Synthesis and characterization of new Oxazine , Thiazine and Pyrazol derived from chalcones

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Abstract:

In this study, chalcones were synthesis by condensing 2-acetylpyridine with aromatic aldehyde derivatives in dilute ethanolic potassium hydroxide solution at room temperature according to Claisen-Schmidt condensation. After that, new heterocyclic derivatives such as Oxazine, Thiazine and Pyrazol were synthesis by reaction between chalcones with urea, thiourea and hydrazine hydrate respectively scheme 1. All these compounds wrer characterization by FTIR, ^{1}H-NMR spectroscopy and elemental analysis.

Key words : 2-acetylpyridine, chalcones, Oxazine, Thiazine, Pyrazol.

Introduction :

Chalcones either natural or synthetic and their heterocyclics are known to exhibit various biological activities [1]. They have been reported to possess antioxidant [2], antimalarial [3], antileishmanial [4], anti-inflammatory [5], antitumour [6] and antibacterial activity [7]. The presence of a reactive α,β-unsaturated keto function in chalcones is found to be responsible for their antimicrobial activity, which may be altered depending on the type and position of substituent on the aromatic rings. In the present communication we report the reaction of 2-acetyl pyridine with different aromatic aldehydes to form chalcones [8-11]. oxazine heterocycles has shown that they possess varied biological properties such as antibacterial [12], analgesic [13], antitubercular [14], anticancer [15] and anticoagulant [16]. Thiazine is a six membered heterocyclic which contains two hetero atoms (N and S) [17]. Thiazine is fairly basic diuretics supplement it reduces water and increase vascularity , so it also use as anabolic agent in medicine [18]. The ability of thiazine to exhibit antibacterial [19,20], anti-inflammatory [21] and used as cannabinoid receptor agonist [22]. Pyrazole is an important class of compounds and attracted widespread attention due to their pharmacological properties [23], being reported to have a large spectrum of biological effects, especially antibacterial [24], antifungal [25] and anti-inflammatory properties [26,27].

Material and Methods:

Melting points were determined on a capillary melting point apparatus and are uncorrected. ^{1} H NMR spectra was recorded in the indicated solvent on Bruker WM 400 MHz spectrometer with TMS as internal standard. Infrared spectra were recorded in KBr on Perkin-Elmer AC-1 spectrophotometer.

1- General procedure for the preparation of chalcones (1-3)

Equimolar quantity (0.001mol) of 2-acetylpyridine and respective aldehydes were mixed and dissolved in minimum amount of alcohol. Aqueous potassium hydroxide solution 40% (15 mL) was added slowly and mixed occasionally for 24 h, at room

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temperature. Completion of the reaction was identified by TLC using Silica gel-G. After completion of the reaction (Scheme 1), the reaction mixture was poured into crushed ice and the precipitate have been obtained and recrystallized from ethanol .

2- General procedure for the Preparation of thiazine/oxazine derivatives [A_1-A_3 , B_1-B_3]

A mixture of Chalcone [1-3] (0.02mol), thiourea/urea (0.02 mol) were dissolved in ethanolic sodium hydroxide (10ml) was stirred about 2-3 hours with a magnetic stirrer. This was then poured into 400 ml of cold water with continuous stirring for an hour and then kept in refrigerator for 24 hours. The precipitate obtained was filtered, washed and recrystallized from ethanol. The completion of the reaction was monitored by TLC (ethyle acetate : toluene).

3- General procedure for the Preparation of pyrazole derivatives [C_1-C_3]

A mixture of Chalcone [1-3] (0.02 mol), hydrazine hydrate (0.02 mol) in ethanol (25 ml) was refluxed for 6hr. The mixture was concentrated by distilling out the solvent under reduced pressure and poured into ice water. The precipitate obtained was filtered, washed and recrystallized from ethanol. The completion of the reaction was monitored by TLC (ethyle acetate: toluene).

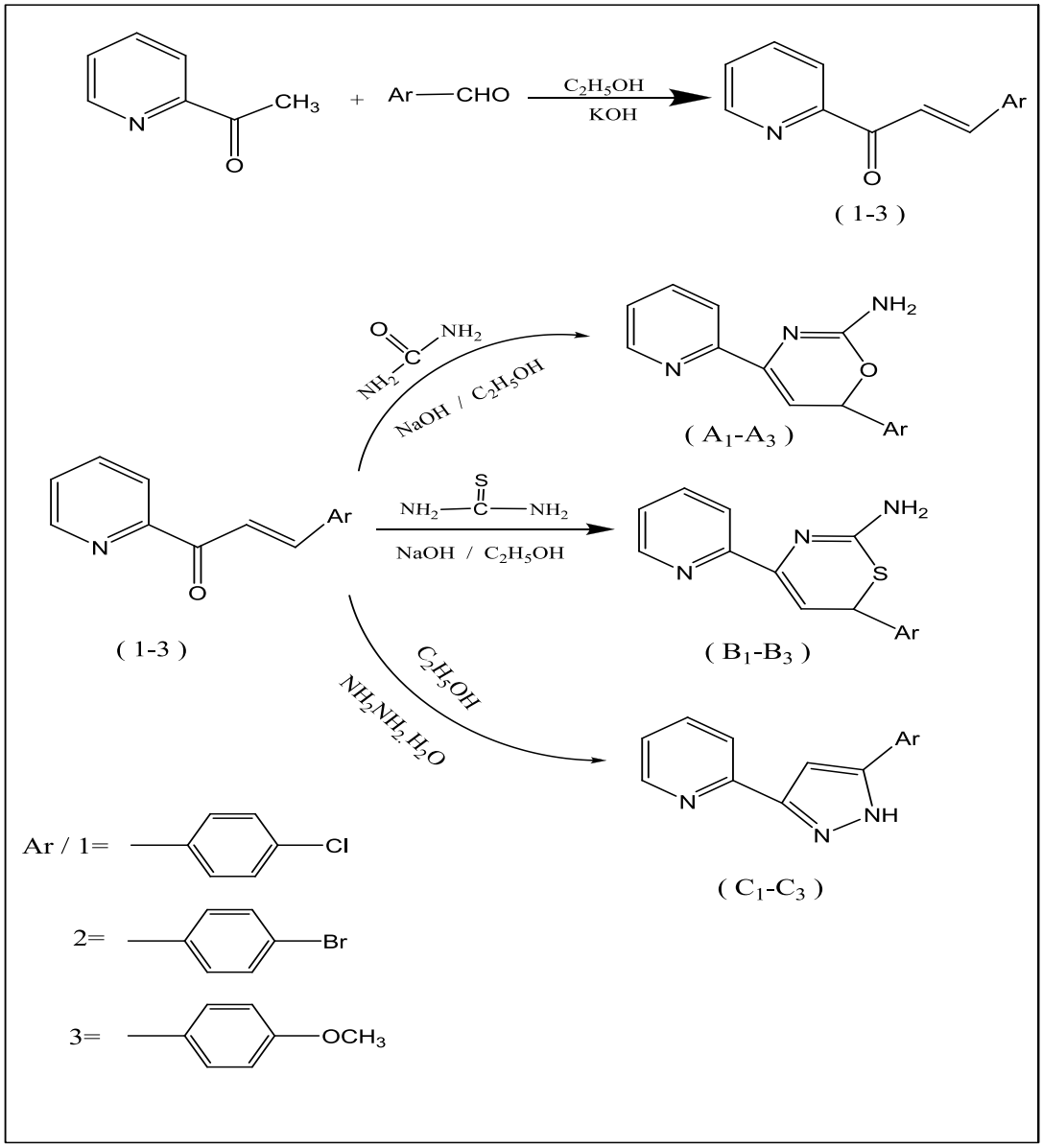
The characterization data of these compounds is described in Table 1 and 2.

Table 1- Physical data and Elemental Analysis of Synthesized Compounds

Comp.	M.F	M.Wt	M.p (^{0}C)	Yield %	Rf	Elemental analysis %					
						C		H		N	
						found	Calcu	found	Calcu	found	Calcu
1	$C_{14}H_{10}ONCl$	243.5	168	80	0.72	69.11	69.00	4.08	4.14	5.51	5.75
2	$C_{14}H_{10}ONBr$	288	139	73	0.65	58.52	58.36	3.55	3.50	4.57	4.86
3	$C_{15}H_{13}O_2\ N$	239	125	79	0.51	75.53	75.30	5.31	5.48	5.93	5.85
A_1	$C_{15}\ H_{12}ON_3Cl$	285.5	204	65	0.63	62.90	63.05	4.15	4.23	14.38	14.71
A_2	$C_{15}H_{12}ON_3Br$	330	198	55	0.70	54.31	54.56	3.73	3.66	12.29	12.73
A_3	$C_{16}H_{15}O_2N_3$	281	220	63	0.68	68.45	68.31	5.14	5.37	15.05	14.94
B_1	$C_{15}H_{12}SN_3Cl$	301	186	57	0.54	59.82	59.70	4.15	4.01	13.63	13.92
B_2	$C_{15}H_{12}SN_3Br$	346	212	70	0.58	52.10	52.03	3.25	3.49	11.96	12.14
B_3	$C_{16}H_{15}SN_3O$	297	253	64	0.78	64.43	64.62	5.18	5.08	14.08	14.13
C_1	$C_{14}H_{12}NCl$	255	190	52	0.76	65.55	65.76	3.67	3.94	16.21	16.43
C_2	$C_{14}H_{10}N_3Br$	300	226	58	0.61	55.88	56.02	3.14	3.36	14.43	14.00
C_3	$C_{15}H_{13}ON_3$	251	180	60	0.56	71.64	71.70	5.49	5.21	16.52	16.72

Results and Discussion

The general synthetic strategy employed synthesis procedure the chalcone derivatives (**1-3**) was based on Claisen-Schmidt condensation, As shown in Scheme1.The structures of all the chalcone derivatives (**1-3**) synthesized in this research were established on the basis of FTIR and ^{1}H-NMR spectral data Table2 and Figure 1,2,3. New heterocyclic derivatives such as Oxazine, Thiazine and Pyrazol were synthesized by reaction between chalcones with urea, thiourea and hydrazine hydrate respectively. The structures of all the heterocyclic derivatives synthesized in this research were established on the basis of FTIR and ^{1}H-NMR spectral data Table2 and Figure 4,5,6,7,8.



Scheme 1- Structure of all synthesized compounds

Table 2- Spectral data of Synthesized Compounds

Comp.	FTIR (KBr,cm^{-1})	^{1}HNMR (ppm)
1	1700 (C=O) , 1607 (–CH=CH) 834 (C–Cl) , 1524 (C=N)	6.95 (1H,d,-CO-CH=), 8.13 (1H,d,=CH-Ar) 6.12-6.90 (8H,m, Ar-H)
2	1704 (C=O) , 1600 (–CH=CH) 827 (C–Br) , 1515 (C=N)	7.12 (1H,d, -CO-CH=), 8.03 (1H,d,=CH-Ar) 6.32-7,10 (8H,m, Ar-H)
3	1660 (C=O) , 1595 (–CH=CH) 1232 (OCH_3) , 1548 (C=N)	6.99 (1H,d, -CO-CH=), 8.42 (1H,d,=CH-Ar) 6.09-6.93 (8H, m, Ar-H) 4.13 (3H, s, OCH_3)
A_1	3324 (1^0NH_2) , 1567 (Ar–C=C) 792 (C–Cl) , 1604 (C=N) 1321 (Ar–C–O)	9.98 (2H, s, NH_2), 7.31 (1H, s, CH) 6.31-7.12 (8H, m, Ar-H)
A_2	3345 (1^0NH_2) , 1551 (Ar–C=C) 829 (C–Br) , 1612 (C=N) 1253 (Ar–C–O)	10.03 (2H, s, NH_2), 7.53 (1H, s, CH) 6.19-7.11 (8H, m, Ar-H)
A_3	3348 (1^0NH_2) , 1541 (Ar–C=C) 1224 (OCH_3) , 1631 (C=N) 1178 (Ar–C–O)	10.45 (2H, s, NH_2), 7.26 (1H, s, CH) 6.77-7.23 (8H, m, Ar-H) 4.27 (3H, s, OCH_3)
B_1	3414 (1^0NH_2) , 1561 (Ar–C=C) 808 (C–Cl) , 1603 (C=N) 2360 (C–S–C)	9.81 (2H, s, NH_2), 7.35 (1H, s, CH) 6,52-7.21 (8H, m, Ar-H)
B_2	3395 (1^0NH_2) , 1573 (Ar–C=C) 871 (C–Br) , 1592 (C=N) 2521 (C–S–C)	10.09 (2H, s, NH_2), 7.32 (1H, s, CH) 6.25-7.15 (8H, m, Ar-H)
B_3	3270 (1^0NH_2) , 1512 (Ar–C=C) 1256 (OCH_3), 1602 (C=N) 2380 (C–S–C)	9.78 (2H, s , NH_2), 7.79 (1H, s, CH) 6.80-7.26 (8H, m, Ar-H) 3.83 (3H, s, OCH_3)
C_1	3352 (2^0NH) , 1586 (Ar–C=C) 853 (C–Cl) , 1212 (C–N,St)	12.03 (1H, s,NH), 6.52 (1H, s, CH) 6.61-7.51 (8H, m, Ar-H)
C_2	3356 (2^0NH) , 1551 (Ar–C=C) 876 (C–Br) , 1270 (C–N,St)	11.52 (1H, s, NH), 6.31 (1H, s, CH) 6.41-7.13 (8H, m, Ar-H)
C_3	3276 (2^0NH) , 1602 (Ar–C=C) 1305 (OCH_3) , 1269 (C–N,St)	11.28 (1H, s, NH), 6.77 (1H, s, CH) 6.78-7.26 (8H, m, Ar-H) 3.67 (3H, s, OCH_3)

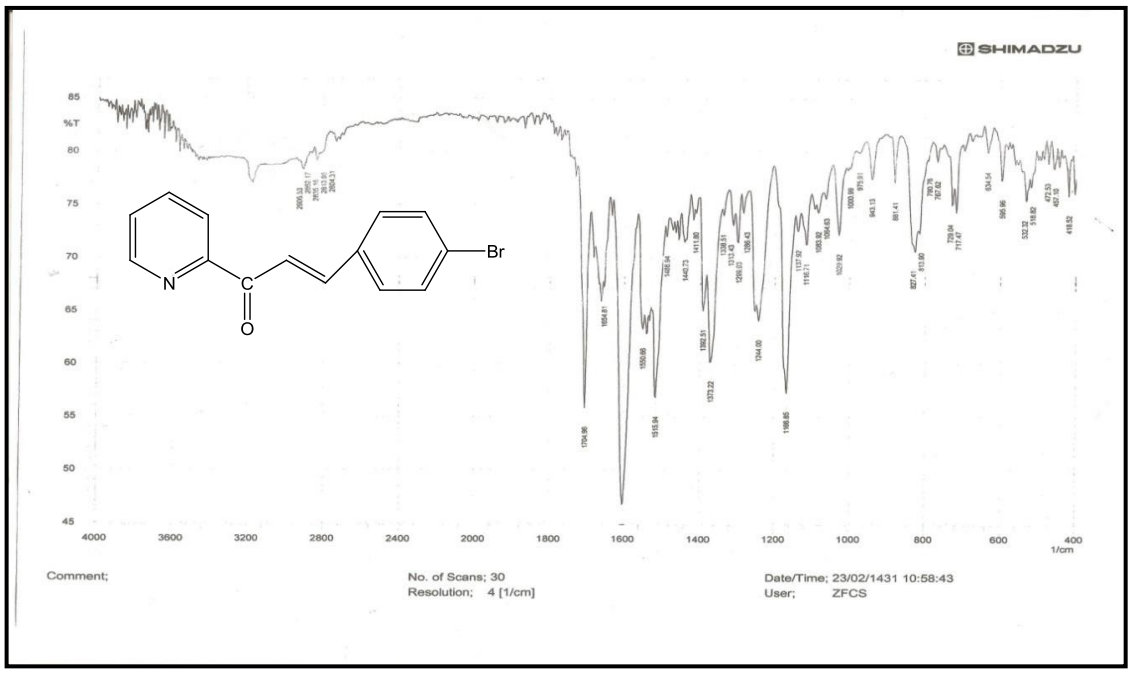


Fig. 1- FT.IR spectrum of compound [2]

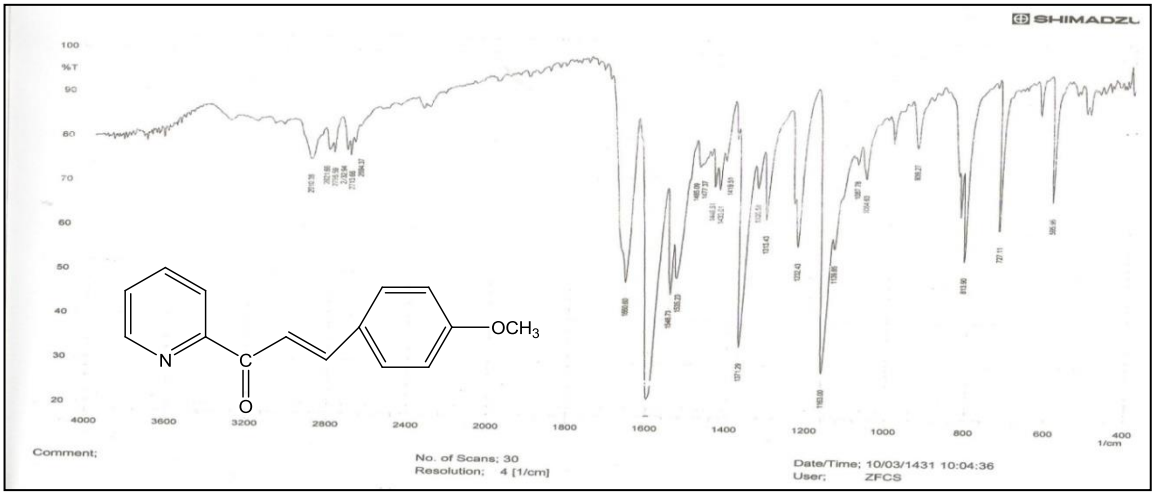


Fig.2- FT.IR spectrum of compound [3]

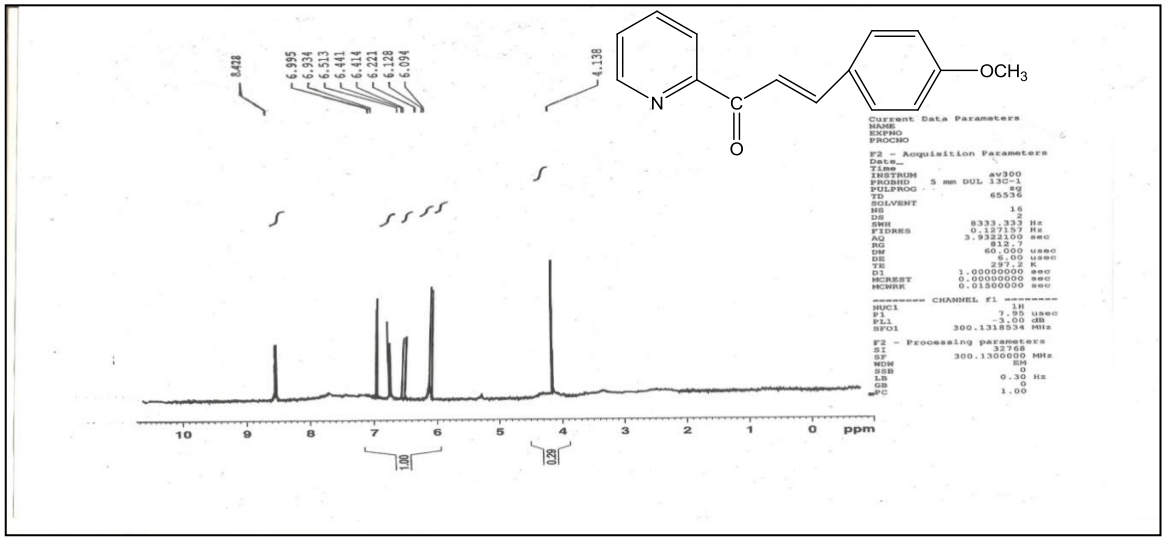


Fig. 3- ^{1}HNMR spectrum of compound [3]

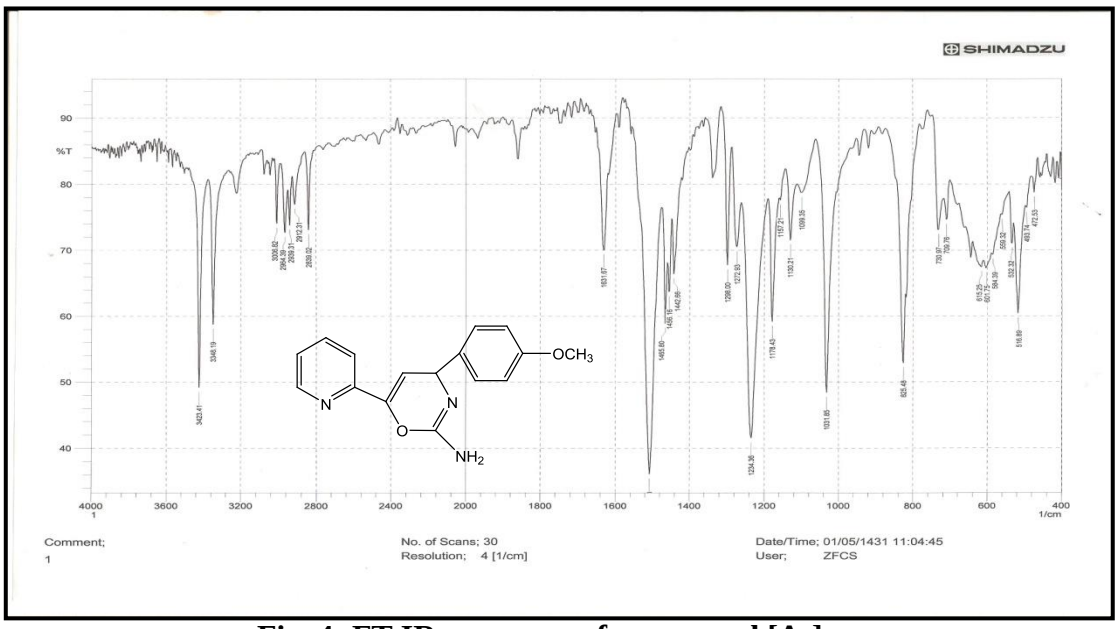


Fig. 4- FT.IR spectrum of compound [A_3]

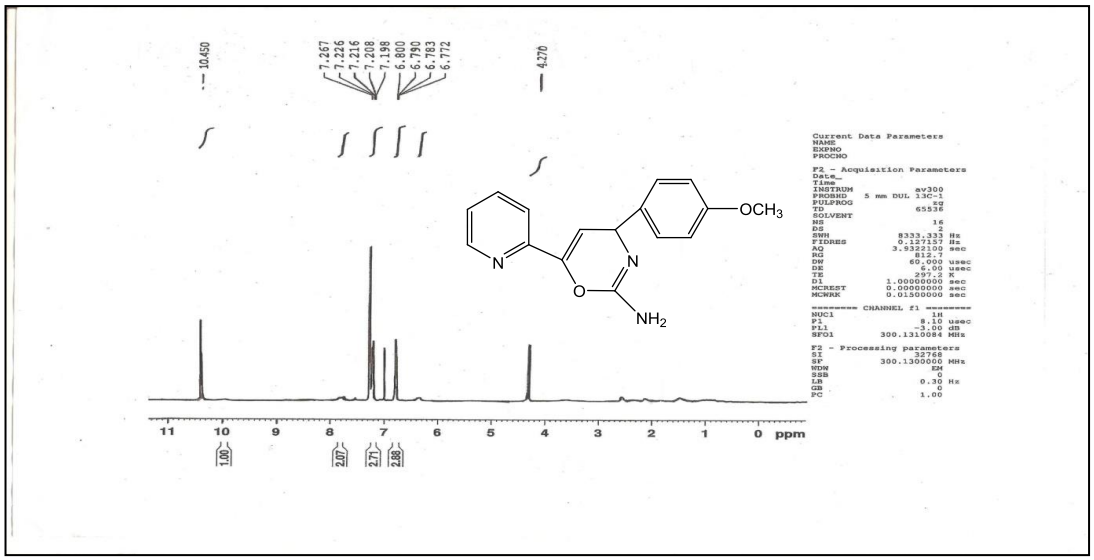


Fig. 5- ^{1}HNMR spectrum of compound [A_3]

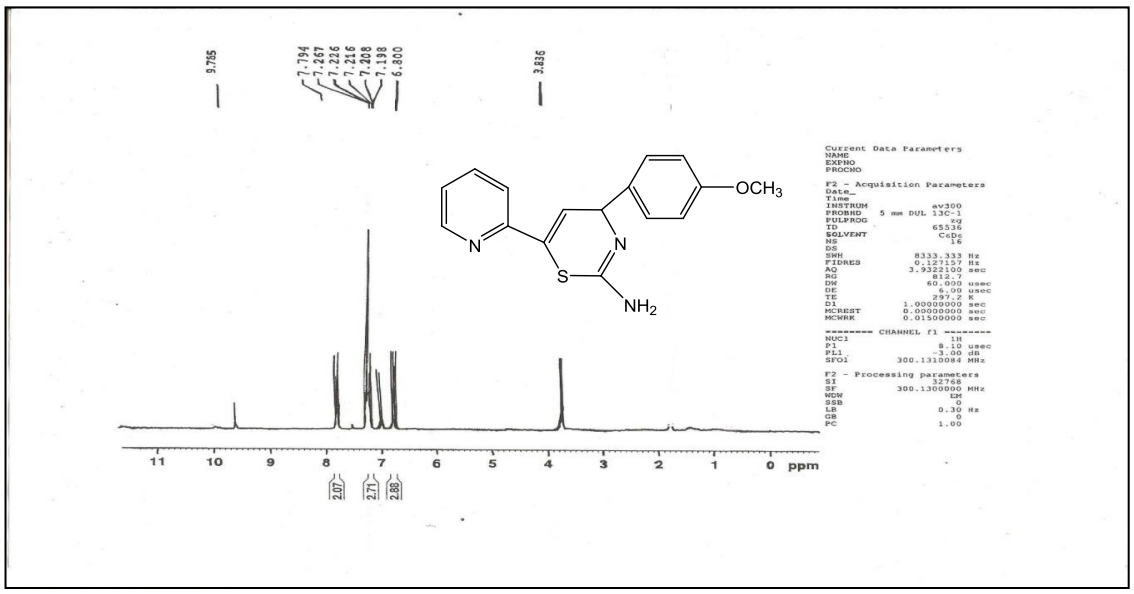


Fig. 6- ^{1}HNMR spectrum of compound [B_3]

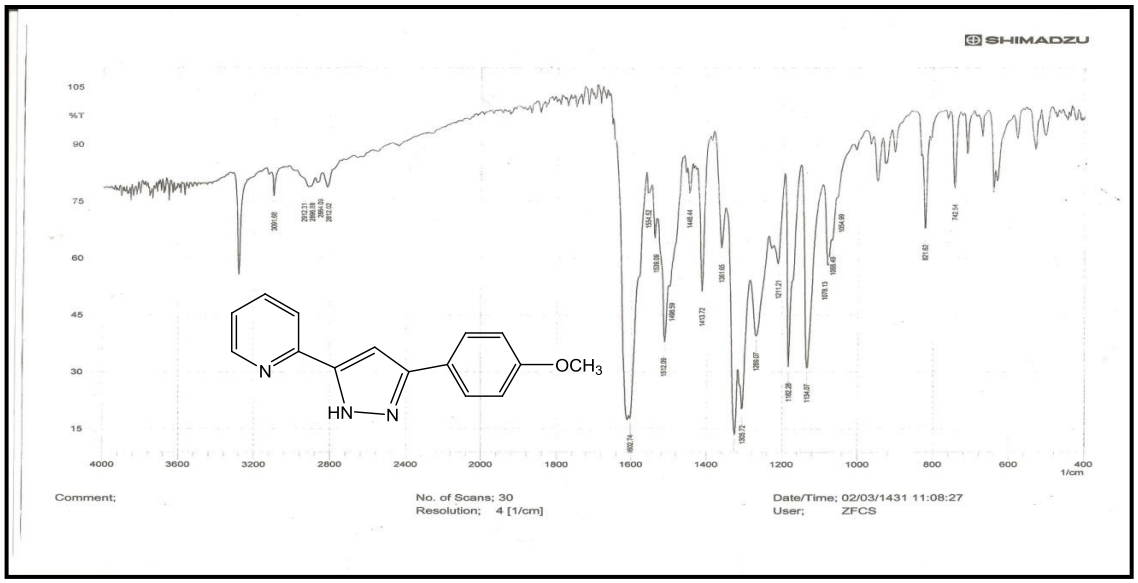


Fig. 7- FT.IR spectrum of compound [C_3]

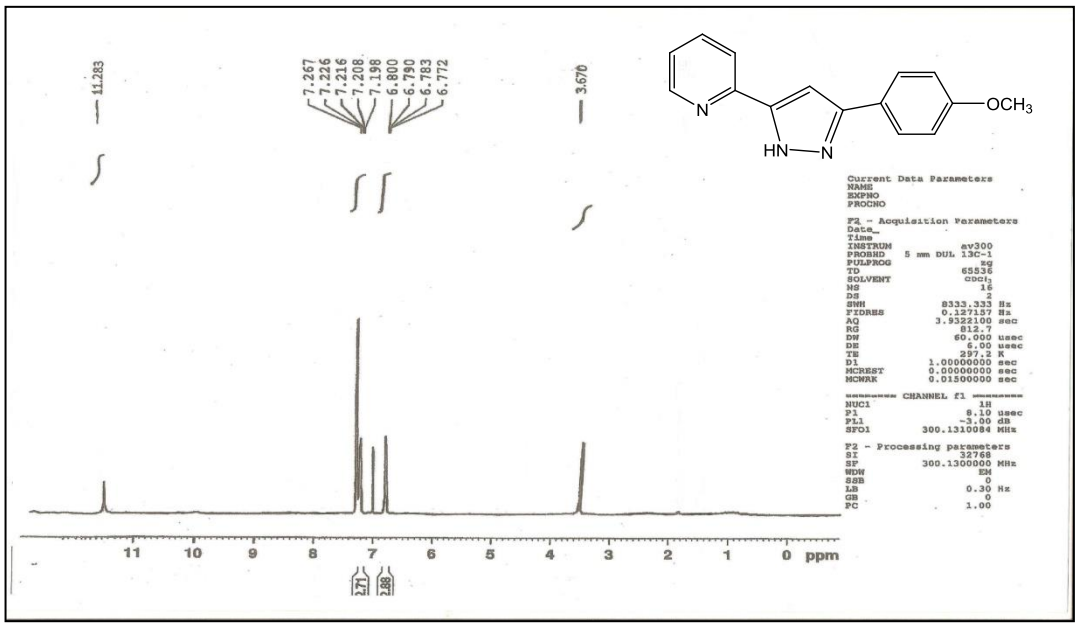


Fig. 8- ^{1}HNMR spectrum of compound [C_3]

References:

1- Satyanarayana M. Tiwari P. Tripathi B. K. Sriwastava A. K. and Pratap R. 2004. Synthesis and antihyperglycemic activity of chalcone based aryloxypropanolamines, Bioorg. Med. Chem. 12(5): 883-889.

2- Mukherjee S. Kumar N. Parasad A. K. Raj H. G. Bracke M. E. Olsen C. E. Jain S. C. and Parmar V. S. 2001. Synthetic and biological activity evaluation studies on novel 1,3-diarylpropenones, Bioorg. Med. Chem. 9(2): 337-345.

3- Ram V. J. Saxena A. S. Srivastava S. and Chandra S. 2000. Oxygenated chalcones and bischalcones as potential antimalarial agents, Bioorg. Med. Chem. Lett. 10(19): 2159-2161.

4- Zhai L. Chen M. Blam J. Theander T. G. Chiristensen S. B. Kharazmi A. and Antimicrob J. 1999. Chemother. 793.

5- Hsieh H. K. Tsao L. T. Wang J. P. and Lin C. N. 2000. Synthesis and anti-inflammatory effect of chalcones, J. Pharm Pharmacol. 52(2): 163-171.

6- Kumar S. K. Hager E. Catherine P. Gurulingappa H. Davidson N. E. and Khan S. R. 2003. Design, synthesis, and evaluation of novel boronic-chalcone derivatives as antitumor agents, J. Med. Chem. 46(14) 2813-2815.

7- Prasad Y R, Prasoona L, Rao A L, Lakshmi K, Kumar P R and Rao B, G. 2005. Synthesis and antibacterial activity of chalcone. Int. J. Chem. Sci. 3(4) 685-689.

8- Prasad Y.P. Kumar P.P. Kumar P.R. and Rao A.S. 2008. Synthesis and Antimicrobial Activity of Some New Chalcones of 2-Acetyl Pyridine, Journal of Chemistry. 5 (1):144-148.

9- Jyothi M.V. Prasad Y. R. Venkatesh P. and Sureshreddy M. 2012. Synthesis and Antimicrobial Activity of Some Novel Chalcones of 3-Acetyl Pyridine and their Pyrimidine Derivatives, Chem Sci Trans. 1(3): 716-722.

10- Mustafa C. and Hayreddin G. 2008. Preparation of 1,5-Diketones by Addition of Cyclohexanone to Chalcones under Solvent-free Phase Transfer Catalyst Condition, Turk J Chem. 32, 55-61.

11- Jayapal M. R. and Sreedhar N. Y. 2011. Synthesis of 2,6-dihydroxy substituted chalcones by ALdol condensation using SOCl2/ETOH, Int J Pharm Pharm Sci. 3(1): 127-129.

12- Sawant R. Bhangale L. Wadekar J. and Gaikwad P. 2012. Substituent Selection for Design and Synthesis of Antimicrobial 1,3 Oxazines, a Topliss Modified Approach. 60, 32-39.

13- Hiroyuki K. Yasuhide M. Yuji K. Kazuya O. and Maki H. 2008. 2-Arylimino-5,6-dihydro-4H-1,3-Thiazines as a New Class of Cannabinoid Receptor Agonists, Bioorg Med Chem Lett. 18, 6444–6447.

14- Li X. Manjunatha U.H. Goodwin M.B. Knox J.E. Lipinski C.A. Keller T.H. Barry C.E. and Dowd C.S. 2008. Synthesis and Antitubercular Activity of 7-(R)-and7-(S)-Methyl-2-nitro-6-(S)-(4-(trifluoromethoxy)benzyloxy)-6,7-dihydro-5H-imidazo[2,1-b][1,3] Oxazines, Bioorg Med Chem Lett. 18, 2256–2262.

15- Ouberai M. Asche C. Carrez D. Croisy A. Dumy P. and Demeunynck M. 2006. 3,4-Dihydro-1H-[1,3]oxazino[4,5-c]acridines as a New Family of Cytotoxic Drugs, Bioorg Med Chem Lett. 16, 4641-4643.

16- Ramesh L.S. Mahesh S.M. and Jyoti B.W. 2012. Anticoagulant potential of Schiff bases of 1,3-Oxazines, Int J Pharm Pharm Sci. 4(4): 320-323.

17- Farooque H. and Zulfequar H. 2012. Synthesis and antimicrobial screening of some 1,3- thiazines, J. Chem. Pharm. Res. 4(4): 2263-2267.

18- Doifode SK, Wadekar MP and Rewatkar S. 2011, Orient. J. Chem., 27(3), 1265-1267.

19- Mohamed J.E. and HUSSNIYIA A.A. 2012. Synthesis of some heterocyclic compounds derived from chalcones, Sci. Revs. Chem. Commun. 2(2): 103-107.

20- Kalirajan R. Sivakumar S.U. Jubie S. Gowramma B. and Suresh B. 2009. Synthesis and Biological evaluation of some heterocyclic derivatives of Chalcones, Int.J. ChemTech Res. 1(1): 27-34.

21- Nagaraj A. and Sanjeeva R.C. 2008. Synthesis and Biological Study of Novel Bis-chalcones, Bis-thiazines and Bispyrimidines, J. Iran. Chem. Soc. 5(2): 262-267.

22- Dabholkar V.V. and Parab S.D., 2011, Heterolett.org., 1, 176-188.

23- George M. N. Horia P. Constantin D. Alexandru V.M. Oana A.C. and Ion F. 2010. Synthesis and pharmacological evaluation of some new Pyrazole derivatives, FARMACIA. 58(2): 190-197.

24- Essam M.S. and Nagwa M. 2012. Synthesis and Antimicrobial Evaluation of Some Pyrazole, Molecules. 17, 4962-4971.

25- Ekhlass N. 2010. Synthesis (in vitro) Antitumor and Antimicrobial Activity of some Pyrazoline, Pyridine, and Pyrimidine Derivatives Linked to Indole Moiety, Journal of American Science. 6(8): 338-347.

26- Bekhit A.A. Ashour H.M.A. Bekhit A.E. Abdel-Rahman H.M. and Bekhit S.A. 2009. Synthesis of some pyrazolyl benzenesulfonamide derivatives as dual anti-inflammatoryantimicrobial agents, J. Enzym. Inhib. Med. Chem. 24(1): 296-309.

27- Bekhit A.A. Ashour H.M. Bekhit A.D. and Bekhit S.A. 2009. Synthesis and biological evaluation of novel pyrazole derivatives as anti-inflammatory antimicrobial agents, Med Chem. 5(2): 103-107.

تحضير وتشخيص مشتقات جديدة للأوكسازاين والثايازاين والبايروزول من الجالكون

*زينب عامر صلال**

*قسم الكيمياء – كلية العلوم- جامعة بغداد

الخلاصة :

تم تحضير الجالكون من تكاثف 2-أسيتال بيريدين مع مشتقات الديهايدية في محلول مخفف من هيدروكسيد البوتاسيوم الكحولي في درجة حرارة الغرفة بالاعتماد على تكاثف كليسن-شمدت. بعدها تم تحضير من خلال التفاعل بين الجالكون مع Pyrazol, Thiazine, Oxazine مشتقات حلقية غير متجانسة جديدة مثل اليوريا والثايوريا والهيدرازين على التوالي. شخصت جميع المركبات المحضرة بواسطة الاشعة تحت الحمراء ومطيافية الرنين النووي المغناطيسي البروتوني والتحليل الدقيق للعناصر (الكاربون والهيدروجين والنيتروجين).