Synthesis of new pyrazoline and oxazoline Derivatives From Indole

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Abstract

The objective of the present work is preparing of new pyrazoline and oxazoline derivatives by reaction of amine derivative(4-aminoacetophenone) with Indole, then complete with next step which include the reaction of the product in the first step with some benzaldehyde derivatives to form chalcones , The final step which include formation cyclization to prepared chalcones to yield pyrazoline and oxazoline derivatives. The structures of the synthesized compounds are established by Elemental Analysis and several technique (TLC, M.p , and IR spectra).

Key words: Indole, Chalcone, pyrazoline, oxazoline.

الخلاصة

تم في هذا البحث تحضير مشتقات جديدة البايرازولين والاوكسازولين وذلك عن طريق تفاعل مشتق الأمين (4-امينواسيتوفينون) مع الاندول كخطوة أولى ثم تفاعل الناتج مع مشتقات بنزلديهايد لتكوين جالكونات, الخطوة الأخيرة من البحث تضمنت غلق حلقي للجالكونات لتكوين مشتقات البايرازولين والاوكسازولين.المركبات المحضرة تم تشخيصها بتقنيات عديدة وهي الأشعة تحت الحمراء IR , تحليل العناصر CHN, درجة الانصهار M.p, كروموتوغرافيا الترشيح بالورقة TLC .

Introduction

A hetero cyclic compound is one that contains a ring made up of more that one kind of atom[1]. Hetero cyclic compounds intermediates are

being used more and more in synthesis as protecting groups, readily generated and, when their job is done, readily removed .In the biological word, as we have seen ,hetero cyclic compounds are every where carbohydrates are hetero cyclic[2,3].

Indole[4] (1) is the commonly used name for the benzopyrrole ring system, consisting of a benzene ring fused to the 2,3-positions of a pyrrole ring[5,6] .one of the most characteristic reactions of indoles is electrophilic substitution at C-3 in the five-membered ring, which is facilitated by electron-release from the heteroatom. This preference can be rationalized by consideration of the wheland intermidate(2), in which the enamine system in the five-membered ring does not disturb the aromaticity of the benzene ring. The positive charge in the intermidate is delocalized and the aromaticity of sex-membered ring can therefore be retained.In contrast, any attack at C-2 cannot derive assistance from the nitrogen without disrupting the aromaticity of the benzene ring. However, electrophilic substitution can occur at C-2, if for instance the C-3 is occupied by a substituent[7] .

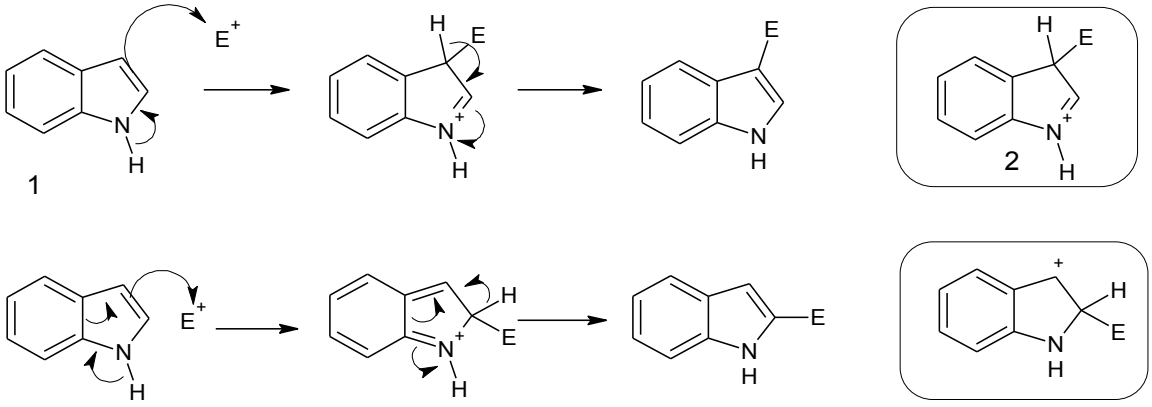


Fig.1: Typical Reactivity of Indoles

Pharmacological Importance of Indole[8]:

Indole possess the following activities that is shown in fig.2

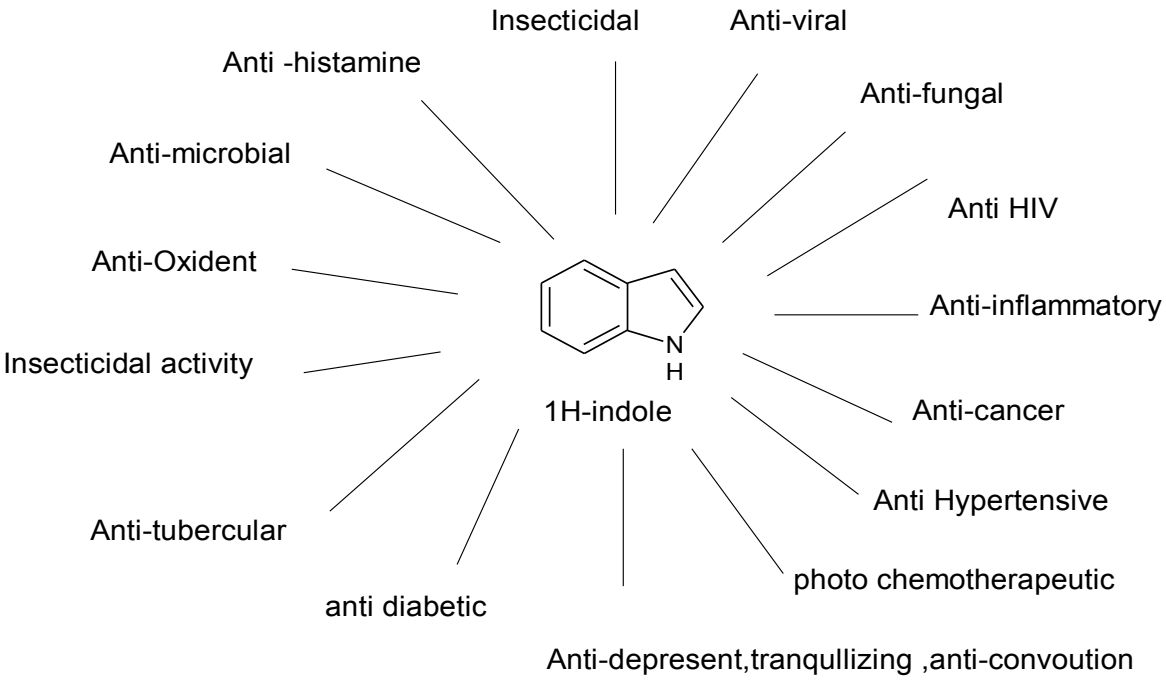


Fig.2: Pharmacological Importance of Indole

Table1: Selected Indole Derivatives and Their Biological Indication[9]

Sequencing	Name	Domain	Reference
1	Indole-3-carbinol	anticancer agent	10
2	Indomethacin	anti-inflammatory agent	11
3	Sumatriptan	treatment of migraine headaches	12
4	Pindolol	beta blocker	13
5	Indole-3-acetic acid	plant growth hormone	14
6	Vincristine	chemotherapeutic agent	15
7	Ellipticine	antitumor agent	16
8	Tryptophan	amino acid	17
9	Serotonin	neuro-transmitter	18
10	Mitomycins	antitumor agent	19

We reported here the synthesis new derivatives of Indole containing azo and chalcone groups .Azo compounds constitute one of the largest classes of industrially synthesized organic compounds .The chalcones are

product of condensation of simple or substituted aromatic with simple or substituted acetophenone in the presence of alkali. Chalcone constitute an impartment group of natural products and some of them possess wide range of biological activities such as antimicrobial[20], anticancer[21], anti tubercular[22] and antiviral.

Experimental

All chemicals used were supplied from Merck , BDH and Fluka chemical company.

Instruments

The following instruments were used to characterize the prepared organic ompounds.

1. Melting point measurement:
   Electro thermal melting point apparatus T1A/UK/Serial No. 10611460 in College of Education / Kufa University was used to measure the melting point of prepared compounds.
2. Infrared spectra:
   Infrared spectra were recorded as KBr discs using Fourier Transform Infrared Spectrophotometer FTIR-8400s SHIMADZU, Kufa University (Iraq).
3. TLC performance

TLC was used for monitoring of reaction progress by preparing of 1 % Indole solution in ethanol and using of Benzene-Methanol (4/1 v/v) as developer, visualization by Iodine vapor.

4. The elemental analysis were recorded using E.A.G.E.R.-100,Carlo Erba, Italy.

Synthesis of Azo Compound (H) .

4- Amino acetophenone (1.35 gm,0.01mole) was dissolved in (3ml) of concentration hydrochloric acid and (10) of distilled water .

The mixture was cooled at ($0C^{O}$) in ice-water bath .Then a solution of sodium nitrite (0.7gm,0.01mole) was dissolved in (10ml) of distilled water .This solution was added a drop wise to the mixture with stirring .In the other beaker indole (1.17gm,0.01mole) was dissolved in (30ml) of ethanol and (5ml) of (10%) sodium hydroxide and place this beaker in ice-water bath to cool ($0C^{O}$).The cold diazonium chloride was added to the coupling agent in small portions and stirred after each addition ,after the addition was completed (pH=9),The reaction mixture was stirred at (0c) for (24hrs).The brown product was precipitated and filtered, washed with distilled water and recrystallized from ethanol ,yield (78%), MP=187-188C^{O} and Rf =0.68 ,used two solvent (benzene :methanol , 4:1).

Synthesis of Chalcones (H1-H2) [23]

General procedure: Azo indole (0.01moles) was dissolved in (20ml) of ethanol ,Then equimolar amount (0.01moles) of benzaldehyde derivatives (4-N,N-dimethyl, 4-N,N-di ethyl, 3-methoxy-4- hydroxyl and 2,4-dichloro) were added , and (5ml) of (10 %) sodium hydroxide was added. The reaction mixture was completed at room temperature for (4-6hrs) . Filtered and recrystallization from ethanol.

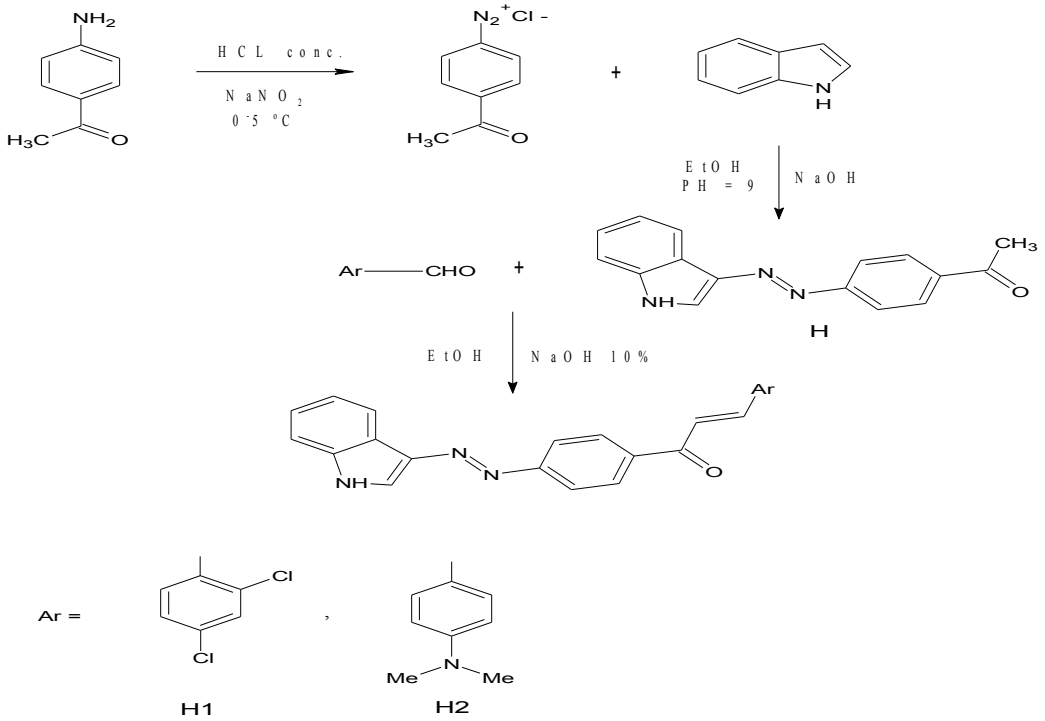
Synthesis Of Pyrazoline and Oxazoline Derivatives (H3-H6)[24,25]

0.01 moles of chalcones (H1-H2) were dissolved in absolute ethanol (50 mL). 0.01moles of (phenyl hydrazine , hydrazine and hydroxylamine) were added to it. The resulting solution was refluxed for 5-6 hrs. The solution was then cooled and the solid obtained was filtered and recrystallized from ethanol.

The physical and spectral data of the compounds are given in Table 2 and Table 3.

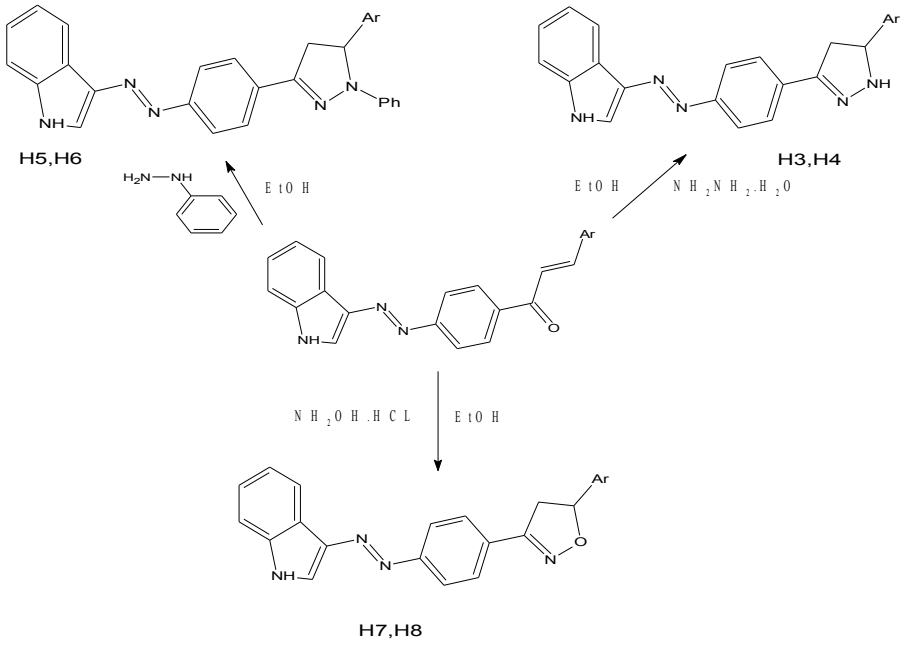
Result and Discussion

4-Amino acetophenone was converted to indole azo by reaction 4-amino acetophenone with concentration hydrochloric acid and sodium nitrite .Diazonium salt was directly introduced in a coupling reaction with indole to produce indole derivatives . Chalcones derivative of indole were synthesized by reaction the indole azo with benzaldehyde derivatives and 10% sodium hydroxide in ethanol. (H1-H2) ,See scheme1



Scheme 1: Synthesis Chalcones Derivative of Indole

Another step ,synthesis new heterocyclic derivatives (pyrazole and isoxazole derivatives) from reaction the chalcones of indole with hydrazine derivatives and hydroxyl amine hydrochloride . see scheme 2



Scheme 2: Synthesis Heterocyclic Compounds

All theses compound were characterized by melting points , thin layer chromotoghraphy and some by Elemental Analysis and FTIR spectra , Table 2.

Table 2 :The physical properties of prepared Indole Derivatives

							Calculated(found)		
	M. F	M.W	M.P	Colour	R_f	Yield%	C%	H%	N%
H	C16H13 N3O	263	187-188	Orange	0.68	78	72.99 73.17	4.98 5.14	15.96 16.23
H1	C23H15N3O Cl2	420	218-219	Red	0.85	81.5	65.73 65.86	3.60 3.80	10.00 10.20
H2	C25H22N4O	394	136-138	Red	0.87	77.3	76.38 76.14	5.67 5.58	14.27 14.21
H3	C23H17Cl2 N5	434	>300	Red	0.66	79	63.60 63.99	3.95 4.14	16.12 16.19
H4	C25H24N6	408	196-198	Brown	0.81	65.7			
H5	C29H21Cl2 N5	510	171-173	Red	0.63	72			
H6	C31H28N6	484	187 decomp.	Brown	0.75	61.8			
H7	C23H16Cl2 N4O	435	223-225	Dark Brown	0.73	80	63.46 63.53	3.70 3.90	12.87 12.99
H8	C25H23N5O	409	195 decomp.	Red	0.77	73			

The FTIR spectra

All thesis derivatives were characterized by FTIR spectrum . Figure (1) showed disappearance of the absorption broad at (3419 cm^{-1}) were due to the stretching vibration of (NH2) group of 4-Aminoacetophenone ,and appearance of the weak absorption band at (2987 cm^{-1}) was due to the CH aliphatic group . The new absorption band at (1395 cm^{-1}) was due to the

Table 3: IR Data of Prepared Indole Derivatives (cm^{-1})

	Ar-CH	N-H	C=O	N=N	C=C	C=N	C-Cl
Indole	3050	3400	------	-----	1620	----	----
H	3055	3221	1665	1395[26]	1597	----	----
H1	3059	3265	1653	1390	1600	----	746
H2	3053	3221	1664	1395	1597	----	----
H3	3040	3280 3402.54	----	1410	1604	1520	740
H4	3060	3277.17 3446.91	----	1405	1597.11	1550	----
H5	3061	3396	----	1417	1597	1558	748
H6	3051	3265	----	1411	1597	1523	
H7	3063	3265.59	----	1400	1593.25	1525.74	748.41
H8	3050	3200	----	1398.79	1604	1525	----

stretching band of (N=N)group. FTIR spectrum also showed the appearance of absorption band at (3221cm^{-1}) for (N-H) of pyrole ring of indole .

Figures (2,3) showed the absorption band at (3130cm^{-1}) due to (C=C-H) group and weak absorption band at (2920cm^{-1})due to the stretching vibration of (CH3) groups.FTIR spectrum also showed the appearance of absorption bands at (3265-3221 cm^{-1}) for (NH) group of indole cyclic and showed the appearance of absorption bands at (1653-1664 cm^{-1}) for (C=O) group of carbonyl .

Figure(4,5) showed the broad absorption bands at (3277-3280cm^{-1})due to the stretching vibration of (NH) group of indole cyclic, appearance of absorption bands at (3446-3400 cm^{-1}) for (NH) group of new pyrazoline ring, disappearance of the absorption sharp of (C=0) at (1653-1664 cm^{-1}) and appearance of moderate band of (C=N) at(1520-1550cm^{-1}).

Figure (6,7,8,9) showed the broad absorption bands at (3200-3396cm^{-1}) due to the stretching vibration of (NH) group of indole cyclic, disappearance the absorption sharp of (C=0) at (1653-1664 cm^{-1}) and appearance of moderate band of (C=N) at (1523-1558cm^{-1}).

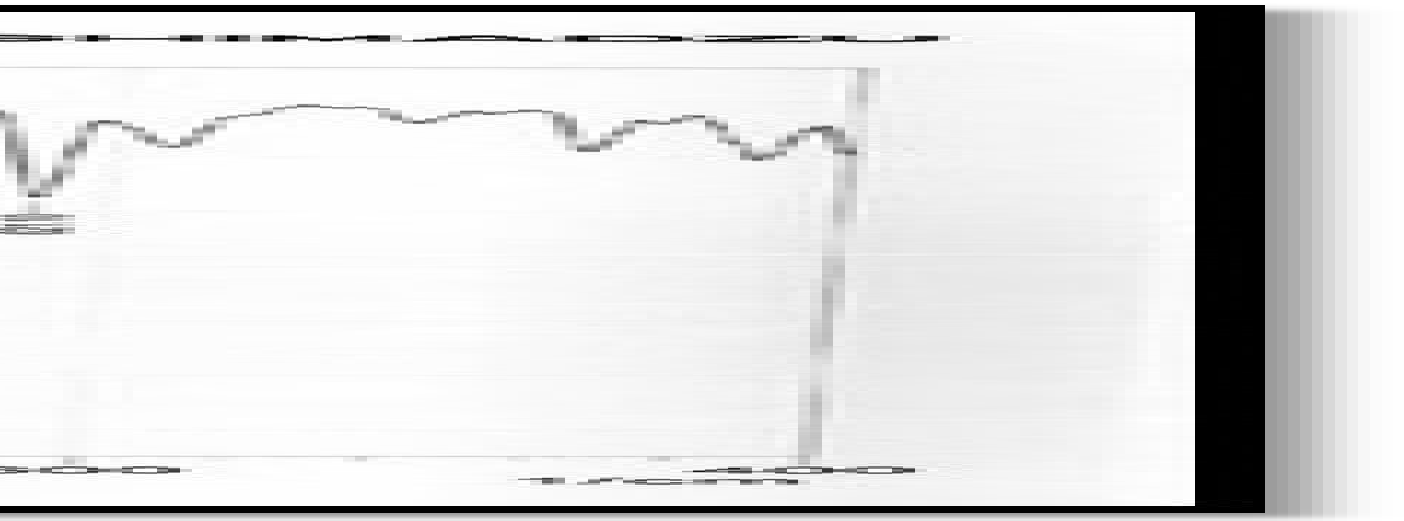


Figure 1. FT.IR spectrum of compound H

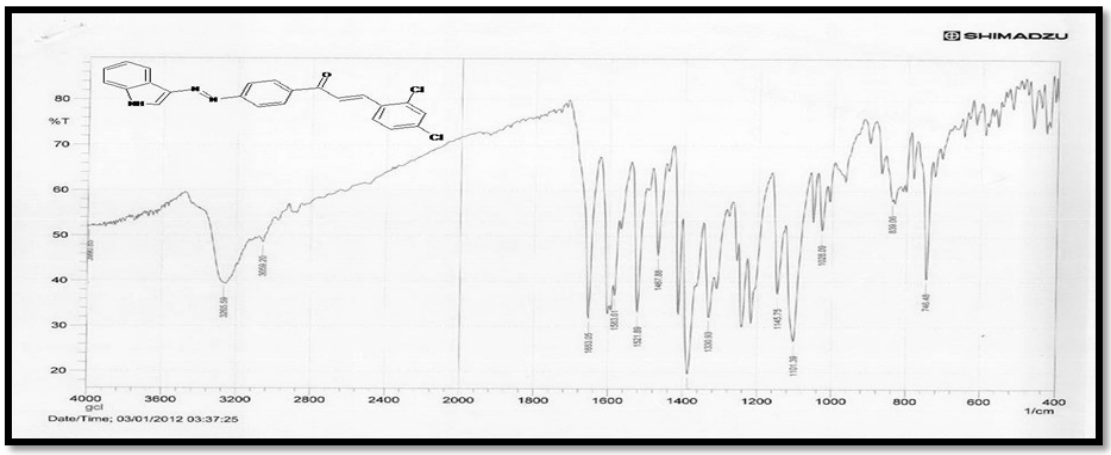


Figure 2. FT.IR spectrum of compound H1

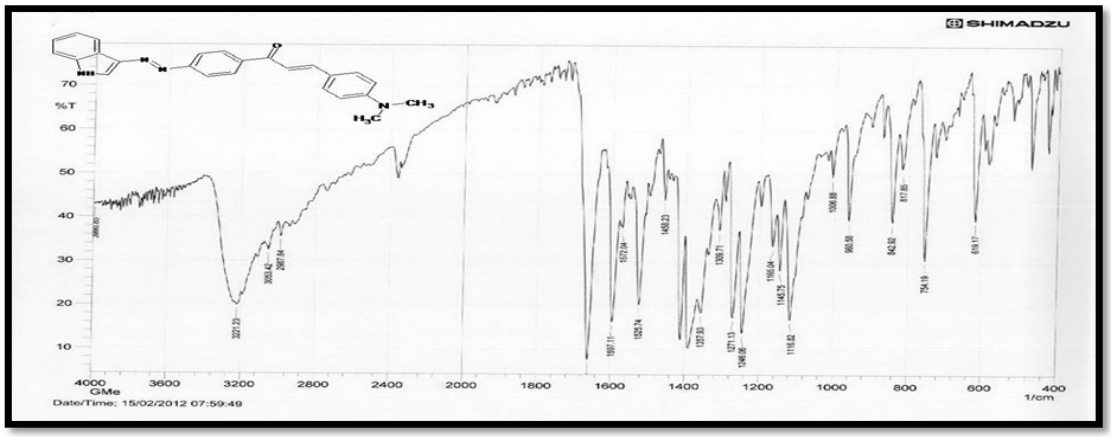


Figure 3. FT.IR spectrum of compound H2

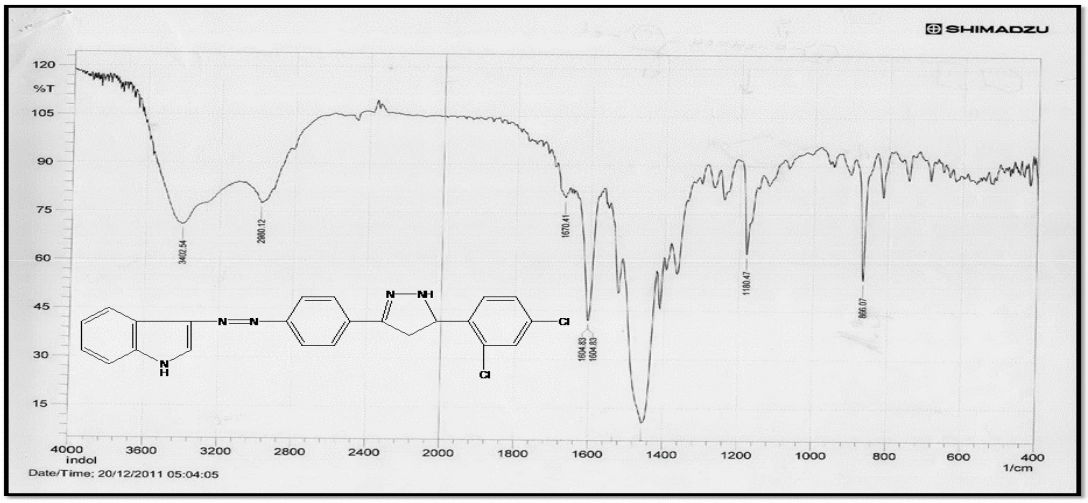


Figure 4. FT.IR spectrum of compound H3

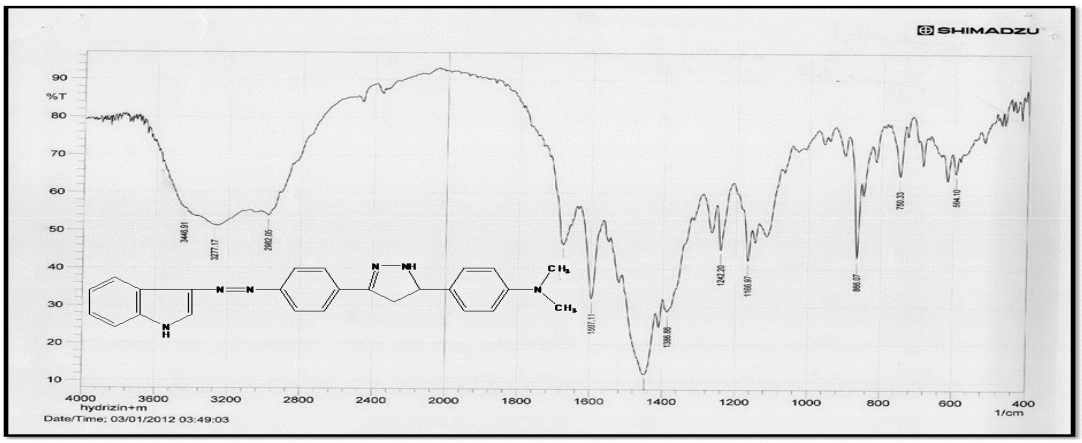


Figure 5. FT.IR spectrum of compound H4

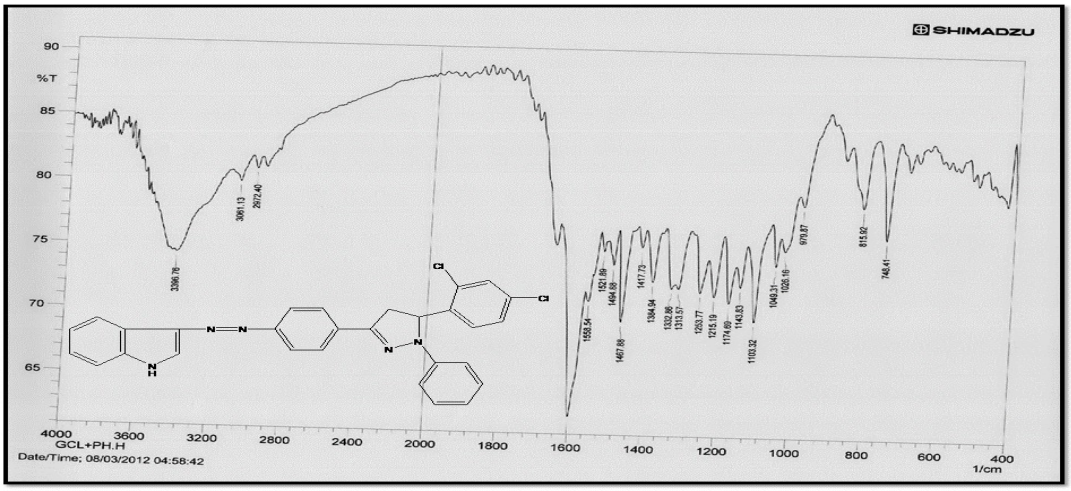


Figure 6. FT.IR spectrum of compound H5

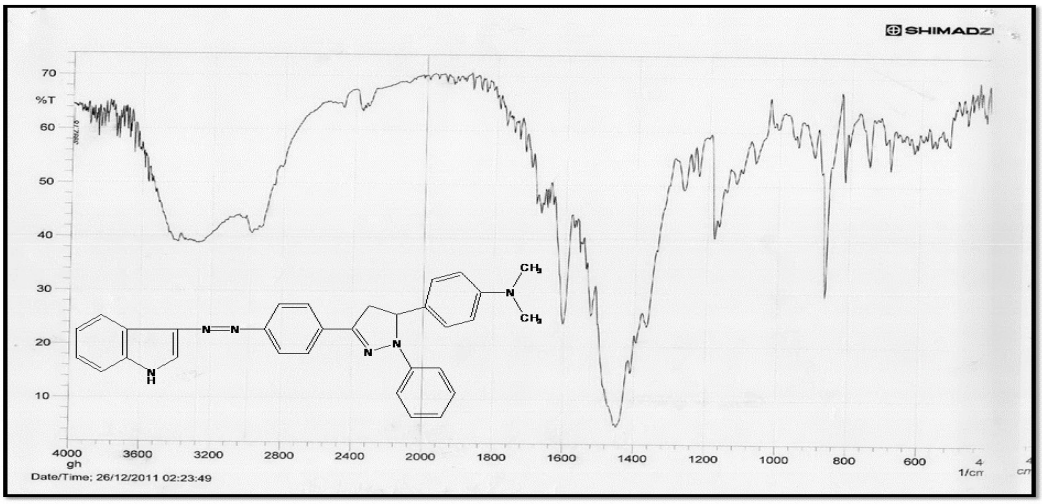


Figure 7. FT.IR spectrum of compound H6

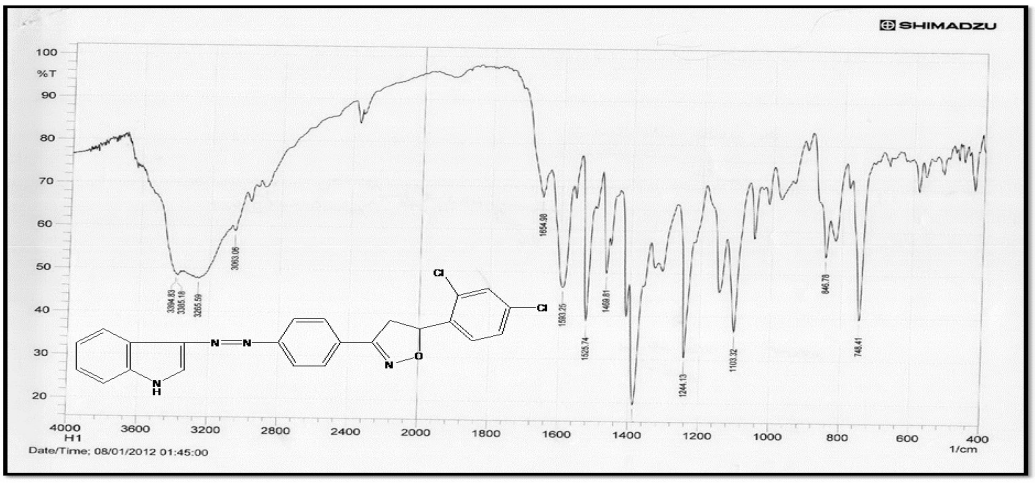


Figure 8. FT.IR spectrum of compound H7

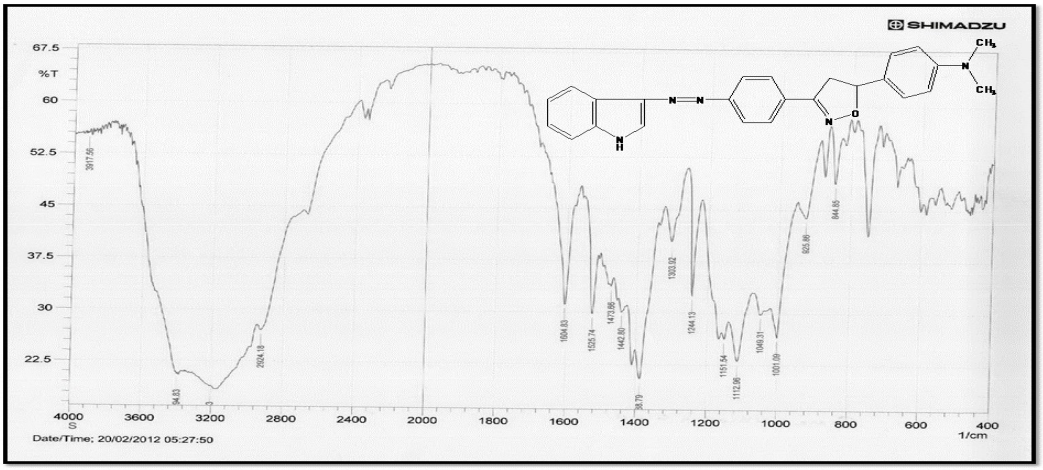


Figure 9. FT.IR spectrum of compound H8

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