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Ministry of Higher Education
and Scientific Research
Al-Nahrain University
College of Science
Department of Chemistry

Synthesis and biological activity of Some amino acid and Barbituric acid derivatives via Schiff's bases

Thesis
Submitted to the College of Science Al-Nahrain University in partial fulfillment of the requirements for the Degree of Master of Science in Chemistry.

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بِسم اللهِ الرَّحمنِ الرَّحيمِ

نَرْفَعُ دَرَجَاتٍ مَنْ نَشَاءُ وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ

صَدَقَ اللهُ العَظِيم

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جزء من آية (٧٦)

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I certify that this thesis was prepared under my supervision at the Department of Chemistry, College of Science, Al-Nahrain University as a partial requirements for **the Degree of Master of Science in Chemistry.**

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We, the Examining Committee, certify that we read this thesis and have examined the student ***"Ahmed Abbas Numan"***, in its contents and that, in our opinion; it is adequate as a thesis for the Degree of Master of Science, in Chemistry.

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Summary

This work involves synthesis and biological activity of some amino and barbituric acid derivatives via shiff bases. This work is divided into six different parts:

Part One:

This part involved the synthesis of different shiff bases [1] by reaction of the aniline with benzaldehyde and its derivatives.

Part Two:

This part involved synthesis of phenoxy acetic acid [II] which converted to phenoxy acid chloride [III]. Reaction of the latter compound with shiff bases resulted in part one yields acetanilide derivatives [2].

Part Three:

This part involved synthesis of amino acid derivatives [3, 4, and 5] by reaction of acetanilide derivatives resulted in part two with different of L-amino acids (Cysteine, Valine, Phenylalanine) as shown in scheme [I].

Part Four:

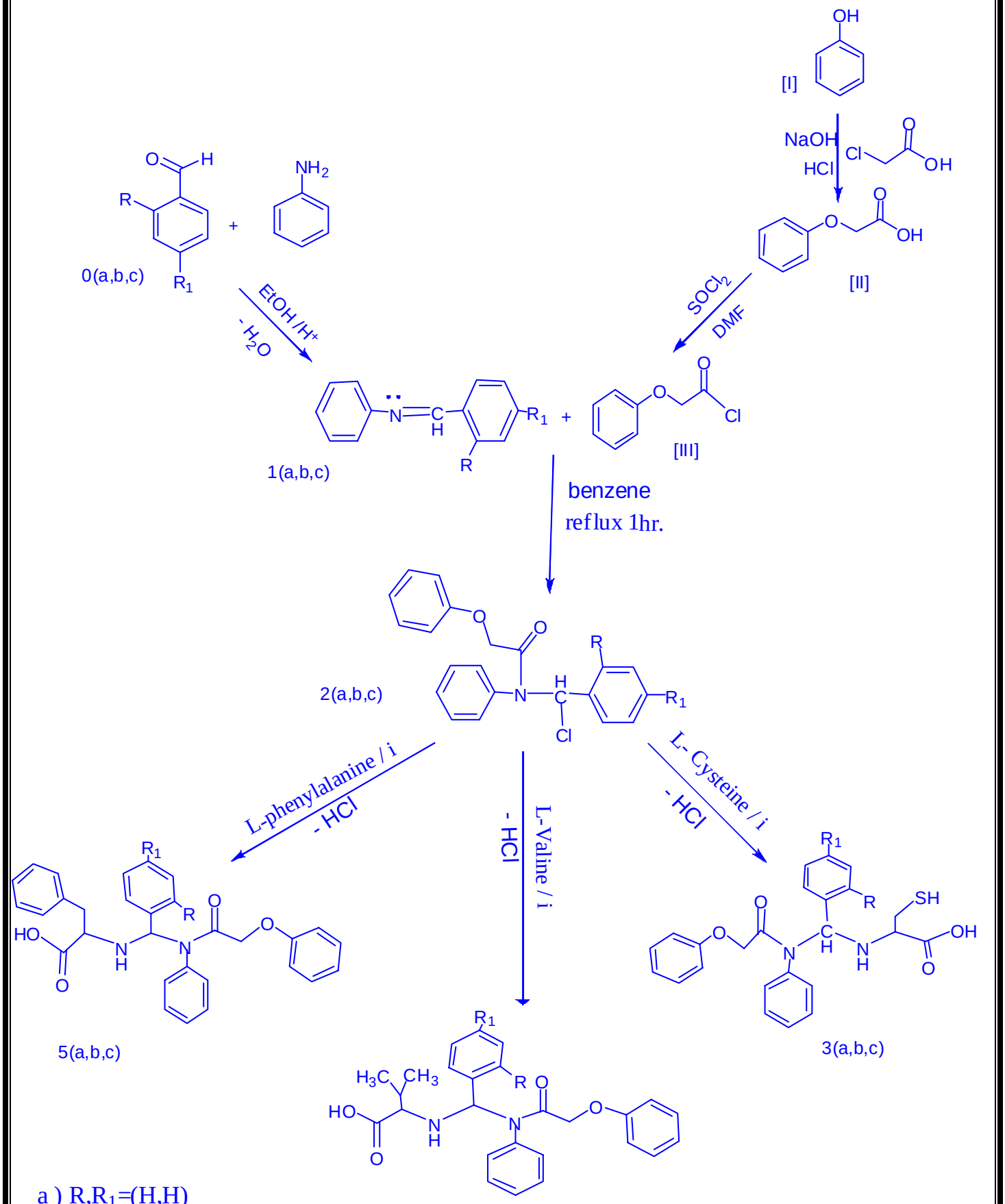
This part involved synthesis of barbituric acid derivatives [7] by reaction of acetanilide derivatives resulted in part two with guanidine carbonate and diethyl malonate (DEM) as shown in scheme [II].

Part Five:

This part involved characterization of the products above by their melting points, elemental analysis and FTIR spectroscopy listed in table 4, 9, and 11.

Part Six:

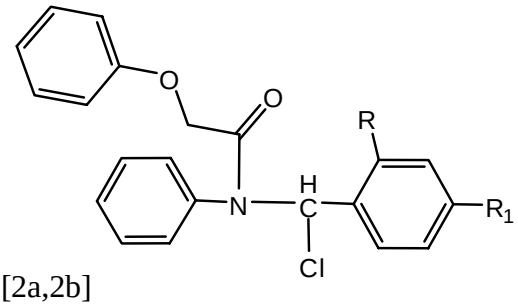
This part involved the evaluation of antibacterial activity of the products. These activities were determined in vitro using disc diffusion method against two pathogenic strains of bacteria {***Pseudomonas aeuroginosa and Staphylococcus aureus***}, as shown in table (4-1).



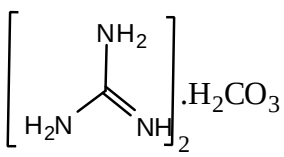
a) R,R_1=(H,H)
b) R,R_1=[H,-N(CH_3)$_2$]
c) R,R_1=(-OCH_3)

i = dioxane / H_2O, reflux 4hr.

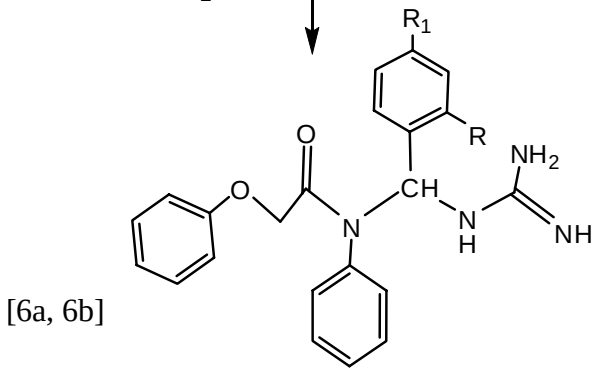
Scheme I



[2a,2b]

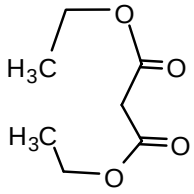


i

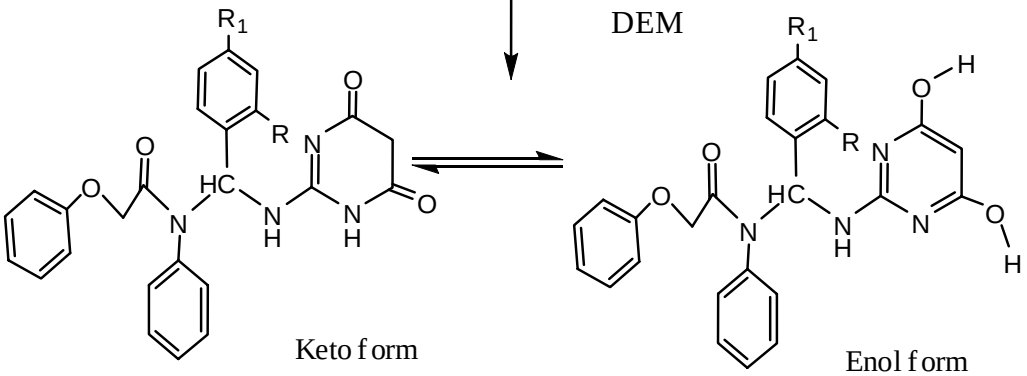


[6a, 6b]

ii



DEM



Keto form

Enol form

[7a, 7b]

a R,R_1 = H, -$N(CH_3)_2$

b R,R_1 = -OCH_3

i = Na_2CO_3 , EtOH

ii = 1. NaOEt / EtOH

2. HCl

Scheme II

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Chapter Four: Biological activity

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Introduction

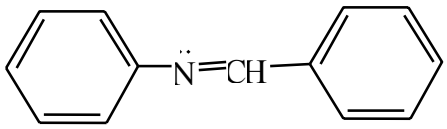
Chapter One

1.1 Schiff Bases

Schiff bases are compounds which contain an azomethine group (—N=C<). They are named according to Schiff who prepared a number of these bases via condensation of aliphatic and aromatic aldehydes and ketones with primary aromatic amines, primary aliphatic amines and amino acids. [1]

There are different nomenclature for Schiff bases such as anils, [2] benzanils, azomethines, imines, ketimine (which derived from ketones), aldimine (which derived from aldehydes).

Aromatic Schiff bases are considered as a chromophore due to conjugation of the electron pair on nitrogen atom with benzene ring of aniline and benzaldehyde [1]. [3]



[1]

Most of aromatic Schiff bases are sparingly soluble in water, while solubility of those having carbohydrate moiety is increased, [4]

Schiff bases are considered as starting materials for synthesis of heterocyclic compounds, [5] and metal complexes[6]. Also Schiff's bases are as important organic compounds for polymerization reactions where they considered as catalyst of reaction.[7, 8]

Also Schiff's bases are used in the industry of ink dyes, [9] Also used to prepare super conducting polymers, [10, 11] and they are highly resistant to heat, light and oxidation.[11]

Schiff bases have two geometric isomers result from stereo distribution of groups attached to double bond [—N̈=C<] which known as Syn-Anti (Cis-trans)-isomerism [2]. [12,13] One of these isomers is more stable than the other result from type of group's distribution about Carbon and Nitrogen atom. [14, 15]

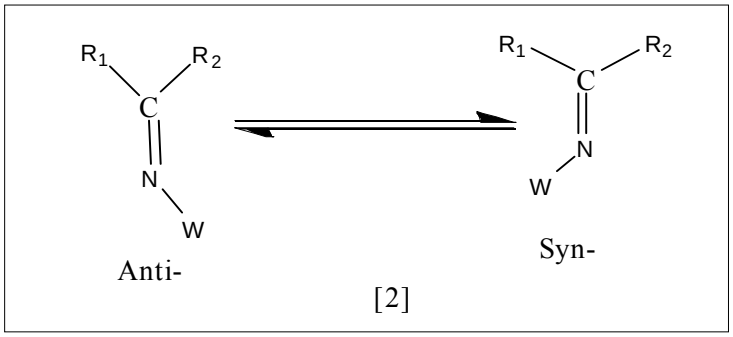
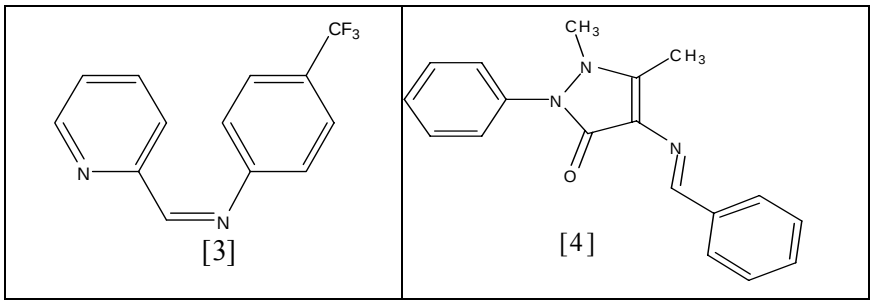


Figure 1-1 geometric isomer of Shiff's bases

Schiff bases exhibit good antimicrobial activity and have pharmacological applications. These compounds show good fungicidal activity, [16] antiviral,[17] antimicrobial, [18] anti -inflammatory, [19] activities and play as antioxidant,[20] anticancer, [21] antibacterial, [22] antifungal, [23] and herbicidal. [24]

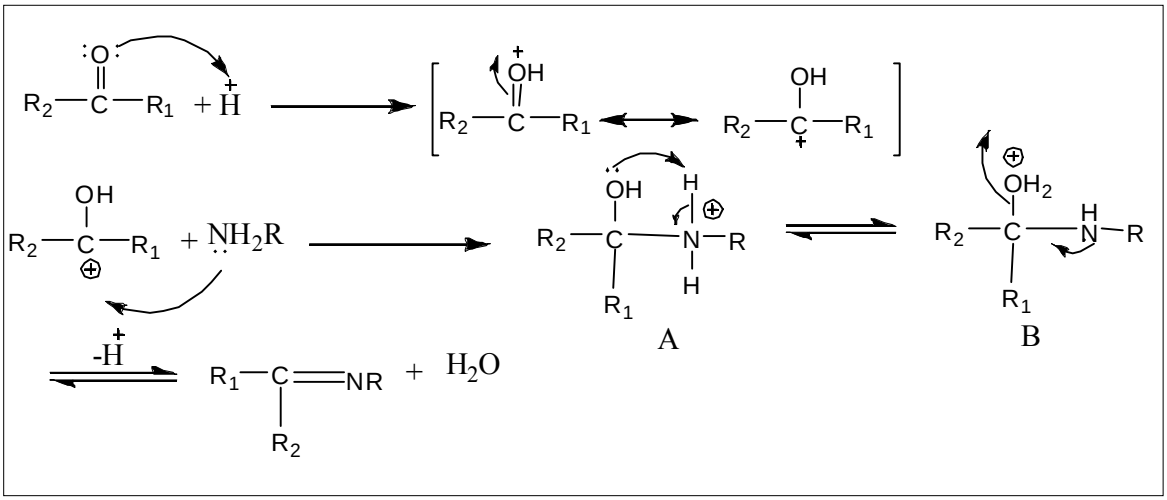
Also the compound 1-pyridin-2-ylmethan imin-1-meth-4-(trifluoromethyl) benzene [3] synthesized to show anti-inflammatory, [25] and (E)-4-(benzylideneamino)-2, 3-dimethyl-1-phenyl-1, 2-dihydropyrazol -5-one [4] found to be antibacterial activity. [26]



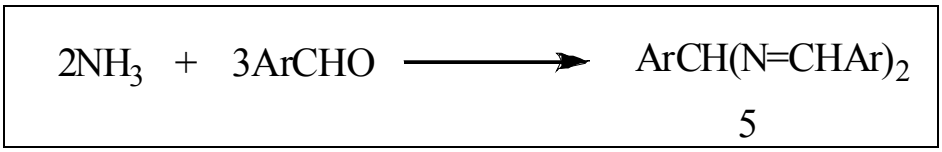
Schiff bases can be synthesized by condensation of aldehyde or ketone with primary amine.

$$R_1R_2CO + RNH_2 \longrightarrow R_1R_2C{=}NR + H_2O$$

Hammett suggested an acid catalyzed reaction includes addition of proton (H) to carbonyl group to form oxonium ion which react with amine group to form [A] which converted to [B] by transition of proton [H] from nitrogen atom to oxygen atom then abstraction of H_2O molecules in the last step to form Schiff base.[27]



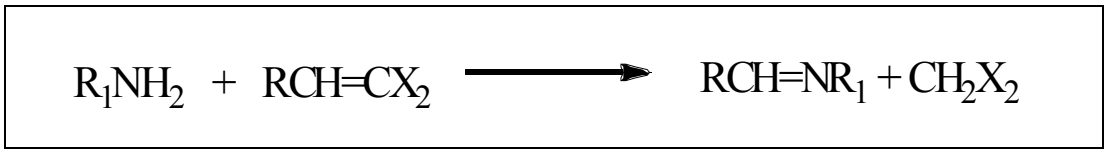
Ammonia does not give azomethine with formaldehyde or aliphatic aldehyde but formed compounds of polymerization [27] while aromatic aldehyde and secondary or tertiary aliphatic aldehyde give condensation products [5] of moles aldehydes with two moles of ammonia. [27]



$$2NH_3 + 3ArCHO \longrightarrow ArCH(N{=}CHAr)_2$$

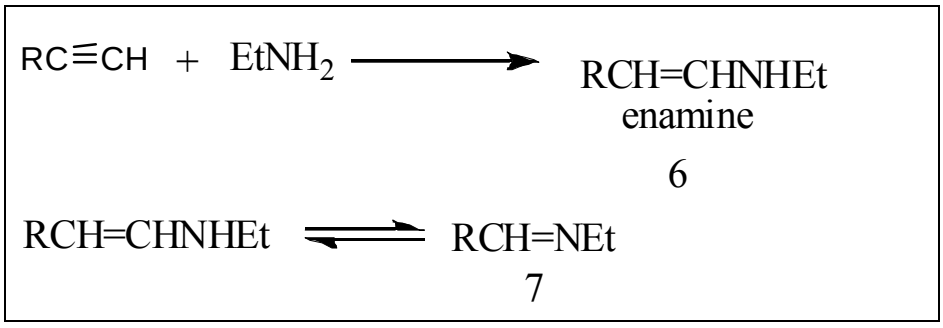
5

Another way for synthesis of shiff bases include used primary amine instead of some groups in this compounds.[27]



$$R_1NH_2 + RCH{=}CX_2 \longrightarrow RCH{=}NR_1 + CH_2X_2$$

Primary amines reaction with acetylenes[27] needed to high temperature and pressure to form enamine [6], which is converted easily to azomethine compound [7].



$$RC{\equiv}CH + EtNH_2 \longrightarrow RCH{=}CHNHEt$$

enamine

6

$$RCH{=}CHNHEt \rightleftharpoons RCH{=}NEt$$

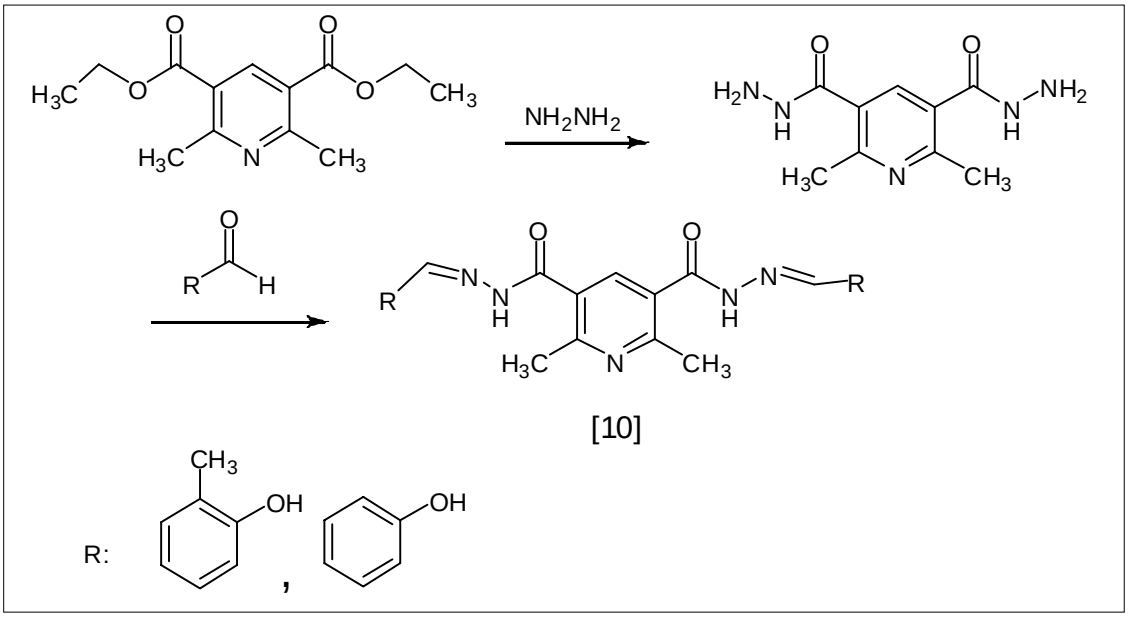
7

Another method includes hydrogenation of phanalnitrile[27] by lithium aluminum hydride where forming mixture of azomethine [8] and primary amine [9].

$$N{\equiv}CPh \xrightarrow{LiAlH_4} PhCH{=}NCH_2Ph + PhCH_2NH_2$$

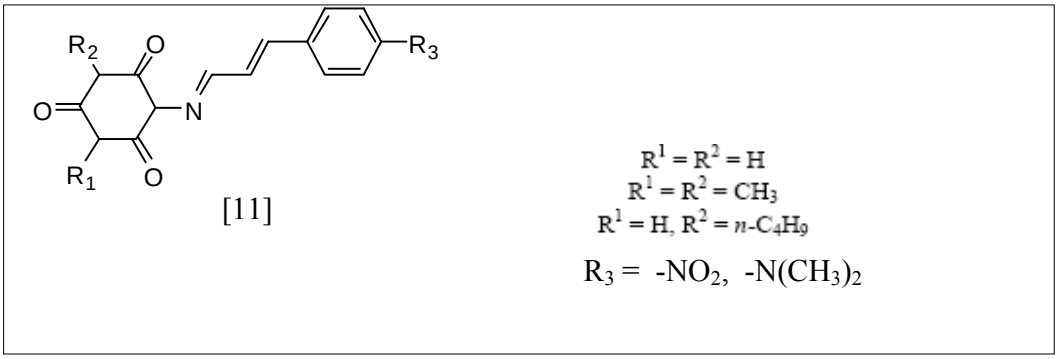
8 9

In 2004 R. Lozytska, [28] has synthesized series of new Schiff bases [10] containing pyridine skeleton by the reaction of suitable aldehyde with 2,6-dimethyl-3, 5-pyridinedicarboxhydrazide.



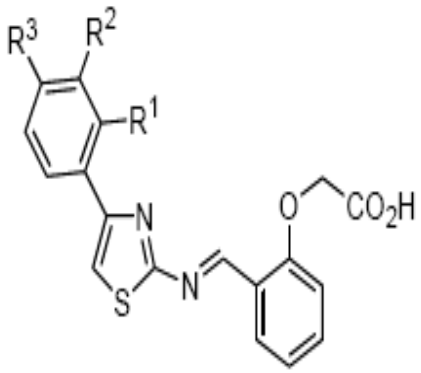
[10]

In 2007 I. Bolz, et. al, [29]have synthesized and characterized novel Schiff bases [11] with multiple binding sites for supramolecular assemblies which used as dyes. For this purpose 1,3- Dimethyl- and 1-Butyl-5- aminobarbituric acids are condensed with p-Nitro- and p-N,N-Dimethylaminocinnamaldehyde respectively.



[11]

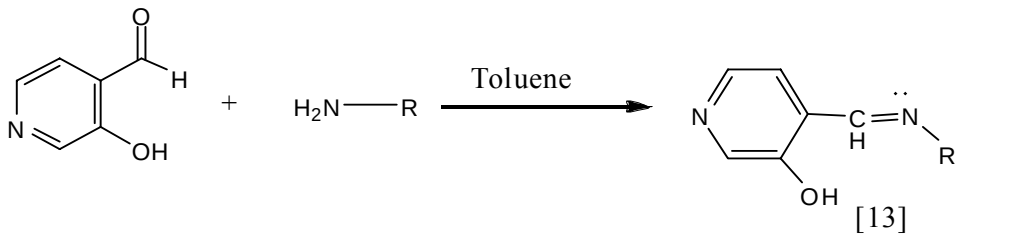
In 2006 Hamid et. al, [30] have synthesized five novel Schiff bases [12] from *o*-Formylphenoxyacetic acid and a series of aminothiazoles to form a number of potentially biologically active compounds.



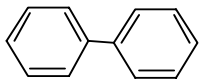
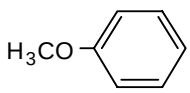
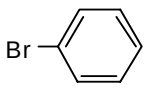
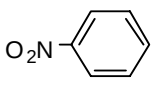
a $R^1 = Br, R^2 = H, R^3 = H$
b $R^1 = H, R^2 = H, R^3 = Br$
c $R^1 = F, R^2 = H, R^3 = H$
d $R^1 = H, R^2 = F, R^3 = H$
e $R^1 = H, R^2 = H, R^3 = F$

[12]

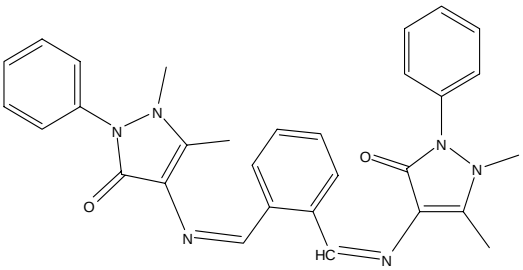
In 2006 Almudena et. al, [31] have synthesized new Schiff bases [13] with antibacterial activity by reacting 3-Hydroxy-4-pyridinecarboxaldehyde with various Amines in toluene.



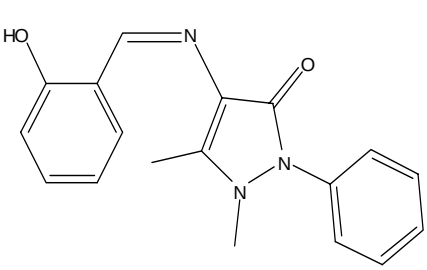
[13]

R:  ,  ,  , 

In 2006 T. Rosu, [32] have synthesized Cu (II) complexes derived from Schiff base [14-15] ligands obtained by the condensation of 2-Hydroxybenzaldehyde or terephthalic aldehyde with 4-aminoantipyrine

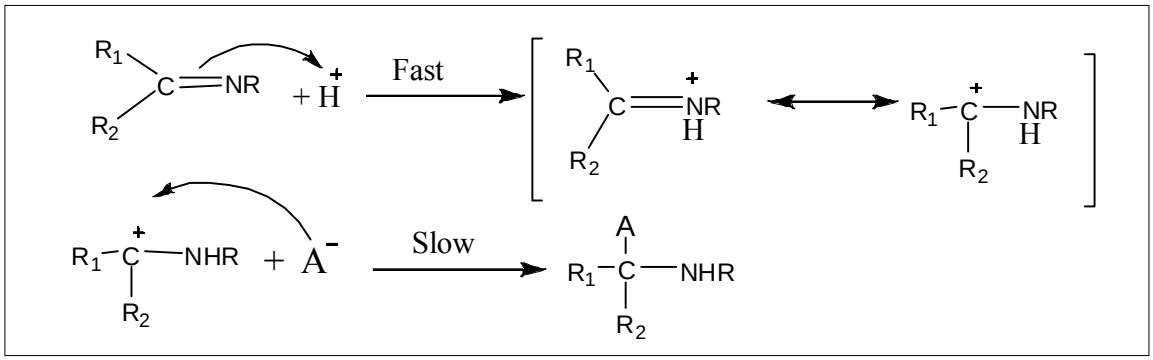


[14]

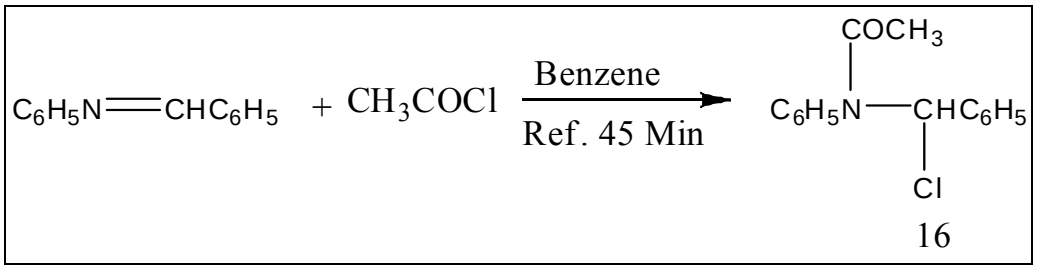


[15]

Schiff bases undergo addition reaction of azomethine, the reagents add to polarized double bond (C=N), therefore nucleophilic reagents attack the carbon atom of the azomethine linkage as described the following mechanism.[33]

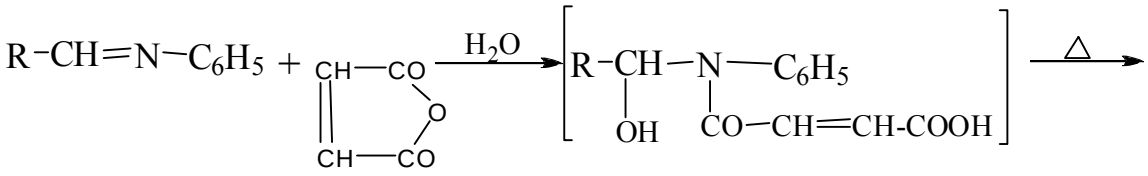


Aromatic Schiff bases are weak bases and weak nucleophiles. This is supported by the fact that they do not react with simple alkyl halides, allyl halides or benzyl halides but they react with the relatively more reactive acid halides. Acetyl chloride, for example, with N-Benzylidene aniline to give N-[chloro (phenyl) methyl]-N-acetanilide [16].[34]

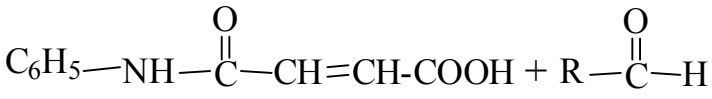


16

Anils react with maleic anhydride in the presence of water to form maleanilic acid [18] and aldehydes[35]

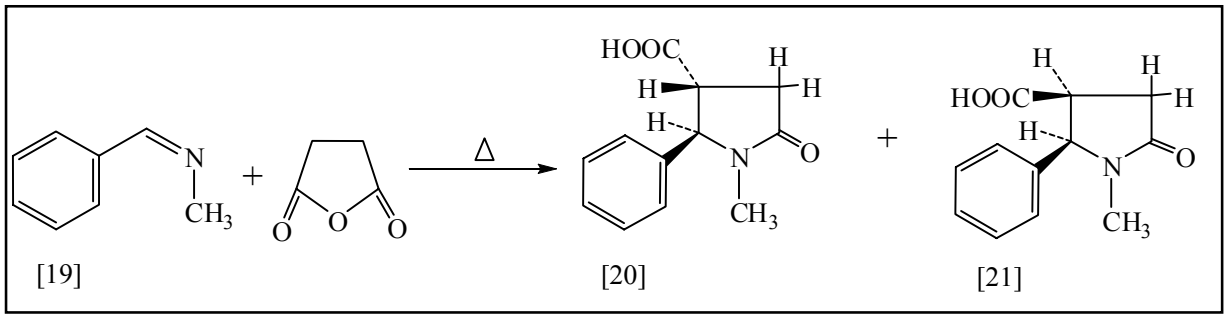


Anil Maleic anhydride [17]



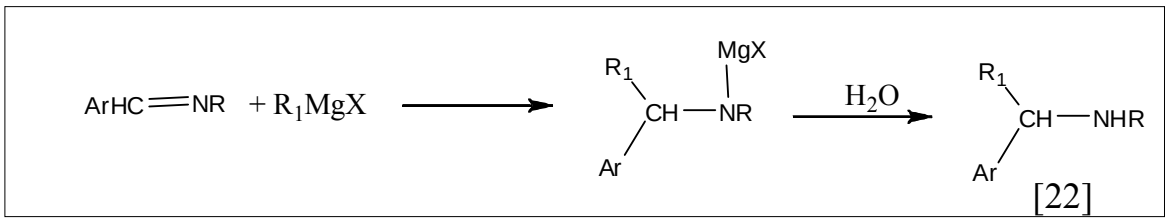
maleanilic acid [18] aldehyde

The condensation of benzylidenemethylamine [19] with succinic anhydride yields trans- and cis- 1- methyl 4- carboxy -5- phenyl -2- pyrrolidinone [20] [21] respectively[36]**:**



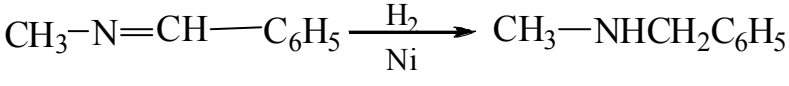
[19] [20] [21]

Grignard reagent reacts with azomethine compounds to form addition products which on hydrolysis result in secondary amines [22][35]. The reaction is usually applied to the Schiff bases which are prepared from aryl aldehydes:



[22]

Schiff bases can be hydrogenated in the presence of catalyst to give the corresponding secondary amines [23][35].



Secondary amine

[23]

1.2 Amino acid derivatives

Proteins are the most abundant organic molecules in animals playing important role in all aspects of cell structures and functions. The physical and chemical properties of proteins are determined by its constituent amino acids. The term amino acids, suggests, every amino acids has an amine group and carboxylic acid group. Both of these functional groups are attached to the same carbon atom which usually also hydrogen atom and another variable group. There are 20 α-amino acids, called the standard amino acids that are found in nearly all proteins. The 20 standard amino acids, grouped according to chemical properties of their side chain.[37]

All amino acids having a free α-amino group except proline, the structure differ slightly from general formula because the amino group and (R) group are part of ring, and this give strength to the proline in peptides that contain it, as shown in Figure (1-2).

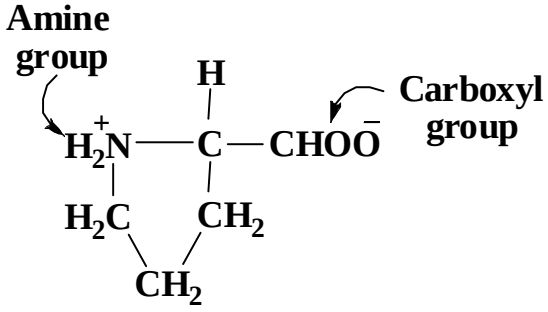


Figure (1-2) Proline

All amino acids in nature except glycine contains on asymmetric carbon (chiral carbon) and so amino acids are optically active.

There are two possible arrangements for molecules with chiral carbon. (Molecules that have only in special arrangement of their atoms are called (stereoisomer). There are two types of stereoisomer [38] of molecules with chiral carbon, D-isomers, L-isomers.

The atoms of two isomers are bonded together in the same pattern except for position of amino group and hydrogen atom. Careful examination reveals that the two isomers in figure (1-3) are mirror images of each other, such molecules called (enantiomers), can not be superimposed on each other.

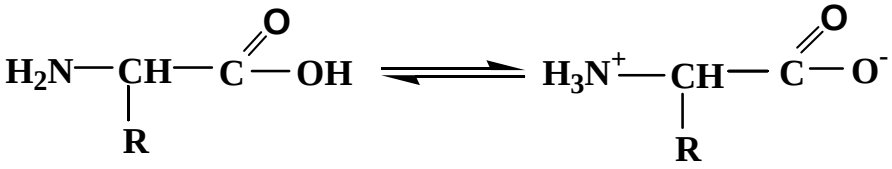
a) L-Alanine **b) D-Alanine**

Figure (1-3) the structural formula (L, D) for alanine

Some of amino acids contain equal quantity from (D) and (L) and this mixture called (Racemic Mixture).

The genetic code use only (L-amino acids) in constructing proteins, although (D-amino acids) may occur as a modification after the genetic code has been transcribed in to proteins, or they are formed by nongenatically directed processes in to (D-amino acids) occur mainly in the lower organisms such as bacteria.[38]

Bjerrume suggest that nearly the whole of neutral aliphatic amino acid is present in solution in the form of the dipolar ion (Zwitter ion), [39] as shown in figure (1- 4) that carries both a positive and negative charge as result of internal acid-base reaction in amino acid molecules.



non ionized form dos not exist

Zwitter ion present in soilds state and solution

Figure (1-4) the Zwitter ion for Amino Acid

A solution of glycine, for example, i.e., $NH_2CH_2CO_2H$ is compared with one of ammonium acetate; if a strong acid is added to the latter, the reaction is with basic $CH_3CO_2^-$ ion and CH_3CO_2H is formed, but a strong base reacts with the acidic $^+NH_4$ ion to yield NH_3.

In the same way, the addition of strong acid to glycine consisting mainly of the dual ion $^+NH_3CH_2CO_2^-$, result in the reaction.

$$^+NH_3CH_2CO_2^- + H_3O^+ \rightleftharpoons {}^+NH_3CH_2CO_2H + H_2O$$

While reaction with alkali is:

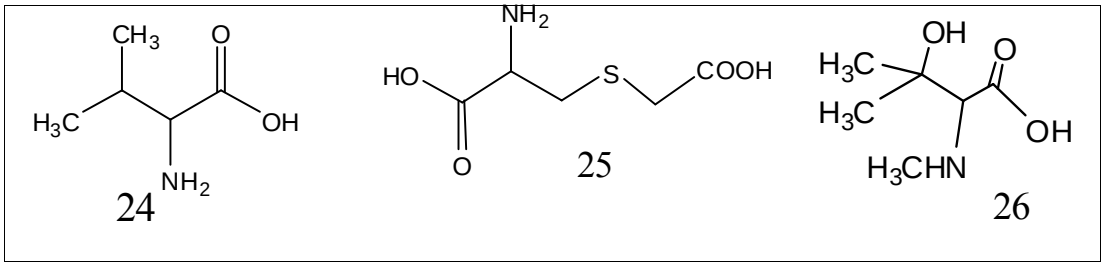
$$^+NH_3CH_2CO_2^- + {}^-OH \rightleftharpoons NH_2CH_2CO_2^- + H_2O$$

There are several other properties of amino acids which are in agreement with the dipolar ion type of structure. These are the high melting point, the sparing solubility in alcohol and acetone, and increased solubility in presence of natural salts, all of these properties associated with ionized substance. [40]

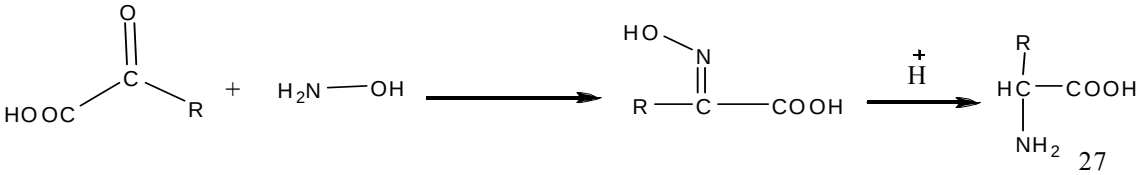
Shown of crystals of glycine by the method of X-ray diffraction indicates that the substance has the structure ($^{+}NH_3CH_2CO_2^{-}$) in the solid state. The high dielectric constant of aqueous solution of aliphatic amino acids lead to that the conclusion molecules have very large dipole moments; such large values can only be explained by the presence within the molecule of unit charges of opposite sign separated by several atomic diameters, as would be expected for dipolar ions. [40]

Amino acids have proven to play significant role in the synthesis of novel drugs. [41] Much Cysteine in a cell culture medium can inactivate the hormone insulin contained in this medium.[42] Another study showed that (L&D) – Cysteine reduced acetaldehyde to ethanol, the human blood was used as medium for this reaction. [43]

Also amino acid derivatives (Valine, phenylalanine) were used in production of drugs for flu, [44] antifungal, [45] cancer therapy, [46] antibodies [47] and antidepressant agent[48] The compound L-Valine (24) was used in biosynthesis of penicillin and cephalosporin,[49] S-carboxymethyl-L-Cysteine (25) was synthesized as antisense compound, [50] and L-N-methyl-β-hydroxy valine (26) synthesized which have antibiotic activity .[51]

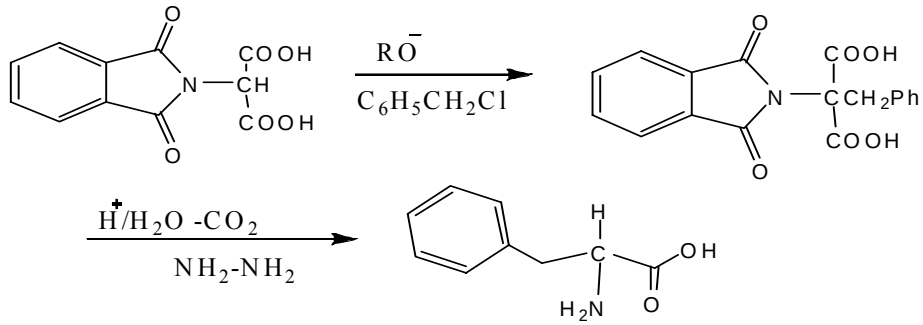


Amino acids can be synthesized from treatment of ∝-keto acids with hydroxylamine to form oxime which was reduced to amino acid [27] as shown below.[52]

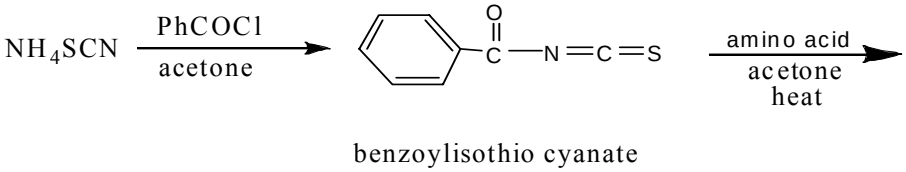


27

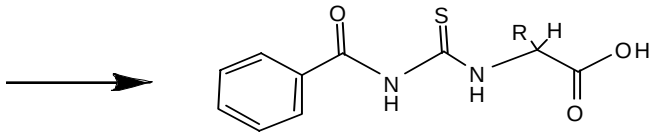
Another way includes using of phthalimidomalonicester.[52]



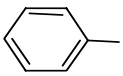
In 2005 A. T. Kabbani et.al, [53] have synthesized new series of potential ligands N-[(benzoylamino)thioxomethyl]amino acid (phenylalanine, Valine, Cysteine) (HL) (28) having biological activity. by the reaction of benzoyl- isthiocyanate with various amino acids.



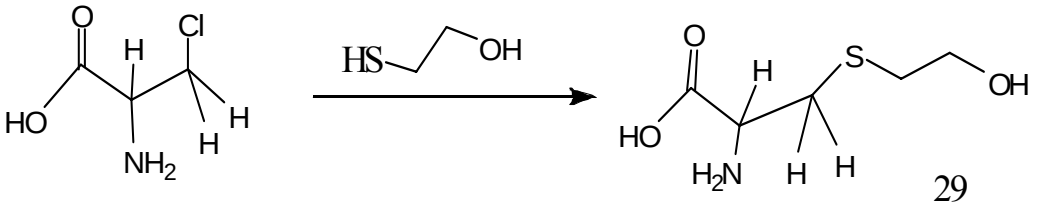
benzoylisothio cyanate



28

R : {$(CH_3)_2$ CH ,  CH_2 , CH_2 SH }

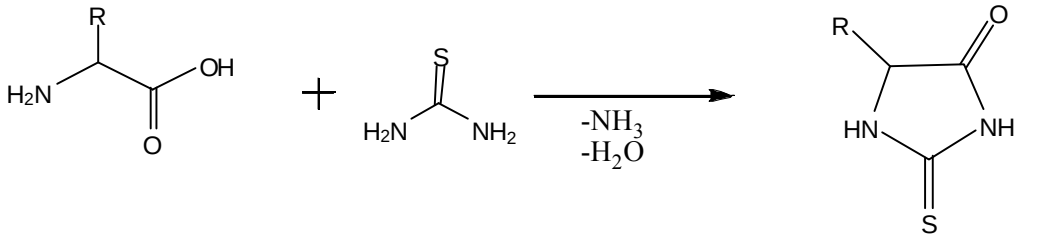
In 2000 B. Adams et.al,[49] have synthesized 3-(2-hydroxy- ethyl) Cysteine (29) from (D&L) Chloro alanine which used as enzymes inhibiter.

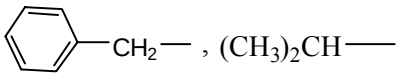


29

3-(2-hydroxy ethyl) cysteine

In 2006 Z. D. Wang et.al, [54] have synthesized 2-thio hydonation derivatives (30) as antiviral activity from ∝- amino acid (valine, phenylalanine) and thiourea.

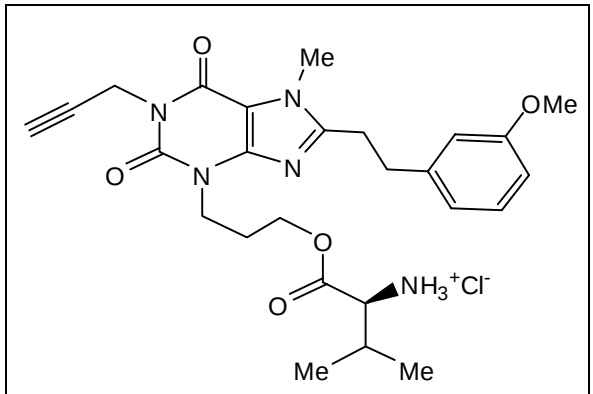


R :  , $(CH_3)_2CH$—

2-thio hydonation

30

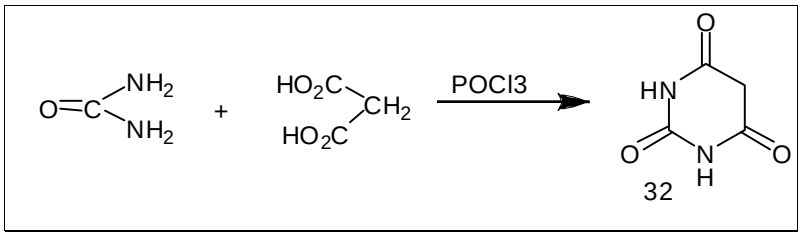
In 2008 K.Vollmann et.al, [55] have synthesized compound L-valine-3-{8-[(E)-2-[3-methoxyphenyl) ethyenyl]-7-methyl-1-propagylxanthine-3-yl} propyl ester hydrochloride (MSX-4) [31] as amino acid ester prodrug of the adenosine A_{2A} receptor antagonist MSX-2. It was found to be stable in artificial gastric acid, but readily cleaved by pig liver esterase.



MSX-4
[31]

1.3 Barbituric acid Derivatives:

Barbituric acid [32] is important members of the pyrimidine family. Barbituric acid was first synthesized by the German chemist Adolf Von Baeyer.This is done by condensing Urea with malonic acid in presence of phosphorus oxychloride ($POCl_3$) as shown below.[56]



Barbituric acid derivatives are solid and have low melting point and low solubility in water. New carbohydrate derivatives having a barbituric acid unit was synthesized in assumption that carbohydrate moiety have higher water solubility and neutral solution, for the new barbituric acid derivatives. The higher solubility will tend to lower the allowed dose and acidic effect of the barbiturate[57].

Because of the acidic effect of the barbiturate can be suggested as shown in Figure (1-5) as the structure of barbituric acid (2, 4, 6-tri hydroxy-pyrimidine).[57]

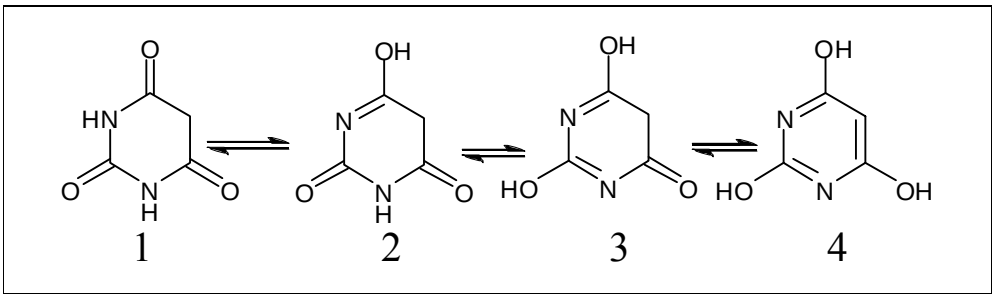
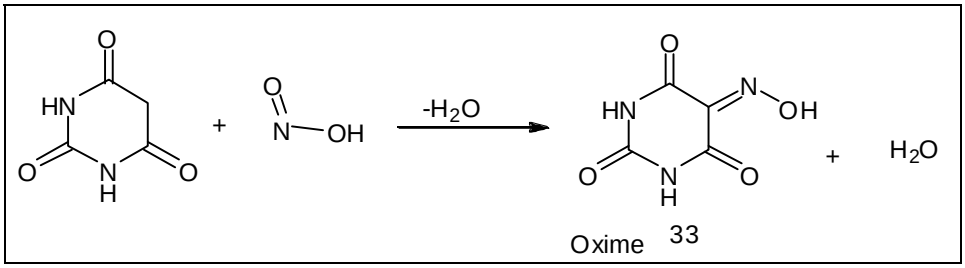


Figure (1-5) the structure of barbituric acid

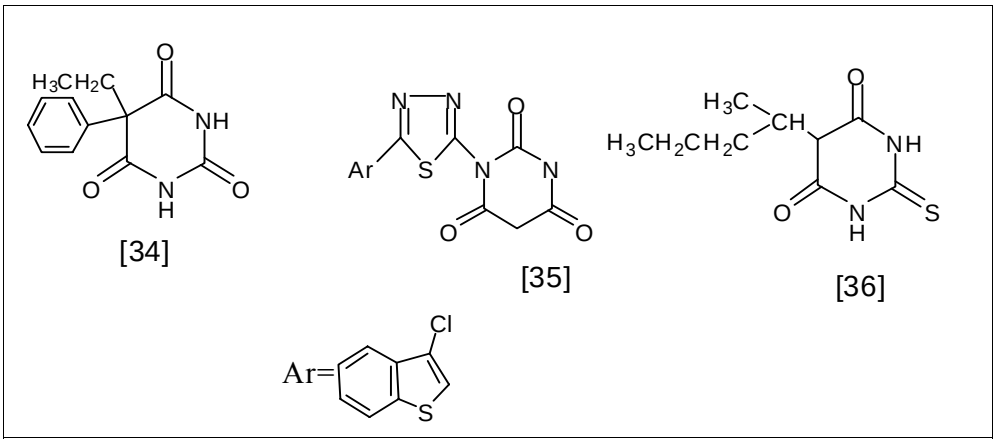
Barbituric acid contains active methylene group therefore methylene easily formed oxime derivative [33] with nitrous acid as shown below [57]



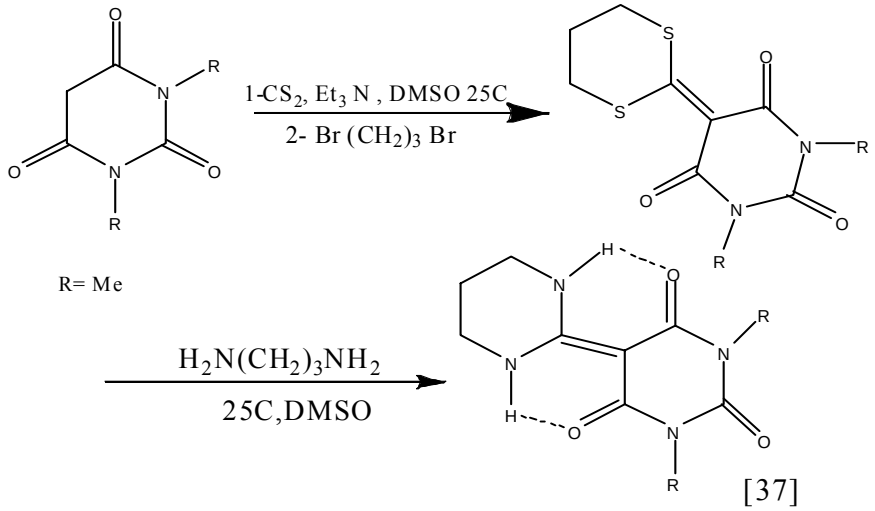
Oxime 33

Barbituric acid itself not pharmacologically active but chemists immediately began making a great variety of derivatives for potential use as drugs. [58] These drugs are used to prepare patients for surgery; other general anesthetics like nitrous oxide are then used to keep the patient from waking up before the surgery is complete. Because barbituric acid derivatives (Pentothal) and other ultra short-acting barbiturates are typically used in hospital settings.[58]

Barbituric acid can be applied as antioxidant, [59] It is important sort for raw material for organic Synthesis.[60] Also barbituric acid derivatives are well known to posses antibacterial, [61] herbicides, [62] fungicide [63] and antiviral agents.[64] The compounds 5- phenyl -5-ethyl barbiturate (Phenobarbital) [34] synthesized as anticonvulsive [65] and 1-]5-(3-chloroben 20(b) (thiophen-Z-yl) -1,3,4- thiadiazol -2-yl] –phenyl –di- hydro pyrimidine -2,4,6 trione [35] as antimicrobial active[66] and thio-5-pentyl barurate (Pentothal) [36] as soporifics and hypnotics since (1903) [67, 68], often used in psychiatry because it tends to release inhibitions and allows patients to talk more ((freely)) (but not necessarily tell the truth). It often produces retrograde amnesia.[69]

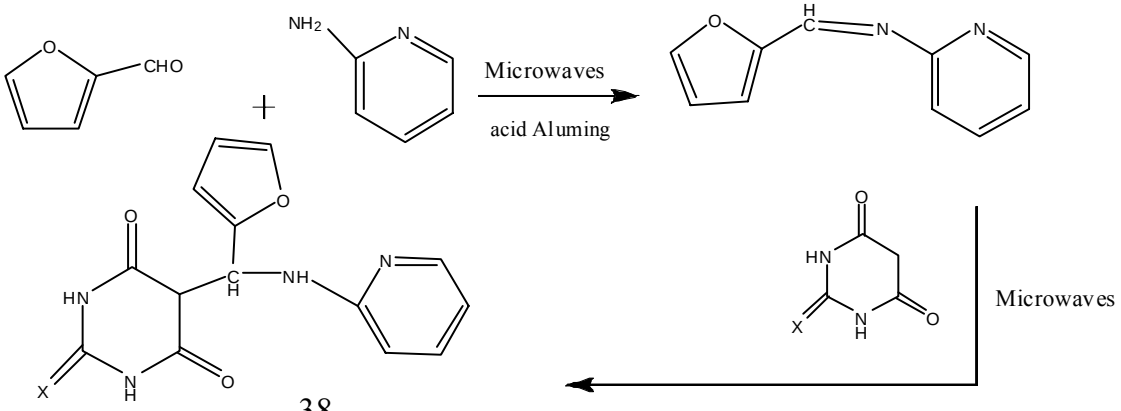


In 2001 Figueroa – villar et. al, [70] have synthesized novel barbiturate derivative (5- Diamino methylidene barbiturates) [37] by the reaction of Diamino propane as nucleophiles with dicyclohexliden barbituric acid.



[37]

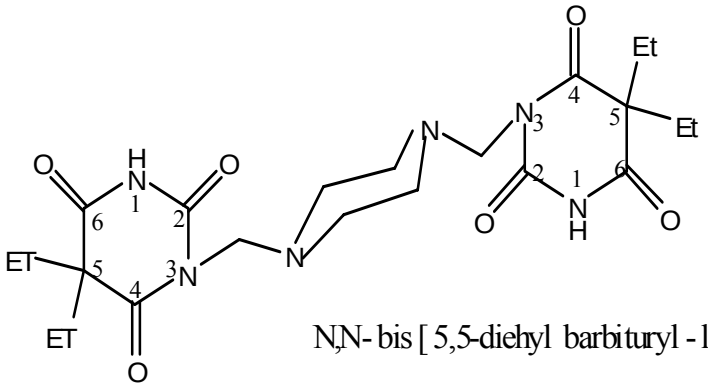
In 2005 Kidwai et. al [71] have synthesized novel mannich base of thiobarbiturates and barbiturates [38] using clay under microwaves. The compound gives good antifungal activity.



38

X = (O,S)

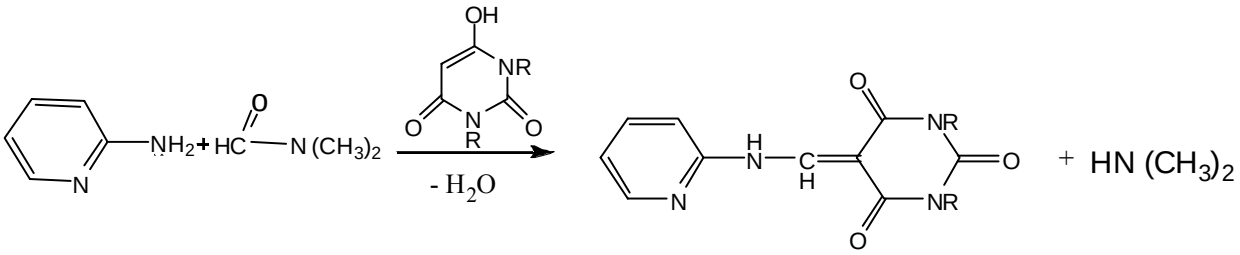
In 2005 C. M. Baucovicean et. al, [72] have Synthesized the ligand N,N Bis (5,5-di ethyl barbituryl -1-methyl) piperazine (VEP) [39] and Cu (II) complex by condensation of 5,5–di–ethyl– barbituric acid (veronal) with formaldehyde and piperazine



N,N- bis [5,5-diehyl barbituryl - l-methyl] Piperazine (VEP)

[39]

In 2004 H. Salgado – Zamora et.al, [73] have synthesized 1, 3-dimethyl -5-methyldene (2-amino Pyridyl) barbituric acid [40] by the reaction of 2-amino pyridine with dimethyl barbituric in DMF.



[40]

Aim of the present work:

Amino acid and barbituric acid derivatives are of great importance because many of these compounds have been found to display biological active, chemotherapeutic and antibiotic.

This work was designed to reach the following targets:

1. Synthesis of amino acid and barbituric acid derivatives via Shiff's bases. Aniline, benzaldehyde derivatives and phenoxy acetic acid have been using the basic materials.
2. Characterization of the products by using elemental analysis (CHN), melting points and FTIR spectroscopy.
3. Exploration the biological activity of synthesized compounds on Pseudomonas aeuroginosa and Staphylococcus aurous.

Experimental part

2.1 Chemicals:

Table (2-1) showed all the used chemicals

Chemicals	purity	Supplied from
Benzaldehyde	99%	BDH
Benzene	Analar	-
Dimethylformamide	Analar	-
1,4-Dioxane	99%	-
Ethanol absolute	99.9%	-
Guanidine Carbonate	65%	-
Hydrochloric acid	37%	-
Thionyl chloride	Analar	-
Aniline	99%	Fluka
Chloroacetic acid	99%	-
L-Cysteine	Analar	-
L-Phenyl alanine	99%	-
L-Valine	-	-
p-Dimethylaminobenzaldehyde	-	Merck
Diethyl malonate	-	-
Glacial acetic acid	90%	-
Phenol	99%	-
Sodium hydroxide	56%	-
2,4-dimethoxy benzaldehyde	99%	-
Sodium carbonate anhydrous	-	LTD

2-2 Apparatus:

1. Melting points were recorded using hot stage Gallen Kamp melting point apparatus were uncorrected.
2. Infrared spectra were recorded on Shimadzu FTIR-8300 spectrometer as potassium bromide disc or thin film was preformed in Chemistry Department, Al-Nahrain University.
3. Thin layer chromatography (TLC) was performed on Alumina plate covered with Silica gel layer, and the spots were developed with iodine vapor.
4. Elemental analyses (CHN) were carried by Eroea Elemental Anlayzer 3000 in Al-Mustansiriya University.

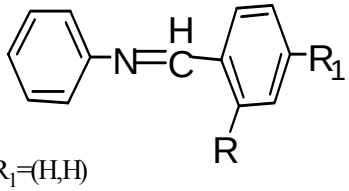
2.3 Procedures:

2.3.1 Synthesis of Schiff Bases: (1a-c) [27]

In a 100 ml round bottomed flask equipped with magnetic stirrer, and double surface condenser with calcium chloride guard tube a mixture of 0.01 mole (1.01g) of freshly distilled aniline, 0.01 mole (0.93g) of benzaldehyde, 10 ml of ethanol and one drop of glacial acetic acid, was refluxed at for 30 min. Then the mixture was left to cool in ice bath, a yellowish crystals were separated out. The crystals were filtered, washed with 2% HCl, then with water and recrystallized from ethanol and in the similar way synthesized another derivatives (1b, 1c) and table 2.2 shown physical properties of synthesis Schiff bases.

Table 2.2 Physical properties of Schiff bases (1a-c)

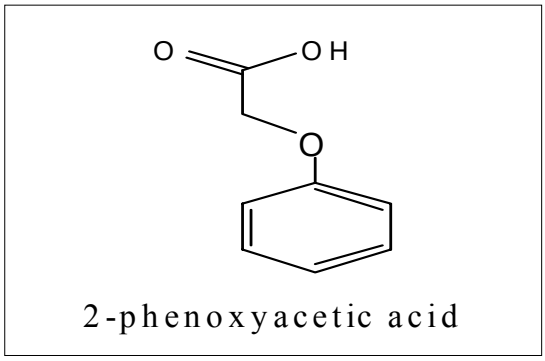
Substituents	Melting points	yields%	Colors	Formula
R,R_1=H	50-52 ºC	88.9	Yellow	$C_{13}H_{11}N$
R,R_1=H,$N(CH_3)_2$	150-154 ºC	86.6	Yellow	$C_{15}H_{16}N_2$
R,R_1=-OCH_3	70-73 ºC	78.6	Yellow	$C_{15}H_{15}NO_2$



1a: R,R_1=(H,H)
1b: R,R_1=[H,-$N(CH_3)_2$
1c: R,R_1=(-OCH_3)

2.3.2 Synthesis of Phenoxyacetic acid: (Π) [42]

In a 100 ml round bottomed flask equipped with magnetic stirrer, and double surface condenser a mixture of monochloroacetic acid 0.05 mole, (4.7g) and phenol 0.05 mole (4.8g), was placed then a solution of sodium hydroxide (0.12 mole in 25 ml water) was added slowly with constant stirring. After completion of addition the mixture was stirred for 2 hrs till solution turn greenish yellow and then the mixture was evaporated till sodium salt precipitated out .The salt was dissolved in water and acidified with Conc. HCl till blue litmus paper turn red. The precipitate filtered off and recrystallized from ethanol, m.p. for [Π] (247-250) ºC, yield (83.6%).



2-phenoxyacetic acid

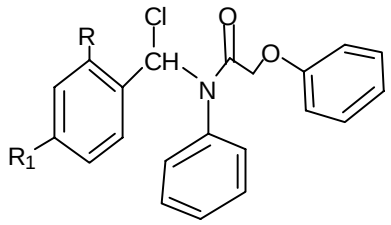
The product Π have been converted into the corresponding acyl chloride as described in 2.3.3.

2.3.3 Synthesis of N-α-(chloro-2, 4-disubstituted phenyl) methyl-N-2-phenoxyacetanilide (2a-c) [42]

In a 100 ml round bottomed flask equipped with magnetic stirrer, and double surface condenser with calcium chloride guard tube a mixture of phenoxyacetic acid (Π) 0.003 mole (0.5g) and of Thionyl chloride (0.22 ml,0.003 mole) was refluxed for 30 min. After cooling in ice-bath a solution of 0.06 moles (1.08g) from Schiff base derivatives (1) in 5ml benzene was added. The mixture was refluxed for 45 min. After cooling the crystals separated out, filtered and washed with 2% Na_2CO_3. The product was washed with water and recrystallized from (1:1) ethanol-water.

Table (2.3) Physical properties of compounds (2a-c)

Substituents	Melting points	**Yields%**	**Formula**
R,R_1=H	**160-164 °C**	**54**	**$C_{21}H_{18}NO_2Cl$**
R,R_1= H,$N(CH_3)_2$	**93-95 °C**	**58**	**$C_{23}H_{23}N_2O_2Cl$**
R,R_1=OCH_3	**150-155 °C**	**74**	**$C_{23}H_{22}NO_4Cl$**



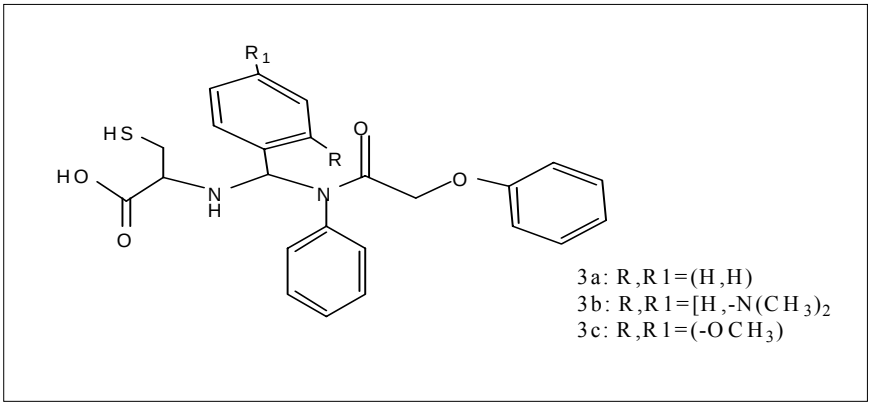
2 a : R ,R_1 = (H ,H)
2 b : R ,R_1 = [H ,-N (CH_3)$_2$
2 c : R ,R_1 = (-O CH_3)

2.3.4 Synthesis of N-[α-(2, 4-disubstituted phenyl- N¯-Cystyl) methyl]-N-2-phenoxyacetanilide: (3a-c)

In a 100 ml round bottomed flask equipped with magnetic stirrer, and double surface condenser a mixture of acid halide (2) 0.0005 mole, L-Cysteine 0.0005 mole (0.06g), in 10 ml (2:1) 1,4-dioxane-water, was refluxed with stirring for 4 hrs. The resulting mixture was cooled and a few drops of water were added, the crystals were separated out, filtered, washed with water. The product was recrystallized from (2:1) 1, 4-dioxane-water.

Table (2.4): Physical properties of compounds (3a-c)

Substituents	Melting points	yields%	Formula
R,R_1=H	78-80ºC	38.3%	$C_{24}H_{24}N_2O_4S$
R,R_1=H,$N(CH_3)_2$	140- 143 ºC	45.8%	$C_{26}H_{29}N_3O_4S$
R,R_1=-OCH_3	93-96 ºC	70.0%	$C_{26}H_{28}N_2O_6S$

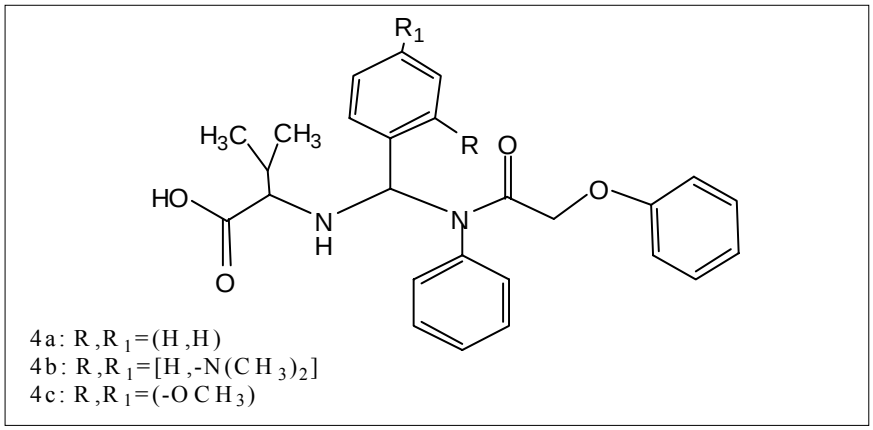


2.3.5 Synthesis of N-[α-(2, 4-disubstituted phenyl- N¯-Valinyl) methyl]-N-2-phenoxyacetanilide :(4a-c)

In a 100 ml round bottomed flask equipped with magnetic stirrer, and double surface condenser a mixture of acid halide (2) 0.0005 mole, L-Valine 0.0005 mole (0.06g), in 10 ml (2:1) 1,4-dioxane-water, was refluxed with stirred for 4hrs. The resulting mixture was cooled and a few drops of water were added, the crystals were separated out, filtered, washed with water. The product was recrystallized from (2:1) 1, 4-dioxane-water.

Table (2.5): Physical properties of compounds (4a-c)

Substituents	Melting points	yields%	Formula
R,R_1=H	150-153 ºC	66.6	$C_{26}H_{28}N_2O_4$
R,R_1=H,N$(CH_3)_2$	178-180 ºC	58	$C_{28}H_{33}N_3O_4$
R,R_1=-OCH_3	118-120 ºC	62.5	$C_{28}H_{32}N_2O_6$



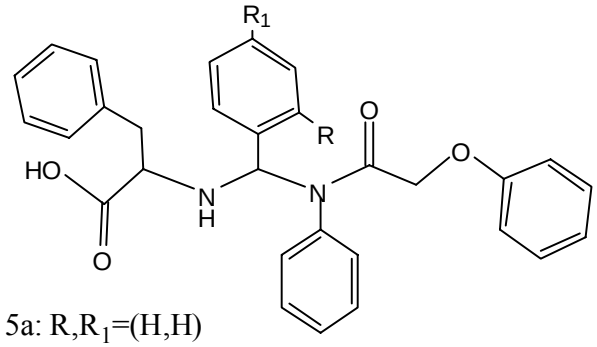
4a: R ,R_1=(H ,H)
4b: R ,R_1=[H ,-N$(CH_3)_2$]
4c: R ,R_1=(-OCH_3)

2.3. Synthesis of N-[α-(2, 4-disubstituted phenyl-N¯ - Phenylalinyl) methyl]-N-2-phenoxyacetanilide: (5a-c)

In a 100 ml round bottomed flask equipped with magnetic stirrer, and double surface condenser a mixture of acid halide (2) 0.0005 mole, phenylalanine 0.0005 mole (0.08 g), in 10 ml (2:1) 1,4-dioxane-water, was refluxed with stirred for 4hrs. The resulting mixture was cooled and a few drops of water were added, the crystals were separated out, filtered, washed with water. The product was recrystallized from (2:1) 1, 4-dioxane-water.

Table (2.6):- Physical properties of compounds (5a-c)

Substituents	Melting points	yields%	Formula
R,R_1=H	160-165 ºC	81.3	$C_{30}H_{28}N_2O_4$
R,R_1=H,$N(CH_3)_2$	78-80 ºC	74	$C_{32}H_{33}N_3O_4$
R,R_1=-OCH_3	87-90 ºC	30.8	$C_{32}H_{32}N_2O_6$



5a: R,R_1=(H,H)
5b: R,R_1=[H,-$N(CH_3)_2$]
5c: R,R_1=(-OCH_3)

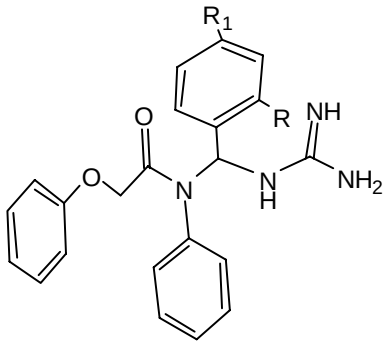
2.3.7 Synthesis of N-[α-(2, 4-disubstituted phenyl- N¯-guanidino) methyl]-N-2-phenoxyacetanilide: (6a, b) [56]

In a 100 ml round bottomed flask equipped with magnetic stirrer, and double surface condenser 0.0007mole (0.3g) of N-α-(chloro-2, 4-disubstitutedphenyl) methyl-N-2-phenoxyacetanilide (2) dissolved in 5ml of absolute ethanol, and 0.0007 mole (0.13g) of guanidine carbonate with 0.0007 mole of anhydrous sodium carbonate dissolved in 5ml absolute ethanol. The reaction mixture was refluxed for 2 hrs. with continuous stirring.

The solvent was evaporated and the remaining colored crystals of the product were filtered, washed with 2% Na_2CO_3 then with distilled water and recrystallized from (1:1) ethanol-water.

Table (2.7): Physical properties of compounds (6a, b)

Substituents	Melting points	Yields%	Formula
R,R_1=H,-N$(CH_3)_2$	152-155̊C	46.7	$C_{24}H_{27}N_5O_2$
R,R_1= -OCH_3	82-85̊C	81.3	$C_{24}H_{26}N_4O_4$



6a:R,R_1[H,-N$(CH_3)_2$]
6b:R,R_1[-OCH_3]

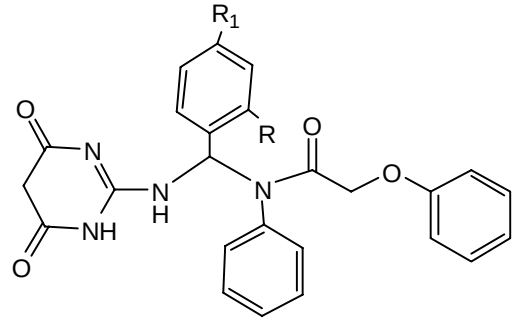
2.3.8 Synthesis of N-[α-(2-aminobarbiturat-2, 4-disubstituted phenyl) methyl]-N-2-phenoxyacetanilide: (7a, b) [56]

In 100ml round bottomed flask, fitted with a double surface condenser, was placed 0.02mole (3ml) of DEM and 10 ml of ethanolic solution of sodium ethoxide [prepared by dissolving 0.64g of dry clean sodium metal in 10 ml absolute ethanol] with continuous stirring for 20 min. 0.02 mole (8.35g) of N-[α-(2, 4-disubstituted phenyl-Ñ-guanidino) methyl]-N-2-phenoxyacetanilide (6) in 10ml of absolute ethanol was added to the mixture. The resulting mixture was refluxed for 8 hrs. with continuous stirring.

When the clear solution was allowing cooling to room temperature, added 20 ml of distilled water was added then acidified with 2ml of concentrated hydrochloric acid. The precipitated colored crystals were filtered, washed with distilled water, dried and recrystallized from (1:1) ethanol-water.

Table (2.8): Physical properties of compounds (7a, b)

Substituents	Melting points	Yields%	Formula
R,R_1=H,-$N(CH_3)_2$	75-79 ̊C	52.2	$C_{27}H_{27}N_5O_4$
R,R_1= -OCH_3	89-92 ̊C	72.4	$C_{27}H_{26}N_4O_6$

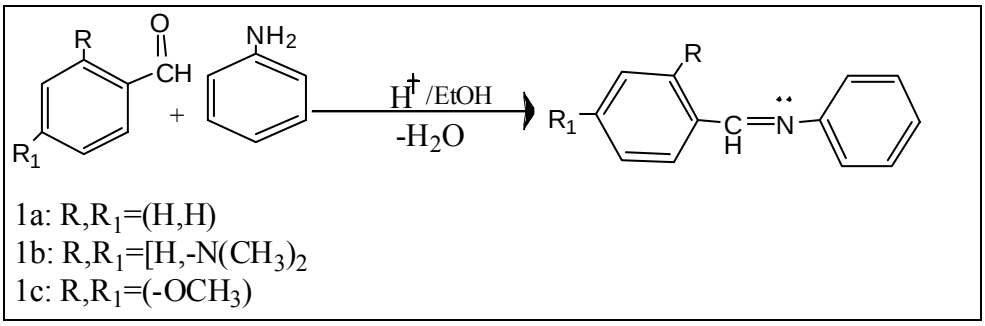


7a:R,R_1[H,-$N(CH_3)_2$]
7b:R,R_1[-OCH_3]

Chapter three

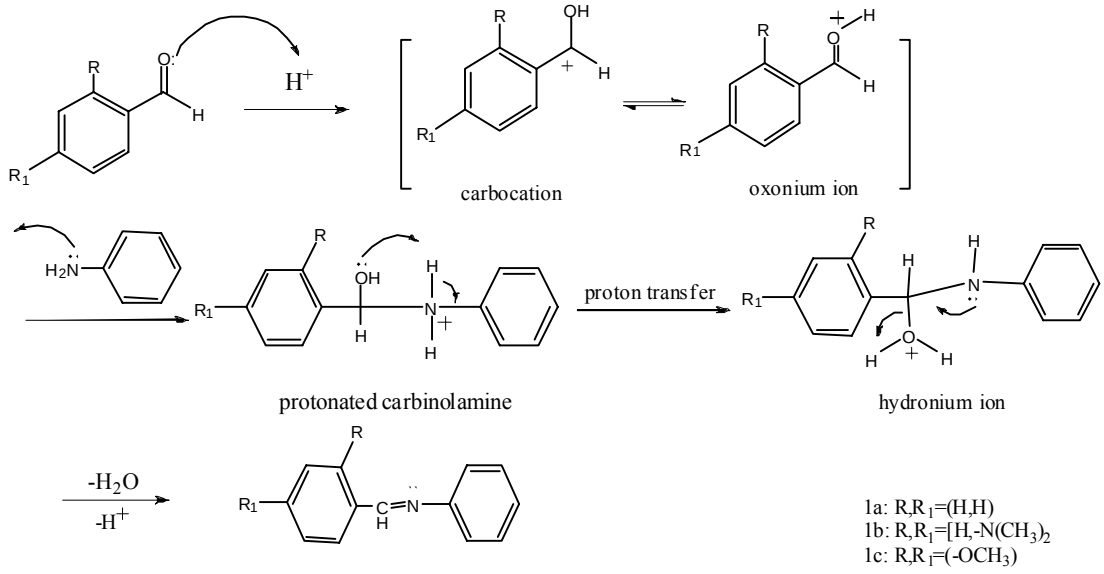
Result & Discussion

3-1 Synthesis of Schiff bases [1]



1a: R,R_1=(H,H)
1b: R,R_1=[H,-N(CH_3)$_2$
1c: R,R_1=(-OCH_3)

The Schiff bases are prepared by the reaction of the primary aromatic amine with different aromatic aldehyde derivatives in absolute ethanol in presence of glacial acetic acid as catalyst. It is believed that the reaction follows tetrahedral mechanism.[74, 75]

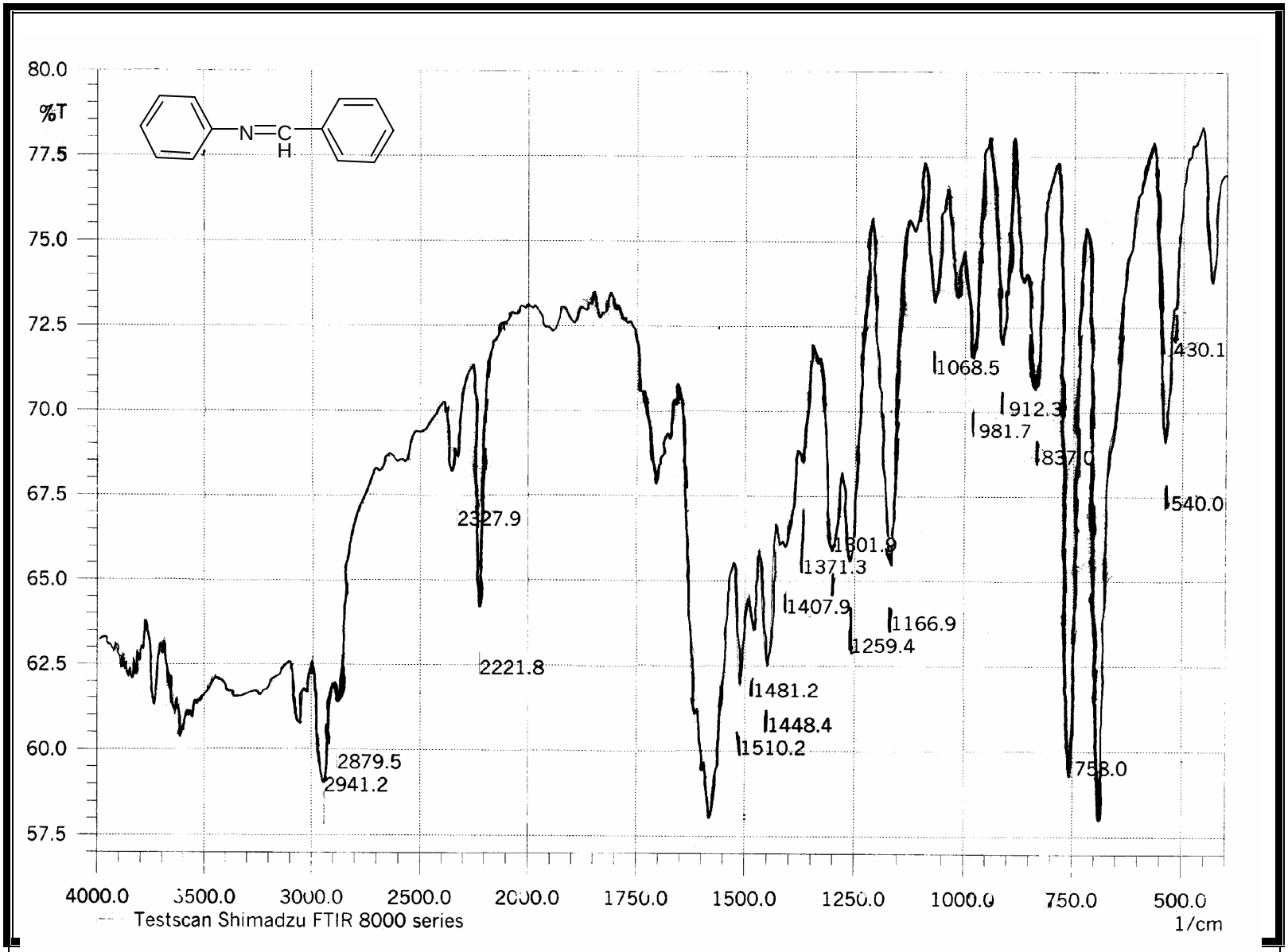


The Schiff bases were characterized by FT-IR spectra which showed disappearance of two bands in [3450 and 3220 cm^{-1}] represent the symmetric and asymmetric stretching vibration for amine group in aniline respectively, disappearance of C=O absorption band of the aldehydes in range [1660-1740 cm^{-1}] and appearance of the stretching vibration of C=N band in [1600 cm^{-1}] indicate the formation of Schiff base. FT-IR spectra of above compounds are shown in figure (3-1, 2and 3) and the purity of the product examined by TLC.

Table (3-1) FT-IR spectral data for Synthesized Schiff bases (3a-c)

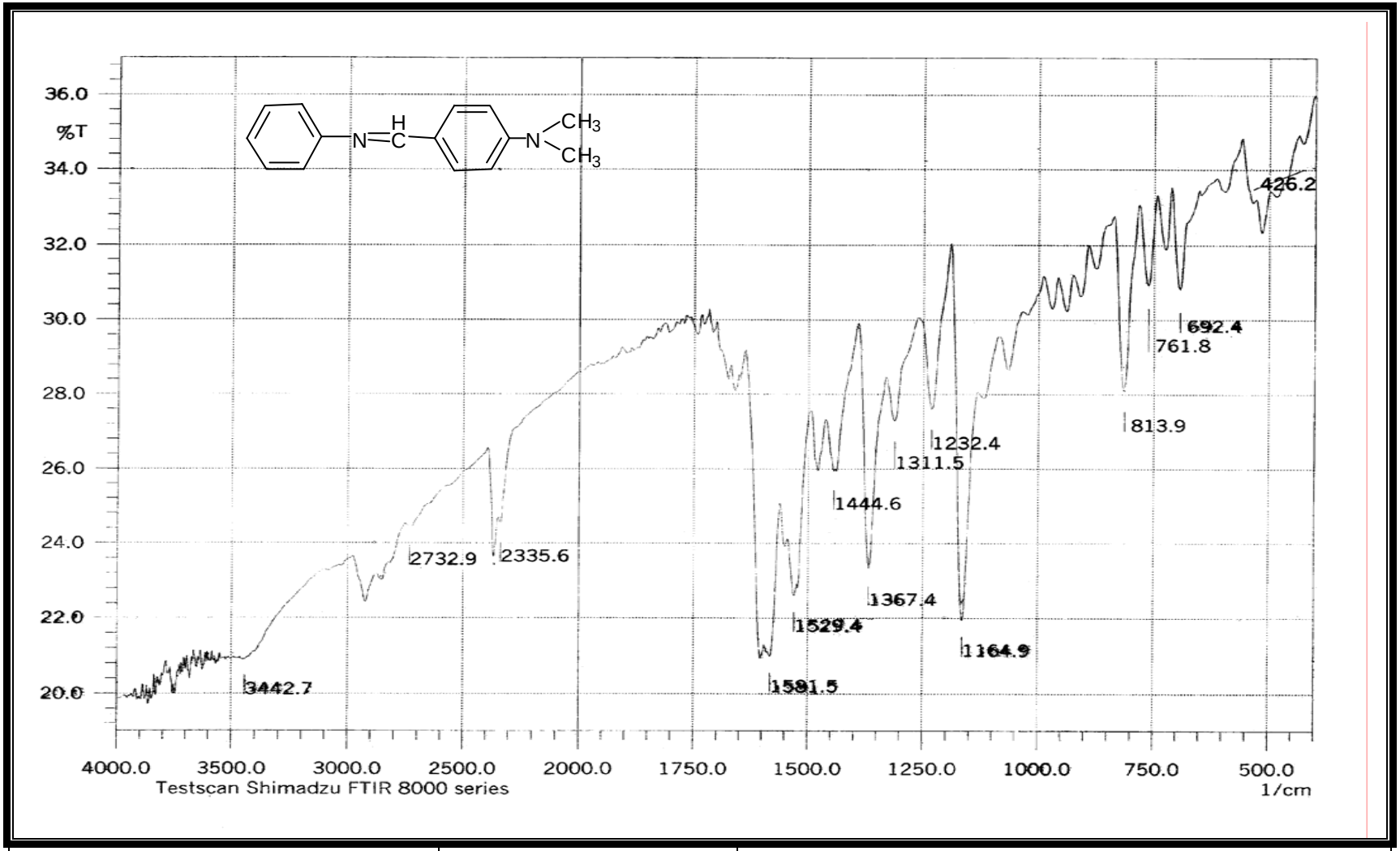
Comp No.	Fig. No.	substituents	ν C-H aromatic	ν C-H aliphatic	ν C=N Schiff	ν C=C aromatic	additional peaks
1a	3-1	R,R_1 = H	3080	2941	1600	1510	-
1b	3-2	R = H $R_1 = N(CH_3)_2$	2910	2850	1610	1529	C-N 1367
1c	3-3	$R,R_1 = -OCH_3$	3100	2889	1627	1583-1461	C-O-C as.st1271 s.st 1020

ν = stretching vibration, as.st = asymmetrical Stretching, s.st = symmetrical Stretching



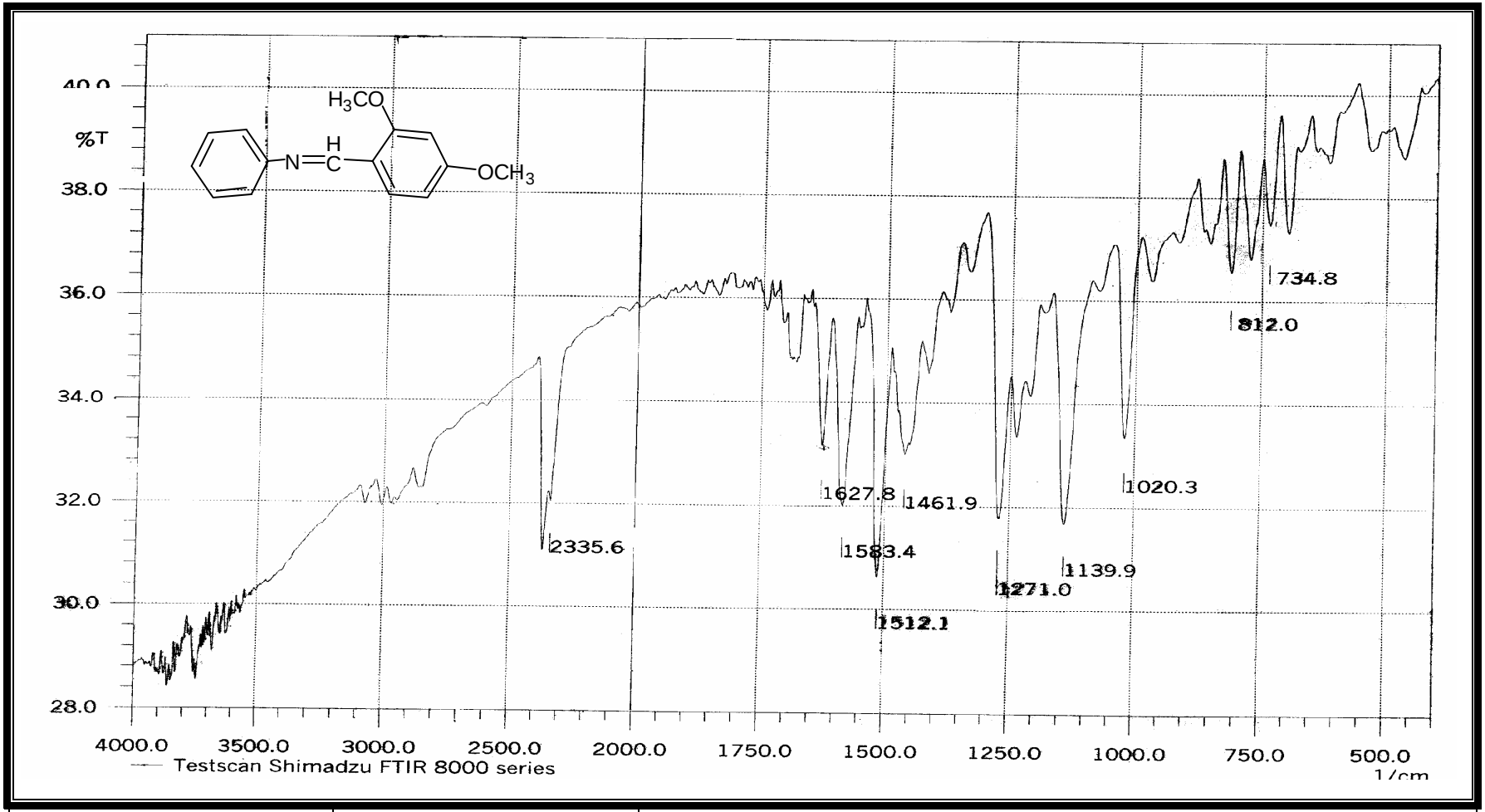
Yield% 88.9%	MP. (50-52)°C	$C_{13}H_{11}N$

Figure(3-1) Structure, melting Point yield% and FT-IR spectra of N-benzylideneaniline(1a)



Yield% 86.6%	MP. (150-154)ºC	$C_{15}H_{16}N_2$

Figure(3-2)Structure, melting Point yield% and FT-IR spectra of N-[(4-dimethyl amino Benzylidene aniline(1b)

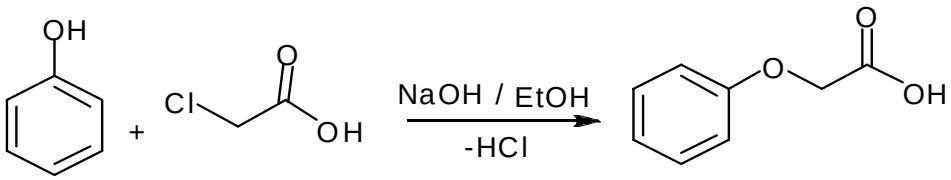


Yield% 78.6%	MP. (70-73)ºC	$C_{15}H_{15}NO_2$

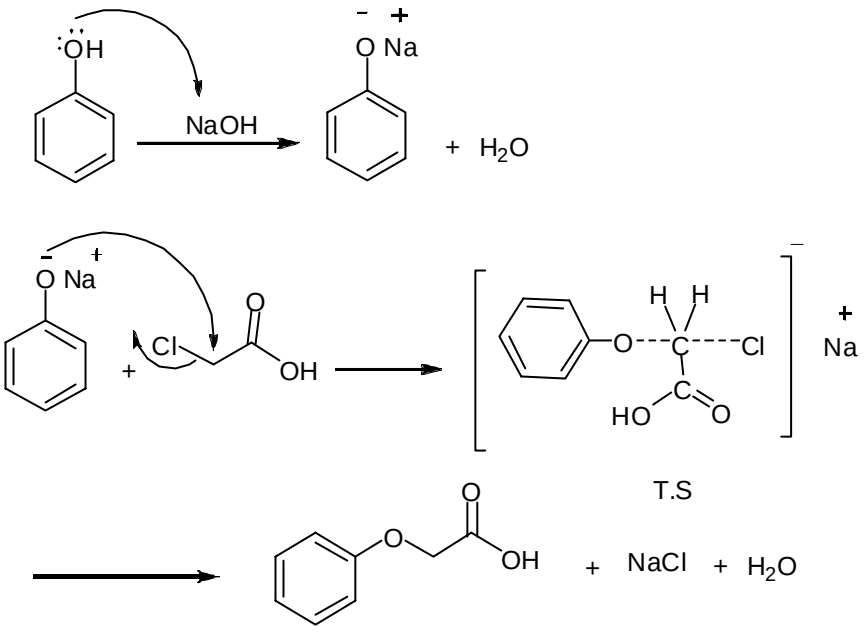
Figure(3-3)Structure, melting Point yield% and FT-IR spectra of N-[(2,4-dimethoxy phenyl)benzylidene aniline)(1C)

3-2 Synthesis of Phenoxyacetic acid [Π]

Phenoxyacetic acid is prepared according to Williamson method [76] by reaction of phenol and mono chloroacetic acid in absolute ethanol in basic medium (sodium hydroxide) as shown in the equation below.



Phenol is a weak acid that react easily with base (NaOH) to give the conjugate base. The reaction follows S_N2 mechanism as shown below:

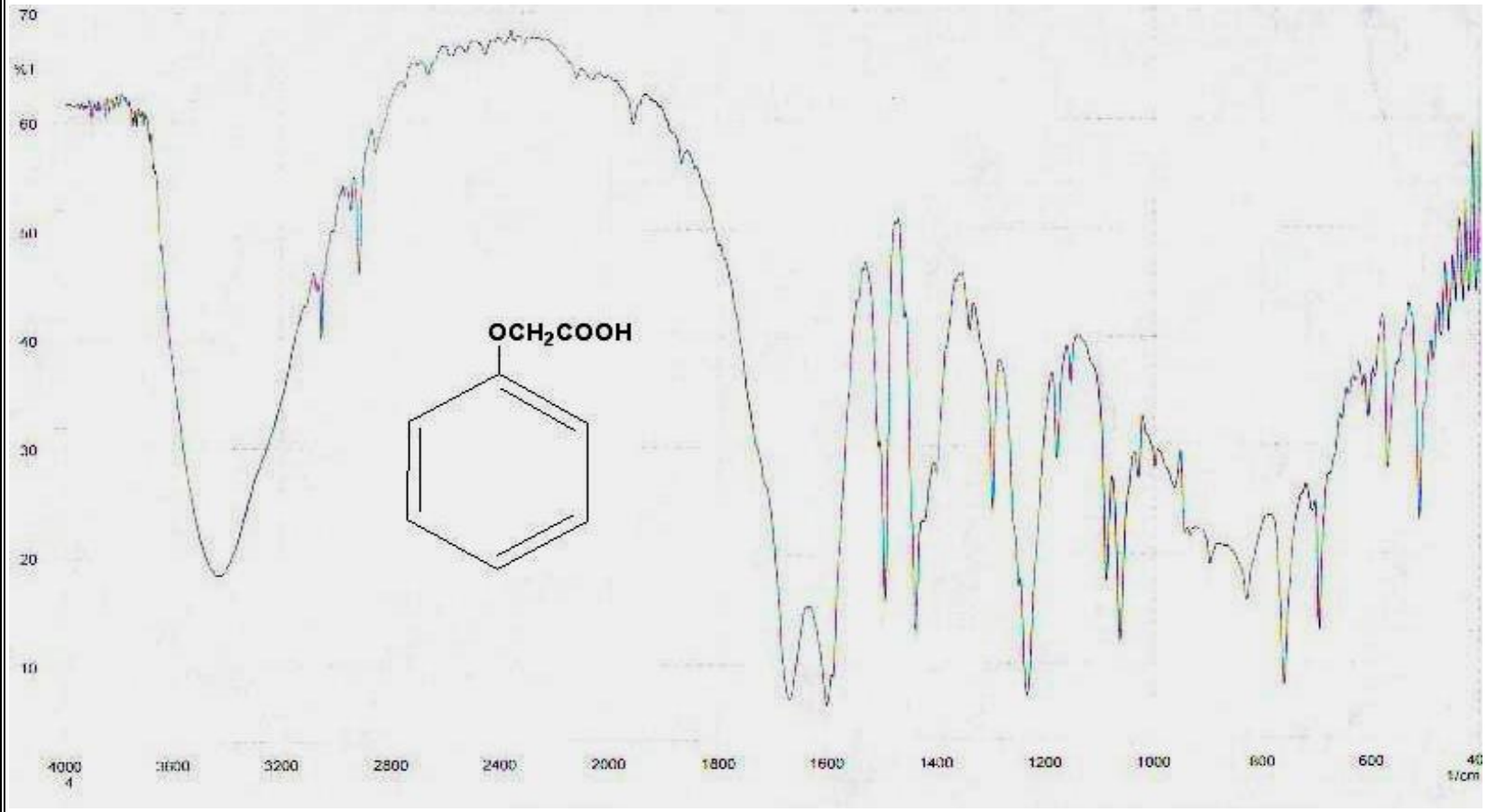


The products was characterized by FT-IR spectra which showed appearance of C=O band for carboxylic acid in [1700 cm^{-1}], appearance of C-O-C absorption band at 1200 and 1045cm^{-1} for symmetric and asymmetric stretching vibration respectively and appearance of typical broad strong band for O-H group at [3400-3350 cm^{-1}]. FT-IR spectra of above compounds are shown in figure (3-4) and the purity of the product was examined by TLC.

Table (3-2) FT-IR spectral data for Phenoxyacetic acid.

Comp No.	Fig. No.	ν O-H	ν C-H aromatic	ν C-H aliphatic	ν C=C aromatic	ν C=O	ν C-O-C
Ц	3-4	3400 - 3350	3100	2900	1600	1700	as.st 1200 s.st 1045

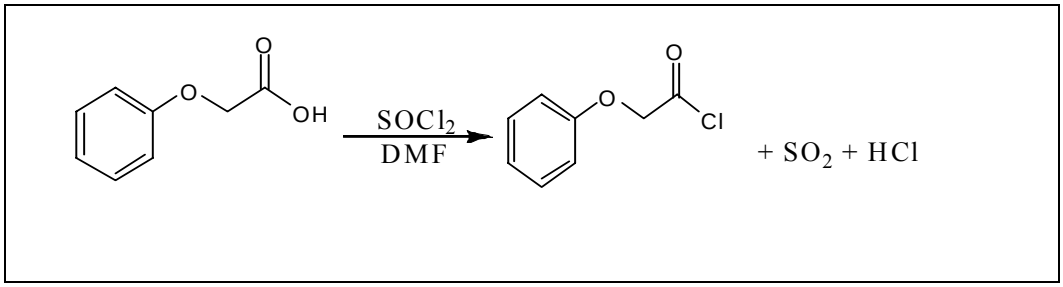
ν = stretching vibration, as.st=asymmetrical Stretching, s.st=symmetrical Stretching



Yield% 83.6%	MP. (247-250)ºC	$C_8H_8O_3$

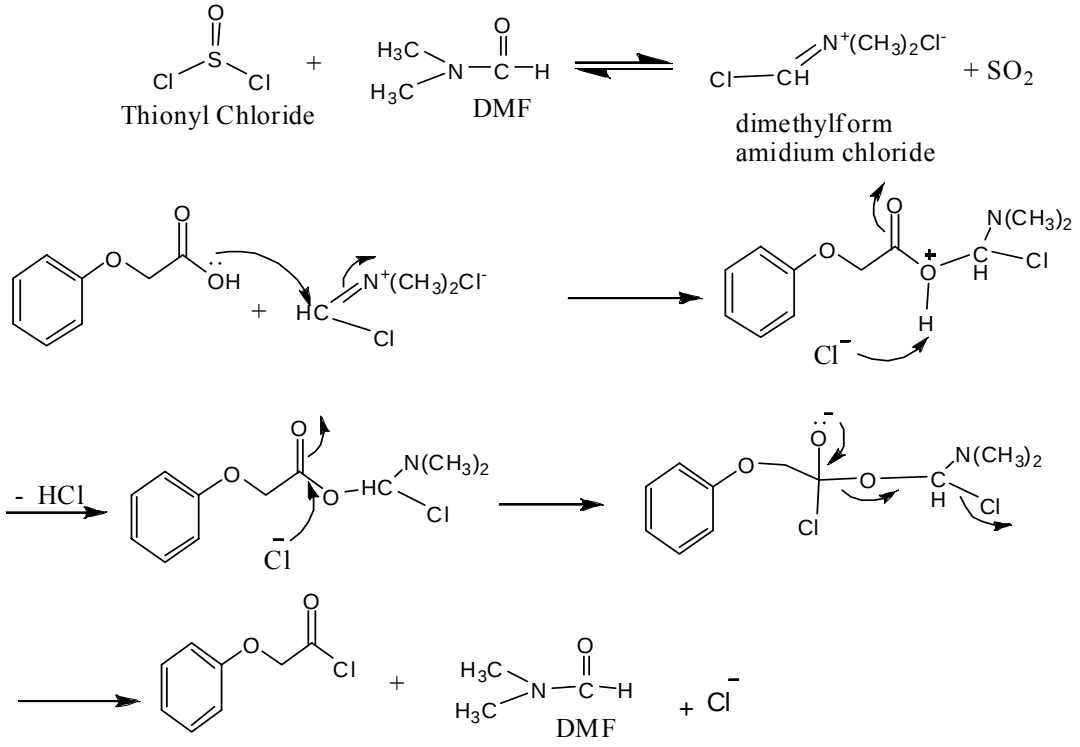
Figure(3-4)Structure, yield, melting Point and FT-IR Spectra of Phenoxyacetic acid (II)

3.3 Synthesis of Phenoxyacetyl Chloride [III]



Phenoxyacetyl Chloride is prepared by the reaction of Phenoxyacetic acid with excess of thionyl chloride in presence of dimethylformamide (DMF) as catalyst.

The suggested mechanism for this reaction involves reaction of thionyl chloride with dimethylformamide (DMF) to yield dimehtylforma-midinium chloride. This complex reacted with Phenoxyacetic acid and then chloride anion attacks the carbonyl carbon displacing dimethylformamide and forming the phenoxyacetyl chloride as shown below.[76]

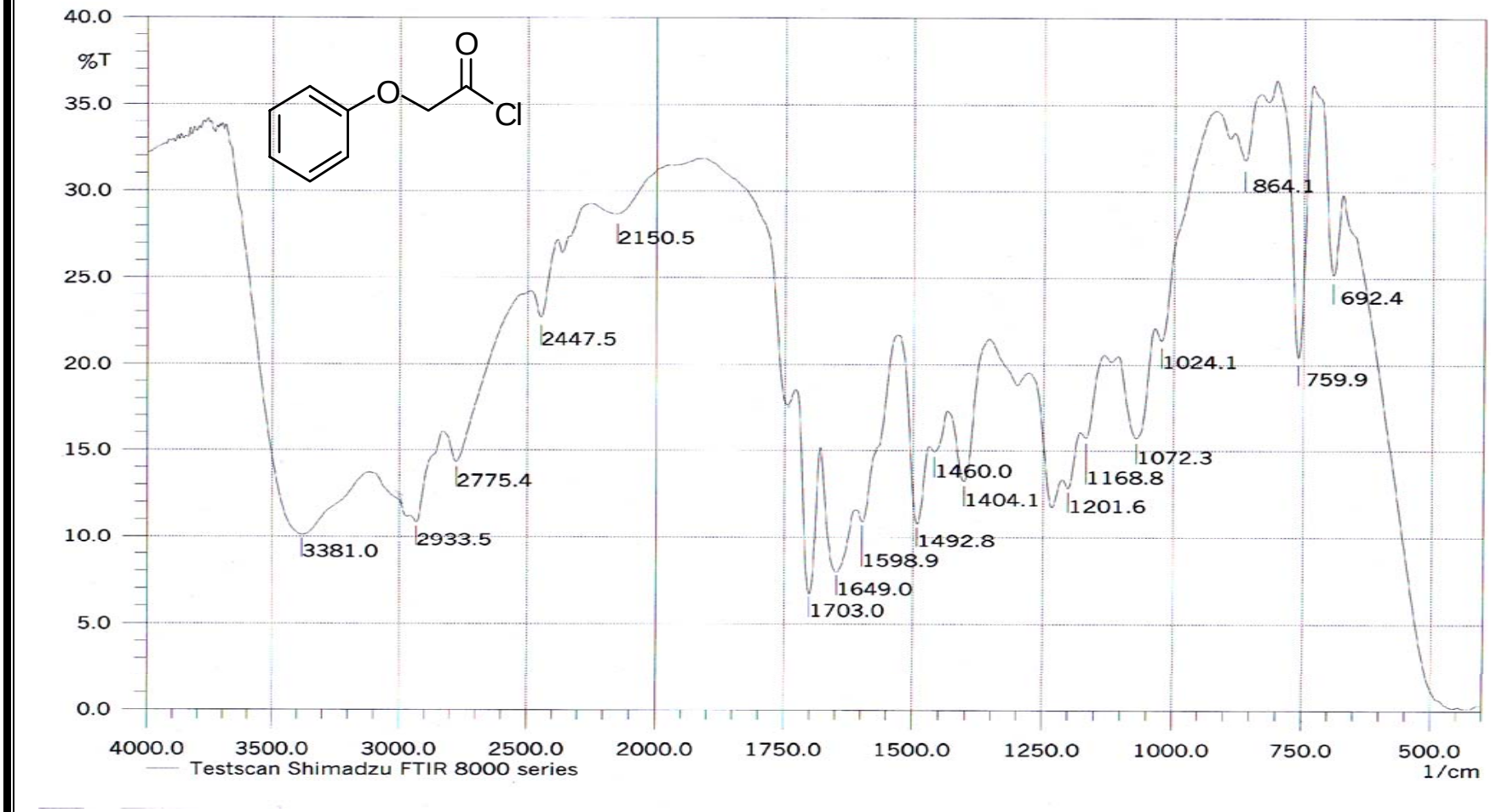


The product was characterized by FT-IR spectra which showed the shifting in the position of stretching vibration of C=O band from 1700 cm^{-1} for the acid to 1748 cm^{-1} for acetyl chloride and appearance of C-Cl band at 759 cm^{-1}. FT-IR spectra also, showed appearance typical broad strong band for O-H group at 3381-3250 cm^{-1} for enol form. The FT-IR spectra of above compounds is shown in figure (3-5) and the purity of the product examined by TLC.

Table (3-3) FT-IR spectral data for synthesized Phenoxyacetyl chloride.

Comp No.	Fig. No.	ν O-H enolat	ν C-H aromatic	ν C-H aliphatic	ν C=C aromatic	ν C=O	ν C-O-C
III	3-5	3381-3250	3010	2933	1598	1748	as.st 1240 s.st 1168

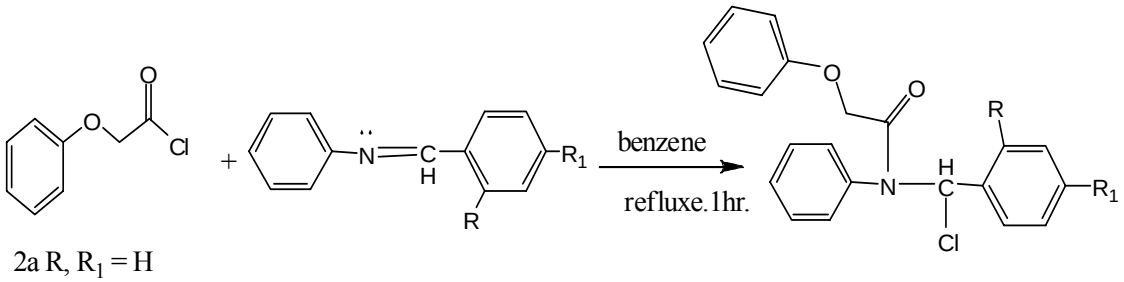
ν = stretching vibration, as.st = asymmetrical Stretching, s.st = symmetrical Stretching



Figure(3-5) FT-IR Spectra of phenoxyacetyl chloride (ΠΙ)

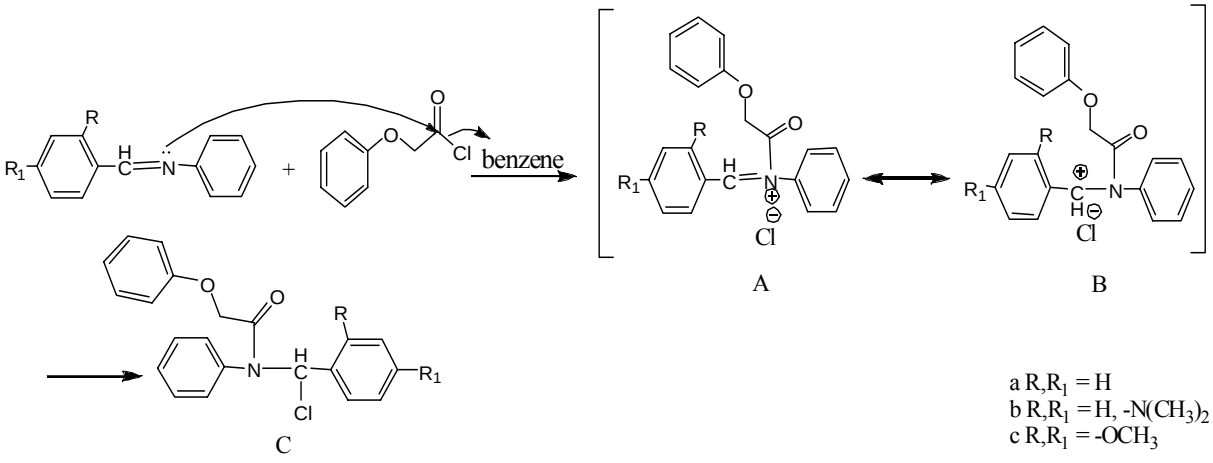
3.4 Synthesis of N-α-(chloro-2, 4-disubstituted phenyl) methyl-N-2-phenoxyacetanilide (2)

N-α-(chloro-2, 4-disubstituted phenyl) methyl-N-2-phenoxyacetanilide can be synthesized by reaction of shiff bases (1) with Phenoxyacetyl Chloride (III) in dray benzene as solvent as shown in the equation below.



2a R, R_1 = H
2b R, R_1 = H, -N$(CH_3)_2$
2c R, R_1 = -OCH_3

The suggested mechanism of this reaction involves S_N2 mechanism[74, 75]. Nucleophilic Nitrogen atom attacks the carbon of the carbonyl group displacing chloride ion and forming the iminum ion (A), which can be represented by structure (B) too. Both structures A and B are unstable because the positively charged nitrogen atom in [A] and the positively charged carbon atom in [B] are linked to three strong electron withdrawing groups [77, 78, 79], for the two reasons above both structure [A and B] give more stable structure [C]



a R,R_1 = H
b R,R_1 = H, -N$(CH_3)_2$
c R,R_1 = -OCH_3

The products identified by Elemental analysis (CHN) and FT-IR spectra. The FT-IR spectra of the products showed appearance of C=O stretching vibration at 1662 cm^{-1} with shifting compared with C=O group of acetyl chloride 1748 cm^{-1}. The peak at 748 cm^{-1} could be attributed to stretching vibration of C-Cl band.

FT-IR spectra also, can clearly point the disappearance of C=N absorption band at 1600 cm^{-1}. The FT-IR spectra of above compounds are shown in figure (3-6, 7 and 8).

The measured results from the elemental analysis (CHN) were in agreement with the calculated values.

The FT-IR results were supported by the elemental analysis (CHN) as shown in table (3-4)

Table (3-5) showed the main FT-IR absorption bands for all Acetanilide derivatives and the other functional groups that found in their structures.

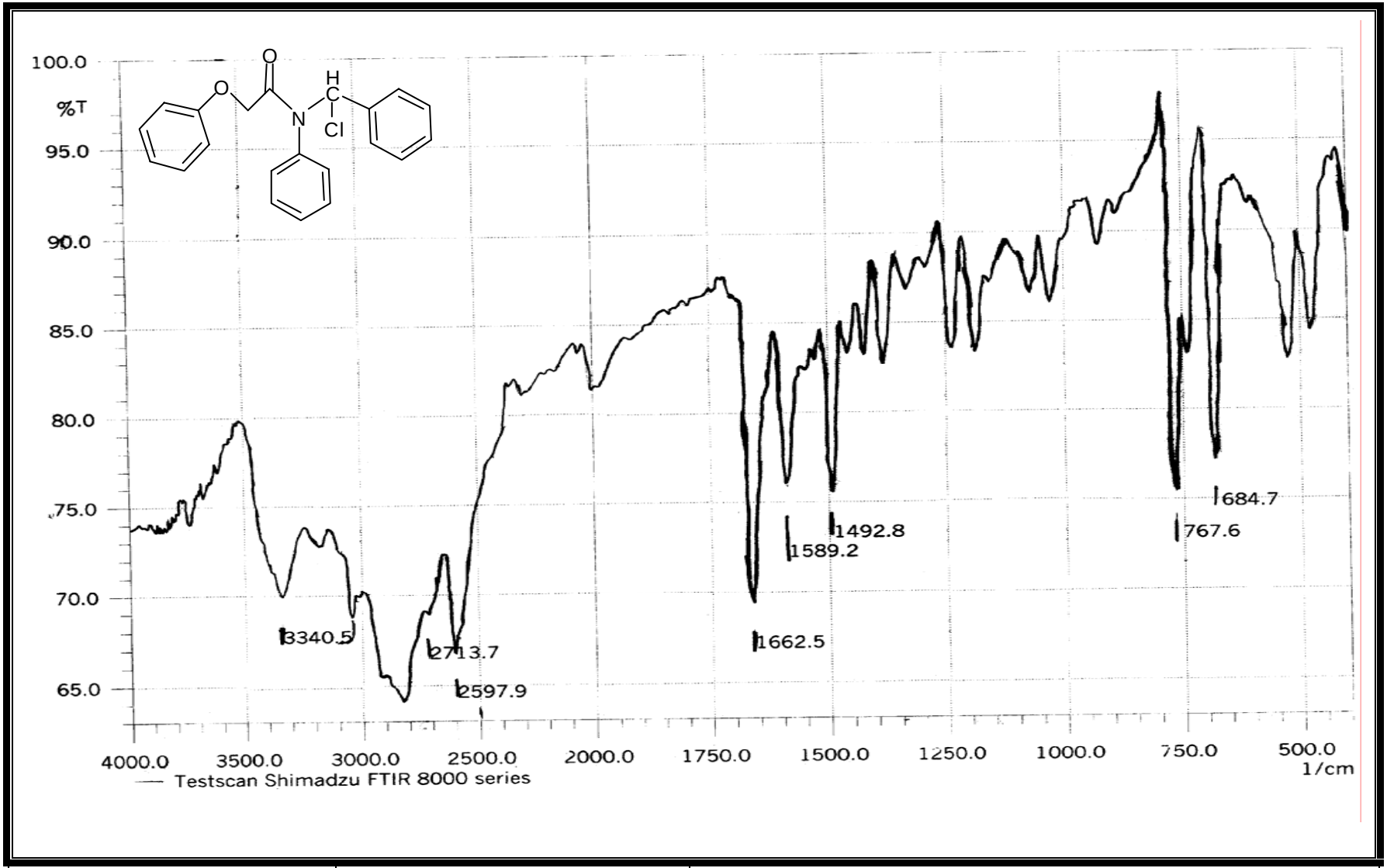
. Table (3-4) Elemental analysis data for acetanilide derivatives (2a-c)

substituents	**Elemental analysis**			
		C%	**H%**	**N%**
R,R_1 = H	**Calculated** **Found**	71.693 71.88	5.120 5.375	3.983 3.637
R = H, **R_1= -$N(CH_3)_2$**	**Calculated** **Found**	69.962 69.43	5.830 5.730	7.098 7.215
R,R_1 = - **OCH_3**	**Calculated** **Found**	67.072 67.105	5.346 5.997	3.402 3.302

Table (3-5) IR spectral data for synthesized acetanilide derivatives (2a-c)

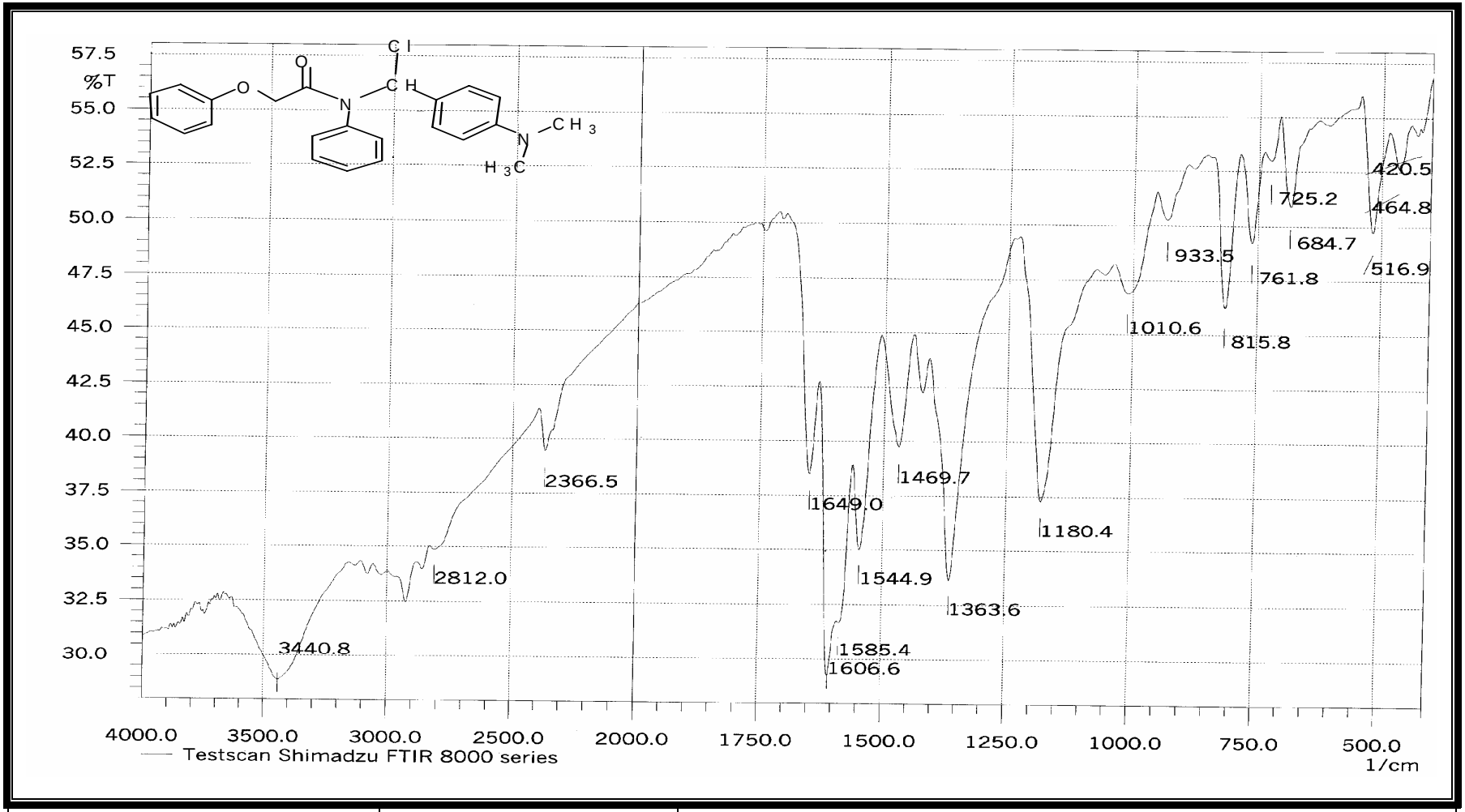
Comp No.	substituents	ν C-H aromatic	ν C-H aliphatic	ν C=O	ν C=C aromatic	ν C-Cl	additional peaks
2a	R,R_1 = H	3020	2820	1662	1589	748	-
2b	R = H, R_1= -N(CH_3)$_2$	3100	2920	1649	1606 - 1544	761	C-N 1363
2c	R,R_1 = -OCH_3	3000	2920	1662	1593 - 1519	752	C-O-C as.st1222 s.st 1149

ν = stretching vibration, as.st = asymmetrical Stretching, s.st = symmetrical Stretching



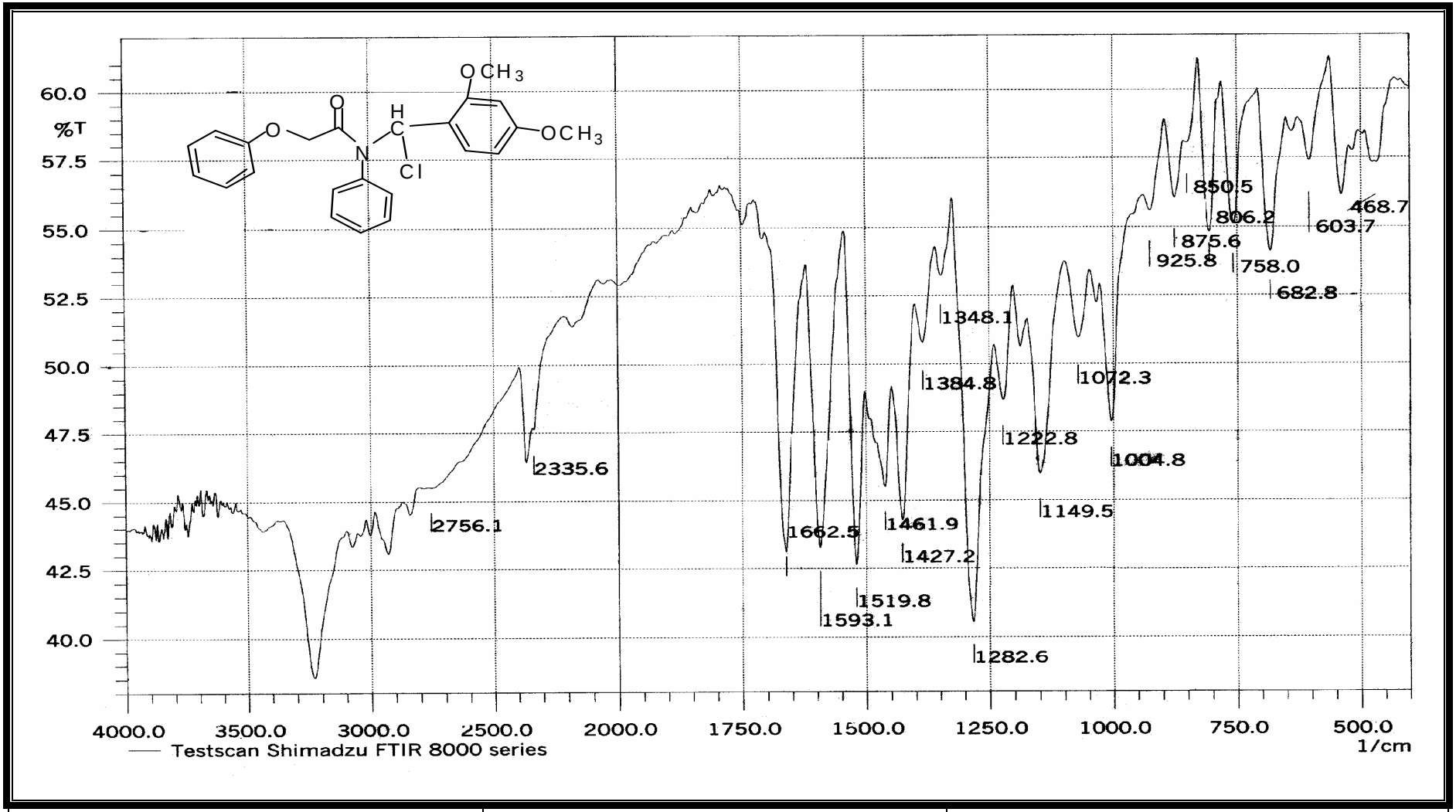
Yield% 54%	MP. (160-164)ºC	$C_{21}H_{18}NO_2Cl$

Figure(3-6)Structure, melting Point yield% and FT-IR Spectra of N-α-(chloro phenyl)methyl N-2-phenoxyacetanilide(2a)



Yield% 58%	MP. (93-95)ºC	$C_{23}H_{23}NO_2Cl$

Figure(3-7)Structure, melting Point yield% and FT-IR Spectra of N-α-(chloro 4-dimethylamino phenyl)methyl N-2-phenoxyacet-anilide(2b)

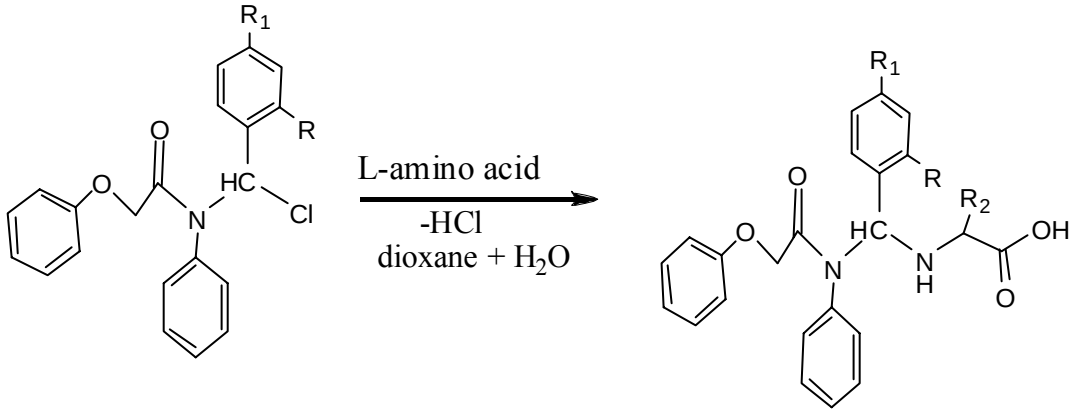


Yield% 74%	MP. (150-155)ºC	$C_{23}H_{22}NO_4Cl$

Figure(3-8)Structure, melting Point yield% and FT-IR Spectrum of N-α-(chloro-2,4-dimethox phenyl)methyl N-2-phenoxyacetanilide(2C)

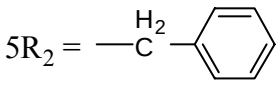
3.3 Synthesis of N-[α-(2, 4-disubstituted phenyl-N¯-Cystyl) methyl]-N-2-phenoxyacetanilide (3):

N-α-(chloro-2, 4-disubstituted phenyl) methyl-N-2-phenoxyacetanilide which are considered as benzyl halide are expected to be relatively reactive toward nucleophiles. In fact they reacted with L-amino acid in basic medium (Na_2CO_3) to give amino acid derivatives in good yields.



$3R_2$ = $-CH_2SH$

$4R_2$ = $-CH(CH_3)_2$

$5R_2$ = 

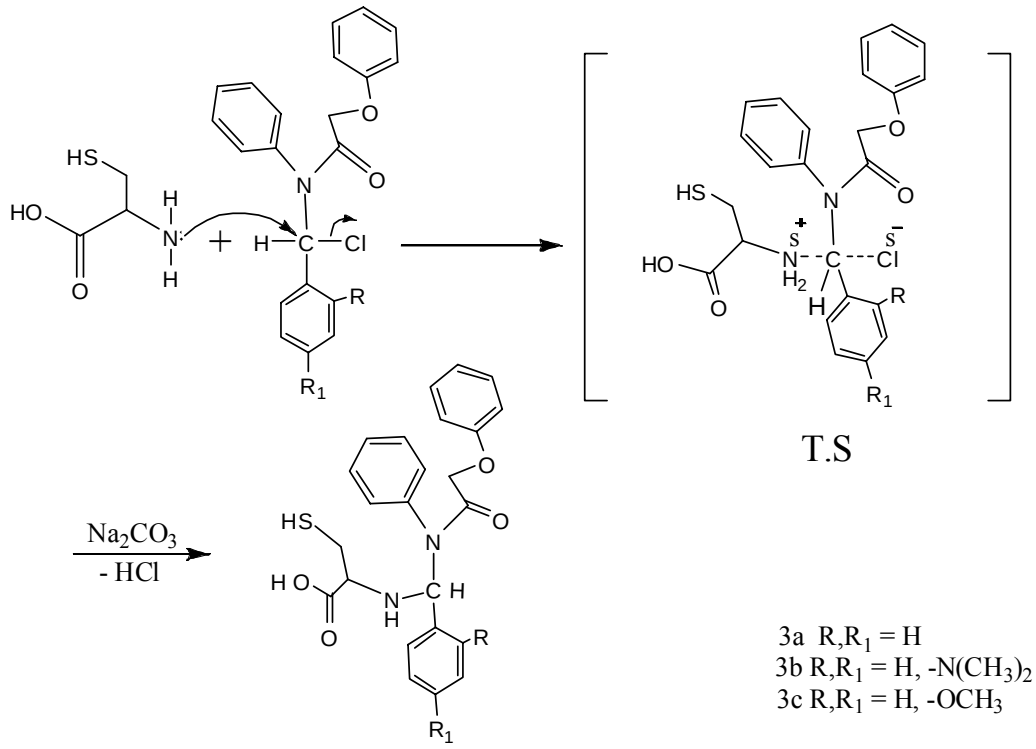
,

a R,R_1 = H

b R,R_1 = H, $-N(CH_3)_2$

c R,R_1 = H, $-OCH_3$

Cysteine derivatives have been synthesized by reaction of L-Cysteine with benzyl chloride derivatives in 2:1 of 1, 4-dioxane-water as a solvent. The suggested mechanism of this reaction may follow S_N2 mechanism as shown below[52].

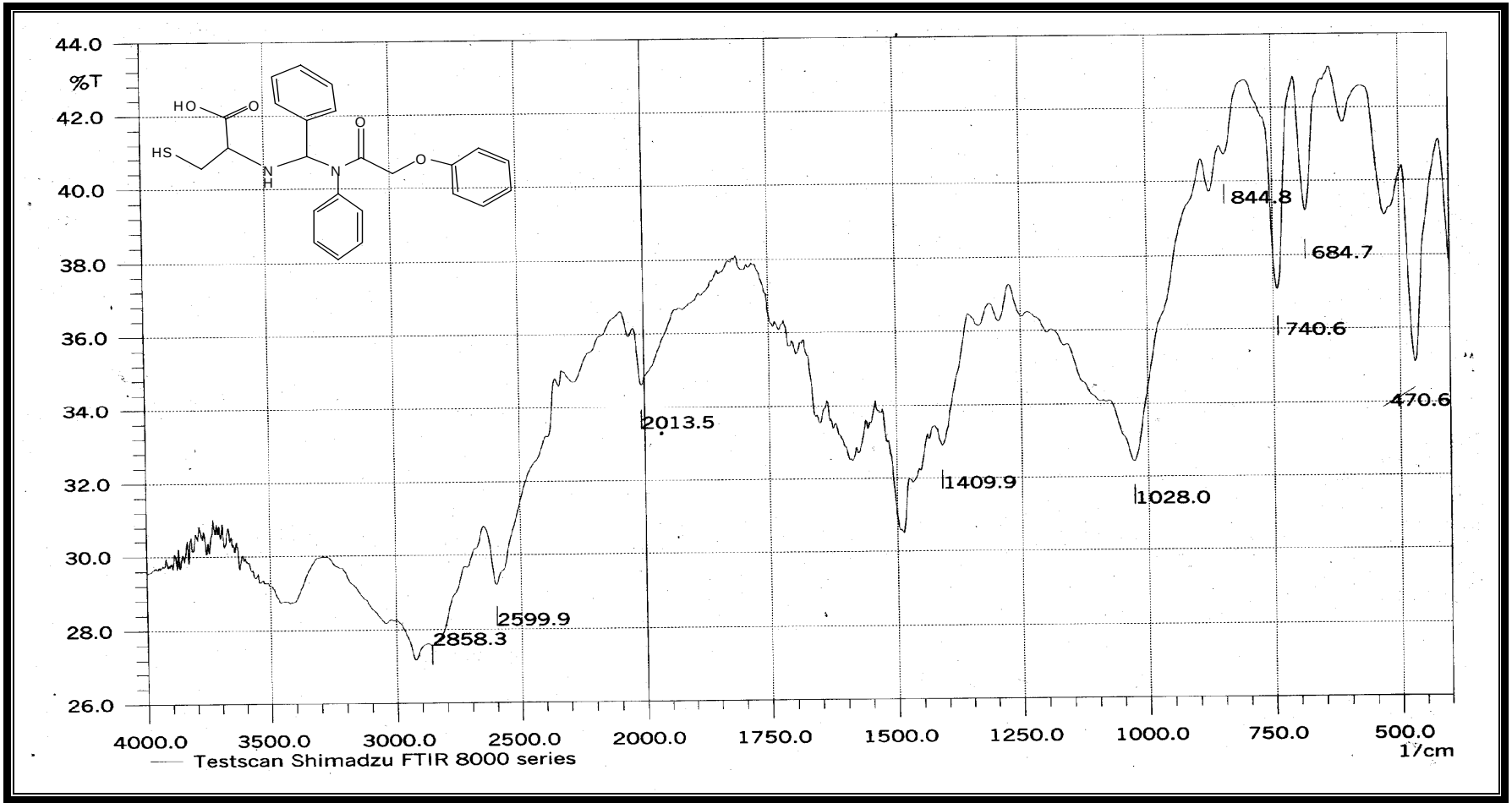


3a R,R_1 = H
3b R,R_1 = H, -$N(CH_3)_2$
3c R,R_1 = H, -OCH_3

The synthesized compounds were identified by FT-IR spectra which showed appearance of N-H stretching vibration band at 3210 cm^{-1}, band at the range 1650-1595 cm^{-1} belong to C=O and disappearance of C-Cl band at 725 cm^{-1}. The FT-IR spectra also showed appearance of stretching vibration band at 2596 cm^{-1} belongs to S-H group of Cysteine. The FT-IR spectra of above compounds is shown in figure [3-(9, 10, 11)]

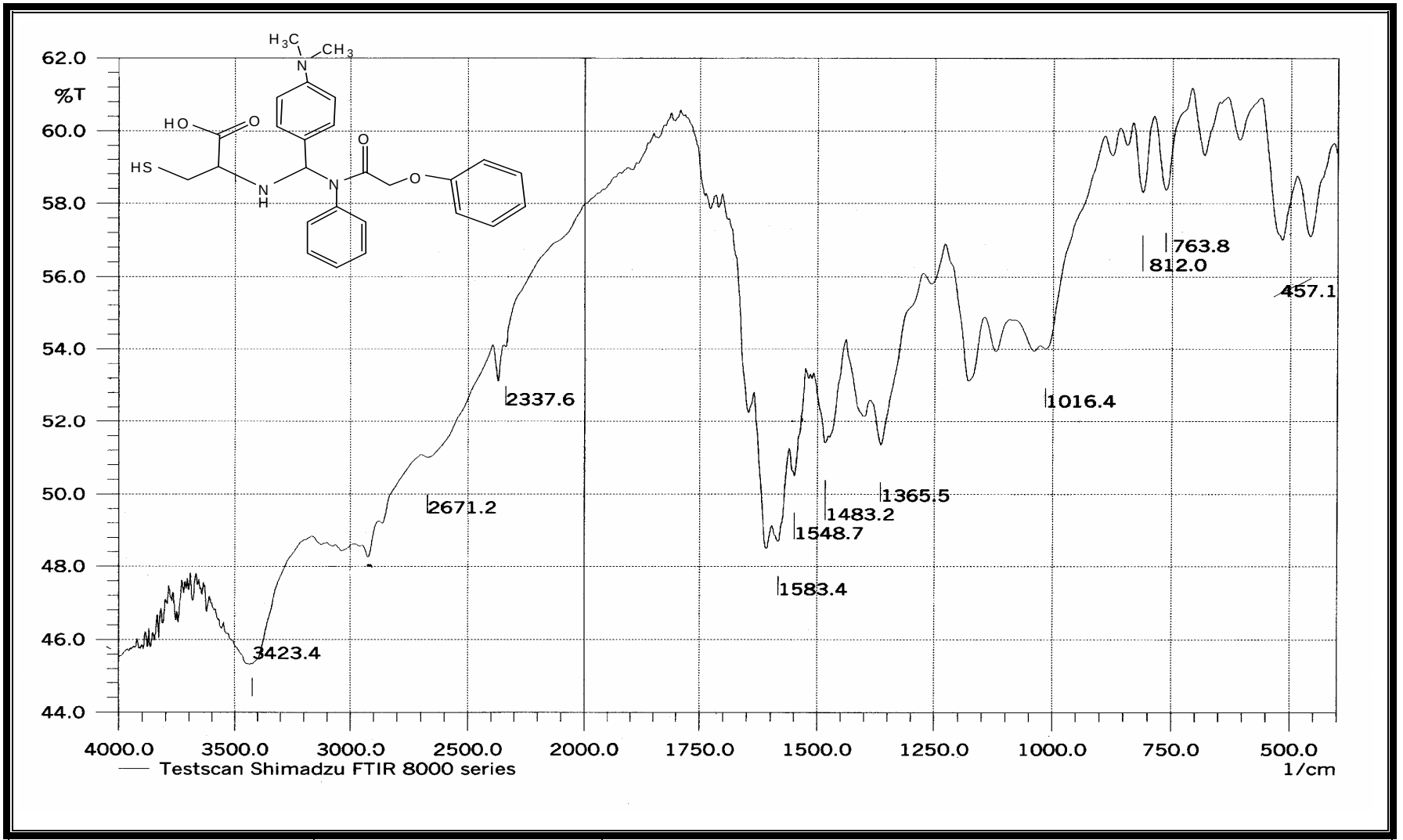
Table (3-6) FT-IR spectral data for synthesized Cysteine derivatives(3a-c)

Comp No.	substituents	ν O-H	ν N-H	ν C-H aromatic	ν C-H aliphatic	ν S-H	ν C=O	ν C=C aromatic	Additional peaks
3a	R,R_1 = H	3423	3210	3015	2858	2599	1595	1600	-
3b	R= H, R_1= $N(CH_3)_2$	3423	3150	3050	2855	2671	1583	1548	C-N 1365
3c	R,R_1=-OCH_3	3423	3250	2900	2842	2596	1648	1595	C-O-C as.st1220 s.st 1016



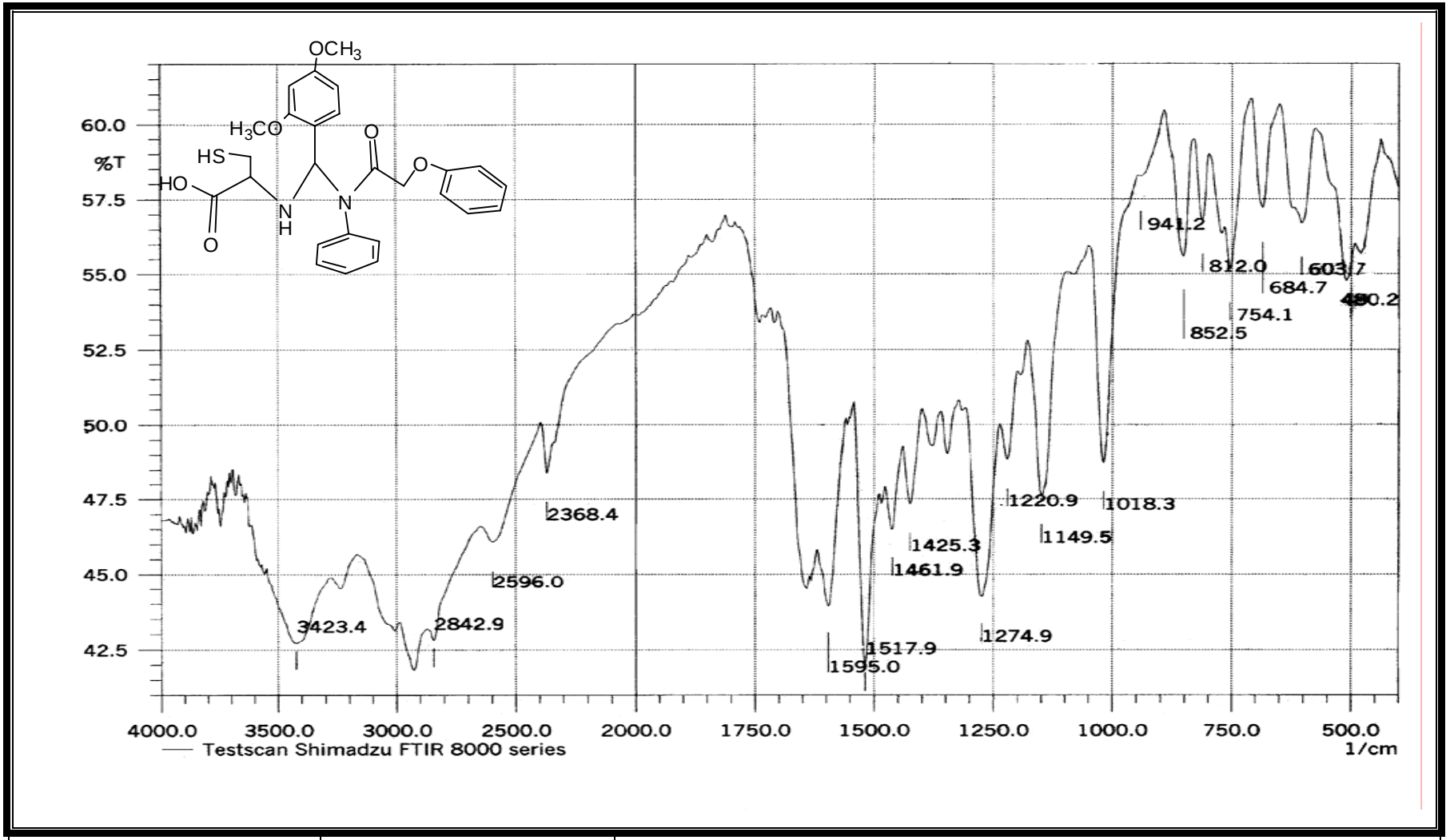
Yield% 38.3%	MP. (78-80)ºC	$C_{24}H_{24}N_2O_4S$

Figure(3-9)Structure, melting Point, yield% and FT-IR Spectra of N-[α- (phenyl Ñ-cystyl) methyl]-N-2-phenoxyacetanilide(3a)



Yield% 45.8%	MP. (140-143)ºC	$C_{26}H_{29}N_3O_4S$

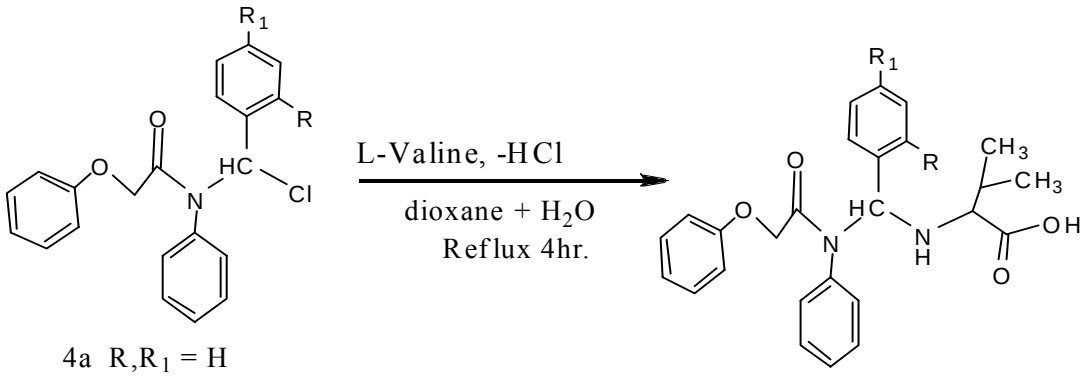
Figure(3-10)Structure, melting Pointe yield% and F.T-.IR Spectrum of N-[α -(4-dimethylamino phenyl Ñ-cystyl)methyl]-N-2-phenoxyacetanilide(3b)



Yield% 70%	MP. (93-96)ºC	$C_{26}H_{28}N_2O_6S$

Figure(3-11)Structure, melting Point, yield% and F.T-.IR Spectra of N-[α- (2,4-dimethoxy phenyl Ñ-cystyl)methyl]-N-2-phenoxyacetanilide(3C)

3.4 Synthesis of N-[α-(2, 4-disubstituted phenyl-N¯-Valinyl) methyl]-N-2-phenoxyacetanilide :(4)



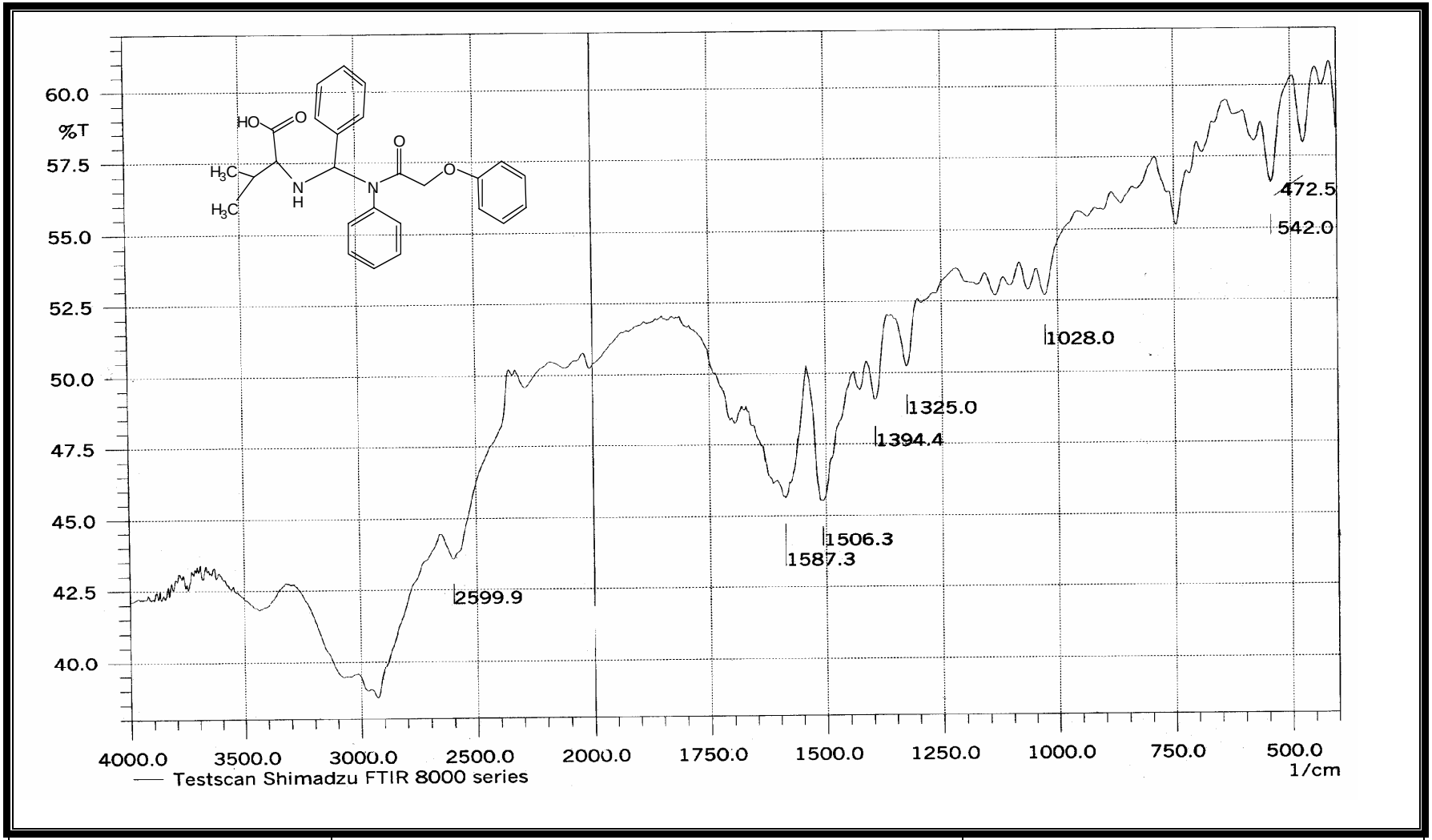
4a R,R_1 = H
4b R,R_1 = H, -$N(CH_3)_2$
4c R,R_1 = H, -OCH_3

The Valine derivatives can be synthesized by reaction of L-Valine with benzyl chloride derivatives (2a-c) in 2:1 of 1, 4-dioxane-water as a solvent. The suggested mechanism of this reaction involves S_N2 mechanism as shown in (3-3).

The synthesized compounds were identified by FT-IR spectra which showed appearance of N-H stretching vibration band at 3100 cm^{-1}, band at range 1650-1700 cm^{-1} belong to C=O and disappearance of C-Cl band at 725 cm^{-1}. FT-IR spectrum of above compounds are shown in figure [3-(12, 13, 14)]

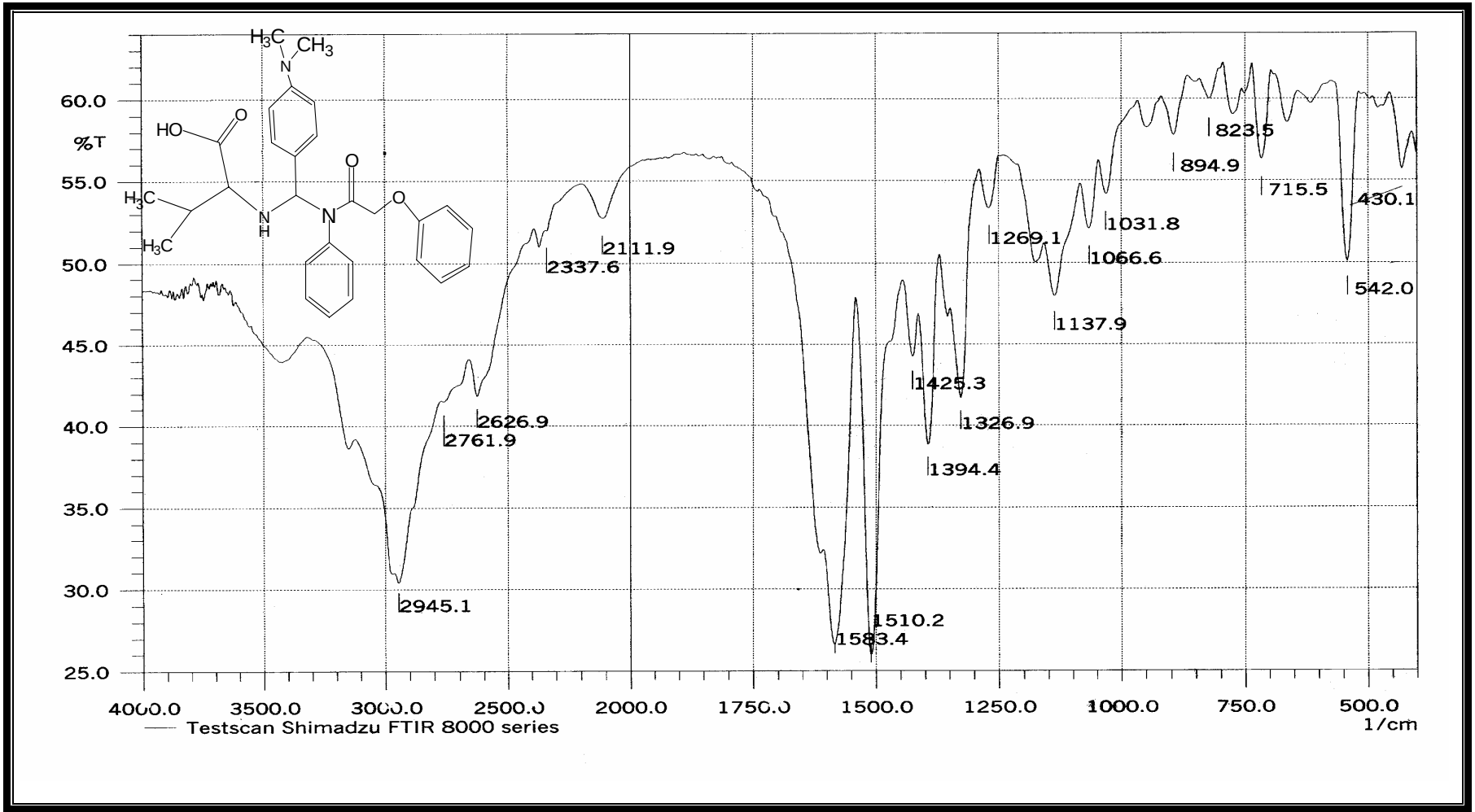
.Table (3-7) FT-IR spectral data for synthesized Valine derivatives (4a-c)

Comp No.	substituents	ν O-H	ν N-H	ν C-H aromatic	ν C-H aliphatic	ν C=O	ν C=C aromatic	Additional peaks
4a	R,R_1 = H	3423	3100	2996	2932	1700	1587	-
4b	R= H, R_1= $N(CH_3)_2$	3415	3150	3050	2945	1610	1510	C-N 1326
4c	R,R_1=-OCH_3	3400	3236	3080	2943	1668	1591	C-O-C as.st1228 s.st 1149



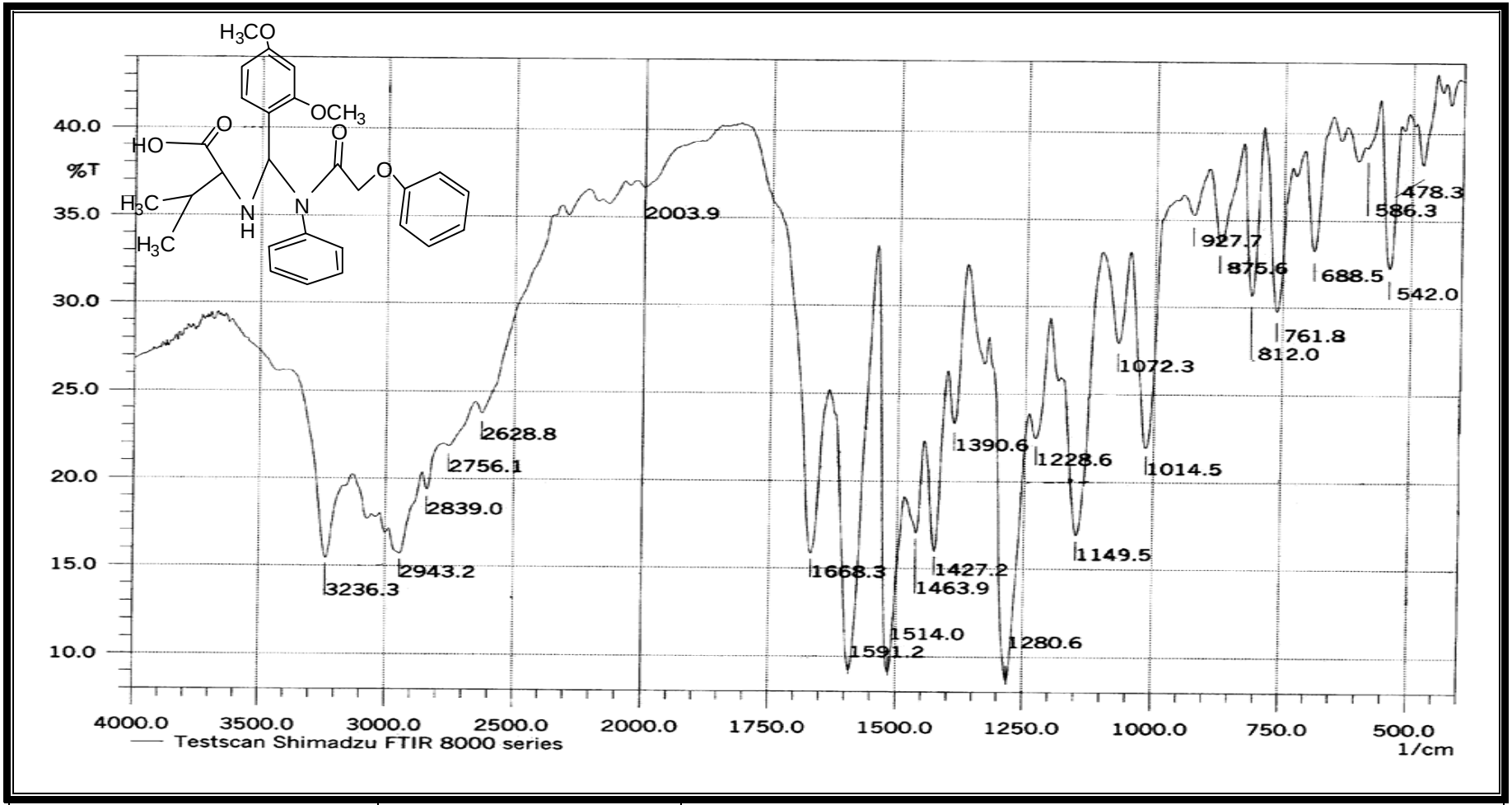
Yield% 66.6%	MP. (150-153)ºC	$C_{26}H_{28}N_2O_4$

Figure(3-12)Structure, melting Point, yield% and FT-IR Spectra of N-[α-(phenyl-Ñ-Vainly) methyl]-N-2-phenoxyacetanilide (4a)



Yield% 58%	MP. (178-180)ºC	$C_{28}H_{33}N_3O_4$

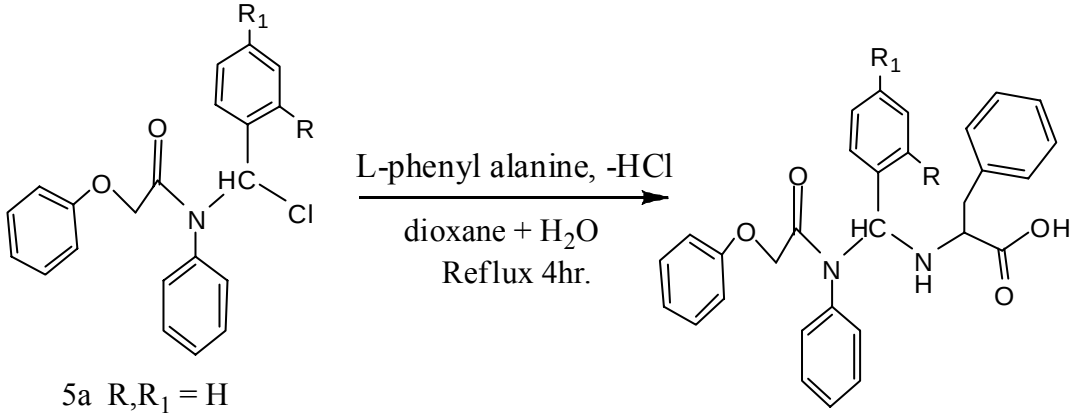
Figure(3-13)Structure, melting Point, yield% and FT-IR Spectra of N- [α-(4-dimethylamino phenyl-Ñ-Vainly) methyl]-N-2-phenoxyacetanilide (4b)



Yield% 62.5%	MP. (118-120)	$C_{28}H_{32}N_2O_6$

Figure(3-14)Structure, melting Point, yield% and FT-IR Spectra of N-[α- (2,4-dimethoxy phenyl-Ñ-Vainly) methyl]-N-2-phenoxyacetanilide (4C)

3.5 Synthesis of N-[α-(2, 4-disubstituted phenyl-N¯-Phenylalinyl) methyl]-N-2-phenoxyacetanilide: (5)



5a R,R_1 = H
5b R,R_1 = H, -$N(CH_3)_2$
5c R,R_1 = H, -OCH_3

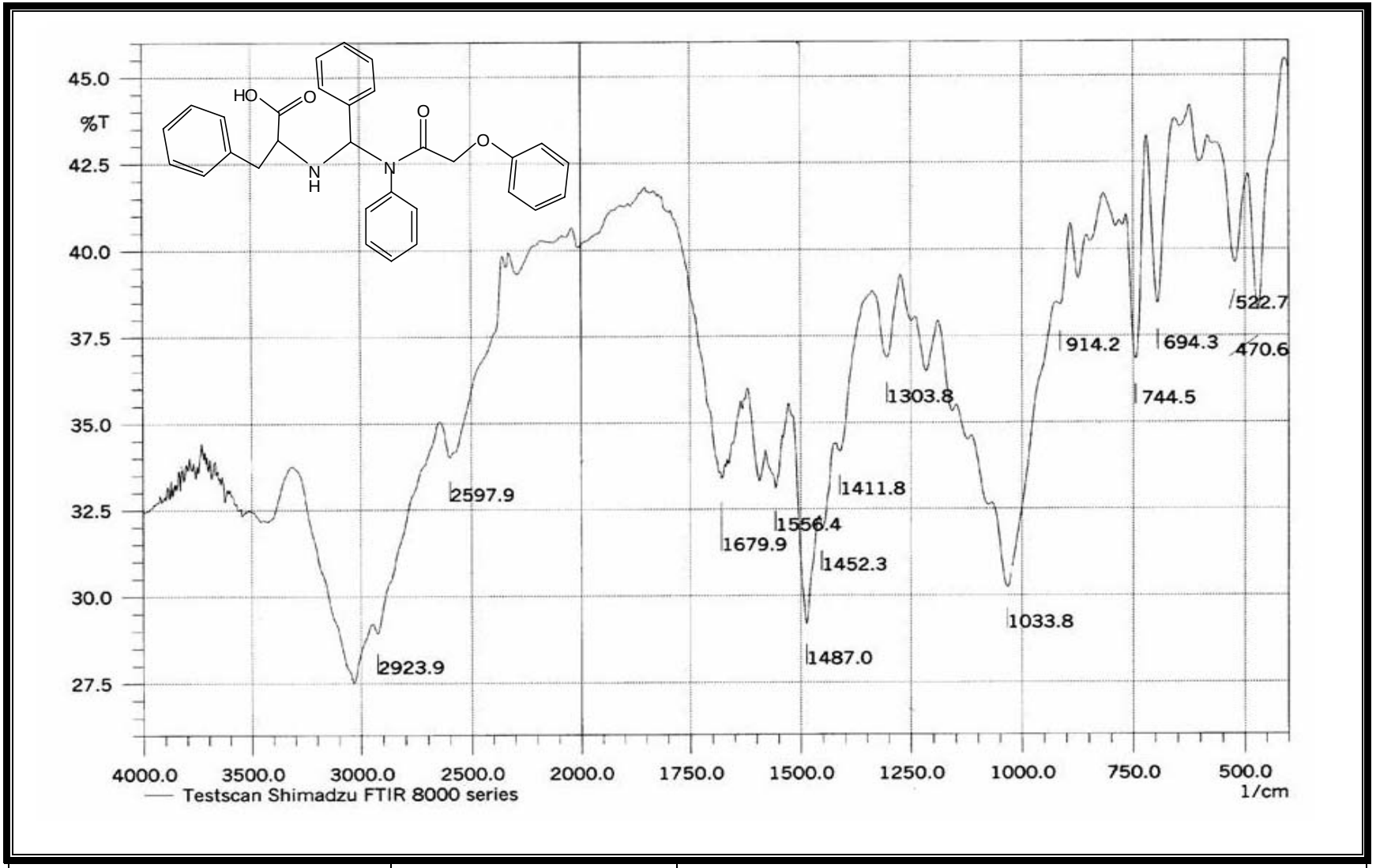
The Phenylalanine derivatives can be synthesized by reaction of L-Phenylalanine with benzyl chloride derivatives (2a-c) in 2:1 of 1, 4-dioxane-water as a solvent.

The suggested mechanism of this reaction involves S_N2 mechanism as shown in (3-3).

The synthesized compounds were identified by FT-IR spectra which showed appearance of N-H stretching vibration band at 3110 cm^{-1}, band at range 1650-1700 cm^{-1} belong to C=O and disappearance of C-Cl band at 725cm^{-1}. The FT-IR spectra of above compounds are shown in figure [3-(15, 16, 17)]

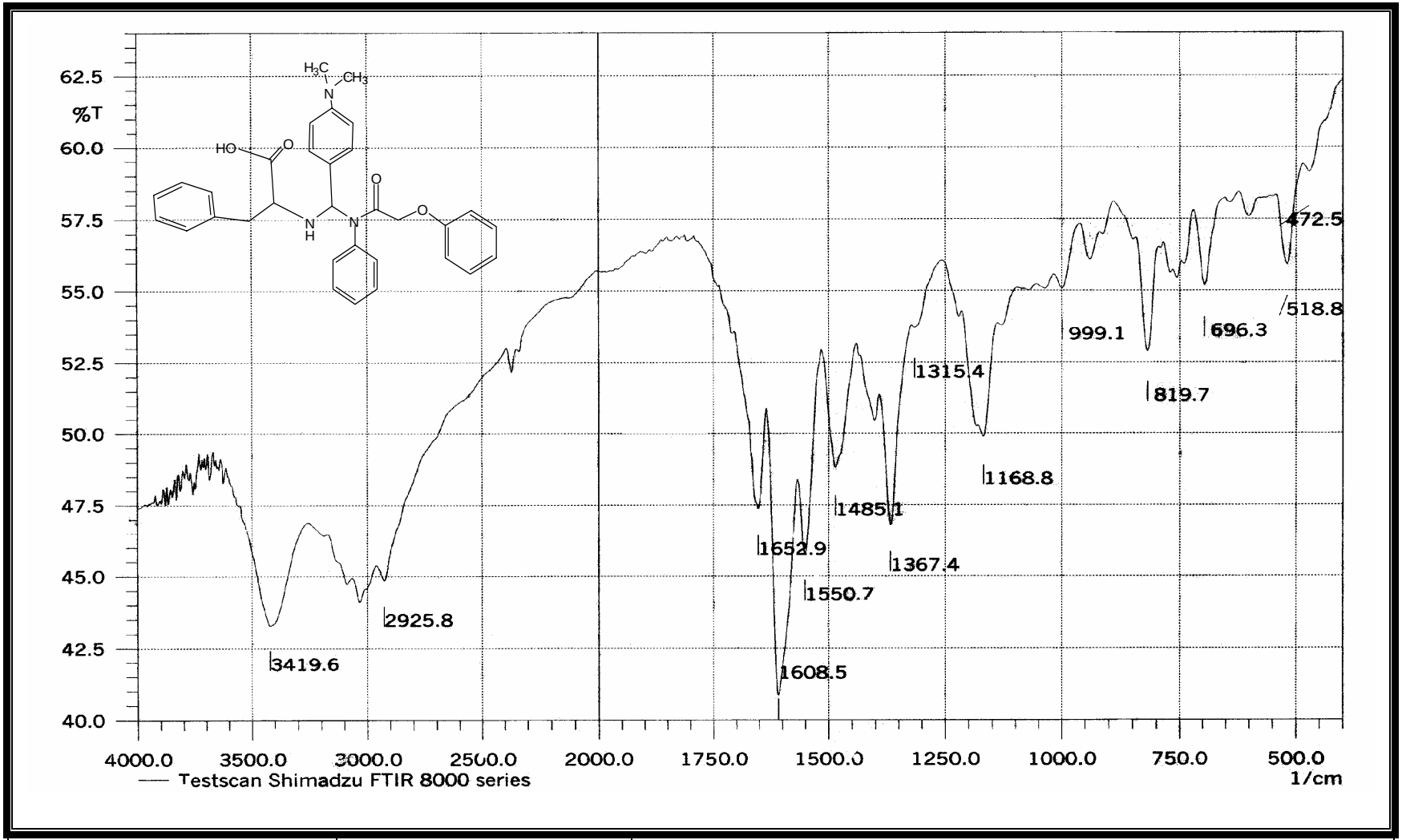
Table (3-8) IR spectral data for synthesized Phenylalanine derivatives

Comp No.	substituents	ν O-H	N N-H	ν C-H aromatic	ν C-H aliphatic	ν C=O	ν C=C aromatic	Additional peaks
5a	R,R_1=H	3420	3110	3020	2923	1679	1600 1556	-
5b	R= H, R_1= $N(CH_3)_2$	3419	3100	3025	2925	1625 1608	1550 - 1485	C-N 1367
5c	R,R_1=-OCH_3	3450	3230	3075	2964	1670	1591 - 1515	C-O-C as.st1278 s.st 1230



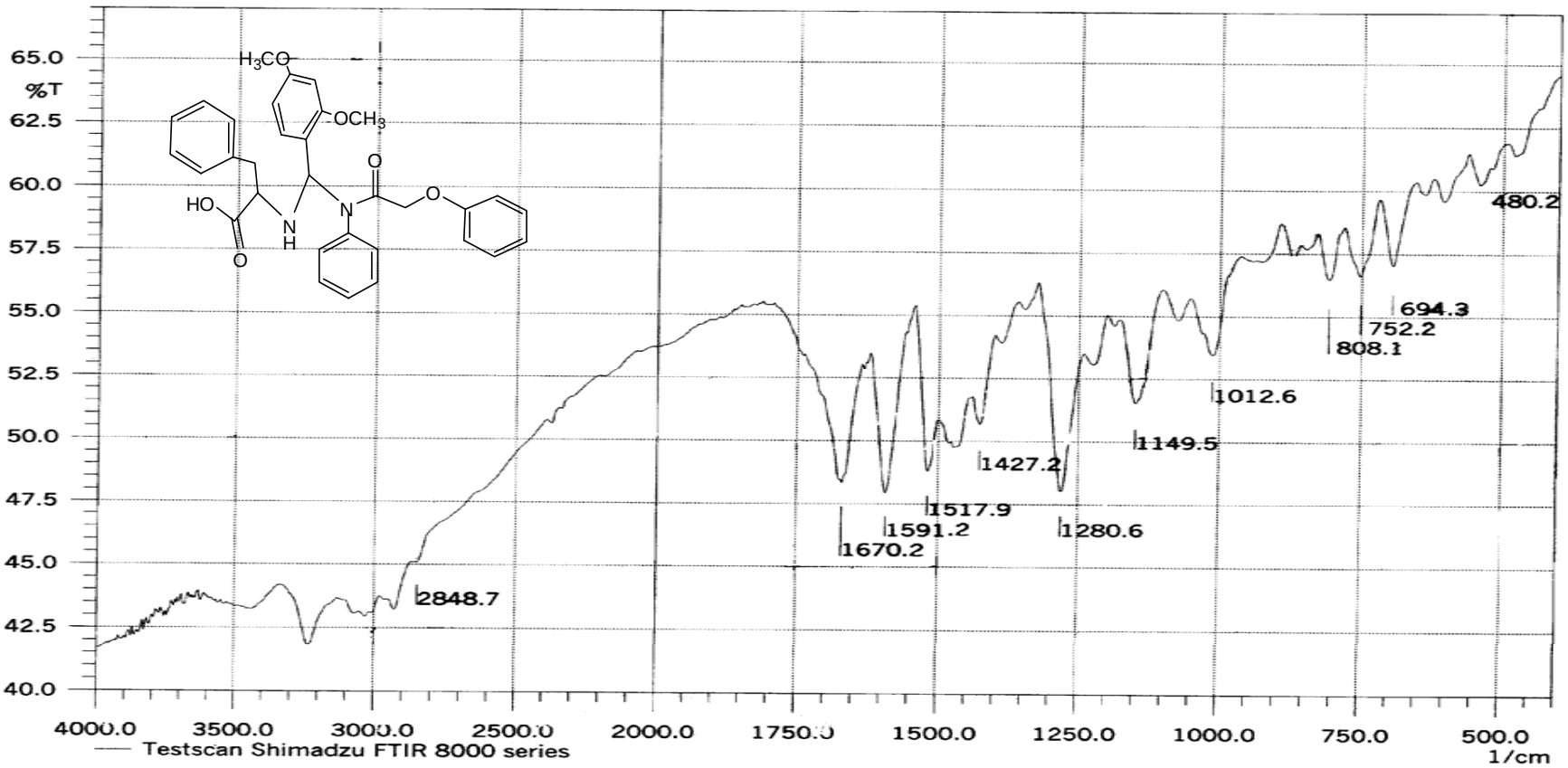
Yield% 81.3 %	MP. (160-165)ºC	$C_{30}H_{28}N_2O_4$

Figure(3-15)Structure, melting Point, yield% and FT-IR Spectra of N-[α-(phenyl-Ñ-Phenyl alinyl) methyl]-N-2-phenoxyacetanilide(5a)



Yield% 74%	MP. (78-80)ºC	$C_{32}H_{33}N_3O_4$

Figure(3-16)Structure, melting Point, yield% and FT-IR Spectra of N-[α-(4-dimethyl amino phenyl-Ñ-Phenyl alinyl) methyl]-N-2-phenoxyacetanilide(5b)

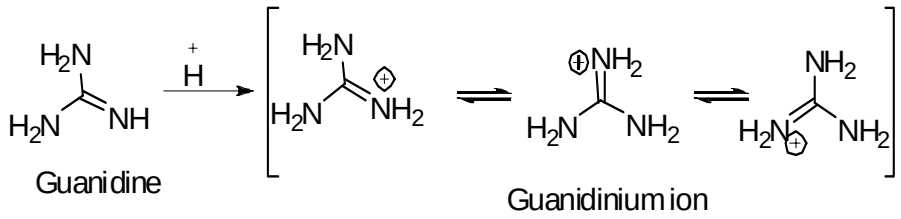


Yield% 30.8%	MP.(87-90) ºC	$C_{32}H_{32}N_2O_6$

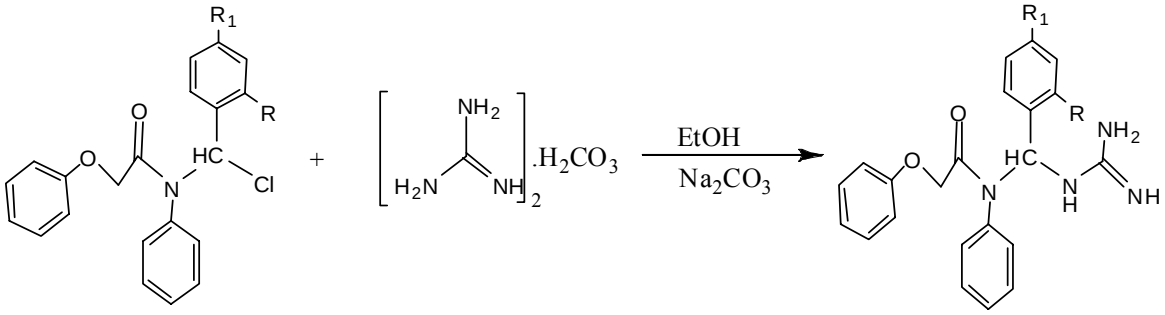
Figure(3-17)Structure, melting Point, yield% and FT-IR Spectra of N-[α-(2,4-dimethoxyphenyl-Ñ-Phenyl alinyl) methyl]-N-2-phenoxyacetanilide (5C)

2.3.7 Synthesis of N-[α-(2, 4-disubstituted phenyl-N¯-guanidino) methyl]-N-2-phenoxyacetanilide: (6)

Guanidine is one of the strongest bases in organic chemistry[80-82], where its pk_a= 13.65 from the extensive delocalization of the positive charge on the protonated cation:

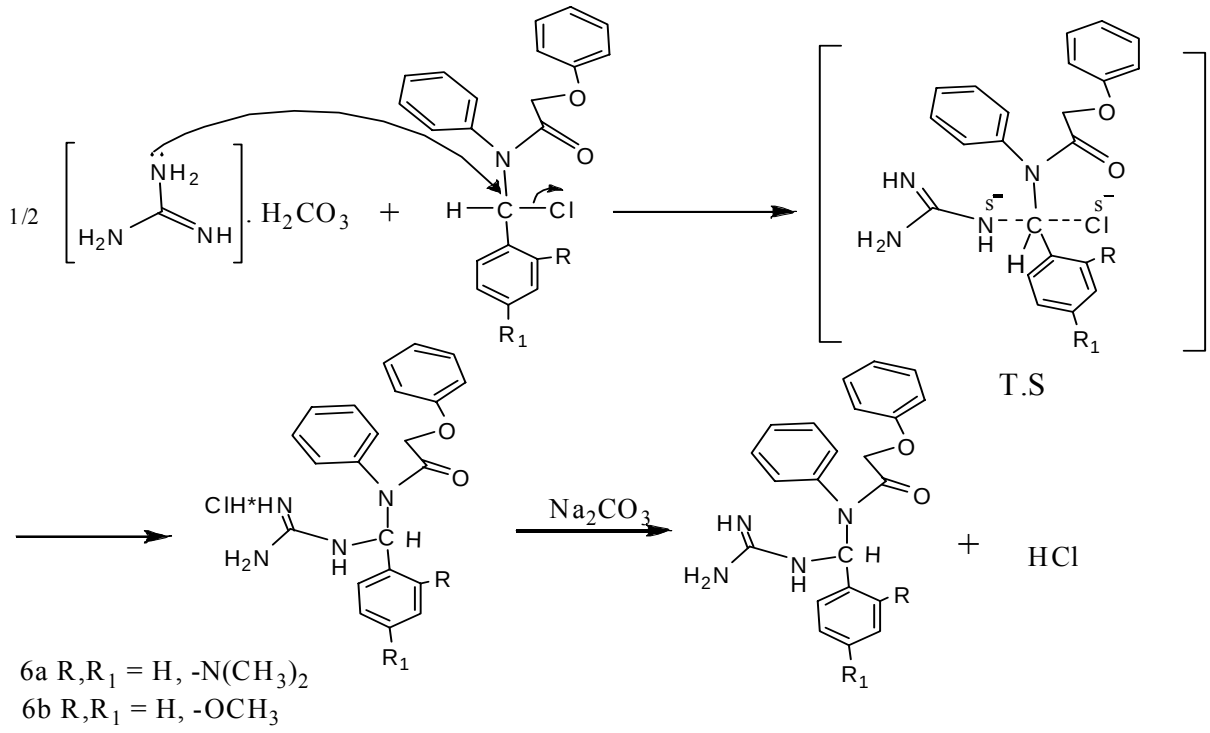


The guanidine derivatives were synthesized by the reaction of guanidine carbonate with benzyl chloride derivatives (2a-c) in absolute ethanol as solvent, the reaction mixture is treated with solution of 2% sodium carbonate, to remove the formed HCl.



6a R,R_1 = H, -$N(CH_3)_2$
6b R,R_1 = H, -OCH_3

The suggested mechanism of this reaction involves S_N2 [52] as shown below



6a R,R_1 = H, -$N(CH_3)_2$
6b R,R_1 = H, -OCH_3

The products were identified by Elemental analysis (CHN) and FT-IR spectroscopy, while the purification of the products where examined by TLC.

The FT-IR spectra showed the band at 1610cm^{-1} which is attributed to the bending vibration of -NH_2 group. Also the bands at 3400 and 3250 cm^{-1} caused by asymmetric and symmetric stretching vibration band of -NH_2 group respectively and disappearance of C-Cl band at 748 cm^{-1} give indication for the formed product. FT-IR spectra of above compounds are shown in figure (3-18 and 19).

The measured results of elemental analysis (CHN) were in agreement with the calculated values.

The FT-IR results were supported by the elemental analysis (CHN) as shown in table (3-9)

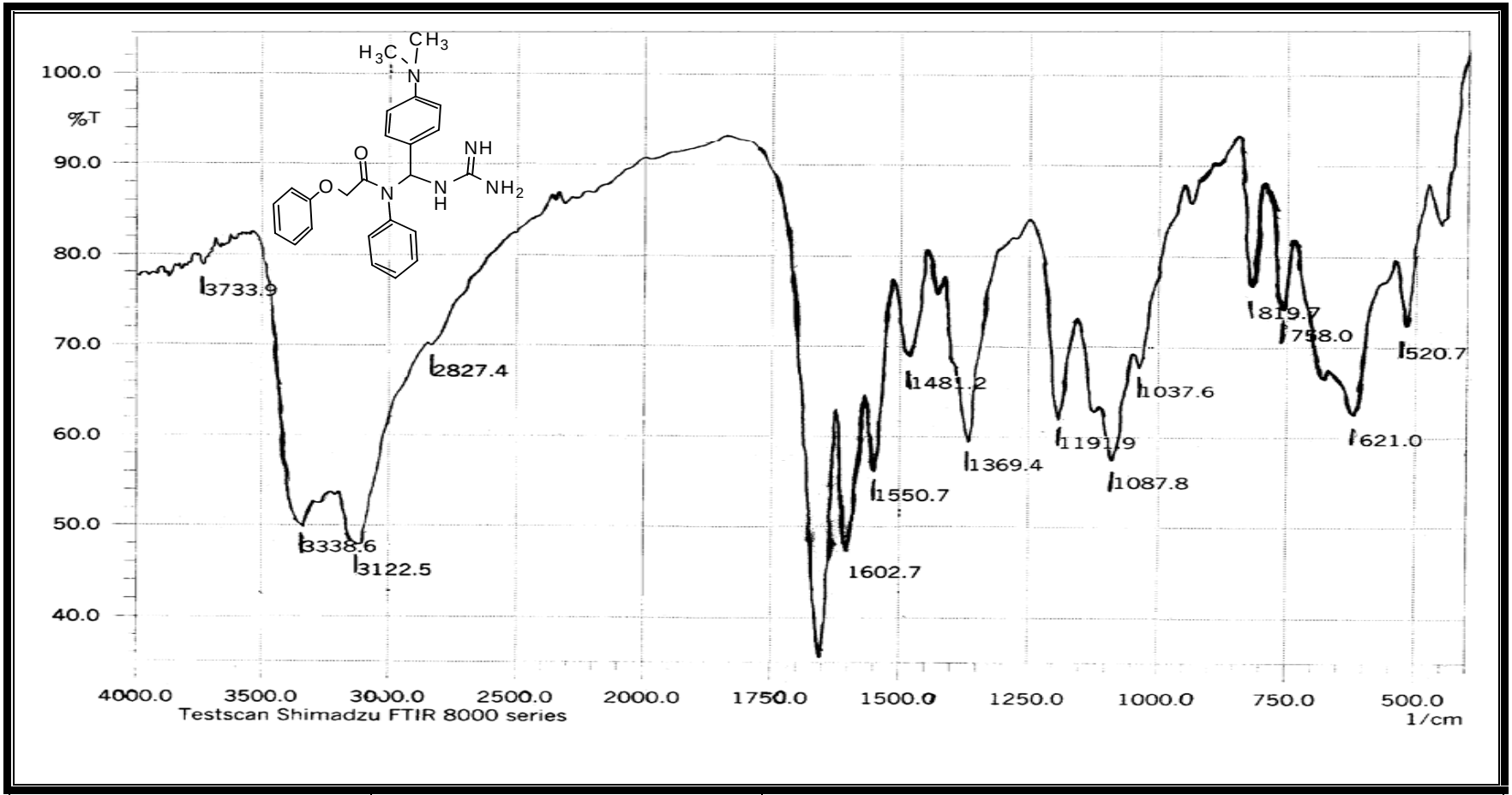
Table (3-9) Elemental analysis data for synthesized guanidine derivatives

substituents	**Elemental analysis**			
		C%	**H%**	**N%**
R = H, **R_1= -$N(CH_3)_2$**	**Calculated** **Found**	69.065 69.124	6.475 6.169	16.787 18.343
R,R_1 = -OCH_3	**Calculated** **Found**	66.359 65.406	6.682 6.530	12.903 12.355

Table (3-10) IR spectral data for synthesized guanidine derivatives

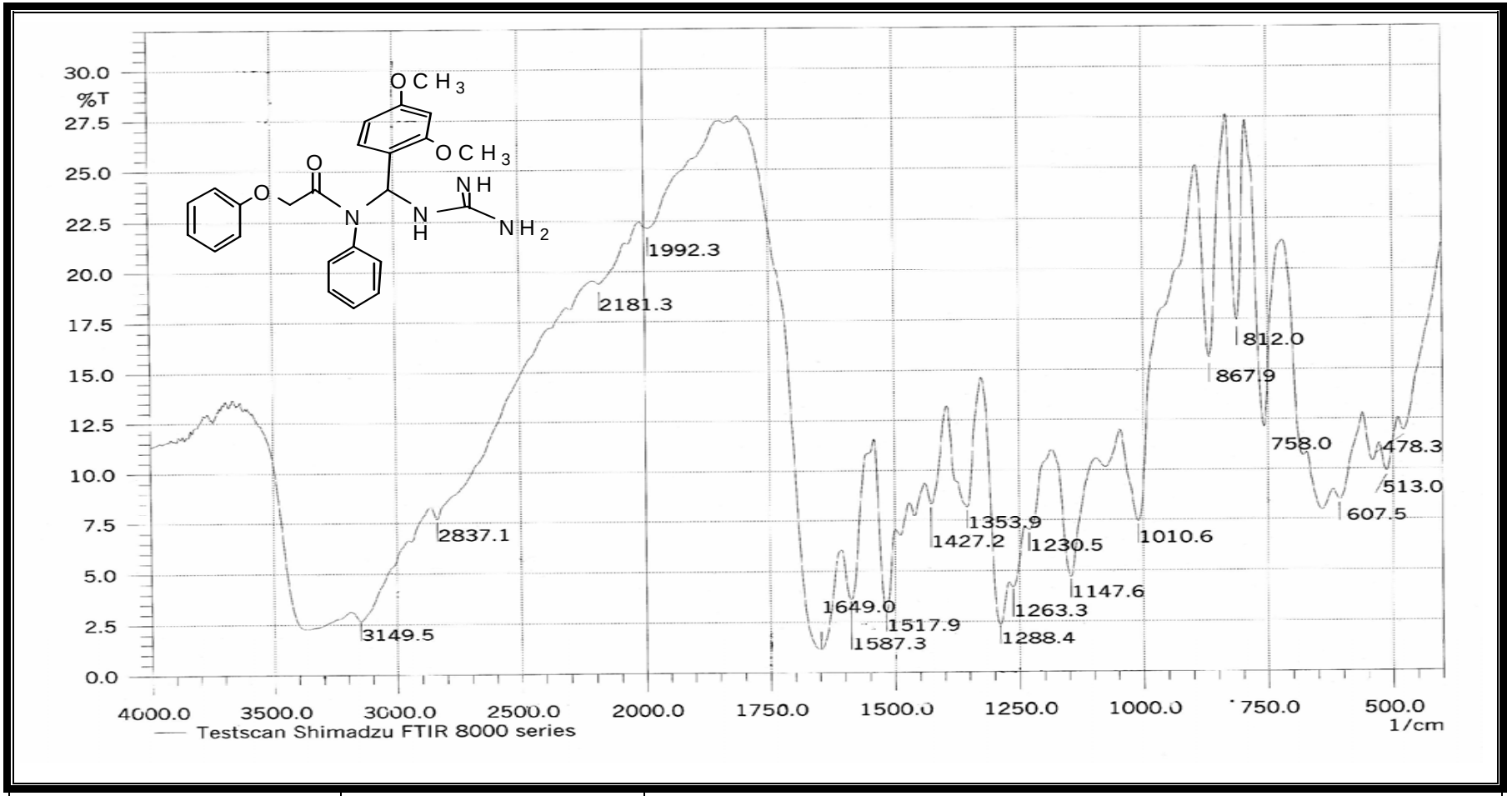
Comp No.	Fig. No.	substituents	ν N-H 1º	ν C-H aromatic	ν C-H aliphatic	ν C=O	ν C=C aromatic	additional peaks
7a	3-12	R = H R_1 = -$N(CH_3)_2$	as.st3338 s.st 3250	3122	2827	1652	1550	C-N 1369
7b	3-13	R,R_1 = -OCH_3	as.st3396 s.st 3300	3149	2837	1649	1517	C-O-C as.st1230 s.st 1147

ν **= stretching vibration, as.st = asymmetrical Stretching, s.st = symmetrical Stretching**



Yield% 46.7%	MP. (152-155)ºC	$C_{24}H_{27}N_5O_2$

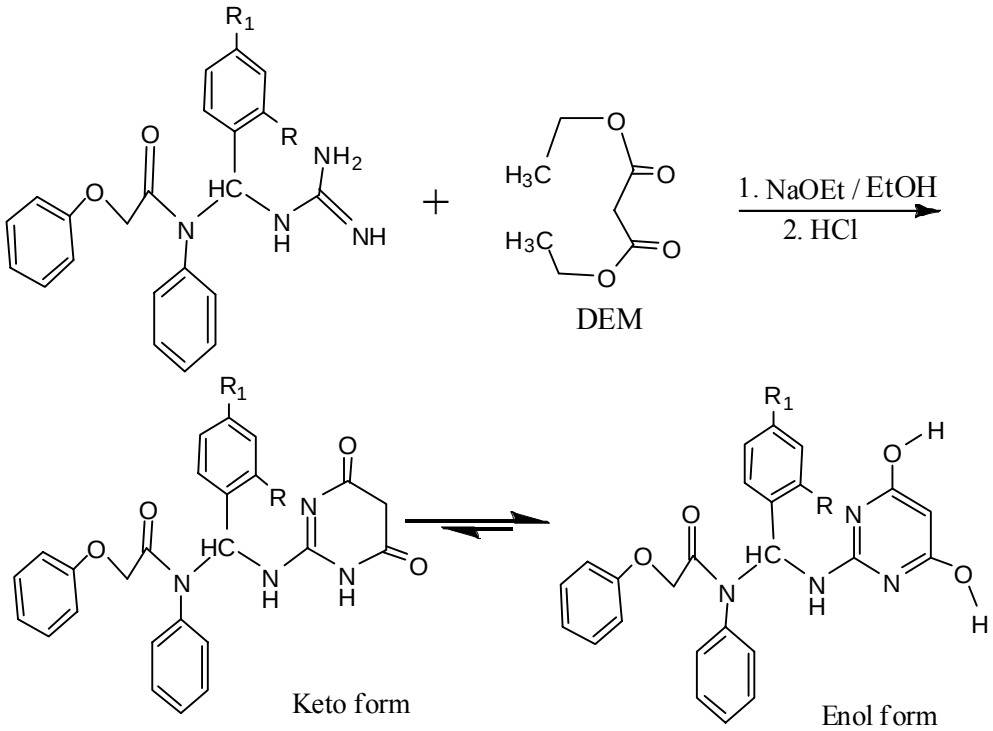
Figure(3-18)Structure, melting Point, yield% and FT-IR Spectra of N-[α (4-dimethyl amino phenyl-Ñ-guanidino)methyl]-N-2-phenoxy acetanilide (6a)



Yield% 81.3%	MP. (82-85)ºC	$C_{24}H_{26}N_4O_4$

Figure(3-19)Structure, melting Point, yield% and FT-IR Spectra of N-[α- (2,4-dimethoxy phenyl-Ñ-guanidino)methyl]-N-2-phenoxy acetanilide (6b)

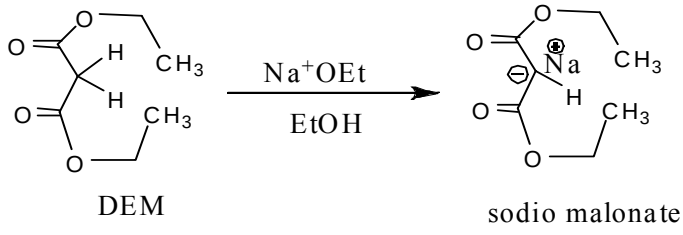
2.3.8 Synthesis of N-[α-(2-aminobarbiturate-2, 4-disubstituted phenyl) methyl]-N-2-phenoxyacetanilide: (7)



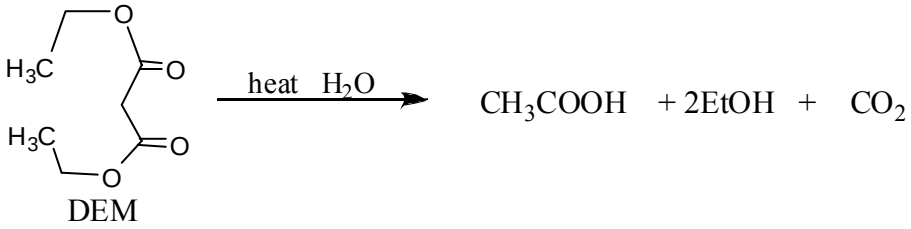
7a R,R_1 = H, -$N(CH_3)_2$
7b R,R_1 = H, -OCH_3

Guanidine derivatives (6) are condensed with diethyl malonate (DEM) under basic conditions to give the corresponding pyrimidine derivative, which is known as barbituric acid derivative. [80-84]

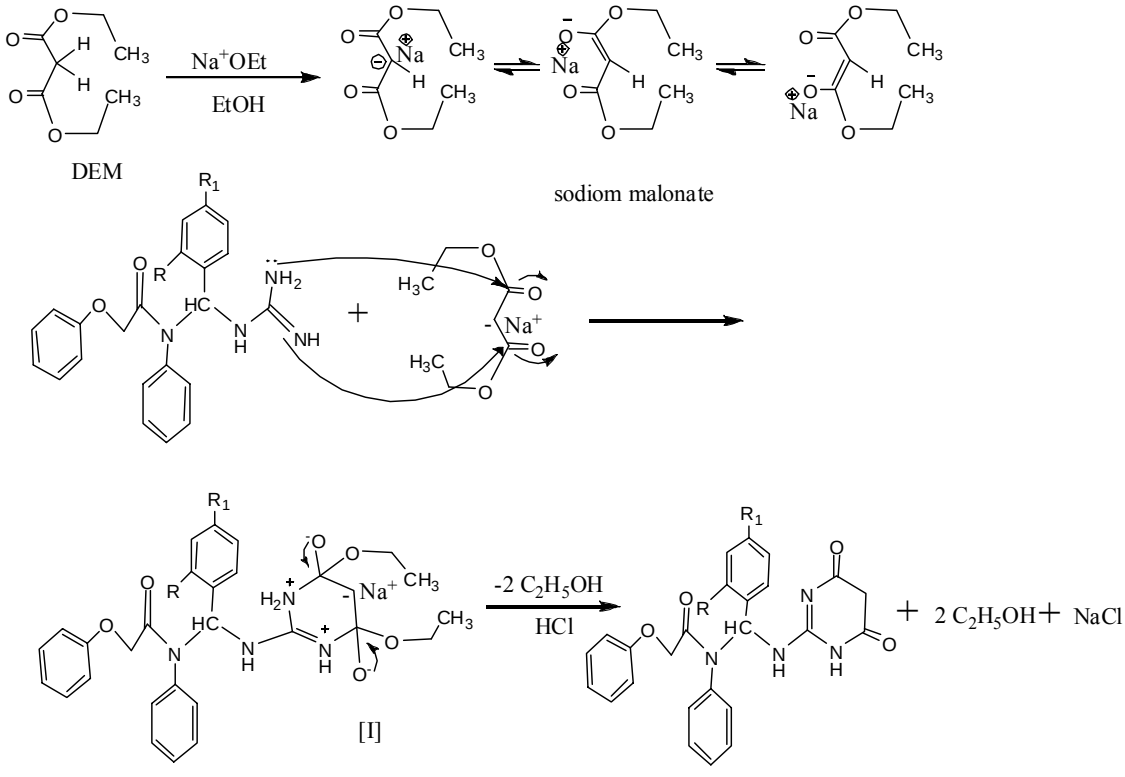
DEM is converted to the sodium malonic ester by sodium ethoxide in absolute ethanol to keep DEM in the solution without decomposition [83, 84]



DEM decomposes, by heating in neutral or acidic medium into acetic acid, ethanol and CO_2, in a decarboxylation process.[83, 84]



Both carbon atoms of the carbonyl groups of DEM is attacked by a nucleophilic group (NH_2 and =NH) of the guanidine to form the intermediate (I), which is stabilized in tetrahedral mechanism into the barbituric derivative. The formation of two ethanol molecules is the driving force for this step. The complete reaction mechanism is shown below. [82-84]



7a R,R_1 = H, -$N(CH_3)_2$
7b R,R_1 = H, -OCH_3

The products were identified by Elemental analysis (CHN) and FT-IR spectroscopy, while the purification of the products where examined by TLC.

The product were identified by FT-IR spectra which showed, appearance of stretching vibration of C=O band at 1730cm^{-1}, appearance of N-H band for secondary amine group at 3200cm^{-1} disappearance of NH_2 band for primary amine group at 1610-1587 cm^{-1} and disappearance of stretching vibration of $N-H_2$ bands at 3400cm^{-1} and 3250cm^{-1} for asymmetric and symmetric stretching vibration band respectively.

The appearance of typical broad strong band for O-H group at 3480-3400 $cm^{-1}$for enol form was seeing in the FT-IR spectra.

FT-IR spectra of above compounds were shown in figure (3-20, 21). The measured results from the elemental analysis (CHN) were in agreement with the calculated values.

The FT-IR results were supported by the elemental analysis (CHN) as shown in table (3-11)

Table (3-12) showed the main FT-IR absorption bands for all synthesized barbituric acid derivatives and the other functional groups that found in their structures.

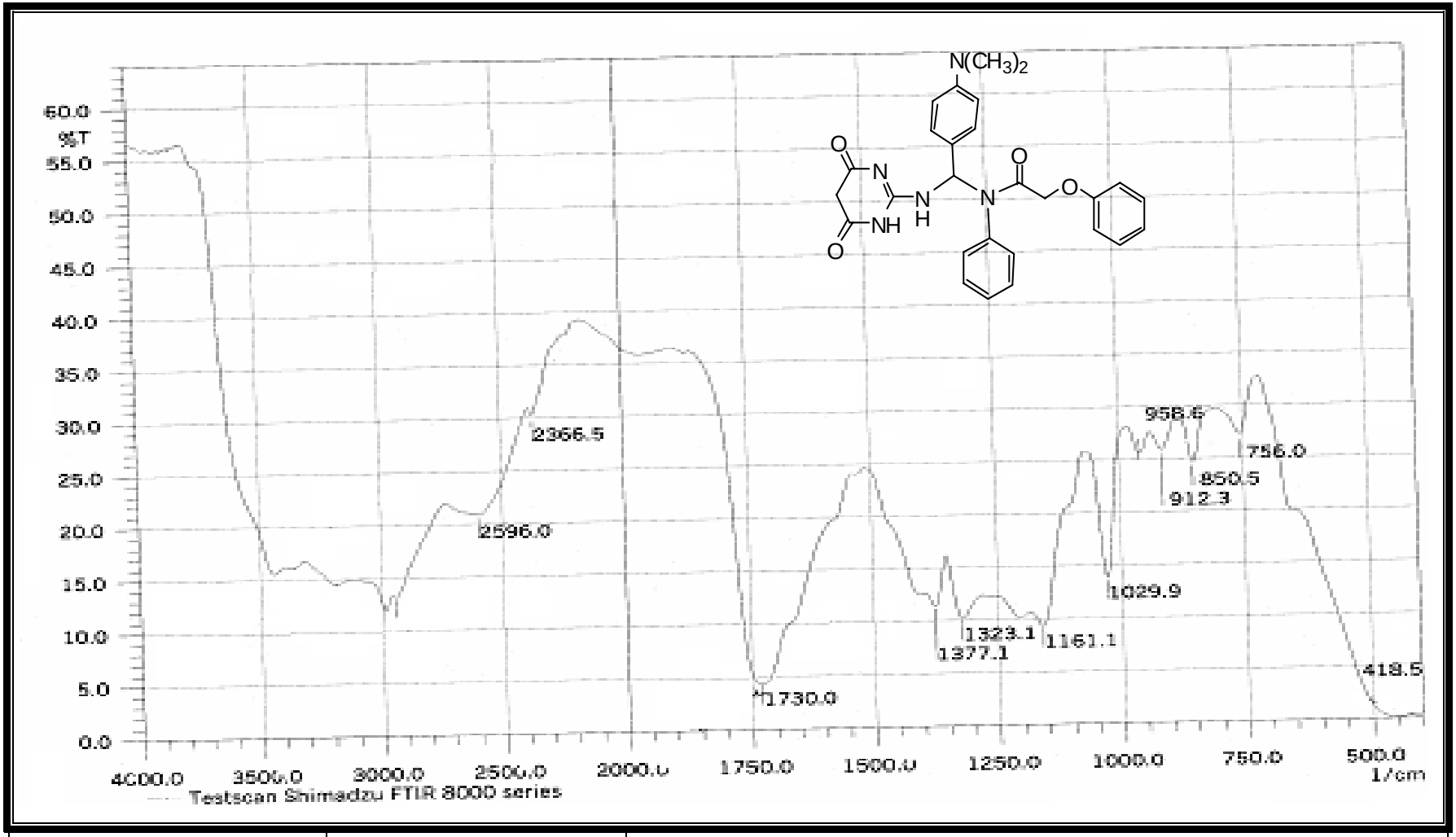
Table (3-11) Elemental analysis data for barbituric acid derivatives

substituents	Elemental analysis			
		C%	H%	N%
R = H, **R_1= -$N(CH_3)_2$**	**Calculated** **Found**	66.804 66.302	5.567 5.734	14.432 13.421
R,R_1 = - **OCH_3**	**Calculated** **Found**	64.541 66.501	5.179 4.109	11.155 11.312

Table (3-12) FT-IR spectral data for barbituric acid derivatives

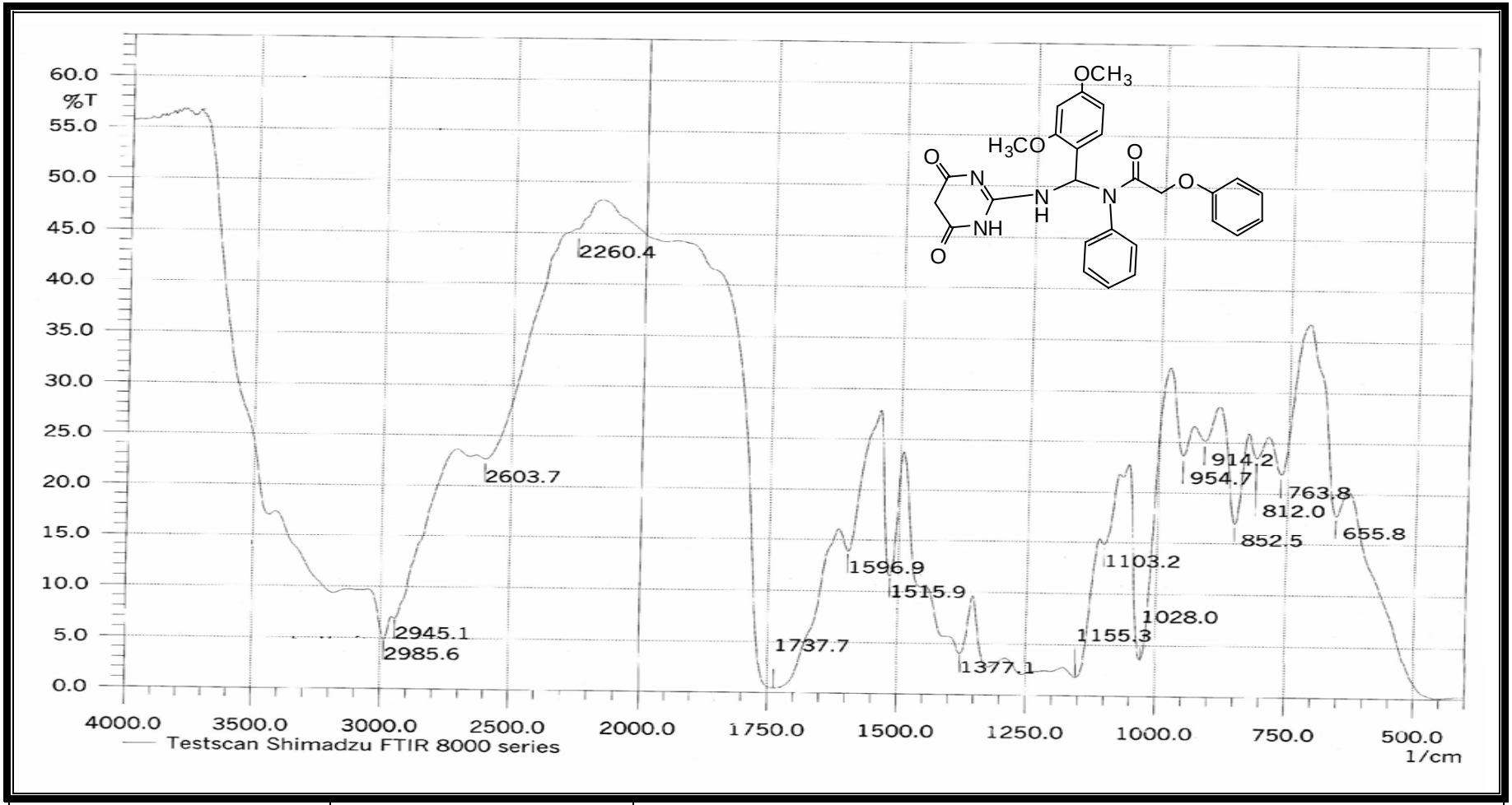
Comp No.	Fig. No.	substituents	ν O-H enolat	ν N-H 2º	ν C-H aromatic	ν C-H aliphatic	ν C=O	ν C=C aromatic	additional peaks
8a	3-14	R = H, R_1= -$N(CH_3)_2$	3480	3200	2997	2943	1730	1577	C-N 1377
8b	3-15	R,R_1= -OCH_3	3480	3200	2985	2945	1737	1515	C-O-C as.st1200 s.st 1155

ν = stretching vibration, as.st = asymmetrical Stretching, s.st = symmetrical Stretching



Yield% 52.2%	MP.(75-79)ºC	$C_{27}H_{27}N_5O_4$

Figure(3-20)Structure, melting Point, yield% and FT-IR Spectra of N-[α-(2-aminobarbiturate-4-dimethyl amino phenyl)methyl]-N-2-phenoxy acetanilide (7a)



Yield% 72.4%	MP. (89-92)ºC	$C_{27}H_{26}N_4O_6$

Figure(3-21)Structure, melting Point, yield% and FT-IR Spectra of N-[α-(2-aminobarbiturate-2,4-dimethoxy phenyl)methyl]-N-2-phenoxy acetanilide (7b)

Chapter Four

Biological activity

4.1 Introduction:

Microorganism cause different diseases to human and animals. Discovery of Chemotherapeutic agents played a very important role in controlling and preventing such diseases.

Chemotherapeutic agents are isolated either from living organism known as antibiotics like penicillin and tetracycline or they are chemical compounds prepared by chemists such as sulfa drugs [85].

Chemotherapeutic agents are chemicals which are intended to be toxic for the infectious organism but innocuous for the host. So that, it can be given in sufficient doses to inhibit or kill the microorganism through out the body without harming the body cell [86].

Amino acid and barbituric acid derivatives are considered an important class of compounds having a wide spectrum of biological activity[52, 68]. There are some types of bacteria:

4.1.1-Pseudomonas aeruginosa:-

Pseudomonas aeruginosa is gram negative rod, motile, non-spore forming. *Pseudomonas aeruginosa* infection can occur at many sites and can lead to urinary tract infections, sepsis, pneumonia, pharyngitis and wound infection [87].

4.1.2-Staphylococcus aurous:-

Staphylococcus aurous is gram positive cluster form, non-motile, non-spore forming. It has been found to be the causative agent in such illness as pneumonia, meningitis, boils, arthritis and osteomyelitis (chronic bone infection) [88]

Most clinical isolates of Staphylococcus *aureus* resistant to benzylpenicillin, due to the production of a beta-lactamase that bind to the antibiotic and destroys its activity by opening it at beta-lactam ring [89]

Resistance to other antibiotics is achieved by a number of different mechanisms depending on the class of antibiotic; these include membrane Impermeability, alteration of the target site, and enzymes degradation of antibiotic.[89]

4.2 Experimental:

4.2.1 Microbiological tests:

In this work, the antibacterial test was performed according to the disc diffusion method [90]. Compounds (3, 4, 5, 6, 7,) were assayed for their antimicrobial activity *in vitro* against one strain of Gram negative bacteria (*Pseudomonas aeuroginosa)* and one strain of Gram positive bacteria *(Staphylococcus aurous).*

4.2.2 Sensitivity test:

The prepared agar and Petri dishes were sterilized by autoclaving for 15 min at 121^{o}C. The agar was surface inoculated uniformly from the broth culture of the tested microorganisms.

In the solidified medium, suitably spaced apart holes were made (6mm in diameter) these holes were filled with (0.02g) of the prepared Compounds dissolved in (1ml) of DMSO solvent, DMSO was used as a solvent. These plates were incubated at 37^{o}C for 24 hour.

4.3 Results and Discussion:

The biological activity of the prepared compounds was determined by measuring the diameter of the empty region around the well (Inhibition zone). The results of preliminary screening tests are listed in table (4-1)

Table (4 - 1) antibacterial activities of the synthesized compounds

Comp. No.	*Pseudomonas aeuroginosa*	*Staphylococcus aurous*
3a	++	++
3b	+++	++
3c	+++	+++
4a	++	++
4b	-	++
4c	+	+++
5a	+	+
5b	++	+++
5c	+++	+++
6b	+++	+++
6c	+++	+++
7b	+	++
7c	+	++

Not:

- = (0) mm No inhibition = inactive

+ = (1-5) mm = weak activity

++ = (6-10) mm = moderate activity

+++ = (11-15) mm = highest activity

From the obtained data in table (4-1), it is found clearly that Cysteine derivatives (3b, 3c) and guanidine derivatives (6b, 6c) have the highest activity against P. ***aeruginosa*** and S. ***aurous***. This result may be attributed to the presence of -SH and -NH_2 groups in these derivatives.

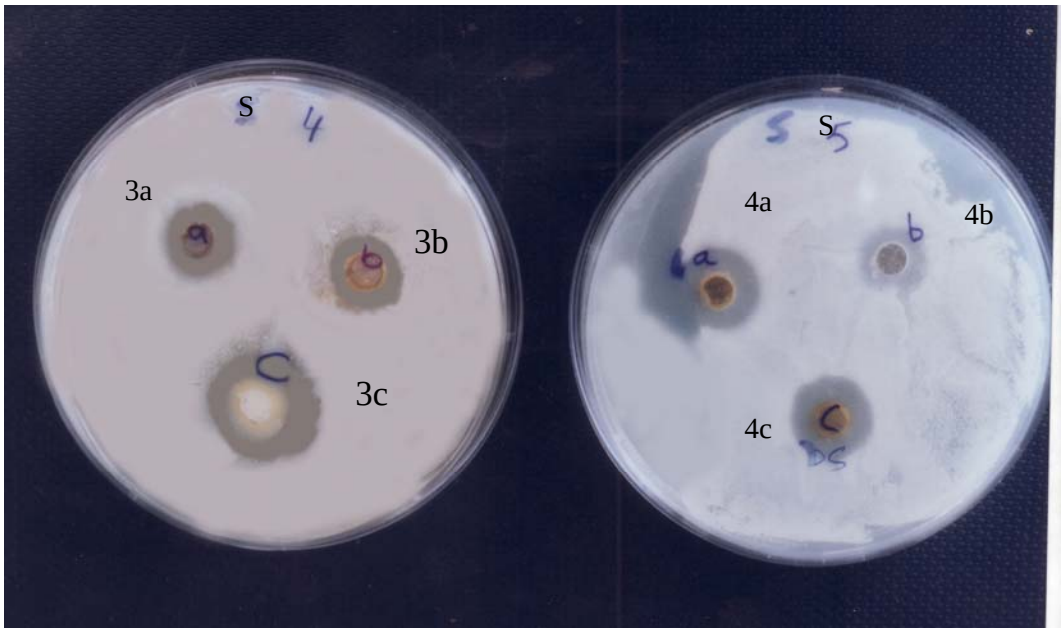


Fig (4-1) Effect of compounds (3, 4) on *Staphylococcus aurous*

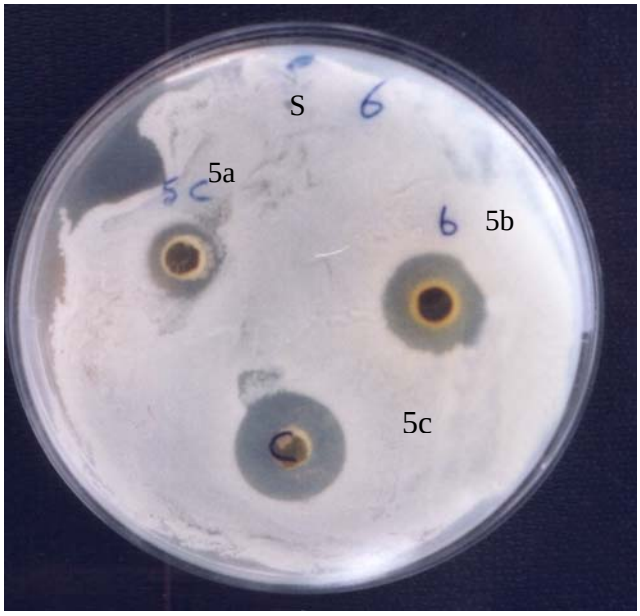


Fig (4-2) Effect of compounds (5) on *Staphylococcus aurous*

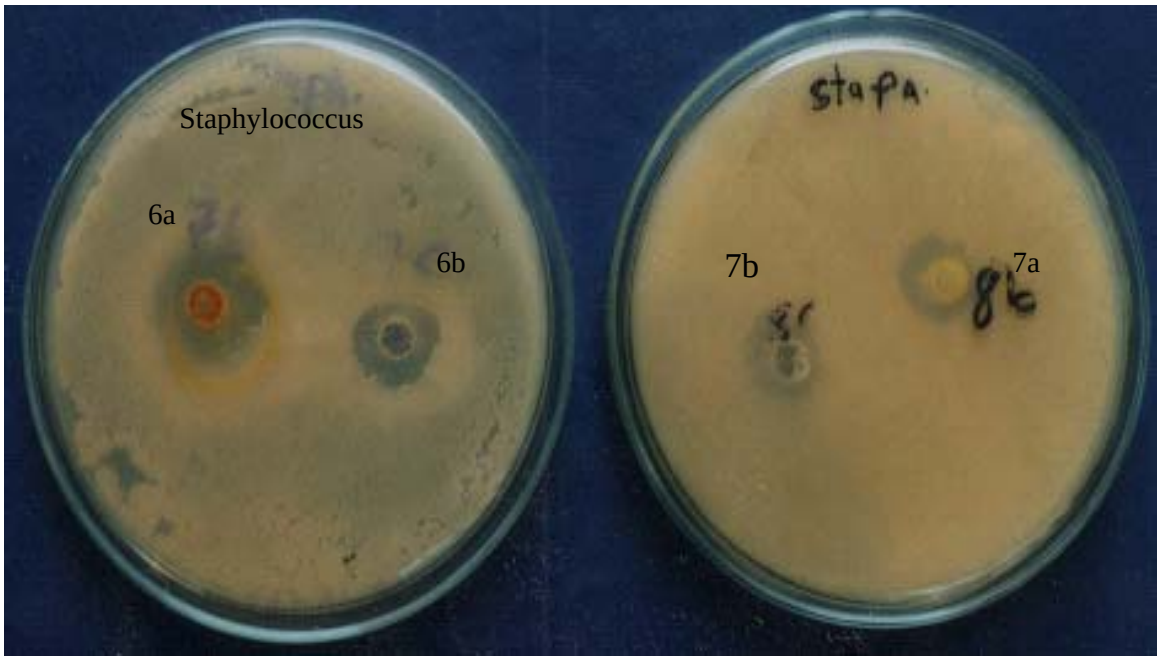


Fig (4 -3) Effect of Compounds (6, 7) on *Staphylococcus aurous*

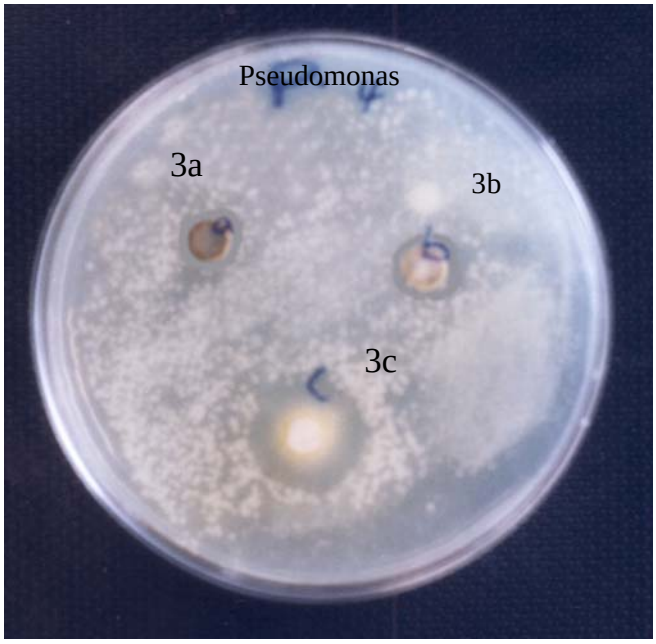


Fig (4-4) Effect o f compounds (3) on *Pseudomonas aeuoginos*

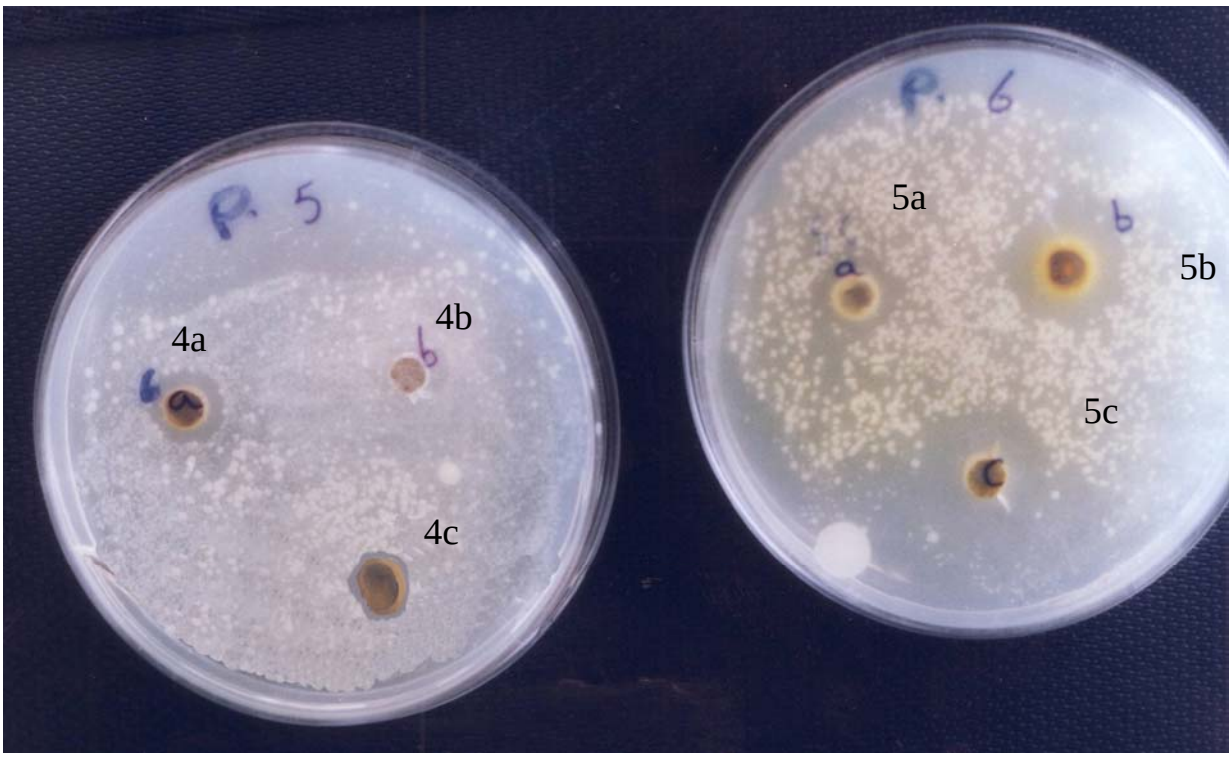


Fig (4-5) Effect of compounds (4, 5) on *Pseudomonas aeuroginosa*

Fig (4-6) Effect of compounds (6, 7) on Pseudomonas *aeuroginosa*

4.4 Conclusion:

1- For *Staphylococcus aurous* (G^+), compounds [3c, 4c, 5, 6 (b, c)] showed highest activity, compounds [3, 4 (a, b), 7] showed moderate activity and compound [5a] showed weak activity on this bacteria.

2- For *Pseudomonas aeuroginosa* (G^-), compound [3(a,b),5c,6] showed highest activity, compounds [3a,4a,5b] showed moderate activity, compounds [5a,7, 4c] showed weak activity and compound [4b] showed no activity on this bacteria.

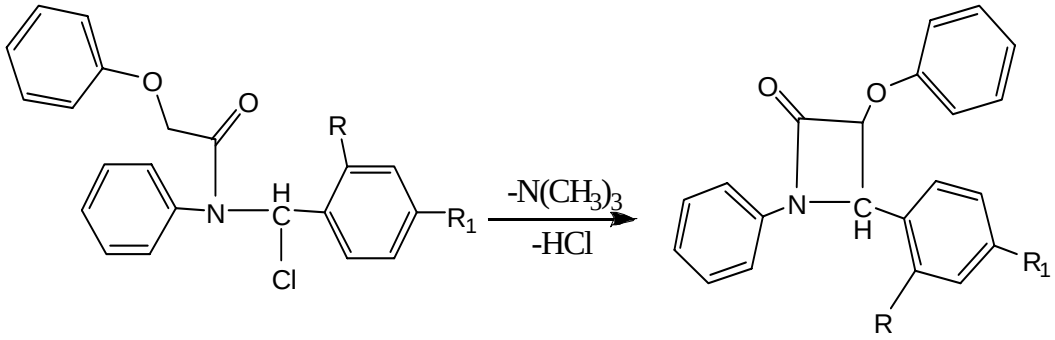
From these results it is shown that most of the new synthesized compounds exhibited high biological activity against both bacteria.

The combination of $–OCH_3$ group with the –SH and $–NH_2$ side chains may enhance the biological activity against both bacteria as seen in compounds [3c, 5c, 6c].

Suggestions for further work:

1- Similar new amino acid derivatives can be synthesized and tested for their biological activity.

2- Heterocyclic rings can be synthesized from compound [3] using different organic reagents as shown in the following equation.



a: $R,R_1=(H,H)$
b: $R,R_1=[H,-N(CH_3)_2]$
c: $R,R_1=(-OCH_3)$

3- Identification the most biologically active products to use in the medicine as drugs.

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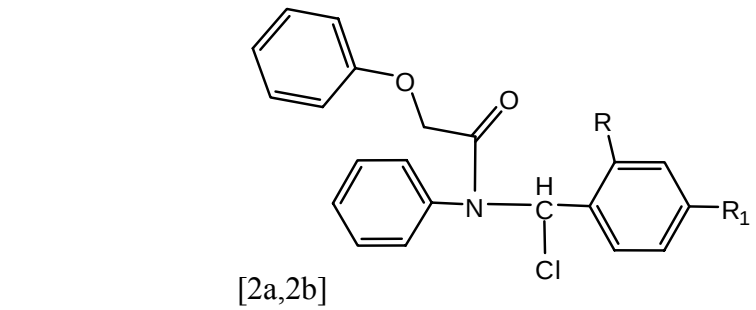
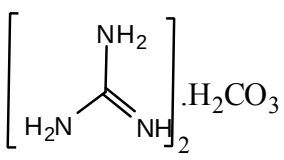
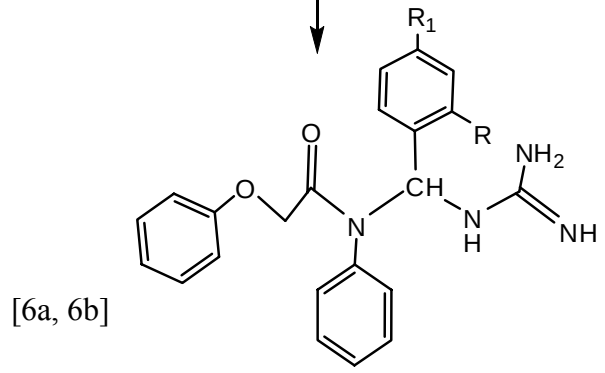


[2a,2b]

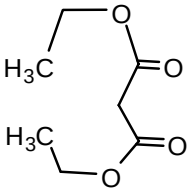


i



[6a, 6b]

ii



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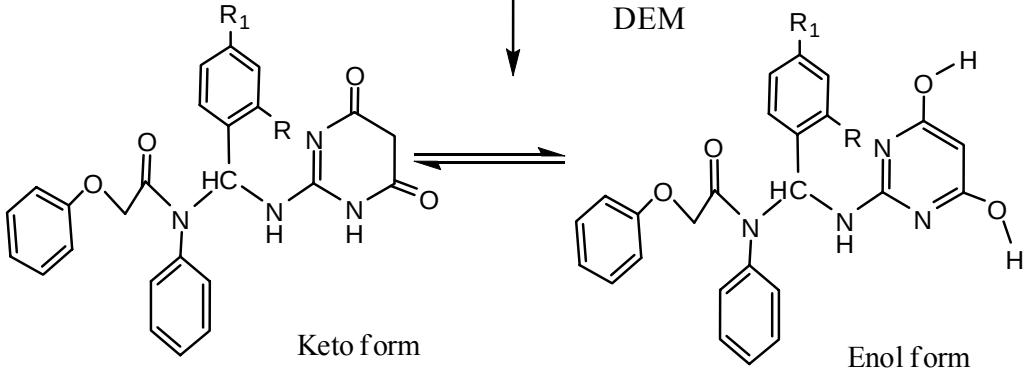


Keto form

Enol form

[7a, 7b]

a R,R_1 = H, $-N(CH_3)_2$

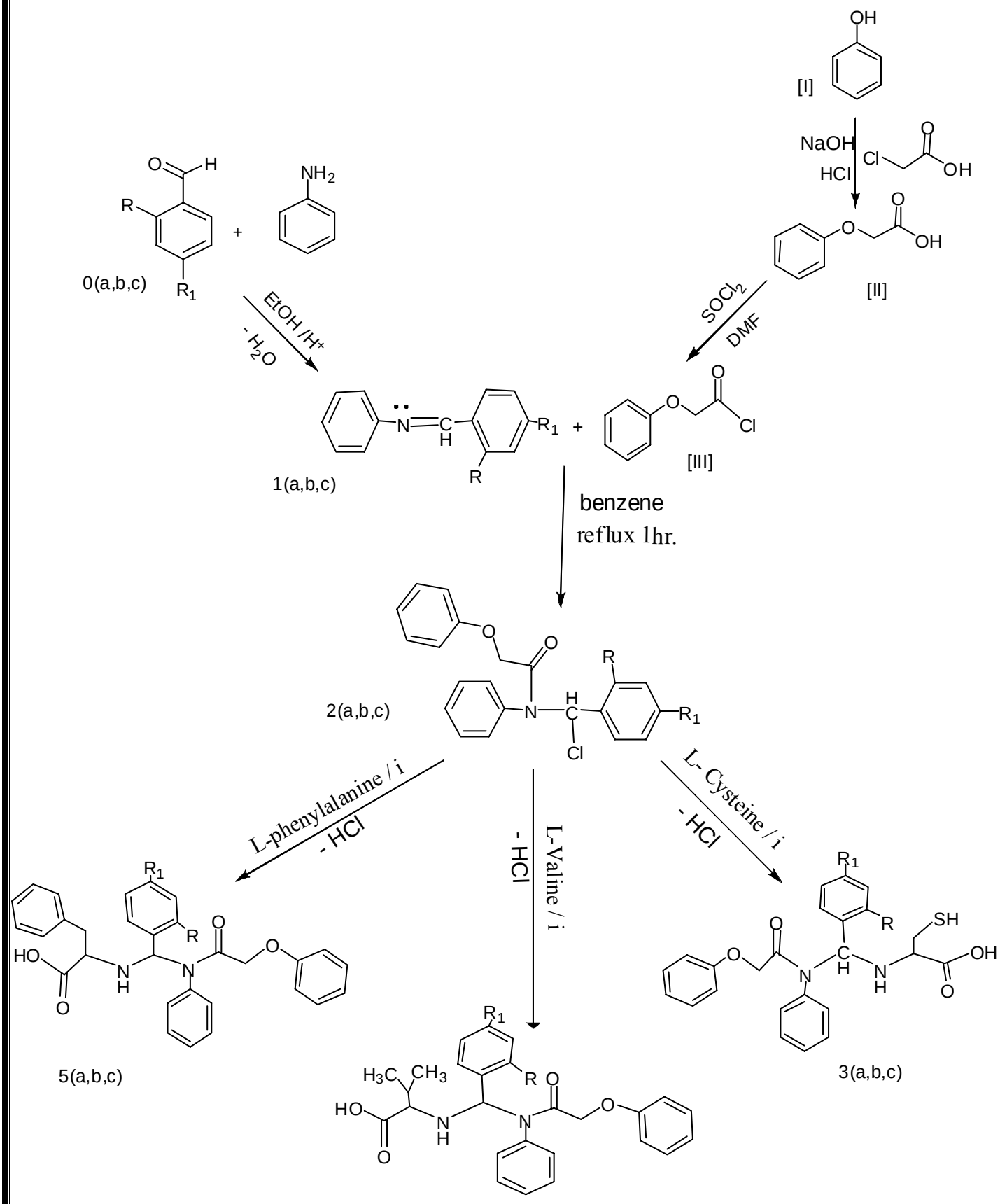
b R,R_1 = $-OCH_3$

i = Na_2CO_3 , EtOH

ii = 1. NaOEt / EtOH

2. HCl

المخطط ٢



a) $R,R_1=(H,H)$
b) $R,R_1=[H,-N(CH_3)_2]$
c) $R,R_1=(-OCH_3)$

i = dioxane / H_2O , reflux 4hr.

المخطط ١

الخلاصـة

يتضمن هذا البحث تحضيرودراسة الفعالية لبعض مشتقات الاحماض الامينية ومشتقات حامض الباربيتيورك عن طريق قواعد شيف. لقد تم تقسيم هذا العمل الى ستة أجزاء:

الجزء الاول:-

يتضمن هذا الجزء تحضير قواعد شيف عن طريق مفاعلة الانيلين مع مشتقات مختلفه من البنزلديهايدات المخطط (I).

الجزء الثاني:-

يتضمن هذا الجزء تحضير فينوكسي حامض الخليك الذي بدوره يتغيرالى ٢- كلورو فينوكسي حامض الخليك والذي بدوره يتفاعل فيما بعد مع قواعد شيف الناتجة في الجزء الاول لكي تنتج مشتقات انليديه المخطط (I).

الجزء الثالث:-

يتضمن تحضير مشتقات الاحماض الامينيه عن طريق تفاعل مشتقات الانليدات الناتج في الجزء الثاني مع الاحماض الامينيه مختلفه (سيستين، فالين، فنيال الينين) كما في المخطط (I).

الجزء الرابع:-

يتضمن تحضير مشتقات حامض الباربيتيوريك بواسطة تفاعل مشتقات الأنليدات الناتجة بالجزء الثاني مع كاربونات الجواندين وثنائي أثيل المالونيت في الوسط القاعدي كما في المخطط (II) .

الجزء الخامس :-

يتضمن تشخيص النتائج و المركبات الوسطية بواسطة درجة الانصهار وتحليل العناصر (CHN) كما في الجدول (4,9,11) وبواسطة مطياف الاشعة الحمرا .

الجزء السادس :-

هذا الجزء يتضمن مع تقدير الفعالية البايولوجية للمركبات المحضرة اعلاة ضد نوعان من البكتريا (*Pseudomonas aeuroginosa and Staphylococcus aureus*) كما في الجدول (٤-١)

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

تحضير ودراسة الفعالية البايولوجية لبعض مشتقات الاحماض الامينية وحامض الباربيتوريك عن طريق قواعد شيف.

رسالة
مقدمة إلى كلية العلوم- جامعة النهرين
وهي جزء من متطلبات نيل درجة الماجستير في الكيمياء

من قِبَلْ
احمد عباس نعمان
بكالوريوس٢٠٠٦ (جامعة النهرين)

تشرين الأول ٢٠٠٨م　　شوال ١٤٢٩