Synthesis of New 1,3-Oxazepine Derivatives Containing Azo Group

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الخلاصة
تم من خلال هذا العمل تحضير مشتقات ٣،١-اوكسازيبين جديدة تحتوي في تركيبها على مجموعة الأزو. الخطوة الأولى تتضمن تحول (٤-ميثوكسي أنلين) إلى ٤-(داي مثيل أمينو)-٣-((٤-ميثوكسي فنيل)) داي ازو) بنزلديهايد [Z]. الخطوة الثانية تتضمن إدخال مجموعة ألديهايد مشتق الأزو الجديد [Z] في تفاعل تكاثف مع أمينات إورماتية أولية مختلفة (٤-ميثوكسي إنلين و ٤-أمينو أسيتوفينون و ٢-أمينو بيرمدين) بوجود الأيثانول المطلق وتم الحصول على مشتقات ازو قواعد شف الجديدة [A_3-A_1] على التوالي. أما الخطوة الثالثة فتتضمن مفاعلة مشتقات إلايمين الناتجة [A_3-A_1] مع كل من إنهدريد المالك وإنهدريد الفثاليك في البنزين الجاف فتم الحصول على مشتقات حلقية جديدة ٣،١-اوكسازيبين-٧،٤-دايون [A_6-A_4] و [A_9-A_7] على التوالي وان المخطط [2] يوضح خطوات تحضير كافة المركبات. إن جميع المركبات المحضرة شخصت بوساطة درجات الأنصهار ومطيافية الأشعة تحت الحمراء والبعض منها شخصت بوساطة مطيافية الرنين النووي المغناطيسي ألبروتوني و التحليل الدقيق للعناصر(كربون والهيدروجين والنيتروجين).

Abstract
In this work new 1,3-oxazepine derivatives containing azo group have been prepared. The first step, 4-methoxyaniline was converted to the 4-(dimethylamino)-3-((4-methoxy phenyl)diazenyl)benzaldehyde [Z]. The second step, aldehyde group of the new azo derivative [Z] was condensed with different primary aromatic amines [4-methoxyaniline, 4-aminoacetophenone and 2-aminopyrimidin] in the presence of absolute ethanol to give azo Schiff bases derivatives [A_1-A_3] respectively. The third step, the resulting imines derivatives [A_1-A_3] were reacted with maleic anhydride and phathalic anhydride in dry benzene to give new 1,3-oxazepine-4,7-dione ring derivatives [A_4-A_6] and [A_7-A_9] respectively scheme[2]. All these compounds were characterized by melting points and FT.IR spectroscopy, some of them were characterized by ^{1}H-NMR spectroscopy and elemental analysis (C.H.N.).

Introduction

Azo compounds constitute one of the largest classes of industrially synthesized organic compounds. Aliphatic azo compound, like azobisisobutylonitrile (AIBN), can be used as radical initiators in polymerization of alkenes to make plastics[(1)]. Aromatic azo compounds are used as acid-base indicators such as methyl red, methyl orange and Congo red [(2)]. Mkpenie et al.[(3)] have prepared 1-(4-methylphenylazo)-2-naphtol and study its inhibition effect on the biological activities of some bacteria like *E.coli* and *S.aureus*. Schiff bases are important intermediates for synthesis of some bioactive compounds[(4)]. Furthermore , they are reported to show a variety of interesting biological actions, including antibacterial[(5,6)], antifungal[(7)], anticonvulsant [(8)], anti-inflammatory [(9)] and antitubercular [(10)]. We reported here the synthesis new 1,3-oxazepine derivatives

containing azo group. Oxazepine is non-homologous seven member ring that contains two heteroatom (Oxygen and Nitrogen). Oxazepine and their derivatives have some important biological pharmacological activities[11] such as enzyme inhibitors[12], analgesic[13], antidepressant[14] and psychoactive drugs[15]. Amoxapine is a group of drugs called tricyclic antidepressants. It is used to treat symptoms of depression, anxiety and agitation [16].

Experimental

- All chemicals used were supplied from merck and BDH chemical compony.
- Thin layer chromatography (TLC) was performed an aluminum plates coated with layer of silica gel.
- Melting points were recorded using Electrothermal melting point apparatus, UK.
- FT.IR spectra were recorded on SHIMADZU FT.IR-8400S infrared spectrophotometer by KBr disc, Kufa University.
- ^{1}H-NMR were recorded on Fourier Transform Varian spectrometer, operating at 300 MH_Z with tetramethylsilane as internal standard, measurements were made on chemistry department, AL-Al-Bayt University, Jordan.
- Elemental analysis were recorded using E.A.G.E.R.-100, Carlo Erba, Italy, Babylon University.

Preparation Methods

- **Synthesis of 4-(dimethylamino)-3-((4-methoxyphenyl)diazenyl) benzaldehyde [Z]:** 4-Methoxyaniline (1.28 gm , 0.01 mole) was dissolved in (2 ml) of concentrated hydrochloric acid and (20 ml) of distilled water. The mixture was cold at (0 ^{0}C) in ice-water bath.Then a solution of sodium nitrite (0.69 gm , 0.01 mole) dissolved in (10 ml) of distilled water was added drop wise to the mixture with stirring. In the other beaker 4-N,N-dimethylaminobenzaldehyde (1.49 gm , 0.01 mole) was dissolved in (20 ml) of ethanol and (5 ml) of (10 %) sodium hydroxide and plase this beaker in ice-water bath to cool to (0 ^{0}C). The cold diazonium chloride was added to the coupling agent in small portions and stirred after each addition, after the addition was completed, the reaction mixture was stirred at (0 ^{0}C) for 2 hours. The orange product that precipitated and filtered, washed well with distilled water and recrystallized from ethanol, yield (2.16 gm , 78 %), m.p.=69 ^{0}C and R_F=0.72 used two solvent (benzene : methanol , 3 : 2).
- **Synthesis of azo Schiff bases derivatives [A_1-A_3]:** Azo benzaldehyde derivative [Z] (1.42 gm , 0.005 mole) was dissolved in (20 ml) of absolute ethanol containing two drops of glacial acetic acid, then equimolar amount (0.005 mole) of aromatic primary amines (4-methoxyaniline, 4-aminoacetophenone and 2-aminopyrimidin) were added. The reaction mixture was refluxed with stirring for (3-4) hours. Then, the TLC showed that the reaction was complete by using (ethyl

acetate : toluene , 1 : 1). The mixture was allowed to cool at room temperature and recrystallized from ethanol.

- **Synthesis of 2-(4-(dimethylamino)-3-((4-methoxyphenyl)diazenyl) phenyl)-3-(aryl)-2-hydro-1,3-oxazepine-4,7-dione [A_4-A_6] :** A mixture of equimolar amounts (0.001 mole) of azo Schiff bases derivatives [A_1-A_3] and (0.098 gm , 0.001 mole) of malic anhydride in (20 ml) of dry benzene, was reflux for (5-7) hrs., the TLC showed that the reaction was complete by used (ethyl acetate : toluene , 1 : 1). Then, the solvent was removed and the resulting colored crystalline solid was recrystallized from dry 1,4-dioxan.
- **Synthesis of 2-(4-(dimethylamino)-3-((4-methoxyphenyl)diazenyl) phenyl)-3-(aryl)-2-hydrobenzo[e]-1,3-oxazepine-4,7-dione[A_7-A_9]:** A mixture of equimolar amounts (0.001 mole) of azo Schiff bases derivatives [A_1-A_3] and (0.148 gm , 0.001 mole) of phthalic anhydride in (20 ml) of dry benzene, was reflux for (6-8) hrs., the TLC showed that the reaction was complete by using (ethyl acetate : toluene , 1 : 1). Then, the solvent was removed and the resulting colored crystalline solid was recrystallized from dry 1,4-dioxan.

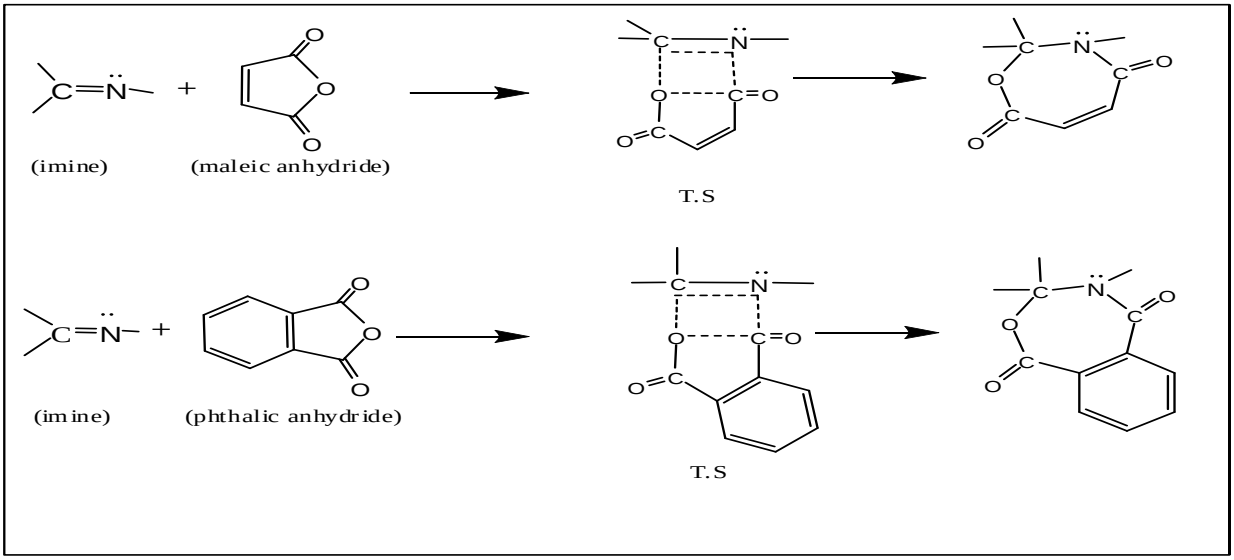
Table [1] shows the molecular weight, m.p., yield, R_F and elemental analysis of the prepared compounds [A_1-A_9].

Table 1: The physical properties and elemental analysis of prepared compounds [A_1-A_9]

Comp. No.	Molecular Formula	M.Wt g/mole	M.P. ^{0}C	Yield %	R_F	C.H.N. analysis					
						calculated			Found		
						C%	H %	N%	C%	H %	N%
A_1	$C_{23}H_{24}N_4O_2$	388	118	63	0.58	-	-	-	-	-	-
A_2	$C_{24}H_{24}N_4O_2$	400	145	58	0.64	72	6	14	72.83	6.42	13.76
A_3	$C_{20}H_{20}N_6O$	360	99	69	0.77	66.67	5.56	23.33	66.94	5.33	22.97
A_4	$C_{27}H_{26}N_4O_5$	486	112	54	0.61	-	-	-	-	-	-
A_5	$C_{28}H_{26}N_4O_5$	498	176	61	0.76	67.46	5.22	11.24	67.13	5.84	11.82
A_6	$C_{24}H_{22}N_6O_4$	458	110	48	0.68	62.88	4.8	18.34	63.21	4.95	18.84
A_7	$C_{31}H_{28}N_4O_5$	536	123	62	0.79	-	-	-	-	-	-
A_8	$C_{32}H_{28}N_4O_5$	548	221	51	0.63	70.07	5.11	10.22	70.87	5.74	10.64
A_9	$C_{28}H_{24}N_6O_4$	508	139	63	0.82	66.14	4.72	16.54	66.51	4.49	16.74

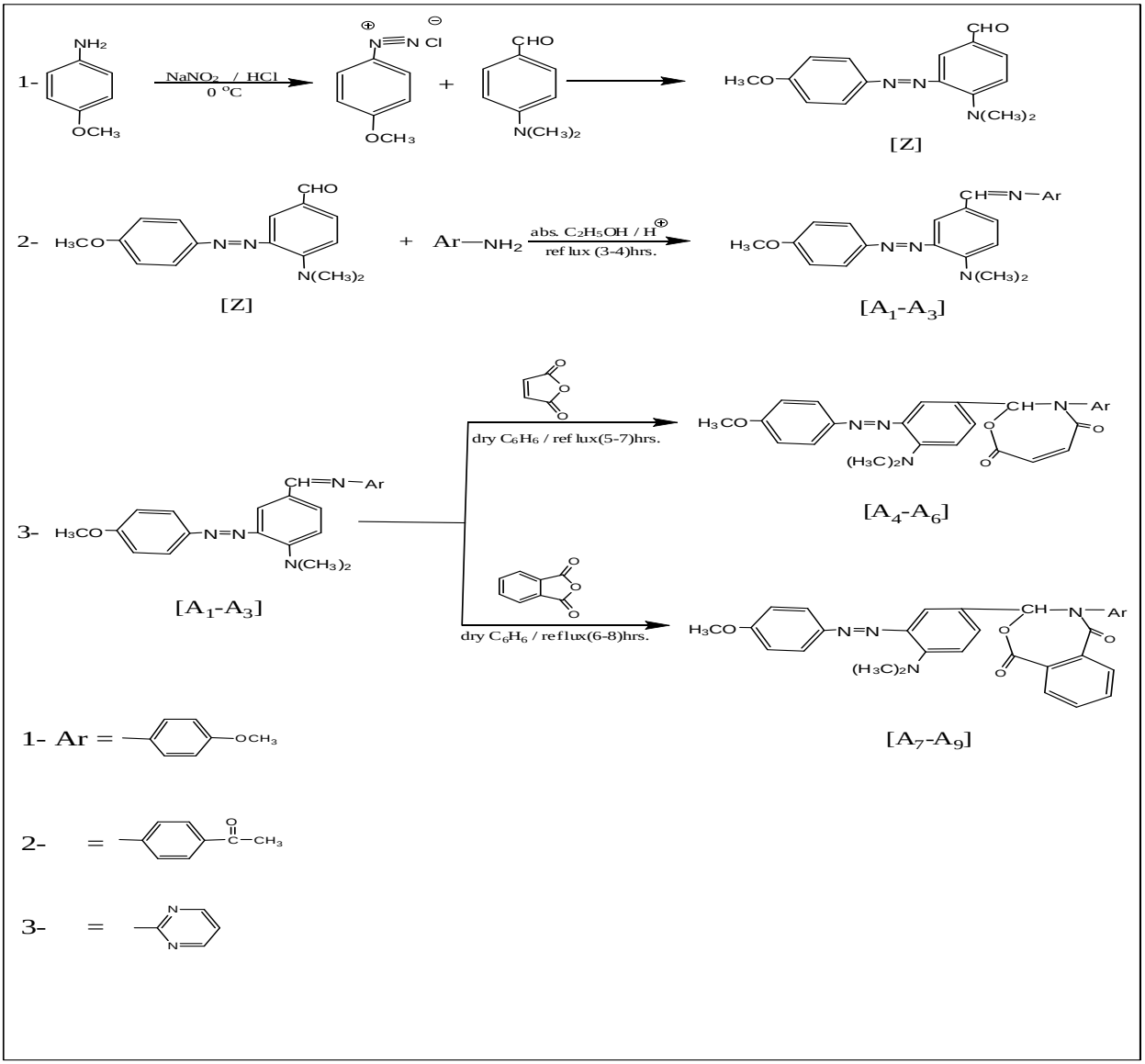
Result and Discussion

4-methoxyaniline was converted to the 4-methoxyphenyl diazonium chloride by the reaction with concentration hydrochloric acid and sodium nitrite. Diazonium salt was directly introduced in a coupling reaction[17] with 4-N,N-dimethylaminobenzaldehyde to produce 4-(dimethylamino)-3- ((4-methoxy phenyl)diazenyl)benzaldehyde [Z]. Azo Schiff bases [A_1-A_3] were synthesized by condensation of equimolar quantity of aromatic primary amines (4-methoxyaniline, 4-aminoacetophenone, 2-aminopyrimidin) with azo benazldehyde derivative [Z] in the presence of two drops of glacial acetic acid as catalyst in absolute ethanol. A pericyclic reactions[18], between imine groups of azo Schiff bases [A_1-A_3] as two-membered components and cyclic acid anhydride [maleic anhydride and phthalic anhydride] as five-membered components in dry benzene, were carried out to synthesis of 1,3-oxazepine derivatives [A_4-A_6] and [A_7-A_9] [19] respectively. Mechanism of the pericyclic reaction for the synthesis 1,3-oxazepine ring is shown in scheme 1.



Scheme 1: Mechanism of synthesis 1,3-oxazepine

The structures of all synthesis compounds were shown in scheme 2.



Scheme 2: Structure of all synthesis compounds

All these compounds were characterized by melting points and FT.IR spectroscopy, some of them were characterized by ^{1}H-NMR spectroscopy and C.H.N analysis. The FT.IR spectra, fig. [1] showed disappearance of the two absorption bands at (3423 cm^{-1}) and (3348 cm^{-1}) was due to the stretching vibrations of (-NH_2) group of 4-methoxyaniline and appearance the sharp strong absorption band at (1660 cm^{-1}) was due to the (C=O) of aldehyde group[20]. The absorption band at (3000 cm^{-1}) was due to the (C-H) aromatic, stretching band at (2910 cm^{-1}) for (C-H) aliphatic and the weak absorption bands at (2821 cm^{-1}) and (2732 cm^{-1}) were attributed to the (C-H) of aldehyde group. FT.IR spectra also showed the appearance of absorption band at (1548 cm^{-1}) for (N=N) group. The absorption band at (1232 cm^{-1}) was duo to the asymmetric stretching vibration of (C-O) ether group. The stretching band at (1600 cm^{-1}) was due to the (C=C) of aromatic rings. The absorption bands at (813 cm^{-1}) and (727 cm^{-1}) were due to the (C-H) aromatic out of plane and stretching vibration at(1371 cm^{-1}) was attributed to the (-$N(CH_3)_2$) aromatic group[21].

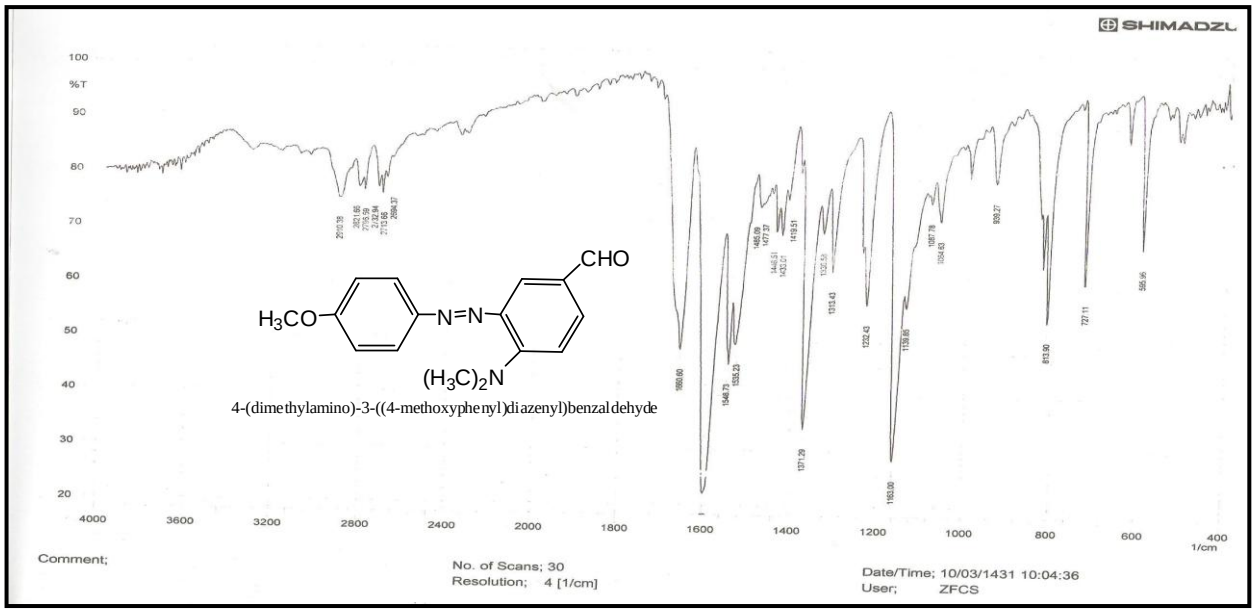


Fig. 1: FT.IR spectra of compound [Z]

The FT.IR spectra of the compounds [A_1-A_3] showed disappearance of the two absorption bands at (3425 cm^{-1}) and (3340 cm^{-1}) were due to the symmetric and asymmetric stretching vibrations of (-NH_2) groups of aromatic amines and disappearance of the strong absorption band at (1660 cm^{-1}) was due to the (C=O) of aldehyde group. The appearance of the stretching vibration between (1600-1604) cm^{-1} was due to the (C=N) of imine group[22], the absorption band at (1363-1367) cm^{-1} was due to of the stretching vibration of the (-$N(CH_3)_2$) aromatic group, and absorption band at (1228-1270) cm^{-1} was due to the stretching vibration of (C-O) ether group, other data of functional group**s** were shown in table [2].

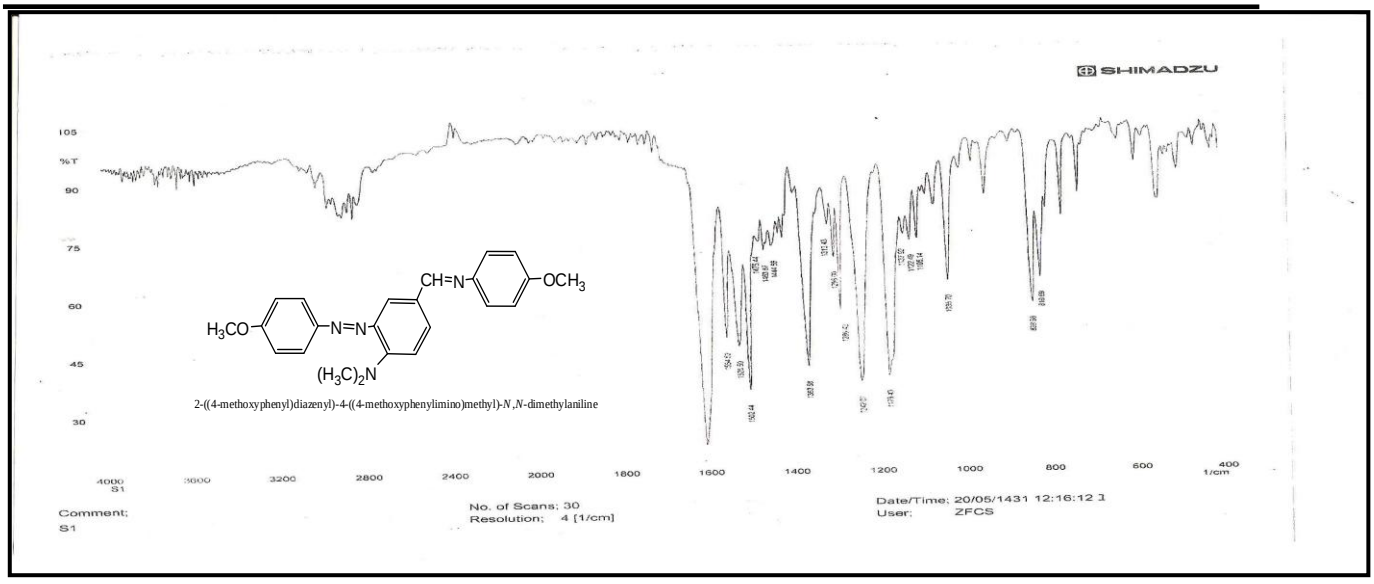


Fig. 2: FT.IR spectra of compound [A_1]

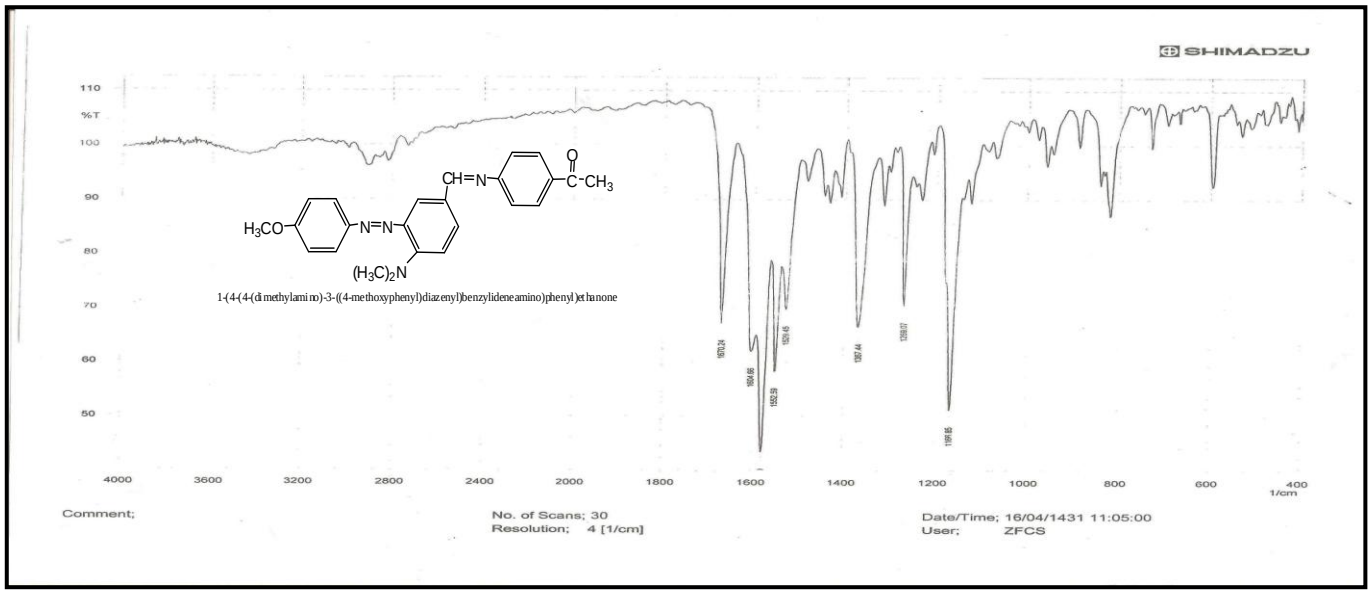


Fig. 3: FT.IR spectra of compound [A_2]

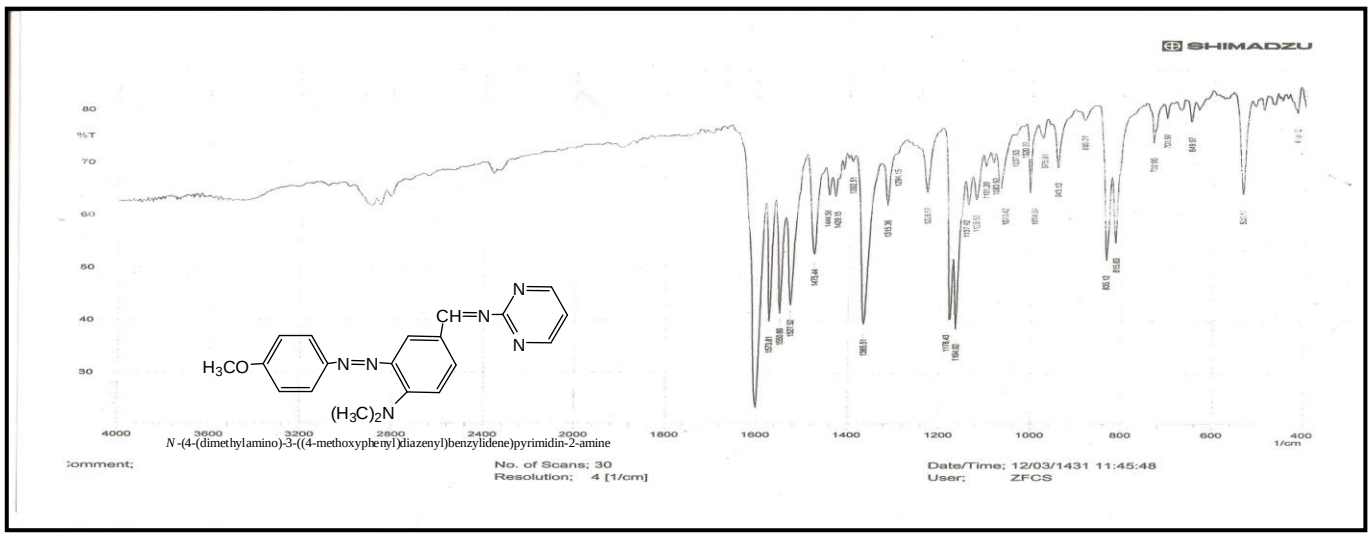


Fig. 4: FT.IR spectra of compound [A_3]

The FT.IR spectra of the compounds [A_4-A_6] and [A_7-A_9] showed disappearance of absorption band at (1600-1604) cm^{-1} was duo to the (C=N) of imine group and appearance of the strong absorption band at (1699-1718) cm^{-1} was due to the stretching vibration of the (C=O) lactone group[21], the appearance of the strong absorption band at (1620-1654) cm^{-1} was due to the stretching vibration of the (C=O) lactam group[21]. It was noticeable that the absorption band of the stretching vibration of the (C-H) benzylic was rather high. This was in fact explained by the shift toward higher frequency, that take place when the benzylic carbon is linked to three electron-withdrawing groups (phenyl, oxygen and nitrogen)[23]. The other data of functional groups were shown in table [2].

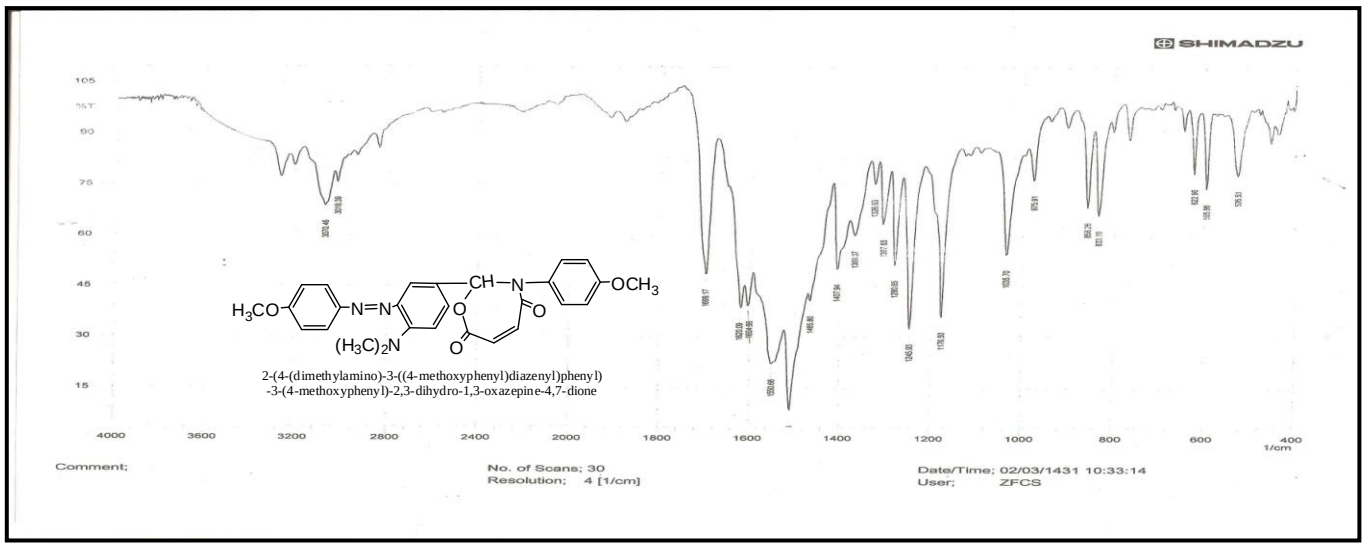


Fig. 5: FT.IR spectra of compound [A_4]

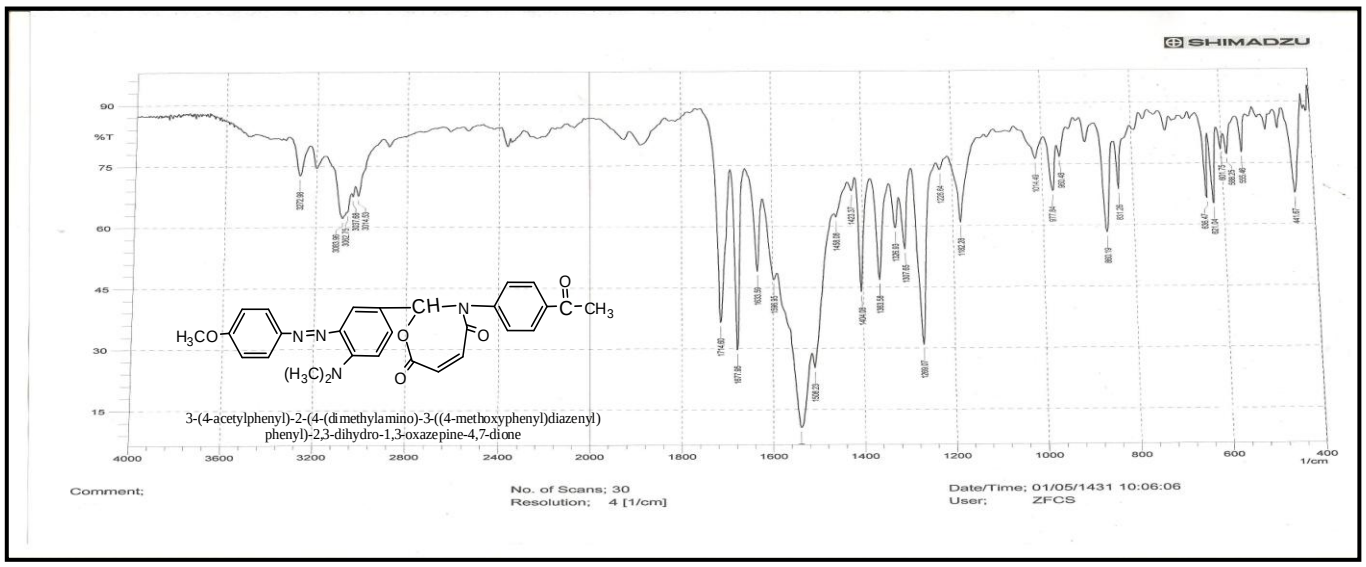


Fig. 6: FT.IR spectra of compound [A_5]

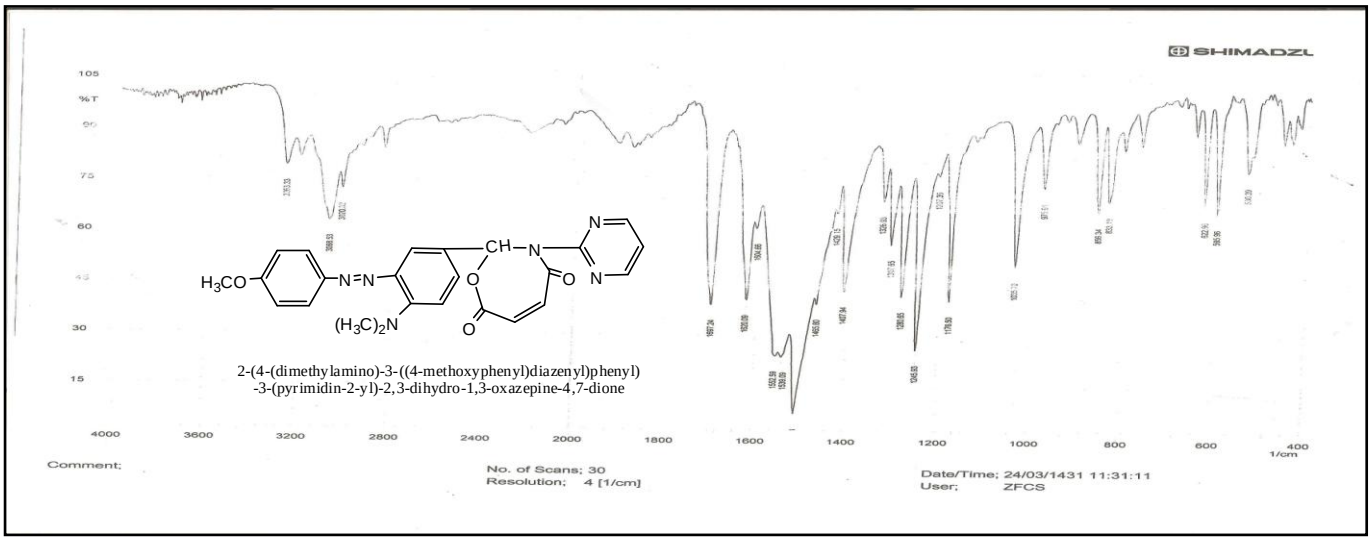


Fig.7: FT.IR spectra of compound [A_6]

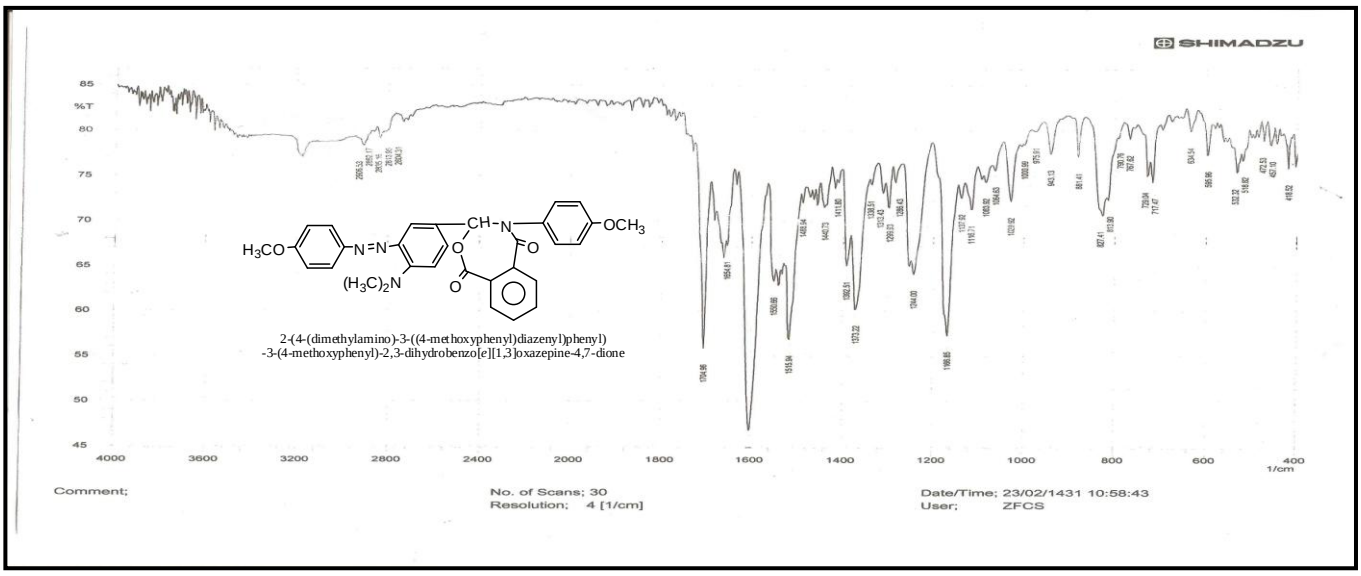


Fig. 8: FT.IR spectra of compound [A_7]

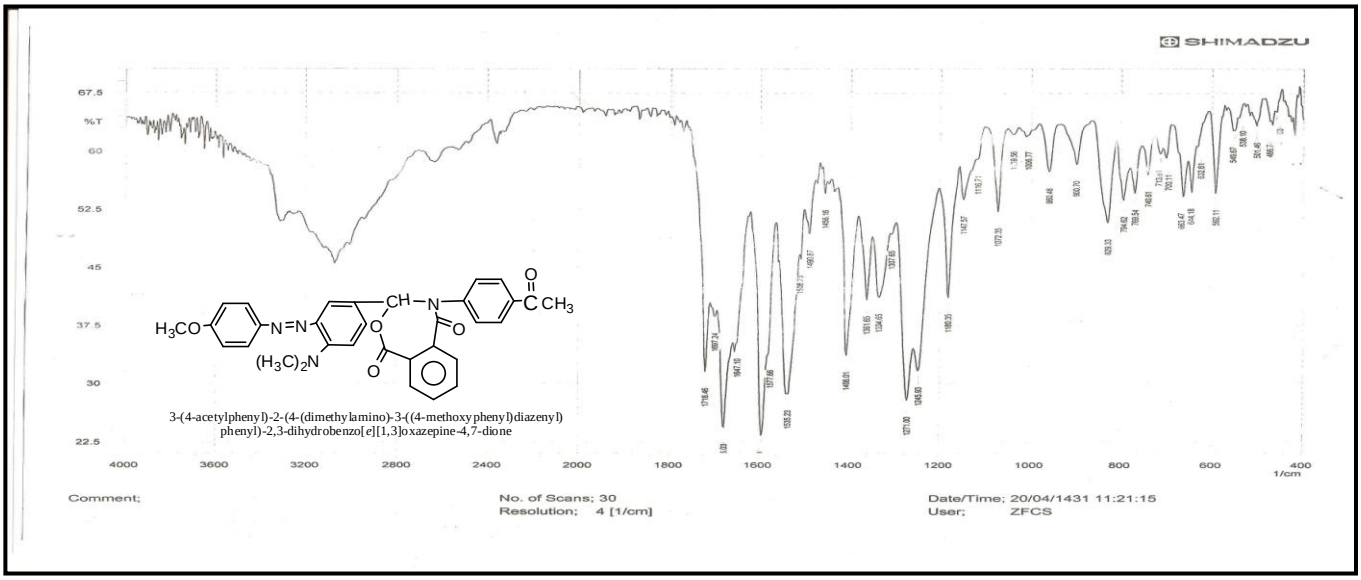


Fig. 9: FT.IR spectra of compound [A_8]

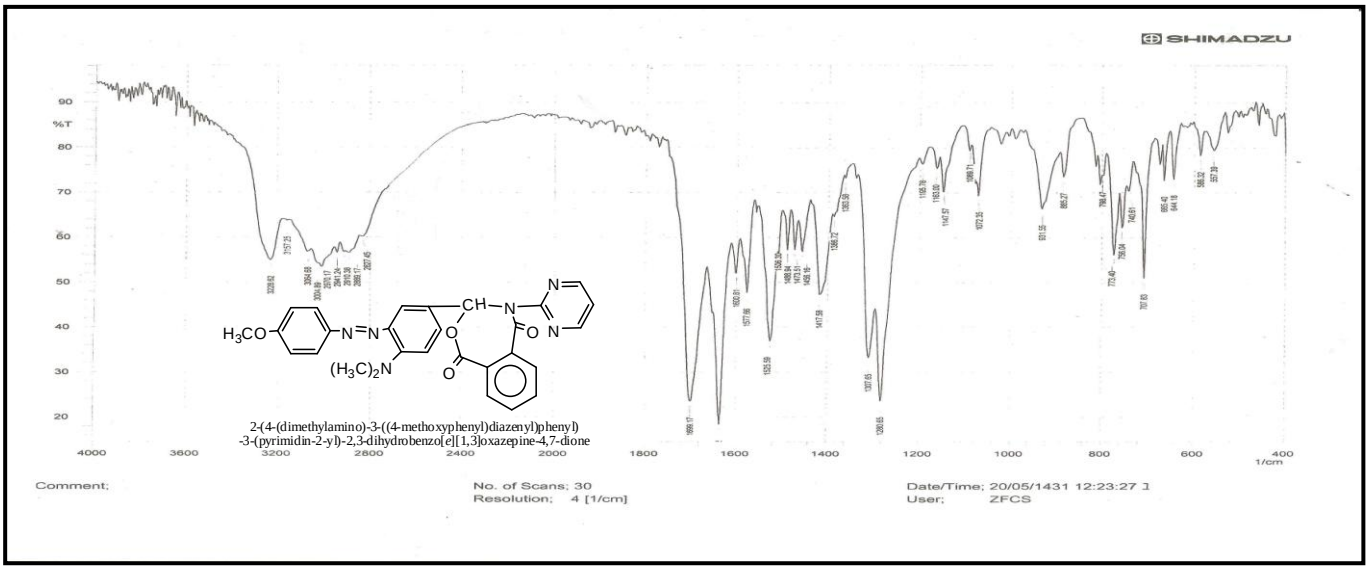


Fig. 10: FT.IR spectra of compound [A_9]

^{1}H-NMR spectra, fig. [11] of compound [A_4] showed the following characteristic chemical shifts (C_6D_6 as a solvent) were appeared: singlet signal at δ(1.15 ppm) that could be attributed to the six protons of (-N(CH_3)$_2$) group[24], singlet signal at δ(3.44 ppm) that could be attributed to the six protons of (O-CH_3) two groups, while the multiplet signal at δ(6.53-7.34)ppm that could be attributed to the aromatic protons for three rings and the doublet signal at δ(7.36-7.39)ppm that could be attributed to the two protons of seven membered ring of oxazepine . The ^{1}H-NMR spectra also showed the singlet signal at δ(9.7 ppm) that could be attributed to the one proton of oxazepine group.

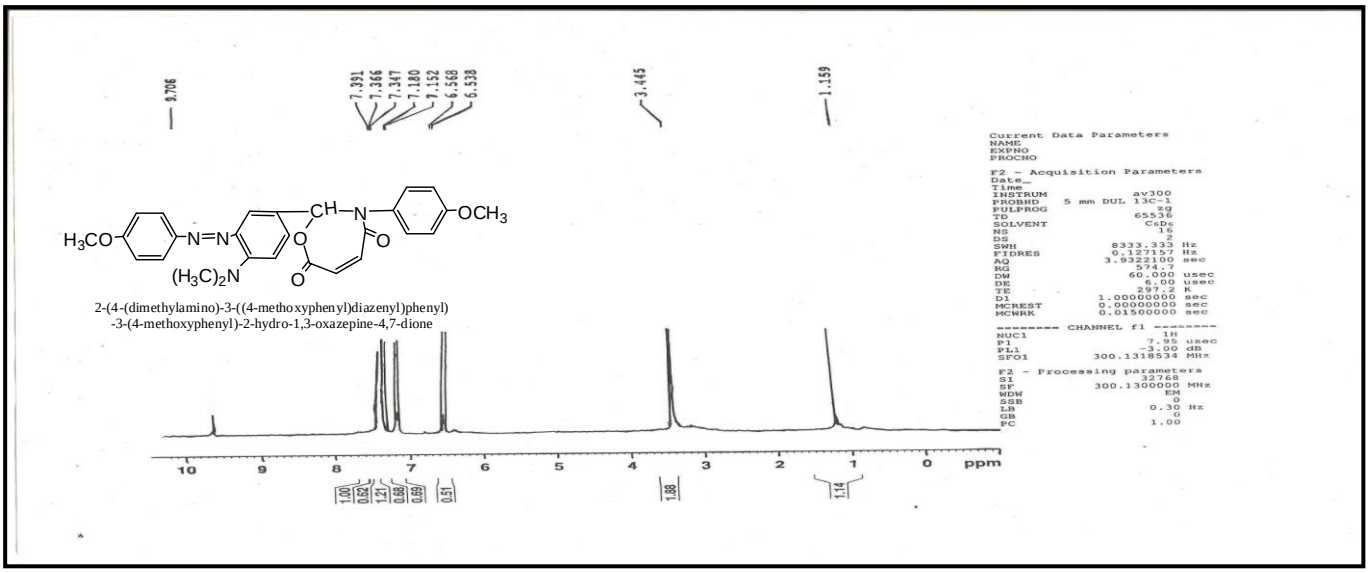


Fig. 11: ^{1}H-NMR spectra of compound [A_4]

^{1}H-NMR spectra, fig. [12] of compound- [A_7] showed the following characteristic chemical shifts (C_6D_6 as a solvent) were appeared: singlet signal at δ(1.5 ppm) that could be attributed to the six protons of (-N(CH_3)$_2$) group, singlet signal at δ(3.41 ppm) that

could be attributed to the six protons of (O-CH_3) two groups, while the multiplet signal at δ(6.55-7.46)ppm that could be attributed to the aromatic protons for four rings[24].The ^{1}H-NMR spectra also showed the singlet signal at δ(9.26 ppm) that could be attributed to the one proton of oxazepine group.

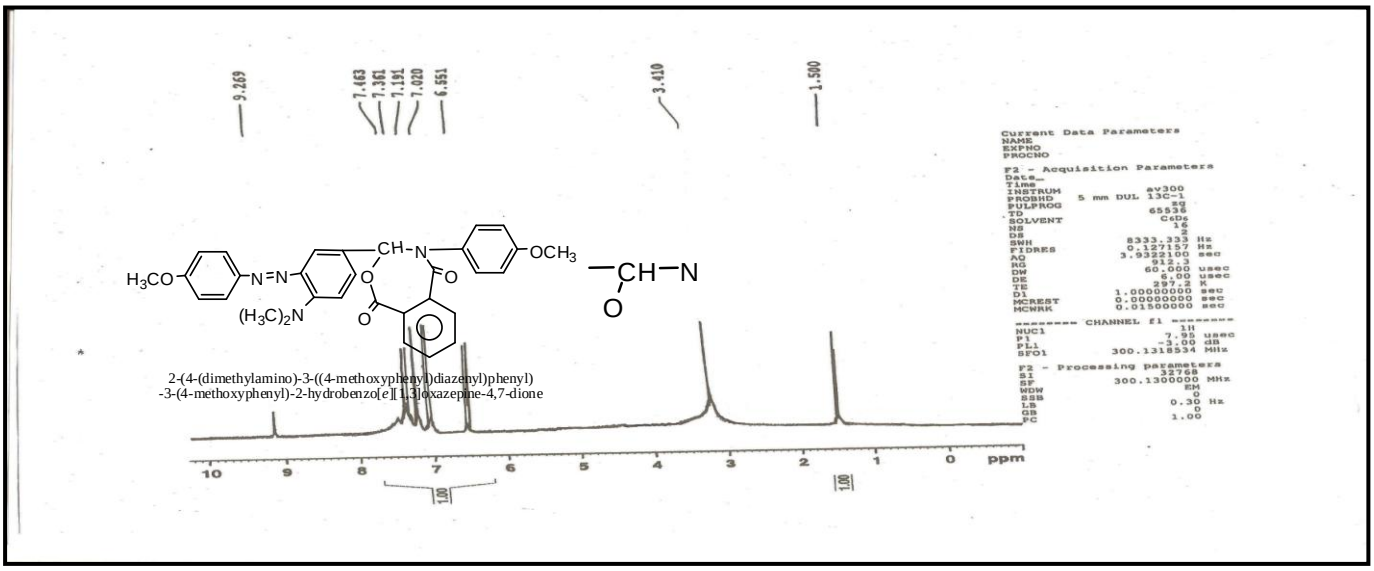


Fig. 12: ^{1}H-NMR spectra of compound [A_7]

Table [2] FT.IR data of the prepard compounds [A_1-A_9]

Comp. No.	υ (C-H) Str. Benzylic cm^{-1}	υ (C-H) Str. Aromati cm^{-1}	υ (C-H) Str. Aliphati cm^{-1}	υ (C=N Str. Imine cm^{-1}	υ (C=O Str. Lacton cm^{-1}	υ (C=C Str. Lactar cm^{-1}	υ (C=C) Str. Aromati cm^{-1}	υ (C-O Str. Lacon cm^{-1}	4-N(CH_3)$_2$ Str. Aromatic cm^{-1}	Others cm^{-1}
A_1	-	3010	2890	1600	-	-	1595	-	1363	-
A_2	-	3000	2910	1604	-	-	1598	-	1367	υ (C=O): 1670
A_3	-	3050	2900	1600	-	-	1590	-	1365	υ (C=N)endo cyclic c pyrimidin : 1550
A_4	3255	3070	2890	-	1699	1620	1600	1245	1369	-
A_5	3272	3083	2910	-	1714	1633	1596	1269	1363	υ (C=O) : 1677
A_6	3263	3068	2860	-	1667	1620	1600	1245	1307	υ (C=N)endo cyclic c pyrimidin : 1552
A_7	3200	3083	2862	-	1704	1654	1600	1244	1373	-
A_8	3240	3058	2908	-	1718	1647	1600	1245	1361	υ (C=O) : 1676
A_9	3232	3066	2941	-	1701	1645	1602	1250	1386	υ (C=N) endo cyclic c pyrimidin 1577

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