*Available online at* www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

**Der Pharma Chemica, 2016, 8(6):40-48**
*(http://derpharmachemica.com/archive.html)*

# Synthesis and Biological Study of Hetero (Atoms and Cycles) Compounds

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**ABSTRACT**

*Our study is concerned with synthesis of (five , sixandseven ) –membered cycles which were prepared from reaction between di ketone compounds like( di phenyl propyl-1,3-di ketone) with ethyl methyl ketone to produce alkene compound containing di ketone groups, which reacts with di amine compounds through closure and cyclization reactions to give various cyclic compounds containing di nitrogen atoms in same cycle like diazepine as seven membered ring and diazine as six membered ring and other various cycles. The structure of compounds [1-10] have been characterized by melting points, TLC and spectral analysis (FT.IR , H.NMR, C.H.N ,$^{13}$C.NMR -Spectra ) , then study of antimicrobial activity.*

**Keywords**: oxazepam, diazepam, anti microb, diazine, Micheal reaction , $^{13}$C.NMR -Spectra.

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## INTRODUCTION

Nitrogen heterocycles are a special interest, one of the most important activities are the effective of anti-viral ,anti-microbial drug. Such as diazepam, oxazepam , which are found to be associated with various biological activities .

Hetero cyclic compounds containing more than one of nitrogen atoms have excellent biological activities which have attracted many researches attention in the last year. These compounds, like the other members of the benzodiazepine series, have been widely applied as therapeutic agents due to their anti-cancer, cardiotonic ,anti inflammatory properties.

Various diaze cycles are well known to possess physiological activities, are widely used in pharmaceutical drugs as muscle relaxant, hypotonic, analgesic.

In the recent years, there has been a growing interest in cyclic compounds thanks to the development of a number of efficient synthetic methods that make their preparation more hetero cyclic compounds.

This reaction supported on micheal addition through reaction between α–carbon atom (bearing hydrogen atom) adjacent carbonyl group with carbonyl group in other compound, after that, cyclization step with di amine compounds to yield diaze compounds [2-10].

## MATERIALS AND METHODS

All chemicals used (purity 99.95 %) , FT.IR- spectra: were recorded on shimadzu 8300 , KBr -disc , H.NMR-spectra & (C.H.N)–analysis , $^{13}$C.NMR -Spectra were recorded in Canada ., melting points were determined in open capillary tubes by electro thermal 9300 LTD , U.K .

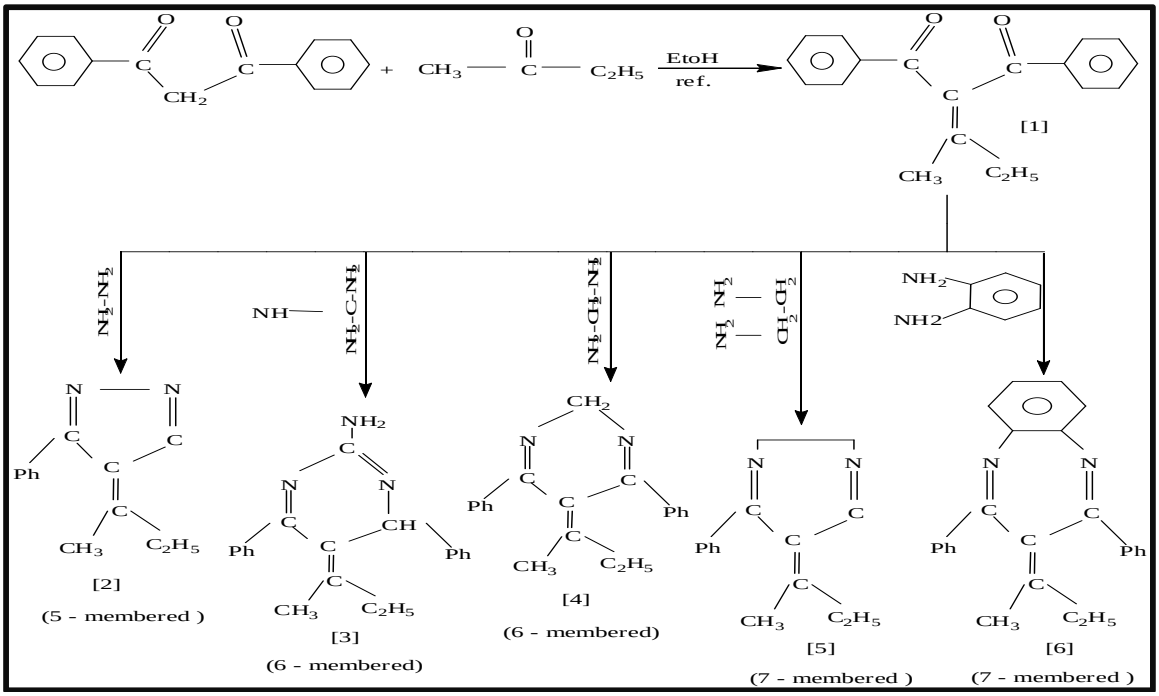
**Synthesis of compound [1] :**
A mixture of benzoyl acetophenone (0.1 mole , 22.4 gm) with 2 –butanone (0.1 mole , 7.2 gm) were reacted under reflux for (2hrs) in presence absolute ethanol , the reaction mixture poured on cold water , precipitate was filtered & recrystallized from ethanol to give compound [1] %89 .

**Synthesis of compounds [2-6] :**
Equimolar amounts (0.01 mole ) of compound [1] (2.7 g) reacted with one of [(0.32 g of hydrazine ) , (0.95 gm of quinidine) , ( 0.46 g of methylene di amine ), ( 0.60 g of ethylene di amine ), ( 1.08 g of phenylene di amine )] were heated under reflux for (3-6) hours in presence of absolute ethanol, after that , the precipitate was filtered & recrystallized from ethanol to yield compounds [2-6] respectively,(86,87,85,86,87)% respectively .

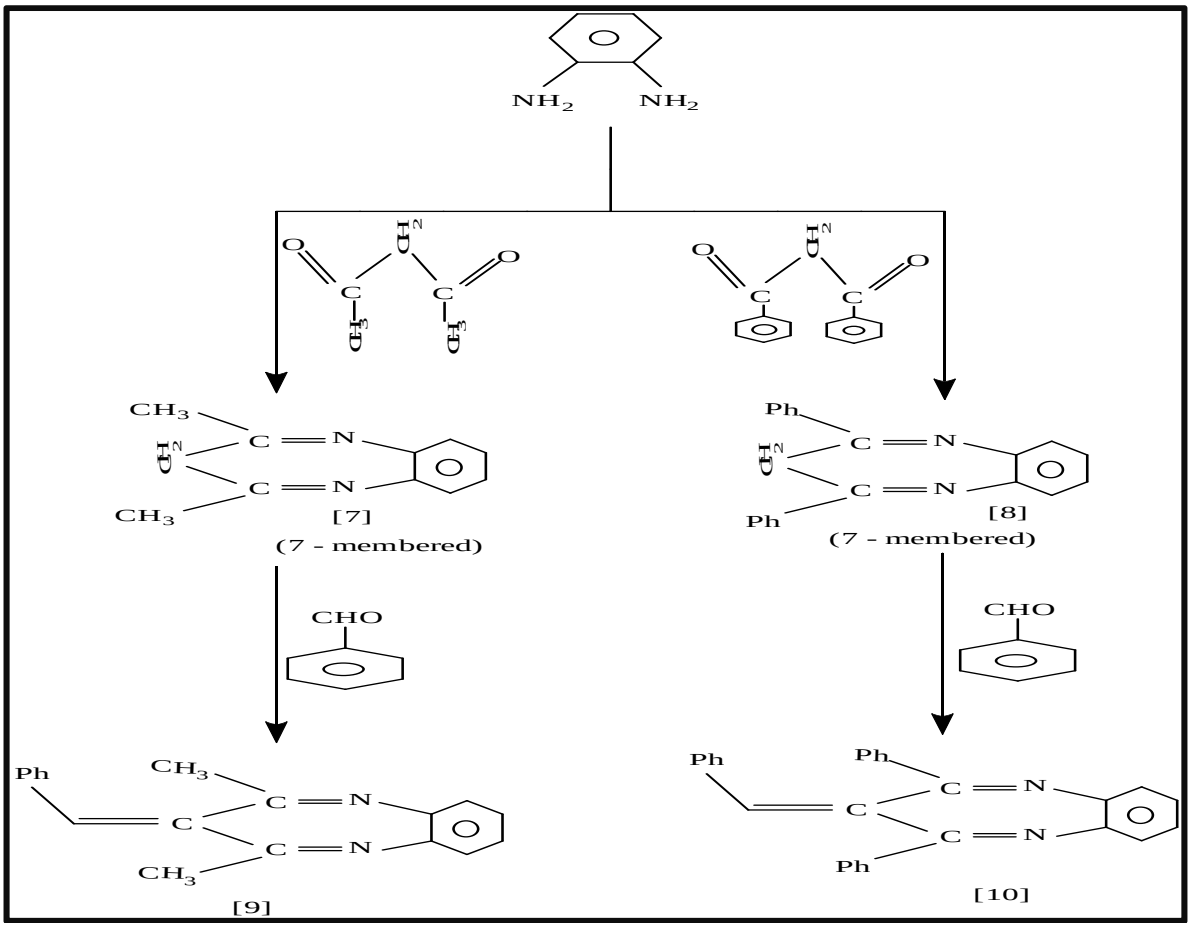
**Synthesis of compounds [7,8] :**
Equimolaramounts (0.1 mole ) of phenylene di amine (10.8 g) was reacted with one of [(10 g of acetyl acetone) ,(22.4 g of benzoyl acetophenone )]under reflux in presence of absolute ethanol , the precipitate was filtered & recrystallized from ethanol to give (85 , 87) % of compounds [ 7,8 ] respectively .

**Synthesis of compounds [ 9,10 ] :**
A mixture of equimolar amounts (0.01 mole ) of benzaldehyde (12 mole) with one of {(1.7 g of compound [7] ) ,( 2.9 g of compound [8] ) } were reacted in basic media , with ethanol as a solvent , the precipitate filtered to yield (88, 86) % of compounds [9,10] respectively .

**Scheme (1) :synthesis of compounds [1-6]**



**Scheme (2) :synthesis of compounds [7-10]**




## RESULTS AND DISCUSSION

The formation of compound [1] proceed via micheal addition followed by cyclization reaction with various di amine compounds to produce series of hetero cyclic compounds [2-10] from (5,6,7) –membered ring .

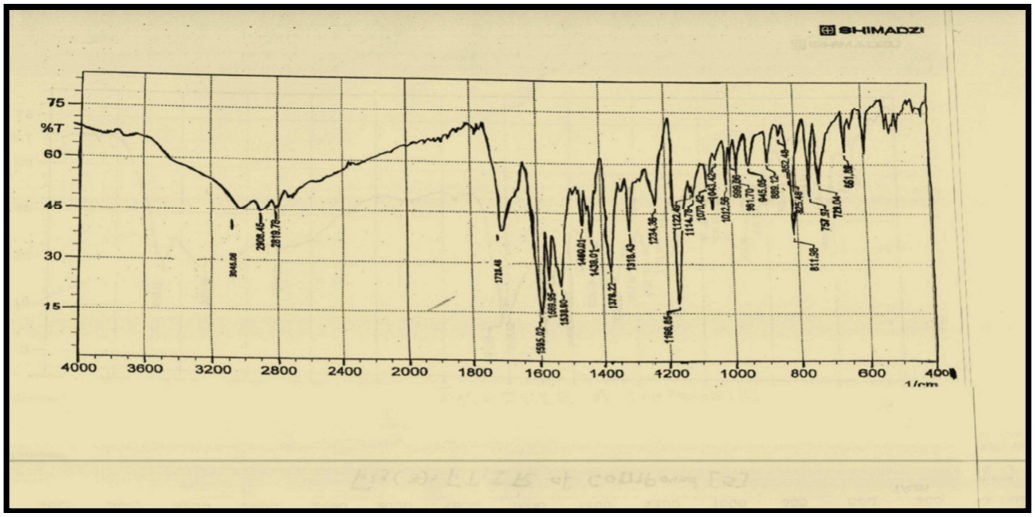
The structures of these compounds were confirmed by {FT.IR ,H.NMR ,$^{13}$C.NMR ,(C.H.N)–analysis}.

**Table (1) : (FT.IR) –data (cm$^{-1}$) of compounds [1-10]**

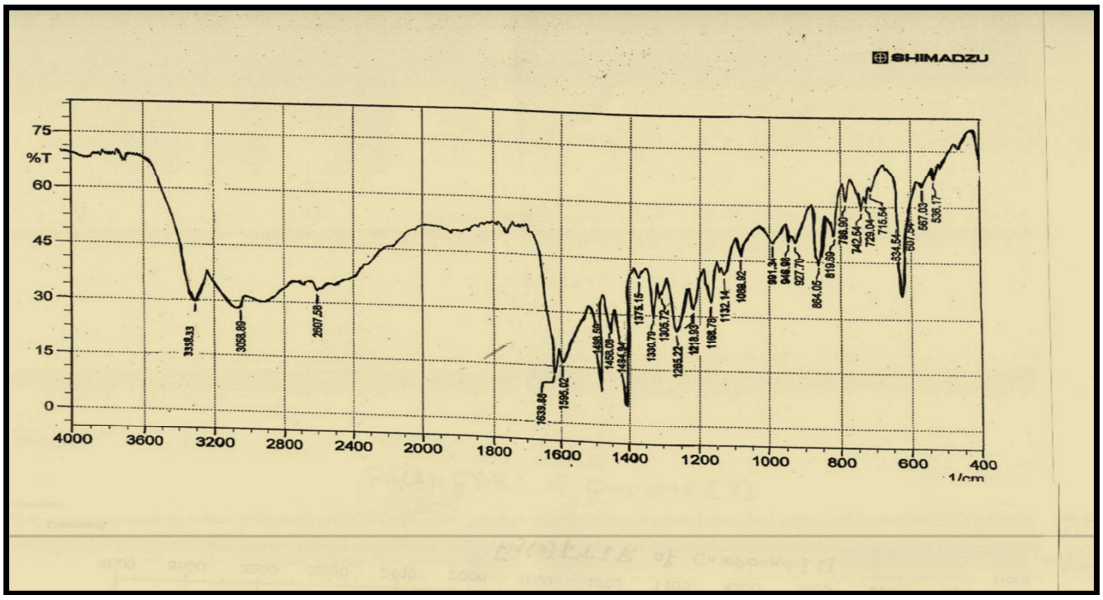
| Comp. No. | I.R$_{(KBr)}$ (Important Group ) |
|---|---|
| **[1]** | (CO) carbonyl of ketone :1728 ,(CH) aliphatic :2908 ,(HC=C) alkene :3046. |
| **[2]** | (C=N) imine group :1616 ,(CH) aliphatic :2930 ,(C=C)alkene :3085 ,(C–N) endocycle :1520 . |
| **[3]** | ($NH_2$) amine :3358 ,(C=N) imine group :1639 ,(C-N) endocycle:1498 ,(HC=C) alkene : 3058 ,(CH) aliphatic : 2900 . |
| **[4]** | (C=N) imine group :1625 ,(C–N) endocycle :1540 ,(CH) aliphatic :2935 ,(HC=C) alkene :3075 . |
| **[5]** | (C=N) iminegroup :1622 , (C–N) endocycle : 1535 , (CH) aliphatic : 2908 , (HC=C) alkene : 3025 . |
| **[6]** | (C=N) imine group :1630 ,(C–N) endocycle : 1538 ,(CH) aliphatic : 2940 , (HC=C) :3097. |
| **[7]** | (C=N) imine group :1622 (C-H) aliphatic : 2920 ,(C–N) endocycle : 1543 |
| **[8]** | (C=N) imine group :1627, (C-H) aliphatic : 2945 ,(C–N) endocycle : 1552 |
| **[9]** | (C=N) imine group :1622 ,(CH) aliphatic :2908 ,(C–N) endocycle :1548 ,(HC=C) alkene :3025 . |
| **[10]** | (C=N) imine group :1620 ,(CH) aliphatic :2972 ,(C–N) endocycle :1533 ,(HC=C) alkene :3095 . |

**Their FT.IR–spectrum ,** showed an absorption band at (1728)cm$^{-1}$ due to (-CO-) carbonyl of ketone in compound [1] , which disappears & other bands appeared at {(1616-1639) , (3025-3097)}cm$^{-1}$ due to (C=N) imine group

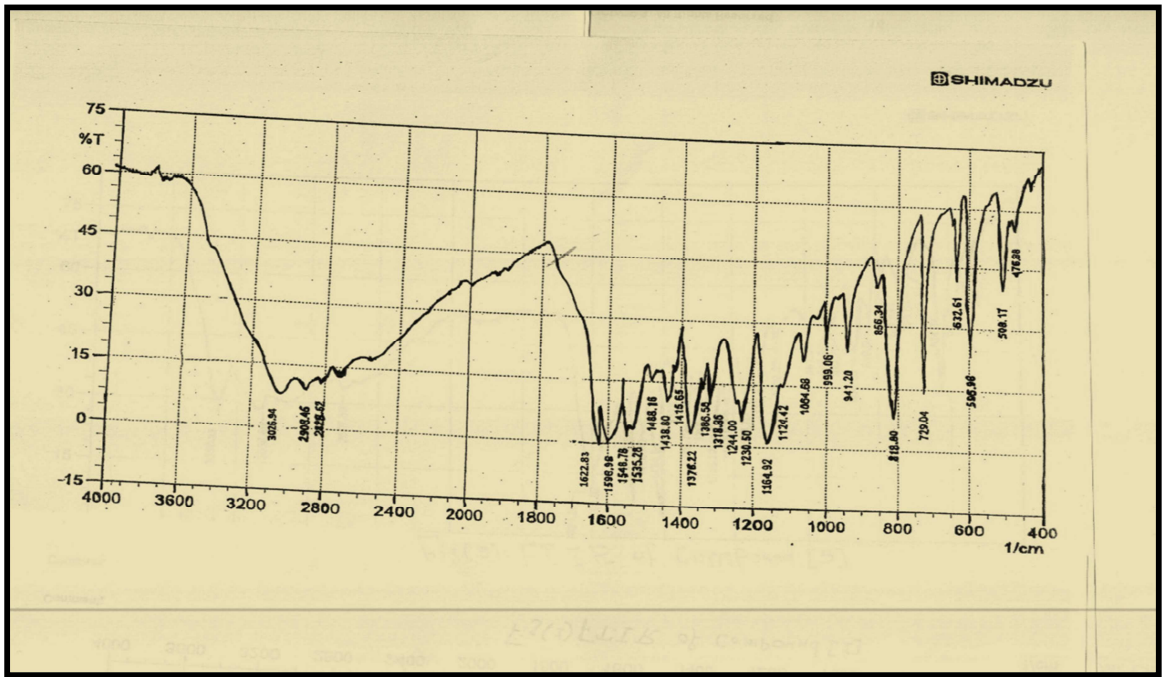
&(C=C) alkene , respectively in compounds [2-10] , absorption band at (3358)$cm^{-1}$ due to ($NH_2$) amine group ( Seema ., AnithaEet al) in compound [3] , and other bands are summarized in table (1) and figures(1-4) .



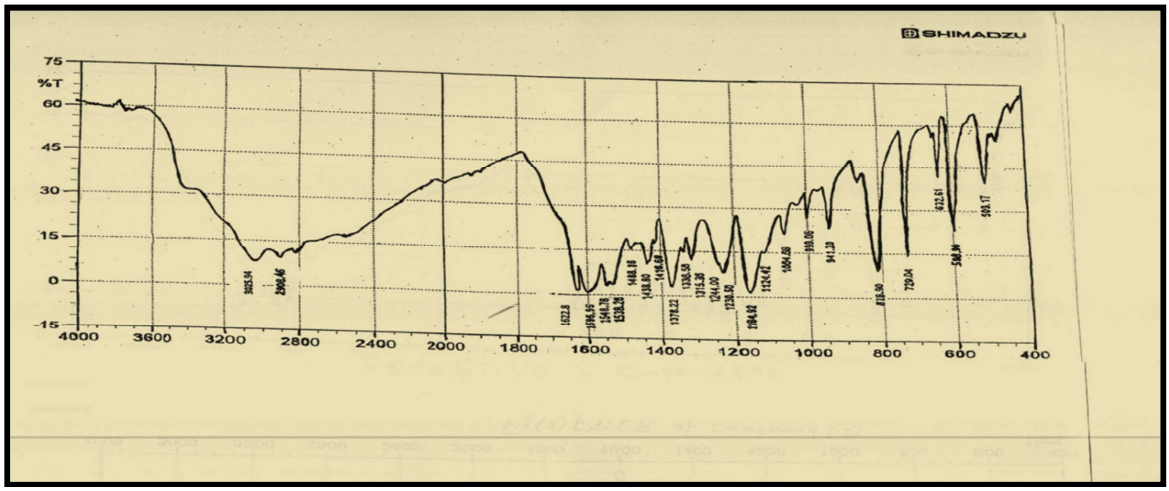

**Fig(1). FT.IR of Compound [1 ]**




**Fig(2). FT.IR of Compound [3 ]**



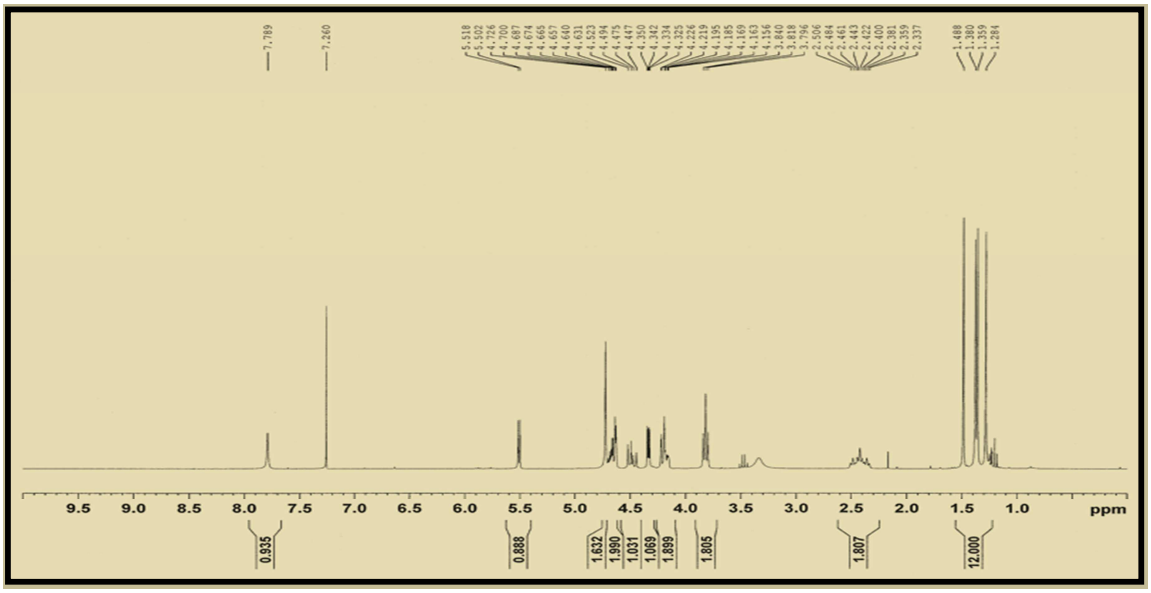

**Fig(3). FT.IR of Compound [5 ]**



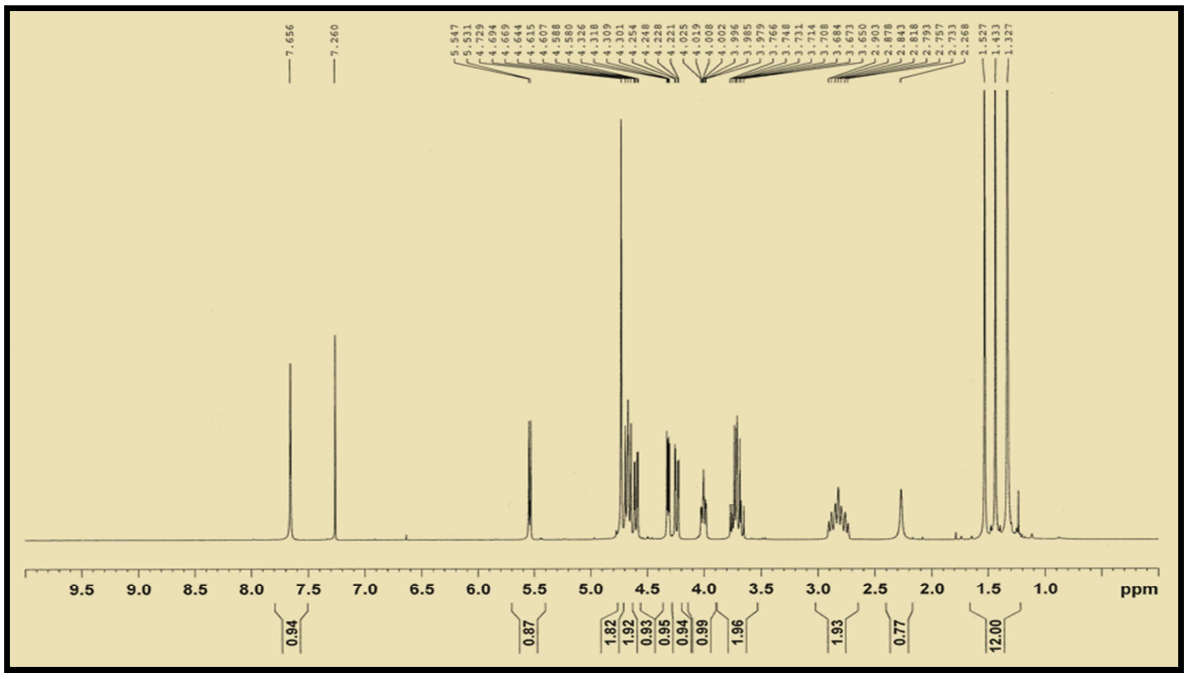

**Fig(4). FT.IR of Compound [9 ]**

**Table (2) : $^1$H.NMR –data ($\delta_{ppm}$) of compounds [1-10]**

| Comp. No. | H.NMR $_{(DMSO)}$ (Importance Peaks ) |
|---|---|
| **[1]** | 1.87(=C-$CH_3$) ; 1.76 ,2.78 (=$CH_2$–$CH_3$) ,7.28–7.67 (ph-) protons of phenyl rings . |
| **[2]** | 1.82 (=C-$CH_3$) ; 1.95 , 2.04 (=$CH_2$–$CH_3$) ; 6.75 –7.40 (ph-) protons of phenyl rings . |
| **[3]** | 4.6 (-$NH_2$) ; 2.78 ($CH_3$) ; 2.25 . 2.35 (-$CH_2$–$CH_3$) , 3.77 (N–CH ) endo cycle ; 6.61 – 7.60 (ph-) protons of phenyl rings . |
| **[4]** | 3.48 (N–$CH_2$–N) ; 2.10 (=C-$CH_3$) , 1.94 , 2.05 (=$CH_2$–$CH_3$) ; 6.76–7.48 (ph-) protons of phenyl rings . |
| **[5]** | 4.20, 3.80 , 3.76 (N–$CH_2$–$CH_2$–N) ; 1.98 (=C-$CH_3$) ; 1.86 , 4.02 (=$CH_2$–$CH_3$); 6.58–7.63 (Ph-) protons of phenyl rings . |
| **[6]** | 1.78 (=C-$CH_3$) ; 1.93 , 4.09(=$CH_2$–$CH_3$) ;6.63–7.37 (Ph-) protons of phenyl rings. |
| **[7]** | 2.02 (N=C-$CH_3$) ; 1.90 (N=C-$CH_2$) ; 7.02–7.39 (Ph-) protons of phenyl rings . |
| **[8]** | 1.97 (N=C-$CH_2$) ; 6.66–7.44 (Ph-) protons of phenyl rings . |
| **[9]** | 2.72 (N=C-$CH_3$) ; 4.36 (CH=C) alkene ., 7.16–7.58 (Ph-) protons of phenyl rings |
| **[10]** | 4.89 (CH =C) alkene ; 6.84–7.58 (Ph-) protons of phenyl rings . |




**Fig(5). $^{1}$H.NMR of compound [3]**

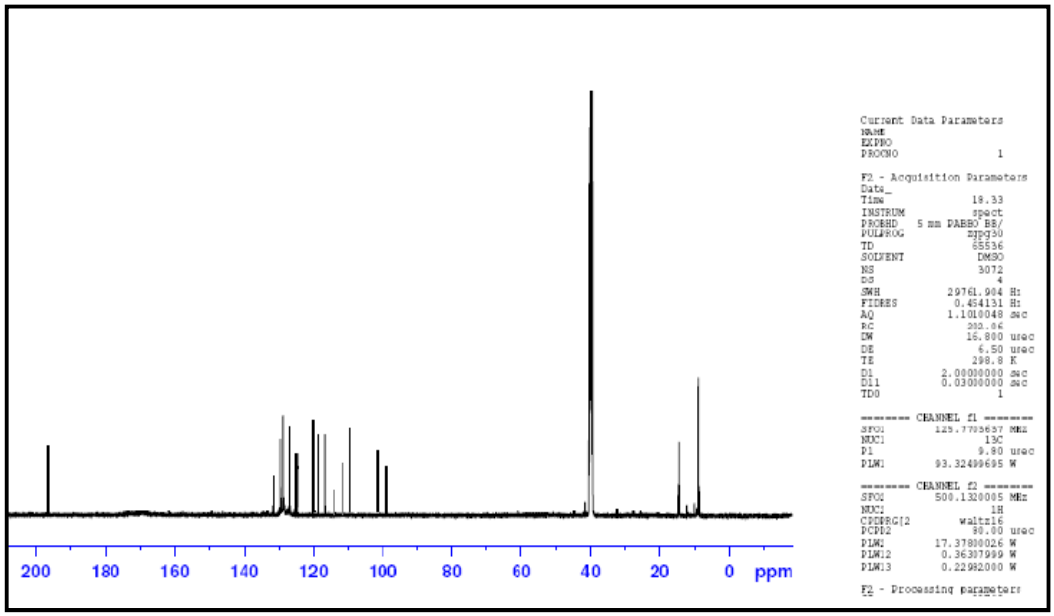



**Fig(6). $^{1}$H.NMR of compound [5]**

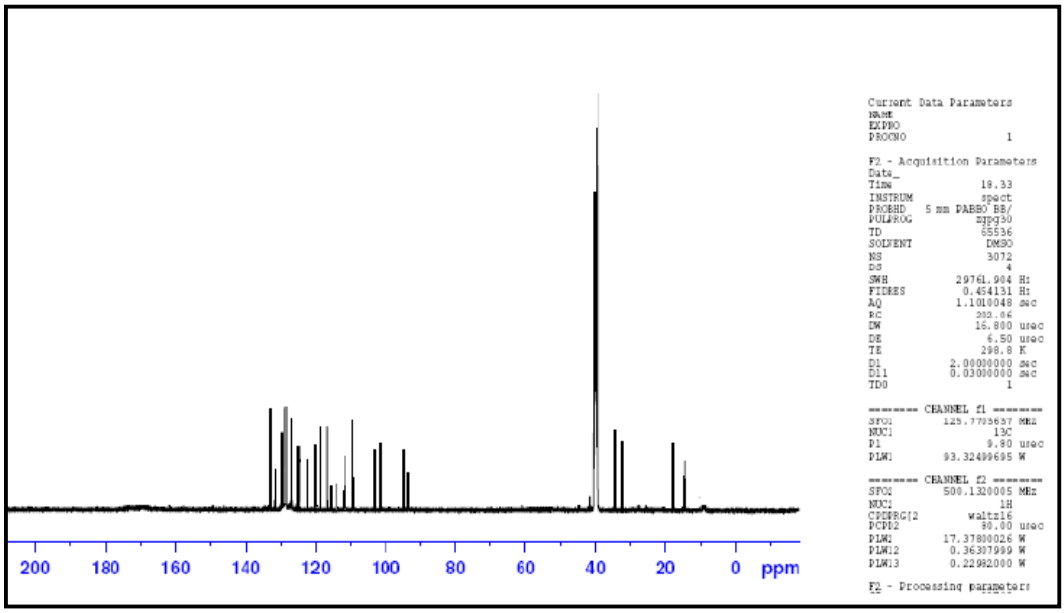
**Their $^{1}$H.NMR–spectra** showed important peaks at ϭ {(1.27–1.95 ) ,(1.76–2.78), (6.56–7.67)} due to protons of {($CH_3$) methyl group[13] , ($C_2H_5$) ethyl group , (ph-) phenyl groups} respectively in compounds [1-10] , peaks at ϭ4.6 , ϭ 3.77 due to (-$NH_2$ , N–NH) in compound [3] , peaks at (3.48) and (3.20 , 3.42) due to {(N–$CH_2$N) & (N–$CH_2$–$CH_2$–N)} respectively in compounds [4,5] respectively , & other signals of functional groups show in the following , table (2) and figures (5 ,6).

**Their $^{13}$C.NMR – Spectra**

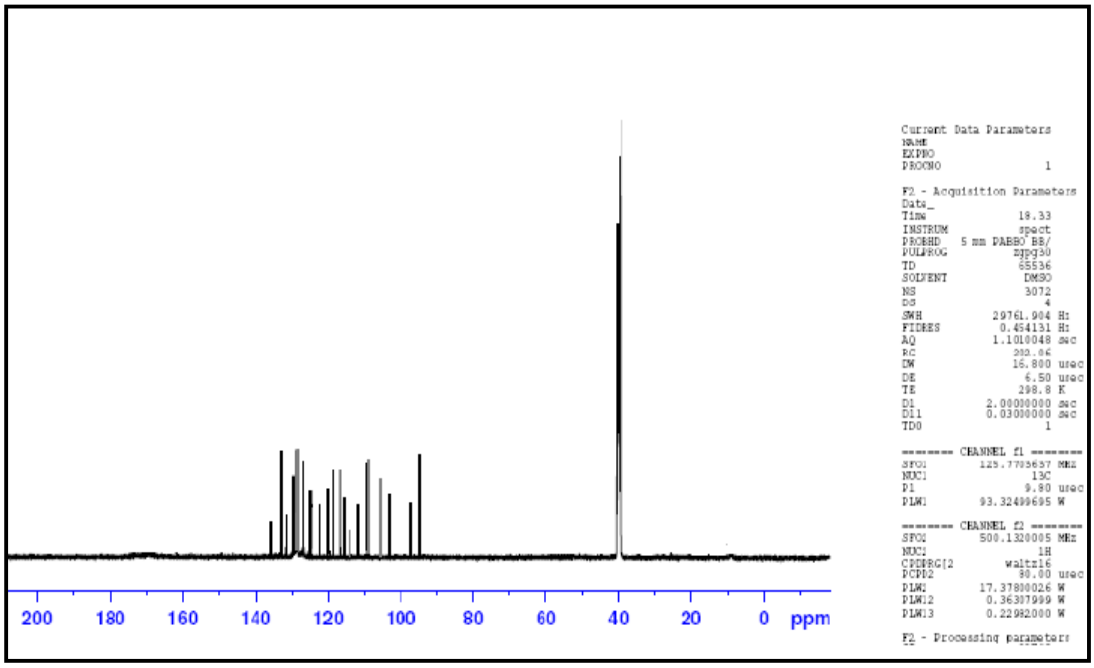
The measurements indicate to formation of compounds in this work ,as shown in figures ( 7 , 8 , 9 ).




**Fig(7 ): 13C.NMR – Spectra of Compound [ 1 ]**




**Fig(8 ): 13C.NMR – Spectra of Compound [ 4 ]**




**Fig(9 ): 13C.NMR – Spectra of Compound [ 10 ]**

**Their (C.H.N)-analysis& melting points :**

it was found from compared the calculated data with experimentally data of these compounds ,the results were compactable , the data of analysis , M.F & melting points are listed in table (3) .

**Table (3) :physical properties & (C.H.N)–analysis of compounds [1-10]**

| Comp. No. | M.F | m.p (+2) C° | Name of compounds | Calc. /Found. | | |
|---|---|---|---|---|---|---|
| | | | | C% | H% | N% |
| [1] | $C_{19}H_{18}O_2$ | 164 | 2–methyl-1–dibenzoylbutene | 82.014<br>81.873 | 6.474<br>6.313 | ---- |
| [2] | $C_{19}H_{18}N_2$ | 189 | 3,5–diphenyl-4–one–isobutyl-1,2 –diazolidine . | 83.211<br>83.042 | 6.569<br>6.385 | 10.218<br>10.089 |
| [3] | $C_{20}H_{21}N_3$ | 220 | 4,6–diphenyl-5–one–isobutyl-2–amino-1,3–diazine . | 79.207<br>79.052 | 6.930<br>6.816 | 13.861<br>13.703 |
| [4] | $C_{20}H_{20}N_2$ | 202 | 4,6–diphenyl-5–one–isobutyl-1,3–diazine . | 83.333<br>83.194 | 6.944<br>6.771 | 9.722<br>9.603 |
| [5] | $C_{21}H_{22}N_2$ | 215 | 5,7–diphenyl-6–one–isobutyl-1,4–diazepine | 83.443<br>83.303 | 7.284<br>7.127 | 9.271<br>9.106 |
| [6] | $C_{25}H_{22}N_2$ | 235 | 5,7–diphenyl-6–one–isobutyl-1,4–benzodiazepine. | 85.714<br>85.532 | 6.285<br>6.067 | 8.000<br>7.823 |
| [7] | $C_{11}H_{12}N_2$ | 222 | 2,4–dimethyl-1,5– benzodiazepine. | 76.744<br>76.537 | 6.976<br>6.715 | 16.279<br>16.115 |
| [8] | $C_{21}H_{16}N_2$ | 250 | 2,4–diphenyl-1,5 – benzodiazepine. | 85.135<br>85.025 | 5.405<br>5.286 | 9.450<br>9.291 |
| [9] | $C_{18}H_{16}N_2$ | 265 | 2,4–dimethyl-3–styrene -1,5– benzodiazepine. | 83.076<br>82.891 | 6.153<br>6.038 | 10.769<br>10.557 |
| [10] | $C_{28}H_{20}N_2$ | 283 | 2,4–diphenyl-3–styrene -1,5–benzodiazepine. | 87.500<br>87.398 | 5.208<br>5.046 | 7.291<br>7.127 |

**Assay of Antimicrobial Activity**

All chemical materials like( agar for bacteria , DMSO ,petri dish ) and bacteria supplied from bio-lab in college of education. Antimicrobial activity was tested by the filter paper disc diffusion method against gram positive bacteria *(Staphylococcus aureus )* and gram negative bacteria (*Pseudomonas aeruginosa*) , 0.1 ml of the bacterial suspensions was seeded on agar .To determine minimum inhibitory concentration(MIC) for each compounds[1-10]

were ranged between (6-28)mg/ml by dissolved in ( DMSO) and preparation 0.1mg/ml standard antibiotic amoxyline as positive standard and reference .

The positive results or sensitivity were established by the presence of clear zone of inhibition around active compounds which were measured with a meter rule and diameters were recorded based on (mm), the assays were performed with two replicates .Generally, The results showed that the compounds[1-10] have goodinhibitory effect against tested bacteria as compared with synthetic antibiotic Amoxyline.

Table (4) showed the zone of inhibition of the compounds[1-10] in this study ranged (from 28 to 6) mm. From results, we noted that the compounds[2-4] have higher antibacterial activity against *S.aureus and P.aeruginosa*is due to the presence more than one of nitrogen atoms(N ) in their structures of five and six membered ring more than seven membered ring as diazepine. Consequently, these compounds become more effective in precipitating proteins on bacteria cell walls. These atoms form hydrogen bonds with cell wall protein and hence ,destroying the cell membranes, these compounds had abroad antibacterial activity .

**Table(4):Antibacterial activity of the compounds[1-10]**.

| **Compounds[1-10]** * | **diameter of zone(mm)** | |
|---|---|---|
| | ***G+: Staphylococcus. aureus*** | ***G-: Pseudomonas. aeruginosa*** |
| compounds[1] | 10 | 6 |
| compounds[2] | 28 | 23 |
| compounds[3] | 24 | 21 |
| compounds[4] | 24 | 20 |
| compounds[5] | 22 | 17 |
| compounds[6] | 20 | 17 |
| compounds[7] | 19 | 14 |
| compounds[8] | 20 | 12 |
| compounds[9] | 18 | 11 |
| compounds[10] | 18 | 8 |
| Amoxyline** | 30 | 26 |
| **Minimum Inhibitory concentration (MIC)of compounds[1] (5mg/ml).* ***Amoxyline (0.1mg/ml) .* | | |

**Acknowledgement**
I would like to express my thanks to Mr. Ahmed in Canada for providing (C.H.N) elements analytical &$^{1}$H.NMR–spectra &$^{13}$C.NMR and melting points & express my thanks to (United Arabic Company ) & ( Zaidan company of chemical ) for supplied some materials .

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