SYNTHESIS, INVESTIGATION AND ANTICANCER EVALUATION OF NOVEL MACROCYCLIC FORMAZAN AND LINEAR FORMAZAN

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Abstract: Innovative Macrocyclic Formazan Compounds as a bio-compounds were generated and advanced globally designed for the initial stage by investigator Professor. Dr. Nagham M. Aljamali in 2019) via more than five steps of reaction with various catalyst like (Sodium- alkali 5% ,Pipridine, trimethyl amine , etc.). For that reason, these invented compounds act one of the advanced and new assemblies which have a deficiency of references and researches which lead us to prepare and create a restraint of these innovated compounds and studied by abundant requests in future literatures represented by biological, pharmaceutical, nano, antimicrobial studies, also as anticancer agents ,Normal Formazan was first synthesis over a century ago, but still attention of chemists ,biologists ,technologists and other specialists and here in this research. A numeral of applied spectroscopic studies have been used to revel their chemical assemblies which delivered to sturdy indications of their chemical assemblies through various technical devices like (FT IR-Ranges, 1H.NMR-Ranges, 13C.NMR-Ranges)., Also anticancer study

Keywords: Macrocyclic Formazan, Normal Formazan ,Schiff base, Azo, Anil, innovative compounds, breast cancer.

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INTRODUCTION

Macrocyclic Formazan Compounds
are Novel-Inventive structures in the arena of organic chemistry and are created a novel modernization by Professor Dr. Nagham Aljamali in 2019 once these structures were originated for the earliest time internationally(1- 3) , and for their literatures and studies are rare in this ground for this purpose the investigator Prof. Dr. Nagham Aljamali industrialized different compounds from Macrocyclic Formazan by using countless conditions and altered basic medium(3-7) like (Pyridine ,Pi.pridine ,5 % Sodium hydroxide , Triethylamine etc.)(1, 2), and linked them with heterocyclic derivatives and pharmaceutical drugs(2-4) with additional than double hetero atoms to rise their usefulness(5-9) , biotic(10-16) besides to Nano with engineering requests(12-17). The structure of Macrocyclic Formazan is (-N=N=C-N- in cyclic structure) or (-N=N-C-N-NH- in cyclic structure) conferring to form of amine in reaction(1, 3) .

Normal Formazan Compounds
the Normal Formazan (Linear not Cyclic Formazan have been prepared by more than methods to have essential medicinal(8-9) application due to their several activities for instance antiviral ,antibacterial, antifungal , anti-inflammatory, analgesic antifungal , antitumor , anti-HIV etc. Several formazan showed talented antifertility, anti-parkinsonian and anticonvulsant(31-37).

Structure of Normal Formazan
Formazan Skeleton is (-N=N-C=N-NH) or (-N=N-C=N-N-) in Normal or Liner structure(4-11) , fragment according to type and structure of reactants from aromatic amine like (aniline , phenyl hydrazine ,etc.) the formazan derivatives are currently commonly applied each in chemistry and biology, the reason for this that it contains two nitrogen atoms(12-33).

Investigational Instruments
All invented compounds measured via :melting points , FT.IR Ranges ,1H.NMR Ranges., 13C.NMR– Ranges .

EXPERIMENTAL METHODS

Preparation of Trimethoprim-Imine [1]
Trimethoprim drug (0.001 mol ,0.290 g) refluxed with (0.002 mol ,0.240 g) of p-methyl benzaldehyde for (4 hrs) with (3 drops) of glacial acetic acid and absolute ethanol (30 ml), the product sifted ,desiccated ,purified to crop Trimethoprim-Imine [1] according to procedures(1 ,3) .

Preparation of Liner Formazan Compound [2]
Solution of Trimethoprim-Imine [1] (0.001 mol , 0.494g) with (5 ml of 5% NaOH) in ice path ,then solution of diazonium salt was added (0.002 mol ,0.218g) of 2-aminophenol in

basic medium to the reaction, after (32 hrs), the product sifted ,craved with distilled water ,desiccated ,purified to crop derivative of Formazan [2] according to procedures(1 ,3) .

Preparation of Liner Formazan Compound [3]
Solution of Trimethoprim-Imine [1] (0.001 mol , 0.494g) with (5 ml of 5% NaOH) in ice path ,then solution of diazonium salt was added (0.002 mol) of 5-methylthiazol-2-amine in basic medium to the reaction, after (52 hrs) , the product sifted ,craved with distilled water ,desiccated ,purified to crop derivative of Formazan [3] according to procedures(1 ,3) .

Preparation of Liner Formazan Compound [4]
Solution of Trimethoprim-Imine [1] (0.001 mol , 0.494g) with (5 ml of 5% NaOH) in ice path ,then solution of diazonium salt was added (0.002 mol , 0.190g) of Pyrimidine-2-amine in basic medium to the reaction, after (48 hrs) , the product sifted ,craved with distilled water ,desiccated ,purified to crop derivative of Linear Formazan [4] according to procedures(1 ,3) .

Preparation of Liner Formazan Compound [5]
Solution of Trimethoprim-Imine [1] (0.001 mol , 0.494g) with (5 ml of 5% NaOH) in ice path ,then solution of diazonium salt was added (0.002 mol , 0.214g) of P-toluidine in basic medium to the reaction, after (52 hrs) , the product sifted ,craved with distilled water ,desiccated ,purified to crop derivative of Linear Formazan [5] according to procedures(1 ,3) .

Preparation 5-(4-aminophenyl)-1,3,4-thiadiazol-2-amine Compound [6]
Anthranilic acid (0.001 mol,0.192g) was reacted with Thiosemicarbazide (0.001 mol,0.091g) in 30 ml absolute ethanol (5ml of H2SO4) with refluxing for 30 hrs in 75 oc then cyclization step, the product sifted , desiccated , purified to crop Cyclic Compound [6] by following innovated procedures in literatures(1 ,3) .

Preparation of Macrocyclic Formazan Compound [7]
Trimethoprim-Imine [1] (0.001 mol , 0.494g) reacted in basic medium of (pyridine) with (0.001 mol , 0.192g) from diazo salt of 5-(4-aminophenyl)-1,3,4-thiadiazol-2-amine in same steps to crop Macrocyclic Formazan Compound [7] by succeeding innovated procedures in collected works(1 ,3) .

Preparation of Imine [8]
5-(4-aminophenyl)-1,3,4-thiadiazol-2-amine [Compound 6] (0.001 mol , 0.192g) refluxed with (0.002 mol , 0.281g) of p-chloro benzaldehyde for (4 hrs) with (3 drops) of glacial acetic acid and absolute ethanol (30 ml), the product sifted ,desiccated ,purified to crop Imine according to procedure(1, 3) .

Preparation of Macrocyclic Formazan Compound [9]
Compound [8] (0.001 mol , 0.437g) reacted in (pyridine) with (0.001 mol , 0.108g) from diazo salt of benzene-1,4-diamine through same steps to crop Invented Macrocyclic Formazan Compound [9] by succeeding innovated procedures in collected works (1 ,3) .

Preparation of Macrocyclic Formazan Compound [10]
Compound [8] (0.001 mol , 0.437g) reacted in (pyridine) with (0.001 mol , 0.290g) from diazo salt of trimethoprime through same steps to crop Invented Macrocyclic Formazan Compound [10] by succeeding innovated procedures in collected works (1 ,3) .

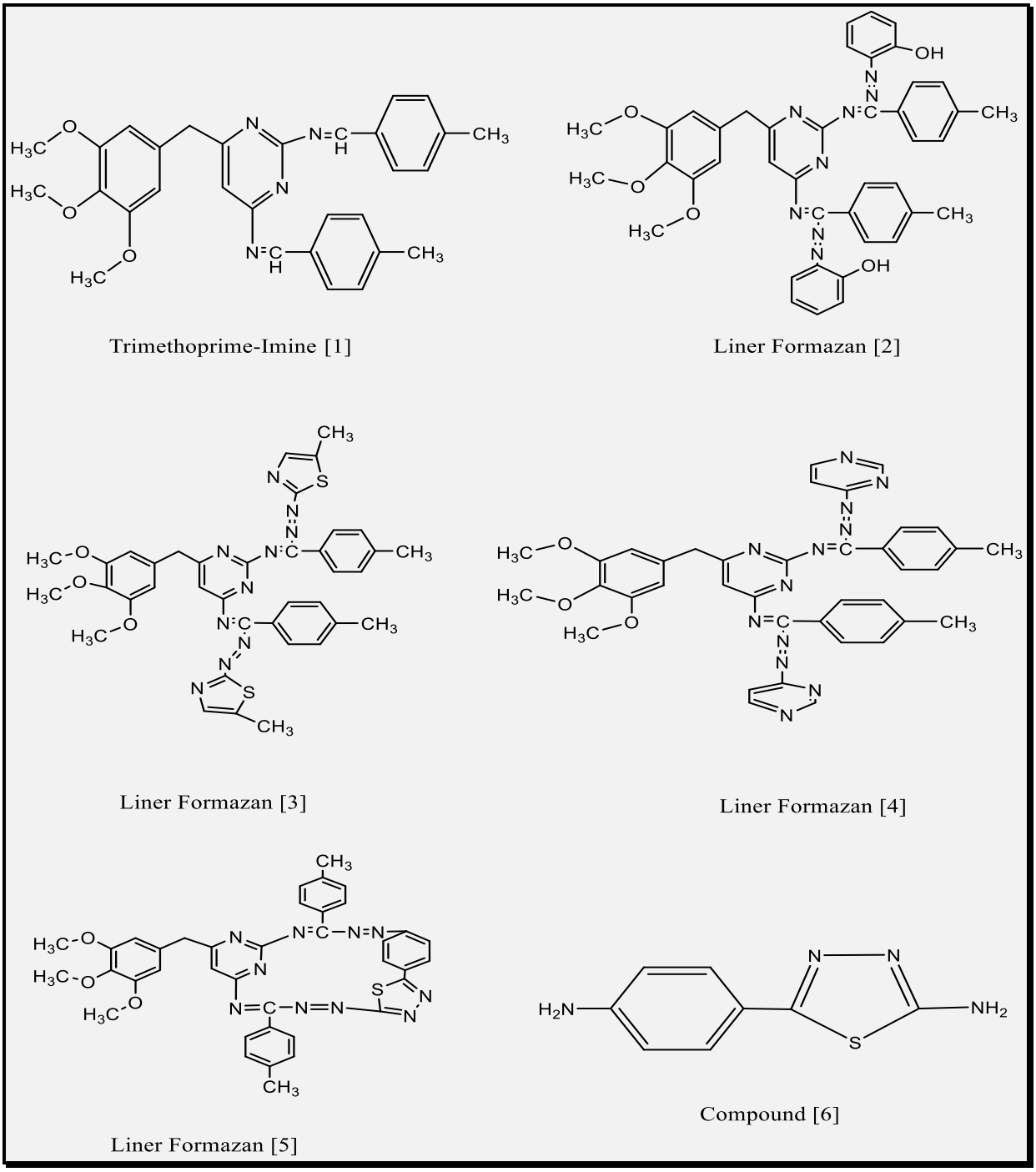
Preparation of 5,5'-(1,4-phenylene)bis(1,3,4-thiadiazol-2-amine) Compound [11]
Terephthalic acid(0.001 mol,0.166g) was reacted with Thiosemicarbazide(0.002 mol,0.182g) in 30 ml absolute ethanol 5ml of H2SO4 with refluxing for 30 hrs in 75 oc then cyclization step, the product sifted , desiccated , purified to crop compound [11] according to procedure(1, 3) .

Preparation Imine Compound [12]
5,5'-(1,4-phenylene)bis(1,3,4-thiadiazol-2-amine) [Compound 11] (0.001 mol , 0.276g) refluxed with (0.002 mol , 0.370g) of 3-bromobenaldehyde for (5 hrs) with (3 drops) of glacial acetic acid and absolute ethanol (30 ml), the product sifted ,desiccated ,purified to crop Imine according to procedure(1, 3) .

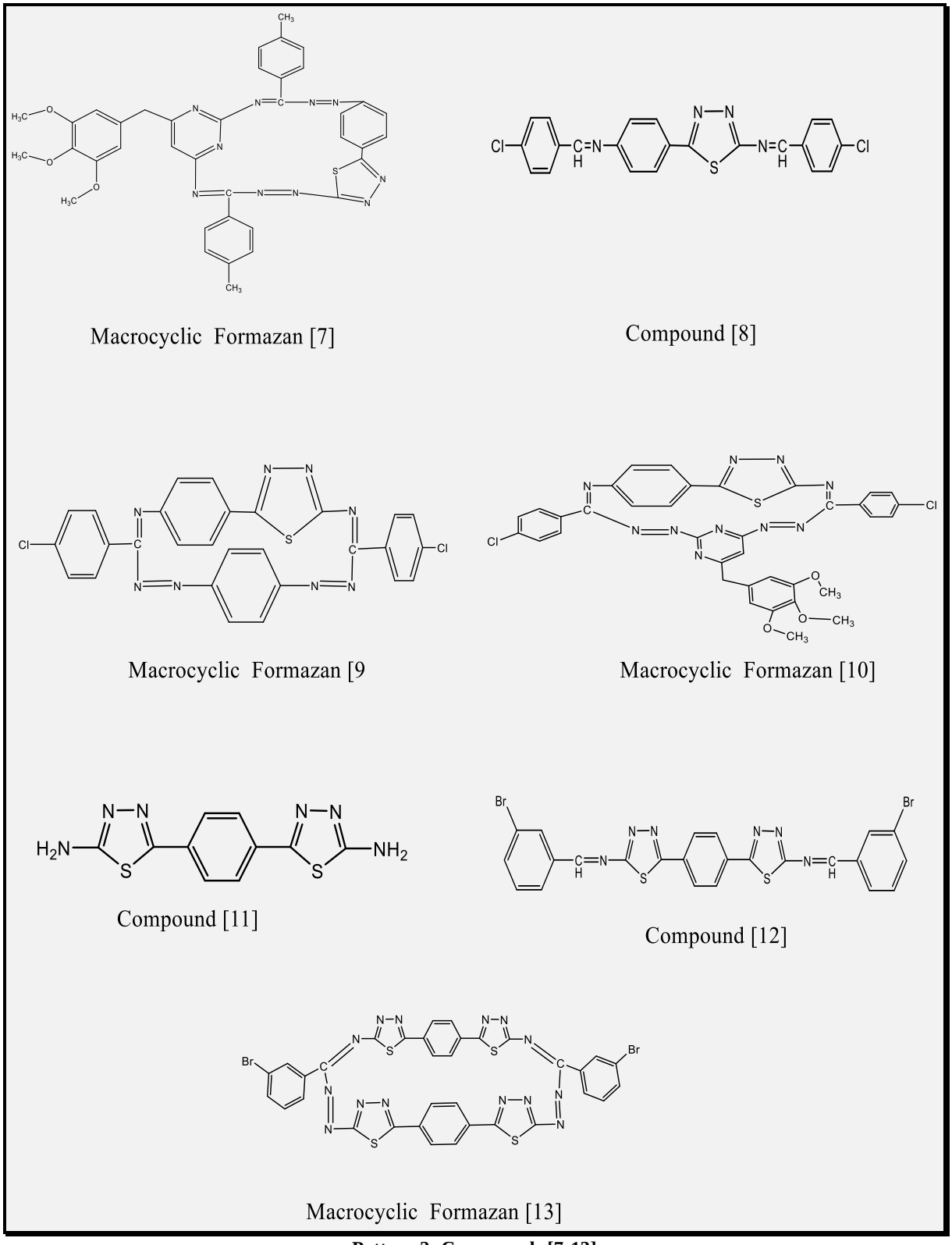
Preparation of Macrocyclic Formazan Compound [13]
Compound [12] (0.001 mol , 0.610g) reacted in (pyridine) with (0.001 mol , 0.276g) from diazo salt of 5,5'-(1,4-phenylene)bis(1,3,4-thiadiazol-2-amine) through many steps to crop Invented Macrocyclic Formazan Compound [13] by succeeding innovated procedures in works (1, 3) .

Preparation of Macrocyclic Formazan Compound [14]
Compound [12] (0.001 mol , 0.610g) reacted in (pyridine) with (0.001 mol , 0.290g) from diazo salt of trimethoprime through same steps to crop Invented Macrocyclic Formazan Compound [14] by following innovated procedures in collected works (1, 3) .

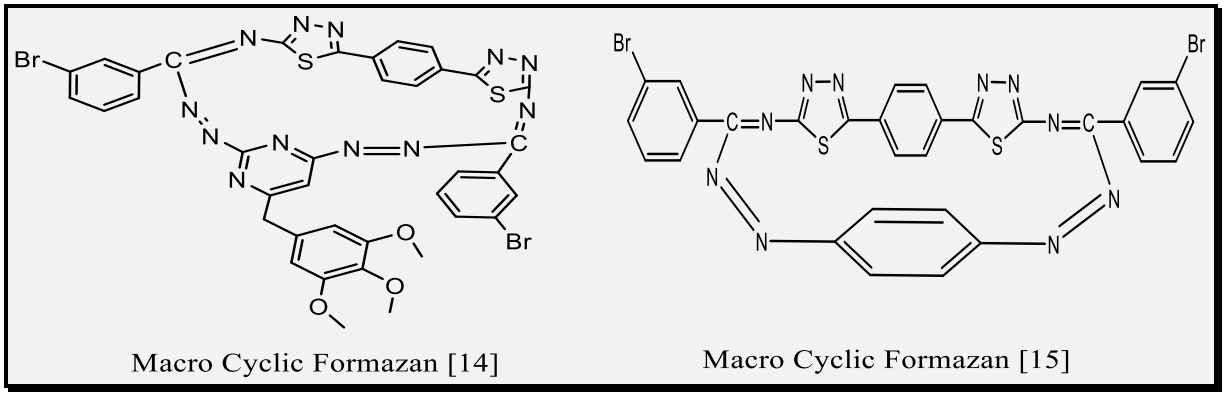
Preparation of Macrocyclic Formazan Compound [15]
Compound [12] (0.001 mol , 0.610g) reacted in (pyridine) in (pyridine) with (0.001 mol , 0.108g) from diazo salt of benzene-1,4-diamin through same steps to crop Invented Macrocyclic Formazan Compound [15] by following innovated procedures in collected works (1, 3) .



Pattern.1: Compounds [1-6]



Pattern.2: Compounds [7-13]



Pattern.3: Compounds [14-15]

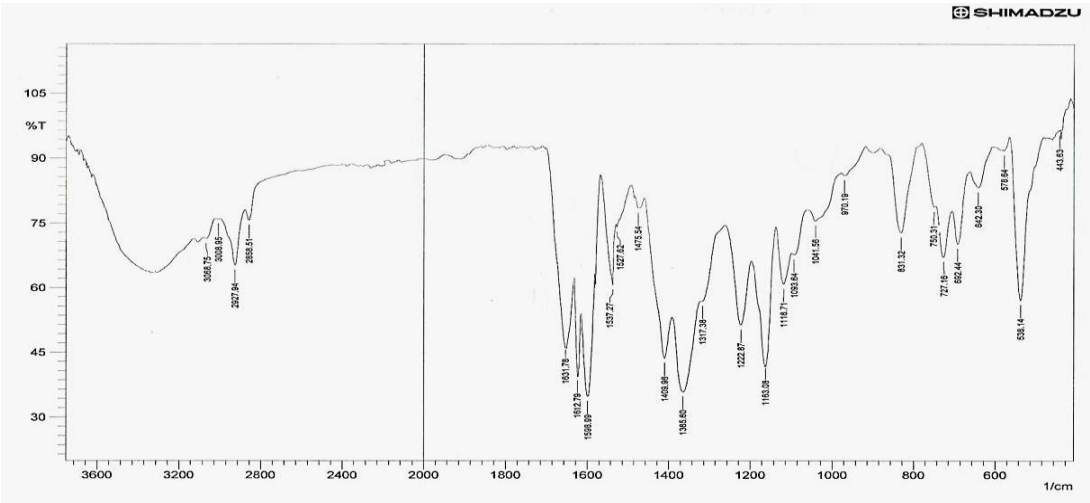
RESULTS AND DISCUSSION

Series of identification – Ranges and anticancer study against Breast Cancer were carried out :

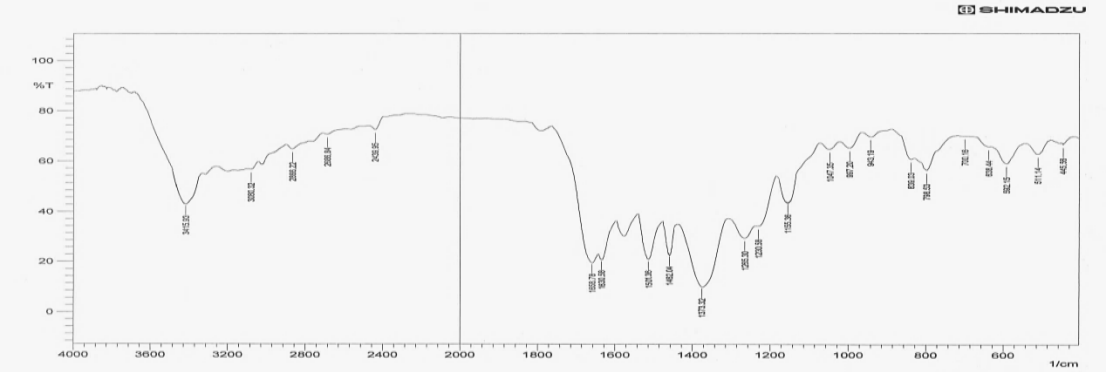
Evidences via Spectra

FT.IR- Indication of Trimethoprim- Imine, Liner Formazan and Invented Macrocyclic Formazan compounds

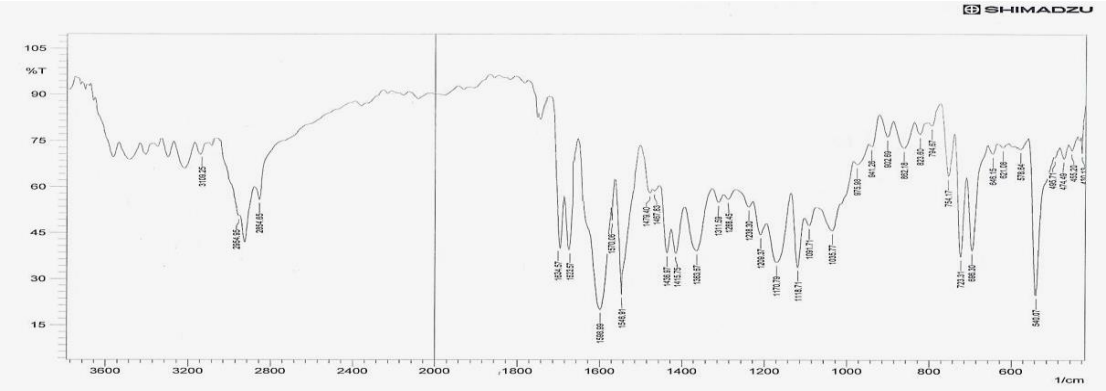
The initial categorization of Trimethoprim- Imine is appearance of Schiff base at [(1621) (1616), (1613) due to (C=N-) in compounds [1-8-12] respectively. Also in same compounds appeared many bands for (C=N-) Imine group and other due to endo cycle at [(1658), (1634), (1646), (1659), (1641), (1648), (1658) (1650) in compounds [2-3-4-5-10-13-14-15] . The disappearance of the COOH group and the appearance of an absorption band for an NH2 group in the (3338 -3398) (3332 – 33353) region, as well as the appearance of a C-S absorption band at (769 , 763) and the appearance of C=N endo cyclic of Thiadiazole absorption at (1639 , 1637) in compound [6 – 11]. Normal or Liner compounds we noted shifting of frequencies of Imine group (CH=N) in starting compounds -Imine compound [1] that were about at (1612) Cm-1 which shifted to (1630 , 1623) (1635 , 15637)Cm-1 for (-C=N-) due to formation of Liner Formazan and appearance Azo group of Formazan (-N=N) at (1462 , 1505) (1436,1479) (1436,1490) (1443,1463) in compounds [2-5] respectively .While the Invented Macrocyclic compounds we noted shifting of frequencies of Imine group (CH=N) in starting compounds -Imine compound [8] that were about at (1616) Cm-1 which shifted to (1635) (1639) (1637)(1629) (1637) Cm-1 for (-C=N-) due to formation of Macrocyclic Formazan in compounds [9-10 -13- 14-15] respectively. Also appearance three new band in each Macrocyclic Formazan compounds[7 and 15] due to Azo group of Formazan at [(1438, 1496) and (1436 ,1465) (1438 , 1481) (1411 , 1448) (1435 , 1485)] respectively in each from Macrocyclic Formazan compounds[7 and 15], all frequencies clarified according to reference(29) , and other functional groups in figures (1-15) :



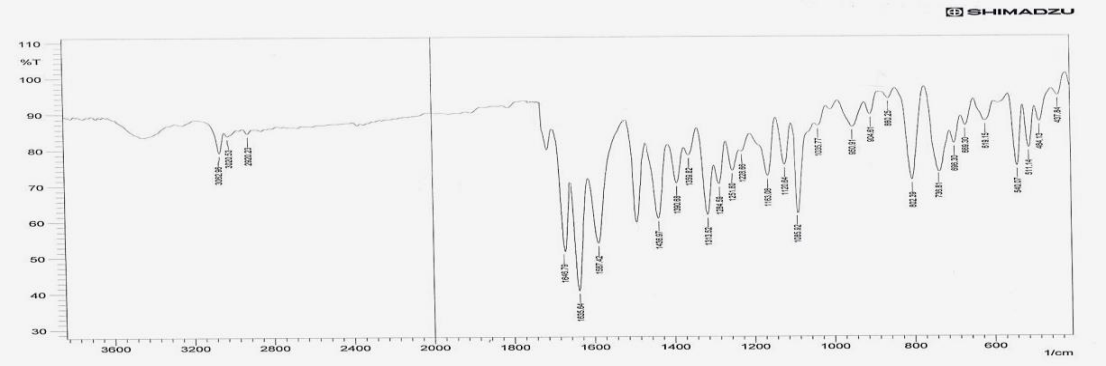
System (1): I.R of [1]



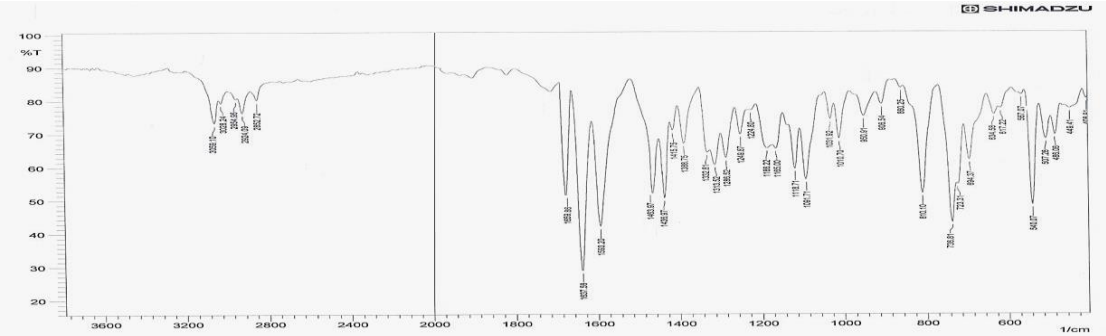
System (2): I.R of [2]



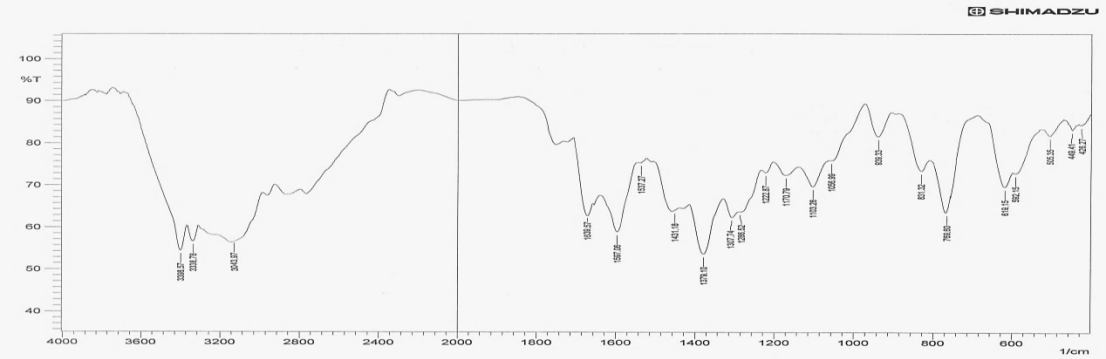
System (3): I.R of [3]



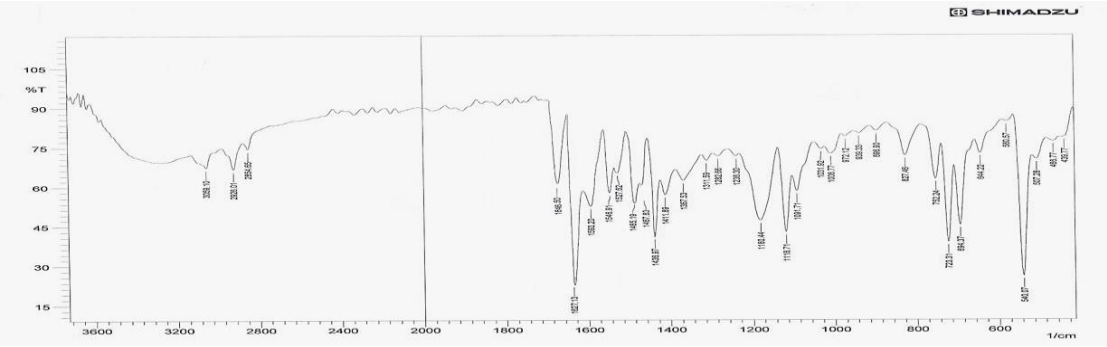
System (4): I.R of [4]



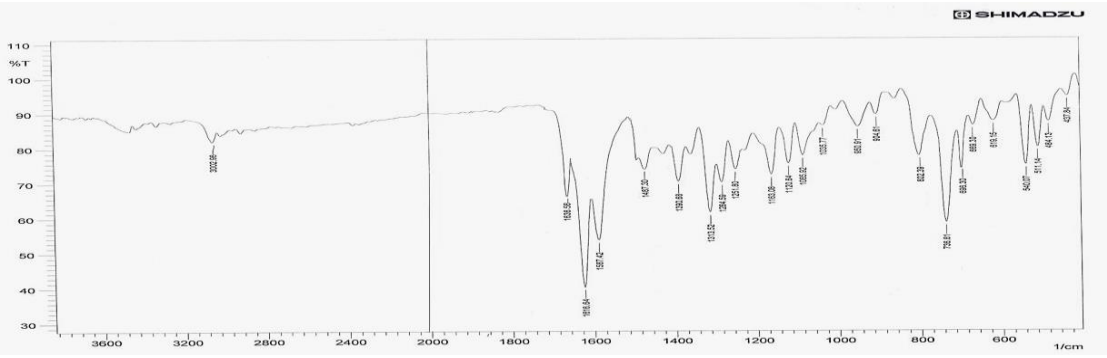
System (5): I.R of [5]



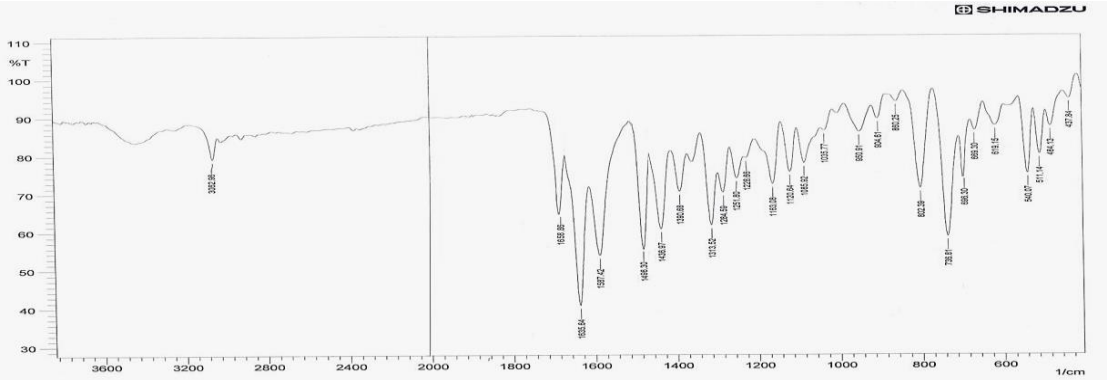
System (6): I.R of [6]



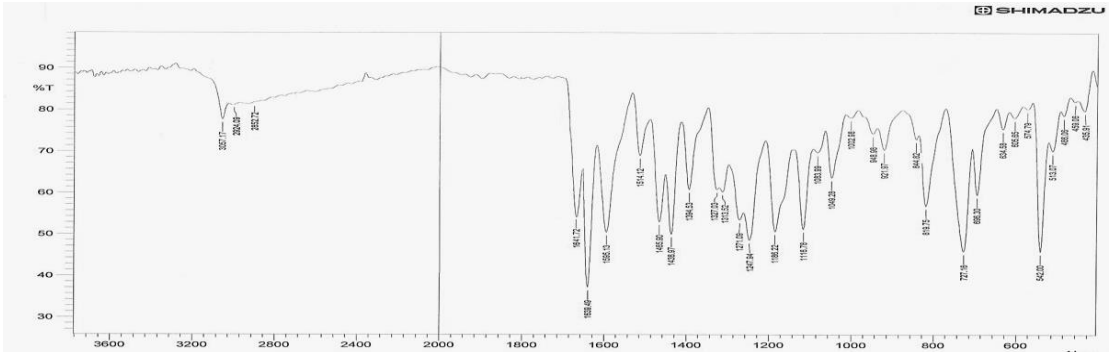
System (7): I.R of [7]



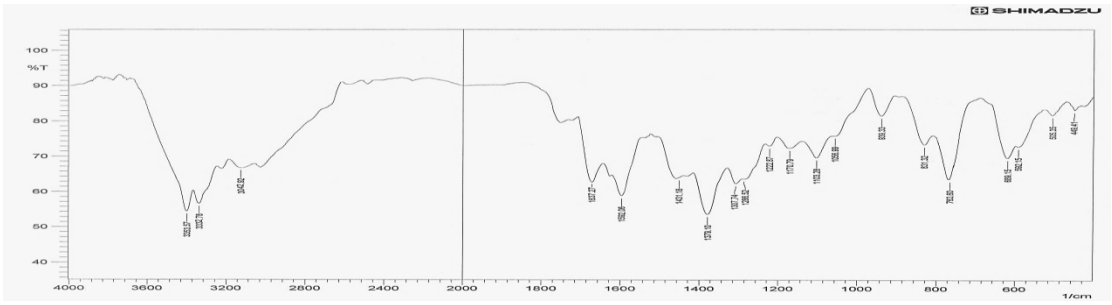
System (8): I.R of [8]



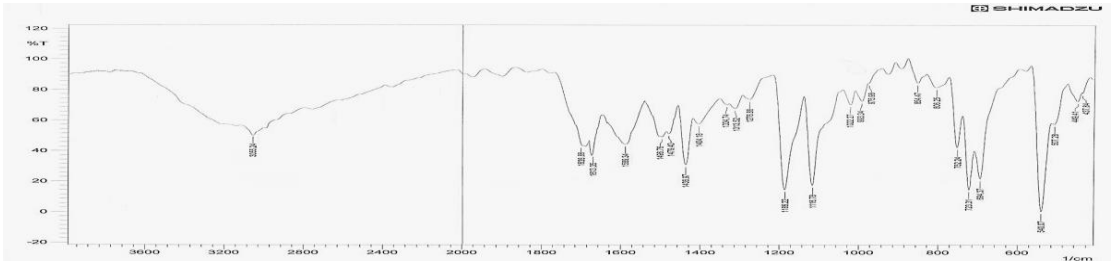
System (9): I.R of [9]



System (10): I.R of [10]



System (11): I.R of [11]



System (12): I.R of [12]

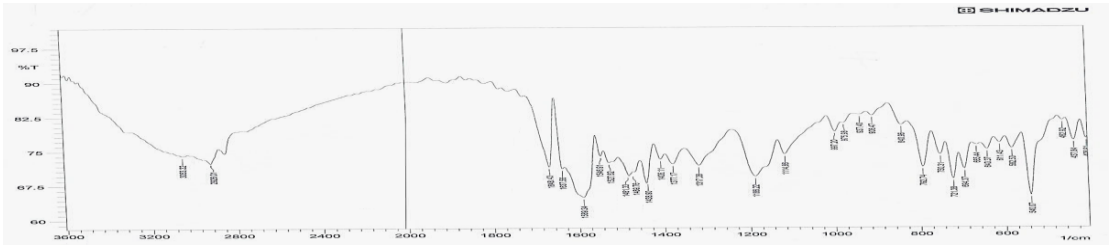
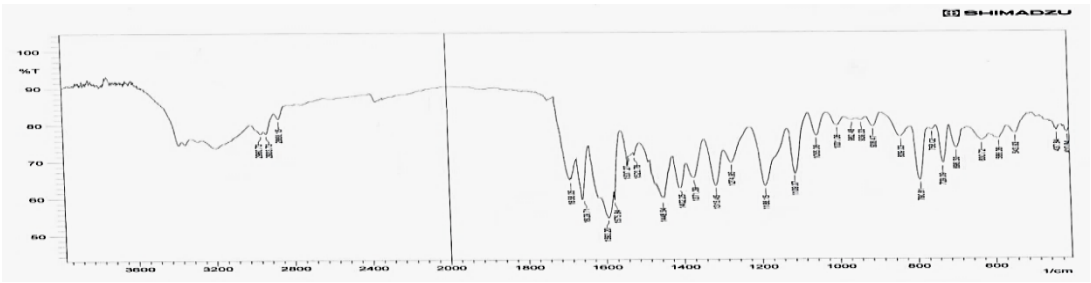
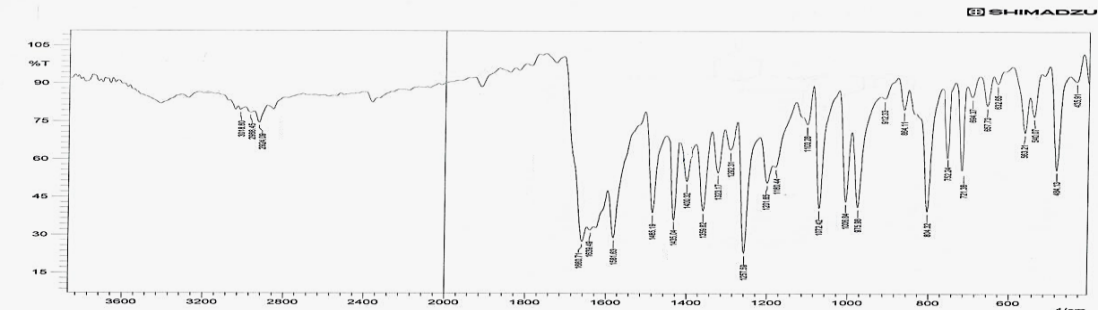


Fig (13): I.R of Compound [13]



System (14): I.R of [14]

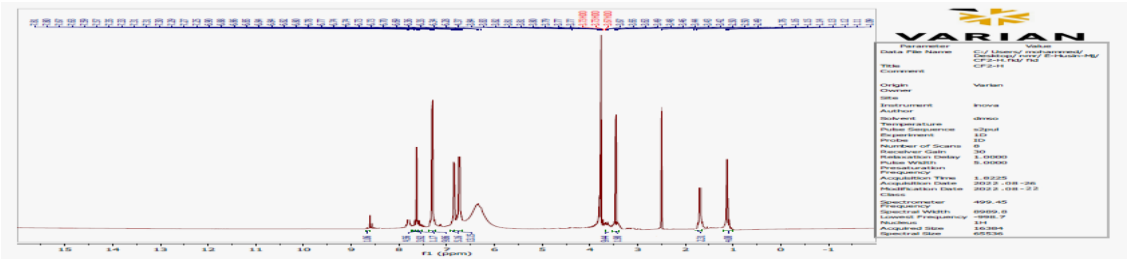


System (15): I.R of [15]

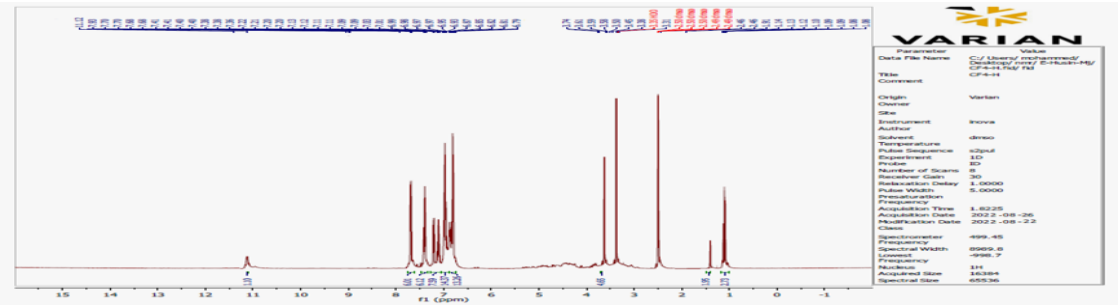
1H.NMR- Indication of Trimethoprim- Imine , Liner and Macrocyclic Formazan

The additional characterization by disappearance of peak for Aldamine group (CH=N) in initial composite (Anil compound) that were at δ (8.60) (8.47,8.43) (8.48) in Compound [1-8 12] respectively as (a starting) due to construction of (N=C-N=N) Formazan group in Liner Formazan and Macrocyclic Formazan compounds [2, 15]. ,

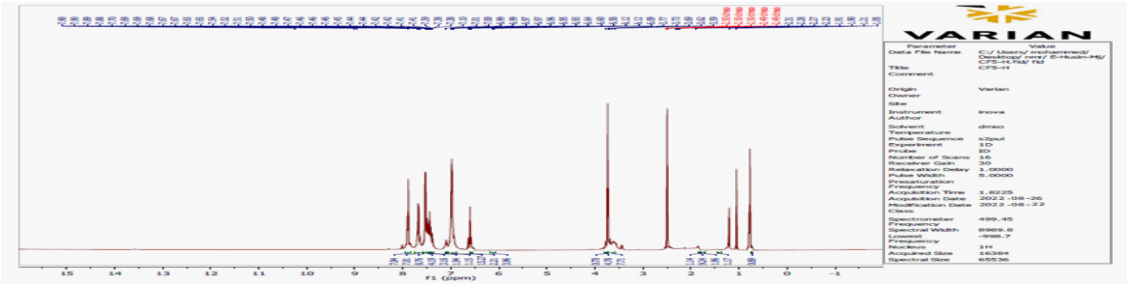
The disappearance of a proton from a Schiff base group is an indication of the formation of compounds [2-15], appearance of signals (NH2) group were at δ(5.41) (5.23) as well as Aromatic Ring signal of proton (6.44 – 7.51) (6.77-7.7) in compounds [6-11] as well appearance of signal (O-CH3) group at δ(3.49) (3.74) (3.76)(3.76) (3.79) in compounds [1-2-7-10-14]. , All signals clarified according to reference (Dr. Nagham Aljamali. 2022)(29) , and other functional groups in figures (16-30) :



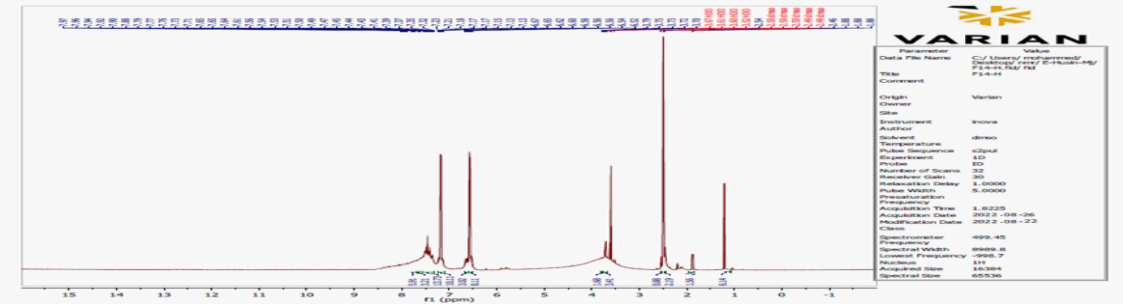
System (16): 1H.NMR of [1]



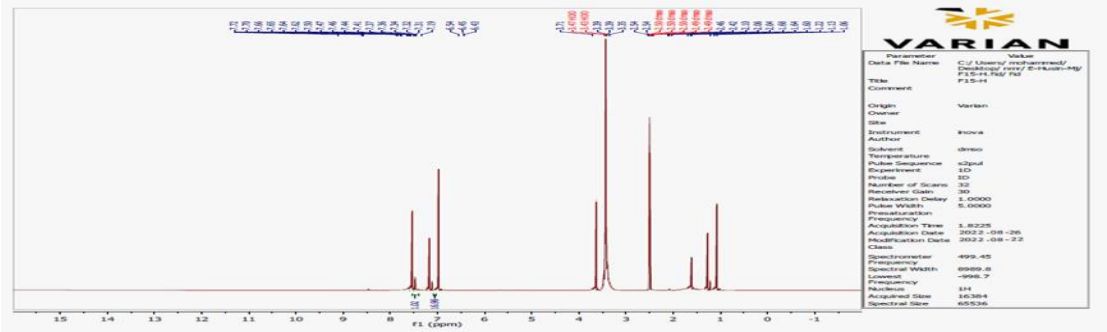
System (17): 1H.NMR- of [2]



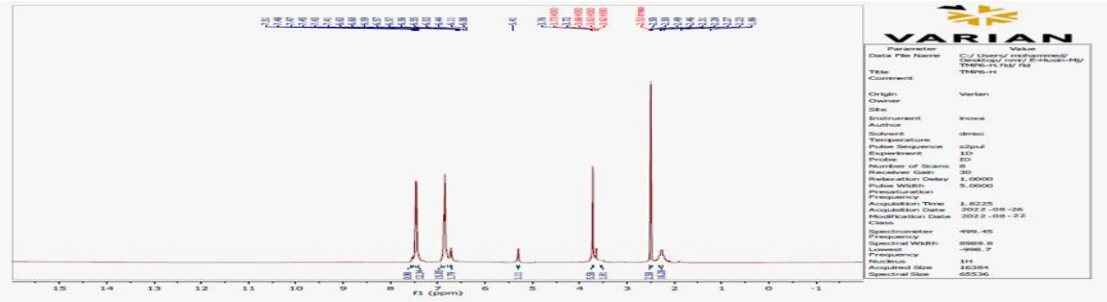
System (18): 1H.NMR- of [3]



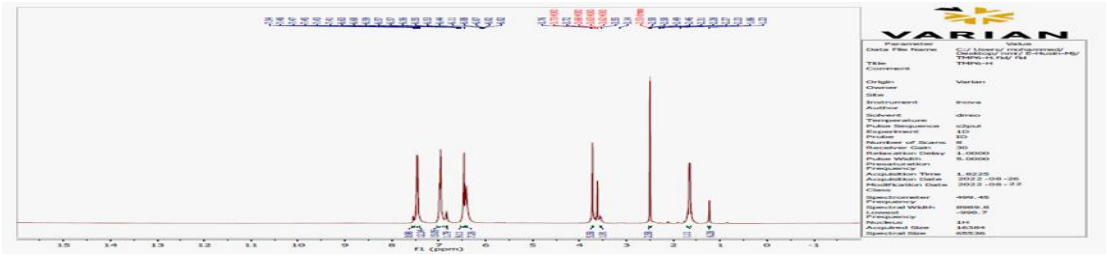
System (19): 1H.NMR- of [4]



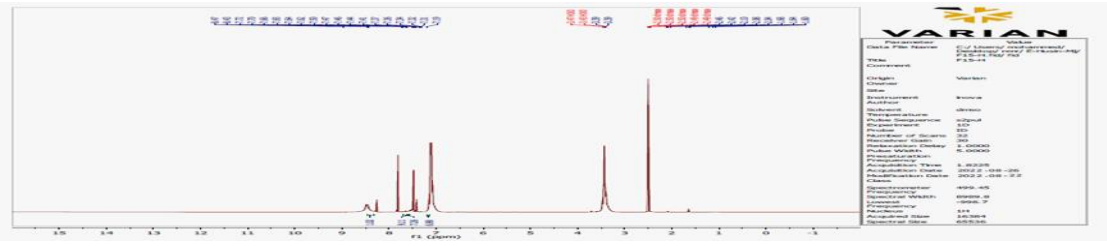
System (20): 1H.NMR- of [5]



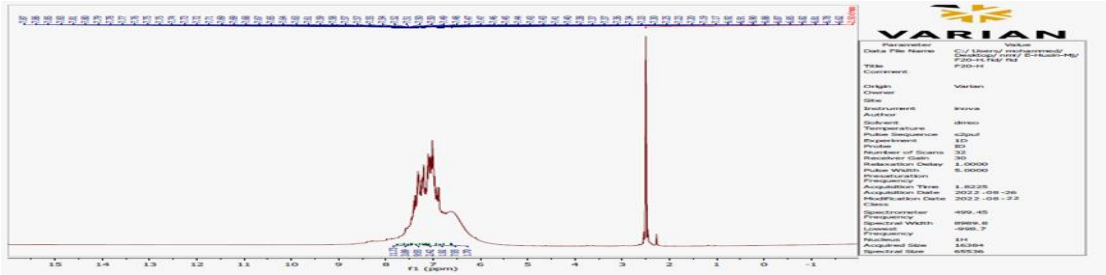
System (21): 1H.NMR- of [6]



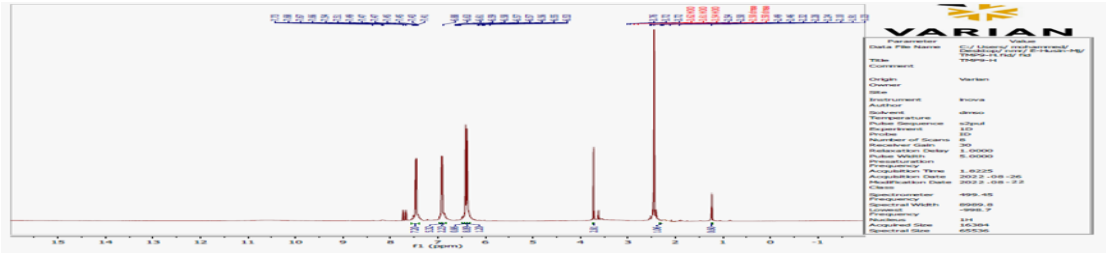
System (22): 1H.NMR- of [7]



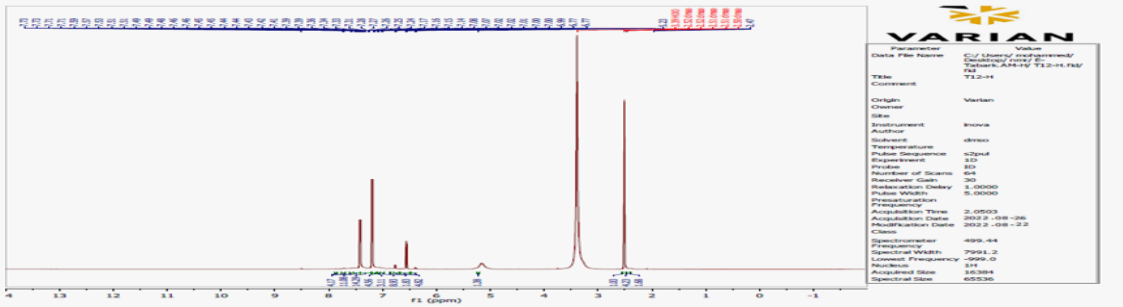
System (23): 1H.NMR- of [8]



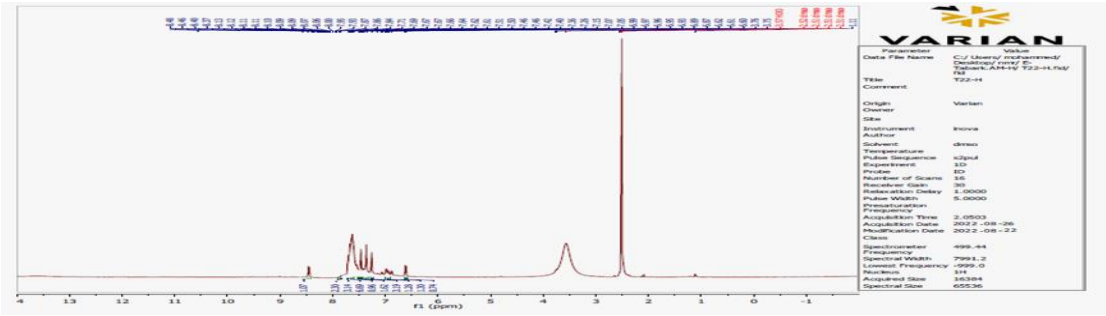
System (24): 1H.NMR- of [9]



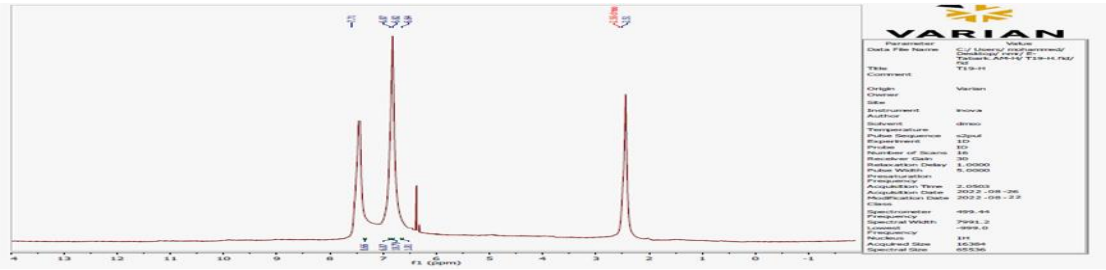
System (25): 1H.NMR- of [10]



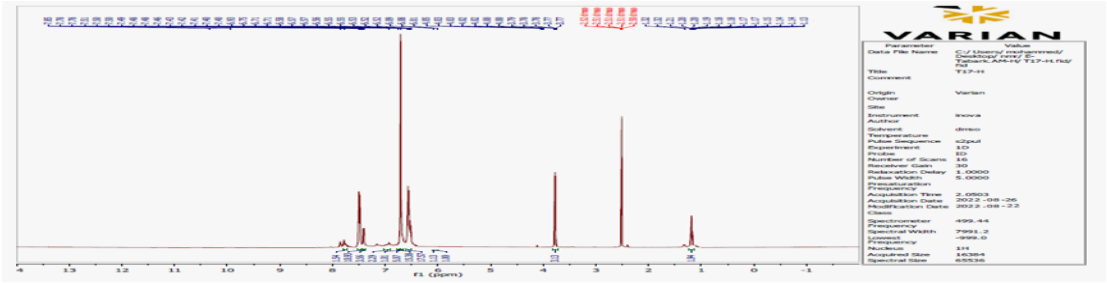
System (26): 1H.NMR- of [11]



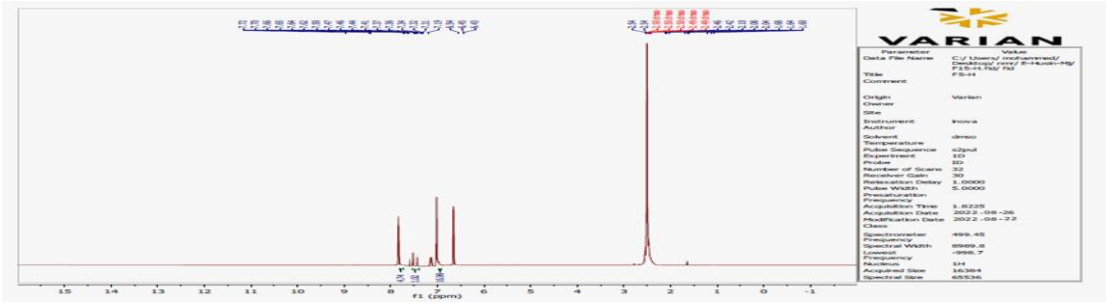
System (27): 1H.NMR- of [12]



System (28): 1H.NMR- of [13]



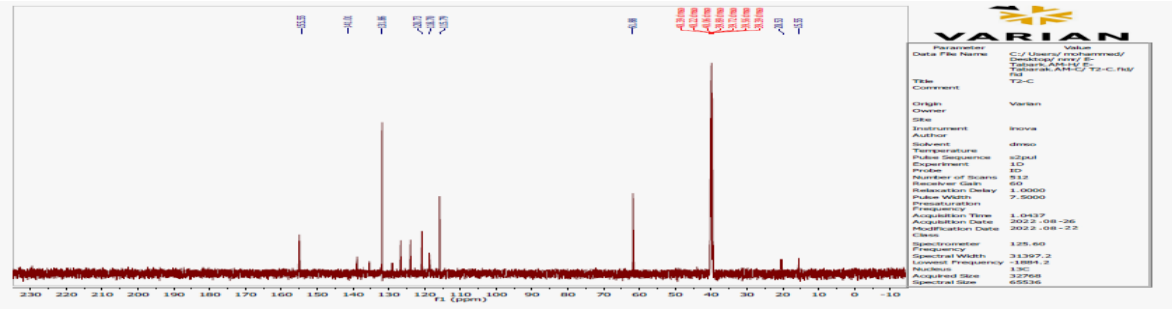
System (29): 1H.NMR- of [14]



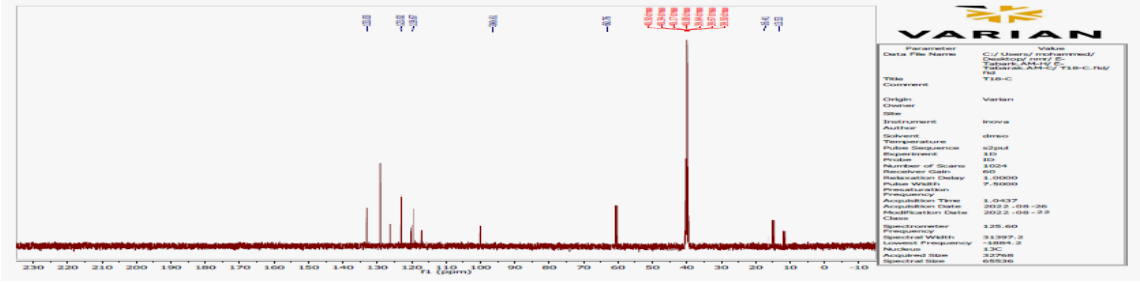
System (30): 1H.NMR- of [15]

C.NMR- Indication of Trimethoprim-Imine, Liner Formazan and Macrocyclic Formazan compounds

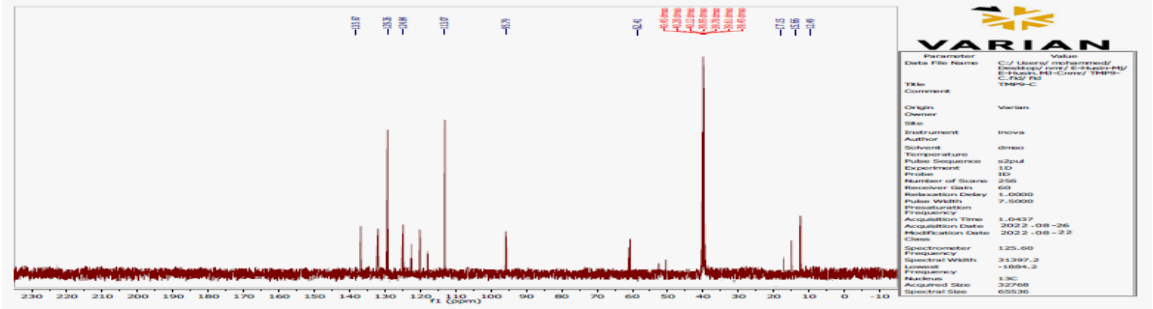
By appearance peak about at δ (155.5) ,(151.5), (156.9 in Imine compound [1] ,[8], and [12] respectively for carbon atom in imine groups for these compounds ,while all these peaks shifted to (100.0), (99.5), (97.7) and like this in Formazan compounds [2], [3],[4],[5] ,[7],[9],[10], [13],[14] and [15] respectively as a result of formation of Formazan compounds, figures(31-38), all these peaks explained according to reference(29) .



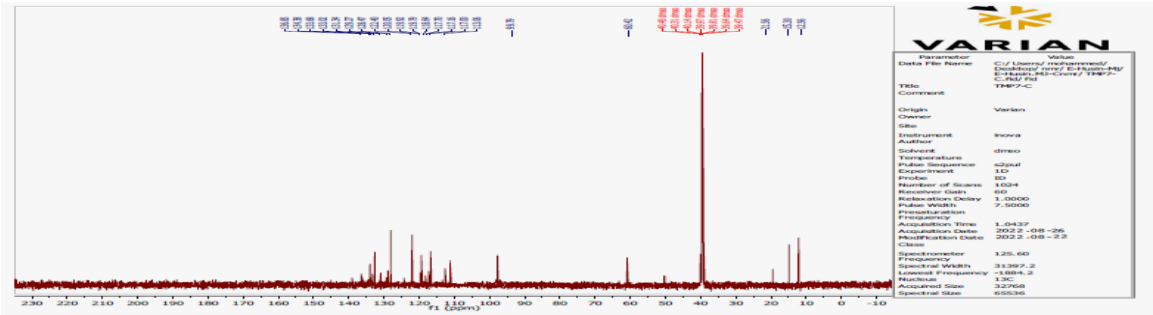
System.(31): C.NMR of [1]



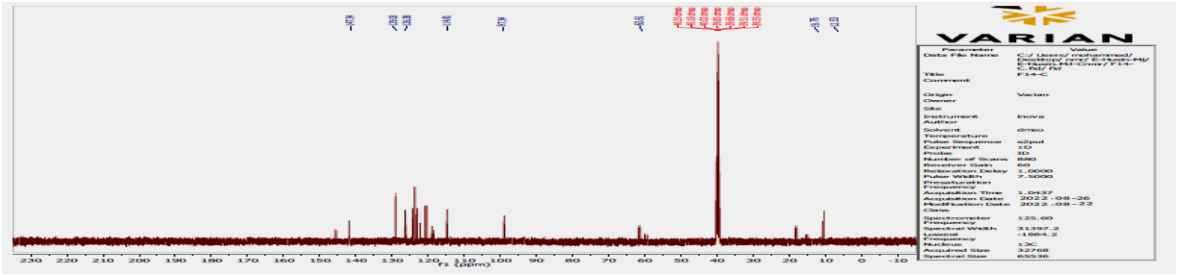
System.(32): C.NMR of [2]



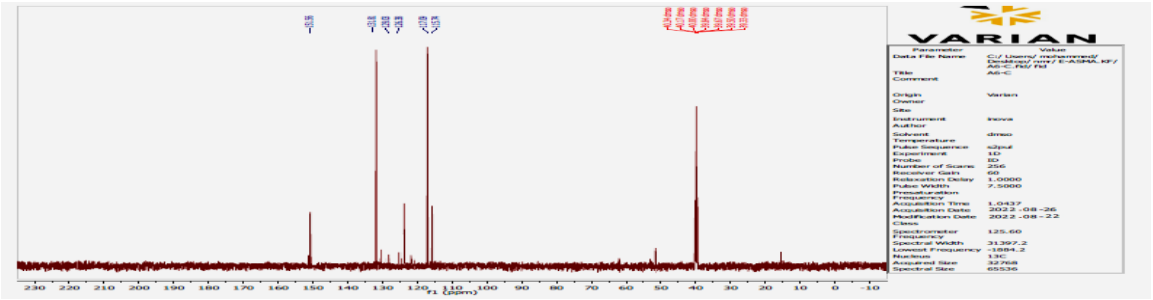
System.(33): C.NMR of [3]



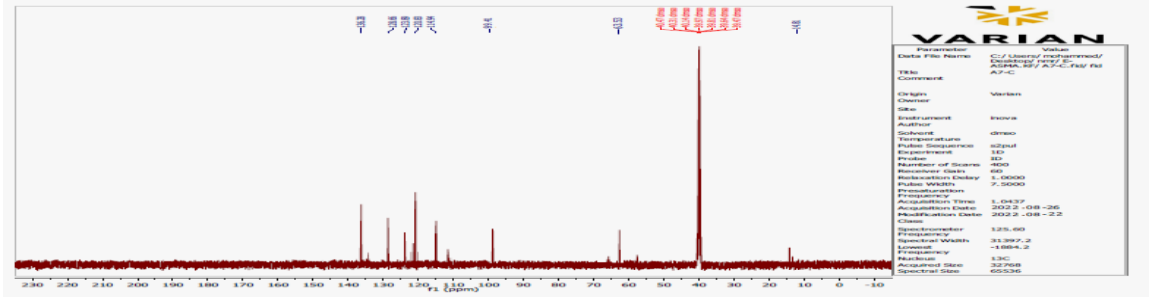
System.(34): C.NMR of [5]



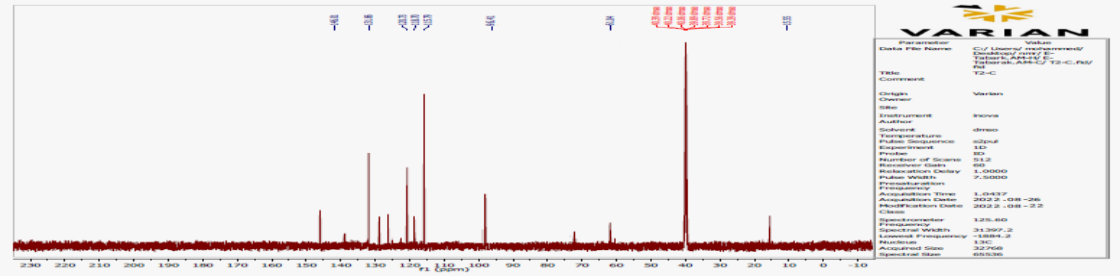
System (35): C.NMR of [7]



System.(36): C.NMR of [8]



System.(37): C.NMR of [10]



System.(38): C.NMR of [14]

Anticancer-Assay(1, 13)

Two compounds were selected for anticancer evaluation (breast cancer) represented by Linear formazan Compound [3] and Macrocyclic Formazan compound [14] by MTT-Test of two types of Cells (MCF-7) as Cancer cell and (MCF- 10 A)as healthy cell according to studies(1, 13) , all data in Figures(39, 40), Tables(1,2).

Table 1 : Cytotoxic Activity of Linear Formazan Compound{3} on Breast Cancer Cells line (MCF-7) and Healthy Cells (MCF-10A) at the same concentration using 24 hrs ., MTT test 370c.

Con. (µg.mL−1)	Mean Percentage (%) for each cell line			
	MCF-7 / IC50= 32.08		MCF-10A / IC50 = 174.87	
Linear Formazan Compound {3}	Cancerous line cells of MCF-7		Normal line cells of MCF-10A	
	Cell Viability	Cell Inhibition	Cell Viability	Cell Inhibition
15. 62	85.72	14.28	92.97	7.03
31. 25	78.23	21.77	92.85	7.15
62. 5	74.74	25.77	92.13	7.87
125.0	71.34	28.66	91.58	8.42
250	60.20	39.8	94.1	5.90
500	57.20	42.8	95.62	4.37
Control	100		93.62	6.32

Table. 2 : Cytotoxic Activity of Macrocyclic Formazan Compound{14} on Breast Cancer Cells line (MCF-7) and Healthy Cells (MCF-10A) at the same concentration using 24 hrs ., MTT test 370c.

Con. (µg.mL−1)	Mean Percentage (%) for each cell line			
	MCF-7 / IC50 = 34.14		MCF-10A / IC50= 170.44	
Macrocyclic Formazan Compound {14}	Cancerous line cells of MCF-7		Normal line cells of MCF-10A	
	Cell Viability	Cell Inhibition	Cell Viability	Cell Inhibition
15. 62	96.21	3.79	95.58	4.42
31. 25	94.43	5.57	96.22	3.78
62. 5	89.19	10.81	94.24	5.76
125.0	87.80	12.2	92.5	7.50
250	83.13	16.87	93.63	6.37
500	72.99	27.01	91.15	8.85
Control	100		93.62	6.38

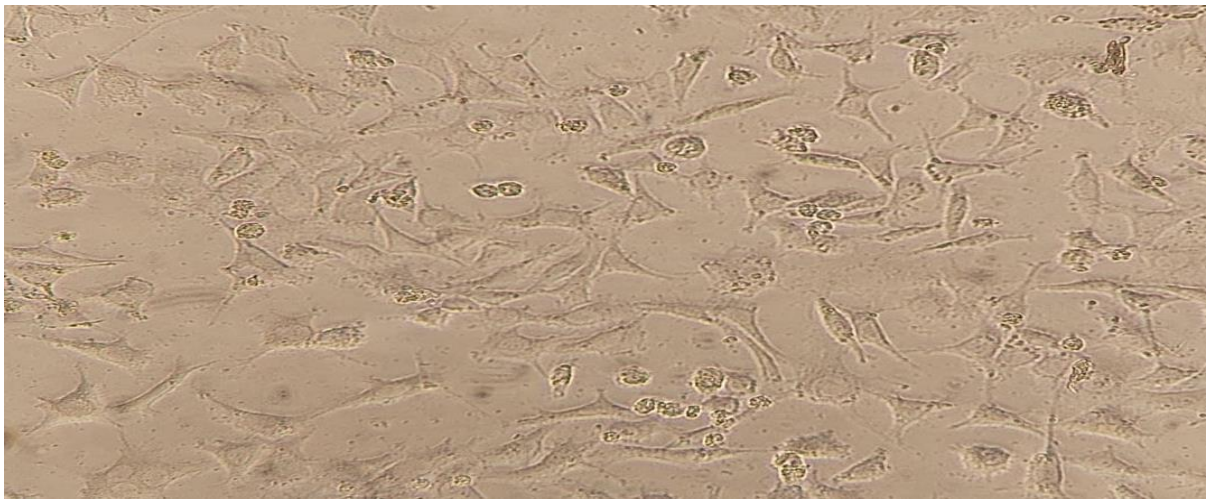


Fig. 39:Anti-cancer activity of Macrocyclic Formazan Compound{14}on (MCF-7) at 500µg/ml

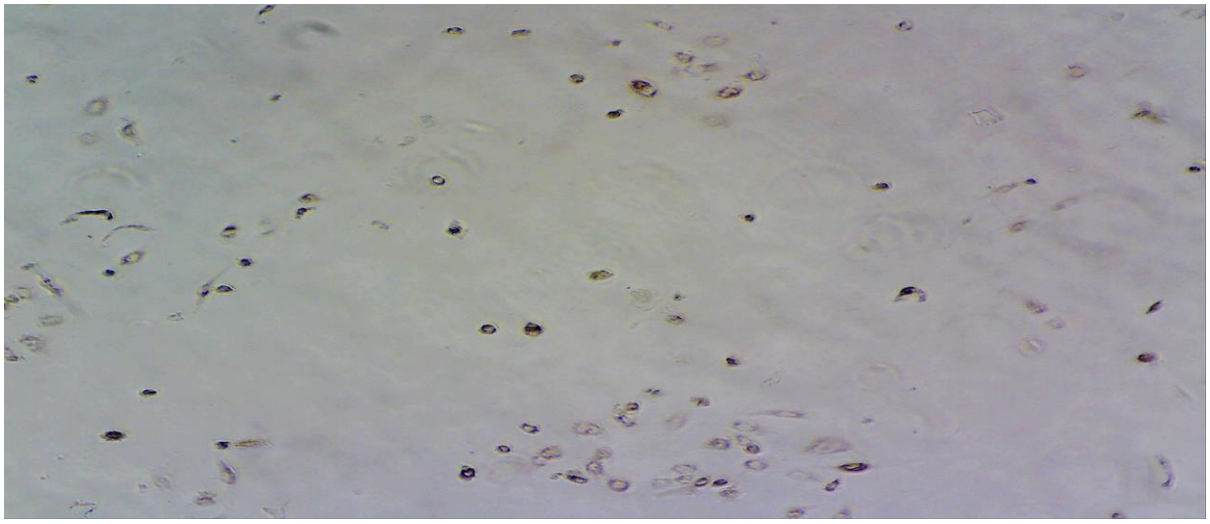


Fig. 40:Anti-cancer activity of Macrocyclic Formazan Compound{14}on (MCF-A 10) at 500µg/ml

CONCLUSIONS

From results of anticancer test ,we noted that Linear Formazan Compound [3] has higher efficiency towards Cancer cells and high inhibition on cancer cells than Macrocyclic Formazan compound [14].

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