

Article

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Construction, Anticancer Assessment and Spectral Study of Novel Cycles-Triazole Derivatives

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Abstract

Triazoles play an essential role in pharmacy, especially when exposed to the chemical structure of the drug, delving into drug metabolism processes, and biological preparations. It is found abundantly in vitamins, dyes and many other natural products. Most heterogeneous organic compounds are extracted from animal or plant sources. It is used in some industries, such as the manufacture of nylon used in the clothing industry, and in the manufacture of vitamin C. It represents the active group in many enzymes, coenzymes, polymers, and the manufacture of nucleic acids. The study also reached the grades of diagnosing and determining the structural formula using the infrared spectrum (FT-IR), the proton magnetic resonance spectrum (¹H-NMR), and the carbon nuclear magnetic resonance spectrum (¹³C-NMR) according to the functional groups and their appearance in each spectrum. Also, when comparing the process of preparing the derivatives, it was found the difference in the substituted groups from the base compound has a clear effect on the time period for completion of the reaction, which was monitored using the TLC –technique (Ethanol: benzene) but the ratio of solvents was according to type of , in addition to the

difference in effectiveness as a result of the difference in these groups. The efficiency of some breeders in inhibiting breast cancer cells and cells affected by the tumour was also evaluated and characterized.

Keywords: triazole , anticancer, heterocyclic ,anile, imine, bicyclic ,five ring , six ring.

Introduction

Triazole is a very important compound in the preparation of many types of pharmaceuticals and antibiotics [1-3]. A cyclic compound is a chemical compound consisting of a chain of atoms linked to each other in a cyclic manner. The majority of cyclic compounds are organic compounds, but there is a small percentage of cyclic compounds that are non-luminous [4,5], including: sulfur, Silicon, which forms the compound saline, and phosphorus [6, 7], which forms phosphine compounds. Some types of cyclic compounds are aromatic, such as benzene [8-11]. The concept of a multi-cyclic compound is used when a single molecule is formed from more than one ring, such as naphthalene [112-18]. The concept of a macro-cyclic compound is also used when it contains more than a dozen atoms [19-21]. Heterocyclic compounds are cyclic compounds that contain atoms of at least two different chemical elements in the aromatic ring [22-27]. So, it consists of a cyclic structure like what is found in benzene, aromatic compounds, or aromatic hydrocarbons [28-32], but it is found in the structure of these.

2. Methodology

2.1 . Experimental Methodologies:

Synthesis of Amino-Triazole Compound{1} :

2-Thiol benzoic acid (0.001 mol) refluxed in (50 ml) absolute ethanol with (3ml of H_2SO_4) for esterification step , then refluxed for (22 hrs) with (0.001 mol) hydrazoguanidine with (2ml of H_2SO_4) for cyclization step to formation triazole ring derivative, product filtered ,desiccated ,purified by using (DMF) as a solvent to yield compound {1} according to procedure [4].

Synthesis of Nitrogen-Triazole Compound{2} :

Amino-Triazole compound {2} (0.001 mol) refluxed with (0.002 mol) of 4-methyl benzaldehyde for (4 hrs) with ethanol (50 ml), the reaction in drops of Glacial acetic acid ,the product filtered ,desiccated ,purified by using (DMF) as a solvent to yield compound {2} as imine compound according to procedures [4-7].

Synthesis of Nitrogen-Triazole Compound[3] :

Cyclic compound {3} prepared from reaction of anil compound {2} that was prepared in second step (0.001 mol) refluxed with (0.001 mol) of thiol acetic acid ,

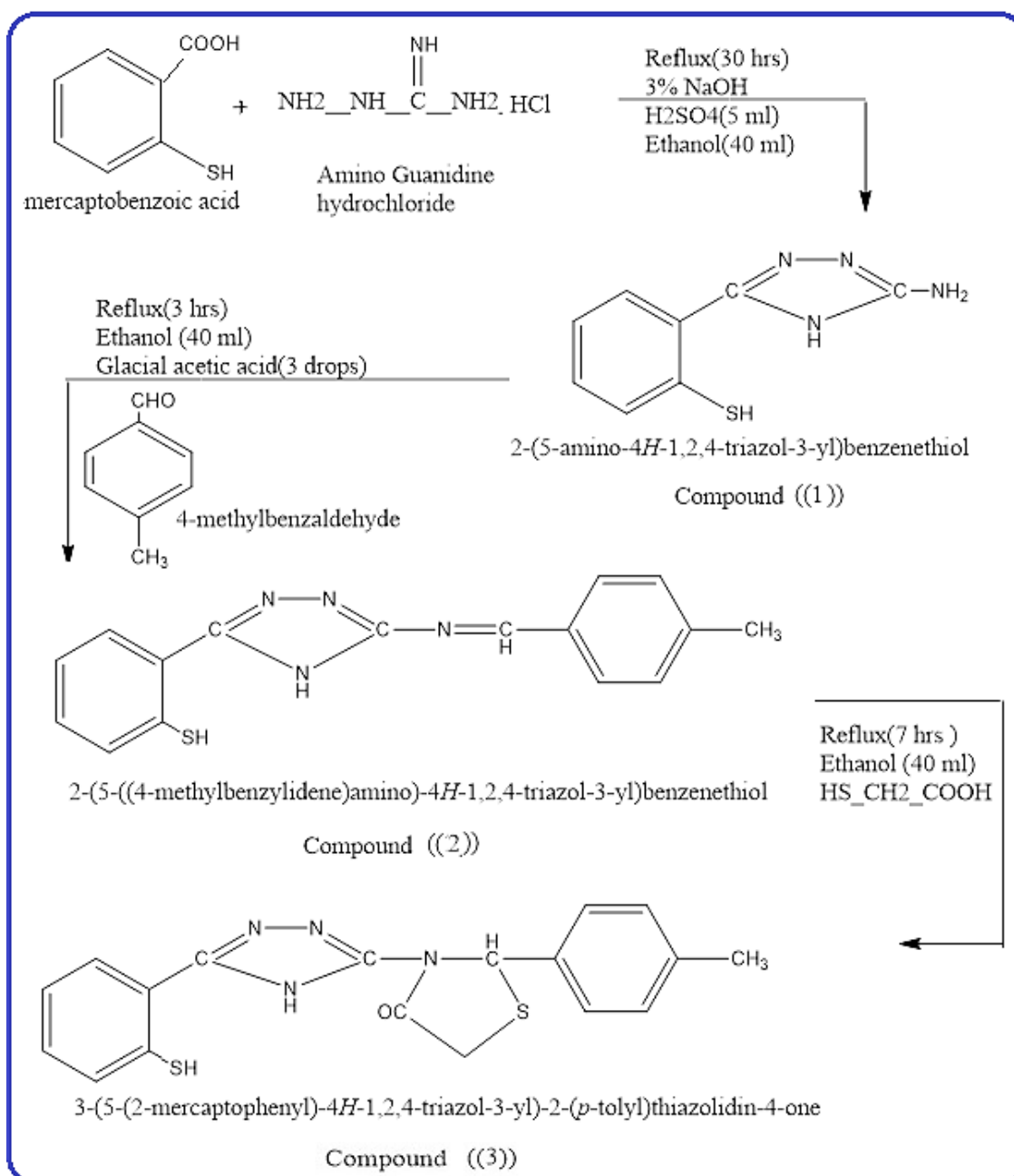
the creation of cyclic compounds ,the product filtered ,desiccated ,purified by using (Eth.OH) as a solvent to yield cyclic compound {3} according to procedures [4-7].

Synthesis of Nitrogen- Triazole Compound[4] :

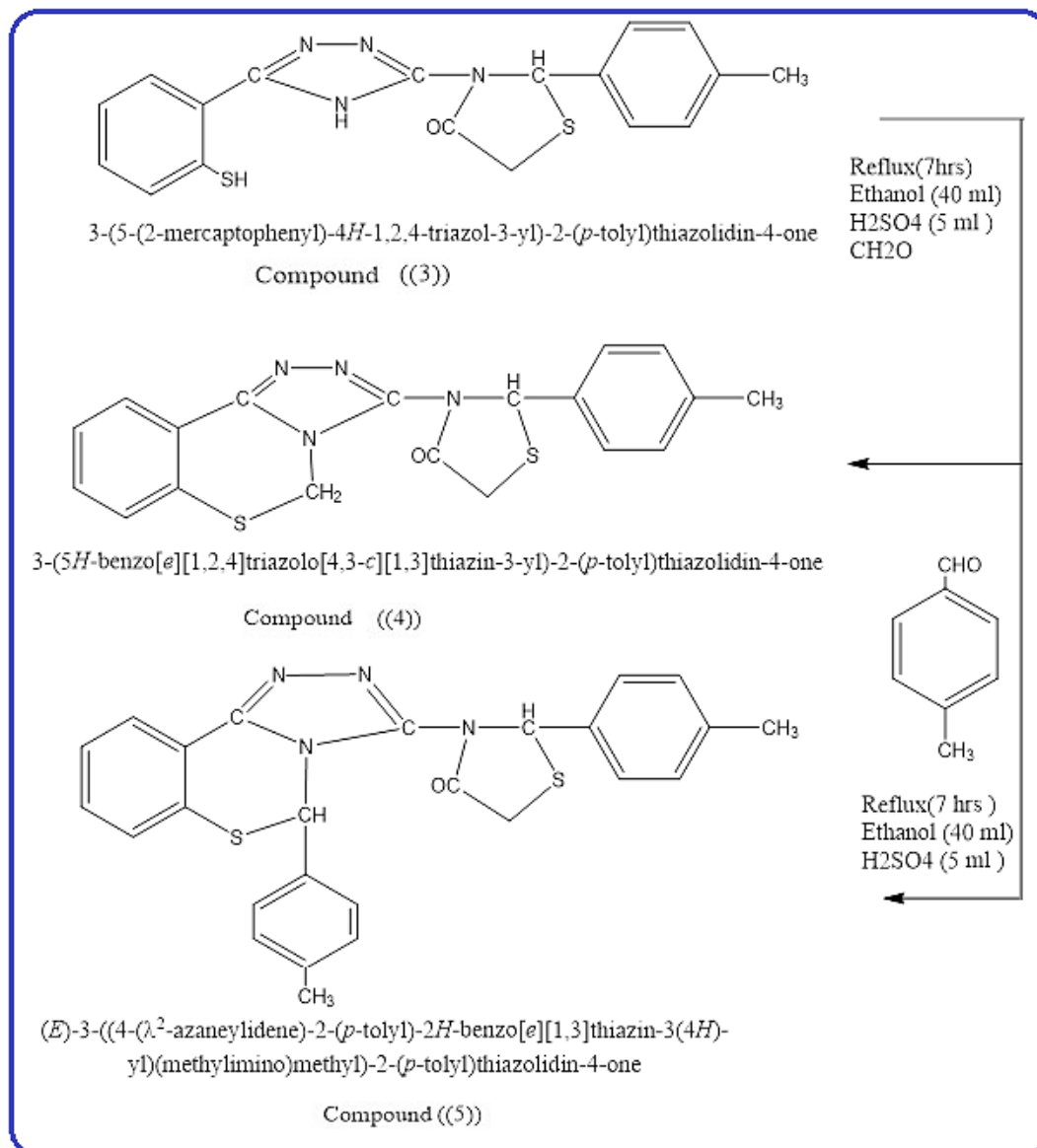
Cyclic compound {4} prepared from reaction of compound {3} that was prepared in third step (0.001 mol) refluxed with (0.001 mol) of formaline for (6 hrs) with ethanol (50 ml), the reaction is shortened in the linkage of the two nucleophiles (in basic medium) with the carbonium ion of the aldehyde (formal), the creation of cyclic compounds ,the product filtered ,desiccated ,purified by using (DMF) as a solvent to yield cyclic compound {4} according to procedures [4].

Synthesis of Nitrogen -Triazole Compound[5] :

Cyclic compound {5} prepared from reaction of compound {3} that was prepared in third step (0.001 mol) refluxed with (0.001 mol) of 4-methyl benzaldehyde for (6 hrs) with ethanol (50 ml), the reaction is shortened in the linkage of the two nucleophiles (in basic medium) with the carbonium ion of the aldehyde (formal), the creation of cyclic compounds ,the product filtered ,desiccated ,purified by using (Eth.OH) as a solvent to yield cyclic compound {5} according to procedures [4-7].



Pattern.1: The Synthesized Nitrogen-Triazole Compounds {1-3}



Pattern.2: The Synthesized Nitrogen–Triazole Compounds{4, 5}

Results And Discussion

These unique organic compounds are of great interest due to their outstanding biological activity and applications in a wide range of fields. In fact, heterocycles represent more than half of the known organic compounds. For over a century, cyclic closure reactions have been used in the construction of organic compounds as a fundamental strategy in heterocyclic chemistry [33-34]. This application has led to the availability of these compounds in a huge variety of uses [35-38]. The development of new methods for the synthesis of heterogeneous rings is still a focused topic for researchers and students in the fields of organic, pharmaceutical, and agricultural chemistry.

Evidences of Nitrogen-Triazole Compounds via Spectral Identification : FT.IR- Spectra :

The spectrum gave absorption bands for (SH) group at (2237 , 2396 , 2381) belongs to the thiol group cm^{-1} triazole in compounds {1 , 2, 3} respectively ,which are disappeared in compounds {4 ,5} as a result of formation cyclic compounds as a six and five –membered ring. All frequencies identified and explained according to reference [13], also there are several bands appeared if spectra like (C=N) endocycle act in { (1653), (1659), (1662), (1648),(1652)} respectively in compounds {1-5},while other bands appeared in spectra like band of amide (CO-N) at {(1698), (1682), (1687)} respectively for compounds {3, 4, 5},and other functional groups in some figures (1-5):

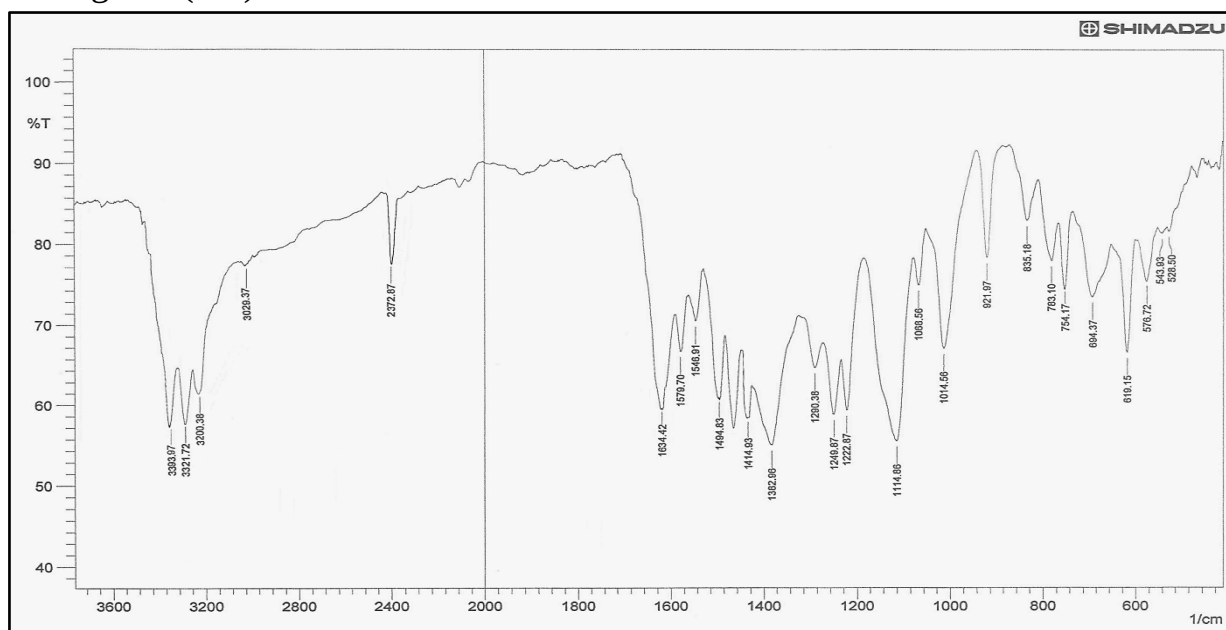


Fig (1): I.R of Compound [1]

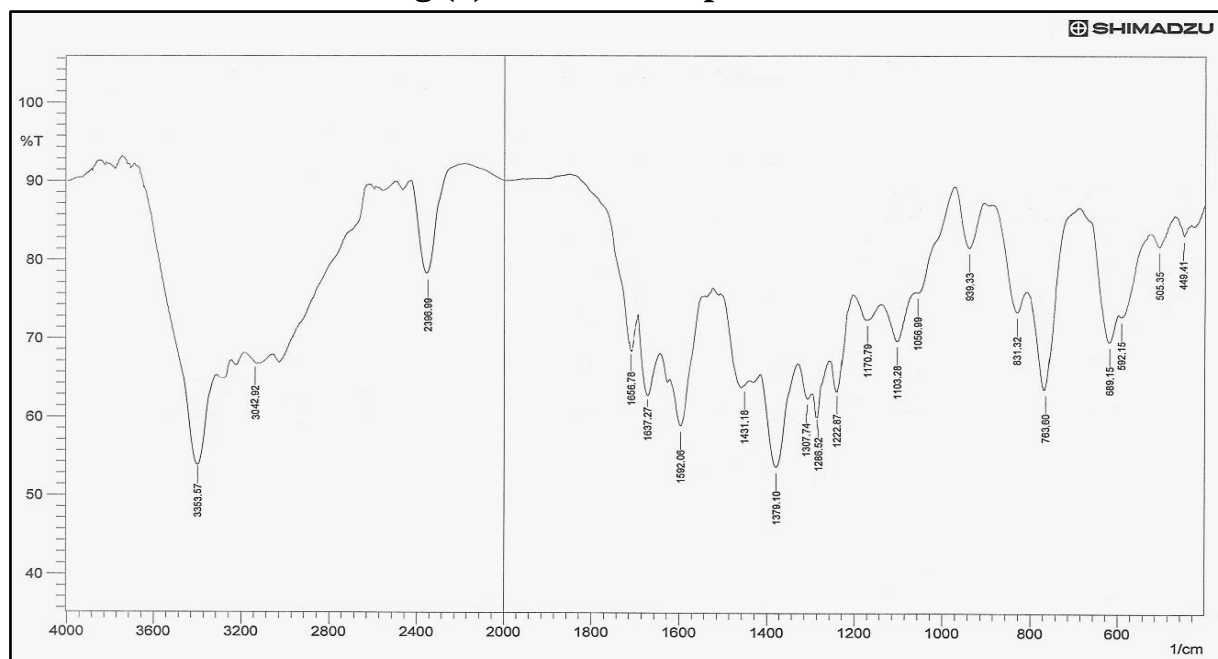


Fig (2): I.R of Compound [2]

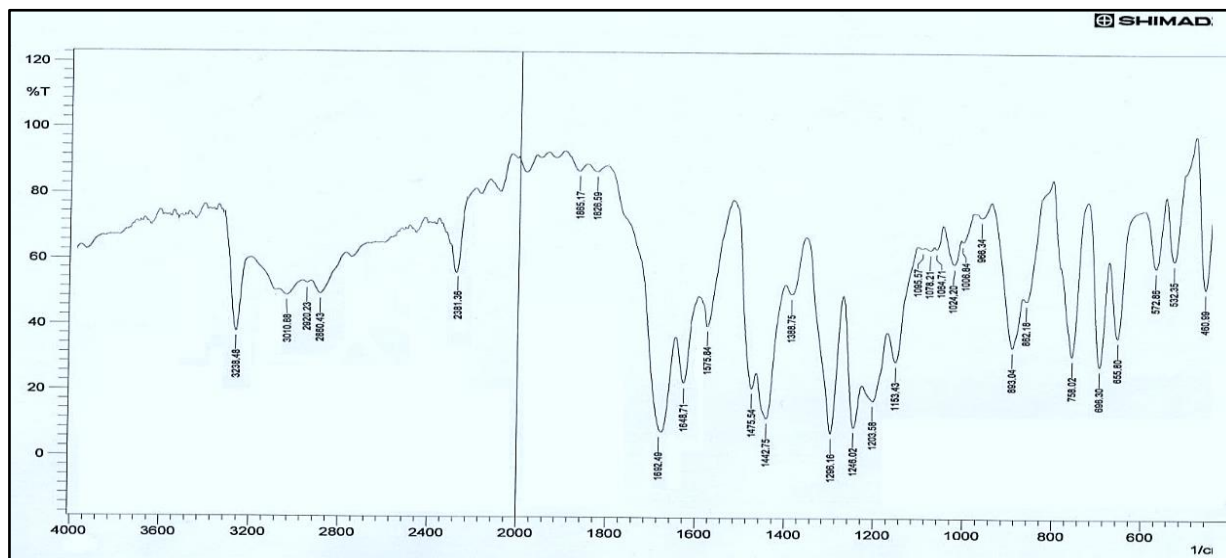


Fig (3): I.R of Compound [3]

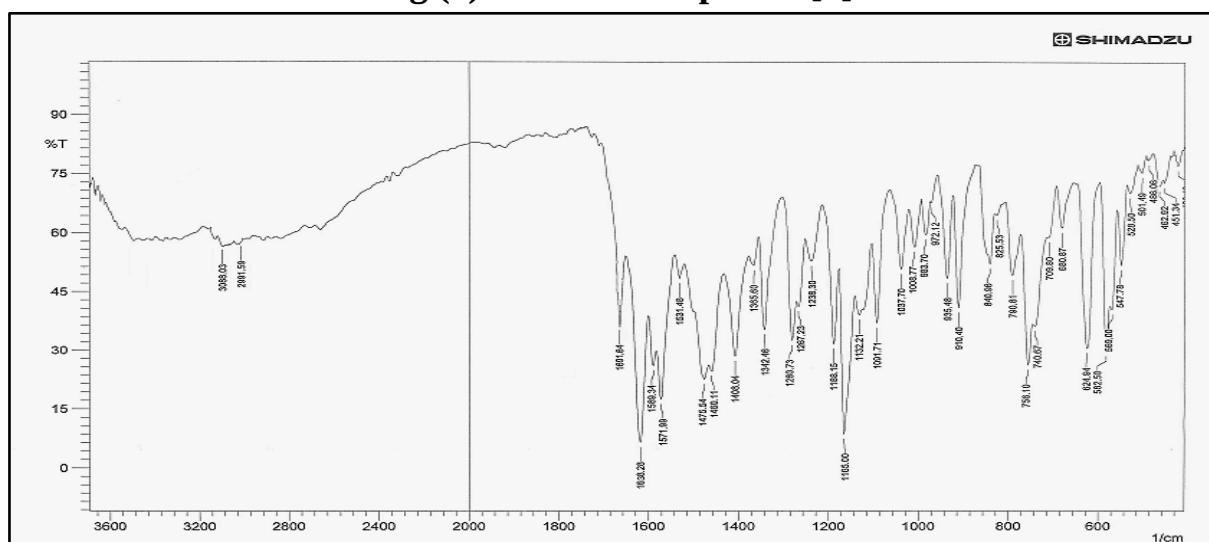


Fig (4): I.R of Compound [4]

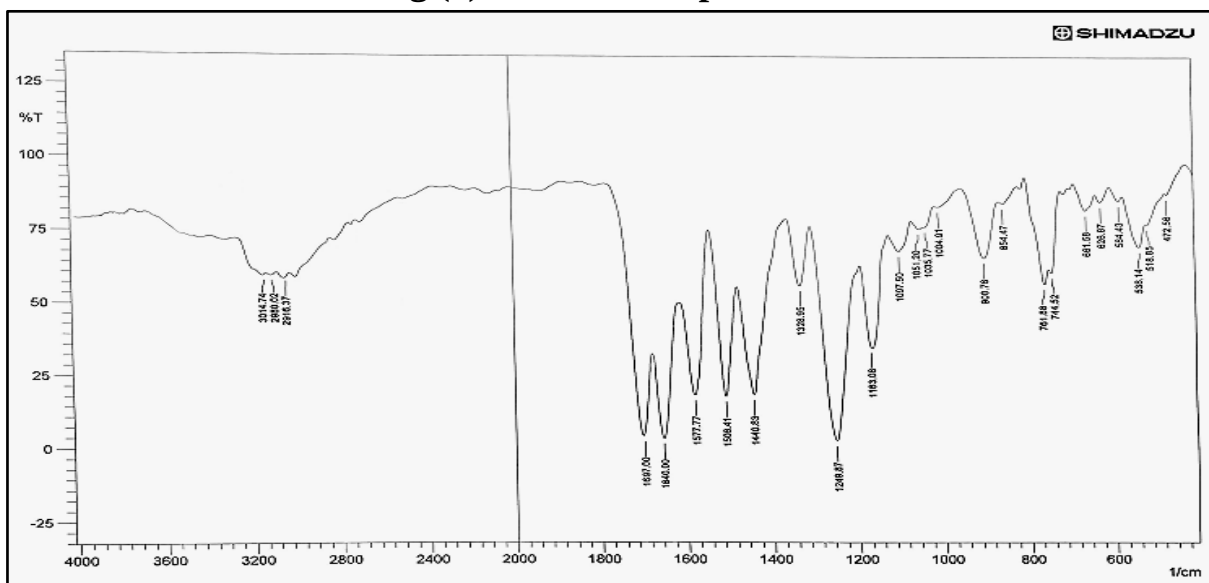
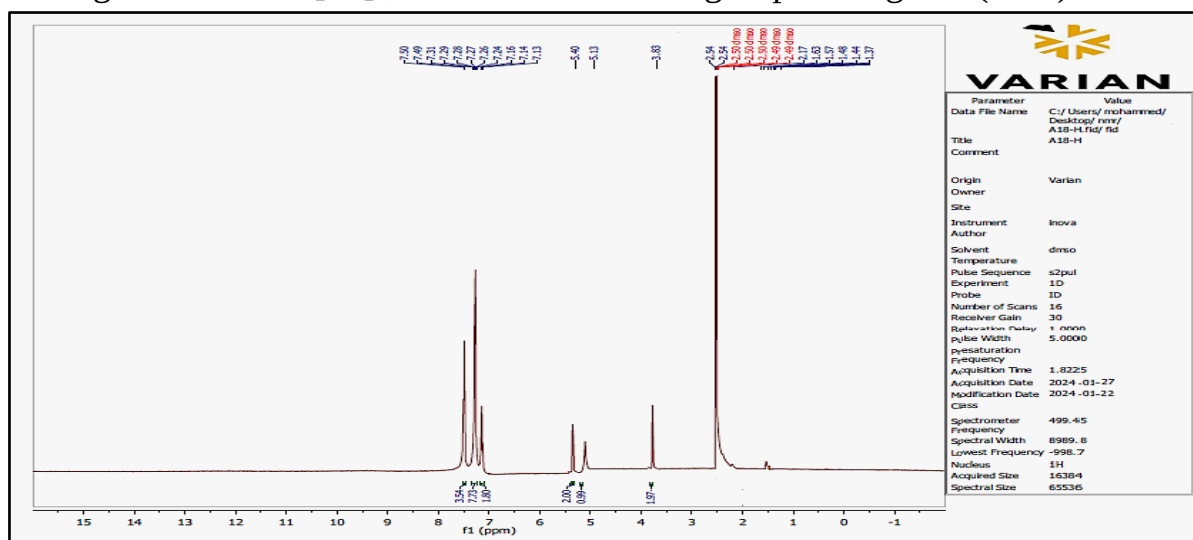
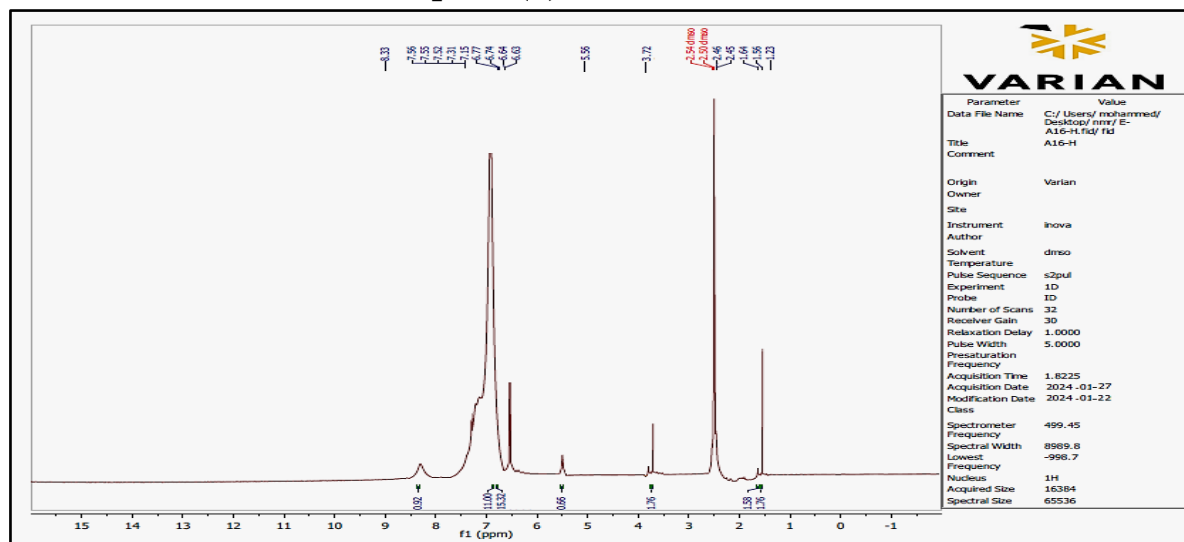
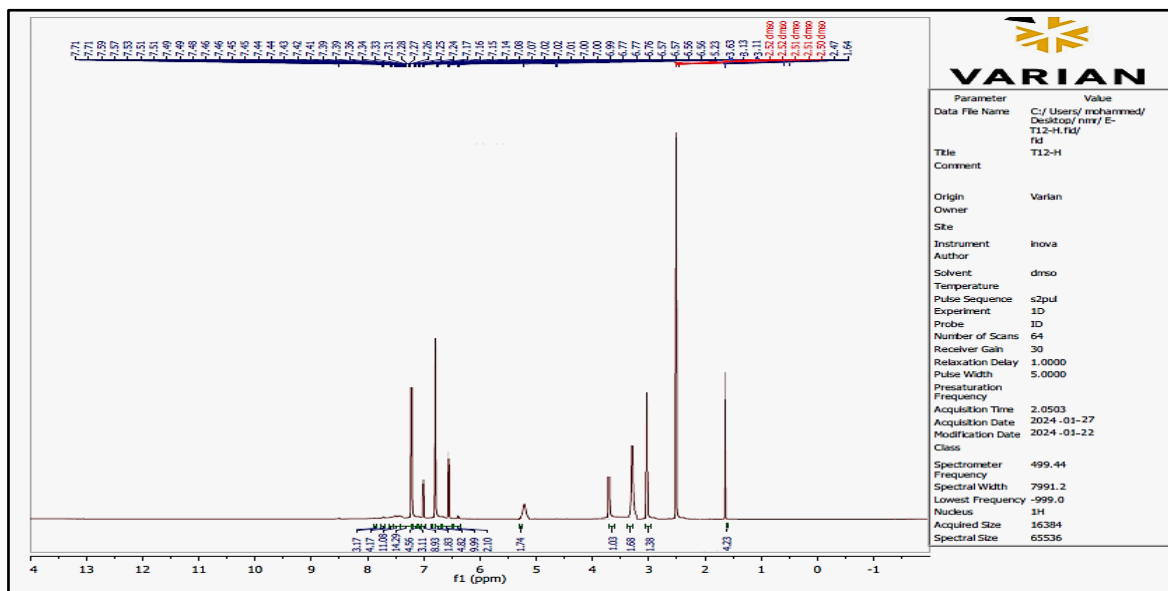
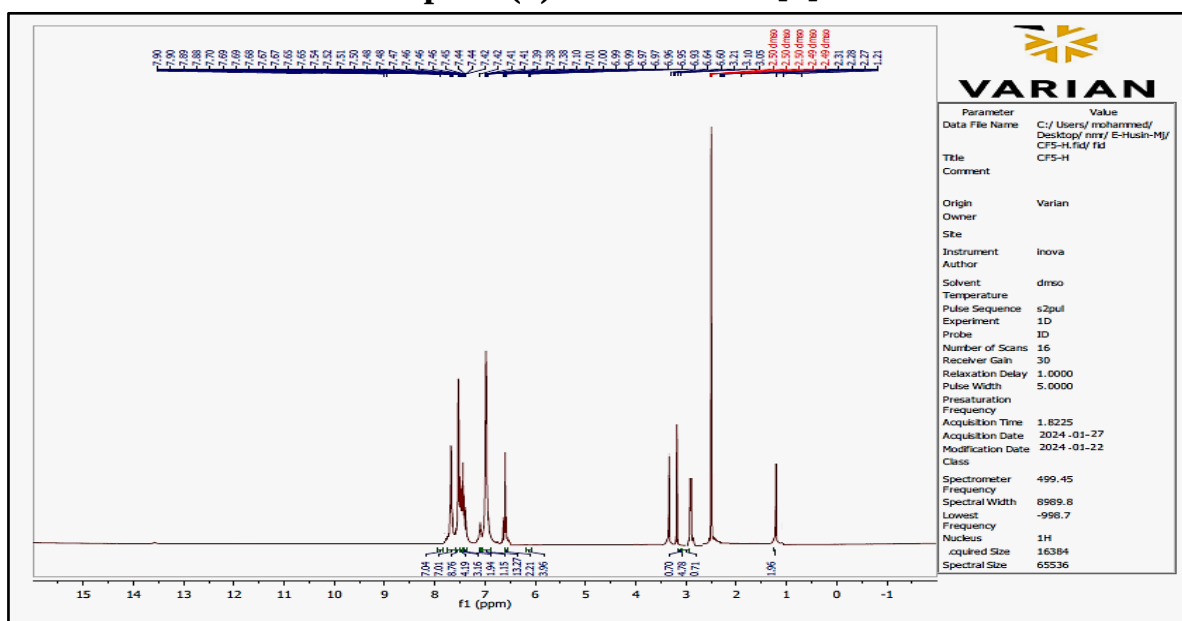


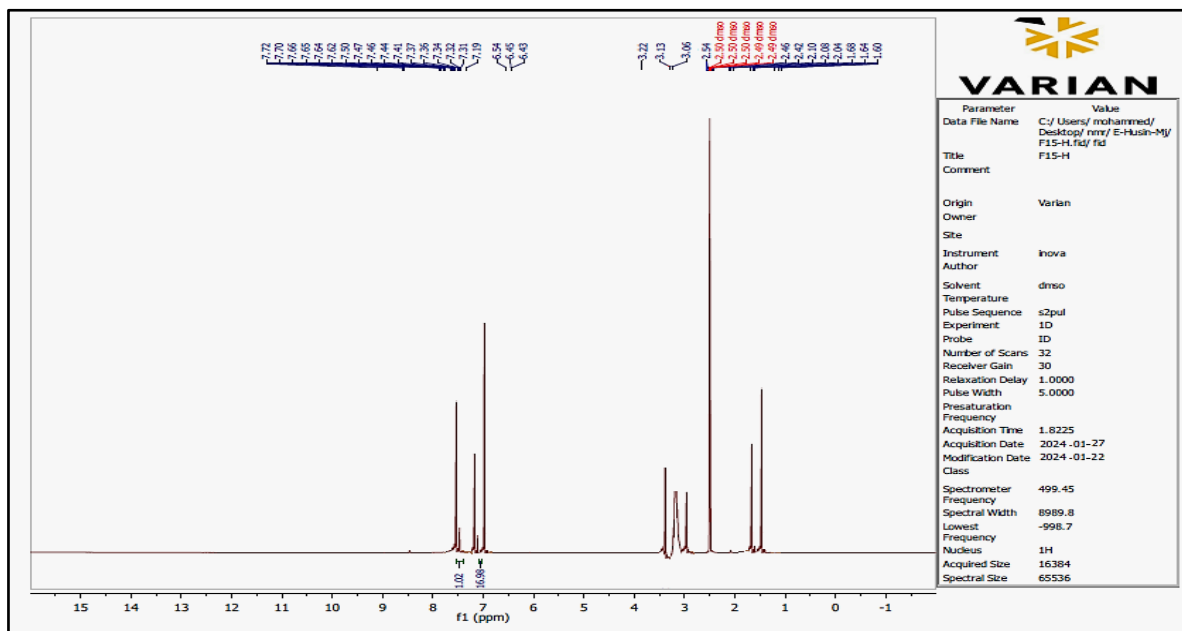
Fig (5): I.R of Compound [5]

¹H.NMR- Indication of Nitrogen –Triazole derivatives :

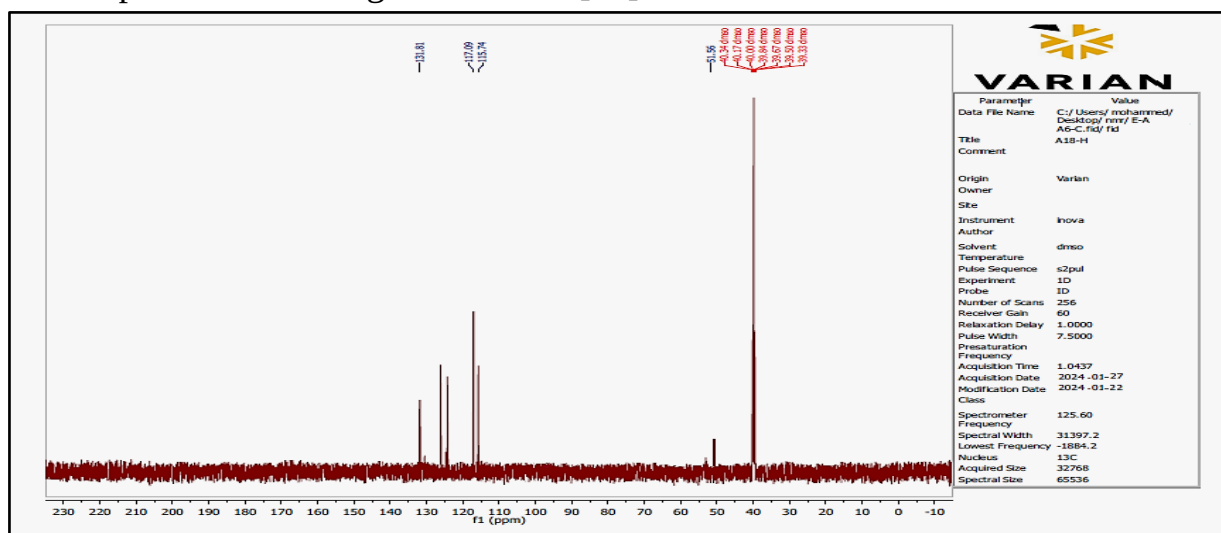
The compounds were also diagnosed by resonance spectra : a single signal appeared (DMSO - d₆) (2.50) belonging to the protons of the solvent used, ppm, the location., The spectrum also showed signal returning to (SH) (3.83 , 3.72 , 3.63) belonging to the proton of the thiol group (ppm) in the site in compounds {1 ,2, 3} respectively , which disappeared in compounds {4,5}. While signals at (6.43- 7.90), the spectrum also gave a single signal (ppm) for the protons of the aromatic rings at the locations Also, a single signal appeared belonging to the (NH₂) group (5.20) and to the protons of the ppm group at the site, belonging to the triazole ring., All signals clarified according to reference [13] ,and other functional groups in figures (6-10):

**Spect. (6): ¹H.NMR of [1]****Spect. (7): ¹H.NMR- of [2]**

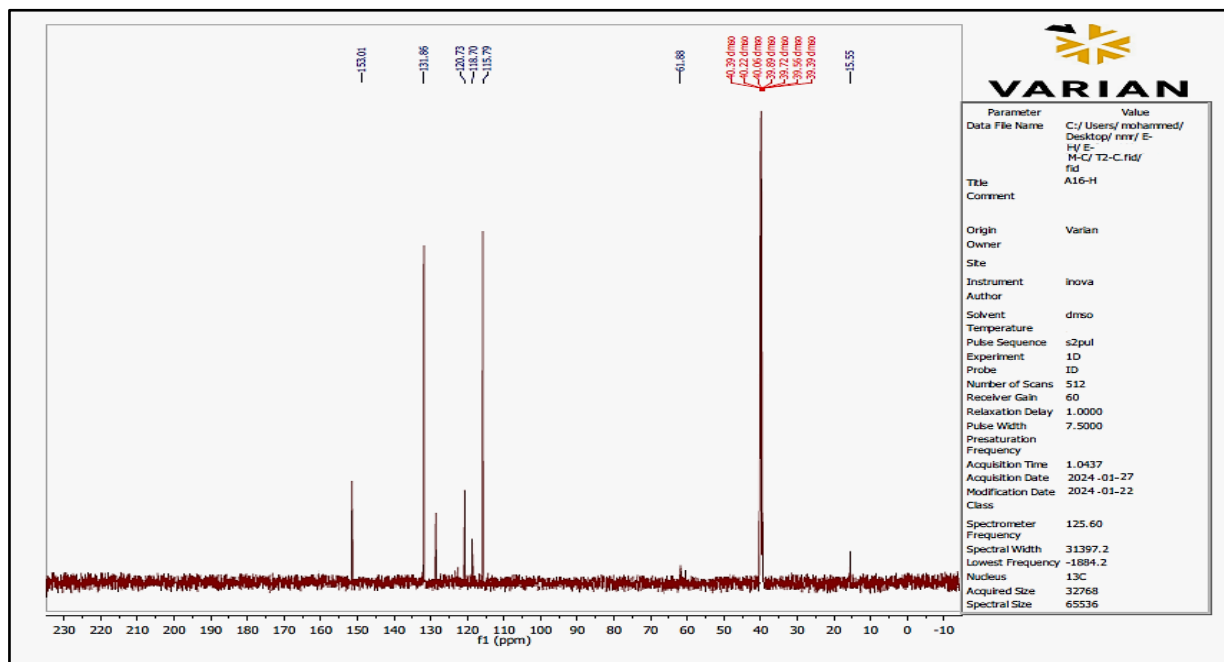
Spect. (8): ^1H .NMR- of [3]Spect. (9): ^1H .NMR- of [4]

Spect. (10): ^1H .NMR- of [5]**C.NMR- Indication of Nitrogen –Triazole Compounds :**

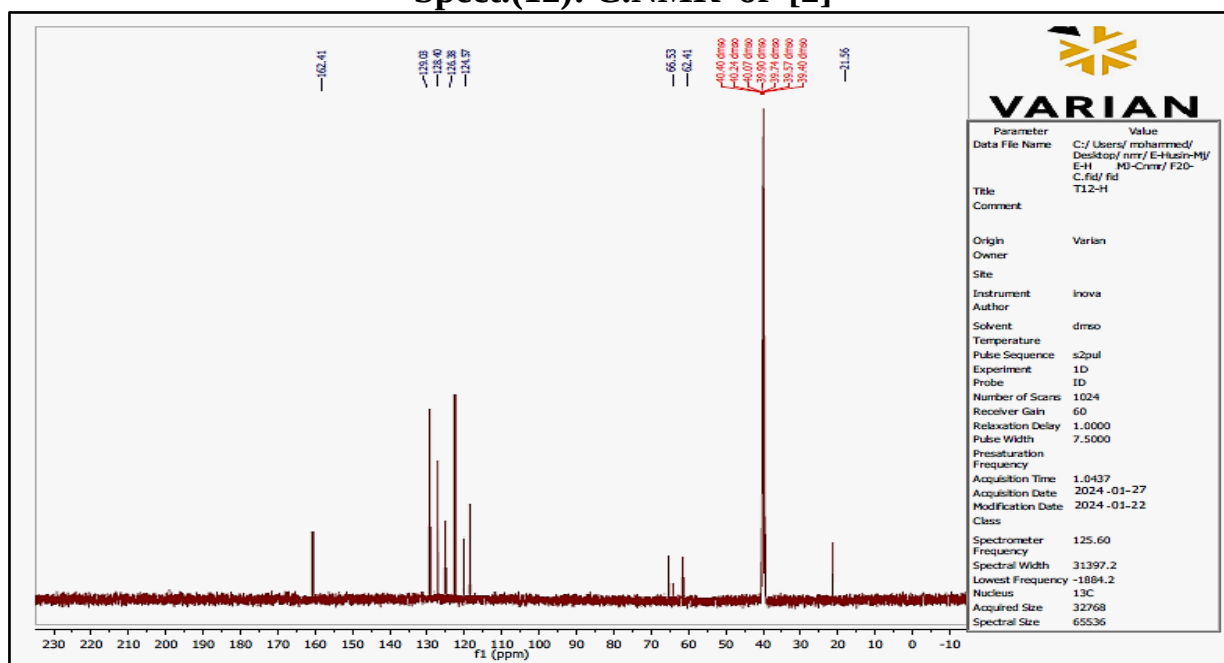
The essential signals appeared in spectrum : A single signal, ^{13}C .NMR, appeared in the nuclear magnetic resonance spectrum at (40.0) , It also appeared in the spectrum only ppm at the site (DMSO - d₆) of the carbon atoms of the solvent used., (131-115) belong to the carbon atoms of the aromatic rings, figures(11-16), all these peaks explained according to reference [13].



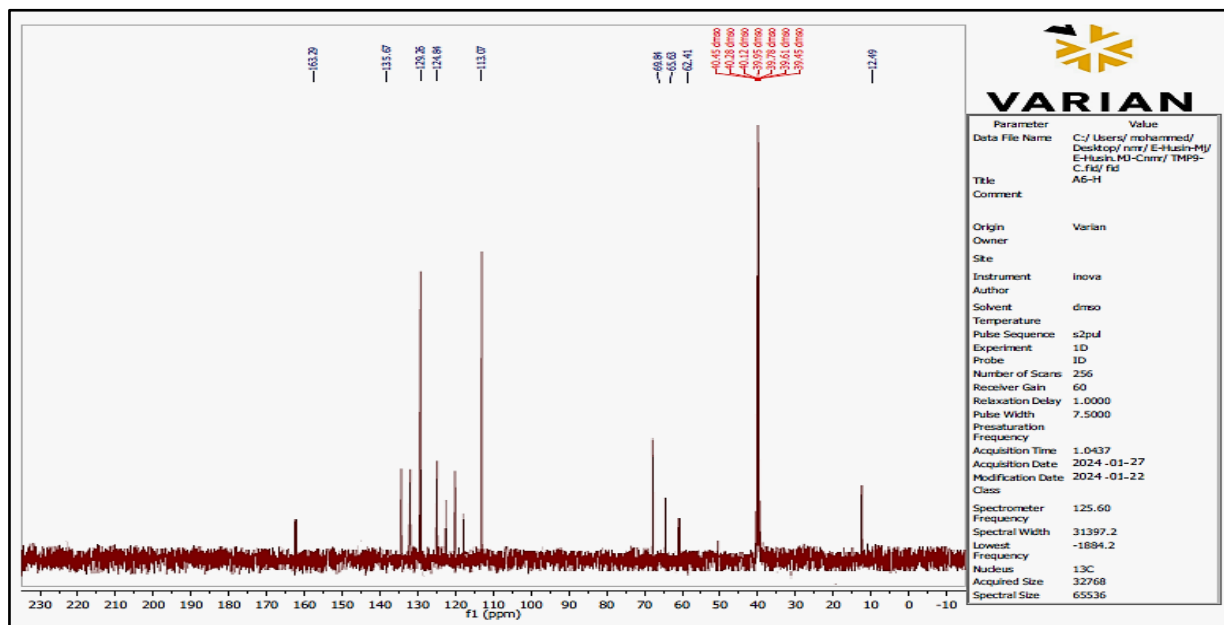
Spect.(11): C.NMR of [1]



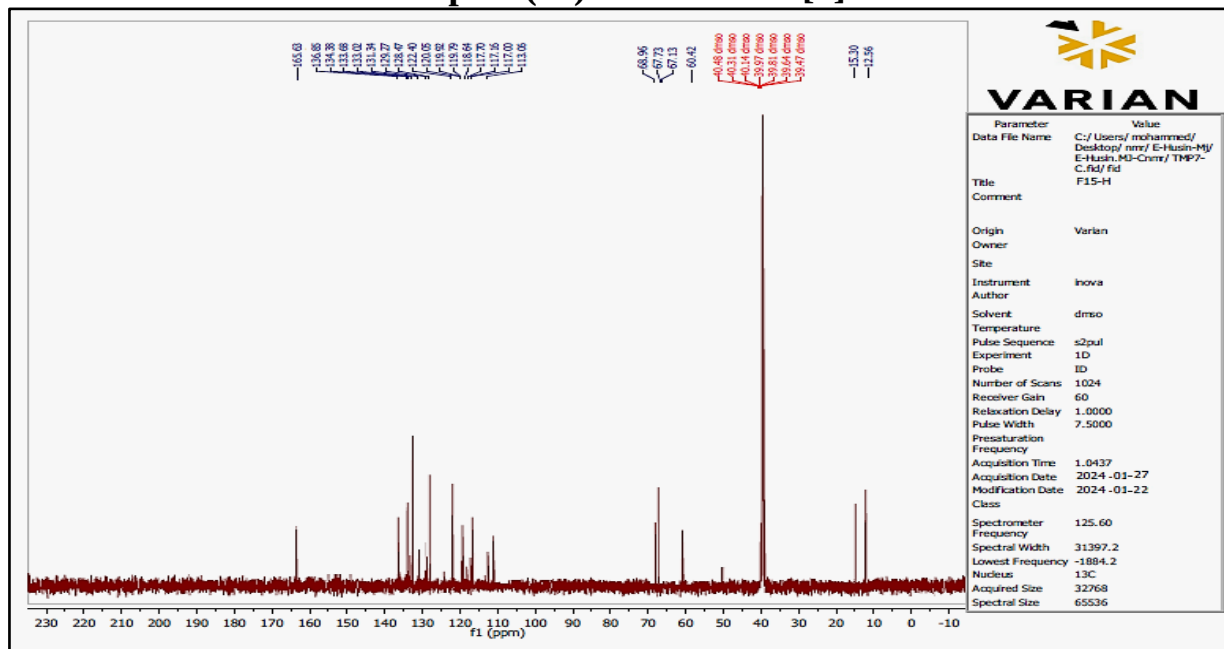
Spect.(12): C.NMR of [2]



Spect.(13): C.NMR of [3]



Spect.(14): C.NMR of [4]



Spect.(15): C.NMR of [5]

Table.(1): Chemical and Physical Properties

No. of Compounds	M.P C ° ±2	R _f	Yield %	Color
Comp. {1}	156	0.58	70	Yellowish
Comp. {2}	174	0.62	72	Bill Orange
Comp. {3}	200	0.60	76	Yellowish Orange
Comp. {4}	210	0.60	84	Reddish Yellow
Comp. {5}	216	0.56	80	Yellowish Orange

Anticancer-Assay :

Cyclic Compounds {4,5} were selected for anticancer evaluation (breast cancer) by MTT-Test of two types of Cells (MCF-7) as Cancer cell and (MCF-10A) as healthy cell according to study⁽¹⁰⁾, all data in photos (1, 2), Tables (2,3). The results gave good data indicated to high inhibition of tumor cells [4]. The suspended cells were centrifuged at (250 g) for (10 minutes) and the supernatant was removed, the cells were re-suspended in a freezing medium, then placed at (-70 °C) in beaker for (1-3) days, the beaker was transferred from the standard freezer boxes to the liquid (N₂) container according to studies [4, 9].

Table. (2): Cytotoxic Activity of Compound [4] continuously Breast Cancer Cells (MCF-7) and Well Cells (MCF-10A) at the equivalent medication exhausting 24 hrs., MTT trial 37⁰c.

Con. ($\mu\text{g.mL}^{-1}$)	Proportion (%) Percentage of every cells			
	MCF-7, $\text{IC}_{50} = 32.03$		MCF-10A, $\text{IC}_{50} = 326.0$	
Compound [4]	Cancer t cells (MCF-7)		Healthy cells (MCF-10A)	
	Cell - Viability	Cell - Inhibition	Cell - Viability	Cell - Inhibition
35.62	90.68	7.62	87.09	8.40
75.00	73.55	15.49	92.38	7.0662
150.00	70.71	34.04	93.84	6.12
300	55.09	50.19	95.01	5.86
600	38.03	52.11	95.41	5.59
Control	100	0.00	92.43	7.57

Table. (3): Cytotoxic Activity of Compound [5] continuously Breast Cancer Cells (MCF-7) and Well Cells (MCF-10A) at the equivalent medication exhausting 24 hrs., MTT trial 37⁰c.

Con. ($\mu\text{g.mL}^{-1}$)	Proportion (%) in percentage of every cells			
	MCF-7, $\text{IC}_{50} = 34.18$		MCF-10A, $\text{IC}_{50} = 210.03$	
Compound [5]	Cancer cells (MCF-7)		Healthy cells (MCF-10A)	
	Cell - Viability	Cell - Inhibition	Cell - Viability	Cell - Inhibition
35.62	86.42	13.76	88.31	6.85
75.00	70.03	20.140	90.07	6.44
150.00	66.09	28.05	94.92	5.00
300	67.75	49.07	95.76	3.52
600	31.48	65.32	96.74	3.62
Control	100.0	0.00	95.44	4.88

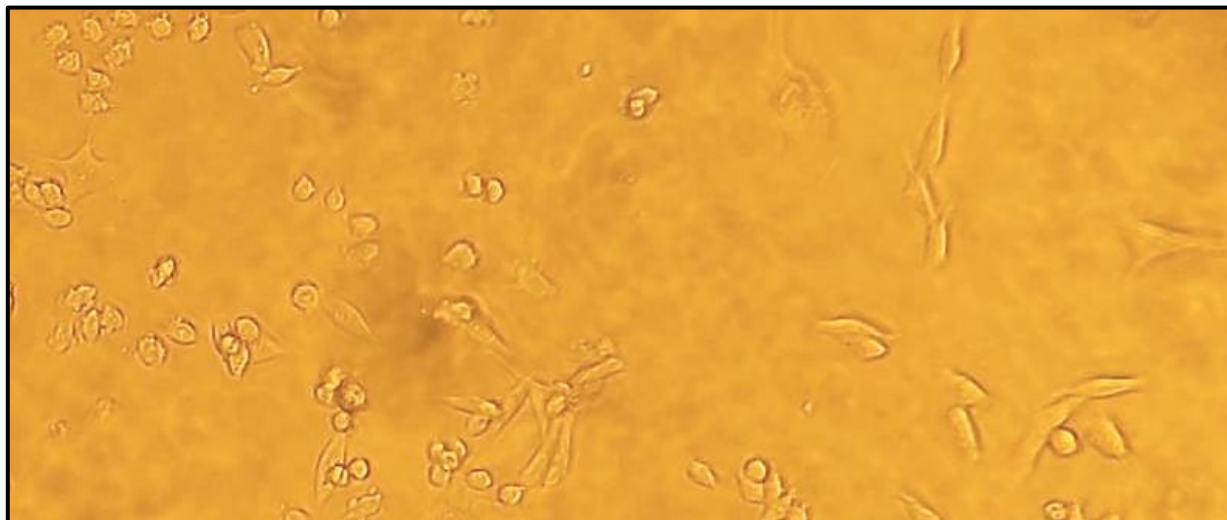


Photo. 1: Anti-cancer commotion of Cyclic {4} on (MCF-7) at 600µg/ml

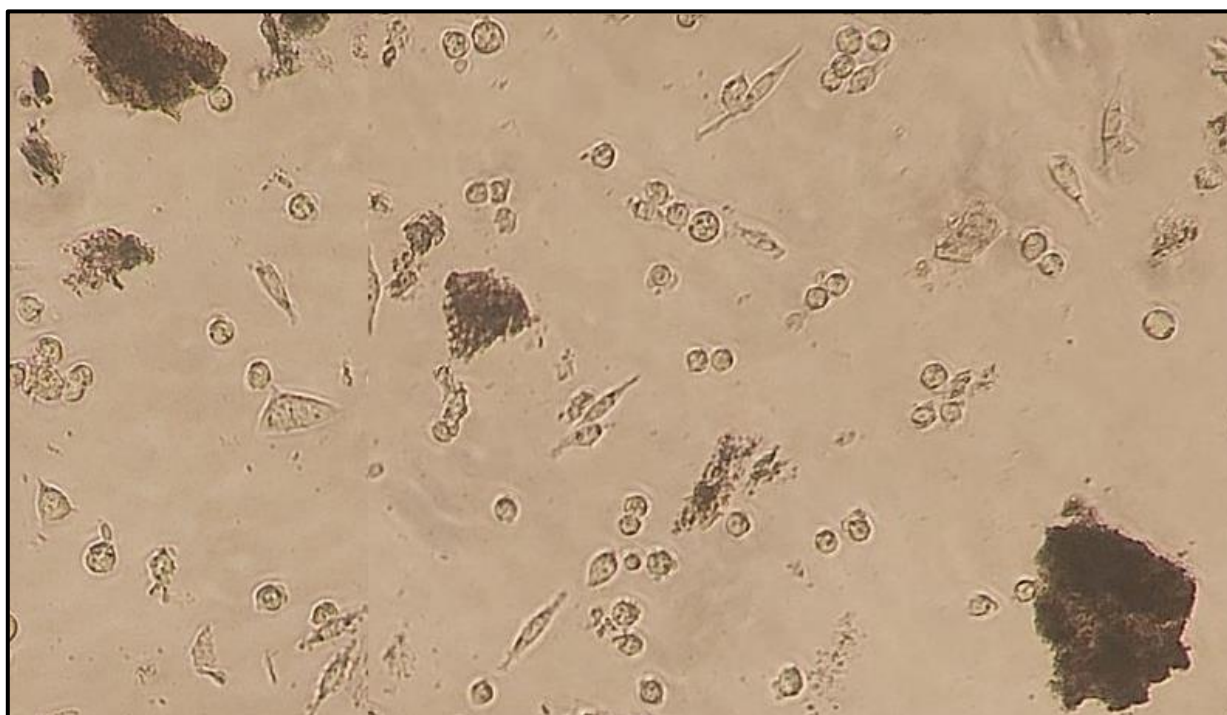


Photo. 2: Anti-cancer commotion of Cyclic {4}on (MCF-A 10) at 600µg/ml

Conclusions

From results of current study ,all spectral techniques pointed to strong evidences for formation of Anile and bicyclic compounds via appearance new bands like (imine $\text{CH}=\text{N}$, endocycle of Nitrogen compounds , other functional bands) via insertion reaction of Nitrogen and sulfur atoms in ring to formation bicyclic–structure.

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تحضير و تقييم فعالية سرطانية ودراسة طيفية لمشتقات حلقية جديدة للترايزول

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الخلاصة :

الترايزولات تلعب دوراً أساسياً في الصيدلة، وبشكل خاص عند التعرض للتركيب الكيميائي للدواء، والتعمق في عمليات الأيض الدوائية، والتحضيرات الحيوية. توجد بكثرة في الفيتامينات، والأصبغ وغيرها العديد من المنتجات الطبيعية. تُستخلص معظم المركبات العضوية غير المتجانسة من مصادر حيوانية أو مصادر نباتية. تدخل في بعض الصناعات، مثل صناعة النايلون المستخدم في صناعة الملابس، وفي صناعة فيتامين C. تمثل المجموعة الفعالة في العديد من الإنزيمات، والإنزيمات المساعدة، والبوليميرات، وصناعة الأحماض النووية. كما توصلت الدراسة إلى درجات تشخيص وتحديد الصيغة البنائية باستخدام طيف الأشعة تحت الحمراء (FT-IR)، وطيف الرنين المغناطيسي البروتوني ($^1\text{H-NMR}$)، وطيف الرنين المغناطيسي النووي الكربوني ($^{13}\text{C-NMR}$) حسب الصيغة الوظيفية. المجموعات وظهورها في كل طيف. كما أنه عند مقارنة عملية تحضير المشتقات تبين أن اختلاف المجموعات المستبدلة من المركب الأساسي له تأثير واضح على المدة الزمنية لاكتمال التفاعل والتي تم رصدها باستخدام تقنية TLC، بالإضافة إلى الفرق في الفعالية نتيجة الاختلاف في هذه المجموعات. كما تم تقييم وتوصيف كفاءة بعض المربين في تثبيط خلايا سرطان الثدي والخلايا المتضررة من الورم.