

Synthesis of Some New Barbiturate Derivatives Via Schiff Bases

Ahlam J. Zaier*

* University of Baghdad - College of Education For Pure Science (Ibn Al - Haitham) -
Department of Chemistry.

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Abstract

A stable Schiff bases were prepared by condensation reaction between equimolar quantities of aromatic aldehydes with aromatic amines. Aromatic Schiff bases were undergo nucleophilic addition with acetyl chloride to give *N*-(chloro(phenyl)methyl)-*N*-phenylacetamides. The reaction of latter with diethylmalonate in basic medium yeild diethyl-2-(phenyl(*N*-phenylacetamido)methyl)malonates. The latter condense with urea in basic medium to give derivatives of barbiturate which used in the medical field as hypnotics. The prepared compounds were identified by FT.IR and UV-Vis spectroscopy.

Key words: Schiff base, Acetamide, Barbiturate, Pyrimidine

تحضير بعض مشتقات الباربيتورات الجديدة عن طريق قواعد شيف

أحلام جاسم

قسم الكيمياء ، كلية التربية للعلوم الصرفة – ابن الهيثم ، جامعة بغداد

الخلاصة

تحضير قواعد شيف المستقرة من تكاثف كميات مولية متكافئة من الالديهيدات الاروماتية مع الامينات الاورماتية اذ تخضع قواعد شيف لتفاعل اضافة نيوكلوфильية عند تفاعلها مع كلوريد الاسيتيل ليعطي : (*N*-(كلورو(فnil)مethyl)-*N*-فnil أسيتاميدات والتي بدورها تتفاعل مع ثنائي ائيل مالونيت في وسط قاعدي لتعطي : ثنائي ائيل-2-(فnil)-*N*-فnil أسيتاميدو) مethyl مالونيات. تتكاثف الاخيرة مع اليوريا في وسط قاعدي لتعطي مشتقات الباربيتورات التي تستعمل في مجال الطب كـ (منومات).

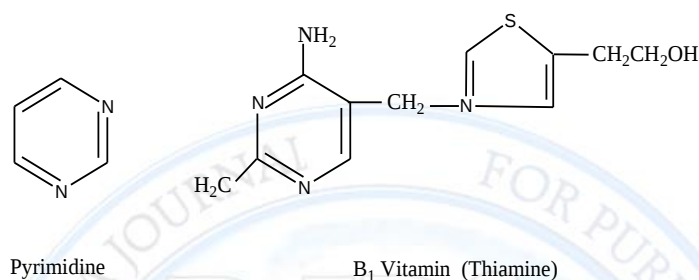
الكلمات المفتاحية: قاعدة شف، أسيتاميد، باربيتورات، بريميدين

Synthesis of Some New Barbiturate Derivatives Via Schiff Bases

Ahlam J. Zaier

Introduction

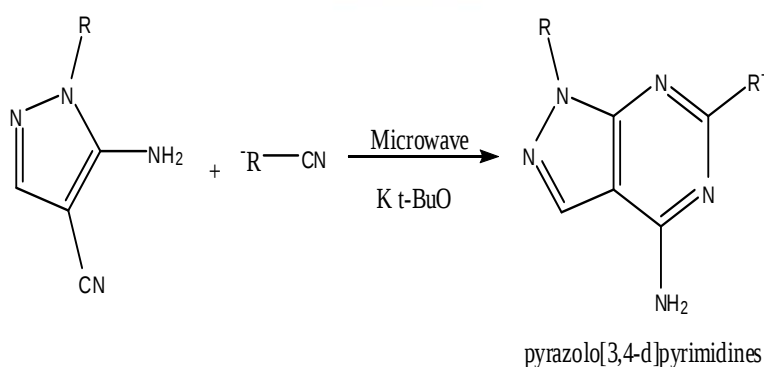
Barbiturates are compounds contain a pyrimidine [1]. Pyrimidine is a six-membered ring with two nitrogen atoms. Pyrimidines are constituent of B₁ and B₂ vitamins, coffee and tea in their caffeine's[2].



A new Schiff base N, N̄-bis (Salicylidene)-1,10-decanediamine has a band or a combination of hydrogen molecular recognition with barbituric acid [3]. The investigated of cyclic polyether Schiff base" N-propylenebis [5, -oxo-bis(hexaethyleneoxy) Salicylideneaminato] " showed a strong correlation with susceptibility barbituric acid by non covalent intermolecular interaction such as hydrogen bonding[4].

In recent years pyrimido pyrimidines are cyclic uracils that have attracted considerable interest [5]. A wide range of pyrimido pyrimidine derivatives are known to display a wide range of pharmacological activities, The strong inhibitory properties in the area like tyrosine kinase of the epidermal growth factor receptor [6].

By using microwave irradiation under solvent-free conditions there are simple methods have been developed for the synthesis of various pyrazolo (3,4-d) pyrimidines [7].



Synthesis of Some New Barbiturate Derivatives Via Schiff Bases

Ahlam J. Zaier

The aim of this work is to prepare and characterize new series of barbiturate derivatives starting from Schiff bases which it were expected to have a biological activity.

Experimental**Instrumental and Chemical**

All chemicals purified before use. By using Gallen Kamp melting point apparatus melting points were recorded, and were without correction. By using FT.IR 8400 shimadzu in the range of $(4000-200) \text{ cm}^{-1}$ FT.IR spectra were recorded by using KBr disc. At room temperature the electronic spectra were measured mediated (U.V-1600) shimadzu spectrophotometer., the used solvent was ethyl alcohol , and the used concentration was $(10^{-3}) \text{ M}$ at $(25)^{\circ}\text{C}$.

Synthesis of Schiff bases [8]

An equal amounts of aromatic aldehyde and primary aromatic amine (0.01 mol) were dissolved in (20 ml) of absolute ethyl alcohol., A few drops of acetic acid snow was added to the mixture. The reaction mixture was refluxed for two hours. To room temperature the reaction mixture was allowed to cool , filtered. Gave re-crystallization from ethyl alcohol of colorful crystals of : N-benzylideneanilines (1-4).

Synthesis of: *N*-(chloro(phenyl)methyl)-*N*-phenylacetamides

A drop wise of the solution of acetyl chloride (0.015 mole, 1.18gm) in (15 ml) benzene was added drop wise to the solution (0.015 mole) *N*-benzylideneanilines thaw in benzene(25 ml). The reaction mixture was refluxed for (2hrs.) with stirring. At room temperature the solution was normally allowed to cool ,and the formed crystals were filtered . Re crystallization from ethyl alcohol to yield colored crystals of: *N*-(chloro(phenyl)methyl)-*N*-phenylacetamides (5-8).

Synthesis of diethyl-2-(phenyl(*N*-phenylacetamido)methyl)malonates

A mixture of (0.01 mole) of diethyl malonate and (15 ml) of ethanolic solution of sodium ethoxide(0.01mole of absolute ethanol + 0.01mole of sodium metal) has been added to a solution of (0.01 mole) of *N*-(chloro(phenyl) methyl)-*N*-phenylacetamides in (15 ml) of absolute ethanol. The reaction mixture was refluxed for (4 hrs.) with stirring. The solvent was evaporated. The precipitated crystals were filtered, washed with 2% Na_2CO_3 solution, then

Synthesis of Some New Barbiturate Derivatives Via Schiff Bases

Ahlam J. Zaier

recrystallized from ethyl alcohol to give: diethyl-2-(phenyl(*N* phenylacetamido) methyl) malonates (9-12).

Synthesis of : *N*-phenyl-*N*-(phenyl-(2,4,6 - trioxohexahydropyrimidine-5-yl)methyl) acetamides (barbituric acids)

A solution of (0.005 mole, 0.3gm) of urea in (15 ml) of dry acetone was added to a solution of (0.005 mole) of diethyl-2-(phenyl(*N*- henylacetamido)methyl) malonate in (15 ml) of dry acetone. The reaction mixture was refluxed for (7 hrs.) with stirring. The solvent was evaporated and the remaining crystals was filtered, re-crystallized from ethanol to yield: *N*-phenyl-*N*-(phenyl-(2,4,6-trioxohexahydropyrimidine-5-yl)methyl)acetamides (13-16).

Results and Discussion

Aromatic Schiff bases are good starting material to prepared heterocyclic compounds[8,9]. Aromatic Schiff bases were prepared by acid catalyzed of aromatic aldehydes with aromatic primary amines in boiling absolute ethanol[10].



Where $\text{Ar} = \text{O} - \text{NO}_2 - \text{C}_6\text{H}_4$, $\text{m} - \text{NO}_2 - \text{C}_6\text{H}_4$,

$\text{p} - \text{NO}_2 - \text{C}_6\text{H}_4$, $2 - \text{NO}_2$, $4 - \text{Cl} - \text{C}_6\text{H}_4$

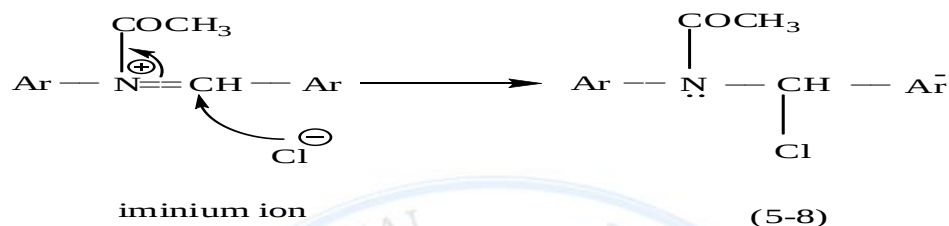
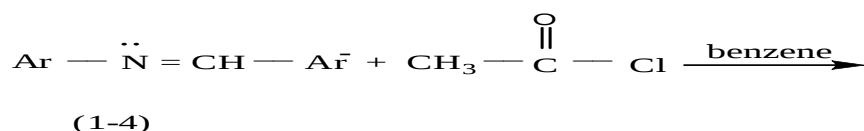
$\text{Ar}^- = \text{p} - \text{N}(\text{CH}_3)_2\text{C}_6\text{H}_4$

The FT.IR spectra showed appearance of ($\text{N} = \text{C}$) absorption band at ($1598 - 1630$) cm^{-1} , while UV-Vis. spectra showed absorption at ($\lambda_{\text{max}} = 238 - 248$ nm), (table - 2), (figs. 1-4).

Schiff bases are reacted with acetyl chloride to yield: *N*-(chloro (phenyl) methyl)-*N*-phenylacetamides (5-8) in good yield[11]

Synthesis of Some New Barbiturate Derivatives Via Schiff Bases

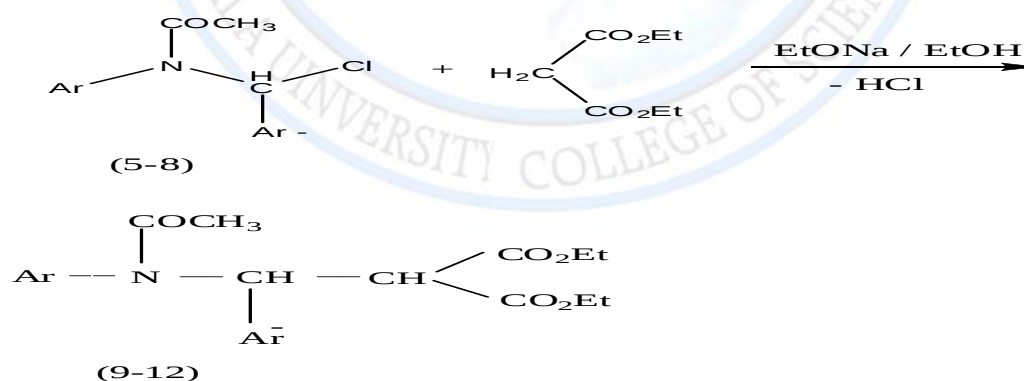
Ahlam J. Zaier



Nitrogen atom attacks carbon atom of the acyl group displacing the chloride ion to form iminium ion. Chloride ion attacks the iminium carbon yields acetamides derivatives (5-8). FT-IR spectra of compounds (5-8) showed an absorption band at (1650-1635) cm^{-1} due to $\nu(\text{C}=\text{O})$ of $(-\text{N}^+-\overset{\text{O}}{\parallel}\text{C}-)$ group and appearance of aliphatic (C-Cl) absorption band at (830-825) cm^{-1} [12]. U.V. spectra of compounds (5-8) showed absorption maxima at (334-335) nm due to charge transfer (table - 3), (figs. 5-8).

N-(chloro(phenyl) methyl)-*N*-phenylacetamides undergo nucleophilic substitution reaction when treated with diethyl malonate in basic medium to yield:

diethyl-2-(phenyl(*N*-phenylacetamido)methyl)malonates (9-12) with elimination of HCl.

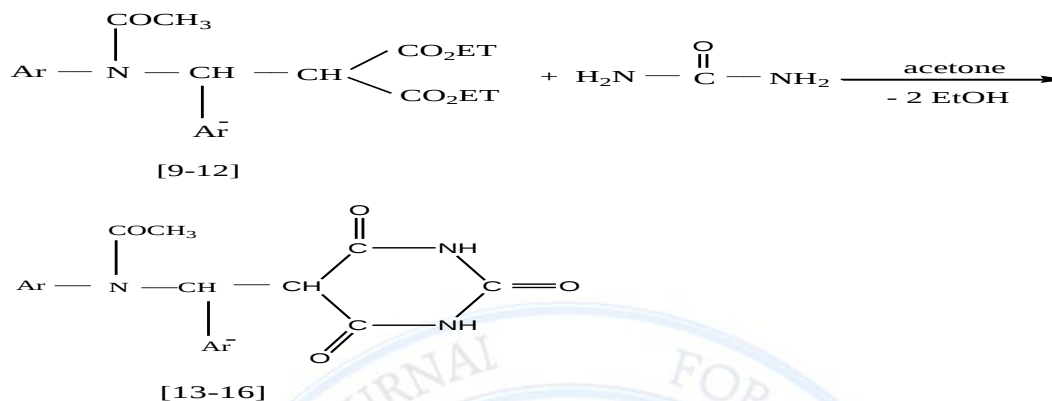


FT-IR spectra of compounds (9-12) gave an absorption band about (1750-1740) cm^{-1} due to $\nu(\text{C}=\text{O})$ of ester, and around (1680-1665) cm^{-1} due to $\nu(\text{C}=\text{O})$ of amide, and disappearance of aliphatic (C-Cl) band at (830-825) cm^{-1} [12]. U.V. spectra showed absorption maxima at (340-411) nm due to charge transfer (table - 4), (figs. 9-12).

Synthesis of Some New Barbiturate Derivatives Via Schiff Bases

Ahlam J. Zaier

Diethyl-2-(phenyl(*N*-phenylacetamido)methyl)malonates (9-12) are condensed with urea by nucleophilic substitution to give the pyrimidine derivatives (barbiturates) (13-16).



FTIR spectra of barbiturate derivatives gave on absorption band at $(3275\text{-}3260) \text{ cm}^{-1}$ due to $\nu(\text{N-H})$ and at $(1685\text{-}1675) \text{ cm}^{-1}$ due to $\nu(\text{C=O})$ of lactam [12]. U.V. spectra of barbiturate derivatives showed absorption maxima at $(300\text{-}235) \text{ nm}$ (table - 5), (figs. 13-16).

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Synthesis of Some New Barbiturate Derivatives Via Schiff Bases

Ahlam J. Zaier

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Table No. (1): Physical properties of the prepared compounds.

Comp No.	The compounds	Molecular formula	Yield %	M.P C ⁰	Color
1	N,N-dimethyl1-4-((2-nitrophenylimino) methyl)aniline	C ₁₅ H ₁₅ N ₃ O ₂	58	103-105	Dark yellow
2	N,N-dimethyl1-4-((3-nitrophenylimino) methyl) aniline	C ₁₅ H ₁₅ N ₃ O ₂	61	148-150	Yellow
3	N,N-dimethyl1-4-((4- nitrophenylimino) methyl)aniline	C ₁₅ H ₁₅ N ₃ O ₂	69	198-200	Yellow
4	4-chloro-N-(4-(dimethylamion)benzylidene)-2nitroaniline	C ₁₅ H ₁₄ N ₃ O ₂ Cl	51	222-224	brown
5	N-(chloro(4-(dimethylamino)phenyl)methyl)-N-(2nitrophenyl)acetamide	C ₁₇ H ₁₈ N ₃ O ₃ Cl	61	159-161	yellow
6	n-(chloro(4-(dimethylamino)phenyl)methyl)-N-(3nitrophenyl)acetamide	C ₁₇ H ₁₈ N ₃ O ₃ Cl	66	173-174	light Yellow
7	n-(chloro(4-(dimethylamino)phenyl)methyl)-N-(4nitrophenyl)acetamide	C ₁₇ H ₁₈ N ₃ O ₃ Cl	65	189-191	light brown
8	N-(chloro(4-(dimethylamino)phenyl)methyl)-N-(4-chloro-2-nitrophenyl)acetamide	C ₁₇ H ₁₇ N ₃ O ₃ Cl ₂	51	263-266	brown
9	diethyl2-((4-(dimethylamino)phenyl)N-(2-nitropheny) acetamido)methyl) malonate	C ₂₄ H ₂₉ N ₃ O ₇	51	210-212	brown
10	diethyl2-((4-(dimethylamino)phenyl)N-(3-nitrophenyl)acetamido)methyl)malonate	C ₂₄ H ₂₉ N ₃ O ₇	68	223-225	brown
11	diethyl2-((4-(dimethylamino)phenyl)N-(4-nitrophenyl) acetamido) methyl) malonate	C ₂₄ H ₂₉ N ₃ O ₇	70	236-238	brown

Synthesis of Some New Barbiturate Derivatives Via Schiff Bases

Ahlam J. Zaier

12	Diethyl 2-((N-(4-chloro-2-nitrophenyl)acetamido)(4-(dimethylamino) phenyl) methyl) malonate	$C_{24}H_{28}N_3O_7Cl$	43	277-280	Light brown
13	N-((4-(dimethylamino)phenyl)(2,4,6-trioxohexahydropyrimidin-5-yl)methyl)-n-(2-nitrophenyl) acetamide	$C_{21}H_{21}N_5O_6$	43	271-273	brown
14	N-((4-(dimethylamino)phenyl)(2,4,6-trioxohexahydropyrimidin-5-yl)methyl)-n-(3-nitrophenyl)acetamide	$C_{21}H_{21}N_5O_6$	63	241-243	brown
15	N-((4-(dimethylamino)phenyl)(2,4,6-trioxohexahydropyrimidin-5-yl) methyl)-N-(4-nitrophenyl)acetamide	$C_{21}H_{21}N_5O_6$	51	254-256	brown
16	N-(4chloro-2-nitrophenyl)-N-((4-(dimethylamino)phenyl)(2,4,6-trioxohexahydropyrimidin-5-yl)methyl)acetamide	$C_{21}H_{20}N_5O_6Cl$	49	243-295	light brown

Table No. (2) :FT.IR and UV.-VIS. spectra for compounds (1-4)

Comp. No.	$\nu(C-H)$ aromatic	$\nu(C-H)$ aliphatic	$\nu(C=N)$	$\nu(C-N)$	$\nu(C-NO_2)$	$\nu(C-Cl)$	UV.-Vis. λ_{Max} (nm)
1	3050	2845	1630	1245	1519 & 1342	-	243
2	3045	2843	1598	1240	1504 & 1334	-	242
3	3050	2845	1598	1243	1504 & 1373	-	248
4	3055	2850	1604	1245	1520 & 1340	817	238

Table No. (3) :FT.IR and UV.-VIS. spectra for compounds (5-8)

Comp. No.	$\nu(C-H)$ aromatic	$\nu(C-H)$ aliphatic	$\nu(C=O)$ amide	$\nu(C-N)$	$\nu(C-NO_2)$	$\nu(C-Cl)$	UV.-Vis. λ_{Max} (nm)
5	3050	2850	1635	1240	1545 & 1335	825	335
6	3050	2855	1630	1240	1540 & 1335	825	334
7	3060	2855	1630	1245	1540 & 1330	825	335
8	3065	2865	1630	1245	1540 & 1335	830	335

Synthesis of Some New Barbiturate Derivatives Via Schiff Bases

Ahlam J. Zaier

Table No. (4) :FT.IR and UV.-VIS. spectra for compounds (9 -12)

Comp. No.	$\nu(\text{C-H})$ Aromatic	$\nu(\text{C-H})$ Aliphatic	$\nu(\text{C=O})$ amide	$\nu(\text{C=O})$ ester	$\nu(\text{C-O-C})$	$\nu(\text{C-N})$	$\nu(\text{C-NO}_2)$	$\nu(\text{C-Cl})$	UV.-Vis. λ_{max} (nm)
9	3050	2845	1665	1745	1240 1125	1235	1540 & 1335	--	371 340
10	3045	2840	1675	1740	1240 1130	1235	1540 & 1330	-	391 344
11	3045	2840	1670	1745	1240 1130	1235	1540 & 1330	-	411 344
12	3055	2843	1680	1745	1240 1135	1235	1545 & 1330	820	400 343

Table No. (5) :FT.IR and UV.-VIS. spectra for compounds (13-16)

Comp. No.	$\nu(\text{C-H})$ Aromatic	$\nu(\text{C-H})$ aliphatic	$\nu(\text{N-H})$	$\nu(\text{C=O})$ amide	$\nu(\text{C=O})$ lactam	$\nu(\text{C-N})$	$\nu(\text{C-NO}_2)$	$\nu(\text{C-Cl})$	UV.-Vis. λ_{max} (nm)
13	3045	2845	3275	1675	1680	1240	1540 & 1330	-	935 374
14	3040	2845	3260	1660	1680	1240	1540 & 1335	-	983 377
15	3040	2845	3260	1665	1675	1235	1540 & 1345	-	920 304
16	3035	2865	3265	1675	1585	1245	1540 & 1335	820	884 300

Synthesis of Some New Barbiturate Derivatives Via Schiff Bases

Ahlam J. Zaier

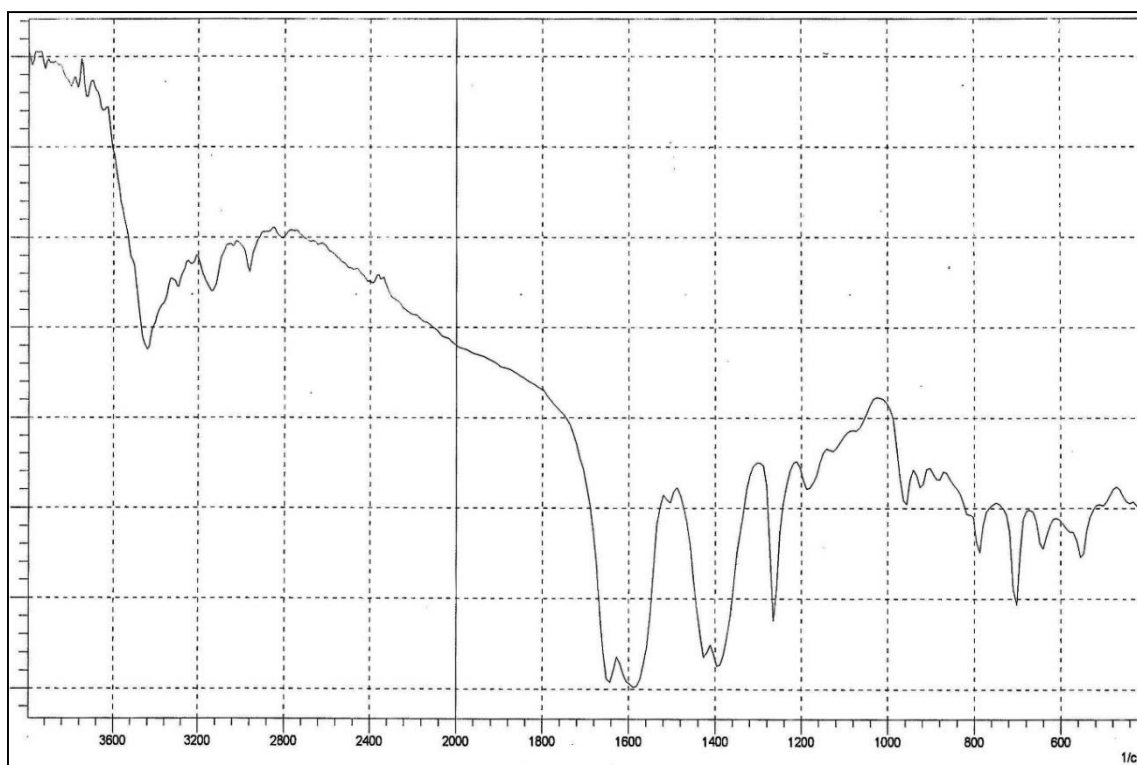


Figure No.(1): FT-IR spectra of compound (1)

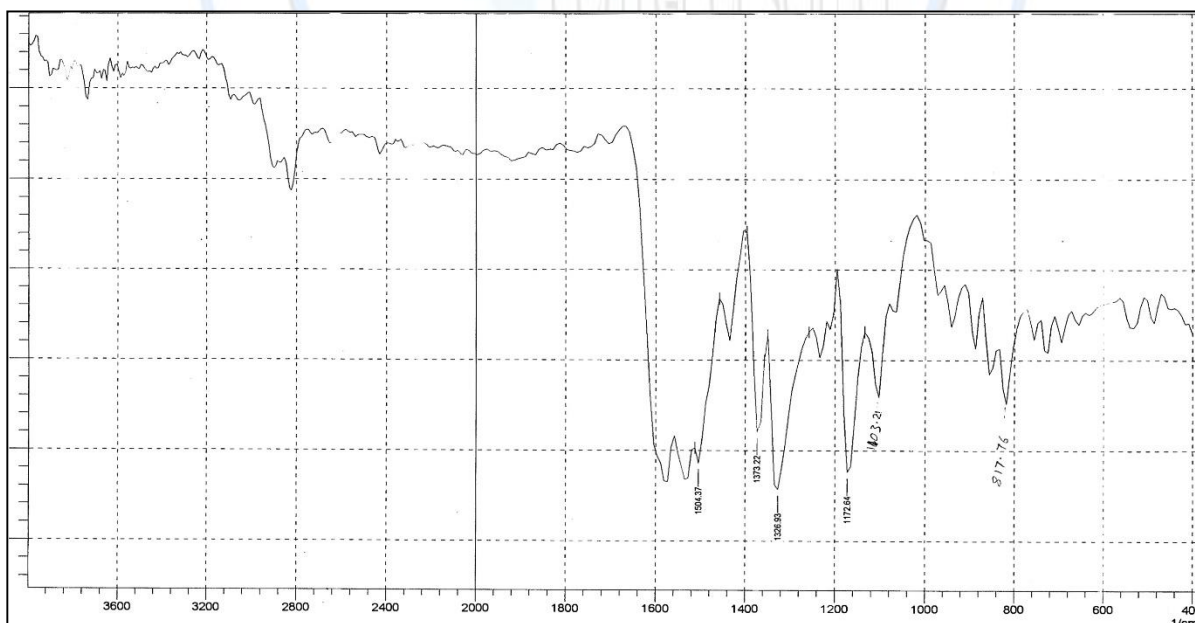


Figure No.(2): FT-IR spectra of compound (2)

Synthesis of Some New Barbiturate Derivatives Via Schiff Bases

Ahlam J. Zaier

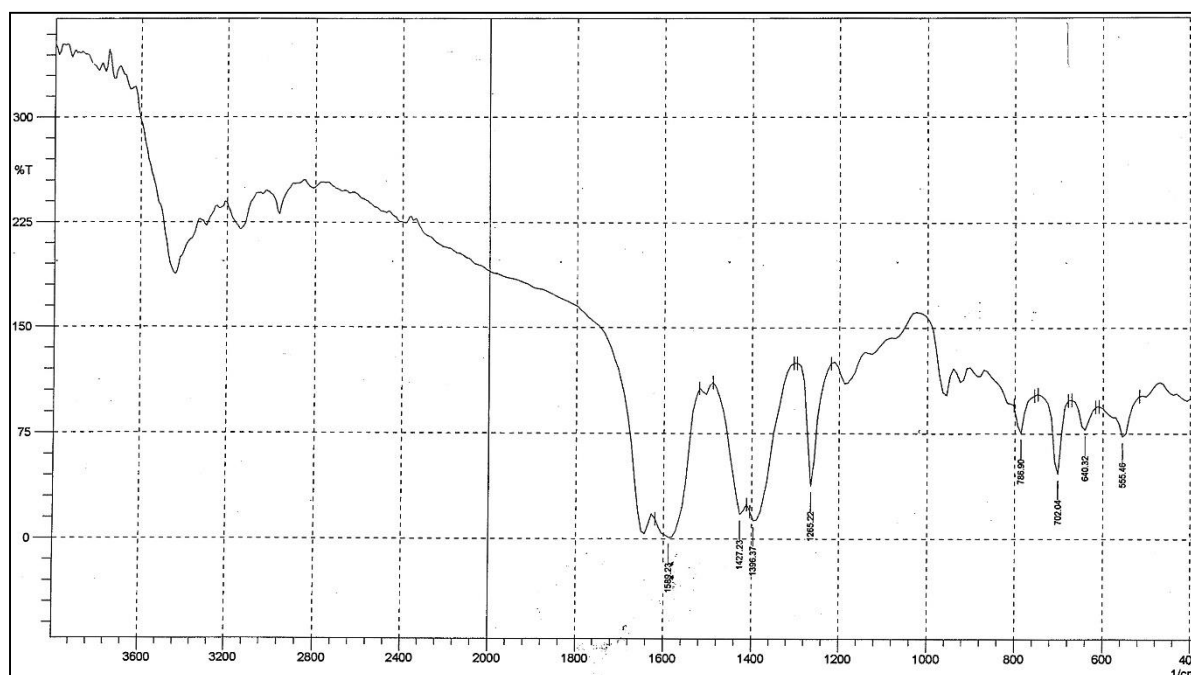


Figure No.(4): FT-IR spectra of compound (4)

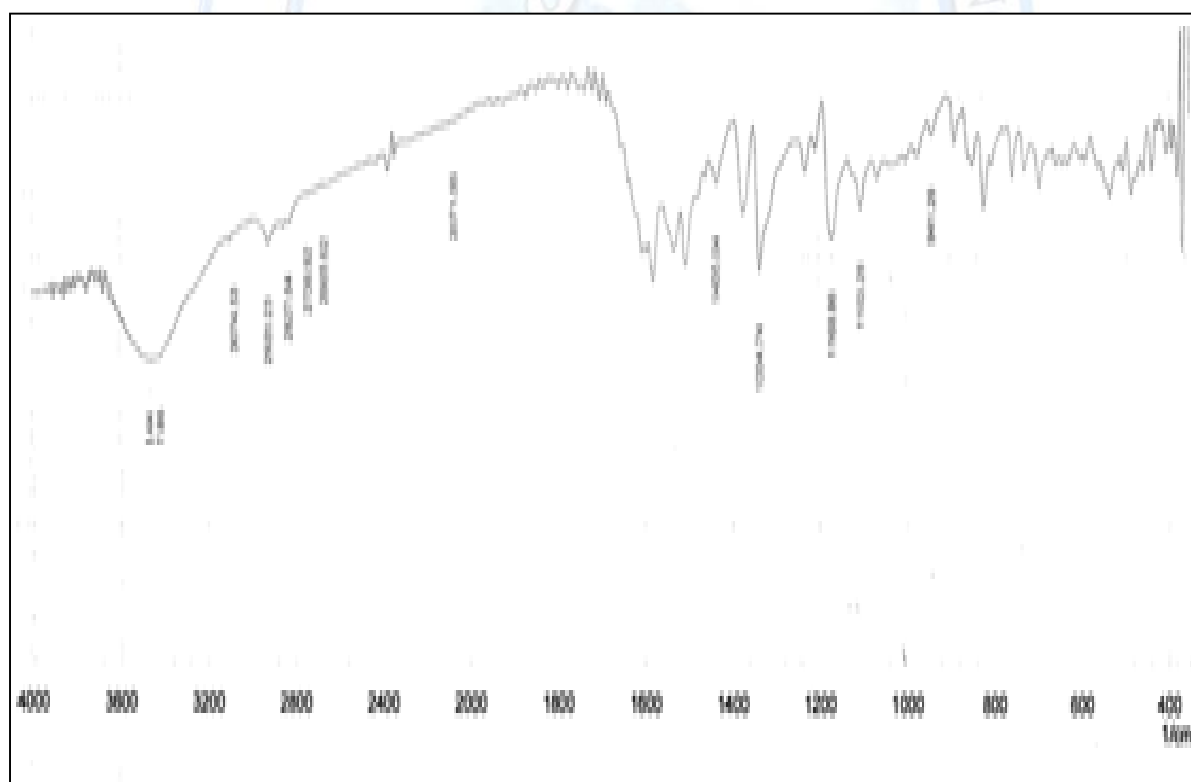


Figure No.(5): FT-IR spectra of compound (5)

Synthesis of Some New Barbiturate Derivatives Via Schiff Bases

Ahlam J. Zaier

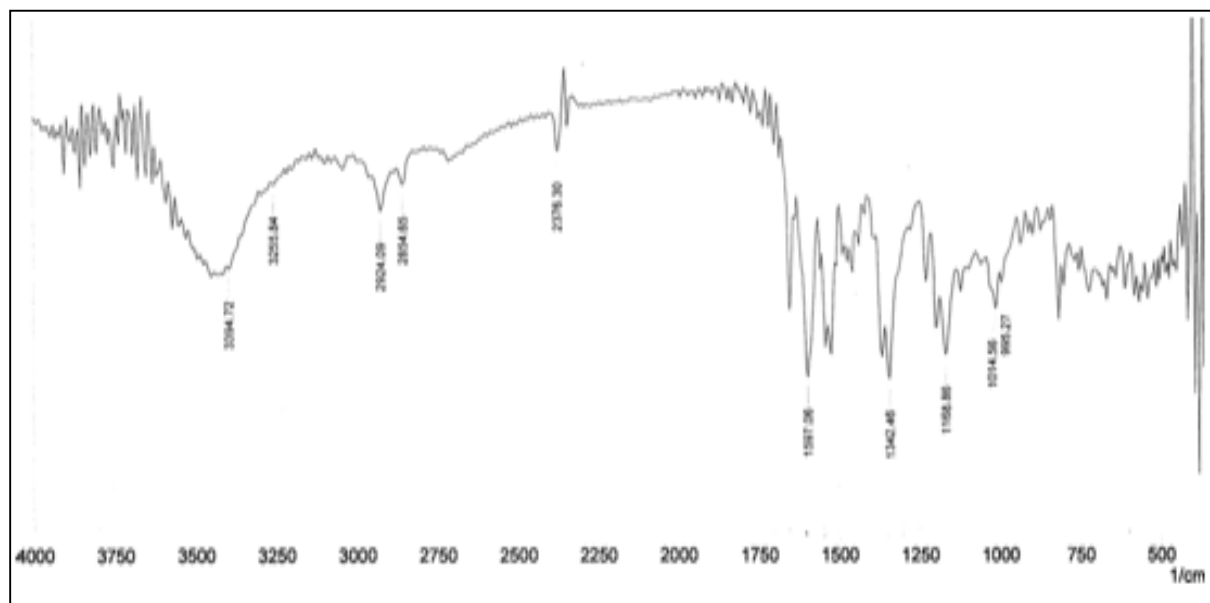


Figure No.(6): FT-IR spectra of compound (6)

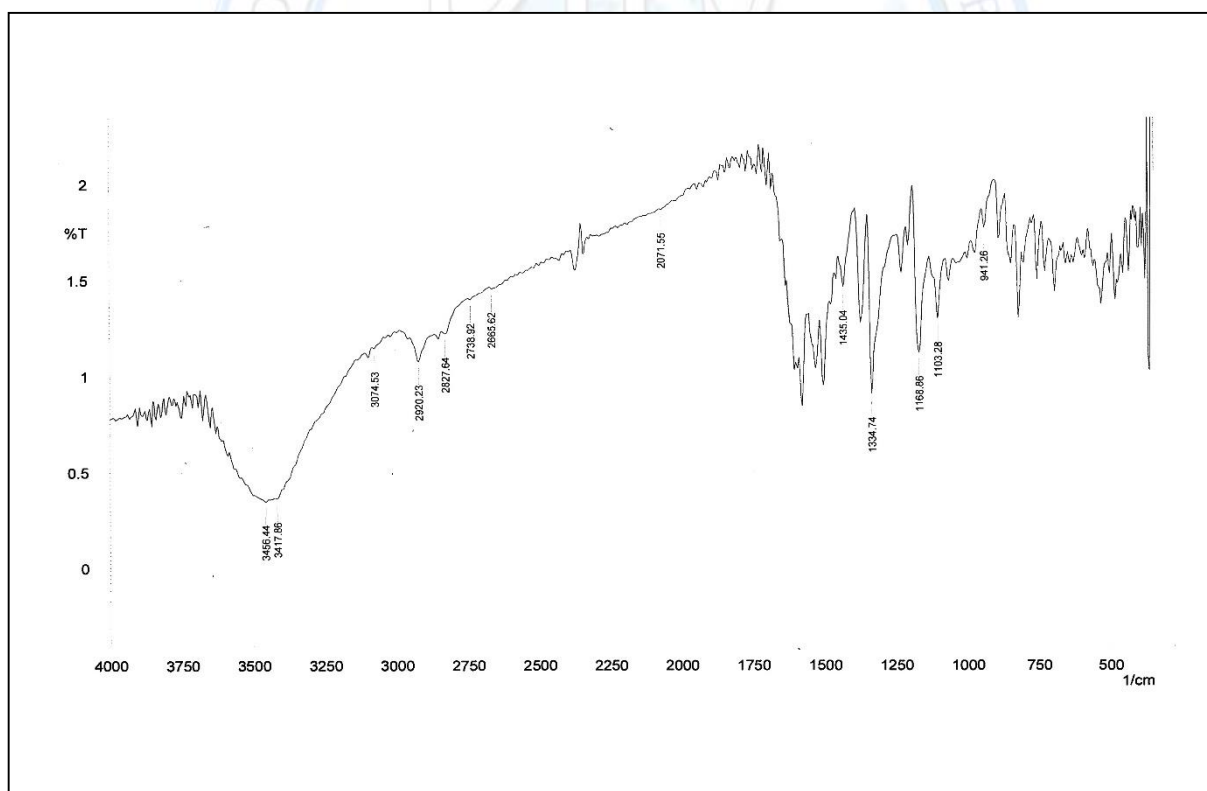


Figure No.(7): FT-IR spectra of compound (7)

Synthesis of Some New Barbiturate Derivatives Via Schiff Bases

Ahlam J. Zaier

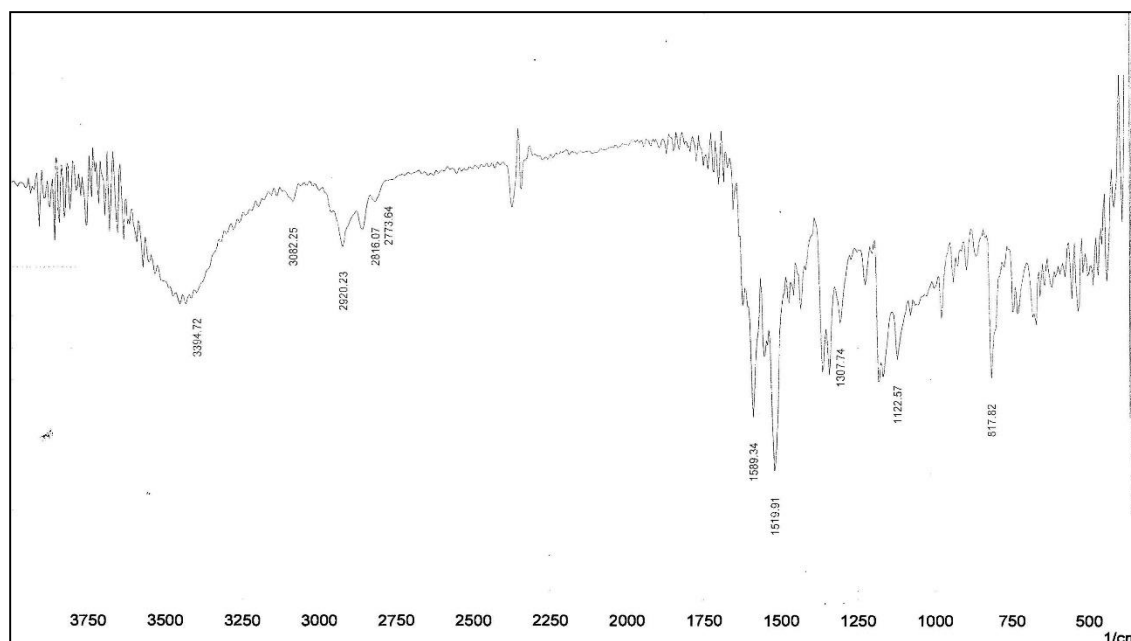


Figure No.(8): FT-IR spectra of compound (8)

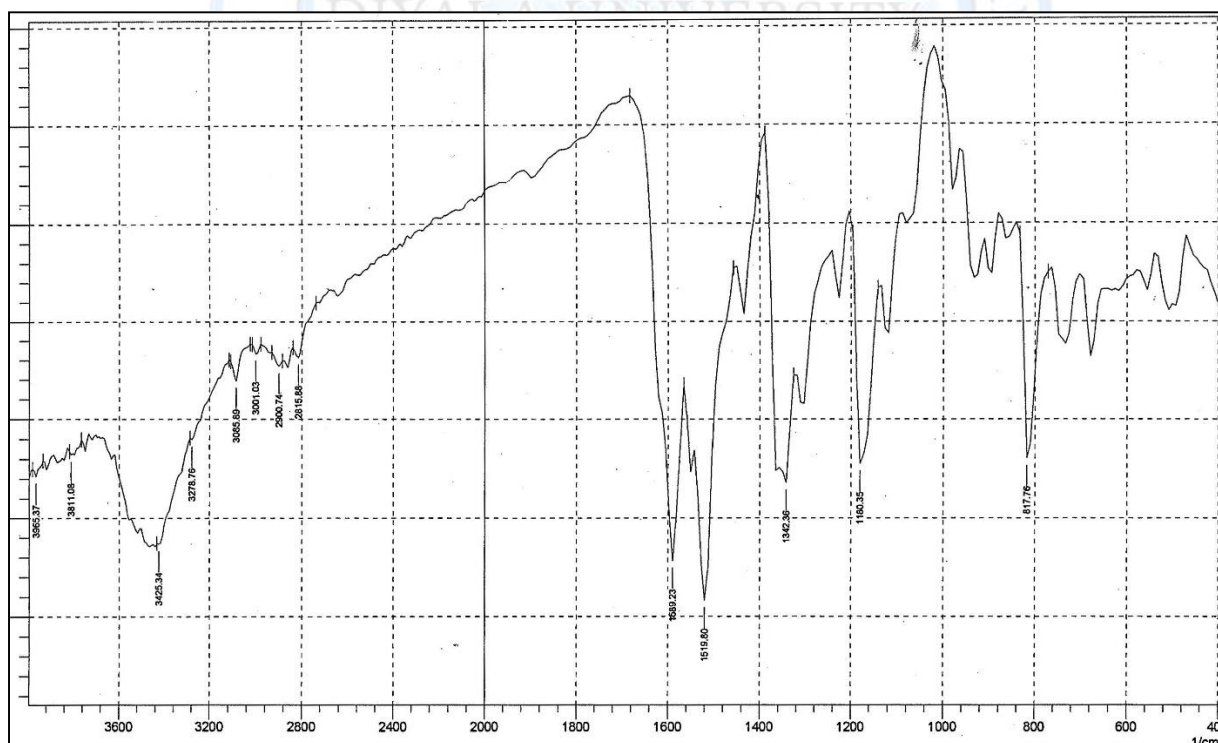


Figure No.(9): FT-IR spectra of compound (9)

Synthesis of Some New Barbiturate Derivatives Via Schiff Bases

Ahlam J. Zaier

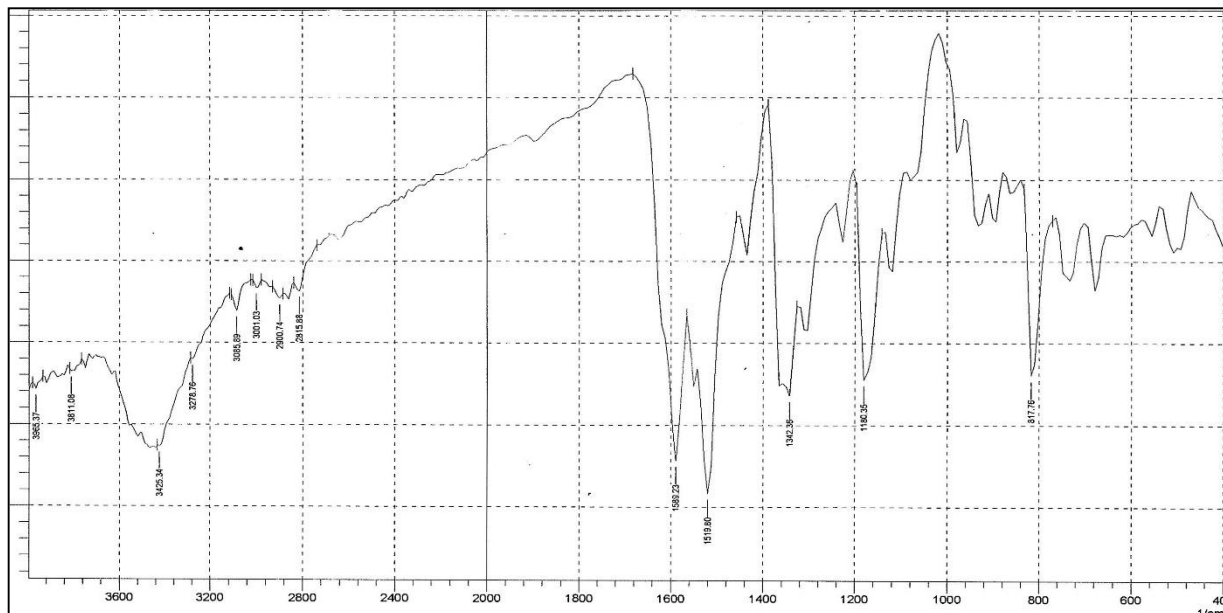


Figure No.(10): FT-IR spectra of compound (10)

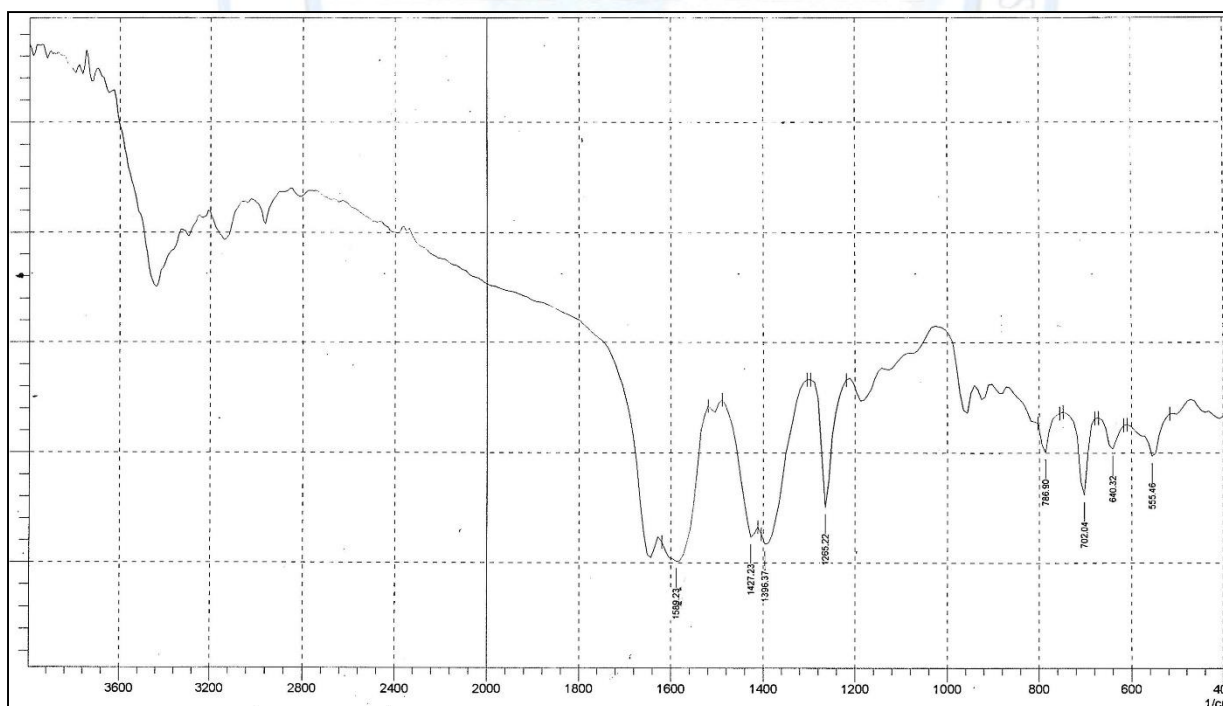


Figure No.(11): FT-IR spectra of compound (11)

Synthesis of Some New Barbiturate Derivatives Via Schiff Bases

Ahlam J. Zaier

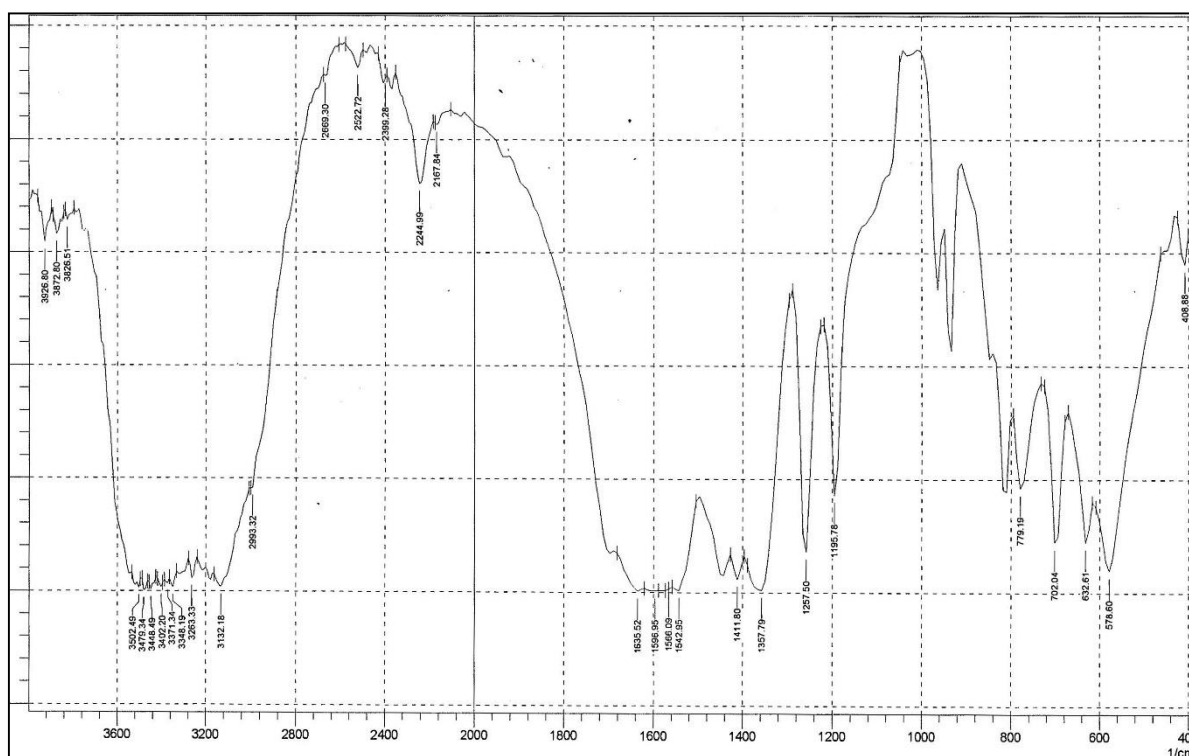


Figure No.(12): FT-IR spectra of compound (12)

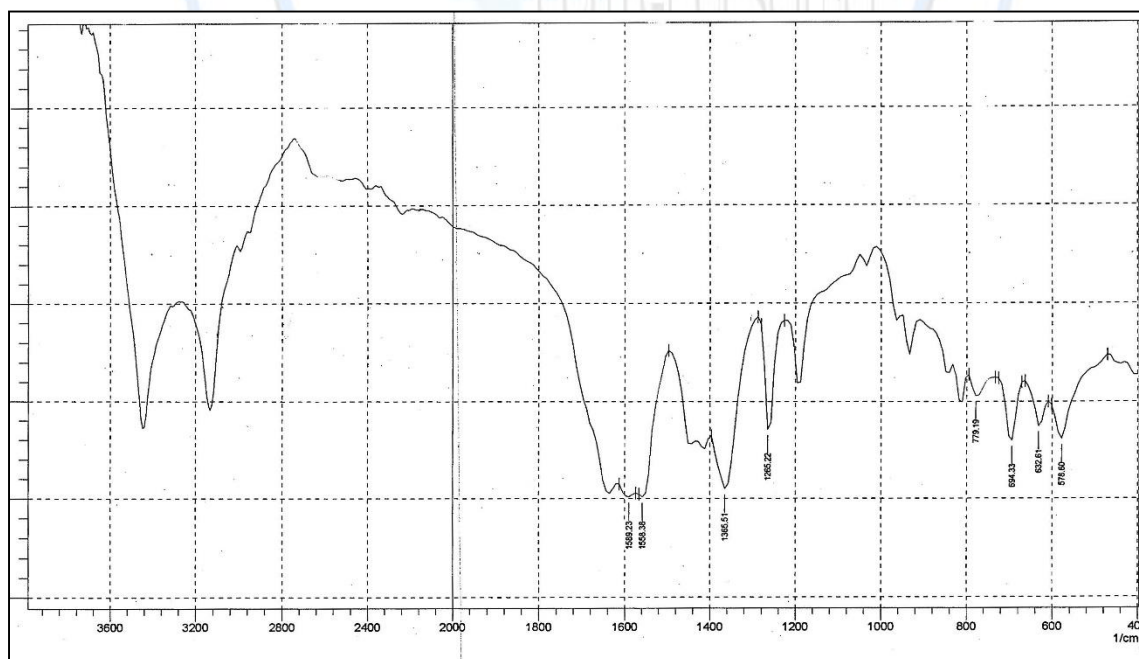


Figure No.(13): FT-IR spectra of compound (13)

Synthesis of Some New Barbiturate Derivatives Via Schiff Bases

Ahlam J. Zaier

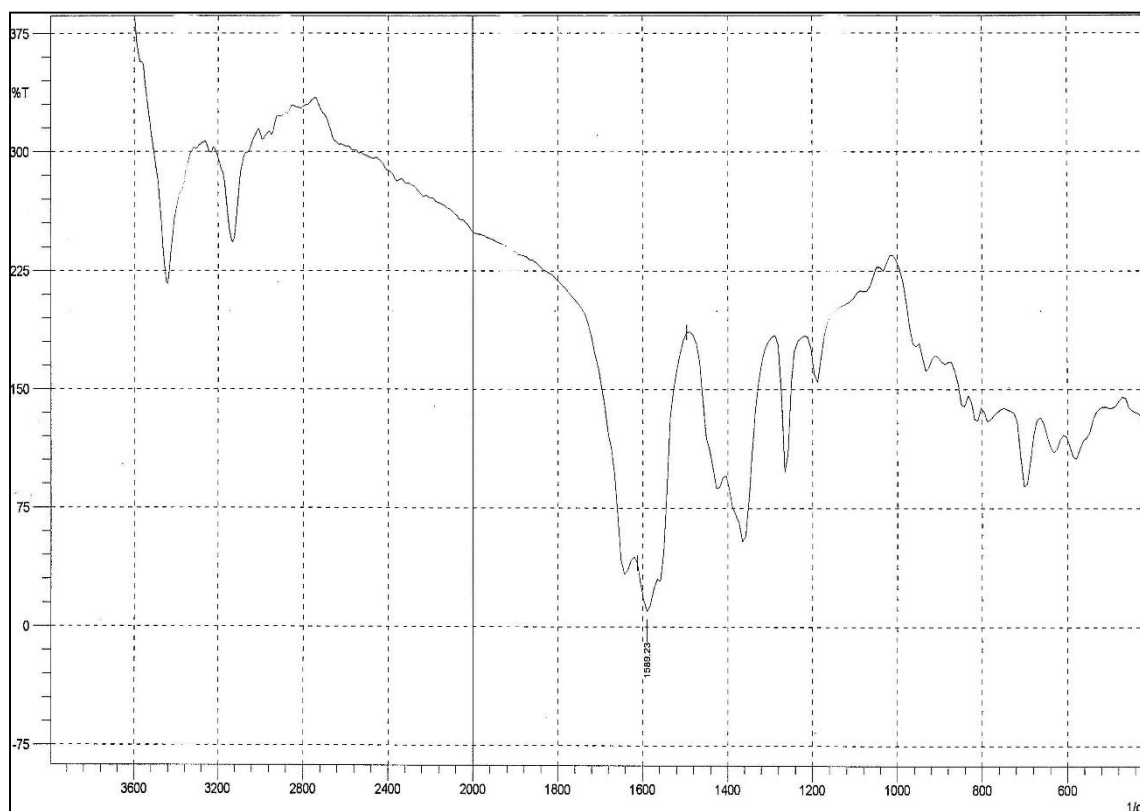


Figure No.(14): FT-IR spectra of compound (14)

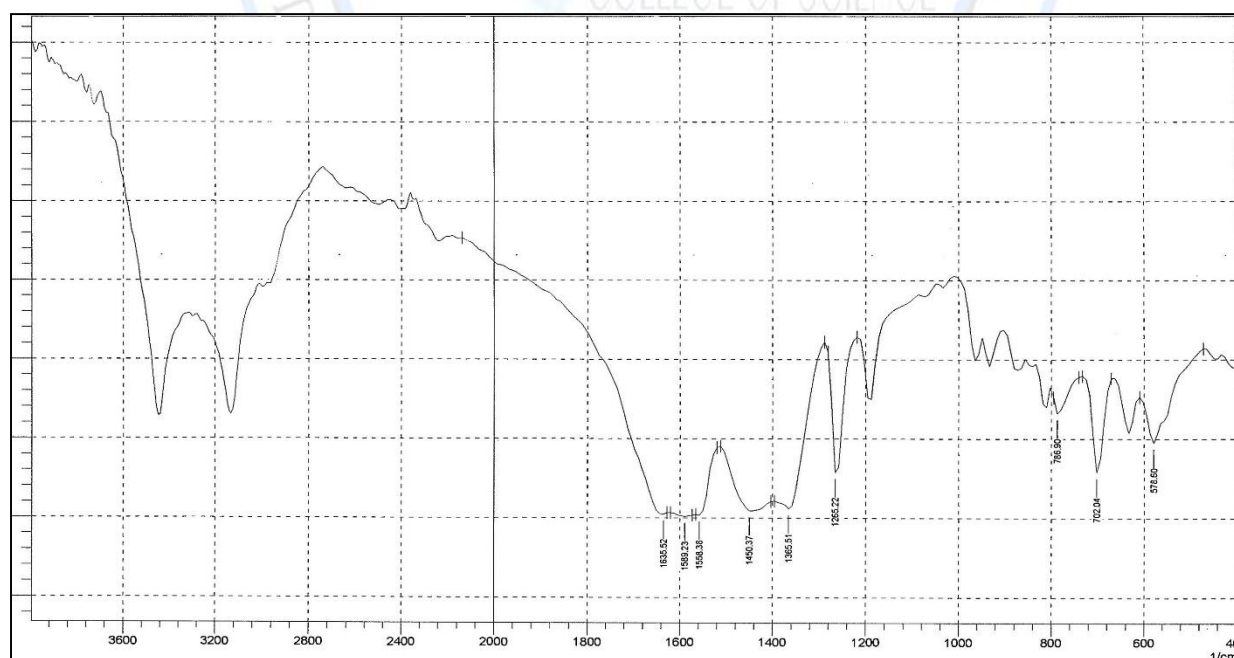


Figure No.(15): FT-IR spectra of compound (15)

Synthesis of Some New Barbiturate Derivatives Via Schiff Bases

Ahlam J. Zaier

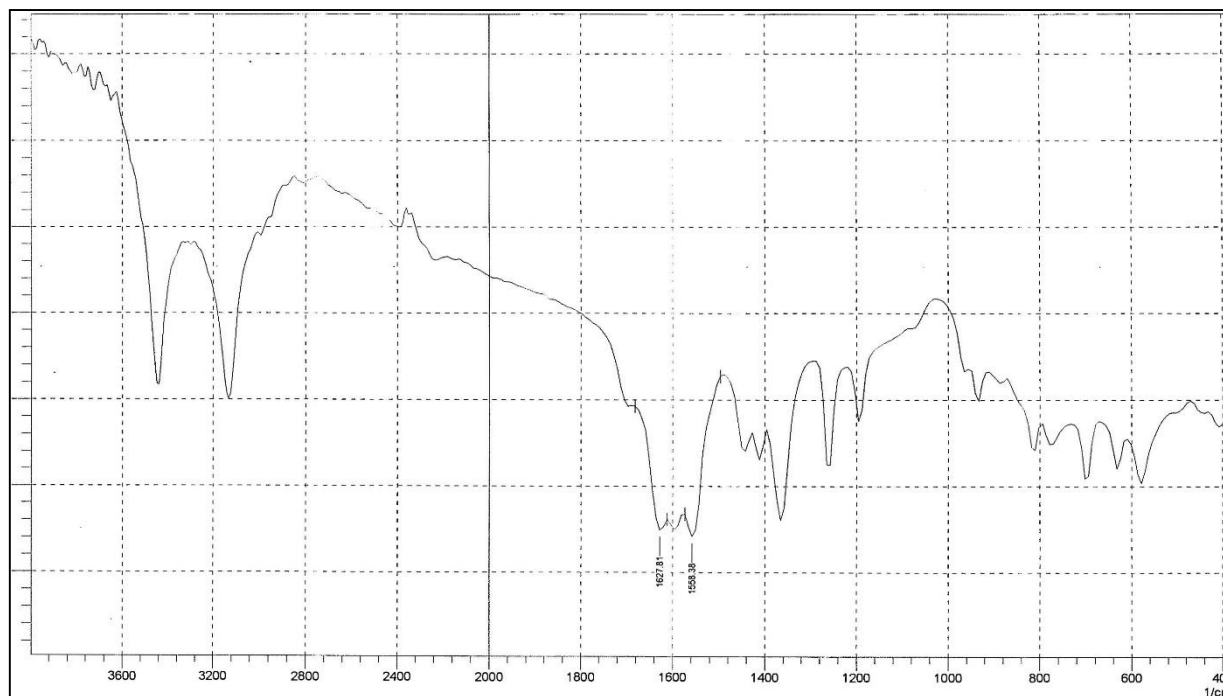


Figure No.(16): FT-IR spectra of compound (16)