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Synthesis and study of the biological activity and molecular Docking of 2-hydrazinobenzothiazole derivatives

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ABSTRACT

In this study, 2-hydrazineylbenzothiazole was synthesized by reacting 2-Mercaptobenzothiazole with N_2H_4 in ethanol as a solvent. All structures were characterized using spectroscopic techniques such as FT-IR, ^{1}H-NMR, and ^{13}C-NMR. The molecular docking showed the inhibitory activity of the synthesized compounds (B1, B2) and (T1, T2) in the activity of the enzyme lactate dehydrogenase (LDH). All Schiff base and tetrazole derivatives showed enzyme inhibitory activity. The anticancer activities of the synthesized compounds were evaluated against MCF-7 strains of human breast cells.

Keywords: 2-hydrazinobenzothiazole, Anticancer, Antibacterial, Molecular Docking.

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INTRODUCTION

Tetrazole is a heterocyclic organic compound that Consists of a five-membered ring. It has four nitrogen atoms and one carbon atom in the same ring. [25] Tetrazole exhibits tautomerism Figure 1 [3].

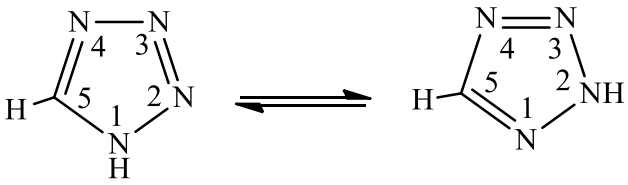

Figure (1) 1H- and 2H-tautomers of tetrazole

The tetrazole molecule has the highest proportion of nitrogen among stable unsubstituted heterocyclic systems, accounting for 80 percent of its total mass [1]. Despite its high nitrogen ratio, tetrazole and the majority of its derivatives remain stable when heated, irradiated with microwaves, or in the presence of other chemical reagents (oxidants, acids, bases, alkylating agents, dienophiles, etc.).[5] The substance is often a white solid that can dissolve in water and ethanol but is extremely difficult to dissolve in ether.[12,8] Tetrazole has weakly acidic characteristics in solutions and has an acid dissociation constant (pKa) of 4.89, which is comparable to acetic acid. [14] Due to its significance in both biological and industrial activity, researchers have given tetrazole compounds a lot of attention. The tetrazole ring's biological activity also increases dramatically. [13] Making tetrazole derivatives has recently been their

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focus. [23] Tetrazoles have many biologically important properties, such as hypotensive, antimicrobial, antiviral, antiallergic, and antitumor activities. [16]

Benzothiazoles and their derivatives are considered as nuclei in the preparation of many organic and pharmaceutical compounds. [19] Benzothiazole derivatives have been used as antibacterial and anticancer agents [20,6] anti-inflammatory [21,22], antiparasitic [17], and antioxidant [4] activities. The idea of preparing a derivative of both tetrazole and benzothiazole and evaluating their biological activity may seem interesting.

Molecular docking is used in drug screening and design to determine how well two molecules bind to one another and forecast how chemicals will interact with biological targets. This technique predicts the interactions between proteins, small molecules, and other compounds. Based on how they seem and how much energy they emit, ligands and receptors can be matched, according to the theory underlying it. [18] Finding the right way for small molecule ligands and protein receptors to bind together in the making of complex structures is the basis for designing drugs and studying how they work.[10] In the present study, three Tetrazole derivatives were synthesized, and their Biological activity was evaluated and study molecular docking.

MATERIAL & METHODS

All of the chemicals were bought from Sigma-Aldrich. The melting points were found in an open capillary tube. The Tensor 27 Bruker Co., Germany spectrometer was used to record infrared spectra FT-IR, range (4000- 600 cm^{-1}).

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The 1HNMR and 13CNMR spectra were taken with a Bruker Ultershield 400MHz NMR spectrometer, Co., Germany, and the DMSO-d6 was used as a solvent. The chemical shifts are given as values in parts per million (ppm).

General procedure for Synthesis 2- hadrazinayl benzothiazole (A)[7]

2-mercaptobenzothiazole (0.06mole, 10g) was dissolved in (0.06mole, 30 ml) of Hydrazine hydrate, the mixture was refluxed for 6 hours. The precipitate was then cooled, filtered, and recrystallized from the ethanol. It has the chemical formula ($C_7H_7N_3S$), is beige in color, and has an 85% yield.

General procedure for Synthesis 2- arylidene-hydrazinobenzothiazole (B1-B3)

A combination of compound (A) (0.03mol, 5 g) dissolved in (20ml) of ethanol absolute and (0.03mol) of different aldehydes derivatives in the presence of drops of glacial acetic acid were refluxed for (6 hours). The product was precipitated and purified by recrystallization from ethanol to give a pure product. The table (1) shows some physical properties of the synthesized compounds (B1-B3).

TABLE (1) Some physical properties of the synthesized compounds (B1-B3)

Com. Symbol	Yields			M.P. ^{O}C	Color
	Formula	Mol. Wt.	%		
B_1	$C_{14}H_{10}FN_3S$	271.31	66	232-235	Yellow
B_2	$C_{15}H_{13}N_3OS$	283.35	71	240-243	Brown
B_3	$C_{14}H_{10}BrN_3S$	332.22	77	222-225	Pale yellow

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General procedure for Synthesis of Tetrazole Derivatives (T1-T3)

A combination of compounds (B1-B3) (0.01mol, 2 g) dissolved in (15ml) of 1-4 dioxane and Sodium azide (0.001mol, 0.1 g) were refluxed for (10 hours) in a water bath at 50 ^{o}C. Upon treatment of the reaction mixture with crushed ice, the product was obtained as a solid which was purified by recrystallization from ethanol to give a pure product. Table (2) shows some physical properties of the synthesized compounds (T1-T3).

TABLE (2) Some physical properties of the synthesized compounds (T1-T3)

Com. Symbol	Yields			M.P. ^{O}C	Color
	Formula	Mol. Wt.	%		
T_1	$C_{14}H_{11}FN_6S$	314.34	73	240-243	Dark blue
T_2	$C_{15}H_{14}N_6OS$	326.38	65	261-263	Light blue
T_3	$C_{14}H_{11}BrN_6S$	375.25	80	251-254	Dark blue

Anti-Bacterial activity

Using the good diffusion method on Muller-Hinton agar, a test was done in the lab to observe the effects of synthesized tetrazole compounds. Five micrograms of synthesized tetrazole compounds were dissolved in DMSO and put in 6 mm wells separately. After 18 hours of incubation at 37 °C, the size of the zone of inhibition was measured in millimeters.

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Molecular Docking Study

To find out more about how lactate dehydrogenase works with the most reactive compound, autodock_vina was used to do a molecular docking study. The PDB (protein data bank) was used to get the 3D crystal structures of lactate dehydrogenase (www.rcsb.org). Chem Bio Draw Ultra (v16.0) was used to make the structures of the ligands.

RESULTS & DISCUSSION

Synthesis and characterization of 2- hadrazinayl benzothiazole (A)

The 2-hadrazinayl benzothiazole (A) was synthesized by reaction of 2-mercaptobenzothiazole and Hydrazine hydrate, (Scheme 1), FTIR spectrum for compounds (A) showed the absence of SH group within stretching vibration bands and revealed a sharp bands at 3317, 3201cm^{-1} which were attributable to the (NH_2) group, and strong absorption at 3056 cm^{-1} attributable to the Aromatic (C-H).

The ^{1}H-NMR spectrum of compound (A) showed a singlet signal at δ 9.01 (s, 1H) ppm was attributed to protons of the secondary amine, the two doublet and two triplet signals at δ7.66, δ7.30, δ7.18, δ6.96 (4H) respectively, were attributed to protons of the phenyl ring, and one singlet signal at δ5.05 (s, 2H) ppm, which is attributed to amine protons.

The ^{13}C-NMR spectrum of compound (A) was comprised of multiple signals within the range δ108.85–121.39ppm, which was attributed to the aromatic carbons. A signal at 125.75 ppm represents C-S group, while the

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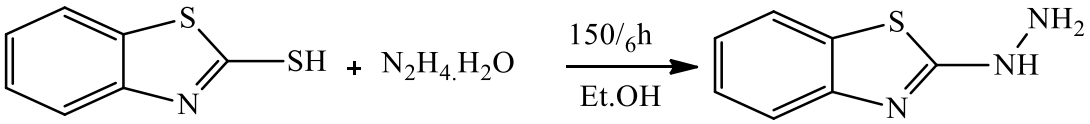
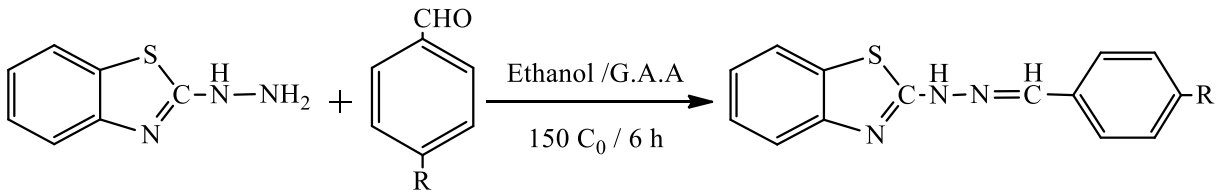
chemical shift δ157.52ppm representing C-N group. Finally, the chemical shift δ174.91ppm represents the carbon atom of the five-membered ring.



Scheme 1: Prepare Compound (A)

Synthesis and characterization of 2-arylidene-hydrazinobenzothiazole derivatives (B_1-B_3)

2-arylidene-hydrazinobenzothiazole derivatives (B1-B3) were synthesized following the reaction of compound (A) with different aldehydes derivatives according to the following (Scheme 2) [2]. The mechanism of imine formation is thoroughly elucidated in the literatures.



B_1, R= 4-F, B_2, R= 4-OCH_3, B_3, R= 4-Br

Scheme 2: Prepare Compounds B1-B3

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The structures of the synthesized 2-arylidene-hydrazinobenzothiazole were confirmed by their FT-IR spectra, which showed the disappearance of the characteristic absorption frequencies of both (C=O) at (1720-1740) cm^{-1} and (-NH_2) at (3317-3201) cm^{-1} of the aldehyde and the primary amine respectively. The stretching absorption bands of azomethine group (C=N) showed within the range (1624-1625) cm^{-1}, the important peaks are listed in Table (3).

TABLE (3) IR characteristic absorption in cm^{-1} of compounds B_1-B_5

Comp. Symb.	-R	νC-H arom	νNH	νC=N	Other
B_1	F	3094	3210	1624	675 C-F 1494-1471 C=C_{ring}
B_2	OCH_3	3072	3191	1625	3958, 1396 CH_3 aliphatic 1589-1489 C=C_{ring}
B_3	Br	3099	3278	1625	499 C-Br 1608-1451 C=C_{ring}

The ^{1}H-NMR spectra of the prepared compounds (B1-B3) were comprised of a single signal at δ11.75, 12.14, 12.34ppm (s, 1H) respectively which ascribed to the secondary amine proton. The spectra showed singlet signals at δ8.12, 8.15, 8.65ppm (s, 1H) respectively which ascribed to the azomethine proton. The different signals within the range δ7.01–8.11ppm (m, 8H) attributed

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to the protons of the aromatic rings. The ^{1}H-NMR data for compounds B1-B3 are listed in table (4).

TABLE (4) ^{1}H-NMR spectra for compounds B_1-B_3

Comp.	NH	OCH_3	CH=N	Ar-H
B1	1 H s	……..	1 H s	8 H m
	11.75		8.15	7.09-7.77
B2	1 H s	3 H s	1 H s	8 H m
	12.14	3.81	8.65	7.01-8.11
B3	1 H s	……	1 H s	8 H m
	12.34		8.12	7.10-7.78

The ^{13}C-NMR spectra of the prepared compounds were comprised of signals within the range δ166.73-169.89ppm, which attributed to the carbon of azomethine. A several signals within the range δ118.34-135.31ppm were attributed to the aromatic carbons. The ^{13}C-NMR data for compounds B1-B3 are listed in table (5).

TABLE (5) ^{13}CNMR spectra for compounds B_1-B_3

Comp.	C-N	OCH_3	Ar-C
B1	166.73	…..	122.06-134.13
B2	169.89	38.28	122.06-135.31
B3	167.60	…….	118.34-134.13

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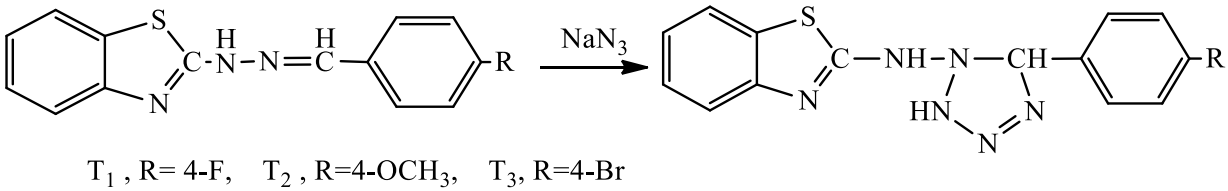
Synthesis and characterization of tetrazole

Tetrazole derivatives (T1-T3) were synthesized by the reaction of (B1-B3) and Sodium azide according of the Scheme (3).



T_1 , R= 4-F, T_2 , R=4-OCH_3, T_3, R=4-Br

Scheme 3: Prepare Compounds T1-T3

The structures of the synthesized tetrazole derivatives (T1-T3) were confirmed by their FT-IR spectra. The disappearance of the characteristic absorption frequencies of azomethine (C=N) at 1624-1625cm^{-1}, and the appearance of characteristic absorption bands for tetrazole at 1292-1369cm^{-1} for -N-N=N-, as well as vibration extension bands for the tetrazole ring at 1571-1573cm^{-1}, evidence of tetrazole ring formation. The FTIR data are listed in Table 6.

Table (6) FTIR data (cm^{-1}) for T1-T3 compounds

Comp.	ν C-$H_{ar.}$	ν N-H	N-N=N	Tetrazole bending Vibrations			ν(Tetrazole Ring)
T1	3002	3201	1292	1029	1071	1110	1573
T2	3066	3197	1369	1022	1068	1128	1571
T3	3053	3211	1340	1026	1069	1111	1571

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The ^{1}H-NMR spectra of the prepared compounds (T1-T2) were showed the singlet signals within the range δ12.39, 12.19, 12.42ppm (s, 1H) respectively which ascribed to the protons of the secondary amine, the singlet signals at δ8.69, 8.45, 8.71ppm (s, 1H) respectively attributed to proton of (NH) of tetrazole ring, the spectra showed the singlet signals at δ8.14, 8.19, 8.12ppm (s, 1H) respectively attributed to proton of (CH) of tetrazole ring, the signals within the range δ7.03– 8.71ppm (m, 8H) were attributed to the protons of the aromatic ring. The ^{1}H-NMR data for compounds T1-T3 are shown in table (4).

TABLE (7) ^{1}H-NMR spectra for compounds T_1-T_3

Comp.	NH	NH ring tetrazole	CH	OCH_3	Ar-H
T1	S, 1H 12.39	S, 1H 8.69	S, 1H 8.14	……..	m, 8H 7.10-7.95
T2	S, 1H 12.19	S, 1H 8.45	S, 1H 8.19	S, 3H 3.81	m, 8H 7.03-7.77
T3	S, 1H 12.42	S, 1H 8.71	S, 1H 8.12	……	m, 8H 7.10-7.78

The ^{13}C-NMR spectra of the prepared compounds were comprised of the single signals within the range δ159.23-167.59ppm which attributed to the N=C-N carbon. The signals within the range δ122.06-149.78ppm were attributed to the aromatic carbons. Tetrazole ring was comprised of a single signal within the range δ92.68- 94.23ppm. The ^{13}C-NMR data for compounds T1-T3 are shown in table (8).

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TABLE (8) ^{13}CNMR spectra for compounds T_1-T_3

Comp.	N=C-N	CH ring tetrazole	OCH_3	Ar-C
T1	164.47	93.22	…..	122.07-134.15
T2	159.23	122.14	36.26	122.14-134.31
T3	167.59	92.68	…….	122.06-149.78

Antibacterial activity

The antibacterial activity of both hydrazones and tetrazole derivatives was tested at different concentrations against all bacteria. The areas of inhibition were measured in mm and the results are shown in Table (9). The results of the antibacterial test indicate that the Tetrazole derivatives show great activity compared to the hydrazone derivatives. Where compounds B2, T1, and T2 showed the highest inhibition against *Klebsiella*, while B3 and T2 compounds showed the highest inhibition against and *Escherichia coli* Show the compounds T2 and T1, the highest inhibition against *Staphylococcus aureus*, and compound T1 showed the highest inhibition against *Streptococcus faecalis*, all that at minimum inhibitory concentration.

Table (9) Antibacterial activity data of prepared compounds

Bacteria	Zone Inhibition in (mm)						
	Conc. mg/l	B1	B2	B3	T1	T2	T3
Klebsiella pneumonia	0.01	19	20	18	22	19	-

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	0.001	18	17	15	20	18	-
	0.0001	16	17	13	18	17	-
Escherichia coli	0.01	17	18	18	19	18	14
	0.001	15	15	16	18	15	11
	0.0001	-	-	15	11	14	-
Staphylococcus aureus	0.01	17	18	-	19	20	20
	0.001	14	-	-	14	17	17
	0.0001	-	12	-	16	17	12
Streptococcus faecalis	0.01	18	18	18	20	18	-
	0.001	14	15	14	18	17	-
	0.0001	-	-	-	17	-	-

Anticancer Activity

The activity of the prepared compounds to inhibit cell growth against human breast cell lines (MCF-7) was measured, using cis-platin as a positive control. The effect of the compounds on the growth of MCF-7 was studied and recorded after 24 hours, and the calculated IC_{50} values were recorded (refer to Tables (10)) shown in (Fig. 2) the compound T1 showed IC_{50} values at 8.27 2.362mM, while the compound T3 showed the least inhibitory effect on the proliferation of cancer cells. When comparing the results of tetrazoles, we find that they have a higher activity than hydrazones, and this is consistent with the literature indicating that compounds containing heterocyclic rings such as tetrazoles are more active [9,11, 24].

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Table (10) IC_{50} values of (B2,B3,T1,T2,T3) against MCF-7 cell line

Compound	IC_{50} value (μM)
B2	89.87 ± 4.049
B3	102.2 ± 4.534
T1	28.27 ± 2.362
T2	38.58 ± 1.835
T3	41.51 ± 2.062
Cis-platin	4.45 ± 0.04

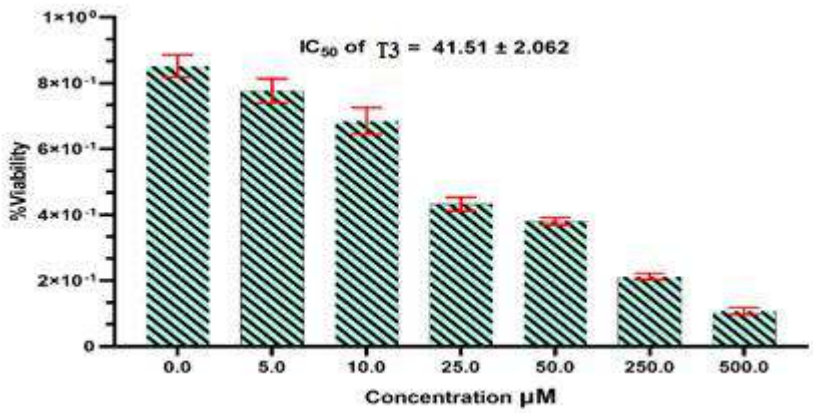

FIGURE (2) MCF-7 cell viability after treatment of compound T3 at different concentrations (μM). P value = 0.005 in each case

Results of molecular docking studies

Molecular docking studies of the prepared derivatives that act as inhibitors of the enzyme lactate dehydrogenase (LDH), gave different types of bonds with the amino acid residues in the active site of the enzyme lactate dehydrogenase (LDH), where the study showed that the derivative B2 interacts with the amino

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acid residues by Its composition is two types of bonds, a carbon-hydrogen bond, which links the ALA2 residues in the C chain located in the active site of the enzyme with the substituted methoxide group on the aromatic ring, and four Pi-Alkyl bonds, two of which link the PRO28 residues in the (A) chains, C, which is present in the active site of the enzyme with the electronic pairs of the aromatic ring of the compound, and two bonds linking the histidine residues ALA247 and histidine VAL243 in the B chain, which are present in the active site of the enzyme with the electronic pairs of the aromatic ring of the compound[15].

The study showed that the derivative B3 interacts with the amino acid residues that are present in the active site of the enzyme (LDH) by forming two types of bonds, a hydrogen bond, which links the residues of the amino acid GLY76 located in the active site of the enzyme with the hydrogen atom of the azomethine group at a distance of 2.45 Å, Four Pi-Alkyl bonds bind the amino acid residues ARG10, VAL11, LEU33, ILE95, which are located in the active site of the enzyme with the electronic pairs of the aromatic ring of the compound with a distance of 5.33,4.81,4.24,5.47 Å, respectively.

The derivative T2 reacts with the amino acid residues that are present in the active site of the enzyme (LDH) by forming two types of bonds, the first three hydrogen bonds linking the amino acid residues LYS225 located in the active site of the enzyme with the methoxide group substituted on the aromatic ring with a distance 2.85 Å, and the second bond linking the amino acid residue ASN229 in the active site of the enzyme with the hydrogen atom in the

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compound with a distance of 2.83 Å and the third bond linking the amino acid residue TYR230 in the active site of the enzyme with the hydrogen atom of the amino group of the heterocyclic five ring with a distance 2.39 Å, and four Pi-Alkyl bonds linking amino acid residues LYS225,ALA227.2(ARG10), which are located in the active site of the enzyme with the electronic pairs of the aromatic ring of the compound with a distance of 5.12,4.82,4.54,4.46 Å, respectively.

As for derivative T3, it reacts with the amino acid residues that are present in the active site of the enzyme (LDH) by forming two types of bonds, the first are two hydrogen bonds, the first linking the amino acid residue ASN229 in the active site of the enzyme with the hydrogen atom of the azomethine group with a distance of 2.80 Å, and the second which binds the amino acid residue TYR230 located in the active site of the enzyme with the hydrogen atom of the amine group of the heterocyclic five ring with a distance of 2.35 Å, and four Pi-Alkyl bonds link the amino acid residues ARG10, which is present in the active site of the enzyme with the electronic pairs of the aromatic ring of the compound and a distance of 4.81 Å. The table (11) shows the values of the docking score and the number and type of bonds for the prepared derivatives (B2, B3,T2,T3).

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TABLE (11) values of the docking score and the number and type of bonds for the prepared derivatives (B2,B3,T2,T3).

Comp. Symb.	RMSD	Docking Score	Hydrogen Bond	carbon-hydrogen bond	Pi-Alkyl
B2	0.044	-7.2	——	ALA2	PRO28 ALA247 VAL243
B3	0.028	-7.4	GLY76	——	ARG10 VAL11 LEU33 ILE95
T2	0.031	-8.7	LYS225 ASN229 TYR230	——	LYS225 ALA227 ARG10
T3	0.018	-8.1	ASN229 TYR230	——	ARG10

These interactions between the prepared organic derivatives and the amino acid residues located in the active site of the lactate dehydrogenase enzyme were also elucidated using 3D and 2D pictures, as illustrated in the figures below:

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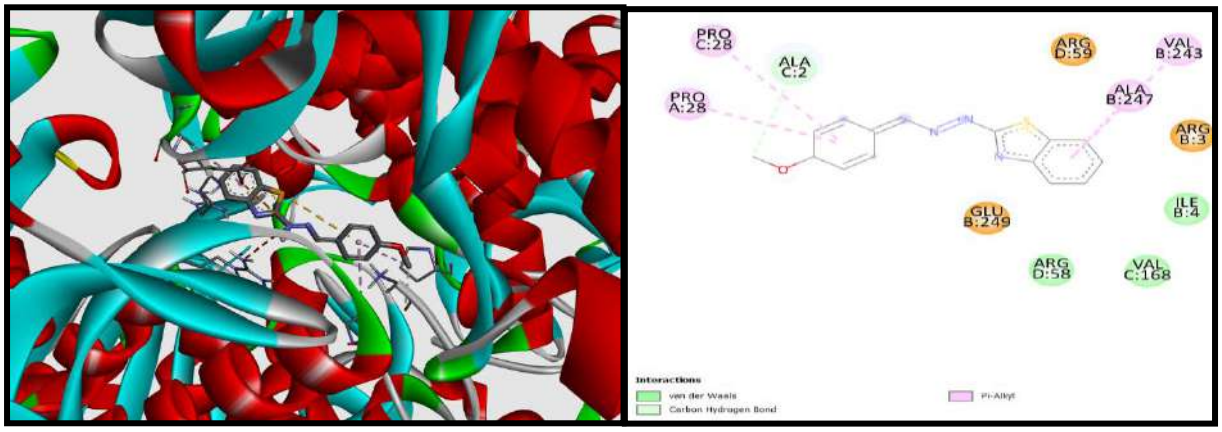

FIGURE (3) 2D,3D Interaction between B2 and LDH.

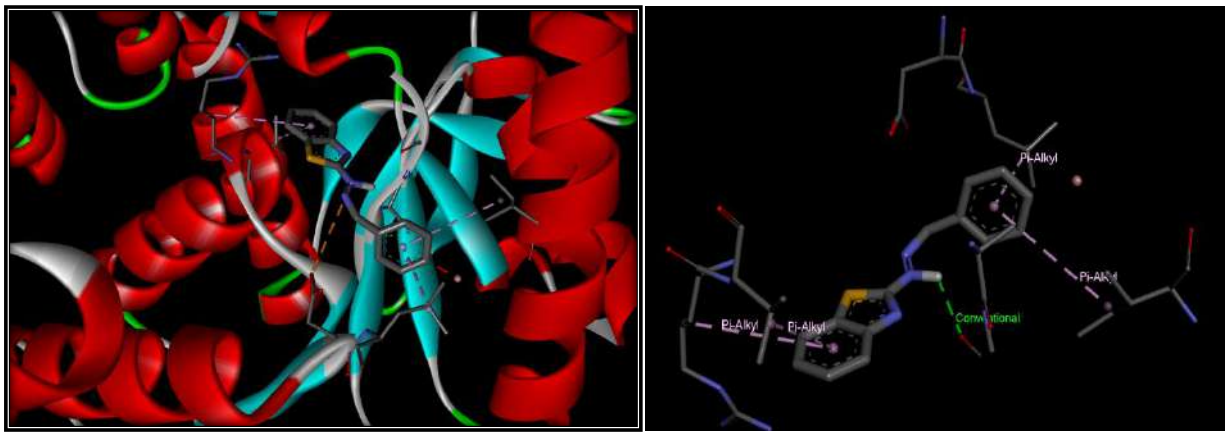

FIGURE (4) 2D,3D Interaction between B3 and LDH.

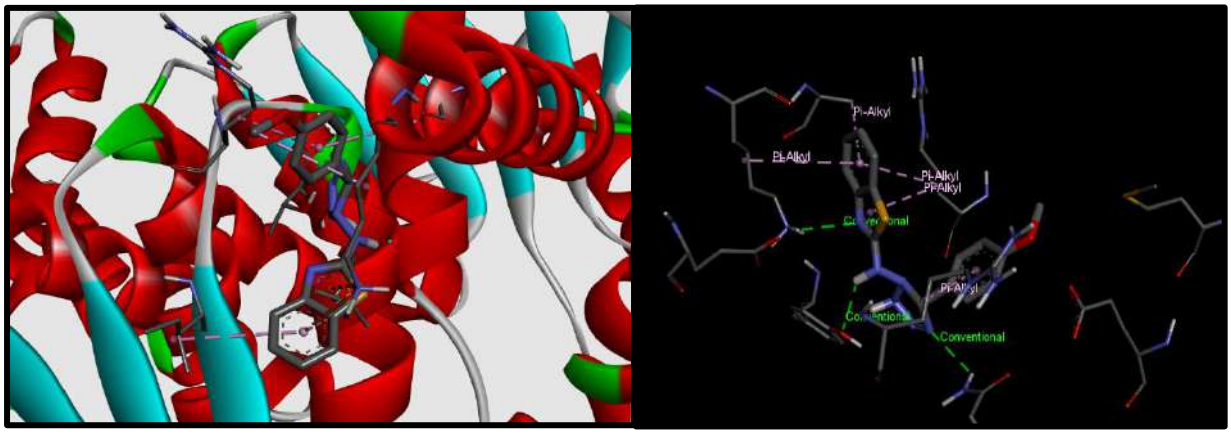

FIGURE (5) 2D,3D Interaction between T2 and LDH.

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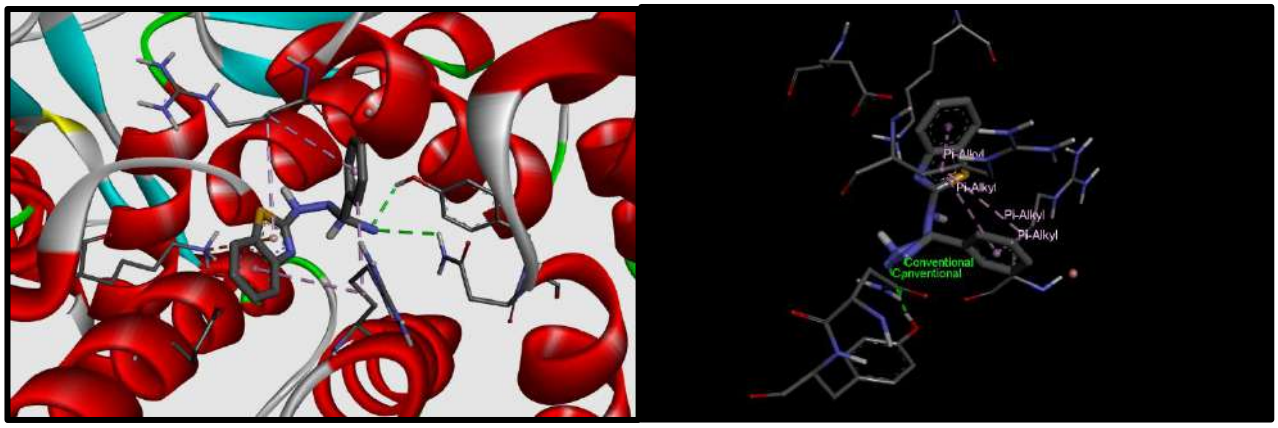

FIGURE (6) 2D,3D Interaction between T3 and LDH.

CONCLUSIONS

Three derivatives of hydrazones and their corresponding tetrazoles were prepared and characterized using spectroscopic and physical measurements, as the prepared compounds do not degrade or change color at laboratory temperatures. The effectiveness of the prepared compounds against four types of bacteria was evaluated, and the tetrazole compounds showed more significant activity than the hydrazones. Its efficacy against human breast cell lines (MCF-7) was also tested in comparison with cis-platin, compound T1 has good activity while T3 has limited activity. The ability of the prepared compounds to prevent and describe the type of interference between them and the cancer protein was also explored by knowing their association with the active side of the cancer proteins using molecular docking.

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تحضير ودراسة النشاط البيولوجي والارساء الجزيئي لمشتقات 2- هيدرازينوبنزوثيازول

سفانة سالم العزاوي [1، a] ، يسرى خلف الاسدي [1، b *]

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خلاصة

في هذه الدراسة ، تم تصنيع 2-هيدرازينيل بنزوثيازول عن طريق تفاعل 2-ميركابتوبنزوثيازول مع الهيدرازين في الإيثانول كمذيب. تم تشخيص جميع التراكيب باستخدام تقنيات التحليل الطيفي مثل FT-IR و ^{1}H-NMR و ^{13}C-NMR. وقد أظهر الارساء الجزيئي النشاط التثبيطي للمركبات المصنعة (B1، B2) و (T1، T2) في نشاط إنزيم اللاكتات ديهيدروجينيز (LDH). وأظهرت جميع مشتقات قاعدة شيف و تترازول نشاطًا مثبطًا للإنزيم. كما تم تقييم الأنشطة المضادة للسرطان للمركبات المصنعة ضد سلالات MCF-7 من خلايا الثدي البشرية.

الكلمات المفتاحية: 2-هيدرازينوبنزوثيازول ، مضاد للسرطان ، مضاد للبكتيريا ، الالتحام الجزيئي.

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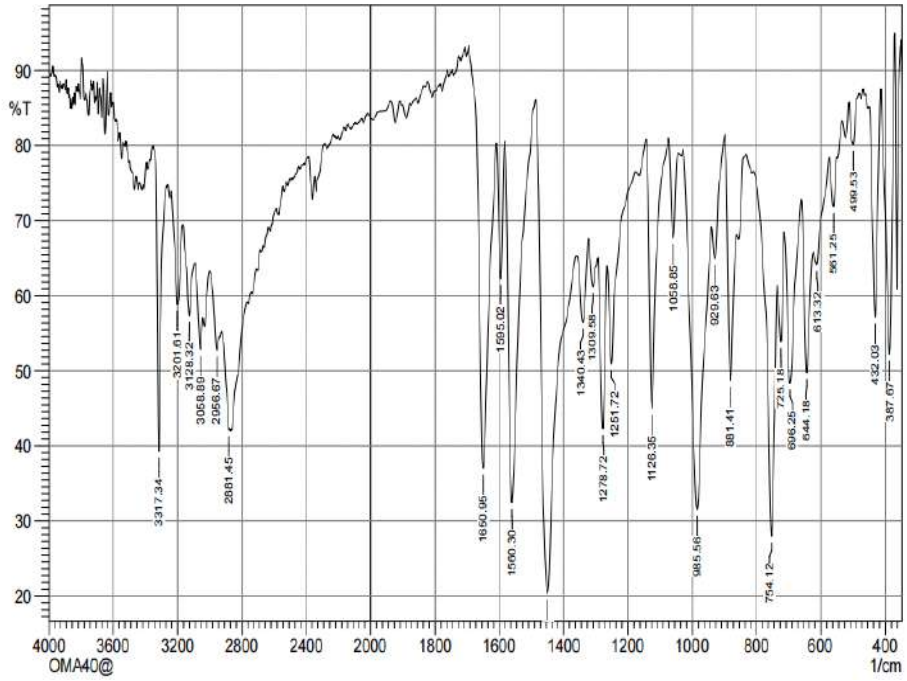
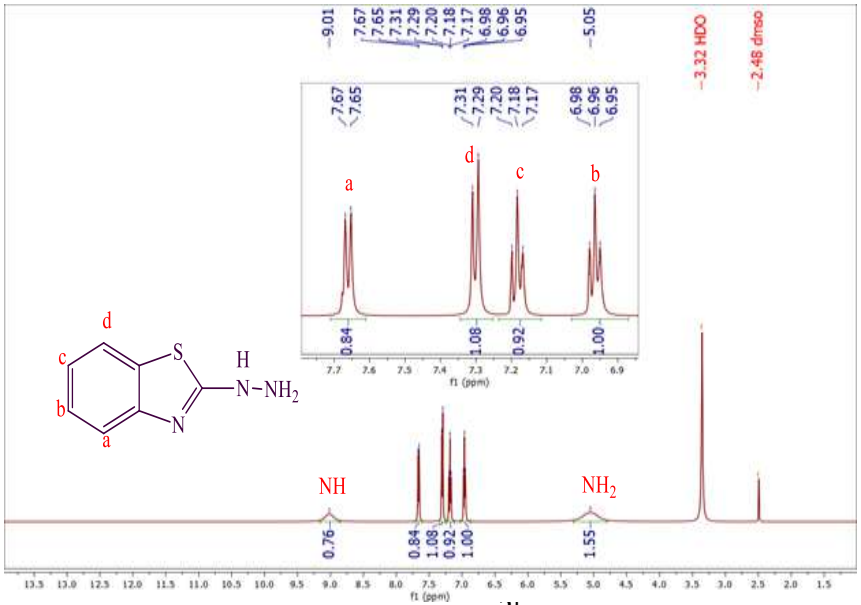
Supporting data



FTIR spectrum of (A) compound



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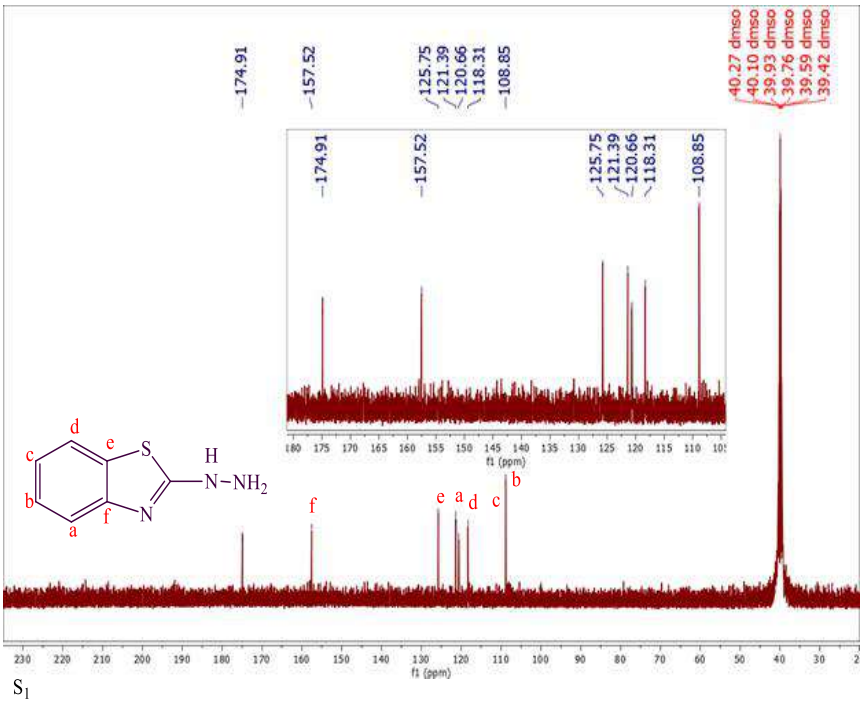
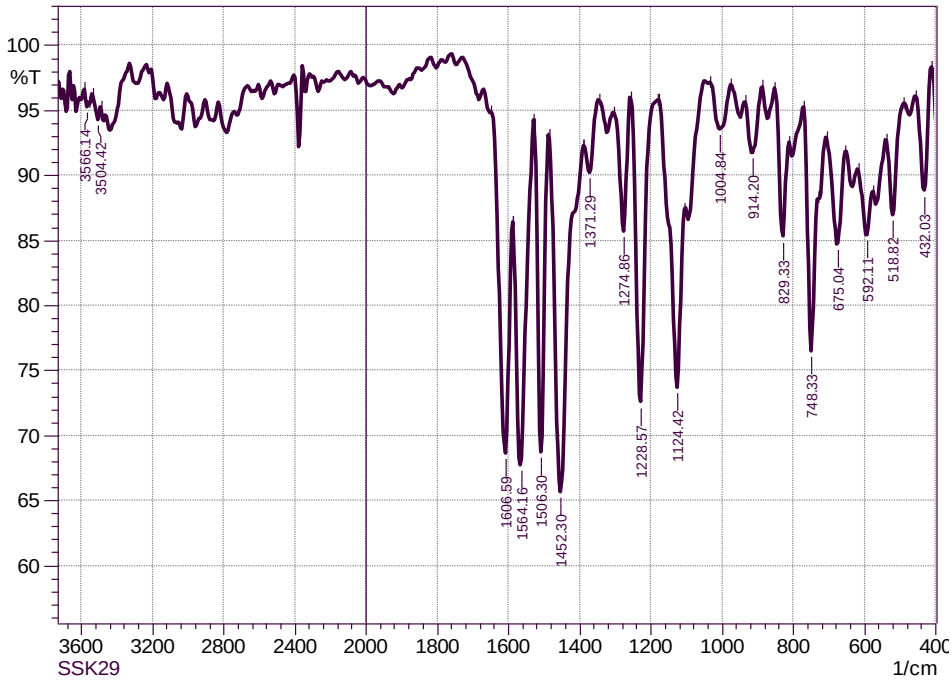


^{13}C-NMR spectrum of (A) compound



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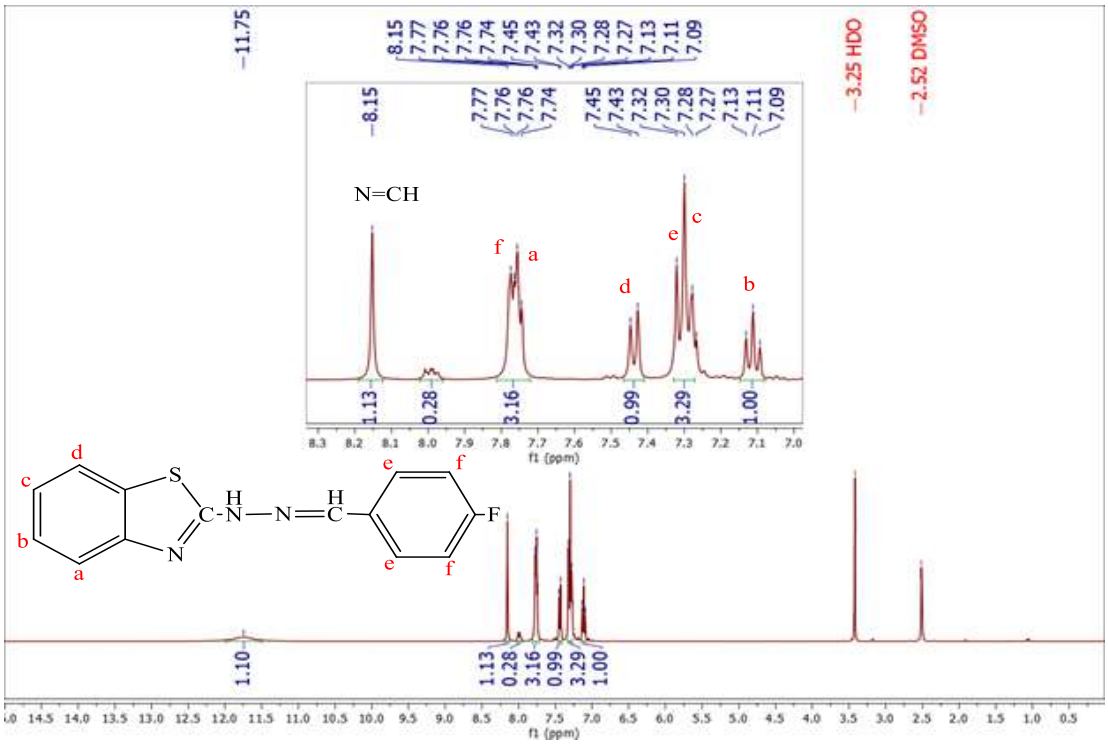
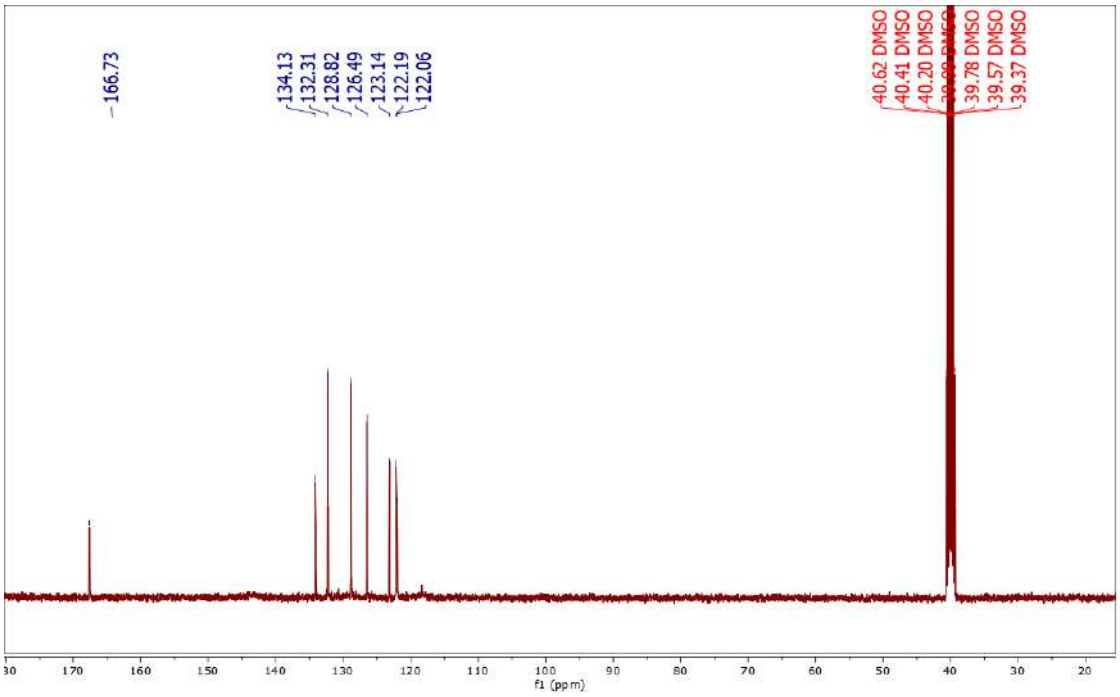
FTIR spectrum of (B1) compound



S_4

^{1}H-NMR spectrum of (B1) compound



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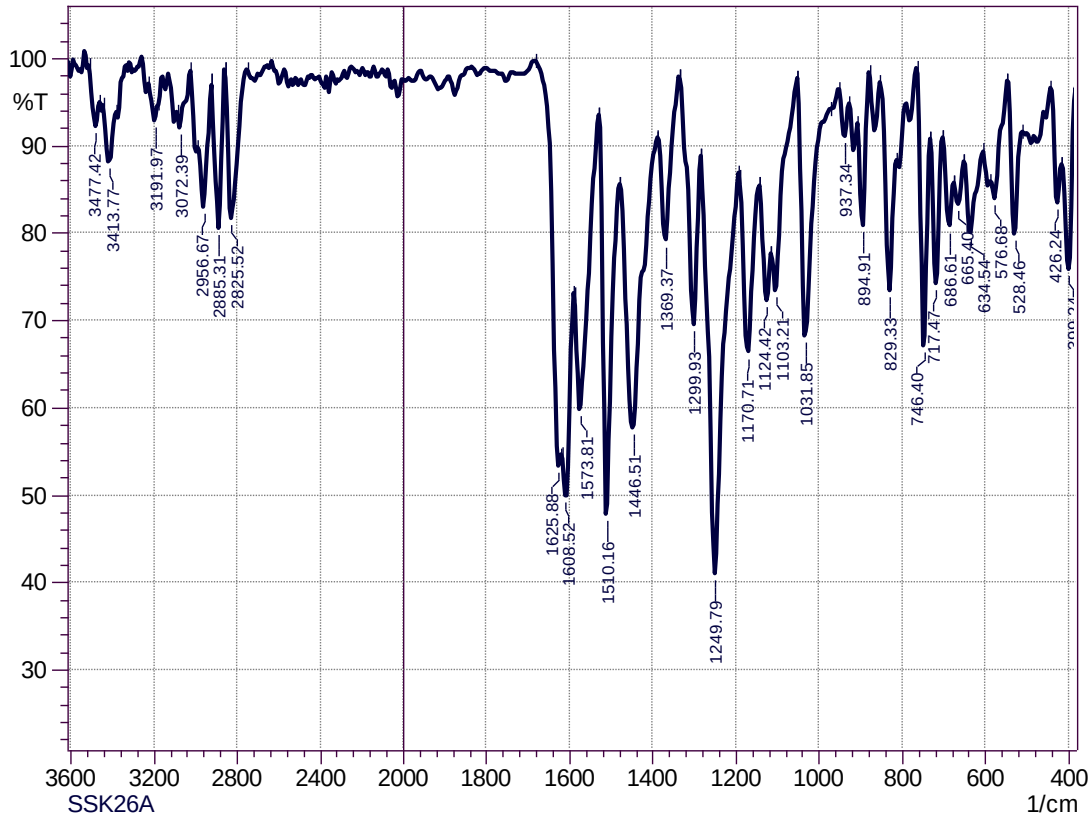
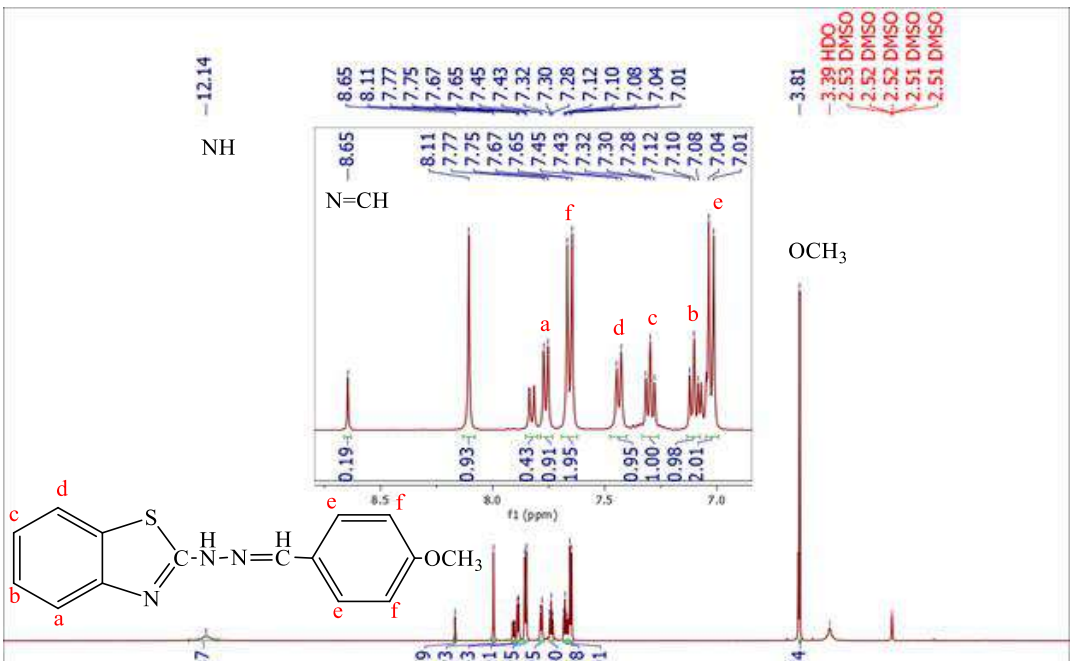
^{13}C-NMR spectrum of (B1) compound



FTIR spectrum of (B2) compound



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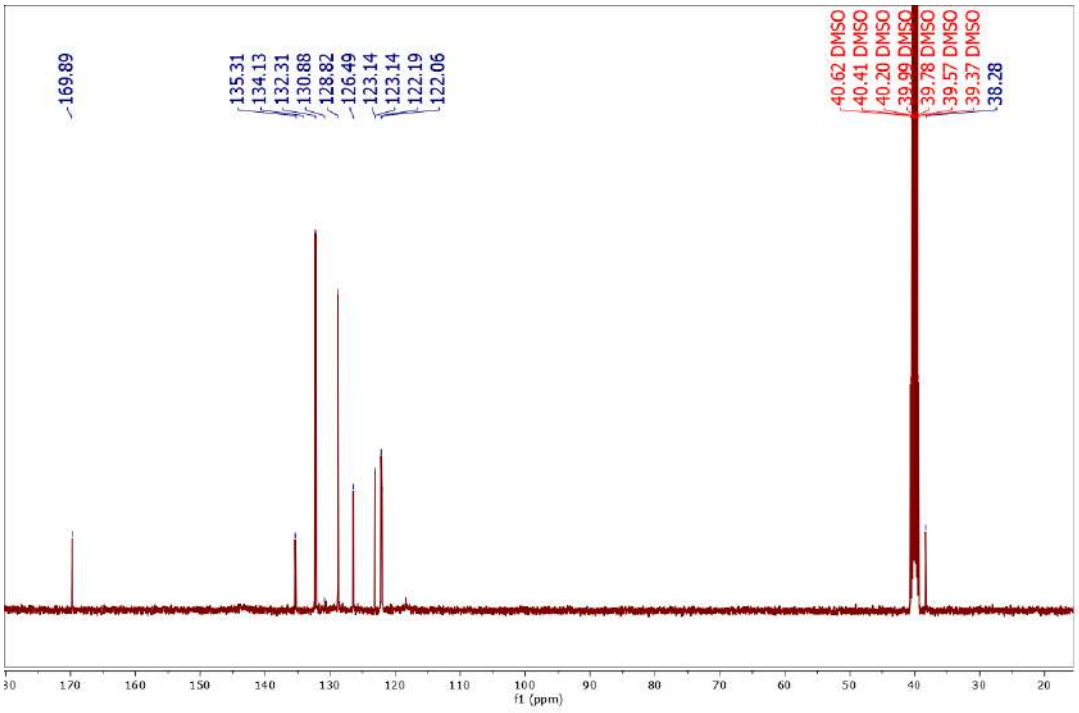
^{1}H-NMR spectrum of (B2) compound



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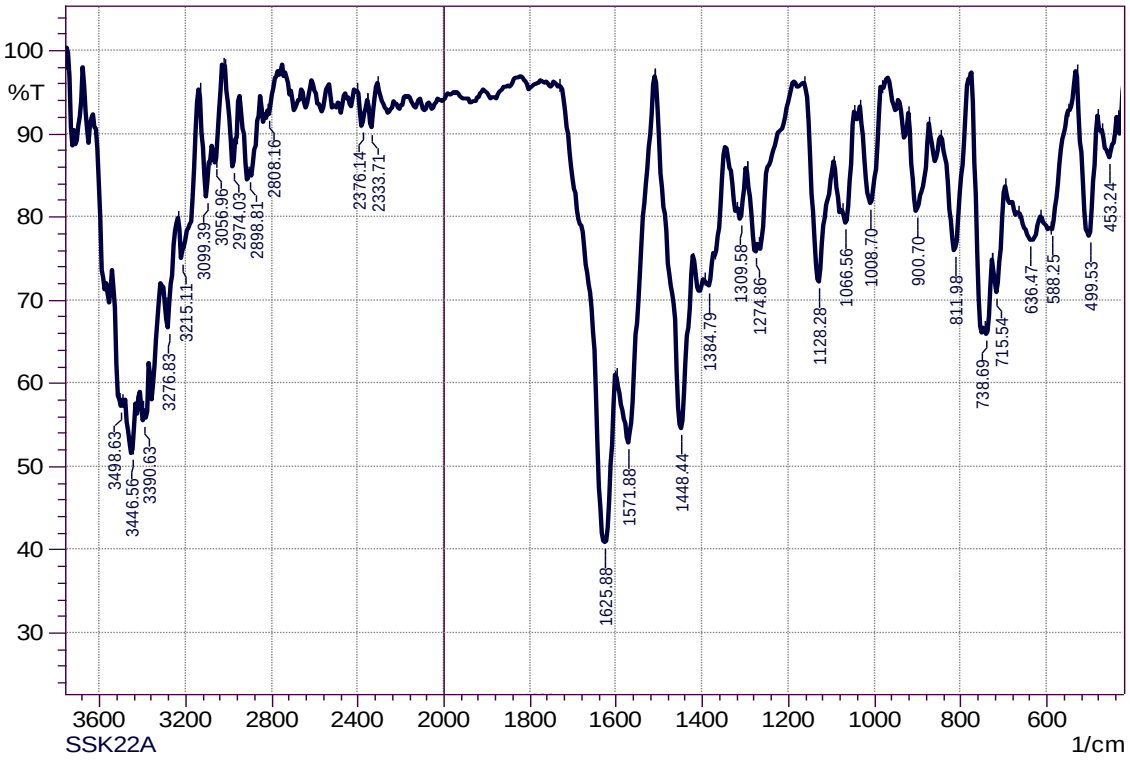

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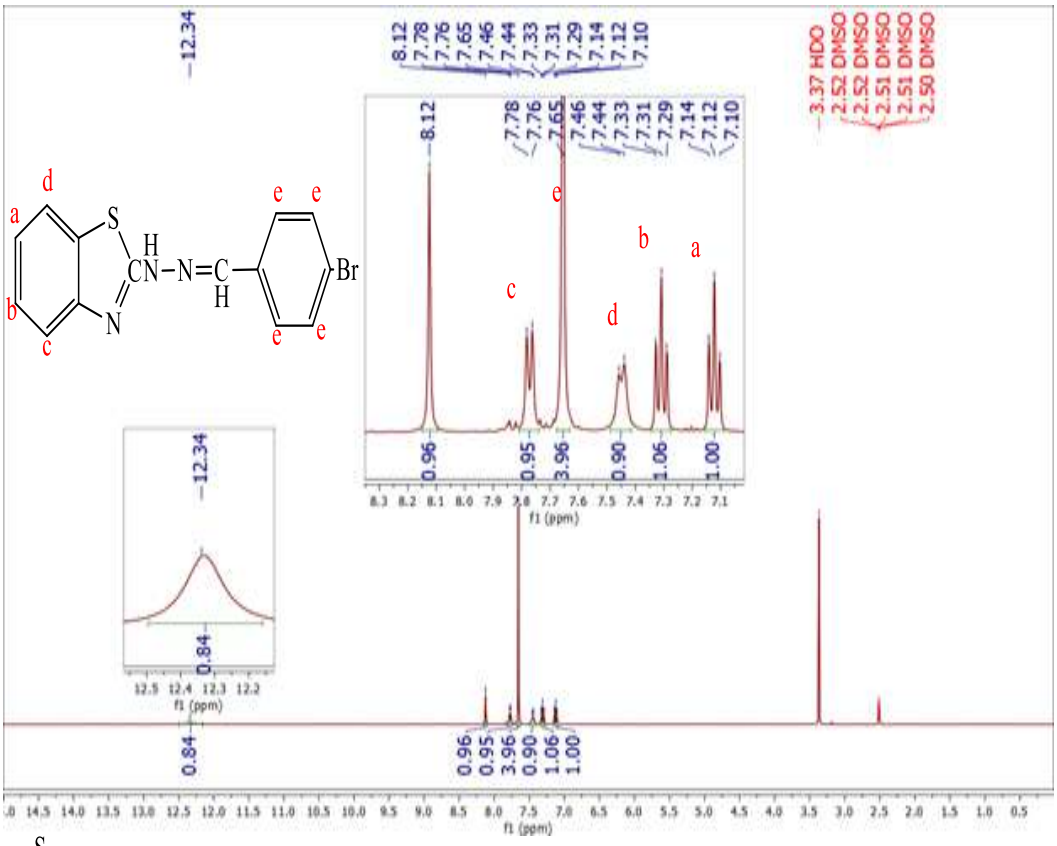
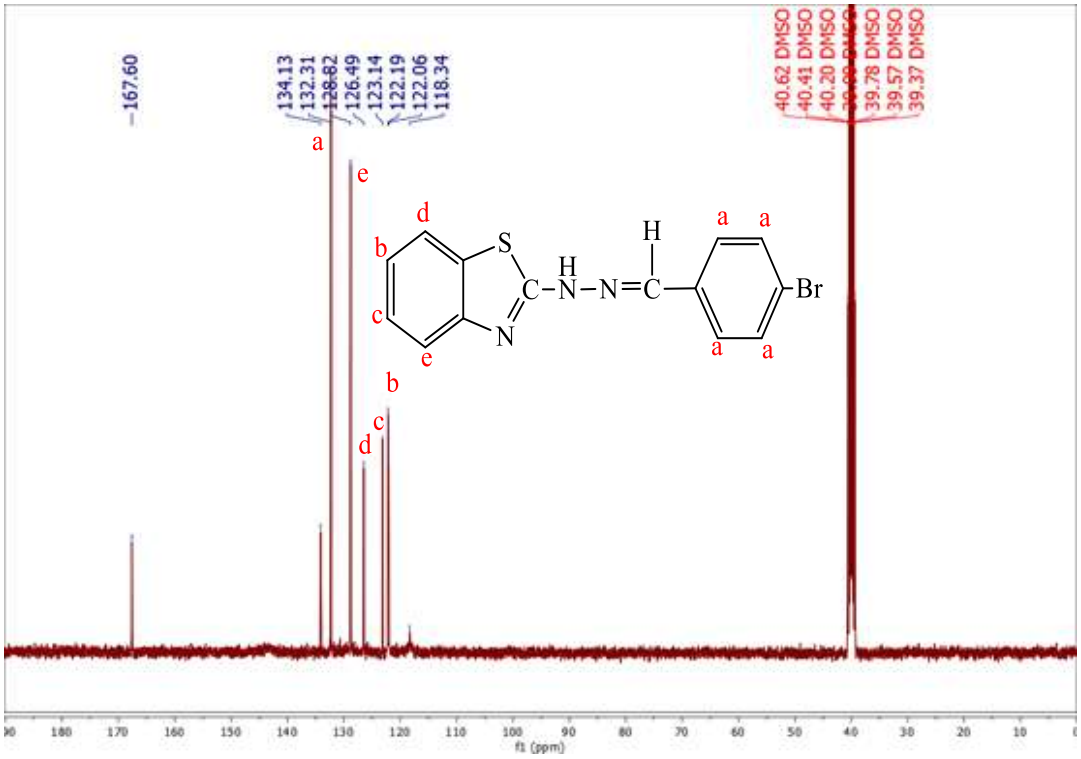
FTIR spectrum of (B3) compound



S_2

^{1}H-NMR spectrum of (B3) compound



S_2

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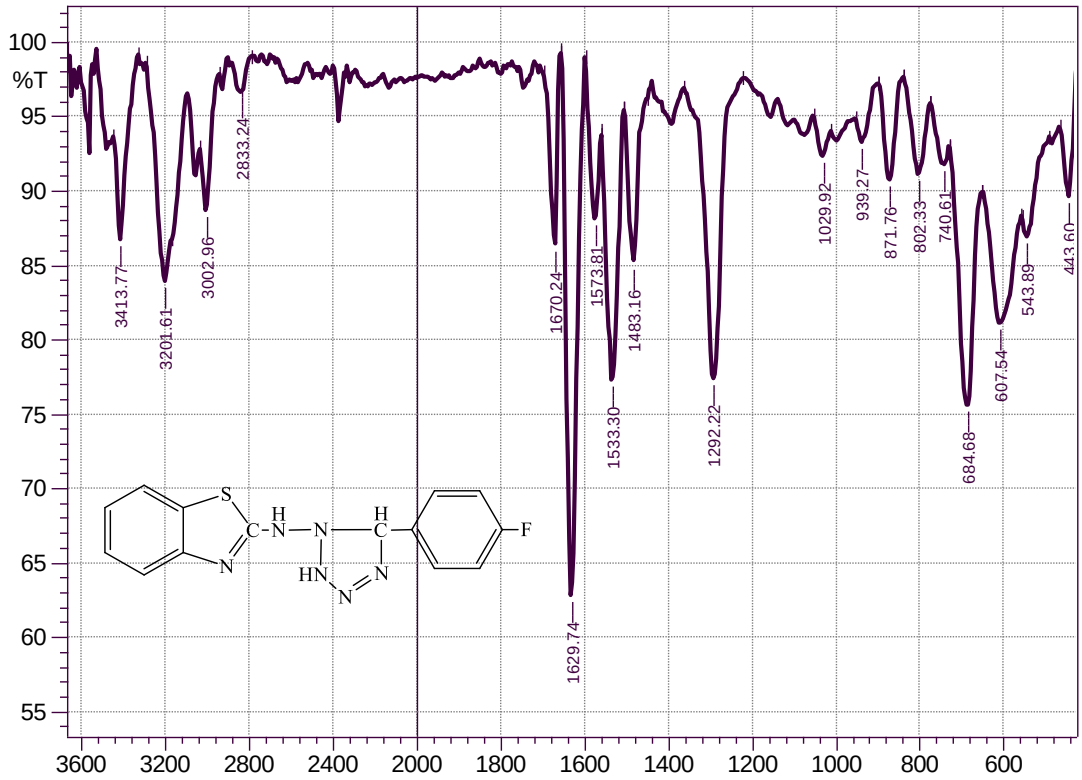
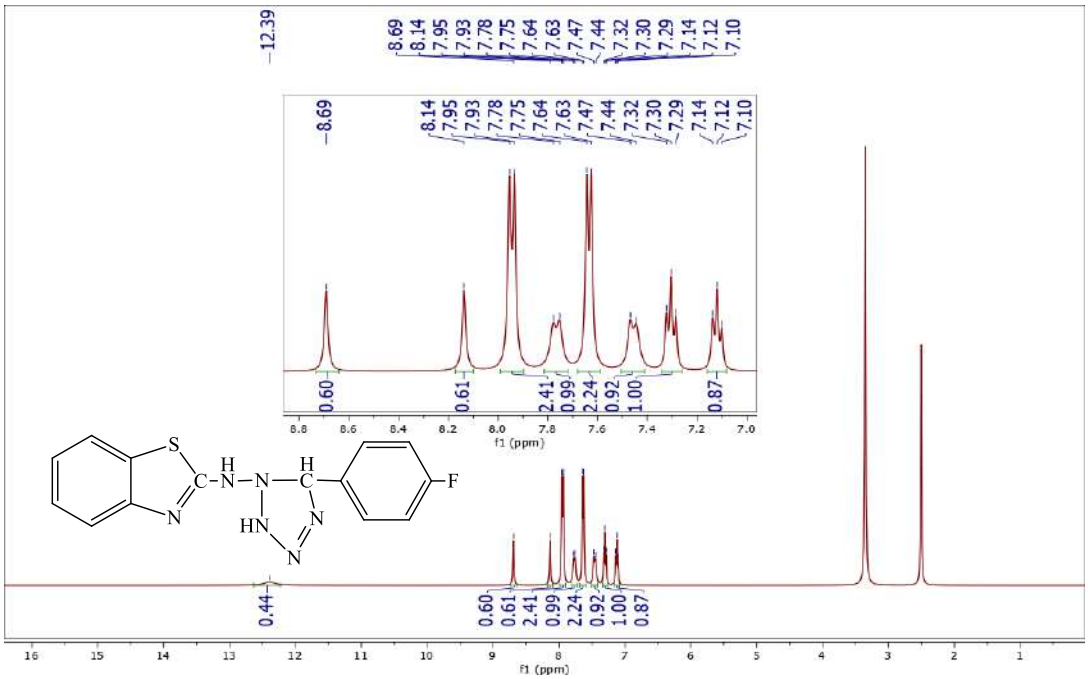
^{13}C-NMR spectrum of (B3) compound



FTIR spectrum of (T1) compound



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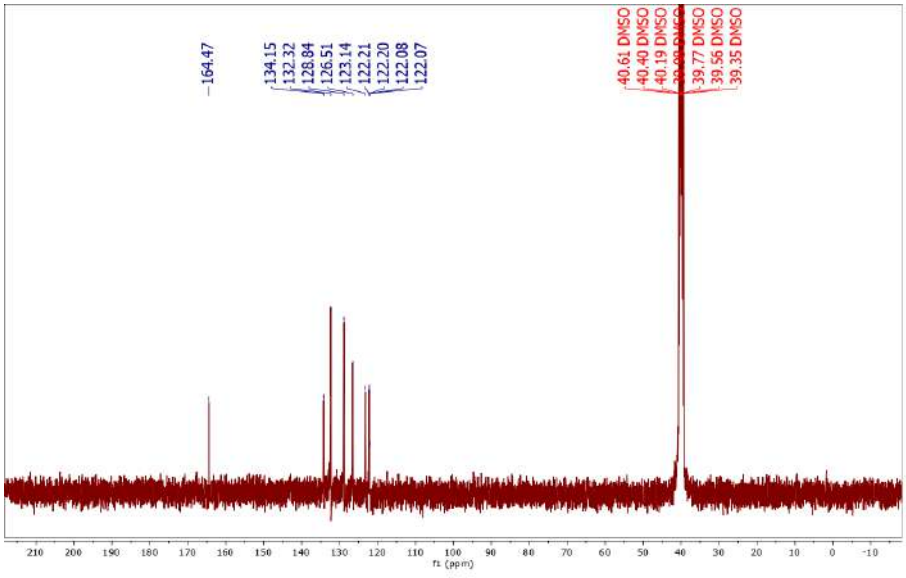
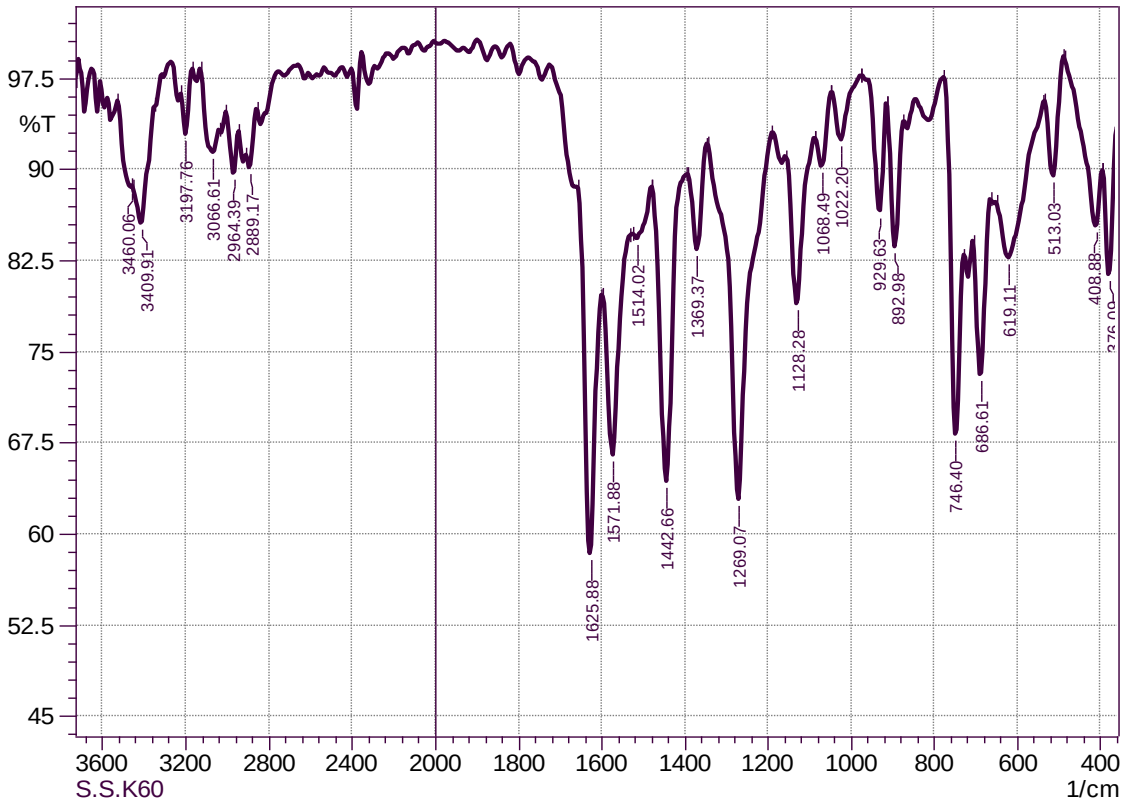
^{1}H-NMR spectrum of (T1) compound



^{13}C-NMR spectrum of (T1) compound



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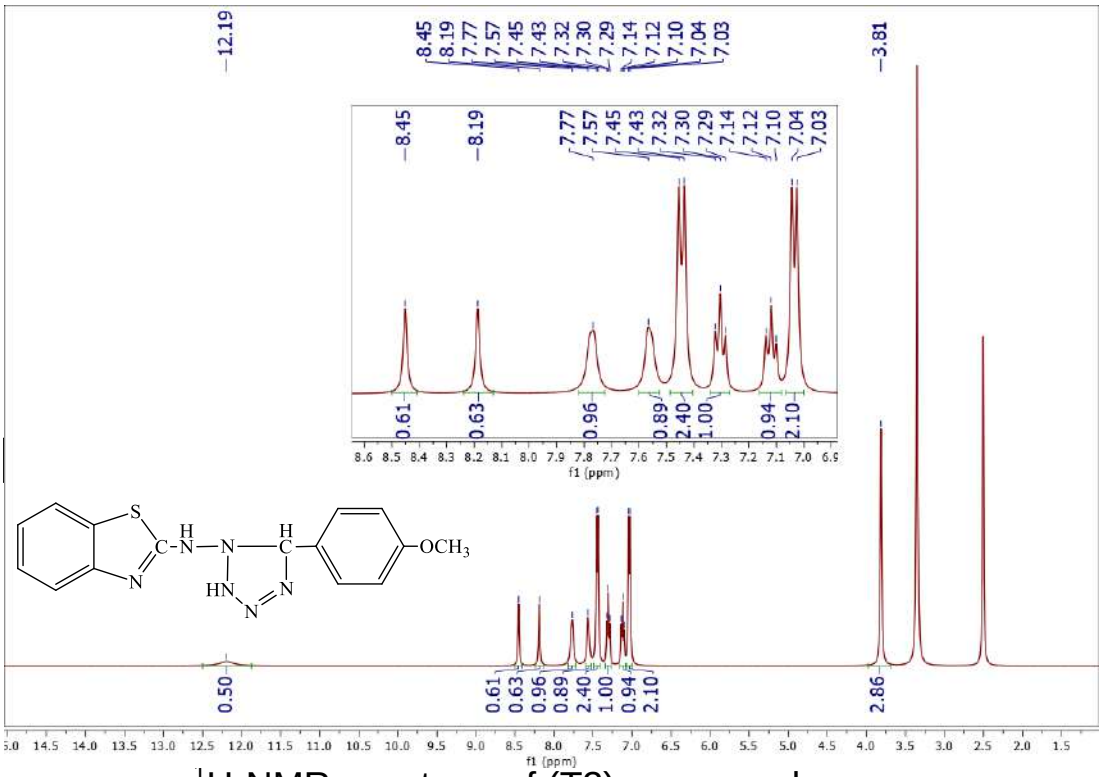
FTIR spectrum of (T2) compound



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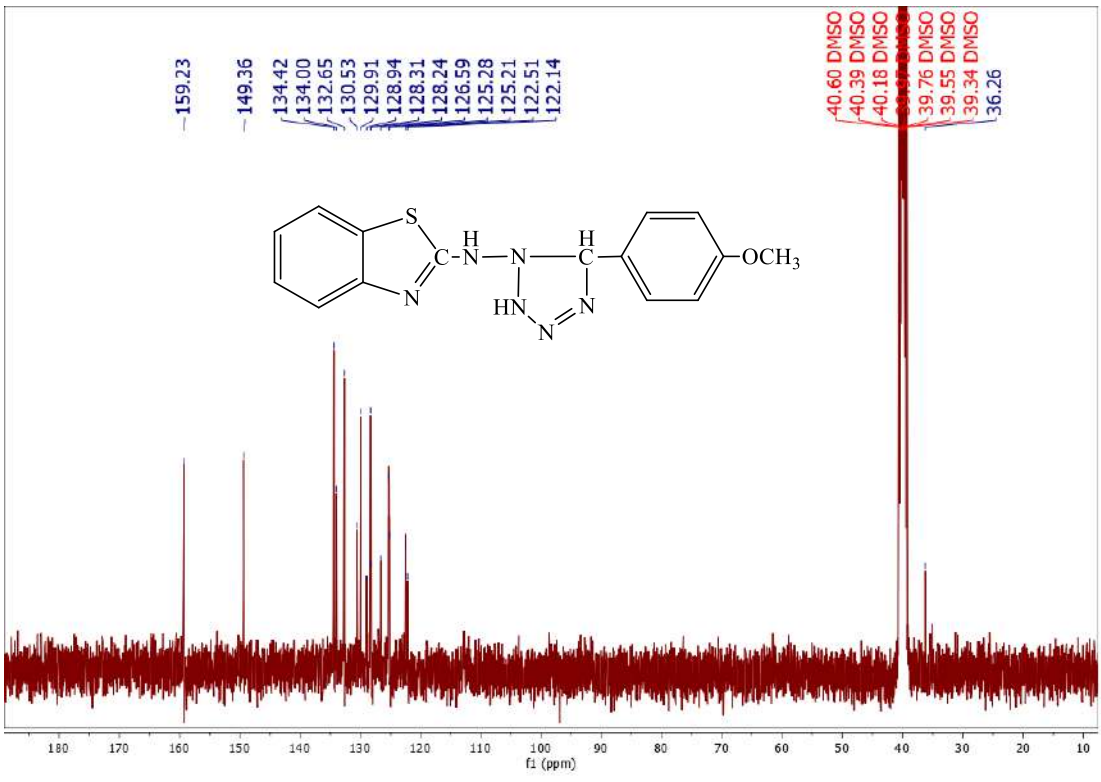

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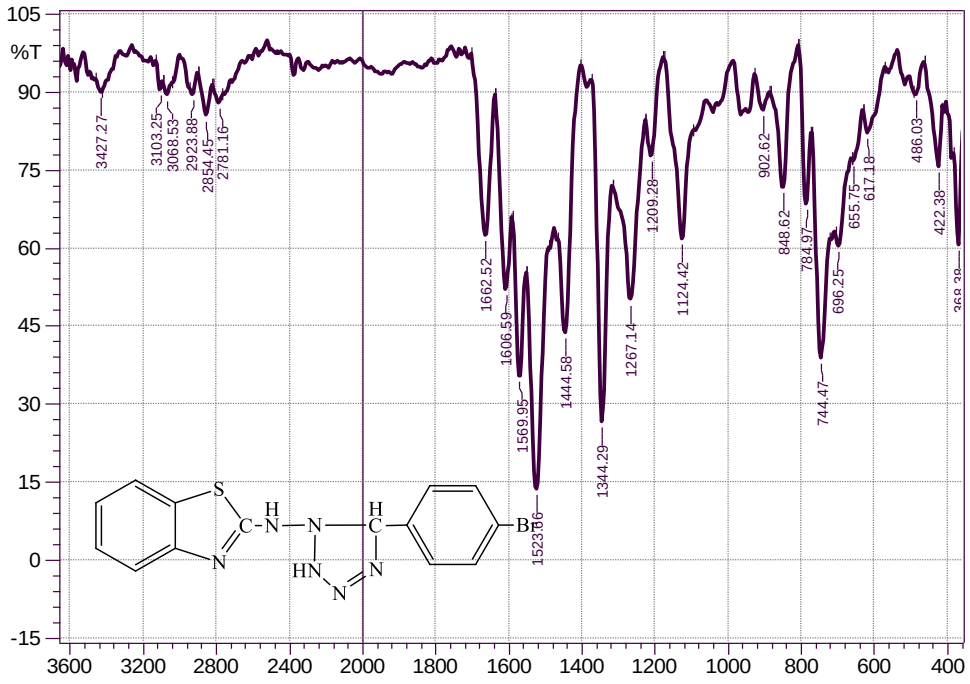
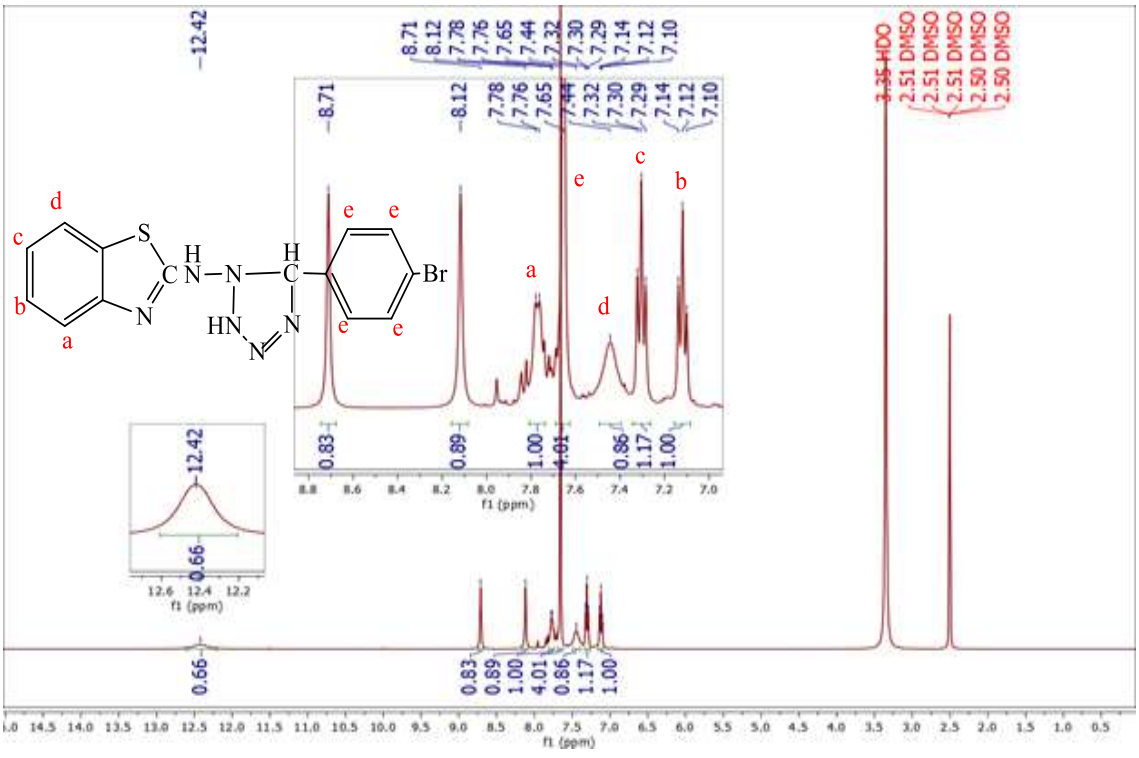
^{13}C-NMR spectrum of (T2) compound



FTIR spectrum of (T3) compound



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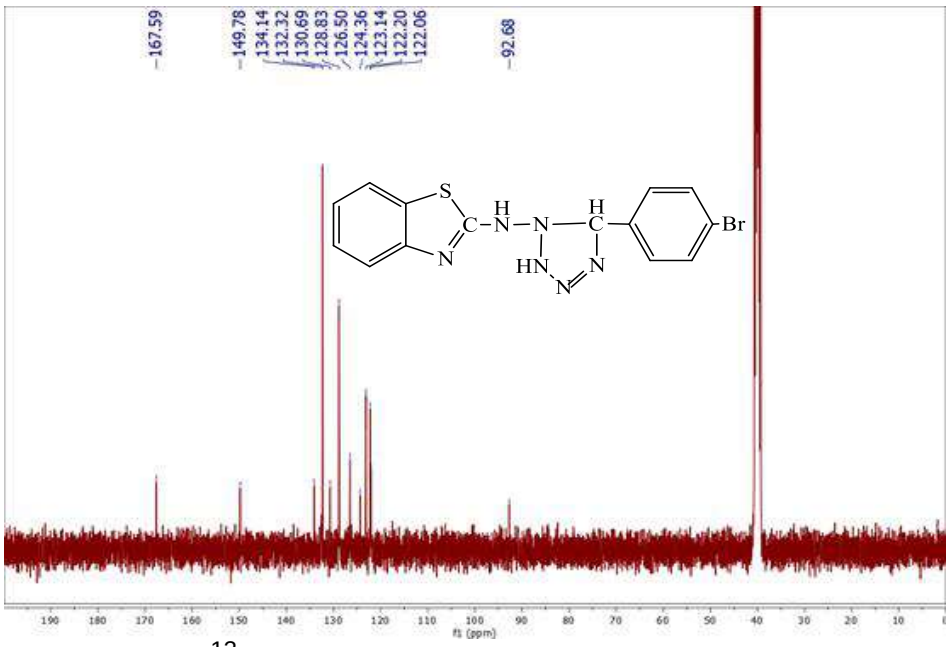
^{1}H-NMR spectrum of (T3) compound



S_{13} ^{13}C-NMR spectrum of (T3) compound