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SYNTHESIS AND CHARACTERIZATION OF NOVEL 1,3-OXAZEPINE DERIVATIVES FROM AMINOPYRAZINE

Hawraa Mohammed Sadiq*

Chemistry Department, College of Science, Kufa University, Iraq.

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***Corresponding Author'**
Hawraa Mohammed Sadiq
Chemistry Department,
College of Science, Kufa
University, Iraq.

ABSTRACT

In this work new 1,3-oxazepine subsidiaries have been readied, by two stages: The initial step incorporate amino gathering of the 2-aminopyrazine was dense with various fragrant aldehydes within the sight of supreme ethanol to give novel Schiff bases subordinates [A_1 – A_5] separately. The second step, the subsequent imines subordinates [A_1-A_5] were responded with maleic anhydride and phathalic anhydride in dry toluene to give new 1,3-oxazepine-4,7-dione ring subsidiaries [B_{1a}-B_{5a}] and [B_{1b}-B_{5b}] individually scheme[I]. Every one of these mixes were described by liquefying focuses and FT.IR spectroscopy, several of them were portrayed by 1H-NMR spectroscopy and C.H.N. S. examination.

KEYWORDS: Aminopyrazine, 1,3-Oxazepine, Schiff bases.

1. INTRODUCTION

Aminopyrazines are spread over numerous normal items, particularly in brilliant marine life forms like jam fish (aequorea) (Head *et al*., 2000), firefly squid (Wataseniascintillans) (Inoue *et al*., 1976) and flying squid Tobiika (Symplectoteu this oualaniensis) (Tsuji & Leisman, 1981; Takahashi & Isobe, 1994; Takahashi & Isobe, 1993), Schiff bases are the imperative compound inferable from their extensive variety of biological activities and mechanical application (Bhausaheb *et al.*, 2012). They have been originate to enjoy the pharmacological actions such as antimalarial (Li. *et al.*, 2003), anticancer (Villar *et al.*, 2004), antibacterial (Venugopal & Jayashree, 2008) and antiviral (Karthikeyan *et al.*, 2006). For quite a while, the blend of 1,3-and 1,4-oxazepine rings depended on two constrained established sorts of responses, the principal response is called Valence bond isomerization which is completed by means of illumination of polyarylpyridine N-oxides. This illumination brings about ring

development to 1, 3-oxazepine in high return and some deoxygenation to the parent amines (Buchardt *et al.*, 1972). The second response is called Enamines buildup which is done by response of Erythro 1,2-diphenyl-2-phenylaminoethanol with diethylacetylene dicarboxylate in methanol at apartment temperature to stretch a blend of the Michael adduct and tetrahydro-1,4-oxazepin-7-one (Tsuge & Ohnishi, 1982). As of late, a pericyclic responses are utilized to union of 1,3-oxazepine ring . This kind of reactions is not limited and gives distinctive 1,3-oxazepine ring auxiliaries. The kind of cyclo alternative reaction that used to union of 1,3-oxazepine ring was assigned (2+5) → 7 cycloaddition reaction in which two particles of imine assembling as two-membered portion was extra to five-membered section, for instance, maleic or phthalic anhydrides to spring a seven-membered heterocycle (K.F. Ali, 2005; N.M. Al-Jamali, 2008; R.T. Haiwal, 2008; Z.H. Abood, 2009). Some oxazepine subsidiaries demonstrated organic exercises against different sorts of microorganisms (M.H. Serrano-Wu *et al.*. 2002) what's more, some of them go about as inhibitors of a few proteins activity (L. Smith *et al.*, 2006).

2. EXPERIMENTAL

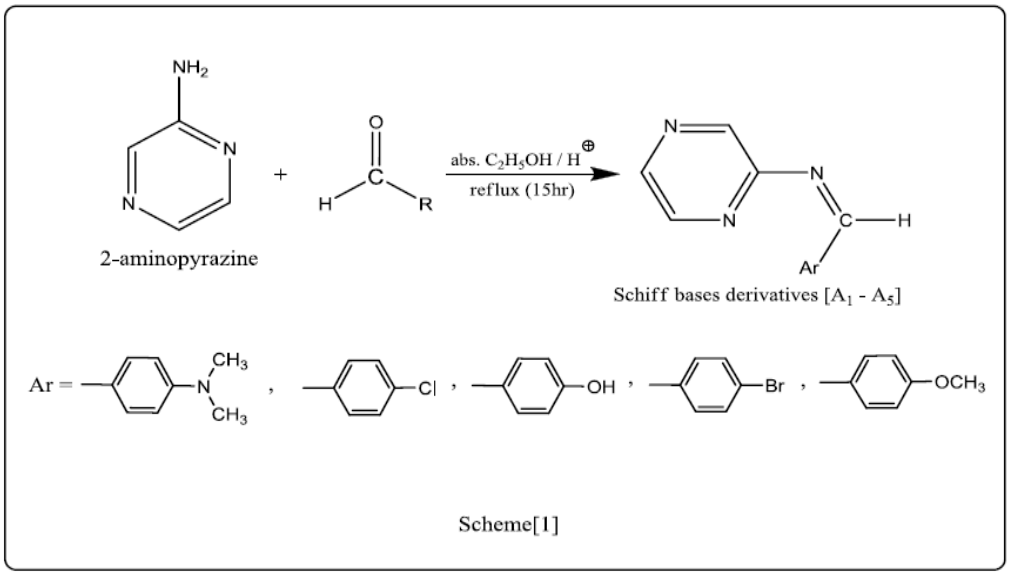
Instruments & Chemicals

All chemical were used supplied from Merck, BDH and Fluke chemicals company. The melting points were chronicled using Electro updraft melting point device, UK. The elemental analyses were noted using E.A.G.E.R.-100, Carlo Erba, Italy. FT.IR spectra were verified using Fourier transform infrared SHIMADZU FT. IR-8400S infrared spectrophotometer by KBr disc. ^{1}H-NMR were logged on Fourier transform Varian spectrometer, operating at 300 MH_Z.

Synthesis Methods

Universal technique for synthesis Schiff bases [$A_1 – A_5$] (Malleshappa et al., 2011)

The 2-aminopyrazine (0.01 mole, 0.95 gm) was additional to a solutione of the distinctive substituted benzaldehydes (0.01mole) in 40ml of absolut ethanol and two drops of glacial acetic acid were additionally added to the above mixture. The mixture was rfluxed for (15hr.) and toward the finish of the reply; solvents were somewhat vanished then filled water. The hastens were gathered by filtration, washed with diethylether, dried and recrystallized from the suitable dissolvable like ethanol or ethanol-water scheme.[1]



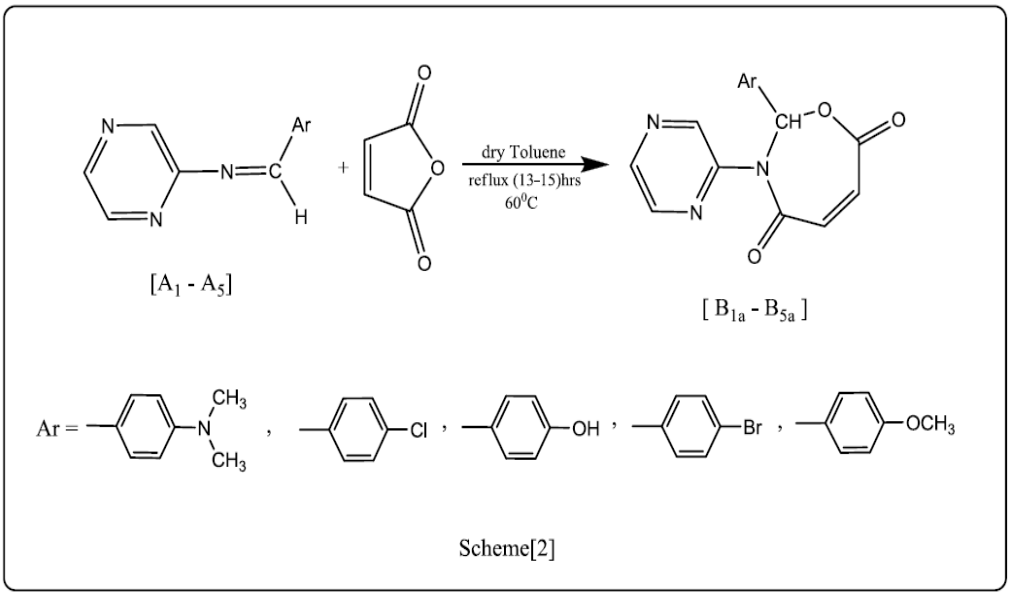
Scheme[1]

Table 1: The physical properties of compounds [A_1-A_5]

Comp. No.	Molecular Formula	M.P. ^{O}C	Yield $^{0}/_{0}$	R_f	Color	$^{0}/_{0}$of C.H.N. Cal./ Found		
						C	H	N
A_1	($C_{13}H_{14}N_4$)	72 – 74	73.2	0.82	Pale brown	69	6.24	24.76
						62.81	5.74	24.25
A_2	($C_{11}H_8ClN_3$)	82	72.5	0.33	Pale orange	60.7	3.7	19.31
						60.1	3.23	18.73
A_3	($C_{11}H_9N_3O$)	130	75.7	0.53	Dark red	66.32	4.55	21.09
						65.88	4.05	20.72
A_4	($C_{11}H_8BrN_3$)	140-142	68.3	0.31	Pale yellow	50.41	3.08	16.03
						49.82	2.63	15.73
A_5	($C_{12}H_{11}N_3O$)	168-170	71.6	0.73	Pale yellow	67.59	5.2	19.71
						67.02	4.78	19.32

Common process for Synthesis 2-argio-3-(pyrazin-2-yl)-2,3-dihydro-1,3-oxazepine-4,7-dione [B_{1a} – B_{5a}]with malic anhydride (Nagham, 2008).

A mix of identical molar amounts (0.001mole) of Schiff bases dervatives [A_1-A_5] and (0.098gm, 0.001 mole) of malic anhydride in (20 ml) of dry toluene, was refluxed with rousing for (13-15) hours at (60 ^{0}C), the TLC displayed that the reaction was ample by using (toluene: ethanol, 3 : 1). Then, the solvent was detached and the subsequent colored crystalline solid was recrystalized from dry 1,4-dioxan scheme.[2]



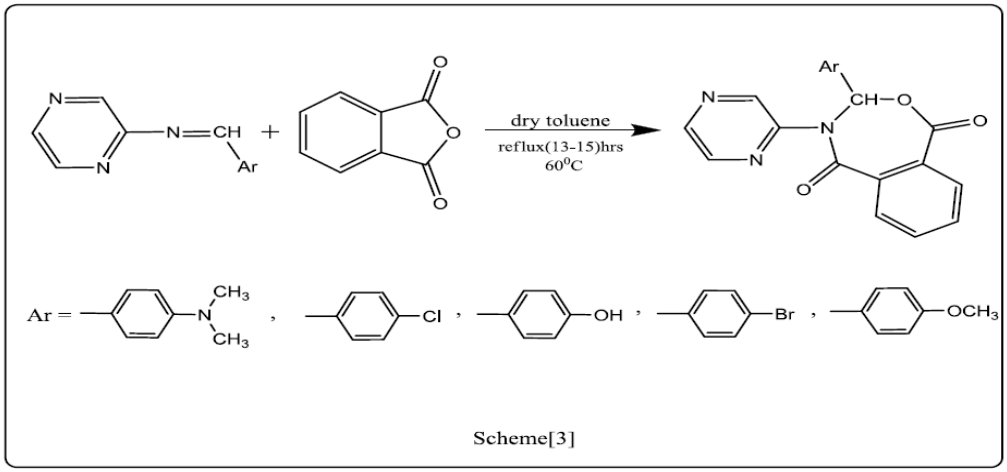
Scheme[2]

Table 2: The physical properties of compounds [B_{1a} – B_{5a}]

Comp. No.	Molecular Formula	M.P. ^{O}C	Yield %	R_f	Color	% of C.H.N. Cal./ Found			
						C	H	N	O
B_{1a}	($C_{17}H_{16}N_4O_3$)	140	90.3	0.78	Orang	62.95	4.97	17.27	14.80
						62.81	5.74	24.25	
B_{2a}	($C_{15}H_{10}ClN_3O_3$)	210	82.1	0.34	Pale yellow	57.06	3.19	13.31	15.20
						60.1	3.23	18.73	
B_{3a}	($C_{15}H_{11}N_3O_4$)	110	79.7	0.47	Brown	60.61	3.73	14.14	21.53
						65.88	4.05	20.72	
B_{4a}	($C_{15}H_{10}BrN_3O_3$)	194	78.4	0.67	Yellow crystal	50.02	2.80	11.67	13.33
						49.82	2.63	15.73	
B_{5a}	($C_{16}H_{13}N_3O_4$)	224	78.5	0.85	Yellow	61.73	4.21	13.50	20.56
						67.02	4.78	19.32	

Universal practice for Synthesis 3-argio-4-(pyrazin-2-yl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione with phthalic anhydride (Fahad & Obaid, 2001)

A mixtur of like molar amounts (0.001mole) of Schiff bases derivatves [A_1-A_5] and (0.148gm, 0.001 mole) of phthalic anhydride in (20 ml) of dry toluene, was refluxed with impassioned for (13-15) hours at (60 ^{0}C), the TLC exposed that the reaction was whole by using (toluene : ethanol , 3 : 1). Then, the solvent was aloof and the consequential colored crystalline solide was recrytallized from dry 1,4-dioxan scheme.[3]



Scheme[3]

Table 3: The physical properties of compounds [B_{1b} – B_{5b}]

Comp. No.	Molecular Formula	M.P. ^{O}C	Yield %	R_f	Color	%of C.H.N. Cal./ Found			
						C	H	N	O
B_{1b}	($C_{21}H_{18}N_4O_3$)	210	80.3	0.72	Pale brown	67,37	4.85	14.96	12.82
						62.81	5.74	24.25	
B_{2b}	($C_{19}H_{12}ClN_3O_3$)	106	58.6	0.57	Pale orange	62.39	3.31	11.49	13.12
						60.1	3.23	18.73	
B_{3b}	($C_{19}H_{13}N_3O_4$)	138	89.2	0.37	Dark red	65.70	3.77	12.10	18.43
						65.88	4.05	20.72	
B_{4b}	($C_{19}H_{12}BrN_3O_3$)	256	77.3	0.41	Pale yellow	55.63	2.95	10.24	11.70
						49.82	2.63	15.73	
B_{5b}	($C_{20}H_{15}N_3O_4$)	210	88.5	0.64	Pale yellow	66.48	4.18	11.63	17.71
						67.02	4.78	19.32	

3. RESULTS AND DISCUSSION

In this exertion, 2-aminopyrazine which on strengthening with sundry particular aromatic aldehydes in the manifestation of absolut ethanol and limited dropes of glacial acetic acid molded Schiff bases drivatives [A_1 – A_5]. The uncomplicated analysis was believed settlement with the intended percentages of C, H and N elements. The spectral data of FT.IR of [A_1 – A_5] revealed band at (1598 – 1698) cm^{-1} endorsing the building of imine (Abdullah & Khadija, 2007) (C=N) and vanishing of NH_2 band of pyrazine. Supplementary ^{1}H-NMR of compounds [A_1 and A_5] publicized the incidence of a singlet signal between δ (8.74 – 8.78) ppm demonstrating the realization of imine (Apoorva *et al.*, 2011) (HC=N), and signal at δ (6.93 – 7.46) ppm exposed the incidence of aromatic protons for compounds [A_1 , A_5 , A_9 and A_{10}]. The synthesized compounds [B_{1a} – B_{5a}] and [B_{1b} – B_{5b}] were considered by FT.IR spectra, particular of them were categorized by ^{1}H-NMR spectra and C.H.N analysis. The FT.IR spectra of the compounds [B_{1a} – B_{5a}] and [B_{1b} – B_{5b}] exhibited desertion of absoption bands at (1598 – 1698) cm^{-1} was owing to the (C=N) of imine group and attendance of the

strong absorption band at (1670-1791) cm^{-1} was attributable to the stretching vibration of the (C=O) lactone group (L. G. Wade, 2001), the arrival of the strong absorption band at (1625-1694) cm^{-1} was due to the widening shaking of the (C=O) lactam group (N. Saemian *et al.*, 2005). ^{1}H-NMR spectrum, exhibited the next characteristic chemical shifts (C_6D_6 as a solvent) doublet signal at δ(7.36-7.39)ppm that could be accredited to the two protons of seven membered ring of oxazepine ( ) group (R. M. Silverstein *et al.*, 2005) . The ^{1}H-NMR spectrum also presented the singlet signal at δ(9.7 ppm) that could be ascribed to the one proton of oxazepine ( ) group (Nagham, 2008).

Table 4: FT.IR data of Schiff bases compounds [$A_1 – A_{10}$]

Com. No.	υ(HC=N) Str. Pyrimidine cm^{-1}	υ(C-H)Str. Aromatic Alifatic cm^{-1}	υ (C=N) Str. Imin cm^{-1}	υ (C=N) Str. Pyrimidine cm^{-1}	υ (C-H) Ben. Aromatic cm^{-1}	Others cm^{-1}
A_1	3100	3051 2950	1662	1552	825	υ(N-CH_3)Str.: 2908asym. υ(N-CH_3)Str.: 2794sym.
A_2	3197	3096 2852asym. 2815sym.	1698	1495	851	υ (C-Cl)Str.: 1089
A_3	3141	3018 2997asym. 2927sym.	1598	1506	822	υ (C-OH)Str.: 3361 υ (C-OH)Ben.: 1238
A_4	3178	3085 2858asym. 2847sym.	1684	1573	811	υ (C-Br)Str. : 1066
A_5	3150	3072 2998asym. 2935sym.	1602	1520	848	(C-OCH_3)Str. : 2833

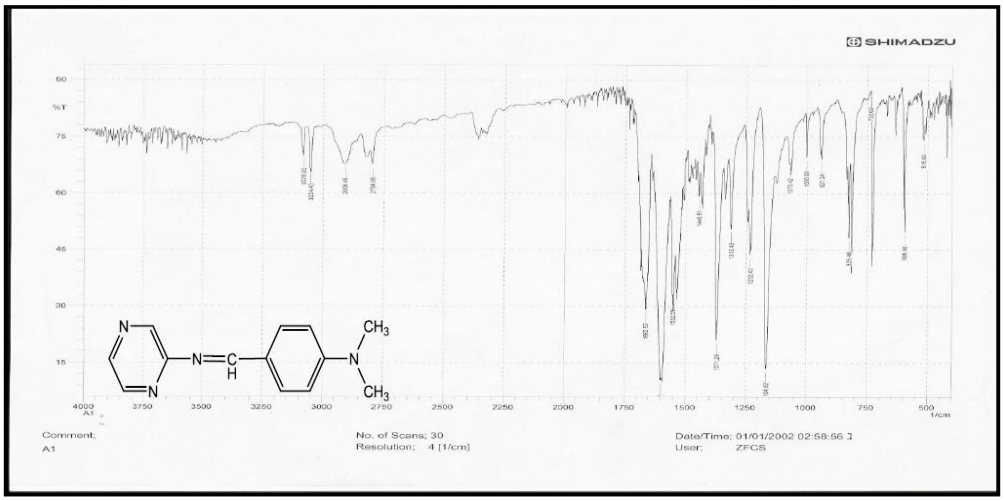


Fig. 1. FT.IR spectrum of compound [A_1]

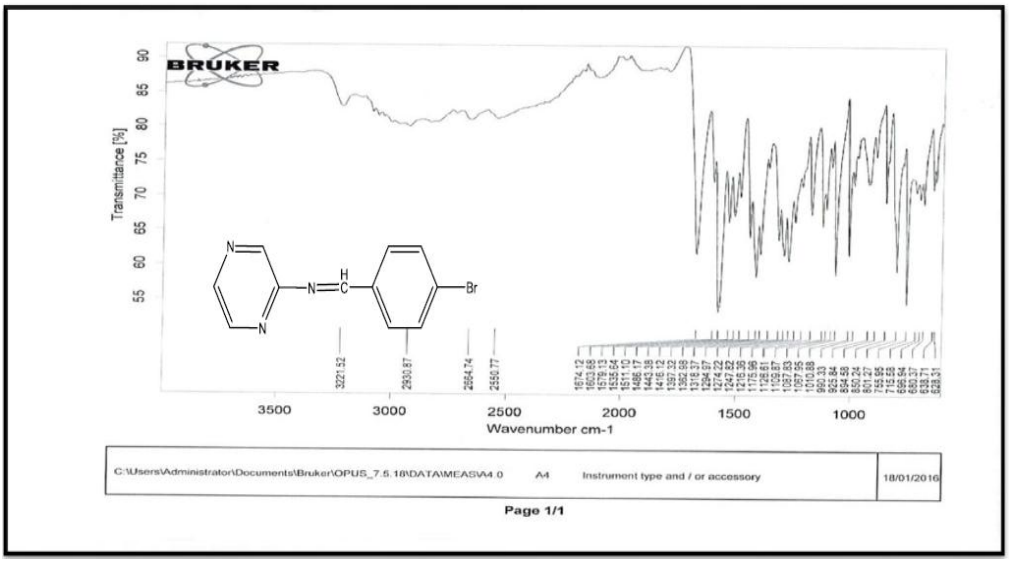


Fig 2: FT.IR spectrum of compound [A_4]

Table 5: ^{1}H-NMR data of Schiff bases compounds [A_1 , A_5]

Comp. No.	δ(C-H) Aromatic ppm m , nH	δ(N=CH) Imine ppm s , 1H	δ(CH=N) pyrimidine ppm m , 3H	Others ppm
A_1	(6.93 – 7.62) 4H	8.78	8.81	(s , 3H , N-CH_3): δ2.34 (s , 3H , N-CH_3): δ2.44
A_5	(6.99 – 7.62) 4H	8.74	8.74	(s , 3H , O-CH_3): δ3.3

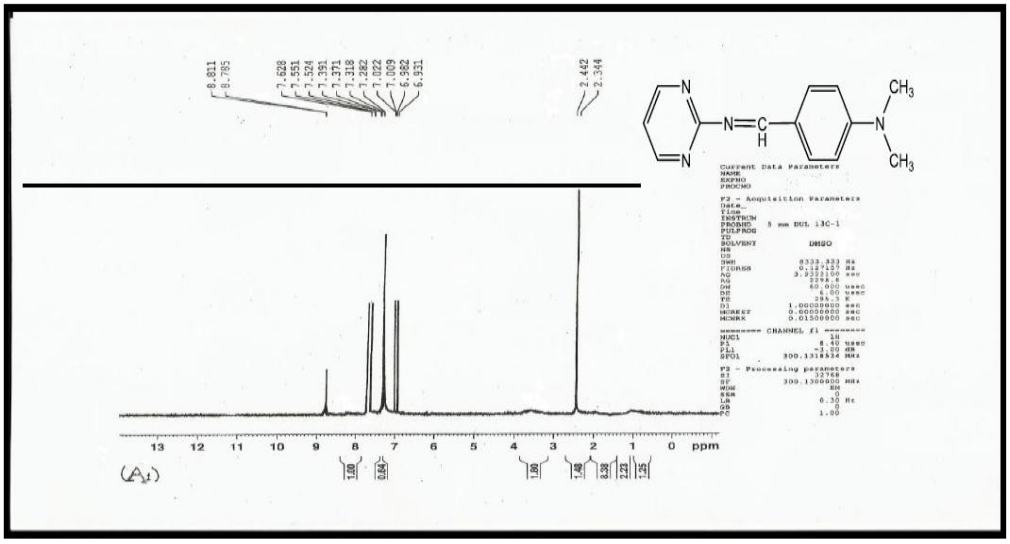


Fig 3: ^{1}H-NMR spectrum of compound [A_1]

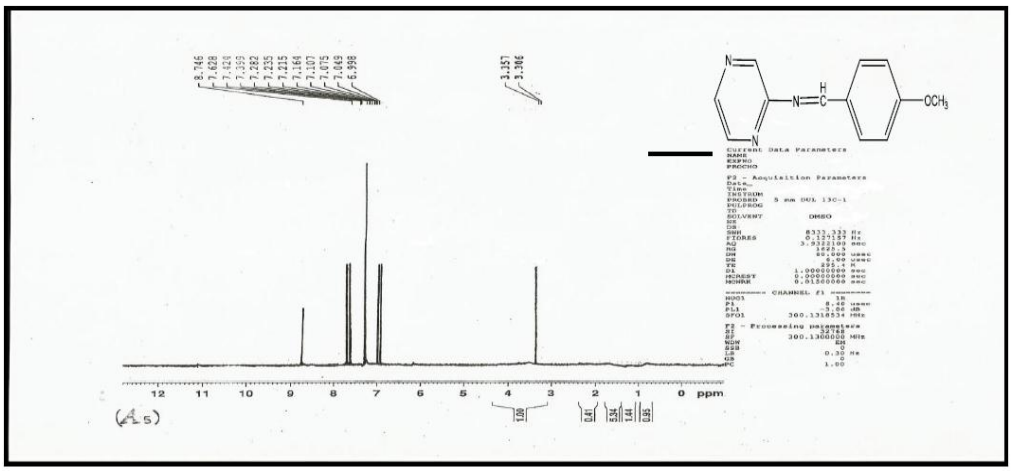


Fig 4: ^{1}H-NMR spectrum of compound [A_5]

Table 6: FT.IR data of 3-aryl-4-(pyrazin-2-yl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione [$B_{1a} – B_{5a}$]

Comp. No.	υ(HC=N) Str. Pyrazine cm^{-1}	υ(C-H) Str. Aromatic Alifatic cm^{-1}	υ(C=O) Str. Lactone Lactam cm^{-1}	υ (C-O) Str. Lactone cm^{-1}	Others cm^{-1}
B_{1a}	3154	2847 2775	1703 1630	1273	υ (N-CH_3)Str.:2603asym. 2477sym.
B_{2a}	3198	2851 2644	1670 1627	1278	υ (C-Cl)Str.: 1092
B_{3a}	3110	2955 2847	1730 1694	1284	υ (C-OH) Str.:3080 Ben. :1211
B_{4a}	3092	3036 2850asym. 2825sym.	1720 1678	1276	υ(C-Br)Str. : 1065
B_{5a}	3081	3051 2830	1791 1694	1254	υ(C-OCH_3)Str.: 2888

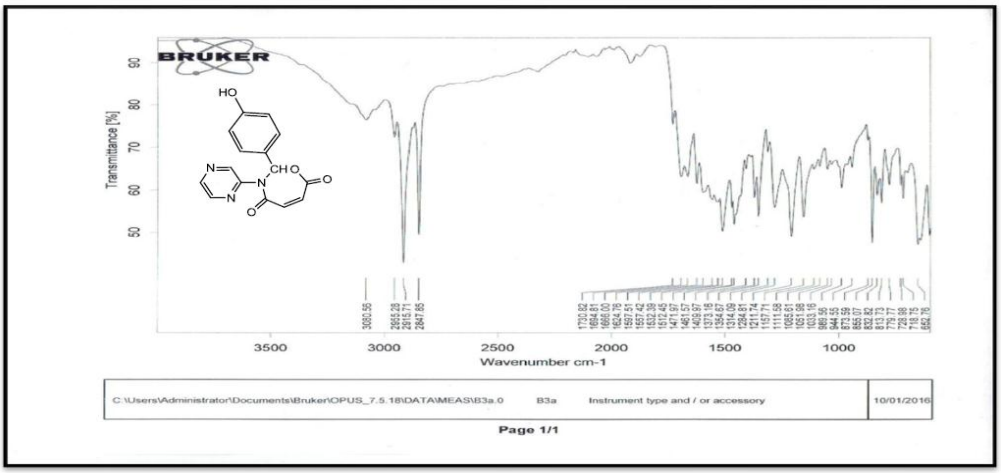


Fig 5: FT.IR spectrum of compound [B_{3a}]

Table 7: ^{1}H-NMR data of 3-aryl-4-(pyrazin-2-yl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione [$B_{1a} – B_{5a}$]

Comp. No.	δ(N-CH) oxazepine ppm s , 1H	δ(HC=CH) oxazepine ppm d , 1H	δ(C-H)Aromatic ppm m , nH	δ(HC=N) Pyrazine ppm m , 3H	Others ppm
B_{1a}	7.85	6.83	(7.86 – 7.98) 4H	8.12	(s , 6H , N-$(CH_3)_2$) : δ 3.37
B_{5a}	7.69	7.57	(7.06 – 7.38) 4H	8.92	(s , 3H , O-CH_3) : δ 3.41

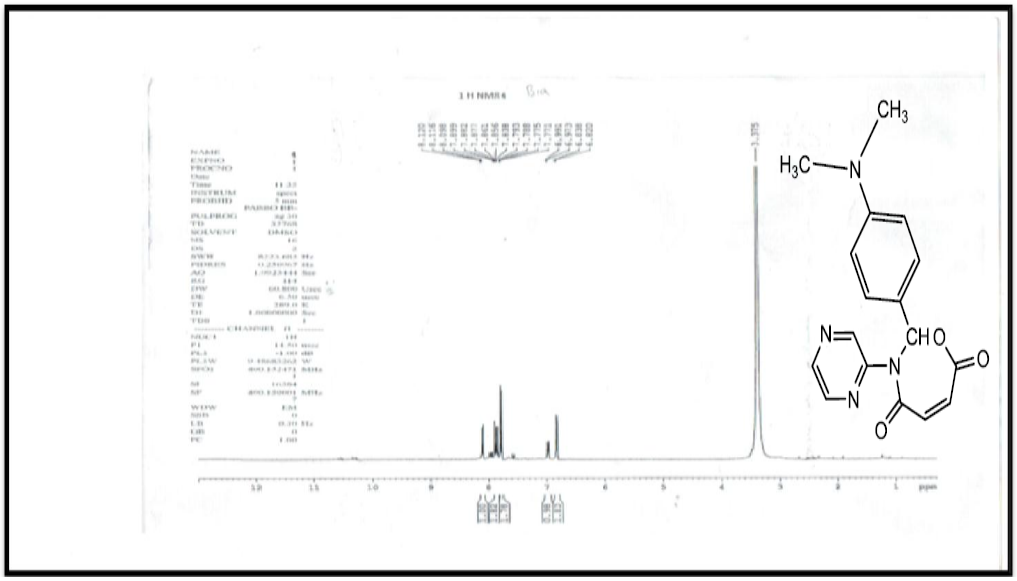


Fig 6: ^{1}H-NMR spectrum of compound [B_1a]

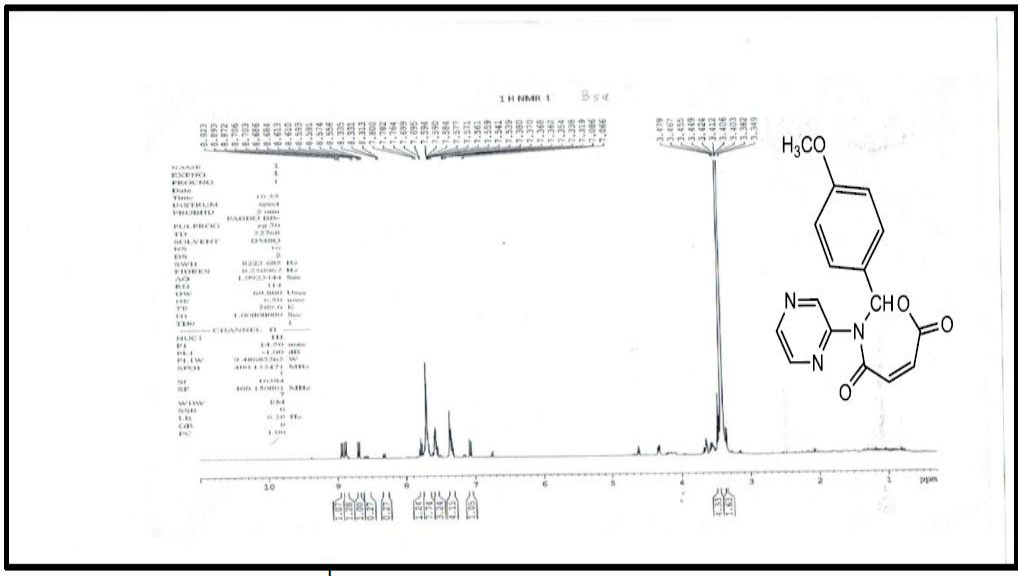


Fig 7: ^{1}H-NMR spectrum of compound [B_5a]

Table 8: FT.IR data of 3-aryl-4-(pyrazin-2-yl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione [B_{1b}– B_{5b}]

Comp. No.	υ(HC=N) Str. Pyrazine cm^{-1}	υ(C-H) Str. Aromatic Alifatic cm^{-1}	υ(C=O) Str. Lactone Lactam cm^{-1}	υ (C-O) Str. Lactone cm^{-1}	Others cm^{-1}
B_{1b}	3430	2916 2849	1703 1629	1230	υ (N-CH_3)Str.:2777asym. 2600sym.
B_{2b}	3436	2894 2649	1671 1630	1263	υ (C-Cl)Str.: 1091
B_{3b}	3154	2922 2851	1789 1665	1257	υ (C-OH) Str.:3406 Ben. :1240
B_{4b}	3309	2849 2653	1674 1640	1274	υ(C-Br)Str. : 1065
B_{5b}	3215	2918 2848	1682 1625	1260	υ(C-OCH_3)Str.: 2373

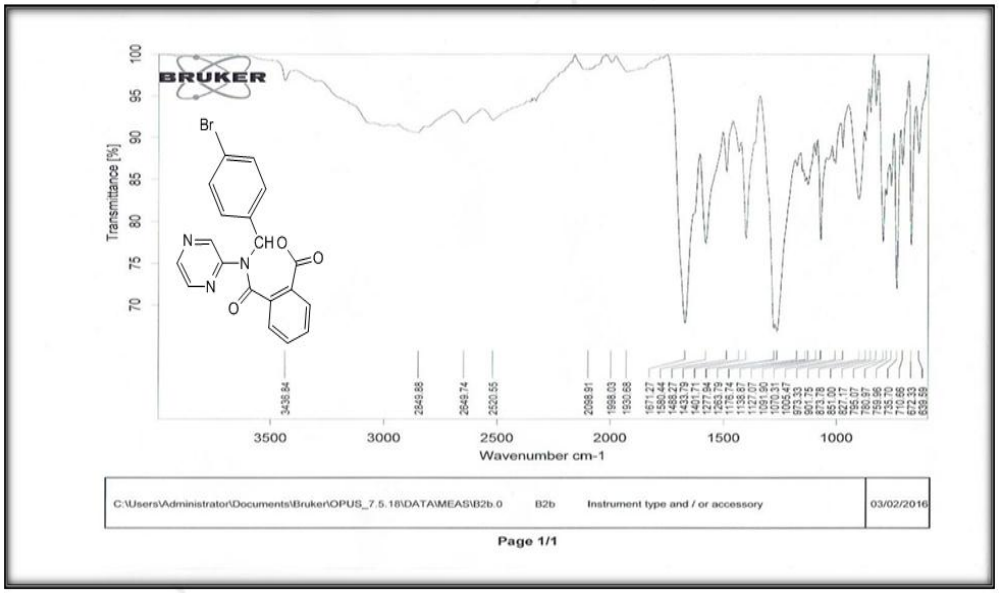


Fig 8: FT.IR spectrum of compound [B_{2b}]

Table 9: ^{1}H-NMR data of 3-aryl-4-(pyrazin-2-yl)-3,4-dihydrobenzo[e][1,3]oxazepine-1,5-dione [B_{1b}– B_{5b}]

Comp. No.	δ(N-CH) oxazepine ppm s, 1H	δ(C-H)Aromatic ppm m, nH	δ(HC=N) Pyrazine ppm m, 3H	Others ppm
B_{1b}	7.88	(6.34 – 7.17) 4H	8.17	(s, 6H, N-$(CH_3)_2$) : δ 3.40
B_{5b}	7.54	(6.97 – 7.32) 4H	8.29	(s, 3H, O-CH_3) : δ 3.43

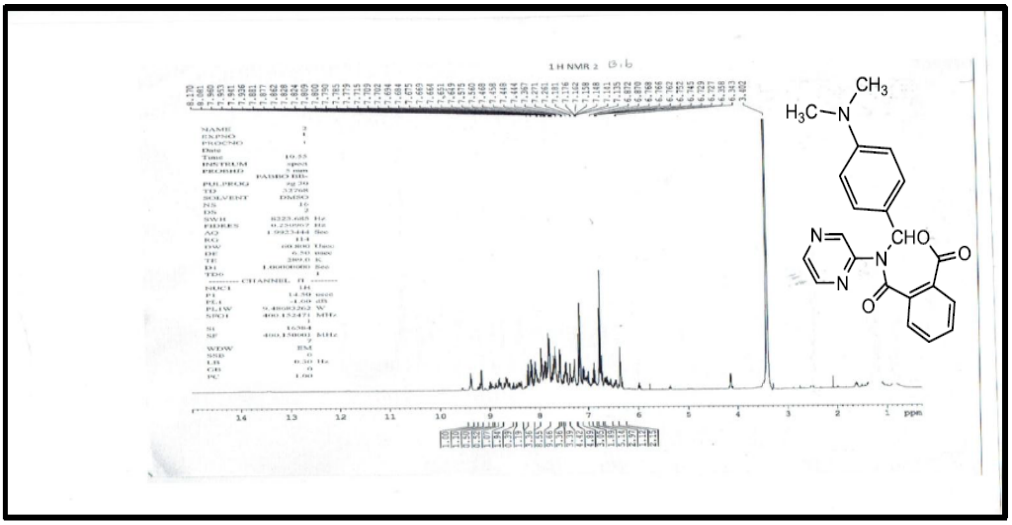


Fig 9: ^{1}H-NMR spectrum of compound [B_1b]

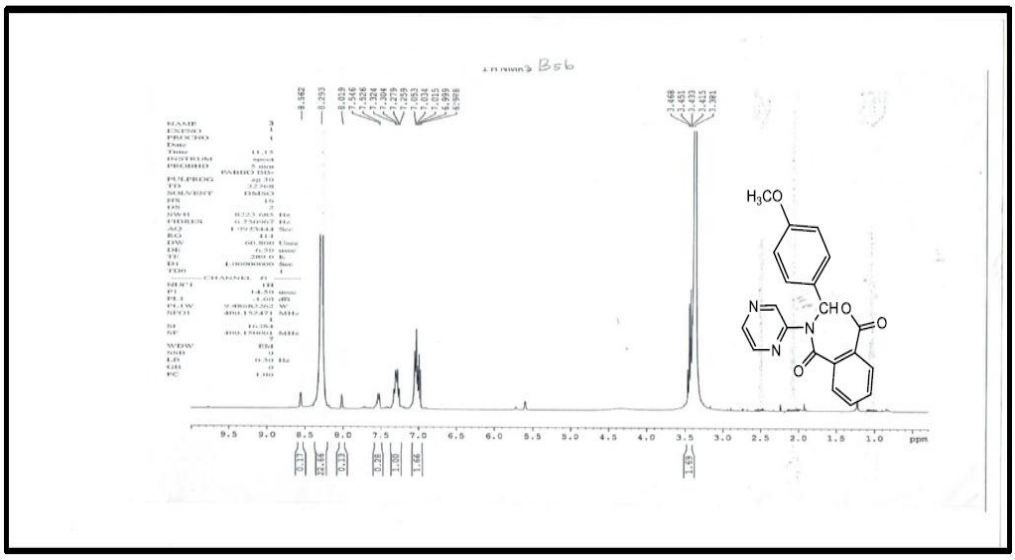


Fig 10: ^{1}H-NMR spectrum of compound [B_5b]

4. CONCLUSIONS

From this review, the accompanying conclusion could be drawn.

1-The electron-giving and the electron-pulling back gatherings impact the assurance of the season of the response. The electron-giving gathering expands the rate of the response, along these lines the season of the response is declines while the electron-pulling back gathering diminishes the rate of the response, accordingly the season of the response was expanded.

2- All incorporated mixes were steady by reverberation and having high softening focuses generally, this is another proof on the degree of the soundness.

REFERENCES

1. Abdullah M. Asiri and Khadija O. Badahdah, *Molecules*, 2007; 12: 1796–1804.
2. Apoorva Upadhyay, S.K. Srivastava, S.D. Srivastava and R. Yadav, *Indian Journal of Chemistry*, 2011; 89-90.
3. Bhausaheb K. Magar, Vijay N. Bhosale, Anil S. Kirdant and Trimbak K. Chondhekar, *J. Chem. Bio. Phy. Sci. Sec. A*, 2012; 2(1): 127–131.
4. Fahad A. Hassein and Obaid H. Abid, *Iraqi Journal of Chemistry*, 2001; 27(3).
5. Head J.F., Inoue S., Teranishi K. and Shimomura O., *Nature*, 2000; 405: 372–376.
6. Inoue S., Kakoi H. and Goto T., *Tetrahedron Lett*, 1976; 2971–2974.
7. Karthikeyan M.S. et al. Synthesis and biological activity of Schiff and Mannich bases bearing 2, 4-dichloro-5-flourophenyl moiety. *Bioorg. and Med. Chem*, 2006; 14: 7482-7489.
8. K. F. Ali, *Ph. D. Thesis*, Baghdad University, 2005.
9. Li. Y. et al. Artemisinin Derivatives Bearing Mannich Base Group: Synthesis and Antimalarial Activity. *Bioorg. and Med. Chem.*, 2003; 11: 4363-4368.
10. L. G. Wade, "Organic Chemistry", 7th Ed, New York, 2001.
11. L. Smith, W.C. Wong, A.S. Kiselyov, S. Burdzovic-Wizemann, Y. Mao, Y. Xu, M.A.J. Duncton, K. Kim, E.L. Piatnitski, J.F. Doody, Y. Wang, R.L. Rosler, D. Milligan, J. Columbus, C. Balagtas, S.P. Lee, A. Konovalov and Y.R. Hadari, Accepted for Publication, 11 July 2006.
12. *Bioorganic and Medicinal Chemistry Letters*, Available Online, 2006.
13. Malleshappa Noolvi et al. Synthesis, antimicrobial and cytotoxic activity of novel azetidine-2-one derivatives of 1*H*- benzimidazole. *Arabian Journal of Chemistry*, 2011; 21: 1, 5.
14. M. H. Serrano-Wu, D.R.St. Laurent, Y. Chen, S. Huang, K.R. Lam, J.A. Matson, C.E. Mazzucco, T.M. Stickle, T.P. Tully, H.S. Wong, D.M. Vyas and B.N. Balasubramanian, *Bioorganic and Medicinal Chemistry Letters*, 2002; 12(19): 2757.
15. Nagham M. Al-Jamali, Ph. D. Thesis, College of Education Ibn-Al-Haitham, University of Baghdad, 2008.
16. N.M. Al-Jamali, *Ph. D. Thesis*, Baghdad University, 2008.
17. N. Saemian, G. Shirvani and H. Matloubi, *Nuklenika*, 2005; 50(40): 139-141.
18. O. Buchardt, C.L. Pedersen and N. Harrit, *J.Org. Chem*, 1972; 37(23): 3592.
19. O. Tsuge, K. Oe and T. Ohnishi, *Heterocycles*, 1982; 19(9): 1609.

20. R. M. Silverstein, F. X. Webster and D. J. Kiemle, "Spectrometric Identification of Organic Compounds" New York, 2005.
21. R.T. Haiwal, *J. Kerbala University*, 2008; 6(4): 216.
22. Tsuji F. I. and Leisman G., *Proc. Natl Acad. Sci. U.S.A.* 1981; 78: 6719–6723.
23. Takahashi H. and Isobe M., *Chem. Lett,* 1994; 843–846.
24. Takahashi H. and Isobe M., *Bio Med. Chem. Lett*, 1993; 3: 2647–2652.
25. Venugopal K.N. and Jayashree B.S. Microwave-induced synthesis of Schiff bases of brom coumarins as antibacterials. *Indian J. Pharm. Sci.*, 2008; 70: 88-91.
26. Villar R. et al. Synthesis and cytotoxic activity of lipophilic sulphanamide derivatives of the benzo [b] thiophene 1,1-dioxode. *Bioorg. and Med. Chem,* 2004; 12: 963-968.
27. Z. H. Abood, *J. Kerbala University*, 2009; 7(1): 297.