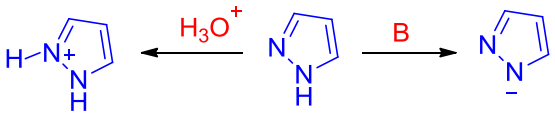
Figure 1.8.



Pyrazole

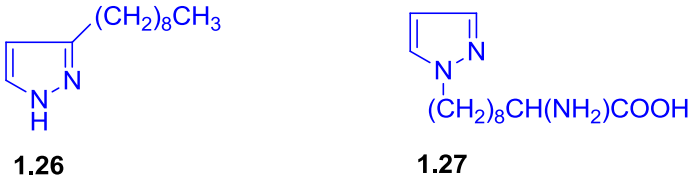
Figure 1.9.

They are a class of well-known nitrogen heterocycles and among the two nitrogen atoms present in pyrazole, nitrogen atom 1 (N1) is "pyrrole-like" because its unshared electrons are conjugated with the aromatic system and nitrogen atom 2 (N2) is "pyridine-like" since the unshared electrons are not compromised with resonance like that of a pyridine system. Due to this difference between the two nitrogen atoms, pyrazoles react with acids as well as with bases (Scheme 1.9).[100]



Scheme 1.9. Cations and anions produced from pyrazole in presence of acid and base.

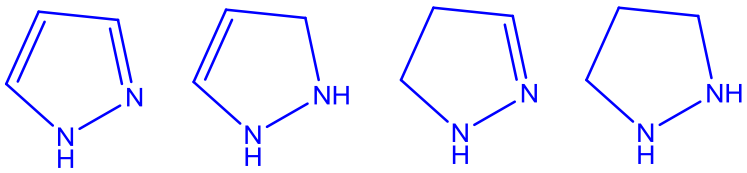
The first natural pyrazole 3-*n*-nonyl-1H-pyrazole (**1.26**) (Figure 1.10) was isolated by Japanese workers from a common plant, *Houttuynia cordata* in tropical Asia and observed its antimicrobial activity.[101] Another natural pyrazole, 1-pyrazolyl-alanine (or β-(1-pyrazolyl)alanine) (**1.27**) (Figure 1.10) was first reported in 1959 which was isolated from seeds of watermelon.[102] Pyrazole is classified as alkaloids because of its many pharmacological effects on humans and are widely found as the core structure in a large variety of compounds that possesses important agrochemical and pharmaceutical activities.[99]



1.26 **1.27**

Figure 1.10. Pyrazoles extracted from natural products.

Pyrazoles are aromatic molecules because of their planar conjugated ring structures with six delocalized π-electrons (**1.28a**). Its aromaticity arises from the four π-electrons and the unshared pair of electrons on the –NH nitrogen. Pyrazole arises in two forms, the partially reduced form is named as pyrazolines being basic in nature (**1.28b** or **1.28c**) while completely reduced form is pyrazolidine (**1.28d**) (Figure 1.11).[103]



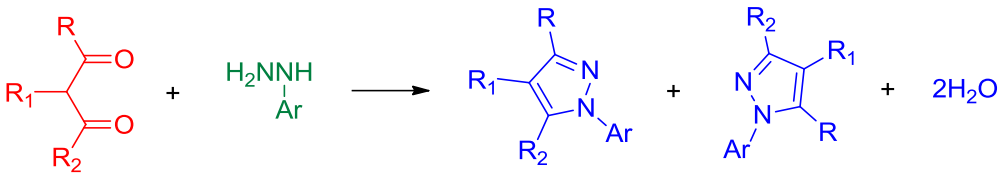
1.28a **1.28b** **1.28c** **1.28d**

Figure 1.11. Structures of pyrazole class.

1.4.2 Pyrazole as Drugs

Pyrazole and its derivatives are known to occupy a leading position in medicinal and pesticide chemistry because of their varied biological activities. They are also used as building blocks in organic synthesis for scheming and designing various pharmaceutical and agrochemical molecules and also as bifunctional ligands for metal catalysis.[103] The pyrazole ring is present as the core in a variety of leading drugs and is reported to possess various biological activities such as anti-microbial,[104] anti-convulsant,[105] anti-cancer,[106] analgesic, anti-inflammatory,[107] anti-tubercular,[108] cardiovascular,[109] etc.

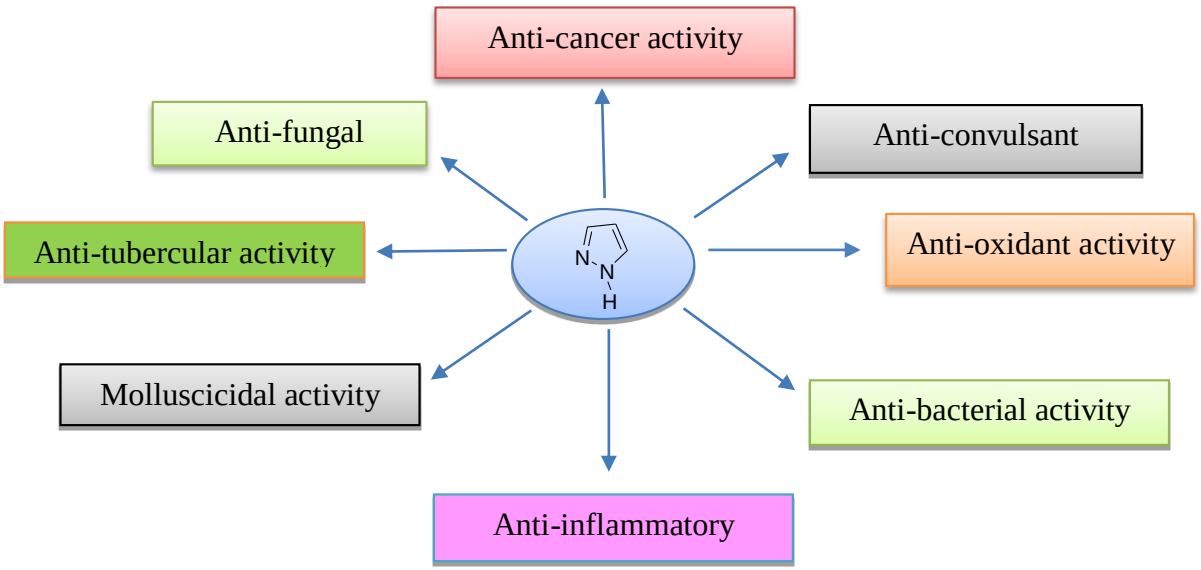
Numerous methods have been developed for the synthesis of substituted pyrazoles of which the classical methods involve the approaches based either on the condensation of hydrazines with 1,3-dicarbonyl compounds or 1,3-dielectrophiles such as the Knorr synthesis (Scheme 1.10), from the reaction of α,β-unsaturated aldehydes and ketones with hydrazines and also from the intermolecular [3+2] cycloadditions of 1,3-dipolar compounds with alkynes, e.g., the Pechmann synthesis.[110]



Scheme 1.10. Knorr synthesis of pyrazoles.

It also gives many reactions with electrophilic reagents such as addition at nitrogen,[111] alkylation at nitrogen,[112] acylation at nitrogen,[113] substitution at carbon,[114] halogenation,[115] acylation,[116] reaction with bases (deprotonation of pyrazole C-hydrogen, deprotonation of pyrazole N-hydrogen),[117] reaction of N-metallated pyrazoles,[118] reaction of C-metallated pyrazoles[119] and reaction with radicals.[120]

1.4.3 Biological Importance of Pyrazole



Pyrazole moieties, being called as pharmacophore have been investigated since long due to its versatile usefulness. They represent key structural motifs in heterocyclic chemistry which constitutes an essential branch of organic chemistry and are known to display an array of biological properties. Among the various bioactive heterocycles, pyrazoles are of special interest because they comprise a significant class of natural as well as non-natural products and therefore represents an interesting template for combinatorial as well as medicinal chemistry. Pyrazole and its derivatives are reported to have exhibited interesting biological properties, unique electrical as well as optical properties.[121] It is also widely applied in the pharmaceutical and agrochemical industry.[122] Much attention is being given to this nitrogen containing

heterocyclic molecule due to its diverse spectrum of therapeutic properties which makes it an indispensable anchor for designing and developing new pharmacological agents.[123] Since the discovery of pyrazole, intense research has been carried out with the aim to find the therapeutic values of pyrazole moiety.[124] These compounds are thus widely used in the development of drug research[125] and consequently various procedures for the syntheses of pyrazoles have been developed.[126] Some of the leading drugs having pyrazole as the core showing good pharmacological activities are represented in Figure 1.12.[127]

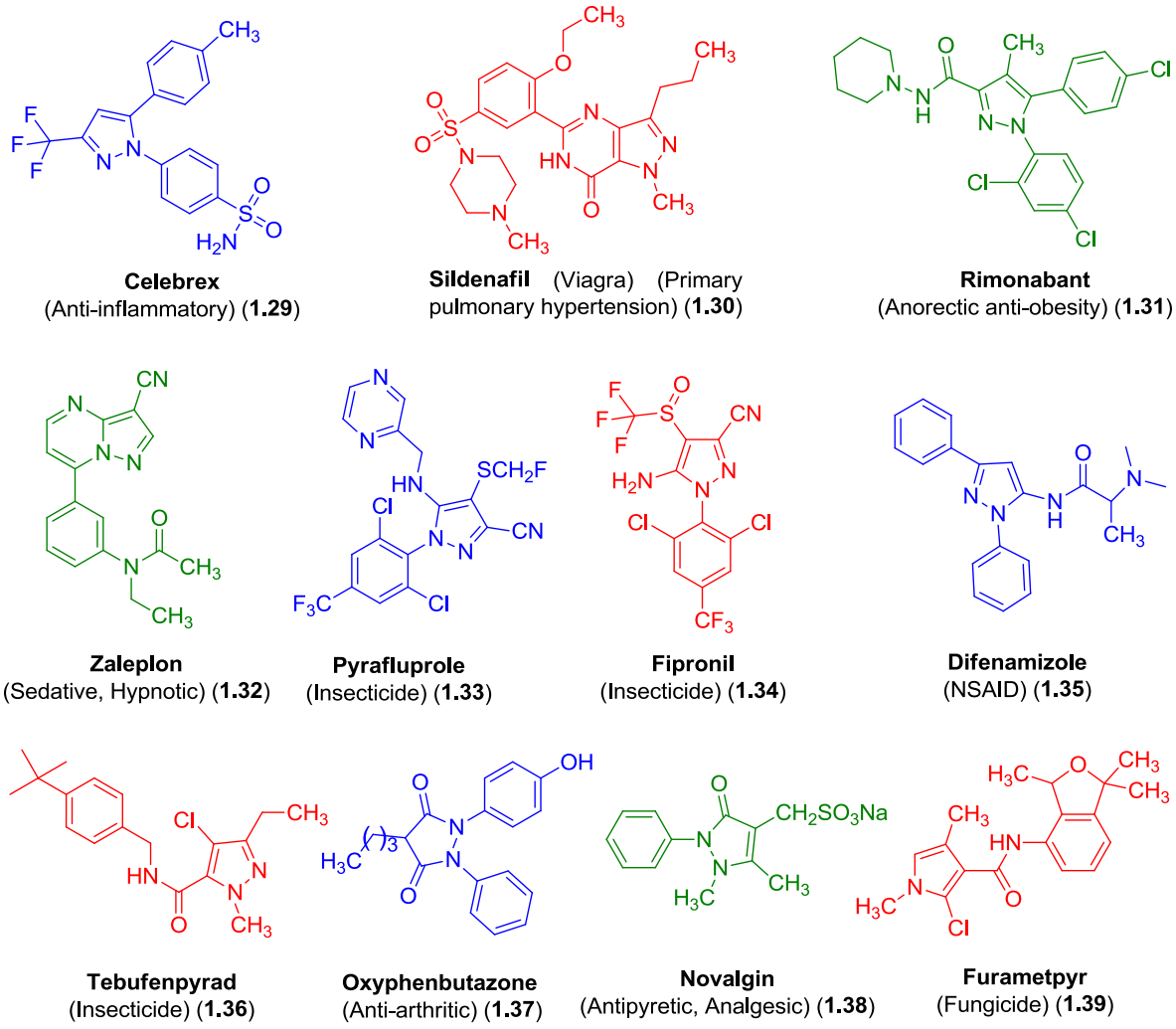


Figure 1.12. Some of the leading drugs having the pyrazole moiety.

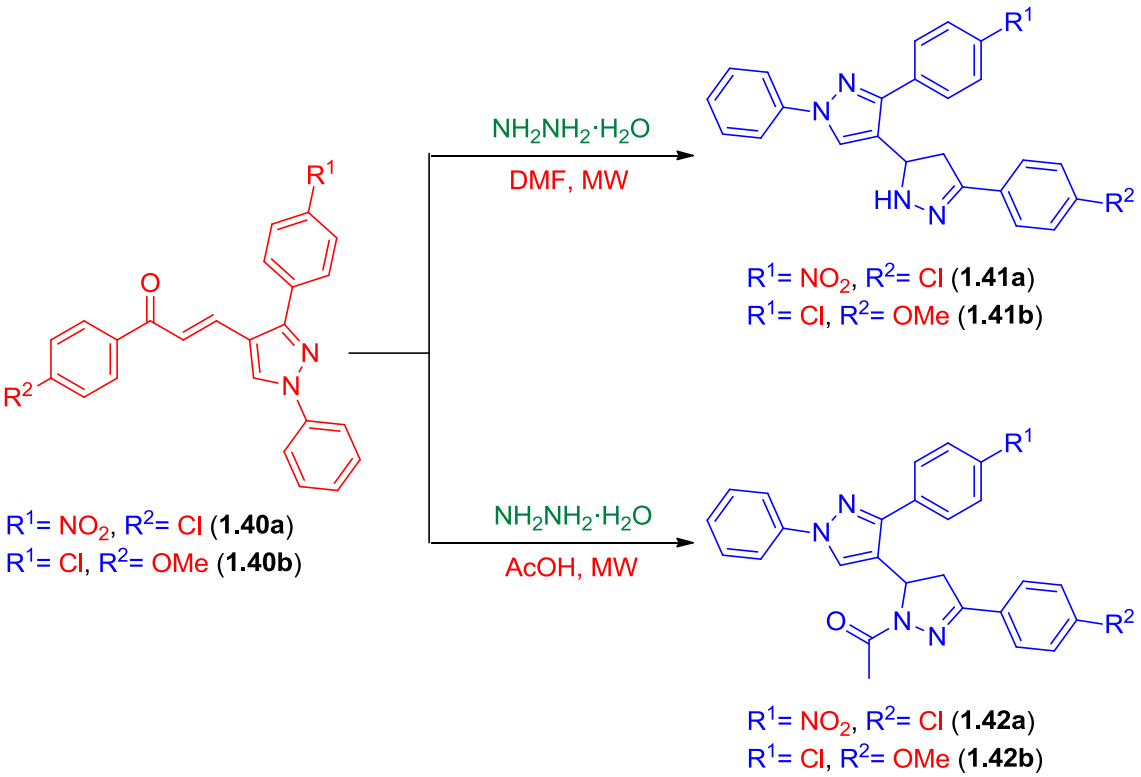
Examination of the existing literature reflects a number of biological activities associated with different pyrazole moiety. Some examples are described below.

1.4.3.1 Pyrazole with Anti-cancer Activity

Worldwide cancer has become the leading cause of death accounting for about 13% and is the second major cause of deaths after cardio and cerebrovascular diseases.[128] The global cancer rate could increase by 50% to 15 million new cases by 2030.[129] The clinical prognosis for treating this disease is very poor. Several reports suggest that pyrazole analogues have been tested for anti-tumor and anti-proliferative activities and resulted as promising anti-cancer agents, indicating their use in designing new anti-cancer agents.[130] The major approach for treating cancer is chemotherapy, using drugs that targets cell division, angiogenesis or that induces cancer cell death by various signaling pathways. However, majority of the cancers have become resistant to chemotherapy or acquires resistance to drug during treatment. A key feature of cancer cells is their uncontrolled proliferation, thus inhibition of proliferative pathways is assumed to be an effective strategy to fight cancer.[131] As a result, the need to design and develop novel potent nontraditional, efficient and more selective chemotherapeutics as anti-cancer agents is the key target for medicinal chemists in the existing research in medicinal chemistry.[132]

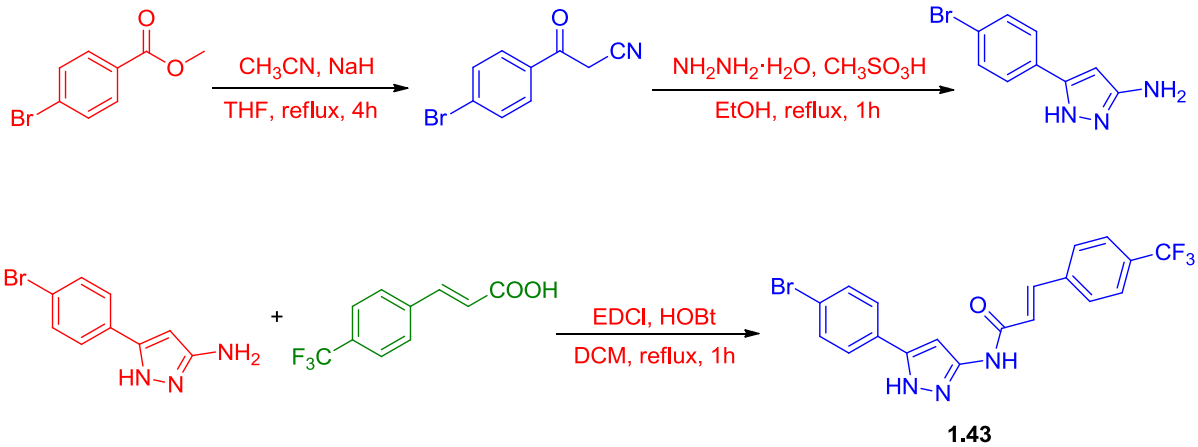
Several recent reports from literature suggest that pyrazole derivatives are promising anti-cancer agents in different cellular lines including melanoma, liver, colon, lung, breast, alveolar adenocarcinoma, renal, neuroblastoma, ovarian and leukaemia human cancer cells.[133] Although the skeleton of pyrazole plays an important role in its biological effects, the type of peripheral substituents is also crucial. Pyrazoles, 1,3-diphenyl pyrazoles have been reported to be highly potent and efficient cytotoxic agents.[134] Of late, it was also reported that the dihydropyrazole derivatives have good potency and is used as selective inhibitors showing great effect on cancer cell death.[135] Some of the reported synthesized pyrazole molecules that show anti-cancer activity against different cancer cell lines are discussed below.

Various (E)-1-aryl-3-(3-aryl-1-phenyl-1H-pyrazol-4-yl)prop-2-en-1-one compounds (pyrazolic chalcones) and their pyrazolyl-pyrazoline derivatives were synthesized by Braulio Insuasty *et al*. (**2010**) (Scheme 1.11) and several of these compounds were screened for various cancer cell lines, of which two molecules **1.40a** and **1.42b** shows remarkable anti-cancer activity mainly against leukemia (K-562 and SR), renal cancer (UO-31) and non-small cell lung cancer (HOP-92) cell lines with the most important GI_{50} values ranging from 0.04 to 11.4 μM from the *in vitro* assays.[136]



Scheme 1.11. Synthesis of pyrazolyl-pyrazoline derivatives from pyrazolic chalcones.

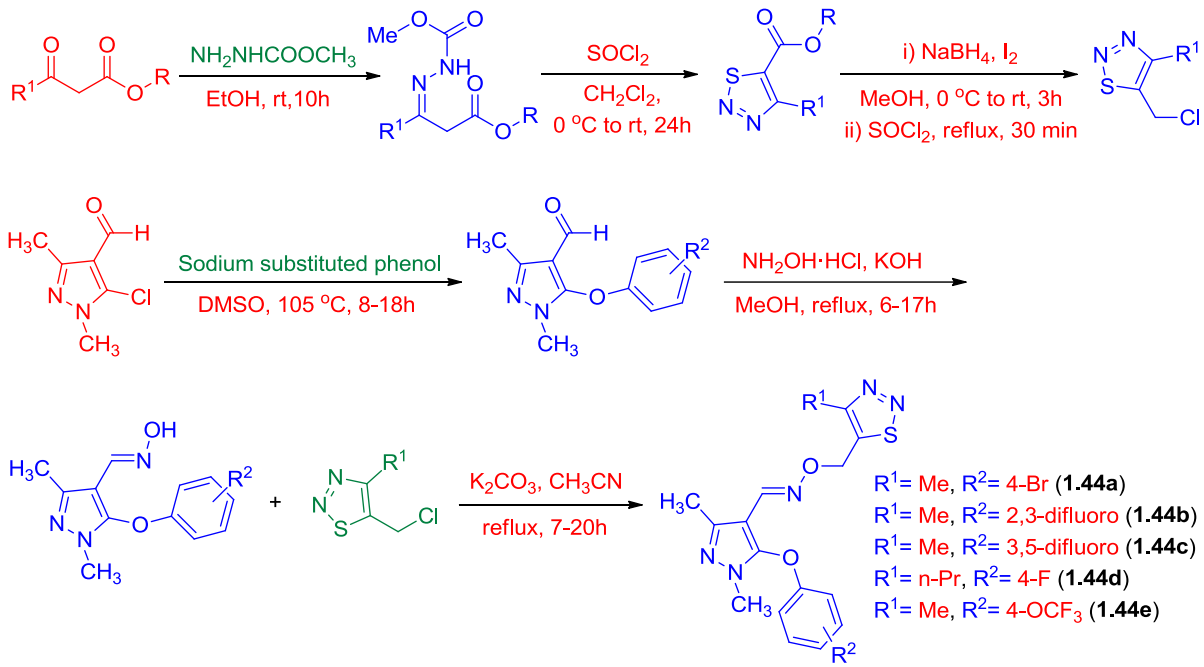
Wang and collaborators in **2015** synthesized a series of pyrazole derivatives that were tested for inhibition of tubulin polymerization in tumor cells. Compound (E)-N-(5-(4-bromophenyl)-1H-pyrazol-3-yl)-3-(4-(trifluoromethyl)phenyl)acrylamide (**1.43**) exhibited the best inhibitory activity against MCF-7 breast cancer cells (Scheme 1.12).[137]



Scheme 1.12. Synthesis of pyrazolyl-acrylamide derivatives.

Dai and co-workers (**2016**) prepared a series of twenty 1,2,3-thiadiazoles bearing pyrazole ring (Scheme 1.13). These compounds were tested for anti-cancer activity against cell

lines HCT-116 and SGC-7901. Among the synthesized pyrazole-thiadiazoles, compounds **1.44a, 1.44b, 1.44c** and **1.44d** showed better inhibitory activities than the standard 5-fluorouracil against HCT-116 cells and compounds **1.44c**, **1.44d** and **1.44e** showed higher inhibitory activities than 5-fluorouracil against SGC-7901 cell lines.[138]



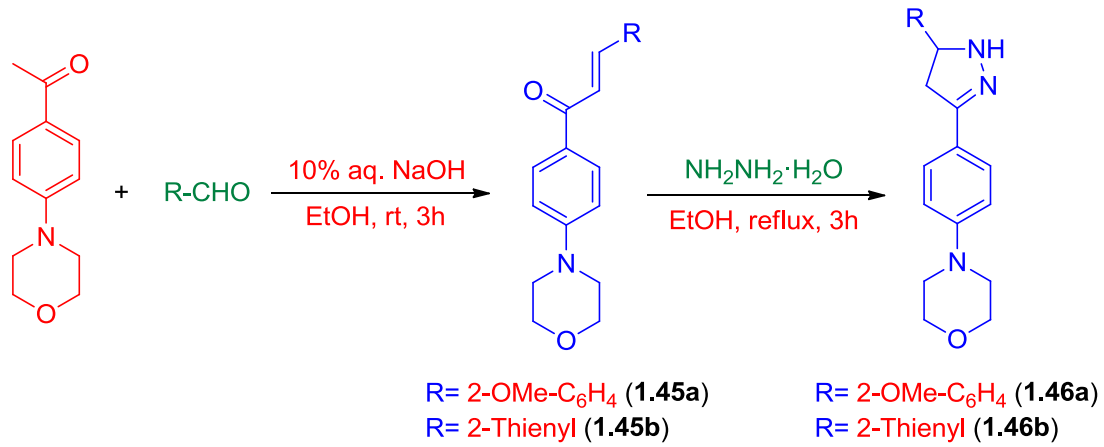
Scheme 1.13. Synthesis of pyrazole-thiadiazole derivatives.

1.4.3.2 Pyrazole with Anti-inflammatory Activity

Inflammation is a normal response to any kind of harmful or toxic stimulus threatening the host and it may vary from a localized response to a generalized one.[139] Relieving pain and to reduce inflammation is an urgent need to reduce such severe symptoms. Developing novel non-steroidal anti-inflammatory drugs (NSAIDs) with improved safety profile is still a challenge for many researchers in pharmaceutical industry. Most non-steroidal anti-inflammatory drugs (NSAIDs) have limitations in their therapeutic use since they cause some side effects like development of peptic and duodenal ulcer (massive gastrointestinal bleed), liver malfunctions and acute renal failure when used for a longer period of time.[140] However, NSAIDs still remains the most commonly prescribed drugs worldwide and have been generally considered as inhibitors of cyclooxygenases (COXs) i.e., they reduce pain and inflammation through inhibition of both cyclooxygenase-1 (COX-1 enzyme expresses their activity by acting as housekeeping enzyme such as protection of gastric mucosa, vascular homeostasis and platelet aggregation) and cyclooxygenase-2 (COX-2, its enzyme is expressed and regulated

during acute and chronic inflammation, pain and oncogenesis). Their therapeutic action is produced by inhibition of COX-2 whereas their side effects arise from the inhibition of COX-1 activity.[141] Therefore, stepwise approach to treat such inflammation disorders is generally applied such as physical therapy, NSAIDs, disease modifying anti-rheumatic drugs (DMARDs), corticosteroids and finally, immunosuppressive agents.[142] Consequently, extensive research for development of novel compounds having anti-inflammatory activity has been directed towards improving their pharmacological profile. Below are some of the synthesized pyrazole molecules that were reported as good anti-inflammatory agents.

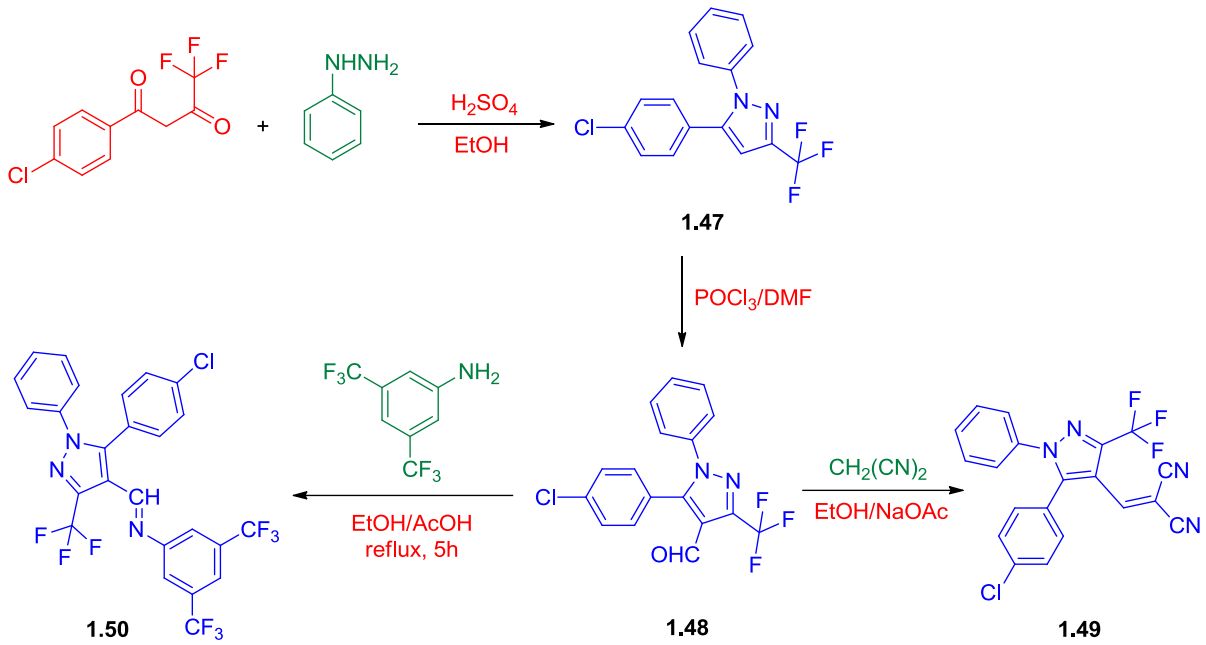
Omneya M. Khalil in **2011** synthesized chalcones and their corresponding pyrazoline products (Scheme 1.14). All these molecules were evaluated for their anti-inflammatory activity carrageenan edema in albino rats at a dose of 10 mg/kg. Screening data revealed that each molecule exhibited considerable anti-inflammatory properties. Except for 3-(2-methoxyphenyl)-1-(4-morpholinophenyl)-2-propen-1-one (**1.45a**), all other chalcone derivatives were found to be more potent than their cyclized pyrazolines. Pyrazoline derivatives 5-(2-methoxyphenyl)-4,5-dihydro-3-(4-morpholinophenyl)-1H-pyrazole (**1.46a**) and 3-(4-morpholinophenyl)-4,5-dihydro-5-(2-thienyl)-1H-pyrazole (**1.46b**) showed comparable activity to control drug indomethacin.[143]



Scheme 1.14. Synthesis of chalcone and pyrazoline derivatives.

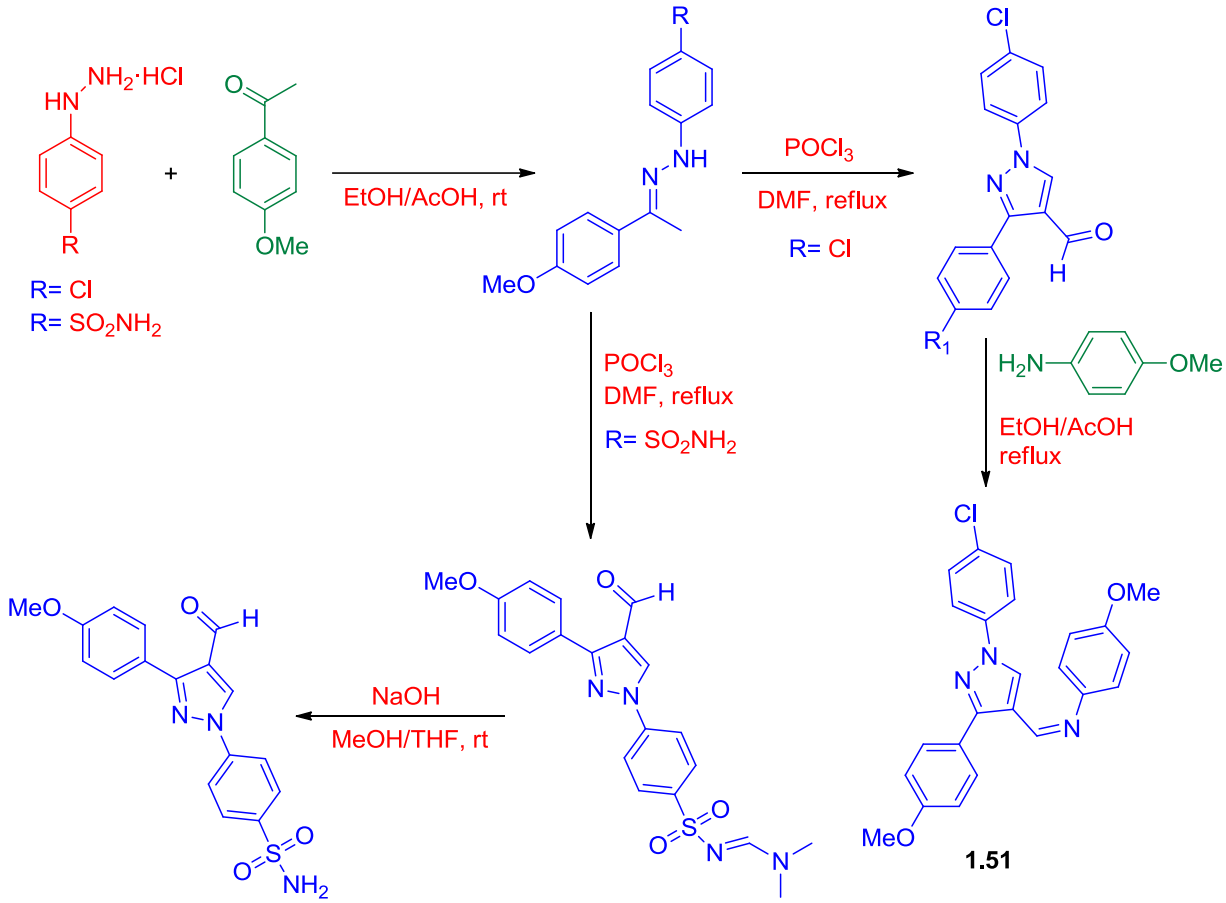
Magda A.-A El-Sayed *et al*. (**2012**) synthesized a series of pyrazole derivatives and these molecules were evaluated for COX-1/COX-2 inhibition and anti-inflammatory activity. It was reported that among all the molecules, N-((5-(4-chlorophenyl)-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)methylene)-3,5-bis(trifluoromethyl)aniline (**1.50**) exhibited

optimal COX-2 inhibitory potency and selectivity equivalent with the reference drug celecoxib (Scheme 1.15).[144]



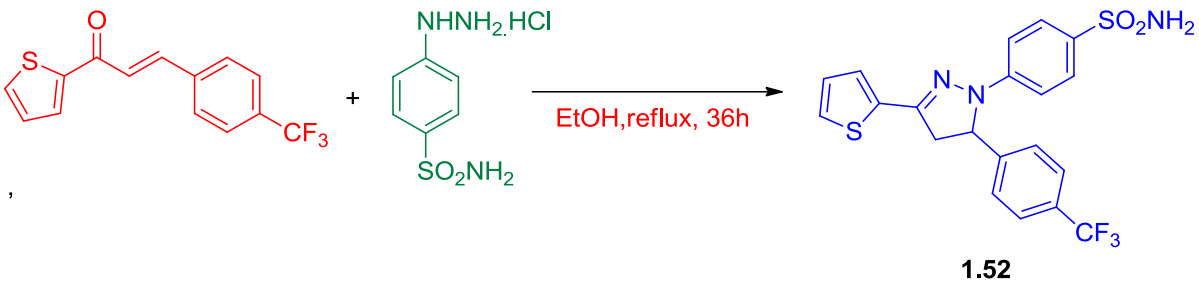
Scheme 1.15. Synthesis of trifluoromethane substituted pyrazole derivatives.

In **2013**, Fatma A. Ragab and group synthesized some 1,3,4-trisubstituted pyrazoles (Scheme 1.16) and all these molecules were evaluated for their anti-inflammatory activity, analgesic as well as ulcerogenic activity. Results showed that these molecules showed anti-inflammatory and analgesic activities with better GIT tolerance than the standard drug phenylbutazone. The IC_{50} reports showed that N-((1-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-4-yl)methylene)-4-methoxyaniline (**1.51**) was the most active anti-inflammatory and analgesic agent.[145]

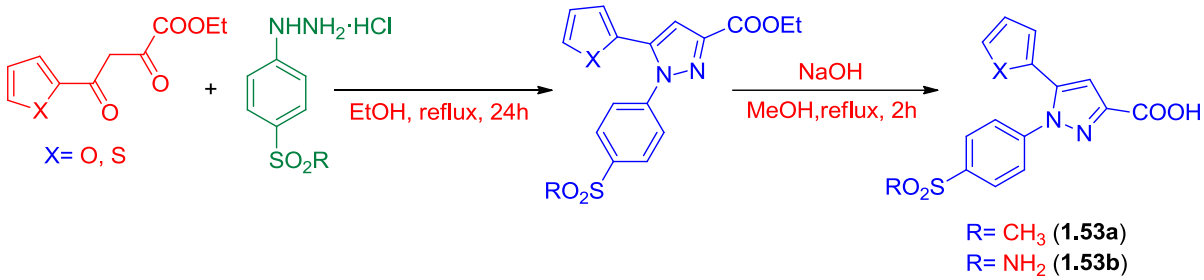


Scheme 1.16. Synthesis of 1,3,4-trisubstituted pyrazole derivatives.

Two series of 1,3,5-triaryl pyrazolines (Scheme 1.17) and 1,3,5-trisubstituted pyrazoles (Scheme 1.18) were synthesized by Abdellatif, K. R. *et al*. in **2015** and each molecules were evaluated for their anti-inflammatory activity and *in vitro* COX-1/COX-2 inhibitory activity. Reports show that all compounds were more COX-2 inhibitors than COX-1. Of all the molecules, 4-[3-thiophen-2-yl-5-(4-trifluoromethyl-phenyl-4,5-dihydro-pyrazol-yl]-benzene sulfonamide (**1.52**) showed good anti-inflammatory activity (ED_{50}= 99 µmol/kg) which is reported to be five times more potent than ibuprofen and half potency than celecoxib (ED_{50}= 47 µmol/kg) in the *in vivo* studies. The analogues with thienyl substitution are found to be more potent than furyl ones.[146]

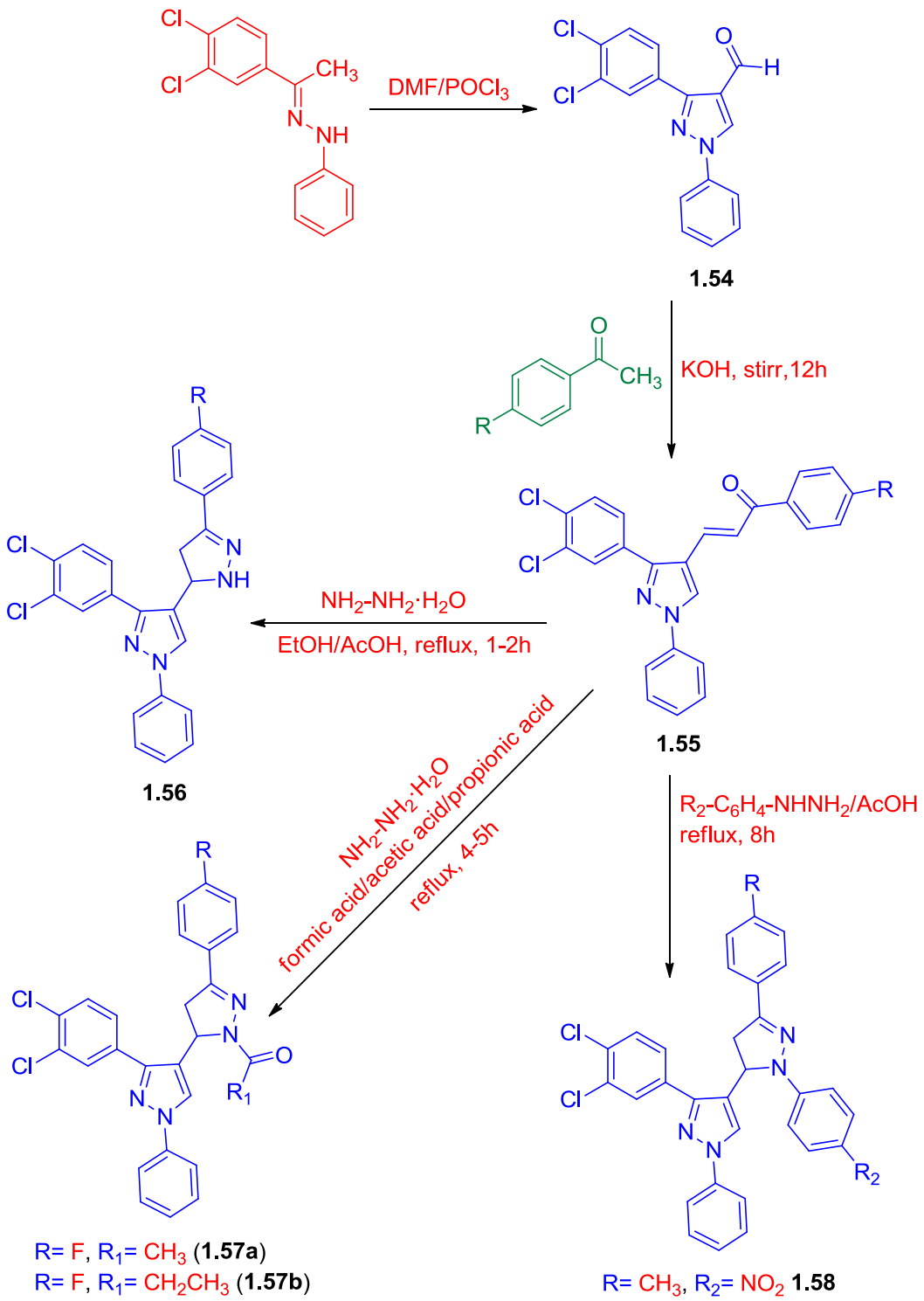


Scheme 1.17. Synthesis of 1,3,5-triaryl pyrazolines.



Scheme 1.18. Synthesis of 1,3,5-trisubstituted pyrazoles.

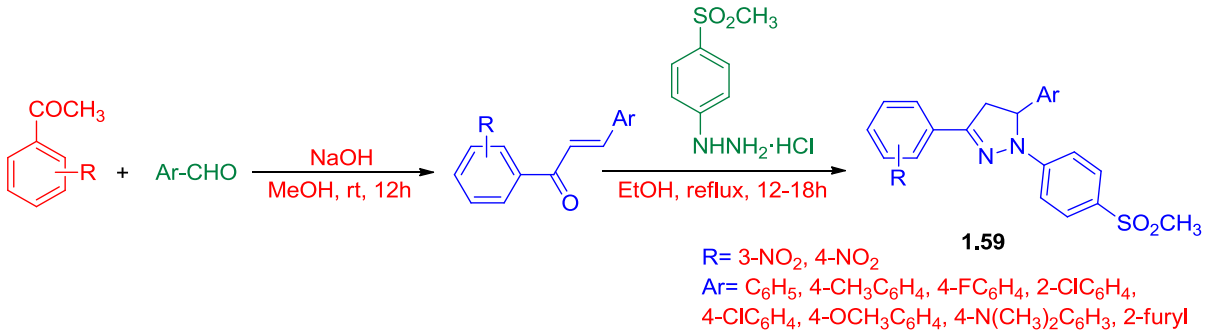
Shivapura Vivek *et al*. (**2015**) synthesized pyrazoline derivatives linked to a substituted pyrazole scaffold (Scheme 1.19) which were evaluated for anti-inflammatory, analgesic and anti-bacterial activities. Results showed that N-acylated pyrazolyl-pyrazolines (**1.57a**, **1.57b)** and nitro substituted pyrazolyl-pyrazoline (**1.58**) exhibited a potent anti-inflammatory activity whereas, compounds **1.57b** and **1.58** shows analgesic activity. The compound with halo substituted phenyl group at C-3 of the pyrazoline ring was reported to show interesting anti-bacterial activity and compound **1.57b** shows dual profile for anti-inflammatory as well as anti-bacterial activity.[147]



Scheme 1.19. Synthesis of pyrazolyl-pyrazoline derivatives.

In **2016**, Khaled R. A. Abdellatif *et al*. prepared a series of 1,3,5-triaryl-4,5-dihydro-1H-pyrazole derivatives (Scheme 1.20). All the synthesized compounds were tested for their cyclooxygenase (COX) inhibition, anti-inflammatory activity and ulcerogenic liability. These

compounds were more potent inhibitors for COX-2 than COX-1. Most of the compounds also showed good anti-inflammatory activity in comparison with the control drug celecoxib.[148]



Scheme 1.20. Synthesis of methanesulfonyl pyrazoline derivatives.

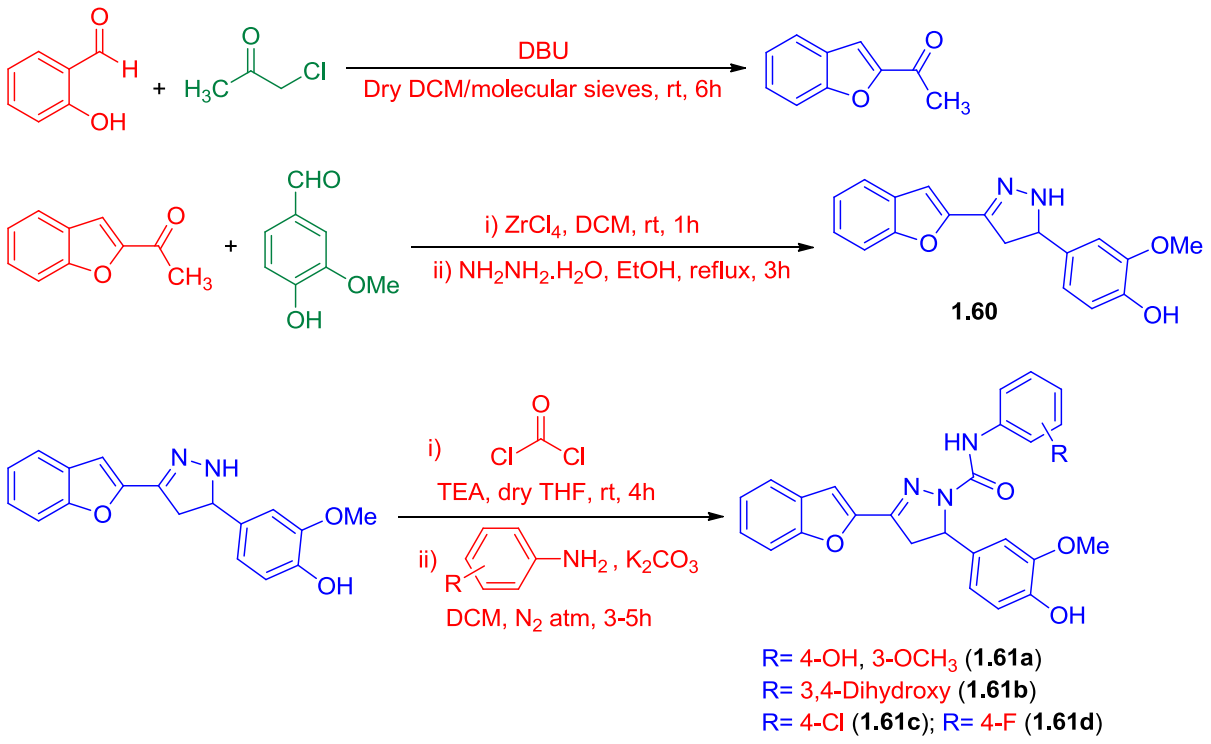
1.4.3.3 Pyrazole with Anti-microbial and Anti-fungal Activity

The problems caused by multi-drug resistant microorganisms have been persisting for a decade and have reached an alarming level in many countries around the world.[149] The first anti-microbial drug therapy began in the year 1929 with the discovery of 'penicillin' by Alexander Fleming in 1928, which is a powerful anti-bacterial substance and also the discovery of chemically synthesized 'sulfonamides' in 1935 by Domagk having broad anti-microbial activity. These drugs were designed to inhibit or kill microorganisms that are causing widespread and serious diseases with minimal or no effect on the receiver. This type of treatment or therapy is known as chemotherapy.[150] Many studies have been done for synthesizing novel molecules for the treatment of several microbial diseases and since pyrazole have been reported to have many biological activity and keeping in view its potential importance and the incorporation of its moiety into various heterocyclic ring system.[151] Some of the synthesized pyrazole moiety with their positive anti-microbial activity reported by different researchers have been explained below.

The emergence and incidence of fungal infection after 1950s has become a worrying threat to human health especially the existence of a more threatening type of fungal infections which are to a large extent iatrogenic. Many patients with decreased immunity such as AIDS, cancer and transplant patients are likely to be more affected by these primary and opportunistic fungal infections and therefore it tends to grow rapidly in them.[152] During the past few decades, a number of anti-fungal drugs such as amphotericin B, fluconazole, miconazole, itraconazole voriconazole, methotrexate, anidulafungin, etc., have helped to fight against fungal infections

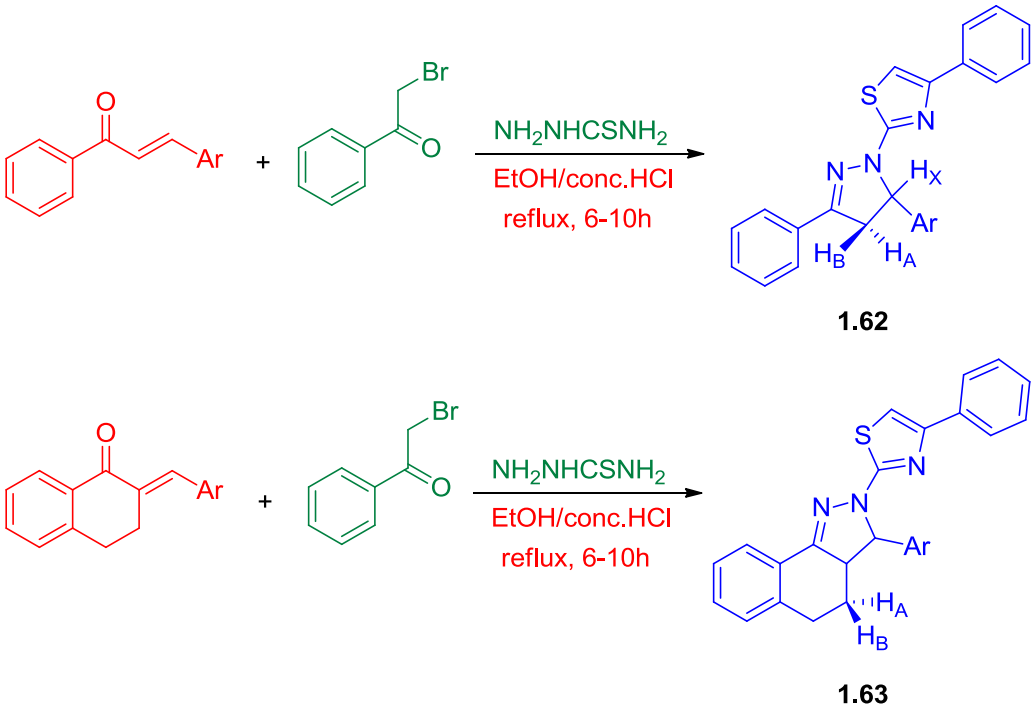
but due to their side effects when used in combination with other drugs and also it involves a number of preparative steps and costly chemicals for preparing this drugs. Therefore, the development of new and effective anti-fungal drugs with low cost effective and reasonably broad spectrum is the need of the hour.[153] Pyrazole derivatives have been proposed as potential drugs for such kind of anti-fungal infections due to their broad range of pharmacological activities.[154] With their growing applications for synthesis and bioactivity, many chemists and biologists in recent years have focused their attention to the research of pyrazole and its analogues.[155] Below are some of the reported synthesis of pyrazole molecules that are studied for their anti-bacterial and anti-fungal activity.

A series of benzofuran and vanillin based 1,3,5-trisubstituted pyrazoline analogues (**1.61**) were synthesized in **2012** by Javarappa Rangaswamy *et al*. (Scheme 1.21) which were further screened for their *in vitro* anti-oxidant and anti-microbial activities. Among all the tested compounds, **1.61a** and **1.61b** (methoxy and hydroxyl substitution) confirmed potent anti-oxidant activity and compounds **1.61c** and **1.61d** (chloro and fluoro substitution) exhibited maximum anti-microbial activity whereas for antifungal studies, **1.61d** showed excellent activity in comparison with the standard streptomycin and fluconazole drugs.[156]



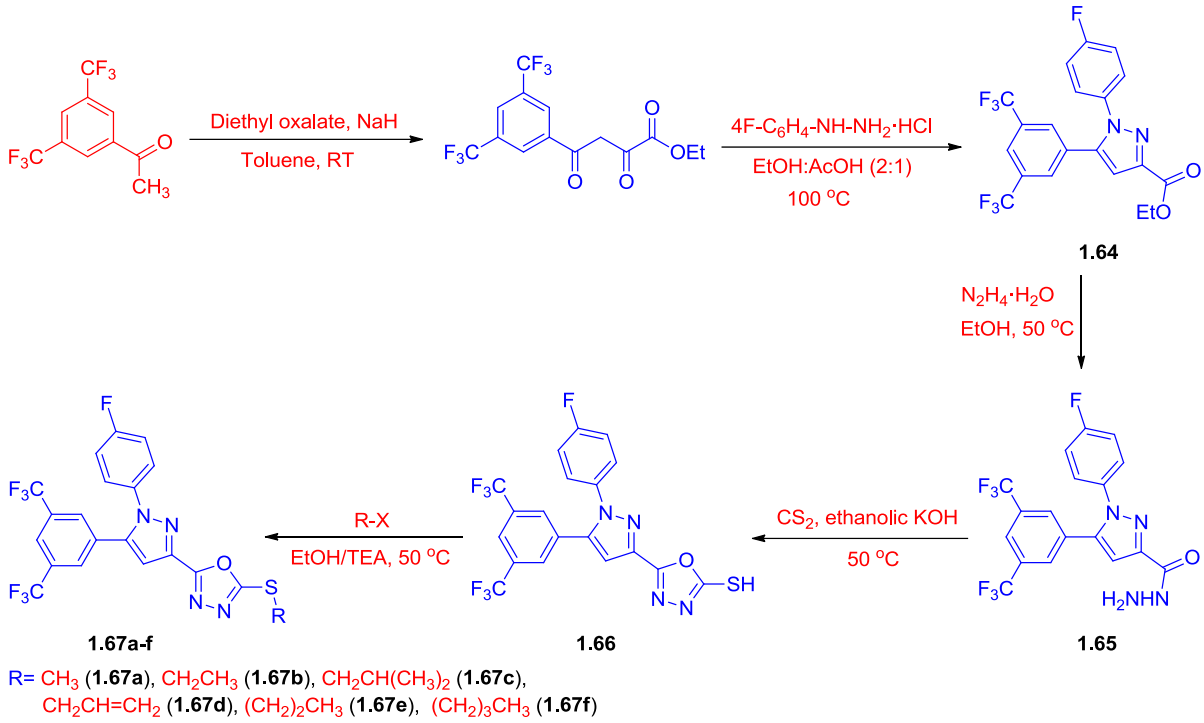
Scheme 1.21. Reaction pathway for the synthesis of benzofuran-pyrazoline derivatives.

In **2013**, Bahman Sharifzadeh and co-workers described the synthesis of a series of 2-(3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)-4-phenylthiazoles prepared by a three-component cyclo-condensation of various chalcones, thiosemicarbazide and phenacyl bromide (Scheme 1.22). Anti-bacterial activities of the compounds **1.62** and **1.63** were evaluated and the study exhibited good anti-bacterial activity against *Pseudomonas aeruginosa*.[157]



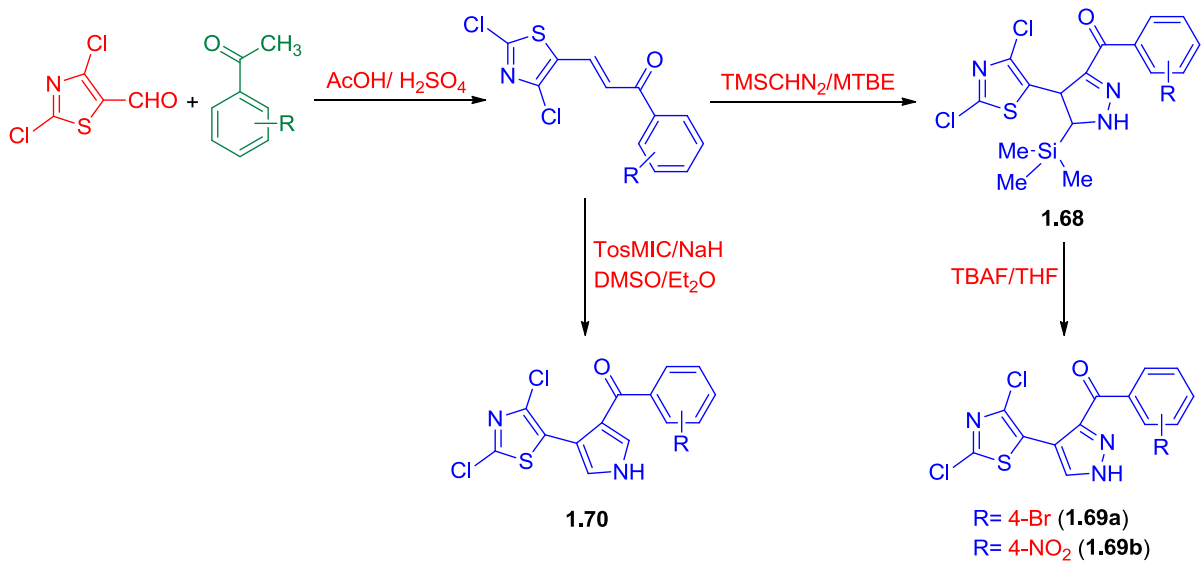
Scheme 1.22. Synthesis of thiazolyl-pyrazoline derivatives.

In **2015**, Amar Patil *et al*. reported the synthesis of a series of six pyrazole-oxadiazole derivatives (Scheme 1.23). These molecules were evaluated for their anti-fungal activity against *Candida albicans*, *Aspergillus flavus*, *Aspergillus fumigates* and *Aspergillus niger*. Their anti-fungal activity was evaluated against fungal pathogenic strains using broth micro dilution method. All compounds were screened for MIC (Minimum Inhibitory Concentration) and MFC (Maximum Fungicidal Concentrations). The synthesized compounds **1.66**, **1.67a**, **1.67b**, **1.67c**, **1.67d** and **1.67e** showed good anti-fungal activity against *Candida albicans*, *Aspergillus flavus*. Compound **1.67a** showed excellent activity against *A. fumigates* whereas compound **1.67f** was inactive against this fungus.[158]



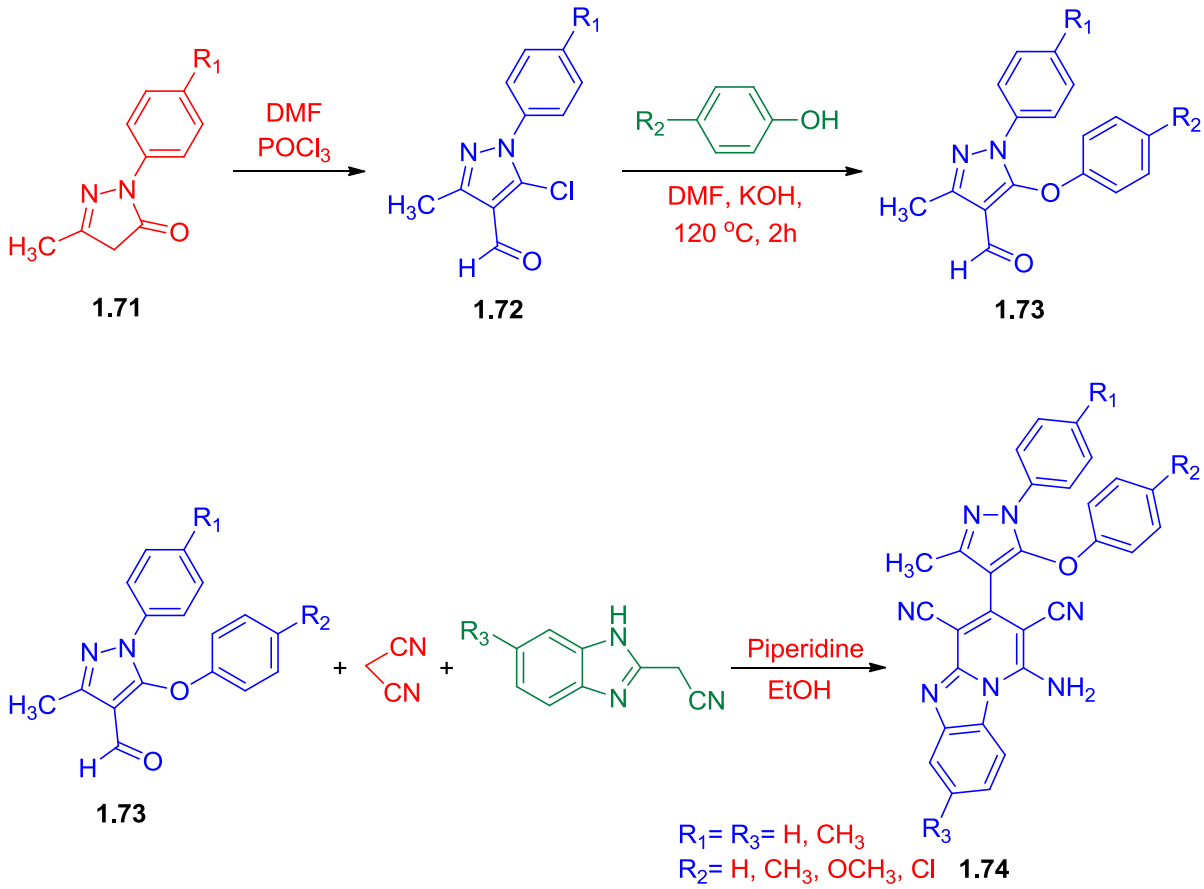
Scheme 1.23. Synthetic pathway for the preparation of pyrazolyl-oxadiazole derivatives.

In **2015**, Shaik Sharafuddin Basha and co-workers developed a variety of bis heterocyclic pyrazoles (**1.69**) and pyrrole derivatives (**1.70**) from heteroaryl chalcones adopting 1,3-dipolar cycloaddition reaction and these molecules were studied for their anti-microbial activity (Scheme 1.24). The compounds **1.69a** and **1.69b** having bromo and nitro substituents on the aromatic ring shows interesting anti-microbial activity against *Bacillus subtilis* and *Aspergillus niger*.[159]



Scheme 1.24. Synthesis of 3-aroyl-4-heteroaryl pyrrole and pyrazole derivatives.

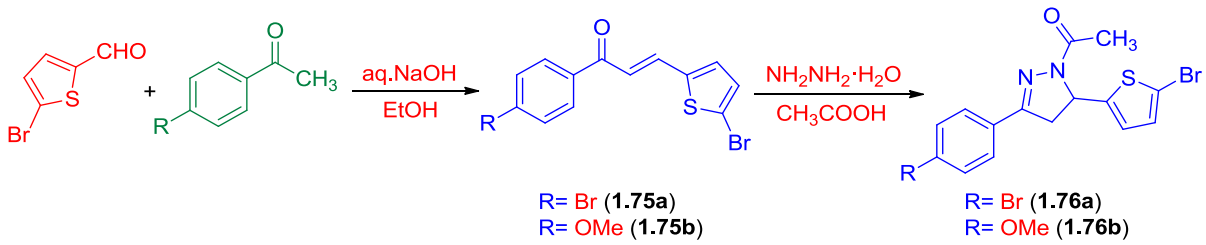
In **2015**, a series of pyrido[1,2-a]benzimidazole derivatives bearing the aryloxypyrazole nucleus (**1.74**) have been synthesized by Hardik H. Jardosh *et al*. Anti-microbial activity screening was done for all the synthesized molecules and it was reported that majority of the compounds were found to be active against employed pathogens and the compounds are strongly dependent on the nature of the substituents at the either linked aryl ring attached to the pyrazole unit or together with the substituent linked to the C5 of the benzimidazole unit (Scheme 1.25).[160]



Scheme 1.25. Synthetic pathway for the synthesis of pyrido[1,2-a]benzimidazole derivatives.

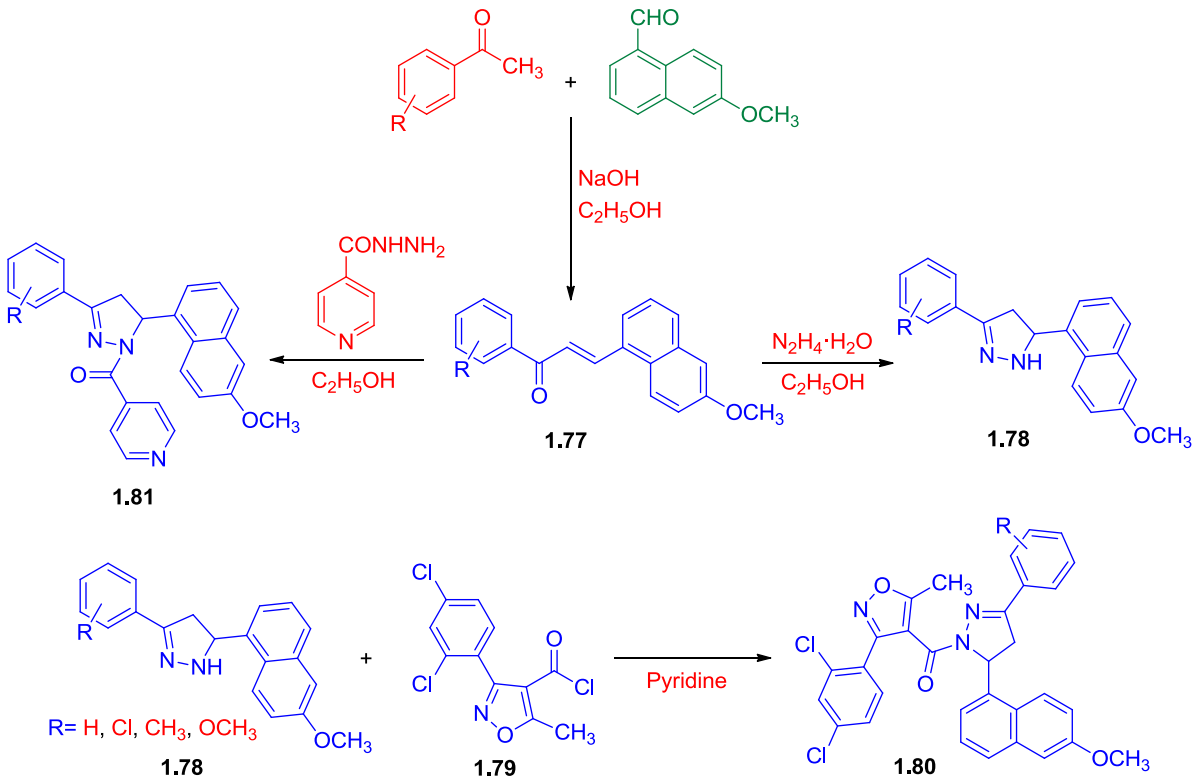
Helmi Mohammed Al-Maqtari and co-workers (**2017**) synthesized a series of chalcone and pyrazoline derivatives (Scheme 1.26). All synthesized compounds were evaluated for their anti-fungal activity on *Candida albicans* and *Aspergillus niger*. The test revealed that compounds **1.75a** and **1.76b** showed significant activity against both tested fungal strains. This report explains that it is important to take into consideration the importance of balancing hydrosolubility/lipophilicity in drug design because of the coexistence of two combined anti-fungal N, O and O, S-pharmacophore sites for pyrazoline series (**1.76**) as in agreement with

the POM analyzer. On the other hand, two coexistent and identical N, Cl-pharmacophore sites have been identified for fluconazole.[161]



Scheme 1.26. Synthesis of chalcone and pyrazoline derivatives.

Recently, a series of (3-(2,4-dichlorophenyl)-5-methylisoxazol-4-yl)(3-(4-substituted phenyl)-5-(6-methoxynaphthalen-1-yl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (**1.80**) and (3-(4-fluorophenyl)-5-(6-methoxynaphthalen-1-yl)-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (**1.81**) were synthesized by reacting 3-(6-methoxynaphthalen-1-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (chalcone) (**1.77**) with hydrazine hydrate followed by 3-(2,4-dichlorophenyl)-5-methylisoxazole-4-carbonyl chloride (**1.79**) and isonicotinohydrazide respectively were synthesized by Satish Babulal Jadhav and co-workers in **2017** (Scheme 1.27). All these synthesized molecules were evaluated for their anti-microbial activity and results showed significant to moderate anti-microbial activity. Anti-bacterial activity was performed against *Staphylococcus aureus, Escherichia coli, Salmonella typhi* and anti-fungal activity against *Aspergillus niger, Aspergillus flavus and Penicillium chrysogenum.* In this study, the pharmacophore which possess pyrazoline moiety coupled with isoxazole ring, pyridyl ring and groups substituted like bromo, chloro, flouro and methoxy provides the positive results.[162]



Scheme 1.27. Synthesis of N-substituted-pyrazoline derivatives.

1.4.3.4 Pyrazole with Anti-tubercular Activity

Another disease that has been a threat to the world is the mycobacterial disease, Tuberculosis (TB). It is a chronic disorder caused by five closely related mycobacteria such as *Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium africanum, Mycobacterium microti and Mycobacterium canetti*. Among these, *Mycobacterium tuberculosis* (*M. tuberculosis*) are organisms that are present almost everywhere and are caused by slow-growing bacteria in parts of the human body becoming important intracellular pathogens that establish an infection in oxygen-rich macrophages of the lung called pulmonary TB.[163] It has been reported by WHO in 2013 that about 8.6 million people of the World's population is currently infected with TB and deaths reaching to about nearly 1.3 million annually in 2012 due to the development of clinical pulmonary TB in infected people. The majority of cases reported worldwide were in the South-East Asia (29%), African (27%) and Western Pacific (19%) regions. India accounted for 29% and China alone accounted for 12% of total cases reported respectively.[164] The *Mycobacterium tuberculosis* usually attacks the lungs, spine, kidney and brain. Therefore, in order to prevent such disease from becoming severe and fatal, it is necessary to treat such disease properly. The need for designing new anti-tubercular drugs that can withstand both chronic and acute growth phases of *Mycobacterium*

giving better treatment against tuberculosis and stop all forms of drug resistant-TB has become a necessity.[165] Below in Figure 1.13 is given some of the lead anti-tubercular agents (**1.82-1.88**) that have been known and used for the treatment of tuberculosis.

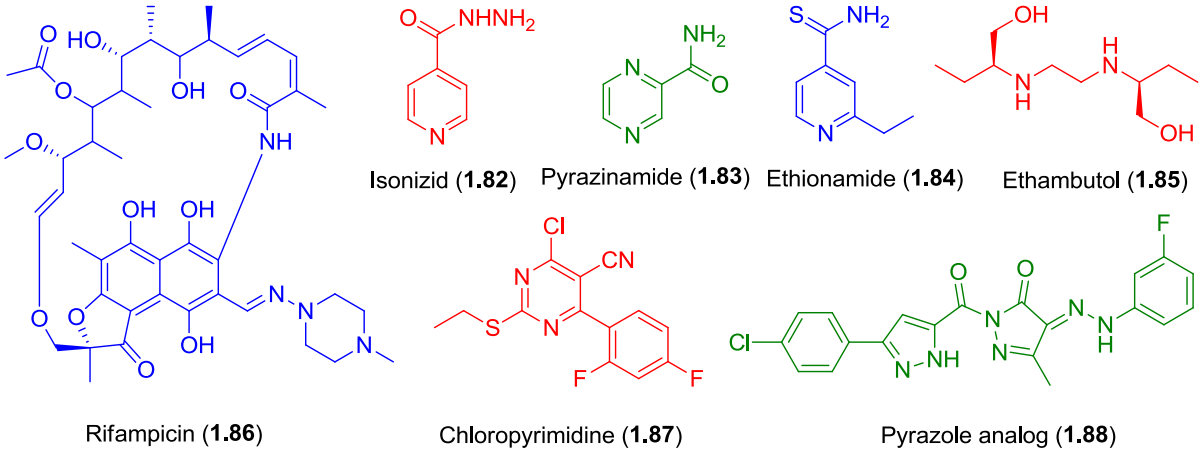
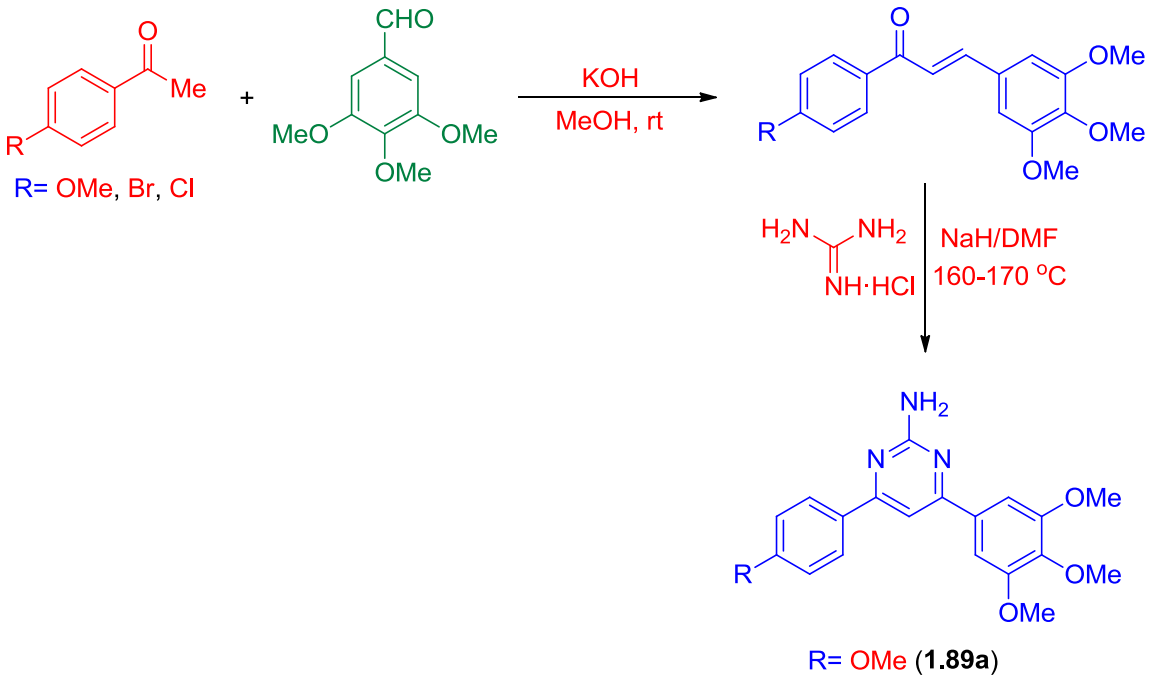


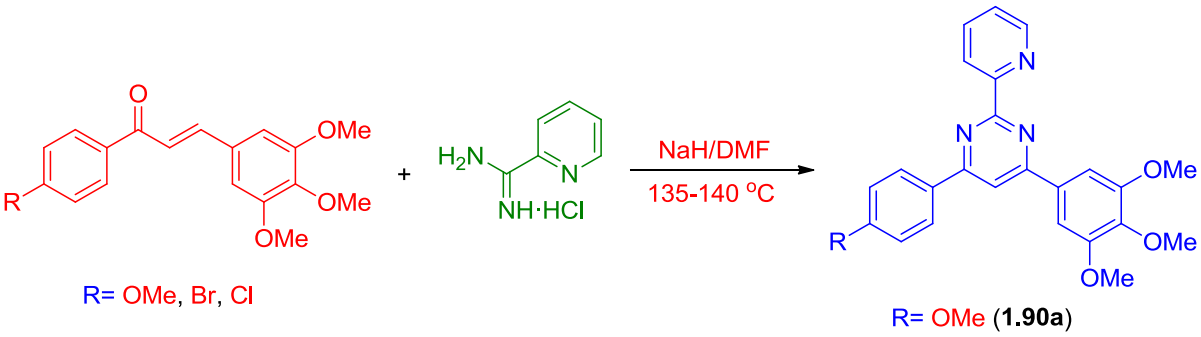
Figure 1.13. Some of the lead anti-tubercular drugs for the treatment of tuberculosis.

Some heterocyclic compounds such as pyrimidine and pyrazole analogs have been reported to have high activity against *Mycobacterium tuberculosis* some of which have been discussed below.

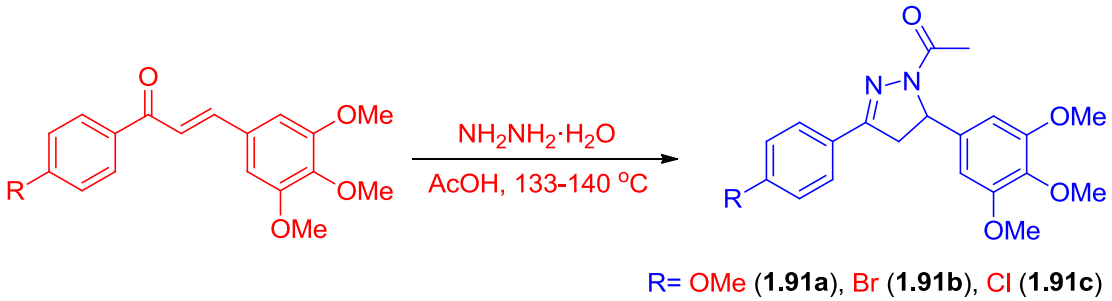
Vinay Pathak *et al*. (**2014**) synthesized various substituted 4,6-diarylpyrimidin-2-amine (**1.89**), 4,6-diaryl-2-(heteroaryl)pyrimidine (**1.90**) and 1-(3,5-diaryl-4,5-dihydro-1H-pyrazol-1-yl)ethanone (**1.91**) derivatives (Scheme 1.28, 1.29 and 1.30) which were screened for their *in vitro* anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv strain. The screening reports showed that compounds **1.89a**, **1.90a**, **1.91b** and **1.91c** exhibited significant anti-tubercular activity at MIC values 25, 25, 12.5 and 12.5 µM concentration. The most active compounds according to their biological activity profile were **1.91b** and **1.91c** which showed eight times significant selectivity towards anti-tubercular activity.[166]



Scheme 1.28. Synthesis of 4,6-diarylpyrimidine-2-amine derivatives.

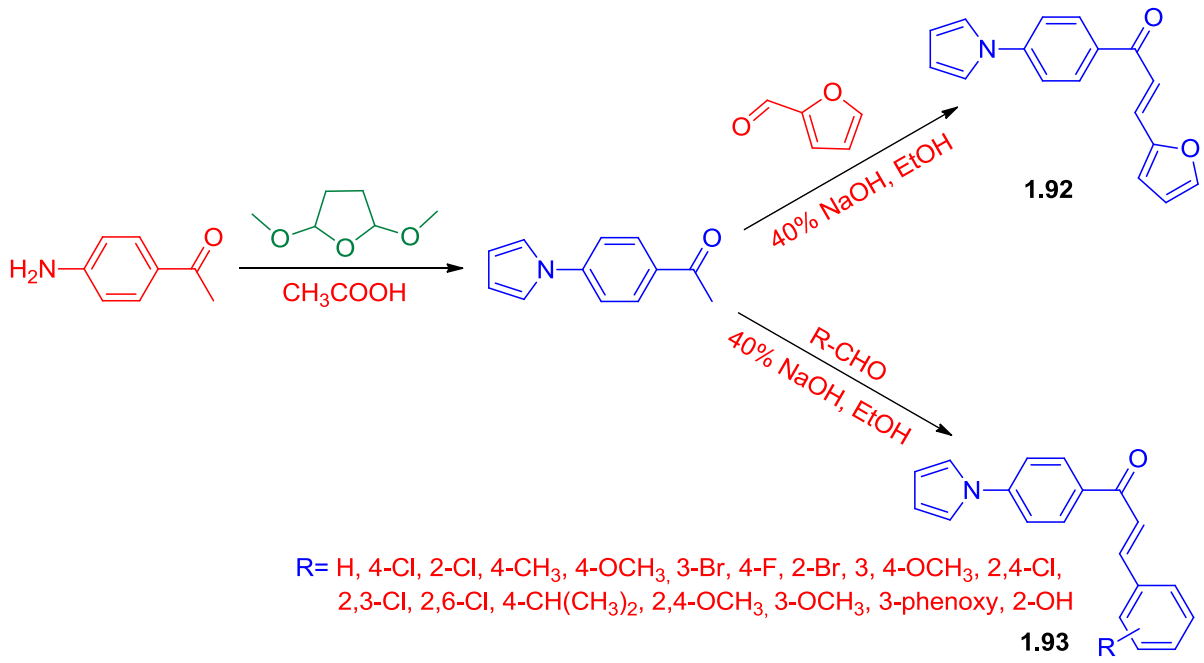


Scheme 1.29. Synthesis of 4,6-diaryl-2-(heretoaryl)pyrimidine derivatives.

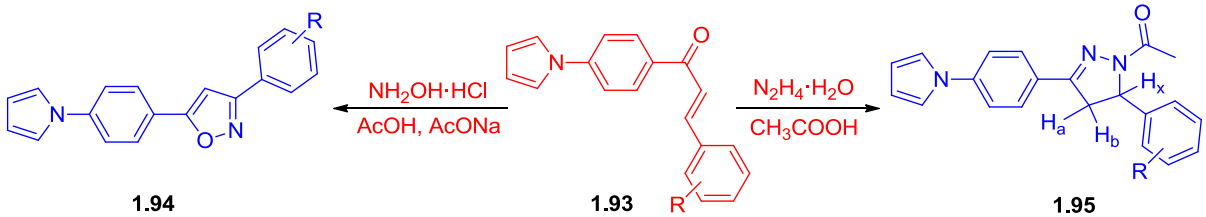


Scheme 1.30. Synthesis of 1-(3,5-diaryl-4,5-dihydro-1H-pyrazol-1-yl)ethanone derivatives.

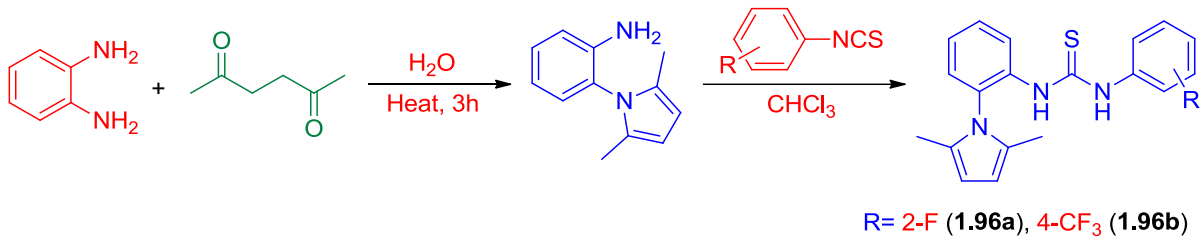
Shrinivas D. Joshi *et al*. in **2015** synthesized 61 pyrrolyl derivatives bearing chalcone, isoxazole, pyrazoline and phenyl thiourea moieties (Scheme 1.31, 1.32 and 1.33) and all the synthesized compounds were evaluated for their anti-bacterial and anti-tubercular activity. Results showed that 1-(2-(2,5-dimethyl-1H-pyrrol-1-yl)phenyl)-3-(2-fluorophenyl)thiourea (**1.96a)** and 1-(2-(2,5-dimethyl-1H-pyrrol-1-yl)phenyl)-3-(4-(trifluoromethyl)phenyl)thiourea (**1.96b**) exhibited the maximum anti-tubercular activity almost close to isoniazid (0.4 µg/mL) with a MIC value of 0.8 µg/mL. All other compounds displayed significant activity with a MIC value of 6.25-100 µg/mL. These drugs were further tested for mammalian cell toxicity using human lung cancer cell lines (A549) but there was no apparent cytotoxicity.[167]



Scheme 1.31. Synthesis of pyrrole chalcone derivatives.



Scheme 1.32. Synthesis of pyrrole isoxazole and pyrrole pyrazoline derivatives.



Scheme 1.33. Synthetic route for the preparation of pyrrolyl phenyl thiourea derivatives.

1.5 Historical Perspective & Chemistry of Anthracene

Structurally, anthracene is a three fused benzene rings belonging to the class of polycyclic aromatic hydrocarbons (PAHs). They are solid PAHs and they do not contain any heteroatoms or carry other substituents.[168] In 1866, Fritzache in his due course of studies on solid hydrocarbons (that can be obtained from coal tar by distillation) discovered that saturated solutions of anthracene upon exposure to sunlight regenerated anthracene upon melting which is a colorless crystalline precipitate. Anthracene is known to be an important component of coal tar (contains 2.0% anthracene) and is classically prepared in the laboratory by cyclodehydration of o-methyl- or o-methylene-substituted diarylketones, common impurities being carbazole and phenanthrene.[169] An important isomer of anthracene is phenanthrene which is a polycyclic aromatic hydrocarbon (PAHs) composed of three fused benzene rings and is more stable than anthracene due to more efficient π bonding (Figure 1.14).[168]

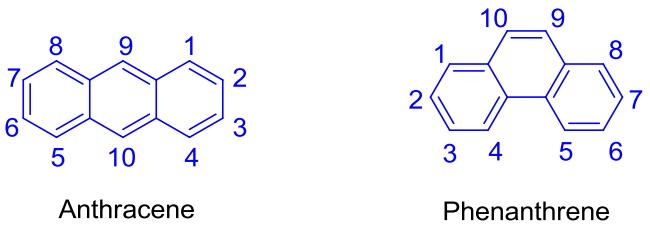


Figure 1.14. Structures of Anthracene and Phenanthrene.

There are five naturally occurring anthracene analogs that have been known to be isolated from a woody plant, *Coussarea macrophylla*. They are 1,4,10-trimethoxyanthracene-2-carbaldehyde (**1.97**), (1,4,10-trimethoxyanthracen-2-yl)methanol (**1.98**), 1,4,8,10-tetramethoxyanthracene-2-carbaldehyde (**1.99**), 1,4,10-trimethoxyanthracene-2-carboxylic acid (**1.100**) and 1,3-dimethoxy-2-methoxymethylanthraquinone (**1.101**) as represented in Figure 1.15.[170]

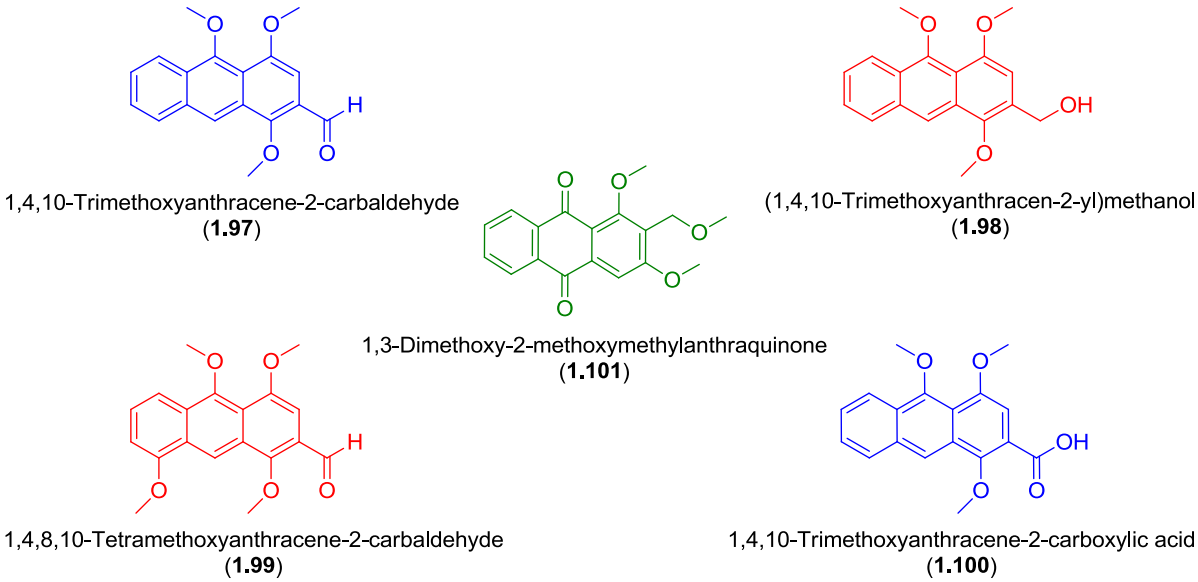


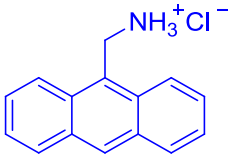
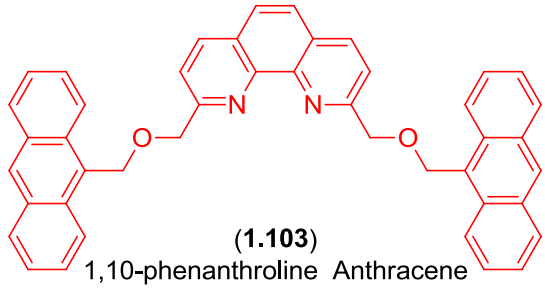
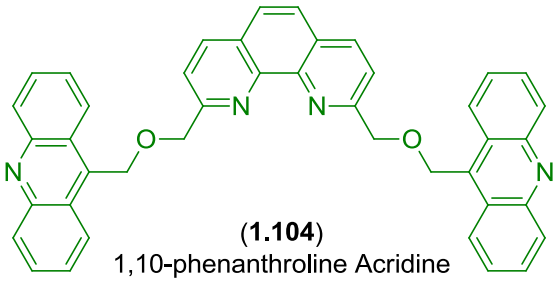
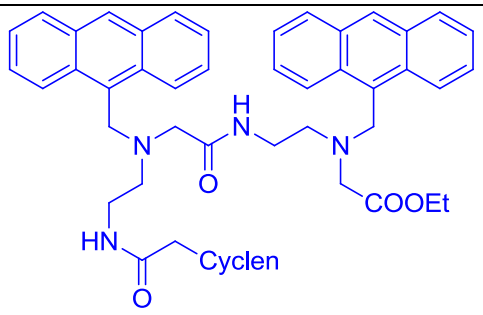
Figure 1.15. Naturally occurring anthracene analogs.

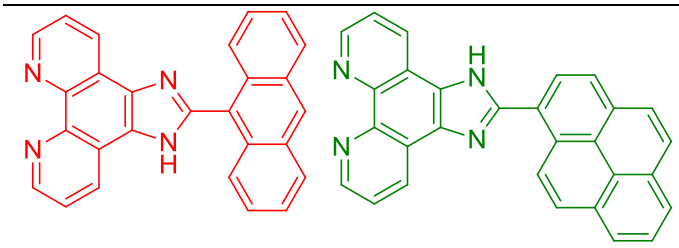
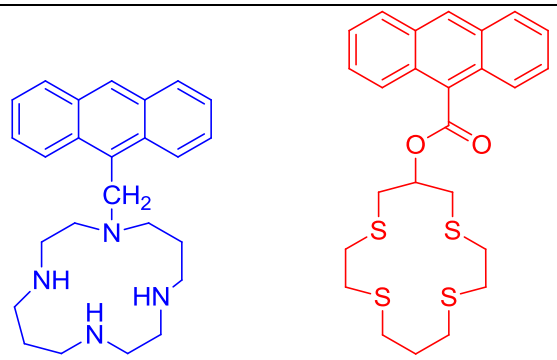
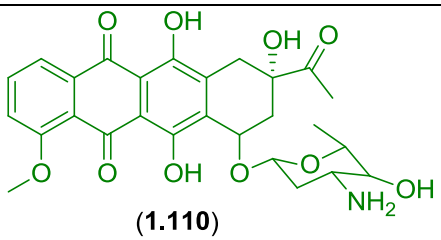
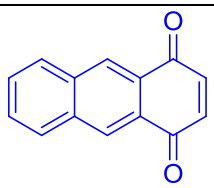
1.5.1 Biological Importance and other Applications of Anthracene

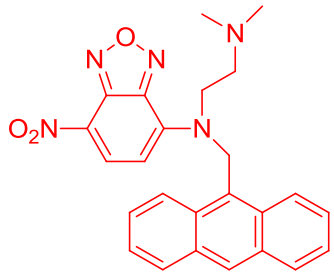
Anthracene are the subject to many research areas because of their applications in the diverse fields such as spectroscopic, bimolecular photoreaction reaction, photochromic properties (used in designing optical, electronic or magnetic switches incorporated in mesophases, polymers, films or crystals) and thermotropic liquid-crystalline to light-light emitting properties.[171] Anthracene also exhibits a 0.99 high quantum efficiency of photoluminescence in the solid state.[172] For the development of functional materials, anthracene containing polymers are of great interest especially the 9,10-dihydroxyanthracene but because of its tendency to easy oxidation, it becomes difficult to purify this molecule and therefore, this limits the synthesis of anthracene containing polymer compounds.[173] Among the many polycyclic aromatic hydrocarbons (PAHs), extensive studies have been done especially on anthracene and its derivatives due to its biological properties that have been reported over the years. Research reports on anthracene and its derivatives shows that anthracene is found to be effective against specific skin ailments (Pseudourea; one of the earliest examples of anthracene-based drugs that was tested in clinical trials).[174] There were also reports on the biological activity of anthracene with amino phosphonic acids which are known for its anti-cancer activity.[175] It also possesses significant biological activity against L1210 *in vitro* tumor cells.[176] Anthracene probes are known to absorb moderately in the near-UV region and gives good fluorescence quantum yields which are used in monitoring ligand binding to DNA by spectroscopic methods.[177] Some of the synthesized anthracene derivatives

(**1.102–1.112**) which are reported to have various applications in different fields are specified in Table 1.1.

Table 1.1. Some of the reported synthetic Anthracene derivatives showing different applications.

Structure of Anthracene	Activity	Reference
 (**1.102**) (9-Anthryl) ammonium chloride	DNA-photo cleavage and photochemical reactivity	[177]
 (**1.103**) 1,10-phenanthroline Anthracene  (**1.104**) 1,10-phenanthroline Acridine	DNA-photo cleavers	[178]
 (**1.105**) Bis-anthryl peptide with cyclen moiety	DNA-binding Activity	[178]

 (**1.106**) (**1.107**) Anthracene and pyrene polypyridyl pyrazoles	DNA- binding Activity	[179]
 (**1.108**) (**1.109**) Anthracene appended cyclam rings	Redox activity in presence of transition metals	[180]
 (**1.110**) Anthracycline	Cancer Chemotherapy	[181]
 (**1.111**) 1,4-Anthracenedione	Anti-tumor Activity	[182]

 (**1.112**) Anthracene 4-amino-7-nitrobenzoxa[1,3]diazole	Fluorescence property	[183]

1.6 Rationale and Aim of the Research

In view of the wide applications and biological activities of various chalcones, pyrazoles, pyrazolines, heterocyclic compounds and anthracenes we thought it will be worthwhile to design and synthesize organic anthracene chalcone scaffolds and its further synthetic extension towards the synthesis of anthracenyl pyrazoline and anthracenyl pyrazole heterocyclic scaffolds to explore their anti-cancer activity. The present research investigation describes the synthesis of natural products-based organic anthracene scaffolds, spectral characterization, results and discussion and some of their anti-cancer activity is detailed in chapters 2–5.

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Chapter 2

Synthesis of Anthracenyl Chalcones by Conventional and Green Synthetic Methods and their Anti-Cancer Activity

Abstract

In this chapter, we aimed at synthesizing a series of anthracenyl chalcone derivatives (**2.10a-p**) using conventional as well as microwave-assisted green synthetic method. Each anthracenyl chalcones were characterized by various spectroscopic techniques and crystal structures of four novel anthracenyl chalcones (**2.10g**, **2.10i**, **2.10m**, **2.10p**) were solved by single crystal X-ray diffraction methods. All the synthesized antracenyl chalcone were evaluated for their anti-cancer activity against four human cancer cell lines, HeLa (cervical cancer cell line), MIAPACA (pancreatic cancer cell line), U-87 (human primary glioblastoma cancer cell line) and SIHA (cervical cancer cell line) using an SRB assay. Taking into account the various universal incidences and tremendous mortality ratio of cancer that makes serious health affair especially in cancers progressive with inflammation; consequential efforts are made and still continuing to characterize new drugs or agents for therapeutic intervention against cancer. The anti-cancer screening results of the newly synthesized anthracenyl chalcones showed good anti-cancer activity and among all the compounds, compounds **2.10g**, **2.10h**, **2.10j** and **2.10k** showed marked anti-cancer activity against HeLa, U-87, MIAPACA and SIHA with GI_{50} values of 5.18 μM, 4.04 μM, 5.31 μM and 4.02 μM respectively.

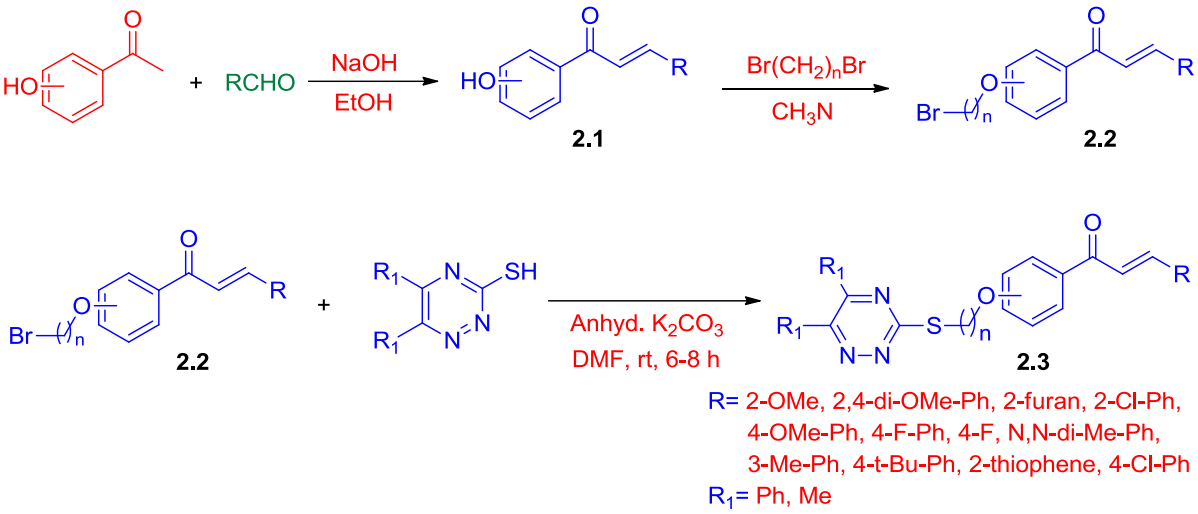
2.1 INTRODUCTION

Chalcones are polyketide natural products also chemically known as (E)-1,3-diaryl-2-propen-1-one are known to be abundantly available in many plant species and are reported to be the precursor of flavonoids and isoflavonoids. They are a class of open-chain flavonoids in which the two aromatic rings are linked by a three-carbon α,β-unsaturated carbonyl bridge enone moiety.[1] It is not only biosynthesized by plants but also can be prepared synthetically by aldol condensation,[2] Suzuki,[3] direct crossed-coupling,[4] Heck,[5] Friedel-Crafts[6] or Julia-Kocienski reaction.[7] Chalcone can also be classically synthesized by Claisen-Schmidt condensation between a benzaldehyde and an acetophenone under homogeneous and heterogeneous conditions in the presence of aqueous bases like NaOH,[8] KOH,[9] $Ba(OH)_2$ etc.[10] There are many other reaction methods that has been carried out using Claisen-Schmidt condensation,[11] grinding,[12] microwave-irradiation,[13] ultrasound irradiation technique,[14]

coupling reactions etc.[15] Chalcone are known to display several promising biological and pharmaceutical activities such as cytotoxic,[16] anti-cancer,[17] anti-oxidant,[18] anti-angiogenic,[19] inhibitory activation,[20] anti-malarial,[21] anti-microbial,[22] anti-mutagenic,[23] radioprotective,[24] anti-inflammatory,[25] anti-diabetic,[26] anti-ulcer activity[27] and many other biological activities.[28] Other applications of chalcones also reported are; they are used as sweeteners in food items, pesticides, skin-lightening agents,[29] photoresists and photographic emulsions.[30] It also possesses some other properties such as non-linear optical properties[31] and their use as fluorescent probe.[32] Due to the plethora of biological and pharmacological applications of chalcone as synthesized and published, many researchers and scientists have put their attention in designing and developing novel chalcone analogues to study their potentiality in these different areas of medicinal as well as other applications.

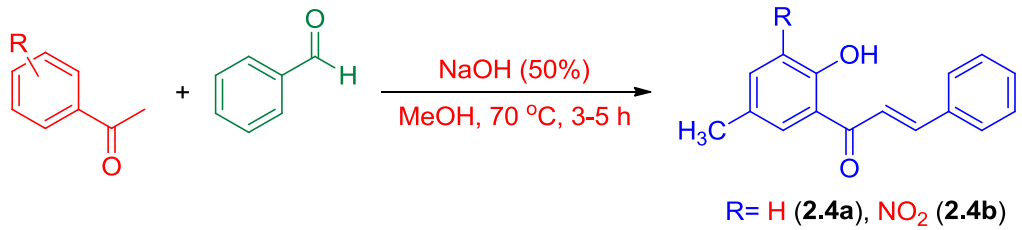
Since the treatment of cancer has been unsatisfactory especially because of its side effects caused by the use of chemotherapeutic compounds, more efforts have been put by researchers globally to study and design new chalcone molecules to study their inhibition at different steps of carcinogenesis, their function in tumor initiation through promotion, progression, angiogenesis and invasion.[33] Laboratory studies shows that chalcone have significant effects on cell growth and proliferation.[34] Despite intense research on designing new chemotherapeutic strategies, it still remains a key concern across the world. Natural products have a long-term history of anti-cancer activity and is the backbone for cancer chemotherapy.[35] Taking in to consideration the various important biological activities and application of chalcones, below are discussed some of the recently reported synthesis of chalcone derivatives and their biological activity.

Xu Tang *et al*. in **2019** reported the synthesis of substituted 1,2,4-triazine containing chalcone derivatives (**2.3**) from a mixture of 5,6-diphenyl-1,2,4-triazine-3-thiol or 5,6-dimethyl-1,2,4-triazine-3-thiol and substituted chalcone (**2.2**) in presence of anhydrous potassium carbonate in dimethylformamide (Scheme 2.1). Anti-viral bioassays results revealed that most of the synthesized compounds exhibited good anti-viral activity against tobacco mosaic virus (TMV) at a concentration of 500 mg/mL.[36]



Scheme 2.1. Synthesis of substituted chalcones and 1,2,4-triazine chalcone derivatives.

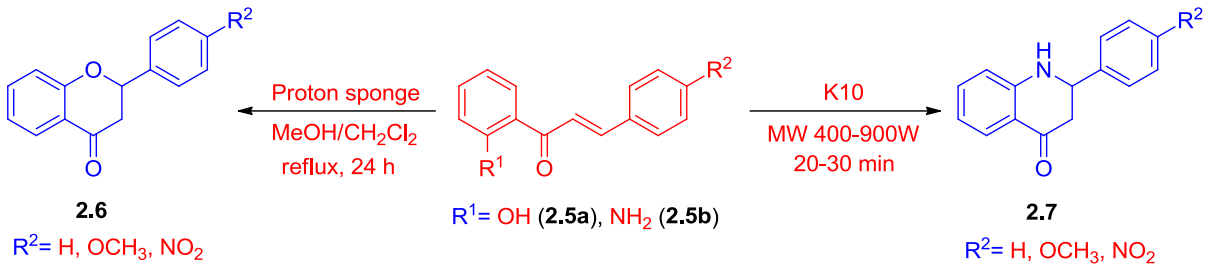
Josefina Higgs and co-workers (**2019**) synthesized a series of chalcones (Scheme 2.2) and studied their ability to bind distinctive receptors such as from rat brain homogenates, by displacement of labeled specific ligands: [3H] FNZ (binding site of benzodiazepines/$GABA_A$), [3H] 8-OH-DPAT (serotonin 5-HT1A) and [3H] DAMGO (m-opioid). The compounds showing better *in vitro* activities were evaluated in mice using different behavioral tasks. *In vivo* results showed that compound 5'-methyl-2'-hydroxychalcone (**2.4a**) exerted anxiolytic like effects in mice in the plus maze test, while chalcone nuclei revealed anti-depressant-like activities in the tail suspension test. In addition to their study, the novel 5'-methyl-2'-hydroxy-3'-nitrochalcone (**2.4b**) exhibited anti-nociceptive activity in acute chemical and thermal nociception tests (writhing and hot plate tests).[37]



Scheme 2.2. Synthesis of chalcone derivatives.

Djenisa H. A. Rocha *et al*. in **2019** reported the synthesis of flavanones (2-aryl-2,3-dihydrochromen-4(1H)-ones) (**2.6**) from the reaction of 2'-hydroxychalcones (**2.5a**) in presence of proton sponge in MeOH/DCM and refluxed for 24 h and also the synthesis of azaflavanones (2-aryl-2,3-dihydroquinolin-4(1H)-ones) (**2.7**) by the isomerization of 2'-aminochalcone (**2.5b**) in presence of montmorillonite K10 under microwave-irradiation

technique at 400-900W for 20-30 min (Scheme 2.3). These molecules are known to be valuable precursors in the synthesis of important pharmacological scaffolds.[38]



Scheme 2.3. Synthesis of flavanones and azaflavanones from substituted chalcones.

Many classes of chalcone with their anti-cancer activities have been reported over the years but research on anthracenyl chalcone derivatives with their anti-cancer activities are not studied much. In this chapter, we focused our research on the synthetic strategies which are employed for designing and developing novel chalcone scaffolds as anti-cancer agents. So, in order to discover the diverse class of chalcone analogues, here we have developed the synthesis of a series of novel anthracenyl chalcone derivatives (**2.10a-p**) under conventional and green synthetic method (microwave irradiation) and screened their *in vitro* anti-cancer activity against four human cancer cell lines, HeLa, MIAPACA, U-87 and SIHA.[39]

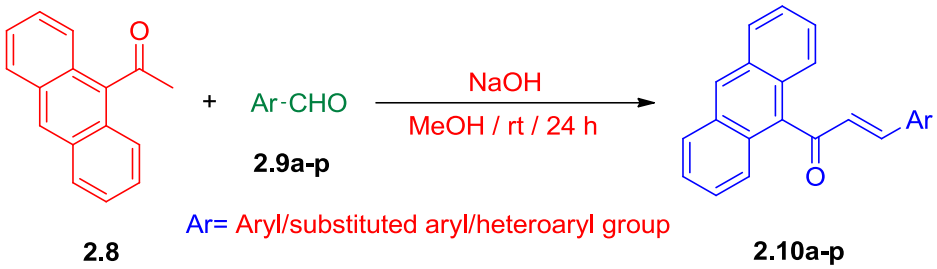
2.2 EXPERIMENTAL SECTION

2.2.1 Materials and Methods

All commercially available chemicals, reagents and solvents were used as received. For thin layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by Iodine and/or by UV light. Microwave experiments were carried out using an Anton Paar (Microwave Synthesis Reactor, Monowave 400). All the newly synthesized anthracenyl chalcones melting points were recorded on an IKON melting point apparatus and are uncorrected. Purity of all the synthesized anthracenyl chalcone products were confirmed by Binary Gradient HPLC-3000 system. IR spectra were recorded on JASCO FT/IR-5300. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded at Bruker 400 MHz and 500 MHz respectively. The chemical shifts are reported in ppm downfield to TMS (d = 0) for ^{1}H-NMR and relative to the central $CDCl_3$ resonance (d = 77.0) for ^{13}C-NMR. High-resolution mass spectra were recorded on micromass ESI-TOF MS.

2.2.2 Conventional synthesis of anthracenyl chalcones (2.10a-p) (*Method I*)

To a mixture of 9-acetyl anthracene (**2.8**) (0.220 g, 1 mmol), benzaldehyde (**2.9a**) (0.106 g, 1 mmol) in methanol solution (5 mL) was added a catalytic amount of NaOH and the reaction mixture was stirred at room temperature for 24 hours. The progress of the reaction was monitored by thin layered chromatography (TLC) and after completion of the reaction was added ice cold water. The solid product was collected by filtration method and at that moment the product was washed with water (3-4 times) and finally washed with methanol to obtain the pure product (**2.10a**). The same synthetic protocol was followed for the synthesis of all the other anthracenyl chalcone derivatives (Scheme 2.4).



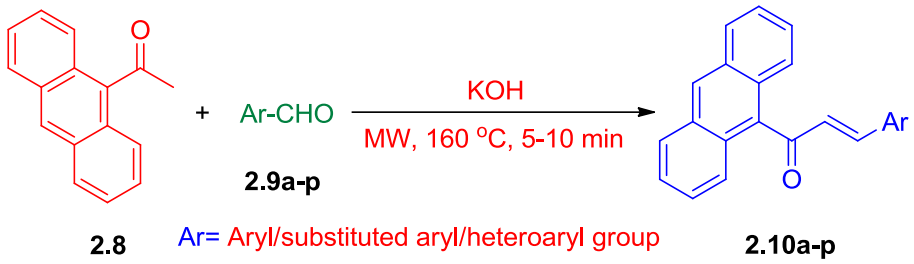
Scheme 2.4. Conventional synthesis of anthracenyl chalcone derivatives (**2.10a-p**).

In continuation with our research work towards the development of new eco-friendly green synthetic methodologies, efforts were made to design new green synthetic method for the synthesis of anthracenyl chalcones. Microwave irradiation method have been reported to have many advantages over conventional method such as short reaction time, economic, solvent-free, giving high reaction rate and ease of purification. Therefore, taking into consideration these various factors, we have designed and reported microwave-assisted fast and efficient synthesis of anthracenyl chalcone derivatives in presence of KOH under solvent-free reaction conditions. We found KOH to be an excellent catalyst for the synthesis of anthracenyl chalcones under solvent-free microwave irradiation reaction at 160 ^{o}C and giving 90-97% yield in a very short reaction time.

2.2.3 Microwave-assisted green synthesis of anthracenyl chalcones (2.10a-p) (*Method II*)

Equimolar quantities of 9-acetyl anthracene **(2.8)** (0.220 g, 1mmol) and respective aldehydes **(2.9a-p)** (1 mmol) were mixed and to it a catalytic amount of KOH was added and the reaction mixture was grinded properly then microwave irradiated for about 5-10 minutes at 160 ^{o}C. The completion of reaction was monitored by thin layer chromatography (TLC)

system. After completion of the reaction, ice cold water was added to the reaction mixture and the solid products were collected by filtration method which was washed with water several times and finally washed with methanol, dried and collected the desired pure products, **2.10a-p** (Scheme 2.5 and Table 2.2).



Scheme 2.5. Microwave-assisted green synthesis of anthracenyl chalcones (**2.10a-p**).

2.3 RESULTS AND DISCUSSION

2.3.1 Chemistry

A series of anthracenyl chalcones were designed and synthesized by Claisen-Schmidt condensation reaction from commercially available 9-acetyl anthracene (**2.8**) with various aromatic/heteroaromatic aldehydes (**2.9a-p**) catalyzed by sodium hydroxide in methanol solution at room temperature for 24 hours giving the desired anthracenyl chalcone derivatives (Scheme 2.4). This method shows that the condensation reactions were found to be quite efficient for the aryl, hetero aryl and tolerated a variety of functional groups on the phenyl ring regardless whether electron-donating or electron-withdrawing in character. Efforts were also made to develop green optimized protocol to synthesize anthracenyl chalcone compounds using microwave irradiation method (Scheme 2.5). As we were emphasizing on one-pot synthesis of anthracenyl chalcone derivatives under solvent-free condition using eco-friendly microwave irradiation method, we studied in detail the use of various catalysts under different microwave reaction conditions in terms of time and temperature. In order to find the most effective condensation, the mixture of 9-acetyl anthracene (**2.8**) and benzaldehyde (**2.9a**) was microwave irradiated at different reaction conditions. In the initial experiment, the reaction was first carried out with 9-acetyl anthracene, (**2.8**) (0.220 g, 1 mmol) and benzaldehyde, (**2.9a**) (0.106 g, 1 mmol) using MgO as the catalyst. TLC was first monitored after grinding the mixture for 10 minutes, but we see no new spot for the reaction mixture. The reaction mixture was then microwave irradiated at intervals of 10 minutes at different temperature and TLC was checked at each interval. We observed that after 20 minutes of MW at 160 ^{o}C, there was only

30% of the product formation. At increased time of 60 minutes, 80% formation of the product can be observed. Due to the increased time taken for formation of product in terms of yield, we studied and monitored the reaction using other catalysts such as boric acid, $BaCl_2$, $Ba(OH)_2$, I_2, $Ca(OH)_2$ and KOH. The use of microwave irradiation was found essential as a control reaction carried out at 160 ^oC. The time and product conversion for each reaction for different catalysts was monitored and the results of each reaction are presented in table 2.1.

Table 2.1 Evaluation of catalysts for the synthesis of anthracenyl chalcone (**2.10a**) using microwave irradiation at 160 ^oC under solvent-free conditions.

Entry	Catalyst	Temperature (^oC)	Time (min)	Yield (%)
1	MgO (80mg)	160	60	80
2	Boric acid (122mg)	160	10	10
3	$BaCl_2$ (416mg)	160	20	5
4	$Ba(OH)_2$ (342mg)	160	20	10
5	I_2 (506mg)	160	10	3
6	$Ca(OH)_2$ (148mg)	160	20	40
7	**KOH** (112mg)	**160**	**5**	**96**

Conditions: 9-acetyl anthracene (**2.8**) (1 mmol), benzaldehyde (**2.9a**) (1 mmol), catalyst, µW, 160 ^oC.

Efforts were made to improve the reaction conditions by applying different temperature and time intervals for improving the product yield. Among all the catalysts used, KOH was found to be the best catalyst for the solvent-free synthesis of anthracenyl chalcone under microwave irradiation at 160 ^oC and the reaction was completed within 5 minutes yielding 96% of the product **2.10a** which is quite excellent compared to the other catalysts and conditions which we have evaluated. The workup involves pouring ice cold water in the reaction mixture and the yellow solid was filtered, washed several times with water, dried and collected. Taking this as the general optimized reaction condition and technique, we further proceeded for the synthesis of other substituted anthracenyl chalcone derivatives using different aldehydes. It was observed that all electron donating and electron withdrawing substituents in the aryl ring of the aldehyde were well tolerated to give moderate to high yields of the desired products (**2.10a-p**). The results obtained from both techniques (*Method I* and *Method II*) shows the formation of the same product but the reaction time and yield varied between conventional and

microwave-assisted reactions. Microwave-assisted reactions were found to be economically more efficient in terms of yield as well as short reaction time. Reactions carried out for other benzaldehyde derivatives also showed reaction time of 5-10 minutes and yield percentage of 90-97% for all anthracenyl chalcone derivatives which showed a marked advantage of ecofriendly microwave irradiation method over conventional method (Table 2.2). All synthesized anthracenyl chalcone compounds structures were confirmed on the basis of its spectroscopic data (IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectra) and structures of four compounds (**2.10g**, **2.10i**, **2.10m** and **2.10p**) were solved by single crystal X-ray crystallographic methods. The chemical structures of the newly synthesized anthracenyl chalcone products are represented in Figure 2.1.

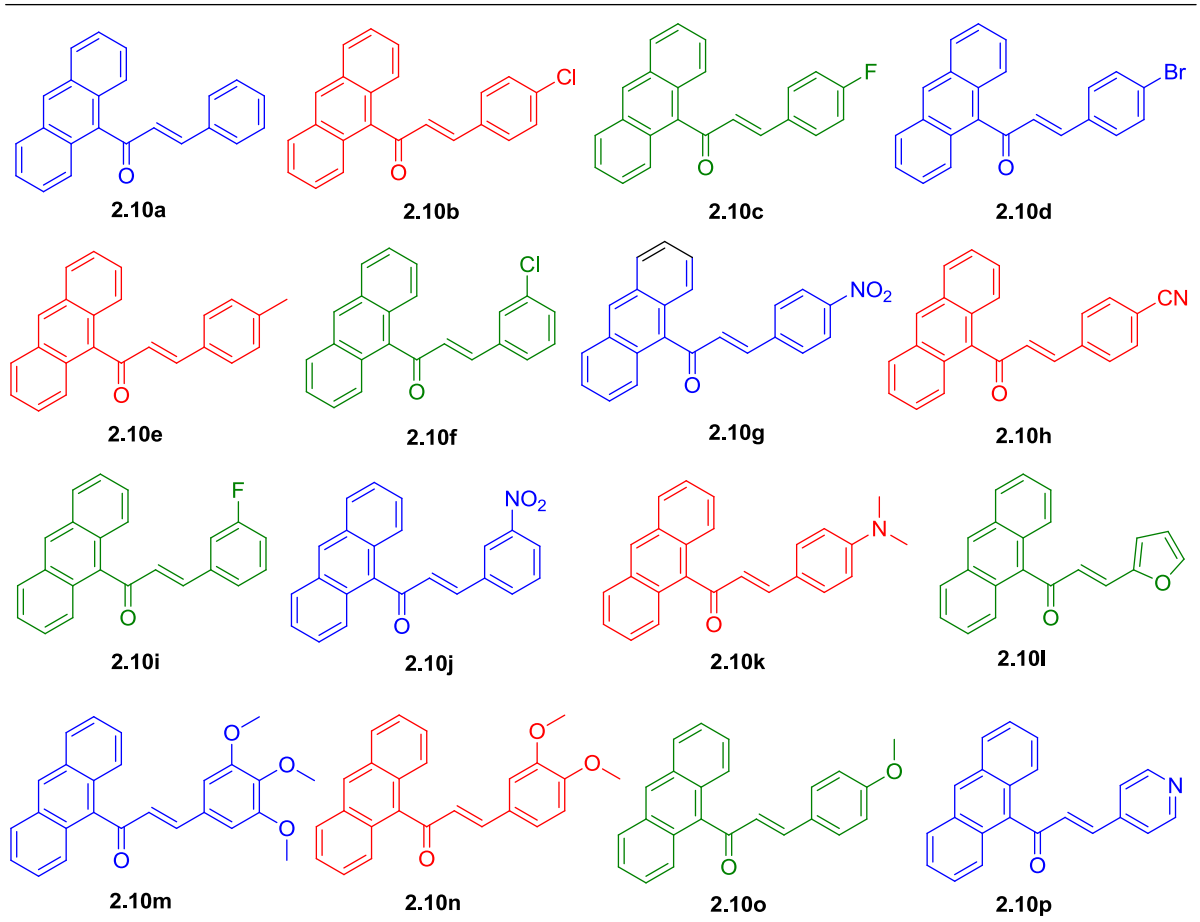
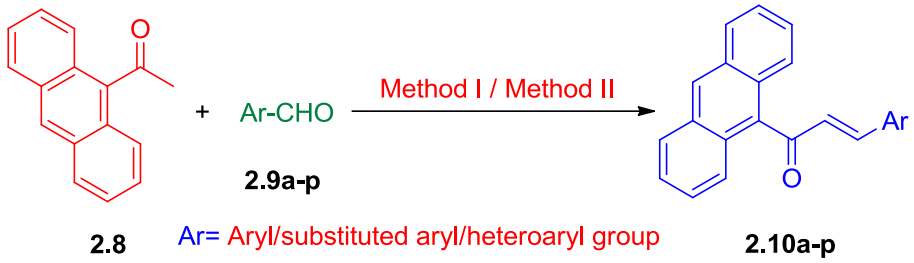


Figure 2.1. Structures of the newly synthesized anthracenyl chalcone derivatives (**2.10a-p**).

Table 2.2. Synthesis of anthracenyl chalcone derivatives (**2.10a-p**) from compound **2.8** and **2.9a-p** at room temperature stirring (24 h in presence of NaOH) and under microwave irradiation conditions (MW, 160 °C in the presence of KOH).



Sl. No.	Ar	Product	Method I Time (h), (Yield)	Method II Time (min), (Yield)	Method I m.p. (°C)	Method II m.p. (°C)
1	C_6H_5	**2.10a**	24 (86%)	5 (96%)	186-189	185-187
2	4-ClC_6H_4	**2.10b**	24 (90%)	5 (97%)	157-160	155-158
3	4-FC_6H_4	**2.10c**	24 (88%)	6 (95%)	109-112	108-110
4	4-BrC_6H_4	**2.10d**	24 (80%)	6 (94%)	167-170	167-170
5	4-MeC_6H_4	**2.10e**	24 (85%)	6 (90%)	114-116	115-117
6	3-ClC_6H_4	**2.10f**	24 (86%)	5 (94%)	145-148	146-149
7	4-$NO_2C_6H_4$	**2.10g**	24 (73%)	5 (95%)	159-162	159-161
8	4-CNC_6H_4	**2.10h**	24 (80%)	5 (95%)	130-133	129-132
9	3-FC_6H_4	**2.10i**	24 (84%)	5 (93%)	165-168	164-167
10	3-$NO_2C_6H_4$	**2.10j**	24 (75%)	5 (94%)	169-172	167-169
11	4-$N(Me)_2C_6H_4$	**2.10k**	24 (80%)	7 (91%)	171-174	170-172
12	2-Fural	**2.10l**	24 (75%)	6 (90%)	119-122	119-121
13	3,4,5-$(OCH_3)_3C_6H_2$	**2.10m**	24 (90%)	10 (94%)	150-153	149-152
14	3,4-$(OCH_3)_2C_6H_3$	**2.10n**	24 (88%)	10 (95%)	104-107	105-107
15	4-$(OCH_3)C_6H_4$	**2.10o**	24 (86%)	6 (92%)	100-103	99-101
16	4-Pyridyl	**2.10p**	24 (73%)	5 (94%)	160-163	161-163

Reaction conditions: *Method I*: (**2.8** (1 mmol), **2.9a-p** (1 mmol), NaOH, MeOH, rt, 24 h); *Method II*: (**2.8** (1 mmol), **2.9a-p** (1 mmol), KOH, solvent-free, MW, 160 °C, 5-10 min).

2.3.2 Biological Activity

2.3.2.1 Materials and Methods

The human cancer cell lines HeLa, MIAPACA, U-87 and SIHA used in this study were purchased from the American Type Culture Collection (ATCC, United States) and were maintained in Dulbecco's modified Eagle's medium (containing 10% FBS in a humidified atmosphere of 5% CO_2 at 37 ºC). The synthesized test compounds were evaluated for their *in vitro* anti-proliferative activity in these four different human cancer cell lines compared with the standard drug Nocodazole. A protocol of 48 h continuous drug exposure was used and an SRB cell proliferation assay was used to estimate cell viability or growth. All the cell lines were grown in Dulbecco's modified Eagle's medium (containing 10% FBS in a humidified atmosphere of 5% CO at 37 ºC). Cells were trypsinized when sub-confluent from T25 flasks/60 mm dishes and seeded in 96-well plates in 100 mL aliquots at plating densities depending on the doubling time of individual cell lines. The microtiter plates were incubated at 37 ºC, 5% CO_2, 95% air and 100% relative humidity for 24 h prior to the addition of experimental drugs and were incubated for 48 h with different doses (0.01, 0.1, 1, 10, 100 mM) of the prepared derivatives. After incubation at 37 ºC for 48 h, the cell monolayers were fixed by the addition of 10% (wt/vol) cold trichloroacetic acid and incubated at 4 ºC for 1 h and were then stained with 0.057% SRB dissolved in 1% acetic acid for 30 min at room temperature. Unbound SRB was washed with 1% acetic acid. The protein-bound dye was dissolved in 10 mMTris base solution for OD determination at 510 nm using a microplate reader (Enspire, Perkin Elmer, USA). Using the seven absorbance measurements [time zero, (Tz), control growth, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth was calculated at each of the drug concentrations levels.

Percentage growth inhibition was calculated as: [(Ti-Tz)/(C-Tz)] x 100 for concentrations for which Ti >/= Tz; [(Ti-Tz)/Tz] x 100 for concentrations for which Ti <Tz.

The dose response parameter, growth inhibition of 50% (GI was calculated from [(Ti-Tz)/(CTz)] x 100 = 50, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. Values were calculated for this parameter if the level of activity is reached; however, if the effect is not reached or is exceeded, the value for that parameter was expressed as greater or less than the maximum or minimum concentration tested.

2.3.2.2 Anti-Cancer Activity

The *in vitro* anti-proliferative activity of the synthesized compounds was evaluated against a panel of four different human cancer cell lines, HeLa, MIAPACA, U-87 and SIHA. The results for compounds **2.10a-p** shown as GI_{50} values calculated using SRB assay are tabulated in Table 2.3.

Table 2.3. Anti-cancer activity of newly synthesized anthracenyl chalcones (**2.10a-p)** against four human cancer cell lines, HeLa, MIAPACA, U-87 and SIHA.

Compound	HELA GI_{50}(µM)	U-87 GI_{50}(µM)	MIAPACA GI_{50}(µM)	SIHA GI_{50}(µM)
2.10a	12.3±0.05	14.44±0.07	11.39±0.06	16.25±0.07
2.10b	17.06±0.07	15.10±0.05	13.06±0.07	14.50±0.06
2.10c	16.10±0.07	13.10±0.05	16.4±0.06	15.22±0.07
2.10d	11.02±0.05	14.80±0.06	15.34±0.03	13.44±0.06
2.10e	18.50±0.06	17±0.06	12.10±0.06	18.29±0.05
2.10f	11.06±0.06	13.48±0.07	15.55±0.08	14.08±0.05
2.10g	5.18±0.05	6.18±0.06	8.41±0.06	7.06±0.06
2.10h	6.47±0.06	4.04±0.06	5.46±0.05	7.24±0.06
2.10i	14.06±0.06	15.06±0.06	12.52±0.06	19.57±0.07
2.10j	6.65±0.05	7.16±0.06	5.31±0.05	6.16±0.06
2.10k	5.65±0.07	7.03±0.07	6.44±0.05	4.02±0.07
2.10l	13.35±0.06	12.55±0.07	12.36±0.08	14.28±0.06
2.10m	12.30±0.6	10.86±0.08	14.31±0.08	11.53±0.05
2.10n	13.08±0.06	14.33±0.05	11.30±0.05	15.02±0.08
2.10o	16.89±0.05	13.65±0.06	18.05±0.05	19.43±0.08
2.10p	15.44±0.05	11.43±0.07	12.64±0.06	17.62±0.07
Nocodazole	0.567±0.2	0.667±0.3	0.782±0.2	0.884±0.1

The GI_{50} concentration for each compound was calculated with reference to a control sample, which represents the concentration that results in a 50% decrease in cell growth/proliferation after 48 h incubation in the presence of drug. The cytotoxic activities of synthesized compounds were compared with the activity exhibited by the reference drug Nocodazole. Based on the data obtained, most of the compounds possess GI_{50} values were at the 4.02 µM to 19.57 µM range. Among all the synthesized anthracenyl chalcones, compounds **2.10g**, **2.10h**, **2.10j** and **2.10k** were found to be the most potent against all the four human

cancer cell lines with the GI_{50} values below 10 µM. ranging from 5.18 to 8.41, 4.04 to 7.24, 5.31 to 7.16 and 4.02 to 7.03 µM respectively.

2.3.3 X-ray Crystallography

Single crystal X-ray diffraction data for the anthracenyl chalcones **2.10g**, **2.10i**, **2.10m** and **2.10p** were collected at 293(2)K using a SuperNova, Dual, Cu at Zero, Eos diffractometer with graphite monochromated Cu-Kα radiation (λ = 1.54184 Å) with ω-scan method. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Integration and scaling of intensity data were accomplished using SAINT program.[39] Using Olex2,[40] the structure was solved by Direct Methods using SHELXT[41] and refinement was carried out by full-matrix least-squares technique using SHELXTL.[42] Anisotropic displacement parameters were included for all non-hydrogen atoms. All the H-atoms were positioned geometrically and treated as riding on their parent C atoms with C-H distances of 0.93-0.97 Å, and with Uiso(H) = 1.2Ueq (C) or 1.5Ueq for methyl atoms. The software used to prepare material for publication was Mercury 2.3 (Build RC4), ORTEP-3 and X-Seed.[43] The suitable single crystals of anthracenyl chalcone **2.10g** were obtained from methanol whereas anthracenyl chalcones **2.10i**, **2.10m** and **2.10p** were obtained from acetonitrile solvents by slow evaporation method.

2.3.3.1 Crystal Structure analysis of anthracenyl chalcone 2.10g

The anthracenyl chalcone **2.10g** crystallizes in centrosymmetric monoclinic $P2_1/c$ space group with one molecule in the asymmetric unit (Table 2.4). The geometry at the C=C double bond is trans (*E*). The anthracenyl group is in perpendicular with the enone moiety. The nitro group is essentially coplanar with the phenyl group (Figure 2.2). The crystal structure analysis shows that the molecules of **2.10g** form two dimensional (2D) corrugated layer structure. The glide related molecules along the crystallographic *c*-axis connect with each other *via* bifurcated C−H···O hydrogen bonds and forms a one dimensional (1D) 'V' shaped tape like structure (Figure 2.3 and Table 2.5). These bifurcated C–H···O hydrogen bonds formed by the interaction of enone carbonyl group and two C–H groups of 4-nitrophenyl and alkene =C-H group (Table 2.5). These 1D-tape like structures are extended along the crystallographic *b*-axis by C–H···O hydrogen bonds[44] and forms a 2D-corrugated layered structure. One of the oxygen atoms of the nitro group is participating in the formation 2D-corrugated layered structure with the bifurcated hydrogen bonds (Figure 2.4 and Table 2.5). Further these corrugated layers are

stabilized by weak C–H···π (C3–H3···$\pi_{C18\text{-}C23}$; d = 2.972 Å, 165.43°) and very weak π···π ($\pi_{C1\text{-}C2\text{-}C3\text{-}C4\text{-}C5\text{-}C6}$···$\pi_{C8\text{-}C9\text{-}C10\text{-}C11\text{-}C12\text{-}C13}$; 3.708 Å) interactions.

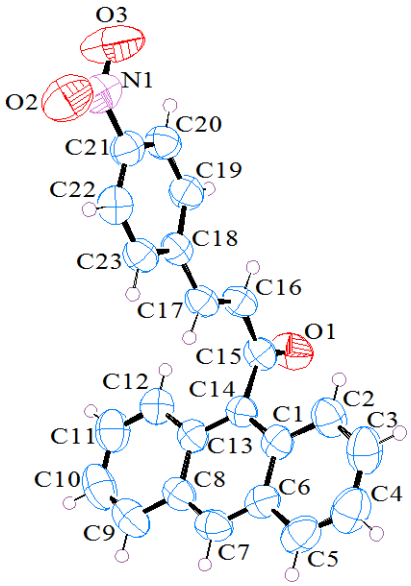


Figure 2.2. ORTEP representation of the anthracenyl chalcone **2.10g**. The thermal ellipsoids are drawn at 50% probability level.

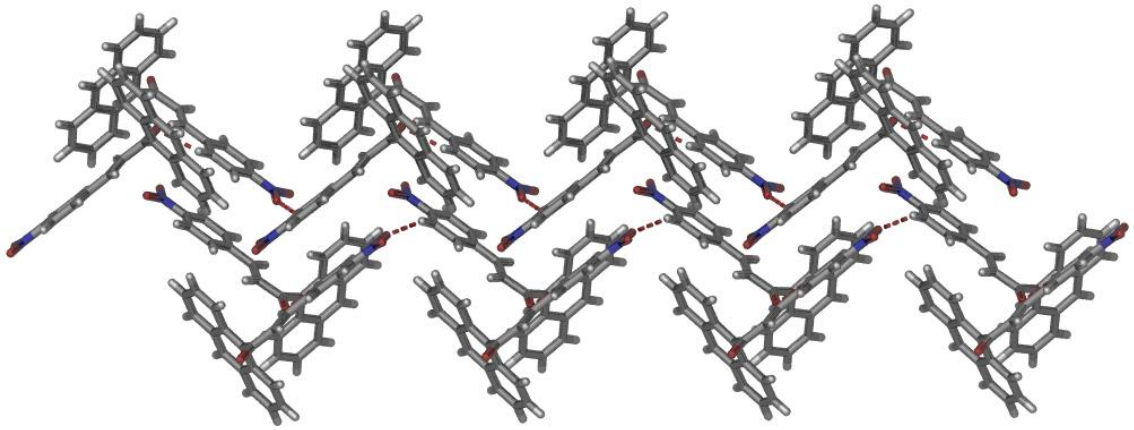


Figure 2.3. These 1D-tape like structures with C–H···O hydrogen bonding in anthracenyl chalcone **2.10g** with are extended along the crystallographic *b*-axis by C–H···O hydrogen bonds and forms a 2D-corrugated layered structure.

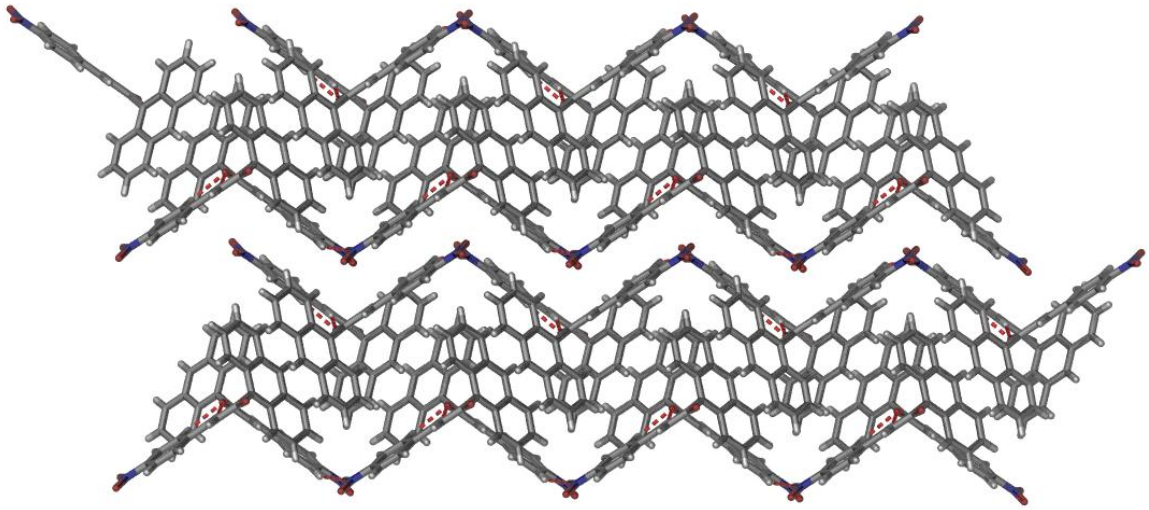


Figure 2.4. 2D-corrugated layered structure in anthracenyl chalcone **2.10g** along the crystallographic *b*-axis by C–H···O hydrogen bonds.

2.3.3.2 Crystal structure analysis of anthracenyl chalcone 2.10i

The anthracenyl chalcone **2.10i** crystallizes in centrosymmetric triclinic *P*-1 space group with one molecule in the asymmetric unit (Table 2.4). The geometry at the C=C double bond is trans *(E)*. The anthracenyl group is in perpendicular with the enone moiety (Figure 2.5). The crystal structure analysis shows that the molecules of chalcone **2.10i** form one dimensional (1D) tape like structure. The inversion related molecules of chalcone **2.10i** form dimers with C–H···O hydrogen bonds (Table 2.5). The carbonyl oxygen of the one molecule interacts with the ortho-position hydrogen of the 3-fluorophenyl ring of the inversion related another molecule to form C–H···O hydrogen bond leading to a dimer (Table 2.5). These dimers are further propagated in to 1D-tape like structure *via* C–H···O hydrogen bonds along the crystallographic *a*-axis (Figure 2.6 and Table 2.5).[44] The anthracenyl aromatic C–H groups are interacting with the oxygen atoms of the enone carbonyl groups to extend into 1D-tape like structure. Further, these 1D-tapes are propagated into second dimension with C–H···F hydrogen bonds and form two dimensional (2D) square grid network structure (Figure 2.7 and Table 2.5). These 2D square grid network structures are stabilized by very weak π···π ($\pi_{C1\text{-}C2\text{-}C3\text{-}C4\text{-}C5\text{-}C6}\cdots\pi_{C8\text{-}C9\text{-}C10\text{-}C11\text{-}C12\text{-}C13}$; 3.750 Å) interactions.

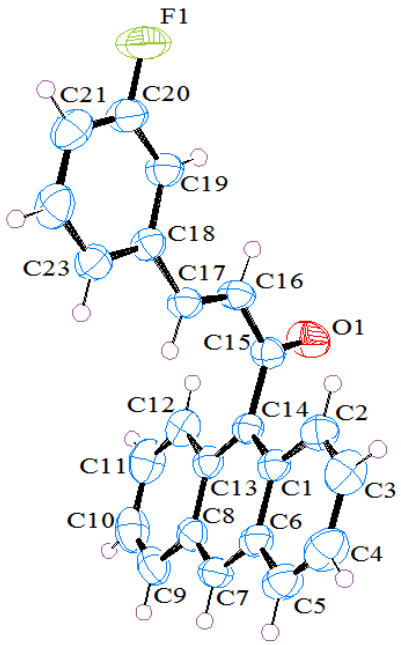


Figure 2.5. ORTEP representation of the anthracenyl chalcone **2.10i**. The thermal ellipsoids are drawn at 50% probability level.

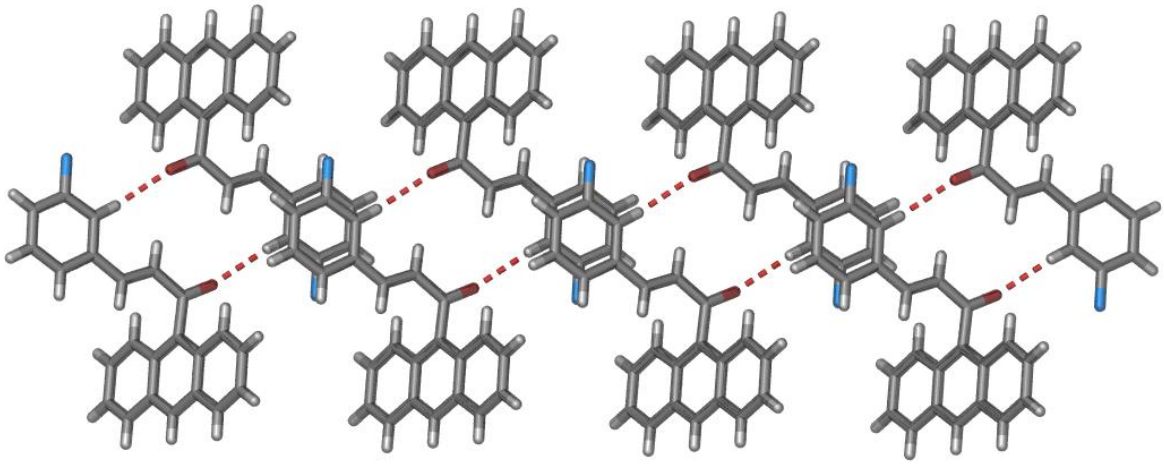


Figure 2.6. Anthracenyl chalcone **2.10i** forms 1D-tape like structure *via* C–H···O hydrogen bonds along the crystallographic *a*-axis.

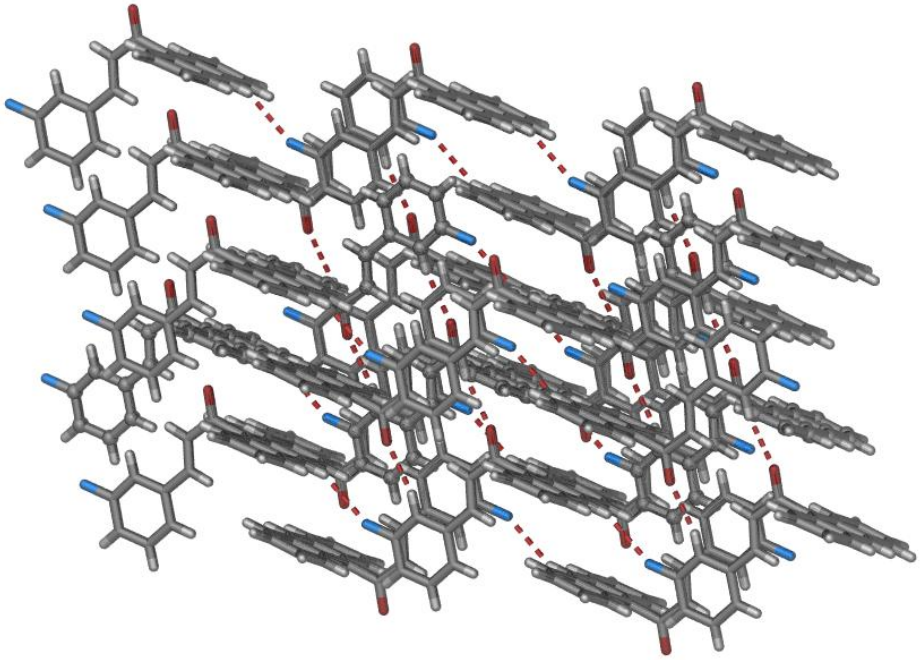


Figure 2.7. Two-dimensional square grid network structure of anthracenyl chalcone **2.10i** along with the crystallographic *c*-axis formed by C–H···F hydrogen bonds.

2.3.3.3 Crystal structure analysis of anthracenyl chalcone 2.10m

The anthracenyl chalcone **2.10m** crystallizes in the centrosymmetric monoclinic $P2_1/n$ space group with one molecule in the asymmetric unit (Table 2.4). The geometry at the C=C double bond is trans *(E)*. The anthracenyl group is in perpendicular with the enone moiety (Figure 2.8). The crystal structure analysis shows that the molecules of **2.10m** form two dimensional (2D) network structure. Initially, inversion related molecules form dimer C–H···O hydrogen bonds (Table 2.5).[44] The C-H hydrogens of the meta-methoxy group interacts with the carbonyl oxygen of the enone moiety *via* bifurcated C–H···O hydrogen bonds to form these dimers (Table 2.5). These dimers extend along the crystallographic *a*-axis by the interaction of *para*-methoxy oxygen and C-H group of anthracene moiety *via* C–H···O hydrogen bonds to form a 1D-square grid networks (Figure 2.9 and Table 2.5). Further, these 1D-square grid networks are propagated into second dimension along the crystallographic *c*-axis to form 2D-network structure (Figure 2.10). Further these networks are stabilized by weak C–H···π (C11–H11···π_{C22}; d = 2.706 Å, 154.84°) and very weak π···π ($\pi_{C1\text{-}C2\text{-}C3\text{-}C4\text{-}C5\text{-}C6}$···$\pi_{C8\text{-}C9\text{-}C10\text{-}C11\text{-}C12\text{-}C13}$; 3.765 Å) interactions.

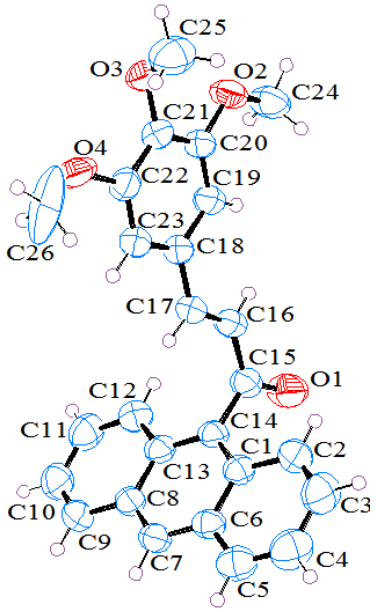


Figure 2.8. ORTEP representation of the anthracenyl chalcone **2.10m**. The thermal ellipsoids are drawn at 50% probability level.

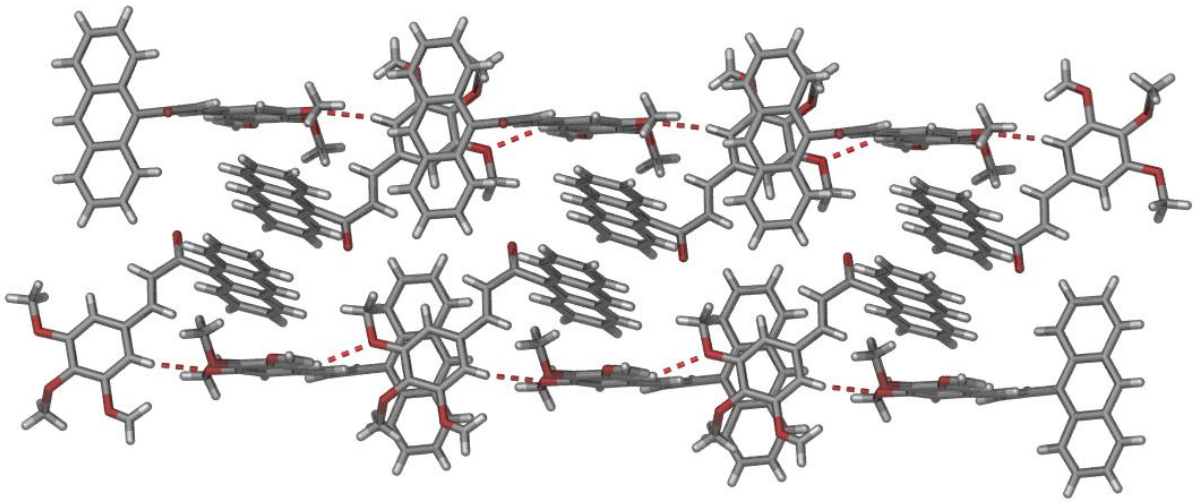


Figure 2.9. One-dimensional (1D) square grid networks along the crystallographic *c*-axis are formed by C–H···O hydrogen bonds in anthracenyl chalcone **2.10m**.

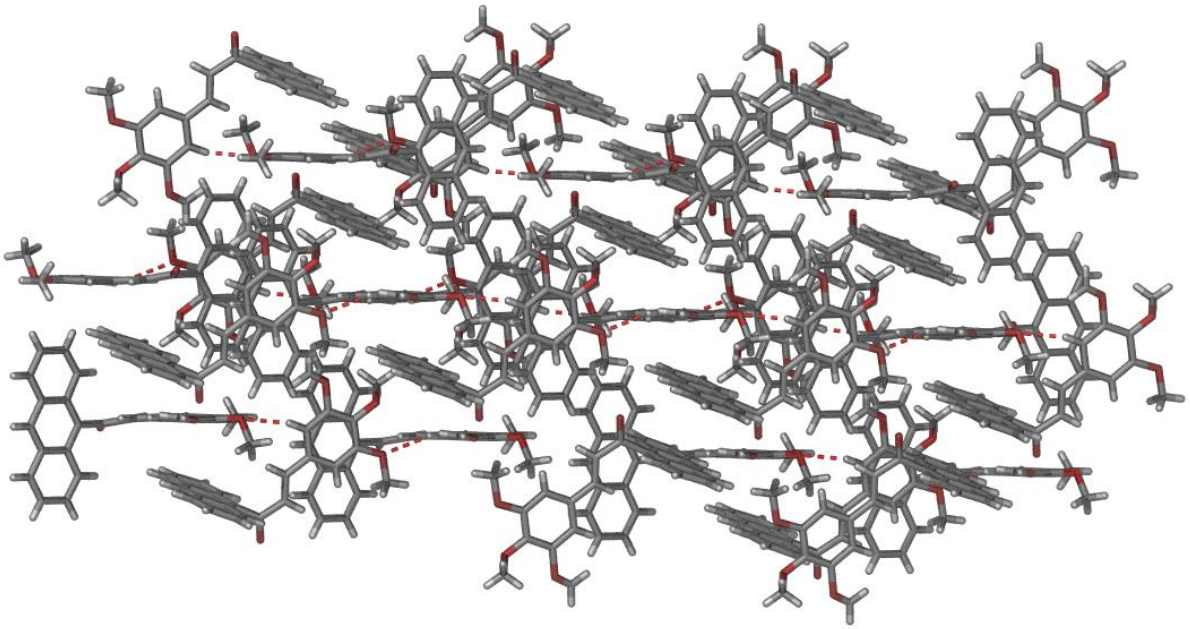


Figure 2.10. Two dimensional **(**2D) network structure in anthracenyl chalcone **2.10m** along the crystallographic *c*-axis.

2.3.3.4 Crystal structure analysis of anthracenyl chalcone 2.10p

The anthracenyl chalcone **2.10p** crystallizes in the centrosymmetric monoclinic *P*-1 space group with one molecule in the asymmetric unit (Table 2.4). The geometry at the C=C double bond is trans *(E)*. The anthracenyl group is in perpendicular with the enone moiety (Figure 2.11). The crystal structure analysis shows that the molecules of **2.10p** form one dimensional (1D) network structure. The two inversion related molecules form a dimer synthon with C–H···O hydrogen bonds (Table 2.5). The carbonyl group of the enone moieties and =C–H groups of the enones interact with each other *via* C–H···O hydrogen bonds to form dimer synthon (Table 2.5).[44] These dimer synthons are propagated along the crystallographic *a*-axis to form one dimensional (1D) tape like structure (Figure 2.12). These 1D-tapes are further, strengthened with C–H···N hydrogen bonds (Table 2.5). Further these 1D tapes are stabilized by weak C–H···π (C21–H21···$\pi_{C2\text{-}C3}$; d = 2.947 Å, 156.30°) interactions (Figure 2.13).

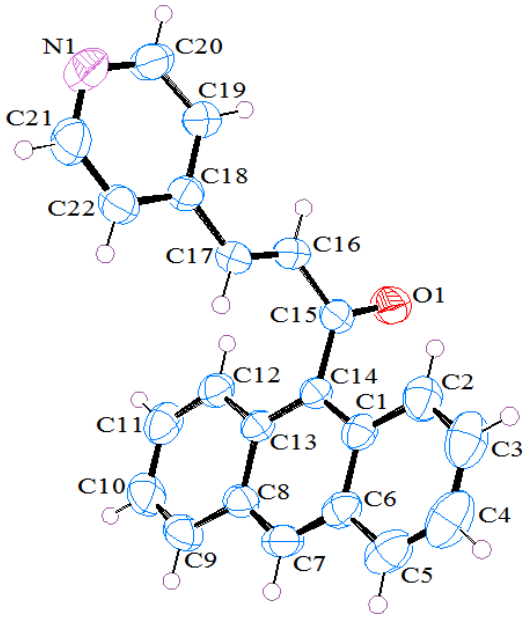


Figure 2.11. ORTEP representation of the anthracenyl chalcone **2.10p**. The thermal ellipsoids are drawn at 50% probability level.

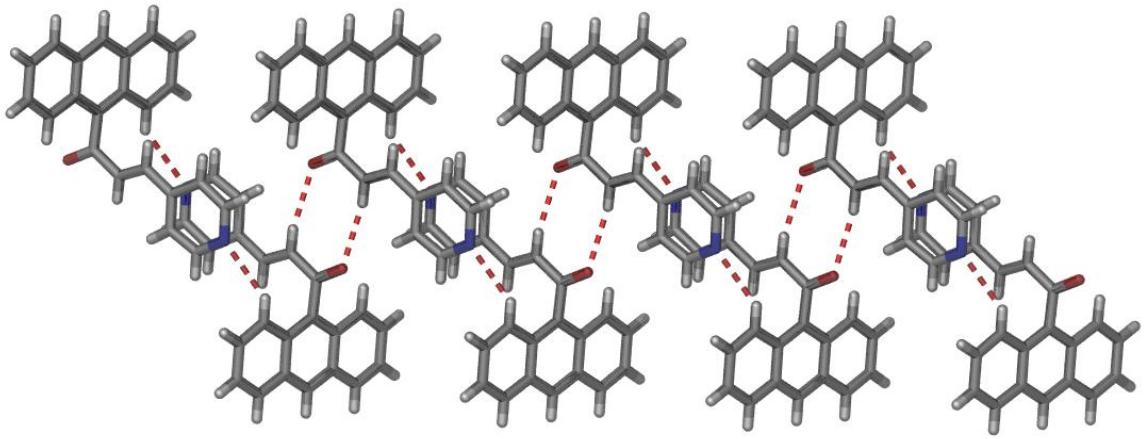


Figure 2.12. The dimer synthons in anthracenyl chalcone **2.10p** are propagated along the crystallographic *a*-axis to form one dimensional (1D) tape like structure.

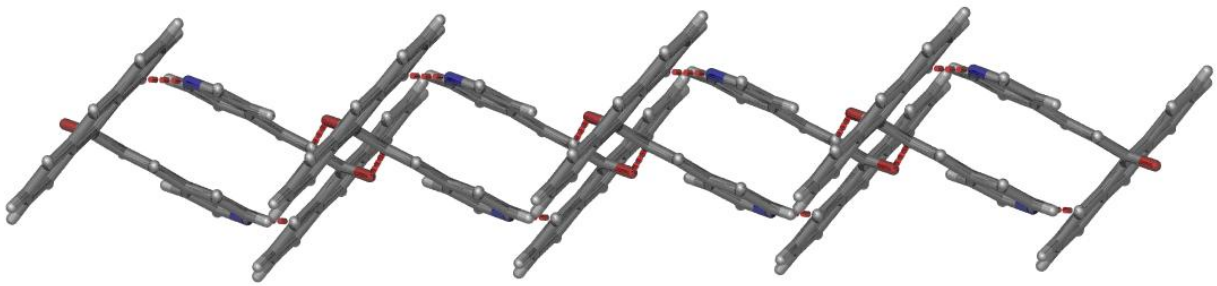


Figure 2.13. One dimensional tape like structure in anthracenyl chalcone **2.10p** along the crystallographic *b*-axis.

Table 2.4 Salient features of crystallographic data and structure refinement parameters of the anthracenyl chalcones **2.10g**, **2.10i**, **2.10m** and **2.10p**.

Parameters	**2.10g**	**2.10i**	**2.10m**	**2.10p**
Empirical formula	$C_{23}H_{15}NO_3$	$C_{23}H_{15}FO$	$C_{26}H_{21}O_4$	$C_{22}H_{15}NO$
Formula weight	353.36	376.35	397.43	309.35
Crystal shape	Rectangular blocks	needles	Rectangular blocks	needles
Colour	Yellow	Bright orange	Yellow	Dark orange
Crystal size/mm^3	0.254 x 0.207 x 0.155	0.231 x 0.158 x 0.077	0.365 x 0.205 x 0.108	0.232 x 0.136 x 0.099
Crystal system	Monoclinic	Triclinic	Monoclinic	Triclinic
Space group	$P2_1/c$	P-1	$P2_1/n$	P-1
T/K	293(2)	293(2)	293(2)	293(2)
a/Å	13.3027(9)	8.5765(7)	12.4705(7)	8.5870(10)
b/Å	12.6151(7)	9.4676(8)	13.6622(7)	9.3595(12)
c/Å	11.0386(6)	10.4464(8)	13.2023(7)	10.2677(10)
α/°	90.00	91.237(7)	90.00	91.018(9)
β/°	105.719(6)	99.652(7)	111.620(6)	102.444(9)
γ/ °	90.00	103.678(7)	90.00	101.283(10)
Z	4	1	4	2
V/Å^3	1783.17(19)	810.86(11)	2091.09(19)	788.71(15)
D_{calc}/ g/cm^3	1.316	1.337	1.262	1.303
F(000)	736	340	836	324
μ/mm^{-1}	0.709	0.710	0.682	0.625
θ/°	3.45 to 66.89	4.30 to 66.86	4.17 to 66.92	4.42 to 66.99
Index ranges	$-12 \le h \le 15$ $-15 \le k \le 12$ $-12 \le l \le 13$	$-10 \le h \le 10$ $-11 \le k \le 10$ $-12 \le l \le 12$	$-11 \le h \le 14$ $-16 \le k \le 13$ $-15 \le l \le 15$	$-10 \le h \le 10$ $-11 \le k \le 11$ $-9 \le l \le 12$
N-total	5788	4562	6712	4573
N-independent	3123	2851	3666	2766
N-observed	2469	2288	2972	1948
Parameters	244	226	273	217
R_1 ($I > 2\sigma(I)$)	0.0423	0.0491	0.0706	0.0492
wR_2 (all data)	0.1126	0.1621	0.2071	0.1222
GOF	1.028	1.200	1.051	1.050
CCDC	1909344	1909345	1909346	1909347

Table 2.5 Geometrical parameters of hydrogen bonds in anthracenyl chalcones **2.10g**, **2.10i**, **2.10m** and **2.10p**.

Chalcone	Interaction	D···A (Å)	H···A (Å)	D–H···A (°)	Symmetry code
2.10g	C10–H10···O2	3.6035(2)	2.61	151	x,-1+y,z
	C17–H17···O1	3.2705(2)	2.26	154	x,1/2-y,1/2+z
	C20–H20···O2	3.361(2)	2.37	152	x,3/2-y,-1/2+z
	C23–H23···O1	3.3996(2)	2.43	148	x,1/2-y,1/2+z
2.10i	C10–H10···O1	3.432(3)	2.50	144	-1+x,y,z
	C19–H19···O1	3.366(3)	2.31	165	1-x,2-y,1-z
	C7–H7···F1	3.460(3)	2.54	142	-1+x,y,-1+z
	C5–H5···F1	3.601(3)	2.73	138	-1+x,y,-1+z
2.10m	C10–H10···O3	3.508(5)	2.67	134	1-x,1-y,1-z
	C17–H17···O2	3.632(3)	2.71	143	-1/2+x,1/2-y,-1/2+z
	C23–H23···O2	3.387(3)	2.41	149	-1/2+x,1/2-y,-1/2+z
2.10p	C12–H12···N1	3.506(3)	2.61	140	-x,1-y,1-z
	C4–H4···O1	3.448(3)	2.53	142	1+x,y,z
	C16–H16···O1	3.493(2)	2.47	158	-x,-y,1-z
	C29–H19···O1	3.362(2)	2.30	168	-x,-y,1-z

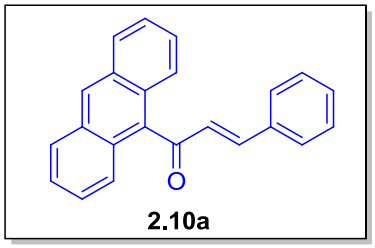
2.4 CONCLUSION

The present study described the synthesis of anthracenyl chalcones by conventional and microwave-assisted green synthetic methods. The microwave-assisted reaction is found to be economically more efficient in terms of yield and short reaction time than the conventional method. All the compounds were well characterized by various spectroscopic techniques and crystal structures of four novel anthracenyl chalcones (**2.10i**, **2.10g**, **2.10m** and **2.10p**) were solved by single crystal X-ray diffraction methods.[46] The anthracenyl chalcones **2.10g** and **2.10m** crystallizes in monoclinic space group and the anthracenyl chalcones **2.10i** and **2.10p** crystallizes in triclinic space groups. Anthracenyl chalcone **2.10g** forms 2D corrugated layer structure with C–H···O hydrogen bonds whereas anthracenyl chalcone **2.10i** forms 1D tape like structure with C–H···O hydrogen bonds. The 1D tape like structure in anthracenyl chalcone **2.10i** propagate in second dimension to 2D square grid network structure with C–H···F hydrogen bonds and the anthracenyl chalcone **2.10m** forms 2D network structure whereas anthracenyl chalcone **2.10p** forms a 1D network structure with C–H···O hydrogen bonds. Each

anthracenyl chalcone derivatives were evaluated for their anti-cancer activity. We have identified that compounds **2.10g**, **2.10h**, **2.10j** and **2.10k** as effective considering their significant cytotoxic activity against the four human cancer cell lines HeLa, MIAPACA, U-87 and SIHA. Further these observations may facilitate a promising approach to design novel anti-cancer agents based on the potent compound by structural modifications of these series of anthracenyl chalcones that can lead to the discovery of better anti-cancer agents as clinical candidates.

2.5 SPECTRAL CHARACTERIZATION DATA

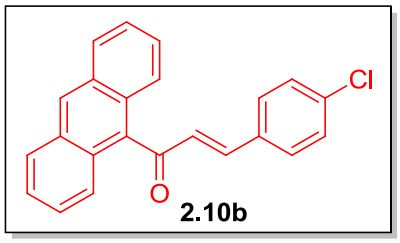
2.5.1 (E)-1-(Anthracen-9-yl)-3-phenylprop-2-en-1-one (2.10a)



2.10a

Bright yellow solid. Yield: 96%. m.p. 186–189 °C. IR (KBr) cm^{-1} 3132 (Aromatic C-H), 1639.54 (C=O), 1520.75 (olefinic C=C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H, Ar-H), 8.08 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.97–7.95 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.53–7.50 (m, 4H, Ar-H), 7.45–7.44 (m, 2H, Ar-H, =CH), 7.38–7.33 (m, 4H,Ar-H), 7.28–7.25 (m, 1H, =CH) ppm. ^{13}C-NMR (400 MHz, $CDCl_3$) δ 200.19, 147.90, 134.62, 134.29, 131.17, 131.01, 129.19, 128.95, 128.69, 128.65, 128.45, 126.60, 126.66, 125.55, 125.31 ppm. HRMS (m/z): 309.1273 (M+1) observed for $C_{23}H_{16}O$.

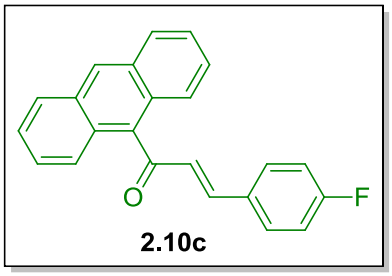
2.5.2 (E)-1-(Anthracen-9-yl)-3-(4-chlorophenyl)prop-2-en-1-one (2.10b)



2.10b

Pale yellow solid. Yield: 97%. m.p. 157–160 °C. IR (KBr) cm^{-1} 3049.52 (Aromatic C-H), 1629.21 (C=O), 1577.57 (olefinic C=C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H, Ar-H), 8.08–8.07 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.92–7.91 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.51–7.50 (m, 5H, Ar-H), 7.38–7.37 (d, *J* = 7.4 Hz, 1H, =CH), 7. 32–7.31 (d, *J* = 7.4 Hz, 1H, =CH), 7.28–7.25 (m, 1H, Ar-H), 7.21–7.18 (m, 1H, Ar-H), 7.20–7.18(m, 1H, Ar-H) ppm. ^{13}C-NMR (400 MHz, $CDCl_3$) δ 199.87, 146.13, 136.96, 134.35, 132.78, 131.14, 129.75, 129.51, 129.22, 128.70, 128.56, 128.39, 126.72, 125.55, 125.17 ppm. HRMS (m/z): 343.0882 (M+1) observed for $C_{23}H_{15}ClO$.

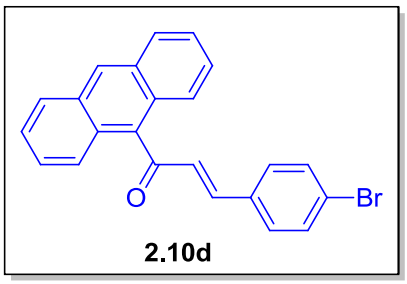
2.5.3 (E)-1-(Anthracen-9-yl)-3-(4-fluorophenyl)prop-2-en-1-one (2.10c)



2.10c

Orange yellow solid. Yield: 95%. m.p. 109–112 °C. IR (KBr) cm^{-1} 3059.97 (Aromatic C-H), 1629.27 (C=O), 1587.95 (olefinic C=C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H, Ar-H), 8.08–8.06 (m, 2H, Ar-H), 7.94–7.90 (m, 2H, Ar-H), 7.53–7.42 (m, 6H, Ar-H), 7.23–7.22 (m, 2H, =CH), 7.06–7.01 (m, 2H, Ar-H) ppm. ^{13}C-NMR (400 MHz, $CDCl_3$) δ 200.00, 165.56, 163.04, 146.49, 134.45, 131.14, 130.66, 130.57, 130.50, 128.92, 128.49, 128.31, 126.69, 125.55, 125.22, 116.25 ppm. HRMS (m/z): 327.1183 (M+1) observed for $C_{23}H_{15}FO$.

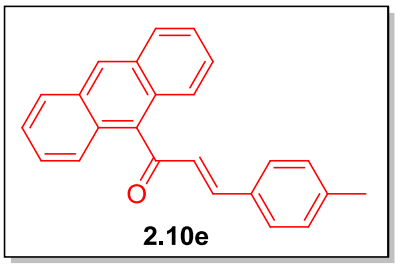
2.5.4 (E)-1-(Anthracen-9-yl)-3-(4-bromophenyl)prop-2-en-1-one (2.10d)



2.10d

Pale yellow solid. Yield: 94%. m.p. 167–170 °C. IR (KBr) cm^{-1} 3054.81 (Aromatic C-H), 1634.43 (C=O), 1582.78 (olefinic C=C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H, Ar-H), 8.09–8.06 (m, 2H, Ar-H), 7.93–7.90 (m, 2H, Ar-H), 7.53–7.45 (m, 7H, Ar-H), 7.31–7.26 (m, 3H, Ar-H, =CH) ppm. ^{13}C-NMR (400 MHz, $CDCl_3$) δ 199.86, 134.34, 134.10, 133.20, 132.19, 131.13, 129.93, 129.59, 128.72, 128.59, 128.40, 126.74, 125.57, 125.36, 125.17 ppm. HRMS (m/z): 388.0409 (M+1) observed for $C_{23}H_{15}BrO$.

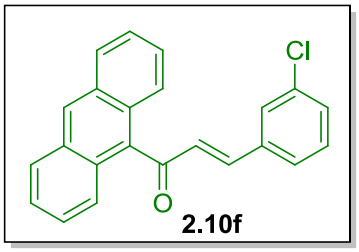
2.5.5 (E)-1-(Anthracen-9-yl)-3-(p-tolyl)prop-2-en-1-one (2.10e)



2.10e

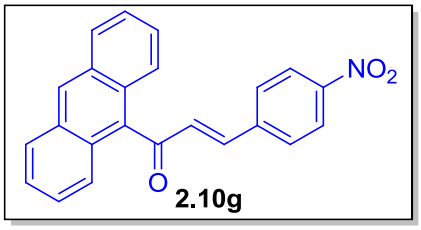
Bright orange solid. Yield: 90%. m.p. 114–116 °C. IR (KBr) cm^{-1} 3044.48 (Aromatic C-H), 1629.27 (C=O), 1580 (olefinic C=C). ^{1}H -NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H, Ar-H), 8.08 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.95–7.92 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.52–7.46 (m, 5H, Ar-H), 7.36–7.33 (m, 2H, Ar-H), 7.27–7.26 (d, *J* = 7.3 Hz, 1H, =CH), 7.27–7.16 (m, 1H, Ar-H), 7.14 (d, *J* = 7.3 Hz, 1H, =CH), 2.35 (s, 3H, -CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$) δ 200.26, 131.56, 131.15, 129.80, 129.68, 129.23, 128.68, 128.62, 128.41, 128.30, 128.09, 127.95, 126.55, 125.50, 125.36, 21.51 ppm. HRMS (m/z): 323.1435 (M+1) observed for $C_{24}H_{18}O$.

2.5.6 (E)-1-(Anthracen-9-yl)-3-(3-chlorophenyl)prop-2-en-1-one (2.10f)



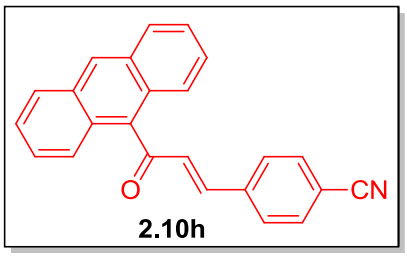
Bright orange solid. Yield: 94%. m.p. 145–148 °C. IR (KBr) cm^{-1} 3054.81 (Aromatic C-H), 1629.27 (C=O), 1562.12 (olefinic C=C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H, Ar-H), 8.08 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.92–7.89 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.53–7.47 (m, 5H, Ar-H), 7.42 (d, *J* = 7.6 Hz, 1H, =CH), 7.41–7.25 (m, 4H, Ar-H, =CH) ppm. ^{13}C-NMR (400 MHz, $CDCl_3$) δ 199.84, 145.89, 144.49, 136.12, 135.00, 134.20, 133.54, 131.13, 130.73, 130.13, 128.73, 128.38, 127.97, 126.77, 126.64, 125.55, 125.11 ppm. HRMS (m/z): 343.0882 (M+1) observed for $C_{23}H_{15}ClO$.

2.5.7 (E)-1-(Anthracen-9-yl)-3-(4-nitrophenyl)prop-2-en-1-one (2.10g)



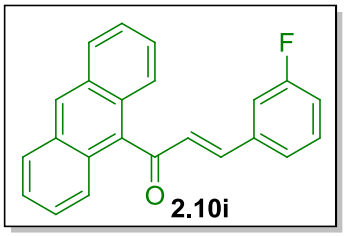
Yellow solid. Yield: 95%. m.p. 159–162 °C. IR (KBr) cm^{-1} 3039.31 (Aromatic C-H), 1639.60 (C=O), 1593.11 (olefinic C=C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H, Ar-H), 8.18–8.16 (d, *J* = 8.2 Hz, 2H, Ar-H), 8.08–8.07 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.90–7.89 (m, 2H, Ar-H), 7.58–7.54 (m, 2H, Ar-H), 7.53–7.49 (m, 4H, Ar-H), 7.34–7.30 (d, *J* = 7.6 Hz, 1H, =CH), 7.28–7.26 (d, *J* = 7.6 Hz, 1H, =CH) ppm. ^{13}C-NMR (400 MHz, $CDCl_3$) δ 199.34, 148.72, 143.87, 140.39, 133.75, 132.35, 131.11, 129.11, 128.99, 128.84, 128.39, 126.98, 125.66, 124.91, 124.07 ppm. HRMS (m/z): 354.1120 (M+1) observed for $C_{23}H_{15}NO_3$.

2.5.8 (E)-4-(3-(Anthracen-9-yl)-3-oxoprop-1-en-1-yl)benzonitrile (2.10h)



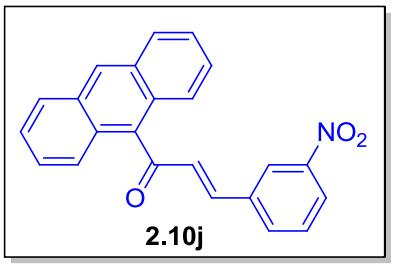
Bright orange solid. Yield: 95%. m.p. 130–133 °C. IR (KBr) cm^{-1} 3054.81 (Aromatic C-H), 2228.41 (CN), 1644.76 (C=O), 1598.28 (olefinic C=C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H, Ar-H), 8.09–8.08 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.89–7.88 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.63–7.62 (m, 2H, Ar-H), 7.54–7.50 (m, 6H, Ar-H), 7.35–7.22 (m, 2H, =CH) ppm. ^{13}C-NMR (400 MHz, $CDCl_3$) δ 199.45, 144.51, 138.58, 132.58, 131.78, 131.11, 128.92, 128.85, 128.81, 128.38, 127.22, 126.93, 125.63, 124.93, 118.19, 113.88 ppm. HRMS (m/z): 334.1223 (M+1) observed for $C_{24}H_{15}NO$.

2.5.9 (E)-1-(Anthracen-9-yl)-3-(3-fluorophenyl)prop-2-en-1-one (2.10i)



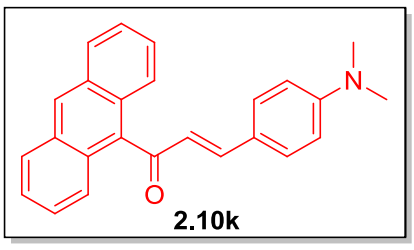
Bright orange solid. Yield: 93%. m.p. 165–168°C. IR (KBr) cm^{-1} 3065.14 (Aromatic C-H), 1634.43 (C=O), 1582.78 (olefinic C=C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H, Ar-H), 8.09 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.90–7.89 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.53–7.47 (m, 4H, Ar-H), 7.34–7.30 (m, 2H, Ar-H), 7.29–7.27 (d, *J* = 7.6 Hz, 1H, =CH), 7.22–7.20 (d, *J* = 7.6 Hz, 1H, =CH), 7.18–7.15 (m, 1H, Ar-H), 7.10–7.05 (m, 1H, Ar-H) ppm. ^{13}C-NMR (400 MHz, $CDCl_3$) δ 199.89, 161.97, 146.11, 134.23, 134.12, 131.13, 130.49, 130.49, 130.42, 130.18, 128.63, 128.39, 128.20, 127.97, 127.29, 126.75, 124.58, 123.86, 122.43 ppm. HRMS (m/z): 327.1180 (M+1) observed for $C_{23}H_{15}FO$.

2.5.10 (E)-1-(Anthracen-9-yl)-3-(3-nitrophenyl)prop-2-en-1-one (2.10j)



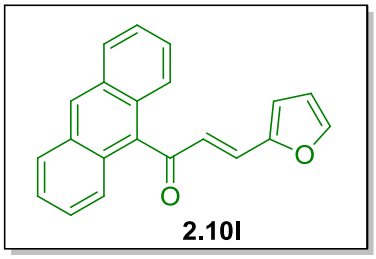
Bright orange solid. Yield: 94%. m.p. 169–172 °C. IR (KBr) cm^{-1} 3054.81 (Aromatic C-H), 1639.60 (C=O), 1520.80 (olefinic C=C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H, Ar-H), 8.22–8.21 (d, *J* = 8.2 Hz, 1H, Ar-H), 8.20–8.19 (d, *J* = 8.4 Hz, 1H, Ar-H), 8.11–8.07 (m, 2H, Ar-H), 7.90–7.88 (m, 2H, Ar-H), 7.80–7.76 (m, 1H, Ar-H), 7.56–7.48 (m, 5H, Ar-H), 7.36 (d, *J* = 7.2 Hz, 1H, =CH), 7.27 (d, *J* = 7.3 Hz, 1H, =CH) ppm. ^{13}C-NMR (400 MHz, $CDCl_3$) δ 199.53, 148.62, 114.23, 136.05, 133.85, 133.75, 131.45, 131.11, 129.97, 128.93, 128.83, 128.38, 128.31, 126.95, 125.64, 125.00, 123.05 ppm. HRMS (m/z): 354.1134 (M+1) observed for $C_{23}H_{15}NO_3$.

2.5.11 (E)-1-(Anthracen-9-yl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (2.10k)



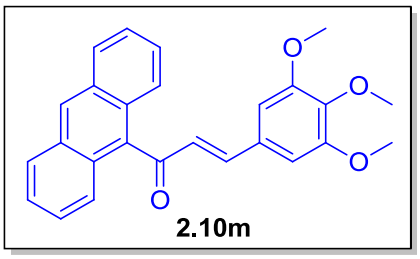
Bright orange solid. Yield: 91%. m.p. 171–174 °C. IR (KBr) cm^{-1} 3054 (Aromatic C-H), 2362.70 (N-CH), 1630 (C=O), 1572.45 (olefinic C=C). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H, Ar-H), 8.06–8.05 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.99–7.97 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.50–7.44 (m, 4H, Ar-H), 7.33–7.28 (m, 2H, =CH), 7.15 (d, *J* = 7.4 Hz, 2H, Ar-H), 6.60–6.59 (d, *J* = 7.4 Hz, 2H, Ar-H), 3.00 (s, 6H, $-CH_3$) ppm. ^{13}C-NMR (500 MHz, $CDCl_3$) δ 199.85, 152.32, 149.18, 135.62, 134.10, 133.56, 130.65, 128.48, 128.44, 127.81, 127.23, 126.27, 128.73, 125.73, 124.37, 111.72, 40.02 ppm. HRMS (m/z): 374.1521 (M+23) observed for $C_{25}H_{21}NO$.

2.5.12 (E)-1-(Anthracen-9-yl)-3-(furan-2-yl)prop-2-en-1-one (2.10l)



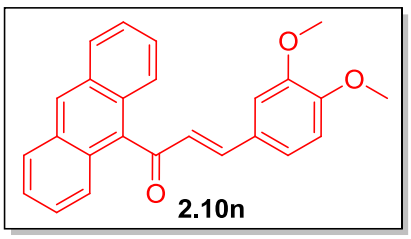
Bright yellow solid. Yield: 90%. m.p. 119–122 °C. IR (KBr) cm^{-1} 3106.46 (Aromatic C-H), 1618.94 (C=O), 1541.46 (olefinic C=C). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H, Ar-H), 8.07 – 8.04 (m, 2H, Ar-H), 7.94–7.91 (m, 2H, Ar-H), 7.52–7.46 (m, 5H, Ar-H), 7.15 (d, *J* = 8.4 Hz, 1H, =CH), 6.97–6.93 (d, *J* = 8.4 Hz, 1H, =CH), 6.53–6.52 (m, 1H, Ar-H), 6.45 (dd, *J* = 6.4 Hz, *J* = 2.7 Hz, 1H, Ar-H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$) δ 199.53, 150.79, 145.67, 134.46, 133.63, 131.13, 128.40, 128.34, 127.23, 126.67, 126.39, 125.51, 125.32, 116.98, 112.80 ppm. HRMS (m/z): 321.0890 (M+23) observed for $C_{21}H_{14}O_2$.

2.5.13 (E)-1-(Anthracen-9-yl)-3-(3, 4, 5-trimethoxyphenyl)prop-2-en-1-one (2.10m)



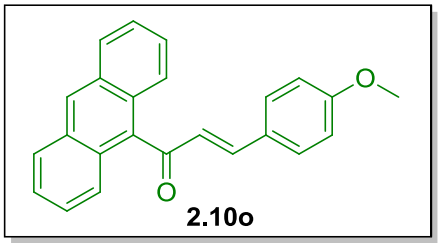
Yellow solid. Yield: 94%. m.p. 150–153 °C. IR (KBr) cm^{-1} 3059.97 (Aromatic C-H), 1629.27 (C=O), 1572.45 (olefinic C=C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H, Ar-H), 8.09 – 8.07 (m, 2H, Ar-H), 7.94–7.91 (m, 2H, Ar-H), 7.54–7.47 (m, 4H, Ar-H), 7.23 (d, *J* = 8.9 Hz, 1H, =CH), 7.14 (d, *J* = 8.9 Hz, 1H, =CH), 6.68 (s, 2H, Ar-H), 3.86 (s, 3H, -OCH_3), 3.83–3.82 (s, 6H, -OCH_3) ppm. ^{13}C-NMR (400 MHz, $CDCl_3$) δ 200.08, 153.50, 153.44, 148.06, 140.86, 134.64, 131.26, 131.16, 129.62, 128.70, 128.63, 128.42, 128.30, 126.64, 125.33, 60.96, 56.17 ppm. HRMS (m/z): 421.1418 (M+23) observed for $C_{26}H_{22}O_4$.

2.5.14 (E)-1-(Anthracen-9-yl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (2.10n)



Pale yellow solid. Yield: 95%. m.p. 104–107 °C. IR (KBr) cm^{-1} 2992.83 (Aromatic C-H), 1624.10 (C=O), 1598.28 (olefinic C=C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H, Ar-H), 8.07– 8.06 (m, 2H, Ar-H), 7.96–7.94 (m, 2H, Ar-H), 7.52–7.46 (m, 6H, Ar-H), 7.20 (s, 1H, Ar-H), 7.18 (d, *J* = 9.1 Hz, 1H, =CH), 6.98 (d, *J* = 9.1 Hz, 1H, =CH), 3.88 (s, 3H, -OCH_3), 3.86 (s, 3H, -OCH_3) ppm. ^{13}C-NMR (400 MHz, $CDCl_3$) δ 200.04, 151.84, 149.29, 148.09, 131.17, 128.83, 128.60, 128.40, 128.19, 127.28, 126.77, 126.54, 125.51, 125.33, 1233.50, 11.06, 110.18, 55.99, 55.89 ppm. HRMS (m/z): 391.1310 (M+23) observed for $C_{25}H_{20}O_3$.

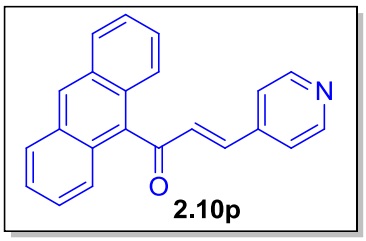
2.5.15 (E)- 1-(Anthracen-9-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (2.10o)



2.10o

Pale yellow solid. Yield: 92%, m.p. 100–103 °C. IR (KBr) cm^{-1} 3059 (Aromatic C-H), 1629.27 (C=O), 1567.29 (olefinic C=C). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H, Ar-H), 8.08–8.05 (m, 2H, Ar-H), 7.96–7.93 (m, 2H, Ar-H), 7.52–7.45 (m, 4H, Ar-H), 7.40–7.38 (d, *J* = 9.4 Hz, 2H, Ar-H), 7.20 (s, 2H, Ar-H), 6.86–6.84 (m, 2H, =CH), 3.81 (s, 3H, $-OCH_3$) ppm. ^{13}C-NMR (500 MHz, $CDCl_3$) δ 200.15, 162.07, 147.95, 134.12, 131.16, 130.49, 128.61, 128.41, 128.07, 127.23, 127.08, 126.52, 125.50, 125.35, 114.42, 55.40 ppm. HRMS (m/z): 361.1203 (M+23) observed for $C_{24}H_{18}O_2$.

2.5.16 (E)-1-(Anthracen-9-yl)-3-(pyridin-4-yl)prop-2-en-1-one (2.10p)

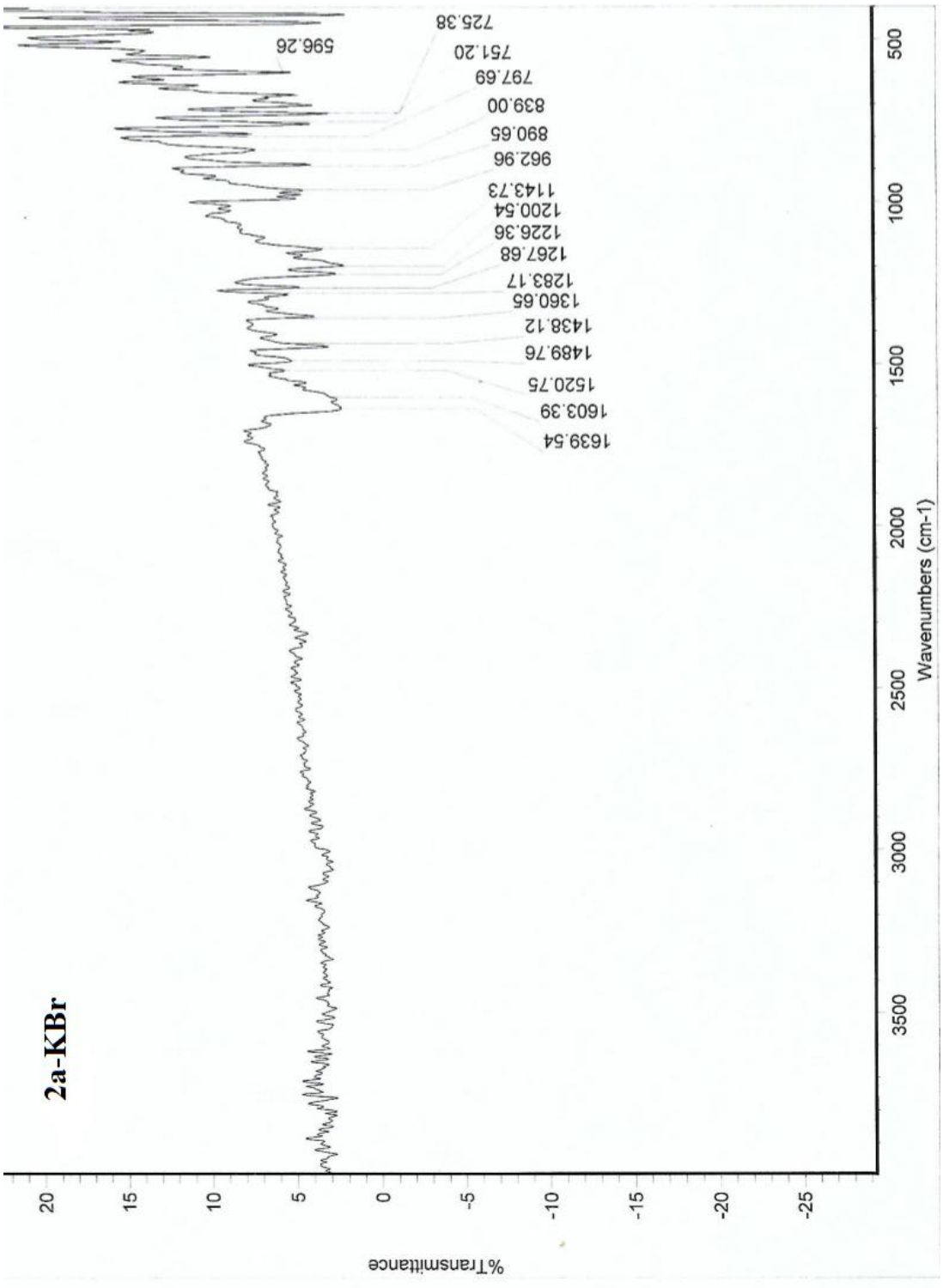


2.10p

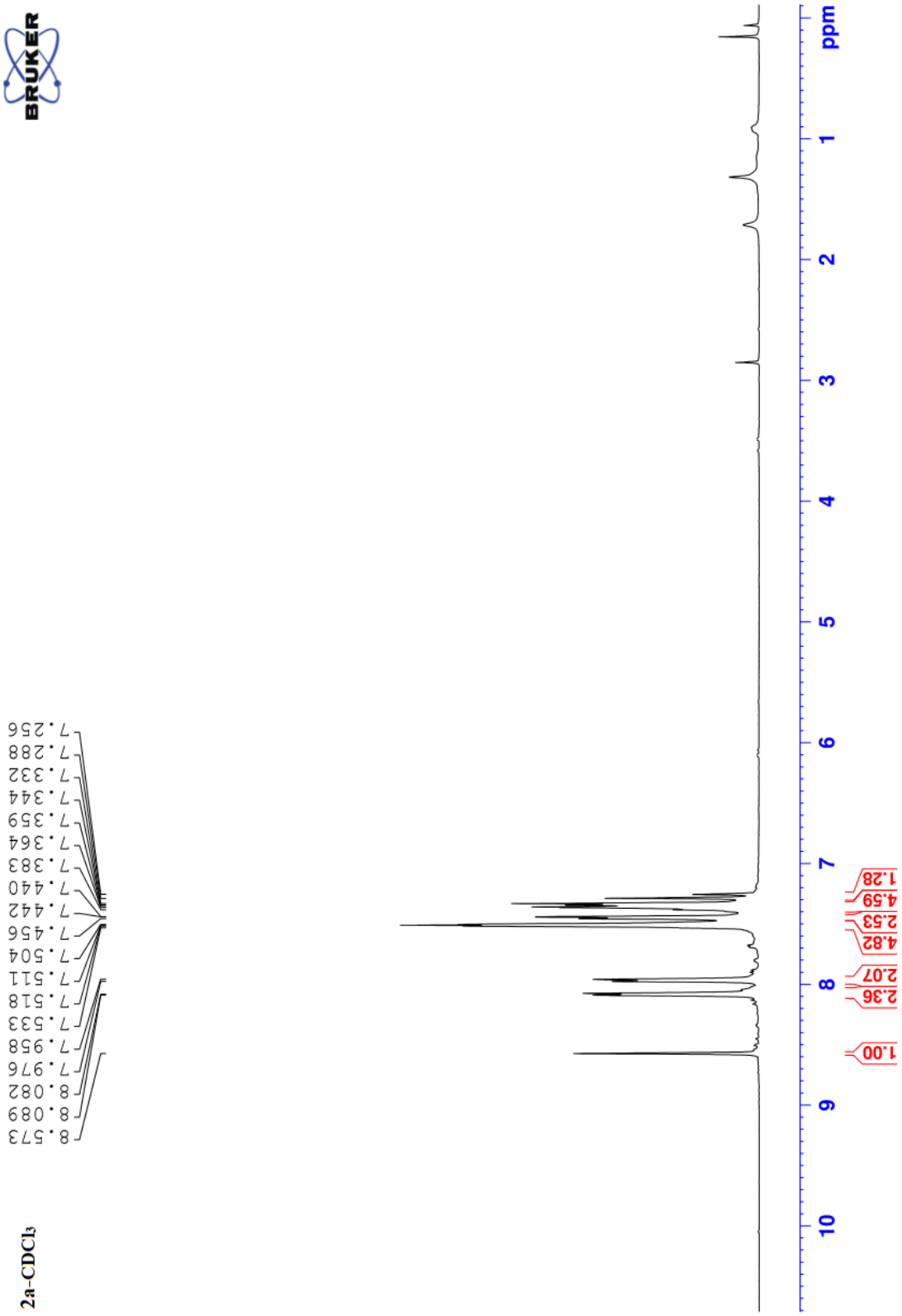
Dark orange solid. Yield: 73%. m.p. 160–163 °C. IR (KBr) cm^{-1} 3049.64 (Aromatic C-H), 1634.43 (C=O), 1582.78 (olefinic C=C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.60–8.58 (m, 3H, Ar-H), 8.08–8.07 (m, 2H, Ar-H), 7.89–7.87 (m, 2H, Ar-H), 7.51–7.48 (m, 2H, Ar-H), 7.41–7.38 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.28–7.27 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.18–7.15 (m, 2H, =CH) ppm. ^{13}C-NMR (400 MHz, $CDCl_3$) δ 199.56, 150.56, 144.04, 141.49, 132.65, 131.09, 128.98, 128.81, 128.39, 127.20, 126.96, 125.64, 124.91, 122.05 ppm. HRMS (m/z): 332.1054 (M+23) observed for $C_{22}H_{15}NO$.

2.6 REPRESENTATIVE SPECTRA OF ANTHRACENYL CHALCONES

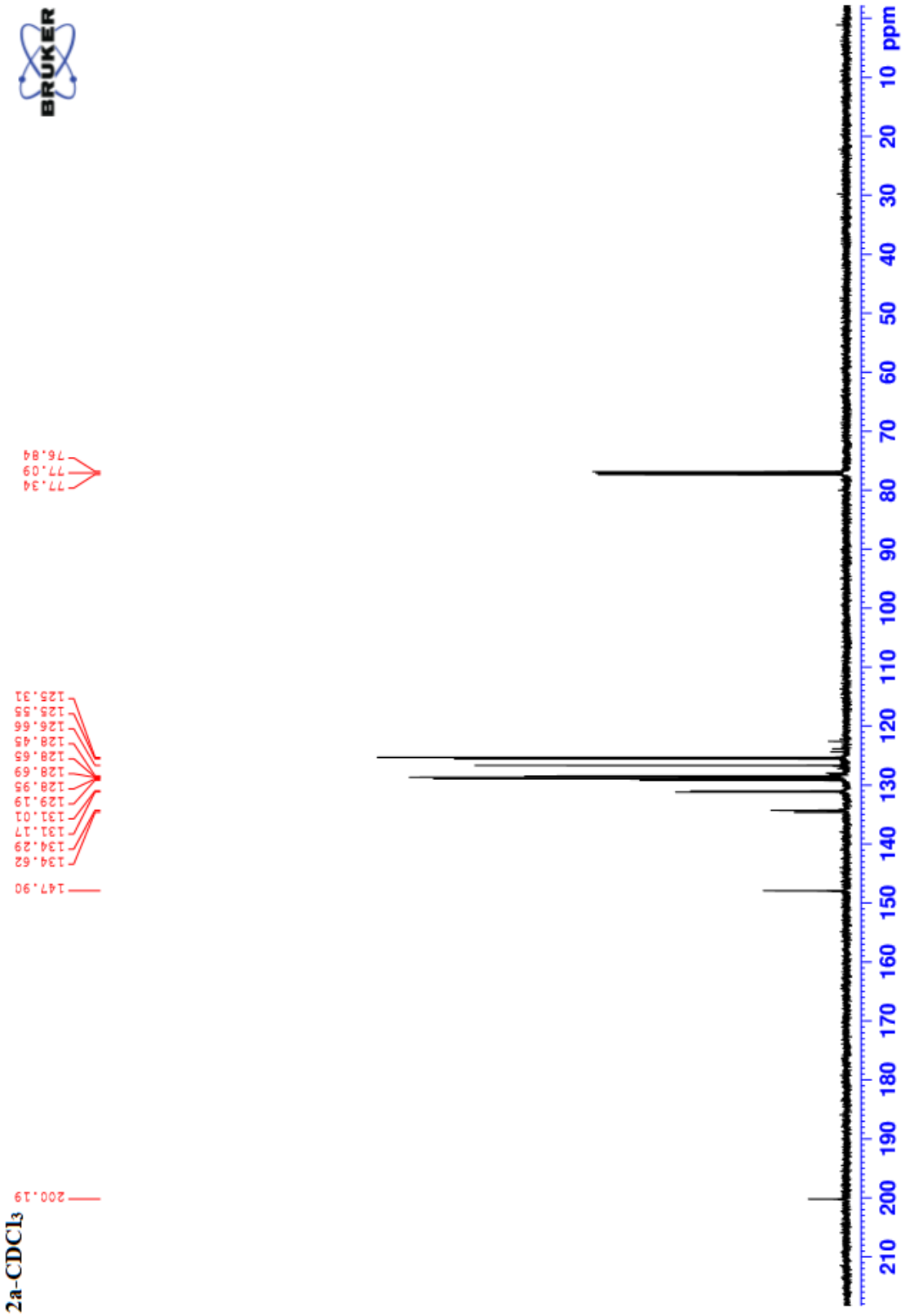
2.6.1 IR (KBr, *v*, cm^{-1}) spectrum of (E)-1-(Anthracen-9-yl)-3-phenylprop-2-en-1-one (2.10a)



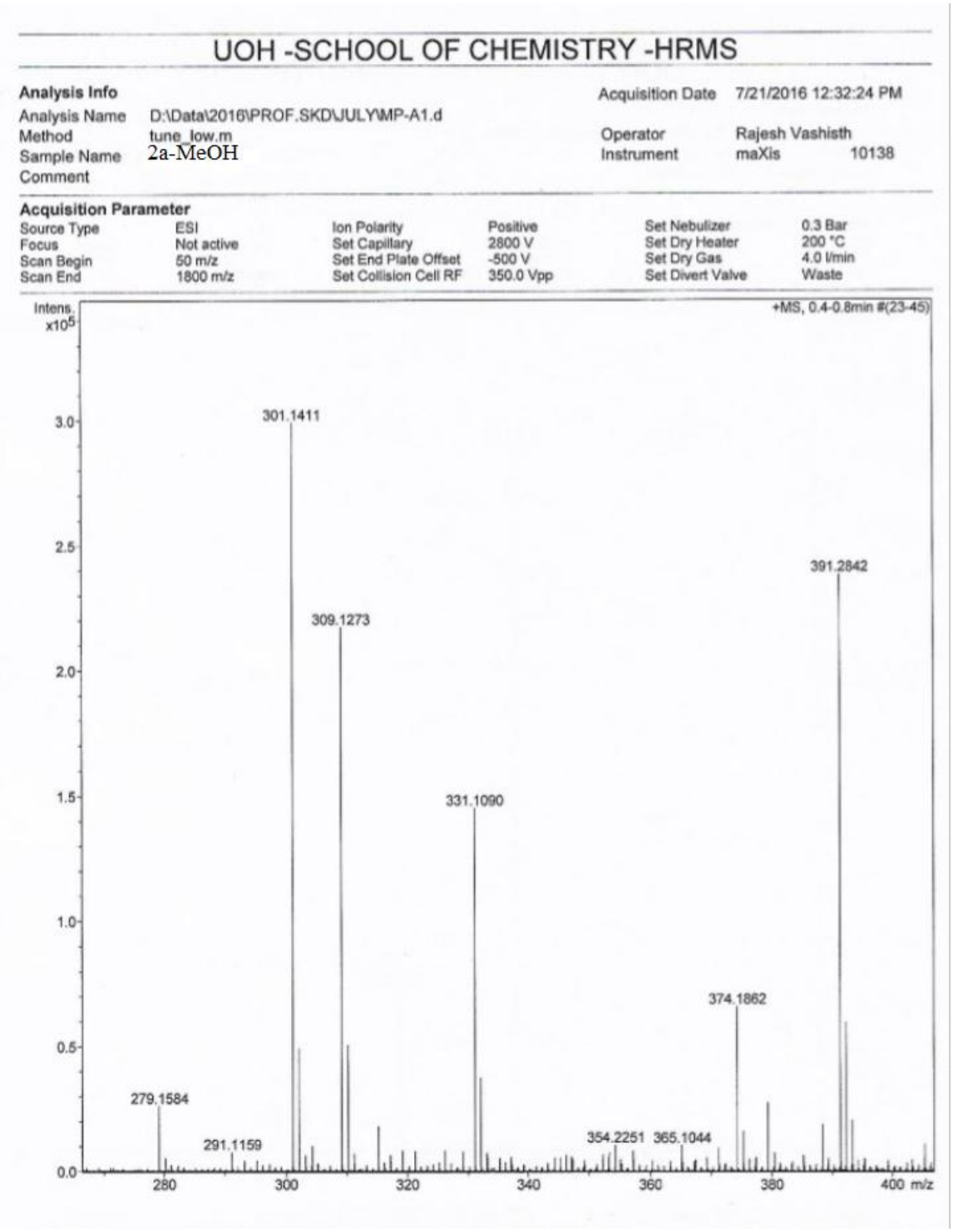
2.6.2 ^{1}H-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-phenylprop-2-en-1-one (2.10a)



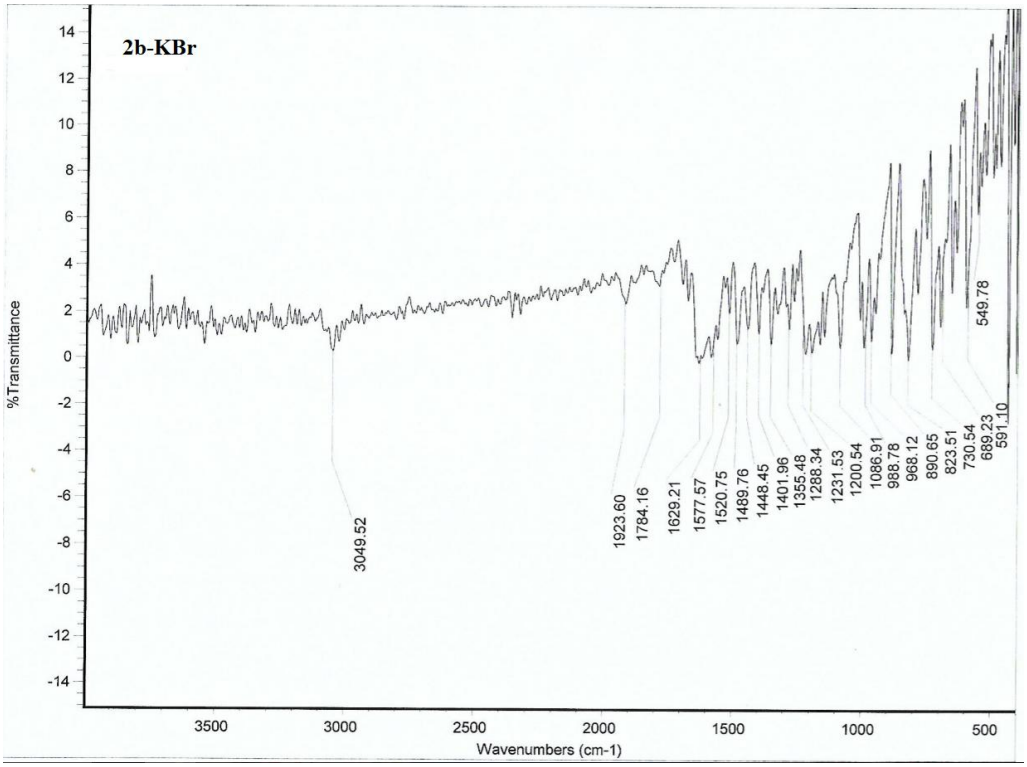
2.6.3 ^{13}C-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-phenylprop-2-en-1-one (2.10a)



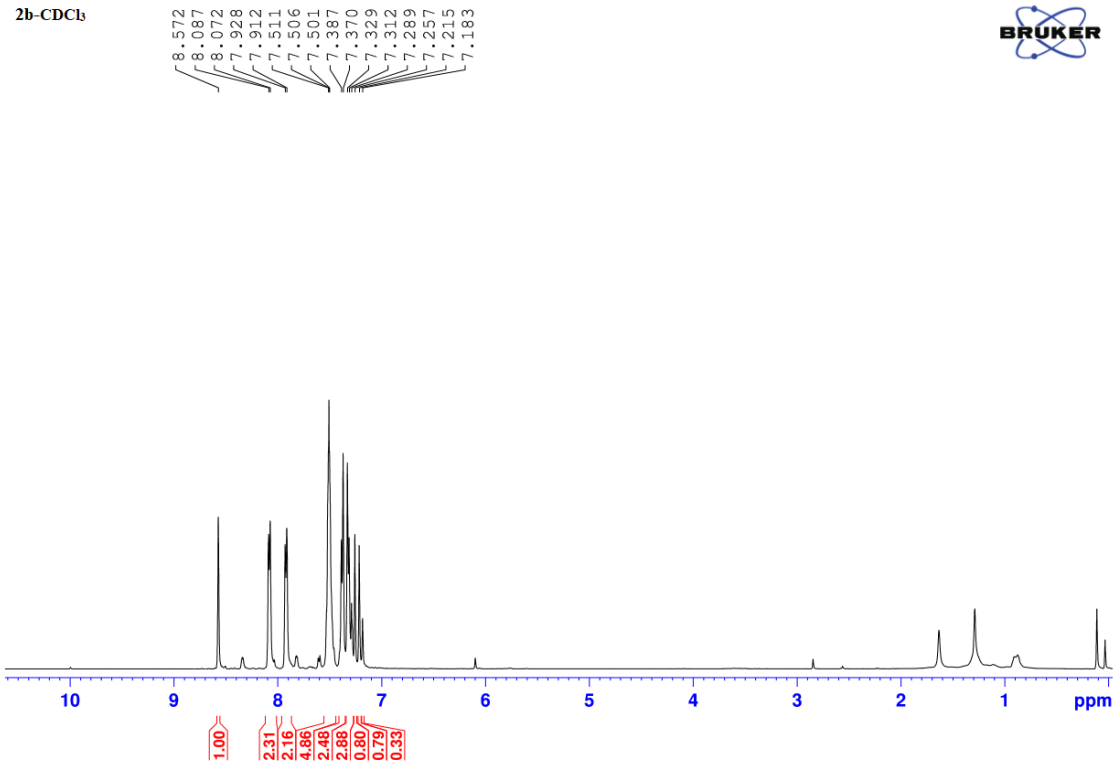
2.6.4 HRMS spectrum of (E)-1-(Anthracen-9-yl)-3-phenylprop-2-en-1-one (2.10a)



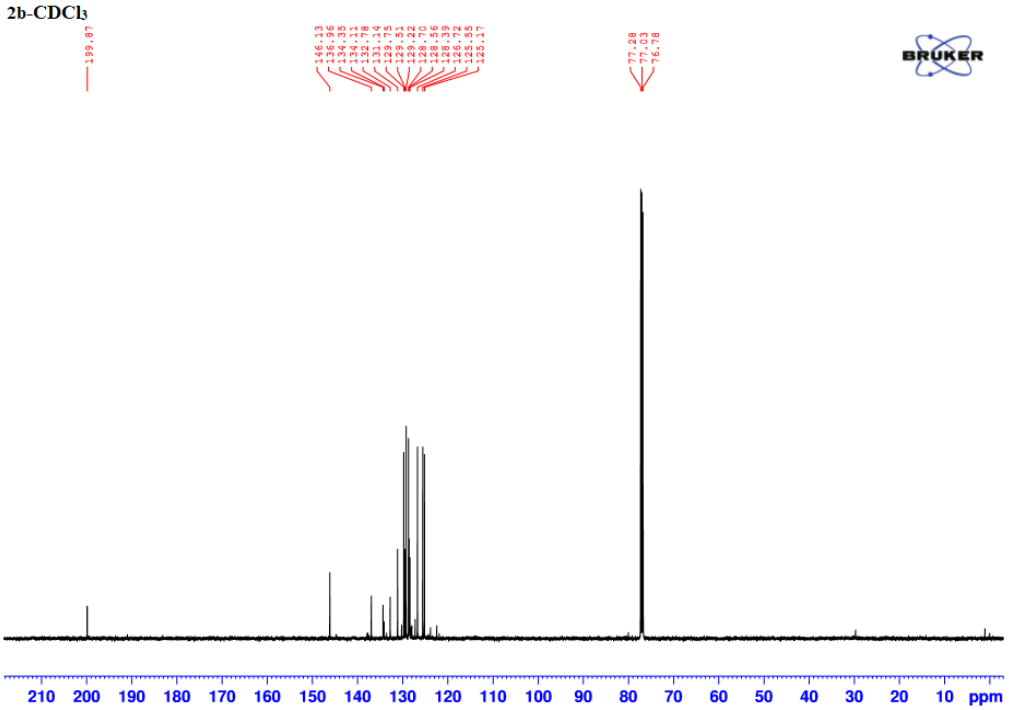
2.6.5 IR (KBr, *v*, cm^{-1}) spectrum of (E)-1-(Anthracen-9-yl)-3-(4-chlorophenyl) prop-2-en-1-one (2.10b)



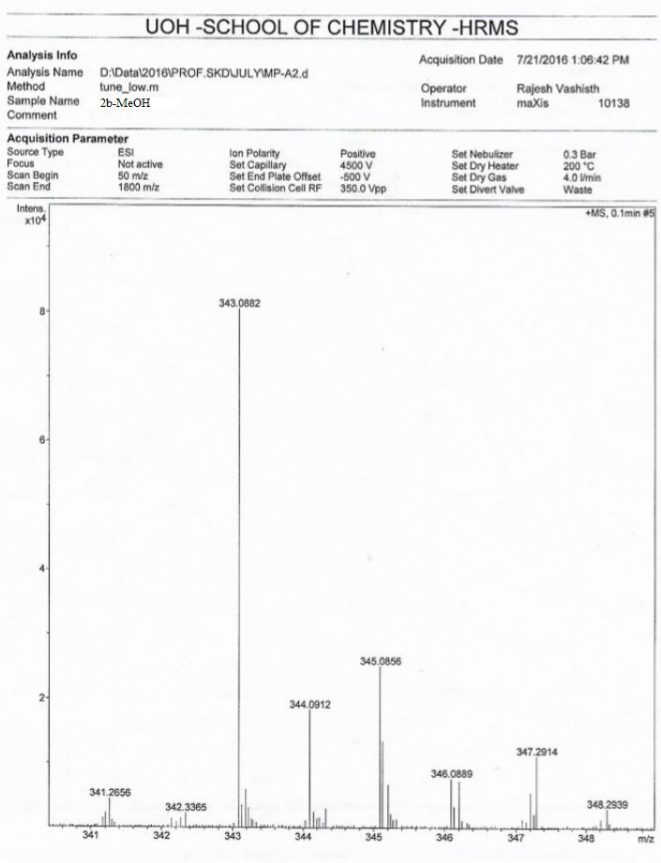
2.6.6 ^{1}H-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(4-chlorophenyl) prop-2-en-1-one (2.10b)



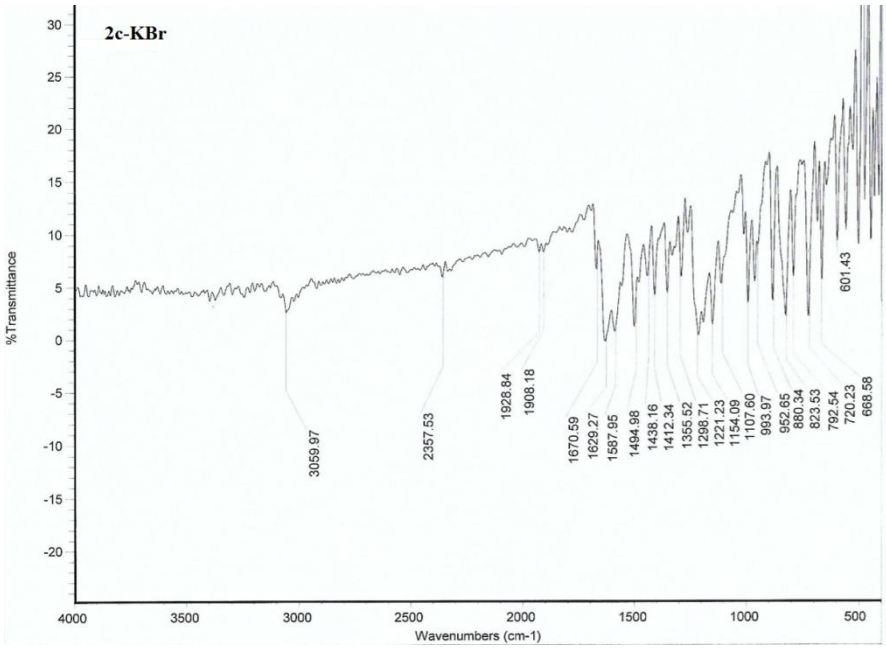
2.6.7 ^{13}C NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(4-chlorophenyl) prop-2-en-1-one (2.10b)



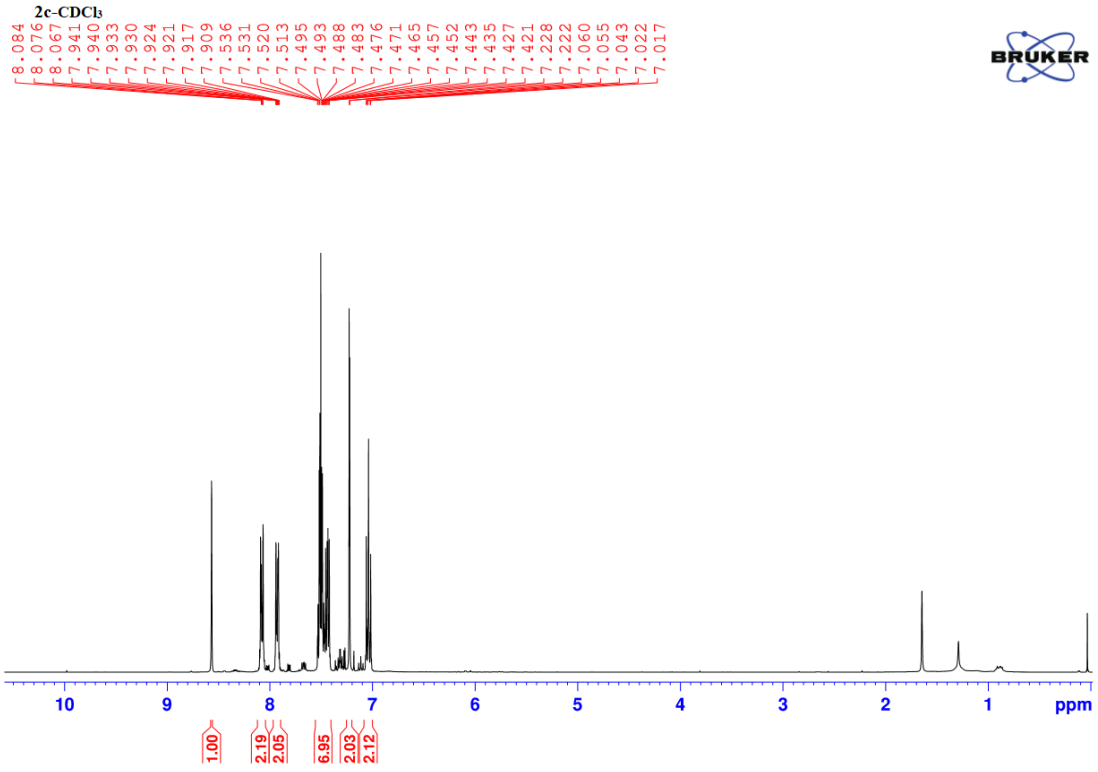
2.6.8 HRMS spectrum of (E)-1-(Anthracen-9-yl)-3-(4-chlorophenyl)prop-2-en-1-one (2.10b)



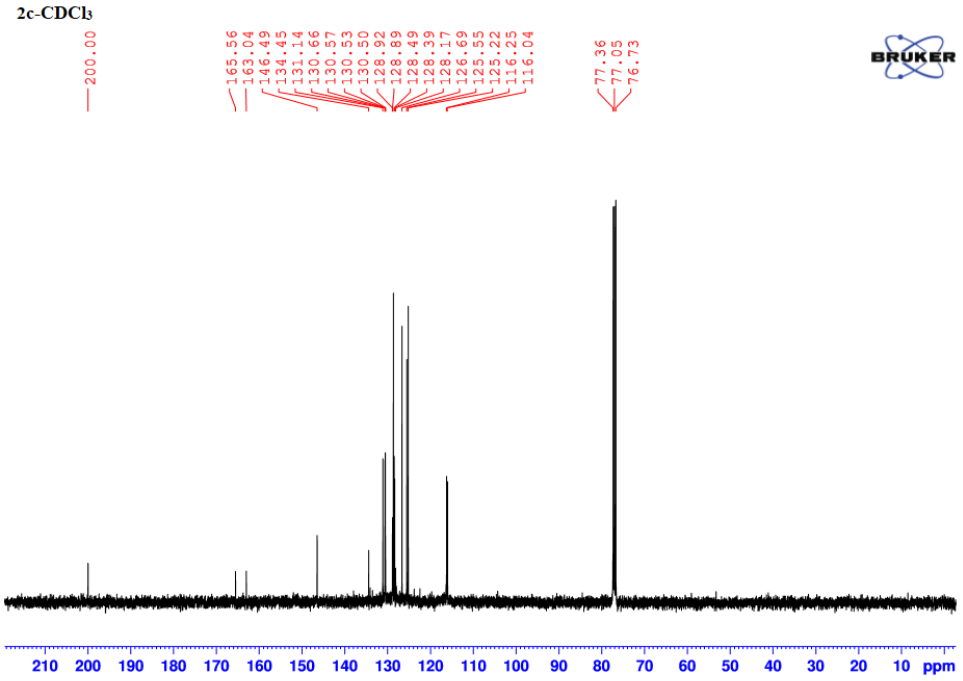
2.6.9 IR (KBr, *v*, cm^{-1}) spectrum of (E)-1-(Anthracen-9-yl)-3-(4-fluorophenyl) prop-2-en-1-one (2.10c)



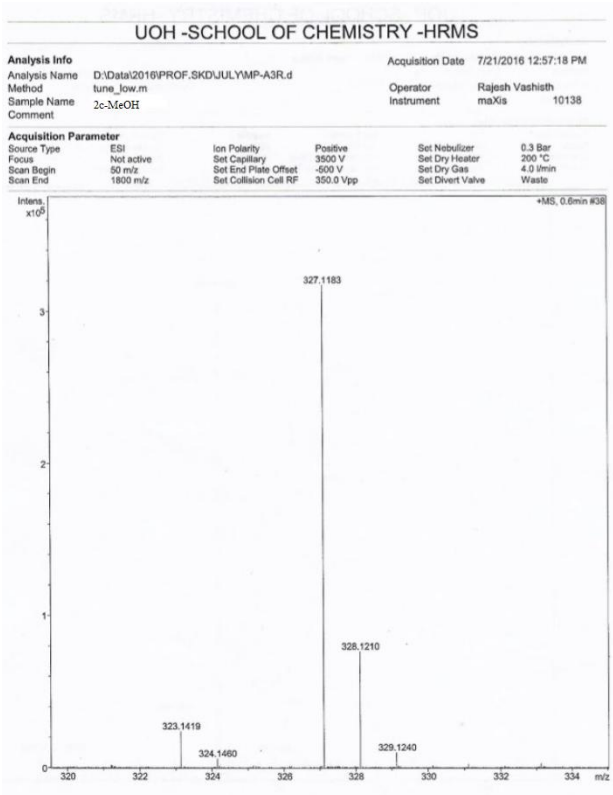
2.6.10 ^{1}H-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(4-fluorophenyl) prop-2-en-1-one (2.10c)



2.6.11 ^{13}C-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(4-fluorophenyl) prop-2-en-1-one (2.10c)



2.6.12 HRMS spectrum of (E)-1-(Anthracen-9-yl)-3-(4-fluorophenyl)prop-2-en-1-one (2.10c)



- All the spectra of other anthracenyl chalcones are represented in Appendix: C-2.

1.7 References

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Chapter 3

Design and Synthesis of Anthracenyl Pyrazolines and their Anti-Cancer Activity

Abstract

A series of anthracenyl pyrazoline derivatives (**3.9a–o**) were synthesized by the reaction of various anthracenyl chalcones and hydrazine hydrate with an aim to evaluate their *in vitro* anti-cancer activity. The structure of each compound is well characterized by IR, ^{1}H-NMR, ^{13}C-NMR, elemental analyses and mass spectroscopic techniques. The molecular structures of compounds **3.9d** and **3.9e** were solved by single-crystal X-ray crystallographic methods. The newly synthesized anthracenyl pyrazoline compounds (**3.9a–o**) were evaluated for their *in vitro* anti-cancer activity studies against four human cancer cell lines MCF-7 (breast cancer cell lines), SK-N-SH (neuroblastoma cancer cell lines), HeLa (cervical cancer cell lines) and HepG2 (liver cancer cell lines) and the screening results show strong cytotoxic effects for most of the synthesized compounds against the three cell lines except SK-N-SH cells. Notably, compounds **3.9a**, **3.9j**, **3.9l**, **3.9m**, **3.9n** and **3.9o** showed a highly potential activity against HeLa cells (IC_{50}: 0.22, 0.3, 0.3, 0.10, 0.25, and 0.25 μM), while compounds **3.9i**, **3.9k**, **3.9l** and **3.9m** showed a significant cytotoxic activity in HepG2 cells (IC_{50}: 0.22, 0.44, 0.40, and 0.22 μM), whereas compounds **3.9a**, **3.9b**, **3.9d** and **3.9e** exhibit a promising cytotoxicity against MCF-7 cells (IC_{50}: 0.73, 0.495, 0.493, and 0.66 μM) respectively.

3.1 INTRODUCTION

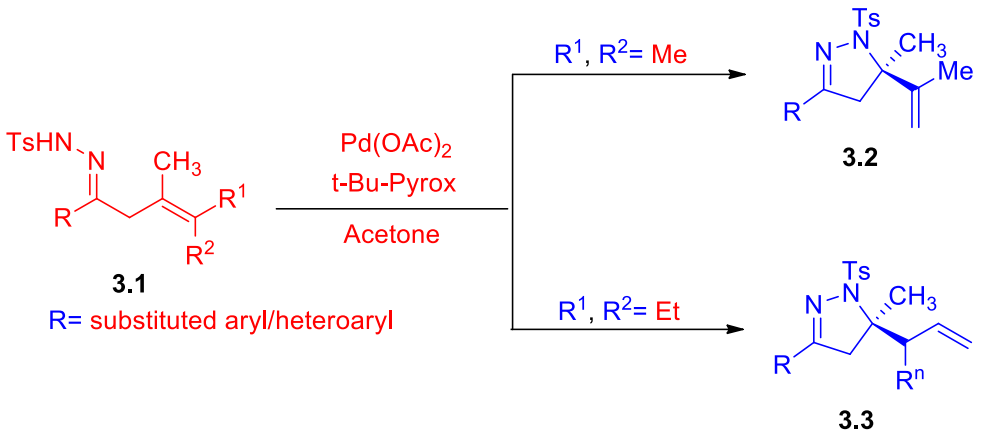
Pyrazole and pyrazoline moieties are nitrogen-containing heterocyclic molecules that are well known for their numerous biological activities and variety of applications. They are by far the most important efficacious molecules in the field of anti-HIV,[1] anti-oxidant,[2] anti-bacterial,[3] anti-inflammatory,[4] anti-cancer,[5] anti-histaminic,[6] sedative-hypnotic,[7] anti-coagulant,[8] anti-tumor,[9] anti-convulsant activities,[10] etc. Pyrazoles are reported to be synthesized *via* a (3+2) cycloaddition reactions[11] and by using different types of catalysts such as copper,[12] Cu_2O,[13] Cu-nanoparticles,[14] CeO_2 nanoparticles,[15] CuO/ZrO_2,[16] $NaHSO_4$-SiO_2,[17] ZrO_2 nanoparticles,[18] $MgCl_2$,[19] L-Proline[20] catalyzed reactions, etc. As mentioned in the first chapter, the easy and convenient preparation and functionalization of pyrazoles associated with the different biological properties have made this class of *N*-heterocycles very striking for the design and development of new synthetic routes and applications.[21] Intense studies have been

done on pyrazole in their structural as well as physical properties and a systematic investigation of this type of heterocyclic molecules containing pharmacoactive agents shows increasing number of publications. The main aim of medicinal chemistry is to design and develop biologically active compounds and to understand their metabolism and to study their mode of action at the molecular level so as to prevent and treat humans as well as animal diseases.[22] Due to the biologically active core pyrazolyl structural unit and their importance in the field of medicinal chemistry, the need for the development of new transformations of the synthesis of pyrazole containing moiety that are not only efficient but also environmentally benign is highly appreciated.[23] A number of pyrazolyl unit containing molecules have also been extensively studied and reported for their anti-cancer activity[24] since we all know that cancer has become one of the most major health problems in the world and has affected people of all ages.[25] The most prominent types of cancer that has been known and reported are lung, bronchus, prostate, breast, colon and rectum.[26] Some of the most common environmental factors that lead to cancer death are chewing of tobacco, dietary habits, obesity, different kinds of infections, exposure to radon, radiation, stress, lack of physical activity and environmental pollutants.[27] Despite the modern advances in cancer treatment and therapy, cancer is still the second leading cause of death next to cardiovascular disorders all over the world.[28] Therefore, the need for potent chemotherapeutic agents still remains a great challenge to fight against different types of cancer.

Taking into consideration the various biological importance of pyrazole, many new potent bioactive pyrazole molecules considering pyrazolines as intermediate compound for synthesis of various heterocyclic compounds have been designed and developed especially in cancer therapy. The most common method that have been used and reported for the synthesis of substituted pyrazoles are condensation of substituted hydrazines with dicarbonyl or intermolecular [3+2] cycloaddition reaction with alkynes to 1,3-dipoles.[29] The recent investigations on the synthesis of pyrazoles and pyrazolines and their biological activities are discussed below.

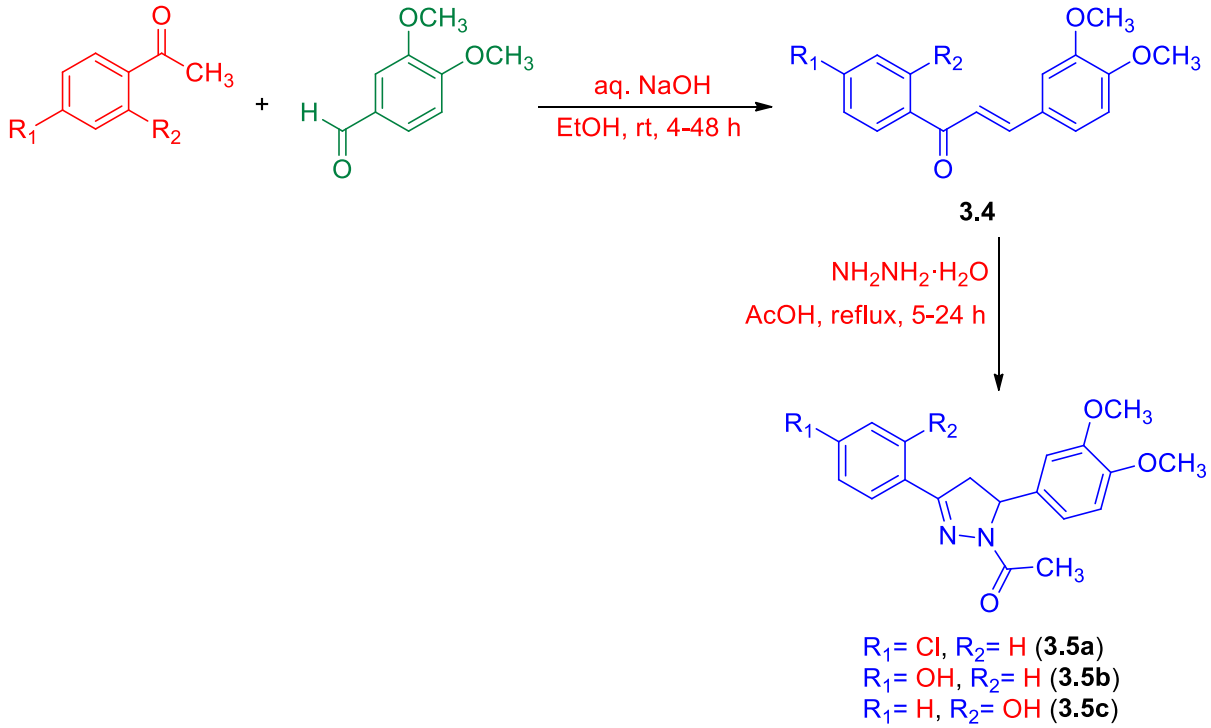
Xuezhen Kou and group in **2018** developed Pd-catalyzed asymmetric aza-Wacker-type cyclization of N-Ts hydrazine-tethered tetrasubstituted olefins is the presence of t-Bu-Pyrox in acetone giving the optically active pyrazolines bearing chiral tetrasubstituted carbon stereocenters (Scheme 3.1). This reaction is tolerant to a broad range of substrates under mild reaction conditions, giving the desired chiral products with good to excellent yields and high enantio-selectivities. This study is one of the rare types for Wacker-type reaction due to the generation of two vicinal stereocenters on the C=C double bonds that is feasible with high

selectivities. A mechanistic study revealed that this aza-Wacker-type cyclization undergoes a *syn*-amino-palladation process.[30]



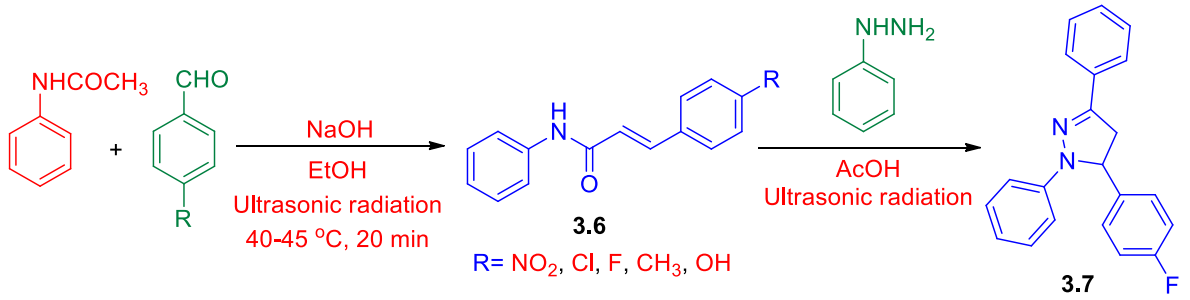
Scheme 3.1. Synthesis of pyrazolines bearing tetrasubstituted chiral carbon stereocenters.

In **2019**, Tutik Dwi Wahyuningsih and co-workers have reported the synthesis of *N*-acetyl pyrazoline derivatives containing methoxy and chloro/hydroxyl substituents. Each of the synthesized compounds was tested for their cytotoxic activities. The precursor chalcones (**3.4**) which were obtained from condensation of veratraldehyde and acetophenone derivatives were than reacted with hydrazine hydrate in the presence of glacial acetic acid to give pyrazolines (Scheme 3.2). Results of cytotoxicity evaluation revealed that 1-(3-(4-chlorophenyl)-5-(3,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (**3.5a**) has moderate activity against breast cancer cell line MCF7 (IC_{50} 40.47 µg/ml), breast cancer cell line T47D (IC_{50} 26.51 µg/ml) and cervical cancer cell line HeLa (IC_{50} 31.19 µg/ml). 1-(5-(3,4-dimethoxyphenyl)-3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (**3.5b**) is inactive against all tested cancer lines (IC_{50}>100 µg/ml). 1-(5-(3,4-dimethoxyphenyl)-3-(2-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (**3.5c**) has moderate activity against MCF7 cancer cell line (IC_{50} 94.02 µg/ml) but inactive against T47D and HeLa cancer cell lines. Docking studies also showed hydrogen bonds and π-cation interaction between pyrazolines and EGFR receptor.[31]



Scheme 3.2. Synthesis of *N*-acetyl pyrazoline derivatives.

J. P. Sethiya *et al*. in **2019** also reported the Claisen-Schmidt condensation of acetanilide and an appropriate aromatic aldehydes giving chalcone molecule as the product. These chalcone derivatives were further cyclized with phenylhydrazine in the presence of glacial acetic acid under ultrasonic radiation giving the new pyrazoline derivatives (Scheme 3.3). All the synthesized chalcone derivatives were evaluated for their anti-microbial activity and the cyclized pyrazoline derivatives were screened for their anti-inflammatory properties. Out of the synthesized pyrazoline derivatives, compound 1,3-diphenyl-5-(4-fluorophenyl)-4,5-dihydro-1H-pyrazole (**3.7**) showed good potential anti-inflammatory activity.[32]



Scheme 3.3. Synthesis of 1,3-diphenyl-5-(p-substituted)-4,5-dihydro-1H-pyrazole derivatives.

In this chapter we have synthesized a series of anthracenyl pyrazoline derivatives by the reaction of anthracenyl chalcones (**2.10**) and hydrazine hydrate (**3.8**). We observed that the introduction of a pyrazoline ring in the chalcones between the two aryl rings gives more scope for the synthesis of new heterocyclic compounds from diverse chalcones. From this findings and in the continuation of our ongoing research in the field of design and synthesis of natural products-based new scaffolds and their biological activity, we reported the synthesis of a new series of anthracenyl pyrazoline derivatives (**3.9a-o**) and their anti-cancer activity evaluation against four different cancer cell lines, MCF-7 (breast cancer cell lines), SK-N-SH (neuroblastoma cancer cell lines), HeLa (cervical cancer cell lines) and HepG2 (liver cancer cell lines).

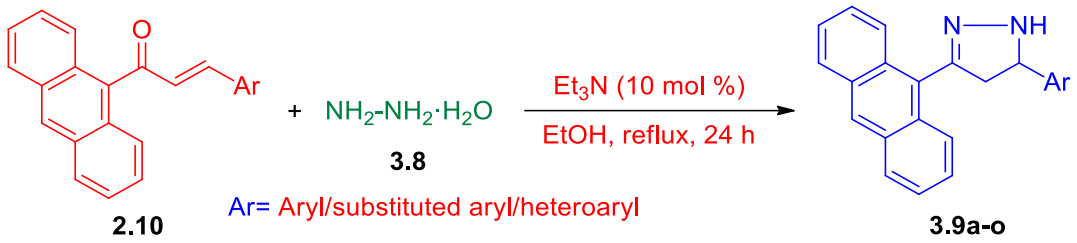
3.2 EXPERIMENTAL SECTION

3.2.1 Materials and Methods

All the reagents and solvents were purchased from commercially available sources and used without further purification. Melting points were recorded in open capillaries using IKON melting point apparatus and are uncorrected. FTIR spectra of the compounds were recorded on Perkin-Elmer spectrophotometer (Spectrum-Two) using KBr disk and values are expressed in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra for the newly synthesized anthracenyl pyrazoline compounds were recorded using Bruker 300 MHz spectrophotometer in $CDCl_3$ as a solvent and TMS as an internal standard, values are given in parts per million (ppm). Mass spectra for the compounds were recorded on PE Sciex API 2000 system. Microanalytical (CHN) data were obtained with a FLASH EA 1112 Series CHNS analyzer. Progress of the reactions was monitored by thin layer chromatography (TLC) with silica gel plates (Merck) using ethylacetate and *n*-hexane (3:7) as a solvent system and visualized under UV-light/iodine vapors.

3.2.2 General procedure for the synthesis of new anthracenyl pyrazolines (3.9a-o)

To a stirred solution of corresponding anthracenyl chalcone (**2.10**) (1 mmol), hydrazine hydrate (**3.8**) (0.500 g, 10 mmol) was added triethylamine (10 mol %) in ethanol (5 mL). The reaction mixture was refluxed for 24 hours with continuous stirring. After completion of the reaction monitored by TLC, the solvent was removed and added ice cold water. The pure solid products were collected by filtration, washed with water (3-4 times) and finally with 50% ethanol and dried. The same synthetic protocol was followed for the synthesis of all other anthracenyl pyrazoline derivatives (**3.9a-o**) (Scheme 3.4 and Figure 3.1).



Scheme 3.4. Synthesis of anthracenyl pyrazoline derivatives (**3.9a-o**).

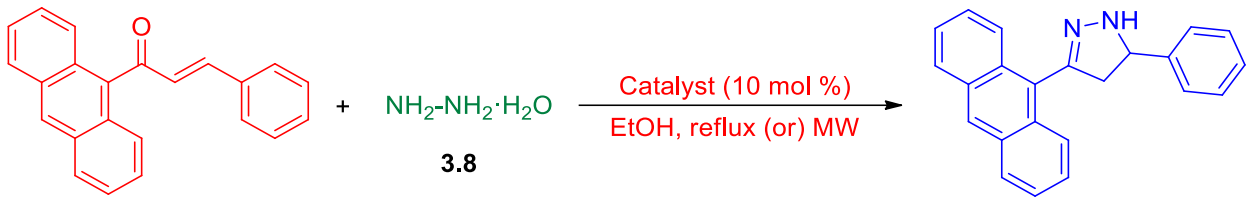
3.3 RESULTS AND DISCUSSION

3.3.1 Chemistry

The synthesis of anthracenyl pyrazoline derivatives (**3.9a–o**) were carried out from the reaction of anthracenyl chalcones (**2.10**)[33] with hydrazine hydrate (**3.8**) in the presence of triethylamine (Et_3N) in ethanol solution at refluxing temperature for 24 h. Initially, attempts were made to synthesize the 3-anthracen-9-yl-5-phenyl-4,5-dihydro-1H-pyrazole (**3.9a**) starting from 1:10 ratio of 1-anthracen-9-yl-3-phenyl-propenone (**2.10a**) with hydrazine hydrate (**3.8**) in the presence of different acid catalysts (AcOH, HCl, H_2SO_4, TsOH, and $FeCl_3$) in ethanol solution under reflux conditions for 24 h, and we observed that the progress of the reactions was very slow and obtained poor yields (Table 3.1, entries 1–5). Further, we carry out the reaction under microwave reaction conditions at 200 °C for 30 min by using different acid catalysts (AcOH, HCl, H_2SO_4, TsOH, and $FeCl_3$); here we observed that the percentage of the yields are not improved much under this methods (Table 3.1, entries 1–5). The aforementioned catalysts and conditions were not attained up to satisfactory yields of the product **3.9a** monitored by thin-layer chromatography (TLC) on time intervals. Then we proceed to carry out the reactions in the presence of base catalysts such as Et_3N (Table 3.1, entry 6), piperidine (Table 3.1, entry 7) and pyridine (Table 3.1, entry 8) under refluxing conditions in ethanol for 24 h and microwave conditions. We found that better yields (96%) were achieved only in the presence of Et_3N under refluxing conditions in ethanol for 24 h (Table 3.1, entry 6). Thus, in order to standardize the reaction, we examined the mole ratio of the reactants (1:1, 1:2, 1:5 and 1:10) for better conversion of the reactant **2.10a** to the anthracenyl pyrazoline product **3.9a** in the presence of Et_3N (10 mol %). We found that better yields (96%) of the product **3.9a** was obtained at 1:10 mole ratio of reactants anthracenyl chalcone (**2.10a**) and hydrazine hydrate (**3.8**) in ethanol at reflux temperature for 24 h (Table

3.1, entry 6). To test the generality and scope of this method, we than examined the reactions with a series of anthracenyl chalcones (**2.10**) and hydrazine hydrate (**3.8**) under the aforementioned standardized reaction conditions for the synthesis of anthracenyl pyrazoline derivatives (**3.9a-o**) as revealed in Table 3.2 and Figure 3.1. All reactions showed to be a good and quite efficient synthetic etiquette for aryl as well as hetero-aryl group and irrespective of the presence of electron-donating and electron-withdrawing functional groups in phenyl ring system.[34]

Table 3.1. Optimization of the reaction conditions and catalysts for the synthesis of anthracenyl pyrazoline (**3.9a**).[a]



2.10a **3.9a**

Entry	Catalyst	Reaction methods, Yields (%)	
		Reflux (24h)	Microwave(200 °C, 30 min)
1	AcOH	30	10
2	TsOH	40	25
3	HCl	35	20
4	H_2SO_4	10	3
5	$FeCl_3$	10	3
6	**Et_3N**	**96**	60
7	Piperidine	40	15
8	Pyridine	25	5

[a]Reaction conditions: Anthracenyl chalcone **2.10a** (1 mmol), hydrazine hydrate **3.8** (10 mmol) and Catalyst (10 mol %) in 5 mL ethanol solution.

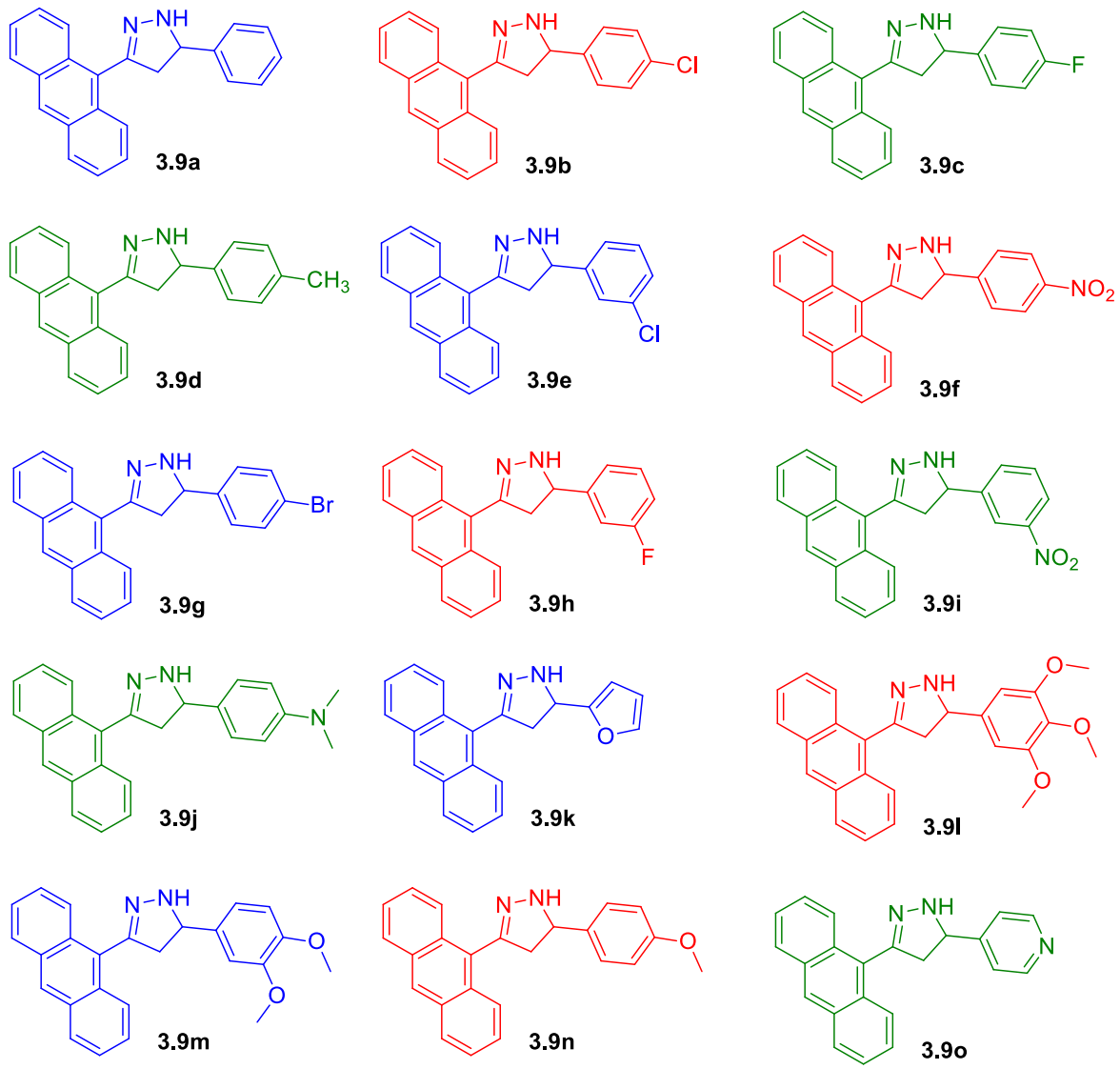
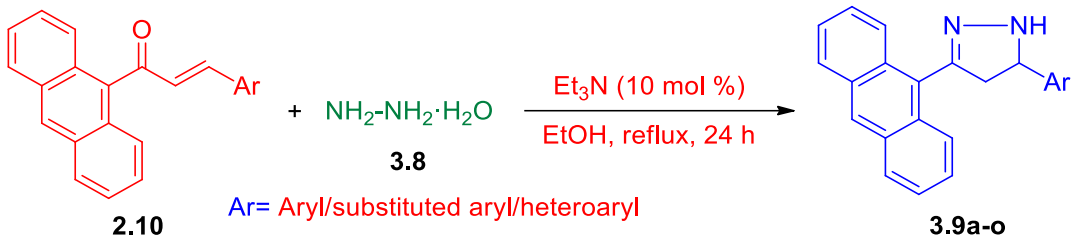


Figure 3.1. Structures of the newly synthesized anthracenyl pyrazoline derivatives (**3.9a–o**).

The structures of the newly synthesized anthracenyl pyrazoline derivatives (**3.9a–o**) were elucidated by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy. The Fourier transform infrared spectra of the anthracenyl pyrazoline compounds endorse the disappearance of two absorption bands of the CH═CH and C═O groups of anthracenyl chalcones and appearance of a new absorption bands of NH and C═N groups at 3343 and 1591 cm^{-1} as well as the aliphatic C–H stretching vibrations at 2985–2930 cm^{-1} respectively.

Table 3.2. Substrate scope for the synthesis of new anthracenyl pyrazoline derivatives (**3.9a-o**).[a]



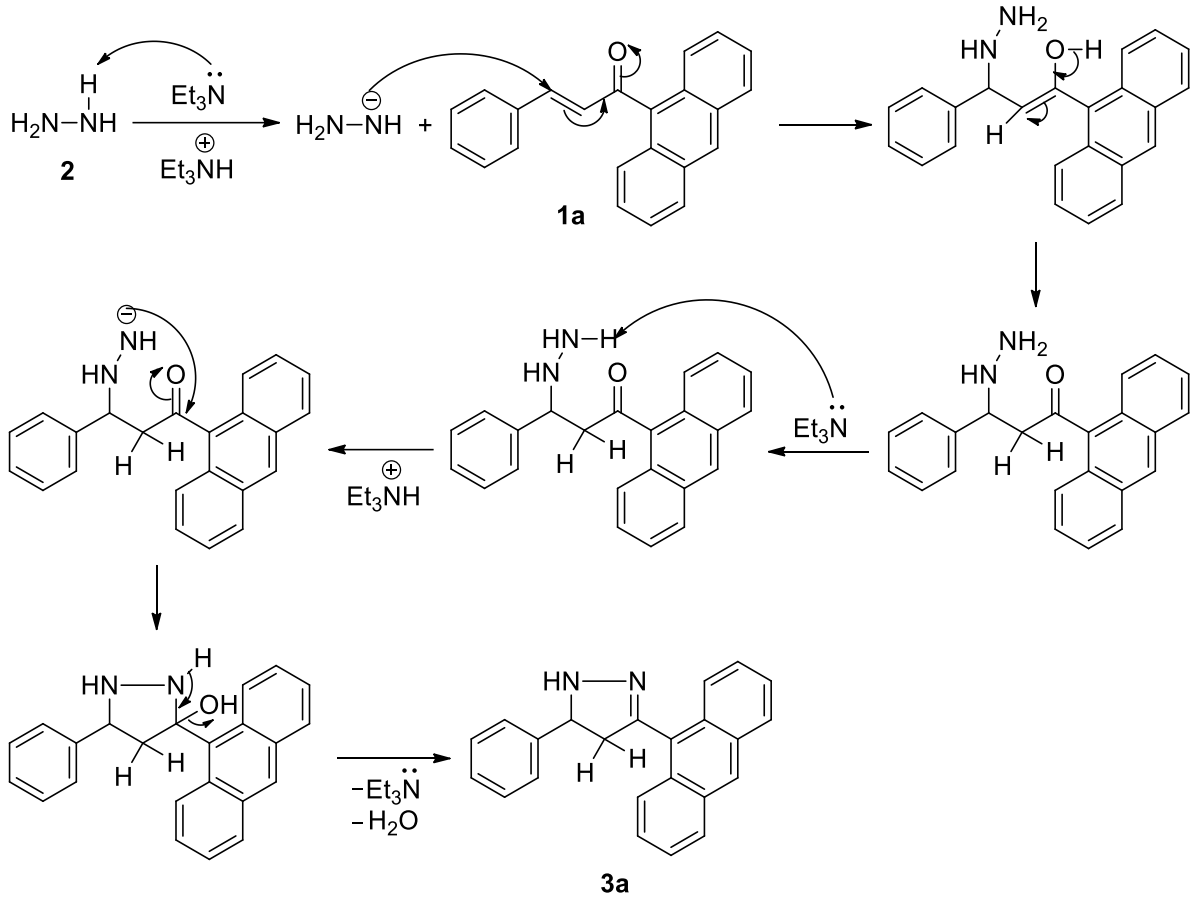
2.10 **3.9a-o**

Entry	Ar	Product	Yield (%)	m.p. (°C)
1	C_6H_5	**3.9a**	96	94–97
2	4-ClC_6H_4	**3.9b**	95	50–53
3	4-FC_6H_4	**3.9c**	94	76–79
4	4-$CH_3C_6H_4$	**3.9d**	96	123–125
5	3-ClC_6H_4	**3.9e**	97	104–106
6	4-$NO_2C_6H_4$	**3.9f**	90	67–70
7	4-BrC_6H_4	**3.9g**	94	57–59
8	3-FC_6H_4	**3.9h**	93	86–89
9	3-$NO_2C_6H_4$	**3.9i**	95	73–75
10	4-$N(CH_3)_2C_6H_4$	**3.9j**	93	114–116
11	2-Furanyl	**3.9k**	90	56–58
12	3,4,5-$(OCH_3)_3C_6H_2$	**3.9l**	95	62–64
13	3,4-$(OCH_3)_2C_6H_3$	**3.9m**	92	63–65
14	4-$(OCH_3)C_6H_4$	**3.9n**	94	103–105
15	4-Pyridinyl	**3.9o**	90	57–60

[a]Reaction conditions: Anthracenyl chalcone (**2.10**) (1 mmol), hydrazine hydrate (**3.8**) (10 mmol), Et_3N (10 mol %) in 5 mL ethanol and reflux for 24 h.

In the ^{1}H-NMR spectra of the anthracenyl pyrazolines (**3.9a-o**), the CH_2 protons of pyrazoline ring resonated as a pair of doublet of doublets at δ 3.16–3.07 ppm, 3.60–3.51 ppm and the CH proton of the compounds appears as a triplet at δ 5.35–5.10 ppm because of the neighboring protons of the methylene (CH_2) group. In the ^{13}C-NMR spectra of the compounds, the characteristic chemical shift values of the pyrazoline ring carbons appear at 47.75–43.71 (C, CH_2 pyrazoline), 64.73–57.48 (C, CH pyrazoline) and 151.80–151.34 (C, C═N pyrazoline)

that agrees with the pyrazoline character deduced from the ^{1}H-NMR spectra. The proposed reaction mechanism for the synthesis of anthracenyl pyrazolines is shown in Scheme 3.5.



Scheme 3.5. Proposed reaction mechanism for the synthesis of anthracenyl pyrazolines (**3.9a–o**).

3.3.2 Biological Activity

3.3.2.1 Materials and Methods

Cytotoxicity assay was performed with MTT (3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide) in four human cancer cell lines (MCF-7, SK-N-SH, HeLa and HepG2 cells). Briefly, cancer cell lines were grown in DMEM media with 10% FBS, approximately 0.02 x10^{6} cells were seeded in 100 µL of complete media. After overnight incubation, cell viability was determined by MTT (3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide) reagent (5 mg/mL) assay. Test compounds (**3a-o**) at different concentrations (25 nM, 250 nM, 2.5 µM, 25 µM and 250 µM) were added and incubated for a period of 48 hours in cell culture incubator at 37 ^{o}C. At the end of the treatment, the medium was removed and the cells were washed with 1xPBS and 20 µL of MTT was added to each

well and incubated for 4 hours in cell culture incubator. Finally, 200 µL of DMSO was added to all the wells, plate was gently swirled and kept in dark for 2 hours at room temperature. Absorbance was measured at 570 nm in a micro titer plate reader and compared with that of the wells in which the drug is omitted (control). Curcumin was used as a positive control. Each assay was repeated at least three times and in triplicates. The IC_{50} (Concentration of 50% Inhibition) value was calculated using Microsoft Excel sheet. All compounds were showed significant anti-proliferative activity (Figure 3.2).

3.3.2.2 Anti-Cancer Activity

The anti-cancer activity of the newly synthesized anthracenyl pyrazoline derivatives (**3.9a-o**) were carried out against four human cancer cell lines MCF-7 (breast cancer cell lines), SK-N-SH (neuroblastoma cancer cell lines), HeLa (cervical cancer cell lines) and HepG2 (liver cancer cell lines). Curcumin was used as a reference drug and the cell viability in presence of test compounds were measured by MTT assay. The anti-cancer activity results revealed that the compounds **3.9a**, **3.9b**, **3.9d** and **3.9e** exhibit highest activity against MCF-7 cells (IC_{50}: 0.73, 0.495, 0.493 and 0.66 µM), compounds **3.9i**, **3.9k** and **3.9l** show significant activity against SK-N-SH cells (IC_{50}: 3.55, 1.88 and 2.00 µM). Whereas compounds **3.9a**, **3.9j**, **3.9l**, **3.9m**, **3.9n** and **3.9o** showed highly potent activity against HeLa cells (IC_{50}: 0.22, 0.3, 0.3, 0.10, 0.25 and 0.25 µM) and compounds **3.9i**, **3.9k**, **3.9l** and **3.9m** showed highest activity against HepG2 cells (IC_{50}: 0.22, 0.44, 0.40 and 0.22 µM) respectively (Table 3.3).[34]

The overall anti-cancer activity screening results of the new anthracenyl pyrazoline compounds (**3.9a-o**) found that (i) substitution on phenyl ring showed marked effect on cytotoxic activity, (ii) presence of nitrogen containing groups, electron donating and withdrawing groups on phenyl ring led to enhanced anti-cancer activity, (iii) replacement of phenyl ring with heterocyclic ring also increases the anti-cancer activity against the cancer cell lines MCF-7 (breast cancer cell lines), SK-N-SH (neuroblastoma cancer cell lines), HeLa (cervical cancer cell lines) and HepG2 (liver cancer cell lines). The anti-cancer activity screening results (IC_{50}; µM) were represented in Table 3.3 and percentage of cancer cells viability of four cell lines were depicted in Figure 3.2.

Table 3.3. Anti-cancer inhibition values (IC_{50}) of new anthracenyl pyrazoline compounds (**3.9a-o**) on four human cell lines.

S. No.	Compounds	Anti-Cancer Activity (IC_{50}; µM)			
		MCF-7	SK-N-SH	HeLa	HepG2
1	**3.9a**	0.73	260.00	0.22	3.86
2	**3.9b**	0.495	290.00	25.00	22.22
3	**3.9c**	3.08	254.22	29.56	3.50
4	**3.9d**	0.493	258.42	2.03	26.44
5	**3.9e**	0.66	254.23	2.58	20.88
6	**3.9f**	1.5	250.66	27.29	20.65
7	**3.9g**	1.5	240.26	1.96	19.22
8	**3.9h**	2.0	250.29	1.10	33.44
9	**3.9i**	26.0	3.55	1.30	0.22
10	**3.9j**	17.0	260.22	0.3	1.58
11	**3.9k**	1.98	1.88	1.88	0.44
12	**3.9l**	23.0	2.00	0.3	0.40
13	**3.9m**	29.0	23.42	0.10	0.22
14	**3.9n**	25.0	25.33	0.25	2.66
15	**3.9o**	2.50	253.88	0.25	3.26
16	Curcumin	50	58.33	35.00	15.23

Table 3.3 is showing IC_{50} (50% Inhibitory Concentration) of the new anthracenyl pyrazoline compounds (**3.9a-o**) at µM concentration. The compounds have 50% cell cytotoxicity at varied concentration depending on the cell lines and curcumin was used as a positive control.

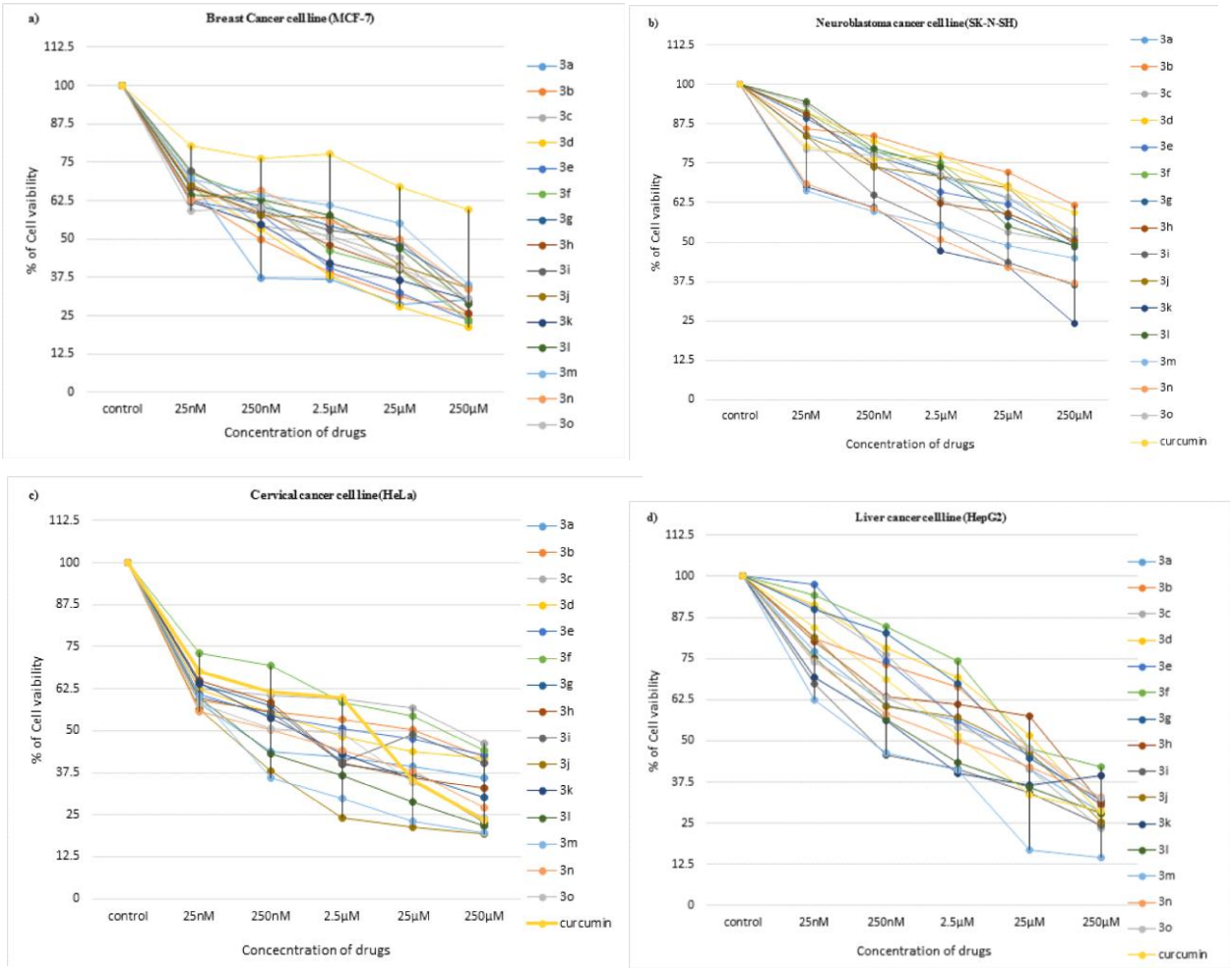


Figure 3.2. The survival curves of the human cancer cells (MCF-7 (**a**), SK-N-SH (**b**), HeLa (**c**), HepG2 (**d**)) for anthracenyl pyrazoline compounds (**3.9a-o**), curcumin was used as a positive control.

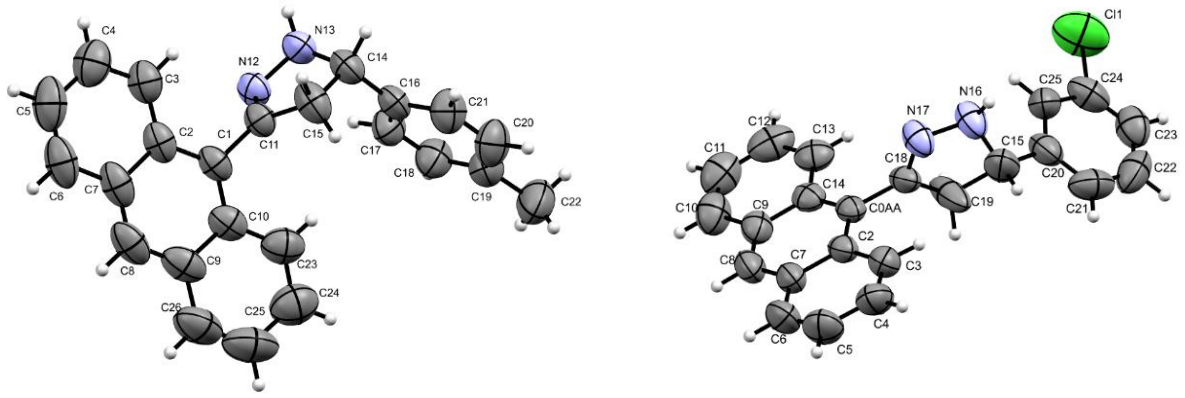
3.3.3 X-Ray Crystallography

Single crystal X-ray diffraction data of **3.9d** and **3.9e** were collected on an Agilent Super Nova diffractometer, equipped with multilayer optics, monochromatic dual source (Cu and Mo) and Eos CCD detector, using Mo-Kα (0.71073 Å) radiation at 293 K. Data acquisition, reduction and absorption correction were performed by using CrysAlisPRO program.[35] The structure was solved with ShelXS and refined on F^2 by full matrix least-squares techniques using ShelXL program provided in Olex^2 (v.1.2) program package.[36,37] Anisotropic displacement parameters were applied for all the atoms, except hydrogen atoms. H atoms were calculated into their positions or located from the electron density map and refined as riding atoms using isotropic displacement parameters. The data collected for **3.9e** were of poor

quality, despite multiple attempts of data collection. It exhibited relatively high R1 and *w*R2 values. The ratio of maximum/minimum residual density was 2.24 in this case.

The molecular structures of the new anthracenyl pyrazoline compounds **3.9d** and **3.9e** were unambiguously deduced by single-crystal X-ray diffraction methods. The crystal structure and refinement data of anthracenyl pyrazoline compounds **3.9d** and **3.9e** are listed in Table 3.4. The complete listing of the bond distances and bond angles is presented in the Appendix-C3, Table AC3.3–AC3.6. ORTEP diagrams of the crystal structures of **3.9d** and **3.9e** with atomic numbering are shown in Figure 3.3. Compound **3.9d** crystallized in orthorhombic Pbca space group. The asymmetric unit of **3.9d** consists of two independent molecules as shown in Figure 3.3 except some minor differences in the corresponding bond lengths and angles. The angles between the planes of the anthracene and benzene rings of the two molecules present in the asymmetric unit are 76.42° and 79.80°. The supramolecular analysis of **3.9d** revealed that the crystal structure is stabilized by a number of C–H···π intermolecular interactions. The strongest interaction among them is C47–H47···Cg1 with an angle of 161.62° and an H···Cg1 distance of 2.718 Å. The other such bonds include C9–H9···Cg1 with an angle of 162.06° and an H···Cg1 distance of 2.798 Å, C46–H46···Cg2 with an angle of 122.17° and an H···Cg2 distance of 3.161 Å and C19–H19···Cg3 with an angle of 171.87° and an H···Cg3 distance of 2.757 Å; see Appendix-C3, Table AC3.1 (Cg1 is the ring centroid of the six-membered C25-38 ring, Cg2 of C25-C30 and Cg3 of C1-C14; see Figure 3.3). The amine-H atom in **3.9d** does not participate in hydrogen bonding interactions. The inter-connection of molecules through such weak bonding interactions leads to a supramolecular sheet-like structure in the crystal lattice (Figure 3.4).

Meanwhile, compound **3.9e** crystallized in orthorhombic Pccn space group. The asymmetric unit consists of one molecule of **3.9e** as shown in Figure 3.3. The planes of the anthracene and phenyl rings in this molecule make an angle of 49° with each other. Structural analyses revealed a number of weak bonding interactions in the crystal. These include various C–H···Cl, N–H···N and C–H···π interactions (Appendix-C3, Table AC3.2). All these interactions stabilizes the crystal structure and lead to the formation of a supramolecular arrangement as shown in Figure 3.5. Crystallographic data for the solved structures **3.9d** and **3.9e** were deposited to the Cambridge Crystallographic Data Center (Numbers: CCDC-1891026 and CCDC-1891027) respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Center *via* www.ccdc. cam.ac.uk.



3.9d **3.9e**

Figure 3.3. X-ray crystal structures of the new anthracenyl pyrazoline compounds **3.9d** and **3.9e**.

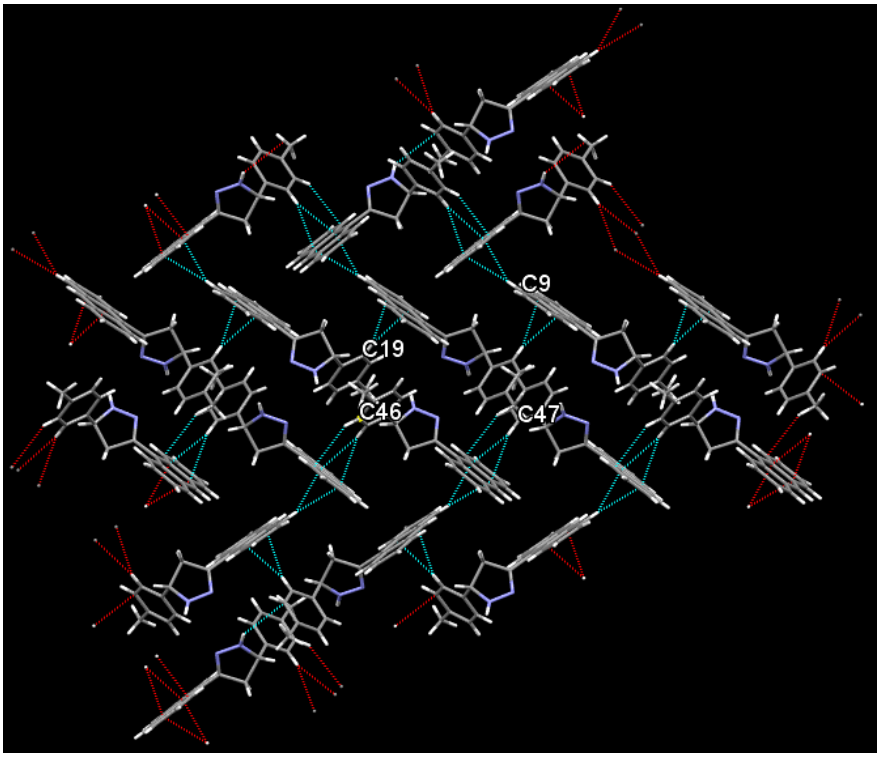


Figure 3.4. Intermolecular C–H···π interactions lead to the formation of supramolecular sheet-like arrangement in **3.9d**. The green dotted lines represent the C–H···π interactions among adjacent molecules and the red dotted lines represent hanging contacts from a molecule. Color code: C-grey, H-white, N-blue.

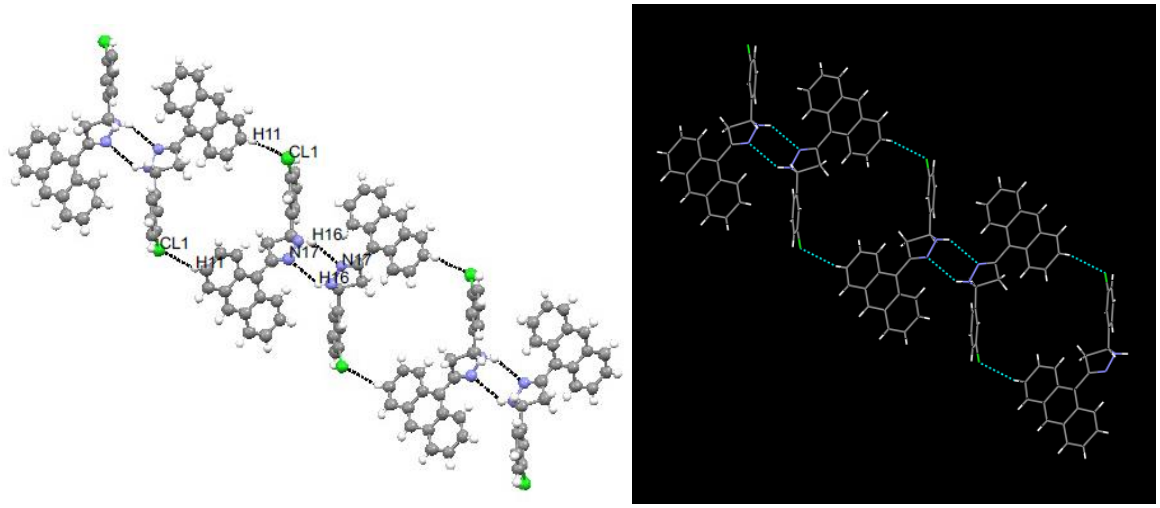


Figure 3.5. Crystal packing and intermolecular hydrogen bonding interactions of **3.9e**.

Table 3.4. The X-ray crystal experimental data of new anthracenyl pyrazolines **3.9d** and **3.9e**.

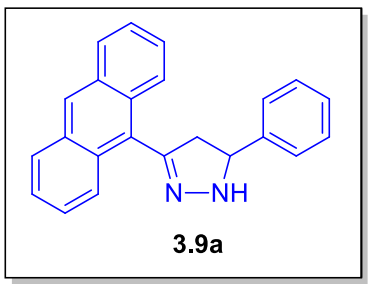
Parameters	**3.9d**	**3.9e**
Empirical formula	$C_{48}H_{40}N_4$	$C_{23}H_{17}ClN_2$
Formula weight	672.84	356.84
Temperature/K	293(2)	293(2)
Crystal system	orthorhombic	orthorhombic
Space group	Pbca	Pccn
a/Å	18.3826(6)	23.7226(9)
b/Å	16.2592(5)	15.2115(7)
c/Å	25.0613(6)	10.1920(4)
α/°	90.00	90.00
β/°	90.00	90.00
γ/°	90.00	90.00
Volume/Å^3	7490.5(4)	3677.8(3)
Z	8	8
ρ_{calc}g/cm^3	1.193	1.289
μ/mm^{-1}	0.538	1.885
F(000)	2848.0	1488.0
Crystal size/mm^3	0.236 × 0.105 × 0.088	0.656 × 0.088 × 0.069
Radiation	CuKα (λ = 1.54184)	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.08 to 133.66	6.9 to 133.72
Index ranges	-13 ≤ h ≤ 21, -19 ≤ k ≤ 16, -22 ≤ l ≤ 29	-22 ≤ h ≤ 28, -14 ≤ k ≤ 18, -12 ≤ l ≤ 11
Reflections collected	15280	7070
Independent reflections	6481 [R_{int} = 0.0434, R_{sigma} = 0.0468]	3214 [R_{int} = 0.0268, R_{sigma} = 0.0304]
Data/restraints/parameters	6481/0/471	3214/0/235
Goodness-of-fit on F^2	1.031	1.606
Final R indexes [I>=2σ (I)]	R_1 = 0.0674, wR_2 = 0.1868	R_1 = 0.1274, wR_2 = 0.3671
Final R indexes [all data]	R_1 = 0.1015, wR_2 = 0.2237	R_1 = 0.1493, wR_2 = 0.3996
Largest diff. peak/hole / e Å^{-3}	0.37/-0.34	2.00/-0.83
CCDC number	1891026	1891027

3.4 CONCLUSION

In conclusion, we have established and reported the Et_3N-prompted efficient synthesis of new anthracenyl pyrazoline derivatives and their anti-cancer activity. The present synthetic protocol is quite simple and obtained yields are good to excellent as pure solids by simple filtration methods. The single-crystal X-ray crystallographic structures show intermolecular C–H···π interactions leading to the formation of supramolecular sheet-like arrangement in **3.9d** and C–H···Cl, N–H···N and C–H···π interactions in **3.9e**. The anti-cancer activity results of the compounds **3.9a**, **3.9b**, **3.9d** and **3.9e** exhibit highest activity against MCF-7 cells, **3.9i**, **3.9k** and **3.9l** show significant activity against SK-N-SH cells. Whereas compounds **3.9a**, **3.9j**, **3.9l**, **3.9m**, **3.9n** and **3.9o** showed remarkable potential activity against HeLa cells ((IC_{50}: 0.22, 0.3, 0.3, 0.10, 0.25 and 0.25 µM)) and **3.9i**, **3.9k**, **3.9l** and **3.9m** showed highest activity against HepG2 cells. In conclusion, the newly synthesized anthracenyl pyrazoline derivatives exhibited remarkable potential activity against cancer and some of them are exclusively potent against breast cancer, cervical cancer and have more scope to explore for further investigations towards the clinical trials.

3.5 SPECTRAL CHARACTERIZATION DATA

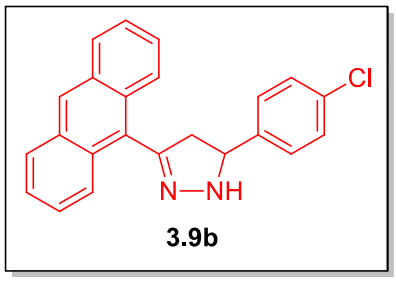
3.5.1 3-Anthracen-9-yl-5-phenyl-4,5-dihydro-1H-pyrazole (3.9a)



3.9a

Yellow solid. Yield: 96%. m.p. 94–97 °C. IR (KBr) cm^{-1} 3052.66 (Aromatic C-H), 3336.68 (NH) and 1590.63 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H, Ar-H), 8.03–8.01 (t, Hz, 4H, Ar-H), 7.60–7.57 (d, *J* = 7.38 Hz , 2H, Ar-H), 7.48–7.45 (m, 6H, Ar-H), 7.39–7.36 (d, *J* = 7.25 Hz , 1H, Ar-H) 6.41 (s, 1H, -NH), 5.29–5.23 (t, 1H, -CH), 3.62–3.53 (dd, 1H, -CH_2), 3.23–3.14 (dd, 1H, -CH_2) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 151.54, 142.22, 134.14, 131.43, 130.24, 128.99, 128.76, 128.05, 127.88, 127.67, 127.25, 126.54, 126.31, 125.38, 64.87, 47.62 ppm. MS (m/z): 323.7 (M+1). Elemental Anal. Calcd for $C_{23}H_{18}N_2$: C, 77.41; H, 4.80; N, 7.85. Found: C, 77.32; H, 4.85; N, 7.79.

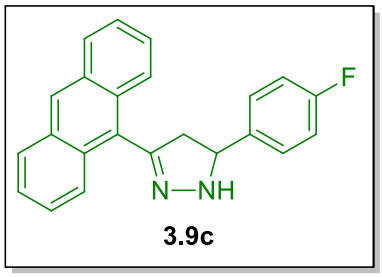
3.5.2 3-Anthracen-9-yl-5-(4-chloro-phenyl)-4,5-dihydro-1H-pyrazole (3.9b)



3.9b

Yellow solid. Yield: 95%. m.p. 50–53ºC. IR (KBr) cm^{-1} 3052 (Aromatic C-H), 3343.44 (NH) and 1591.30 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1H, Ar-H), 8.01–8.00 (d, *J* =3.46 Hz, 4H, Ar-H), 7.53–7.40 (m, 8H, Ar-H), 6.37 (s, 1H, -NH), 5.26–5.19 (t,1H, -CH), 3.60–3.51 (dd, 1H, $-CH_2$), 3.16–3.07 (dd, 1H, $-CH_2$) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 151.56, 140.63, 133.54, 131.41, 130.18, 129.07, 128.82, 128.16, 128.01, 127.37, 126.41, 125.42, 125.22, 64.31, 47.65 ppm. MS (m/z): 357.4 (M+). Elemental Anal. Calcd for $C_{23}H_{17}N_2Cl$: C, 85.68; H, 5.63; N, 8.69. Found: C, 85.52; H, 5.68; N, 8.61.

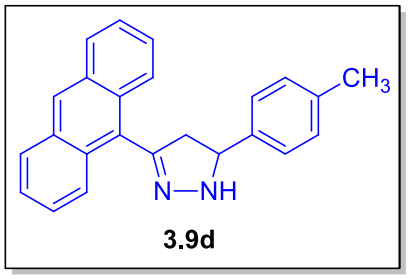
3.5.3 3-Anthracen-9-yl-5-(4-fluoro-phenyl)-4,5-dihydro-1H-pyrazole (3.9c)



3.9c

Yellow solid. Yield: 94%. m.p. 76–79 ºC, IR (KBr) cm^{-1} 3053.99 (Aromatic C-H), 3342.95 (NH) and 1600.83 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1H, Ar-H), 8.02–8.00 (t, Hz, 4H, Ar-H), 7.57–7.46 (m, 6H, Ar-H), 7.16–7.10 (t, 2H, Ar-H), 5.27–5.21 (t, 1H, -CH), 3.59–3.50 (dd, 1H, $-CH_2$), 3.17–3.08 (dd, 1H, $-CH_2$) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 151.69, 137.83, 134.23, 131.46, 128.85, 128.33, 128.22, 128.18, 126.42, 125.46, 125.28, 116.00, 115.71, 64.37, 47.77 ppm. MS (m/z): 341.5 (M+1). Elemental Anal. Calcd for $C_{23}H_{17}N_2F$: C, 81.16; H, 5.03; N, 8.23. Found: C, 81.26; H, 5.09; N, 8.27.

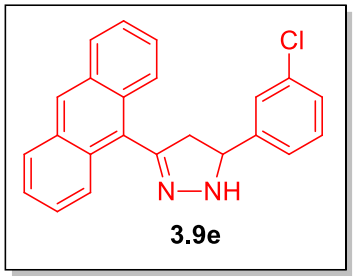
3.5.4 3-Anthracen-9-yl-5-p-tolyl-4,5-dihydro-1H-pyrazole (3.9d)



3.9d

Yellow solid. Yield: 96%. m.p. 123–125 ºC. IR (KBr) cm^{-1} 30544.09 (Aromatic C-H), 3326.74 (NH) and 1589.75 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H, Ar-H), 8.03–8.02 (d, *J* =2.03 Hz, 4H, Ar-H), 7.48–7.46 (t, 6H, Ar-H), 7.27–7.25 (d, J=6.92 Hz, 2H, Ar-H), 6.34 (s, 1H, -NH), 5.25-5.19 (t, 1H, -CH), 3.59–3.50 (dd, 1H, $-CH_2$), 3.20–3.12 (dd, 1H, $-CH_2$), 2.40 (s, 3H, Ar-CH_3) ppm.^{13}C- NMR (300 MHz, $CDCl_3$) δ 151.58, 139.29, 137.65, 131.49, 130.30, 129.69, 128.79, 128.03, 127.86, 126.53, 126.31, 125.47, 125.41, 64.78, 47.68, 21.27 ppm. MS (m/z): 337.5 (M+1). Elemental Anal. Calcd for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.33. Found: C, 85.56; H, 5.91; N, 8.27.

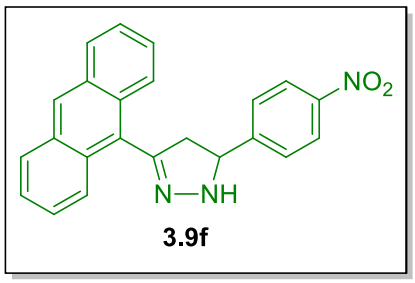
3.5.5 3-Anthracen-9-yl-5-(3-chloro-phenyl)-4,5-dihydro-1H-pyrazole (3.9e)



3.9e

Brown solid. Yield: 90%. m.p. 67–70 ºC. IR (KBr) cm^{-1} 3053.07 (Aromatic C-H), 3343.93 (NH) and 1587.78 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.48–8.45 (d, J= 8.69 Hz, 1H, Ar-H), 8.28–8.25 (d, *J* = 8.59 Hz, 1H, Ar-H), 8.02–7.97 (m, 4H, Ar-H), 7.74–7.72 (d, J= 8.46 Hz, 1H, Ar-H), 7.50–7.33 (m, 5H, Ar-H), 6.76–6.73 (d, J= 8.16 Hz, 1H, Ar-H), 6.56–6.48 (t, 1H, -NH), 5.35–5.10 (tt, 1H, -CH), 3.73–3.44 (m, 1H, $-CH_2$), 3.18–3.04 (m, 1H, $-CH_2$) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 151.34, 149.48, 131.34, 130.08, 128.85, 128.70, 128.29, 127.53, 127.45, 126.50, 126.25, 125.45, 125.00, 124.01, 115.45, 64.16, 47.60 ppm. MS (m/z): 356.4 (M+). Elemental Anal. Calcd for $C_{23}H_{17}N_2Cl$: C, 77.41; H, 4.80; N, 7.85. Found: C, 77.32; H, 4.86; N, 7.81.

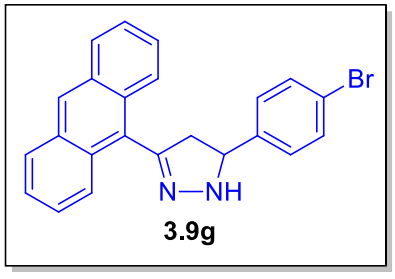
3.5.6 3-Anthracen-9-yl-5-(4-nitro-phenyl)-4,5-dihydro-1H-pyrazole (3.9f)



3.9f

Yellow solid. Yield: 97%. m.p. 104–106 ºC. IR (KBr) cm^{-1} 3053.73 (Aromatic C-H), 3324.08 (NH) and 1591.85 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H, Ar-H), 8.02–7.99 (t, 4H, Ar-H), 7.60 (s, 1H, Ar-H), 7.49–7.31 (m, 7H, Ar-H), 6.37 (s, 1H, -NH), 5.25–5.18 (t, 1H, -CH), 3.60–3.51 (dd, 1H, $-CH_2$), 3.16–3.07 (dd, 1H, $-CH_2$) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 151.51, 144.32, 134.86, 131.42, 130.27, 128.82, 128.17, 128.02, 126.87, 126.43, 125.44, 125.26, 124.81, 64.45, 47.61 ppm. MS (m/z): 368.4 (M+2). Elemental Anal. Calcd for $C_{23}H_{17}N_3O_2$: C, 75.19; H, 4.66; N, 11.44. Found: C, 75.24; H, 4.71; N, 11.32.

3.5.7 3-Anthracen-9-yl-5-(4-bromo-phenyl)-4,5-dihydro-1H-pyrazole (3.9g)

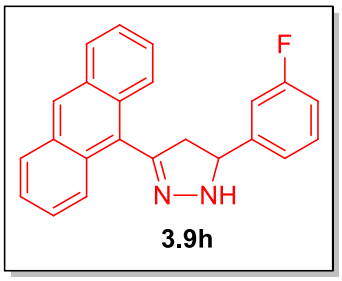


3.9g

Yellow solid. Yield: 94%. m.p. 56–59 ºC. IR (KBr) cm^{-1} 3052.47 (Aromatic C-H), 3343.23 (NH) and 1589.42 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H, Ar-H), 8.00–7.99 (d, *J* = 3.16 Hz, 4H, Ar-H), 7.57–7.43 (m, 8H, Ar-H), 6.37 (s, 1H, -NH), 5.23–5.16 (t, 1H, -CH), 3.58–3.49 (dd, 1H, $-CH_2$), 3.14–3.05 (dd, 1H, $-CH_2$) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 151.56, 141.13, 132.00, 131.38, 130.14, 128.81, 128.34, 128.16, 127.27, 126.40,

125.40, 125.18, 121.60, 64.31, 47.59 ppm. MS (m/z): 401.3 (M+). Elemental Anal. Calcd for $C_{23}H_{17}N_2Br$: C, 68.84; H, 4.27; N, 6.98. Found: C, 68.75; H, 4.31; N, 6.92.

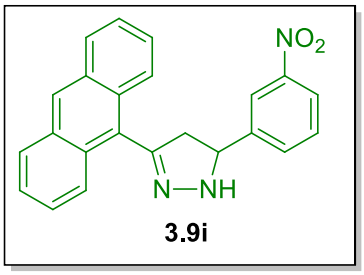
3.5.8 3-Anthracen-9-yl-5-(3-fluoro-phenyl)-4,5-dihydro-1H-pyrazole (3.9h)



3.9h

Brown solid. Yield: 93%. m.p. 86–89 °C. IR (KBr) cm^{-1} 3055.58 (Aromatic C-H), 3328.34 (NH) and 1587.74 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H, Ar-H), 8.02–7.99 (t, 4H, Ar-H), 7.48–7.02 (m, 8H, Ar-H), 6.37 (s, 1H, -NH), 5.27–5.20 (t, 1H, -CH), 3.60–3.51 (dd, 1H, -CH_2), 3.17–3.08 (dd, 1H, -CH_2) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 151.51, 131.40, 130.57, 130.46, 130.19, 128.79, 128.13, 126.39, 125.40, 125.23, 122.24, 114.88, 114.60, 113.75, 113.46, 64.44, 47.62 ppm. MS (m/z): 341.4 (M+1). Elemental Anal. Calcd for $C_{23}H_{17}N_2F$: C, 81.16; H, 5.03; N, 8.23. Found: C, 81.23; H, 5.08; N, 8.29.

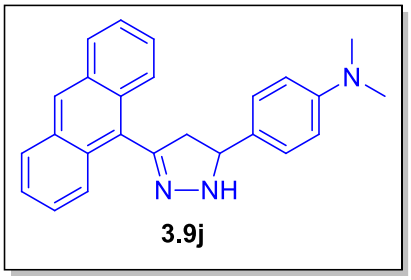
3.5.9 3-Anthracen-9-yl-5-(3-nitro-phenyl)-4,5-dihydro-1H-pyrazole (3.9i)



3.9i

Yellow solid. Yield: 95%. m.p. 73–75 °C. IR (KBr) cm^{-1} 3049.76 (Aromatic C-H), 3339.50 (NH) and 1589.69 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H, Ar-H), 8.03–8.02 (d, *J* = 3.14 Hz, 4H, Ar-H), 7.48–7.45 (q, 5H, Ar-H),7.25–7.19 (t, 2H, Ar-H),7.25–7.19 (t, 2H, Ar-H) 6.33 (s, 1H, -NH), 5.18–5.12 (t, 1H, -CH), 3.58–3.49 (dd, 1H, -CH_2), 3.21–3.13 (dd, 1H, -CH_2) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 151.73, 147.10, 143.62, 131.45, 130.27, 129.98, 128.77, 128.50, 128.03, 126.31, 126.15, 125.41, 116.61, 114.56, 112.89, 64.85, 47.52 ppm. MS (m/z): 367.3 (M+). Elemental Anal. Calcd for $C_{23}H_{17}N_3O_2$: C, 75.19; H, 4.66; N, 11.44. Found: C, 75.26; H, 4.59; N, 11.51.

3.5.10 [4-(5-Anthracen-9-yl-3,4-dihydro-2H-pyrazol-3-yl)-phenyl]-dimethyl-amine (3.9j)

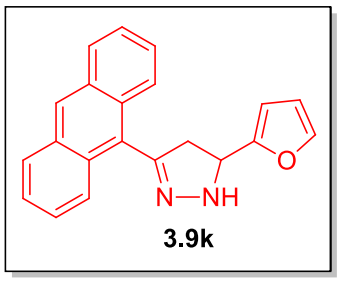


3.9j

Orange solid. Yield: 93%. m.p. 114–116 °C. IR (KBr) cm^{-1} 3048.31 (Aromatic C-H), 3297.26 (NH) and 1588.02 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.51–8.47 (d, J= 12.45 Hz ,1H, Ar-H), 8.08–7.94 (m, 4H, Ar-H), 7.48–7.44 (m, 5H, Ar-H),7.32–7.25 (t, 2H, Ar-H), 6.83–6.80 (d, J= 8.56, 1H, Ar-H), 6.60–6.57 (d, J= 8.75, 1H, Ar-H), 5.21–5.14 (t, 1H, -CH), 3.55–3.46 (dd, 1H, -CH_2), 3.22–3.13 (dd, 1H, -CH_2), 2.99 (s, 6H, Ar-

$N(CH_3)_2$) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 151.37, 149.38, 130.76, 128.74, 128.58, 127.92, 127.43, 126.38, 125.81, 125.50, 124.42, 112.96, 111.78, 64.65, 47.54, 40.79, 40.13 ppm. MS (m/z): 366.4 (M+1). Elemental Anal. Calcd for $C_{25}H_{23}N_3$: C, 82.16; H, 6.34; N, 11.50. Found: C, 82.25; H, 6.38; N, 11.43.

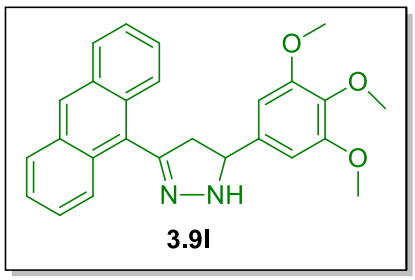
3.5.11 3-Anthracen-9-yl-5-furan-2-yl-4,5-dihydro-1H-pyrazole (3.9k)



3.9k

Yellow solid. Yield**:** 90%**.** m.p. 56–59 °C. IR (KBr) cm^{-1} 3053.20 (Aromatic C-H), 3410.42 (NH) and 1586.72 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.49–8.43 (d, *J* = 17.51 Hz, 1H, Ar-H), 8.02–8.01 (d, *J* = 3.12 Hz, 4H, Ar-H), 7.50–7.46 (m, 7H, Ar-H), 6.43–6.41 (d, *J* = 4.11 Hz, 1H, -NH), 5.25–5.19 (q, 1H, -CH), 3.77–3.70 (m, 1H, $-CH_2$), 3.58–3.47 (m, 1H, $-CH_2$) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 151.38, 142.64, 134.22, 131.10, 128.87, 128.76, 126.86, 126.37, 125.59, 125.45, 124.54, 110.55, 106.51, 57.48, 43.71 ppm. MS (m/z): 313.4 (M+1). Elemental Anal. Calcd for $C_{21}H_{16}O$: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.65; H, 5.19; N, 8.91.

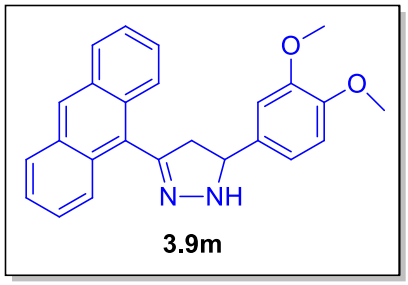
3.5.12 3-Anthracen-9-yl-5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-1H-pyrazole (3.9l)



3.9l

Yellow solid. Yield: 95%. m.p. 62–64 °C. IR (KBr) cm^{-1} 3053.05 (Aromatic C-H), 3333.35 (NH) and 1590.28 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1H, Ar-H), 8.06–8.01 (q, 4H, Ar-H), 7.48–7.45 (q, 4H, Ar-H), 6.80 (s, 2H, Ar-H), 5.22–5.15 (t, 1H, -CH), 3.95–3.89 (t, 9H, Ar-OCH_3), 3.62–3.53 (dd, 1H, $-CH_2$), 3.23–3.14 (dd, 1H, $-CH_2$) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 153.77, 151.68, 138.29, 134.20, 131.46, 130.28, 128.86, 128.15, 127.30, 126.33, 125.43, 125.33, 103.26, 65.06, 61.03, 56.34, 47.75 ppm. MS (m/z): 413.4 (M+1). Elemental Anal. Calcd for $C_{26}H_{24}N_2O_3$: C, 75.71; H, 5.86; N, 6.79. Found: C, 75.62; H, 5.82; N, 6.71.

3.5.13 3-Anthracen-9-yl-5-(3,4-dimethoxy-phenyl)-4,5-dihydro-1Hpyrazole (3.9m)

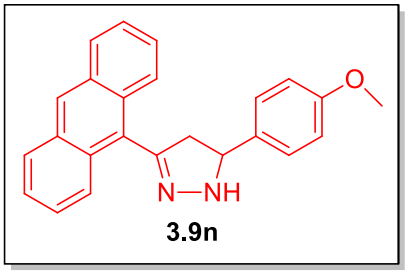


3.9m

Yellow solid. Yield: 92%. m.p. 63–65 °C. IR (KBr) cm^{-1} 3053.51 (Aromatic C-H), 3343.60 (NH) and 1590.43 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.53–8.42 (t, 1H, Ar-H), 8.02 (s, 3H, Ar-H), 7.88–6.80 (m, 8H, Ar-H), 5.22–5.15 (t, 1H, -CH), 3.94–3.83 (m, 6H, Ar-OCH_3), 3.59–3.50 (dd, 1H, $-CH_2$), 3.21–3.12 (dd, 1H, $-CH_2$) ppm. ^{13}C-NMR (300

MHz, $CDCl_3$) δ 151.80, 134.96, 131.49, 130.30, 128.84, 128.58, 128.28, 128.11, 126.52, 126.35, 126.05, 125.67, 125.44, 118.78, 111.46, 109.36, 64.73, 56.12, 47.74 ppm. MS (m/z): 383.4 (M+1). Elemental Anal. Calcd for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.32. Found: C, 78.39; H, 5.75; N, 7.38.

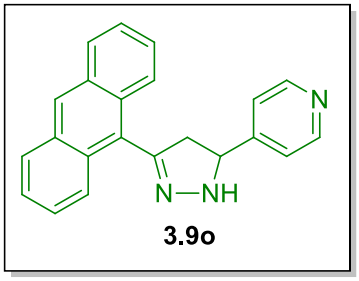
3.5.14 3-Anthracen-9-yl-5-(4-methoxy-phenyl)-4,5-dihydro-1H-pyrazole (3.9n)



3.9n

Yellow solid. Yield: 94%. m.p. 103–105 ºC. IR (KBr) cm^{-1} 3052.61 (Aromatic C-H), 3299.86 (NH) and 1581.20 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H, Ar-H), 8.02–7.99 (d, J= 7.35 Hz, 4H, Ar-H), 7.51–7.45 (m, 6H, Ar-H), 6.99–6.96 (d, J= 8.53 Hz, 2H, Ar-H), 5.24–5.17 (t, 1H, -CH), 3.84 (s, 3H, Ar-CH_3), 3.56–3.47 (dd, 1H, -CH_2), 3.19–3.10 (dd, 1H, -CH_2) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 159.26, 151.53, 134.11, 131.40, 130.20, 128.73, 127.96, 127.82, 127.68, 126.26, 125.39, 125.35, 114.28, 64.43, 55.40, 47.57 ppm. MS (m/z): 353.4 (M+1). Elemental Anal. Calcd for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72; N, 7.95. Found: C, 81.66; H, 5.67; N, 7.89.

3.5.15 4-(5-Anthracen-9-yl-3,4-dihydro-2H-pyrazol-3-yl)-pyridine (3.9o)

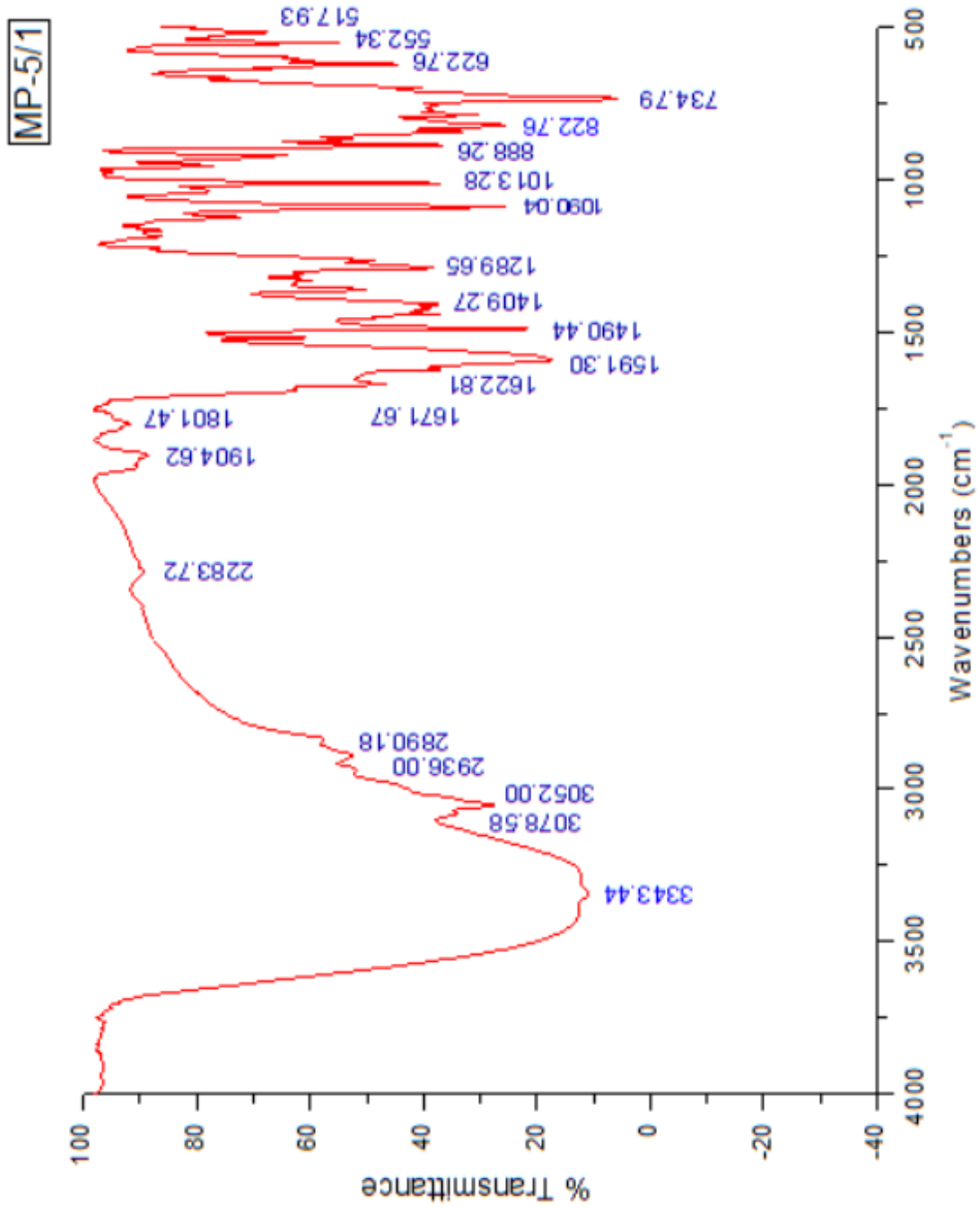


3.9o

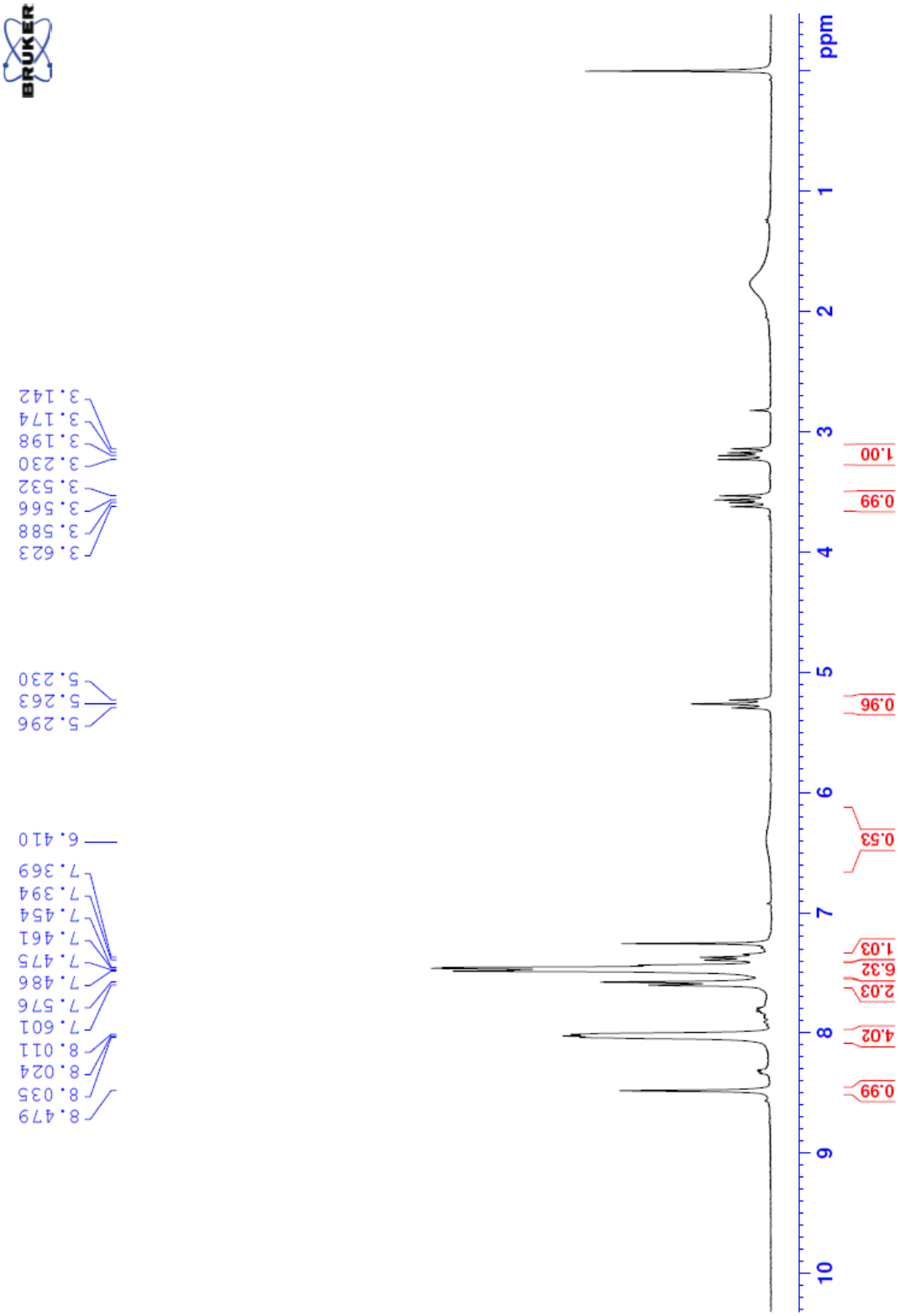
Brown solid. Yield: 90%. m.p. 57–60 ºC. IR (KBr) cm^{-1} 3053.10 (Aromatic C-H), 3412.73 (NH) and 1599.03 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.64–863 (d, J= 4.34 Hz, 2H, Ar-H), 8.48 (s, 1H, Ar-H), 8.05–7.94 (m, 3H, Ar-H), 7.80–7.79 (d, J= 4.89 Hz, 1H, Ar-H), 7.49–7.46 (q, 6H, Ar-H), 6.43 (s, 1H, -NH), 5.25–5.18 (t, 1H, -CH), 3.65–3.56 (dd, 1H, -CH_2), 3.15–3.06 (dd, 1H, -CH_2) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 151.36, 150.18, 134.17, 131.37, 130.13, 128.86, 128.58, 128.32, 126.51, 125.45, 125.01, 121.72, 63.64, 47.26 ppm. MS (m/z): 323.4 (M+). Elemental Anal. Calcd for $C_{22}H_{17}N_3$: C, 81.71; H, 5.30; N, 12.99. Found: C, 81.65; H, 5.36; N, 12.89.

3.6 REPRESENTATIVE SPECTRA OF ANTHRACENYL PYRAZOLINES

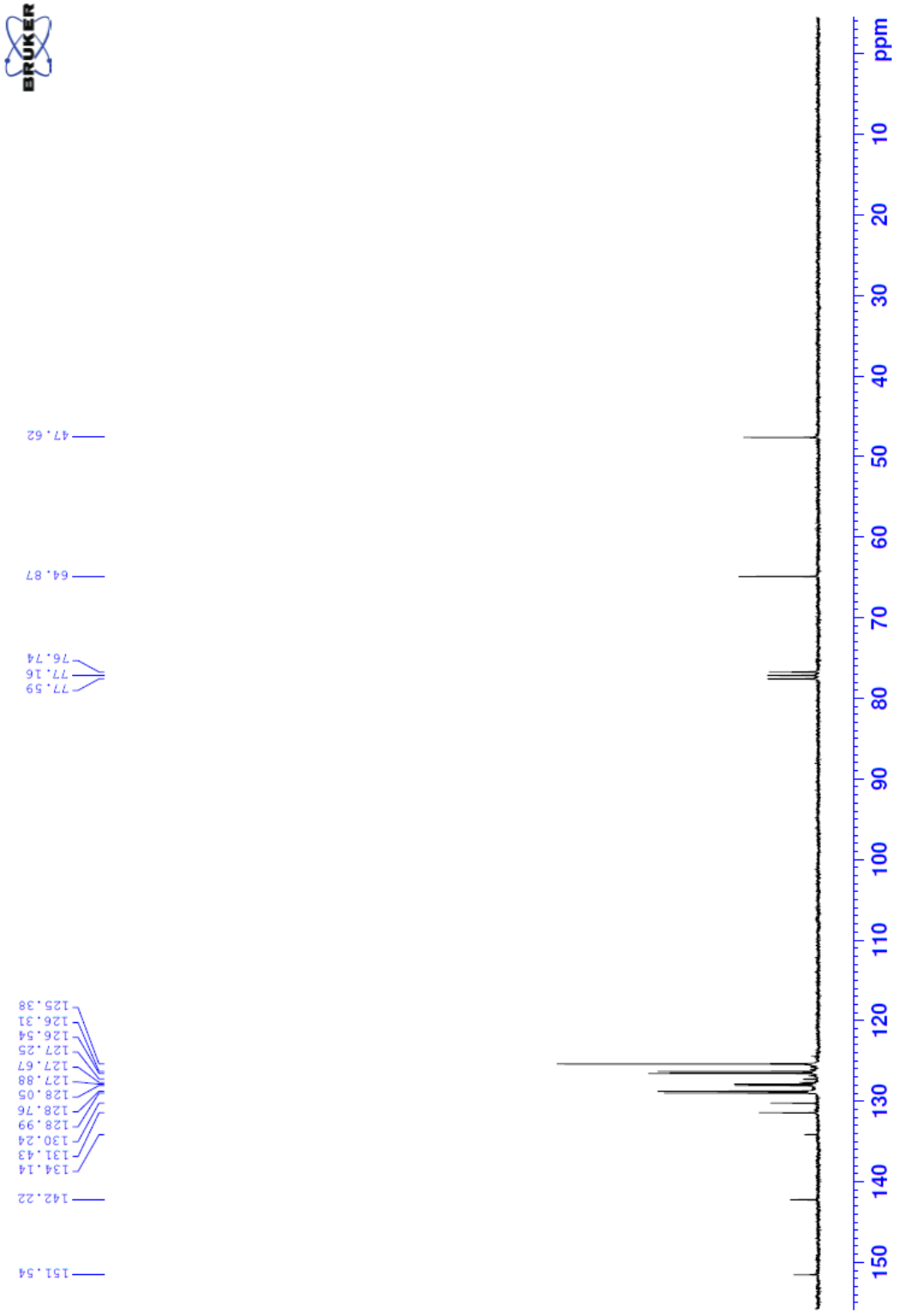
3.6.1 IR (KBr, *ν*, cm^{-1}) spectrum of 3-Anthracen-9-yl-5-phenyl-4,5-dihydro-1H-pyrazole (3.9a)



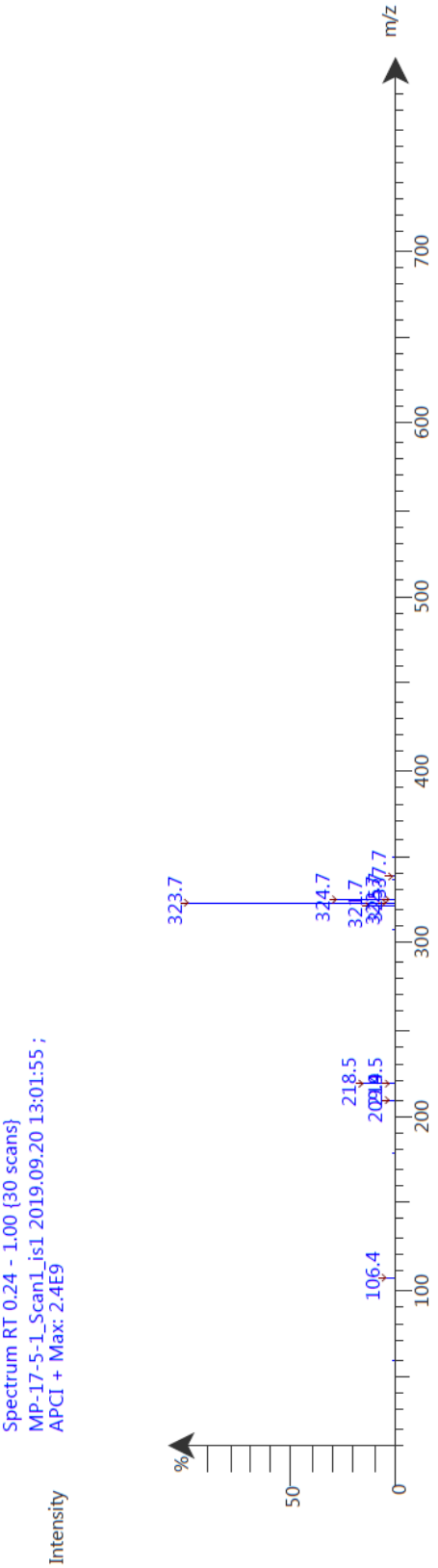
3.6.2 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-phenyl-4,5-dihydro-1H-pyrazole (3.9a)



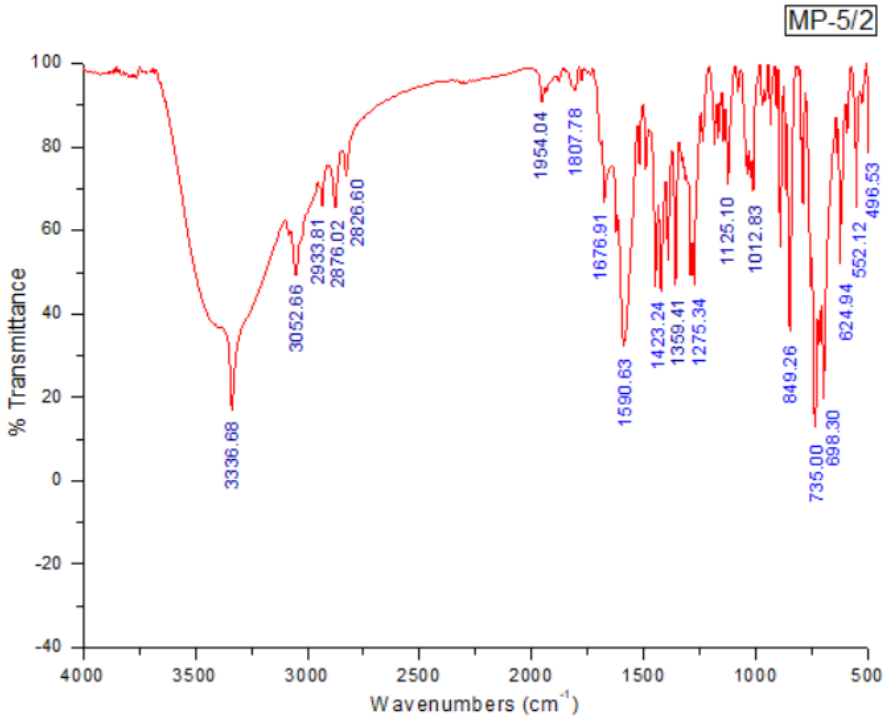
3.6.3 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-phenyl-4,5-dihydro-1H-pyrazole (3.9a)



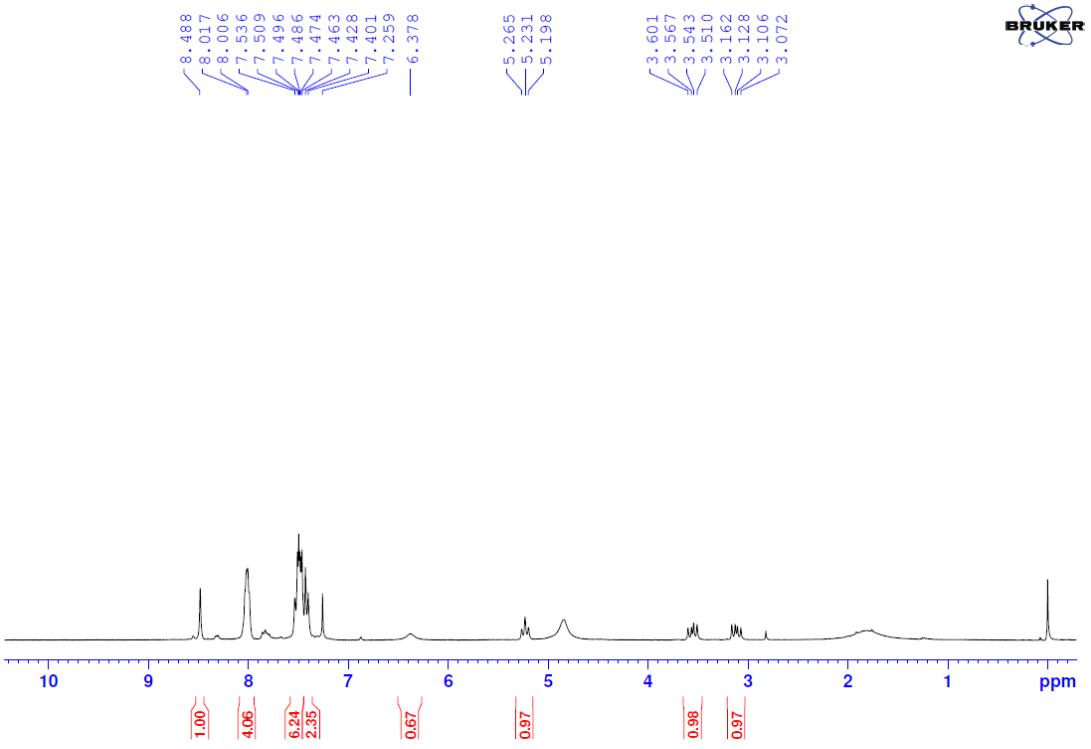
3.6.4 MS spectrum of 3-Anthracen-9-yl-5-phenyl-4,5-dihydro-1H-pyrazole (3.9a)



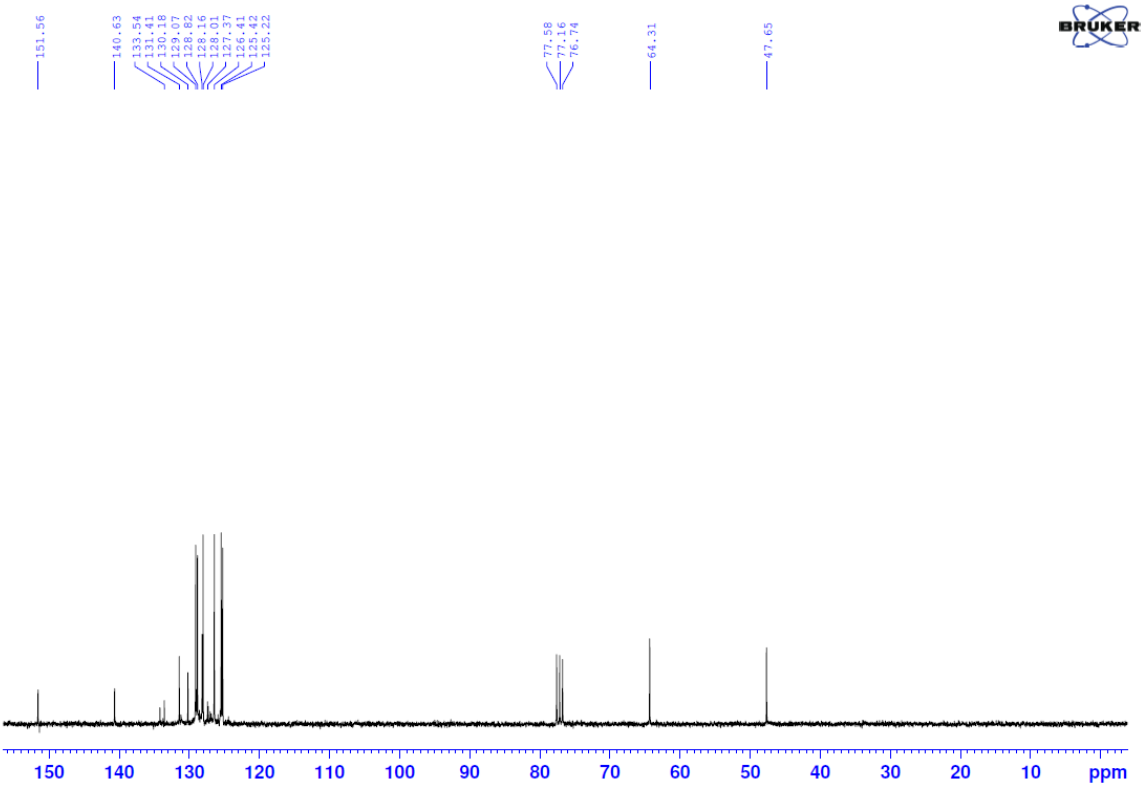
3.6.5 IR (KBr, *v*, cm^{-1}) spectrum of 3-Anthracen-9-yl-5-(4-chloro-phenyl)-4,5-dihydro-1H-pyrazole (3.9b)



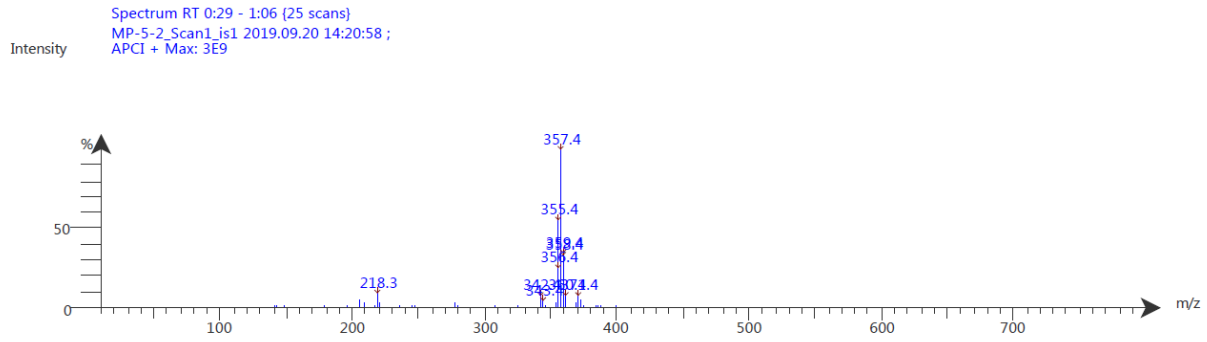
3.6.6 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(4-chloro-phenyl)-4,5-dihydro-1H-pyrazole (3.9b)



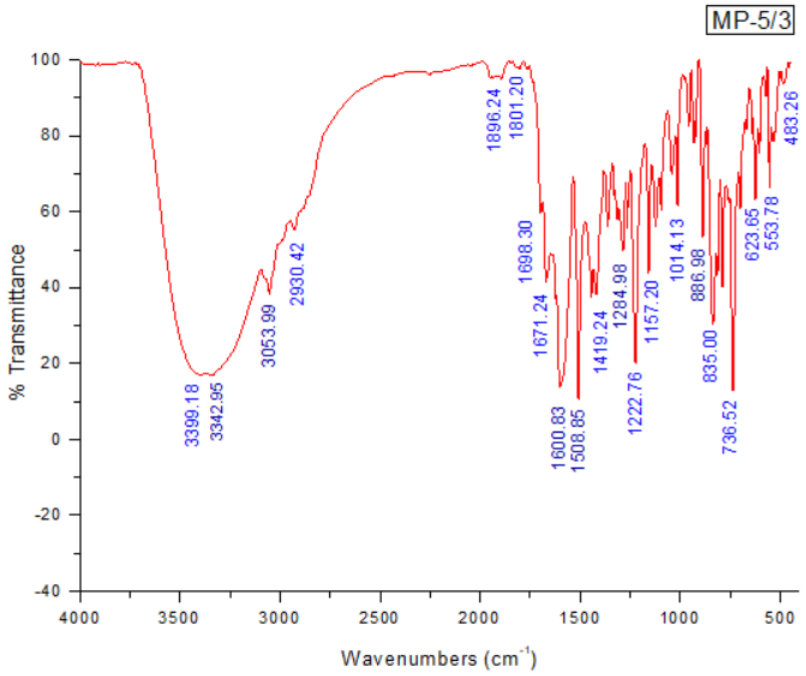
3.6.7 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(4-chloro-phenyl)-4,5-dihydro-1H-pyrazole (3.9b)



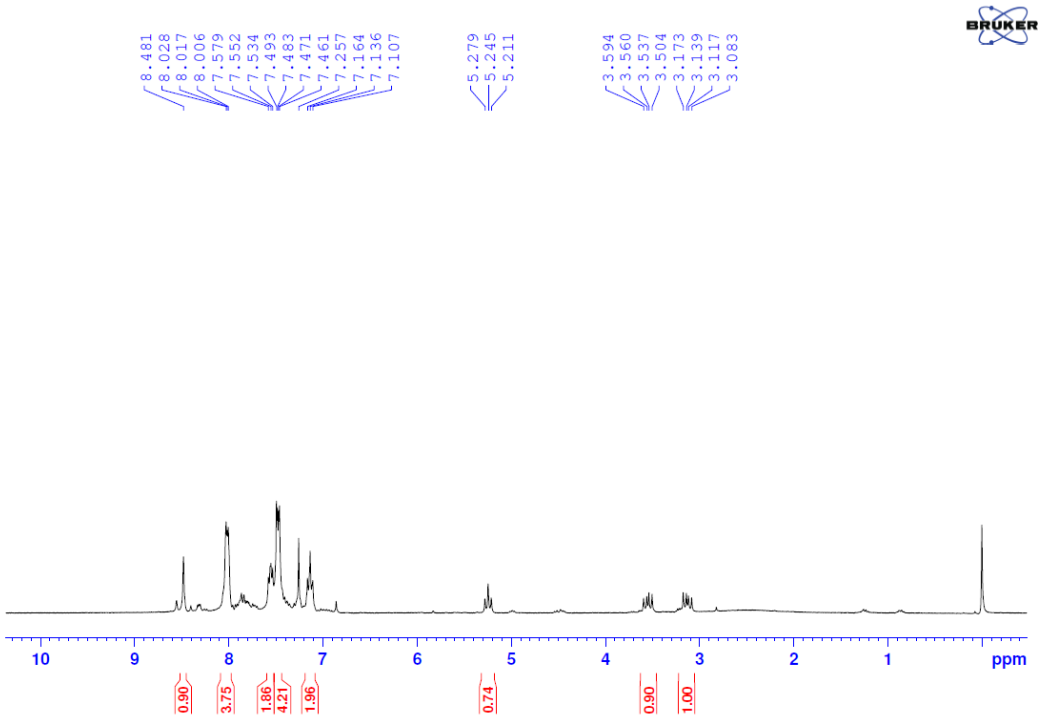
3.6.8 MS spectrum of 3-Anthracen-9-yl-5-(4-chloro-phenyl)-4,5-dihydro-1H-pyrazole (3.9b)



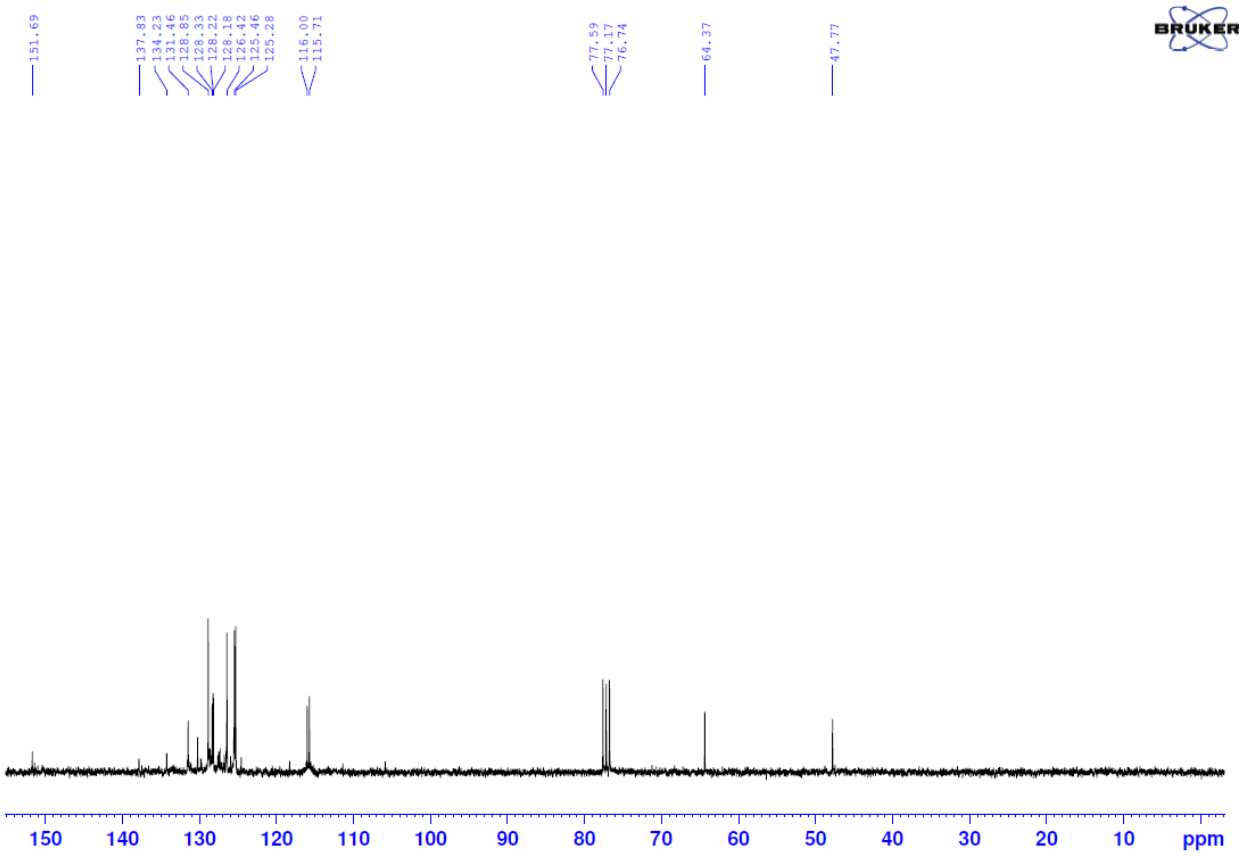
3.6.9 IR (KBr, *ν*, cm^{-1}) spectrum of 3-Anthracen-9-yl-5-(4-fluoro-phenyl)-4,5-dihydro-1H-pyrazole (3.9c)



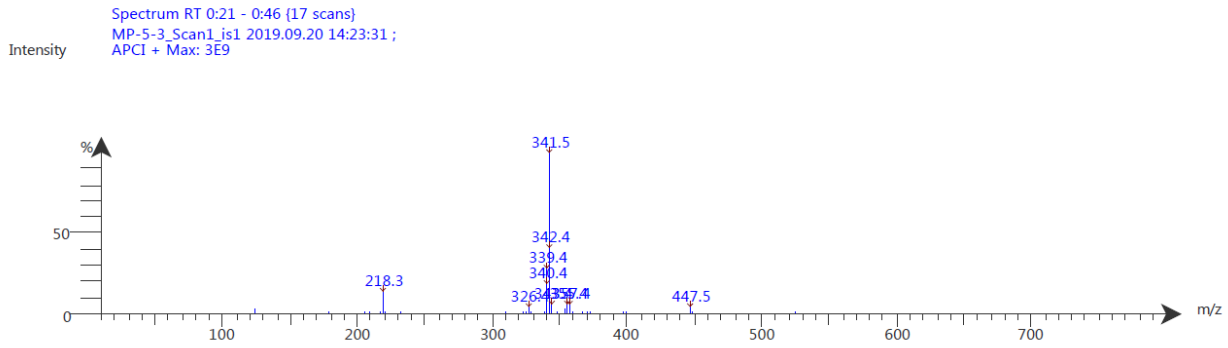
3.6.10 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(4-fluoro-phenyl)-4,5-dihydro-1H-pyrazole (3.9c)



3.6.11 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(4-fluoro-phenyl)-4,5-dihydro-1H-pyrazole (3.9c)



3.6.12 MS spectrum of 3-Anthracen-9-yl-5-(4-fluoro-phenyl)-4,5-dihydro-1H-pyrazole (3.9c)



- All the spectra of other anthracenyl pyrazolines are represented in Appendix: C-3.

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Chapter 4

Green Oxidation Reaction for the Synthesis of Anthracenyl Pyrazoles from Anthracenyl Pyrazolines

Abstract

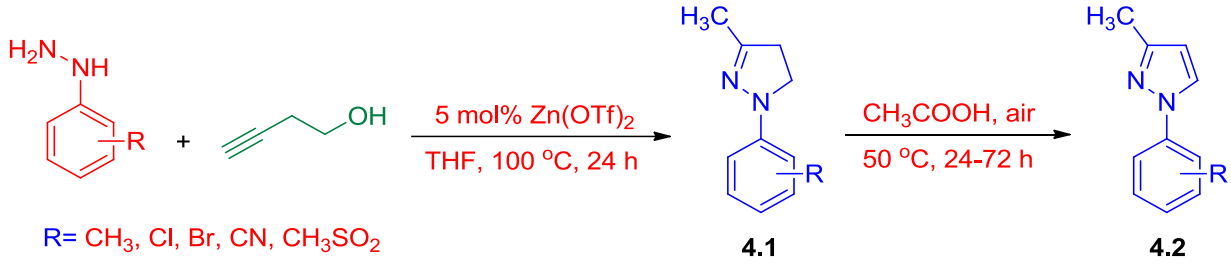
In this chapter, we aimed at developing a simple and efficient green synthetic method for the synthesis of a series of anthracenyl pyrazole derivatives by simple oxidation of anthracenyl pyrazoline derivatives using I_2-DMSO as the oxidizing agent under microwave irradiation at 140 ºC for 3 min. This method accounts for its less temperature and short reaction time that marks the advantage of using microwave-irradiation as a green synthetic method.

4.1 INTRODUCTION

Pyrazoles being one of the most important 5-membered heterocyclic compounds and their derivatives are well known for its pharmaceutical and agrochemical sciences.[1] Pyrazole and pyrazoline skeletons are known to exist in various bioactive compounds.[2] Pyrazoles and their reduced forms pyrazolines are known to show a wide range of biological activities such as anti-depressant, anti-cancer, analgesic, anti-inflammatory, anti-pyretic, anti-arrhythmic, muscle relaxant, psychoanaleptic, anti-diabetic, anti-bacterial activity, etc.[3] Pyrazoles on the other hand is present in a number of commercial drugs such as celecobix (Celebrex),[4] sildenafil (Viagra),[5] Acomplia,[6] rimonabant (Acomplia)[7] and the insecticide Fipronil.[8] Literature reports also shows that a number of substituted pyrazole derivatives have been used as ligands for transition-metal-catalyzed cross coupling reactions,[9] directing groups for C−H activation[10] and precursors to N-heterocyclic carbenes (NHCs).[11] A number of methods have been reported for the synthesis of pyrazoles due to its high functional versatility.[12] Pyrazoles are usually obtained by the condensation of 1,3-diketones with hydrazine derivatives.[13] However, this reaction results in a mixture of regioisomers. Till date, the most convenient method that has been employed for the synthesis of pyrazole involves the annulations which is initiated by the condensation of a monosubstituted hydrazine with a carbonyl (such as the cyclocondensation of 1,3-dicarbonyl or α,β-unsaturated carbonyl compounds) leading to the construction of the pyrazole rings. However, with the different reaction conditions and the requirements of the chemist for reaction of their molecules, different methods have been employed for the synthesis of pyrazoles under different solvent media and acidic or basic conditions.[14] Pyrazoles can also

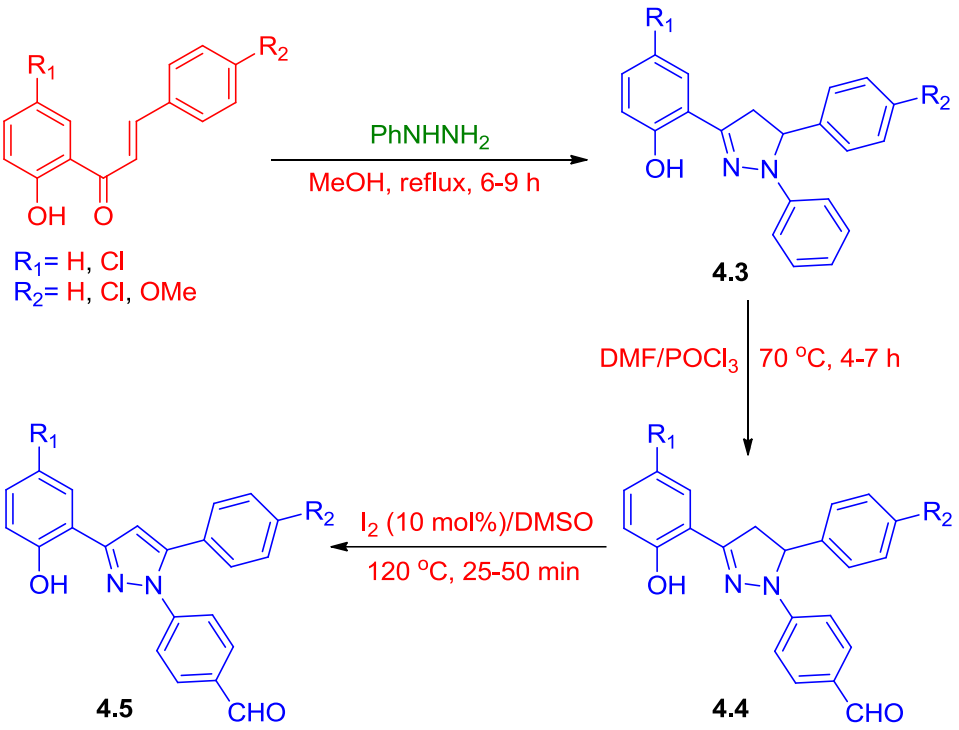
be prepared by the oxidation of pyrazolines by a number of oxidizing agents such as lead dioxide, mercuric oxide, bromine, potassium permanganate, chromium oxide, silver nitrate, manganese dioxide, lead tetraacetate, potassium hexacyanoferrate (III), *N*-bromosuccinimide and chloranil.[15] Other suitable oxidants that has also been used and reported for the oxidation of 2-pyrazolines as well as 1,3,5-trisubstituted pyrazolines are $Zr(NO_3)_4$,[16] Pd/C,[17] HNO_2/AcOH,[18] $KMnO_4$,[19] Co(II)/O_2,[20] p-chloranil,[21] MnO_2,[22] $PhI(OAc)_2$,[23] claycop,[24] $Pb(OAc)_4$,[25] HgO,[26] $AgNO_3$,[27] I_2,[28] I_2-DMSO,[29] TBPA cation radical,[30] 1,3-dibromo-5,5-dimethylhydantoin (DBH)[31] and $Zr(NO_3)_4$.[32] There are also reports on conversion of pyrazolines to pyrazole in acetic acid with or without the use of Pd/C catalyst.[17] An aerobic oxidation of pyrazoline to pyrazole has also been reported using activated carbon,[33] cobalt salts,[34] $HAuCl_4$[35] and $FeCl_3$.[36] Literature studies of some of the reported synthesis of pyrazoles by the oxidation of pyrazolines have been discussed in the schemes given below.

Karolin Alex and group reported a regioselective synthesis of aryl-substituted pyrazolines and pyrazoles in **2008**. The reactions were carried out from a stoichiometric amount of phenylhydrazine with 3-butynol in the presence of zinc triflate ($Zn(OTf)_2$) resulting in the formation of pyrazolines (**4.1**) which occurred *via* hydrohydrazination of the alkyne. This products were further used for the one-pot oxidation in acetic acid in presence of air leading to the formation of the corresponding pyrazoles (**4.2**) as shown in Scheme 4.1.[37]



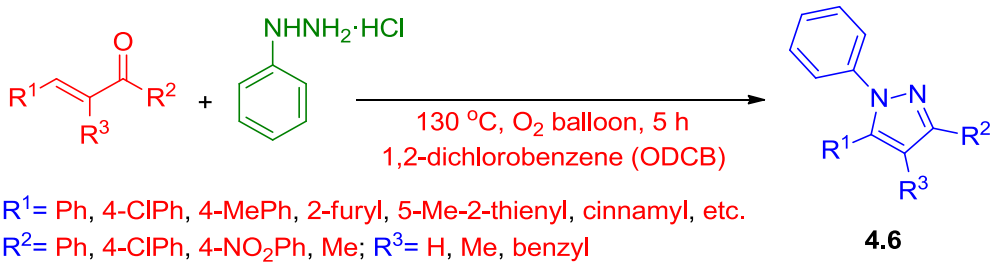
Scheme 4.1. Synthesis of aryl-substituted pyrazoline and pyrazole derivatives.

In **2011**, a regioselective formylation (**4.4**) of 1,3,5-triarylpyrazoline (**4.3**) by the Vilsmeier-Haack reaction and followed by chemoselective oxidation of 1,3,5-triaryl pyrazolines to 1,3,5-triaryl pyrazoles (**4.5**) by using catalytic amount of iodine in dimethylsulfoxide (Scheme 4.2) was reported by Pradeep D *et al.*[38]



Scheme 4.2. Synthesis of 1,3,5-triaryl pyrazoline and 1,3,5-triaryl pyrazole derivatives.

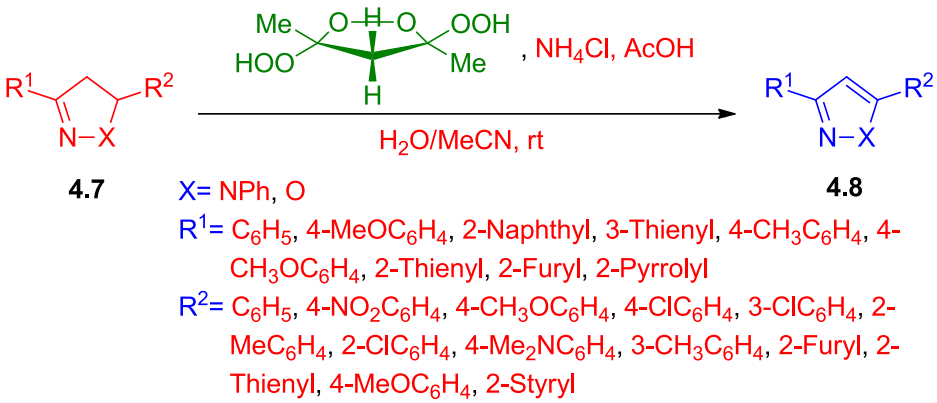
Jin Yu and group in **2014** reported an efficient one-pot synthesis of 1,3,5-trisubstituted pyrazoles from α,β-enones and arylhydrazine. The mechanism of the reaction proceeds by the formation of pyrazolines and an acid-catalyzed aerobic oxidation process giving pyrazoles (**4.6**). Many 1,3,5-trisubstituted and 1,3,4,5-tetrasubstituted pyrazoles could be synthesized by this method in good to excellent yields; however, this protocol failed for the synthesis of N-unsubstituted pyrazoles (Scheme 4.3).[39]



Scheme 4.3. Synthesis of trisubstituted and tertasubstituted pyrazole derivatives.

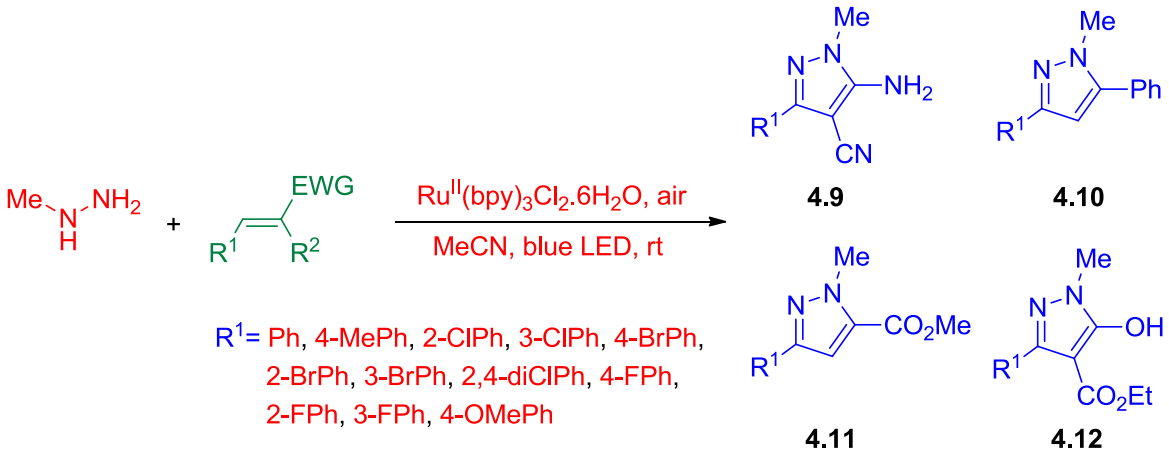
Kaveh Khosravi *et al.* in **2014** developed a method involving the oxidative aromatization of 2-pyrazolines and isoxazolines yielding the corresponding 2-pyrazoles and isoxazoles (**4.8**). No toxic solvents were used and the acetylacetone that was probably produced in the reaction and NH_4Cl, are easily washed with water. In this procedure, trans-3,5-

dihydroperoxy-3,5-dimethyl-1,2-dioxalane–NH_4Cl–HOAc was used as an effective oxidant in water–acetonitrile at room temperature (Scheme 4.4).[40]



Scheme 4.4. Synthesis of 2-pyrazole and isoxazole derivatives.

Ya Ding and co-workers in **2016** reported a selective and high yielding synthesis of polysubstituted pyrazoles by Ru(II) catalyst *via* a VLPC (visible light photoredox catalysis)-promoted reaction of hydrazine with Michael acceptors using air as the terminal oxidant. The reaction proceeds by VLPC-promoted oxidation of hydrazine to diazene followed by addition to Michael acceptors rather than the usual conventional condensation of hydrazine with carbonyls (Scheme 4.5).[41]



Scheme 4.5. Synthesis of polysubstituted pyrazole derivatives.

The history and the importance of pyrazole and pyrazolines prompted us to synthesize a series of anthracenyl pyrazolines as reported[42] which on further oxidation leads to the formation of anthracenyl pyrazoles. The reactions that were reported for the oxidation of

pyrazolines to pyrazoles however faced a number of disadvantages such as long reaction time, harsh reaction conditions, toxicity because of the toxic reagents, difficulty in performing workup for the reaction and poor yields. Therefore, in order to overcome these drawbacks and disadvantages, the need for new environmentally safe, cheap reagents and high satisfactory yielding of products is needed. Here in this chapter, a series of anthracenyl pyrazole derivatives were synthesized by microwave-assisted green oxidation reaction from anthracenyl pyrazolines using I_2-DMSO as the oxidizing agent at a very short reaction time. All the synthesized anthracenyl pyrazole compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, Mass and elemental analysis.

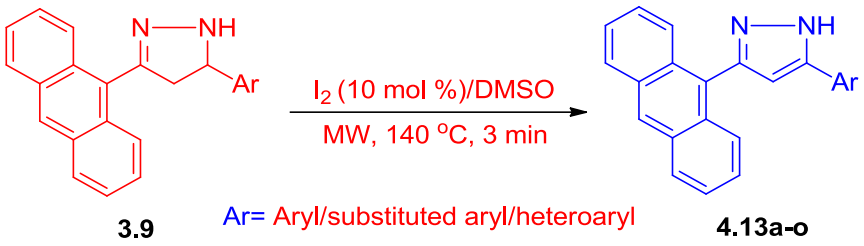
4.2 EXPERIMENTAL SECTION

4.2.1 Materials and Methods

All commercially available chemicals, reagents and solvents were used as received. For thin layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by Iodine and/or by UV light. All melting points were determined in open capillaries on an IKON melting point apparatus and are uncorrected. Silica gel (60-120 mesh) was used for column chromatography. Purity of all the synthesized anthracenyl pyrazole products were confirmed by Binary Gradient HPLC-3000 system. IR spectra were recorded on Perkin-Elmer spectrophotometer (Spectrum-Two) using KBr disk and values are expressed in cm^{-1}. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded at Bruker 300 MHz. The chemical shifts (δ) are reported in parts per million (ppm) downfield to TMS (d = 0) and coupling constants (J) are expressed in Hertz (Hz) for ^{1}H-NMR and relative to the central $CDCl_3$ resonance (d = 77.0) for ^{13}C-NMR. Mass spectra for the compounds were performed on Advion Expression-S CMS system. Microwave experiments were carried out using an Anton Paar (Microwave Synthesis Reactor, Monowave 400).

4.2.2 Microwave-assisted oxidation for the synthesis of anthracenyl pyrazoles (4.13a-o)

To anthracenyl pyrazoline derivatives (**3.9**) (1 mmol) in DMSO (0.5 mL) was added I_2 (10 mol %) and the reaction mixture was microwave irradiated at 140 ºC for 3 min. The completion of the reaction was monitored by thin layer chromatography (TLC) and after completion of the reaction, the reaction mixture was cooled to room temperature and added ice cold water. The resulting solids were filtered, washed with water several times, air dried to afford the resulting anthracenyl pyrazole products (Scheme 4.6 and Figure 4.1).

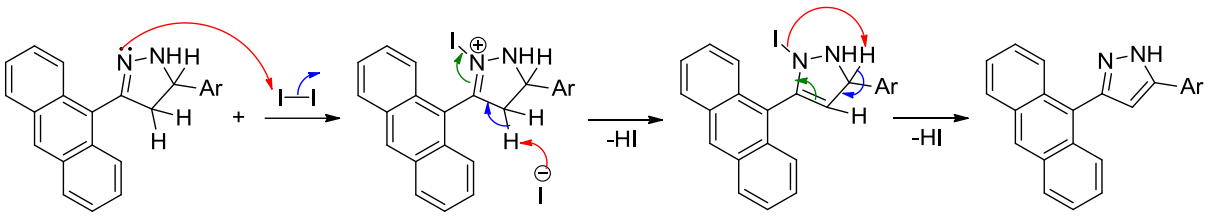


Scheme 4.6. Microwave-assisted oxidation for the synthesis of anthracenyl pyrazoles.

4.3 RESULTS AND DISCUSSION

Microwave-assisted method for the synthesis of many organic molecules have been reported to be one of the most powerful, efficient, safe, fast reaction time, economic as well as environmental friendly to carry out different types of reactions especially governing a flexible platform for the formation of heterocyclic ring. Due to the increased pressure in the area of research in industry, a lot of efforts have been given in improvising the synthetic methods in order to reduce the amount of pollutants and also the over usage of organic solvents in chemical synthesis. Thus, for this very purpose, microwave-assisted synthetic methods are significantly useful in carrying out efficient synthetic reactions which takes lesser time and also enhances the conversions of the desired product finding broad applications, attracting much attention in organic synthesis applications.[43] In this chapter, microwave irradiation has been employed for a rapid and efficient synthesis of anthracenyl pyrazoles (**4.13a-o**). Initially, we have started the synthesis of 3-(anthracen-10-yl)-5-(4-chlorophenyl)-1H-pyrazole (**4.13a**) by the oxidation of 3-(anthracen-10-yl)-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole **(3.9a**) using I_2/DMSO under extremely facile and environmental friendly microwave method. The time and temperature for this reaction was monitored at time intervals of 1 min under different temperatures confirming the conversion of our desired product using thin layer chromatography technique (TLC). But we observed very less conversion of the product. After several experiments to improve the product yields at different conditions, we observed that the reaction carried out at 140 ^oC and time 3 min gives better conversion (94%) of the desired anthracenyl pyrazole product (**4.13a**) which is quite satisfactory. Iodine mediated dehydrogenations of pyrazolines[44] have been reported to be controllable for different types of substrates. As given in Scheme 4.6, all the derivatives of anthracenyl pyrazolines (**3.9**) have been easily oxidized in presence of I_2 (10 mol%) in DMSO under microwave irradiation at 140 ^oC to our desired anthracenyl pyrazole products (**4.13a-o**) giving 90-96% yields at a very short reaction time of 3 min (Figure 4.1 and

Table 4.1). The proposed reaction mechanism for the I_2-catalyzed green oxidation reaction for the synthesis of anthracenyl pyrazoles from anthracenyl pyrazolines is shown in Scheme 4.7. All the solid compounds were collected by simple workup with water followed by filtration method as pure products except compounds **4.13i**, **4.13k** and **4.13l**, which were purified from column chromatography (Hex/EtOAc 7:3). All the synthesized anthracenyl pyrazole compounds were identified on the basis of its spectroscopic data (IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectra).



Scheme 4.7. Proposed Reaction Mechanism for the Synthesis of Anthracenyl Pyrazoles.

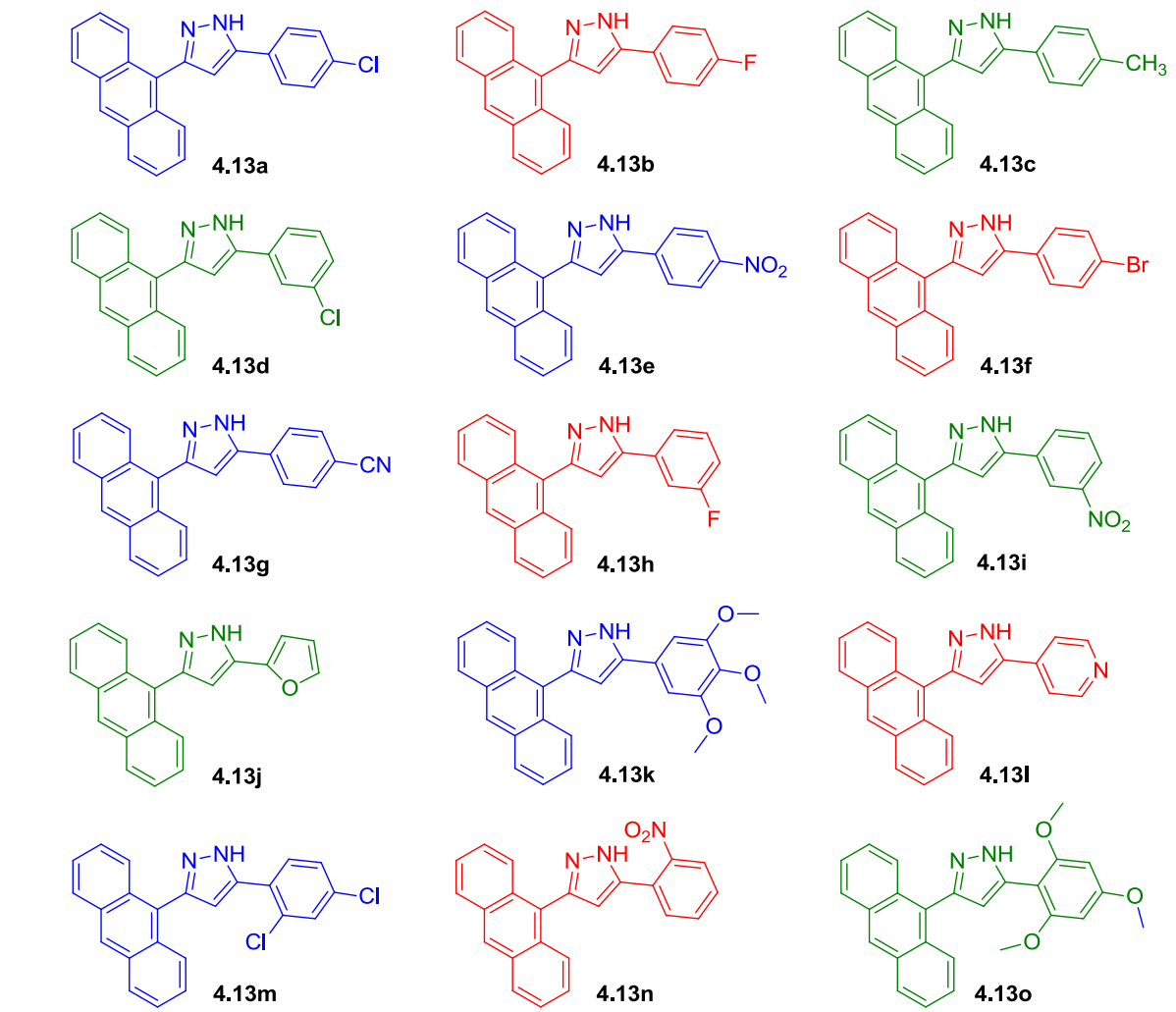


Figure 4.1. Synthetic structures of anthracenyl pyrazole derivatives.

The IR spectroscopic analysis of the pyrazole molecules shows the appearance of a C=C absorption band at 1599.25 cm^{-1} and disappearance of CH_2 stretching frequencies which confirms the oxidized product. In the ^{1}H-NMR spectra of the anthracenyl pyrazole molecules, the spectra shows the disappearance of the pair of doublet of doublets of the CH_2 protons of pyrazoline ring and also the disappearance of the CH proton of the compounds that appears as a triplet in the pyrazoline molecule which evidences the formation of the pyrazole products.

Table 4.1. Microwave-assisted oxidative synthesis of anthracenyl pyrazole derivatives.[a]

Entry	Ar	Product	Yield (%)	m.p. (ºC)
1	4-ClC_6H_4	**4.13a**	94	89–91
2	4-FC_6H_4	**4.13b**	95	90–92
3	4-$CH_3C_6H_4$	**4.13c**	95	91–93
4	3-ClC_6H_4	**4.13d**	94	86–88
5	4-$NO_2C_6H_4$	**4.13e**	95	146–148
6	4-BrC_6H_4	**4.13f**	94	96–98
7	4-CNC_6H_4	**4.13g**	96	200–202
8	3-FC_6H_4	**4.13h**	96	79–81
9	3-$NO_2C_6H_4$	**4.13i**	94	198–200
10	2-Furanyl	**4.13j**	92	106–108
11	3,4,5-$(OCH_3)_3C_6H_2$	**4.13k**	93	99–101
12	4-Pyridinyl	**4.13l**	92	154–156
13	2,4-$(Cl)_2C_6H_3$	**4.13m**	93	70–72
14	2-$NO_2C_6H_4$	**4.13n**	90	70–72
15	2,4,6-$(OCH_3)_3C_6H_2$	**4.13o**	91	81–83

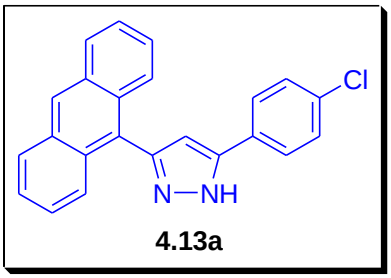
[a]Conditions: Anthracenyl pyrazolines (**3.9**) (1 mmol), DMSO (0.5 mL), I_2 (10 mol %), MW, 140 ºC, 3 min.

4.4 CONCLUSION

In conclusion, to explore different anthracenyl pyrazole derivatives, we have developed and described a microwave-assisted environmental friendly, simple and efficient green oxidation protocol for the synthesis of anthracenyl pyrazole derivatives (**4.13a-o**) *via* I_2/DMSO in a very short reaction time (3 min) and product yields were good to excellent. The structures of all the anthracenyl pyrazole compounds were characterized and confirmed by different spectroscopic methods. These anthracenyl pyrazole products can be further studied for their various applications and their biological activities towards certain diseases.

4.5 SPECTRAL CHARACETERIZATION DATA

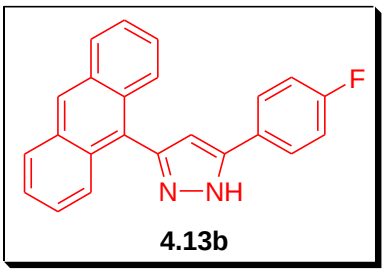
4.5.1 3-(Anthracen-10-yl)-5-(4-chlorophenyl)-1H-pyrazole (4.13a)



4.13a

Brown solid, Yield: 94%, m.p. 89–91 ^oC, IR (KBr) cm^{-1} 3052.57 (Aromatic C-H), 3137.74 (Aromatic C-H), 3400.51 (NH), 1661.10 (C=N) and 1599.25 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.28–8.11 (m, 1H, Ar-H), 8.09–8.02 (m, 2H, Ar-H), 7.95–7.67 (m, 3H, Ar-H), 7.55–7.07(m, 9H, Ar-H), 5.98–5.85 (s, 1H, -NH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 144.55, 134.49, 134.27, 131.16, 129.94, 129.55, 129.20, 128.76, 127.85, 127.36, 126.88, 125.65, 125.24, 101.13, 40.46 ppm. MS (m/z): 355.7 (M+1) observed for $C_{23}H_{15}N_2Cl$.

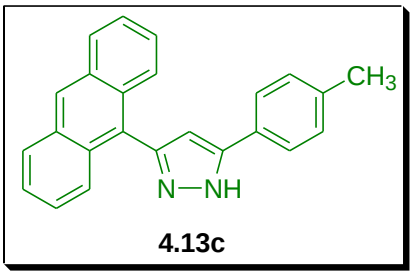
4.5.2 3-(Anthracen-10-yl)-5-(4-fluorophenyl)-1H-pyrazole (4.13b)



4.13b

Brown solid, Yield: 95%, m.p. 90–92 ^oC, IR (KBr) cm^{-1} 3052.25 (Aromatic C-H), 3200.72 (Aromatic C-H), 3399.5 (NH) and 1662.24 (C=N) and 1598.51 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.18–8.10 (t, 1H, Ar-H), 8.07–7.99 (m, 2H, Ar-H), 7.88–7.77 (m, 2H, Ar-H), 7.65–7.63 (d, J=7.42 Hz, 1H, Ar-H), 7.52–7.39 (m, 5H, Ar-H), 7.17–6.99 (m, 2H, Ar-H), 6.89–6.80 (m, 1H, Ar-H), 6.16 (s, 1H, -NH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 146.96, 143.80, 142.69, 134.28, 131.14, 130.45, 129.44, 128.82, 127.58, 125.68, 125.27, 116.44, 115.75, 101.39, 40.37 ppm. MS (m/z): 339.7 (M+1) observed for $C_{23}H_{15}N_2F$.

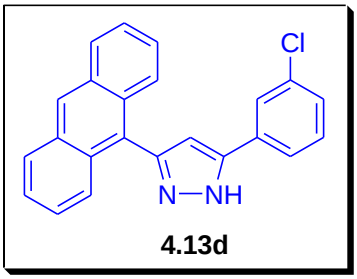
4.5.3 3-(Anthracen-10-yl)-5-p-tolyl-1H-pyrazole (4.13c)



4.13c

Yellow solid, Yield: 95%, m.p. 91–93 ºC, IR (KBr) cm^{-1} 3026.67 (Aromatic C-H), 3401.18 (NH), 1658.85 (C=N) and 1599.11 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H, Ar-H), 8.12–8.09 (d, *J* =7.78 Hz, 1H, Ar-H), 7.89–7.86 (t, 2H, Ar-H), 7.73–7.63 (dd, 3H, Ar-H), 7.51–7.35 (m, 4H, Ar-H), 7.17–7.14 (m, 3H, Ar-H), 6.96–6.93 (d, *J* =8.00 Hz, 1H, Ar-H), 6.05 (s, 1H, -NH), 2.39–2.23 (t, 3H, Ar-CH_3) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 144.36, 134.47, 130.76, 130.14, 129.55, 129.10, 128.71, 127.39, 127.10, 126.67, 125.47, 124.74, 106.78, 100.73, 40.42, 21.62 ppm. MS (m/z): 335.7 (M+1) observed for $C_{24}H_{18}N_2$.

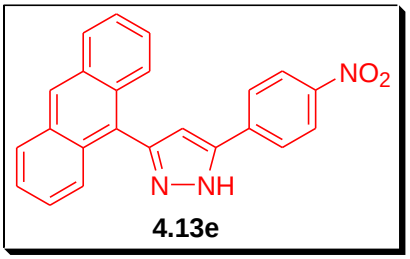
4.5.4 3-(Anthracen-10-yl)-5-(3-chlorophenyl)-1H-pyrazole (4.13d)



4.13d

Yellow solid, Yield: 94%, m.p. 86–88 ºC, IR (KBr) cm^{-1} 3063.63 (Aromatic C-H), 3401.49 (NH), 1657.47 (C=N) and 1599.32 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.30–8.27 (m, 1H, Ar-H), 8.17–8.15 (m, 1H, Ar-H), 8.10–7.94 (m, 1H, Ar-H), 7.80–7.63 (m, 3H, Ar-H), 7.52–7.36 (m, 6H, Ar-H), 7.18–7.11 (m, 1H, Ar-H), 7.08–6.91 (m, 1H, Ar-H), 6.43–6.39 (s, 1H, -NH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 144.81, 134.42, 131.09, 130.54, 129.26, 129.11, 128.78, 128.39, 127.48, 127.10, 126.50, 125.69, 125.45, 124.54, 124.08, 106.94, 40.56 ppm.MS (m/z): 355.6 (M+1) observed for $C_{23}H_{15}N_2Cl$.

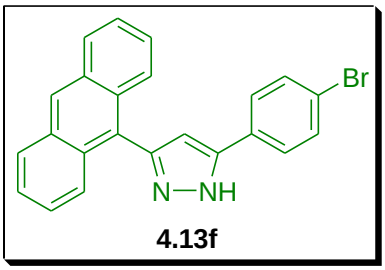
4.5.5 3-(Anthracen-10-yl)-5-(4-nitrophenyl)-1H-pyrazole (4.13e)



4.13e

Brown solid, Yield: 95%, m.p. 146–148 ºC, IR (KBr) cm^{-1} 3052.42 (Aromatic C-H), 3379.22 (NH), 16601.11 (C=N) and 1600.47 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.25–8.22 (m 1H, Ar-H), 8.07–7.99 (m, 2H, Ar-H), 7.81–7.73 (m, 3H, Ar-H), 7.63–7.57 (m, 1H, Ar-H), 7.51–7.44 (m, 4H, Ar-H), 6.97 (s, 1H, Ar-H) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 139.32, 134.27, 131.24, 130.96, 129.18, 128.76, 127.38, 126.91, 126.32, 125.70, 125.57, 124.31, 114.88, 106.96, 41.16 ppm.MS (m/z): 366.6 (M+1) observed for $C_{23}H_{15}N_3O_2$.

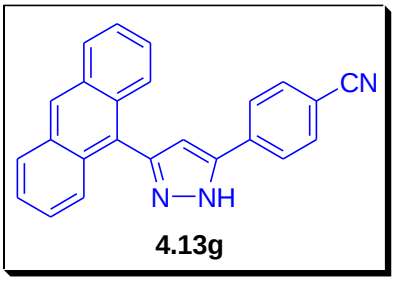
4.5.6 3-(Anthracen-10-yl)-5-(4-bromophenyl)-1H-pyrazole (4.13f)



4.13f

Brown solid, Yield: 94%, m.p. 96–98 ^{o}C, IR (KBr) cm^{-1} 3052.46 (Aromatic C-H), 3401.29 (NH), 1662.55 (C=N) and 1599.33 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.52–8.42 (t, 1H, Ar-H), 8.30–8.27 (q, 1H, Ar-H), 8.18–7.93 (m, 2H, Ar-H), 7.85–7.77 (m, 1H, Ar-H), 7.70–7.67 (d, J=7.73 Hz, 2H, Ar-H), 7.55–7.35 (m, 5H, Ar-H), 7.32–7.22 (m, 1H, Ar-H), 5.41 (s, 1H, -NH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 146.69, 134.69, 134.28, 132.34, 131.98, 130.13, 129.90, 128.84, 127.37, 127.05, 126.91, 125.70, 125.23, 107.32, 40.53 ppm. MS (m/z): 399.6 (M^+) observed for $C_{23}H_{15}N_2Br$.

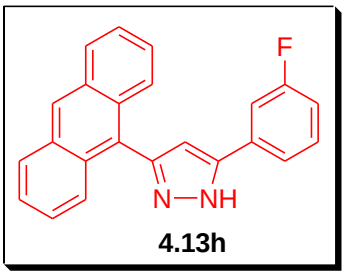
4.5.7 4-(3-(Anthracen-10-yl)-1H-pyrazol-5-yl)benzonitrile (4.13g)



4.13g

Brown solid, Yield: 96%, m.p. 200–202 ^{o}C, IR (KBr) cm^{-1} 3050.73 (Aromatic C-H), 3392.23 (NH), 1661.42 (C=N) and 1610.07 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.43–8.32 (m, 1H, Ar-H), 8.31–8.29 (m, 1H, Ar-H), 8.16–7.99 (m, 3H, Ar-H), 7.87–7.68 (m, 3H, Ar-H), 7.52–7.44 (m, 5H, Ar-H), 7.04–6.95 (m, 1H, Ar-H), 2.30 (s, 1H, -NH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 143.71, 134.27, 132.79, 131.27, 129.62, 129.22, 128.76, 128.30, 127.71, 127.38, 126.88, 126.29, 125.69, 106.65, 40.49 ppm. MS (m/z): 346.6 (M+1) observed for $C_{23}H_{15}N_2CN$.

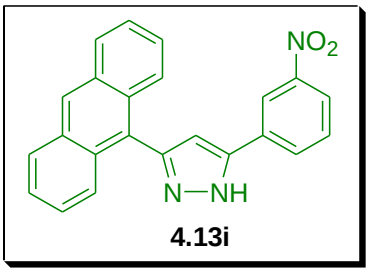
4.5.8 3-(Anthracen-10-yl)-5-(3-fluorophenyl)-1H-pyrazole (4.13h)



4.13h

Yellow solid, Yield: 96%, m.p. 79–81 ^{o}C, IR (KBr) cm^{-1} 3053.56 (Aromatic C-H), 3397.00 (NH), 1664.05 (C=N) and 1589.07 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.53–8.27 (m, 1H, Ar-H), 8.19–7.77 (m, 3H, Ar-H), 7.67–7.62 (m, 2H, Ar-H), 7.50–7.38 (m, 5H, Ar-H), 7.14–7.07 (m, 2H, Ar-H), 6.97–6.88 (m, 1H, Ar-H), 6.50 (s, 1H, -NH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 144.33, 134.69, 134.27, 130.96, 129.61, 128.79, 127.36, 127.17, 126.36, 125.66, 125.29, 122.34, 116.62, 113.64, 107.13, 101.32, 40.32 ppm. MS (m/z): 339.6 (M+1) observed for $C_{23}H_{15}N_2F$.

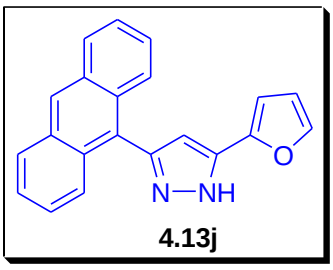
4.5.9 3-(Anthracen-10-yl)-5-(3-nitrophenyl)-1H-pyrazole (4.13i)



4.13i

Brown solid, Yield: 94%, m.p. 198–200 ^{o}C, IR (KBr) cm^{-1} 3050.27 (Aromatic C-H), 3367.73 (NH), 1661.83 (C=N) and 1599.03 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.54–8.49 (m, 1H, Ar-H), 8.32–8.31 (m, 1H, Ar-H), 8.06–8.03 (m, 2H, Ar-H), 7.85–7.80 (m, 2H, Ar-H), 7.50–7.47 (m, 4H, Ar-H), 1.91 (s, 1H, -NH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 144.71, 134.80, 134.28, 133.92, 131.22, 130.30, 129.38, 128.64, 127.66, 127.39, 126.92, 126.02, 125.65, 125.23, 124.42, 101.23, 41.10 ppm. MS (m/z): 366.6 (M+1) observed for $C_{23}H_{15}N_3O_2$.

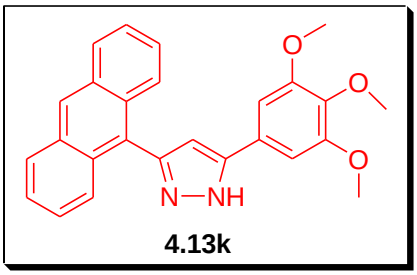
4.5.10 3-(Anthracen-10-yl)-5-(furan-2-yl)-1H-pyrazole (4.13j)



4.13j

Brown solid, Yield**:** 92%**,** m.p. 106–108 ^{o}C, IR (KBr) cm^{-1} 3052.25 (Aromatic C-H), 3396.7 (NH), 1676.57 (C=N) and 1591.71 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.57–8.42 (m, 1H, Ar-H), 8.32–8.23 (m, 2H, Ar-H), 8.05–7.98 (m, 2H, Ar-H), 7.81–7.70 (m, 3H, Ar-H), 7.50–7.34 (m, 5H, Ar-H), 3.03 (s, 1H, -NH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 142.71, 134.27, 133.66, 130.77, 128.97, 128.29, 127.38, 127.10, 126.35, 125.74, 125.47, 125.03, 124.46, 102.22, 42.81 ppm. MS (m/z): 311.5 (M+1) observed for $C_{21}H_{14}N_2O$.

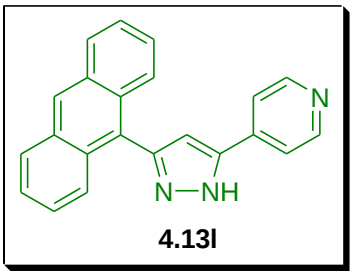
4.5.11 3-(Anthracen-10-yl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (4.13k)



4.13k

Yellow solid, Yield: 93%, m.p. 99–101 ^{o}C, IR (KBr) cm^{-1} 3051.82 (Aromatic C-H), 3408.00 (NH), 1669.42 (C=N) and 1588.83 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.54–8.19 (m, 2H, Ar-H), 8.10–8.93 (m, 2H, Ar-H), 7.86–7.78 (m, 1H, Ar-H), 7.62–7.36 (m, 6H, Ar-H), 7.12 (s, 1H, Ar-H), 5.52 (s, 1H, -NH), 3.94–3.69 (m, 9H, Ar-OCH_3) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 153.44, 143.99, 134.28, 131.05, 129.46, 129.28, 128.78, 127.59, 127.37, 126.91, 125.57, 105.64, 101.14, 61.12, 56.92, 56.56, 56.33 ppm. MS (m/z): 411.6 (M+1) observed for $C_{26}H_{22}N_2O_3$.

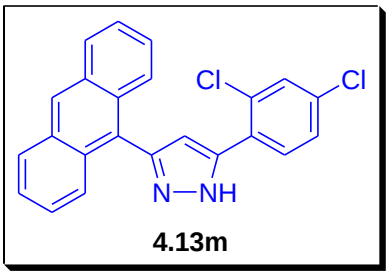
4.5.12 4-(3-(Anthracen-10-yl)-1H-pyrazol-5-yl)pyridine (4.13l)



4.13l

Yellow solid, Yield: 92%, m.p. 154–156 ^{o}C, IR (KBr) cm^{-1} 3059.57 (Aromatic C-H), 3389.91 (NH), 1660.56 (C=N) and 1634.88 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.63–8.30 (m, 3H, Ar-H), 8.10–7.99 (m, 1H, Ar-H), 7.83–7.76 (q, 4H, Ar-H), 7.60–7.45 (m, 1H, Ar-H), 1.60 (s, 1H, -NH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 145.25, 134.29, 133.72, 131.68, 129.02, 128.72, 128.31, 127.40, 127.06, 126.17, 125.49, 124.86, 101.89, 40.35 ppm. MS (m/z): 322.5 (M+1) observed for $C_{22}H_{15}N_3$.

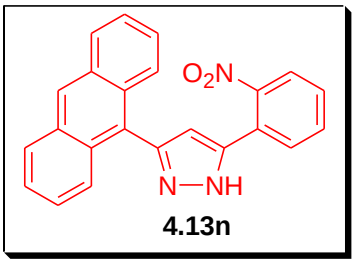
4.5.13 3-(Anthracen-10-yl)-5-(2,4-dichlorophenyl)-1H-pyrazole (4.13m)



4.13m

Yellow solid, Yield: 93%, m.p. 70–72 ^{o}C, IR (KBr) cm^{-1} 3054.49 (Aromatic C-H), 3419.09 (NH), 1666.52 (C=N) and 1598.27 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.17–7.99 (m, 2H, Ar-H), 7.86–7.67 (m, 2H, Ar-H), 7.62–7.09 (m, 7H, Ar-H), 7.04–6.94 (m, 1H, Ar-H) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 143.61, 134.27, 131.61, 131.10, 130.53, 129.48, 128.98, 12875, 127.85, 127.36, 127.12, 126.97, 125.71, 125.48, 124.16, 110.46, 40.50 ppm. MS (m/z): 389.5 (M+1) observed for $C_{22}H_{14}N_3Cl_2$.

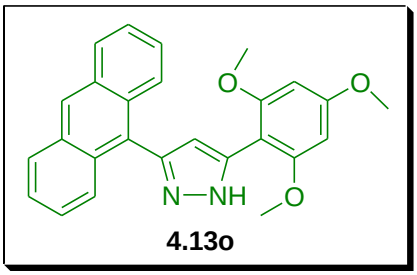
4.5.14 3-(Anthracen-10-yl)-5-(2-nitrophenyl)-1H-pyrazole (4.13n)



4.13n

Brown solid, Yield: 90%, m.p. 70–72 ^{o}C, IR (KBr) cm^{-1} 3051.44 (Aromatic C-H), 3399.00 (NH), 1669.89 (C=N) and 1612.29 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.68–8.42 (m, 2H, Ar-H), 8.32–7.99 (m, 4H, Ar-H), 7.91–7.75 (m, 3H, Ar-H), 7.68–7.39 (m, 6H, Ar-H) ppm.^{13}C-NMR (300 MHz, $CDCl_3$) δ 146.04, 134.28, 129.28, 128.97, 128.74, 128.28, 127.37, 127.24, 127.06, 126.93, 125.74, 125.64, 124.74, 124.45, 122.14, 112.62, 40.68 ppm. MS (m/z): 366.8 (M+1) observed for $C_{22}H_{15}N_3O_2$.

4.5.15 3-(Anthracen-10-yl)-5-(2,4,6-trimethoxyphenyl)-1H-pyrazole (4.13o)

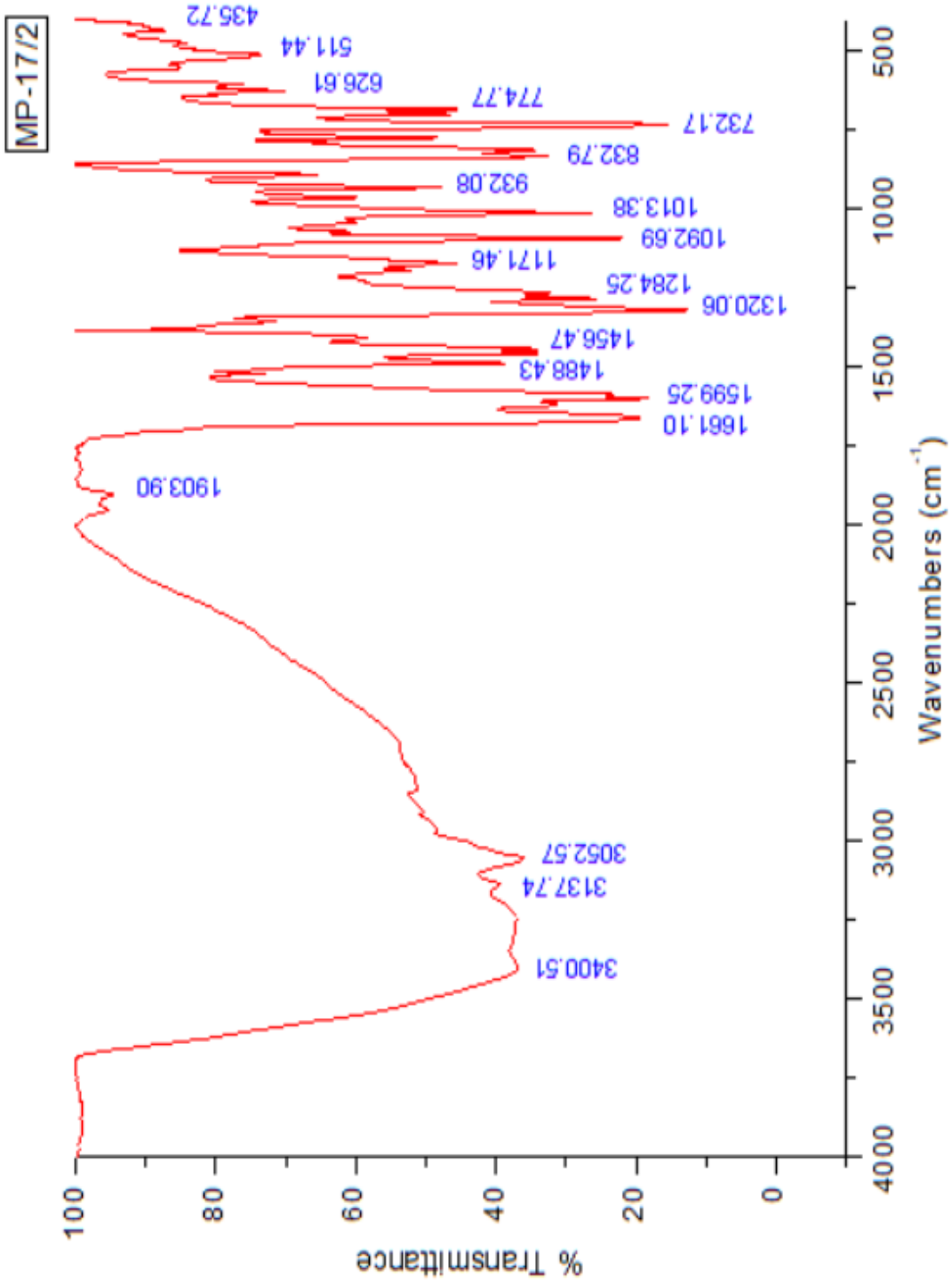


4.13o

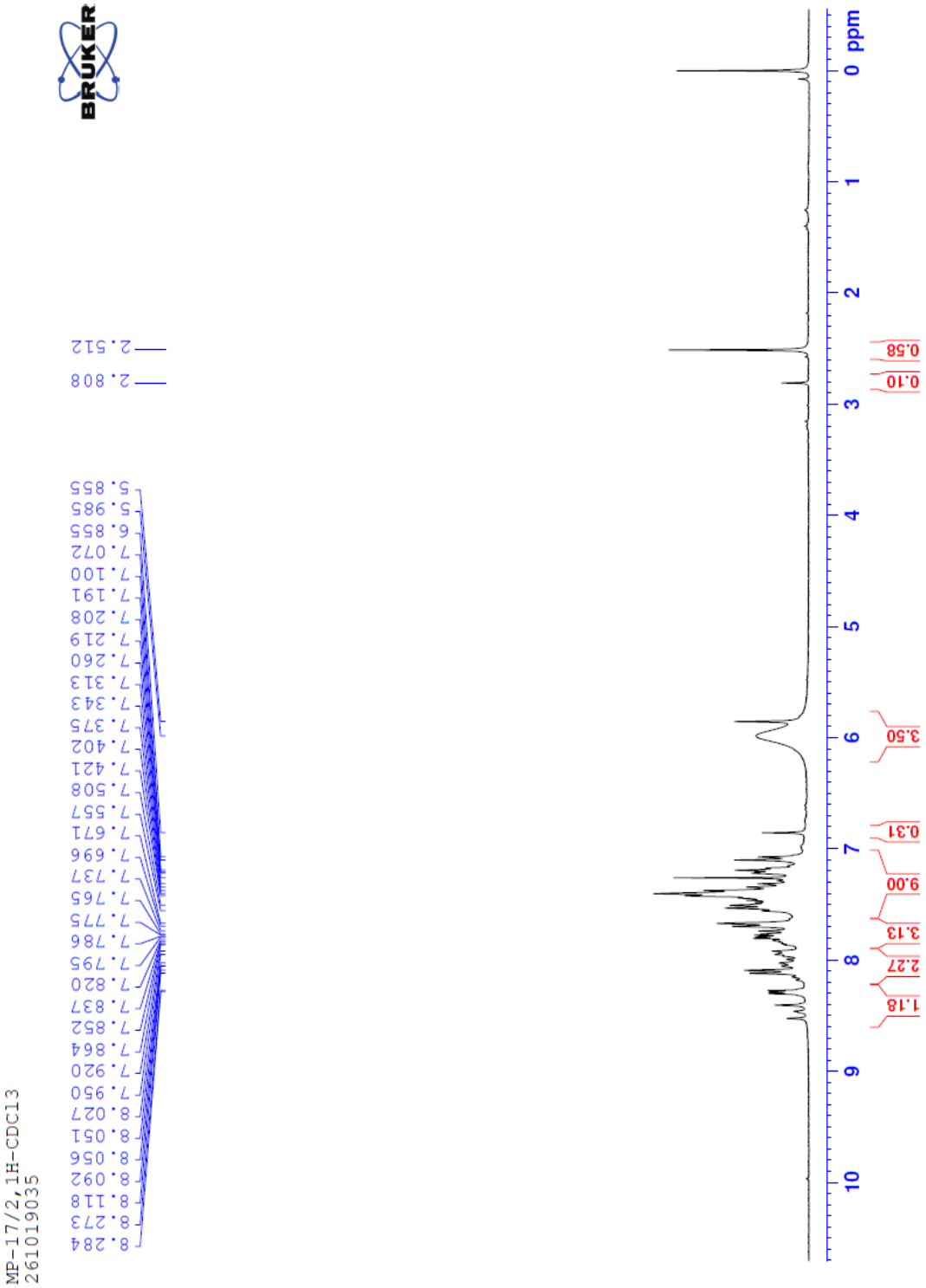
Brown solid, Yield: 91%, m.p. 81–83 ^{o}C, IR (KBr) cm^{-1} 3051.82 (Aromatic C-H), 3437.50 (NH), 1669.8 (C=N) and 1579.16 (C=C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.50–8.48 (m, 1H, Ar-H), 8.33–8.30 (m, 1H, Ar-H), 8.04–7.74 (m, 4H, Ar-H), 7.66–7.57 (m, 1H, Ar-H), 7.51–7.32 (m, 5H, Ar-H), 6.23 (m, 1H, Ar-H), 6.02–5.98 (m, 1H, Ar-H), 5.00 (s, 1H, -NH), 3.95–3.58 (m, 9H, Ar-OCH_3) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 140.97, 134.28, 131.23, 129.01, 128.72, 128.55, 127.84, 127.37, 126.45, 126.20, 126.04, 125.65, 125.47, 100.12, 91.91, 90.65, 61.52, 56.71, 56.07, 55.86 ppm. MS (m/z): 412.4 (M+2) observed for $C_{26}H_{23}N_2O_3$.

4.6 REPRESENTATIVE SPECTRA OF ANTHRACENYL PYRAZOLES

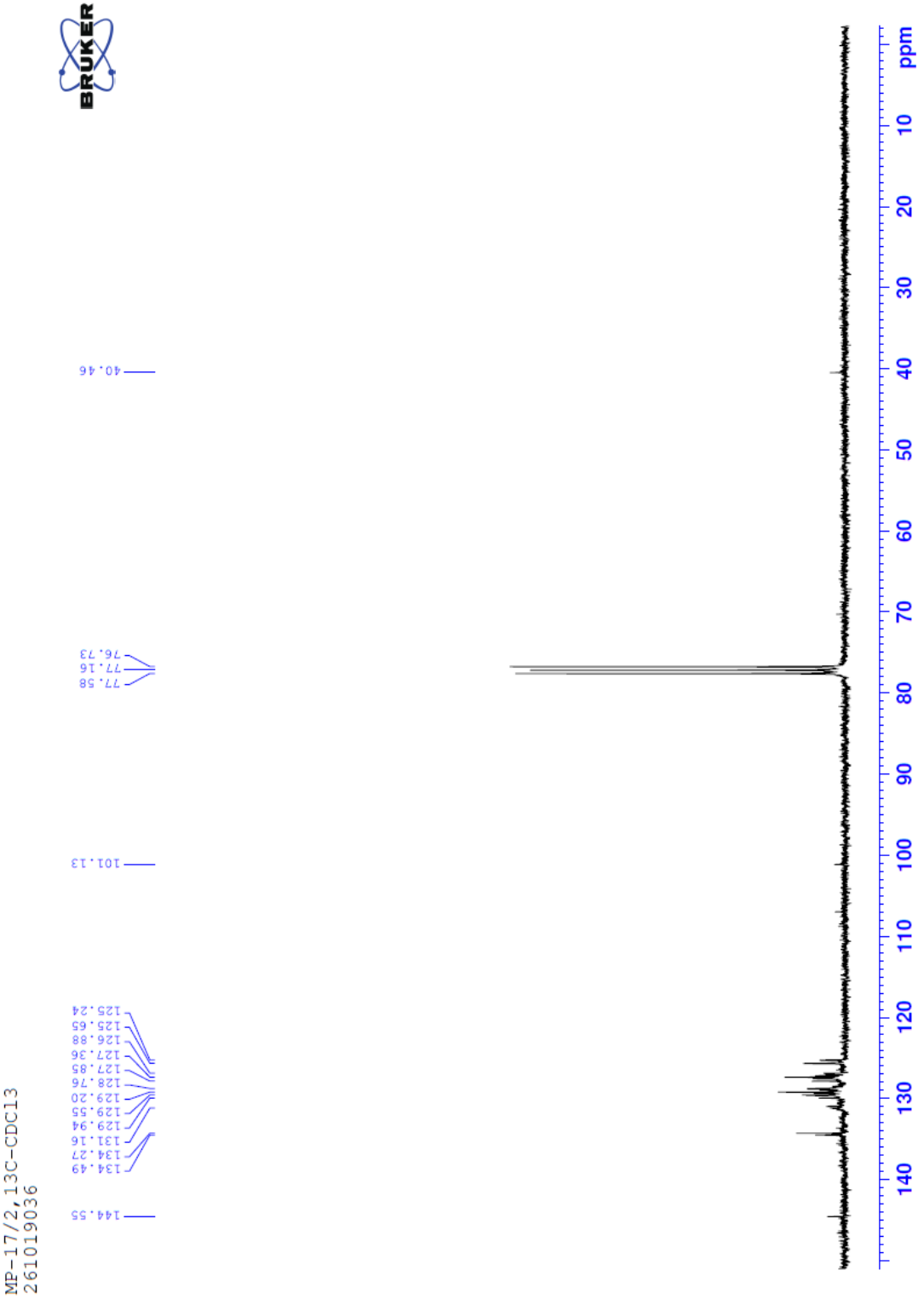
4.6.1 IR (KBr, *v*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-5-(4-chlorophenyl)-1H-pyrazole (4.13a)



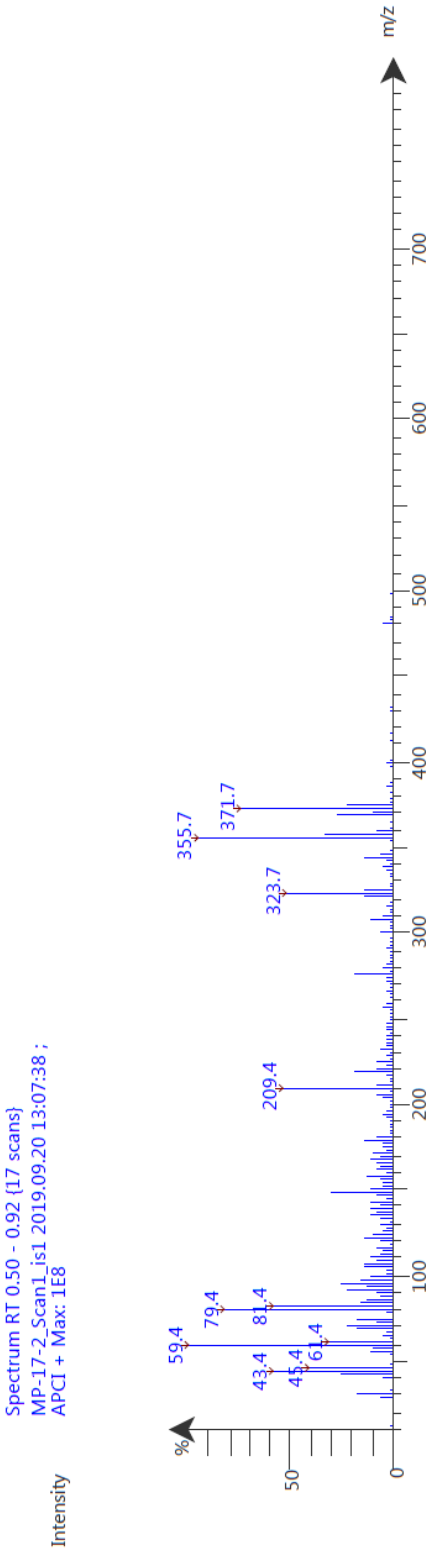
4.6.2 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(4-chlorophenyl)-1H-pyrazole (4.13a)



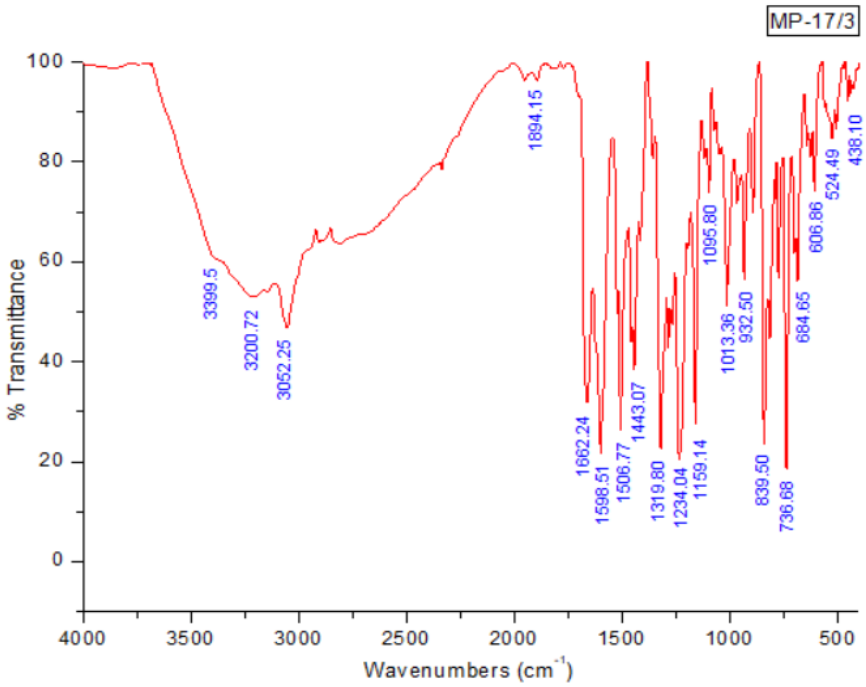
4.6.3 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(4-chlorophenyl)-1H-pyrazole (4.13a)



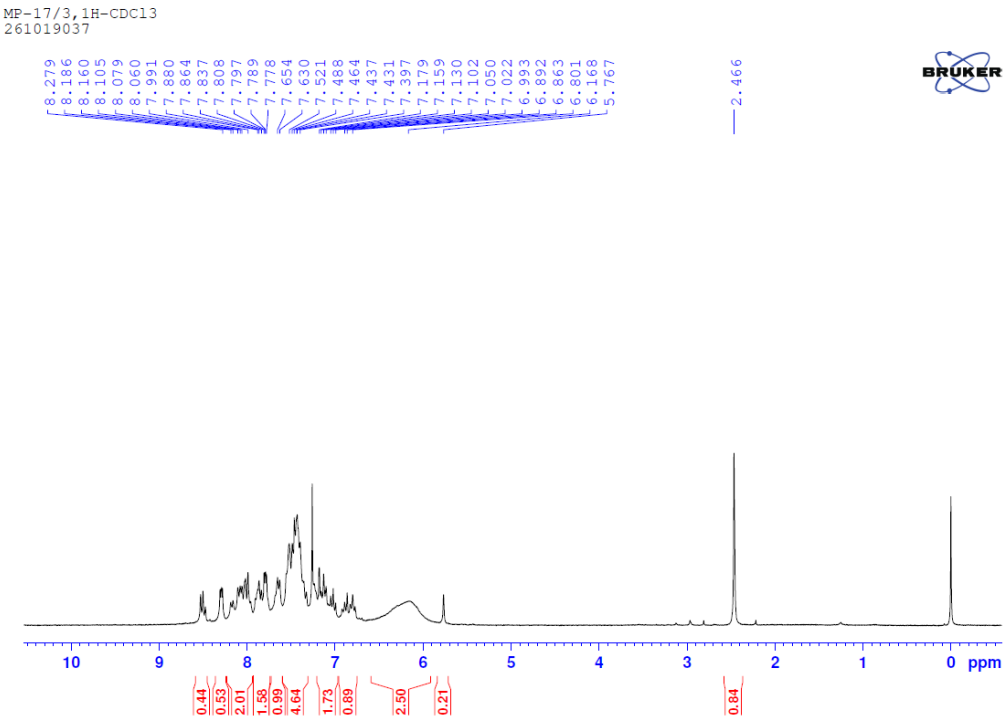
4.6.4 MS spectrum of 3-(Anthracen-10-yl)-5-(4-chlorophenyl)-1H-pyrazole (4.13a)



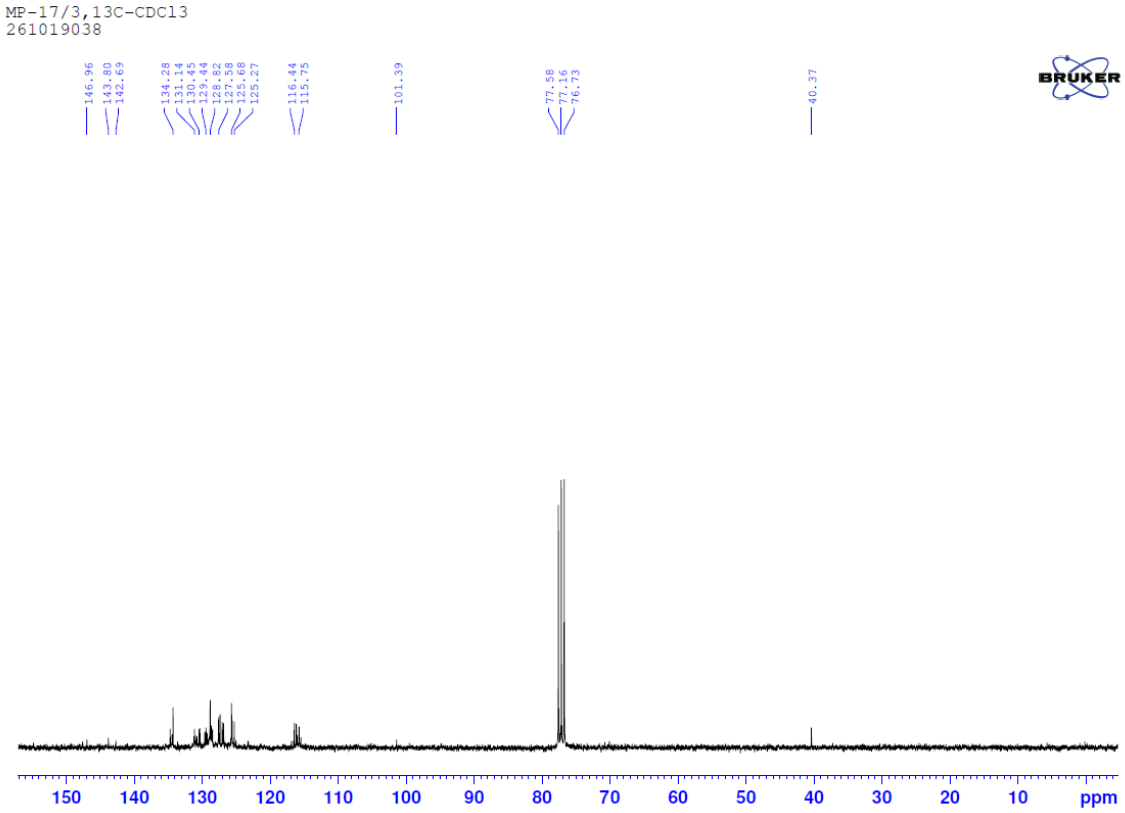
4.6.5 IR (KBr, *v*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-5-(4-fluorophenyl)-1H-pyrazole (4.13b)



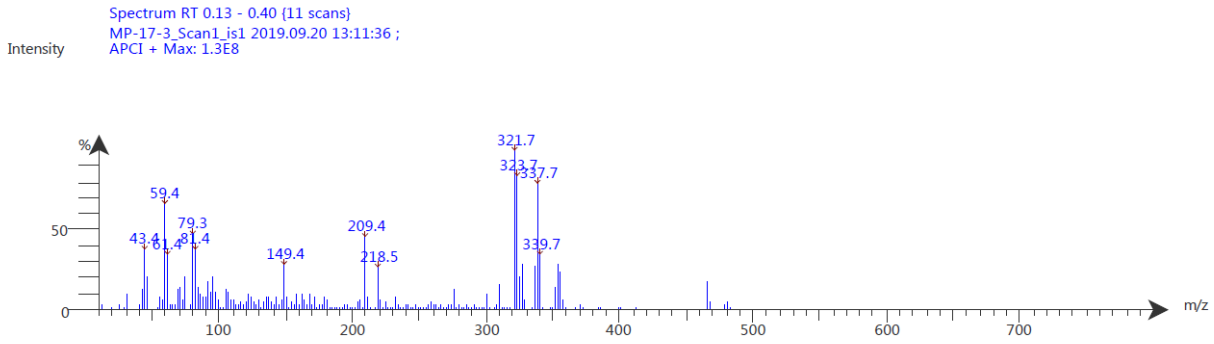
4.6.6 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(4-fluorophenyl)-1H-pyrazole (4.13b)



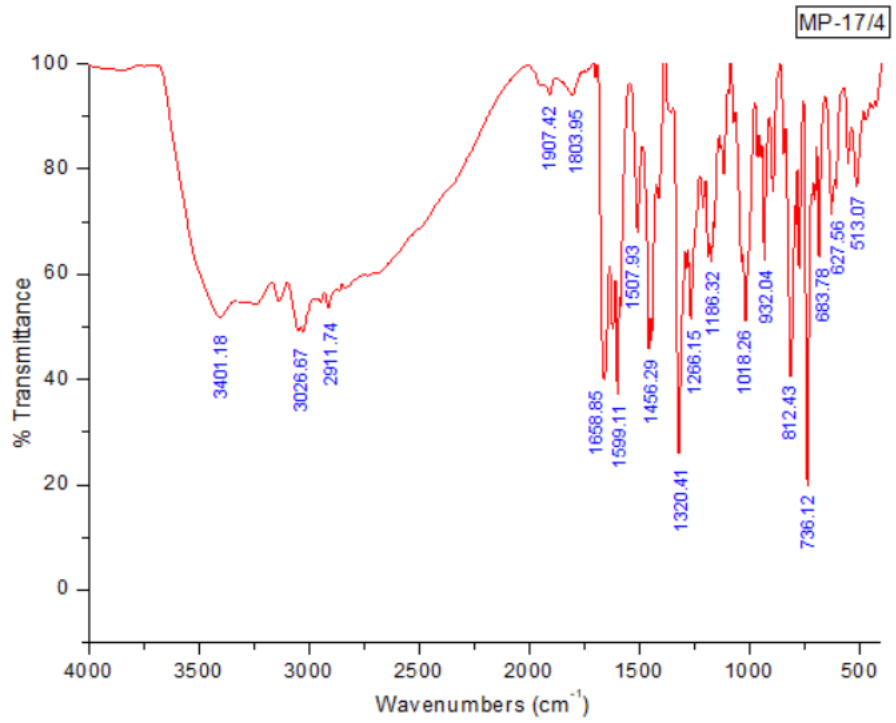
4.6.7 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(4-fluorophenyl)-1H-pyrazole (4.13b)



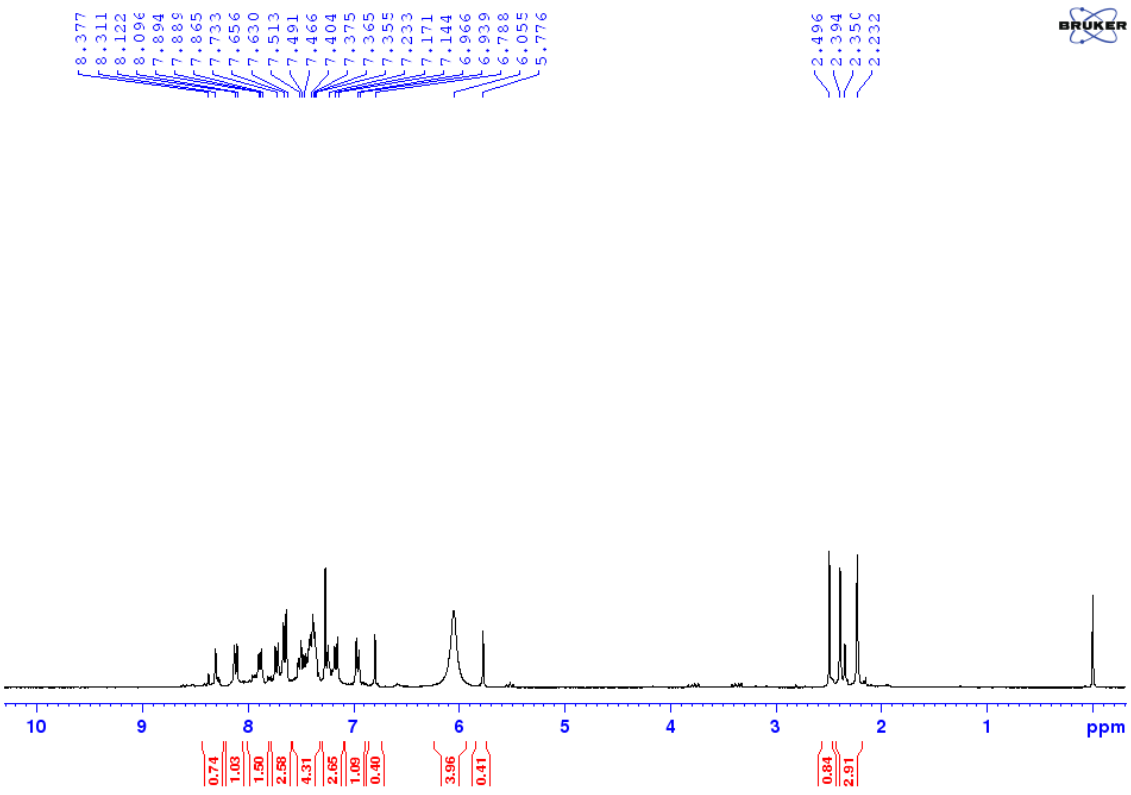
4.6.8 MS spectrum of 3-(Anthracen-10-yl)-5-(4-fluorophenyl)-1H-pyrazole (4.13b)



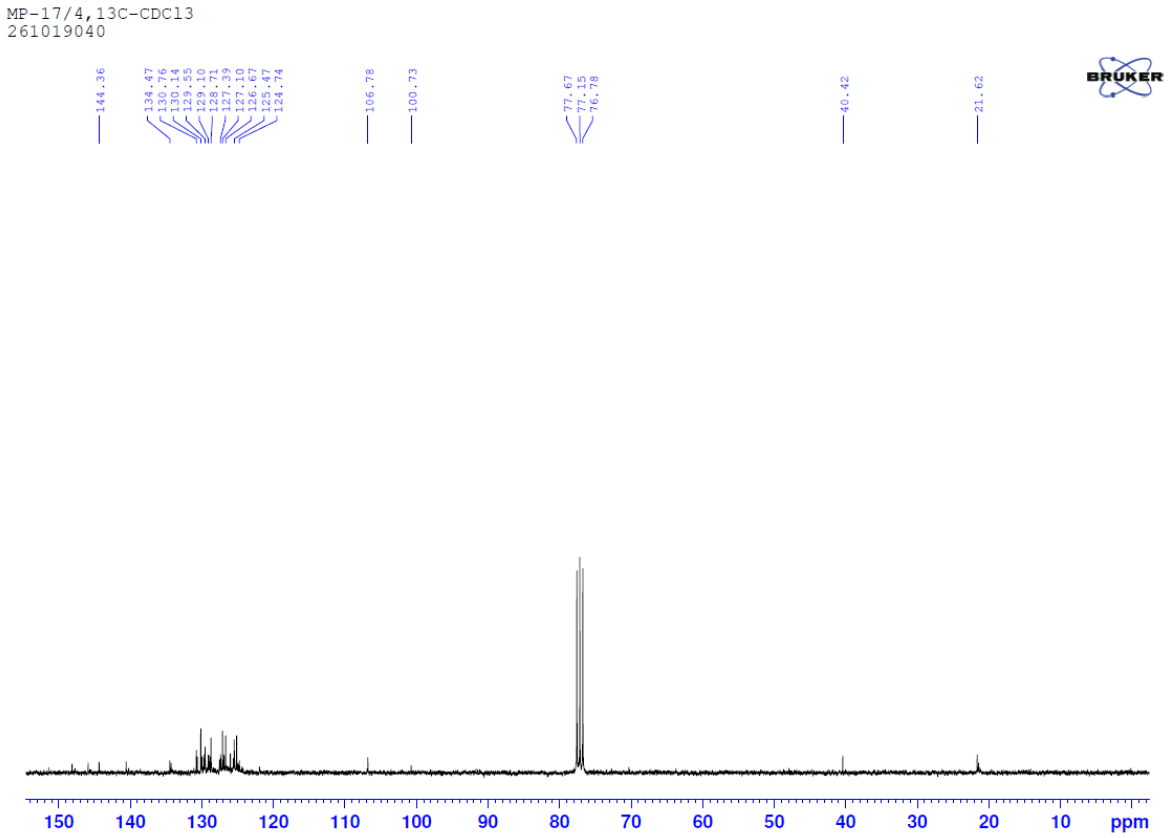
4.6.9 IR (KBr, *v*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-5-p-tolyl-1H-pyrazole (4.13c)



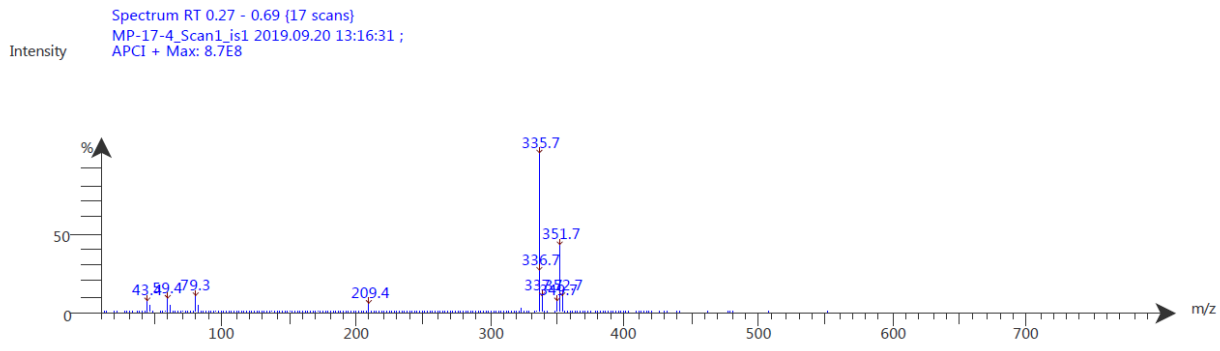
4.6.10 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-p-tolyl-1H-pyrazole (4.13c)



4.6.11 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-p-tolyl-1H-pyrazole (4.13c)



4.6.12 MS spectrum of 3-(Anthracen-10-yl)-5-p-tolyl-1H-pyrazole (4.13c)



- All the spectra of other anthracenyl pyrazoles are represented in Appendix: C-4.

4.7 References

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Chapter 5

Synthesis of Anthracene-based 1,3,5-Trisubstituted Pyrazolines and their Structural Characterization

Abstract

A new series of anthracene scaffold containing 1,3,5-trisubstituted pyrazoline derivatives (**5.10a-p**) were synthesized and characterized. The reactions were carried out starting from anthracenyl pyrazolines (**3.9**) and benzoyl chloride (**5.9**) in presence of anhydrous K_2CO_3 in acetone under reflux conditions for 2-7 hours. The obtained yields were good to excellent (80-94%). The newly synthesized pyrazoline compounds (**5.10a-p**) were well characterized by ^{1}H-NMR, ^{13}C-NMR, FTIR, mass spectroscopic and elemental analysis methods.

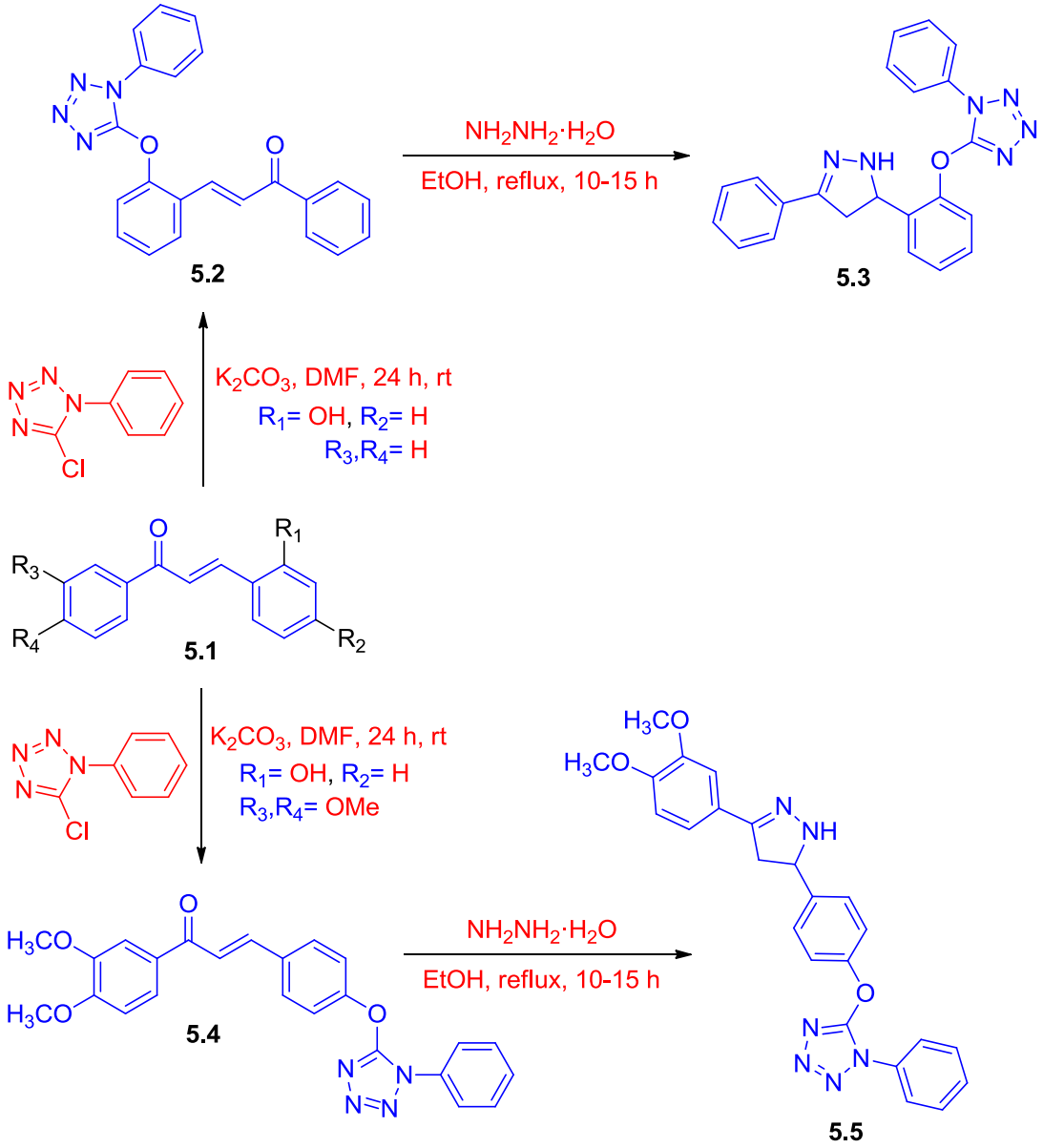
5.1 INTRODUCTION

The pyrazoline nucleus which is an elegant member of the heterocyclic family is known to be the core feature of various organic compounds exhibiting diverse pharmacological, physiological and tunable properties depending on the nature of the molecular structure and mode of synthesis and is therefore useful materials in discovery of new drug. Pyrazoline with functional substituents are also reported to occupy a leading role in medicinal and pesticide chemistry because of their many biological activities. Therefore, it comes as no surprise that pyrazolines and its derivatives are widely incorporated in a number of important and diverse medical and biochemical agents. Among the various pyrazoline derivatives, 2-pyrazolines seem to be the most commonly studied pyrazoline type compounds. Literature review also reported that different substituted 2-pyrazolines possess a vast number of biological activities such as anti-microbial,[1] anti-convulsant,[2] anti-tubercular,[3] anti-cancer,[4] analgesic,[5] anti-diabetic[6] and insecticidal agents.[7] Literature survey also gives a good report of many pyrazolines as anti-inflammatory agents (Anti-pyrine, 2,3-dimethyl- 1-phenyl-3-pyrazolin-5-one, was the first pyrazolone derivative that was used in the management of pain and inflammation).[8] In 2000 Davood *et al.* synthesized 3,5-dinaphthalene-1-yl-substituted-2-pyrazolines showing anti-bacterial activity.[9] Another report also shows a modification of 2-pyrazolines nucleus that is the synthesis of 1-acetyl-5-(substitutedaryl)-3-(*β*- aminonaphthyl)-2-pyrazolines that showed anti-inflammatory activity against standard drugs phenyl butazone

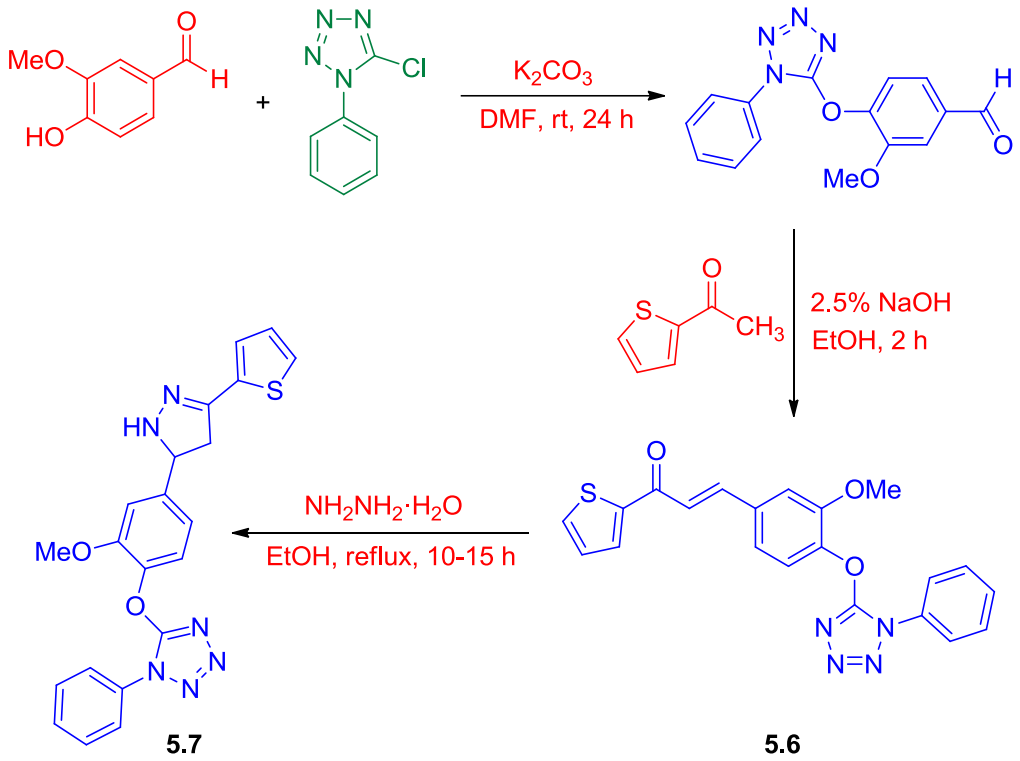
and indomethacin.[10] In 2008, Budakoti A. and group synthesized 3-(3-bromophenyl)-5-phenyl-1-(thiazolo[4,5-*b*]quinoxaline-2-yl)-2-pyrazoline derivatives and screened for their antamoebic activity against HMI: IMSS strain of *Entamoeba histolytica.* All the compounds were found to be non-toxic.[11] Understanding the synthetic routes of pyrazolines, the most common method that has been employed is the reaction of an α,β-unsaturated ketones and aldehydes with hydrazines under different reaction conditions (conventional or green synthesis). In this procedure, hydrazones are formed as intermediates which on cyclization with a suitable cyclizing agent (eg. acetic acid) gives 2-pyrazolines. Till date, this simple method have been the most popular method for the synthesis of 2-pyrazolines. Other modified synthesis of 2-pyrazolines have also been reported by different researchers.[12]

Research studies on pyrazoline derivatives have been carried out for many years by various chemists, aiming at finding ways to utilize this pyrazoline molecules with changes in its substitutents to replace some heterocyclic rings that are not as efficient as this compound as it has been justified by many recent publications with simpler conditions, synthetic modification and the various properties reported.[13] The need for developing and synthesizing lesser toxic and environmental friendly novel pyrazoline molecules is mandate in order to understand its applications in different areas and to evaluate its biological activity against various kinds of diseases. Recent literature studies of the synthesis of pyrazolines and its derivatives have been discussed below.

A report on the synthesis of new hybrids of tetrazole-pyrazoline derivatives by the reaction of chalcones with hydrazine hydrate was prepared by Heidi S. Abd ElMonaem and group in **2018**. Screening for the *in vitro* anti-proliferative activity for all the compounds were evaluated against three cancer cell lines and *Vero-B* normal cell line using MTT-based assay. Most of the chalcone derivatives showed more activity against colon *HCT-116* and prostate *PC-3* cell lines when compared with the standard drug cisplatin (IC_{50}= 20 μg/ml and 5 μg/ml) and 5-FU (IC_{50}= 17.3 μg/ml and 21.4 μg/ml). Compound **5.2** (Scheme 5.1) was found to be the most active against colon *HCT-116* and prostate *PC-3* cell lines (IC_{50}= 0.6 μg/ml and 1.6 μg/ml) and compound **5.6** (Scheme 5.2) showed excellent activity against breast *MCF-7* cell lines with SI= 2.75.[14]

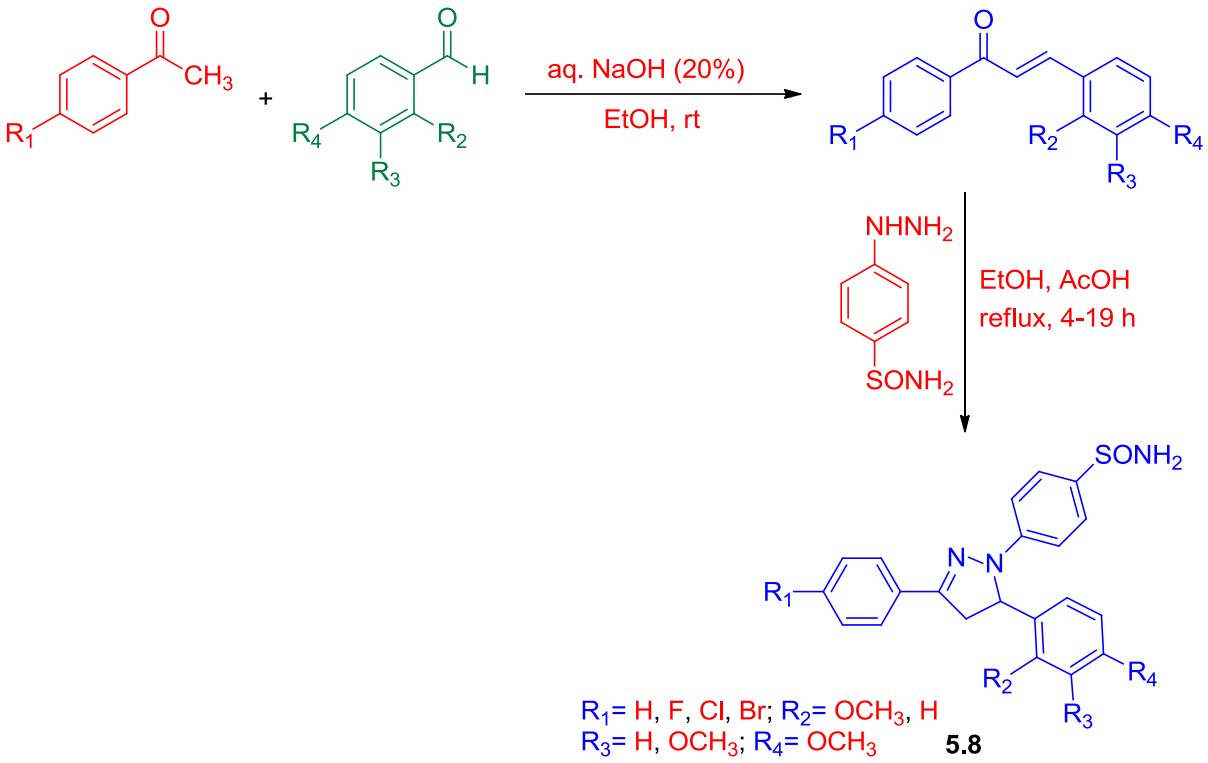


Scheme 5.1. Synthesis of new hybrids of tetrazole-pyrazoline derivatives.



Scheme 5.2. Synthesis of new hybrids of tetrazole-pyrazoline derivatives.

Dilan Ozmen Ozguna and co-workers in **2019** synthesized chalcone derivatives which was further reacted with p-hydrazinobenzenesulfonamide hydrochloride in presence of acetic acid in ethanol affording 4-(3-Substitutedphenyl-5-polymethoxyphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)benzenesulfonamide derivatives (**5.8**). The compounds that were designed also include pyrazoline and sulfonamide pharmacophores in a single molecule (Scheme 5.3). Results of inhibition potency shows that sulfonamides evaluated against human CA isoenzymes (hCA I and hCA II) and acetylcholinesterase (AChE) enzyme gives a strong inhibition with Ki value ranging from 37.7 ± 14.4–89.2 ± 30.2 nM. The cytotoxicity screening results towards oral squamous cancer cell carcinoma (OSCC) cell lines (Ca9-22, HSC-2, HSC-3 and HSC-4) and non-tumor cells (HGF, HPLF and HPC) are low except for compounds bearing 3,4-dimethoxyphenyl.[15]



Scheme 5.3. Synthesis of chalcones and pyrazolyl benzenesulfonamide derivatives.

It is evident from the literature findings that pyrazolines and their derivatives possess a wide variety of biological activities. A number of anthracenyl pyrazoline derivatives (**3.9**) earlier synthesized and discussed in previous chapter showing significant anti-cancer activity and in continuation of that work, we aimed to synthesize anthracene-based 1,3,5-trisubstituted pyrazoline derivatives (**5.10a-p**). All the synthesized new pyrazoline compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and Mass elemental analysis methods.

5.2 EXPERIMENTAL SECTION

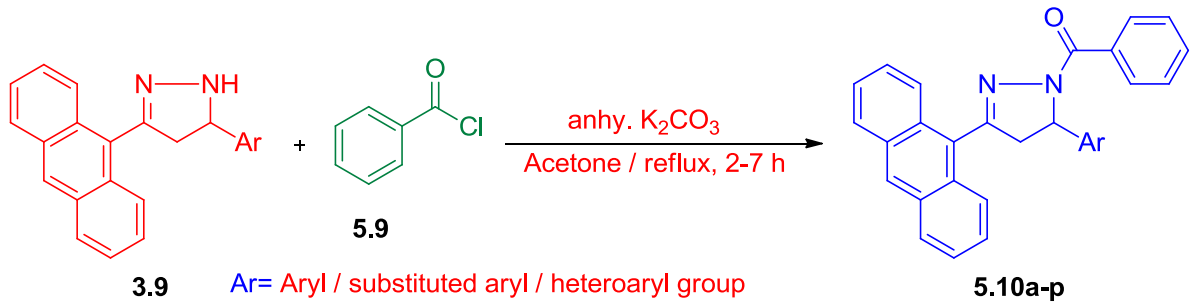
5.2.1 Materials and Methods

All the basic reagents and solvents were purchased from commercially available sources and used without further purification. Anthracenyl pyrazolines (**3.9**) were synthesized according to our previous reported procedures.[16] Progress of the reactions was monitored by thin layer chromatography (TLC) with silica gel plates (Merck) using ethylacetate and *n*-hexane (3:7) as a solvent system and visualized under UV-light/iodine vapors. Silica gel (60-120 mesh) was used for column chromatography. Melting points were recorded in open capillaries using IKON melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra for the newly synthesized anthracene-based 1,3,5-trisubstituted pyrazoline compounds

were recorded using Bruker 300 MHz spectrometer in $CDCl_3$ as a solvent and TMS as an internal standard, values are given in parts per million (ppm). FTIR spectra of the compounds were recorded on Perkin-Elmer spectrophotometer (Spectrum-Two) using KBr disk and values are expressed in cm^{-1}. Micro analytical (CHN) data were obtained with a FLASH EA 1112 Series CHNS analyzer. Mass spectra for all the newly synthesized compounds were recorded on Advion Expression-S CMS system.

5.2.2 General procedure for the synthesis of anthracene-based 1,3,5-trisubstituted pyrazolines (5.10a-p)

To a stirred solution of corresponding anthracenyl pyrazoline (**3.9**) (1 mmol), benzoyl chloride (**5.9**) (1 mmol) in acetone (10 mL) was added catalytic amount of anhydrous K_2CO_3. The reaction mixture was refluxed for 2-7 hours with continuous stirring. After completion of the reaction monitored by TLC, the solvent was removed and added ice cold water. The pure solid products of new anthracenyl pyrazolines (**5.10a-p**) were collected by filtration methods, washed with water (3-4 time) and air dried at RT (Scheme 5.4).

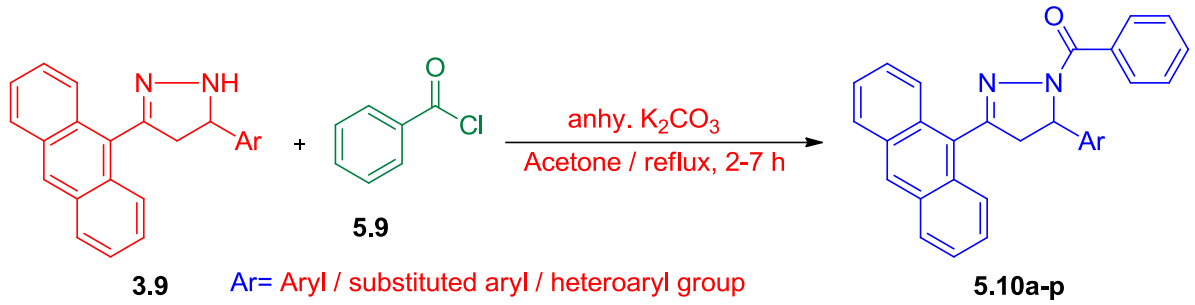


Scheme 5.4. Synthesis of anthracene-based 1,3,5-trisubstituted pyrazolines (**5.10a-p**).

5.3 RESULTS AND DISCUSSION

The anthracene-based 1,3,5-trisubstituted pyrazoline derivatives (**5.10a-p**) were synthesized by carrying out the reaction starting from our previously reported anthracenyl pyrazolines (**3.9**)[16] with benzoylchloride (**5.9**) in presence of anhydrous K_2CO_3 in acetone solution under reflux conditions for 2-7 h (Scheme 5.4, Figure 5.1 and Table 5.1) and the obtained yields are good to excellent (80-94%). The structures of the latter products were generated from their spectroscopic analysis. When different anthracenyl pyrazoline derivatives were used for the reaction, we observed that the time taken for each reaction to complete was different depending on the functional groups present in the aromatic ring and the progress of each reaction was monitored by thin layer chromatography (TLC) at different time intervals. The obtained yields and time taken for each reaction to complete is listed in Table 5.1.

Table 5.1. Synthesis and physicochemical features of new anthracene-based 1,3,5-trisubstituted pyrazoline derivatives (**5.10a-p**).[a]



3.9 **5.9** Ar= Aryl / substituted aryl / heteroaryl group **5.10a-p**

S. No.	Ar	Product	Time (h)	Yield (%)	m. p. (°C)
1	-C_6H_5	**5.10a**	2	80	100-102
2	-4-ClC_6H_4	**5.10b**	3	93	84-86
3	-4-FC_6H_4	**5.10c**	4	92	85-87
4	-4-$CH_3C_6H_4$	**5.10d**	2	94	195-197
5	-3-ClC_6H_4	**5.10e**	4	86	86-88
6	-4-$NO_2C_6H_4$	**5.10f**	7	91	80-82
7	-4-BrC_6H_4	**5.10g**	5	93	92-94
8	-4-CNC_6H_4	**5.10h**	2	91	106-108
9	-3-FC_6H_4	**5.10i**	3	85	55-57
10	-3-$NO_2C_6H_4$	**5.10j**	5	92	102-104
11	-2-Furan	**5.10k**	4	83	84-86
12	-3,4,5-$(OCH_3)_3C_6H_2$	**5.10l**	3	90	68-70
13	-3,4-$(OCH_3)_2C_6H_3$	**5.10m**	3	85	65-67
14	-4-$(OCH_3)C_6H_4$	**5.10n**	3	94	151-153
15	-4-Pyridine	**5.10o**	2	90	84-86
16	-2,4-$(Cl)_2C_6H_3$	**5.10p**	2	92	60-62

[a]Reaction conditions: Anthracenyl pyrazolines (**3.9**) (1 mmol), benzoyl chloride (**5.9**) (1 mmol), anhyd. K_2CO_3 in 10 mL acetone and reflux for 2-7 h.

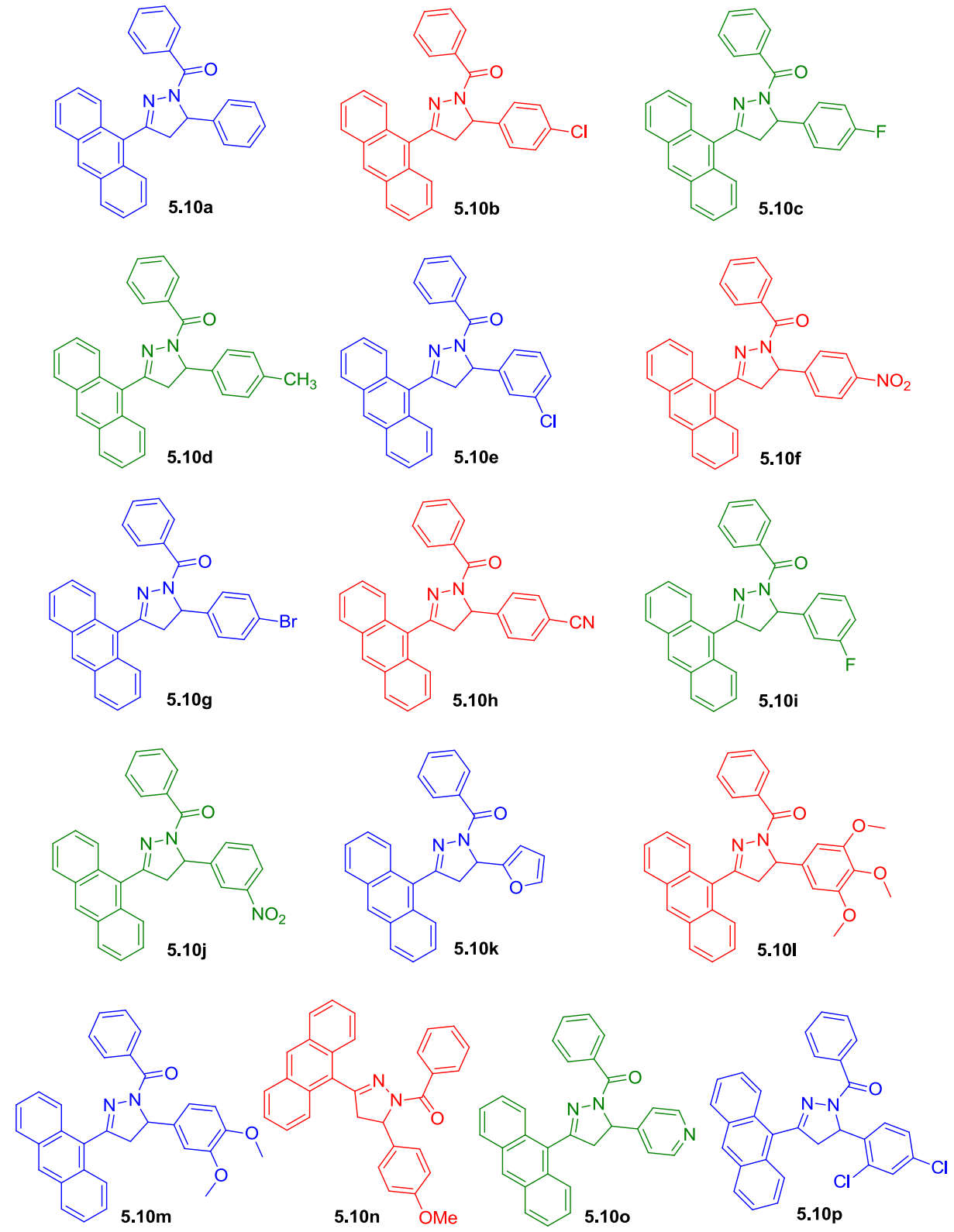


Figure 5.1. Synthetic structures of new anthracene-based 1,3,5-trisubstituted pyrazolines(**5.10a-p**).

All the solid compounds were collected by simple workup with water followed by filtration method as pure products except compounds **5.10h**, **5.10j** and **5.10k**, which were purified from column chromatography (Hex/EtOAc 7:3). The structures for all the molecules were obtained by spectroscopic analysis method (IR, ^{1}H-NMR, ^{13}C-NMR and Mass elemental analysis). In general, all the newly synthesized anthracene-based 1,3,5-trisubstituted pyrazoline compounds revealed the comparable characteristic spectral features. For instance, the IR spectra of anthracene-based 1,3,5-trisubstituted pyrazoline compound **5.10a** showed the characteristics bands for aromatic C-H at 3053.77 cm^{-1} and aliphatic C-H stretching frequency at 2927.90 cm^{-1}, C=O at 1709.77 cm^{-1} and C=N stretching at 1641.75 cm^{-1}. The disappearance of the absorption band of NH of the anthracenyl pyrazoline (**3.9**)[16] and appearance of strong C=O absorption band at 1709.77 cm^{-1} confirmed the formation of our expected product.

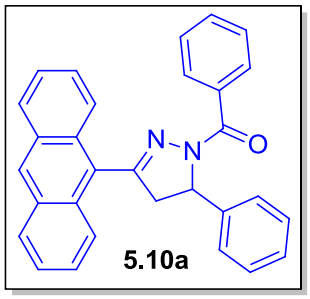
Its ^{1}H-NMR spectrum displayed a pair of doublet of doublet signals of methylene protons at δ 3.98–3.88 ppm for -CH_B, δ 3.32–3.24 ppm for -CH_A and a double doublet peaks at δ 6.10–6.04 ppm for methyl proton -CH_X because of the neighboring protons of the methylene (CH_2) group. Coming to the ^{13}C-NMR spectra, the distinctive chemical shift values of the pyrazoline ring carbons appears at δ 47.92 ppm (C, CH_2 pyrazoline), δ 61.50 ppm (C, CH pyrazoline), δ 156.03 ppm (C, C=N pyrazoline) and δ 167.09 ppm (C, C=O) which gives the characteristic features for the formation of the corresponding anthracene-based 1,3,5-trisubstituted pyrazoline product **5.10a**.

5.4 CONCLUSION

In summary, in this chapter we developed a novel efficient synthesis of anthracene-based 1,3,5-trisubstituted pyrazolines derivatives (**5.10a-p**) and their structural characterization studies by various spectroscopic methods. The present protocol is simple, easy workup procedure and obtained yields were good to excellent with a simple filtration method. In future, these newly synthesized anthracene-based 1,3,5-trisubstituted pyrazolines may be of value for numerous applications in various scientific areas.

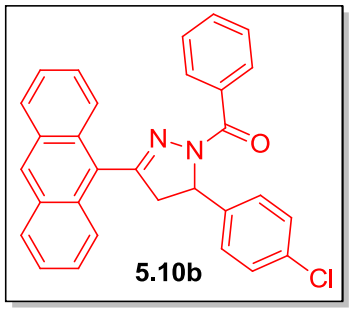
5.5 SPECTRAL CHARACTERIZATION DATA

5.5.1 (3-(Anthracen-10-yl)-4,5-dihydro-5-phenylpyrazol-1-yl)(phenyl)methanone (5.10a)



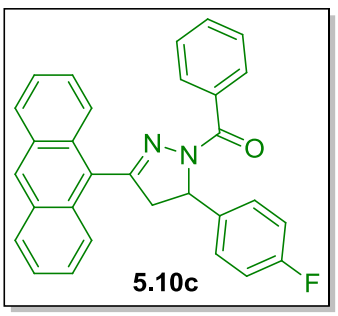
Brown solid. Yield: 79%. m.p. 100–102 °C. IR (KBr) cm^{-1}: 3053.77 (Aromatic C-H), 2927.90 (Aliphatic C-H), 1709.77 (C=O) and 1641.75 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.51 (s, 1H, Ar-H), 8.06–8.01 (q, 4H, Ar-H), 7.93–7.90 (t, 2H, Ar-H), 7.80–7.77 (m, 8H, Ar-H), 7.38–7.33 (m, 4H, Ar-H), 6.10–6.04 (dd, 1H, -CH), 3.98–3.88 (dd, 1H, -CH), 3.32–3.24 (dd, 1H, -CH).^{13}C-NMR (300 MHz, $CDCl_3$) δ 167.09, 156.03, 141.75, 134.26, 131.34, 131.22, 130.22, 129.95, 129.35, 129.03, 128.97, 127.98, 127.89, 127.36, 126.95, 125.68, 125.60, 124.77, 61.50, 47.92 ppm. MS (*m/z*): 427.5 (M+1). Elemental Anal. Calcd for $C_{30}H_{22}N_2O$: C, 84.48; H, 5.20; N, 6.57. Found: C, 84.36; H, 5.26; N, 6.65.

5.5.2 (3-(Anthracen-10-yl)-5-(4-chlorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10b)



Brown solid. Yield: 93%. m.p. 84–86 °C. IR (KBr) cm^{-1} 3053.11 (Aromatic C-H), 1709 (C=O) and 1641.47 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.55–8.53 (d, J=6.29 Hz, 1H, Ar-H), 8.06–7.99 (t, 4H, Ar-H), 7.94–7.88 (t, 2H, Ar-H), 7.82–7.36 (m, 11H, Ar-H), 6.07–6.01 (dd, 1H, -CH), 3.99–3.3.79 (dd, 1H, -CH), 3.30–3.21 (dd, 1H, -CH).^{13}C-NMR (300 MHz, $CDCl_3$) δ 167.08, 155.98, 140.30, 134.25, 133.05, 131.77, 131.34, 130.23, 129.54, 129.10, 127.94, 127.15, 127.06, 126.67, 125.63, 125.41, 124.59, 60.89, 47.83 ppm. MS (*m/z*): 461.6 (M+1). Elemental Anal. Calcd for $C_{30}H_{21}N_2OCl$: C, 78.17; H, 4.59; N, 6.08. Found: C, 78.25; H, 4.52; N, 6.15.

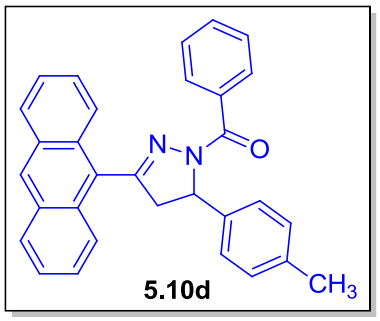
5.5.3 3-(Anthracen-10-yl)-5-(4-fluorophenyl)-4,5-dihydropyrazol-1-yl) (phenyl)methanone (5.10c)



Yellow solid. Yield: 92%. m.p. 85–87 °C. IR (KBr) cm^{-1} 3053.76 (Aromatic C-H), 2895.77 (Aliphatic C-H), 2833.68 (Aliphatic C-H), 1708.40 (C=O) and 1640.78 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H, Ar-H), 8.03–7.78 (m, 7H, Ar-H), 7.50–7.37 (m, 8H, Ar-H), 7.16 (s, 1H, Ar-H), 6.06–6.04 (dd, 1H, -CH), 3.98–3.88 (dd, 1H, -CH), 3.28–3.21 (dd, 1H, -CH)

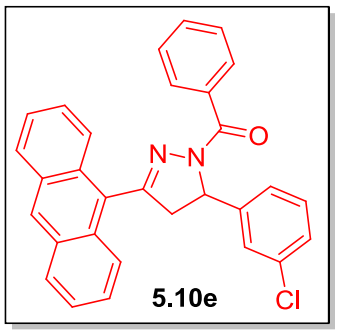
ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 167.52, 155.97, 137.52, 134.26, 131.77, 131.35, 130.23, 129.93, 129.09, 128.86, 127.93, 127.50, 127.39, 127.02, 125.63, 124.63, 116.40, 116.11, 111.25, 60.89, 47.83 ppm. MS (*m/z*): 445.6 (M+1). Elemental Anal. Calcd for $C_{30}H_{21}N_2OF$: C, 81.06; H, 4.76; N, 6.30. Found: C, 80.92; H, 4.81; N, 6.25.

5.5.4 (3-(Anthracen-10-yl)-4,5-dihydro-5-p-tolylpyrazol-1-yl)(phenyl)methanone (5.10d)



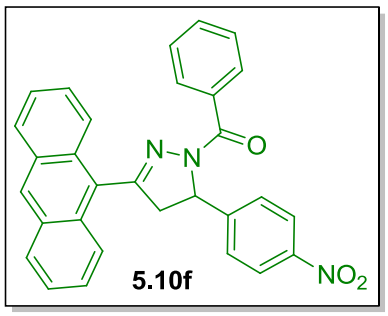
Yellow solid. Yield: 95%. m.p. 195–197 ºC. IR (KBr) cm^{-1} 3054.72 (Aromatic C-H), 2945.17 (Aliphatic C-H), 2916.42 (Aliphatic C-H), 1721.42 (C=O) and 1643.06 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) 8.50 (s, 1H, Ar-H), 8.12–7.92 (m, 6H, Ar-H), 7.50–7.28 (m, 12H, Ar-H), 6.06–6.01 (dd, 1H, -CH), 3.96–3.86 (dd, 1H, -CH), 3.31–3.23 (dd, 1H, -CH), 2.38 (s, 3H, -CH_3) ppm.^{13}C-NMR (300 MHz, $CDCl_3$) δ 167.08, 156.08, 138.84, 137.61, 134.34, 133.75, 131.34, 131.16, 130.21, 129.99, 129.95, 129.01, 128.93, 127.85, 126.92, 125.63, 125.58, 124.80, 61.33, 47.94, 21.31 ppm. MS (*m/z*): 441.6 (M+1). Elemental Anal. Calcd for $C_{31}H_{24}N_2O$: C, 84.52; H, 5.49; N, 6.36. Found: C, 84.45; H, 5.53; N, 6.29.

5.5.5 3-(Anthracen-10-yl)-5-(3-chlorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10e)



Yellow solid. Yield: 86%. m.p. 86–88 ºC. IR (KBr) cm^{-1} 3053.19 (Aromatic C-H), 2837.26 (Aliphatic C-H), 1709.81 (C=O) and 1641.42 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 1H, Ar-H), 8.06–8.02 (t, 4H, Ar-H), 7.92–7.89 (d, J=7.97 Hz, 2H, Ar-H), 7.53–7.32 (m, 11H, Ar-H), 6.06–6.00 (dd, 1H, -CH), 3.98–3.88 (dd, 1H, -CH), 3.29–3.21 (dd, 1H, -CH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 167.11, 156.00, 143.81, 135.28, 134.26, 131.41, 131.34, 130.69, 130.26, 129.93, 129.09, 128.24, 127.96, 127.07, 126.05, 125.65, 124.63, 123.82, 61.06, 47.68 ppm. MS (*m/z*): 461.5 (M+1). Elemental Anal. Calcd for $C_{30}H_{21}N_2OCl$: C, 78.17; H, 4.59; N, 6.08. Found: C, 78.32; H, 4.52; N, 6.15.

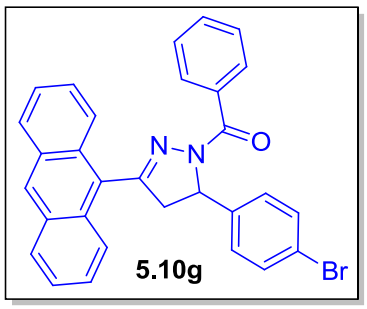
5.5.6 (3-(Anthracen-10-yl)-4,5-dihydro-5-(4-nitrophenyl)pyrazol-1-yl)(phenyl)methanone (5.10f)



5.10f

Brown solid. Yield: 95%. m.p. 80–86 °C. IR (KBr) cm^{-1} 3055.43 (Aromatic C-H), 1714.57 (C=O) and 1639.97 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 1H, Ar-H), 8.31 (s, 1H, Ar-H), 8.04–7.70 (m, 8H, Ar-H), 7.50–7.25(m, 9H, Ar-H), 6.13–6.01 (dd, 1H, -CH), 3.97–3.91 (dd, 1H, -CH), 3.26–3.20 (dd, 1H, -CH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 167.19, 156.02, 143.87, 147.72, 134.25, 133.45, 131.70, 131.31, 130.27, 129.18, 129.01, 128.04, 127.21, 126.68, 125.68, 124.76, 124.33, 121.24, 61.10, 47.32 ppm. MS (*m/z*): 472.5 (M+1). Elemental Anal. Calcd for $C_{30}H_{21}N_3O_3$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.32; H, 4.53; N, 8.86.

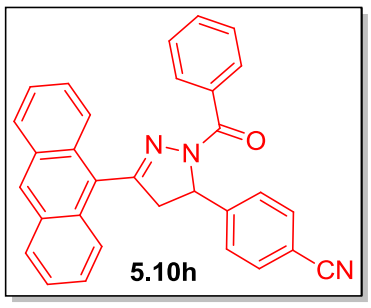
5.5.7 3-(Anthracen-10-yl)-5-(4-bromophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10g)



5.10g

Brown solid. Yield: 93%. m.p. 92–94 °C. IR (KBr) cm^{-1} 3061.57 (Aromatic C-H), 1721.87 (C=O) and 1599.39 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 1H, Ar-H), 8.17–7.99 (m, 5H, Ar-H), 7.90–7.68 (m, 1H, Ar-H), 7.65–7.31 (m, 11H, Ar-H), 6.07–6.01 (dd, 1H, -CH), 3.99–3.89 (dd, 1H, -CH), 3.29–3.21 (dd, 1H, -CH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 172.02, 162.52, 134.69, 133.92, 132.50, 132.20, 131.43, 130.72, 130.35, 129.45, 129.03, 128.63, 127.96, 127.50, 127.08, 125.65, 125.41, 124.59, 61.04, 47.64 ppm. MS (*m/z*): 505.4 (M+). Elemental Anal. Calcd for $C_{30}H_{21}N_2OBr$: C, 71.29; H, 4.19; N, 5.54. Found: C, 71.16; H, 4.13; N, 5.59.

5.5.8 3-(Anthracen-10-yl)-5-(4-cyanophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10h)

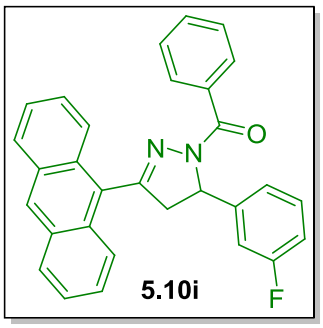


5.10h

Orange solid. Yield: 91%. m.p. 106–108 °C. IR (KBr) cm^{-1} 3055.20 (Aromatic C-H), 1714.17 (C=O) and 1641.46 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.79–8.41 (m, 1H, Ar-H), 8.17–7.87 (m, 8H, Ar-H), 7.80–7.47 (m, 11H, Ar-H), 6.19–6.07 (dd, 1H, -CH), 4.00–3.91 (dd, 1H, -CH), 3.36–3.20 (dd, 1H, -CH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 170.85, 167.22, 133.63,

133.28, 131.65, 131.32, 130.70, 130.27, 129.93, 129.10, 128.55, 127.99, 127.12, 126.57, 125.65, 125.46, 124.59, 124.38, 61.28, 47.64 ppm. MS (m/z): 452.5 (M+1). Elemental Anal. Calcd for $C_{31}H_{21}N_3O$: C, 82.46; H, 4.69; N, 9.31. Found: C, 82.35; H, 4.62; N, 9.38.

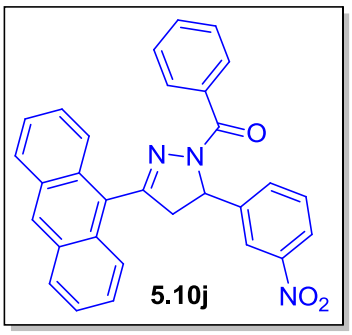
5.5.9 3-(Anthracen-10-yl)-5-(3-fluorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10i)



5.10i

Brown solid. Yield: 85%. m.p. 55–57 °C. IR (KBr) cm^{-1} 3054.62 (Aromatic C-H), 2904.65 (Aliphatic C-H), 2836.38 (Aliphatic C-H), 1712.07 (C=O) and 1641.16 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.51 (s, 1H, Ar-H), 8.07–8.00 (q, 4H, Ar-H), 7.91–7.88 (d, J=7.64 Hz, 2H, Ar-H),7.76–7.73 (d, J=8.47 Hz, 2H, Ar-H), 7.50–7.31 (m, 9H, Ar-H), 7.08–7.03 (t, 1H, Ar-H), 6.08–6.02 (dd,1H, -CH), 3.97–3.87 (dd, 1H, -CH), 3.29–3.21 (dd, 1H, -CH) ppm.^{13}C-NMR (300 MHz, $CDCl_3$) δ 167.14, 165.15, 161.88, 156.02, 144.28, 134.24, 133.96, 131.79, 131.39, 130.23, 129.07, 127.94, 127.04, 125.62, 124.60, 121.26, 115.11, 112.94, 61.04, 47.69 ppm. MS (*m/z*): 445.5 (M+1). Elemental Anal. Calcd for $C_{30}H_{21}N_2OF$: C, 81.06; H, 4.76; N, 6.30. Found: C, 81.23; H, 4.72; N, 6.25.

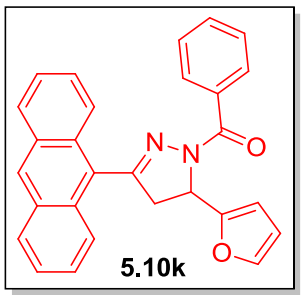
5.5.10 (3-(Anthracen-10-yl)-4,5-dihydro-5-(3-nitrophenyl)pyrazol-1-yl)(phenyl)methanone (5.10j)



5.10j

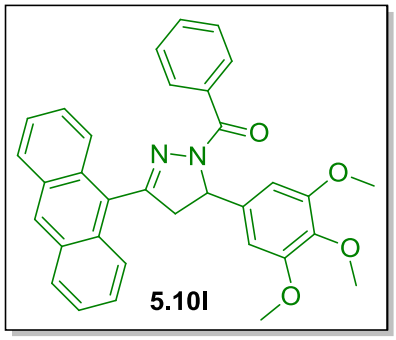
Yellow solid. Yield: 92%. m.p. 102–104 °C. IR (KBr) cm^{-1} 3054.06 (Aromatic C-H), 1708.59 (C=O) and 1639.00 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H, Ar-H), 8.25 (s, 1H, Ar-H), 8.03–7.74 (m, 7H, Ar-H), 7.53–7.30 (m, 11H, Ar-H), 5.99–5.94 (dd, 1H, -CH), 3.92–3.82 (dd, 1H, -CH), 3.33–3.25 (dd, 1H, -CH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 167.17, 156.52, 142.73, 139.17, 135.08, 134.14, 131.86, 131.30, 130.31, 129.94, 128.97, 127.90, 127.32, 125.63, 124.86, 121.26, 119.88, 117.85, 61.57, 47.86 ppm. MS (*m/z*): 472.5 (M+1). Elemental Anal. Calcd for $C_{30}H_{21}N_3O_3$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.32; H, 4.53; N, 8.85.

5.5.11 3-(Anthracen-10-yl)-5-(furan-2-yl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10k)



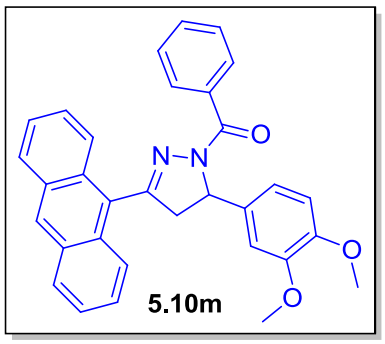
Brown solid. Yield: 83%. m.p. 84–86 °C. IR (KBr) cm^{-1} 3053.62 (Aromatic C-H), 2904.60 (Aliphatic C-H), 1697.66 (C=O) and 1639.75 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.53–8.42 (t, 1H, Ar-H), 8.32–8.30 (t,1H, Ar-H), 8.08–7.78 (m, 5H, Ar-H), 7.57–6.80 (m, 10H, Ar-H), 6.58–6.44 (m, 1H, Ar-H), 6.18–6.12 (q, 1H, -CH), 3.79–3.72 (dd, 1H, -CH), 3.62–3.55 (dd, 1H, -CH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 167.09, 156.03, 141.5, 134.26, 131.37, 131.20, 130.75, 130.23, 128.95, 128.91, 128.29, 127.83, 127.37, 126.93, 125.64, 125.47, 125.04, 124.38, 61.50, 47.92 ppm. MS (*m/z*): 417.4 (M+1). Elemental Anal. Calcd for $C_{28}H_{20}N_2O_2$: C, 80.75; H, 4.84; N, 6.73. Found: C, 80.65; H, 4.79; N, 6.81.

5.5.12 3-(Anthracen-10-yl)-4,5-dihydro-5-(3,4,5-trimethoxyphenyl)pyrazol-1-yl)(phenyl) methanone (5.10l)



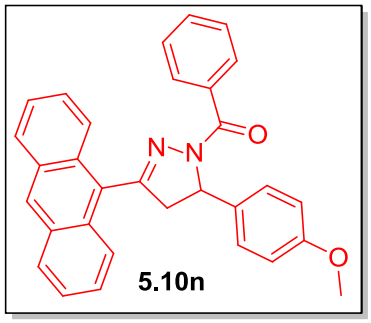
Brown solid. Yield: 90%. m.p. 68–70 °C. IR (KBr) cm^{-1} 3054.36 (Aromatic C-H), 2963.45 (Aliphatic C-H), 2906.03 (Aliphatic C-H), 2834.64 (Aliphatic C-H), 1710.13 (C=O) and 1641.57 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 1H, Ar-H), 8.03 (m,1H, Ar-H), 7.78 (s, 1H, Ar-H), 7.48–7.25 (m, 8H, Ar-H),6.75 (s, 2H, Ar-H), 6.03–5.98 (dd, 1H, -CH), 3.92–3.69 (d, J=11.23 Hz, 9H, Ar-OCH_3; dd, 1H, -CH), 3.34–3.27 (dd, 1H, -CH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 167.00, 156.48, 154.06, 137.60, 134.25, 131.76, 131.33, 131.26, 130.05, 129.11, 127.97, 127.34, 126.93, 125.61, 125.44, 124.65, 103.85, 102.29, 61.55, 60.98, 56.40, 56.24, 47.87 ppm. MS (*m/z*): 517.5 (M+1). Elemental Anal. Calcd for $C_{33}H_{28}N_2O_4$: C, 76.73; H, 5.46; N, 5.42. Found: C, 76.65; H, 5.41; N, 5.48.

5.5.13 3-(Anthracen-10-yl)-4,5-dihydro-5-(3,4-dimethoxyphenyl)pyrazol-1-yl)(phenyl) methanone (5.10m)



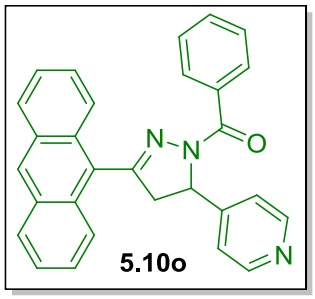
Yellow solid. Yield: 85%. m.p. 65–67 ^{o}C. IR KBr) cm^{-1} 3053.23 (Aromatic C-H), 2906.07 (Aliphatic C-H), 2833.98 (Aliphatic C-H), 1705.07 (C=O) and 1640.77 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 1H, Ar-H), 8.02–7.79 (m, 5H, Ar-H), 7.48–6.81 (m, 9H, Ar-H), 6.05–6.00 (dd, 1H, -CH), 3.95–3.67 (d, 6H, Ar-OCH_3; dd, 1H, -CH), 3.34–3.18 (dd, 1H, -CH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 167.44, 156.44, 141.46, 134.26, 131.77, 131.18, 130.13, 129.08, 128.82, 127.91, 126.93, 125.61, 124.74, 119.62, 117.84, 111.89, 111.36, 108.82, 61.20, 56.16, 56.05, 47.86 ppm. MS (*m/z*): 487.5 (M+1). Elemental Anal. Calcd for $C_{32}H_{26}N_2O_3$: C, 78.99; H, 5.39; N, 5.76. Found: C, 78.89; H, 5.34; N, 5.81.

5.5.14 3-(Anthracen-10-yl)-4,5-dihydro-5-(4-methoxyphenyl)pyrazol-1-yl)(phenyl) methanone (5.10n)



Yellow solid. Yield: 94%. m.p. 151–153 ^{o}C. IR (KBr) cm^{-1} 3055.93 (Aromatic C-H), 2963.02 (Aliphatic C-H), 2910.91 (Aliphatic C-H), 2834.98 (Aliphatic C-H), 1721.60 (C=O) and 1644.22 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.51 (s, 1H, Ar-H), 8.17–7.95 (m, 5H, Ar-H), 7.94–7.92 (d, J=7.67 Hz, 2H, Ar-H), 7.64–7.57 (q, 6H, Ar-H), 7.51–7.32 (m, 3H, Ar-H), 7.01–6.98 (d, J=8.44 Hz, 2H, Ar-H), 6.06–6.01 (dd, 1H, -CH), 3.96–3.86 (dd, 1H, -CH), 3.83 (s, 3H, Ar-OCH_3), 3.31–3.23 (dd, 1H, -CH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 167.12, 159.31, 156.08, 134.67, 134.34, 133.89, 131.35, 131.17, 130.20, 129.95, 129.03, 128.94, 127.86, 127.00, 126.94, 125.59, 124.78, 114.71, 61.01, 55.51, 47.93 ppm. MS (*m/z*): 457.5 (M+1). Elemental Anal. Calcd for $C_{31}H_{24}N_2O_2$: C, 81.56; H, 5.30; N, 6.14. Found: C, 81.45; H, 5.36; N, 6.21.

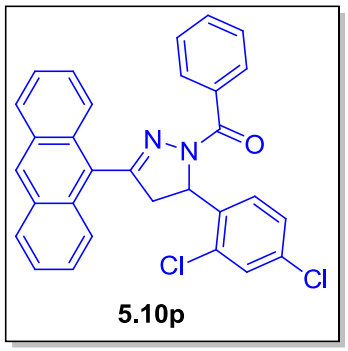
5.5.15 (3-(anthracen-10-yl)-4,5-dihydro-5-(pyridin-4-yl)pyrazol-1-yl)(phenyl)methanone (5.10o)



5.10o

Brown solid. Yield: 90%. m.p. 84–86 °C. IR (KBr) cm^{-1} 3052.5 (Aromatic C-H), 2963.96 (Aliphatic C-H), 2906.71 (Aliphatic C-H), 1713.19 (C=O) and 1641.78 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.72 (s, 1H, Ar-H), 8.56–8.54 (d, J=8.50 Hz, 1H, Ar-H), 8.316 (s, 1H, Ar-H), 8.05–7.99 (m, 4H, Ar-H), 7.85–7.70 (q,3H, Ar-H),7.49–7.45 9 (m, 7H, Ar-H), 7.12–7.02 (m, 1H, Ar-H), 6.07–6.01 (dd, 1H, -CH),4.01–3.91 (dd, 1H, -CH), 3.28–3.19 (dd, 1H, -CH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 167.89, 155.99, 150.60, 134.27, 131.81, 130.28, 129.15, 128.93, 128.10, 128.03, 127.18, 126.61, 125.69, 125.47, 125.25, 124.42, 120.77, 111.42, 60.58, 47 10 ppm. MS (*m/z*): 428.4 (M+1). Elemental Anal. Calcd for $C_{29}H_{21}N_3O$: C, 81.48; H, 4.95; N, 9.83. Found: C, 81.36; H, 4.91; N, 9.94.

5.5.16 (3-(anthracen-10-yl)-5-(2,4-dichlorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl) methanone (5.10p)

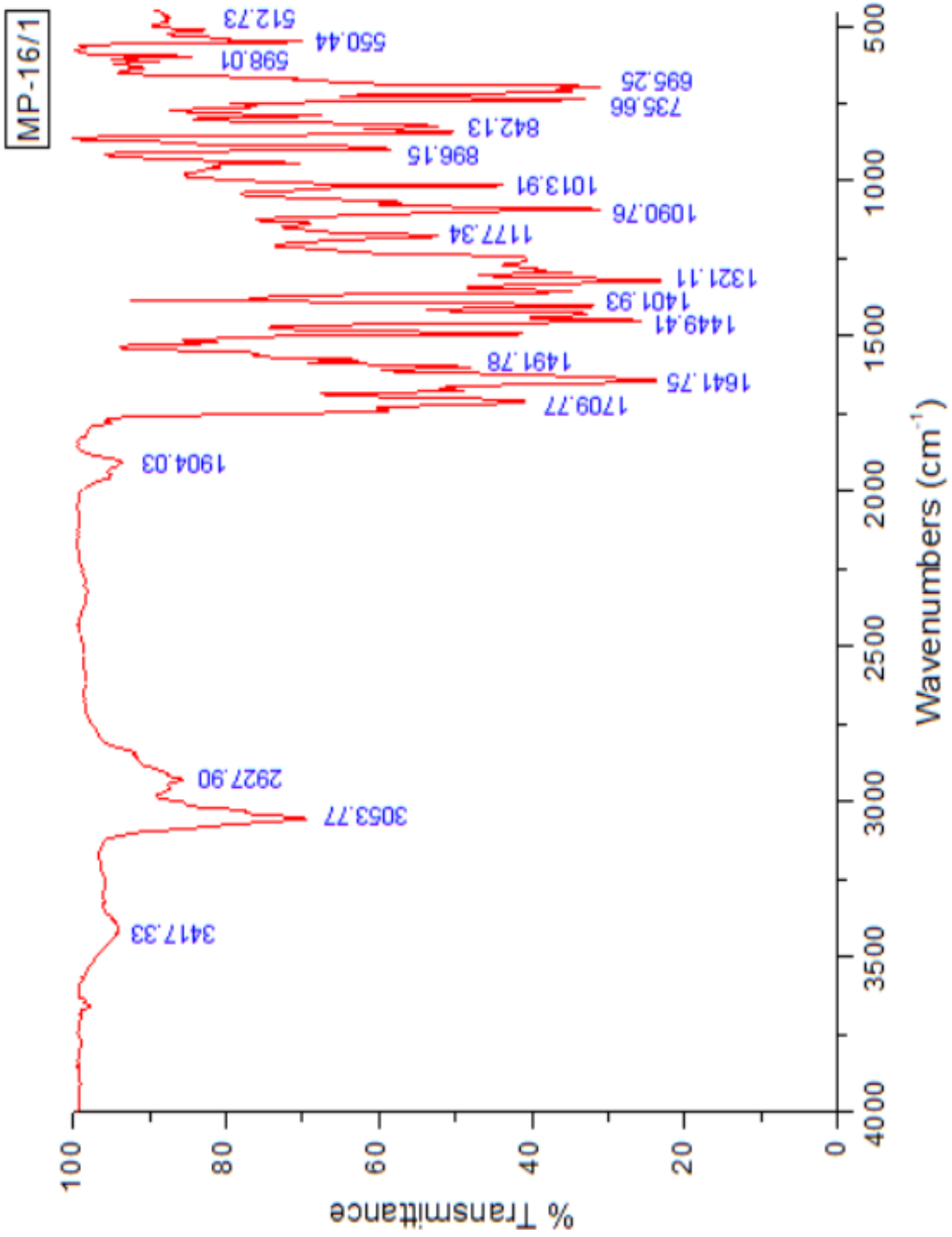


5.10p

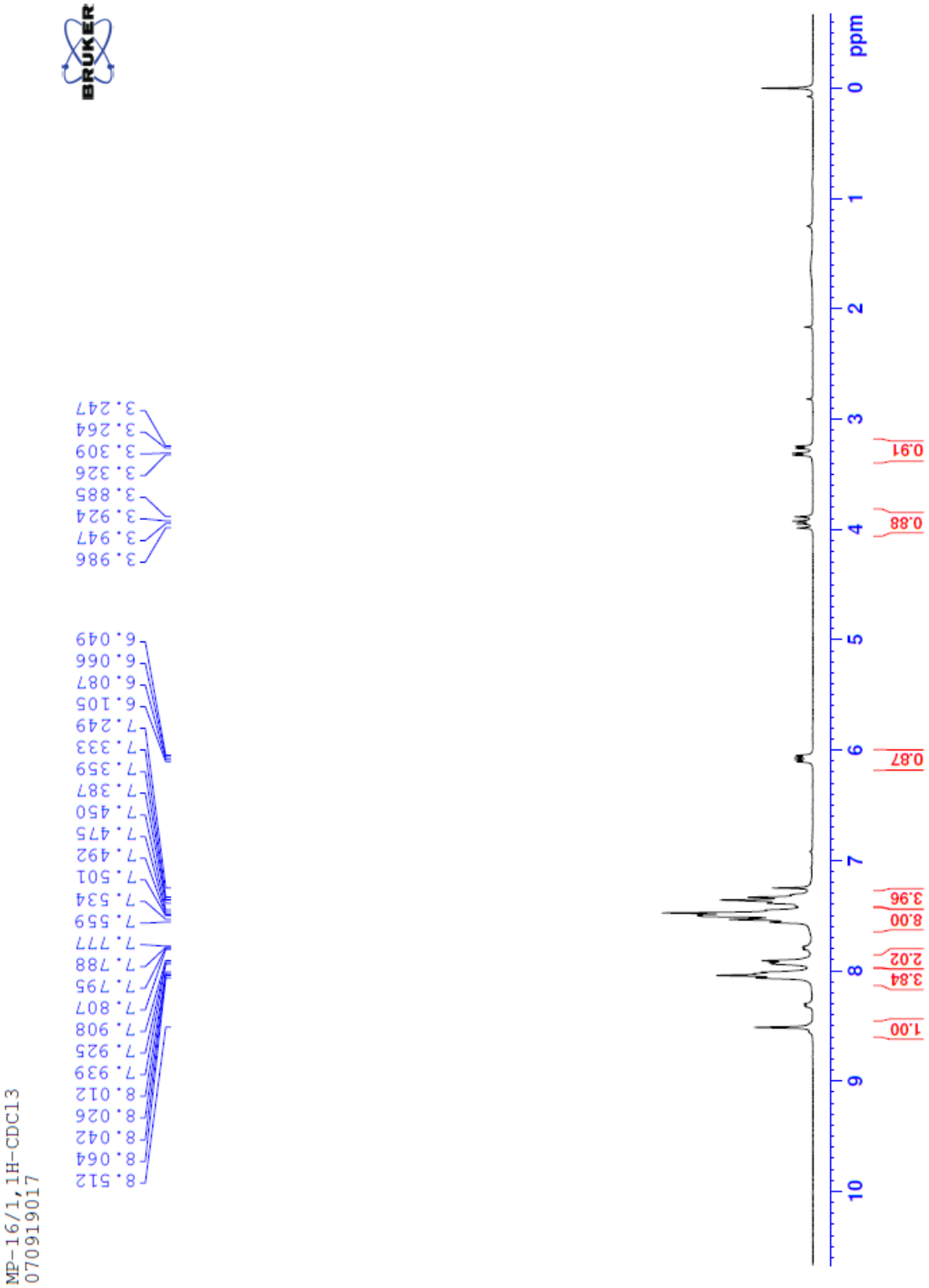
Yellow solid. Yield: 92%. m.p. 60–62 °C. IR (KBr) cm^{-1} 3058.79 (Aromatic C-H), 2929.81 (Aliphatic C-H), 1724.91 (C=O) and 1644.50 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H, Ar-H), 8.33–8.01 (m, 5H, Ar-H), 7.85–7.82 (q, 1H, Ar-H), 7.70–7.33 (m, 10H, Ar-H), 6.35–6.29 (q, 1H, -CH), 4.08–3.98 (dd, 1H, -CH), 3.21–3.13 (dd, 1H, -CH) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 171.63, 162.51, 156.74, 137.31, 134.67, 133.86, 131.55, 131.30, 130.71, 130.32, 129.10, 129.01, 128.61, 128.01, 127.95, 127.06, 125.63, 124.51, 59.05, 46.49 ppm. MS (*m/z*): 495.1 (M^+). Elemental Anal. Calcd for $C_{30}H_{20}N_2OCl_2$: C, 72.73; H, 4.07; N, 5.65. Found: C, 72.65; H, 4.12; N, 5.62.

5.6 REPRESENTATIVE SPECTRA OF NEWLY SYNTHESIZED ANTHRACENE–BASED 1,3,5-TRISUBSTITUTED PYRAZOLINES

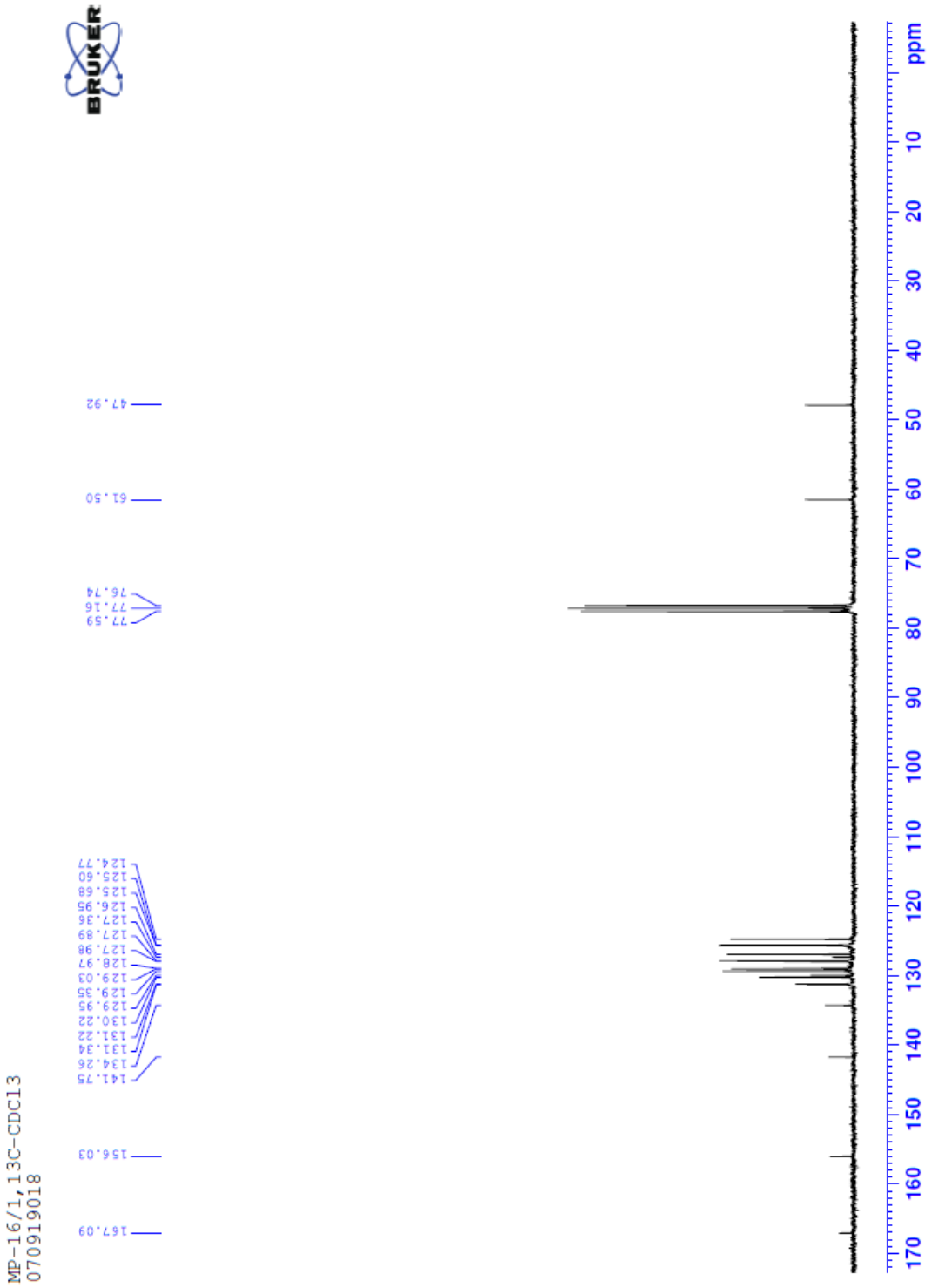
5.6.1 IR (KBr, *v*, cm^{-1}) spectrum of (3-(Anthracen-10-yl)-4,5-dihydro-5- phenylpyrazol-1-yl)(phenyl)methanone (5.10a)



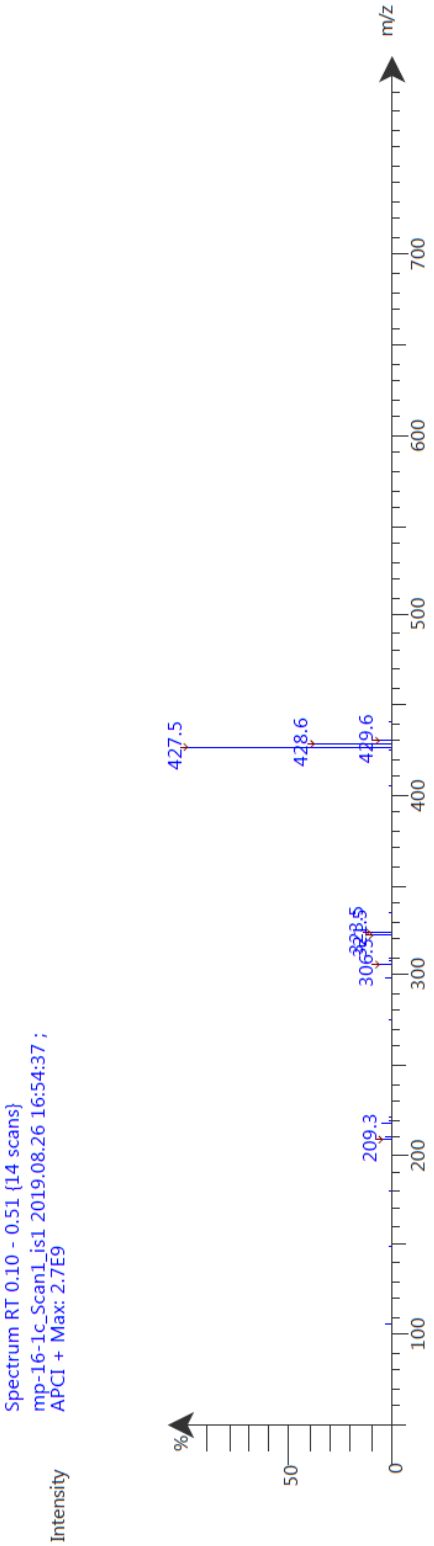
5.6.2 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of (3-(Anthracen-10-yl)-4,5-dihydro-5-phenylpyrazol-1-yl)(phenyl)methanone (5.10a)



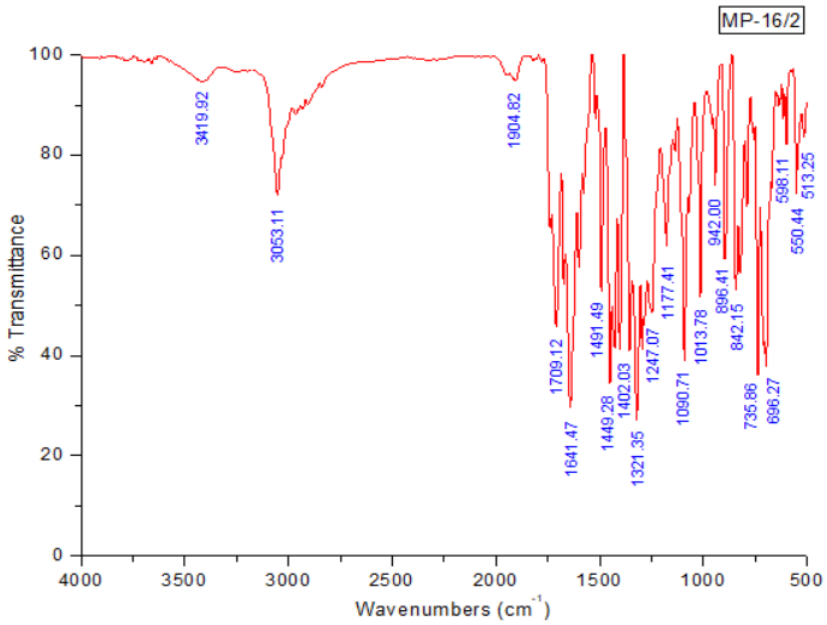
5.6.3 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of (3-(Anthracen-10-yl)-4,5-dihydro-5-phenylpyrazol-1-yl)(phenyl)methanone (5.10a)



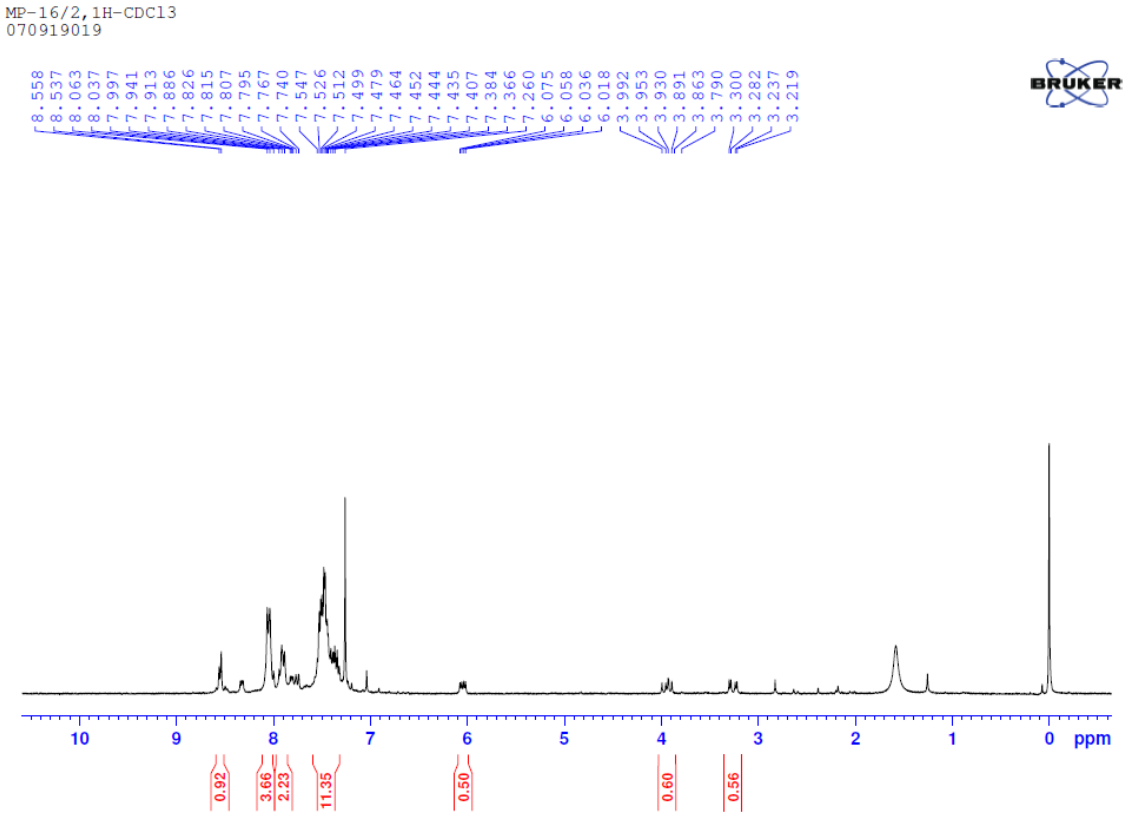
5.6.4 MS spectrum of (3-(Anthracen-10-yl)-4,5-dihydro-5-phenylpyrazol-1-yl)(phenyl) methanone (5.10a)



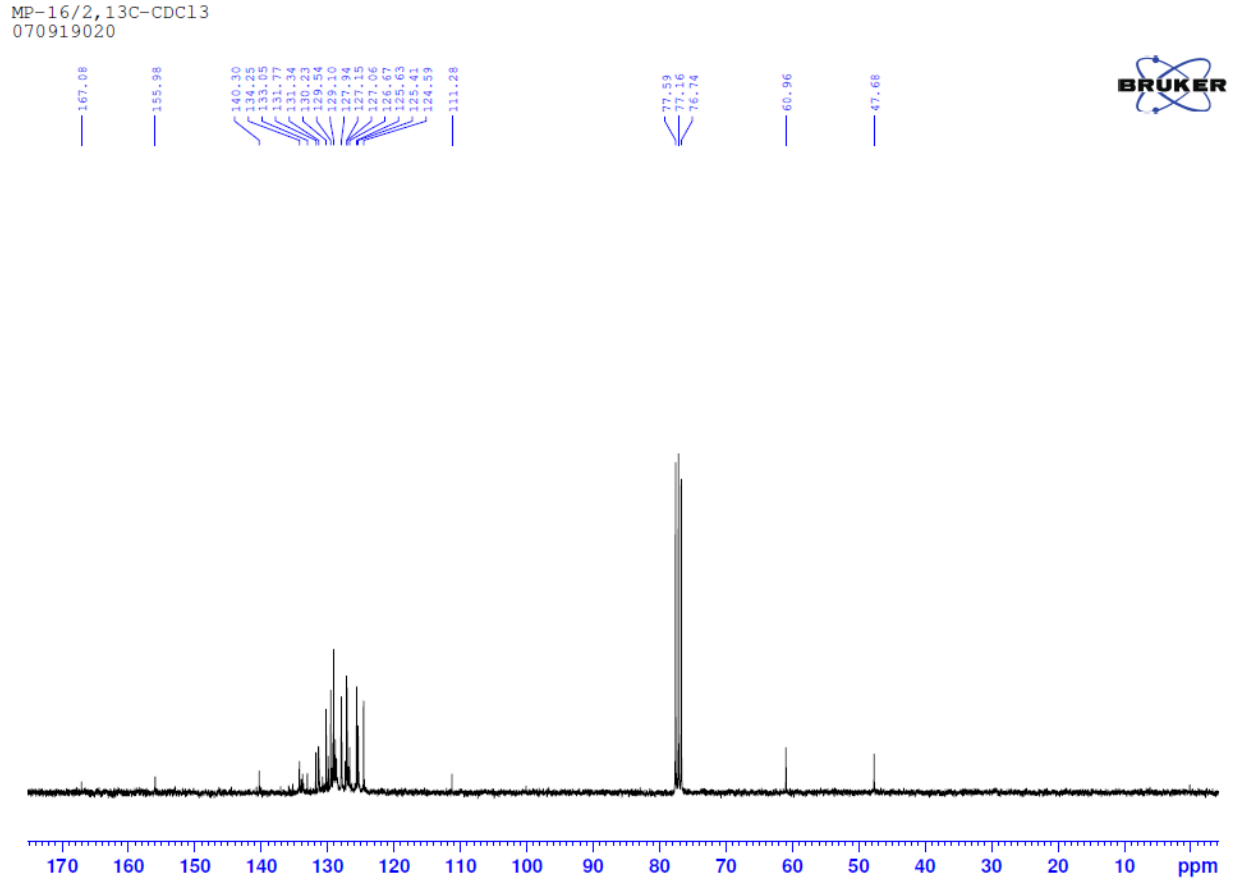
5.6.5 IR (KBr, *v*, cm^{-1}) spectrum of (3-(Anthracen-10-yl)-5-(4-chlorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10b)



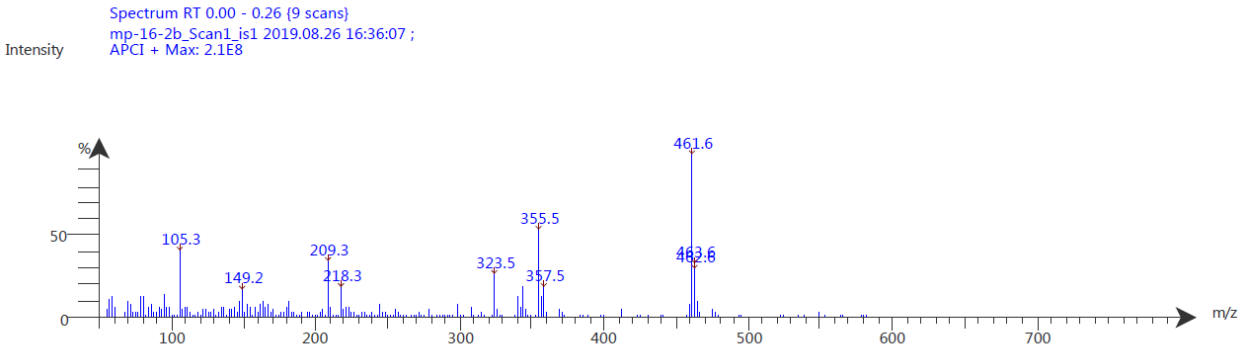
5.6.6 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of (3-(Anthracen-10-yl)-5-(4-chlorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10b)



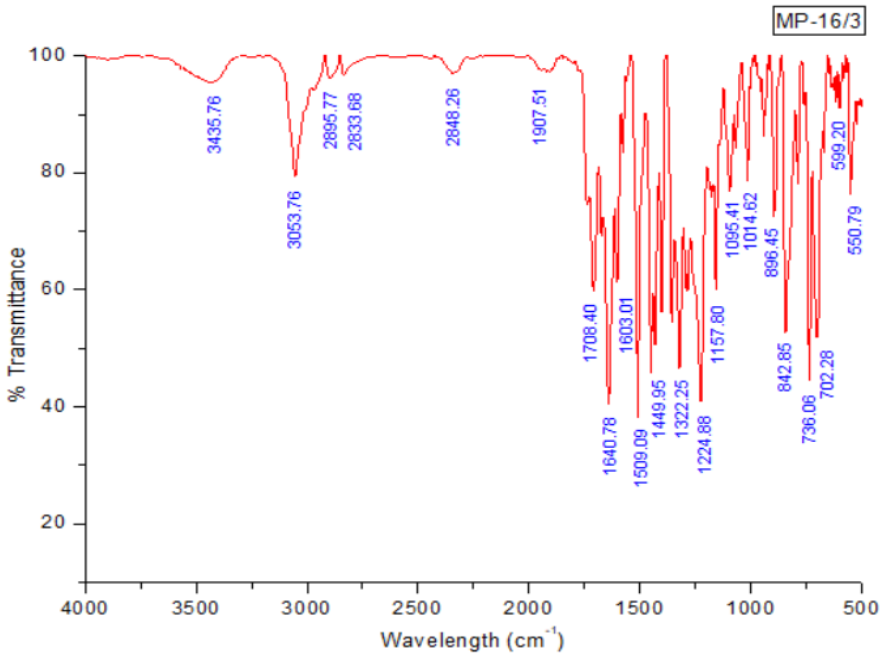
5.6.7 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of (3-(Anthracen-10-yl)-5-(4-chlorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10b)



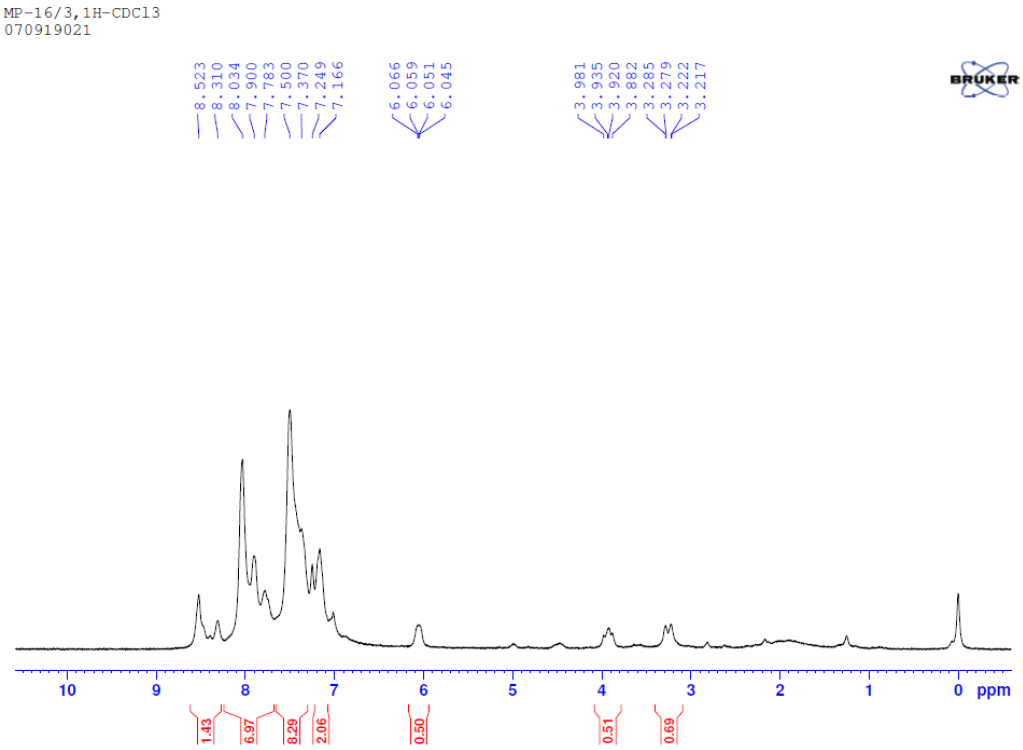
5.6.8 MS spectrum of (3-(Anthracen-10-yl)-5-(4-chlorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10b)



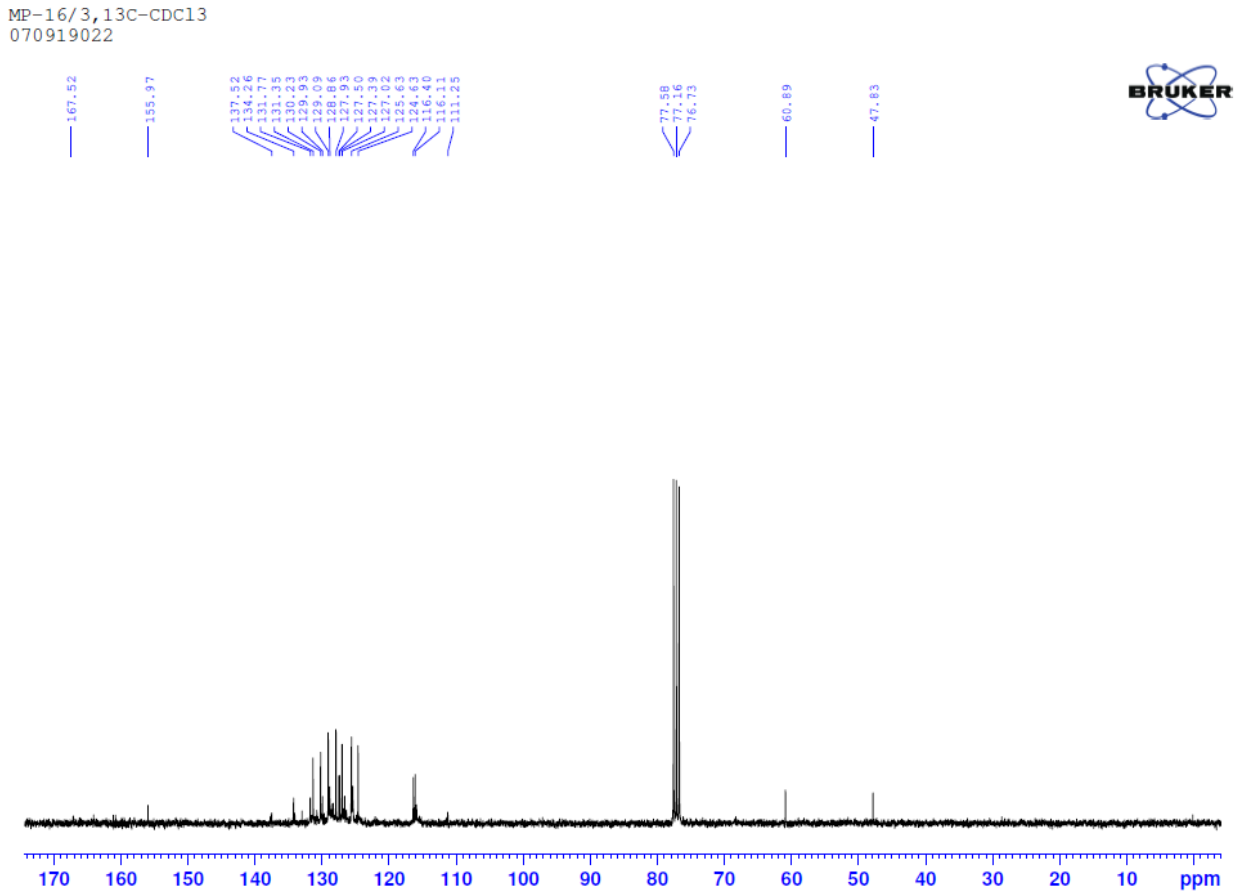
5.6.9 IR (KBr, *v*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-5-(4-fluorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10c)



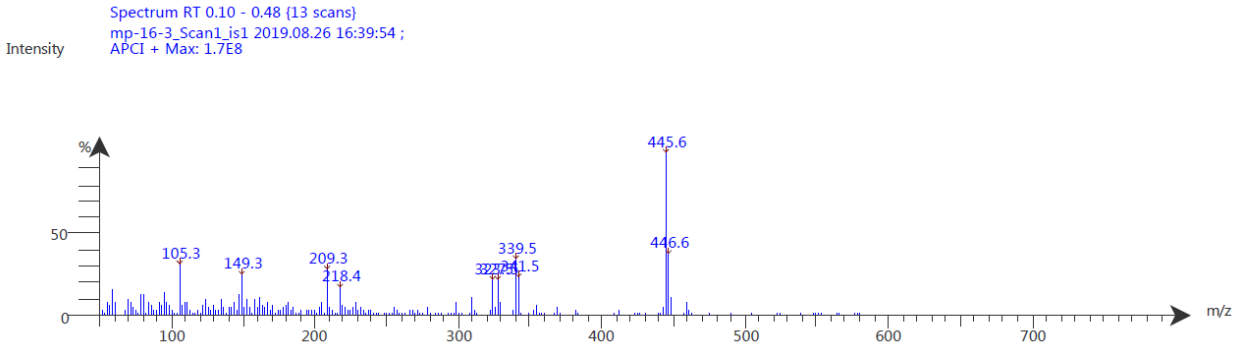
5.6.10 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(4-fluorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10c)



5.6.11 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(4-fluorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10c)



5.6.12 MS spectrum of 3-(Anthracen-10-yl)-5-(4-fluorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10c)



- All the spectra of other anthracene-based 1,3,5-trisubstituted pyrazolines are represented in Appendix: C-5.

5.7 References

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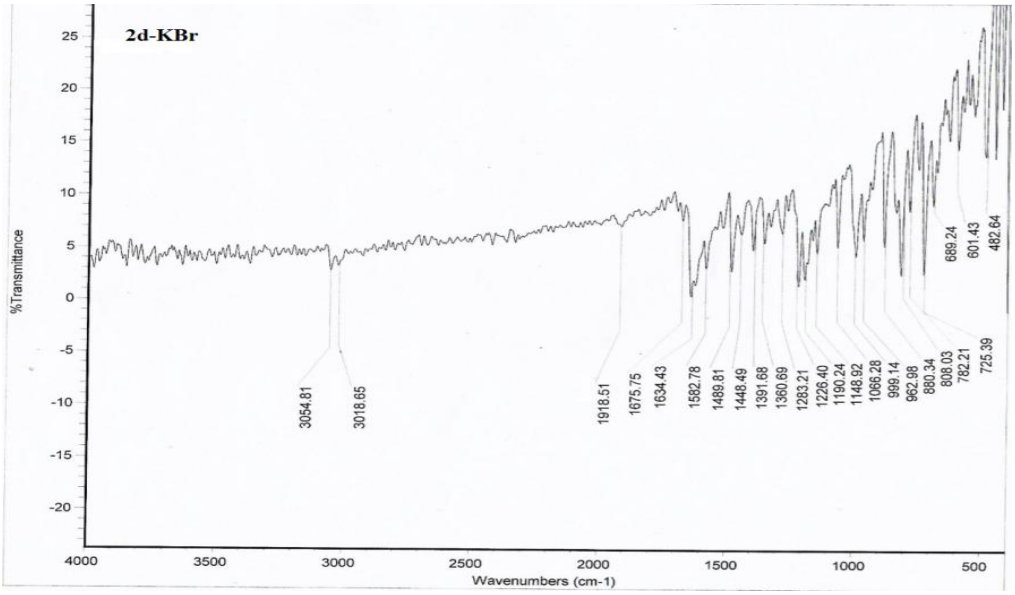
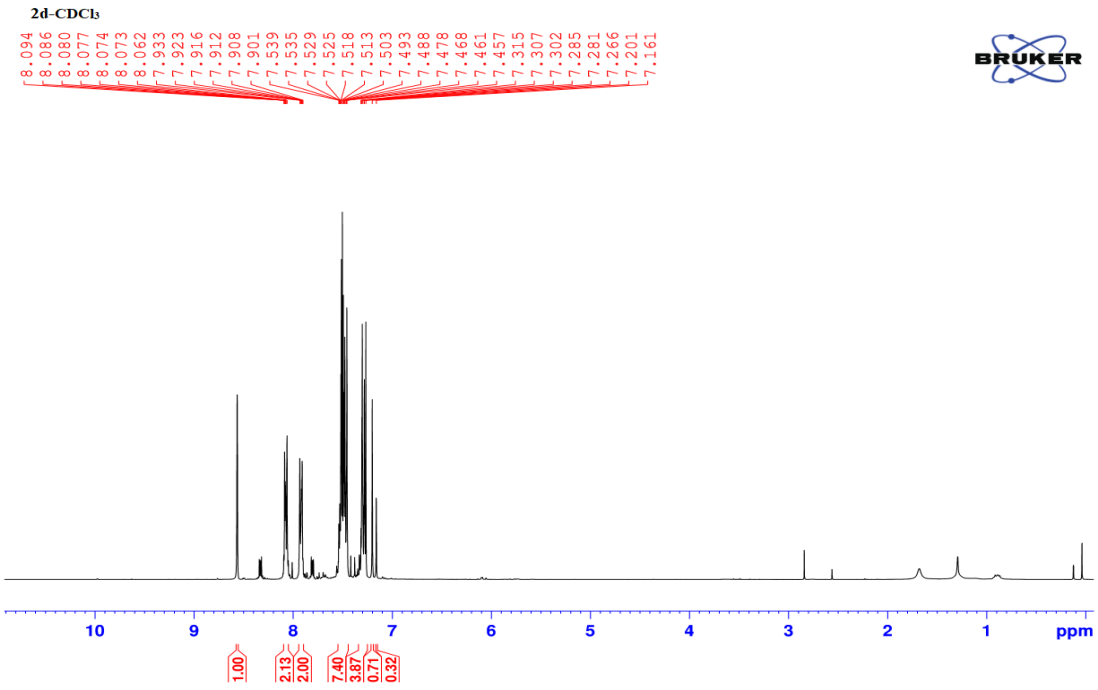
Appendix: C-2

AC2. REPRESENTATIVE SPECTRA OF NEWLY SYNTHESIZED ANTHRACENYL CHALCONES

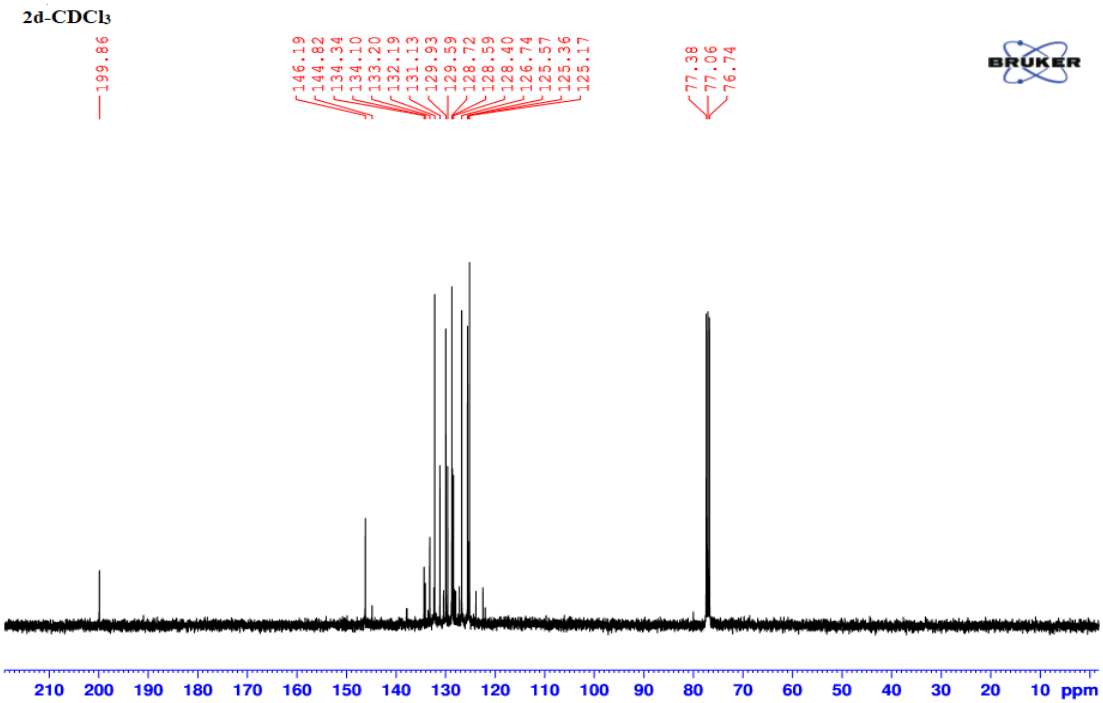
AC2.1 IR (KBr, *v*, cm^{-1}) spectrum of (E)-1-(Anthracen-9-yl)-3-(4-bromophenyl)prop-2-en-1-one (2.10d)



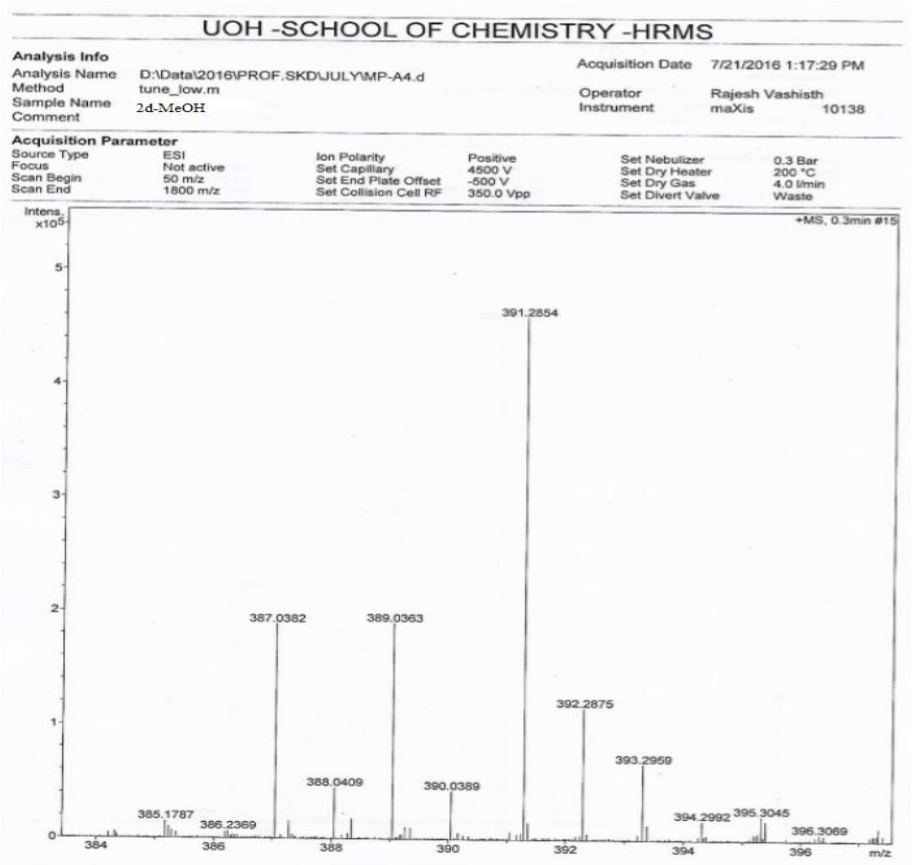
AC2.2 ^{1}H-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(4-bromophenyl)prop-2-en-1-one (2.10d)



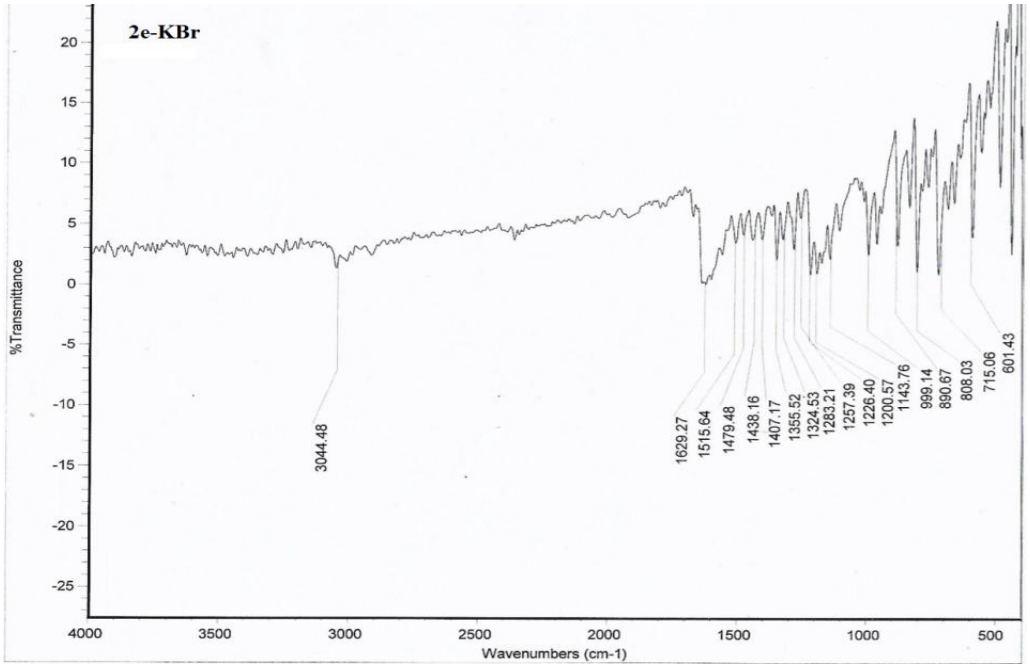
AC2.3 ^{13}C-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(4-bromophenyl)prop-2-en-1-one (2.10d)



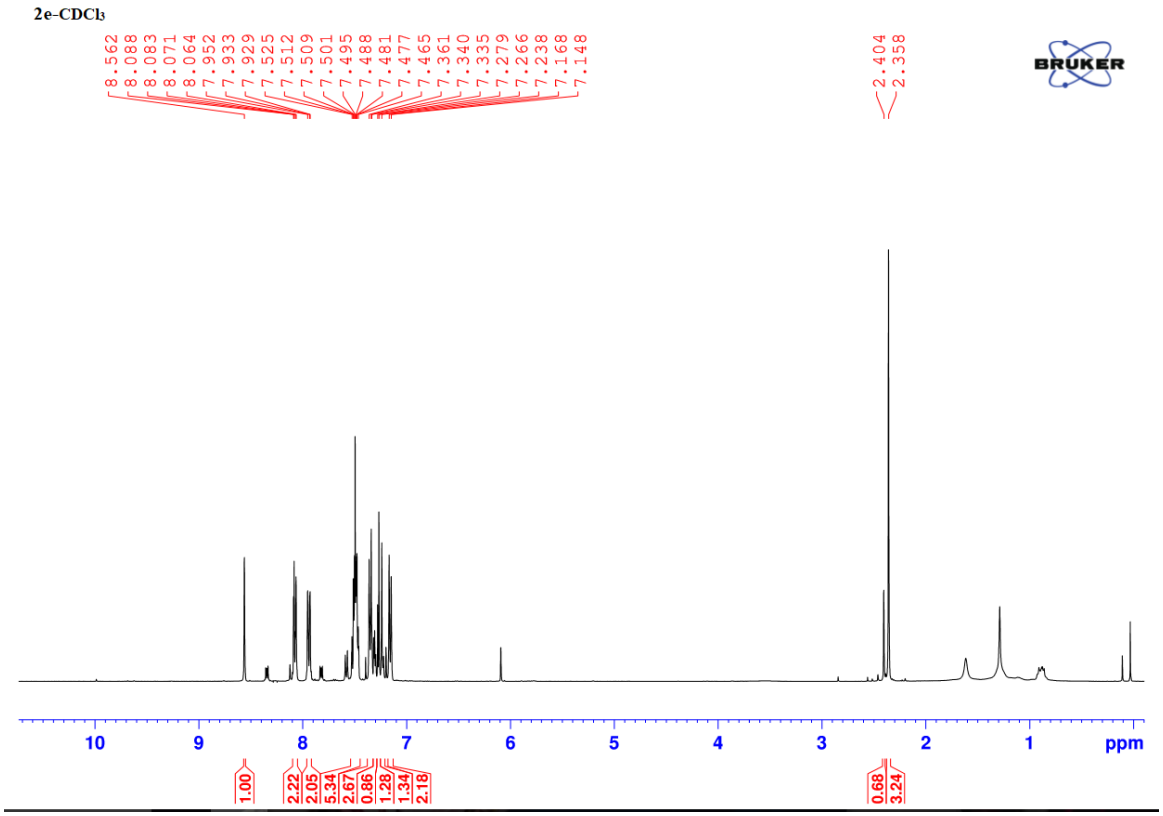
AC2.4 HRMS spectrum of (E)-1-(Anthracen-9-yl)-3-(4-bromophenyl)prop-2-en-1-one (2.10d)



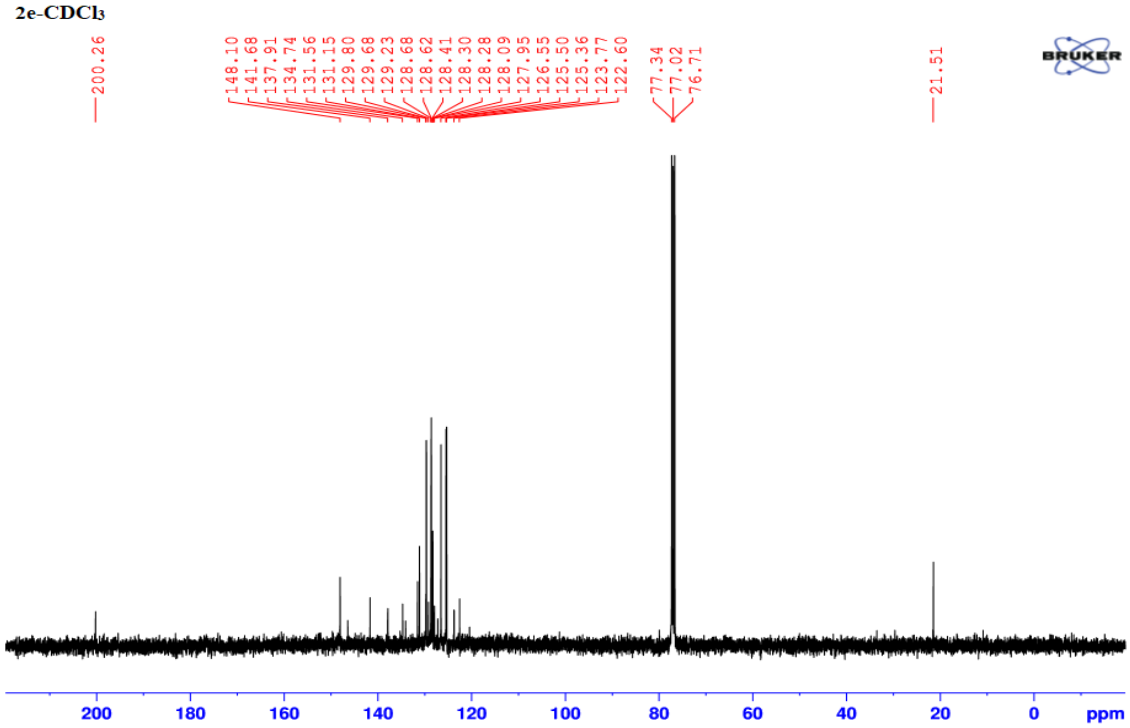
AC2.5 IR (KBr, *v*, cm^{-1}) spectrum of (E)-1-(Anthracen-9-yl)-3-(p-tolyl)prop-2-en-1-one (2.10e)



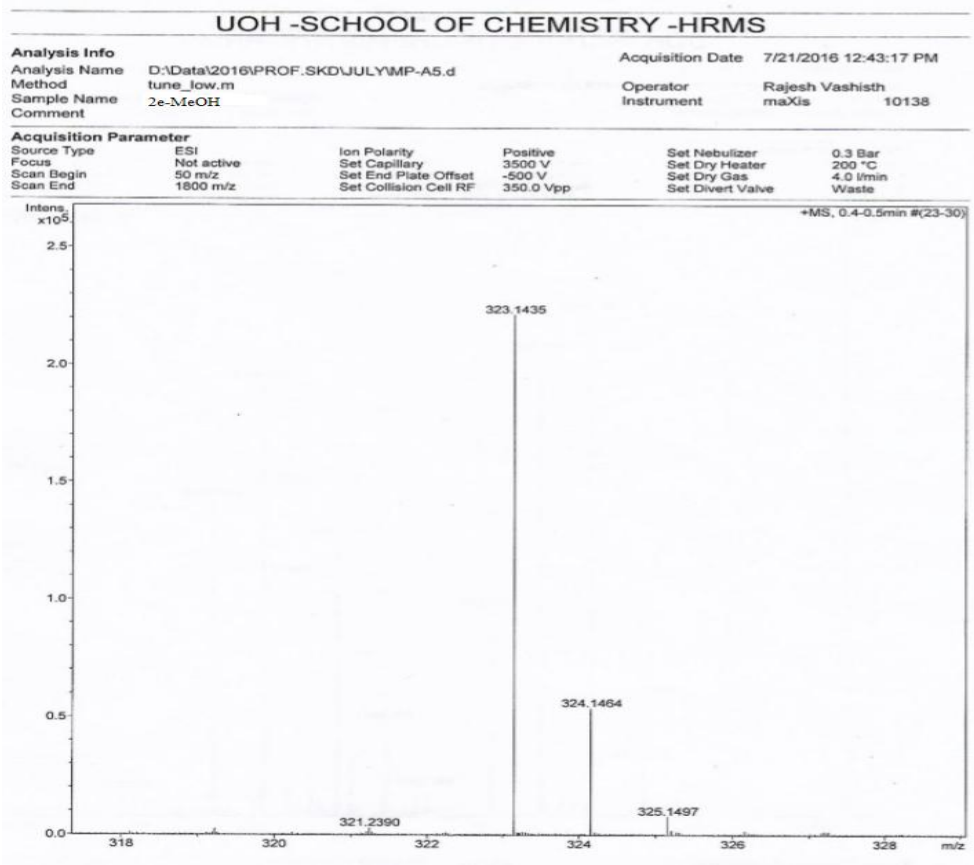
AC2.6 ^{1}H-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(p-tolyl)prop-2-en-1-one (2.10e)



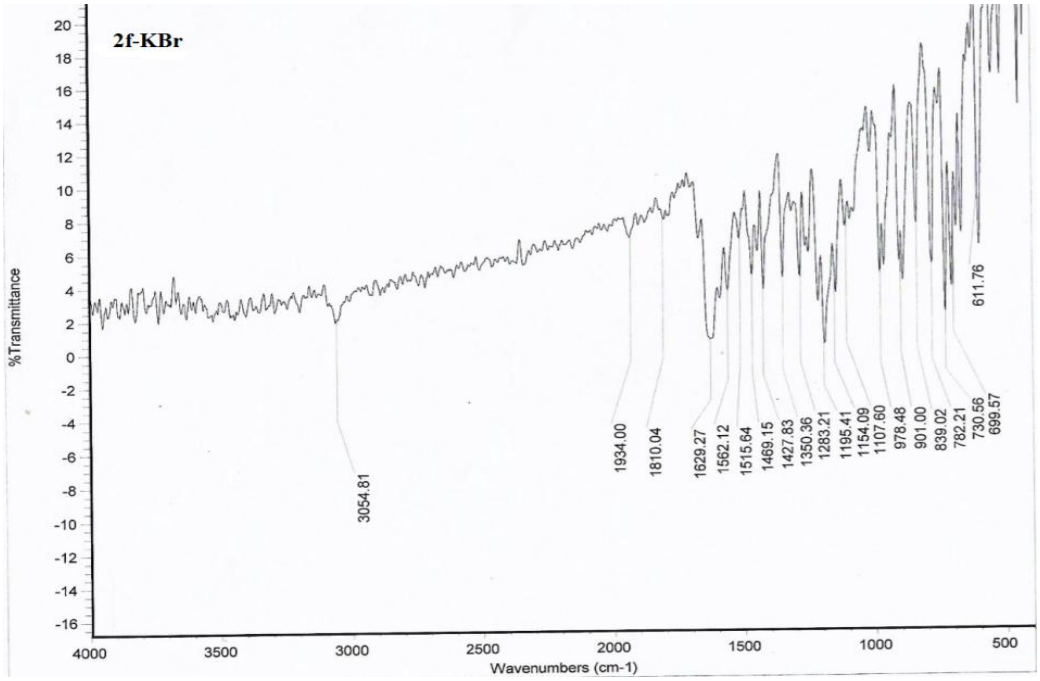
AC2.7 ^{13}C-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(p-tolyl)prop-2-en-1-one (2.10e)



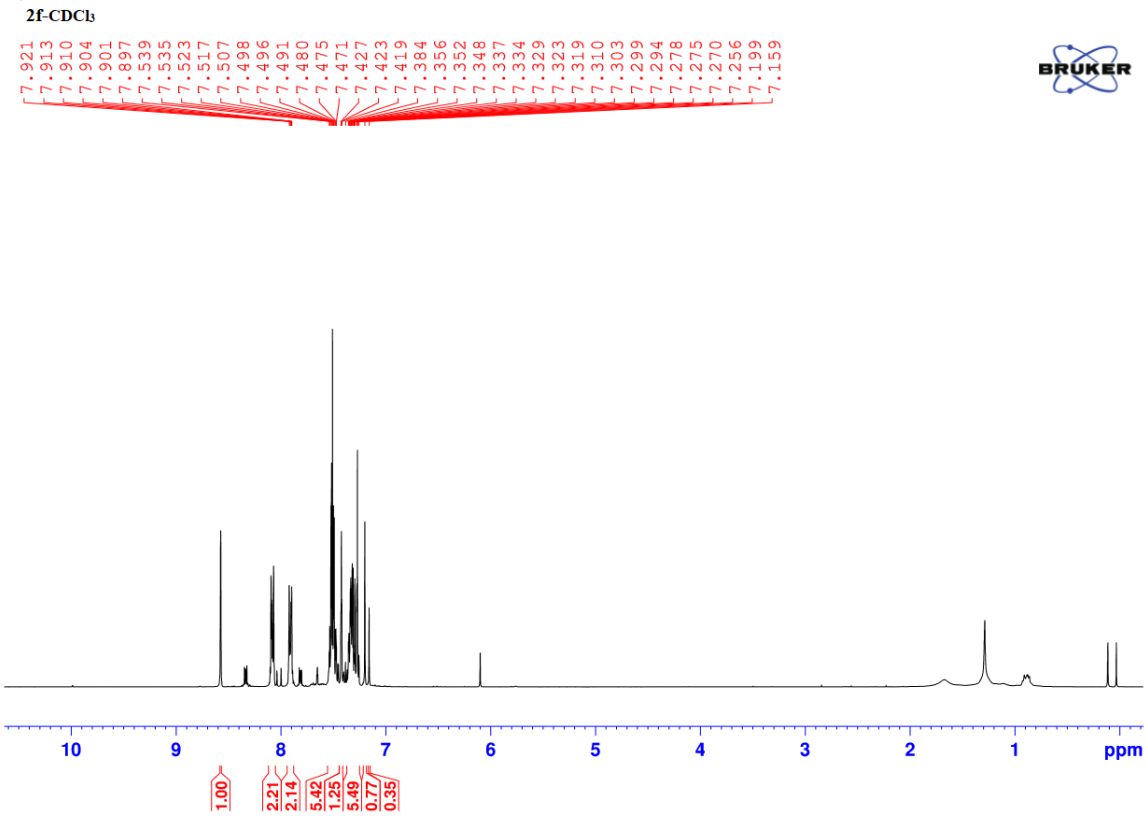
AC2.8 HRMS spectrum of (E)-1-(Anthracen-9-yl)-3-(p-tolyl)prop-2-en-1-one (2.10e)



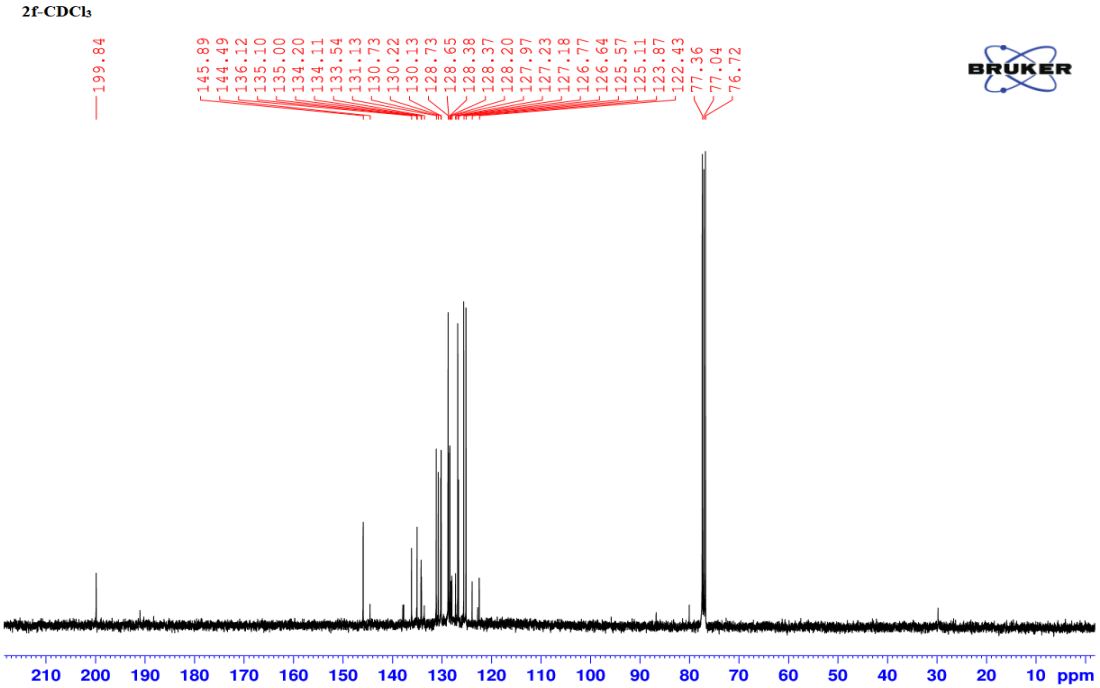
AC2.9 IR (KBr, *v*, cm^{-1}) spectrum of (E)-1-(Anthracen-9-yl)-3-(3-chlorophenyl)prop-2-en-1-one (2.10f)



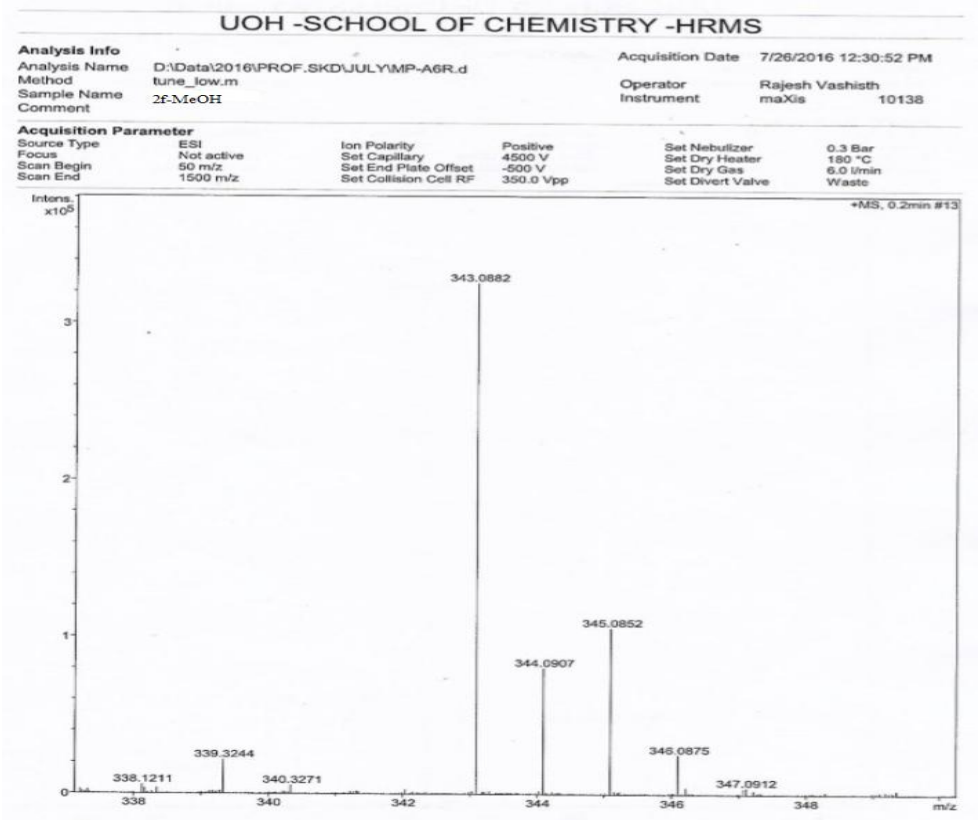
AC2.10 ^{1}H-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(3-chlorophenyl)prop-2-en-1-one (2.10f)



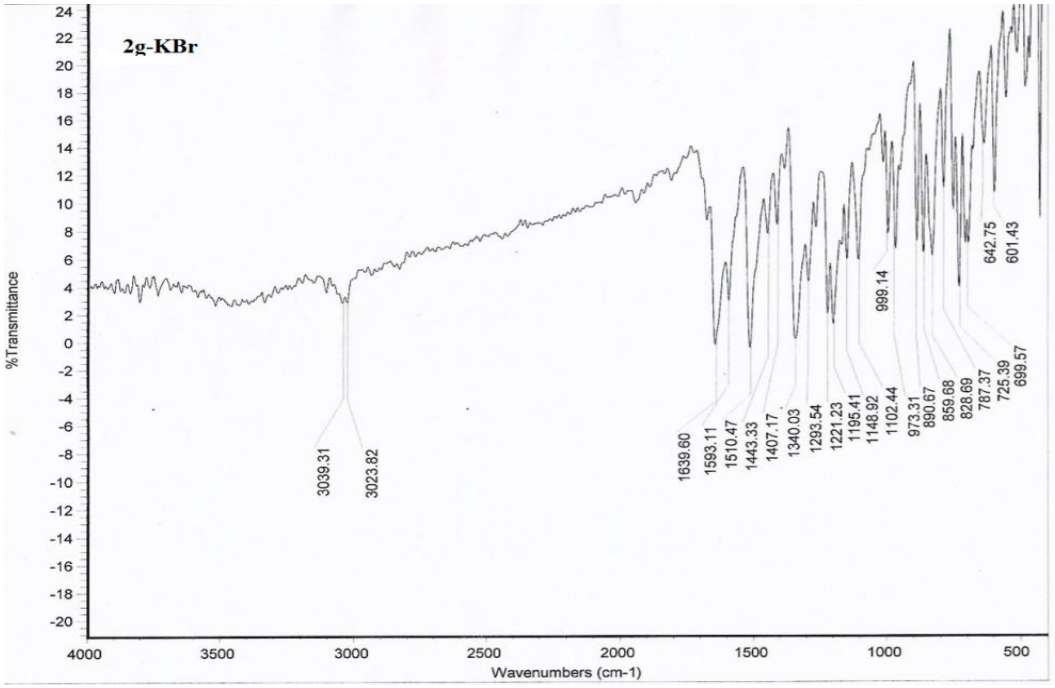
AC2.11 ^{13}C-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(3-chlorophenyl)prop-2-en-1-one (2.10f)



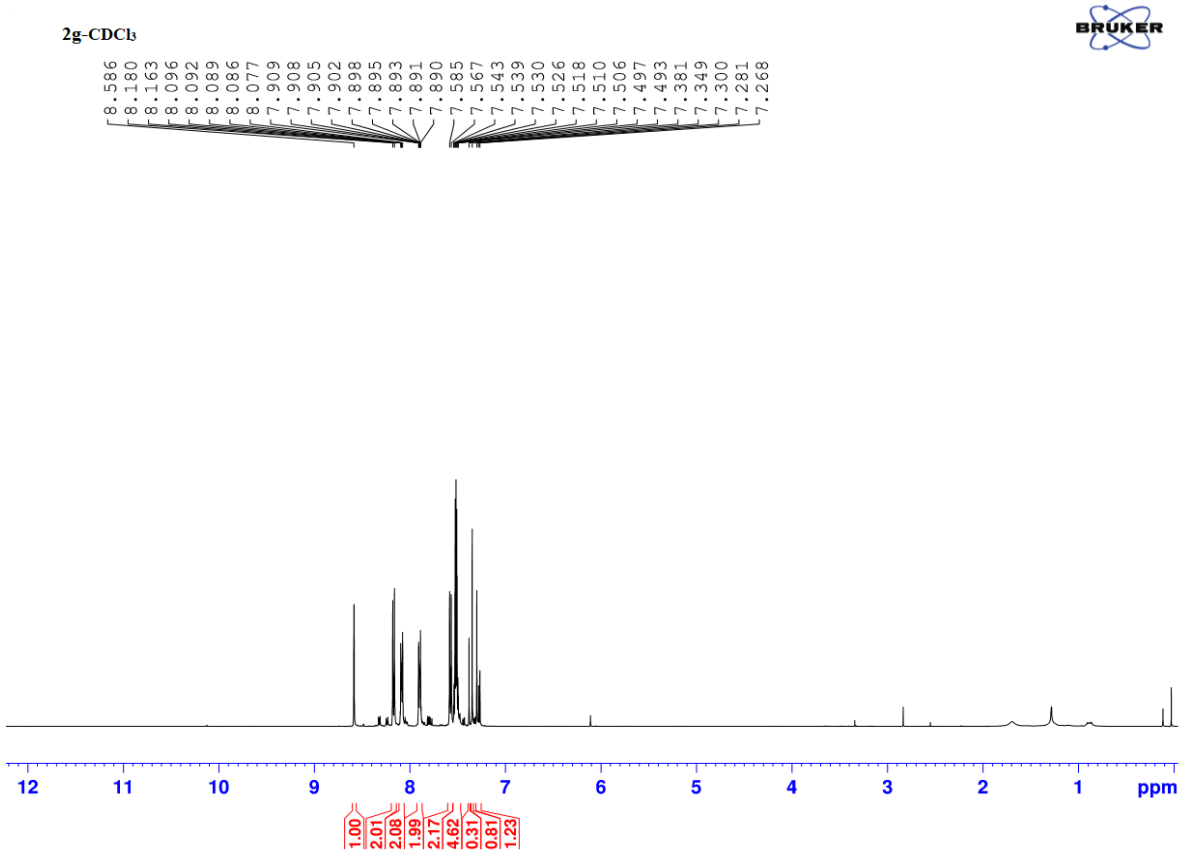
AC2.12 HRMS spectrum of (E)-1-(Anthracen-9-yl)-3-(3-chlorophenyl)prop-2-en-1-one (2.10f)



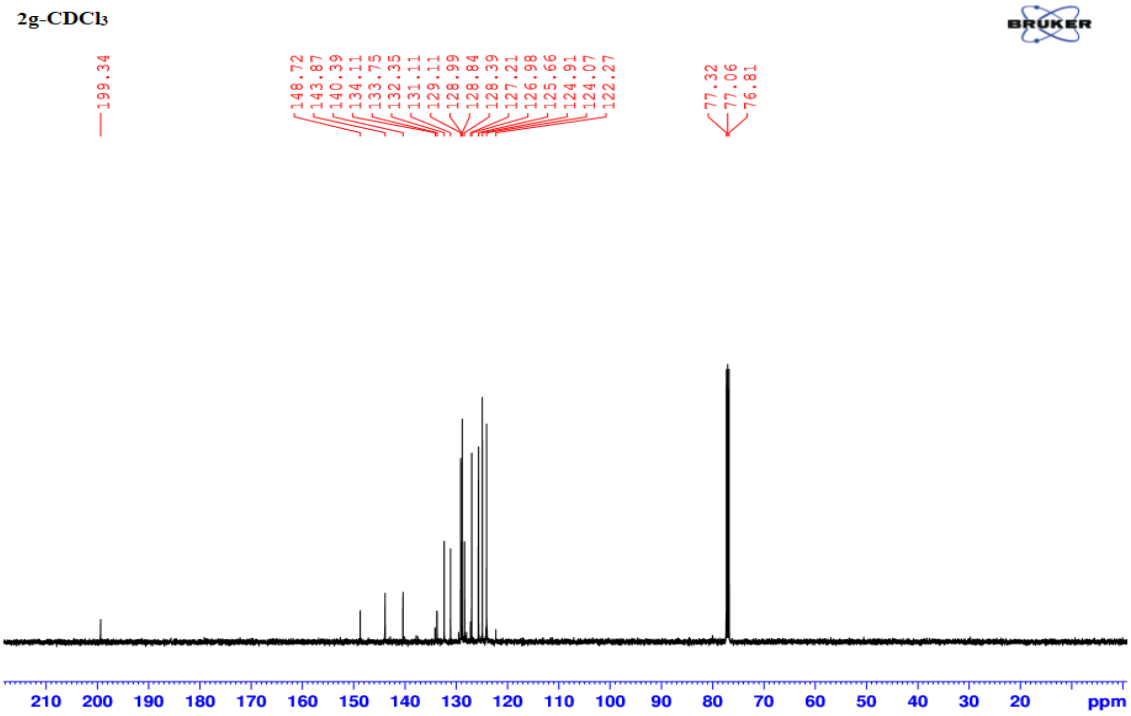
AC2.13 IR (KBr, *v*, cm^{-1}) spectrum of (E)-1-(Anthracen-9-yl)-3-(4-nitrophenyl)prop-2-en-1-one (2.10g)



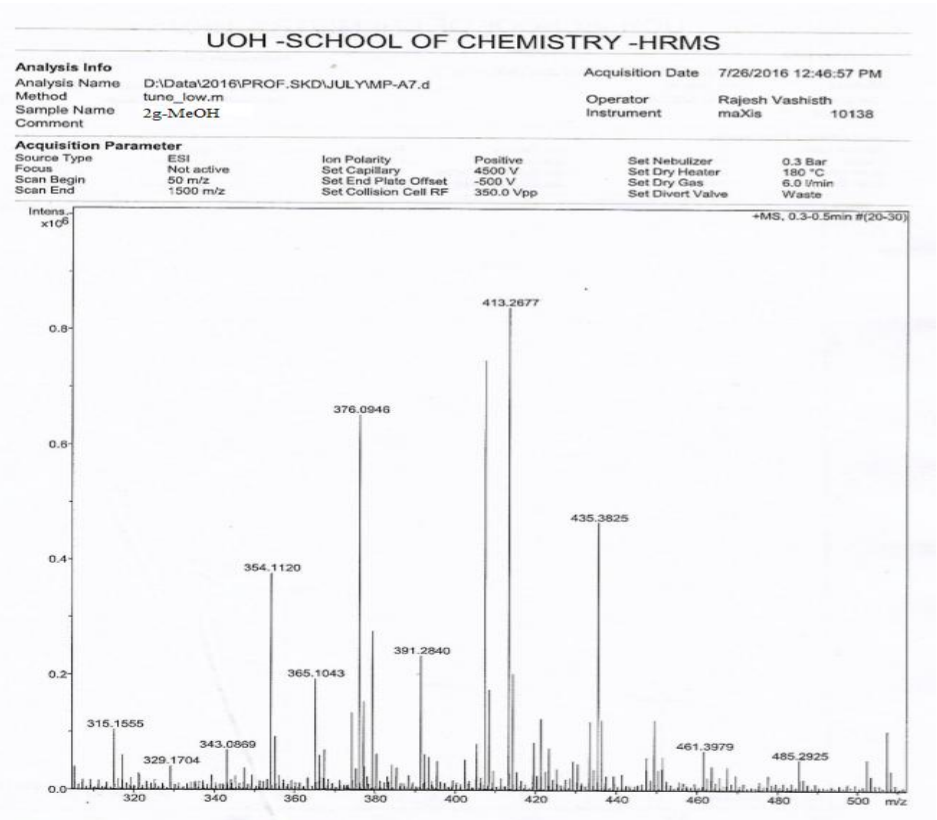
AC2.14 ^{1}H-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(4-nitrophenyl)prop-2-en-1-one (2.10g)



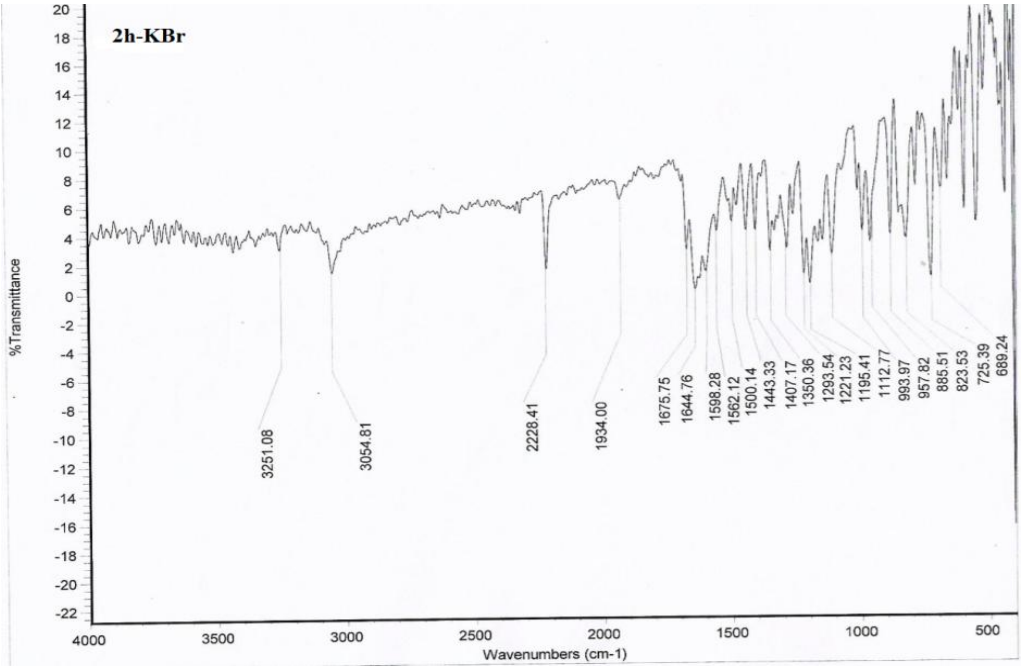
AC2.15 ^{13}C-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(4-nitrophenyl)prop-2-en-1-one (2.10g)



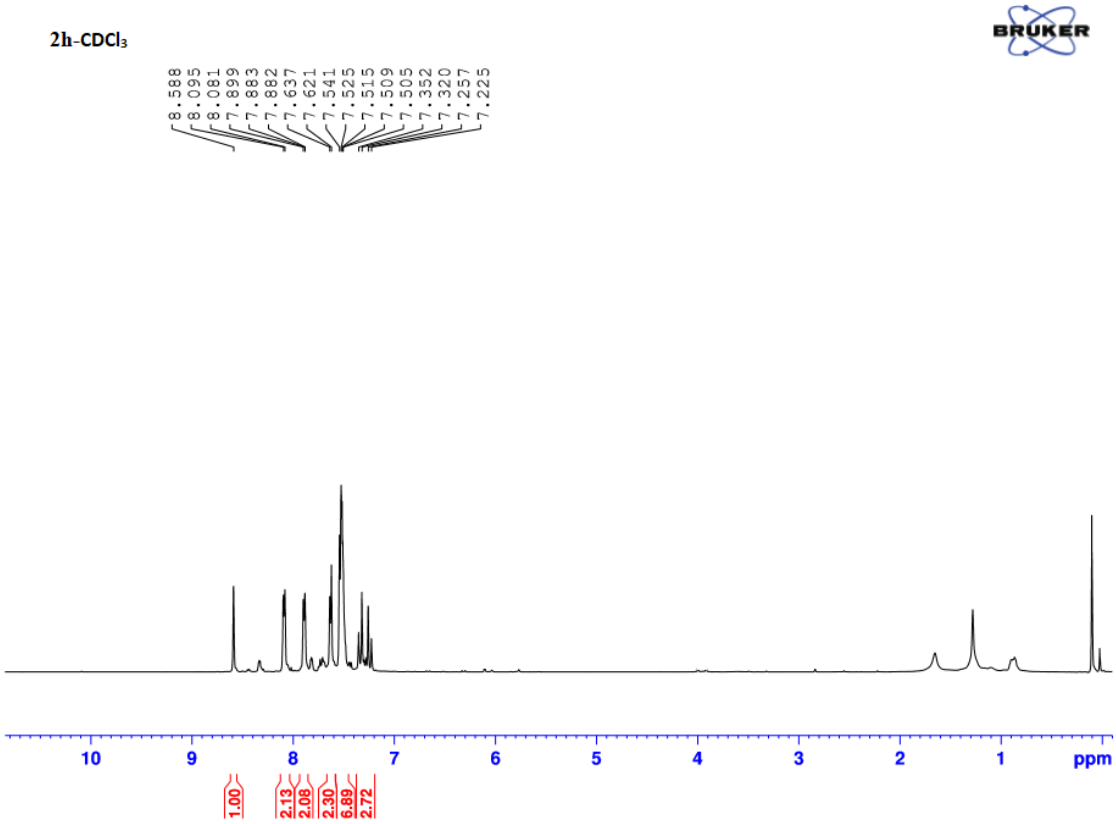
AC2.16 HRMS spectrum of (E)-1-(Anthracen-9-yl)-3-(4-nitrophenyl)prop-2-en-1-one (2.10g)



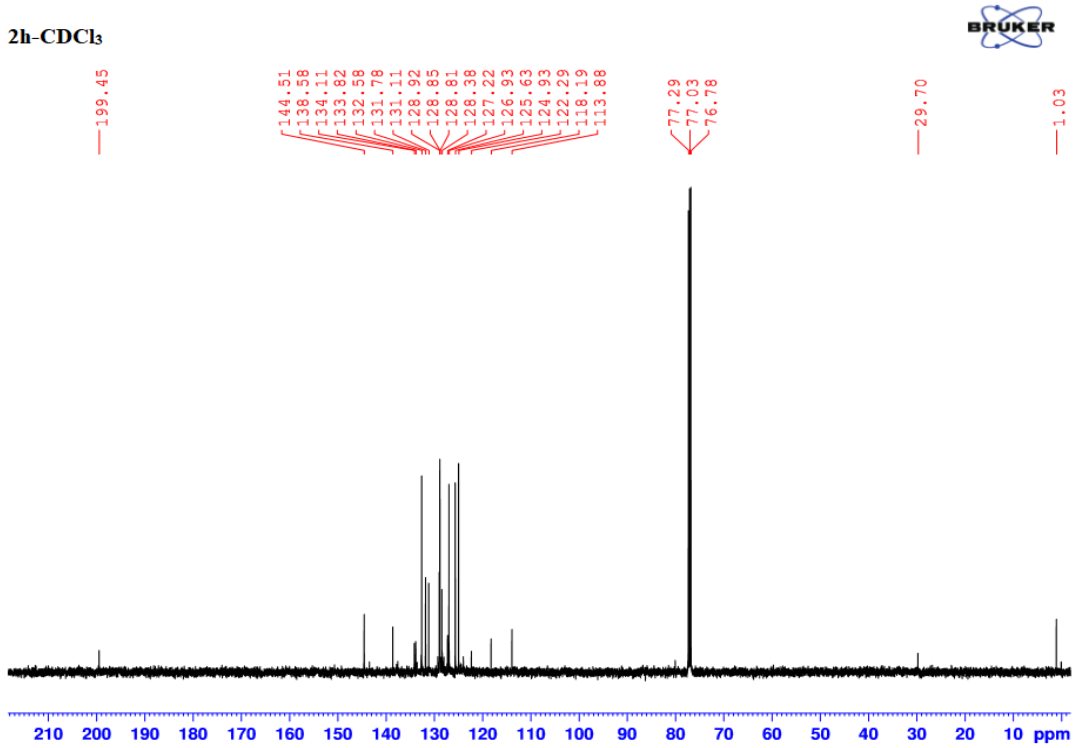
AC2.17 IR (KBr, *ν*, cm^{-1}) spectrum of (E)-4-(3-(Anthracen-9-yl)-3-oxoprop-1-en-1-yl)benzonitrile (2.10h)



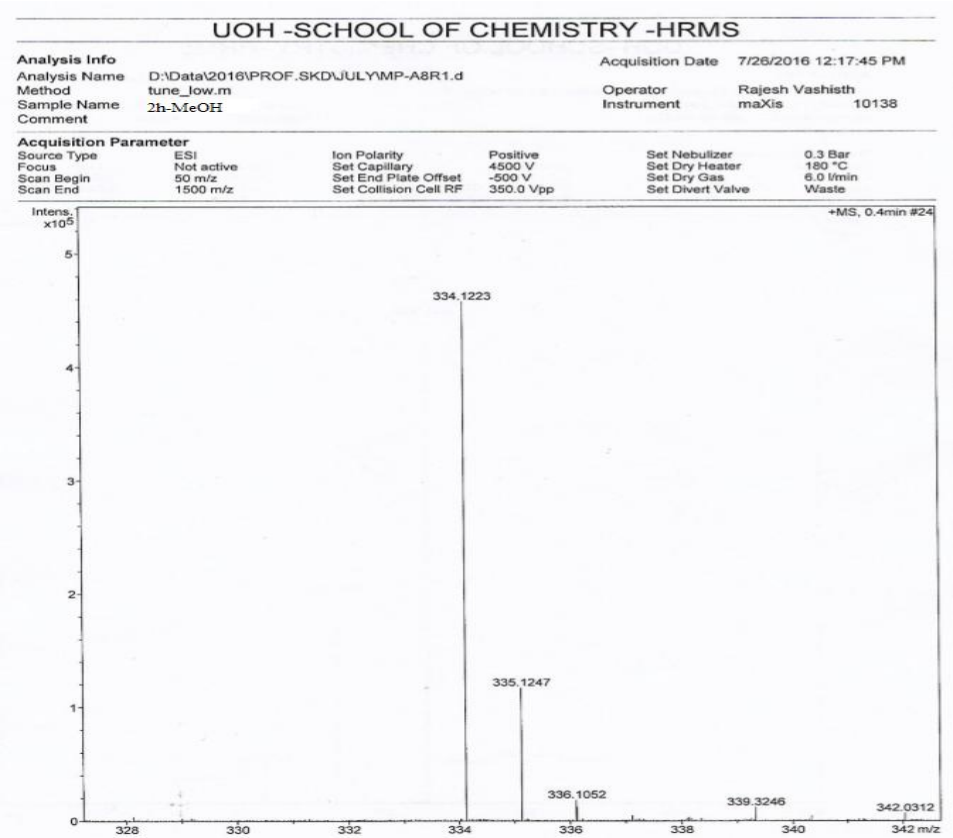
AC2.18 ^{1}H-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-4-(3-(Anthracen-9-yl)-3-oxoprop-1-en-1-yl)benzonitrile (2.10h)



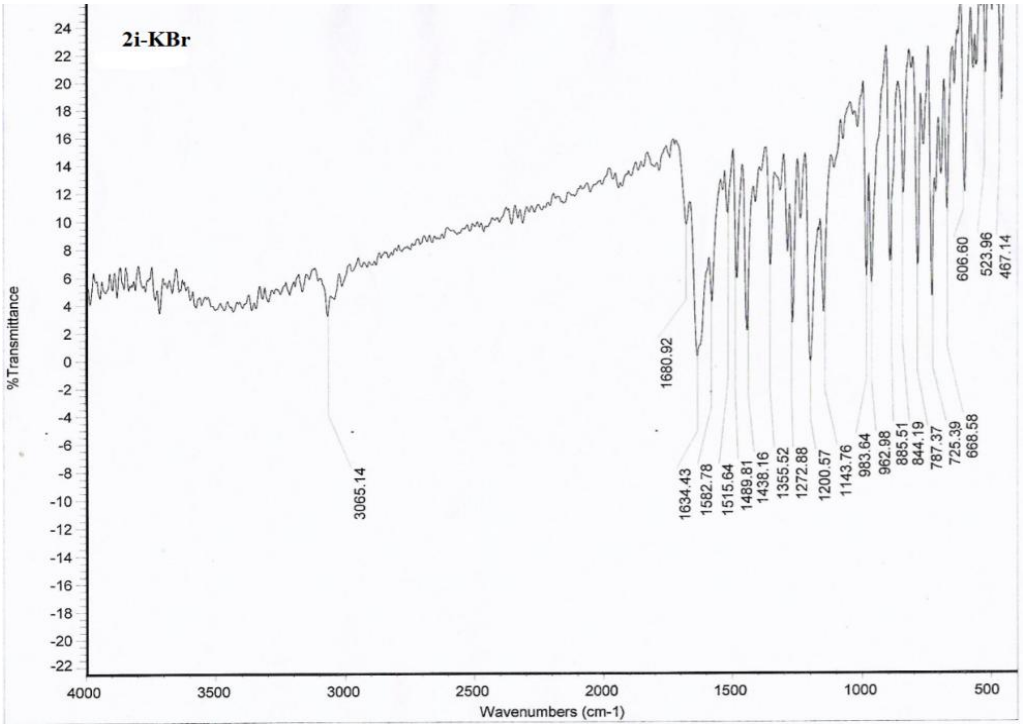
AC2.19 ^{13}C-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-4-(3-(Anthracen-9-yl)-3-oxoprop-1-en-1-yl)benzonitrile (2.10h)



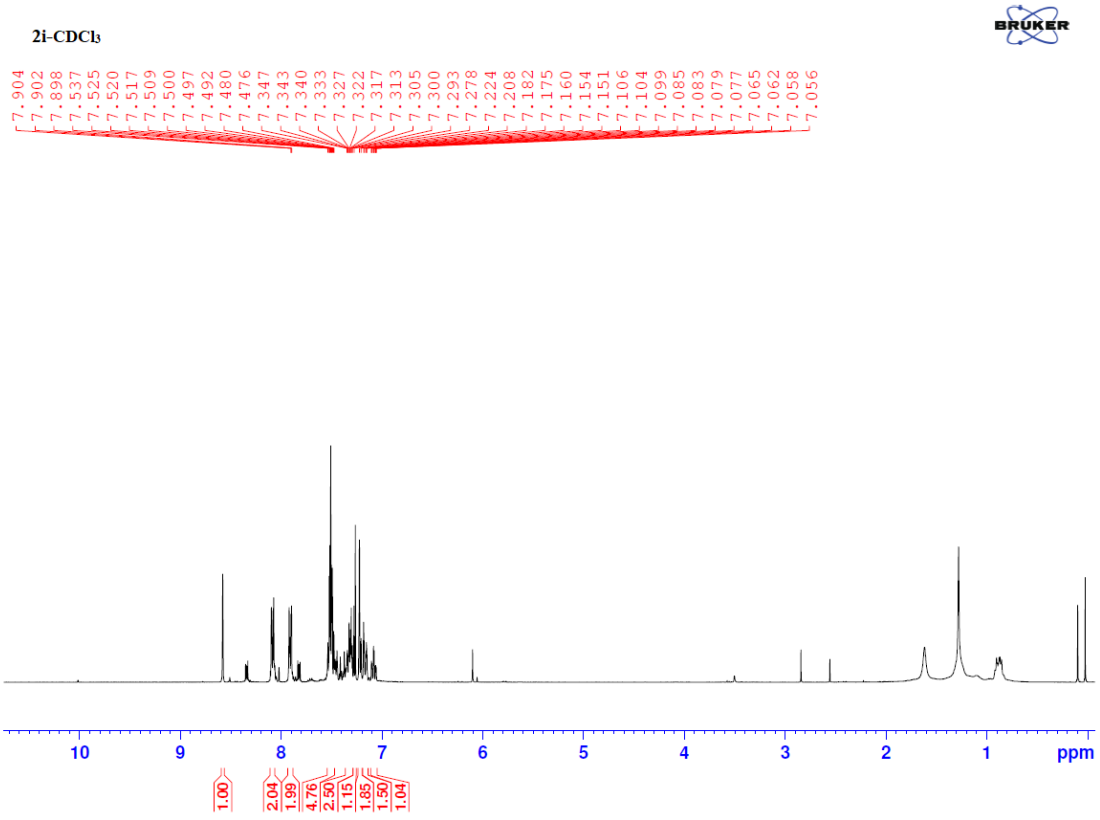
AC2.20 HRMS spectrum of (E)-4-(3-(Anthracen-9-yl)-3-oxoprop-1-en-1-yl)benzonitrile (2.10h)



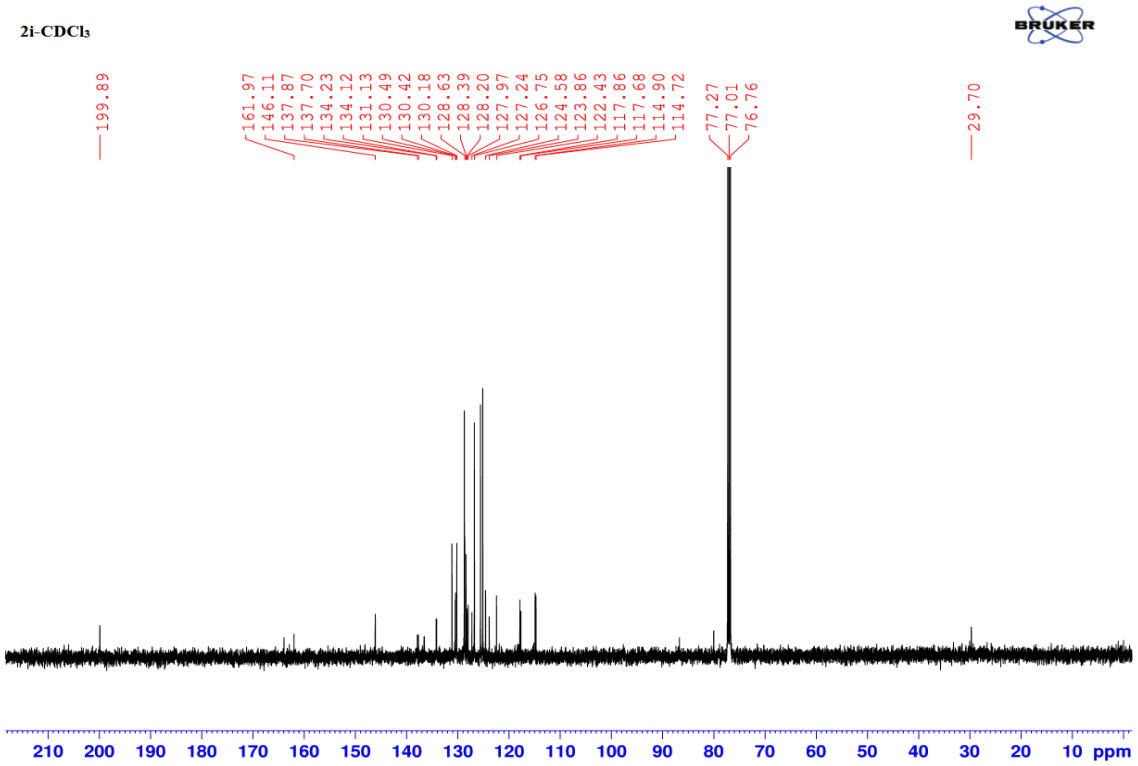
AC2.21 IR (KBr, *v*, cm^{-1}) spectrum of (E)-1-(Anthracen-9-yl)-3-(3-fluorophenyl)prop-2-en-1-one (2.10i)



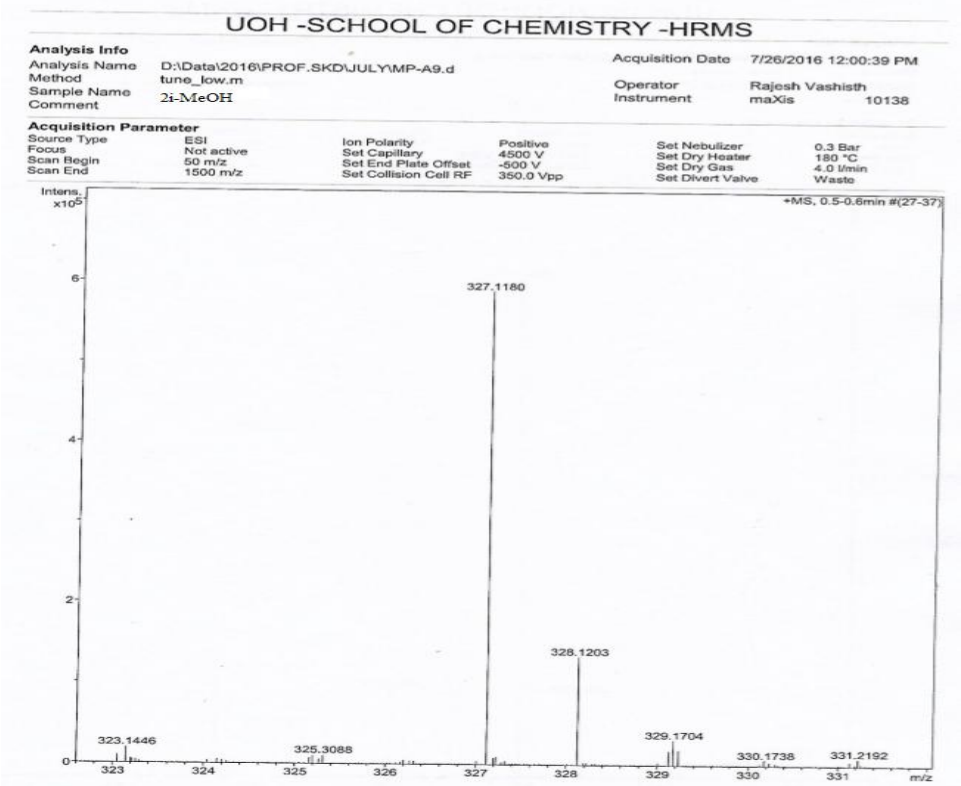
AC2.22 ^{1}H-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(3-fluorophenyl)prop-2-en-1-one (2.10i)



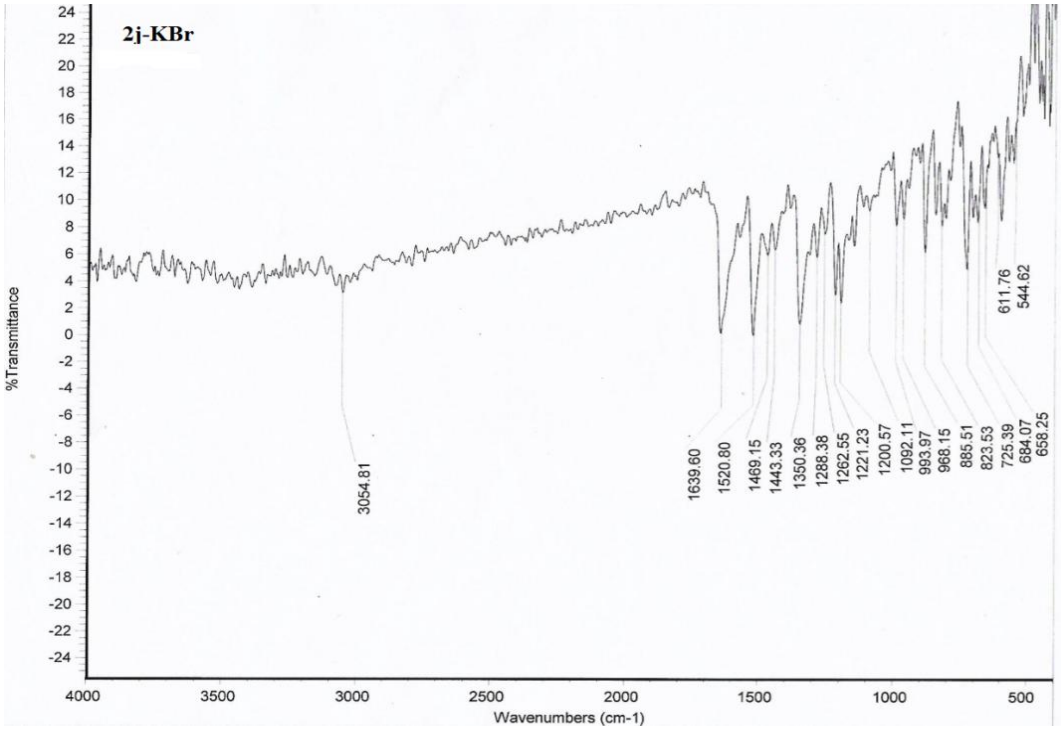
AC2.23 ^{13}C-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(3-fluorophenyl)prop-2-en-1-one (2.10i)



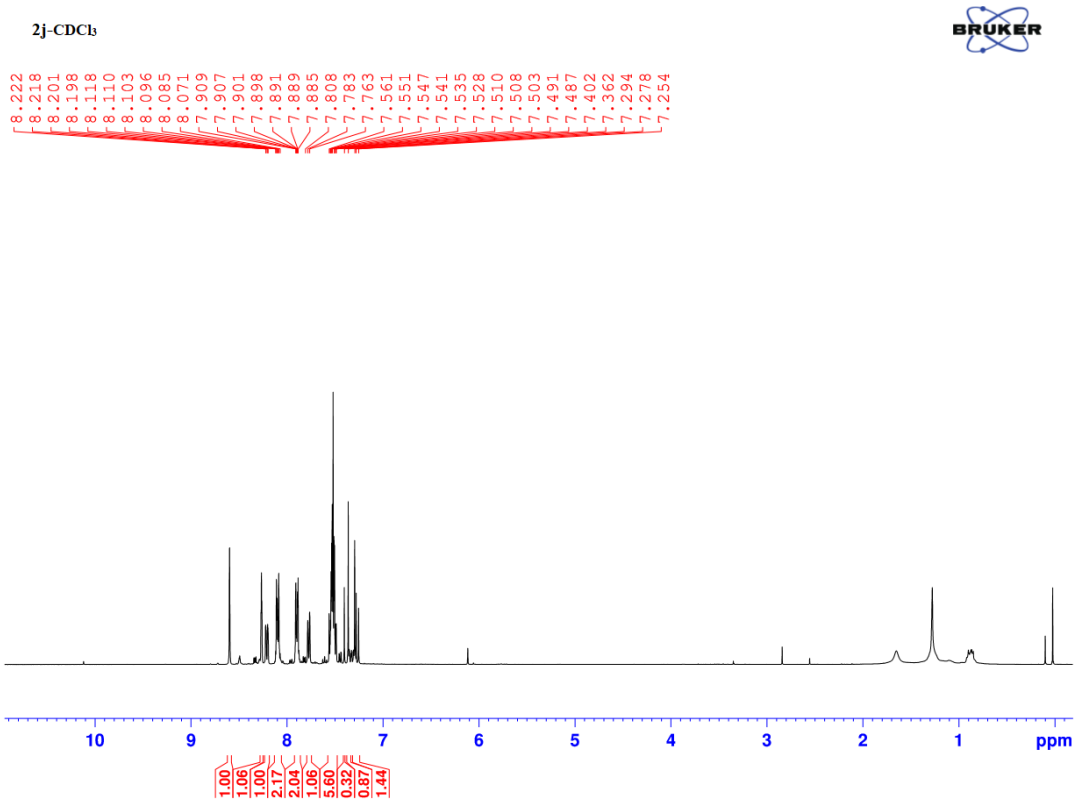
AC2.24 HRMS spectrum of (E)-1-(Anthracen-9-yl)-3-(3-fluorophenyl)prop-2-en-1-one (2.10i)



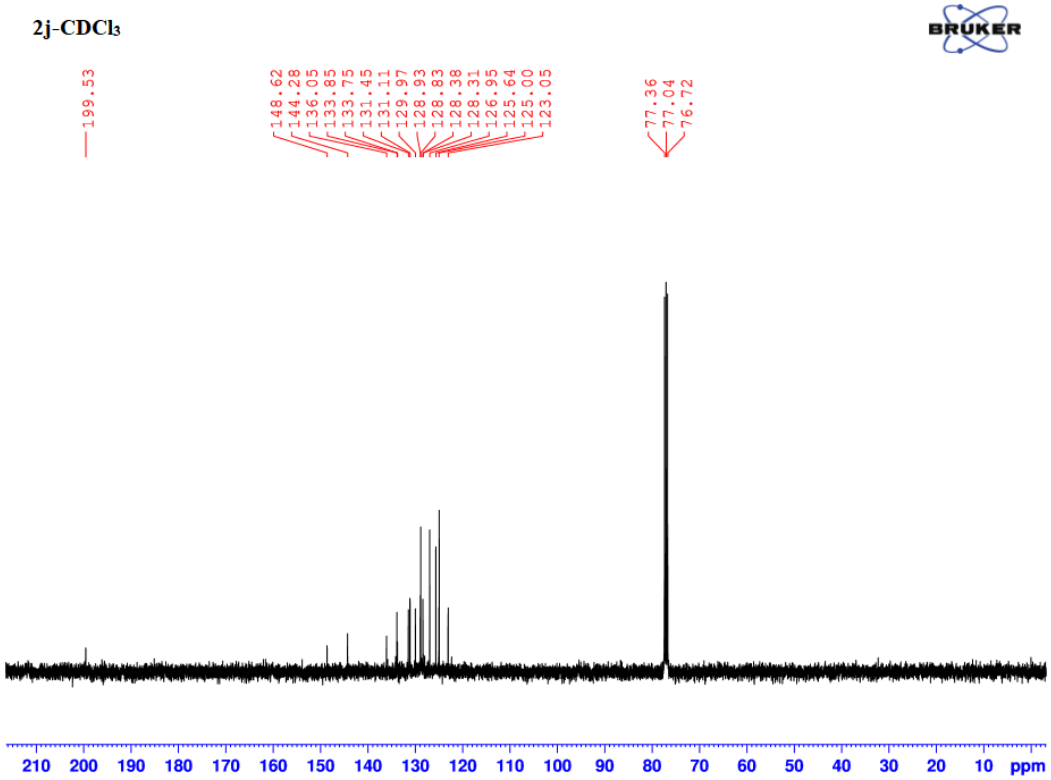
AC2.25 IR (KBr, *v*, cm^{-1}) spectrum of (E)-1-(Anthracen-9-yl)-3-(3-nitrophenyl)prop-2-en-1-one (2.10j)



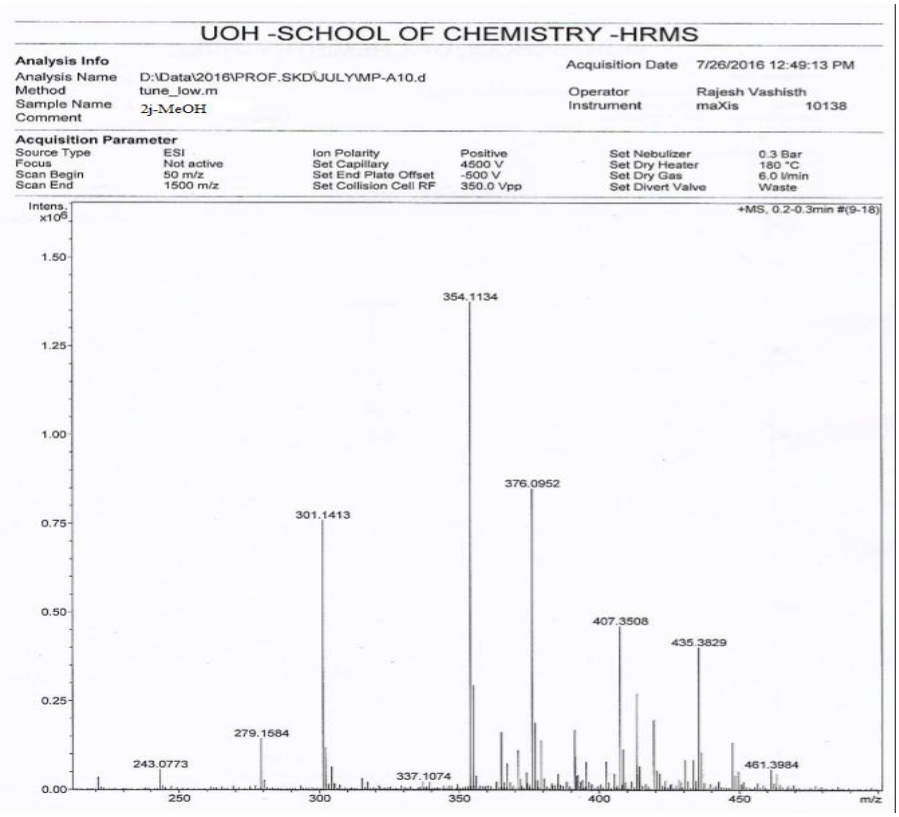
AC2.26 ^{1}H-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(3-nitrophenyl)prop-2-en-1-one (2.10j)



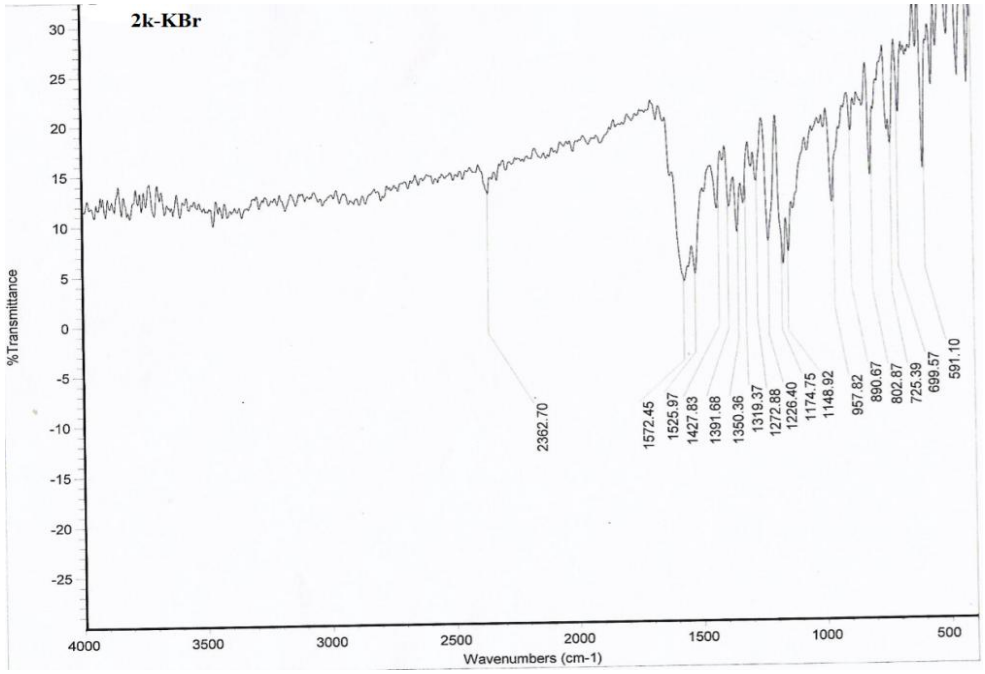
AC2.27 ^{13}C-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(3-nitrophenyl)prop-2-en-1-one (2.10j)



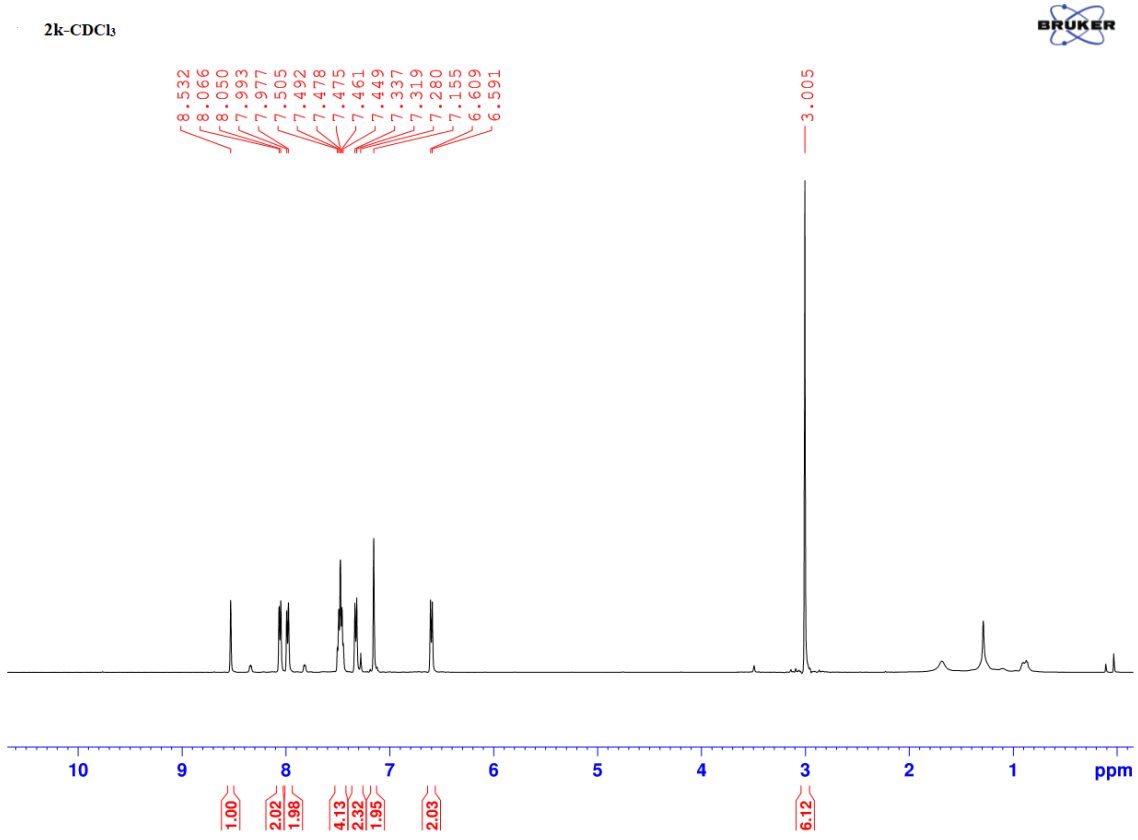
AC2.28 HRMS spectrum of (E)-1-(Anthracen-9-yl)-3-(3-nitrophenyl)prop-2-en-1-one (2.10j)



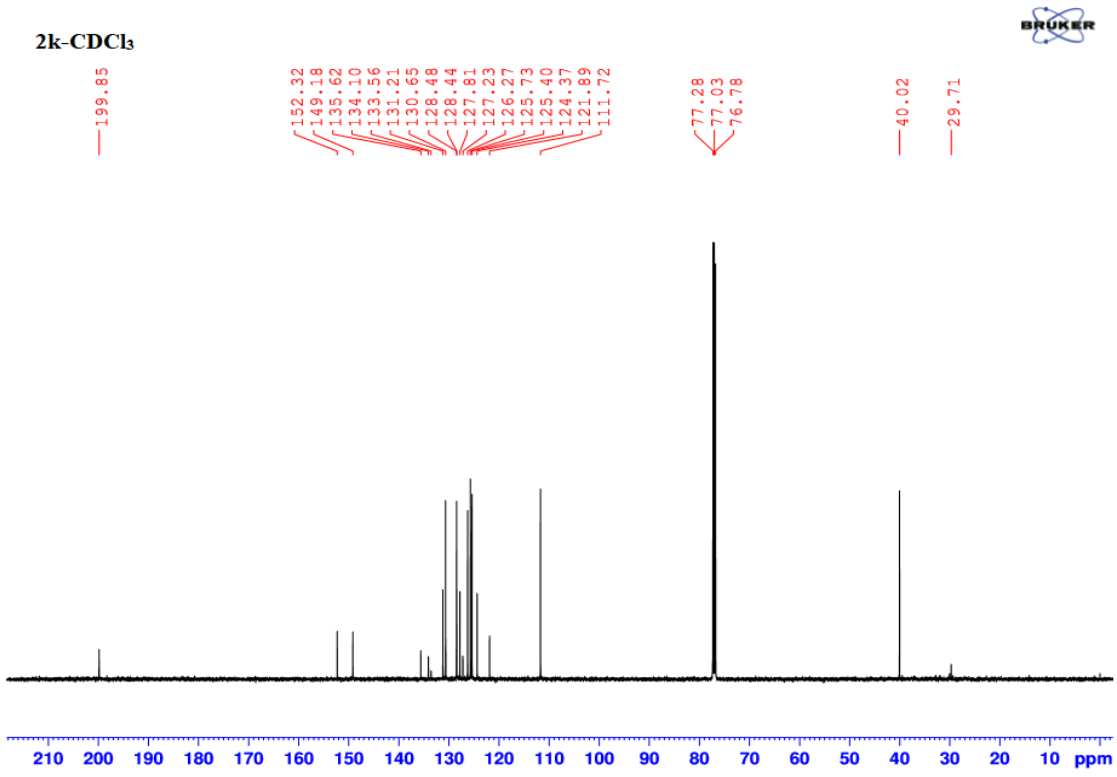
AC2.29 IR (KBr, *ν*, cm^{-1}) spectrum of (E)-1-(Anthracen-9-yl)-3-(4-(dimethylamino) phenyl)prop-2-en-1-one (2.10k)



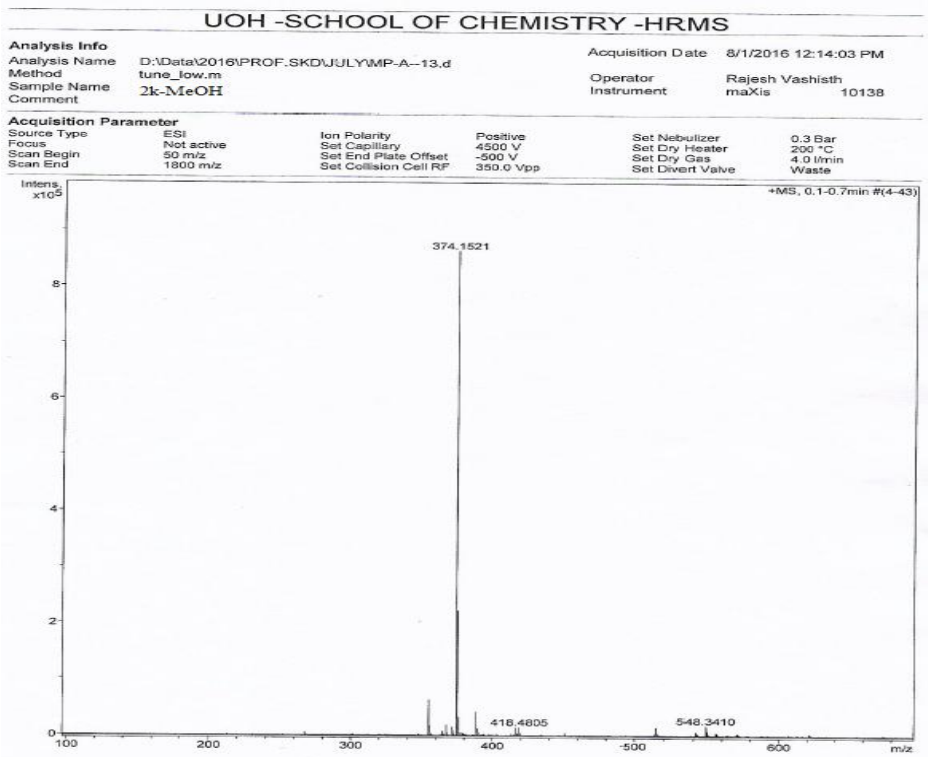
AC2.30 ^{1}H-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (2.10k)



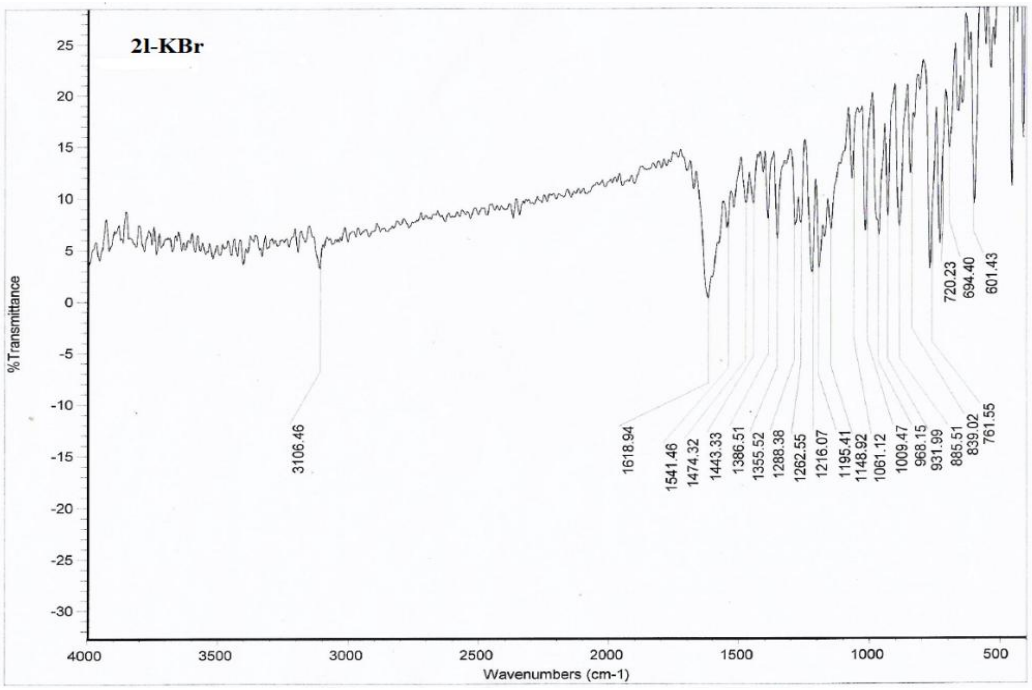
AC2.31 ^{13}C-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (2.10k)



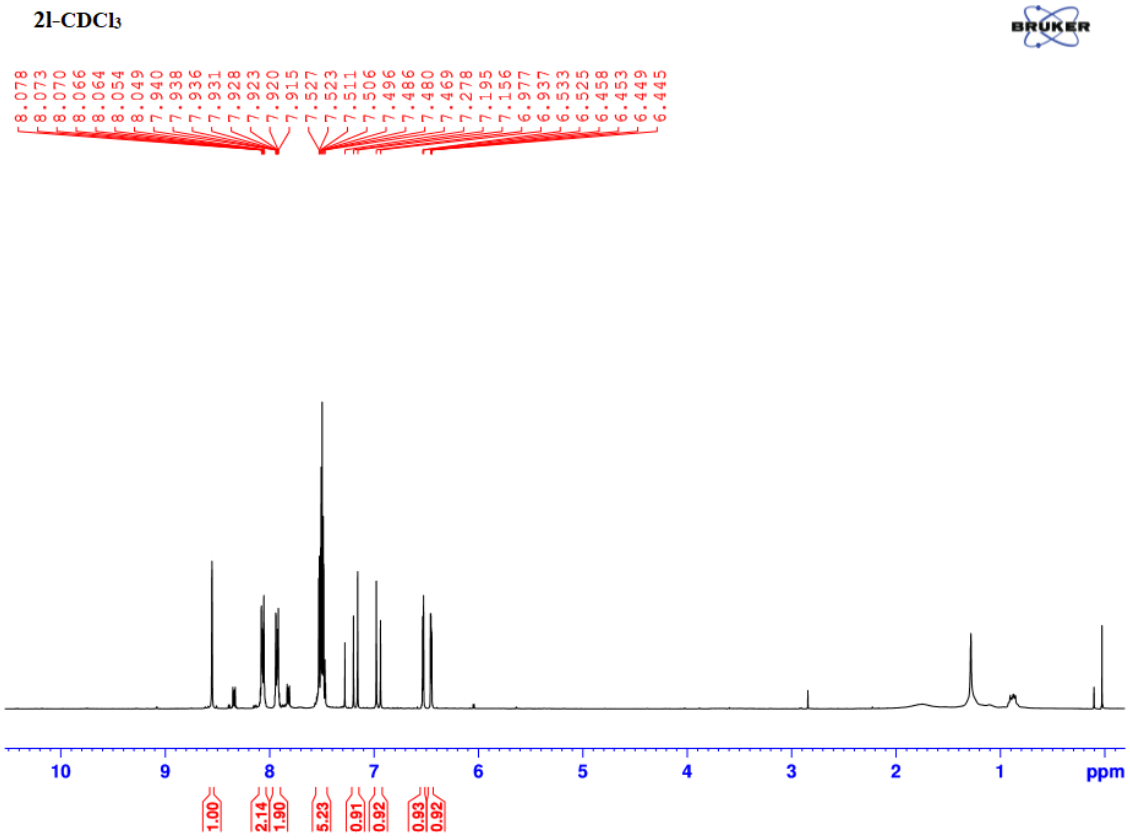
AC2.32 HRMS spectrum of (E)-1-(Anthracen-9-yl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (2.10k)



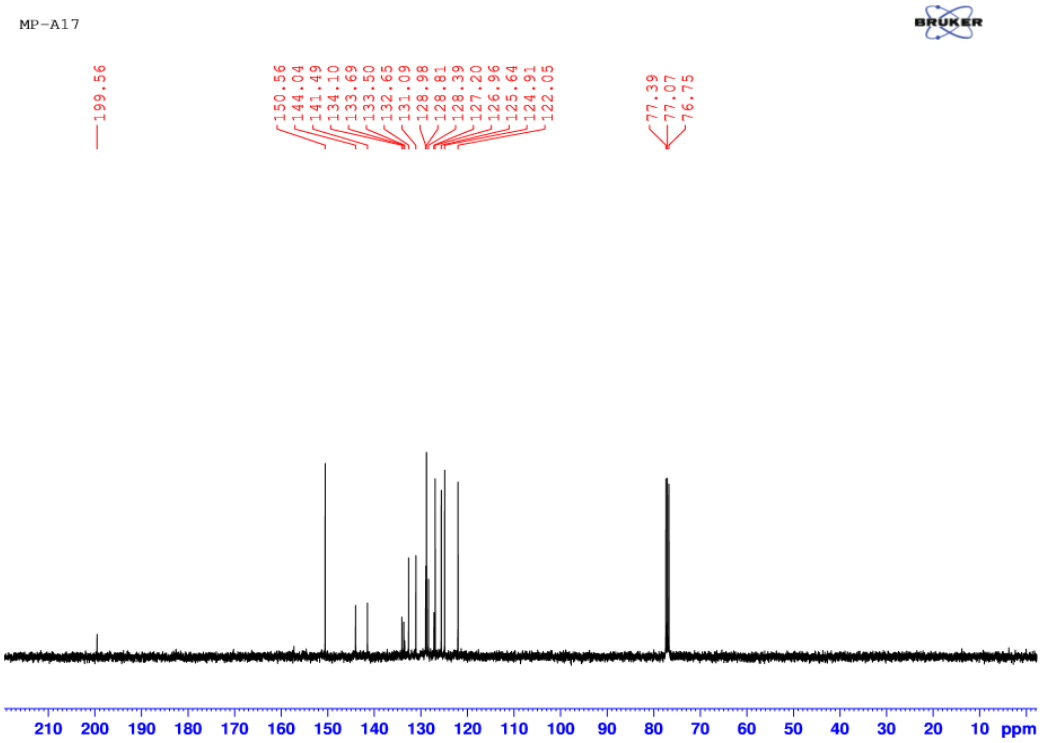
AC2.33 IR (KBr, *v*, cm^{-1}) spectrum of (E)-1-(Anthracen-9-yl)-3-(furan-2-yl)prop-2-en-1-one (2.10l)



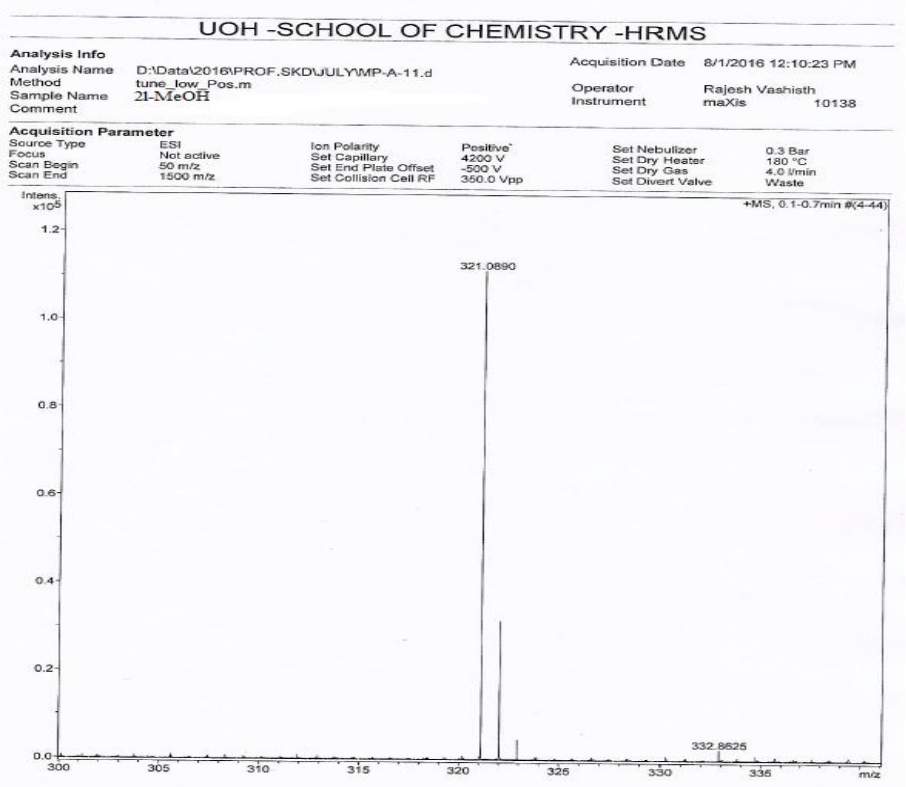
AC2.34 ^{1}H-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(furan-2-yl)prop-2-en-1-one (2.10l)



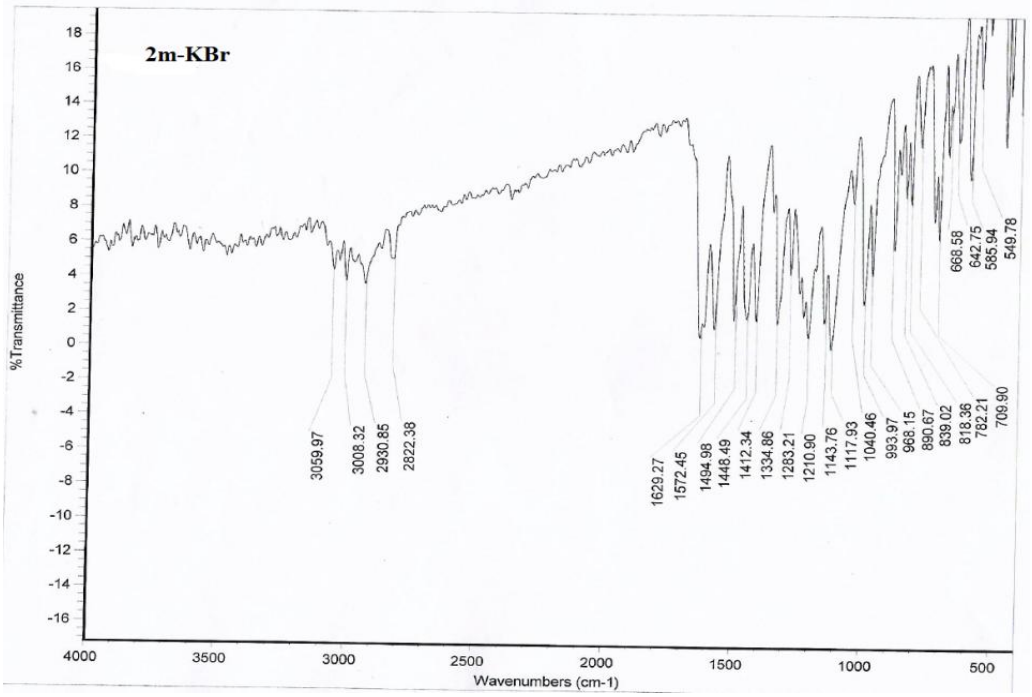
AC2.35 ^{13}C-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(furan-2-yl)prop-2-en-1-one (2.10l)



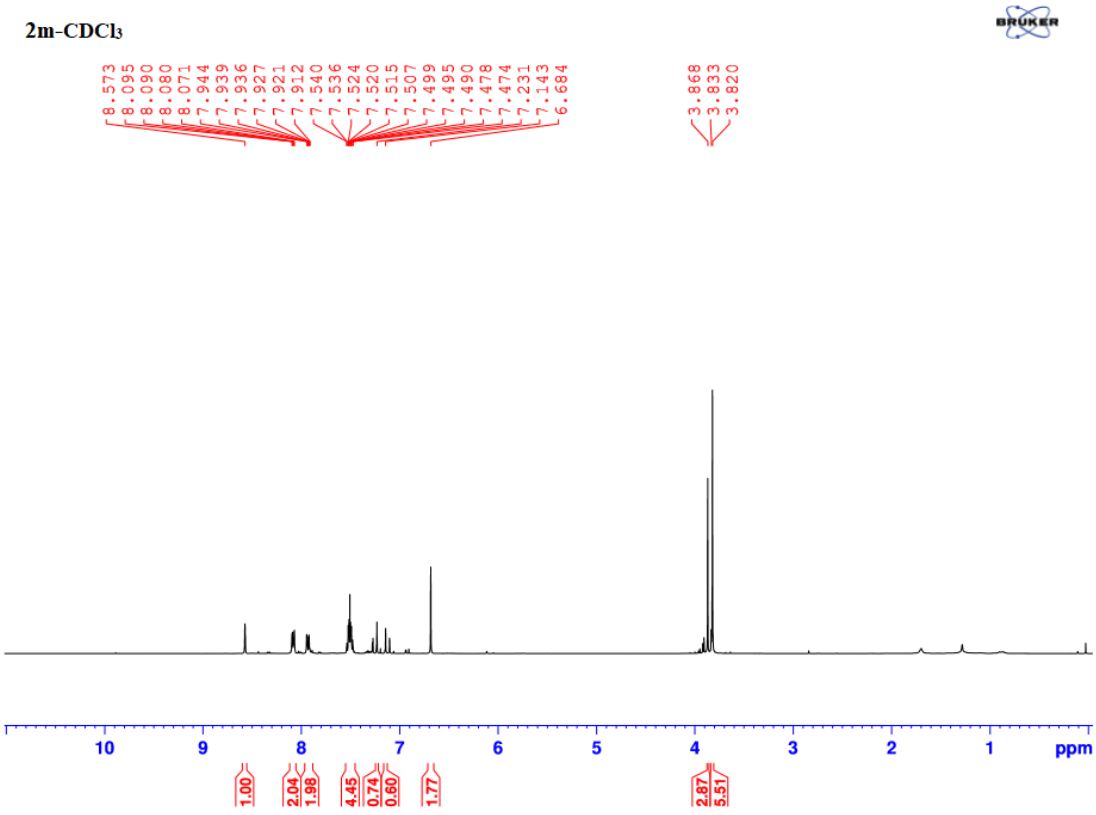
AC2.36 HRMS spectrum of (E)-1-(Anthracen-9-yl)-3-(furan-2-yl)prop-2-en-1-one (2.10l)



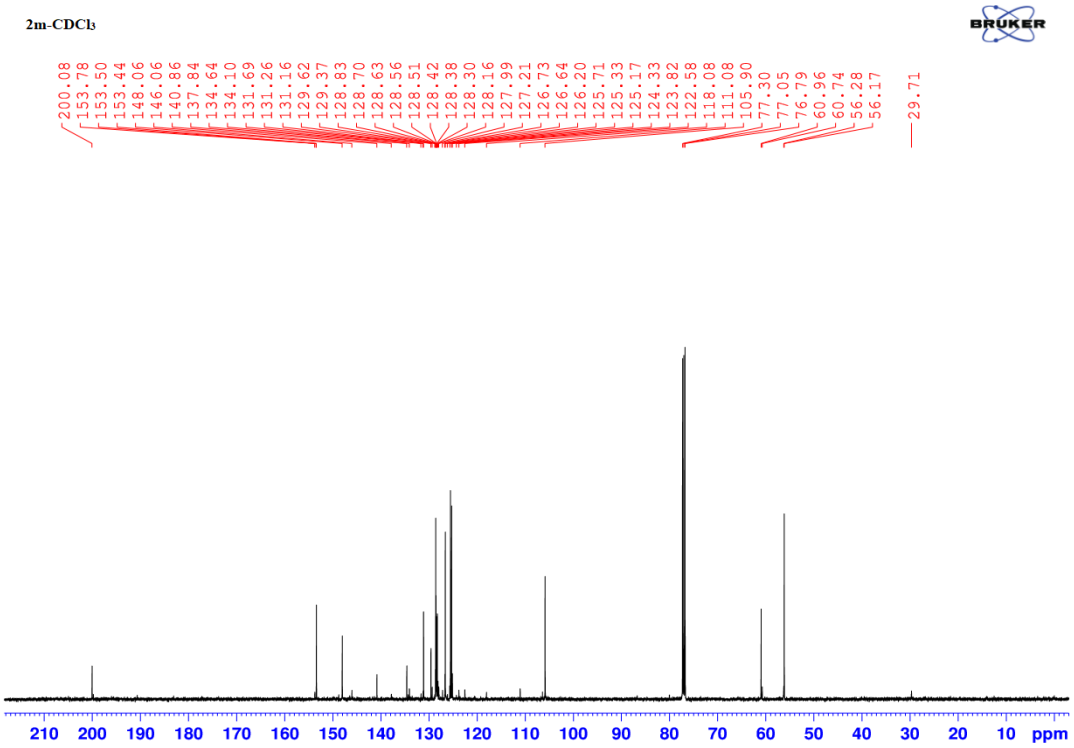
AC2.37 IR (KBr, *ν*, cm^{-1}) spectrum of (E)-1-(Anthracen-9-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (2.10m)



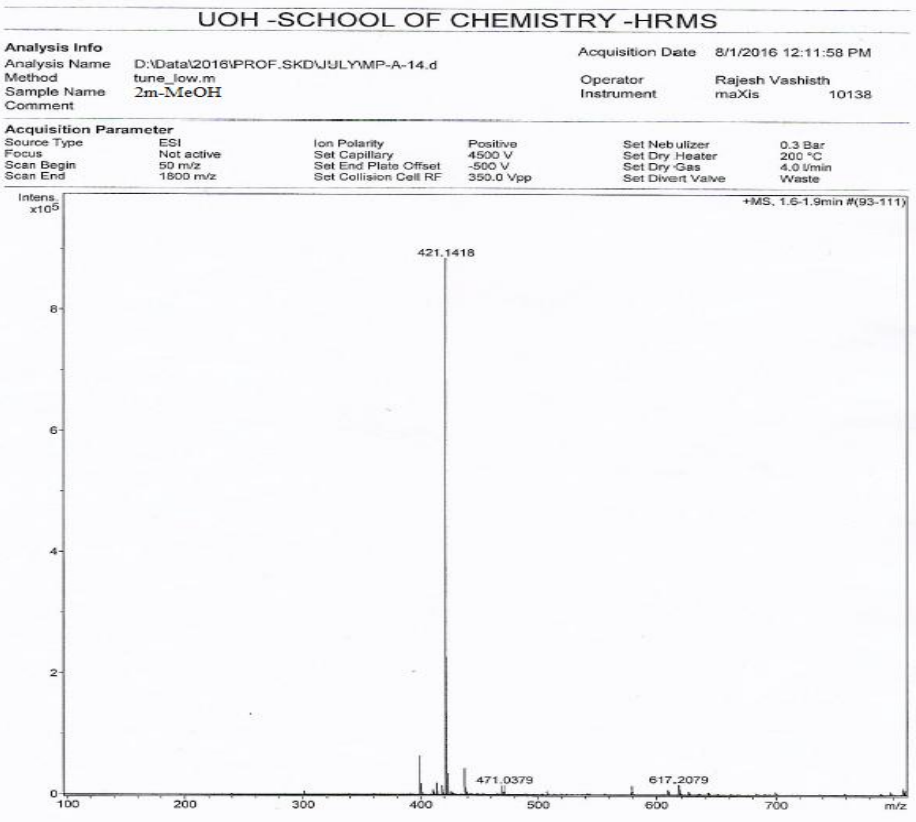
AC2.38 ^{1}H-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (2.10m)



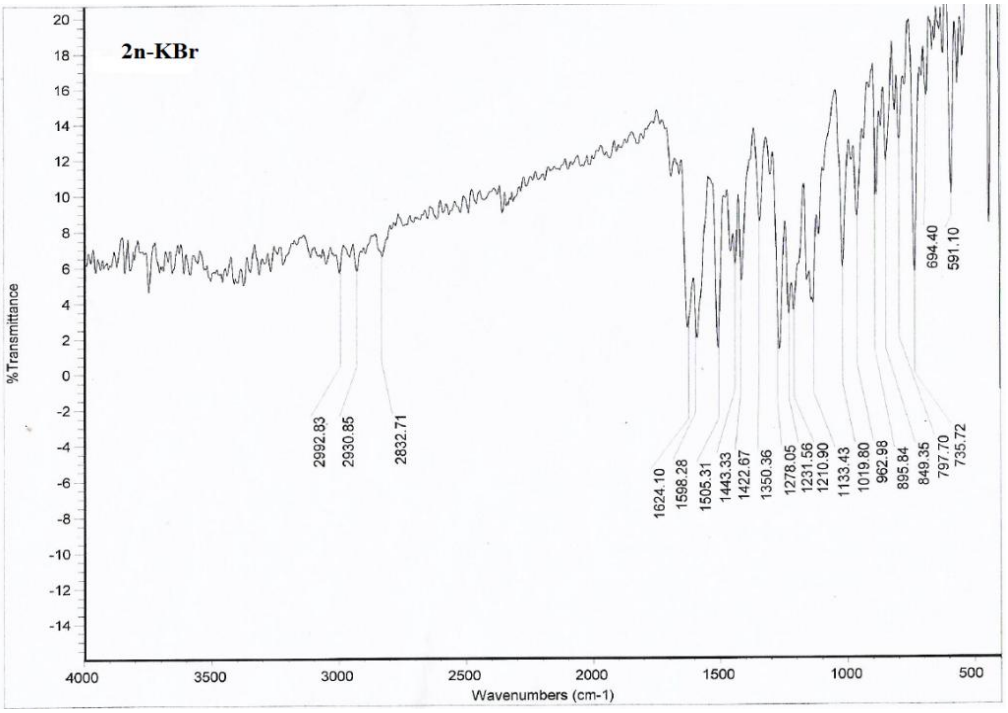
AC2.39 ^{13}C-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (2.10m)



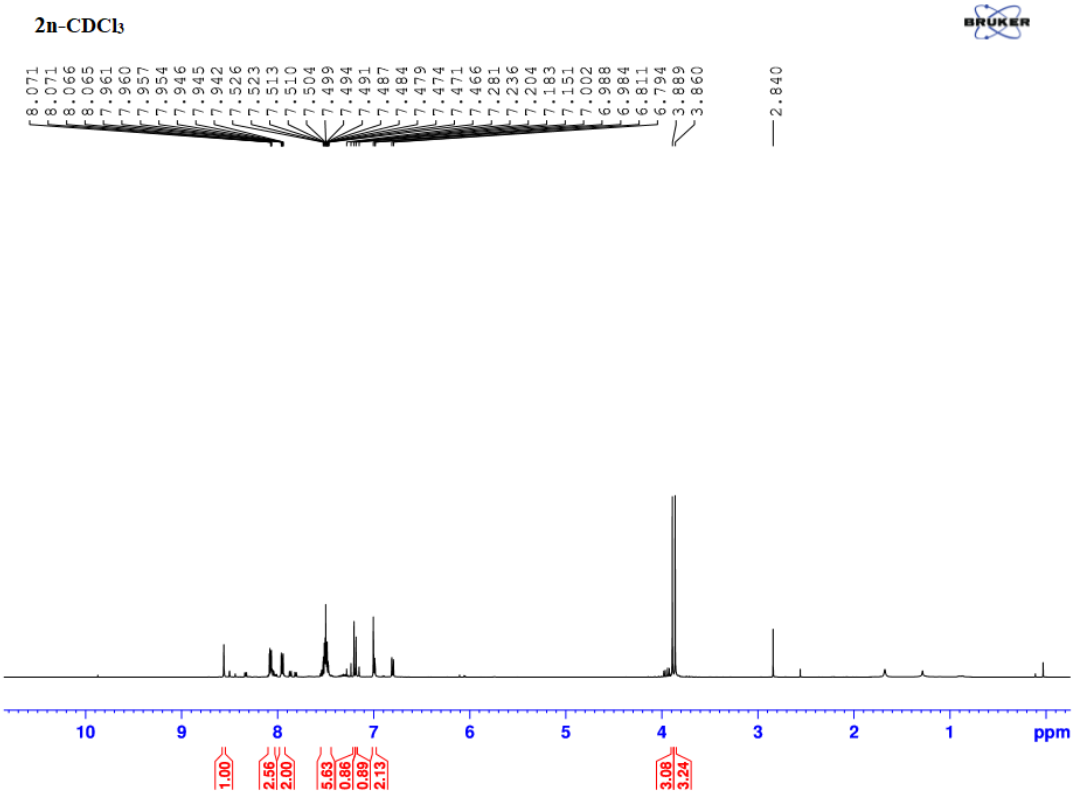
AC2.40 HRMS spectrum of (E)-1-(Anthracen-9-yl)-3-(3,4,5-trimethoxyphenyl) prop-2-en-1-one (2.10m)



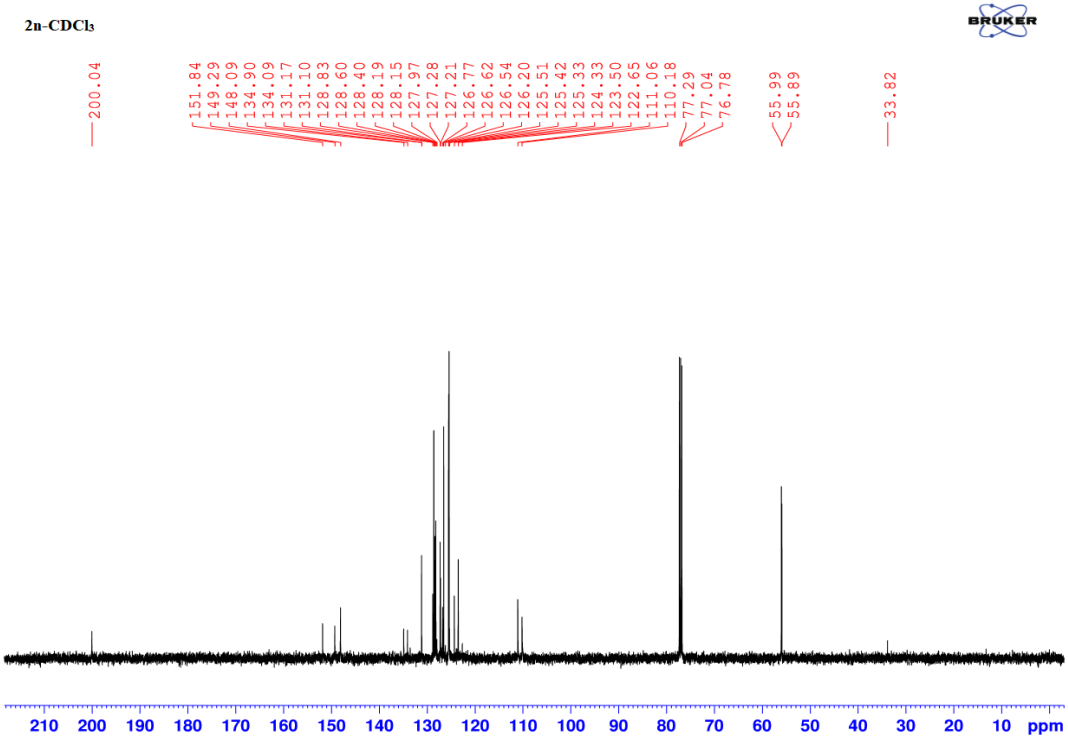
AC2.41 IR (KBr, *v*, cm^{-1}) spectrum of (E)-1-(Anthracen-9-yl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (2.10n)



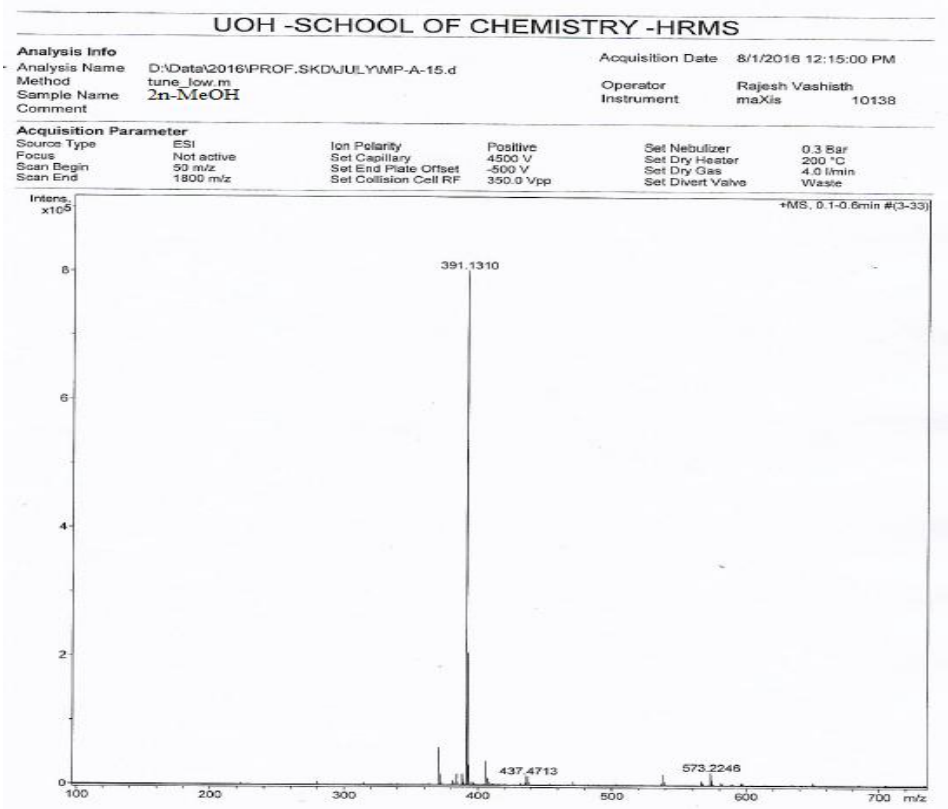
AC2.42 ^{1}H-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (2.10n)



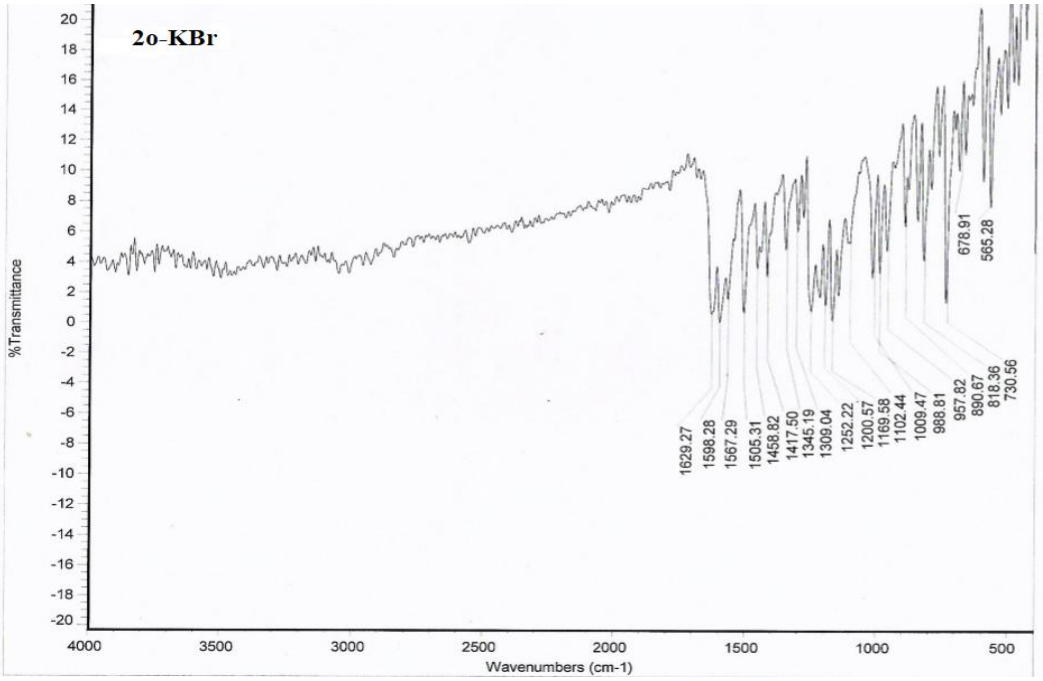
AC2.43 ^{13}C-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (2.10n)



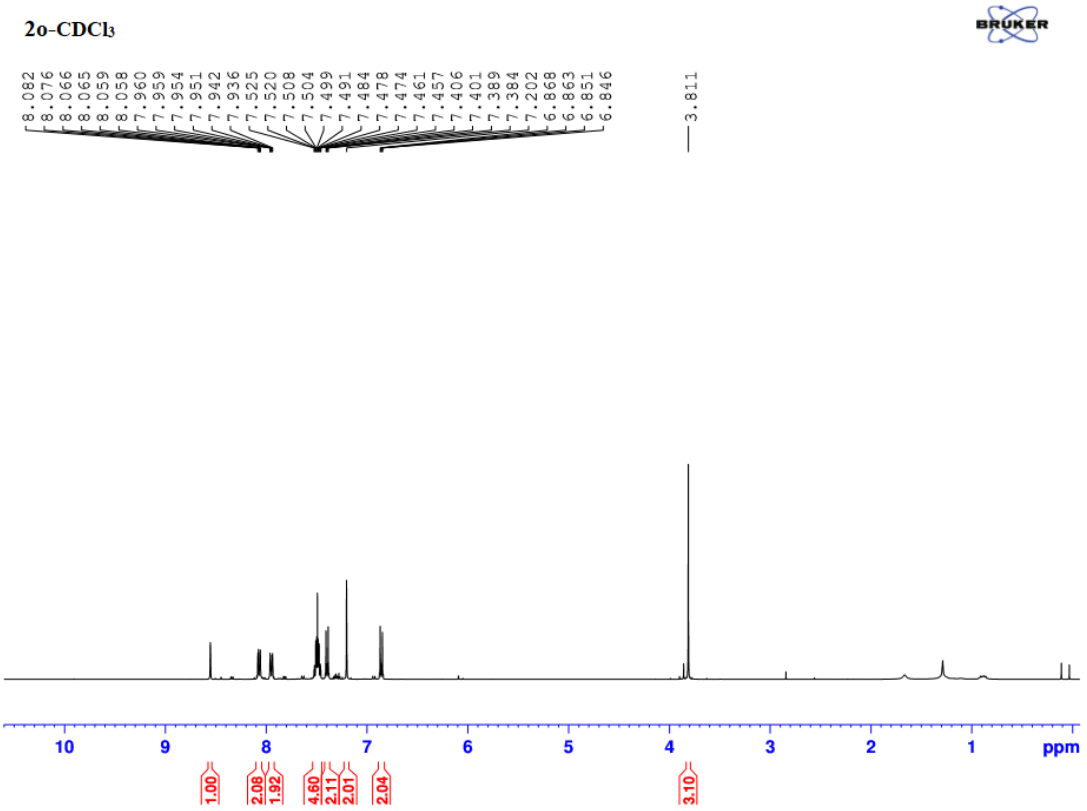
AC2.44 HRMS spectrum of (E)-1-(Anthracen-9-yl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (2.10n)



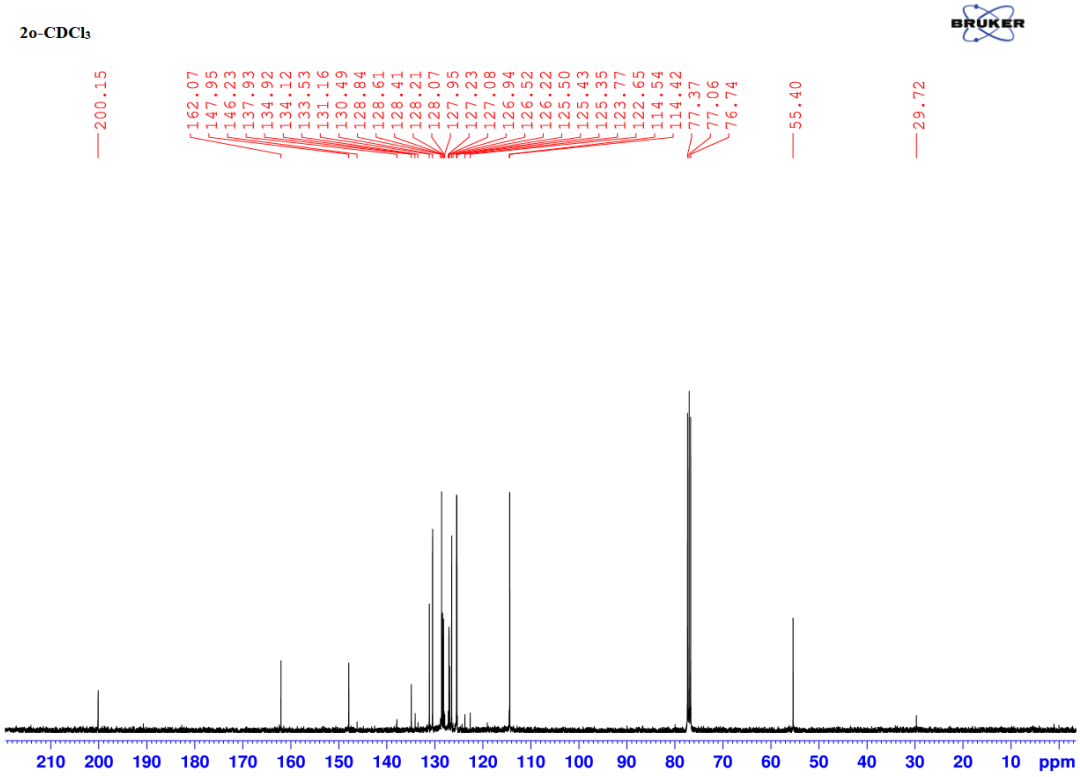
AC2.45 IR (KBr, *v*, cm^{-1}) spectrum of (E)-1-(Anthracen-9-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (2.10o)



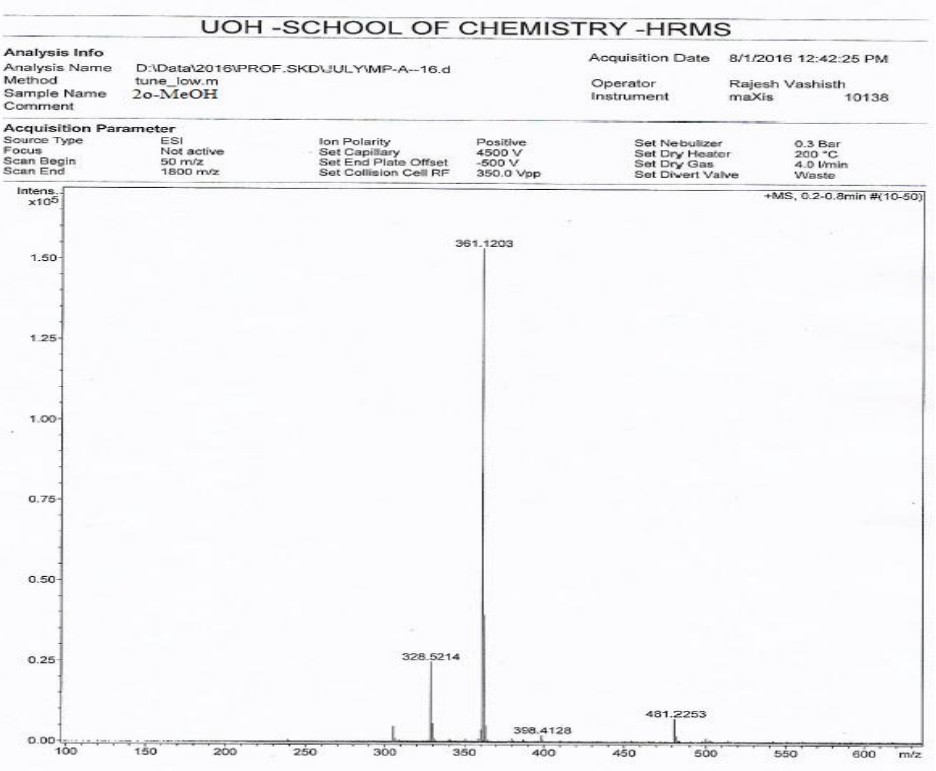
AC2.46 ^{1}H-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (2.10o)



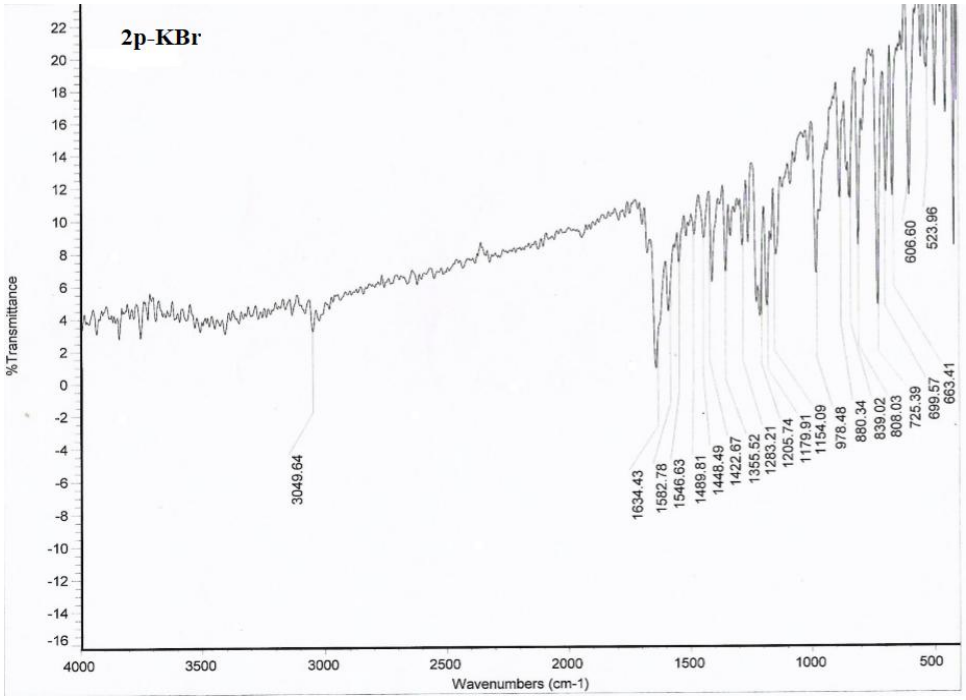
AC2.47 ^{13}C-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (2.10o)



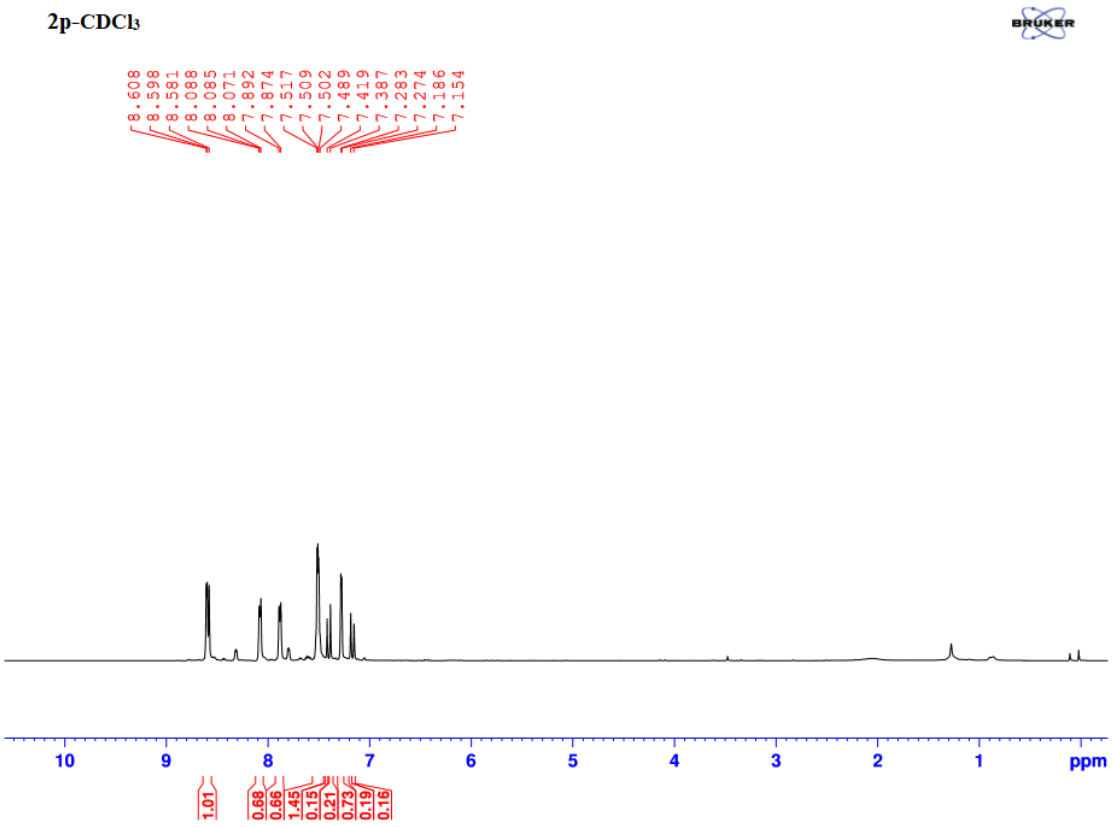
AC2.48 HRMS spectrum of (E)-1-(Anthracen-9-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (2.10o)



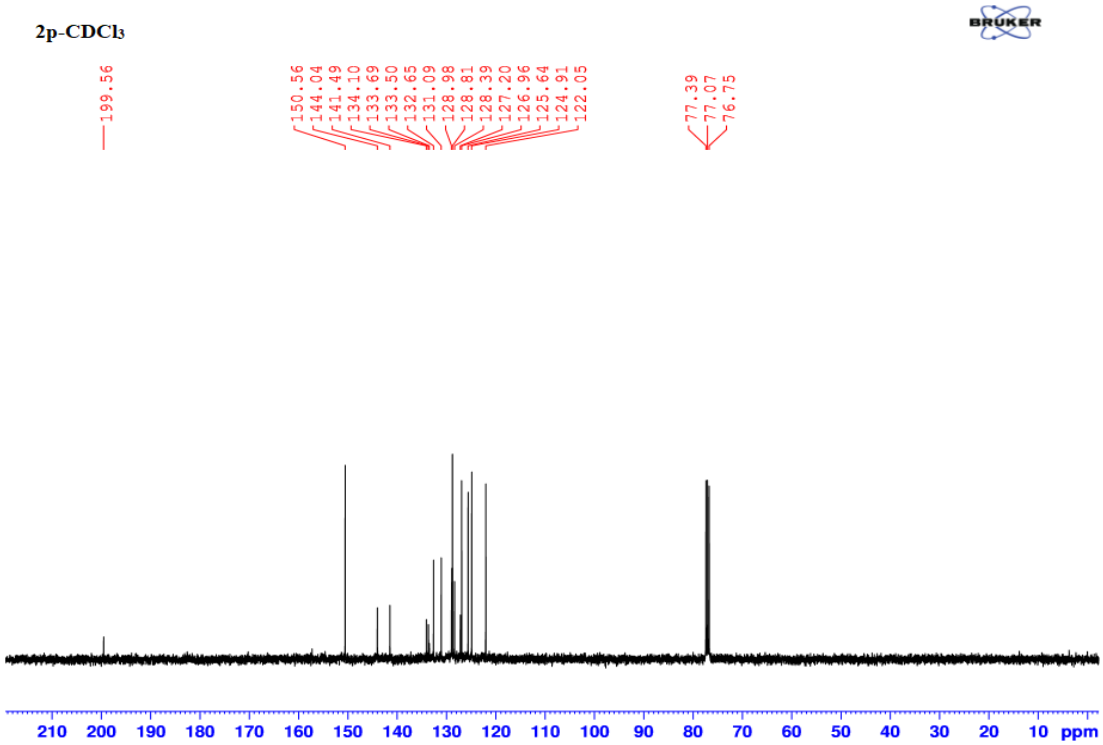
AC2.49 IR (KBr, *v*, cm^{-1}) spectrum of (E)-1-(Anthracen-9-yl)-3-(pyridin-4-yl)prop-2-en-1-one (2.10p)



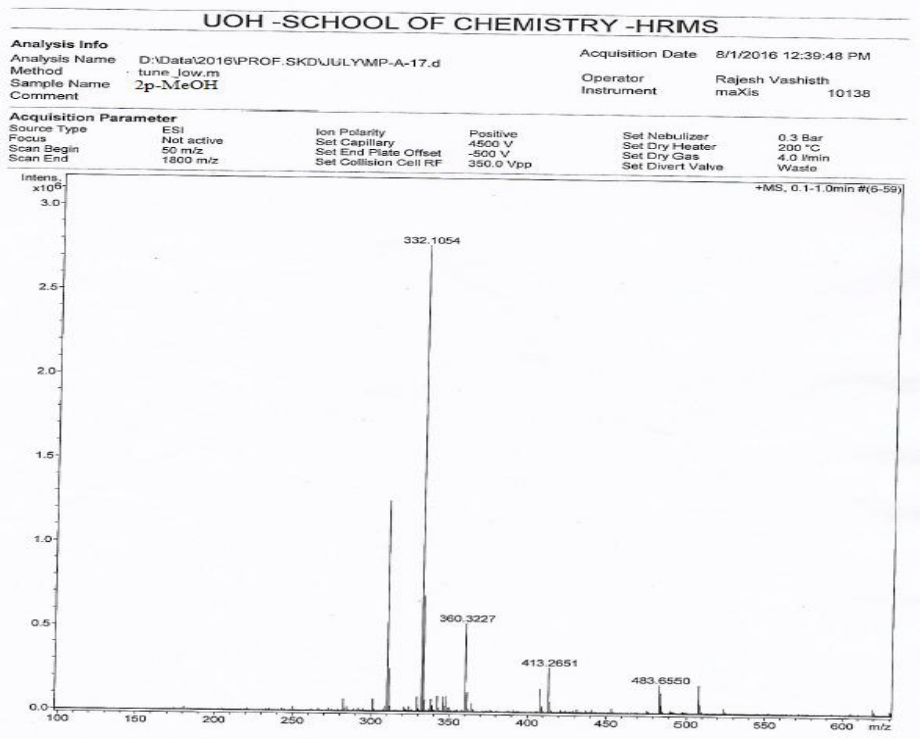
AC2.50 ^{1}H-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(pyridin-4-yl)prop-2-en-1-one (2.10p)



AC2.51 ^{13}C-NMR (400 MHz, δ(ppm), $CDCl_3$) spectrum of (E)-1-(Anthracen-9-yl)-3-(pyridin-4-yl)prop-2-en-1-one (2.10p)

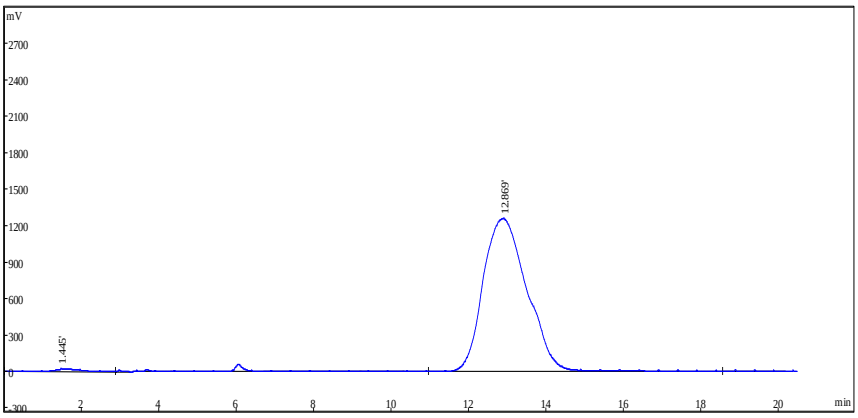


AC2.52 HRMS spectrum of (E)-1-(Anthracen-9-yl)-3-(pyridin-4-yl)prop-2-en-1-one (2.10p)



AC2.53 HPLC-Analysis spectrum of (E)-1-(anthracen-9-yl)-3-(4-chlorophenyl) prop-2-en-1-one (2.10b)

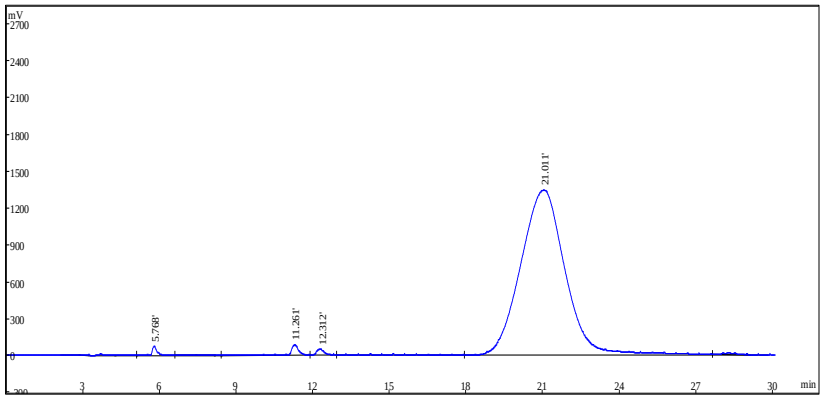
Dr. M. Prabhakar's Lab, Dept. Chemistry, Nagaland University
Detector: Wavelength 270 nm;
Column: C18
Water: Methanol 3:7; 1 mL/Min



Rank	Time	Name	Conc.	Area
1	1.445		1.948	1964814
2	6.022		0.9035	911352
3	12.869		97.15	97992614
Total			100	100868780

AC2.54 HPLC-Analysis spectrum of (E)-1-(Anthracen-9-yl)-3-(p-tolyl)prop-2-en-1-one (2.10e)

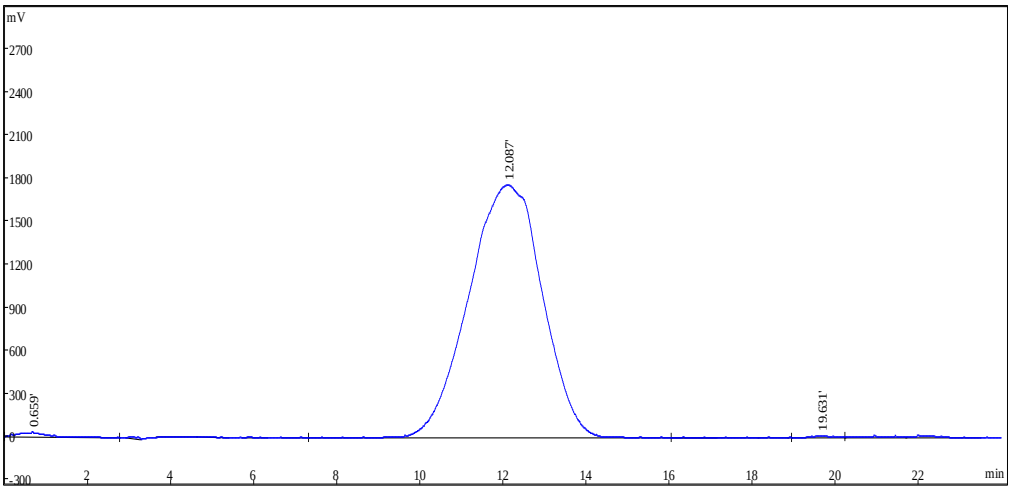
Dr. M. Prabhakar's Lab, Dept. Chemistry, Nagaland University
Detector: Wavelength 270 nm
Column: C18
Water: Methanol 3:7; 1 mL/Min



Rank	Time	Name	Conc.	Area
1	5.768		0.8306	1384296
2	11.261		1.34	2233109
3	12.312		0.8129	1354937
4	21.011		97.02	161691930
Total			100	166664272

AC2.55 HPLC-Analysis spectrum of (E)-1-(Anthracen-9-yl)-3-(3-fluorophenyl)prop-2-en-1-one (2.10i)

Dr. M. Prabhakar's Lab, Dept. Chemistry, Nagaland University
Detector: Wavelength 270 nm
Column: C18
Water: Methanol 3:7; 1 mL/Min

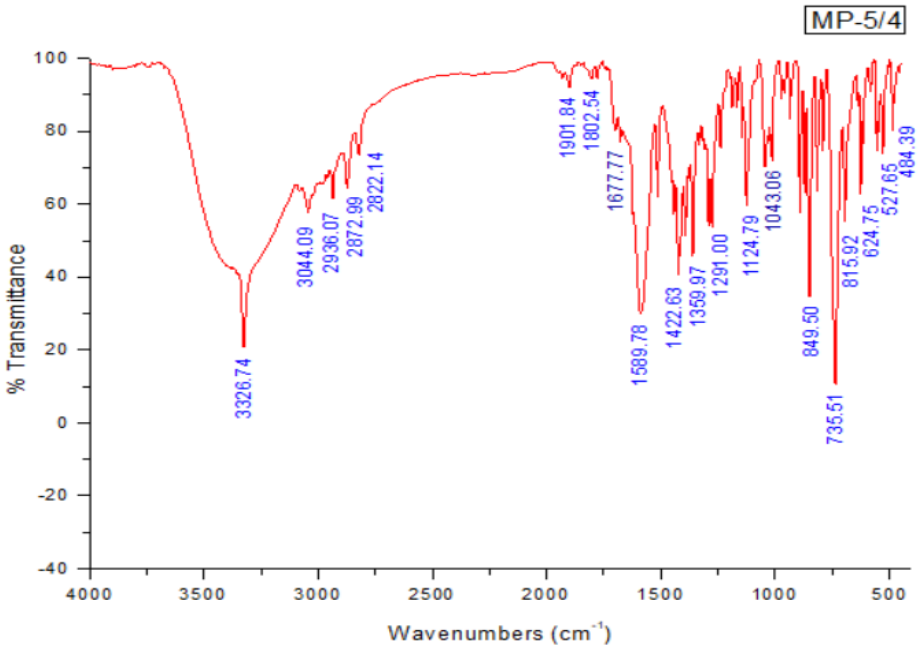


Rank	Time	Name	Conc.	Area
1	0.659		0.8162	1793180
2	12.087		98.87	217214080
3	19.631		0.3154	692991
Total			100	219700251

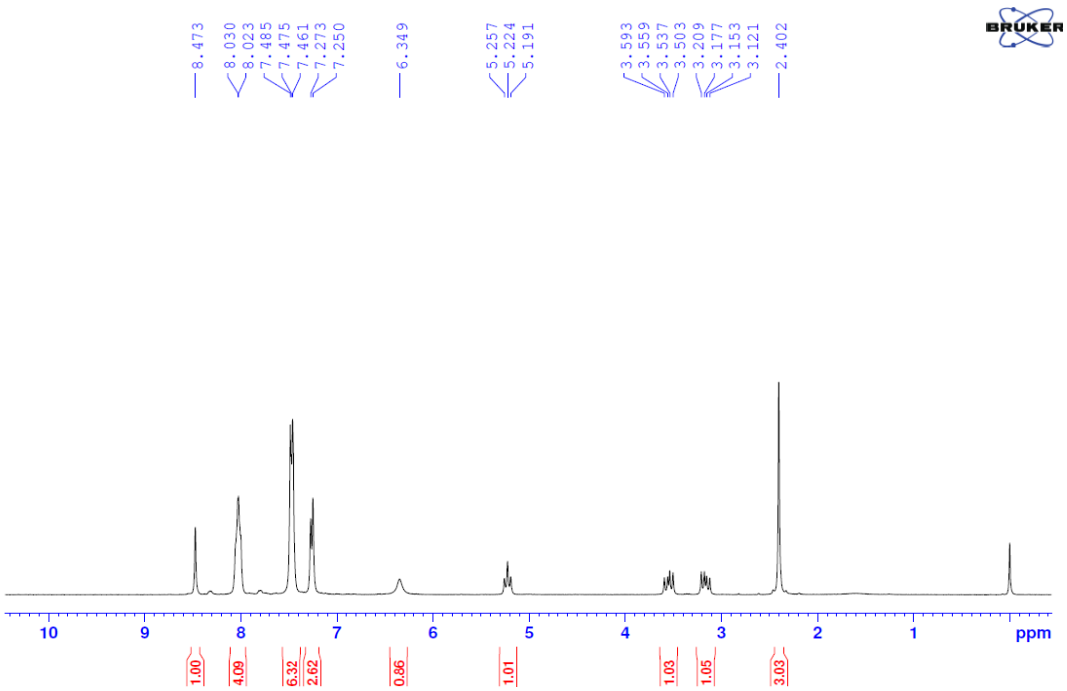
Appendix: C-3

AC3. REPRESENTATIVE SPECTRA OF NEWLY SYNTHESIZED ANTHRACENYL PYRAZOLINES

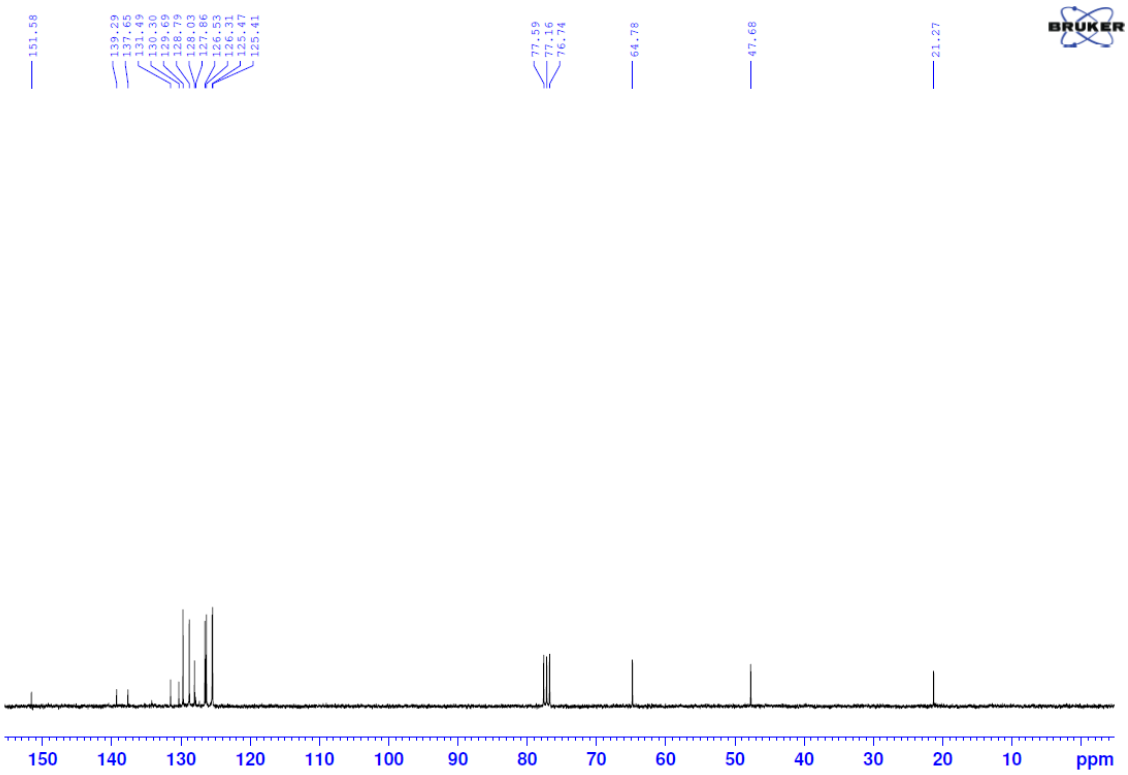
AC3.1 IR (KBr, *v*, cm^{-1}) spectrum of 3-Anthracen-9-yl-5-p-tolyl-4,5-dihydro-1H-pyrazole (3.9d)



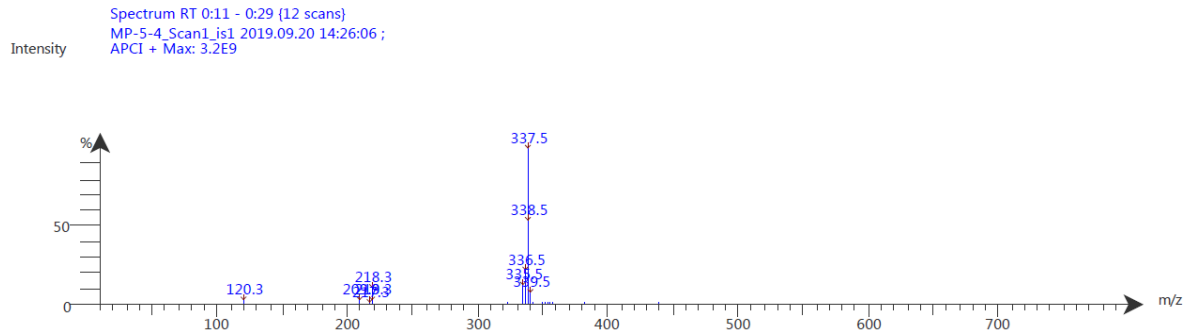
AC3.2 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-p-tolyl-4,5-dihydro-1H-pyrazole (3.9d)



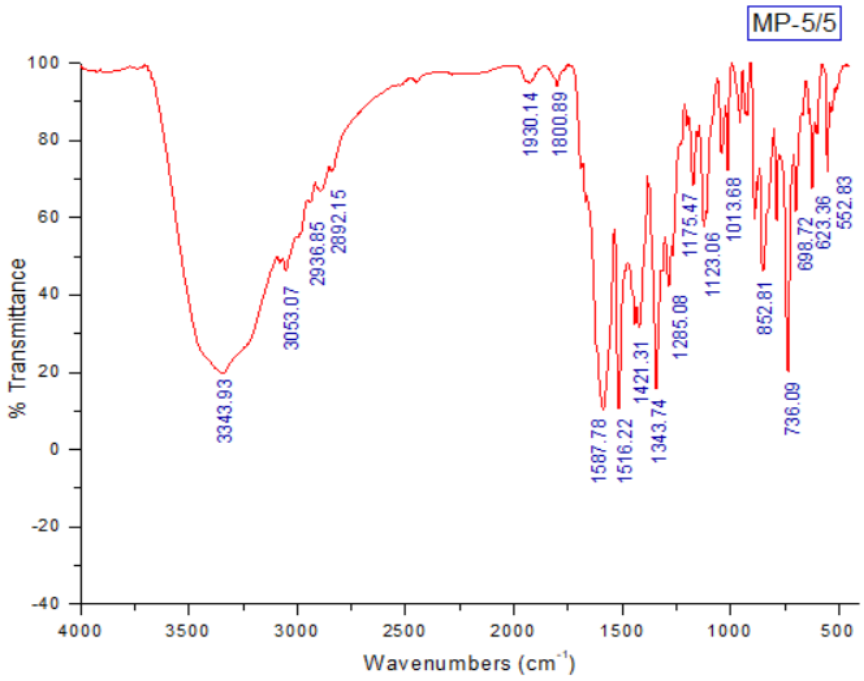
AC3.3 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-p-tolyl-4,5-dihydro-1H-pyrazole (3.9d)



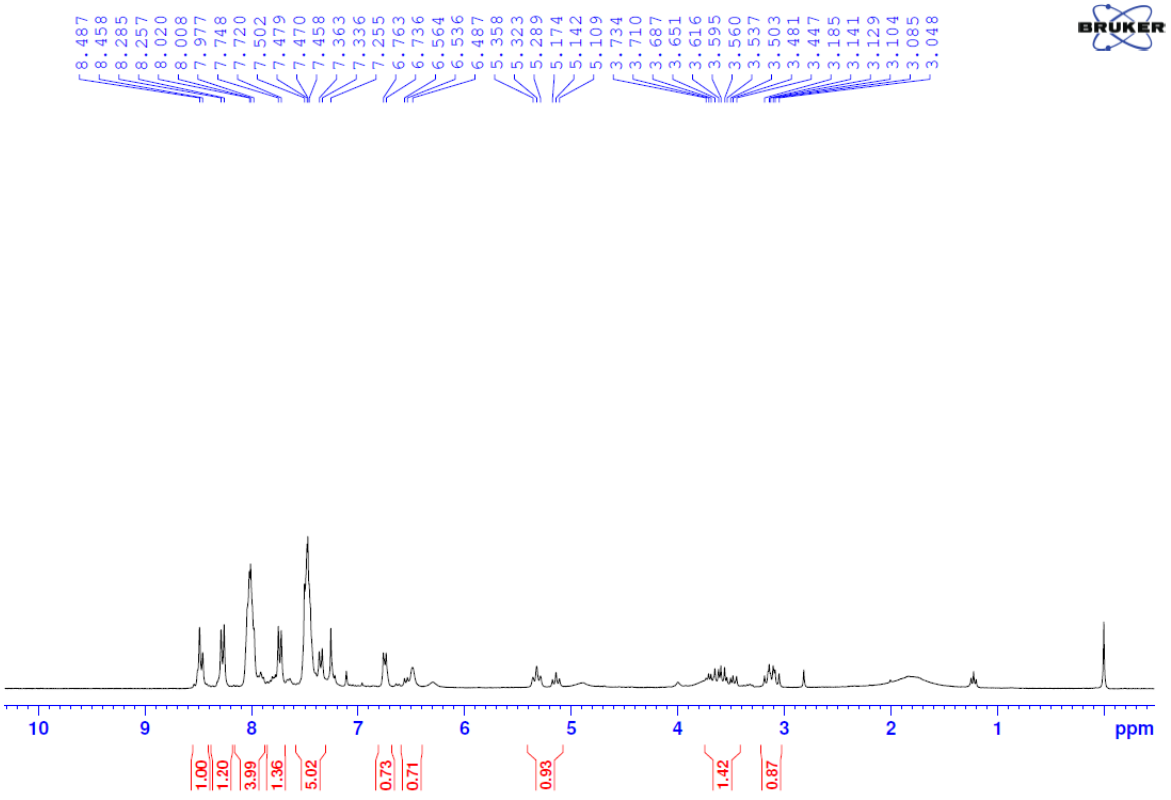
AC3.4 MS spectrum of 3-Anthracen-9-yl-5-p-tolyl-4,5-dihydro-1H-pyrazole (3.9d)



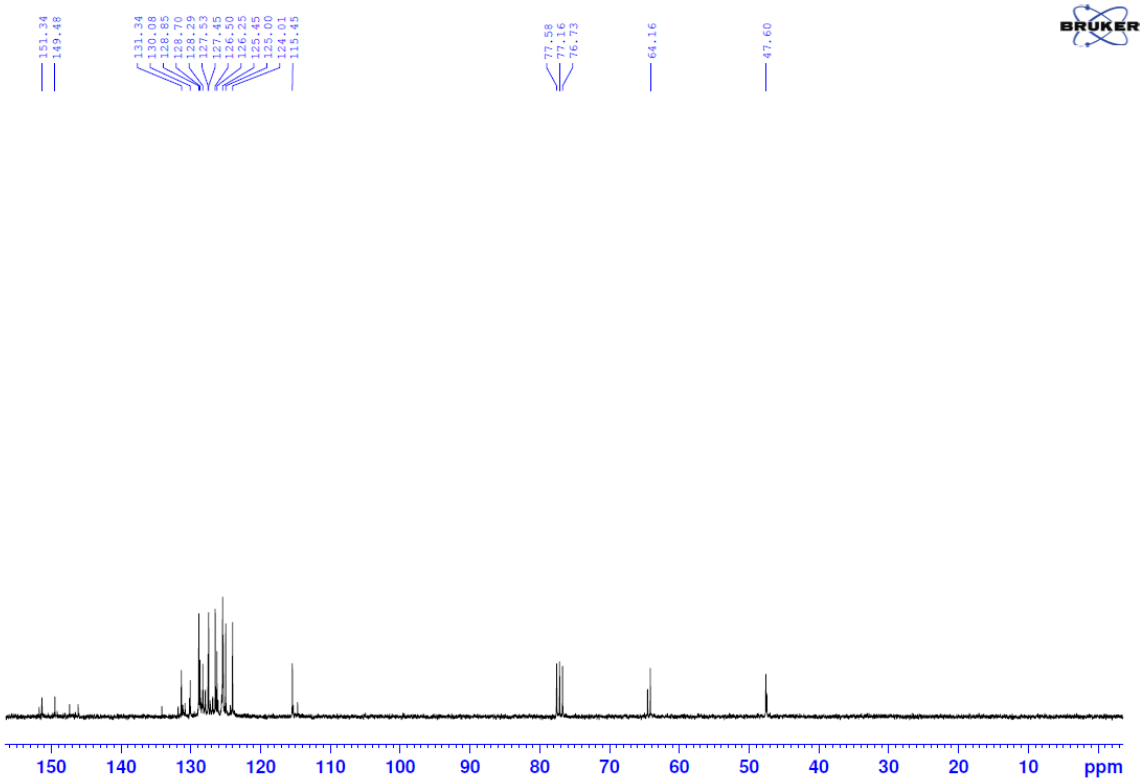
AC3.5 IR (KBr, *v*, cm^{-1}) spectrum of 3-Anthracen-9-yl-5-(3-chloro-phenyl)-4,5-dihydro-1H-pyrazole (3.9e)



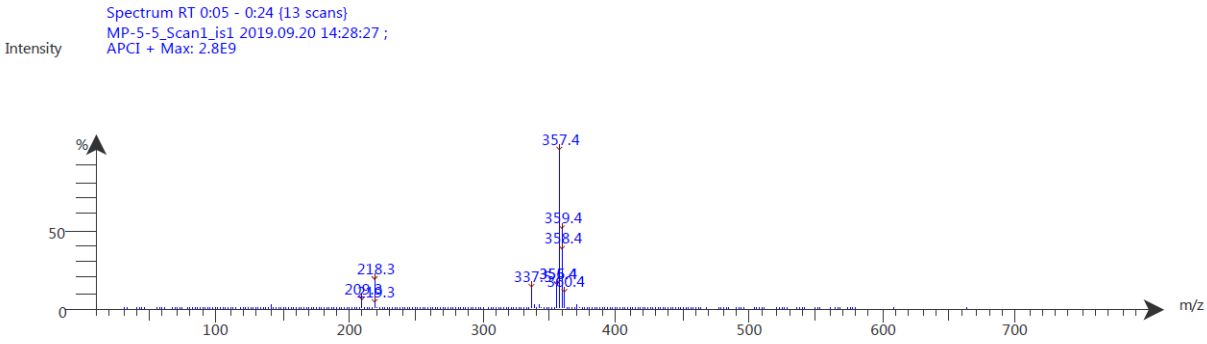
AC3.6 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(3-chloro-phenyl)-4,5-dihydro-1H-pyrazole (3.9e)



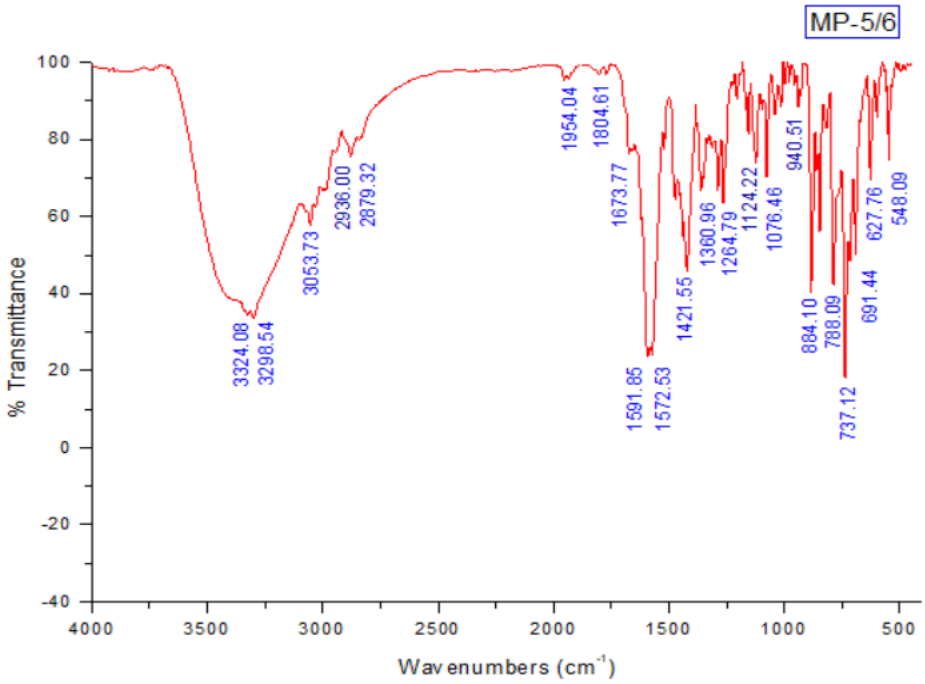
AC3.7 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(3-chloro-phenyl)-4,5-dihydro-1H-pyrazole (3.9e)



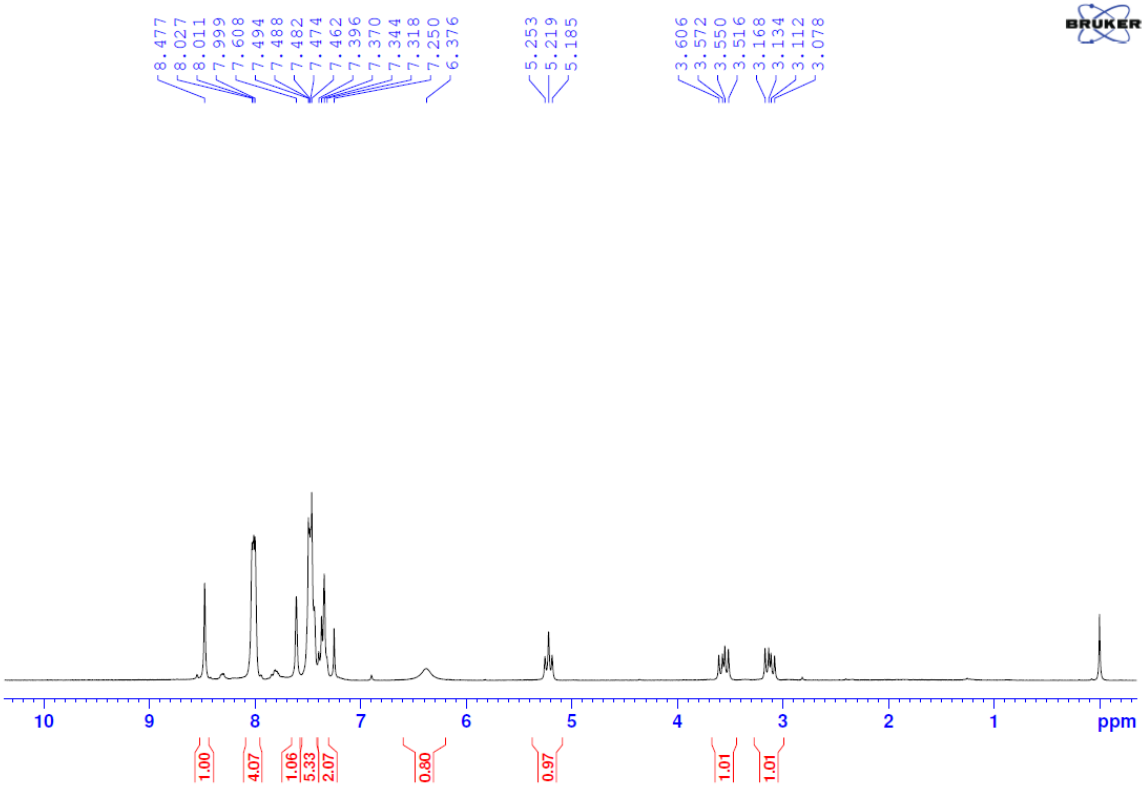
AC3.8 MS spectrum of 3-Anthracen-9-yl-5-(3-chloro-phenyl)-4,5-dihydro-1H-pyrazole (3.9e)



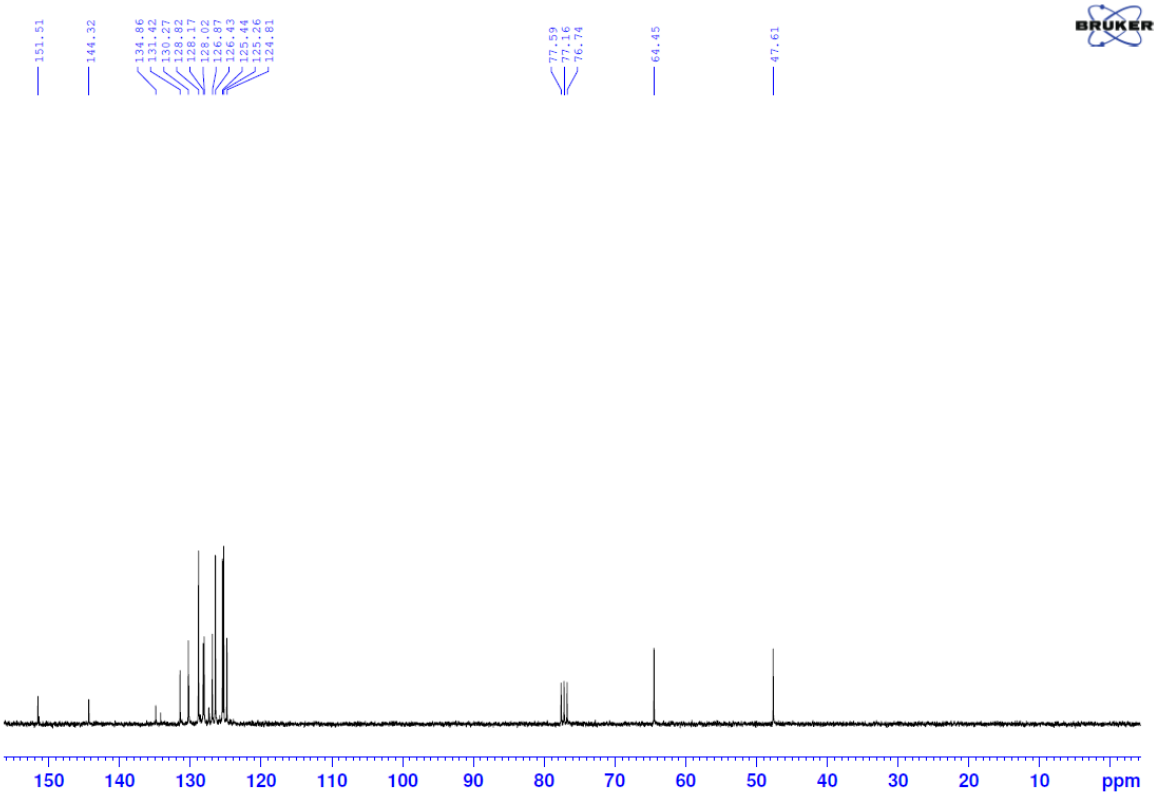
AC3.9 IR (KBr, *v*, cm^{-1}) spectrum of 3-Anthracen-9-yl-5-(4-nitro-phenyl)-4,5-dihydro-1H-pyrazole (3.9f)



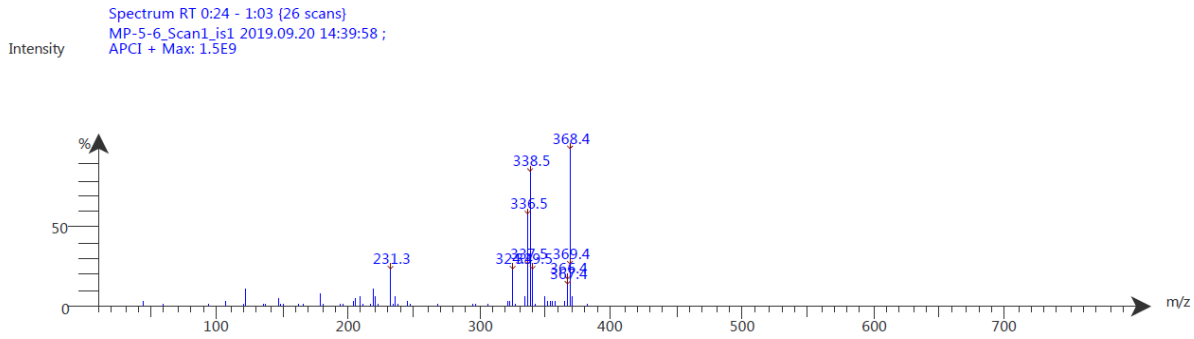
AC3.10 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(4-nitro-phenyl)-4,5-dihydro-1H-pyrazole (3.9f)



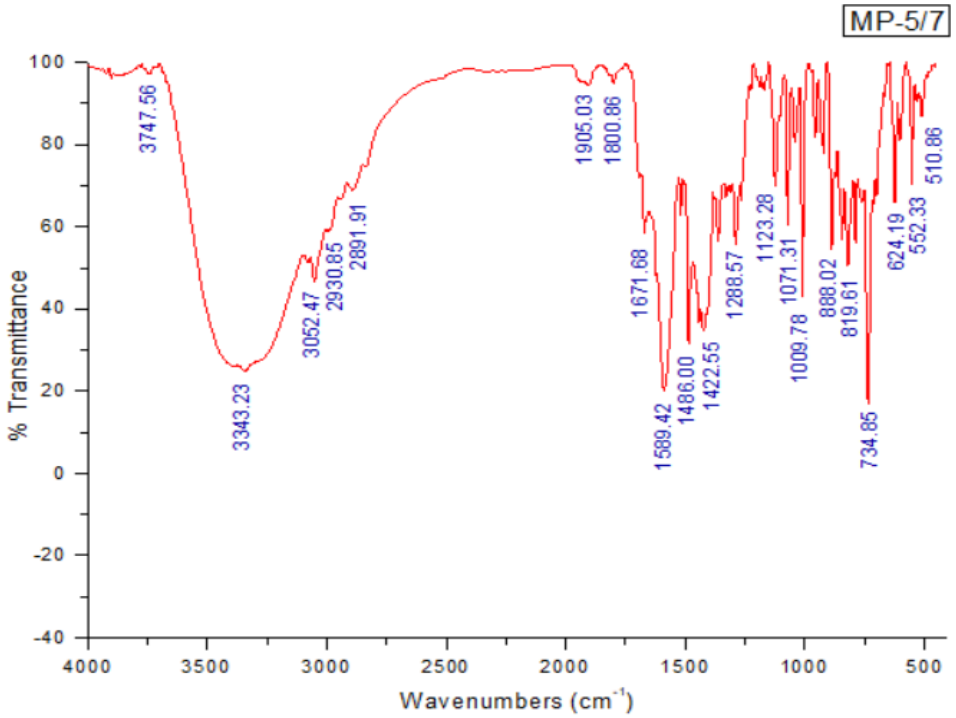
AC3.11 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(4-nitro-phenyl)-4,5-dihydro-1H-pyrazole (3.9f)



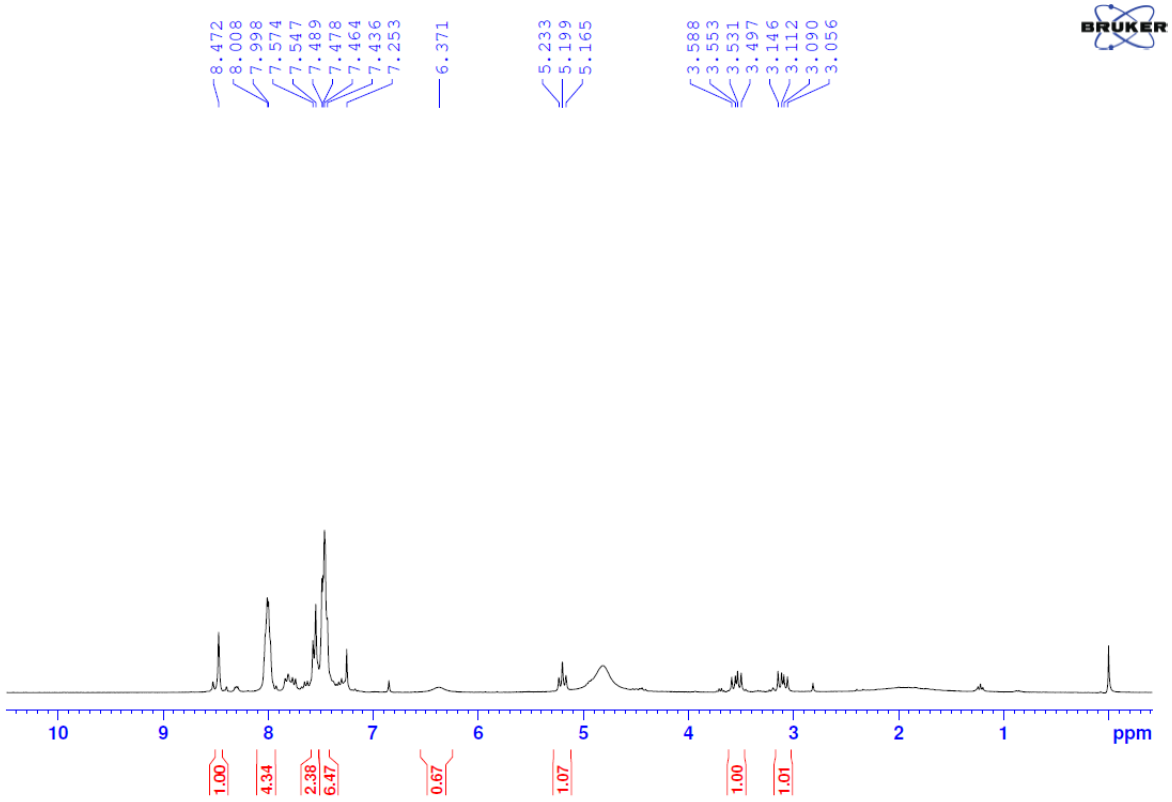
AC3.12 MS spectrum of 3-Anthracen-9-yl-5-(4-nitro-phenyl)-4,5-dihydro-1H-pyrazole (3.9f)



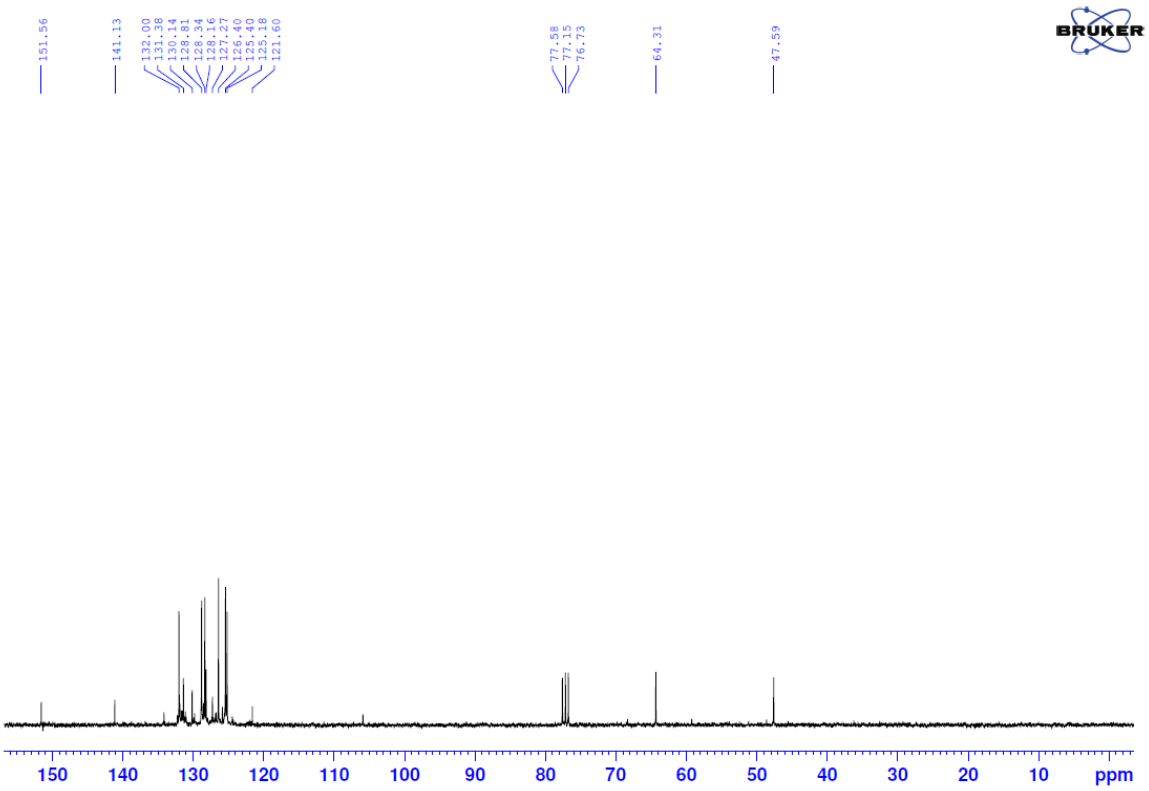
AC3.13 IR (KBr, *v*, cm^{-1}) spectrum of 3-Anthracen-9-yl-5-(4-bromo-phenyl)-4,5-dihydro-1H-pyrazole (3.9g)



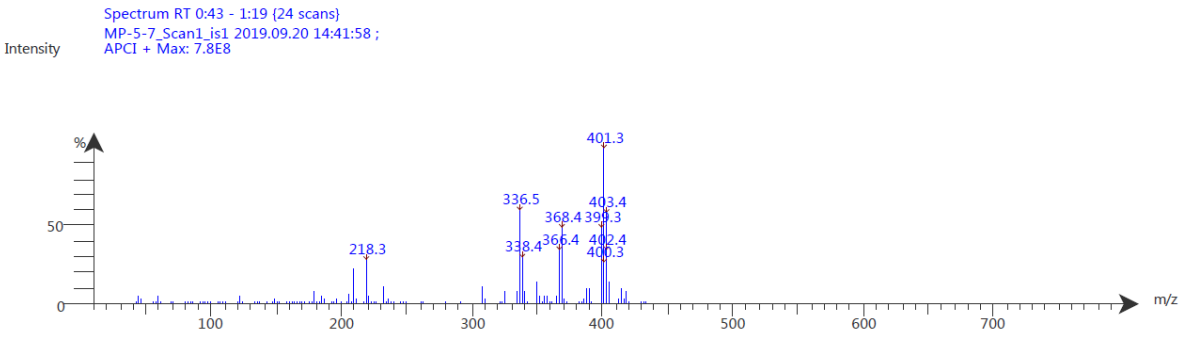
AC3.14 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(4-bromo-phenyl)-4,5-dihydro-1H-pyrazole (3.9g)



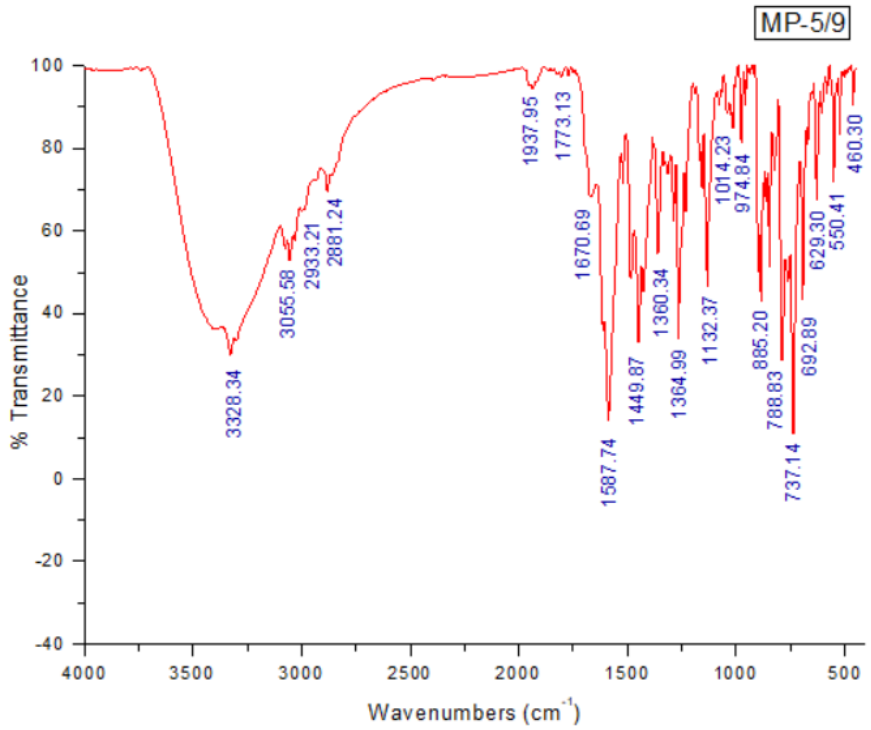
AC3.15 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(4-bromo-phenyl)-4,5-dihydro-1H-pyrazole (3.9g)



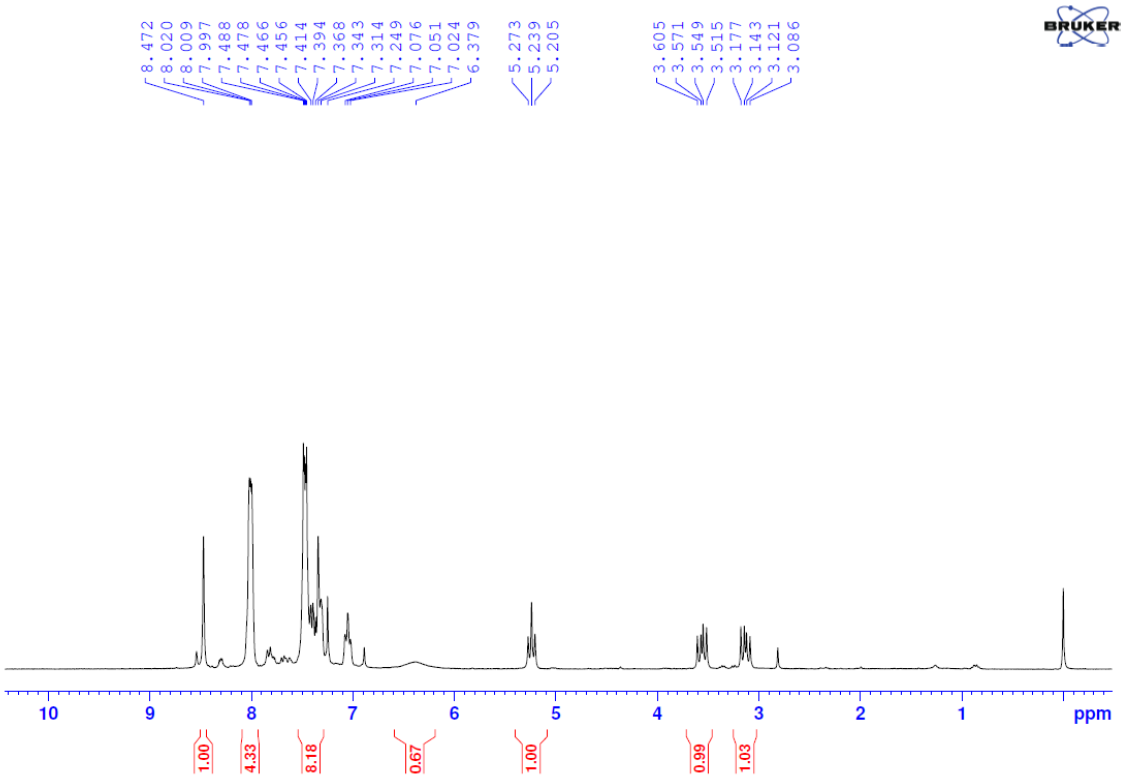
AC3.16 MS spectrum of 3-Anthracen-9-yl-5-(4-bromo-phenyl)-4,5-dihydro-1H-pyrazole (3.9g)



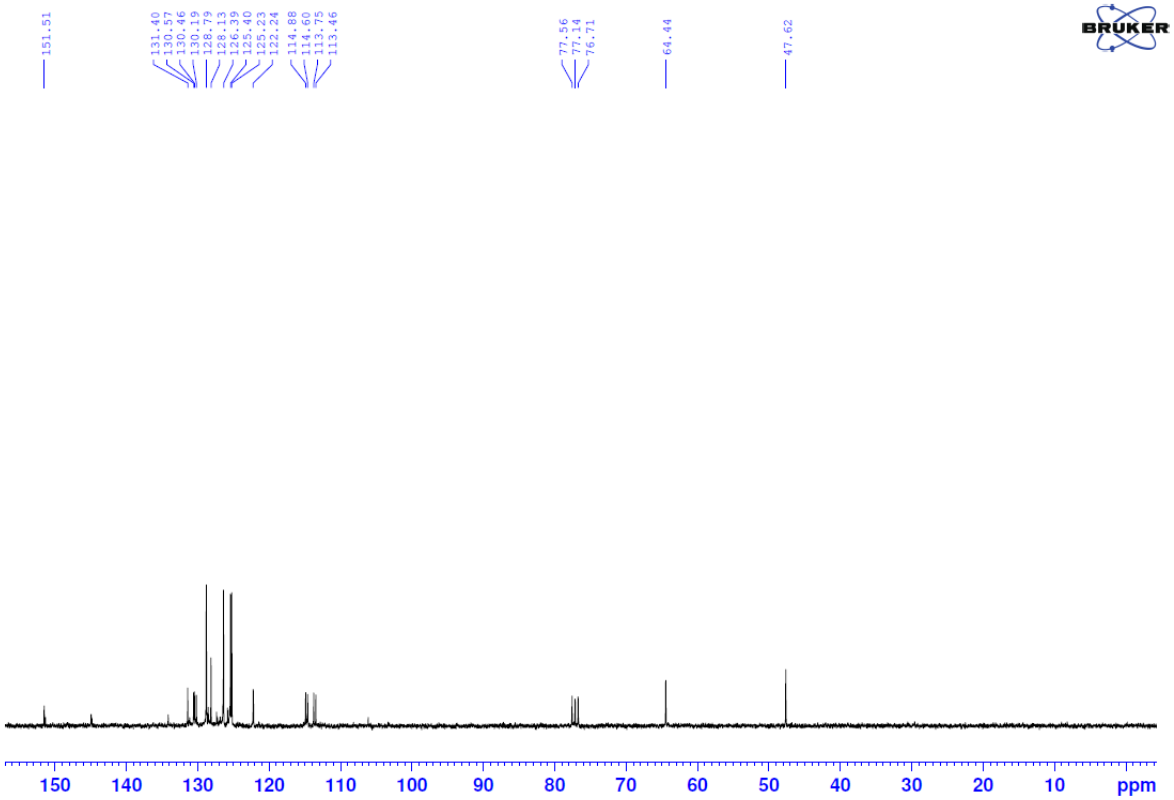
AC3.17 IR (KBr, *v*, cm^{-1}) spectrum of 3-Anthracen-9-yl-5-(3-fluoro-phenyl)-4,5-dihydro-1H-pyrazole (3.9h)



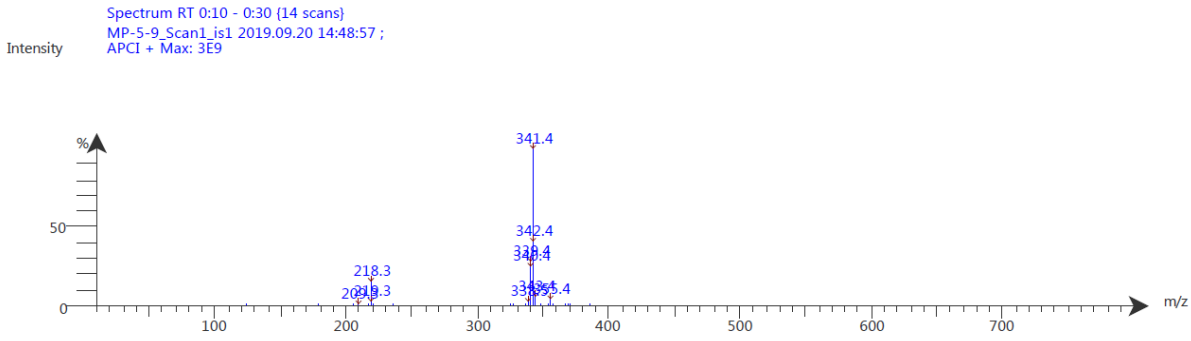
AC3.18 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(3-fluoro-phenyl)-4,5-dihydro-1H-pyrazole (3.9h)



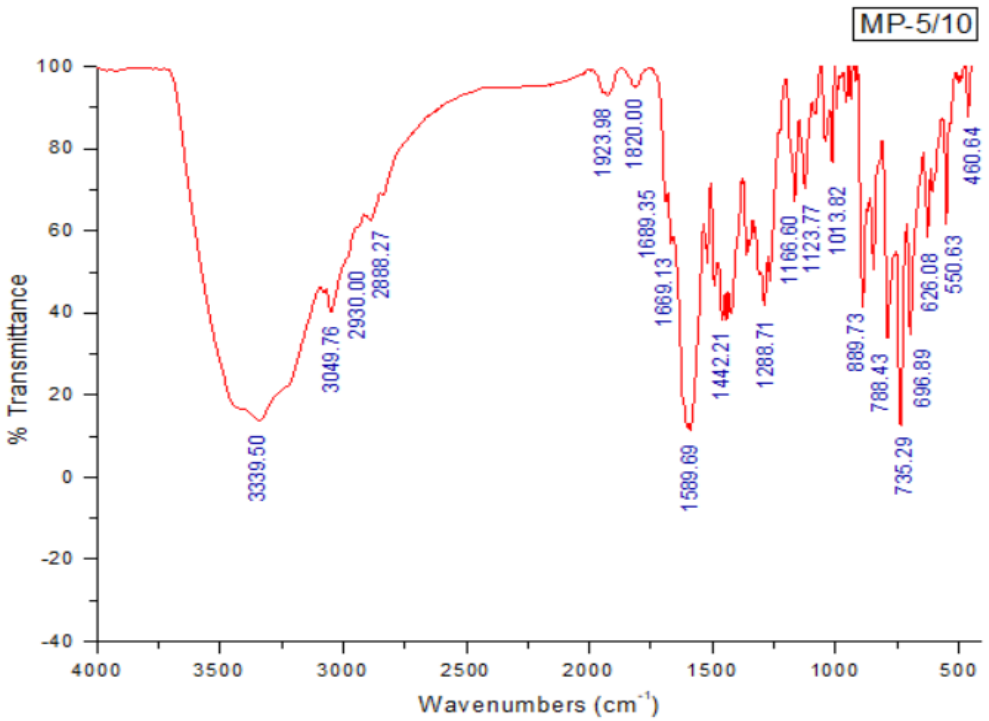
AC3.19 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(3-fluoro-phenyl)-4,5-dihydro-1H-pyrazole (3.9h)



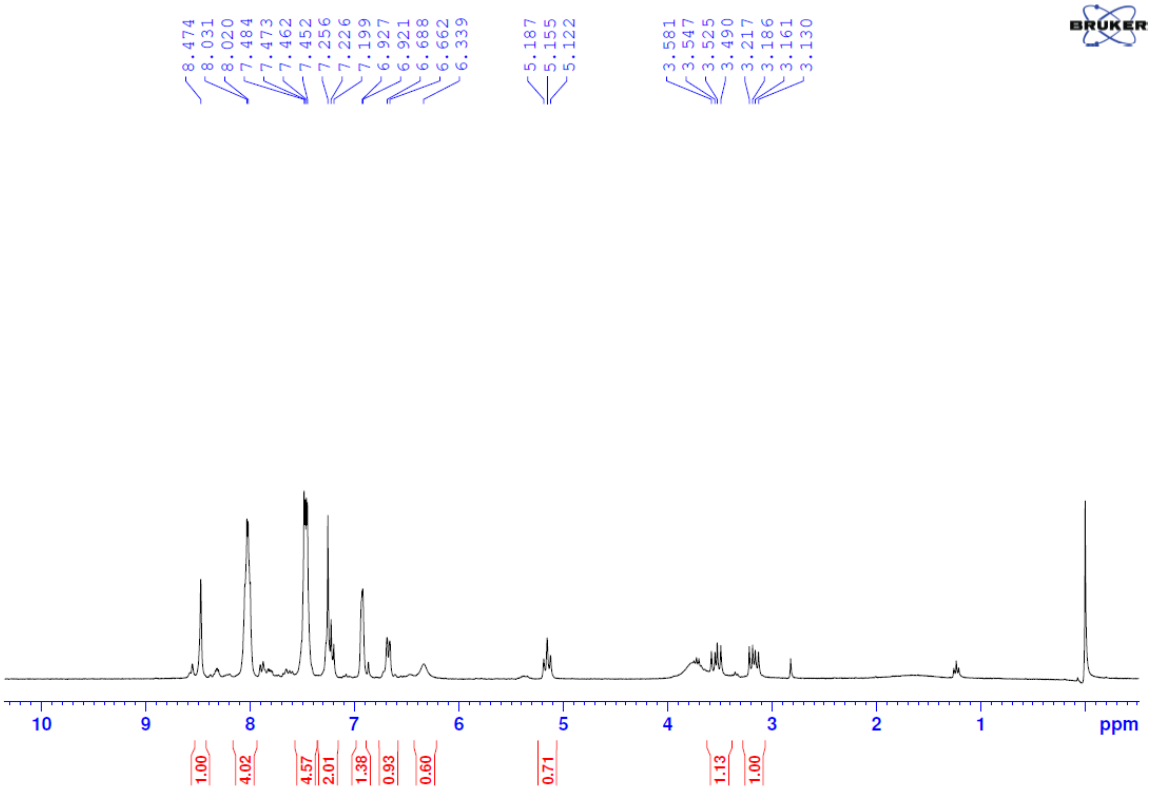
AC3.20 MS spectrum of 3-Anthracen-9-yl-5-(3-fluoro-phenyl)-4,5-dihydro-1H-pyrazole (3.9h)



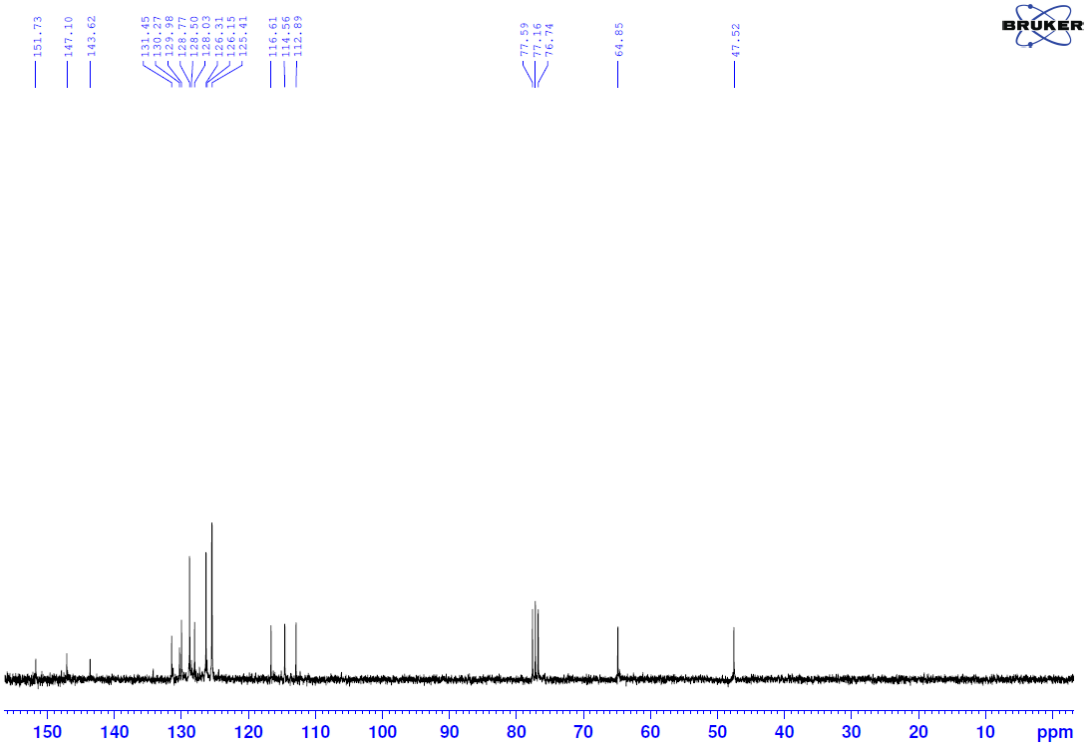
AC3.21 IR (KBr, *v*, cm^{-1}) spectrum of 3-Anthracen-9-yl-5-(3-nitro-phenyl)-4,5-dihydro-1H-pyrazole (3.9i)



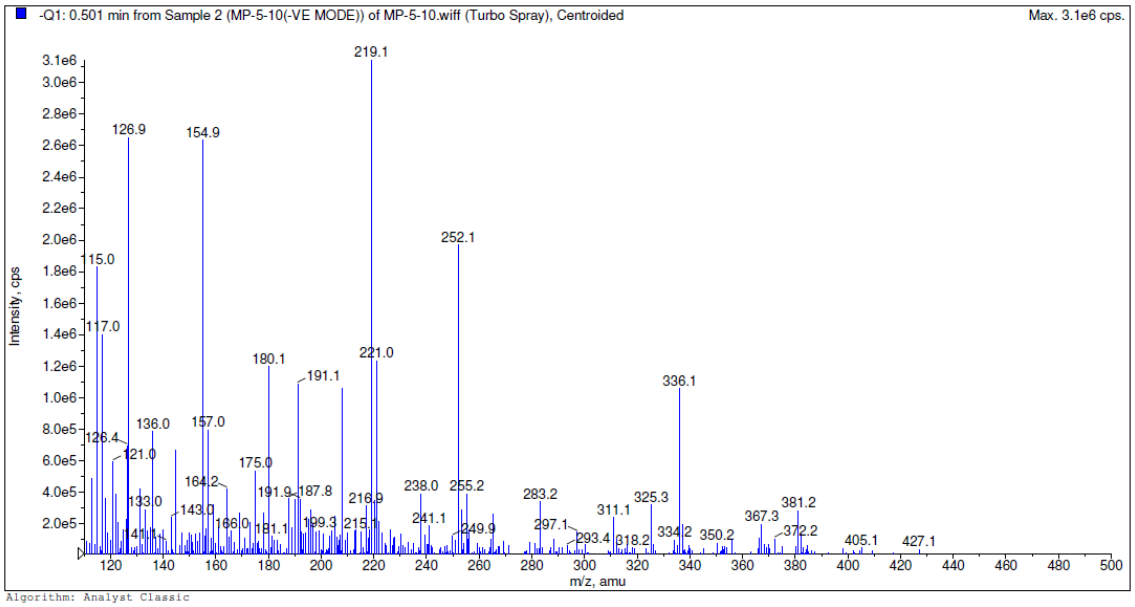
AC3.22 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(3-nitro-phenyl)-4,5-dihydro-1H-pyrazole (3.9i)



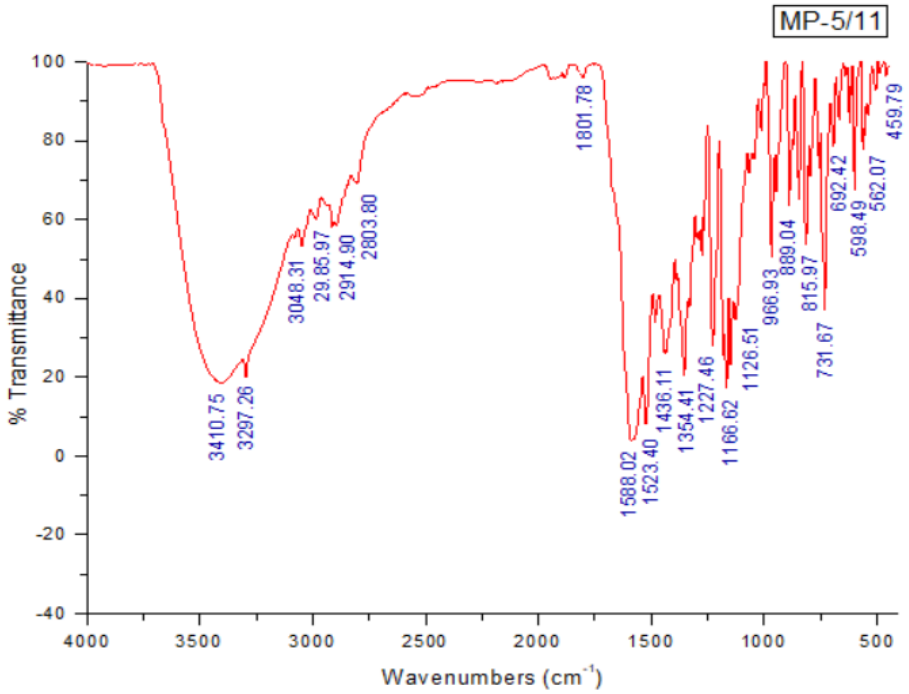
AC3.23 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(3-nitro-phenyl)-4,5-dihydro-1H-pyrazole (3.9i)



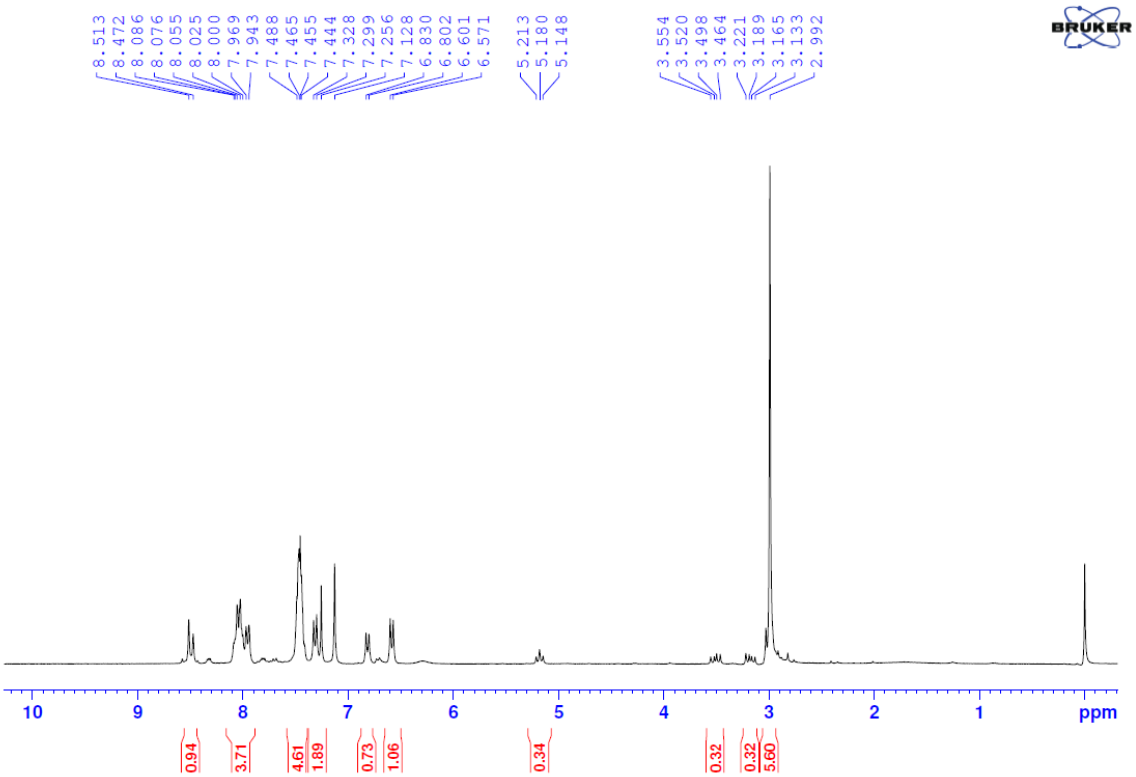
AC3.24 MS spectrum of 3-Anthracen-9-yl-5-(3-nitro-phenyl)-4,5-dihydro-1H-pyrazole (3.9i)



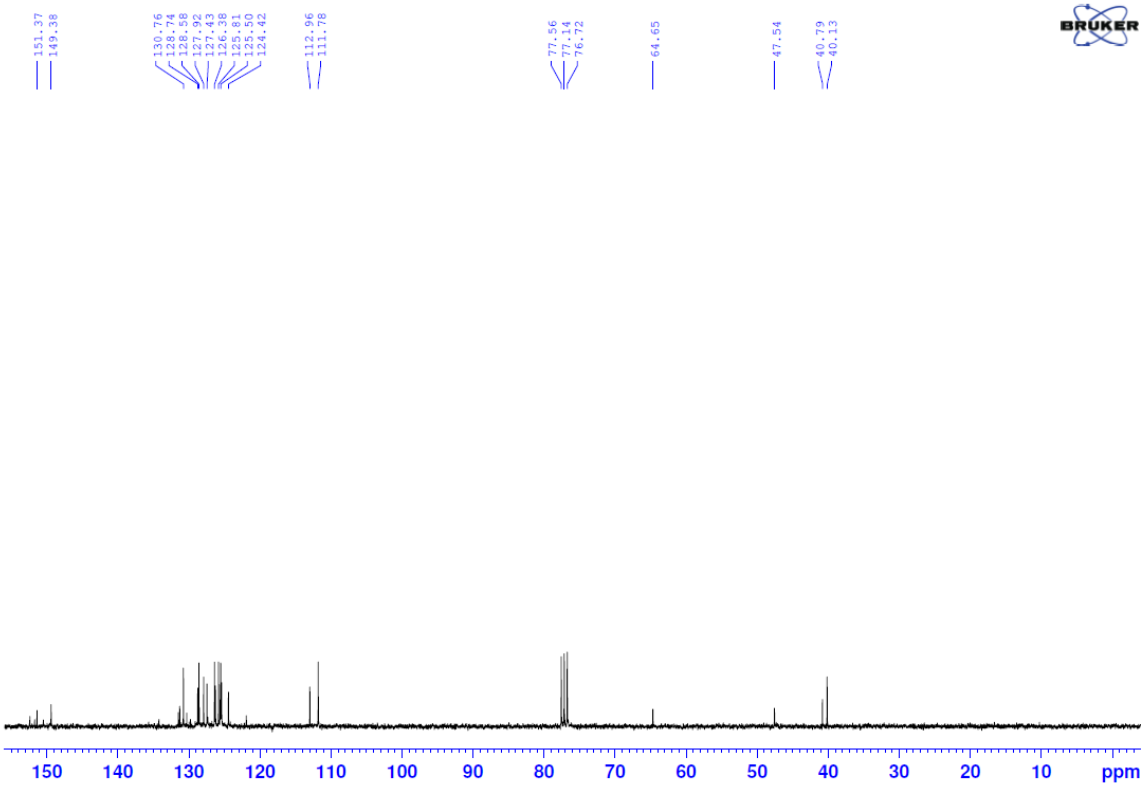
AC3.25 IR (KBr, *v*, cm^{-1}) spectrum of [4-(5-Anthracen-9-yl-3,4-dihydro-2H-pyrazol-3-yl)-phenyl]-dimethyl-amine (3.9j)



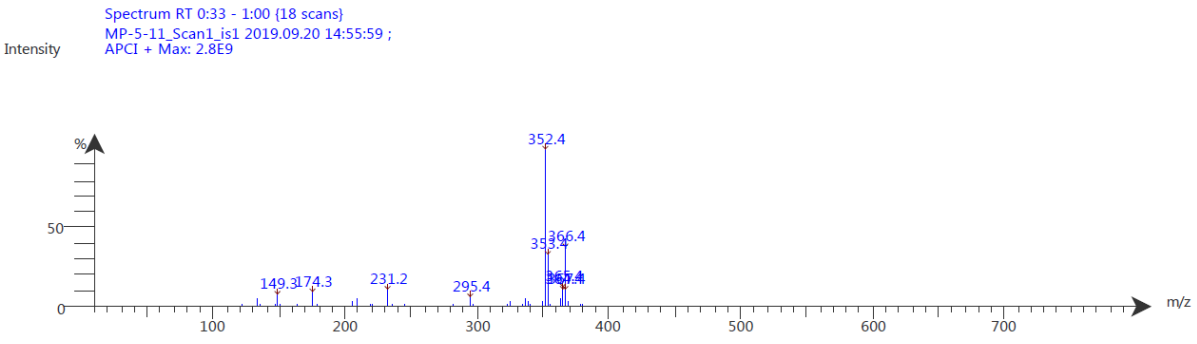
AC3.26 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of [4-(5-Anthracen-9-yl-3,4-dihydro-2H-pyrazol-3-yl)-phenyl]-dimethyl-amine (3.9j)



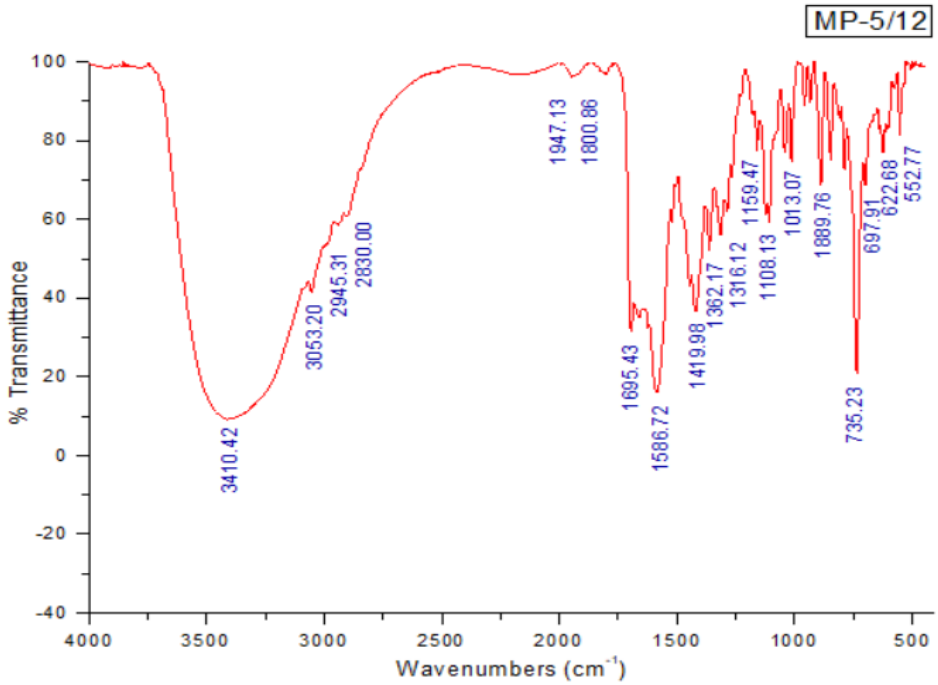
AC3.27 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of [4-(5-Anthracen-9-yl-3,4-dihydro-2H-pyrazol-3-yl)-phenyl]-dimethyl-amine (3.9j)



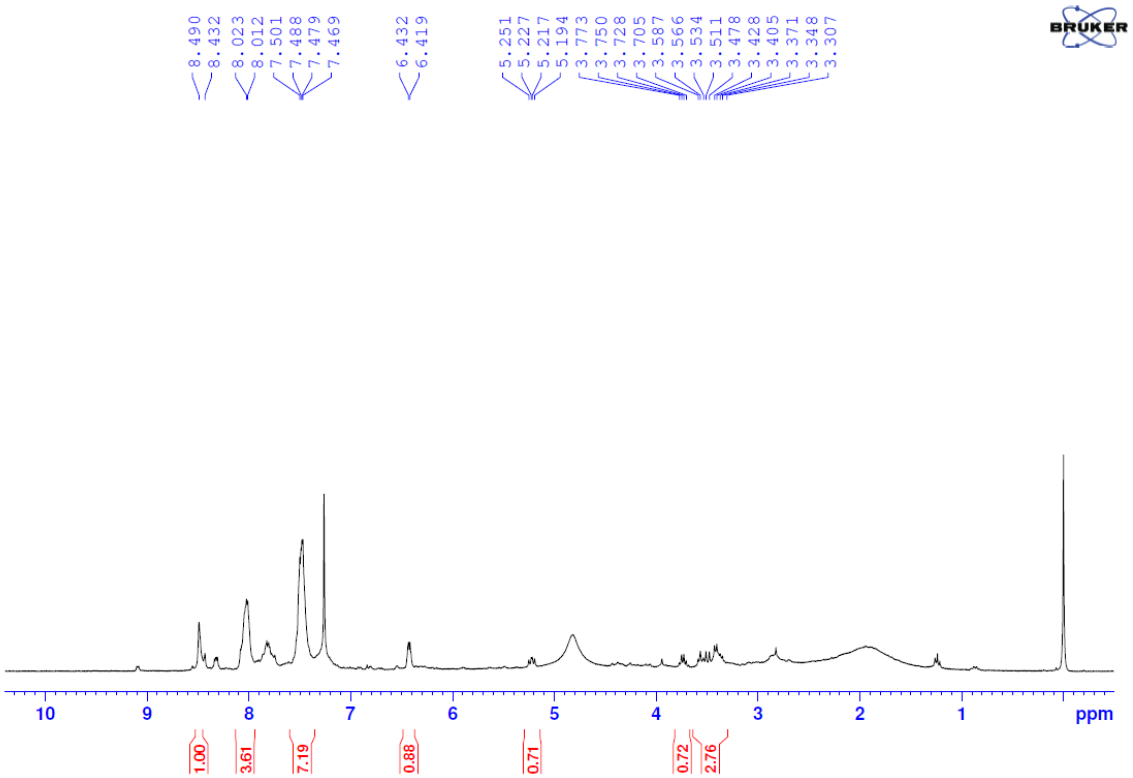
AC3.28 MS spectrum of [4-(5-Anthracen-9-yl-3,4-dihydro-2H-pyrazol-3-yl)-phenyl]-dimethyl-amine (3.9j)



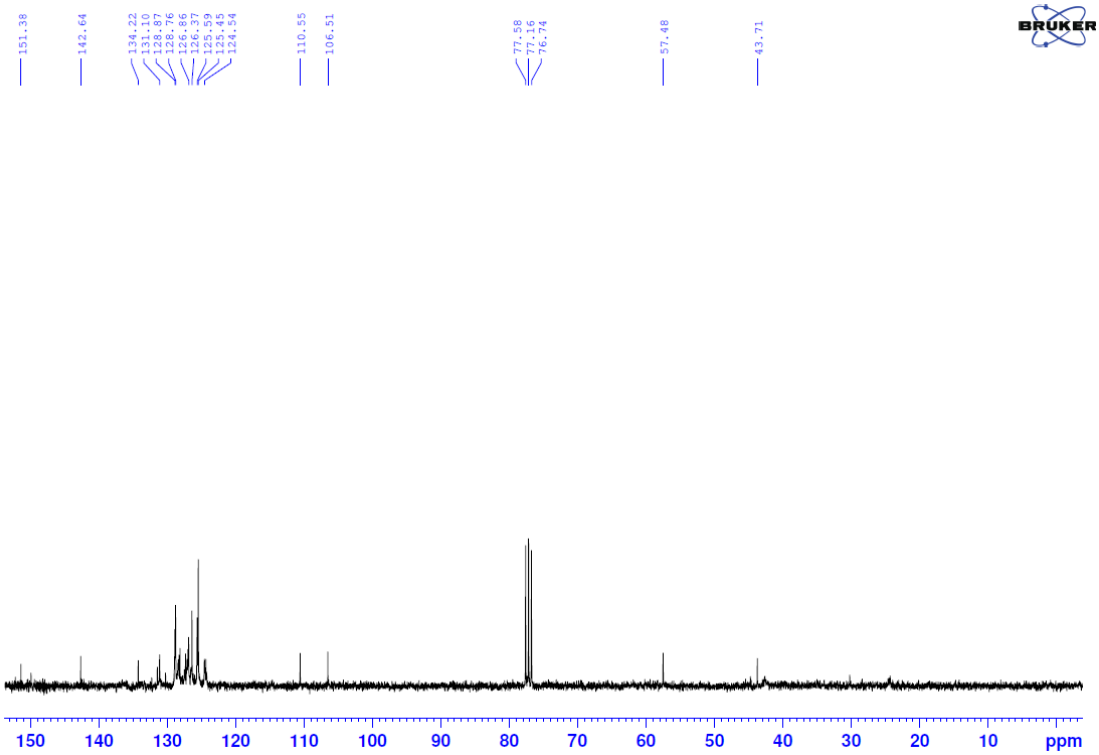
AC3.29 IR (KBr, *v*, cm^{-1}) spectrum of 3-Anthracen-9-yl-5-furan-2-yl-4,5-dihydro-1H-pyrazole (3.9k)



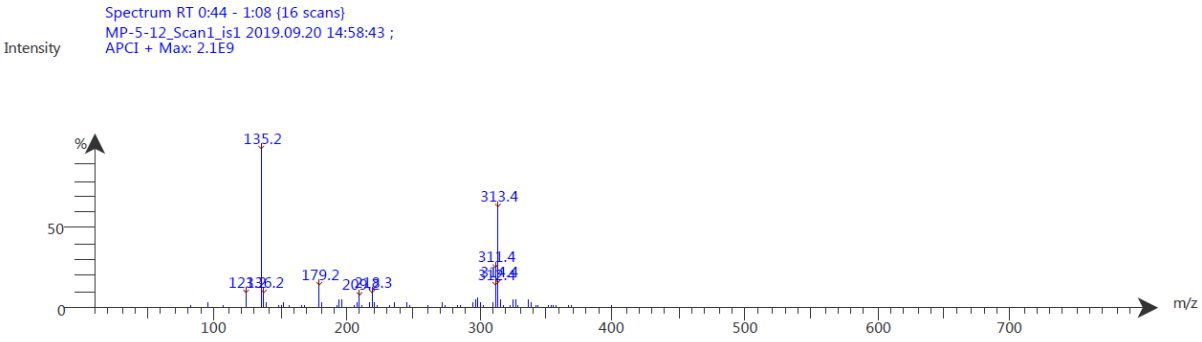
AC3.30 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-furan-2-yl-4,5-dihydro-1H-pyrazole (3.9k)



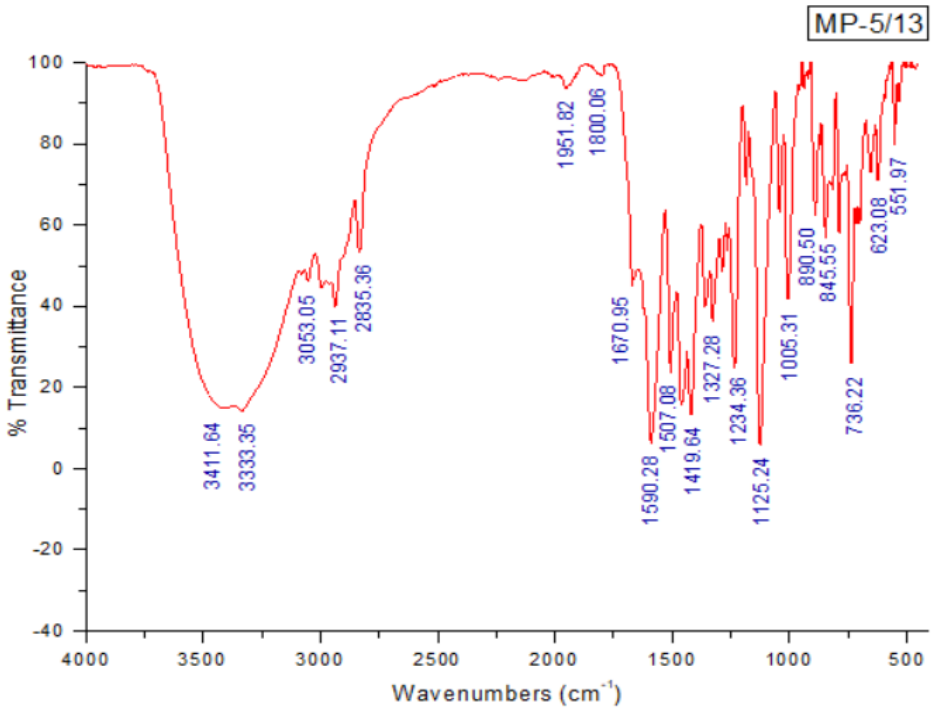
AC3.31 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-furan-2-yl-4,5-dihydro-1H-pyrazole (3.9k)



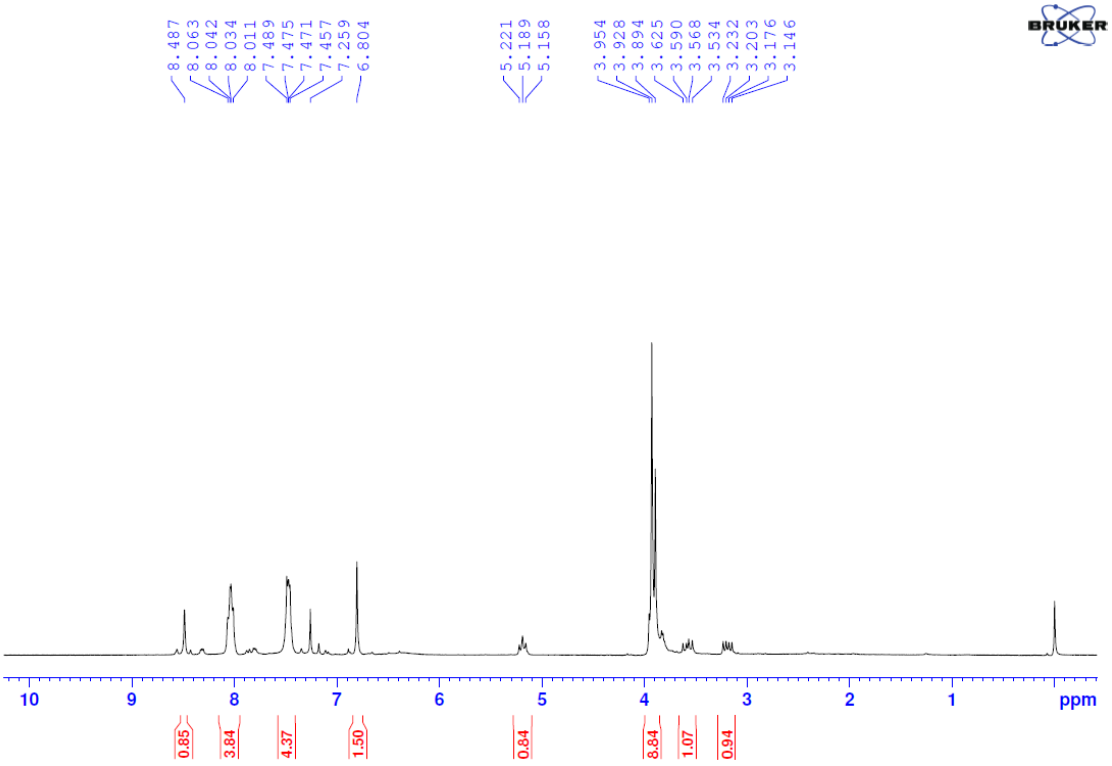
AC3.32 MS spectrum of 3-Anthracen-9-yl-5-furan-2-yl-4,5-dihydro-1H-pyrazole (3.9k)



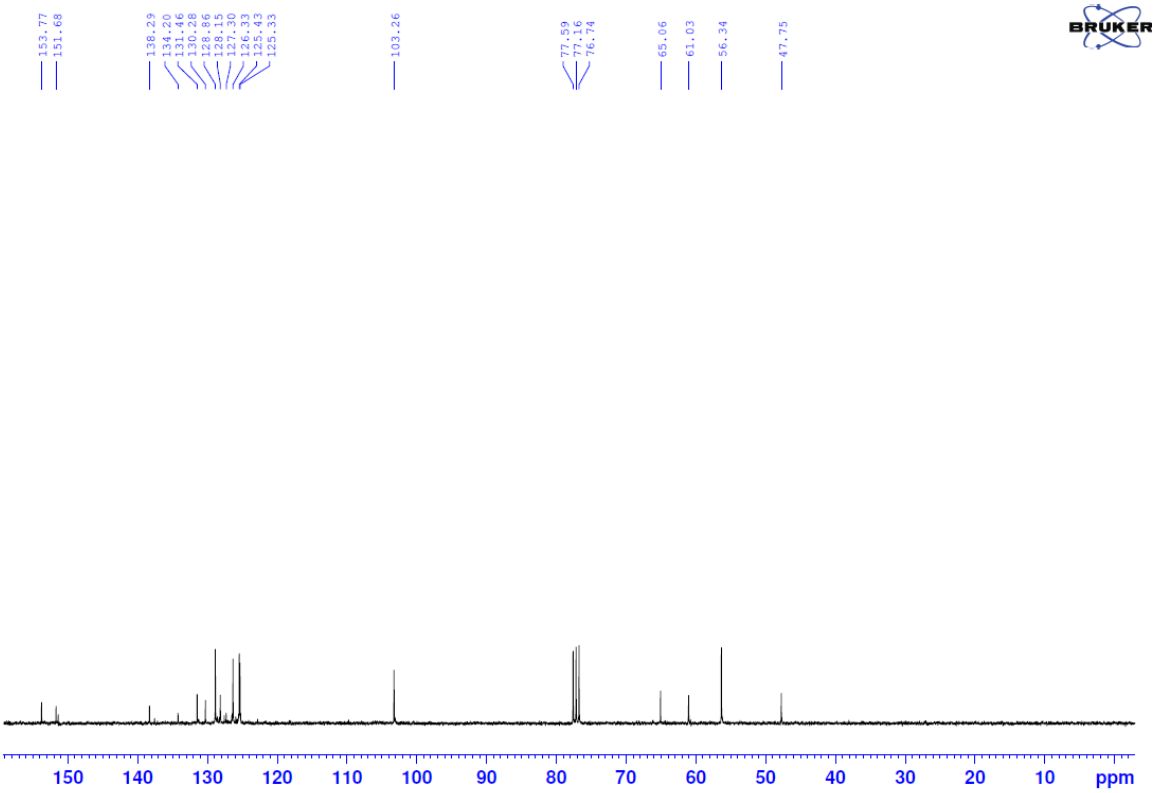
AC3.33 IR (KBr, *v*, cm^{-1}) spectrum of 3-Anthracen-9-yl-5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-1H-pyrazole (3.9l)



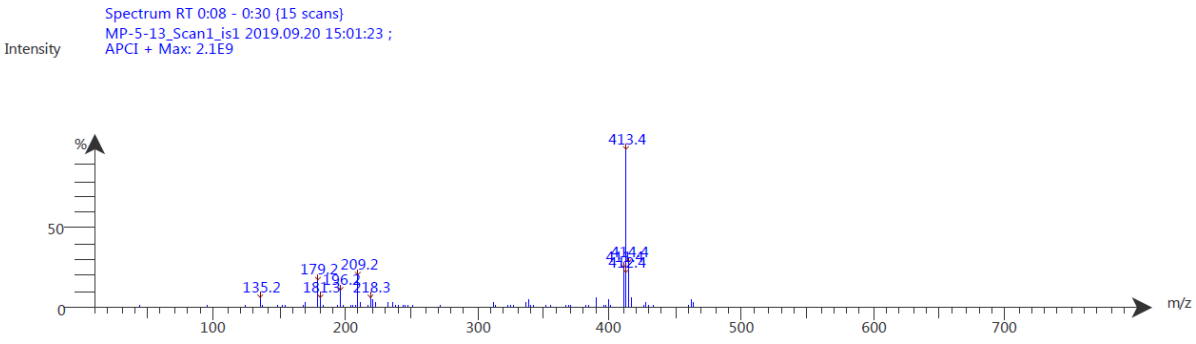
AC3.34 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-1H-pyrazole (3.9l)



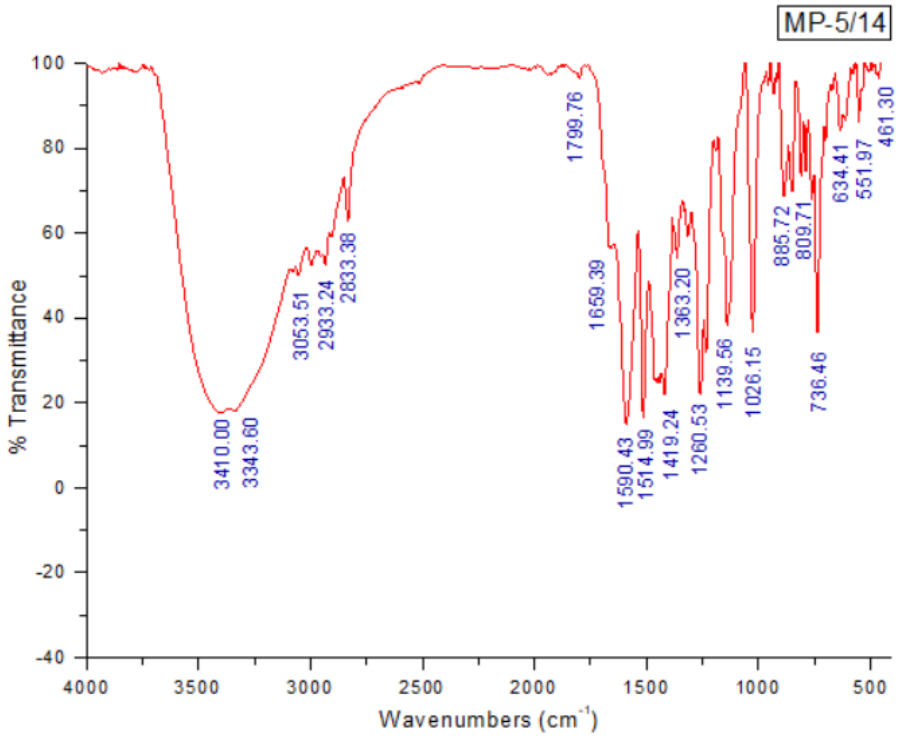
AC3.35 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-1H-pyrazole (3.9l)



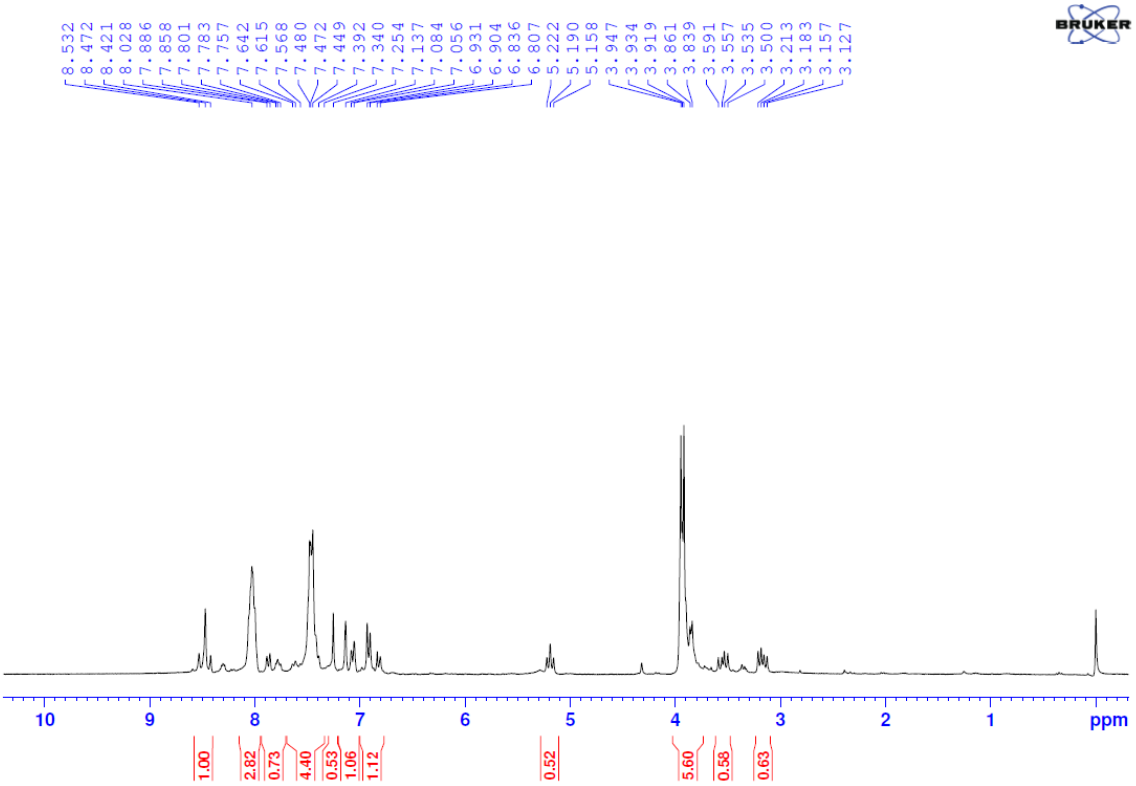
AC3.36 MS spectrum of 3-Anthracen-9-yl-5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-1H-pyrazole (3.9l)



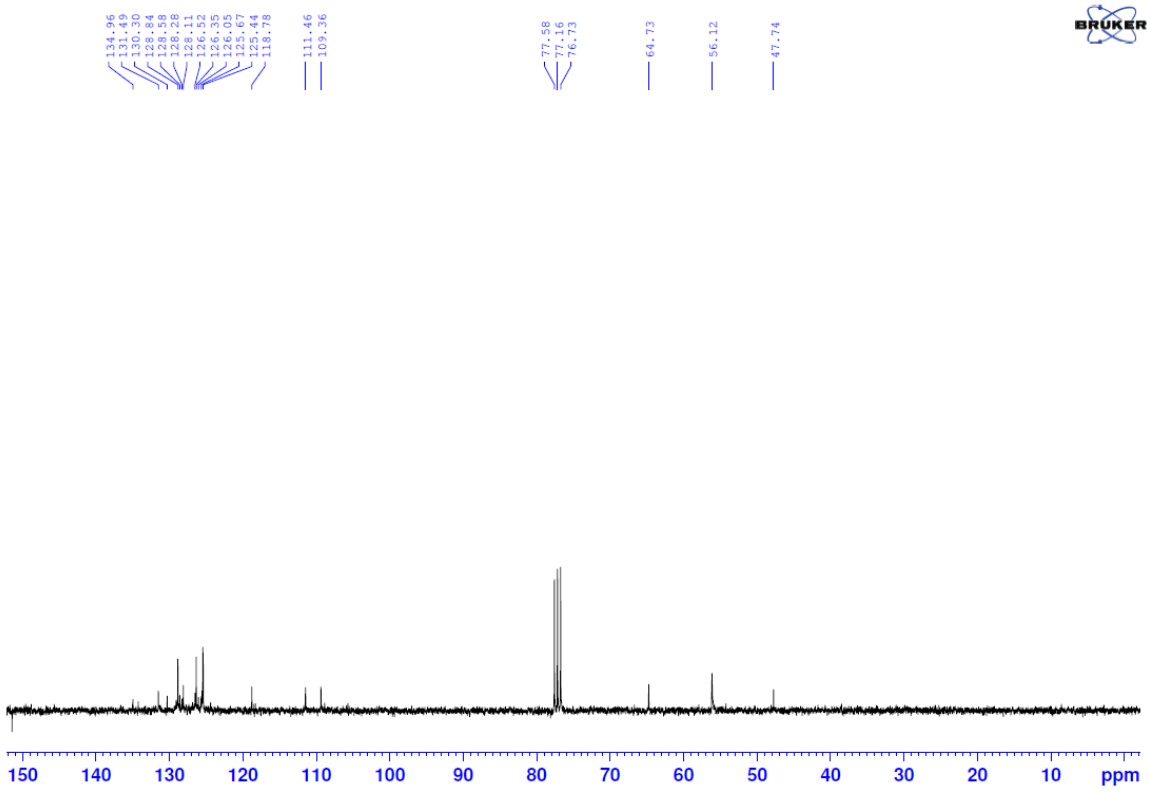
AC3.37 IR (KBr, *v*, cm^{-1}) spectrum of 3-Anthracen-9-yl-5-(3,4-dimethoxy-phenyl)-4,5-dihydro-1H-pyrazole (3.9m)



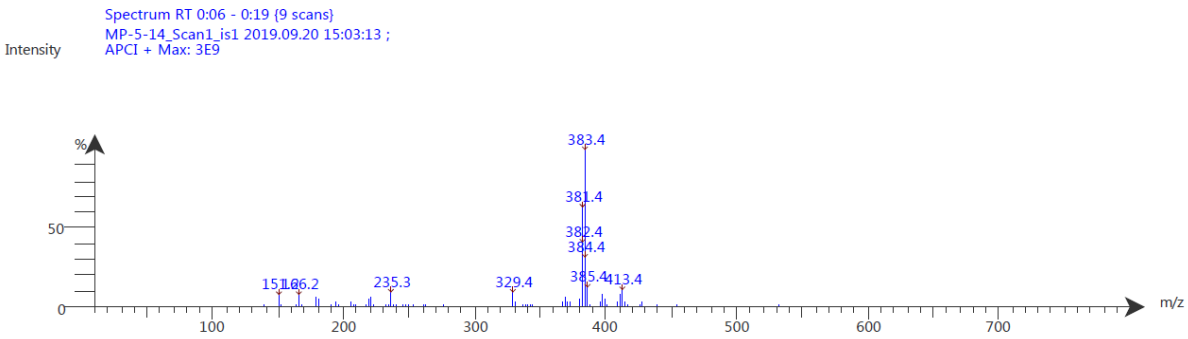
AC3.38 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(3,4-dimethoxy-phenyl)-4,5-dihydro-1H-pyrazole (3.9m)



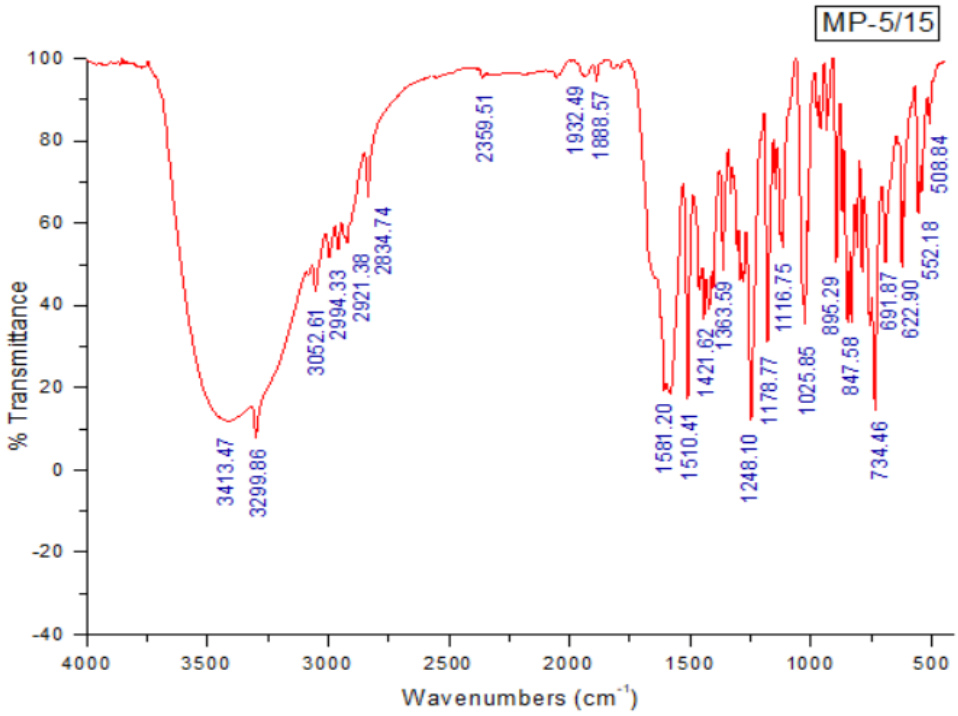
AC3.39 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(3,4-dimethoxy-phenyl)-4,5-dihydro-1H-pyrazole (3.9m)



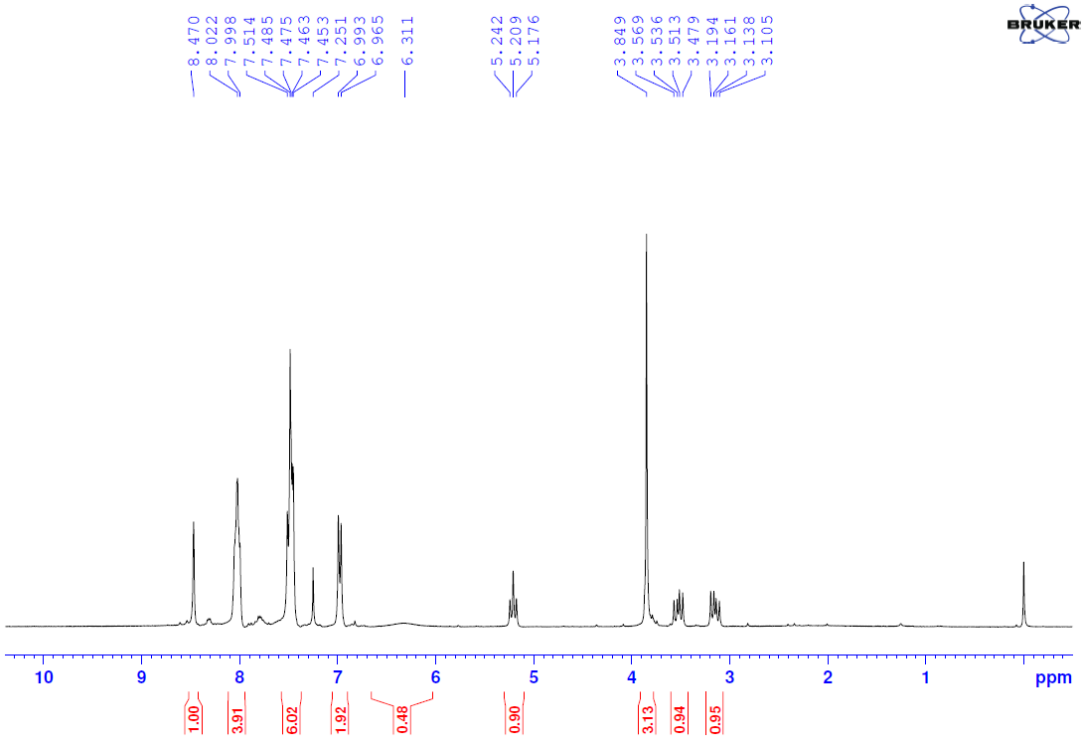
AC3.40 MS spectrum of 3-Anthracen-9-yl-5-(3,4-dimethoxy-phenyl)-4,5-dihydro-1H-pyrazole (3.9m)



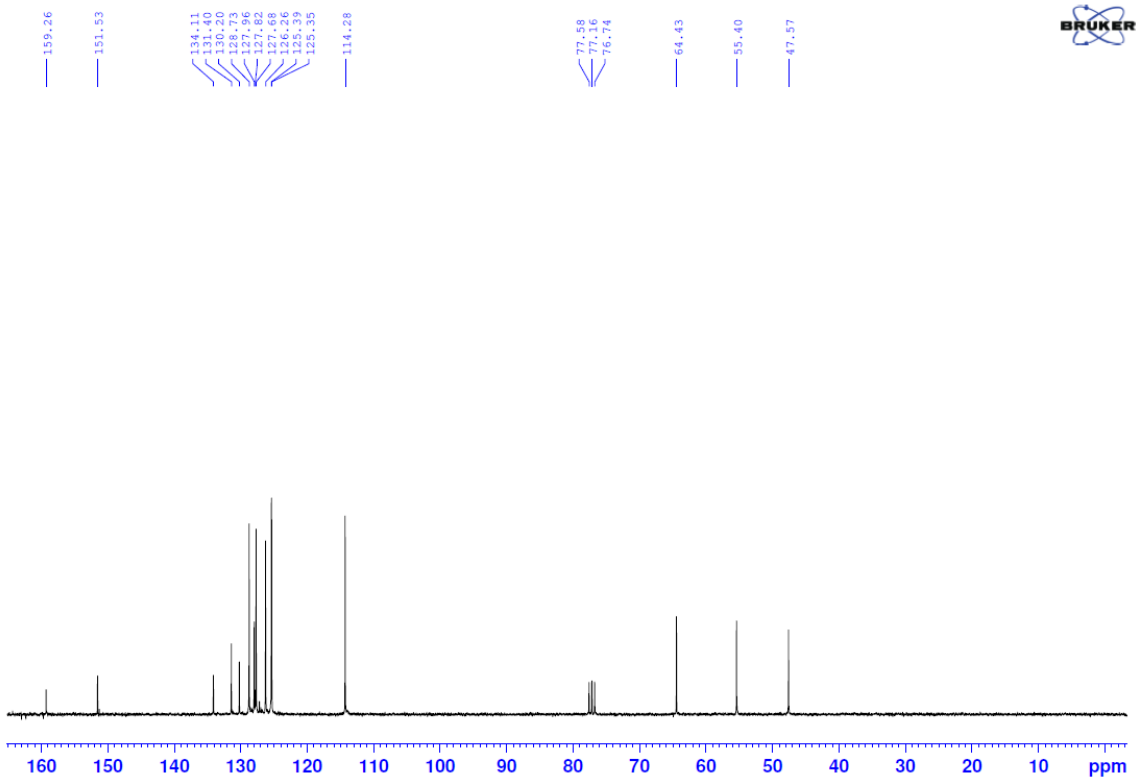
AC3.41 IR (KBr, *v*, cm^{-1}) spectrum of 3-Anthracen-9-yl-5-(4-methoxy-phenyl)-4,5-dihydro-1H-pyrazole (3.9n)



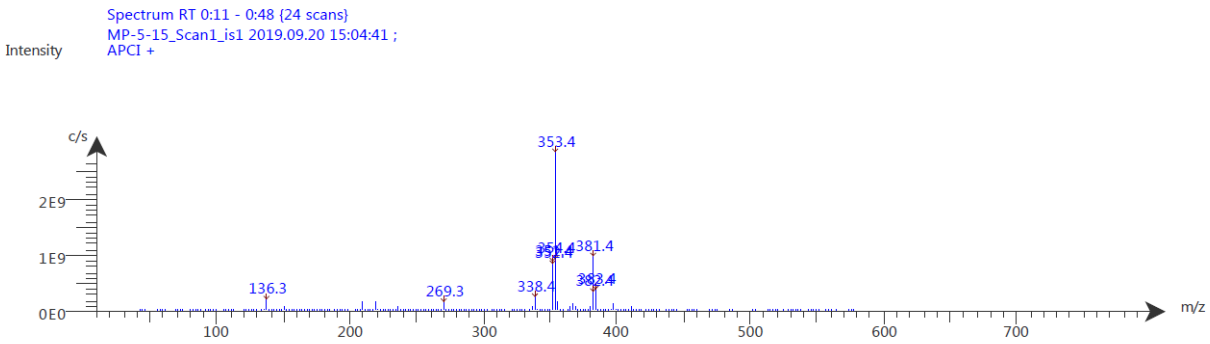
AC3.42 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(4-methoxy-phenyl)-4,5-dihydro-1H-pyrazole (3.9n)



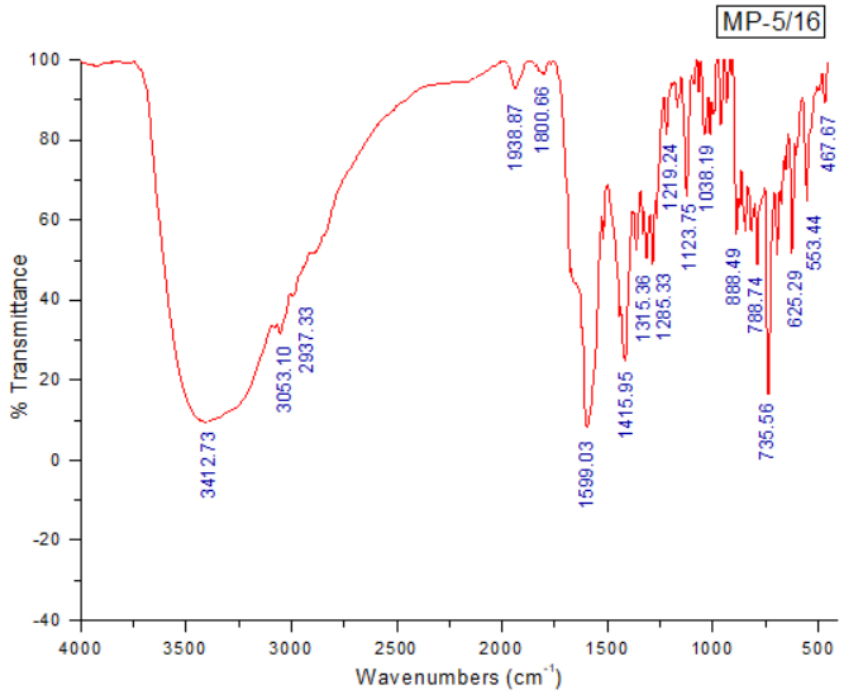
AC3.43 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-Anthracen-9-yl-5-(4-methoxy-phenyl)-4,5-dihydro-1H-pyrazole (3.9n)



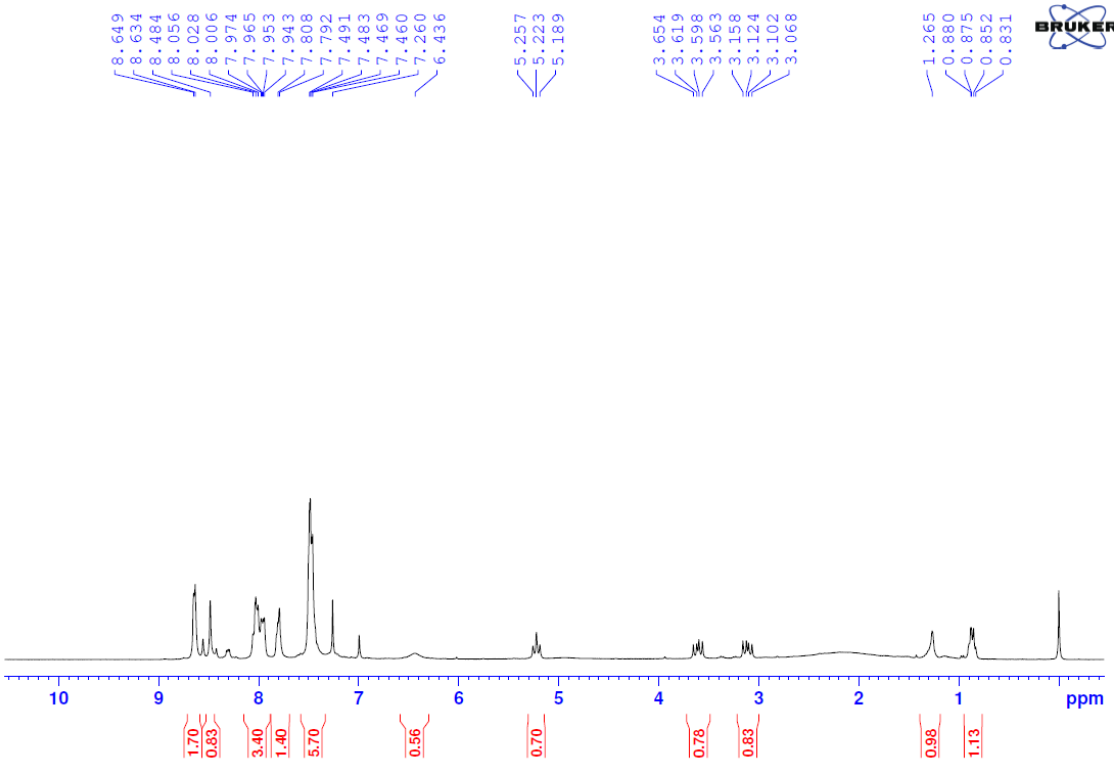
AC3.44 MS spectrum of 3-Anthracen-9-yl-5-(4-methoxy-phenyl)-4,5-dihydro-1H-pyrazole (3.9n)



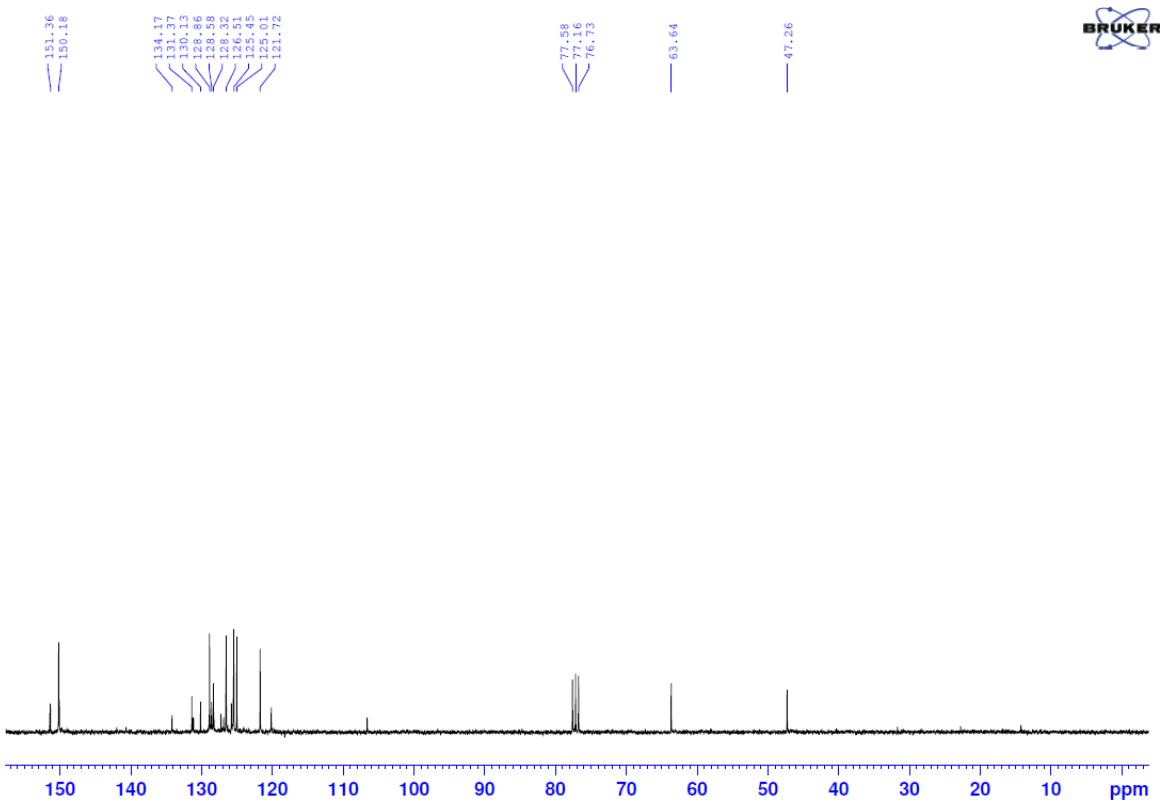
AC3.45 IR (KBr, *v*, cm^{-1}) spectrum of 4-(5-Anthracen-9-yl-3,4-dihydro-2H-pyrazol-3-yl)-pyridine (3.9o)



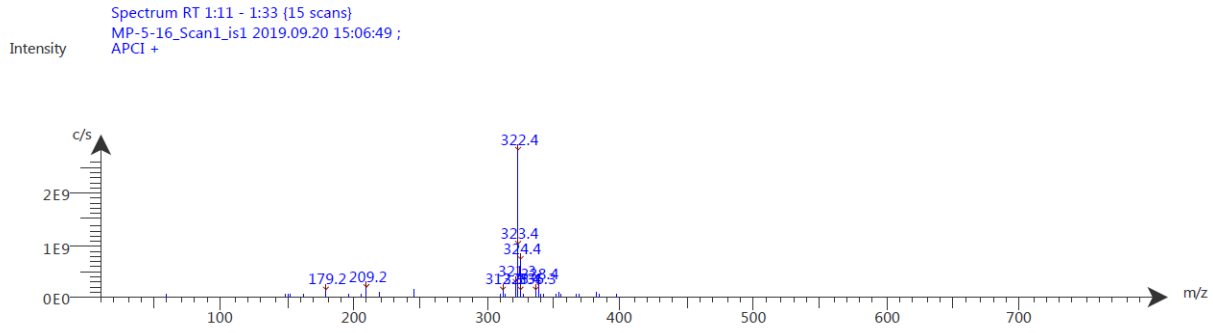
AC3.46 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 4-(5-Anthracen-9-yl-3,4-dihydro-2H-pyrazol-3-yl)-pyridine (3.9o)



AC3.47 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 4-(5-Anthracen-9-yl-3,4-dihydro-2H-pyrazol-3-yl)-pyridine (3.9o)

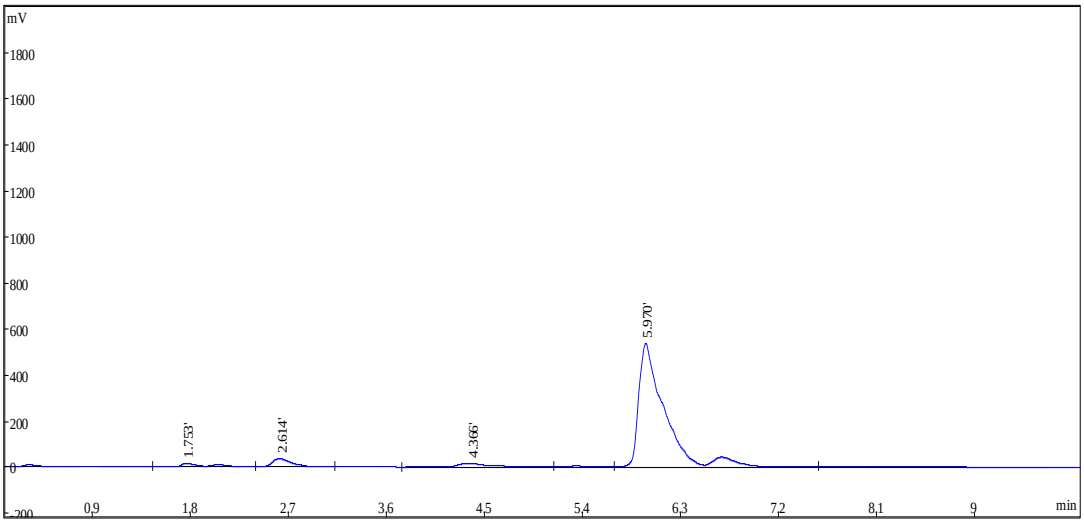


AC3.48 MS spectrum of compound 4-(5-Anthracen-9-yl-3,4-dihydro-2H-pyrazol-3-yl)-pyridine (3.9o)



AC3.49 HPLC Analysis spectrum of 3-Anthracen-9-yl-5-p-tolyl-4,5-dihydro-1H-pyrazole (3.9d)

Dr. M. Prabhakar's Lab, Dept. Chemistry, Nagaland University
Detector: Wavelength 270 nm
Column: C18
Water: Methanol 3:7; 1 mL/Min



Rank	Time	Name	Conc.	Area
1	1.753		3.682	394538
2	2.614		5.149	551651
3	4.366		7.01	751071
4	5.970		84.16	9016512
Total			100	10713772

Table AC3.1 Hydrogen bonding geometry of **3.9d**. Cg1, Cg2 and Cg3 are the centroids of the C25-38, C25-C30 and C1-C14, respectively

D–H···A	**D–H /Å**	**H···A / Å**	**D–H···A / Å**	**∠ D–H···A /º**
C9–H9···Cg1[1]	0.93	2.798	3.694	162.06
C47–H47···Cg1[2]	0.93	2.718	3.612	161.62
C46–H46···Cg2[2]	0.93	3.161	3.739	122.17
C19–H19···Cg3[3]	0.93	2.757	3.680	171.87

[1]x,1/2-y,-1/2+z; [2]3/2-x,-1/2+y,z; [3]3/2-x,1/2+y,z

Table AC3.2 Hydrogen bonding geometry of **3.9e**. Cg1 is the centroid of the six membered ring containing C9-14

D–H···A	**D–H /Å**	**H···A / Å**	**D–H···A / Å**	**∠ D–H···A /º**
N1–H1···N2[1]	0.86	2.55	3.263(5)	141.0
C21–H21···Cl1[2]	0.93	2.89	3.672(5)	142.5
C11–H11···Cl1[3]	0.93	2.92	3.804(6)	160.0
C16–H16B···Cg1[4]	0.97	2.88	3.701	143.03
C4–H4···Cg2[1]	0.93	3.042	3.781	137.68

[1]3/2-x,3/2-y,+z; [2]+x,1/2-y,1/2+z; [3]1-x,1-y,-z; [4]x,1.5-y,1/2+z

Table AC3.3 Bond Lengths of compound **3.9d**

Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**
N3	N4	1.393(3)	C1	C2	1.420(5)
N3	C39	1.288(3)	C32	C31	1.371(5)
N1	N2	1.393(3)	C32	C33	1.427(5)
N1	C15	1.282(3)	C45	C44	1.372(4)
N4	C41	1.456(4)	C45	C46	1.380(4)
N2	C17	1.458(4)	C45	C48	1.507(5)
C38	C25	1.414(4)	C8	C7	1.365(6)
C38	C39	1.481(3)	C8	C9	1.434(6)
C38	C37	1.386(4)	C26	C27	1.360(4)
C14	C15	1.481(3)	C17	C16	1.546(4)
C14	C13	1.414(4)	C12	C11	1.369(5)
C14	C1	1.397(4)	C43	C44	1.370(4)
C25	C30	1.435(4)	C47	C46	1.370(5)
C25	C26	1.412(4)	C21	C20	1.385(5)
C39	C40	1.494(3)	C21	C22	1.382(5)
C15	C16	1.496(4)	C21	C24	1.492(5)
C42	C41	1.513(4)	C23	C22	1.373(5)
C42	C43	1.375(4)	C6	C7	1.373(6)
C42	C47	1.393(4)	C6	C5	1.419(7)
C37	C32	1.450(4)	C36	C35	1.355(5)
C37	C36	1.428(4)	C19	C20	1.359(5)
C18	C17	1.514(4)	C29	C28	1.340(6)
C18	C23	1.374(4)	C2	C3	1.361(6)
C18	C19	1.386(4)	C27	C28	1.399(6)
C13	C8	1.443(4)	C33	C34	1.331(6)
C13	C12	1.402(5)	C9	C10	1.315(7)
C41	C40	1.548(4)	C34	C35	1.431(7)
C30	C31	1.371(5)	C11	C10	1.405(7)
C30	C29	1.437(5)	C5	C4	1.336(8)
C1	C6	1.443(4)	C3	C4	1.403(8)

Table AC3.4 Bond angles of compound **3.9d**

Atom	**Atom**	**Atom**	**Angle/°**	**Atom**	**Atom**	**Atom**	**Angle/°**
C39	N3	N4	108.4(2)	C44	C45	C46	116.7(3)
C15	N1	N2	108.7(2)	C44	C45	C48	122.1(3)
N3	N4	C41	109.21(19)	C46	C45	C48	121.2(3)
N1	N2	C17	108.0(2)	C7	C8	C13	119.6(3)
C25	C38	C39	118.7(2)	C7	C8	C9	123.3(4)
C37	C38	C25	121.0(2)	C9	C8	C13	117.0(4)
C37	C38	C39	120.2(2)	C27	C26	C25	121.9(3)
C13	C14	C15	118.4(3)	C30	C31	C32	122.6(2)
C1	C14	C15	121.1(2)	N2	C17	C18	114.9(2)
C1	C14	C13	120.6(2)	N2	C17	C16	100.9(2)
C38	C25	C30	118.8(3)	C18	C17	C16	111.7(3)
C26	C25	C38	123.3(2)	C11	C12	C13	121.3(3)
C26	C25	C30	117.9(3)	C39	C40	C41	100.0(2)
N3	C39	C38	121.7(2)	C44	C43	C42	121.3(2)
N3	C39	C40	112.9(2)	C46	C47	C42	121.1(3)
C38	C39	C40	125.1(2)	C20	C21	C24	120.9(4)
N1	C15	C14	121.7(2)	C22	C21	C20	116.5(3)
N1	C15	C16	113.1(2)	C22	C21	C24	122.5(4)
C14	C15	C16	125.0(2)	C15	C16	C17	99.0(2)
C43	C42	C41	124.5(2)	C22	C23	C18	120.8(3)
C43	C42	C47	116.9(2)	C7	C6	C1	119.0(3)
C47	C42	C41	118.6(2)	C7	C6	C5	122.8(4)
C38	C37	C32	118.9(3)	C5	C6	C1	118.2(4)
C38	C37	C36	122.6(2)	C35	C36	C37	120.9(3)
C36	C37	C32	118.4(3)	C20	C19	C18	121.6(3)
C23	C18	C17	123.9(2)	C43	C44	C45	122.2(3)
C23	C18	C19	117.3(3)	C19	C20	C21	121.6(3)
C19	C18	C17	118.7(2)	C28	C29	C30	121.7(3)
C14	C13	C8	118.6(3)	C8	C7	C6	122.8(3)
C12	C13	C14	123.0(2)	C47	C46	C45	121.8(3)
C12	C13	C8	118.4(3)	C3	C2	C1	119.8(4)
N4	C41	C42	115.0(2)	C23	C22	C21	122.1(3)
N4	C41	C40	100.5(2)	C26	C27	C28	120.3(4)
C42	C41	C40	113.0(2)	C34	C33	C32	121.4(4)
C25	C30	C29	117.7(3)	C29	C28	C27	120.5(3)
C31	C30	C25	119.5(3)	C10	C9	C8	122.5(4)
C31	C30	C29	122.8(3)	C33	C34	C35	121.2(4)
C14	C1	C6	119.4(3)	C12	C11	C10	120.1(5)
C14	C1	C2	122.2(3)	C36	C35	C34	120.0(4)
C2	C1	C6	118.4(3)	C4	C5	C6	121.8(5)
C31	C32	C37	119.2(3)	C2	C3	C4	121.8(5)

C31	C32	C33	122.8(3)	C9	C10	C11	120.7(4)
C33	C32	C37	118.0(3)	C5	C4	C3	120.0(5

Table AC3.5 Bond Lengths of compound **3.9e**

Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**
N2	N1	1.410(5)	C3	C4	1.361(7)
N2	C15	1.253(5)	C18	C19	1.414(7)
N1	C17	1.386(7)	C18	C23	1.374(8)
C1	C2	1.406(5)	C18	C17	1.536(7)
C1	C15	1.481(5)	C13	C12	1.368(8)
C1	C14	1.411(5)	C19	C20	1.348(8)
C2	C7	1.435(5)	C4	C5	1.411(8)
C2	C3	1.423(6)	C6	C5	1.353(9)
C15	C16	1.488(6)	C20	C21	1.328(9)
C14	C9	1.441(5)	C20	Cl1	1.782(6)
C14	C13	1.419(6)	C21	C22	1.295(10)
C7	C8	1.397(7)	C10	C11	1.341(10)
C7	C6	1.410(7)	C23	C22	1.409(11)
C9	C8	1.377(7)	C12	C11	1.413(10)
C9	C10	1.441(6)	C16	C17	1.614(8)

Table AC3.6 Bond angles of compound **3.9e**

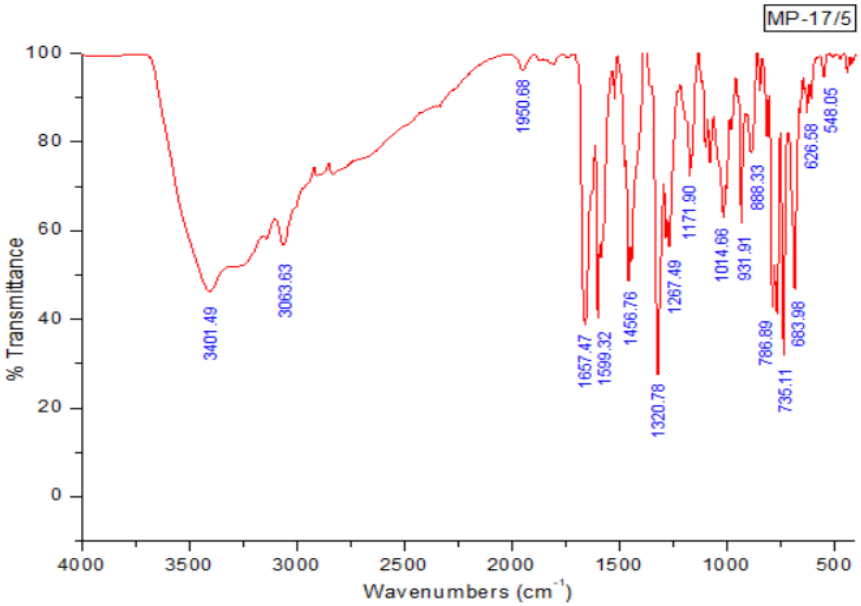
Atom	**Atom**	**Atom**	**Angle/°**	**Atom**	**Atom**	**Atom**	**Angle/°**
C15	N2	N1	108.8(3)	C23	C18	C19	117.2(5)
C17	N1	N2	109.7(3)	C23	C18	C17	117.2(5)
C2	C1	C15	119.9(3)	C12	C13	C14	120.9(5)

C2	C1	C14	120.8(3)	C9	C8	C7	122.3(4)
C14	C1	C15	119.3(3)	C20	C19	C18	119.0(4)
C1	C2	C7	119.8(4)	C3	C4	C5	120.3(4)
C1	C2	C3	122.8(3)	C5	C6	C7	121.2(4)
C3	C2	C7	117.4(4)	C19	C20	Cl1	112.1(5)
N2	C15	C1	123.5(3)	C21	C20	C19	123.5(5)
N2	C15	C16	111.7(3)	C21	C20	Cl1	124.4(5)
C1	C15	C16	124.9(3)	C22	C21	C20	119.0(5)
C1	C14	C9	118.5(3)	C11	C10	C9	120.3(6)
C1	C14	C13	122.7(4)	C18	C23	C22	118.9(5)
C13	C14	C9	118.7(4)	C13	C12	C11	120.0(5)
C8	C7	C2	118.6(4)	C21	C22	C23	122.5(4)
C8	C7	C6	122.1(4)	C10	C11	C12	121.8(5)
C6	C7	C2	119.3(4)	C6	C5	C4	120.3(5)
C8	C9	C14	119.9(4)	C15	C16	C17	98.5(4)
C8	C9	C10	121.8(4)	N1	C17	C18	116.4(4)
C10	C9	C14	118.3(5)	N1	C17	C16	97.3(4)
C4	C3	C2	121.5(4)	C18	C17	C16	108.9(5)
C19	C18	C17	125.6(4)				

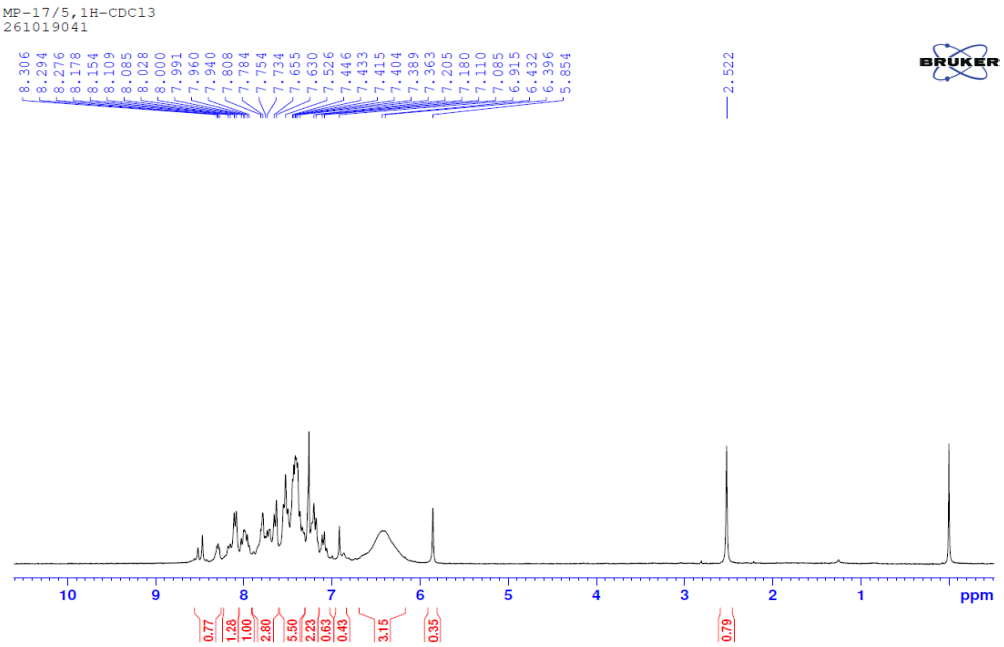
Appendix: C-4

AC4. REPRESENTATIVE SPECTRA OF ANTHRACENYL PYRAZOLES

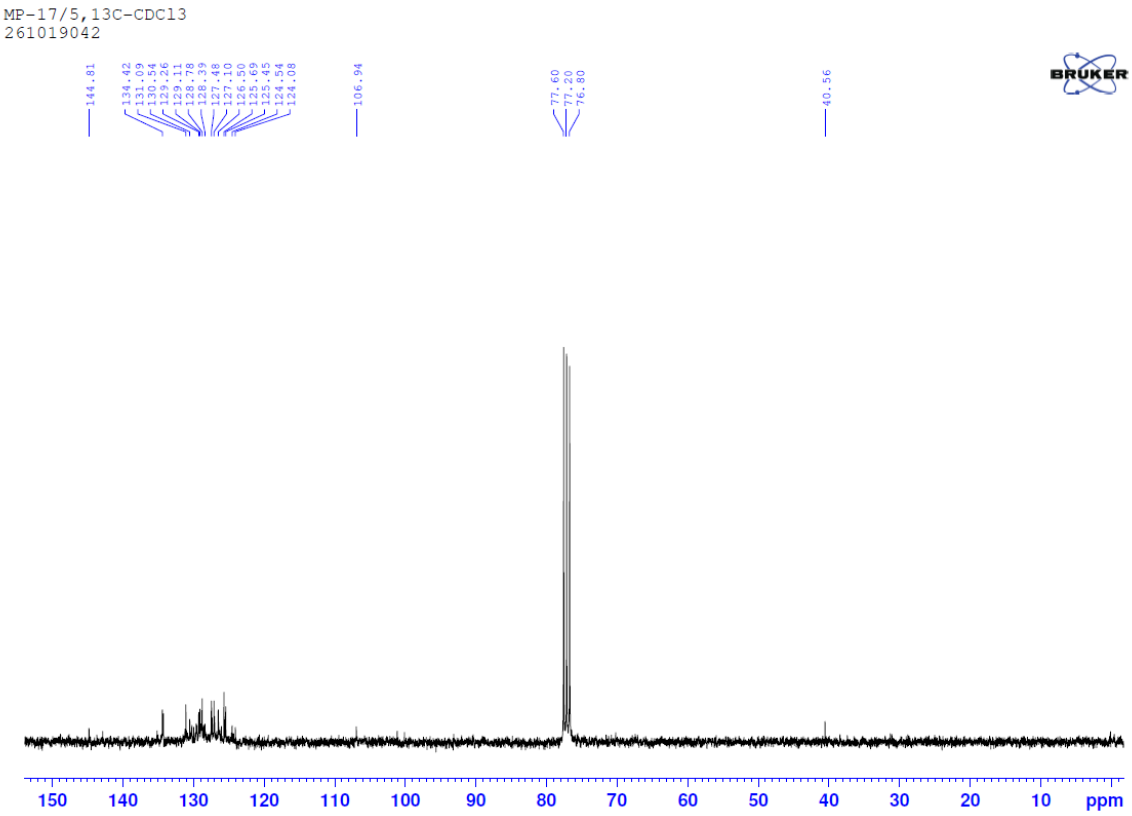
AC4.1 IR (KBr, *v*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-5-(3-chlorophenyl)-1H-pyrazole (4.13d)



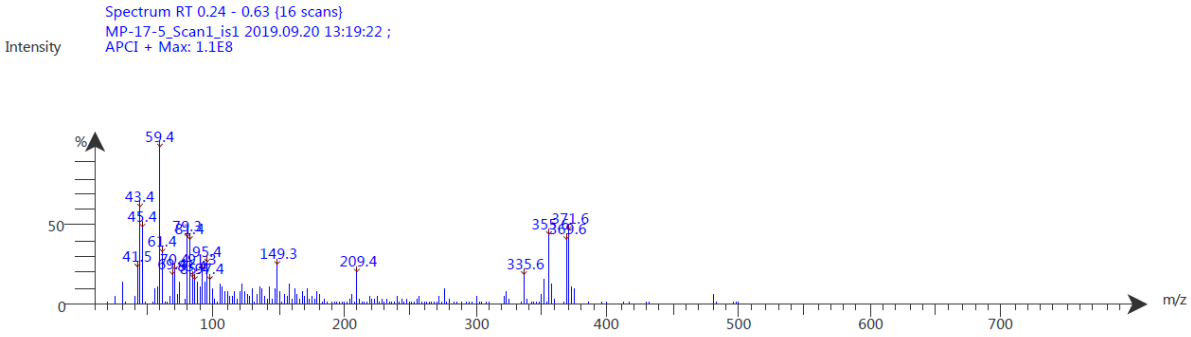
AC4.2 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(3-chlorophenyl)-1H-pyrazole (4.13d)



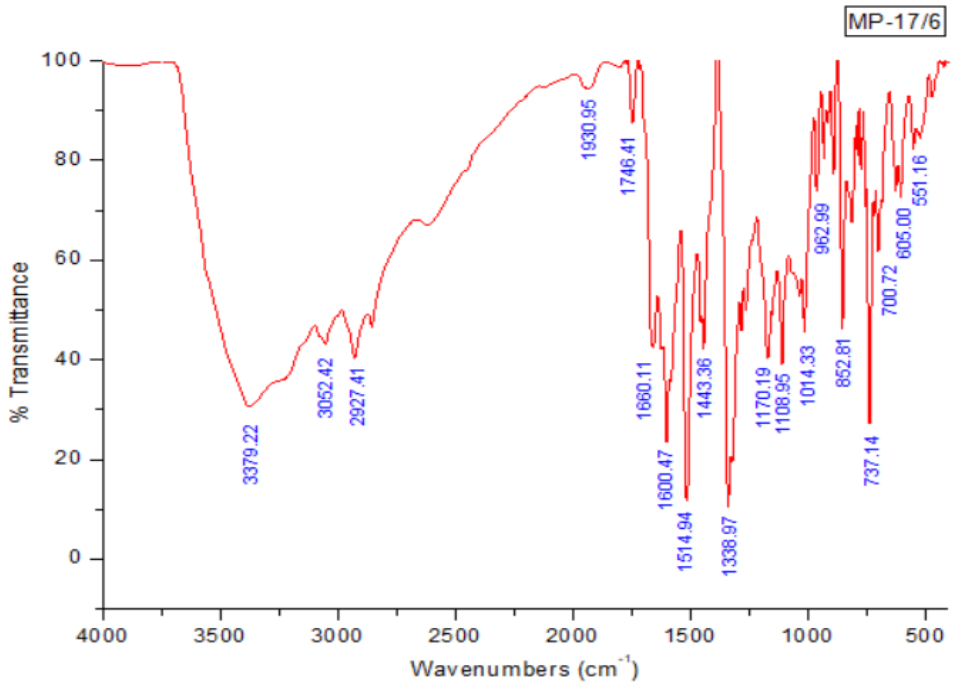
AC4.3 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(3-chlorophenyl)-1H-pyrazole (4.13d)



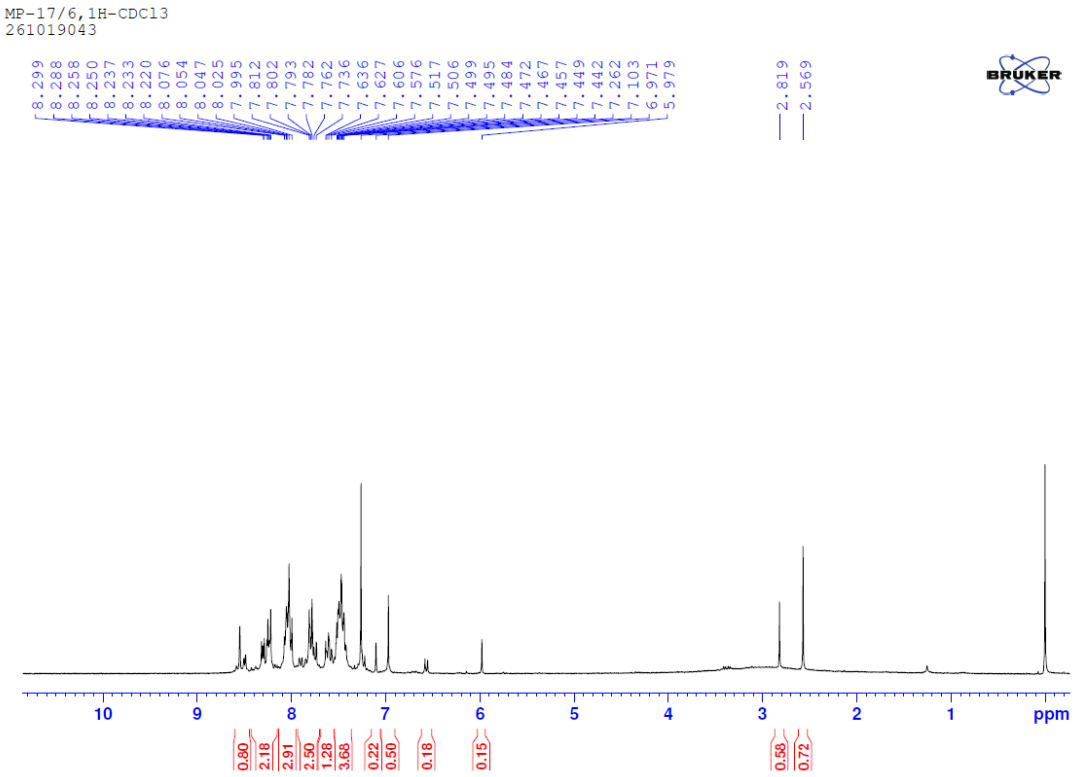
AC4.4 MS spectrum of 3-(Anthracen-10-yl)-5-(3-chlorophenyl)-1H-pyrazole (4.13d)



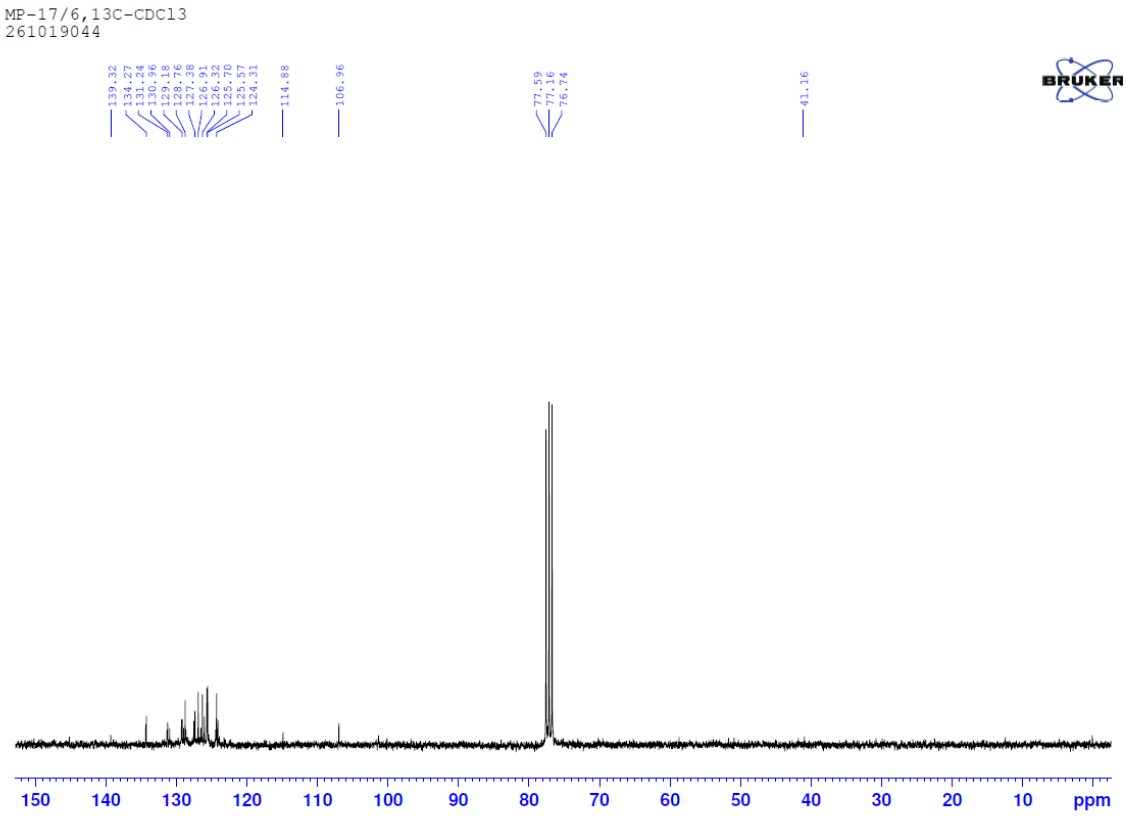
AC4.5 IR (KBr, *v*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-5-(4-nitrophenyl)-1H-pyrazole (4.13e)



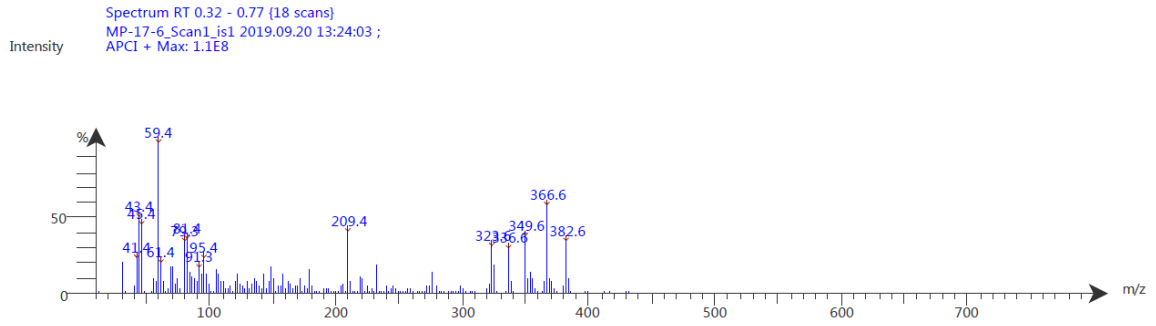
AC4.6 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(4-nitrophenyl)-1H-pyrazole (4.13e)



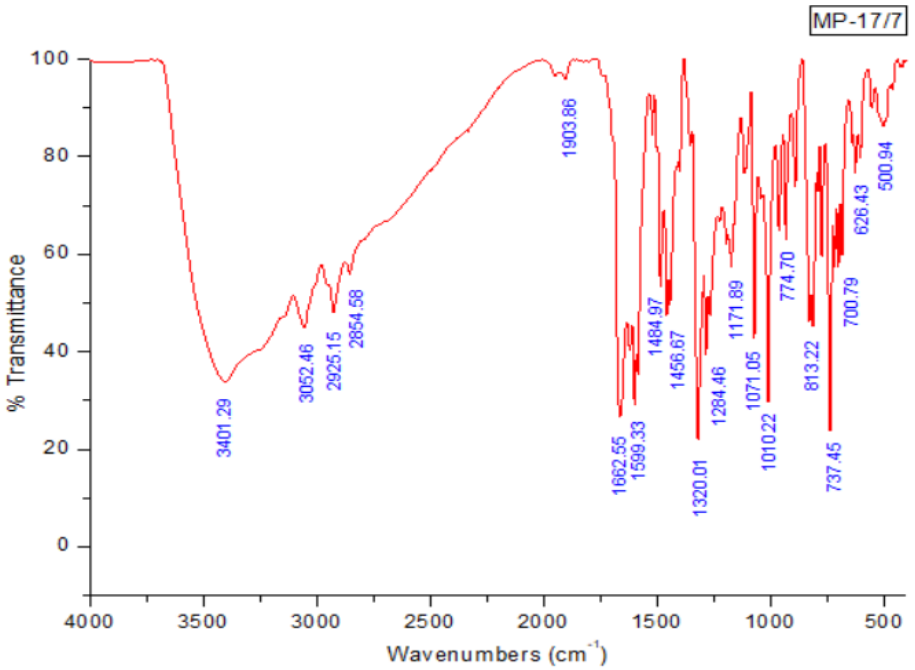
AC4.7 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(4-nitrophenyl)-1H-pyrazole (4.13e)



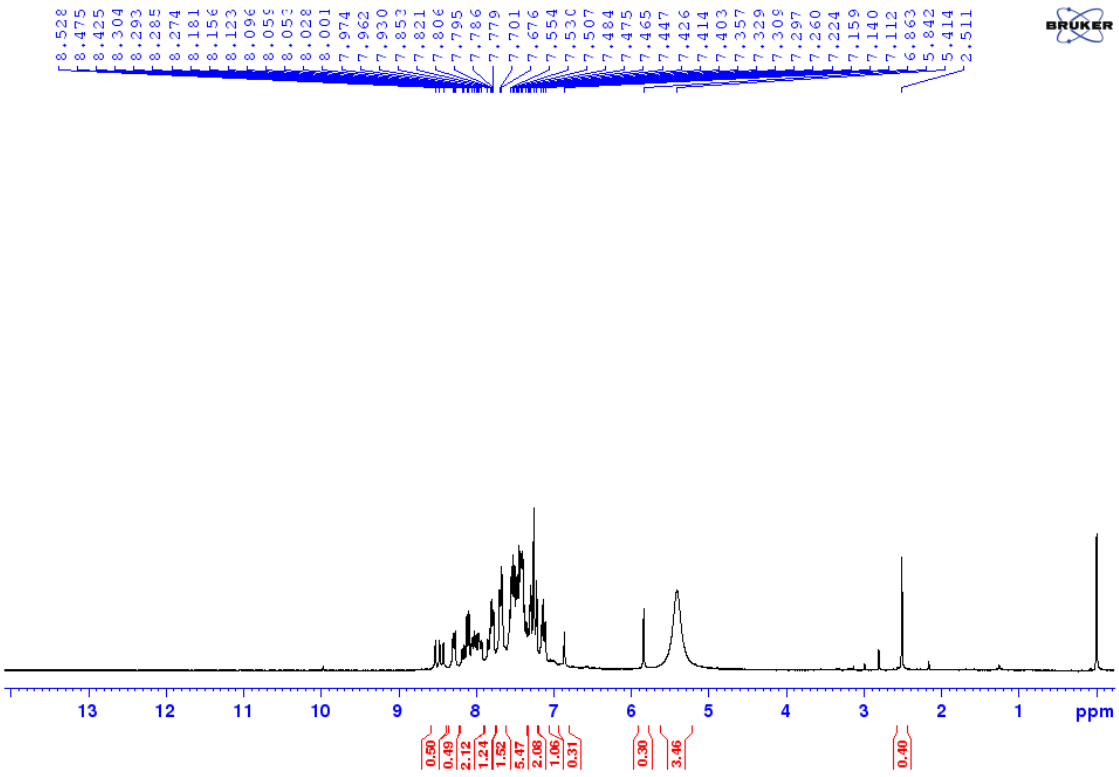
AC4.8 MS spectrum of 3-(Anthracen-10-yl)-5-(4-nitrophenyl)-1H-pyrazole (4.13e)



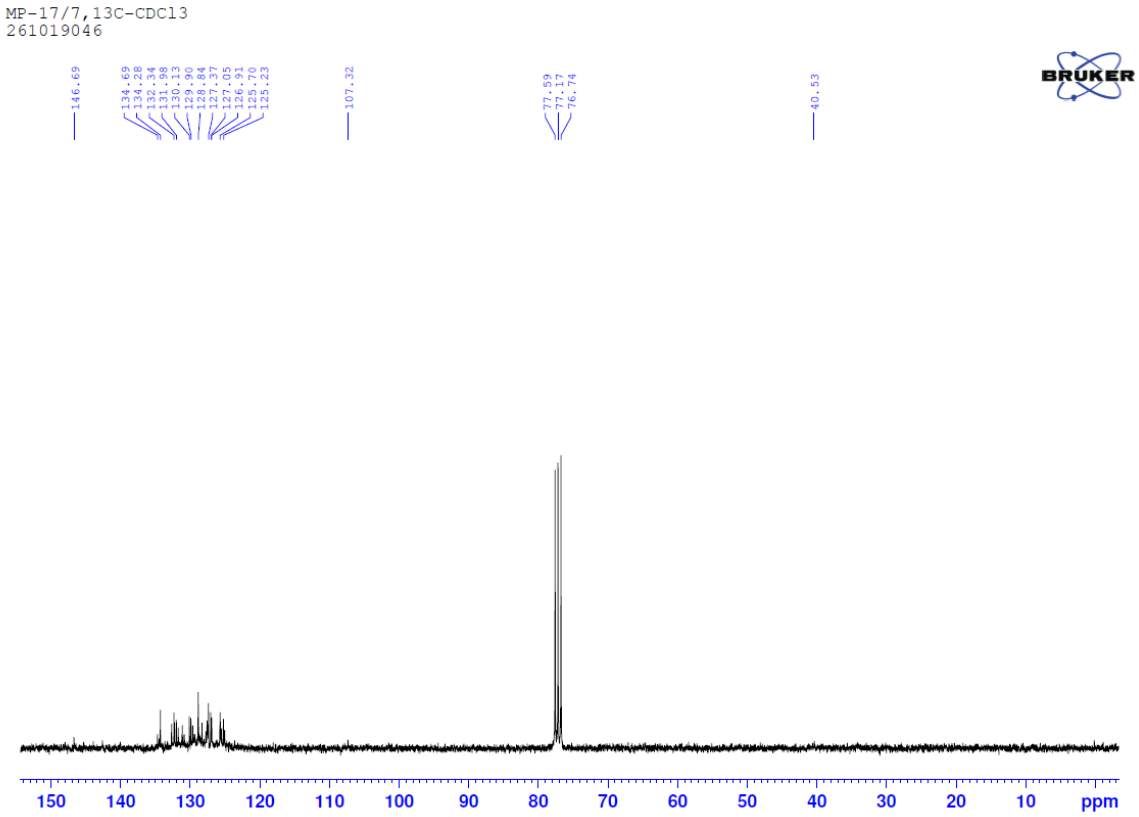
AC4.9 IR (KBr, *v*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-5-(4-bromophenyl)-1H-pyrazole (4.13f)



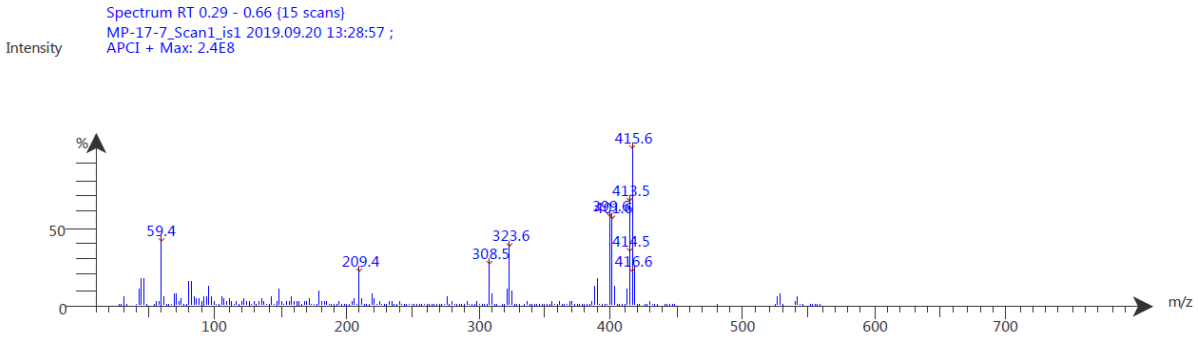
AC4.10 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(4-bromophenyl)-1H-pyrazole (4.13f)



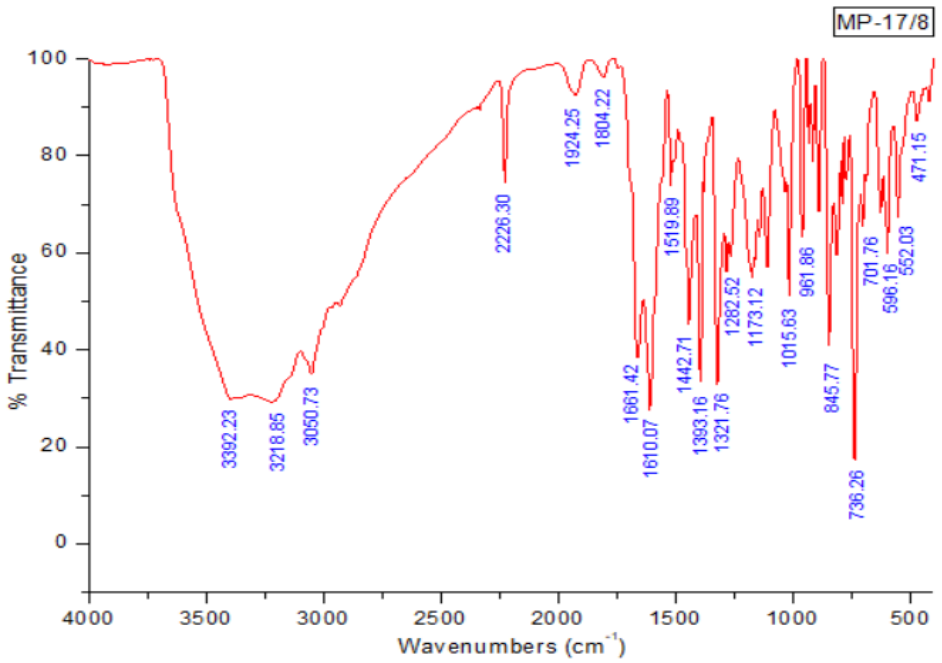
AC4.11 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(4-bromophenyl)-1H-pyrazole (4.13f)



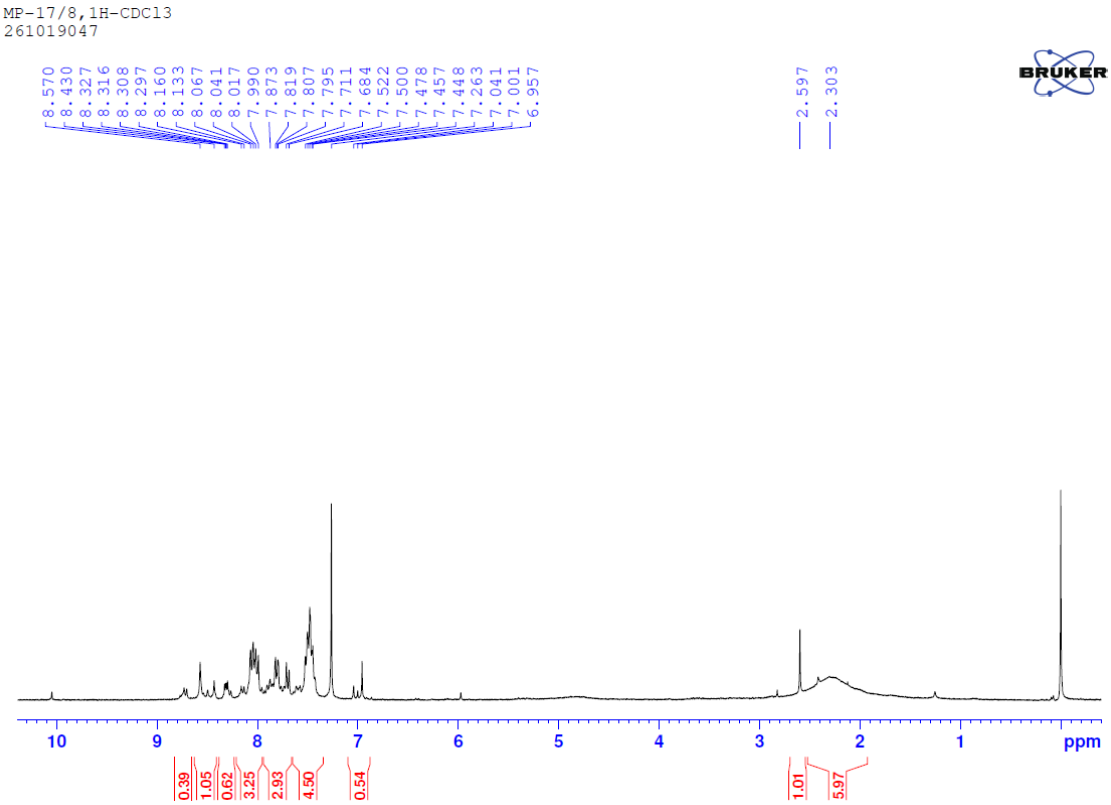
AC4.12 MS spectrum of 3-(Anthracen-10-yl)-5-(4-bromophenyl)-1H-pyrazole (4.13f)



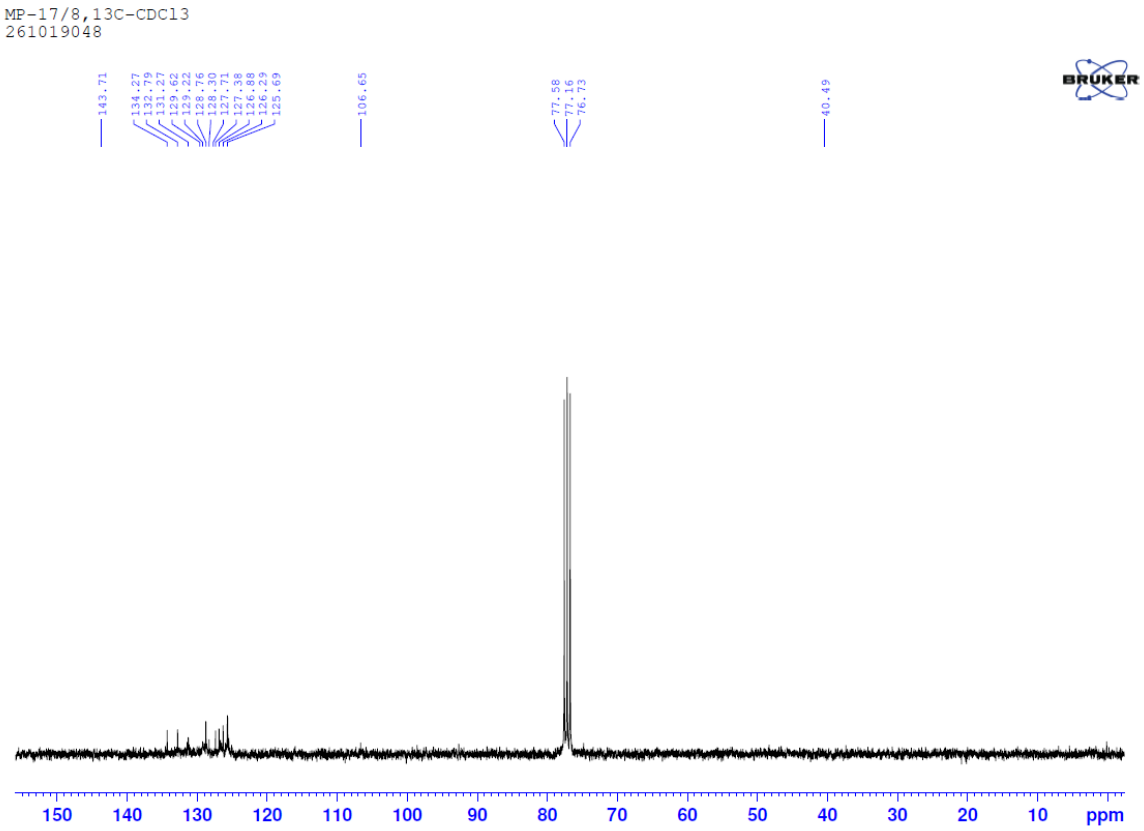
AC4.13 IR (KBr, *ν*, cm^{-1}) spectrum of 4-(3-(Anthracen-10-yl)-1H-pyrazol-5-yl)benzonitrile (4.13g)



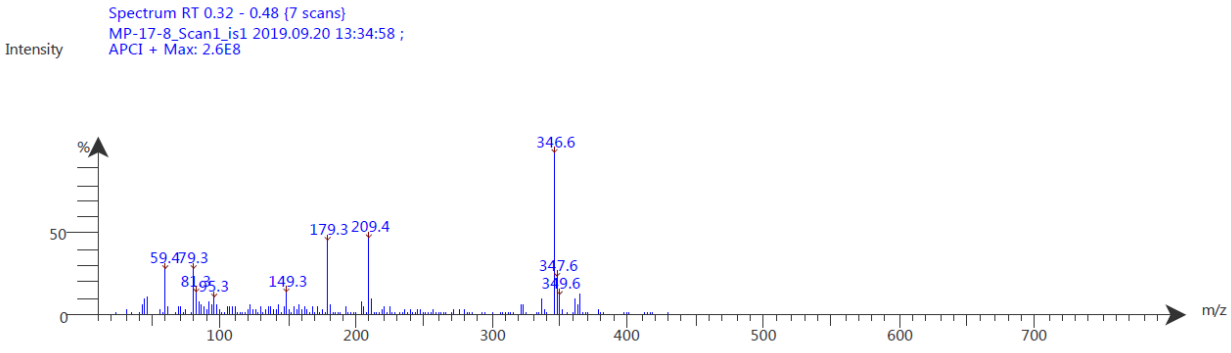
AC4.14 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 4-(3-(Anthracen-10-yl)-1H-pyrazol-5-yl)benzonitrile (4.13g)



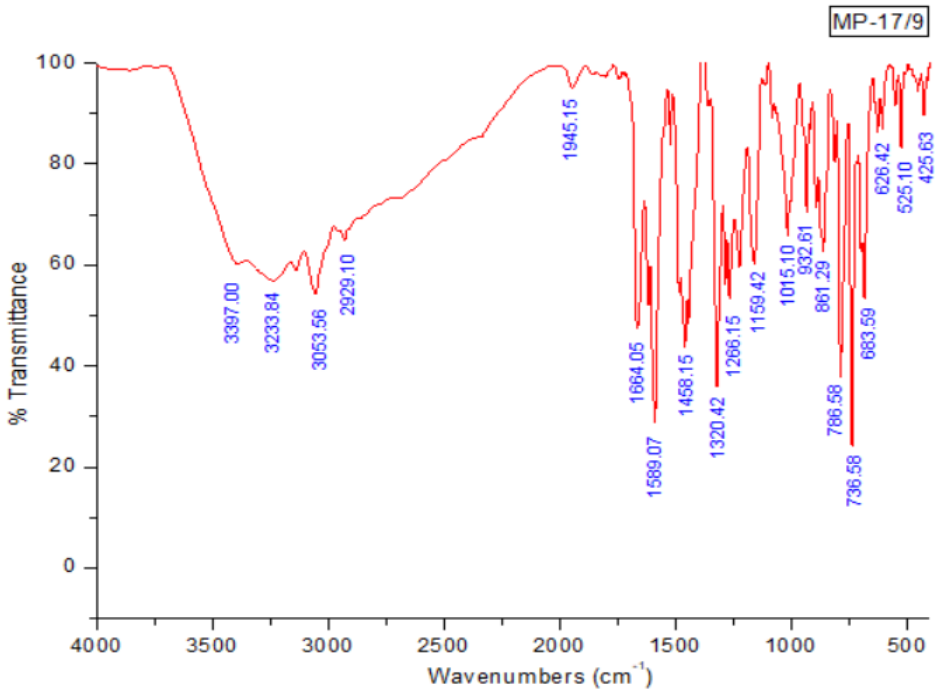
AC4.15 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 4-(3-(Anthracen-10-yl)-1H-pyrazol-5-yl)benzonitrile (4.13g)



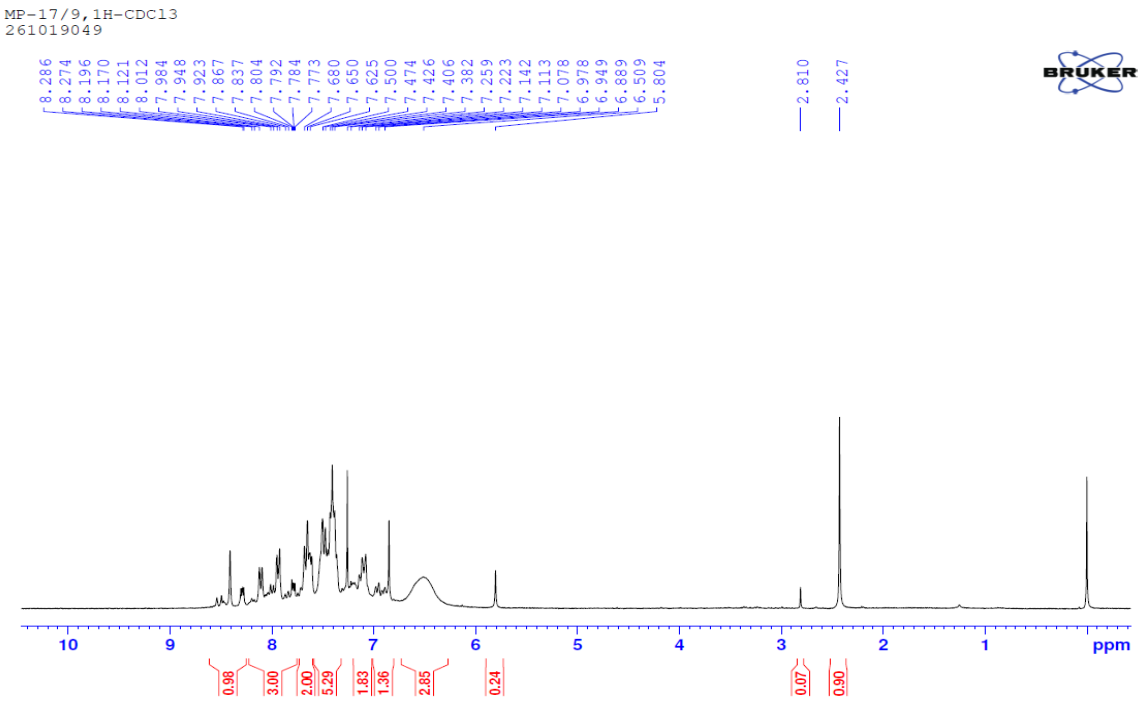
AC4.16 MS spectrum of 4-(3-(Anthracen-10-yl)-1H-pyrazol-5-yl)benzonitrile (4.13g)



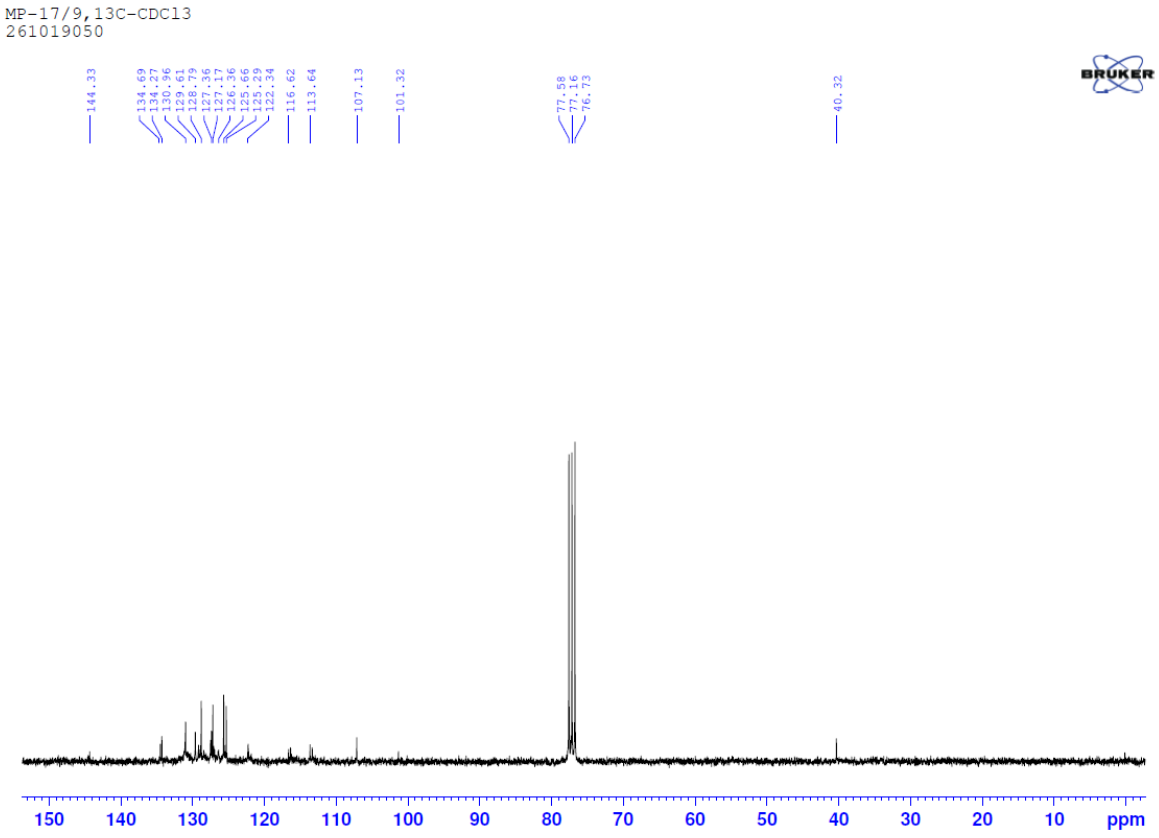
AC4.17 IR (KBr, *ν*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-5-(3-fluorophenyl)-1H-pyrazole (4.13h)



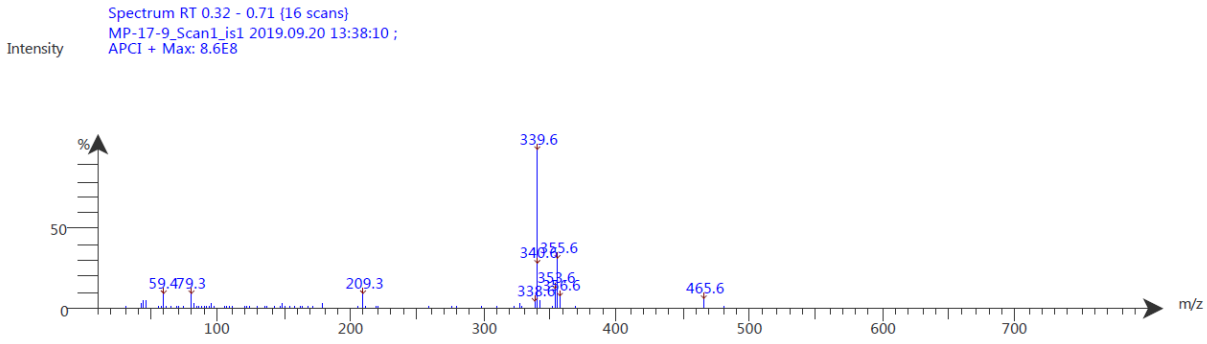
AC4.18 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(3-fluorophenyl)-1H-pyrazole (4.13h)



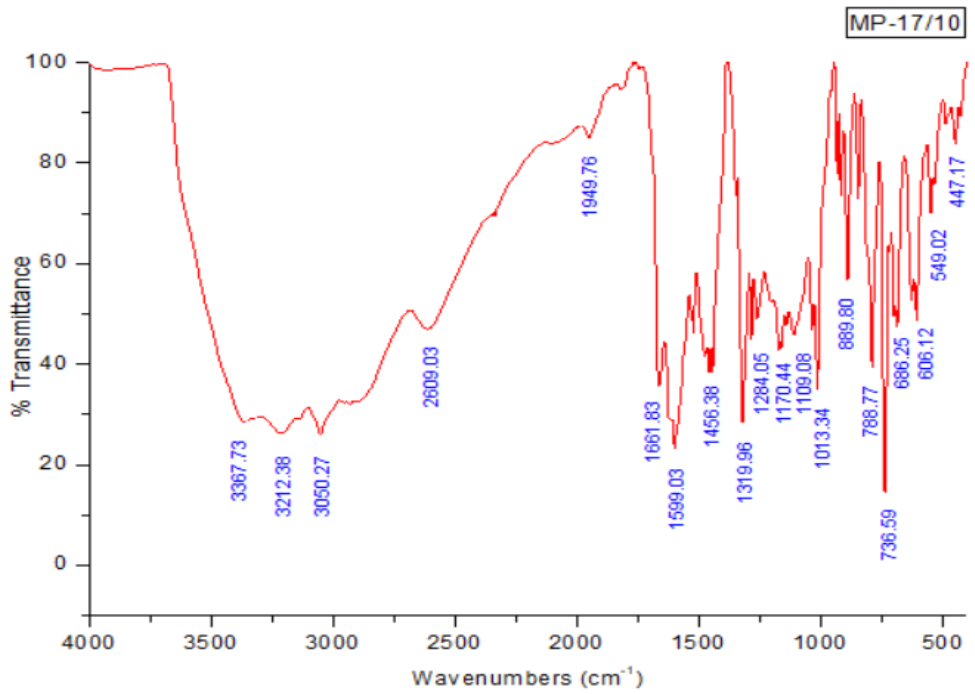
AC4.19 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(3-fluorophenyl)-1H-pyrazole (4.13h)



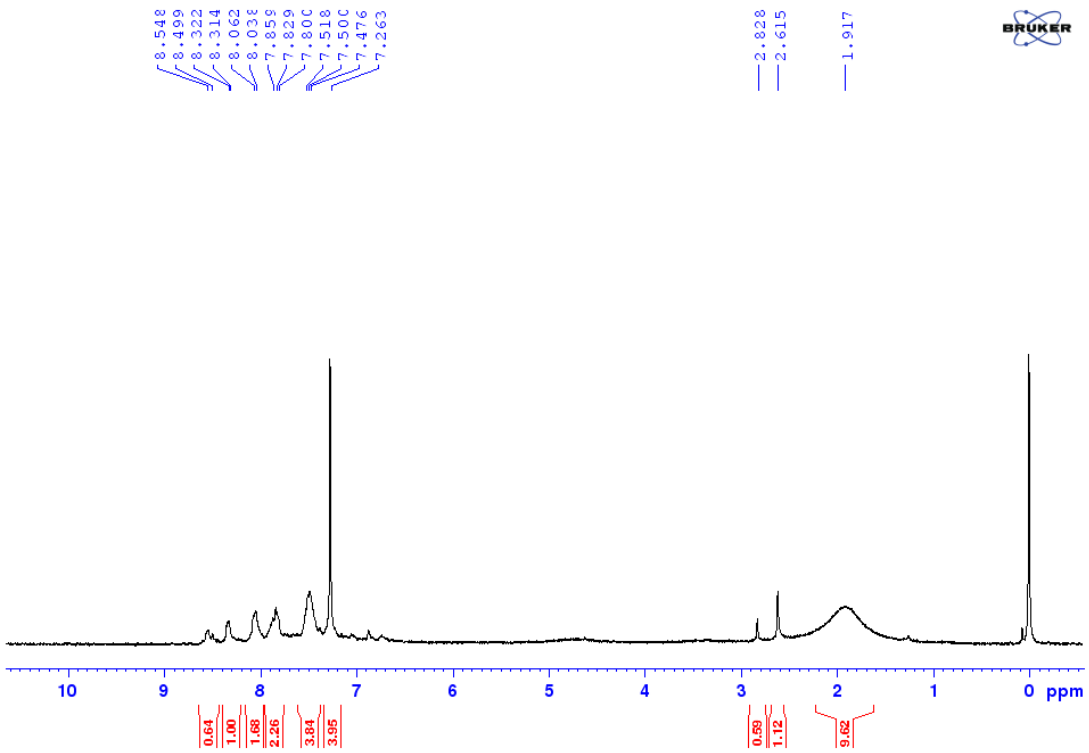
AC4.20 MS spectrum of 3-(Anthracen-10-yl)-5-(3-fluorophenyl)-1H-pyrazole (4.13h)



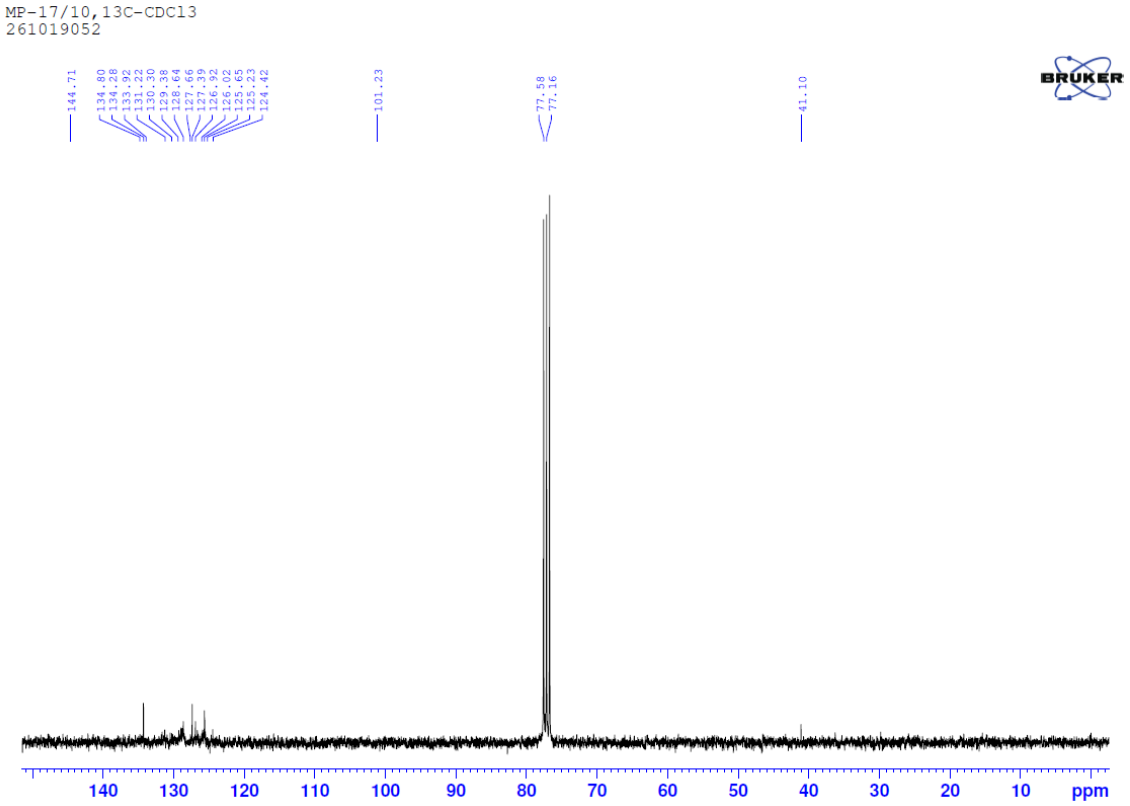
AC4.21 IR (KBr, *ν*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-5-(3-nitrophenyl)-1H-pyrazole (4.13i)



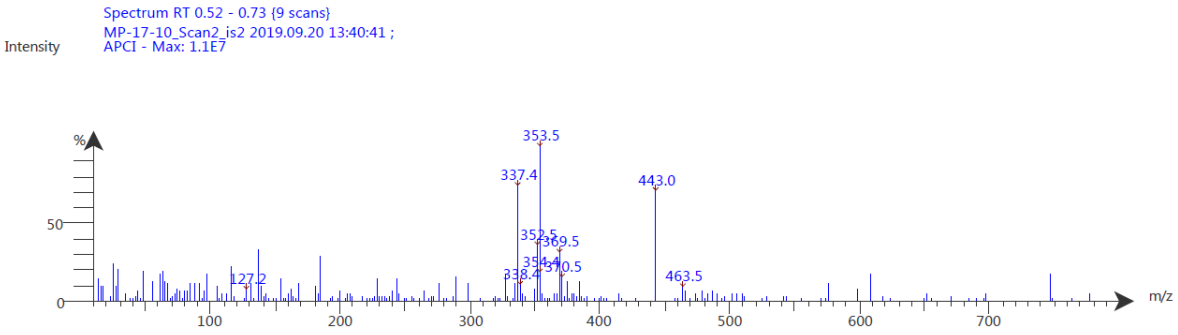
AC4.22 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(3-nitrophenyl)-1H-pyrazole (4.13i)



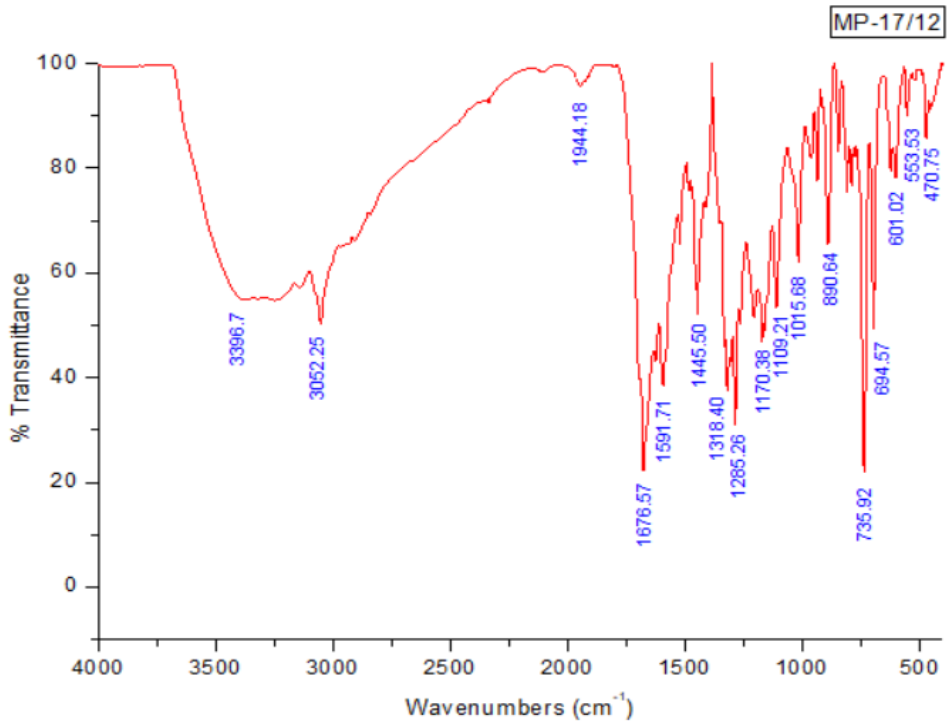
AC4.23 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(3-nitrophenyl)-1H-pyrazole (4.13i)



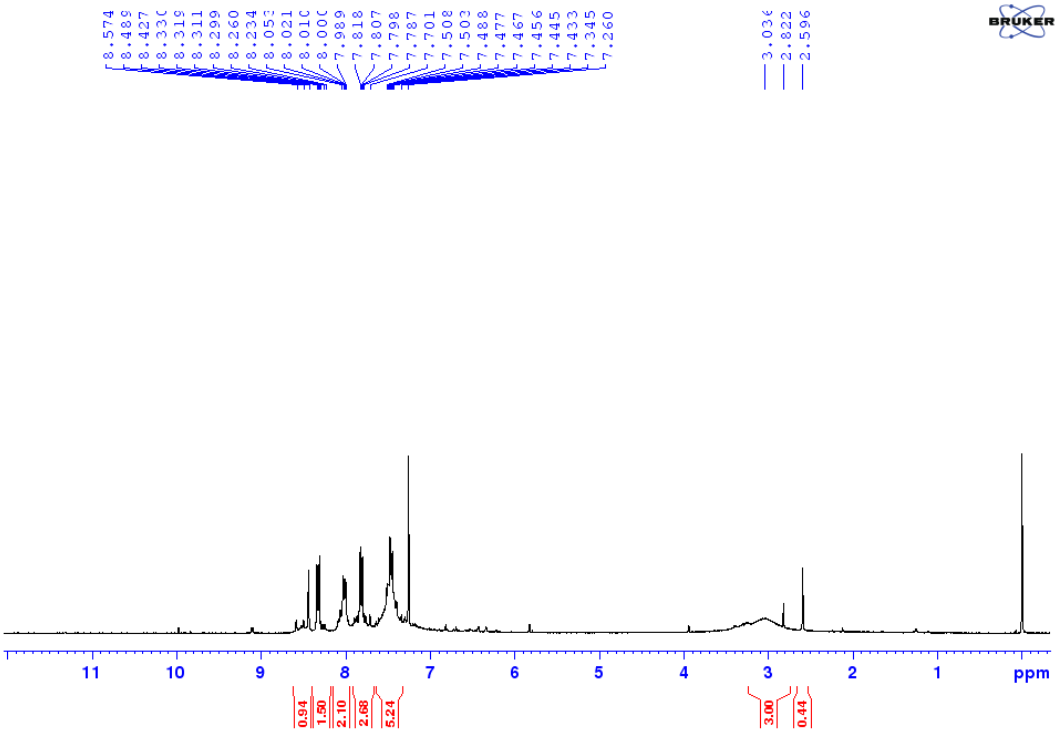
AC4.24 MS spectrum of 3-(Anthracen-10-yl)-5-(3-nitrophenyl)-1H-pyrazole (4.13i)



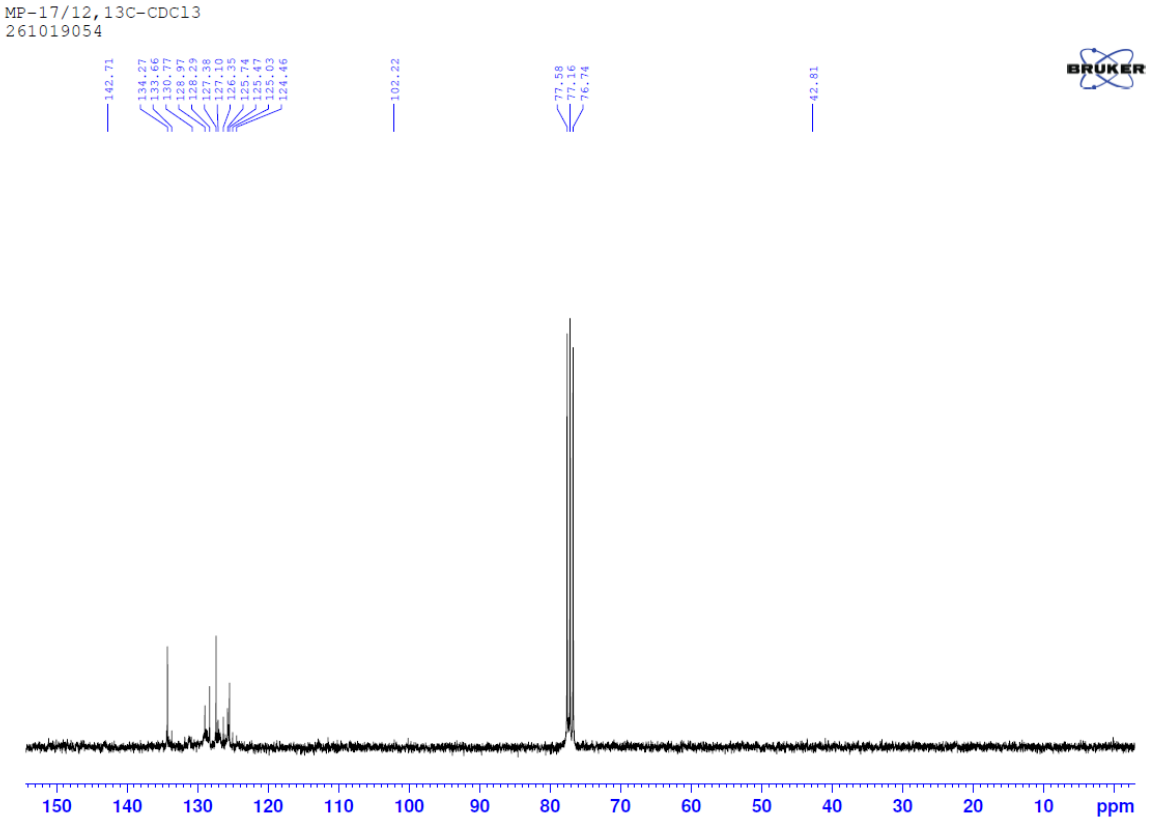
AC4.25 IR (KBr, *v*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-5-(furan-2-yl)-1H-pyrazole (4.13j)



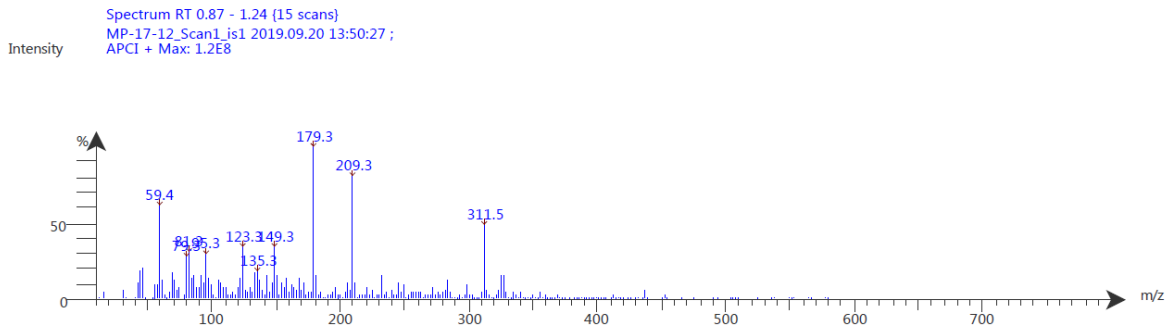
AC4.26 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(furan-2-yl)-1H-pyrazole (4.13j)



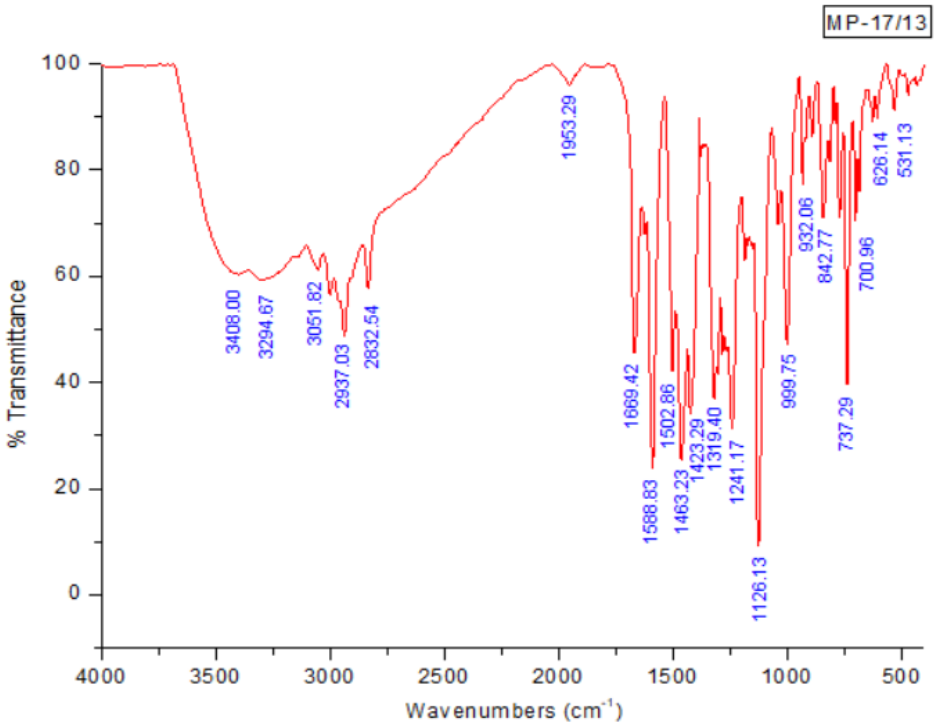
AC4.27 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(furan-2-yl)-1H-pyrazole (4.13j)



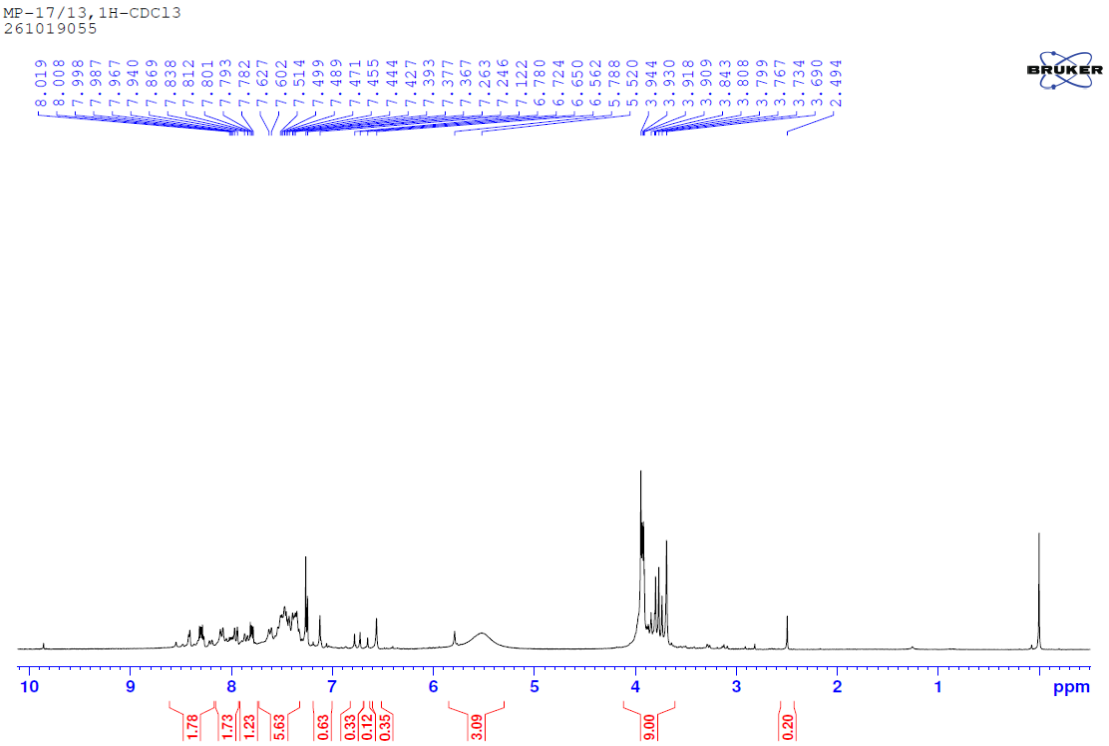
AC4.28 MS spectrum of 3-(Anthracen-10-yl)-5-(furan-2-yl)-1H-pyrazole (4.13j)



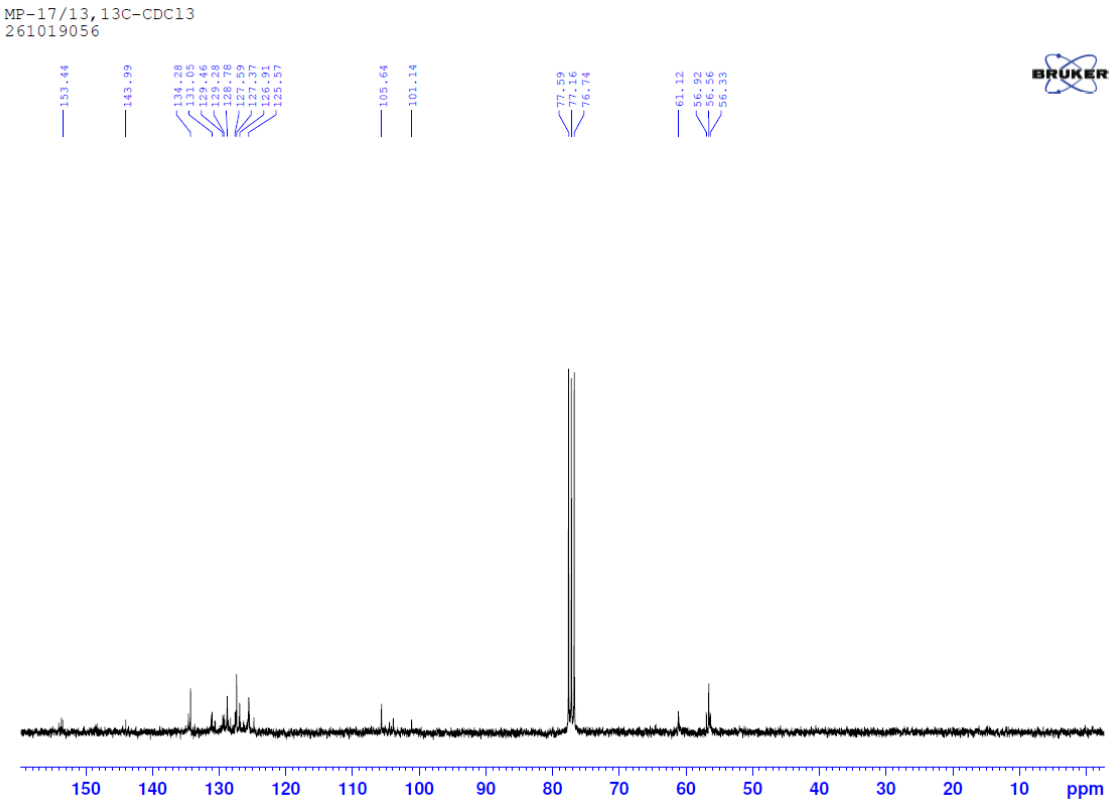
AC4.29 IR (KBr, *v*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-5-(3,4,5-trimethoxyphenyl)-1H-(4.13k)



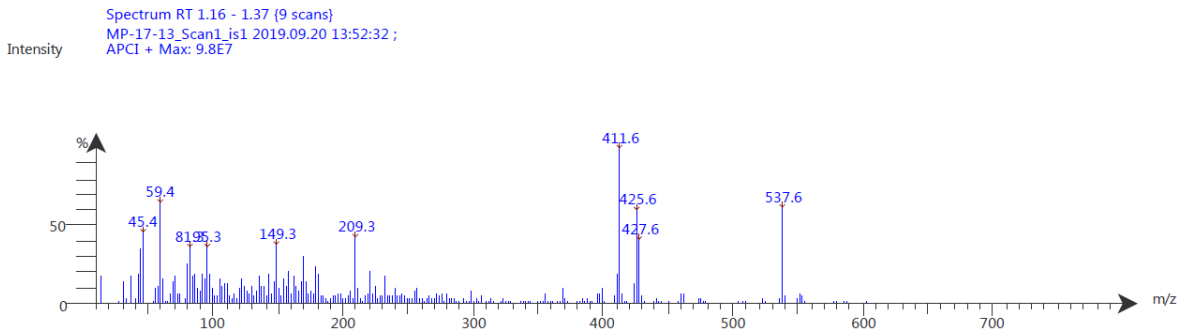
AC4.30 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (4.13k)



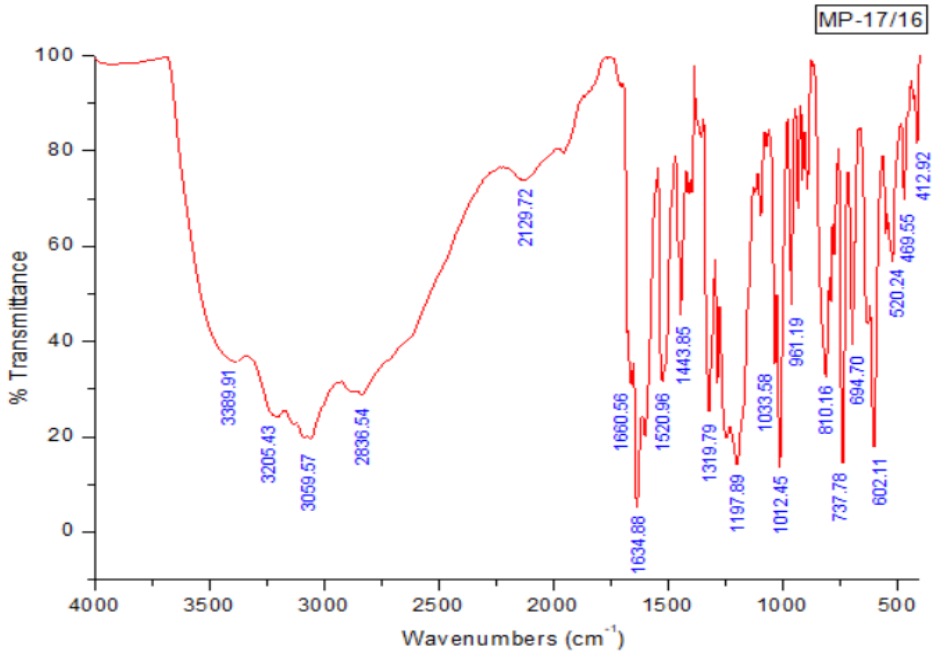
AC4.31 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (4.13k)



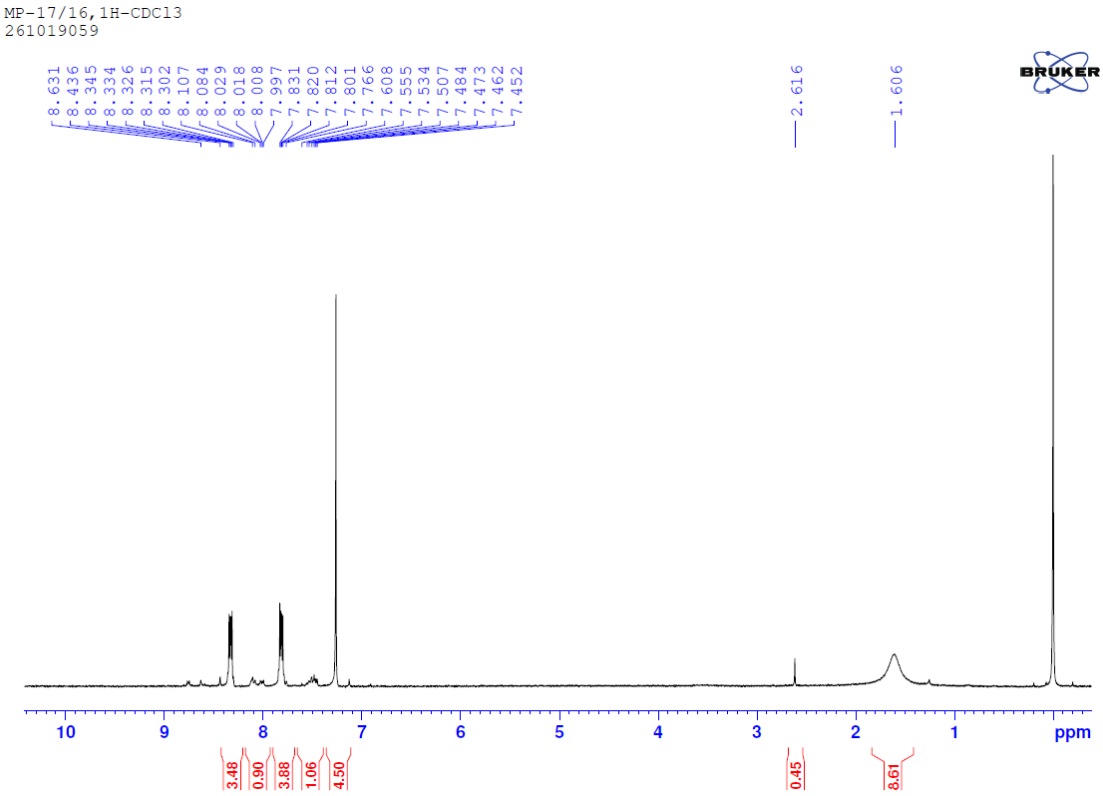
AC4.32 MS spectrum of 3-(Anthracen-10-yl)-5-(3,4,5-trimethoxyphenyl)-1H-pyrazole (4.13k)



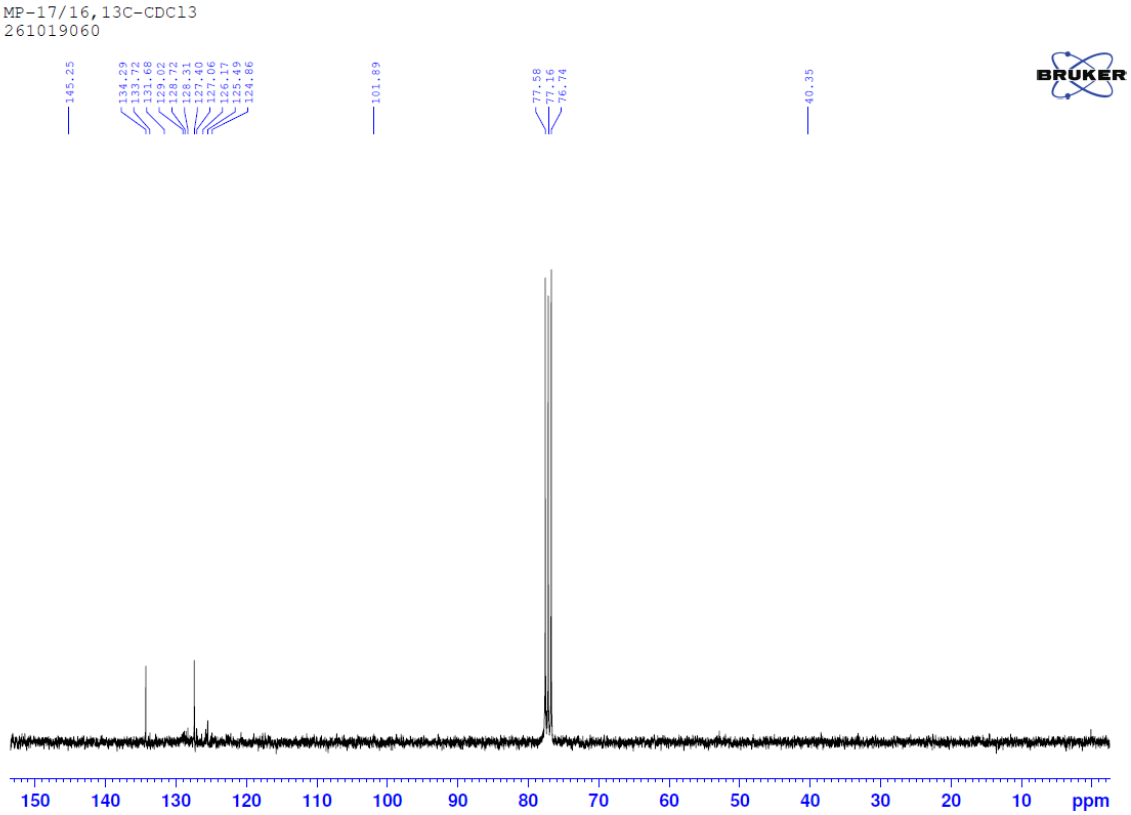
AC4.33 IR (KBr, *ν*, cm^{-1}) spectrum of 4-(3-(Anthracen-10-yl)-1H-pyrazol-5-yl)pyridine (4.13l)



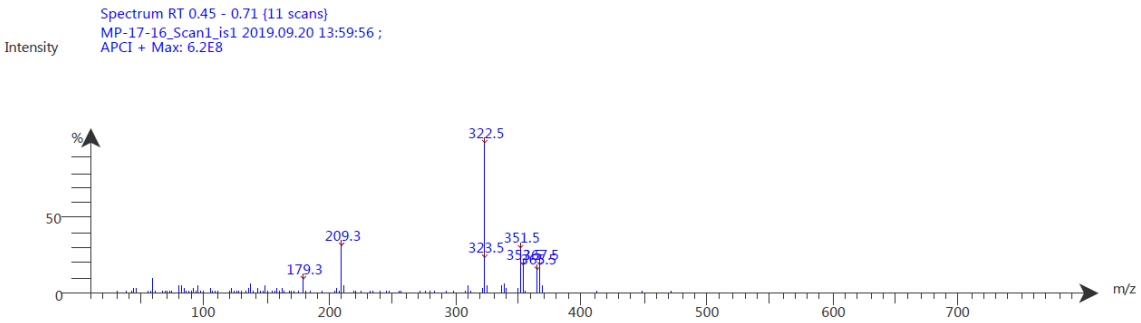
AC4.34 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 4-(3-(Anthracen-10-yl)-1H-pyrazol-5-yl)pyridine (4.13l)



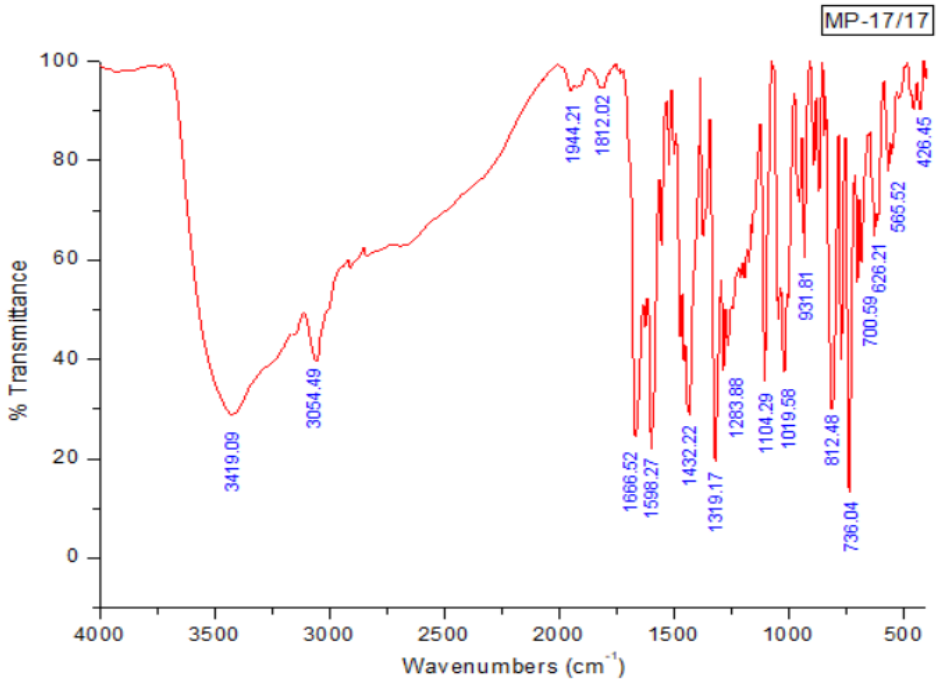
AC4.35 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 4-(3-(Anthracen-10-yl)-1H-pyrazol-5-yl)pyridine (4.13l)



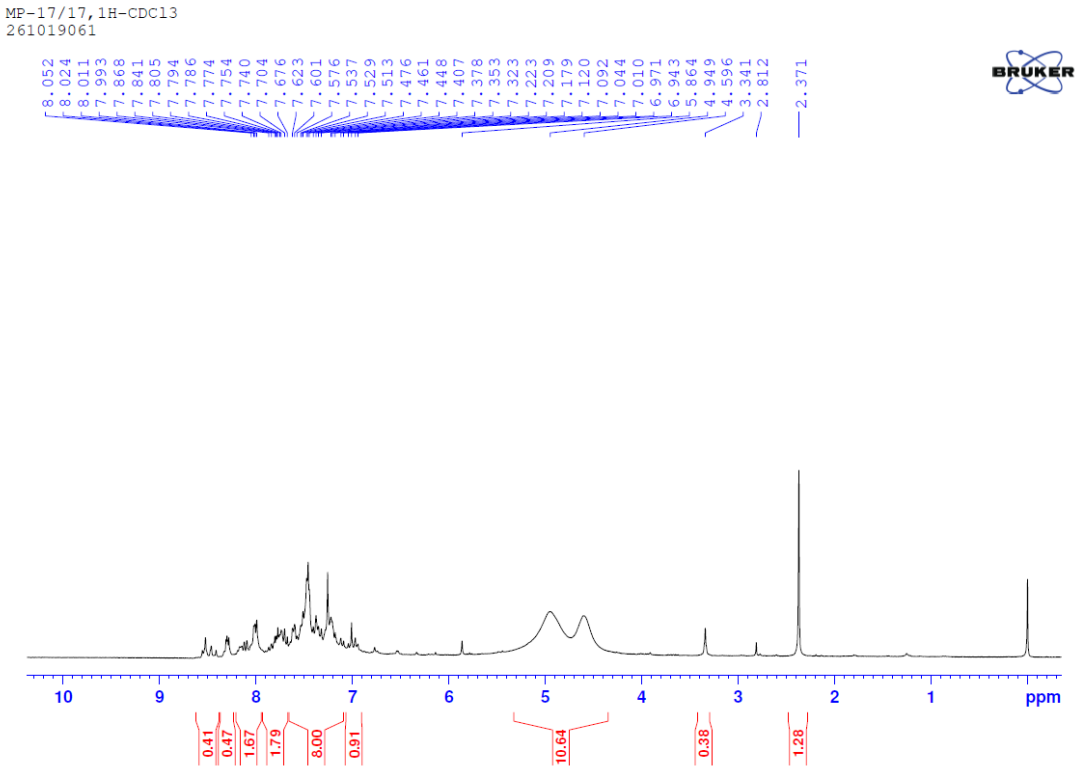
AC4.36 MS spectrum of 4-(3-(Anthracen-10-yl)-1H-pyrazol-5-yl)pyridine (4.13l)



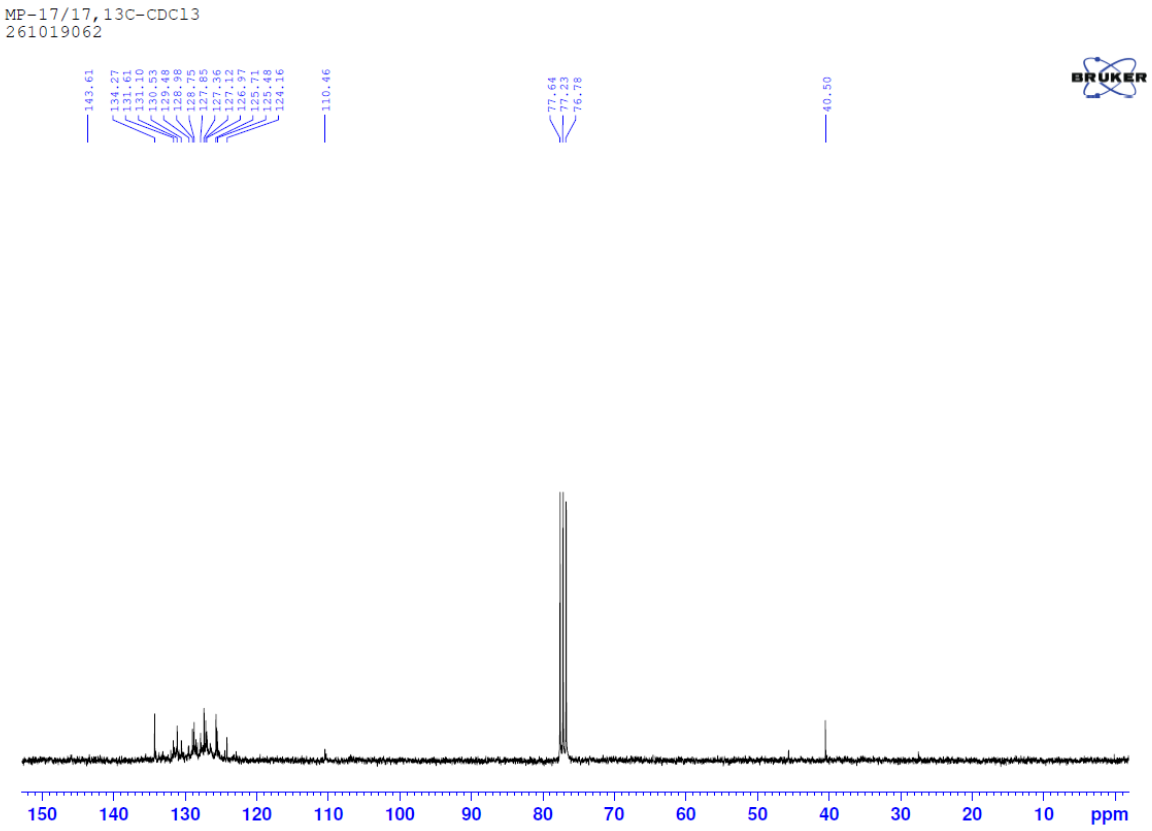
AC4.37 IR (KBr, *v*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-5-(2,4-dichlorophenyl)-1H-pyrazole (4.13m)



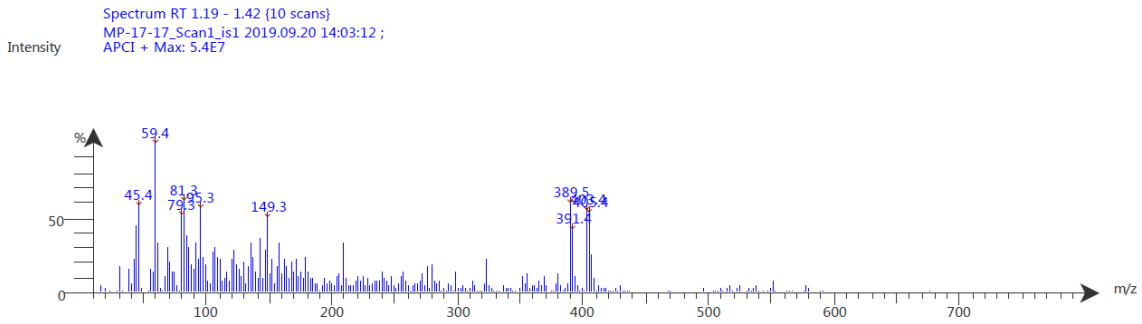
AC4.38 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(2,4-dichlorophenyl)-1H-pyrazole (4.13m)



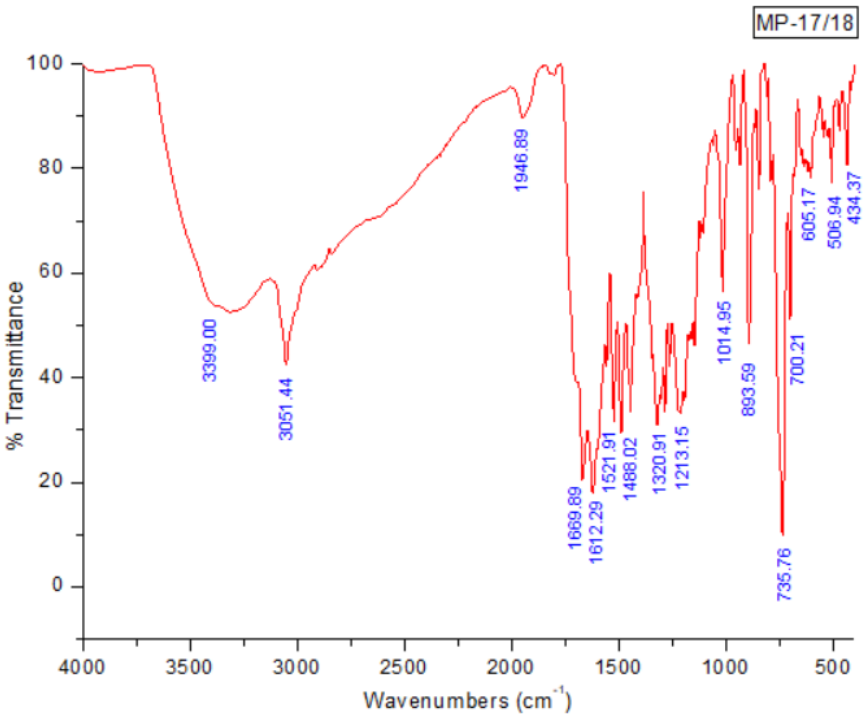
AC4.39 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(2,4-dichlorophenyl)-1H-pyrazole (4.13m)



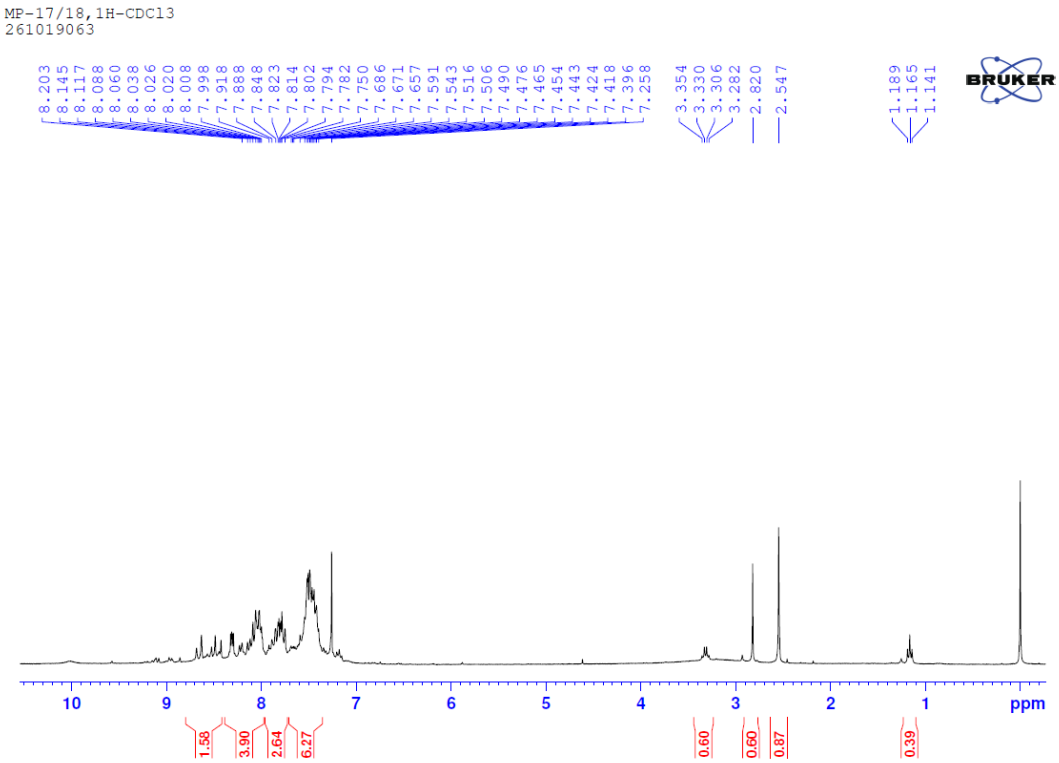
AC4.40 MS spectrum of 3-(Anthracen-10-yl)-5-(2,4-dichlorophenyl)-1H-pyrazole (4.13m)



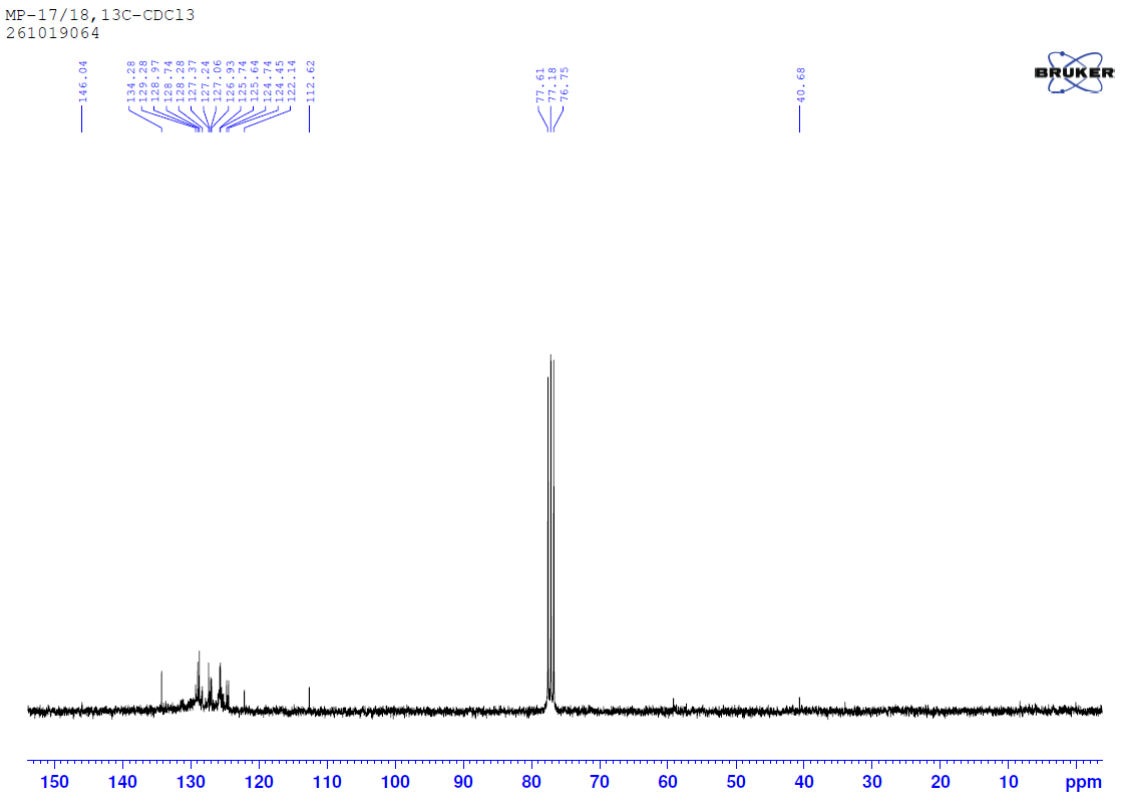
AC4.41 IR (KBr, *ν*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-5-(2-nitrophenyl)-1H-pyrazole (4.13n)



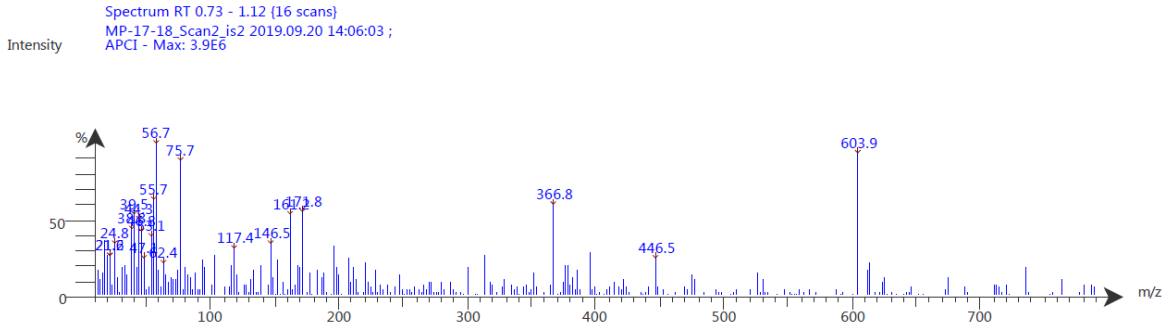
AC4.42 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(2-nitrophenyl)-1H-pyrazole (4.13n)



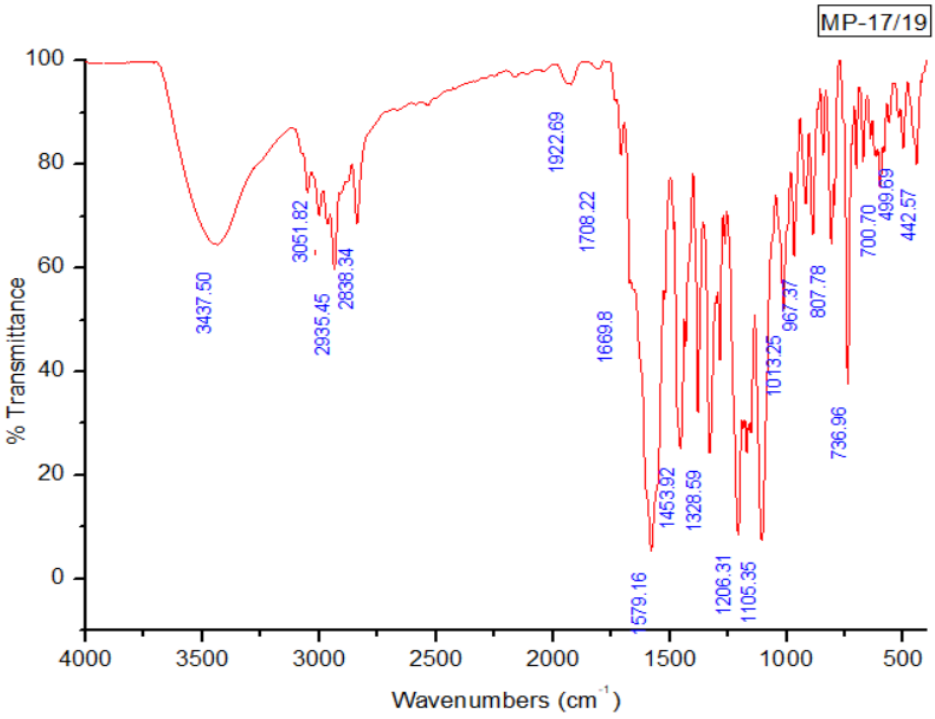
AC4.43 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(2-nitrophenyl)-1H-pyrazole (4.13n)



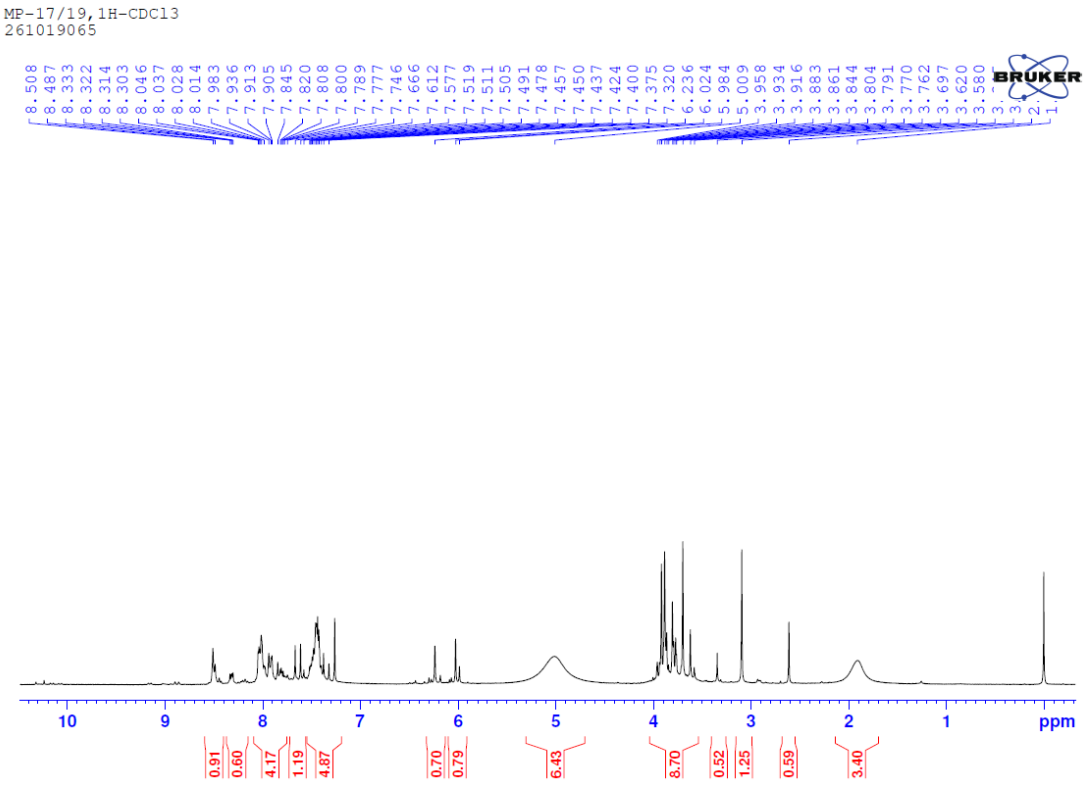
AC4.44 MS spectrum of 3-(Anthracen-10-yl)-5-(2-nitrophenyl)-1H-pyrazole (4.13n)



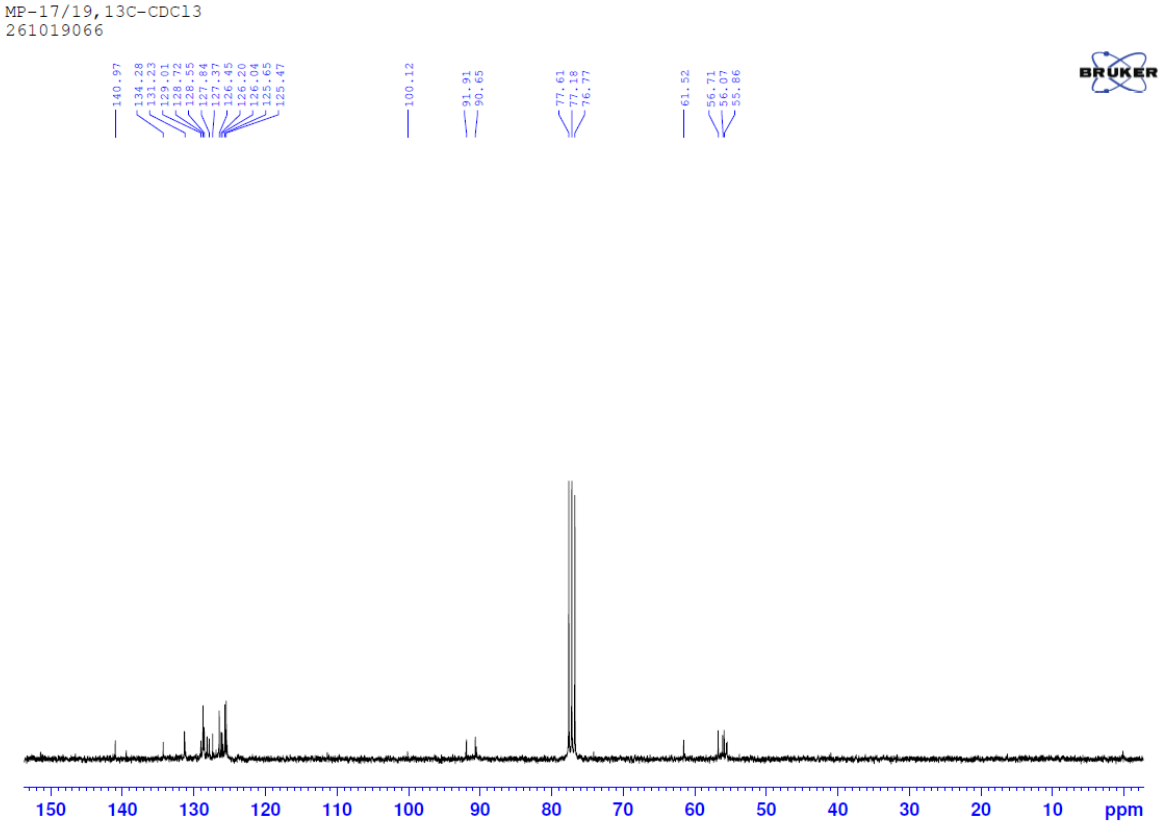
AC4.45 IR (KBr, *v*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-5-(2,4,6-trimethoxyphenyl)-1H-pyrazole (4.13o)



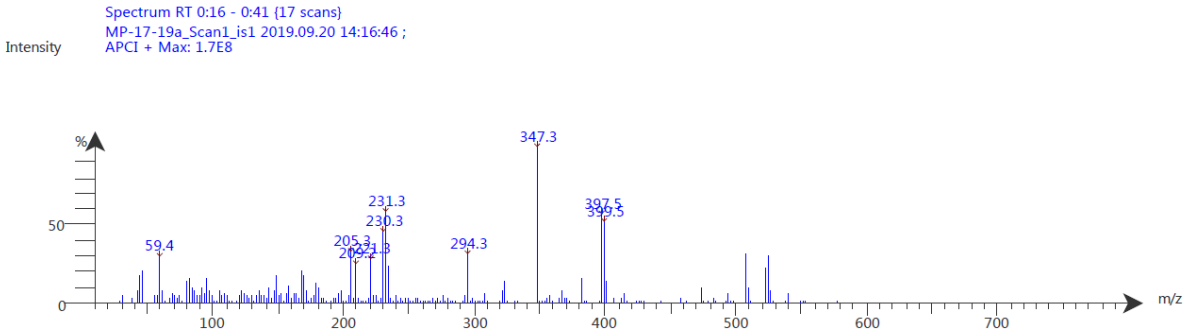
AC4.46 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(2,4,6-trimethoxyphenyl)-1H-pyrazole (4.13o)



AC4.47 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(2,4,6-trimethoxyphenyl)-1H-pyrazole (4.13o)



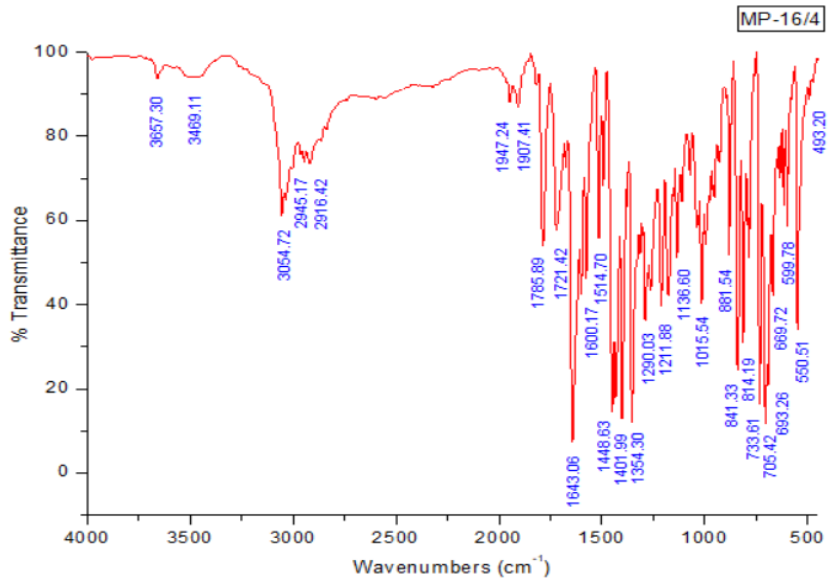
AC4.48 MS spectrum of 3-(Anthracen-10-yl)-5-(2,4,6-trimethoxyphenyl)-1H-pyrazole (4.13o)



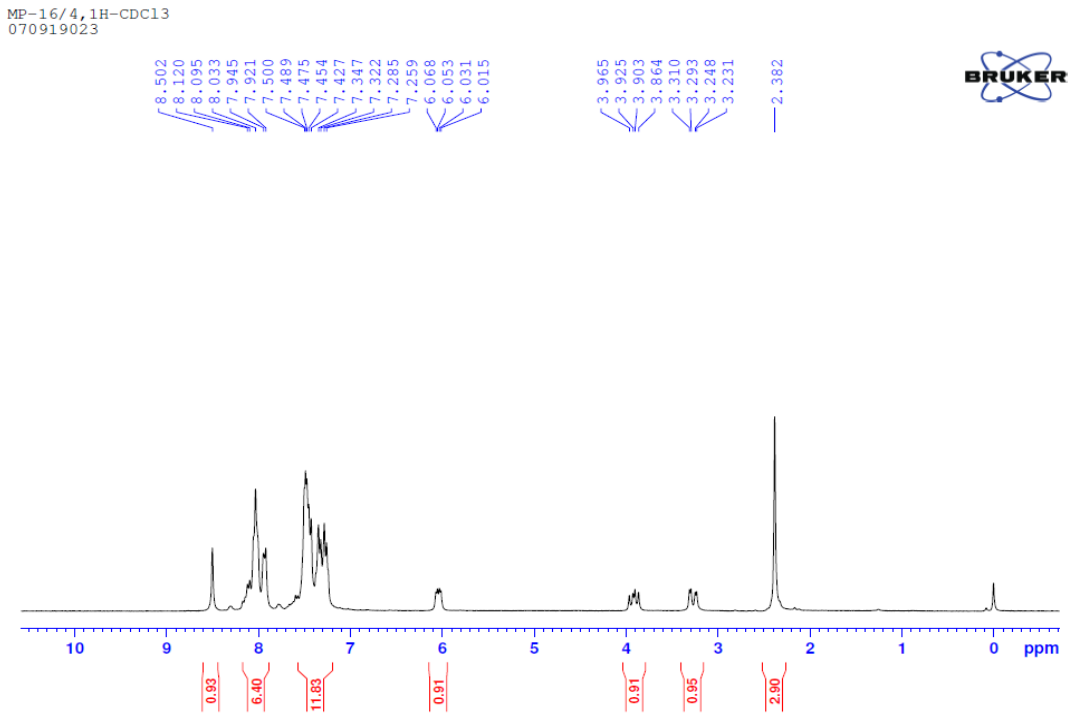
Appendix: C-5

AC5. REPRESENTATIVE SPECTRA OF NEWLY SYNTHESIZED ANTHRACENE-BASED 1,3,5-TRISUBSTITUTED PYRAZOLINES

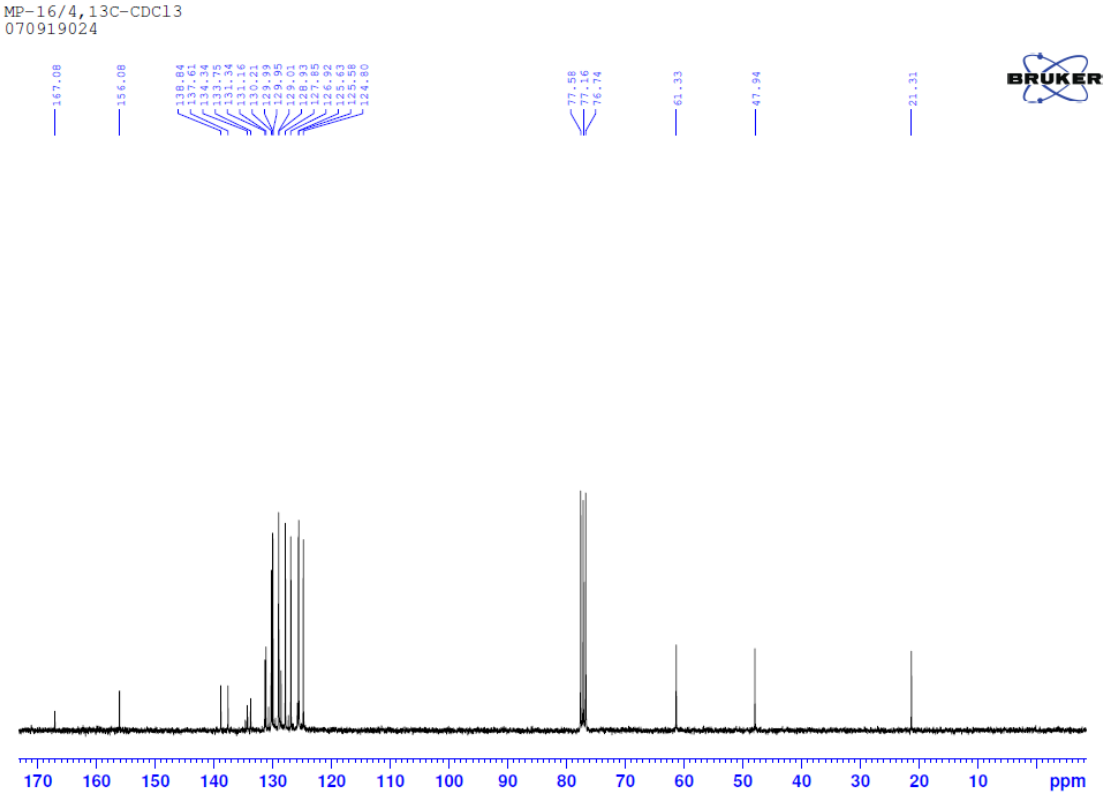
AC5.1 IR (KBr, *v*, cm^{-1}) spectrum of (3-(anthracen-10-yl)-4,5-dihydro-5-p-tolylpyrazol-1-yl)(phenyl)methanone (5.10d)



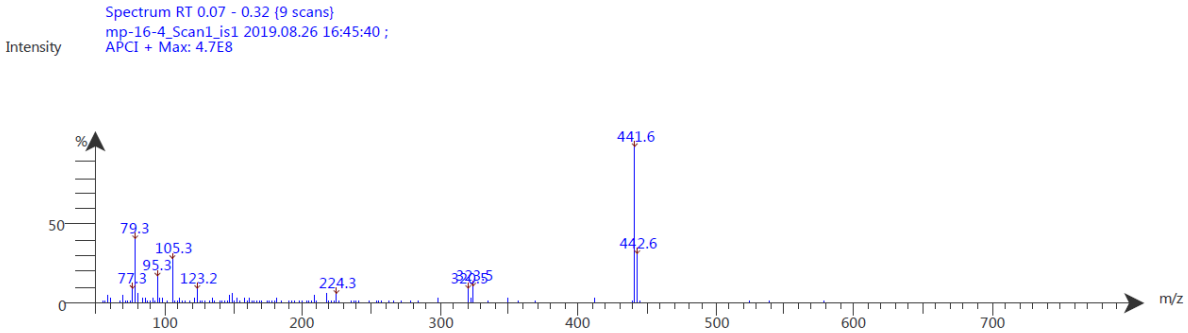
AC5.2 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of (3-(anthracen-10-yl)-4,5-dihydro-5-p-tolylpyrazol-1-yl)(phenyl)methanone (5.10d)



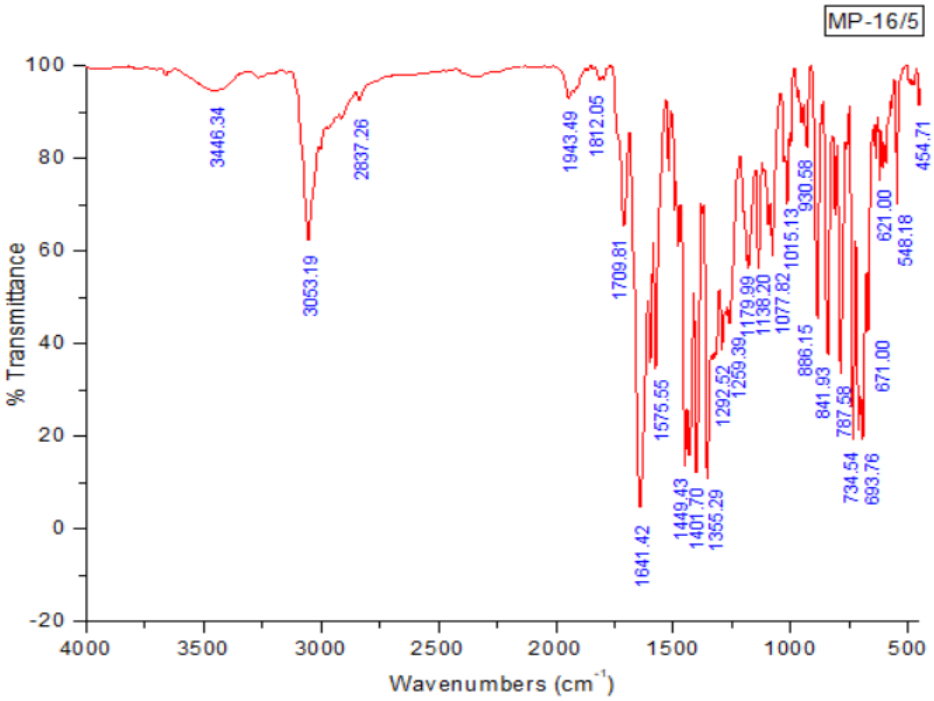
AC5.3 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of (3-(anthracen-10-yl)-4,5-dihydro-5-p-tolylpyrazol-1-yl)(phenyl)methanone (5.10d)



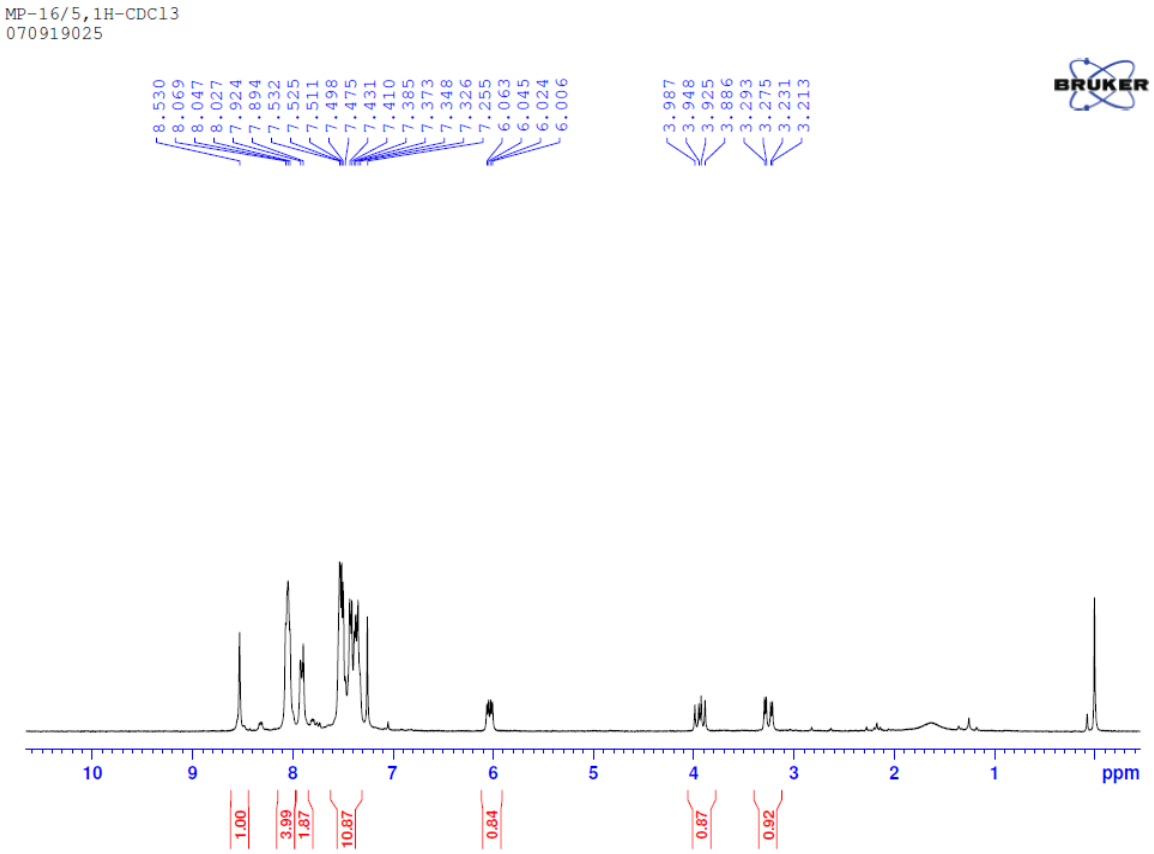
AC5.4 MS spectrum of (3-(anthracen-10-yl)-4,5-dihydro-5-p-tolylpyrazol-1-yl)(phenyl)methanone (5.10d)



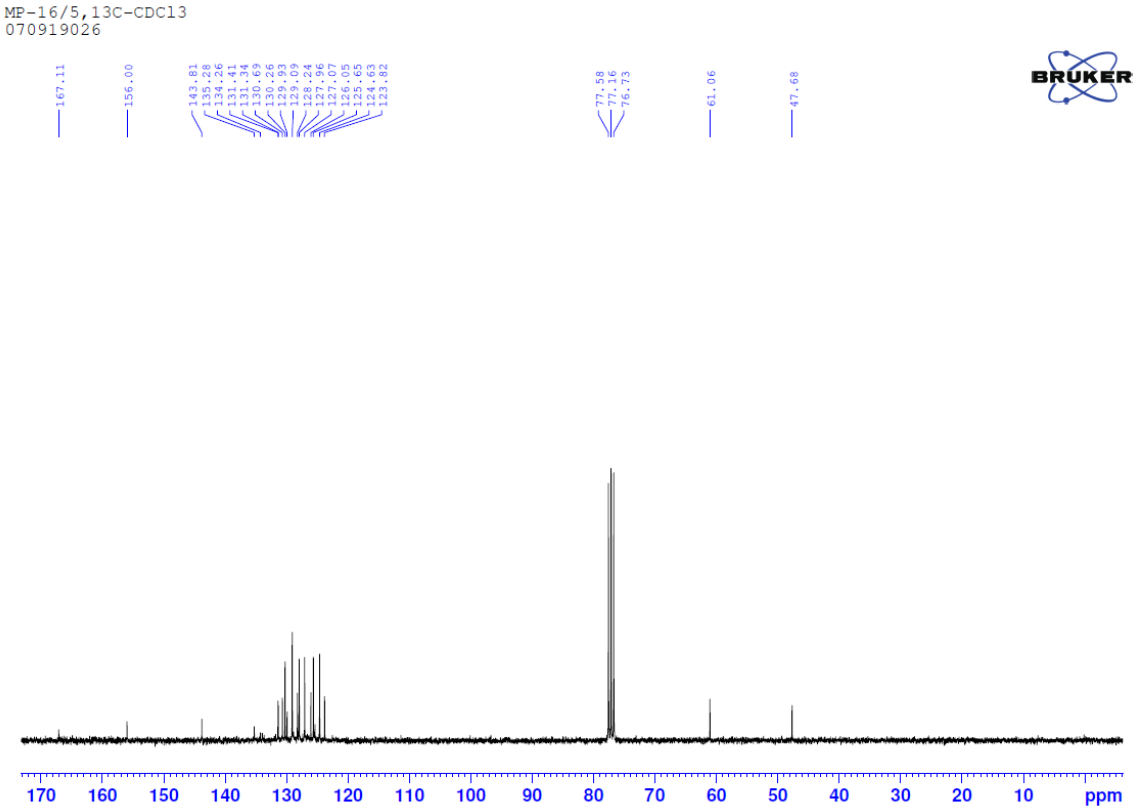
AC5.5 IR (KBr, *ν*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-5-(3-chlorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10e)



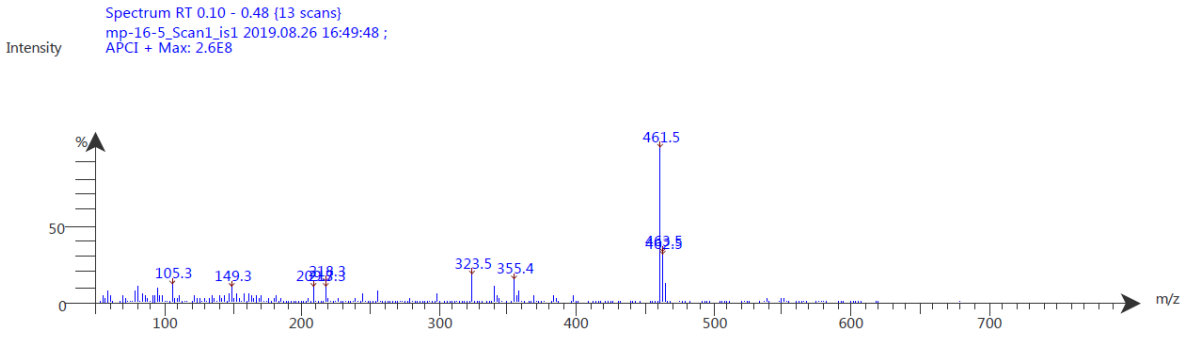
AC5.6 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(3-chlorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10e)



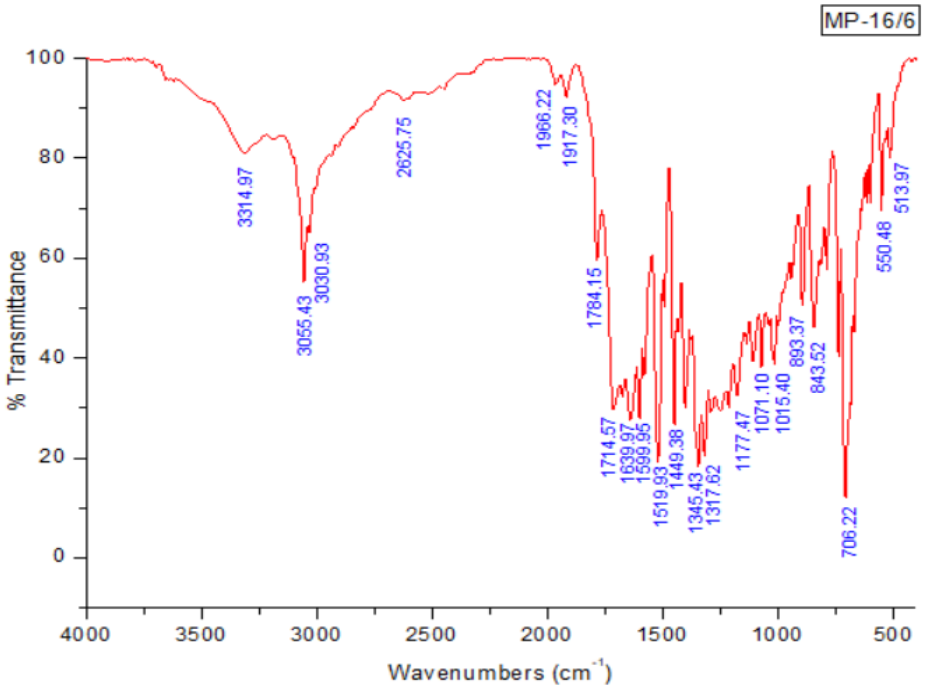
AC5.7 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(3-chlorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10e)



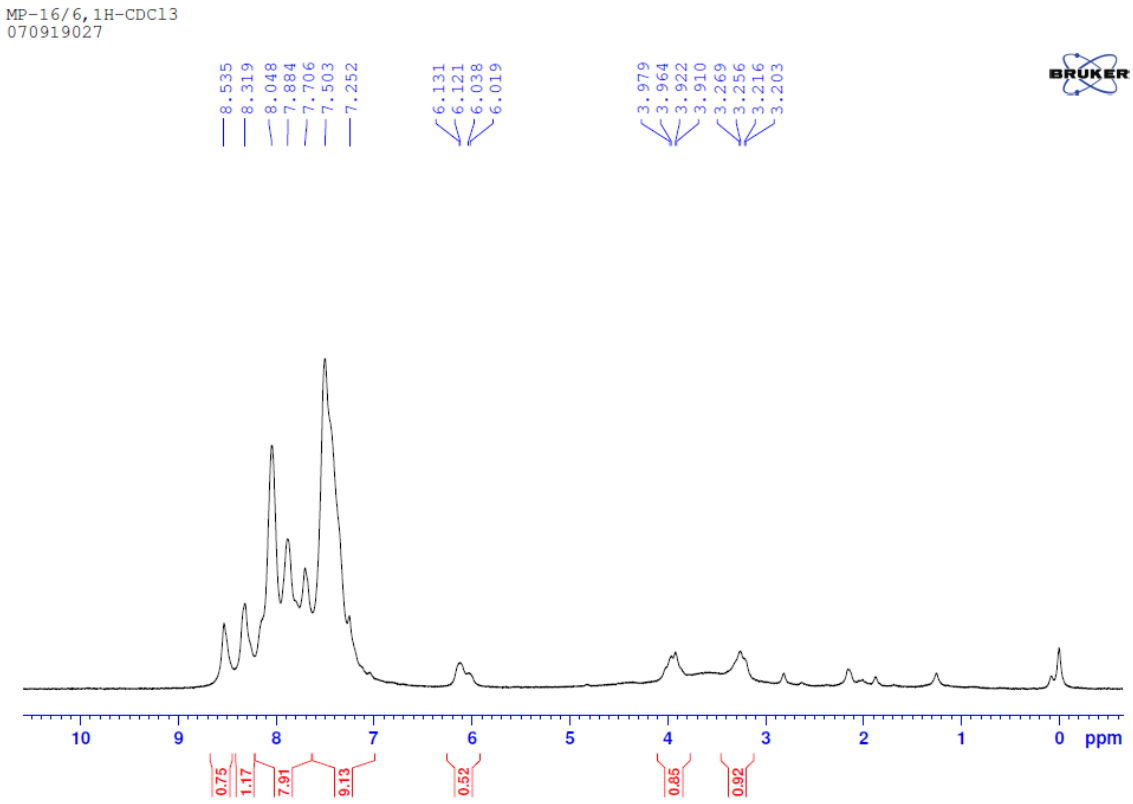
AC5.8 MS spectrum of 3-(Anthracen-10-yl)-5-(3-chlorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10e)



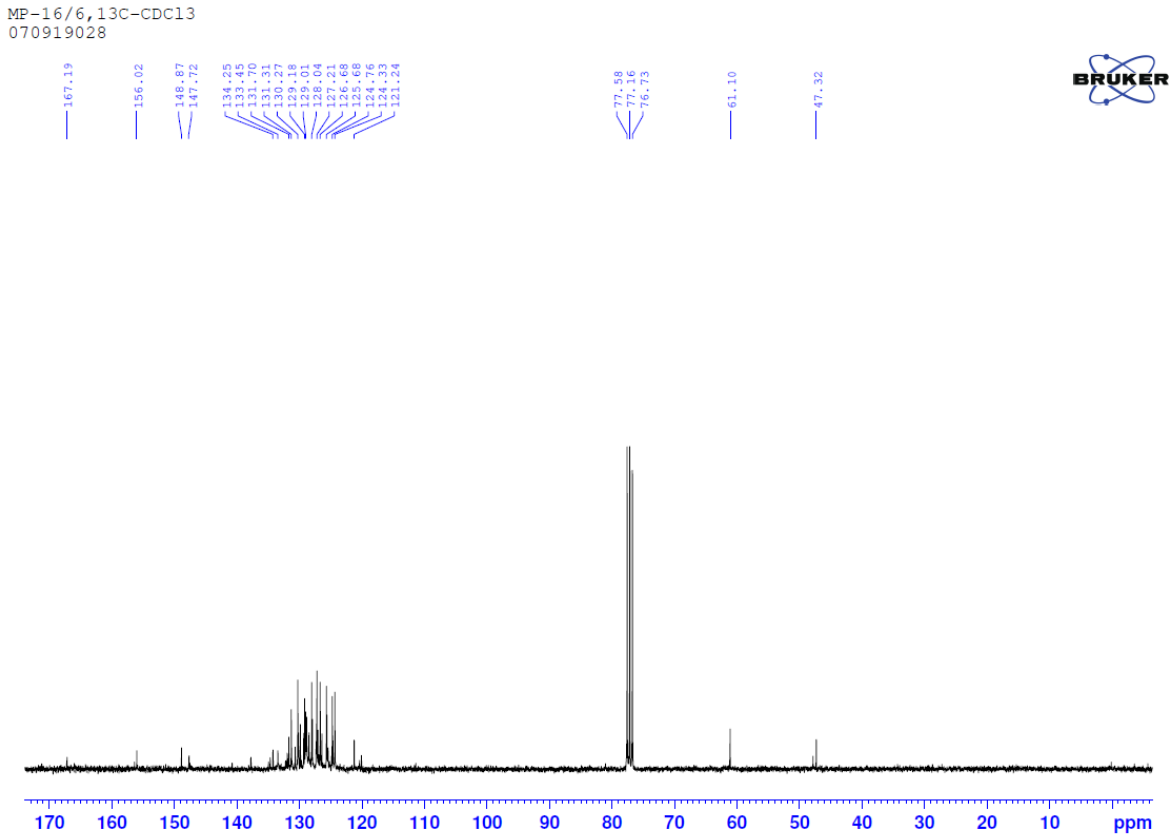
AC5.9 IR (KBr, *v*, cm^{-1}) spectrum of (3-(anthracen-10-yl)-4,5-dihydro-5-(4-nitrophenyl) pyrazol-1-yl)(phenyl)methanone (5.10f)



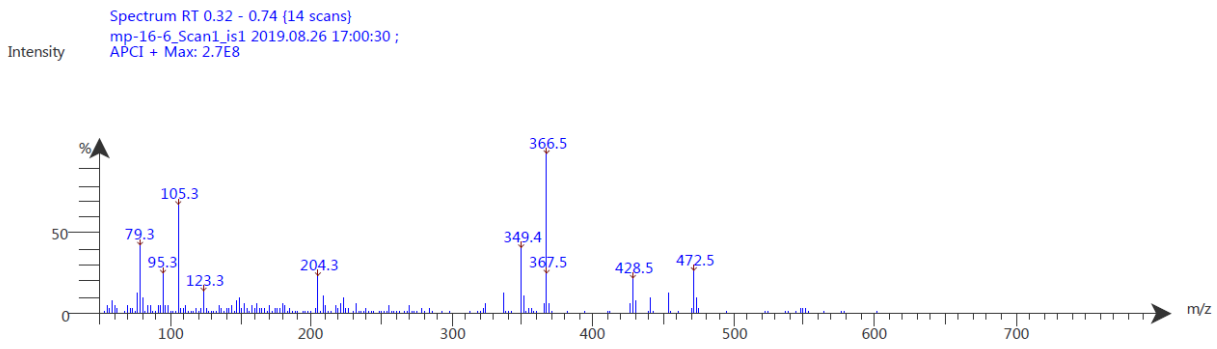
AC5.10 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of (3-(anthracen-10-yl)-4,5-dihydro-5-(4-nitrophenyl) pyrazol-1-yl)(phenyl)methanone (5.10f)



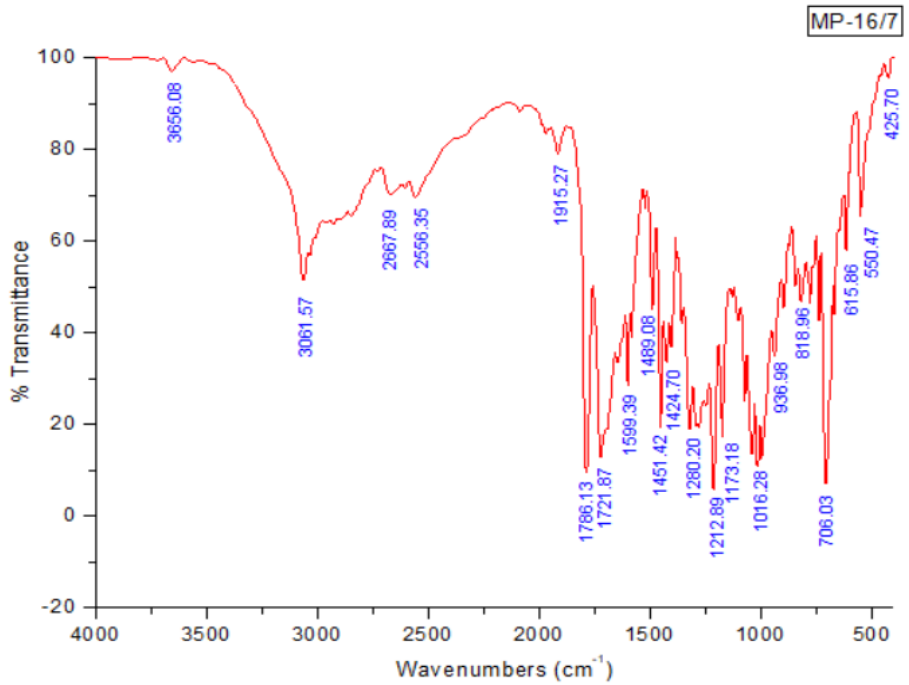
AC5.11 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of (3-(anthracen-10-yl)-4,5-dihydro-5-(4-nitrophenyl) pyrazol-1-yl)(phenyl)methanone (5.10f)



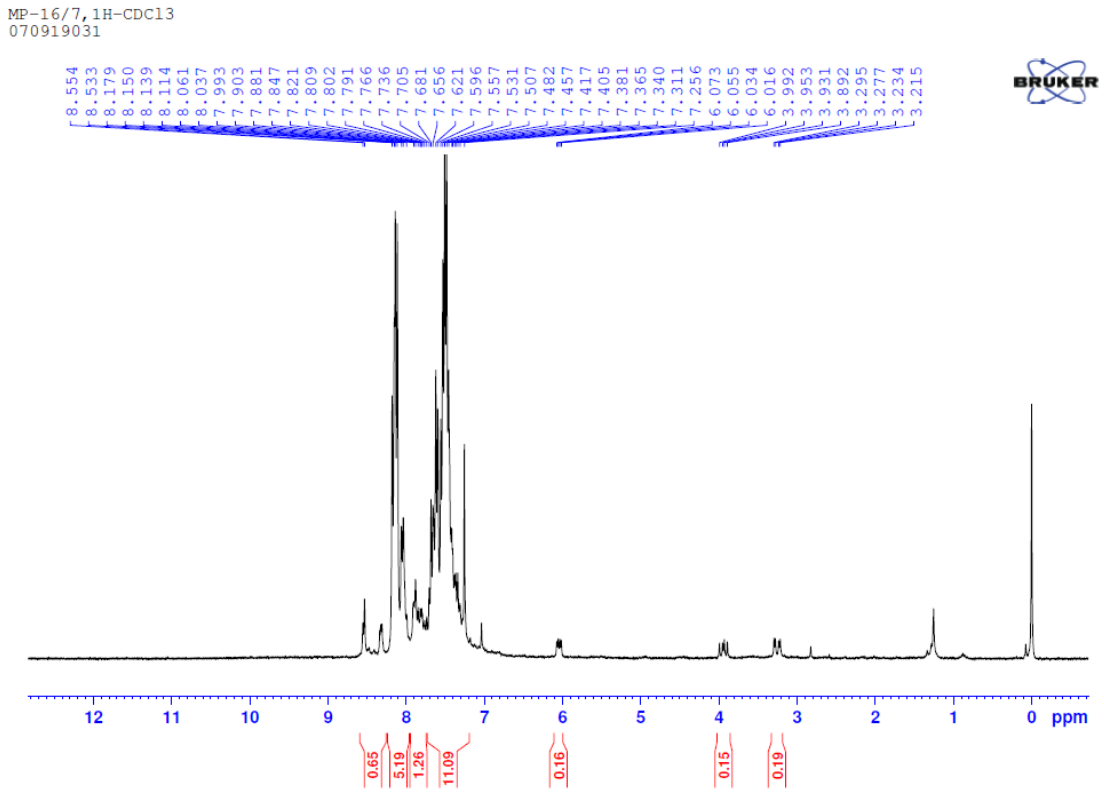
AC5.12 MS spectrum of (3-(anthracen-10-yl)-4,5-dihydro-5-(4-nitrophenyl) pyrazol-1-yl)(phenyl)methanone (5.10f)



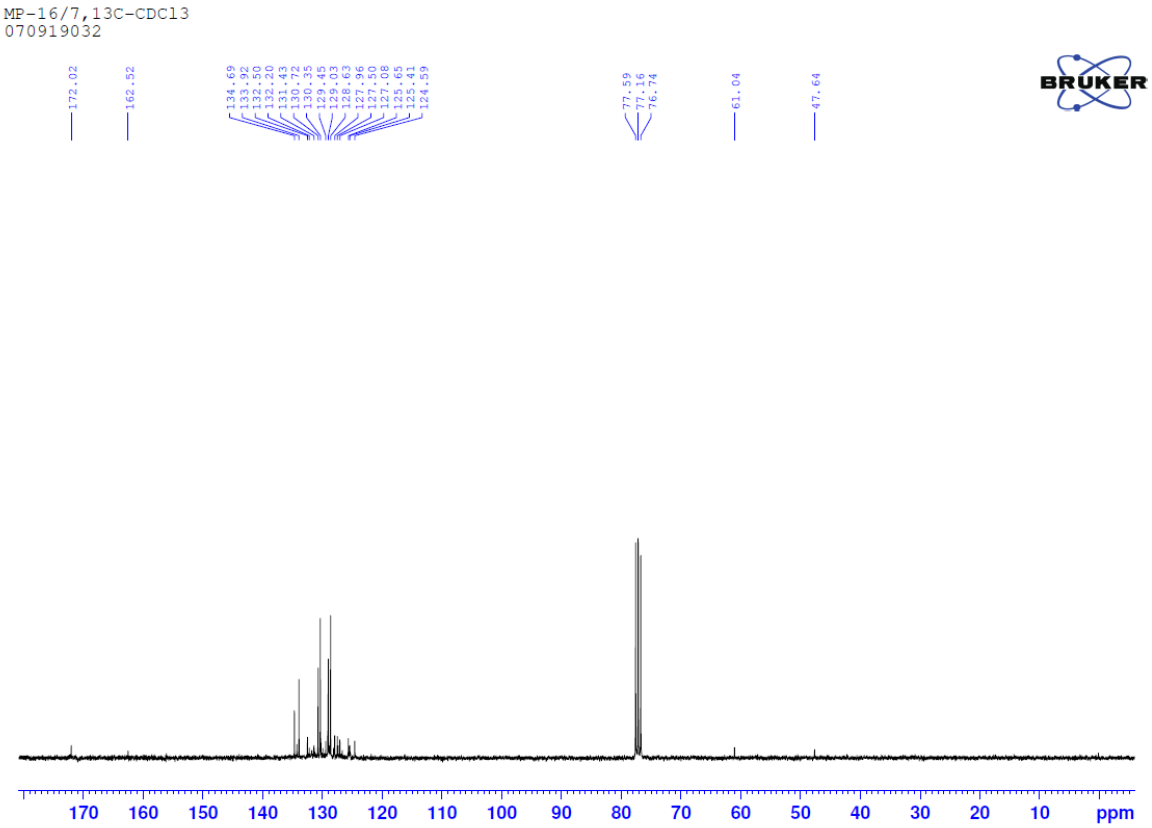
AC5.13 IR (KBr, *v*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-5-(4-bromophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10g)



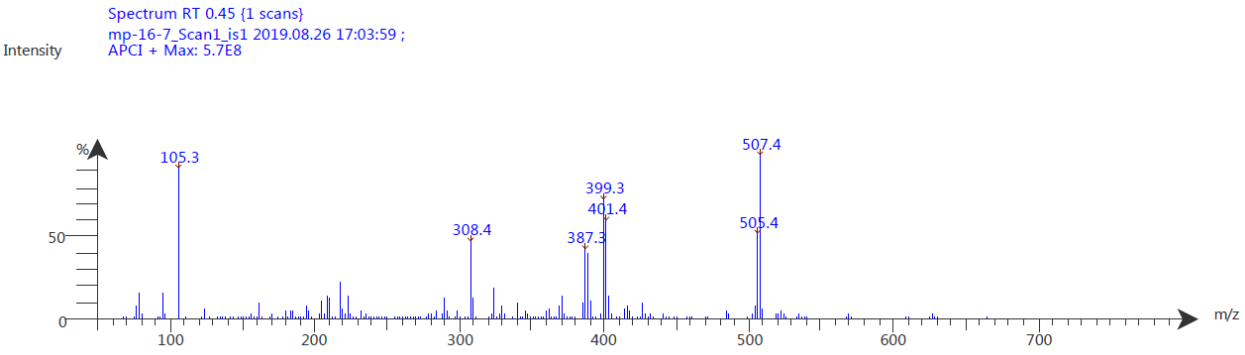
AC5.14 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(4-bromophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10g)



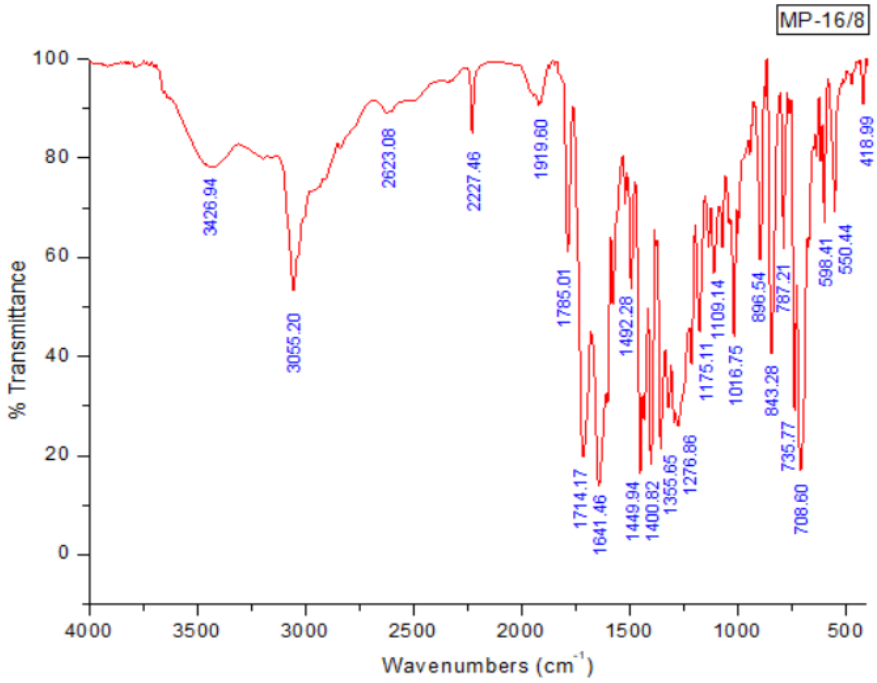
AC5.15 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(4-bromophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10g)



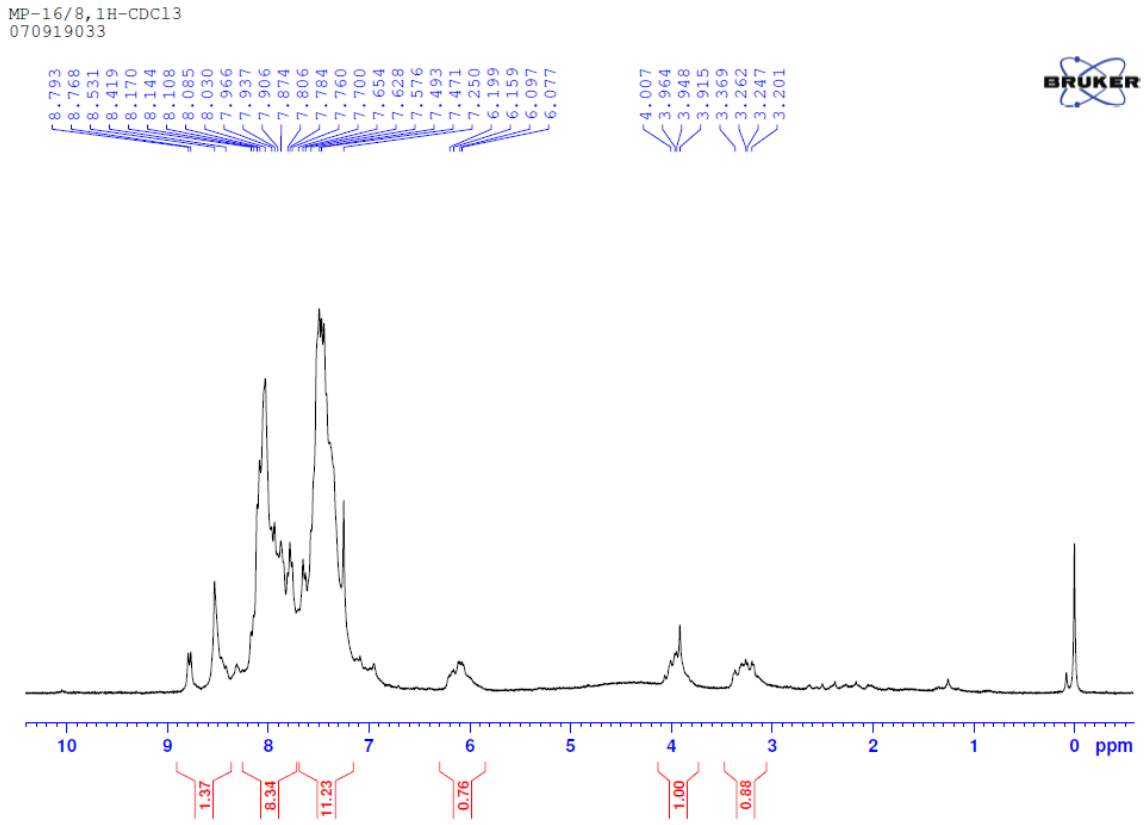
AC5.16 MS spectrum of 3-(Anthracen-10-yl)-5-(4-bromophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10g)



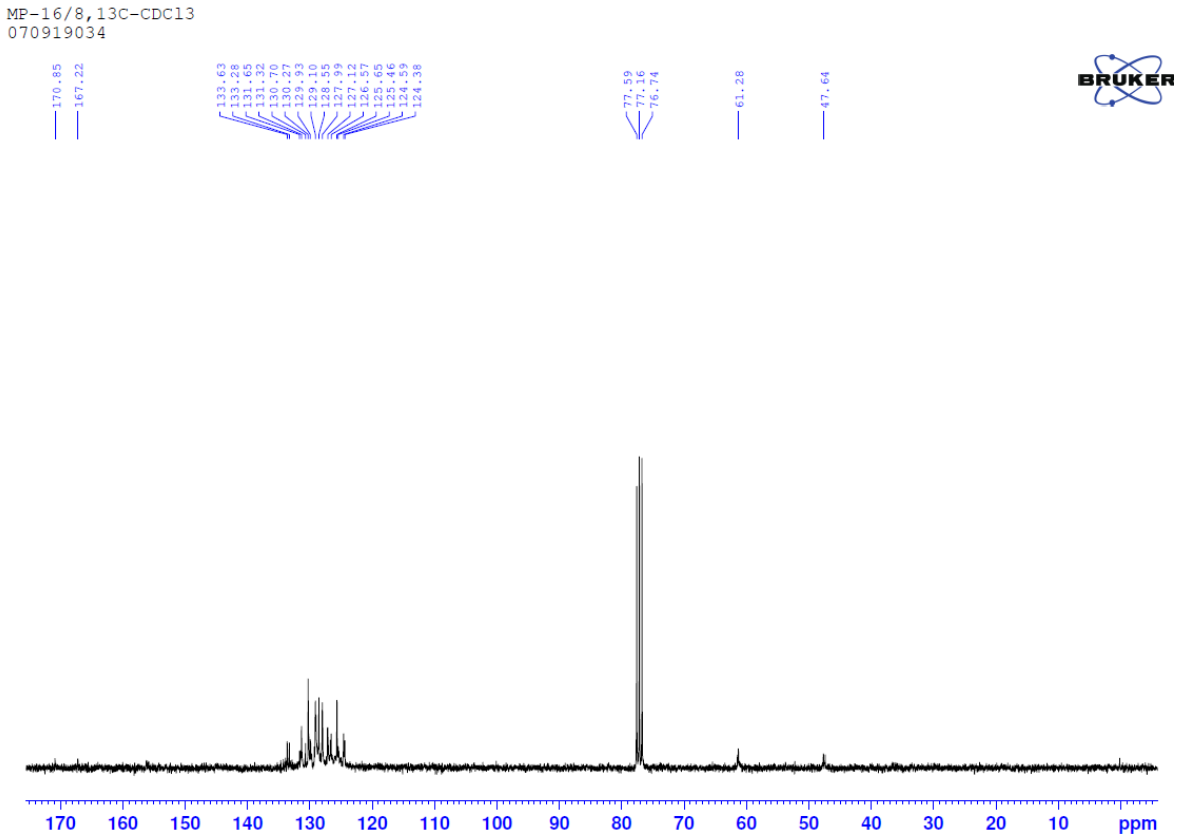
AC5.17 IR (KBr, *ν*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-5-(4-cyanophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10h)



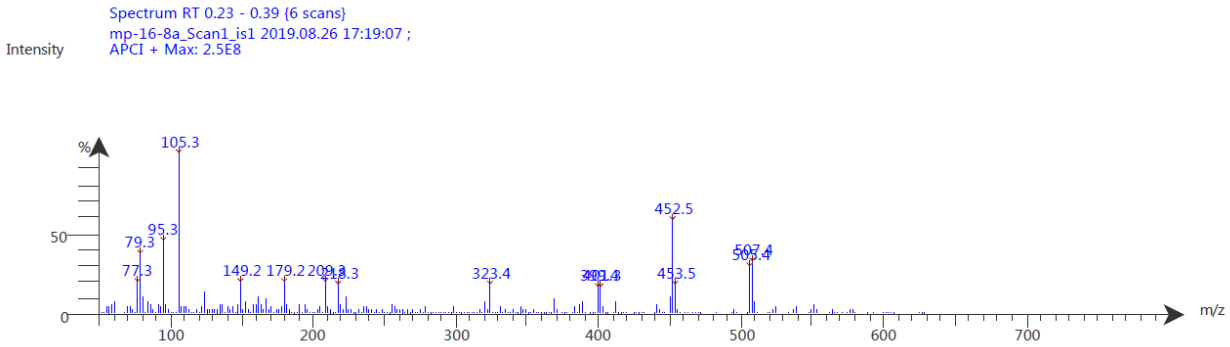
AC5.18 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(4-cyanophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10h)



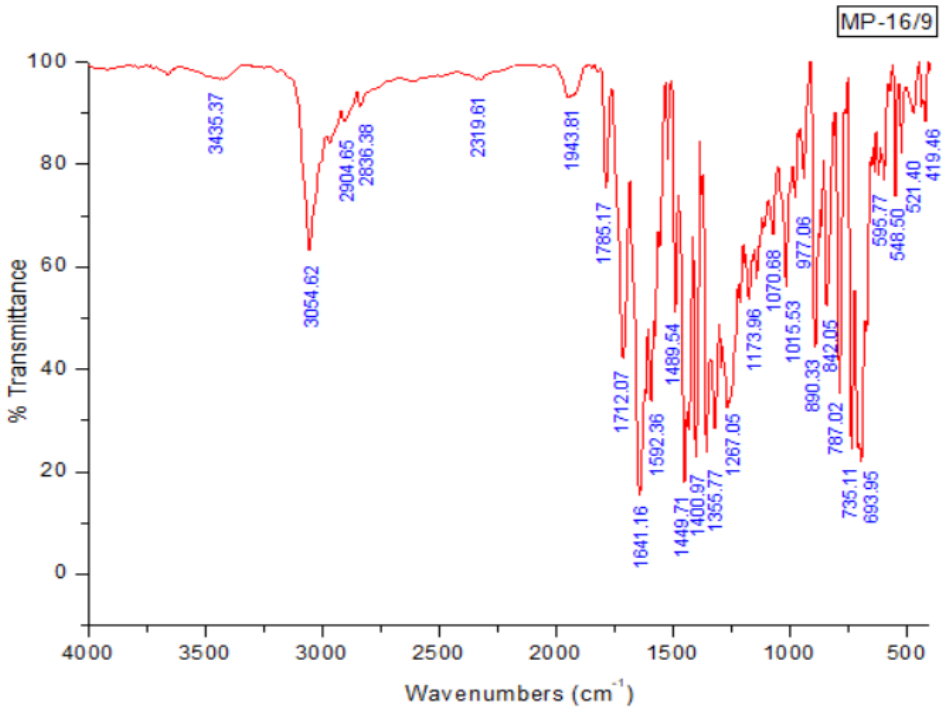
AC5.19 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(4-cyanophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10h)



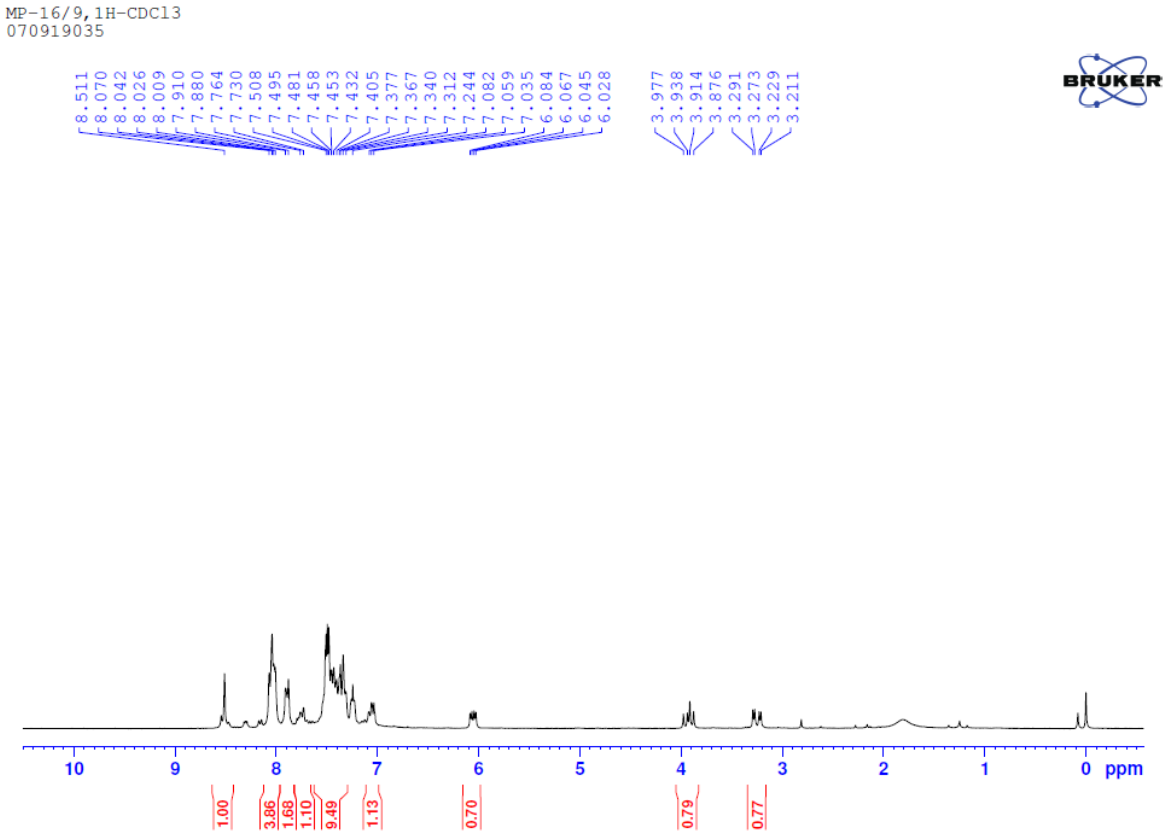
AC5.20 MS spectrum of 3-(Anthracen-10-yl)-5-(4-cyanophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10h)



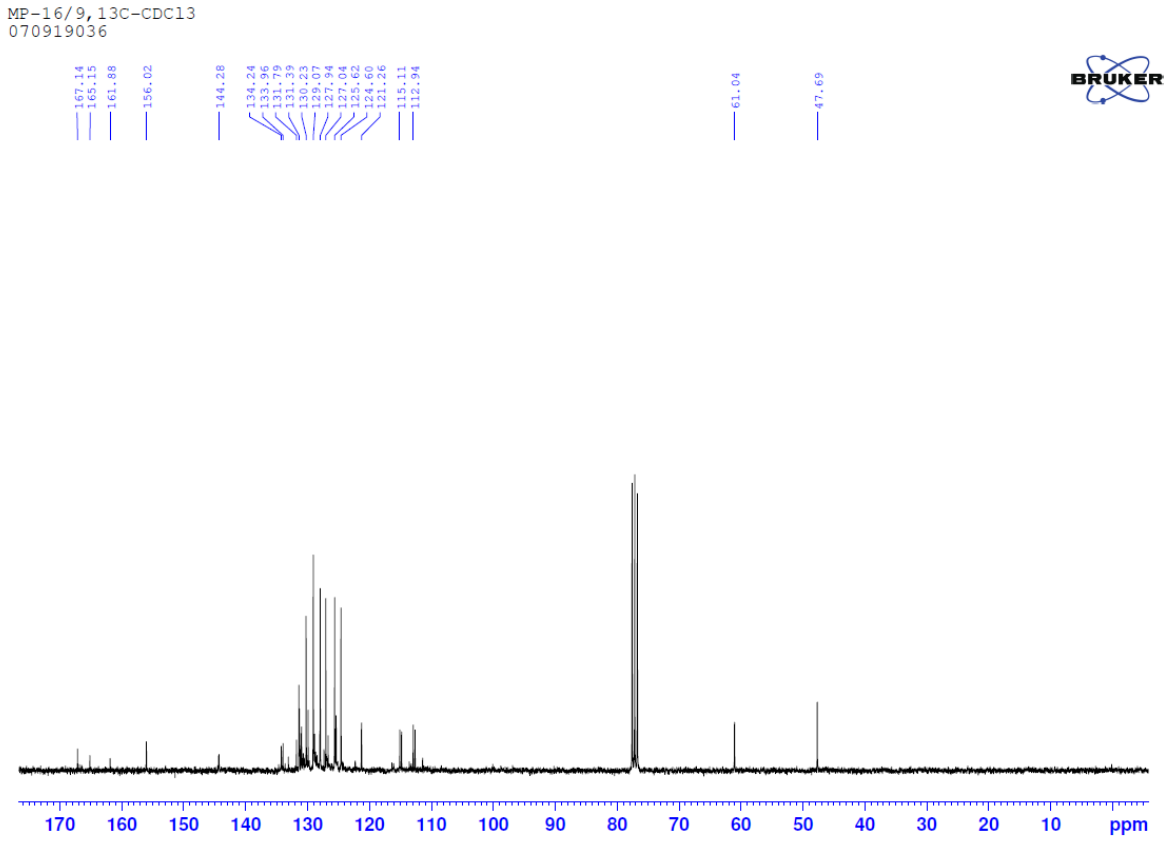
AC5.21 IR (KBr, *ν*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-5-(3-fluorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10i)



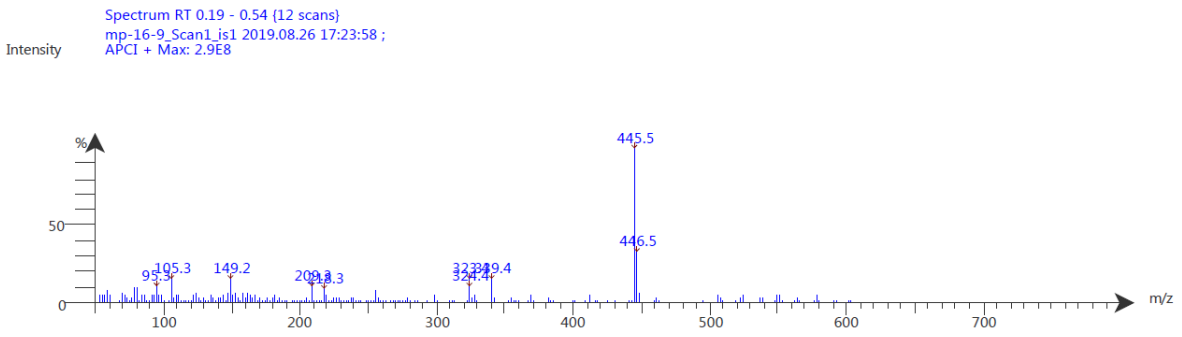
AC5.22 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(3-fluorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10i)



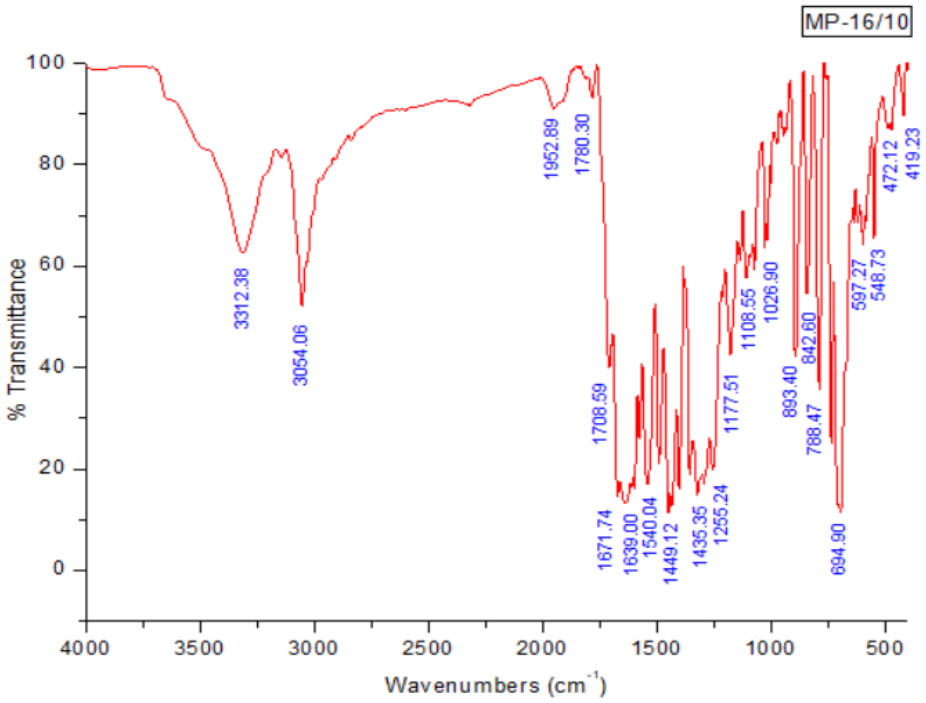
AC5.23 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(3-fluorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10i)



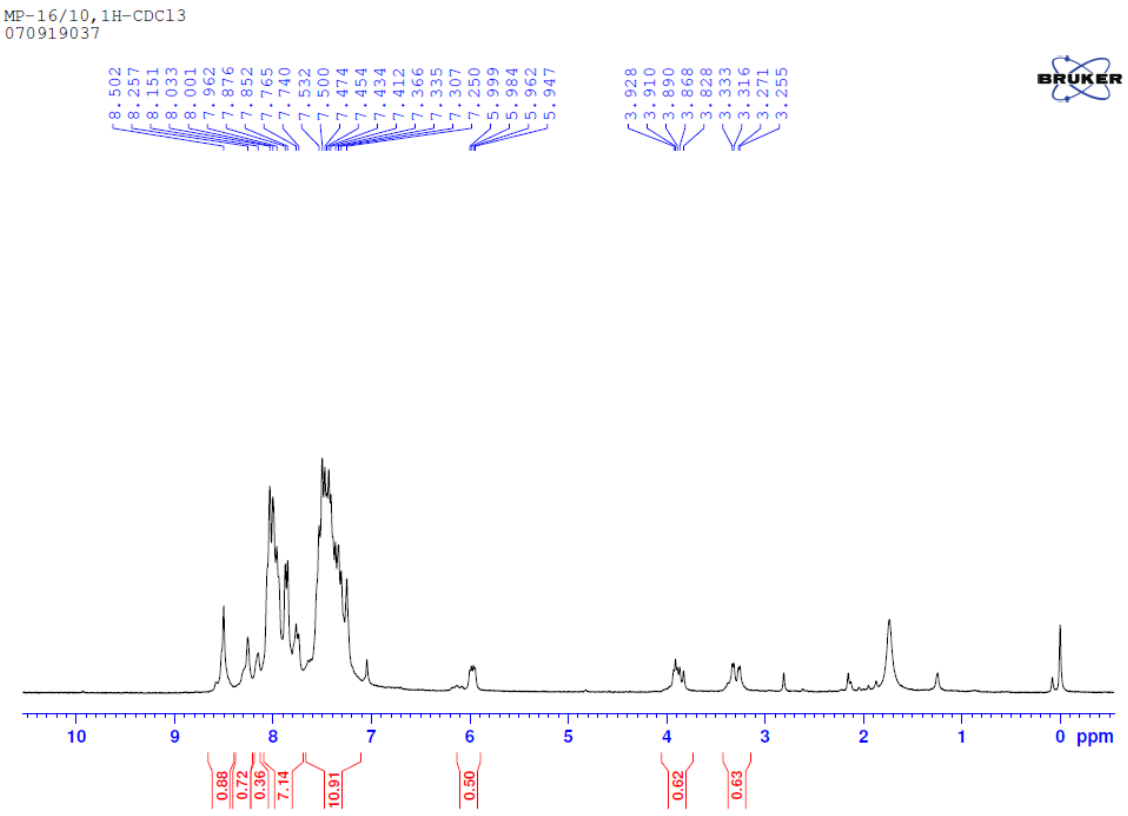
AC5.24 MS spectrum of 3-(Anthracen-10-yl)-5-(3-fluorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10i)



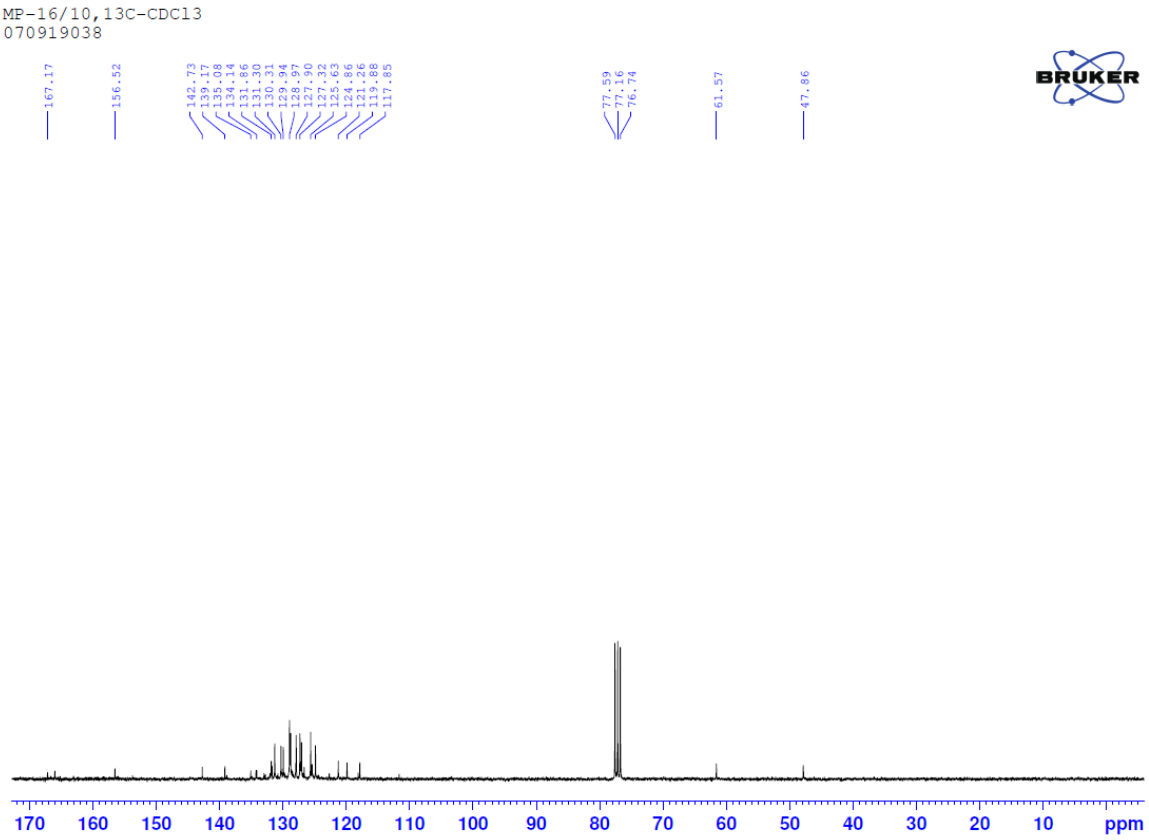
AC5.25 IR (KBr, *ν*, cm^{-1}) spectrum of (3-(anthracen-10-yl)-4,5-dihydro-5-(3-nitrophenyl)pyrazol-1-yl)(phenyl)methanone (5.10j)



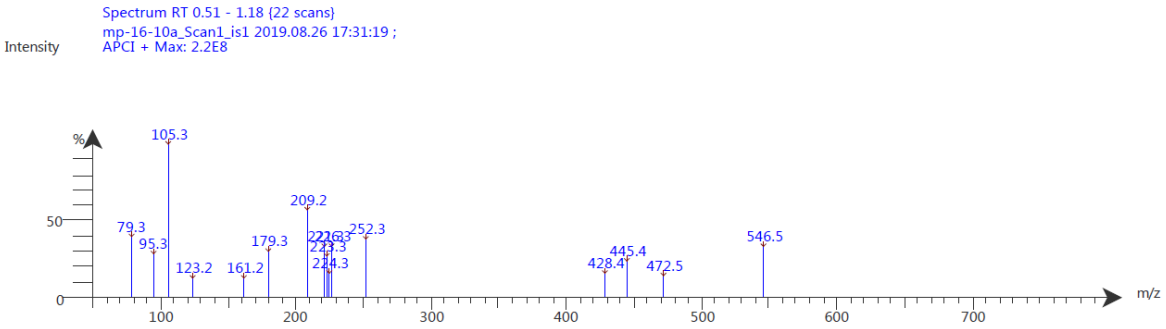
AC5.26 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of (3-(anthracen-10-yl)-4,5-dihydro-5-(3-nitrophenyl)pyrazol-1-yl)(phenyl)methanone (5.10j)



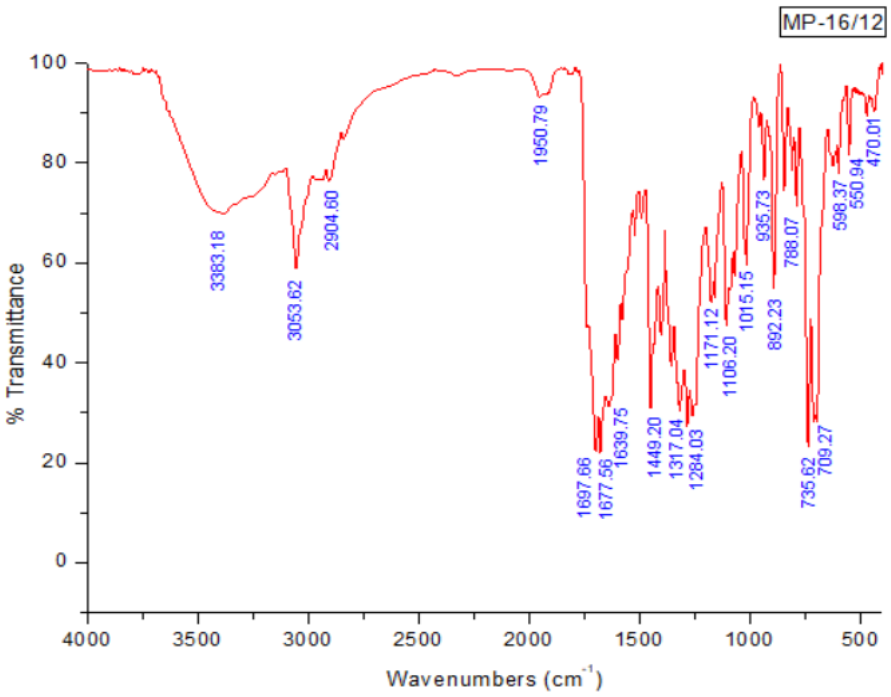
AC5.27 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of (3-(anthracen-10-yl)-4,5-dihydro-5-(3-nitrophenyl)pyrazol-1-yl)(phenyl)methanone (5.10j)



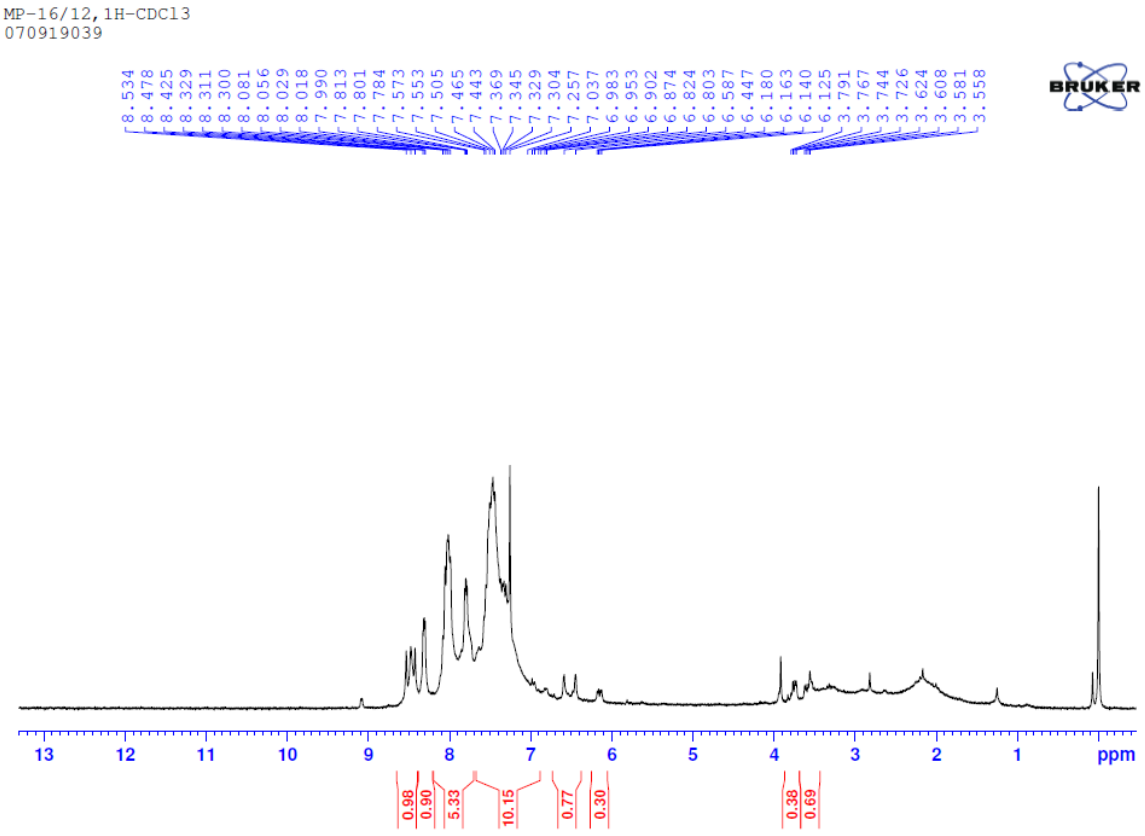
AC5.28 MS spectrum of (3-(anthracen-10-yl)-4,5-dihydro-5-(3-nitrophenyl)pyrazol-1-yl)(phenyl)methanone (5.10j)



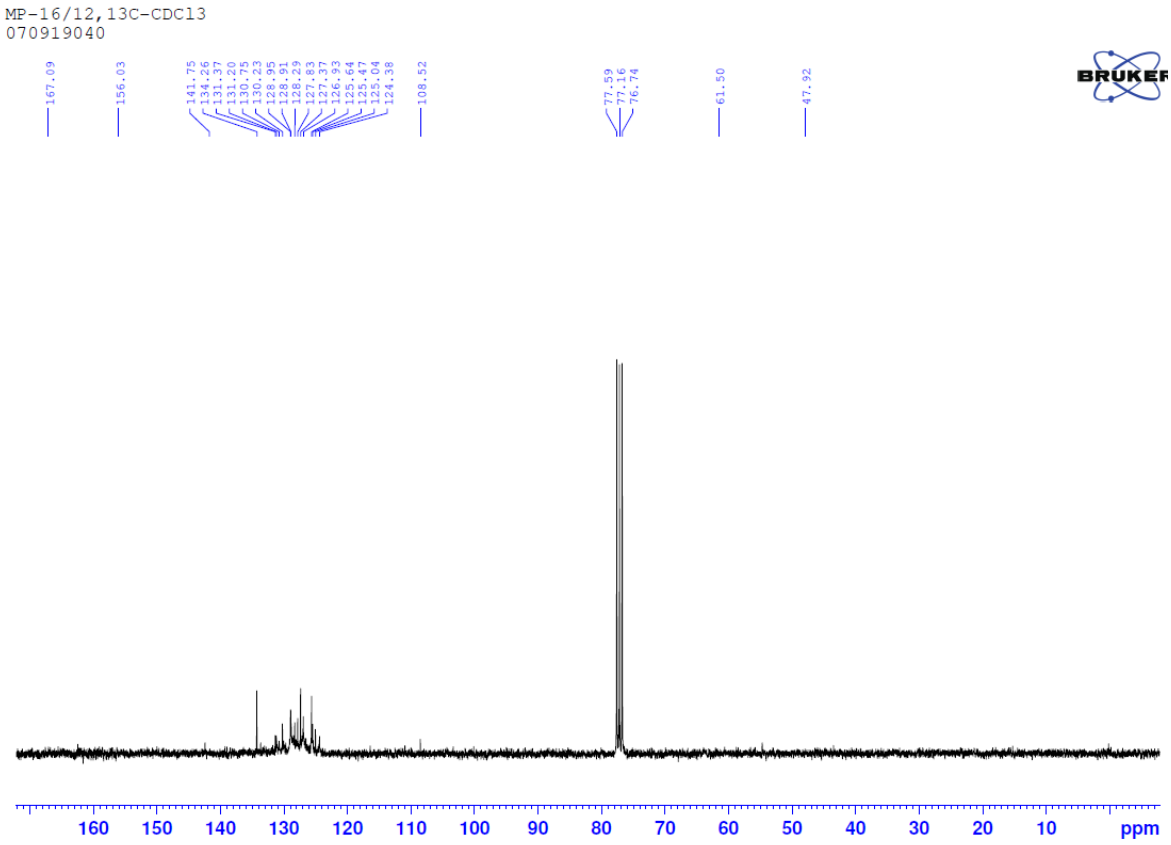
AC5.29 IR (KBr, *ν*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-5-(furan-2-yl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10k)



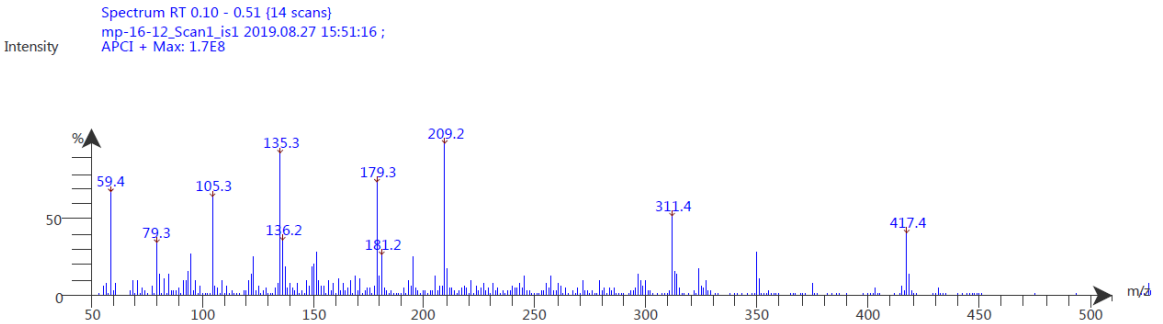
AC5.30 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(furan-2-yl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10k)



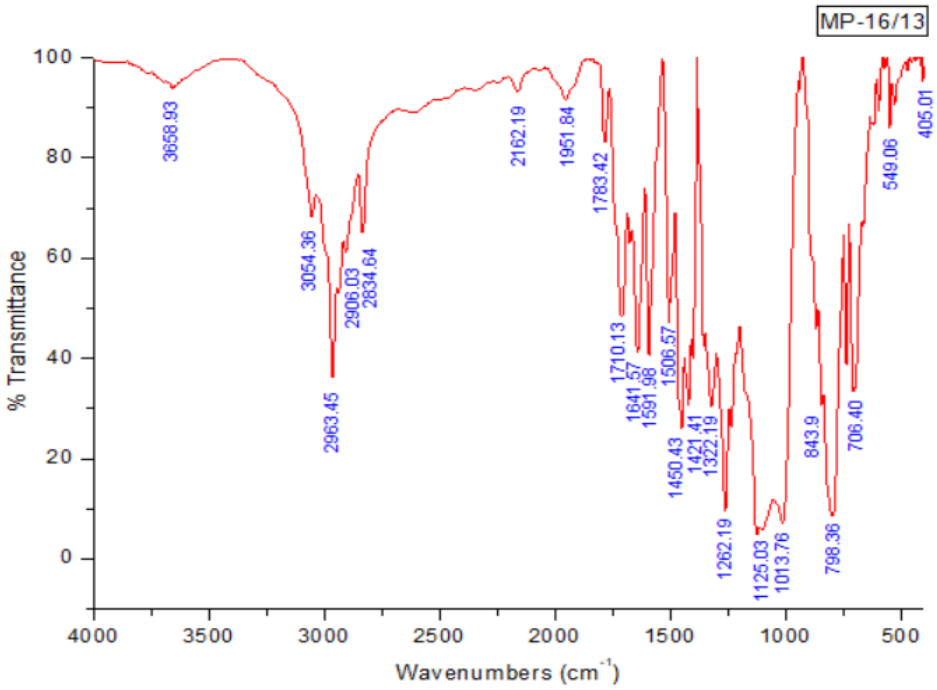
AC5.31 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-5-(furan-2-yl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10k)



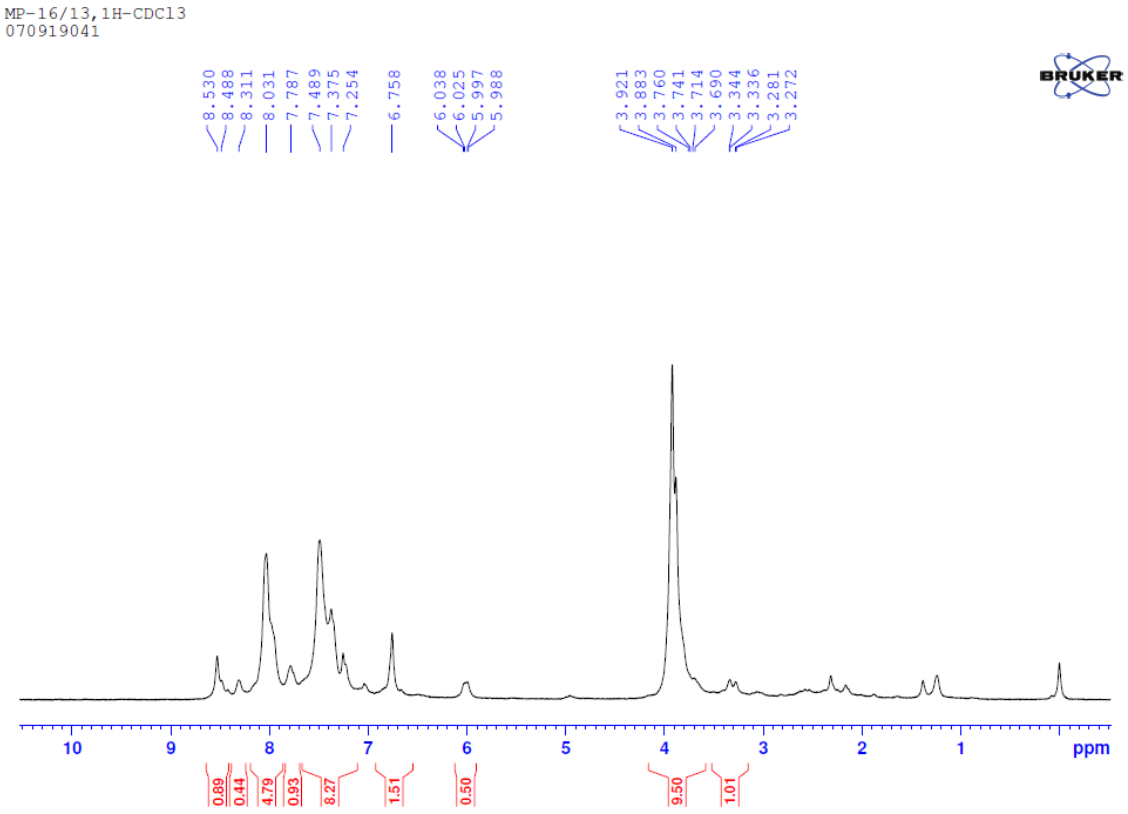
AC5.32 MS spectrum of 3-(Anthracen-10-yl)-5-(furan-2-yl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10k)



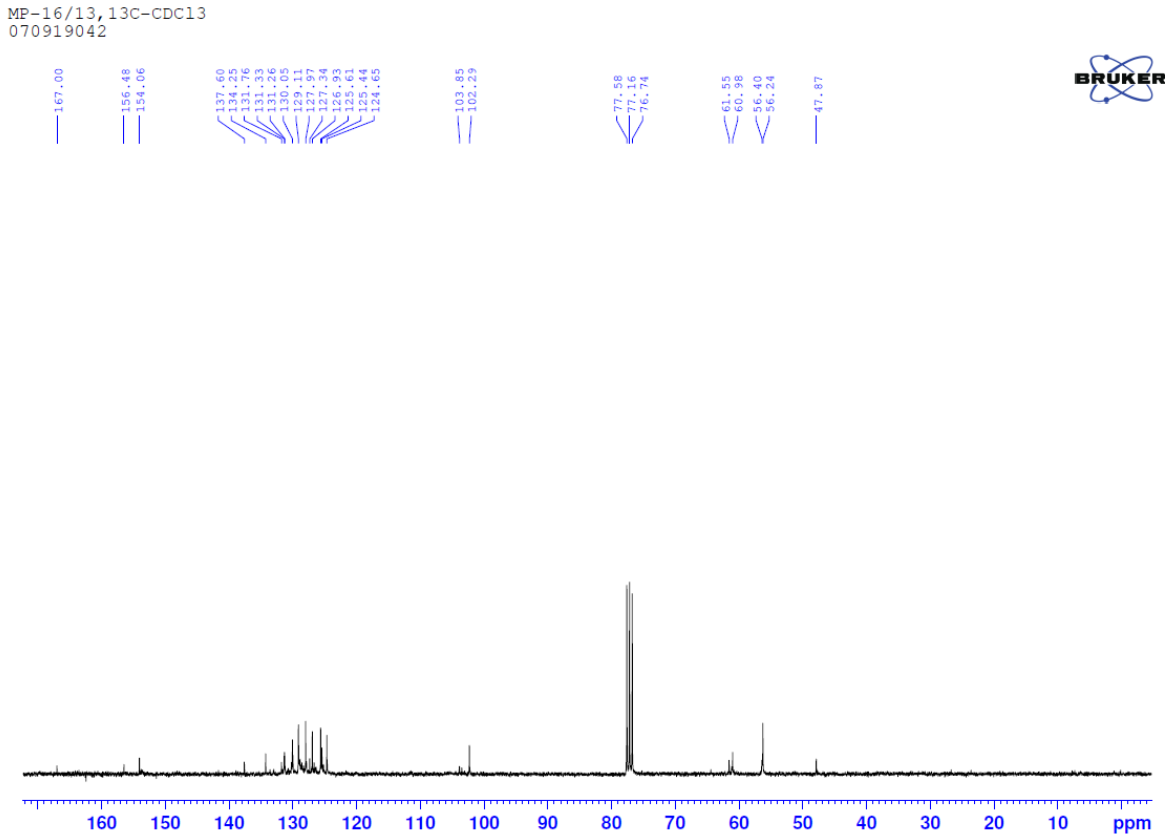
AC5.33 IR (KBr, *ν*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-4,5-dihydro-5-(3,4,5-trimethoxyphenyl)pyrazol-1-yl)(phenyl)methanone (5.10l)



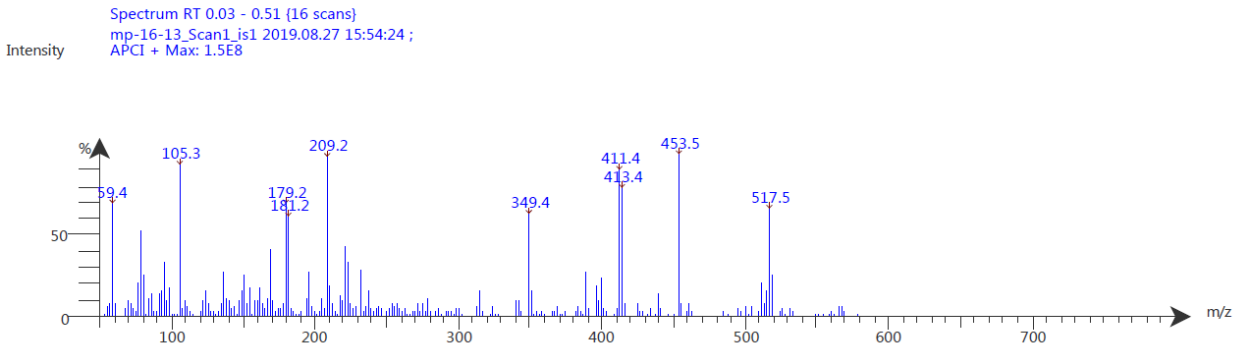
AC5.34 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-4,5-dihydro-5-(3,4,5-trimethoxyphenyl)pyrazol-1-yl)(phenyl)methanone (5.10l)



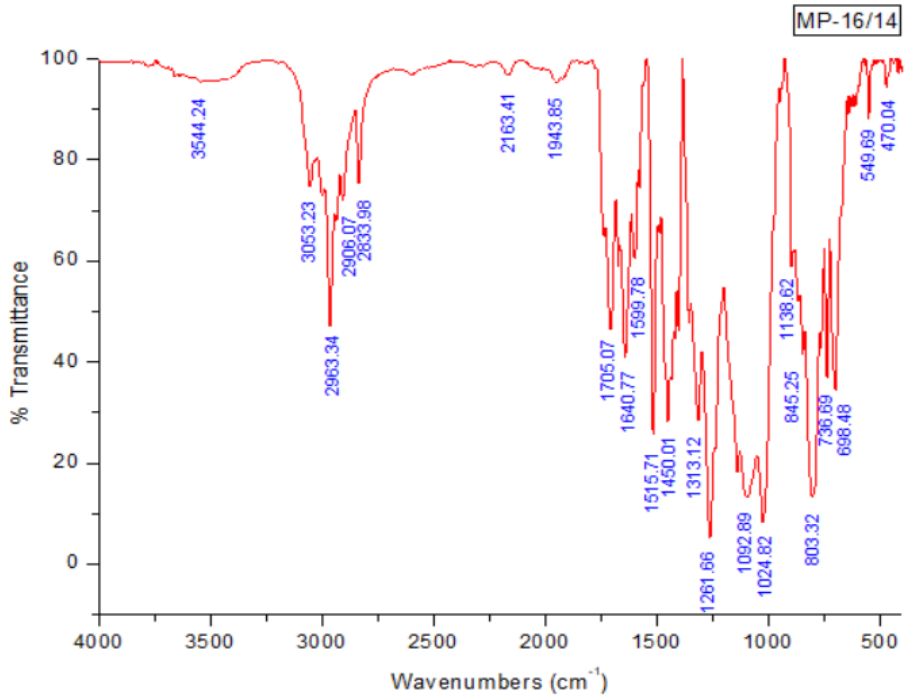
AC5.35 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-4,5-dihydro-5-(3,4,5-trimethoxyphenyl)pyrazol-1-yl)(phenyl)methanone (5.10l)



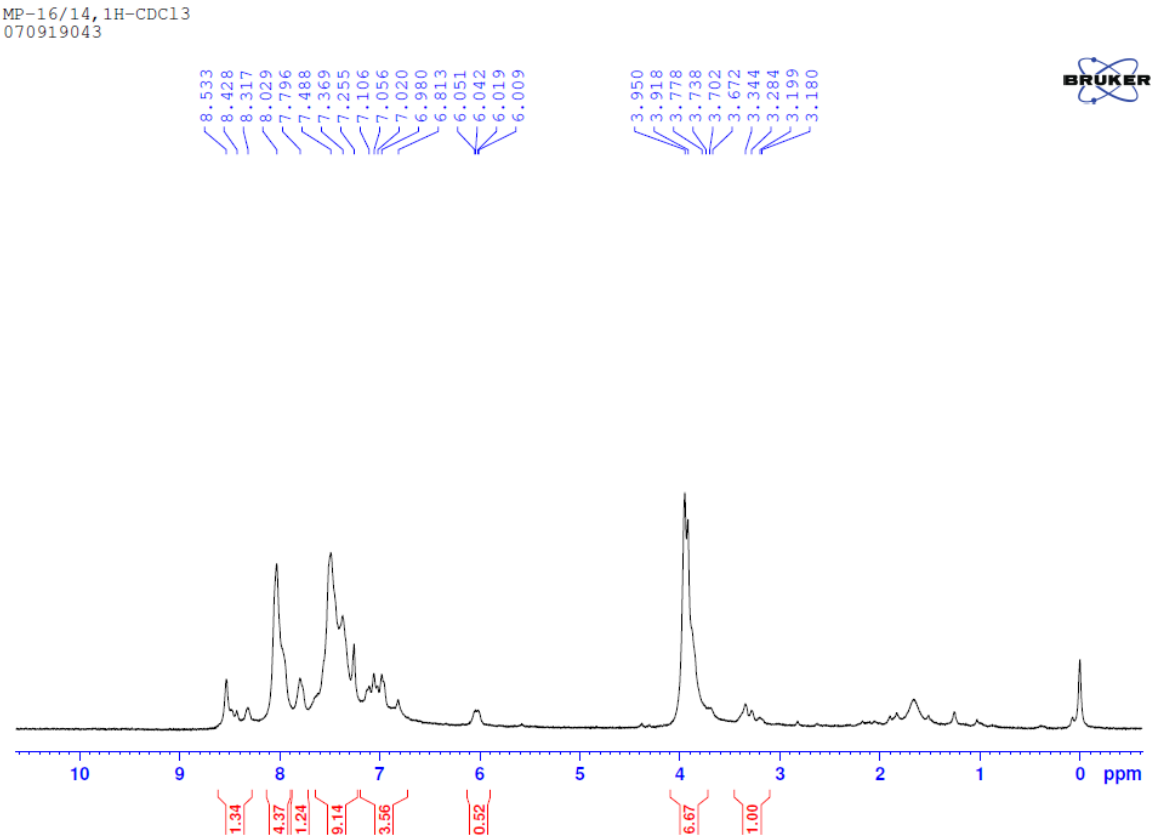
AC5.36 MS spectrum of 3-(Anthracen-10-yl)-4,5-dihydro-5-(3,4,5-trimethoxyphenyl)pyrazol-1-yl)(phenyl)methanone (5.10l)



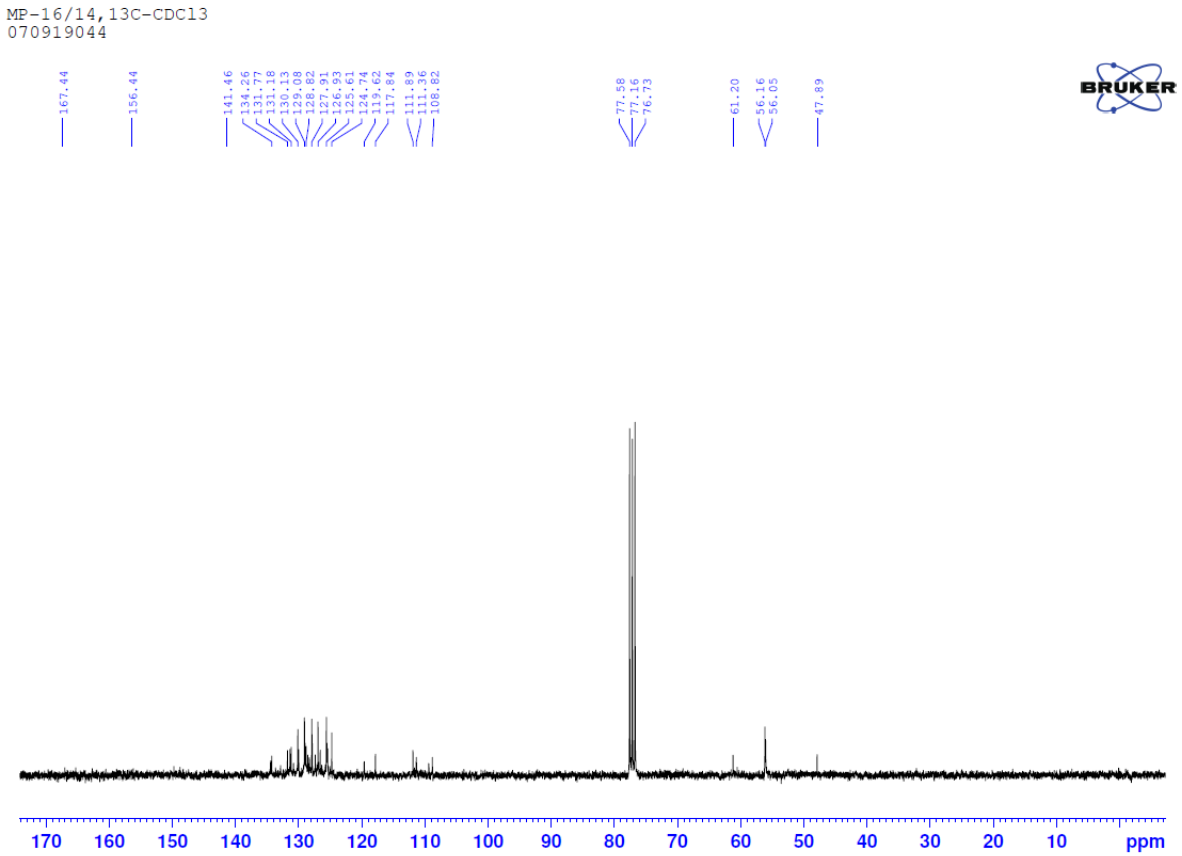
AC5.37 IR (KBr, *ν*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-4,5-dihydro-5-(3,4-dimethoxyphenyl)pyrazol-1-yl)(phenyl)methanone (5.10m)



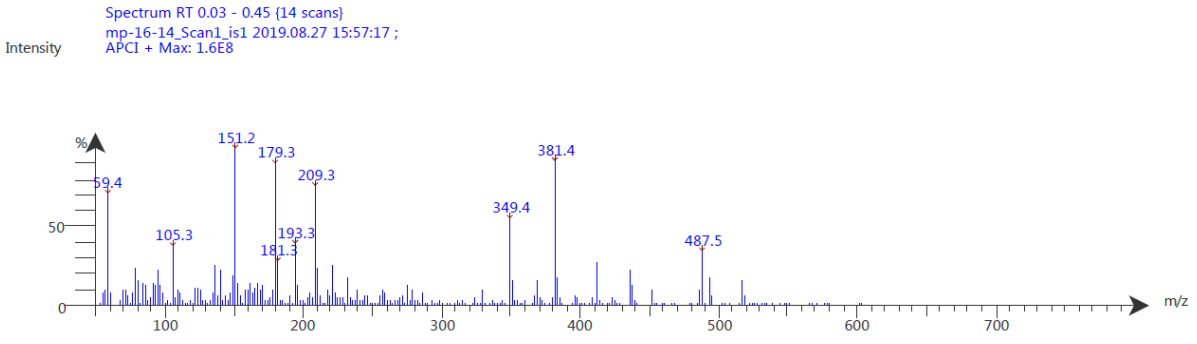
AC5.38 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-4,5-dihydro-5-(3,4-dimethoxyphenyl)pyrazol-1-yl)(phenyl)methanone (5.10m)



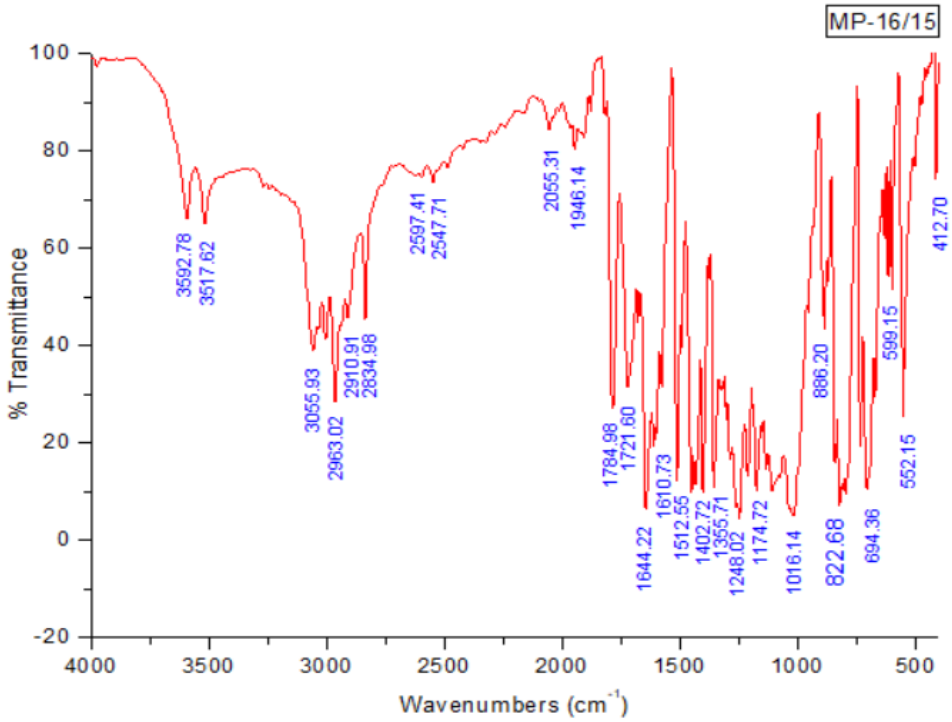
AC5.39 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-4,5-dihydro-5-(3,4-dimethoxyphenyl)pyrazol-1-yl)(phenyl)methanone (5.10m)



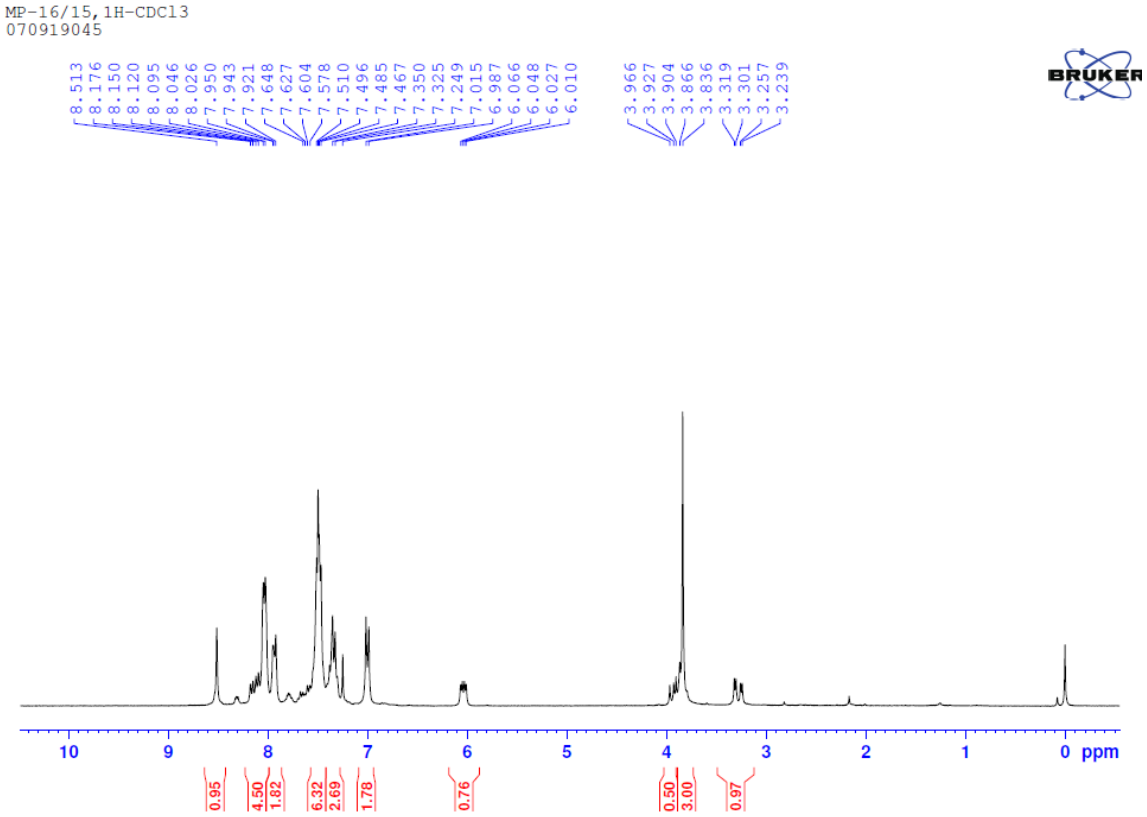
AC5.40 MS spectrum of 3-(Anthracen-10-yl)-4,5-dihydro-5-(3,4-dimethoxyphenyl)pyrazol-1-yl)(phenyl)methanone (5.10m)



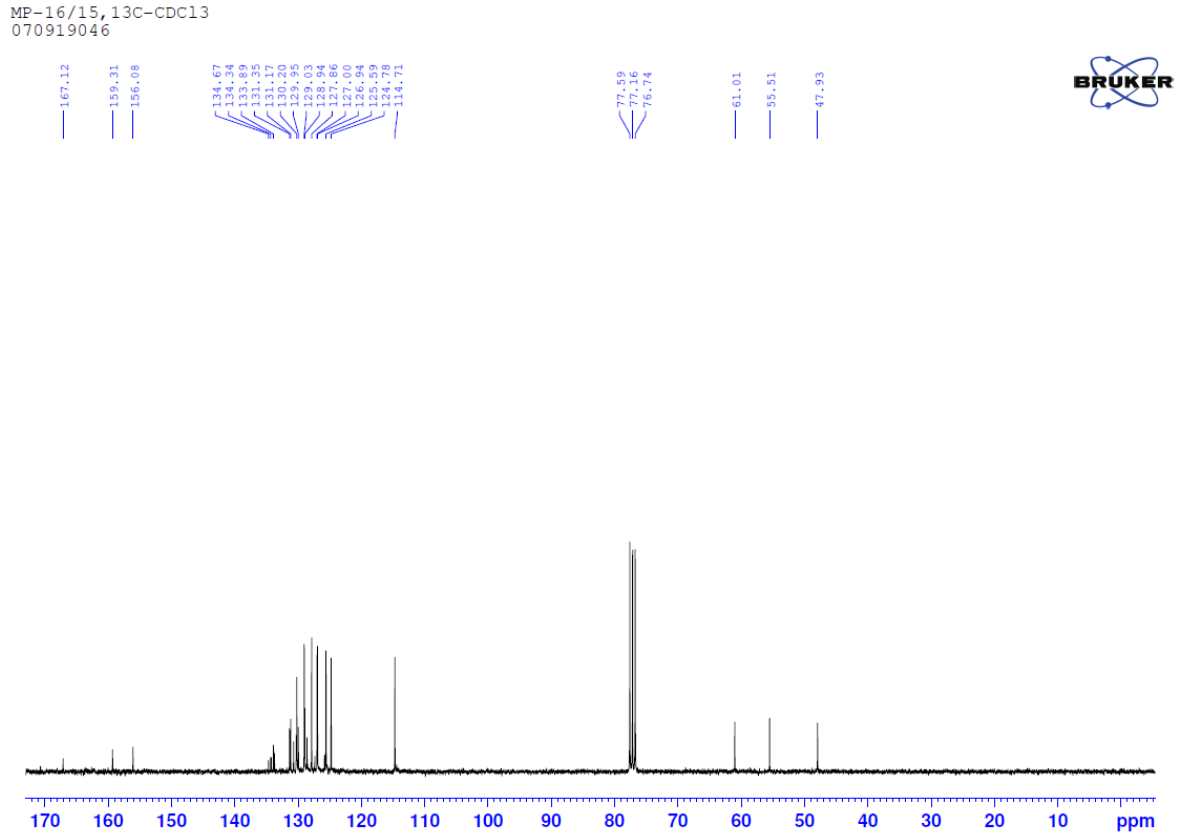
AC5.41 IR (KBr, *ν*, cm^{-1}) spectrum of 3-(Anthracen-10-yl)-4,5-dihydro-5-(4-methoxyphenyl)pyrazol-1-yl)(phenyl)methanone (5.10n)



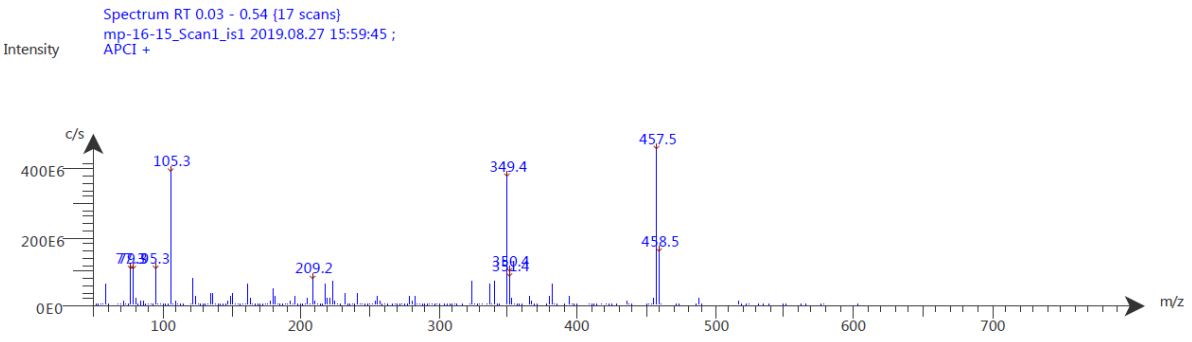
AC5.42 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-4,5-dihydro-5-(4-methoxyphenyl)pyrazol-1-yl)(phenyl)methanone (5.10n)



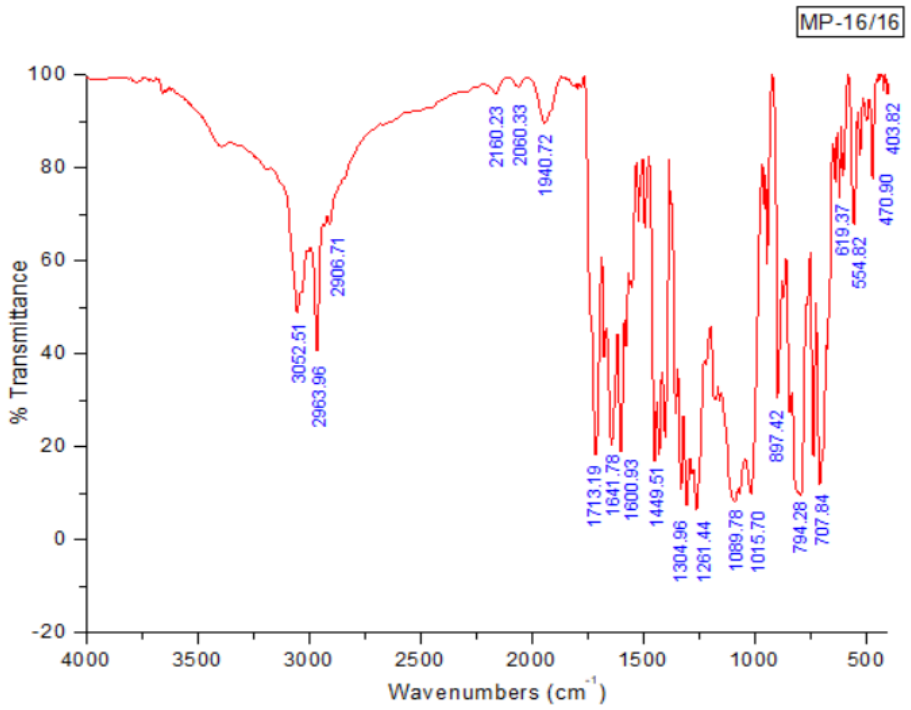
AC5.43 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of 3-(Anthracen-10-yl)-4,5-dihydro-5-(4-methoxyphenyl)pyrazol-1-yl)(phenyl)methanone (5.10n)



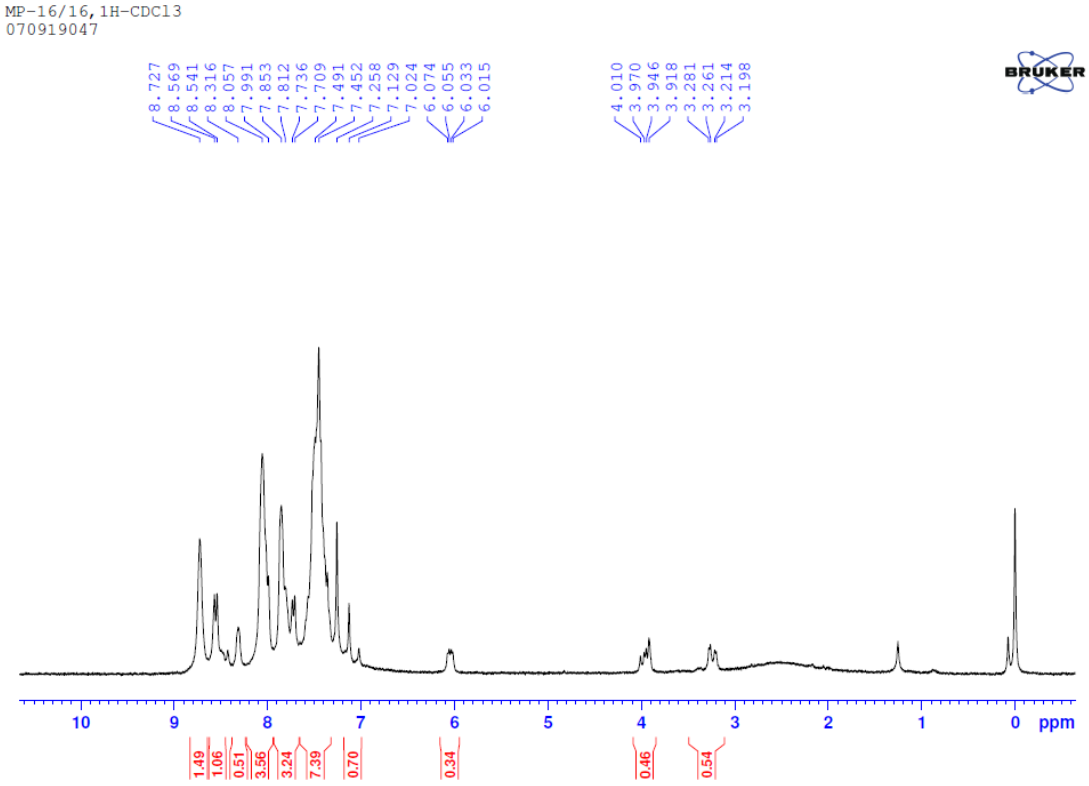
AC5.44 MS spectrum of 3-(Anthracen-10-yl)-4,5-dihydro-5-(4-methoxyphenyl)pyrazol-1-yl)(phenyl)methanone (5.10n)



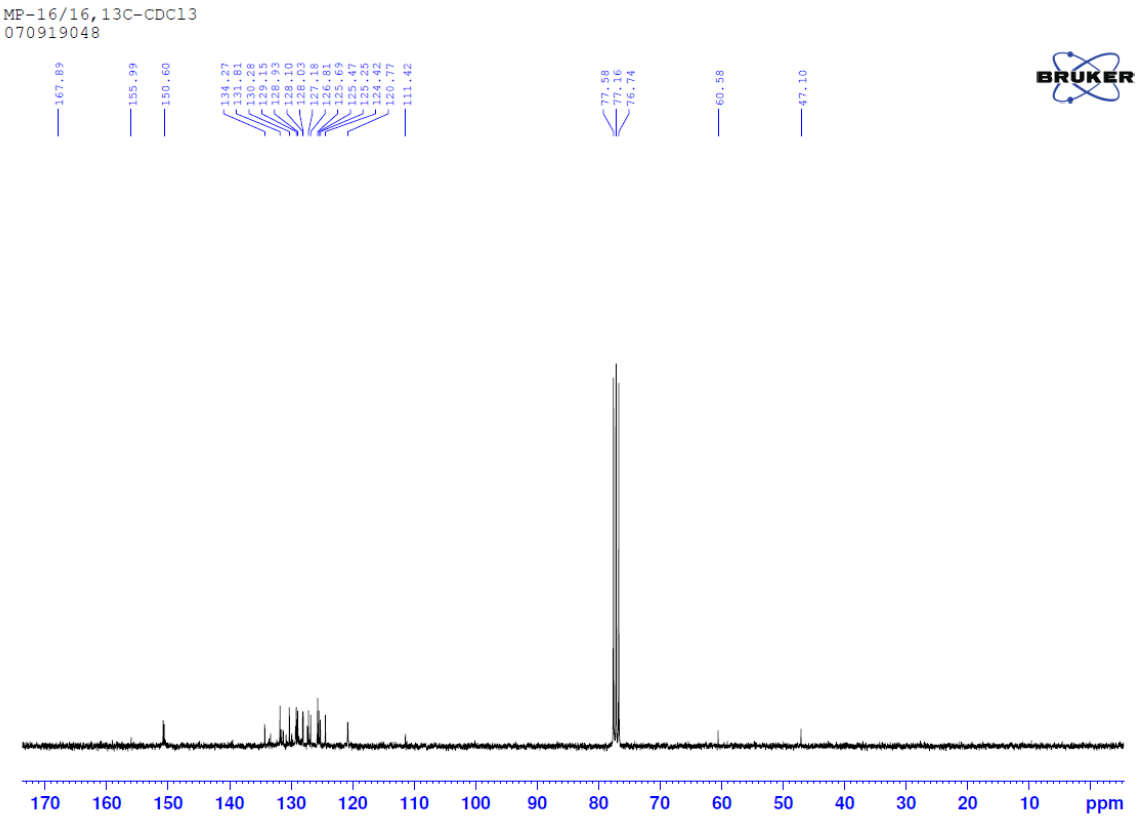
AC5.45 IR (KBr, *v*, cm^{-1}) spectrum of (3-(anthracen-10-yl)-4,5-dihydro-5-(pyridin-4-yl)pyrazol-1-yl)(phenyl)methanone (5.10o)



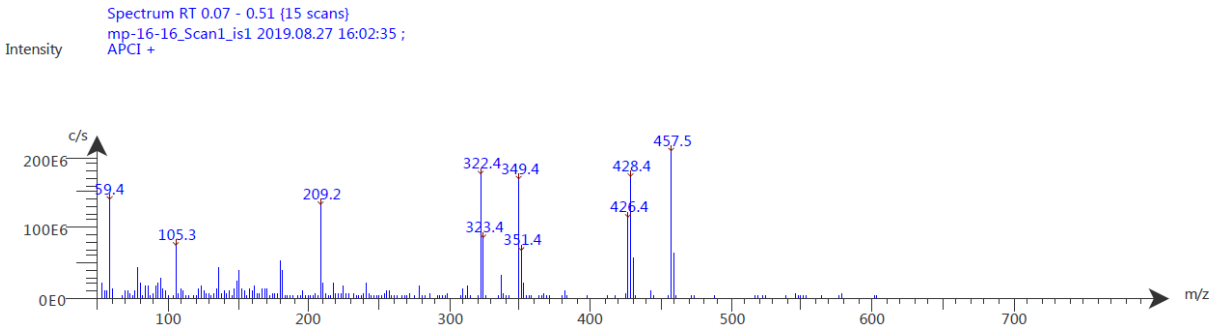
AC5.46 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of (3-(anthracen-10-yl)-4,5-dihydro-5-(pyridin-4-yl)pyrazol-1-yl)(phenyl)methanone (5.10o)



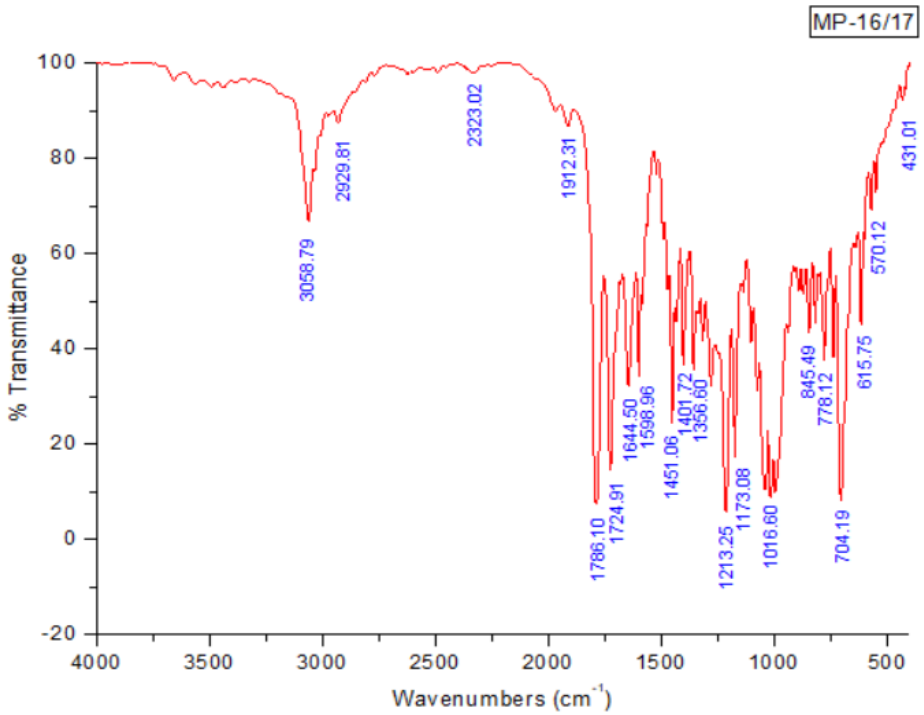
AC5.47 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of (3-(anthracen-10-yl)-4,5-dihydro-5-(pyridin-4-yl)pyrazol-1-yl)(phenyl)methanone (5.10o)



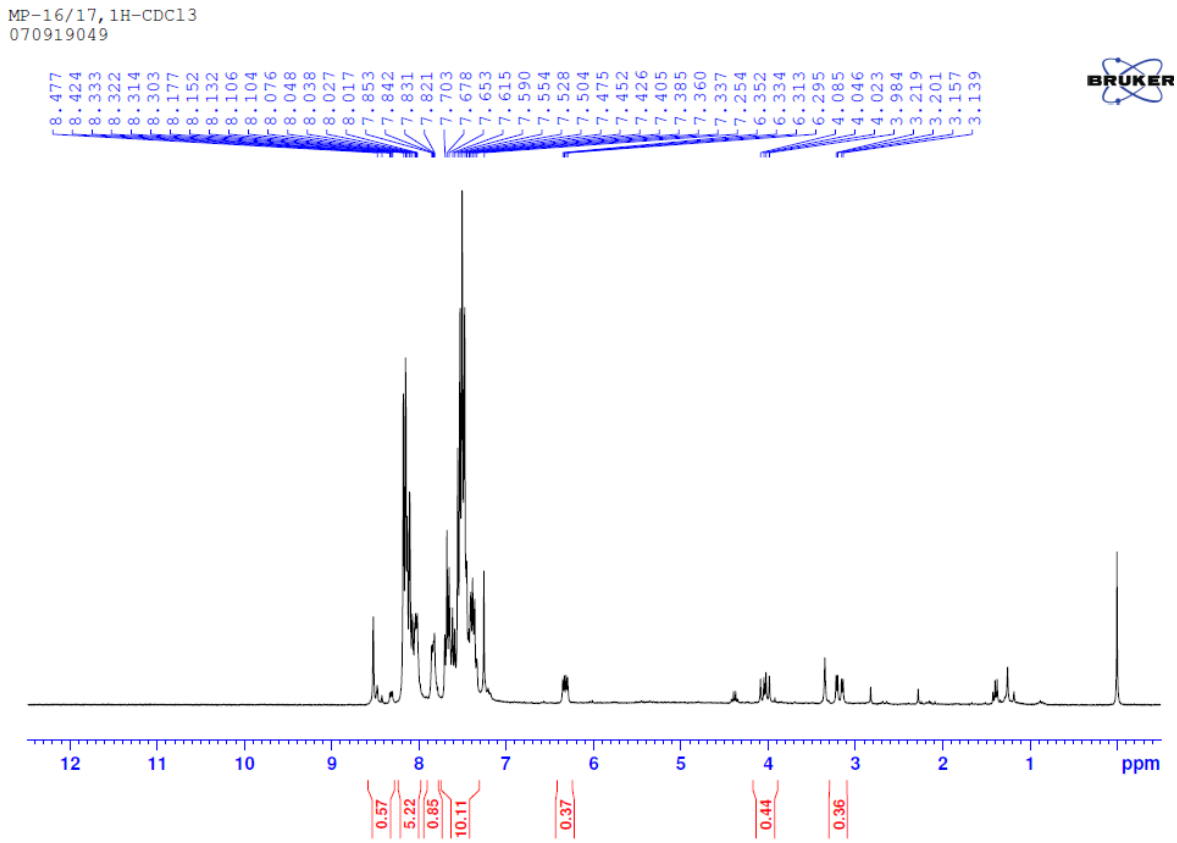
AC5.48 MS spectrum of (3-(anthracen-10-yl)-4,5-dihydro-5-(pyridin-4-yl)pyrazol-1-yl)(phenyl)methanone (5.10o)



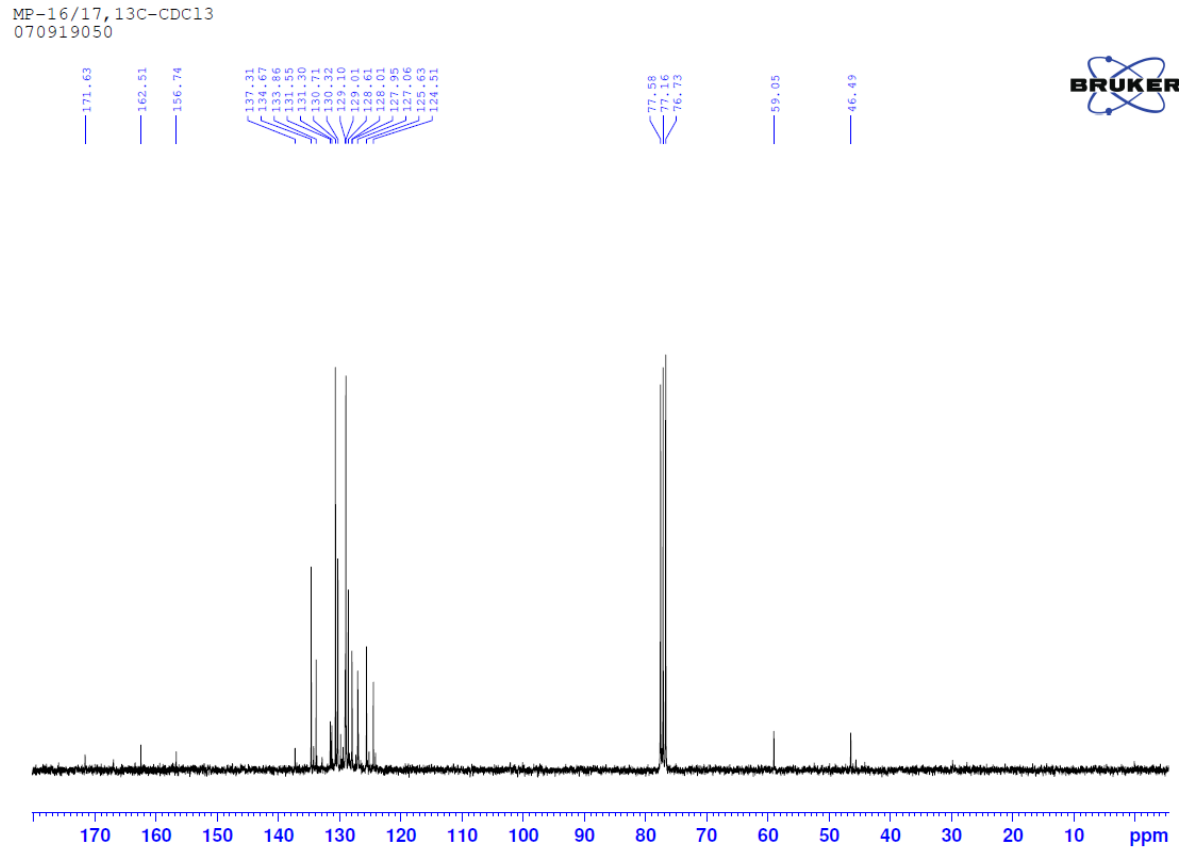
AC5.49 IR (KBr, v, cm-1) spectrum of (3-(anthracen-10-yl)-5-(2,4-dichlorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10p)



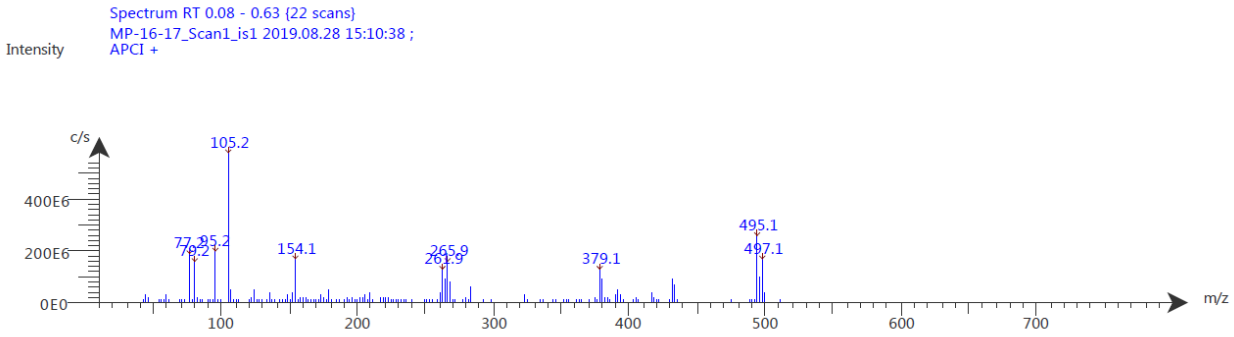
AC5.50 ^{1}H-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of (3-(anthracen-10-yl)-5-(2,4-dichlorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10p)



AC5.51 ^{13}C-NMR (300 MHz, δ(ppm), $CDCl_3$) spectrum of (3-(anthracen-10-yl)-5-(2,4-dichlorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10p)



AC5.52 MS spectrum of (3-(anthracen-10-yl)-5-(2,4-dichlorophenyl)-4,5-dihydropyrazol-1-yl)(phenyl)methanone (5.10p)



List of Publications

Journal Publications

1. **Thechano Merry**, Prabhakar Maddela. Efficient Synthesis and Characterization of Anthracene based 1,3,5-Trisubstituted Pyrazoline Derivatives. *Asian J. Chem*. **2021**, *33(3)*, 600−604.
2. **Thechano Merry**, Prabhakar Maddela, Chullikattil P. Pradeep, Ranjit Singh and Srinivas Basavoju. Synthesis and Novel Crystal Structure Analysis of Anthracene-based Chalcone Derivatives. *Mol. Cryst. Liq. Cryst*. **2019**, *692(1)*, 13−24.
3. **Thechano Merry**, Prabhakar Maddela, Kiran Devaraya, Anand K. Kondapi and Chullikkattil P. Pradeep. Et_3N-Prompted Efficient Synthesis of Anthracenyl Pyrazolines and Their Cytotoxicity Evaluation against Cancer Cell Lines. *J. Heterocycl. Chem*. **2019**, *56*, 2469−2478.
4. Maddela Prabhakar, **Thechano Merry**, Ruokuosenuo Zatsu, Shurhovolie Tsurho and Ramchander Merugu. Microwave-assisted Fast and Efficient Green Synthesis of 9-Anthracenyl Chalcones and their Anti-Bacterial Activity. *IOSR Journal of Pharmacy,* **2017**, *7(12),* 24−32.
5. Maddela Prabhakar, **Thechano Merry**, Shurhovolie Tsurho, Ruokuosenuo Zatsu, Nishant Jain, Aaysha Sataniya and Sreenivas Enaganti. Synthesis Characterization and Biological Evaluation of 9-Anthracenyl Chalcones as Anti-Cancer Agents. *J. Chem. Pharm. Res*., **2017**, *9(6)*, 185−192.
6. **Thechano Merry**, Maddela Prabhakar, Palakolanu. S. Reddy and Anand K. Kondapi. Water-Mediated Green Economical Synthesis of Biscoumarins and their Cell Cytotoxic Activity. *J. Applicable Chem.* **2014**, *3(6)*, 2592−2597.

Seminar Presentations

1. Presented an Oral presentation on "Synthesis, Characterization and Evaluation of new 9-Anthracenyl Chalcones as Anti-Cancer Agents" at the National Seminar On "Chemistry In Interdisciplinary Research" (Nscir-2018) organized by Department of Chemistry, Nagaland University on 9^{th}–10^{th} November, 2018.
2. Presented an Oral presentation on "Microwave-assisted new Synthetic Methodology for the Synthesis of Curcumin Derivatives" at the National Seminar On "Chemistry In Interdisciplinary Research" (Nscir-2017) organized by Department of Chemistry, Nagaland University held on 16^{th}–17^{th} March, 2017.

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URKUND

Urkund Analysis Result

Analysed Document:	5d-plagcheck.pdf (D66292523)
Submitted:	3/24/2020 10:28:00 AM
Submitted By:	prabhakem@gmail.com
Significance:	1 %