SYNTHESIS OF SOME NEW THIAZOLIDINONE COMPOUNDS DERIVED FROM SCHIFF BASES COMPOUNDS AND EVALUATION OF THEIR LASER AND BIOLOGICAL EFFICACY

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ABSTRACT

In this work 6-fuloro-2-aminobenzothazol compound (R_1) have been prepared from the reaction of aniline with appropriate potassium thiocyanate in presence cooled glacial acetic acid in such a way to temperature not exceeded above room temperature, Solution of 1.6ml of bromine in 6ml of glacial acetic acid, the reaction 6-fuloro-2-aminobenzothazol of with Hydrazine hydrate 6-fluoro-2-hydrazineylbenzo thiazole yielded compounds (R_2). The research included synthesis of schiff base from the reaction of with appropriate aromatic aldehydes in presence of glacial acetic acidyieldeds compounds (R_3-R_7) 2-(2-benzylidenehydrazineyl)-6-chlorobenzo thiazole, and synthesis of thiazolidinone from the reaction of thioglycolic acid with schiff base,yieldeds compounds (R_8-R_{12}) chloro-N-(5-phenyl-2,5-dihydro-tetrazol-1-yl) benzo thiazol-2. The prepared compounds have been characterized by melting points and some physical properties besides the FT-IR, H-NMR spectra and quantitative analysis of elements (C.H.N.). The purity for these compounds was checked by TLC. The study is showed biological activity for chemical compounds, at three concentrations (10^{-2},10^{-3},10^{-4}) mg/ml The minimum inhibitory concentration [MIC] have been determined with the reference of stander drugs the results showed that the thiazolidinone derivatives are better than growth of both types of bacteria gram-positive and gram–negative compared to drug, and evaluation of laser efficacy.

Keywords: Schiff bases, aminobenzothiazole, thiazolidinone

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INTRODUCTION

The synthesis of benzothiazole is an area of current interest because it belongs to an important class of heterocyclic compounds that found to be effective as antimicrobial and anti –inflammatory agents [1]. At present several methods from the synthesis and cyclization of benzothiazole have been reported. Since

individual method has its own advantages and disadvantages, but the most common classical method for the synthesis of benzothiazole recently in use is based on cyclization through oxidation by bromine. The biological activity associated with them, including anti-inflammatory [2], antitubercular, cytotoxic, anti-HIV antioxidant, analgesic, antiviral and antimicrobial [3], analgesic, anti-tuberculosis, anti-fungal, anti-malarial [4], anti-tumor, and antioxidant [5]. Schiff bases are an important class of ligands in coordination chemistry and find extensive application in different fields [6]. Some of these bases exhibited antimicrobial and anticancer activities the thiazolidin-4-one ring have reported to a wide range of pharmacologic activities whichinclude antimicrobial [7], antifungal, antitumor, antidiabetic activity [8], anti-inflammatory and stomach toxicity [9].

MATERIALS AND METHODS

All the chemicals and solvents used were of Aldrich and Fluka products and were used without further purification**.** Melting points are uncorrected and were recorded in an open capillary tube on Stuart melting point apparatus. Infrared spectra have been recorded on a Shimadzo FTIR-8100 spectrophotometer using KBr discs–and ^{1}HNMR Spectra have been measured on a MH_Z spectrometer using (DMSO-d_6) as solvent. reaction monitoring and verification of the purity of the compounds was done by TLC on silica gel-percolated alumni sheets (type 60 F254 Merck, Darmstadt, Germany).

Synthesis of 2-Amino-6-flouro benzothiazoles (R_1) [10]: To a solution of (0.1 mole) of substituted anilines and (0.4mole) of potassium thiocyanate in 150m1 of 96% acetic acid glacial was add drupe wise, with stirrings 16g. (0.1mole) of bromine dissolved in 100 ml of glacial acetic acid while the temperature was kept below (10°C). After all the bromine solution had been added the mixture was stirred for 10 hr. The combined filtered are dissolved in warm water. The combined filtrate and neutralized with 10% Na OH. The precipitate was collected on a filter and dried recrystallized from a suitable solvent. The physical properties of the synthesized compound (R_1) are color white, M.P. (183-185) ^{OC} and yield 76%.

Synthesis of 2-hedruzeno-6-fulorobenzothiazole (R_2) [11]: To a solution of (0.006mol) of substituted benaothiazole in (25ml) ethylene glycol and added (1:1) HCl and aqueous hydrazine with stirring the mixture ascends was refluxed for 8 hrs. The precipitate was collected on a filter and dried. recrystallization from a suitable solvent. The physical properties of (R_2) is color gray, M.P. (234 -236) ^{O}C and yield 68%.

Synthesis of schiff base (R_3-R_7) [12]: In round bottomed flask equipped with double surface condenser fitted with calcium chloride guard tube, a mixture of 2-Hedruzeno-6- sub. Benzothiazole (0.001 mole, 0.165 gm) and aromatic benzaldehyde (0.01mol) in ethanol 30 ml containing a drop of acetic acid was refluxed for 12 hrs. the mixture was poured on ice water to give precipitate which was recrystalized from acetic acid. The physical properties of the synthesized compound are given in table (1).

Table 1: The physical properties of compounds(R_3-R_7)

Comp. No.	X	Molecular formula	M.P (C)^{o}	Yield (%)	Color
R_3	Cl	$C_{14}H_9ClN_3SF$	45-48	63	White
R_4	Br	$C_{14}H_9BrN_3SF$	110-112	68	White
R_5	OCH_3	$C_{15}H_{12}N_3SOF$	73-75	67	White
R_6	F	$C_{14}H_9N_3SFF$	83-86	78	Yellow
R_7	$N(CH_3)_2$	$C_{16}H_{15}N_4SOF$	118-120	70	White

Synthesis of thiazolidin-4-one derivatives (R_8-R_{12})[13]: A mixture of Schiff bases(R_3-R_7) [(0.02mol) and thioglycolic acid (0.02 mole) was refluxed in drybenzene (15 mL) for 16 hrs. The solvent was evaporated and the reaction mixture wasneutralized with sodium bicarbonate solution, the product was filtered off and recrystallizedfrom acetone. The physical properties are listed in table 2.

Table 2: The physical properties of compounds (R_8-R_{12})

Comp. No.	X	Molecular formula	M.P (C)^o	Yield (%)	Color
R_8	Cl	$C_{16}H_{11}ClN_3OS_2F$	86-89	60	Yellow
R_9	Br	$C_{16}H_{11}BrN_3OS_2F$	73-75	58	Red
R_{10}	OCH_3	$C_{17}H_{14}N_3O_2S2F$	92-95	74	Yellow
R_{11}	F	$C_{16}H_{11}FN_3OS_2F$	78-80	60	Red
R_{12}	$N(CH_3)_2$	$C_{18}H_{17}N_4OS_2F$	104-106	70	Yellow- Red

The biological activity [14]:

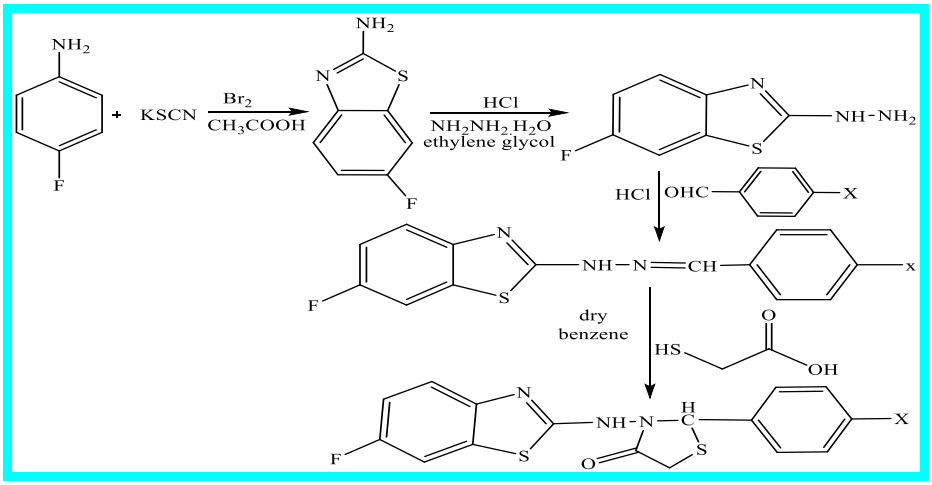
The bacteria species used are listed in table (7). All strains were obtained from College of Sciences, Tikrit University. They were grown up to the stationary phase nutrient bath at 37 ^{O}C and a sample of 0.5 ml of each bacteria was spread over a surface of a nutrient agar plate.

Antibacterial assay [15]:

Disc of filter paper (6 mm diameter) is sterilized at 140 ^{O}C for 1hr., and impregnated with the germs. DMSO was used as a solvent for compounds (R_1-R_{12}). The same solvent was used for antibiotics (Amoxicillin, Ampicillin). Blank paper discs of DMSO was used as control. The inoculated plates are incubated at 37 ^{O}C for 24 hrs., and the inhibition zone (mm) were measured. In all experiments the mean of each triplicate was measured.

RESULTS AND DISCUSSION

In this work many compounds were synthesized who Amino-6-flouro benzothiazoles, 2-hedruzeno-6-fulorobenzothiazole, schiff bases and thiazolidin-4-one and as in the following scheme:



Scheme 1: synthesis of compounds (R_1-R_{12}).

Characterization of 2-amino-6-flouro benzothiazoles (R_1):

The structures of the prepared compounds were confirmed by spectroscopic methods such as:

FT-IR, ^{1}H-NMR. The IR spectrum of compound (R_1) shows a starting compound 2-amino-6-flourobenzothiazolesrequired for the preparation of schiff base was obtained by the hydrazinolysis of 2-amino-6- flouro benzothiazoles the, IR spectra of these compounds showed a band at (1625 cm^{-1}) due to stretching (C=N) group. band at (1446-1581cm^{-1}) for **(C=C)** group at (1267cm^{-1}) for (C-Br) at. band at (1038 cm^{-1}) for (C-S-C) group bat, (3180cm^{-1}) for (Ar-H) at (3455-3355cm^{-1}) for (NH_2) group. IR data showed in the fig. (3).

The H^1-NMR Spectrum ($CDCl_3$) of compounds (R_1) Show signal at (2.50ppm) for (DMSO), signal at (3.50 ppm) for (HDO), signal at (6.98toppm) for (NH2), signal at (7-7.98ppm) for (forphenyl), figure (4).

Characterization of 6-Fluoro-2-hydrazineylbenzo [d] thiazole (R_2):

The IR data showed in the figure (2), the reaction of 2- Amino-6-flouro benzothiazoles the, with hydrazine yielded the compounds (**R_2**). The IR spectral data of these compound showed band at (3455-3355cm^{-1}) due to stretching (NH-NH_2) group. The IR data showed in the figure (5).

The ^{1}HNMR spectrum ($CDCl_3$) of compounds (R_2) showed signal at (1.53ppm) for (HDOO), signal at (4.00 ppm) for (NH_2), signal at (7.00 to 7.54ppm) for phenol, signal at (7.89 ppm) for (NH), figure (6).

Characterization of schiff base (R_3-R_7):

The 2-hydrazinobenzothiazole compound converted to schiff base by condensation with aromatic aldehyde the compounds (R_3-R_7). The IR spectrum showed disappearance of the (NH2) group stretching bands (symmetrical & unsymmetrical) at (3450-3550 cm^{-1}) and appearance of (C=N) absorption band at (1610-1650 cm^{-1}). the IR DATA showed in the figure (7) table (3).

The H^1-NMR Spectrum ($CDCl_3$) of compounds (R_3-R_7) show signal at (2.50ppm) for (DMSO), signal at (3.30-3.44 ppm) for (HDO), signal at (6.98to7,95ppm) for phenyl, signal at(7.98ppm) for (H-C=N) signal at (12ppm) for (NH_2), figure (8).

Characterization of thiazolidin-4-one derivatives (R_8-R_{12}):

The FTIR spectra of compounds (R_8-R_{12}) showed the disappearance of a stretching band of imine group and appearance of stretching band due to a carbonyl group of thiazolidinone around (1710-1705) cm^{-1} and the FTIR spectra showed a band in (904-898) cm-1 for C-S stretching the IR data showed in the figure (9), table (4).

The H^1-NMR Spectrum ($CDCl_3$) of compound (R_1) Show signal at (26ppm) for (O=C-CH), signal at (7.65 to 7.42 ppm) for phenyl, signal at (7.67 to 8.05ppm) for (HC=CH)) figure (3), the H^1NMR spectrum ($CDCl_3$) of compound (R_{11}) Showed signal at (3.35) for (HDO), Signal at (3.40 ppm) for (-C=O-CH), Signal at (6.00) for (N-CH). ppm) for, signal at (6.56 to7.42ppm) for (phenyl), signal at (7.97 ppm) for (NH) figure (10)**.**

Table 3: Spectral data of compounds (R_3-R_7)

Comp. No.	X	FT-IR cm^{-1} (KBr)					
		C=N	C-F	υ(Ar-H)	υ(NH)	υ(C=C)	Others cm^{-1}
R_3	Cl	1655	1050	3057	3421	1446	1020υ(Cl)
R_4	Br	1658	1143	3051	3412	1571	1080υ(Br)
R_5	OCH_3	1644	1116	3062	3430	1574	1150sy υ(OCH_3)
R_6	F	1660	1230	3055	3446	1452	υ (C-Cl) 1200
R_7	$N(CH_3)_2$	1654	1030	3031	3479	1509	υ (C-N)1380

Table (4) Spectral data of compounds (R_8-R_{12})

Comp. No.	X	FT-IR cm^{-1} (KBr)						
		C-S-C	C-F	υ(Ar-H)	υ (NH)	C=O	υ(C=C)	Others cm^{-1}
R_8	Cl	920	1050	3021	3445	1705	1442	1021 υ(Cl)
R_9	Br	894	1143	3045	3417	1713	1556	1060 υ(Br)
R_{10}	OCH_3	932	1116	3069	3429	1720	1521	1050sy υ(OCH_3)
R_{11}	F	968	1230	3062	3411	1731	1452	1200 υ(C-Cl)
R_{12}	$N(CH_3)_2$	865	1030	3013	3466	1727	1506	1380 υ(C-N)

Table 5: Elemental analysis of some of the prepared compounds.

Comp. No.	Molecular Formula	Found					Calculated				
		C%	H%	N%	O%	S%	C%	H%	N%	O%	S%
R_1	$C_7H_5FN_2S$	55.13	2.98	16.60	---	18.88	49.99	3.00	16.66	---	19.06
R_2	$C_7H_6FN_3S$	45.74	3.25	23.07	---	17.61	45.89	3.30	22.94	---	17.50
R_3	$C_{14}H_9ClFN_3S$	55.17	3.00	13.65	---	10.60	55.00	2.97	13.74	---	10.49
R_5	$C_{15}H_{12}FN_3OS$	59.68	3.99	13.40	5.30	10.52	59.79	4.01	13.94	5.31	10.64
R_7	$C_{16}H_{15}FN_4S$	61.25	4.85	18.03	---	10.05	61.13	4.81	17.82	---	10.20

R_9	$C_{16}H_{11}BrFN_3OS_2$	45.42	2.60	10.00	3.80	15.21	45.29	2.61	9.90	3.77	15.11
R_{11}	$C_{16}H_{11}F_2N_3OS_2$	53.13	3.03	11.49	4.42	17.58	52.88	3.05	11.56	4.40	17.64
R_{12}	$C_{18}H_{17}FN_4OS_2$	55.55	4.43	14.35	4.14	16.60	55.65	4.41	14.42	4.12	16.51

Influence of lasers on prepared compounds (R_1-R_2) [19]: A laser apparatus with a capacity of (5) milliwatt which gives laser rays in the visible area of the spectrum with a wavelength (600-700) nm in continuous waves. The compounds (R_1-R_{12}) were radiated by laser for (10-30) seconds. It was observed that the compounds were not affected. They did not disintegrate or polymerize when the melting point and color were measured. If some minor changes were found in some of them, they would have been neglected. This denotes that the compounds were not affected by the laser beams used. Since they are stable, as shown in the table (6).

Table 6: The results of the irradiation of the compounds by laser beams

Comp. No.	10 S		20 S		30 S	
	M.P. ^{0}C	**Color**	**M.P. ^{0}C**	**Color**	**M.P. ^{0}C**	**Color**
R_1	183-185	White	183-185	White	183-184	White
R_2	234 -236	Gray	234 -235	Gray	234 -235	Gray
R_3	45-48	White	45-48	White	46-48	White
R_4	110-112	White	110-112	White	111-113	White
R_5	73-75	White	73-75	White	75-77	White
R_6	83-86	Yellow	83-84	Yellow	83-84	Yellow
R_7	118-120	White	118-120	White	118-121	White
R_8	86-89	Yellow	86-88	Yellow	86-88	Yellow
R_9	73-75	Red	71-72	Red	70-71	Red
R_{10}	92-95	Yellow	94-95	Yellow	95-97	Yellow
R_{11}	78-80	Red	78-80	Red	78-80	Red
R_{12}	104-106	Yellow- Red	104-106	Yellow- Red	106-108	Yellow- Red

Evaluation of the biological efficacy of prepared compounds (R_1-R_{12}) [20]: The biological activity of prepared compounds (R_1-R_{12}) were evaluated against Gram positive and negative bacteria. Results in Table (7) indicate that these compounds possessed the ability of inhibiting the growth of the used bacteria. Amoxicillin and Ampicillin were used as control samples based on what is used in the laboratories of the Ministry of Health; which is based on the tests of the World Health Organization. Table (8) shows the anti-bacterial activity of prepared compounds.

Table 7: The antibacterial activity of the prepared compounds against Gram positive and negative bacteria (inhibitory zones are in mm).

Comp. No.	Conc. mg/ml	*E. Coil*	*K. Pneumonia*	Inhibition Distance
R_1	25	+	+	5-11

	50	+	+	7-17
	100	+++	+	16-49
R_2	25	+	-	0-8
	50	++	+	10-30
	100	+++	++	35-50
R_3	25	+	-	0-8
	50	+	-	0-12
	100	+	-	0-20
R_4	25	+	+	6-11
	50	+	+	7-13
	100	++	+	19-30
R_5	25	-	++	0-29
	50	-	+++	0-40
	100	-	+++	0-50
R_6	25	-	-	0
	50	+	+	13
	100	++	+	20-35
R_7	25	+	+	11-14
	50	++	++	26-33
	100	+++	+++	50
R_8	25	+	++	14-30
	50	+	+++	20-35
	100	++	+++	31-50
R_9	25	+	-	0-16
	50	++	+	12-27
	100	+++	+++	45-50
R_{10}	25	+	-	0-14
	50	+	-	0-20
	100	++	+	15-35
R_{11}	25	-	+	0-20
	50	+	++	18-34
	100	++	+++	31-44
R_{12}	25	-	-	0
	50	+	+	16-20
	100	++	++	30-35

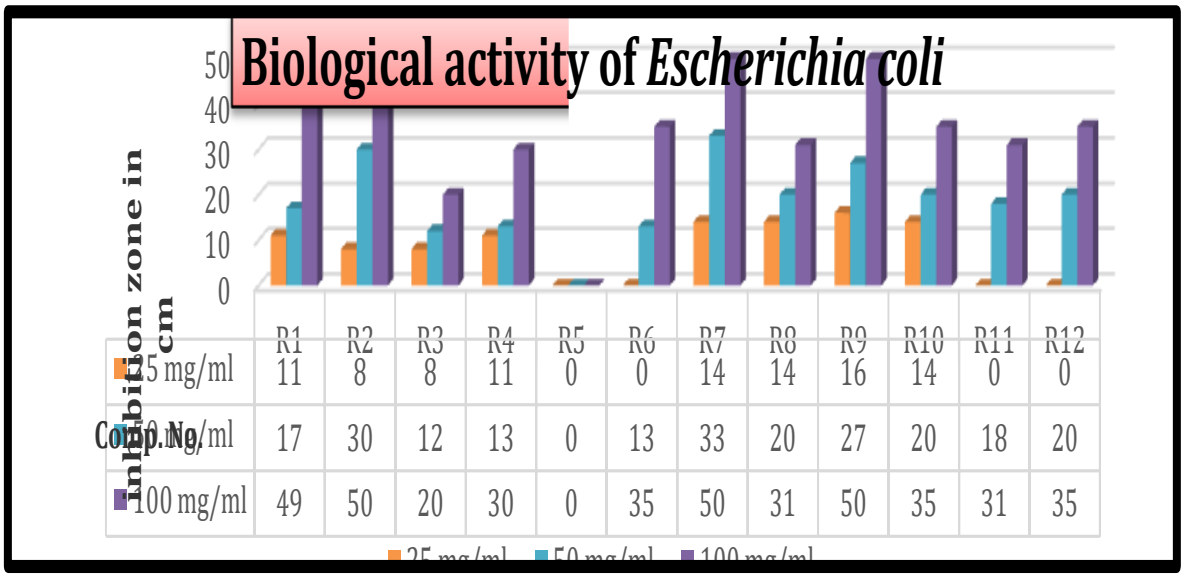
(-) : No inhibition(++): inhibition zone of 21-35 mm

(+): inhibition zone of 5-20 mm(+++): inhibition zone of 36-50 mm

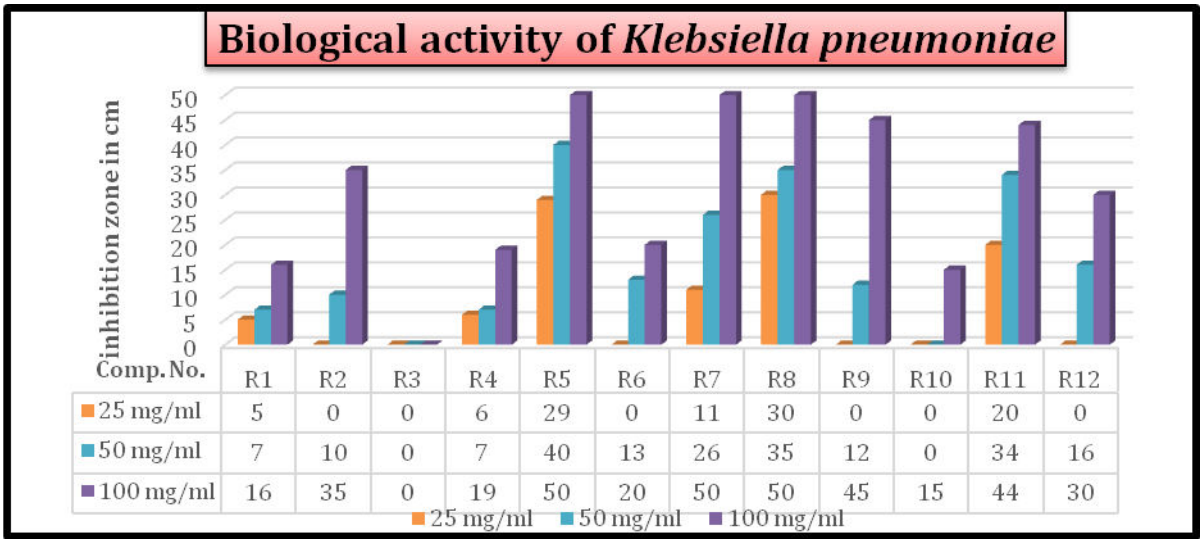
Table 8: Antibacterial efficacy of control treatments (antibiotics) in the growth of a number of negative and positive bacteria (diameter of the inhibition circuit measured by mm).

Comp. No.	*Name*	*E. Coil*	*K. pneumonia*
1	Amoxicillin	38	40
2	Ampicillin	43	37
3	Blank disk	0	0

The following figures show the inhibitory activity values of bacterial compounds:



Scheme 2: Evaluation of inhibitory activity of compounds prepared for *Escherichia coli.*



Scheme 3: Evaluation of inhibitory activity of compounds prepared for *K. pneumonia.*

Below are pictures of some compounds showing the inhibitory activity against the used bacteria:

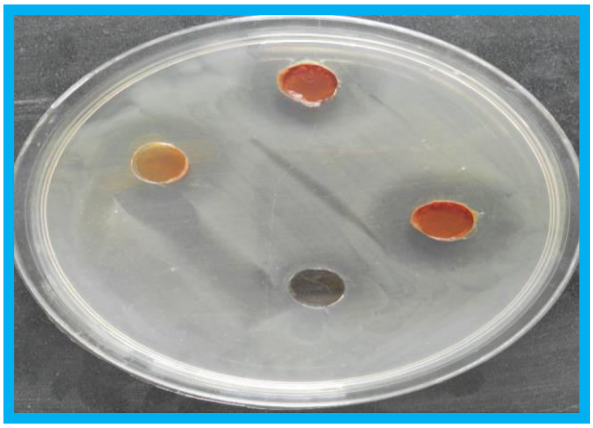
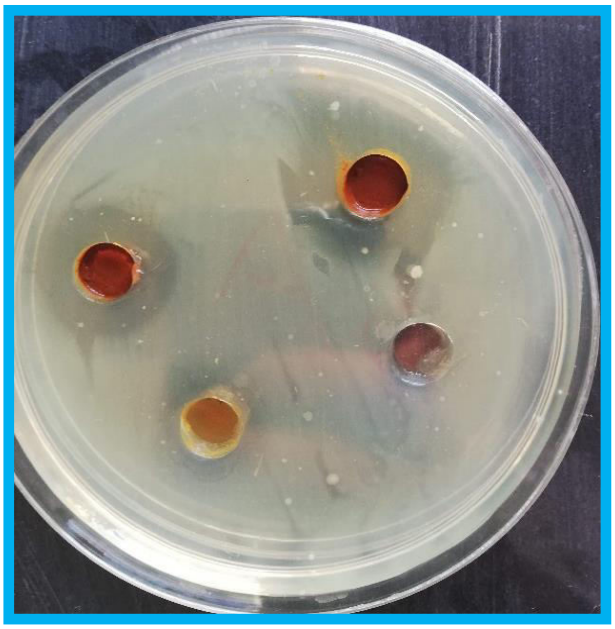


Fig. 1: Antibacterial activity ofcompound [R_2] against *E. coli*.

Fig. (2): Antibacterialactivity ofcompound [R_7] against *K. pneumonia*.



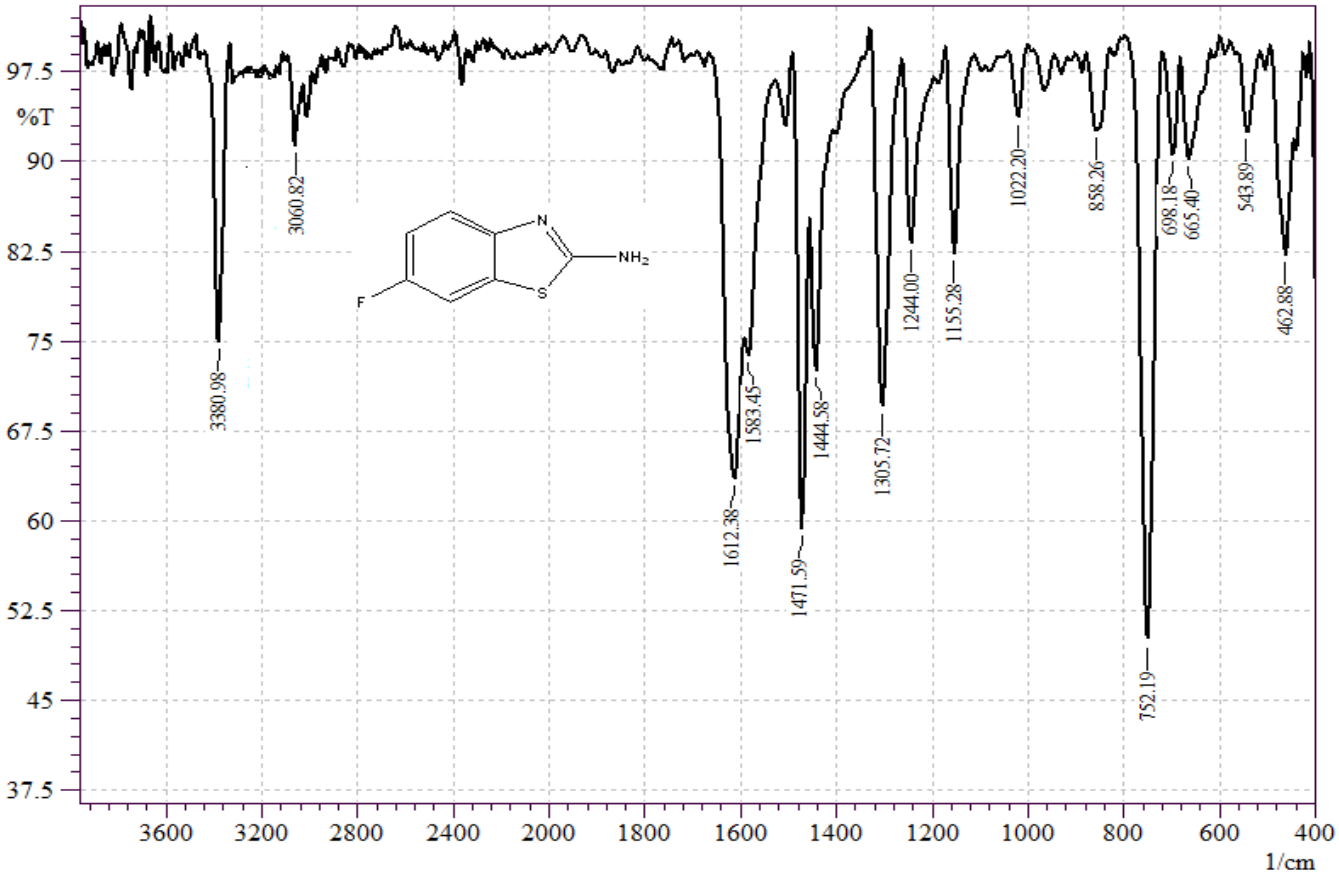


Fig. 3: FT-IR spectrum of compound [R_1]

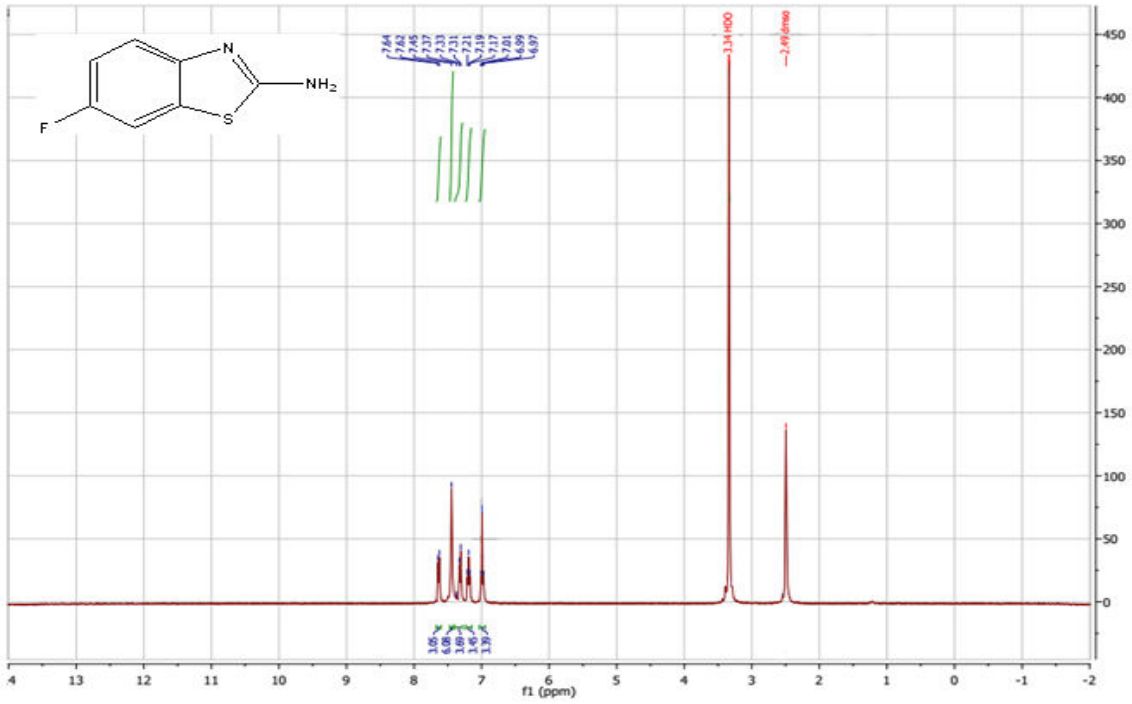


Fig. 4: ^{1}H-NMR spectrum of compound [R_1]

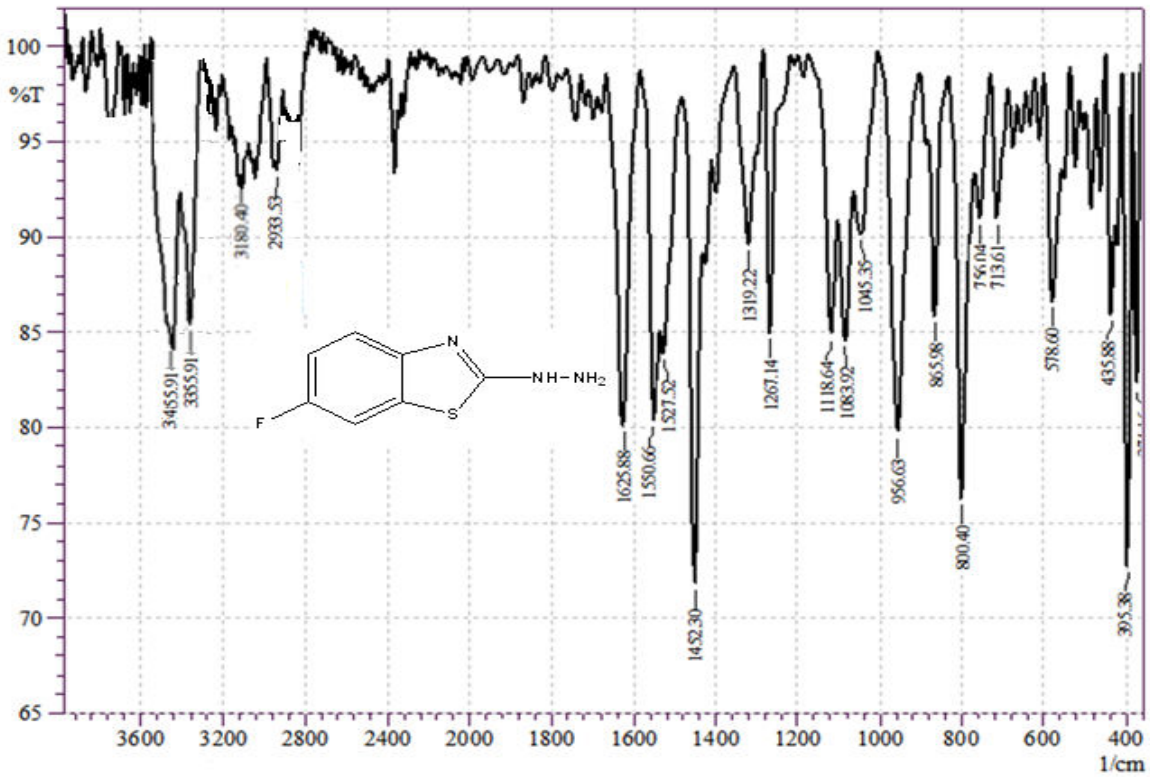


Fig. 5: FT-IR spectrum of compound [R_2]

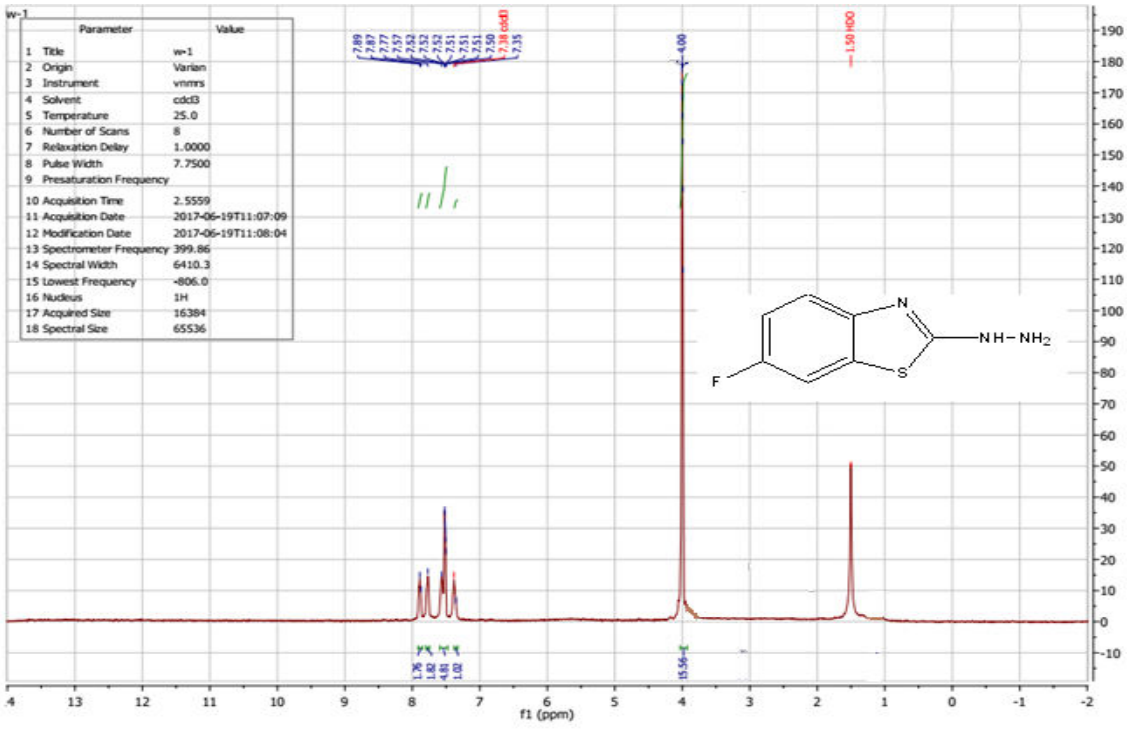


Fig. 6: ^{1}H-NMR spectrum of compound [R_2]

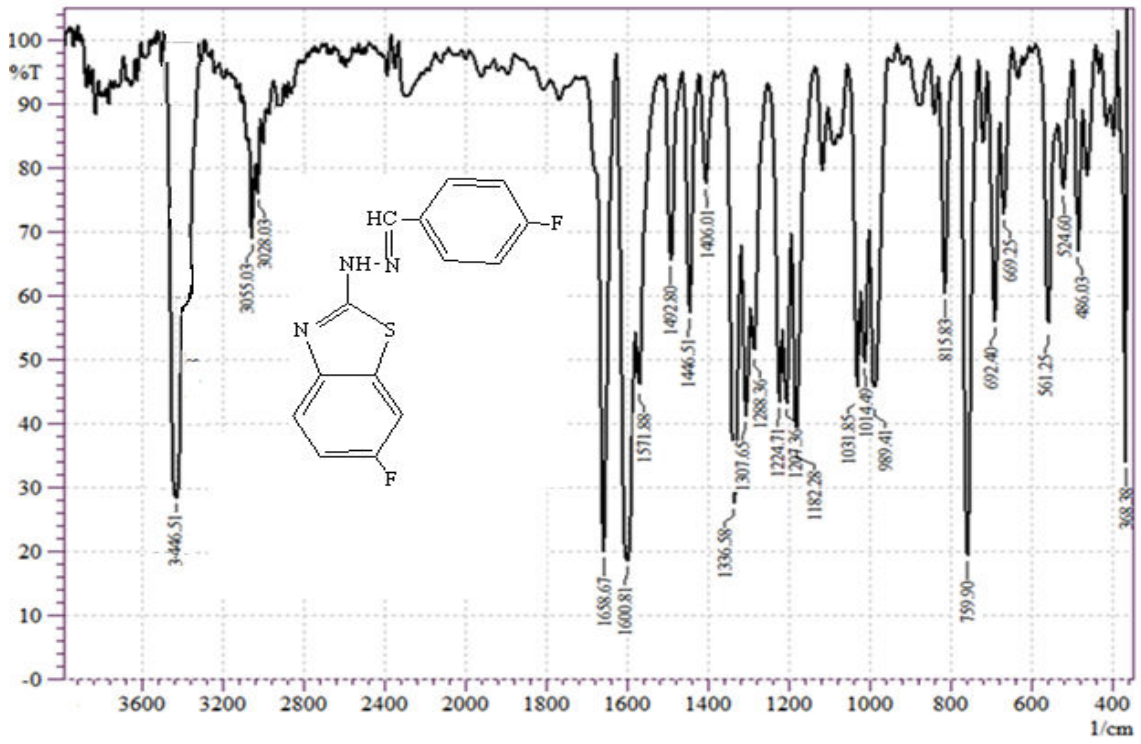


Fig. 7: FT-IR spectrum of compound [R_6]

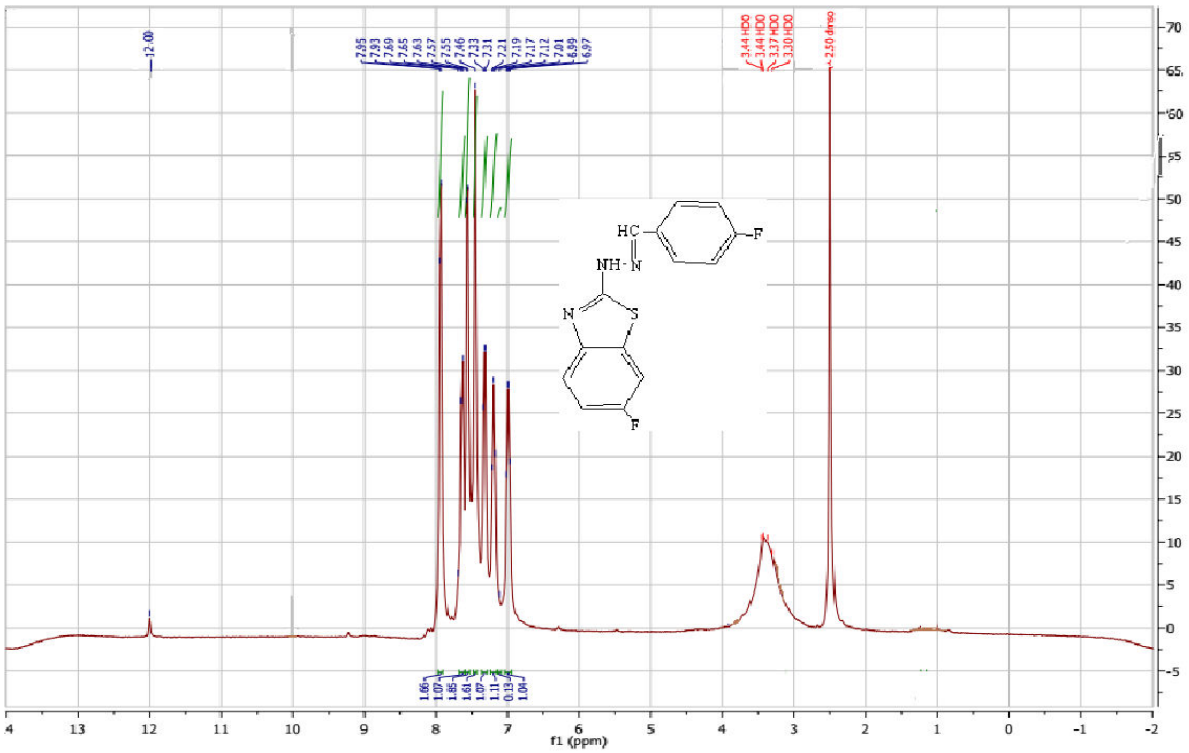


Fig. 8: ^{1}H-NMR spectrum of compound [R_6].

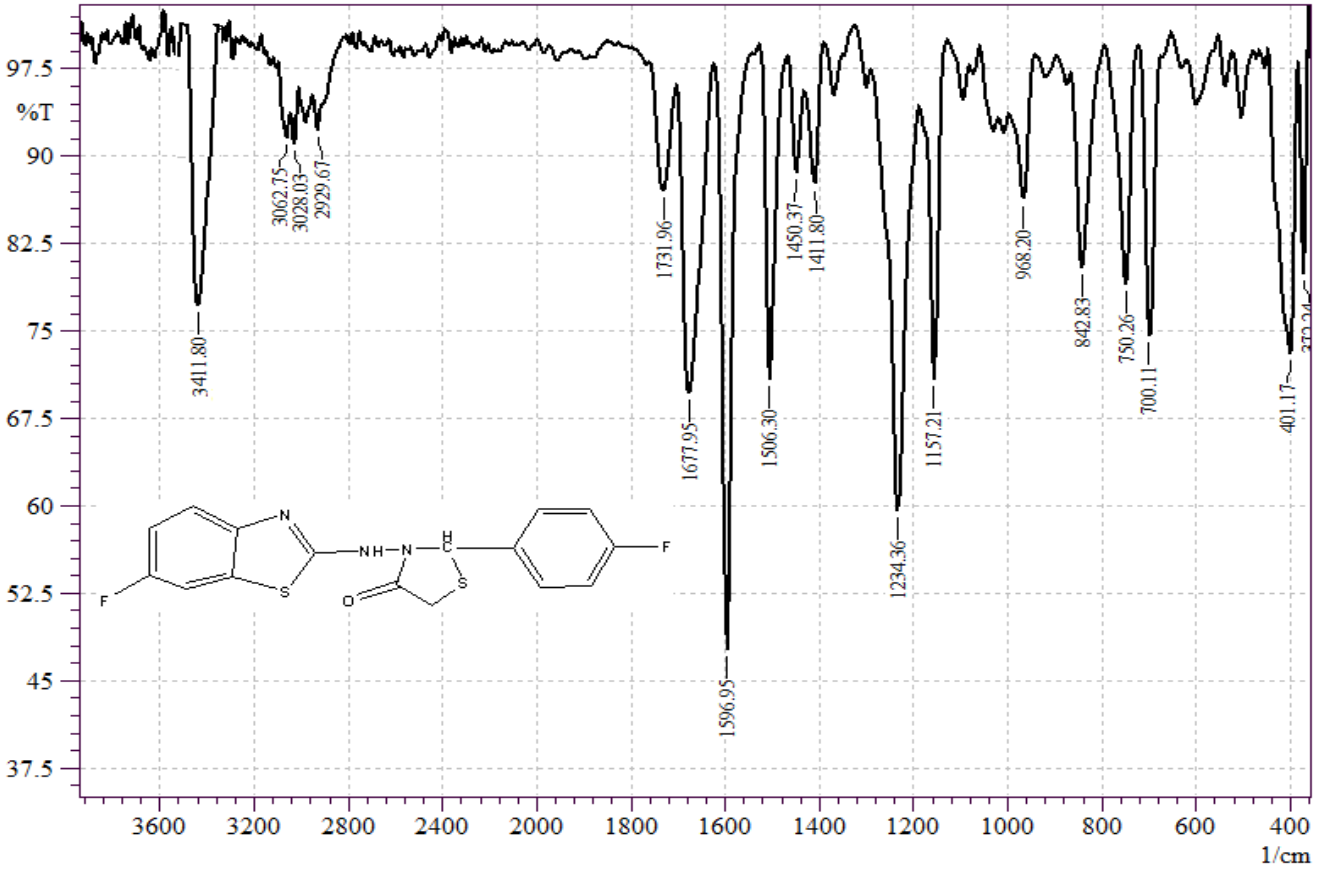


Fig. 9: FT-IR spectrum of compound [R_{11}]

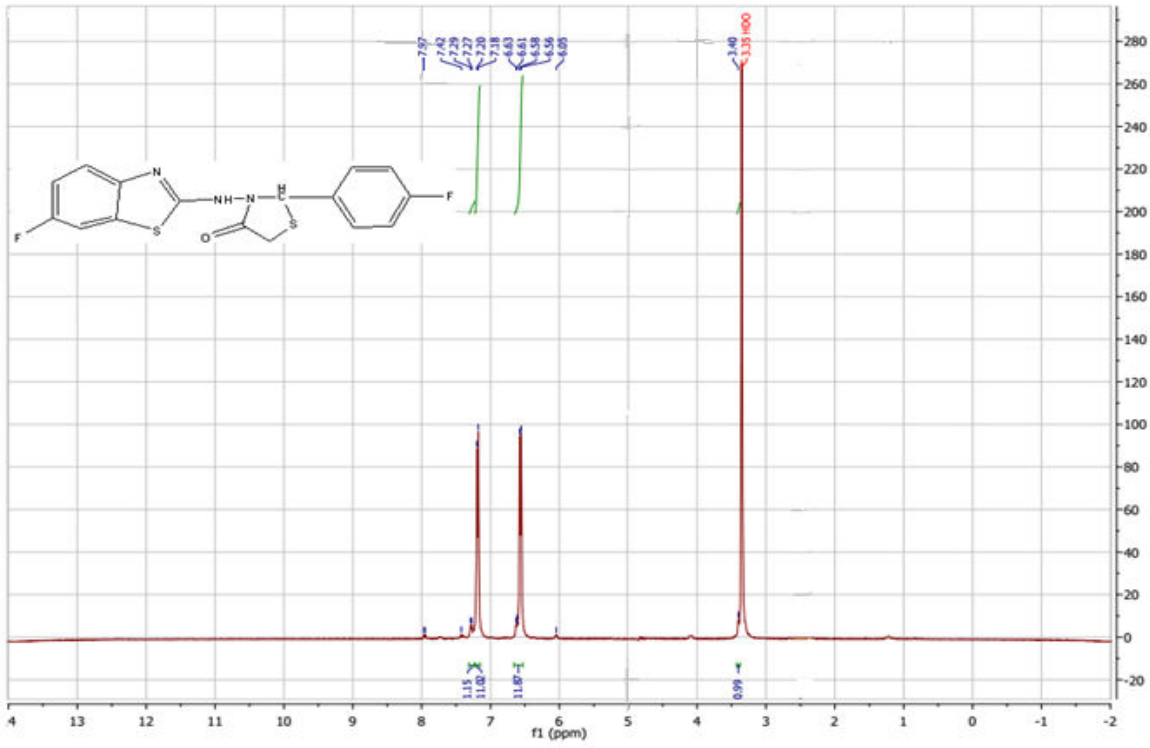


Fig. 10: ^{1}H-NMR spectrum of compound [R_{11}].

CONCLUSION

The biological activity for chemical compounds on growthof both types of bacteria gram-positive and gram–negative, showed that the thiazolidinone derivatives are better drug, and evaluation of laser efficacy.

ETHICAL CLEARANCE

The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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