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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF SOME NEW HETEROCYCLIC COMPOUNDS DERIVED FROM 4-AMINOACETOPHENONE

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ABSTRACT : Our work aimed for organic synthesis and biological investigation of some new heterocyclic derivatives by three steps : the first step included synthesis of some five-membered and six-membered heterocyclic derivatives (Pyrazole, Isoxazole, Oxazine and Thiazine) from Chalcone. The second step included synthesis of some 1,3-Oxazipene derivatives from Schiff's bases derived from Azo compound. The third step included the assay of biological activity of all compounds against four types of pathogens bacteria (*Staphylococcus aureus*, *Granutice tella adiacens*) gram positive and (*E. coli, Proteus mirabilis*) gram negative the results exhibited excellent biological activity for all derivatives compared to antibiotics (Ampicillin and Ciprofloxacin). These compounds were identified and confirmed by FT- IR, 1HNMR, 13CNMR and elemental analysis.

Key words : Synthesis, heterocyclic derivatives, chalcone, antibacterial.

INTRODUCTION

Heterocyclic compounds are very broadly distributed in nature, and are important to life in different ways (Dhar, 1981). Mainly these compounds are essential because of the inclusive and variety of physiological activities associated with this part of substances. Heterocyclic rings are present in some compounds like most of the members of antibiotics, vitamin B complex, hemi, chlorophyll, other plant pigments, amino acids, proteins, enzymes, drugs, the genetic material DNA and dye stuffs (Wilson and Gisvold, 1966; Wunsche and Button, 1967). The chief importance of hetero cycles in nature product chemistry and pharmacology constantly drive the search for new ways for the building of heterocyclic five-membered rings like unit isoxazoles, pyrazoles (Granero *et al*, 1999), six-membered rings as oxazine and thiazine as well as seven-membered rings for example 1,3- oxazipene .These isoxazoles, pyrazoles, oxazine and thiazine were synthesized from chalcones which are main intermediate products and they too possess biological and pharmacological effectiveness (Modi and Naik, 1994). The another class reactions is not limited and gives typical 1,3-oxazepine rings derived from Schiff's bases. This kind of cyclo another reaction that used to amalgamation of 1,3-oxazepine ring was determined (2+5) $\rightarrow$ 7 cyclo addition reaction in which two units of imine accumulating as two-membered part was additional to five-membered portion, for example, maleic or phthalic anhydrides to obtain a seven-membered hetero cycle (Sadiq, 2017; Sallal and Ghanem, 2011). Oxazepine is non-homologous seven member ring that includes two heteroatom (Oxygen and Nitrogen). Oxazepine and their derivatives require some essential biological pharmacological activities (Fadi *et al*, 2003) like analgesic (Mikim *et al*, 2002), enzyme inhibitors (Moawad, 1989), psychoactive drugs (Bilgic *et al*, 2009) and antidepressant (Jiu *et al*, 1977; Elarfi *et al*, 2012).

MATERIAL AND METHODS

Reagents and reactants are used like obtained fromcommercial providers without further purification. Solvents were purified before hand. The purity of derivatives and path ofreaction were monitored using thin layer chromatography on silicagel-G (Merck grade) with ethanol and benzene mixture asmobile phase. The meltingpoints were measured in open capillaries, with the help of (Stuart) melting point (SMP30, England) melting point apparatus are uttered in ^{i}C and are uncorrected. Infrared spectra (IR) were recorded on Shimadzu Prestige-21 Spectrophotometer by using potassium bromide (KBr pellets) and the values are uttered in cm^{-1}, 1H NMR and 13CNMR spectra of the derivatives were recorded on Bruker (Avance III, Bruker 300MHz NMR spectrophotometer using TMS as an interior standardand the values are expressed in ä ppm in university of Toronto in Canada and elemental analyses were completed on a Flash EA1112 C.H.N analyzer (Thermo Electron Corporation).

General procedure for synthesis of Chalcone (F)

1-(4-aminophenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one

Vanillin (0.01 mol) and 4-amino acetophenone (0.01 mol) were dissolved in absolute ethanol (30 mL).Sodium hydroxide solution 10% (5 mL) was added gradually and the mixture stirred for 5-6 hrs then it was constant stirring and put overnight in Refrigerator. The precipitate found was filtered, washed and recrystallized from ethanol (Bera and Roy, 2009).

Synthesis of Oxazine / Thiazine derivatives (F_1, F_2)

4-(2-amino-6-(4-aminophenyl)-6H-1,3-oxazin-4-yl)-2-Methoxyhenol

4-(2-amino-6-(4-aminophenyl)-6H-1,3-thiazin-4-yl)-2Methoxyphenol

A mixture of chalcone F (0.03 mol), thiourea/urea (0.03 mol) were dissolved in (30 mL) of absolute ethanol and sodium hydroxide solution 10% (5 mL) was stirred for 4hrs, after that it was transferred into 20 mL of ice water with continuous stirring for 1 hrs, then left overnight. The precipitate made was filtered, washed and recrystallized by ethanol (Kalirajan *et al*, 2009).

Synthesis of Pyrazole derivative(F_3)

4-(5-(4-aminophenyl)-1H-pyrazol-3-yl)-2-Methoxy phenol

A derivative (F) (0.001 mol) and hydrazine hydrate (0.20 mL, 0.002 mol) was refluxed for 10 h, in 30 mL absolute ethanol then cooled and the residual material (F_3) was filtered off and recrystallized from ethanol (Hamada and Sharshira, 2011).

Synthesis of Isoxazole derivative (F_4)

4-(5-(4-aminophenyl)-4.5-di-hydroisoxazol-3-yl)-2-Methoxy phenol

A compound of Chalcone (F) (0.01 mol), hydroxylamine hydrochloride (0.01 mol) and sodium acetate in ethanol (30 mL) was refluxed for 8 h, then the reaction mixture was cooled. The precipitate obtained was filtered, washed and recrystallized from ethanol (Turki *et al*, 2012).

Synthesis of Azo compound (N)

1-(4-((5-amino-4-hydroxy-2-methylphenyl) diazenyl) phenyl ethanone

A solution of 4- amino acetophenone (10 mmol) and 11.5M HCl (10 mL) then water (20 mL) was added in order to dissolve the amine . The mixture was cooled to 0°C in an ice bath with stirring. the reaction will still work well if it is stirred. Newly prepared 1M sodium nitrite solution (10 mL) was then added gradually with stirring. the temperature of the solution remnants below 10 °C. The solution was kept in an ice bath and used directly in the next step . Coupling with 2- amino-5- methyl phenol (10 mmol) in 1M NaOH (30 mL) was synthesized and cooled in an ice bath. The diazonium salt from step 1 was then added slowly with stirring to the phenol solution. The reaction mixture was then left standing in the ice bath for at 3h until the crystallization is complete The brown azo dye was then collected and washed with cold water (Al-Hamdani *et al*, 2010).

Synthesis of Schiff's bases (N_1, N_2)

1-(4-hydroxy-2-methyl-5-(4-nitrobenzylidene amino) phenyl) diazenyl) phenyl) ethanone.

5-((5-((4-acetophenyl)diazenyl)-2-hydroxy-4-methylphenylimino) methyl)-2hydroxy benzoic acid.

0.01mol from 4-nitro benzaldehyde, 3-carboxy-4-hydroxyl benzaldehyde, which was mixed with 20 ml ethanol. After that 2-3 drops of glacial acetic acid and (0.01mol) from azo compound (N) was added to this alcoholic solutions. The whole mixture were stirred under refluxed for 10 hours. After reflux the products were obtained, filtered and dried for further use (Muzammil *et al*, 2015).

Synthesis of 1,3- Oxazipene derivatives (N_3,N_4)

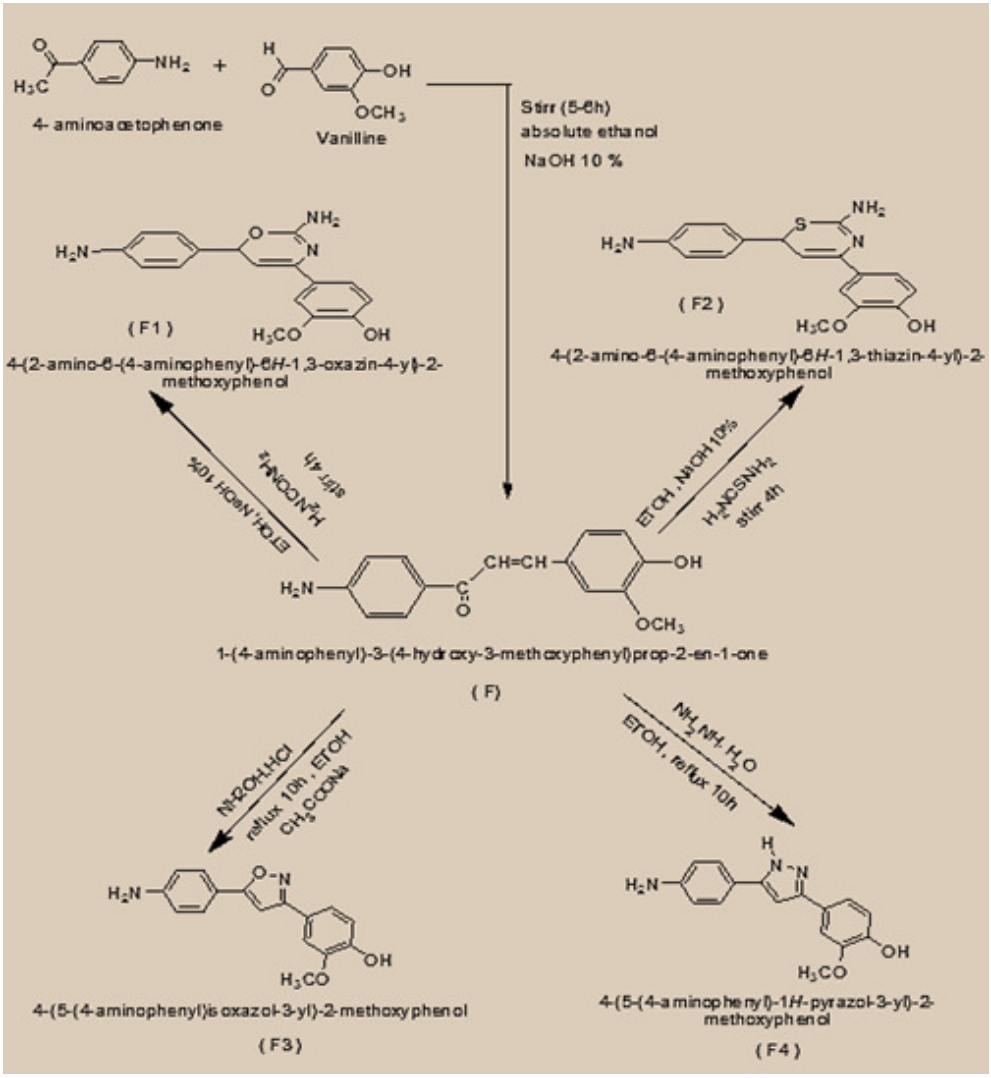
4-(5-((4-acetylphenyl)diazenyl)-2-hydroxy-4-methyl phenyl)-3-(4-nitrophenyl)-3,4-dihydro benzo [1,3] Oxazepine-1,5-dione

5-(4-(5-((4-acetyl phenyl)diazenyl)-2-hydroxy-4-Methyl phenyl)-1,5-dioxo-1,3,4,5-tetra hydro benzo[1,3] oxazepine (-3-yl)-2-hydroxy benzoic acid.

A mix of equal molar amounts (0.001mole) of Schiff's bases derivatives [N_1,N_2] and (0.001 mole) of phathalic anhydride in (30 ml) of dry benzene, were refluxed for (24) hours at (50 0C), the TLC displayed that the reaction was ample by using (benzene : ethanol, 2 : 3). Then, the solvent was separated and crystalline solid was recrystallized from dry 1,4-dioxan (Samir *et al*, 2017).

Biological activity assay

Antibacterial activity of the heterocyclic compounds [F-F_4 and N-N_4] have been carried out against four types of bacteria like, *(staphylococcusaureus*, *Granutice tella adiacens*) gram positive and (*E. coli, Proteus mirabilis*) gram negative using nutrient agar medium via well diffusion method[21]. All derivatives were suspended in aqueous solutions in dissimilar concentrations ranged from 1µg, 0.5 µg and 0.1 µg in 100 ml of water, the results are voiced on MIC (minimal inhibitory concentration),



Scheme 1 : Synthesis some heterocyclic compounds from Chalcone.

and exhibited high biological activity of all these synthesized compounds of these microorganisms more than the effectiveness of antibiotics (Ciprofloxacin and Ampicillin drugs). The biological investigation data is given in Table 3.

RESULTS AND DISCUSSION

In this study, the synthesis and identification of some compounds have been presented. These derivatives were prepared from Chalcone and Schiff's bases which are important intermediate products as they have different pharmacological and biological activities. They can found by two paths, the first path included condensation of 4-aminoacetophenone with vanillin in the presence of base as a catalyst by Aldol-Condensation Reaction to yield the Chalcone compound F (scheme 1).

The suggestion mechanism for synthesis of Chalcone (Jafar and Majeed, 2016) F:

Then, we can be obtained several five-membered rings derivatives (Pyrazole, Isoxazole) and six-membered rings derivatives (Oxazine, Thiazine) from Chalcone in absolute ethanol and sodium hydroxide 10% as a catalyst (Scheme 1).

The suggestion mechanism for cyclization of thiazine compound (Jafar and Majeed, 2017) F_2:

The assignment of FT-IR for compound (F) appeared absorption band (õ=cm^{-1}) at 1653 for C=O (ketone) and exhibited band at 1589 related to CH=CH (alkene) but these bands were disappeared in the spectra of compounds (F_1, F_2, F_3, F_4) and appeared new bands at 1602-1629 for C=N (endocyclic) and 1577-1597 for C=C(endocyclic), the structures of compounds (F-F_4) were identified by the ^{1}H-NMR spectra and showed the compound F spectrum exhibited singlet signal at 11.0 ppm for the hydrogen of hydroxyl group in phenol and singlet signal at 4.6 ppm related to free amine group NH_2 as

Table 1 : Elemental analysis of synthesized derivatives.

No.	Chemical formula	M.W gm/mol	Calcu. % C	Found % C	Calcu. % H	Found % H	Calcu. % N	Found % N	Calcu. %S	Found
F	$C_{16}H_{15}NO_3$	269	71.37	71.41	5.57	5.77	5.20	5.61		
F_1	$C_{17}H_{16}N_3O_3$	310	65.80	65.39	5.16	5.23	13.54	13.65		
F_2	$C_{17}H_{16}N_3O_2S$	326	62.57	62.66	4.90	4.78	12.88	12.65	9.81	9.98
F_3	$C_{16}H_{14}N_2O_3$	282	68.08	68.23	4.96	4.75	9.92	9.80		
F_4	$C_{16}H_{15}N_3O_2$	281	68.32	68.17	5.33	5.62	14.94	14.68		
N	$C_{15}H_{15}N_3O_2$	269	66.91	66.70	5.57	5.81	15.61	15.42		
N_1	$C_{22}H_{18}N_4O_4$	402	65.67	65.91	4.47	4.28	13.93	13.75		
N_2	$C_{23}H_{19}N_3O_5$	417	66.18	66.37	4.55	4.71	10.07	10.19		
N_3	$C_{30}H_{22}N_4O_7$	550	65.45	65.81	4.00	4.24	10.18	10.02		
N_4	$C_{31}H_{23}N_3O_8$	565	65.84	65.49	4.07	4.32	7.43	7.68		

Table 2 : Physical properties of synthesized derivatives.

No.	M.F	M.W gm/mol	M.P °C	Yield %	R*f* (3:3) Eth:benz	Color
F	$C_{16}H_{15}NO_3$	269	121-123	68	0.63	Light brown
F_1	$C_{17}H_{16}N_3O_3$	310	193-195	73	0.74	brown
F_2	$C_{17}H_{16}N_3O_2S$	326	205-207	78	0.54	Dark brown
F_3	$C_{16}H_{14}N_2O_3$	282	138-140	80	0.60	Dark brown
F_4	$C_{16}H_{15}N_3O_2$	281	142-144	82	0.65	Grey
N	$C_{15}H_{15}N_3O_2$	269	110-112	72	0.81	Dark red
N_1	$C_{22}H_{18}N_4O_4$	402	180-182	66	0.57	Brown
N_2	$C_{23}H_{19}N_3O_5$	417	185-187	52	0.84	Black
N_3	$C_{30}H_{22}N_4O_7$	550	265-267	70	0.49	Dark Brown
N_4	$C_{31}H_{23}N_3O_8$	565	275-277	57	0.76	Brown

of alkene CH=CH but these peaks were disappeared from spectra of another derivatives. The second line included reaction 4-aminoacetophenone with sodium nitrite solution and hydrochloric acid in ice bath 0-5 °C which coupling with 2- amino-5- methyl phenol solution in the presence of sodium hydroxide in order to form azo compound **N** which reacts with aromatic aldehyde in the manifestation of Absolut ethanol and limited drops of glacial acetic acid molded Schiff bases derivatives N_1 and N_2 as in Scheme 2.

Table 3 : Zone inhibition (mm) of all derivatives against various microorganisms and compression the biological activity of these compounds with biological activity of Ampicillin and Ciprofloxacin.

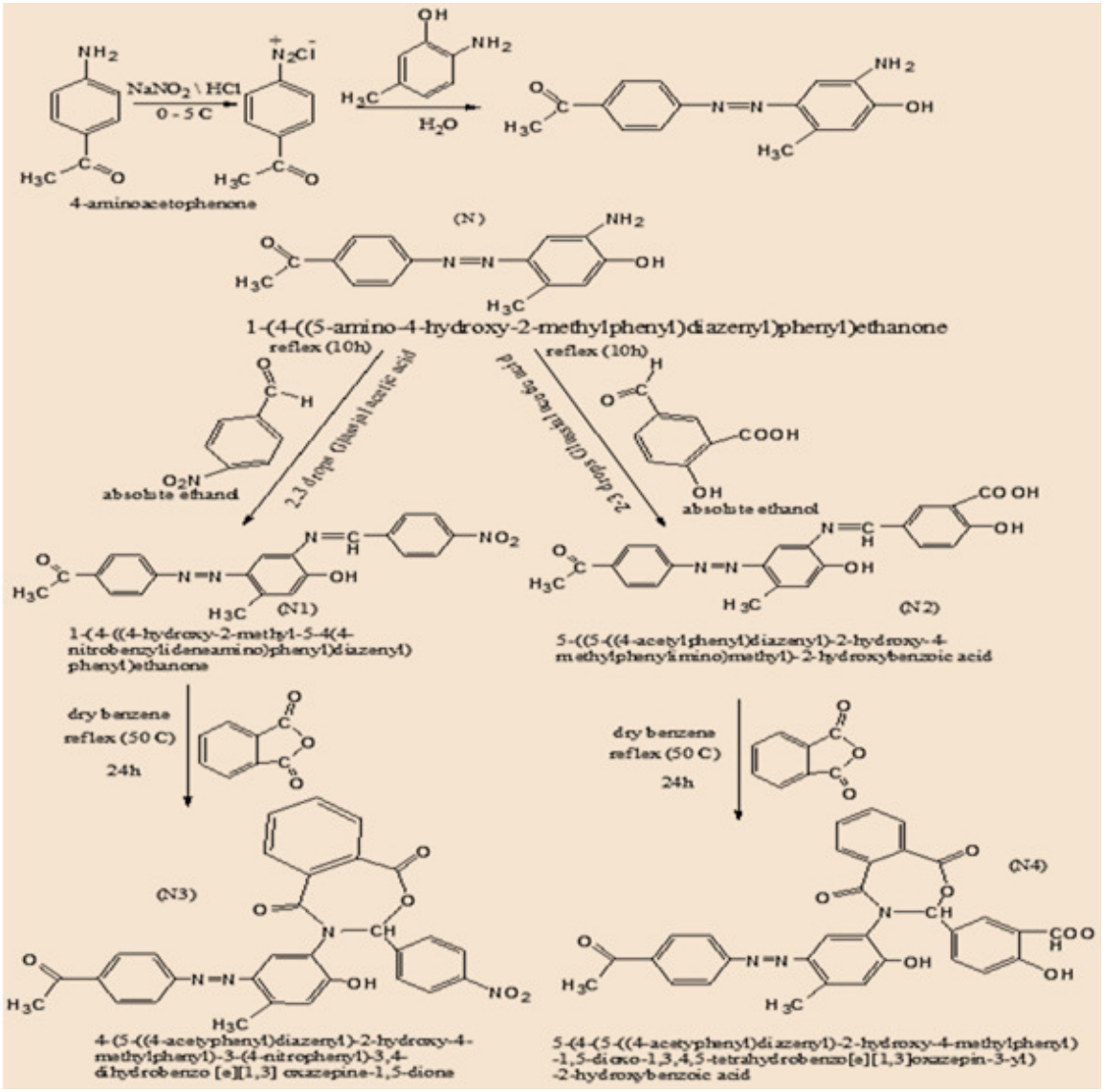
No.	Concentrations (µg/L)			Inhibition zone (mm)											
				StaphylococcusAureus			*Granutice tellaadiacens*			*Escherichia coli*			*Proteus mirabilis*		
F	1	0.5	0.1	20	16	12	18	16	14	25	22	16	22	18	14
F_1	1	0.5	0.1	22	18	14	21	18	14	23	16	14	20	16	13
F_2	1	0.5	0.1	26	18	15	24	14	12	22	18	14	25	19	14
F_3	1	0.5	0.1	18	16	12	20	16	12	18	17	15	21	18	15
F_4	1	0.5	0.1	25	20	21	24	18	19	22	20	20	23	22	18
N	1	0.5	0.1	30	24	22	32	26	22	28	25	20	30	24	21
N_1	1	0.5	0.1	22	20	16	22	18	14	17	13	11	18	14	16
N_2	1	0.5	0.1	24	12	9	18	14	12	16	14	19	24	13	10
N_3	1	0.5	0.1	28	14	12	26	14	12	25	14	10	16	12	10
N_4	1	0.5	0.1	30	22	18	26	20	18	28	12	10	26	13	11
Amp.*	1	0.5	0.1	12	11	13	12	11	10	12	13	10	10	11	13
Cip.*	1	0.5	0.1	13	10	8	12	10	9	14	11	8	17	13	11

*Ampicillin antibiotics *Ciprofloxacin antibiotics

well as the spectrum appeared doublet signals at 5.5 ppm for protons of alkene CH=CH while in others compounds the spectra showed disappeared protons of alkene CH=CH group because of the cyclization of compounds. In ^{13}C-NMR spectra, compound F exhibited peak at 187ppm for carbon of ketone (C=O) so appeared two peaks at 129 ppm and 131 ppm respectively for carbons

The suggestion mechanism of synthesis Schiff's bases N_1, N_2 compounds :

The FT-IR spectrum of compounds (N_1,N_2) showed disappearance the band of free amine group (NH_2) which was appeared in original compound (N) at 3367 and exhibited new absorption bands at 1629 and 1625 related



Scheme 2 : Synthesis of some new 1,3-Oxazepine derivatives from Schiff's bases derived from Azo compound.

to imine group (C=N) so the spectra of these compounds appeared absorption bands for (C=O) ketone at 1707 and 1680 respectively as well as exhibited bands for (N=N) azo group at 1519 and 1521.

The ^{1}H-NMR spectrum of compound N exhibited single signal at 11.05 ppm related to the hydrogen of phenol and appeared single signal for free amine group (NH_2) at 5.32 ppm so appeared quartet signal at 7.06-7.60 ppm for hydrogen of aromatic rings as well as this compound N showed single signals at 2.00 ppm and 3.32 ppm related to hydrogen of CH_3 group but in ^{1}H-NMR spectrum of compound N_2 exhibited single signal at 12.60 ppm related to the hydrogen of hydroxyl group of carboxylic acid and appeared single signal at 11.3 ppm and 10.7 ppm for hydrogen of hydroxyl group of phenol so the spectrum of compound N_2 showed single signal at 8.64 ppm related to imine group (N=CH) as well as appeared single signal at 2.30 ppm and 3.77 ppm for CH_3 group respectively while disappearance the single signal for free amine NH_2 group in original compound N at 5.32 ppm while in ^{13}C-NMR spectra while in ^{13}C-NMR spectrum the compound N exhibited clear band in 181ppm related to (C=O) ketone and appeared multiplied bands for carbon of aromatic rings at 112-133ppm so exhibited clear bands at 12ppm and 17ppm for carbon of methyl group CH_3 respectively but in ^{13}C-NMR spectrum of compound N_2 exhibited clear band at 189ppm for carbon of ketone so appeared new band at 173ppm related to carbon of carboxylic acid COOH also the spectrum of compound N_2 showed to appear new band at 149ppm for carbon of imine group (C=N) at 111-132ppm appeared multiplied bands related to carbon of aromatic rings. These compounds (N_1,N_2) react with phathalic anhydride to produce new derivatives of seven-membered rings 1,3-

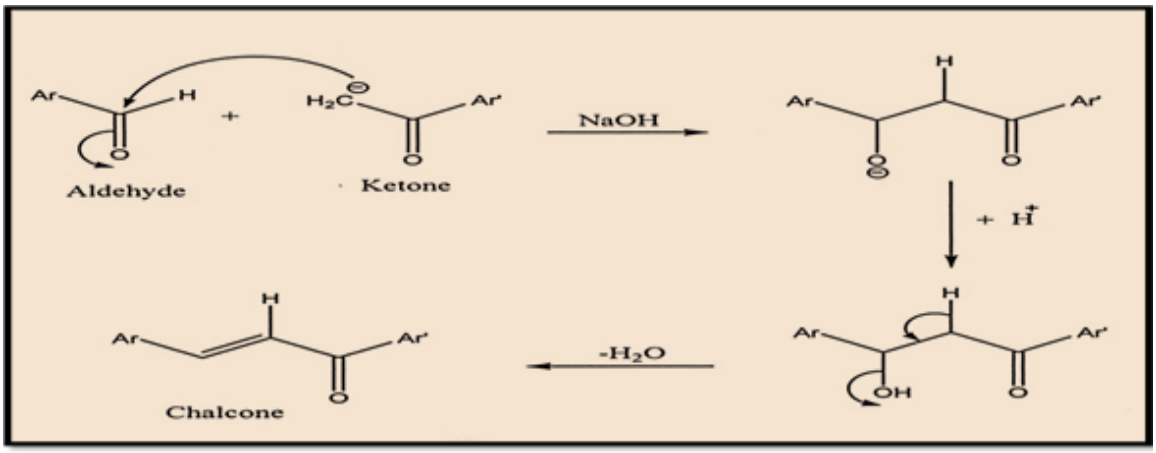


Fig. 1 :

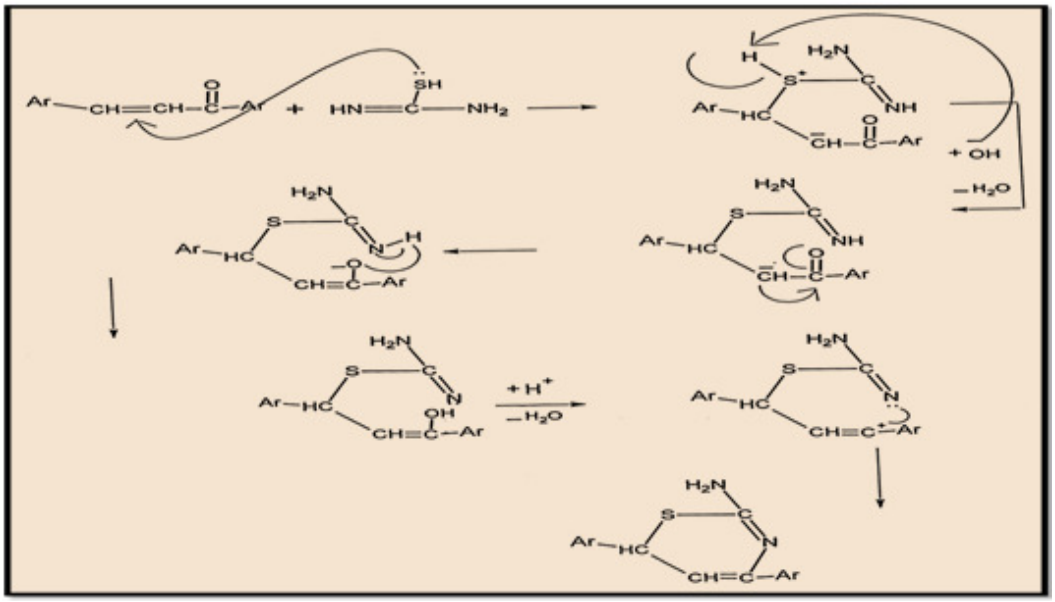


Fig. 2 :

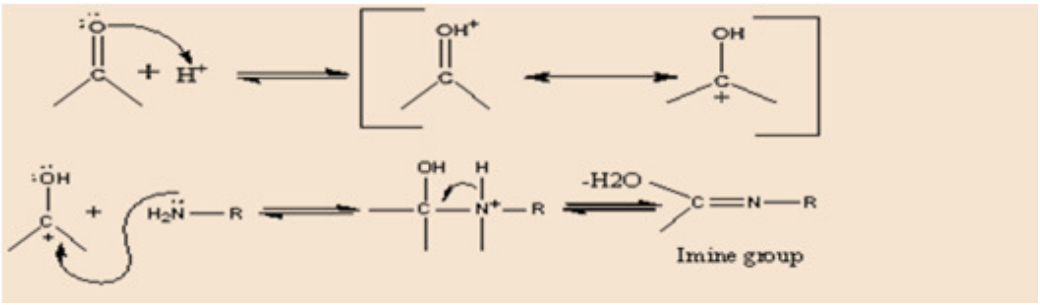


Fig. 3 :

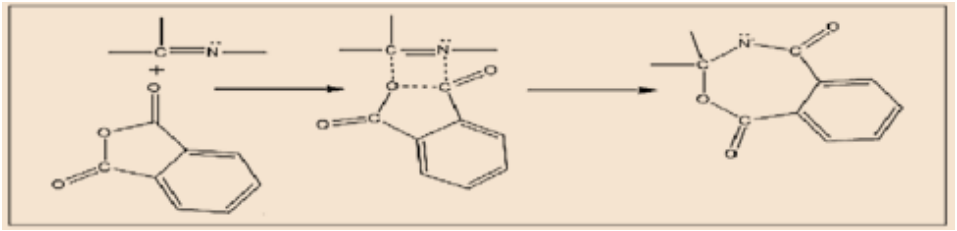


Fig. 4 :

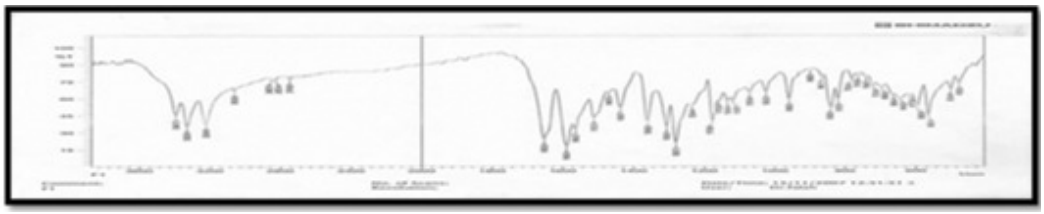


Fig 5 : FT-IR spectrum for compound F.

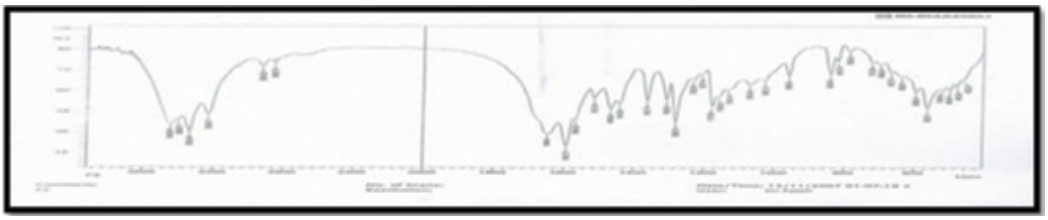


Fig. 6 : FT-IR spectrum for compound F_1.

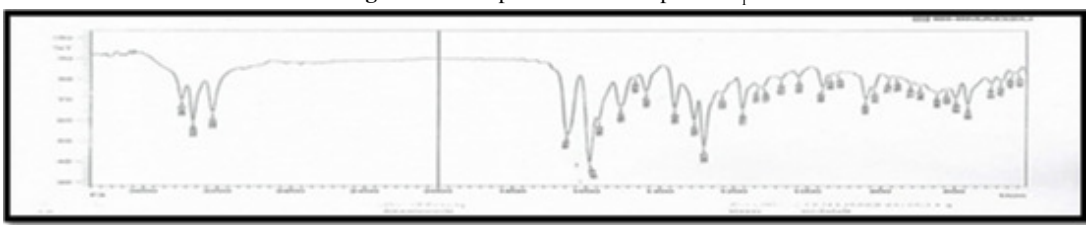


Fig. 7 : FTIR spectrum for compound F_2.

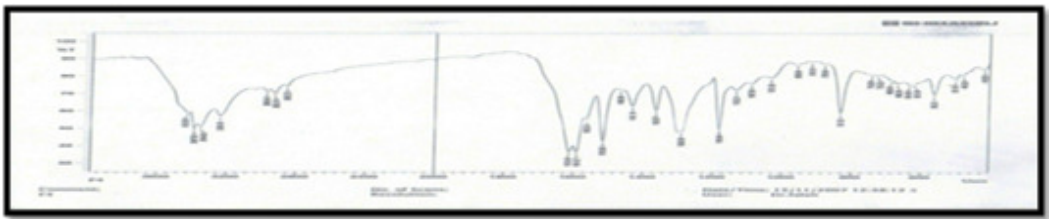


Fig. 8 : FT-IR spectrum for compound F_3.

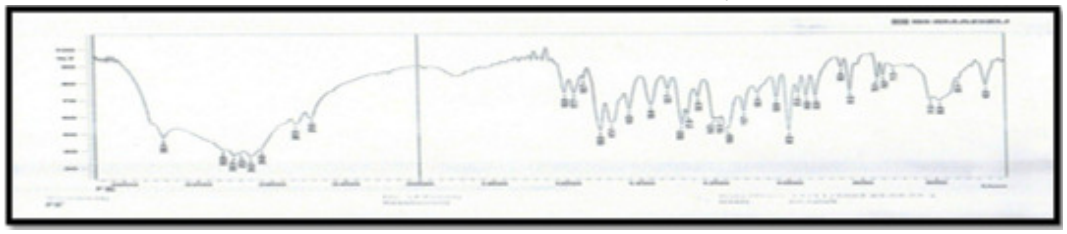


Fig. 9 : FT-IR spectrum for compound F_4.

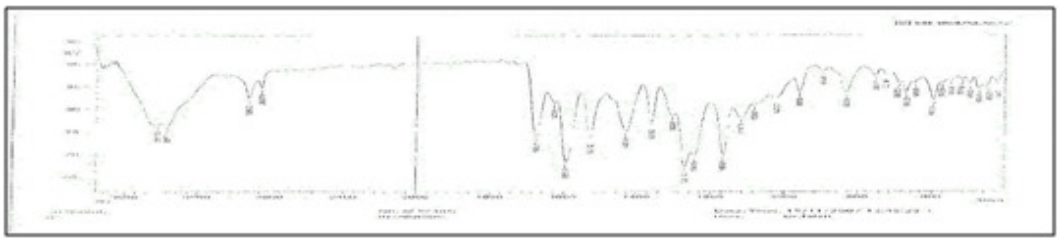


Fig. 10 : FT-IR spectrum for compound N.

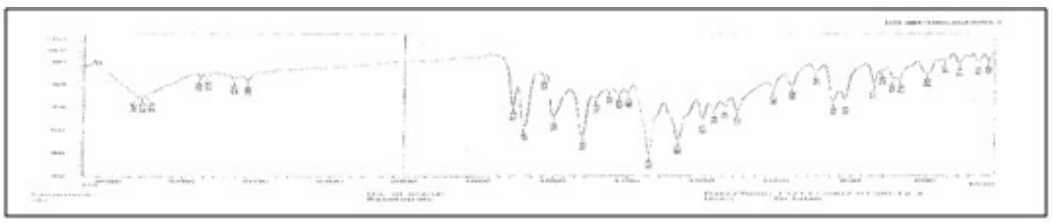


Fig. 11 : FT-IR spectrum for compound N_1.

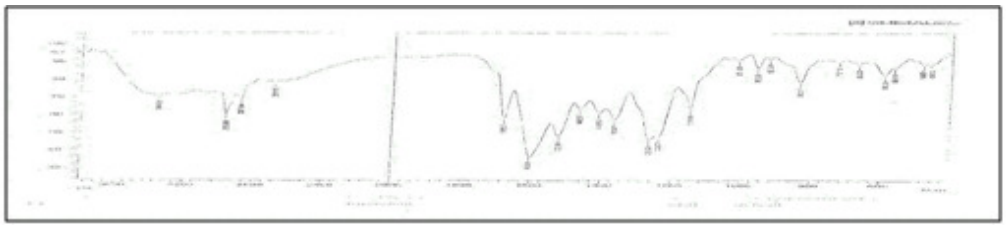


Fig. 12 : FT-IR spectrum for compound N_2.

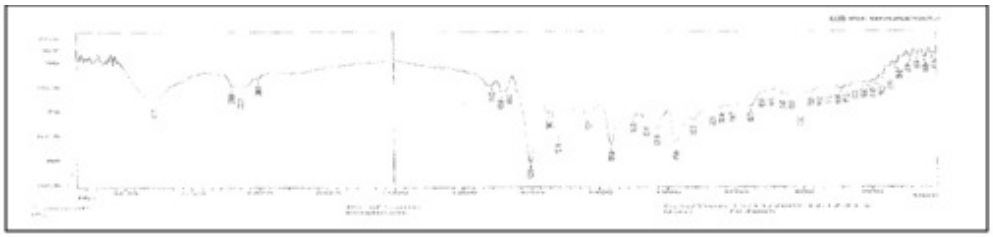


Fig. 13 : FT-IR spectrum for compound N_3.

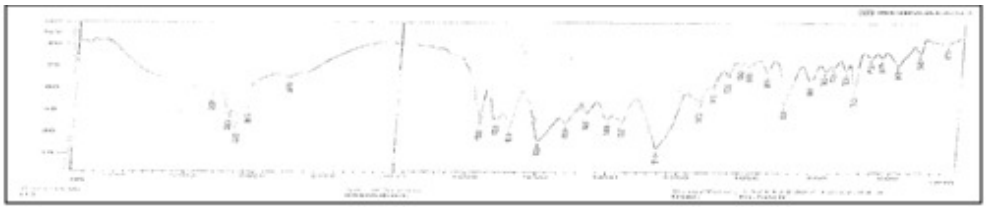


Fig. 14 : FT-IR spectrum for compound N_4.

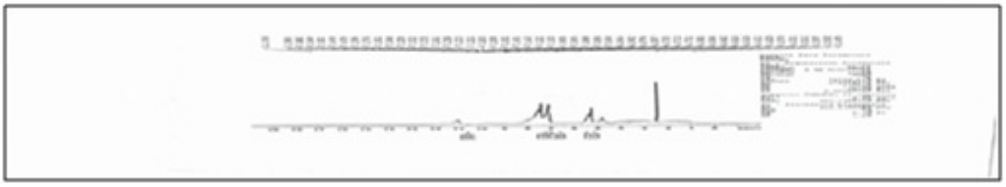


Fig. 15 : 1H-NMR spectrum for compound F.

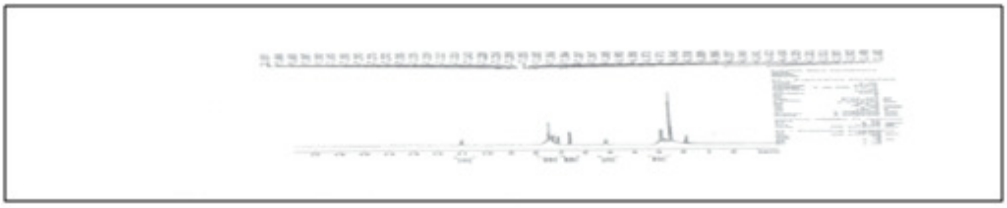


Fig. 16 : 1H-NMR spectrum for compound F_2.

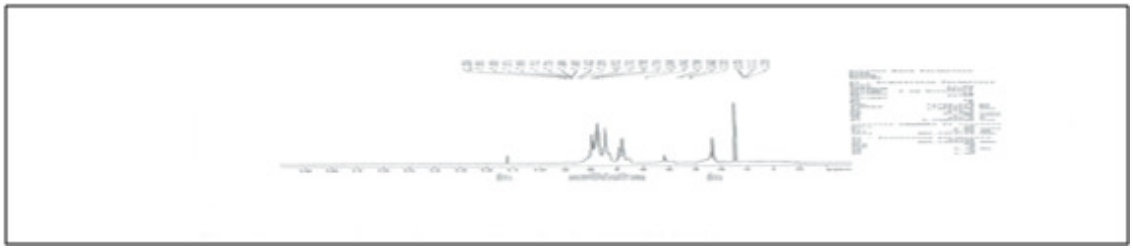


Fig. 17 : 1H-NMR spectrum for compound F_4.

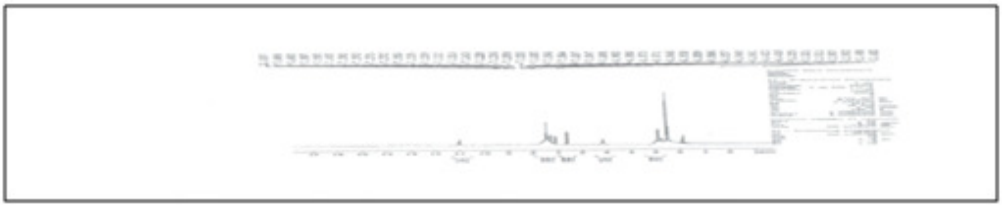


Fig. 18 : 1H-NMR spectrum for compound N.

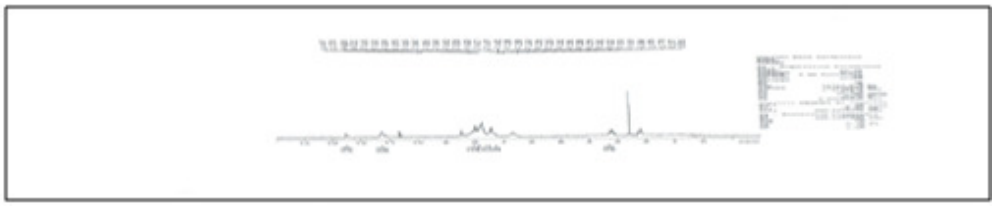


Fig. 19 : 1H-NMR spectrum for compound N_2.

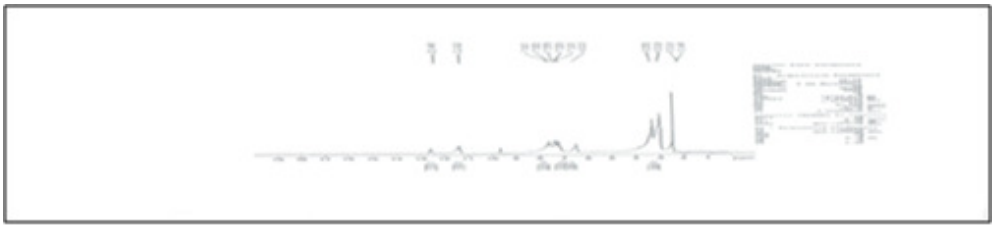


Fig. 20 : 1H-NMR spectrum for compound N_4.

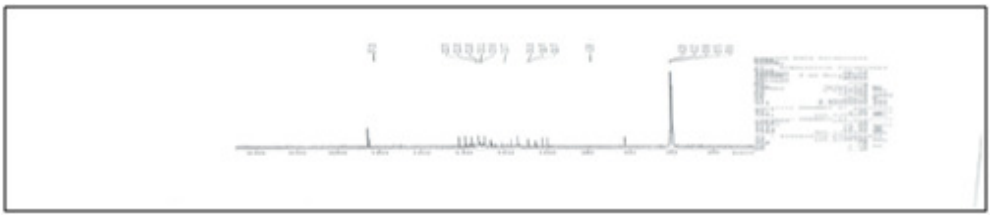


Fig. 21 : 13C-NMR spectrum for compound F.

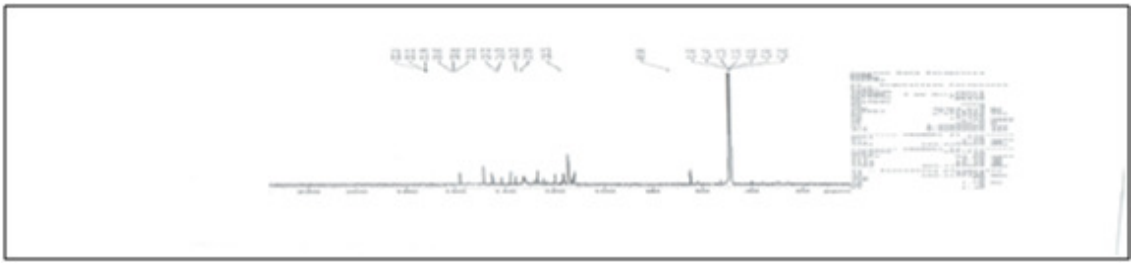


Fig. 22 : 13C-NMR spectrum for compound F_2.

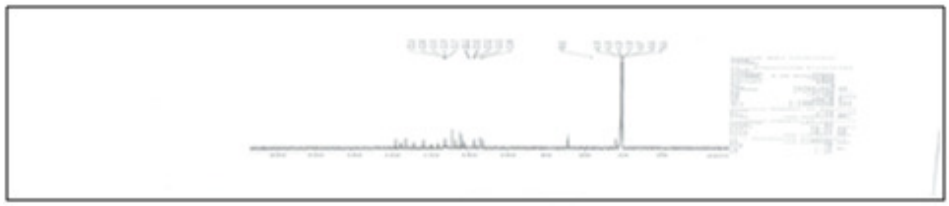


Fig. 23 : 13C-NMR spectrum for compound F_4.

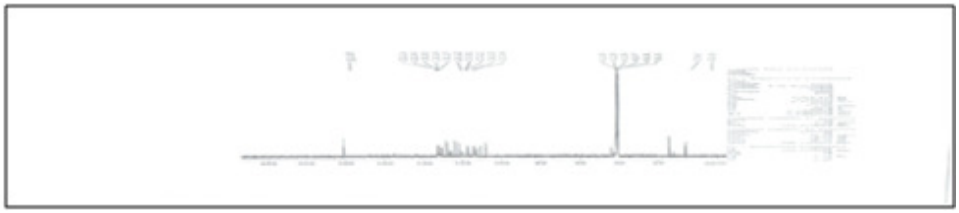


Fig. 24 : 13C-NMR spectrum for compound N.

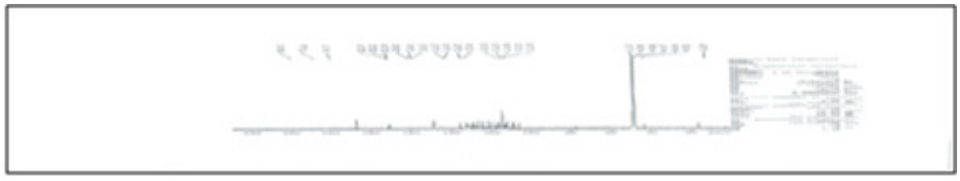


Fig. 25 : 13C-NMR spectrum for compound N_2.

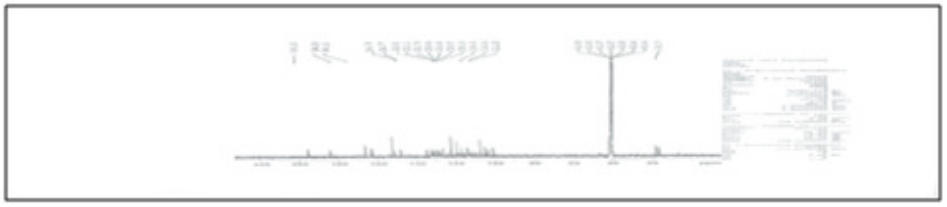


Fig. 26 : 13C-NMR spectrum for compound N_4.

oxazepine (N_3, N_4) as in scheme (2). The suggestion mechanism for cyclization of seven-membered ring 1,3-Oxazepine:

The spectral data of FT-IR for compounds (N_3, N_4) exhibited absorption bands (õ=cm^{-1}) at 3421 and 3345 for hydroxyl group (OH) and the spectrum of these compounds showed disappearance absorption bands at 1629 and 1625 respectively related to (C=N) imine group which was appeared in compounds N_1, N_2 while exhibited new absorption bands at 1714 and 1766 for lactone (O=C-O-) groups and also appeared new absorption bands at 1668 and 1681 for lactam (O=C-N-) group as well as the spectrum exhibited absorption bands at 1683 and 1720 for (C=O) ketone so the spectra of these compounds appeared absorption bands related to (C=C) aromatic rings at 1602 and 1598. The ^{1}H-NMR spectrum of compound N_4 appeared single signal at 12-16ppm for hydrogen of hydroxyl group of carboxylic acid and single signals at 11.51 ppm and 9.80 ppm for hydrogen of hydroxyl group of phenol also this spectrum showed multiplied signals at 6.51-7.61 ppm related to hydrogen of aromatic rings so exhibited multiplied signals at 3.01-3.33 ppm for CH_3 methyl group . In ^{13}C-NMR spectrum compound N_4 exhibited clear band at 195 ppm for (C=O) ketone and 185 ppm for carbon lactone group also at 166 ppm for carbon carboxylic acid so the spectrum of compound N_4 showed single signal at 164 ppm related to carbon of lactam and appeared multiplied signals at 111-154 ppm for carbons of aromatic rings finally, the spectrum exhibited single signals at 16 and 18 ppm for carbons of CH_3 methyl group.

Biological activity

The development of antibiotics for bacterial pathogenesis has a special importance in the treatment of infection diseases (Jafar and Majeed, 2016; Jafar and Majeed, 2017). The important conclusion is that the biological effectiveness of the best in the compound (F_2) and (F_4) because their constituents including organic heterocyclic rings which containing sulphuer atoms. All of these compounds showed high effective even at low concentrations. The results also showed that all compounds are effectively much higher than the effectiveness of Ciprofloxacin (Jetti *et al*, 2016) and Ampicillin (Jimenez *et al*, 2016). Some compounds like (N), (N_2), (N_3) and (N_4) are a promising agent for further structural modiûcation and pharmacological evaluation as target treatment of infections caused by these types of bacteria (Table 3).

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