بسم الله الرحمن الرحيم

Sudan University of Science and Technology

College of Graduate Studies

Preparation of some mefenamic acid derivatives

تحضير بعض مشتقات حمض الميفيناميك

By

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الآية

قَالَ تَعَالَىٰ:

﴿ لَا يُكَلِّفُ ٱللَّهُ نَفْسًا إِلَّا وُسْعَهَا ۚ لَهَا مَا كَسَبَتْ وَعَلَيْهَا مَا ٱكْتَسَبَتْ ۗ رَبَّنَا لَا تُؤَاخِذْنَآ إِن نَّسِينَآ أَوْ أَخْطَأْنَا ۚ رَبَّنَا وَلَا تَحْمِلْ عَلَيْنَآ إِصْرًا كَمَا حَمَلْتَهُۥ عَلَى ٱلَّذِينَ مِن قَبْلِنَا ۚ رَبَّنَا وَلَا تُحَمِّلْنَا مَا لَا طَاقَةَ لَنَا بِهِۦ ۖ وَٱعْفُ عَنَّا وَٱغْفِرْ لَنَا وَٱرْحَمْنَآ ۚ أَنتَ مَوْلَىٰنَا فَٱنصُرْنَا عَلَى ٱلْقَوْمِ ٱلْكَٰفِرِينَ ﴾

صدق الله العظيم

سورة البقرة: الآية ﴿٢٨٦﴾

Dedication

I Dedicate this work with deep love and respect to

My parents

My brother

And to My friends

Acknowledgment

Thanks to Allah the most gracious, the compassionate for giving me strength and health to complete this work.

I am deeply grateful to my supervisor: Prof. Dr. Ahmed Elsadig Mohammed Saeed, for his fruitful guidance.

I wish to thanks UstazFathi Abbas for being available willingly to provide help when being asked.

I am grateful to the chemistry laboratory staff for their great help.

Finally, special thanksfor all those who have kindly helped me.

Abstract

Nine new substituted mefenamic acid derivatives were synthesized by the reaction between the amino group in mefenamic acid and acyl chloride to give tertiary amine and reaction of free carboxylic acid of mefenamic acid with alcohol to give ester, ACD/Lab program method for Moleculardesign was described. The results on application of ACD/Lab program in calculation and correlation of structure properties of the some mefenamic acid derivatives reported. The synthetic design of these compounds was achieved through retrosynthetic analysis (RSA) approach.

The reaction progress for all synthesized compounds was checked by (TLC) and m.p. techniques, and the structures of the synthesized compounds were confirmed using IR, ^{1}HNMR, UV, and GC-MS.

الخـــــلاصــة

تسع من بعض مستبدلات حمض الميفيناميك الجديدة تم تخليقها بواسطة التفاعل بين مجموعة الامين في حمض اليفيناميك وكلوريد اسيل لإعطاء أمين ثالثوي و تفاعل مجموعة الكاربوكسيل الحره لحمض الميفيناميك مع الكحول لإعطاء إسترات، بطريقة برامج ACD/Lab للمركبات المختلفة التي تم وصفها.النتائج ركزت علي تطبيق برنامجACD/Labفي حساب الخصائص التركيبية وإيجاد العلاقة بينها لبعض مشتقات حمضالميفيناميك.

التصميم التخليقي لهذه المركبات تم التحقق منه من خلال نهج تحليل التخليق الرجعي، عند تقدم التفاعل للمركبات المخلقة تمت متابعتها بواسطة تقنيتي كروموتوغرافيا الطبقة الرقيقة ودرجة الإنصهار، تم التأكد من البنيه التركيبية للمركبات بإستخدام طريقة طيف الإشعة تحت الحمراء، طيف الرنين النووي المغناطيسي للبروتون ، طيف الاشعة فوق البنفسجية وبعض من المركبات حللت بكروموتوغرافيا الغاز المقترن مع طيف الكتلة.

List of Contents

List of Figures and Schemes

List of Tables

List of abbreviation

Term	abbreviation
Ar	Aromatic
D	Density
M	Multiple
M.wt	Molecular weight
MA	Mefenamic Acid
MF	Molecular Formula
MV	Molar Volume
Name S.	Name for structure
NSAIDs	Non-steroidal Anti-Inflammatory Drugs
Rec.	Recrystallization
s	single
st.vib.	stretching vibration
t	Triple
Temp.	Temperture

Chapter One

Introduction

1. Introduction

1.1. Non-Steroidal Anti-inflammatory Drugs (NSAIDS)

The non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of minor pain and for the management of edema and tissue damage resulting from inflammatory joint disease (arthritis), a number of these drugs possess antipyretic activity in addition to having analgesic and anti-inflammatory actions, and thus have utility in the treatment of fever, most of these drugs express their therapeutic actions by inhibition of prostaglandin biosynthesis (Manjanna and Shivakumar, 2011).

1.1.1. General Structure and Properties of the NSAIDs:

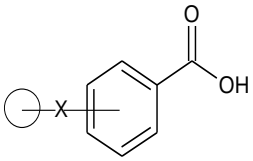


Figure (1.1) NSAIDs General Structure

The NSAIDs are characterized by the following chemical/ pharmacologic properties:

All are relatively strong organic acids with *pKa* in the range 3-5. Thus, salts forms can be generated upon treatment with base and all of these compounds are extensively ionized at physiologic *pH.* The acidic group is essential for COX inhibitory activity.

The NSAIDs differ in their lipophilicities based on the lipophilic character of their aryl groups and additional lipophilic moieties and substituents.

The acidic group in these compounds serves as a major binding group (ionic binding) with plasma proteins.

Thus all NSAIDs are highly bound by plasma proteins.

The acidic group also serves as a major site of metabolism by conjugation. Thus a major pathway of clearance for many NSAIDs is glucuronidation (and inactivation) followed by renal elimination. (Nishimori *et al.*, 2006)**.**

1.1.2. Uses:

NSAIDs are used to relieve pain and reduce signs of inflammation fever, swelling and redness. People may take NSAIDs for temporary conditions such as sprains, strains, flares of back pain, headache and painful menstrual periods. NSAIDs also are a common treatment for

chronic (long-term) health problems such as arthritis (rheumatoid arthritis, osteoarthritis and others) and lupus (Gigante *et al,* 2012).

1.1.3. NSAID Mechanism of Action

Traditionally, the analgesic action of non-steroidal anti-inflammatory drugs (NSAIDs) has been explained on the basis of their inhibition of the enzymes that synthesis prostaglandins. However, it is clear that NSAIDs exert their analgesic effect not only through peripheral inhibition of prostaglandin synthesis but also through a variety of other peripheral and central mechanisms (Gigante *et al,* 2012).

It is now known that there are two structurally distinct forms of the cyclo-oxygenase enzyme (COX-1 and COX-2). COX-1 is a constitutive member of normal cells and COX-2 is induced in inflammatory cells. Inhibition of COX-2 activity represents the most likely mechanism of action for NSAID-mediated analgesia, while the ratio of inhibition of COX-1 to COX-2 by NSAIDs should determine the likelihood of adverse effects. In addition, some NSAIDs inhibit the lipoxygenase pathway, which may itself result in the production of algogenic metabolites. Interference with G-protein-mediated signals transduction by NSAIDs may form the basis of an analgesic mechanism unrelated to inhibition of prostaglandin synthesis (Cashman, 1996).

There is increasing evidence that NSAIDs have a central mechanism of action that augments the peripheral mechanism. This effect may be the result of interference with the formation of prostaglandins within the CNS. Alternatively, the central action may be mediated by endogenous opioid peptides or blockade of the release of serotonin (5-hydroxytryptamine; 5-HT). A mechanism involving inhibition of excitatory amino acids or *N*-methyl-D-aspartate receptor activation has also been proposed (Cashman, 1996).

1.1.4. Classification OF NSAIDs:

1.1.4.1. Salicylates:

The salicylates are derivatives of 2-hydroxybenzoic acid (salicylic acid).The salicylates were discovered in 1838 following the extraction of salicylic acid from willow bark. Salicylic acid was used medicinally as the sodium salt but replaced therapeutically in the late 1800s by the acetylated derivative, acetylsalicylic acid (ASA) or aspirin. Therapeutic utility is

enhanced by esterification of the phenolic hydroxyl group as in aspirin, and by substitution of a hydrophobic/lipophilic group at C-5 as in diflunisal (Bhushan and Martens, 2007):

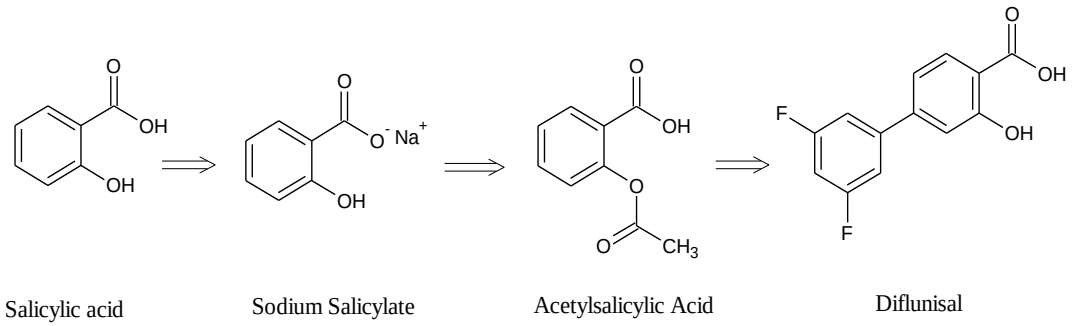


Figure (1.2): Salicylates Structure

The salicylates are strong organic acids and readily form salts with alkaline materials. The carboxyl group is substantially more acidic and ionizes readily at physiologic pH than the phenolic hydroxyl group (Singh, 2004):

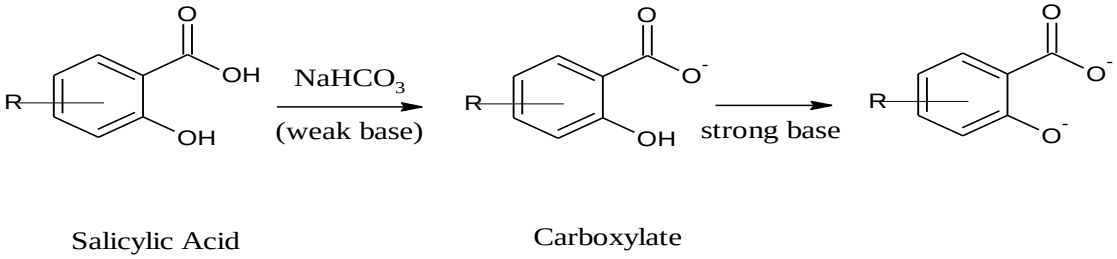


Figure (1.3): Reaction Salicylates with sodium carbonate

1.1.4.2. Propionic Acid Derivatives ("Profens"):

Some of the most useful NSAIDs are structurally derived from arylaceticacids. These compounds are often referred to as the "profens" based on the suffix of the prototype member, ibuprofen.

Like the salicylates these agents are all strong organic acids (*pKa* = 3-5) and thus form water soluble salts with alkaline reagents. The aryl propionic acids are characterized by the general structure Ar-CH (CH_3)-COOH which conforms to the required general structure. All of these compounds are predominantly ionized at physiologic pH and more lipophilic than acetyl salicylic acid (ASA) or salicylic acid. (Bhushan and Martens, 2007)

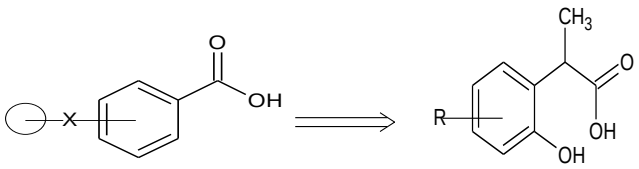


Figure (1.4) General Structure of Propionic Acids

The α-CH_3 substituent presents in the profens increases cyclooxygenase inhibitory activity and reduces toxicity of the profens. The α-carbon in these compounds is chiral and the S-(+)-enantiomer of the profens is the more potent cyclooxygenase inhibitor.

Most profen products, except naproxen, are marketed as the racemates. In addition to the metabolism described below, the profens undergo a metabolic inversion at the chiral carbon involving stereo specific transformation of the inactive R-enantiomers to the active S-enantiomers. This is believed to proceed through an activated (more acidic α-carbon) intermediate. Normally only the S-(+) isomer is present in plasma.

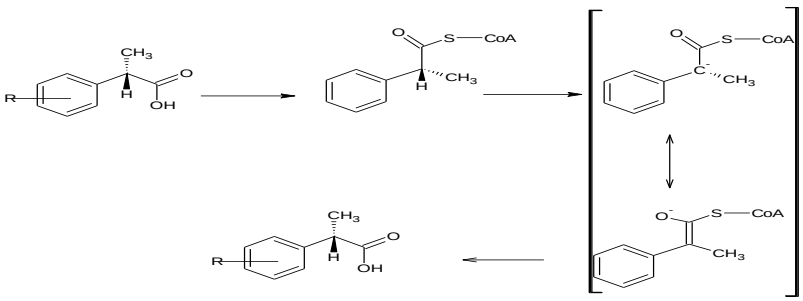


Figure (1.4): Structure enantiomers

1.1.4.3. Aryl and Hetero aryl acetic Acids:

These compounds are also derivatives of acetic acid, but in this case the substituent at the 2-position is a hetero cycle or related carbon cycle. This does not significantly affect the acidic properties of these compounds. The hetero aryl acetic acid NSAIDs marketed in this class can be further sub classified as the indene/indoles, the pyrroles and the oxazoles as shown below (Baldo and Pham, 2013):

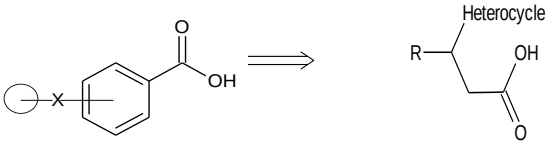
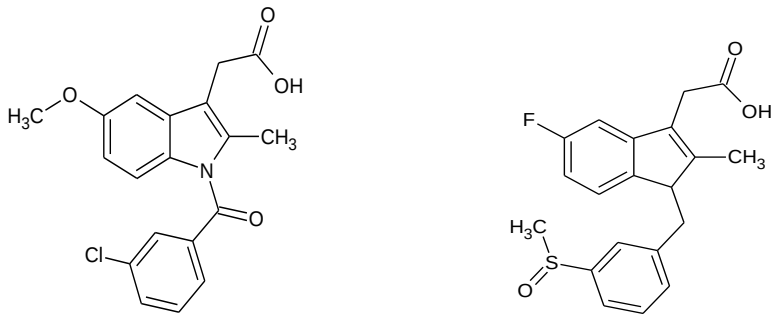


Figure (1.5) NSAID General Structure for Hetero cyclic Acetic Acids

A. Indene and Indole Acetic Acids:

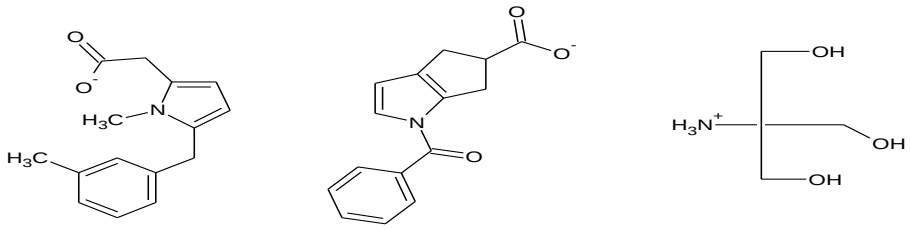


Indomethacin (Indocin) Sulindac (Clinoril)

Figure (1.6) Structure Indene and Indole

Indomethacin contains abenzoylatedindole nitrogen. The methyl group at the two position of the indole ring prevents free rotation about the C-N bond and keeps the two aromatic rings in the correct relationship for COX binding and therapeutic activity.

B. Aryl acetic Acids: The Pyrrole Acetic Acids



Tometin(Tolectin) Ketorolac Tromethamine

Figure (1.7) Structure Aryl acetic Acids

Tolmetin (Tolectin): Non-selective COX inhibitor with actions similar to other members in this class and it is used for Rheumatoid Arthritis (RA), Osteoarthritis (OA). It is the shortest acting member of this class due in part to rapid Phase I oxidation of the p-methyl group to a benzylic alcohol initially and eventually to the acid. These metabolites are subsequently glucuronidated and eliminated. As a result of this, tolmetin's half-life is typically less than 5 hours.

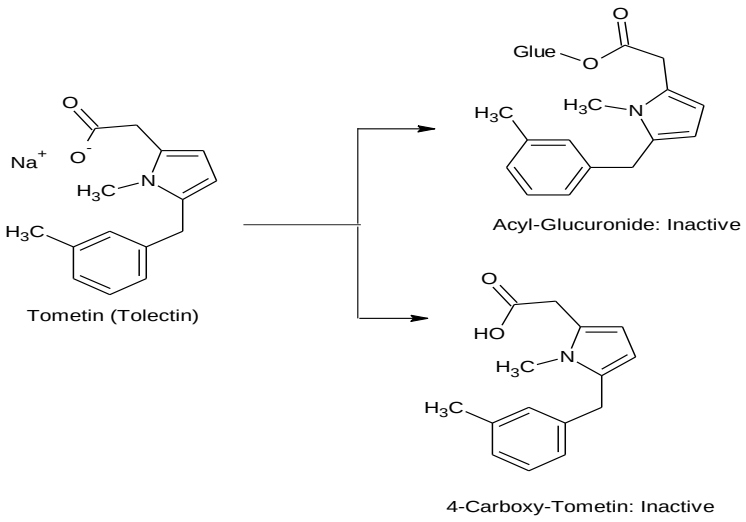
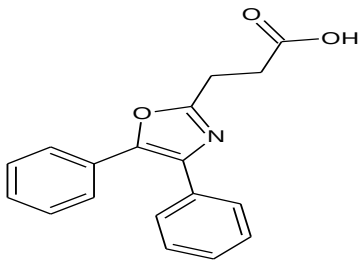


Figure (1.8) Structure of Aryl acetic Acids

C. Arylacetic Acids: Oxazole Acetic Acids

Addition to this class of agents is oxaprozin another nonselective COX inhibitor. It differs slightly in that substitution of the propionic moiety is at the three position rather than that at the two position as in other agents of this class. It is metabolized byglucuronidation and uncharacterized oxidation products.



Oxaprozin (Daypro)

Figure (1.9) Structure of Oxazole Acetic Acids

1.1.4.4. Anthranilates:

These agents are considered to be N-aryl substituted derivatives of anthranilic acid which is itself a bioisostere of salicylic acid. These agents retain the acid properties that are characteristic of this class of agents; however, mefenamic acid and meclofenamic acid are derivatives of anthranilic acid, diclofenac is derived from 2-arylacetic acid. The most active fenamates have small alkyl or halogen substituent at the two, three and/or six position of the N-aryl moiety (meclofenamate is 25 times more potent than mefenamate).

Hence this steric effect is proposed to be important in the effective interaction of the fenamates at their inhibitory site on cyclooxygenase.

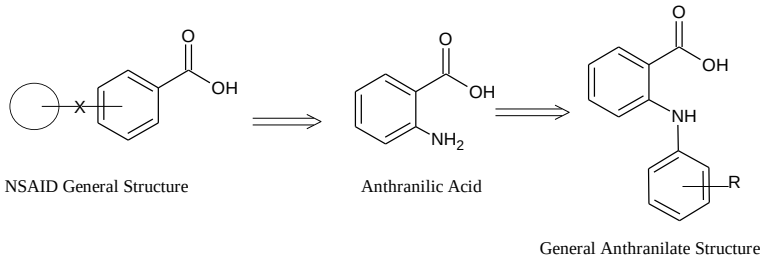
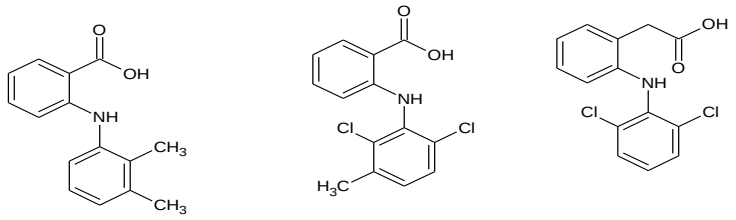


Figure (1.10) Structure of Anthranilates

The anthranilates have primarily anti-inflammatory with some analgesic and antipyretic activity and are non-COX selective. The anthranilates are used as mild analgesics and occasionally to treat inflammatory diseases. (Cashman *et al*, 2013)



1.1.4.5. Oxicams (Enolic Acids)

Oxicams (Piroxicam and Meloxicam) are characterized by the 4-hydroxybenzothiazine heterocycle. The acidity of the oxicams is attributed to the four-OH with the enolate anion being stabilized by Intramolecular H-bonding to the amide N-H group.

The presence of the carboxamide substituent at the three-position of the benzothiazine ring contributes toward acidity by stabilizing the negative charge formed during ionization (resonance stabilization).

Although these compounds are acidic (*pKa* = 6.3), they are somewhat less acidic than carboxylic acids NSAIDs. Yet the oxicams are primarily ionized at physiologic pH and acidity is required for COX inhibitory activity. (Cashman *et al*, 2013)

Higher COX-2 selectivity than many other NSAIDs, particularly meloxicam. These agents have utility in treatment of RA and OA.

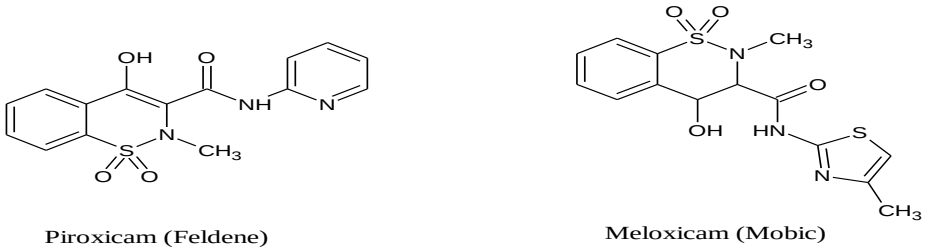


Figure (1.11) Structure of Oxicams

1.1.4.6. Phenylpyrazolones:

This class of agents is characterized by the 1-aryl-3, 5-pyrazolidinedione structure. The presence of a proton which is situated to two electron withdrawing carbonyl groups renders these compounds acidic. The *pKa* for phenylbutazoneis 4.5Oxyphenbutazone is a hydroxylated metabolite of phenylbutazone (Manjanna and Shivakumar, 2011).

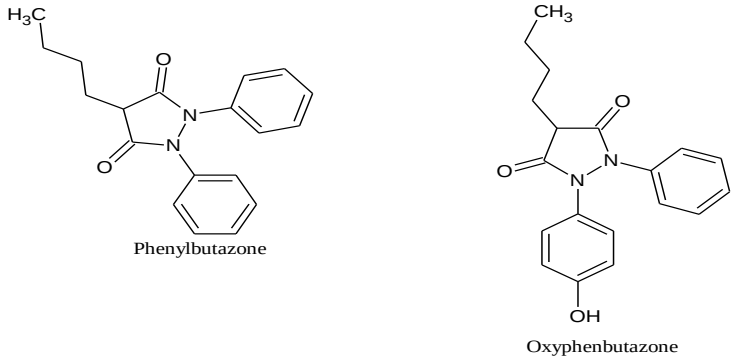


Figure (1.12) Structure of Phenylpyrazolones

1.1.5. Side effects:

All drugs have a risk of side effects, including NSAIDs. It is important to understand the risks and benefits of a drug before deciding to take it (Gigante *et al*, 2012).

Possible risks of all NSAIDs include, among others:

Stomach problems like bleeding, ulcer and stomach upset, high blood pressure, fluidretention, kidneyproblems, heartproblems, rashes.

1.2. Mefenamic acid

1.2.1. Description:

Mefenamic acid is a member of the fenamate group of non-steroidal anti-inflammatory drugs (NSAIDs). Mefenamic acid is a white to greyish-white, odorless, microcrystalline powder with a melting point of 230°-231°C and water solubility of 0.004% at pH 7.1. The chemical name is N-2,3xylylanthranilic acid. The molecular weight is 241.29. (Kovala-Demertzi, 2006) Its molecular formula is $C_{15}H_{15}N0_2$ and the structural formula of mefenamic acid is:

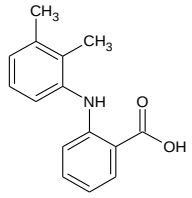


Figure (1.13) Structure of Mefenamic acid

1.2.2. Pharmacodynamics:

Mefenamic acid is a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and anti-pyretic activities in animal models. The mechanism action of mefenamic acid, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthesize inhibition. (Chakraborty *et al*, 2008)

1.2.3. Pharmacokinetics:

Mefenamic acid is rapidly absorbed after oral administration. In two 500 mg single oral dose studies, the mean extent of absorption was 30.5 mg/hr/mL (17%CV) (Neuvonen *et al*, Aug1994) (Tali *et al*, 1975).

The bioavailability of the capsule relative to a dose or an oral solution has not been studied. Following a single one gram oral dose, mean peak plasma levels ranging from 10-20 mg/mL have been reported (Helal and Lane, 2014)

Peak plasma levels are attained in two to four hours and the elimination half-life approximates two hours. Following multiple doses, plasma levels are proportional to dose with no evidence of drug accumulation. (Yan *et al.*, 2006)

In a multiple dose trial of normal adult subjects(n=six) receiving one gram doses of mefenamic acid four times daily, steady-state concentrations of 20 mg/mL were reached on the second day of administration, consistent with the short half-life. The effect of food on the rate and extent of absorption of mefenamic acid has not been studied. Concomitant ingestion of anti-acids containing magnesium hydroxide has been shown to significantly increase the rate and extent of mefenamic acid absorption (Winder *et al.*, 1966).

Metabolism: Mefenamic acid is metabolized by cytochrome P450 enzyme CYP2C9 to 3-hydroxymethylmefenamic acid (Metabolite I). Further oxidation to a 3-carboxymefenamic acid (Metabolite II) may occur. (Venkataraman *et al.*, 2014) .The activity of these metabolites has not been studied. The metabolites may undergo glucuronidation and mefenamic acid is also glucuronidated directly. A peak plasma level approximating twenty mg/mL was observed at three hours for the hydroxyl metabolite and its glucuronide (n=six) after a single one gram dose. Similarly, a peak plasma level of eight mg/mL was observed at six to eight hours for the carboxy metabolite and its glucuronide (Huskey *et al.*, 2015).

Excretion: Approximately fifty-two percent of a mefenamic acid dose is excreted into the urine primarily asglucuronides of mefenamic acid (6%), 3-hydroxy mefenamic acid (25%) and 3-carboxymefenamic acid (21%).The fecal route of elimination accounts for up to 20% of the dose, mainly in the form of unconjugated 3-carboxymefenamic acid. The elimination half-life of mefenamic acid is approximately two hours. Half-life of metabolites I and II have not been precisely reported, but appear to be longer than the parent compound (Winder *et al,* 1966).

The metabolites may accumulate in patients with renal or hepatic failure. The mefenamic acid glucuronide may bind irreversibly to plasma proteins. Because both renal and hepatic excretions are significant pathways of elimination, dosage adjustments in patients with renal or hepatic dysfunction may be necessary. Mefenamic acid should not be administered to patients with preexisting renal disease or in patients with significantly impaired renal function (Onay *et al,* 2009).

1.2.4. Distribution:

Mefenamic acid has been reported as being greater than 90% bound to albumin (Champion *et al,* 1978). The relationship of unbound fraction to drug concentration has not been studied. The apparent volume of

distribution (Vz/F) estimated following a 500-mg oral dose of mefenamic acid was 1.06 L/kg. Based on its physical and chemical properties, mefenamic acid is expected to be excreted in human breast milk.

1.3. Molecular Modeling and Computational Chemistry:

1.3.1. The definition:

Molecular modeling is anything that requires the use of a computer to paint, describe or evaluate any aspect of the properties of the structure of a molecule (Ramachandran *et al*., 2008).Methods used in the molecular modeling arena regard automatic structure generation, analysis of three-dimensional (3D) databases, construction of protein models by techniques based on sequence homology, diversity analysis, docking of ligands or continuum methods. Thus, today molecular modeling is regarded as a field concerned with the use of all sort of different strategies to model and to deduce information of a system at the atomic level. On the other hand, this discipline includes all methodologies used in computational chemistry, like computation of the energy of a molecular system, energy minimization, Monte Carlo methods or molecular dynamics. In other words, it is possible to conclude that computational chemistry is the nucleus of molecular modeling. Identification of biomolecular moieties involved in the interaction with a specific receptor permits to understand the molecular mechanism responsible of it specific biological activity. In turn, this knowledge is aimed at designing new active molecules that can be successfully used as drugs. Due to the fact that simulation accuracy is limited to the precision of the constructed models, when it is possible, computational simulations have to be compared with experimental results to confirm model accuracy and to modify them if necessary, in order to obtain better representations of the system (Barril *et al*, 2006).

1.3.2. The major computational requirements are:

- Molecular energies and structures.
- Geometry optimization from an empirical input.
- Energies and structures of transition states.
- Bond energies.
- Reaction energies and all thermodynamic properties.
- Molecular orbitals.
- Multipolar moments.

- Atomic charges and electrostatic potential.
- Vibrational frequencies.
- IR and Raman spectra.
- NMR spectra.
- CD spectra.
- Magnetic properties.
- Polarizabilities and hyperpolarizabilities.
- Reaction pathway.
- Properties such as the ionization potential electron affinity proton affinity.
- Modeling excited states.
- Modeling surface properties and so on meeting these challenges could eliminate time-consuming and costly experimentations.
- Software tools for computational chemistry are often based on empirical information.

To use these tools effectively, need to understand the method of implementation of this technique and the nature of the database used in the parameterization of the method. With this knowledge, can redesign the tools for specific investigations and define the limits of confidence in results (Ramachandran *et al*, 2008).

1.3.3. Quantitative Structure-Activity Relationships (QSARs)

Many types of model are possible, with mathematical and statistical models being particularly common. Such models are often referred to as Quantitative Structure-Activity Relationships (QSARs) or Quantitative Structure–Property Relationships (QSPRs). (Tropsha *et al*, 2003).Hansch was the first one to use QSARs to explain the biological activity of series of structurally related molecules (Kubinyi, 2008). Hansch pioneered the use of descriptors related to a molecule's electronic characteristics and to its hydrophobicity. This led him to propose that biological activity could be related to the molecular structure.

Via equations of the following form:

$$\text{Log } (1/C) = k1 \log P + k2\sigma + k3$$

C= the concentration of compound required to produce a standard response a given time.

Log *P*= the logarithm of the molecule's partition coefficient between 1-octanol and water.

σ = the appropriate Hammett substitution parameter.

k_1, k_2, k_3=constants derived from regression analysis

This formalism expresses both sides of the equation in terms of free energy.

Hansch's rationale for suggesting the parabolic dependence on log *P* was that the drug's hydrophobicity should not be so low that the drug did not partition into the cell membrane nor so high that once in the membrane it simply remained there.

An early example of such a non-linear relationship between a biological response and the partition coefficient is the following equation derived for the narcotic effect of thirteen barbiturates on mice (Kubinyi, 2008): $\log (1/C) = -0.44 (\log P)\, 2 + 1.58 (\log P) + 1.93$

The electronic characteristics of a molecule are also important in determining its activity against the target; the Hammett parameters provided a concise and convenient way to quantify these. Hammett and others had shown that for related compounds reaction rates (e.g. for the hydrolysis of benzoate esters) and positions of equilibrium (e.g. the ionization constants of substituted benzoic acids) could be quantified using equations of the following form (Leach and Gillet, 2007):

$$\text{Log } (k/k0) = \rho\sigma$$

$$\text{Log } (K/K0) = \rho\sigma$$

k =these equations express the rate or equilibrium

K= constant for a particular substituent relative to that for a reference compound (indicated using the subscript 0 and typically that for which the substituent is hydrogen).

The substituent parameter σ is determined by the nature of the substituent and whether it is *meta* or *para* to the carboxylic acid or ester group on the aromatic ring.

The so-called 3D-QSAR models, however, are more representative of these new QSAR methods, and the *Comparative Molecular Field Analysis* (CoMFA) method is probably one of the most popular of these.

In the CoMFA method, the molecular descriptors are taken as steric and electric fields calculated at a large number of points surrounding each molecule (Cramer*et al*, 1989).

The main problem with 3D-QSAR methods such as CoMFA is the alignment of the molecules in the test set (Sullivan *et al*., 2000).

- It must be assumed that each of the molecules binds to the enzyme at the same site.
- It is not always clear that all the molecules bind to the active site in the same overall orientation.
- If the molecule has several conformations available, one has to guess or estimate which conformation actually binds to the enzyme.

1.4. Aim and objectives:

The main objectives of the research are to synthesis some mefenamic acid derivatives and characterize the compounds by using IR, H^1NMR, GC mass and UV spectroscopy.

Using ACD/Lab program to designed and examined, in order to select specific compounds to synthesize them, and predict and calculation of molecular properties.

Chapter Two

Materials and Methods

2.1. Materials

2.1.1. Solvents:

- Acetone Assay >99.7% Romil India.
- Methanol Assay 97% and Chloroform Assay 99.5% Alpha chemika India.

2.1.2. Chemicals:

- Acetanilide Alpha chemika India.
- Benzoyl chloride Assay 98% Lab chemie pvt. Ltd. India.
- Benzyl alcohol Assay 97% Lab chemie pvt. Ltd. India.
- Benzyl chloride Assay (G.C) 98.5% Lab chemie pvt. Ltd. India.
- Chlorosulphonic acid Assay > 97% Alpha chemika India.
- Dichloromethane Assay (G.C) 98% Alpha chemika India.
- Ethanol Assay (G.C) 99% Alpha chemika India.
- Ethyl chloroformate Assay (G.C) 98% Alpha chemika India.
- Hydrochloric acid (35-38%) Lab chemie pvt. Ltd. India.
- Sodium carbonate and potassium carbonate Assay 99.5% Central Drug Hous.
- Sodium hydroxide Central Drug, New Delhi 110002 India.
- Sulphuric acid Assay 98% Lab chemie pvt. Ltd. India.

2.2. Thin layer chromatography (TLC):

TLC was carried out using silica gel Fertigfolien(Merck Germany) coated sheets ALUGRAM SIL G/UV_{254}

2.3. Instruments:

2.3.1. Infrared Spectrophotometer (IR):

Infra-red spectroscopy was recorded on FTIR-8400s instrument (Shamazu, Japan) using KBr disc**.**

2.3.2. Ultraviolet Spectrophotometer (UV-VIS):

Ultraviolet spectral date analyses were carried out uses **6505 UV-VIS** Spectrophotometer Jenway, England.

2.3.3. Gas chromatography-mass spectroscopy:

Gas chromatography mass spectroscopy (GC-MS) was recorded on QP 2010 GC instrument (Shimadzu, Japan) and the following conditions have been adopted:

- Injection temp = 290-100 °C
- Injection mode = split
- Total flow = 1.24ml/min
- Ion source temp = 200-100 °C
- Solvent cut time = 2.5min
- Start time = 3min
- Oven temp program was illustrated below:

Rate	Temperature (°C)	Hold time (min)
-	100	00.00
30	160	00.00
15	92	20.00

2.3.4. H^1- Nuclear magnetic resonance Spectroscopy (H^1-NMR):

^{1}H Nuclear magnetic resonance spectroscopy (^{1}HNMR) was recorded on Ultrashield-500 plus instrument (BRUKER, Germany) using DMSO as solvent and operating at 500.13MHz for protons.

Employing a 5mm high-resolution broad-band TMS gradients probe, the 30 g pulse program was used. Spectra were recorded over a sweep width of (10330.57 Hz) at 293.4K temperature and time domain data points giving an acquisition time of 1.00 seconds.

2.4 ACD lab program:

ACD lab free ware 2015 downloaded from www.acd labs.com.

2.5. Apparatus and equipment:

- Hot plate stirrer, Scott Science UK.
- Melting point apparatus, BIBBY STERILN LTD, UK.
- Ultraviolet lamp, 254/365nm UV, Upland CA, USA.

2.6. Glassware:

All glass wares are Pyrex type.

2.7. General method of ACD/ lab program:

There were two modes to ACD/chemo sketch, namely structure and draw, structure mode was used to draw chemical molecules, while draw mode used to create and edit graphical objects. Upon startup, the draw normal mode and carbon automatically selected. By clicking and dragging the cursor in the windows, C-C bonds were created. Clicking on carbon atom produced a braced structure. The change was made by selecting heteroatom from the element list in the lift lobar and clicking on an atom in the structure to replace it. Radicals were made by selecting it from table which including carbon ring, carbon-based side chain and functional groups. A reaction requires were drawing by using the reaction arrow and reaction plus icons. Bond lengths and bond angles standardized by clicking on clean structure. The calculated properties were inserted into the chemo sketch window as text field; on the tools menu, point to calculate and choose the desired property. By selecting a structure and clicking on generating name for structure, the IUPC name was generated as text field underneath the structure (table No 3-1)

2.8. Synthetic methods:

2.8.1. Preparation of N-substituted mefenamic acid derivatives (I, II, III)

0.24 g (0.001 mole) of mefenamic acid was weighted in conical flask, followed by addition of (0.002 mole) (benzylchloride, benzoyl chloride, Ethyl chloroformate), 0.55g (0.004 mole) of potassium carbonate and 10ml of acetone. The reaction mixture was stirred at room temperature for 24 hours .The mixture was filtered, washed with acetone and concentrated at room temperature. The product was recrystallized from ethanol, for physical and chemical properties see tables (2-1) (2-2)**.**

2.8.2. Preparation of 2-[Benzyl (2,3-dimethyl phenyl) Amino]benzoic acid(IV)

0.42 g (0.001mole) of compound (I) was weight in conical flask, dissolved by 10 ml of hydrochloric acid (1:1), the mixture was heating in water bath for four hour. The mixture was cooled at room temperature and sodium hydroxide solution was added until pH equal to 4.5. Filtrated the product and recrystallization by cold water for physicals and chemicals properties see tables (2.1) (2.2).

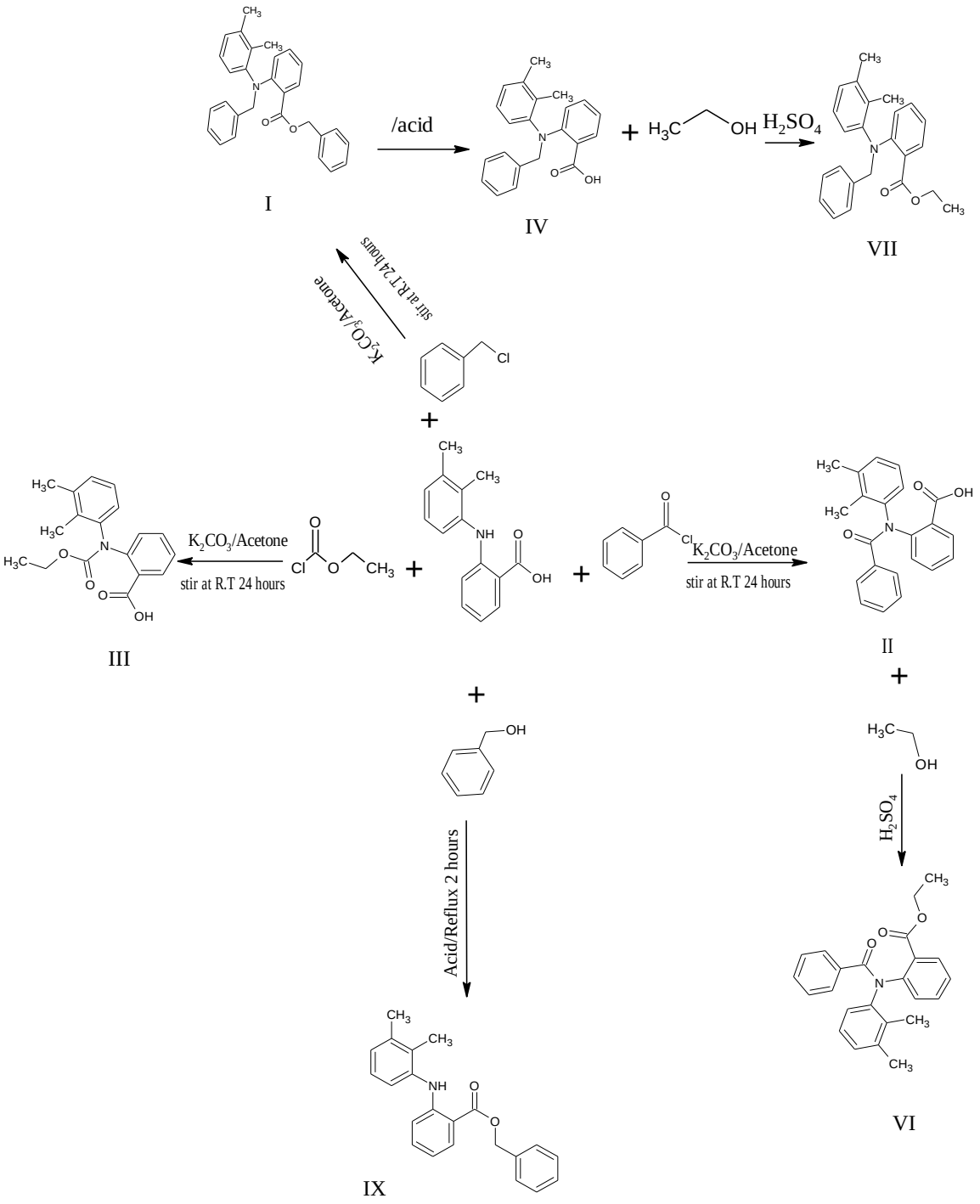
2.8.3. Preparation of 2-[(4-acetamidophenyl) (2,3-dimethyl phenyl) amino] benzoic acid (V)

0.7g (0.0052 mole) of dry acetanilide was weighted and transferred into 50ml conical flask, 1.5ml (0.023 mole) of chlorosulphonic acid was added gradually with continuous shaking. When addition had been made, the mixture was heated on water bath for one hour. The Oily mixture was cooled and poured into 10.2 g of crushed ice; the solid material was broken up and the mixture was stirred for several minute in order to obtain an even suspension of the granular white solid. The p-acetamidobenzenesulphanyl chloride was filtered and washed with a little cold water pressed and drained.

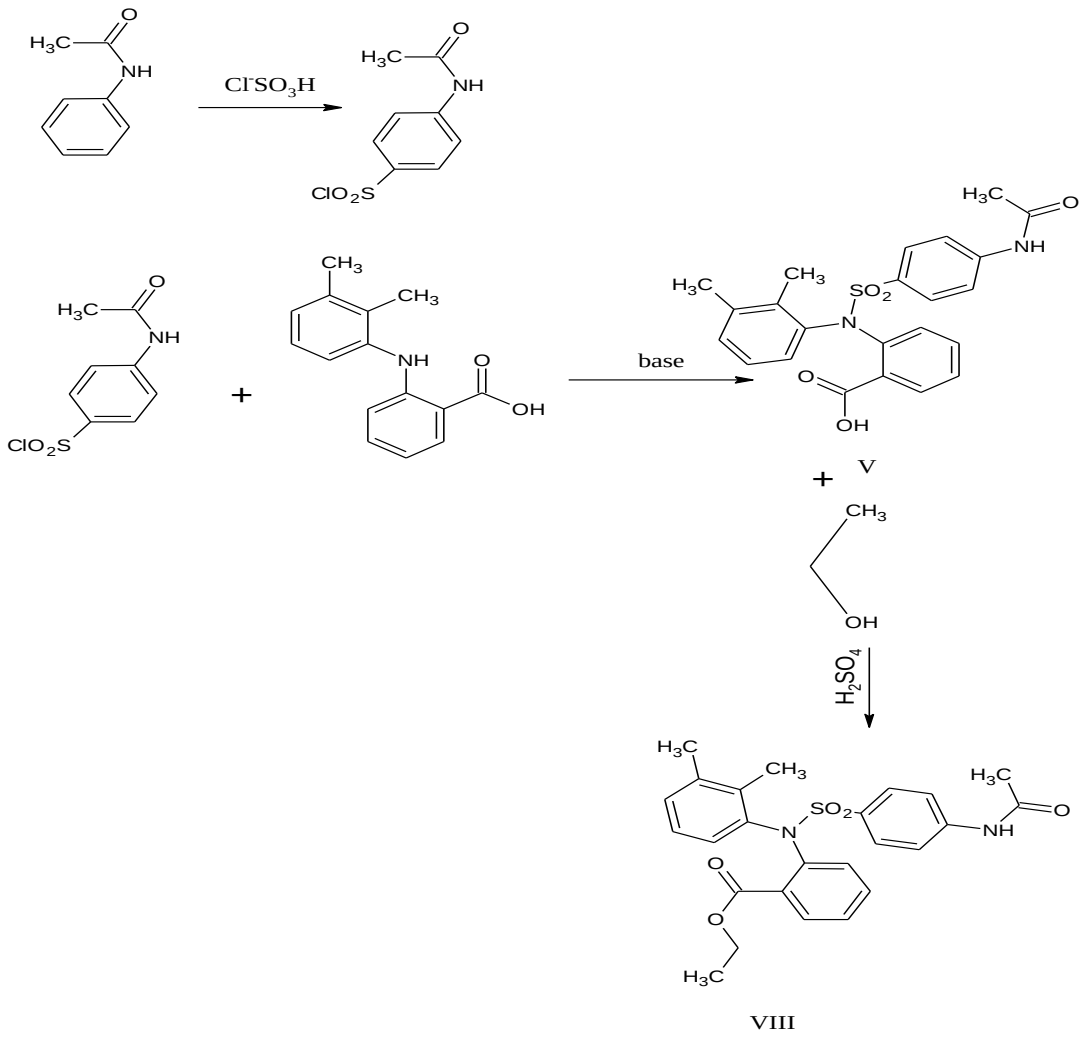
The previous prepared compound was moved into 100 ml beaker, 3.6 g (0.015 mole) of mefenamic acid was added, and the mixture was heated to just below the boiling point, for two hours then cooled at room temperature. 20ml of sodium hydroxide; 1.2 g (0.03mole) was added to the mixture with continuous shaking for 5min, then warm the mixture for 15 minute to hydrolyze it; the mixture was cooling and acidify by added hydrochloric acid (1M) with shaking, until the crystals were form, filtered the crystal and was recrystallized from cold water, for physical and chemical properties see tables (2-1) (2-2).

2.8.4. Preparation of alkyl-N-substitute mefenamic acid derivatives (VI, VII, VIII, IX):

0.24 g (0.001 mole) of (Derivative II, VI, V, mefenamic acid), 5 ml (0.055 mole) of (Ethanol, Benzyl alcohol) and 3 drops of sulphuric acid in round bottom were refluxed for two hours. The mixture was poured in to baker contained solution of sodium carbonate, organic layer was separated, concentrated at room temperature, the product was recrystallized from ethanol, for physical and chemical properties see tables (2-1)(2-2).

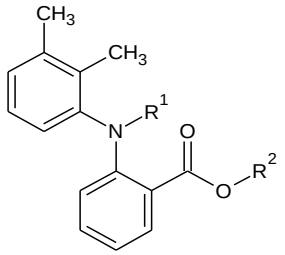


Scheme (2-1) Preparation of alkyl-N-substitute mefenamic acid derivative (VI, VII, IX) and N-substitute mefenamic acid derivative (I, II, III, IV)



Scheme (2-2) preparation of 2-[(4-acetamidophenyl) (2, 3-dimethyl phenyl) amino] benzoic acid (V) and 2-[(4-actamidophenyl) (2, 3-dimethyl phenyl) (ethyl) amino] benzoate (VIII)

Table (2.1): Chemical names of the prepared compounds:



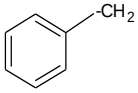
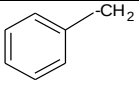
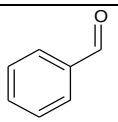
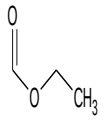
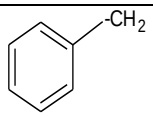
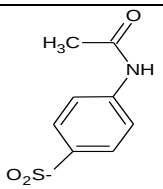
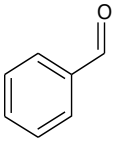
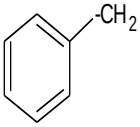
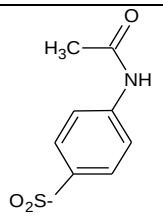
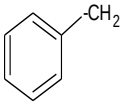
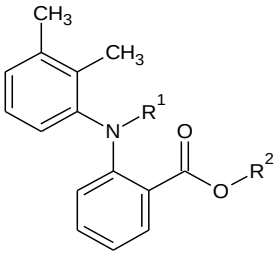
Compound No.	R^1	R^2	Chemical name
I.			Benzyl 2-[(2,3-dimethyl phenyl)(benzyl) Amino]benzoate
II.		H	2-[benzoyl(2,3-dimethylphenyl)amino] benzoic acid
III.		H	2-[(2,3-dimethylphenyl)(ethoxycarbonyl)amino] benzoic acid
IV.		H	2-[Benzyl (2,3-dimethyl phenyl) Amino]benzoic acid
V.		H	2-[(4-actamidophenyl)(2,3-dimethyl phenyl)amino]benzoic acid
VI.		CH_2CH_3	2-[benzoyl(2,3-dimethylphenyl)(ethyl)amino] benzoate
VII.		CH_2CH_3	Benzyl 2-[(2,3-dimethyl phenyl)(ethyl) Amino]benzoate
VIII.		CH_2CH_3	2-[(4-actamidophenyl)(2,3-dimethyl phenyl)(ethyl)amino]benzoate
IX.	H		benzyl2-[(2,3-dimethylphenyl)amino]benzoate

Table (2.2) Reaction conditions of prepared compounds:



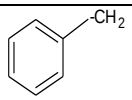
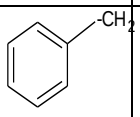
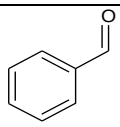
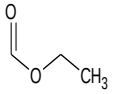
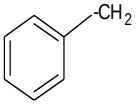
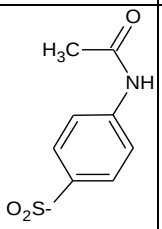
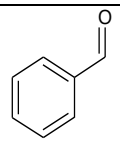
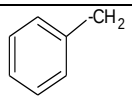
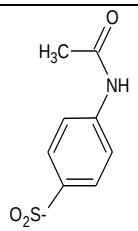
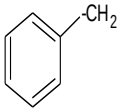
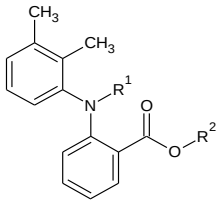
Compound No.	R^1	R^2	Reaction temp.(°C)	Time(h)	Rec. solvent	Yield(g)	Yield (%)	Color	Melting point °C
I.			Room	24	Ethanol	0.4	95	Pale-grey	250-255
II.		H	Room	24	Ethanol	0.287	84.6	yellow	245-250
III.		H	Room	24	Ethanol	0.3	95	yellow	165-170
IV.		H	100	4	Water	0.29	70.5	yellow	200-205
V.		H	80	1	water	1.03	66.7	white	235-240
VI.		CH_2CH_3	Reflux	3	Ethanol	0.16	81.33	Green	255-260
VII.		CH_2CH_3	Reflux	3	Ethanol	0.25	61.7	White-gray	240-245
VIII.		CH_2CH_3	Reflux	3	Ethanol	0.34	75.38	Pale cream	265-270
IX.	H		Reflux	4	Ethanol	-		Liquate green	

Table (2.3) Infra-red spectral data of the compounds:



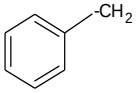
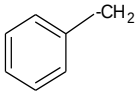
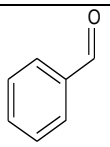
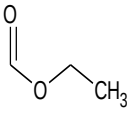
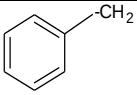
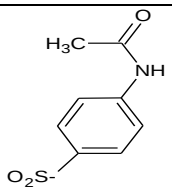
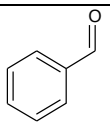
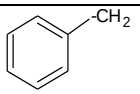
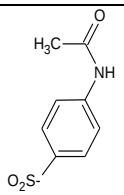
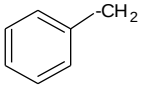
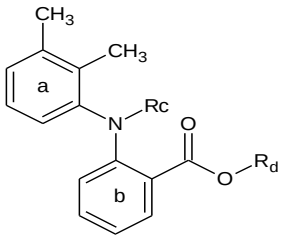
No. Comp.	R^1	R^2	C=O st.vib.	C-N st.vib.	C-C st.vib.	Other
I.			1676	1364	1495	2964 C-H st.vib.
II.		H	1668, 1652	1290, 1259	1423, 1452	3068 OH st.vib.
III.		H	1726, 1700	1194	1506, 1446	1008 C-O st.vib. 3331OHst.vib.
IV.		H	1650	1250	1475	3325OHst.vib
V.		H	1610 amide 1700 carboxylic acid	1286,1188,1159	1473,1577,1496	3427NHst.vib. 3070 $CH_{aromatic}$ 1045 S=O st.vib.
VI.		CH_2CH_3	1635 amide 1750 ester	-	1577, 1506, 1488	2921C-Hst.vib.
VII.		CH_2CH_3	1716ester	1338,1373	1577,256,1496	3060 CH $_{aromatic}$
VIII.		CH_2CH_3	1610 amide 1740 ester	-	1577,1496,1558	1340 S=O st.vib.
IX.	H		1720	-	1358, 1452, 1495	3473 NH st.vib. 3030 C-H $_{aromatc}$ 2854 $C\text{-}H_{alphtic}$ 1873,1956,1808 Disubstitutedaromtic

Table (2.4):H^1Nuclar Magnetic Resonance data of the compounds:



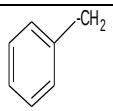
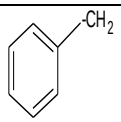
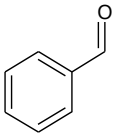
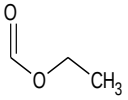
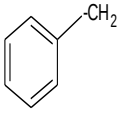
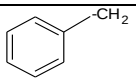
No. comp.	R1	R2	δ Value ppm intensity, multiplicity				
			H_a	H_b	H_c	H_d	other
I.			(6.5-6.7,m,3H)H_{Ar}	(6.7-6.9,s,4H) H_{Ar}	(3.4,s,2H)CH_2 (7-7.3,t,5H)H_{Ar}	(5.3,s,2H)CH_2 (7.4-7.9,t,5H)H_{Ar}	(2-2.5,S,6H)CH_3,CH_3
II.		H	(6.7-7.1,m,3H)$H_{Ar.}$	(7.2-7.6,s,4H) H_{Ar}	(7.7-8.1,s5H)HAr	(9.1,s,1H)OH	(2-2.5,S,6H)6H
III.		H	(6.5-6.9,m,3H)H_{Ar}	(7-7.8,s,4H) H_{Ar}	(2.5-2.38,m,2H)CH_2 (2.1-2.2,m3H) CH_3	(11.8,s,1H)OH	(1-2,s,6H)CH_3CH_3
IV.		H	(6.6-6,m,3H)H_{Ar}	(7.3-7.9,s4H) H_{Ar}	(7.1-7.3,t,5H)H_{Ar}	(9.4,s,1H)OH	(2-3.3,s,6H)CH_3 CH_3
IX.	H		(7.1-7.2,m,3H)H_{Ar}	(7.2-7.3,s,4H) H_{Ar}	(4.5,s,1H)NH	(7.3,s,4H)H_{Ar}	(2-4,s,6H)CH_3, CH_3

Table (2.5) Gas Chromatography–mass spectral data of the prepared mefenamic acid derivatives:

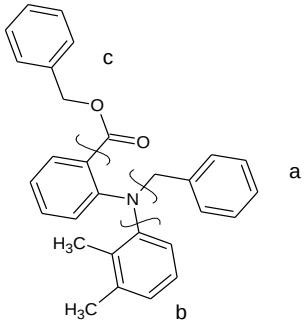
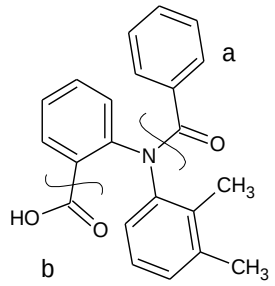
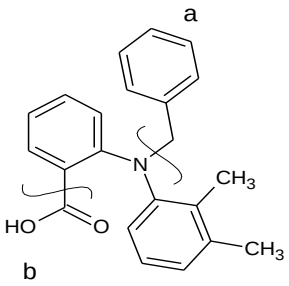
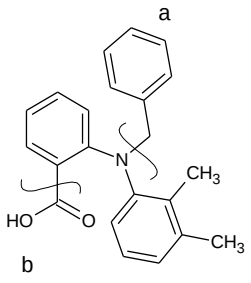
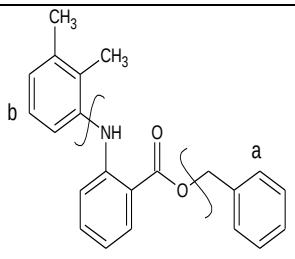
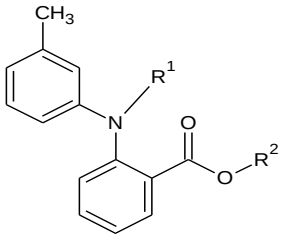
Compound No.	Structure of compound	Retention time/min	M.wt calculated		Massspectral fragmentation	
				M^+ m/z	Path of fragment lost	m/z
I.		3.4	421.53	406	a=[M⁻ (3ph+C_3H_8 NO_2)] b=[]M^+-(ph+C_2H_6) c=[M+-(3ph+C_2H_6+N)]	91 208 122
II.		3.3	345.39	345	a=[M^+-(2ph+$C_3H_7O_2$)] b=[M^+-(CO_2H)]	105 300
III.		5.6	313.34	313	a=[M^+-C_3H_502] b=[M^+-CO_2H] c=[M^+-(ph+C_2H_6)]	241 369 103
IV.		1.8	331.40	331	a=[M^+-(2ph+$C_3H_7O_2N$)] b=[M^+-CHO_2]	91 286S
IX.		3.7	331.40	313	a=[M^+-(2ph+C_2H_7N)] b=[M^+-(ph+C_2H_6)]	91 208

Table (2.6) Ultra Violet spectroscopy data of the prepared mefenamic acid derivatives:



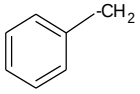
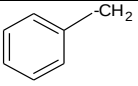
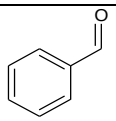
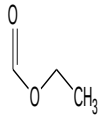
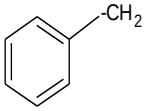
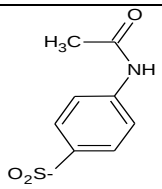
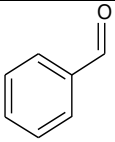
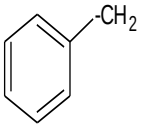
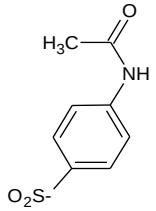
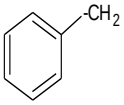
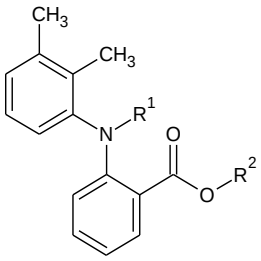
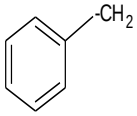
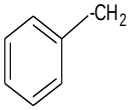
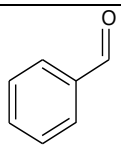
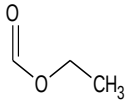
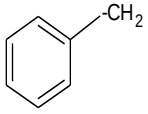
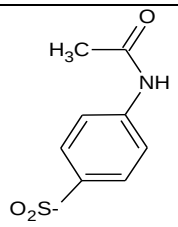
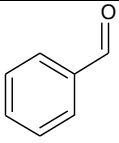
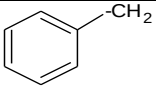
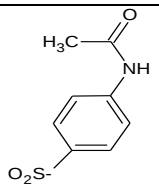
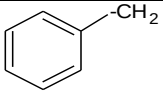
Compound No.	R^1	R^2	λ_{max}
I.			275
II.		H	300
III.		H	320
IV.		H	275
V.		H	255
VI.		CH_2CH_3	220
VII.		CH_2CH_3	
VIII.		CH_2CH_3	290
IX.	H		300

Table (2.7) Thin-layer chromatography data of the compounds prepared:



Solvent system: methanol absolute

No. Comp.	R^1	R^2	Solvent system Chloroform: methanol	Rf
I.			9.8:.2	0.88
II.		H	9.8:0.2	0.64
III.		H	9.8:0.2	0.71
IV.		H	9.8:0.2	0.66
V.		H	9.6:0.4	0.87
VI.		CH_2CH_3	9.6:0.4	0.54
VII.		CH_2CH_3	9.6:0.4	0.50
VIII.		CH_2CH_3	9.6:0.4	0.64
IX.	H		9.8:0.2	0.90

Chapter Three

Discussion

3.1. Introduction:

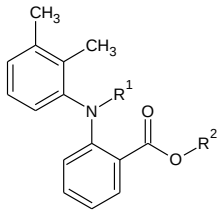
Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed drugs in modern medicine. NSAIDs are very effective in the alleviation of pain, fever and inflammation.

NSAID use is however associated with several serious treatment side effects, with considerable associated morbidity and mortality. (Meek *et al*., 2010).

3.2. ACD/lab program:

In the present work several mefenamic acid derivatives were designed and examined, in order to select specific compound to synthesize, depend on first step was designing about 30 compounds derivatives from different amines and esters, (table No.3-3) using chemo sketch program (ACD/lab); there are free ware was used to draw chemical structure ,calculation of molecular properties (molecular formula, molecular weight, molar volume, density, polarizability and parachor) Log p and naming structure(table No.3-1). After that the compounds were selective depend on Log p, molar volume and polorizability; in drug design compound with high value of Log weak absorption or permeation. So compounds were selected with low Log p value, high molar volume and large polerizability.

Table (3.1): ACD/lab data



No.	R1	R2	Log P	M.wt	D ±0.06 g/cm^3	M.V± 3 cm^3	Polarizability±0.05 10^{-24} cm^3	Parachor ±4 cm^3	Name S.	M.F
1	CH_3	H	4.3/-0.33	225.3	1.16	219	30.49	581	2-[(2,3-dimethyl phenyl)(methyl)amino]benzoic acid	$C_{16}H_{17}NO_2$
2	CH_2CH_3	H	4.84\-0.33	269.33	1.14	335.5	32.32	620.9	2-[(2,3-dimethyl phenyl)(ethyl)amino]benzoic acid	$C_{17}H_{19}NO_2$
3	$CH_3CH_2CH_3$	H	5.19/-0.33	283.36	1.12	252.4	24.14	658.1	2-[(2,3-dimethyl phenyl)(propan-2-yl)amino]benzoic acid	$C_{18}H_{21}NO_2$

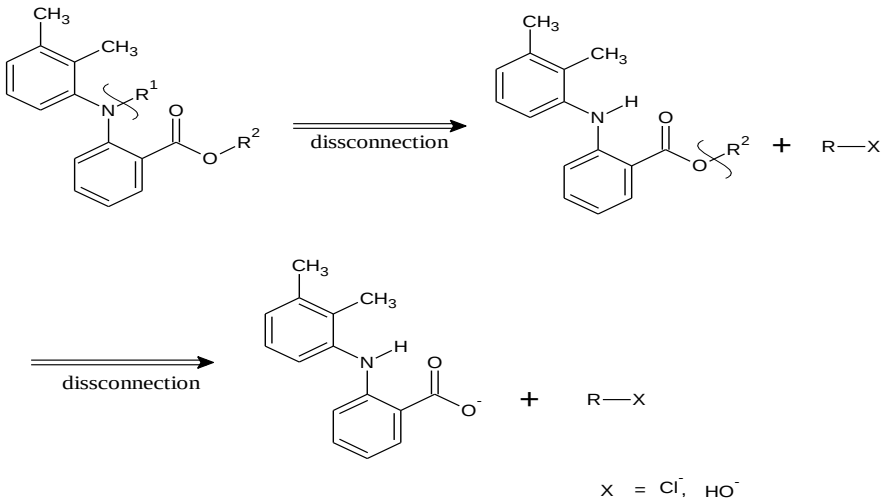
4	$CH_3CHCH_2CH_3$	H	5.72/-0.33	297.39	1.10	268.9	35.98	697.9	2-[(2,3-dimethyl phenyl)(2-methyl propyl)amino]benzoic acid	$C_{19}H_{23}NO_2$
5	$CH_3CH_2CH_2CH_2CH_2CH_2$	H	6.43/-0.33	311.41	1.09	285.1	37.83	740.3	2-[(2,3-dimethyl phenyl)(pentyl)amino]benzoic acid	$C_{20}H_{25}NO_2$
6	CH_3CH_2CO	H	2.99/-0.33	297.34	1.19	249.2	34.17	665.8	2-[(2,3-dimethyl phenyl)(propanayl)amino]benzoic acid	$C_{18}H_{19}NO_3$
7	CH_3CO	H	2.46/-0.33	283.32	1.21	232.32	32.33	626.0	2-[acetyl(2,3-dimethyl phenyl)amino]benzoic acid	$C_{17}H_{17}NO_3$
8	$(CH_3)_2CHCH_2CO$	H	3.34/-0.33	311.37	1.17	266.1	35.99	702.9	2-[(2,3-dimethyl phenyl)(2-methyl propanoyl)amino]benzoic acid	$C_{19}H_{21}NO_3$
9	$(CH_3)_2CHCH_2CH_2CO$	H	3.87/-0.33	325.40	1.15	282.6	37.83	742.7	2-[(2,3-dimethyl phenyl)(3-methyl butanoyl)amino]benzoic acid	$C_{20}H_{23}NO_3$
10	$CH_3(CH_2)_3CO$	H	4.05/-0.33	325.4	1.15	282.2	37.84	745.3	2-[(2,3-dimethyl phenyl)(pentanoyl)amino]benzoic acid	$C_{20}H_{23}NO_3$
11	$CH_3CH_2CH_2$	H	3.52/-0.33	311.37	1.17	265.7	36.01	705.5	2-[butanoyl(2,3-dimethyl phenyl) amino]benzoic acid	$C_{19}H_{21}NO_3$
12	$C_6H_5SO_2$	H	4.57/-0.60	381.4	1.32	280.4	42.57	804.3	2-[(2,3-dimethyl phenyl)(phenoxysulfinyl)amino]benzoic acid	$C_{21}H_{19}NO_4S$
13	$C_5H_4SO_2$	H	3.58/-0.61	369.43	1.39	265.2	40.59	778.1	2-{[(cyclopenta-2,4dien-1-yloxy)sufinyl](2,3-dimethyl phenyl) amino}benzoic acid	$C_{20}H_{19}N_4S$
14	C_6H_5CO	H	4.9/-0.55	245.39	1.24	278.5	40.38	761.9	2-[benzoyl(2,3-dimethyl phenyl) amino]benzoic acid	$C_{22}H_{19}NO_3$
15	$C_6H_5CH_2$	CH_3	6.78/-0.35	359.46	1.11	321.6	43.95	835.8	Methyi2-[benzyl(2,3-dimethyl phenyl) amino]benzaoate	$C_{24}H_{25}NO_2$
16	$C_6H_5CH_2$	H	5.94/-0.35	331.40	1.184	279.7	40.19	735.3	2-[benzyl(2,3-dimethyl) amino]benzoic acid	$C_{22}H_{21}NO_2$
17	CH_3OCO	H	4.13/-0.56	313.34	1.22	255.5	34.86	685.4	2-[l(2,3-dimethyl)(ethoxy carbonyl) amino]benzoic acid	$C_{18}H_{19}NO_4$
18	H	$(CH_3)_2CHCH_2$	6.40/-0.38	297.39	1.07	275.8	36.03	697.4	2-methyl propyl 2-[(2,3-dimethyl) anilino]benzoate	$C_{19}H_{23}NO_2$
19	H	CH_3CH_2	5.52/-0.37	269.33	1.11	242.4	32.3	620.5	Ethyl 2-[(2,3-dimethyl) anilino]benzoate	$C_{17}H_{19}NO_2$
20	H	(CH3)2CH	5.87/-0.38	283.36	1.09	259.3	34.2	657.7	Propan-2-yl 2-[(2,3-dimethyl) anilino]benzoate	$C_{18}H_{21}NO_2$
21	H	$C_6H_5CH_2$	6.76/-0.39	331.40	1.15	386.6	40.25	752.9	benzyl 2-[(2,3-dimethyl) anilino]benzoate	$C_{22}H_{21}NO_2$
22	H	$CH_3(CH_2)_3$	6.58/-0.37	297.39	1.07	275.4	36.05	700.1	butyl 2-[(2,3-dimethyl) anilino]benzoate	$C_{19}H_{23}NO_2$
23	H	-Cl	5/-0.62	259.73	1.21	214.4	29.93	559.7	2-[(2,3-dimethyl phenyl) amino]benzoyl	C15H14NO
24	C_6H_5	H	6.15/-0.35	317.38	1.19	265.6	38.32	715.6	2-[(2,3-dimethy phenyl) amino]benzoic acid	$C_{21}H_{19}NO_2$

25	CH3	$C_6H_5CH_2$	6.38-0/.34	345.43	1.13	305.1	42.11	796	benzyl2-[(2,3-dimethyl phenyl)(methyl) amino]benzoate	$C_{23}H_{23}NO_2$
26	H	$C_6H_5CH_2$	6.76/-0.39	331.40	1.15	286.6	40.25	752.9	Benzyl 2-[(2,3-dimethylphenyl)amino]benzoate	$C_{22}H_{21}NO_2$
27	$C_6H_5CH_2$	$C_6H_5CH_2$	8.02/-0.39	421.35	1.15	365.8	51.82	968.1	Benzyl 2-[(2,3-dimethylphenyl)amino]benzoate	$C_{29}H_{27}NO_2$
28	$C_6H_5SO_2CH_3CONH$	H	-	438.49	-	-	-	-	2-[(4-acetomido phenyl)(2,3-dimethylphenyl)amino]benzoic acid	$C_{23}H_{22}NO_3S$
29	C_6H_5CO	CH_2CH_3	5.73/-0.55	373.44	1.16	320.3	44.14	844.2	2-[benzoyl(2,3-dimethylphenyl)(ethyl)amino]benzoate	$C_{24}H_{23}NO_3$
30	$C_6H_5CH_2$	CH_2CH_3	6.78/-0.35	359.46	1.11	321.6	43.95	845.8	2-[benzyl(2,3-dimethylphenyl)(ethyl)amino]benzoate	$C_{24}H_{25}NO_2$
31	$C_6H_4SO_2H_3CONH$	CH_2CH_3	-	-	-	-	-	-	2-[(4-acetomido phenyl)(2,3-dimethylphenyl)(ethyl)amino]benzoate	$C_{25}H_{26}N_2O_5$

Accordingly, the alkyl-N-substitute, N-substitute, mefenamic acid derivatives were selected for synthetic work

3.3. Retro synthetic analysis (RSA):

Retro synthetic analysis (RSA), aid in the establishment of good synthetic scheme in (RSA), key steps are developed by examine important structural element in the final product and figuring out how specific reaction could lead to the product. The procedure is performed it relatively so that a complex final molecule is reduced to simpler intermediates. The advantage of such an approach is that greatly simplifies planning the synthesis of a complex product and readily leads to a convergent synthesis (Golan *et al*, 2008). In performing (RSA), it may also be useful to disconnect a bond showing the fragment not as real compounds but only as an electrophile and nucleophile (synthons). This may help bring to mind other reaction that can be used to reassemble the fragment (Hornback, 2005).



Scheme (3.1): Retro synthetic analysis of Alkyl-N-substitute mefenamic acid derivatives (I, II, III, IV, V, VI, and VIII)

3.4. Reaction mechanism:

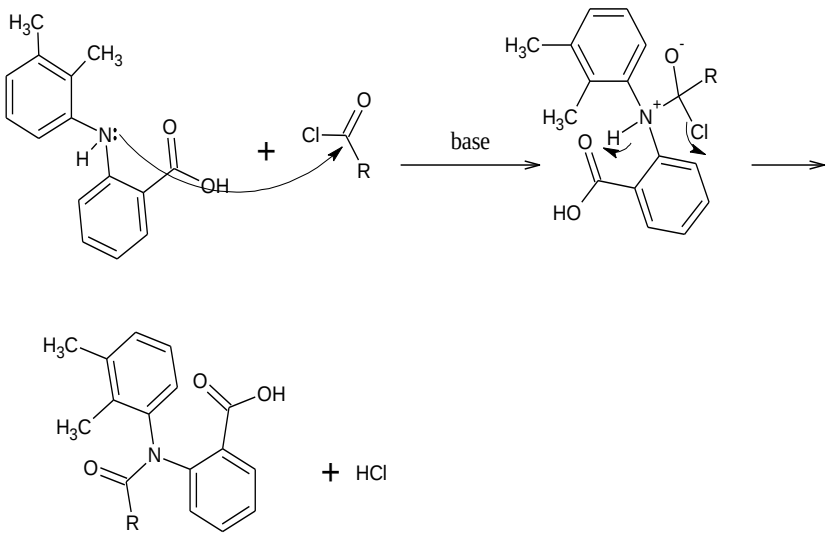
3.4.1. Reaction mechanism of N-substituted mefenamic acid derivatives (I, II, III)

Acyl chlorides can be used to prepare ester or amide by react with carboxylic acid or amine in basic media.

Acyl chlorides are very reactive than hydroxide group in free carboxylic acid in mefanamic acid, and good leaving group.

The carbonyl group is highly polarized and the positive carbon is attacked by the nuleophlilic amine molecule, acting as an electron pair in amine.

The intermediate is highly unstable ionic via C-N bond and simultaneously the π electron pair of the C=O bond moves on to the oxygen atom to give it a full negative charge. C-Cl bond pair into the chlorine and leaves chloride ion, one lone pairs of electron from negative oxygen shift to complete the C=O.



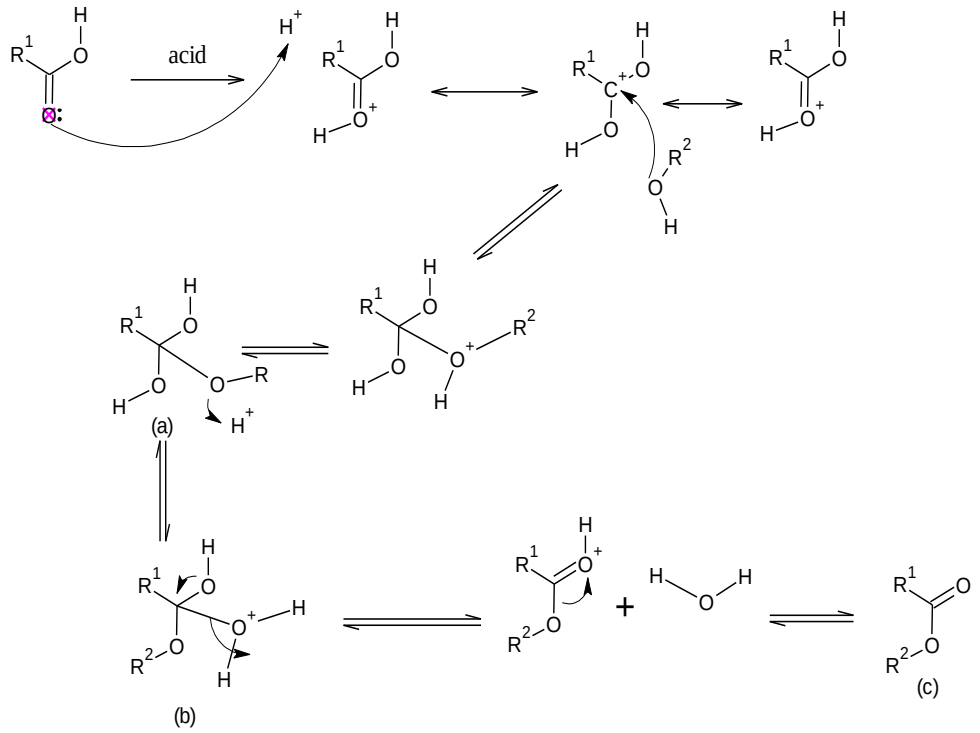
Scheme (3.2): Reaction mechanism of N-substitute mefenamic acid derivatives (I,II,III)

3.4.2. Reaction mechanism of Alkyl N-substitute mefenamic acid derivatives (V, VI, IX, and VIII):

The reaction between alcohol (Ethanol, benzyl alcohol) and free carboxylic acid in mefanamic acid in strong acid (H_2SO_4) is produced by protraction of the carbonyl oxygen of carboxylic acid, thereby giving intermediate ion. This protonation greatly enhances affinity of carbonyl carbon for an electron pair on the oxygen of the alcohol.

A proton is transferred from the OR^2 to a hydroxide group (a) to give (b). This process converts the hydroxide into a good leaving (H_2O).

When H_2O leaves the product (c) is the conjugate acid of the ester.



Scheme (3.3): Reaction mechanism of derivatives (V, VI, and IX)

3.4.3. Reaction mechanism of derivatives (IV, VIII):

Chlorosulfonic acid is very strong acid; it is capable of pate thing itself. It then loses water, yielding an electroplilic chlorsulfonium species which then attacked by a pair of pi electrons in the mate-para position of the acyl ring (the acetamido group is directing, but due to steric hindrance and other electronic effect, directs mainly para)

Purity of synthesized compound was ascertained by melting point and thin layer chromatography (TLC).the synthesized compound were confirmed by FTIR, H^1NMR and Mass spectroscopy.

3.5 Rf-values:

Thin layer chromatography is method for analyzing the purity of the compound and monitors the progress of reaction.

Use chloroform and methanol is solvent system and record Rf- values in table (3-2)

3.6. IR, H^1NMR, GC -MS and UV spectral data of the compounds:

Infrared spectroscopy in one of the most important tool in structure elucidation it provide an excellent means identification of the different functional groups associated with in molecule. In the present work, IR analysis was carried out using FTIR -8400s instrument (Shamazu, Japan)

using KBr disc**.** The results were tabulated in table (3-3) and the IR spectra of some representative were given in appendix A.

The characteristics peak for mefenamic acid were observed for aromatic ring C=$C_{st.vib}$ at (1575-1547cm^{-1}), C-$H_{st.vib}$ at 3010cm^{-1}, CH_3alaphatic C-H (2974 -2940cm^{-1}), C=O $_{st.vib}$ at 1650cm^{-1} Carboxylic acid and $OH_{st.vib}$ at 3300$cm^{-1.}$

Compound (**I**) showed the band of aromatic C=$C_{st.vib}$ which were observed at (1495cm^{-1}), the band of C-$N_{st.vib}$ observed at (1364cm^{-1}), the band of C=$O_{st.vib}$ observed at (1676cm^{-1}), and the band of C-$H_{st.vib}$ observed at (2964cm^{-1}) for benzene ring.

Compound (**II, III, IV**) showed the band of aromatic C=$C_{st.vib}$ which were observed at (1495-1506cm^{-1}), the band of C-$N_{st.vib}$ observed at (1364-1194cm-1), the band of C=$O_{st.vib}$ observed at (1668-1700cm^{-1}), and the broad band of $OH_{st.vib}$ observed at (2964-3300cm^{-1}).

Compound (**V, VI, VIII**) showed the band of aromatic C=$C_{st.vib}$ which were observed at (1496-1577cm^{-1}), the band of aromatic C-$H_{st.vib}$ observed at (2921-3060cm^{-1}), the two band of C=$O_{st.vib}$ observed at (1635-1740cm^{-1}) one of them is ester and other is amid. In Compound (VIII) showed other band of S=$O_{st.vib}$ observed at (1340cm^{-1}), and the band of $NH_{st.vib}$ observed at (3421cm^{-1}).

Compound (**IX**) showed the band of aromatic C=$C_{st.vib}$ which were observed at (1358-1495cm^{-1}), the band of C=$O_{st.vib}$ observed at

(1720cm^{-1}), the band of $NH_{st.vib}$ observed at (3473cm^{-1}), and the band of C-$H_{st.vib}$ observed at (3030cm^{-1}).

Compound (**V**) showed the band of aromatic C=$C_{st.vib}$ which were observed at (1473-1577cm^{-1}), the two band of C=$O_{st.vib}$ observed at (1610-1700cm^{-1}) one of them is carboxylic acid and other is amid, the band of $NH_{st.vib}$ observed at (3427cm^{-1}), the band of S=$O_{st.vib}$ observed at (1045cm^{-1}), and the band of C-$H_{st.vib}$ observed at (3070cm^{-1}).

Nuclear magnetic resonance (NMR) is spectroscopic method that even more important to organic chemist then infrared spectroscopy where IR revel the type of functional group in a molecule, NMR give information about the number of each distant type of nuclei or well as obtain information regarding the nature of the immediate environment of each

type. The combination of IR and NMR date is often sufficient to determine completely the structure of unknown molecule (Pavia et al; 2001).

H^1NMR spectrum data of mefenamic acid showed(s, 3H), (s, 3H) for aliphatic proton at δ (2.182-2.350ppm), (m, 7H) for seven proton for aromatic ring at δ (6.655-8.044ppm), and (s, 1H) for carboxylic group at δ (9.39ppm).

Compound (**I, II, III, IV, IX**) showed (m, $3H_a$), (s, $5H_b$) for seven protons of benzene ring at δ (6.5-6.8ppm), (s, 6H) for six aliphatic protons at δ (2-4ppm).

Compound (**II, III, and IV**) showed (s, 1H) for one protons of hydroxyl group at δ (9.1-11.8 ppm).

Compound (**I**) showed (s, $3H_d$, H_C), for 14 protons of aliphatic at δ (3.4-5.3ppm), and (t, 5H) for ten aromatic protons at δ (7.4-7.9ppm).

Compound (**IX**) showed (s, $1H_c$) for one protons of amine group at δ (2.5ppm), (s, 4H) for four protons of aromatic ring at δ (7.3ppm).

Compound (**II**) showed (s, $3H_c$) for five protons of benzene ring at δ (7.7-8.1ppm).

The technique of gas chromatography with its exceptional separation potential and mass spectrometry which provides unique structural determinations are ideally suited to be used in combination as an analytical technique (**GC-MS**).

Compound in table (3-6) showed this MS spectral analysis, compound (**I**),(**II**),(**III**),(**IV**)and (**IX**)showed retention time (3.4,3.3,5.6,1.8and3.7min) respectively, and base peak at (406,345,331,313,and313m/z).

Conclusion and recommendation

The following points can be concluded and recommended according to this study:

- The planning prepared in the work were obtained in a two steps reaction, for prepared the tertiary amine and esterification the carboxylic group by ethanol.
- I am recommend using chemo sketch program (ACD/lab) in organic synthesis because it provides vital information which saves time and effort.
- From the synthetic point of view the retro synthetic analysis adopted in this work proved to be correct and good, in accordance with the proposed mechanism.
- Highly recommended in order to apply other analytical technique like HPLC, X-ray.
- Testing for reasonable biogical activates was strongly recommended.
- Using microwave irradiation to minimize the time reaction.

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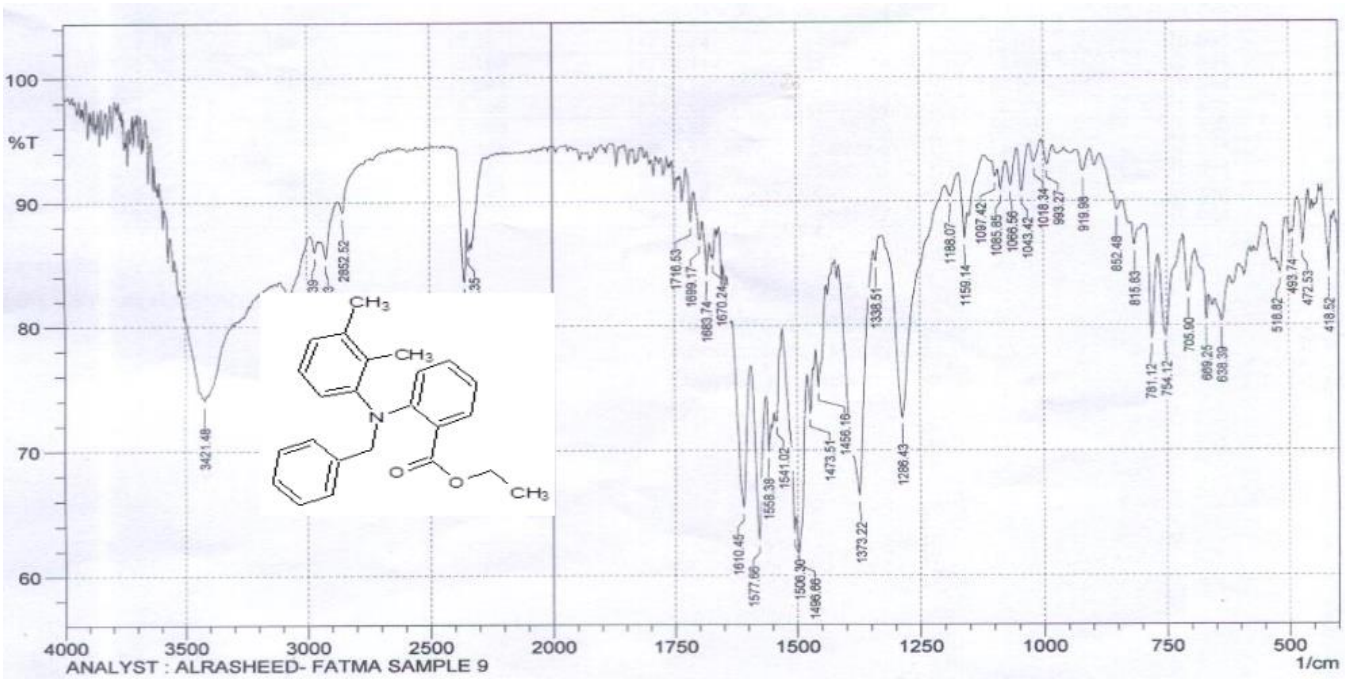
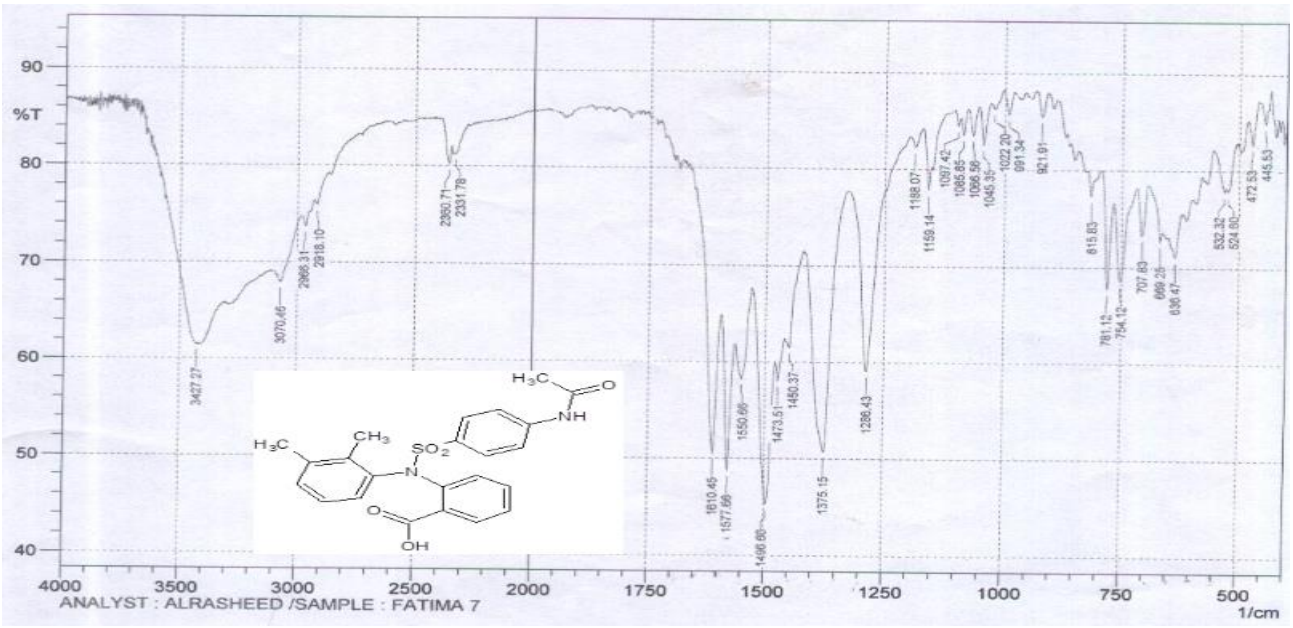
Appendix

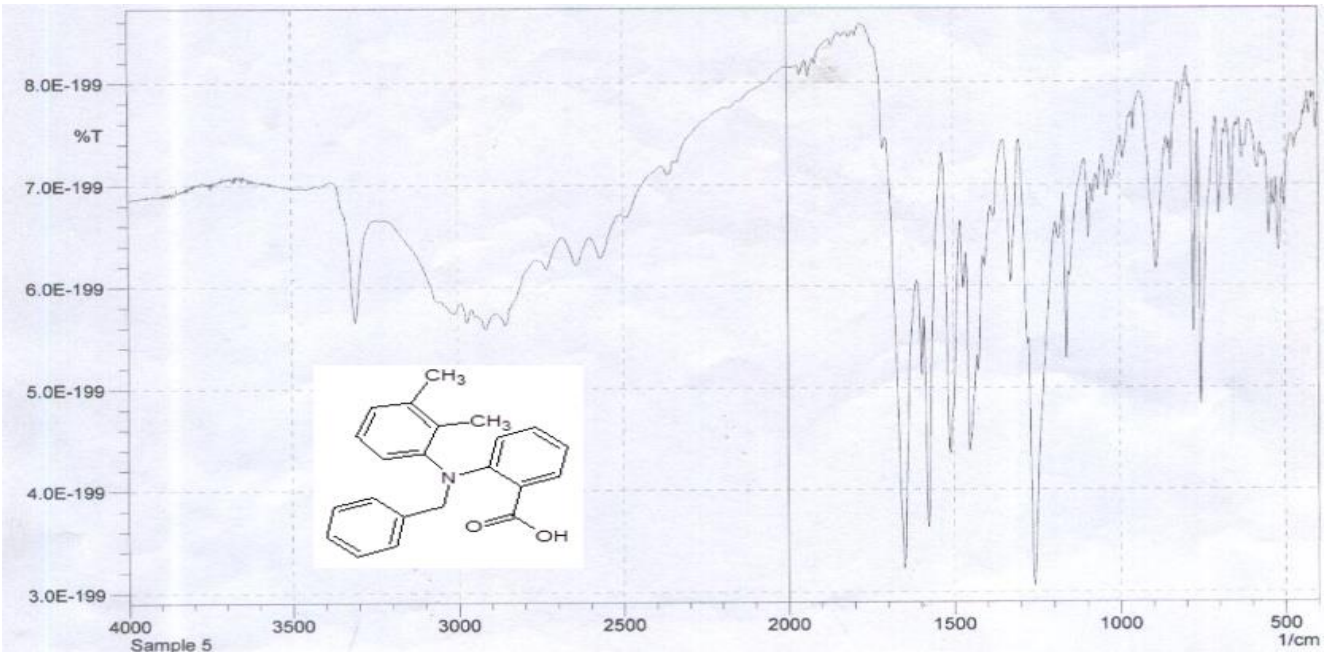
Appendix A



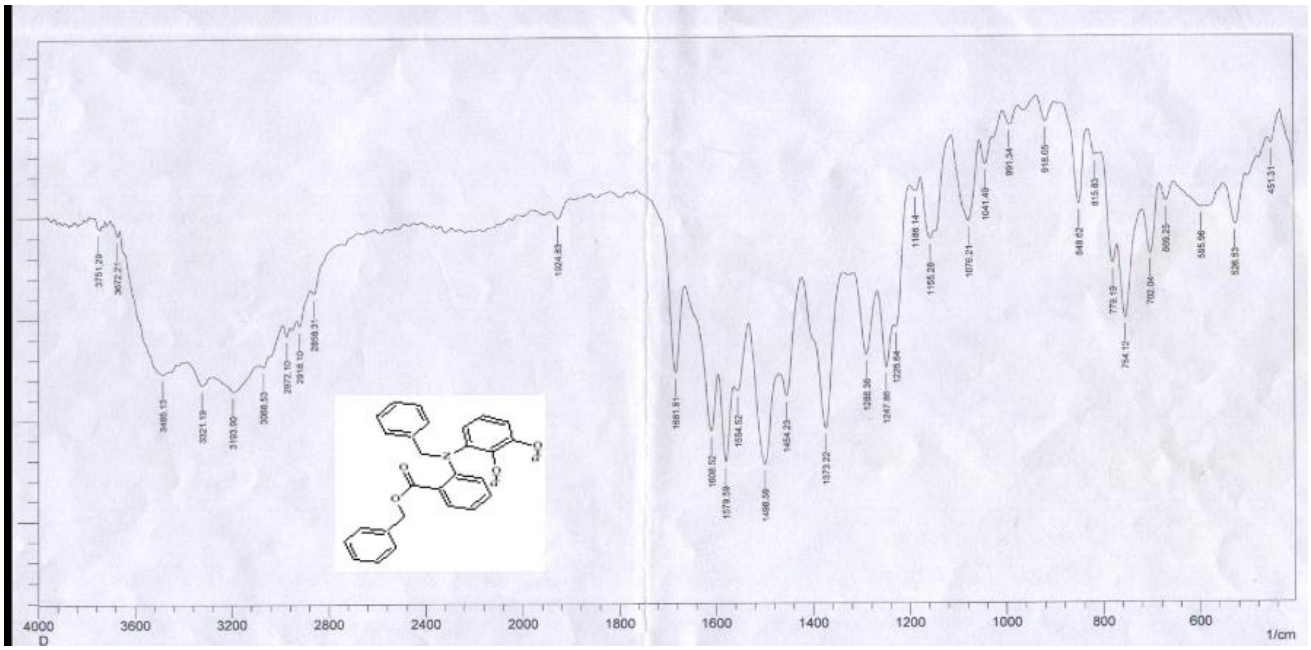
Appendix A-1 IR spectrum of Benzyl 2-[(2,3-dimethyl phenyl)(ethyl) Amino] benzoate



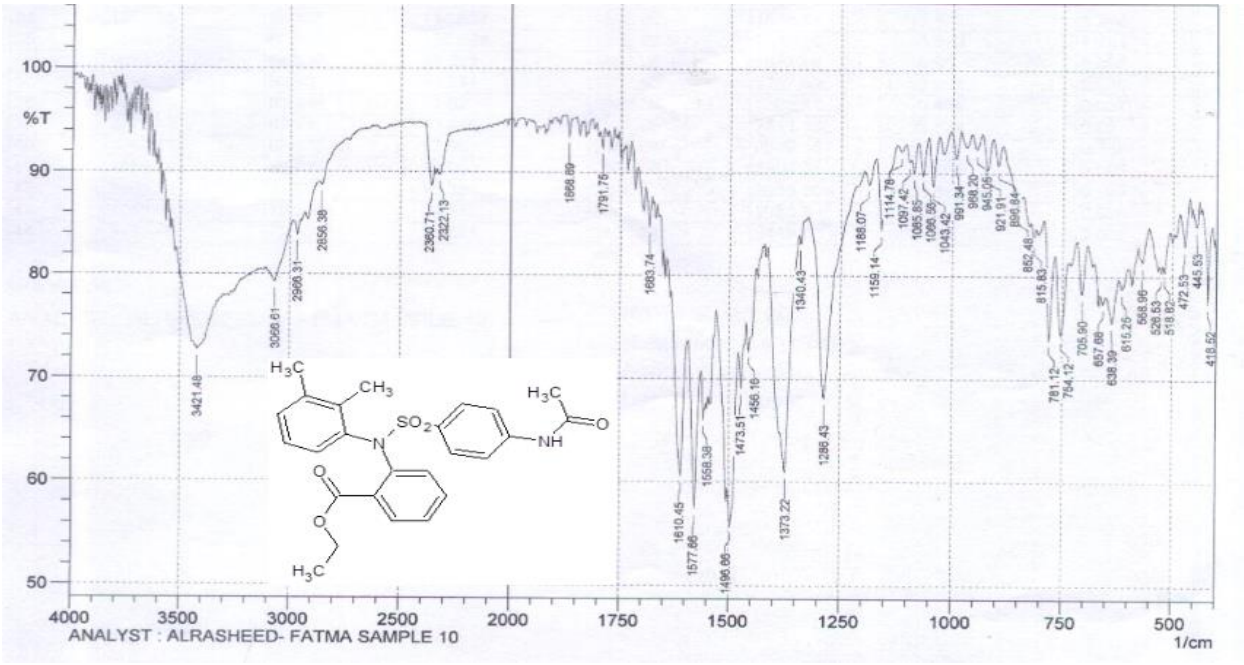
Appendix A-2 IR spectrum of 2-[(4-actamidophenyl) (2, 3-dimethyl phenyl) amino] benzoic acid



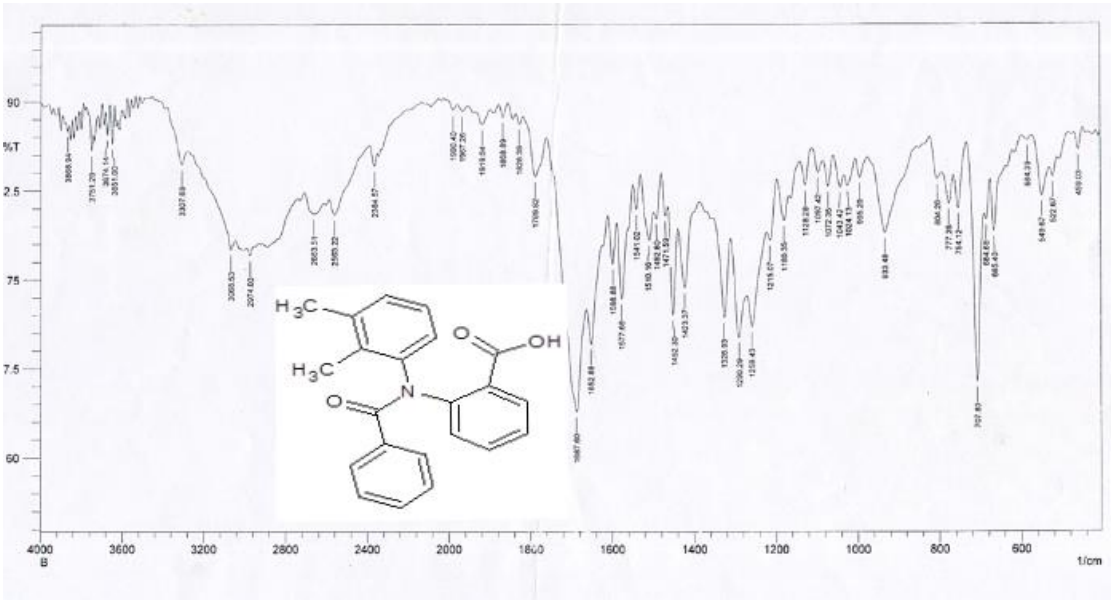
Appendix A-3 IR spectrum of 2-[Benzyl (2, 3-dimethyl phenyl) Amino] benzoic acid



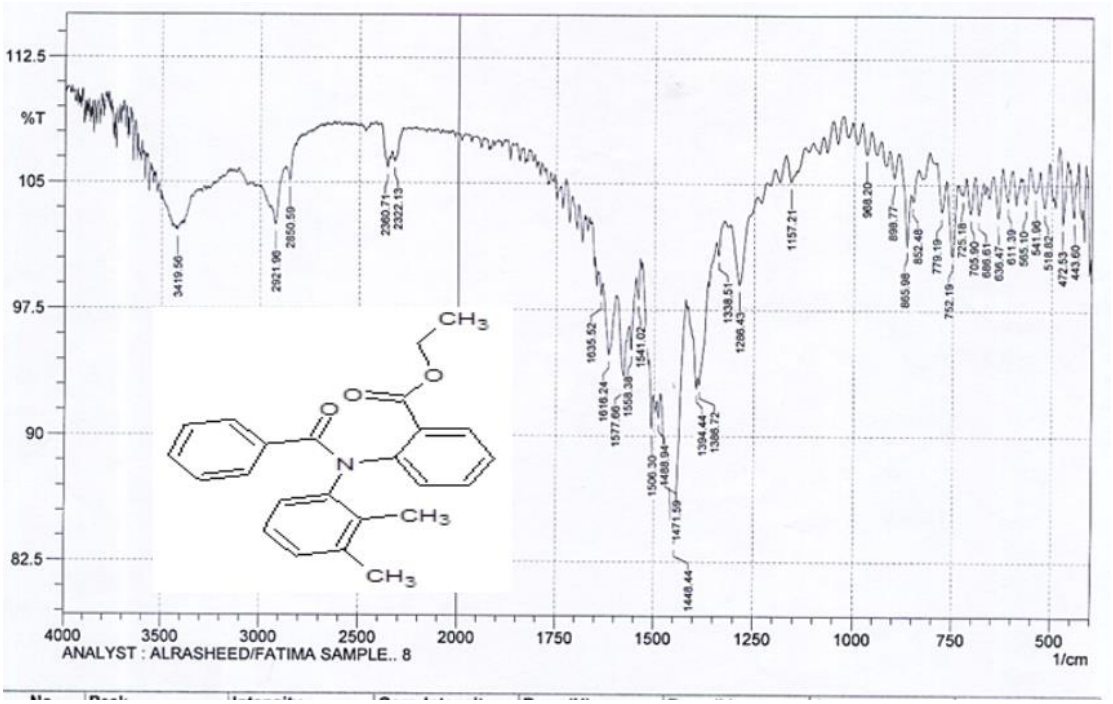
Appendix A-4 IR spectrum of Benzyl 2-[(2,3-dimethyl phenyl)(benzyl) Amino] benzoate



Appendix A-5 IR spectrum of 2-[(4-actamidophenyl) (2,3-dimethyl phenyl) (ethyl) amino] benzoate

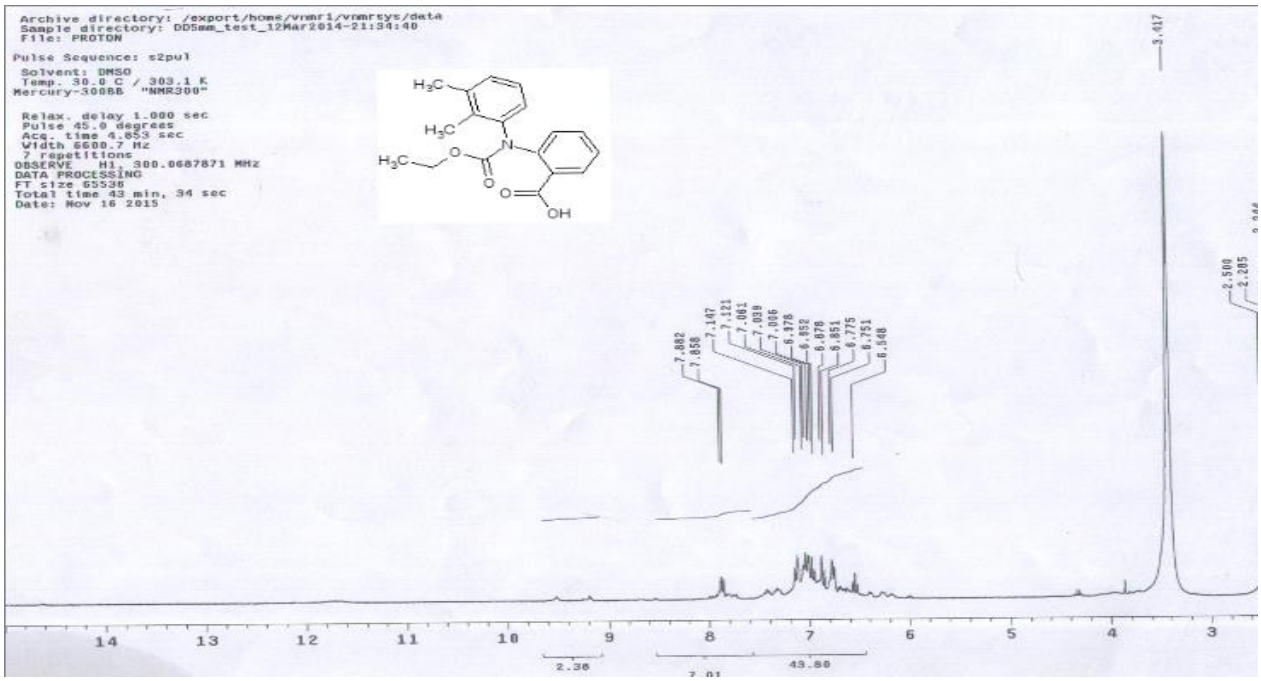


Appendix A-6 IR spectrum of 2-[benzoyl (2,3-dimethylphenyl)amino] benzoic acid

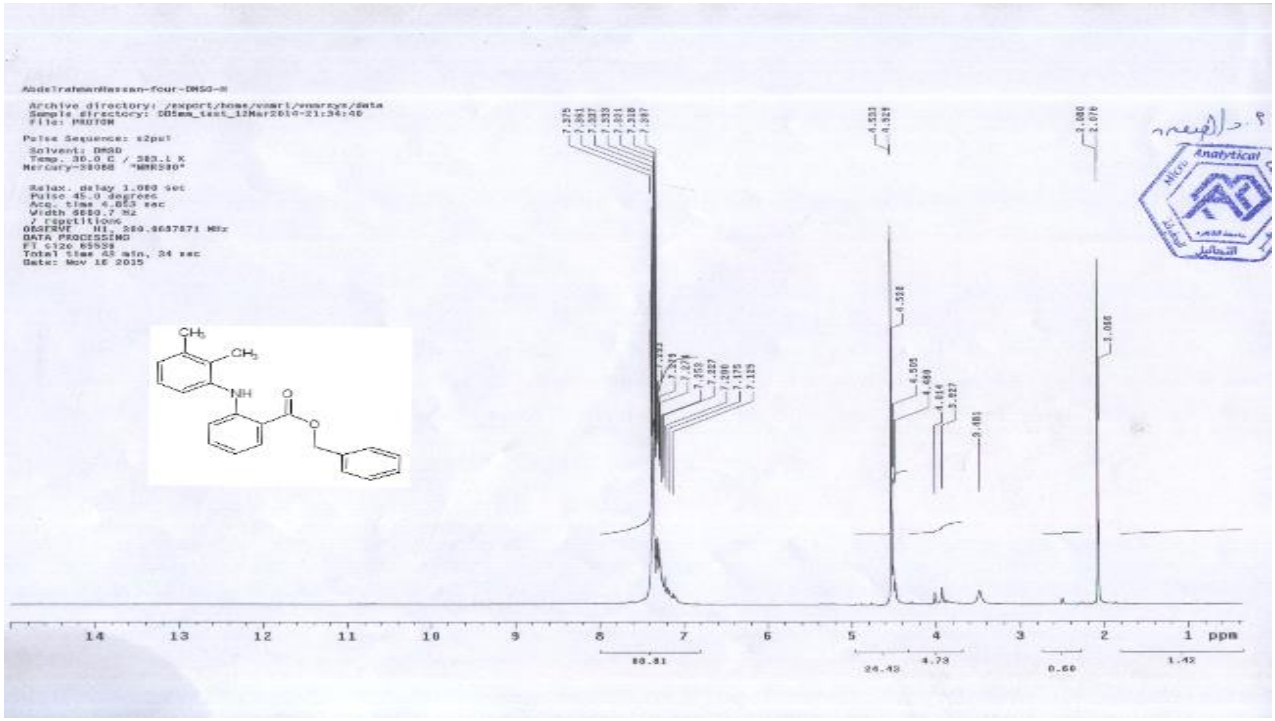


Appendix A-7 IR spectrum of 2-[benzoyl(2,3-dimethylphenyl)(ethyl)amino] benzoate

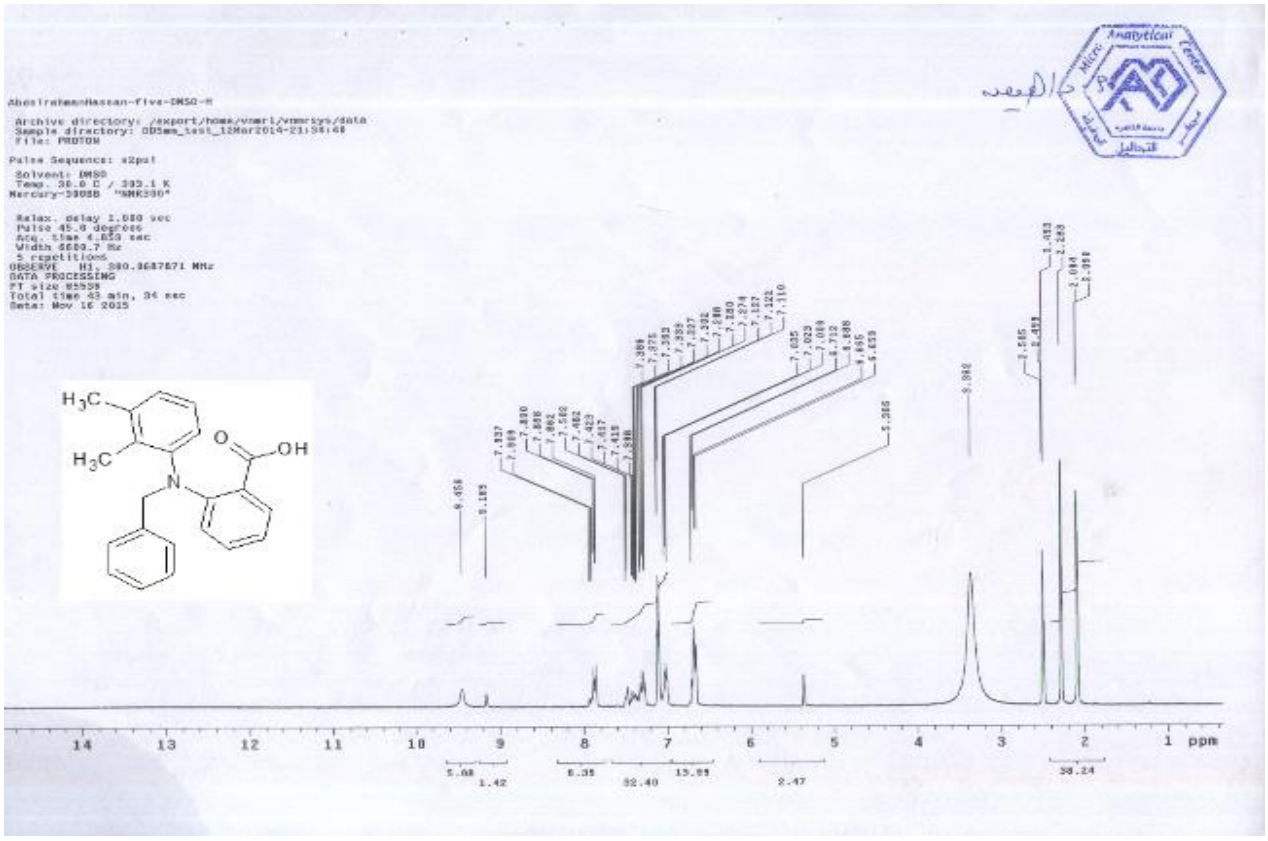
Appendix B



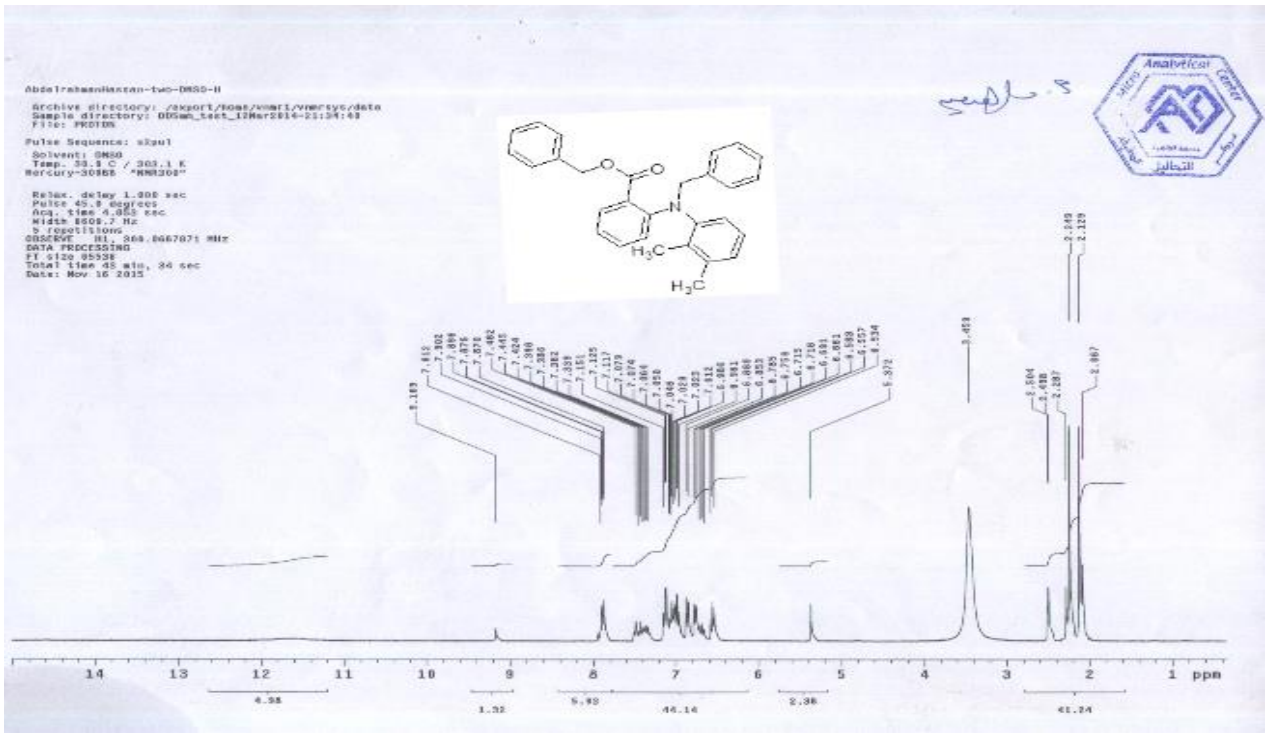
Appendix B-1 H^1NMR spectrum of 2-[(2,3-dimethylphenyl)(ethoxycarbonyl)amino] benzoic acid



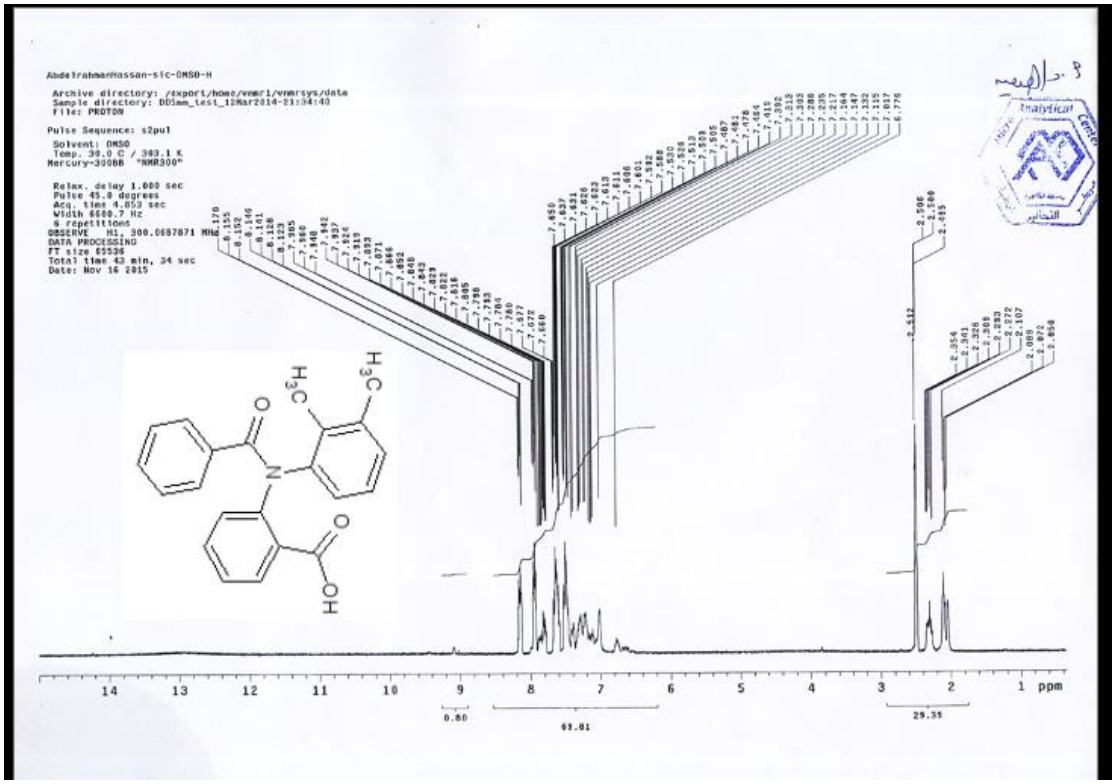
Appendix B-2 H^1NMR spectrum of benzyl2-[(2,3-dimethylphenyl)amino]benzoate



Appendix B-3 H^1NMR spectrum of 2-[Benzyl (2,3-dimethyl phenyl)Amino]benzoic acid

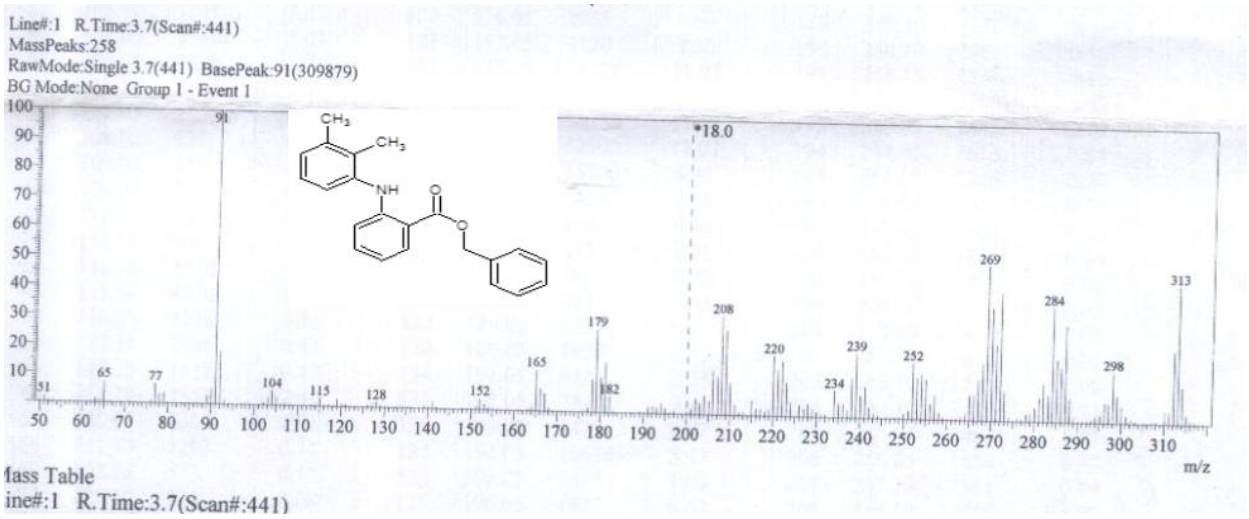


Appendix B-4 H^1NMR spectrum of Benzyl 2-[(2,3-dimethyl phenyl)(benzyl) Amino] benzoate

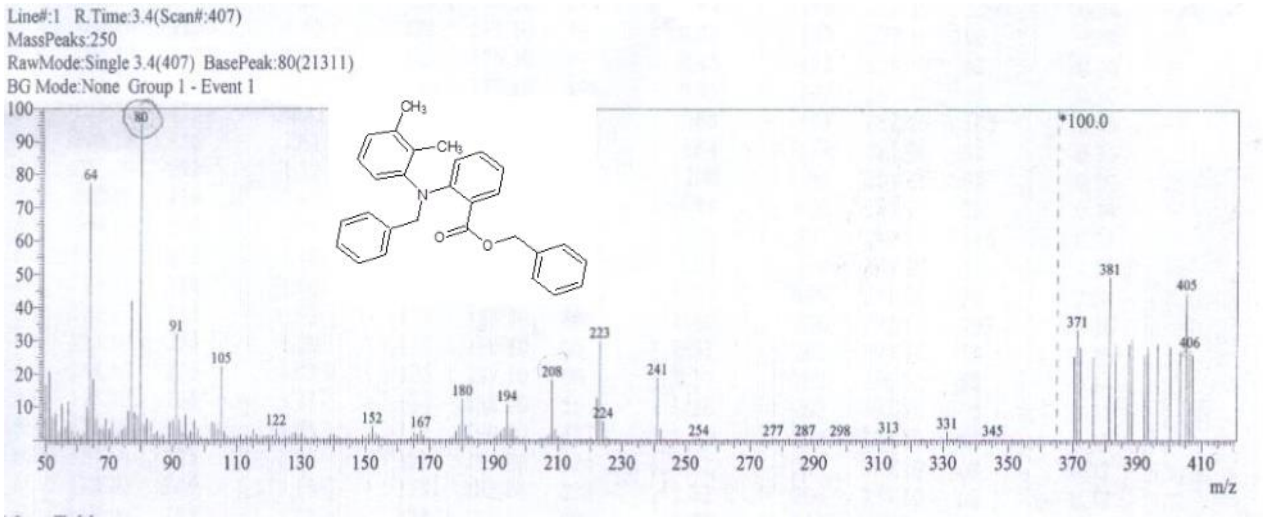


Appendix B-5H[1]NMR spectrum of2-[benzoyl (2,3-dimethylphenyl)amino] benzoic acid

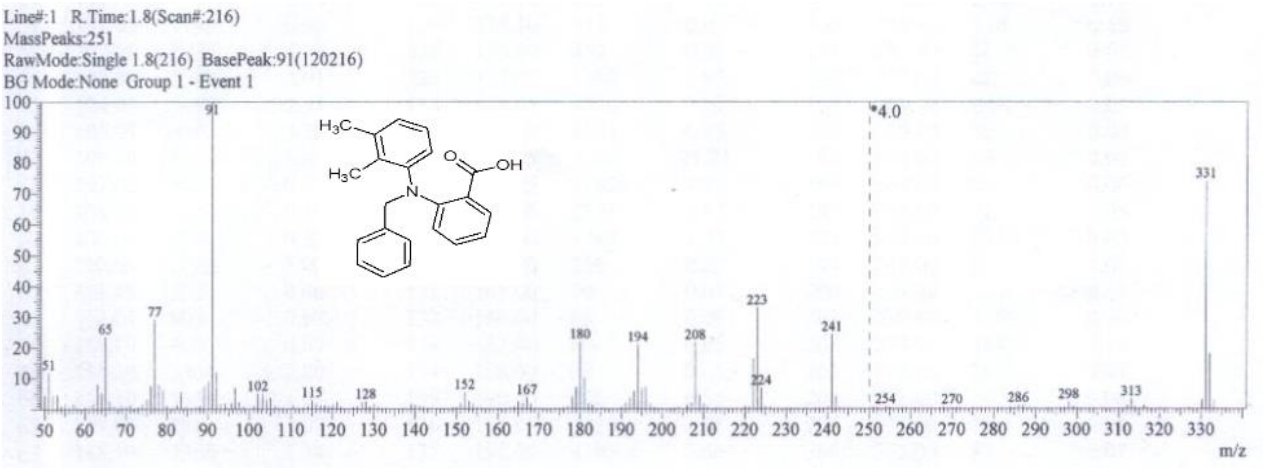
Appendix C



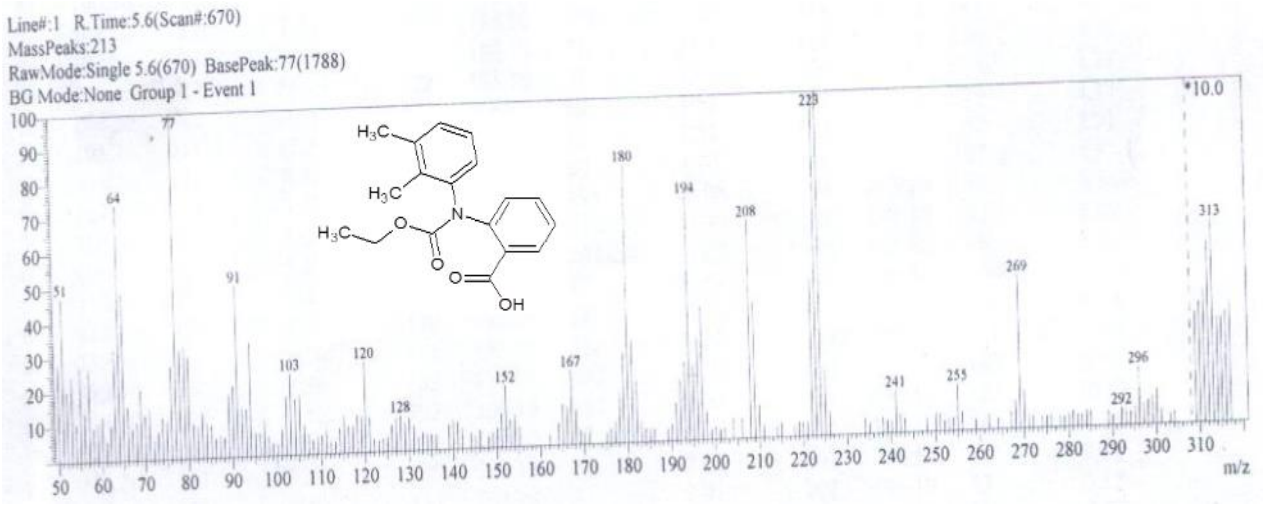
Appendix C-1 GC. Mass spectrum of benzyl2-[(2,3-dimethylphenyl)amino]benzoate



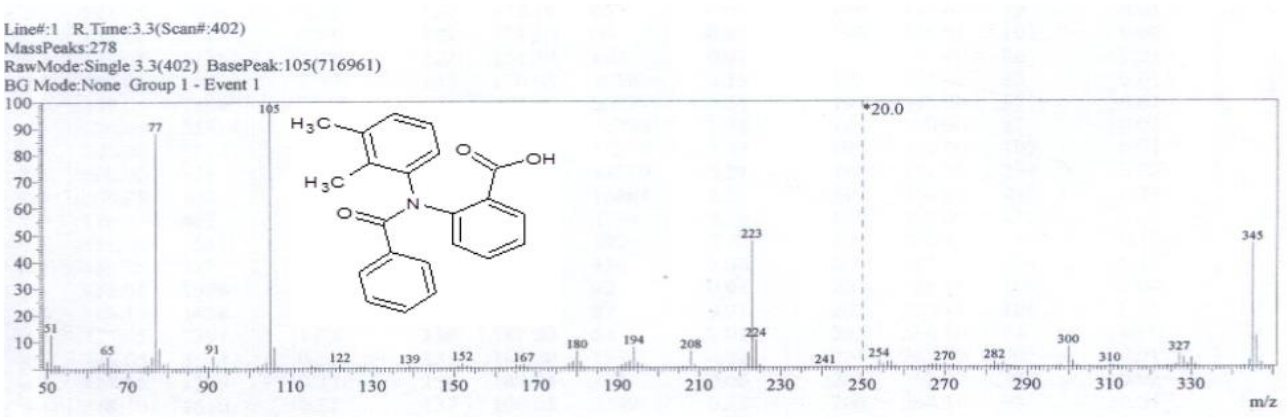
Appendix C-2 GC. Mass spectrum of Benzyl 2-[(2,3-dimethyl phenyl)(benzyl) Amino] benzoate



Appendix C-3 GC. Mass spectrum of 2-[Benzyl (2,3-dimethyl phenyl)Amino]benzoic acid

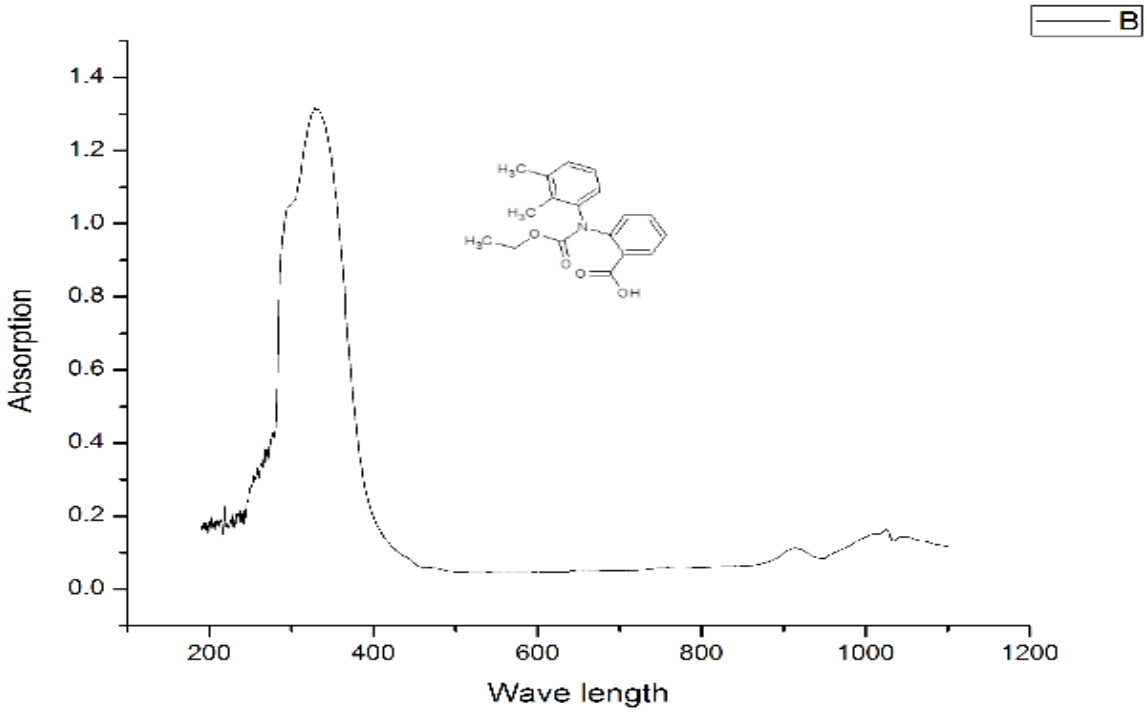


Appendix C-4 GC. Mass spectrum of 2-[(2,3-dimethylphenyl)(ethoxycarbonyl)amino] benzoic acid

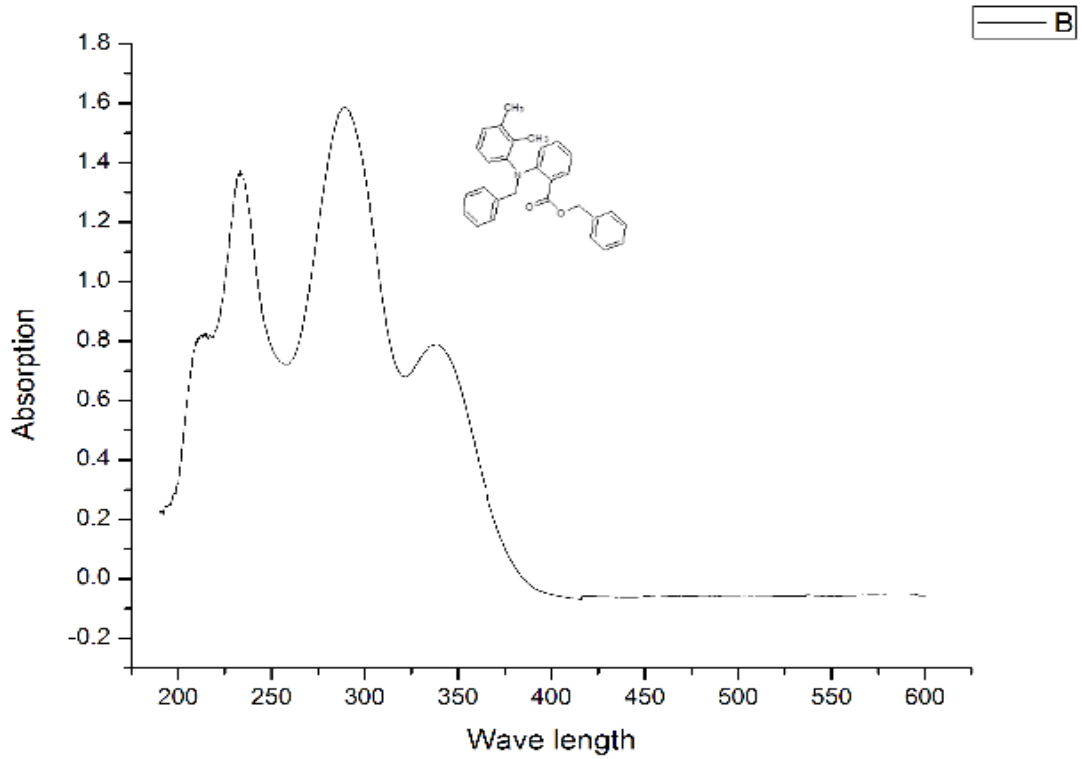


Appendix C-5 GC. Mass spectrum of 2-[benzoyl(2,3-dimethylphenyl)amino] benzoic acid

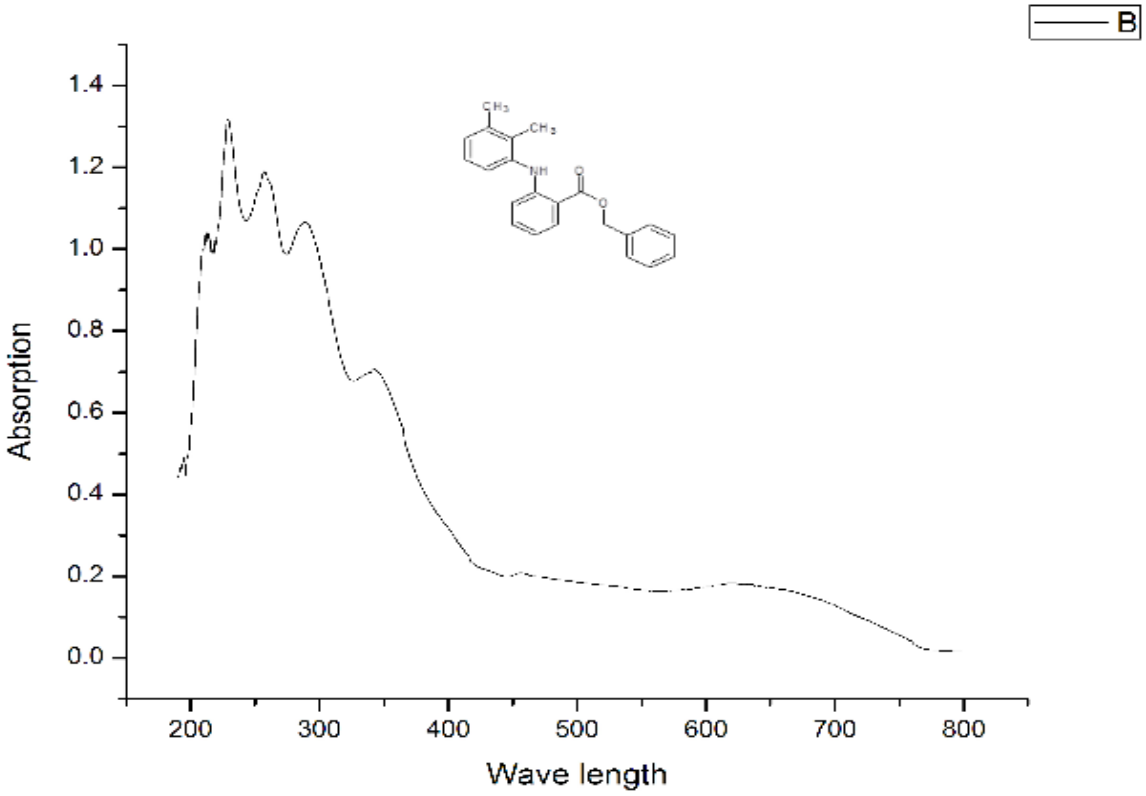
Appendix D



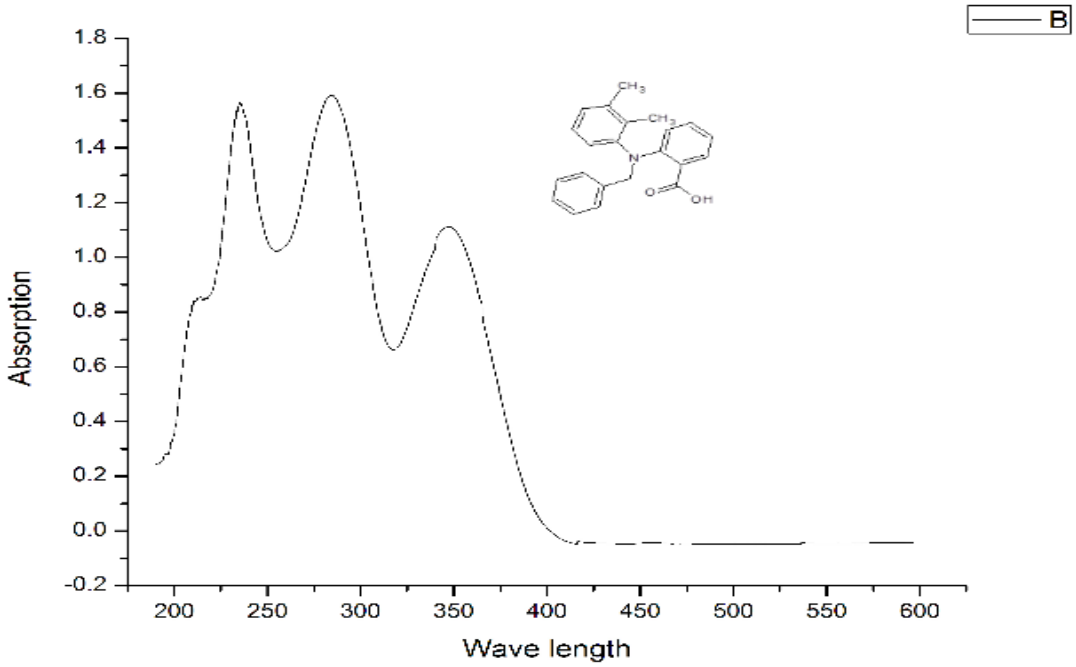
Appendix D-1 UV spectrum of 2-[(2,3-dimethylphenyl)(ethoxycarbonyl)amino] benzoic acid



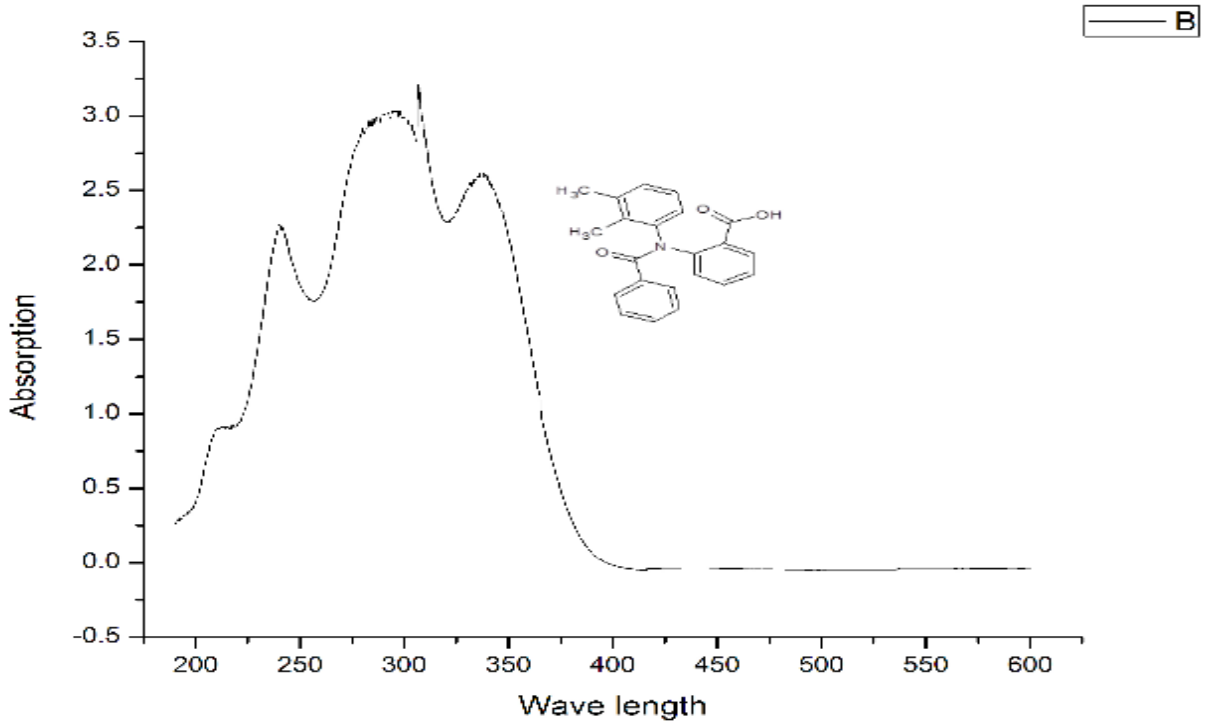
Appendix D-2 UV spectrum of Benzyl 2-[(2,3-dimethyl phenyl)(benzyl) Amino] benzoate



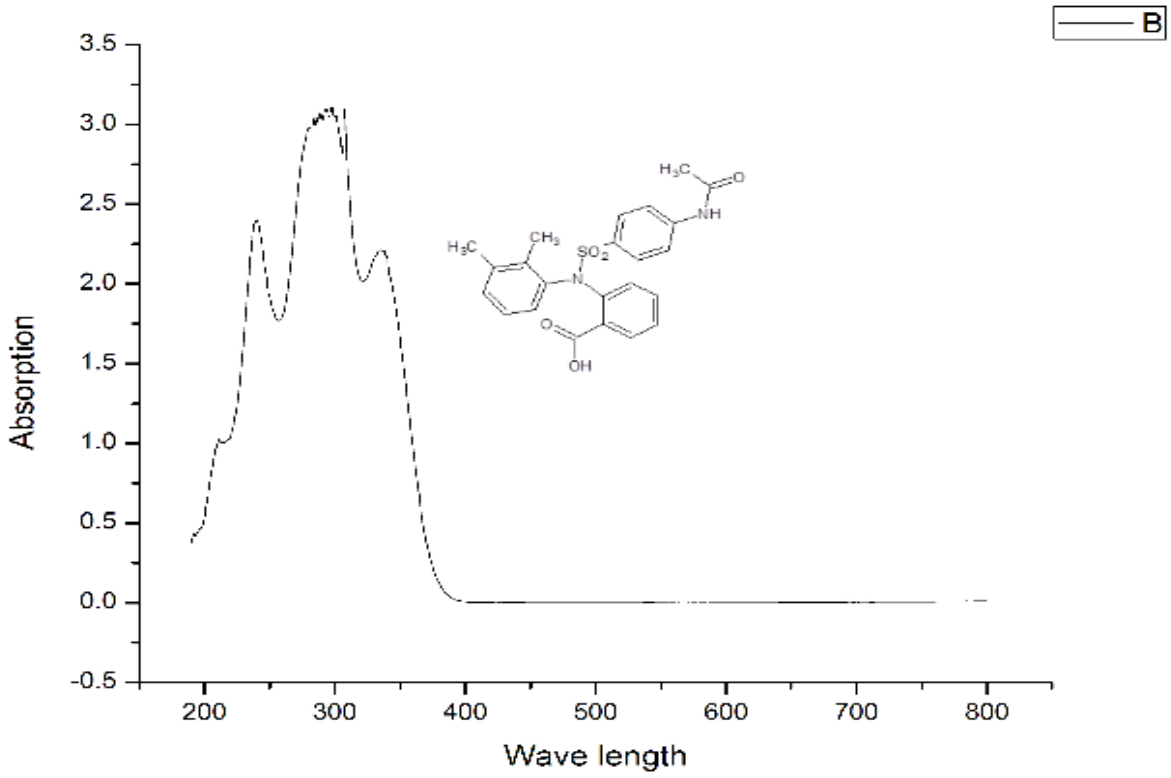
Appendix D-3 UV spectrum of benzyl2-[(2,3-dimethylphenyl)amino]benzoate



Appendix D-4 UV spectrum of 2-[Benzyl (2,3-dimethyl phenyl)Amino]benzoic acid



Appendix D-5 UV spectrum of 2-[benzoyl (2,3-dimethylphenyl)amino] benzoic acid



Appendix D-6 UV spectrum of 2-[(4-actamidophenyl) (2,3-dimethyl phenyl) amino] benzoic acid