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Synthesis and Biological Activity Study of Some New Pyrazoline and Pyrimidine Derivatives

A Thesis Submitted to

The College of Science / University of Misan as Partial Fulfillment of the Requirements for the Master Degree of Science in Chemistry

By

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2023 A.D **1444 A.H**

Dedication

To my life's light, who are always lighting my way even in the darkest night, to the safest haven.....

My Father & My Mother

To those who have supported me and are waiting for my Success…..

My Brothers & My Close Friends

To everyone who stood by me... To everyone who supported me, even with a word, I dedicate what my Lord has guided me to

Hadeel

Acknowledgements

Firstly, very much thanks for Allah the most merciful for his blessings, who gave me health, strength, and facilitated the ways for me to accomplish this work, and the prayer and peace of Allah be upon our Master and prophet Muhammad and his divine good family. I would like to express my sincere gratitude to my supervisors, **Professor Dr. Karim S. Abbas** and **Dr. Yusra S. Abdul-Saheb** for highly inspiring guidance, patience, motivation, enthusiasm and immense knowledge, continuous support for completing this thesis. Much appreciation is offered to the head of The Department of Chemistry, Assistant Professor **Asst. Prof. Dr. Tahseen S. Fendi** for help to complete my work. Many thanks offered to **Asst. Prof. Dr. Usama A. Muhsen** for his help to complete my work. Also I express my sincere thanks and gratitude to my family for their help me in providing the appropriate ambiences for study .Finally, I'd like to thank my post graduate classmates, best friends, apology to all whom I have not mentioned with my respect. Thanks for all.

Hadeel

"Supervisors certification"

We are the supervisors of **Ms. Hadeel Saad Jasim** , certify that the thesis (**Synthesis and Biological Activity Study of Some New Pyrazolines and Pyrimidine Derivatives)** was done and written under our supervision as a partial fulfillment of the requirements for the Master degree of Science in Chemistry.

Signature.....

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Date: / /2023

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College of Pharmacy \ Misan University

Date: / /2023

Head of Chemistry Department Recommendation

According to the recommendation of supervisors , this thesis is forwarded to the examination committee for approval .

Signature.....

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Date: / /2023

"Examining Committee Certificate"

We the examining committee members, certify that we have read this thesis entitled **(Synthesis and Biological Activity Study of Some New Pyrazoline and Pyrimidine Derivatives)** and examined the student **(Ms. Hadeel Saad Jasim)** in its contents and in our opinion it meets the standard of a thesis for the degree of master in Chemistry with **(Excellent)** estimation .

Signature.....

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Abbreviations

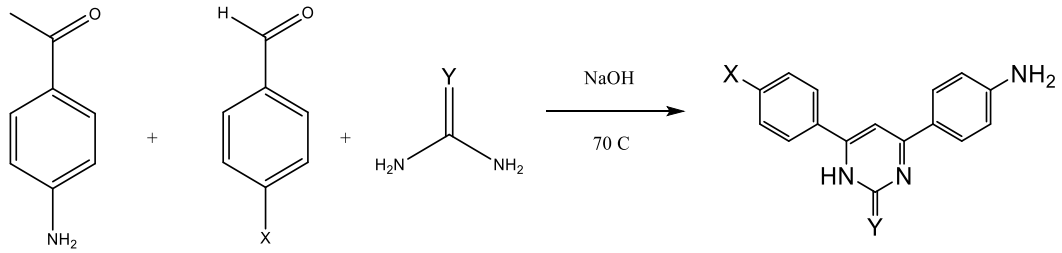
THF	Tetrahydrofuran
DMF	Dimethyl formamide
EtOH	Ethanol
EtOAC	Ethyl Acetate
Pet.Ether	Petroleum ether
r.t	room temperature
h.	hour
uv	Ultraviolet
DMSO	Dimethyl sulfoxide
MHz	megahertz
^{1}H-NMR	Proton Nuclear Magnetic Resonance
^{13}C-NMR	Carbon 13 Nuclear Magnetic Resonance
FT-IR	Fourier-Infrared transform
ppm	Part per Million
s	singlet
t	triplet
d	doublet
m	multiplet
m.p	Melting Point
β	beta
α	alpha
°C	Degrees Celsius
δ	Chemical Shift
µL	Microliter
µg	Microgram
Cm^{-1}	Wave Number Unit
g	gram

m	medium
s	strong
w	weak
Str.	Stretching
%	percentage
Ar	Aromatic group
TMS	Tetra methylsilane
TLC	Thin layer chromatography
min	minute
mL	milliliter
t-BuOK	Potassium tert-butoxide
t-BuOH	tert-Butyl alcohol
DMAP	4-Dimethylaminopyridine

SUMMARY

The first step in our study is include the preparation of precusors which are:

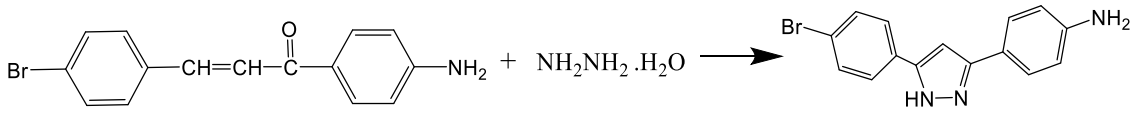
a. Some oxopyrimidines (**I - III**) and thiopyrimidines (**IV - VI**) from the reaction of p–aminoacetophenone and p- substituted benzaldehyde with urea or throurea in basic medium :



X = Cl , Br , NO_2 **Y= O , S**

I-III ,Y= O
IV-VI , Y= S

b. Pyrazoline derivative (**VIII**) by Claisen - Schmidt condensation of p-aminoacetophenone and P-bromobenzaldehyde by base catalysted followed by dehydration to yield the desire chalcone **VII** . The chalcone was further reacted with hydrazine hydrate in ethanol absolute to yield the corresponding pyrazoline derivative.

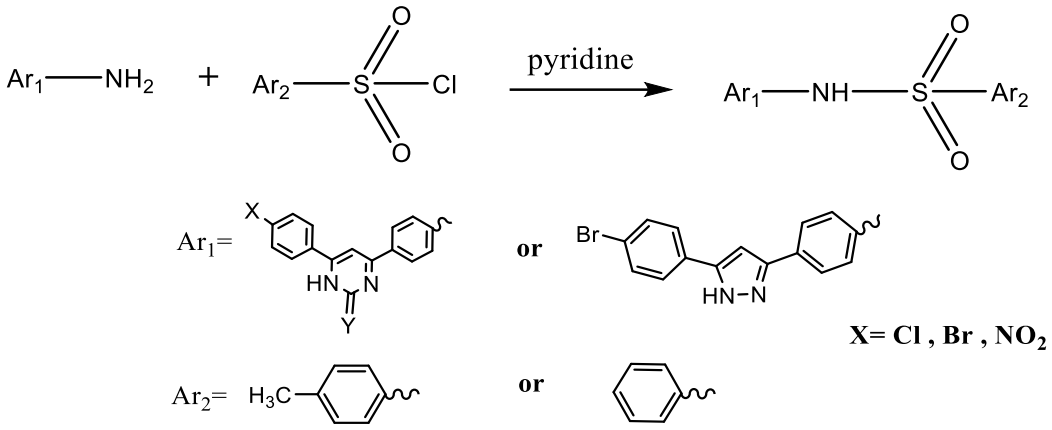


VII **VIII**

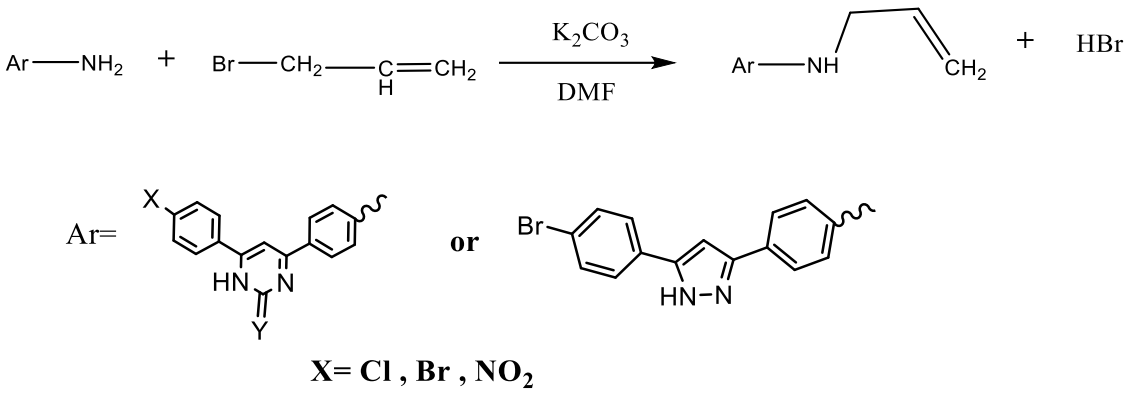
The starting materials are characterized by IR , ^{1}H - NMR and ^{13}C-NMR techniques .

The second step is represent by the synthesis of products which are:

a. Aryl sulfonamide derivatives (H_1 - H_{11}) by the reaction of benzensulfonyl chloride or p-toluenesulfonyl chloride with precursors (**I– VI,VIII**) in the presence of pyridine as base and solvent according to the following reaction:



b. Ally derivatives (H_{12} – H_{18}) by mixing (**I – VI, VIII**) compounds with allyl bromide and potassium carbonate in dry DMF, as explained in the below reaction:



Aryl sulfonyl derivatives (H_1- H_{11}) and allyl derivatives (H_{12}- H_{18}) are characterized by elemental analysis and IR , ^{1}H-NMR and ^{13}C-NMR Spectroscopies. Elemental analysis for C , H , N , S of the synthesized derivatives

showed that the difference with calculated values falls with the range , which confirms the correctance of the suggested structures of the prepared samples . The IR spectra in solid state of aryl salfanyl derivatives and ally derivatives are characterized by the ten bands corresponding to the stretching vibrations of the NH , Ar-H , Aliph-H , C = O , C = N , C = C , C = S , S = O , C - N and C - X (X = Cl , Br , NO_2) groups The resonance signals for the ^{1}H - NMR of the aryl sulfonyl derivatives (H_1 - H_{11}) are: δ (1.07- 2.34) , (6.59-8.50) , (10.92-10.99) , (10.98-11.01) ppm, which are attributed to , -CH_3 , Ar-H , O=C-NH and S=C-NH respectively .

^{1}H-NMR spectra of allyl derivatives (H_{12}- H_{18}) appeared singlet signal at the range δ(6.64-6.74) ppm relates to a proton of NH group , which confirms that the substitution is made for mono- allyl group instead of one proton of amino group (-NH_2) .

^{13}C - NMR Spectral data of aryl sulfonyl derivatives (H_1 – H_{11}) appeared δ (21.40-21.43) , (118.26-144.26) , (139.74- 143.23) , (144.22-148.32) , (187.78-187.89) and (124.36-142.64) ppm which attributed to –CH_3 , aromatic ring , hetero C-N , C=N , C=O , C = S and C - X (X = Cl , Br , NO_2) respectively.

While allylic substitution derivatives (H_{12} –H_{18}) Provided us with their resonance spectra of ^{13}C-NMR by signals relates to -CH_2 , Aromatic ring , C - N , C=N , C = 0 , C = S and C-X (X=Cl , Br , NO_2) .

Finally, the biological activity of these compounds was estimated, including antitumor and antibacterial activity; these activities were determined in vitro using the cytotoxicity assay (MTT cell viability assay) in MCF7 Cells to detect the anticancer activity, and Kirby-Bauer disc diffusion method used for antibiotic sensitivity test against different pathogenic strains of bacteria.

In this study, the **MCF-7** cell line was used to assay the antiproliferative activity of compounds (H_1-H_9, H_{11}, H_{12}, H_{14}, H_{15}, H_{17} and H_{18}) , compound H_4 was the

most potent in this group with **IC_{50}** value of 8.66 μg/mL and compound H_8 was the lowest in potency with **IC_{50}** value of 52.29 μg/mL.

Also, the antibacterial properties of the produced compounds were tested against six Gram positive and Gram negative bacteria that were multidrug resistant, and the results indicated varying degrees of efficacy.

Chapter One

The Introduction

1. Introduction

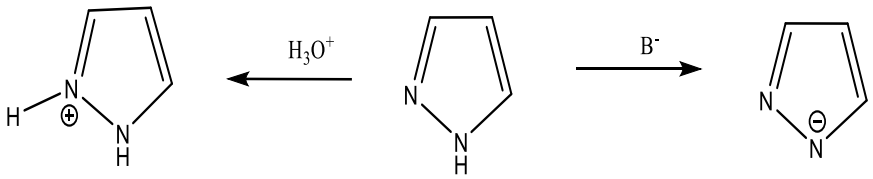
1.1 Heterocyclic Compounds

The term "heterocyclic compounds" refers to organic cyclic molecules with at least one heteroatom. Though heterocyclic rings with other hetero atoms are as well-known, nitrogen, oxygen, and sulfur are the most common heteroatoms. A carbocyclic compound is an organic compound with rings made entirely of carbon atoms.[1]. Heterocycles, a hugely important and distinctive family of compounds with a wide range of physical, chemical, and biological properties spanning a broad spectrum of reactivity and stability, account for more than half of all known organic molecules. [2]. Because their structural subunits are present in a variety of natural products, such as vitamins, hormones, antibiotics, and alkaloids, as well as in pharmaceuticals, agrochemicals, dyes, and many other substances, heterocycles are widely distributed in nature and play a significant role in metabolism[3]. Many synthetic heterocyclic compounds with significant physiological and pharmacological effects are also known in addition to naturally occurring molecules[4]. In a huge variety of pharmacological and commercial uses, heterocyclic derivatives a significant group of organic compounds are used. They are renowned for their biological and pharmacological qualities, which include anti-inflammatory, antibacterial, anticancer, antitumor, and antiviral activity[5]. The majority of heterocycles have significant uses in materials science, such as analytical reagents, fluorescence sensors, brightening agents, information storage, and dyes. They also have uses in polymer and supramolecular chemistry, particularly with conjugated polymers. Additionally, they function as liquid crystalline compounds, organic

conductors, semiconductors, molecular wires, photovoltaics, organic light-emitting diodes (OLEDs), lighting equipment, optical data carriers, and chemically programmable switches. Due to their synthetic value as organic catalysts, protecting groups, chiral auxiliaries, synthetic intermediates, and metal ligands in asymmetric catalysts in organic synthesis, heterocycles are also of great interest. Therefore, there has been a lot of focus on creating new, effective ways to create heterocycles[6]. In addition to being widely present in both natural and synthetic chemicals, heterocyclic systems are also used as building blocks in the synthesis of organic compounds. A heterocyclic fragment is present in the structures of more than 90% of novel medicines [7].

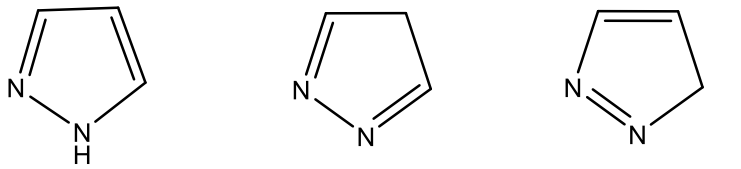
1.2. Pyrazolines

A member of the azole class, pyrazole is an aromatic heterocyclic system. Three carbon atoms and two nitrogen atoms are joined together to form a five-membered ring. Due to the conjugation of its unshared electrons with the aromatic system, nitrogen atom 1 (N1) is said to be "pyrrole-like." As in pyridine systems, the unshared electrons of nitrogen atom 2 (N2) are not compromised by resonance, making it "pyridine-like." Pyrazoles react with both acids and bases because of the variations between the nitrogen atoms (Scheme 1.1) [8]. Pyrazole has prototropic tautomerism, another significant structural feature. Unsubstituted pyrazoles have a three tautomer potential (Fig. 1.1), whereas monosubstituted pyrazoles have a five tautomer potential (Fig. 1.2). Due to their ability to maintain aromaticity, structures 1a, 2a, and 2b are the most important.[9,10].



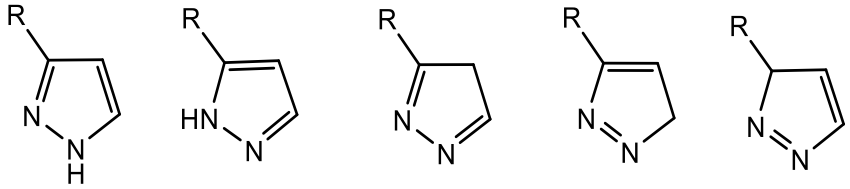
(1)

Scheme 1.1: Cations and anions produced from pyrazole.



1H-Pyrazole (1a) 4H-Pyrazole (1b) 3H-Pyrazole (1c)

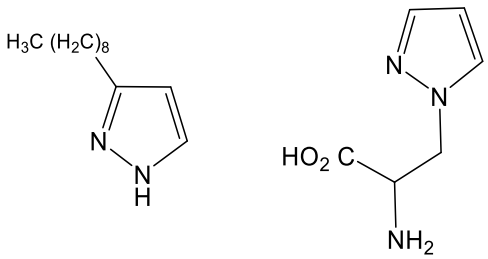
Fig. 1.1: Tautomers of unsubstituted pyrazole.



(2a) **(2b)** **(2c)** **(2d)** **(2e)**

Fig. 1.2 : Tautomers of 3(5)-monosubstituted pyrazoles.

3-n-nonyl-1H-pyrazole **4**, which was taken from the widespread tropical Asian plant Houttuynia cordata, was the first pyrazole to be isolated from natural sources. In watermelon seeds, was found (1-pyrazolyl)alanine **3** (Fig. 1.3) [10].



(3) **(4)**

Fig. 1.3: Pyrazoles extracted from natural products.

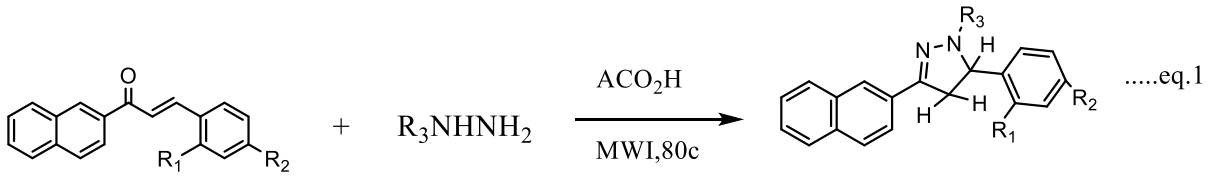
In the field of heterocyclic chemistry, the synthesis and characterization of pyrazoline derivatives were developing, and the pyrazoline attracted the attention of organic chemists due to its diverse properties, reasonably assessable synthesis route, wide range of therapeutic activities, and variety of industrial applications [11][12].

1.2.1. Synthesis of Pyrazolines

Pyazolines are made in a variety of ways, some of which are listed below:

A: The most prevalent approach for this appears to be the treatment of α ,ß - unsaturated ketones with hydrazines. This reaction has been tested under a variety of circumstances, [13],[14] including:

Reaction of chalcones (1) and hydrazine (2) in acetic acid under microwave irradiation (MWI) yielded new pyrazolines (3)[15].(eq.1)



.....eq.1

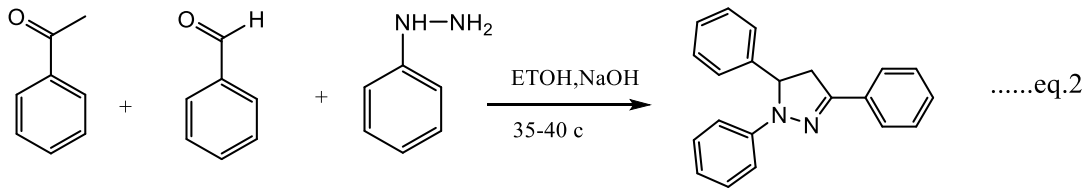
(1) **(2)** **(3)**

R_1= H , Cl

R_2= Me , OMe , Cl

R_3= H , Ph , $CONH_2$

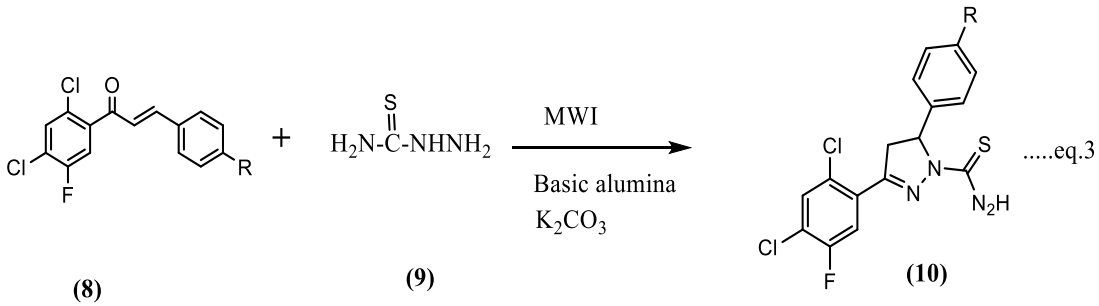
Traven and Ivanov synthesis 1, 3, 5-triaryl-2-pyrazolines (7), from the reaction of aryl aldehydes (4), acetophenone (5), and phenylhydrazine (6) in the presence of sodium hydroxide (NaOH) [16]. (eq.2)



.....eq.2

(4) **(5)** **(6)** **(7)**

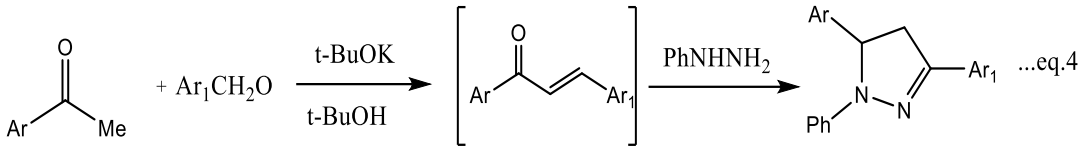
In addition, the reaction of chalcone (8) and thiosemicarbazide (9) was adsorbed over K_2CO_3 and exposed to MWI, yielding pyrazolines (10)[17].(eq.3)



.....eq.3

(8) **(9)** **(10)**

The treatment of phenylhydrazine with different chalcone derivatives yielded a more convenient approach for producing 3,5- diaryl-1-phenyl-2-pyrazoline (12) through derivatives (11). The reaction was completed in 3-13 minutes at r.t (25°C) in the presence of t-BuOK and anhydrous t-BuOH, yielding 69-89%[18]. (eq.4)

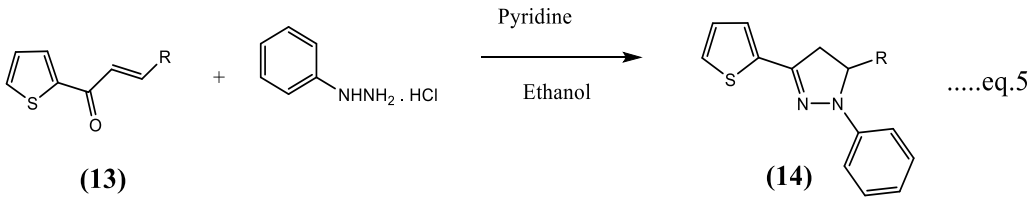


(11) **(12)**

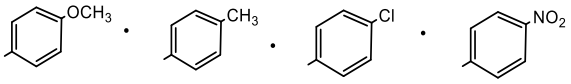
Ar=Ph , 4-MePh , 4-ClPh , 4-OMePh

Ar_1=Ph , 4-MeOPh , 4-ClPh , 4-BrPh , 4-No_2Ph , 9-Anthranyl

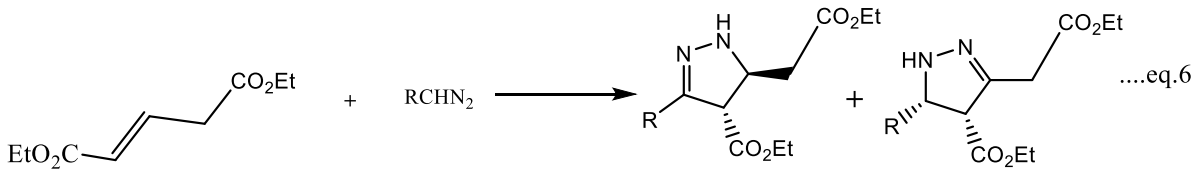
Ramash *et.al* [19], made pyrazoline derivatives (14) by reacting chalcones (13) with phenyl hydrazine hydrochloride in the presence of pyridine.(eq.5)



(13) **(14)**

R= 

B: Pyrazolines (17) and (18) are made through 1,3 - dipolar cyclo addition [20] between trans - diethyl glutaconate (15)and diazoalkanes (16). (eq.6)

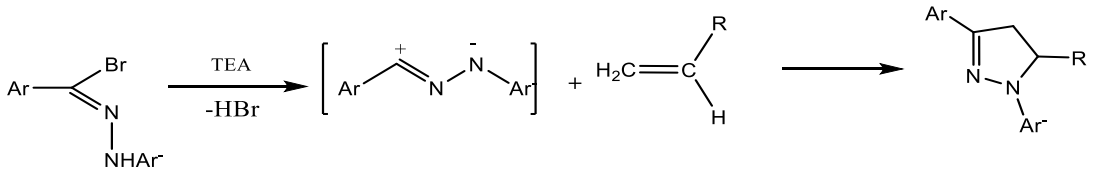


....eq.6

(15) **(16)** **(17)** **(18)**

R= H , Ph , CO_2Et

C: Pyrazolines (22) were obtained in good quantities by reacting equimolar amounts of compounds (20) with either of acrylonitrile, acrylamide, or ethyl acrylate (21) in dry benzene using tri ethyl amine (TEA) as catalyst scheme (1.2) [21].



(19) **(20)** **(21)** **(22)**

Ar= 4-FC_6H_4 , 2,4-$Cl_2C_6H_3$
Ar⁻= 4-$NO_2C_6H_4$
R= -CN , -$CONH_2$, -COOEt

Scheme 1.2 : Synthesis of pyrazoline

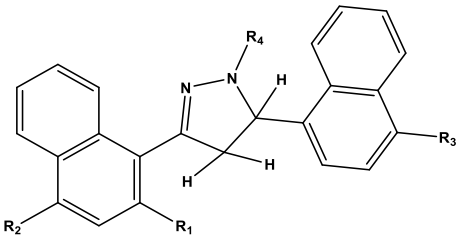
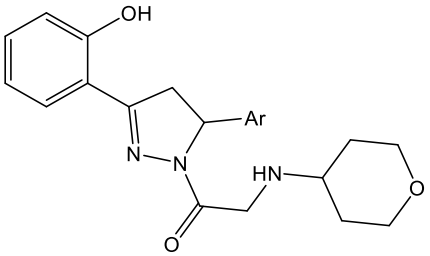
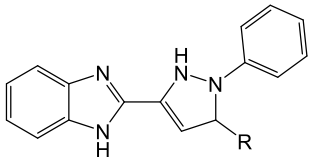
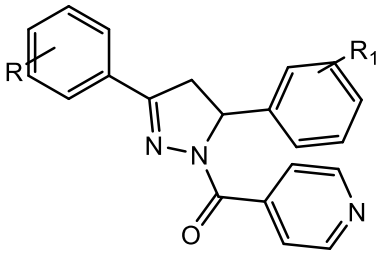
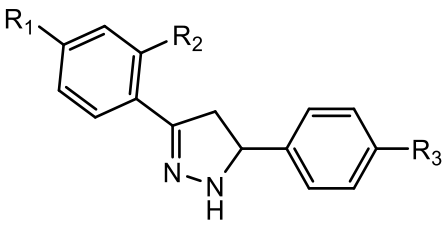
1.2.2. Biological activity of pyrazolines

The derivatives of pyrazoles are nitrogen heterocycles with abundant electrons are involved in a variety of biological processes. Vitamins, pigments, plant and animal cells, and alkaloids all include nitrogen heterocycles. Because of their wide range of pharmacological effects, such as anti-bacterial, antifungal, herbicidal, and anti-

choligenic, substituted pyrazoline derivatives are important[22]–[25].The biological activities displayed by the pyrazoline derivatives were noteworthy, which inspired researchers to step up their research in this area. There have been reports of pyrazolone scaffold used for a variety of biological activities. Such as anti-convulsant,[26] anti-fungal,[27] anti-bacterial,[28], anti-hyperglycemic,[29], anti-amoebic,[30] antiepileptic,[31] anti-malarial,[32], anti-pyretic,[33], anti-histaminic,[16] anticholinesterase,[34] anti-depressant,[35], analgesic,[36], anti-adhesive,[37] anti-oxidant,[38], anti-trypanosomal,[39] anti-tubercular,[40] and anticancer,[41] activities. Pyrazine is a pyrazoline derivative.

Table (1.1) lists the biological activity and structural formula of derivatives.

Table (1.1): Biological activity of pyrazoline

Comp. No.	Structural Formula	R	Biological activity	Ref.
1		R_1= H , OH R_2 = H , Cl R_3 = H , NMe_2 R_4 = H , C_6H_5	antimicrobial	[42]
2		Ar=3,4-diMeOC_6H_3, 4-$NMe_2C_6H_3$	antibacterial	[43]
3		R=Phenyl,4 Chlorophenyl,4-Bromophenyl,4-Methoxyphenyl	Anti-tubercular	[44]
4		R=P-CH_3 , M-NO_2 , P-OCH_3 R_1=P-OH , C_6H_5 ,P-Cl	antimicrobial	[45]
5		R_1=H,4-OCH_3,4-CH_3 R_2=2-OH, H R_3=4-NO_2,4-Cl,4-$N(CH_3)_2$	Antibacterial and antiflammatory	[46]

1.3. Pyrimidine and its Derivatives

Pyrimidine is a heterocyclic aromatic chemical that is similar to pyridine in structure (Fig. 1.4a). Containing two nitrogen atoms in positions 1 and 3, it is one of three diazines (an unsaturated 6 ring with two nitrogen atoms). Molecules having pyrimidine rings that are heterocyclic are extremely important since they constitute a diverse family of natural and manufactured chemicals, many of which have clinical uses and bioactivities [47].

The majority of substituted pyrimidines and purines are found in living things and are among the most popular substances that chemists study[48]. Thymine (Fig. 1.4b), uracil (Fig. 1.4c), and cytosine (Fig. 1.4d) are important building blocks of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), making pyrimidines the most prevalent members of the diazine class. Additionally, the pyrimidine moiety is found in a number of naturally occurring substances, such as vitamin B1 (thiamine), and a number of synthetic substances, including veronal and barbituric acid, which are utilized as sophrotic medicines (sleeping pills)[49].

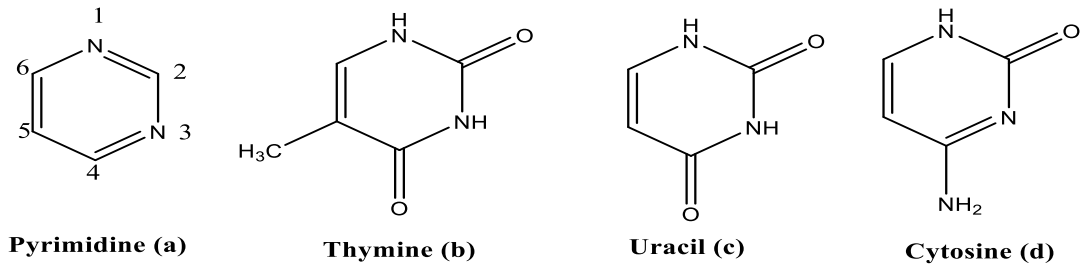
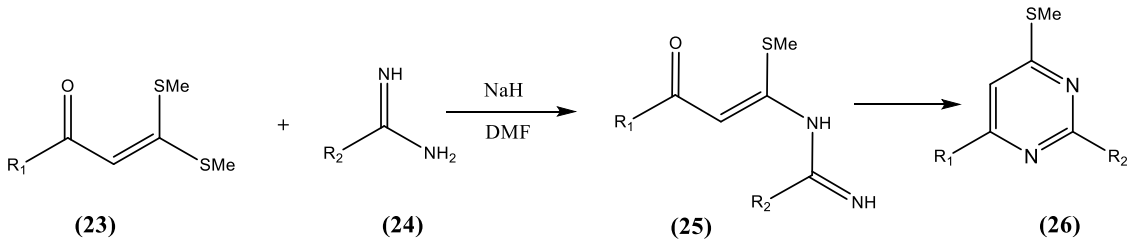


Fig. 1.4: Chemical structures of pyrimidine

Starting materials like as pyrimidines and pyrimidinones have been employed to create new scaffolds that are the parents of DNA nitrogenated bases, with the goal of identifying potential biological and/or pharmacological features of newly synthesized molecules [50]. Compounds with a pyrimidine ring in their structures, for example, have been discovered to be antiplasmodials [51], as well as inhibitors of caspase [52], hepatitis C [53], [54], NTPDase [55],and cancer [56].Several technologies that may aid synthetic organic chemists have emerged as powerful operating instruments for heterocyclic synthesis in the last 20 years, [57].

1.3.1. Synthesis of pyrimidines

In the presence of sodium hydride, α- oxoketene dithioacetals (23) interacted with an amidine, guanidine, or thiourea (24) to create an enaminone intermediate (25), which cyclizes to 4 - methyl thiopyrimidine (26) in moderate to fair yield scheme (1.3) [58].



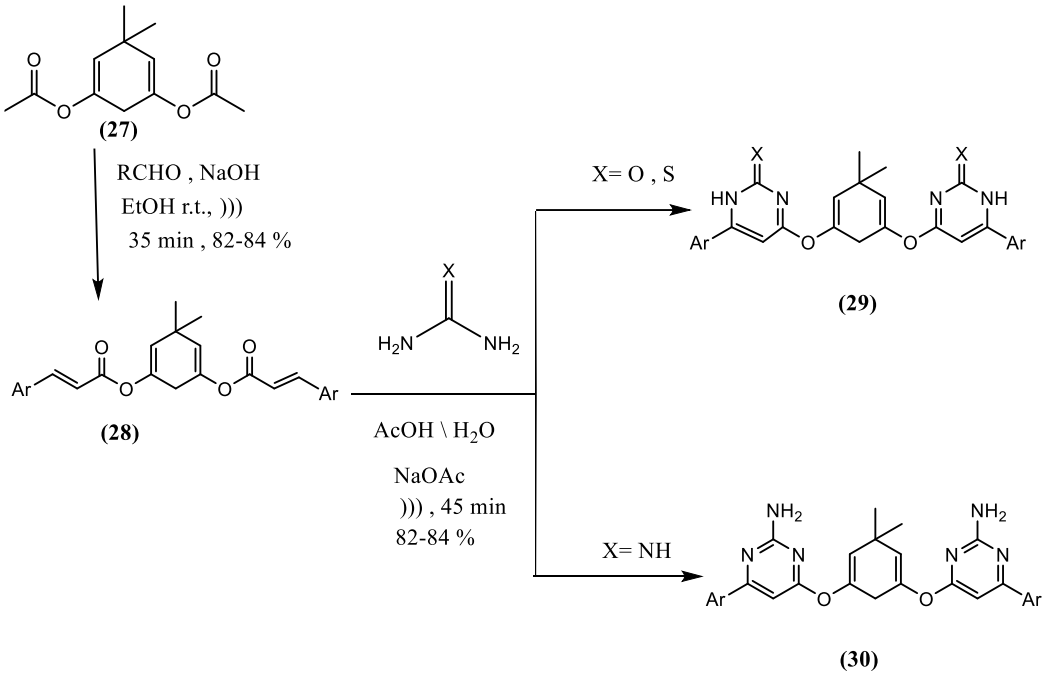
(23) **(24)** **(25)** **(26)**

R_1= alkyl , aryl

R_2= alkyl , aryl , NH_2 , SH

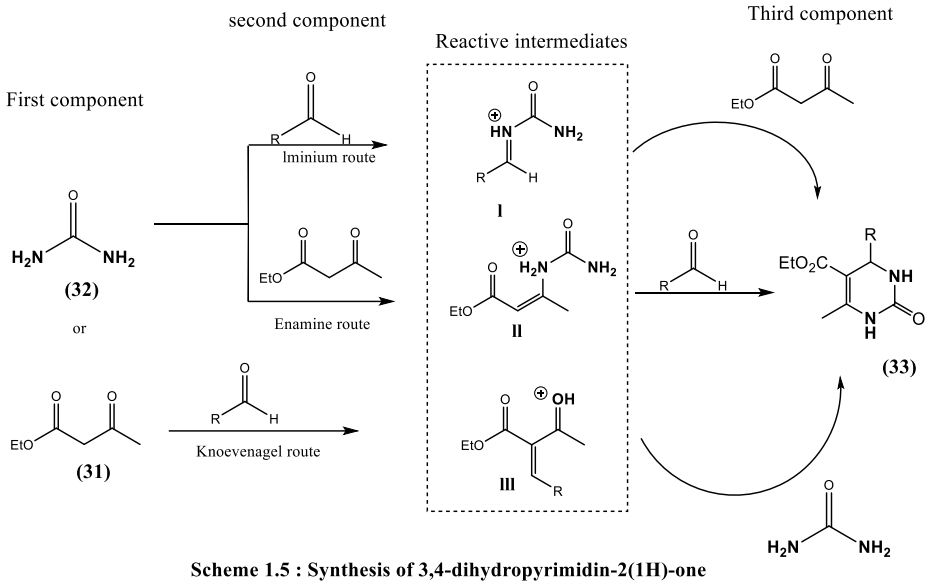
Scheme 1.3 : synthesis of 4 - methyl thiopyrimidine

To make bis-pyrimidine derivatives, a totally ultrasound-based method was used, with diester (27) as the starting material. Initially, an aldol condensation between the ester and aldehydes was carried out in basic media (NaOH, EtOH,)) for 45 minutes, yielding α, β-unsaturated esters (28) in 82–84% yields. The bis-pyrimidines (29,30) were then obtained by cyclocondensation with NCN-dinucleophiles (urea, thiourea, and guanidine) in 82–84 % yields scheme (1.4) [59].



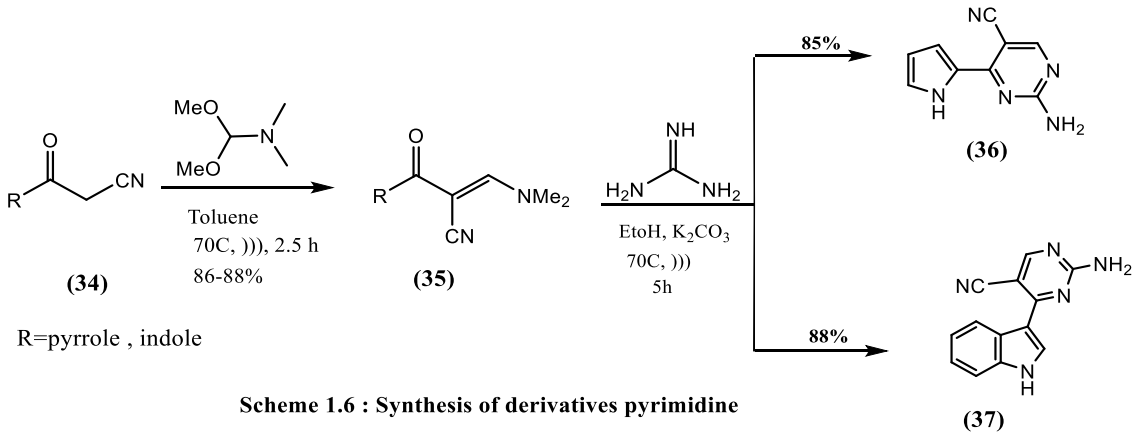
Scheme 1.4: Synthesis of bis-pyrimidine derivatives

In addition, the 3,4-dihydropyrimidin-2(1H)-one(33) scheme(1.5) has been assembled effectively using the Biginelli reaction, a three-component reaction between an aldehyde, a 1,3- dicarbonylic molecule (31) (or its equivalent), and a (thio)urea derivative (32). [60-62].



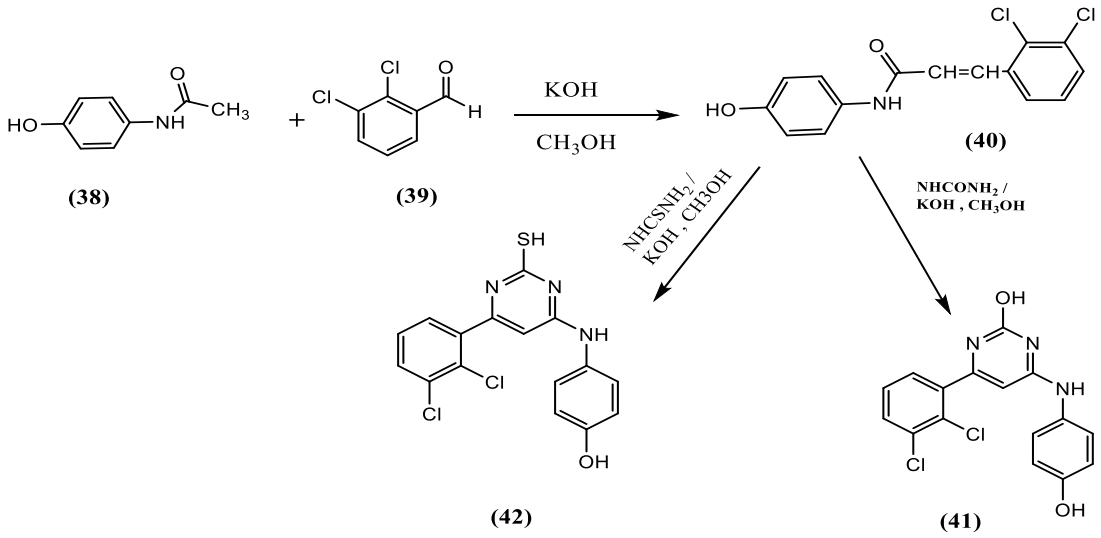
Scheme 1.5 : Synthesis of 3,4-dihydropyrimidin-2(1H)-one

Also, α-cyano ketones (34) were used as starting materials for the synthesis of pyrimidines conjugated with 1H-pyrrole and 1H-indole cores. These were given 86-88% yields of α-cyano-β-enaminones(35) after being treated with N,N-dimethylformamide dimethylacetal (toluene, 70 °C, 2.5 h). The 6-azolyl-2-amino-4-cyanopyrimidines (36) and (37) were subsequently cyclocondensed with guanidine (EtOH, K_2CO_3, 70 °C, 5 h) to provide 85–88% yields scheme (1.6) [63].



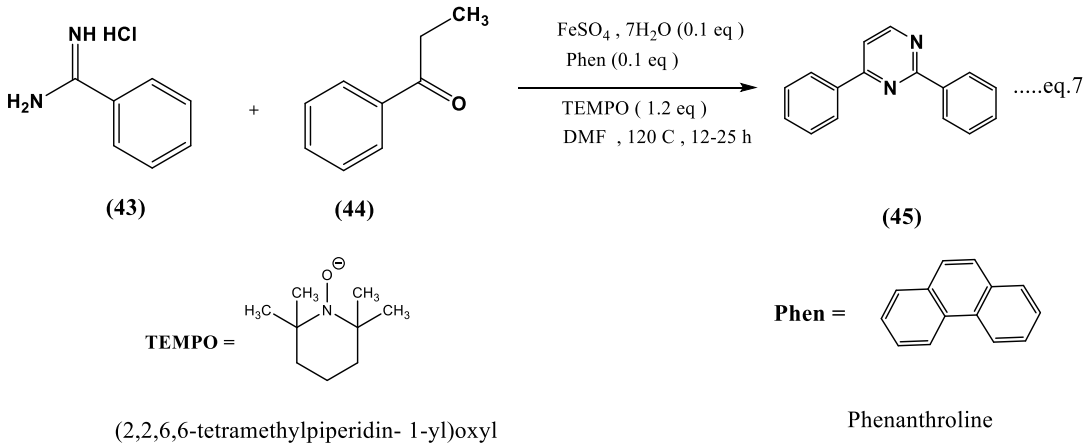
Scheme 1.6 : Synthesis of derivatives pyrimidine

Paracetamol (38) is treated with 2,3-dichlorobenzaldehyde(39) in KOH solution at 298K to produce chalcone (40). The equivalent pyrimidine (41) is obtained by reacting them with urea and potassium hydroxide in methyl alcohol In addition, chalcone (40) can be treated with thiourea and KOH in methyl alcohol to produce(42) scheme (1.7) [64].

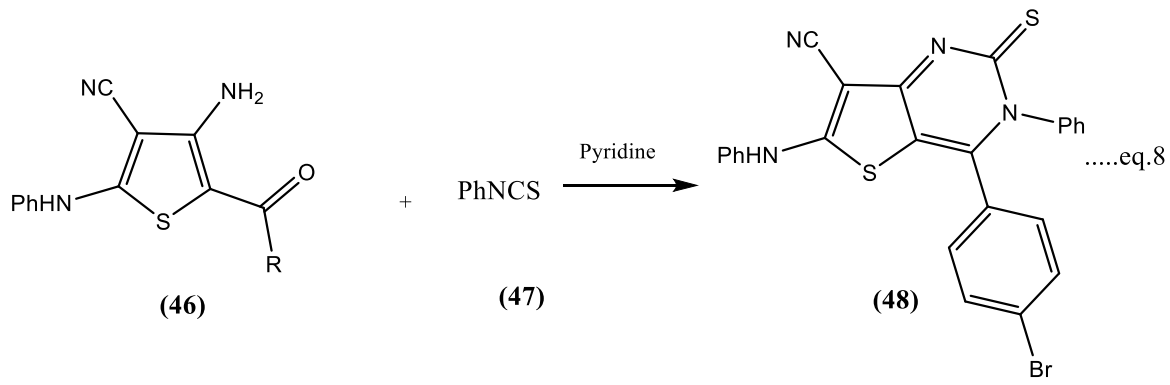


Scheme 1.7 : Reactions of derivative chalcones

Also, for the production of many pyrimidine (45) analogs, the regioselective reaction of carbonyl compounds (esters, aldehydes, and ketones) (43) with amidines (44) in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) an in situ generated recyclable iron(II)-complex has been described. The processes took place in the following order TEMPO complexation, enamine addition, temporary a-occupation, b-TEMPO removal, and cyclization, according to the mechanism[65]. (eq.7)



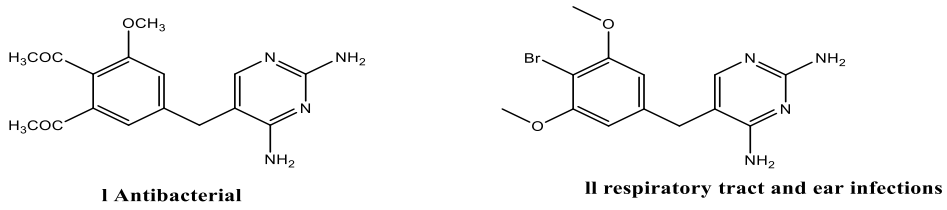
By reacting thiophene (46) with phenyl isothiocyanate (47) in pyridine, El-Saghier *et al* [23] created pyrimidine derivatives (48). (eq.8).



R = 4-BrC_6H_4 , CH_3

1.3.2. Biological activity of pyrimidines

Pyrimidines are employed as antituberculosis , antioxidants, and antidiabetics because of their diverse inherent biological qualities. Ant allergic, antioxidant, antiviral, antihistaminic, cytostatic, immunomodulating herbicidal, anticonvulsant actions are all medicinal capabilities of pyrimidine-containing heterocycles. Antimicrobial properties of pyrimidines include fungicidal, antitoxoplasma, antimalarial, antibacterial, antifilerial and antileishmanial. (Fig. 1.5) Trimethoprim (l) is an antibacterial and antifungal drug, and brodimoprim (ll) treats respiratory tract and ear infections [64].

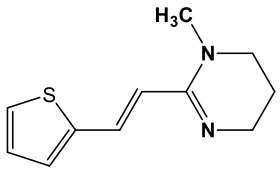
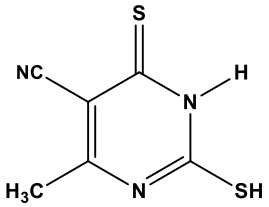
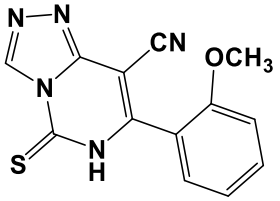
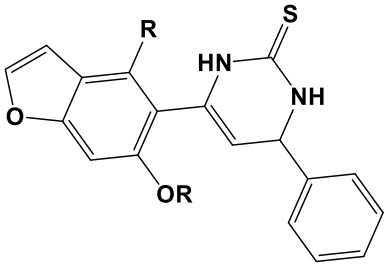
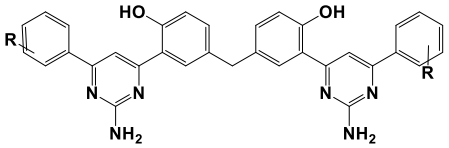


l Antibacterial **ll respiratory tract and ear infections**

Fig. 1.5. Pyrimidine compounds that show pharmacological activity

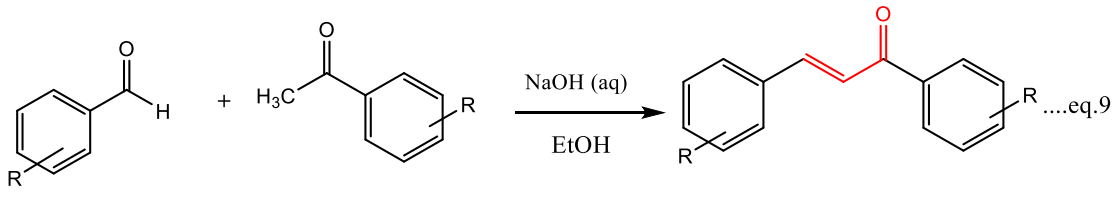
The biological activity and structural formula of pyrimidine derivatives are given in Table (1.2)

Table (1.2): Biological activity of some pyrimidines

Comp. No.	Structural Furmula	R	Biological activity	Ref.
1			anthlemintic	[66]
2			antisecticidal	[67]
3			anticancer and antibacterial	[68]
4		R= $COCH_3$, CH_3 , OCH_3	antimicrobial	[69]
5		R=H , 4-OMe , 4-Cl , 4-NO_2 , 4-Br , 2-Cl	antifungal and antibacterial	[70]

1.4. Chalcones

Chalcone is a chemical made up of two aromatic rings connected by an unsaturated α,β-ketone and different substituents on the two aromatic rings **eq..9**. Chalcone is a naturally occurring intermediate precursor of flavonoids and isoflavonoids that is present in the majority of plants[71]. It was claimed to have a wide range of applications in the disciplines of biology and biochemistry [72,73]including anticancer[74,75], antiinflammatory[76-78],and antimalarial agents. Additionally, it has been noted for its photochemical and photophysical properties, including its application as a photoalignment and photocrosslinking component in the polymerization process[79] , fluorescent dyes, light-emitting diodes (LEDs), and other things [80].

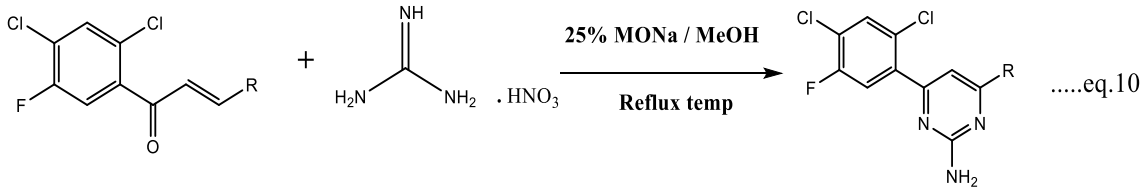


(49) **(50)** **(51)**

Chalcone
R = Various substituted

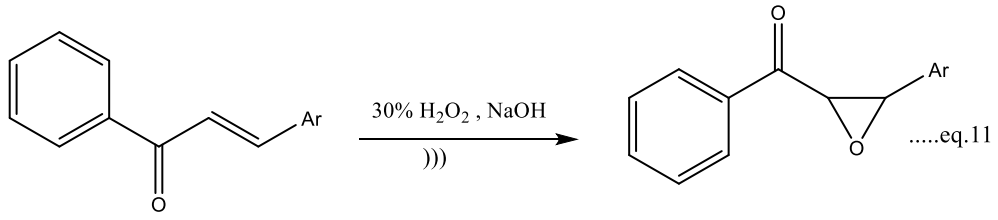
1.4.1 Reactions of chalcones.

When chalcone (52) when guanidine nitrate (53), sodium methoxide (25%) and methanol are refluxed together for six hours. 2-Amino-4-(2,4-dichloro-5-fluorophenyl)(2,4-dichloro-5-fluoro phenyl)-6-(aryl)-pyrimidine(54)is produced[81].(eq.10)



(52) **(53)** **(54)**

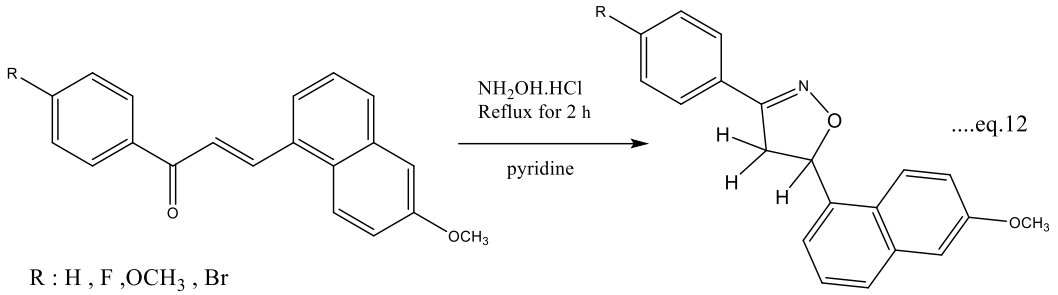
Under ultrasonic irradiation, epoxidation of the chalcone (55) with 30 percent aqueous hydrogen peroxide employing benzyl dimehtyl tetra decyl ammonium chloride as phase transfer catalyst generated 2,3-epoxy-1- phenyl- 3- aryl-1 – propanones(56)[82].(eq.11)



(55) **(56)**

Ar= C_6H_5 , 4-ClC_6H_4 , 3- or 4- $NO_2C_6H_4$, 2- or 4-$MeOHC_6H_4$ and 2,4-$Cl_2C_6H_4$

To obtain 2-isoxazoline (58) chalcones(57)were reacted with hydroxylamine hydrochloride in pyridine with reflux for 2h[83].(eq.12)

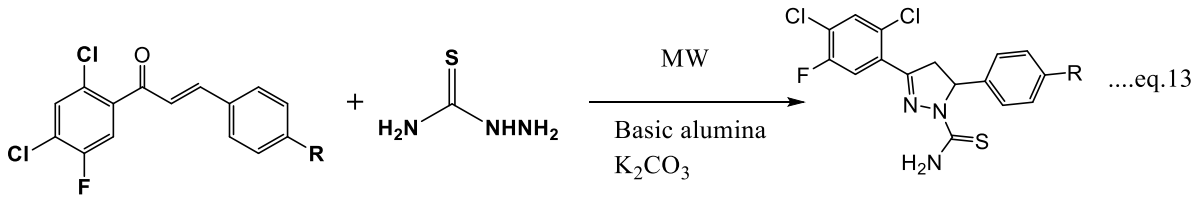


....eq.12

R : H , F ,OCH_3 , Br

(57) **(58)**

By employing a microwave to induce solvent-free condensation of chalcones (59) with thiosemicarbazide over K_2CO_3, the following novel pyrazolines derivatives (60) were obtained[17].(eq.13)



....eq.13

(59) **(60))**

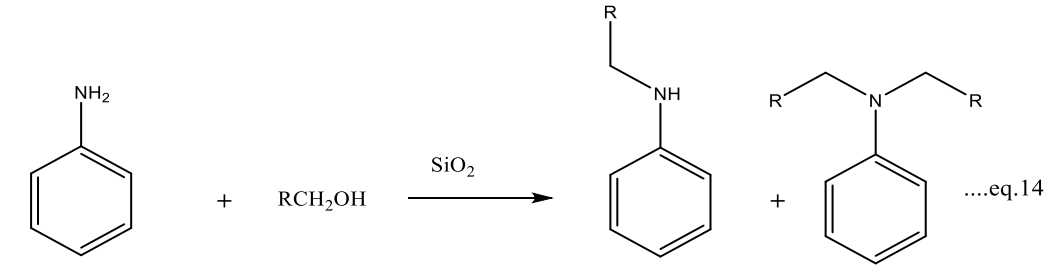
R= H , OCH_3

1.5. Amino group

Chemistry of nitrogen-containing compounds such as amides, amines, and other is crucial to the process of creating organic molecules. Urine was actually the first organic substance to be produced[84].The significance of this type of nitrogen-containing molecule stems from a number of elements. The first is that various nitrogen derivatives, including amino acids and nucleotides, have been selected by nature as their characteristic building blocks for the creation of life[85].This category should also contain other significant minor compounds, such as neurotransmitters, naturally occurring toxins, alkaloids, and other active biomolecules, in addition to the main components of nature[86]. An essential step in organic synthesis is the N-alkylation of aniline derivatives, which is frequently used to make dyes, fluorescent probes, agrochemicals, and medicines [87]. The difficulty with this reaction is getting good selectivity for mono- or dialkylation products while avoiding the production of matching quaternary ammonium salts from N, N-dialkylaryl amines. A wide range of techniques have been examined for the synthesis of substituted amines[88,89]. They still have certain issues, though, namely the employment of hazardous chemicals[90] and the management of the selectivity of mono and dialkylation-aniline derivatives[91]. In attempt to solve these issues, numerous homogeneous phase reports on noble metal complexes and salts using alcohols as alkylating agents and Ru[92], Ir[93,94], Pt[95], Au[96 ,97], and Pd[98 ,99] as catalysts have been published. Development of methods for preparing amines is great importance due to the wide spread of amine cracks inside natural products, medicines and fine chemicals[100].

1.5.1 Reactions of amino group

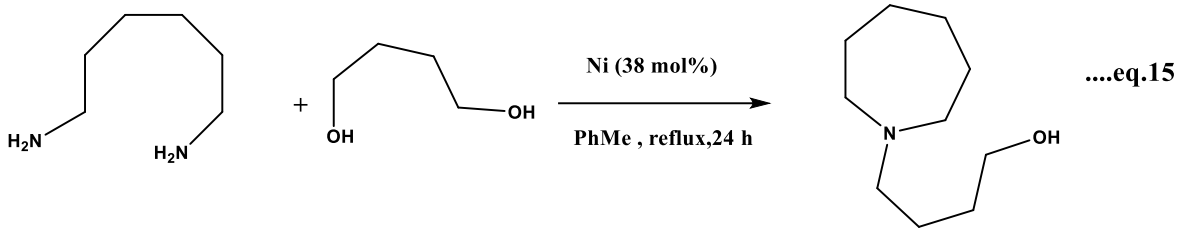
An mixture of substituted anilines (62), (63) produced by the high-temperature alkylation of aniline (61), with primary alcohols[101]. (eq.14)



(61) **(62)** **(63)**

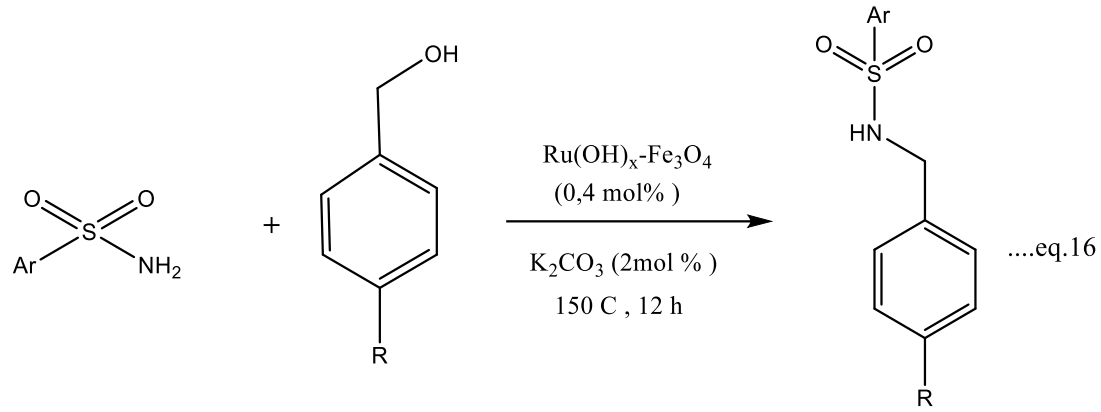
R= H , Me , Et

Also, the alkylation of 1,6-hexandiamine (64) with 1,4-butanediol (65) and the Dean-Stark apparatus, the azepa derivative (66) containing a hydroxy and an amine group was unexpectedly produced [102].(eq.15)



(64) **(65)** **(66)**

Gabriela Guillena *et.al*, has synthesized (69) from the alkylation of sulfonamides (67), the reaction at 150 °C in the absence of solvent employing an excess of benzylic alcohol (68), substoichiometric concentrations of Ru(OH)x- Fe_3O_4 and K_2CO_3 [86].(eq.16)



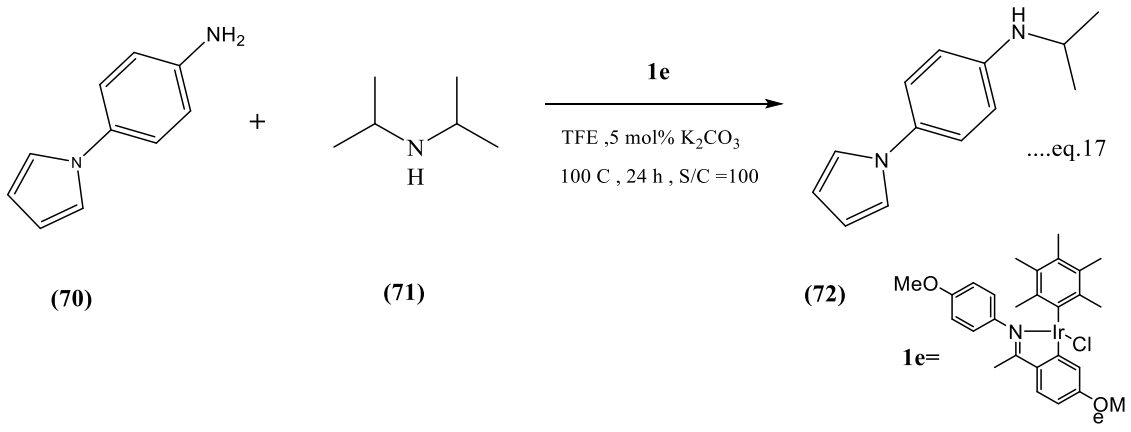
....eq.16

(67) **(68)** **(69)**

X= N ,CH

R= H ,Cl , Me , OMe

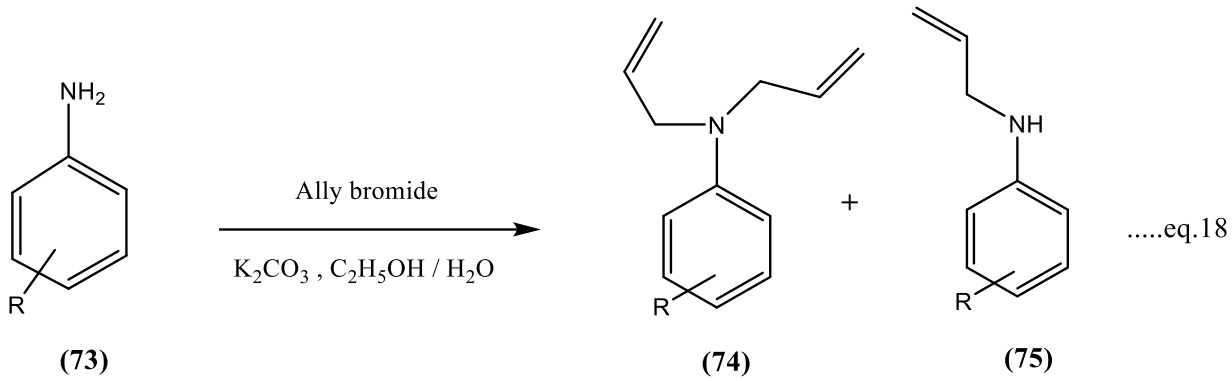
In addition, reaction of 4-(1H-pyrrol-1-yl) aniline (70) with diisopropylamine (71), K_2CO_3, TFE give N-isopropyl-4-(1H-pyrrol-1-yl) aniline (72) [103].(eq.17)



....eq.17

(70) **(71)** **(72)**

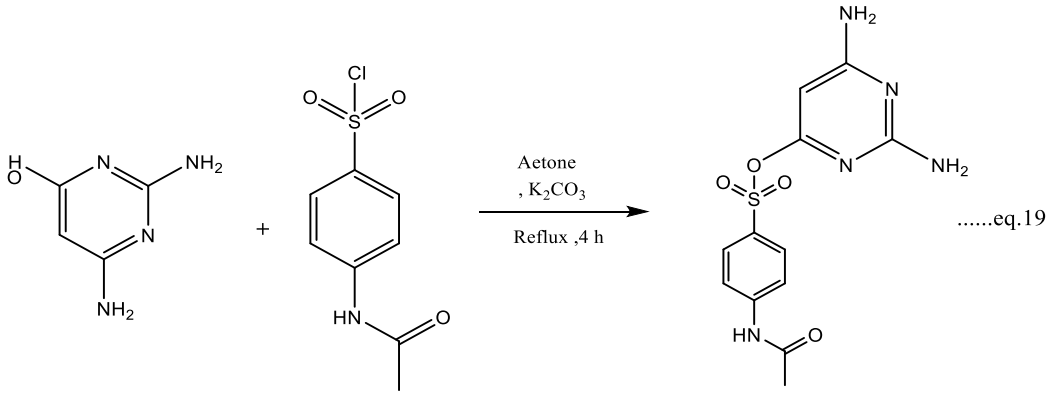
The reaction of inexpensive aniline (73) with allyl bromide in ethanol \ water and K_2CO_3 give mix of N,N-diallylaniline (74) and N-allylaniline (75)[87].(eq.18)



(73) **(74)** **(75)** eq.18

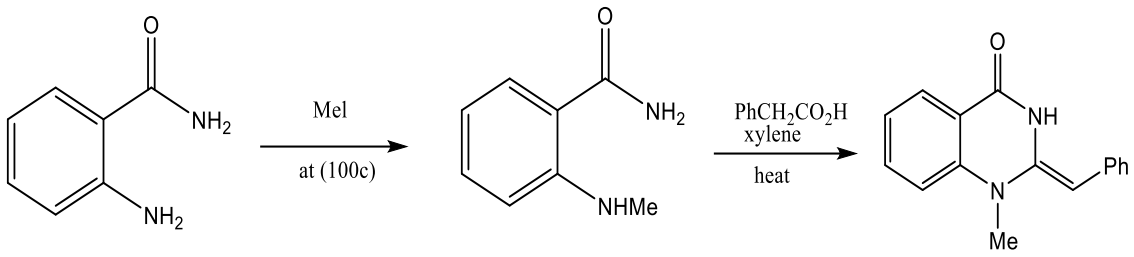
R= H and various subtituents

Prepartion of 2,6-diaminopyrimidin-4-yl 4-acetamidobenzenesulfonate (78) from the reaction of 4-acetamidobenzenesulfonyl chloride (77) with 2,6-diaminopyrimidin-4-ol (76) in acetone[104].(eq.19)



(76) **(77)** **(78)** eq.19

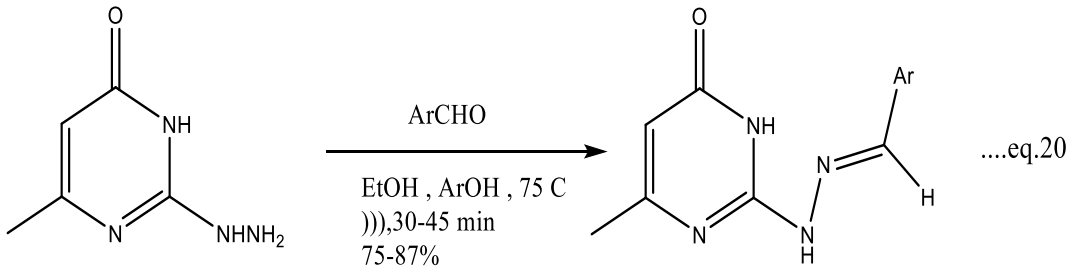
Methylation of 2-aminobenzamide (79) scheme(1.8) with Mel in sealed tube leads to the N- methylanthranilamide (80), which undergoes ring closure to glycosine(8) upon heating with $PhCH_2COOH$ and P_2O_5[105].



(79) **(80)** **(81)**

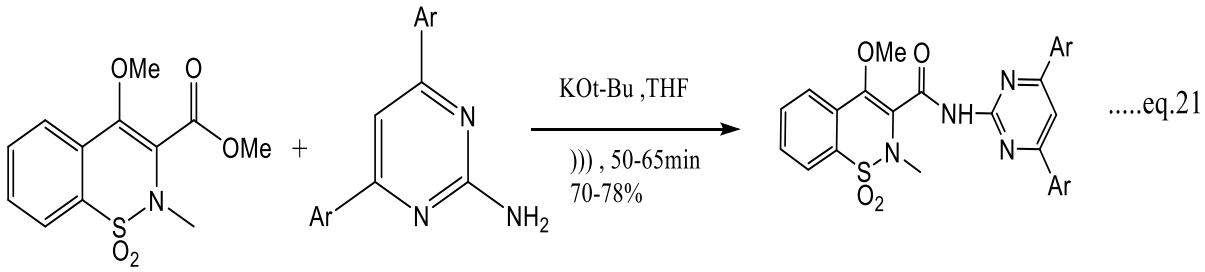
Scheme 1.8 : Synthsis of glycosine

When aromatic aldehydes were added to 2-hydrazinopyrimidin-4(3H)-one (82), benzylidene hydrazones (83) were obtained with yields of 75-87%[57]. (eq.20)



(82) **(83)** eq.20

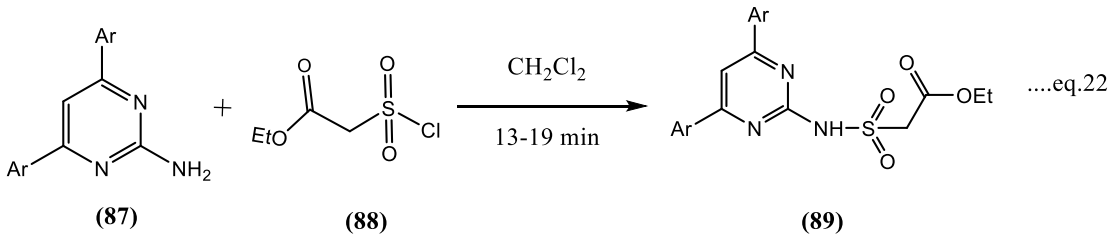
The pyrimidine ring's amino group at position 2 allows for additional derivatizations, such as the creation of amides (86). Benzothiazine 3-carboxylate (84) was aminolyzed using 2-aminopyrimidines (85), it took between 50 and 65 minutes to complete the reaction with potassium tert-butoxide in THF. A yield of 70–78% was achieved for the comparable carboxamides[82]. (eq.21)



.....eq.21

(84) **(85)** **(86)**

Divya *et.al.* reported the synthesis of 4,6 - diaryl-2 - ethylacetate sulfony amino Pyrimidine (89) from the reaction of 4,6 - diaryl- 2 - amino pyrimidine (87) and ethyl acetate sulfony chloride (88) in the Presence of methylene chloride [106].(eq.22)

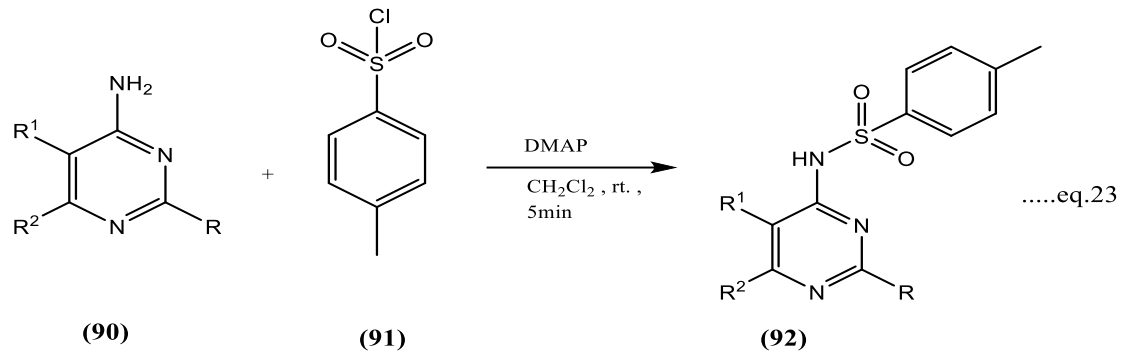


....eq.22

(87) **(88)** **(89)**

Ar =4-Me.Ph , 4-Cl.Ph

N-tosylated derivative (92) was synthesized from 2,5,6-trialkyl-4-amino pyrimidine (90) and p-toluene sulfonyl chloride (91) in the presence of DMAP and methylene chloride of r.t [107].(eq.23)

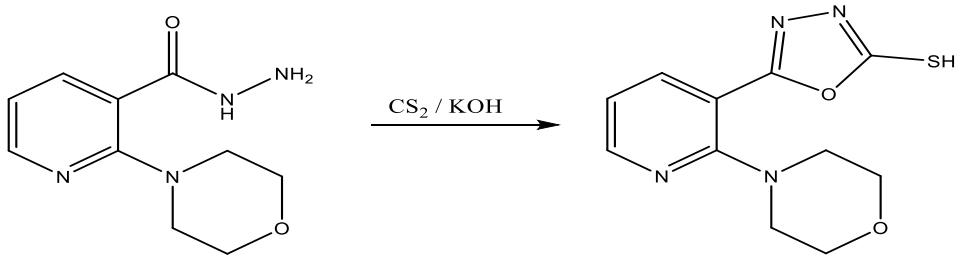


.....eq.23

(90) **(91)** **(92)**

R= H and various subtituents

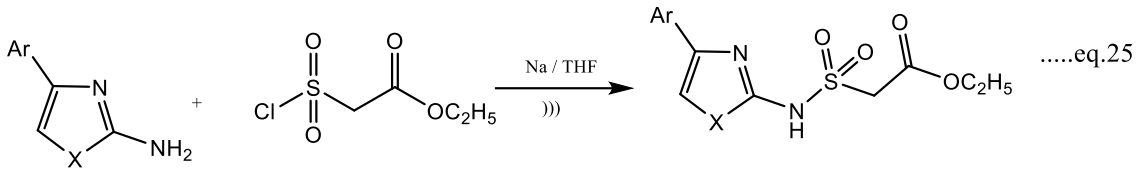
Synthesis of 5-(2-morpholinopyridin-3-yl)-1,3,4-oxadiazole-2-thiol (94) from reaction 2-morpholinonicotinohydrazide (93) with CS_2, KOH [81].(eq.24)



.....eq.24

(93) **(94)**

Synthesis of sulfonamides(97) using dispersed sodium from reaction ethyl 2-(chlorosulfonyl)acetate (96) with compounds (95) [108].(eq.25)



.....eq.25

(95) **(96)** **(97)**

X = O , S , NH

Ar =4-Me.Ph , 4-Cl.Ph , 4-NO_2.Ph

Other literatures of tosylation compounds have been reported in the review[109-113].

The Aim of the Study

The aim of this study is to prepare of some new aryl sulfonyl derivatives and allyl derivatives via the introducing a sulfonyl- or an ally - group instead of the protons of amino group, which attached to the phenyl ring of some oxopyrimidines, thiopyrimidines and pyrrazoline compounds. These modifications will help us to obtain derivatives with high biological activity properties and development of compounds of chemotherapeutic interest.

Chapter Two

The experimental

2.1 Chemicals and Techniques

2.2 Chemicals

The following substances were purchased from various companies. To achieve the maximum purity, some of these were cleansed. The solid and liquid compounds are listed in Table (2.1).

Table (2.1) Liquid and solid chemicals

Name of material	Name of company
Ethanol absolute 99.8%	Scharlau
Chloroform 99.4%	Merck
Petroleum ether 66-80°C	ROMIL
Ethyl acetate 99%	ROMIL
Pyridine 80 %	MERK
Hydrochloric acid 37%	Riedel-De Haen
Hydrazine hydrate 55%	Aldrich
Allyl bromide	Fluorochem
Dimethylformamide	Merck
Acetone	J.T.Baker
Benzene sulfonyl chloride	Merck
Urea	TOMAS BAKER
Thiourea	THOMAS BAKER
Sodium hydroxide 97%	THOMAS BAKER
Potassium hydroxide	THOMAS BAKER
4-Chlorobenzaldehyde 99%	TCI
4-Bromobenzaldehyde 99%	Fluorochem
4-Nitrobenzaldehyed 98%	TCI
4-Aminoacetophenone 98%	Aldrich
4-Toluene sulfonyl chloride	Fluorochem

2.3 The Techniques

2.3.1 The Spectroscopy

a: Fourier Transform Infra - Red Spectrophotometer (FTIR)

FTIR spectra were recorded using potassium bromide discs on a 8400s Shimadzu spectrophotometer and FTIR spectrophotometer, Shimadzo (Ir prestige - 21)**.**These spectra are achieved in Medicine College, Maysan University-Iraq.

b: Nuclear Magnetic Resonance Spectrometer

^{1}H-NMR and ^{13}C-NMR the spectra were measured by Bruker using the ultra shield 400 MHz model, and they are shown in parts per million (ppm). The Chemistry Department at Al-Basra University in Iraq made use of DMSO as a solvent and TMS as an internal standard.

2.3.2 Elemental analysis

Elemental analysis was Performed at Micro Analytical Center, Sience College, Cairo University by Euro Vector 3000 A Elemental Analysis (Italy).

2.3.3 Thin layer chromatography (TLC)

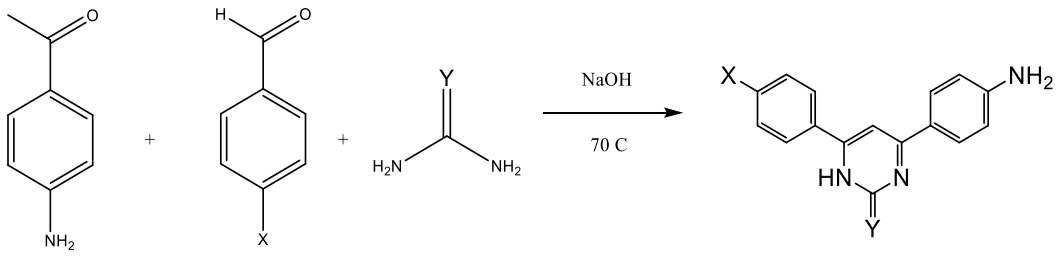
When performing thin layer chromatography (TLC), TLC grade silica gel 'G' is used (Acme Synthetic Chemicals). Unless otherwise specified, the spots are eluted with petroleum ether: ethyl acetate 3:2 mixes and made visible by exposing plates to UV light.

2.3.4 Melting points

Stuart SMP11 melting point equipment was used to calculate uncorrected melting points. They are evaluated in the Chemistry Department of the College of Science at the University of Misan in Iraq.

2.4 Synthetic Methods

2.4.1 Preparation of 4[6- (4-substituted phenyl) -2 –oxo or thio-1, 2,-dihydropyrimidine- 4-yl] aniline (I-VI) [114]

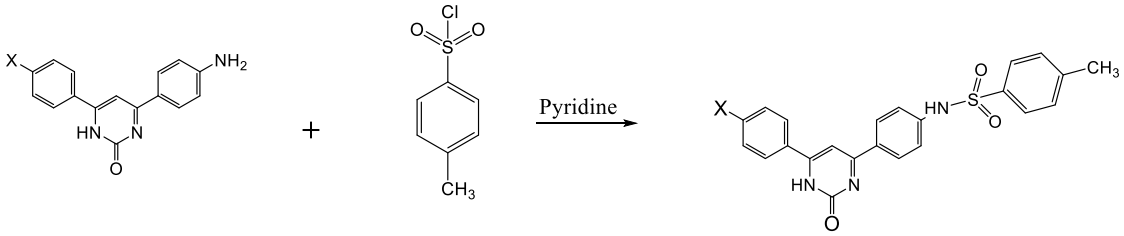


X = Cl , Br , NO_2 **Y= O , S**

I-III ,Y= O
IV-VI , Y= S

A mixture of 4-aminoacetophenone (0.281g, 2mmol), 4-substituted benzaldehyde (chloro, bromo, nitro) (2mmol), and urea or thiourea (3mol), were added in a mortar. The mixture was blended together and then shifted into a round flask and mix it with 50ml of 0.4% aqueous NaOH solution. The mixture was heated about 70°C under atmospheric conditions, and the reaction could be finished within 3-4 h. After being put into water, the reaction mixture underwent filtering, drying, and recrystallization from ethanol.

2.4.2 Preparation of N-(4-(6-(4- substituted phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)phenyl)-4-methylbenzenesulfonamide (H_1-H_3). [115]

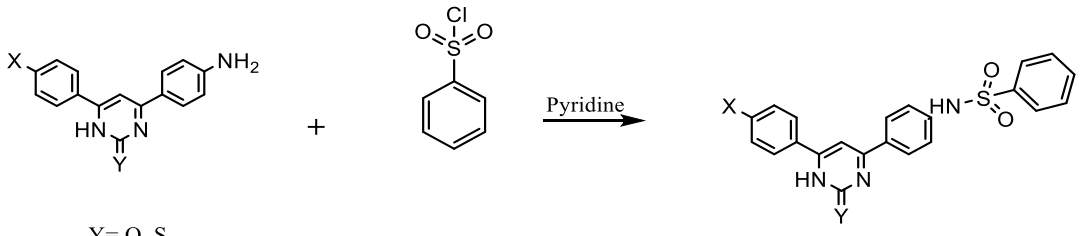


(H_1 - H_3)

X = Cl , Br , NO_2

A mixture of (I , II or III) (0.01mol) and 4-toluene sulfonyl chloride (0.381g, 0.01 mol), in pyridine (20 mL) was refluxed for (2-4) h in a water bath. TLC was kept an eye on in between to make sure the reaction was finished. After the reaction was finished, the fluid was chilled to room temperature before being put into ice water. The produced precipitate was filtered, water washed, and dried. From ethanol, the product underwent recrystallization.

2.4.3 Preparation of N-(4-(6-(4- substituted phenyl)-2-thioxo or oxo-1,2-dihydropyrimidin-4-yl)phenyl)benzenesulfonamide (H_4-H_9) [115]



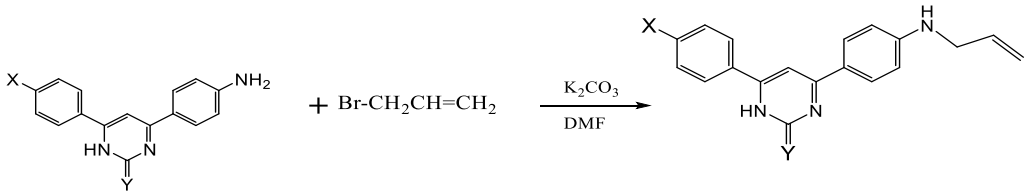
Y= O ,S

(H_4 - H_9)

X = Cl , Br , NO_2

A mixture of (I, II ,III ,IV ,V or VI) (0.01 mol) and benzene sulfonyl chloride (0.01 mol) in pyridine (20 mL) was refluxed on water bath for (2-4)h. until the T.L.C showed no more reactants. The reaction mixture was cooled to r.t when it was finished, and then put into ice-cold water. The precipitate was collected, filtered, water washed, and dried. The product was re-crystallized from ethanol.

2.4.4 Preparation of 4-(4-(allylamino) phenyl)-6-(4- substituted phenyl) pyrimidin-2(1H)-one (H_{12}-H_{17}). [116]



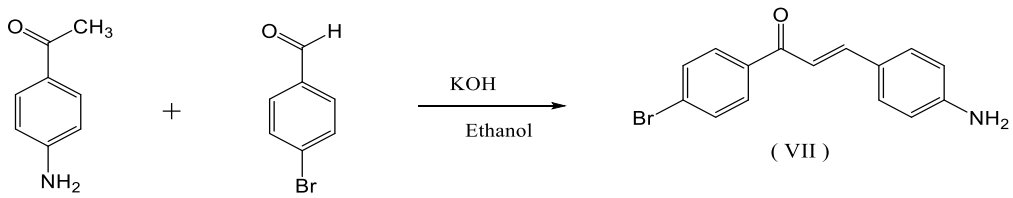
Y = O , S

X = Cl , Br , NO_2

(H_{12} -H_{17})

A mixture of (I , II ,III , IV , V or VI) (0.01mol) and allyl bromide (0.01 mmol) was refluxed overnight, in dry DMF (20 mL) in the presence of K_2CO_3 (0.01 mol). The reaction mixture was cooled to r.t. and filtered. The solvent was evaporated under reduced pressure. The crude product was purified using column chromatography (5%-10% EtOAc in Pet. Ether) to afford the desired product (60-82% yields).

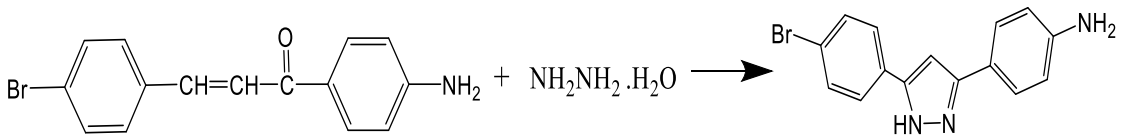
2.4.5 Preparation of (E)-3-(4-aminophenyl)-1-(4-bromophenyl) prop-2-en-1-one (VII). [117]



(VII)

4-aminocetophenone (1.361g,0.01mol) 4-bromobenzaldehyde (1.850g, 0.01mol), were mixed and dissolved in ethanol (10 ml). To this aqueous potassium hydroxide solution 40% (W/V) (10 ml) was added slowly with constant stirring. The reaction mixture was stirred continuously for 3 h at r.t. The completion of reaction was confirmed by monitoring Thin layer Chromatography (TLC). After completion of the reaction, the reaction mixture was kept in refrigerator overnight. The product was filtered and washed with cold water and neutralized by adding dilute HCI. The product was dried and recrystallized from ethanol to get pale yellow coloured solid chalcone.

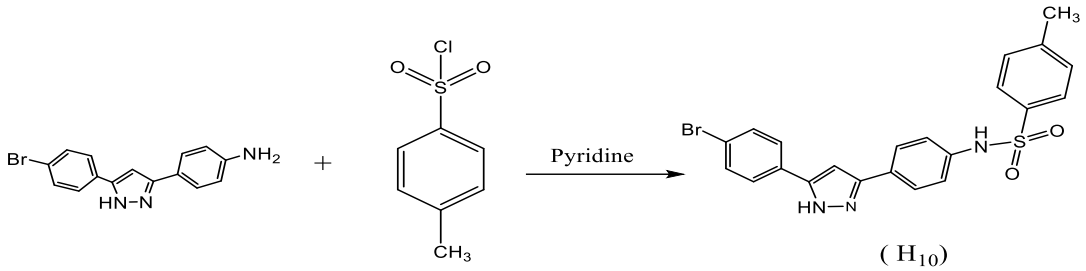
2.4.6 Preparation of 4-(3-(4-bromophenyl)-1H-pyrazol-5-yl) aniline (VIII). [117]



VIII

Chalcone (VII) (0.366g, 0.001mol), Hydrazine hydrate (0.01mol) were mixed and dissolved in ethanol (10 ml). To this 40% aqueous potassium hydroxide solution 10 ml was added slowly with constant stirring. The reaction mixture was refluxed on water bath for 3 h. In between TLC was monitored to check the completion of reaction. After completion of reaction, the reaction mixture was cooled to room temperature. And then poured in to ice cold water and neutralized by adding dilute HCl. The Precipitate obtained was filtered, washed with water and dried. The product was recrystallized from ethanol.

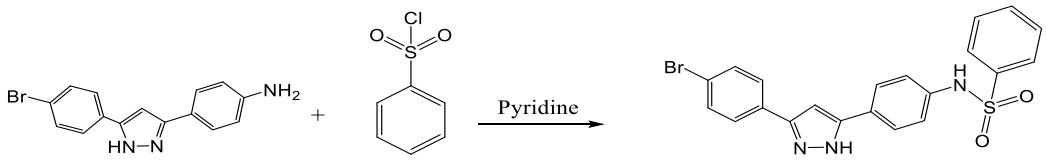
2.4.7 Preparation of N-(4-(3-(4-bromophenyl)-1H-pyrazol-5-yl) phenyl)-4-methylbenzene sulfonamide (H_{10}). [115]



(H_{10})

A mixture of (VIII) (0.342g, 0.001 mol) and 4-toluene sulfonyl chloride (0.381g, 0.01 mol) in pyridine (20 mL) was refluxed on water bath for (2-4)h. .In between TLC was monitored to check the completion of reaction. After completion of reaction, the reaction mixture was cooled to room temperature. And then poured in to ice cold water. The Precipitate obtained was filtered, washed with water and dried. The product was recrystallized from ethanol.

2.4.8 Preparation of N-(4-(3-(4-bromophenyl)-1H-pyrazol-5-yl) phenyl) benzene sulfonamide (H_{11}). [115]

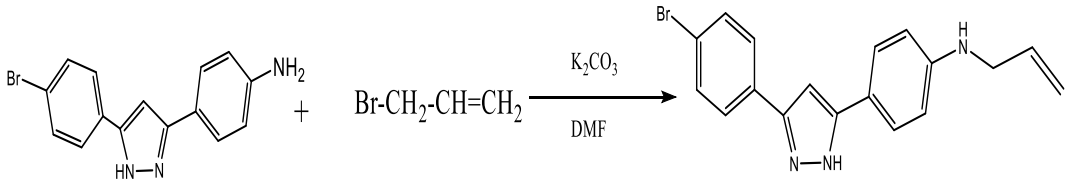


(H_{11})

A mixture of (VIII) (0.342g, 0.001 mol) and benzene sulfonyl chloride (0.01 mol),(in pyridine (20 mL) was refluxed on water bath for (2-4)h. .In between TLC was monitored to check the completion of reaction. After completion of reaction, the reaction mixture was cooled to room temperature. And then poured in to ice cold water. The Precipitate

obtained was filtered, washed with water and dried. The product was recrystallized from ethanol.

2.4.9 Preparation of N-allyl-4-(3-(4-bromophenyl)-1H-pyrazol-5-yl) aniline (H_{18}). [116]



(H_{18})

A mixture of (VIII) (0.342g, 0.01mol) and allyl bromide (0.01 mol) was refluxed overnight, in dry DMF (10 mL) in the presence of K_2CO_3 (0.01 mol). The reaction mixture was then cooled to r.t. and filtered. The solvent was evaporated under reduced pressure. The crude product was purified using column chromatography (5%-10% EtOAc in Pet. Ether) to afford the desired product (60% yield).

2.5 Biological part

2.5.1 Antibacterial activity assay

2.5.1.1 Bacterial isolates

The bacteriological unit of Al-Saddar Teaching Hospital provided all the isolates, which were later reidentified [118] in bacteriological laboratory in Pharmacy College\ Misan University. Following identification, one collection was placed in a test tube with 5 ml of nutritional broth and cultured for 24 h at 37 ℃. To acquire pure and isolated collections from each bacterium for the sensitivity test, the tested bacteria were strict on blood or chocolate agar and likewise incubated at 37°C for 24 h.

2.5.1.2 Preparation of bacterial suspension

Bacteria suspension was created by taking [119-121] isolated collections from each microorganism and transferring them to a test tube with 5 ml of normal saline after shaking. This suspension was then compared and adjusted with the tube containing (0.5) ml of the McFarland standard, which results in a cell density of 1.5 x 108 cells/ml.

2.5.1.3 Antibiotic sensitivity test

Antibiotic sensitivity testing is done using the Kirby-Bauer disc diffusion method [121]. After evenly swabbing a Muller-Hinton agar plate with a sterile cotton swab dipped in bacterial solution, the plates were incubated at 37°C for 30 minutes. The antibiotic discs (used as a control) are placed on the agar with a forceps firmly pressed to ensure contact with the agar, and then the plate is inverted and incubated. After incubation for 24 h at 37 °C, the inhibition zone around the disc is read. According to NCCLS criteria, isolates were classified as either sensitive or resistant [120].

2.5.1.4 Biological activity evaluation by agar diffusion well assay.

Agar diffusion well experiment [121] was used to examine the chemical compounds' biological activity in vitro against 10 microorganisms, including eight bacterial isolates (four of them were Gram negative, and four of them Gram positive). A Muller-Hinton agar plate's surface is equally covered with a sterile cotton swab soaked in the prepared suspension, with seven 7 mm-diameter holes spaced 20 mm apart in the agar gel. The prepared diluted concentrations (12.5, 25, 50, 100, 150, and 200 mg/ml) were then applied to each well in a volume of 100 mL.

One of these holes was filled with either DMSO or ethanol (20% each) to observe the effect of the solvent. The plates that weren't converted were incubated at 37°C for 24 h. After incubation, growth was seen, and the amount by which it was inhibited was measured in millimeters.

2.5.2 Cytotoxic activity

2.5.2.1 Cell lines and culture .

The MCF7 (a human breast cancer cell line) was purchased from National Cell Bank of Iran (Pasteur Institute, Iran). Cells were grown in RPMI-1640 medium (Gibco) with 10% FBS (Gibco) supplemented with antibiotics (100 U/ml penicillin and 100 µg/ml streptomycin). Cells were maintained at 37 °C under humidified air containing 5% CO2 and were passaged using trypsin/EDTA (Gibco) and phosphate-buffered saline (PBS) solution.

2.5.2.2 The MTT cell viability assay in MCF7 Cells.

Cell growth and cell viability were quantified using the MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium Bromide] (Sigma-Aldrich) assay. In brief, for monolayer culture, cells (MCF7) were digested with trypsin, harvested, adjusted to a density of 1.4 × 104 cells/well and seeded to 96-well plates filled with 200 µl fresh medium per well for 24 h. When cells formed a monolayer, they were treated with 100-6.25 µg/ml of the compounds for 24 h at 37 °C in 5% CO2. At the end of the treatment (24 h), while the monolayer culture was left untouched in the original plate, the supernatant was removed and 200 µl/well of MTT solution (0.5 mg/ml in phosphate-buffered saline [PBS]) was added and the plate was incubated at 37 °C for an additional 4 h. MTT solution (the supernatant of cells was removed and dimethyl

sulfoxide was added (100 µl per well). Cells were incubated on a shaker at 37 °C until crystals were completely dissolved. Cell viability were quantified by measuring absorbance at 570 nm using an ELISA reader (Model wave xs2, BioTek, USA). The concentration of the compounds that resulted in 50% of cell death (IC50) was determined from respective dose-response curves

Table (2.2) : Some physical properties of starting materials

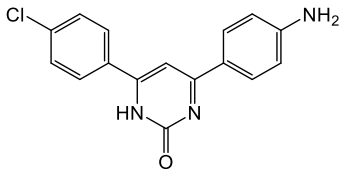
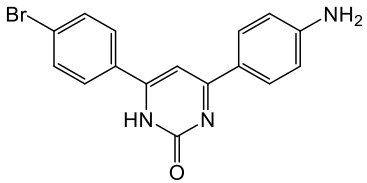
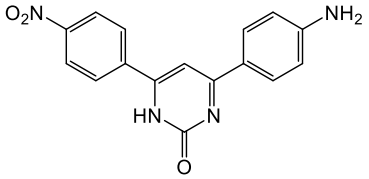
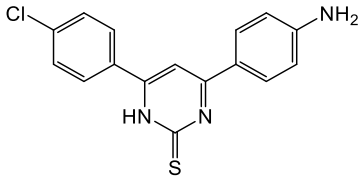
Comp. Symbol	Nomenclature	Structural formula	Molecular formula	M.P °C	Yield %	Color
(I)	4-(4-aminophenyl)-6-(4-chlorophenyl)pyrimidin-2(1H)-one		$C_{16}H_{12}ClN_3O$	155-158	67.06	Yellow
(II)	4-(4-aminophenyl)-6-(4-bromophenyl)pyrimidin-2(1H)-one		$C_{16}H_{12}BrN_3O$	156-160	85	Yellow
(III)	4-(4-aminophenyl)-6-(4-nitrophenyl)pyrimidin-2(1H)-one		$C_{16}H_{12}N_4O_3$	205-208	96	Dark orange
(IV)	4-(4-aminophenyl)-6-(4-chlorophenyl)pyrimidine-2(1H)-thione		$C_{16}H_{12}ClN_3S$	149-152	94	Pale yellow

Table (2.2) : Continued

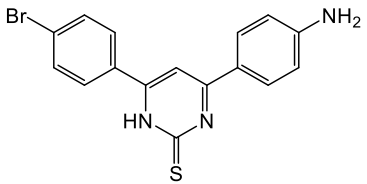
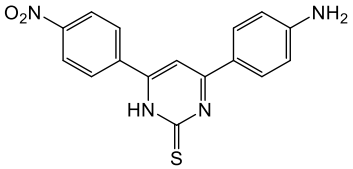
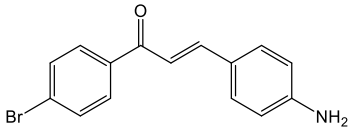
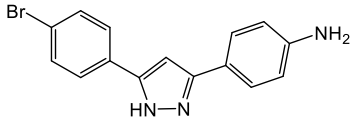
(V)	4-(4-aminophenyl)-6-(4-bromophenyl)pyrimidine-2(1H)-thione		$C_{16}H_{12}BrN_3S$	145-148	88	Pale yellow
(VI)	4-(4-aminophenyl)-6-(4-nitrophenyl)pyrimidine-2(1H)-thione		$C_{16}H_{12}N_4O_2S$	198-200	92	Pale brown
(VII)	(E)-3-(4-aminophenyl)-1-(4-bromophenyl)prop-2-en-1-one		$C_{15}H_{12}BrNO$	163-165	76	Yellow
(VIII)	4-(3-(4-bromophenyl)-1H-pyrazol-5-yl)aniline		$C_{15}H_{12}BrN_3$	209-212	59	Pale yellow

Table (2.3) : Some physical properties of sulfonyl derivatives

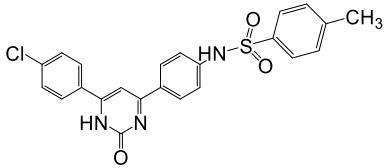
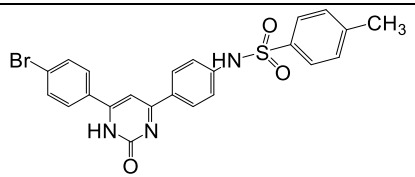
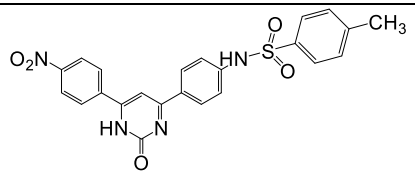
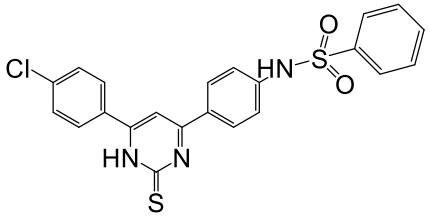
Comp. Symbol	Nomenclature	Structural formula	Molecular formula	M.P °C	Yield %	Color
H_1	N-(4-(6-(4-chlorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)phenyl)-4-methylbenzenesulfonamide		$C_{23}H_{18}ClN_3O_3S$	198-200	68	Yellow
H_2	N-(4-(6-(4-bromophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)phenyl)-4-methylbenzenesulfonamide		$C_{23}H_{18}BrN_3O_3S$	193-195	74	Pale yellow
H_3	4-methyl-N-(4-(6-(4-nitrophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)phenyl)benzenesulfonamide		$C_{23}H_{18}N_4O_5S$	211-214	65	Pale orange
H_4	N-(4-(6-(4-chlorophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)phenyl)benzenesulfonamide		$C_{22}H_{16}ClN_3O_2S_2$	203-205	70	White

Table (2.3) : Continued

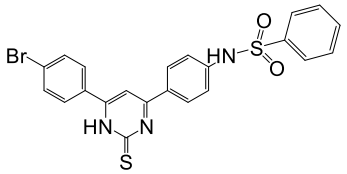
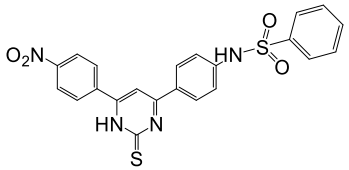
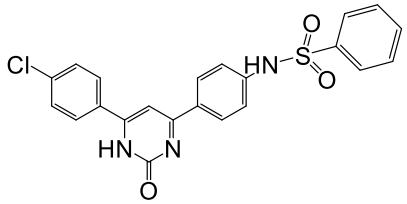
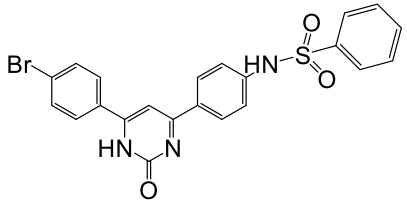
H_5	N-(4-(6-(4-bromophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)phenyl)benzenesulfonamide		$C_{22}H_{16}BrN_3O_2S_2$	208-211	76	Pale yellow
H_6	N-(4-(6-(4-nitrophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)phenyl)benzenesulfonamide		$C_{22}H_{16}N_4O_4S_2$	221-223	81	Pale orange
H_7	N-(4-(6-(4-chlorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)phenyl)benzenesulfonamide		$C_{22}H_{16}ClN_3O_3S$	200-203	70	white
H_8	N-(4-(6-(4-bromophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)phenyl)benzenesulfonamide		$C_{22}H_{16}BrN_3O_3S$	211-213	76	Crystal white

Table (2.3) : Continued

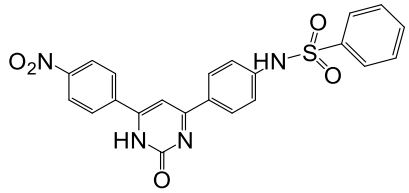
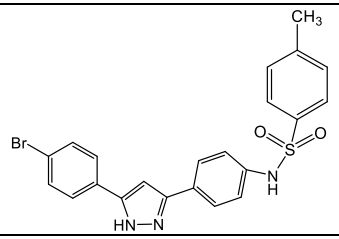
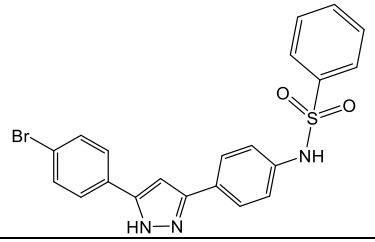
H_9	N-(4-(6-(4-nitrophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)phenyl)benzenesulfonamide		$C_{22}H_{16}N_4O_5S$	215-218	81	Pale yellow
H_{10}	N-(4-(3-(4-bromophenyl)-1H-pyrazol-5-yl)phenyl)-4-methylbenzenesulfonamide		$C_{22}H_{18}BrN_3O_2S$	180-184	62	Yellow
H_{11}	N-(4-(3-(4-bromophenyl)-1H-pyrazol-5-yl)phenyl)benzenesulfonamide		$C_{21}H_{16}BrN_3O_2S$	225-229	70	Brown

Table (2.4) : Some physical properties of allyl derivatives

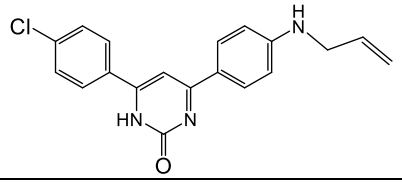
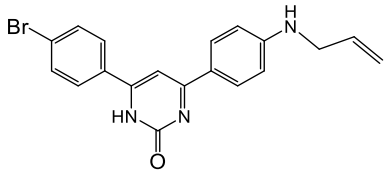
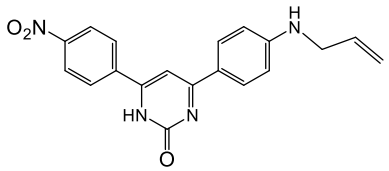
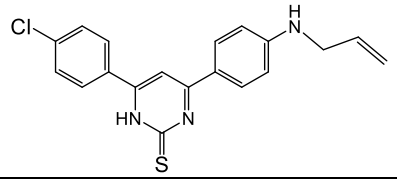
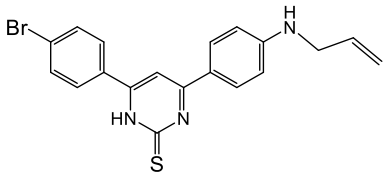
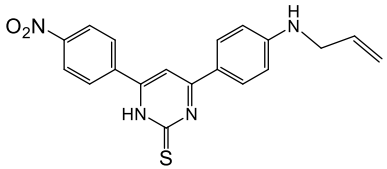
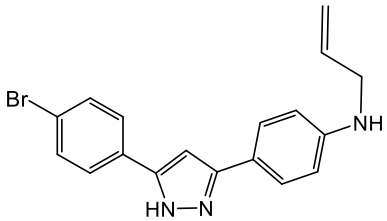
Comp. Symbol	Nomenclature	Structural formula	Molecular formula	M.P ℃	Yield %	Color
H_{12}	4-(4-(allylamino)phenyl)-6-(4-chlorophenyl)pyrimidin-2(1H)-one		$C_{19}H_{16}ClN_3O$	80-83	60	Yellow
H_{13}	4-(4-(allylamino)phenyl)-6-(4-bromophenyl)pyrimidin-2(1H)-one		$C_{19}H_{16}BrN_3O$	85-88	82	Yellow
H_{14}	4-(4-(allylamino)phenyl)-6-(4-nitrophenyl)pyrimidin-2(1H)-one		$C_{19}H_{16}N_4O_3$	96-100	68	Orange
H_{15}	4-(4-(allylamino)phenyl)-6-(4-chlorophenyl)pyrimidine-2(1H)-thione		$C_{19}H_{16}ClN_3S$	80-83	70	Yellow

Table (2.4) : Continued

H_{16}	4-(4-(allylamino)phenyl)-6-(4-bromophenyl)pyrimidine-2(1H)-thione		$C_{19}H_{16}BrN_3S$	98-101	65	Pale orange
H_{17}	4-(4-(allylamino)phenyl)-6-(4-nitrophenyl)pyrimidine-2(1H)-thione		$C_{19}H_{16}N_4O_2S$	122-125	69	Dark orange
H_{18}	N-allyl-4-(3-(4-bromophenyl)-1H-pyrazol-5-yl)aniline		$C_{18}H_{16}BrN_3$	81-83	60	Pale yellow

Chapter Three

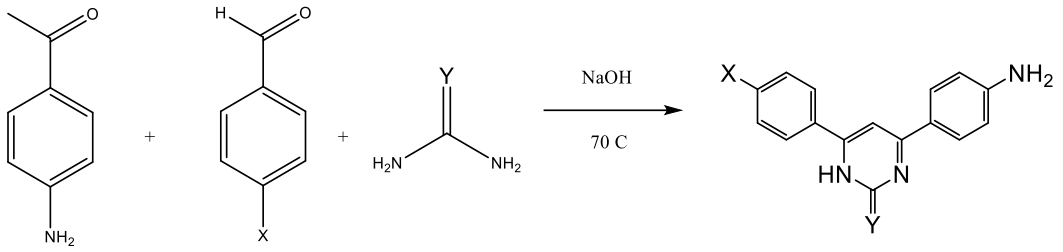
The results and discussion

3.1 Reactions and mechanisms

3.1.1 Preparation of 2-oxopyrimidines and 2-thiopyrimidines

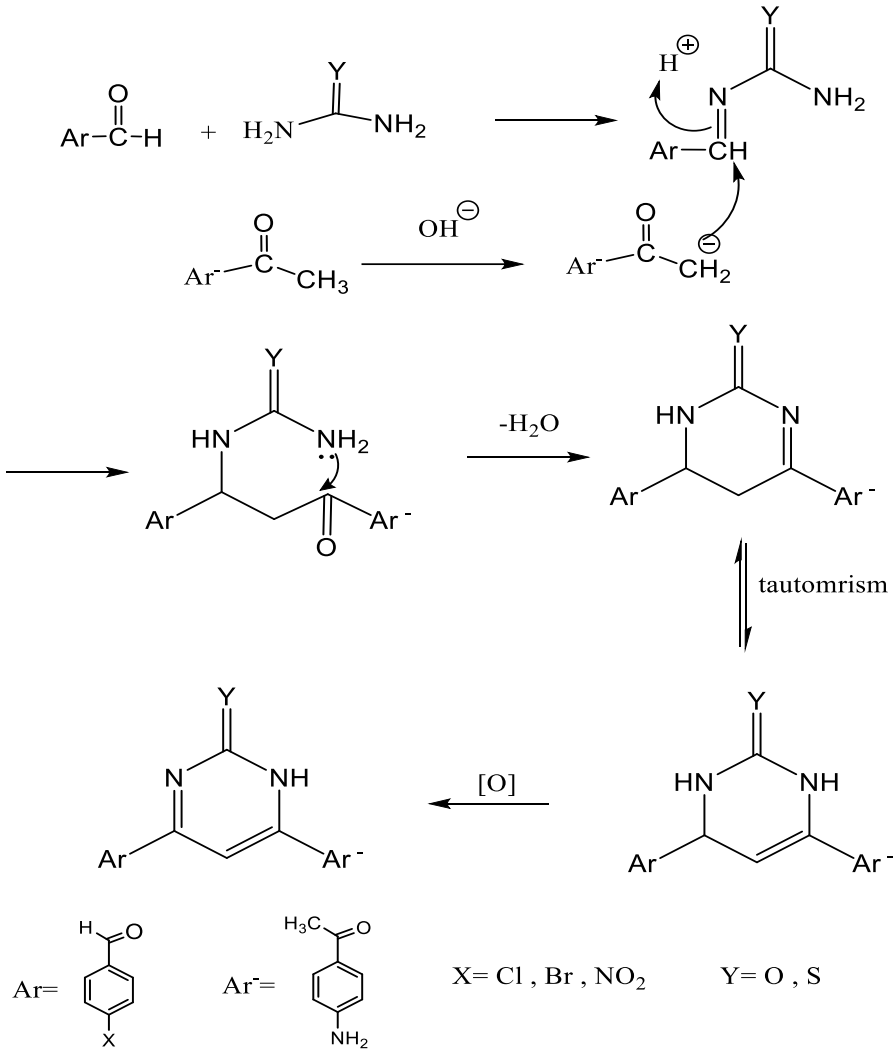
Oxopyrimidines (I)-(III) and thiopyrimidines (IV)-(VI) were synthesized from the reaction of 4-Aminoacetophenoe and 4-substitutedbenzaldehyde with urea or thiourea in basic medium.

General reaction :



X = Cl , Br , NO_2 Y= O , S

The possible mechanism involves in the formation of dihydropyrimidine derivatives (I)-(VI) showed Scheme (3-1) as:



Scheme (3.1)

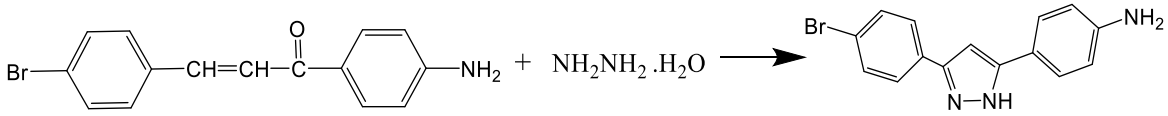
3.1.2 Preparation of pyrazolines (VIII)

Chalcone was chosen as the starting material for the synthesis of, pyrazoline by using approperative reagents for that purpose.

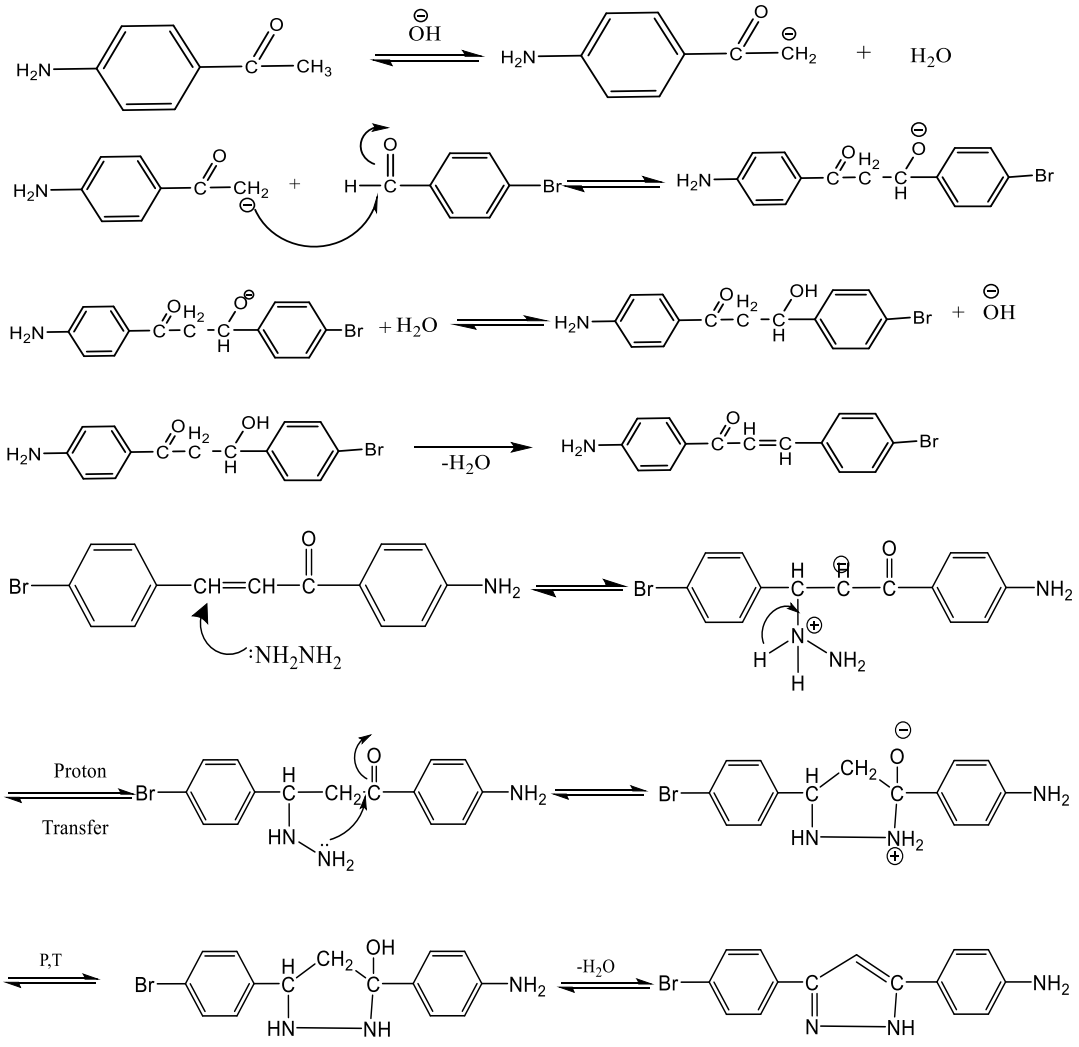
Chalcone (VII) is prepared by Claisen - Schmidt condensation of 4 - aminoacetophenone and 4-bromobenzaldehyde by base catalyzed followed by dehydration to yield the desired chalcone. The suggesting mechanism of this reaction may be outlined as follows in Scheme (3.2).

The chalcone (VII) was further reacted with hydrazine hydrate in ethanol absolute to yield the corresponding pyrazoline derivative (VIII) by the following reaction mechanism, Scheme (3.2).

General reaction:



The expected mechanism:

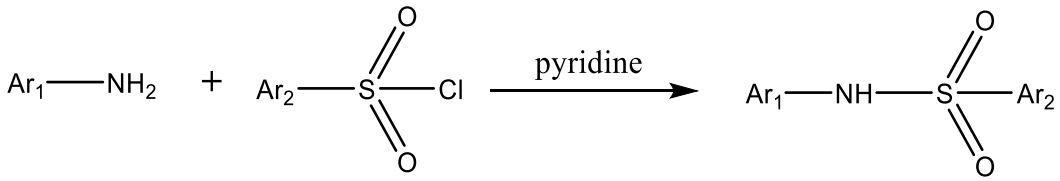


Scheme (3.2)

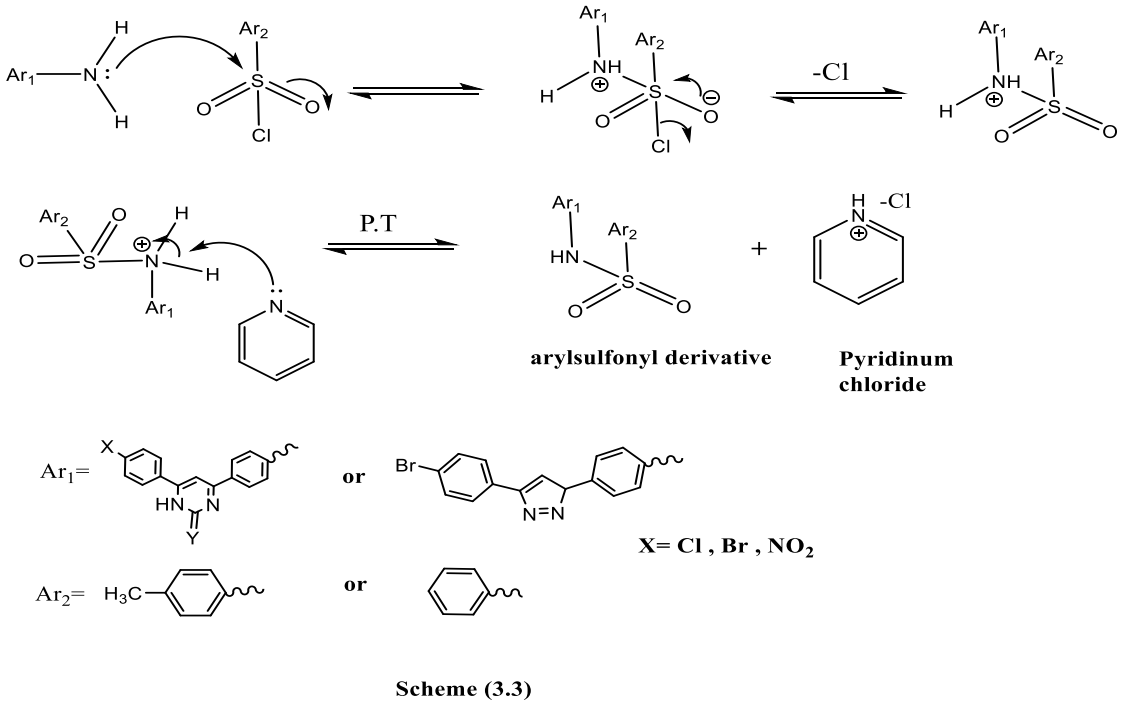
3.1.3 Synthesis of arylsulfonyl derivatives (H_1-H_{11})

Aryl sulfonyl derivatives (H_1-H_{11}) are synthesed by the reaction of benzene sulfonyl chloride or P-toluene sulfonyl chloride with compounds (**I - VI**) and **VIII** in the presence of pyridine as solvent and base according to the following reaction mechanism , Scheme (3 . 3) .

General reaction:



The expected mechanism:

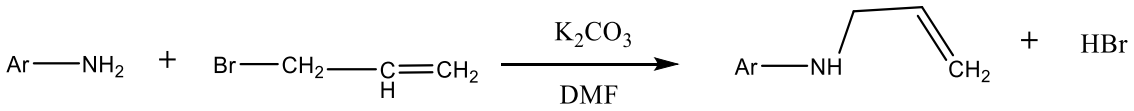


Scheme (3.3)

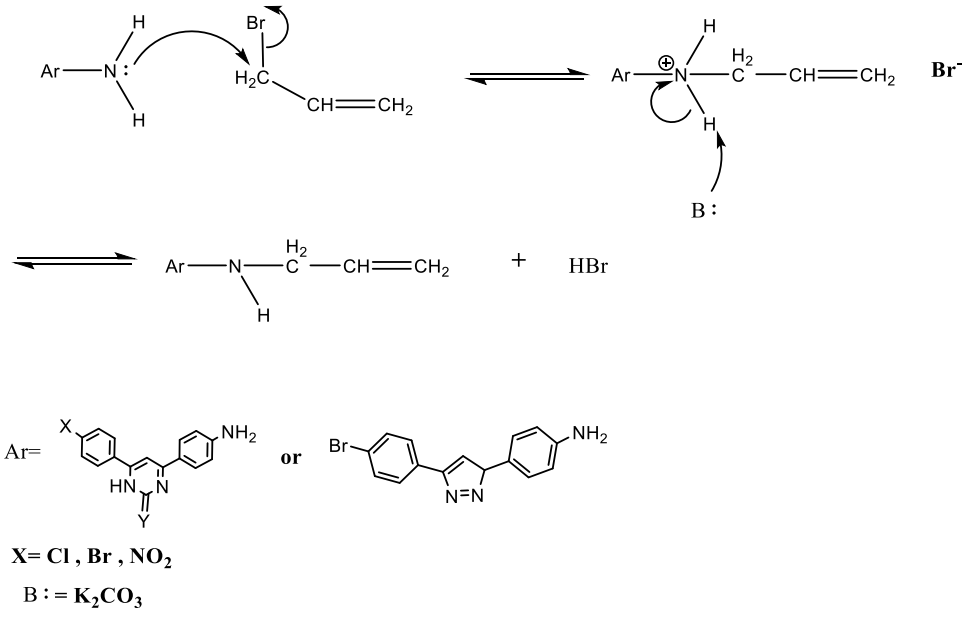
3.1.4 Synthesis of allyl derivatives (H_{12}-H_{18})

The synthesis of allyl derivatives (H_{12}-H_{18}) is acheived by mixing (**I-VI)** or V**III** compounds with allyl bromide and potassium carbonate in dry DMF , as explained in the below mechanism ,Scheme (3.4).

General reaction:



The expected mechanism:



Scheme (3.4)

3.2 Characterization of the prepared compounds

3.2.1 Characterization of the precursors

The starting materials (**I - VIII**) were characterized by some physical measurement, such as melting points besides the spectroscopic techniques, IR, ^{1}H-NMR and ^{13} C-NMR.

The IR spectra of the starting materials are studied as KBr disc as shown in Table (3.1) and in Figs. (3.1 -3.8). These compounds are characterized by eight bands corresponding to the stretching vibrations of the NH_2 ,-NH , aromatic C - H , C = O , C = N , C = C , C -N , C-S and C-X groups , which occur within the ranges (3487.3 – 3342.64) , (3230.77-3118.80), (3107.32 – 3037.77) , (1647.21-1629.85) , (1647.21-1583.59) , (1629.85-1487.12) , (1400.32-1340.53) , (1182.36-1178.51) , (1344.46-617.22) cm^{-1} , respectively .

Also the starting materials were identified by ^{1}H-NMR spectra which appeared four signals shown in Table (3.2) and Figs (3.9- 3.16) . The range of the signals are δ (4.24 – 6.21) , (6.23 - 8.64) , (9.97- 11.43) , and (8.64 -10.17)ppm which are represented the -NH_2 , Ar-H , O=C-NH and S=C-NH respectively .

Whereas the ^{13}C-NMR spectra of starting materials showed seven signals ascribed to the C - N , C = C , C = N , C=O , C=S and C-X as clarified in Table (3.3) and Figs(3.17-3.24) .

Table (3.1) : FT-IR spectra of the stretching vibrations of starting materials (cm^{-1})

Com. No.	Symbol	-NH_2	-NH-C=O	C-H Aromatic	C=N	C=C	C=O	C=S	C-N	C-X
1	**(I)**	3460.30 3344.57 (m)	3217.27 (w)	3066.82 (w)	1604.77 (m)	1573.91 (m)	1629.85 (m)	…….	1346.31 (s)	(C-Cl) 840.96 (w)
2	**(II)**	3462.22 3342.64 (m)	3215.34 (w)	3049.46 (w)	1606.7 (m)	1487.12 (m)	1647.21 (s)	…….	1340.53 (m)	(C-Br) 642.30 (s)
3	**(III)**	3482.37 3390.88 (s)	3230.77 (w)	3037.77 (w)	1583.59 (s)	1506.41 (s)	1637.58 (s)	……	1342.46 (m)	($C-NO_2$) 1344.46 (s)
4	**(IV)**	3460.3 3342.64 (s)	3217.27 (w)	3051.39 (w)	1647.21 (m)	1629.85 (m)	……	1178.51 (m)	1346.31 (m)	(C-Cl) 813.96 (s)
5	**(V)**	3462.22 3342.64 (m)	3215.34 (w)	3047.53 (w)	1647.21 (m)	1627.92 (m)	……	1180.44 (m)	1340.53 (m)	(C-Br) 671.23 (m)
6	**(VI)**	3487.3 3388.93 (s)	3230.77 (w)	3107.32 (w)	1610.56 (s)	1610.56 (m)	……..	1182.36 (m)	1342.46 (s)	($C-NO_2$) 1342.46 (s)
7	**(VII)**	3462.22 3342.64 (m)	…….	3047.53 (w) Alkene 2929.87 (w)	……	1575.84 (s) Alkene 1606.70 (s)	1647.21 (m)	……	1400.32 (m)	(C-Br) 688.59 (m)
8	**(VIII)**	3373.50(w) 3203.76 3118.90 (m)	3118.80 (w)	3070.68 (w)	1624.06 (s)	1504.48 (s)	……..	…….	1340.53 (m)	(C-Br) 617.22 (m)

s = strong , m = medium , w = weak

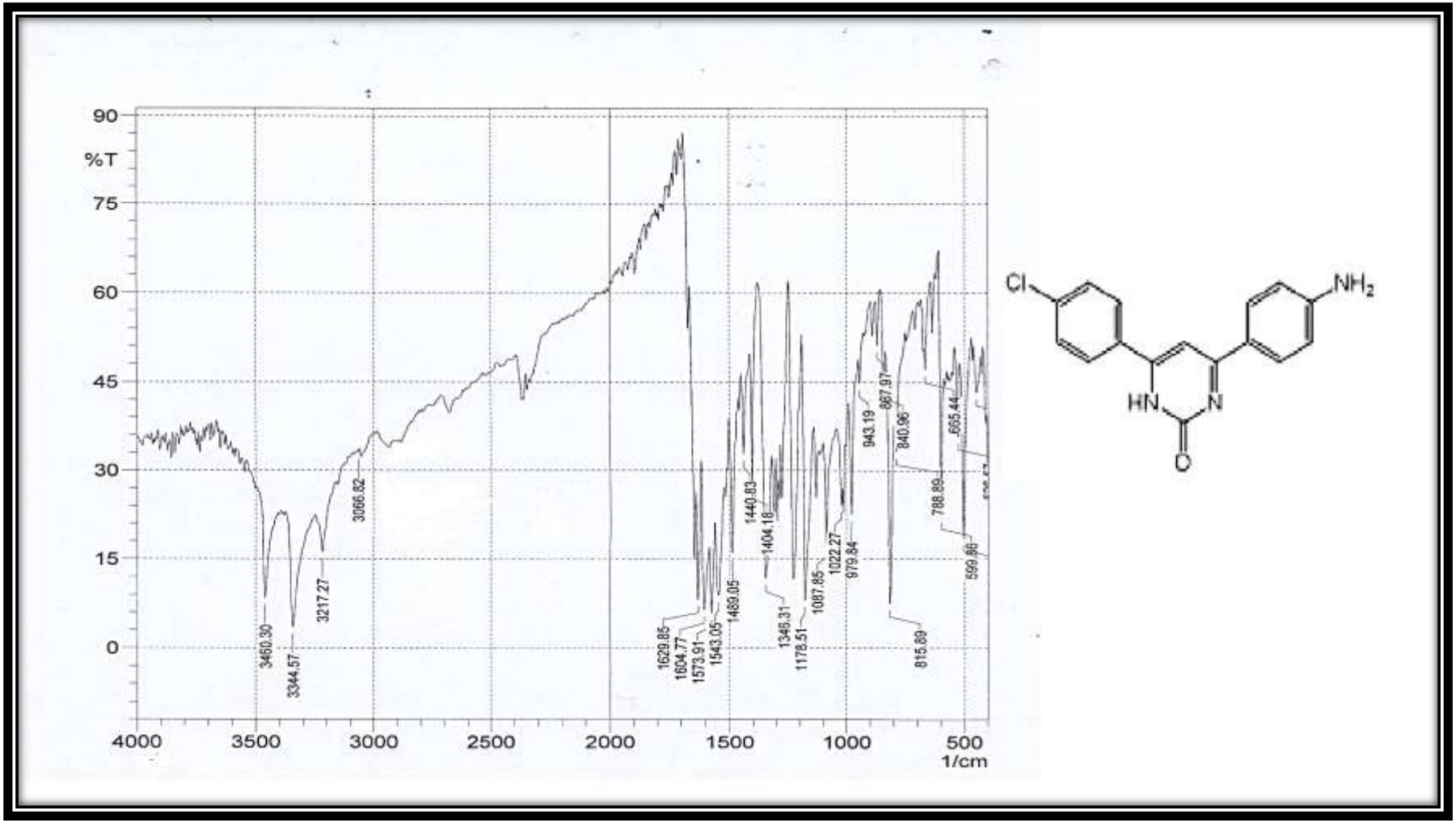


Fig (3.1) :FT-IR spectrum of 4-(4-aminophenyl)-6-(4-chlorophenyl)pyrimidin-2(1H)-one (I)

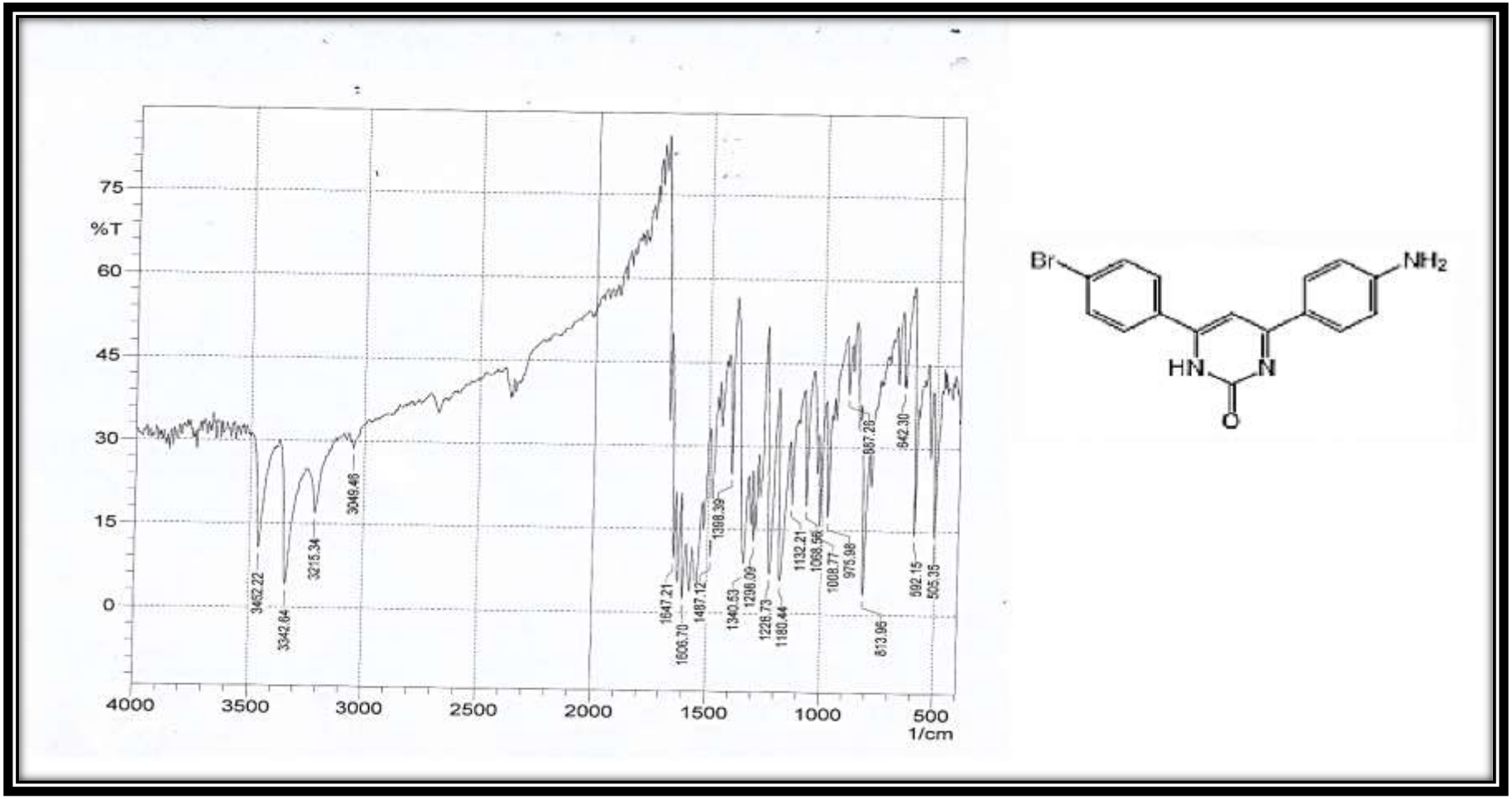


Fig (3.2) : FT-IR spectrum of 4-(4-aminophenyl)-6-(4-bromophenyl)pyrimidin-2(1H)-one (II)

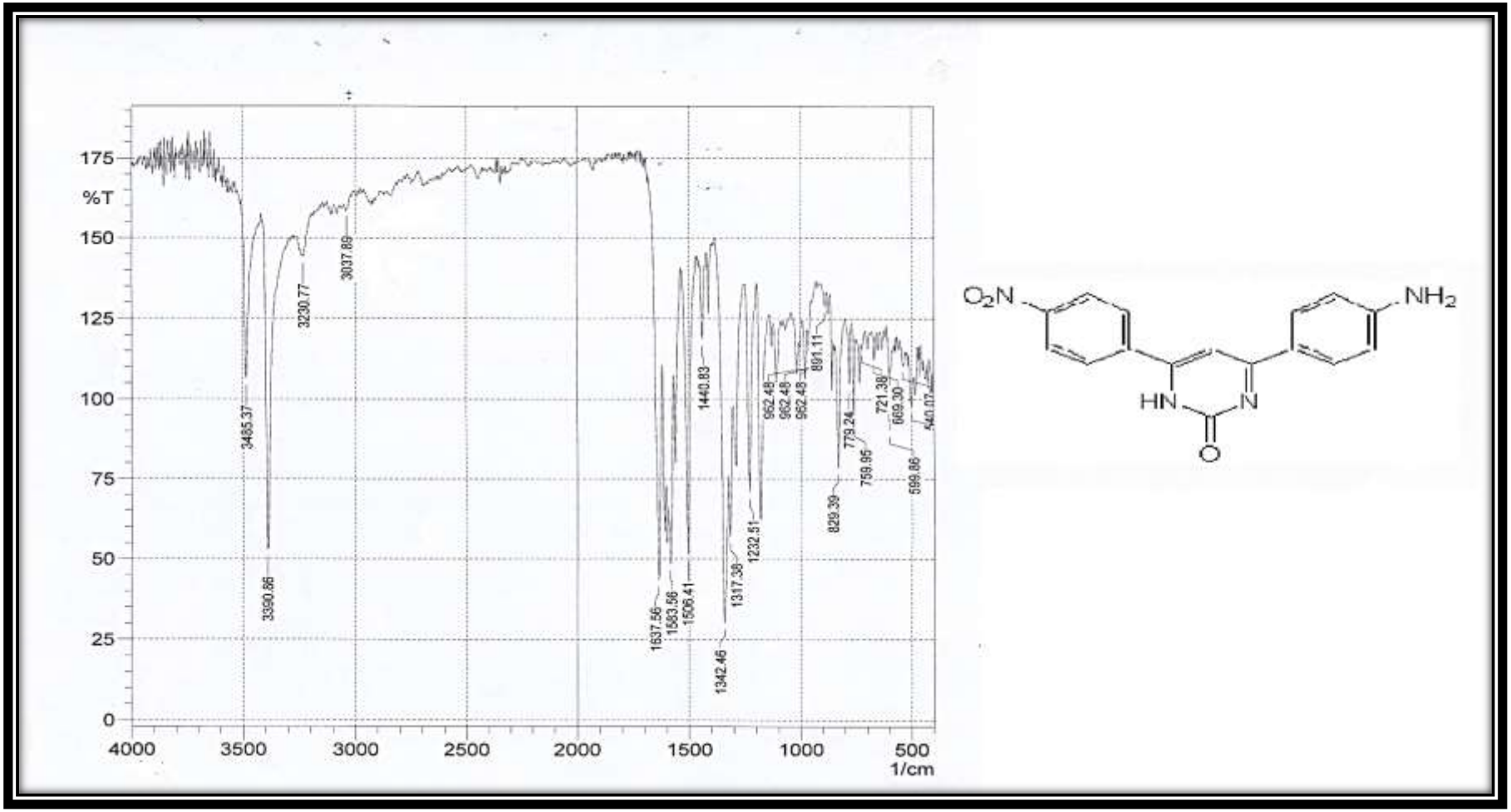


Fig (3.3) : FT-IR spectrum of 4-(4-aminophenyl)-6-(4-nitrophenyl)pyrimidin-2(1H)-one (III)

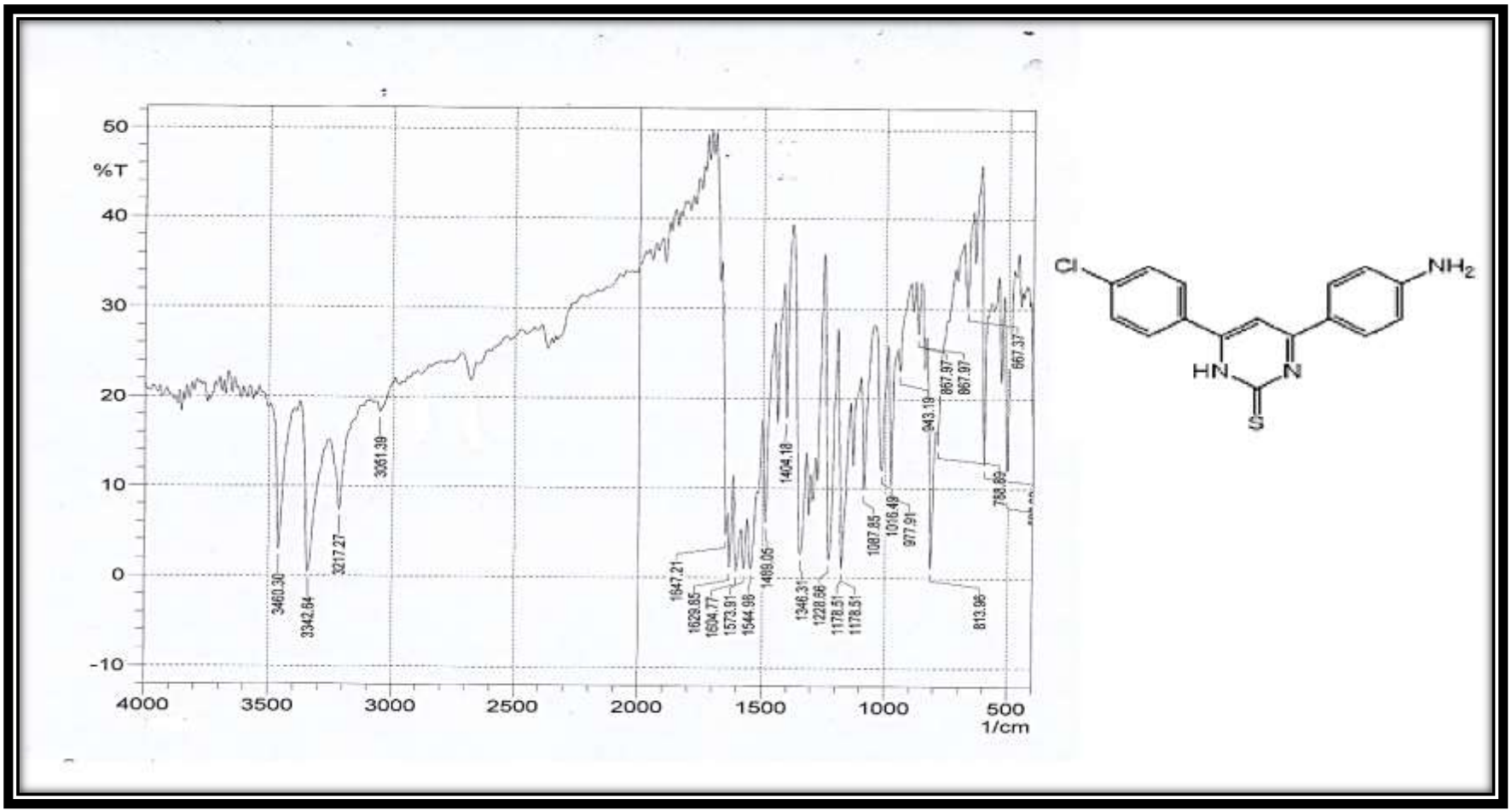


Fig (3.4) : FT-IR spectrum of 4-(4-aminophenyl)-6-(4-chlorophenyl)pyrimidine-2(1H)-thione (IV)

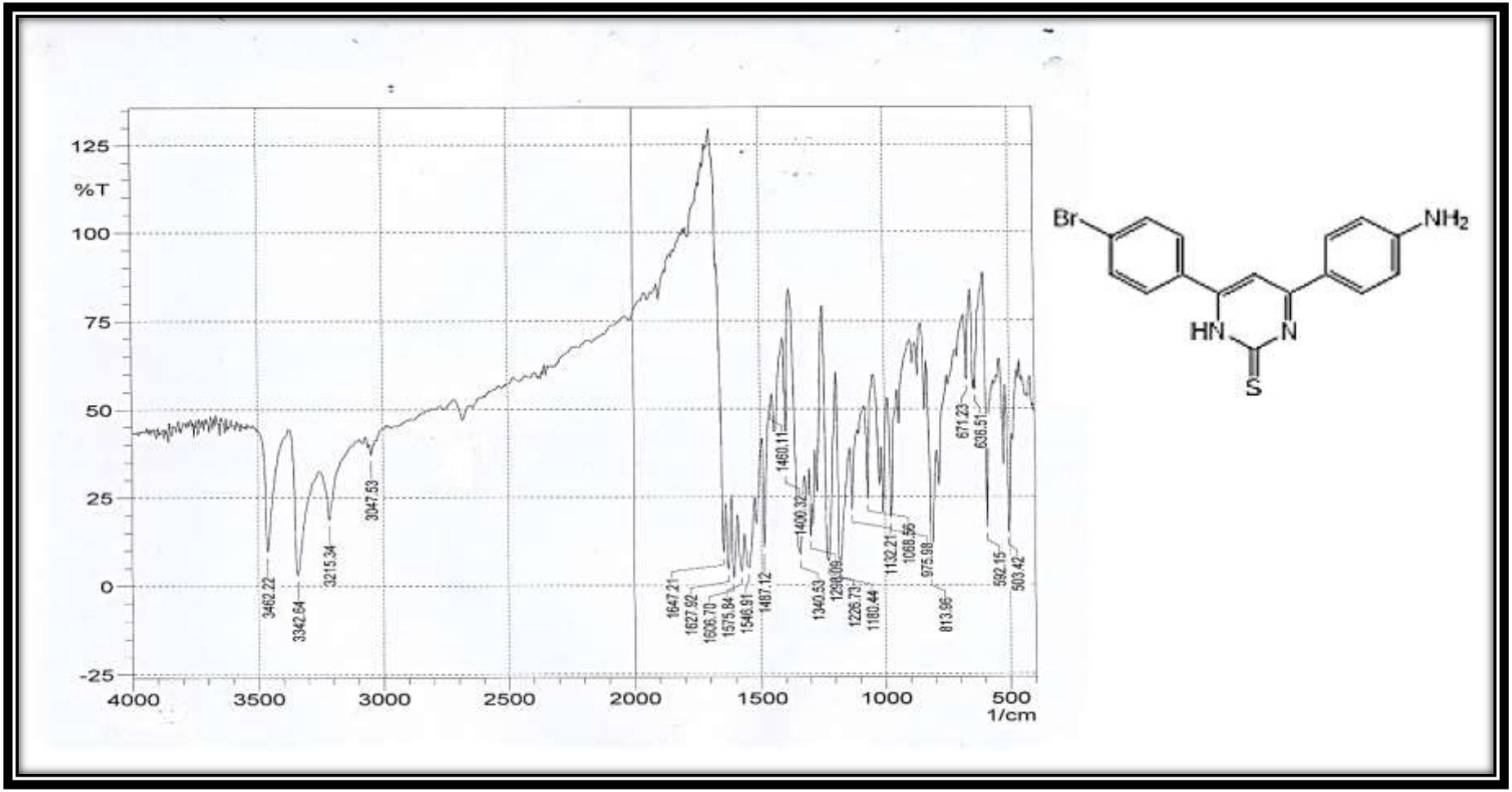


Fig (3.5) : FT-IR spectrum of 4-(4-aminophenyl)-6-(4-bromophenyl)pyrimidine-2(1H)-thione (V)

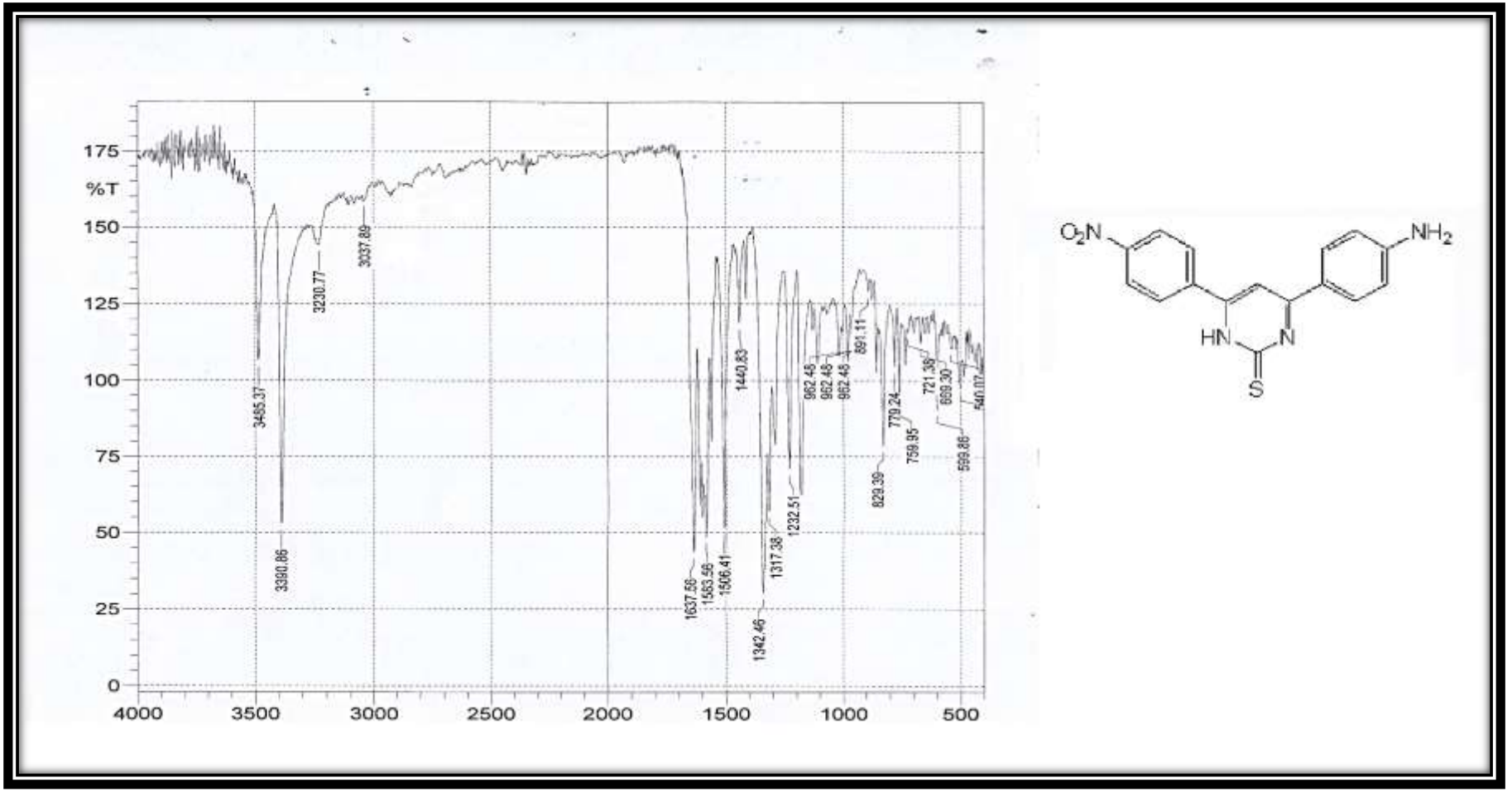


Fig (3.6) : FT-IR spectrum of 4-(4-aminophenyl)-6-(4-nitrophenyl)pyrimidine-2(1H)-thione (VI)

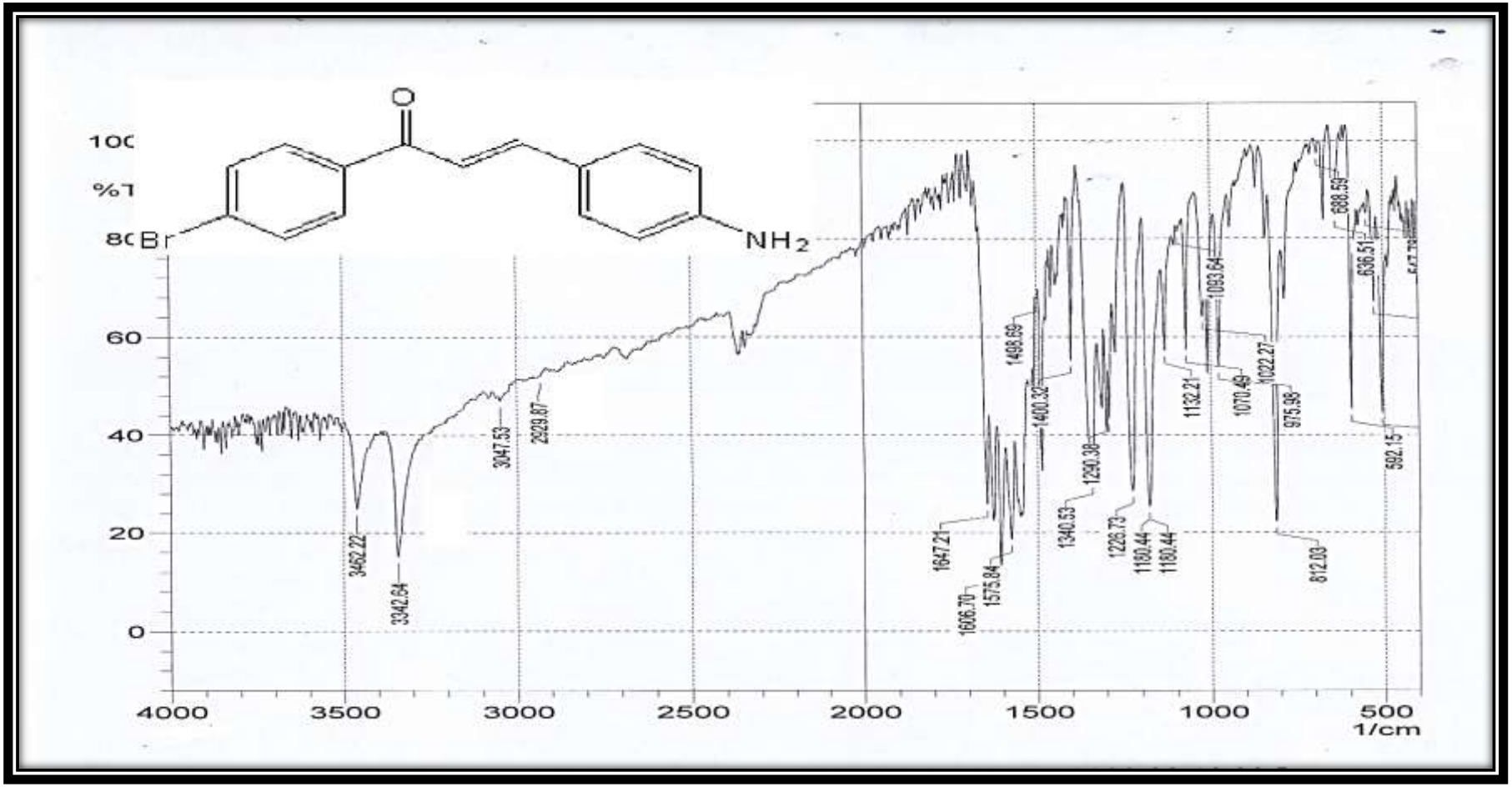


Fig (3.7) : FT-IR spectrum of (E)-3-(4-aminophenyl)-1-(4-bromophenyl)prop-2-en-1-one(VII)

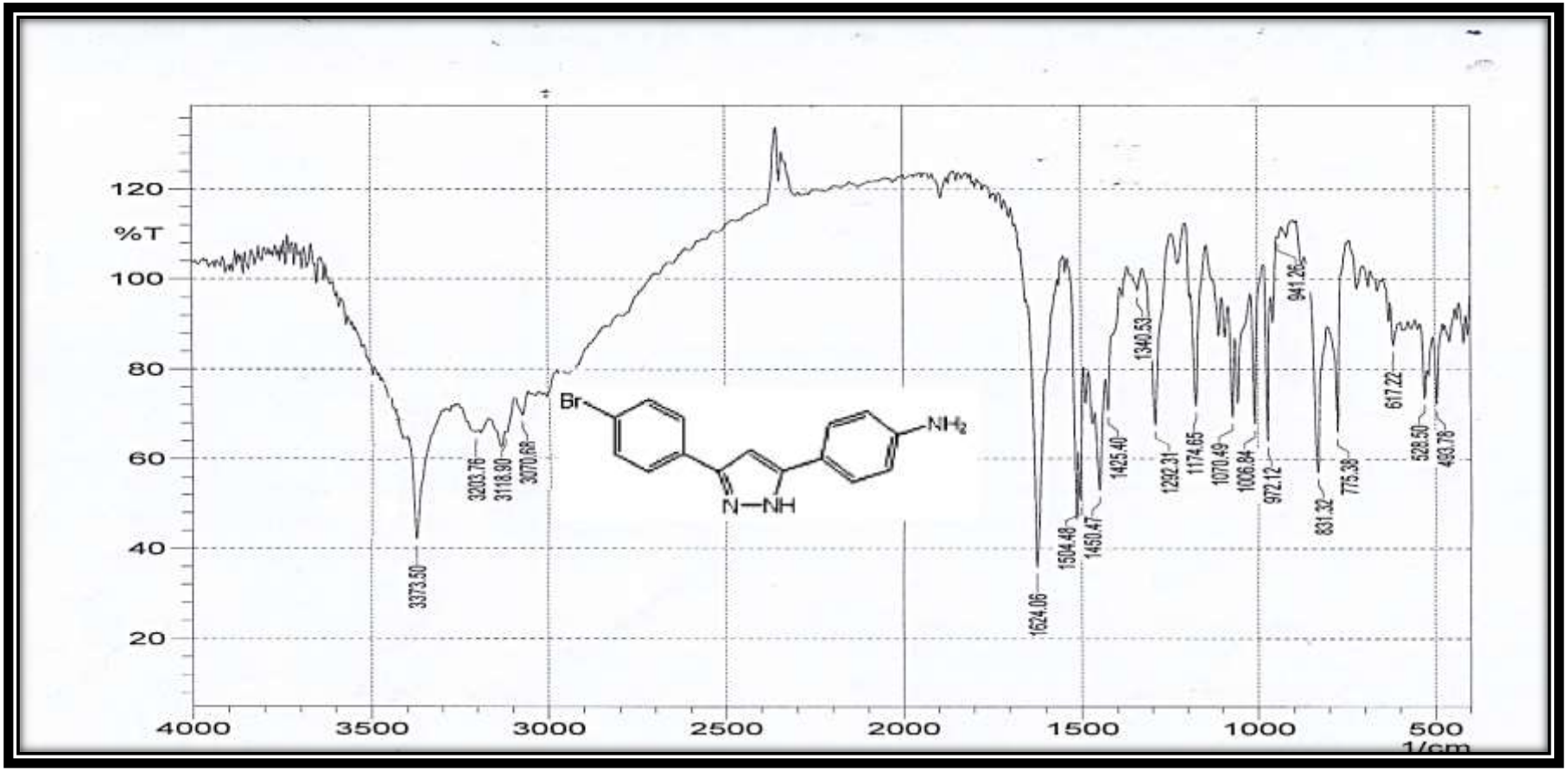


Fig (3.8) : FT-IR spectrum of 4-(3-(4-bromophenyl)-1H-pyrazol-5-yl)aniline(VIII)

Table (3.2) : ^{1}H-NMR spectra data of the starting materials(ppm)

Com. No.	Symbol	-NH_2 (s)	C-H Heterocycle	Aromatic Protons and Pyrimidine-NH (m,s)
1	**(I)**	4.24	6.70	7.27-8.08
2	**(II)**	6.23	7.35	7.35-8.03
3	**(III)**	5.19	6.75	7.56-8.08
4	**(IV)**	6.20	6.65	7.43-7.94
5	**(V)**	6.21	6.67	7.35-8.64
6	**(VI)**	5.33	6.30	7.69-8.31
7	**(VII)**	6.15	6.09	6.11-8.00
8	**(VIII)**	4.70	7.65	7.66-7.87

s = singlet , m = multiplet

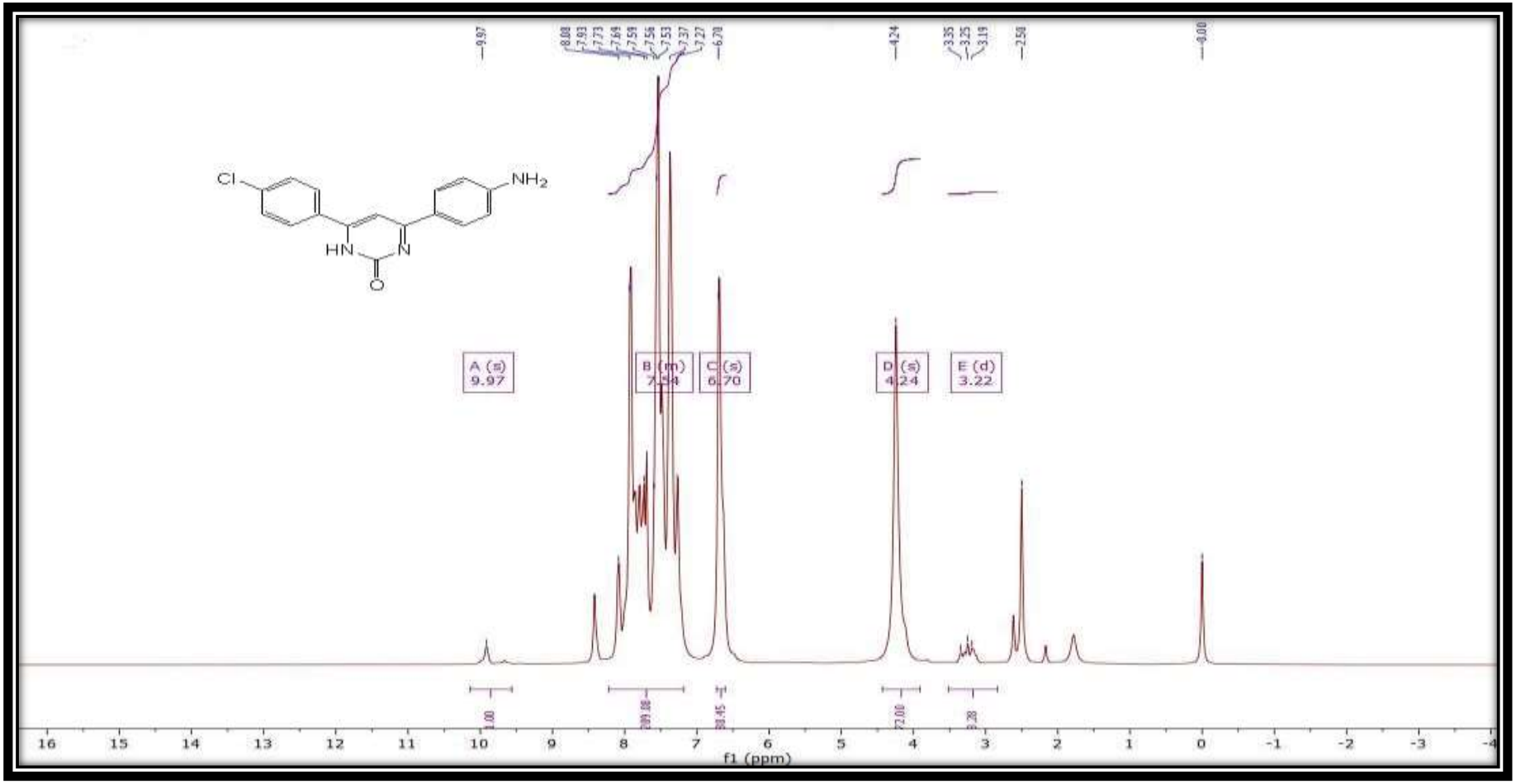


Fig (3.9) : ^{1}H-NMR Spectrum of 4-(4-aminophenyl)-6-(4-chlorophenyl)pyrimidin-2(1H)-one (I)

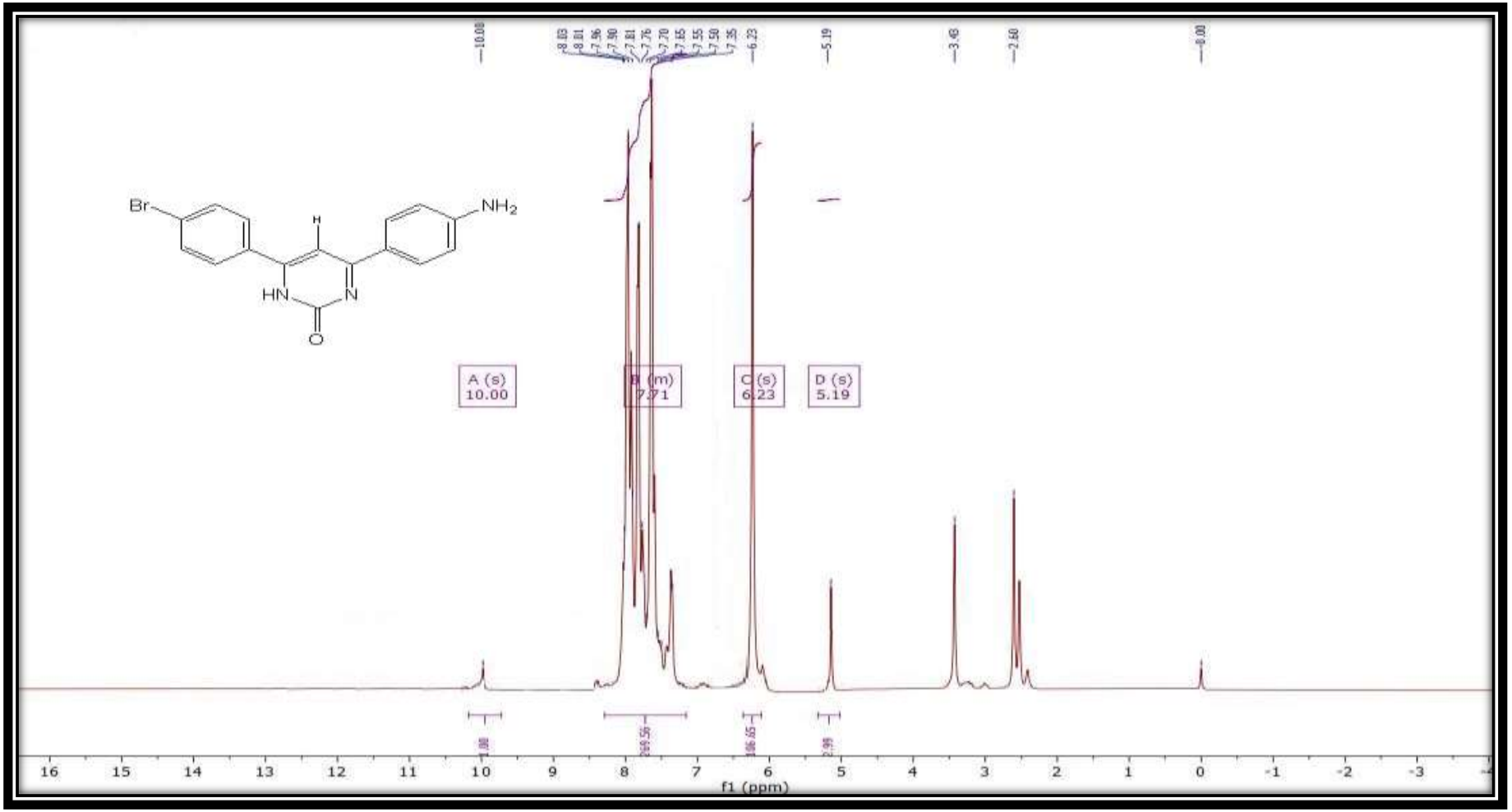


Fig (3.10) : ^{1}H-NMR Spectrum of 4-(4-aminophenyl)-6-(4-bromophenyl)pyrimidin-2(1H)-one (II)

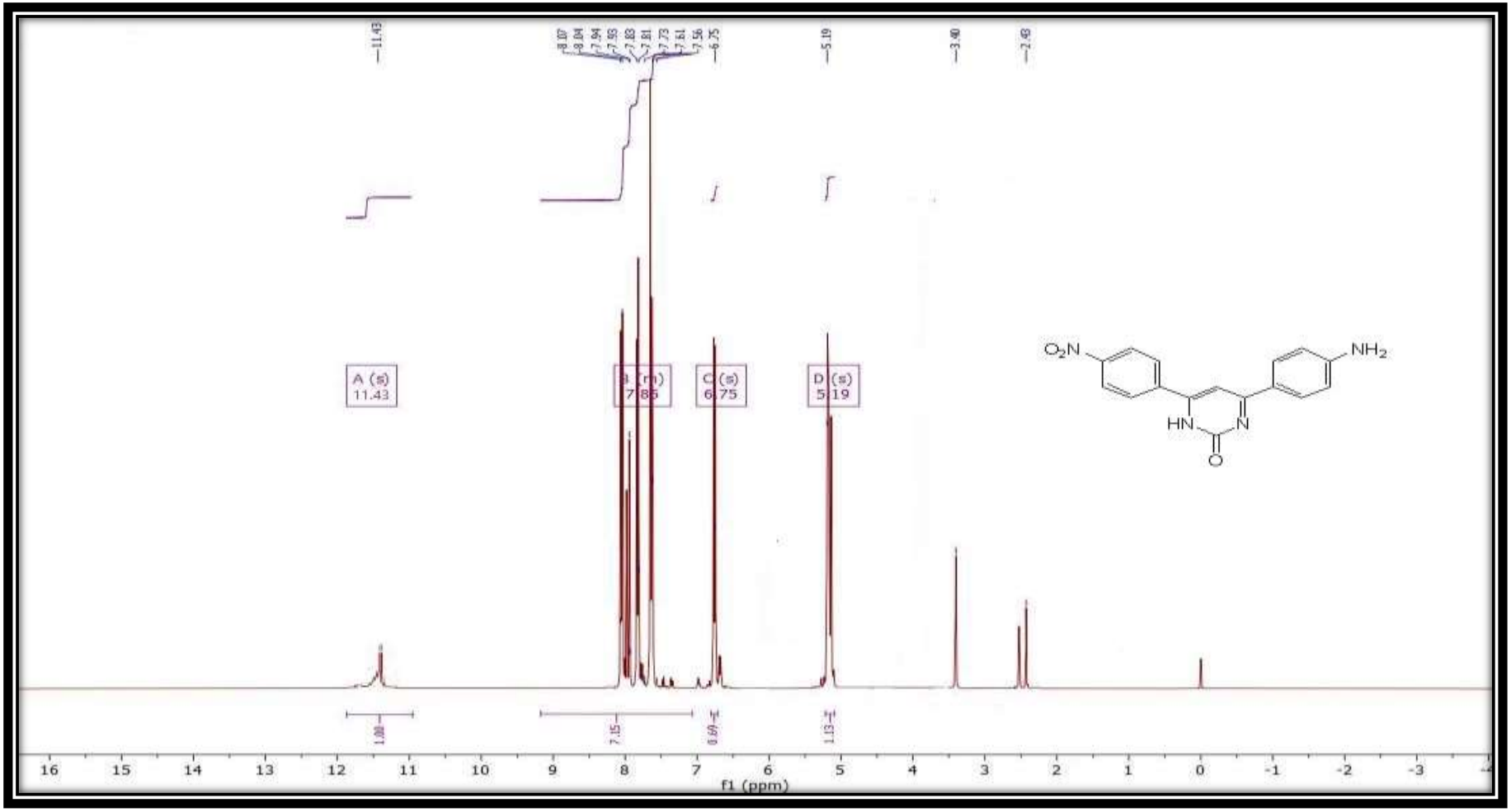


Fig (3.11) : ^{1}H-NMR Spectrum of 4-(4-aminophenyl)-6-(4-nitrophenyl)pyrimidin-2(1H)-one (III)

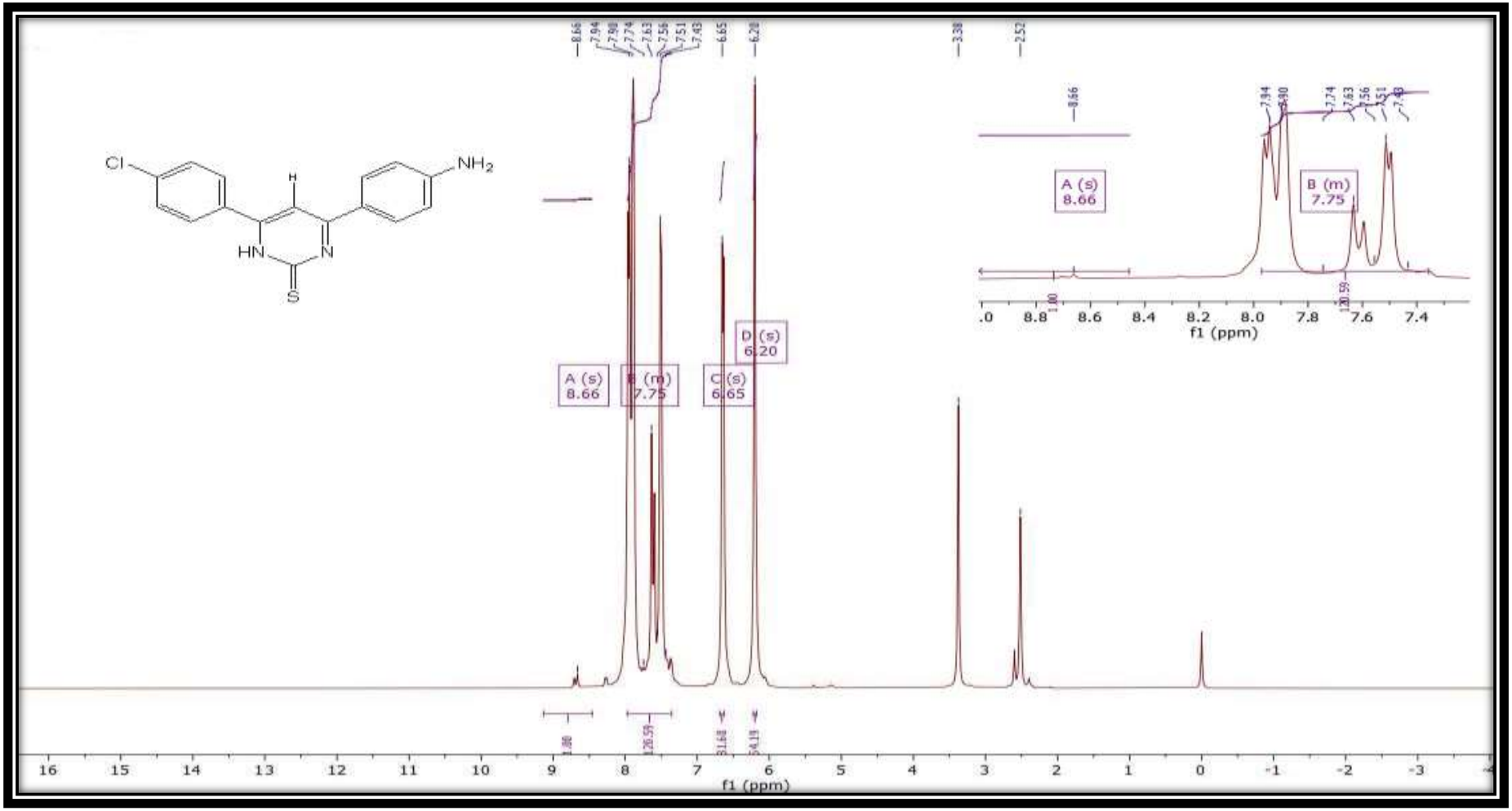


Fig (3.12) : ^{1}H-NMR Spectrum of 4-(4-aminophenyl)-6-(4-chlorophenyl)pyrimidine-2(1H)-thione (IV)

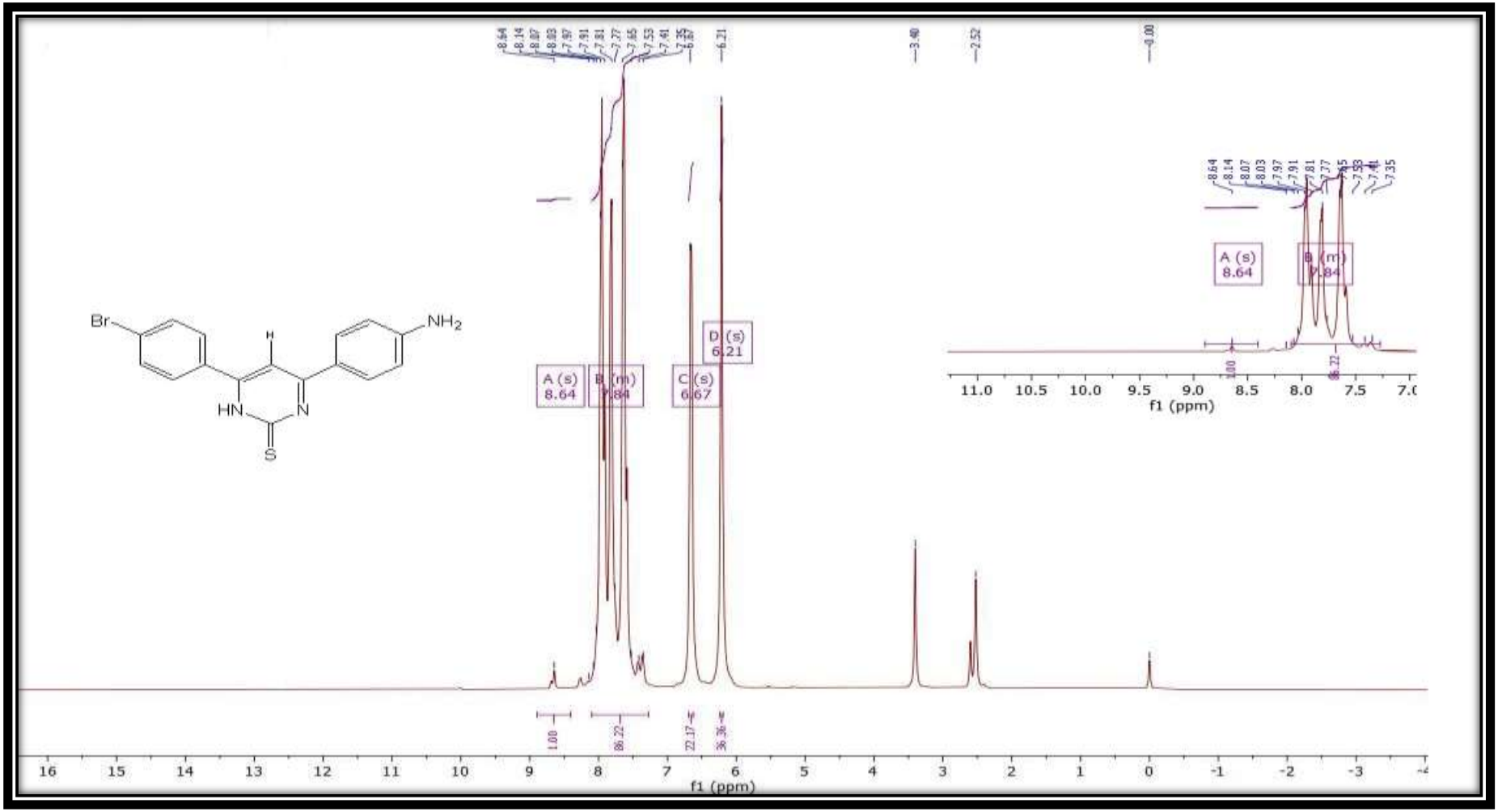


Fig (3.13) : ^{1}H-NMR Spectrum of 4-(4-aminophenyl)-6-(4-bromophenyl)pyrimidine-2(1H)-thione (V)

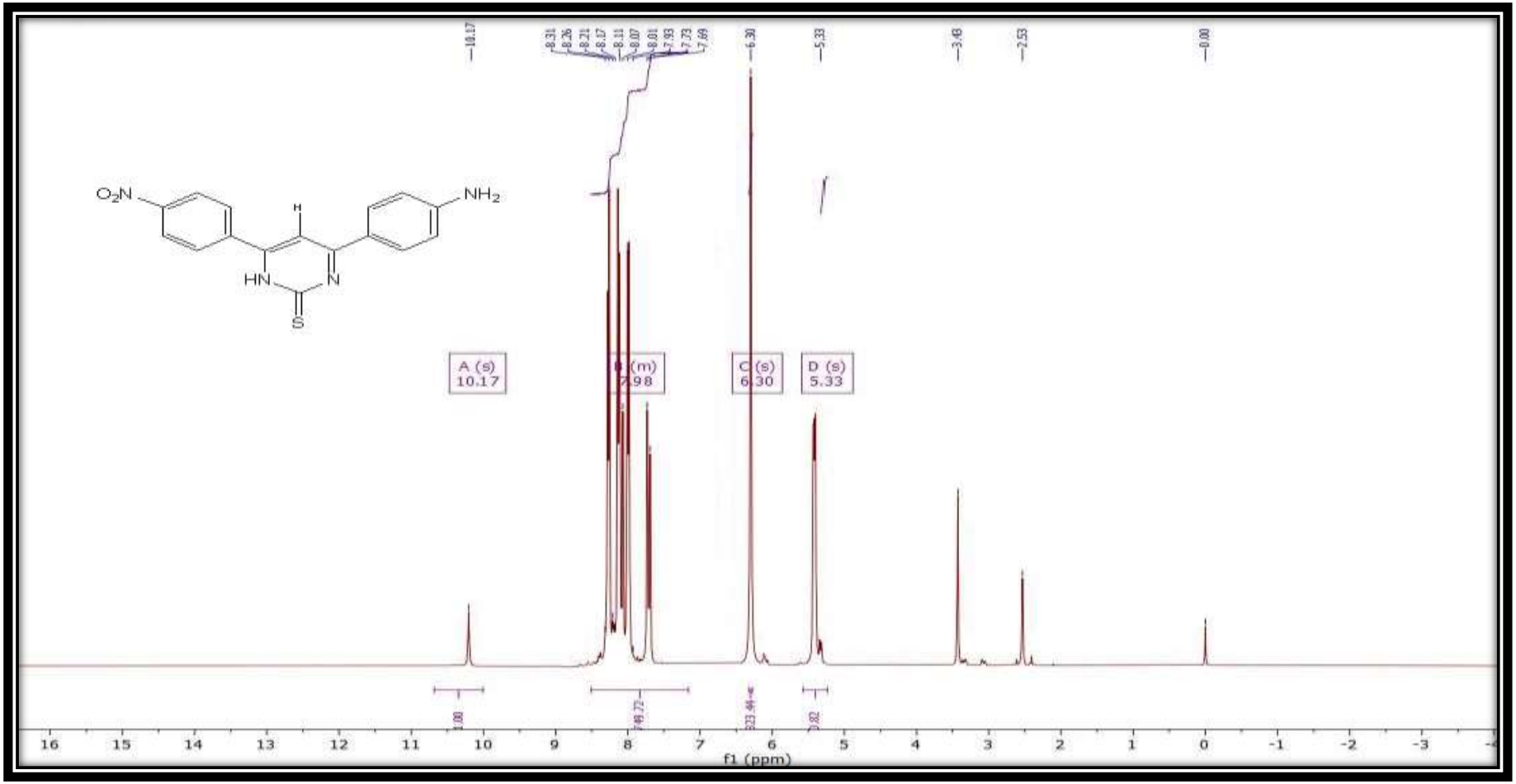


Fig (3.14) : ^{1}H-NMR Spectrum of 4-(4-aminophenyl)-6-(4-nitrophenyl)pyrimidine-2(1H)-thione (VI)

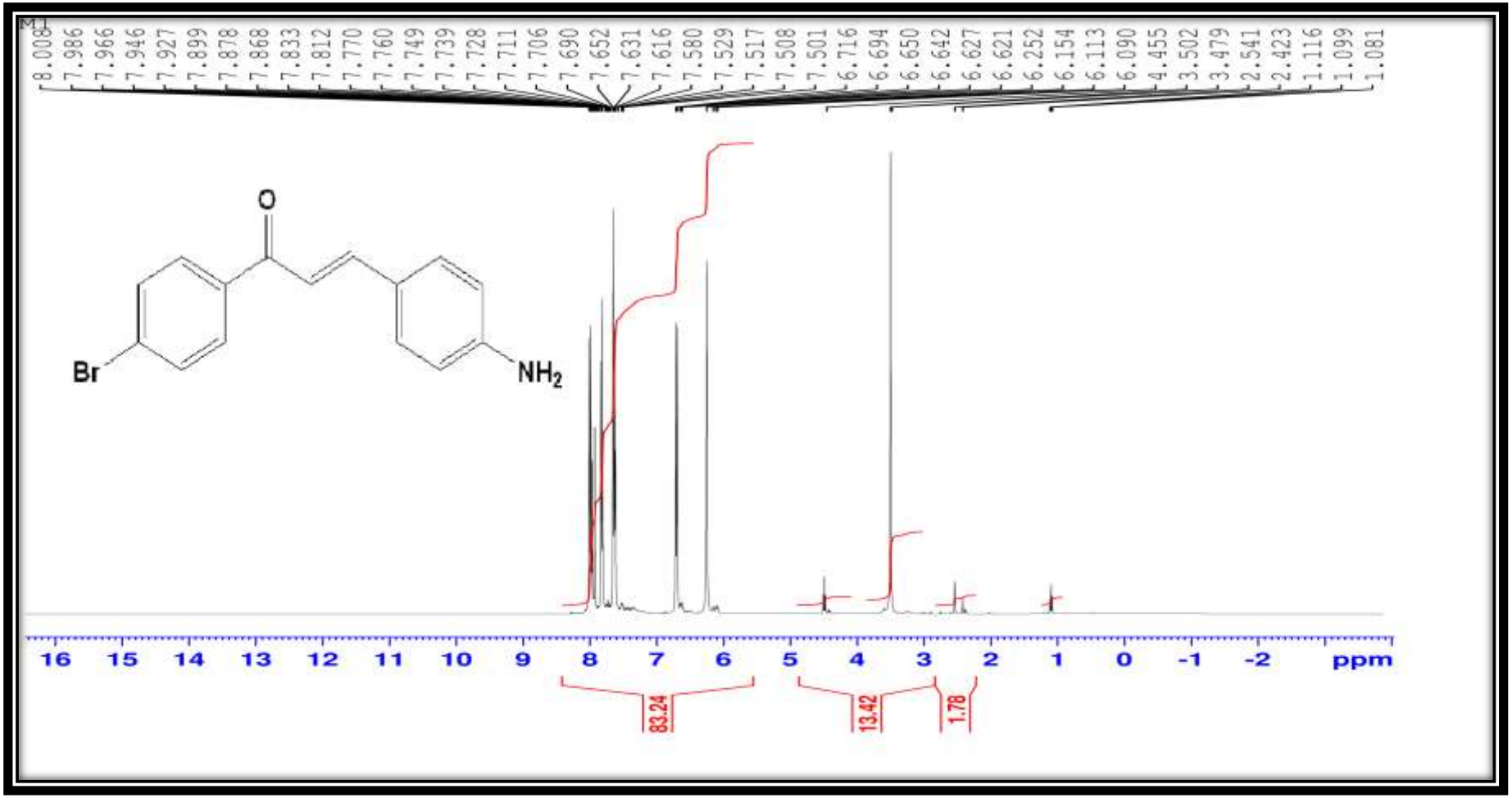


Fig (3.15) : ^{1}H-NMR Spectrum of (E)-3-(4-aminophenyl)-1-(4-bromophenyl)prop-2-en-1-one(VII)

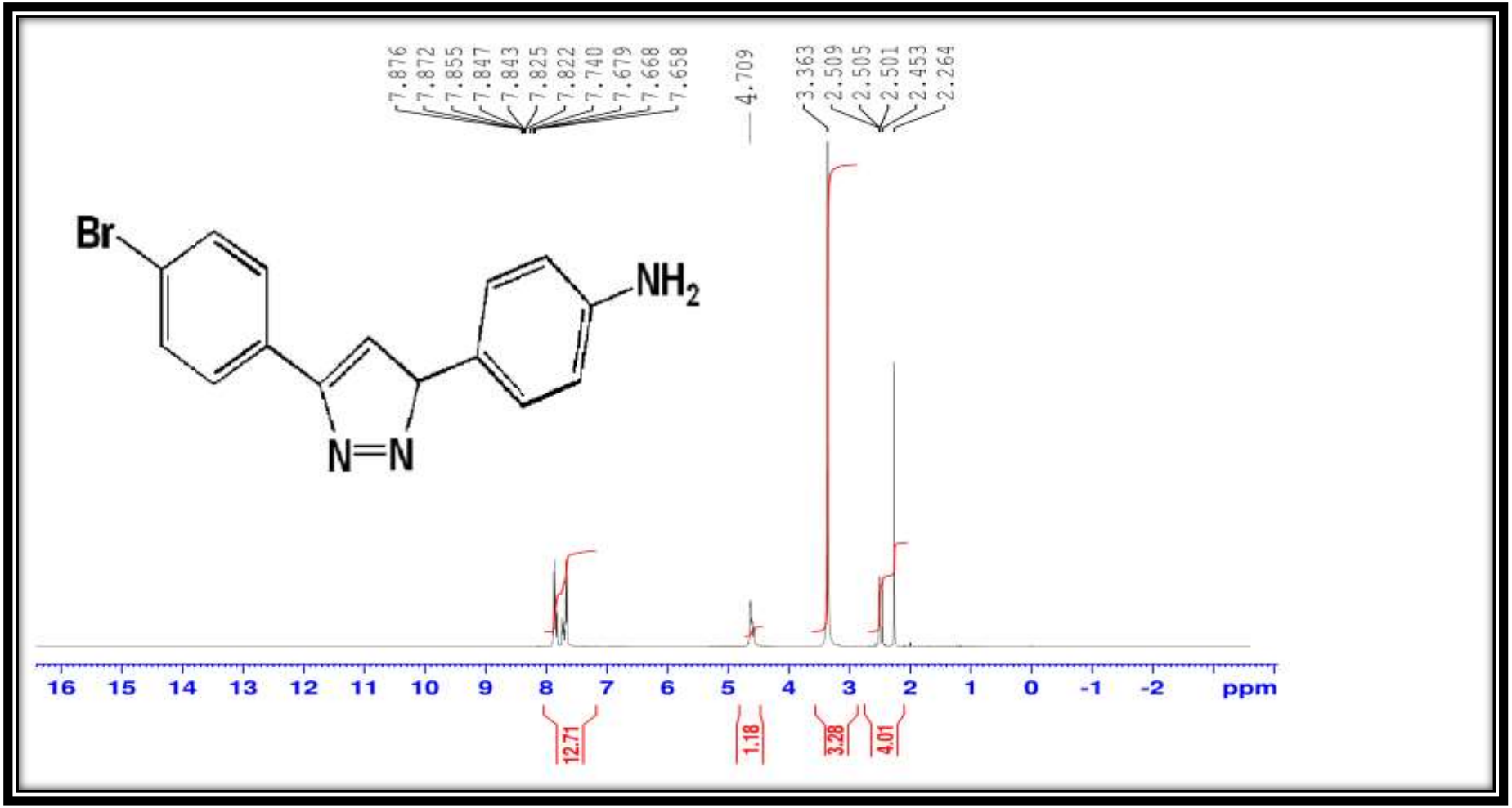


Fig (3.16) : ^{1}H-NMR Spectrum of 4-(3-(4-bromophenyl)-1H-pyrazol-5-yl)aniline(VIII)

Table (3.3) : ^{13}C-NMR spectra data of the starting materials(ppm)

Com. No.	Symbol	C-NH_2	Aromatic	C-N (Heterocycle)	C=N	C=O	C=S	C-X
1	**(I)**	141.62	113.95-151.35	155.90	160.33	187.76	……..	C-Cl 135.89
2	**(II)**	140.49	113.23-140.49	154.47	161.85	186.17	……..	C-Br 125.73
3	**(III)**	140.74	111.27-134.91	152.37	167.39	186.35	……..	C-NO_2 134.91
4	**(IV)**	140.39	113.21-134.86	154.46	166.84	…….	186.17	C-Cl 134.86
5	**(V)**	140.49	113.22-140.49	154.47	161.87	……	186.17	C-Br 125.70
6	**(VI)**	142.26	113.25-139.10	154.72	166.39	……	185.87	C-NO_2 139.10
7	**(VII)**	140.52	113.01-154.48	……..	……	186.24	…….	C-Br 125.73
8	**(VIII)**	145.15	129.05-148.34	148.34	……	……	…….	C-Br 129.28

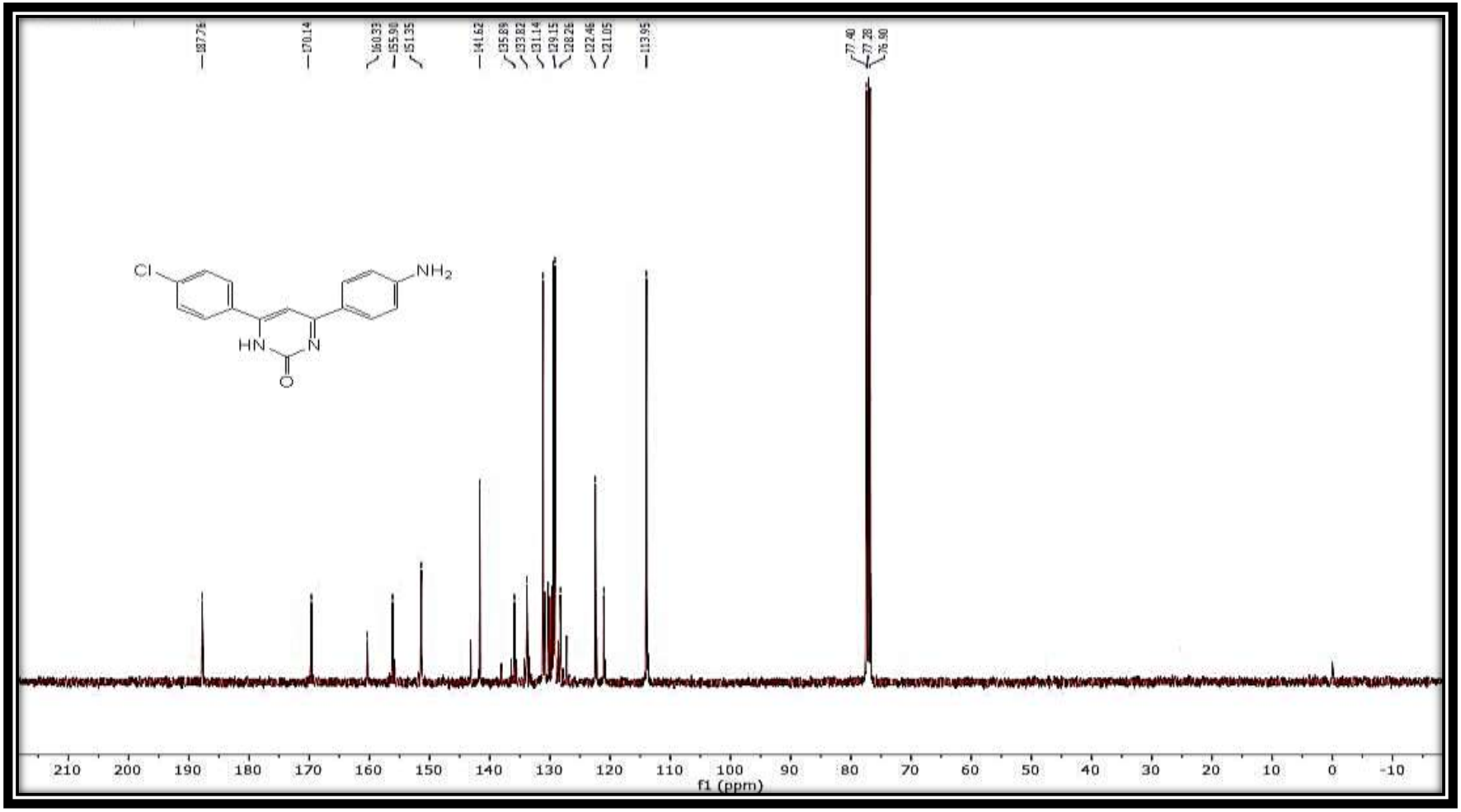


Fig (3.17) : ^{13}C-NMR Spectrum of 4-(4-aminophenyl)-6-(4-chlorophenyl)pyrimidin-2(1H)-one (I)

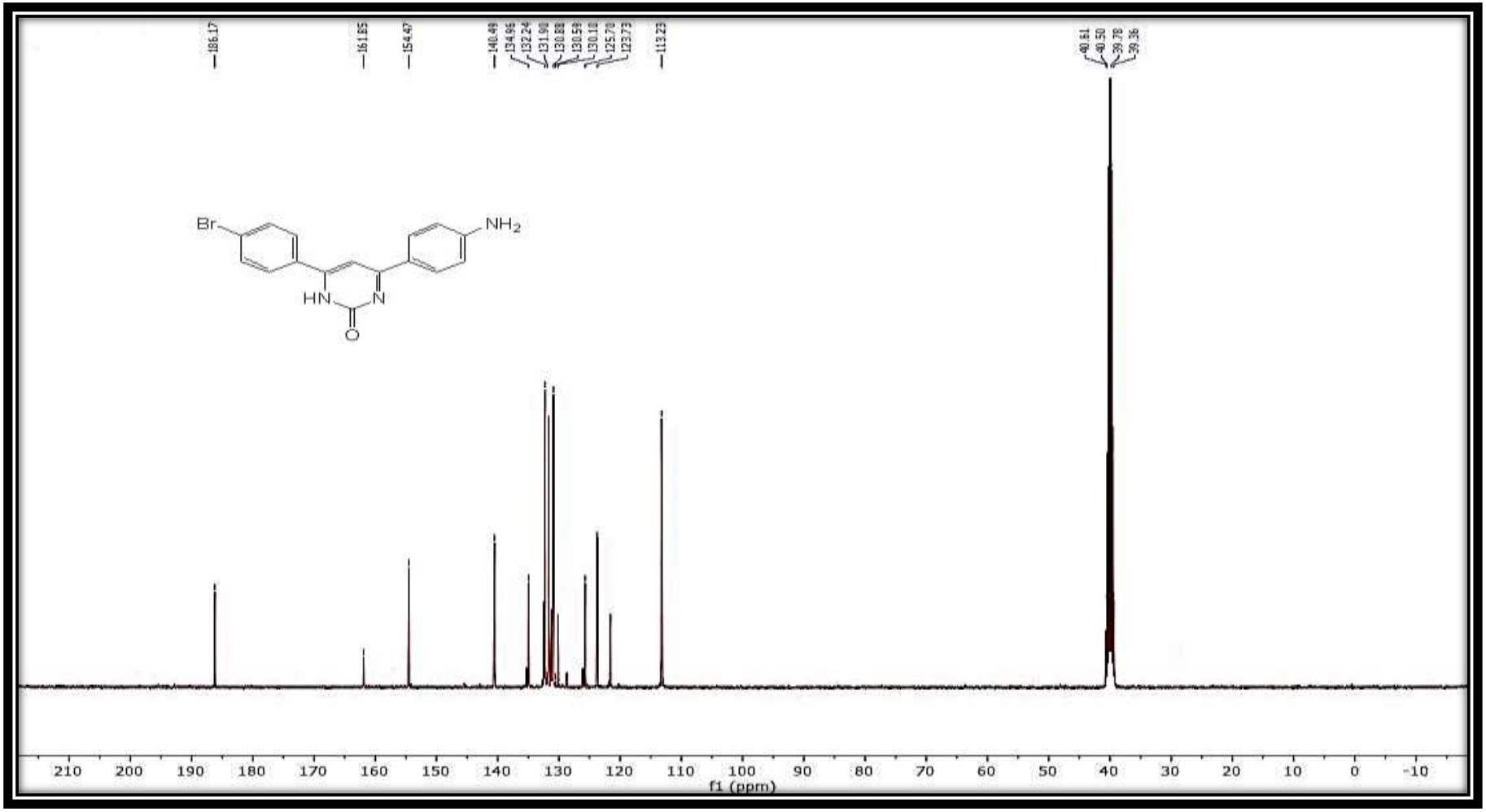


Fig (3.18) : ^{13}C-NMR Spectrum of 4-(4-aminophenyl)-6-(4-bromophenyl)pyrimidin-2(1H)-one (II)

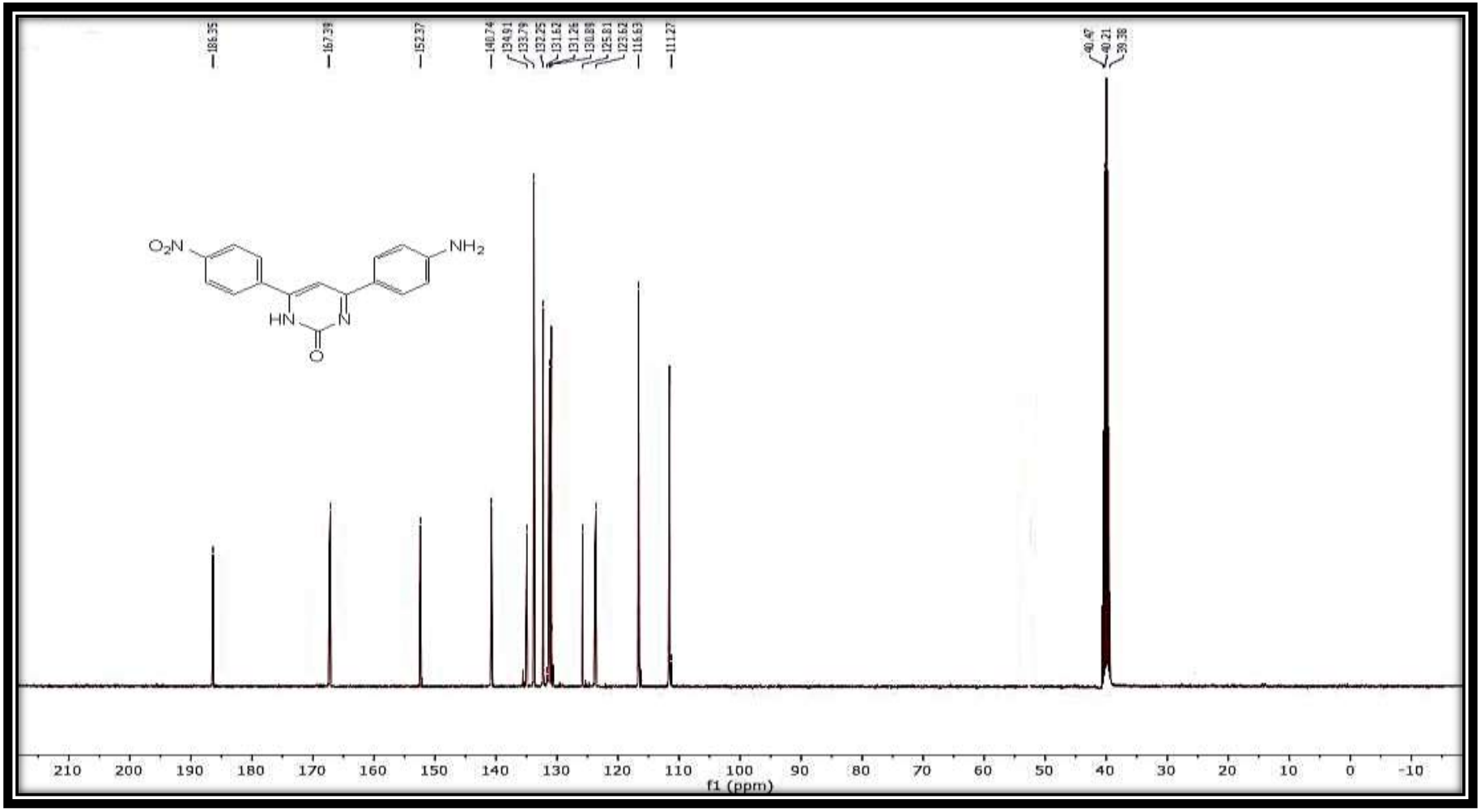


Fig (3.19) : ^{13}C-NMR Spectrum of 4-(4-aminophenyl)-6-(4-nitrophenyl)pyrimidin-2(1H)-one (III)

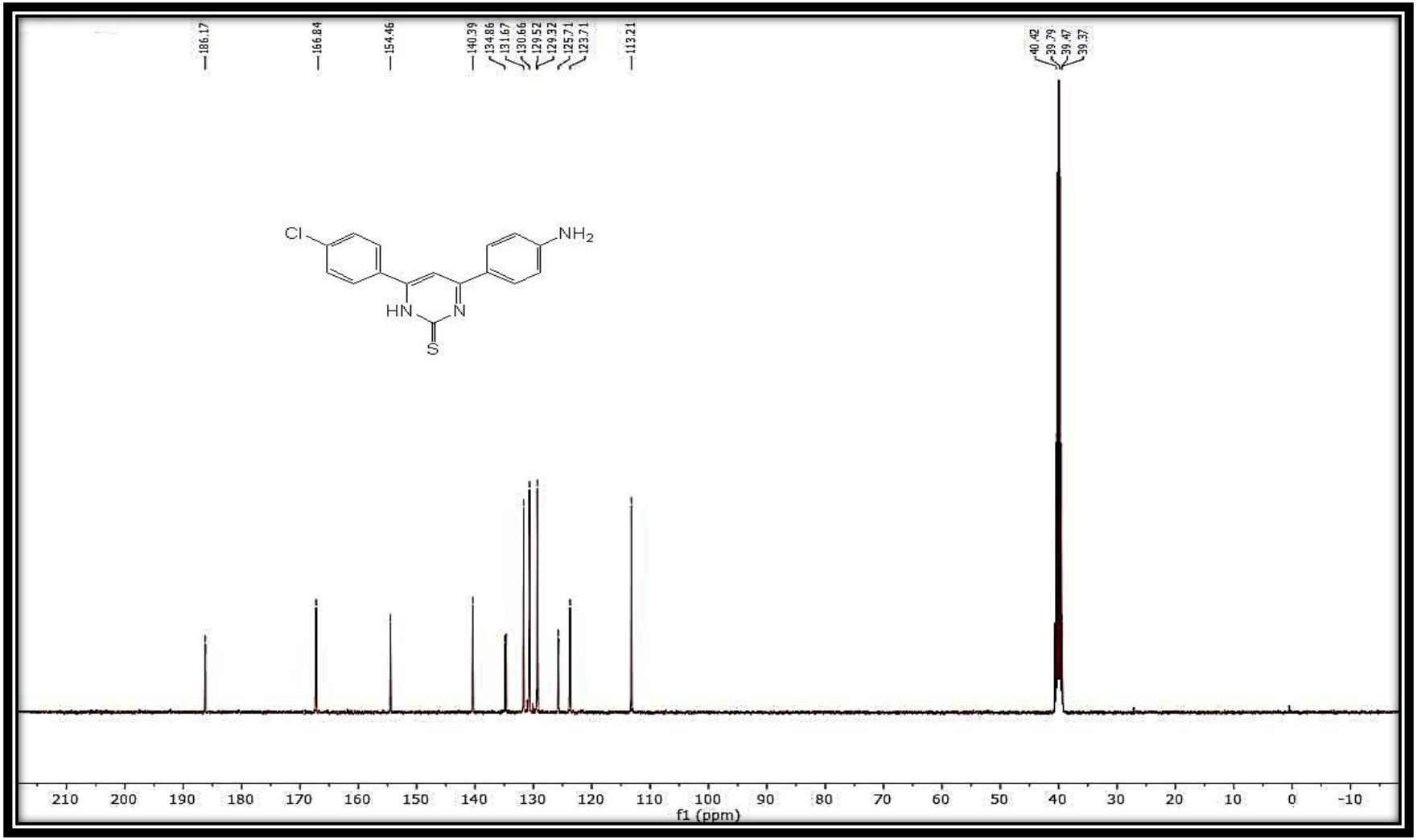


Fig (3.20) : ^{13}C-NMR Spectrum of 4-(4-aminophenyl)-6-(4-chlorophenyl)pyrimidine-2(1H)-thione (IV)

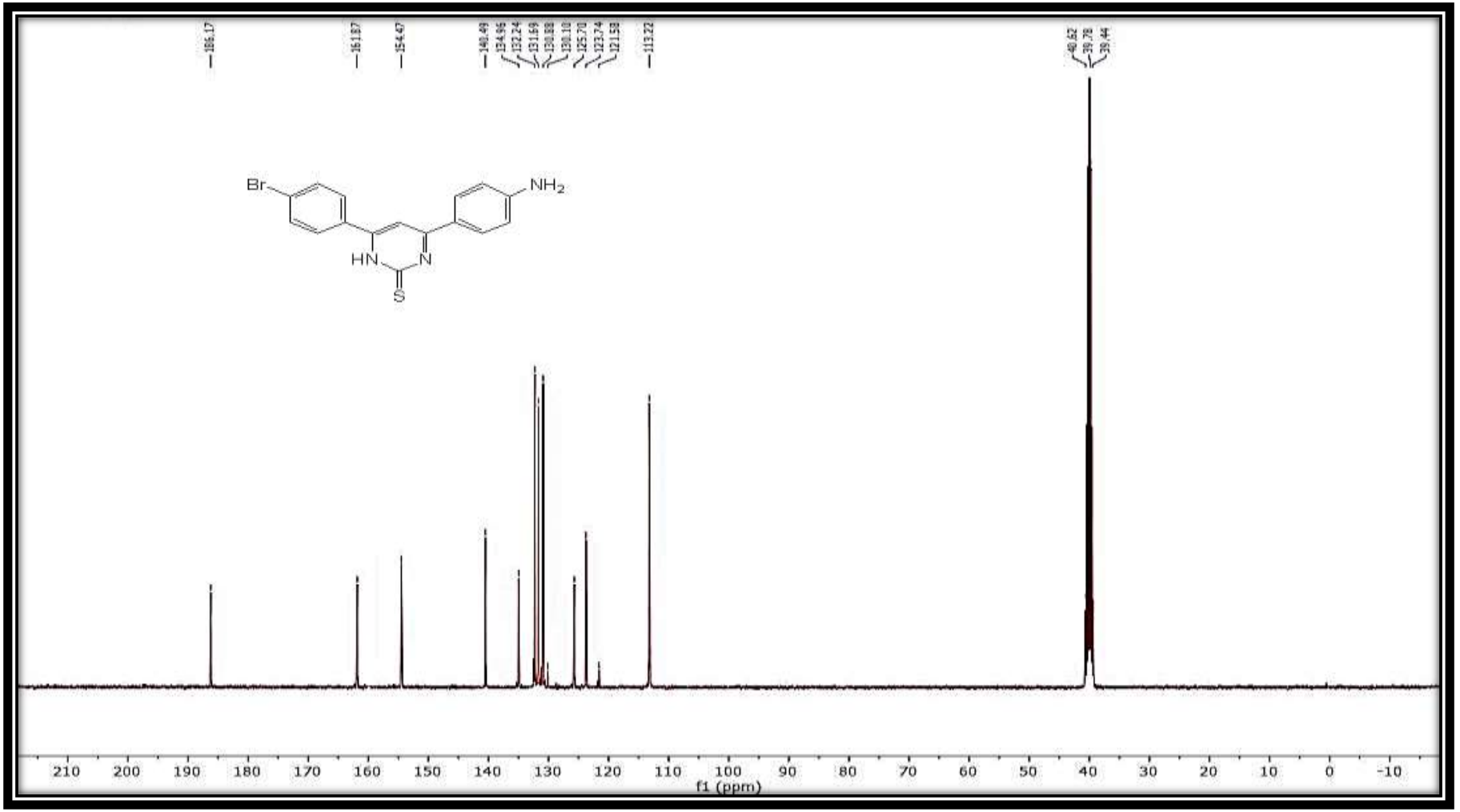


Fig (3.21) : ^{13}C-NMR Spectrum of 4-(4-aminophenyl)-6-(4-bromophenyl)pyrimidine-2(1H)-thione (V)

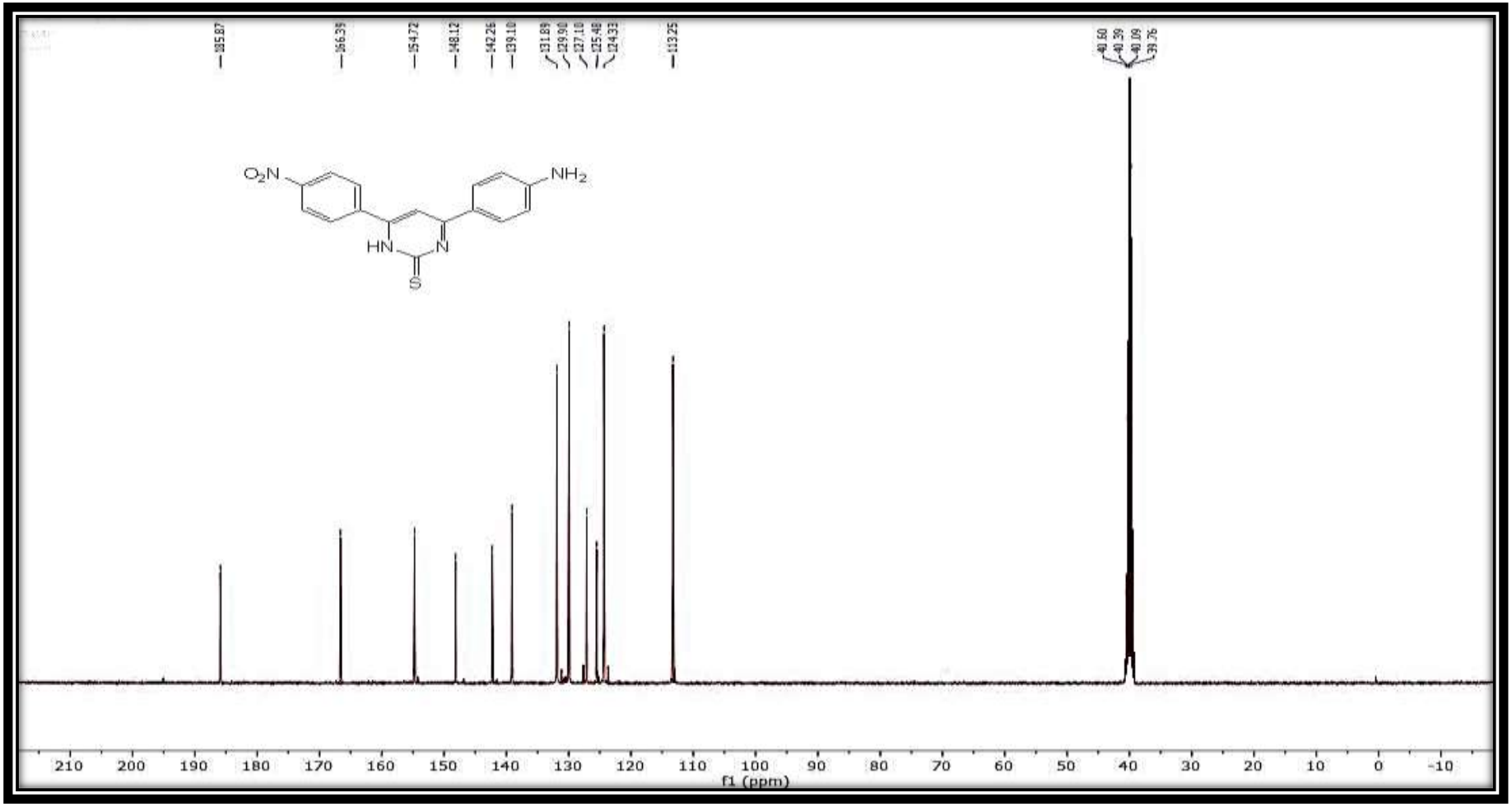


Fig (3.22) : ^{13}C-NMR Spectrum of 4-(4-aminophenyl)-6-(4-nitrophenyl)pyrimidine-2(1H)-thione (VI)

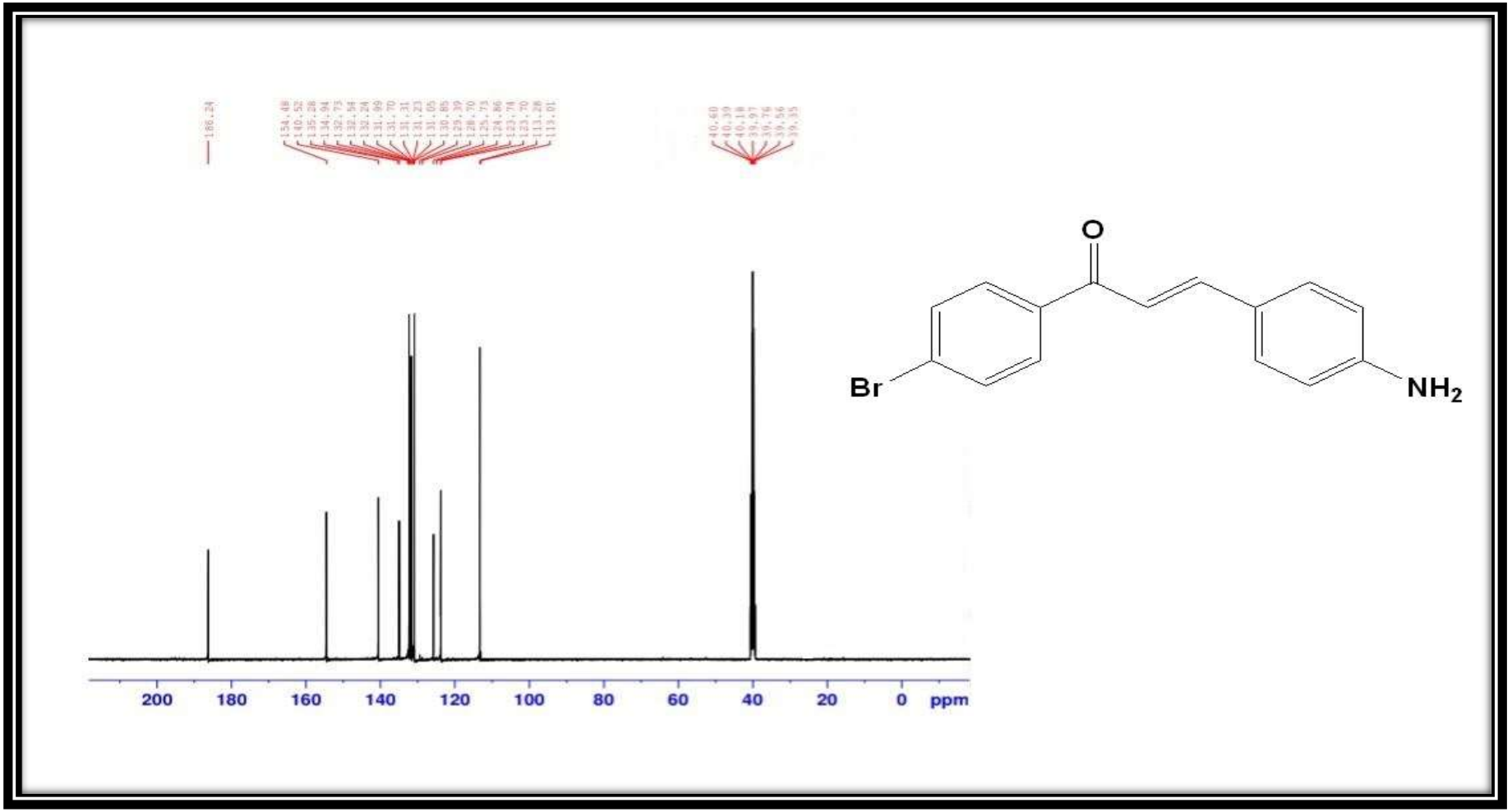


Fig (3.23) : ^{13}C-NMR Spectrum of (E)-3-(4-aminophenyl)-1-(4-bromophenyl)prop-2-en-1-one(VII)

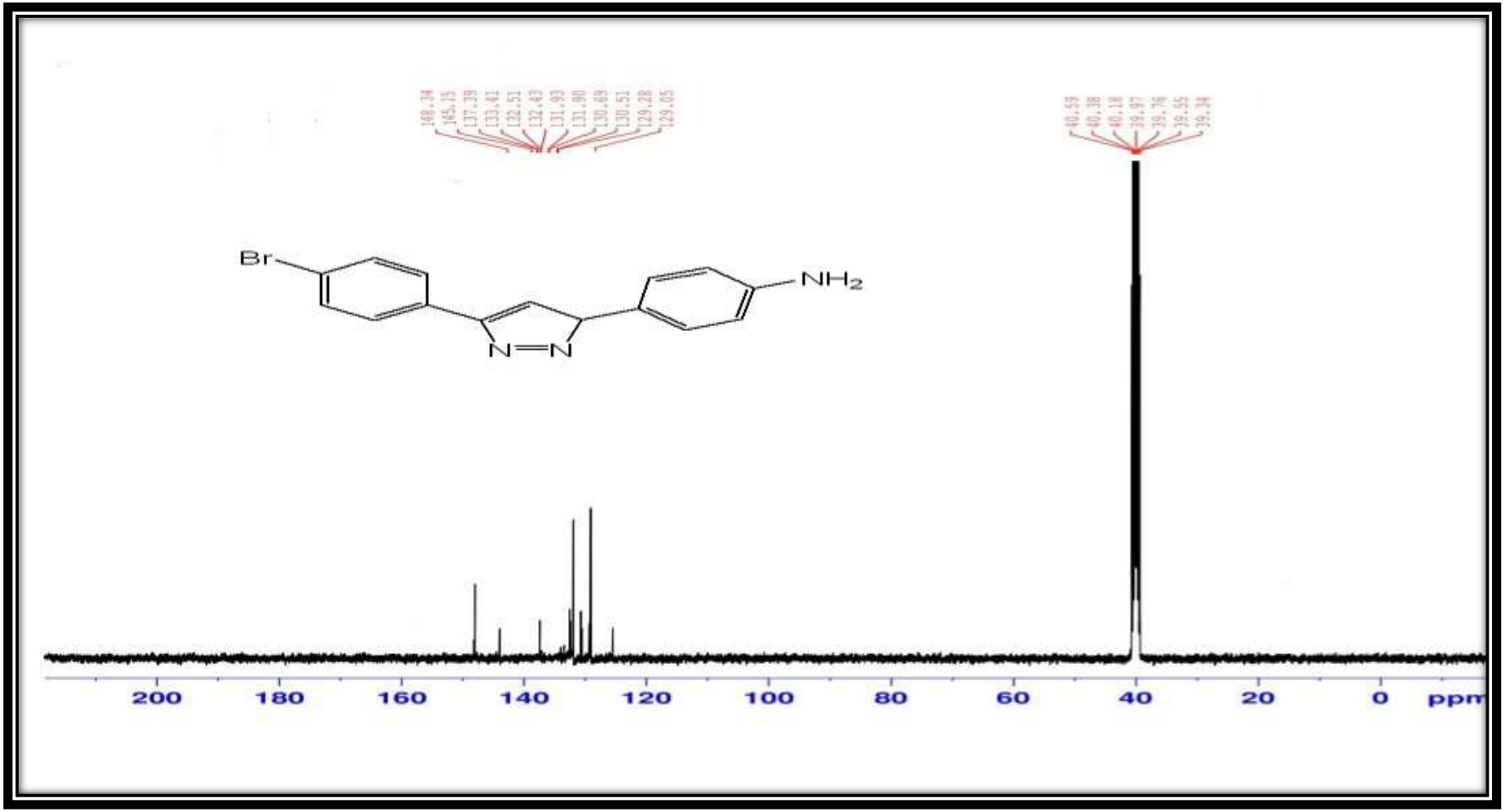


Fig (3.24) : ^{13}C-NMR Spectrum of 4-(3-(4-bromophenyl)-1H-pyrazol-5-yl)aniline (VIII)

3.2.2 Characterization of the synthesized derivatives

3.2.2.1 Elemental Analysis

The Practical values of the Precise elemental analysis for C , H , N , S of the prepared compounds showed that the difference with calculated values falls within the range , which confirms the correctance of the suggested Structures of the prepared samples Table (3.4) .

3.2.2.2 Infrared spectra (IR) of aryl sulfonyl derivatives (H_1-H_{11}) [122]

Infrared spectra of the synthesized compounds (H_1 - H_{11}) showed a similarity in the stretching absorption bands.

These spectra of derivatives (H_1-H_{11}) showed the monosappearance of one of the stretching vibration bands into a group (NH_2) which appeared within the range (3118.90-3487.30) cm^{-1}, Table (3.1). On the other hand, new medium bands appeared within the range (1400.32-1485.19) cm^{-} , which belongs to the stretching vibration of the S = O of sulfonyl group, which confirmed the occurence of a monosubstitution reaction between the amino groups of the compounds (**I-VIII**) and benzenesulfonyl chloride or P-toluene sulfonyl chloride. The other stretching vibrations of the prepared derivatives (H_1-H_{11}) are occur within the ranges (3219.19-3369.64) ,(3037.99-3128.54),(2840.61-2972.01) ,(1653.00-1660.71) ,(1595.18-1616.35),(1487.17-1598.99), (1328.95-1344.38) , (1157.33-1222.87) and (663.51-1344.38) cm^{-1} which are corresponding with –NH , Ar-H , Aliph-H , C=O , C=N ,C=C , C-N , C=S and C-X groups respectively , as illustrated in Table (3.5) and Figs (3.25-3.43).

3.2.2.3 Infrared spectra (IR) of allyl derivatives (H_{12}-H_{18})

The Spectra of N- allylated derivatives (H_{12}-H_{18}) are characterized by (nine) bands corresponding to the stretching vibrations of the –NH , Ar-H , Aliph-H , C=O , C=N ,C=C , C-N, C=S and C-x groups which occur within the ranges (3215.34-3655.23),(3037.99-3086.11),(2846.39-2980.02) , (1641.48-1647.26),(1589.40-1651.07),(1504.53-1606.70),(1329.00-1348.29),

(1174.65-1188.15) and (686.66-1338.60) cm^{-1} respectively.

We also notice that these spectra showed the absorption of a group NH- and this indicates that the reaction between (**I-VI, VIII**) and allyl bromide is mono substitution, as shown in Table (3.5) and Figs. (3.44-3.62).

Table (3.4) : Elemental analysis of the products

No.	Symbol	Molecular formula	Mol. Wt g/mole	C %		H %		N %		S %	
				Cal.	Fou.	Cal.	Fou.	Cal.	Fou.	Cal.	Fou.
1	**H_{10}**	$C_{22}H_{18}BrN_3O_2S$	464.16	56.45	56.00	3.84	3.64	8.97	9.11	6.84	6.59
2	**H_{11}**	$C_{21}H_{16}BrN_3O_2S$	454.15	55.53	55.93	3.52	3.63	9.24	9.44	7.05	7.19
3	**H_{12}**	$C_{19}H_{16}ClN_3O$	337.63	67.58	67.91	4.73	4.60	12.43	12.09	……..	…….
4	**H_{13}**	$C_{19}H_{16}BrN_3O$	382.08	59.72	60.10	4.18	4.28	10.99	10.71	……..	…….
5	**H_{14}**	$C_{19}H_{16}N_4O_3$	348.16	65.54	65.32	4.59	4.64	16.08	15.70	……..	…….
6	**H_{15}**	$C_{19}H_{16}ClN_3S$	353.70	64.51	64.80	4.52	4.66	11.87	11.60	9.06	9.25
7	**H_{16}**	$C_{19}H_{16}BrN_3S$	398.15	57.31	56.92	4.01	3.89	10.54	10.20	8.05	8.34
8	**H_{17}**	$C_{19}H_{16}N_4O_2S$	364.23	62.64	62.32	4.39	4.48	15.37	14.88	8.80	9.01
9	**H_{18}**	$C_{18}H_{16}BrN_3$	354.08	61.05	60.78	4.51	4.58	11.86	12.17	……..	……

Table (3.5) : Infrared spectra (IR) of the product (cm^{-1})

No.	Symbol	-NH-	Ar-H	Aliph-H	C=O	C=N	C=C	C=S	S=O	C-N	C-X
1	**H_1**	3356.14 (w)	3126.91 (m)	$-CH_3$ 2972.01(w)	1653.00 (s)	1597.95 (s)	1490.97 (m)	……	1409.97 (m)	1328.95 (s)	812.03 (s) X=Cl
2	**H_2**	3369.64 (w)	3128.54 (m)	$-CH_3$ 2970.08(w)	1653.00 (s)	160863 (s)	1597.06 (m)	……..	1402.25 (m)	1328.95 (s)	663.51(s) X=Br
3	**H_3**	3313.71 (s)	3078.39, 3043.67(w)	$-CH_3$ 2930.05(w)	1660.71 (s)	1604.77 (s)	1519.91 (s)	…….	1406.11 (m)	1342.46 (s)	1342.46(s) $X=NO_2$
4	**H_4**	3265.49 (m)	3080.32, 3035.96(w)	…….	…….	1604.77 (s)	1595.13 (s)	1219.01 (m)	1402.25 (s)	1344.38 (m)	813.96 (s) X=Cl
5	**H_5**	3277.06 (m)	3101.54 (w)	……	…….	1606.70 (s)	1510.26 (s)	1219.01 (m)	1400.32 (s)	1344.38 (s)	688.59(m) X=Br
6	**H_6**	3273.20 (m)	3113.11 (w)	……	…….	1604.77 (m)	1514.12 (s)	1222.87 (s)	1400.32 (w)	1342.46 (s)	1342.46(m) $X=NO_2$
7	**H_7**	3365.78 (m)	3082.25 (w)	…….	1654.92 (s)	1604.77 (s)	1595.13 (s)	……	1402.25 (m)	1344.38 (s)	719.45(m) X=Cl
8	**H_8**	3277.06 (s)	3082.25 (w)	…….	1656.85 (s)	1606.70 (s)	1598.99 (s)	…..	1400.32 (s)	1344.38 (s)	688.54(m) X=Br
9	**H_9**	3219.19 (s)	3066.82 (w)	……..	1656.85 (s)	1616.35 (m)	1597.06 (m)	…..	1411.89 (m)	1344.38 (s)	1344.38(s) $X=NO_2$

Table (3.5) : Continued

No.	Symbol	-NH-	Ar-H	Aliph-H	C=O	C=N	C=C	C=S	S=O	C-N	C-X
10	**H_{10}**	3286.81 (w)	3068.85 (w)	$-CH_3$ 2840.61(w)	……	1595.18 (w)	1487.17 (w)	1157.33 (m)	1426.20 (w)	1329.00 (m)	677.04 (m) X=Br
11	**H_{11}**	3230.87 (w)	3037.99 (w)	…….	…….	1602.90 (m)	1504.53 (m)	1159.26 (s)	1420.12 (m)	1334.78 (m)	686.68(m) X=Br
12	**H_{12}**	3655.23 (w)	3074.63 (w)	2918.40 (w)	1647.26 (w)	1589.40 (m)	1535.39 (w)	…….	…….	1329.00 (m)	804.34(m) X=Cl
13	**H_{13}**	3348.54 (m)	3049.56 (w)	2912.61 (w)	1641.48 (m)	1602.90 (m)	1550.82 (s)	…….	……..	1348.29 (w)	777.34(w) X=Br
14	**H_{14}**	3360.00-3307.92(m)	3078.39 (w)	2927.94, 2846.93(w)	1647.21 (s)	1604.77 (s)	1556.55 (s)	……	……	1338.60 (s)	1338.60(s) X=NO_2
15	**H_{15}**	3321.42, (m)	3086.11 (w)	2980.02, 2920.23(w)	…….	1649.14 (s)	1507.77 (m)	1178.58 (m)	…..	1344.38 (m)	810.10(m) X=Cl
16	**H_{16}**	3215.34 (m)	3078.39 (w)	2924.09, 2864.29(w)	…….	1651.07 (s)	1606.70 (m)	1188.15 (m)	…….	1334.74 (m)	686.66(m) X=Br
17	**H_{17}**	3361.93, 3302.13(m)	3080.32 (w)	2920.23, 2854.65(w)	…….	1647.21 (s)	1597.27 (m)	1174.65 (m)	……..	1338.60 (m)	1338.60(m) X=NO_2
18	**H_{18}**	3230.87 (w)	3037.99 (w)	2914.54 (w)	…….	1602.90 (m)	1504.53 (m)	……..	…….	1334.78 (m)	686.68(m) X=Br

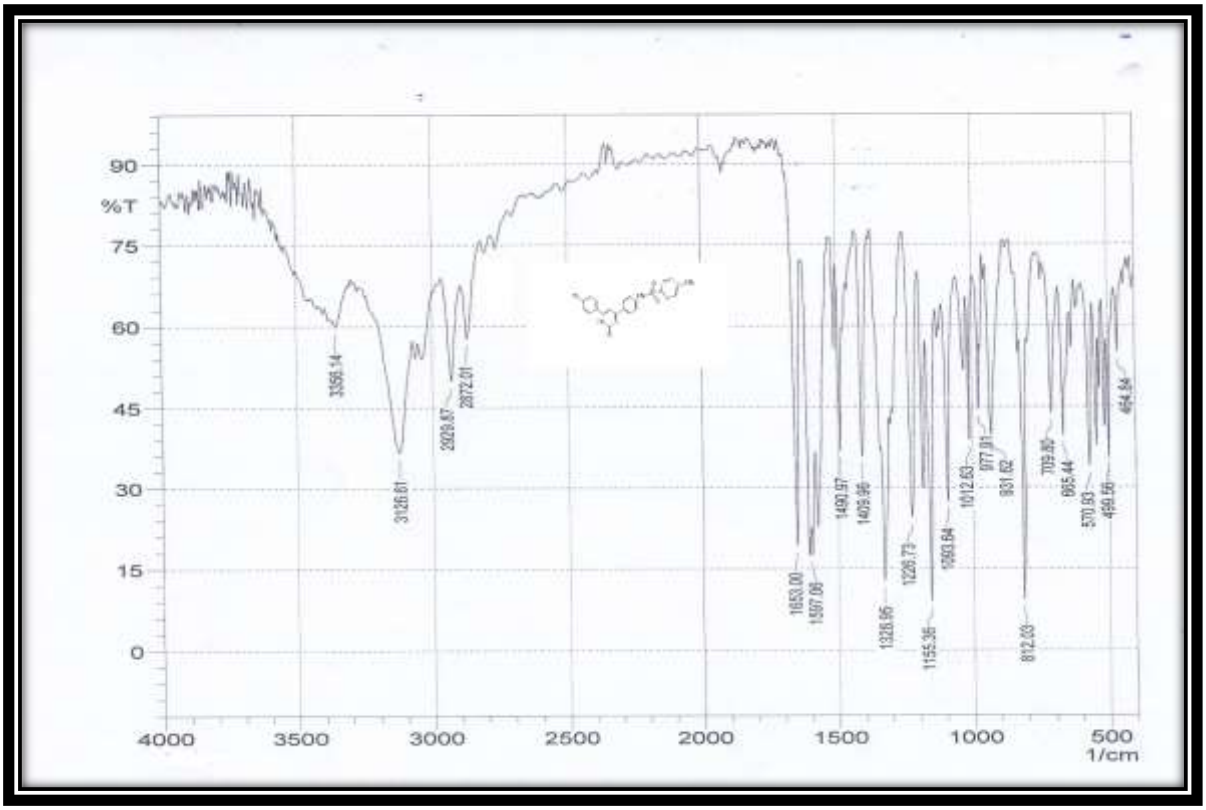


Fig (3.25) : IR spectrum of compound (H_1)

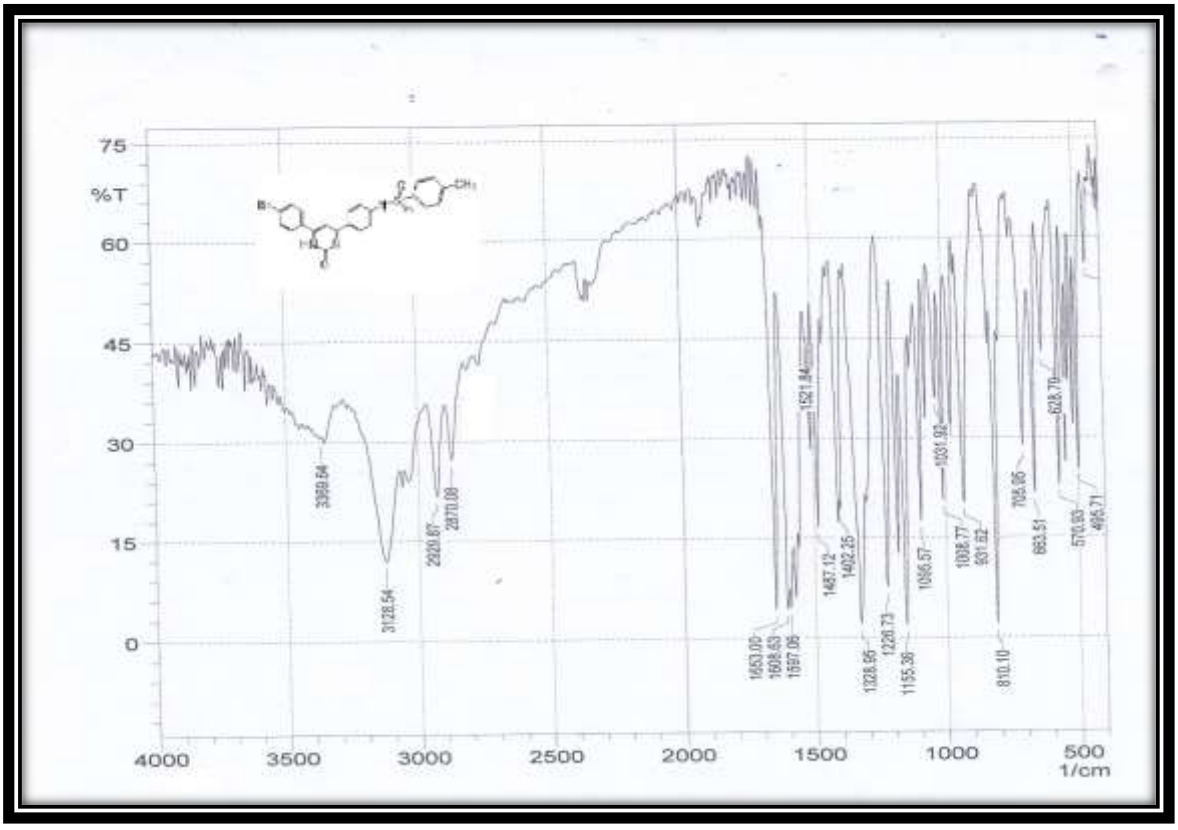


Fig (3.26) : IR spectrum of compound (H_2)

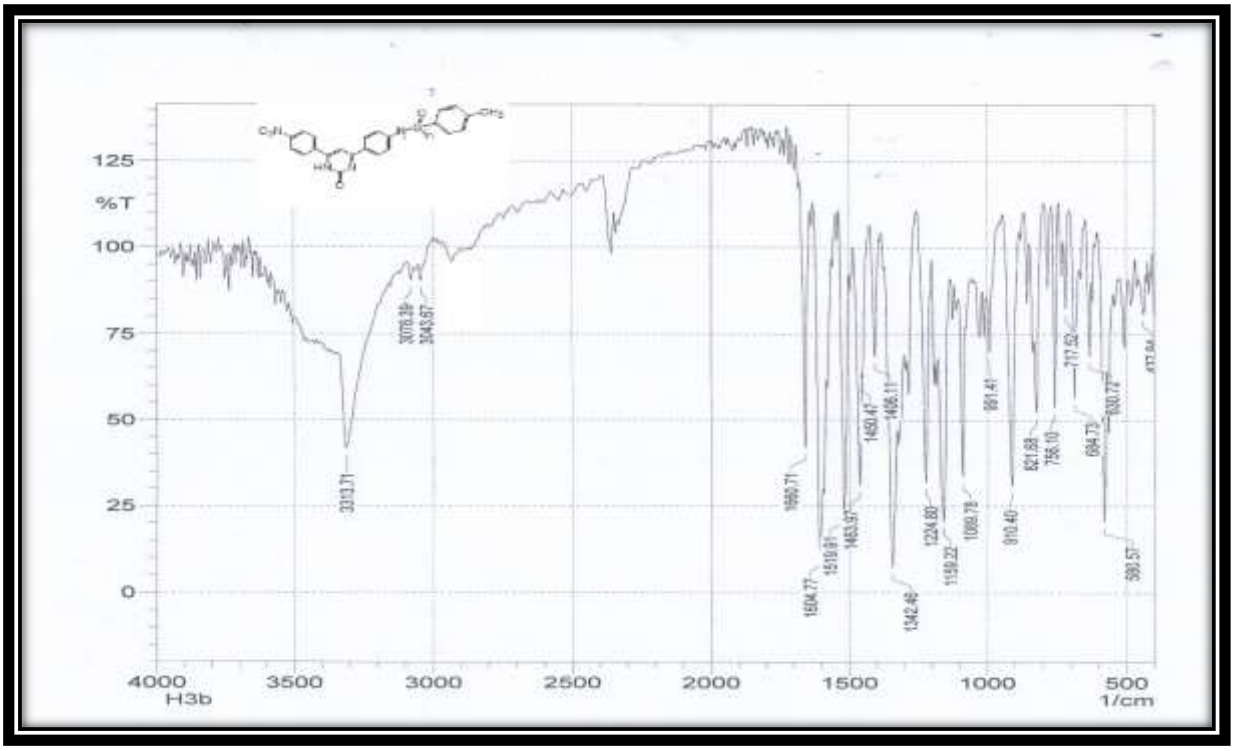


Fig (3.27) : IR spectrum of compound (H_3)

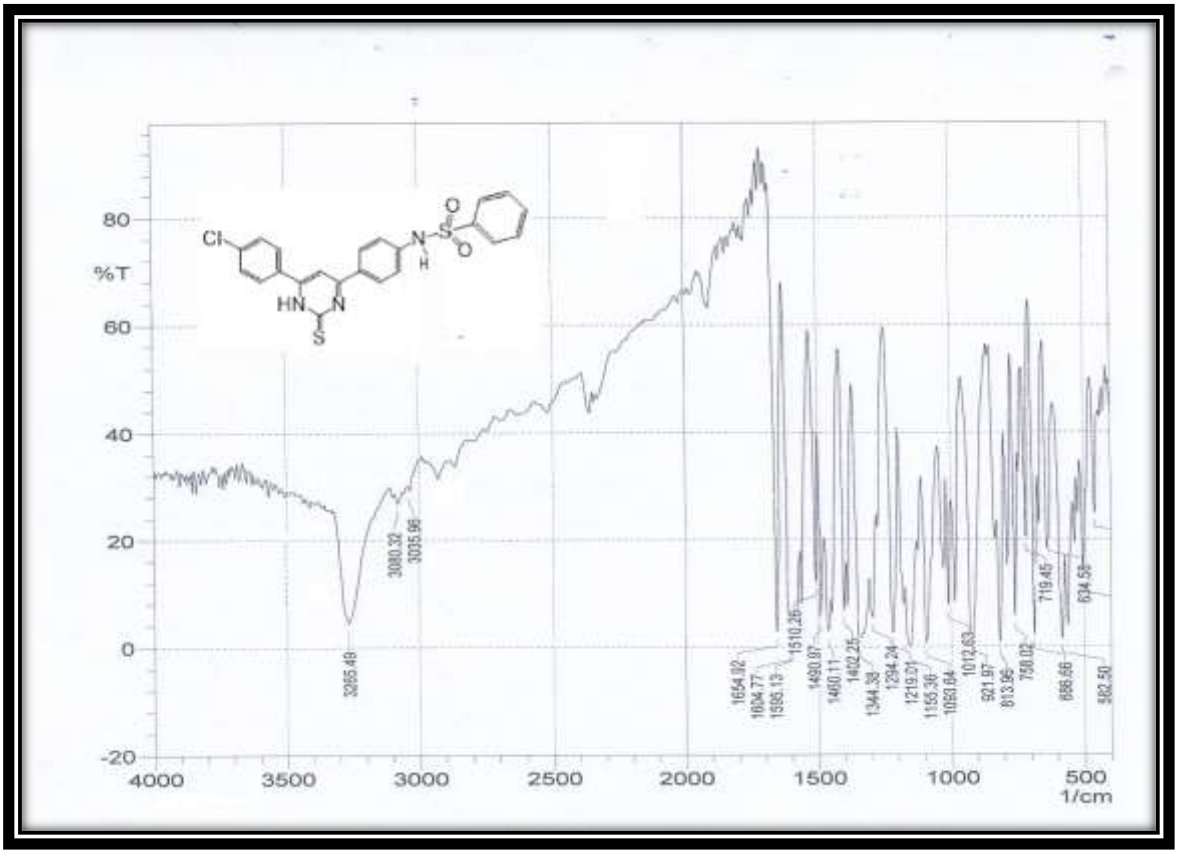


Fig (3.28) : IR spectrum of compound (H_4)

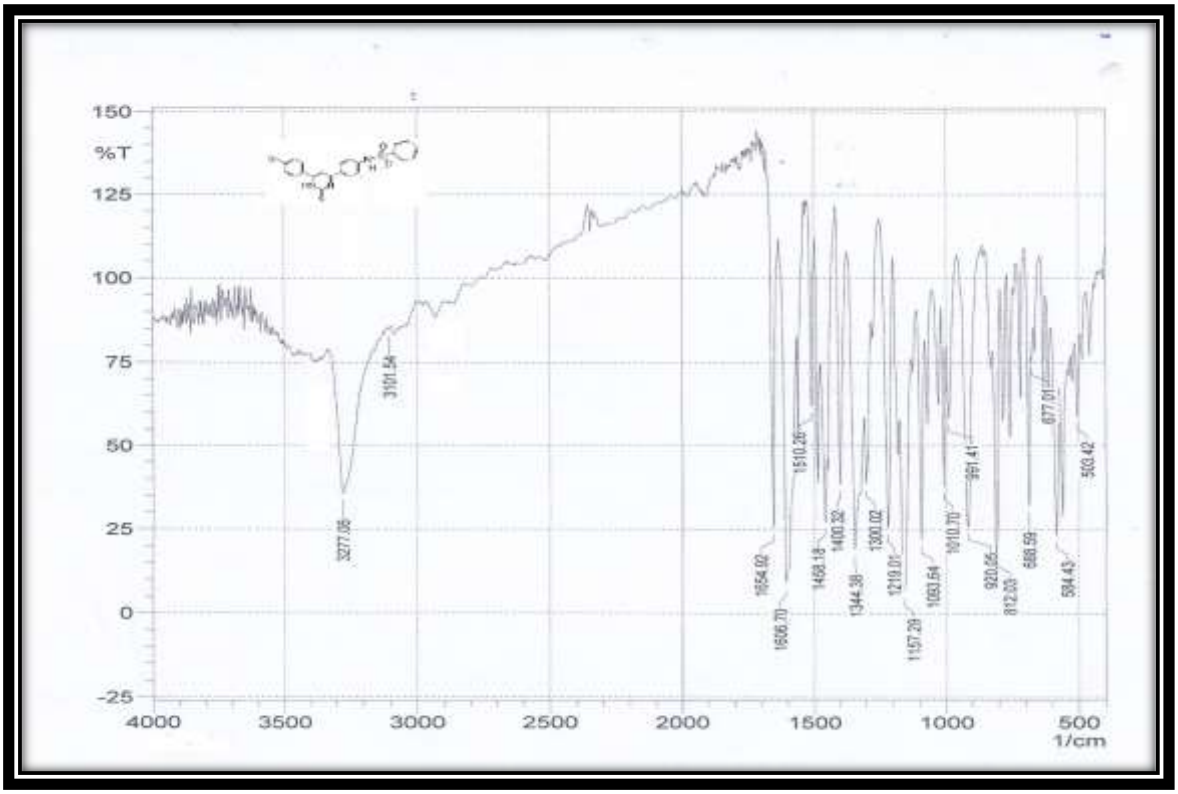


Fig (3.29) : IR spectrum of compound (H_5)

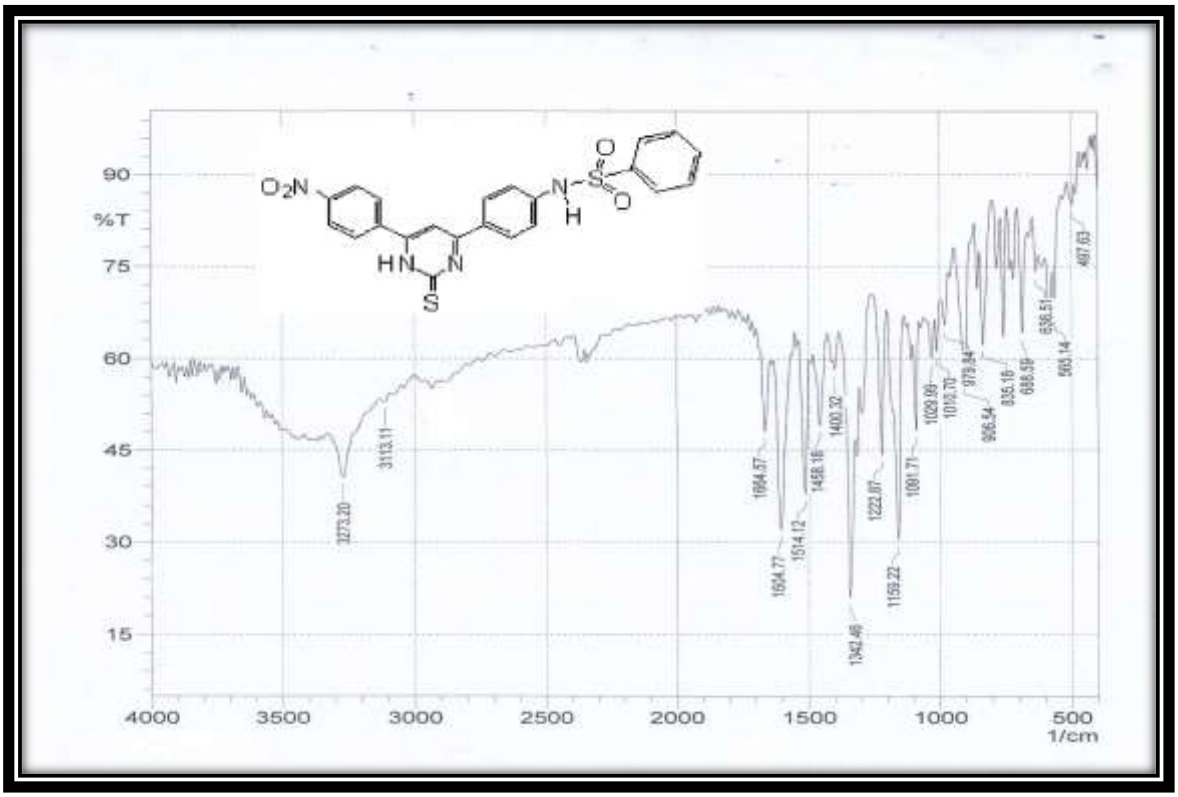


Fig (3.30) : IR spectrum of compound (H_6)

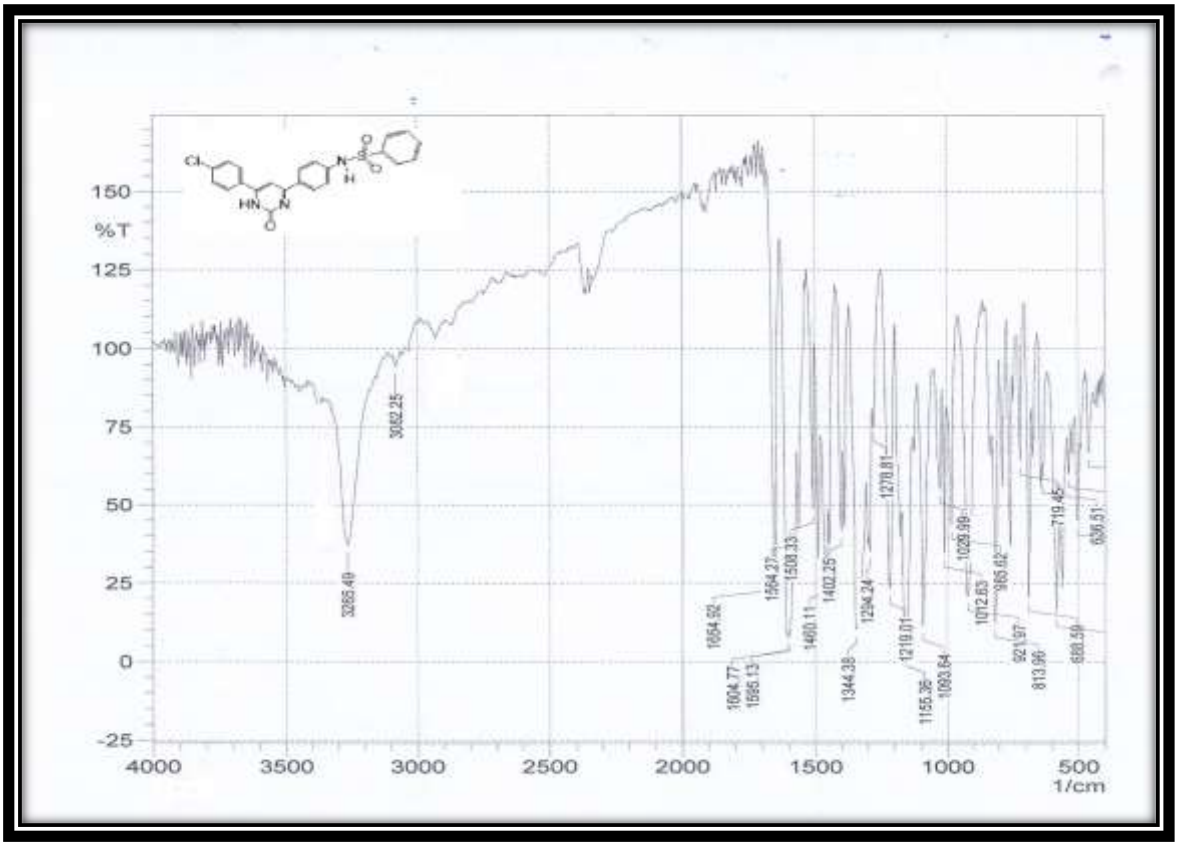


Fig (3.31) : IR spectrum of compound (H_7)

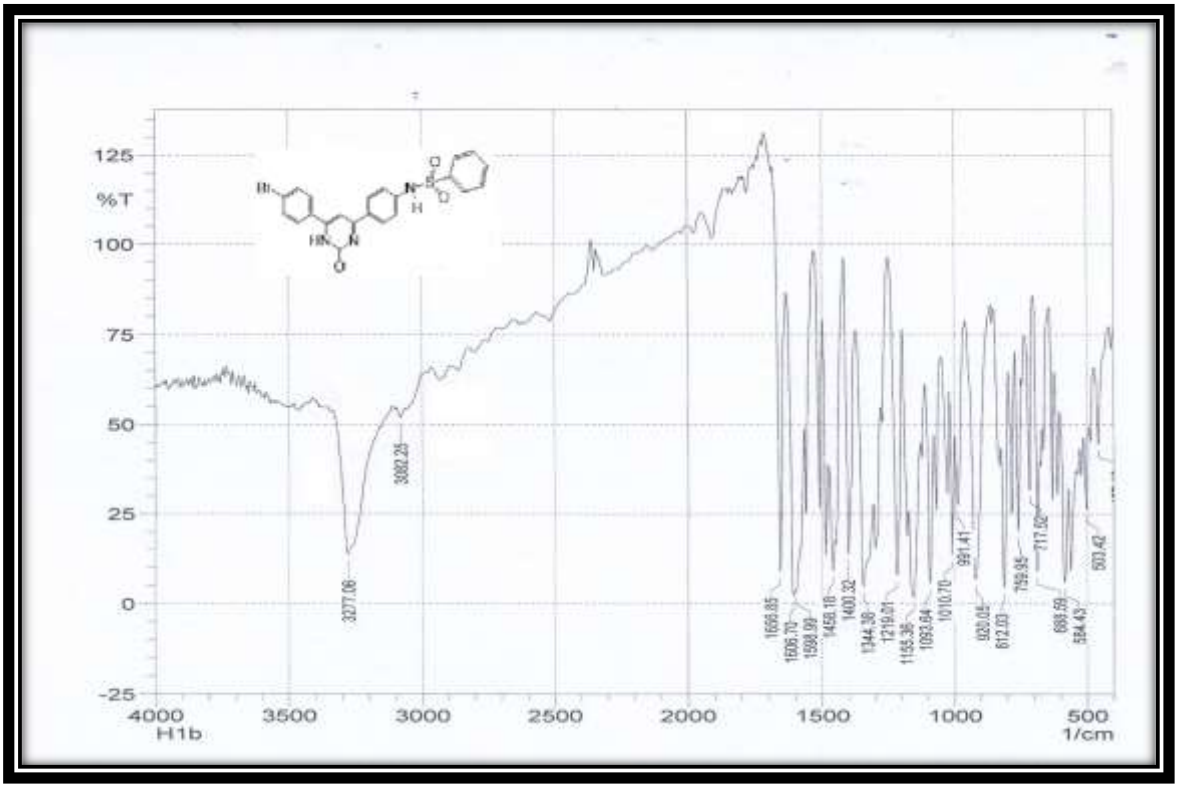


Fig (3.32) : IR spectrum of compound (H_8)

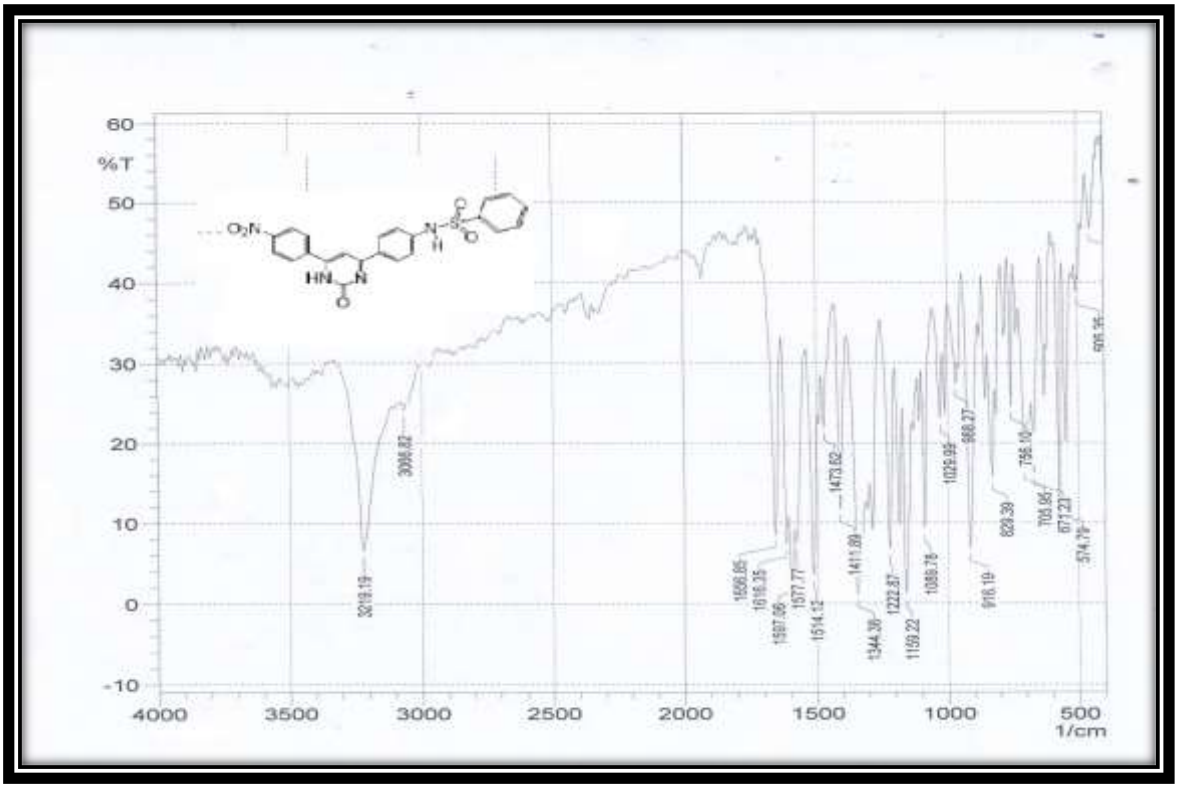


Fig (3.33) : IR spectrum of compound (H_9)

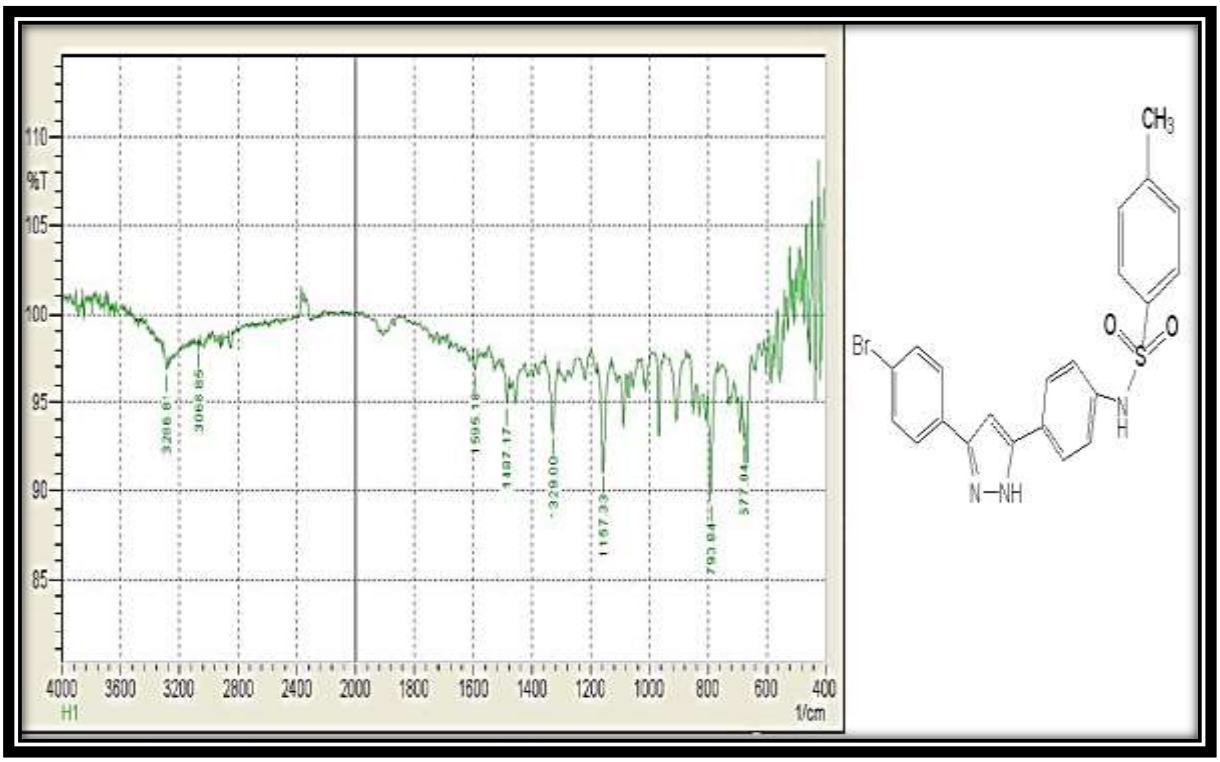


Fig (3.34) : IR spectrum of compound (H_{10})

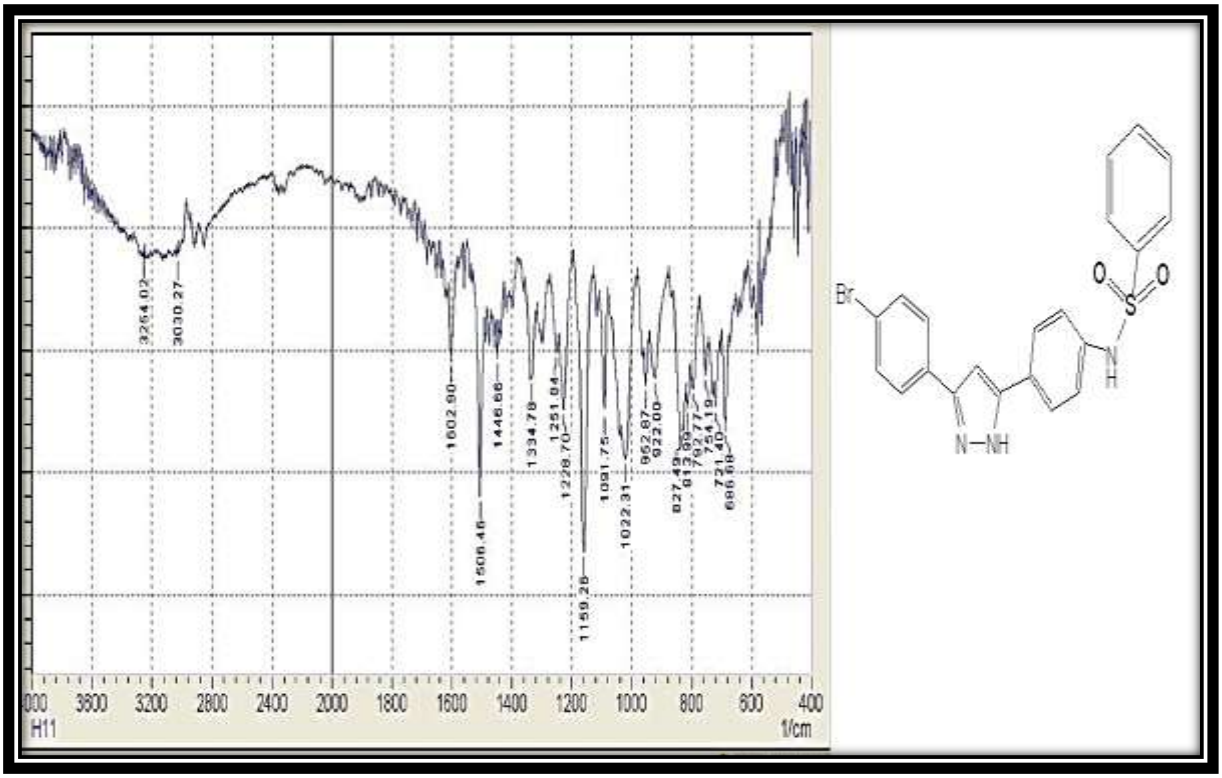


Fig (3.35) : IR spectrum of compound (H_{11})

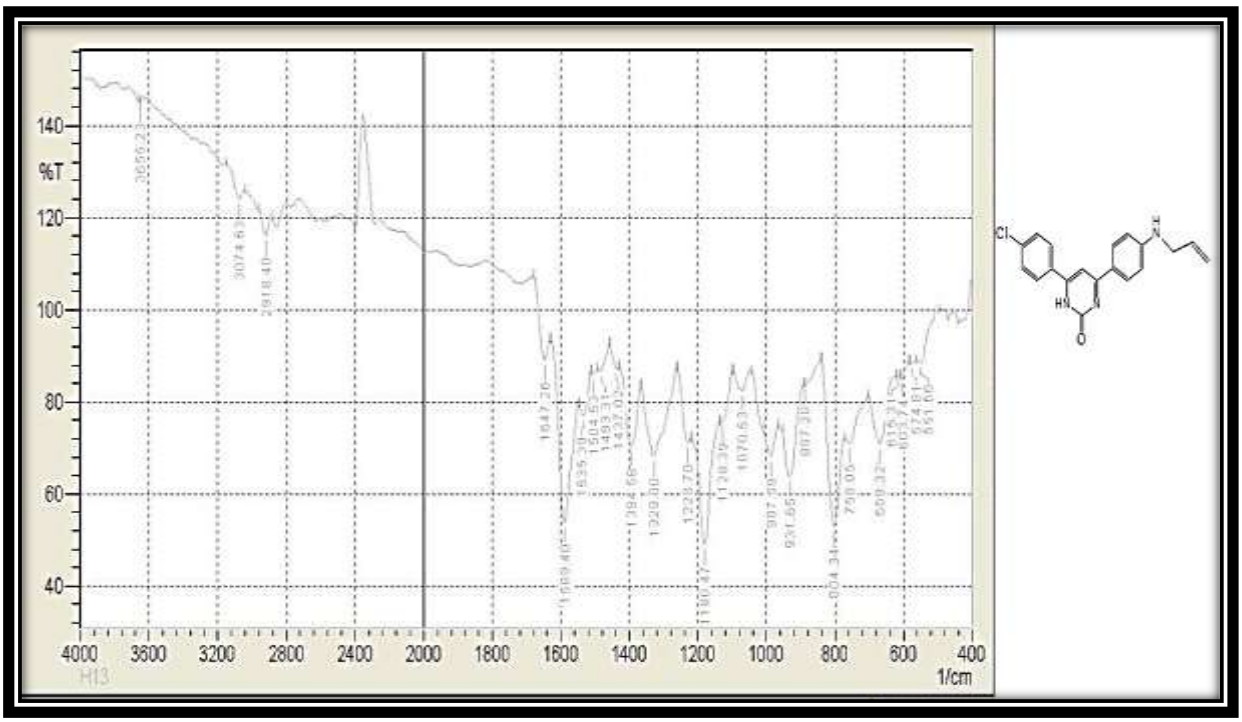


Fig (3.36) : IR spectrum of compound (H_{12})

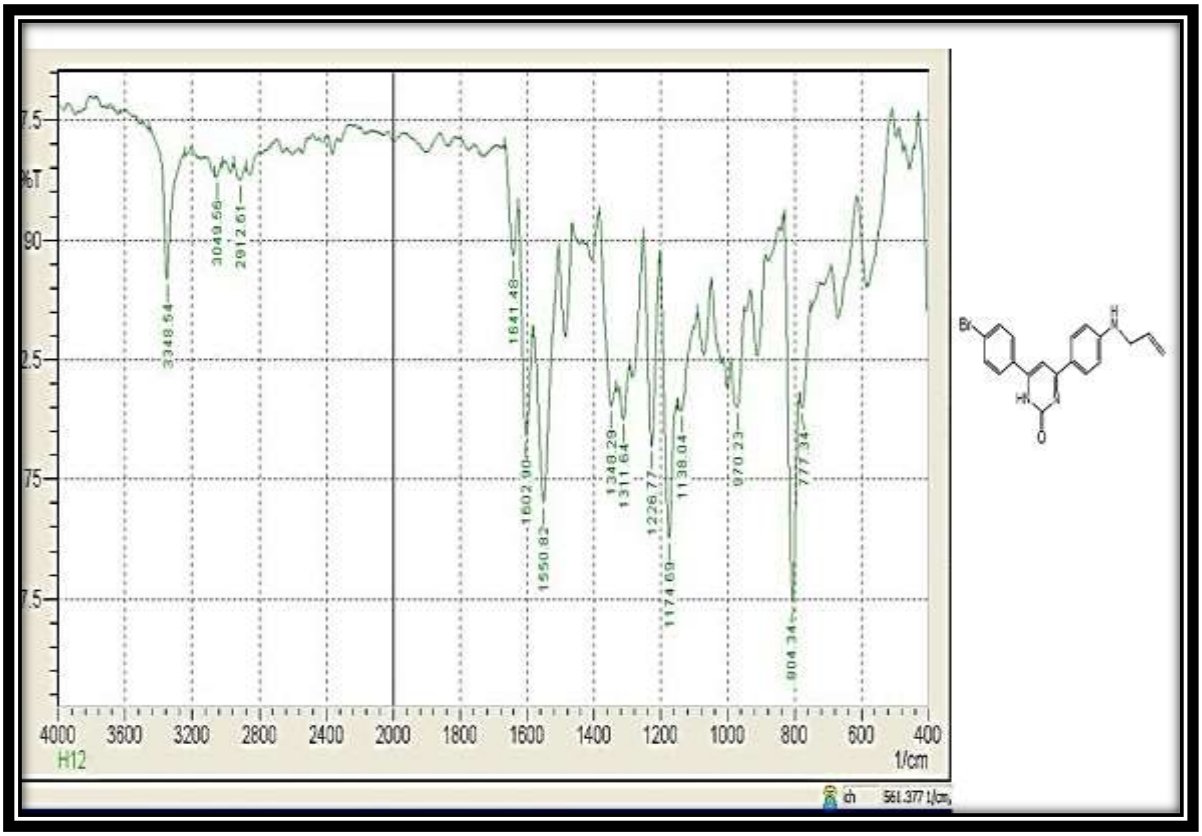


Fig (3.37) : IR spectrum of compound (H_{13})

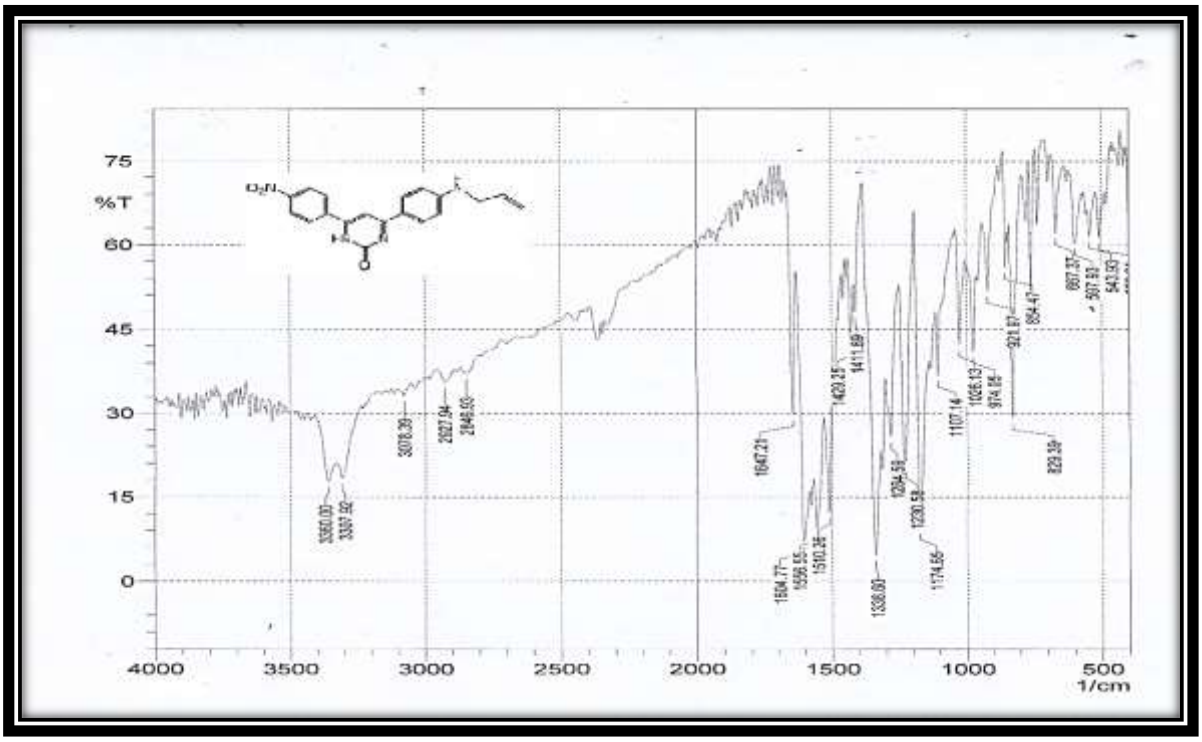


Fig (3.38) : IR spectrum of compound (H_{14})

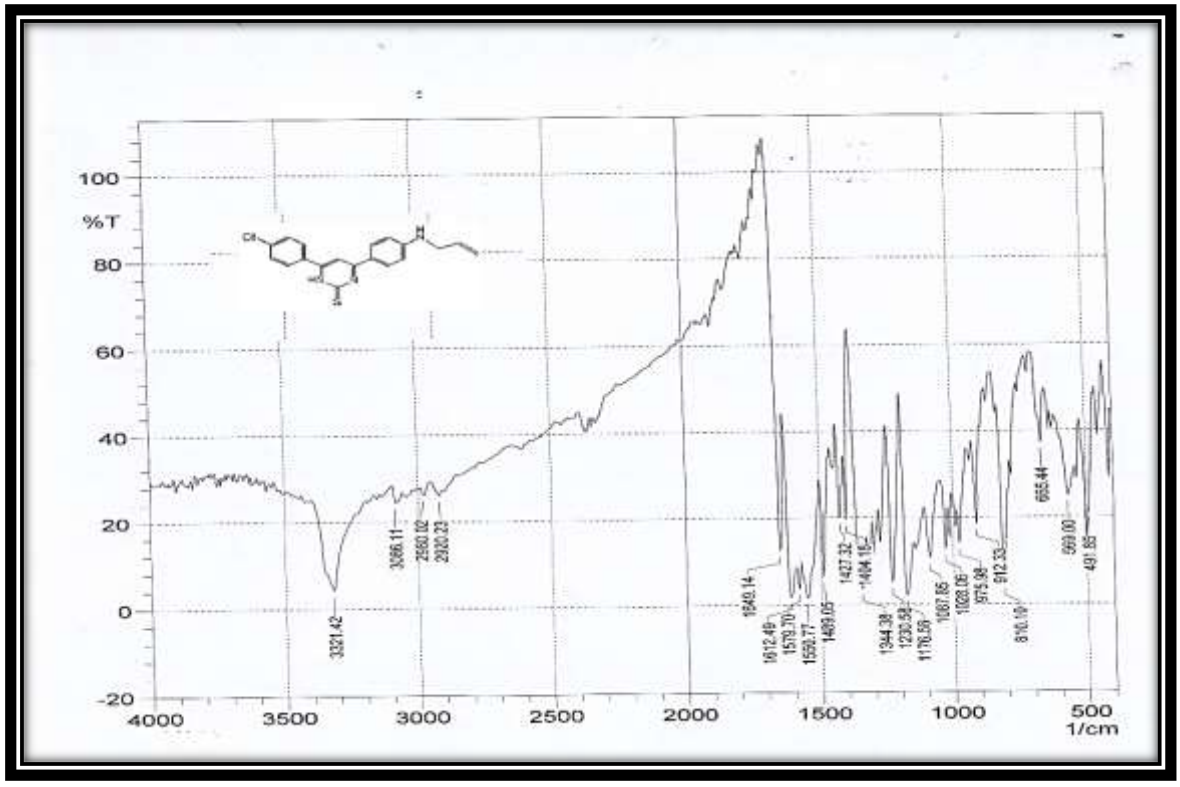


Fig (3.39) : IR spectrum of compound (H_{15})

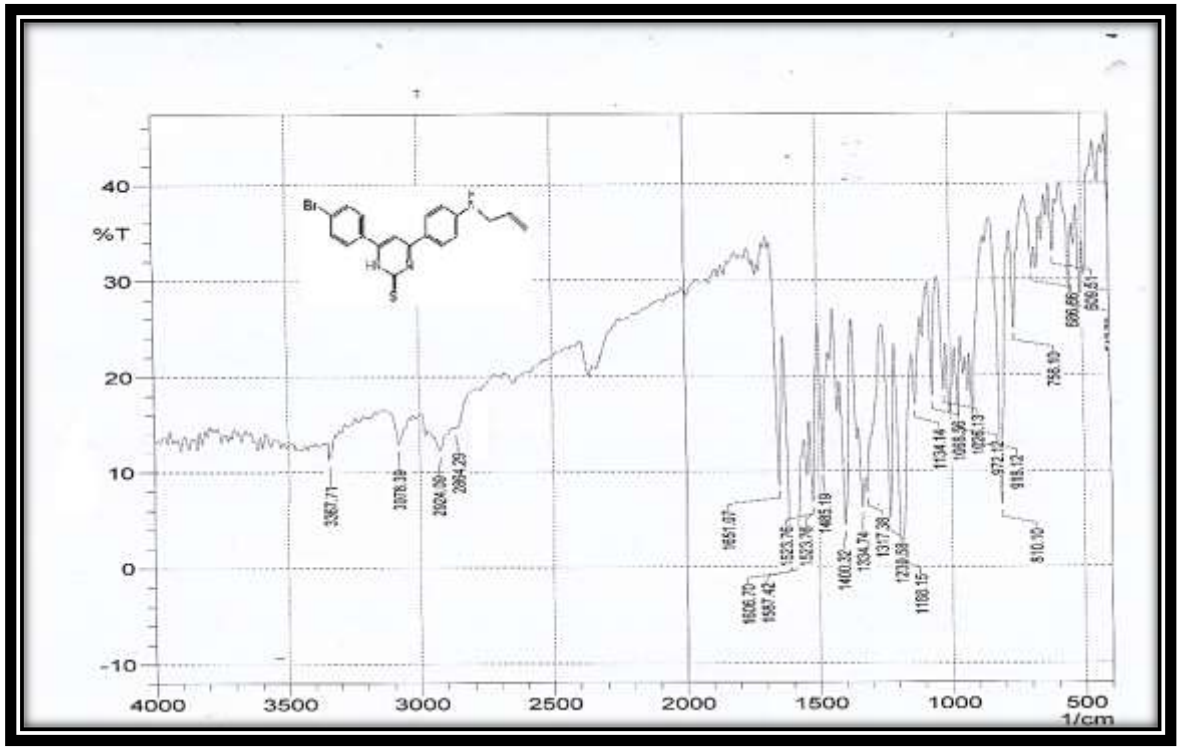
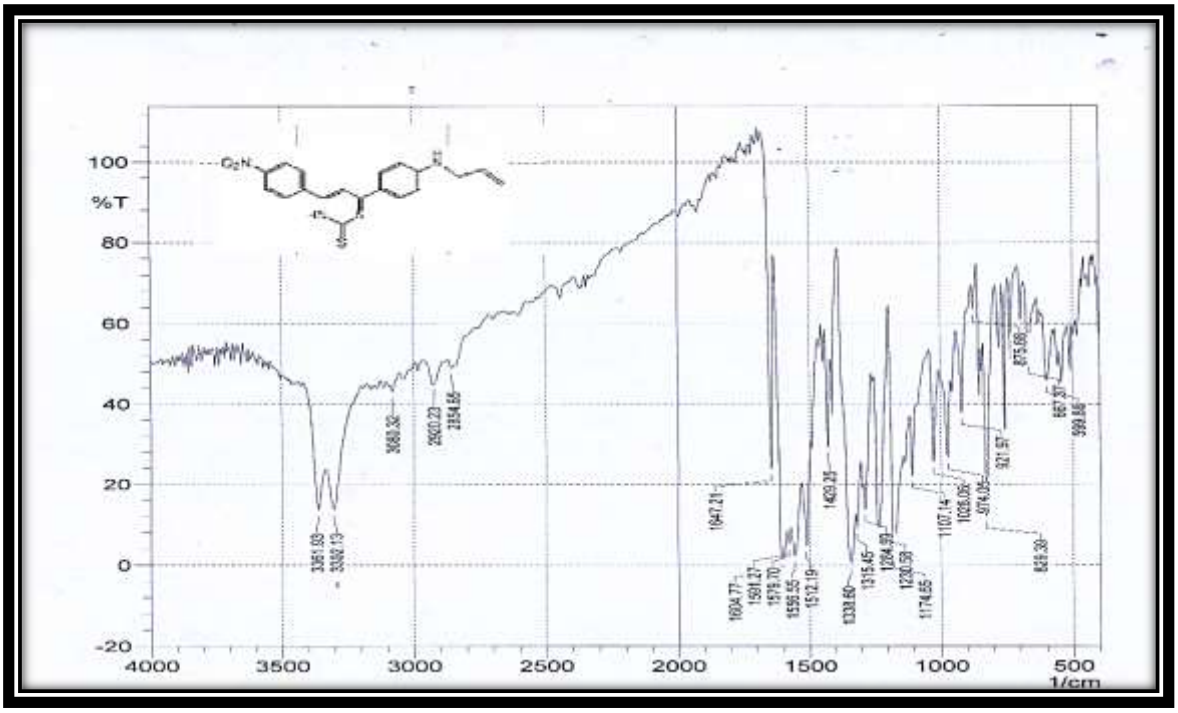


Fig (3.40) : IR spectrum of compound (H_{16})



Fig(3.41) : IR spectrum of compound (H_{17})

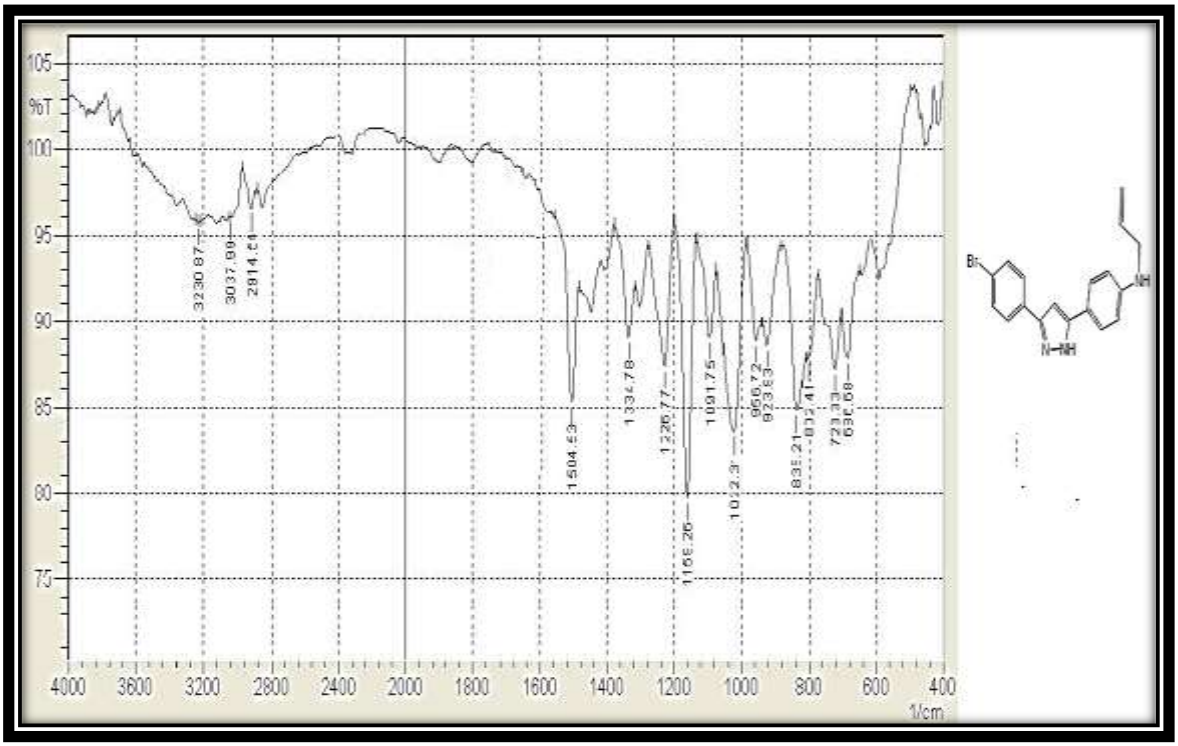


Fig (3.42) : IR spectrum of compound (H_{18})

3.2.2.4 ^{1}H-NMR of aryl sulfonyl derivatives (H_1-H_{11})[123]

The most important characteristic of the ^{1}H-NMR spectra of the aryl sulfonyl derivatives was monosappearance of one of the singlet signal of the amino group (NH_2), belonging to the starting materials (**I - VI**) at the range δ (4.24-6.21) ppm, Table (3.2). Which is consistent with the data, we obtained from the spectra of IR. These data (IR, ^{1}H-NMR) confirmed that the reaction has taken place and that is monosubstitution. The rest of the resonance signals are for aryl sulfonyl derivative (H_1-H_{11}) as appear in a Table (3.6) and the Figs (3.43-3.60) are δ (1.07-2.34) , (6.59-8.50) , (7.92-18.14) ,(7.88-8.12) ,(10.14-11.04) and (13.23-13.34) ppm which are attributed to CH_3 , Ar-H , O=C-NH , S=C-NH , NH-S=O and pyrrole-NH respectively .

3.2.2.5 ^{1}H-NMR of ally derivatives (H_{12}-H_{18})[124]

Table (3.7) and Figs.(3.61-3.78) of the derivatives (H_{12} – H_{18}) appeared singlet signal at the range (6.64-6.74) ppm that relates to a Proton of NH group which confirms that the substitution is made for mono - ally group instead of one Proton of amino group (-NH_2) .The spectra of N - allylated derivatives (H_{12}-H_{18}) are similar and especially concerned with the signals of the allyl group –NH-CH_2-CH=CH_2 as shown in Table (3.7). This allyl group showed three resonance signals , the first(a) is doublet in the range δ (4.95-5.25) ppm which belongs to the protons of the = CH_2 group , the second (b)is doublet doublet at the range δ (5.19-5.94)ppm which belongs to the protons of the - CH= group and the third (c) is doublet in the range δ (3.82-4.02)ppm and it returns to the protons of the group -CH_2 attached to the nitrogen atom.

Table (3.6) : ^{1}H-NMR Spectral data of aryl sulfonyl derivatives(ppm)

Com. No.	Symbol	-CH_3 (s)	C-H Heterocycle (s)	Aromatic Protons Pyrimidine -NH (m, s)	—NH-S(=O)(=O)— (s)	Py-NH (s)
1	**H_1**	2.33	7.66	7.72-8.09	10.92	……
2	**H_2**	2.34	7.69	7.30-8.41	10.93	…..
3	**H_3**	1.07	7.78	7.21-8.50	10.95	……
4	**H_4**	…….	7.54	7.30-8.10	11.00	…..
5	**H_5**	…….	7.28	6.64-8.08	10.98	……
6	**H_6**	…….	7.30	6.59-8.28	11.01	……
7	**H_7**	…...	7.61	7.27-8.09	10.99	……
8	**H_8**	……	7.51	7.30-8.09	10.99	……
9	**H_9**	……	7.65	7.31-8.27	11.04	……
10	**H_{10}**	1.34	7.09	7.15-7.75	10.14	13.34
11	**H_{11}**	…..	7.30	7.40-8.41	10.41	13.23

s = singlet , m = multiplet

Table (3.7) : ^{1}H-NMR Spectral data of N-allylated derivatives (ppm)

Com. No.	Symbol	-NH- (t)	C-H Aromatic (s)	Aromatic Protons (m)	O=C-NH (s)	S=C-NH (s)	$-CH_2-CH=CH_2$ c b a
1	**H_{12}**	6.74	7.33	7.50-8.33	12.02	…….	a (5.19)d b (5.80)m c (4.01)t
2	**H_{13}**	6.64	6.94	7.37-8.16	10.22	…….	a (5.25)d b (5.19)m c (3.82)t
3	**H_{14}**	6.68	7.05	7.10-8.26	10.93	……	a (5.21)d b (5.94)m c (3.84)t
4	**H_{15}**	6.65	6.95	7.39-8.00	……	10.68	a (5.19)d b (5.92)m c (3.82)t
5	**H_{16}**	6.67	6.95	7.39-8.00	……	10.93	a (5.19)d b (5.92)m c (3.82)t
6	**H_{17}**	6.70	7.02	7.32-8.37	…….	10.17	a (5.24)d b (5.94)m c (3.85)t
7	**H_{18}**	6.79	7.02	7.15-7.92	……	…….	a (4.95) b (5.92) c (4.02)

s = singlet , m = multiplet , d = doublet , t = triblet

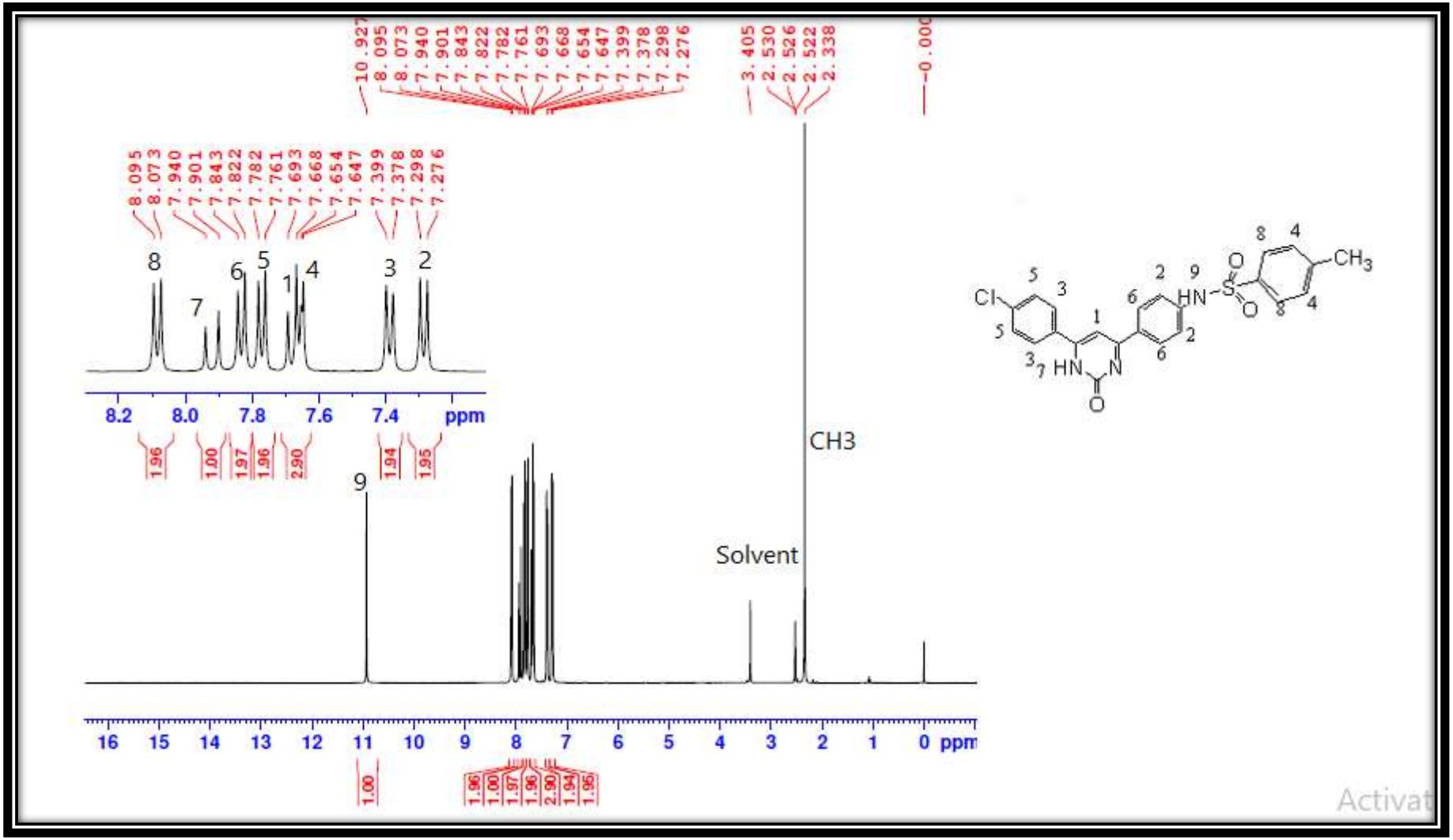


Fig (3.43) : ^{1}H-NMR spectrum of compound (H_1)

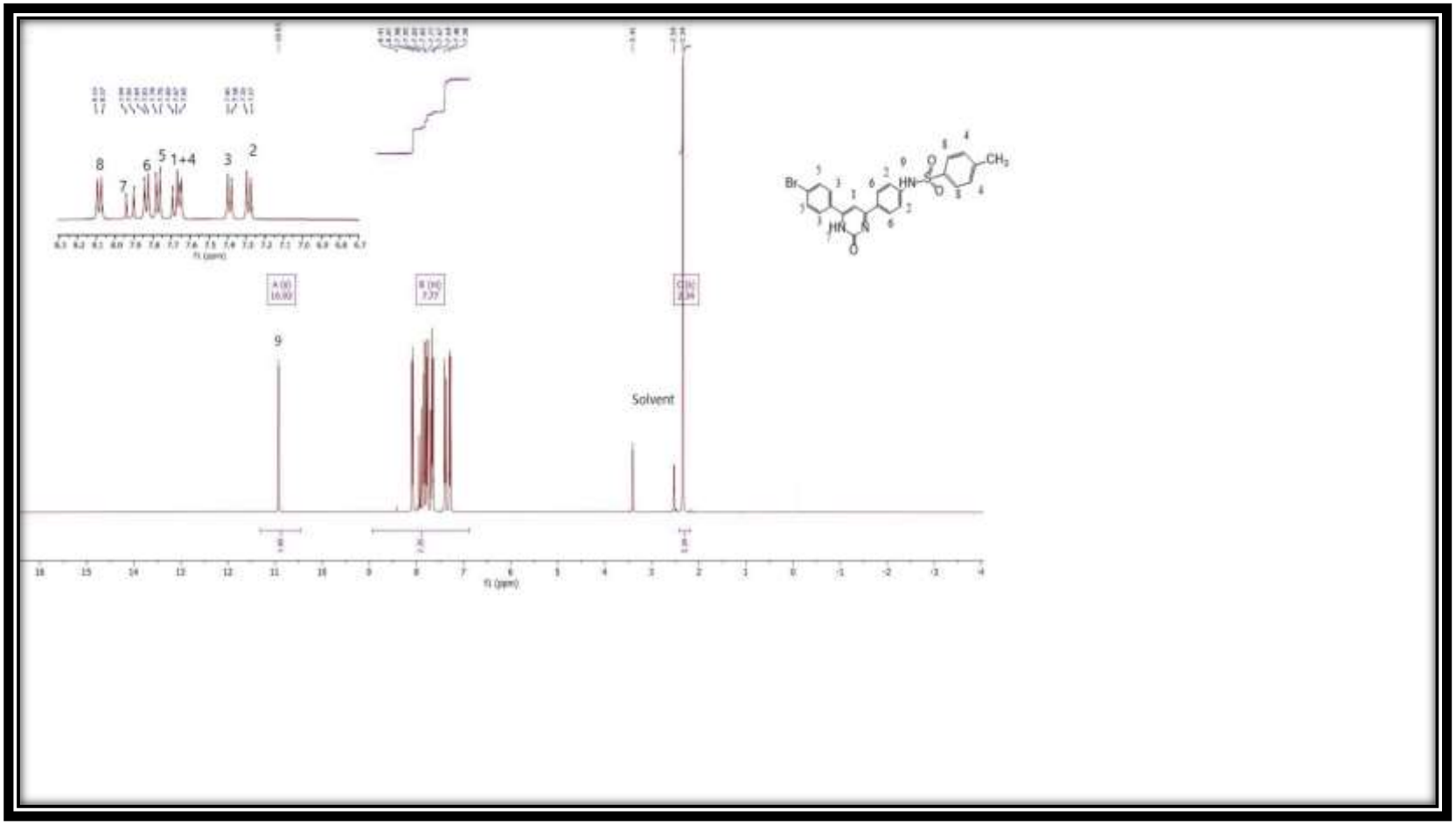
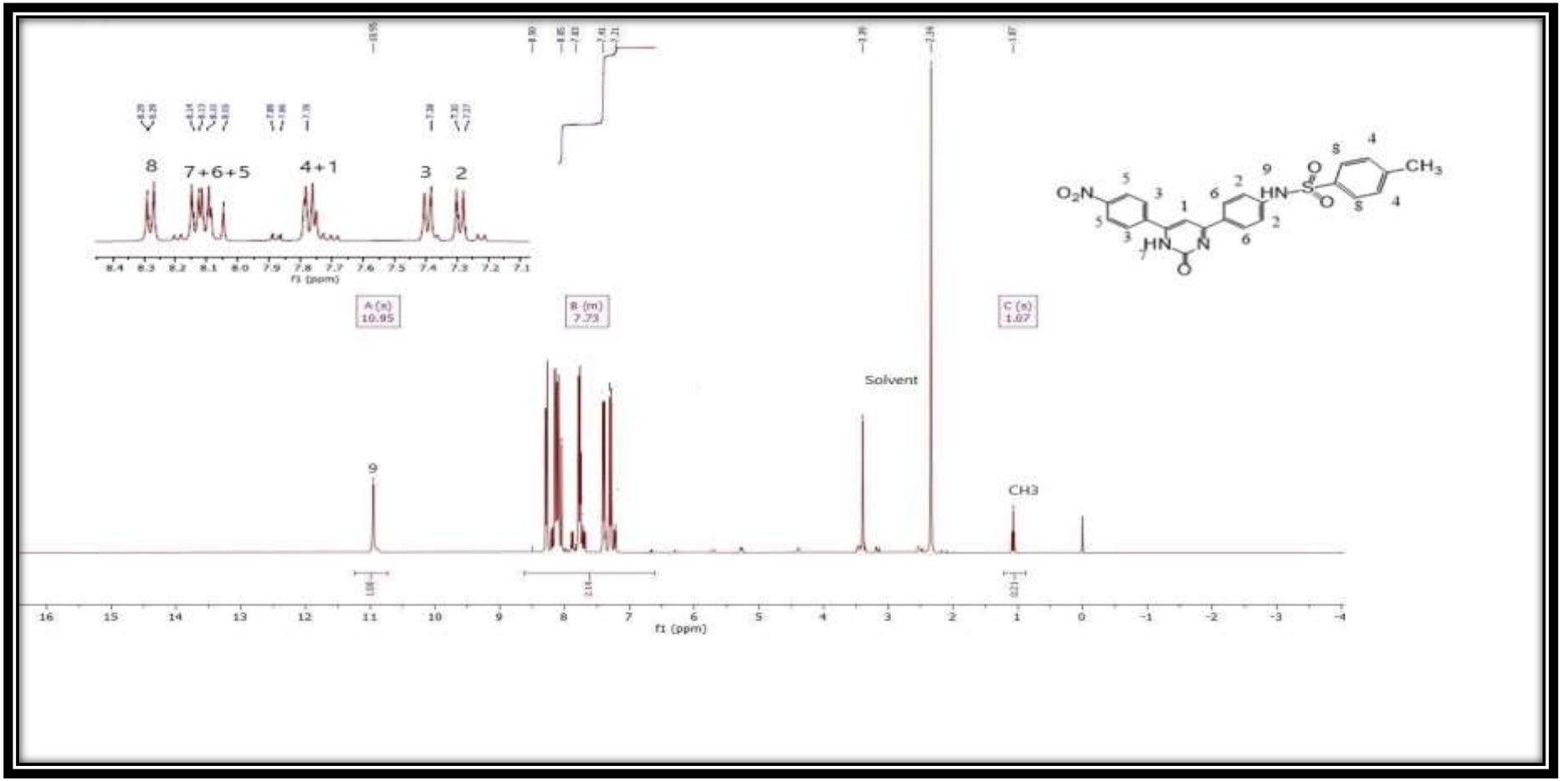


Fig (3.44) : ^{1}H-NMR spectrum of compound (H_2)



Fig(3.45) : 1H-NMR spectrum of compound (H3)

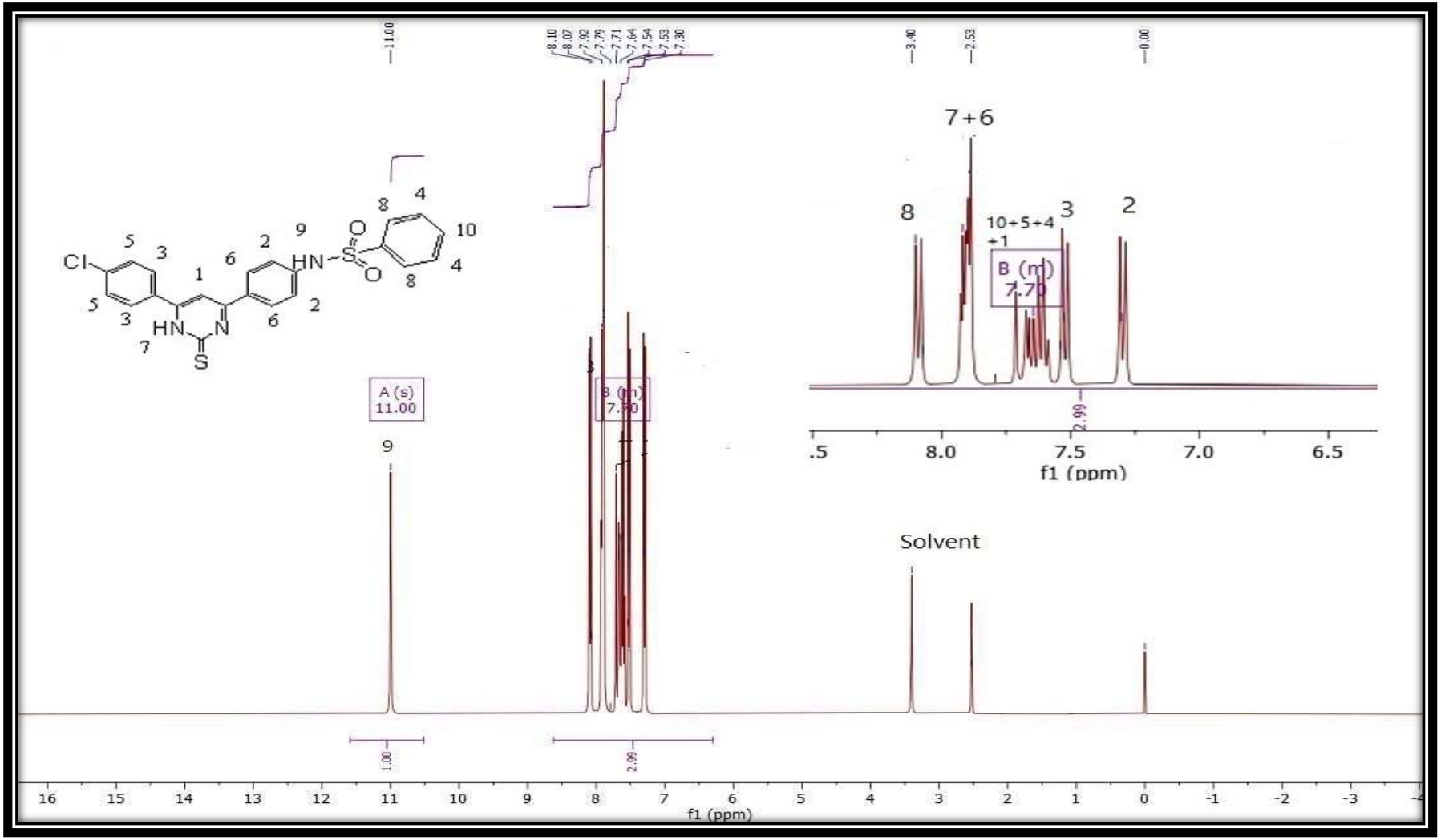


Fig (3.46) : ^{1}H-NMR spectrum of compound (H_4)

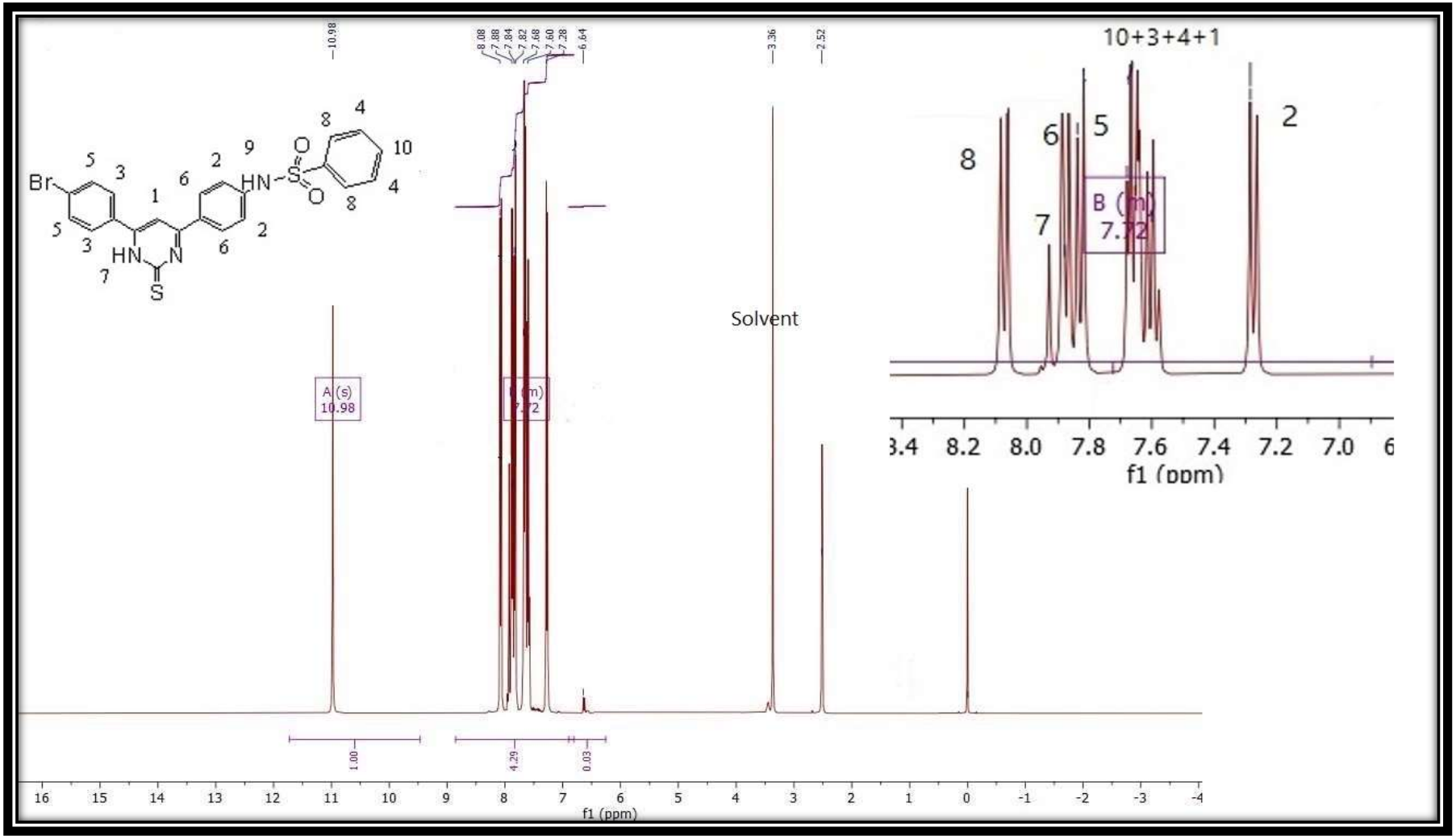


Fig (3.47) : ^{1}H-NMR spectrum of compound (H_5)

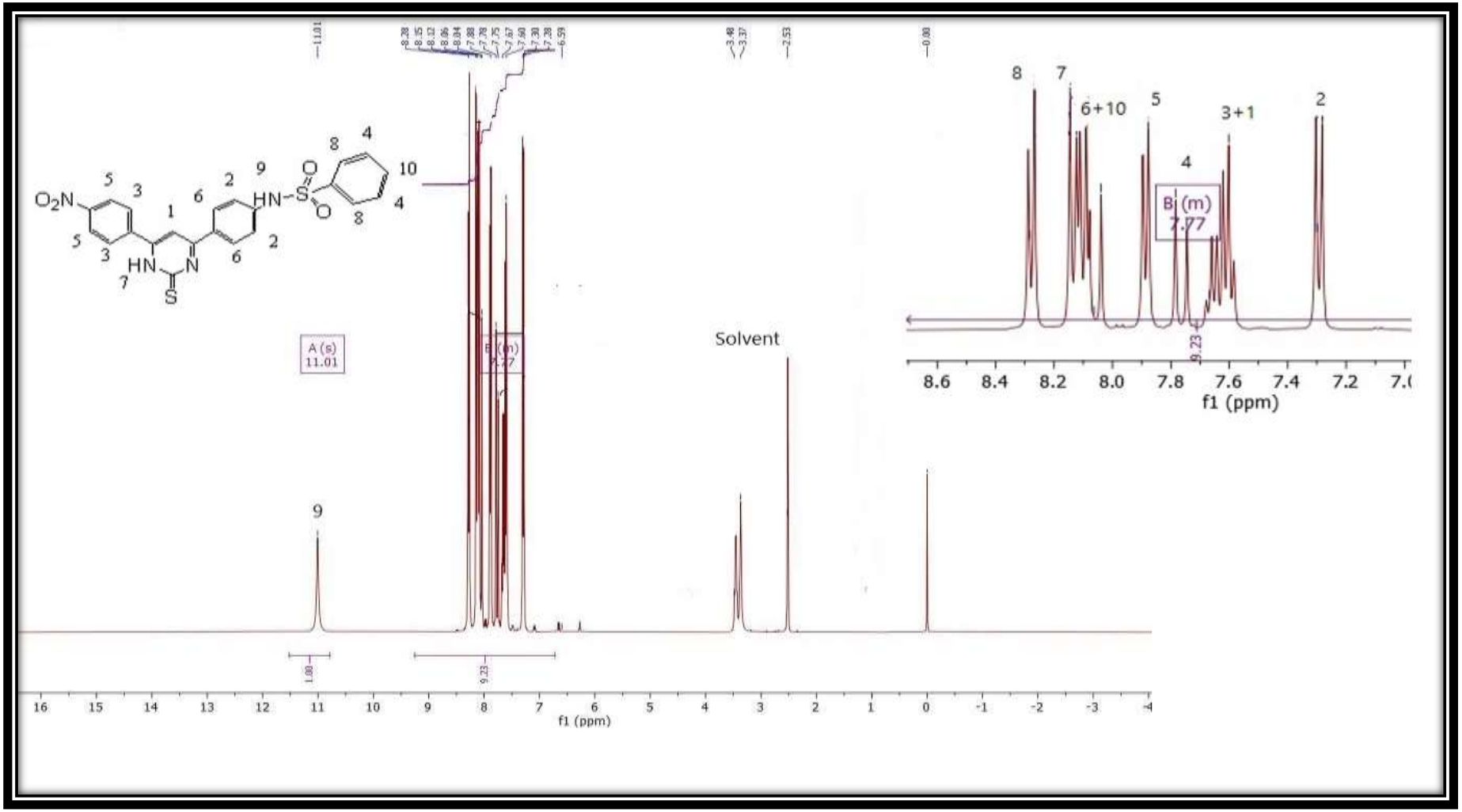


Fig (3.48) : ^{1}H-NMR spectrum of compound (H_6)

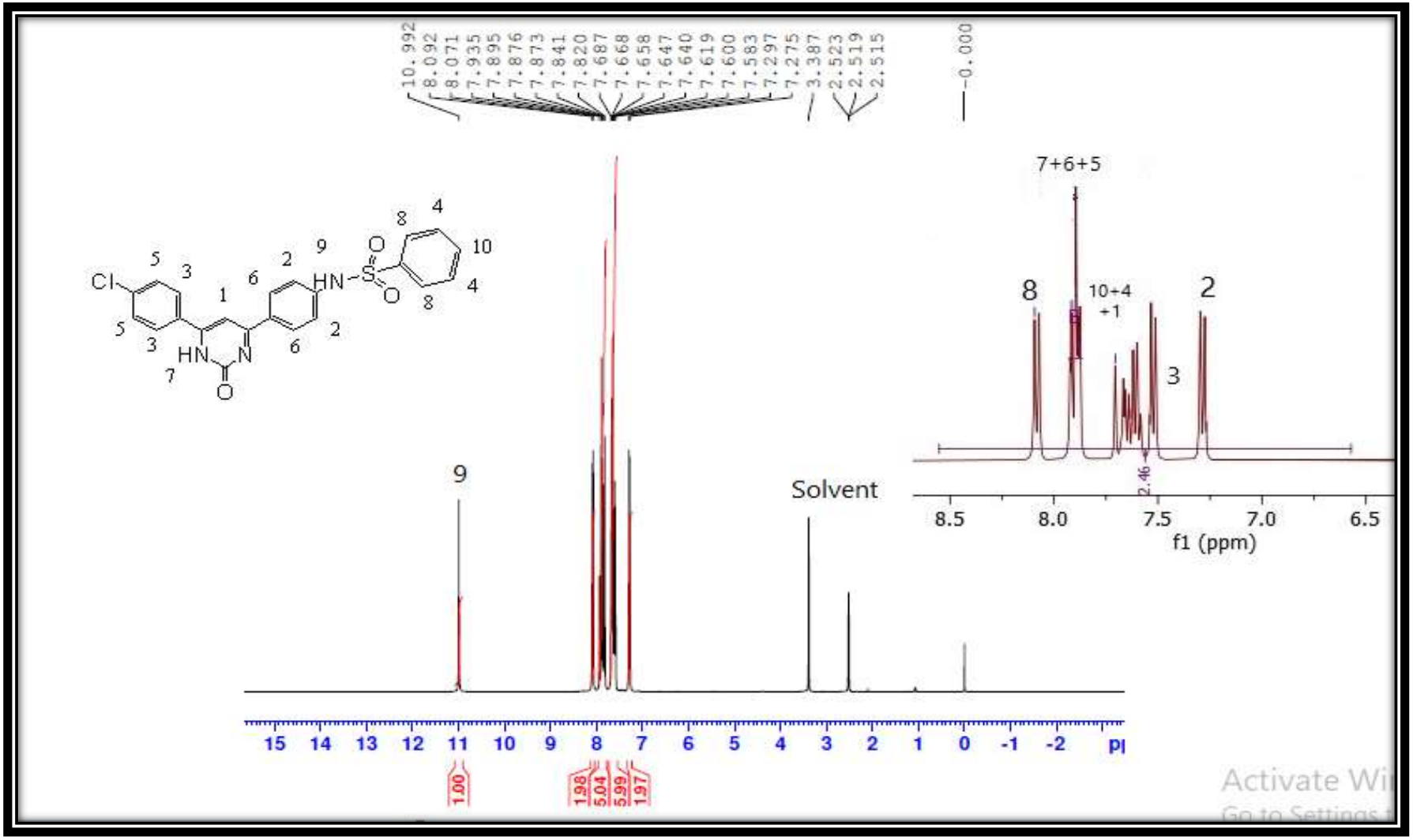


Fig (3.49) : ^{1}H-NMR spectrum of compound (H_7)

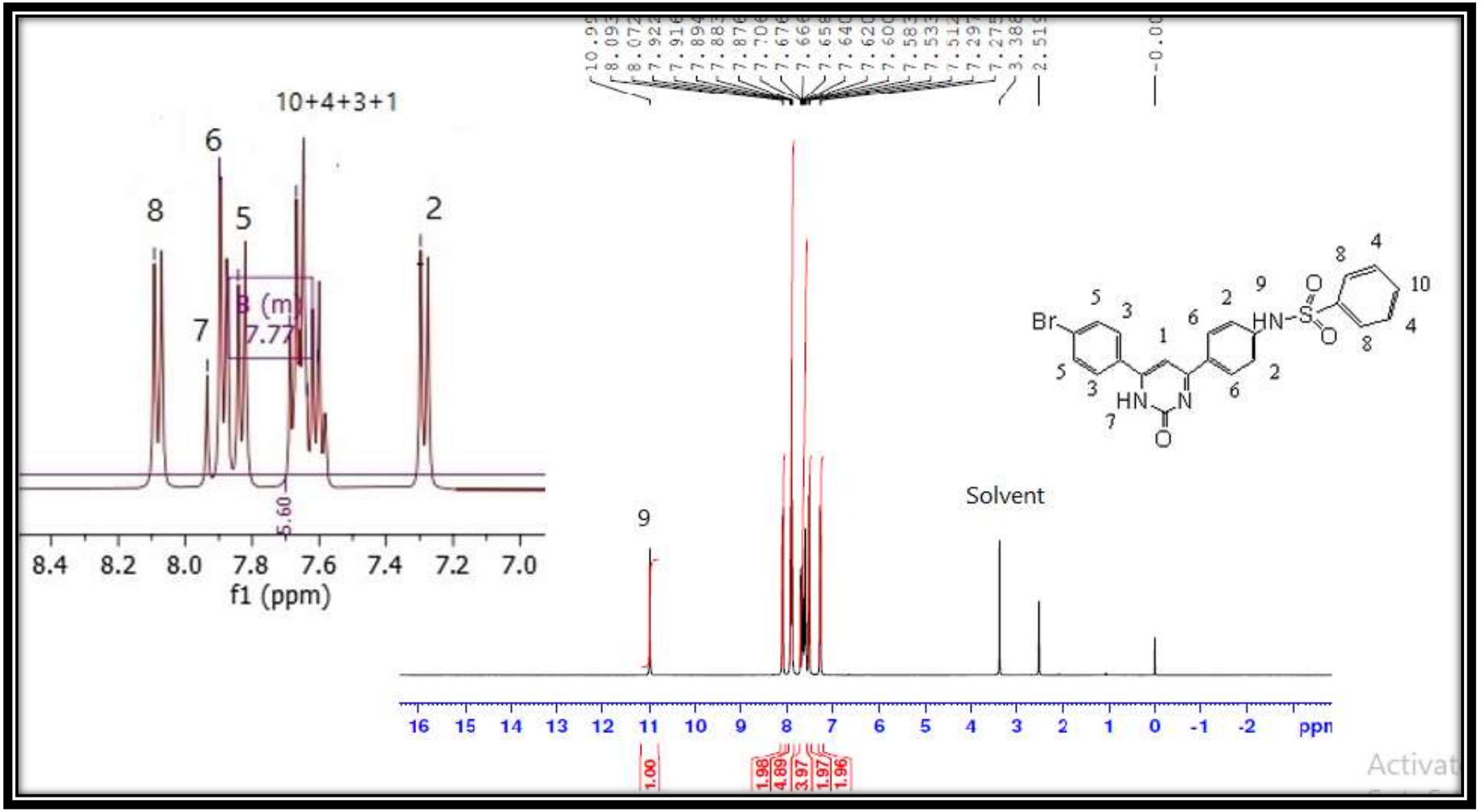


Fig (3.50) : ^{1}H-NMR spectrum of compound (H_8)

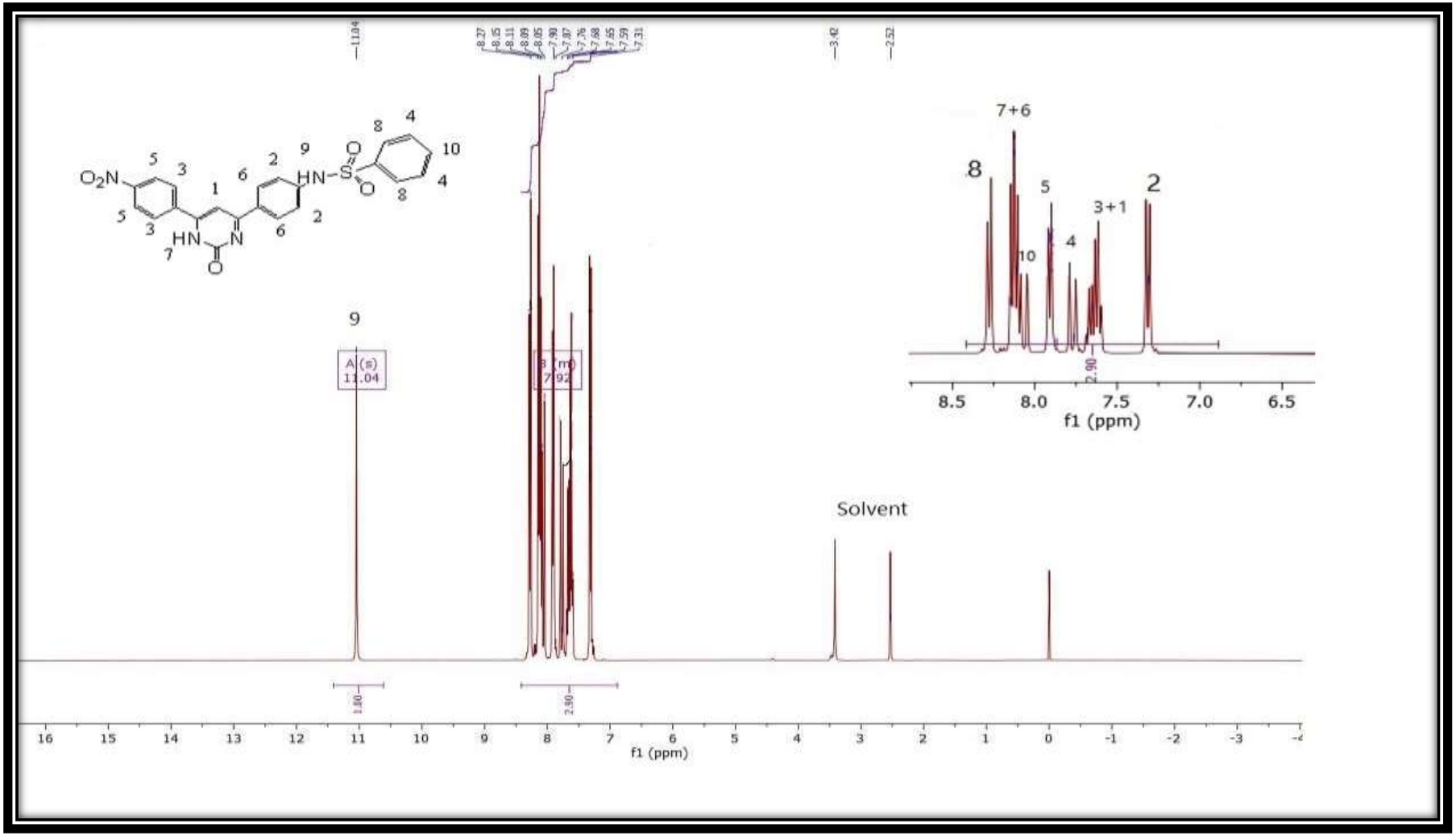


Fig (3.51) : ^{1}H-NMR spectrum of compound (H_9)

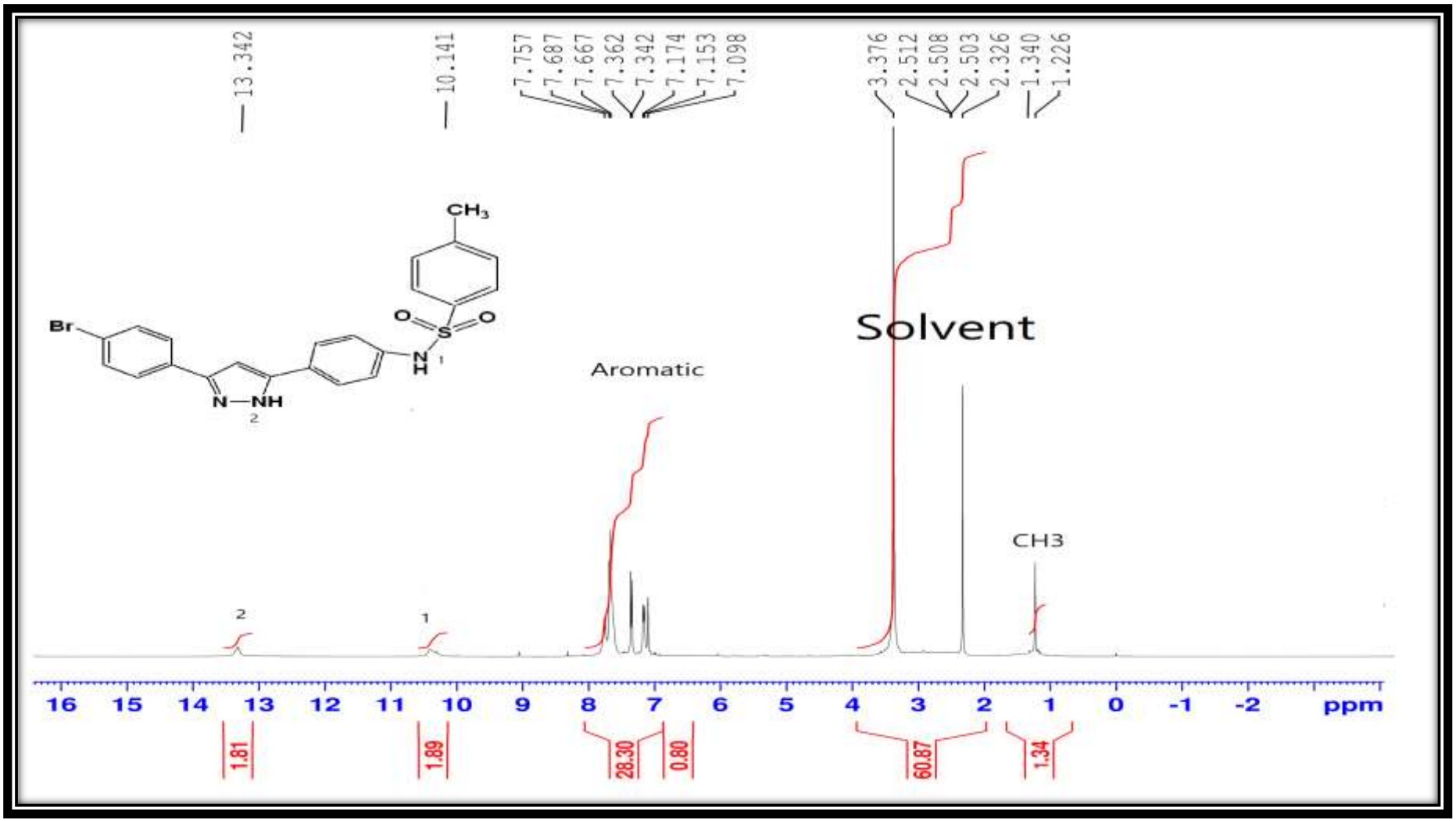


Fig (3.52) : ^{1}H-NMR spectrum of compound (H_{10})

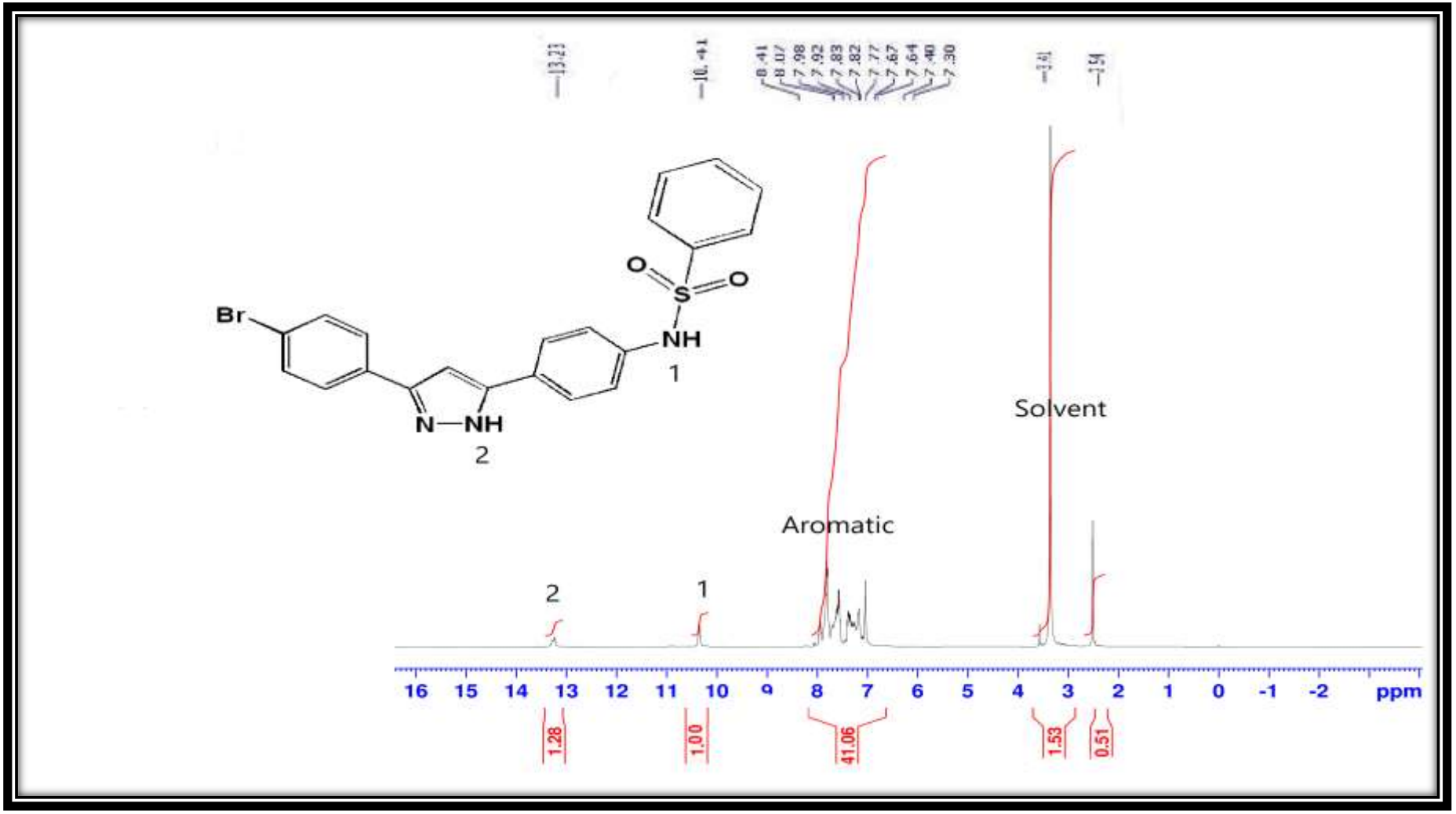


Fig (3.53) : ^{1}H-NMR spectrum of compound (H_{11})

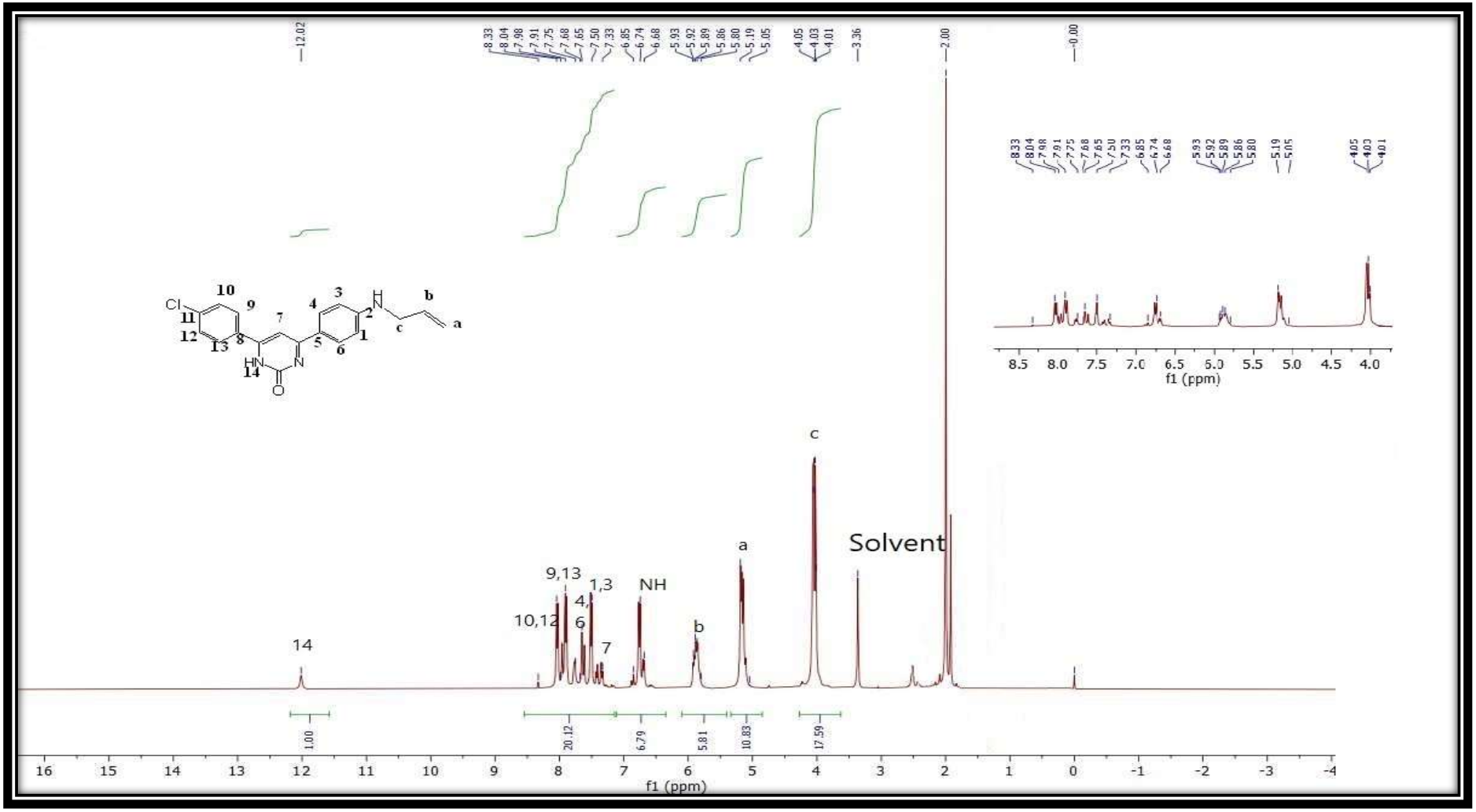


Fig (3.54) : ^{1}H-NMR spectrum of compound (H_{12})

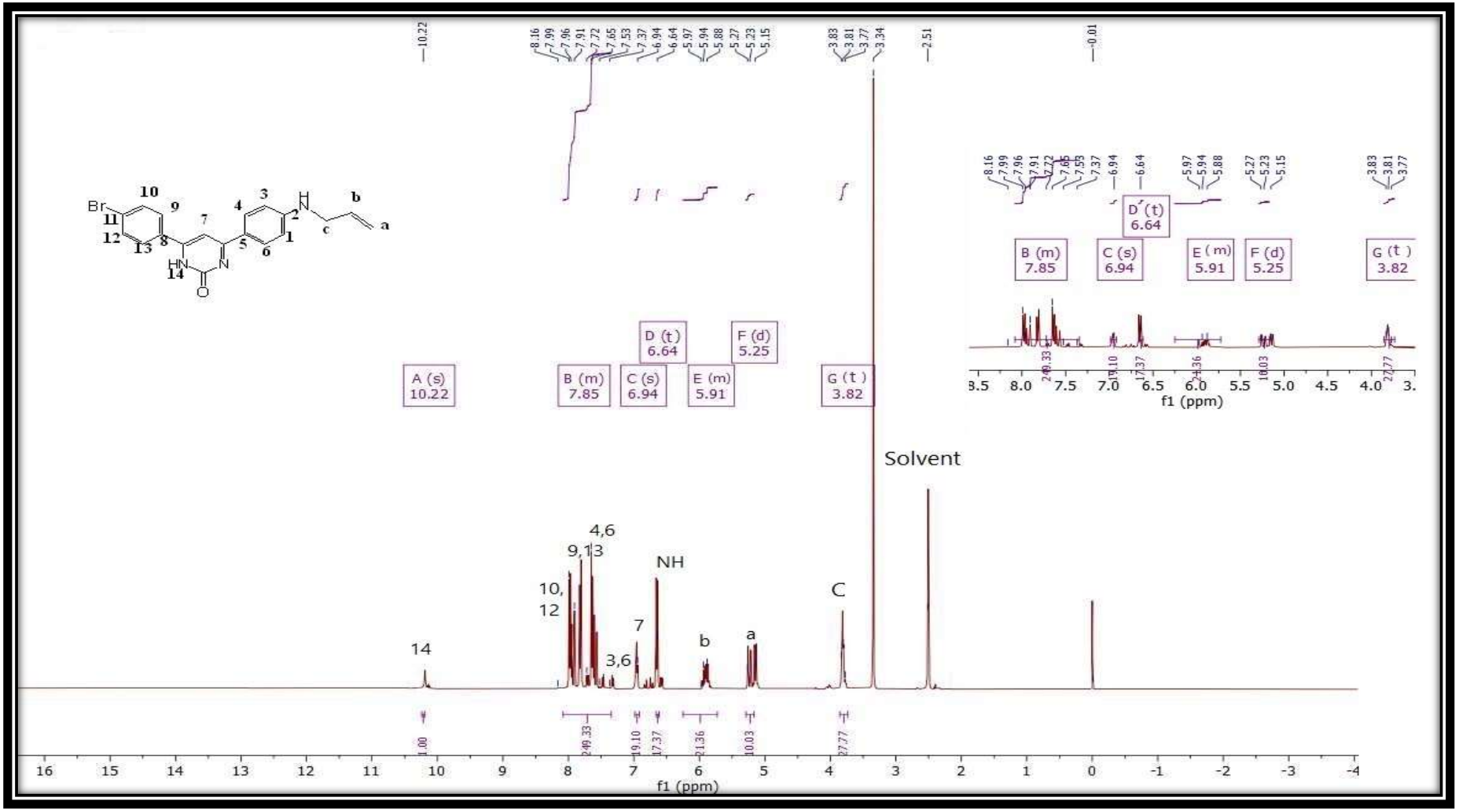


Fig (3.55) : ^{1}H-NMR spectrum of compound (H_{13})

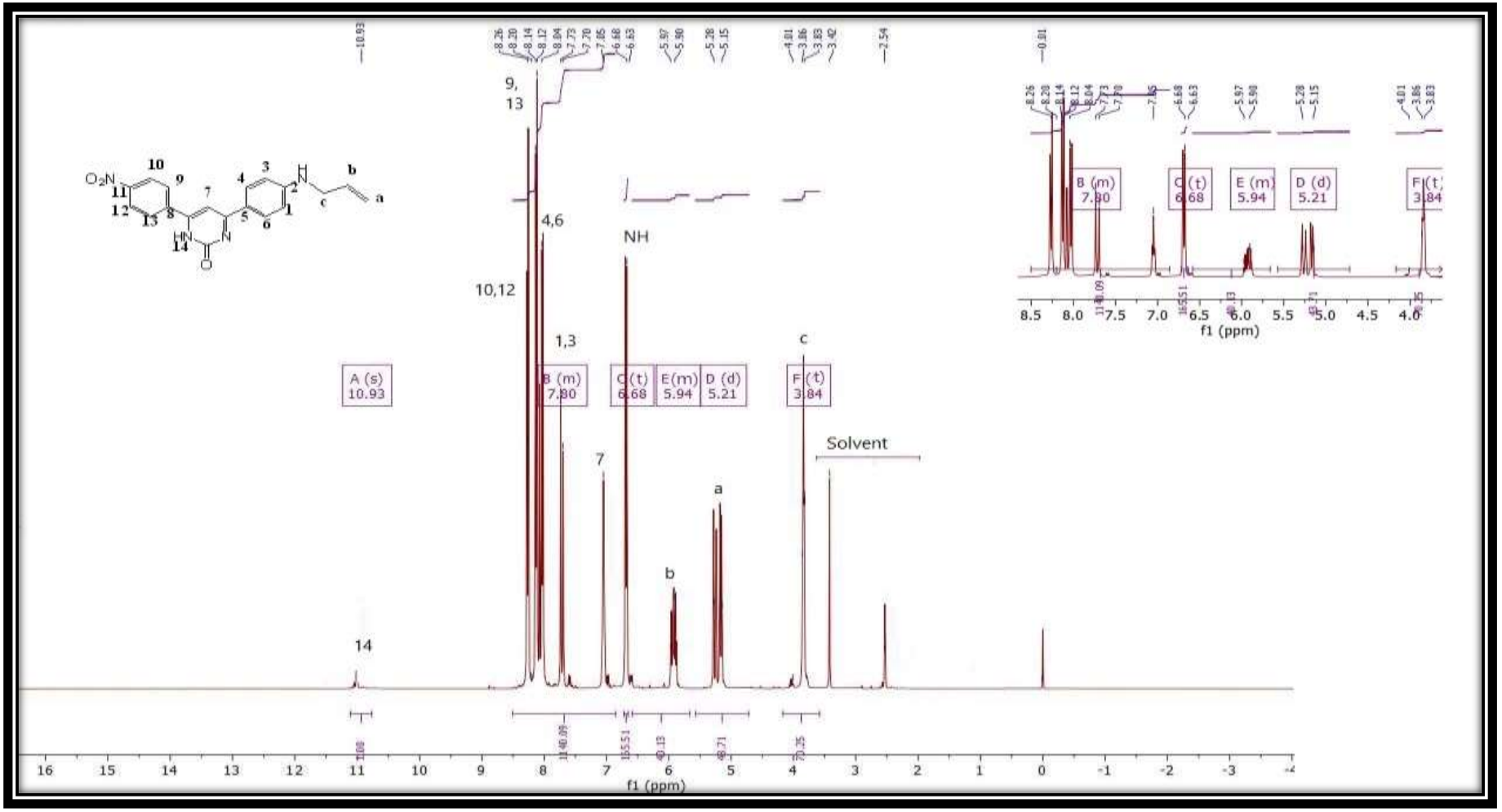


Fig (3.56) : ^{1}H-NMR spectrum of compound (H_{14})

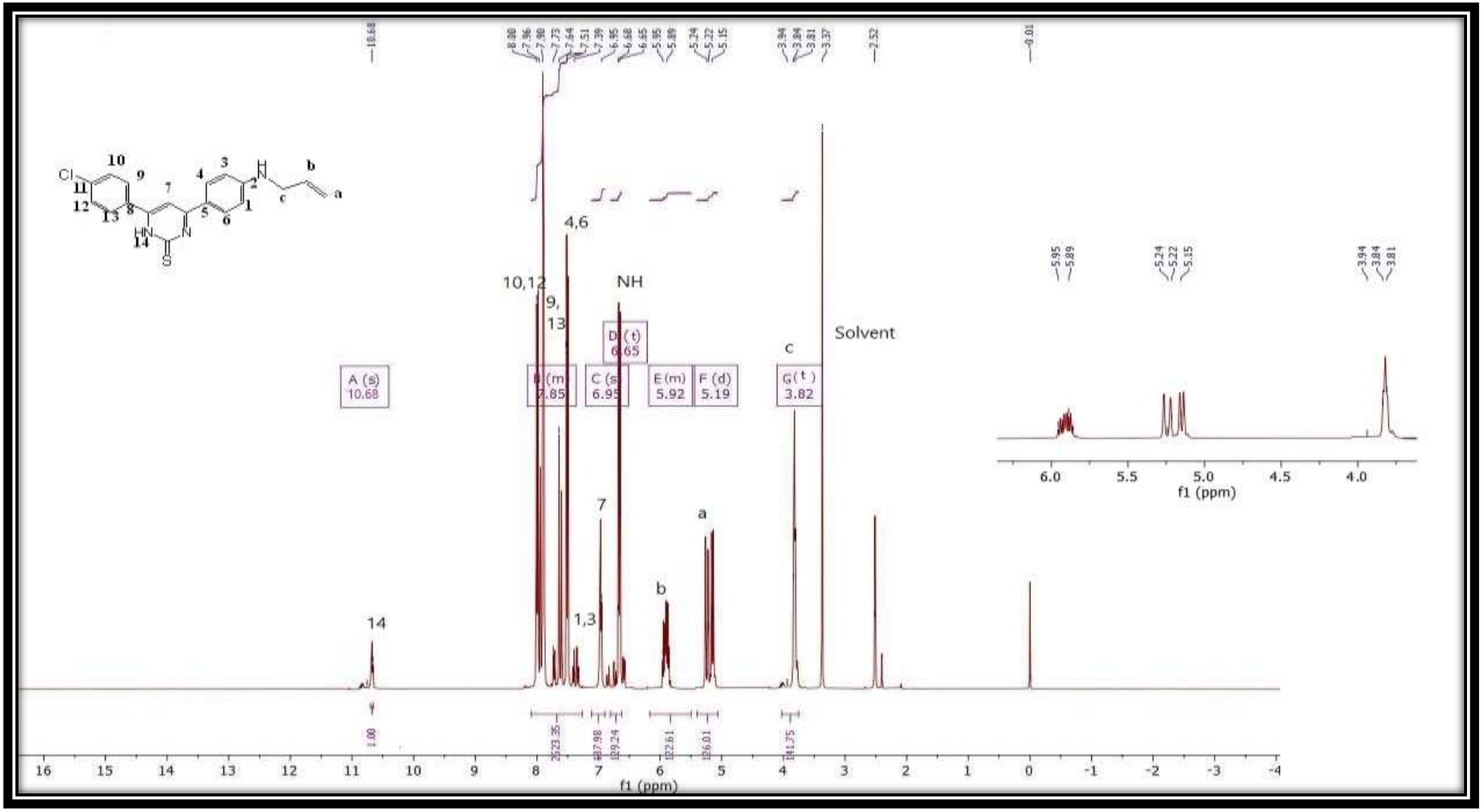


Fig (3.57) : ^{1}H-NMR spectrum of compound (H_{15})

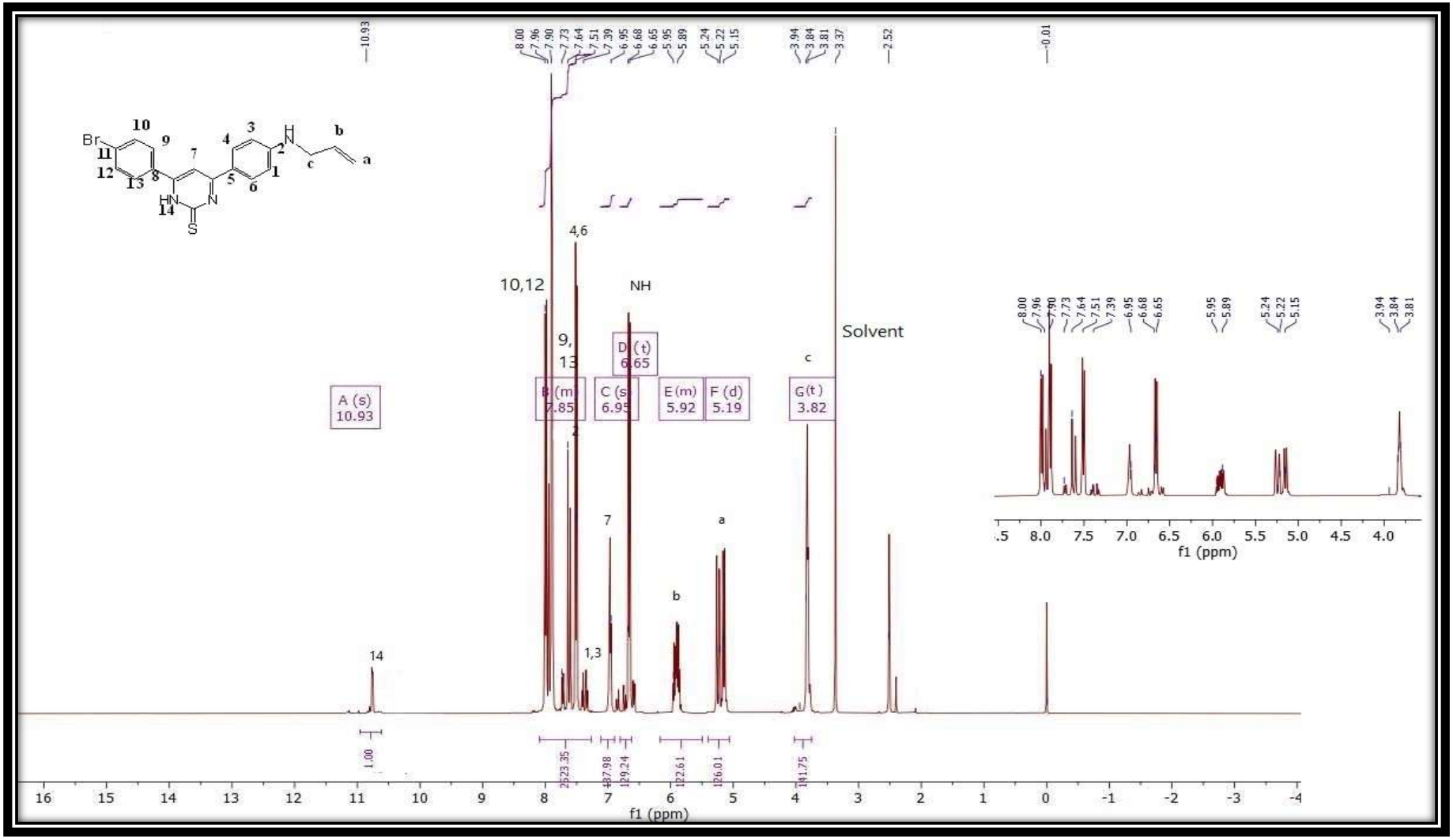


Fig (3.58) : ^{1}H-NMR spectrum of compound (H_{16})

Fig (3.59) : ^{1}H-NMR spectrum of compound (H_{17})

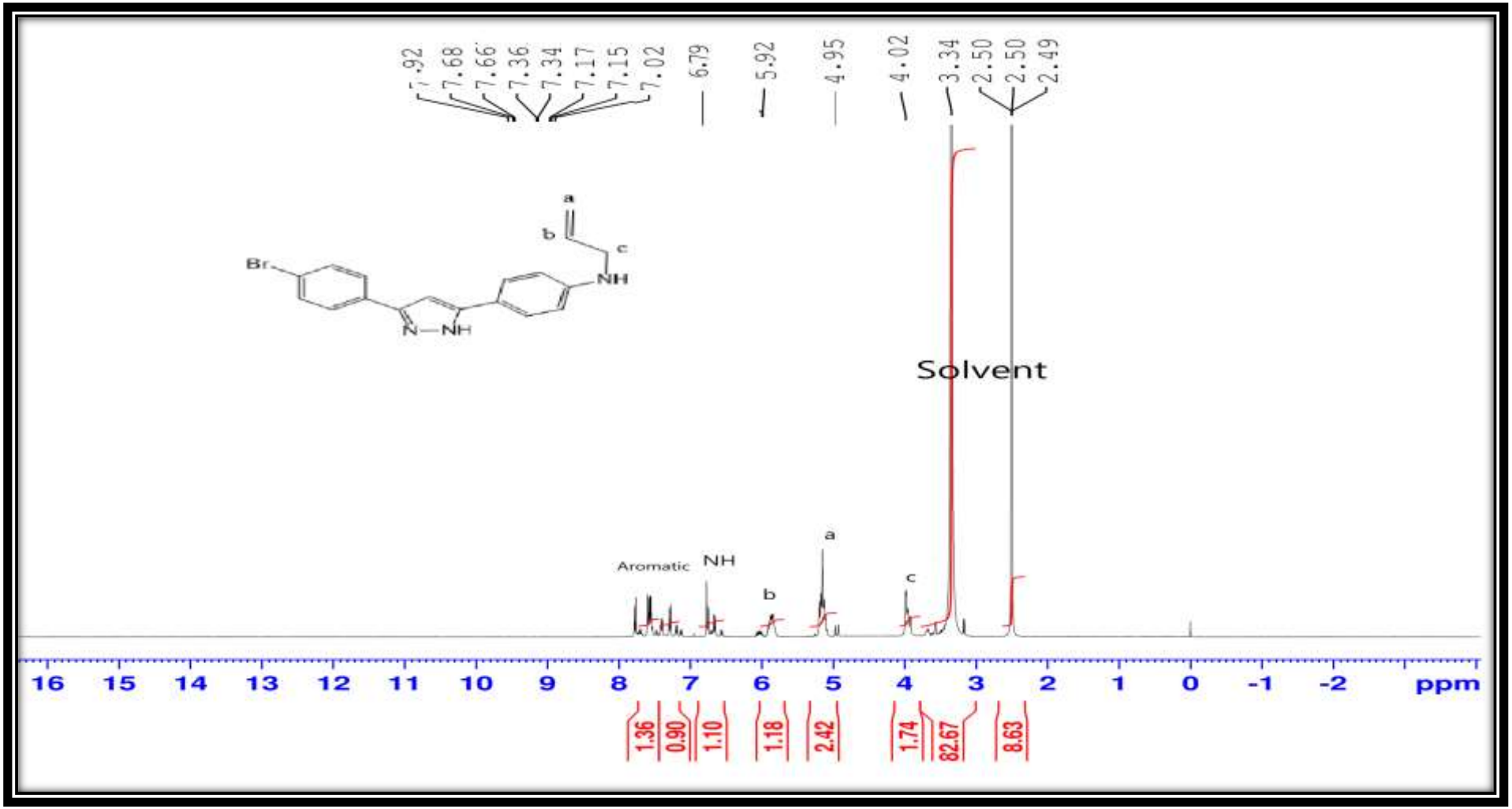


Fig (3.60) : ^{1}H-NMR spectrum of compound (H_{18})

3.2.2.6 ^{13}C - NMR of the synthesized derivatives (H_1 - H_{18})

The ^{13}C - NMR spectral data of aryl sulfonyl derivatives(H_1 - H_{11}) are illustrated in Table (3.8) and Figs (3.61-3.71).

The resonance signals shown by these spectra of the derivatives synthesized above are: δ (21.40-21.43) , (118.26-144.26) , (136.60-143.23) , (144.22-148.49) , (187.78-187.89) , (187.81-187.89) and (126.45-143.23)ppm which ascribes to -CH_3 , Aromatic ring, C-N, C=N , C=O , C=S and C-X respectively .

Whereas allylic substitution derivatives (H_{12} - H_{18}) provided us with their resonance spectra by signals which relates to as explained in Table (3.9) and Figs (3.72-3.78).

Table (3.8) : ^{13}C-NMR Spectral data of aryl sulfonyl derivatives(ppm)

Comp. No.	Symbol	-CH_3	Aromatic	Py-CH	C-N	C=N	C=O	C=S	C-X
1	**H_1**	21.43	118.34-142.55	118.34	142.99	144.22	187.87	……	C-Cl 134.48
2	**H_2**	21.43	118.35-136.88	118.35	142.55	144.22	187.87	……	C-Br 127.24
3	**H_3**	21.40	118.26-144.26	118.26	143.23	148.47	187.78	……	C-NO_2 143.23
4	**H_4**	…….	118.48-135.48	118.48	139.76	142.85	…….	187.89	C-Cl 135.48
5	**H_5**	…….	118.47-134.49	118.47	142.84	142.85	…….	187.89	C-Br 129.97
6	**H_6**	…….	118.46-113.18	118.47	143.18	148.49	…….	187.81	C-NO_2 141.70
7	**H_7**	…….	118.48-135.48	118.48	142.84	142.85	187.89	……..	C-Cl 133.78
8	**H_8**	……	118.48-139.75	118.48	142.58	142.86	187.89	……..	C-Br 129.97
9	**H_9**	……	118.42-141.67	118.48	143.10	148.45	187.78	……..	C-NO_2 141.67
10	**H_{10}**	21.41	99.99-137.09	99.99	140.80	143.80	……	…….	C-Br 126.47
11	**H_{11}**	……	115.26-139.92	115.26	136.60	150.07	……	…….	C-Br 126.45

Table (3.9) : ^{13}C-NMR Spectral data of N-allylated derivatives(ppm)

Comp. No.	Symbol	Aromatic ring	Py-CH	-CH_2-CH=CH_2 c b a	C-N	C=N	C=O	C=S
1	**H_{12}**	111.30-135.05	111.30	a (111.57) b (135.05) c (52.68)	140.64	152.12	170.78	…….
2	**H_{13}**	111.72-135.62	111.72	a (116.22) b (135.62) c (45.05)	140.54	153.55	186.22	…….
3	**H_{14}**	111.76-142.25	111.76	a (116.23) b (142.25) c (45.05)	148.12	153.74	185.92	…….
4	**H_{15}**	111.72-135.61	111.72	a (116.21) b (135.61) c (45.05)	140.46	153.78	……	186.22
5	**H_{16}**	113.24-142.27	113.24	a (123.69) b (142.27) c (47.00)	148.14	154.72	……	185.86
6	**H_{17}**	111.76-142.24	111.76	a (116.22) b (142.24) c (45.06)	148.10	153.74	…..	185.92
7	**H_{18}**	118.18-149.80	118.18	a (118.18) b (138.09) c (52.73)	149.80	149.80	…….	……

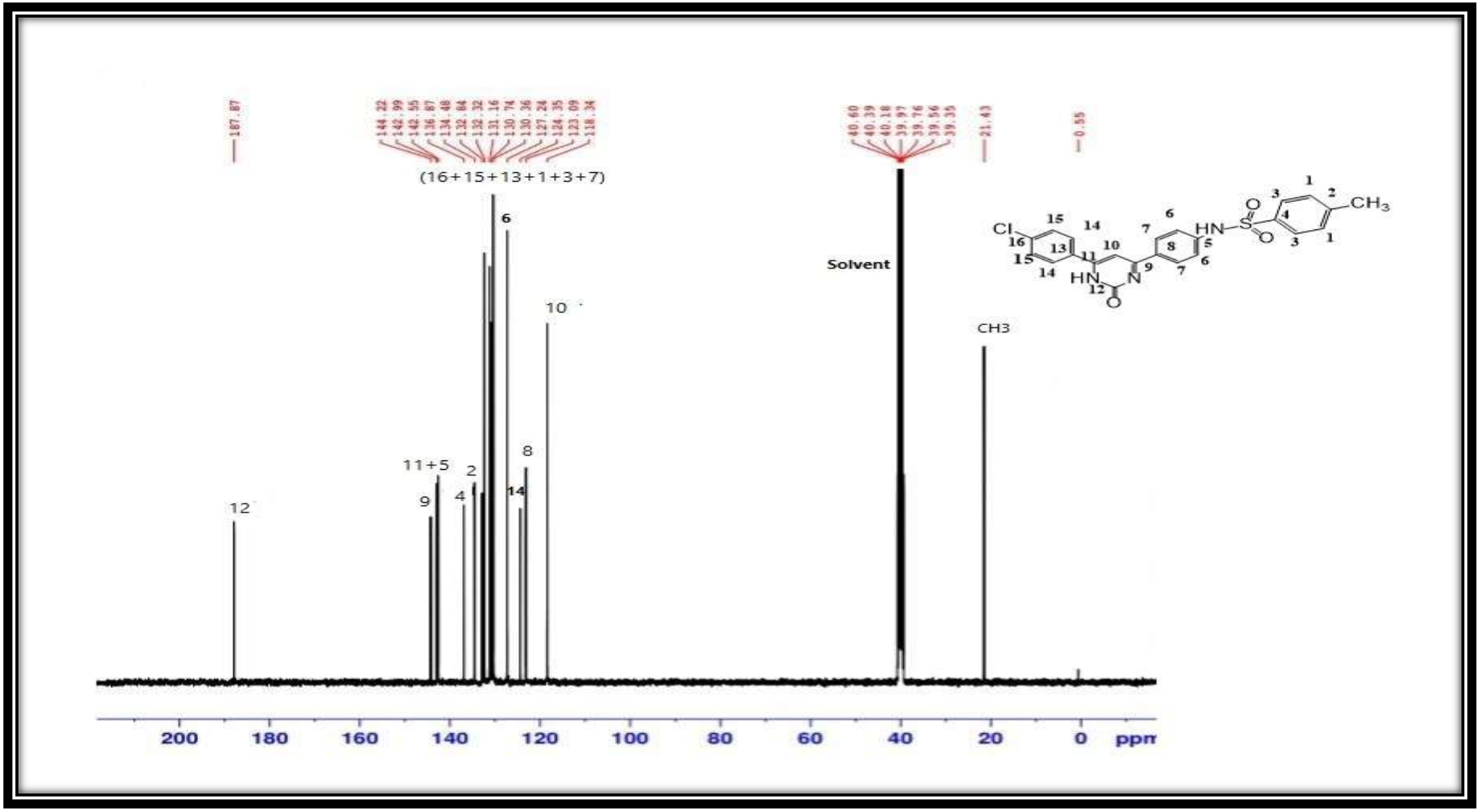


Fig (3.61) : ^{13}C-NMR spectrum of compound (H_1)

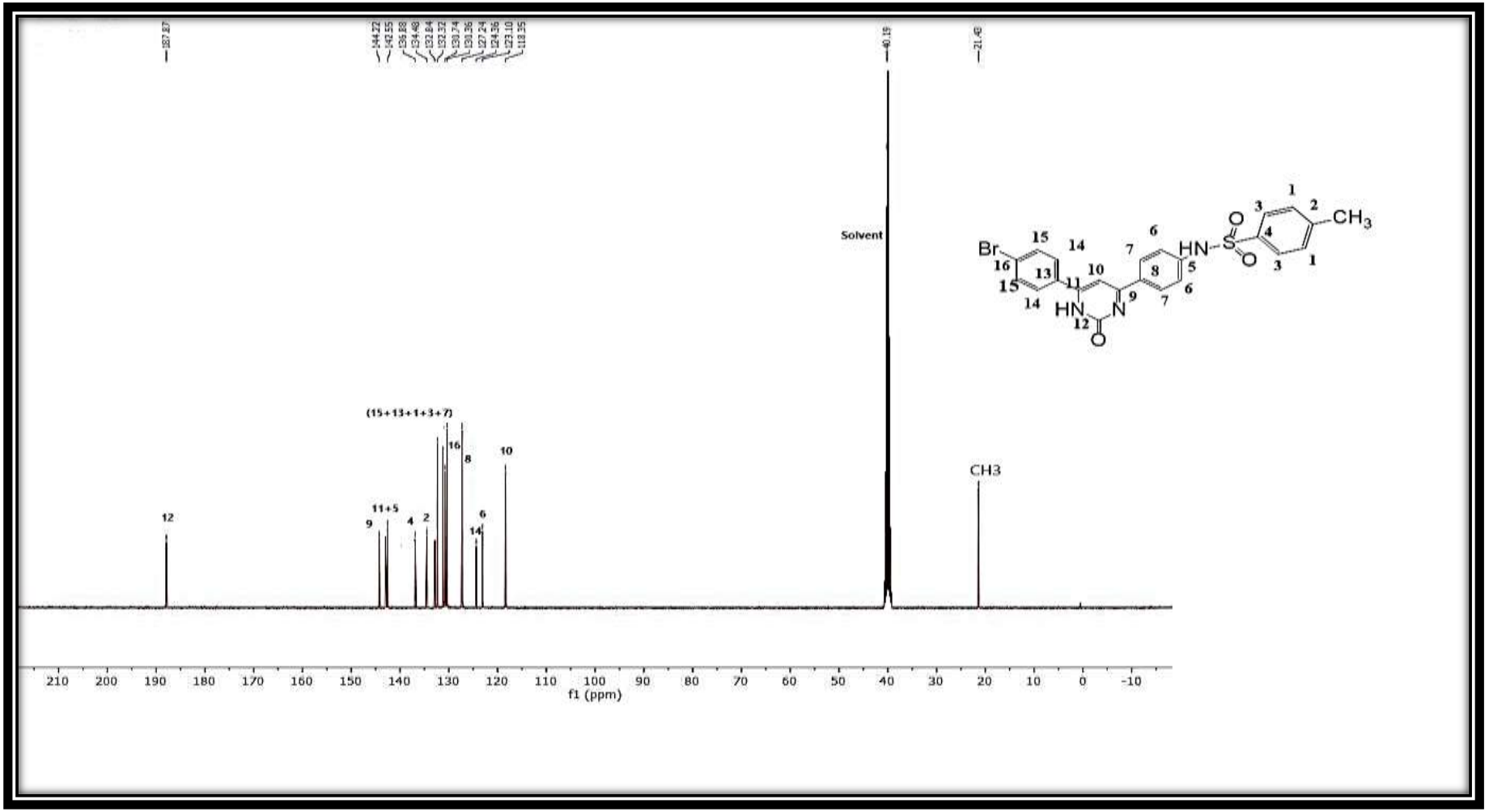


Fig (3.62) : ^{13}C-NMR spectrum of compound (H_2)

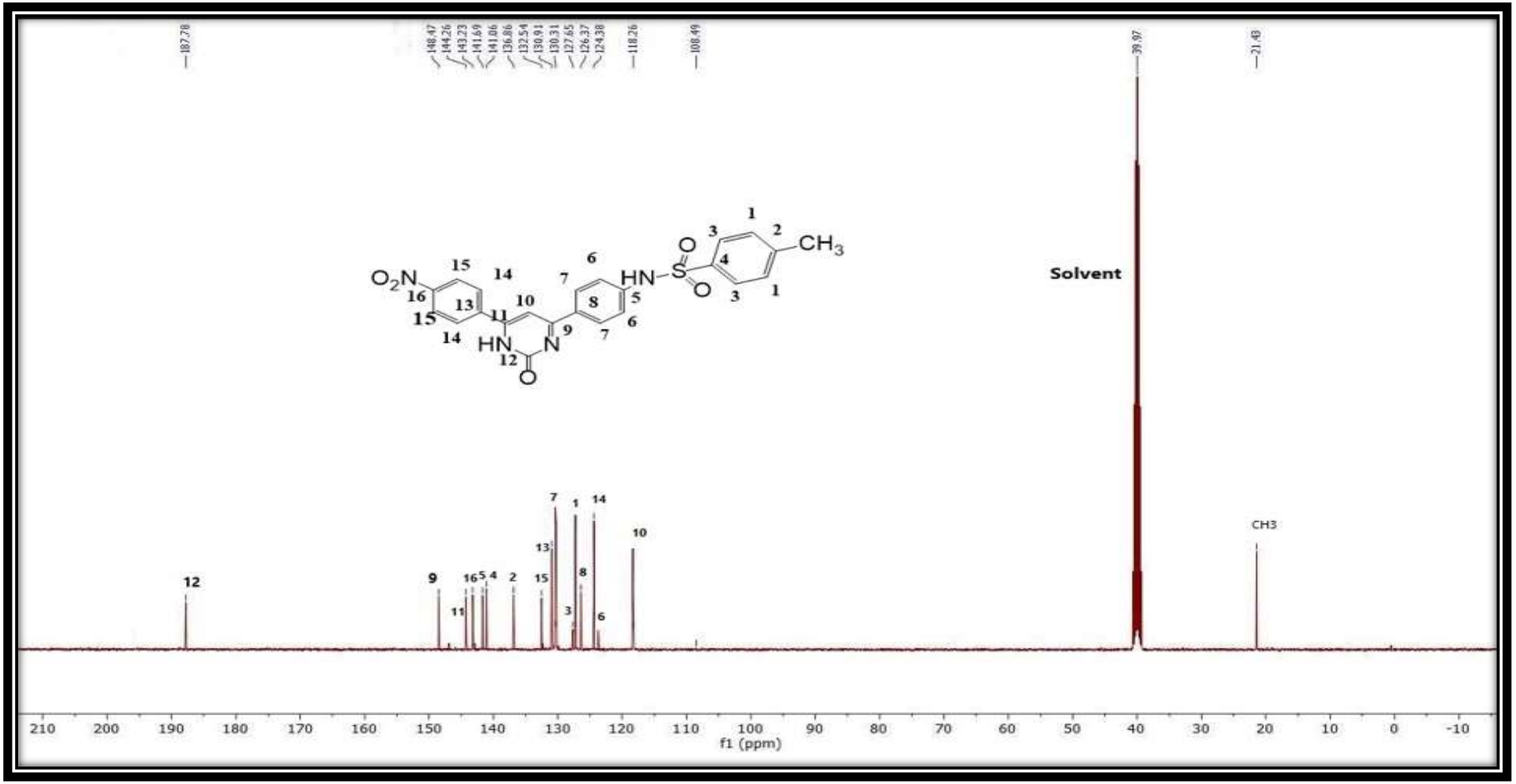


Fig (3.63) : ^{13}C-NMR spectrum of compound (H_3)

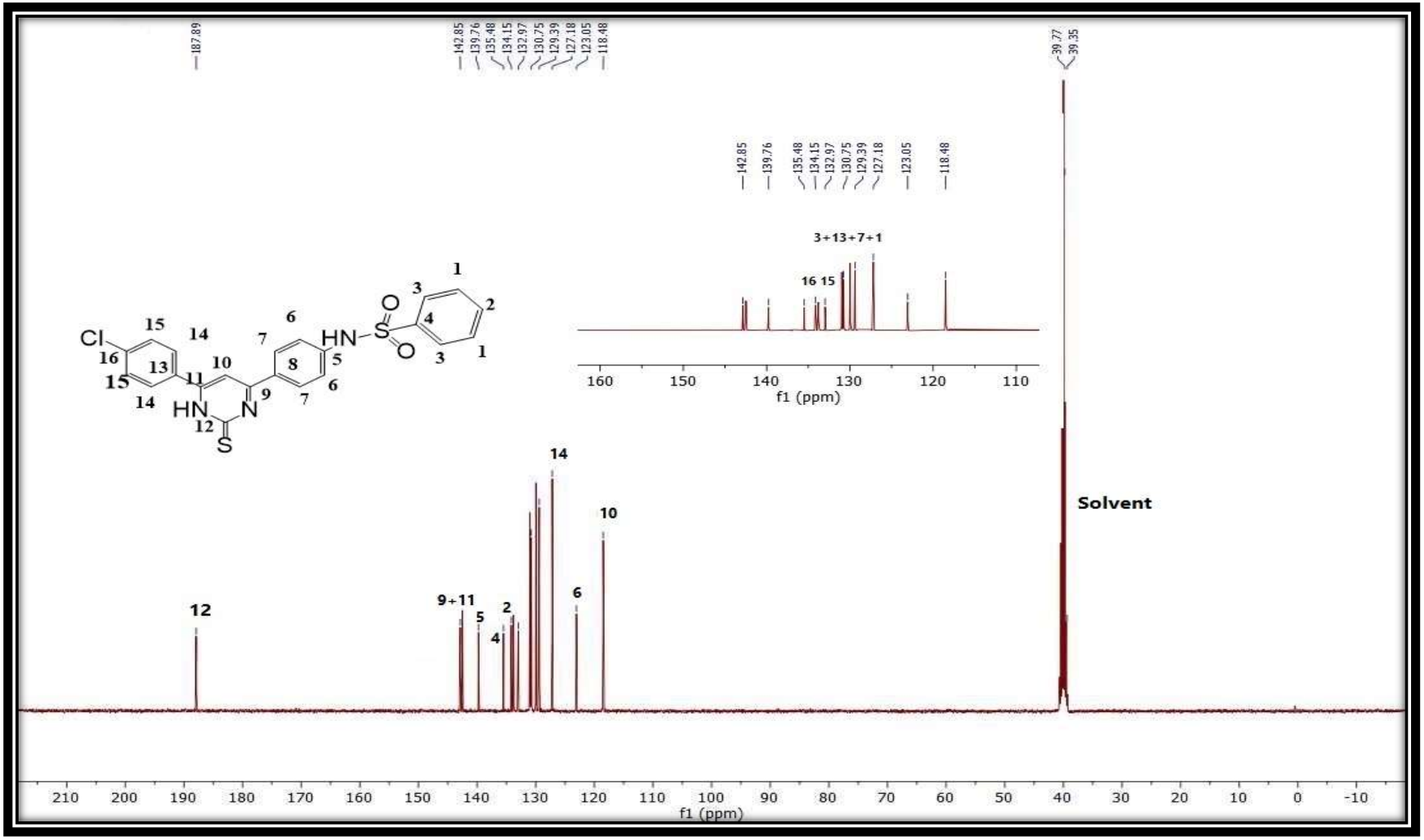


Fig (3.64) : ^{13}C-NMR spectra of compound (H_4)

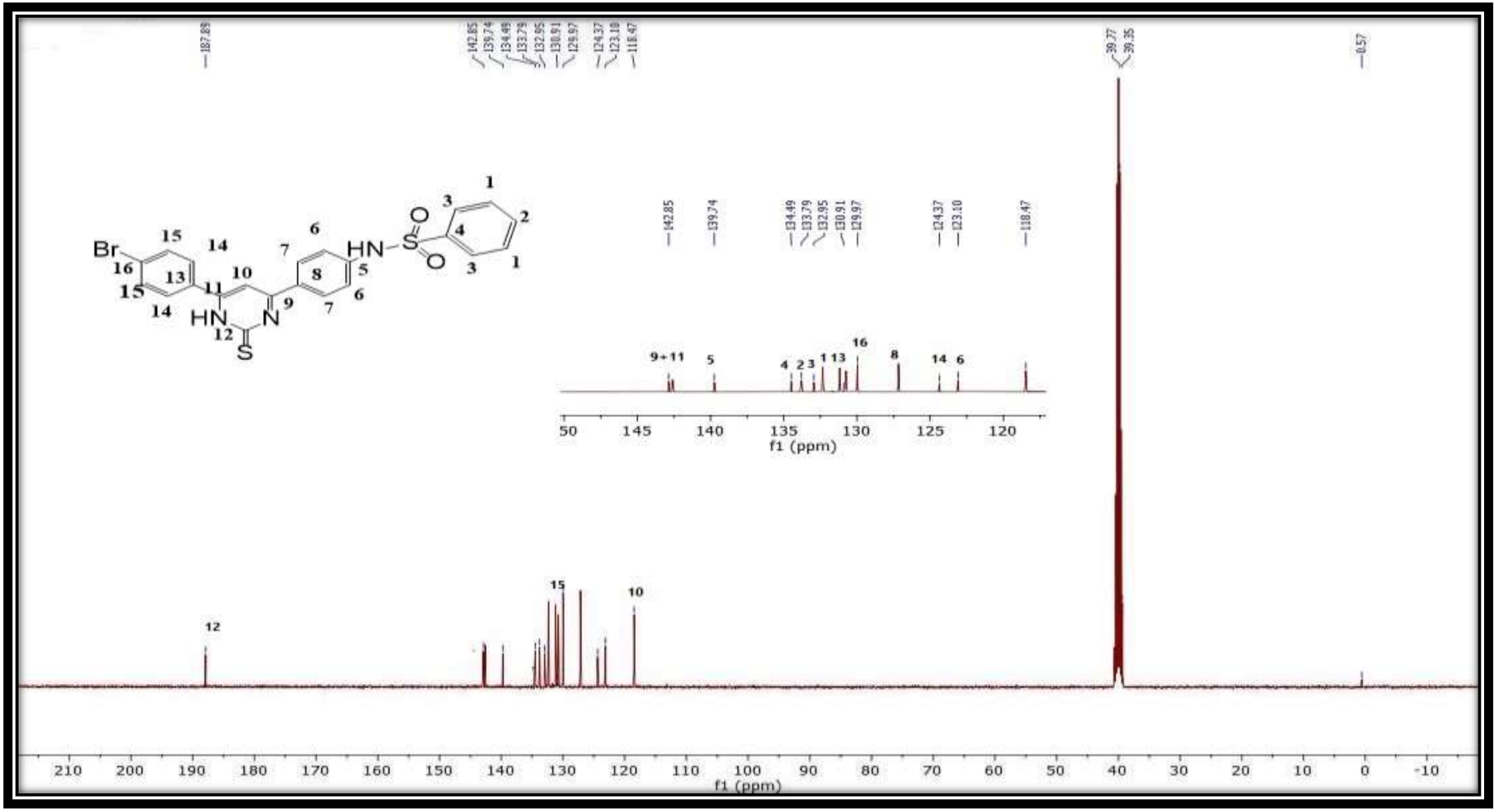


Fig (3.65) : ^{13}C-NMR spectrum of compound (H_5)

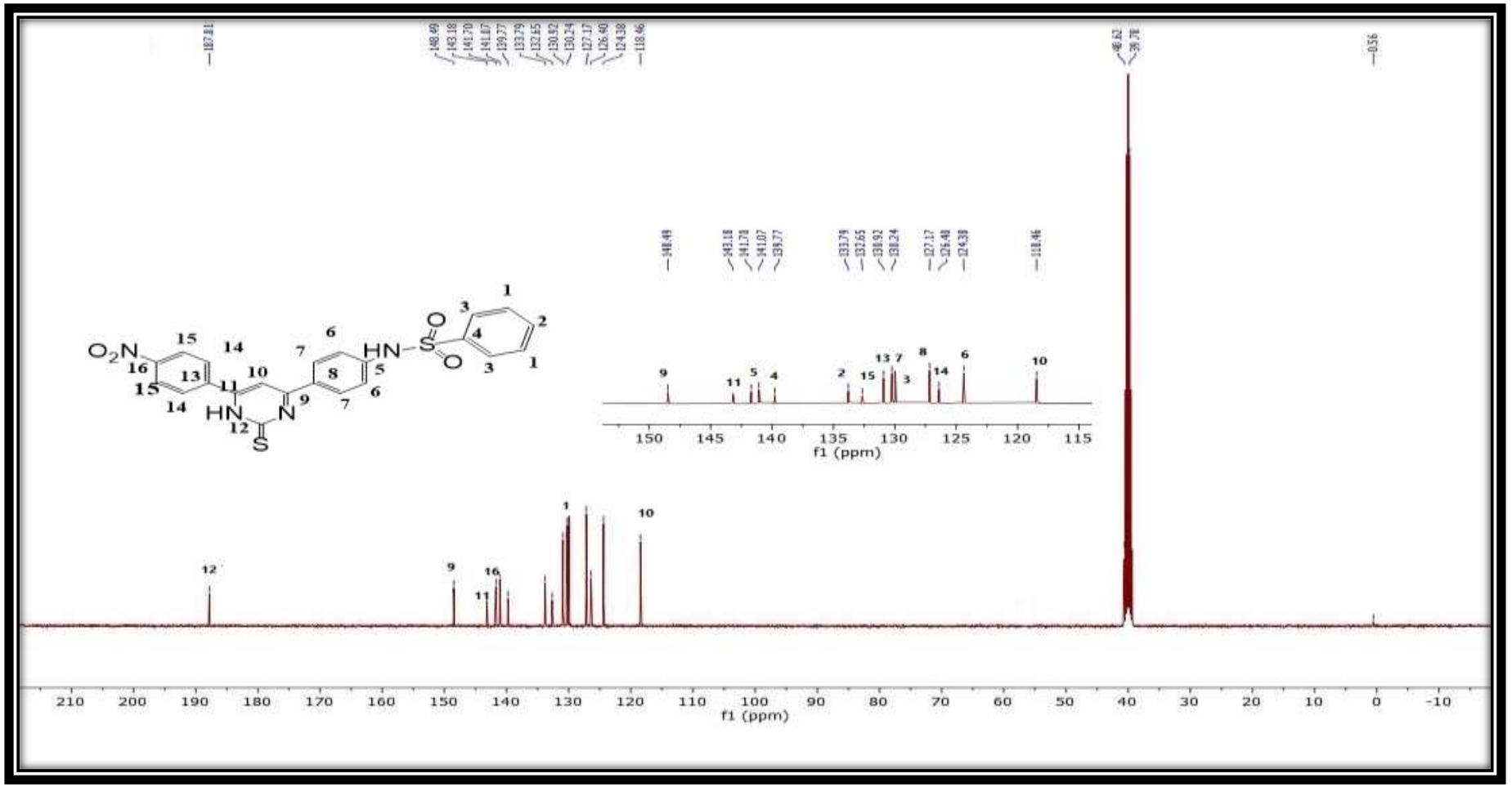


Fig (3.66) : ^{13}C-NMR spectrum of compound (H_6)

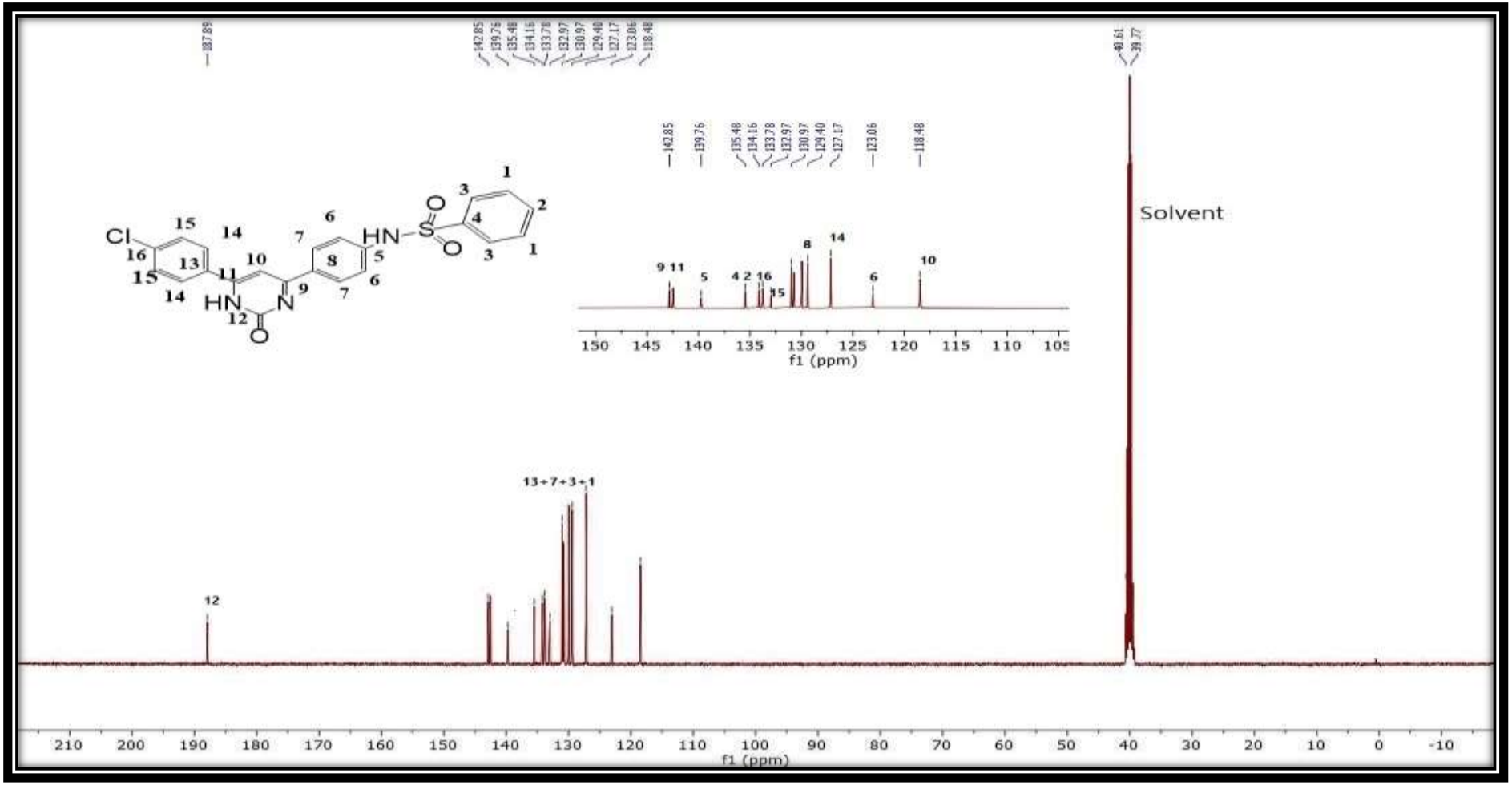


Fig (3.67) : ^{13}C-NMR spectrum of compound (H_7)

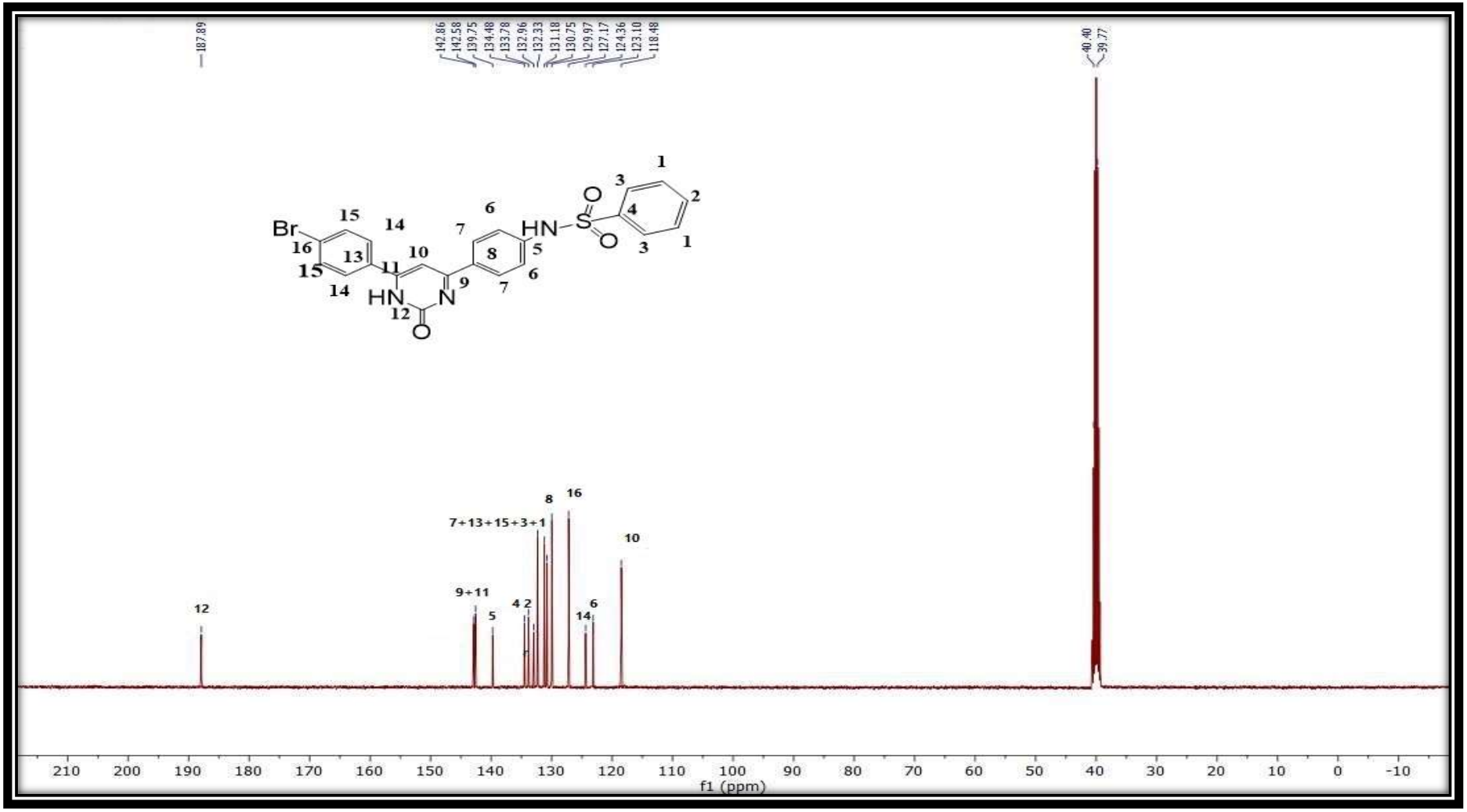


Fig (3.68) : ^{13}C-NMR spectrum of compound (H_8)

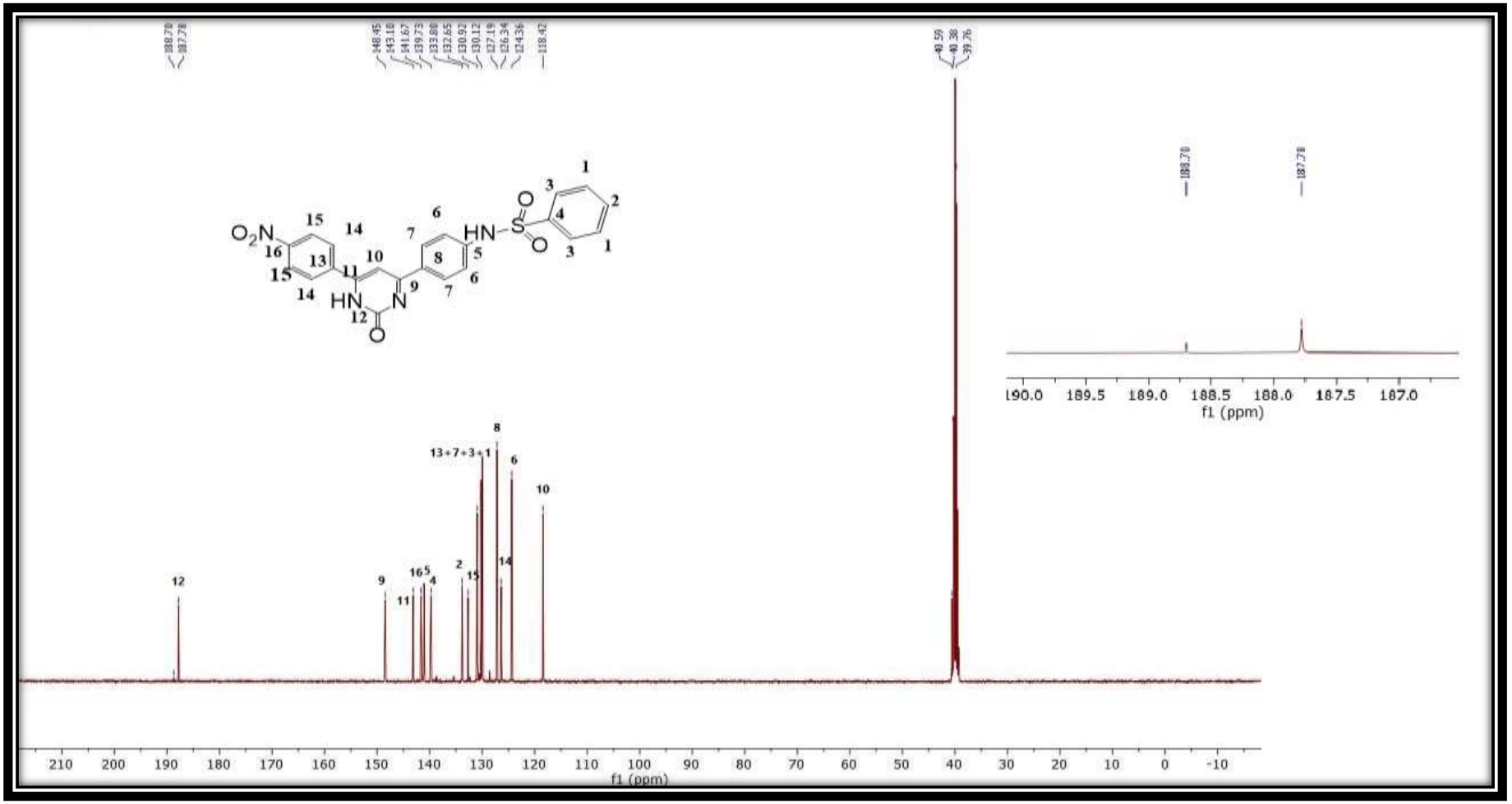


Fig (3.69) : ^{13}C-NMR spectrum of compound (H_9)

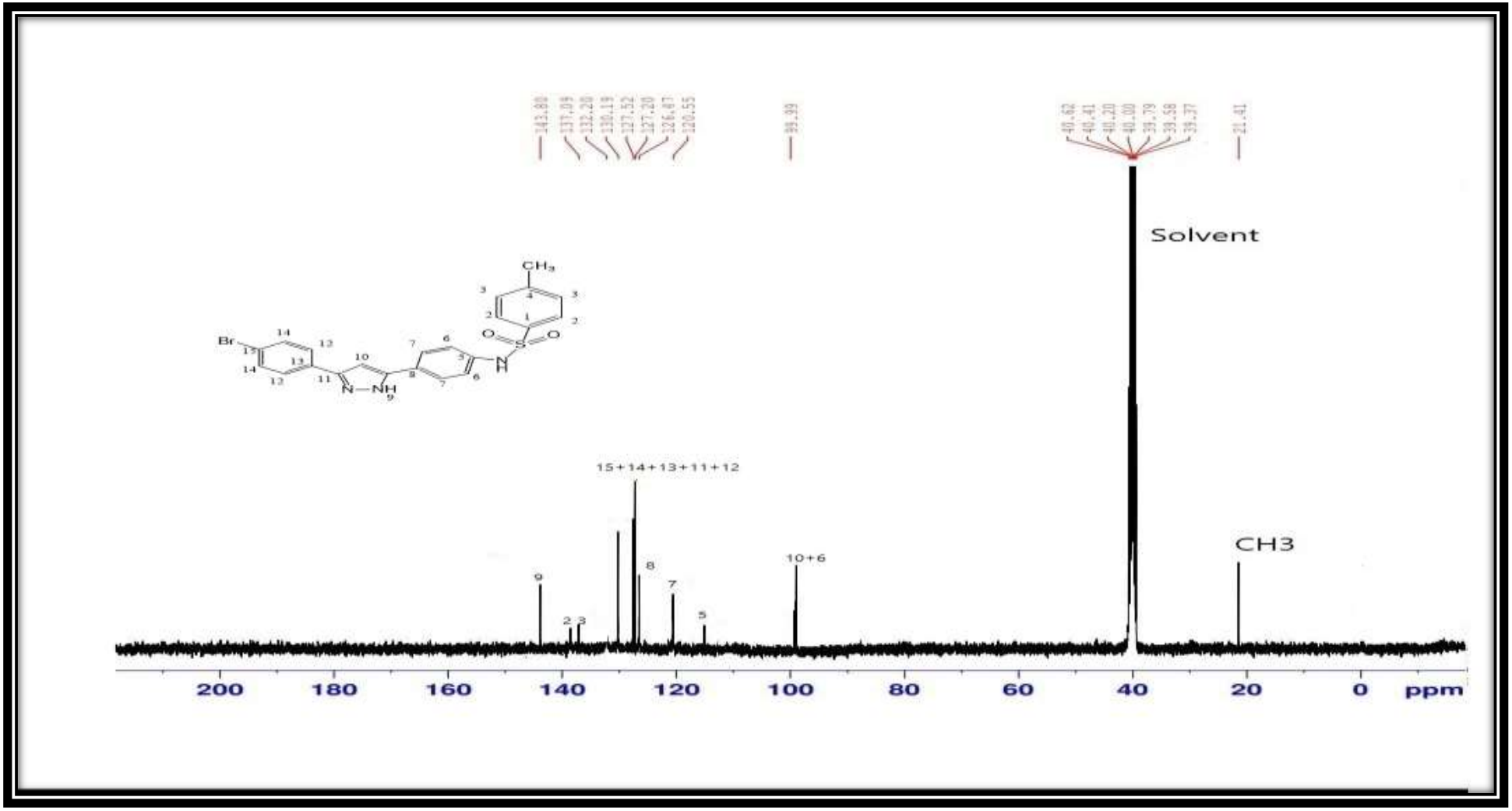


Fig (3.70) : ^{13}C-NMR spectrum of compound (H_{10})

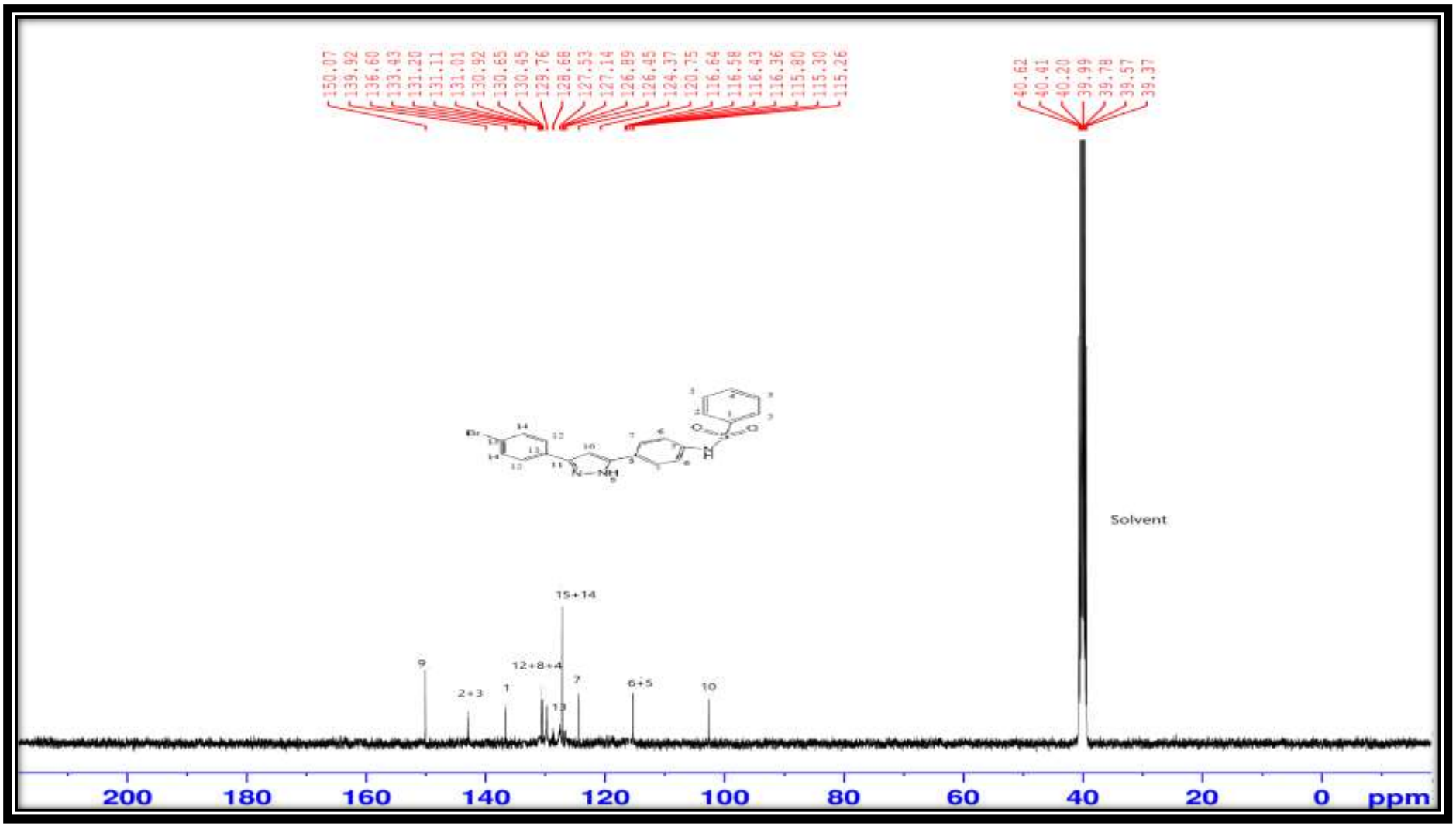


Fig (3.71) : ^{13}C-NMR spectrum of compound (H_{11})

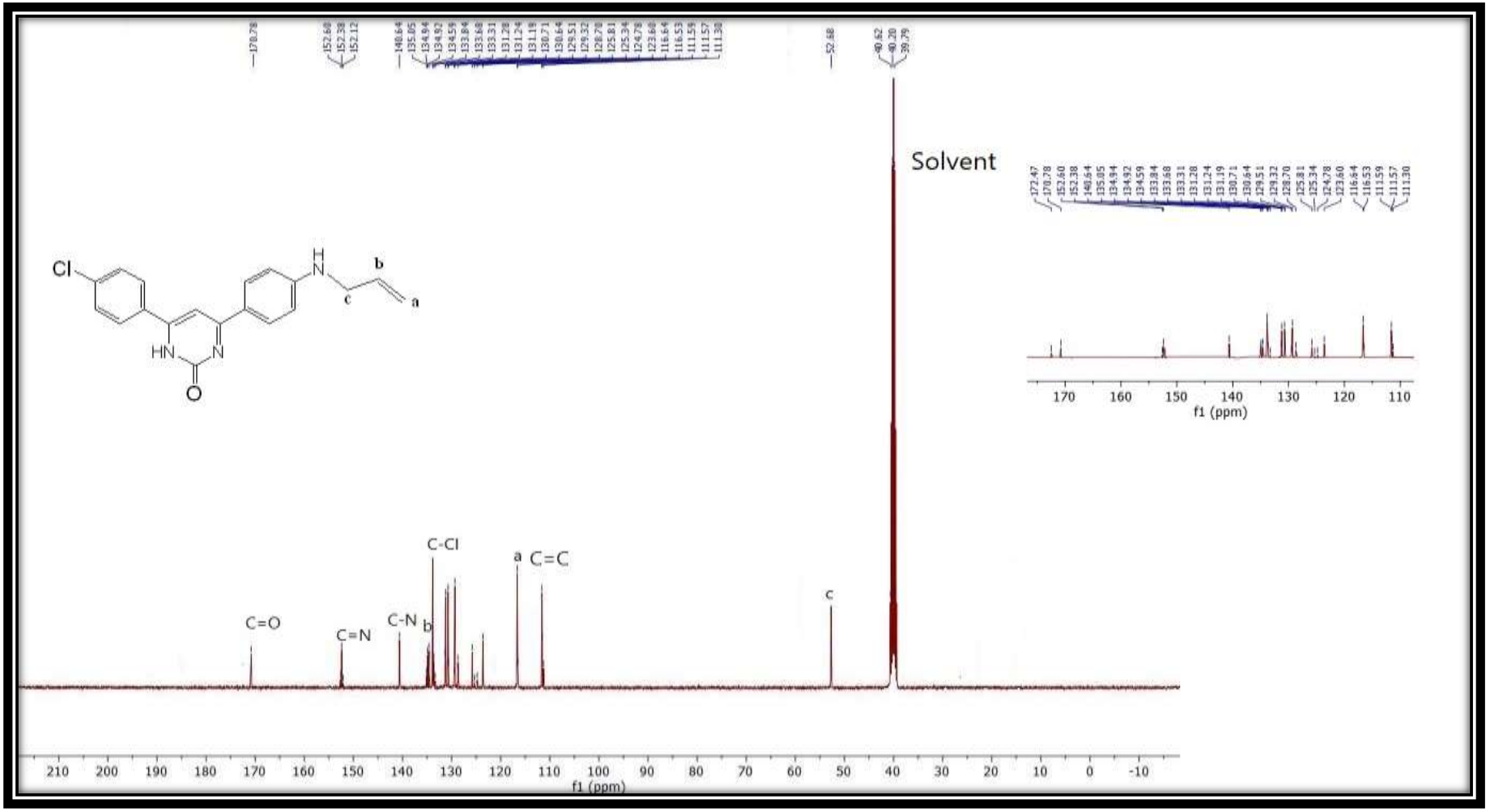


Fig (3.72) : ^{13}C-NMR spectrum of compound (H_{12})

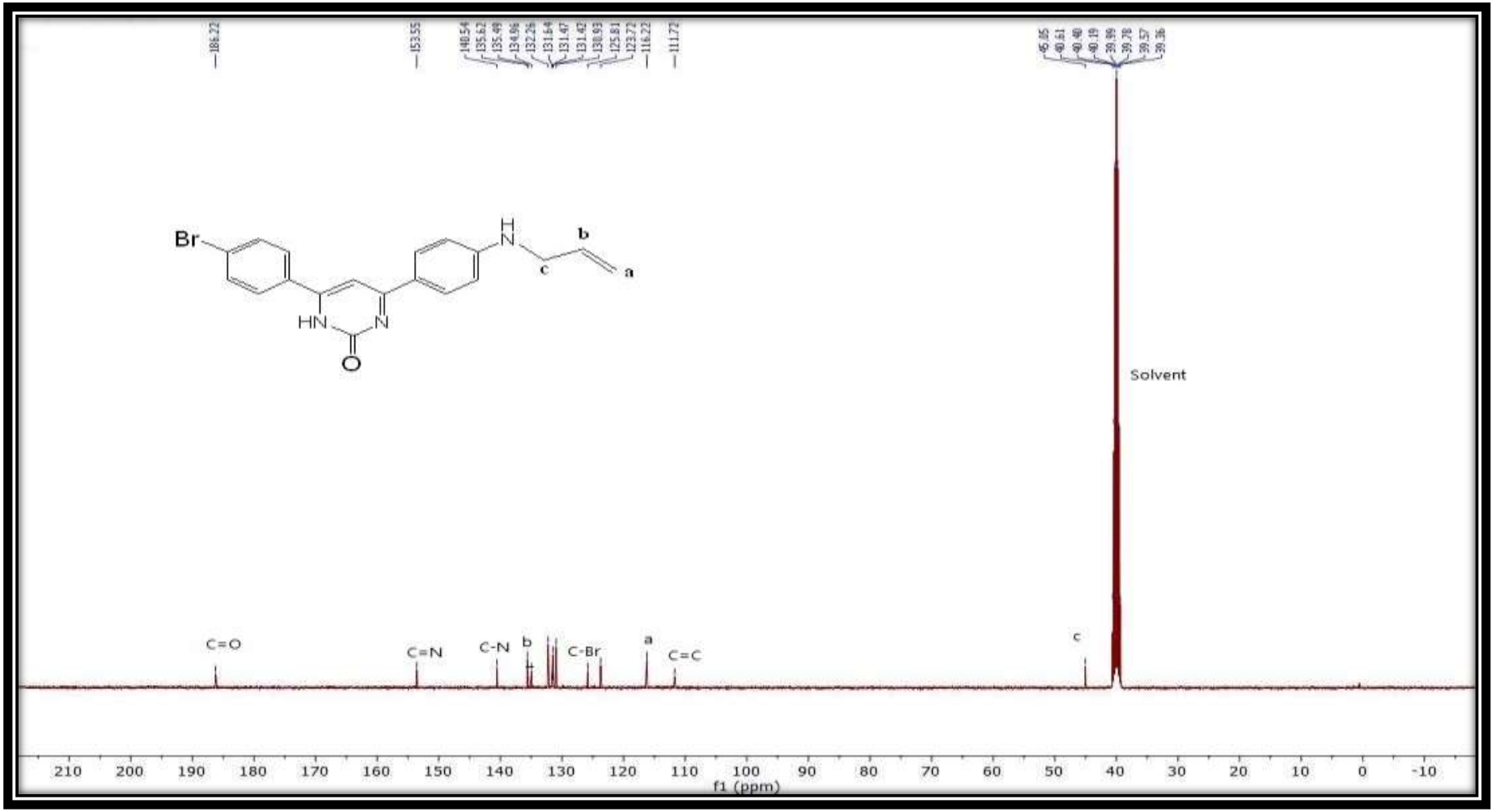


Fig (3.73) : ^{13}C-NMR spectrum of compound (H_{13})

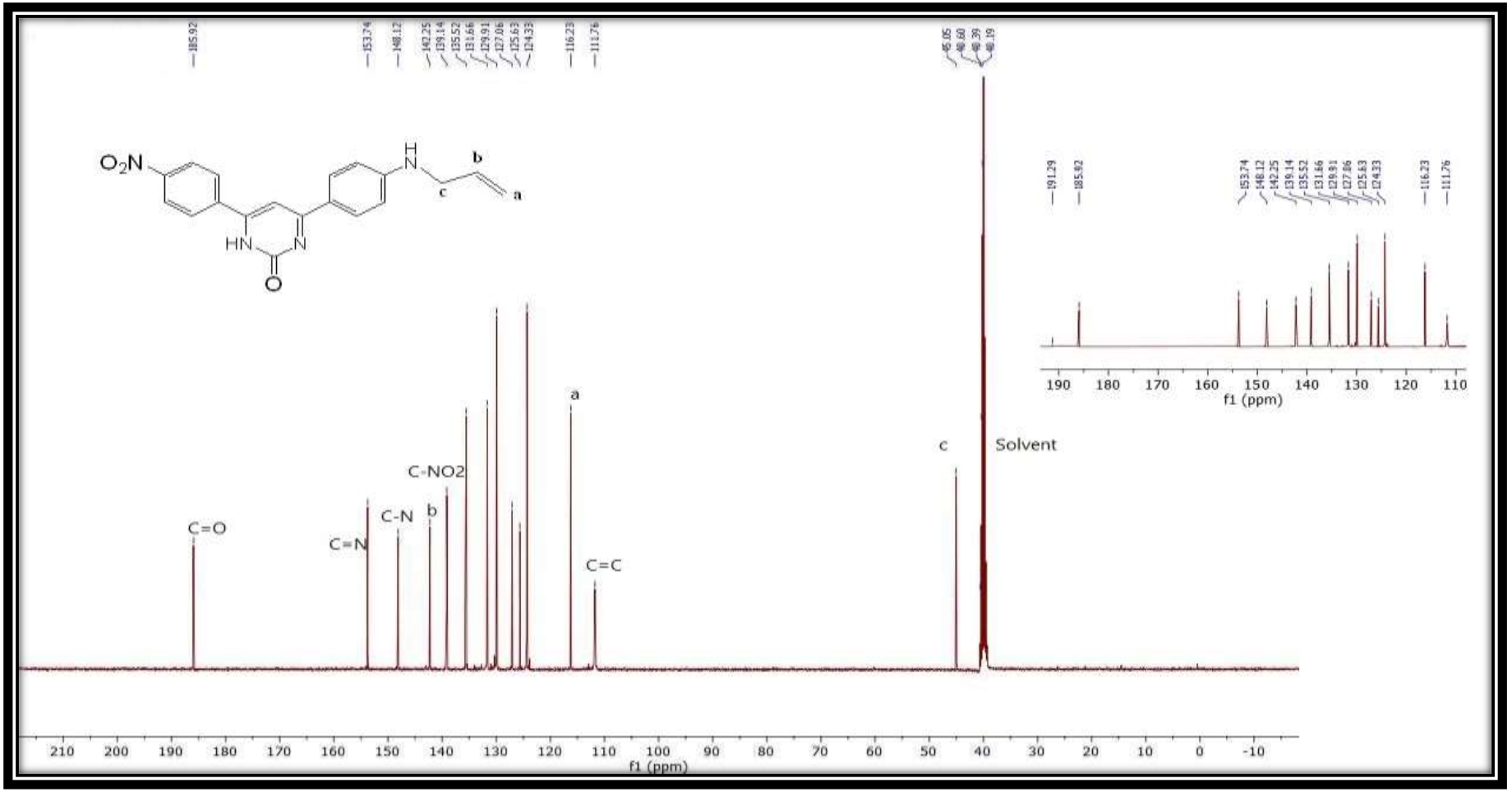


Fig (3.74) : ^{13}C-NMR spectrum of compound (H_{14})

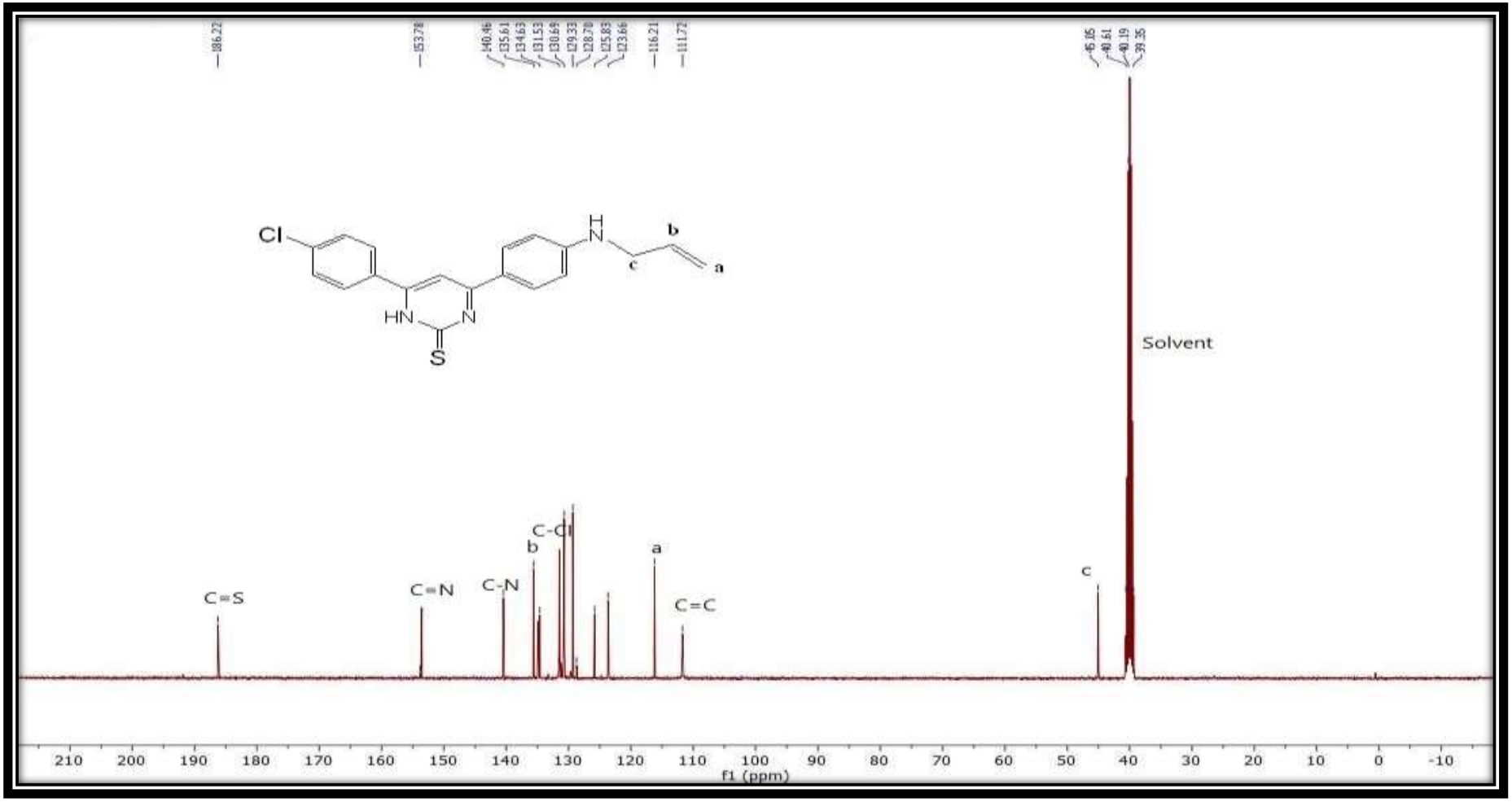


Fig (3.75) : ^{13}C-NMR spectrum of compound (H_{15})

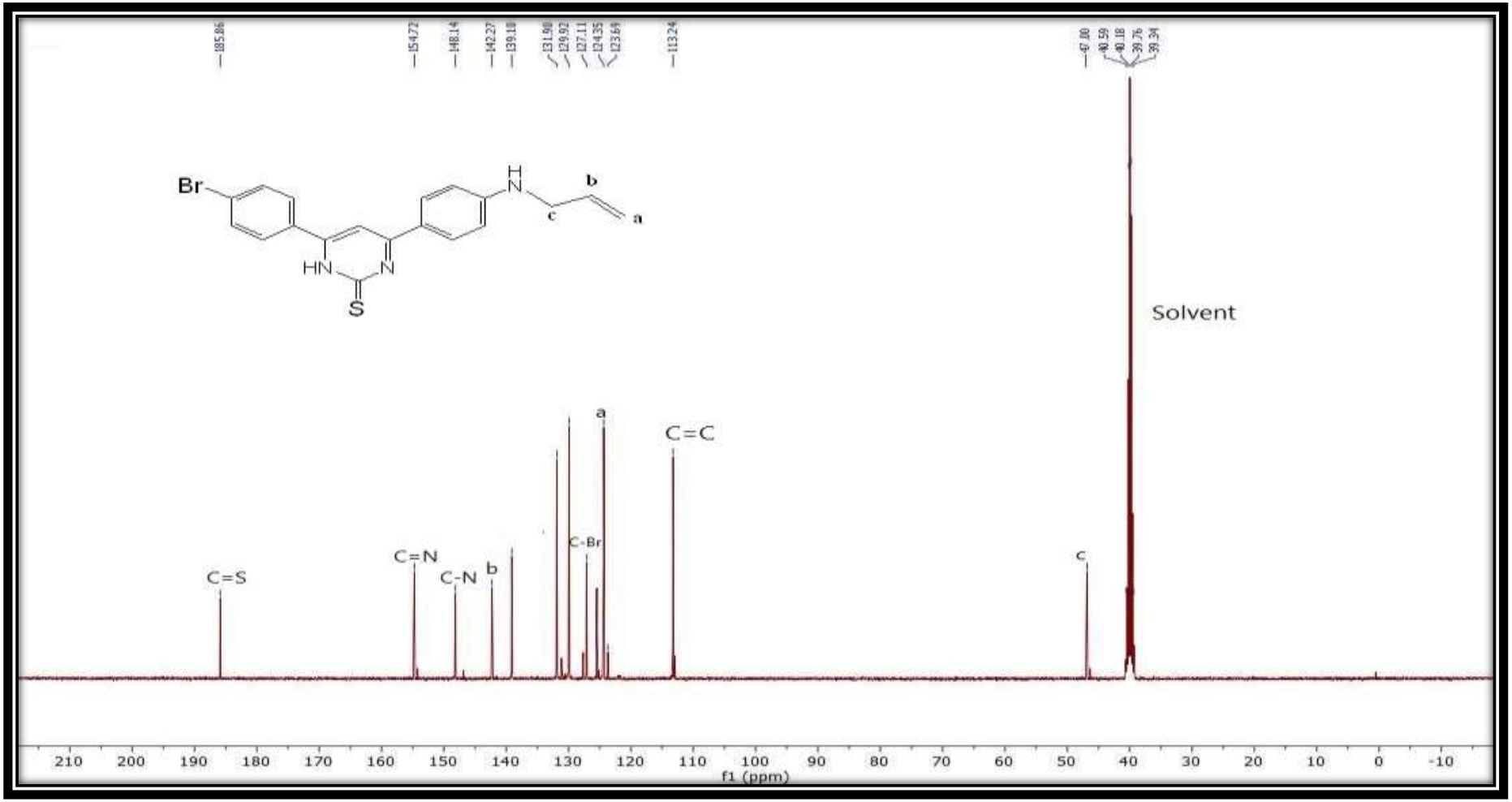


Fig (3.76) : ^{13}C-NMR spectrum of compound (H_{16})

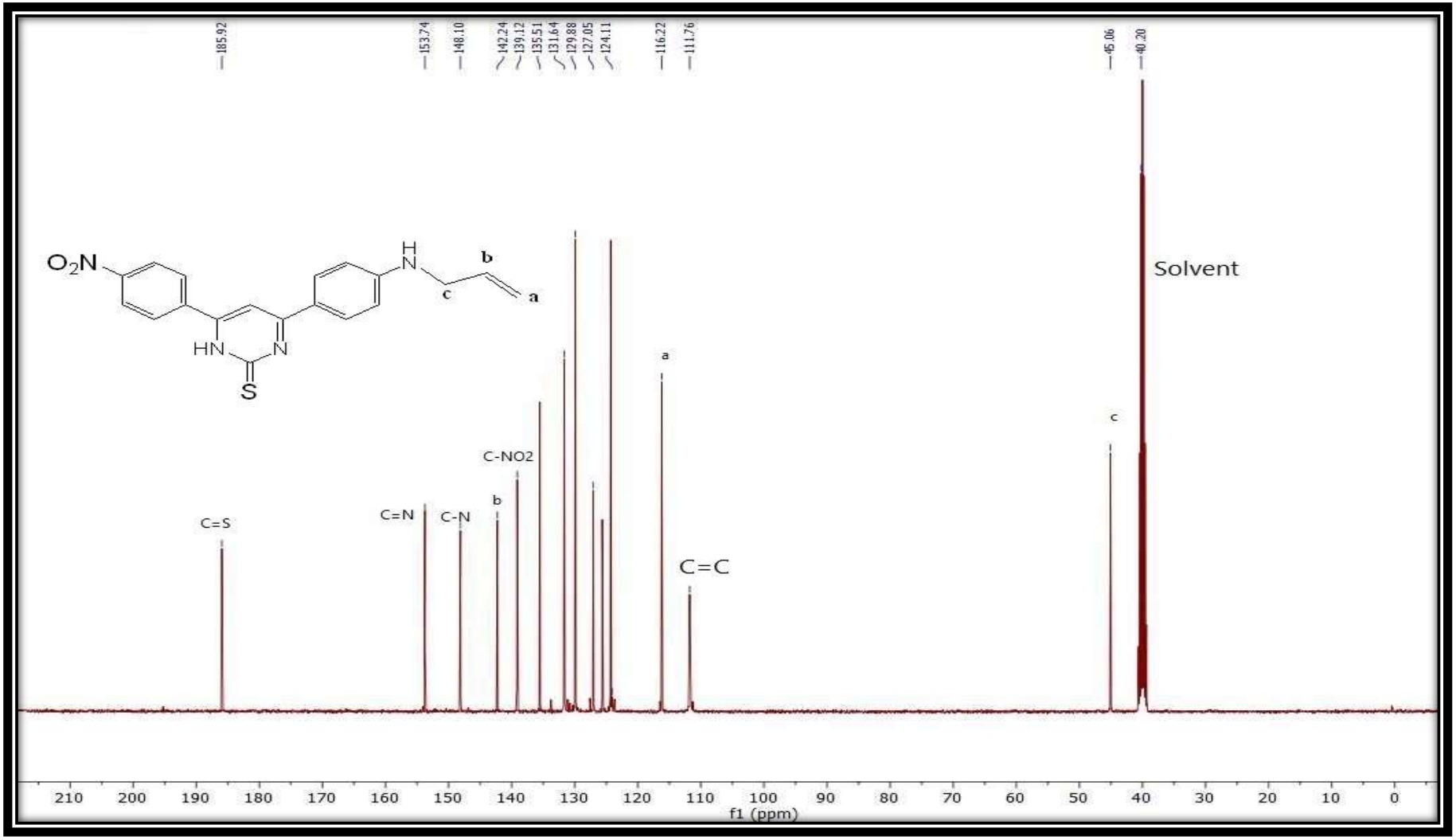


Fig (3.77) : ^{13}C-NMR spectrum of compound (H_{17})

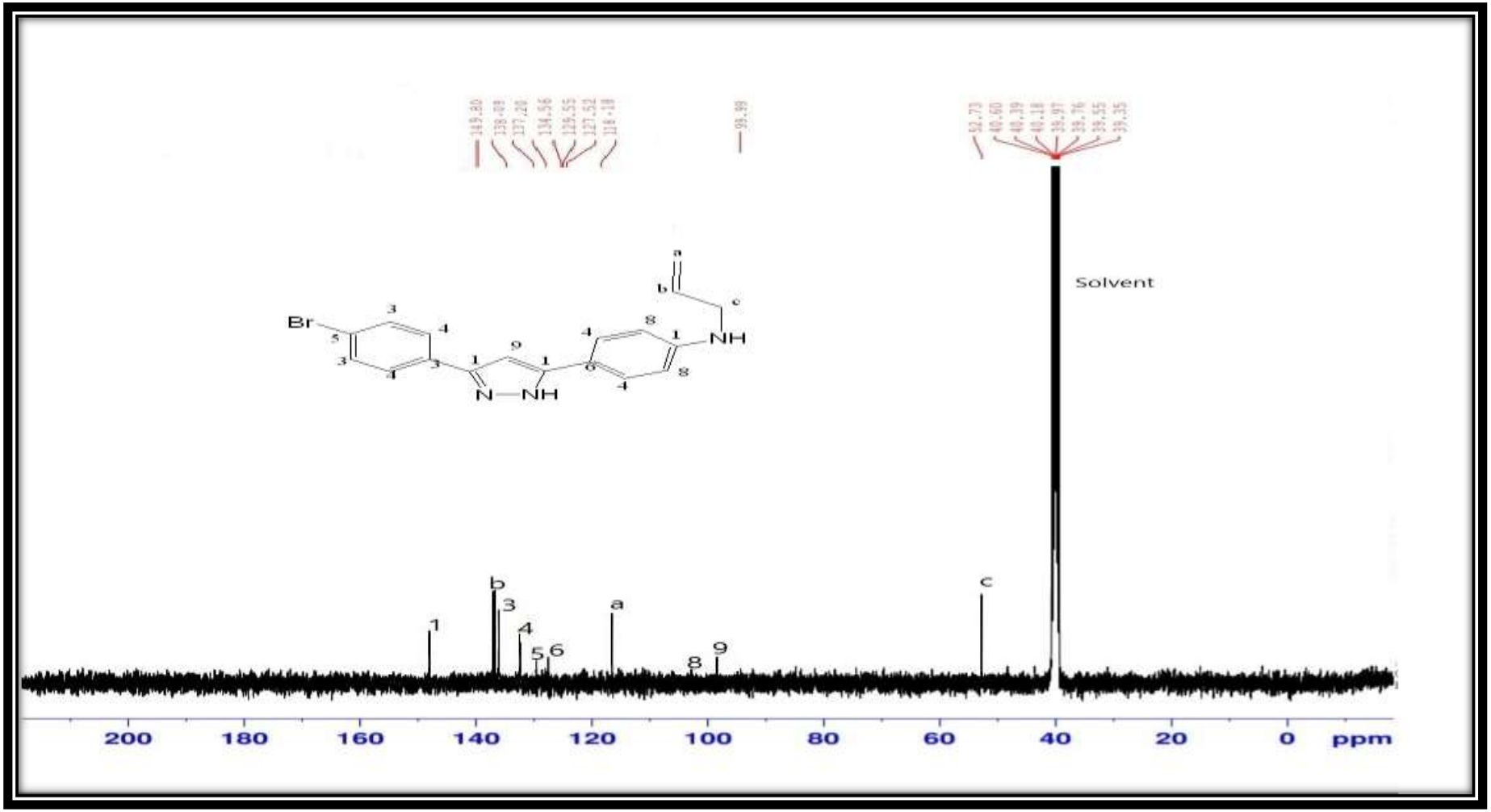
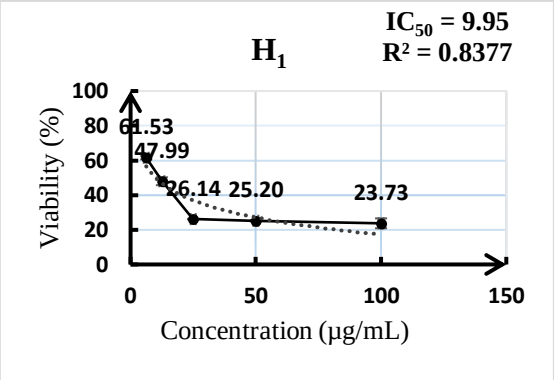


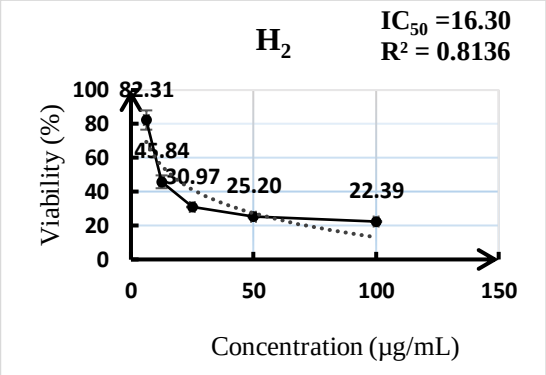
Fig (3.78) : ^{13}C-NMR spectrum of compound (H_{18})

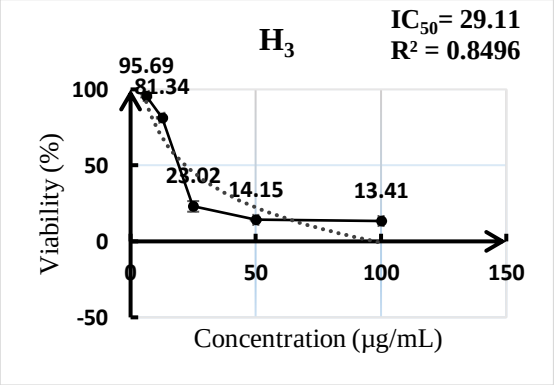
3.3 Biological activity

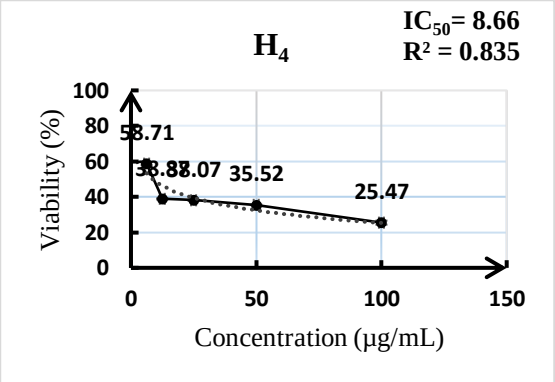
3.3.1 The cytotoxic activity for the synthesized compounds against human breast cancer cells line (MCF-7).

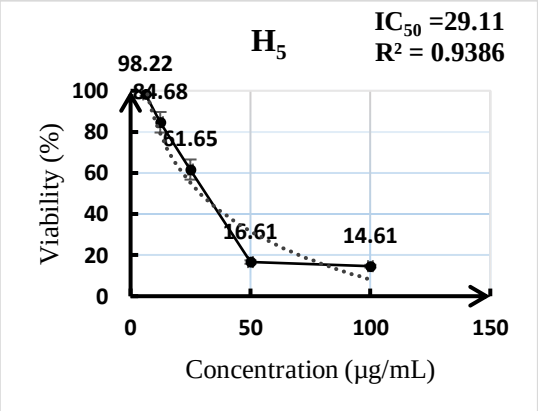
The concept of **IC_{50}** is widely used in the pharmaceutical field as an inhibition efficiency indicator of a biological and biochemical material, and its value shows the inhibitory concentration that is required to halve a specific biological substance or biochemical function. The high **IC_{50}** values indicate low inhibitory activity with the material in contrast to the materials with low **IC_{50}** values [125]. In this study, the **MCF-7** cell line was used to assay the antiproliferative activity of compounds (H_1-H_9, H_{11}, H_{12}, H_{14}, H_{15}, H_{17} and H_{18}) , compound H_4 was the most potent in this group with **IC_{50}** value of 8.66 μg/mL and compound H_8 was the lowest in potency with **IC_{50}** value of 52.29 μg/mL, Figure (3.79). Microscopical examination of the tested compounds in the cell line at 100 μg/mL used to confirm the calculation of the **IC_{50}**, Figure (3.80).

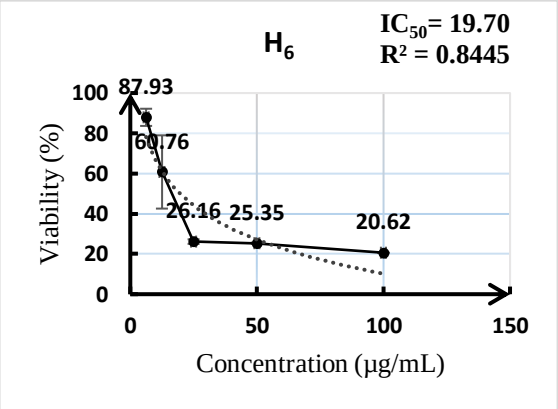

H1
IC50 = 9.95
R² = 0.8377
Viability (%)
Concentration (µg/mL)
61.53
47.99
26.14
25.20
23.73

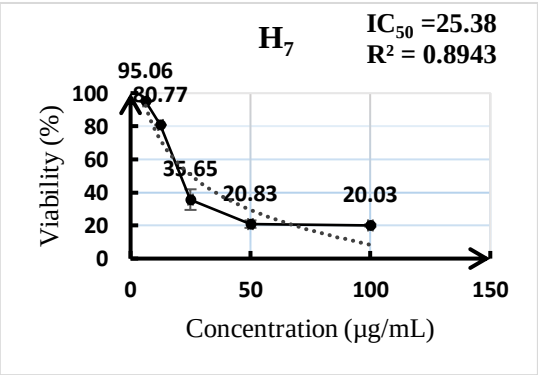

H2
IC50 =16.30
R² = 0.8136
Viability (%)
Concentration (µg/mL)
82.31
45.84
30.97
25.20
22.39

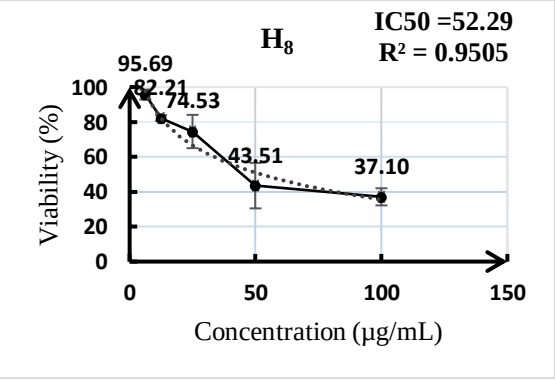

H3
IC50= 29.11
R² = 0.8496
Viability (%)
Concentration (µg/mL)
95.69
81.34
23.02
14.15
13.41


H4
IC50= 8.66
R² = 0.835
Viability (%)
Concentration (µg/mL)
58.71
38.88
38.07
35.52
25.47


H5
IC50 =29.11
R² = 0.9386
Viability (%)
Concentration (µg/mL)
98.22
84.68
61.65
16.61
14.61


H6
IC50= 19.70
R² = 0.8445
Viability (%)
Concentration (µg/mL)
87.93
60.76
26.16
25.35
20.62


H7
IC50 =25.38
R² = 0.8943
Viability (%)
Concentration (µg/mL)
95.06
80.77
35.65
20.83
20.03


H8
IC50 =52.29
R² = 0.9505
Viability (%)
Concentration (µg/mL)
95.69
82.21
74.53
43.51
37.10

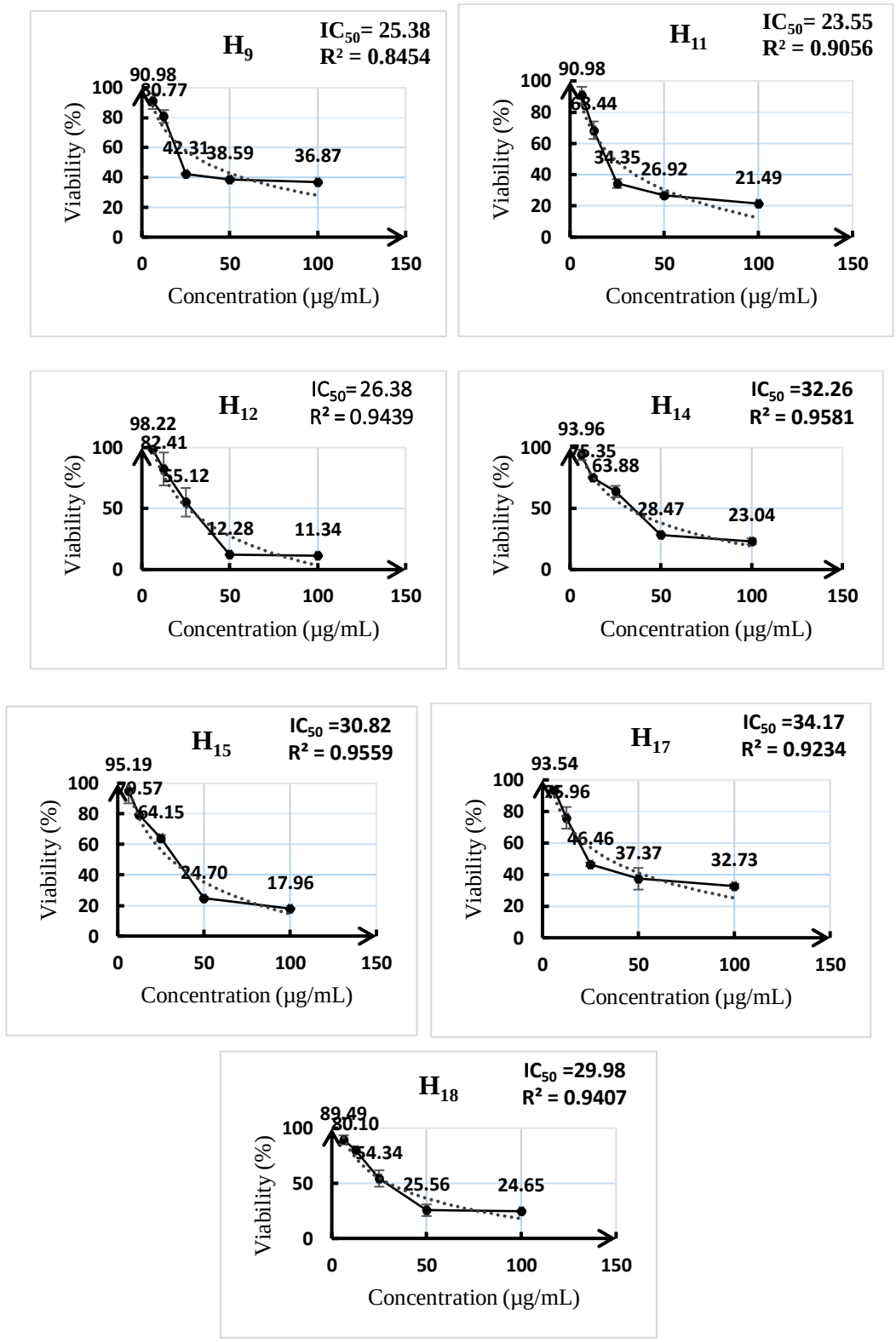
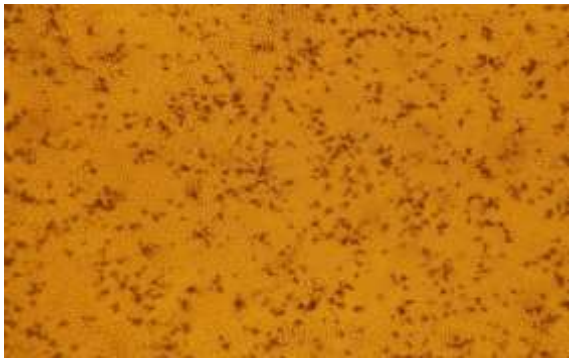


Fig (3.79) : The IC_{50} Values of compounds against MCF-7 Cell line

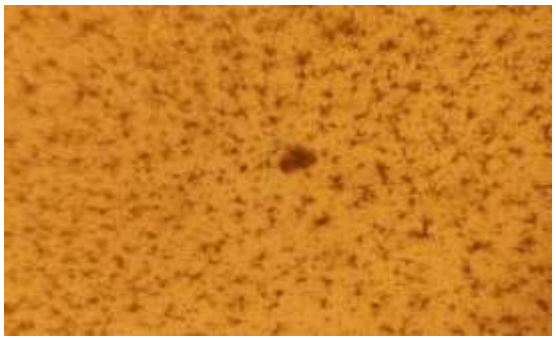
Control

H_1

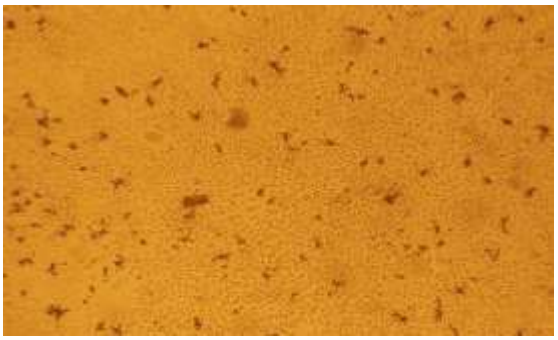


H_2

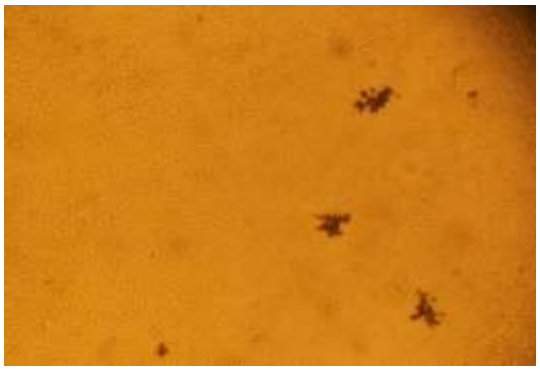
H_3



H_4



H_5



H_6

H_7

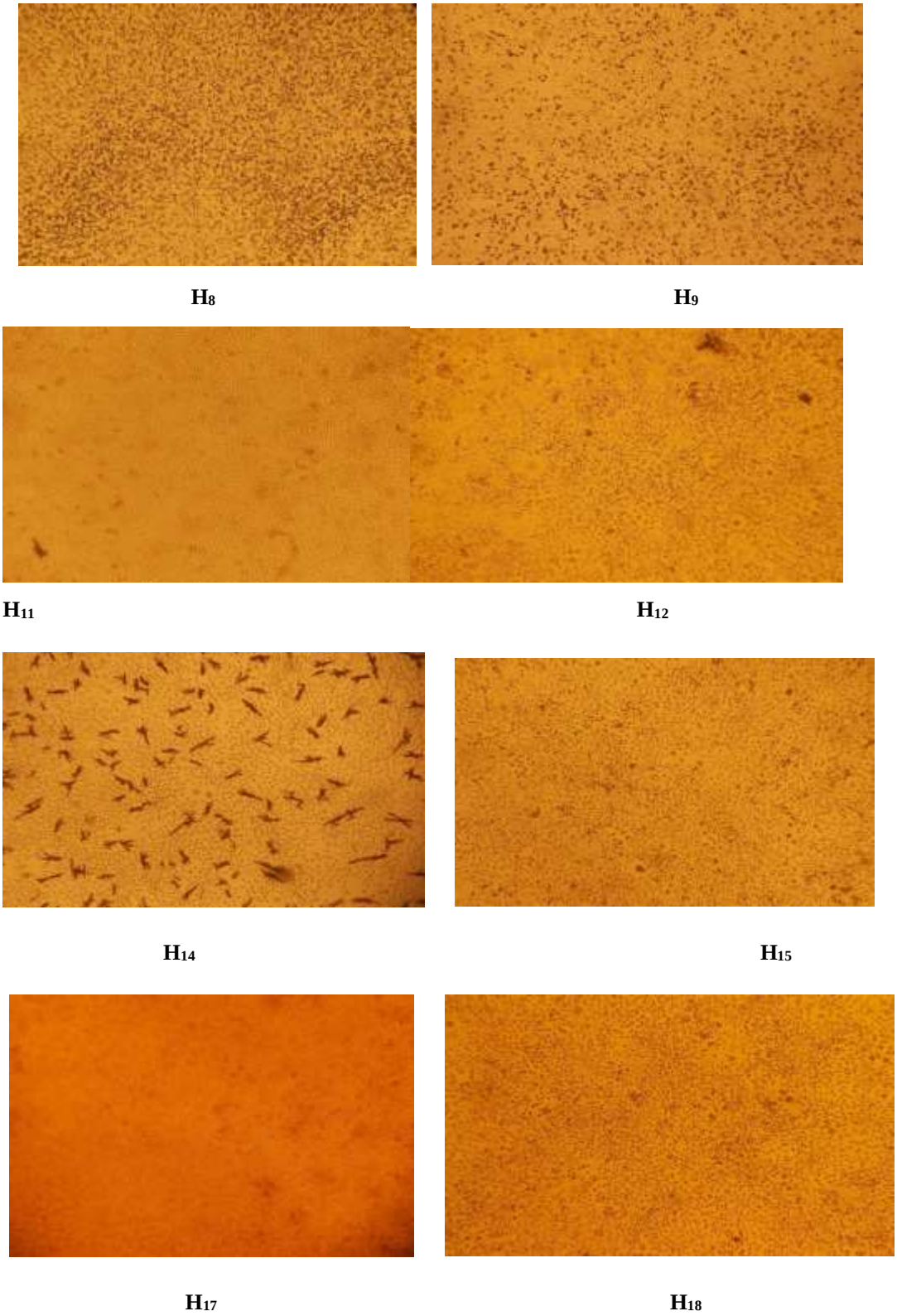


Fig (3.80) : MCF-7 cell line under microscopic examination of control and compounds at 100 µm concentration

3.3.2 Antibacterial Activity of the Compounds:

Due to their extensive spectrum of biological activity, organic molecules with heterocyclic ring structures continue to garner a lot of attention [126]. In this work, six gram positive and gram negative bacteria with multidrug resistance were examined using heterocyclic compounds and their treatments (3.10). The outcomes in Table (3.11) demonstrated varying levels of efficacy against the tested bacteria;

1. The **IV** compound at concentration 5,10,15,20 and 30 mg/mL inhibited the growth of *Escherichia coli* 1 and *Escherichia coli* 2 with zone (10, 12) mm respectively, in *Staphylococcus aureus* 1 only the (20, 30) mg/mL displayed inhibition zone (15, 18) mm respectively, While *Streptococcus agalactiae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* 2 show less sensitivity against this compound.
2. The **VI** compound at concentration 10,15,20 and 30 mg/mL inhibited the growth of *Escherichia coli* 1with zone (12,15, 20) mm respectively, although, showed the inhibited (12,13, 15,15) mm of the growth of this compound at 30 mg/mL concentration for *Pseudomonas aeruginosa, Escherichia coli* 2, *Staphylococcus aureus* 1, and *Staphylococcus aureus* 2 respectively. No effect was observed of *Streptococcus agalactiae* against this compound.
3. The **VIII** compound at concentration 10 and 20 mg/mL inhibited the growth of *Escherichia coli* 1, *Escherichia coli* 2, *Staphylococcus aureus* 1 and *Streptococcus agalactiae* (20,20,22, 18) mm respectively. Whereas this compound at 5 mg/mL inhibited the growth of *Escherichia coli* 1, *Staphylococcus aureus* 1 and *Streptococcus agalactiae* (15,10,15) mm respectively. Also, no effect was observed of *Staphylococcus aureus* 2 and *Pseudomonas aeruginosa.*

4. The H_1, H_2, H_3 and H_5 compounds at concentration 5 mg/mL inhibited only the growth of *Streptococcus agalactiae* and *Pseudomonas aeruginosa* (20,47) mm correspondingly. Although the H_1 at (20, 30 mg/mL) increased the inhibition zone to (15,18) mm of *Staphylococcus aureus* respectively.
5. The H_4 and H_7 compounds at concentration 5 mg/mL inhibited only the growth of *Staphylococcus aureus* 1 (15 mm) for each one.
6. The H_3 compound at concentration 5 mg/mL inhibited only the growth of *Staphylococcus aureus* and *Pseudomonas aeruginosa* (20 mm) for each one.
7. The H_8 compound at concentration 5,10,20 and 30 mg/mL inhibited only the growth of *Escherichia coli* 1 (12,15,15,20) mm respectively.

Table (3.10): Biological activity of the precures compound on tested bacteria.

Sample	Conc. mg/ml	Diameter of inhibition zone (mm)					
		E.coli 1	Phsed.	Staph.1	Psd.monous	E.coli 2	Staph. 2
IV	30	10	0.00	18	0.00	12	0.00
IV	20	10	0.00	15	0.00	12	0.00
IV	5,10,15	10	0.00	0.00	0.00	12	0.00
VI	30	20	0.00	15	12	13	15
VI	20,10	15	0.00	0.00	0.00	0.00	0.00
VI	15	12	0.00	0.00	0.00	0.00	0.00
VIII	20,10	20	18	22	0.00	20	0.00
VIII	5	15	10	15	0.00	0.00	0.00

Table (3.11) : Biological Activity of Synthesis Compound on Tested Bacteria.

Sample	Conc. mg/ml	Diameter of inhibition zone (mm)					
		E.coli 1	Phsed.	Staph.1	Psuelo.1	E.coli 2	Staph.2
H_1	5	0.00	20	0.00	45-47	0.00	0.00
H_2	5	0.00	20	0.00	45-47	0.00	0.00
H_3	5	0.00	20	0.00	45-47	0.00	0.00
H_5	5	0.00	20	0.00	45-47	0.00	0.00
H_1,H_5,H_{14}	5	0.00	20	20	0.00	0.00	0.00
H_1	30	0.00	0.00	18	0.00	0.00	0.00
H_1	20	0.00	0.00	15	0.00	0.00	0.00
H_4	5	0.00	0.00	15	0.00	0.00	0.00
H_7	5	0.00	0.00	15	0.00	0.00	0.00
H_7	10	0.00	0.00	0.00	0.00	0.00	0.00
H_8	20,10	15	0.00	0.00	0.00	0.00	0.00
H_8	5	12	0.00	0.00	0.00	0.00	0.00
H_8	30	20	0.00	0.00	0.00	0.00	0.00

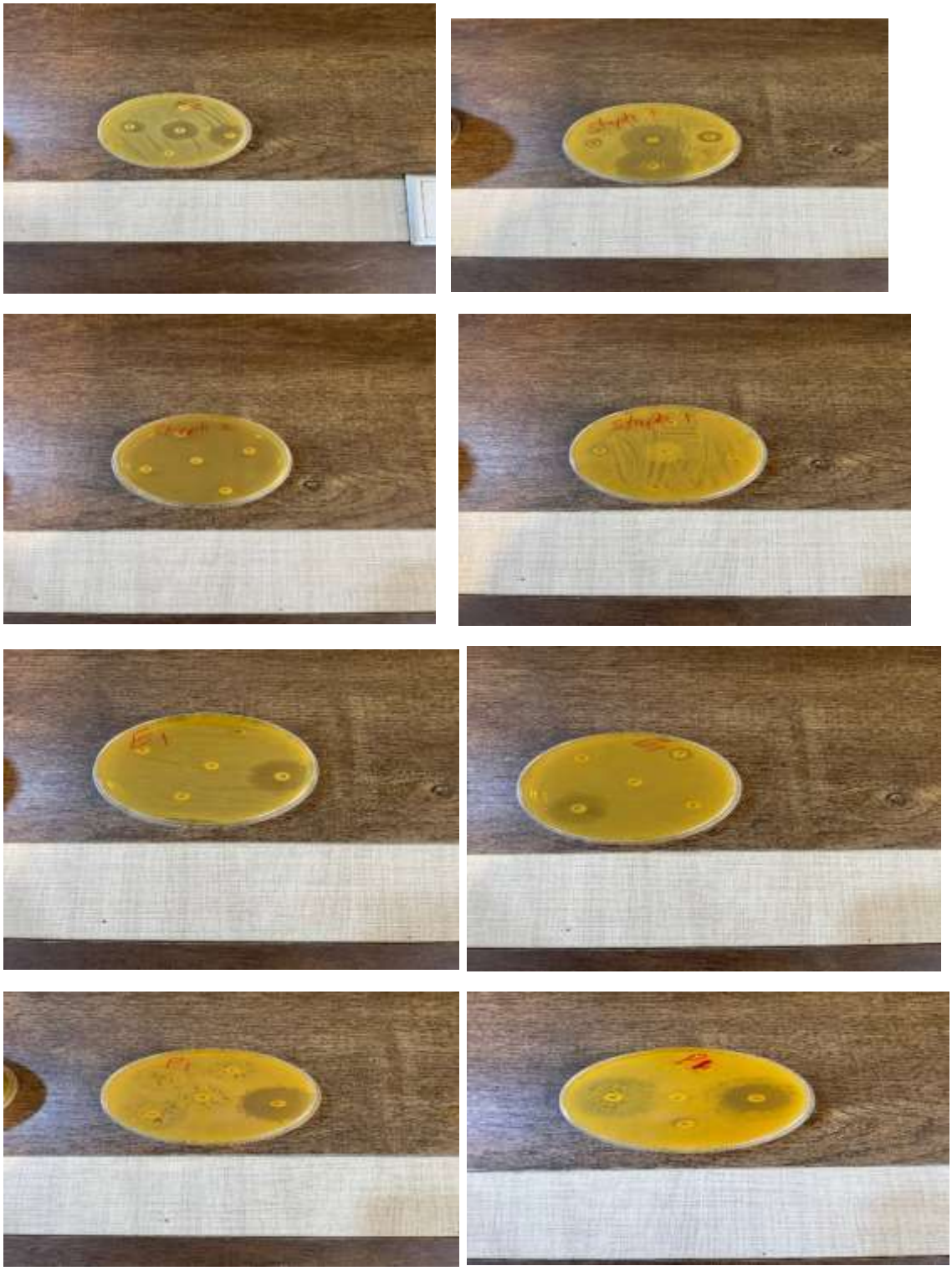


Fig (3.81): The Effect of Synthesis Compound and their Precures Compound on Tested Bacteria. (H_1-H_5 ,H_7 ,H_8 ,H_{14})

Conclusions And Recommendations

Conclusions

1. The aryl sulfonyl derivatives gave higher yields compared to the yields given by the ally derivatives.
2. It was observed that the starting material containing a pyrimidine ring Substituted with a thioxo group gave a greater amount of product compared to the one containing an oxo group.
3. The preparation of the aryl sulfonyl derivatives takes much less time than the preparation of the ally derivatives.
4. The use of the reagent benzene sulfonyl chloride leads to the production of products in a greater Proportion than if the reagent p - toluene sulfonyl chloride was used in preparation.
5. The ally derivatives require more effort in purification compared to the aryl sulfonyl derivatives.
6. The biological activity of the prepared antibacterial compounds appeared to be much higher than that shown by the starting materials.
7. In general the prepared Compounds showed acceptable anti - breast cancer activity.

Recommendations

1. The use of potassium Carbonate as powder besides the allyl bromide (reagent) and acetone (solvent) in the preparation of N-allyl derivatives may be gives products with high yield compound with the use of the solution of potassium Carbonate.
2. We can use the method of the synthesis of N - allyl derivatives to prepae nucleosides from nitrogen bases by using derivatives of halosugar instead of allyl bromide.
3. It is possible to use other nitrogenous bases such as purines and quinolines substituted with amine group in the preparation of aryl sulfonyl derivative using p-aminobenzene sulfonyl chloride for the purpose of obtaining biologically active compounds.
4. Our study recommends to complete the estimation of MIC and ID_{50} of the starting materials and synthesised derivatives.

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اخيرًا ، بعد تخليق المركبات وتصنيفها بتقنيات مختلفة، تم تقدير النشاط البيولوجي لهذه المركبات ، بما في ذلك النشاط المضاد للاورام والبكتيريا ؛ تم تحديد هذه الأنشطة في المختبر باستخدام قياس السمية الخلوية (قياس قابلية الخلية MTT) في خلايا MCF7 لاكتشاف النشاط المضاد للاورام ، وطريقة انتشار قرص كيربي باور المستخدمة لاختبار حساسية المضادات الحيوية ضد سلالات البكتيريا المسببة للأمراض المختلفة.

في هذه الدراسة ، تم استخدام خط الخلايا لفحص النشاط المضاد للمركبات (H_{11} , H_1 - H_9 H_{18} , H_{17} , H_{15} , H_{14} , H_{12},) وكان المركب H_4 الاكثر فاعلية في هذه المجموعة بقيمة IC_{55} 8.66 ميكروغرام \مل ومركب H_8 هو الاقل فاعلية مع قيمة IC_{50} 52.29 ميكروغرام \مل.

كما تم فحص المركبات المحضرة بحثًا عن مضادات البكتريا ضد ستة أنواع من البكتيريا المقاومة للأدوية المتعددة إيجابية الجرام وسالبة الجرام ، وأظهرت النتائج فعالية مختلفة ضد البكتيريا المفحوصة.

ان الارايل مشتقات سلفونايل (H_1-H_{11}) و مشتقات الاليل (H_{12}-H_{18}) شخصت بواسطة التحليل العنصري الدقيق ومطيافيات ^{13}C-NMR , ^{1}H-NMR , IR .

ان التحليل العنصري الدقيق لعناصر C , H , N , S للمشتقات المحضره اظهرت بأن الفرق بين القيم النظرية و العملية يقع ضمن المدى المطلوب الذي يؤكد صحة التراكيب المقترحه للنماذج المحضره .

اما اطياف IR التي قيست في الحالة الصلبة لمشتقات الارايل سلفونايل و مشتقات الاليل شخصت بعشر حزم تعود الى الترددات الاتساعية للمجاميع NH_2 , Ar-H , Aliph-H , C=C , C=S , S=O , C-N , C-X (X=Cl , Br), C=O , C=N .

الاشارات الرنينية لاطياف الرنين النووي المغناطيسي للبروتون (^{1}H-NMR) العائده لمشتقات الارايل سلفونايل (H_1-H_{11})هي : (1.07- 2.34) , (6.59-8.50) , (10.92-10.99) , (10.98-11.01) جزء لكل مليون (ppm) تعود الى بروتونات المجاميع :

$-CH_3$, Ar-H , O=C-NH , S=C-NH على التوالي .

بينما اطياف الرنين النووي المغناطيسي (^{1}H-NMR) لمشتقات الاليل (H_{12}-H_{18}) اظهرت اشاره احادية عند المدى (6.64-6.74) جزء لكل مليون تمثل بروتون المجموعة NH , والذي يؤكد بأن التعويض احادي لمجموعة الاليل كل بروتون مجموعة الامين $-NH_2$.

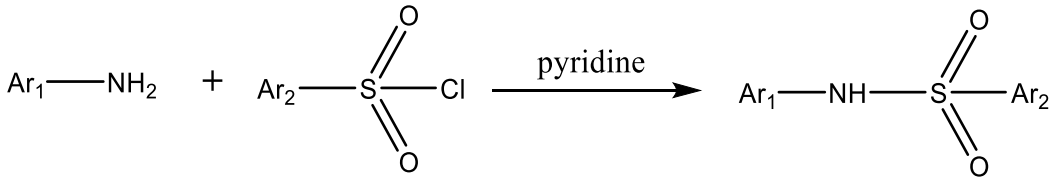
ان اطياف الرنين النووي المغناطيسي للكاربون -13 لمشتقات الارايل سلفونايل (H_1-H_{11}) اظهرت δ (21.40-21.43) , (118.26-144.26) , (139.74-143.23) , (144.22-148.49) , (187.89-187.78) , (124.36-141.69) والتي تعود الى $-CH_3$, الحلقة الاروماتية , الحلقة الغير متجانسة , C=N ,C=O ,C=S ,C=X(X=Cl , Br , NO_2) على التوالي .

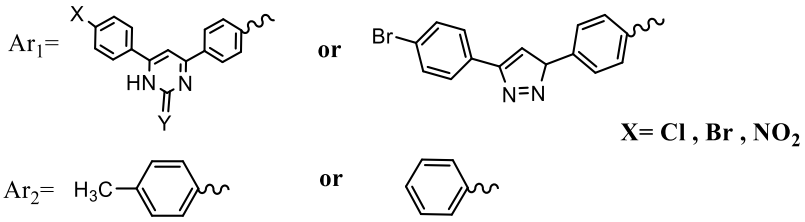
بينما مشتقات التعويض الاليلي (H_1-H_{18}) زودتنا اطيافها الرنينية ل ^{13}C-NMR باشارات تعود الى مجاميع : C-X (X=Cl , Br , NO_2) , C=S , C=O , C=N ,Ar-C , $-CH_3$

ان المواد الاولية شخصت بواسطه التقنيات الطيفية IR , ^{1}H-NMR , ^{13}C-NMR

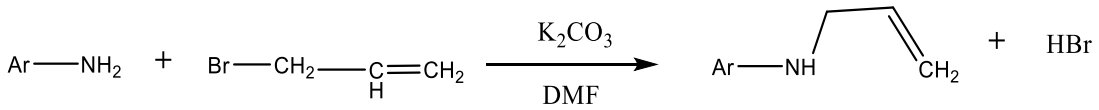
اما الخطوه الثانيه فتتمثل بتخليق النواتج وهي:

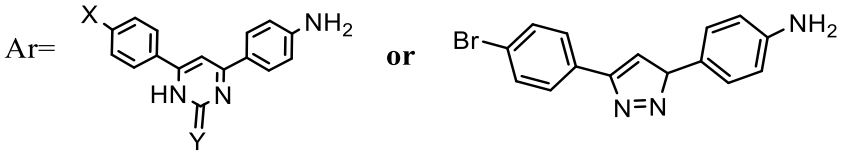
a-مشتقات الارايل سلفونايل (H_1-H_{11}) من خلال مفاعلة البنزين سلفونايل كلورايد او بارا تلوين سلفونايل كلورايد بوجود البريدين كمذيب وقاعده استنادا الى التفاعل التالي :





a-مشتقات الاليل(H_{12}-H_{18}) من مزج المركب (I-VI ,VIII) مع بروميدالاليل وكاربونات البوتاسيوم في ثنائي ميثل فورمايد (DMF) الجاف كما موضح في التفاعل التالي:



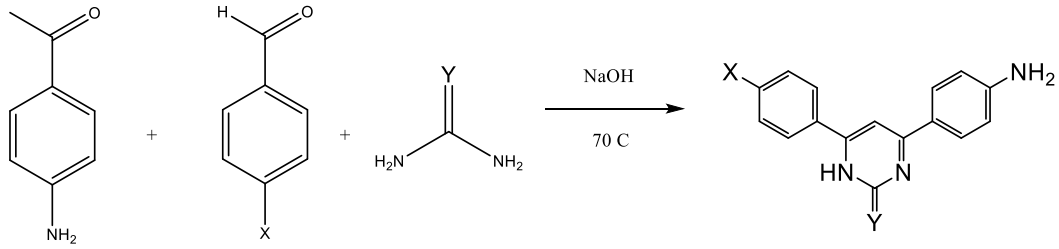


X= Cl , Br , NO_2

الخلاصة

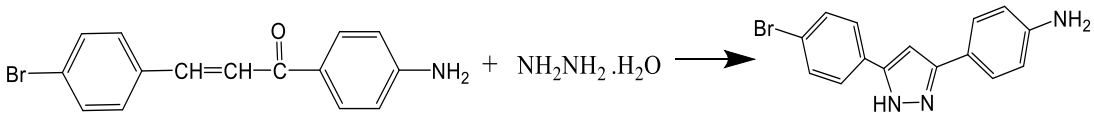
ان الخطوه الاولى في هذه الدراسة تتضمن تحضير المواد الاولية وهي:

a- بعض المركبات الاوكسو بريميدين(I-III) والثايو بريميدين(IV-VI) من تفاعل بارا - امينو اسيتو فينون وبنزالديهايد معوض في موقع بارا مع اليوريا او الثايويوريا وفي وسط قاعدي.



X = Cl , Br , NO_2 Y= O , S

b- مشتق البايرازولين(VIII) بواسطة تكثيف كلاسين - شميدت لبارا امينو اسيتو فينون وبارا برومو بنزالديهايد بتحفيز قاعدي يتبعه عملية ازالة الماء الانتاج الجالكون المطلوب (VII). يتفاعل الجالكون مع الهيدرازينالمائي في الايثانول لاعطاء مشتق البايرازولين.



بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

(قُلْ هَلْ يَسْتَوِي الَّذِينَ يَعْلَمُونَ وَالَّذِينَ لَا يَعْلَمُونَ ۗ إِنَّمَا يَتَذَكَّرُ أُولُو الْأَلْبَابِ)

صدق اللة العظيم

سورة الزمر-الاية(9)

جمهورية العراق

وزارة التعليم العالي والبحث العلمي

جامعة ميسان

كلية العلوم

قسم الكيمياء

تحضير و دراسة الفعالية البايلوجية لبعض مشتقات البايرازول والبريميدين الجديدة

الرسالة مقدمة الى

كلية العلوم \ جامعة ميسان جزء من متطلبات نيل

شهادة الماجستير في علوم الكيمياء

من الطالبة

هديل سعد جاسم حسين

بكالوريوس علوم كيمياء \جامعة ميسان (2018)

باشراف

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يسرى صبري عبد الصاحب

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