Ministry of Higher Education
and Scientific Research
University of Baghdad
College of Science
Department of Chemistry

Synthesis, Characterization and Anti-Inflammatory Evaluation of Some New 2-(3-Fluorobiphenyl-4-yl) Propanoic Acid Derivatives

A Thesis
Submitted to the College of Science, University of Baghdad
in Partial Fulfillment of the Requirements for the Degree of Master of Science in organic Chemistry

By

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2017 A.D **1438 A.H**

بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

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مَا لَمْ يَعْلَمْ ٥

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Head of the department of Chemistry /College of Science/ University of Baghdad

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We certify that we have read this thesis, entitled " *Synthesis, Characterization and Anti-Inflammatory Evaluation of Some New 2-(3-Fluorobiphenyl-4-yl) Propanoic Acid Derivatives* ",and as Examining Committee,examined the student ***Ahmed Jaafar Qasim*** on its content, and that in our opinion it is adequate for the partial fulfillment of the requirements for the degree of **Master of Science in Chemistry / Organic chemistry.**

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ᔓ *Acknowledgments* ᔓ

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☙ *Abstract* ❧

Throughout this work some new heterocyclic compounds have been synthesized from 2-(3-flourobiphenyl-4-yl) propanohydrazide as a starting material and study anti-inflammatory activities of some them. This work is divided into three parts; the reaction steps for each part are summarized as shown below:

Part one: (scheme 1)

This part involves the synthesis of compounds [1-17]:

1- Synthesis of ethyl-2-(3-flourobiphenyl-4-yl) propanoate [1] from the reaction of flurbiprofen with absolute ethanol, in presence concentrated H_2SO_4
2- Synthesis of 2-(3-flourobiphenyl-4-yl) propano hydrazide [2] from the reaction of ethyl-2-(3-flourobiphenyl-4-yl) propanoate [1] with excess of 80% hydrazine hydrate.
3- Synthesis of cyclic imide derivatives [3-5] *via* the reaction of compound [2] with some cyclic acid anhydrides, such as maleic anhydride, succinic anhydride and phthalic anhydride.
4- Synthesis of hydrazone derivatives [6-9] *via* the reaction of compound [2] with some aromatic aldehydes; such as 2,4-dimethoxy benzaldehyde, 4-(N,N-dimethylamino) benzaldehyde, 2-hydroxy benzaldehyde and 3-hydroxy benzaldehyde.
5- Synthesis 1,2,4-triazole derivatives [10] from the reaction of [2] with CS_2 in the presence of potassium hydroxide and 80% hydrazine hydrate.
6- Synthesis of cyclic imide derivatives [11-13] *via* the reaction of compound [10] with some cyclic acid anhydrides, such as maleic anhydride, succinic anhydride and phthalic anhydride.

7- Synthesis Schiff bases [14-17] *via* the reaction of 1,2,4- trizole [10] with some aromatic aldehydes; such as 2,4-dimethoxybenzaldehyde, 4-(N,N-dimethylamino) benzaldehyde, 2-hydroxybenzaldehyde and 3-hydroxy-benzaldehyde

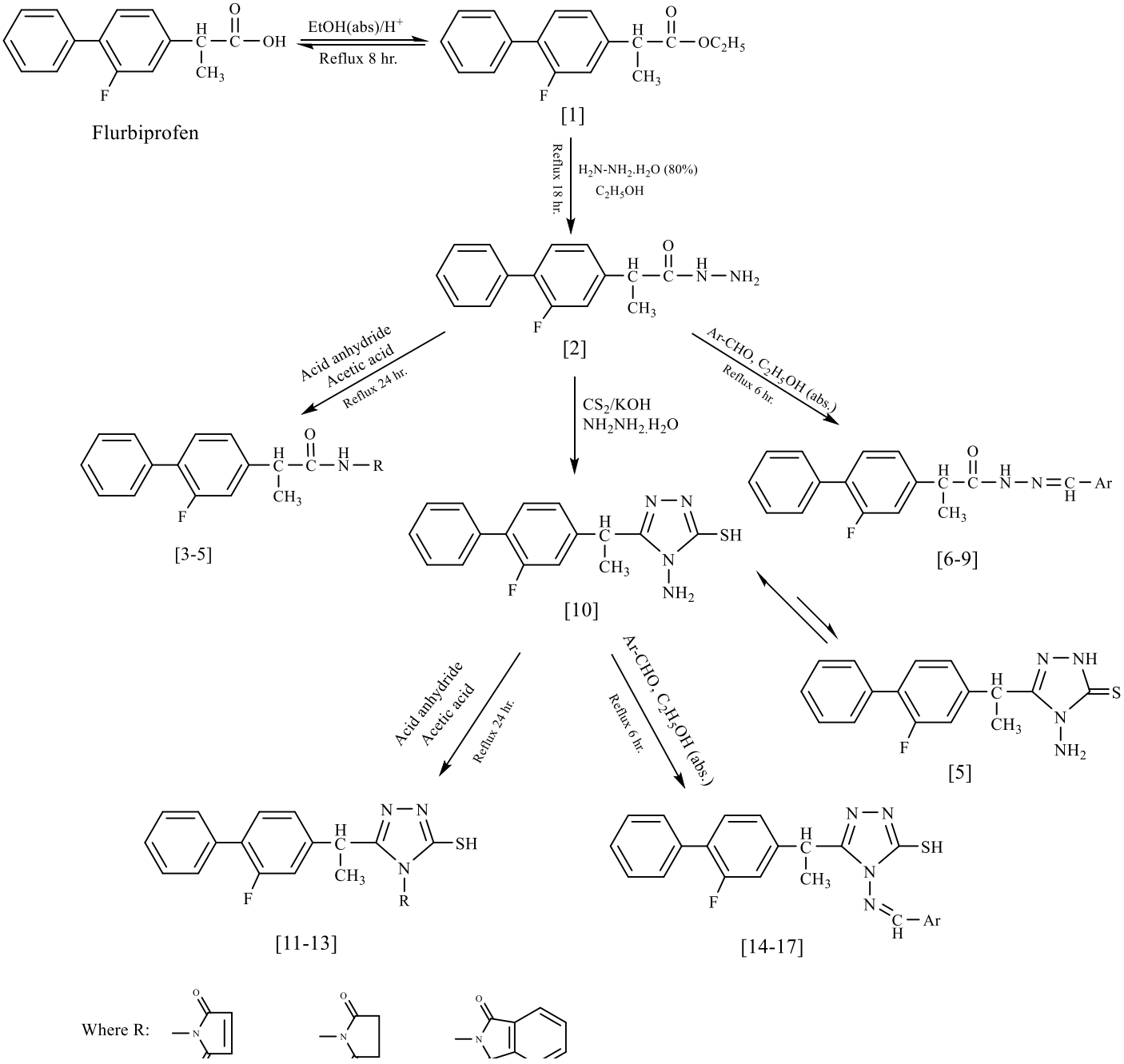
Part two: (scheme 2)

This part involves synthesis of compounds [18-33]:

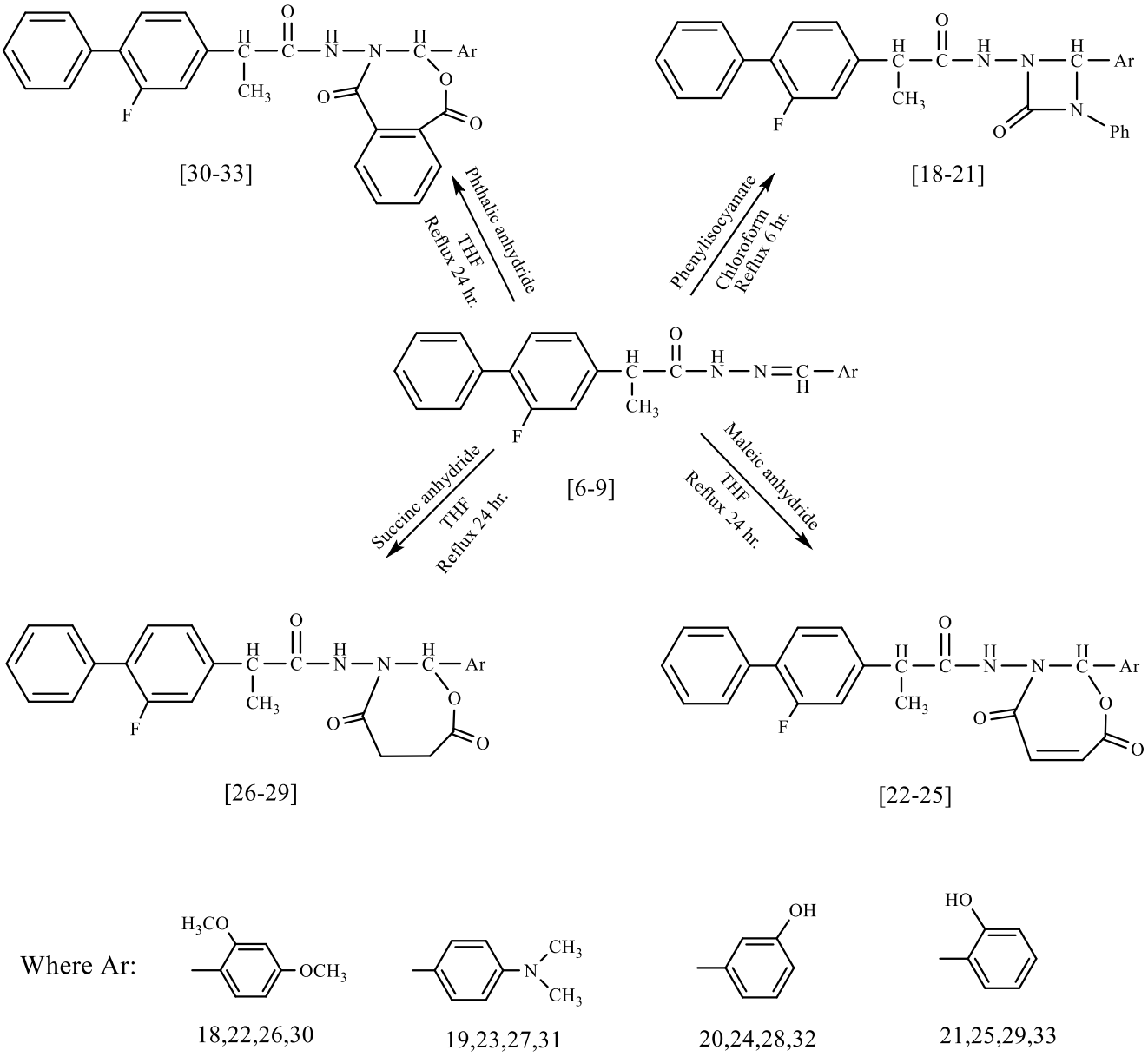
1- Synthesis of diazitidinone derivatives [18-21] from the cyclization of new hydrazone derivatives [6-9] with phenylisocyanate.
2- Synthesis of oxazpein derivatives [22-25], [26-29] and [30-33] from the cyclization of prepared hydrazone derivitives [6-9] with some cyclic acid anhydrides, such as maleic anhydride, succinic anhydride and phthalic anhydride.

Part three:

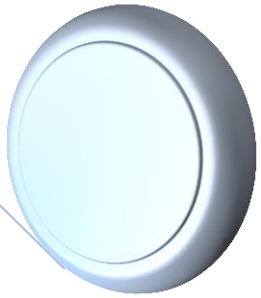
This part involves evaluation of anti-inflammatory activity of compounds [5], [7], [8], [21] and [25]; in the egg-albumin induced paw-edema in rats. The tested compounds showed weak inhibition except compound [25] named 2-(2-hydroxyphenyl)-3-[2-(3-fluorobiphenyl-4-yl)]propanamido-2,3-dihydro-1,3-oxazepine -4,7-dione showed inhibition more than stander drug flurbiprofen.



Scheme (1): Synthetic route of compounds [3-5], [6-9], [10],[11-13] and [14-17].



Scheme (2): Synthetic route of compounds [18-21], [22-25], [26-29] and [30-33].



CHAPTER ONE

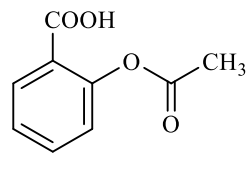
INTRODUCTION

❧ Introduction ❧

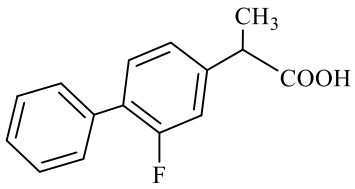
1.1- Non-steroidal anti-inflammatory drugs (NSAIDs)

(NSAIDs) are among the most widely prescribed drugs worldwide. Through their anti-inflammatory, antipyretic and analgesic activities, they represent a choice treatment of rheumatic arthritis (RA), osteoarthritis (OA) and other degenerative inflammatory joint diseases [1,2]. Although NSAIDs are very effective in relieving mild to moderate pains and inflammation, their use is also often associated with many undesirable side effects, including gastrointestinal (GI) irritation and bleeding, platelet dysfunction, kidney damage, and bronchospasm[1-4].

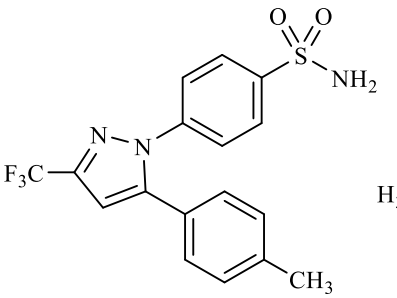
The design and the synthesis of nonsteroidal anti-inflammatory drugs (NSAIDs) have been given much attention by medicinal chemists, especially in the last decade. As a therapeutic group, NSAIDs are among the most widely used prescribed. Some of NSAID drugs are shown below [5,6]:



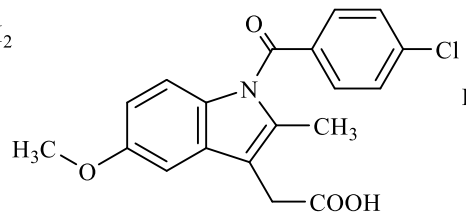
Aspirin



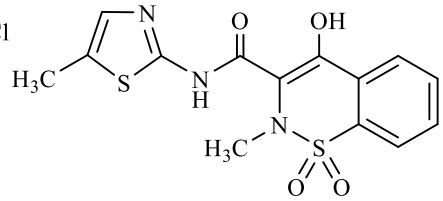
Flurbiprofen



Celecoxib



Indometacin



Meloxicam

1.2- Mechanism of NSAIDs Action:

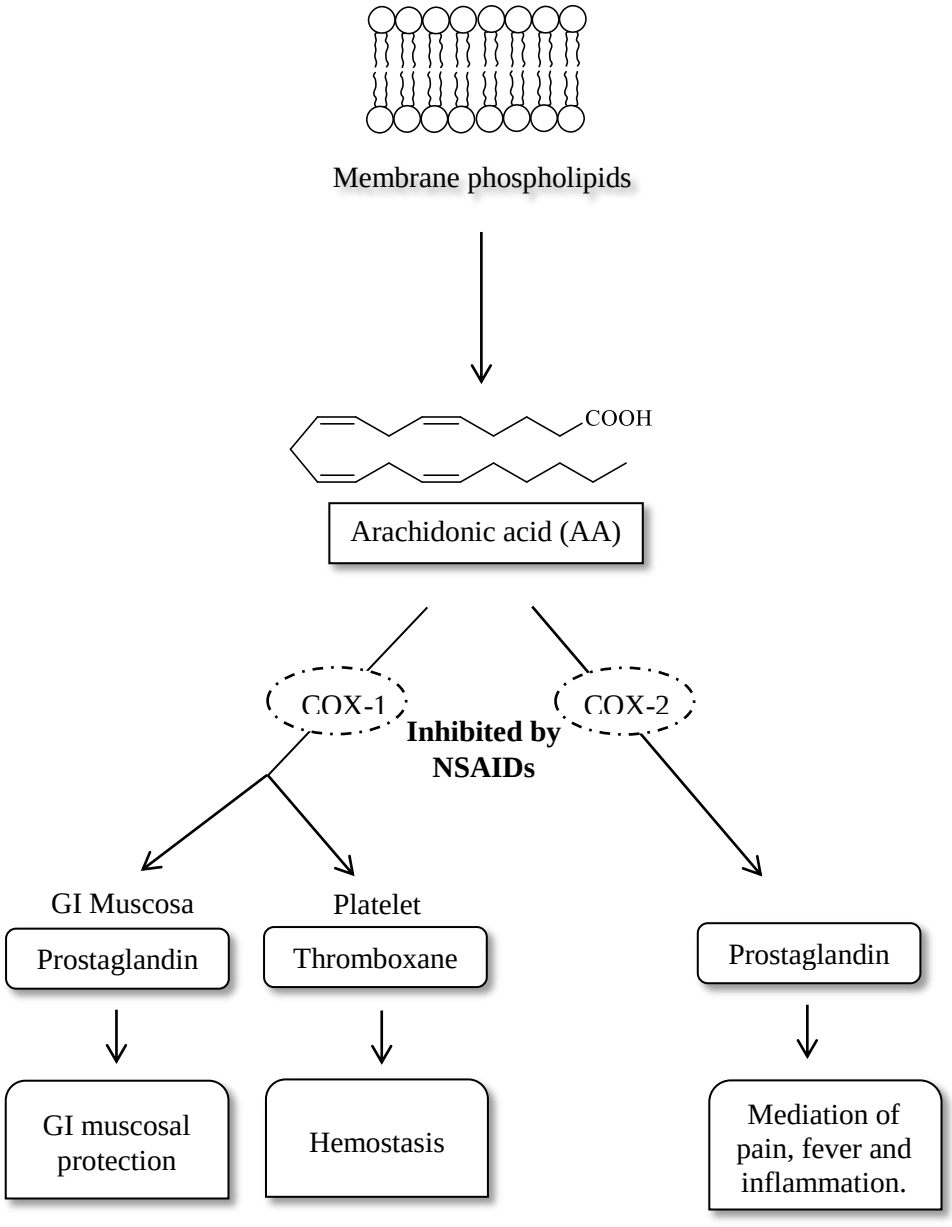
The mechanism of action of anti-inflammatory and analgesic agents such as aspirin, flurbiprofen and indomethacin remained elusive. This all changed in the seventies when John Vane (1971) discovered the mechanism of action of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) thereby increasing our ability to develop novel anti-inflammatory therapies [8]. The conventional NSAIDs exert their therapeutic action by inhibiting two isoforms of cyclooxygenase (COX-1, the constitutive isoenzyme and COX-2, the inducible isoenzyme). Cyclooxygenase also known as prostaglandin endoperoxide synthase or PGH synthase, which is the rate-limiting enzyme responsible for the biosynthesis of the prostaglandins (PGs) from arachidonic acid (AA), and thereby modulating pain transmission, attenuating inflammation, and reducing fever [8,9]. As stated earlier, all classes of NSAIDs strongly inhibit prostaglandin synthesis in various tissues, especially at the site of the tissue damage or inflammation. This inhibition occurs at the stage of oxidative cyclization of AA, catalyzed by the rate-limiting enzyme, cyclooxygenase (or PGH synthase), as shown in figure (1.2) [10,11].

They also produce their undesirable side effects such as gastrointestinal (GI) bleeding, ulcerations, or renal impairments by blocking the same cyclooxygenases responsible for synthesizing PGs that modulate platelet activity, gastric acid secretion and cytoprotection, and renal blood flow [12-14].

Constitutive COX-1 has a housekeeping function; including gastro-protective and kidney function regulation PGs, whereas COX-2 is induced in inflammatory cells and generate PGs that help mediate the inflammatory response [15].

Classical NSAIDs such as Aspirin and Ibuprofen are selective inhibitors of COX-1 isoenzyme and cause a gastric failure like bleeding and ulcer [16,17].

In contrast, selective COX-2 inhibitors such as Celecoxib, Rofecoxib, and Valdecoxib exert anti-inflammatory and analgesic activity with markedly less gastrointestinal toxicity than the traditional NSAIDs [18].



Figure(1.1): Conversion of arachidonic acid to prostaglandins and Thromboxane

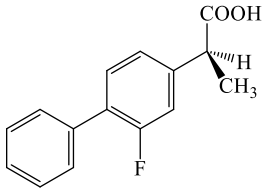
1.3- Inflammation and anti-inflammatory evaluation:

Inflammation is a biological response to noxious stimuli such as pathogens that cause tissue and cell damage [19]. It is considered a protective measure taken by the organism to remove harmful stimuli and to begin the healing process. It is classified as either acute or chronic, depending on whether it involves a short response or a prolonged one, respectively [20]. Inflammatory response is affected area redness, swollen, to feel pain and to have a rise in body temperature. The level of dermal tissue cells found Mast cell (produce histamine), dendretique cells (secrete prostaglandins) and phagocytic cells big (secrete chimiokine). Wound allow bacteria to seep into the body and multiply, that it stimulates the mast cells to sort histamine cells and macrophages to swallow some bacteria and secretion prostaglandins [21]. Histamine and prostaglandins stimulate blood vessels to stretch in the injury and increased permeability and this is what explains the bulge the affected area, phagocytic cells moving toward the germs to be swallowed and excreted (chimiokine), this chemical mediator is working on attracting leukocytes ubiquitous in the capillaries into the injury site to operate on ingest bacteria[22].

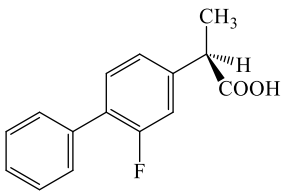
Among the many methods used for screening and evaluation of anti-inflammatory drugs, one of the most commonly employed technique is based upon the ability of such agents to inhibit the edema produced in the hind paw of the rat by injection of a phlogistic agent. The most frequently used phlogistic materials include brewer's yeast, formalin, dextran and egg albumin. The doses of anti-inflammatory drugs which have been employed to demonstrate inhibition of edema have been almost without exception within the toxic range[23].

1.4- Flurbiprofen and some their derivatives:

2-(3-Fluorobiphenyl-4-yl) propanoic acid (flurbiprofen) is a member of the phenyl alkanoic acid derivative family, having molecular weight 244.3 g/mol with a molecular formula of $C_{15}H_{12}O_2F$. Flurbiprofen is commercially available as a racemate mix of (+) *S* and (-) *R* enantiomers[24,25], as shown below:



(*S*)-Flurbiprofen



(*R*)-Flurbiprofen

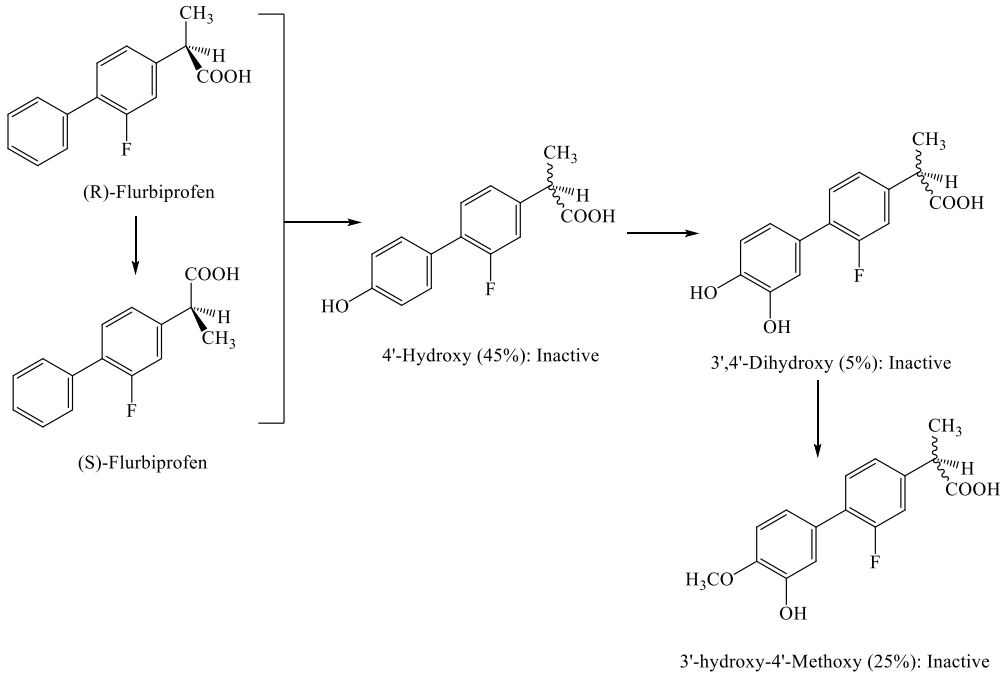
Flurbiprofen is a non-steroidal anti-inflammatory drugs (NSAIDs), which has an anti-inflammatory, antipyretic and analgesic agent, used in the treatment of pain or inflammation, in humans. Flurbiprofen tablets are used in the management of acute or longterm treatment of osteoarthritis, rheumatoid arthritis, joint stiffness and dysmenorrhea, gout, ankylosing spondylitis, periodontitis, reduction postoperative pain, and in initially treated pain induced from cancer [26,27]. The compound efficiently works in pain management and has, therefore, gained wide use in the preparation of anti-inflammatory medicines [28-31].

Flurbiprofen inhibits the isoenzyme cyclooxygenase I (COX-1) and cyclooxygenase II (COX-2) to make the prostaglandins which result in the valuable reduction in the concentrations of prostaglandins [32-34].

The α-CH_3 substituent present in the flurbiprofen increases cyclooxygenase inhibitory activity and reduces the toxicity of the flurbiprofen. The α-carbon in these compounds is chiral [35], (+) *S* and (-) *R* enantiomers, both flurbiprofen enantiomers block COX-2 induction [36]; therefore, both enantiomers are believed to contribute to its overall anti-inflammatory action[36], but *S*-enantiomer of flurbiprofen is more active than the *R*-enantiomer on both COX-1 and COX-2 activities.

(*R*)-flurbiprofen is actually a strong clinical candidate for the treatment of Alzheimer disease because it has been shown to reduce Amyloid beta-42 aminoacid (Aβ42) production by human cells [37].

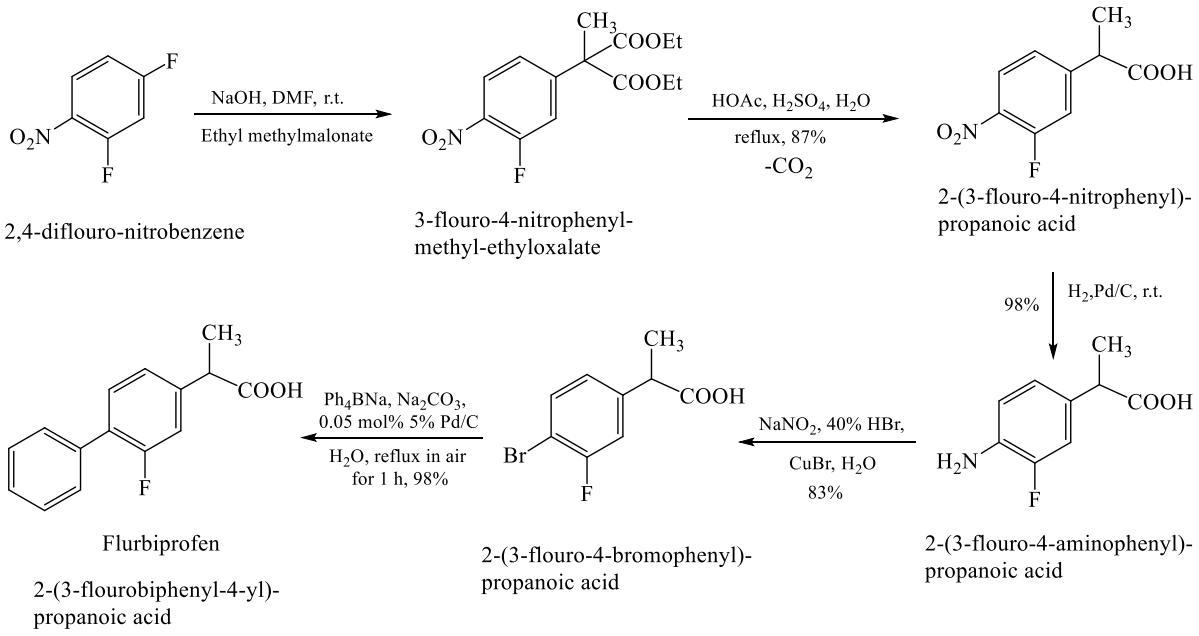
The metabolic transformations of flurbiprofen and their derivitives undergo are determined by the structure of the additional lipophilic functionality present in each compound. Flurbiprofen undergo to Ring oxidation (loss of activity) and can be summarized as follows:



Scheme (1.1): The metabolic transformations of flurbiprofen

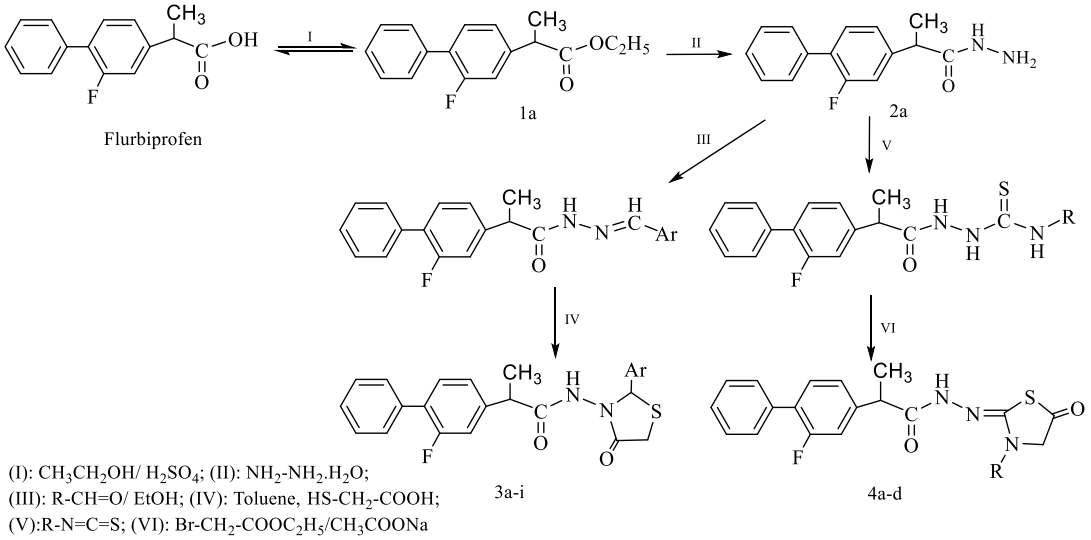
There are several methods to prepare flurbiprofen, one of them synthesis *via* Suzuki coupling reaction by palladium charcoal Pd/C-catalyzed in water using sodium tetraphenylborate as phenylation reagent, in 5 steps in 69% overall yield. The bromoaryl carboxylic acid 2-(3-flouro-4-bromophenyl) propanoic acid was used as a key intermediate, which was easily synthesized from 2,4-difluoronitrobenzene and ethyl methylmalonate. Thus, 2-(3-flouro-4-bromophenyl) propanoic acid was coupled with sodium tetraphenylborate, a highly reactive and non-toxic phenylation reagent, in water in the presence of 0.05 mol 5% Pd/C.

This Suzuki coupling reaction could complete within 1 hour in the air and the target compound (flurbiprofen) was obtained in excellent yield (98%) with high purity determined by high-performance liquid chromatography (HPLC) [38].



Scheme (1.2): Synthesis of flurbiprofen.

Several derivatives of flurbiprofen have been synthesized in the last years, and study their biological activity because of their medicine important as an (NSAIDs). Çıkla et al. [39] synthesized new derivatives of flurbiprofen **3a-i** and **4a-d**, with potential anti-hepatitis C virus (anti-HCV), anticancer and antimicrobial agents.

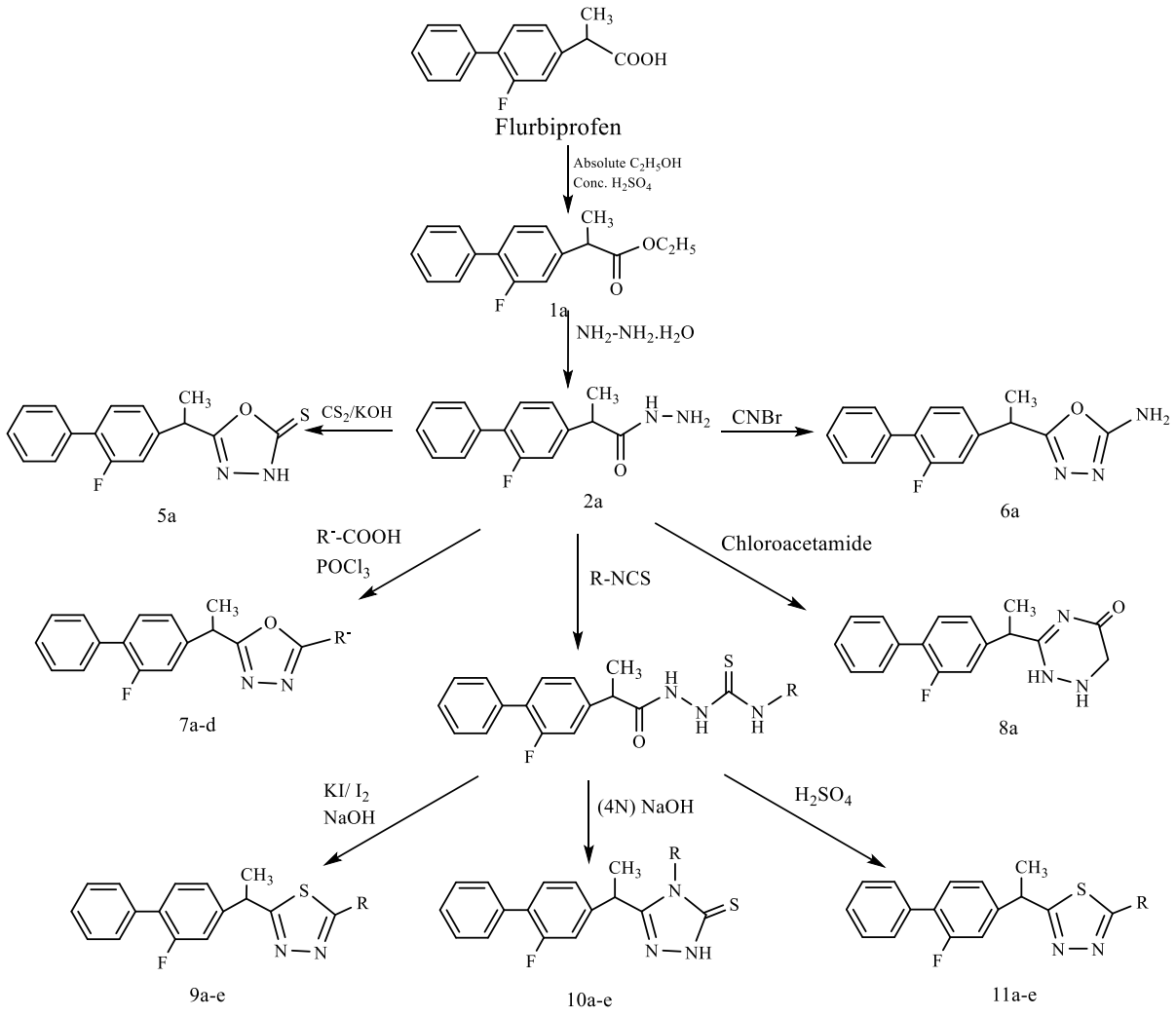


Where R(Ar): **3a**: 5-nitro-2-furyl; **3b** -$C_6H_4NO_2$ (4); **3c** -C_6H_4 (CF_3) (4) ;**3d** -C_6H_4F (2); **3e** -C_6H_4F (3); **3f** -C_6H_4F (4); **3g** -$C_6H_3F_2$ (2,6); **3h** -C_6H_4Cl (4); **3i** -C_6H_4Cl (2); **4a** -CH_3;**4b** -CH_2CH_3; **4c**-$CH_2CH{=}CH_2$;**4d** -$CH_2C_6H_5$

Scheme (1.3): Synthesis of compound 3a-i and 4a-d by Çıkla et al.

The compounds tested were showed weak inhibitors of Nonstructural protein 5B (NS5B) –which is a protein found in the hepatitis C virus (HCV) - activity, but it showed significant inhibition of several cancer cell lines. Additionally, compounds **3a** and **3i** were determined to have anti-bacterial properties.

Mohammad and Kumar [40] synthesized new derivatives of flurbiprofen **5-11**, derived from flurbiprofen hydrazide **2a** and then studied their Anti-inflammatory activity, Analgesic activity, Acute ulcerogenesis and Lipid peroxidation.

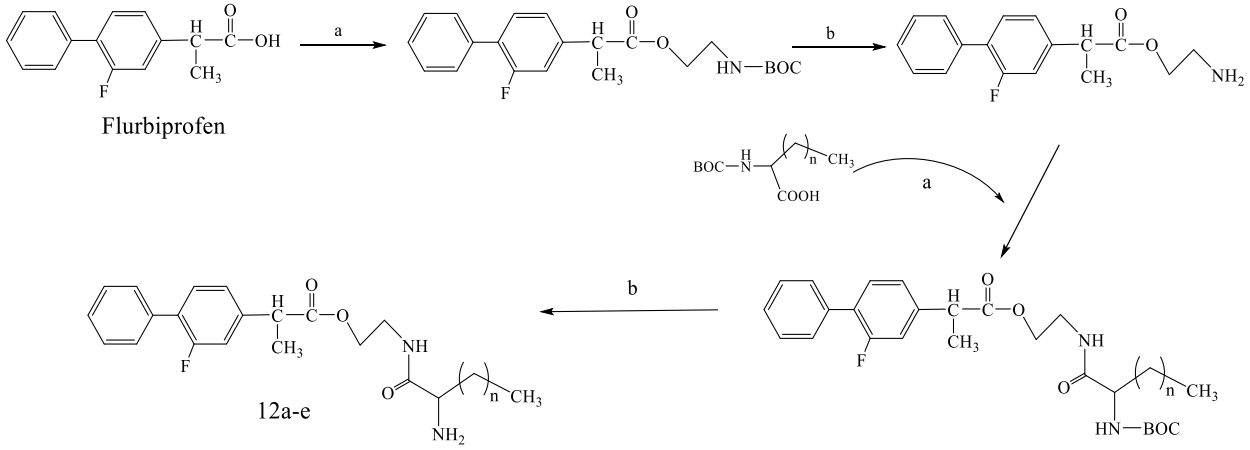


Where R(R⁻): 7b -$C_6H_3Cl_2$ (2,4); **7c** -H_2CO-$C_6H_3Cl_2$ (2,4); **7d** -$C_6H_4NH_2$ (4); **10a** n-C_4H_9;**10b** -C_6H_{10}; **9a,11a** -NH-(n)C_4H_9 ; **9b, 11b** -NH-C_6H_{10}; **10d** -C_6H_4F (4); **10e** -$C_6H_4(CH_3)$ (4); **9c,11c** -NH-C_6H_4Cl (4); **9d,11d** -NH-C_6H_4F (4); **9e,11e** -NH-$C_6H_4(CH_3)$ (4); **10c,7a** -C_6H_4Cl (4)

Scheme (1.4): Synthesis of compounds 5a-11 by Mohammad and Kumar

The tested compounds showed an anti-inflammatory activity ranging from 66.07% to 94.11% inhibition. The compounds, which showed anti-inflammatory activity close to standard drug flurbiprofen, namely compounds **9a, 9e, 10a** and **11a,** were tested for analgesic activity, ulcerogenic activity and lipid peroxidation. The tested compounds showed analgesic activity ranging from 18.13% to 84.06% inhibition, whereas the standard drug flurbiprofen showed 51.09%. The tested compounds showed a reduction in ulcerogenic activity and lipid peroxidation than flurbiprofen.

Pignatello et al. [41] synthesized lipoamino acid of flurbiprofen **12a-e**, and studied their chemical; plasmatic stability, pharmacokinetic assay and biological assessment.



Where Boc is tert.butyloxycarbonyl.

a) Anhydrous dichloromethane (DCM) ; 1-hydroxybenzotrizaole (HOBt) triethylamine (TEA); 1-ethyl-3-(3-dimethylaminopropyl)carbodiimine hydrochloride (EDAC); N-Boc-ethanolamine[tert.butyl-N-(2-hydroxyethyl)carbamate.

b) Anhydrous dichloromethane (DCM); tetraflouroacetic acid (TFA).

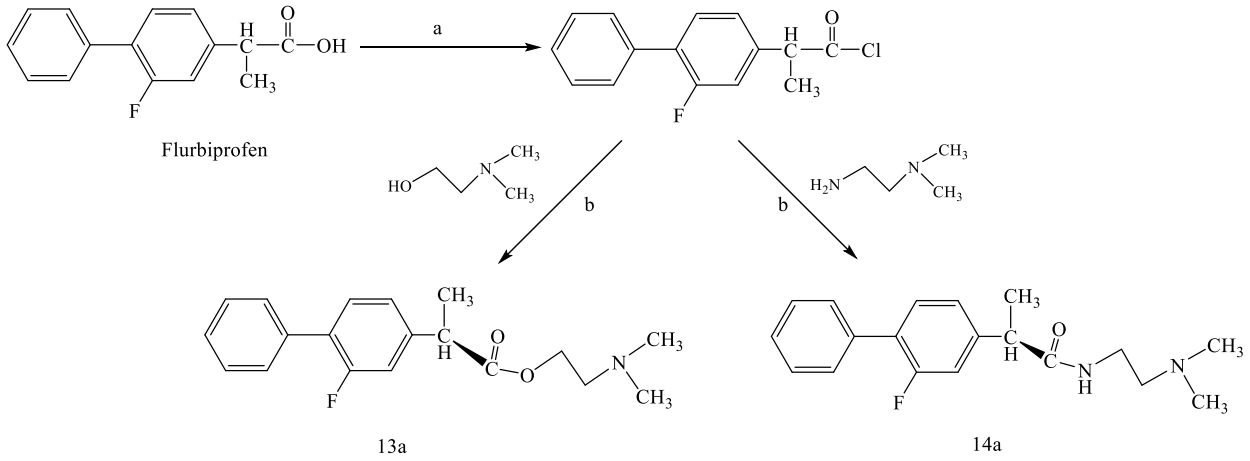
n: a=3; b=5; c=7; d=9; e=11

Scheme (1.5): Synthesis of compounds 12a-e by Pignatello et al.

The tested compounds showed a typical prodrug stability, being stable in phosphate buffer saline (PBS) at Ph 7.4 and release the active drug in plasma. All prodrugs except for the prodrug with the longest alkyl side chain **12e** were effective as inhibitors binding of [F-18]FDDNP to *in vitro* formed a *β*-amyloid protein (A*β* fibrils). [F-18]FDDNP (2-(1-{6-[(2-[F-18]fluoroethyl)(methyl) amino]-2-naphthyl}ethylidene)malononitrile) is a positron-emitting radio-

fluorinated molecular imaging probe with binding affinity for neuropathological lesions found in Alzheimer's disease (AD), *β*-amyloid senile plaques, and neurofibrillary tangles, used for *in vivo* positron emission tomography (PET) imaging of the neuropathology load in AD patients' brains

R-flurbiprofen was acknowledged as a promising candidate in Alzheimer's disease (AD). Zheng et al. [42] synthesized two flurbiprofen derivatives **13a** and **14a** with improved brain delivery and evaluated their *in vitro* and *in vivo* to find a compound with safe and effective therapeutic agent for Alzheimer's disease.



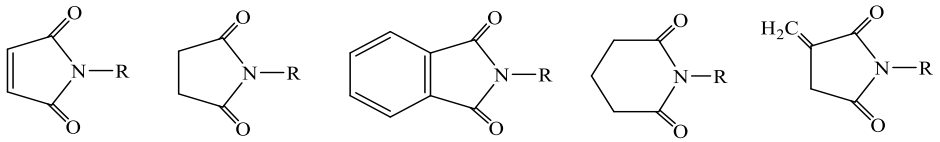
(a): $SOCl_2$, DMF, Reflux 2 hrs. at 60 °C;
(b): CH_2Cl_2, Et_3N, stirring at 35 °C for 1 hr.

Scheme (1.6): Synthesis of compounds 13a and 14a by Zheng et al.

These derivatives showed a good safety level *in vitro* and they possessed much higher cellular uptake efficiency in brain endothelial cells than flurbiprofen did. Biodistribution studies in rats also illustrated a remarkably enhanced accumulation of these derivatives in the brain. Compound **13a**, the ester linkage form of these derivatives, achieved a higher brain-targeting efficiency. Moreover, **13a** could be easily hydrolized to the parent flurbiprofen when being distributed to the target sites. All these findings indicate that **13a** is promising to be developed into a safe and an effective therapeutic agent for Alzheimer's disease.

1.5- Cyclic imide derivatives:

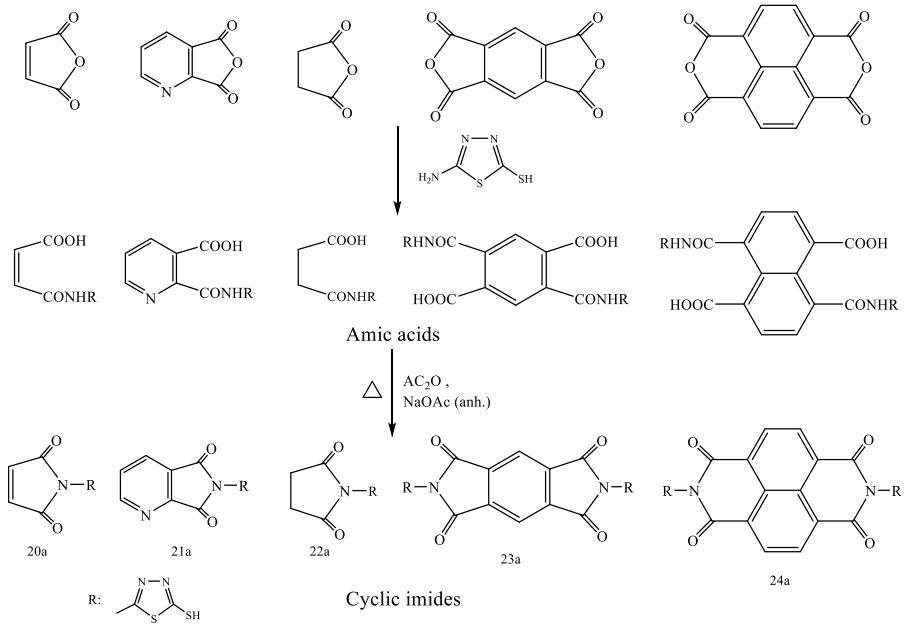
Organic compounds contain two carbonyl groups (C=O) which attach with the nitrogen atom in cyclic ring, such as maleimide **15a**, succinimide **16a**, phthalimide **17a**, glutarimide **18a** and itaconimide **19a** [43], as shown below:



15a 16a 17a 18a 19a

R: H or alkyl or aromatic substituted

Generally, aromatic or aliphatic cyclic imide was prepared by the reaction a primary amine with a cyclic anhydride used reagent or not. The classical synthetic pathway for N- substituted imides synthesis consists of the formation of amic acids -organic compounds containing both carboxyl and amide groups in their molecules- *via* the reaction of amines and anhydrides followed by dehydration of amic acids by several agents such as acetic anhydride with anhydrous sodium acetate [44-50], thionyl chloride[51-53], acetyl chloride with triethyl amine [54,55], phosphorus trichloride [56,57] or phosphorus pentaoxide [58], to the desired cyclic imides, as shown below [59].

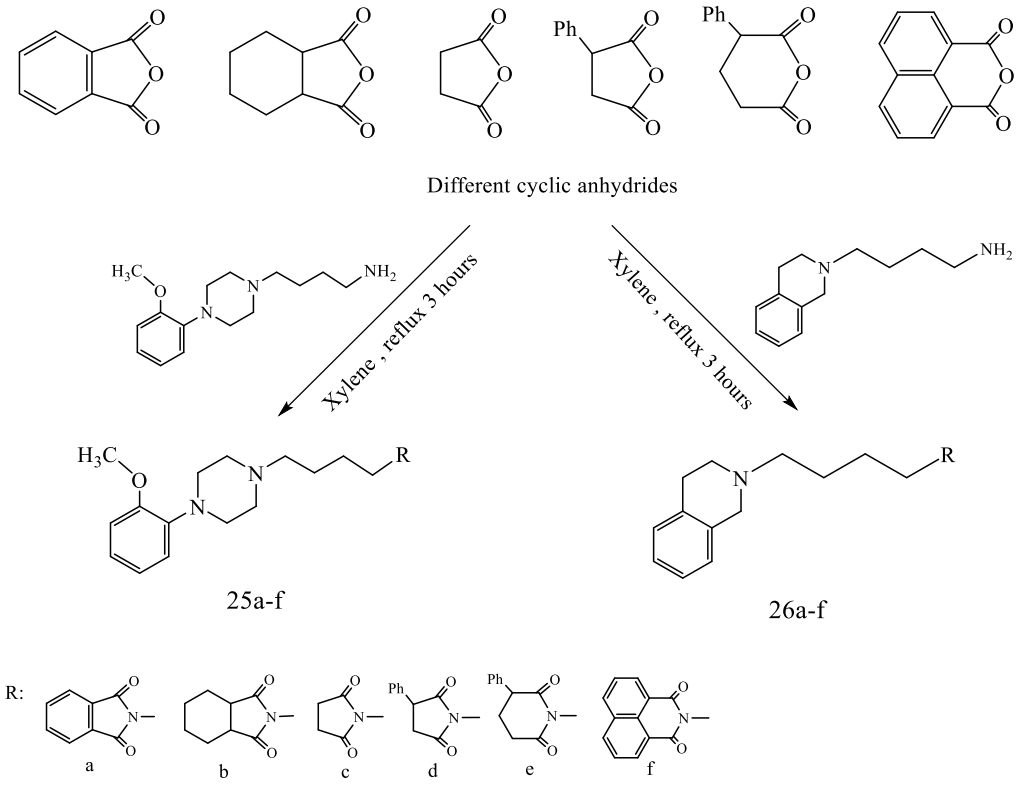


Scheme (1.7): Synthesis of compounds 20a-24a by Al-Azzawi and Hamed

The thermal process can be used instead of using a dehydrating agent to prepare cyclic imides from the corresponding amic acids [60]. Also, cyclic imides can be directlyprepared by reflux cyclic anhydride with a primary amine in an appropriate solvent [61].

Cyclic imides represent an important class of bioactive molecules that shows a wide range of biological and pharmacological activities such as anti-inflammatory, anxiolytic, anti-fungal, antiviral, analgesic, anti-tumor, anti-cancer, anti-convulsant and anti-bacterial properties [62-69].

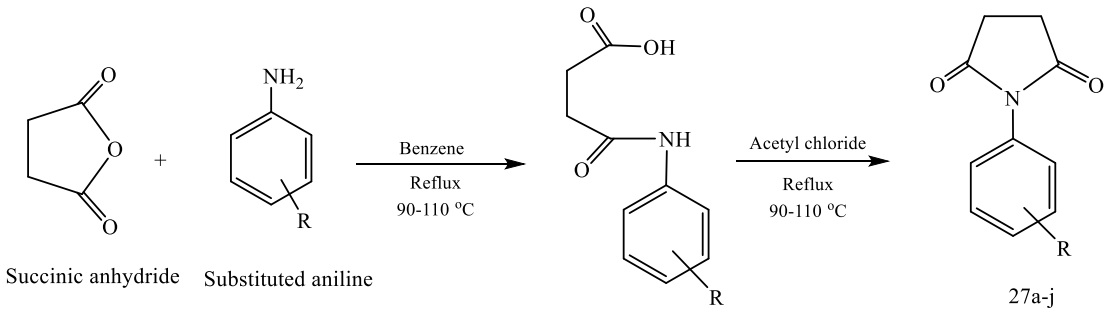
Bojarski et al. [70] synthesized two sets of new *o*-methoxyphenyl piperazine derivatives **25a-f** and 1,2,3,4-tetrahydroisoquinoline **26a-f** derivatives, containing various cyclic imide moieties and evaluated *in vitro* for their ability to bind to the serotonin 5-HT_{1A} and 5-HT_{2A} receptors.



Scheme (1.8): Synthesis of compounds 25a-f and 26a-f by Bojarski et al.

All new derivatives from **25a-f** demonstrated high 5-HT_{1A} affinities, whereas **26a-f** analogs were much less active.

Dhivare and Rajput [71] synthesized new N- substituted succinimides **27a-j** from reflux succinic anhydride with substituted aniline to give N- substituted phenyl succinamic acid and then cyclic imide by reflux with acetyl chloride, and study their anti-bacterial and anti- fungal activities.



Where R:

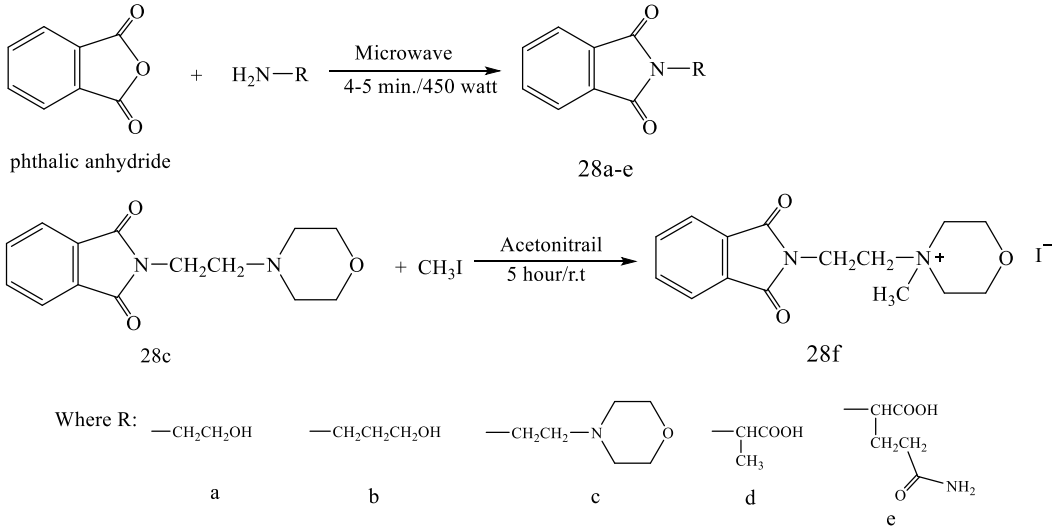
a= -H, b= -Br(4), c= -Cl(4), d= -CH_3(4), e= -OCH_3(4)

f= -F(4), g= -NO_2(4), h= - phenyl, i= -Cl(3), -F(4). j= -Cl(2,4,5)

Scheme (1.9): Synthesis of compounds 27a-j by Dhivare and Rajput

The tested compounds were found significantly active against gram-positive *Bacillus subtilis* and gram-negative *Escherichia coli* bacterial strains. In the same way, they showed the prominent antifungal activity against *Candida albicans* and *Aspergillus niger* fungal strains.

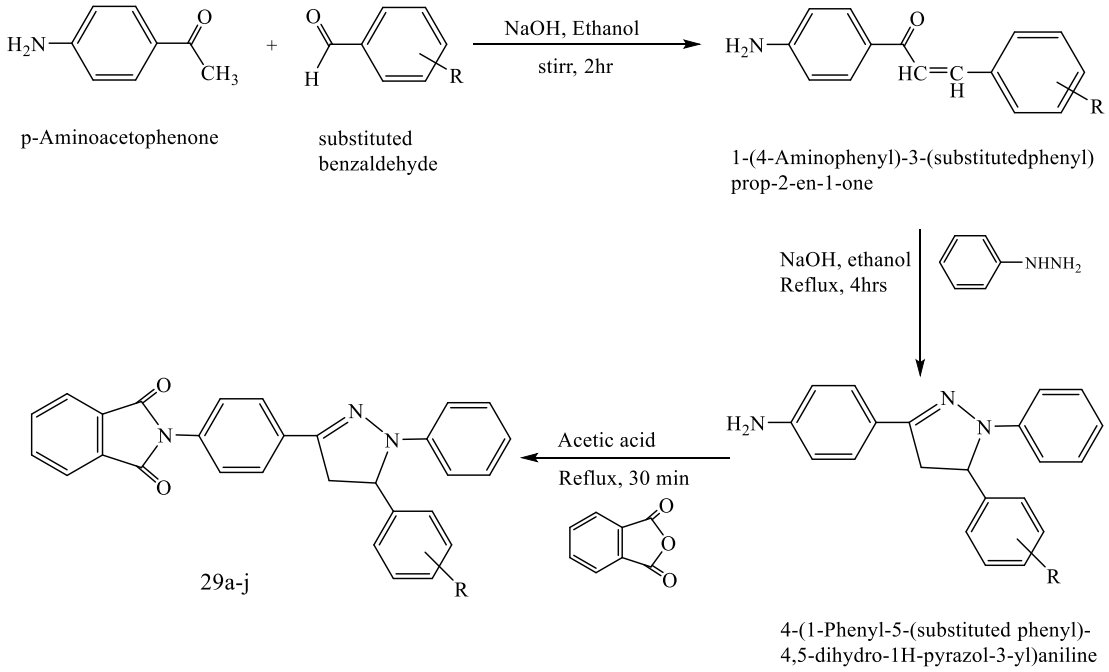
Fhid et al. [72] synthesized new phthalimide derivatives **28a-f** by treating phthalic anhydride with various aliphatic amines (aminoethanol, aminopropanol, amino ethyl morphline, and some amino acids) *via* microwave and reflux. All the synthesized compounds were evaluated *in vivo* for analgesic activity by using standard experimental models.



Scheme (1.10): Synthesis of compounds 28a-f by Fhid et al.

The compounds **28a, 28c** and **28d** showed a significant analgesic effect with hot plate and acetic acid induced writhing test in mice compared to the control group.

Pophale and Deodhar [73] synthesized a series of phthalimide derivatives **29a-j** and evaluated their analgesic and anti-inflammatory activity

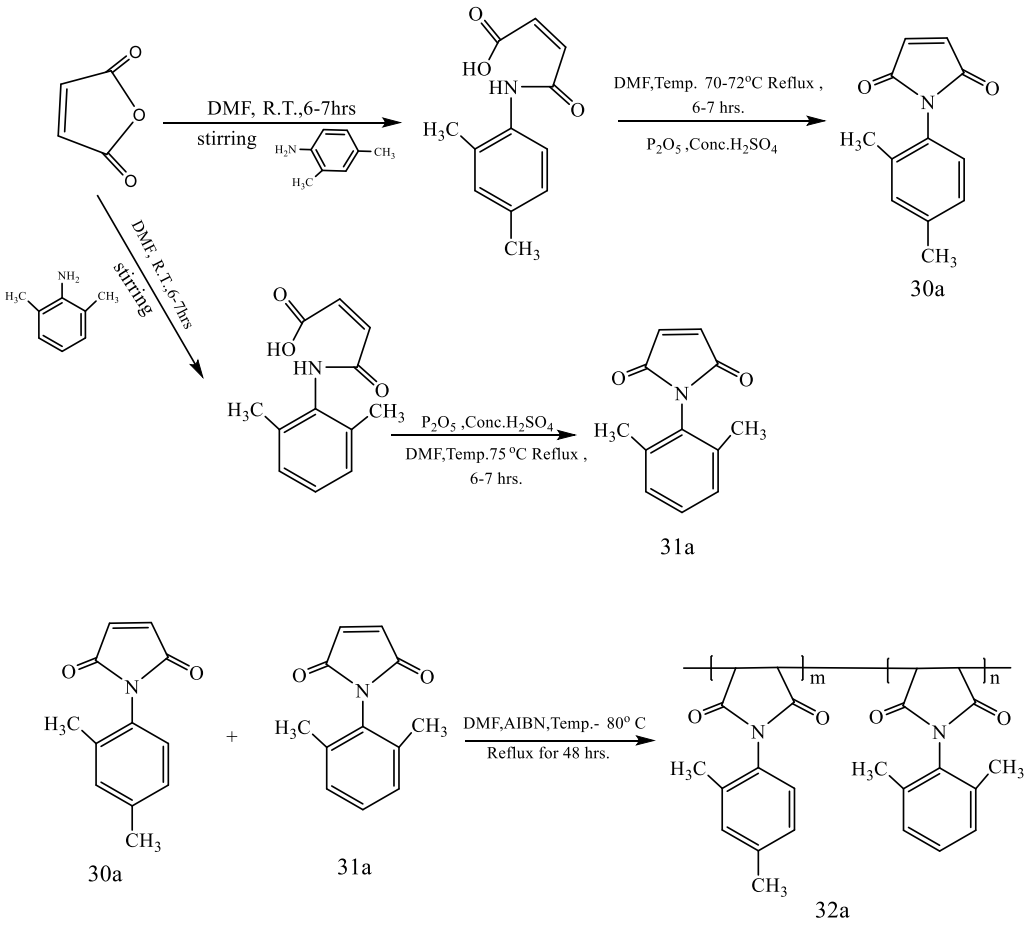


Where R:a= p-Cl; **b**= o-Cl; **c**= m-Cl; **d**= o-NO_2; **e**= p-NO_2;
f= p-OCH_3; **g**= 3,4,5$(OCH_3)_3$; **h**= H; **i**= p-Br; **j**= m-Br

Scheme (1.11): Synthesis of compounds 29a-j by Pophale and Deodhar

Compounds **29a-j** were screened for anti-inflammatory activity against carrageenin-induced rat paw edema. Except for compound **29b** all exhibited a good anti-inflammatory activity, while compounds **29d, 29h** and **29j** exhibited a good analgesic activity when screened against acetic acid induced writhing in mice.

Hiran et al. [74] synthesized new maleimide monomers **30a** and **31a**, and then both maleimide monomers were copolymerized with each other using azobisisobutyronitrile (AIBN) as a free radical initiator to give poly imide **32a**



Scheme (1.12): Synthesis of compounds 30a, 31a and 32a by Hiran et al.

1.6- Hydrazone derivatives:

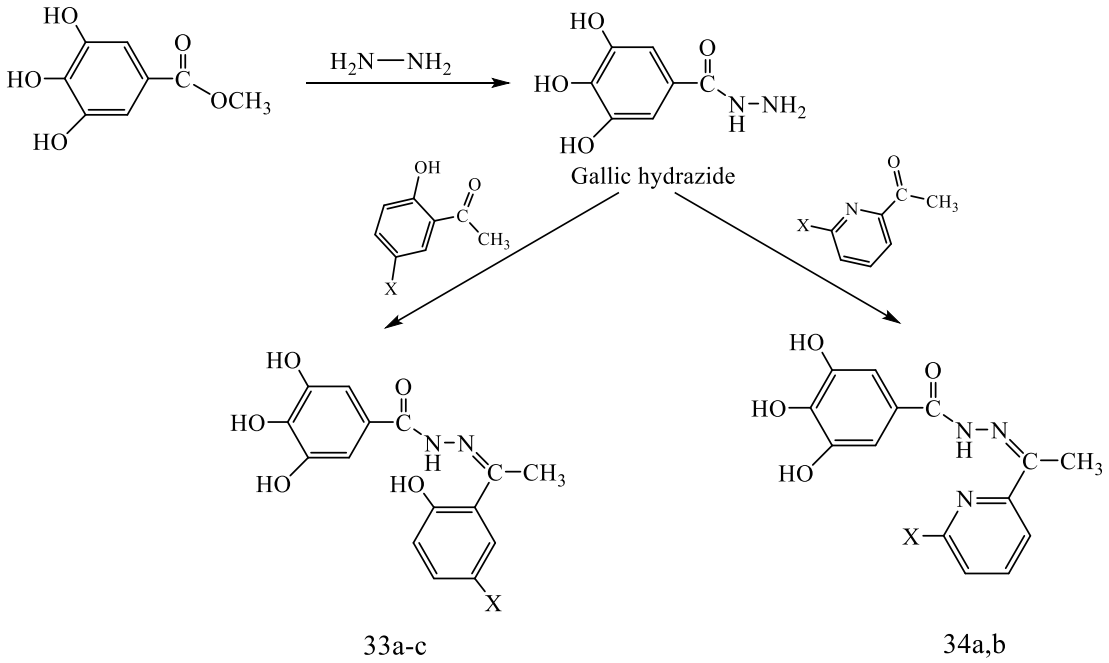
Hydrazones are a special class of organic compounds in the Schiff-base family. Hydrazones constitute a versatile compound of the organic class having azomethine group (-NHN=CH-) [75]. The active centers of hydrazone, that is, carbon and nitrogen, are mainly responsible for the physical and chemical

properties of the hydrazone and due to the reactivity toward electrophiles and nucleophiles. Hydrazone are used for the synthesis of organic compounds such as heterocyclic compounds with a variety of biological activities [76,77].

Hydrazone and their derivatives are known to exhibit a wide range of interesting biological activities like anti-tumor [78], anti-inflammatory [79], analgesic [80], antitubercular [81], anticancer [82], antibacterial [83], antioxidant [84], antifungal activities [85].

Hydrazones are derived from the reaction of aldehydes or ketones with hydrazide derivatives [86]

Gwaram et al. [87] synthesized new hydrazone derivatives **33a-c** and **34a,b** from the reaction of gallic hydrazide with different ketones, and evaluated for their antioxidant activities, *in vitro* and *in silico* acetyl cholinesterase inhibition and possible treatment for Alzheimer's disease (AD).



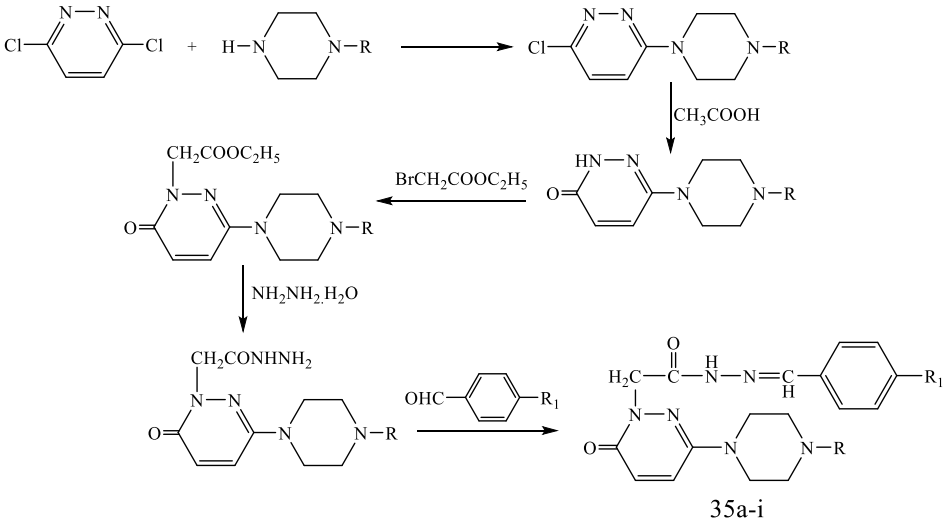
Where X: **33a=** Br; **33b=** Cl; **33c=** OCH_3; **34a=** H; **34b=** $COCH_3$

Scheme (1.13): Synthesis of compounds 33a-c and 34a,b by Gwaram et al.

All synthesized compounds show strong antioxidant activities. N-(1-(5-bromo-2-hydroxyphenyl)-ethylidene)-3,4,5-trihydroxybenzohydrazide **33a** was the most potent inhibitor of human acetyl cholinesterase.

In silico molecular modeling revealed that the compounds may position themselves in the enzyme's active-site gorge, interacting with residues in the peripheral anionic subsit (PAS) and acyl binding pocket (ABP).

Gökçe, Utku and Küpeli [88] synthesized new hydrazone derivatives **35a-i,** and studied their analgesic and anti-inflammatory activities.

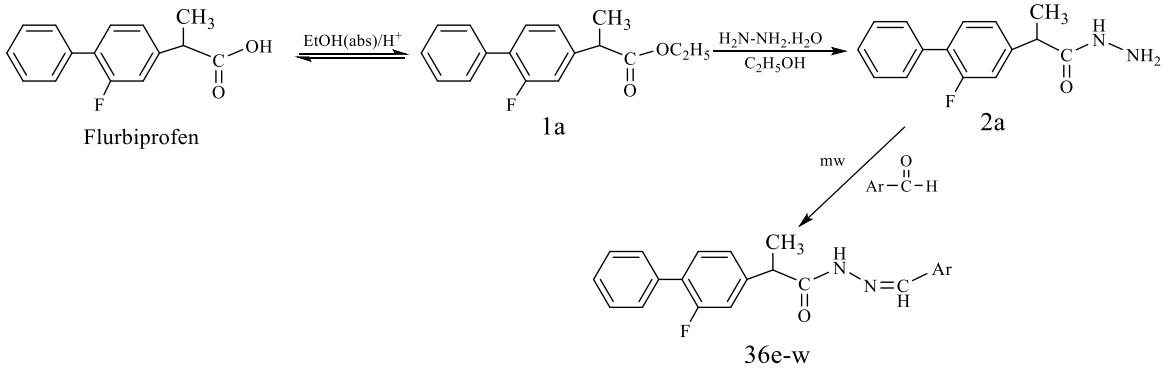


Where: a:R –Chlorophenyl(3), R_1 -H; **b**: R –Chlorophenyl(4), R_1 H; **c**: R –pyridyl(2), R_1 -H; **d**: R –Chlorophenyl(3), R_1 -CH_3; **e**: R –Chlorophenyl(4), R_1 -CH_3;**f** :R –pyridyl(2), R_1 -CH_3; **g** R-Chlorophenyl (3), R_1 -OCH_3; **h** R –Chlorophenyl(4), R_1 -OCH_3; **i** R –pyridyl(2), R_1 -OCH_3

Scheme (1.14): Synthesis of compounds 35a-I by Gökçe, Utku and Küpeli

All the newly synthesized compounds were tested for anti-inflammatory and analgesic activities. These results of anti-inflammatory and analgesic activities of all compounds are statistically significant. **35a**, **35b** and **35c** derivatives have shown better an analgesic activity than reference compound acetylsalicylic acid (ASA) and showed a good anti-inflammatory activity.

Aydın et al. [89] synthesized new hydrazone **36e-w** derived from flurbiprofen by microwave- assisted irradiation, and studied their anti-hepatitis C virus non-structure 5B protein (anti-HCV NS5B) and anticancer agents

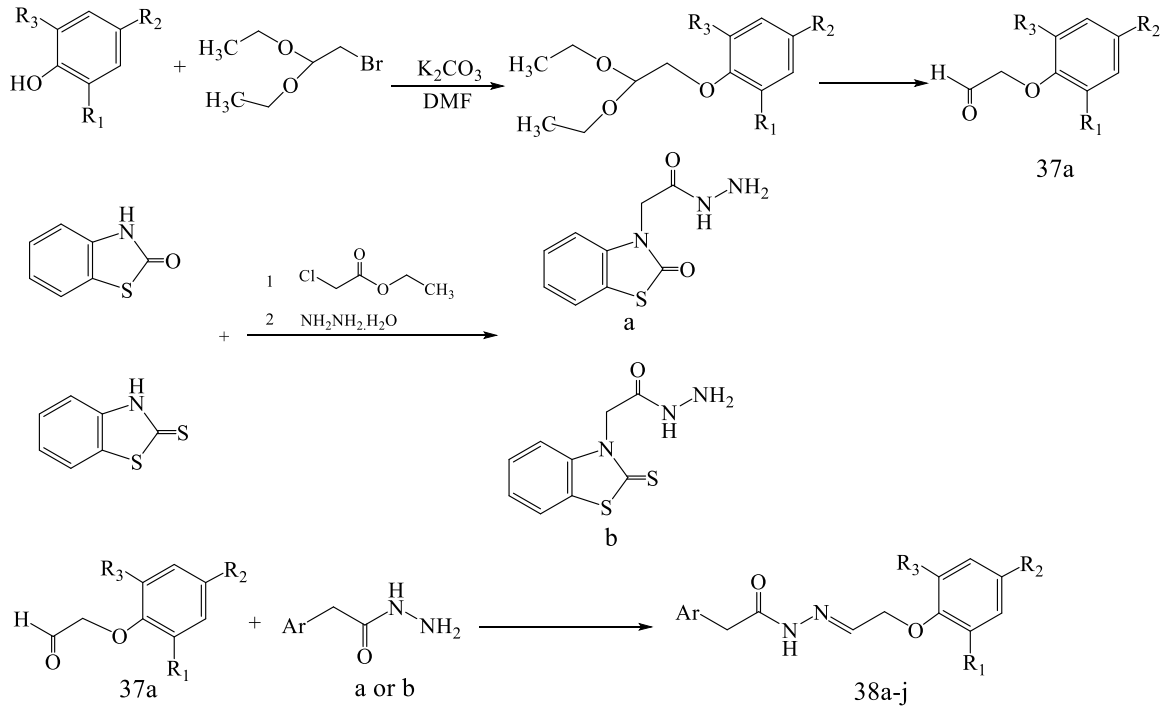


Where Ar: e 4-pyridinyl; **f** 3-pyridinyl; **g** 2-pyridinyl; **h** 2-thiophenyl; **i** 3-methyl-2-thiophenyl; **j** 5-methyl-2-thiophenyl; **k** 5-ethyl-2-thiophenyl; **l** 5-nitro-2-thiophenyl; **m** 2-furanyl; **n** 3-furanyl; **o** 5-bromo-2-furanyl; **p** 5-chloro-2-furanyl;**q** 5-ethyl-2-furanyl;**r** 5-(2-nitrophenyl)-2-furanyl;**s** 4-bromo-2-thiophenyl; **t** phenylmethyl; **u** 2,4-dinitrophenyl; **v** 2-chloro-6-fluorophenyl; **w** 4-trifluoromethoxyphenyl

Scheme (1.15): Synthesis of compounds 36e-w by Aydın et al.

The microwave- assisted (mw) method gives higher yields, in a faster time and with less chemical waste compared to traditional techniques. Two compounds **36t** and **36v** inhibited the growth of a leukemia cancer cell (Tuberculosis) and an ovarian cancer cell line, respectively, but had no significant effect on a panel of sixty human tumor cell lines. Although the compounds were found to exhibit weak inhibition of HCV NS5B polymerase activity.

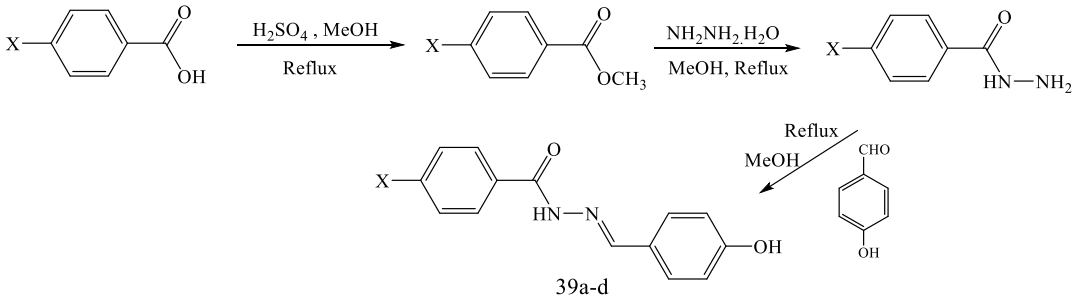
Özdemir et al. [90] synthesized of some new hydrazone derivatives **38a-j** containing the benzothiazole



Where: R_1, R_3: H, CH_3; **R_2:** H, CH_3, OCH_3, $C(CH_3)_3$

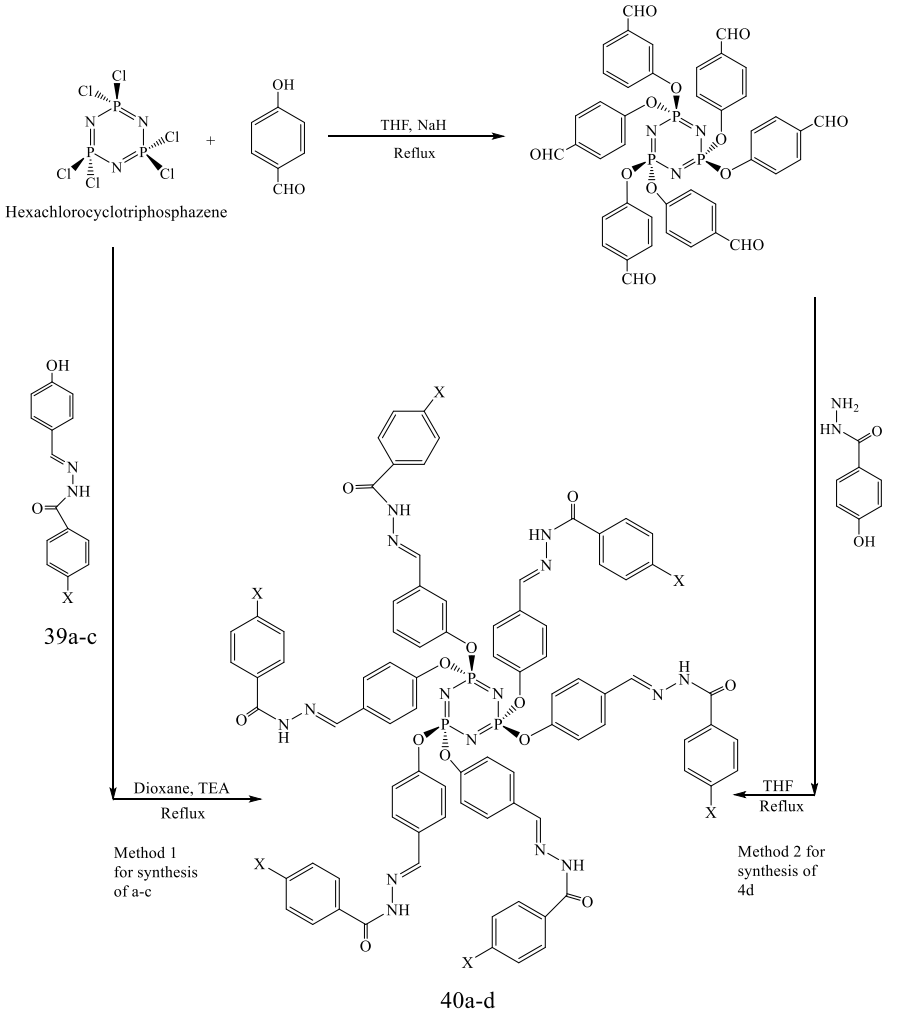
Scheme (1.16): Synthesis of compounds 38a-j by Özdemir et al.

Basavaraj et al. [91] synthesized of hexasubstituted cyclotriphosphazene hydrazone **40a-d**, and evaluated for their antiproliferative activity *in vitro* against the human liver carcinoma cell line (HepG2) and Human cervix carcinoma cell line (HeLa).



Where: X: **a** $-OCH_3$; **b** $-CH_3$; **c** $-NO_2$; **d** -OH

Scheme (1.17): Synthesis of compounds 39a-d by Basavaraj et al.



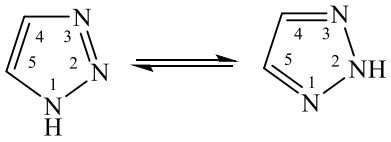
Where: X: **a** $-OCH_3$; **b** $-CH_3$; **c** $-NO_2$; **d** -OH

Scheme (1.18): Synthesis of compounds 40a-d by Basavaraj et al.

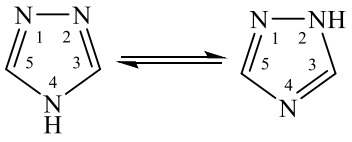
The condensation of 4-hydroxybenzaldehyde with the 4-substituted-benzoic hydrazides lead to aromatic hydrazones **39a-d**. Cyclotriphosphazene hydrazones **40a-d** are prepared by the reaction of hexachlorocyclotriphosphazene with N'-(4-hydroxybenzylidene)-4-substitutedbenzohydrazides. The present compounds exhibited lower activity against HeLa cell lines, but reasonably moderate *in vitro* cytotoxicity against HepG2 cell lines.

1.7- 1,2,4- Triazole and their derivatives:

Triazole derivatives are heterocyclic compounds featuring a five-member ring of two carbon atoms and three nitrogen atoms as part of the aromatic five-member ring. According to the position of nitrogen atoms, the triazoles exists in two isomeric forms with molecular formula $C_2H_3N_3$. Two structural isomeric triazoles are known, the 1,2,3-triazole and the 1,2,4-triazole, each exists in two dissimilar tautomeric forms [92-94].



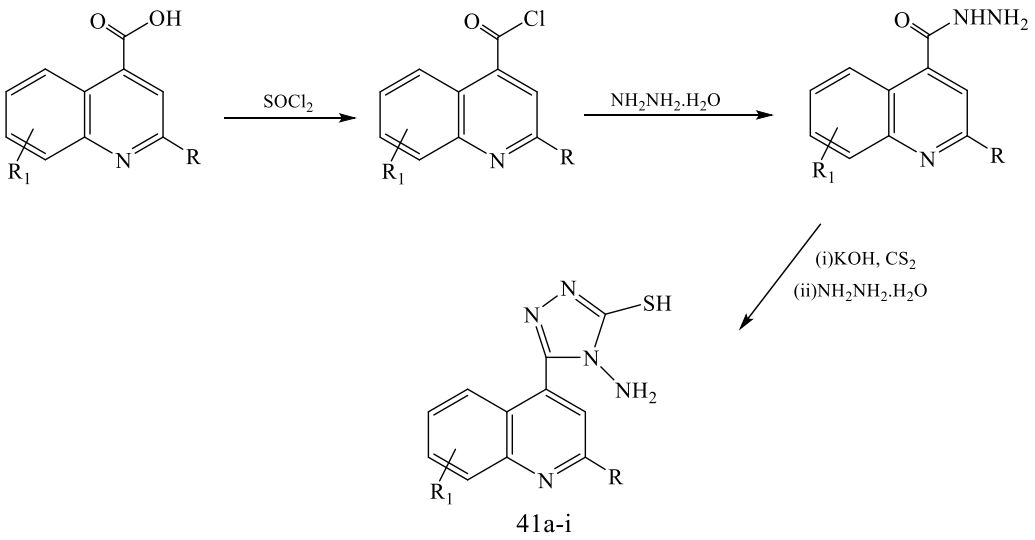
1,2,3-Triazole



1,2,4-Triazole

Amongst the five-member nitrogens containing heterocyclic, the position of nitrogen atom at 1,2 and 4 activates the ring [95], thus triazole and its derivatives have a wide range of the biological activities such as antibacterial [96,97], antifungal [98,99], anti-inflammatory [100,101], anti-tubercular [102], anticonvulsant [103], antioxidant [104], anti-malarial [105], antiproliferative [106], anticancer [107] and antitumor [108].

Vaghasiya et al. [109] synthesized new 4-amino-1,2,4-triazole derivatives **41a-i** and screened for their *in vitro* antimicrobial assay against gram (+ve), gram (-ve) bacteria and fungi activity compared with standard drugs Ampicillin, Chloramphenicol, Ciprofloxacin, Norfloxacin, Griseofulvin and Nystatin at different concentrations.

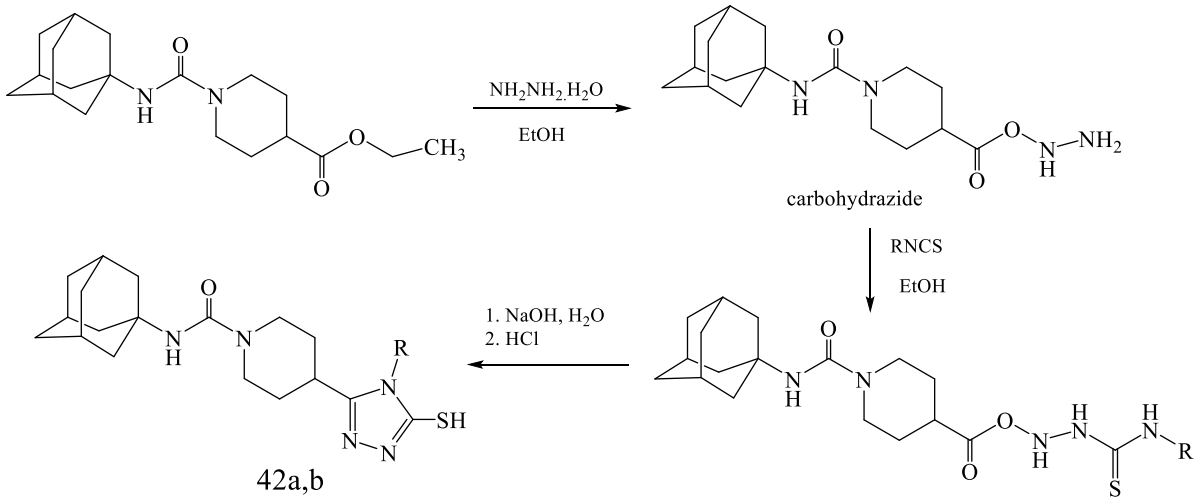


Where R= 4-Cl-C_6H_4, 4-F-C_6H_4, 4-CH_3-C_6H_4
R_1=4-F, 4-Cl, 4-NO_2

Scheme (1.19): Synthesis of compounds 41a-i by Vaghasiya et al.

The high bioactivity of these compounds makes them suitable hits for additional *in vitro* and *in vivo* evaluations, in order to develop a new class of antimicrobial and antimycobacterial drugs or prodrugs with a potential use in the antibacterial, antifungal and tuberculosis treatment.

Al-Abdullah et al. [110] synthesized new 1,2,4-trizole **42a,b** from the reaction of the carbohydrazide with methyl or phenyl isothiocyanate followed by heating in aqueous sodium hydroxide to give 1,2,4-triazole analogues **37a** and **42b**, and then tested for *in vitro* antimicrobial activity against certain strains of pathogenic Gram-positive and Gram-negative bacteria and the yeast-like fungus *Candida albicans.*

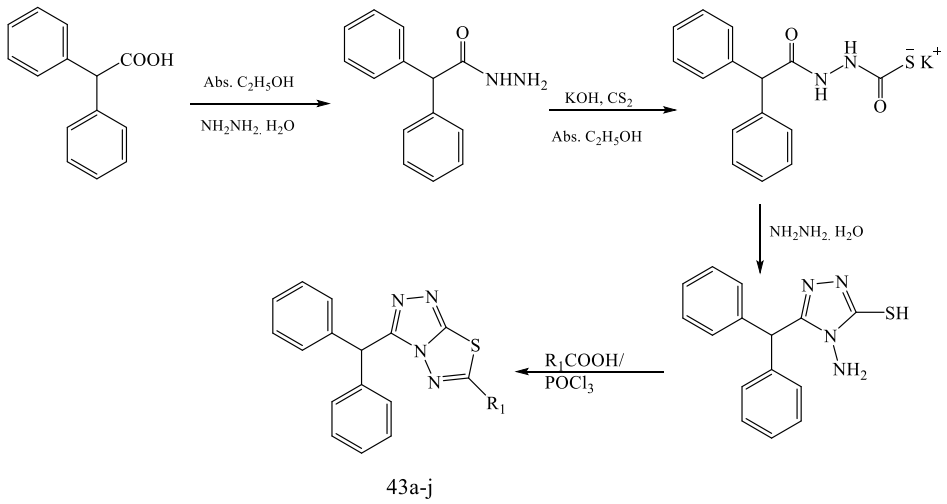


Where R: a= -CH_3; **b**= -C_6H_5

Scheme (1.20): Synthesis of compounds 42a,b by Al-Abdullah et al.

The tested compounds **42a and 42b** showed a low activity when determined in streptozotocin (STZ) –induced diabetic rats.

Akhter, Hassan and Amir [111] synthesized a series of 3-diphenylmethyl-6-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives **43a–j**. These compounds were tested *in vivo* for their anti-inflammatory activity. The compounds which showed activity comparable to the standard drug ibuprofen were screened for their analgesic, ulcerogenic, lipid peroxidation and hepatotoxic effects.

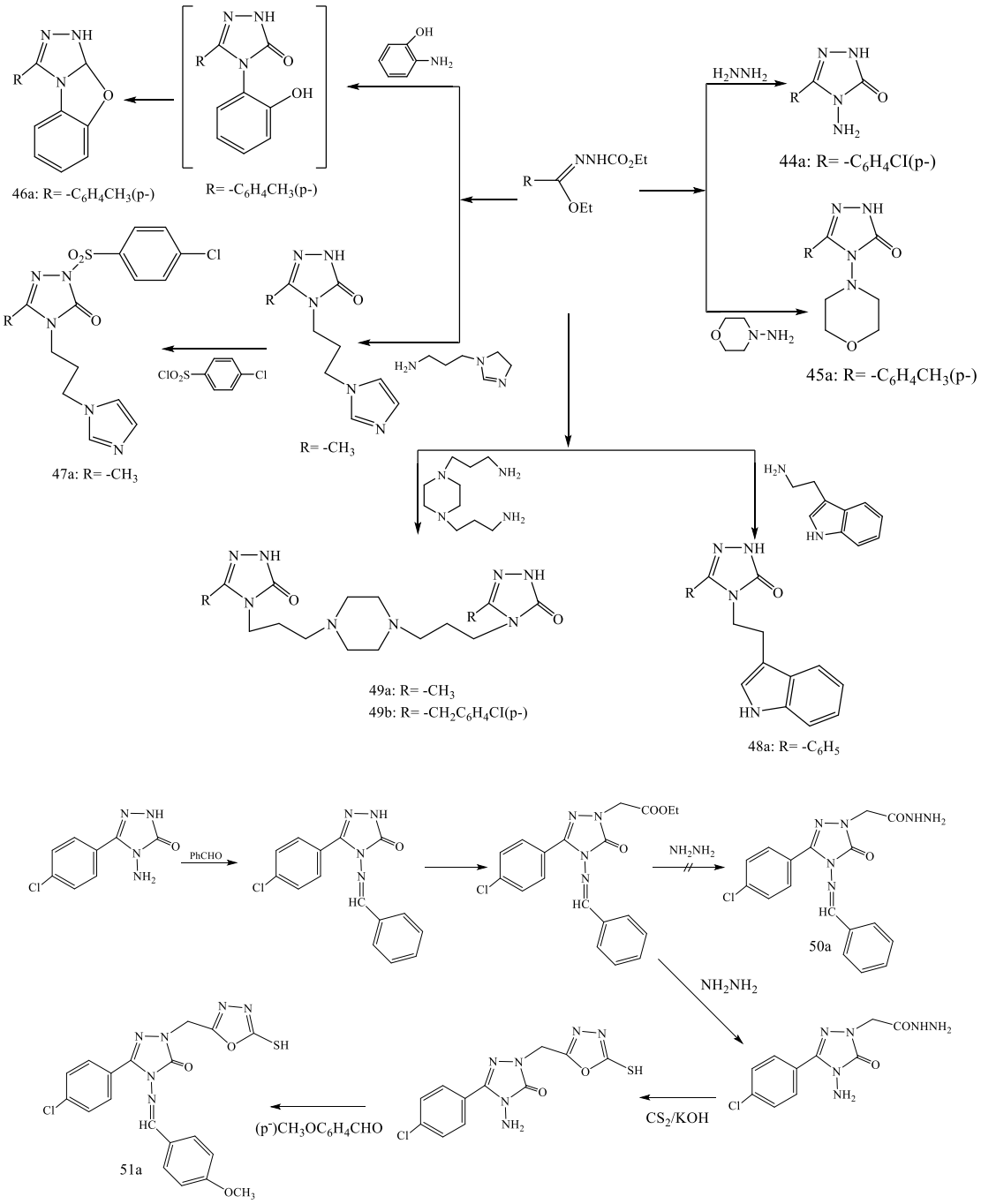


Where R1 = **a**: 4-Cl-C_6H_4; **b**: 2-Cl-C_6H_4; **c**: 2,4-$(Cl)_2$-C_6H_3; **d**: 2-CH_3-C_6H_4; **e**: 4-NH_2-C_6H_4; **f**: 4-NO_2-C_6H_4; **g**: 2-Br-C_6H_4; **h**: 4-Br-C_6H_4; **i**: 2-Cl-4-Br-C_6H_3; **j**: 2,4-$(Cl)_2$-C_6H_3-OCH_2;

Scheme (1.21): Synthesis of compounds 43a-j Akhter, Hassan and Amir

The Compounds 6-(4-chlorophenyl)-3-diphenylmethyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole **43a** and 6-(2,4-dichlorophenyl)-3-diphenylmethyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole **43c** emerged as the most active compounds of the series and were moderately more potent than the standard drug ibuprofen.

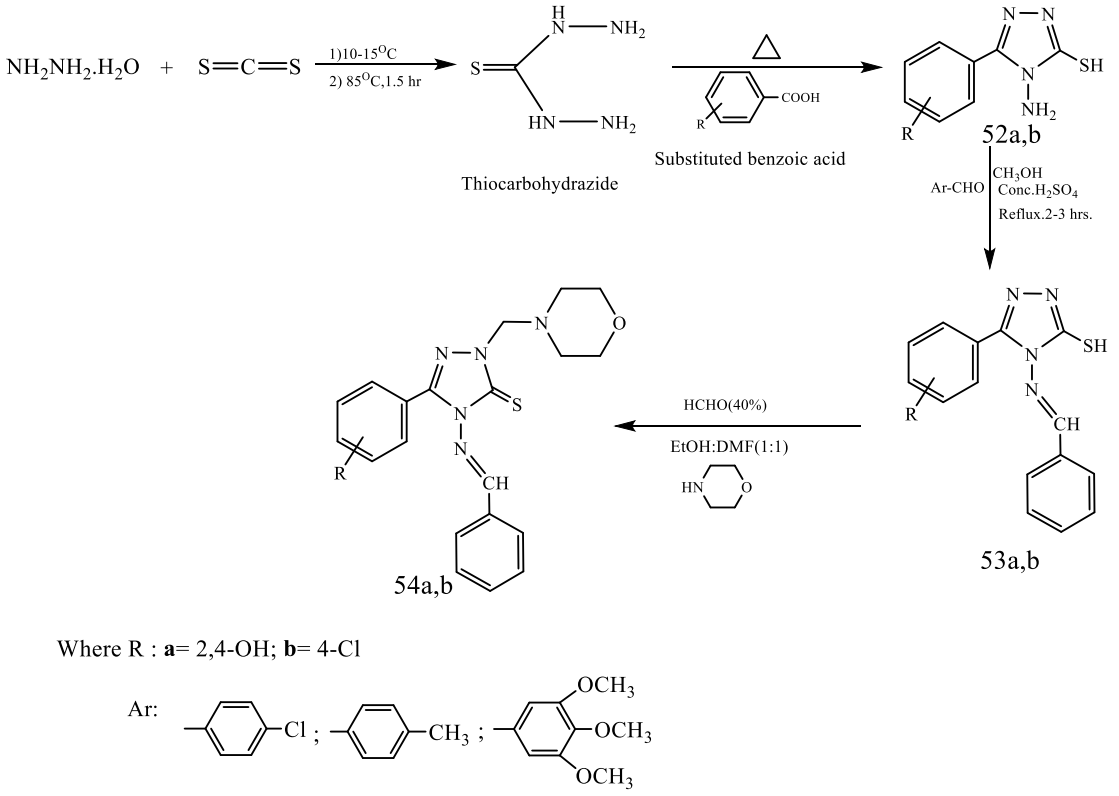
Bektaş et al. [112] synthesized new derivatives of 1,2,4-triazole **44a-51a**, and screened for their antimicrobial activities.



Scheme (1.22): Synthesis of compounds 44a-51a by Bektaş et al.

The antimicrobial screening suggests that among the newly synthesized compounds, the compounds **44a** and **45a** exhibited moderate activities towards *Escherichia coli* (Ec) and *Klebsiella pneumoniae* (Kp), similarly, good antimicrobial activities were found for compounds **51a** against the test microorganisms. On the other hand, none of the synthesized compounds showed antimicrobial activity against *Candida tropicalis* (Ct) and *Candida albicans* (Ca).

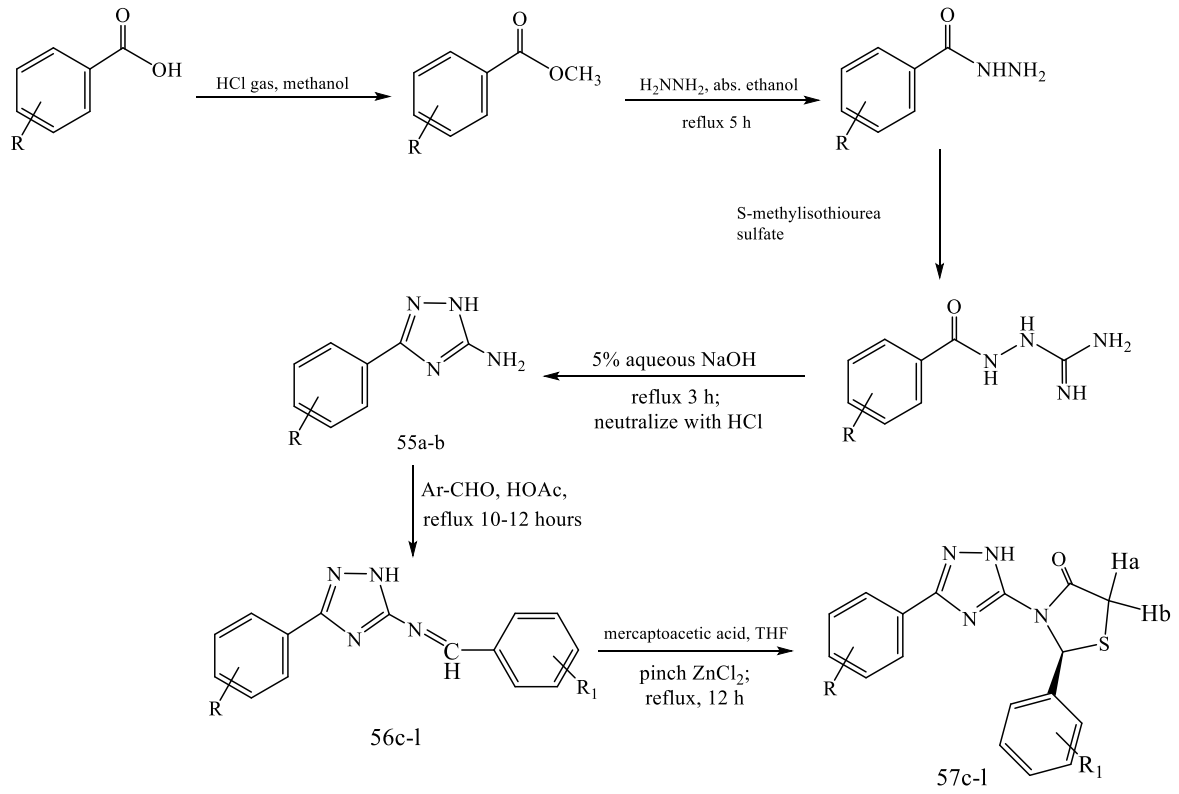
Gupta et al. [113] synthesized of some new 1,2,4-triazole **52a,b** and their Schiff bases **53a,b** and **54a,b** by the cyclization of thiocarbohydrazide and substituted benzoic acid by fusing method, and then studied their antifungal activity.



Scheme (1.23): Synthesis of compounds 54a, b by Gupta et al.

Some of the tested compounds showed good and moderate antifungal activity against various antifungal strains.

Ahmed et al. [114] synthesized of some new 1,2,4-triazole **55a,b** and their Schiff bases **56c-l** and **57c-l**, and studied their antibacterial and antifungal activities.

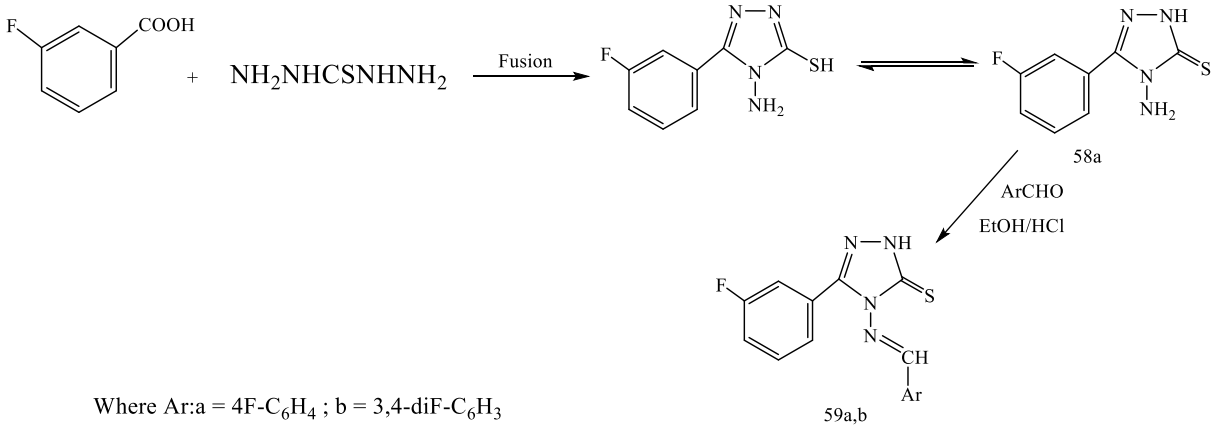


Where a: R = 3-Cl ; **b**: R = 4-OCH_3
c R = 3-Cl, R1 = 4-Cl ; **d** R = 3-Cl, R1 = 4-F
e R = 3-Cl, R1 = 4-NO_2 ; **f** R = 3-Cl, R1 = 4-OCH_3
g R = 3-Cl, R1 = 4-CH_3 ; **h** R = 4-OCH_3, R1 = 4-Cl
i R = 4-OCH_3, R1 = 4-F ; **j** R = 4-OCH_3, R1 = 4-NO_2
k R = 4-OCH_3, R1 = 4-OCH_3 ; **l** R = 4-OCH_3, R1 = 4-CH_3

Scheme (1.24): Synthesis of compounds 57c-I by Ahmed et al.

Compound **57h** followed by **57j** gave the most potent activity against *Staphylococcus aureus*. Compounds **57h–l** showed a good antifungal activity against *Candida albicans*. The *in vitro* studies demonstrated that **57h**, **57j** and **57c** showed promising inhibitory activities against *Mycobacterium fortuitum*.

Aouad [115] synthesized of Schiff bases **59a,b** derived from 1,2,4-triazoles **58a**, and evaluated for their biological activities.

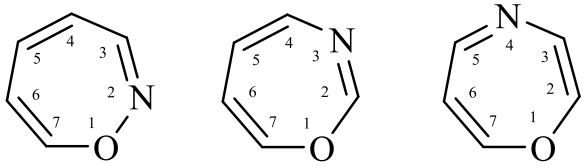


Scheme (1.25): Synthesis of compounds 59a,b by Aouad

The tested compounds **59a** and **59b** showed a comparatively good activity against Gram-positive bacterial strains and excellent activity towards fungal strains.

1.8- Oxazepine derivatives:

Oxazepine is the parent compounds of the seven-membered heterocycles with two heteroatoms; oxygen and nitrogen. There are three isomers for oxazepine compounds: 1,2-oxazepine (a), 1,3-oxazepine (b) and 1,4-oxazepine (c) [116] as shown below:



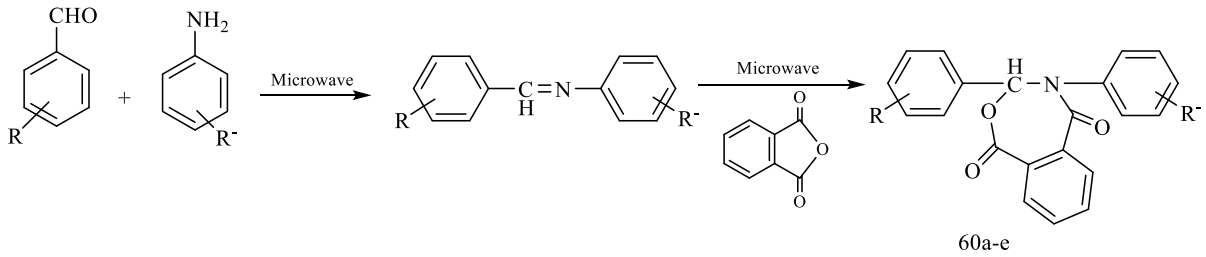
Oxazepine compounds have a medical and biological importance and they have medical and pharmaceutical application. Among the wide chemical derivatives are a heteropolymer which have an activity and effect against cancer [117]. They are also effective against fungi [118] and bacteria [119], hypnotic muscle relaxant[120], antagonistic [121], anti-inflammatory[122], telomerase inhibitors [123] and antiepileptic [124], found that some Oxazepine derivatives are considered a medical drug against the disease [125] and also that (dibenzoxazepine) mental

depression as in the derivative is a cyclic compound containing a heterogeneous (Amoxapine) compound.

Oxazepine derivatives are found to be effective against anxiety and associated with schizophrenia [126].It was also found that (7-hydroxyamoxapine) is a pharmaceutical composite affecting the nervous center (CNS) [127].

Oxazepine can be prepared by condensation cyclization of cyclic anhydride with the imine group (C=N), by direct addition use reflux or microwave technique[128].

Al-Jibory, abdulkareem and Al-Samarraie [129] synthesized new derivatives of 1,3-oxazepine-4,7-dione compounds **60a-e** by modern Microwave technique.

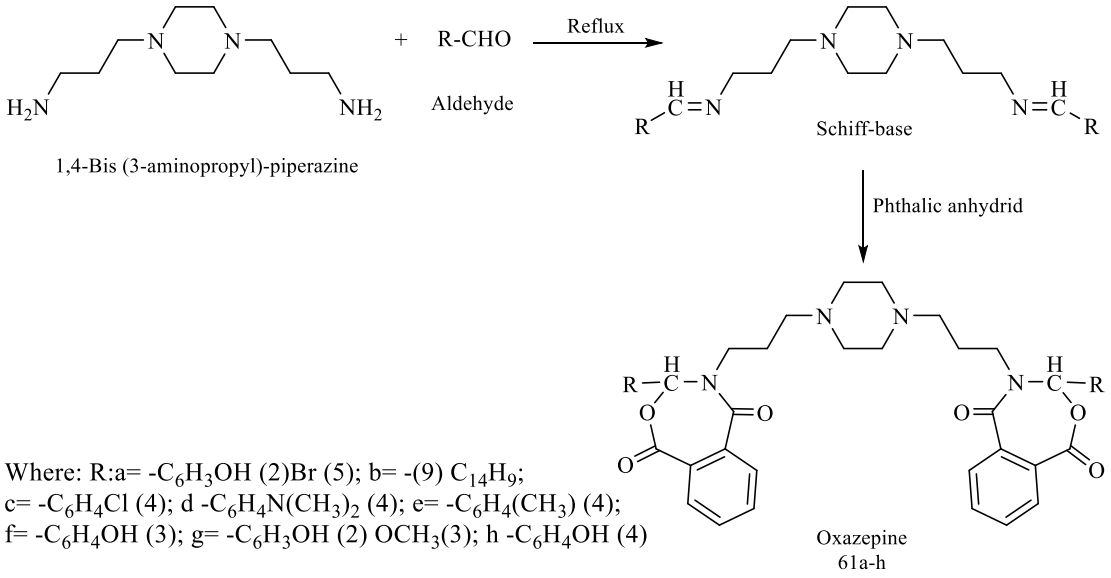


60a-e

Where: a: R -N(CH_3)$_2$ (4), R$^-$ -F (2), -NO_2 (6); **b**:R -NO_2 (3), R$^-$ -F (2), -NO_2 (6); **c**:R -OH (3), R$^-$ -NO_2 (4); **d**:R -Br (4), R$^-$ -F (2), -NO_2 (6); **e**:R -Br (4), R$^-$ -NO_2 (4)

Scheme (1.26): Synthesis of compounds 60a-e by Al-Jibory, abdulkareem and Al-Samarraie

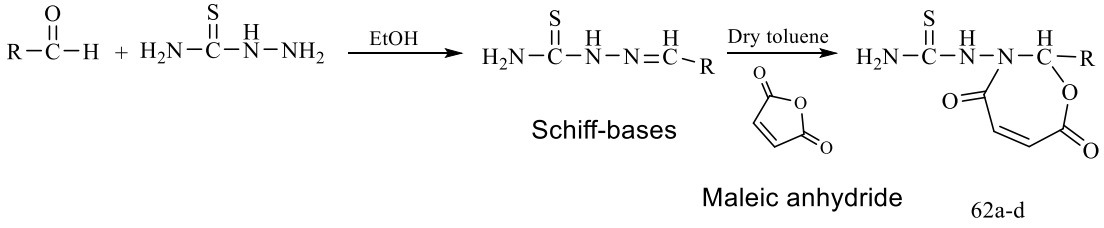
Hamak and Eissa [130] synthesized a series of compounds of oxazepine **61a-h** derived from 1,4-bis(3-aminopropyl)piperazine by Schiff-bases. The synthesized compounds were evaluated for their *in vitro* activity against several microbes and tested to determine their ability to inhibit corrosion of mild steel.



Scheme (1.27): Synthesis of compounds 61a-h by Hamak and Eissa

Compounds **61e-h** which contain electron donating functional moiety is most potent against bacterial they showed a good antimicrobial activity. All eight studied compounds function as effective corrosion inhibitors, with compounds **61b**, **61f** and **61h** being the best of eight compounds.

Sunil et al. [131] synthesized new four oxazepine derivatives **62a-d** by the cycloaddition reaction between Schiff-bases and maleic anhydride. All the synthesized compounds were studied for their anticancer properties in HCT116 (human colon-cancer) cells, molecular modeling and docking studies.



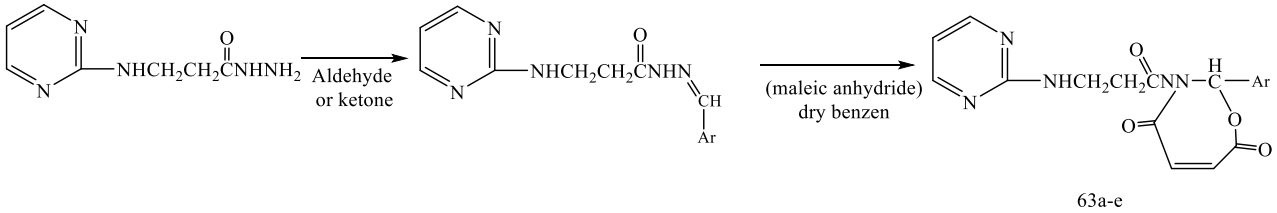
Where R: **a**: 4-hydroxyphenyl; **b**: 3-indolyl; **c**: 2,3-dimethoxyphenyl; **d**: 3-methoxy-4-hydroxyphenyl

Scheme (1.28): Synthesis of compounds 62a-d by Sunil et al.

Four new oxazepine were displayed cytotoxic and antimigratory properties. Oxazepine **62b** with an indole substitute was found to be the most potent among all four oxazepine against HCT116. The docking studies revealed the compound

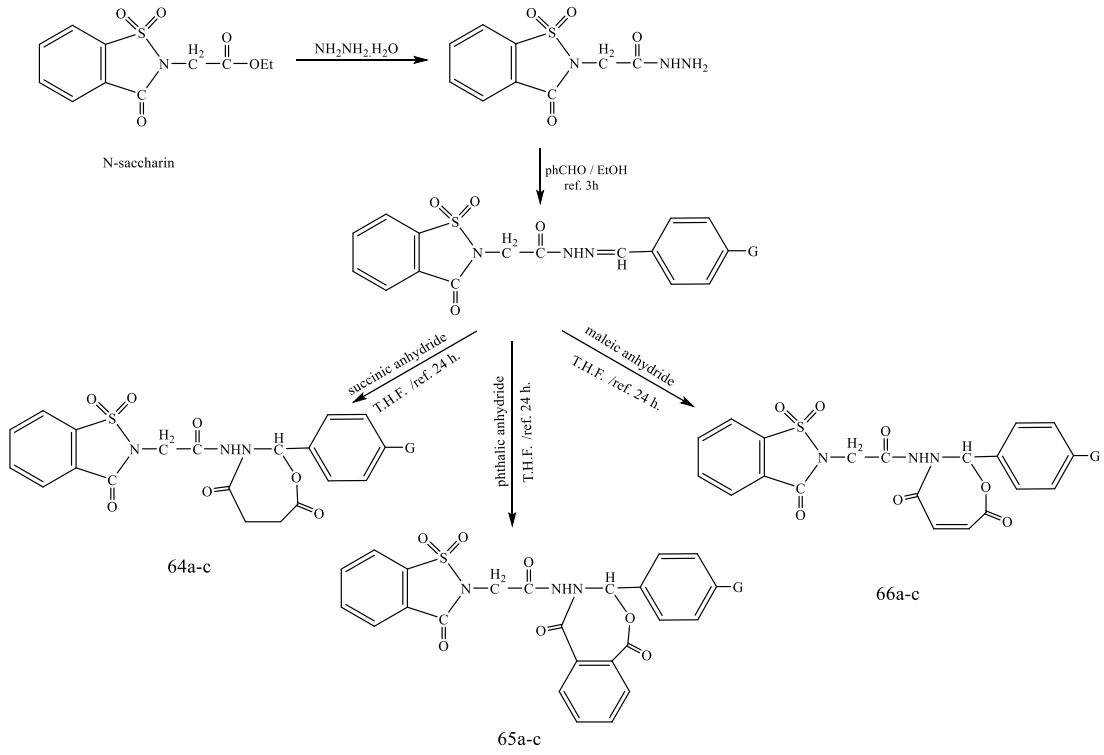
as an excellent snail1 inhibitor. The docking studies of **62b** with the active site of snail1 suggest it to be a potent chemotherapeutic agent in the treatment of colorectal cancer.

Abood [132] synthesized new oxazepine**63-e** from pyrazole derivative used maleic anhydride.



Scheme (1.29): Synthesis of compounds 63a-e by Abood

Naser and Abdullah [133] synthesized new oxazepine **64-66** from reacting N-saccharin derivatives with a succinic, maleic and phthalic anhydride.

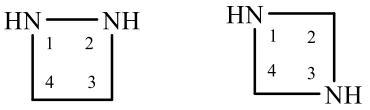


Where G : **a**= Br; **b**= Cl; **c**=OCH_3

Scheme (1.30): Synthesis of compounds 64-66 by Naser and Abdullah

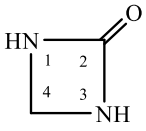
1.9- 1,3-diazetidinone (aza-*β*-lactams):

Diazetidin is one of the important heterocyclic compounds with four member rings containing two nitrogen atoms and two carbon atoms, in two isomers: 1,2-diazetidin and 1,3-diazetidin as shown below [134]:



1,2-Diazetidin 1,3-Diazetidin

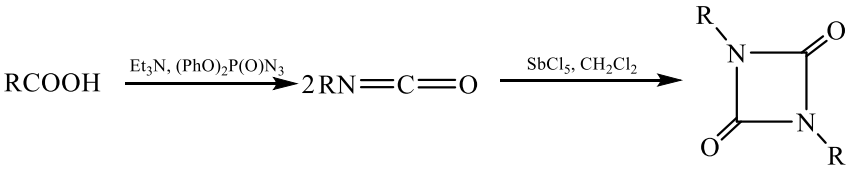
Azetidinones are the carbonyl derivatives of azetidines containing carbonyl group at the position 2. These are also known as 2-azetidinones or more commonly aza-*β*-1actams [135].



1,3-Diazetidin-2-one

1,3-Diazetidins exhibit activities including antibacterial [136,137] and anti-inflammatory activity [138]. They have been found to be potent serine peptidase, transpeptidase, and aza-*β*-lactamase enzyme inhibitors [139,140]. 1,3-Diazetidinone derivatives are also used in polyester polyurethane resins which offer good abrasion resistance [141] and heat resistance [142].

Aoyama et al. [143] synthesized 1,3-diazetidine-dione, Compound **67a** displayed high activity against human cathepsin G and α-chymotrypsin, Compound **67h** was a selective inhibitor against human neutrophil elastase.

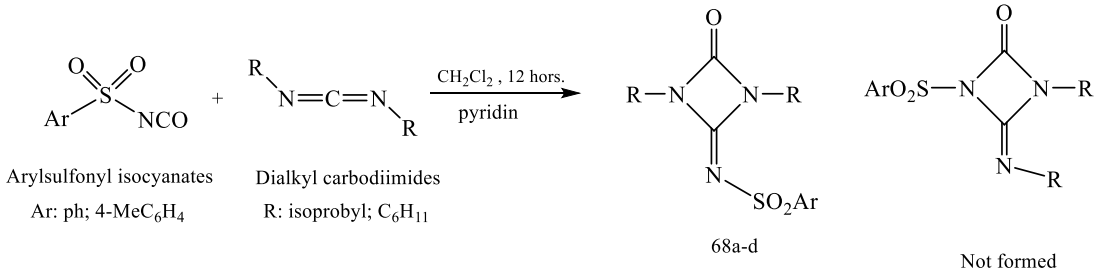


67a-h

Where R: **a**= $C_6H_5CH_2$; **b**= 4-MeO-$C_6H_4CH_2$; **c**= 3-MeO-$C_6H_4CH_2$;
d= 3,4-OCH_2O-$C_6H_3CH_2$; **e**= 4-Me-C_6H_4; **f**= 3,4-OCH_2O-C_6H_3; **g**= EtO_2CCH_2; **h**= Et

Scheme (1.31): Synthesis of compounds 67a-h by Aoyama et al.

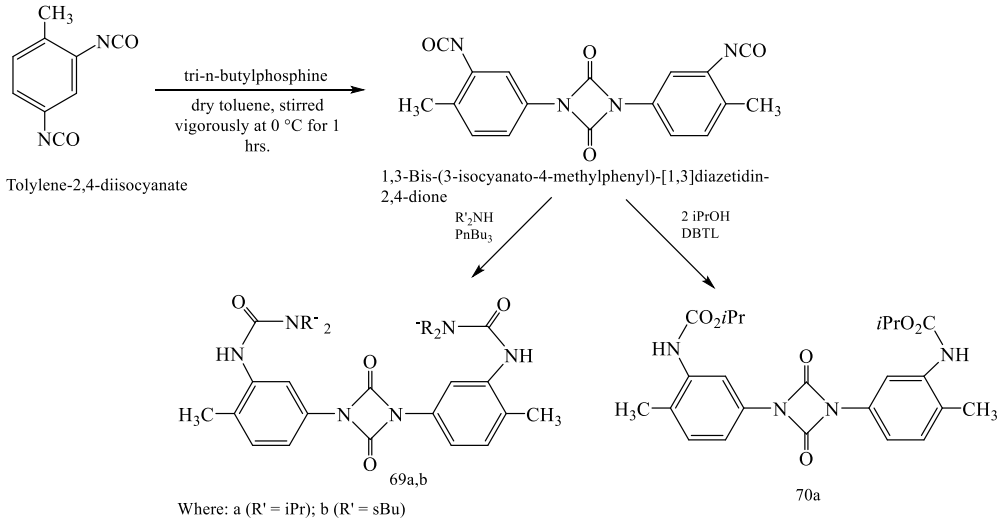
Alizadeh et al. [144] synthesized new 1,3-diazetidin-2-one **68a-d** from the polar cycloaddition reaction of arylsulfonyl isocyanates with dialkyl carbodiimides



Where R &Ar: **a**: Ar= 4-MeC_6H_4 , R= C_6H_{11}; **b**: Ar= 4-MeC_6H_4, R= isoprobyl; **c**: Ar= Ph, R= C_6H_{11}; **d**: Ar= Ph, R= isoprobyl

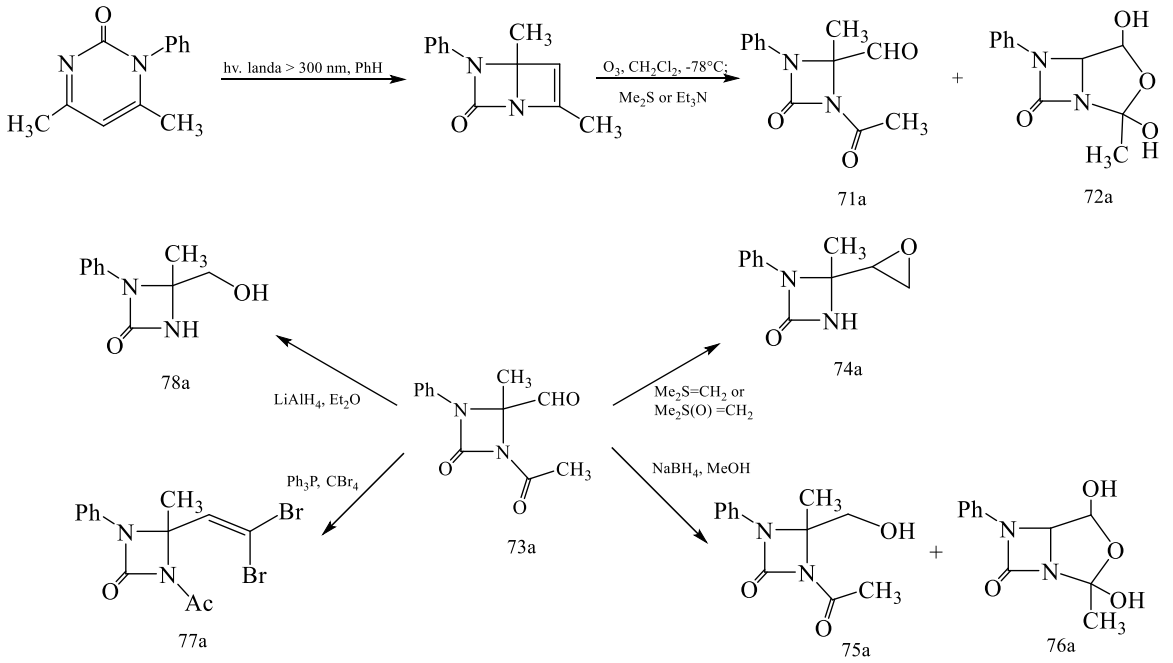
Scheme (1.32): Synthesis of compounds 68a-d by Alizadeh et al.

Risch et al. [145] synthesized new 1,3-diazetidine-2,4-dione **69** and **70a**, from tolylene-2,4-diisocyanate with tri-*n*-butylphosphine to give 1,3-bis-(3-isocyanato-4-methylphenyl)-[1,3]diazetidin-2,4-dione and then react with secondary amine or isopropylalcohol to give compounds **69** and **70a**



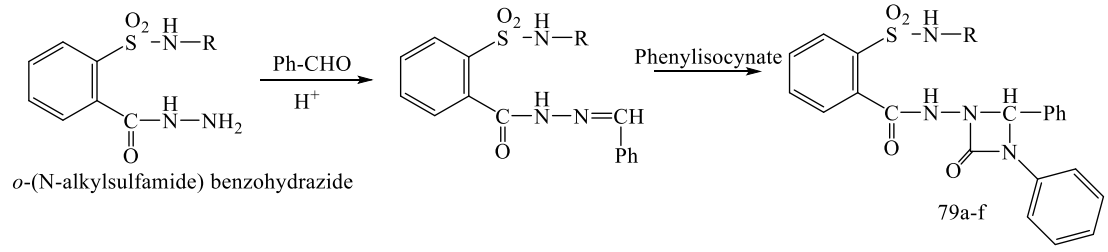
Scheme (1.33): Synthesis of compounds 60a,b and 70a by Risch et al.

Nangia and Chandrakala [146] synthesized diazetidinone **71a-78a** from Pyrimidinone



Scheme (1.34): Synthesis of compounds 72a-78a by Nangia and Chandrakala

Naser and Hussien [147] synthesized new diazetidin-2-one **79a-f** derived from o-(N-alkylsulfamide) benzohydrazide as a starting material.



Wher R: benzyl, n-propyl

Ph:

p-methoxy phenyl ,R=benzyl(79a) *p*-methoxy phenyl , R=n-ropyl(79b) *p*-bromo phenyl , R=benzyl(79c)

p-bromo phenyl , R= n-propyl(79d) *o*-hyderoxy phenyl , R=benzyl(79e) *o*-hyderoxy phenyl , R=n-ropyl(79f)

Scheme (1.35): Synthesis of compounds 79a-f by Naser and Hussien

Aim of the work:

Since heterocyclic compounds exhibited a wide range of biological and pharmacological activities, the target of the present work is directed towards the synthesis of new derivatives of flurbiprofen, and study of the anti-inflammatory activities of some synthesized compounds, this work involves:

1- Synthesis of some new hydrazone and Schiff-base derivatives.
2- Synthesis of some new substituted five-member heterocyclic compounds such as 1,2,3-triazole and cyclic imide derivatives.
3- Synthesis of some new diazetidinone (Aza-*β*-lactam) derivatives.
4- Synthesis of some new oxazepine derivatives.
5- Study the anti-inflammatory activity of some synthesized compounds.

CHAPTER TWO

EXPERIMENTAL

Experimental

2.1- Instruments and Chemicals:

2.1.1- Instruments:

1- Melting point (M.P.) instrument:

Melting points, were recorded using electrothermal melting point apparatus [Gallen Kamp].

2- Fourier transforms infrared spectrophotometer (FT-IR):

FT-IR spectra were recorded using KBr discs on SHIMADZU FT-IR-8400, in the College of Science, Baghdad University and Ibn Sina Center Baghdad-Iraq.

3- Nuclear magnetic resonance spectrophotometer (NMR):

NMR (^{1}H-NMR & ^{13}C-NMR) 400 MHz, use (DMSO-d_6) was used as a solvent, taken with ultrashield (Bruker-Germany), University of Isfahan- Iran.

2.1.2- Chemicals:

All chemicals used in this work were supplied by FDC limited, CDH, BDH, Fluka and Merck.

2.2- Synthetic methods of compounds [1-11]:

2.2.1- Synthesis of ethyl-2-(3-fluorobiphenyl-4-yl) propanoate [1][148]:

To a solution of flurbiprofen (0.004 mol) in absolute ethanol (30 mL), concentrated H_2SO_4 (5 mL) was added and the mixture was refluxed for 8 hours. Then the solution was concentrated and neutralized by $NaHCO_3$ (saturated solution). The oily crude product was extracted with (2 X 20 mL) diethyl ether. The organic layer was evaporated to obtain compound [1].

Physical properties of compound [1] are shown in the table (2.1).

2.2.2- Synthesis of 2-(3-fluorobiphenyl-4-yl) propanohydrazide [2][40]:

Ethyl-2-(3-fluorobiphenyl-4-yl) propanoate [1] (0.004 mol) and hydrazine hydrate 80% (8 mL) were refluxed in an absolute ethanol (30 mL) for 18 hours. The mixture was concentrated, coled and poured over crushed ice in small portions while stirring and kept for (3–4) hours at room temperature. The solid thus separated out filtered, dried and recrystallized from ethanol to give compound [2].

Physical properties of compound [2] are shown in the table (2.1).

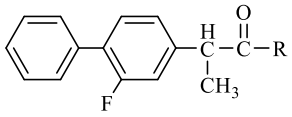


Table (2.1): Physical properties of compounds [1] & [2]:

Com. No.	R	M.F.	M.P. (℃)	Color	Yield (%)
1	$-OC_2H_5$	$C_{17}H_{17}O_2F$	Oil	Colorless	55
2	$-NHNH_2$	$C_{15}H_{15}ON_2F$	98-100	White	85

2.2.3- Synthesis of cyclic imide derivatives [3-5][133]:

A mixture of compound [2] (0.004 mol) and acids anhydride (0.004), namely: maleic anhydride, succinic anhydride and phthalic anhydride (0.004 mol) in (20mL) acetic acid, were refluxed for 24 hours. The formed precipitate was filtered, dried and recrystallized from ethanol to give compounds [3-5] respectively.

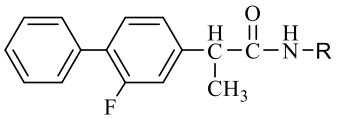
Physical properties of compounds [3-5] are shown in table (2.2)

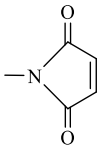
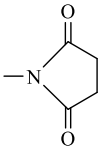
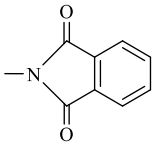
2-(3-Fluorobiphenyl-4-yl)propanamidomaleimide [3]

2-(3-Fluorobiphenyl-4-yl)propaneamidosuccinimide [4]

2-(3-Fluorobiphenyl-4-yl)propaneamidophthalimide [5]

Table (2.2): Physical properties of compounds [3-5]:



Com. No.	R	M.F.	M.P. (℃)	Color	Yield %
3		$C_{19}H_{15}O_3N_2F$	122-124	Red	60
4		$C_{19}H_{17}O_3N_2F$	118-120	White	64
5		$C_{23}H_{17}O_3N_2F$	120-122	White	75

2.2.4- Synthesis of hydrazone derivatives [6-9][149]:

2-(3-Fluorobiphenyl-4-yl) propanohydrazide [2] (0.004 mol) was dissolved in a boiling absolute ethanol. Then, aromatic aldehyde namely 2,4-dimethoxybenzaldehyde, 4-(N,N-dimethylamino)benzaldehyde, 3-hydroxy-benzaldehyde and 2-hydroxybenzaldehyde (0.004 mol) and (2-3) drops of glacial acetic acid were added and refluxed for 6 hours. The formed precipitate after cooling was filtered, dried and recrystallized from ethanol to give compounds [6-9].

Physical properties of compounds [6-9] are listed in Table (2-3).

N-(2,4-dimethoxybenzalidene)-2-(3-fluorobiphenyl-4-yl)propanamide [6]

N-(4-(N,N-dimethylamino)benzalidene)-2-(3-fluorobiphenyl-4-yl)propanamide [7]

N-(3-hydroxybenzalidene)-2-(3-fluorobiphenyl-4-yl)propanamide [8]

N-(2-hdroxybenzalidene)-2-(3-fluorobiphenyl-4-yl)propanamide [9]

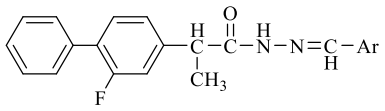
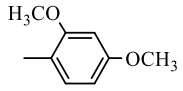
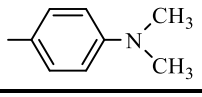
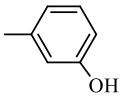
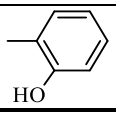


Table (2.3): Physical properties of compounds [6-9]:

Com. No.	Ar	M.F.	M.P. (℃)	Color	Yield (%)
6		$C_{24}H_{23}O_3N_2F$	106-108	Yellow	75
7		$C_{24}H_{24}ON_3F$	124-126	Red	70
8		$C_{22}H_{19}O_2N_2F$	110-112	Brown	65
9		$C_{22}H_{19}O_2N_2F$	120-122	Brown	60

2.2.5- Synthesis of 1-(3-flurobiphenyl-4-yl)-1-(3-mercapto-4-amino-1,2,4-triazole-5-yl)ethane [10][(150)]:

A mixture of 2-(3-fluorobiphenyl-4-yl) propanohydrazide [2] (0.004 mol), potassium hydroxide KOH (0.0045 mol) and (0.0045 mol) carbon disulfide CS_2 were dissolved in absolute ethanol (30 mL) and refluxed for 2 hour in a water bath. After that excess carbon disulfide was removed by distillation. Hydrazine hydrate (80%) (5 mL) was added to the solution and refluxed for 4 hours. After cooling, acidification by 20% HCl, the formed precipitate was filtrated and recrystallized from ethanol to give compound [10]. White solid, M.P. 140-142 ℃, M.F. $C_{16}H_{15}N_4SF$, yield 80%

2.2.6- Synthesis of cyclic imide [11-13] derived from compound [10][(133)]:

Compounds [11-13] were prepared by the same method described for the preparation of compounds [3-5].

Physical properties of compounds [11-13] are listed in Table (2.4).

1-[(3-fluorobiphenyl-4-yl)-1-{3-mercapto-4-(cyclomaleimide)}-1,2,4-triazole-5-yl]ethane [11]

1-[(3-fluorobiphenyl-4-yl)-1-{3-mercapto-4-(cyclosuccinimide)}-1,2,4-triazole-5-yl]ethane [12]

1-[(3-fluorobiphenyl-4-yl)-1-{3-mercapto-4-(cyclophthalimide)}-1,2,4-triazole-5-yl]ethane [13]

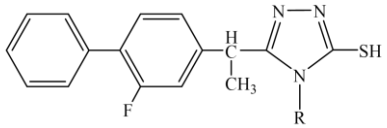
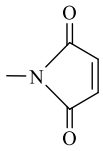
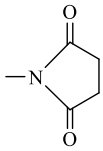
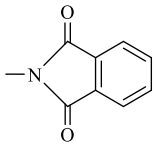


Table (2.4): Physical properties of compounds [11-13]:

Com. No.	R	M.F.	M.P. (℃)	Color	Yield (%)
11		$C_{20}H_{15}O_2N_4SF$	134-136	Yellow	60
12		$C_{20}H_{17}O_2N_4SF$	130-132	Yellow	66
13		$C_{24}H_{17}O_2N_4SF$	150-152	Brown	70

2.2.7- Synthesis of Schiff bases [14-17] derived from compound [10][(149)]:

Compounds [14-17] were prepared by the same method described for the preparation of compounds [6-9].

Physical properties of compounds [14-17] are shown in table (2.5)

1-[(3-fluorobiphenyl-4-yl)-1-{3-mercapto-4-(2,4-dimethoxybenzalidene)}-1,2,4-triazole-5-yl]ethane [14]

1-[(3-fluorobiphenyl-4-yl)-1-{3-mercapto-4-(4-(N,N-dimethylaminobenzalidene))}-1,2,4-triazole-5-yl]ethane [15]

1-[(3-fluorobiphenyl-4-yl)-1-{3-mercapto-4-(3-hydroxybenzalidene)}-1,2,4-triazole-5-yl]ethane [16]

1-[(3-fluorobiphenyl-4-yl)-{3-mercapto-4-(2-hydroxybenzalidene)}-1,2,4-triazole-5-yl]ethane [17]

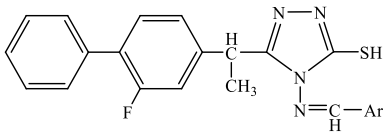
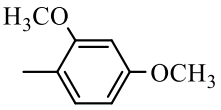
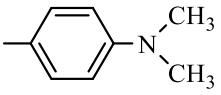
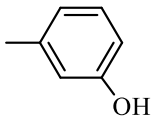
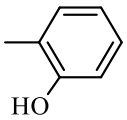


Table (2.5): Physical properties of compounds [14-17]:

Com. No.	Ar	M.F.	M.P. (℃)	Color	Yield (%)
14		$C_{25}H_{23}O_2N_4SF$	130-132	Yellow	60
15		$C_{25}H_{24}N_5SF$	116-118	Red	50
16		$C_{23}H_{19}ON_4SF$	124-126	Yellow	66
17		$C_{23}H_{19}ON_4SF$	132-134	Brown	73

2.2.8- Synthesis of 1,3-diazetidine-2-one (Aza-β-lactam) derivatives [18-21][147]

A mixture of hydrazone compounds [6-9] (0.004 mol) and phenyl isocyanate (0.004 mole) in chloroform (15mL) was refluxed for 6 hrours. The solvent was removed and the residue treated with a mixture of (1:1) ethyl acetate and petroleum ether. The resultingt precipitate was filtered and dried to give compounds [18-21] respectively.

Physical properties of compounds [18-21] are shown in table (2.6)

N-[{2-oxo-3-phenyl-4-(2,4-dimethoxyphenyl)-1,3-diazetidin-1-yl}-2-(3-fluorobiphenyl-4-yl)]-propane amide [18]

N-[{2-oxo-3-phenyl-4-(4-(N,N-dimethyamino)phenyl)-1,3-diazetidin-1-yl}-2-(3-fluorobiphenyl-4-yl)]-propane amide [19]

N-[{2-oxo-3-phenyl-4-(3-hydroxyphenyl)-1,3-diazetidin-1-yl}-2-(3-fluorobiphenyl-4-yl)]-propane amide [20]

N-[{2-oxo-3-phenyl-4-(2-hydroxyphenyl)-1,3-diazetidin-1-yl}-2-(3-fluorobiphenyl-4-yl)]-propane amide [21]

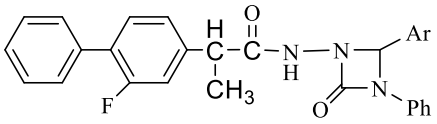
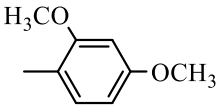
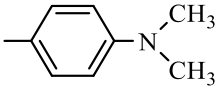
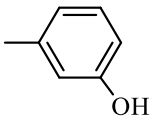
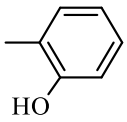


Table (2.6): Physical properties of compounds [18-21]:

Com. No.	Ar	M.F.	M.P. (℃)	Color	Yield (%)
18		$C_{31}H_{28}O_4N_2F$	150-152	Brown	70
19		$C_{31}H_{29}O_2N_3F$	130-132	Red	75
20		$C_{29}H_{24}O_3N_2F$	142-144	Brown	77
21		$C_{29}H_{24}O_3N_2F$	148-150	White	73

2.2.9- Synthesis of oxazepine derivatives [22-25], [26-29] and [30-33][(151)]:

A mixture of hydrazone compounds [6-9] (0.004 mol) and appropriate acid anhydride, namely maleic anhydride, succinic anhydride and phthalic anhydride (0.004 mol) in (20mL) tetrahydrofuran (THF), was refluxed for 24 hours. After cooling the formed precipitate was filtered, dried and recrystallized from ethanol to give compounds [22-25], [26-29] and [30-33].

Physical properties of compounds [22-25] are shown in table (2.7)

2-[(2,4-Dimethoxyphenyl)-3-{2-(3-fluorobiphenyl-4-yl)propanamido}]-2,3-dihydro-1,3-oxazepine-4,7-dione [22]

2-[4-(N,N-Dimethylaminophenyl)]-3-[2-(3-fluorobiphenyl-4-yl)]propanamido-2,3-dihydro-1,3-oxazepine-4,7-dione [23]

2-[(3-Hydroxyphenyl)-3-{2-(3-fluorobiphenyl-4-yl)}propanamido]-2,3-dihydro-1,3-oxazepine-4,7-dione [24]

2-(2-Hydroxyphenyl)-3-[2-(3-fluorobiphenyl-4-yl)]propanamido-2,3-dihydro-1,3-oxazepine-4,7-dione [25]

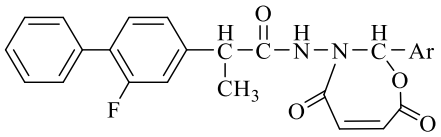
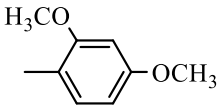
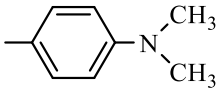
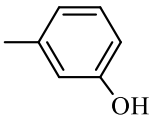
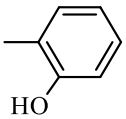


Table (2.7): Physical properties of compounds [22-25]:

Com. No.	Ar	M.F.	M.P. (℃)	Color	Yield (%)
22		$C_{28}H_{25}O_6N_2F$	122-124	Red	75
23		$C_{28}H_{26}O_4N_3F$	146-148	Red	68
24		$C_{26}H_{21}O_5N_2F$	130-132	Yellow	71
25		$C_{26}H_{21}O_5N_2F$	128-130	Brown	64

Physical properties of compounds [26-29] are shown in table (2.8)

2-[(2,4-Dimethoxyphenyl)-3-{2-(3-fluorobiphenyl-4-yl)propanamido}]-2,3,5,6-tetrahydro-1,3-oxazepine-4,7-dione [26]

2-[4-(N,N-Dimethylaminophenyl)-3-{2-(3-fluorobiphenyl-4-yl)}propanamido]-2,3,5,6-tetrahydro-1,3-oxazepine-4,7-dione [27]

2-[(3-Hydroxyphenyl)-3-{2-(3-fluorobiphenyl-4-yl)propanamido}]-2,3,5,6-tetrahydro-1,3-oxazepine-4,7-dione [28]

2-[(2-Hydroxyphenyl)-3-{2-(3-fluorobiphenyl-4-yl)propanamido}]-2,3,5,6-tetrahydro-1,3-oxazepine-4,7-dione [29]

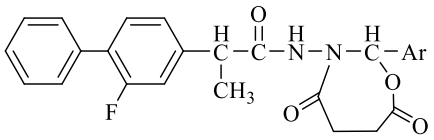
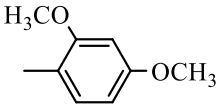
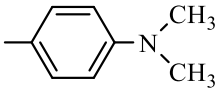
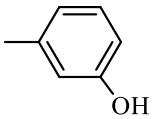
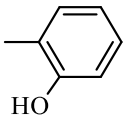


Table (2.8): Physical properties of compounds [26-29]:

Com. No.	Ar	M.F.	M.P. (℃)	Color	Yield (%)
26		$C_{28}H_{27}O_6N_2F$	110-112	Yellow	74
27		$C_{28}H_{28}O_4N_3F$	122-124	Yellow	70
28		$C_{26}H_{23}O_5N_2F$	138-140	Brown	71
29		$C_{26}H_{23}O_5N_2F$	140-142	White	69

Physical properties of compounds [30-33] are shown in table (2.9)

2-[(2,4-Dimethoxyphenyl)-3-{2-(3-fluorobiphenyl-4-yl)propanamido}]-2,3-dihydro(5,6,e)benzo-1,3-oxazepine-4,7-dione [30]

2-[4-(N,N-Dimethylaminophenyl)-3-{2-(3-fluorobiphenyl-4-yl)]propanamido}]-2,3-dihydro(5,6,e)benzo -1,3-oxazepine-4,7-dione [31]

2-[(3-Hydroxyphenyl)-3-{2-(3-fluorobiphenyl-4-yl)]propanamido}]-2,3-dihydro(5,6,e)benzo -1,3-oxazepine-4,7-dione [32]

2-[(2-Hydroxyphenyl)-3-{2-(3-fluorobiphenyl-4-yl)propanamido}]-2,3-dihydro(5,6,e)benzo-1,3-oxazepine-4,7-dione [33]

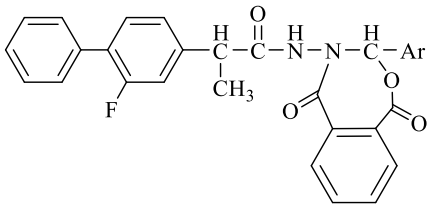
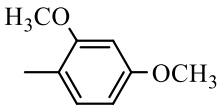
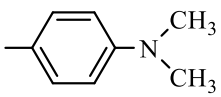
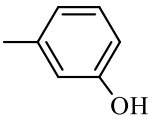
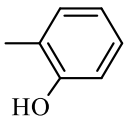


Table (2.9): Physical properties of compounds [30-33]:

Com. No.	Ar	M.F.	M.P. (℃)	Color	Yield (%)
30		$C_{24}H_{27}O_6N_2F$	116-118	Yellow	76
31		$C_{24}H_{28}O_4N_3F$	130-132	Red	69
32		$C_{22}H_{23}O_5N_2F$	118-120	Brown	74
33		$C_{22}H_{23}O_5N_2F$	118-120	Yellow	71

2.3- Evaluation of the anti-inflammatory activity of the synthesized compounds [5], [7], [8], [21] and [25]:

Albino rats of both sexes with the weight (180-220 g), were supplied by the Animal House of the College of Pharmacy, University of Baghdad, and housed in the same location under standardized conditions. Animals were fed standard and drink water *ad libitum*. They were allocated into six groups (six rats each) as follows:

Group I: Six rats that received an appropriate volume of dimethyl sulfoxide (DMSO) (according to the body weight of each rat). This group served as negative control.

Group II: Six rats treated with flurbiprofen as reference substance in a dose of 9mg/kg, dissolved in (DMSO).

Group III-VII: Six rats/group treated with the tested compounds (5, 7, 8, 21, and 25), in a dose 9mg/kg and each dissolved in (DMSO).

The anti-inflammatory activity of the tested compounds was studied using the egg-albumin induced-edema model [(23)]. Acute inflammation was induced by a subcutaneous injection (S.C.) of undiluted egg-albumin (0.05 mL) into the plantar side of the left-hand paw of the rats 30 minutes after intraperitoneal (I.P.) administration of each compound, drugs or the vehicle. The paw thickness was measured by means of vernea at five-time intervals (30, 60, 120, 180 and 240 mintuse) after drug administration. The data were expressed as the mean ± SEM.

2.3.1- Statistical Analysis:

The significance of the differences between the mean value was calculated using unpaired Student t-test. Comparison among multiple groups was made by using analysis of variance (ANOVA). A *p*-value less than 0.05 were considered significant for all data showed in the study part of anti-inflammatory activity. The percent of anti-inflammatory activity was calculated according to the following equation:

Percentage of inhibition (%) = 100 X [1-(X/Y)]

Where:

X= mean increase in paw volume, the thickness of treated rats of either (group II, III, IV, V, VI, VII).

Y= mean increase in paw volume, the thickness of group I rats (negative control).

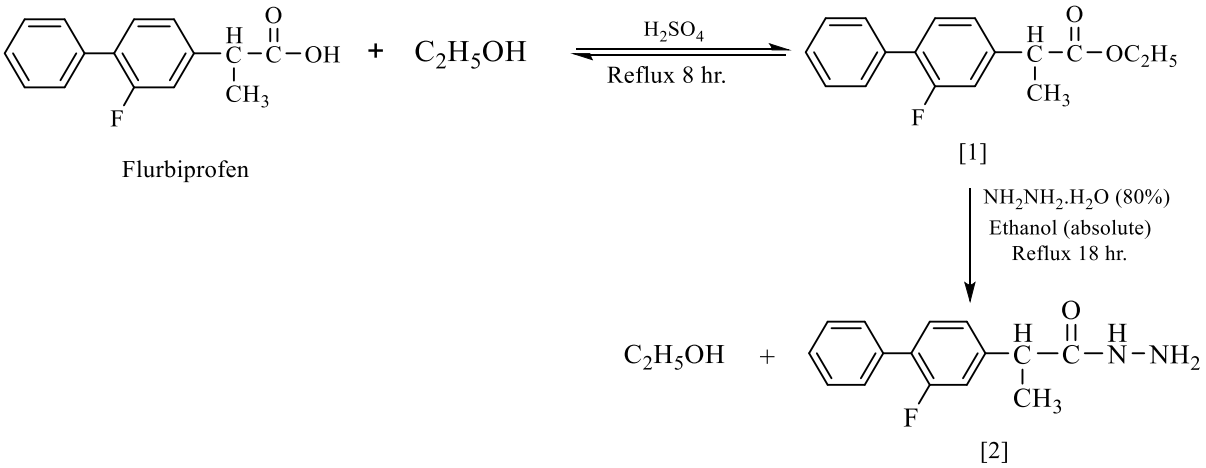
CHAPTER THREE

RESULTS AND DISCUSSION

☙ Results and Discussion ❧

3.1- Synthesis of 2-(3-fluorobiphenyl-4-yl) propanohydrazide [2]:

To synthesize compound [2], the flurbiprofen was first converted to ethyl-2-(3-fluorobiphenyl-4-yl) propanoate [1] *via* esterification of flurbiprofen with absolute ethanol in acid media (concentrated H_2SO_4), then compound [1] reacted with excess of hydrazine hydrate (80%) to give compound [2]



The FT-IR [152] of compound [1] as showen in Figure (3.1) that showed strong absorption bands at 1731 cm^{-1} due to (C=O ester) and 1242 cm^{-1} due to (C-O ester), is good evidence for the formation of the ester derivative [1]. Reaction of compound [1] with 80% of hydrazine hydrate in absolute ethanol gives 2-(3-fluorobiphenyl-4-yl)- propanohydrazide [2]. The disappearance of (C=O ester) at 1731 cm^{-1} and the appearance of stretching bands at (3313, 3184) cm^{-1} and (1637) cm^{-1} which are due to (-$NHNH_2$) and (C=O amide) respectively is good evidence for the formation of the hydrazide compound as showen in Figure (3.2).

All FT-IR spectra bands of compounds 1 and 2 are listed in table (3.1)

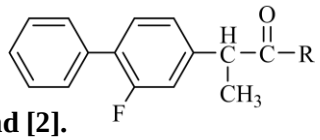


Table (3.1): Characteristic FT-IR absorption bands of compounds [1] and [2].

Com. No.	R	FT-IR spectral data (ν cm^{-1})								
		(-$NHNH_2$) Hydrazine	(C-H) Aromatic	(C-H) Aliph.	(C=C) Aromatic	(C=O) Ester	(C=O) Amide	(C-O) Ester	(C-F)	Other
1	-OC_2H_5	---	3031	2979, 2935	1623, 1581	1731	---	1242, 1182	1074	---
2	-$NHNH_2$	3184, 3313	3031	2977, 2937	1523, 1600	---	1680	---	1072	C-N 1267

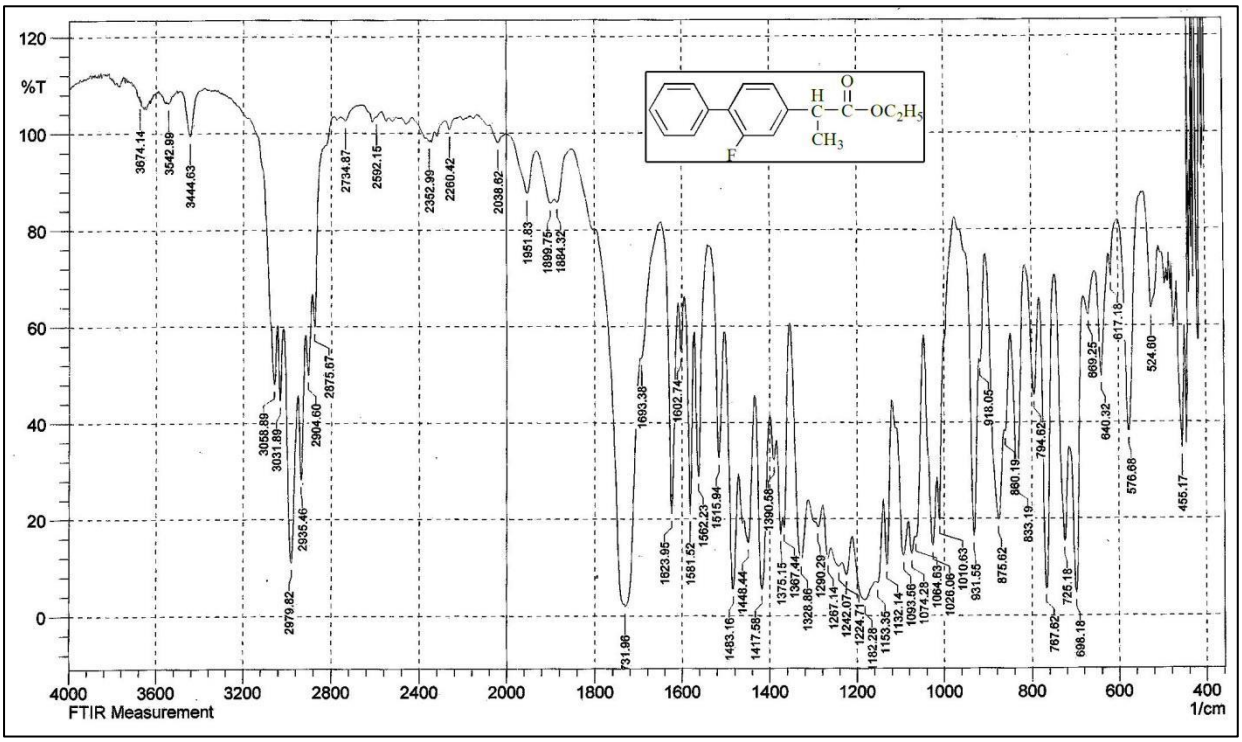


Figure (3.1): FT-IR spectrum of compound [1].

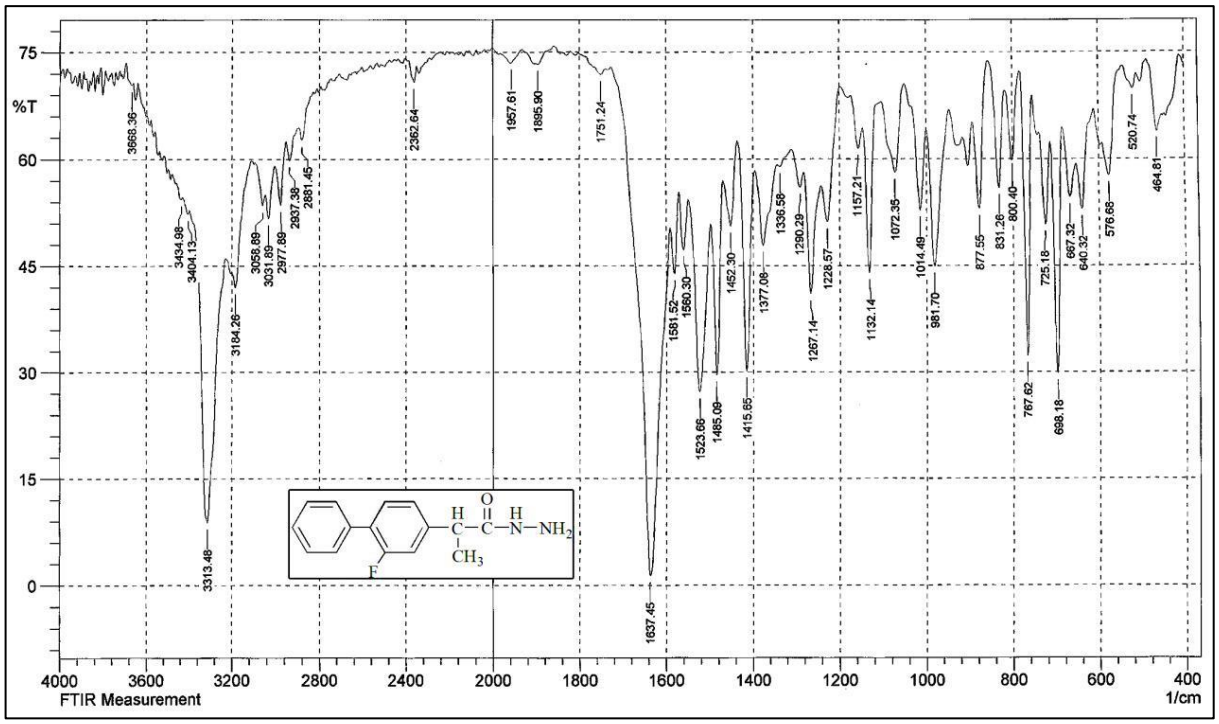
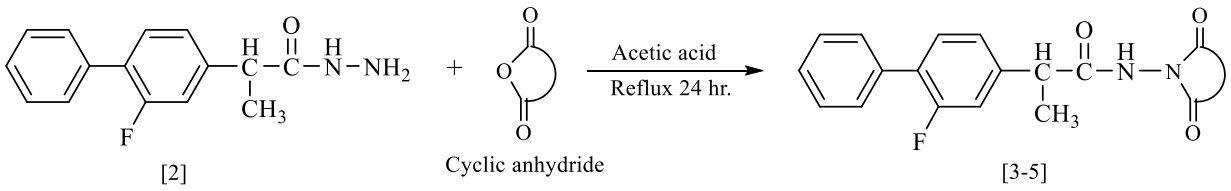
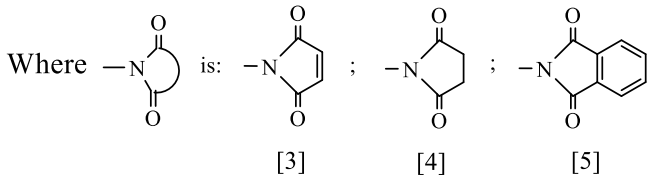


Figure (3.2): FT-IR spectrum of compound [2].

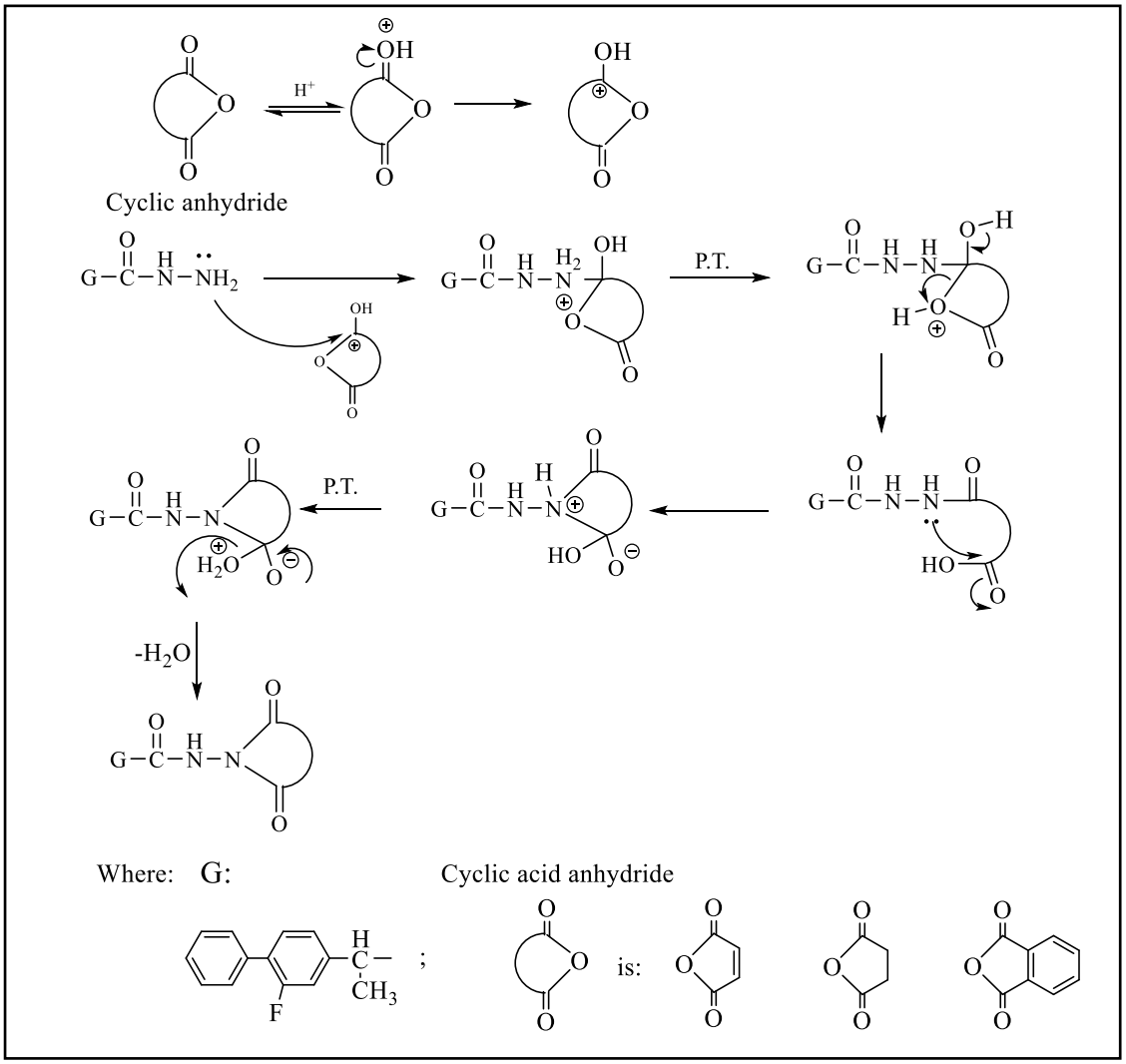
3.2- Synthesis of cyclic imide derivatives [3-5]:

Compounds [3-5] was prepared by the reaction of a compound [2] with different cyclic acids anhydride namely maleic anhydride, succinic anhydride and phthalic anhydride in acetic acid.





The mechanism synthesis of formation cyclic imide derivatives [3-5], as shown in scheme (3.1), involves protenation carbon carbonyl group of acid anhydride, and then nucleophilic attack of amino group of compound [2] on carbonyl group [153]



Scheme (3.1): Mechanism of synthesis compounds [3-5].

The FT-IR spectra Figures (3.3, 3.4 and 3.5) showed the absence of a stretching band at 3313 cm^{-1} and 3184 cm^{-1} due to amino group and the appearance new absorption bands due to (-NH-) at (3211-3280) cm^{-1} and (C=O imide) at (1716-1741) cm^{-1}. It was good evidence for the formation of the cyclic imide derivatives.

All details of FT-IR spectral data of compounds [3-5] are listed in table (3.2).

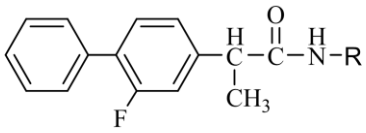
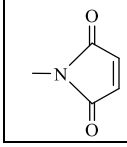
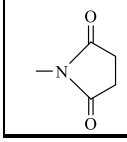
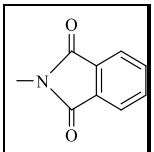


Table (3.2): Characteristic FT-IR absorption bands of compounds [3-5].

Com. No.	R	FT-IR spectral data (ν cm^{-1})							
		(NH)	(C-H) Aromatic	(C-H) Aliph.	(C=O) Imide	(C=O) Amide	(C=C) Aromatic	(C-F)	Others
3		3280	3028	2943, 2916	1739	1629	1514, 1600	1074	C=C 1681
4		3222	3037	2979, 2933	1716	1620	1485, 1602	1072	$-CH_2-$ 1415
5		3271	3026	2979, 2945	1741	1674	1600, 1514	1072	---

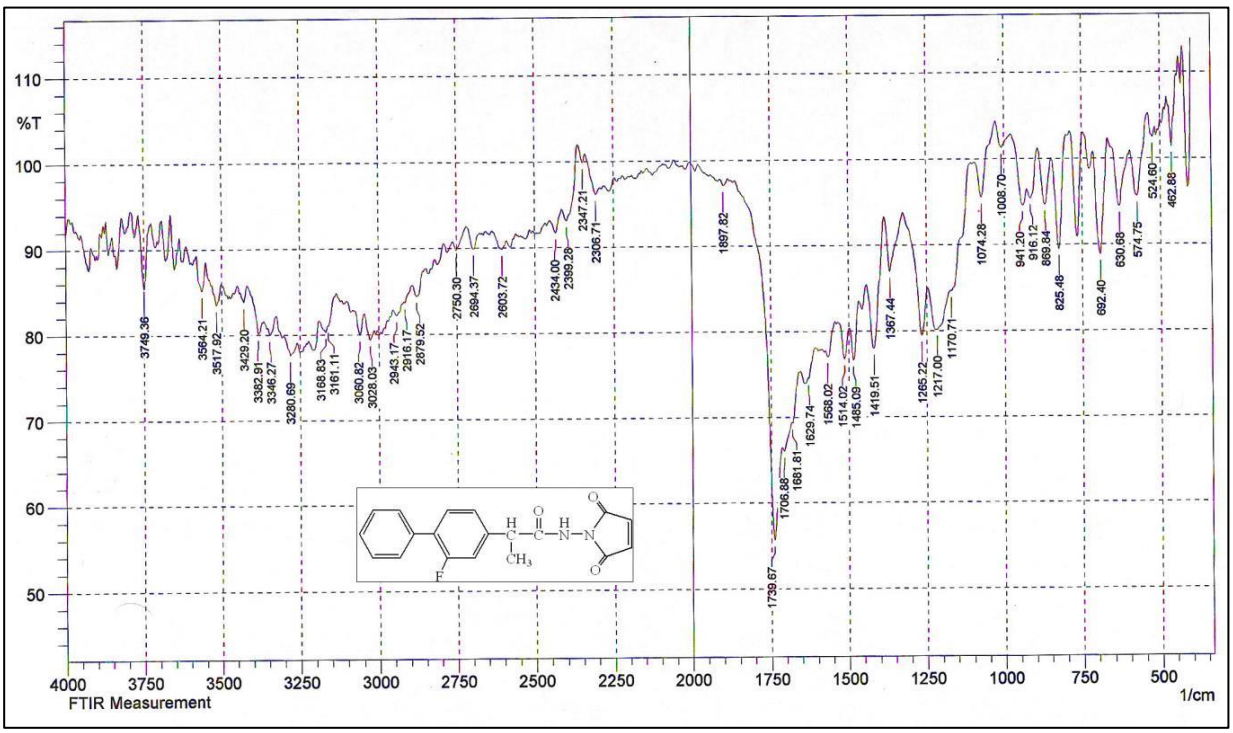


Figure (3.3): FT-IR spectrum of compound [3].

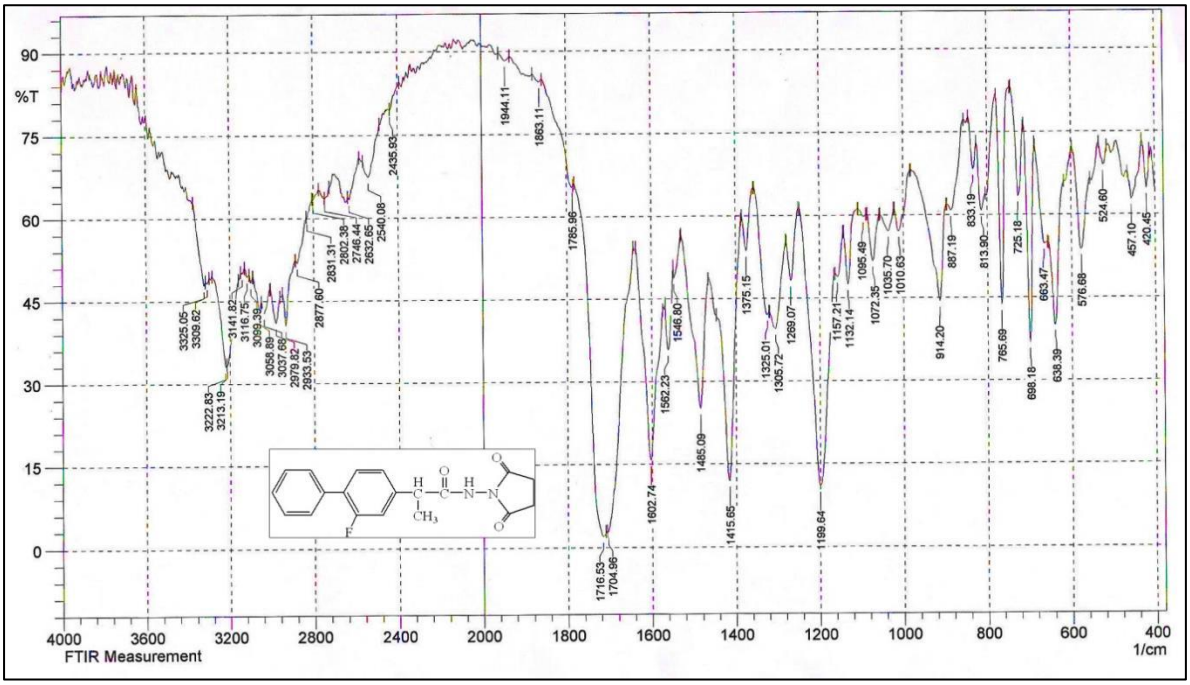


Figure (3.4): FT-IR spectrum of compound [4].

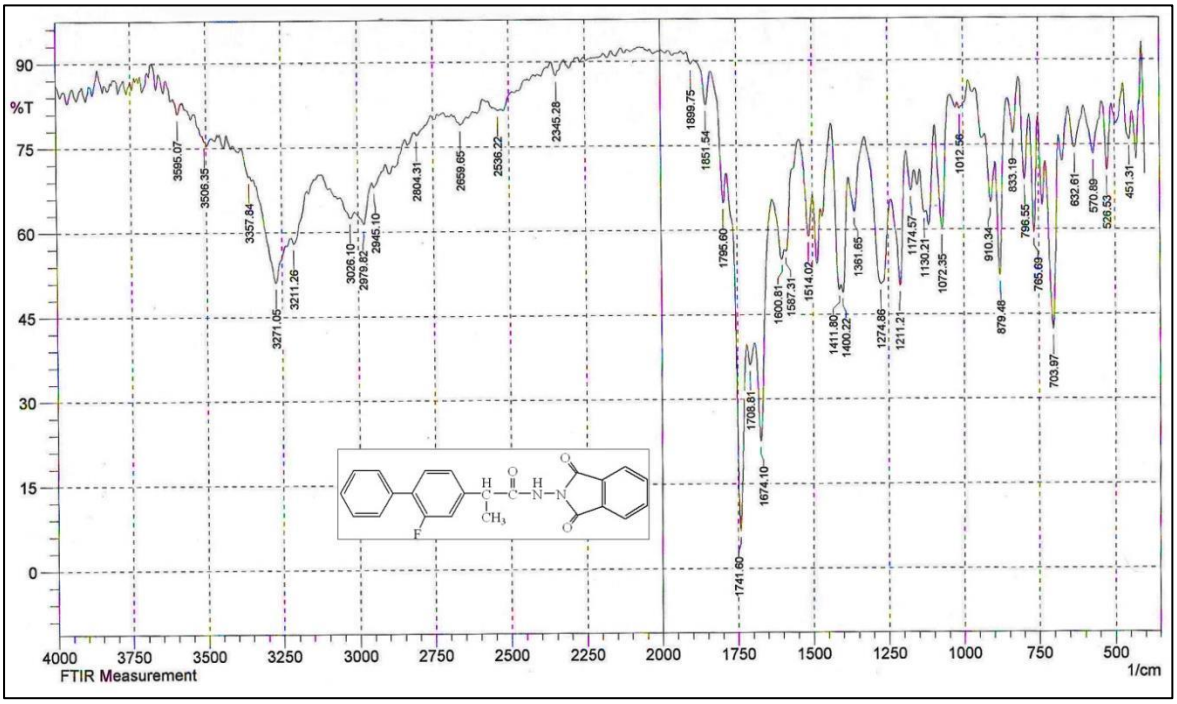
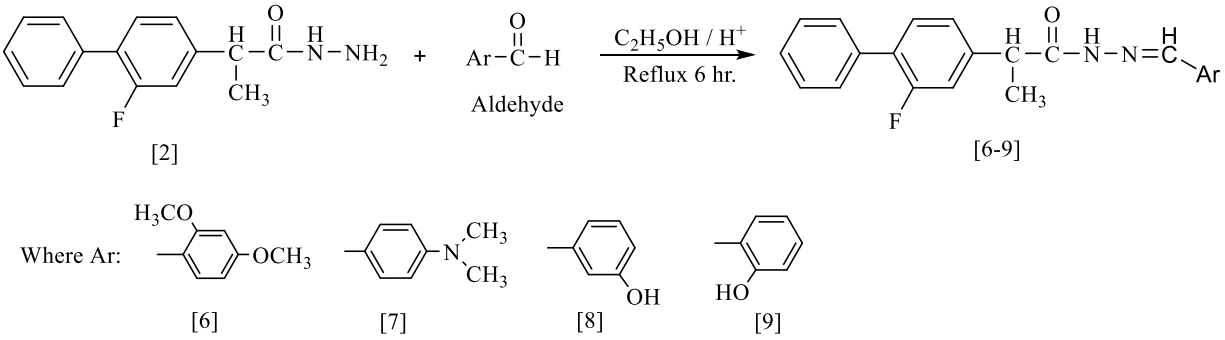


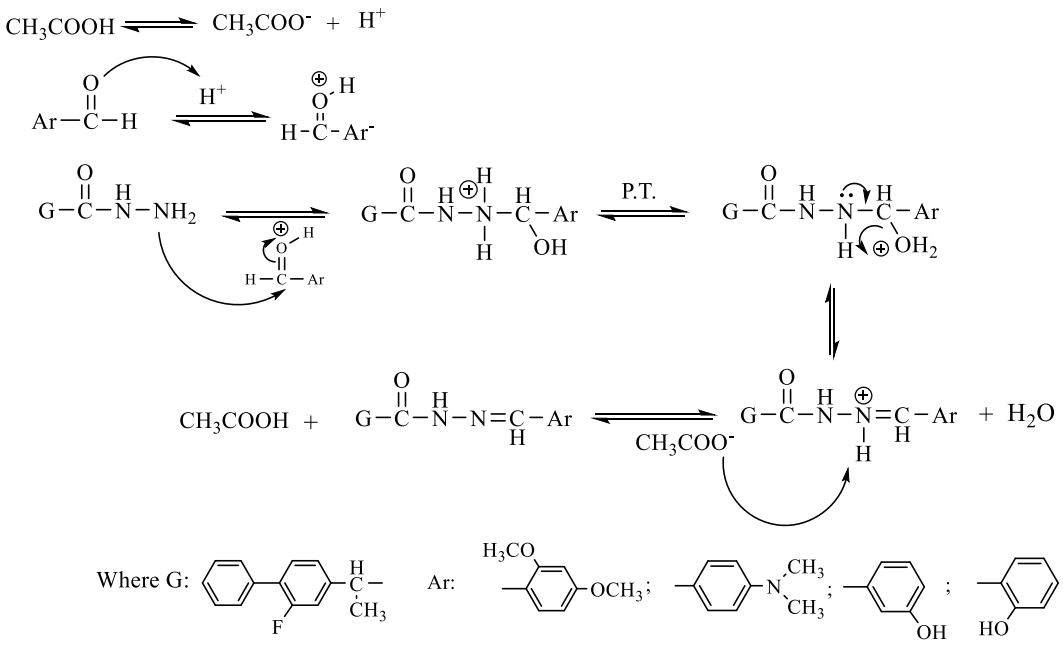
Figure (3.5): FT-IR spectrum of compound [5].

3.3- Synthesis of hydrazone derivatives [6-9]:

Compounds [6-9] was prepared *via* the condensation of compound [2] with different aromatic aldehydes namely 2,4-dimethoxybenzaldehyde, 4-(N,N-dimethylamino) benzaldehyde, 2-hydroxybenzaldehyde and 3-hydroxy-benzaldehyde, in acid media (glacial acetic acid) as a catalyst.



The mechanism of synthetic compounds [6-9], as shown in scheme (3.4), involves protenation of the aromatic aldehyde by glacial acetic acid, and then nucleophilic attack of the amino group of compound [2] on the carbonyl group in aromatic aldehyde to give hydrazone compounds [(154)] after elimination of water.



Scheme (3.2): Mechanism of synthesis compounds [6-9].

The absence of the (-NH_2) stretching band at (3313 and 3184) cm^{-1} Figures (3.6, 3.7, 3.8 and 3.9) and the appearance of (C=N) stretching band at (1581-1620) cm^{-1}, while ^{1}H-NMR spectrum of compound [6] and [7], Figures (3.10 and 3.12), showed singlet signal for imine (CH=N) at 9.72-10.23 ppm and ^{13}C-NMR spectrum Figures (3.11 and 3.13) showed single for (CH=N) at 170 ppm which indicate the formation of hydrazone derivatives[155].

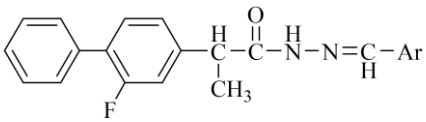


Table (3.3): Characteristic FT-IR absorption bands of compounds [6-9].

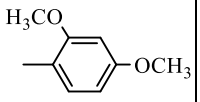
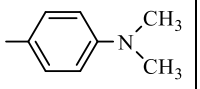
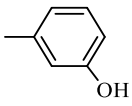
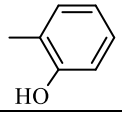
Com No.	Ar	FT-IR spectral data (ν cm^{-1})							
		(NH)	(C-H) Aromatic	(C-H) Aliph.	(C=O) Amide	(C=N)	(C=C) Aromatic	(C-F)	Others
6		3197	3020	2993, 2968	1658	1620	1577, 1602	1078	C-O Ether 1209
7		3186	3033	2970, 2906	1662	1545	1485, 1598	1068	C-N Amine 1205
8		3107	3031	2975, 2835	1668	1581	1492, 1600	1076	-OH 3207
9		3120	3032	2939, 2985	1662	1620	1485, 1605	1076	-OH 3221

Table (3.4): ^{1}H-NMR spectral data (δ ppm) of compounds [6] and [7]:

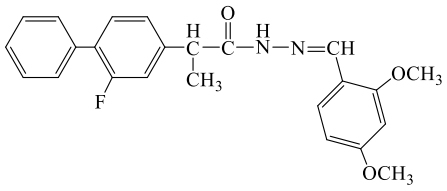
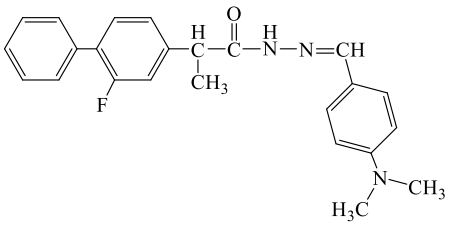
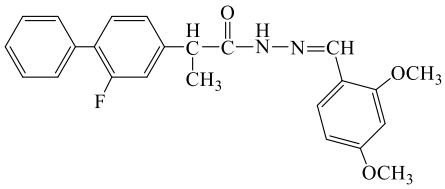
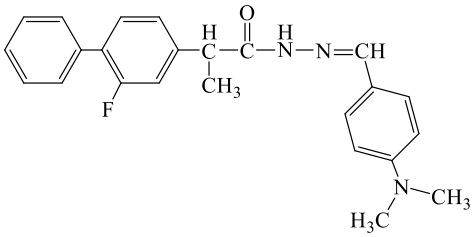
Com. No.	Structure	^{1}H-NMR spectral data (δ ppm)
6		1.46-1.50 (d, 3H, $\underline{CH_3}$-CH), 3.76(s, 6H, $2CH_3O$-), 4.78-4.79 (q, 1H, $\underline{CH}$-CH_3), 6.64-8.26 (m, 11H, Ar-H), 10.23 (s, 1H, CH=N), 11.25 (s, 1H, NH)
7		1.46-1.50 (d, 3H, $\underline{CH_3}$-CH), 3.00 (s, 6H, $(\underline{CH_3})_2$-N), 3.09-3.78 (q, 1H, $\underline{CH}$-CH_3), 6.76-8.12(m, 12H, Ar-H), 9.72 (s, 1H, CH=N), 11.15 (s, 1H, NH),

Table (3.5): ^{13}C-NMR spectral data (δ ppm) of compounds [6] and [7]:

Com. No.	Structure	^{13}C-NMR spectral data (δ ppm)
6		18 ($\underline{C}H_3$-CH), 43 ($\underline{C}H$-CH_3), 55 ($2OCH_3$), (98-166) aromatic ring carbons, 168 (C=N imine), 173 (C-F), 187 (C=O amide).
7		18 ($\underline{C}H_3$-CH), 43 ($\underline{C}H$-CH_3), 43 ($(CH_3)_2N$) 160 aromatic ring carbons, 168 (C=N imine), 173(C-F), 189 (C=O amide).

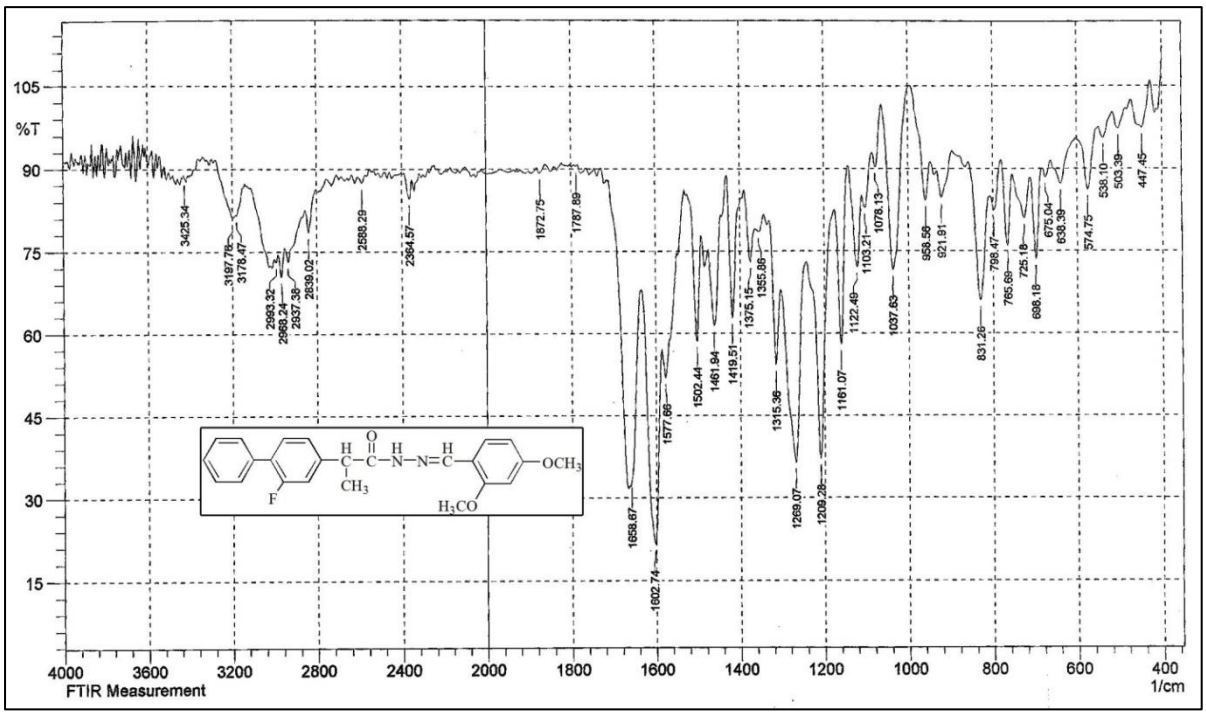


Figure (3.6): FT-IR spectrum of compound [6].

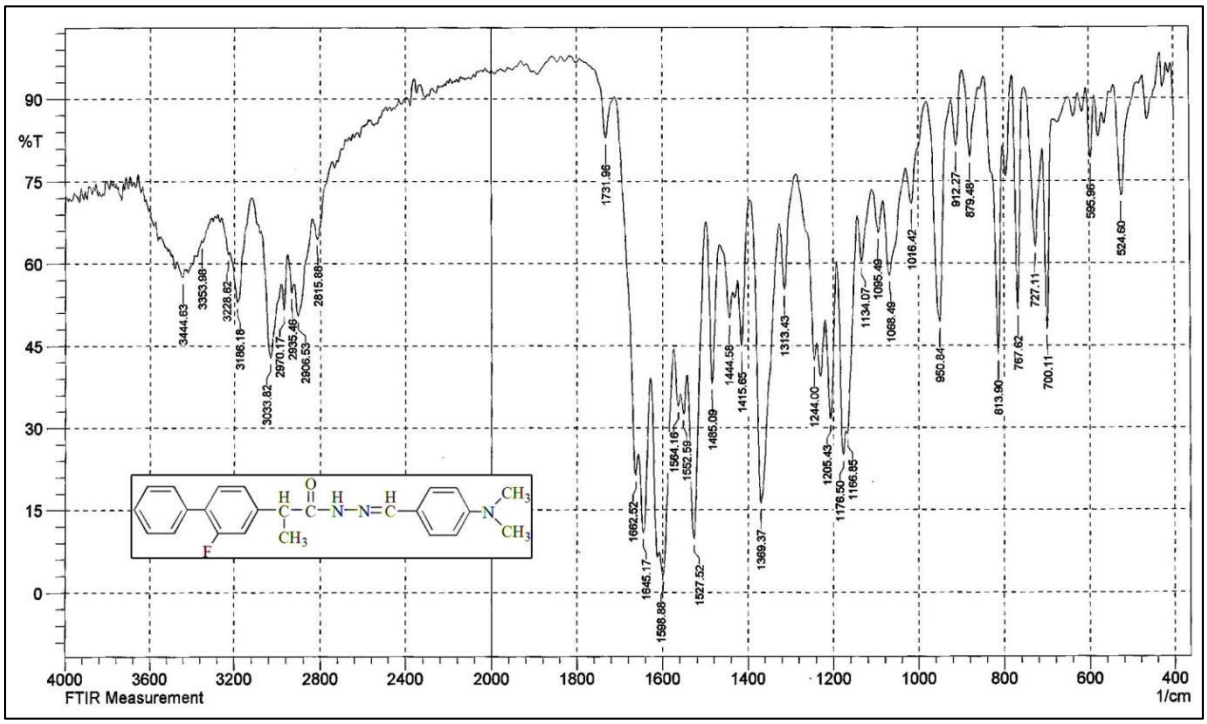


Figure (3.7): FT-IR spectrum of compound [7].

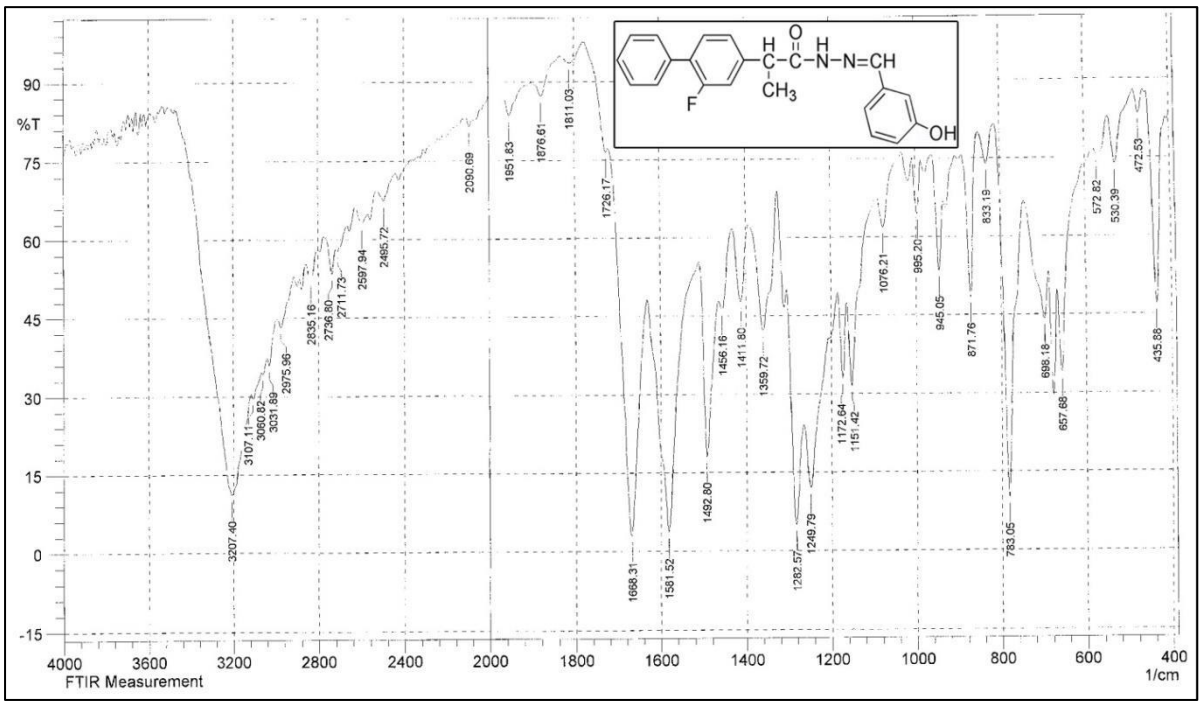


Figure (3.8): FT-IR spectrum of compound [8].

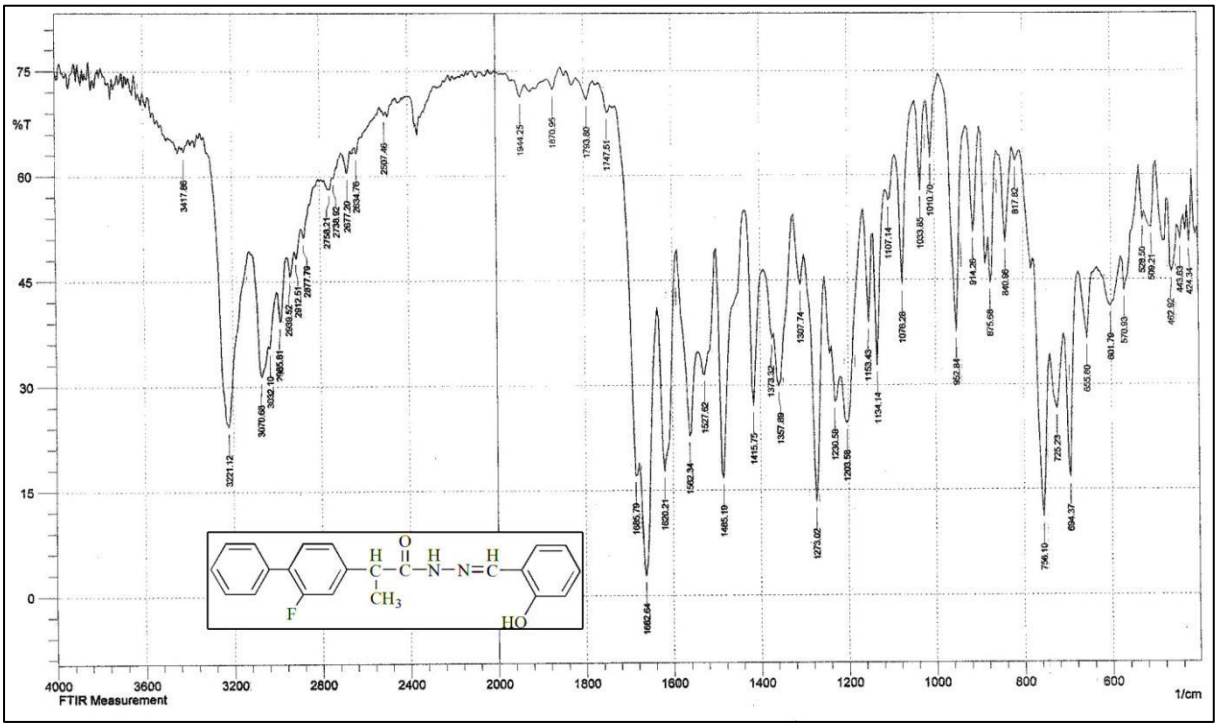


Figure (3.9): FT-IR spectrum of compound [9].

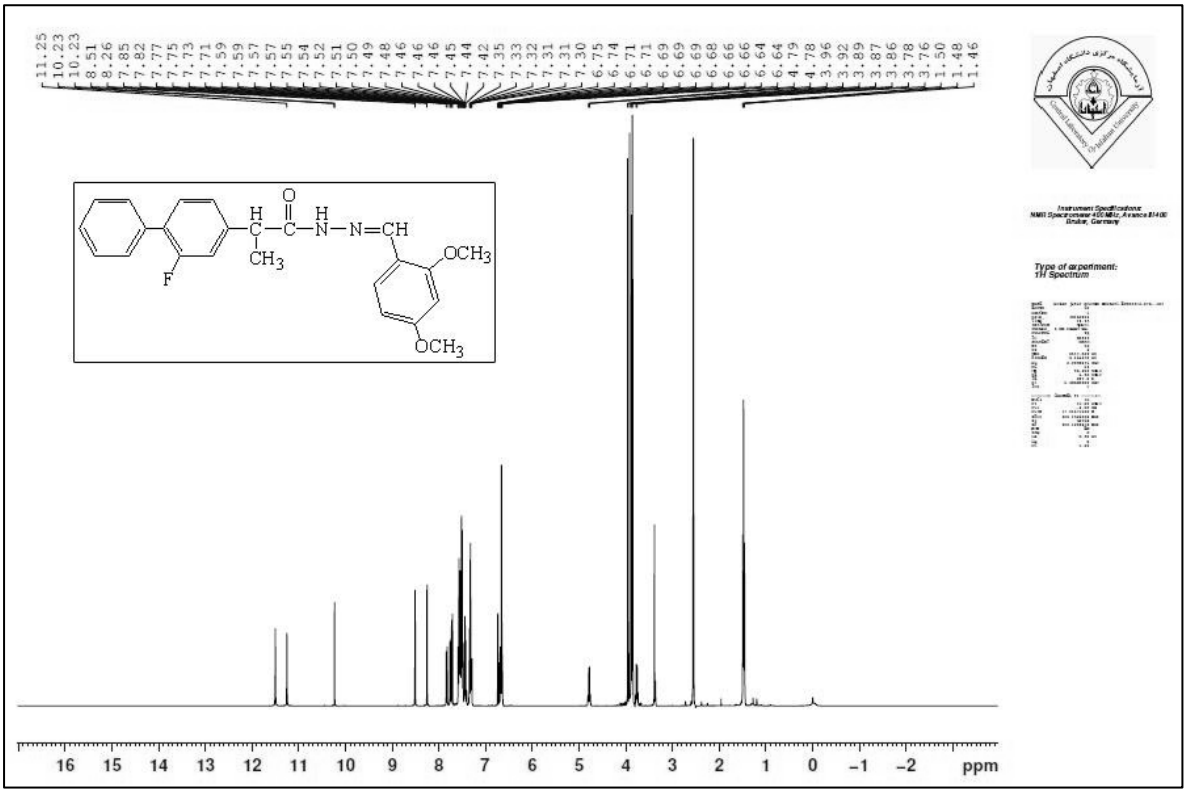


Figure (3.10): ^{1}H-NMR spectrum of compound [6].

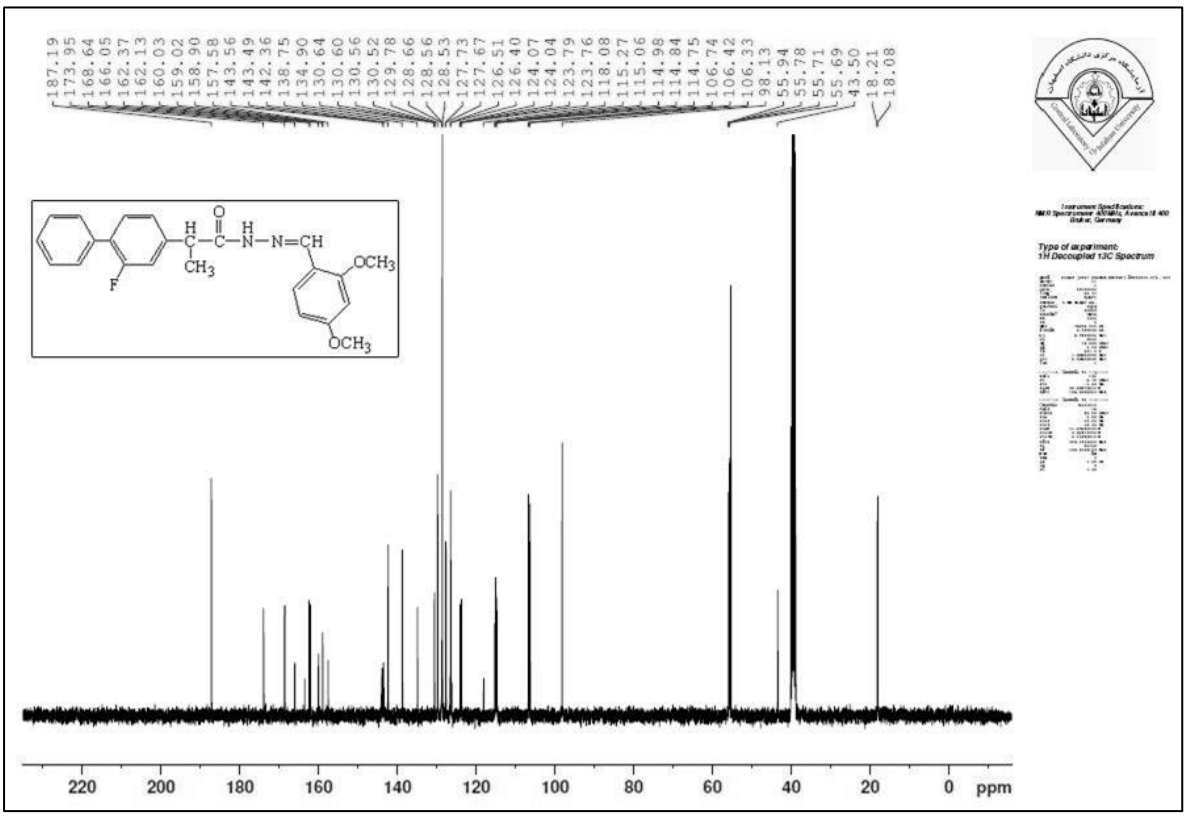


Figure (3.11): ^{13}C-NMR spectrum of compound [6].

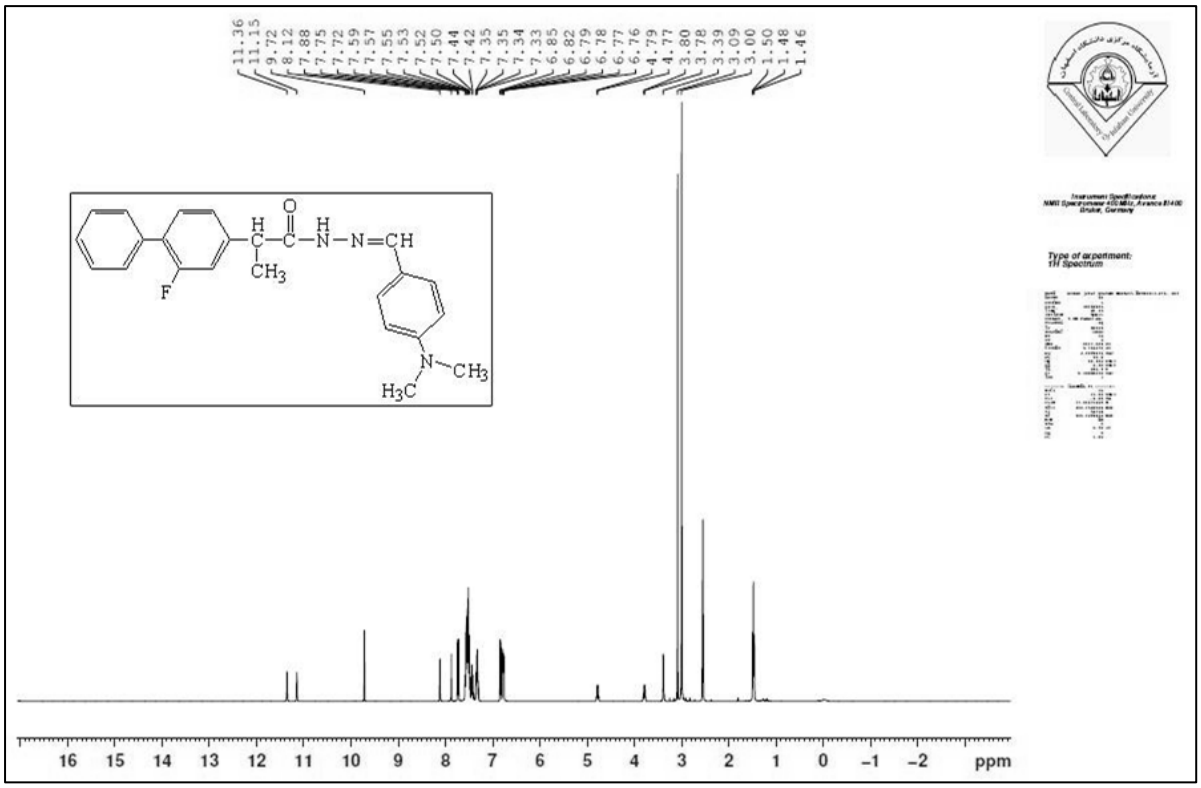


Figure (3.12): ^{1}H-NMR spectrum of compound [7].

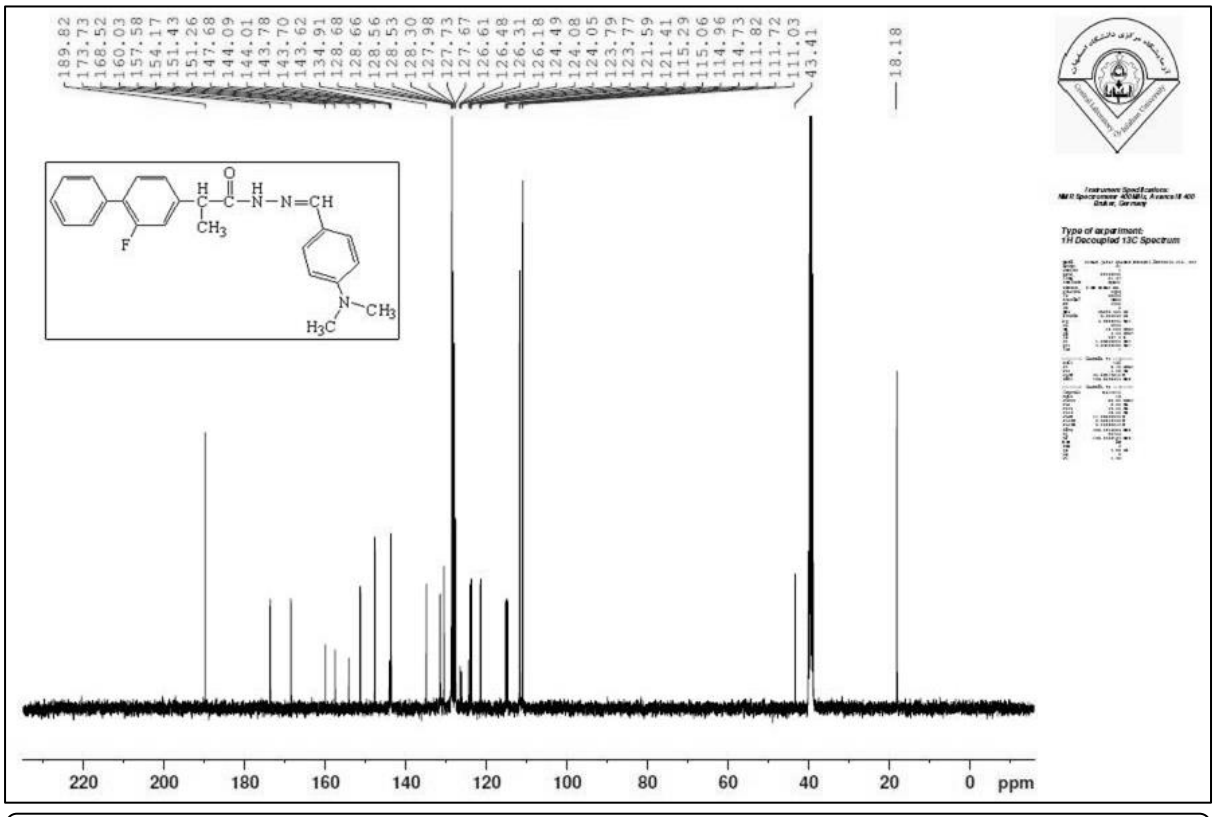
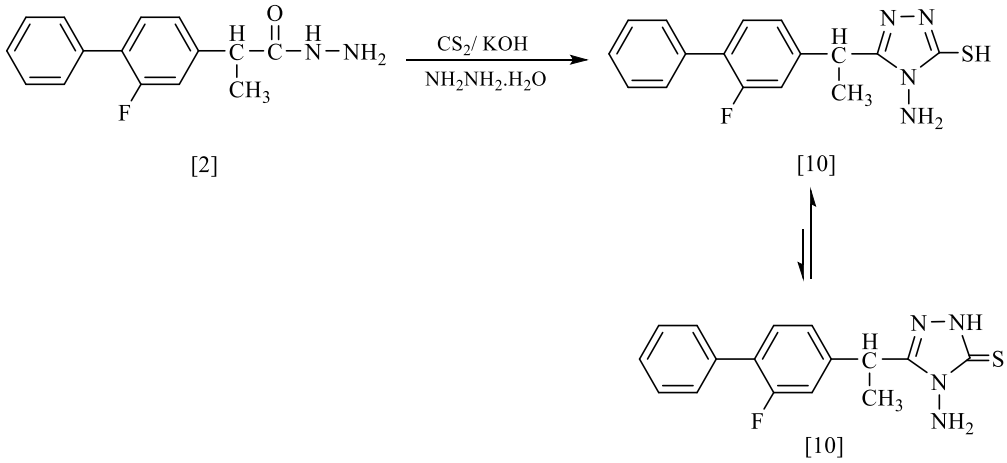


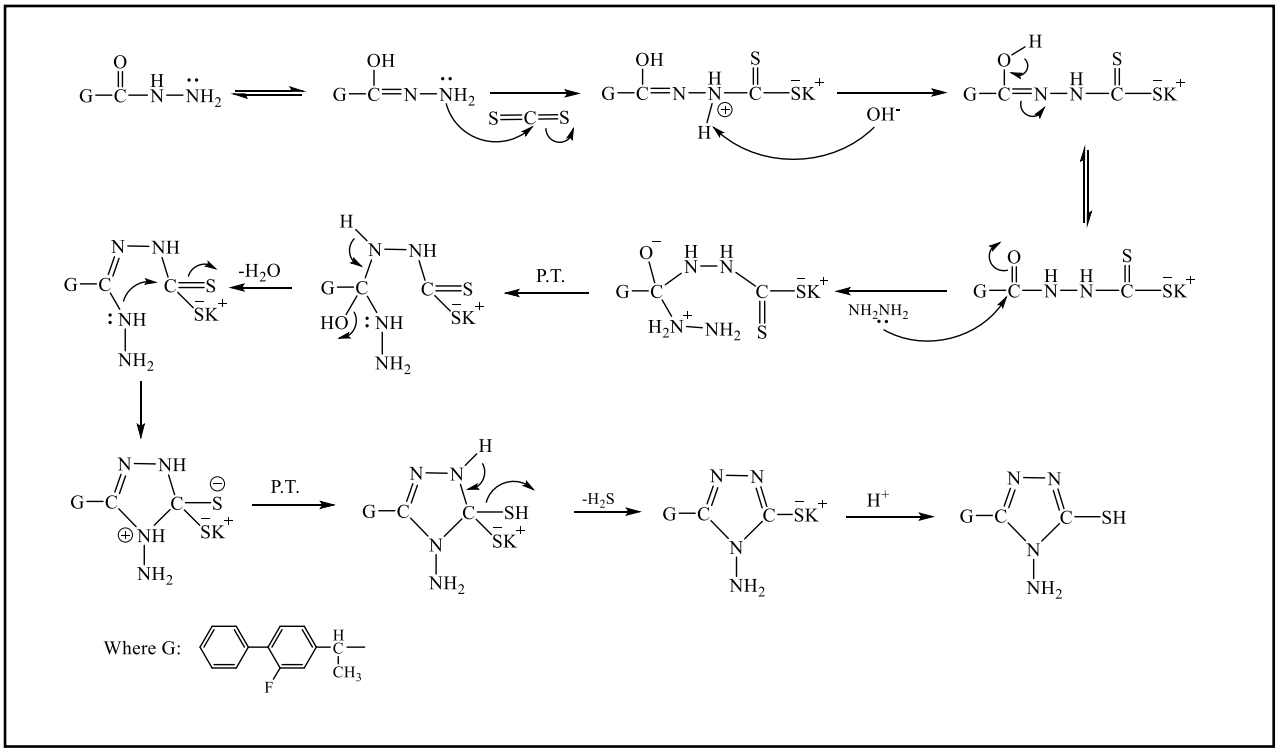
Figure (3.13): ^{13}C-NMR spectrum of compound [7].

3.4- Synthesis of 1-(3-flurobiphenyl-4-yl)-1-(3-mercapto-4-amino-1,2,4-triazole-5-yl)ethane [10]:

4-Amino-1,2,4-triazole-3-thiol derivative was prepared by the ring closure reaction of compound [2] with carbon disulphide in the presence of potassium hydroxide and 80% hydrazine hydrate.



The reaction mechanism [156] of formation of compound [10] involves the neucleophilic addition of hydrazine to CS_2 and then cyclization of the product.



Scheme (3.3): Mechanism synthesis of compound [10].

The FT-IR spectra Figure (3.14) showed the disappearance of the stretching band at 1637 cm^{-1} for (C=O amide) and the appereance of stretching band for thiol group (SH) at 2773 cm^{-1} and a stretching band for (C=N ring) at 1612 cm^{-1} and these bands was confirmed the structure of compound [10].

^{1}H-NMR spectrum Figure (3.15) and ^{13}C-NMR Figure (3.16) showed following characteristic signals: 1.61-1.66 (d, 3H, $\underline{CH_3}$-CH), 3.41 (s,2H, NH_2), 4.47-4.54 (q, 1H, $\underline{CH}$-CH_3), 7.23-8.07 (m, 8H, Ar-H), 14.29 (s, 1H, SH), 18 ($\underline{CH_3}$-CH), 34 ($\underline{CH}$-CH_3), (115-160) aromatic ring carbons, 157 (C-F) and 177 (C=N).

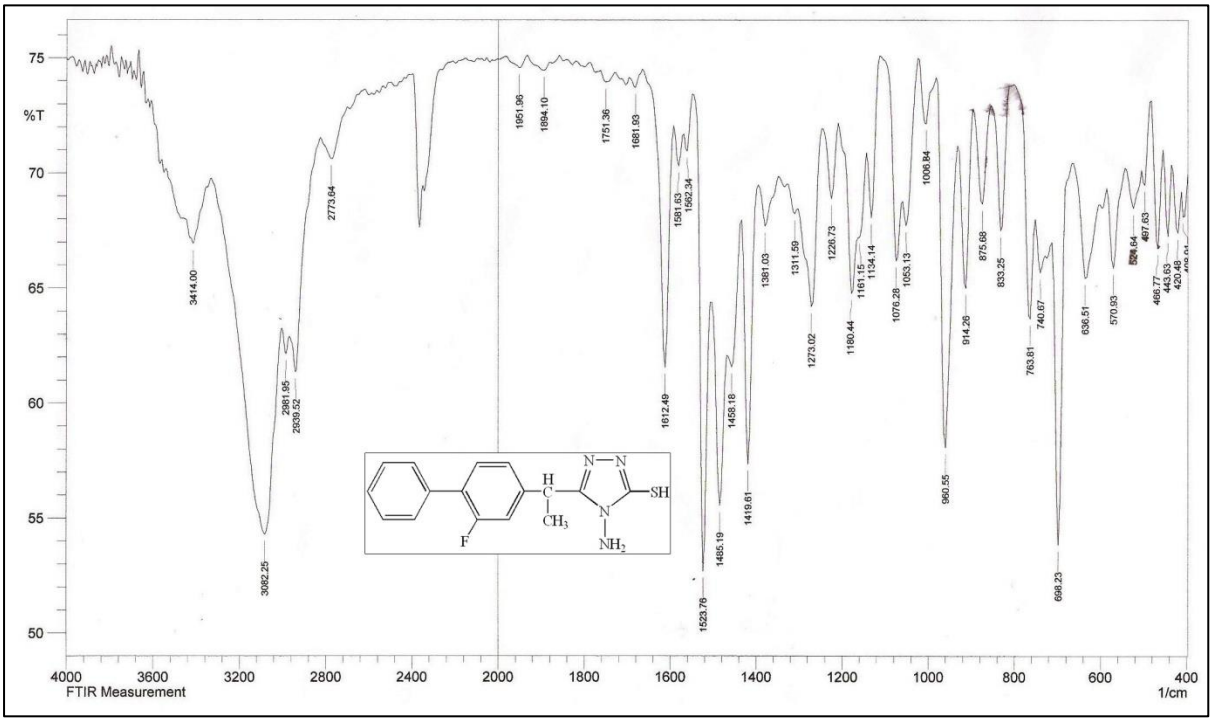


Figure (3.14): FT-IR spectrum of compound [10].

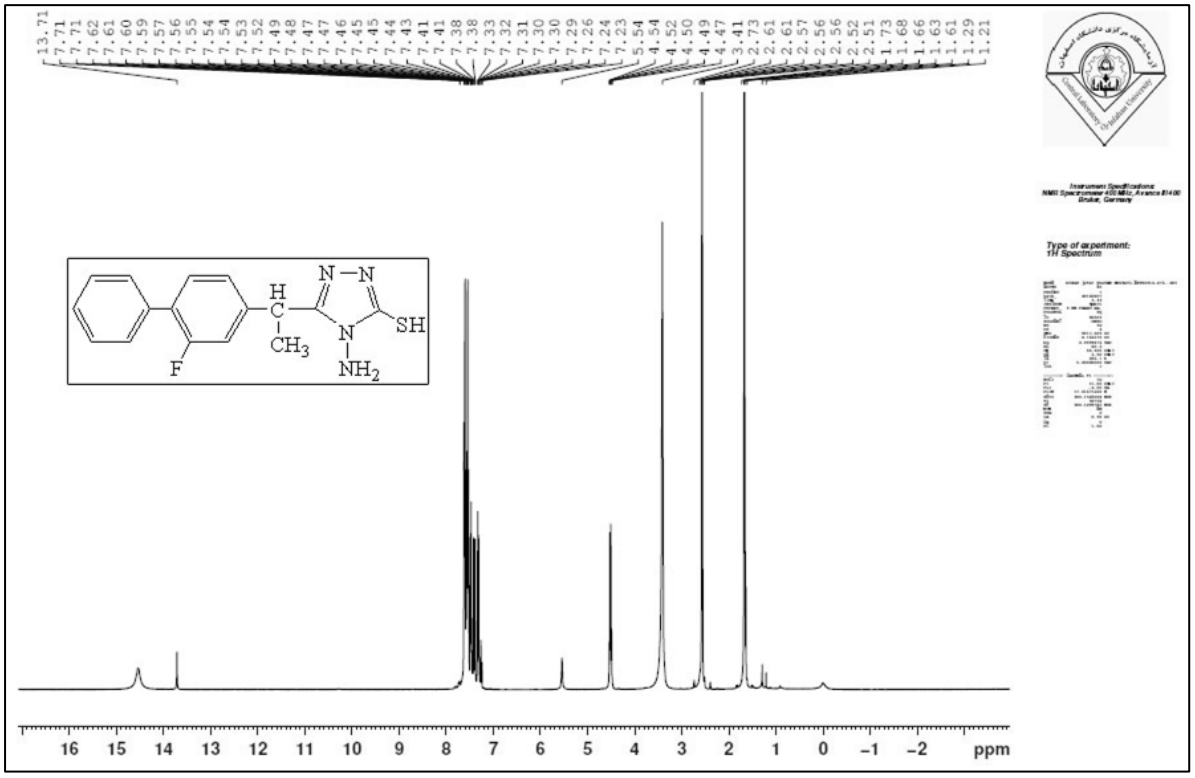


Figure (3.15): ^{1}H-NMR spectrum of compound [10].

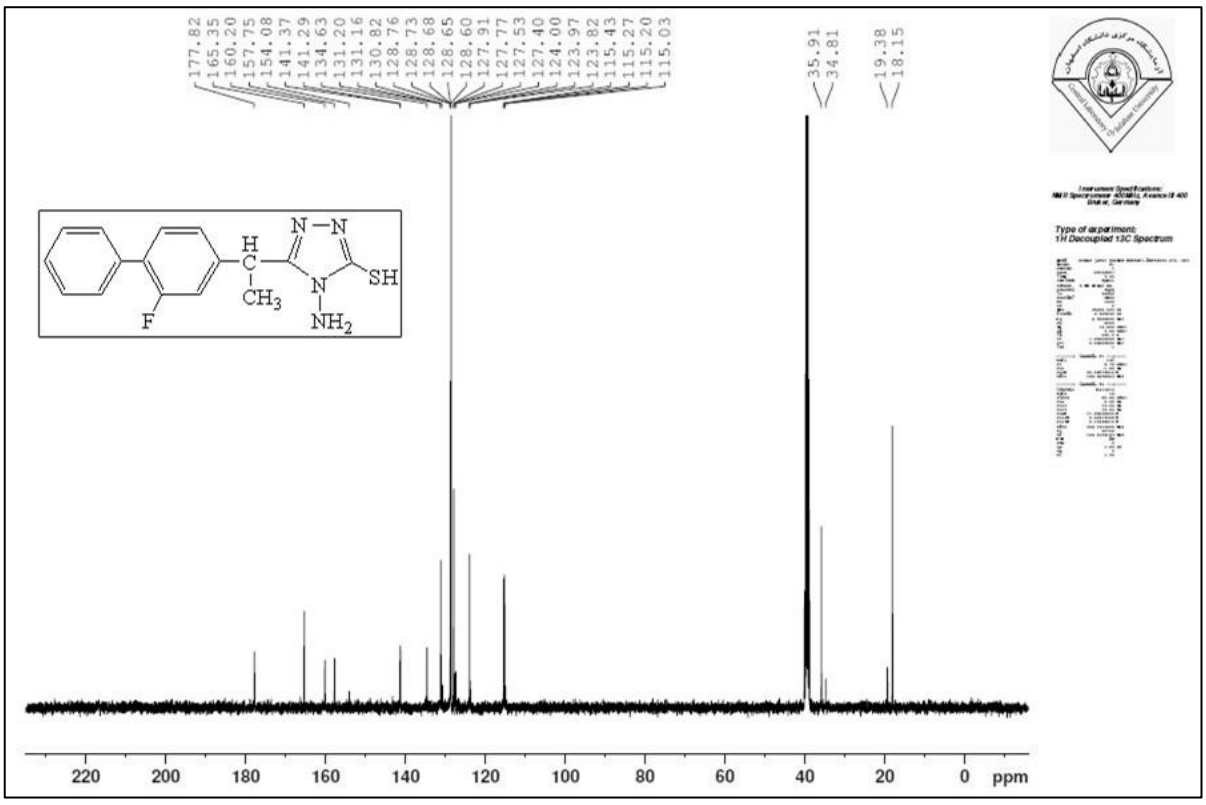
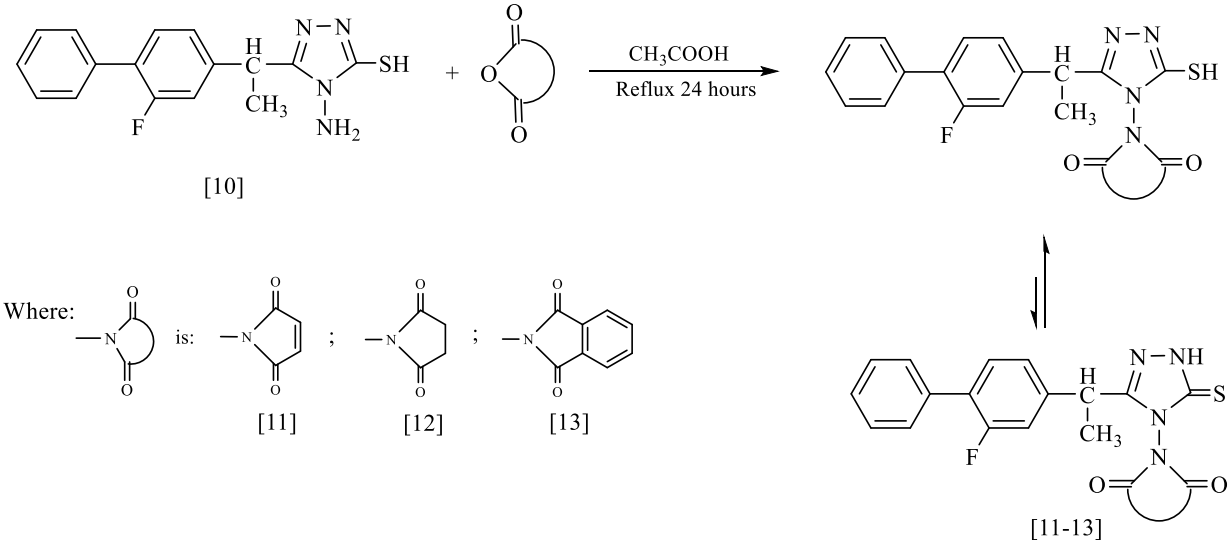


Figure (3.16): ^{13}C-NMR spectrum of compound [10].

3.5- Synthesis cyclic imide derivatives [11-13] derived from compound [10]:

Cyclic imide [11-13] was prepared by the condensation of 1,2,4-triazol derivative [10] with acid anhydrides namely maleic anhydride, succinic anhydrideand phthalic anhydride



The FT-IR spectra show the absence of a stretching bands at 3313 cm^{-1} and 3184 cm^{-1} due to amino group and the appearance of absorption bands, which are due to (-NH-) at (3263-3272) cm^{-1}, (C=O imide) at (1709-1741) cm^{-1} and (C=S) at (1685-1706) cm^{-1} they are good evidence for the formation of the cyclic imide derivatives. Figures (3.3, 3.4 and 3.5)

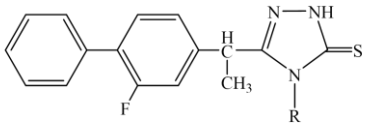
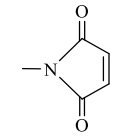
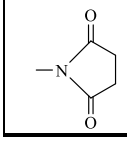
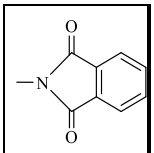


Table (3.6): Characteristic FT-IR absorption bands of compounds [11-13].

Com No.	R	FT-IR spectral data (ν cm^{-1})								
		(NH)	(C-H) Aromatic	(C-H) Aliph.	(C=O) Imide	(C=S)	(C=N)	(C=C) Aromatic	(C-F)	Others
11		3267	3082	2909, 2879	1737	1706	1625	1517, 1600	1076	C=C 1630
12		3263	3109	2985, 2929	1709	1685	1622	1483, 1600	1072	$-CH_2-$ 1417
13		3272	3020	2977, 2881	1741	1695	1622	1485	1070	---

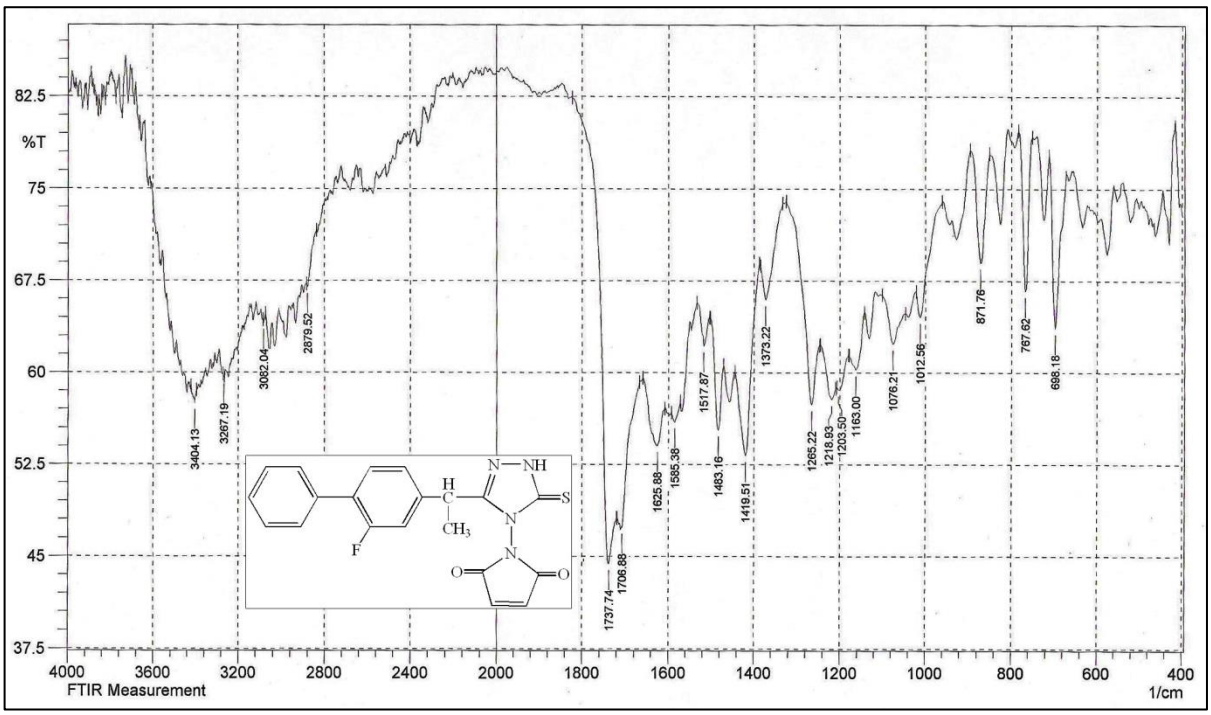


Figure (3.17): FT-IR spectrum of compound [11].

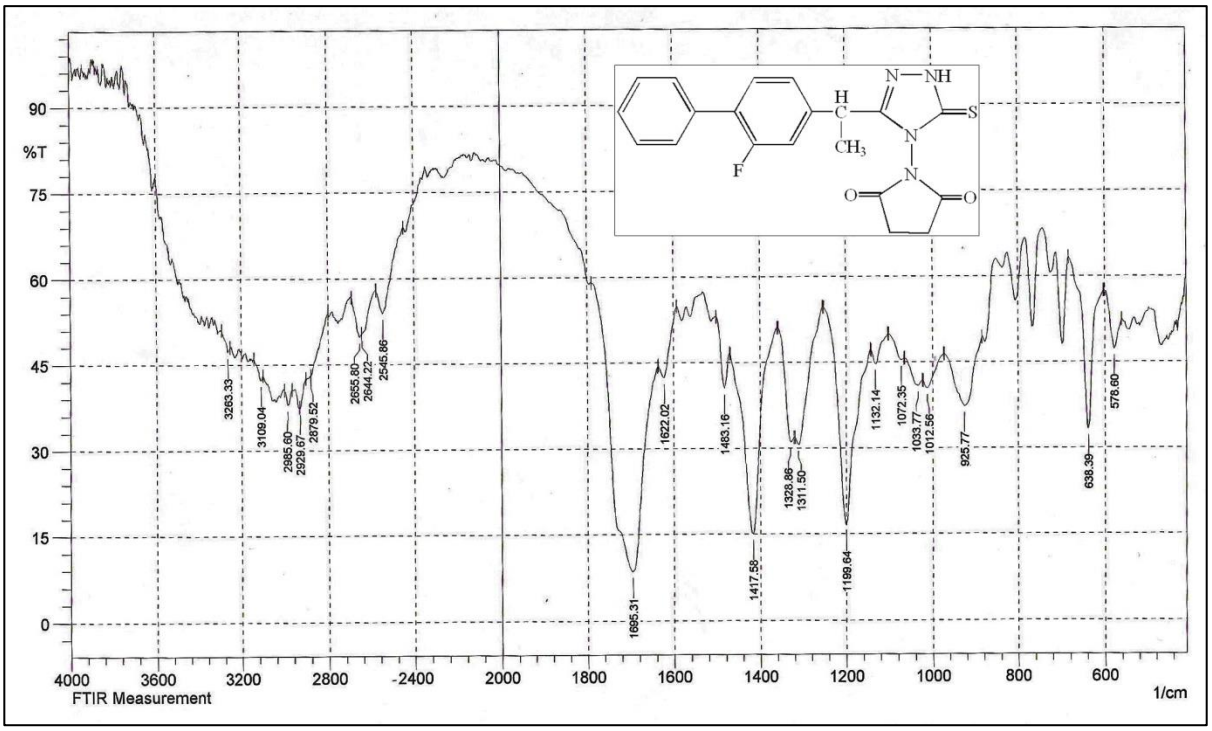


Figure (3.18): FT-IR spectrum of compound [12].

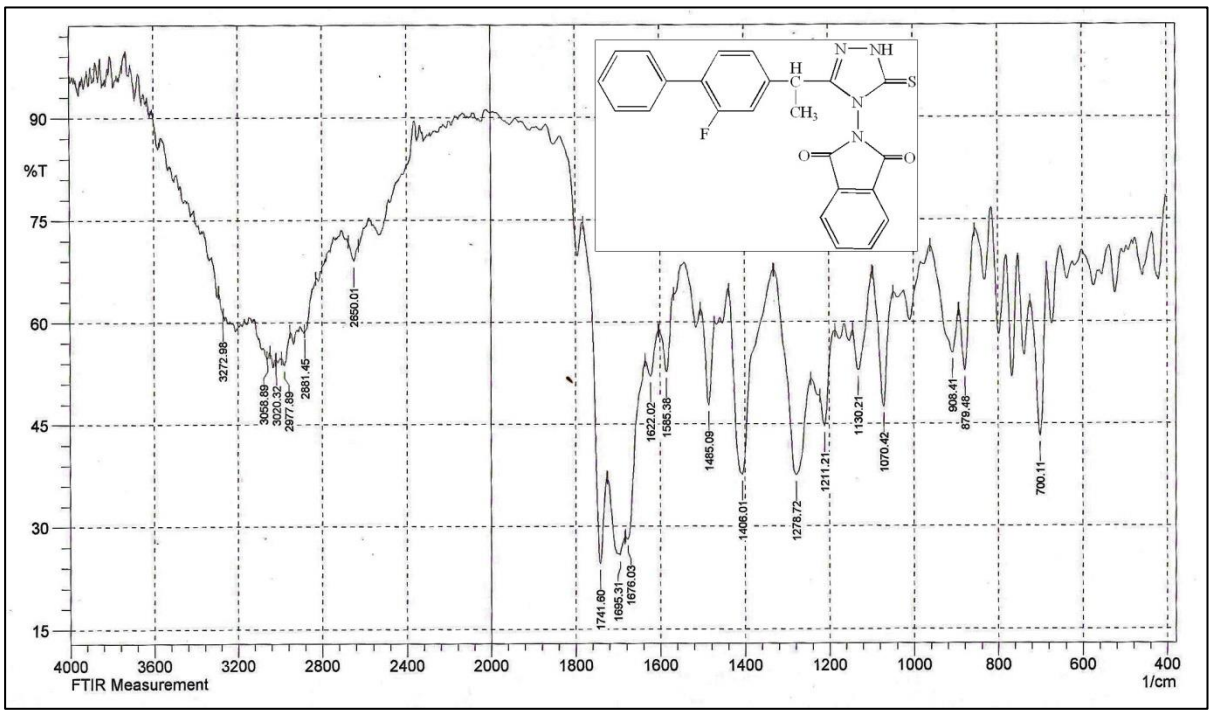
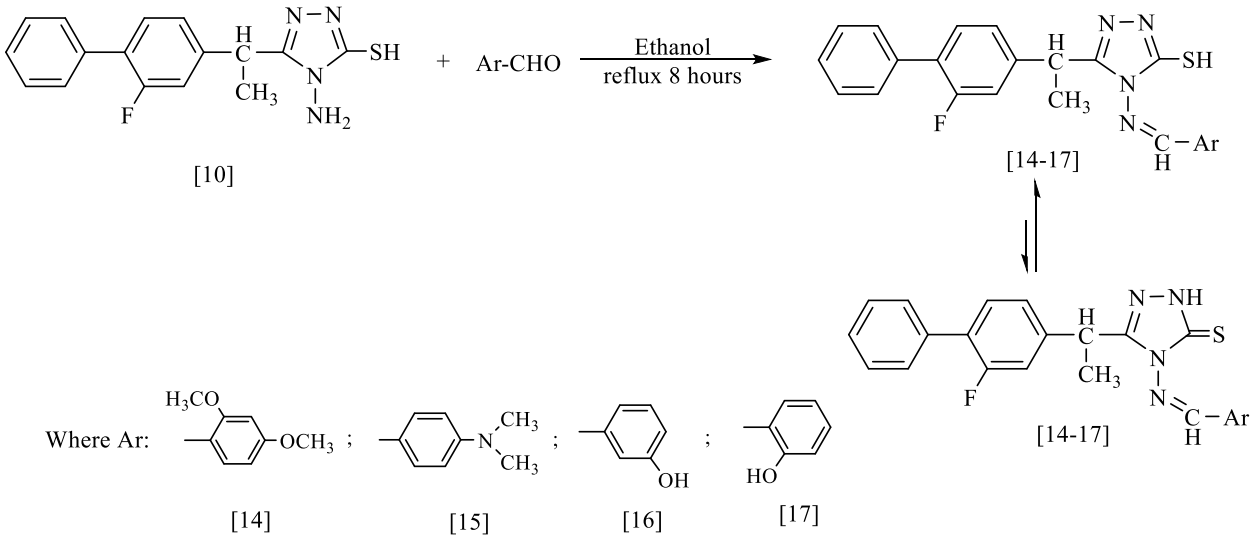


Figure (3.19): FT-IR spectrum of compound [13].

3.6- Synthesis of Schiff bases [14-17] derived from compound [10]:

Schiff bases [14-17] were prepared by the condensation of 1,2,4-triazol derivative [10] with different aromatic aldehydes namely 2,4-dimethoxybenzaldehyde, 4-(N,N-dinitroamino)benzaldehyde, 3-hydroxy-benzaldehyde and 2-hydroxy- benzaldehyde, in presence of glacial acetic acid as catalyst



The FT-IR spectrum, Figures (3.20, 3.21, 3.22 and 3.23) showed the appearance of absorption band for imine group (C=N) from 1581 cm^{-1} to 1639 cm^{-1} and the absence of the band for amino group at 3313 cm^{-1}. While ^{1}H-NMR spectra of compound [15] Figure (3.24) and ^{13}C-NMR spectra Figure (3.25) showed the following characteristic signals: 1.15-1.22 (d, 3H, $\underline{CH_3}$-CH), 3.01 (N-($\underline{CH_3}$)$_2$), 4.45-4.65 (q, 1H, $\underline{CH}$-CH_3), 6.77-8.57 (m, 12H, Ar-H), 9.68 (s, 1H, CH=N), 14.10 (s, 1H, SH), 18 ($\underline{C}H_3$-CH), 35 ($\underline{C}H$-CH_3), (111-141) aromatic ring carbons, 168 (C=N imine) and 160 (CH=N).

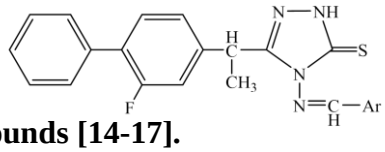
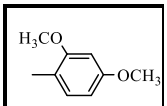
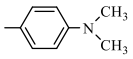
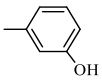


Table (3.7): Characteristic FT-IR absorption bands of compounds [14-17].

Com. No.	Ar	FT-IR spectral data (ν cm^{-1})								
		(NH)	(C-H) Aromatic	(C-H) Aliph.	(C=N) Ring	(C=S)	(C=N)	(C=C) Aromatic	(C-F)	Others
14		3194	3062	2966, 2939	1678	1640	1597	1500, 1602	1072	C-O Ether 1265
15		3414	3062	2978, 2931	1658	1639	1697	1523, 1612	1076	C-N Amine 1273
16		3186	3064	2964, 2939	1670	1630	1581	1523, 1614	1076	O-H 3213
17		3240	3074	2931, 2940	1662	1635	1581	1523, 1616	1076	O-H 3248

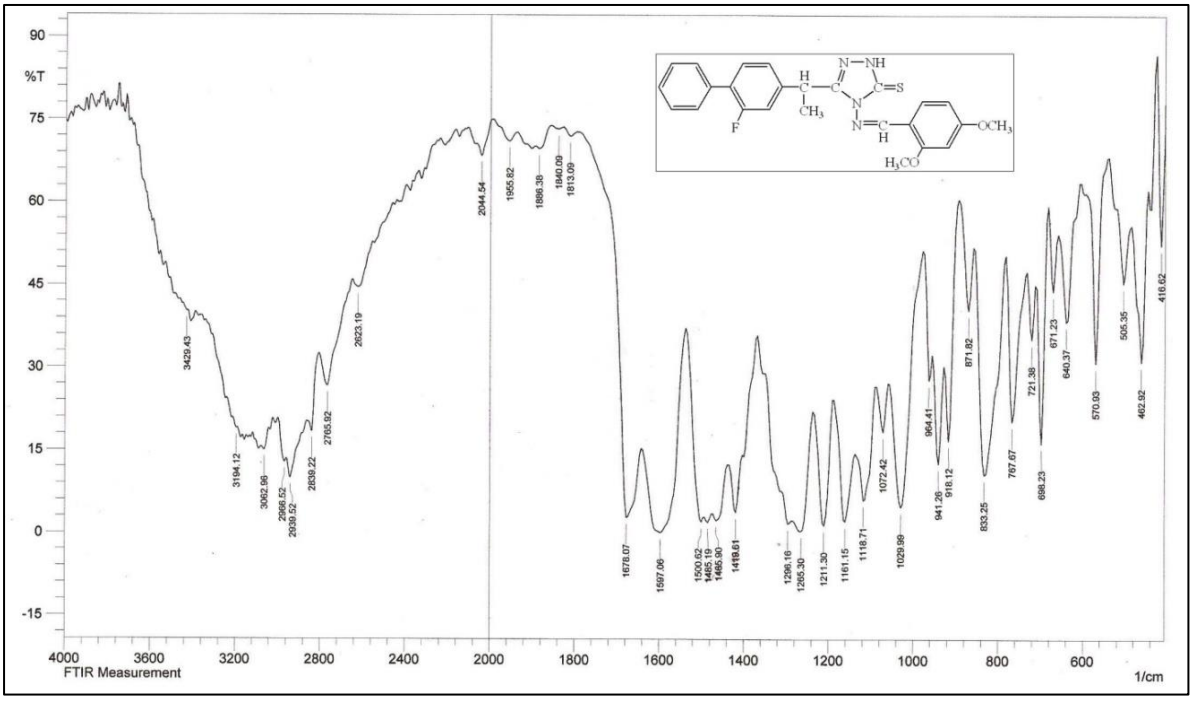


Figure (3.20): FT-IR spectrum of compound [14].

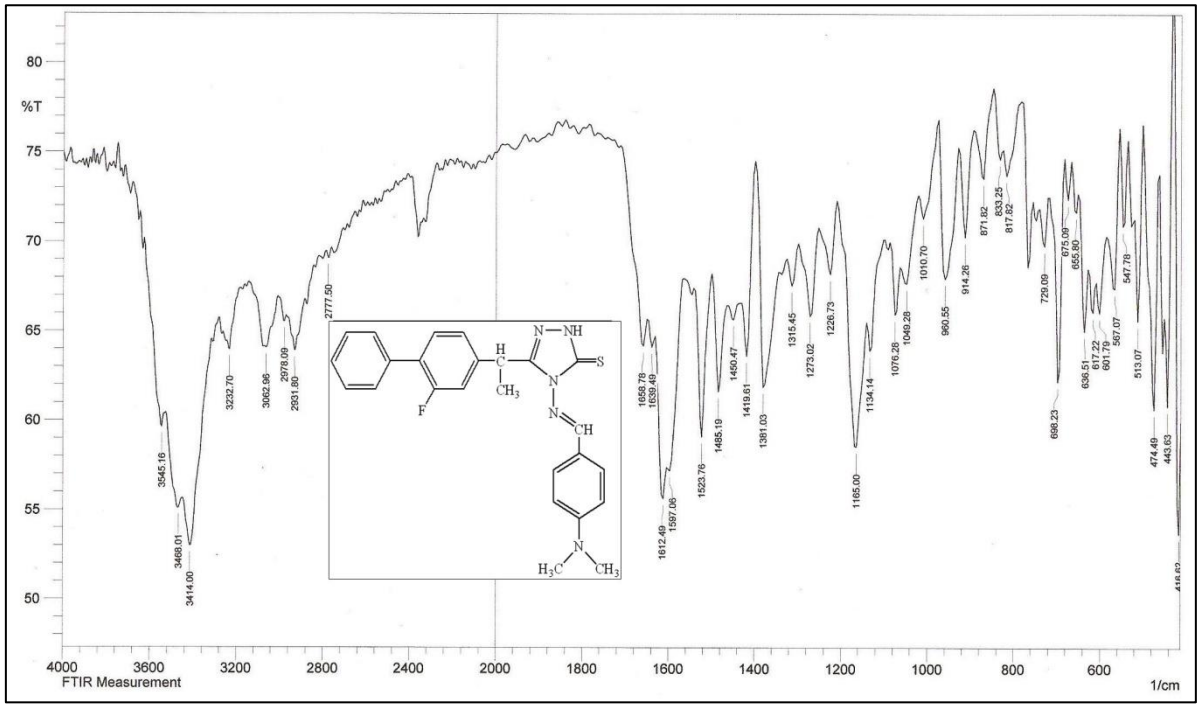


Figure (3.21): FT-IR spectrum of compound [15].

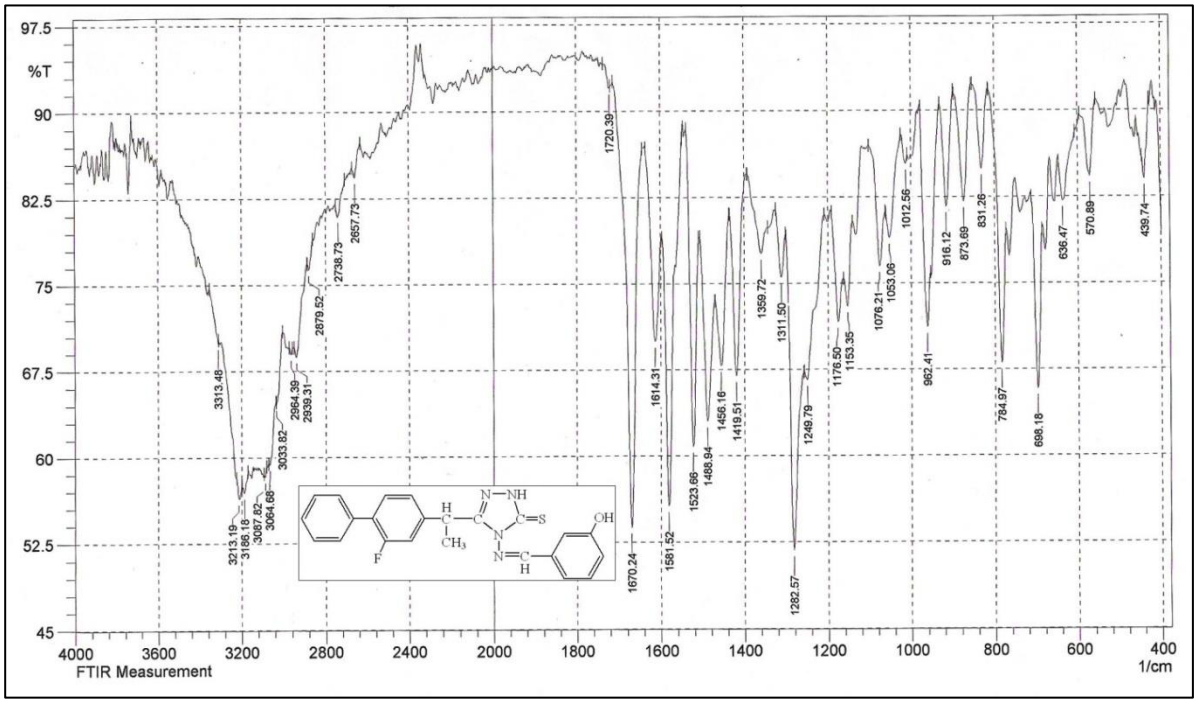


Figure (3.22): FT-IR spectrum of compound [16].

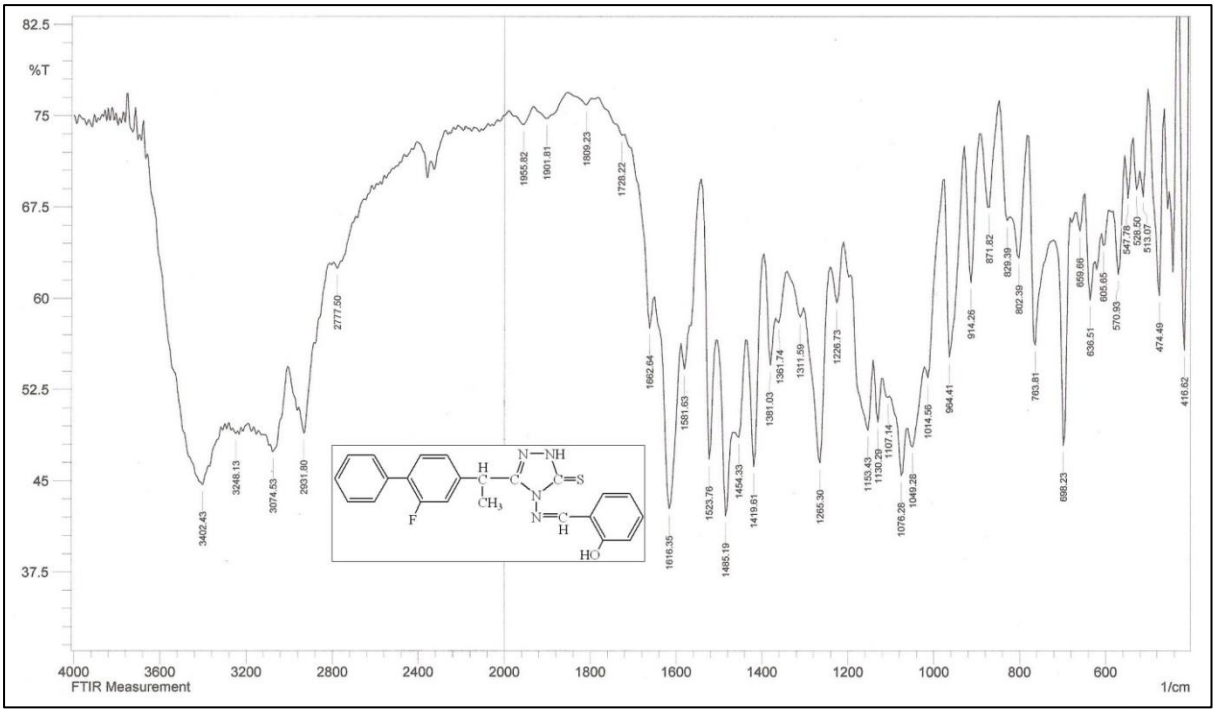


Figure (3.23): FT-IR spectrum of compound [17].

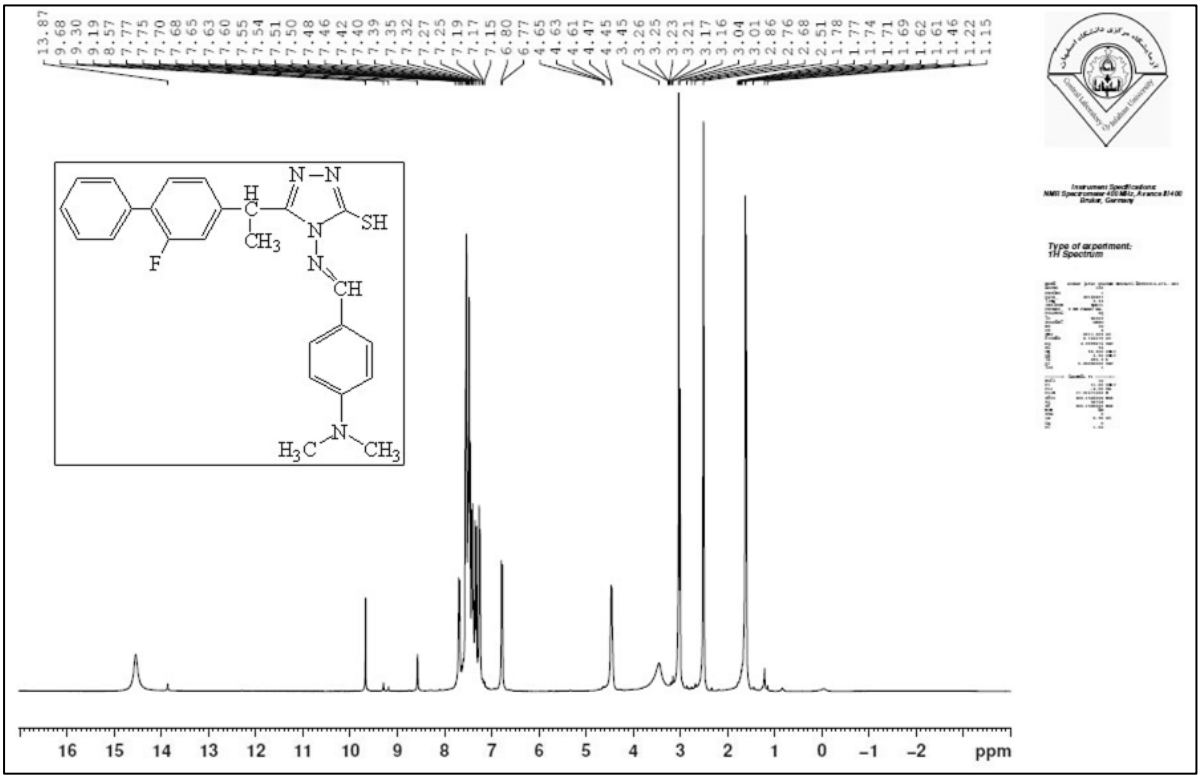


Figure (3.24): ^{1}H-NMR spectrum of compound [15].

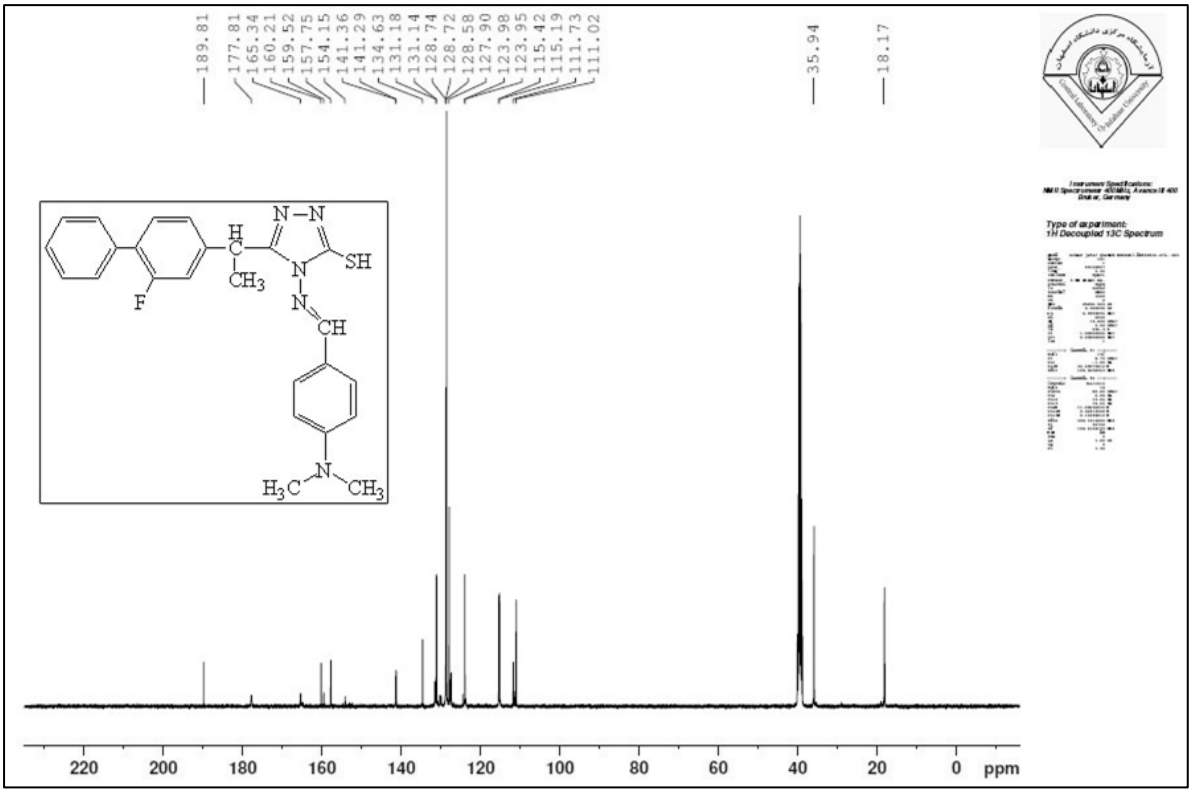
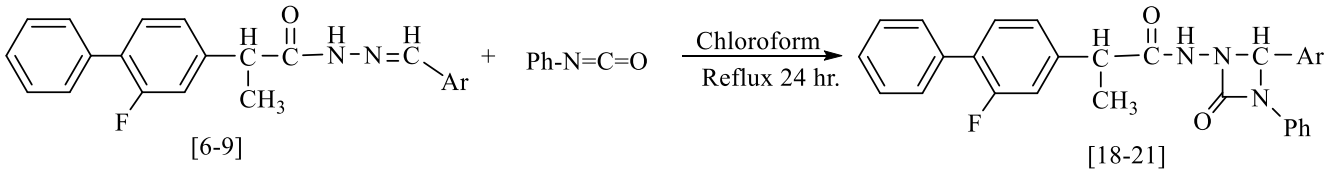


Figure (3.25): ^{13}C-NMR spectrum of compound [15].

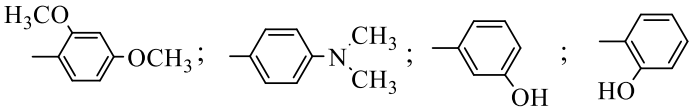
3.7- Synthesis of 1,3-diazetidine-2-one (Aza-β-lactam) derivatives [18-21]

Aza-*β*-lactam derivatives were prepared by the cycloaddition of hydrazone derivatives [6-9] with phenylisocynate *via* [2+2] cycloaddition reaction



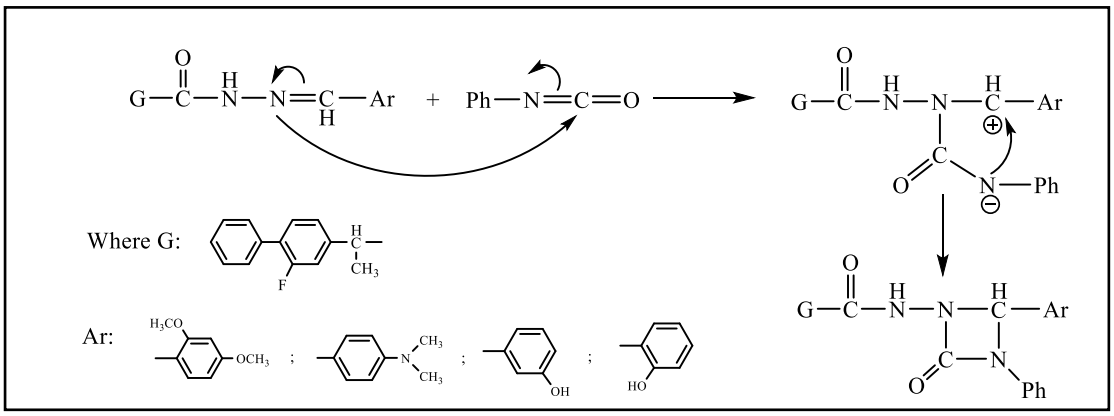
[6-9] [18-21]

Where Ar:



[18] [19] [20] [21]

Mechanism for the synthesis of aza-*β*-lactam compounds are shown in scheme (3.6) [157]:



Scheme (3.4): Mechanism synthesis of compounds [18-21].

The FT-IR spectra of derivatives [18-21], Figures (3.26 to 3.29) showed the absence of imine group (CH=N) absorption band at (1581-1620) cm^{-1} and the appearance of new absorption band of carbonyl group (C=O aza-β-lactams) at (1708-1745) cm^{-1}.^{1}H-NMR of compound [21], is shown Figures (3.30) ^{13}C-NMR Figures (3.30 and 3.31) showed following characteristic signals: 1.46-1.52 (d, 3H, $\underline{CH_3}$-CH), 3.41-4.73 (q, 1H, $\underline{CH}$-CH_3), 6.92 (s, 1H, CH ring), 6.96-8.46 (m,12H, Ar-H), 11.11 (s, 1H, NH), 11.87 (s, 1H, OH), 18 ($\underline{C}H_3$-CH), 43 ($\underline{C}H$-CH_3), 114-160 aromatic carbons,157 (C-OH), 160 (C=O ring), 168 (C-F), 173 (C=O amide). These results gave a good evidence for the formation of the aza-*β*-lactam derivatives

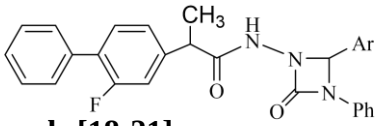
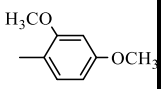
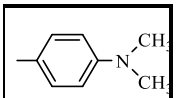
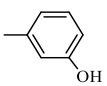


Table (3.8): Characteristic FT-IR absorption bands of compounds [18-21].

Com No.	Ar	FT-IR spectral data cm^{-1}							
		(NH)	(C-H) Aromatic	(C-H) Aliph.	(C=O) Amide	(C=O) Lactam	(C=C) Aromatic	(C-F)	Others
18		3236	3059	2974, 2935	1662	1735	1504, 1604	1064	C-O Ether 1211
19		3309	3062	2981, 2939	1658	1728	1597, 1600	1064	C-N Amine 1226
20		3261	3074	2933, 2975	1691	1745	1600	1500, 1066	O-H 3323
21		3129	3074	2908, 2939	1662	1708	1616	1076	O-H 3228

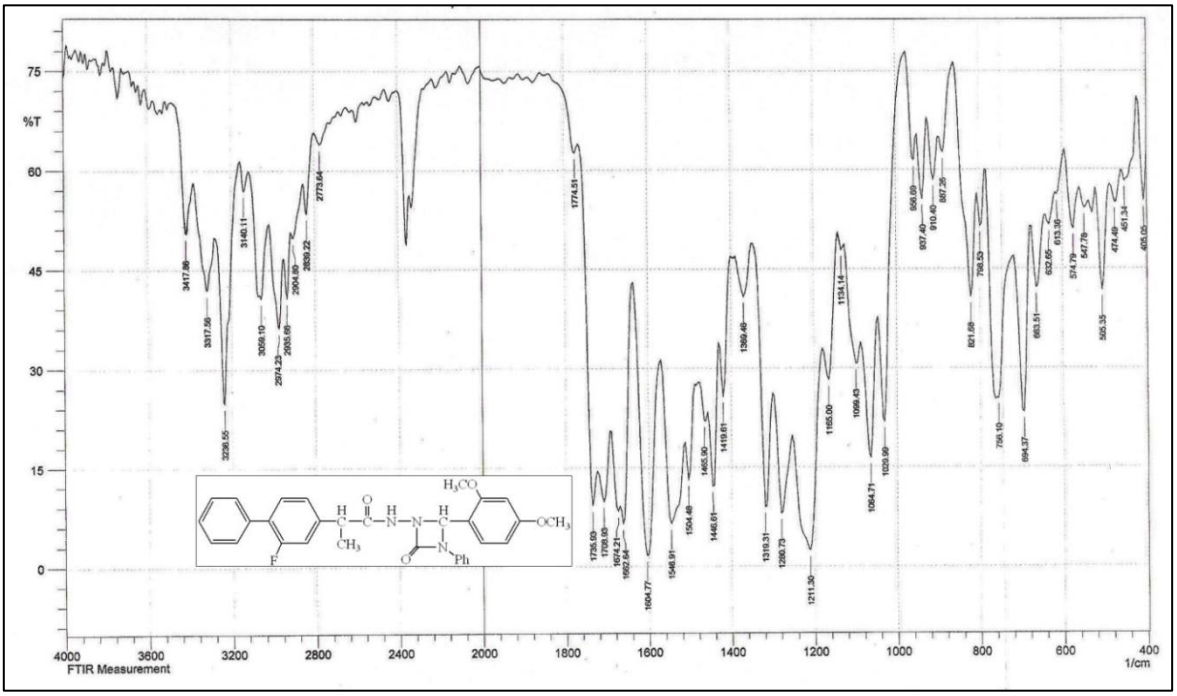


Figure (3.26): FT-IR spectrum of compound [18].

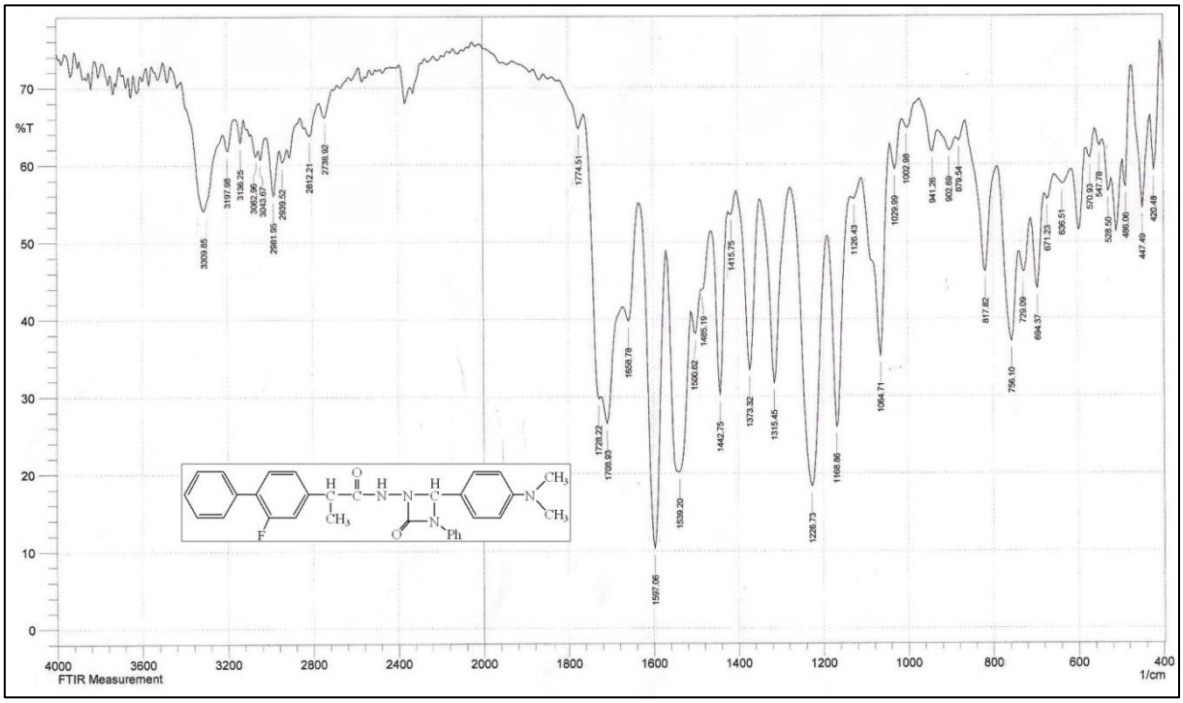


Figure (3.27): FT-IR spectrum of compound [19].

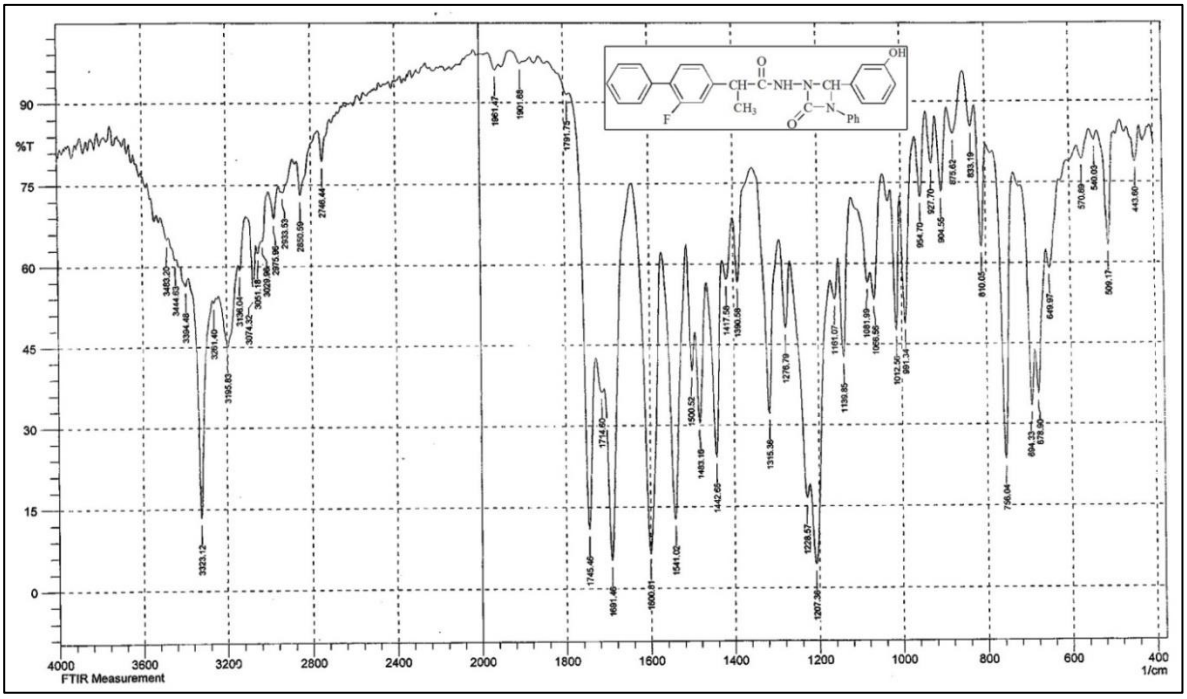


Figure (3.28): FT-IR spectrum of compound [20].

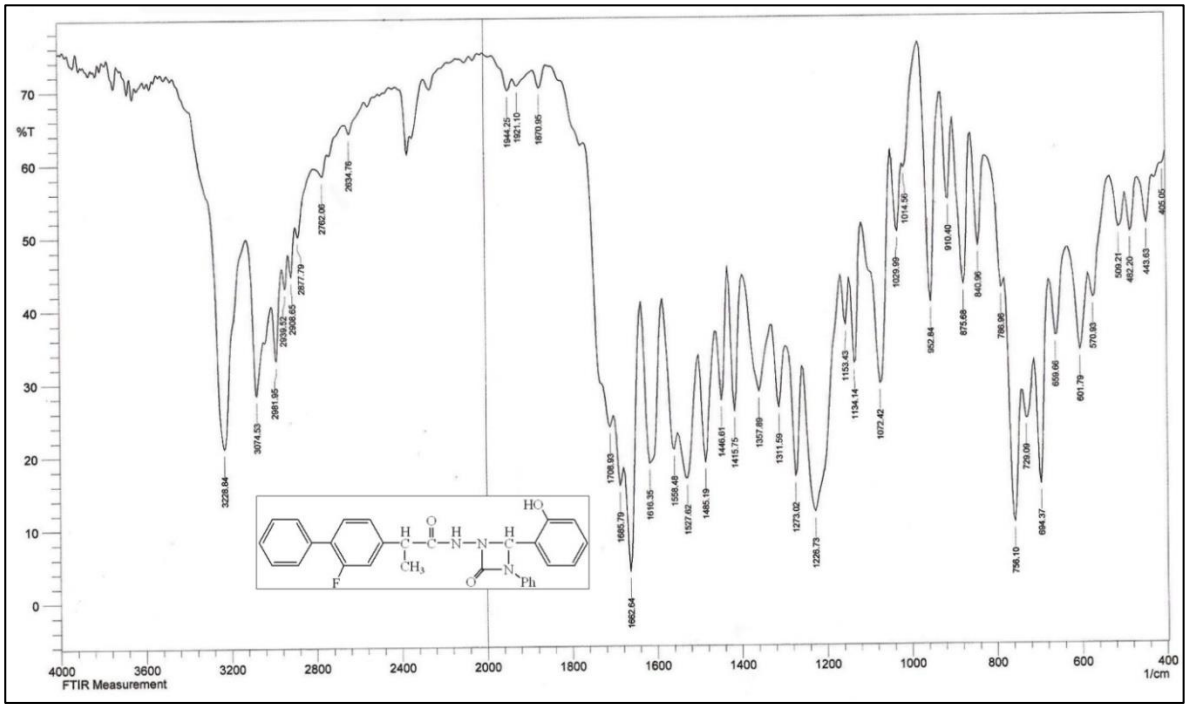


Figure (3.29): FT-IR spectrum of compound [21].

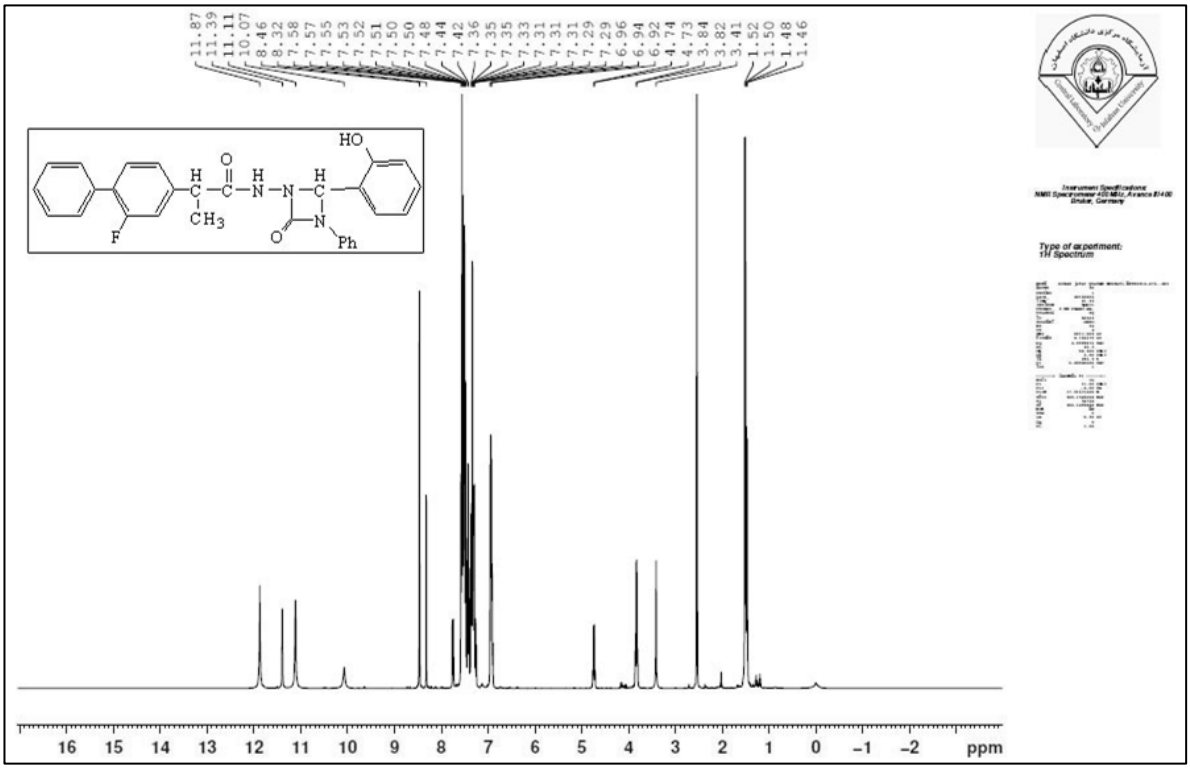


Figure (3.30): ^{1}H-NMR spectrum of compound [21].

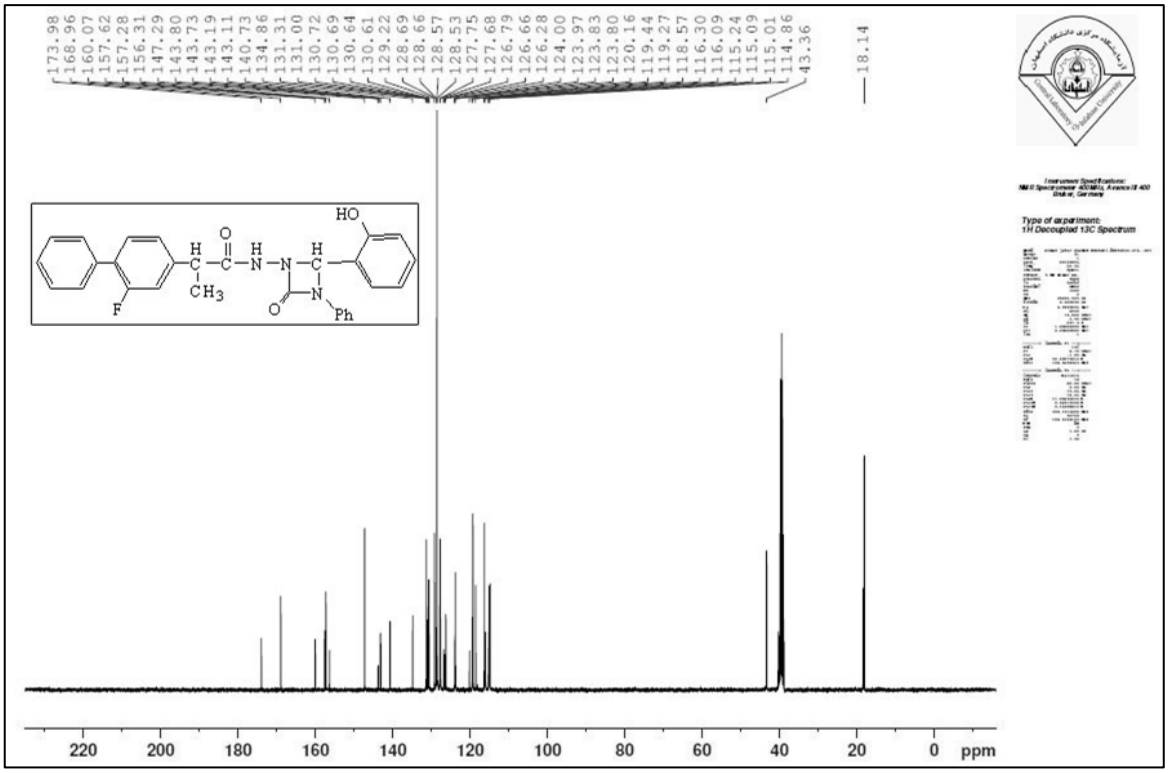
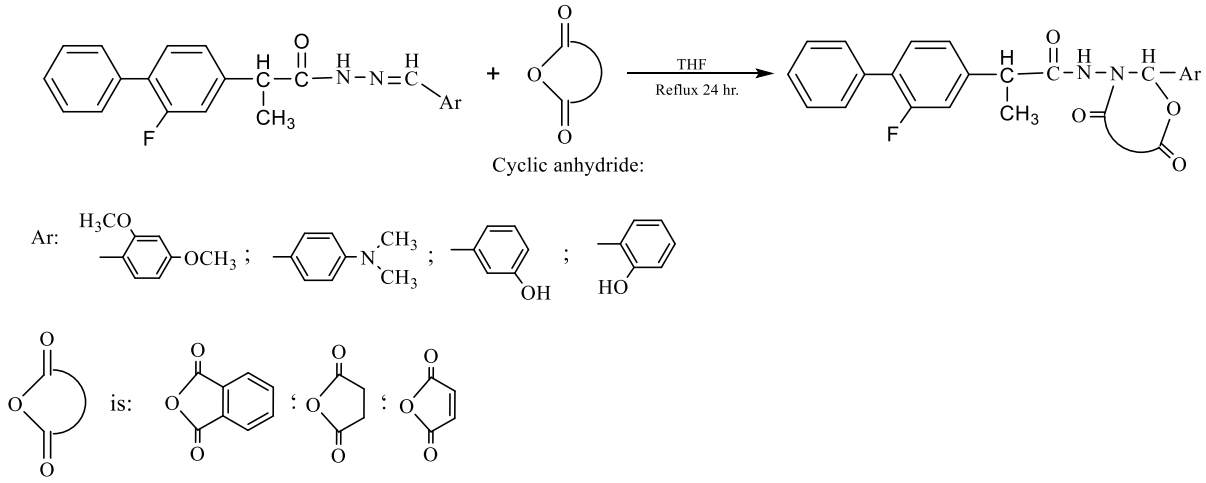


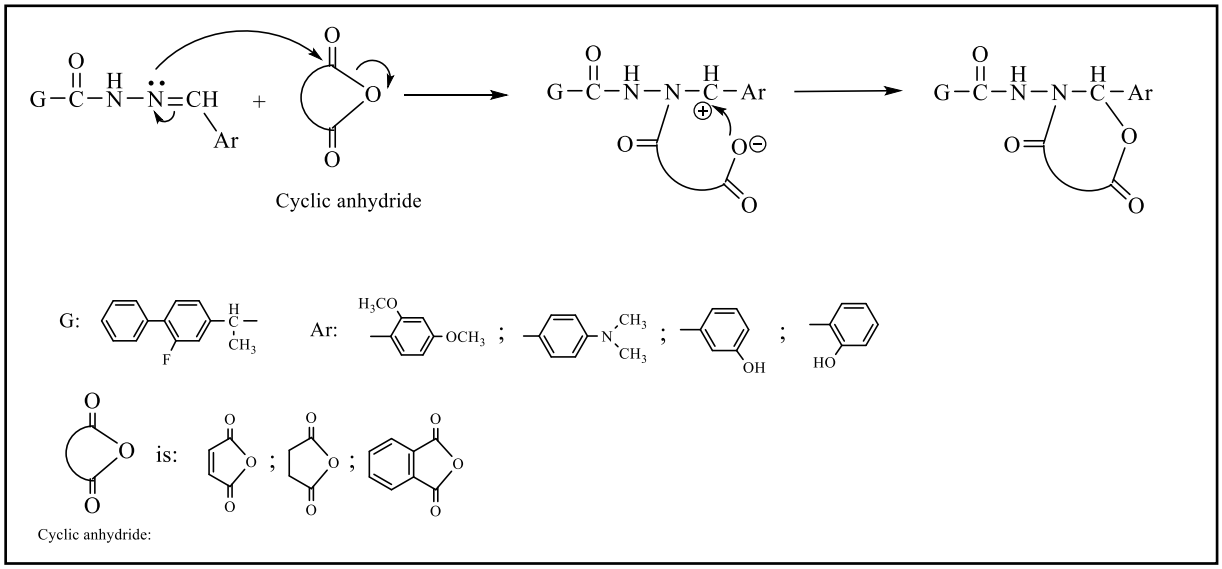
Figure (3.31): ^{13}C-NMR spectrum of compound [21].

3.8- Synthesis of oxazepine derivatives [22-25], [26-29] and [30-33]:

The cyclization of hydrazone derivatives [6-9] with acids anhydrides namely maleic anhydride, succinic anhydride and phthalic anhydride, give the coresponding oxazepine derivatives [22-25], [26-29] and [30-33].



The suggested mechanism for this reaction is shown below [158]:



Scheme (3.5): Mechanism synthesis of compounds [22-25], [26-29] and [30-33].

The absence of the imine group (CH=N) stretching band at (1581-1620) cm^{-1} and the appearance of the (C=O oxazepine ring) stretching band at (1703-1733) cm^{-1} indicate the formation of the oxazepine derivatives Figure (3.29-3.40).

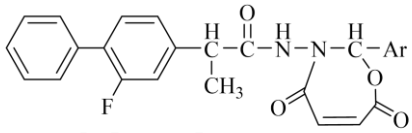
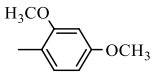
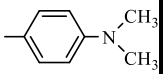
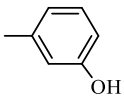
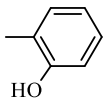


Table (3.9): Characteristic FT-IR absorption bands of compounds [22-25].

Com No.	Ar	FT-IR spectral data (ν cm^{-1})								
		(NH)	(C-H) Aromatic	(C-H) Aliph.	(C=O) Ring	(C=O) Amid	(C=C)	(C═C) Aromatic	(C-F)	Other
22		3382	3004	2879, 2972	1733	1677	1602	1506, 1600	1070	C-O Ether 1271
23		3419	3008	2887, 2972	1730	1660	1595	1537, 1520	1062	C-N Amine 1234
24		3168	3024	2879, 2954	1714	1671	1591	1483, 1600	1056	O-H 3230
25		3186	3024	2958, 2983	1740	1666	1622	1485, 1622	1068	O-H 3215

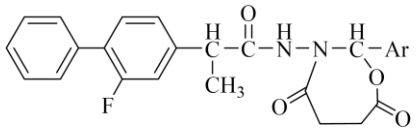
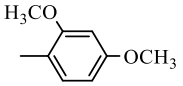
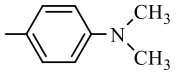
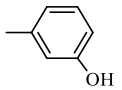
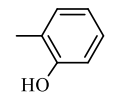


Table (3.10): Characteristic FT-IR absorption bands of compounds [26-29].

Com. No.	Ar	FT-IR spectral data (ν cm^{-1})							
		(NH)	(C-H) Aromatic	(C-H) Aliph.	(C=O) Ring	(C=O) Amid	(C=C) Aromatic	(C-F)	Other
26		3236	3053	2974, 2997	1730	1660	1504, 1602	1074	C-O Ether 1280
27		3188	3049	2966, 2995	1748	1645	1529, 1598	1066	C-N Amine 1203
28		3200	3059	2931, 2981	1700	1585	1481, 1600	1076	O-H 3205
29		3184	3043	2904, 2935	1720	1620	1519, 1620	1076	O-H 3245

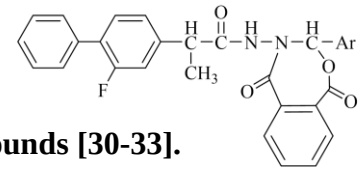
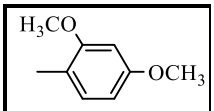
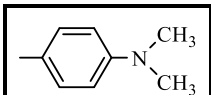
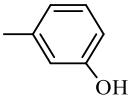
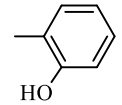


Table (3.11): Characteristic FT-IR absorption bands of compounds [30-33].

Com. No.	Ar	FT-IR spectral data (ν cm^{-1})							
		(NH)	(C-H) Aromatic	(C-H) Aliph.	(C=O) Ring	(C=O) Amid	(C=C) Aromatic	(C-F)	Others
30		3236	3053	2937, 2972	1768	1677	1504, 1600	1070	C-O Ether 1280
31		3320	3040	2951, 2900	1720	1658	1546, 1597	1068	C-N Amine 1257
32		3200	3035	2945, 2979	1770	1650	1583, 1608	1072	O-H 3270
33		3200	3059	2958, 2885	1724	1620	1516, 1581	1072	O-H 3282

The characteristic signals ^{1}H-NMR and ^{13}C-NMR spectram of compounds [25], [27] and [29] are shown in tables (3.11 and 3.12).

Table (3.12): ^{1}H-NMR spectral data (δ ppm) of compounds [25], [27] and [29]:

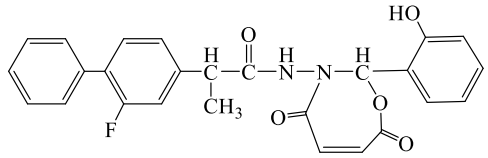
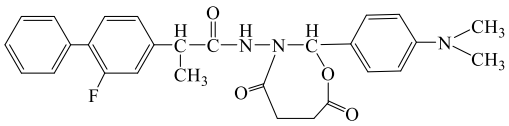
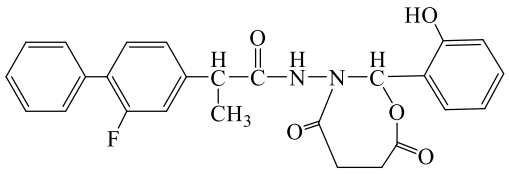
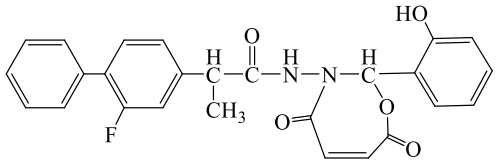
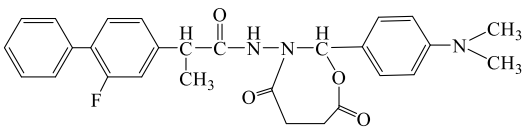
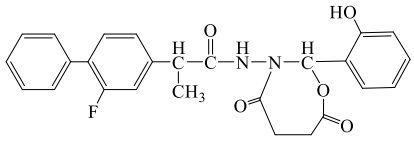
Com. No.	Structur	^{1}H-NMR data (δ ppm)
25		1.42-1.79 (d, 3H, $\underline{CH_3}$-CH), 3.58-3.74 (q, 1H, $\underline{CH}$-CH_3), 3.91 (s,1H,CH oxazepine ring),), 6.87-7.71 (m, 12H, Ar-H), 8.27-8.43 (d.d, 2H, CH=CH oxazepine ring), 11.87 (s, 1H, NH), 12.23 (s, 1H, OH).
27		1.40-1.44 (d, 3H, $\underline{CH_3}$-CH), 2.93 (s, 6H, N-$(CH_3)_2$), 3.91-4.05 (q, 1H, $\underline{CH}$-CH_3), 4.71-4.75 (t, 4H, $2CH_2$ oxazepine ring), 6.69-8.05 (m, 12H, Ar-H), 3.9 (s, 1H, CH oxazepine ring) 11.05 (s, 1H, NH).
29		1.13-1.47 (d, 3H, $\underline{CH_3}$-CH), 2.47-2.57 (t, 4H, $2CH_2$ oxazepine ring), 3.75-4.06 (q, 1H, $\underline{CH}$-CH_3) , , 6.59-8.41 (m, 12H, Ar-H) , 3.9(s,1H, CH oxazepine ring), 11.34 (s, 1H, NH), 11.89 (s, 1H, OH).

Table (3.13): ^{13}C-NMR spectral data (δ ppm) of compounds [25], [27] and [29]:

Com. No.	Structur	^{13}C-NMR data (δ ppm)
25		18 ($\underline{C}H_3$-CH), 45 ($\underline{C}$H-CH_3), 67 (CH ring), 78 (C=C), (114-160) aromatic ring carbons, 140 (C-OH), 147 (C-F), 168 (C=O ring), 173 (C=O amide).
27		18 ($\underline{C}H_3$-CH), 28 ($(CH_3)_2$N) 42 ($\underline{C}$H-CH_3), 60 (CH ring), (110-134) aromatic ring carbons, 130 (C-F) 143 (C=O ring), 173(C=O amide).
29		18 ($\underline{C}H_3$-CH), 28 ($\underline{C}$H-CH3), 43 (CH ring), (118-160) aromatic ring carbons, 169(C=O ring), 173(C=O amide).

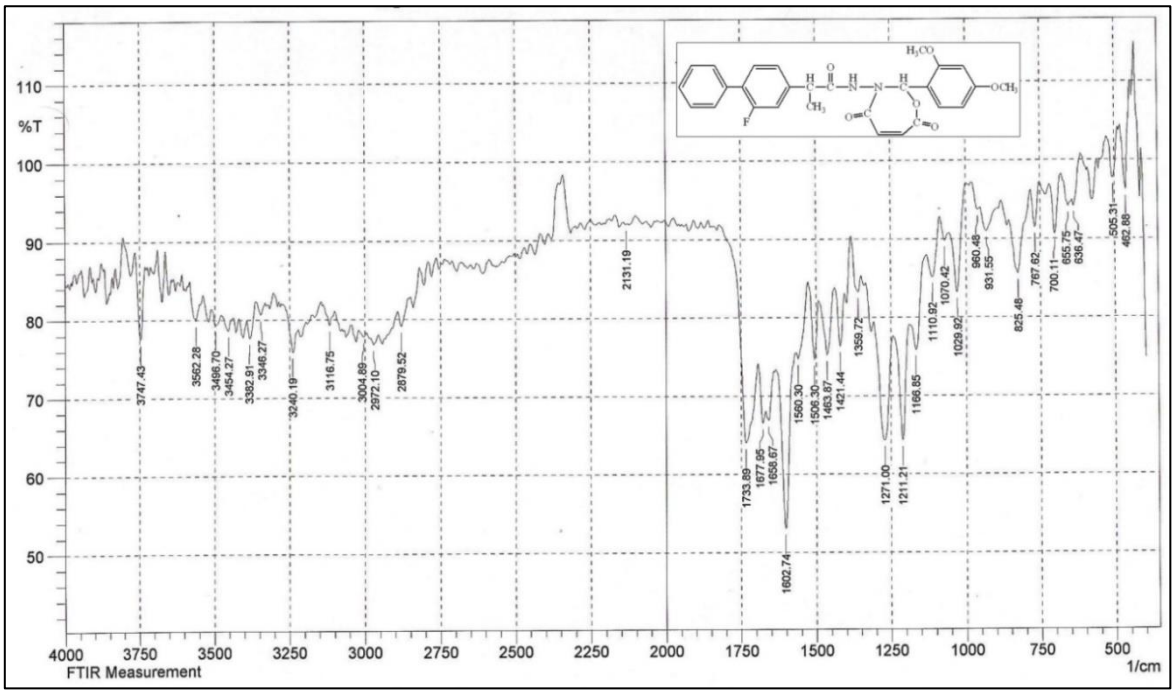


Figure (3.32): FT-IR spectrum of compound [22].

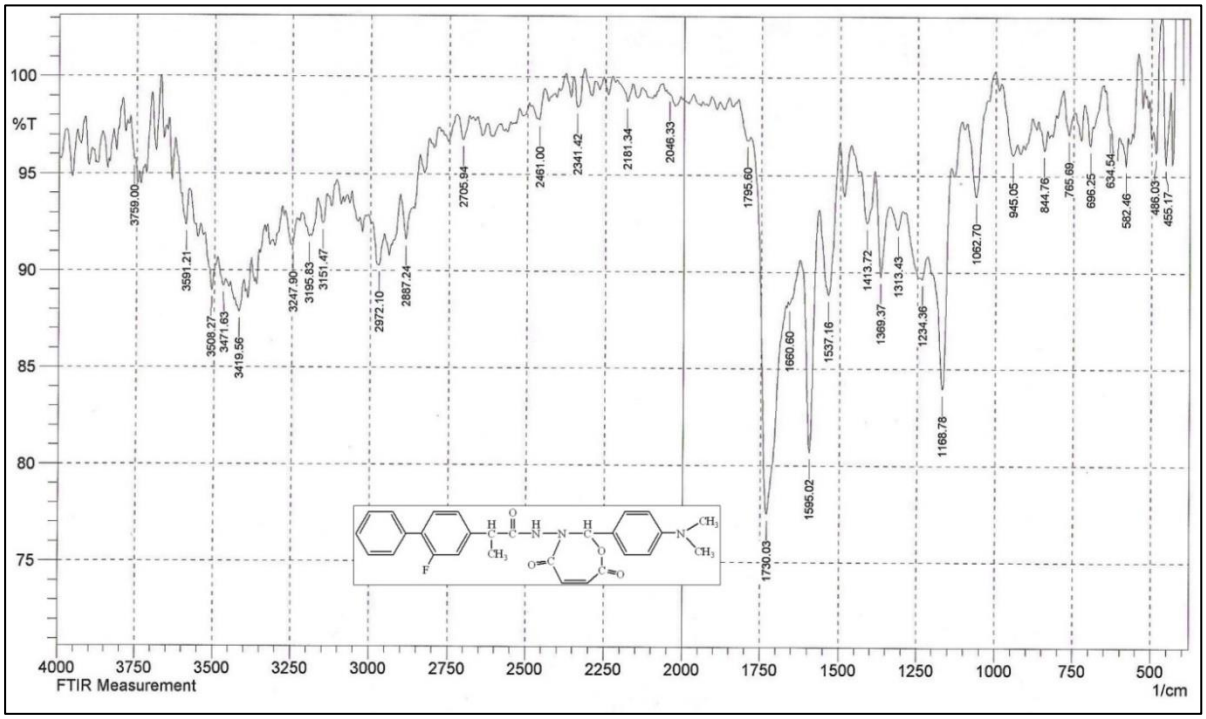


Figure (3.33): FT-IR spectrum of compound [23].

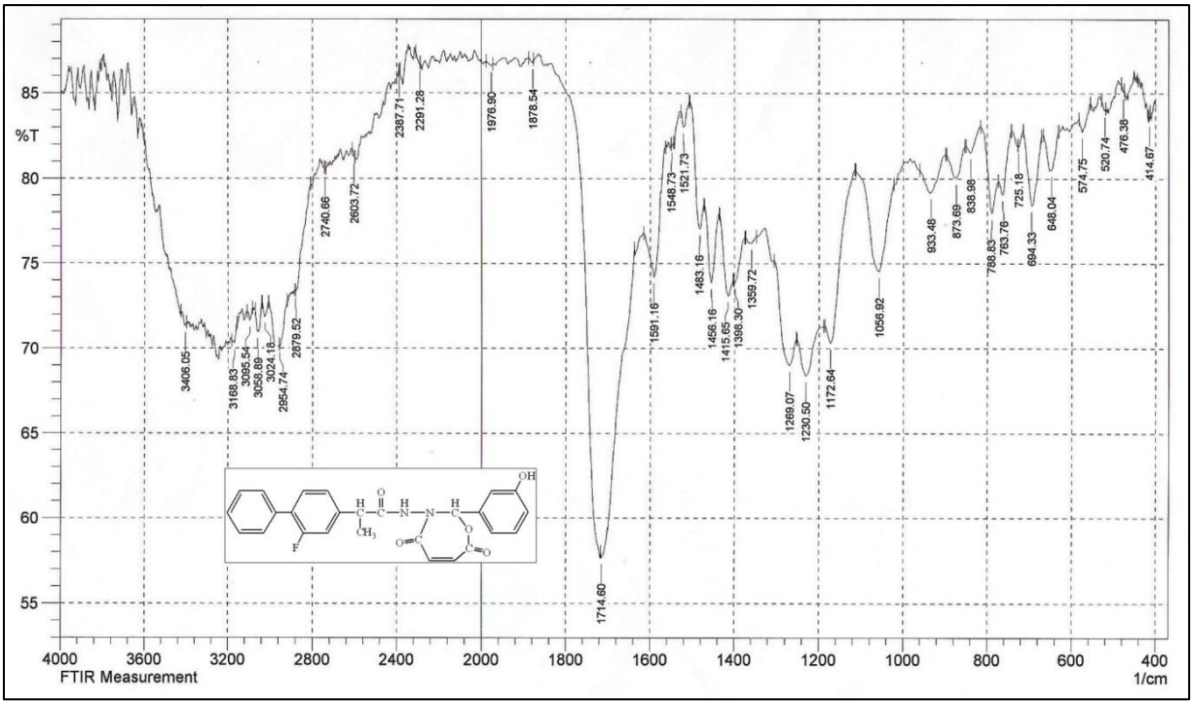


Figure (3.34): FT-IR spectrum of compound [24].

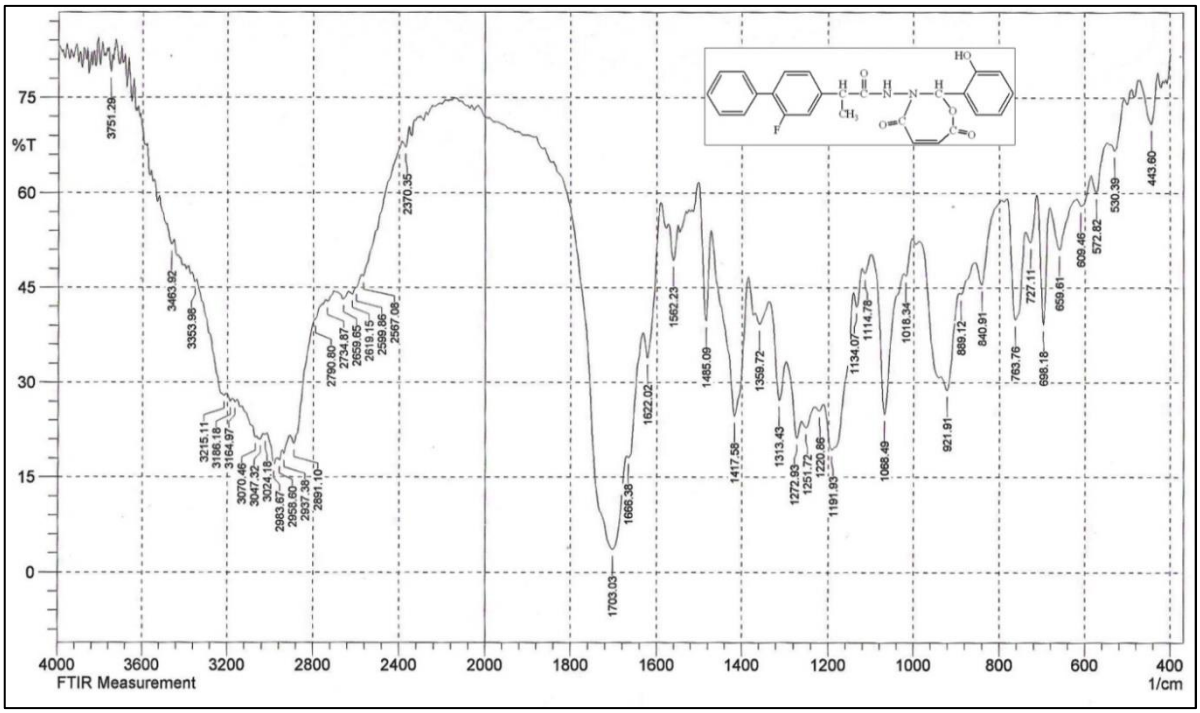


Figure (3.35): FT-IR spectrum of compound [25].

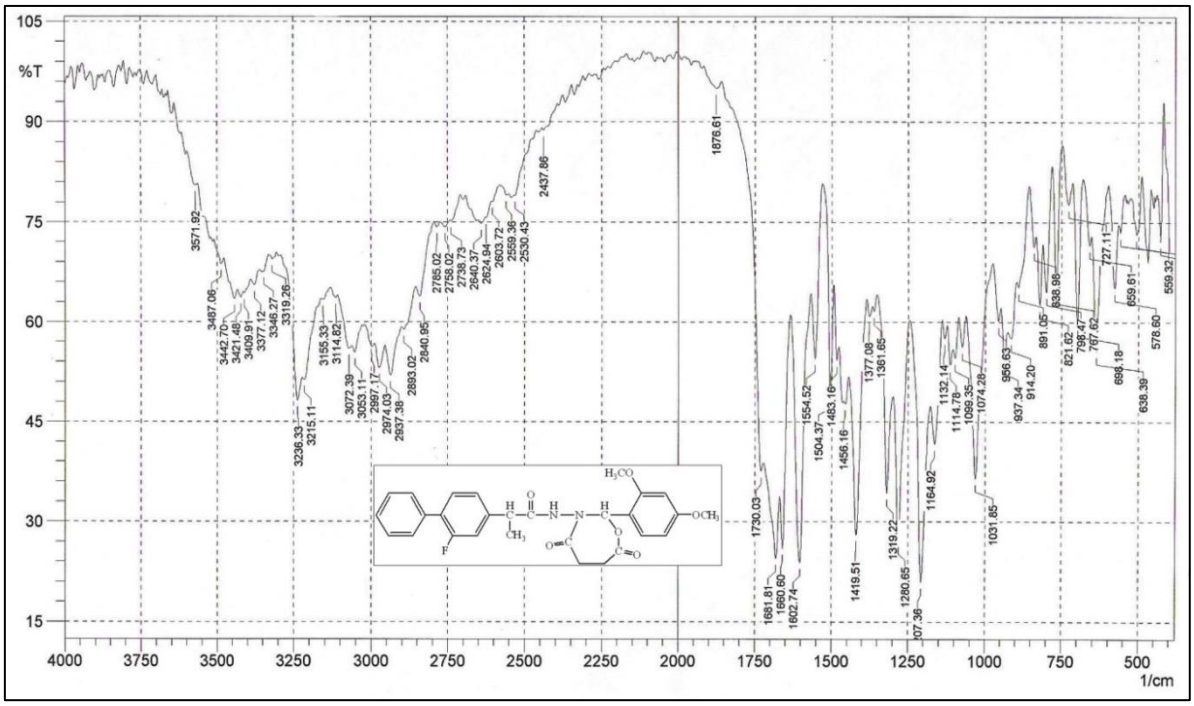


Figure (3.36): FT-IR spectrum of compound [26].

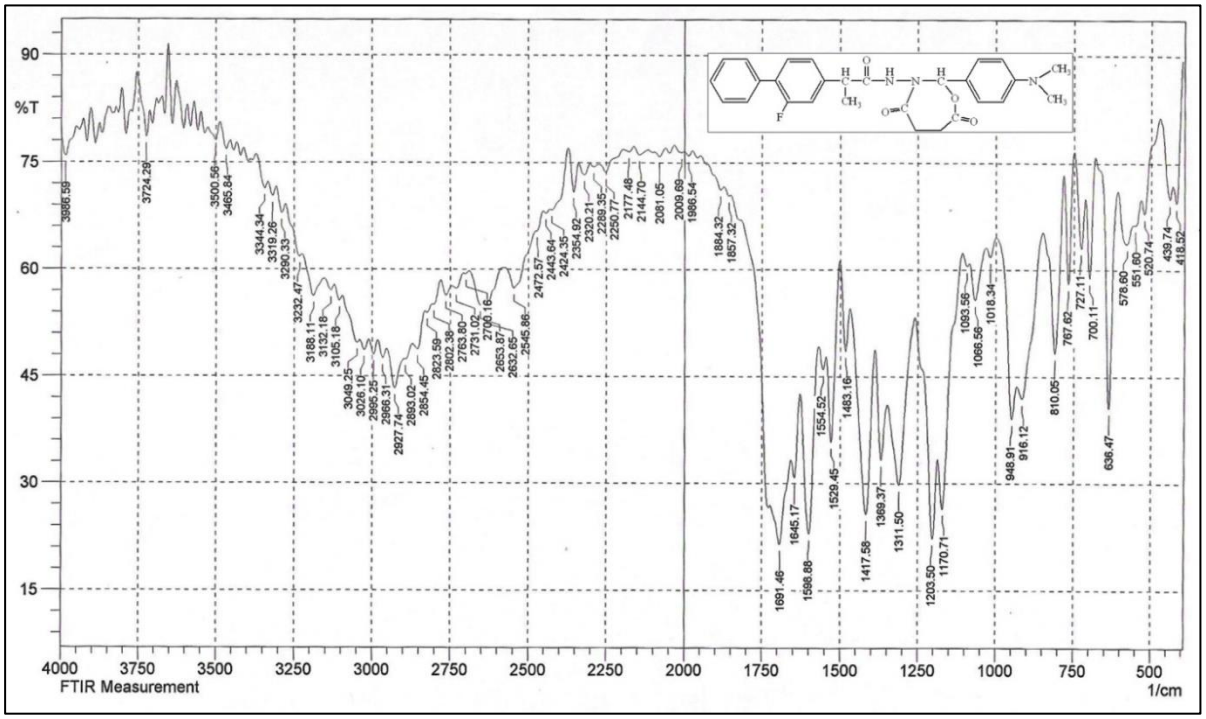


Figure (3.37): FT-IR spectrum of compound [27].

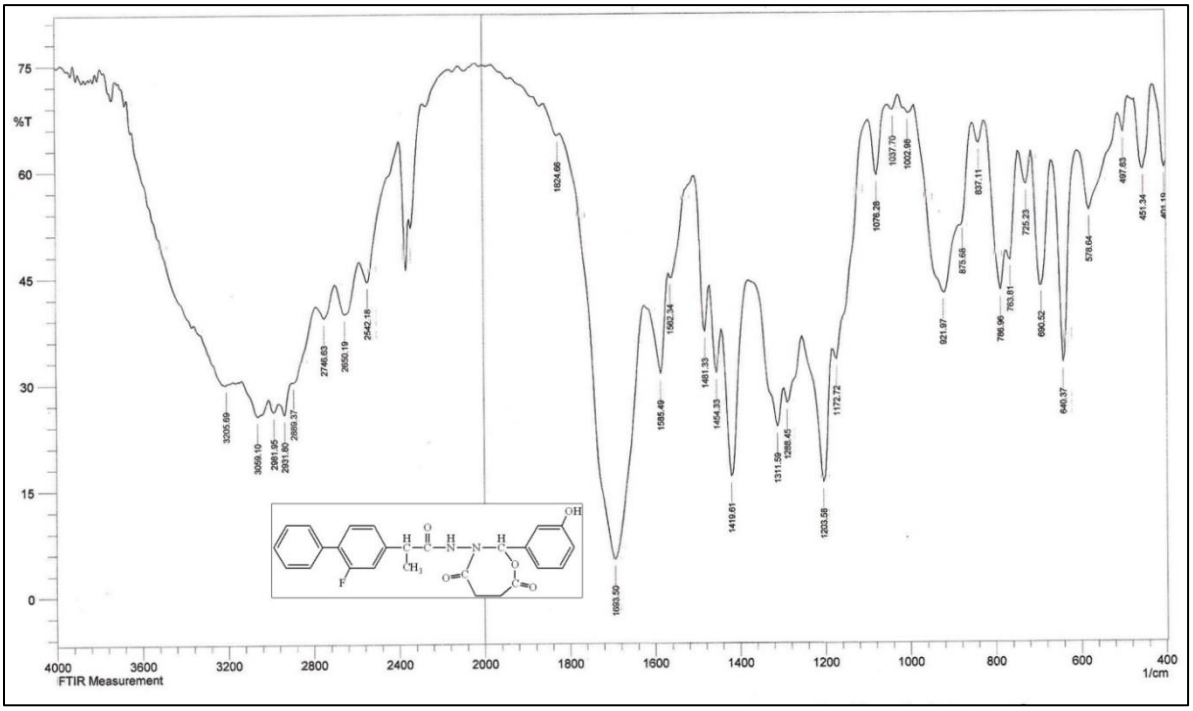


Figure (3.38): FT-IR spectrum of compound [28].

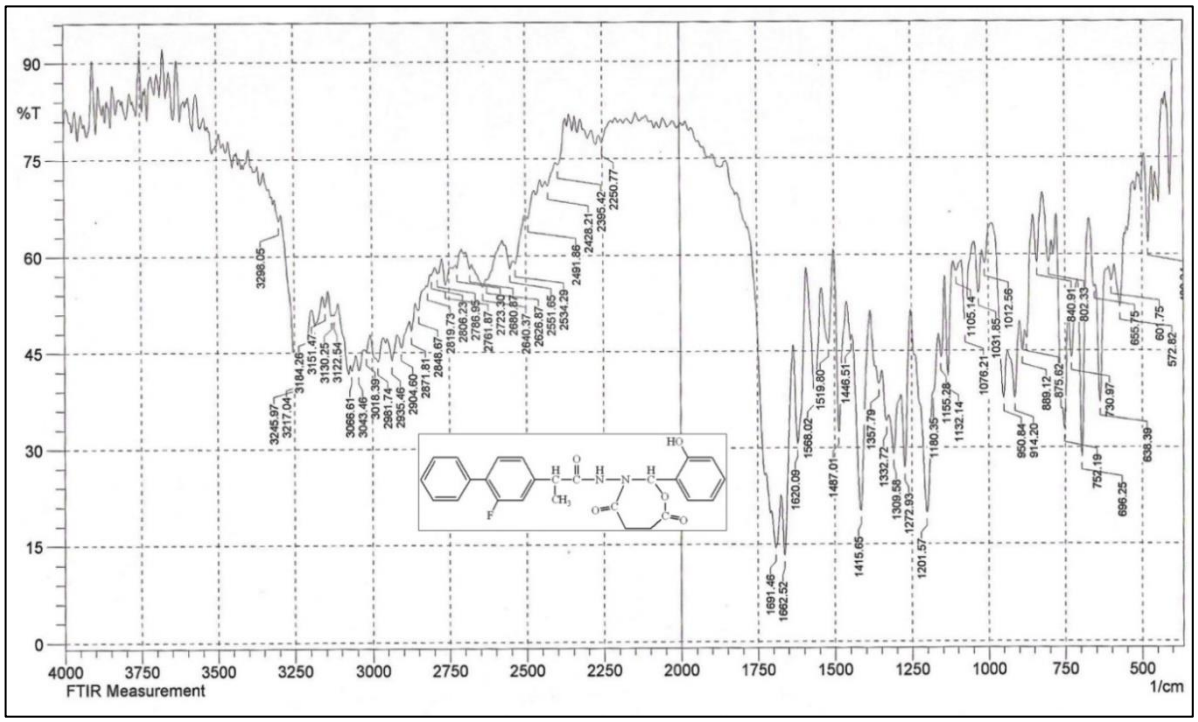


Figure (3.39): FT-IR spectrum of compound [29].

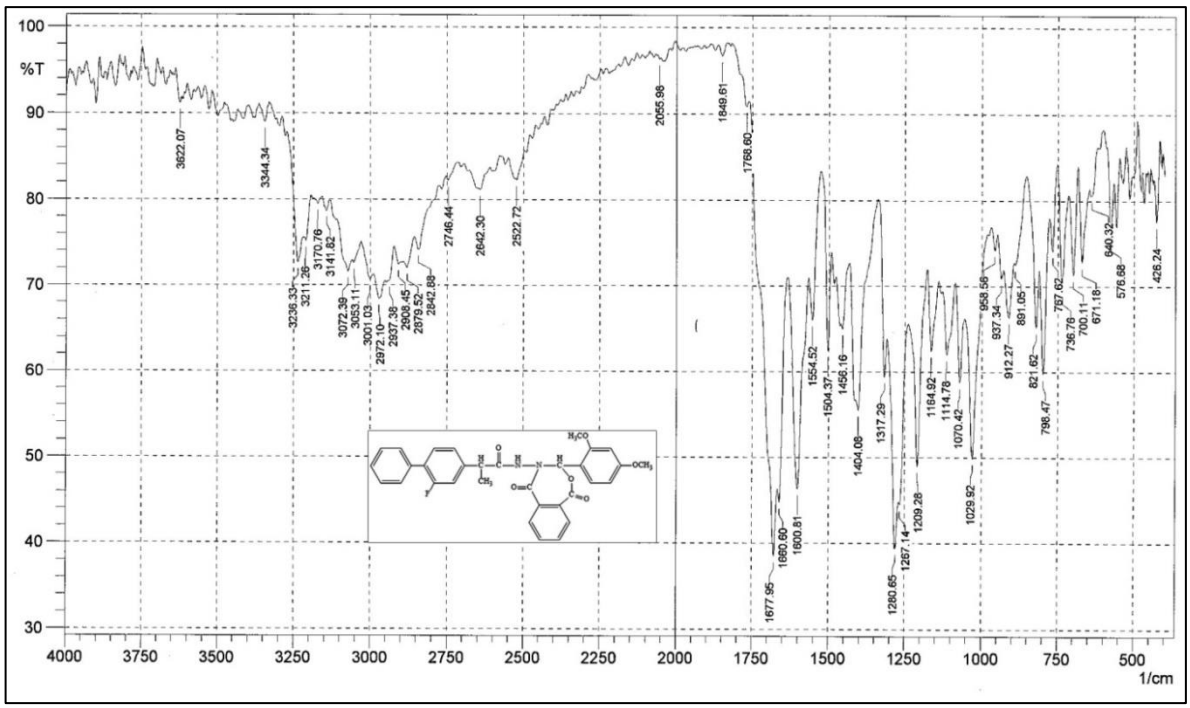


Figure (3.40): FT-IR spectrum of compound [30].

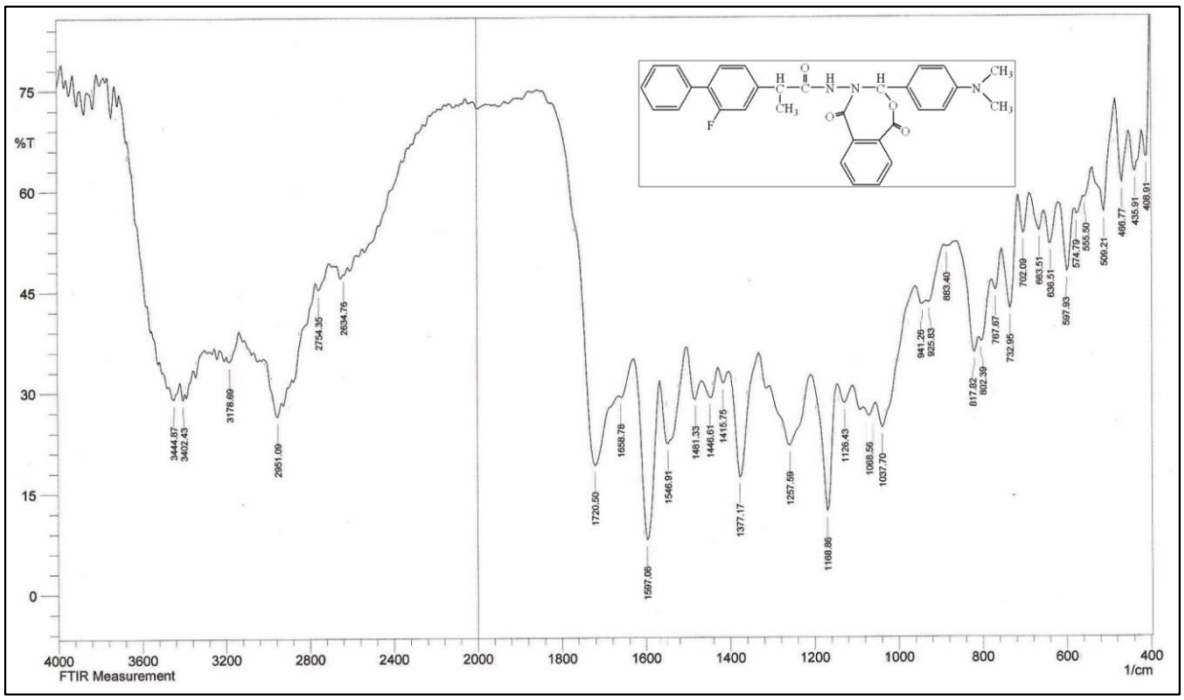


Figure (3.41): FT-IR spectrum of compound [31].

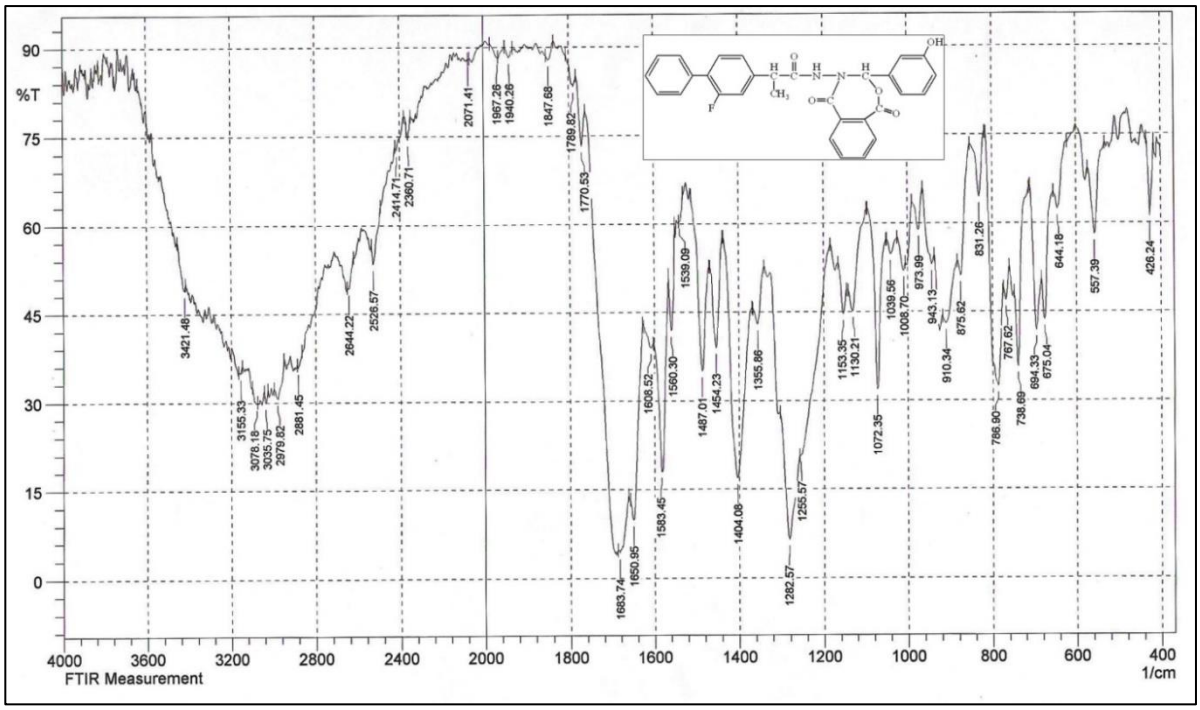


Figure (3.42): FT-IR spectrum of compound [32].

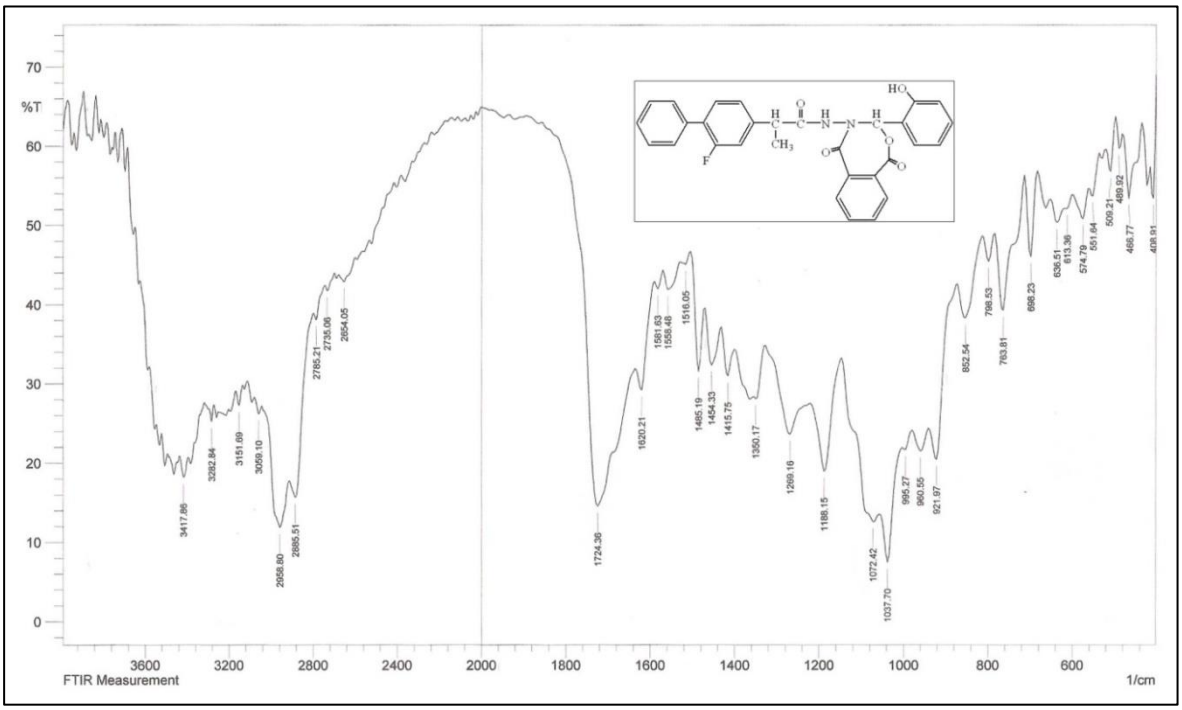


Figure (3.43): FT-IR spectrum of compound [33].

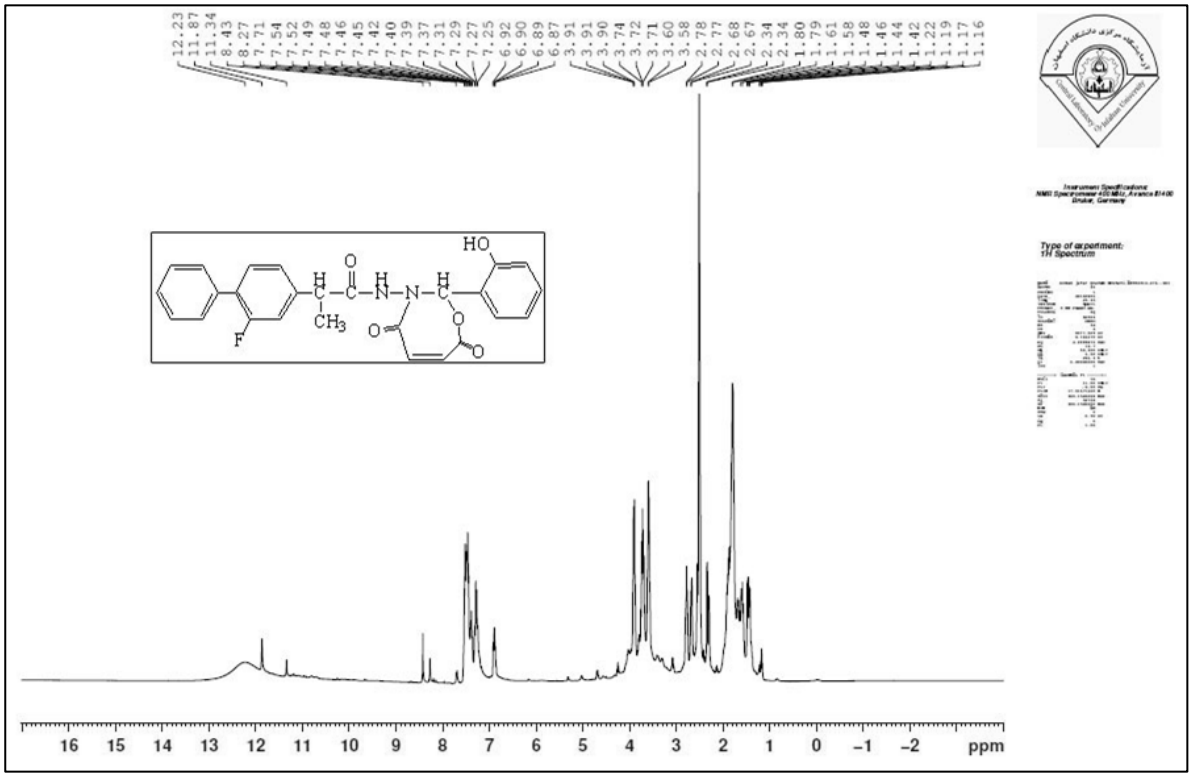


Figure (3.44): ^{1}H-NMR spectrum of compound [25].

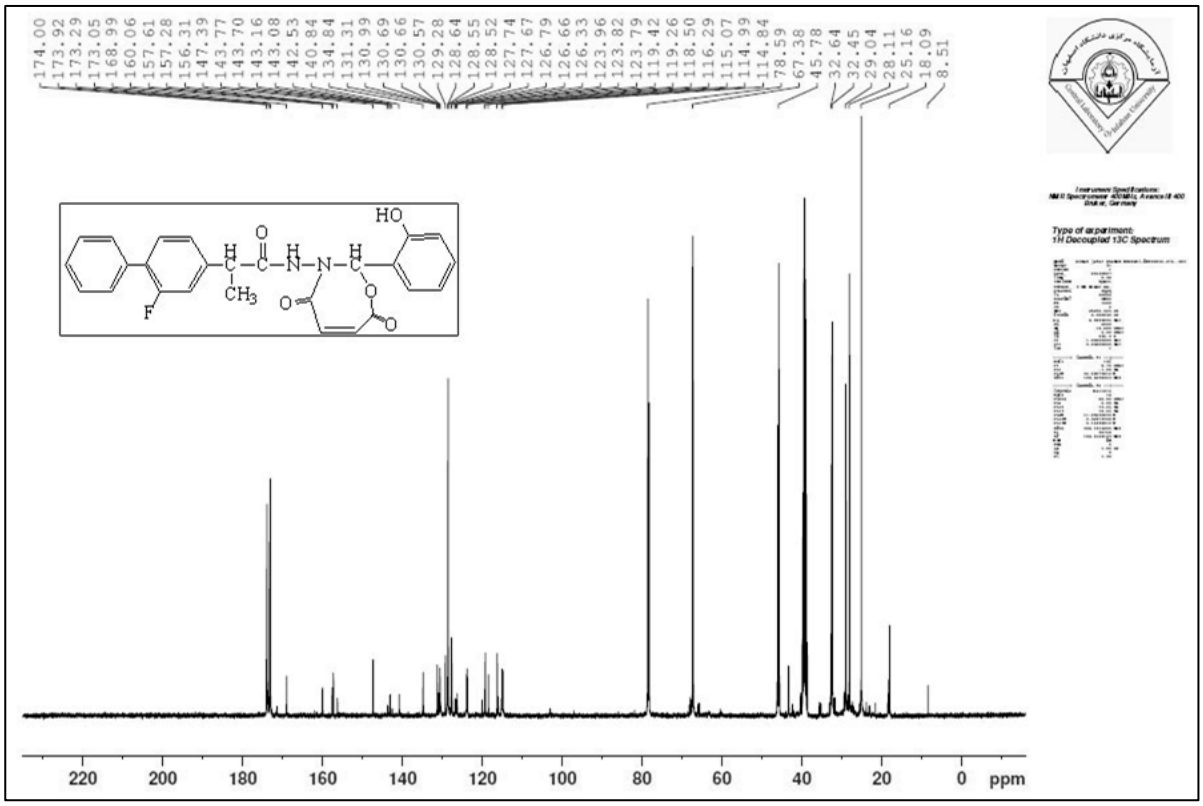


Figure (3.45): ^{13}C-NMR spectrum of compound [25].

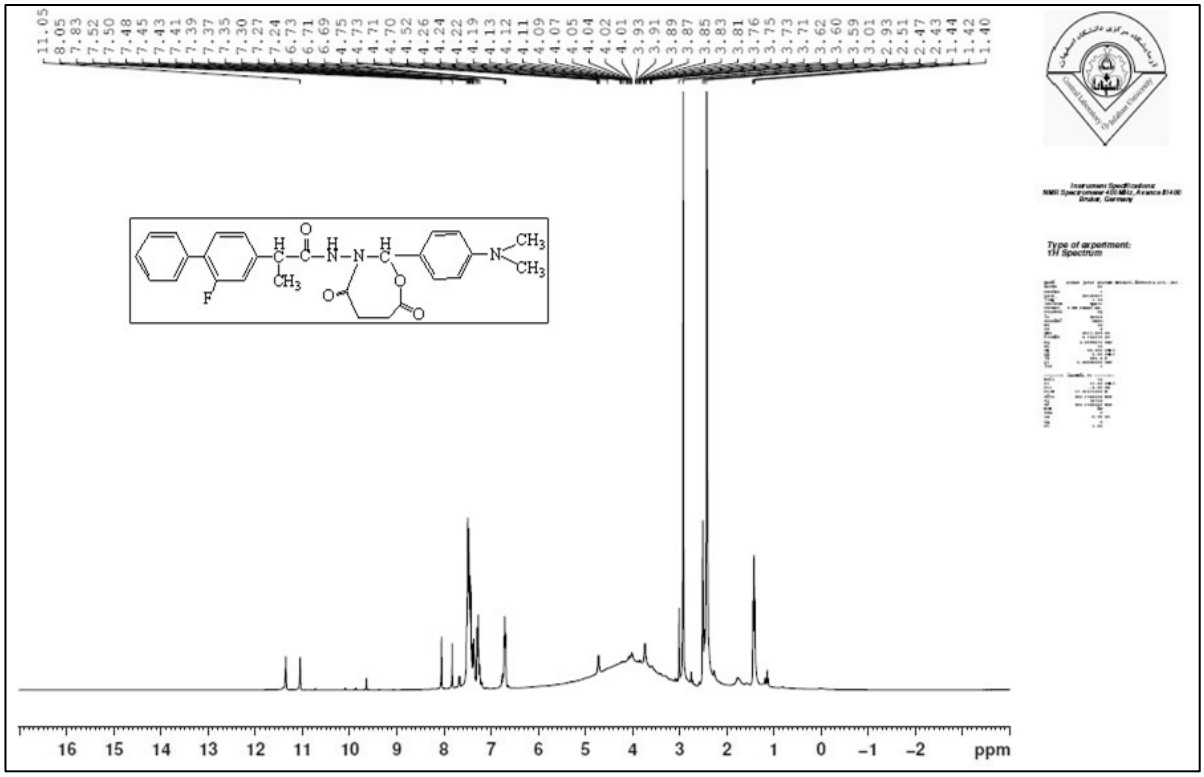


Figure (3.46): ^{1}H-NMR spectrum of compound [27].

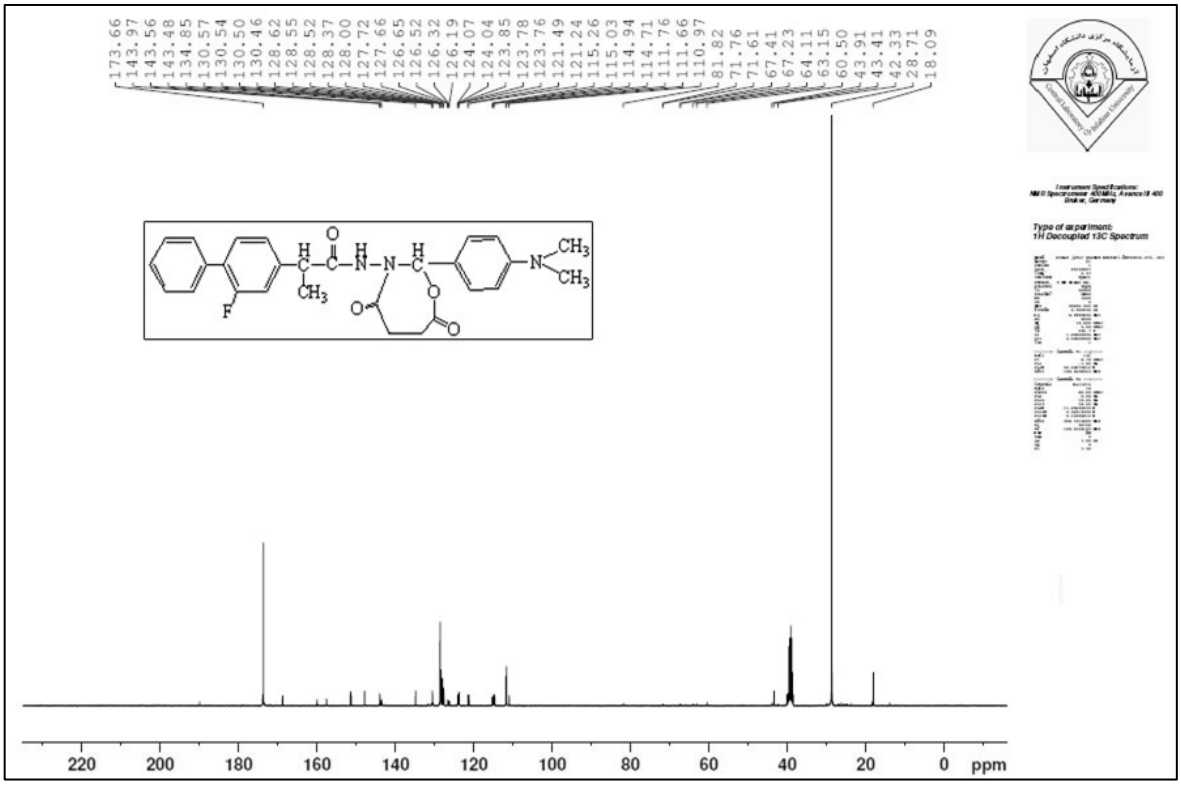


Figure (3.47): ^{13}C-NMR spectrum of compound [27].

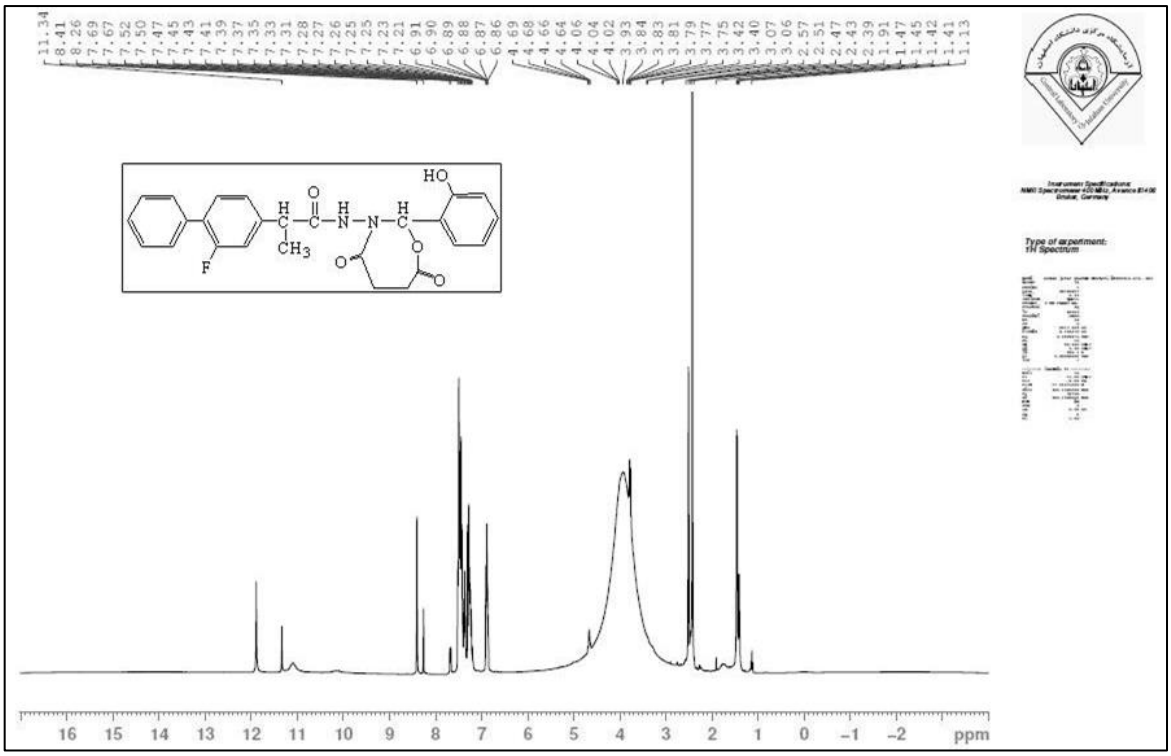


Figure (3.48): ^{1}H-NMRspectrum of compound [29].

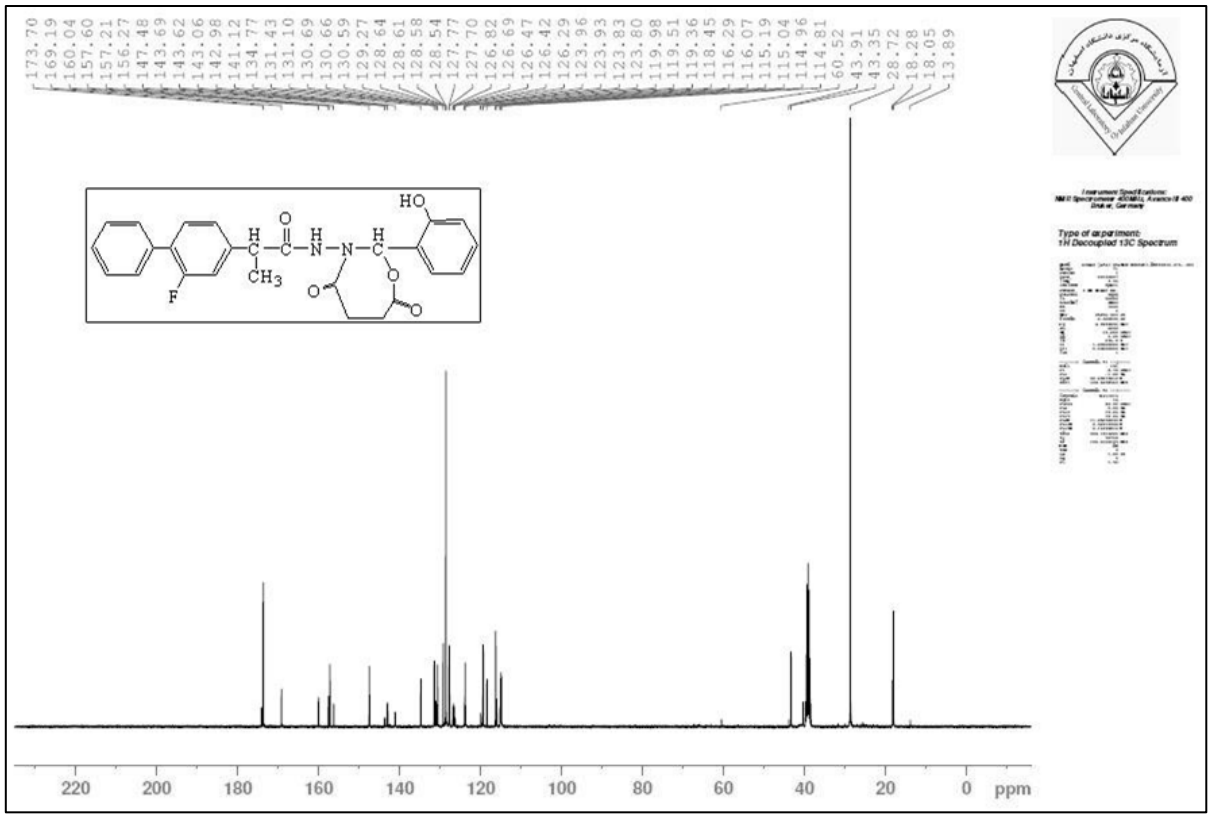


Figure (3.49): ^{13}C-NMR spectrum of compound [29].

3.9- Evaluation of anti-inflammatory of the compounds [5], [7], [8], [21] and [25]

3.9.1- anti-inflammatory effect of standard drug (flurbiprofen) on paw-edema:

The paw - edema method was used for the evaluation anti-inflammatory activity of some new synthesized compounds. Flurbiprofen was used as a reference compound. Table (3.14) showed that the intra-planter injection of (0.05 ml) egg-albumin at a time 30 minutes into the left hind paw produced a significant increase in paw thickness in all animals designed as a control (4.95±0.11 mm.) and flubiprofen (4.67±0.12 mm.) groups; significant difference in the induced the paw-edema was observed among these two groups.

In the control group, paw-edema was shown to be continually elevated reaching maximum (5.17±0.06 mm.) after 60 minutes. For this reason, this time interval is used for the comparative analysis of the anti-inflammatory effect of the reference drug and of the tested compounds.

However; paw thickness was reduced back to the lower value (4.67±0.11 mm.) after 240 minutes (the end of experiment) as shown in figure (3.50). While paw-edema in animals that treated with flurbiprofen (9mg/kg, I.P.) reached (5.53±0.25 mm.) after 120 minutes, which is significantly higher when compared to that in negative control (DMSO) (P<0.05), and reduced back to (4.53±0.16 mm.) after 180 minutes, which is significantly lower in comparison with that in negative control (DMSO) (P<0.05).

Table (3.14): The effect control and flurbiprofen on egg-albumin induced paw edema in rats.

Time (min.)	Mean increase in paw thickness (mm)	
	Negative control (DMSO)	Flurbiprofen
30	4.95±0.11	4.67±0.12*
60	5.17±0.06	5.21±0.22
120	5.06±0.11	5.53±0.25*
180	4.87±0.09	4.53±0.16*
240	4.67±0.11	4.67±0.14

-Data were expressed as mean ± SEM
-*P<0.05: significant difference compared to the negative control group.
-Number of animals= 6/ group

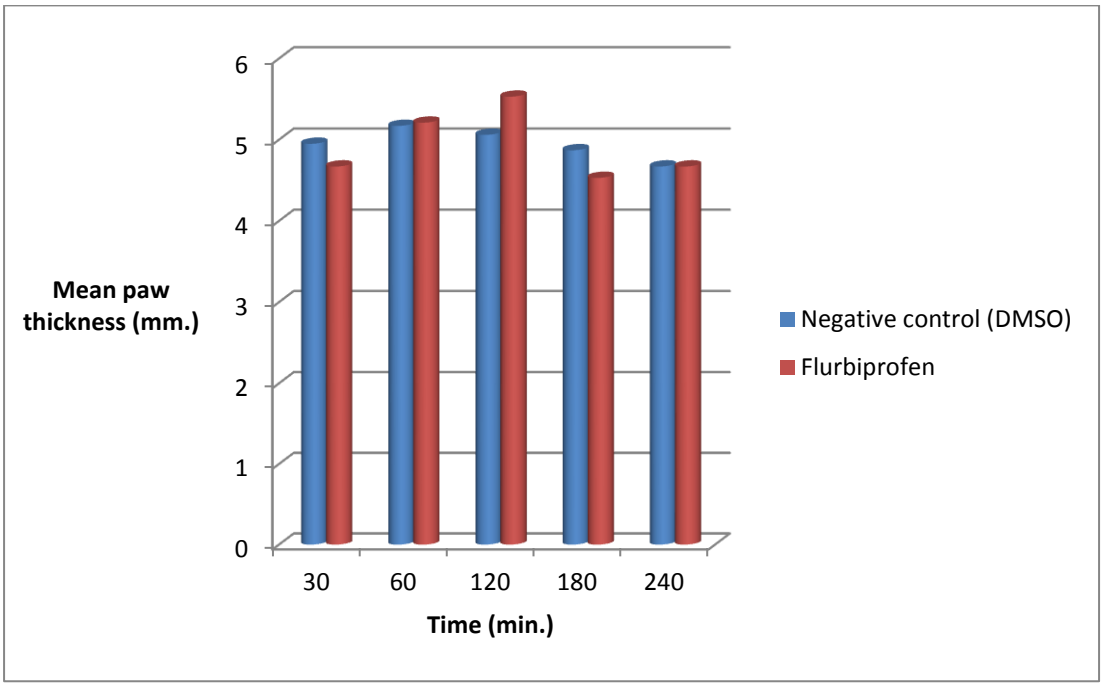


Figure (3.50): The effect control and flurbiprofen on egg-albumin induced paw edema in rats.

3.9.2- Anti-inflammatory Effect of tested compounds [5], [7], [8], [21] and [25] on paw-edema:

Table (3.15) showed the effect of the tested compounds on the paw-edema thickness after intra-planter injection of (0.05 ml) egg-albumin. Paw-edema in animals treated with compound [5] named 2-(3-Fluorobiphenyl-4-yl)propaneamidophthalimide; reached (5.76±0.19 mm.) after 60 minutes of injection, which is significantly lower in comparison to that in the nagetive control (P<0.05) and reduced back to (4.67±0.13 mm.) after 180 minute, which is significantly lower in comparison to that in the negative control (P<0.05), as shown in figure (3.51). (4.11)% inhibition of inflammation after 180 minutes, as shown in table (3.15).

On the other hand, animals treated with compound [8] named N-(3-hydroxybenzalidene)-2-(3-fluorobiphenyl-4-yl) propanamide; exhibited (5.3±0.1 mm.) elevation in paw thickness after 60 minutes of induction, a value that is significantly lower in comparison to that in the negative control (P<0.05)

and reduced back to (4.19±0.12 mm.) at the end of the experiment, a value that is significantly lower in comparison to that in the negative control ($P<0.05$). Higher percentage inhibitaion of compound [8] is (10.28%) after 240 minutes of injection.

Animals treated with compounds [7] named N-(4-(N,N-dimethylamino)benzalidene)-2-(3-fluorobiphenyl-4-yl)propanamide and [21] named N-[2-oxo-3-phenyl-4-(2-hydroxyphenyl)-1,3-diazetidin-1-yl]-2-(3-fluorobiphenyl-4-yl)propane amide, reached [21] (5.65±0.11mm.) and [7] (5.48±0.09 mm.) elevation in paw thickness after 60 minutes of induction, a value that is significantly higher in comparison to that in the negative control ($P<0.05$), and reduced back to [21] (4.39±0.1 mm.) and [7] (4.37±0.08 mm.) at the end of experiment a value that is significantly higher in comparison to that in the negative control ($P<0.05$). Higher percentage inhibitaion of compound [21] is (5.99%) after 240 minutes of injection, while compound [7] reached 6.77% of inhipition after 180 minuts and then reduce back to 6.42 at 240 minutes.

Compound [25] named 2-(2-hydroxyphenyl)-3-[2-(3-fluorobiphenyl-4-yl)]propanamido-2,3-dihydro-1,3-oxazepine-4,7-dione, showed anti-inflammatory more than standard drug (flurbiprofen) in all times. Reached (5.06±.023) elevation in paw thickness after 60 minutes of induction, a value that is significantly lower in comparison to that in the negative control ($P<0.05$), and reduced back to (4.21±0.19) after 240 minutes if injection. Precentage of compound [25] reached (12.9 %) at 180 minutes after injection and reduce back to (9.8%) at 240 minutes (end of experiment).

This study showed that when changing the carboxylic group in drug (flurbiprofen); its effects of activity of the compound and some changes increase the activity of compound as shown in compound [25], inhibition arachidonic acid by compound [25] shown below:

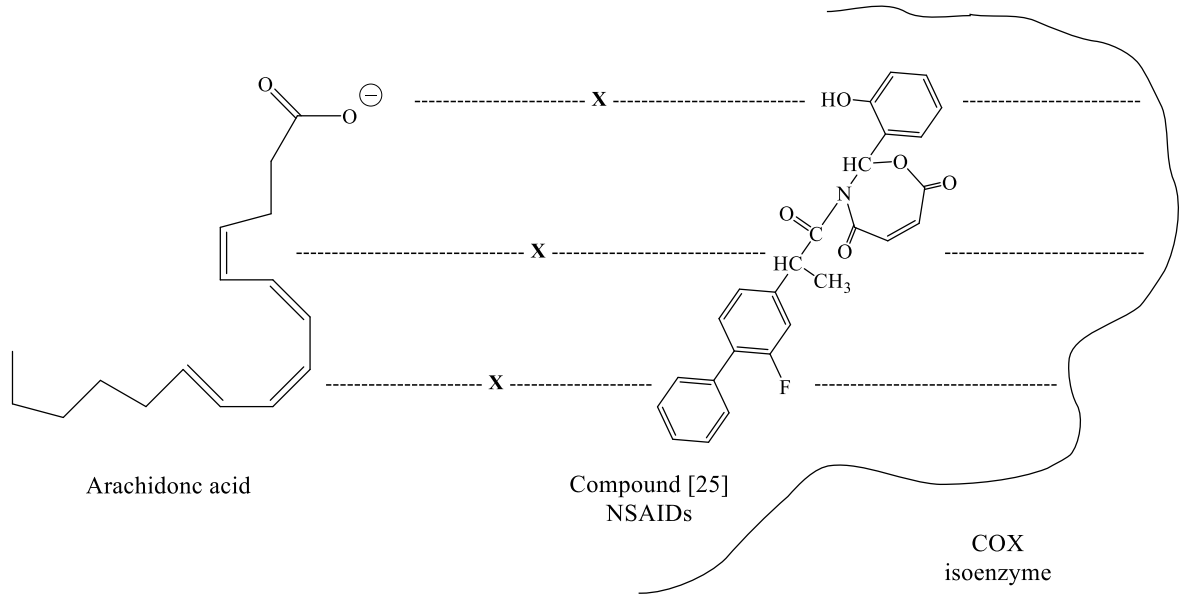


Table (3.15): The effective control, flurbiprofen and compounds [5], [7], [8], [21] and [25] on egg-albumin induced paw edema in rats.

Group	Mean increase in paw thickness (mm)					% of inhibition				
	30 Min.	60 Min.	120 Min.	180 Min.	240 Min.	30 Min.	60 Min.	120 Min.	180 Min.	240 Min.
GI Negative control (DMSO)	4.95± 0.11	5.17± 0.06	5.06± 0.11	4.87± 0.09	4.67± 0.11	---	---	---	---	---
GII Flurb.	4.67± 0.12*A	5.21± 0.22A	5.53± 0.25*A	4.53± 0.16*A	4.67± 0.14A	5.66	---	---	6.98	---
GIII 5	5.49± 0.14*B	5.76± 0.19*B	5.07± 0.17B	4.67± 0.13*B	4.89± 0.19*B	---	---	---	4.11	---
GIV 8	5.02± 0.17C	5.3± 0.1C	4.99± 0.15*C	4.46± 0.11*C	4.19± 0.12*C	---	---	3.29	8.42	10.28
GV 25	4.79± 0.16D	5.06± 0.23D	4.59± 0.211*D	4.24± 0.19*D	4.21± 0.19*D	3.23	2.12	9.28	12.9	9.8
GVI 21	5.24± 0.078E	5.65± 0.11*E	5.19± 0.07E	4.69± 0.13B	4.39± 0.1*E	---	---	---	3.69	5.99
GVII 7	5.25± 0.12*E	5.48± 0.09*C	5.08± 0.1C	4.54± 0.09*C	4.37± 0.08*E	---	---	---	6.77	6.42

-Data were expressed as mean ± SEM

-*P<0.05: significant difference compared to the negative control group.

-Values with non-identical subscripts (A, B, C, D and E) among different groups are considered significantly different (P<0.05) in each time column.

-Percent inhibition (%) compared to the negative control (group I).

-Number of animals= 6/ group.

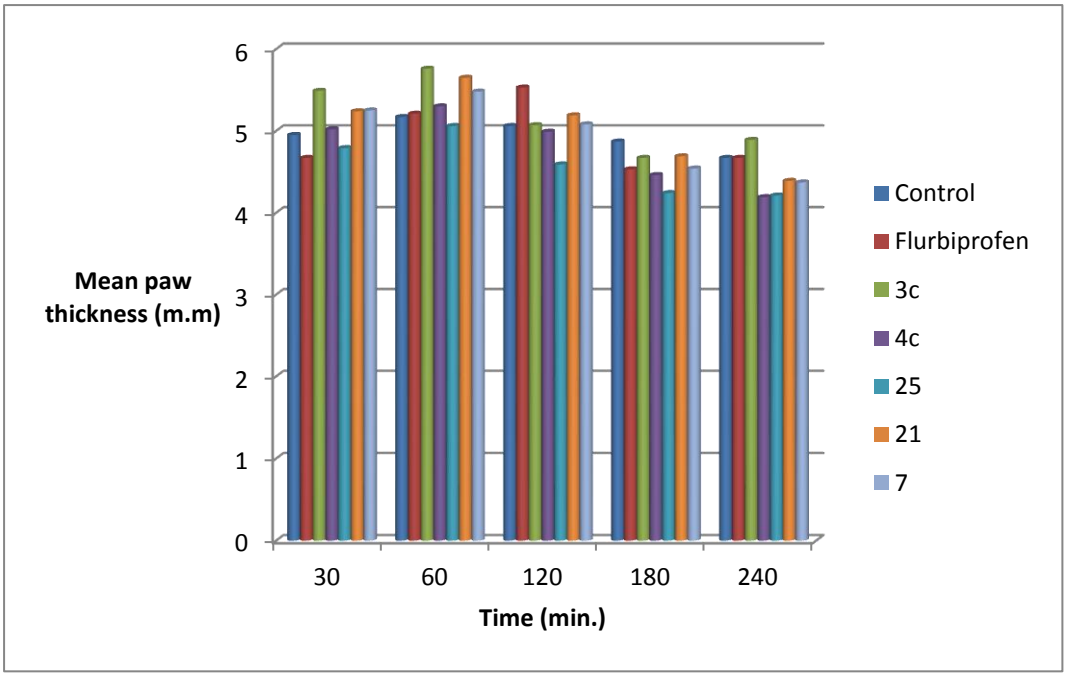


Figure (3.51): The effect control, flurbiprofen and compounds [5], [8], [7], [21] and [25] on egg-albumin induced paw edema in rats.

3.9.3- Comparative analysis:

Multi-way comparison between reference drug and tested compounds revealed the following:

1- All tested compounds were effectively limited the increase in paw-edema and their effect started 30 minutes after induction and continued till the end of the experiment as shown in figure (3.50 and 3.51).
2- Tested compounds [5], [7], [8], [21] and [25] showed a comparable effect to that of flurbiprofen in all time of the experiment.
3- Compound [25] give effect more than in flurbiprofen after 60 minutes and continue till the end of the experiment.

Future work:

1- Synthesis N-phenyl-1,2,4-triazol derivatives from the reaction of compound [2] with phenylisocynate and then with sodiumhydroxide.

2- Synthesis 1,3-thiazole derivatives from the reaction of compound [2] with chloroacetylchloride and then with thiourea.

3- Synthesis new β-lactam derivatives from the reaction of compound [6-9] with chloroacetylchloride.

4- Study biological activities analgesic activity, anticancer, antibacterial, antifungal activities of new synthesized compounds.

5- Perform dose-response curve for [25] compound against inflammation-induced by egg-albumin.

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جمهورية العراق
وزارة التعليم العالي والبحث العلمي
جامعة بغداد/ كلية العلوم
قسم الكيمياء

تحضير وتشخيص وتقييم مضاد للالتهاب لبعض المشتقات الجديده لـ ٢-(٣-فلوروباي فنيل-٤-يل)حامض البروبانويك

رسالة

مقدمة إلى كلية العلوم، جامعة بغداد

وهي جزء من متطلبات نيل درجة الماجستير في علوم الكيمياء العضوية

قدمها

أحمد جعفر قاسم الموسوي

(بكالوريوس كيمياء، كلية العلوم، جامعة ميسان/2013 م)

بإشراف

أ.د.احمد وحيد ناصر

1438هـ

2017م

إلى ينبوع الحنان وملاذ الأمان ..... أمي العزيزة

إلـــى مـــتكـــأي وســنـــدي ..... أبي العزيز

إلـــى من أحببتهم وأحبوني ..... أخوتي

إلـــى من احتضنوني بكل حنان ..... أقاربي

الى من فاضت روحه الى الباري..... المرحوم عمي

أليك يا رسول الله

والى الشجرة النبوية والدوحة الهاشمية المضيئة بالنبوة الموقنة بالإمامة

والى كل مؤمن فتح للإنسانية بابا للرقي العلمي

اهدي هذا الجهد المتواضع

الـبـاحـث

شكر وتقدير

الحمد والشكر الى الباري جل وعلا لما ذلل له لي من العقبات ووفقني لاكمل دراستي، وانا على ابواب اكمال رسالتي اتقدم بوافر الشكر والتقدير الى مشرفي العزيز *الاستاذ الدكتور احمد وحيد* لموافقته الاشراف عليه واختيار البحث ولما قدمه من الملاحظات والتصحيحات للارتقاء بالبحث الى المستوى المطلوب، سائلين المولى ان ينعم عليه بالخير والعطاء لما فيه مصلحة عراقنا الحبيب. كما اتقدم بوافر الشكر والاحترام الى الدكتوره ندى الشاوي والاستاذ عمار عامر من كلية الصيدله لمشاركتهم الكبيره في البحث باجراء الجزء التطبيقي من العمل. لا انسى بالشكر، الفضل الذي قدمه لي *الاستاذ الدكتور كريم سالم* الذي بنى لي اساس في العضويه في الدراسات الاوليه لانطلق منها، تمنياتي له بالموفقيه والرقي. كما اتقدم بالشكر والتقدير الى *عمادة كلية العلوم وقسم الكيمياء* لجهودهم المبذوله لتذليل العقبات امام البحث واخص بالشكر كذلك مسؤولة المختبر الخدمي *الست منيره* لاجرائها قياسات FT-IR وعلى كل المعلومات التي قدمتها فيما يخص طريقة القياس.

تتناثر الكلمات حبرا وحبا ..

على صفائح الأوراق ..

لكل من علمني ..

ومن أزال غيمة جهل مررت بها ..

برياح العلم الطيبة ..

ولكل من أعاد رسم ملامحي ..

وتصحيح عثراتي ..

أبعث تحية شكر واحترام

الخلاصه

خلال هذا العمل تم تحضير بعض المركبات غير المتجانسه المشتقه من 2-(3-فلوروباي فنيل-4-يل) بروبانوهيدرازايد كمركب اساس، ودراسة الفعاليه المضاده للالتهابات لبعض منها. وتضمن هذا العمل ثلاث اجزاء وان خطوات تفاعلات كل جزء موضحه في ادناه:

الجزء الاول: (مخطط 1)

هذا الجزء يتضمن تحضير المركبات [1-17]وكما يلي :

1- تحضير اثيل 2-(3-فلوروباي فنيل-4-يل) بروبانوت [1] بتفاعل فلوربايبروفين مع الايثانول بوجود كميه من حامض الكبريتيك المركز.
2- تحضير 2-(3-فلوروباي فنيل-4-يل) بروبونوهيدرازايد [2] بتفاعل اثيل 2-(3-فلوروباي فنيل-4-يل) بروبانوت [1] مع 80 % هيدرازين المائي.
3- تحضير مشتقات الايمايدات الحلقيه [3-5] من خلال تفاعل المركب [2] مع بعض الحوامض اللامائيه مثل حامض الماليك، حامض السكسنيك وحامض الفثالك.
4- تحضير مشتقات الهيدرازون [6-9] من خلال تفاعل المركب [2] مع بعض الالديهايدات الاروماتيه مثل: 4,2-ثنائي ميثوكسي بنزالديهايد، 4-(N,N-ثنائي مثيل امينو)بنزالديهايد، 2-هيدروكسي بنزالديهايد و 3-هيدروكسي بنزالديهايد.
5- تحضير مشتقات 4,2,1-ثلاثي ازول [10] من تفاعل [2] مع CS_2 ،بوجود هيدروكسيد البوتاسيوم و 80% هيدرازين المائي.
6- تحضير مشتقات الايمايدات الحلقيه [11-13]من خلال تفاعل المركب [10]مع بعض الحوامض اللامائيه مثل حامض الماليك، حامض السكسنيك وحامض الفثالك
7- تحضير قواعد شف [14-17] بتفاعل المركب 4,2,1-ثلاثي ازول [10] مع بعض الالديهايدات الاروماتيه مثل: 4,2-ثنائي ميثوكسي بنزالديهايد، 4-(N,N-ثنائي مثيل امينو)بنزالديهايد، 2-هيدروكسي بنزالديهايد و 3-هيدروكسي بنزالديهايد.

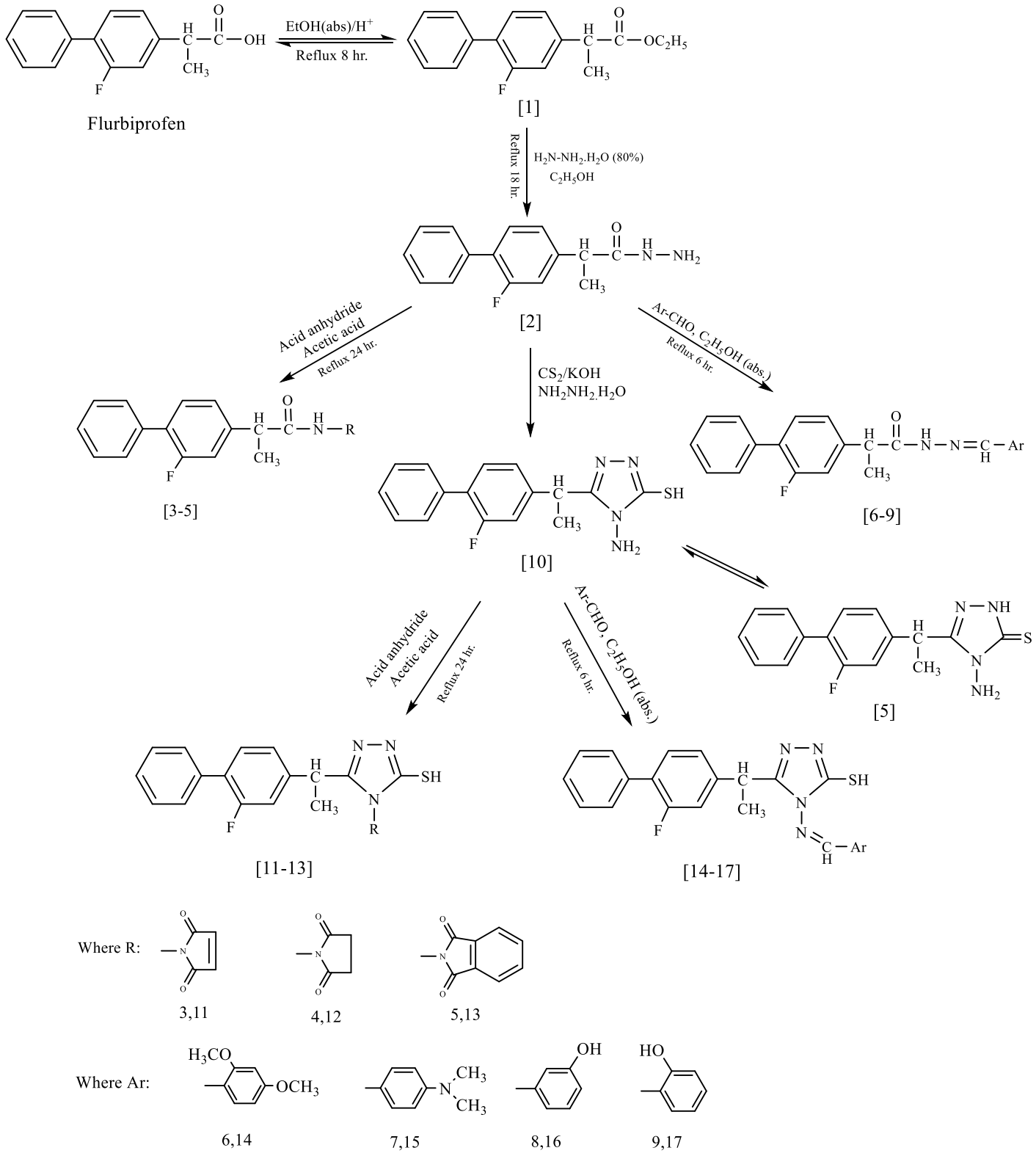
الجزء الثاني: (مخطط 2)

هذا الجزء يتضمن تحضير المركبات [18-33] وكما يلي:

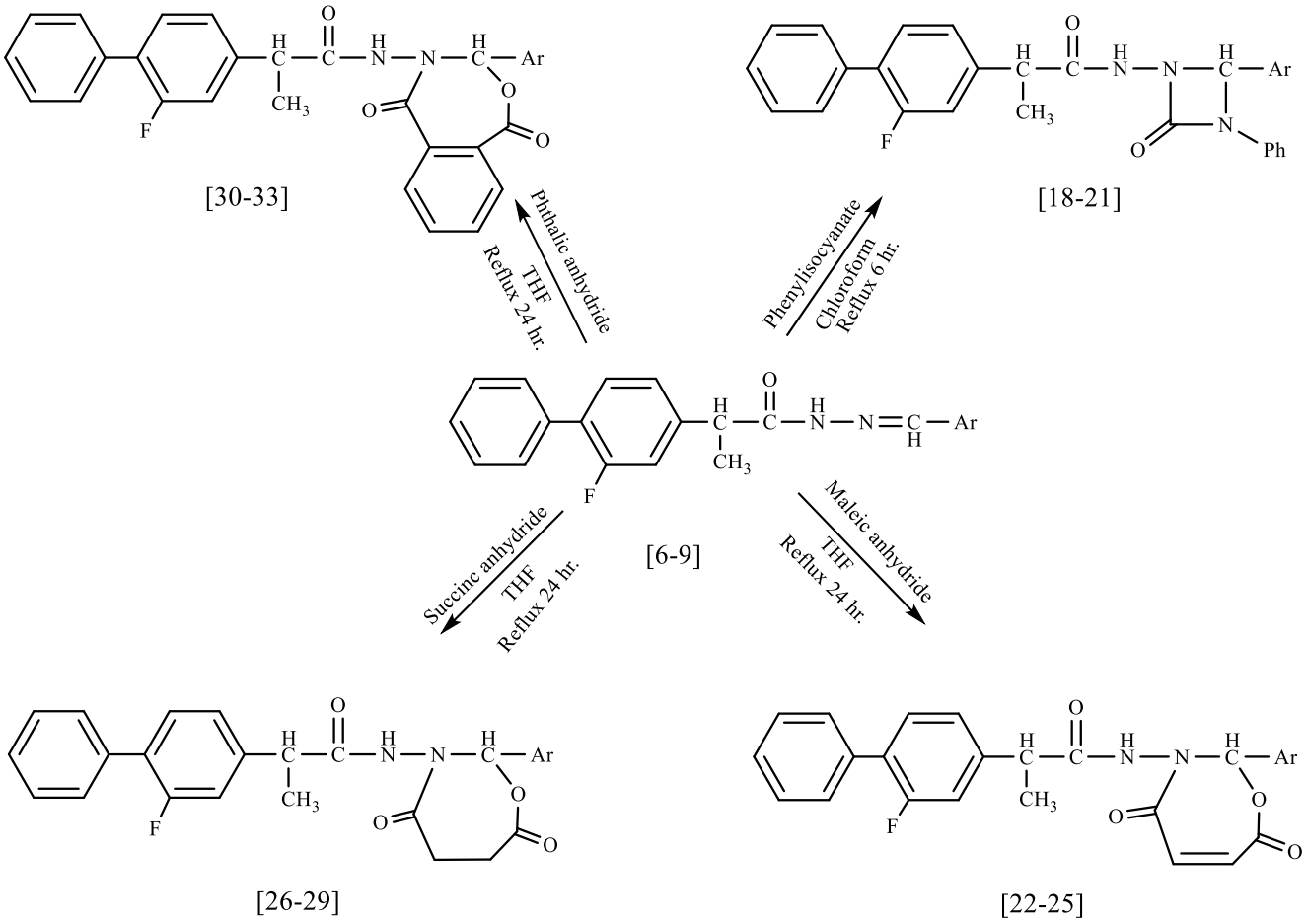
1- تحضير مشتقات ثنائي ازيتيداون [18-21] من الغلق الحلقي لمشتقات الهيدروزن [6-9] مع فنيل ايزوسيانات.
2- تحضير مشتقات اوكسازبين [22-25]، [26-29] و [30-33] من الغلق الحلقي لمشتقات الهيدرازون المحضره [6-9] مع بعض الانهايدريدات مثل: ماليك انهايدريد، ساكسنيك انهايدريد و فثالك انهايدريد.

الجزء الثالث:

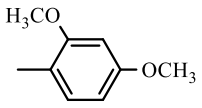
هذا الجزء يتضمن تقدير الفعاليه المضاده للالتهاب للمركبات [5]، [7]،[8]، [21]، [25] ،بواسطه البومين البيض تحت جلد الجرذ. مركب [25] اظهر فعاليه مضاده للالتهاب اعلى من الدواء القياسي الفلورباي بروفين.



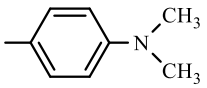
مخطط (1): تحضير المركبات [3-5]، [6-9]،[10] ، [11-13] و [14-15].



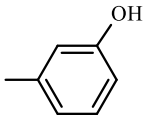
Where Ar:



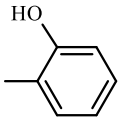
18,22,26,30



19,23,27,31



20,24,28,32



21,25,29,33

مخطط (2): تحضير المركبات [18-21]، [22-25]، [26-29] و [30-33].