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Synthesis of some New 4,6-dichloro-2-aminobenzothiazole compensators with expected biological

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Abstract

was prepared from the reaction of compensated aniline with potassium thiocyanate in the presence of bromine. Unsaturated Alpha-Beta (E2-6) compounds were obtained from the reaction of aromatizing aldehydes with para –hydroxyacetophenone in a basal medium. The interaction of alpha-beta - unsaturated compounds with 4,6-dichloro-2-aminobenzothiazole gives compounds (E7-11) 4-(1-(4,6-dichlorobenzothiazole-2-El amino) - 3-aryl) phenol. The bioavailability of compounds prepared on two types of Gram-negative and Gram-positive bacteria was tested using a lower inhibitory concentration and compared with standard antibiotics. The prepared compositions were validated using physical and spectral methods using FT-IR,H1-NMR,C13NMR technology

Introduction

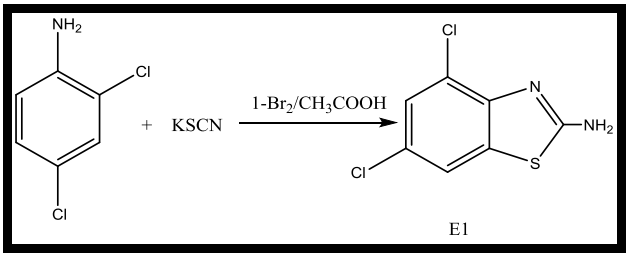
In the last few years, researchers have taken an interest in benzothiazole derivatives, which have found many chemical applications as well as wide uses in the biological field[(1)] , such as their use as an antagonist (anti-inflammatory , anti-cancer , antiviral[(2)], anti-Parkinson's disease, anti-chamanea disease and antimicrobial[(3)], as well as galcones have shown therapeutic benefit as anti-inflammatory, anti-cancer, antiviral and antihypertensive[(4)]. chalcones derivatives have displayedwiderangeof biological ,,andpharma ,activity eschars ecological ,antimmunmodulatory, antiulcerative , antianolgesic,antioxidant[(5]anti-bacterial,andantifungal[(6)]anticyltoxicantitumor[(7)],antimeal[(8)]antimalarlal[(9)]antispasmodic[(10)]antiTuberculer[(11)]anticonvulsant[(12)] antibioic[(13)] anti-Epileptics[(14)] enzyme inhibito[(15)]asaresult Varius procedure have been worked out for their synthesis. Numerous derivatives have been published[(16)] · Schiff bases are formed when any primary amine reacts with an aldehyde or ketone under specific conditions. Studies show that Schiff base ligands together with their complexes have many biological applications ranging from antimicrobial[(17)] , anti-tumor and antifungal[(18)]anti-inflammatory[(19)]antimalarial[(20)] antiproliferative [(-21)]

Materials &methods:

Chemicals and instruments

Melting points are uncorrected and were recorded in an open capillary tube on Stuart melting point apparatus. Infrared spectra have been recorded on a ShimadzoFTIR-8100 spectrophotometer using KBr discs–and H^1-NMR Spectra have been measured on a MHZ spectrometer using (DMSO). All solvents and chemical reagents have been purchased from Aldrich, alfa aesar ,sigma.

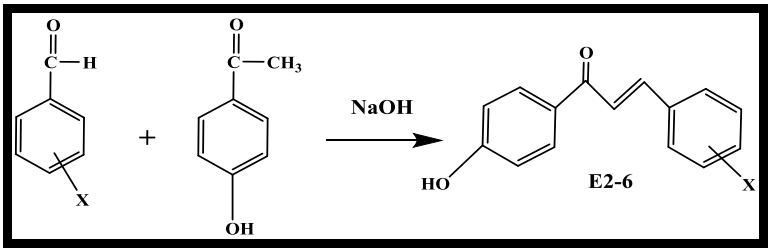
Preparation of 2 - amino - 4,6 - dichlorobenzothiazole (E1)[22]



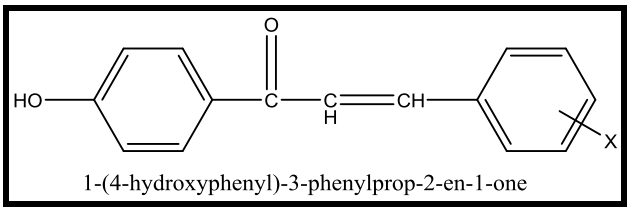
E1

Dissolve (0.03 Mol, 5 g) of 2,4 – dichloroaniline and (0.16 Mol, 11.6 g) of potassium thiocyanate in 50 ml of snow acetic acid and add (0.03 Mol, 4.8 g) of bromine added to 25 ml of snow acetic acid stirring at a temperature below 5 M for 30 minutes after completing the addition of bromine stir for 10 hours at Laboratory temperature, ml of warm water, separated the precipitate and neglected and equalized the filtrate with a solution of 10% sodium hydroxide, separated the precipitate and dried and recrystallized with ethanol to be a white precipitate (4.6 g 70%) melting degree 269 – 270 C.

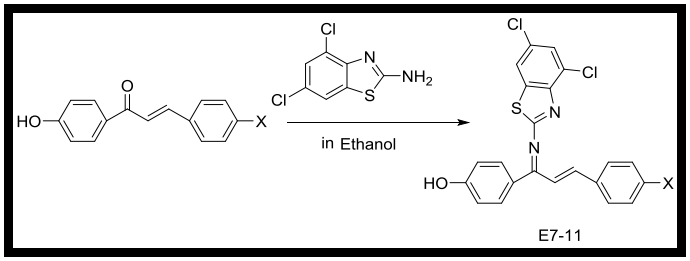
Synthesis of chalcones (E_2-6) [23]



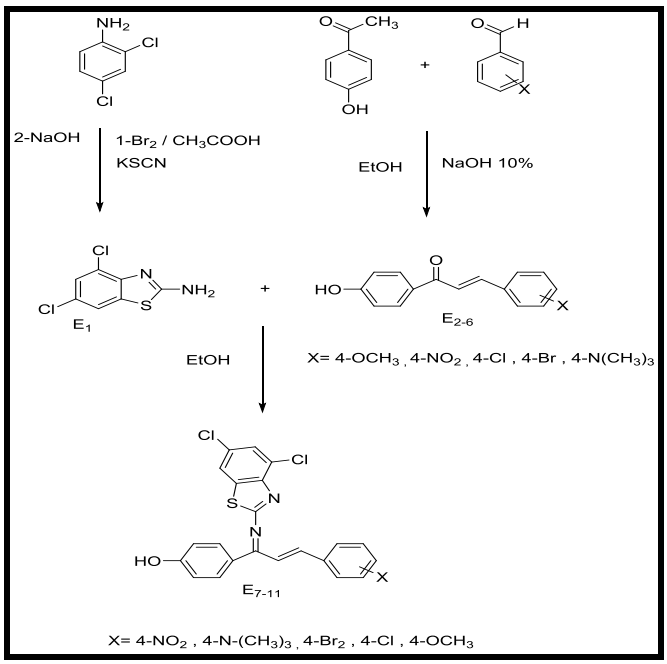
Amixture of 4-hydroxe acetophenone (0.01mole) and aromatic benzaldehyde (0.01mole) have been added to a solution of (10%) sodium hydroxide (5ml), and (3ml) of ethanol. The mixture was stirred for (2-3) hr at (20-40) C ° and kept in a refrigerator for (12) hr. Then it was diluted with ice-cold distilled water (30ml), filtered washed with cold water, dried and recrystallized by ethanol. The physical properties are shown in table (1)



Preparation of 4-1-(4.6 dichlorobenzothiazole-2-El amino)-3 - phenylalyl) phenol:[24]



Dissolve (0.001 Mol, 0.219 g) of 2-amino benzothiazole in 10 ml of ethanol, then add to it (0.001 Mol, 0.269 g) of one of the galcon compensators (E2-6) dissolved in 10 ml of ethanol, ascend the mixture for 6 hours, then filter the solution and dry. The physical properties are shown in table (2)



Scheme (1): Route of prepared compounds [E_1-E_{11}]

Evaluation of biological activity[25]

The biological activity has been estimated by using the propagation method whereas the biological activity has been estimated by the Kirby Bauer movement, where 0.1 ml of bacterial suspension has spread to the ager Muller Hinton dishes and left for 5 minutes to absorb the suspension . After that, holes were prepared for each dish using a Cork Porer and a diameter of (5) mm per hole (0. 1) ml of the prepared solutions of the fourth hole using(DMSO) as acontrol sample and incubated the dishes for(24) hours at 37℃ . The inhibition zone diameters around each holes has been measured in milmeter, depending on the method of Prescott .

3. Results and Discussion

3.1. Characterization of 2 - amino - 4,6 - dichlorobenzothiazole (E1)[26]

Aniline substituted potassium thiocyanate and bromine were stirring at room temp. To give the expected 2 - amino - 4,6 - dichlorobenzothiazole The structure of the synthesized compounds were confirmed by their melting point and IR spectroscopy. The characteristic absorption bands (KBr cm^{-1}) are shown in Table (1) The -2 - amino - 4,6 - dichlorobenzothiazole. The IR spectrum of this compound -4,6-dichloro 2-amino benzothiazoles is showed a band at 3456 (N-H str. Of 1º amine) cm^{-1} a band 3074 (arom. –CH str) band at 1461 (C=C str in aromatic hydrocarbons),band at 1269 (C-N str. Of amino grp),aband, 850 (C-Cl str), 1635(C=N str. the IR DATA showed in the figure (1)

The H^1-NMR Spectrum ($CDCl_3$) of compounds (E_1) Show signal at (2.50ppm) for (DMSO), signal at (8.2-7.5 ppm) for (Ar,H), signal at (4.4 ppm) for (NH_2), Thespectrum ($CDCl_3$) of compounds (E_1) Showed signal at (2.53 ppm) for (2H) pyrazoline ring, Signal at (9.68 ppm) for (H_2,NH_2), Signal at (7.33 to 7.54 ppm) for phenol, signal at (6.59to7.64 ppm) for (H=CH) [30], the H^1-NMR showed in the figure (2) .The 13C NMR spectra of all compound (E1) were characterized characterized (cf. Exper. Part). The resonances in the range (166.4–ppm) due to carbon thiazoles rings (C-A), showed signal (δ= 124.7ppm) due to (carbon -B), as well as signal δ=(125.5) due to (carbon –C), showed signal (δ= 120.1 ppm) due to (carbon -D) , as well as signal δ=(132.7) due to (carbon –E), and signal at (δ=121.8 ppm) due to (carbon -F) as well as singlet signal at δ=39.49-40.49 ppm due to $DMSOd^6$,[13] the 13C NMR showed in the figure (3).

3.2. Characterization of chalcones [27]

The synthesis of chalcones derivatives were performed as Shown in scheme (1). The reaction of acetophenon with aromatic aldehydes yielded the compounds (E_2-$_6$) , the IR spectra of compounds (E_2-$_6$) showed characteristic (C=O) stretching at (1649cm^{-1}) and (C=C) stretching frequencies at (1597cm^{-1}), band at (1510cm^{-1}) for**(C=-=C)** group band at (3030-3074 cm^{-1}) for (Ar-H) group figure(4). ^{1}H NMR Spectrum of compound (E_6), (Figure 5),Showed the following signals : a singlet signal at(

δ 3.3-4.2 ppm) due to a proton of (6H,N-$(CH_3)_3$) group , sharp signal at δ 2.66 ppm due to a proton of phenyl, signal at (7 to 8. 5 ppm) for (HC=CH)) figure (2).

3.3. Characterization of Schiff Bases (E6-E11) [28]:

Schiff Bases derivatives have synthesized from the reaction of compound (E10) with deferentes aromatic amines. The infrared spectrum showed beams at the frequency (1599-1643 cm-1) belonging to the stretching of the pinches (C = N)), beams stretching the pinches (C=C) at the frequency (1487-1543 cm-1), and beams at the frequency (3097 cm-1) returning To the aromatic pinch stretch (Ar - H), and a beam at frequency (1033 cm-1) belonging to the stretch stretch of the pinch (C - S - C), and the bundle stretching of the pinus (C-Cl) at frequency (813 cm-1), and showed the resonance spectrum Nuclear magnetic H1-NMR of compound E47, a signal at frequency (δ = 3.4 ppm) of a proton (H, CH = C), a signal at frequency (= 4.4ppm) of a proton (H, CH-phenyl), and a signal at range (δ = 6.7-8 ppm) belonging to (H, phenyl) protons, and a signal at frequency (= 9.9 ppm) belonged to (H-OH) proton, and the C13-NMR spectrum of compound E47 showed a signal at frequency (= 115ppm) returning To C (CH = CH), a signal within the range (δ = 123-135 ppm) refers to carbon atoms in benzene rings, a sign at frequency (= 141ppm) returns to C in (C = N), and a sign at frequency (= 163ppm) refers to C (C-OH), and a signal at frequency (δ = 187ppm) refers to C2 in benzothiazole.

3.4.-Evaluation of Biological activity :

The antimicrobial activities of the synthesized compounds were determined in vitro against several pathogenic representative microorganism (*Escherichia coli* and *Proteus spp)* , using Agar well-diffusion method[40]. Ciprofloxacin were used as standard drugs for studying the potential activities of these compounds, All the compounds were tested at different concentration level (0.01, 0.001, 0.0001 mg / ml), DMSO was used as solvent and as control. The inhibition zone diameter in mm (IZD) was used as a criterion for the antimicrobial activity. The lowest concentration required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (MIC, µg/mL), was determined for all the compounds and compared with the control. The investigation of antibacterial screening data revealed that diazine derivatives (E_1-E_{11}). Compounds (E_1-E_2-E_3-E_4-E_5-E_6, E_7-E_8-E_9-E_{10}-E_{11}) exhibited good antibacterial activity towards the both gram negative bacteria (*Escherichia coli*). Compounds (E_1-E_2-E_3-E_4-E_5-E_6, E_7-E_8-E_9-E_{10}-E_{11}) have also exhibited good antibacterial activity towards gram positive bacteria(*Proteus spp)* , showed high activity against all the microorganisms employed in contrast with the ciprofloxacin derivatives. The maximum activity (MIC = 12.5 µg/mL) was indicated for compounds[41] . he results are summarized in Table .

The table (1) the physical properties of compounds (E_{2-6})

Compd. No.	X	m.p.(°C)	Yield (%)	Colour	Molecular Formula
E2	4-OCH_3	69-70	80	Yellow	$C_{16}H_{14}O_3$
E3	4-NO_2	128-130	50	Orange	$C_{15}H_{11}NO_4$
E4	4-Cl	30-31	40	White	$C_{15}H_{11}O_2Cl$
E5	4-Br	61-63	35	Yellow	$C_{15}H_{11}O_2Br$
E6	4-$N(CH_3)_2$	139-140	70	Yellow	$C_{17}H_{17}NO_2$

Table (2) The physical properties of compounds (E_{7-11})

Compd. No.	X	m.p.(°C)	Yield (%)	Color	Molecular Formula
E7	4-$N(CH_3)_2$	115-118	74	Yellow	$C_{22}H_{13}N_3O_3SCl_2$
E8	4-NO_2	217-220	80	Orange	$C_{24}H_{19}N_3OSCl_2$
E9	4-Br	232-235	50	White	$C_{22}H_{13}N_2OSBrCl_2$
E10	4-Cl	196-198	82	Yellow	$C_{22}H_{13}N_2OSCl_3$
E11	4-OCH_3	83-85	62	White	$C_{23}H_{16}N_2O_2SCl_2$

Table (3) IR –spectral data of Compounds (E_1-E_6)

Comp .No	X	FT.IR **cm^{-1} (KBr)**				
		-C=O	**υ (Ar-H)**	**υ (C=C) olefin**	**υ(C⎓C)**	**Others** cm^{-1}
E2	4-OCH_3	1670	3002	1602	1537	2820 for C-H aliphatic
E3	4-NO_2	1649	3030	1597	1510	3365 for OH
E4	4-Cl	1662	3010	1594	1537	844 – 790 for Cl
E5	4-Br	1663	2987	1604	1522	773 for C - Br
E6	4-$N(CH_3)_2$	1687	2912	1599	1543	2837 for C-H aliphatic

Table (4) IR –spectral data of Compounds (E_7-E_{11})

Comp .No	X	FT.IR **cm^{-1} (KBr)**				
		C-S-C	**υ (Ar-H)**	**υ (C=N)**	**υ(C⎓C)**	**Others** cm^{-1}
E7	4-NO_2	1010	3074	1610	1514	1338sy for –NO_2
E8	4-$N(CH_3)_2$	1097	3076	1614	1510	2920 for C-H aliphatic
E9	4-Br	1107	3072	1635	1431	779 for C-Br
E10	4-Cl	1033	3097	1634	1487	813 for C-Cl
E11	4-OCH_3	1020	3074	1648	1510	2922 for C-H aliphatic

Table No. (5): antibacterial activity of the synthesized compounds (E_{1-11})

Comp .No	antibacterial activity (zone of inhibition in mm)		
	Conc. mg/m	*E. coil*	*Proteus spp*
E_1	0.01	10	15
	0.001	15	15
	0.0001	15	10
E_3	0.01	15	10
	0.001	25	30
	0.0001	30	30
E_5	0.01	15	10
	0.001	30	10
	0.0001	20	10
E_7	0.01	20	20
	0.001	15	30
	0.0001	15	30
E_8	0.01	10	25
	0.001	20	10
	0.0001	20	10
E_9	0.01	27	15
	0.001	20	17
	0.0001	25	28
E_{11}	0.01	15	20
	0.001	20	10
	0.0001	25	10
Ciprofloxacin	**MIC**	12.5	12.5

Slight activity 15-18 mm, moderate activity 18-20 mm and high activity 21-25 mm; MIC: minimum inhibition concentration (μ g / mL).

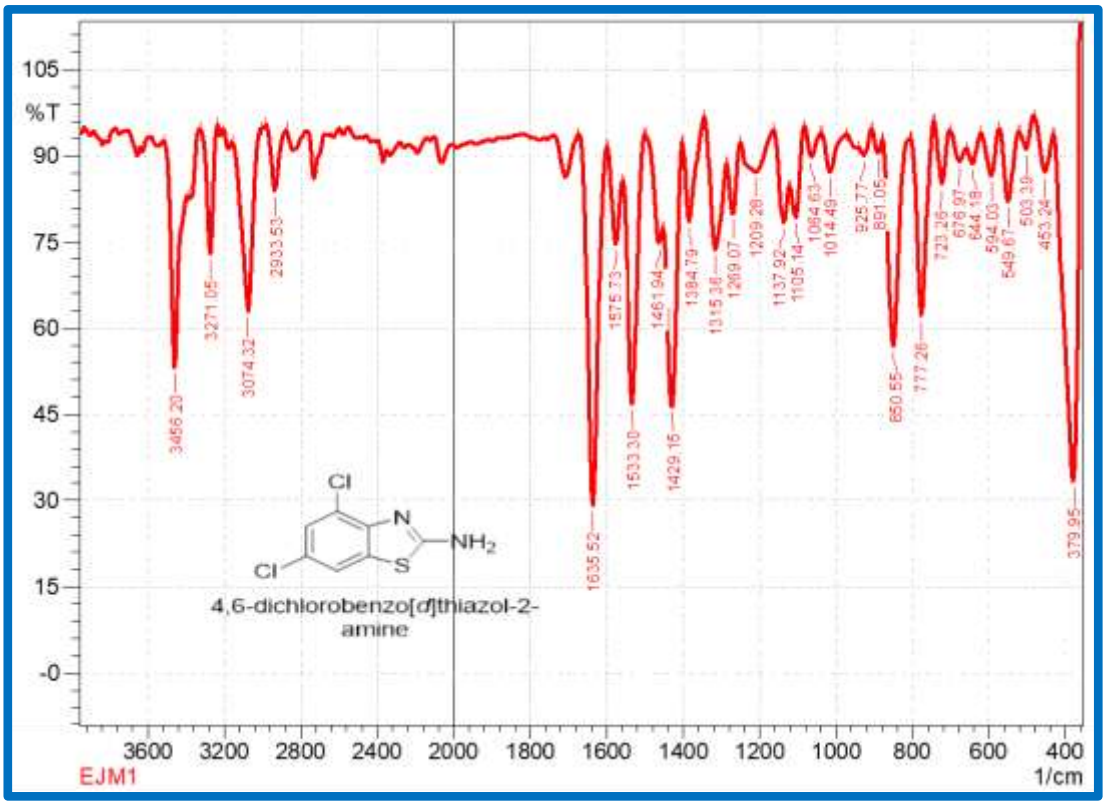


Figure (1) F-TIR spectrum of E_1

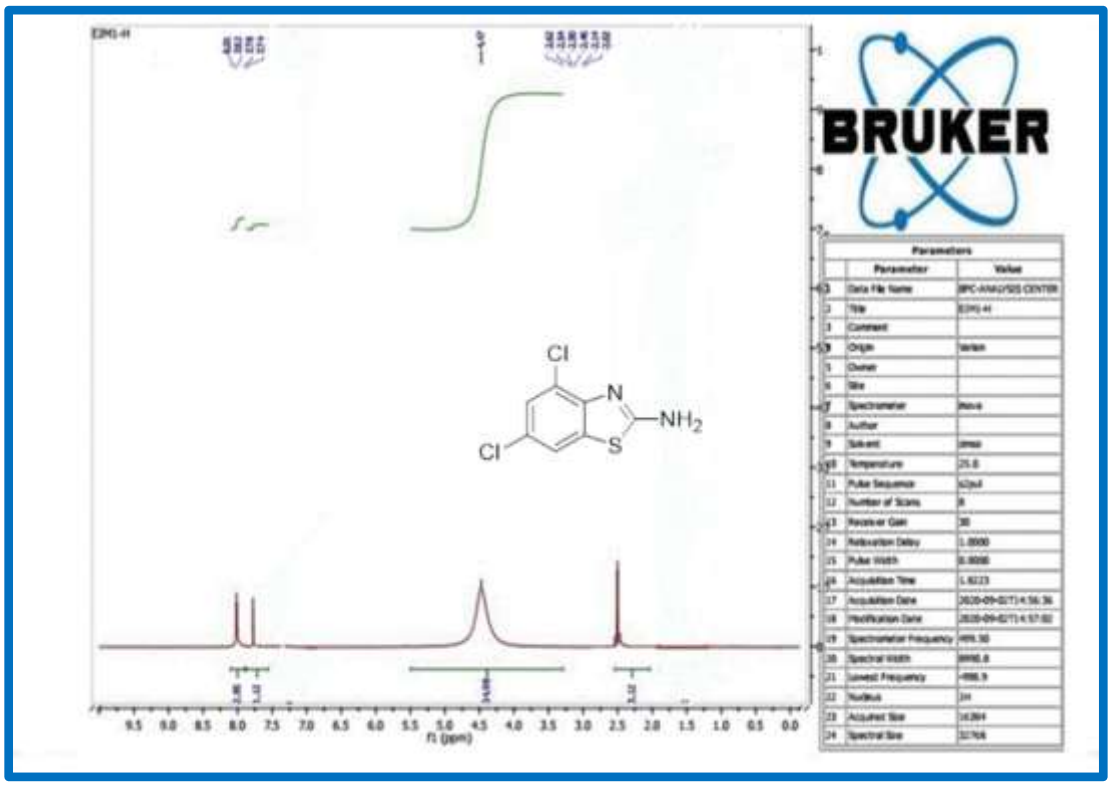


Figure (2) H^1 NMR spectrum of E_1

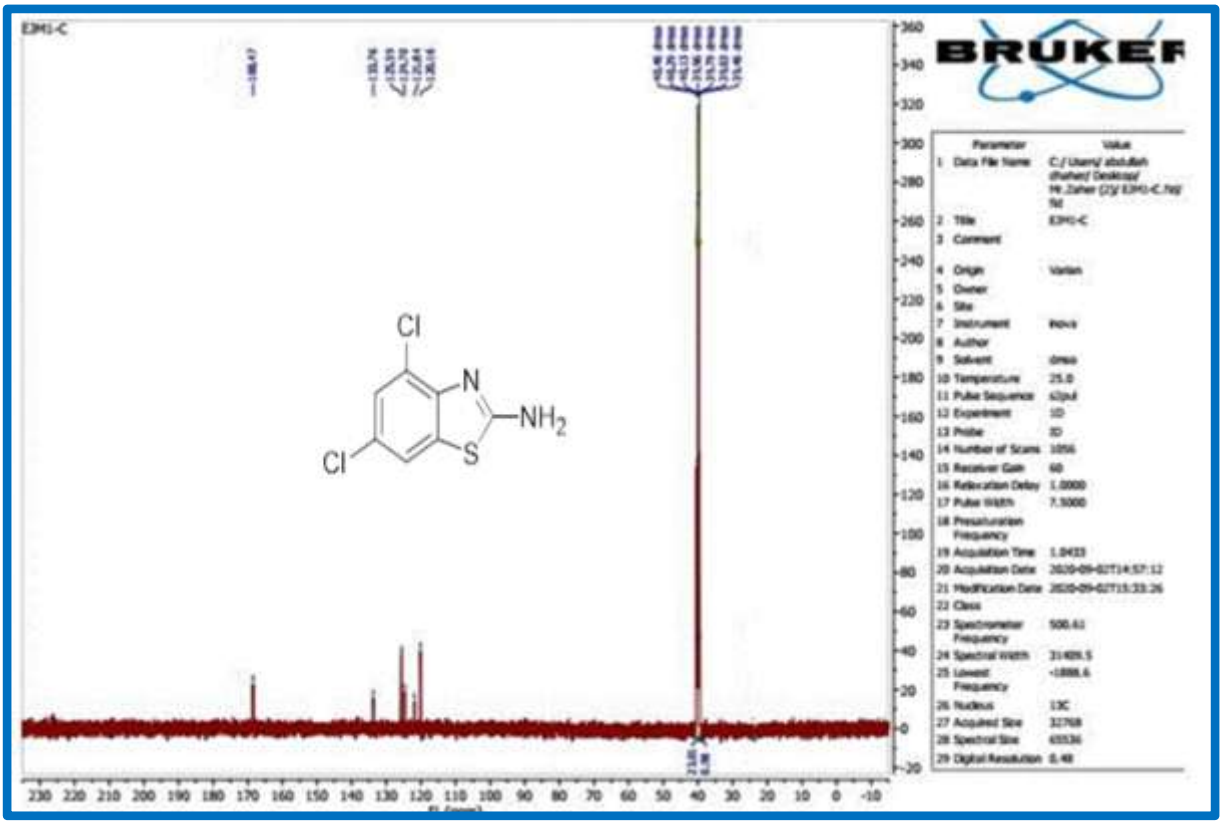


Figure (3) C^{13} NMR spectrum of E_1

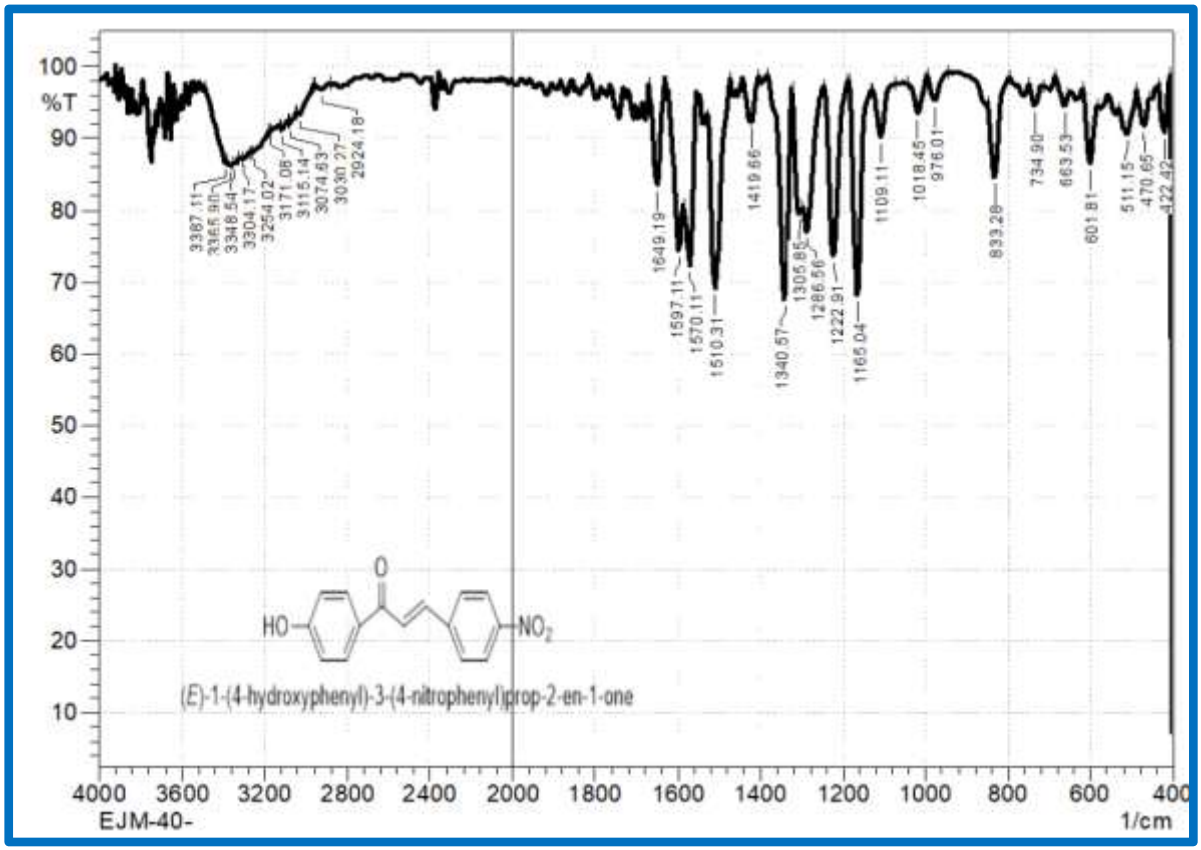


Figure (4) F-TIR spectrum of E_3

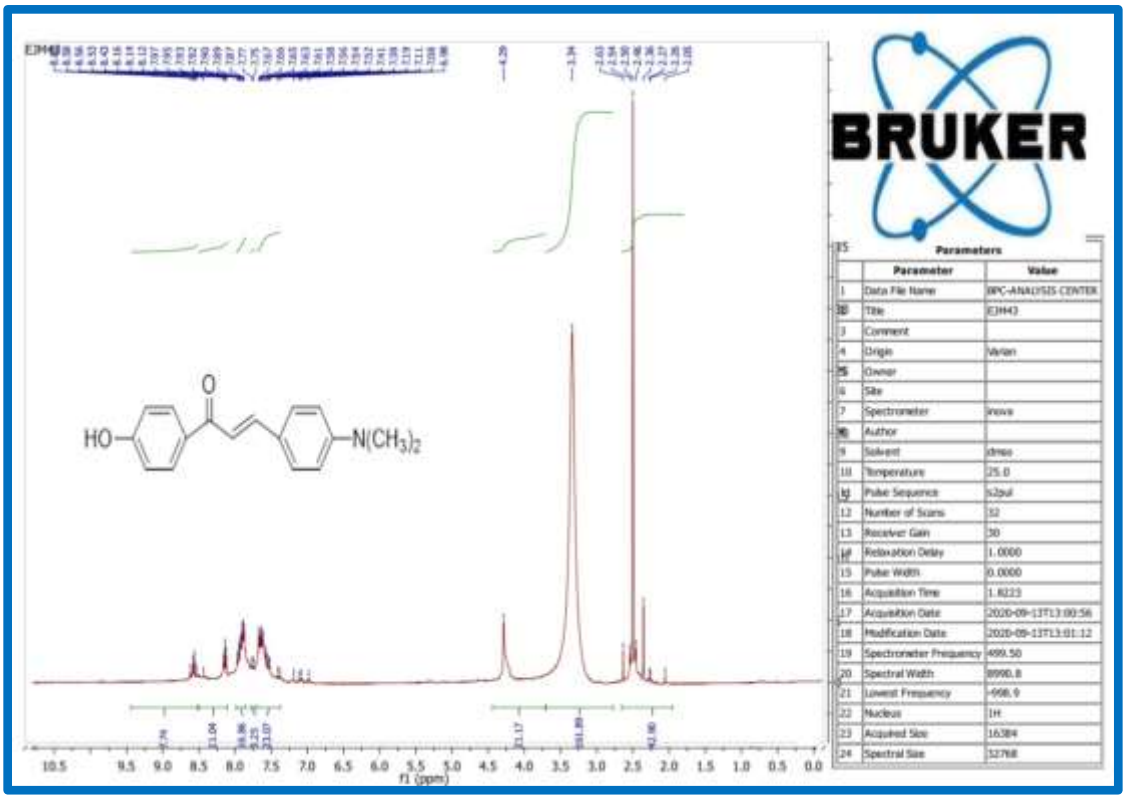


Figure (5) H^1 NMR spectrum of E_6

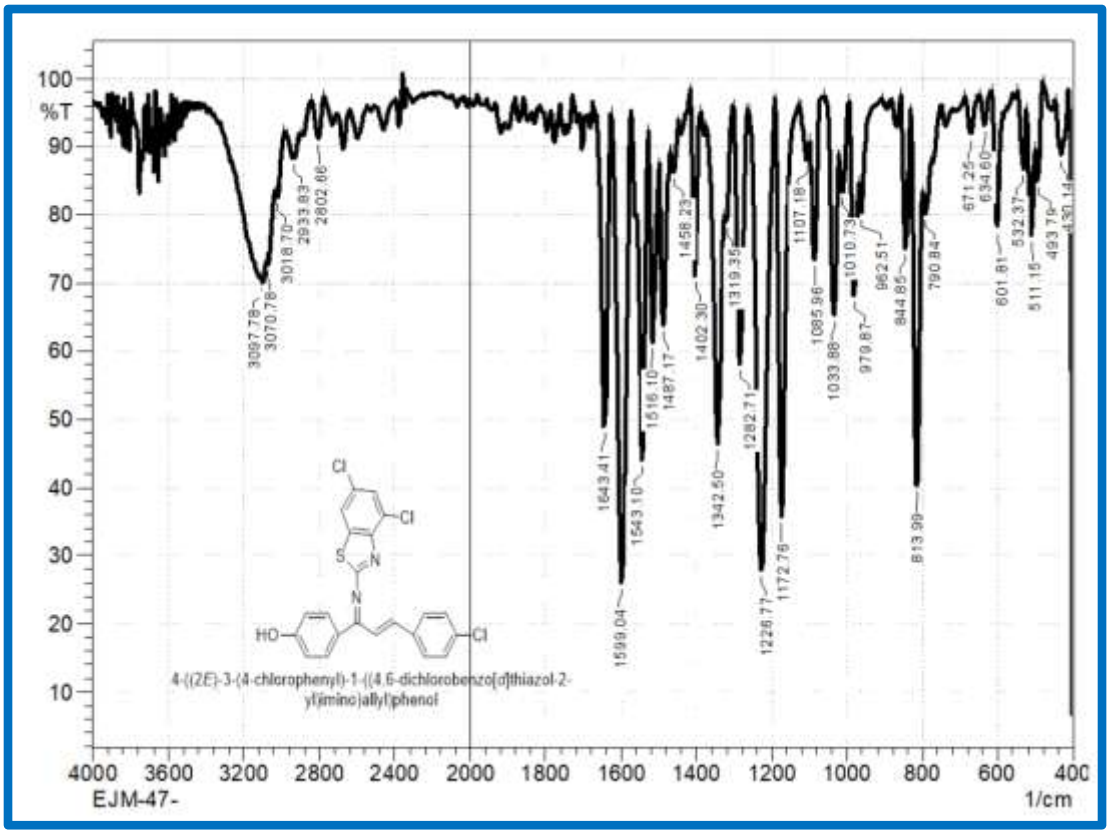


Figure (6) F-TIR spectrum of E_{10}

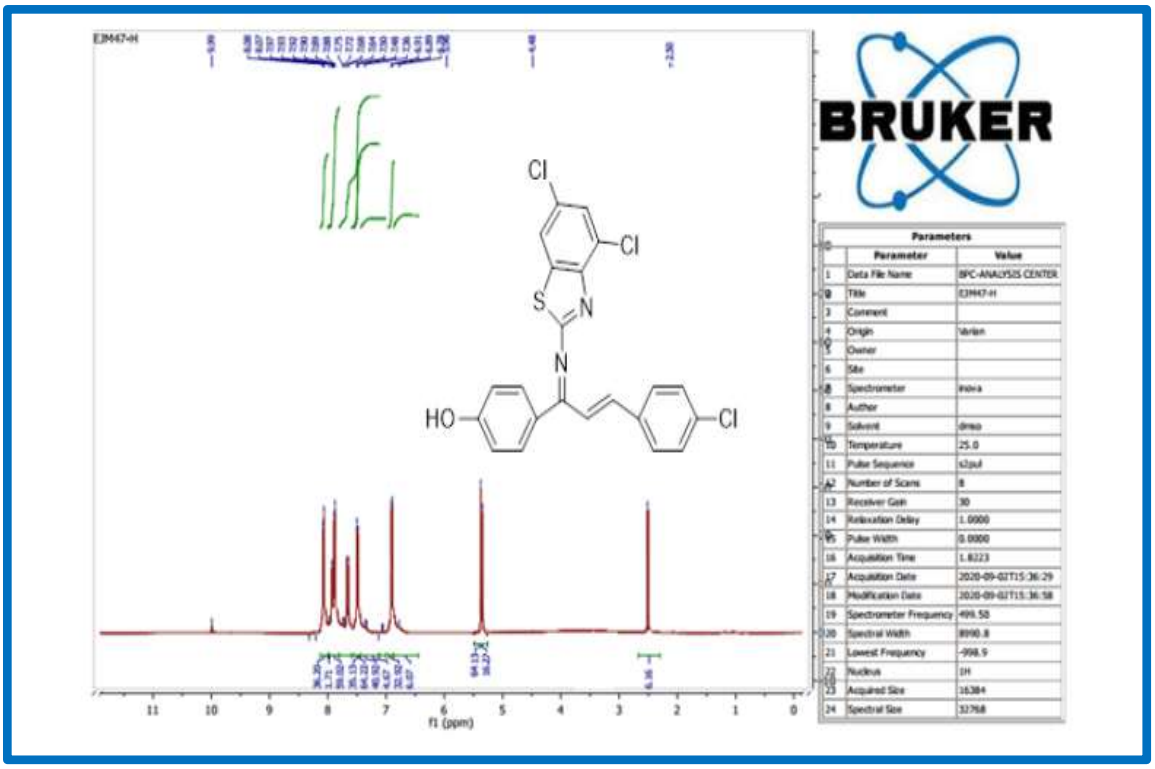


Figure (7) H^1 NMR spectrum of E_{10}

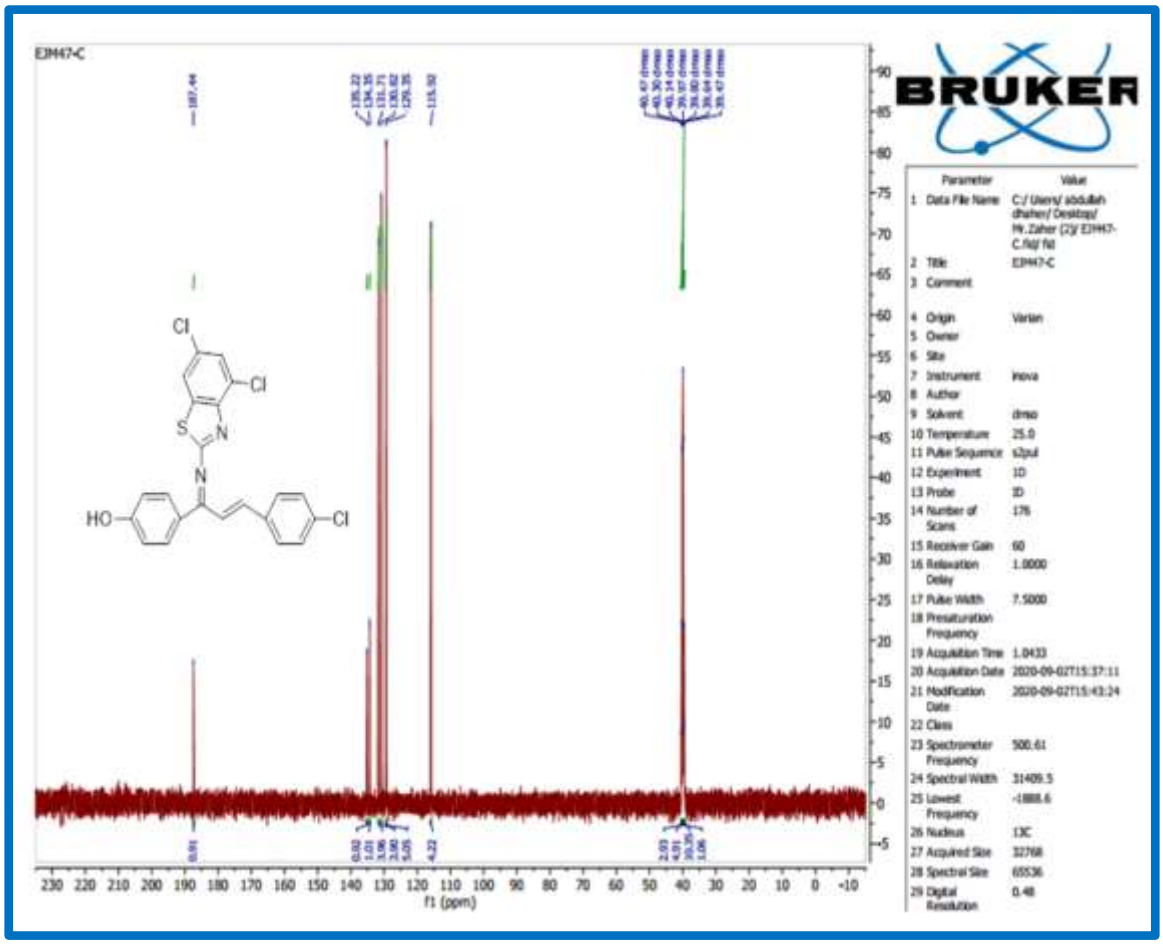


Figure (8) C^{13} NMR spectrum of E_{10}

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