Synthesis , characterization of dihydrozones derived terazole compounds and evaluation of their biological activity

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ABSTRACT

This research included the synthesis of new heterocyclic compounds, the compound [S1] was synthesized by the reaction of a carboxylic acid (1,1-biphenyl-4,4'-dicarboxylic acid) with an increase in absolute ethanol and (4-5 ml) of sulfuric acid Center. The compound [S2] was then made by reacting this mixture. The molecule [S1] was combined with aqueous (95%) hydrazine in absolute ethanol, and the hydrazone derivatives [S3-S8] were created by reacting the chemical [S2] created in the second phase with a few benzaldehyde replacements in absolute ethanol. Tetrazole derivatives [S9-S14] were produced by reacting the sodium azide-prepared hydrazones [S3-S9] with tetrahydrofuran in an acidic medium. After the product had been thoroughly cleaned, the synthetic compounds were identified using spectral techniques like UV-Vis, FTIR, ^{1}H,^{13}C-NMR,, Additionally, utilizing TLC to trace the course of the reactions and evaluate the resulting compounds' melting and purity levels. Two types of bacterial isolates known to be resistant to antibiotics, Pseudomonas aeruginosa, which tested negative for Gram stain [Gr-ve], and Staphylococcus aurous, which tested positive for Gram stain [Gr + ve], were examined for how some prepared compounds affected the growth using the antibiotics amoxicillin and ampicillin. The composition of chemicals produced at the lower energy level was also studied. The studied microorganisms were successfully inhibited by some of the produced chemical substances.

Keywords: hydrazones, tetrazole derivatives, 1,1-biphenyl-4,4'-dicarboxylic acid , antibacterial activity.

1- Introduction

The Tetrazole compounds are well-known for using it frequently in compounds that are intended to represent diverse aspects of science and life [1]. This five-membered aromatic heterocycle has drawn interest in an increasing number of research over the past several years due to its bioisosterism to carboxyl and amide groups, among other things. Following coordination chemistry and materials chemistry as the most significant areas of tetrazole study, respectively, comes general medicine [2]. The hydrazones family of chemicals includes a special class of molecules called hydrazones, which are important for drug design because of their wide variety of pharmacological effects, potential as ligands for metal complexes, organocatalysis, as well as for the production of heterocyclic compounds [3]. One of the most important chemicals is sodium azide, which has a variety of applications and influences incubation. [4]. It was utilized in the creation of substances known as tetrazoles because of its importance [5]. For instance, substituted amines, triethyl orthoformate, and sodium azide might be combined to create

tetrazoles in dimethyl sulfoxide [6Additionally, the 1,3-dipolar cycloaddition method was first used to make the tetrazole ring by coupling an imine as a 1,3-dipolarphile reaction with an azide group as a 1,3-dipolar molecule. [7,8]. Clearly, a crucial problem in contemporary pharmaceutical chemistry is the synthesis of tetrazole derivatives[9]. Due to its numerous uses, tetrazoles are a kind of heterocycle that has grown in prominence. Pharmacologically, because antimicrobial studies are the best method to astonish bacteria resistance and enhance efficient medicines [10], Synthesis is required for certain potential products. Tetrazole includes substances that have been demonstrated to have antibacterial [11] and antifungal activities [12]. The potent cytotoxicity and growth-inhibitory effects of medicines containing tetrazoles were highlighted by Jackman et al. [13]. Drug candidates with antifungal and antibacterial properties are not the subject of many systematic reports. We describe in this work how produced hydrazone chemicals and sodium azide may be used to create tetrazole derivatives. Gram-negative, Gram-positive, and fungal bacteria were all susceptible to the antimicrobial effects of compounds S1–S6 and S10. On the phenyl ring, alterations have an impact on activity.

Materials

Without any additional purification, all compounds were obtained commercially and used.

Physical measurements

Melting Points were measured using an Electro Thermal 9300 without any corrections. On the FTIR 8400si Shimadzu spectrometer, IR spectra in the 400–4000 cm-1 range were captured as KBr discs. Shimadzu's UV-Vis 1800PC spectrophotometer was used to analyze electronic spectra between 200 and 400 nm using 10^{-3}M solutions in spectroscopic-grade dmso-d^6 Solvent. Brukeravance 400 MHz spectrometers were used to perform NMR spectra (^{1}Hand^{13}C-NMR) in DMSO-d6 solutions. Chemical shifts are measured from an internal standard called given in parts per million downfield for tetramethylsilane (TMS).

2- Synthesis Methods:

2-1 Synthesis of compound [S_1][14]

1,1-biphenyl-4,4'-dicarboxylic acid (0.01 mol) was combined with an increase of absolute ethanol, and (4-5 ml) of concentrated sulfuric acid was added. The mixture was then stirred continuously for (6-7) hours, the solvent was then distilled, the residue was then washed with a saturated solution of sodium bicarbonate, the ester was then separated and extracted with diethyl ether, and the washing and separation process was then repeatedIt has a pale yellow color, a disability coefficient (Rf) of 0.81, the chemical formula C18H18O4, and a molecular weight of 298.34 g/mol. Table 2 has IR data.

2-2 Synthesis of compound [S_2][15]

The carboxylic acid ester [S1] (0.09 mol, 26.82 g) was dissolved in (25 ml) of 100% ethanol, and then (0.018 mol, 5.679 g) of aqueous hydrazine (95%) was added. After being kept at an increased temperature for six hours, it was determined that the reaction was complete. After the reaction was finished, the mixture was cooled using the TLC method. The precipitate was then filtered, and the product was then recrystallized using 100% ethanol and dried at a temperature of 50°C. The product had an 80% content and a melting point between 170 and 172 °C. With a light beige tint, the blocking coefficient (Rf) of 0.89, and the chemical formula $C_{14}H_{14}N_4O_2$, its weight 270.29 g/mol is the molecular weight.

2-3 Synthesis of hydrazones derivatives [S_3-S_8][16]

(60.02 mol) of para-benzaldehyde replacements were combined with (0.03mol 3.51gm) of compound [S2], which was dissolved in (20 ml) of 100% ethanol. 4-5 drops of glacial acetic acid were then added, and the mixture was climbed for (6-7) hours. TLC technology was used to check when the reaction had ended. Following the reaction's conclusion, the mixture was allowed to cool before being filtered, the precipitate was collected, recrystallized with 100% ethanol, and dried at 50 °C. Some physical characteristics, percentages, and Rf of the prepared hydrozones [S8 - S3] are shown in Table (1-2). Table 2 has IR data.

.**2-4 Synthesis of tetrazole derivatives [S_9-S_{14}][17]**

The compounds [S9-S14] were produced by refluxing a combination of schiff base derivatives [S3-S8] (0.0016mol) with sodium azide (0.208gm, 0.0032mol) in 30 ml of tetrahydrofuran (THF) for (5–6) hours. In order to recrystallize the raw material from 100% ethanol, it was dried (Scheme1). Table 1: Compounds' physical characteristics (S9–S14). See Table (2) for FTIR data.

3- Anti-bacterial activity

Using the well agar diffusion technique with nutritional agar as the medium, gram-positive and gram-negative microorganisms were examined, including Pseudomonas aeruginosa and Staphylococcus aureus. Compounds were created at different doses using DMSO at 100 mg/ml as the solvent. There are 5ml of nutritious broth in each solution of the fabricated concentration that was added to test tubs. Two test tubes were used, one with no additives and the other with simply DMSO added to serve as a control. After the bacterial solution was thinned, one milliliter of the diluted bacterial suspension was introduced to the control tubes. In several wells of nutritional agar media that had been infected with new bacteria, disks of each concentration were arranged in pairs. One day was spent incubating the bacteria at 37 °C. The inhibitory zones' widths were measured across mm-long distances for assessment. Amoxicillin and ampicillin trihydrate were used as benchmarks for all other drugs that were investigated.The incubation period at 37°C was one day. The inhibitory zones' widths were measured across mm-long distances for assessment. Amoxicillin and ampicillin trihydrate were used as benchmarks for all other drugs that were investigated.

4- Results and Discussion

"When the UV-Vis spectra of the compounds [S_3-S_{14}] produced using ethanol as a solvent was investigated, all compounds showed absorption peaks in the range (217-261) nm into the transitions and absorption peaks in the range (305-393) nm into the", as shown in Figure (1-4).

(1,1-biphenyl-4,4'-dicarbohydrazide) [S_1] was prepared by the reaction of the carboxylic acid (1,1-biphenyl-4,4'-dicarboxylic acid) was mixed with an increase of absolute ethanol and (4-5 ml) of concentrated sulfuric acid was added as showed in Scheme (1). [S_1] The elimination of the (C-H) group's severe stretching band at (2947,2816) cm-1, as well as the strong stretching bands at (1735 cm-1 for C=O) and (1531,1579) cm-1 for C=C, were attributed to the uracil ring in Figure (5). The compound's 1HNMR spectra [S_1] is shown: ^{1}H-NMR (400 MHz, DMSO) δ(2.50 ppm, 4.05 ppm (CH_3, 6H, t, J = 7.1 Hz) , 4.27-4.30 ppm (CH_2,4H, q, J = 7.1 Hz), 7.05-7.07 ppm dd, J = 8.0, 7.2, Hz), 7.51-7.53 (dd, J = 7.2, 1.6,) shown in Figure (6). The ^{13}C-NMR spectra [S_1] is shown: DMSO-d^6 δ 59.54 ppm (1C, s), 13.91 ppm (2C, s), 59.93 ppm (7C, s), 129.33 ppm (6C, s), 131.44 ppm (5C, s), 134.71 ppm (1C, s), 167.72 ppm (3C, s) shown in Figure (7). Compound [S_2] was prepared by reacting one mole of compound [S_1] with 2 moles of $NH_2NH_2.H_2O$ as showed in Scheme (1). Figure (8) demonstrates how the compound[S2] FTIR spectra indicated the disappearance of the (O-C2H5) band at (2947,2816) cm-1 and the formation of a stretching band with sym. and asym. stretch at (3306,3267 cm-1)(NH2).Additionally, the FTIR spectra showed bands at 3149 cm-1 (N-H), 2977 cm-1 (C-H) aliphatic, 1585 cm-1 (C=C), 1703, 1668 cm-1 (C=O), and (1242 cm-1 (C-N) attributed to [S2], as shown in Figure 9.

The ^{1}HNMR spectra for [S_2] is shown: ^{1}H NMR (400 MHz, DMSO) δ (2.50 ppm, (4.05ppm (4H,CH_2, s), 4.27 ppm (4H,NH_2, s), 11.09 ppm (2H,NH,s), 7.38-7.73ppm (4H, dd, J =11.0, 11.0 Hz), shown in Figure (10). The ^{13}C-NMR spectrum of the compound [S_2] is shown: DMSO-d^6 δ 124.71ppm (5C, s), 128.55 ppm (4C, s), 130.91 ppm (3C, s), 132.53ppm (2C, s), 165.65ppm (1C, s), shown in Figure (11). The hydrazone derivatives [S3-S8] are depicted in Scheme (1) in the presence of 2moles of aromatic benzaldehyde substitutions and one mole of compound [S2], a solvent of ethanol, a few drops of CH_3COOH glacial, and the reaction. The Hydrazone FTIR spectrum (S3–S9) no longer displays the two amine group (NH2) stretching bands that were visible at (3267)

and (3306) cm-1 in the molecule [S2], the appearance of absorption bands at the range of (3155–3208) cm-1 due to the stretching of the (NH) bond, and the disappearance of the two amine group (NH2) stretching bands that were visible at (3306, 3267) cm-1 that belonged to the substance [S2]. In addition, the stretching of the (NH) bond produced absorption bands in the (3101-3201) cm-1 range.

The ^{1}HNMR spectrum of the compound [S_3] is shown: ^{1}H NMR (400 MHz, DMSO) δH (7.10-7.12ppm(d,4H,C-H-Ar) (dd, J = 8.5, 1.8Hz), 7.30-7.32ppm(d , 4H,C-H-Ar) (dd, J = 8.5, 1.8, 0.6 Hz), 7.40-7.41 (d, J = 11.0, Hz), (d , 4H,C-H-Ar) (dd, J = 8.5, 1.5, Hz), 7.44 (ddd, J = 8.5, 1.5, 0.6 Hz), 8.94ppm (s ,2H,N=CH, J = 11.0 Hz) 11.32ppm (s,4H,NH). shown in Figure (12). The ^{13}C-NMR spectrum of the compound [S_5] is shown δ 125.09ppm (9C, s), 125.35ppm (8C, s), 127.70ppm (2C, s), 129.47ppm (1C, s), 130.96ppm (3C, s), 133.80ppm (4C, s), 139.10ppm (7C, s), 147.35 (6C, s), 148.91ppm (10C, s), 163.57ppm (5C, s), [18] shown in Figure (13).

According to Scheme (1), the tetrazole derivatives [S9-S14] were created by reacting one mole of the obtained hydrazones [S3-S8] with two moles of sodium azide (NaN_3) in (THF) (19). According to the FTIR spectrum of the produced Hydrazones compounds [S9-S3], the stretch band of the azomethine group (C=N), which showed at the range (1651-1620 cm-1), has disappeared. Furthermore, in the range (1430-1475 cm-1), a medium band belonging to the group (N=N) appeared. For the FTIR results presented in Figure (14), see (Table 3).

^{1}H-NMR (400 MHz, DMSO) δ 4.27(s,2H,C-$H_{Tetrazole}$), δ 5.58ppm(s , 2H, N-$H_{Tetrazole}$), δ 7.34-7.36, (d , 4H,C-H-Ar, ddd, J = 8.4, 1.6 Hz), δ 7.51-7.53ppm (d , 4H,C-H-Ar ,J = 10.7 Hz), δ 7.65-7.67 ppm (d , 4H,C-H-Ar ,J = 10.8 Hz), δ 7.94-7.96(d , 4H,C-H-Ar ,J = 10.7 Hz), 10.48ppm (s,1H,NH),shown in Fig.(15).

The^{13}C-NMR spectrum of the compound [S_{13}] is shown δ18.97(11C,s), 88.68 ppm (6C,s),164.60ppm(5C,C=O,s),128.25(1C,s), 128.13(2C,C-H-Ar,s), 130.81ppm(3C, s), 139.00 (4C, s),137.02(7C,s),126.06(8C,s),129.23(8C,s), 131.61 (10C, s)[19] shown in Figure (16).

5-Determination of antibacterial activity[20,21].

The antibacterial effects of the tetrazole and hydrazone derivatives (S1, S2, S7, S8, S12, and S14) against the staphylococcus aureus and pseudomonas aeruginosa gram-positive and gram-negative pathogens are displayed in (Table 4) in the appropriate ways. To screen for bacteria, nutrient agar, controls of Ciprofloxacin, Ampicillin, and Amoxicillin (1x10-1,1x10-2 g/m1), and solvent DMSO were utilized.

Young bacterial cultures suspension that matched 0.5 tube McFarland turbidity criteria (108 cfu/ml) were put to Muller-Hinton agar plates using sterile cotton brushes. 6mm-diameter wells in solidified agar were bored, and 50 l of each concentration were added .

As a control, dimethyl sulfoxide is also employed. After 24 hours of aerobic incubation at 37°C, the plates' inhibition zones around the wells were measured using a rule to determine their diameter (mm). There were three duplicates of each test run.

The antibacterial activity of the produced compounds [S1, S2, S4, S6, S11, S14] against Pseudomonas aeruginosa and Staphylococcus aureus, two different bacterial species, was evaluated using the agar diffusion technique.. According to the findings, several of the chemicals that were tested had microbiological activity against the tested bacteria. [S1, S2, S4, S14] chemicals have antibacterial properties. Figures (17–20) provide an assessment of the drugs' inhibitory activity.

6-Conclusion:

The results showed that hydrazone derivatives were more active against bacteria than tetrazole derivatives in terms of biological activity.

7- The stereochemistry of some synthetic substances that is the most stable [21]:

Using the 2016 edition of the chem Draw professional 16.0 program, some of the produced compounds [S_1-S_{14}] were examined at the lowest energy level, as shown in Fig. (21-34).

Table 1- The substances' physical characteristics [S_3-S_{14}]

Comp. No.	R	Molecular Formula/ M.Wt g/mol	Color	M.P. (°C)	Yield (%)	R_f	T.R hour
S_3	Cl	$C_{28}H_{20}N_4O_2Cl_2$ 515.39	Yellowish white	-212 208	71	0.72	**7**
S_4	Br	$C_{28}H_{20}N_4O_2Br_2$ 604.30	Light yellow	-227 225	85	0.93	**6**
S_5	NO_2	$C_{28}H_{20}N_6O_6$ 536.50	Light orange	-225 223	60	0.79	**6**
S_6	$N(CH_3)_2$	$C_{32}H_{32}N_6O_2$ 532.65	Red	-221 219	75	0.87	**7**
S_7	CH_3	$C_{30}H_{26}N_4O_2$ 474.56	Yellow	-213 211	84	0.90	**6**
S_8	OH	$C_{28}H_{22}N_4O_4$ 478.51	Orange	-230 228	71	0.87	**7**
S_9	Cl	$C_{28}H_{22}N_{10}O_2Cl_2$ 601.45	Light Yellow	-279 277	90	0.95	**6**
S_{10}	Br	$C_{28}H_{22}N_{10}O_2Br_2$ 690.36	Light brown	-207 205	75	0.80	**6**
S_{11}	NO_2	$C_{28}H_{22}N_{12}O_6$ 622.56	Yellow	-229 227	78	0.68	**5**
S_{12}	$N(CH_3)_2$	$C_{32}H_{34}N_{12}O_2$ 618.71	Light brown	-230 228	65	0.65	**6**
S_{13}	CH_3	$C_{30}H_{28}N_{10}O_2$ 560.62	White	-276 274	80	0.83	**6**
S_{14}	OH	$C_{28}H_{24}N_{10}O_4$ 564.57	Deep yellow	-218 214	70	0.79	5

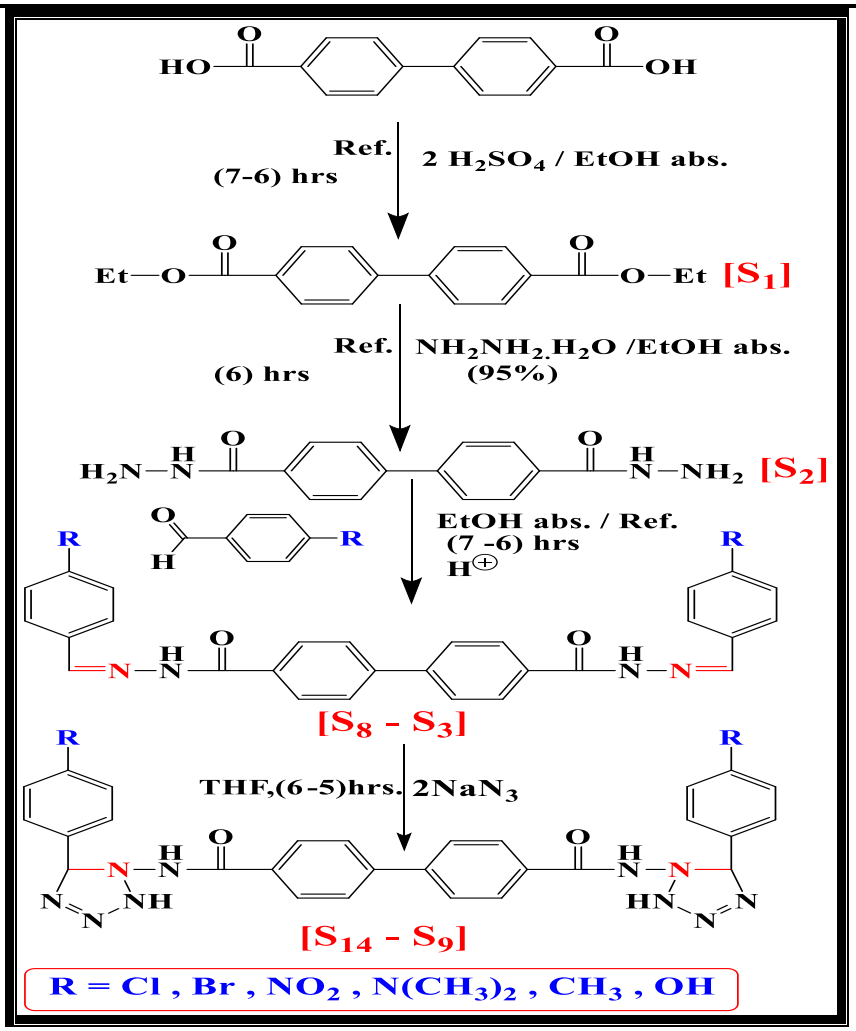
Table 2: FT-IR & UV-Vis spectral data of hydrazones [S_1-S_8].

Comp. No.	λ max1 λ max2 EtOH nm	R	IR (KBr) cm^{-1} ν (C-H) ν Arom. νAliph. Sym. /asy.	ν (C=O) Amid ν (N-H)	ν(C=N)	ν (C=C) Arom.	ν(C-N) ν (N-N)	Others
S_1	256 323	-----	3016 2816 2947	1735 ------	-----	1531 1579	----- -----	-----
S_2	255 353	-----	3032 2816 2947	1668 3149	-----	1581 1618	1531 1093	
S_3	261 393	Cl	3024 2839 2945	1676 3155	1631	1523 1597	1209 1107	(844) υ (C-Cl)
S_4	227 322	Br	3030 2891 2912	1676 3101	1620	1579 1512	1240 1105	(987) υ (C-Br)

S_5	227 322	NO_2	3010 2899 2945	1680 3195	1630	1570 1585	1214 1118	NO_2 υSmy. 1322 υAsmy. 1584
S_6	218 390	$N(CH_3)_2$	3024 2839 2945	1676 3156	1631	1523 1597	1209 1107	-------
S_7	239 305	CH_3	3028 2867 2938	1690 3201	1626	1545 1589	1287 1137	-------
S_8	217 370	OH	3101 2848 2981	1681 3200	1651	1579 1597	1251 1105	(3480) υ (OH)

Table 3: Data on the FT-IR and UV-Vis spectrum of tetrazole [S_9-S_{14}].

			IR (KBr) cm^{-1}					
Comp. No.	**λmax_1 λmax_2 EtOH nm**	**R**	**ν (C-H) ν Arom. νAliph. Sym. /asy.**	**ν (C=O) Amid**	**ν N-(N) ν (N=N)**	**ν (C=C) Arom.**	**ν(C-N) ν (N-H) ν (N-H) tatrazole**	**Others**
S_9	261 393	Cl	3053 2806 2941	1672	1130 1452	1550 1610	1298 3211 3324	υ (C-Cl)(792)
S_{10}	217 370	Br	3014 2874 2914	1685	1109 1440	1573 1614	1246 3176 3369	υ (C-Br)(840)
S_{11}	227 322	NO_2	3010 2848 2918	1695	1105 1450	1512 1579	1251 3194 3346	NO_2 υSmy. 1346 υAsmy. 1415
S_{12}	227 322	$N(CH_3)_2$	3024 2839 2945	1676	1107 1442	1523 1597	1209 3156 3324	-------
S_{13}	242 317	CH_3	3080 2850 2918	1685	1101 1475	1566 1612	1265 3215 3308	-------
S_{14}	232 389	OH	3066 2823 2935	1672	1130 1430	1550 1610	1298 3211 3343	υ (3553) (OH)



Scheme (1): The scheme of Synthetic compounds

Table 4: Six heterocyclic compounds' growth inhibition zones against two pathogenic bacterial species were measured in millimeters.

Compounds NO.	*Conc. Mg per ml*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*
	0.1	*1.5*	*3.5*
S1	*0.01*	*1*	*2*
	0.001	*-*	*5*
	0.1	*3*	*2*
S2	*0.01*	*1*	*4*
	0.001	*1.5*	*5.5*
	0.1	*2*	*5*
S4	*0.01*	*1*	*3.5*
	0.001	*-*	*3*
	0.1	*4*	*2*
S6	*0.01*	*2*	*4*
	0.001	*2*	*1.5*
	0.1	*4*	*3.5*
S11	*0.01*	*2*	*3.5*
	0.001	*2*	*1*
	0.1	*1*	*4.5*
S14	*0.01*	*2.5*	*1.5*
	0.001	*1*	*1.5*

DMSO (Control)	*0.00*	*0.00*	*0.00*
Amoxicillin	*26*	*45*	*24*
Ampicillin	*25*	*39*	*52*

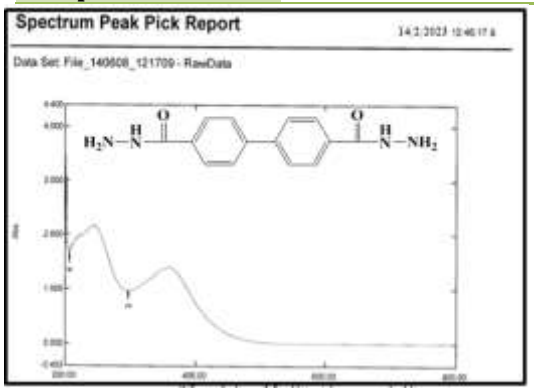


Fig.(2) ultraviolet-visible spectrum [S_2]

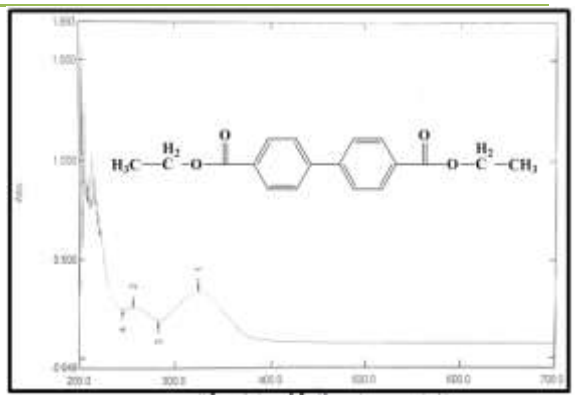


Fig.(1) ultraviolet-visible spectrum [S_1]

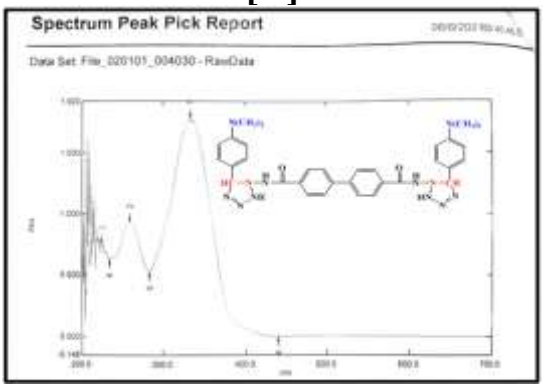


Fig.(4) ultraviolet-visible spectrum [S_{12}]

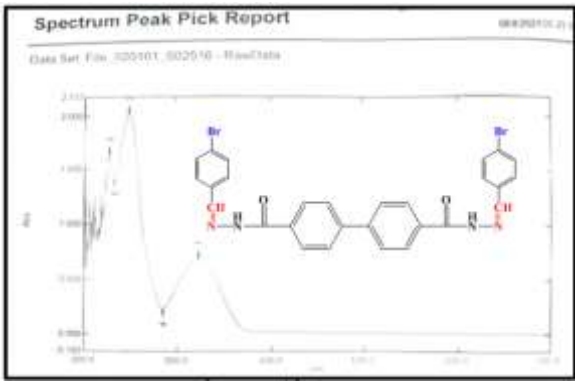


Fig.(3) ultraviolet-visible spectrum [S_4]

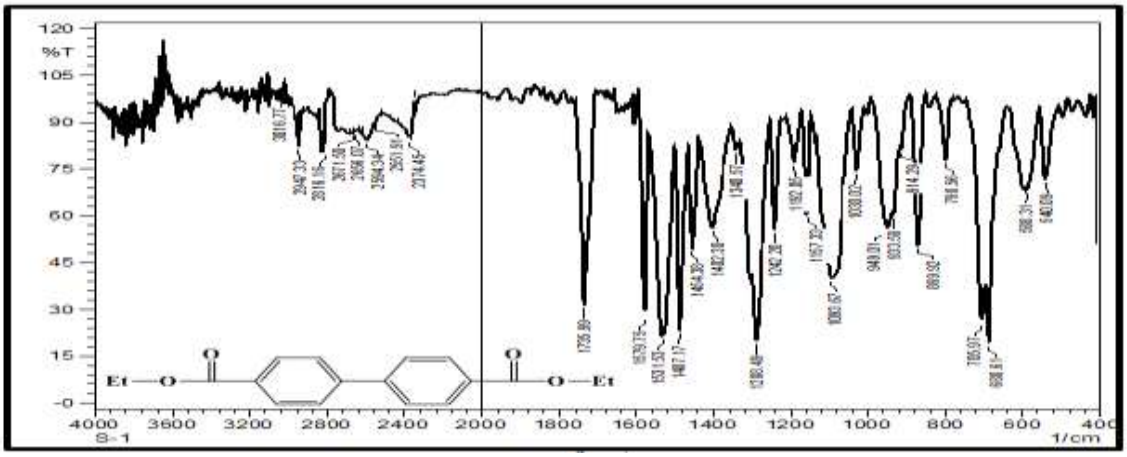


Fig. (5) FTIR spectrum **[S_1]**

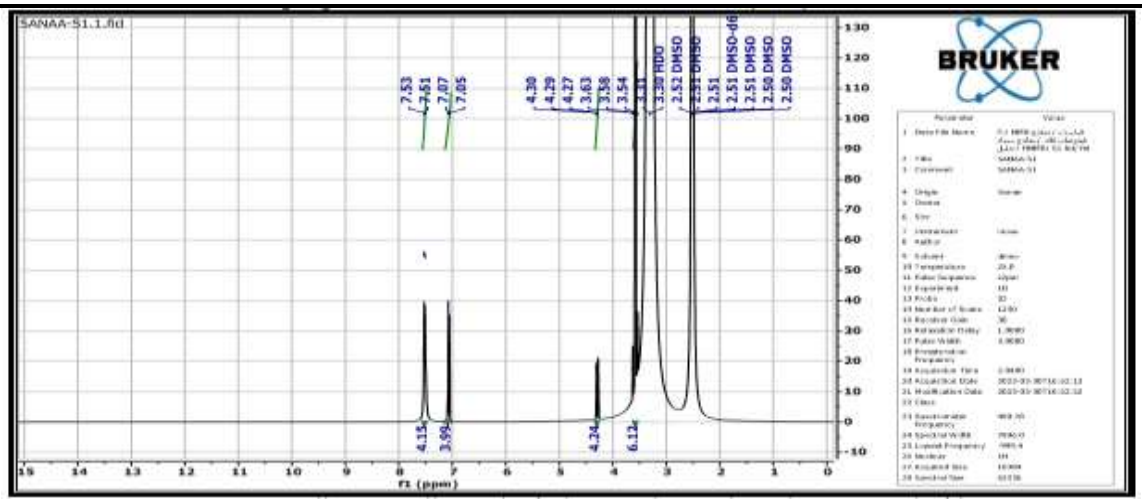


Fig.(6) ^{1}H-NMR spectrum [S_1]

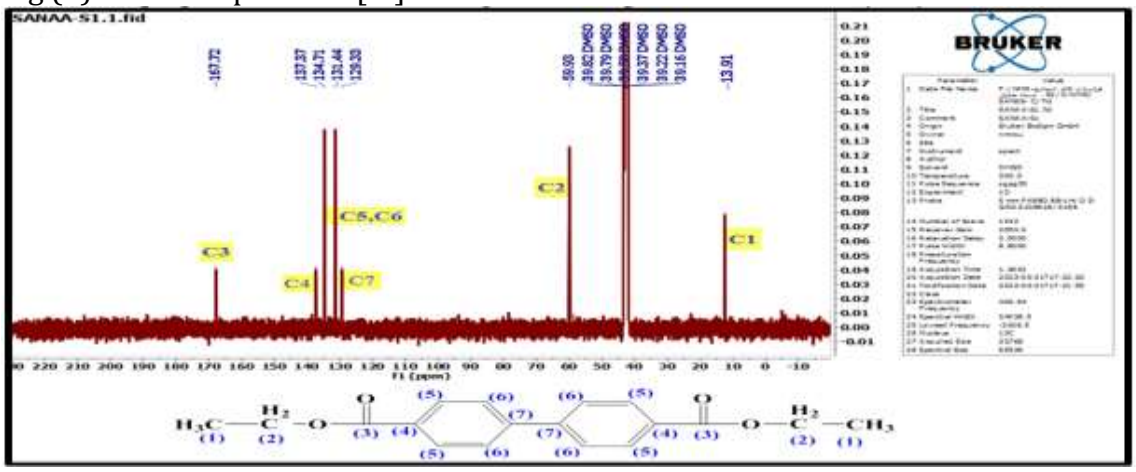


Fig. (7) ^{13}C-NMR spectrum [S_1]

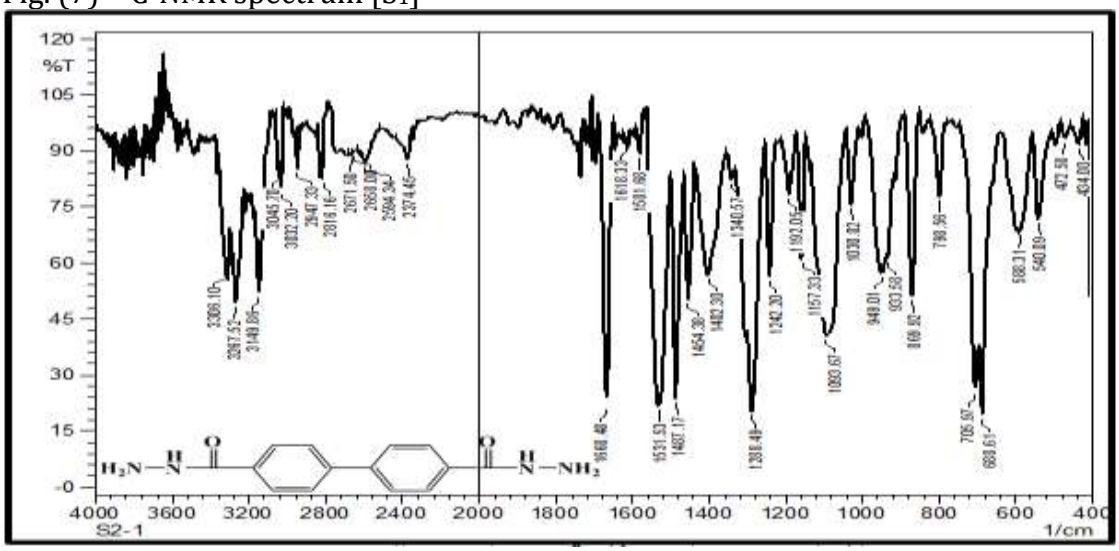


Fig. (8) FTIR [S_2]

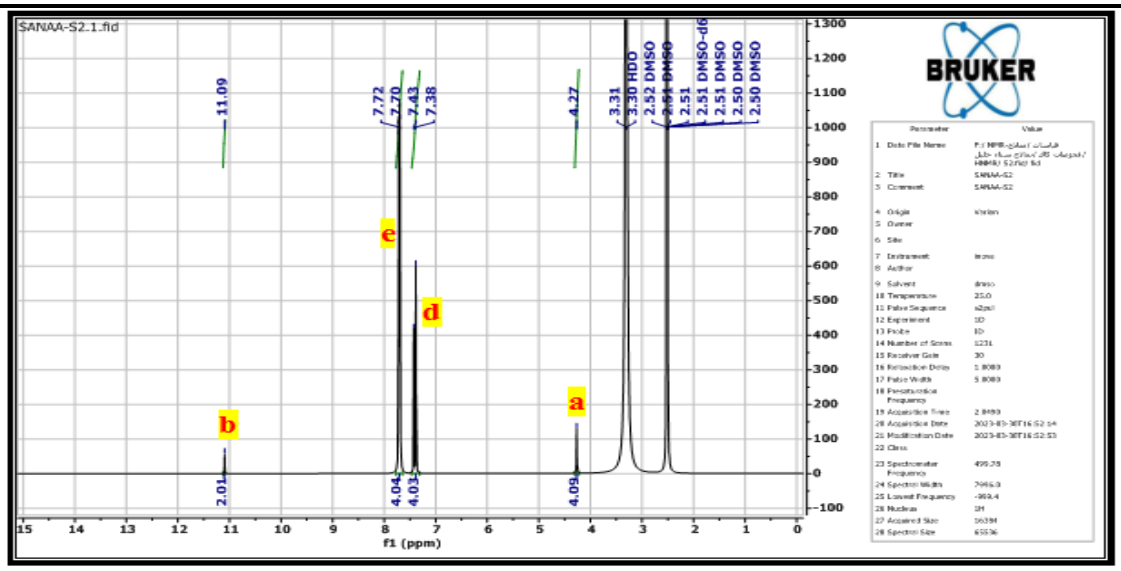
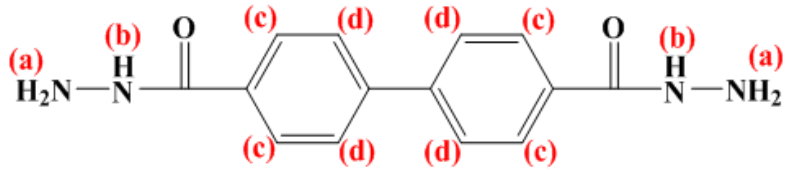


Fig.(9) ^{1}H-NMR [S_2]



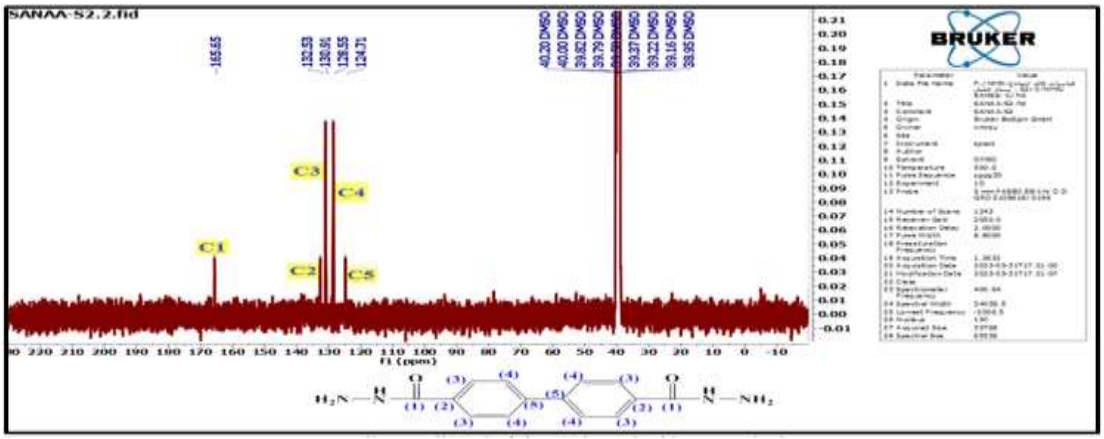


Fig. (10) ^{13}C-NMR spectrum [S_2]

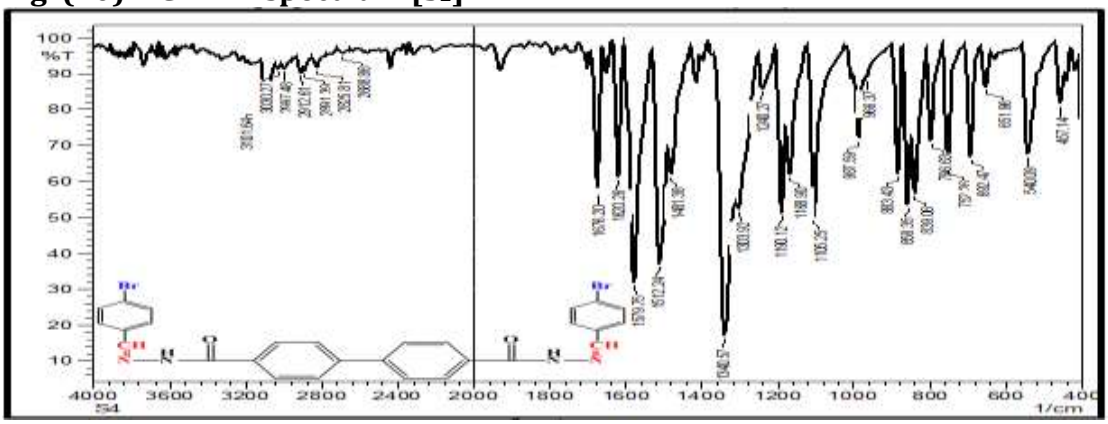


Fig. (11) FTIR [S_4]

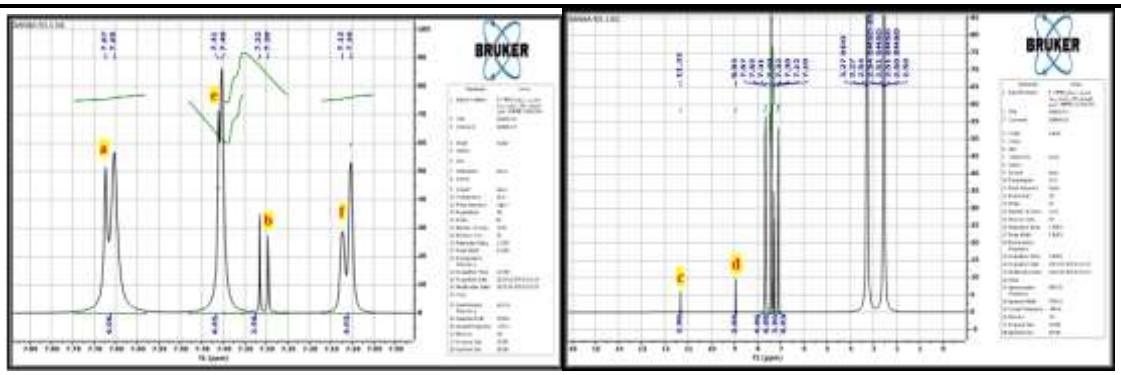
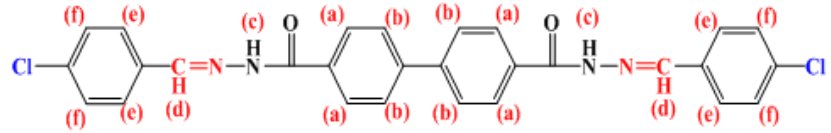


Fig.(12) ^{1}H-NMR [S_3]



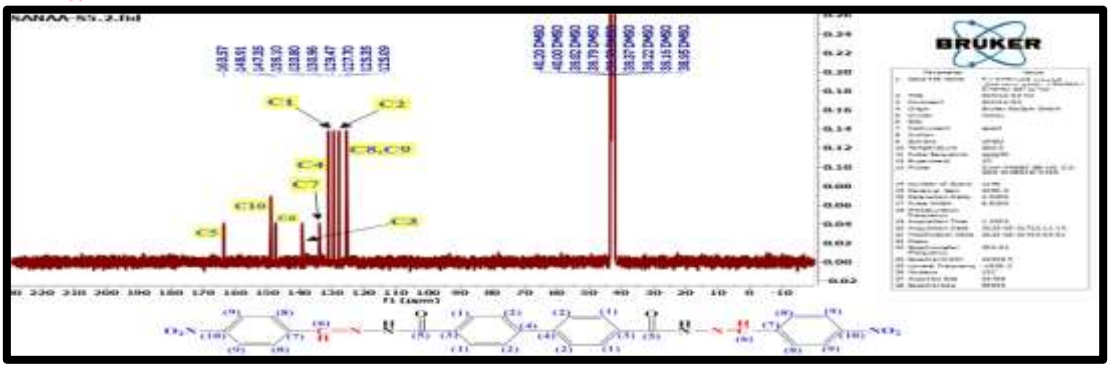


Fig. (13) ^{13}C-NMR [S_5]

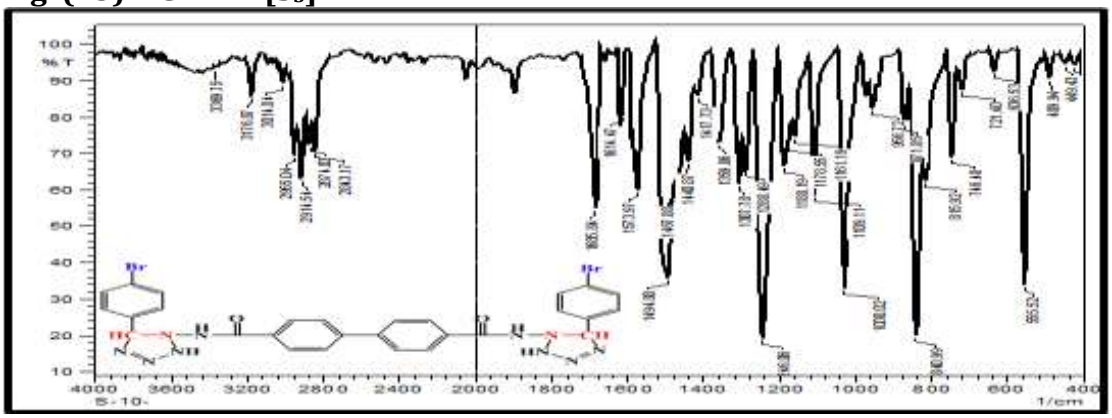


Fig. (14) FTIR [S_{10}]

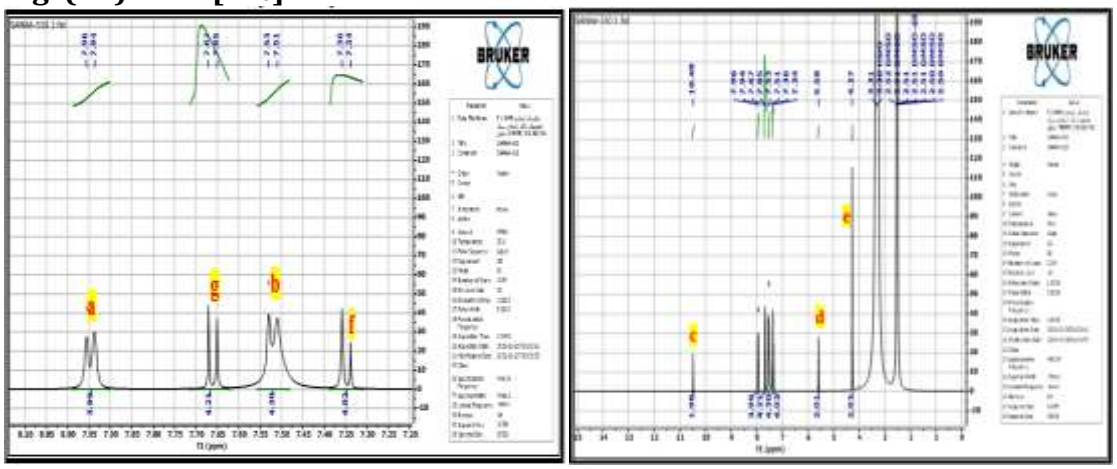
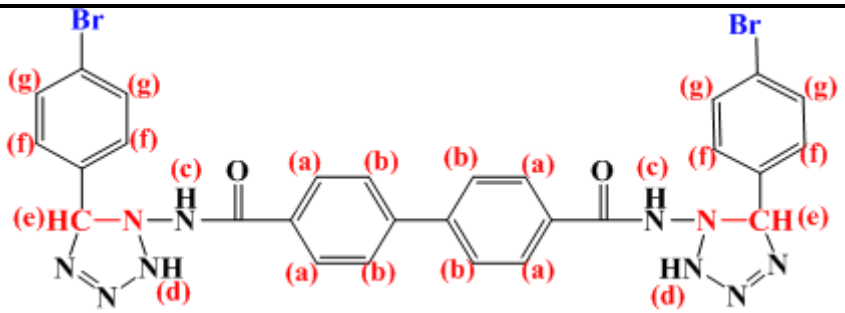


Fig. (15) ^{1}H-NMR of the compound [S_{10}]



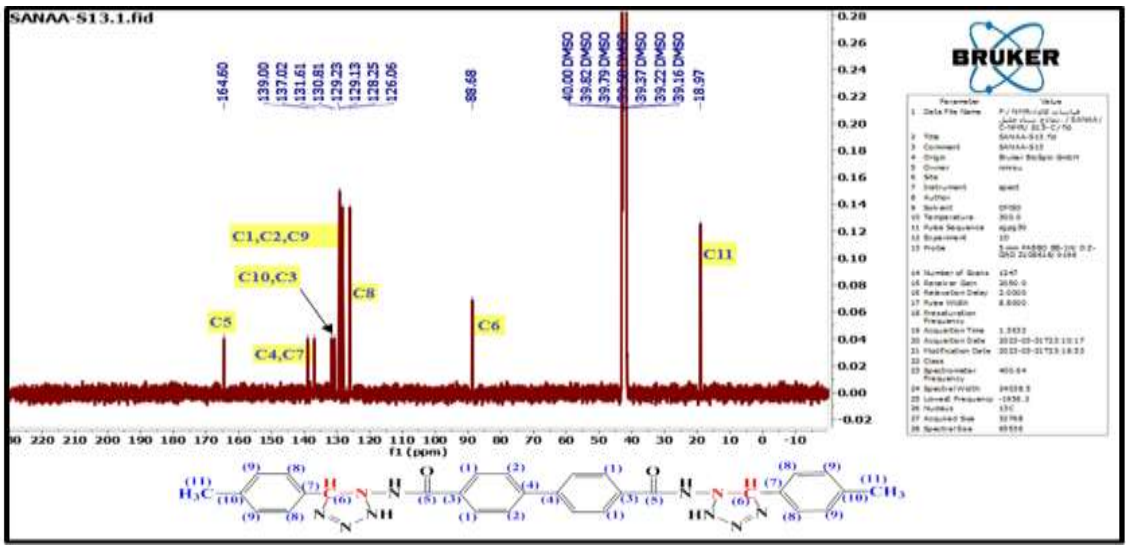


Fig. (16) ^{13}C-NMR [S$_{13}$]

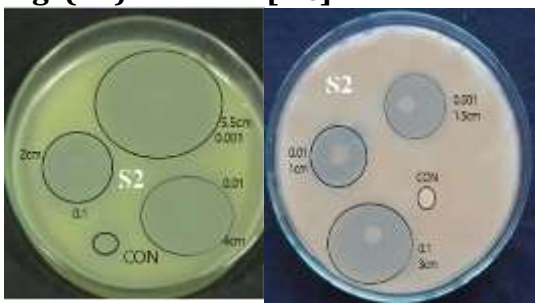


Fig. (18) Pseudomonas aeruginosa and staphylococcus aureus are two bacteria that the chemical [S2] inhibits.

Fig. (17) Pseudomonas aeruginosa and staphylococcus aureus are two bacteria that the chemical [S1] inhibits.

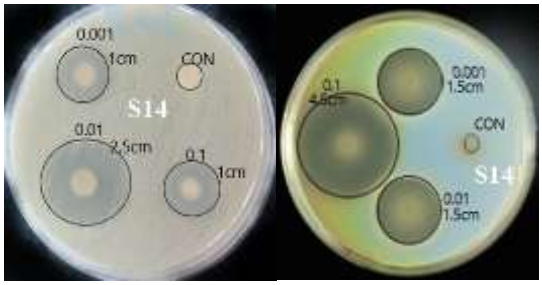


Fig. (20) Pseudomonas aeruginosa and staphylococcus aureus are two bacteria that the chemical [S14] inhibits.

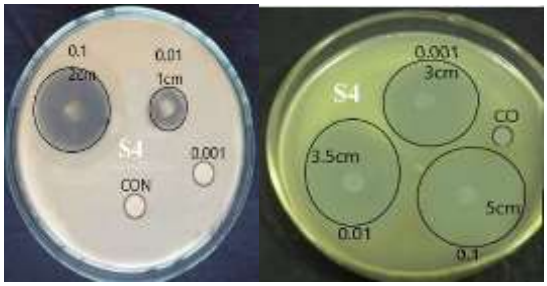


Fig. (18) Pseudomonas aeruginosa and staphylococcus aureus are two bacteria that the chemical [S4] inhibits.

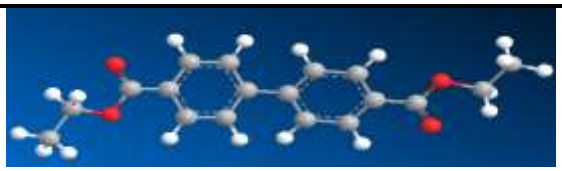
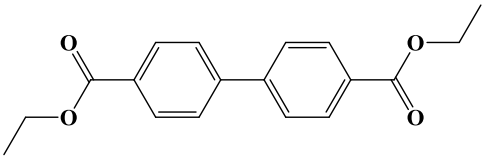



Fig. (21) the molecule with energy structure lower [S_1]

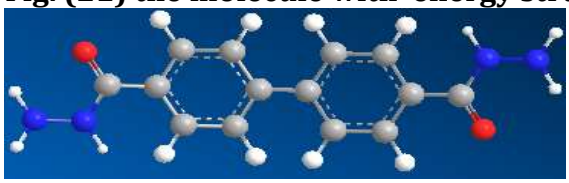
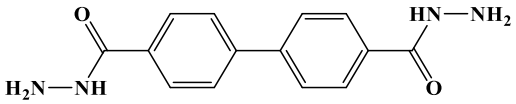



Fig. (22) the molecule with energy structure lower [S_2]

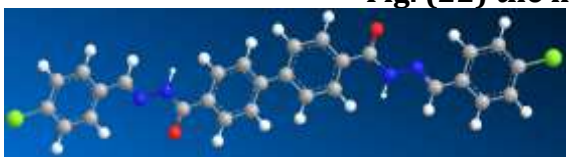
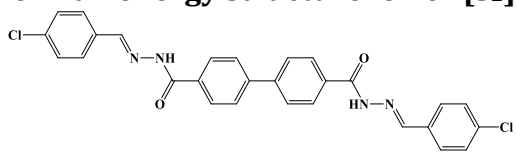



Fig. (23) the molecule with energy structure lower [S_3]

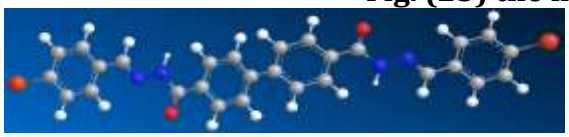
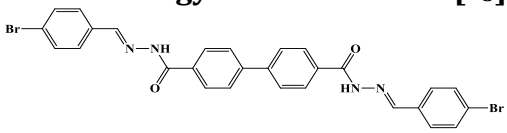



Fig. (24) the molecule with energy structure lower [S_4]

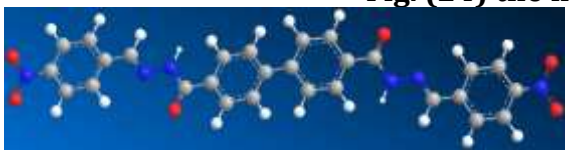
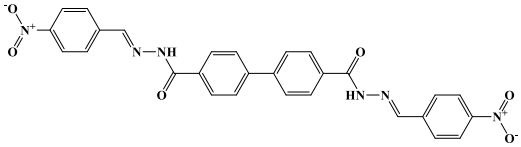



Fig. (25) the molecule with energy structure lower [S_5]

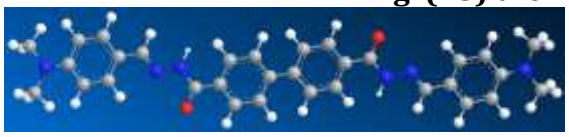
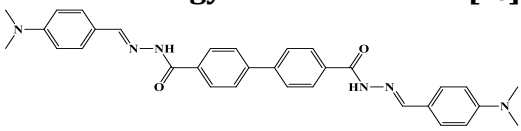



Fig. (26) the molecule with energy structure lower [S_6]

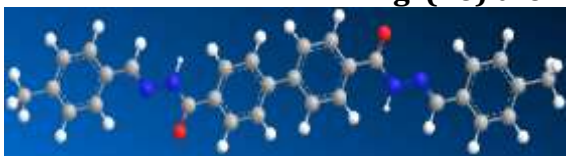
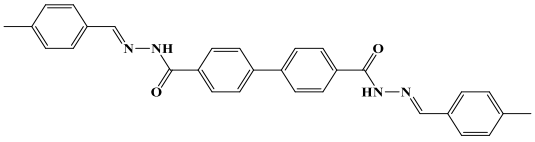



Fig. (27 the molecule with energy structure lower [S_7]

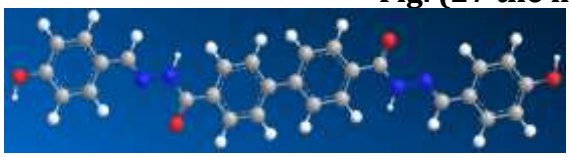
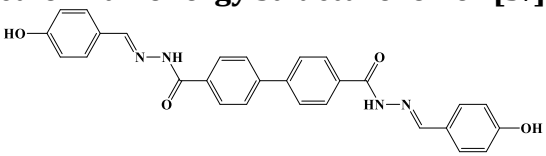



Fig. (28) the molecule with energy structure lower [S_8]

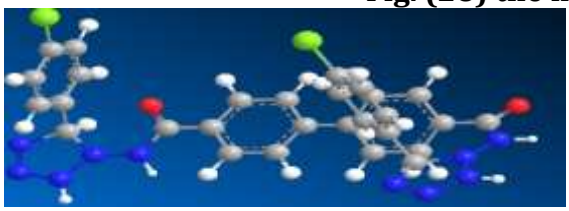
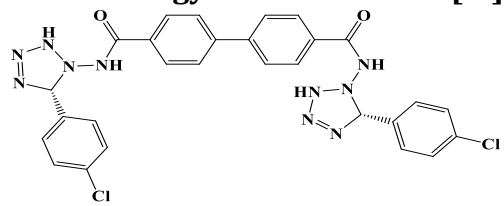



Fig. (29) the molecule with energy structure lower [S_9]

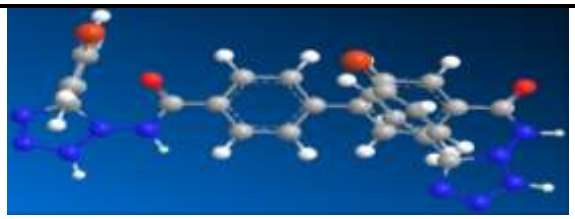
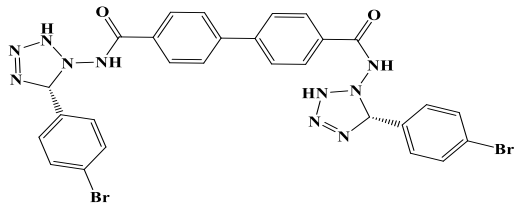



Fig. (30) the molecule with energy structure lower [S10]

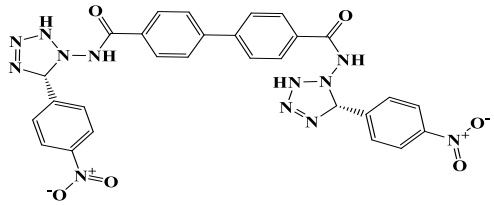



Fig. (31) the molecule with energy structure lower [S11]

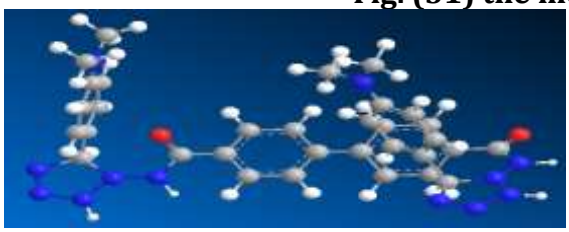
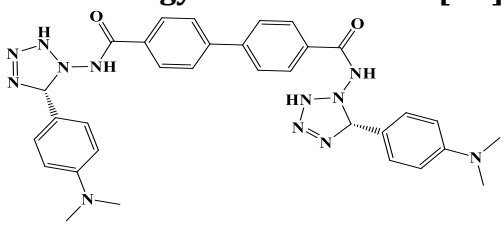



Fig. (32) the molecule with energy structure lower [S12]

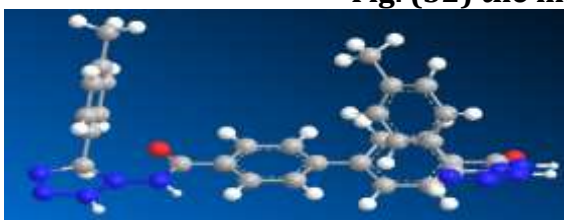
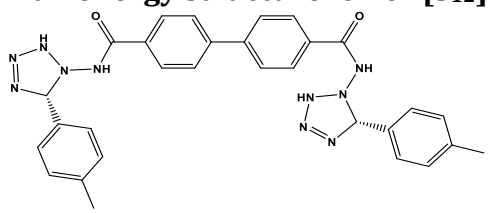



Fig. (33) the molecule with energy structure lower [S13]

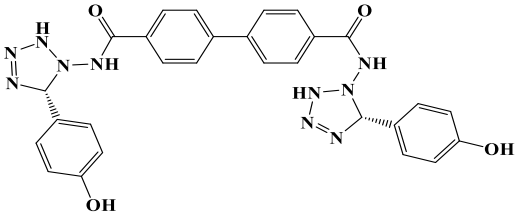



Fig. (34) the molecule with energy structure lower [S14]

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