Synthesis of new Heterocyclic Compounds Containing an Imine Group

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Abstract

This research includes , synthesis of new heterocyclic derivatives,and the first step Involves preparation of chalcone compounds through a reaction between m-amino acetophenone with p-chloro benzaldehyde and p-nitro benzaldehyde which is then used for preparation of new chalcones ,the second step of this study leads for preparation of new shiff bassesThe last step includes preparation of thiazine , oxazine , isoxazole and pyrazole derivatives..Thin layer cromotography was used to follow the reactionsAll the compounds have been characterized by melting points and FT-IR Spectroscopy, some of them characterized by (H^1-NMR)-spectra and Elemental Analysis(C.H.N).

Keywords: Synthesis chalcone, thiazine,oxazine, isooxazole , pyrazole

الخلاصة :-

تضمن البحث تحضير مركبات حلقية غير متجانسة جديدة حيث تم في الخطوة الاولى تحضير مركبات الجالكونات من تفاعل ميتا-أمينو أسيتوفينون مع بارا-كلورو بنزلديهايد و بارا-نايترو بنزلديهايد أما الخطوة الثانية من البحث فتضمنت تحضير قواعد شف جديدة و الخطوة الاخيرة من البحث فقد تضمنت تحضير مركبات الثيازين والاوكسازين والايزواوكسازول والبايرازول وقد تم متابعة سير التفاعلات بأستخدام تقنية كروموتوكرافيا الطبقة الرقيقة, شخصت المركبات المحضرة من خلال قياس درجات الانصهار, مع بعض الطرق الطيفية المتمثلة بـ (طيف الأشعة تحت الحمراء لجميعها) وطيف الرنين النووي المغناطيسي البروتوني وكذلك التحليل الدقيق للعناصر لبعض منها .

Introduction

Chalcones were prepared by condensation of acetophenone with aromatic aldehydes in presence of suitable condensing agent which then undergoes avariety of chemical reactions which leads to many heterocyclic compounds .[1,2] The presence of reactive α,β – unsaturated keto group in chalcones is found to be responsible for biological and pharmacological activities such as antibacterial , antitumor and antioxidant [3,4] The Schiff bases are also called as imine[5], and characterized by the-N=CH-,which is important in educidating the mechanism of transamination and vacemmisation reactions in biological systems[6,7]. Schiff bases are known to be neoplasm inhibitors[5], Pyrazole and its derivatives are an important class of compounds and attracted widespread attention due to their pharmacological properties , being reported to have alonge spectrum of biological effects , especially analgesic and anti inflammatory properties[8].

Experimental

Materials

All chemicals were of highest purity and used as supplied by the manufactures.MeasurementsMelting points(m.p.) of the synthesized compounds were determined in open capillary tube and are uncorrected by Bio Cote,BIBBY SCIENTIFIC,LIMITEDSTONE,STAFFORDSHIRE,ST15 OSA,UK(230V,50HZ,75W)Elemental C.H.N analysis were carried out by EUROEA Elemental analyzer,Kufa university/Bio chemical laboratory.IR spectra were recorded on(Shimadzu 8400 series),in the 4000-400cm-1 range using KBr disk.H-NMR spectra were recorded on(Bruker, Ultra Shield 300 MHZ , Switzerland),Al-biayt

university-Jordon ,by using DMSO as solvent.Thin layer chromatography(T.L.C)was preformed on silica gel G for (T.L.C) and spots were visualized by Iodine vapors.

Preparation of [1-(3-aminophenyl)-3-(4-chlorophenyl)prop-2-en-1-one] A

m-aminoacetophenone (0.01mole,1.35gm) was dissolved in absolute EtOH(30ml) and was added to amix of p-chloro benzaldehyde (0.01mole,1.4gm) in 5ml (10% NaOH) . The mixture was Sterried for 5hr at room tempreture.The reaction was monitored by TLC using (benzene : methanol)(4:1)ml Rf(0.8). The solvent was evaporated and the resulted 304recipitate was recrystallized from absolute EtOH to give(2.1gm,76.3%) , m.p.(114-116) °C.

Preparation of [1-(3-aminophenyl)-3-(4-nitrophenyl)prop-2-en-1-one] B

m-aminoacetophenone (0.01mole,1.35gm) was dissolved in absolute EtOH(30ml) and was add to aimx of p-nitro benzaldehyde (0.01mole,1.51gm)in 5ml (10% NaOH) . The mixture was Sterried for 5hr at room tempreture.The reaction was monitored by TLC using (benzene: methanol)(3.5:1.5)ml Rf(0.55). The solvent was evaporated and the resulted 304recipitate was recrystallized from absolute EtOH toxgive(2.3gm,80.4%),m.p.(130-132) °C.

Preparation of [1-{3-[(2,4-dichlorobenzylidene)amino]phenyl}-3-(4-chlorophenyl)prop-2-en-1-one] A_1

Ethanolic mixture of compound A (0.005mole,1.28gm)with2,4-dichloro benzaldehyde (0.005mole,0.87gm)were refluxed for 8hr at 65°C in presence of EtOH(30 ml) with addition 2 drops of glacial acitic acid. The reaction was monitored by TLC using (benzene :methanol) (3:2)ml Rf(0.9) . The solvent was evaporated and the resulted 304recipitate was re crystallized from absolute EtOH to give compound A_1 (1.6gm, 74.4%) , m.p. (120-122) ° C.

Preparation of [1-{3-[(2,4-dichlorobenzylidene)amino]phenyl}-3-(4-chlorophenyl)prop-2-en-1-one] B_1

Ethanolic mixture of compound B (0.005mole,1.39gm)with2,4-dichloro benzaldehyde (0.005mole,0.85gm)were refluxed for 8hr at 65°C in presence of EtOH(30 ml) with addition 2 drops of glacial acitic acid. The reaction was monitored by TLC using (benzene :methanol) (4:1)ml Rf(0.95)). The solvent was evaporated and the resulted 304recipitate was re crystallized from absolute EtOH to give compound B_1 (1.75gm, 68.89%) , m.p. (106-108) ° C.

Preparation of [6-(4-chlorophenyl)-4-{3-[(2,4-dichlorobenzylidene) amino]phenyl}-6*H*-1,3-oxazin-2-amine] A_2[(1)]

Amixture of compound A_1 (0.414gm, 0.001mole) and urea(0.06gm,0.001mole) were reacted in presence of ethanolic sodium hydroxide(5ml)with mechanical stirring for (6h).then the resulting solution was poured into 20ml of cold water with continuous stirring for an hour and then kept in refrigerator for 24 hours. The solvent was evaporated and the resulted 304recipitate was recrystallized from absolute EtOH .The completion of the reaction was monitored by T.L.C. using (benzene : methanol) (3:2)ml, Rf (0.54) to give[A_2(0.35gm, 76%),m.p. (175-177)°C

Preparation of [6-(4-nitrophenyl)-4-{3-[2,4-dichlorobenzylidene)amin o]phenyl}-6*H*-1,3-oxazin-2-amine] B_2

Amixture of compound B_1 (0.425gm, 0.001mole) and urea(0.06gm,0.001mole) were reacted in presence ethanolic sodium hydroxide(5ml)with mechanical stirring for (6h). then the resulting solution was poured into 20ml of cold water with continuous stirring for an hour and then kept in refrigerator for 24 hours. The solvent was evaporated and the resulted 305recipitate was recrystallized from absolute EtOH .The completion of the reaction was monitored by T.L.C. using (benzene : methanol) (3.5:1.5)ml, Rf (0.75) to give[B_2(0.34gm,70%),m.p. (160-162)°C

Preparation of [*N*-{3-[5-(4-chlorophenyl)isoxazol-3-yl]phenyl}-*N*-(2,4-dichlorobenzylidene)amine] A_3

Amixture of Chalcone A_1 (0.414gm, 0.001mole), hydroxyl amine hydrochloride (0.069gm, 0.001mole) and sodium acetate in ethanol (25ml) was refluxed for (6h) . The solvent was evaporated and the resulted 305recipitate was recrystallized from absolute EtOH .The completion of the reaction was monitored by T.L.C. using (benzene : methanol) (4:1)ml, Rf (0.7) to give[A_3(0.3gm,62 %),m.p. (118-120)°C

Preparation of [*N*-{3-[5-(4-nitrophenyl)isoxazol-3-yl]phenyl}-*N*-(2,4-dichlorobenzylidene)amine] B_3

Amixture of Chalcone B_1 (0.425gm, 0.001mole), hydroxyl amine hydrochloride (0.07gm, 0.001mole) and sodium acetate in ethanol (25ml) was refluxed for (6h) . The solvent was evaporated and the resulted 305recipitate was recrystallized from absolute EtOH .The completion of the reaction was monitored by T.L.C. using (benzene : methanol) (3:2)ml, Rf (0.83) to give[B_3(0.32gm,64.6%),m.p. (149-151)°C

Preparation of [*N*-{3-[5-(4-chlorophenyl)-1*H*-pyrazol-3-yl]phenyl}-*N*-(2,4-dichlorobenzylidene)amine] A_4[9]

Amixture of Chalcone A_1 (0.414gm, 0.001mole), hydrazine hydrate (0.05gm, 0.001mole) in ethanol (25ml) was refluxed for (7h) . The solvent was evaporated and the resulted 305recipitate was recrystallized from absolute EtOH .The completion of the reaction was monitored by T.L.C. using (benzene : methanol) (4:1)ml, Rf (0.71) to give[A_4(0.3gm, 63%),m.p. (179-181)°C

Preparation of [4-(3-aminophenyl)-6-(4-chlorophenyl)-6*H*-1,3-thiazin-2-amine]B_4

Amixture of compound B (1.11gm, 0.004mole) and thiourea(0.36gm,0.004mole) were reacted in presence of ethanolic sodium hydroxide(5ml)with mechanical stirre for (6h). then the resulting solution was poured into 20ml of cold water with continuous stirring for an hour and then kept in refrigerator for 24 hours. The solvent was evaporated and the resulted 305recipitate was re crystallized from absolute EtOH .The completion of the reaction was monitored by T.L.C. using (benzene : methanol) (3:2)ml, Rf (0.85) to give[B_4(1.2gm, 74.5%),m.p. (188-190)°C

Results and Discussion :-

In the present work , compounds (A) and (B) were used as the key intermediates for synthesis of new heterocyclic derivatives . These compounds were prepared by the reaction of compounds {A, B, 2,4-dichloro benzaldehyde, urea, hydroxyl amine hydrochloride and thiourea , Scheme (3) the physical parameters of newly synthesized are reported in table (1) . The elemental analysis data of the prepared compounds was shown as in table (4) . The reaction are followed by (TLC) , (Benzene: MeOH) .

FT-IR Spectra : -

FT-IR spectra of the compounds (A and B) fig. (1,2) shown disappearance of (CH) absorption bands in benzaldehyde derivatives, The absorption band of carbonyl group was appear at 1670cm^{-1} and 1656cm^{-1} , the absorption band of (NH_2) group appear at 3373cm^{-1} and 3239cm^{-1} [10] . The FT-IR spectra of compounds (A_1 and B_1) shown disappearance absorption bands of (NH_2) group fig (3,4) , The FT-IR spectra of compounds (A_2 and B_2) shown appear of (NH_2) absorption bands at 3430cm^{-1} and 3254cm^{-1} fig(5, 6) . The FT-IR spectra of compounds (A_3 and B_3) shown disappearance of carbonyl group absorption band at 1670cm^{-1} and 1653cm^{-1} fig (7,8) The FT-IR spectrum of compound (A_4) shown new absorption bands of 3446cm^{-1} , 3375cm^{-1} and 3254cm^{-1} for (NH_2) groups . fig (9) . The FT-IR spectrum of compound (B_4) shown new band at 3385cm^{-1} for the (NH) group of pyrazole derivatives and disappearance of absorption band at 1675cm^{-1} for carbonyl group fig (10). .

H^1-NMR Spectra:-

H^1-NMR spectrum of compound (A_1) showed signal at 8.7-8.8 ppm due to proton of imine group and signals at 6.8-8.2 ppm[11] due to protons of phenyl groups fig (11) . H^1-NMR spectrum of compound (B_2) showed signal at 9.9ppm due to (NH_2) group and the proton of imine group appear at 8.9 ppm , the signals at 6.3-7.8 ppm due to protons of phenyl groups fig (12) . H^1-NMR spectrum of compound (B_3) showed singlet signal at 8.8 ppm due to proton of imine group , but the signal at 6.7-7.8 ppm due to protons of phenyl group , and the proton of isoxazole cycle appear at 5.9 ppm fig (13)

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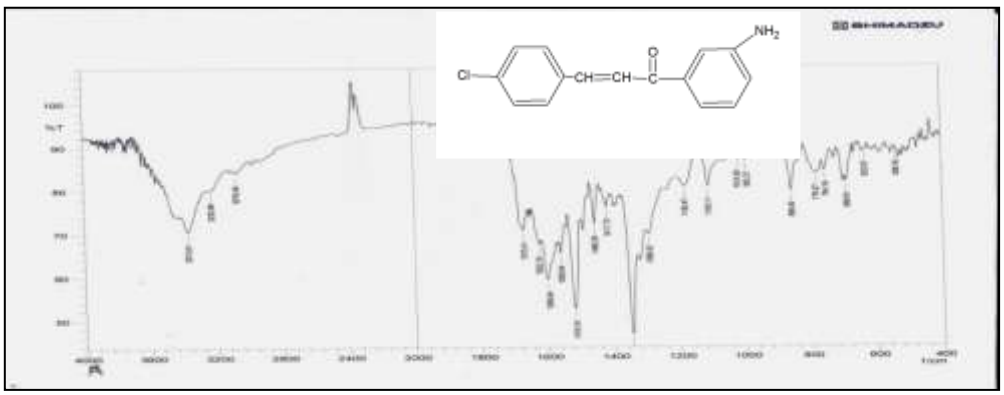


Figure(1) FT-IR Spectrum for Comp. (A)

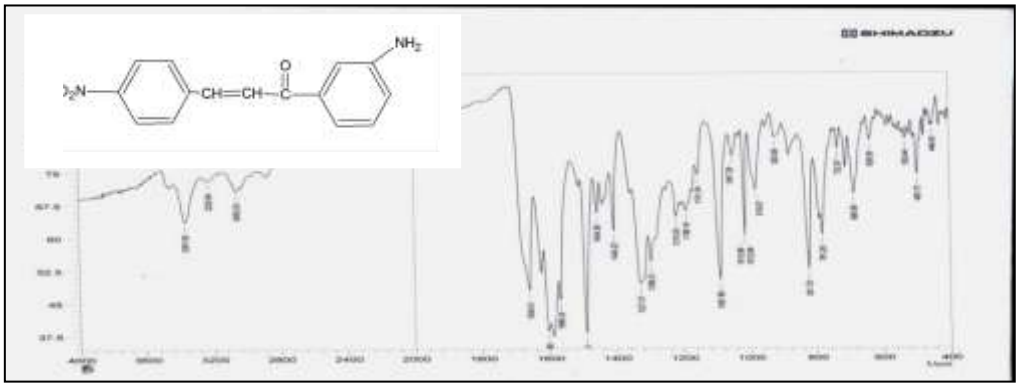


Figure (2) FT-IR Spectrum for Comp. (B)

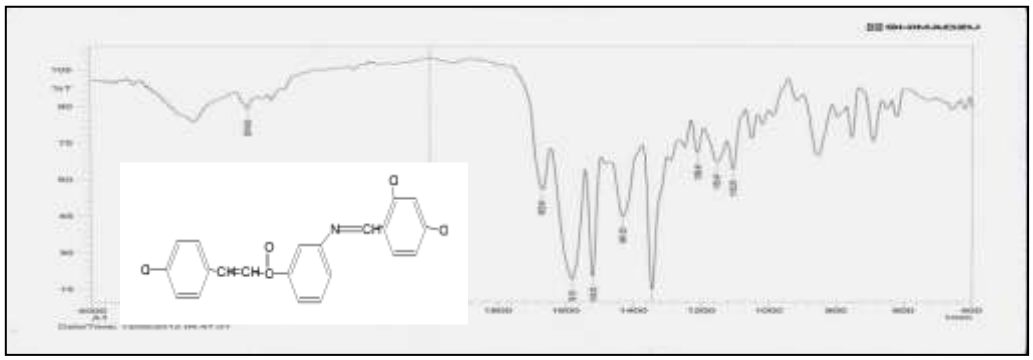


Figure (3) FT-IR Spectrum for Comp. (A_1)

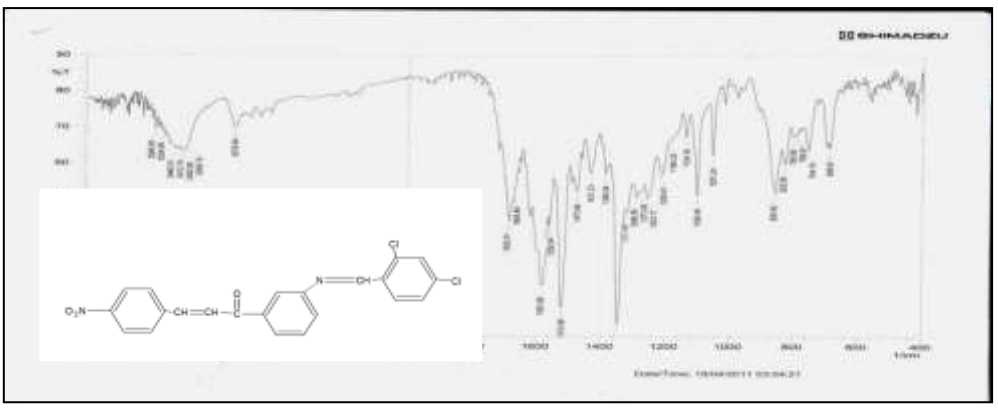


Figure (4) FT-IR Spectrum for Comp. (B_1)

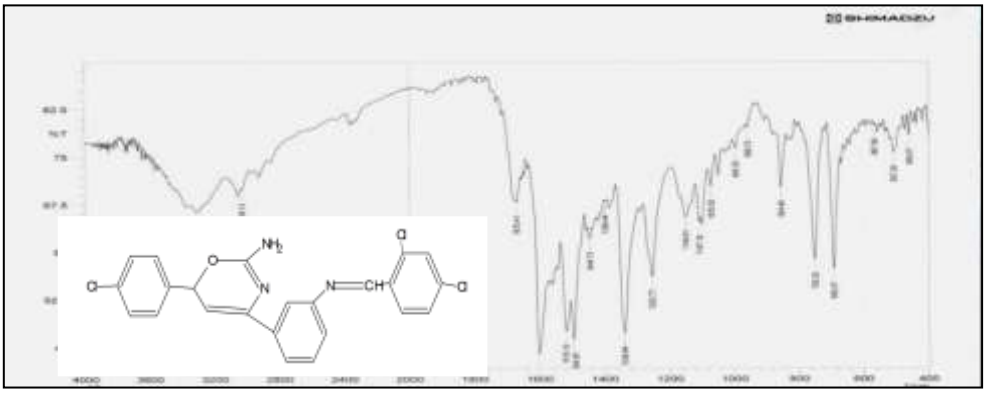


Figure (5) FT-IR Spectrum for Comp. (A_2)

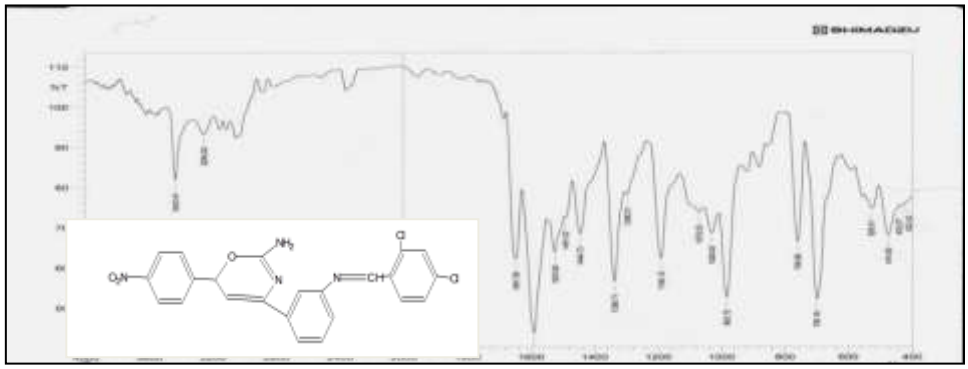


Figure (6) FT-IR Spectrum for Comp. (B_2)

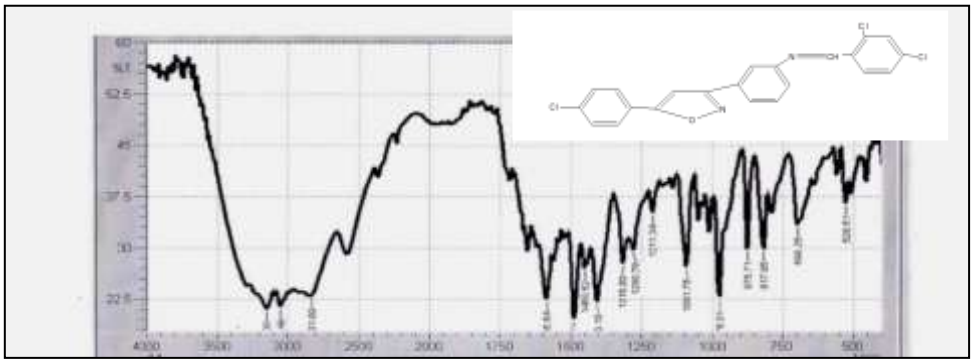


Figure (7) FT-IR Spectrum for Comp. (A_3)

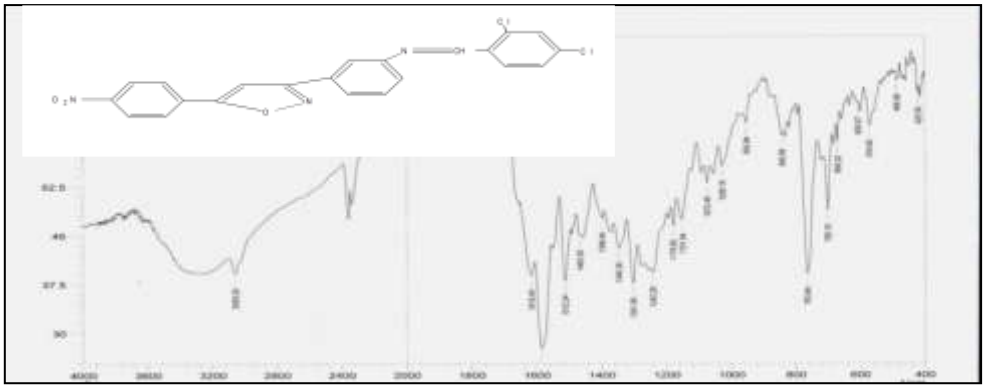


Figure (8) FT-IR Spectrum for Comp. (B_3)

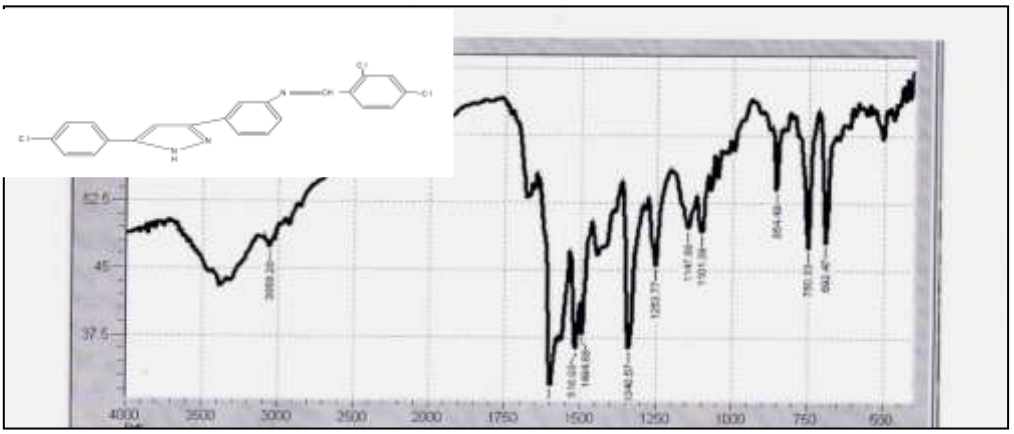


Figure (9) FT-IR Spectrum for Comp. (A_4)

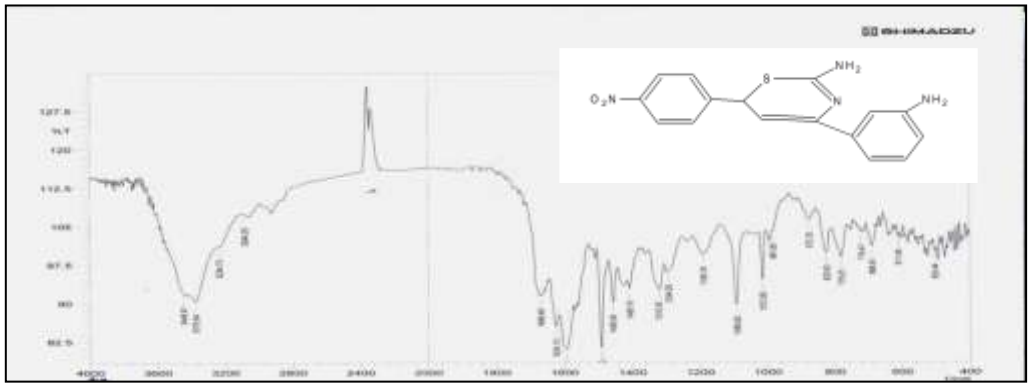
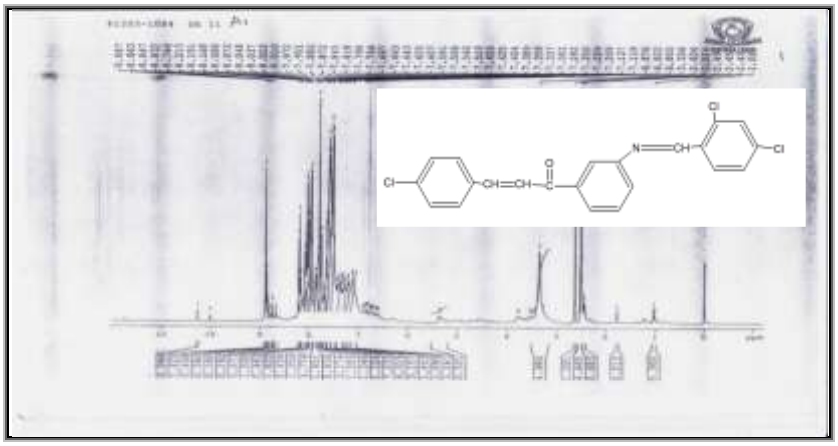
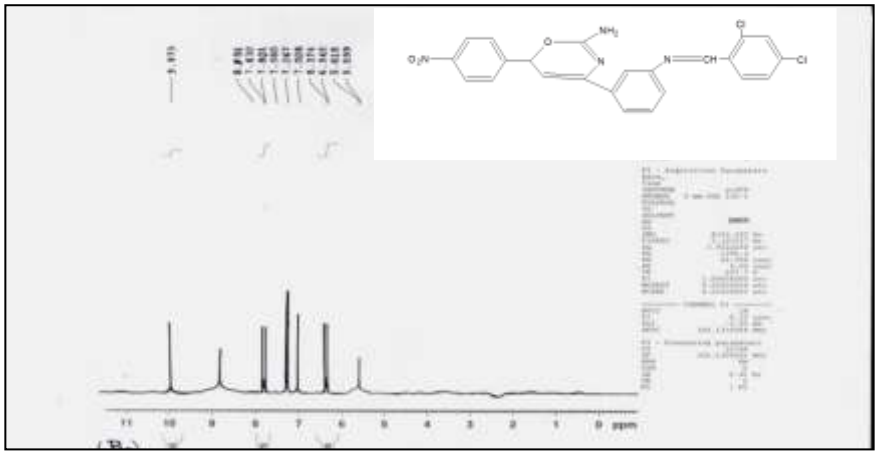


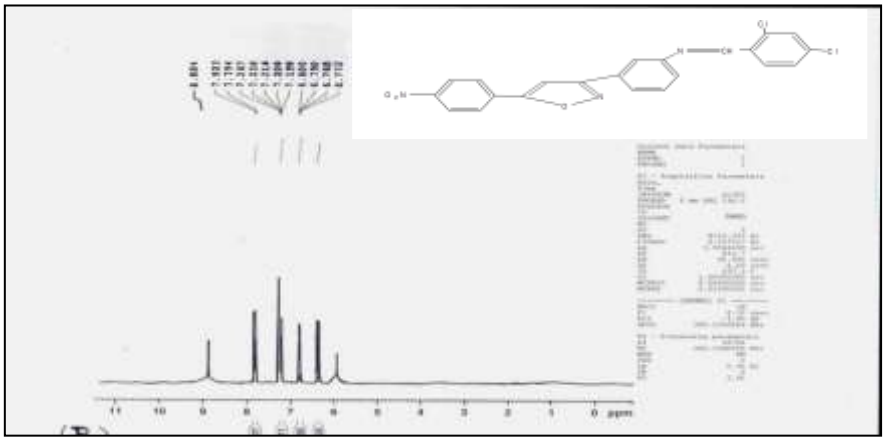
Figure (10) FT-IR Spectrum for Comp. (B_4)



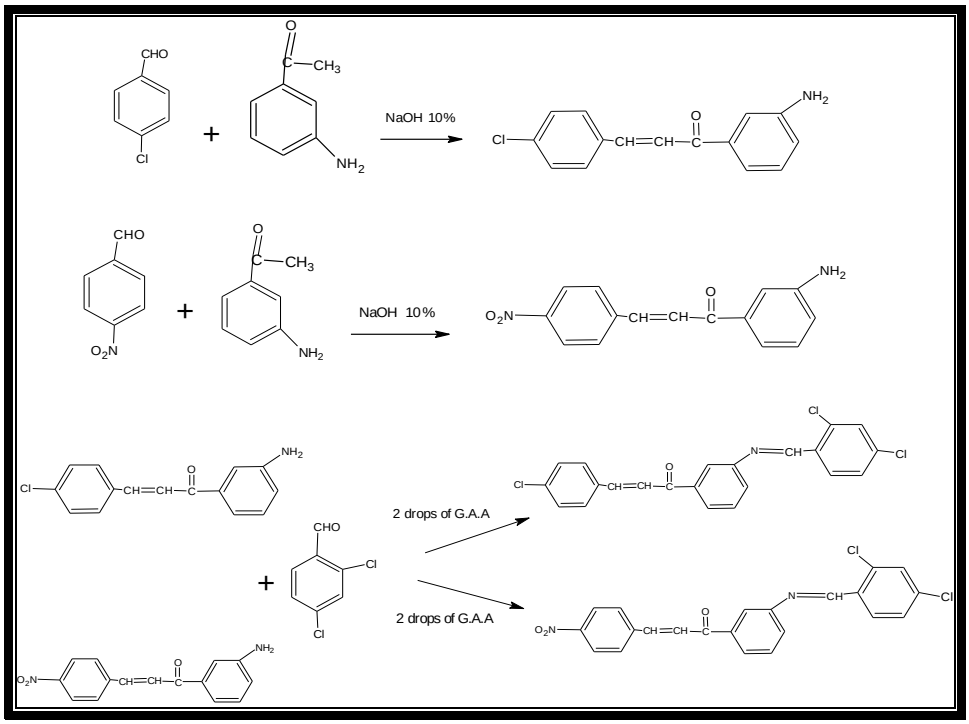
Figure(11) H-NMR Spectrum for Comp. (A_1)



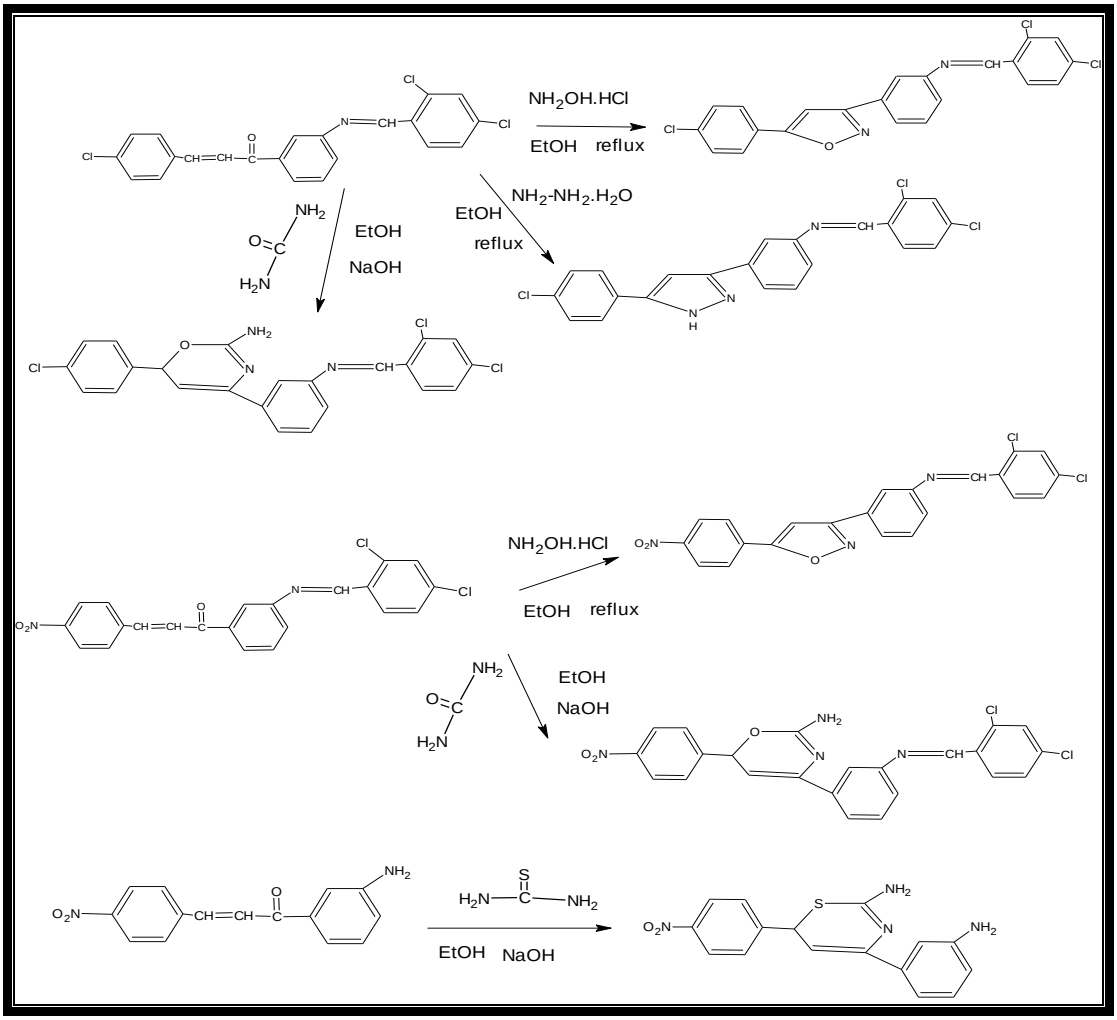
Figure(12) H-NMR Spectrum for Comp. (B_2)



Figure(13) H-NMR Spectrum for Comp. (B_3)

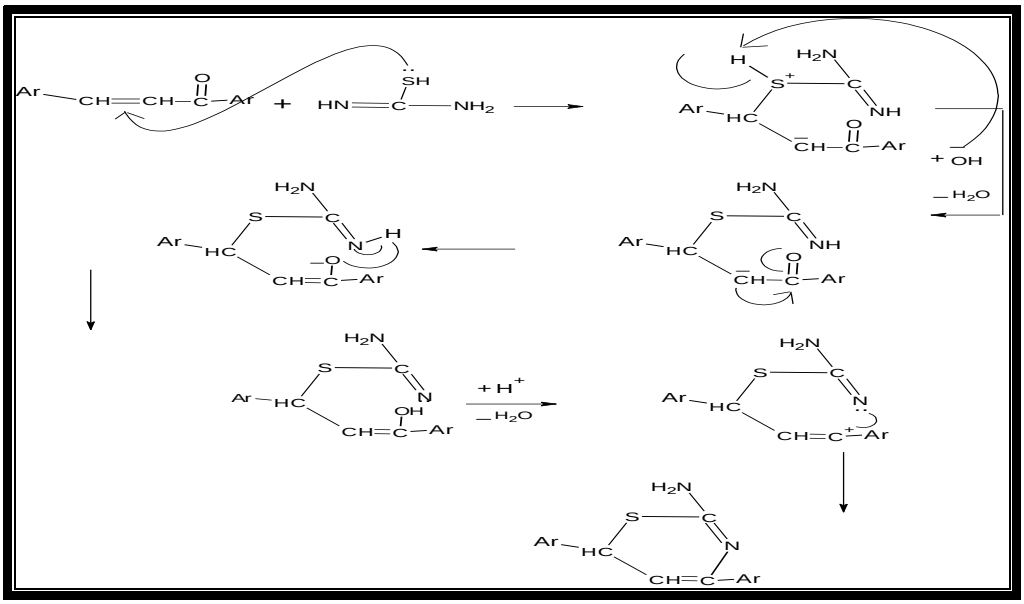


Scheme(1)preparation Comp.(A,B,A_1,B_1)



Scheme(2)preparation Comp.(A_2,A_3, A_4, B_2, B_3,B_4)

The suggestion mechanism[12] of formation for six membered ring



Scheme(3)

Table(1)physical properties from prepared compounds.

Comp.	M.f	M.Wt	R_f	Ben;met (T.L.C)	m.p C°	Colour
A	$C_{15}H_{12}NOCl$	257.5	0.9	3:2	(114-116)	Yellow
B	$C_{15}H_{12}N_2O_3$	268	0.78	3:2	(130-132)	Light yellow
A_1	$C_{22}H_{14}NOCl_3$	414.5	0.9	3:2	(120-122)	Brown
B_1	$C_{22}H_{14}N_2O_3Cl_2$	425	0.95	4:1	(106-108)	dark brown
A_2	$C_{23}H_{16}N_3OCl_3$	456.5	0.54	3:2	(175-177)	Black
B_2	$C_{23}H_{16}N_4O_3Cl_2$	467	0.75	3.5:1.5	(160-162)	dark brown
A_3	$C_{22}H_{13}N_2OCl_3$	427.5	0.7	4:1	(118-120)	Light brown
B_3	$C_{22}H_{13}N_3O_3Cl_2$	438	0.83	3:2	(149-151)	Light yellow
A_4	$C_{22}H_{14}N_3Cl_3$	426.5	0.71	4:1	(179-181)	Red
B_4	$C_{16}H_{14}N_4O_2S$	265	0.85	3:2	(188-190)	Brown

Table(2):(FT-IR)-data(Cm^{-1})of compounds(A-A_4 and B-B_4).

Comp.No	I.R(KBr) (Only Important Groups)
A	1670(C=O,ketone),1622(C=C, alkene), 1599(C=C aromatic),3232,3373(NH_2)
B	1656(C=O,ketone),1630(C=C, alkene), 1600(C=C aromatic),3225,3367(NH_2)
A_1	1670(C=O,ketone) interference with(C=N imine) ,1595(C=C, alkene), 1518(C=C aromatic)
B_1	1683(C=O,ketone) 1668(C=N imine) ,1581(C=C, alkene), 1558(C=C aromatic)
A_2	1670(C=N,oxazine) 1600(C=N imine) , 1590(C=C aromatic) , 3250, 3400(NH_2)
B_2	1647(C=N,oxazine) 1598(C=N imine) , 1523(C=C aromatic) , 3254, 3433(NH_2)
A_3	1660(C=N,oxazole) 1596(C=N imine) , 1500(C=C aromatic) , 3060(C-H) aromatic
B_3	1616(C=N,oxazole) 1595(C=N imine) , 1512(C=C aromatic) , 3059(C-H) aromatic
A_4	1650(C=N,pyrazole) 1600(C=N imine) , 1518(C=C aromatic) , 3059(C-H) aromatic, 3446(N-H, pyrazole)
B_4	1668(C=N,thiazine) , 1624(C=C aromatic) , 3234, 3446(NH_2) , 3084(C-H) aromatic

Table (3) : C.H.N –analysis of some compounds

Compound	C%		H%		N%	
	calculated	Found	calculated	Found	calculated	Found
A	69.902	69.841	4.660	4.594	5.436	5.355
A_4	61.899	61.665	3.282	3.090	9.847	9.477
B	67.164	66.448	4.477	4.501	10.447	10.277

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