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College of Pharmacy

Synthesis and Evaluation of 4-Thiazolidinone Derivatives of Naproxen as Potential Improvement of it is Anti-Inflammatory Effect

A Thesis

Submitted to the Department of Pharmaceutical Chemistry and the Committee of Graduate Studies of the College of Pharmacy-University of Al-Mustansiriyah in Partial Fulfillment of the Requirement for the Degree of Master in Pharmacy "Pharmaceutical Chemistry"

By

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Certification

We certify that this thesis, ***"Synthesis and Evaluation of 4-Thiazolidinone Derivatives of Naproxen as Potential Improvement of it is Anti-Inflammatory Effect"****, was prepared under our supervision at the Department of pharmaceutical Chemistry, College of Pharmacy- University of AL-Mustansiriyah as a partial fulfillment of the requirements for the degree of Master in Pharmacy (Pharmaceutical chemistry).*

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Dedication

To.....

My parents

My husband and my lovely daughters

My sister and brothers

With all my love

Farah

Acknowledgments

*Praise is to almighty **Allah** gracious for enabling me to finish what I started and for helping me to present this work.*

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List of Abbreviations

AA	*Arachidonic acid*
^{1}H-NMR	*Proton nuclear magnetic resonance*
ANOVA	*Analysis of variance*
Arg.	*Arginine*
COX	*Cyclooxygenase*
DCC	*Dicyclohexyl carbodiimide*
DCM	*Dichloromethane*
DCU	*Dicyclohexylurea*
FT-IR	*Fourier transform infrared spectroscopy*
GI	*Gastrointestinal*
Glu.	*Glutamic acid*
His.	*Histidine*
HIV	*human immunodeficiency virus*
i.p.	*Intraperitoneal*
IC_{50}	*Inhibitory concentration by 50%*
IL	*Interleukin*

Leu.	*Leucine*
MES	*Maximal Electroshock Seizure*
NSAIDs	*Non-steroidal anti-inflammatory drugs*
P	*Probability*
PG	*Prostaglandin*
Phe.	*Phenylalanine*
s.c.	*Subcutaneous*
SEM	*Standard error of mean*
Ser.	*Serine*
TLC	*Thin Layer Chromatography*
TXA2	*Thromboxane A2*
Tyr.	*Tyrosine*

ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) represent one of the most widely used classes of drugs, and are used primarily for the treatment of rheumatoid arthritis and other inflammatory disorders; however, the use of NSAIDs is significantly limited by their ability to induce the formation of erosions and ulcers in the gastrointestinal tract. The inhibition of COX-2 produced the therapeutic anti-inflammatory action of NSAIDs, while the undesired side effects arise from inhibition of COX-1 activity. Thus, COX-2 selective inhibitors would have reduced side effects.

Preferential inhibition of COX-2 is due to the additional space in the COX-2 hydrophobic channel, as well as to the presence of a side pocket in the channel therefore, a group of (4-thiazolidinone) pharmacophore incorporated to the naproxen; to increase its size were designed, synthesized and evaluated as potential anti-inflammatory agents with expected inhibitory selectivity toward COX-2 enzyme.

Synthetic procedures have been successfully developed for the synthesis of the intermediates and target compounds which includes:

1. ethyl 2-aminoacetate hydrochloride (I)
2. S-ethyl- 2-[2-(6-methoxynaphthalen-2-yl)-propanamido]acetate (II)
3. S-N-(2-hydrazinyl-2-oxoethyl)-2-(6-methoxynaphthalen-2-yl)propanamide (III)
4. S-2-(6-methoxynaphthalen-2-yl)-N-(2-(2-(4-benzylidene)hydrazinyl)-2-oxoethyl)propanamide (IV_{a-f})
5. S-2-(6-methoxynaphthalen-2-yl)-N-(2-((2-(4-aryl)-4-oxothiazolidin-3-yl)amino)-2-oxoethyl)propanamide (V_{a-f})

Synthesis of the designed compounds (V_{a-f}) has been successfully achieved. Purity and characterization of the synthesized compounds were confirmed by determination of physical properties (melting points & R_f values), Fourier transform infrared spectroscopy (FT-IR), ^{1}H-Nuclear magnetic resonance (^{1}H-NMR) spectroscopy and elemental microanalysis

In vivo potent anti-inflammatory effects of the synthesized compounds were evaluated in rats using egg-white induced edema model of inflammation.

The tested compounds (V_{a-f}) and the reference drug (naproxen) produced significant reduction of paw edema with respect to the effect of control group (propylene glycol 50%v/v). Compounds (V_{a-e}) exhibited higher anti-inflammatory effect than naproxen (50mg/kg, i.p.) at 180-240 min., while compound V_f exhibited lower anti-inflammatory effect.

These results encourage further evaluation of these compounds to demonstrate or identify their selectivity toward COX-2 isoenzyme.

CHAPTER ONE

INTRODUCTION

Introduction

1.1. General Consideration:

In 1899, Aspirin (acetylsalicylic acid) was introduced as the first potent drug to treat rheumatic diseases. Between the 1960s and 1980s, numerous anti-inflammatory agents were developed and reached the market, e.g. ibuprofen, indomethacin, diclofenac and naproxen, as shown in (Figure 1-1) [(1)].

Non-steroidal anti-inflammatory drugs (NSAIDs) represent one of the most widely used classes of drugs, and are used primarily to alleviate the symptoms (eg. pain and swelling) of osteoarthritis, rheumatoid arthritis and other inflammatory disorders. However, the use of NSAIDs is significantly limited by their ability to induce erosions and ulcers in the gastrointestinal (GI) tract [(2)].

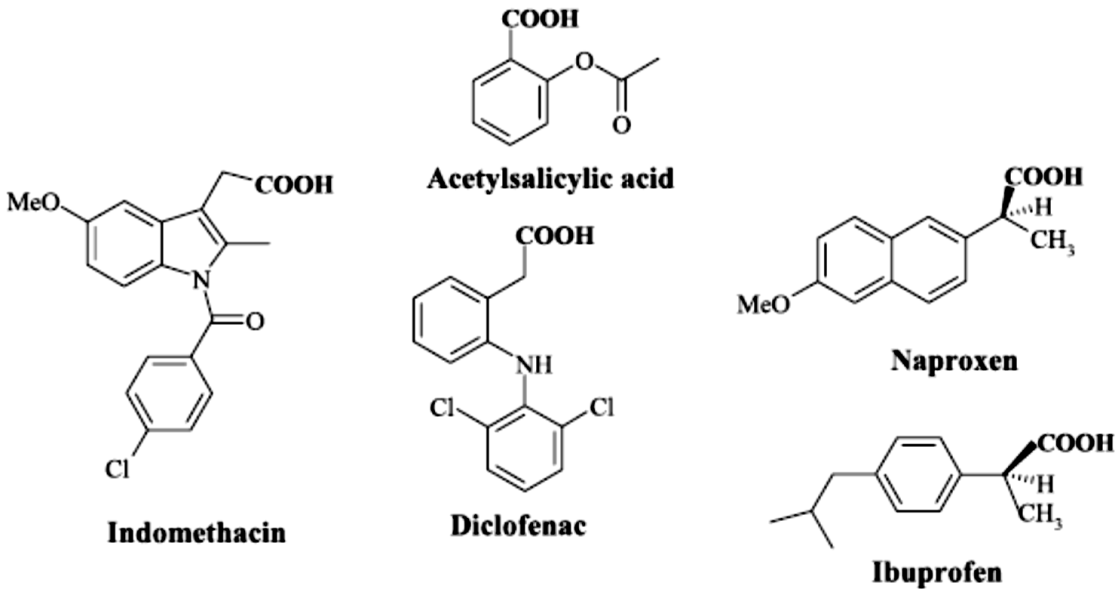


Figure (1-1): Some examples of classical NSAIDs

The mechanism of action principally responsible for most of the NSAIDs seems to act by inhibition of prostaglandin (PG) synthesis causing almost complete blockade of the activity of the precursor enzymes, cyclooxygenases which are the rate limiting enzymes for Prostaglandin synthesis [3&4].

The three isotypes of COX (COX-1, COX-2 and COX-3) have been identified [5]. COX-1 is constitutively expressed, widely distributed and has "housekeeping" function. It is of particular importance in maintaining gastric mucosal integrity, renal function and homeostasis [6]. COX-2 is highly induced in settings of inflammation by cytokines and inflammatory mediators or physiological stress [7].

The prostaglandins (PGs) produced by COX-2 play a major role in inflammatory reactions and are responsible for the characteristic inflammatory symptoms (redness, pain, edema, fever and loss of function). The inducible isozyme has also been implicated in pathological processes such as various cancer types (colorectal, breast), Alzheimer and Parkinson's diseases [8].

However, COX-2 also is constitutively expressed in certain areas of kidney, brain, reproductive tract, the vascular system, in wound healing, lung and bone [9].

There is no clear-cut division between biological function of COX-1 and COX-2. Experimental evidence indicates that a full inflammation response is likely sustained by prostanoids generated by both enzymes. In this sense, drugs inhibiting both enzymes are theoretically more effective in inflammatory disease treatment. Moreover, COX-2 selective inhibitors may theoretically lead to problem in thrombosis, salt and water balance and healing. With all these aspects considered, developing new drugs that preferentially inhibit COX-2 with moderate selectivity may be more promising [10].

1.2. Inflammation and Inflammatory Response:

The inflammatory response has different phases:

An acute phase: typically lasts 1–3 days and is characterized by the five classic clinical signs: heat, redness, swelling, pain, and loss of function. The acute response to tissue injury occurs in the microcirculation at the site of injury. Initially, there is a transient constriction of arterioles; however, within few minutes, chemical mediators released at the site of injury induced relaxation of arteriolar smooth muscle, leading to vasodilation and increased capillary permeability. Protein-rich fluid then exudes from capillaries into the interstitial space. This fluid contains many of the components of plasma including albumin, fibrinogen, kinins, complement, and immunoglobulins that mediate the inflammatory response [(11)].

A sub-acute phase: may last from 3–4 days to ~1 month, characterized by movement of phagocytic cells to the site of injury. In response to adhesion of phagocytic cell, molecules released from activated endothelial cells, leukocytes, platelets, and erythrocytes in injured vessels become sticky and adhere to the endothelial cell surfaces. If the cause of injury is eliminated, the sub-acute phase of inflammation may be followed by a period of tissue repair. Blood clots are removed by fibrinolysis, and damaged tissues are regenerated or replaced with fibroblasts, collagen, or endothelial cells.

A chronic proliferative phase: If the sub-acute phase is not resolved within ~1 month, then inflammation is said to become chronic and can last for several months, if inflammation becomes chronic further tissue destruction and / or fibrosis occurs [(12)].

1.3. Mode of Action of NSAIDs :

The principle therapeutic effect of NSAIDs derives from their ability to inhibit PG production. The first enzyme in the PG synthetic pathway is COX. This enzyme converts arachidonic acid AA to the unstable intermediates PGG_2 and PGH_2 and leads to the production of prostanoids, TXA_2, and variety of PGs as shown in Figure (1-2) [(13)]. These prostanoids have a variety of physiological functions and are also believed to be responsible for causing pain and swelling in inflammatory conditions [(14)].

NSAIDs vary in their selectivity for the COX-1 and COX-2 isoforms, and are categorized as either non-selective NSAIDs or selective COX-2 inhibitors (coxib). Non-selective NSAIDs generally block both COX-1and COX-2, whereas the coxib have higher selectivity for COX-2 isoform [(15)].

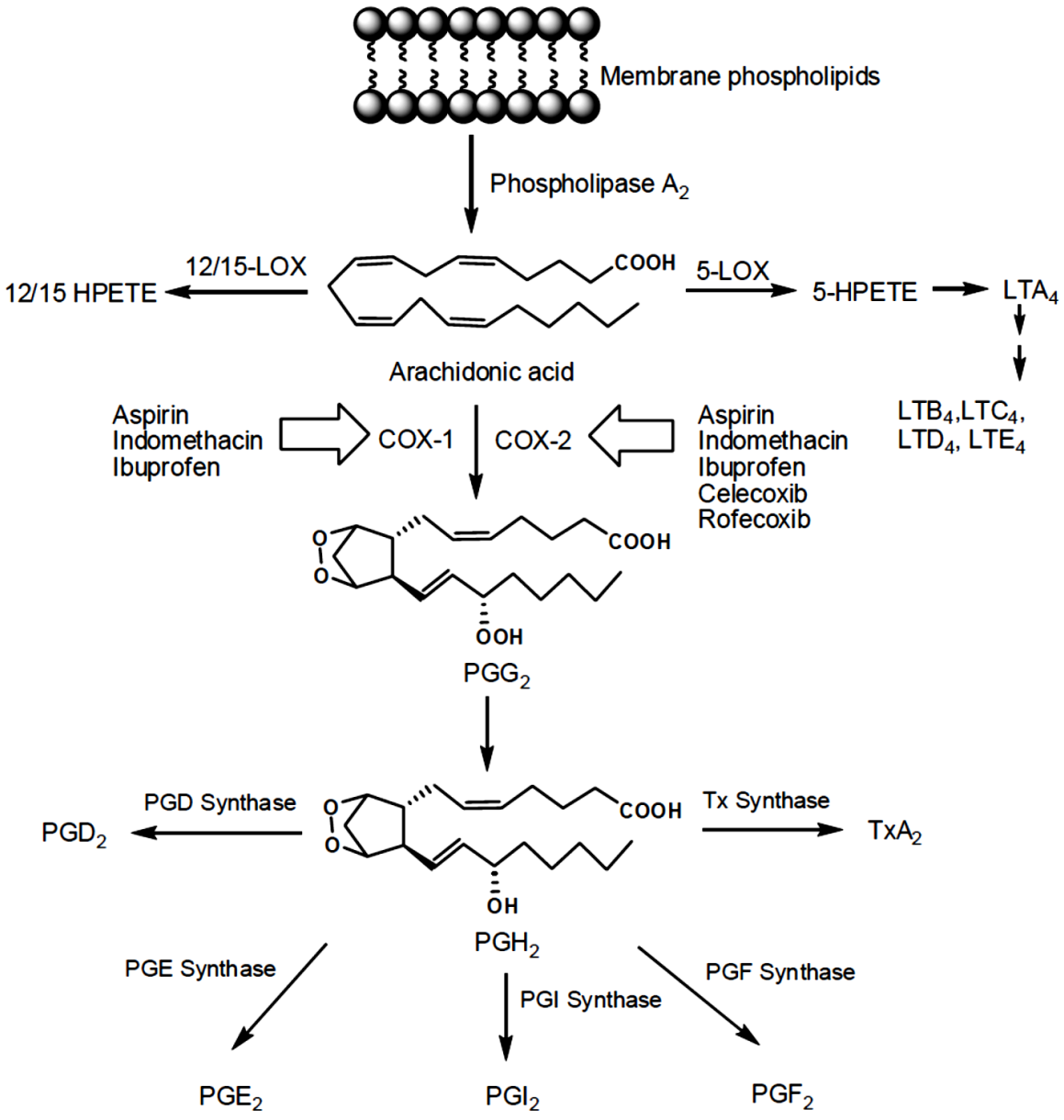


Figure (1-2): Representative biosynthetic pathway of prostaglandin (PG) biosynthesis from arachidonic acid (AA) via COX-1/COX-2 isoform catalysis

1.4. Therapeutic Action of NSAIDs:

NSAIDs have three major pharmacological desirable actions all of which result mainly from the inhibition of COX-2 in inflammatory cells and the resultant decrease in prostanoid synthesis; they are:

Anti-inflammatory effect: the decrease in vasodilator PGs (PGE2, prostacyclin) means less vasodilation and, indirectly, less edema [(16)].

Analgesic effect: decreased prostaglandin generation means less sensitization of nociceptive nerve endings to inflammatory mediators such as bradykinin and 5-hydroxytryptamine [(17)].

Antipyretic effect: NSAIDs exert their antipyretic effect by inhibition of prostaglandin E2 (PGE2) synthesis, which is responsible for triggering the hypothalamus to increase body temperature during inflammation [(18).]

Moreover Reports have shown the ability of many anti-inflammatory agents, especially the NSAIDs, to inhibit tumor growth. NSAIDs have also been reported to inhibit the migration of tumor cells as well as increase of the rate of apoptosis. Several studies have revealed a substantial decrease in the mortality from colorectal cancer in association with the use of aspirin and other NSAIDs [(19).]

1.5. Structural Properties of COX Enzyme Responsible for Substrate and Inhibitor Binding:

The primary structures of COX-1 and COX-2 from numerous species are known. Mature mammalian COX-1 and COX-2 contain 576 and 587 amino acids, respectively. They share a high degree of sequence identity (about 60-65%) [(20)].

COXs are heme-containing integral membrane proteins, located on the luminal surface of the endoplasmic reticulum and also, for COX-2 mainly, on the nuclear envelope. They both exist as homodimers, each monomer comprised of three folding units as shown in Figure (1-3) [(21)]: (1) an N-terminal epidermal growth factor (EGF)-like module; (2) an α-helical membrane-binding domain, which anchors the protein to one leaflet of the lipid bilayer (monotopic membrane attachment); and (3) a large C-terminal globular catalytic domain with the COX active site which accommodates the substrate or the inhibitors and the peroxidase one which contains the heme cofactor. These sites are distinct but functionally and structurally Interconnected [(22)].

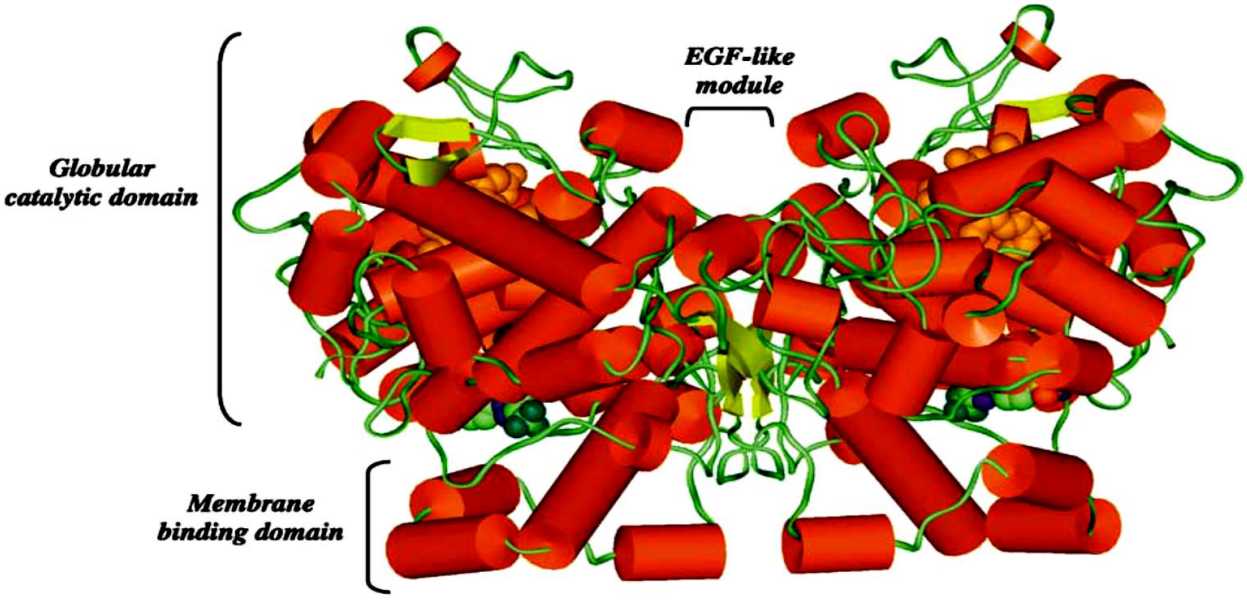


Figure (1-3): Structure of mouse COX-2 homodimer

The COX active site, quite similar in both isozymes, consists of a long narrow hydrophobic channel extending from the membrane-binding domain (the lobby) to the core of the catalytic one. The arachidonate-binding site is located in the upper half of the canal, from Arg-120 to near Tyr-385. Ser-530, positioned in the middle of the channel is the site of acetylation by aspirin [(23)].

Despite their similarity, the COX-2 active site is about 20% larger and has a slightly different form than that of COX-1as shown in Figure (1-4). These size and shape differences are caused mainly by two changes in the amino acid sequence.

1- Ile-523 in COX-1 is replaced by a valine in COX-2. This difference opens up a small hydrophilic side pocket off the main channel, appreciably increasing the volume of the COX-2 active site. Access to this nook is sterically denied in COX-1 by the longer side chain of Ile-523. In addition, the exchange of Ile-434 for a valine in COX-2 allows a neighboring residue Phe-518 to swing out of the way, increasing further access to the side cavity.

2-Within the side pocket of COX-2 is an arginine in place of His-513 in COX-1, which can interact with polar moieties.

These differences between the COX active sites have major implications for the selectivity profile of inhibitors [(24)].

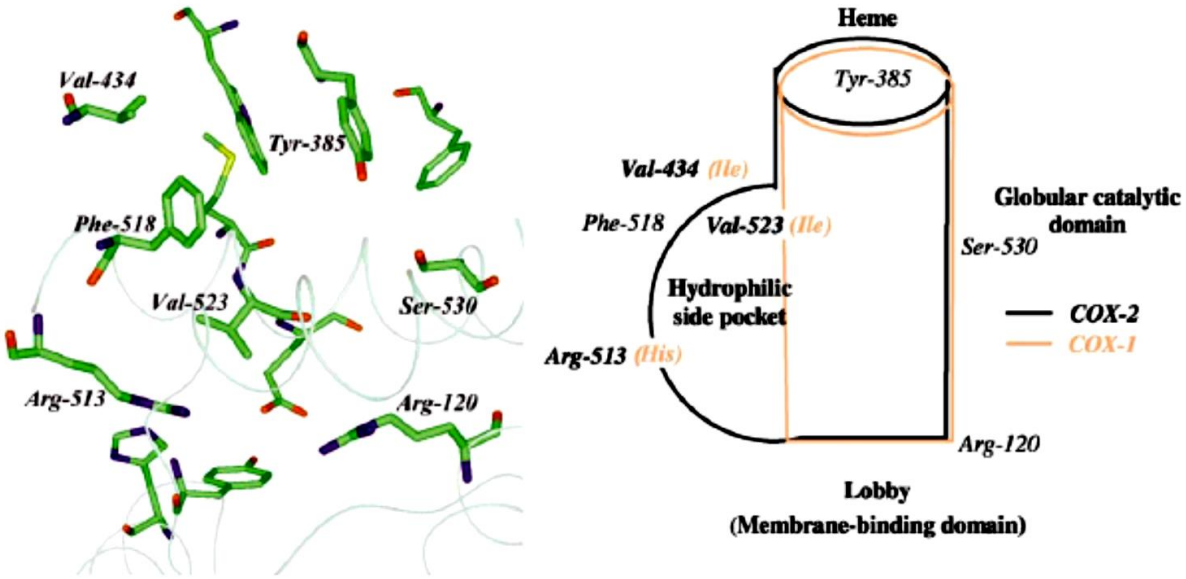


Figure (1-4): The COX-2 active site and its schematic representation

COX-3, which contributes about 5% of total COX-1, whose cyclooxygenase activity is about 80% lower than that of COX-1. This suggests that intron 1 retention may modify the conformation of the active site. Preferential expression of COX-3 in the brain and heart has been reported. The distinctive characteristic of COX-3 as compared to COX-1 and COX-2 is greater sensitivity to acetaminophen. Different studies have shown that acetaminophen has only weak inhibitory actions on both COX-1 and COX-2 when tested on *in-vitro* experimental systems. However, it is a potent, selective inhibitor of COX-3 and most likely produces analgesia by inhibiting this enzyme [(25)].

1.6. COX-1:COX-2 Selectivity:

The selectivity of NSAIDs is based on an IC_{50} value (the concentration at which an NSAID produces 50% inhibition of COX-1 and/or COX-2). A selectivity ratio is then calculated, namely COX-2 IC_{50} / COX-1 IC_{50} or *vice versa*, using the IC_{50} values for both of the COX enzymes [(26)].

The higher the IC_{50}, the more drugs necessary to inhibit the particular enzyme. Therefore, a COX-1: COX-2 ratio greater than 1 would indicate more drugs are necessary to inhibit COX-1 than COX-2 and that drug would selectively inhibit COX-2 and spare COX-1[(27)].

1.7. COX-2 Selective Inhibitors:

Traditional NSAIDs work by blocking both COX-1 and COX-2 enzymes. The COX-2 inhibitors work by blocking only the COX-2 enzyme. By blocking the COX-2 enzyme, these new drugs can help block pain and inflammation and still allow the COX-1 enzyme to work. This is important because COX-1 enzymes help protect the stomach lining, which decreases the chance of having a stomach ulcer and / or bleeding [(28)].

The two enzymes (COX-1&COX-2) share 60 percent homology in amino acid sequence. However, the conformation for the substrate-binding sites and catalytic regions are slightly different.COX-2 has a larger and more flexible substrate channel than COX-1 has, and COX-2 has a large space at the site where inhibitors bind as shown in Figure (1-5). These structural differences between COX-1 and COX-2 permitted the development of COX-2 selective inhibitors [(29)].

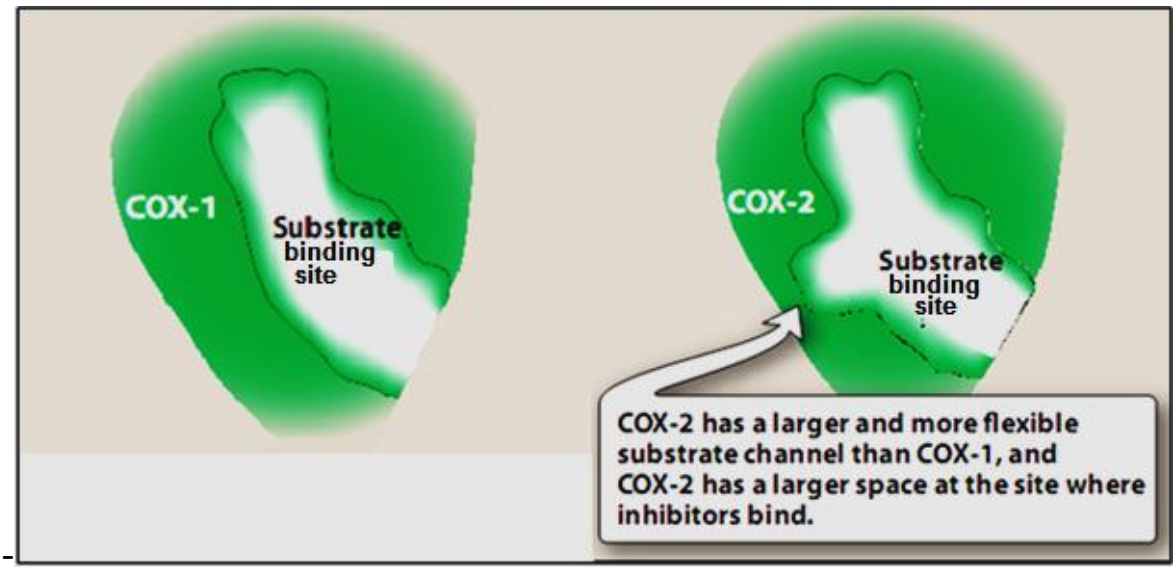


Figure (1-5): Difference between COX-1 and COX-2 in size of active center

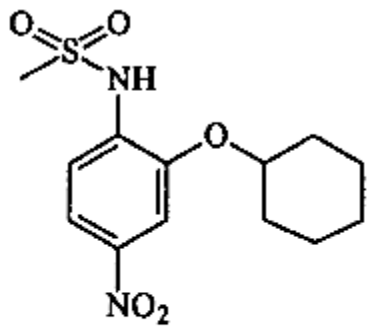
1.8. Chemical Classification of Selective COX-2 Inhibitors:

The identification and characterization of the COX-2 isoenzyme stimulated investigations to develop efficient non-steroidal anti-inflammatory drugs with reduced side effects compared to standard NSAIDs. This will focus on the structural features needed to achieve COX-2 selectivity. Numerous structural classes can be identified together with a class bearing little or no resemblance to one another in their molecular structure. The most interesting point is the very distinct structure/activity relationship. On the one hand only minor modifications to a particular compound induce a drastic change in its COX-2 selectivity and on the other hand the structural requirements in terms of molecular shape, lipophilicity, electron density, flexibility, polarity and H-bonding dynamics allow a wide range of diversity [(30)].

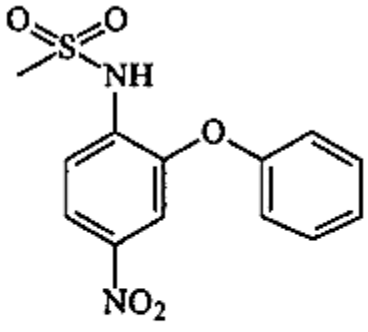
1.8.1. Diaryl- or Aryl-Heteroaryl Ether and Thioether Derivatives:

A selective COX-2 inhibitor at the beginning of this era was the compound NS-398 **(1)** with a completely different structure from classic NSAIDs. The compound showed inhibition of PG synthesis in inflammatory cells and was largely free of unwanted GI effects in animal models. Moreover, NS-398 did not affect PG production in the stomach or kidney [31].

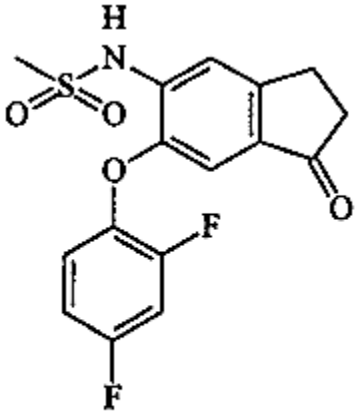
On recognizing that NS-398 was a preferential more or less selective inhibitor of COX-2, new interest in this class of anti-inflammatory agents evolved. Structurally, closely related to NS-398 there are two other compounds, nimesulide **(2)** and flosulide **(3)**, diaryl ether and thioether structure, respectively, which bear a methansulfonanilide moiety [32]. It appears that nimesulide was the first member of this class of drugs, its mechanism of action, pharmacology and clinical results in rheumatic diseases, osteoarthritis and acute inflammation demonstrated that nimesulide possesses novel anti-inflammatory qualities. Flosulide is similar to nimesulide; the main difference between them is the incorporation of the electron-withdrawing substituent into the five-membered carbocyclic ring [33].



(1)



(2)

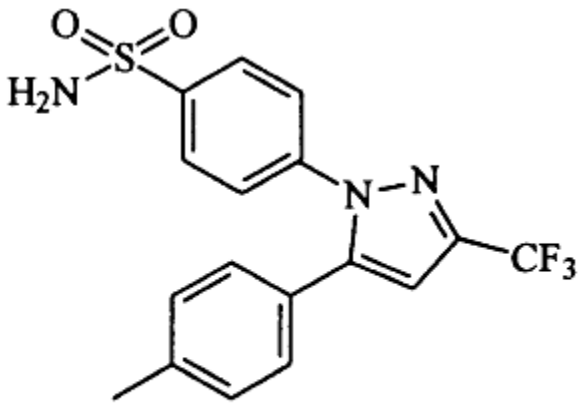


(3)

1.8.2. Carbocycles and Heterocycles with Vicinal Aryl Substitution:

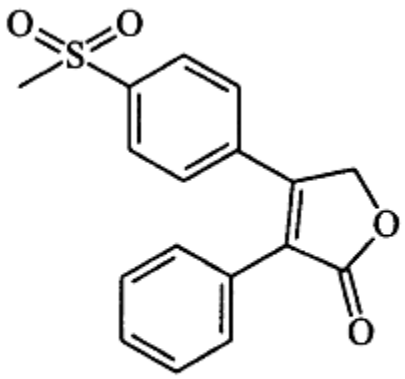
The greatest amount of research in the COX-2 area has been performed in the preparation and evaluation of this class of compounds. These compounds represent the most important group of COX-2 inhibitors. The compounds are characterized by a central carbocyclic or heterocyclic ring system bearing two vicinal aryl moieties. Wide variety of heterocycles can serve as a template for COX-2 inhibitor. For optimal activity, one aromatic ring must be substituted with a methylsulfonyl or a sulfonamide substituent in para position which is essential for COX-2 selectivity [(34)]. Replacement of the methylsulfonyl group by a sulfonamide group reduces COX-2 selectivity but improves oral bioavailability [(35)].

The pyrazole derivative, celecoxib **(4)** the first diarylheterocyclic selective COX-2 inhibitor approved for the treatment of osteoarthritis and rheumatoid arthritis [(36).]



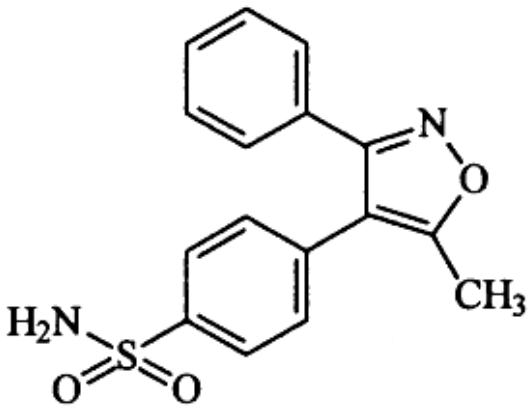
(4)

The furanone derivative rofecoxib **(5)** exhibited effective anti-inflammatory and analgesic activity with reduced GI toxicity and is a selective COX-2 inhibitor [37].



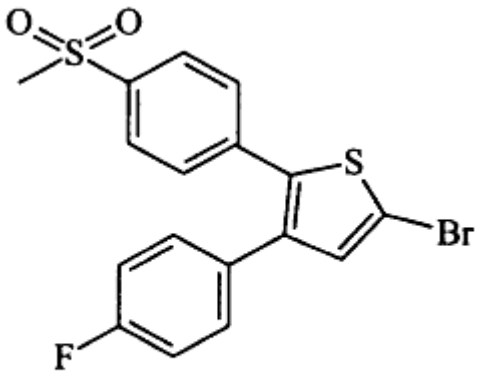
(5)

The isoxazole derivative, valdecoxib **(6)** a second generation COX-2 selective inhibitor with analgesic and anti-inflammatory properties [38]. It is effective as non-selective NSAIDs for treatment of rheumatoid arthritis with no effect on platelet aggregation or bleeding time, therefore caused an increased number of adverse cardiovascular events when used for pain management in coronary artery bypass surgery [39].



(6)

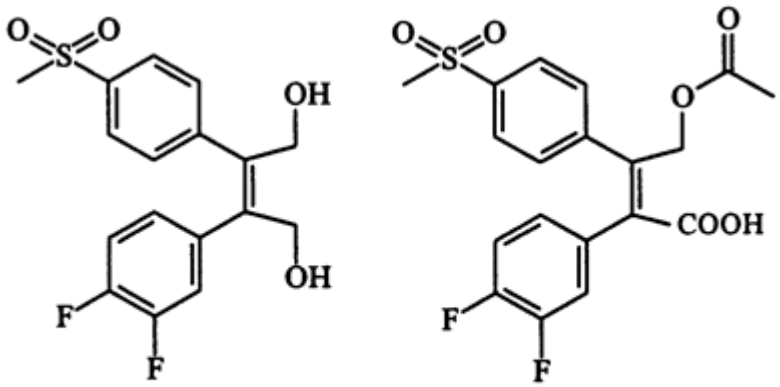
The substitution pattern on the heterocyclic ring is also important for the efficacy as demonstrated in the series of bromo-substituted thiophene derivatives as selective COX-2 inhibitors with the 5-bromothiophene derivative, Dup-697**(7)** being the most potent compound in acute and chronic anti-inflammatory *in vivo* models with high selectivity [40].



(7)

1.8.3. 1, 2 Diarylethylene Derivatives (Cis-Stilbene Derivatives):

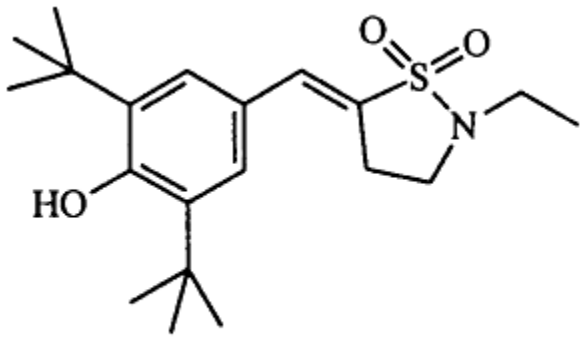
Reduction of the furanone ring led to active inhibitors with a ring open diol structure. Ring opening and elimination of the heteroatom led to *cis*-stilbene derivatives **(8)** which still contain the pre-requisites for COX-2 inhibition: vicinal orientation of two aromatic rings, substitution pattern at the aryl moiety as seen in potent COX-2 inhibitors, i.e. methylsulfonyl moiety in combination with a halogen. However, all derivatives are only in an early stage of development (biological testing) or pre-clinical study [41].



(8)

1.8.4. Compounds with an Antioxidative Moieties:

These compounds develop their mode of action by an antioxidative mechanism. Since COX enzyme catalysis involves radical intermediates, a radical scavenging moiety such as a di-*tert*-butylphenol interferes with the cyclooxygenase reaction. Linkage of phenolic substructure with a thiazole, oxazole derivatives produces non-ulcerogenic, orally active anti-inflammatory agents as a novel class of COX-2 inhibitors, like S-2474 **(9)**. However, according to patent applications this group of compounds is presently undergoing biological testing [(42&43)].



(9)

1.8.5. Aryl -Heteroaryl Ketones:

The ketone function link between an aryl ring and a heterocycle is extended known in the class of anti-inflammatory drugs, such as zomepirac **(10)**, the desired COX-2 selectivity was achieved by replacing the acetic acid group by other moieties such as an *N*-acyl aminosulfonyl phenyl group in RS-1048934 **(11)** or the pyridazinone ring in RS-57067**(12)**, as shown in Figure (1-6) [44].

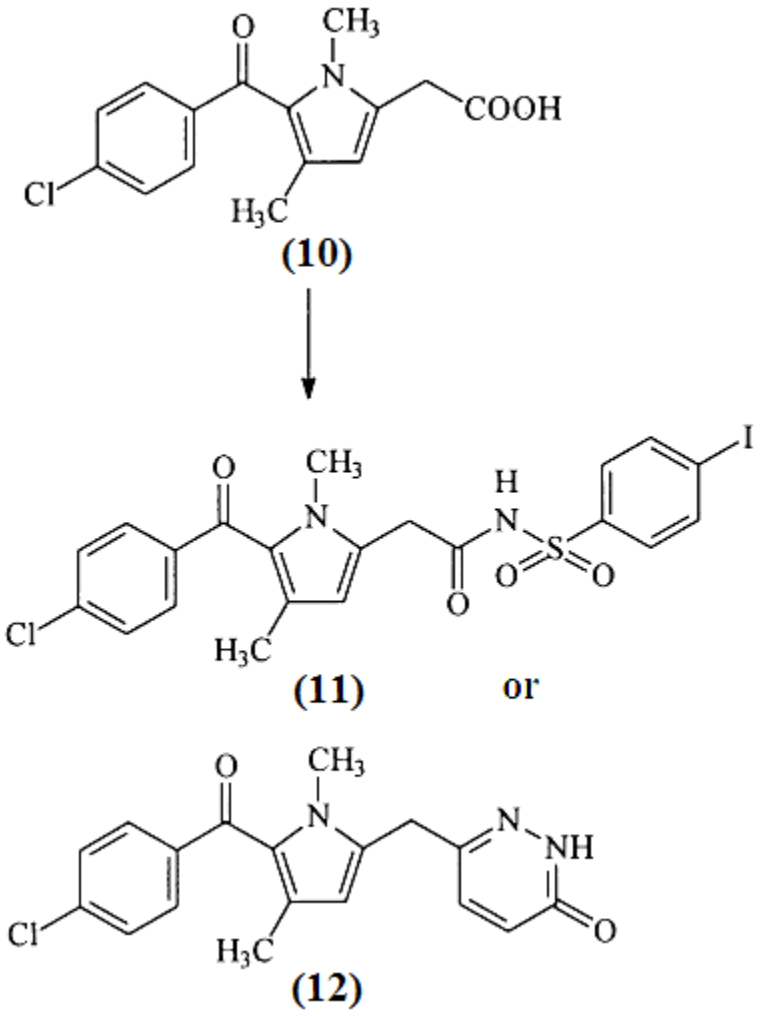
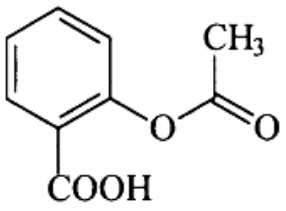


Figure (1-6): Conversion of zomepirac to COX-2 selective inhibitors

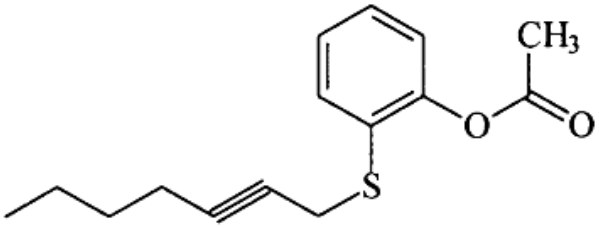
1.8.6. Modification of Known NSAIDs and Compounds without Common Structural Features:

Modifying well known NSAIDs into selective COX-2 inhibitors represents an interesting strategy. Indomethacin and aspirin have been successfully elaborated into selective COX-2 inhibitors [45].

Aspirin **(13)** is the only known NSAID that covalently binds to serine and more significantly inhibits COX-1 than COX-2. A lot of structural modifications have been made resulting in the development of APHS **(14)** [*O*-(acetoxyphenyl)-hept-2-ynyl sulfide] characterized by a 60 times more selective towards COX-2 than aspirin and its selective inhibition toward COX-2 was resulted from the acetylation of the same serine residue that aspirin acetylates indicating that APHS is the first selective covalent inhibitor of COX-2 [46].



(13)



(14)

Classic NSAIDs such as indomethacin **(15)** possess both COX-1 and COX-2 inhibiting activity. Various attempts have been made to shift the enzyme selectivity of indomethacin from COX-1 to COX-2 while keeping the potency on the same level and reducing the unwanted side-effects at the same time.

In principle, the strategy consisted of introducing a larger trichlorobenzoyl analogue instead of the chlorobenzoyl analogue to fit into the active site volume of COX-2 and optimized COX-2selectivity L-748780 **(16)** [47].

Altering the side chain by a beta-branched butyric acid and replacing the benzoyl group of indomethacin by a 4-bromo benzyl-substituent finally produced compound L-761066 **(17)** with a high potency and a remarkable COX-2 selectivity [48].

Transformation of the aryl acetic acid moiety of indomethacin to esters or amide **(18)** provides molecules capable of binding tightly to COX-2 but not COX-1. Moreover, it was shown that the 2-methyl group at the indole ring is essential for the potency as shown in Figure (1-7) [49].

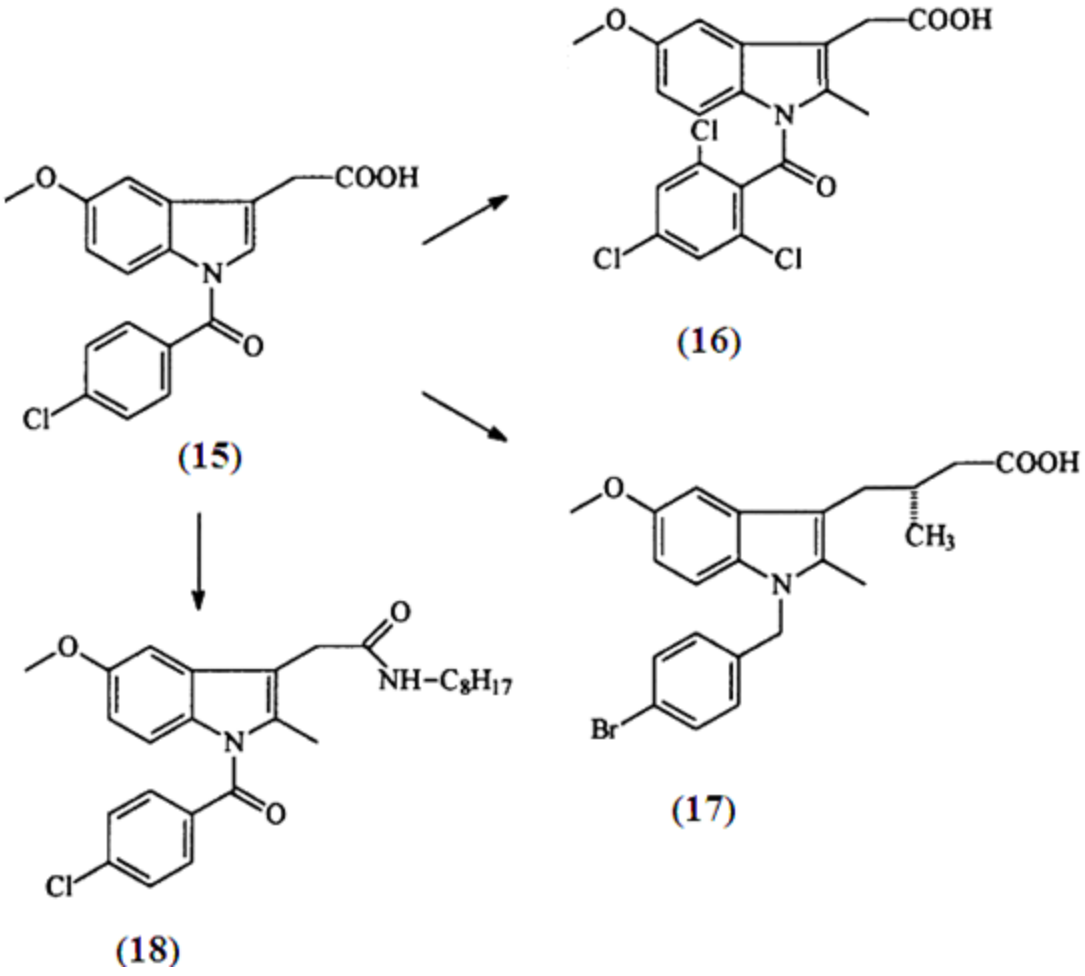
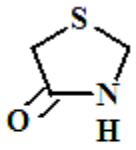


Figure (1-7): Conversion of indomethacin to selective COX-2 inhibitors.

1.9. Thiazolidinones:

There are numerous biologically active molecules which contain various heteroatoms such as nitrogen, sulphur and oxygen, always drawn the attention of chemist over the years mainly because of their biological importance. Thiazolidinones are thiazolidine derivatives and have an atom of sulfur at position 1, an atom of nitrogen at position 3 and a carbonyl group at position 2, 4, or 5 [(50)].

However, its derivatives belong to the most frequently studied moieties and its presence in penicillin was the first recognition of its occurrence in nature. The 4-thiazolidinone scaffold **(19)** is very versatile and has featured in a number of clinically used drugs. They have found uses as antibacterial [(51)], antitubercular [(52)], anti-inflammatory [(53)] and as antiviral agents, especially as anti-HIV agents [(54)].



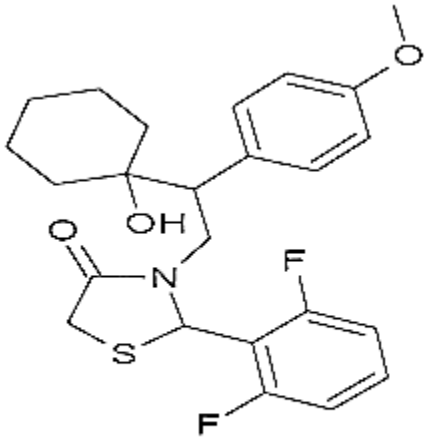
(19)

1.10. Biological Activities of 4-thiazolidinones:

The thiazolidinones ring has been incorporated into a broad range of known biologically active compounds, either as a substituent group or as a replacement of another ring inspired researchers to synthesize several compounds containing this moiety.

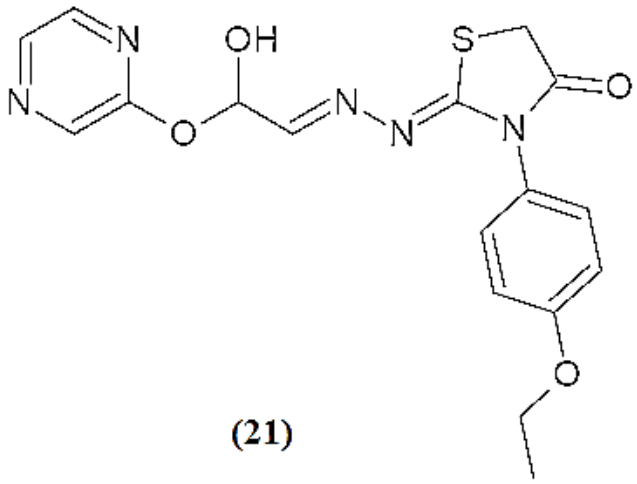
1.10.1. Antibacterial Activity:

Studies have shown that thiazolidinones were more active than thiazoles against some common bacteria. Kavitha reported more than 20 thiazolidinone derivatives were tested against *Bacillus subtilis* and *Escherichia coli*. He concluded that synthesized compounds exhibited powerful activity.This significant inhibitory activity can be attributed to fluorine atoms and has been observed in thiazolidinone derivatives with different positions **(20)** [55].



(20)

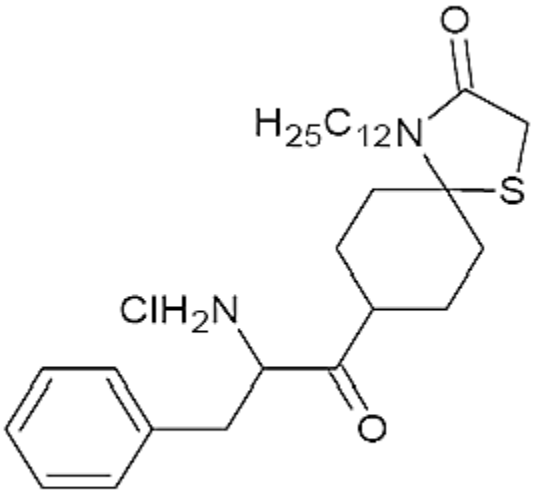
Several analogues of 4-thiazolidinones **(21)** were synthesized and employed for their antibacterial studies against different strains like *S. aureus, B. subtilis, S. typhi and E. coli* of bacteria and were found to have significant antibacterial activity. It was seen that the presence of thiazolidinone ring was essential for antibacterial activity [56].



(21)

1.10.2. Antifungal Activity:

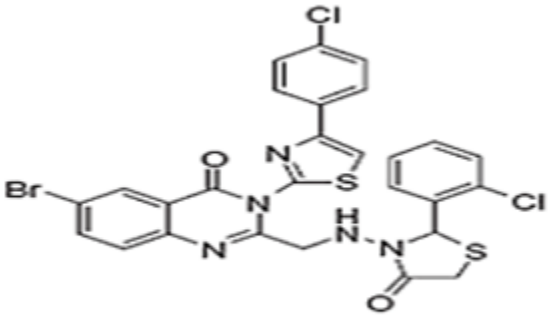
Compound **(22)** and its derivatives were prepared and screened by Katti *et al*. against two strains of *C. albicans* and one strain of *C. neoformans*, and found that the antifungal activity was of average to higher level against the various fungal strains [(57)].



(22)

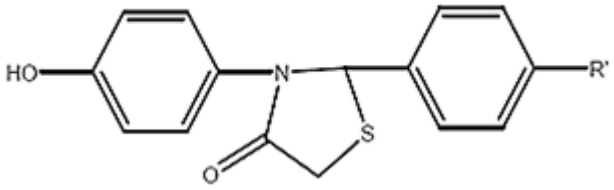
1.10.3. Anti-inflammatory and Analgesic Activity:

Arylalkanoic acids constitute the basis for the widely used nonsteroidal anti-inflammatory agents naproxen and ibuprofen; these drugs inhibit the COX enzymes, the mode of action of these drugs is correlated with unwanted side-effects such as gastrointestinal and renal toxicities, to overcome these side effects anti-inflammatory and analgesic activity of new series of quinazolinone derivatives having thiazolidinone at 2nd position was reported by Kumar *et al*. Interestingly compound **(23)** which was substituted with chloro group at 2nd position of phenyl ring, showed almost equal anti-inflammatory activity to that of phenylbutazone at 50 mg/kg [(58)].



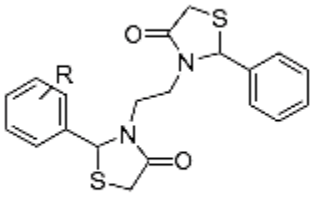
(23)

Taranalli AD *et al.* synthesized a series of thiazolidine-4-one derivatives from sulfanilamide and evaluated for anti-inflammatory, analgesic and anti-ulcer activity. The compound **(24)** and compound **(25)** with substitution R'-CH_3 showed potential activity [(59)].

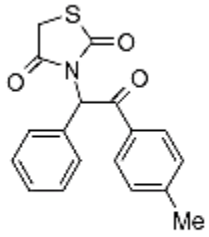


(24) R'= H
(25) R' = CH_3

Ottana et al. investigated compound **(26)**, a thiazolidinone derivative, which show interesting stereo selective anti-inflammatory/analgesic activities and suggested that these derivatives might preferentially interact with inducible COX-2 isoform [60]. Absence of 5-arylmethylidene moiety in compound **(27)** enhanced its anti-inflammatory activity and decreased the analgesic activity [61].



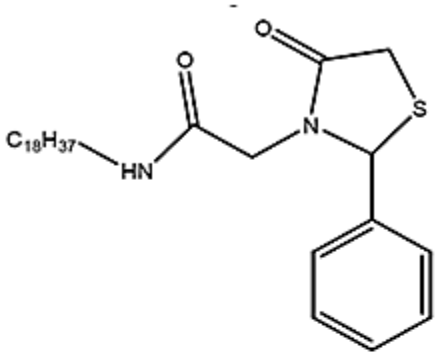
(26)



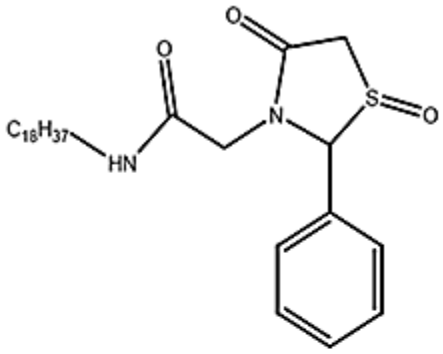
(27)

1.10.4. Anticancer Activity:

Gududuru *et al.* described the synthesis and biological evaluation of new 2-aryl-4-oxothiazoilidin- 3-yl amides against prostate cancer cells. Three potent compounds have been identified (2**8**, 2**9** and **30)**, which are effective in killing Prostate cancer cells with improved selectivity compared to serine amide phosphates (SAPs) [(62)].



(28)



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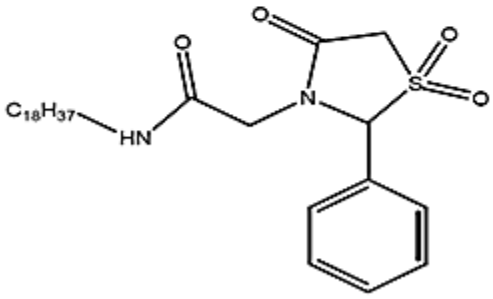
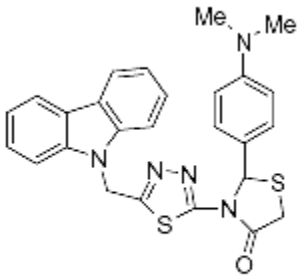


(30)

1.10.5. Anticonvulsant and Antidepressant Activity:

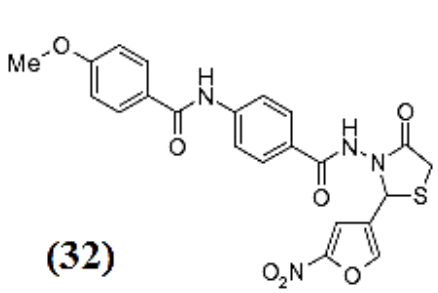
A number of substituted thiazolidinonyl carbazol derivatives are potent antipsychotic and anticonvulsant agent. Compounds having thiazolidinone ring demonstrated more potent antipsychotic as well as anticonvulsant activities as compared to compounds having azetidinone ring. Among these, compound **(31)** exhibited very good response against psychotic disorders by recording their responses towards amphetamine induced stereotyped, cataleptic behavior by Rota rod performance and MES test for anticonvulsant activity [(63)].



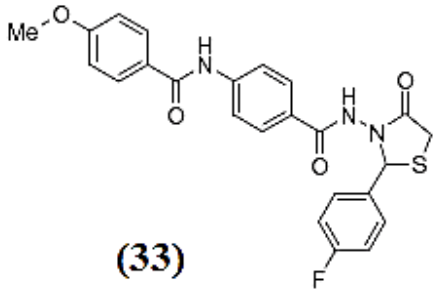
(31)

1.10.6. Antitubercular Activity:

Kucukguzel et al. reported antimycobacterial activity against Mycobacterium tuberculosis $H37_{Rv}$ of substituted 4-thiazolidinones and found that only compounds **(32)** and **(33)** showed 90 and 98% inhibitions at 6.25µg mL^{-1}, respectively [(64)].



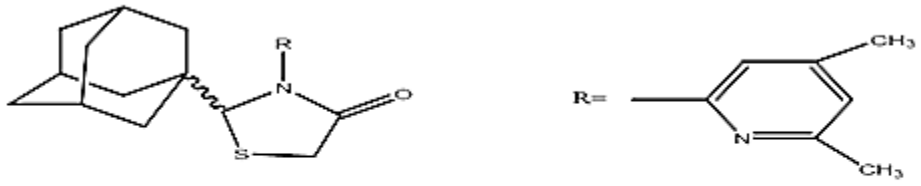
(32)



(33)

1.10.7. Antiviral Activity:

Jan Balzarini *et al*. synthesized a series of novel thiazolidin-4-ones bearing a lipophilic adamantyl substituent at position 2, and versatile substituents on the nitrogen atom of the thiazolidine ring were synthesized whereas several compounds exhibited a modest anti-HIV-1 activity, compound **(34)** was endowed with a remarkable antiviral potency [65].



(34)

1.11. Strategy of the Work:

The direction of the present work is to synthesize potential non-steroidal anti-inflammatory agents that are derivatives of some NSAIDs like (Naproxen) which is a well-known non-steroidal anti-inflammatory drug and the chemical structure has no additional functional groups that may undergo conversion to other intermediates throughout the overall reaction, so it will undergo straight line reaction.

These newly synthesized compounds may represent potent anti-inflammatory agents and exhibit expected selectivity towards COX-2 enzyme due to the fact that COX-2 has a larger and more flexible substrate channel than that in COX-1 and a larger space at the site where inhibitors bind as seen in Figure (1-9) [(66)].

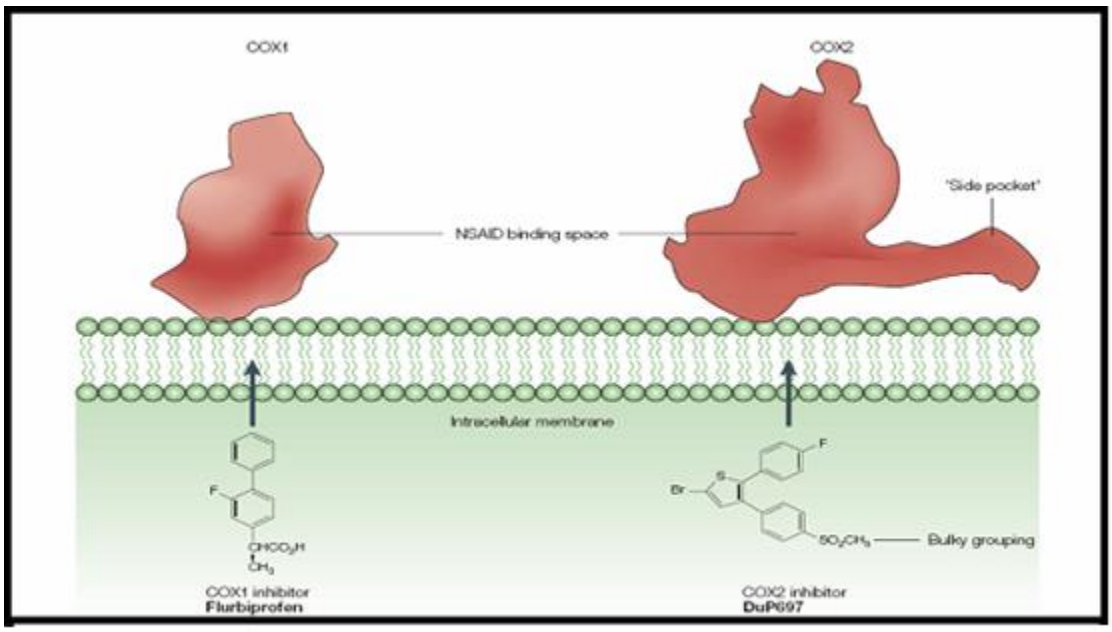


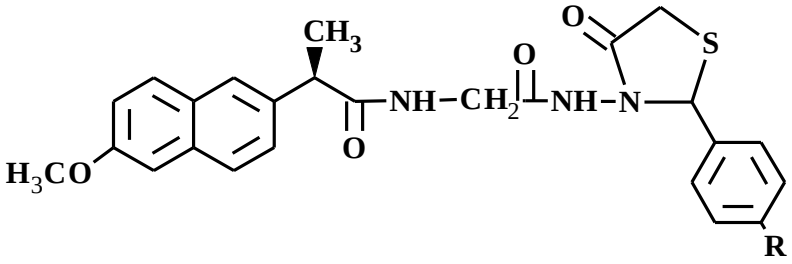
Figure (1-8): comparison of NSAIDs binding sites of COX-1 and COX-2

Preferential inhibition of COX-2 is due to the additional space in the COX-2 hydrophobic channel, as well as to the presence of a side pocket in the channel. Therefore, a group of 4-thiazolidinone derivatives incorporated in the carboxylate group of a (Naproxen) was synthesized and evaluated as anti-inflammatory agents with expected inhibitory selectivity towards COX-2 enzyme [(67)].

1.12. Aim of the Work:

The aim of this work is to synthesize and anti-inflammatory evaluation of 4-thiazolidinone derivatives of Naproxen with expected selectivity towards COX-2 enzyme.

The general structure of these compounds:



Compound No.	R
V_a	H
V_b	Cl
V_c	NO_2
V_d	OH
V_e	OCH_3
V_f	$N(CH_3)_2$

CHAPTER TWO

EXPERIMENTAL

Materials & Methods

2.1. Chemicals:

The specific chemicals used in this work are listed with their suppliers in Table (2-1).

Table (2-1): Chemicals with their Suppliers.

Materials	Company	Origin
Benzaldehyde	BDH	England
Dicyclohexylcarbodimide	Sigma-Aldrich	Germany
Glacial acetic acid	BDH	England
Glycine	Fluka	Switzerland
Hydrazine hydrate 90%	Fluka	Switzerland
(+)-(s)-Naproxen working standard	SDI	Iraq
p-Chlorobenzaldehyde	BDH	England
p-Dimethylaminobenzaldehyde	BDH	England
p-Hydroxybenzaldehyde	Himedia	India
p-Methoxybenzaldhyde	Himedia	India
p-Nitrobenzaldehyde	Himedia	India
Thioglycolic acid	Sigma-Aldrich	Germany
Thionyl chloride	BDH Chemicals Ltd.	England
Triethyl amine	Avochem	UK

All of the solvents and materials used were of analar type and used without further purification.

2.2. Equipment and Instruments:

The equipment and instruments that used in this work are listed in Table (2-2).

Table (2-2): Equipment and Instruments with their suppliers.

Equipment	Company	Country
Electrical melting point apparatus	Stuart	UK
Ultrasonic bath	SB25-12 DTDN	China
FT- IR spectrophotometer	SHIMADZU 8100s	Japan
^{1}H-NMR	SHIMADZU	Japan
C.H.N. analyzers	Euro-Vector EA3000 A	Italy

2.3. Methods of Characterization and Identification:

General methods for identification of the synthesized compounds include:

2.3.1. Thin Layer Chromatography:

Thin layer chromatography was run on TLC silica gel (60) $F_{254,}$ Merck (Germany), for checking the purity of the products as well as monitoring the progress of the reaction. Compounds were revealed upon irradiation with UV light.

Chromatograms were eluted by the following systems:

A: Methanol: Acetic acid: Ether: Benzene (02:18:60: 20) [68].

B: Chloroform: Methanol (85:15) [69].

2.3.2. Melting Point:

Electro thermal melting point apparatus and open capillary tubes were used to determine the melting points and are uncorrected.

2.3.3. Infrared Spectra:

Infrared spectra were recorded as KBr disc by using FT- IR spectrophotometer, in College of Pharmacy, AL-Mustansiriyah University.

2.3.4. ^{1}H-NMR:

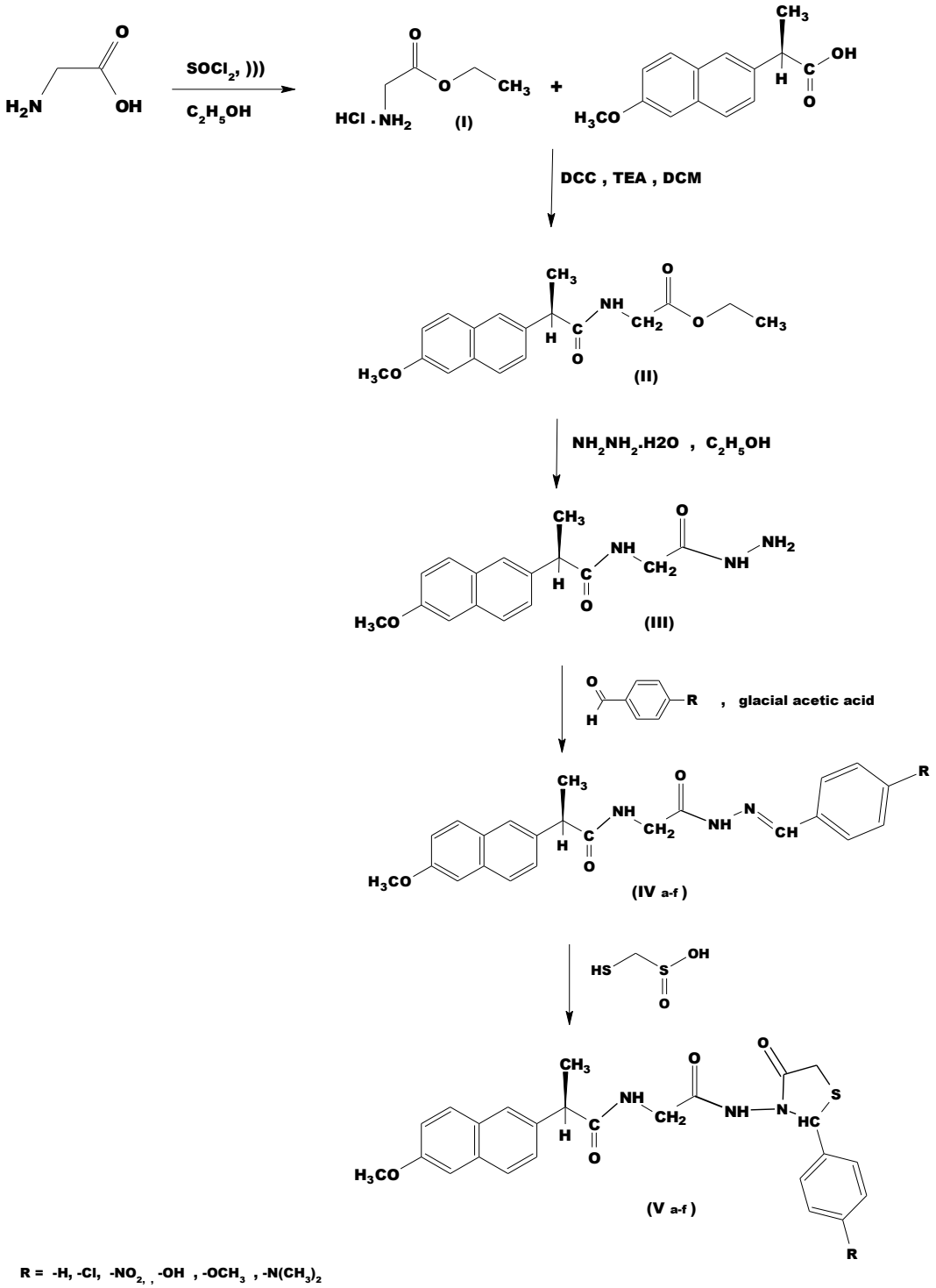
The ^{1}H-NMR spectra was performed at The University of Jordan, Faculty of Science, and Department of Chemistry. Instrument Model: Bruker 500 MHz-Avanc III.

2.3.5. Elemental Microanalysis (CHN):

The CHN analysis was done by using Euro-Vector EA3000 A in College of Science, AL-Mustansiriyah University.

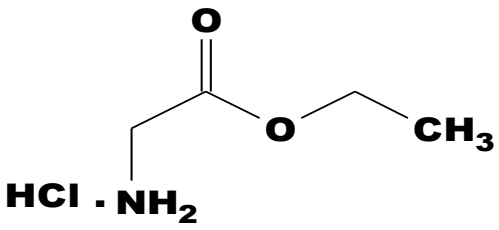
2.4. Chemical Synthesis:

The synthesis of intermediates and target compounds was achieved following procedures illustrated in Scheme (2-1).



Scheme (2-1): Synthesis of intermediates and target compounds

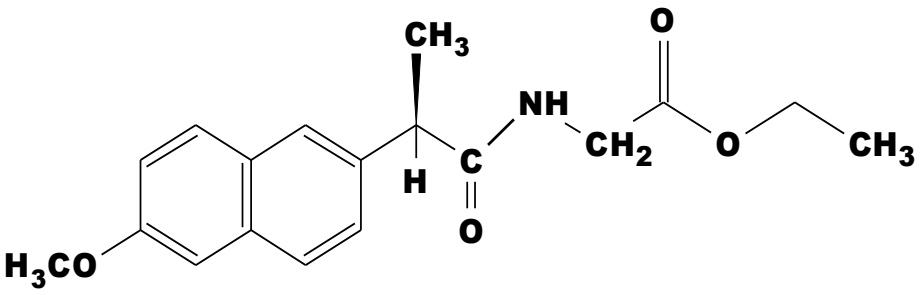
2.4.1. Synthesis of ethyl 2-aminoacetate hydrochloride (I):



(11mmol, 0.8mL) thionyl chloride was added gradually to absolute ethanol (10 mL) cooled to (0C°). 2-Aminoacetic acid (10 mmol, 0.75gm) was suspended in the reaction mixture and subjected to ultra-sonication at room temperature for (45 min.). On completion of the reaction, the solvent was removed under reduced pressure and the residue was purified by recrystallization from methanol: diethyl ether [70].

The percent yield, physical data and R_f values are given in Table (3-1).FT- IR spectrum for this compound is shown in Figure (3-3).

2.4.2. Synthesis of (s)-ethyl-2-[2-(6-methoxynaphthalen-2-yl)-propanamido] acetate (II):

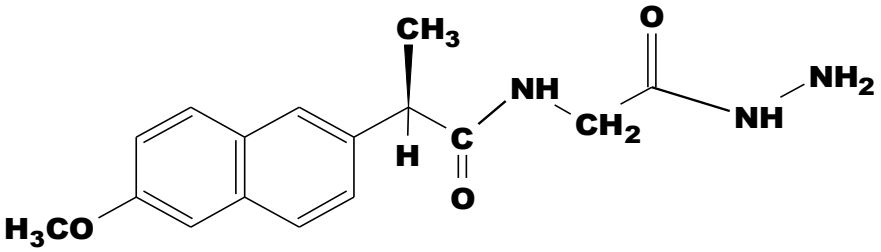


(20mmol, 2.8gm) compound (I), (21mmol, 3mL) triethylamine and (20mmol, 4.12gm) Naproxen were dissolved in dry DCM (40 mL). The reaction mixture was stirred at (0°C) for (30 min.).To this solution (20mmol, 4.8gm) DCC in dry DCM (10 mL) was added slowly in a drop wise manner.

Reaction mixture was stirred for 3 days at (0°C). Precipitated DCU was filtered off and the solvent was distilled off under reduced pressure. The product obtained was dissolved in ethyl acetate (30mL) and filtered. Ethyl acetate layer was washed with 10% aqueous solution of sodium bicarbonate (3x30mL) and distilled water (3x30mL). Ethyl acetate layer was dried over anhydrous magnesium sulphate and filtered to get a clear solution of product in ethyl acetate. Solvent was evaporated under reduced pressure and the crude product was recrystallized by using hexane: ethyl acetate [71].

The percent yield, physical data and R_f values are given in Table (3-1).FT- IR spectrum and ^{1}H-NMR spectra for this compound is shown in Figures (3-4 & 3-18).

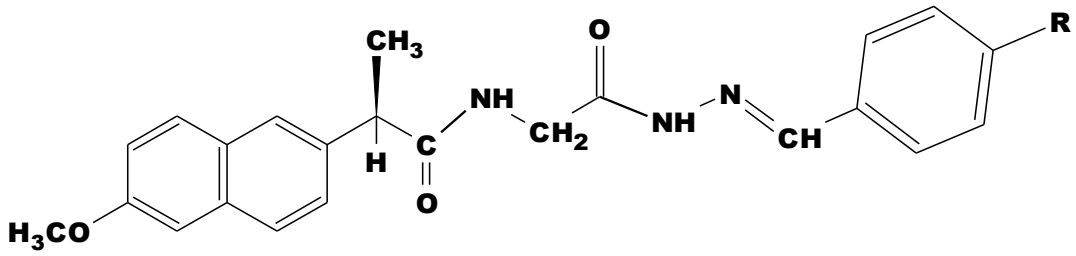
2.4.3. Synthesis of (*s*)-*N*-(2-hydrazinyl-2-oxoethyl)-2-(6-methoxy-naphthalen-2-yl) propanamide (III):



(3mmol, 1gm) compound (II) was dissolved in (15 mL) methanol and (14mmol, 0.7mL) of hydrazine hydrate (90%) was added. The reaction mixture was stirred at room temperature overnight. On the next day the solvent was removed under reduced pressure and the crude product was washed with ether under stirring to afford the product in pure state [72].

The percent yield, physical data and R_f values are given in Table (3-1).FT- IR spectrum and ^{1}H-NMR spectra for this compound is shown in Figures (3-5 & 3-19).

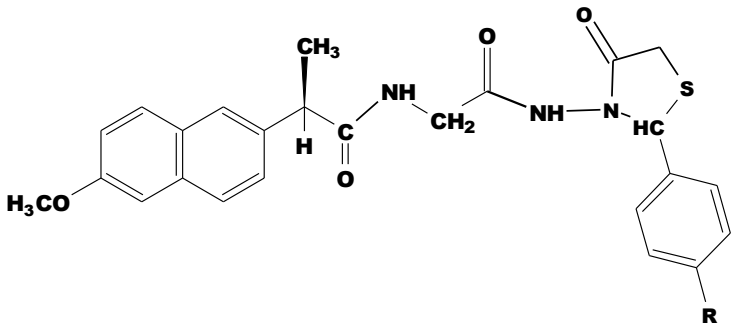
2.4.4. Synthesis of (s)-2-(6-methoxynaphthalen-2-yl)-N-(2-(2-(4-benzylidene) hydrazinyl)-2-oxoethyl) propanamide (IV_{a-f}):



(1mmol, 0.3gm) compound (III) and (1.1mmol) appropriate aromatic aldehydes in absolute ethanol (25mL) were heated under reflux on a water bath for (4hrs.), during the refluxing period (2-3) drops of glacial acetic acid were added. The solvent was distilled off under reduced pressure to a possible extent and residue was poured into ice cooled water to get the product. It was filtered, washed with cold water and dried. The crude product was purified by recrystallization from ethanol [73].

The percent yield, physical data and R_f values are given in Table (3-1).FT- IR spectrums for these compounds are shown in Figures (3-6 to 3-11) and ^{1}H-NMR spectra for the compound IV_a is shown in Figure (3-20).

2.4.5. Synthesis of (s)-2-(6-methoxynaphthalen-2-yl)-N-(2-((2-(4-aryl)-4-oxothiazolidin-3-yl) amino)-2-oxoethyl) propanamide (V_{a-f}):



A mixture of (3mL) thioglycolic acid and (1mmol) of either compound (IV_{a-f}) were heated at (60°C) until reaction was complete about (3hrs.). Ethyl acetate (5mL) was added to the reaction mixture; the organic layer was washed with saturated sodium bicarbonate (3x20mL) and water (10mL), dried with anhydrous magnesium sulfate, and concentrated to give an oil. The oil washed with ether to give the final compounds [74].

The percent yield, physical data and R_f values are given in Table (3-1).FT- IR spectrums for these compounds are shown in Figures (3-12 to 3-17) and ^{1}H-NMR spectra for these compounds are shown in Figures (3-21 to 3-26).

Table (2-3): Names of the synthesized compounds.

Compounds No.	R	Names of the synthesized compounds
I	-	ethyl 2-aminoacetate hydrochloride
II	-	(s)-ethyl-2-[2-(6-methoxynaphthalen-2-yl)-propanamido] acetate
III	-	(s)-N-(2-hydrazinyl-2-oxoethyl)-2-(6-methoxy naphthalene -2-yl) propanamide)
IV_a	H	(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-(2-(4-benzylidene) hydrazinyl)-2-oxoethyl) propanamide

IV_b	Cl	(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-(2-(4-chloro benzylidene) hydrazinyl)-2-oxoethyl)propanamide
IV_c	NO_2	(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-(2-(4-nitro benzylidene)hydrazinyl)-2-oxoethyl) propanamide
IV_d	OH	(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-(2-(4-hydroxy benzylidene)hydrazinyl)-2-oxoethyl)propanamide
IV_e	OCH_3	(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-(2-(4-methoxy benzylidene)hydrazinyl)-2-oxoethyl) propanamide
IV_f	$N(CH_3)_2$	(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-(2-(4-dimethyl aminobenzylidene)hydrazinyl)-2-oxoethyl)propanamide
V_a	H	(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-((2-(4-phenyl)-4-oxothiazolidin-3-yl)amino)-2-oxoethyl)propanamide
V_b	Cl	(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-((2-(4-chloro phenyl)-4-oxothiazolidin-3-yl)amino)-2-oxoethyl) propanamide
V_c	NO_2	(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-((2-(4-nitro phenyl)-4-oxothiazolidin-3-yl)amino)-2-oxoethyl) propanamide
V_d	OH	(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-((2-(4-hydroxy phenyl)-4-oxothiazolidin-3-yl)amino)-2-oxoethyl) propanamide
V_e	OCH_3	(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-((2-(4-methoxy phenyl)-4-oxothiazolidin-3-yl)amino)-2-oxoethyl) propanamide
V_f	$N(CH_3)_2$	(s)-2-(6-methoxynaphthalen-2-yl)-N-(2-((2-(4-dimethyl aminophenyl)-4-oxothiazolidin-3-yl)amino)-2-oxoethyl) propanamide

2.5. Preliminary Pharmacological Studies:

2.5.1. Anti-inflammatory Evaluation Study:

In vivo anti-inflammatory effects of the synthesized compounds (V_{a-f}) were evaluated by using egg-white induced paw edema model [75]. Their evaluation for their ant-inflammatory activity based on measuring the decreases of paw thickness.

2.5.1.1. Methods:

A. Animals:

Albino rats of either sex weighing (170 ± 10 gm) were supplied by Iraqi center for cancer and medical genetic research and were housed in college of pharmacy-AL-Mustansiriyah University under standardized conditions for 10 days for acclimatization. Animals were fed commercial chaw and had free access to water ad *libitum*. Animals were brought to the laboratory, one hour before the experiment, and were divided into eight groups (each group consist of 6 rats) as follows:

Group A: six rats served as control and treated with the vehicle (propylene glycol 50% v/v).

Group B: six rats treated with (s)-Naproxen as reference substance in a dose of 50mg/kg dissolved in Propylene glycol [76].

Group C-H: six rats /group treated with the tested compounds (V_{a-f}) respectively in dose that determined below, also dissolved in propylene glycol.

B. Calculations for Dose Determination:

M.Wt. of (s)-Naproxen = 230.26

50mg / kg / 230.26 = Dose / M.Wt. of the tested compound [77].

Table (2-4): Compounds with their molecular weight and dose:

Compounds	Molecular Weight	Dose mg/ kg
(s)-Naproxen	230	50
V_a	463	101
V_b	498	108
V_c	508	110
V_d	479	104
V_e	493	107
V_f	506	110

C. Experimental Design:

The anti-inflammatory activity of the tested compounds was studied using the egg-white induced edema model. The paw thickness was measured by vernea at seven time intervals (0, 30, 60, 120, 180, 240, and 300 min) after drug administration. Acute inflammation was produced by a subcutaneous injection of (0.05 ml) of undiluted egg-white into the plantar side of the left hind paw of the rats; 30 min after intra-peritoneal administration of the drugs or their vehicle [78].

2.5.1.2. Statistical Analysis:

The data was expressed as the mean ± SEM and results were analyzed for statistical significance using student *t*-test (Two Sample Assuming Equal Variances) for comparison between mean values. While comparisons between different groups were made using ANOVA: Two factors without replication. Probability (P) value of less than 0.05 was considered significant.

CHAPTER THREE

RESULTS & DISCUSSION

Results & Discussion

The synthesis of the target compounds (V_{a-f}) through their intermediates will be discussed as well as the results of their characterization, identification and evaluation as anti-inflammatory agents.

3.1. Synthetic Studies:

The synthetic procedures for the intermediates and target compounds (V_{a-f}) are illustrated in Scheme (2-1). The characterization and purity of these compounds and their intermediates (percent yields, melting points and R_f values) were given in Table (3-1).

The functional groups of the synthesized compounds were identified using FT-IR spectroscopy, as shown in Figures (3-3 to 3-17). The chemical structures were confirmed using ^{1}H-NMR spectroscopy as shown in Figures (3-18 to 3-26).

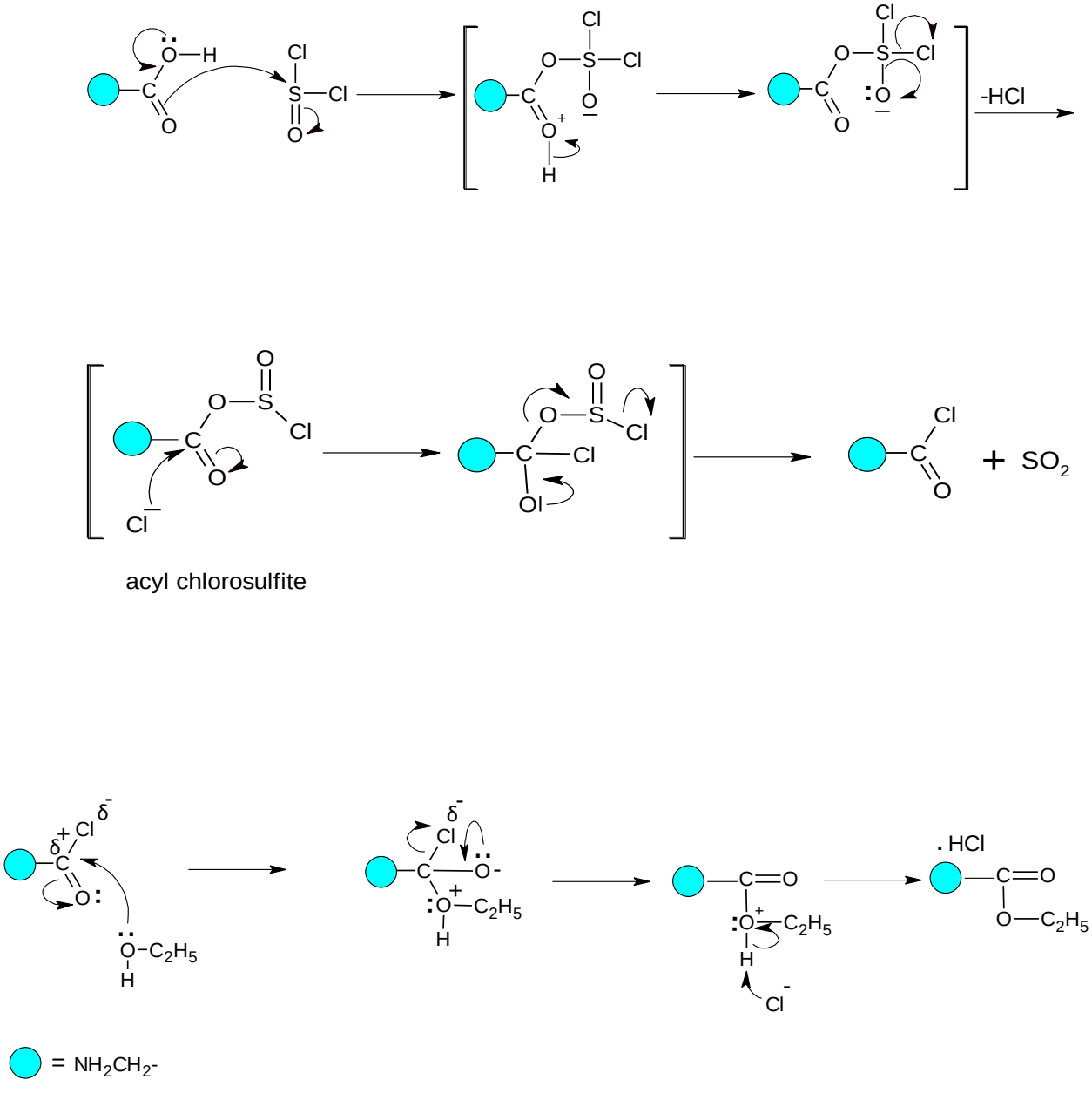
3.1.1. Synthesis of Amino Acid Ester Hydrochloride (I):

The standard procedure for the synthesis of amino acid esters involves the refluxing of a reaction mixture of an amino acid and ethanol for about 2-4 hr. or stirring of a mixture for over (24hr.) at room temperature. In the present study, the esterification reactions have been carried out in an ultrasonic bath at ambient temperature. It has been demonstrated that the esterification can be significantly accelerated by the use of ultrasound [(70)].

The mechanism of esterification of amino acid with thionyl chloride in the presence of alcohol first takes place by S_N2 mechanism. The reaction occurs by nucleophilic acyl substitution pathway in which the carboxylic acid is converted into a chlorosulfite (-OSOCl) intermediate, thereby replacing the (-OH) of the acid with a much better leaving group. The chlorosulfite then react with a nucleophilic chloride ion to produce the acyl chloride of the amino acid.

Second the acyl chloride undergoes addition of hydroxyl group of alcohol at the carbonyl group followed by elimination of chloride ion to form an ester of amino acid (c-protected amino acid) as shown in Scheme (3-1) [79&80].

The structure of compound (I) was identified by melting point and R_f values given in Table (3-1) as well as the appearance of the FT-IR characteristic absorption bands of $\upsilon_{C=O}$ stretching of ester at 1748cm^{-1}, υ_{C-O-C} stretching of ester at 1250cm^{-1} as in Table (3-2).



Scheme (3-1): Mechanism of amino acid ester hydrochloride synthesis

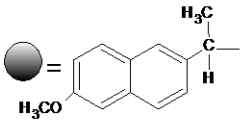
3.1.2. Synthesis of Compound (II); Formation of Amide Bond:

Treatment of carboxylic acid of (Naproxen) and c-protected amino acid with DCC leads directly to amide formation. Mechanism below in Scheme (3-2) shows how DCC promotes the condensation of an amine and the carboxylic acid to give an amide [81].

The structure of compound (II) was identified by melting point and R_f values given in Table (3-1) as well as the appearance of the FT-IR characteristic absorption bands of υ_{NH} stretching of amid at 3293cm^{-1} and $\upsilon_{C=O}$ stretching of ester and amide at 1740cm^{-1} and 1649cm^{-1} respectively as in Table (3-2) and ^{1}H-NMR spectra showed broad singlet for NH amide proton at 8.40 (δ,ppm) as in Table (3-3).

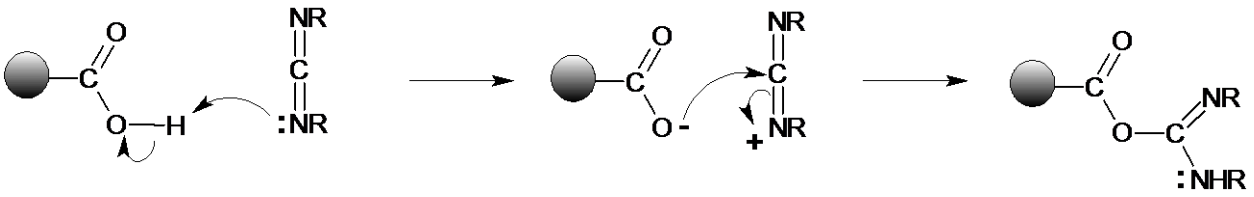
Overall reaction:

Carboxylic acid Amino acid ester DCC Amide *N,N'*-Dicyclohexylurea



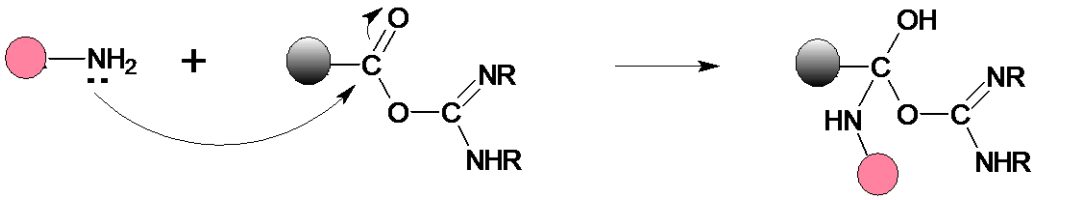
= $CH_3CH_2OC(O)CH_2$- DCC = *N,N'*-dicyclohexylcarbodiimide R = cyclohexyl

Step 1: In the first stage of the reaction, the carboxylic acid adds to one of the double bonds of DCC to give an *o*-acylisourea.



o- Acylisourea

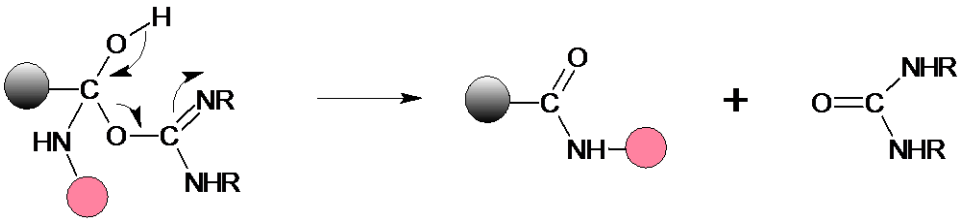
Step 2: structurally, *o*-acylisoureas resemble carboxylic acid anhydride and are powerful acylating agents. In the reaction's second stage the amine adds to the carbonyl group of the *o*-acylisourea to give a tetrahedral intermediate.



Tetrahedral intermediate

Step 3: Thetetrahedral intermediate dissociates to an amide and

N,*N*' -dicyclohexylurea.



N,*N*' -Dicyclohexylurea

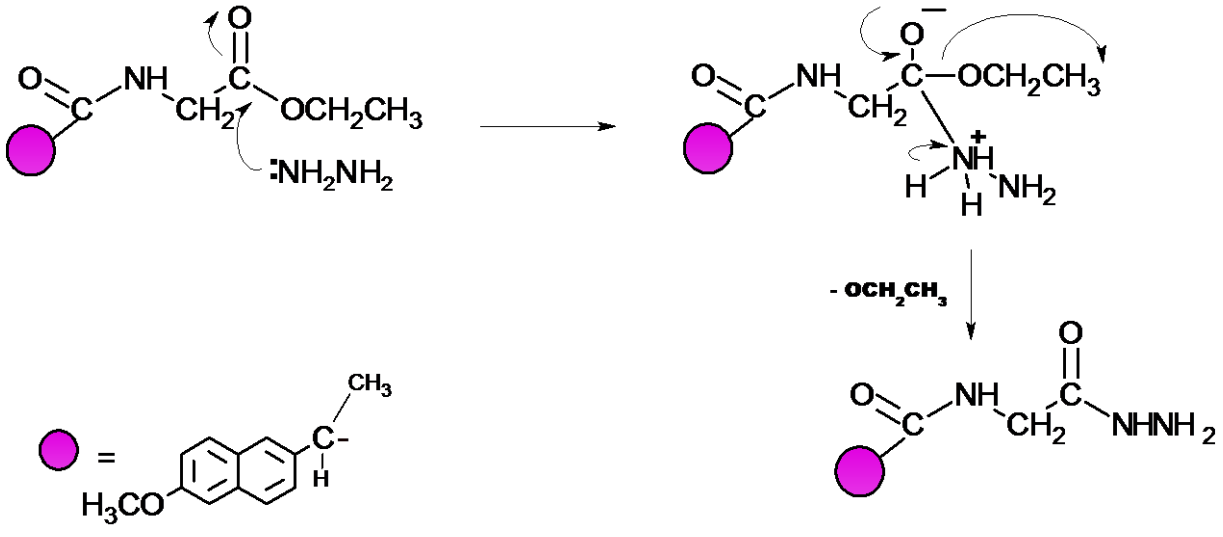
Scheme (3-2): Mechanism of amide synthesis

3.1.3. Synthesis of Compound (III); Formation of Hydrazide:

Compound (III) was synthesized by the reaction of compound (II) with hydrazine hydrate (90%) in absolute methanol.

The reaction of hydrazine hydrate with ester is one of the most common reactions to synthesize the acid hydrazide; it is a tetrahedral nucleophilic substitution reaction. The mechanism of this reaction outlined as follow in Scheme (3-3) [82].

The structure of compound (III) was identified by melting point and R_f values given in Table (3-1) as well as the appearance of the FT-IR characteristic absorption bands of υ_{NHNH2} stretching at 3339 and 3277cm^{-1} and $\upsilon_{C=O}$ stretching of amidic and amide at 1678cm^{-1} and 1645cm^{-1} respectively as in Table (3-2) and ^{1}H-NMR spectra showed broad singlet for NH_2 protons of hydrazide at 4.20(δ,ppm), broad singlet for NH amide proton at 8.20(δ,ppm) and singlet for NH proton of hydrazide at 9.01(δ,ppm) as in Table (3-4).

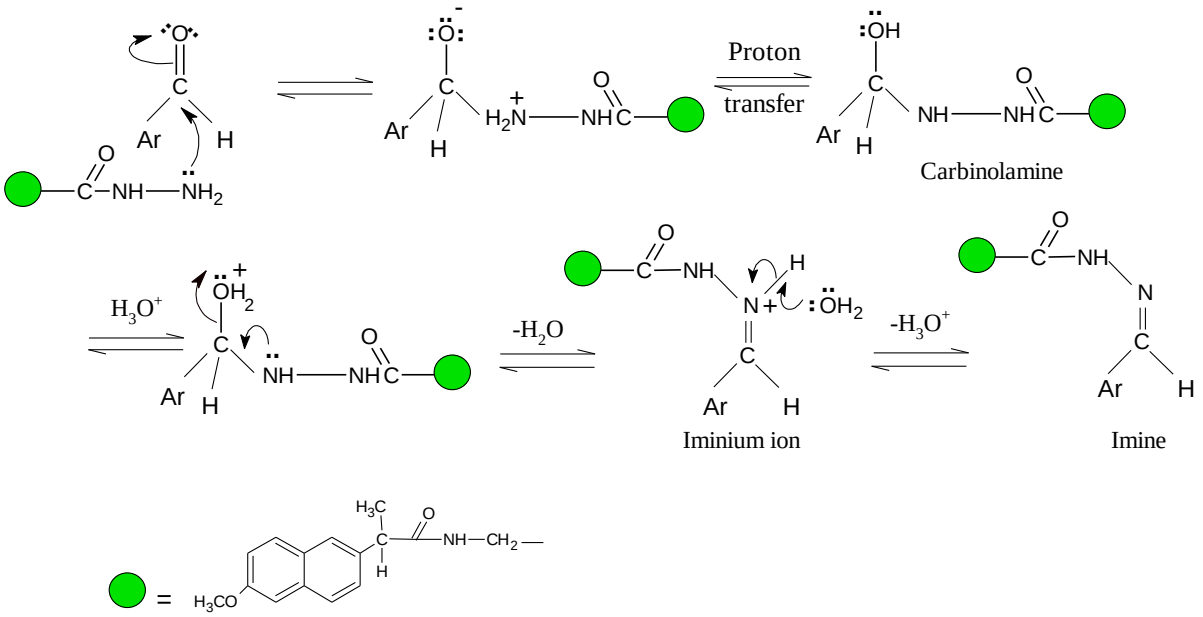


Scheme (3-3): Mechanism of hydrazide synthesis

3.1.4. Synthesis of Compounds (IV_{a-f}); Formation of Schiff base:

The reaction of aromatic aldehyde with acid hydrazide is the most common reactions to synthesize hydrazone compound (Schiff base or imine). Imines are formed in a reversible, acid catalyzed process that begins with nucleophilic addition of the primary amine to the carbonyl group, followed by the transfer of a proton from nitrogen to oxygen to yield a neutral amino alcohol, or carbinolamine. Protonation of the carbinolamine oxygen by an acid catalyst then converts the –OH into a better leaving group (-OH_2), and loss of water produces an iminium ion. Loss of a proton from nitrogen gives the final product and regenerates the acid catalyst as shown in Scheme (3-4) [(83)].

The structure of compound (IV_{a-f}) was identified by melting point and R_f values given in Table (3-1) as well as the appearance of the FT-IR characteristic absorption bands of υ_{NH} stretching of amide at 3319-3271 cm^{-1}, $\upsilon_{C=O}$ stretching of amidic at 1690-1680 cm^{-1} and combination band of $\upsilon_{C=O}$ stretching of amide and $\upsilon_{C=N}$ stretching at 1656-1643cm^{-1} as in Table (3-2) and ^{1}H-NMR spectra of compound (IV_a) showed singlet for N=CH-Ar proton at 8.20 (δ,ppm), singlet for NH-N proton at 8.36(δ,ppm) and broad singlet for NH amide proton at 11.41(δ,ppm) as in Table (3-5).



Scheme (3-4): Mechanism of Schiff base synthesis

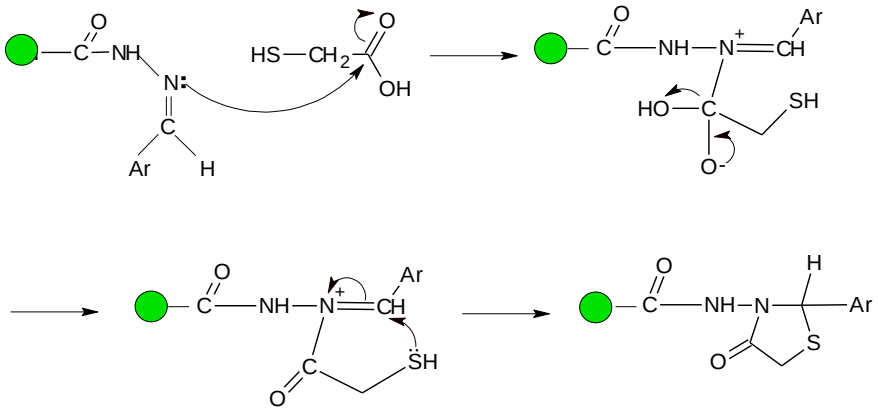
3.1.5. Synthesis of compounds (V_{a-f}); formation of 4-thiazolidinone:

The final compounds (V_{a-f}) were obtained by stirring excess of thioglycolic acid and either of the compounds (IV_{a-f}) without used any solvent [84].

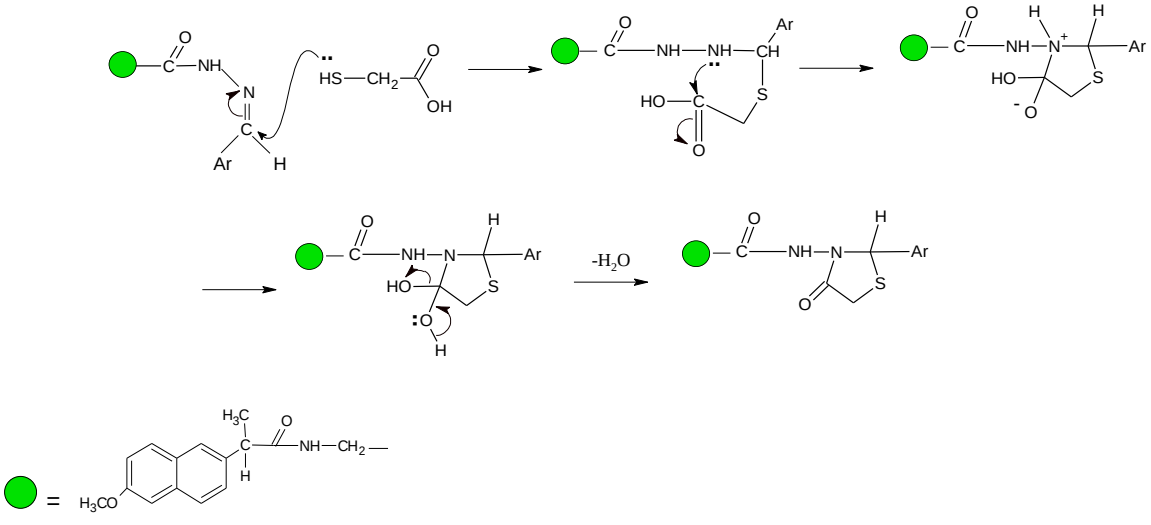
Two suggested mechanisms for the formation of final compounds were proposed as follow in Scheme (3-5) [85] and Scheme (3-6) [86].

The mechanism in Scheme (3-5) was more probable for the formation of the final compounds sine the carbon of carbonyl more electrophilic than carbon of imine, so unshared pair of electron of nitrogen atom will attack carbon atom of carbonyl faster than the probability of attack of imine carbon by unshared pair of electron of sulfhydryl group.

The structure of compounds (V_a-$_f$) was identified by melting point and R_f values given in Table (3-1) as well as the appearance of the FT-IR characteristic absorption bands of υ_{NH} stretching of amide at 3310-3181cm^{-1}, $\upsilon_{C=O}$ stretching of thiazolidinone at1732-1715cm^{-1}, $\upsilon_{C=O}$ stretching of amidic at 1680-1699cm^{-1}, $\upsilon_{C=O}$ stretching of amide at 1661-1649cm^{-1} and υ_{C-S} stretching band at 1213cm^{-1} as in Table (3-2) and ^{1}H-NMR spectra showed singlet for CH proton of thiazolidinone in the range of 5.73-5.92(δ,ppm) as in Tables (3-6 to 3-11).



Scheme (3-5): First Mechanism of 4-thiazolidinone synthesis



Scheme (3-6): Second Mechanism of 4-thiazolidinone synthesis

3.2. Characterization and Identification of the Target Compounds and their Intermediates:

The physical appearance, melting point and R_f values of the target compounds and their intermediates were listed in Table (3-1). TLC was performed in two different solvent systems in order to follow up the reaction pattern and reveal purity of the target compounds and their intermediates by the present of one spot with different R_f values.

3.2.1. Interpretation of the Results of Infrared Spectra:

The FT-IR spectra of the target compounds and their intermediates showed characteristic absorption bands by which their functional groups were identified. The values of the characteristic bands of these spectra have been discussed according to the literature survey of analogous compounds [87-92] and references book [93], and summarized in Table (3-2).

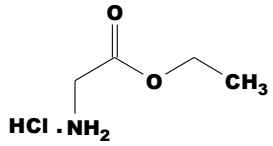
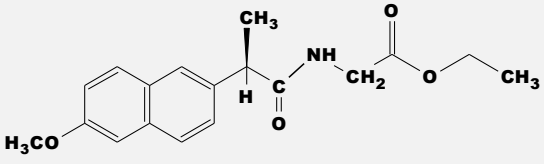
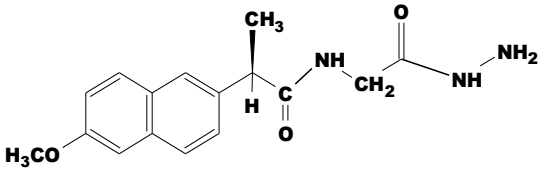
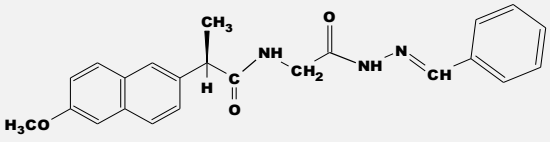
3.2.2. Interpretation of the results of ^{1}H-NMR

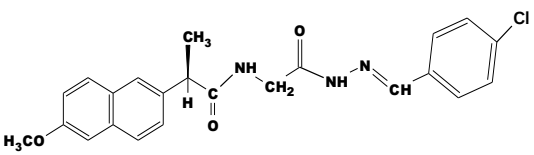
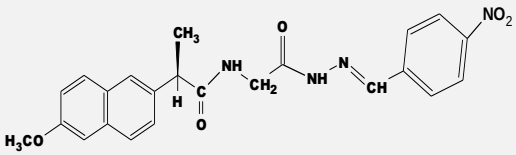
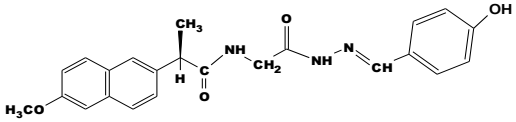
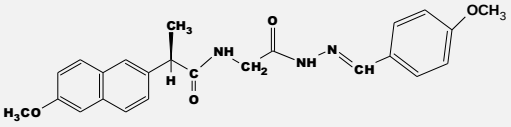
The ^{1}H-NMR analysis was used to identify the target compounds and their intermediates. The spectra were recorded in DMSO solvent. The values of characteristic chemical shifts have been discussed according to the literature survey of analogous compounds [87-92] and references book [93&94] and summarized in Tables (3-3 to 3-11).

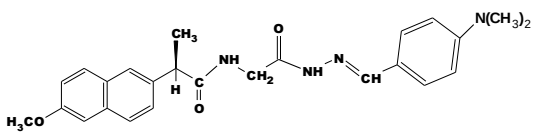
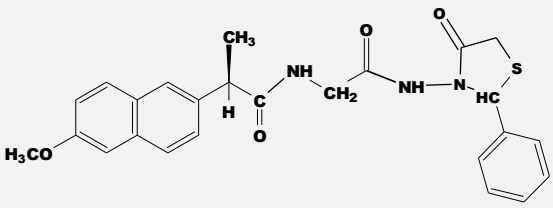
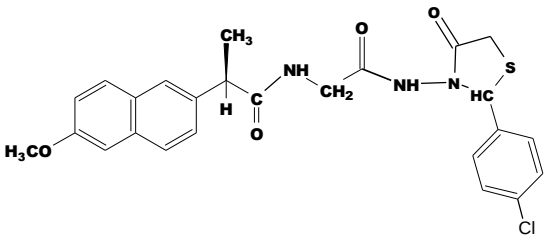
Table (3-1): The characterization and physical parameters of the target compounds and their intermediates

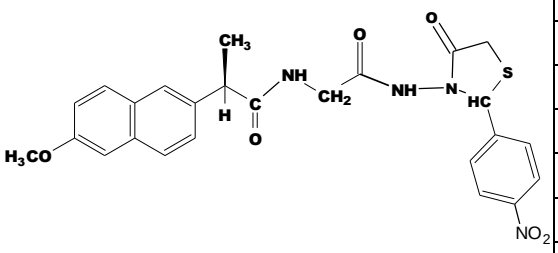
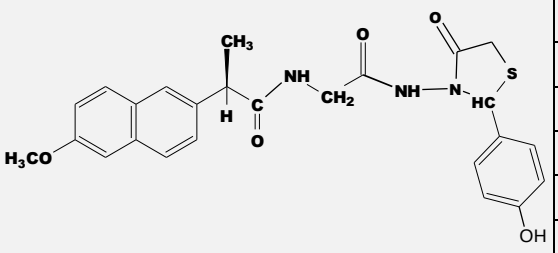
No.	Molecular Formula	Molecular Weight	Description	% yield	Melting point (°C)	R_f
I	$C_4H_{10}NO_2Cl$	139	White crystals	90	145-147	A=0.70 B=0.48
II	$C_{18}H_{21}NO_4$	315	Off white powder	65	84-86	A=0.92 B=0.55
III	$C_{16}H_{19}N_3O_3$	301	Yellow powder	78	158-160	A=0.80 B=0.51
Iv_a	$C_{23}H_{23}N_3O_3$	389	white fluffy powder	70	211-213	A=0.65 B=0.70
IV_b	$C_{23}H_{22}N_3O_3Cl$	424	white fluffy powder	71	188-190	A=0.51 B=0.68
IV_c	$C_{23}H_{22}N_4O_5$	434	Yellow fluffy powder	78	180-182	A=0.45 B=0.60
IV_d	$C_{23}H_{23}N_3O_4$	405	White fluffy powder	68	227-229	A=0.28 B=0.42
IV_e	$C_{24}H_{25}N_3O_4$	419	White fluffy powder	74	177-179	A=0.22 B=0.35
IV_f	$C_{25}H_{28}N_4O_3$	432	yellow fluffy powder	69	190-192	A=0.52 B=0.44
V_a	$C_{25}H_{25}N_3O_4S$	463	Off white powder	65	118-120	A=0.76 B=0.62
V_b	$C_{25}H_{24}N_3O_4SCl$	498	Off white powder	62	109-111	A=0.88 B=0.57
V_c	$C_{25}H_{24}N_4O_6S$	508	Yellow powder	68	134-136	A=0.92 B=0.68
V_d	$C_{25}H_{25}N_3O_5S$	479	White powder	61	188-190	A=0.71 B=0.53
V_e	$C_{26}H_{27}N_3O_5S$	493	White powder	63	186-188	A=0.82 B=0.48
V_f	$C_{27}H_{30}N_4O_4S$	506	Yellow powder	65	185-187	A=0.91 B=0.64
Nap.	$C_{14}H_{14}O_3$	230	White powder	-	157-158	A=0.95 B=0.11
Gly.	$C_2H_5NO_2$	75	White powder	-	233-234	A=0.98 B=0.38

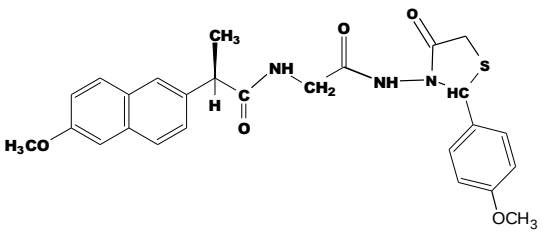
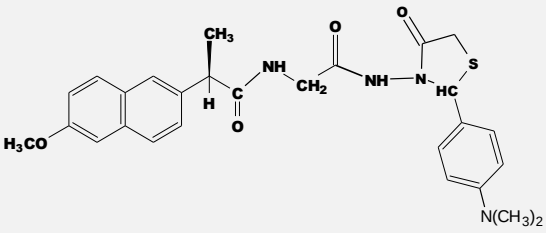
Table (3-2): Characteristic FT-IR absorption bands of the target compounds and their intermediates

Compounds	Bands (cm^{-1})	Interpretation
 **I**	2978	Stretching vibration of primary amine salt
	2675	CH asymmetric stretching of CH_3
	2637	CH symmetric stretching of CH_3
	1748	C=O stretching of ester
	1250	C-O-C stretching of ester
	1136	C-N stretching
 **II**	3293	NH stretching of amide
	3069	C-H stretching of aromatic
	2974	CH asymmetric stretching of CH_3
	2934	CH symmetric stretching of CH_3
	1740	C=O stretching of ester
	1649	C=O stretching of amide
	1610	Aromatic C=C stretching
 **III**	3339 3277	$NHNH_2$ stretching
	3036	C-H stretching of aromatic
	2986	CH asymmetric stretching of CH_3
	2940	CH symmetric stretching of CH_3
	1678	C=O stretching of amidic
	1645	C=O stretching of amide
	1607	Aromatic C=C stretching
 **IV_a**	3291	NH stretching of amide
	3065	C-H stretching of aromatic
	2972	CH asymmetric stretching of CH_3
	2936	CH symmetric stretching of CH_3
	1686	C=O stretching of amidic
	1643	C=O stretching of amide & C=N stretching
	1609	Aromatic C=C stretching

Compounds	Bands (cm^{-1})	Interpretation
 **IV_b**	3293	NH stretching of amide
	3067	C-H stretching of aromatic
	2970	CH asymmetric stretching of CH_3
	2935	CH symmetric stretching of CH_3
	1684	C=O stretching of amidic
	1645	C=O stretching of amide & C=N stretching
	1607	Aromatic C=C stretching
	1092	C-Cl stretching
 **IV_c**	3314	NH stretching of amide
	3082	C-H stretching of aromatic
	2967	CH asymmetric stretching of CH_3
	2939	CH symmetric stretching of CH_3
	1690	C=O stretching of amidic
	1643	C=O stretching of amide & C=N stretching
	1524	NO_2 asymmetric stretching
	1343	NO_2 symmetric stretching
	1607	Aromatic C=C stretching
 **IV_d**	3362	Phenolic O-H stretching
	3271	NH stretching of amide
	3123	C-H stretching of aromatic
	2980	CH asymmetric stretching of CH_3
	2941	CH symmetric stretching of CH_3
	1686	C=O stretching of amidic
	1656	C=O stretching of amide & C=N stretching
	1605	Aromatic C=C stretching
 **IV_e**	3306	NH stretching of amide
	3066	Aromatic CH stretching
	2969	CH asymmetric stretching of CH_3
	2938	CH symmetric stretching of CH_3
	1682	C=O stretching of amidic
	1643	C=O stretching of amide & C=N stretching
	1607	Aromatic C=C stretching
	1254	C-OCH_3 stretching

Compounds	Bands (cm^{-1})	Interpretation
 **IV_f**	3319	NH stretching of amide
	3086	C-H stretching of aromatic
	2974	CH asymmetric stretching of CH_3
	2934	CH symmetric stretching of CH_3
	1680	C=O stretching of amidic
	1643	C=O stretching of amide & C=N stretching
	1607	Aromatic C=C stretching
	1362	C-$N(CH_3)_2$ stretching
 **V_a**	3306	NH stretching of amide
	3055	C-H stretching of aromatic
	2976	CH asymmetric stretching of CH_3
	2936	CH symmetric stretching of CH_3
	1726	C=O stretching of thiazolidinone
	1680	C=O stretching of amidic
	1655	C=O stretching of amide
	1601	Aromatic C=C stretching
	1213	C-S stretching
 **V_b**	3254	NH stretching of amide
	3057	C-H stretching of aromatic
	2976	CH asymmetric stretching of CH_3
	2934	CH symmetric stretching of CH_3
	1728	C=O stretching of thiazolidinone
	1684	C=O stretching of amidic
	1655	C=O stretching of amide
	1605	Aromatic C=C stretching
	1213	C-S stretching
	1088	C-Cl stretching

Compounds	Bands (cm^{-1})	Inter-pretation
 **V_c**	3277	NH stretching of amide
	3113	C-H stretching of aromatic
	2976	CH asymmetric stretching of CH_3
	2936	CH symmetric stretching of CH_3
	1732	C=O stretching of thiazolidinone
	1690	C=O stretching of amidic
	1661	C=O stretching of amide
	1605	Aromatic C=C stretching
	1524	NO2 asymmetric stretching
	1346	NO2 symmetric stretching
	1213	C-S stretching
 **V_d**	3308	Phenolic O-H stretching
	3181	NH stretching of amide
	3051	C-H stretching of aromatic
	2978	CH asymmetric stretching of CH_3
	2938	CH symmetric stretching of CH_3
	1717	C=O stretching of thiazolidinone
	1697	C=O stretching of amidic
	1649	C=O stretching of amide
	1601	Aromatic C=C stretching
	1211	C-S stretching

Compounds	Bands (cm^{-1})	Interpretation
 **V_e**	3310	NH stretching of amide
	3053	C-H stretching of aromatic
	2978	CH asymmetric stretching of CH_3
	2938	CH symmetric stretching of CH_3
	1715	C=O stretching of thiazolidinone
	1697	C=O stretching of amidic
	1649	C=O stretching of amide
	1601	Aromatic C=C stretching
	1267	C-OCH_3 stretching
	1213	C-S stretching
 **V_f**	3310	NH stretching of amide
	3053	C-H stretching of aromatic
	2978	CH asymmetric stretching of CH_3
	2938	CH symmetric stretching of CH_3
	1720	C=O stretching of thiazolidinone
	1699	C=O stretching of amidic
	1649	C=O stretching of amide
	1601	Aromatic C=C stretching
	1390	C-$N(CH_3)_2$ stretching
	1213	C-S stretching

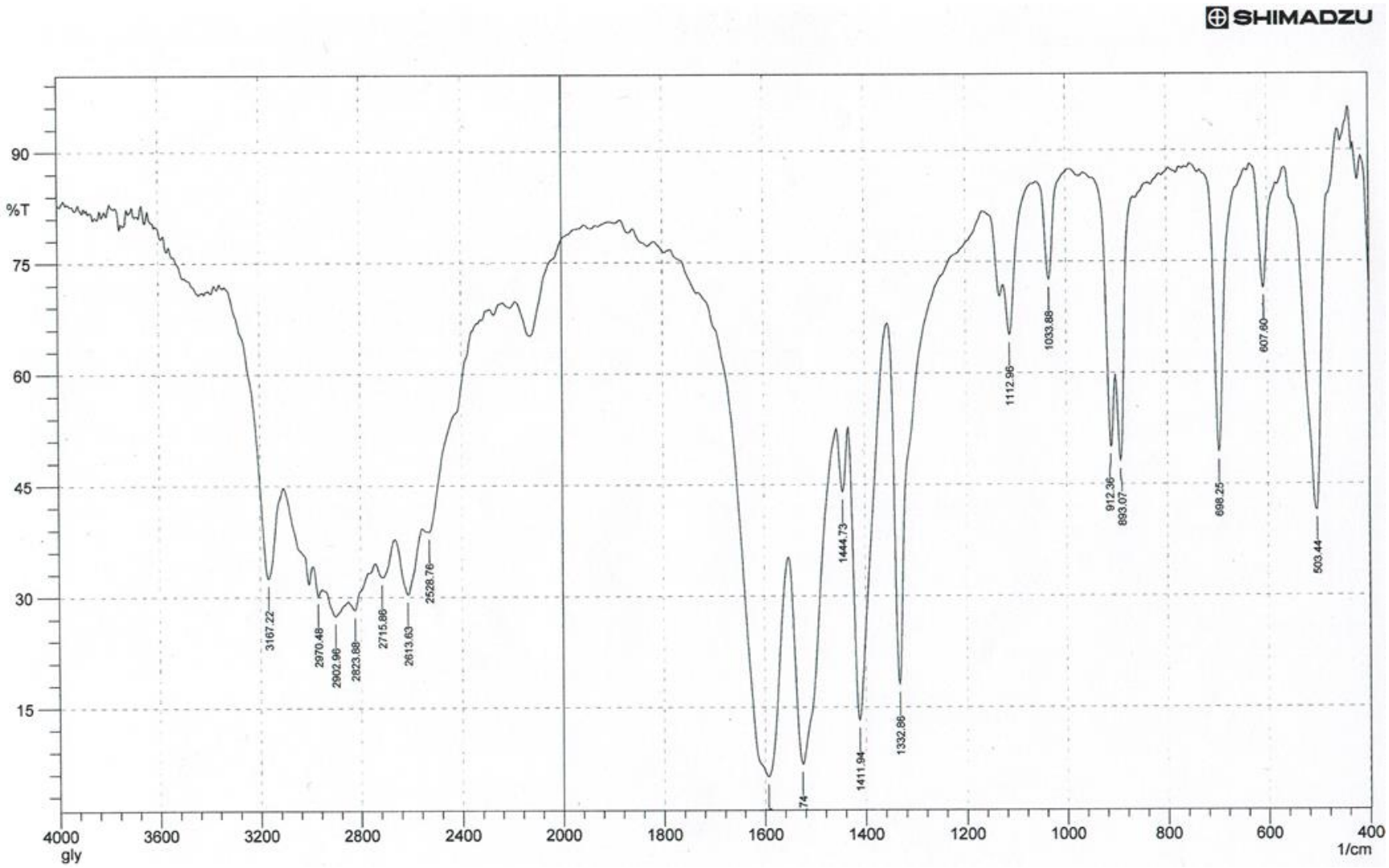


Figure (3-1): FT-IR spectrum of Glycine using KBr dis

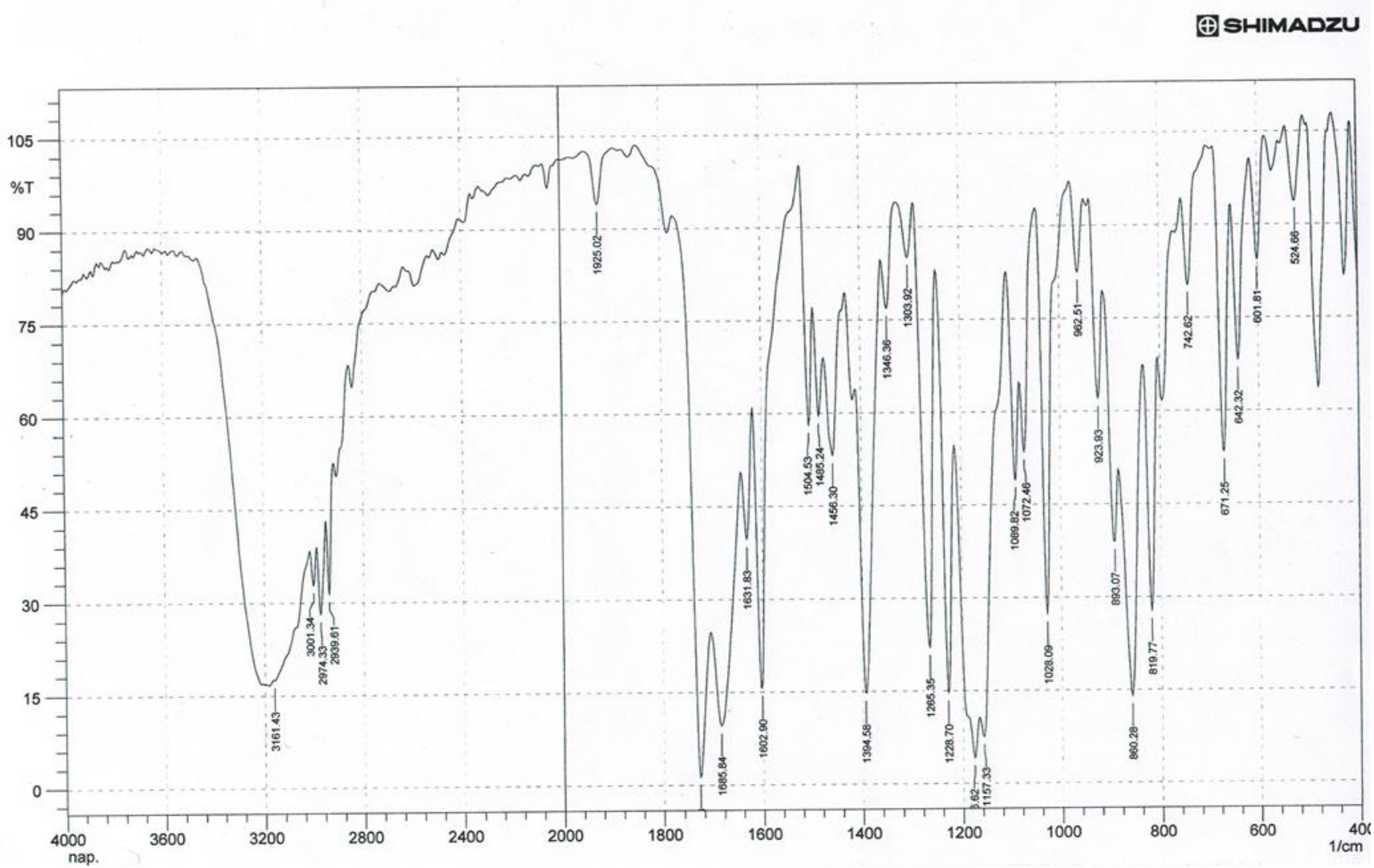


Figure (3-2): FT-IR spectrum of (s)- Naproxen using KBr disc

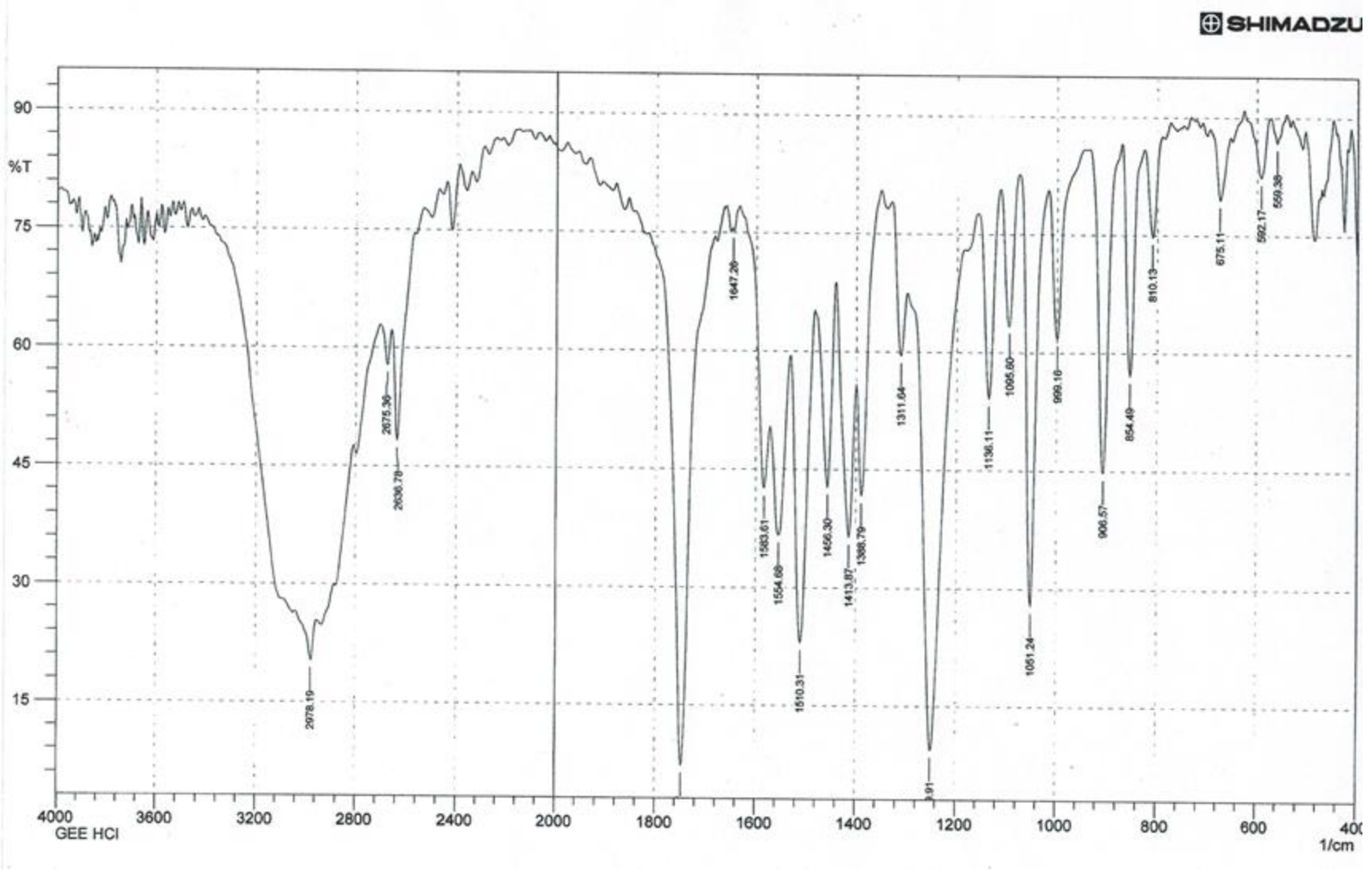


Figure (3-3): FT-IR spectrum of compound (I) using KBr disc

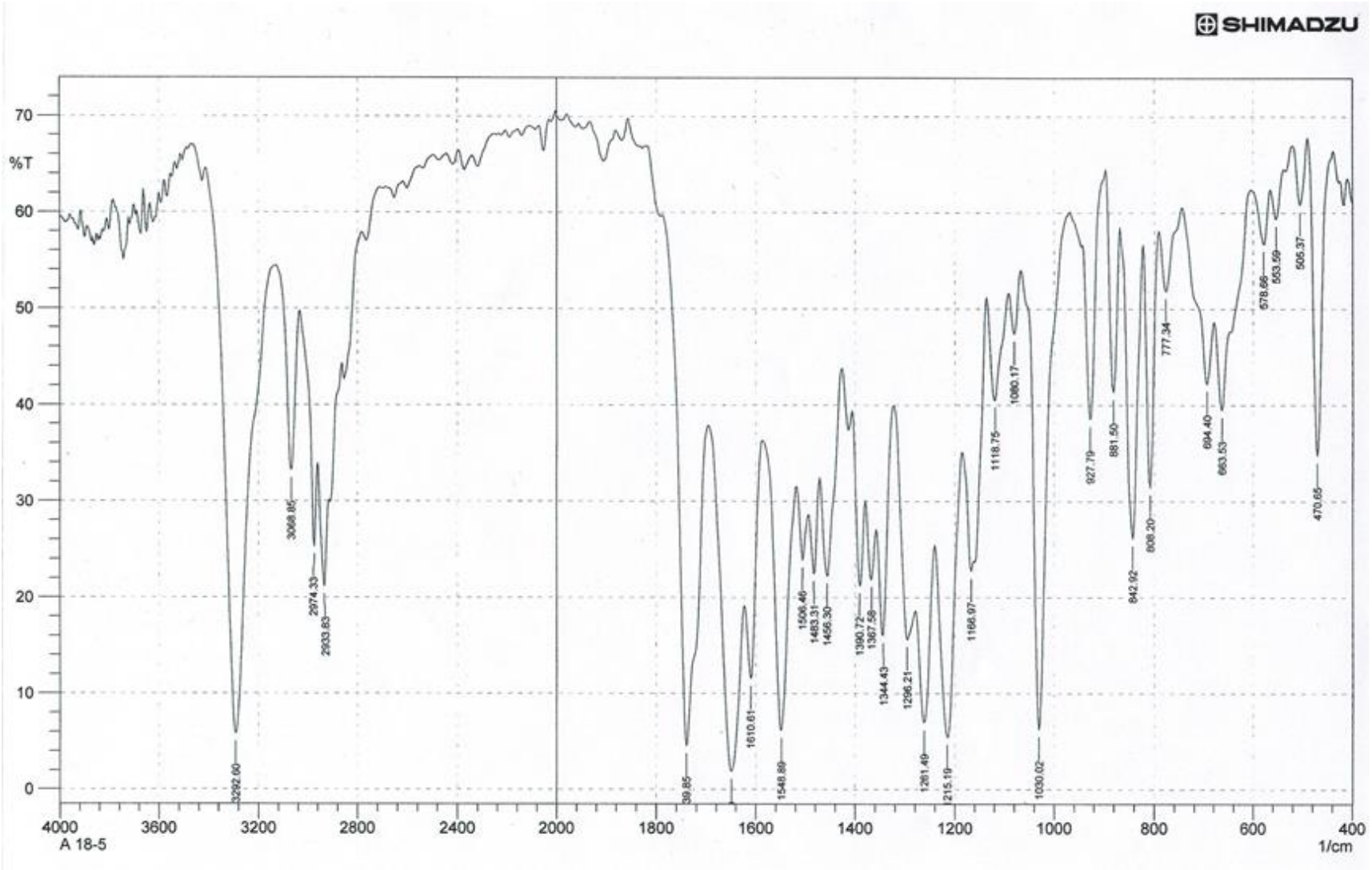


Figure (3-4): FT-IR spectrum of compound (II) using KBr disc

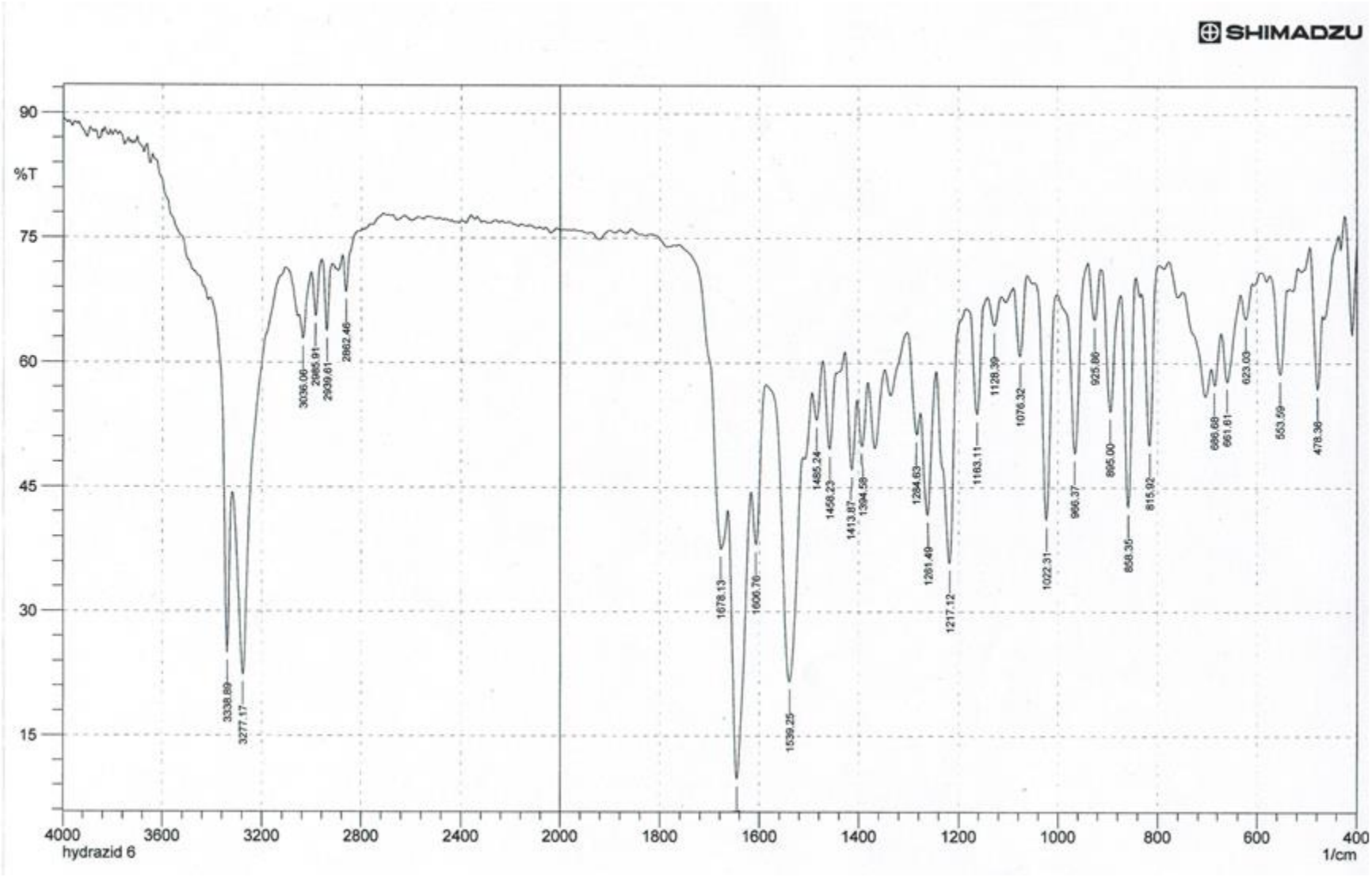


Figure (3-5): FT-IR spectrum of compound (III) using KBr disc

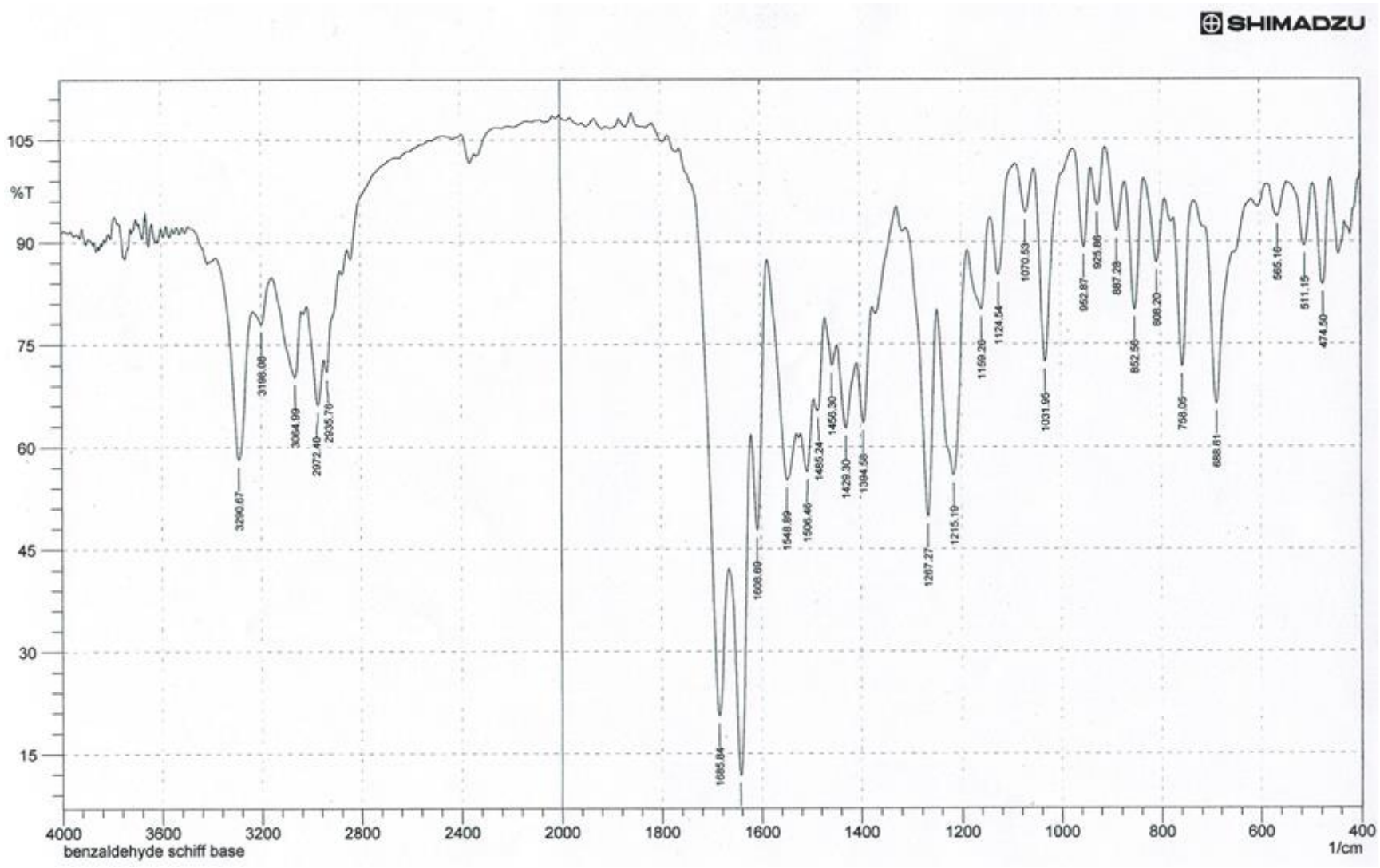


Figure (3-6): FT-IR spectrum of compound (IV_a) using KBr disc

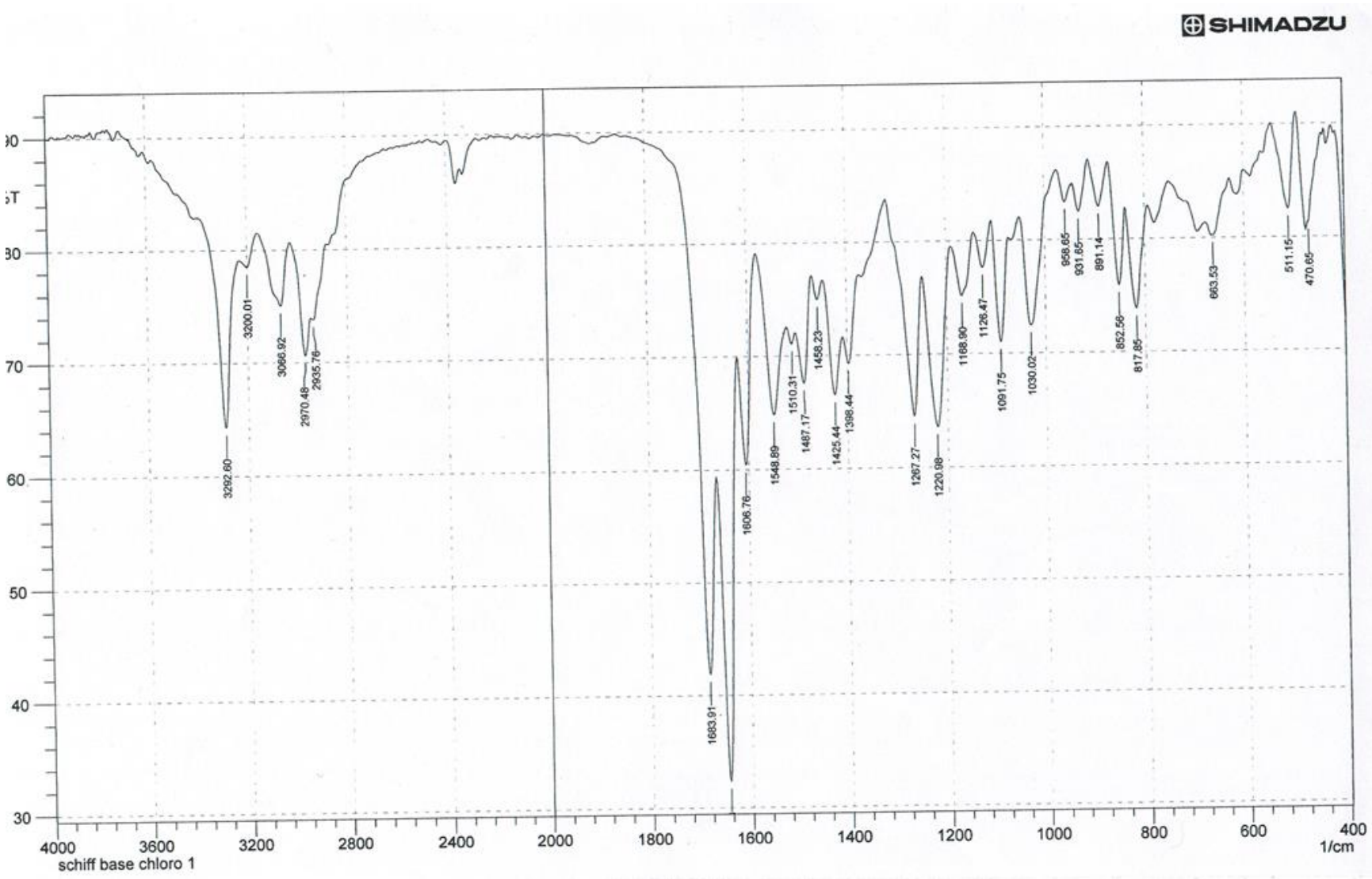


Figure (3-7): FT-IR spectrum of compound (IV_b) using KBr disc

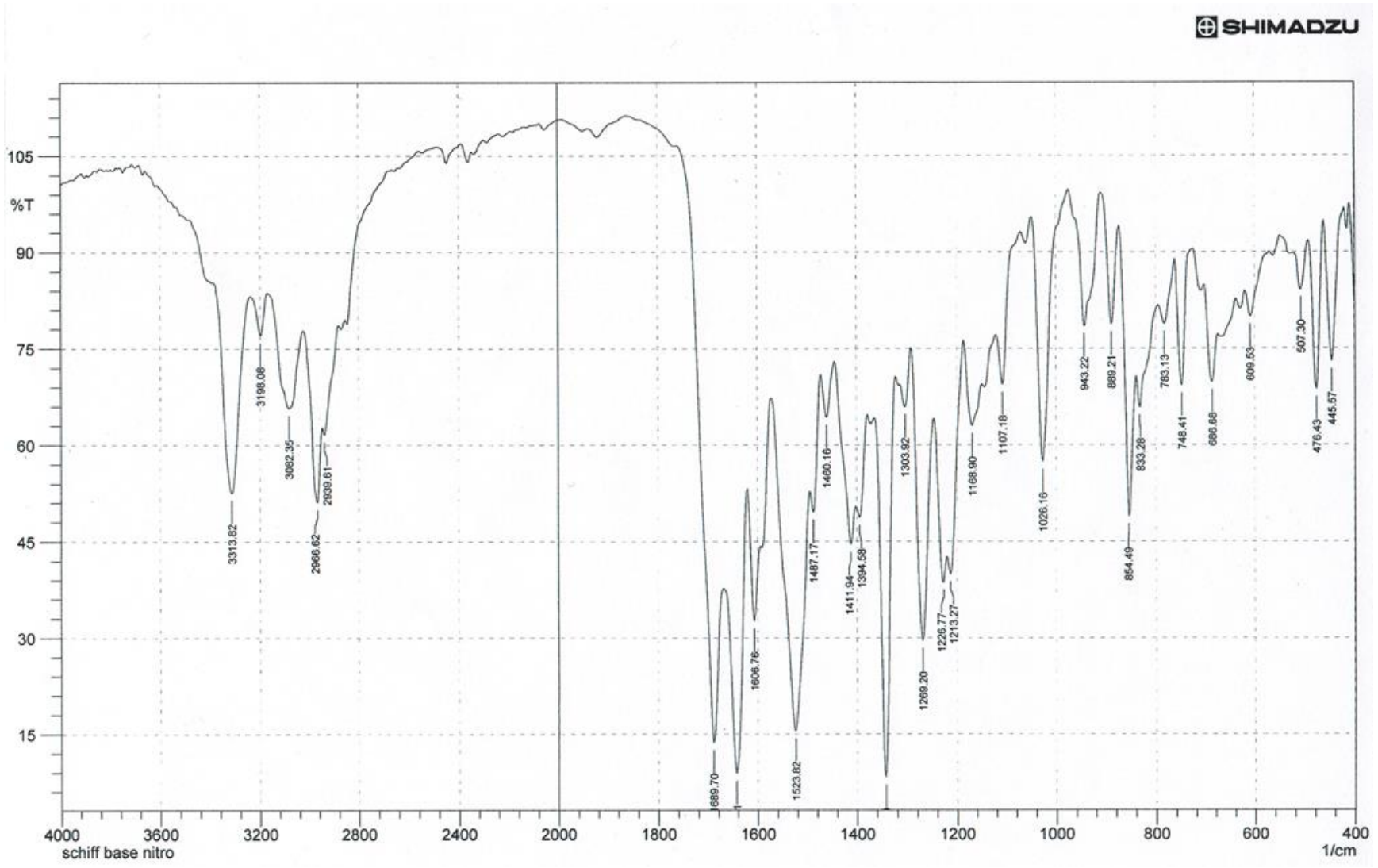


Figure (3-8): FT-IR spectrum of compound (IV_c) using KBr disc

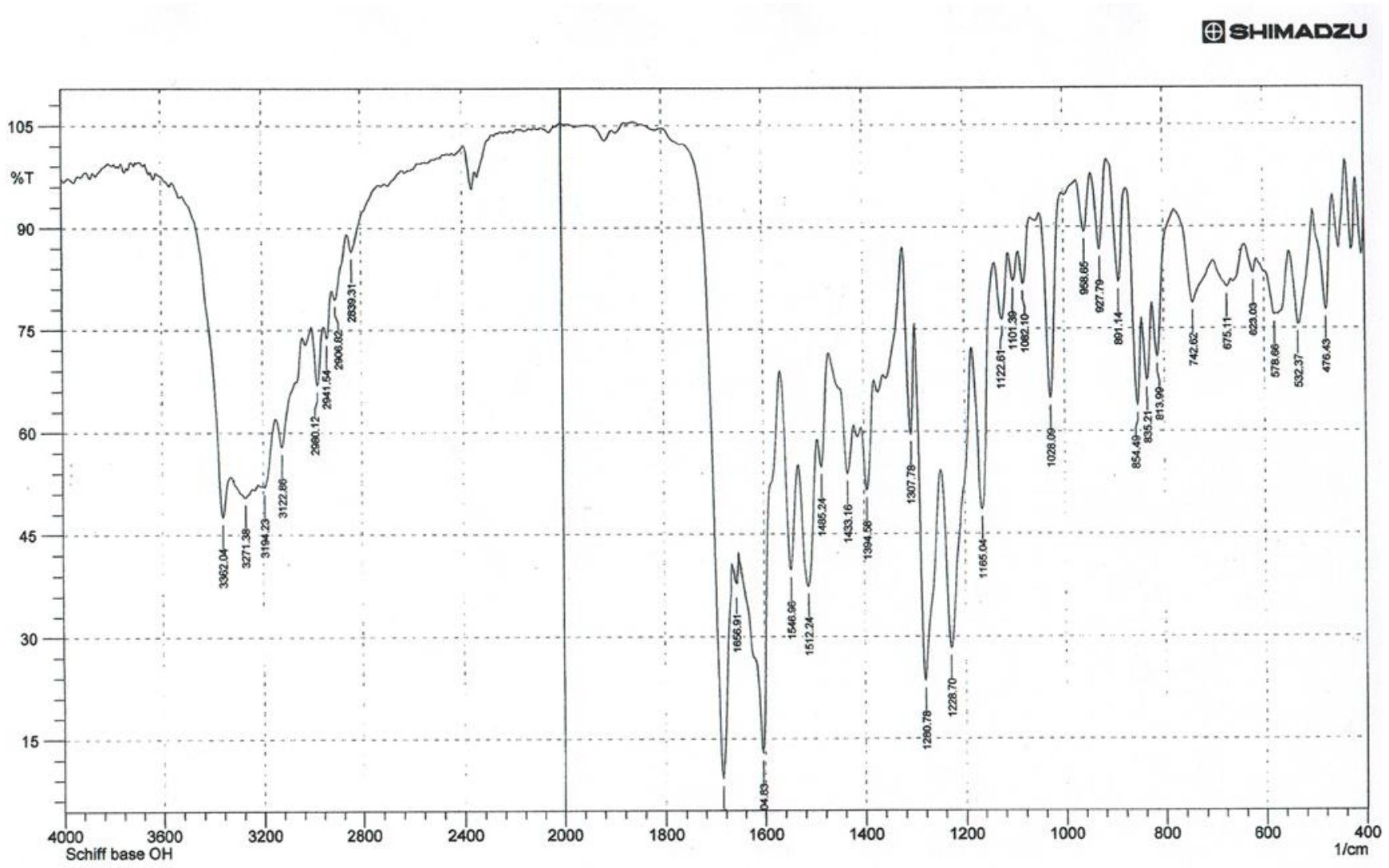


Figure (3-9): FT-IR spectrum of compound (IV_d) using KBr disc

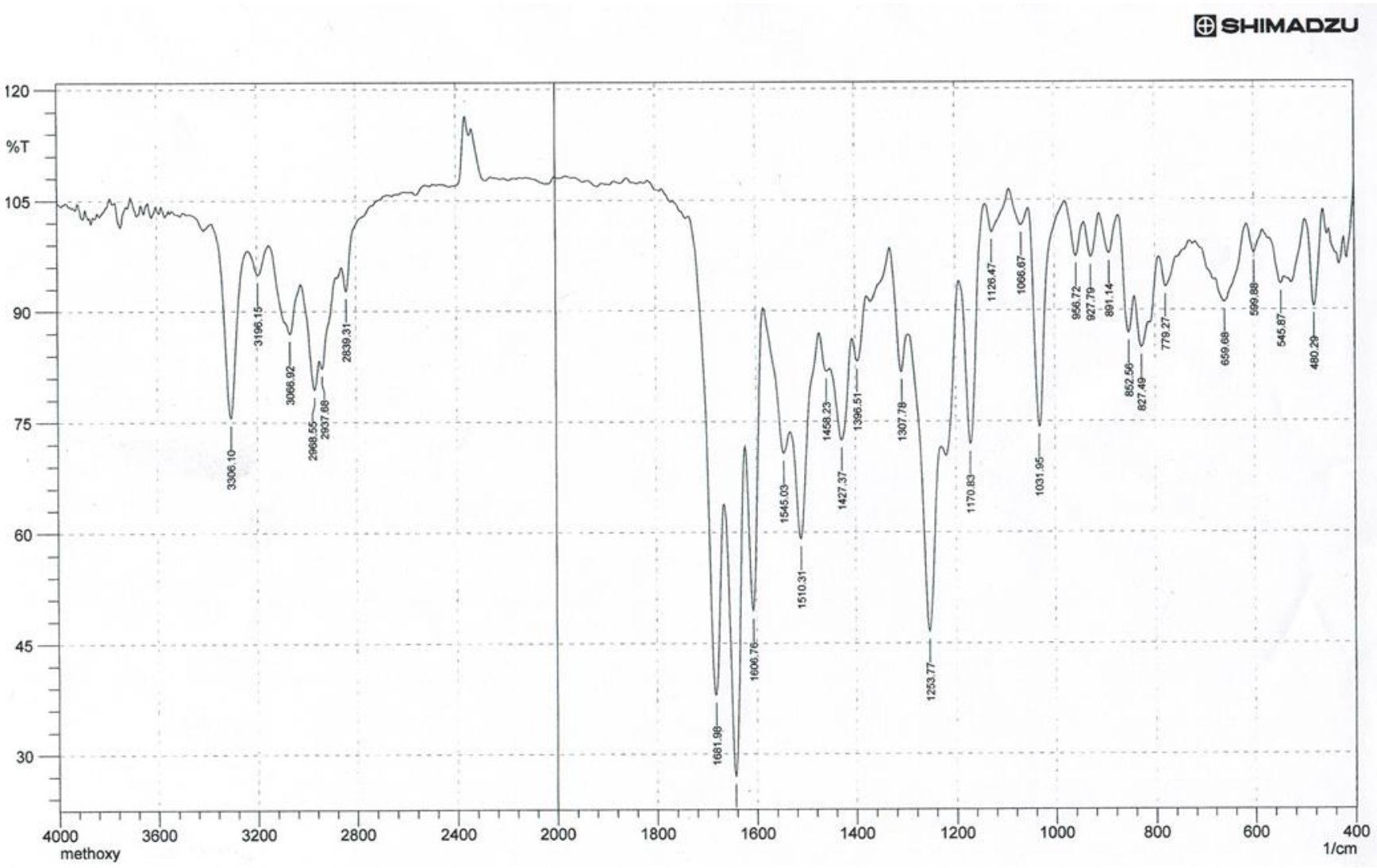


Figure (3-10): FT-IR spectrum of compound (IV_e) using KBr disc

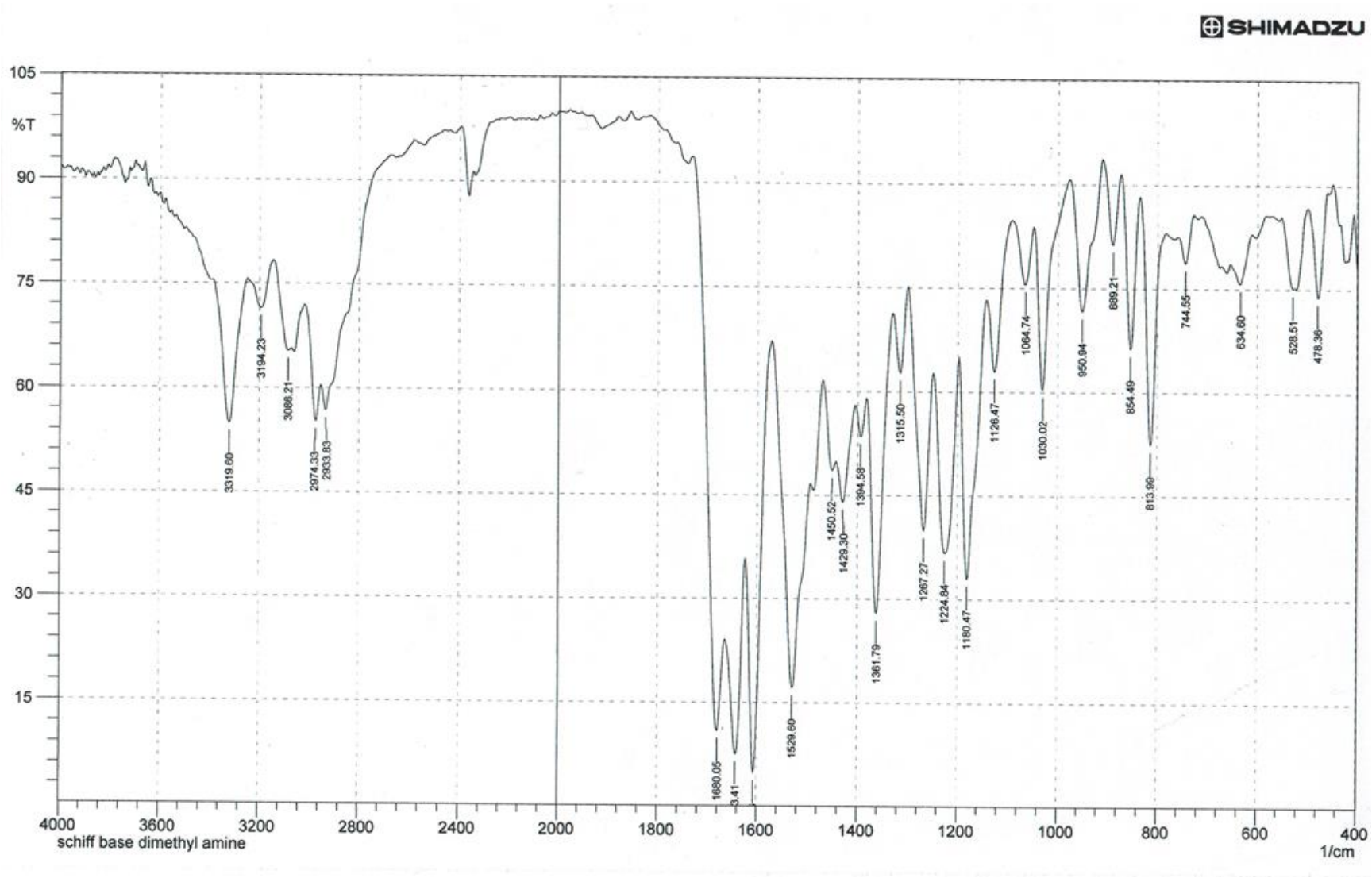


Figure (3-11): FT-IR spectrum of compound (IV_f) using KBr disc

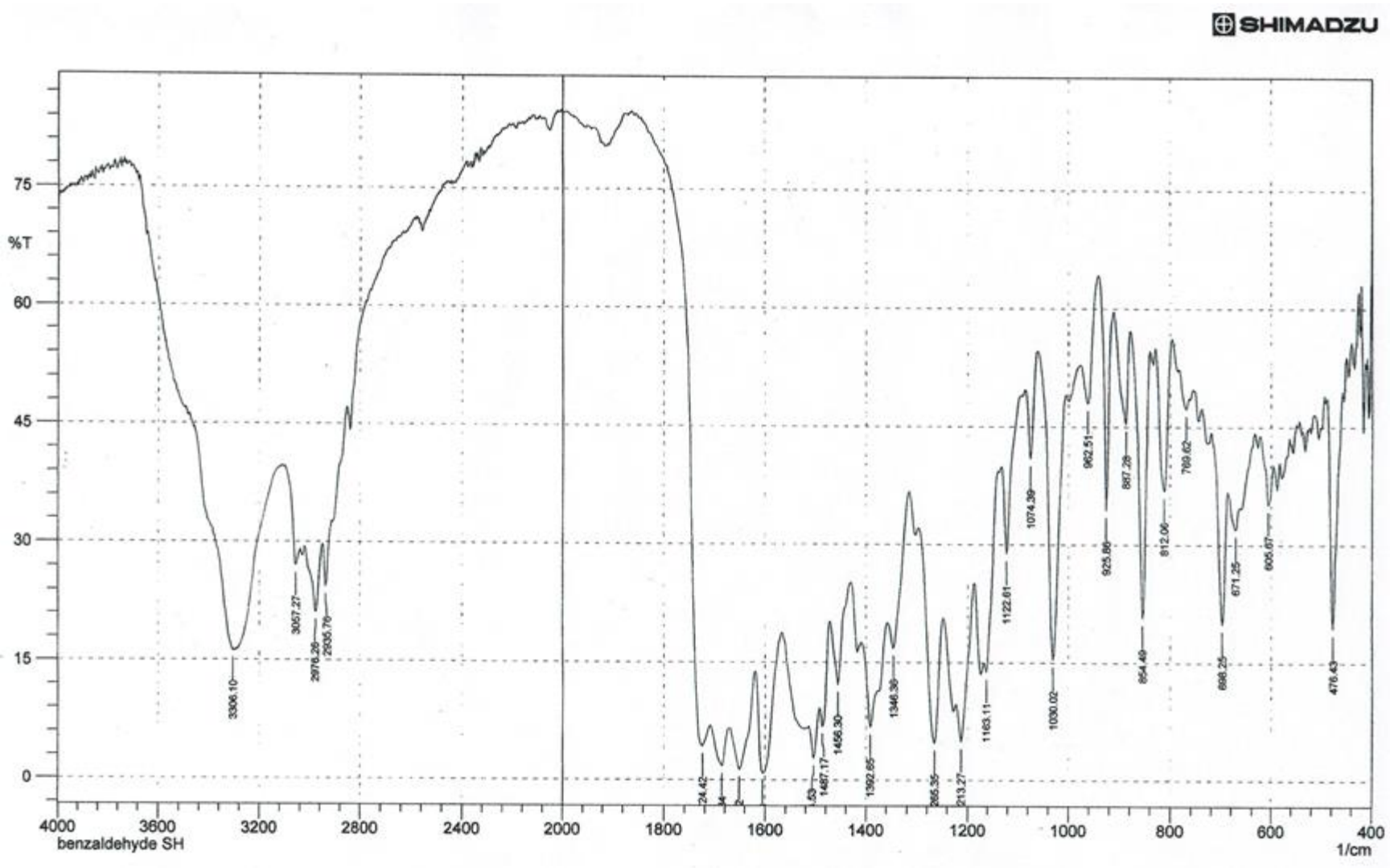


Figure (3-12): FT-IR spectrum of compound (V_a) using KBr disc

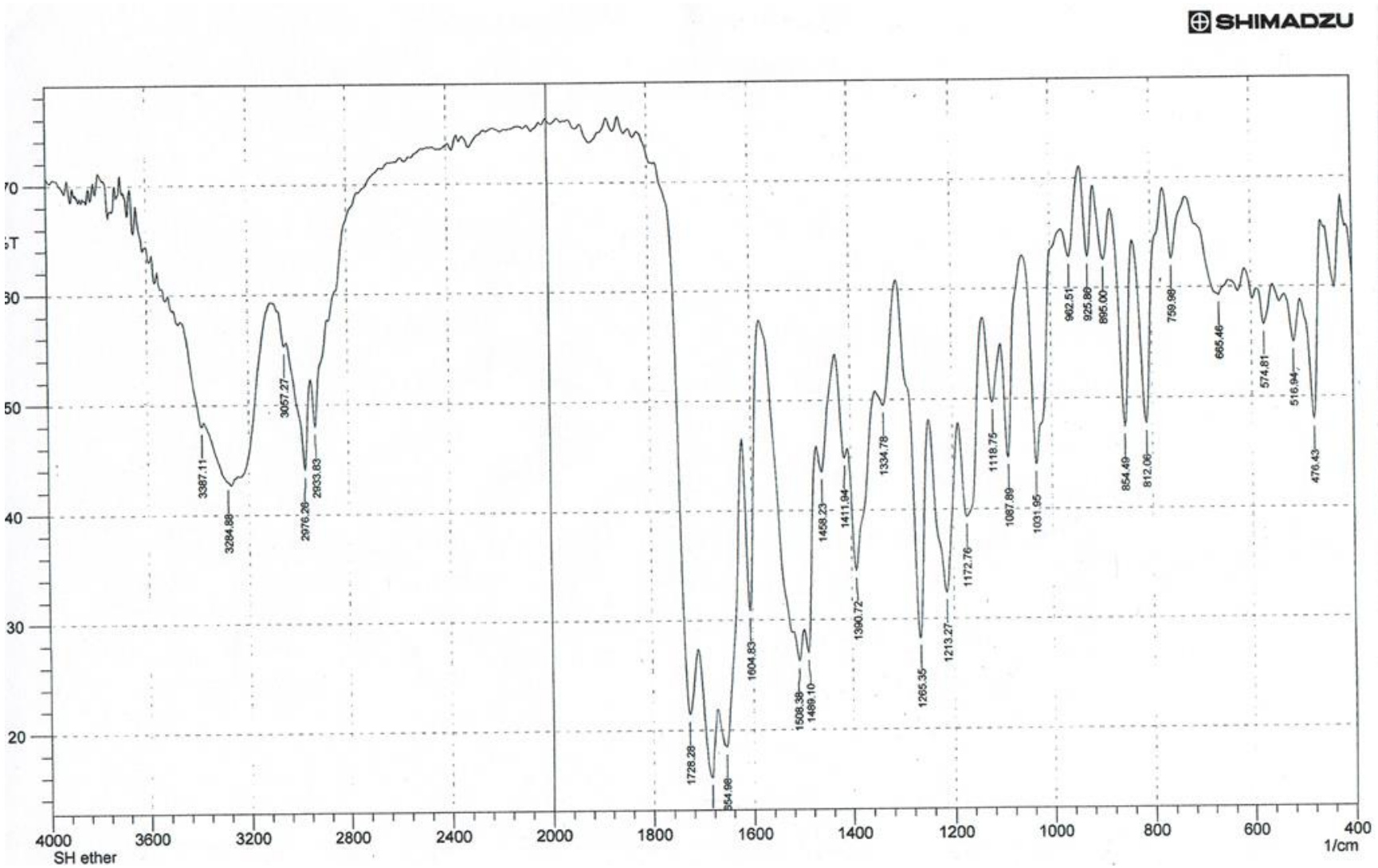


Figure (3-13): FT-IR spectrum of compound (V_b) using KBr disc

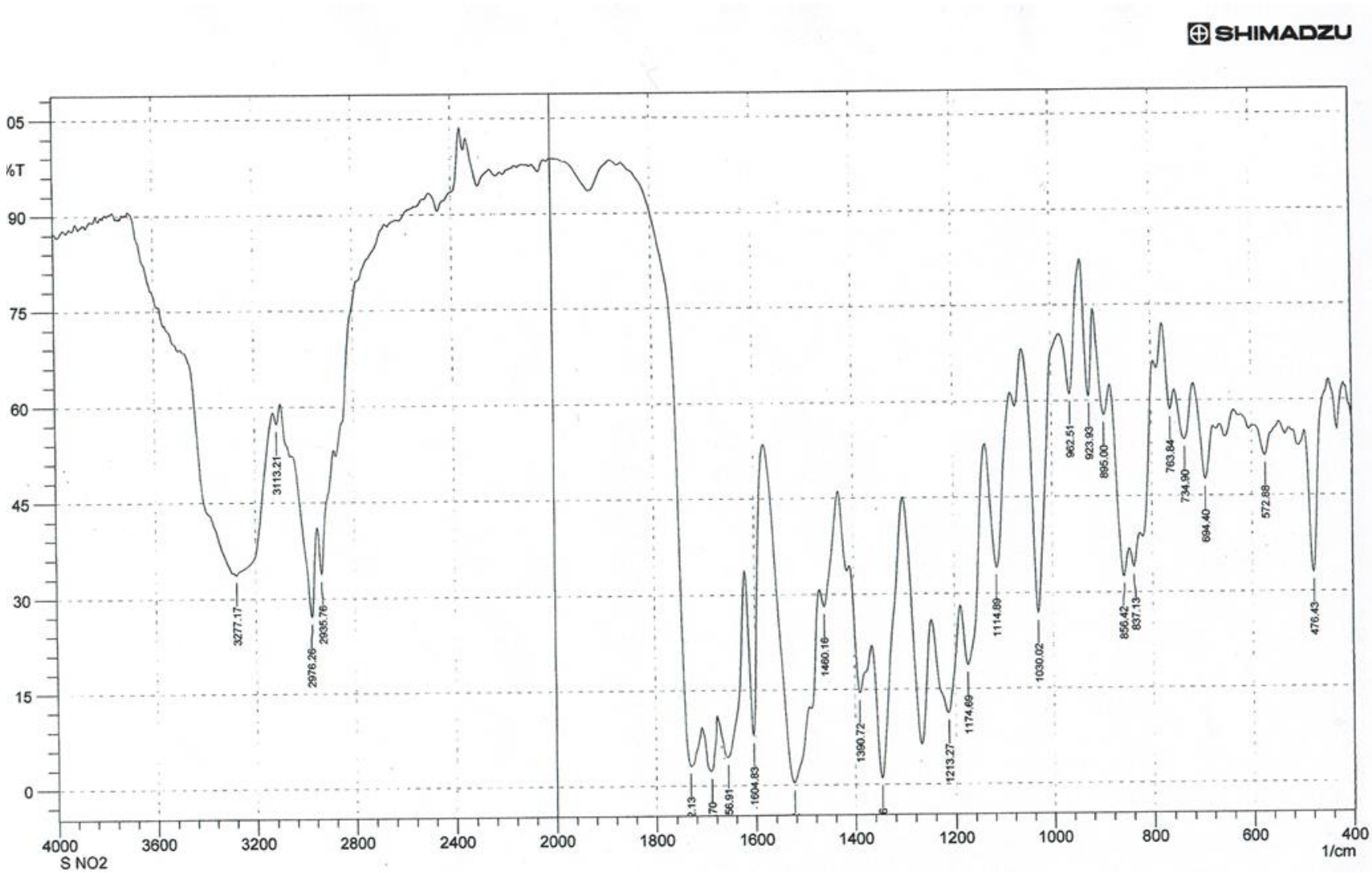


Figure (3-14): FT-IR spectrum of compound (V_c) using KBr disc

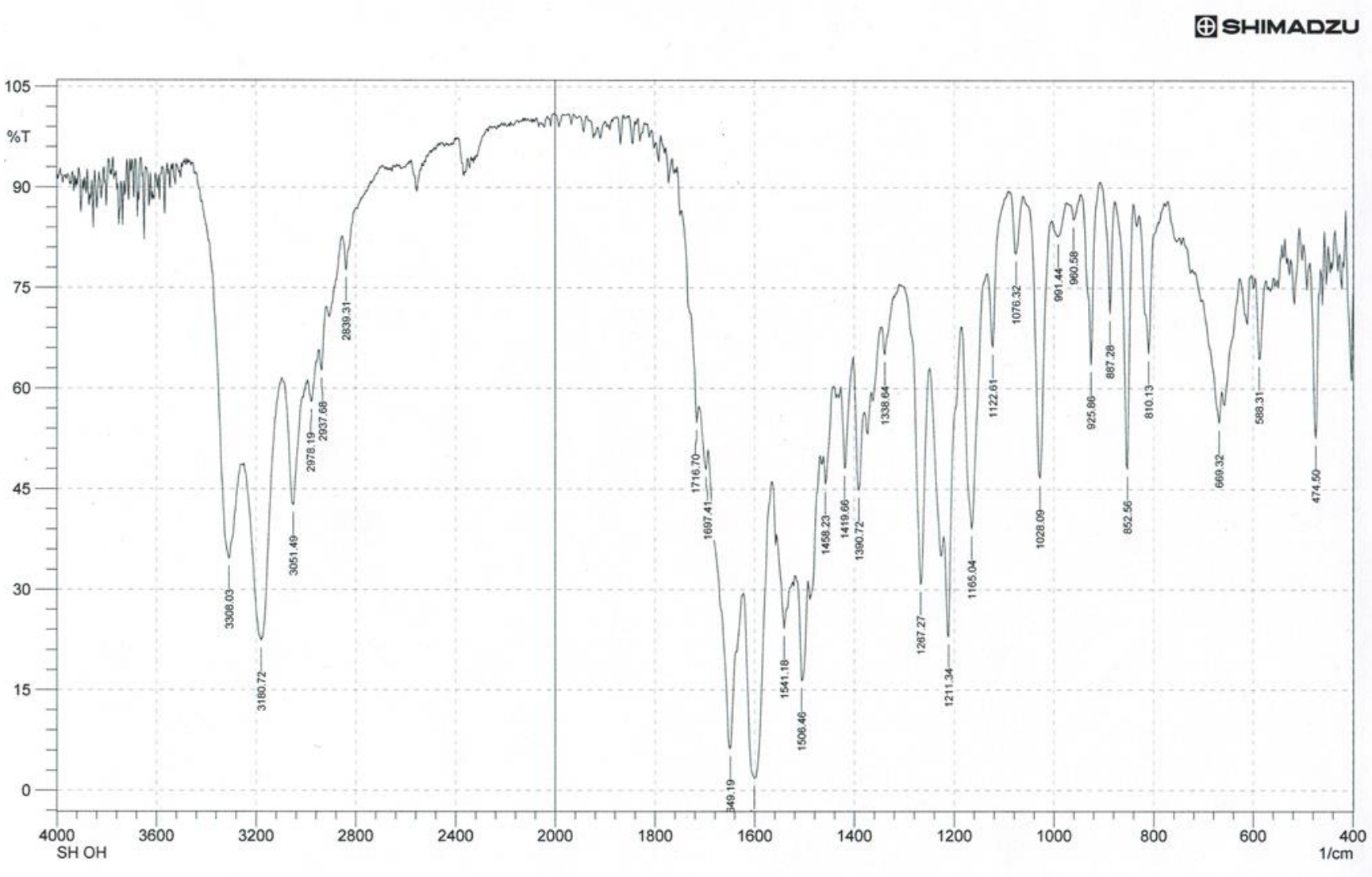


Figure (3-15): FT-IR spectrum of compound (V_d) using KBr disc

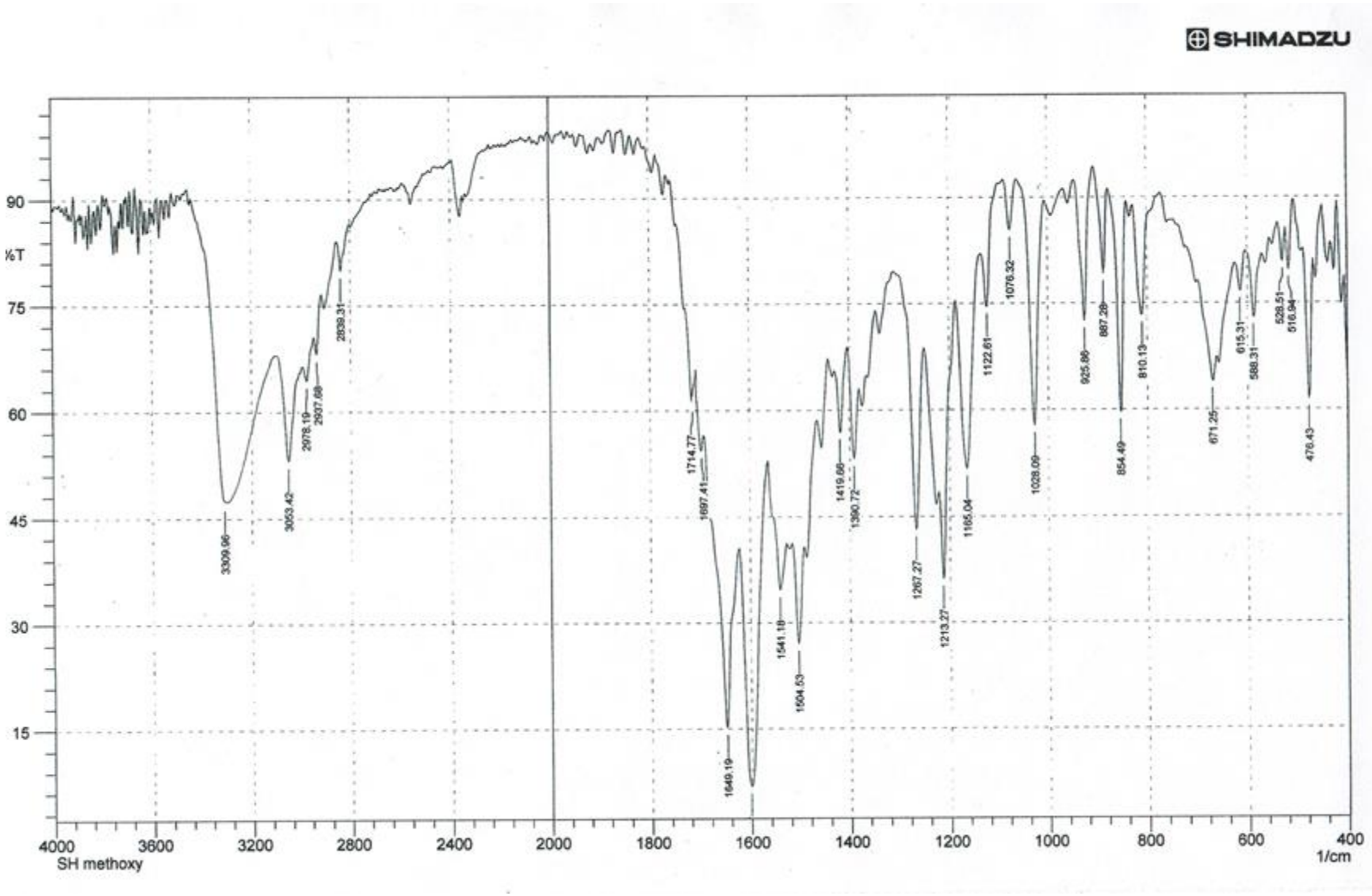


Figure (3-16): FT-IR spectrum of compound (V_e) using KBr disc

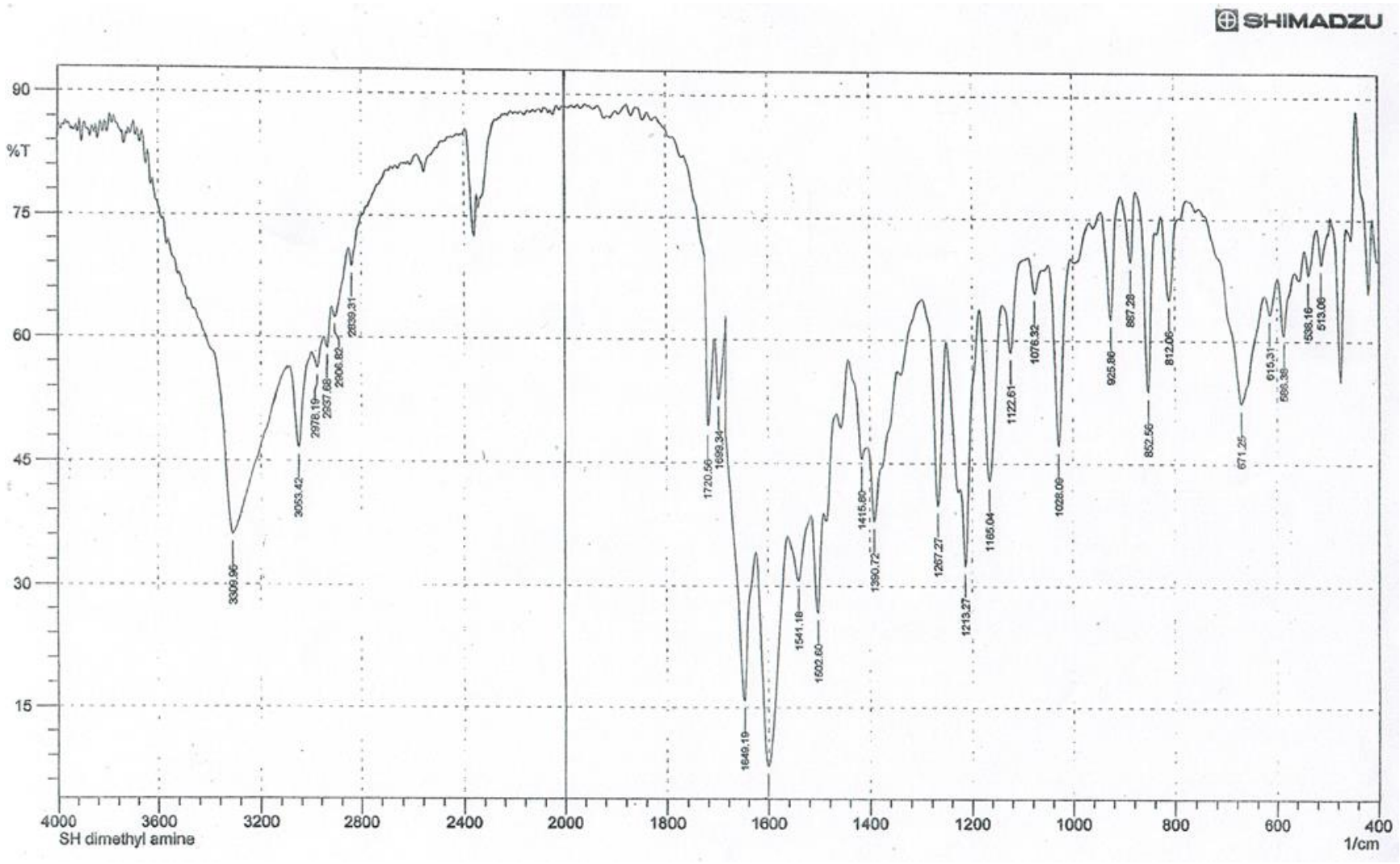
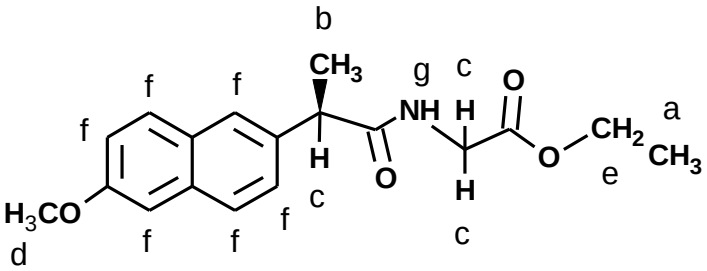


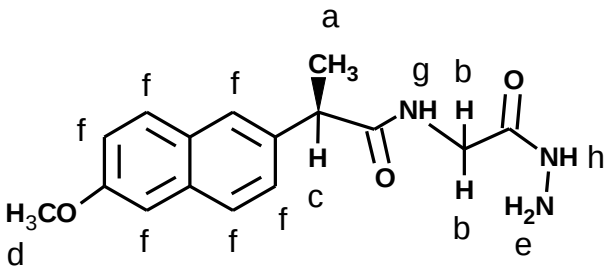
Figure (3-17): FT-IR spectrum of compound (V_f) using KBr disc

Table (3-3): ^{1}H-NMR data and their interpretation of comound (II)



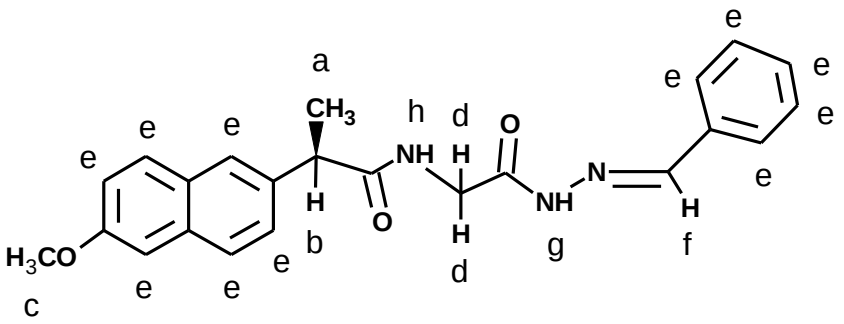
Group	Chemical shift ppm	No. of H	Interpretation
a	1.14	3	Triplet, for CH_3 protons of ester
b	1.42-1.43	3	Doublet, for CH_3 protons of naproxen
c	3.80-3.84	3	Multiplet,for CH proton of naproxen and CH_2protons of glycine
d	3.87	3	Singlet,for -OCH_3 protons of naproxen
e	4.04-4.08	2	Quartate, for CH_2 protons of ester
f	7.14-7.79	6	Multiplet, for naphthalene protons
g	8.40	1	Broad singlet for NH amide proton

Table (3-4): ^{1}H-NMR data and their interpretation of comound (III)



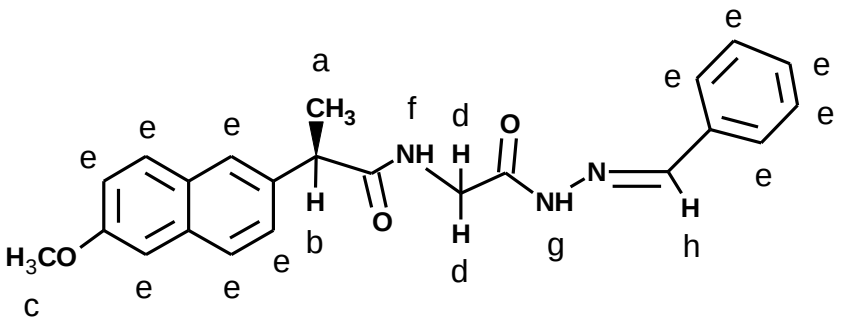
Group	Chemical shift ppm	No. of H	Interpretation
a	1.41-1.42	3	Doublet, for CH_3 protonsof naproxen
b	3.55-3.73	2	Multiplet, for CH_2 protons of glycine
c	3.81-3.87	1	Quartate, for CH proton of naproxen
d	3.91	3	Singlet,for -OCH_3 protons of naproxen
e	4.20	2	Broad singlet, for NH_2 protons of hydrazide
f	7.13-7.79	6	Multiplet, for naphthalene protons
g	8.20	1	Broad singlet for NH amide proton
h	9.01	1	Singlet, for NH proton of hydrazide

Table (3-5): ^{1}H-NMR data and their interpretation of comound (IV_a)



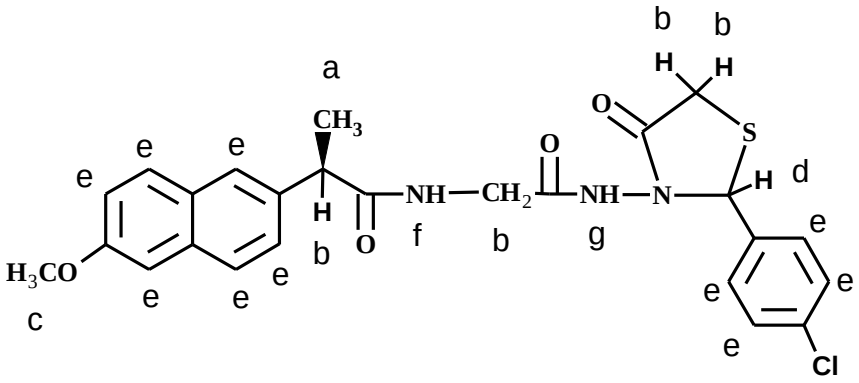
Group	Chemical shift ppm	No. of H	Interpretation
a	1.43-1.45	3	Doublet, for CH_3 protonsof naproxen
b	3.78	1	Quartate, for CH proton of naproxen
c	3.87	3	Singlet,for -OCH_3 protons of naproxen
d	4.17-4.32	2	Multiplet, for CH_2 protons of glycine
e	7.14-7.79	11	Multiplet, for naphthalene &aromatic protons
f	8.20	1	Singlet for N=CH-Ar proton
g	8.36	1	Singlet for NH-N
h	11.41	1	Broad singlet for NH amide proton

Table (3-6): ^{1}H-NMR data and their interpretation of comound (V_a)



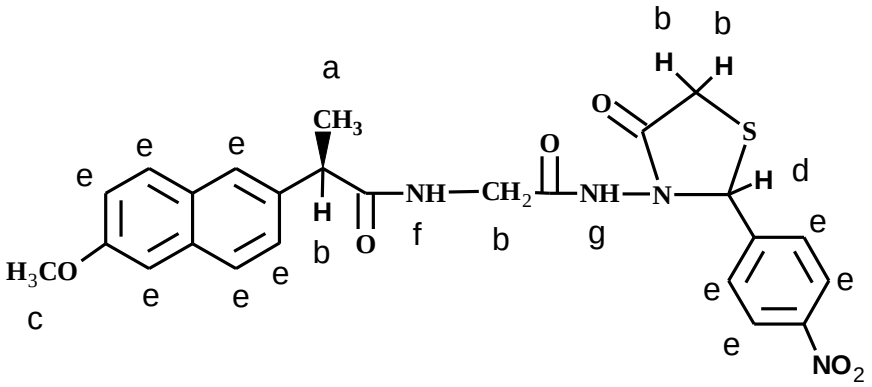
Group	Chemical shift ppm	No. of H	Interpretation
a	1.41-1.43	3	Doublet, for CH_3 protonsof naproxen
b	3.62-3.84	5	Multiplet, due to overlap of CH_2 protons of thiazolidinone and CH_2 protons of glycine and CH proton of naproxen
c	3.90	3	Singlet,for -OCH_3 protons of naproxen
d	5.76	1	Singlet, for CH proton of thiazolidinone
e	7.14-7.78	11	Multiplet, for naphthalene &aromatic protons
f	8.26	1	Broad singlet for NH amide proton
g	10.21	1	Singlet for NH-N

Table (3-7): ^{1}H-NMR data and their interpretation of comound (V_b)



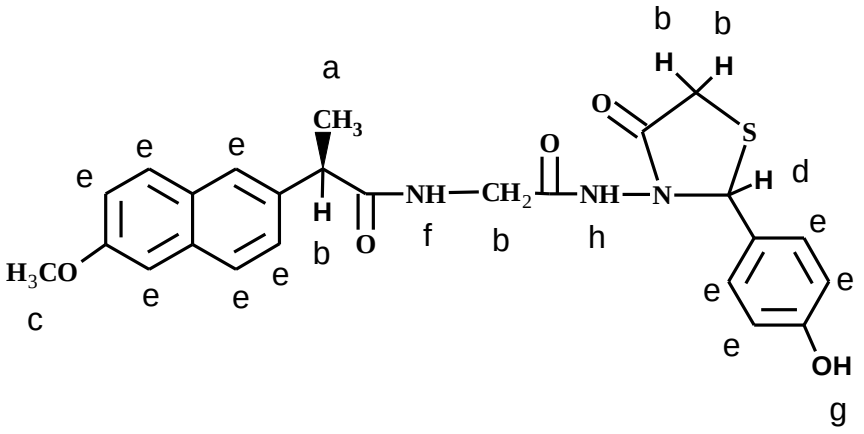
Group	Chemical shift ppm	No. of H	Interpretation
a	1.41-1.43	3	Doublet, for CH_3 protonsof naproxen
b	3.71-3.88	5	Multiplet, due to overlap of CH_2 protons of thiazolidinone and CH_2 protons of glycine and CH proton of naproxen
c	3.91	3	Singlet,for -OCH_3 protons of naproxen
d	5.77	1	Singlet, for CH proton of thiazolidinone
e	7.13-7.79	10	Multiplet, for naphthalene &aromatic protons
f	8.24	1	Broad singlet for NH amide proton
g	10.20	1	Singlet for NH-N

Table (3-8): ^{1}H-NMR data and their interpretation of comound (V_c)



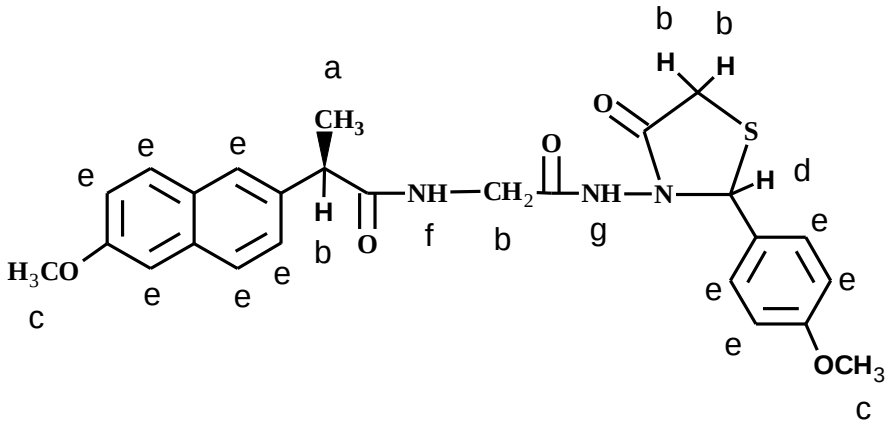
Group	Chemical shift ppm	No. of H	Interpretation
a	1.44-1.45	3	Doublet, for CH_3 protonsof naproxen
b	3.61-3.87	5	Multiplet, due to overlap of CH_2 protons of thiazolidinone and CH_2 protons of glycine and CH proton of naproxen
c	3.97	3	Singlet,for -OCH_3 protons of naproxen
d	5.92	1	Singlet, for CH proton of thiazolidinone
e	7.13-7.78	10	Multiplet, for naphthalene &aromatic protons
f	8.24	1	Broad singlet for NH amide proton
g	10.30	1	Singlet for NH-N

Table (3-9): ^{1}H-NMR data and their interpretation of comound (V_d)



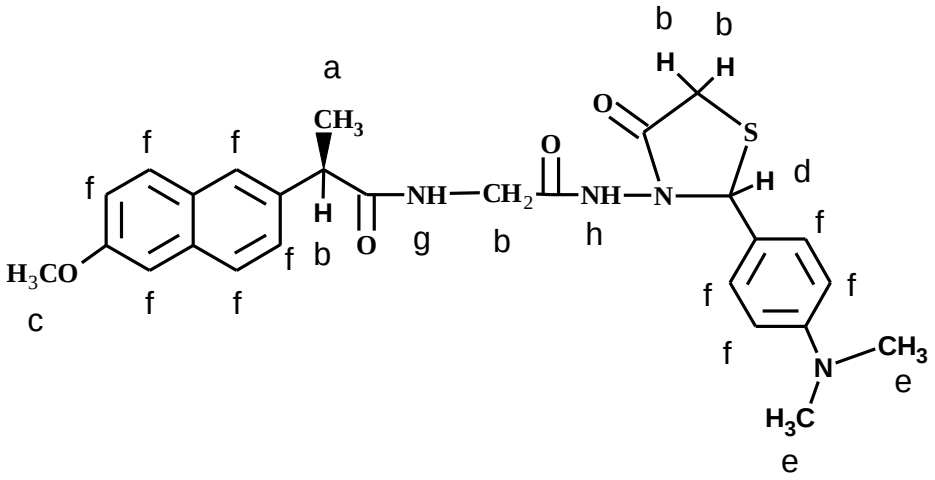
Group	Chemical shift ppm	No. of H	Interpretation
a	1.41-1.43	3	Doublet, for CH_3 protonsof naproxen
b	3.57-3.85	5	Multiplet, due to overlap of CH_2 protons of thiazolidinone and CH_2 protons of glycine and CH proton of naproxen
c	3.87	3	Singlet,for -OCH_3 protons of naproxen
d	5.74	1	Singlet, for CH proton of thiazolidinone
e	7.13-7.79	10	Multiplet, for naphthalene &aromatic protons
f	8.29	1	Broad singlet for NH amide proton
g	9.90	1	Broad singlet for OH proton
h	10.00	1	Singlet for NH-N

Table (3-10): ^{1}H-NMR data and their interpretation of comound (V_e)



Group	Chemical shift ppm	No. of H	Interpretation
a	1.41-1.42	3	Doublet, for CH_3 protonsof naproxen
b	3.53-3.84	5	Multiplet, due to overlap of CH_2 protons of thiazolidinone and CH_2 protons of glycine and CH proton of naproxen
c	3.87	6	Singlet,for 2 -OCH_3 protons
d	5.90	1	Singlet, for CH proton of thiazolidinone
e	7.05-7.79	10	Multiplet, for naphthalene &aromatic protons
f	8.28	1	Broad singlet for NH amide proton
g	10.04	1	Singlet for NH-N

Table (3-11): ^{1}H-NMR data and their interpretation of comound(V_f)



Group	Chemical shift ppm	No. of H	Interpretation
a	1.41-1.43	3	Doublet, for CH_3 protonsof naproxen
b	3.65-3.84	5	Multiplet, due to overlap of CH_2 protons of thiazolidinone and CH_2 protons of glycine and CH proton of naproxen
c	3.86	3	Singlet,for -OCH_3 protons of naproxen
d	5.73	1	Singlet, for CH proton of thiazolidinone
e	6.66	6	Singlet, for $N(CH_3)_2$ protons
f	7.13-7.79	10	Multiplet, for naphthalene &aromatic protons
g	8.27	1	Broad singlet for NH amide proton
h	9.50	1	Singlet for NH-N

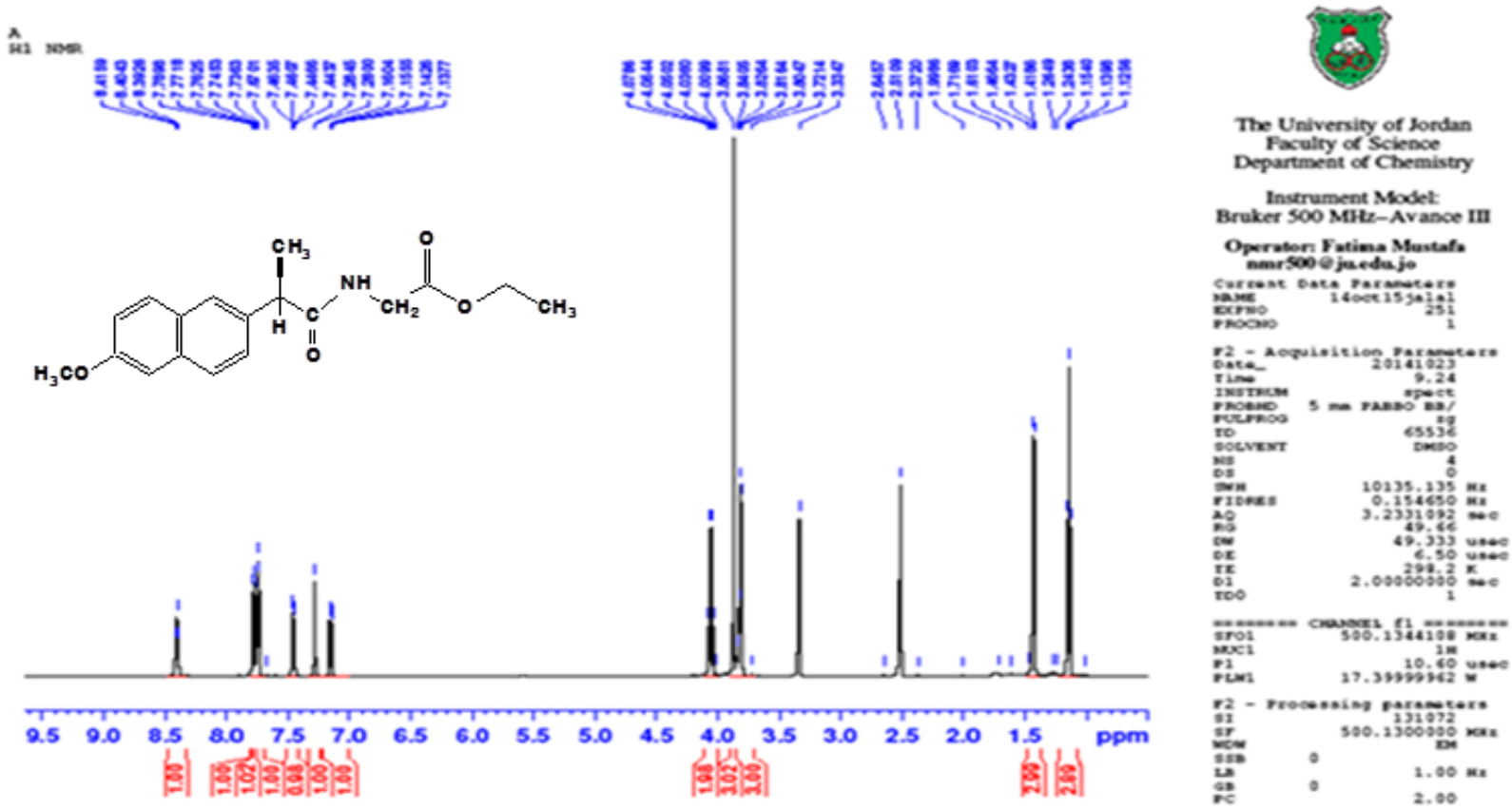


Figure (3-18): ^{1}H-NMR spectrum of compound (II)

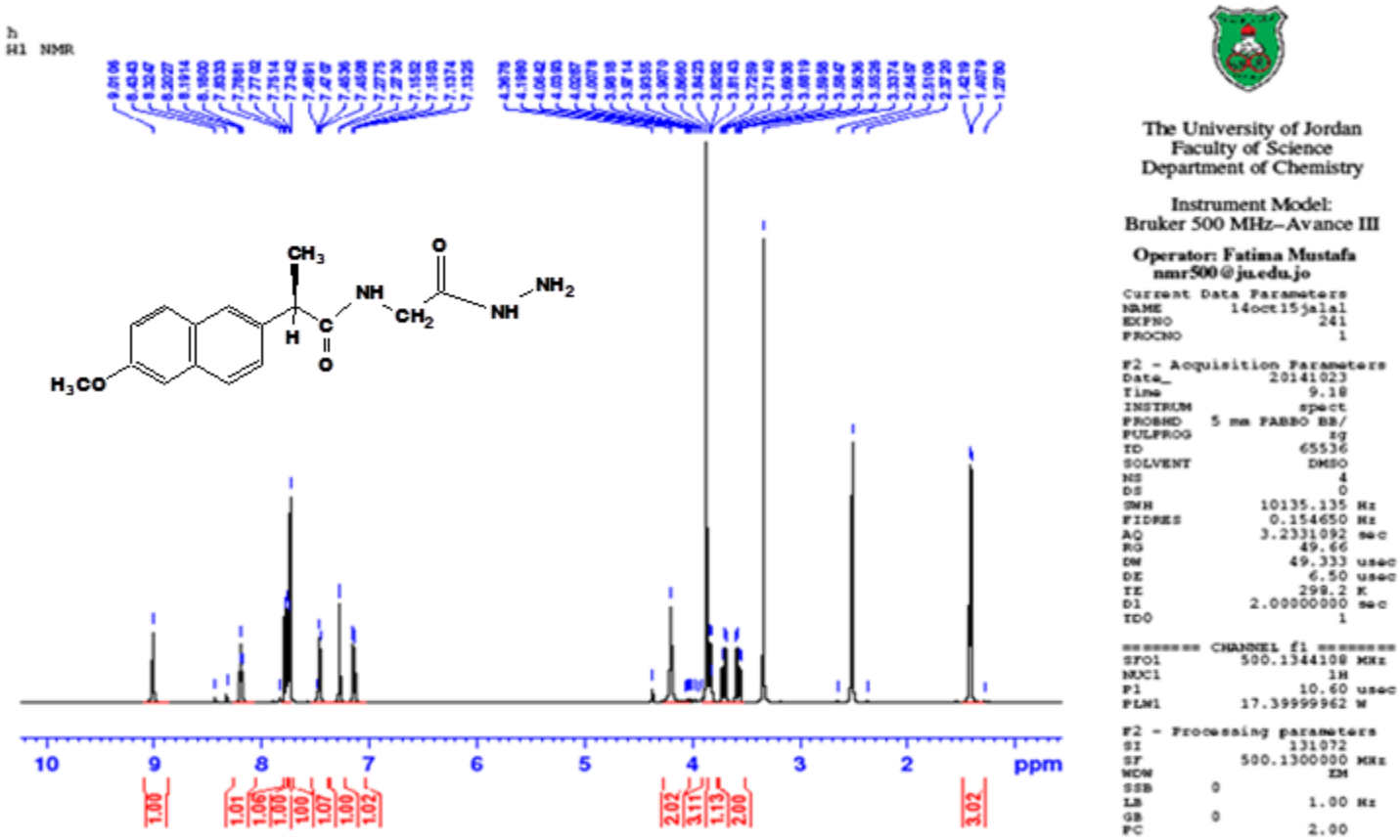


Figure (3-19): ^{1}H-NMR spectrum of compound (III)

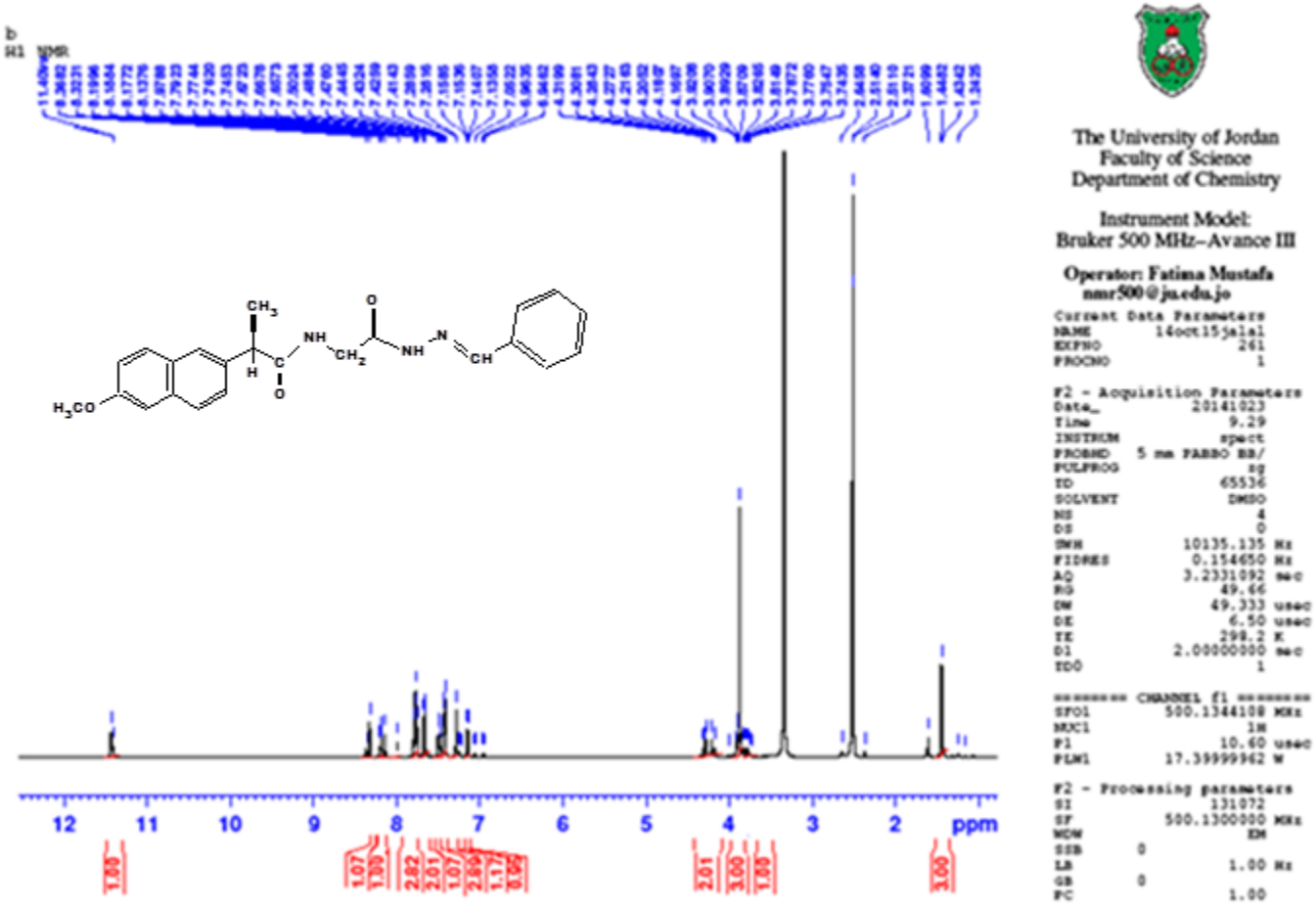


Figure (3-20): ^{1}H-NMR spectrum of compound (IV_a)

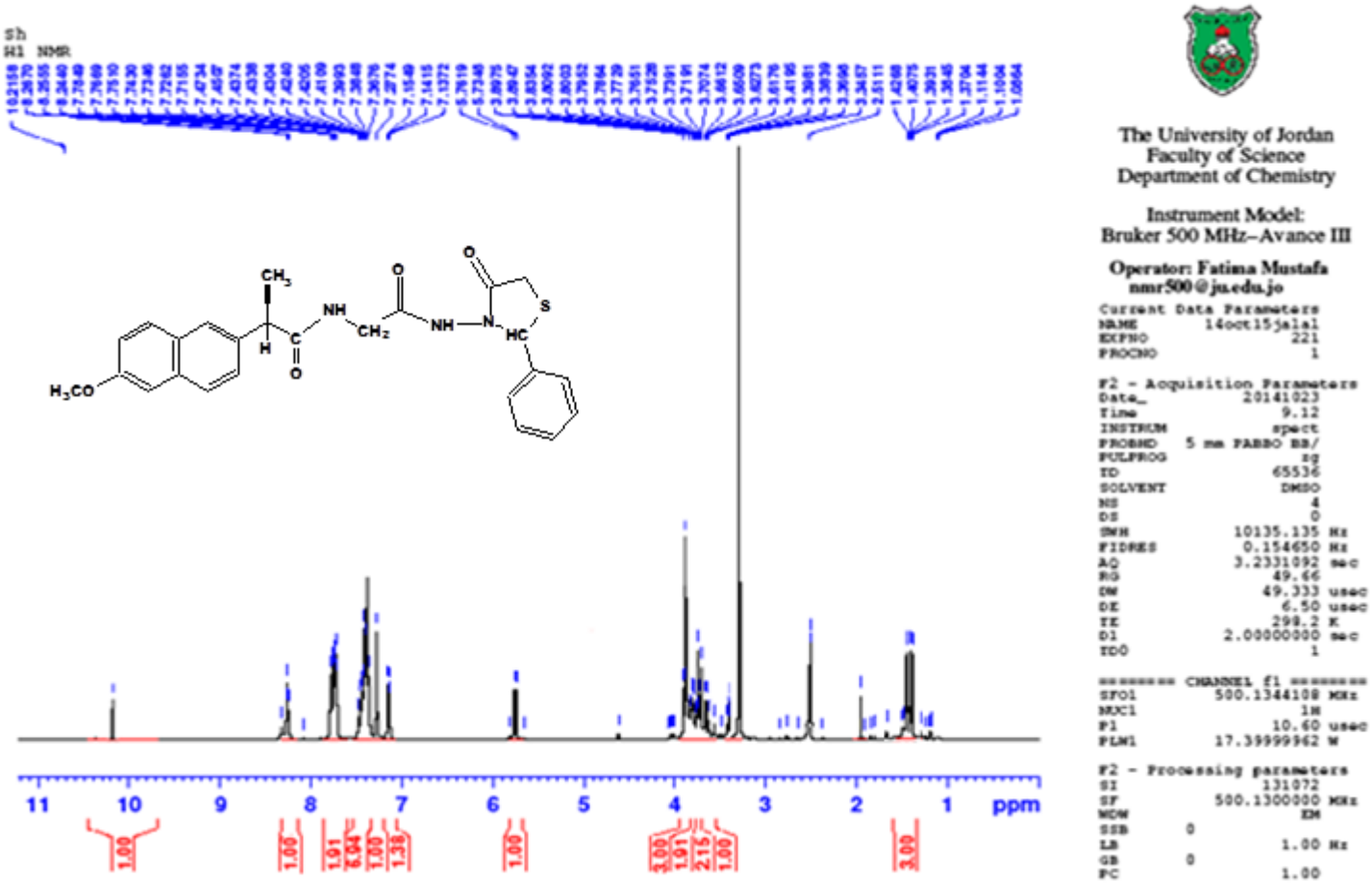


Figure (3-21): ^{1}H-NMR spectrum of compound (V_a)

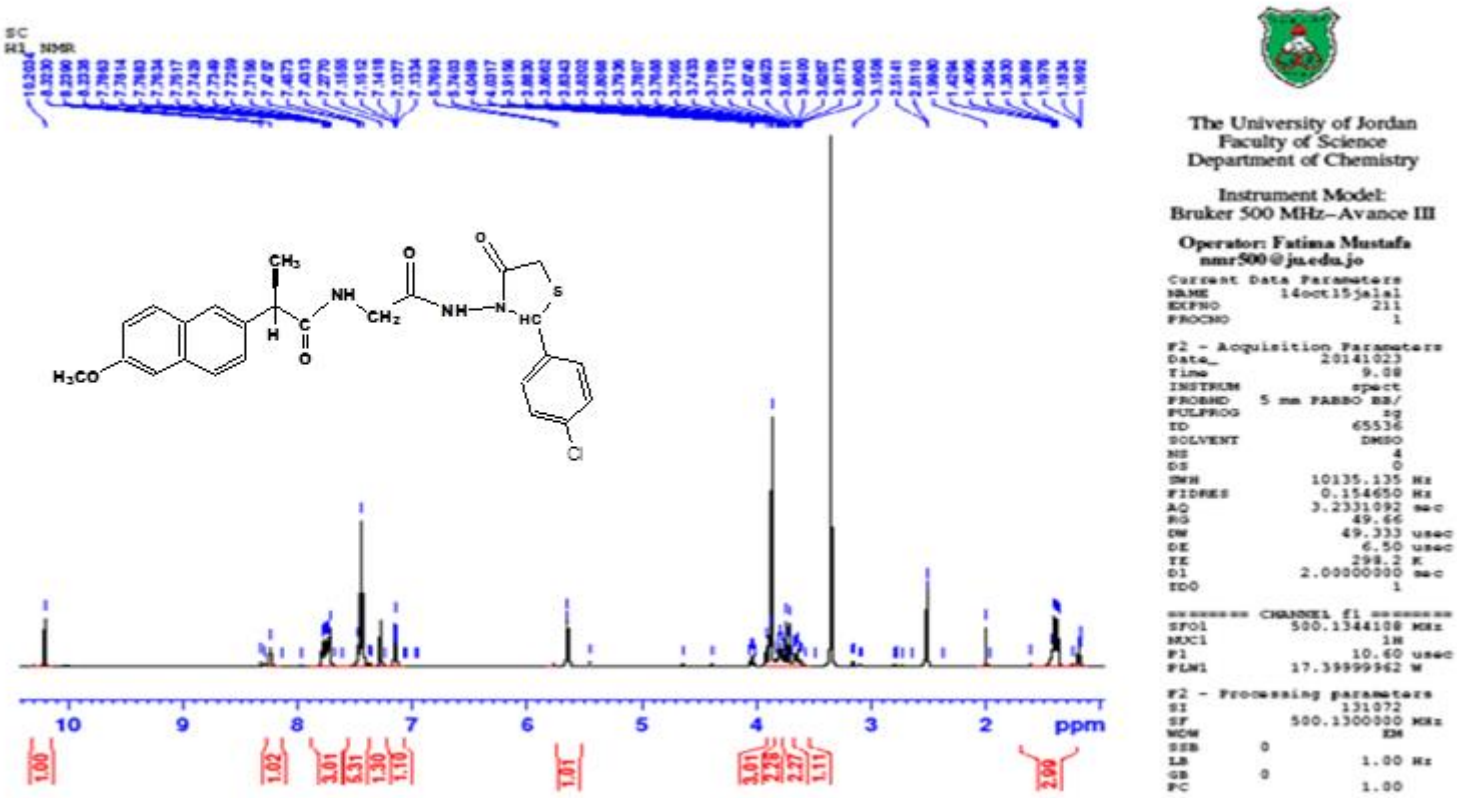


Figure (3-22): ^{1}H-NMR spectrum of compound (V_b)

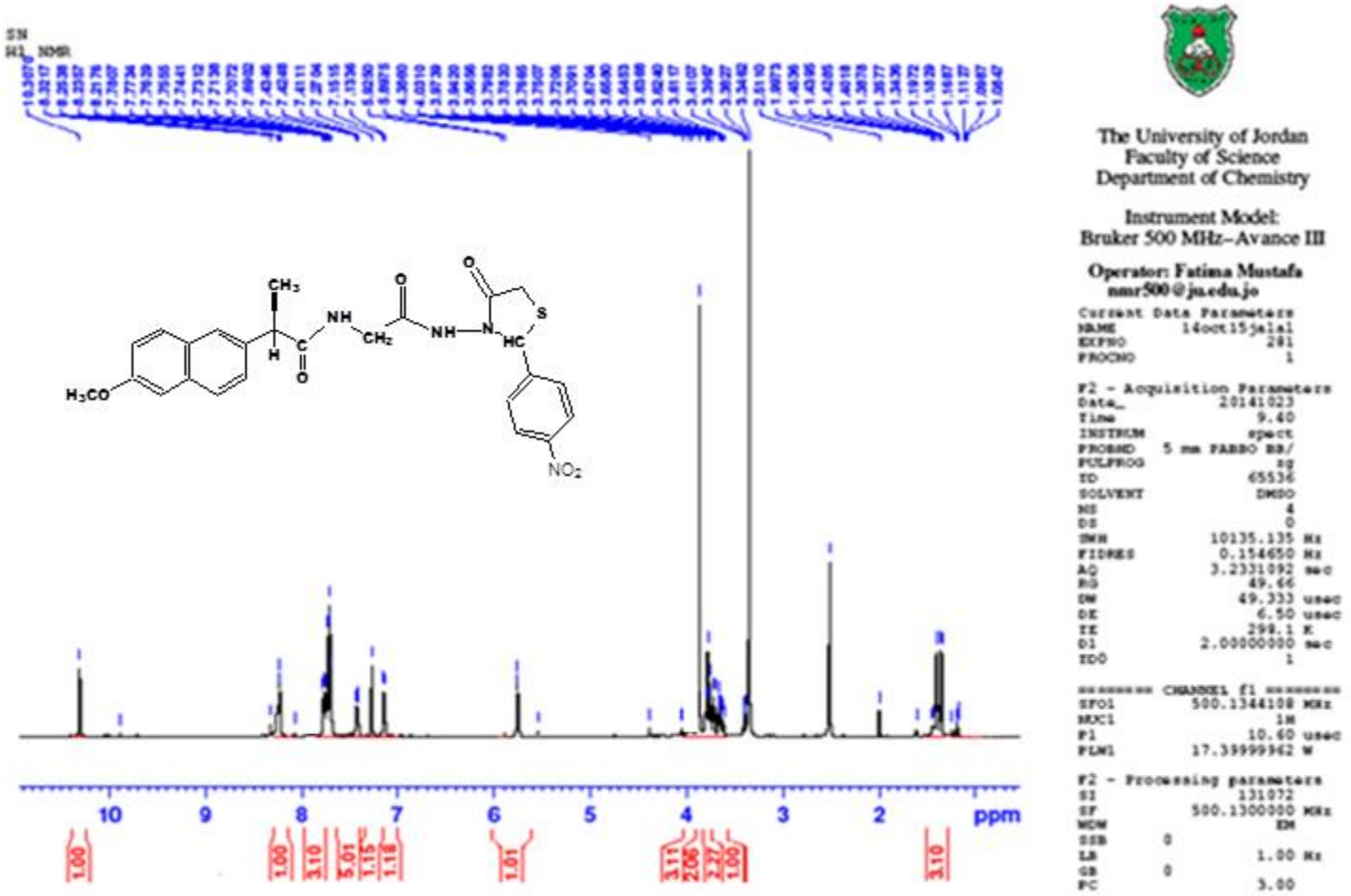


Figure (3-23): ^{1}H-NMR spectrum of compound (V_C)

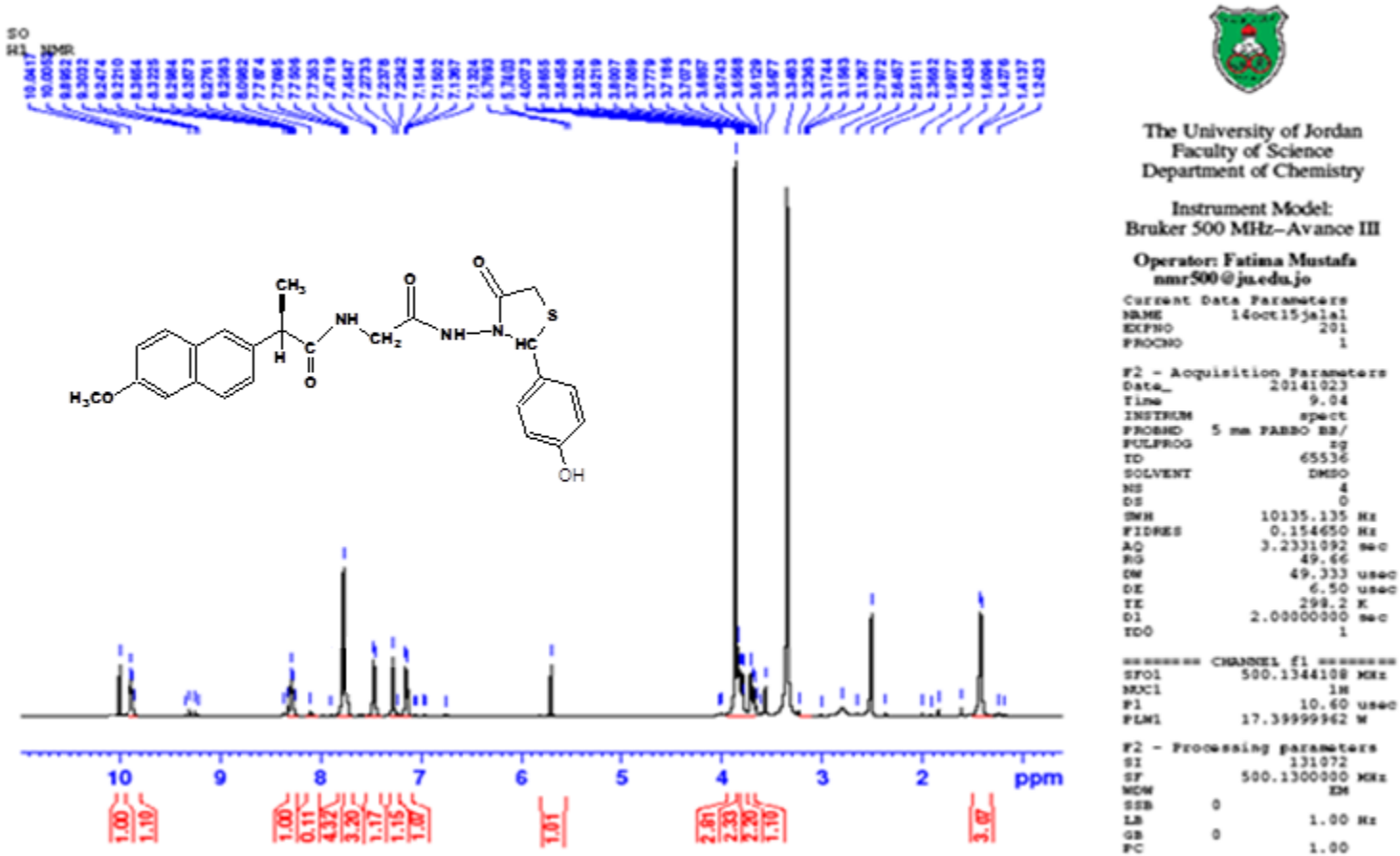


Figure (3-24): ^{1}H-NMR spectrum of compound (V_d)

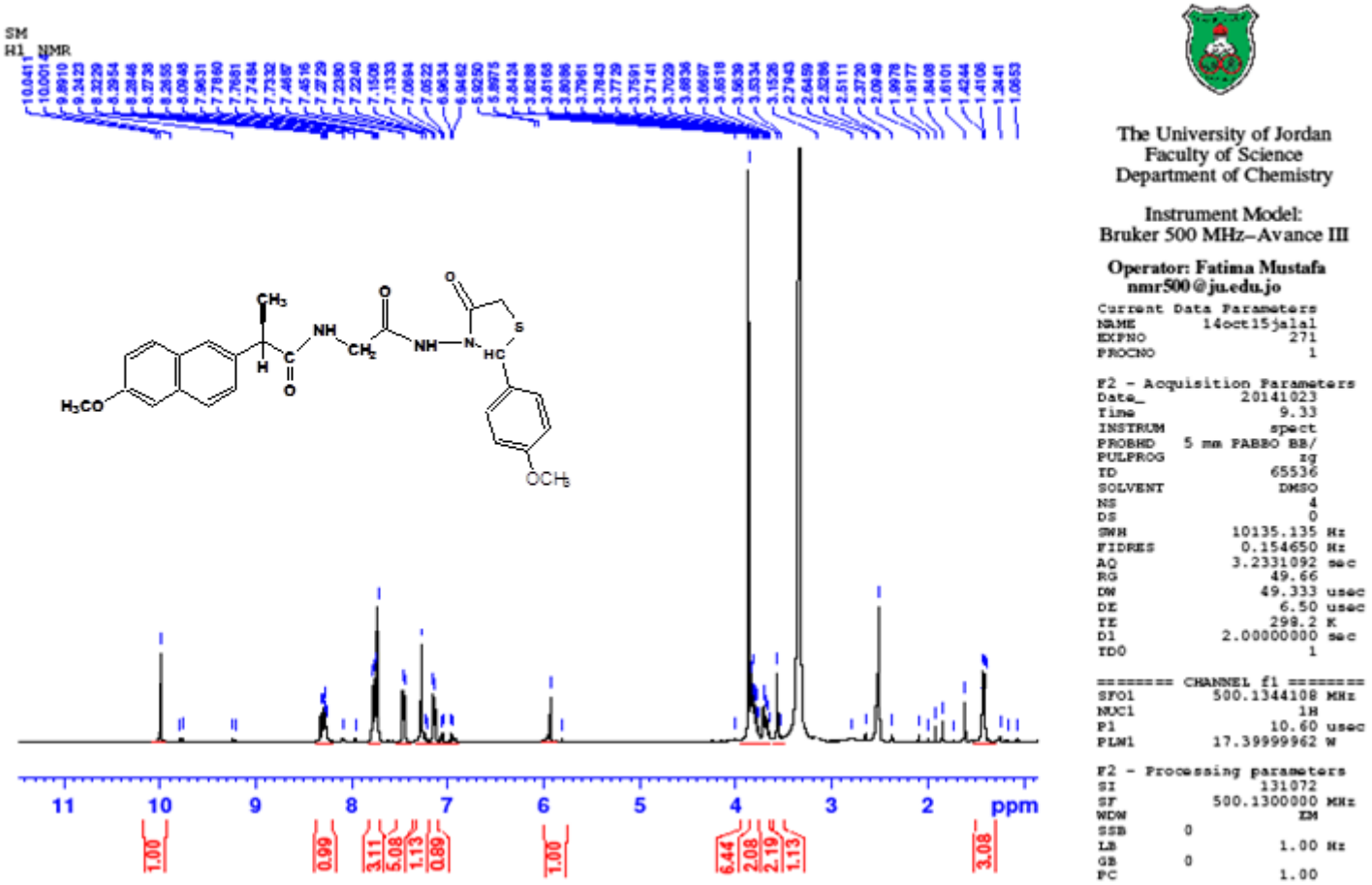


Figure (3-25): ^{1}H-NMR spectrum of compound (V_e)

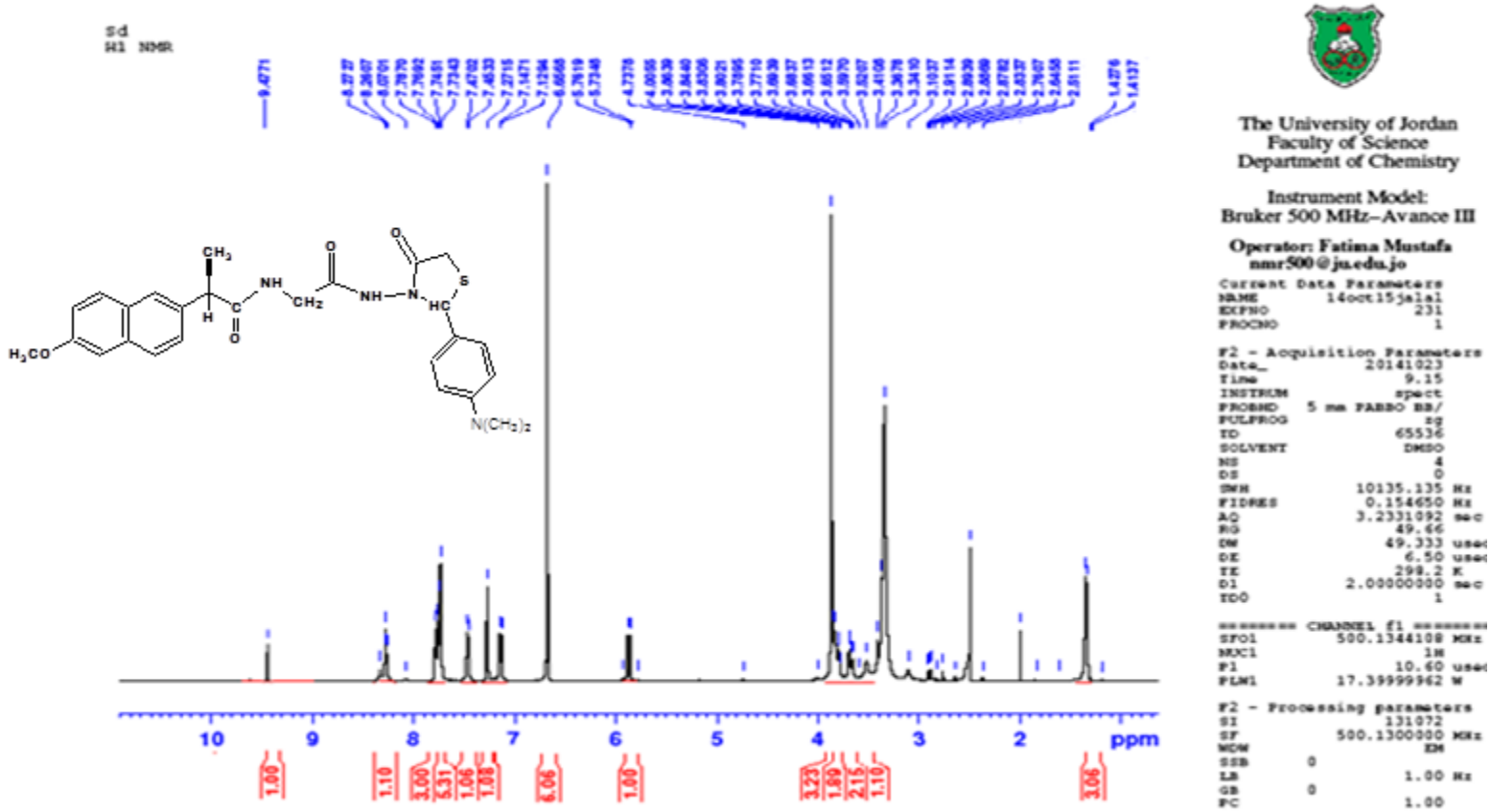


Figure (3-26): ^{1}H-NMR spectrum of compound (V_f)

Table (3-12): Elemental microanalysis of the final compounds.

No.	Molecular Formula	Molecular Weight	Calculated/Found		
			C%	H%	N%
V_a	$C_{25}H_{25}N_3O_4S$	463	64.78 65.51	5.44 5.37	9.06 9.43
V_c	$C_{25}H_{24}N_4O_6S$	508	59.04 60.11	4.76 4.65	11.02 11.22
V_d	$C_{25}H_{25}N_3O_5S$	479	62.61 64.01	5.25 5.13	8.76 8.90
V_e	$C_{26}H_{27}N_3O_5S$	493	63.27 64.88	5.51 5.42	8.51 8.76
V_f	$C_{27}H_{30}N_4O_4S$	506	64.01 65.74	5.97 5.86	11.06 11.33

3.3. Pharmacological Study:

This section concerned with the results of preliminary pharmacological evaluation of tested compounds as anti-inflammatory agents using paw-edema method following intra-plantar injection of egg-white into rat hind paw.

3.3.1. Dose Determination of the Tested Compounds:

The determination of the dose of the newly synthesized compounds (**V_{a-f}**) was depending on the dose of the Naproxen (reference compound) in which the tested compounds are derived from it.

Then according to molecular weight of the tested compound the dose was calculated using the following equation:

$$\frac{\textit{Dose of reference compound}}{\textit{Molecular weight of reference compound}} = \frac{\textit{Dose of tested compound}}{\textit{Molecular weight of tested compound}}$$

3.3.2. *In Vivo* Method for Evaluation of Anti-inflammatory Activity:

The most widely used primary test to screen new anti-inflammatory agents measures the ability of the compound to reduce local edema induced in the rat paw by injection of an irritant agent [(95)]. Many irritant agents have been used in the paw-edema method like dextran, egg-white and carrageenan solution. The paw edema induced by carrageenan has been extensively studied in the assessment of the anti-inflammatory action of steroidal and non-steroidal drugs involving several chemical mediators such as histamine, serotonin, bradykinin and prostaglandins [(96)].

Subcutaneous injection of irritant agent into the rat paw produces inflammation resulting from plasma extravasations, increased tissue water and plasma protein exudation along with neutrophil extravasations, all due to the metabolism of arachidonic acid [(97)].

Carrageenan induced edema has been commonly used as an experimental animal model for acute inflammation and is believed to be biphasic. The early phase 1–2 hr. of the carrageenan model is mainly mediated by histamine, serotonin and increased synthesis of prostaglandins in the damaged tissue surroundings. The late phase is sustained by prostaglandin release and mediated by bradykinin, leukotrienes, polymorph nuclear cells and prostaglandins produced by tissue macrophages[(95)].

3.3.3. Evaluation of the Anti-inflammatory Activity of the Tested Compounds:

The anti-inflammatory activity of the tested compounds has been evaluated in comparison with their vehicle (control group) and Naproxen. Table (3-12) explains the effect of tested compounds (**V_{a-f}**) in comparison to control and Naproxen.

The tested compounds and the reference drug produced significant reduction of paw edema with respect to the effect of propylene glycol 50%v/v (control group). All tested compounds significantly limited the inflammation in paw edema, the onset of compound **V_d** started at time 60 min. while the remaining compounds and Naproxen started at 120 min.

Compounds **V_{a-e}** exhibited potent anti-inflammatory effect than Naproxen (50mg/kg, i.p.) at 180-240 min., while compound **V_f** exhibited lower anti-inflammatory effect.

However, the effect of all tested compound continued till the end of experiment with statistically significant (P<0.05) reduction in paw edema thickness as shown in Figure (3-27).

Table (3-13): The anti-inflammatory effect of control, Naproxen and tested compounds V_a-$_f$ on egg-white induced paw edema in rats

	compounds	Time (min)						
		0	30	60	120	180	240	300
Paw Thickness (mm) / n=6	Control	4.40±0.08	5.43±0.10	6.18± 0.09	6.96±0.06	7.05±0.10	6.71±0.05	5.39±0.04
	Naproxen	4.36±0.07	5.48±0.08	6.11±0.10	5.71±0.08^{*a}	5.54±0.09^{*a}	5.27±0.10^{*a}	4.73±0.05^{*a}
	V_a	4.37±0.10	5.41±0.05	5.97±0.09	5.66±0.04^{*a}	5.11±0.06^{*b}	4.86±0.05^{*b}	4.52±0.07^{*a}
	V_b	4.40±0.06	5.40±0.10	5.99±0.04	5.68±0.07^{*a}	5.21±0.09^{*b}	4.94±0.05^{*b}	4.61±0.08^{*a}
	V_c	4.38±0.05	5.42±0.04	6.06±0.06	5.73±0.10^{*a}	5.23±0.08^{*b}	4.96±0.09^{*b}	4.55±0.10^{*a}
	V_d	4.35±0.04	5.41±0.10	5.82±0.07*	5.51±0.06^{*a}	5.12±0.05^{*b}	4.88±0.08^{*b}	4.53±0.10^{*a}
	V_e	4.39±0.09	5.40±0.05	6.02±0.06	5.69±0.05^{*a}	5.22±0.07^{*b}	4.93±0.04^{*b}	4.59±0.10^{*a}
	V_f	4.35±0.04	5.39±0.05	5.98±0.07	6.25±0.08^{*b}	5.85±0.10^{*c}	5.57±0.06^{*c}	5.05±0.09^{*b}

Non-identical superscripts (a,b&c) among different tested compounds are considered significantly different (P<0.05); *significantly different compared to control (P<0.05).Data are expressed in mm paw thickness as mean ± SEM. n= number of animals.Time (0) is the time of i.p. injection of Naproxen and propylene glycol.
Time (30) is the time of injection of egg white (induction of paw edema).

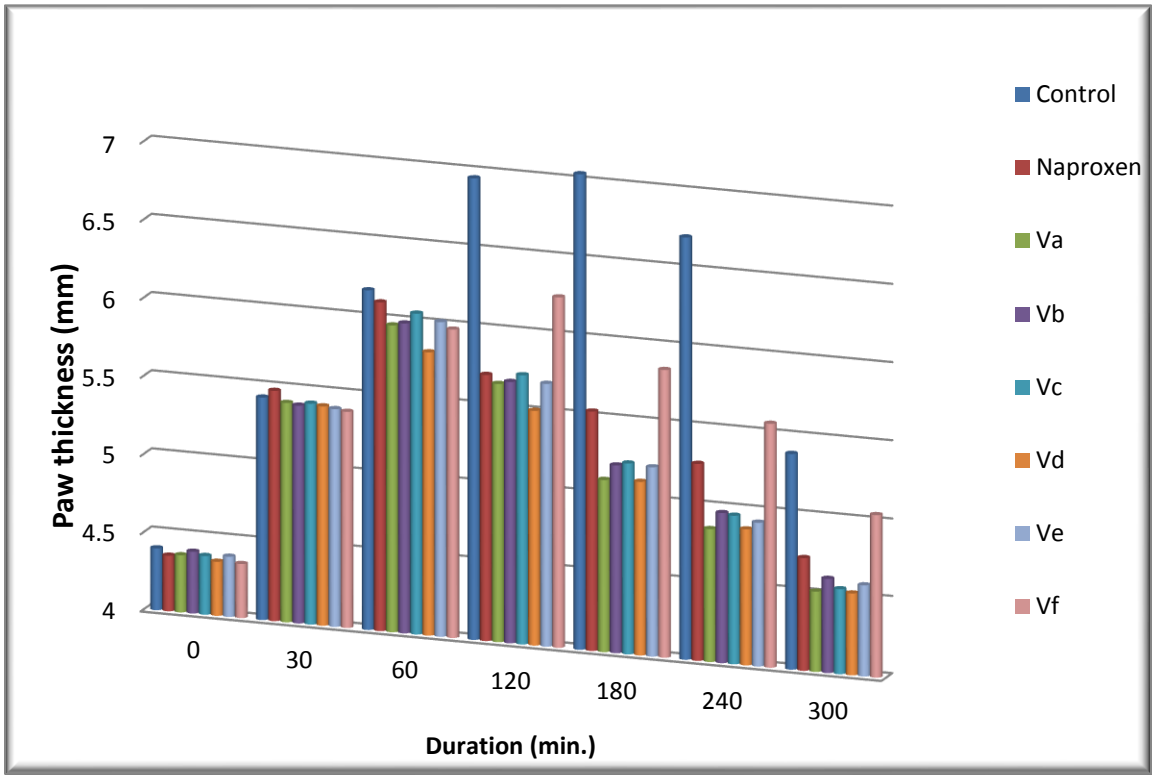


Figure (3-27): Effect of Naproxen, propylene glycol and tested compounds (V_a-$_f$) on egg-white induced paw edema in rats

3.3.4. Comparative Analysis:

The comparison explains that at 0-30 min. there are no differences among all groups. Compounds (**V_a-V_e**) at time 120-300 minutes show comparable effect to Naproxen; however at interval 180-240 minutes show significantly higher effect. Although; compound **V_f** significantly limited the increase in paw edema in comparison to control group, but it is significantly lesser effect than Naproxen and tested compounds (**V_a-V_e**) at interval of 120-300 minutes.

3.4. Conclusions:

1. The synthesis of the designed compounds has been successfully achieved.

2. Characterization and identification of the synthesized compounds were confirmed by determination of physical properties, FT-IR spectroscopy, ^{1}H-NMR spectra and elemental microanalysis.

3. Anti-inflammatory study using egg white induced edema model of inflammation revealed that the incorporation of (4-thiazolidinone) derivatives into a Naproxen maintained or enhanced it is anti-inflammatory activity.

4. Our study of the anti-inflammatory activity indicated that Compounds (**V_a-$_e$**) can be further explored as anti-inflammatory agents.

3.5. Further Study:

1. Study the ulcerogenic side effects of these compounds.

2. Determination of COX-2 selectivity of the target compounds by assessing COX-2: COX-1 inhibitory ratio using human whole blood assay.

3. Evaluation of antimicrobial activity for the target compounds.

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5- س-2-(6-ميثوكسي نفثالين-2-يل)-ن-(2-((2-(4-اريل)-4-اوكسوثايازوليدين-3-يل)امينو)-2-اوكسو اثيل)بروبان امايد(V_{a-f}).

ان تخليق المركبات المصممة قد أنجز بنجاح. تم التأكد من نقاوة وخواص المركبات المصنعة وذلك بقياس الخواص الفيزيائية (درجات الانصهار و معامل التعويق)، و قياس اطياف الأشعة تحت الحمراء و أطياف التردد المغناطيسي والتحليل الدقيق للعناصر.

وجرى تقييم تأثيرات مضادة للألتهابات الحادة للمركبات المحضرة في الجسم الحي (الجرذان) باستخدام زلال البيض لأستحداث وذمة تحت الجلد كنموذج للألتهاب.

ان المركبات المختبرة و الدواء المقارن اظهر أنخفاض مؤثر للوذمة مقارنة مع البروبلين كلايكول كمجموعة ضابطة.

المركبات (V_{a-e}) أظهرت فعالية مضادة للألتهاب أقوى من النابروكسن و لفترة اختبار تراوحت من 180- 240 دقيقة، بينما المركب(V_f) أظهر فعالية أقل كمضاد للألتهاب.

هذه النتائج تشجع على إجراء تقييمات إضافية على هذه المركبات لإظهار أو تشخيص درجه انتقائيتها المثبطة لإنزيم كوكس-2.

الخلاصة

الادوية المضادة للالتهاب غير الستيرويدية تمثل واحدة من أكثر فئات الأدوية استخداما على نطاق واسع، وتستخدم في الدرجة الأولى لعلاج التهاب المفاصل الروماتويدي والاضطرابات الالتهابية الأخرى؛ ومع ذلك، فإن استخدام مضادات الالتهاب غير الستيرويدية يواجه تحديدات كبيرة في الاستخدامات الطبية بسبب قابليتها على احداث تقرحات في مسالك الجهاز الهضمي.

ان تثبيط أنزيم كوكس-2 هو المسؤول عن الفعالية العلاجية كمضاد للالتهاب بينما تظهر الاثار الجانبة بسبب تثبيط نشاط أنزيم كوكس-1 وهكذا فأن مثبطات أنزيم كوكس- 2 الأنتقائية قد خفضت الاثار الجانبية.

التثبيط التفضيلي لكوكس-2 يعتقد انه بسبب الحيز الاضافي في قناة الكوكس-2 الهيدروفوبية وكذلك الى وجود جيب جانبي في القناة وبالتالي،فأن المجموعة الدوائية (4-ثايازوليدينونز) أدمجت الى النابروكسين لزيادة حجمه قد صممت وخلقت لتقييمها كعوامل مؤثرة للالتهابات مع انتقائية مثبطة متوقعة نحو أنزيم كوكس-2 .

ان طرق التحضير قد نجحت بتصنيع المركبات الوسطية و النهائية والتي تتضمن:

1- اثيل 2- امينو استيت هايدروكلورايد (I).

2- س-اثيل-2-[2-(6-ميثوكسي نفثالين-2-يل)-بروبان اميدو]اسيتيت(II).

3- س-ن-(2-هيدرازينال-2-اوكسواثيل)-2-(6-ميثوكسينفثالين-2-يل)بروبان امايد(III).

4- س-2-(6-ميثوكسي نفثالين-2-يل)-ن-(2-(2-(4-بينزليدين)هيدرازينال)-2-اوكسواثيل)بروبان امايد (IV_{a-f}).

جمهوريه العراق

وزارة التعليم العالي والبحث العلمي

الجامعه المستنصريه

كلية الصيدله

تصنيع وتقييم مشتقات 4-ثايازوليدينونز للنابروكسين لامكانية تحسين فعاليتها كتأثير مضاد للألتهاب

رسالة مقدمه الى فرع الكيمياء الصيدلانية والى لجنة الدراسات العليا في كلية الصيدله – الجامعه المستنصرية كجزء من متطلبات الحصول على درجة الماجستير في الصيدلة (الكيمياء الصيدلانية)

من قبل

فرح عبد الحليم كاظم

بكلوريوس صيدله 2009

باشراف

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