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Anticancer Study of Innovative Macrocyclic Formazan Compounds from Trimethoprim Drug

Nagham Mahmood Aljamali[*a] and Zainab Mohamed Farhan[b]

[*a]*Professor ,Ph. D, Organic Chemistry ,Synthetic Chemistry Field, Iraq.*

[b]*M.Sc –Student ,First Part of Thesis ,Chemistry Department, College of Education for Girls, Iraq.*

Abstract

Innovative Macrocyclic Formazan Compounds were generated and advanced globally for the first time by researcher (Prof. Dr. Nagham Aljamali in April 2019) via more than five steps of reaction with various catalyst like (tri ethyl amine, pipyridine ,…)., Therefore, these compounds considered one of the developed and modern compounds in organic chemistry., These biochemical Compounds were synthesized via many steps of reaction with various catalytic agent such as {$(CH_3)_3N$, pi.pyridine ,…}., Hence, these compounds deliberated one of the industrialized and modern compounds which have absence of literatures and researches which clue us to prepare and create a chain of these Modernized compounds and studied by abundant uses in future literatures represented by biological, pharmaceutical , nano , antimicrobial studies, also as anticancer agents, and here in this research. A numeral of applied identical studies have been used to revel their structures which delivered to strong indications of their structures through different methodical routes like Spectra Depiction., other studies represented by physical with chemical belongings., and anticancer study for biochemical compounds through (MTT)-Method was used to conclude cell viability by chromatic inspection (64-70) of types (MCF-7 and MCF- 10 A lines) for compounds [9 , 10].

Key words: Anticancer study, breast cancer, Macrocyclic Formazan, Anil, innovative compounds ,MTT , MCF-7 ,MCF-A 10 .

1.Introduction

Macrocyclic Formazan Compounds :are Original-Innovative compounds in the field of organic chemistry and are considered a new innovation by Dr. Nagham Aljamali in April 2019 when these compounds were prepared for the first time globally[1, 2] , and because their references and papers are a few in this field for this reason the researcher Prof. Dr. Nagham Aljamali developed different compounds from Macrocyclic Formazan by using various conditions and different basic medium[3-7] with various catalytic agent such as {$(CH_3)_3N$, pi.pyridine, Pyridine , $(C_2H_5)_3N$,…}[1, 2], and linked them with heterocyclic compounds and pharmaceutical drugs[2-6] with more than two hetero atoms to increase their effectiveness[7-13] , biological[14-20] and Nano[21-24] with industrial applications[26-30].

Structure of Macrocyclic Formazan : It has cyclic structure of (-N=N=C-N- in cyclic structure) or (-N=N-C-N-NH- in cyclic structure) according to type of amine in reaction[1, 2]., They were considered among the organic compounds of importance[18-23] in organic chemistry because they contain two highly effective groups in several fields of chemistry[1, 24-30], especially in coordination chemistry[31-37], as a ligands because they contain free electrons of donor atoms to coordinate[38-42] with ions to form complexes[43-49].

Instruments and Experimental Part :

All types of analysis were carried out as chemical identifications and Melting points, other studies represented by physical with chemical properties.,

*Corresponding author e-mail dr.nagham_mj@yahoo.com ; (Nagham Mahmood Aljamali).

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Also anticancer study that carried out in Tehran University (Chemistry Research Center).

Experimental Methods:

Preparation of Trimethoprim Derivative {1}

Trimethoprim drug (0.01 mole) dissolved in hydrochloric acid in ice path ,then solution of sodium nitrite added ,after this step we added (0.02 mol) of acetyl acetone in alkaloid medium to the mixture, after (52 hrs) , the product filtered ,wished with condensed water ,desiccated , purified to revenue derivative of Trimethoprim Derivative [1] conferring to routes[38-41] .

Preparation of Trimethoprim-Seven Membered Ring Derivative {2}

Trimethoprim Derivative [1] (0.01 mol) refluxed with (0.02 mol) of phenyl diamine for (3 hrs) with (3 drops) of of (GAA) and absolute ethanol (30 ml), the product filtered ,desiccated ,recrystallized to revenue Trimethoprim-Seven Membered Ring Derivative {2} conferring to routes[38-41] .

Preparation of Trimethoprim-Five Membered Ring Derivative {3}

Trimethoprim Derivative [1] (0.01 mol) refluxed with (0.02 mol) of hydrazine for (2 hrs) with (3 drops) of of (GAA) and absolute ethanol (30 ml), the product filtered ,desiccated ,recrystallized to revenue Trimethoprim-Five Membered Ring Derivative {3} conferring to routes[38-41] .

Preparation of Trimethoprim-Seven Membered Ring Derivative {4}

Trimethoprim Derivative [1] (0.01 mol) refluxed with (0.02 mol) of o-mercapto aniline for (4 hrs) with (3 drops) of of (GAA) and absolute ethanol (30 ml), the product filtered ,desiccated ,recrystallized to revenue Trimethoprim-Seven Membered Ring Derivative {4} conferring to routes [38-41] .

Preparation of Trimethoprim-Six Membered Ring Derivative {5}

Trimethoprim Derivative [1] (0.01 mol) refluxed with (0.02 mol) of thiourea for (3 hrs) with (3 drops) of of (GAA) and absolute ethanol (30 ml), the product filtered ,desiccated ,recrystallized to revenue Trimethoprim -Six Membered Ring Derivative {5} conferring to route[38] .

Preparation of Trimethoprim-Imine Pyridine Derivative {6}

Trimethoprim Derivative [1] (0.01 mol) refluxed with (0.04 mol) of 2-amino 5-carboxy pyridine for (3 hrs) with (3 drops) of of (GAA) and absolute ethanol (30 ml), the product filtered ,desiccated ,recrystallized to revenue Trimethoprim-Imine pyridine Derivative {6} conferring to route[39] .

Preparation of Trimethoprim-Imine Thiazole Derivative {7}

Trimethoprim Derivative [1] (0.01 mol) refluxed with (0.04 mol) of 2-aminothiazole for (4 hrs) with (3 drops) of of (GAA) and absolute ethanol (30 ml), the product filtered ,desiccated ,purified to revenue Trimethoprim-Imine thiazole Derivative {7} conferring to route[38] .

Preparation of Trimethoprim-Imine Phenol Derivative {8}

Trimethoprim (0.01 mol) refluxed with (0.02 mol) of p-hydroxy benzaldehyde for (3 hrs) with (3 drops) of (GAA) and absolute ethanol (30 ml), the product filtered ,desiccated ,purified to revenue Trimethoprim-Imine phenol Derivative {8} conferring to route[39] .

Preparation of Developed Macrocyclic Formazan Compound {9}

Trimethoprim-Imine phenol Derivative {8} (0.01 mole) reacted with (0.01 mole) from azonium salt of trimethoprim in (tri ethyl amine) through five steps in alkaloid medium to formation Developed Macrocyclic Formazan after (30 hrs), the product filtered ,desiccated ,washed by distilled water, recrystallized to revenue Developed Macrocyclic Formazan Compound [9] by following Modernized routes in literatures [38-41] .

Preparation of Developed Macrocyclic Formazan Compound {10}

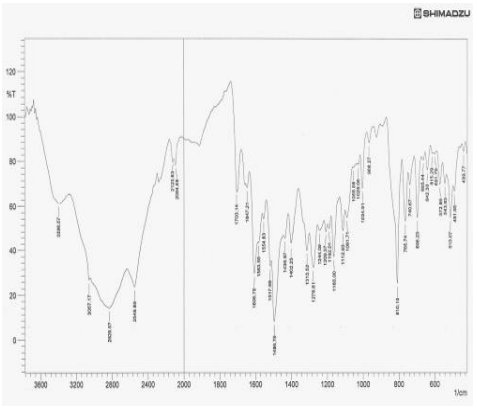
Trimethoprim-Imine phenol Derivative {8} (0.01 mole) reacted with (0.01 mole) from azonium salt of m-phenyl diamine in (pyridine) through five steps in alkaloid medium to formation Developed Macrocyclic Formazan after (42 hrs), the product filtered ,desiccated ,washed by condensed water, purified to revenue Developed Macrocyclic Formazan Compound [10] by succeeding Modernized routes in literatures [38-41] .

RESULTS AND DISCUSSION:

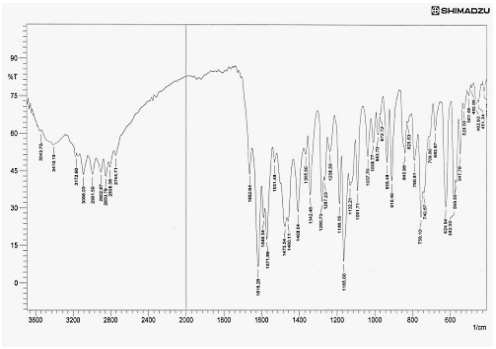
In recently scientific study, a number of Trimethoprim- heterocyclic Derivatives and Innovated Macrocyclic Formazan compounds have been formed in similar route that followed and Developed[1, 38-40] by (Professor .Dr. Nagham in April 2019) for the first time in world as original compounds in organic chemistry that named ((Macrocyclic Formazan compounds)), then different studies were carried out to improve these innovative compounds by the expending of spectral depiction, with anticancer study, all the results are shown in Tables and figures:

Spectral Evidences:

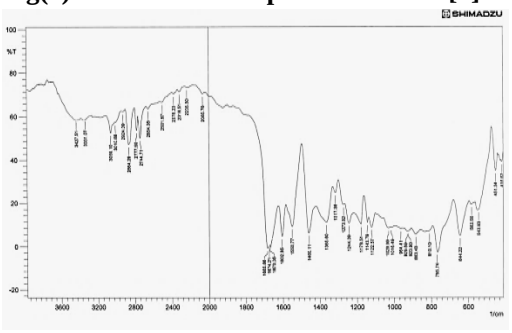
FT.IR- Spectral Indication of Trimethoprim-heterocyclic Derivatives and Industrialized Macrocyclic Formazan compounds : The primary depiction of Trimethoprim- Derivatives is entrance of Azo groups at [(1496 , 1517), (1475 , 1571) ,(1460 , 1550) ,(1442 , 1512) ,(1442 ,1474) ,(1444 ,1465), (1384 ,.1496)] in line for to (-N=N-) in compounds {1-7] respectively., Also in same compounds entranced many bands for (C=N-) anil group and other in line for to endo cycle at [(1618), (1602), (1622), (1612), (1625), (1606), (1616) in compounds {2-8] respectively., While the Developed Macrocyclic compounds we noted shifting of frequencies of aldamine group (CH=N) in initial compounds -Imine compound [8] that were about at (1616) Cm^{-1} which shifted to (1631 , 1635) Cm^{-1} for (-C=N-) in line for to formation of Macrocyclic Formazan in compounds [9 , 10] respectively., Also entrance three new band in each Macrocyclic Formazan compounds{ 9 and 10 } in line for to Azo group of Formazan at [(1355, 1429 ,1517) and (1435 ,1462 , 1512)] respectively in each from Macrocyclic Formazan compounds{ 9 and 10 }, all frequencies clarified conferring to reference (Dr. Nagham Aljamali. 2022)[26] , and other functional groups in figures (1-10):



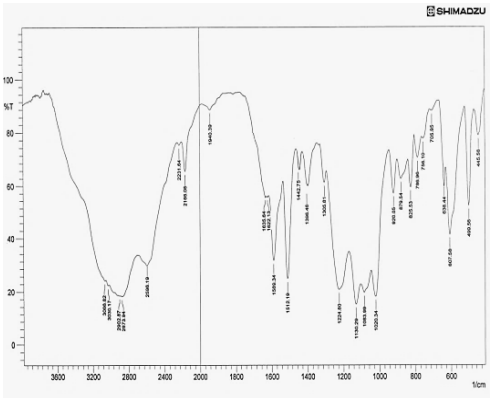
Fig(1):FT.IR-Trimethoprim Derivative[1]



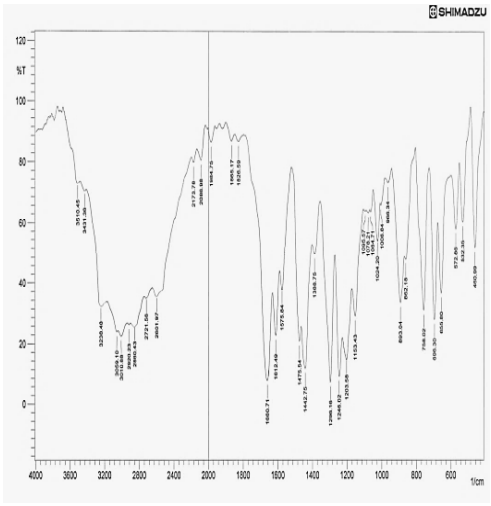
Fig(2):FT.IR-Trimethoprim Derivative[2]



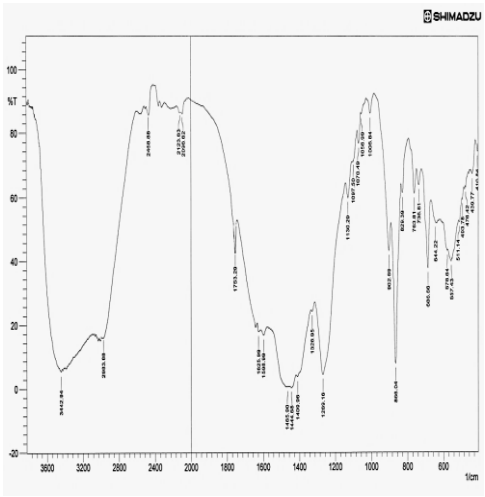
Fig(3): FT.IR of Trimethoprim Derivative[3]



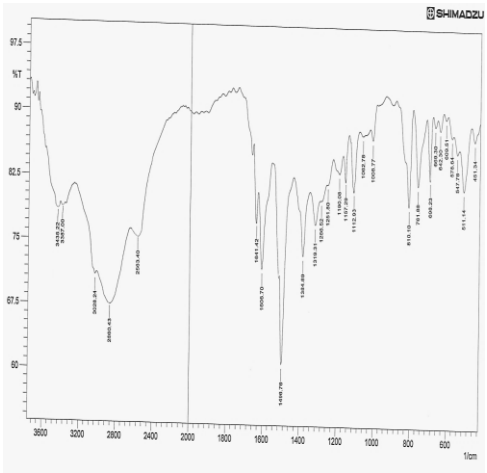
Fig(4):FT.IR-Trimethoprim Derivative[4]



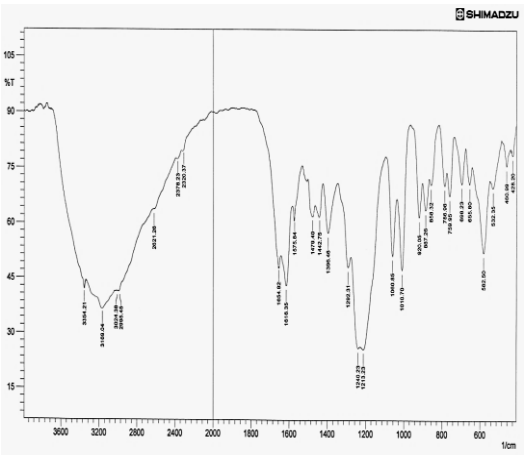
Fig(5):FT.IR-Trimethoprim Derivative[5]



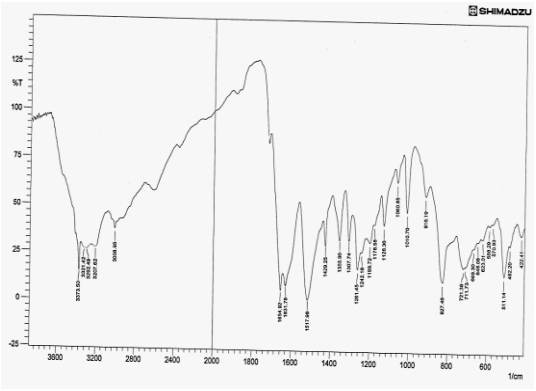
Fig(6):FT.IR-Trimethoprim Derivative[6]



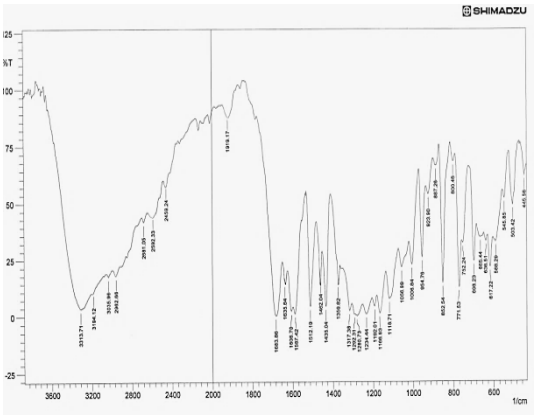
Fig(7):FT.IR-Trimethoprim Derivative[7]



Fig(8):FT.IR-Trimethoprim Derivative[8]



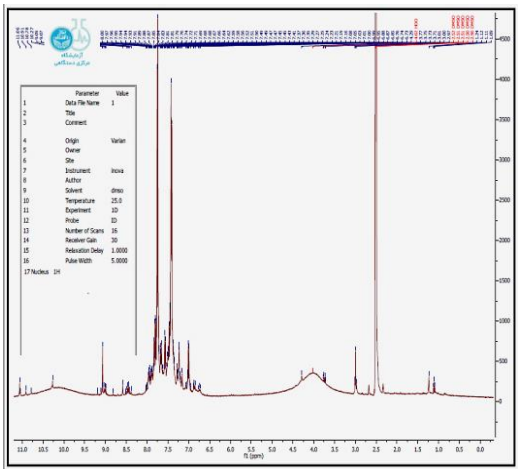
Fig(9):FT.IR-Trimethoprim Derivative[9]



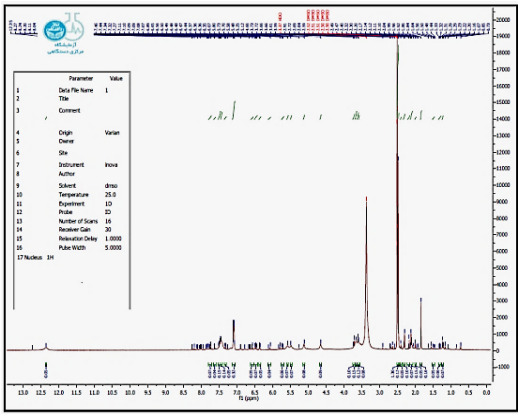
Fig(10):FT.IR-Trimethoprim Derivative[10]

^{1}H.NMR- Spectral Indication of Trimethoprim-heterocyclic Derivatives and Developed Macrocyclic Formazan compounds : The another depiction of innovative Trimethoprim Derivatives by disentrance of peak for Aldamine group (CH=N) in starting compound (Aldamine compound) that were at δ (8.34) in Compound {8} as (initial compound) in line for to formation of (N=C-N=N) Formazan group in Modernized Macrocyclic

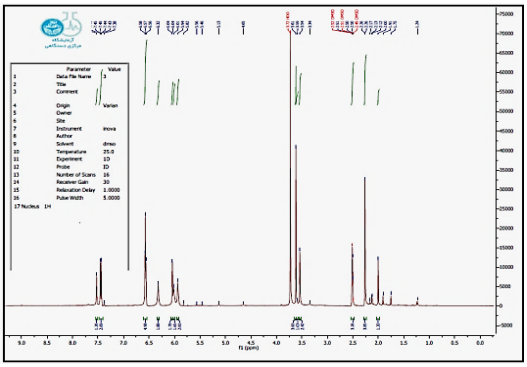
Formazan compounds [9 , 10], also in compound [1] entranced signal at δ (2.02) in line for to protons of Methyl groups of Ketone (CO-CH_3) ,while it shifted (CH_3) groups to (1.22) in compound {2} as a result to formation seven membered ring in compounds [2 ,3, 4, 5 ,6] ,all peaks explained conferring to references[26 ,39].



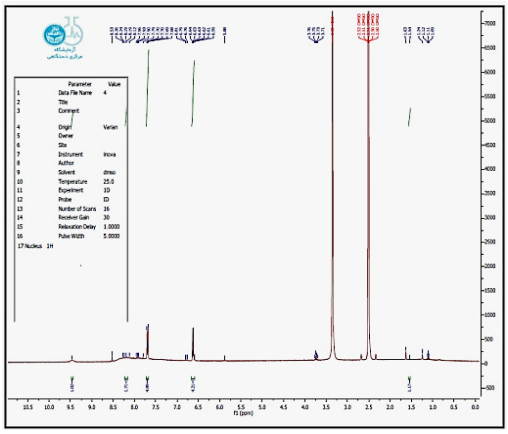
Fig(11):H.NMR- Spectrum of Trimethoprim Derivative[1]



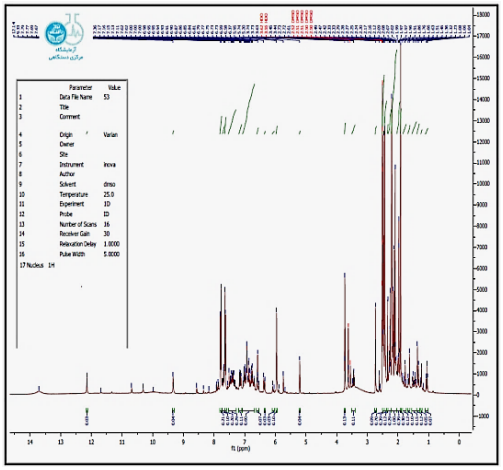
Fig(12):H.NMR- Spectrum of Trimethoprim Derivative[2]



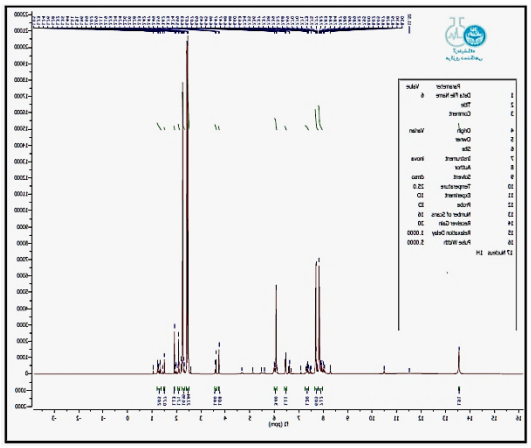
Fig(13):H.NMR- Spectrum of Trimethoprim Derivative[3]



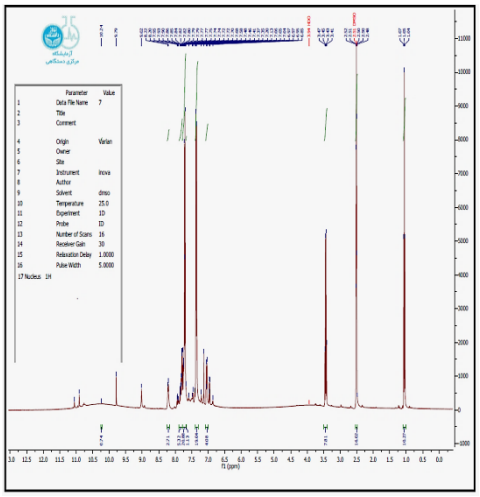
Fig(14):H.NMR- Spectrum of Trimethoprim Derivative[4]



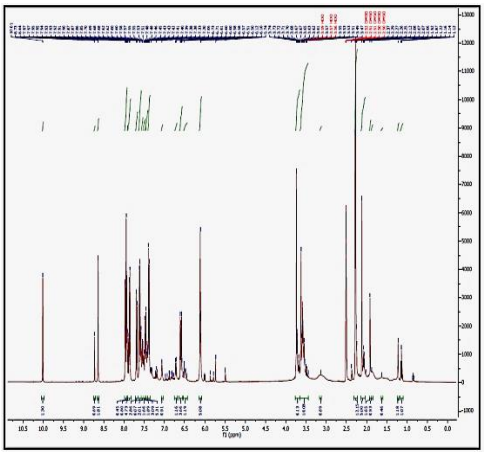
Fig(15):H.NMR- Spectrum of Trimethoprim Derivative[5]



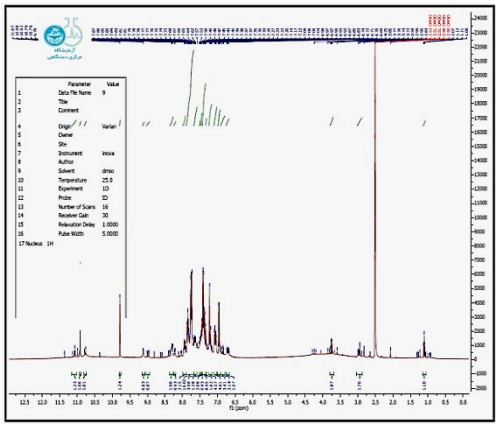
Fig(16):H.NMR- Spectrum of Trimethoprim Derivative[6]



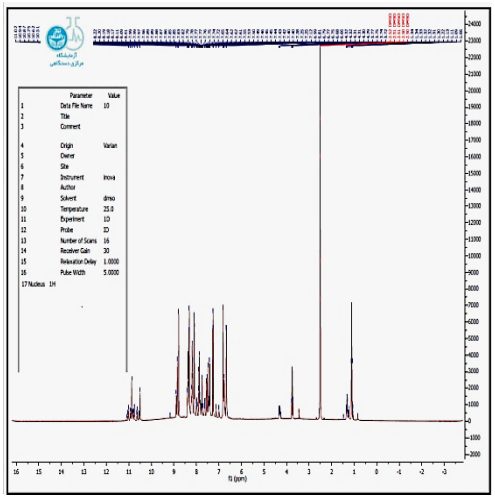
Fig(17):H.NMR- Spectrum of Trimethoprim Derivative[7]



Fig(18):H.NMR- Spectrum of Trimethoprim Derivative[8]

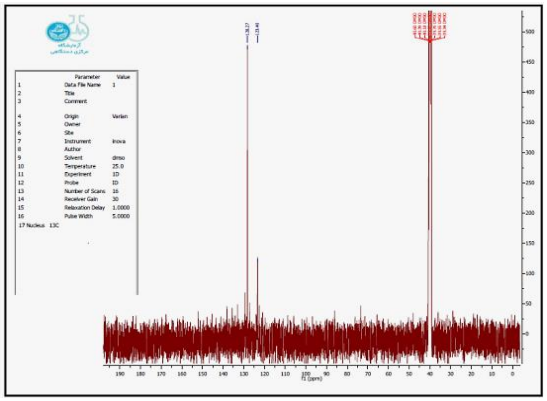


Fig(19):H.NMR- Spectrum of Trimethoprim Derivative[9]

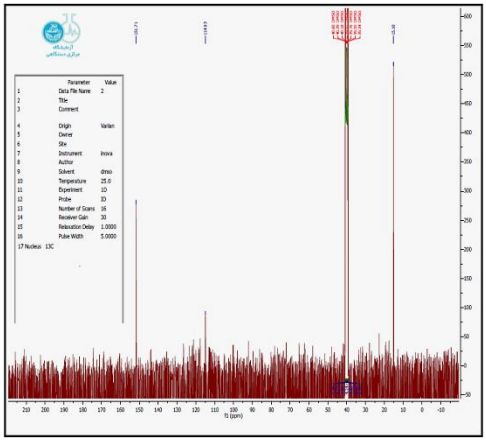


Fig(20):H.NMR- Spectrum of Trimethoprim Derivative[10]

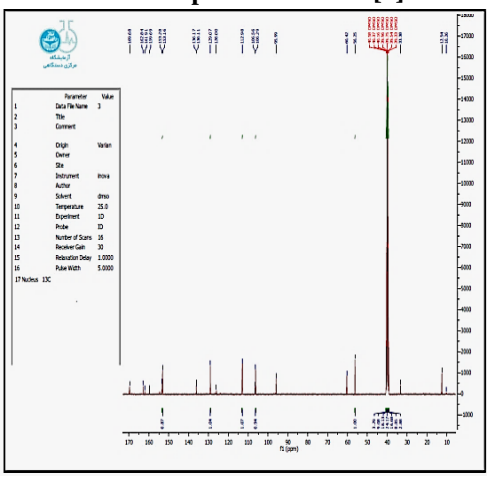
^{13}C.NMR- Spectral Indication of Trimethoprim-heterocyclic Derivatives and Developed Macrocyclic Formazan compounds : The other depiction of innovative Trimethoprim Derivatives by entrance peak of carbon atom for Aldamine group (CH=N) in starting compound (Aldamine compound) that were at δ (159.03) in Compound {8} as (a initial compound) which shifted to δ (102. 09) in line for to formation (N=C-N=N) Formazan group in Modernized Macrocyclic Formazan compounds [9 , 10], besids to in compound [1] entranced signal at δ (184. 97) in line for to carbon atom of carbonyl in ketone ,while it shifted to δ (157. 95 , 155. 23 , 159. 33 , 156. 28) respectively in compounds {2 , 3, 4, 5, 6} as a result to formation imine group (C=N) in compounds [2 ,3, 4, 5 ,6] ,all signals explained conferring to references[26 ,38].



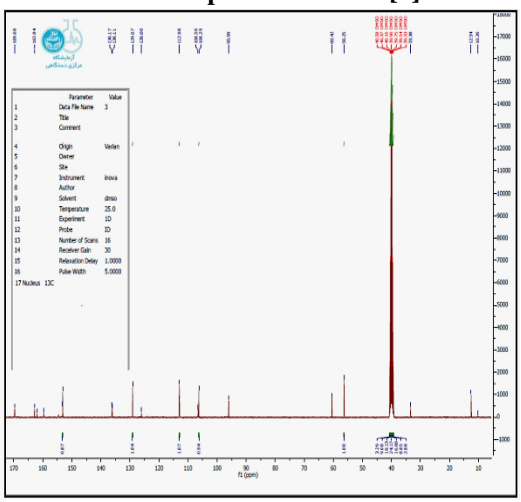
Fig(21):C.NMR- Spectrum of Trimethoprim Derivative[1]



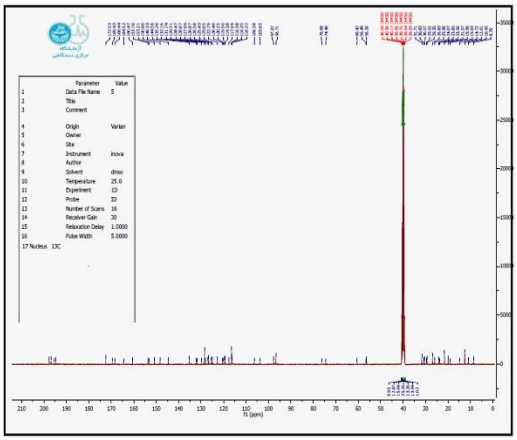
Fig(22):C.NMR- Spectrum of Trimethoprim Derivative[2]



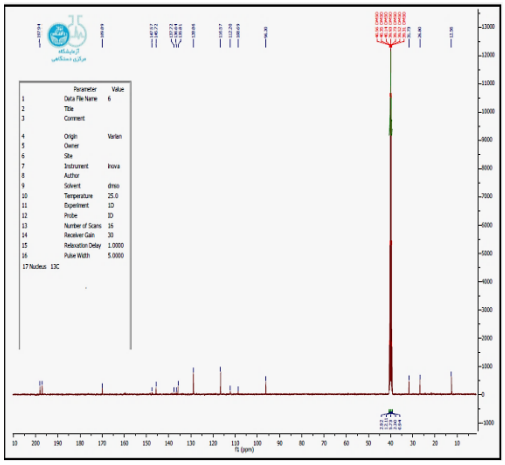
Fig(23):C.NMR- Spectrum of Trimethoprim Derivative[3]



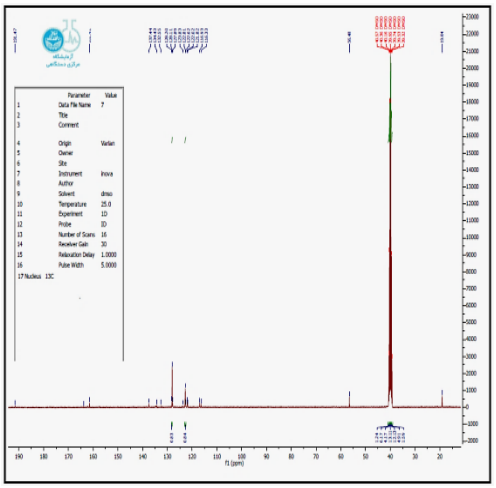
Fig(24):C.NMR- Spectrum of Trimethoprim Derivative[4]



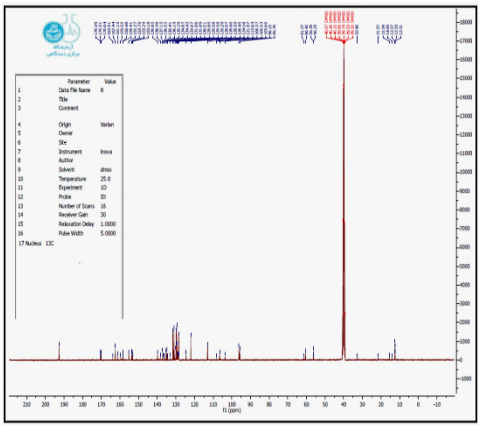
Fig(25):C.NMR- Spectrum of Trimethoprim Derivative[5]



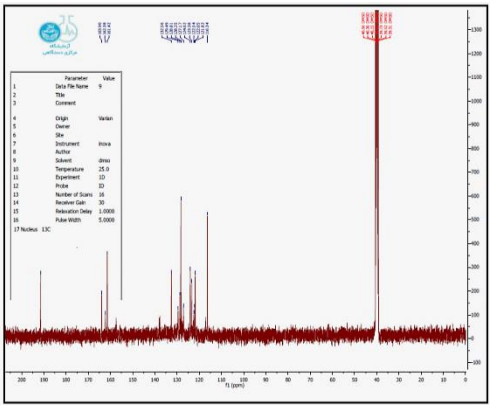
Fig(26):C.NMR-Spectrum of Trimethoprim Derivative[6]



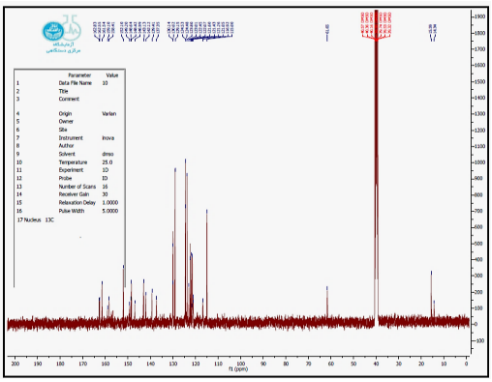
Fig(27):C.NMR-Spectrum of Trimethoprim Derivative[7]



Fig(28):C.NMR- Spectrum of Trimethoprim Derivative[8]



Fig(29):C.NMR- Spectrum of Trimethoprim Derivative[9]



Fig(30):C.NMR-Spectrum of Trimethoprim Derivative[10]

Other Depiction:

All biochemical compounds (Trimethoprim Derivatives with Macrocyclic Formazan) were screend and tested to accumulate in table(1) :

Table.1: Additional depiction of Developed Macrocyclic Formazan and Trimethoprim Derivatives

Trimethoprim Derivatives	*P %*	*Color*	*M .P C °*	*Rf*
Innovated Comp.{1}	82	Deep Yellow	166	-----
Innovated Comp.{2}	78	Yellowish Brown	188	0.60
Innovated Comp.{3}	74	Reddish Brown	172	0.64
Innovated Comp.{4}	70	Yellowish Brown	194	0.56
Innovated Comp.{5}	68	Reddish Orange	180	0.60
Innovated Comp.{6}	72	Reddish Brown	190	0.58
Innovated Comp.{7}	70	Reddish Orange	186	0.60
Innovated Comp.{8}	78	Yellow	164	0.62
Innovated Comp.{9}	86	Yellowish Red	236	0.64
Innovated Comp.{10}	84	Yellowish Orange	208	0.56

Influence of Macrocyclic Formazan In contradiction of Breast Cancer[37, 39] :

(MTT)-Method[37 , 39] was used to conclude cell viability by chromatic inspection (64-70) of types (MCF-7 and MCF- 10 A lines) for compounds [9 , 10], all data in Figures(31 , 32), Tables(2, 3).

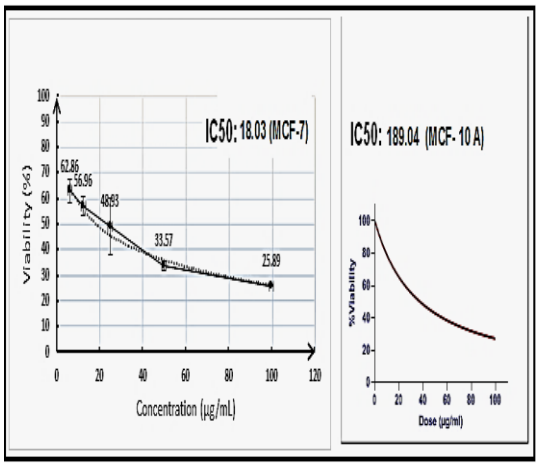


Fig.(31):IC_{50} for Cancer Cells and Healthy Cells for Formazan Compound{9}

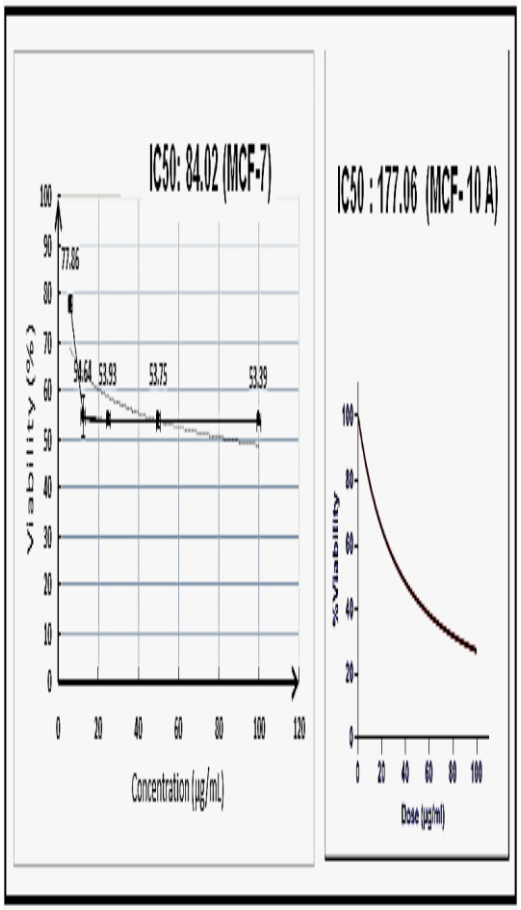


Fig.(32):IC_{50} for Cancer Cells and Healthy Cells for Macrocyclic Formazan Comp.{10}

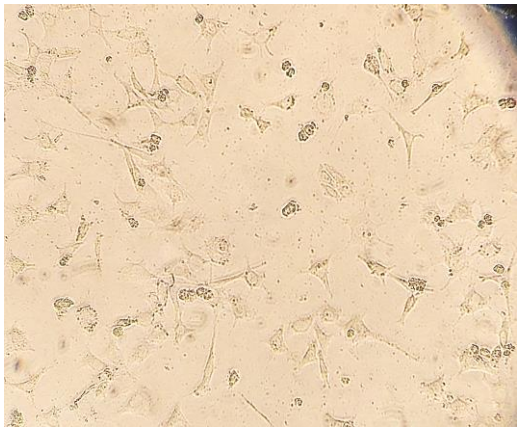


Fig.33:Anti-cancer activity of Compound {10} on (MCF-7) at 25µg/ml

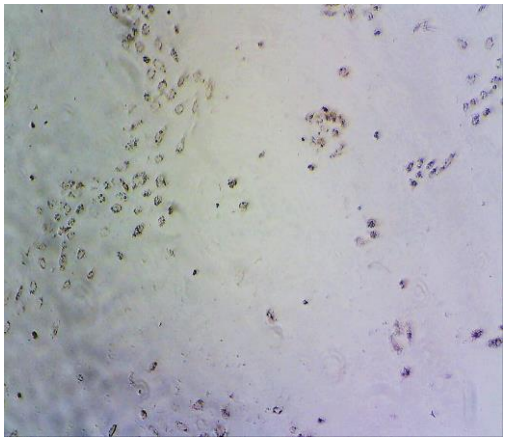


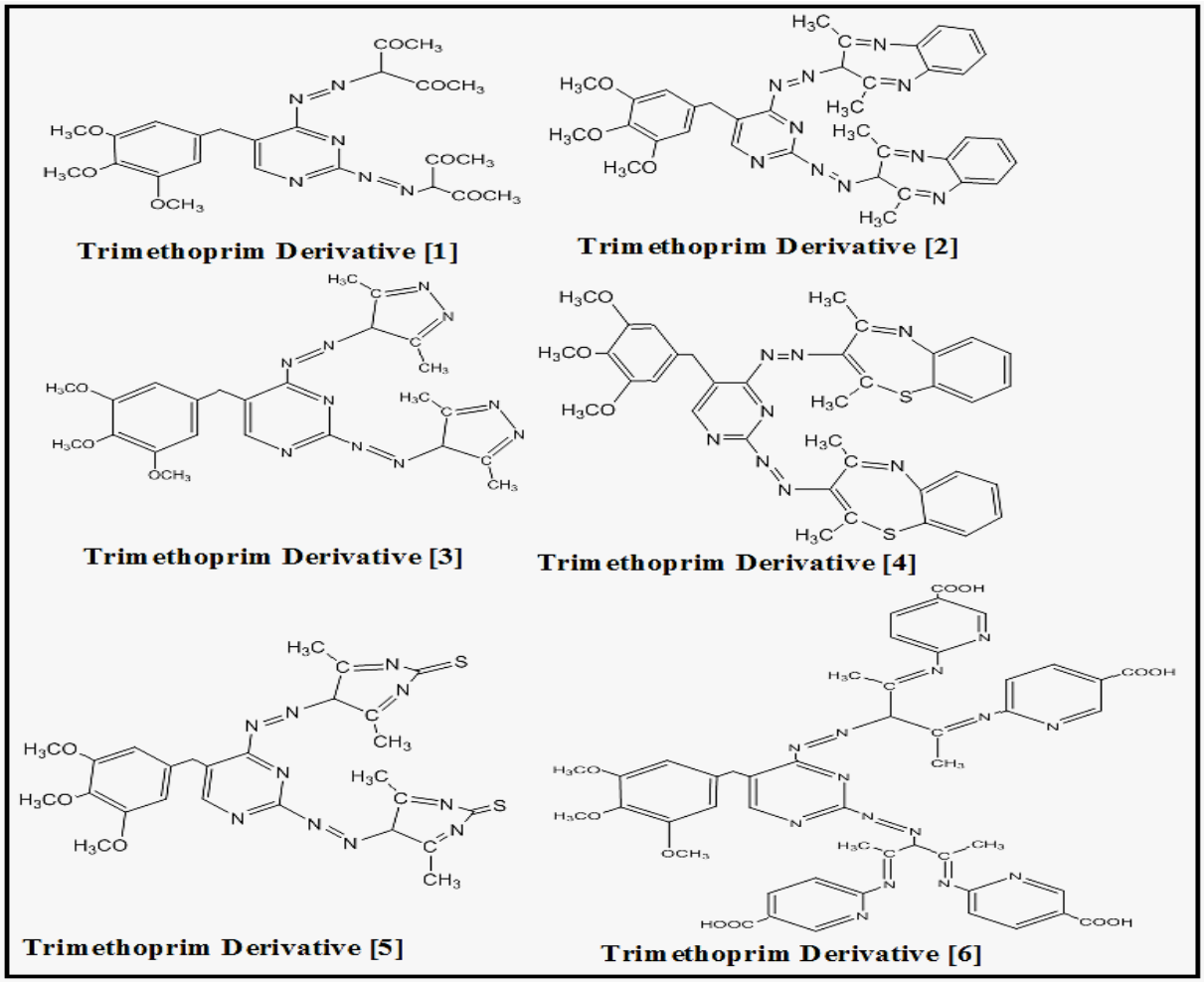
Fig.34:Anti-cancer activity of Compound {10} on (MCF- A 10) at 25µg/ml

Table. (2): Cytotoxic Activity of Formazan Compound{9} on Breast Cancer Cells line (MCF-7) and Healthy Cells (MCF-10A) at the same concentration using 24 hrs ., MTT test 37^0c.

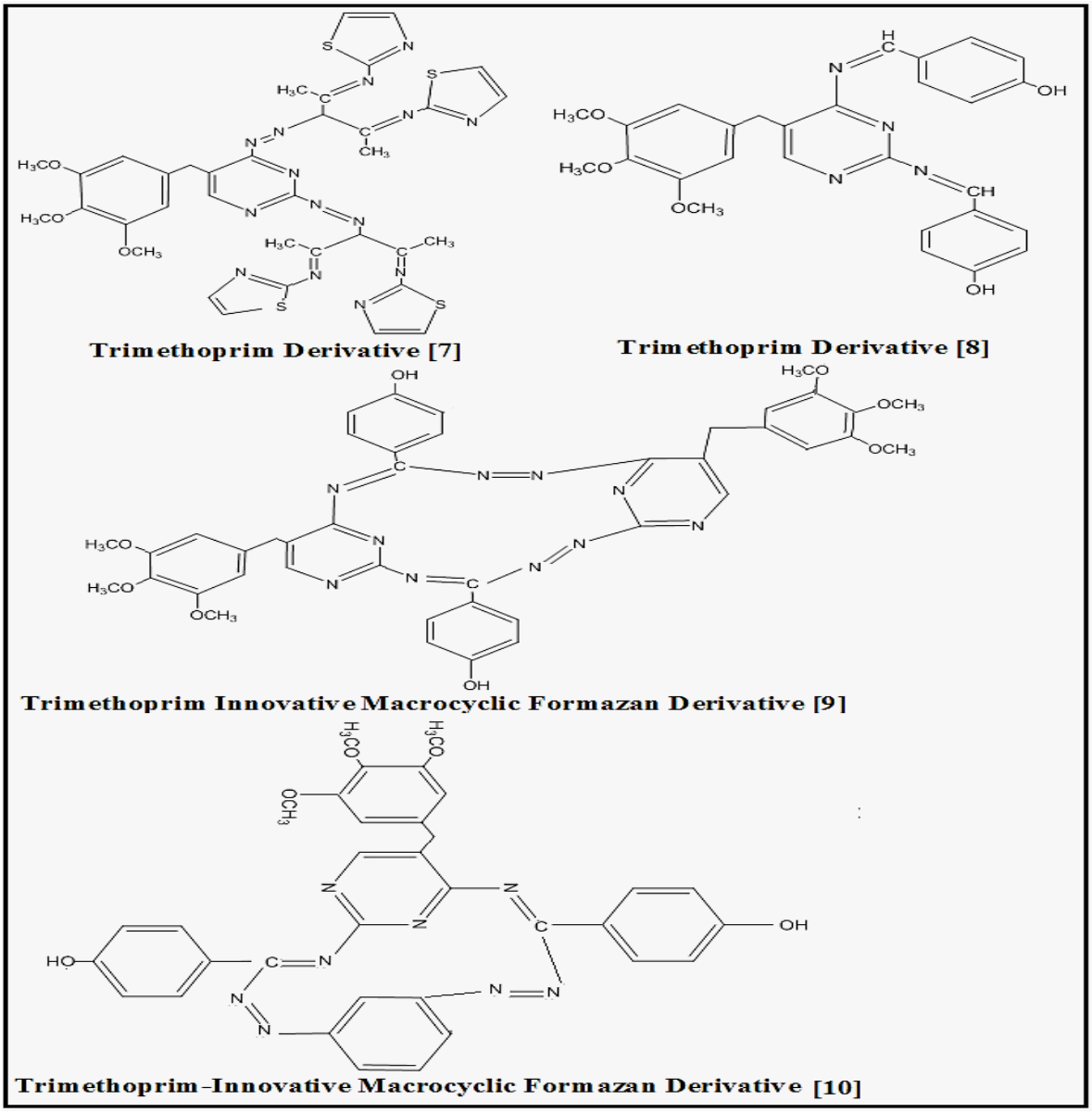
Con. (µg.mL^{-1})	Mean Percentage (%) for each cell line			
	MCF-7		MCF-10A	
Macrocyclic Formazan Compound {9}	Cancerous line cells of MCF-7		Normal line cells of MCF-10A	
	Cell Viability	Cell Inhibition	Cell Viability	Cell Inhibition
6.25	62.86	37.14	95.06	4.94
12.5	56.96	43.04	94.41	5.59
25	48.93	41.07	85.69	14.31
50	33.57	66.43	75.83	24.17
100	25.89	74.11	66.01	33.99

Table. (3): Cytotoxic Activity of Formazan Compound{10} on Breast Cancer Cells line (MCF-7) and Healthy Cells (MCF-10A) at the same concentration using 24 hrs ., MTT test 37^0c.

Con. (µg.mL^{-1})	Mean Percentage (%) for each cell line			
	MCF-7		MCF-10A	
Innovative Macrocyclic Formazan Compound {10}	Cancerous line cells of MCF-7		Normal line cells of MCF-10A	
	Cell Viability	Cell Inhibition	Cell Viability	Cell Inhibition
6.25	77.86	22.14	94.83	5.17
12.5	54.64	45.36	94.95	5.05
25	53.93	46.07	92.44	7.56
50	53.75	46.25	85.57	14.43
100	53.39	46.61	75.81	24.19



Scheme.1: Synthesis of Trimethoprim Derivatives {1-6}



Scheme.2: Creation of Trimethoprim-Developed Macrocyclic Formazan Derivatives {7-10}

Conclusions :

From the results ,we noted that Innovative Formazan Compound {9} is more activity in inhibition of Cancer cells than Formazan Compound {10} which in line for to Formazan compound (N-C-N=N- Ar) linked with two groups of trimethoprim is more active than other compound {10}

Conflict of interest : The authors declare that there is no conflict of interest.

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REFERENCES

1. Nagham Mahmood Aljamali . Inventing of Macrocyclic Formazan Compounds and Studying Them Against Breast Cancer for The first Time Globally . Annals of pharma research **.,9 ,7,** (2021). Pp 525-533., Available at:https://www.annalsofpharmaresearch.com/index.php?journal=apr&page=article&op=view&path%5B%5D=38
2. Imd Karm, Hasan Kudhair Abdullabass ,Nagham Mahmood Aljamali . Invention of (Gluta.Sulfazane-Cefixime) Compounds as

Inhibitors of Cancerous Tumors., Journal of Cardiovascular Disease Research, 2020,11, 2., 44-55 ., DOI: 10.31838/jcdr.2020.11.02.09 .

3. Nagham Mahmood Aljamali. Creation of Modernized Macrocyclic Sulfazan-Formazan Compounds and Linear Sulfazan-Formazan for the first Time Globally with their Assay as Antifungal ., **Biomedical Journal of Scientific & Technical Research,** 2021, Volume 40- Issue 3 , P: 32266-32272 ., DOI: 10.26717/BJSTR.2021.40.006453
4. Nagham Mahmood Aljamali. Experimental Methods for Preparation of Mannich Bases, Formazan, Normal and Cyclic Sulfur Compounds., 1st edition Evince pub Publishing House; 2018, ISBN: 978-93-87905-19-1.
5. Nagham Mahmood Aljamali. Review on (Azo, Formazane, Sulfazane)-Compounds ., International Journal of Innovations in Scientific Engineering., 2019, Vol. No. 10, Jul-Dec ., 19-45.
6. Nagham Mahmood Aljamali. Alternative Methods in Organic Synthesis .,1th–Edition, Eliva Press SRL, 2020 ., ISBN: 9798680201176.
7. Nagham Mahmood Aljamali . Effect of Conditions and Catalysis on Products ., 2021; 1st Ed, Eliva Press SRL., ISBN: 9781636482286 .
8. Nagham Mahmood Aljamali. The Various Preparation Methods in Synthetic Chemistry .,1 Edt. ,Evincepub Publishing house, 2019., ISBN :978-93-88277-82-2.
9. Nagham Mahmood Aljamali, Imd Karm. Development of Trimethoprim Drug and Innovation of Sulfazane-Trimethoprim Derivatives as Anticancer Agents ., Biomedical & Pharmacology Journal, March 2020., Vol. 13, (2), p. 613-625 ., http://dx.doi.org/10.13005/bpj/1925 .
10. Nagham Mahmood Aljamali. Reactions and Mechanisms.,1 Edt., IJMRA Publication ,2018 .,ISBN : 978- 93-87176-25-6 .
11. Matheus ME, de Almeida Violante F, Garden SJ. Isatins inhibit cyclooxygenase-2 and inducible nitric oxide synthase in a mouse macrophage cell line. Eur J Pharmacol. 2007; 556 :200–6.
12. Nagham Mahmood Aljamali. 2016. Synthesis and Biological Study of Hetero (Atoms and Cycles) Compounds , Der Pharma Chemica, 8,6, 40-48.
13. Nagham Mahmood Aljamali., 2015. Synthesis and Chemical Identification of Macro Compounds of (Thiazol and Imidazol)".,Research J. Pharm. and Tech, 8,1, 78-84., DOI: 10.5958/0974-360X.2015.00016.5.
14. Nagham Mahmood Aljamali., (2015). Review in Azo Compounds and its Biological Activity. Biochem Anal Biochem, 4, 169, doi:10.4172/2161-1009.1000169.
15. Nagham Mahmood Aljamali. Synthesis of Antifungal Chemical Compounds from Fluconazole with (Pharma-Chemical) Studying ., Research journal of Pharmaceutical, biological and chemical sciences, 2017, 8 (3), 564 -573.
16. Mieaad M, Nagham Mahmood Aljamali, Wassan Ala Shubber., Sabreen Ali Abdalrahman ."New Azomethine- Azo Heterocyclic Ligands Via Cyclization of Ester"., Research Journal of Pharmacy and Technology, 2018, 11,6, 2555-2560 ., DOI : 10.5958/0974-360X. 2018. 00472.9 .
17. Nagham Mahmood Aljamali, S Jawad., (2022) . Preparation, Spectral Depiction, Thermal *Study, and Antifungal Assay of (Formazane -Mefenamic acid)- Derivatives.*, Egyptian Journal of Chemistry , *411, Volume 65, Issue 2, February 2022,* DOI: 10.21608/EJCHEM.2021.88727.4266 .
18. Hasaneen Kudhair Abdullabass, Aseel Mahmood Jawad ,Nagham Mahmood Aljamali . Synthesis of drugs derivatives as inhibitors of cancerous cells., Biochem. Cell. Arch, Vol. 20 (2) – October 2020., **DocID:** https://connectjournals.com/03896.2020.20.5315 .
19. Nagham Mahmood Aljamali, Husen Mebel Azez. Synthesis and Depiction of Some New Formazan - Cefixime and Study of Against Breast Cancer Cells., Annals of the Romanian Society for Cell Biology, Vol. 25, Issue 4, 2021., P: 8562–8578. Retrieved from https://www.annalsofrscb.ro/index.php/journal/article/view/2400 .
20. Nagham Mahmood Aljamali, Asmaa Kefah Mahdi. Synthesis, Identification and Anticancer Studying of Heterocyclic- Mefenamic Drug via Thiosemicarbazide., Annals of the Romanian Society for Cell Biology, 8521–8537., Vol. 25, Issue 4, 2021., p: , 8521–8537 ., Retrieved from

https://www.annalsofrscb.ro/index.php/journal/article/view/2398 .

21. F. Jawad, Nagham Mahmood Aljamali . Preparation, Investigation and Study of Biological Applications of Tyrosine Derivatives against Breast Cancer Cells ., NeuroQuantology ,September 2021 ,Volume 19 , Issue 9 , Page 117-125 .,doi: 10.14704/nq.2021.19.9.NQ21144
22. Nagham Mahmood Aljamali, Intisar Obaid Alfatlawi. Synthesis of Sulfur Heterocyclic Compounds and Study of Expected Biological Activity ., Research J. Pharm. and Tech., 2015, 8,9 ,1225-1242 , DOI: 10.5958/0974-360X.2015 .00224.3.
23. Intisar Obaid Alfatlawi, Nuha S S, Zainab M J ,Nagham Mahmood Aljamali. Synthesis of New Organic Compounds Via Three Components Reaction with Studying of (Identification, Thermal Behavior, Bioactivity on Bacteria of Teeth)"., Journal of Global Pharma Technology. 2017;11,9, 157-164.
24. Nagham Mahmood Aljamali.; Saher Mahmood Jawd.; Zainab M J.; Intisar, Obaid. Alfatlawi.; 2017, "Inhibition activity of (Azo–acetyl acetone) on bacteria of mouth"., Research Journal of Pharmacy and Technology 10(6):1683-1686, DOI: 10.5958/0974-360X.2017.00297.9
25. Aseel Mahmood Jawad., Nagham Mahmood Aljamali, Saher Mahmood Jawd. Development and Preparation of ciprofloxacin Drug Derivatives for Treatment of Microbial Contamination in Hospitals and Environment, Indian Journal of Forensic Medicine & Toxicology, 2020 ,14, 2, p:1115-1122.
26. Nagham Mahmood Aljamali. Spectral and Laboratory Diagnostics of Compounds ., 1th – Edition, 2022, Eliva Press SRL., ISBN: 9781636482118.
27. Shireen R. Rasool, Nagham Mahmood Aljamali ,Ali Jassim Al-Zuhairi., Guanine substituted heterocyclic derivatives as bioactive compounds., *Biochem. Cell. Arch.* Vol. 20, Supplement 2, pp. 3651-3655, 2020 ., DocID: https://connectjournals.com/03896.2020.20.3651
28. Deniz Ar, Alexander F. R. Kilpatrick, Beatrice Cula, Christian Herwig, Christian Limberg. Transformation of Formazanate at Nickel(II) Centers to Give a Singly Reduced Nickel Complex with Azoiminate Radical Ligands and Its Reactivity toward Dioxygen. Inorganic Chemistry 2021, 60 (18) , 13844-13853. https://doi.org/10.1021/acs.inorgchem.0c03761
29. Francesca Milocco, Folkert de Vries, Harmke S. Siebe, Silène Engbers, Serhiy Demeshko, Franc Meyer, Edwin Otten. Widening the Window of Spin-Crossover Temperatures in Bis(formazanate)iron(II) Complexes via Steric and Noncovalent Interactions. Inorganic Chemistry 2021, 60 (3) , 2045-2055. https://doi.org/10.1021/acs.inorgchem.0c03593
30. Nagham Mahmood Aljamali , Nemah Sahib Muhammed . Chemo - Spectral and Biological Studying of New Ligands ., Research Journal of Pharmaceutical, Biological and Chemical Sciences ., May – June, 2017 , RJPBCS ,8,(3) ,Page No. 674.
31. Nor A., Sud S., Nagham Mahmood Aljamali., Synthesis, Depiction and Thermal Analysis for New Amoxil Ligands, Asian Journal of Chemistry; 31, 5, 1022-1026, (2019).
32. Nagham Mahmood Aljamali. (Synthesis, Investigation, Chromatography, Thermal)-Behavior of (Five, Seven)- Membered Ring with Azo and Anil Compounds", *Pak. J. Biotechnol.;* **15**(1): 219-239 (2018).
33. Mhammd Abdul, Abd Ali H , Nagham Mahmood Aljamali . (2021). Synthesis, Spectral, Bio Assay, Chromatographic - Studying of New Imidazole Reagents Via Three Components Reaction . NeuroQuantology ,July 2021 , Volume 19 , Issue 7 ,Page 115-122 ., doi: 10.14704/nq.2021.19.7.NQ21092
34. Amen Abd , Nagham Mahmood Aljamali . Triazole-Anil and Triazol-Azo Reagents (Creation, Spectral Categorization, Scanning Microscopy, Thermal Analysis)., NeuroQuantology , 2021; 19(11):84-94 ., DOI Number: 10.14704/nq.2021.19.11.NQ21178 .
35. Rajaa Abdul Ameer Ghafil, Nor A Alrab, Nagham Mahmood Aljamali. Synthesis of Triazole Derivatives via Multi Components Reaction and Studying of (Organic Depiction, Chromatographic Behavior, Chem-Physical Properties)., Egyptian Journal of Chemistry .

Vol. 63, No. 11, pp. 4163 - 4174 (2020). DOI: 10.21608/EJCHEM.2020.23541.2399 .

36. Nagham Mahmood Aljamali, Tabark Emad Al-Faham. Synthesis, Identification, Chromatographic Studying of Formazane – Phenylenediamine Derivatives., Annals of the Romanian Society for Cell Biology, Vol. 25, Issue 4, 2021., p: Retrieved from https://www.annalsofrscb.ro/index.php/journal/article/view/2399 .
37. Nagham Mahmood Aljamali, Jad F. Preparation, Diagnosis and Evaluation of Cyclic-Tryptophan Derivatives as Anti Breast Cancer Agents. Biomed Pharmacol J ., 2021; 14(4)., Available from: https://bit.ly/3HuvlVG
38. Nagham Mahmood Aljamali . Designation of Macrocyclic Sulfazan and Triazan as Modernized Compounds with Their Estimation in Nano-Activities by the Scanning Microscope ., International Journal of Convergence in Healthcare, January-June 2022, Vol. 02, No. 01., P: 25-34 , Available at : https://www.ijcih.com/index.php/ijcih/article/view/21
39. Nagham Mahmood A. Origination of Macrocyclic Formazan with Macrocyclic Sulfazan and Triazan as Modernized Compounds and Compared Their efficiency Against Breast Cancer. Open Access Journal of Biomedical Science, 2022, 4(1) OAJBS.ID.000383. DOI: 10.38125/OAJBS.000383
40. Nagham Mahmood Aljamali. Synthesis Innovative Cyclic Formazan Compounds for the First Time and Evaluation of Their Biological Activity. International Journal of Polymer Science & Engineering . 2021; 7(2): 5–14p., DOI: https://doi.org/10.37628/ijpse.v7i2.830 .; Available at : http://materials.journalspub.info/index.php?journal=JPMSE&page=article&op=view&path%5B%5D=830
41. Nagham Mahmood Aljamali. Inventing of Macrocyclic Formazan Compounds with Their Evaluation in Nano- Behavior in the Scanning Microscope and Chromatography. Biomedical Journal of Scientific & Technical Research . 41, (3), 2022., P: 32783-32792 .; BJSTR. MS.ID.006616 .; DOI: 10.26717/BJSTR.2022.41.006616 .
42. J W LEWI S and C SANDORFY. "Infrared absorption and resonance Raman scattering ofphotochromic triphenylformazans" *Can. J. Chem*. (1983). 61,pp. 809 -816.
43. L Hunter and C B Roberts" The associating effect of the hydrogen atom. Part IX. The N-H-Nbond. Virtual tautomerism of the formazyl compounds" *journal of the Chemical Society*.1941, Pages 820-823.
44. Mhand K , Saden Ab, Nour Alrazzaka , Nagham Mahmood Aljamali. 2021 ., Synthesis, Characterization and Biological activity study for new hybridpolymers by grafting 1,3,4-triazole and 1,2,4-oxadiazle moieties ontopolyvinyl chloride ., Egyptian Journal of Chemistry ., Vol. 64, No. 3 pp. 1273 – 1283 ., DOI: 10.21608/EJCHEM.2021.27879.2584
45. A A Abbas" New synthesis of 28- and 30-crown-formazans and bis formazans" *Tetrahedron*.October 1998.Vol. 54, Issue 40, Pages 12421-12428.
46. S A Khan, S Shahid, S Kanwal and G Hussain " Synthesis depiction and antibacterial activity of Cr (III), Co (III), Fe (II), Cu (II), Ni (III) complexes of 4-(2-(((2-hydroxy- 5-nitrophenyl) diazenyl) (phenyl) methylene) hydrazinyl) benzene sulfonic acid based formazandyes and their applications on leather"*Dyes and Pigments*. January 2018, Vol. 148,Pages 31-43.
47. A K .Abdul Rahim. “Metal complexes of formazans ” Thesis. Department of Chemistry,University of Calicut, 2000.
48. H Tezcan" Synthesis and spectral properties of some bis-substituted formazans" *Spectrochim Acta* (2008), Part A, 69 pp. 971-979.
49. A Bamoniri,B FMirjalili and N M Arani" Nano BF3·SiO2: A green heterogeneous solid acid for synthesis of formazan dyes under solvent-free condition" *Journal of Molecular Catalysis A: Chemical*. 1 November 2014, Vol. 393, Pages 272-278.