J. Cardiovasc Disease Res., 2020; 11(2): 44 – 55
A Multifaceted Peer Reviewed Journal in the field of Cardiology
www.jcdronline.org | www.journalonweb.com/jcdr
P – ISSN: 0975 – 3583 Online: 0976 – 2833

Invention of (Gluta. Sulfazane-Cefixime) Compounds as Inhibitors of Cancerous Tumors

Dr. Imad Kareem Alwan Alsabri[1], Dr. Hasaneen Kudhair Abdullabass[2], Dr. Nagham Mahmood Aljamali*[3]
[1]Master in Oncology, College of Medicine, Kufa University, Iraq.
[2]Lecturer, Medical Microbiology, Clinical Immunology, Pharmacy Department, Alkut University College.
*[*3]Professor, Synthetic Chemistry Field, Department of Chemistry, Iraq, E-mail: dr.nagham_mj@yahoo.com**

ABSTRACT

Back ground: Clinical trials are testing many types of treatment such as new drugs, new methods of surgery or radiotherapy, new combinations or new methods such as gene therapy, and clinical trials are one of the final stages of a long and accurate cancer research process.

Methods: As the search for new treatments begins in the laboratory, scientists invent and test new ideas first. If this approach is promising, the next step will be animal testing to see how it affects cancer in an organism, and whether it has harmful effects. Of course, treatments that work well in the laboratory or in animals may not work well in humans.

Results: The research aimed find better ways to treat cancer patients for this the studies are carried out on cancer patients to see if the treatment is promising, safe and effective. We attended three innovative derivatives in which two important pharmaceutical drugs were linked to the innovative sulfazane group for development and obtaining three pharmaceutical compounds developed for cancer treatment, via a series of chemical reactions to prepare the derivatives and linking them to two pharmaceutical drugs for their development and the use of non-previously used catalysis agents and innovative reaction conditions to ensure an ideal preparation method and as a reference for the upcoming research of such sulfazane compounds.

Conclusions: The derivatives (Gluta. Cefixime-Sulfazane) were proven by several diagnostic methods to prove their chemical composition act ((FT.IR - Spectra, H.NMR – Spectra, HMBC-Spectrum, Mass Spectra), chemical properties, Flowing via TLC. Then studies of cancerous cells (Throat Cancer) and other normal cells were conducted to determine their efficiency in treatment and their toxic effect, all these evidences gave good data proved invented drugs.

Keywords: Throat Cancer, Sulfazane, glutathione, cefixime, innovation, new reaction of diazonium, sulfide-azo, (-S-N=N-), invented compounds, tumor, cancer, toxicity.

Correspondence:
Dr. Nagham Mahmood Aljamali
Professor, Synthetic Chemistry Field
Department of Chemistry
Iraq
E-mail Address:
dr.nagham_m@yahoo.com

Submitted: 25-04-2020
Revision: 20-05-2020
Accepted Date: 10-06-2020

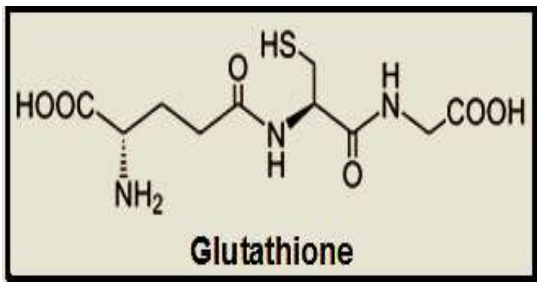
DOI: 10.31838/jcdr.2020.11.02.09

INTRODUCTION

In view of the success achieved by the innovative sulfazane compounds by the researcher (Dr. Nagham Aljamali in 2019) and the innovated preparation procedure[1, 2] of these compounds by using several laboratory experiments, through which they demonstrated the efficiency of the innovative sulfazane compounds as fungicides, antibacterial agents[1, 2] ,inhibitors of cancerous tumors during studies of cancerous cells that proven Its elimination and killing of cancerous cells, as its efficiency and effectiveness are attributed to the presence of the active sulfazane group within its chemical composition (-S-N=N-) which gave the compounds the therapeutic property. Therefore, our research included linking two pharmaceutical drugs to the sulfazane group, which are (Glutathione and Cefixime), through a series of chemical reactions to prepare three pharmaceutical sulfazane derivatives as anticancer drugs, which are (Gluta.Sulfazane-Cefixime) compounds to develop their therapeutic efficacy from antibiotics to anticancer through this research and previous research For the same field.

Glutathione

{($C_{10}H_{17}N_3O_6S$), M.Wt= 307.32 g/mole, m.p= 195 C°, its scientific name: 2*S*)-2-Amino-[(1*R*)-1-[(carboxymethyl) carbamoyl]-2-sulfanylethyl] carbamoyl} butanoic acid}. It is considered[3-8] one of the natural substances secreted by the liver, and this substance consists of three essential amino acids: (glutamic, cysteine and glycine)[9-15], and the work of this substance is related to the work of enzymes that work as antioxidants to protect cells from free radical damage, that work in the production of red blood cells and protect cells from damage and damage in addition to fatty membranes in the body[16-21]. Also Glutathione has many benefits as it protects the body from damage to the surrounding environment caused by pollution and radiation, and reduces the effects[22-30] associated with chemotherapy for cancer patients, besides to it helps the body resist external toxins[31-40].

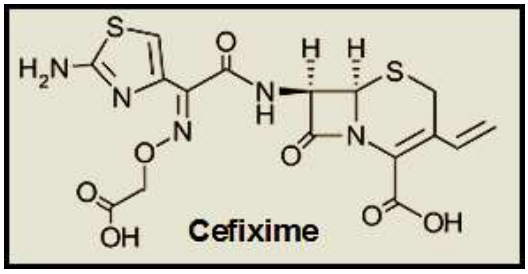


Glutathione

Cefixime

{$C_{16}H_{15}N_5O_7S_2$), M.Wt. = 453.452 g/mol}. It is an antibiotic from the Cephalosporins family[41-43], used to treat children and adults with severe infections of the respiratory tract, urinary tract, pharynx and middle ear. It can also be used to treat patients with gonorrhea[44-50]. Cefixime belongs to a relatively new generation of cephalosporins, which could have been taken by injection only until recently[51-57]. As with all other antibiotics, Cefixime may only be used to treat bacterial infections that are able to resist other antibiotics of a narrower effect, in order to prevent the development of a new generation of bacteria that are able to resist advanced

antibiotics[58-66]. Today, this antibiotic can only be used when there are no other alternatives[76-72], in anticipation of the emergence of a generation of bacteria able to resist antibiotics[73-81].



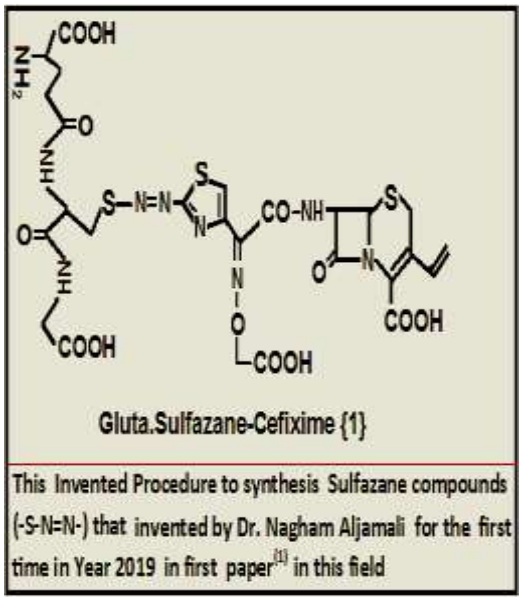
EXPERIMENTAL PART

A recent studies were conducted in year 2019 to find and delineate the scientific fundamentals[1, 2] and the ideal way to prepare newly innovative sulfazane compounds, so the same approach was taken in preparing innovative pharmaceutical compounds in this study and then studied them as treatments for cancerous tumors in many studies and experiments. The preparation of the innovative compounds has been demonstrated through numerous spectral techniques to demonstrate the correct chemical composition and correct association with the sulfazane group (FT-IR spectra (FT-IR 8300 Shimadzu)in range (400-4000)$cm^{-1}$with discs of KBr., 1H.NMR–Spectra in solvent (d-DMSO) Fourier transformation broker spectrometer ,operating at (400MHz)., HMBC- Spectrum ,Mass spectra for some of them)in Kashan university, and the synthesis of compounds was followed via (TLC), then a laboratory experiments of cancer cells line(Throat Cancer)to screen efficiency of the innovative compounds.

Innovative Method of Preparation [1, 2]

Synthesis of Gluta.Sulfazane- Cefixime {1}

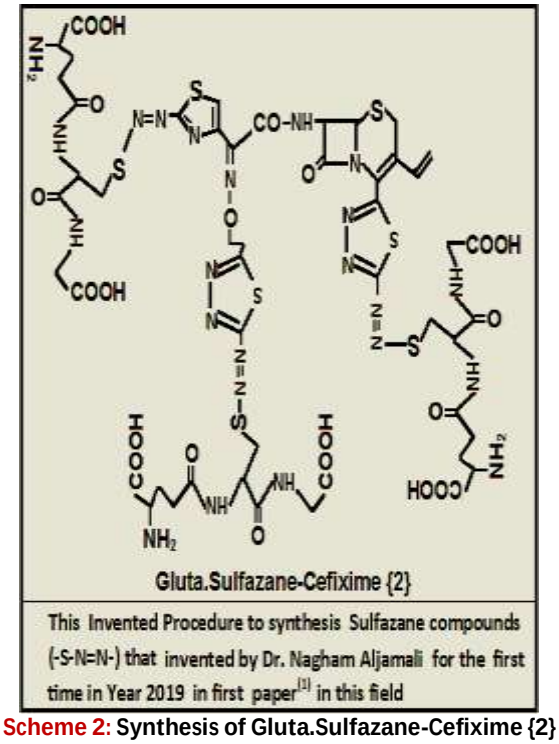
According to fundamental approach in previously studies[1, 2] to prepare newly innovative sulfazane compounds, so the same approach was taken in preparing innovative pharmaceutical compounds in this study via series of chemical reactions by reaction of cefixime (0.01 mole) after diazotation steps with glutathione (0.01 mole) with basic conditions through series organic reactions to obtain precipitation after (56 hrs), filtered, washed, dried, recrystallized to yield Gluta.Sulfazane-Cefixime {1}.



Scheme 1: Synthesis of Gluta.Sulfazane-Cefixime {1}

Synthesis of Gluta. Sulfazane-Cefixime {2}

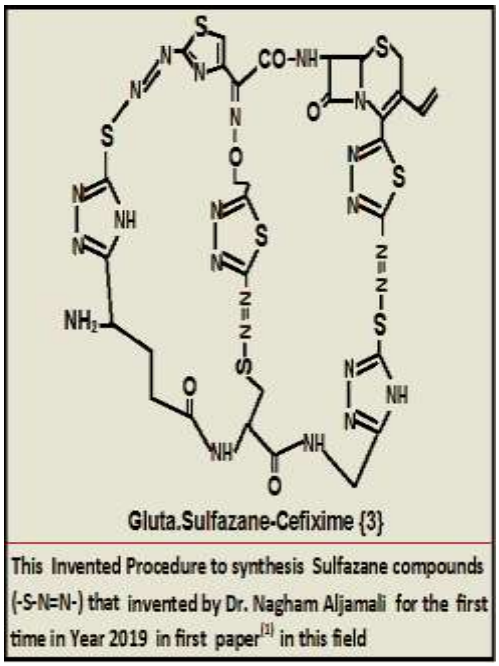
According to fundamental approach in previously studies[1, 2] to prepare newly innovative sulfazane compounds, so the same approach was taken in preparing innovative pharmaceutical compounds in this study via series of chemical reactions by cyclization of cefixime (0.01 mole) with thiosemicarbazide with catalysis after formation of thiadiazole –cefixime, it reacts (0.01 mole) in azotation steps inbasic medium of glutathione (0.03mole) in many organic reactions to obtain precipitation after (7 days), filtered, washed, dried, recrystallized to yield Gluta. Sulfazane-Cefixime {2}.



Scheme 2: Synthesis of Gluta.Sulfazane-Cefixime {2}

Synthesis of Gluta. Sulfazane-Cefixime {3}

According to original approach in previously studies[1, 2] to prepare newly innovative sulfazane compounds, so the same approach was taken in preparing innovative pharmaceutical compounds in this study via series of chemical reactions by cyclization of cefixime (0.01 mole) with thiosemicarbazide with catalysis after formation of thiadiazole–cefixime ,then cyclization of glutathione in basic medium to yield Glutamercapto-triazole that reacted (0.01 mole) in basic medium with diazonium salt of thiadiazole-cefixime from first step (0.01mole) in numerous organic reactions to obtain precipitation after (7 days), filtered, washed, dried, recrystallized to yield Gluta. Sulfazane-Cefixime {3}.



Scheme.3: Synthesis of Gluta.Sulfazane-Cefixime {3}

RESULTS AND DISCUSSION

In this research, innovative compounds (Gluta.Sulfazane-Cefixime) were prepared from the liking of two important drugs (cefixime and glutathione) in the medicine field by using the active sulfazane groupas a first and Original preparation (that acts An original creation of these a pharmaceutical compounds), which have proven its composition through several recent evidences and techniques in this field, and we mention among them:

Spectral Investigation Evidences

FT.IR- Spectra

It represents the first spectral evidence to prove the preparation of innovative compounds, and it gave excellent results that prove the preparation of the compounds, as it showed spectral bands and frequencies that belong to effective functional groups present within the compositions of the prepared compounds, including:

Gluta. Sulfazane-Cefixime {1}

bands for sulfazne group(-N=N-S-) as Azo-Sulfide: (1413, 1462, 1515), (S-CH_2-) Sulfide: 1228, (C-S) endocyle of thiazole: 664, (C=N) endocycle of thiazole: 1622, (-NH_2) amine group: (3320, 3240), (NH) amine of amide group: 3200, (-CH=CH_2) alkene : 3094, (CH) aliphatic: 2944, (CO-O-) carbonyl of carboxyl group: 1714, (CO-N-) carbonyl of amide: 1684, (C=N): 1611

Gluta.Sulfazane-Cefixime {2}

bands for sulfazne group (-N=N-S-) as Azo-Sulfide: (1440, 1498, 1520), (S-CH_2-) Sulfide: 1240, (C-S) endocyle of thiazole: 690, (C-S) endocyle of thiadiazole: 710, (C=N) endocycle of thiazole: 1640, (-NH_2) amine group: (3210, 3190), (NH)amine of amide group: 3100, (-CH=CH_2) alkene: 3090, (CH) aliphatic: 2900, (CO-O-) carbonyl of carboxyl group: 1720, (CO-N-) carbonyl of amide: 1680, (C=N): 1610.

Gluta.Sulfazane-Cefixime {3}

bands for sulfazne group (-N=N-S-) as Azo-Sulfide: (1432, 1477, 1513), (S-CH_2-) Sulfide: 1254, (C-S) endocyle of thiazole: 686, (C=N) endocycle of thiazole: 1635, (-NH_2) amine group: (3270, 3220), (NH) amine of amide group: 3150, (-CH=CH_2) alkene: 3097, (CH) aliphatic: 2915, (CO-O-) carbonyl of carboxyl group: 1717, (CO-N-) carbonyl of amide: 1685, (C=N): 1610, (C-S) endocyle of thiadiazole: 710, (NH) amine of triazole: 3120., Other active groups are appeared in some selected spectra (1, 2).

Fig 1: I. R Spectrum of Innovated Gluta.Sulfazane-Cefixime {1}

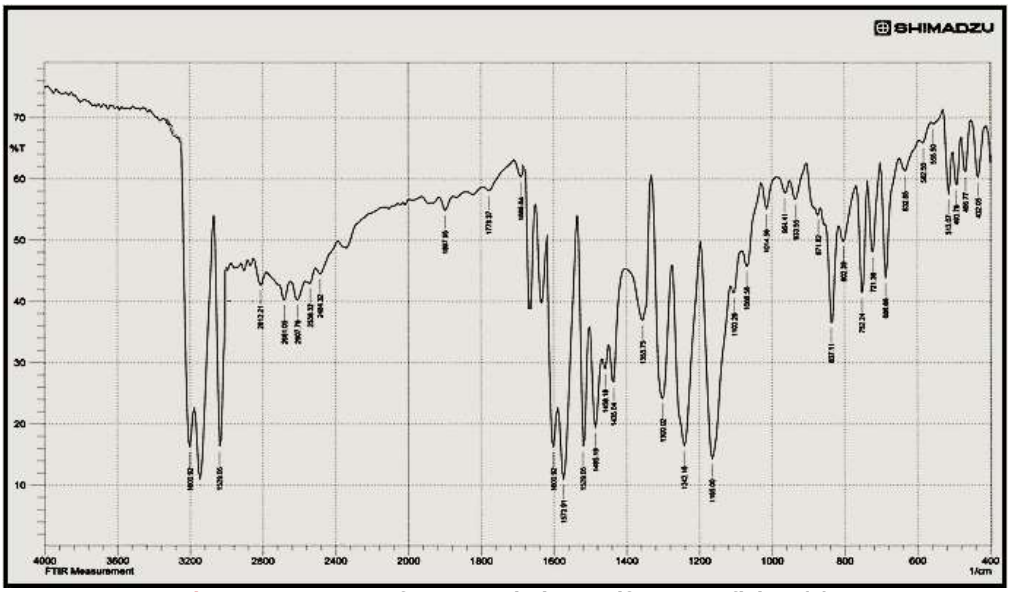


Fig 2: I.R Spectrum of Innovated Gluta.Sulfazane-Cefixime {2}

^{1}H.NMR- Spectra

It represents the second spectral evidence to prove the preparation of innovative compounds, and it gave excellent results that prove the preparation of the compounds, as it showed spectral many peaks that belong to effective functional groups present within the compositions[1,2] of the prepared compounds, all spectra gave signals at (2.50) for solvent (d-DMSO), in addition to other signals such:

Gluta. Sulfazane-Cefixime {1}

It appeared peaks at (5. 02) due to protons of amine group (NH_2), (COOH) proton of carboxyl group: (11.80), (-CH_2-S-) protons: (3.81), (NH-CO-) proton of amide in lactam ring: (9.82), (NH-CO-) proton of amide from linkage with glutathione: (9.76), (N-CH_2-COO-): (2.40), (CO-CH_2-CH_2): (3.3, 3.75), (-CH=CH_2) protons of alkene: (2.80, 3.0, 3.02), (-O-CH_2-COO-) protons of methylene : (3.5).

Gluta. Sulfazane-Cefixime {2}

It appeared peaks at (5.01) due to protons of amine group (NH_2), (COOH) proton of carboxyl group: (11.81), (-CH_2-S-) protons: (3.82), (NH-CO-) proton of amide in lactam ring: (9.40), (NH-CO-) proton of amide from linkage with glutathione: (9.08), (N-CH_2-COO-): (2.40), (CO-CH_2-CH_2): (3.76, 3.35), (-CH=CH_2) protons of alkene: (2.60, 2.82, 3.00), (-O-CH_2-C-) protons of methylene: (3.60).

Gluta.Sulfazane-Cefixime {3}

It appeared peaks at (5.12) due to protons of amine group (NH_2), (COOH) proton of carboxyl group: (11.63), (-CH_2-S-) protons: (3.67), (NH-CO-) proton of amide in lactam ring: (9.54), (NH-CO-) proton of amide from linkage with glutathione: (9.15), (N-CH_2-COO-): (2.29), (CO-CH_2-CH_2): (3.31, 3.28), (-CH=CH_2) protons of alkene: (2.73, 2.79, 3.11), (-O-CH_2-C-) protons of methylene: (3.58)., Other protons of active groups appeared in some spectra (3, 4).

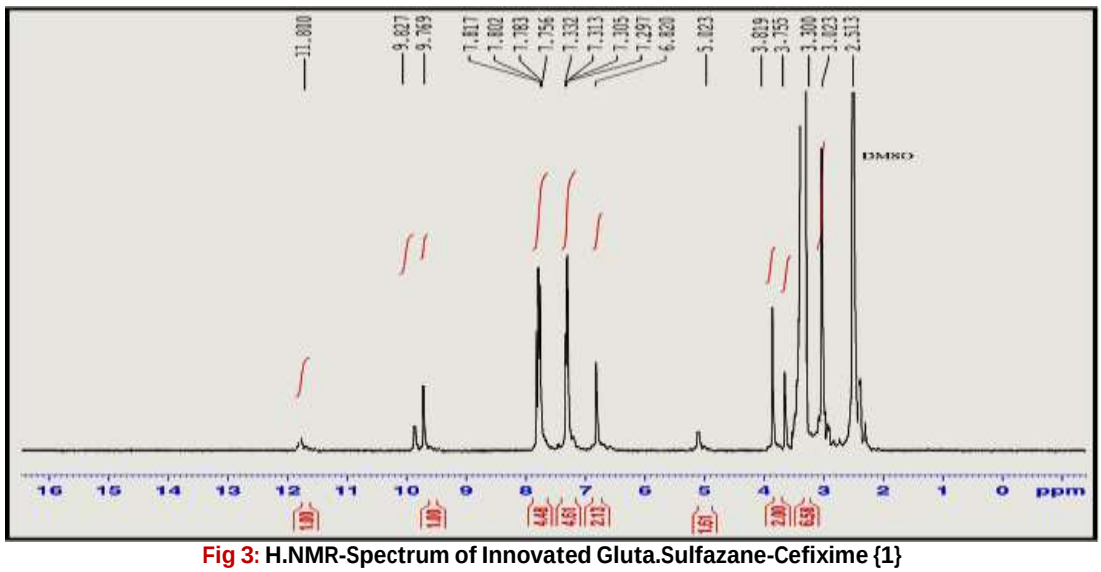


Fig 3: **H.NMR-Spectrum of Innovated Gluta.Sulfazane-Cefixime {1}**

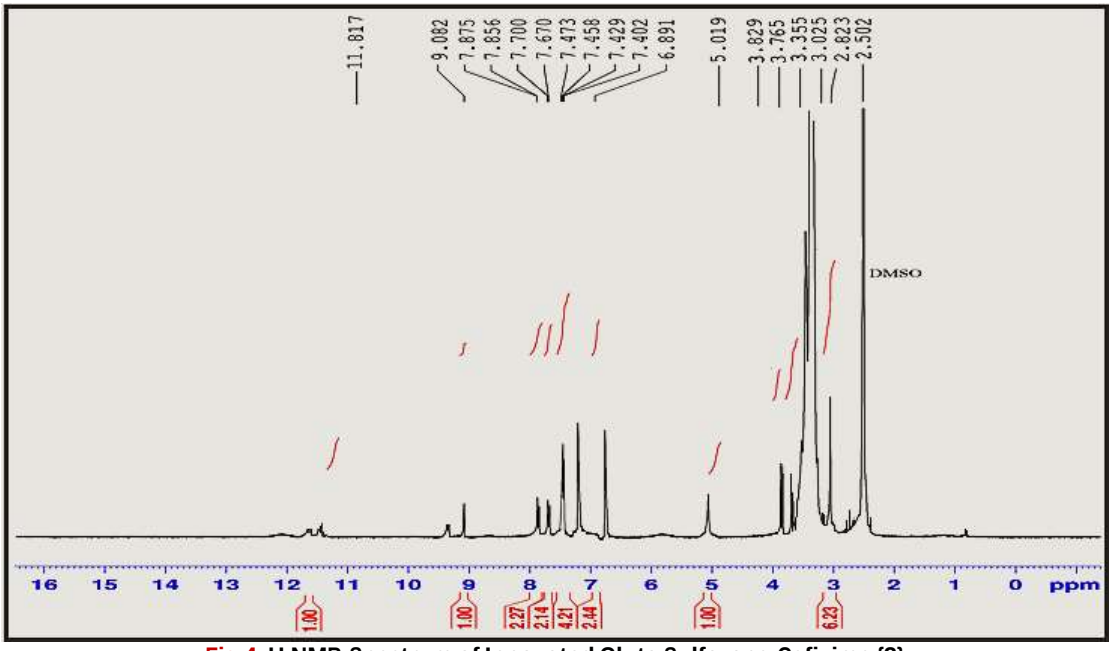


Fig 4: **H.NMR-Spectrum of Innovated Gluta.Sulfazane-Cefixime {2}**

HMBC- Spectrum

The HMBC- spectrum represents the third spectral evidence to prove the preparation of innovative compounds, and it gave excellent results that prove the preparation of the compounds, as it showed many signals that belong to effective functional groups present within the compositions[1,2] of the prepared compounds, spectrum (5).

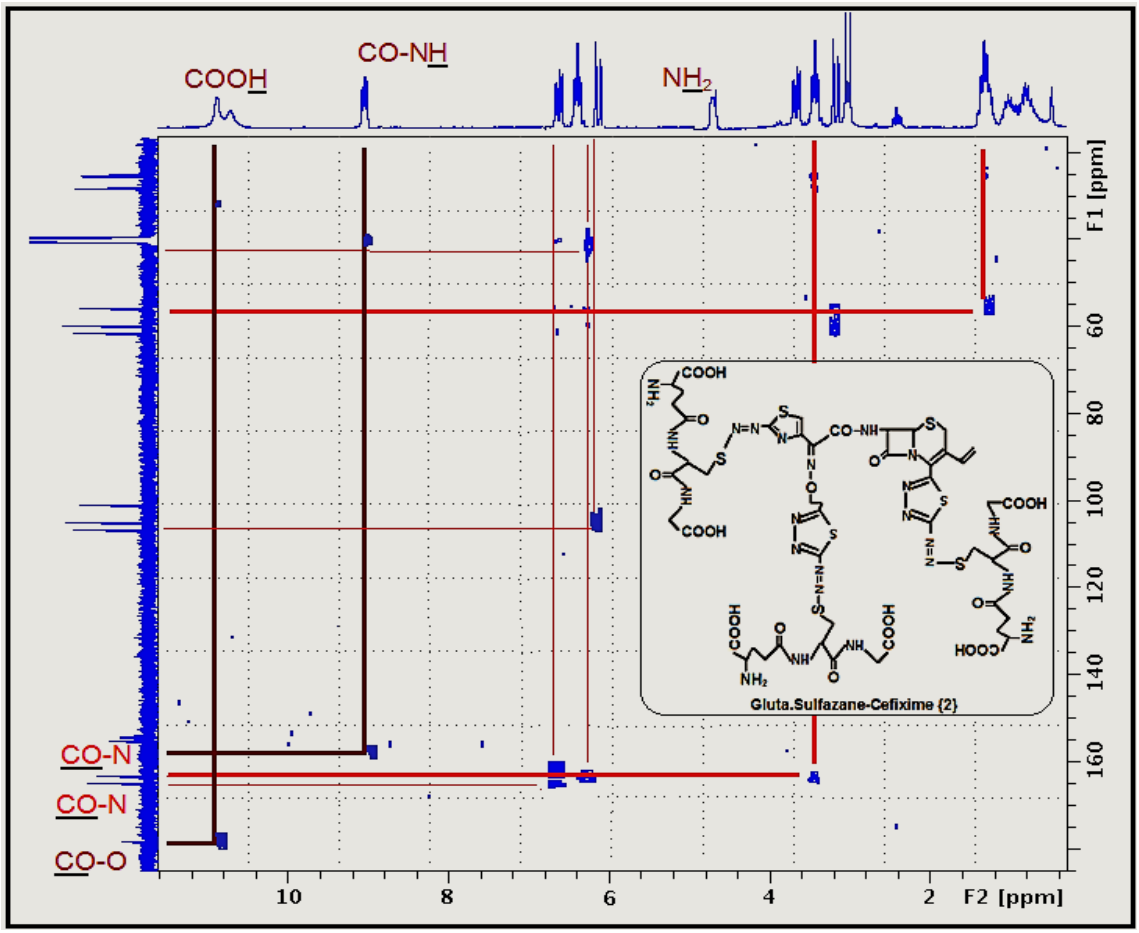


Fig 5: HMBC-Spectrum of Innovated Gluta.Sulfazane-Cefixime {2}

Mass Spectra of Gluta.Sulfazane –Cefixime Derivatives

It represents the fourth spectral evidence to prove the preparation of innovative compounds, and it gave excellent results that prove the preparation of the compounds, as it showed fragments that belong to the compositions[1,2] of the prepared compounds, Some of invented derivatives, Figures (6, 7):

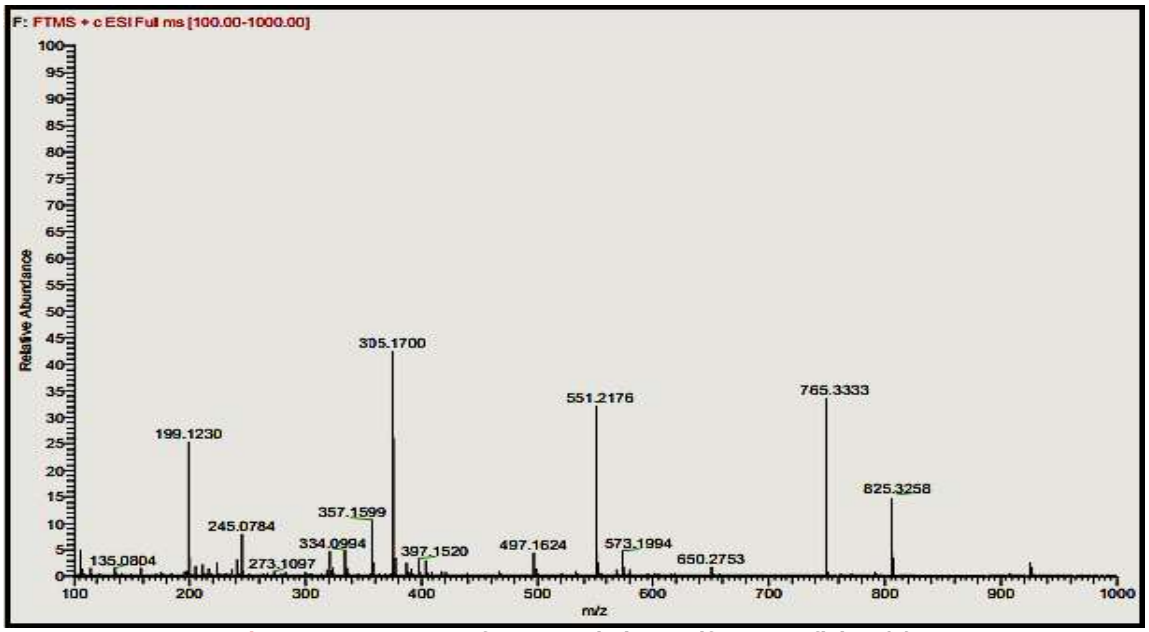


Fig 5: Mass Spectrum of Innovated Gluta.Sulfazane-Cefixime {1}

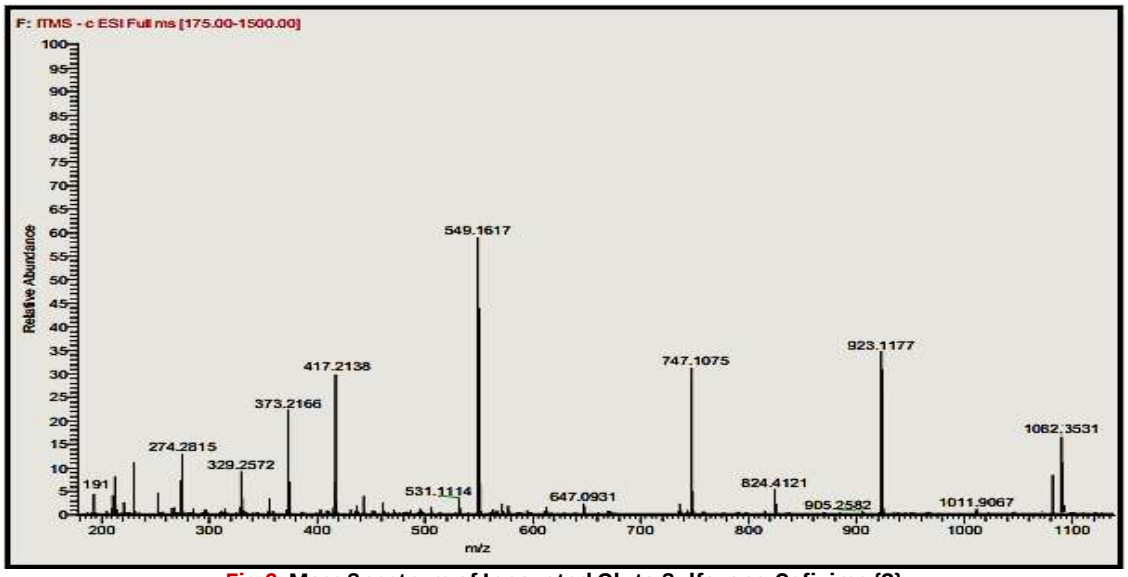


Fig 6: Mass Spectrum of Innovated Gluta.Sulfazane-Cefixime {3}

The chemical and physical properties for invented derivatives abstracted in Table(1)

Table 1: All chemical with physical properties

Invented Derivatives	Product %	Color	M.P (C °)
Gluta.Sulfazane-Cefixime {1}	70	Yellow	238
Gluta.Sulfazane-Cefixime {2}	76	Yellowish Orange	>250
Gluta.Sulfazane-Cefixime {3}	74	Deep Yellowish	244

Innovated Drugs Test against Throat Cancer

Initialization of Throat Cancer Cell Line[39]

Line processing and implantation of Throat Cancercells with live cell line were carried out at Biotechnology Center - the Nahrain (Hep-2 cell line) and (normal cell line grew in RPMI Media1640) supplemented with (10% FBS), cell suspension and incubation[39] at (37 °C) in incubator {(CO_2) % 5}. The suspended cells were centrifuged IN (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 (N_2) container.

Processing Method

MTT was used to determine cell viability via chromatic examination[39] for two (Hep-2 cell line and normal cell lines):

1- Cell suspension (100 µL) was added to the wells of a small flat plate bottom.

2- The solution was prepared via dissolving the crystals of 5 mg MTT in 1 ml of PBS solution (phosphate buffer solution).

3- The concentrations of all innovative derivative of the prepared derivatives were used in this research (500, 250, 125, 62.5, 31.5, 15.6) µg/ml of methanol, which were added to each well (three replicates per concentration).

4- A 10 ml MTT solution was added to each well of a plate including 96 wells then incubated for 4 hours with a test sample at 37 °C (the solution became yellow).

5- DMSO was added (200 µL)to each hole and stirred for 5 minutes (to become a purple DMSO solution).

6- After the complete dissolution of the dye, the absorption of the colored solution from the living cells was read at (575 nm) using the ELISA reader.

7- The mean absorption was calculated for all groups of iterations with the validity ratio of the cells exposed to different treatments was obtained as follows[39]

Cell Vitality% = [(Absorption from the treated sample /Absorption from the untreated sample) X 100

Table 2: Mean Percentage (%) to all cell line (Respond to Treatment) for Innovated {1}

	IC_{50} (µg/ml) : (238. 2084) Mean Percentage (%)for each cell line (Respond to treatment)		
	Conc (µg/ml)	Killing and inhibition of Carcinoma Cells %	Toxic Effect on Normal Cell Line
Gluta.Sulfazane-Cefixime{1}	500	60 %	22 %
	250	50 %	18 %
	125	42 %	12 %
	62.5	40%	10%
	31.5	30 %	10 %
	15.6	30%	10 %

Table 3: Mean Percentage (%) for all cell line (Respond to Treatment) for Innovated {2}

	IC_{50} (µg/ml) : (186. 3182) Mean Percentage (%) for each cell line (Respond to treatment)		
Gluta.Sulfazane-Cefixime{2}	Conc (µg/ml)	Killing and inhibition of Carcinoma Cells %	Toxic Effect on Normal Cell Line
	500	70 %	28 %
	250	64 %	22 %
	125	54%	20 %
	62.5	48%	14 %
	31.5	46 %	14 %
	15.6	46 %	12 %

Table 4: Mean Percentage (%) for each cell line (Respond to Treatment) for Innovated {3}

	IC_{50} (µg/ml) : (214. 6401) Mean Percentage (%) for each cell line (Respond to treatment)		
Gluta.Sulfazane-Cefixime{3}	Conc (µg/ml)	Killing and inhibition of Carcinoma Cells %	Toxic Effect on Normal Cell Line
	500	64 %	24 %
	250	56 %	20 %
	125	50 %	16 %
	62.5	44 %	14 %
	31.5	44 %	12 %
	15.6	36 %	12%

Cancer treatment with drugs is a drug treatment that uses strong chemicals to kill rapidly growing cells in the body. Chemotherapy is often used to treat cancer, as cancer cells grow and multiply much more quickly than most cells of the body. Several different chemotherapy drugs are available. The innovated drugs can be used alone or in combination with other treatments to treat a variety of cancers. Through our research, we were able to link two pharmaceutical drugs with the sulfazane group (-S-N=N-) to raise and increase the efficiency of innovative pharmaceuticals in this study. Indeed, we obtained good results in killing and inhibition of cancer cells (Throat Cancer) for all innovative pharmaceutical compounds that prepared in this research, and compound {2} was the most efficient for the association of three sulfazane groups with three molecules of glutathione and one molecule of sefixime, which is the reason for the increased effectiveness of this compound against cancer cells (Throat Cancer).

ACKNOWLEDGMENTS

we would like to express our heartfelt thanks to Biotechnology Center-the Nahrain for providing assistance samples of cells and bioinformatics analysis.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING SOURCE

None

REFERENCES

1. AfaqJaberKadhium, Ahmed Adnan Abdul Hussein, NaghamMahmoodAljamali, Afaq J K, Ahmed A A H, Invention of Imidazole &Thiazole-Sulfazane Ligands(Synthesis, Spectral Investigation, Microbial Behavior) for the First Time.,International Journal of Pharmaceutical Research ,2020 ,12 ,I 2, 989-998 .,doi.org/10.31838/ijpr/2020.12.02.0151.
2. Jelal H M,AleaJwadKadheim, Nagham M A, NaghamMahmoodAljamali.,Thiophene-Cyclic and Sulfazane Derivatives (Preparation, Spectral Analysis, The Behavior in Organic Solvents ,Microbial Testing).,Indian Journal of Forensic Medicine & Toxicology, 2020, 14, 2, p: 1593-1600.
3. Haynes, W M., ed. (2016). CRC Handbook of Chemistry and Physics (97th ed.). CRC Press. p. 3.284. ISBN 9781498754293.
4. Pompella A, Visvikis A, Paolicchi A, De Tata V, Casini AF (October 2003). "The changing faces of glutathione, a cellular protagonist". Biochemical Pharmacology. 66(8): 1499–503. doi:10.1016/S0006-2952(03)00504-5.PMID 14555227.
5. White CC, Viernes H, Krejsa CM, Botta D, Kavanagh TJ (July 2003). "Fluorescence-based microtiter plate assay for glutamate-cysteine ligase activity". Analytical Biochemistry. 318 (2): 175–80. doi:10.1016/S0003-2697(03)00143-X. PMID 12814619.
6. Chen Y, Yang Y, Miller ML, Shen D, Shertzer HG, Stringer KF, Wang B, Schneider SN, Nebert DW, Dalton TP (May 2007). "Hepatocyte-specific Gclc deletion leads to rapid onset of steatosis with mitochondrial injury and liver failure". Hepatology. 45(5): 1118–28. doi:10.1002/hep.21635. PMID 17464988.
7. Sies H (1999). "Glutathione and its role in cellular functions". Free Radical Biology & Medicine. 27 (9–10): 916–21. doi:10.1016/S0891-5849(99)00177-X. PMID 10569624.
8. Alaa J K, Nagham M A, Jelal H M, NaghamMahmoodAljamali., Thiazole Amide Derivatives (Synthesis, Spectral Investigation, Chemical Properties, Antifungal Assay).,

NeuroQuantology , 2020, 18, 1 ,Page 16-25 ., doi: 10.14704/nq.2020.18.1.NQ20102
9. Guoyao Wu, Yun-Zhong Fang, Sheng Yang, Joanne R. Lupton, Nancy D. Turner (2004). "Glutathione Metabolism and its Implications for Health". Journal of Nutrition. 134 (3): 489–92. doi:10.1093/jn/134.3.489. PMID 14988435.
10. Copley SD, Dhillon JK (29 April 2002). "Lateral gene transfer and parallel evolution in the history of glutathione biosynthesis genes". Genome Biology. 3 (5): research0025. doi:10.1186/gb-2002-3-5-research0025. PMC 115227. PMID 12049666.
11. Wonisch W, Schaur RJ (2001). "Chapter 2: Chemistry of Glutathione". In Grill D, Tausz T, De Kok L (eds.). Significance of glutathione in plant adaptation to the environment. Springer. ISBN 978-1-4020-0178-9 – via Google Books.
12. Pastore A, Piemonte F, Locatelli M, Lo Russo A, Gaeta LM, Tozzi G, Federici G (August 2001). "Determination of blood total, reduced, and oxidized glutathione in pediatric subjects". Clinical Chemistry. 47 (8): 1467–9. PMID 11468240.
13. Lu SC (May 2013). "Glutathione synthesis". BiochimicaetBiophysicaActa. 1830 (5): 3143–53. doi:10.1016/j.bbagen.2012.09.008. PMC 3549305. PMID 22995213.
14. Halprin KM, Ohkawara A (1967). "The measurement of glutathione in human epidermis using glutathione reductase". The Journal of Investigative Dermatology. 48 (2): 149–52. doi:10.1038/jid.1967.24. PMID 6020678.
15. Couto N, Malys N, Gaskell SJ, Barber J (June 2013). "Partition and turnover of glutathione reductase from Saccharomyces cerevisiae: a proteomic approach". Journal of Proteome Research. 12 (6): 2885–94. doi:10.1021/pr4001948. PMID 23631642.
16. Michael Brownlee (2005). "The pathobiology of diabetic complications: A unifying mechanism". Diabetes. 54 (6): 1615–25. doi:10.2337/diabetes.54.6.1615. PMID 15919781.
17. Dalle-Donne, Isabella; Rossi, Ranieri; Colombo, Graziano; Giustarini, Daniela; Milzani, Aldo (2009). "Protein S-glutathionylation: a regulatory device from bacteria to humans". Trends in Biochemical Sciences. 34 (2): 85–96. doi:10.1016/j.tibs.2008.11.002. PMID 19135374.
18. Dringen R (December 2000). "Metabolism and functions of glutathione in brain". Progress in Neurobiology. 62 (6): 649–71. doi:10.1016/s0301-0082(99)00060-x. PMID 10880854.
19. Scholz, RW. Graham KS. Gumpricht E. Reddy CC. (1989). "Mechanism of interaction of vitamin E and glutathione in the protection against membrane lipid peroxidation". Ann NY Acad Sci. 570 (1): 514–7. Bibcode:1989NYASA. 570.514S. doi:10.1111/j.1749-6632.1989.tb14973.x.
20. Hughes RE (1964). "Reduction of dehydroascorbic acid by animal tissues". Nature. 203 (4949): 1068–9. Bibcode:1964Natur.203.1068H. doi:10.1038/2031068a0. PMID 14223080.
21. Ha SB, Smith AP, Howden R, Dietrich WM, Bugg S, O'Connell MJ, Goldsbrough PB, Cobbett CS (June 1999). "Phytochelatin synthase genes from Arabidopsis and the yeast Schizosaccharomycespombe". The Plant Cell. 11 (6): 1153–64. doi:10.1105/tpc.11.6.1153. JSTOR 3870806. PMC 144235. PMID 10368185.
22. Grant CM (2001). "Role of the glutathione/glutaredoxin and thioredoxin systems in yeast growth and response to stress conditions". Molecular Microbiology. 39 (3): 533–41. doi:10.1046/j.1365-2958.2001.02283.x. PMID 11169096.
23. Hayes, John D.; Flanagan, Jack U.; Jowsey, Ian R. (2005). "Glutathione transferases". Annual Review of Pharmacology and Toxicology. 45: 51–88. doi:10.1146/annurev.pharmtox.45.120403.095857. PMID 15822171.
24. Steullet P, Neijt HC, Cuénod M, Do KQ (February 2006). "Synaptic plasticity impairment and hypofunction of NMDA receptors induced by glutathione deficit: relevance to schizophrenia". Neuroscience. 137 (3): 807–19. doi:10.1016/j.neuroscience.2005.10.014. PMID 16330153.
25. Varga V, Jenei Z, Janáky R, Saransaari P, Oja SS (September 1997). "Glutathione is an endogenous ligand of rat brain N-methyl-D-aspartate (NMDA) and 2-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors". Neurochemical Research. 22 (9): 1165–71. doi:10.1023/A:1027377605054. PMID 9251108.
26. AseelMahmoodJawad, NaghamMahmoodAljamali, SaherMahmoodJwad ,Aseel M J, Saher M J, 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.
27. Janáky R, Ogita K, Pasqualotto BA, Bains JS, Oja SS, Yoneda Y, Shaw CA (September 1999). "Glutathione and signal transduction in the mammalian CNS". Journal of Neurochemistry. 73 (3): 889–902. doi:10.1046/j.1471-4159.1999.0730889.x. PMID 10461878.
28. Oja SS, Janáky R, Varga V, Saransaari P (2000). "Modulation of glutamate receptor functions by glutathione". Neurochemistry International. 37 (2–3): 299–306. doi:10.1016/S0197-0186(00)00031-0. PMID 10812215.
29. Freitas HR, Ferraz G, Ferreira GC, Ribeiro-Resende VT, Chiarini LB, do Nascimento JL, Matos Oliveira KR, Pereira Tde L, Ferreira LG, Kubrusly RC, Faria RX, Herculano AM, Reis RA (14 April 2016). "Glutathione-Induced Calcium Shifts in Chick Retinal Glial Cells". PLOS ONE. 11 (4): e0153677. Bibcode:2016PLoSO.1153677F. doi:10.1371

/journal.pone.0153677. PMC 4831842. PMID 27078878.

30. NaghamMahmoodAljamali; Intisar ObaidAlfatlawi., "Synthesis of Sulfur Heterocyclic Ligands and Study of Expected Biological Activity",Research J. Pharm. and Tech.,2015, 8,9 ,1225-1242 , DOI: 10.5958/0974-360X.2015.00224.3.
31. NaghamMahmoodAljamali.,"(Synthesis, Investigation, Chromatography, Thermal)- Behavior of (Five, Seven)- Membered Ring with Azo and Anil Compounds", Pak. J. Biotechnol. ,2018; 15(1): 219-239.
32. Freitas HR, Reis RA (1 January 2017). "Glutathione induces GABA release through P2X7R activation on Müller glia". Neurogenesis. 4 (1): e1283188. doi:10.1080/23262133.2017.1283188. PMC 5305167. PMID 28229088.
33. Noctor G, Foyer CH (June 1998). "Ascorbate and Glutathione: Keeping Active Oxygen Under Control". Annual Review of Plant Physiology and Plant Molecular Biology. 49 (1): 249–279. doi:10.1146/annurev.arplant.49.1.249. PMID 15012235.
34. Ha SB, Smith AP, Howden R, Dietrich WM, Bugg S, O'Connell MJ, Goldsbrough PB, Cobbett CS (June 1999). "Phytochelatin synthase genes from Arabidopsis and the yeast Schizosaccharomycespombe". The Plant Cell. 11 (6): 1153–64. doi:10.1105/tpc.11.6.1153. PMC 144235. PMID 10368185.
35. NaghamMahmoodAljamali., Synthesis of Antifungal Chemical Compounds from Fluconazole with (Pharma-Chemical) Studying, Research journal of Pharmaceutical, biological and chemical sciences, 2017, 8 (3), 564 -573.
36. Parisy V, Poinssot B, Owsianowski L, Buchala A, Glazebrook J, Mauch F (January 2007). "Identification of PAD2 as a gamma-glutamylcysteinesynthetase highlights the importance of glutathione in disease resistance of Arabidopsis" (PDF). The Plant Journal. 49 (1): 159–72. doi:10.1111/j.1365-313X.2006.02938.x. PMID 17144898.
37. Rouhier N, Lemaire SD, Jacquot JP (2008). "The role of glutathione in photosynthetic organisms: emerging functions for glutaredoxins and glutathionylation". Annual Review of Plant Biology. 59 (1): 143–66. doi:10.1146/annurev.arplant.59.032607.092811. PMID 18444899.
38. Allen J, Bradley RD (September 2011). "Effects of oral glutathione supplementation on systemic oxidative stress biomarkers in human volunteers". Journal of Alternative and Complementary Medicine. 17 (9): 827–33. doi:10.1089/acm.2010.0716. PMC 3162377. PMID 21875351.
39. Witschi A, Reddy S, Stofer B, Lauterburg BH (1992). "The systemic availability of oral glutathione". European Journal of Clinical Pharmacology. 43 (6): 667–9. doi:10.1007/bf02284971. PMID 1362956. "Acetylcysteine Monograph for Professionals - Drugs.com".
40. AseelMahmoodJawad, NaghamMahmoodAljamali, Aseel M J .,"Innovation, Preparation of Cephalexin Drug Derivatives and Studying of (Toxicity & Resistance of Infection)"., International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 04, 2020 , 3754-3767 .
41. Zhang J, Zhou X, Wu W, Wang J, Xie H, Wu Z (2017). "Regeneration of glutathione by α-lipoic acid via Nrf2/ARE signaling pathway alleviates cadmium-induced HepG2 cell toxicity". Environ ToxicolPharmacol. 51: 30–37. doi:10.1016/j.etap.2017.02.022. PMID 28262510.
42. Garcion E, Wion-Barbot N, Montero-Menei CN, Berger F, Wion D (April 2002). "New clues about vitamin D functions in the nervous system". Trends in Endocrinology and Metabolism. 13 (3): 100–5. doi:10.1016/S1043-2760(01)00547-1. PMID 11893522.
43. NaghamMahmoodAljamali .,"Synthesis and Chemical Identification of Macro Compounds of (Thiazol and Imidazol)".,Research J. Pharm. and Tech, 2015, 8,1,78-84., DOI: 10.5958/0974-360X.2015.00016.5 .
44. Van Groningen L, Opdenoordt S, van Sorge A, Telting D, Giesen A, de Boer H (April 2010). "Cholecalciferol loading dose guideline for vitamin D-deficient adults". European Journal of Endocrinology. 162 (4): 805–11. doi:10.1530/EJE-09-0932. PMID 20139241.
45. Lieber CS (November 2002). "S-adenosyl-L-methionine: its role in the treatment of liver disorders". The American Journal of Clinical Nutrition. 76 (5): 1183S–7S. doi:10.1093/ajcn/76.5.1183s. PMID 12418503.
46. Vendemiale G, Altomare E, Trizio T, Le Grazie C, Di Padova C, Salerno MT, Carrieri V, Albano O (May 1989). "Effects of oral S-adenosyl-L-methionine on hepatic glutathione in patients with liver disease". Scandinavian Journal of Gastroenterology. 24 (4): 407–15. doi:10.3109/00365528909093067. PMID 2781235.
47. Loguercio C, Nardi G, Argenzio F, Aurilio C, Petrone E, Grella A, Del Vecchio Blanco C, Coltorti M (September 1994). "Effect of S-adenosyl-L-methionine administration on red blood cell cysteine and glutathione levels in alcoholic patients with and without liver disease". Alcohol and Alcoholism. 29 (5): 597–604. doi:10.1093/oxfordjournals.alcalc.a045589. PMID 7811344.
48. Dröge W, Holm E (November 1997). "Role of cysteine and glutathione in HIV infection and other diseases associated with muscle wasting and immunological dysfunction". FASEB Journal. 11 (13): 1077–89. doi:10.1096/fasebj.11.13.9367343. PMID 9367343.
49. Tateishi N, Higashi T, Shinya S, Naruse A, Sakamoto Y (January 1974). "Studies on the regulation of glutathione level in rat liver". Journal of

Biochemistry. 75 (1): 93–103. doi:10.1093/oxfordjournals.jbchem.a130387. PMID 4151174.
50. Meyer AJ, May MJ, Fricker M (July 2001). "Quantitative in vivo measurement of glutathione in Arabidopsis cells". The Plant Journal. 27 (1): 67–78. doi:10.1046/j.1365-313x.2001.01071.x. PMID 11489184.
51. Sebastià J, Cristòfol R, Martín M, Rodríguez-Farré E, Sanfeliu C (January 2003). "Evaluation of fluorescent dyes for measuring intracellular glutathione content in primary cultures of human neurons and neuroblastoma SH-SY5Y". Cytometry. Part A. 51 (1): 16–25. doi:10.1002/cyto.a.10003. PMID 12500301.
52. NaghamMahmoodAljamali., "The Various Preparation Methods in Synthetic Chemistry".,1Edt. ,Evincepub Publishing house, 2019., ISBN :978-93-88277-82-2 .
53. NaghamMahmoodAljamali,RashaNeama H,AafaqJaberAlnajem, Ali JassimAlzuhairi, AfaqJaberKadhium, Afaq J K., Studying of (Chemical ,Physical ,Biological)–Applications of Oxo- Sulfur Derivatives., Journal of Natural Sciences Research., 6, 7, 2016.
54. NaghamMahmoodAljamali. "Reactions and Mechanisms".,1 Edt., IJMRA Publication ,2018 .,ISBN : 978-93-87176-25-6 .
55. Aseel M J ,Mostafa N. Mohamed Salih ,Nagham M A, Nadia Hussein Obaid, AseelMahmoodJawad, Thanaa A. Helal, NaghamMahmood Aljamali.,2019., Review on Chalcone (Preparation ,Reactions, Medical and Bio Applications). International Journal of Chemical Synthesis and Chemical Reactions.; 5,(1):16–27p.
56. Lantz RC, Lemus R, Lange RW, Karol MH (April 2001). "Rapid reduction of intracellular glutathione in human bronchial epithelial cells exposed to occupational levels of toluene diisocyanate".Toxicological Sciences. 60 (2): 348–55. doi:10.1093/toxsci/60.2.348. PMID 11248147.
57. Jiang X, Yu Y, Chen J, Zhao M, Chen H, Song X, Matzuk AJ, Carroll SL, Tan X, Sizovs A, Cheng N, Wang MC, Wang J (March 2015). "Quantitative imaging of glutathione in live cells using a reversible reaction-based ratiometric fluorescent probe". ACS Chemical Biology. 10 (3): 864–74. doi:10.1021/cb500986w. PMC 4371605. PMID 25531746.
58. Jiang X, Chen J, Bajić A, Zhang C, Song X, Carroll SL, Cai ZL, Tang M, Xue M, Cheng N, Schaaf CP, Li F, MacKenzie KR, Ferreon AC, Xia F, Wang MC, Maletić-Savatić M, Wang J (July 2017). "Quantitative imaging of glutathione". Nature Communications. 8: 16087. doi:10.1038/ncomms16087. PMC 5511354. PMID 28703127.
59. Chen J, Jiang X, Zhang C, MacKenzie KR, Stossi F, Palzkill T, Wang MC, Wang J (2017). "Reversible Reaction-Based Fluorescent Probe for Real-Time Imaging of Glutathione Dynamics in Mitochondria". ACS Sensors. 2 (9): 1257–1261. doi:10.1021/acssensors.7b00425. PMC 5771714. PMID 28809477.
60. Meyer AJ, Brach T, Marty L, Kreye S, Rouhier N, Jacquot JP, Hell R (December 2007). "Redox-sensitive GFP in Arabidopsis thaliana is a quantitative biosensor for the redox potential of the cellular glutathione redox buffer". The Plant Journal. 52 (5): 973–86. doi:10.1111/j.1365-313X.2007.03280.x. PMID 17892447.
61. Nawfel M B ,Hayder H K, Noor H D, NawfelMuhammedBaqer ,NaghamMahmoodAljamali., "Preparation of Chemical Inhibitors to Treat the Corrosion and Erosion of Machines", International Journal of Engineering, Applied and Management Sciences Paradigms., 2019, 54, 3,89-93p.
62. NaghamMahmoodAljamali. "Synthesis and Biological Study of Hetero (Atoms and Cycles) Compounds", Der PharmaChemica, 2016, 8,6, 40-48.
63. Maulucci G, Labate V, Mele M, Panieri E, Arcovito G, Galeotti T, Østergaard H, Winther JR, De Spirito M, Pani G (October 2008). "High-resolution imaging of redox signaling in live cells through an oxidation-sensitive yellow fluorescent protein". Science Signaling. 1 (43): pl3. doi:10.1126/scisignal.143pl3. PMID 18957692.
64. Giustarini D, Dalle-Donne I, Milzani A, Fanti P, Rossi R (September 2013). "Analysis of GSH and GSSG after derivatization with N-ethylmaleimide". Nature Protocols. 8 (9): 1660–9. doi:10.1038/nprot.2013.095. PMID 23928499.
65. Schwarzländer M, Dick T, Meyer AJ, Morgan B (April 2016). "Dissecting Redox Biology Using Fluorescent Protein Sensors". Antioxidants & Redox Signaling. 24(13): 680–712. doi:10.1089/ars.2015.6266. PMID 25867539.
66. Farkas E, Buglyó P (2017). "Chapter 8. Lead(II) Complexes of Amino Acids, Peptides, and Other Related Ligands of Biological Interest". In Astrid S, Helmut S, Sigel RK (eds.). Lead: Its Effects on Environment and Health. Metal Ions in Life Sciences. 17. de Gruyter. pp. 201–240. doi:10.1515/9783110434330-008. ISBN 9783110434330. PMID 28731301.
67. Balendiran GK, Dabur R, Fraser D (2004). "The role of glutathione in cancer". Cell Biochemistry and Function. 22 (6): 343–52. doi:10.1002/cbf.1149. PMID 15386533.
68. Visca A, Bishop CT, Hilton SC, Hudson VM (2008). "Improvement in clinical markers in CF patients using a reduced glutathione regimen: An uncontrolled, observational study". Journal of Cystic Fibrosis. 7 (5): 433–6. doi:10.1016/j.jcf.2008.03.006. PMID 18499536.
69. NaghamMahmoodAljamali, ManarGhyathAbd-AlmutalibAlmosawy, Ahmed Adnan Abdul Hussein, NourAlhuda Abdul Abbas Bahar ,Rajaa Abdul AmeerGhafil, Noorhan Ali Hamza, Manar G AA, Ahmed A A H, Nouralhuda A A B, Rajaa A A, Noorhan A H., Review on Chemical-Biological Applications of Thiazole Derivatives.,

Forefront Journal of Engineering &Technology,Volume 2, Issue 3, Mar 2020, 9-22 .

70. Bishop C, Hudson VM, Hilton SC, Wilde C (January 2005). "A pilot study of the effect of inhaled buffered reduced glutathione on the clinical status of patients with cystic fibrosis". Chest. 127 (1): 308–17. doi:10.1378/chest.127.1.308. PMID 15653998.
71. Mandal PK, Tripathi M, Sugunan S (January 2012). "Brain oxidative stress: detection and mapping of anti-oxidant marker 'Glutathione' in different brain regions of healthy male/female, MCI and Alzheimer patients using non-invasive magnetic resonance spectroscopy". Biochemical and Biophysical Research Communications. 417 (1): 43–48. doi:10.1016/j.bbrc.2011.11.047. PMID 22120629.
72. Mandal PK, Saharan, S, Tripathi M, Murari G (October 2015). "Brain Glutathione Levels – A Novel Biomarker for Mild Cognitive Impairment and Alzheimer's Disease". Biological Psychiatry. 78 (10): 702–710. doi:10.1016/j.biopsych.2015.04.005. PMID 26003861.
73. NaghamMahmoodAljamali ,AlaaJawadKadhim, JelalHasenMuhamad, Rajaa Abdul AmeerGhafil, Rajaa A A G . Review on Preparation and Applications of Formazan Ligands. International Journal of Thermodynamics and Chemical Kinetics. 2019; 5(2): 23–33p.
74. Intisar ObaidAlfatlawi ,Nuha Salman S, ZainabMahmoodJawad , NaghamMahmoodAljamali., Synthesis of New Organic Ligands 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.
75. MieaadMohamd, NaghamMahmoodAljamali ,WassanAlaShubber ,Sabreen Ali Abdalrahman .,"New Azomethine- Azo Heterocyclic Ligands Via Cyclization of Ester"., Research J. Pharm. and Tech. 11, 6 , 2018 .
76. Rigaud J, Cheynier V, Souquet J, Moutounet M (1991). "Influence of must composition on phenolic oxidation kinetics". Journal of the Science of Food and Agriculture. 57 (1): 55–63. doi:10.1002/jsfa.2740570107.
77. Vallverdú-Queralt A, Verbaere A, Meudec E, Cheynier V, Sommerer N (January 2015). "Straightforward method to quantify GSH, GSSG, GRP, and hydroxycinnamic acids in wines by UPLC-MRM-MS". Journal of Agricultural and Food Chemistry. 63(1): 142–9. doi:10.1021/jf504383g. PMID 25457918.
78. Malathi, M; Thappa, DM (2013). "Systemic skin whitening/lightening agents: what is the evidence?". Indian Journal of Dermatology, Venereology and Leprology. 79 (6): 842–6. doi:10.4103/0378-6323.120752. PMID 24177629.
79. NaghamMahmoodAljamali, AseelMahmoodJawad, AseelFadhil K, NourAlhuda Abdul Abbas Bahar,Nour A AA, Aseel M J. (2019). Review in Chemical Structures of Common Compounds. International Journal of Chemical Synthesis and Chemical Reactions.; 5 (1) 1–15p.
80. Dilokthornsakul, W; Dhippayom, T; Dilokthornsakul, P (June 2019). "The clinical effect of glutathione on skin color and other related skin conditions: A systematic review". Journal of Cosmetic Dermatology. 18 (3): 728–737. doi:10.1111/jocd.12910. PMID 30895708.
81. Sonthalia, Sidharth; Daulatabad, Deepashree; Sarkar, Rashmi (2016). "Glutathione as a skin whitening agent: Facts, myths, evidence and controversies". Indian J. Dermatol. Venereol. Leprol. 82 (3): 262–72. doi:10.4103/0378-6323.179088. PMID 27088927.

Cite this article: Nagham Mahmood Aljamali Invention of (Gluta. Sulfazane – Cefixime) Compounds as Inhibitors of Cancerous Tumors. J. Cardiovascular Disease Res. 2020; 11 (2): 44 – 55