IJBPAS, June, 2016, 5(6): 1375-1396

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

SYNTHESIS AND IDENTIFICATION OF NEW VARIOUS ENAMINE DERIVATIVES

Dr. NAGHAM MAHMOOD ALJAMALI[*1] AND AHMED ADNAN ABDULHUSSEIN[2]

Chemistry Department, Factuality of Education for women, Iraq

***Corresponding Author E-mail: Dr.Nagham_mj@yahoo.com**

ABSTRACT

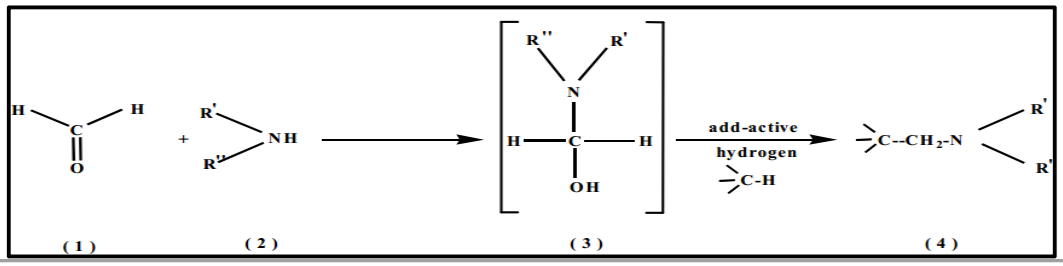
The present work includes the synthesis of Mannich base by reaction of three components ((aldehydes, ketones and secondary amine)) to yield new Mannich base derivatives the general formula (R-CH_2NR_2) , the product of Mannich reaction is a β-amino carbonyl compounds . All steps of reactions are followed by TLC papers and all the synthesized compounds have been investigated using different chemical techniques, such as (1H.NMR-spectra , (C.H.N)-analysis , FT.IR- spectra) , melting points and biological study .

Keywords: Reaction; Mannich bases; β-Amino carbonyl compounds; Enamine compounds

INTRODUCTION

Mannich bases are important compounds act starting materials for many reactions , which were firstly prepared by Mannich[1] in 1933, from simple condensation reactions of three components : formaldehyde (or some time another aldehyde) with an amine and compound containing an active hydrogen to introduce aminomethyl as the functional group in structure compound; (- CH_2-N).

The most common method of obtaining a Mannich base is through a condensation reaction between carbonyl compound (1) and secondary amine (2) with the formation of an intermediate alcohol(3), followed by a nucleophilic substitution reaction to produce (4)[2] ,The following equation describes the Mannich reaction :



The Mannich reaction is one of the most important fundamental carbon-carbon bond-forming reactions in organic chemistry[3].The products of Mannich reaction are mainly β-amino carbonyl compounds and 1, 2-amino alcohol derivatives[4],Mannich base compounds have been studied intensively mainly because of their application of organic synthesis , especially for preparing dyes[5,6] , industrial[6] , pharmacological effects[7] , polymers , resins , surface active agents [8], antimalarial [9,10] ,antibacterial[11,12], antifungal[13,14] ,antiviral agents[15] , antioxidants[16] .

A Mannich-type reaction is a multicomponent reactions (MCRs) have recently received the interest of organic chemists because of the many advantages of these reactions offered over conventional multi-step synthesisas well as their potential applications in medicinal chemistry in order to generation of diverse props and combinatorial libraries for the developmentdrugs[17-19].

In this type of reactions three or more components are reacted to form ideally one product, which containing the essential parts of all the initial reactants. MCRs contribute to the terms of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production[20] .

Experimental Section

General Procedures. All the chemicals used were of highest purity available. The Fourier Transform Infrared Spectrophotometer (FT.IR-spectra) were recorded on shimadzu 8300 with sample prepared as KBr discs , the proton nuclear magnetic spectrophotometer (^{1}H NMR- spectra) were recorded on Varian 300MHz spectrometer using TMS as an internal standard and elemental (analyses system GmbH)-measurements and ^{13}C.NMR-spectra, and elemental analysis (C.H.N.)-elemental (analyses system GmbH)-measurements ,were measured in Canada.

Melting points were recorded on an electro thermal type Gallenkamp M.F.B. 600-010f melting point apparatus . After completion of the reaction,as indicated by TLC (Thin-layer chromatography) , the precipitated solid was collected by filtration, washed with distilled water. All compounds were purified by re crystallization to afford the pure products .

General Synthesis of Compounds [1-3]

benzene-1,2-diamine (0.01mol) reacts with 2-mercaptoacetic acid (0.01mol) in present of hydrochloric acid (4N) after that were refluxed for (4hrs) in ethanol abs. , under magnetic stirrer to produce (80%) of compound **[1]**we've got this percentage after

filtered and dried with recrystallized . (0.001mol) of compound **[1]** reacts with (0.001mol) ethyl 2-chloroacetate ,the existence of (0.0005mol) Potassium carbonate as a catalyst after that were refluxed for (3hrs) in ethanol abs. ,under magnetic stirrer ,after that filtered and dried with recrystallized the product we got on(74%) of compound **[2]**, which reacts with (0.002mol) of 4-nitro acetophenone and (0.003mol) of formaldehyde ,under magnetic stirrer in Ice path after that filtered and dried with recrystallized the product (82%) of compound **[3]** .

Synthesis of Compounds [4-6]

Reaction of (0.001mol) from compound **[3]** and (0.001mol) from 4-methoxyaniline, then were refluxed for (2hrs) in ethanol abs. , with magnetic stirrer to yield the product (72%) of compound **[4]**after filtered and dried with recrystallized . Now we reacted (0.001mol) from compound **[4]**, (0.001mol) from phthalamide and (0.003mol) of formaldehyde the existence of (0.0005mol)Potassium carbonate as a catalyst under magnetic stirrer in the Ice path ($0C^{\circ}$ /2hrs) in ethanol abs. ,we got the product (78%) of compound **[5]** after filtered and dried with recrystallized . To get compound **[6]** reacts (0.001mol) from compound **[4]** with (0.001mol) saccharin and (0.003mol) of formaldehyde the existence of (0.0005mol) Potassium carbonate as a catalyst under magnetic stirrer in the Ice path ($0C^{\circ}$ /3hrs) in ethanol abs. to precipitate the product (80%) of compound **[6]** after filtered and dried with recrystallized.

Synthesis of Compounds [7-9]

2,4-dimethylaniline (0.01mol) reacts with thio ammonium cyanate (0.01mol) and existence bromine /Glacial acetic acid (10ml)with mechanical stirring for(2hrs.) to produce (76%) of compound **[7]** we've got this percentage after filtered and dried with recrystallized .(0.01mol) of compound **[7]** reacts with (0.01mol) ethyl 2-chloroacetatethe existence of (0.0005mol)Potassium carbonate as a catalyst after that were refluxed for (3hrs) in ethanol abs. , under magnetic stirrer , after that filtered and dried with re crystallized the product we got on (80%) of compound **[8]**, which reacts with (0.01mol) of 1,4-dimethoxybenzene and (0.003mol) of formaldehyde refluxed for (7 hrs.) in ethanol abs., under magnetic stirrer after that filtered and dried with recrystallized the product (74%) of compound **[9]** .

Synthesis of Compounds [10-11]

React (0.001mol) from compound **[9]** and (0.001mol) from p-toluidine, then were refluxed for (3hrs) in ethanol abs. , with

magnetic stirrer we got the product (82%) of compound **[10]** after filtered and dried with recrystallized . Now compound **[10]** reacts (0.001mol) with (0.001mol) Piperidine and (0.003mol) of formaldehyde under magnetic stirrer in the Ice path ($0C^{\circ}$ /3hrs) in ethanol abs. to produce product (80%) of compound **[11]** .

Synthesis of Compounds [12-13]

Also compound **[9]** reacts (0.001mol) with (0.001mol) from compound **[7]** which refluxed for (4hrs) in ethanol abs. , with magnetic stirrer we got the product (80%) of compound **[12]** after filtered and dried with recrystallized . Compound **[12]** with (0.001mol)1,3-diphenylpropane-1,3-dione and (0.003mol) of formaldehyde refluxed for (9hrs) in ethanol abs., under magnetic stirrer , to yield the product (82%) of compound **[13]** .

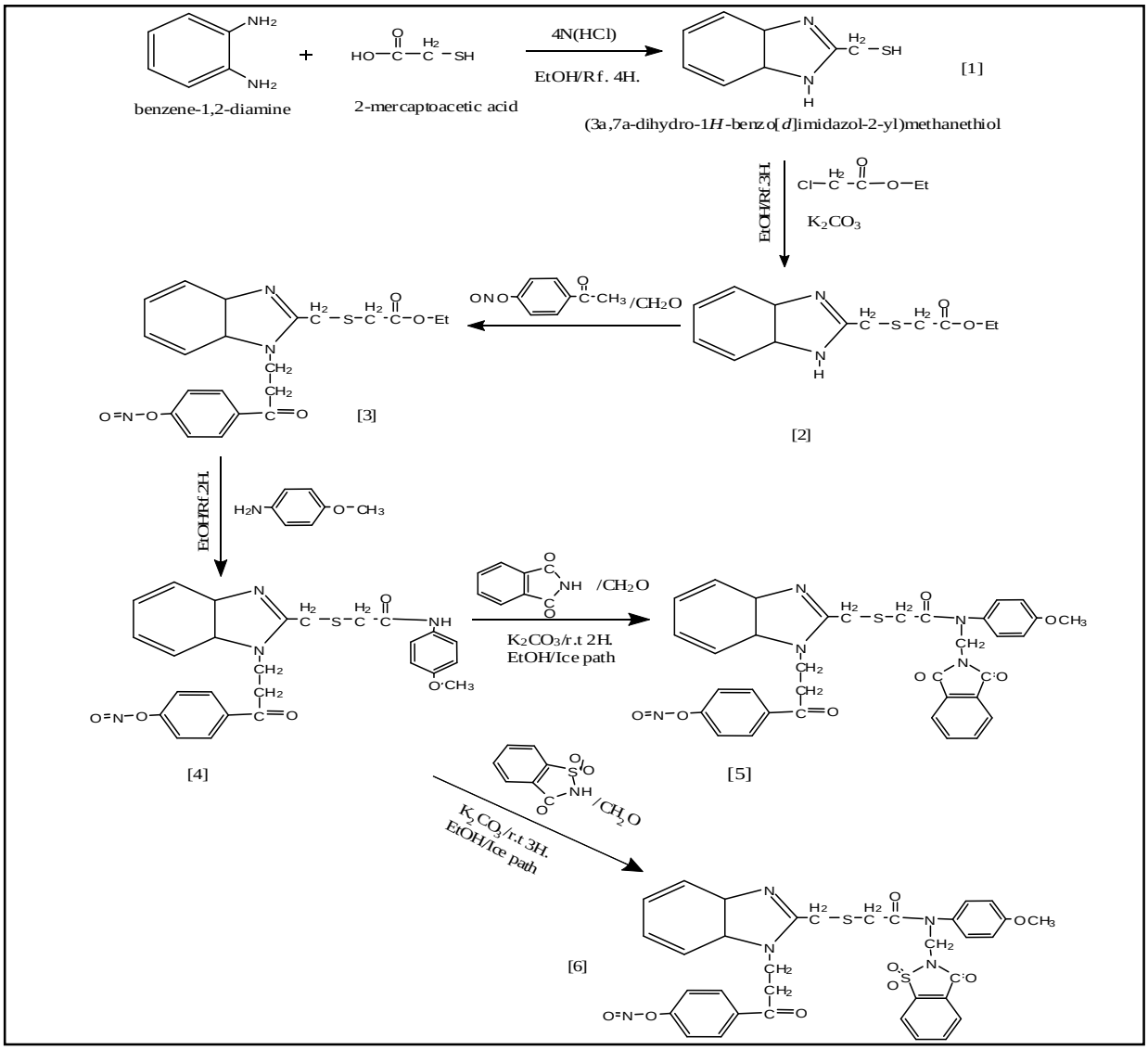
Synthesis of Compounds [14-17]

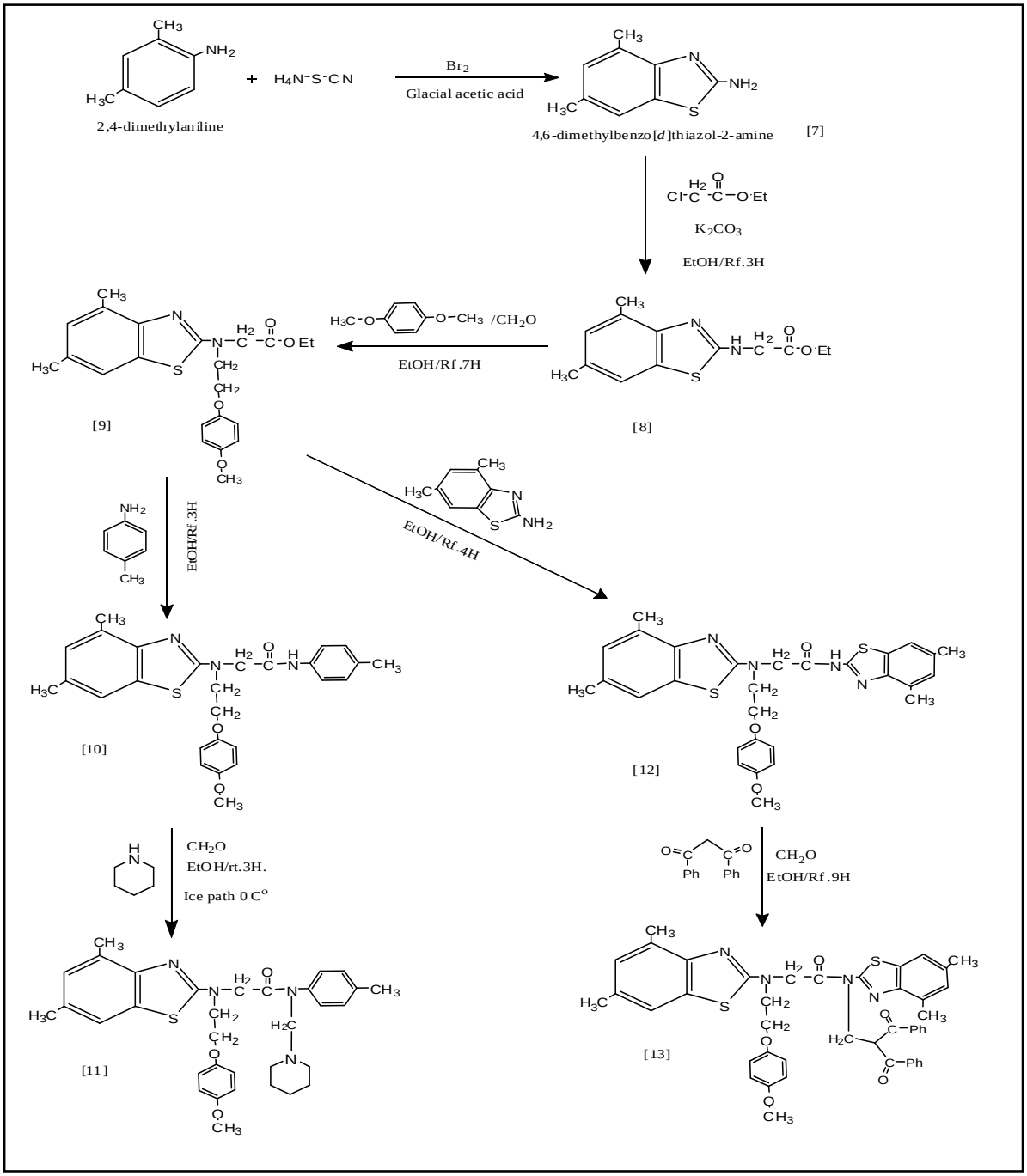
Benzene-1,4-diamine (0.01mol) reacts with thio ammonium cyanate (0.02mol) and existence bromine /Glacial acetic acid with mechanical stirring for(2hrs.) in Ice path ($10C^{\circ}$) to produce (82%) of compound **[14]** after filtered and dried with recrystallized . (0.01mol) of compound **[14]** reacts with (0.01mol) propyl chloride the existence of (0.0005mol)Potassium carbonate as a catalyst after that were refluxed for (3hrs) in ethanol abs. , after that filtered and dried with re crystallized the product to yield (84%) of compound **[15]** , which reacts with (0.01mol) of 4-acetylphenyl nitriteand (0.003mol) of formaldehyde refluxed for (7hrs.) in ethanol abs., under magnetic stirrer after that filtered and dried with recrystallized the product (78%) of compound **[16]**. Also (0.01mol) from compound **[15]** reacts with (0.01mol) of diphenylamine and (0.003mol) of formaldehyde under magnetic stirrer in the Ice path ($0C^{\circ}$ /3hrs) in ethanol abs. , to yield (76%) of compound **[17]** , after dried with re crystallized .

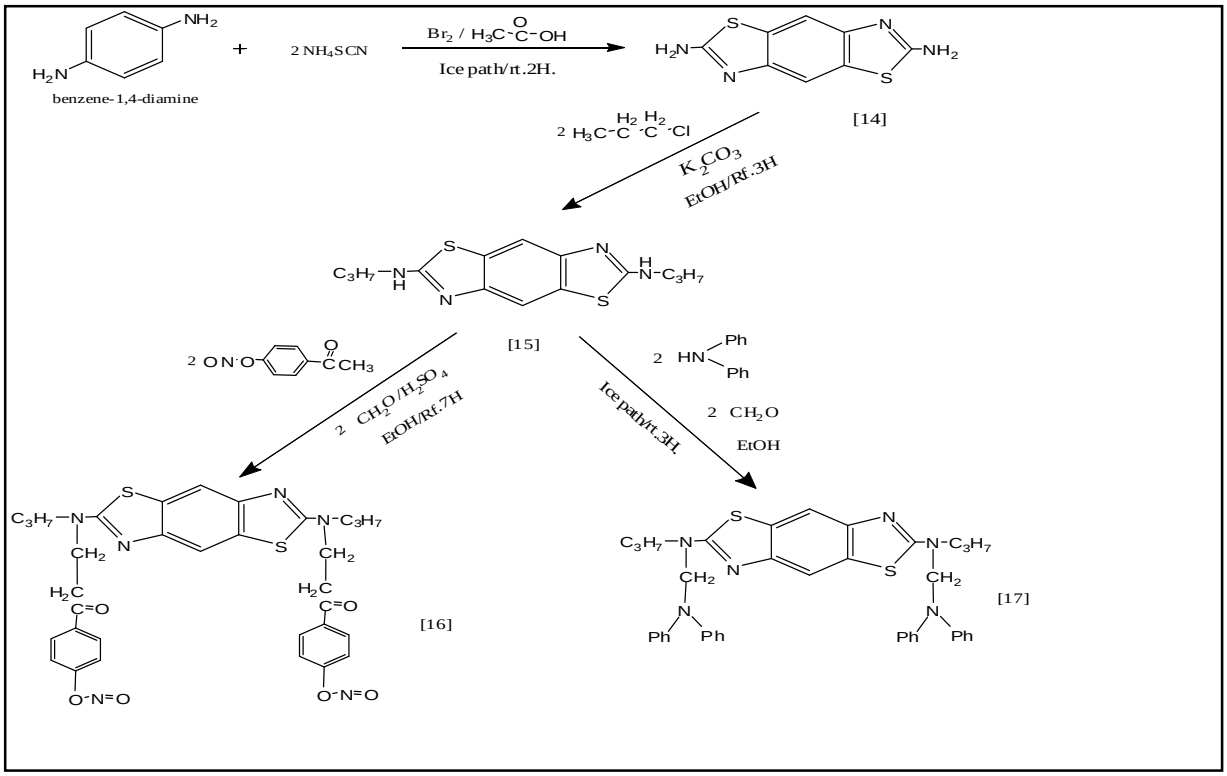
Synthesis of Compounds [18-20]

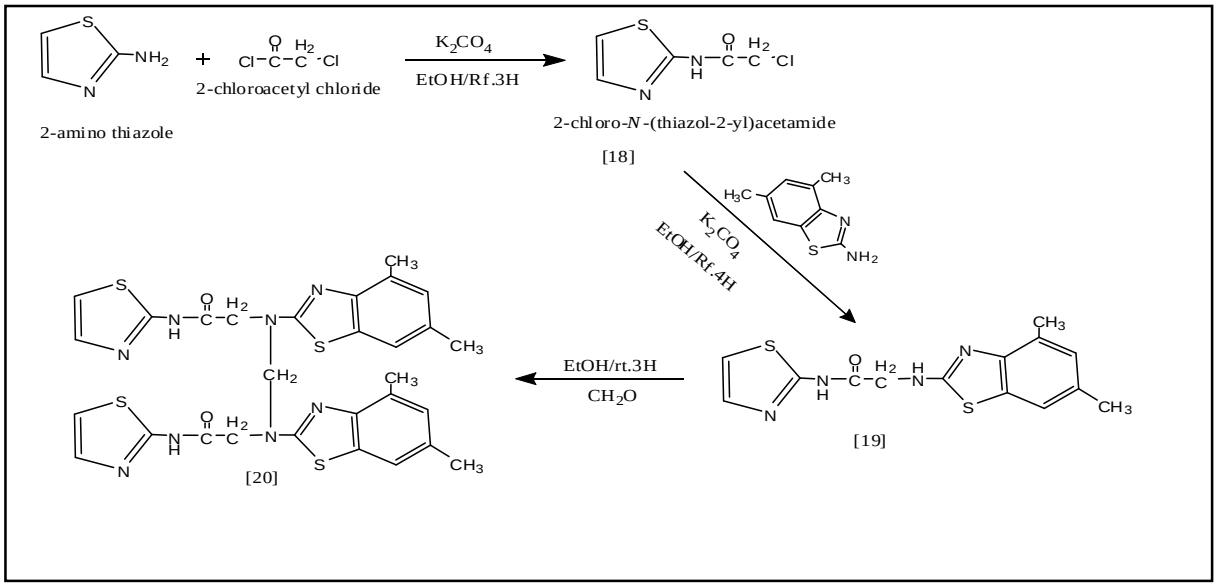
2-amino thiazol(0.001mol) reacts with 2-chloroacetyl chloride (0.001mol) and existence of (0.0005mol)Potassium carbonate as a catalyst after that were refluxed for (3hrs) in ethanol abs. , after that filtered and dried with re crystallized the product (80%) of compound **[18]** ,which reacts with (0.001mol) of compound **[7]** and (0.0005mol)Potassium carbonate as a catalyst were refluxed for (4hrs) in ethanol abs. ,we got the product (72%) of compound **[19]** , . Now we react (0.002mol) from compound **[19]** with (0.003mol) of formaldehyde under magnetic stirrer in the ice path ($0C^{\circ}$ /3hrs) in ethanol abs. , after that

filtered and dried with recrystallized the product (70%) of compound **[20]** .




2,4-dimethylaniline
H_4N-S-CN
Br_2
Glacial acetic acid
4,6-dimethylbenzo[d]thiazol-2-amine
[7]
K_2CO_3
EtOH/Rf.3H
[8]
[9]
EtOH/Rf.7H
EtOH/Rf.4H
EtOH/Rf.3H
[10]
[12]
CH_2O
EtOH/rt.3H.
Ice path 0 C°
CH_2O
EtOH/Rf.9H
[11]
[13]


benzene-1,4-diamine
2 NH4SCN
Br2 / H3C-C(=O)-OH
Ice path/rt.2H.
[14]
2 H3C-C(=O)-CH2-Cl
K2CO3
EtOH/Rf.3H
[15]
2 ON-O-C6H4-C(=O)-CH3
2 CH2O/H2SO4
EtOH/Rf.7H
2 HN(Ph)2
2 CH2O
EtOH
Ice path/rt.3H
[16]
[17]


2-amino thiazole
2-chloroacetyl chloride
K2CO4
EtOH/Rf.3H
2-chloro-N-(thiazol-2-yl)acetamide
[18]
K2CO4
EtOH/Rf.4H
EtOH/rt.3H
CH2O
[19]
[20]

RESULTS AND DISCUSSION

The Mannich reaction is a three-component condensation among an amine component, an enolizable carbonyl compound (donor), and a non enolizable carbonyl compound (acceptor) to form a β-amino carbonyl compound, with the concomitant formation of both carbon–carbon and carbon–nitrogen bonds. For example, aniline compounds, phenol compounds and aldehydes can act as the amine component, donor and acceptor in Mannich reaction, respectively. This reaction can occur under any pH conditions. The Mannich reaction is extendedly employed in many fields such as drug synthesis, agro chemicals synthesis and especially chemical modification of proteins.

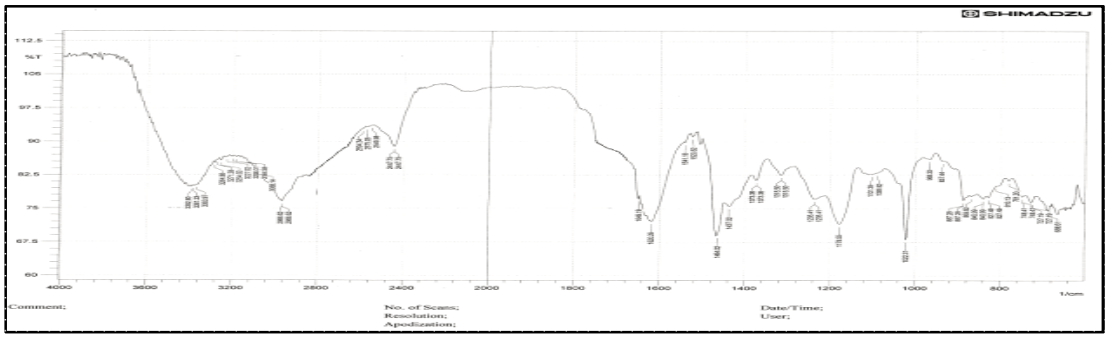
FT.IR-Spectra:

From the FT.IR-Spectra of compound **[1]** we noted appearance absorption bends at (3363)cm^{-1} due to (NH)[21], (1620) cm^{-1} due to (C=N) endow cycle, (2447) cm^{-1} due to (SH). for compound**[2]**appearance absorption bends at (3360)cm^{-1} due to (NH), (1626) cm^{-1} due to (C=N) endow cycle, (1188) cm^{-1} due to (S-CH_2), (1730) cm^{-1} due to (-COO-) ester. For compound**[3]** appearance absorption bends at (1622) cm^{-1} due to (C=N) endow cycle, (1161) cm^{-1} due to (S-CH_2), (1724) cm^{-1} due to (-COO-) ester, (1716) cm^{-1} due to (-CO-) ketone, (1320) cm^{-1} due to (-NO_2-). For compound**[4]** appearance absorption bends at (3306) cm^{-1} due to (NH), (1606) cm^{-1} due to (C=N) endow cycle, (1176) cm^{-1} due to (S-CH_2), (1616) cm^{-1} due to (-CO-) ketone, (1662) cm^{-1} due to(-CO-NH), (1388) cm^{-1} due to (-NO_2-), (1116) cm^{-1} due to (-OCH_3). For compound**[5]** appearance absorption bends at (1631) cm^{-1} due to (C=N) endo cycle, (1176) cm^{-1} due to (S-CH_2), (1712) cm^{-1} due to (-CO-) ketone , (1681) cm^{-1} due to (-CO-NH), (1348) cm^{-1} due to (-NO_2-), (1118) cm^{-1} due to (-OCH_3).For compound**[6]** appearance absorption bands at (1628) cm^{-1} due to (C=N) endo cycle, (1174) cm^{-1} due to (S-CH_2), (1714) cm^{-1} due to (-CO-) ketone, (1683) $cm^{-1}$and (1658) cm^{-1}due to (-CO-NH), (1398) cm^{-1} due to (-NO_2-), (1109) cm^{-1} due to (-OCH_3), (1271) cm^{-1} due to (-SO_2). For compound**[7]** appearance absorption bends at (3306) cm^{-1} and (3375) cm^{-1} due to (NH),(1628) cm^{-1} due to (C=N) endo cycle, (706) cm^{-1} due to (C-S) endo cycle, (2900) cm^{-1} due to (-CH) alp., (3051) cm^{-1} due to (-CH) Ar. For compound**[8]** appearance absorption bends at (3298) cm^{-1} due to (NH), (1631) cm^{-1} due to (C=N) endo cycle, (1712) cm^{-1}due to(-COO), (754) cm^{-1} due to (C-S) endo cycle , (2945) cm^{-1} due to (-CH) alp.,(3063) cm^{-1} due to (-CH) Ar. For compound**[9]** appearance absorption bends at (1631) cm^{-1} due to (C=N) endo cycle, (1728)

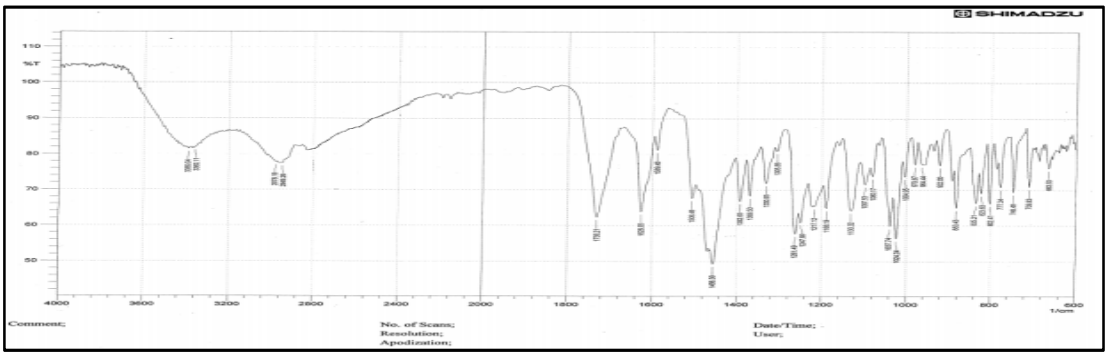
cm^{-1} due to (-COO), (694) cm^{-1} due to (C-S) endo cycle, (1710) cm^{-1} due to (-CO-) ketone , (1118) cm^{-1} due to ($-OCH_3$).For compound**[10]** appearance absorption bends at (3381) cm^{-1} due to (NH) [21], (1606) cm^{-1} due to (C=N) endo cycle, (767) cm^{-1} due to (C-S) endo cycle, (1716) cm^{-1} d'2ue to (-CO-) ketone ,(1682) cm^{-1} due to (-CO-NH),(1116) cm^{-1} due to ($-OCH_3$).For compound**[11]** appearance absorption bends at (1613) cm^{-1} due to (C=N) endo cycle, (765) cm^{-1} due to (C-S) endow cycle, (1714) cm^{-1} due to (-CO-) ketone , (1672) cm^{-1} due to (-CO-NH), (1159) cm^{-1} due to ($-OCH_3$). For compound **[12]** appearance absorption bends at (3153) cm^{-1} due to (NH), (1614) cm^{-1} due to (C=N) endow cycle, (761) cm^{-1} due to (C-S) endo cycle, (1701) cm^{-1} due to (-CO-) ketone , (1666) cm^{-1} due to (-CO-NH), (1174) cm^{-1} due to ($-OCH_3$). For compound**[13]** appearance absorption bands at (1626) cm^{-1} due to (C=N) endo cycle, (767) cm^{-1} due to (C-S) endo cycle, (1714) cm^{-1} due to (-CO-) ketone , (1683) cm^{-1} due to (-CO-NH), (1174) cm^{-1} due to ($-OCH_3$). for compound **[14]** appearance absorption bands at (3232) $cm^{-1}$and (3336) cm^{-1}due to (NH), (1643) cm^{-1} due to (C=N) endow cycle, (727) cm^{-1} due to (C-S) endo cycle. for compound**[15]** appearance absorption bands at (3408) cm^{-1} due to (NH), (1631) cm^{-1} due to (C=N) endo cycle, (746) cm^{-1} due to (C-S) endo cycle, (2943) cm^{-1} due to (-CH)alp. For compound **[16]** appearance absorption bands at (1654) cm^{-1} due to (C=N) endo cycle, (711) cm^{-1} due to (C-S) endow cycle, (1708) cm^{-1} due to (-CO-) ketone, (1384) cm^{-1} due to ($-NO_2$-), (2928) cm^{-1} due to (-CH)alp. For compound **[17]** appearance absorption bands at (1624) cm^{-1} due to (C=N) endo cycle, (777) cm^{-1} due to (C-S) endo cycle, (3018) cm^{-1} due to (-CH)Ar, (2978) cm^{-1} due to (-CH)alp. For compound **[18]** appearance absorption bands at (3134) cm^{-1} due to (NH), (1641) cm^{-1} due to (C=N) endo cycle, (765) cm^{-1} due to (C-S) endo cycle, (1660) cm^{-1} due to (-CO-NH), (2924) cm^{-1} due to (-CH)alp.[23],(698) cm^{-1} due to (C-Cl). For compound **[19]** appearance absorption bands at (3425) cm^{-1} due to (NH), (1617) cm^{-1} due to (C=N)endo cycle, (771) cm^{-1} due to (C-S) endo cycle, (1668) cm^{-1} due to (-CO-NH), (2929) cm^{-1} due to (-CH)alp., (3050) cm^{-1} due to (-CH)Ar. For compound **[20]** appearance absorption bands at (3390) cm^{-1} due to (NH), (1608) cm^{-1} due to (C=N) endo cycle, (767) cm^{-1} due to (C-S) endo cycle, (1682) cm^{-1} due to (-CO-NH), (2999) cm^{-1} due to (-CH)alp., (3020) cm^{-1} due to (-CH)Ar.

Table (1):FT.IR-data(cm^{-1})of compounds [1-20]

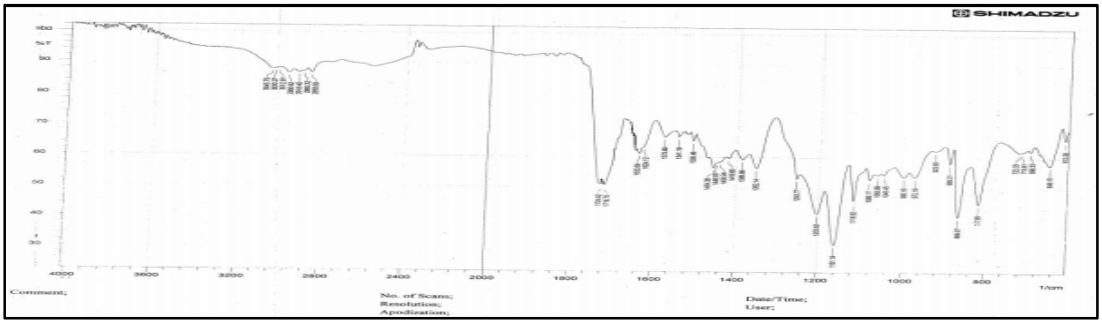
Comp.	NH	(C=N) Endo cycle	(S-CH_2)	(-COO) ester	(-CO) ketone	(CO-NH) carbonyl amide	(C-S) Endo cycle	Other
[1]	3363	1620						SH: 2447
[2]	3360	1626	1188	1730				
[3]			1161	1724	1716			NO_2:1320
[4]	3306	1606	1176		1616	1662		NO_2:1388 OCH_3:1116
[5]		1631	1176		1712	1681		NO_2:1348 OCH_3:1118
[6]		1628	1174		1714	1683 1658		NO_2:1398 OCH_3:1109 -SO_2:1271
[7]	3306 3375	1604					706	(CH)alp:2900 (CH)Ar:3051
[8]	3298	1631		1712			754	(CH)alp:2945 (CH)Ar:3063
[9]		1631		1728	1710		694	OCH_3:1118
[10]	3381	1606			1716	1682	767	OCH_3:1116
[11]		1613			1714	1672	765	OCH_3:1159
[12]	3153	1614			1701	1666	761	OCH_3:1174
[13]		1626			1614	1683	767	OCH_3:1174
[14]	3232 3336	1643					727	
[15]	3408	1631					746	(CH)alp:2943
[16]		1645			1708		711	NO_2:1384 (CH)alp:2928
[17]		1624					777	(CH)alp:2978 (CH)Ar:3018
[18]	3134	1641				1660	765	(CH)alp:2924 (C-Cl):698
[19]	3425	1617				1668	771	(CH)alp:2929 (CH)Ar:3050
[20]	3390	1608				1682	767	(CH)alp:2999 (CH)Ar:3020



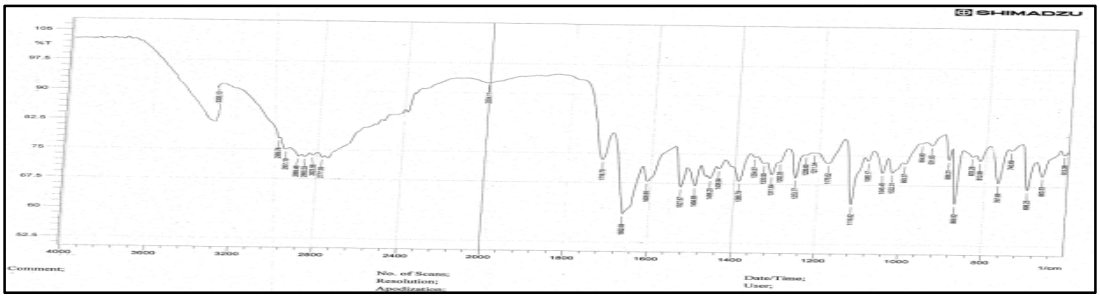
Fig(1): FT.IR of Compound [1]



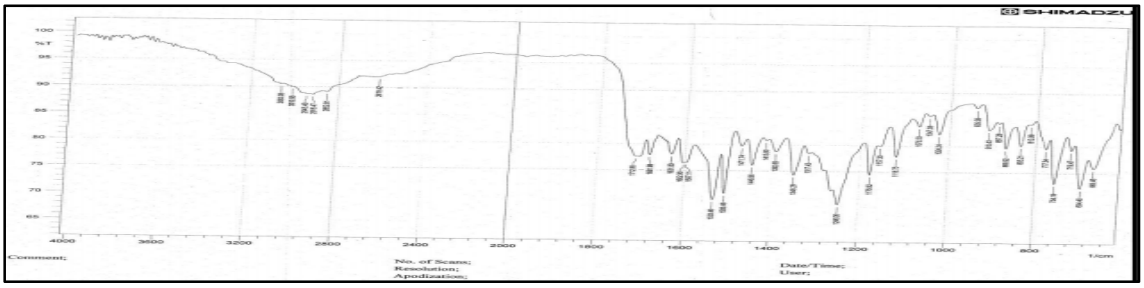
Fig(2): FT.IR of Compound [2]



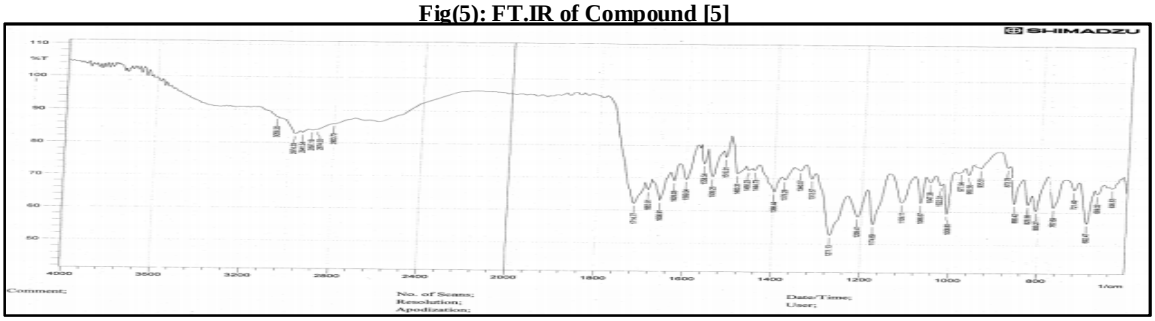
Fig(3): FT.IR of Compound [3]



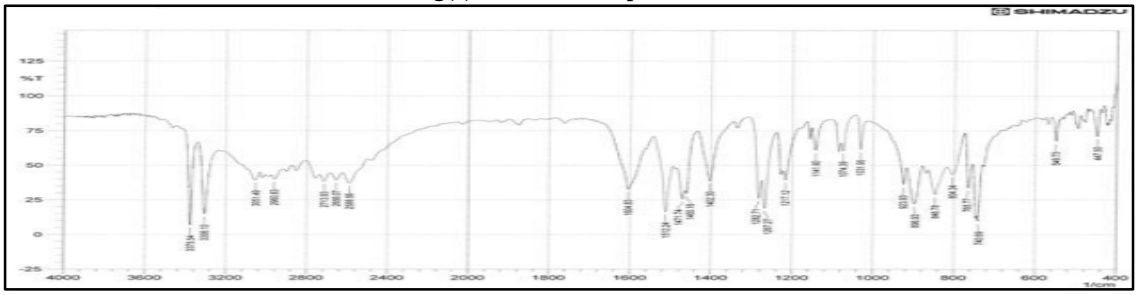
Fig(4): FT.IR of Compound [4]



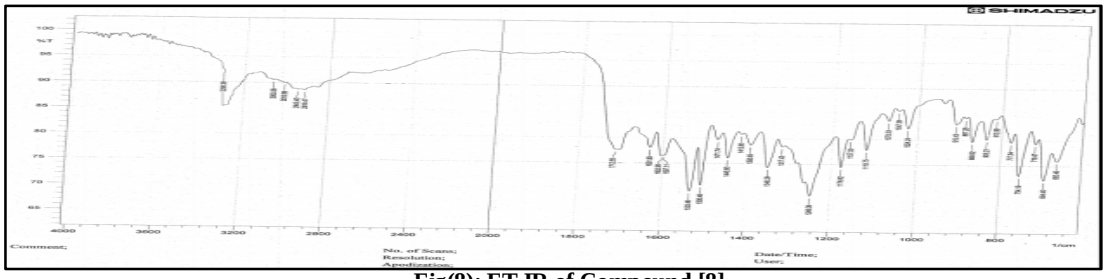
Fig(5): FT.IR of Compound [5]



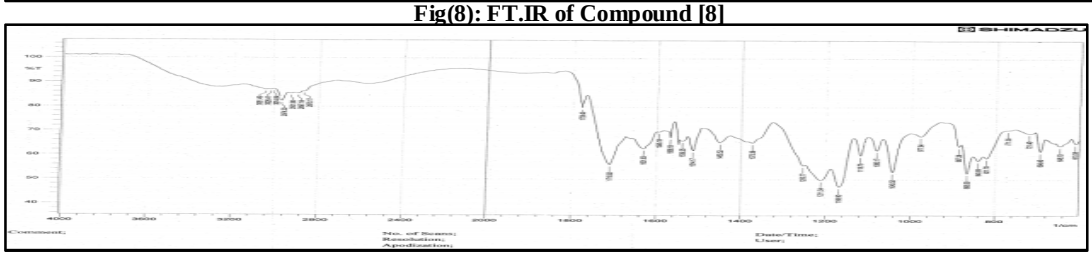
Fig(6): FT.IR of Compound [6]



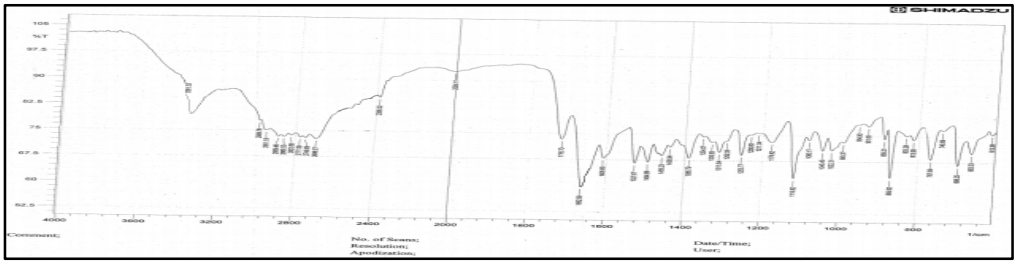
Fig(7): FT.IR of Compound [7]



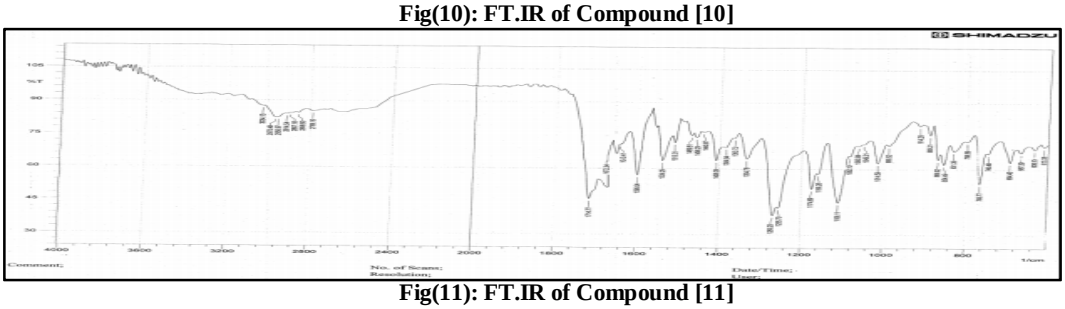
Fig(8): FT.IR of Compound [8]



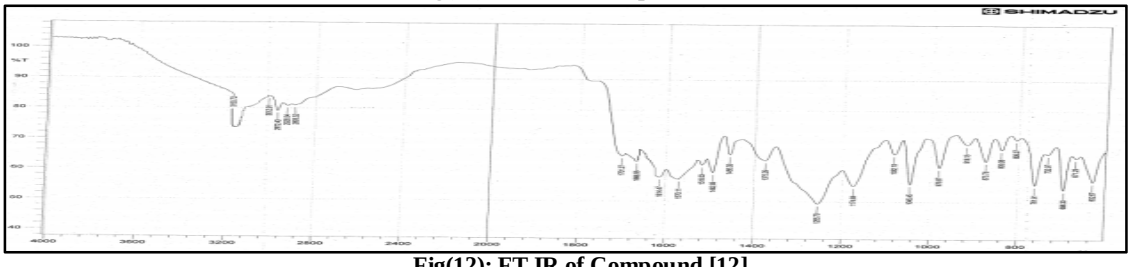
Fig(9): FT.IR of Compound [9]



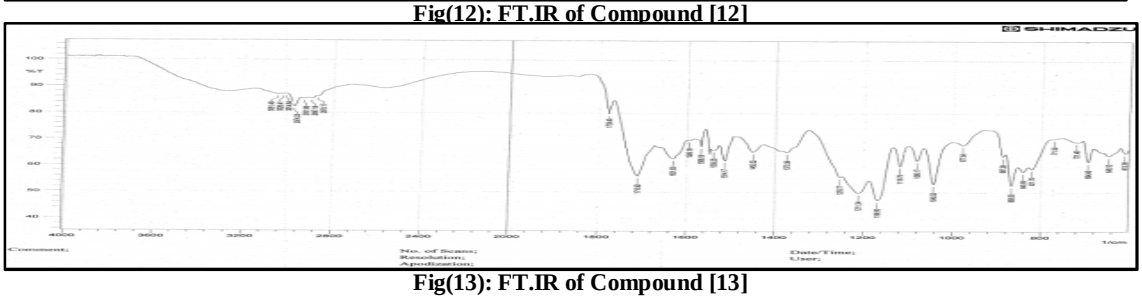
Fig(10): FT.IR of Compound [10]



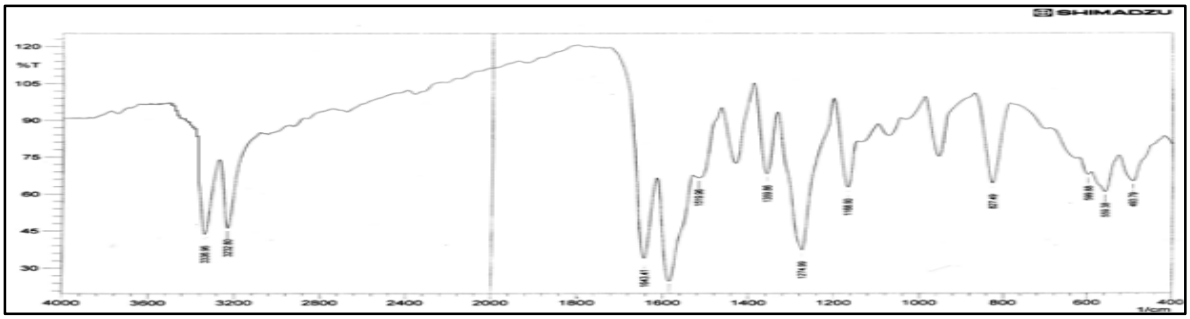
Fig(11): FT.IR of Compound [11]



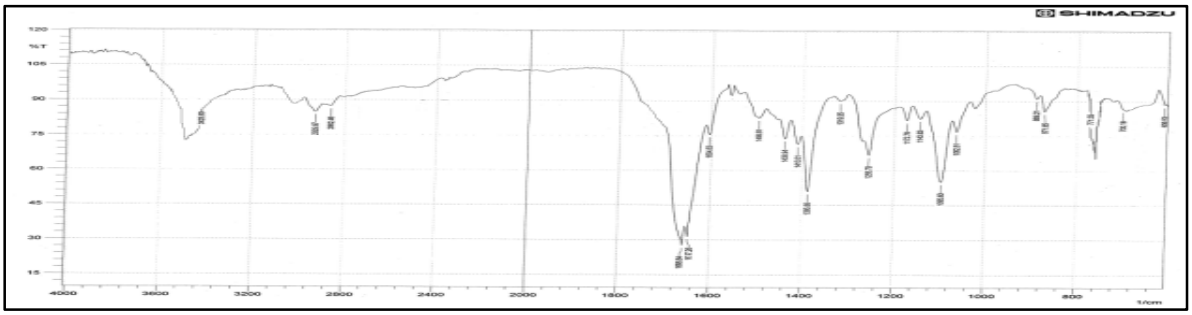
Fig(12): FT.IR of Compound [12]



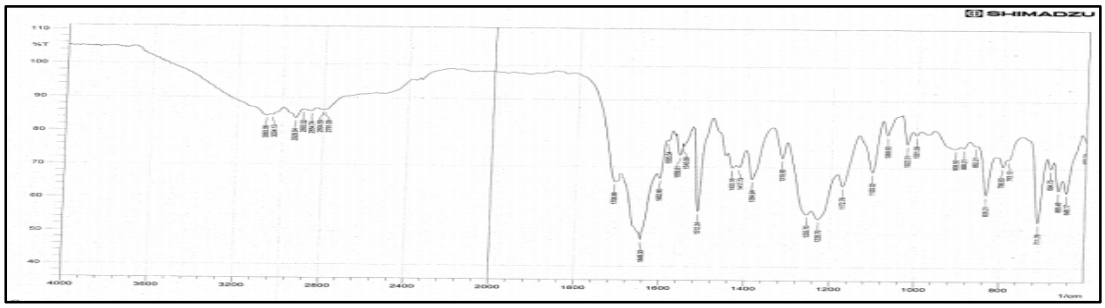
Fig(13): FT.IR of Compound [13]



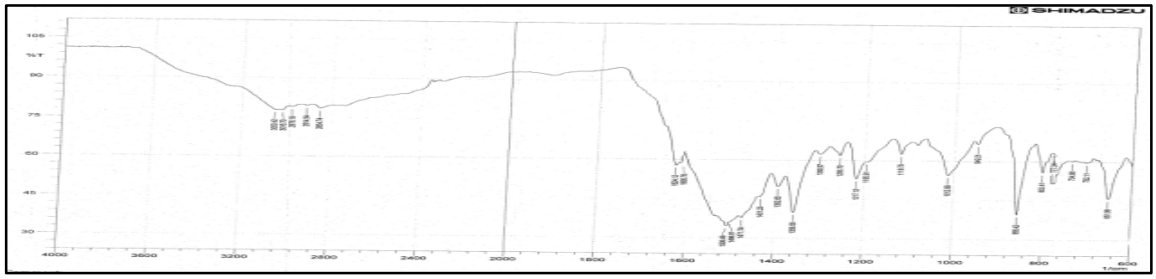
Fig(14): FT.IR of Compound [14]



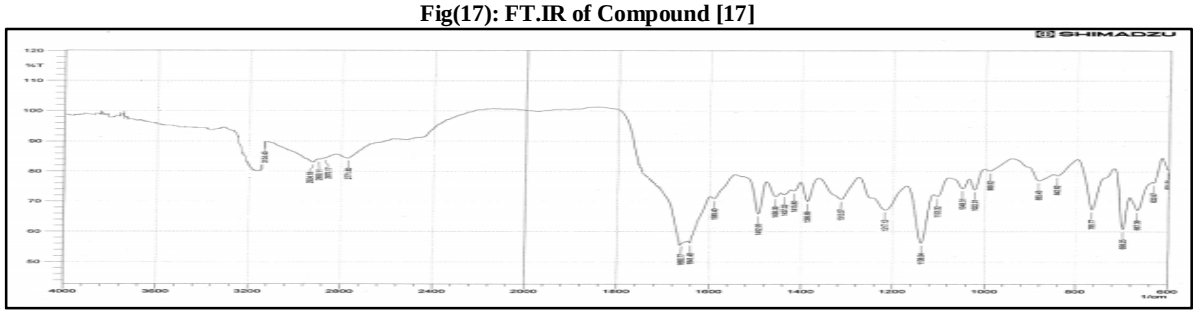
Fig(15): FT.IR of Compound [15]



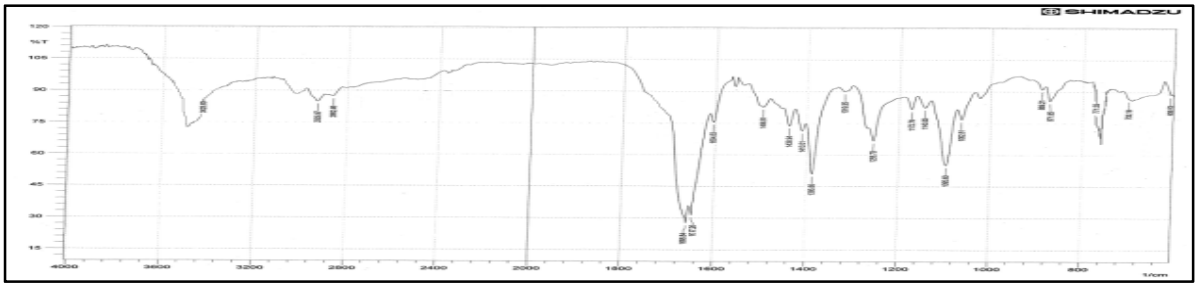
Fig(16): FT.IR of Compound [16]



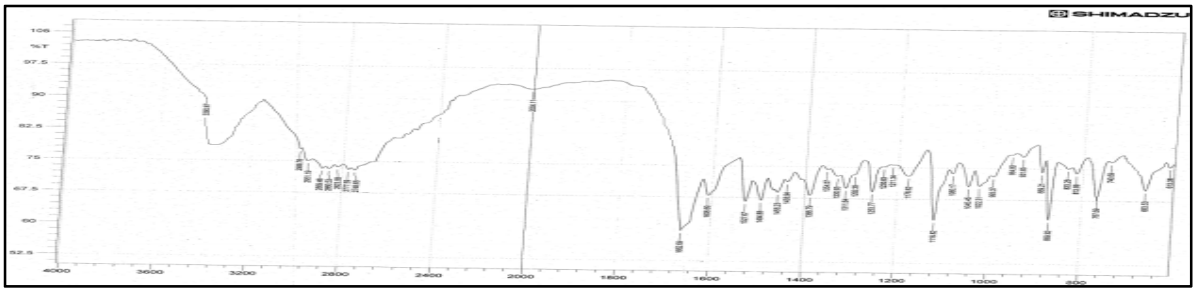
Fig(17): FT.IR of Compound [17]



Fig(18): FT.IR of Compound [18]



Fig(19): FT.IR of Compound [19]



Fig(20): FT.IR of Compound [20]

(C.H.N.S)- Analysis:

We also used C.H.N- Analysis from comparison results were comparable, the data of analysis, the compound calculated with found data of these compounds and melting points are in table (2)

Table (2): Melting point and (C.H.N.S)-Analysis of compound [1-20].

Comp.	M.F	M.P °C	Cal / Found			
			%C	%H	%N	%S
[1]	$C_8H_8N_2S$	158	58.536 58.141	4.878 4.632	17.073 16.823	19.512 19.188
[2]	$C_{12}H_{14}N_2O_2S$	172	57.600 57.290	5.600 5.360	11.200 11.086	12.800 12.460
[3]	$C_{21}H_{21}N_3O_5S$	190	59.016 58.740	4.918 4.630	9.836 9.470	7.494 7.120
[4]	$C_{26}H_{24}N_4O_5S$	198	61.904 61.434	4.761 4.291	11.111 11.01	6.349 6.940
[5]	$C_{35}H_{29}N_5O_7S$	206	63.348 63.108	4.374 4.114	10.558 10.181	4.826 4.416
[6]	$C_{34}H_{29}N_5O_8S_2$	218	58.369 58.051	4.148 4.010	10.014 9.950	9.155 8.940
[7]	$C_9H_{10}N_2S$	152	60.674 60.213	5.617 5.318	15.730 15.4244	17.977 17.541
[8]	$C_{13}H_{16}N_2O_2S$	182	59.090 58.820	6.060 5.841	10.606 10.104	12.121 11.983
[9]	$C_{23}H_{26}N_2O_4S$	204	64.788 64.460	6.103 5.932	6.572 6.214	7.511 7.196
[10]	$C_{28}H_{27}N_3O_3S$	196	69.278 69.013	5.567 5.224	8.659 8.316	6.597 6.177
[11]	$C_{34}H_{38}N_4O_3S$	200	70.103 69.737	6.529 6.158	9.621 9.248	5.498 5.119
[12]	$C_{30}H_{30}N_4O_3S_2$	228	64.516 64.139	5.376 5.118	10.035 9.876	11.469 11.165
[13]	$C_{46}H_{42}N_4O_5S_2$	240	69.521 69.128	5.289 5.054	7.052 6.893	8.060 7.868
[14]	$C_8H_6N_4S_2$	192	43.243	2.702	25.225	28.828

			42.890	2.230	25.040	28.401
[15]	$C_{14}H_{18}N_4S_2$	222	54.901 54.180	5.882 5.270	18.300 18.090	20.915 20.500
[16]	$C_{32}H_{32}N_6S_2O_6$	234	58.181 57.790	4.848 4.430	12.727 12.180	9.696 9.160
[17]	$C_{40}H_{40}N_6S_2$	248	71.856 71.150	5.988 5.270	12.574 12.210	9.580 9.130
[18]	$C_5H_5N_2SO$ Cl	158	33.994 33.361	2.832 2.514	15.864 15.296	18.130 18.014
[19]	$C_{14}H_{14}N_4OS_2$	194	52.830 52.141	4.402 4.053	17.610 17.123	20.125 19.862
[20]	$C_{29}H_{28}N_8O_2S_4$	230	53.703 53.314	4.320 4.093	17.284 17.001	19.753 19.113

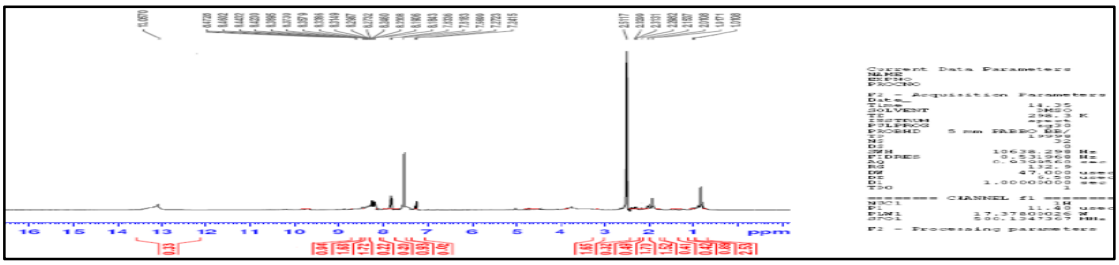
^{1}H NMR- Spectra Analysis:

Also we used ^{1}H NMR (DMSO, 300 MHz, δ ppm) to make sure compounds and we noted appearance peaks of compound **[1]** (13.06) proton of thiol (SH), (8.47) proton of amine in ring (NH), (7.53) proton of phenyl ring (ph).For compound **[2]**(8.7) proton of amine in ring (NH), (7.42) proton of phenyl ring (ph), (3.68-4.20) proton of Ethyl in ester (CO_2Et), (2.07) solvent, (2.10,2.14) proton of methyl sulfide (CH_2-S-CH_2).For compound **[3]** (6.55-7.95) proton of phenyl ring (ph), (3.30-4.00) proton of Ethyl in ester (CO_2Et), (2.80,2.90) proton of methyl sulfide (CH_2-S-CH_2), (4.59-4.98) proton of (N-CH_2-CH_2-CO-), (2.50) solvent . For compound **[4]** (6.19-6.64) proton of phenyl ring (ph), (9.06) proton of amide (CO-NH), (2.90) of (CH_2-S), (4.59-4.98) proton of (N-CH_2-CH_2-CO-),(3.30-4.00) proton of Ethyl in ester (CO_2Et), (2.80,2.90) proton of methyl sulfide (CH_2-S-CH_2),(3.5) of (S-CH_2-CO), (4.0)of (-OCH_3) , (1.50) solvent . For compound **[5]** (6.98-7.66) proton of phenyl ring (ph) [24], (4.06)of (-OCH_3) ,(2.70) of (CH_2-S), (3.06-3.91) proton of (N-CH_2-CH_2-CO-), (4.02) of(N-CH_2-N) [21], (3.96) of (S-CH_2-CO), (2.50) solvent . For compound **[7]** (7.16-7.36) proton of phenyl ring (ph)[22], (4.22)of (-NH_2) ,(1.57,1.96) of (CH_3), (2.50) solvent . For compound **[8]** (7.28-7.62) proton of phenyl ring (ph), (4.60)of (-NH) ,(3.80-4.10) proton of Ethyl in ester (CO_2Et), (1.30,1.40) of (CH_3), (2.14) solvent. For compound **[9]** (6.36-7.67) proton of phenyl ring (ph), (3.10-3.67) proton of Ethyl of ester (CO_2Et), (3.93-4.50) proton of (N-CH_2-CH_2-CO-), (4.90)of (-OCH_3),(1.00,1.10) of (CH_3), (2.14) solvent. For compound **[10]** (6.41-7.95) proton of phenyl ring (ph), (9.17) proton of amide (CO-NH), (3.00-3.60) proton of (N-CH_2-CH_2-CO-), (4.98) of (-OCH_3), (1.00, 1.30, 1.55) of (CH_3), (4.00) of (N-CH_2-CO). For compound **[11]** (6.98-7.95) proton of phenyl ring (ph), (2.80-3.96) proton of (N-CH_2-CH_2-CO-), (4.15) of (-OCH_3), (1.20, 1.90, 1.95) of (CH_3), (2.70) of (N-CH_2-CO), (4.20) of (N-CH_2-N) [21], (2.5) solvent . For compound

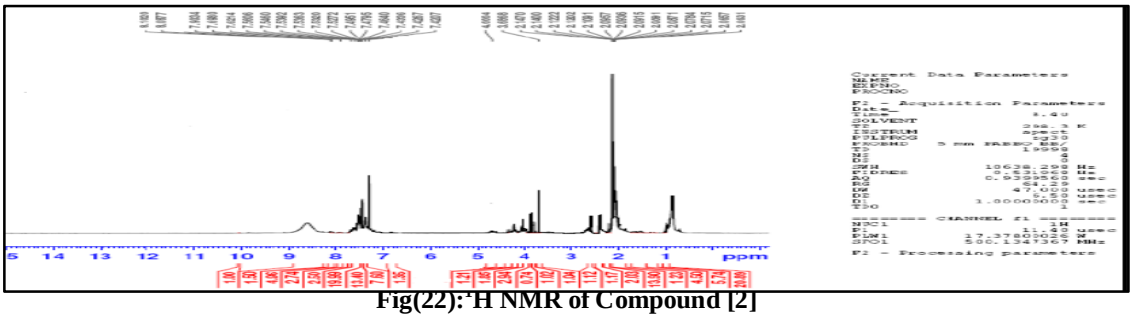
[14] (6.64-7.28) proton of phenyl ring (ph), (4.48)of ($-NH_2$), (2.48) solvent . For compound **[16]** (6.65-7.42) proton of phenyl ring (ph), (3.41-4.05) proton of ($N-CH_2-CH_2-CO-$),(1.02-2.25) of ($N-C_3H_7$), (2.51) solvent. For compound **[19]** (6.64-7.84) proton of phenyl and thiazol ring, (9.41) proton of amide ($CO-NH$)[23], (4.48) of ($-NH_2$), (2.48) of($CO-CH_2$), (1.40, 1.58) of (CH_3), (2.46) solvent. For compound **[20]** (6.55-7.61) proton of phenyl and thiazol ring , (9.06) of ($NH-CO$), (1.0-1.60) of (CH_3), (2.70) of ($CO-CH2-N-$), (3.5) of ($N-CH_2-N$)[24] .

Table (3):^{1}H NMR-data (δ- ppm) of Compounds

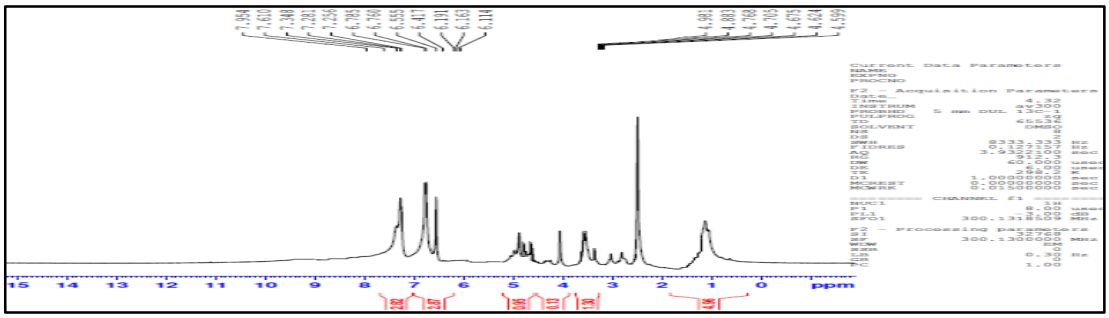
Comp.	^{1}H NMR
[1]	(13.06) proton of thiol (SH), (8.47) proton of amine in ring (NH), (7.53) proton of phenyl ring (ph).
[2]	(8.7) proton of amine in ring (NH), (7.42) (ph), (3.68-4.20) (CO_2Et), (2.10,2.14) (CH_2-S-CH_2) .
[3]	(6.55-7.95) (ph), (3.30-4.00) (CO_2Et), (2.80,2.90) (CH_2-S-CH_2), (4.59-4.98) ($N-CH_2-CH_2-CO-$) .
[4]	(6.19-6.64) (ph), (9.06) (CO-NH), (2.90) (CH_2-S), (4.59-4.98) ($N-CH_2-CH_2-CO-$),(3.30-4.00) (CO_2Et), (2.80,2.90) (CH_2-S-CH_2),(3.5) ($S-CH_2-CO$), (4.0) ($-OCH_3$) .
[5]	(6.98-7.66) proton of phenyl ring (ph), (4.06) ($-OCH_3$) ,(2.70) (CH_2-S), (3.06-3.91) ($N-CH_2-CH_2-CO-$), (4.02) ($N-CH_2-N$), (3.96) ($S-CH_2-CO$).
[7]	(7.16-7.36) proton of phenyl ring (ph), (4.22)of ($-NH_2$) ,(1.57,1.96) of (CH_3).
[8]	(7.28-7.62) proton of phenyl ring (ph), (4.60)of (-NH) , (3.80-4.10) proton of Ethyl of ester (CO_2Et), (1.30,1.40) of (CH_3).
[9]	(6.36-7.67) proton of phenyl ring (ph), (3.10-3.67) (CO_2Et), (3.93-4.50) ($N-CH_2-CH_2-CO-$), (4.90) of ($-OCH_3$), (1.00,1.10) (CH_3).
[10]	(6.41-7.95) proton of phenyl ring (ph), (9.17) proton of amide (CO-NH), (3.00-3.60) ($N-CH_2-CH_2-CO-$), (4.98) ($-OCH_3$), (1.00, 1.30, 1.55) (CH_3), (4.00) ($N-CH_2-CO$).
[11]	(6.98-7.95) proton of phenyl ring (ph), (2.80-3.96) ($N-CH_2-CH_2-CO-$), (4.15) ($-OCH_3$), (1.20, 1.90, 1.95) (CH_3), (2.70) ($N-CH_2-CO$), (4.20) ($N-CH_2-N$),
[14]	(6.64-7.28) proton of phenyl ring (ph), (4.48) of ($-NH_2$).
[16]	(6.65-7.42) proton of phenyl ring (ph), (3.41-4.05) proton of ($N-CH_2-CH_2-CO-$), (1.02-2.25) of ($N-C_3H_7$).
[19]	(6.64-7.84) proton of phenyl and thiazol ring , (9.41) (CO-NH), (4.48) ($-NH_2$), (2.48) ($CO-CH_2$), (1.40, 1.58) (CH_3).
[20]	(6.55-7.61) proton of phenyl and thiazol ring , (9.06) (NH-CO), (1.0-1.60) (CH_3), (2.70) (CO-CH2-N-), (3.5) ($N-CH_2-N$) .



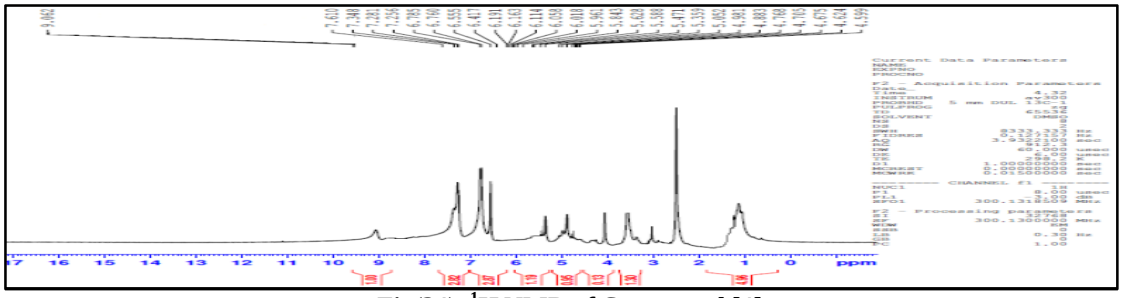
Fig(21):^{1}H NMR of Compound [1]



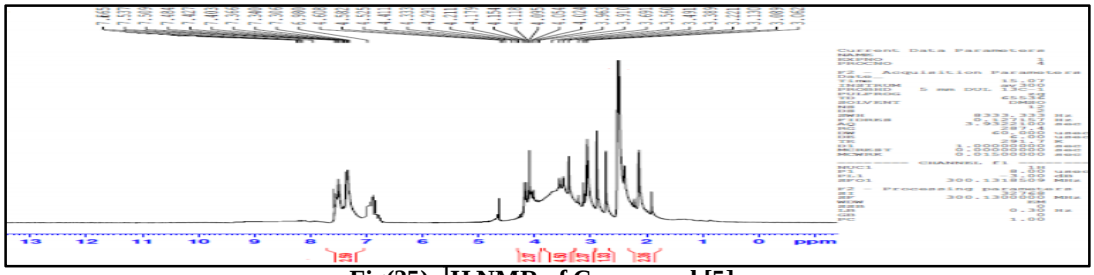
Fig(22):^{1}H NMR of Compound [2]



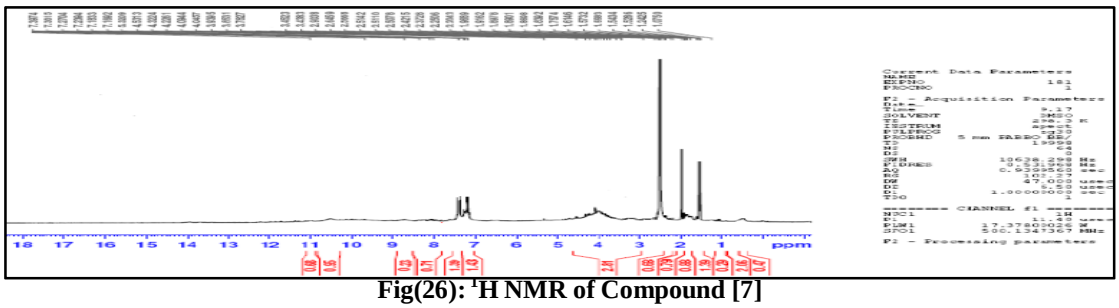
Fig(23):^{1}H NMR of Compound [3]



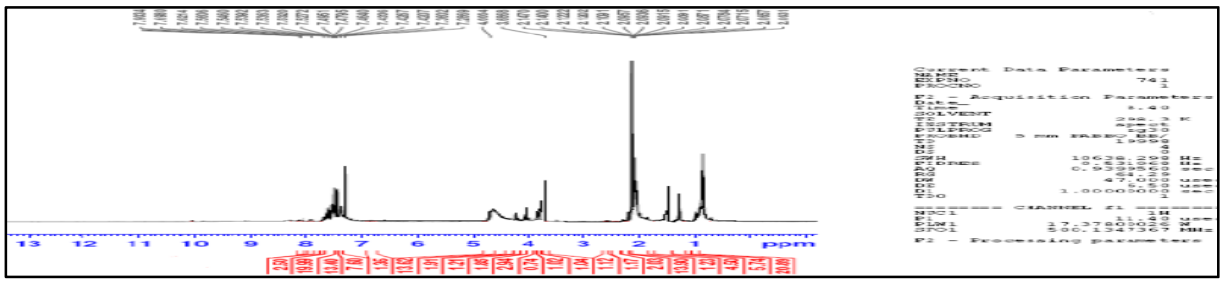
Fig(24): ^{1}H NMR of Compound [4]



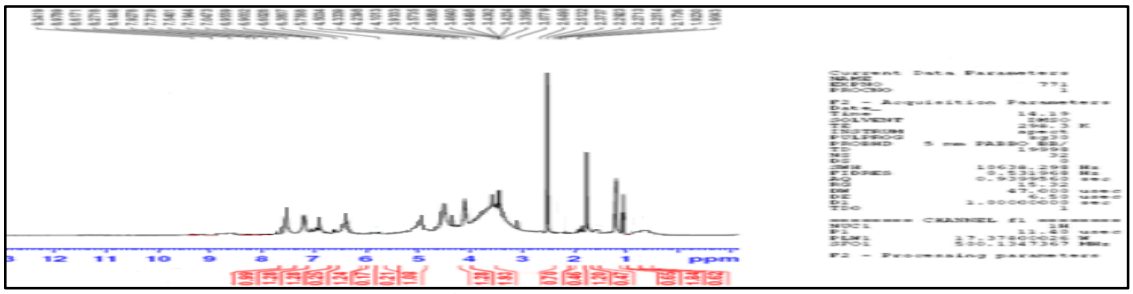
Fig(25): ^{1}H NMR of Compound [5]



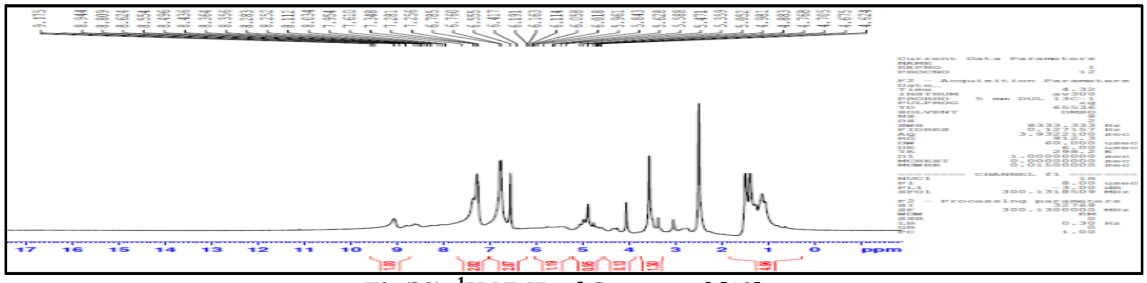
Fig(26): ^{1}H NMR of Compound [7]



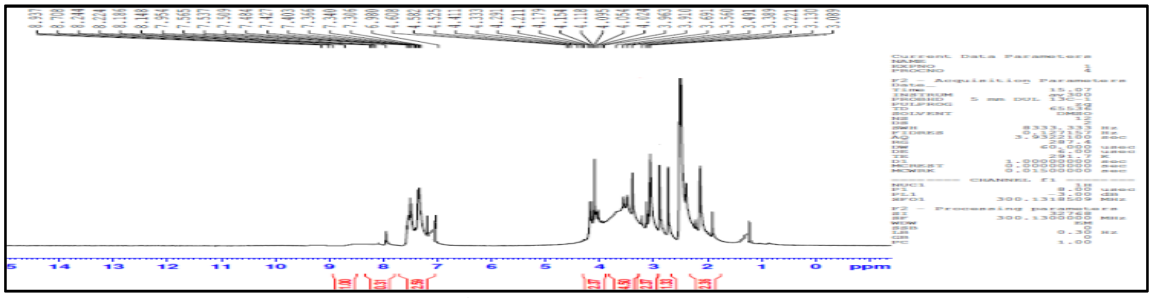
Fig(27): ^{1}H NMR of Compound [8]]



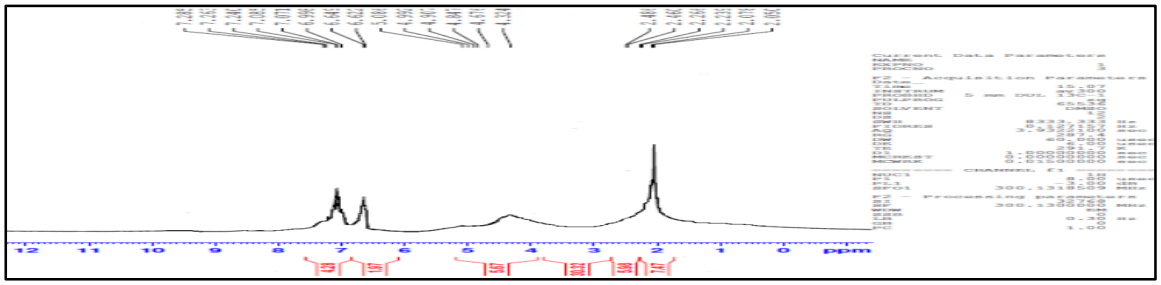
Fig(28): ^{1}H NMR of Compound [9]



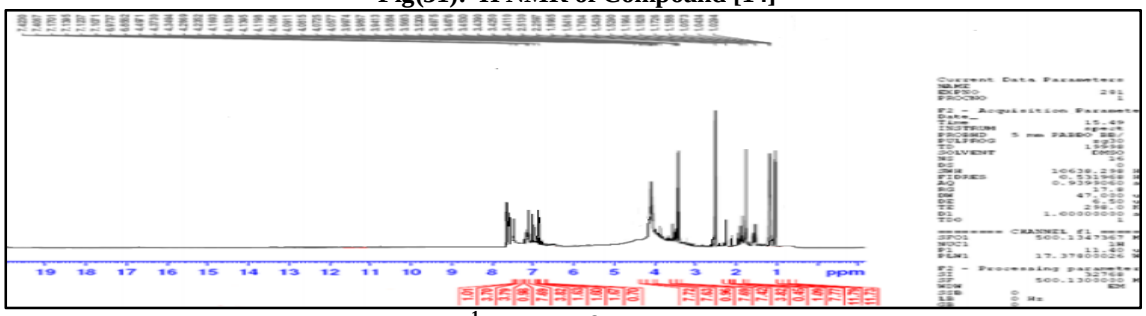
Fig(29): ^{1}H NMR of Compound [10]



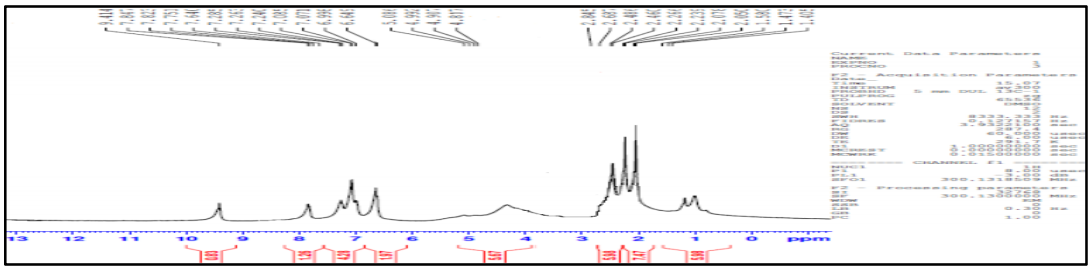
Fig(30): ^{1}H NMR of Compound [11]



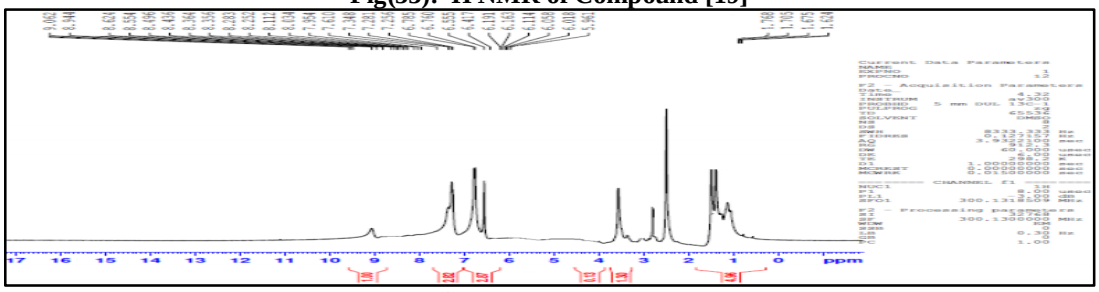
Fig(31): ^{1}H NMR of Compound [14]



Fig(32): ^{1}H NMR of Compound [16]



Fig(33): ^{1}H NMR of Compound [19]

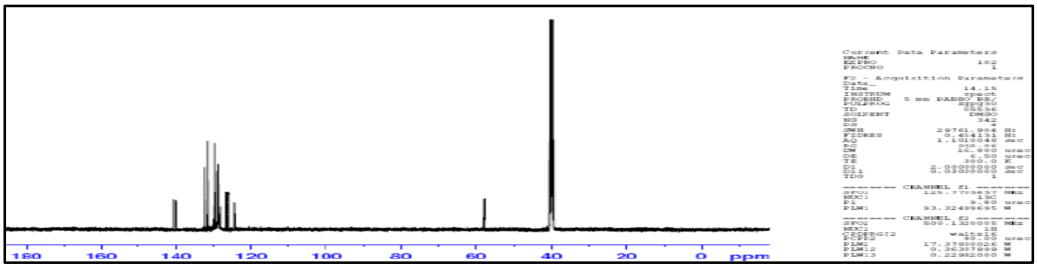


Fig(34): ^{1}H NMR of Compound [20]

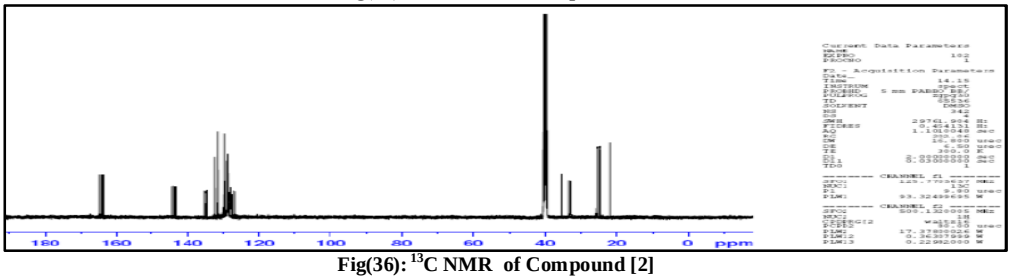
The ^{13}C N.M.R- Spectra: which used to indicate to functional groups[25, 26] in formated compounds as in Table (4):

Table (4) : ^{13}C N.M.R- data of compounds

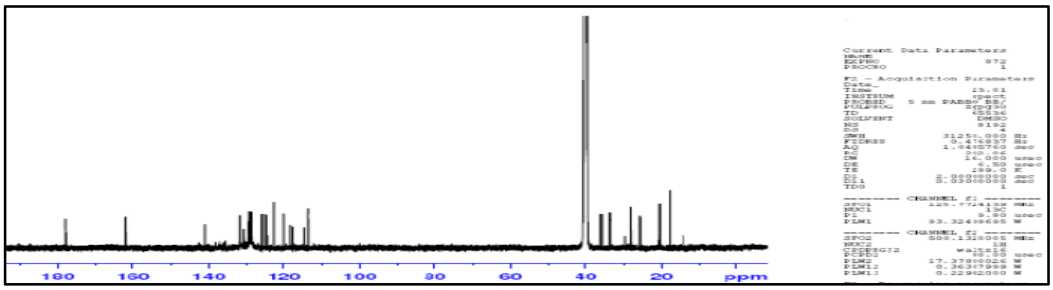
Comp.	^{13}C N.M.R - data
[1]	56.0 :(CH_2-SH), (125-132) :carbon atoms of (ph), 140: carbon of imidazole.
[2]	(34.0,36.0): (-CH_2-S-CH_2), (22.0, 24.0) :(Ethyl), 128-134 :(ph-), 144 :imidazole, 164:(COO) ester.
[3]	(20, 22): Ethyl group(ester),(36,38):(-CH_2-S-CH_2), (28,30): (-N-CH_2-CH_2-), (116-132): (ph), 142 imidazole, 164 :ester , 180:(CO) ketone .
[5]	(34,36) :(-CH_2-S-CH_2) , 30,28 (N-CH_2-CH_2), (110-130): (ph), 142 imidazole, (158,160): (-CO-N) amide , 182 :((CO) ketone , 32.0: (N-CH_2-N) , 65: (-OCH_3).
[8]	(10, 14): (CH_3), (18 ,20): (C_2H_5), 36 (–CH_2), (118-130): (ph), 144 :thiazol , 168 : (COO)ester.
[9]	(6, 10): (CH_3), (16, 30): (C_2H_5), 30 (-CH_2-), 36, 38 (-N-CH_2-CH_2), 64 (-OCH_3), 142 thiazol, (110-130): (ph), 164 : (COO)ester, 182: (CO) ketone.
[10]	(6, 8, 10): (CH_3), 32 (N-CH_2-CO), 34, 38 (-N-CH_2-CH_2), 60 (-OCH_3), 144 thiazol, 112-132 (ph), 158 :(-CO-NH) amide , 180: (CO) ketone .
[15]	(4-12): propyl group, 144 : carbon atom in thiazol, 124-134 (ph).
[16]	(8-16)(C_3H_5), 22-28 (-N-CH_2-CH_2-), 140 :thiazol, 184 : (CO)ketone, 116-132 (ph).
[17]	(10-18):(C_3H_5), 36 (N-CH_2-N), 142 thiazol , (116-130): (ph) .



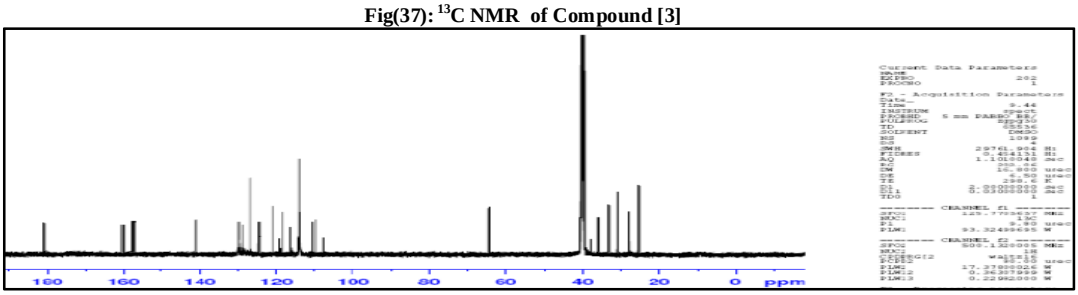
Fig(35): ^{13}C NMR of Compound [1]



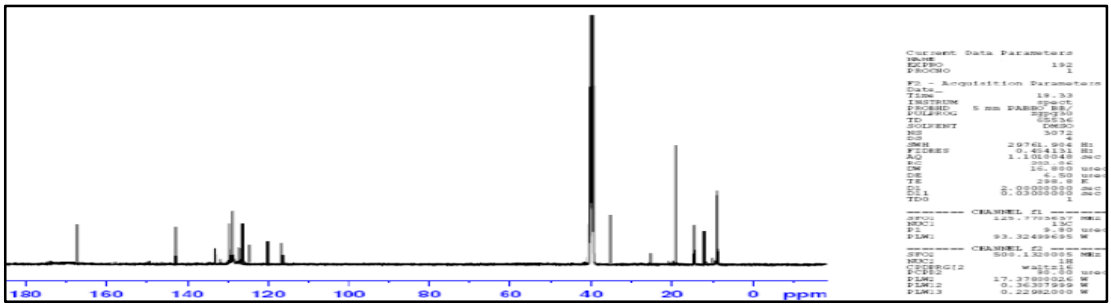
Fig(36): ^{13}C NMR of Compound [2]



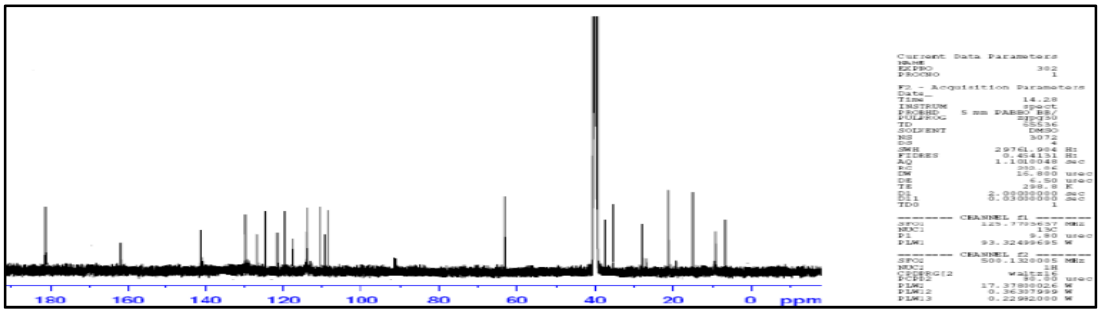
Fig(37): ^{13}C NMR of Compound [3]



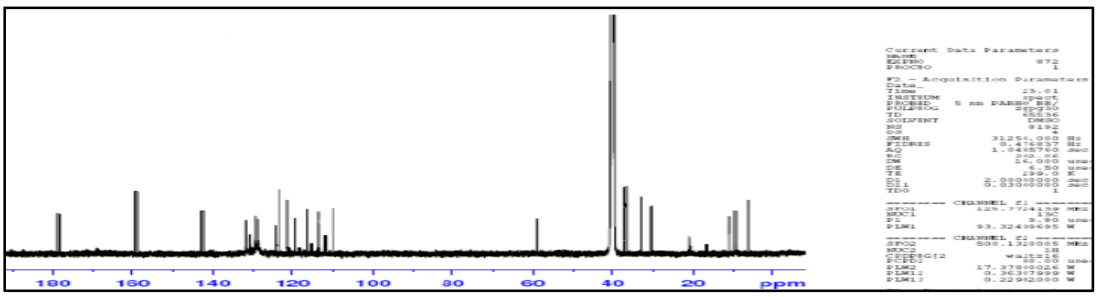
Fig(38): ^{13}C NMR of Compound [5]



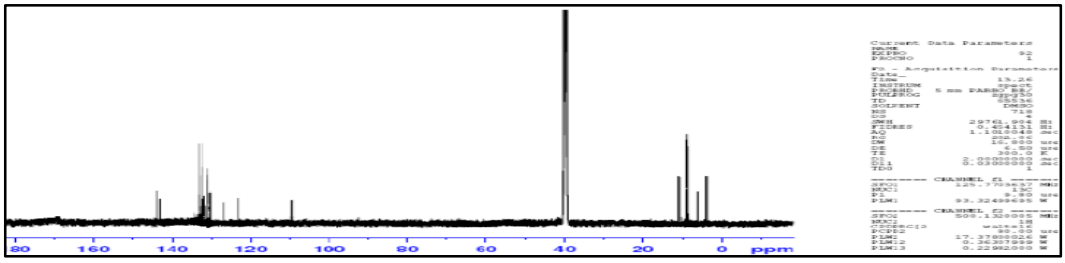
Fig(39): ^{13}C NMR. of Compound [8]



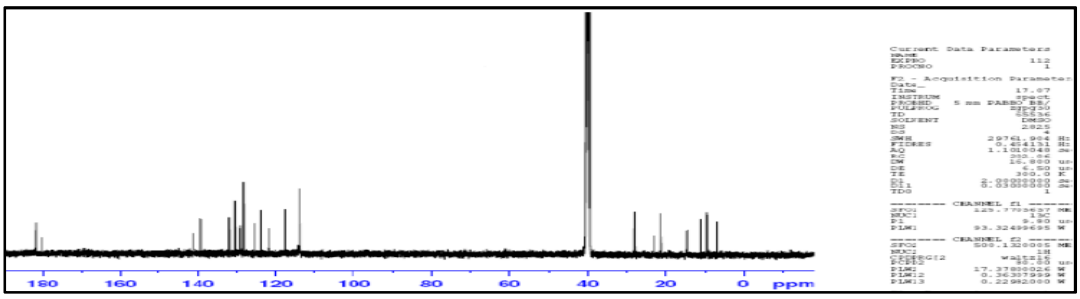
Fig(40): ^{13}C NMR of Compound [9]



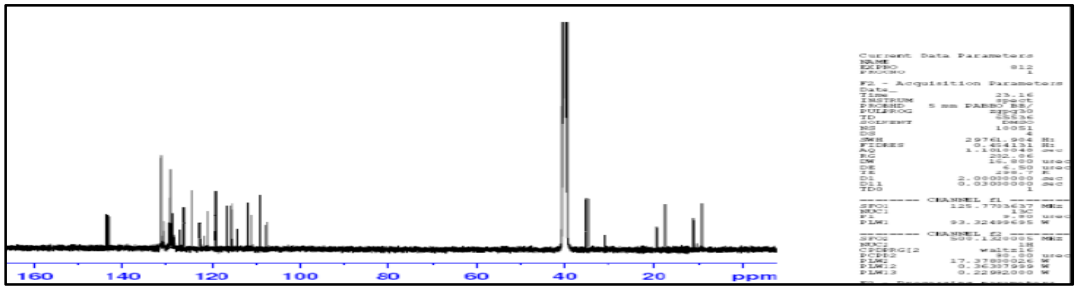
Fig(41): ^{13}C N.M.R. of Compound [10]



Fig(42): ^{13}C N.M.R. of Compound [15]



Fig(43): ^{13}C NMR. of Compound [16]



Fig(44): ^{13}C NMR. of Compound [17]

ACKNOWLEDGEMENTS

The authors thank Dr. Ahmed Aljanabi for providing all measurements in Canada .

REFERENCES

[1] C. Mannich and W. Krpsche, *Arch Pharm*, 250, 647, (1933) .

[2] B.B. Thmpron , *J , Pham.Sci.* , 57, 715 ,(1968) .

[3] M. Arend, B. Westermann, N. Risch, "*Angew.Chem. Int. Ed.*", 37, 1044 , (1998) .

[4] V. Aberg, H. Almstedt, A. Westermark, F. Almqvist, *J. Org. Chem.* 69 , 7830 , (2004).

[5] W. E. Bachmann , J. R. Johson , H. R. Sngder , "*Organic reaction 6th ed. ,Wiley Sonc. Inc*". , Newyork , (1957) .

[6] H. P. S. Ghawla , *J. Med. Chem.*,13 , (1970) .

[7] W. J. Gottstein and L. C.*J.Med.Chem.* ,13 ,480 , (1970) .

[8] R. E. Karll , R.Lee , , *J. US. Patent.* , US 4 384 138 , (1983) .

[9] G. B. Barlin ,C. Jiravinya , . *Aus. J. Chem.* , 43 , 1175 , (1990) .

[10] G. B. Barlin , C. Jiravinya , J. H. Yan , *Aus. J. Chem.* , 44 , 677 , (1991) .

[11] S. K. Sridhar , M. Saravanan , A.Ramesh , *Eur. J. Med. Chem.,* 36 , 615-625 , (2001) .

[12] S. Joshi ,N. Khosla , D. Khare , R. Sharda , *Bio. Org. Med. Chem. Lett.,* 15 , 221-226 , (2005).

[13] A. Chipeleme, J. Gut , P. J.Rosenthal , K.Chibale , *Bio. Org. Med. Chem.,* 15, 273-282 , (2007) .

[14] V. Ravichandran, S.Mohan ,K. Suresh Kumar , *Arkivoc Newslett* , 14 , 51-57 , (2007) .

[15] M. V. Mezentseva, I. S. Nikolaeva, E. A. Golovanova,L. Yu. Krylova, A. N. Fomina , *Khim. Farm. Zhur.,* 25 , 35 , (1991) .

[16] A. G.Horodysky, Kaminski , *J. M. US Patent* , US 4 394 278 , (1983) .

[17] L. A. Thomson ,J. A. Ellman, *Chem. Rev*., 96, 555 , (1996).

[18] A. Dömling, I. Ugi, *"Angew. Chem. Int. Ed."*, 39, 3169, (2000).

[19] A. Dandia, R. Singh, P. Sarawgi, S.Khaturia, *Chin. J. Chem.,* 24, 950, (2006).

[20] Abolghasem Davoodnia,Afsaneh Tavakoli-Nishaburi , Niloofar Tavakoli-Hoseini , *Bull. Korean Chem. Soc*.,32 , 635 , (2011) .

[21] Subbiah Ramasamy , Tanmoy Guria , Tanushree Singha , Puspita Roy, Benu P. Sahu , Jayatri Naskar , Avijit Das and Tapan K. Maity ,*Der Pharma Chemica*, 8(4) , 446-452 , (2016) .

[22] Srinivasa Rao Jetti, Anjna Bhatewara, Tanuja Kadre and Shubha Jain , *Der Pharma Chemica* , 8(5) , 98-106, (2016) .

[23] M. A. Salem, *Der Pharma Chemica* , 8(4) , 363-376, (2016) .

[24] Shaukath Ara Khanum, Noor Fatima Khanum , Mohammed Al-Ghorbani and Zabiulla **,***Der Pharma Chemica* , 8(4) , 453-461, (2016) .

[25] Y. Filali Baba, H. Elmsellem, Y. Kandri Rodi, H. Steli, C. AD, Y. Ouzidan,F. Ouazzani Chahdi, N. K. Sebbar, E. M. Essassiand B. Hammouti , *Der Pharma Chemica* , 8(4) , 159-169, (2016) .

[26] Elsherbiny H. Elsayed and Eman M. Radwan , *Der Pharma Chemica* , 8(4) , 399-413, (2016) .