International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 04, 2020
ISSN: 1475-7192

Innovation, Preparation of Cephalexin Drug Derivatives and Studying of (Toxicity & Resistance of Infection)

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Abstract--- *The current study developed new drugs and new pharmaceutical derivatives against infection and toxicity via Invention and preparation of medication through various chemical reactions and bio-medical studies to improve its efficiency which involved study of resistance of infection and toxicity effect. The invented Cephalexin derivatives have been prepared through many reactions with many steps, which identified through several techniques represented by (Infrared spectra, carbon and proton magnetic resonance)– spectrophotometric identification methods, then bio- medical studying via several experiment in this field like cytotoxicity, resistance of bacteria.*

Keywords--- *Cephalexin, Infection, Contamination, Drug, Toxicity, Formazane.*

I. INTRODUCTION

Cephalexin is the antibiotic involves a beta lactam besides a dihydrothiazide ((6R,7R)-7-[[(2R)-2-amino-2-phenylacetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid) which is used to medicate a numeral[1-3] of susceptible bacterial poisons and toxicities via reserve and decreasing of cell wall production[4-8] followed by the inhibition.

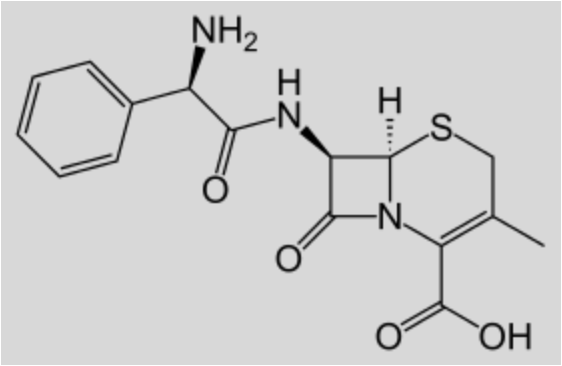

Fig. 1: Cephalexin Drug

Cephalexin (besides that termed Cefalexin) is a main group cephalosporin antibiotic drug. It is one of the greatest commonly approved antibiotics[9-15], often applied for the cure of superficial toxicities that product as problems of slight injuries or cuts(lacerations). It is active compared to various gram(+) bacteria via its reserve of the irritated relating reaction[16-22] among N-acetyl muramic acid and N-acetyl glucosamine in wall of the cell, prominent to cell lysis.

Cephalexin drug is used to inhibit toxicities and infection which produced via bacteria like pneumonia,

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DOI: 10.37200/IJPR/V24I4/PR201489
Received: 16 Jan 2020 | Revised: 17 Feb 2020 | Accepted: 26 Feb 2020

additional or respirational area toxicities or infections[23-29]; contaminations of the bone, membrane(skin), ears, genital, joint, bladder and urinary area which works via killing microbes and bacteria. Cephalexin cannot work for viral diseases[30-35], like the flu or cold.

Cephalexin is an antibiotic that use to treat a numeral of bacterial contamination[36-40]. It destroys gram-positive with a number of gram-negative bacteria via disturbing the growing wall of the bacterial cell[41-47]. Cefalexin drug was industrialized in 1967, which was first advertised in 1969 and 1970 below the terms Keflex also Ceporex, and other names[48-54] (trade names).

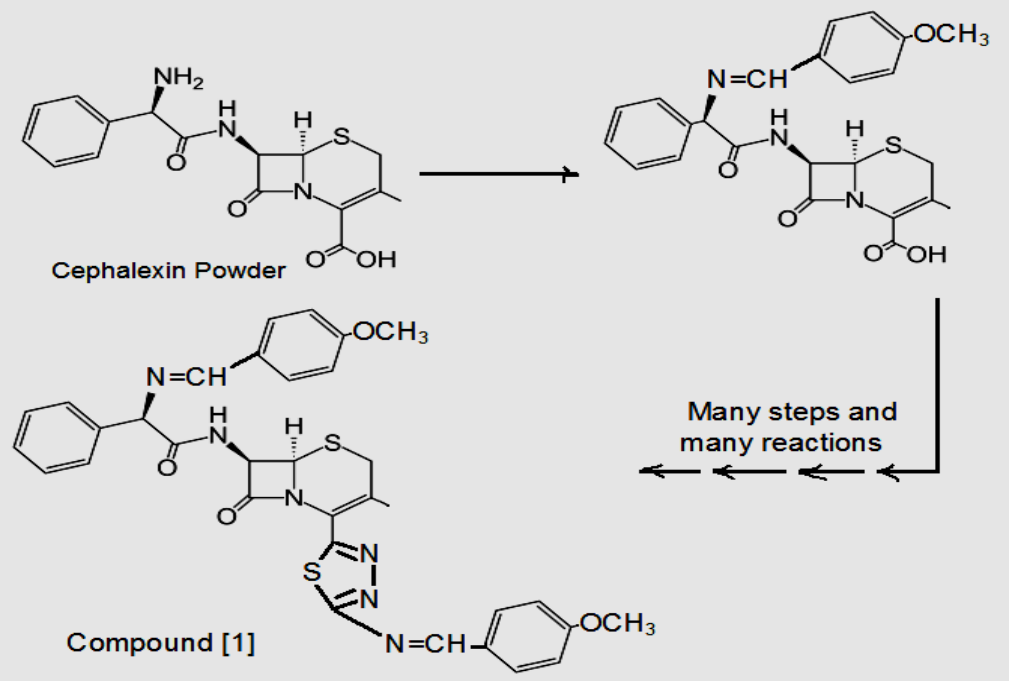
II. EXPERIMENTAL PART

Invented drug derivatives prepared by several chemical reactions, checked and investigated by many techniques represented in: FT-IR spectra (FT-IR 8300 -Shimadzu) with range (400-4000) cm^{-1} in KBr discs., 1H.NMR–Spectra also C.NMR in DMSO–solvent., in addition to resistance studies of Cephalexin derivatives against several kinds of bacteria, beside to toxicity studies of our invented drugs derivatives.

Preparation of Invented drug derivatives[55-60]:

Preparation Invented drug derivative {1}

Cephalexin powder(0.01 mole)condensed with p-methoxy benzaldehyde with two drops of acid, the precipitation dried and re-crystallized, then (0.01 mole) from it reacted with thiosemicarbazide with cupper acetate, dried and re-crystallized, then the resulting compound reacted with p-methoxy benzaldehyde in presence acid by flowing procedures[55-60],the precipitation, filtered, dried and re-crystallized to format drug derivative {1}.

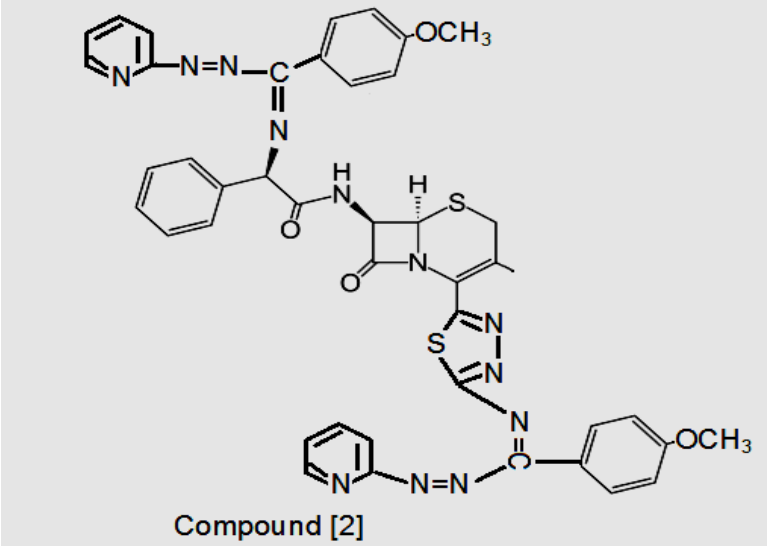


DOI: 10.37200/IJPR/V24I4/PR201489
Received: 16 Jan 2020 | Revised: 17 Feb 2020 | Accepted: 26 Feb 2020

Scheme 1: Preparation of Invented drug derivative {1}

Preparation Invented drug derivative {2}

Invented Drug{1} (0.01 mole) reacted with (0.02 mole) of pyridyl azo salt in basic medium via many steps and several reactions to yield new invented drug according to procedures[55-60] the formatted precipitation, filtered, dried and re-crystallized to give invented drug {2} which represented (formazan compounds).



Scheme 2: Preparation of Invented drug derivative {2}

Preparation Invented drug derivative {3}

Invented Drug{1} (0.01 mole) reacted with (0.02 mole) of thiophenyl azo salt in basic medium via many steps and several reactions to yield new invented drug according to procedures[55-60] the formatted precipitation, filtered, dried and re-crystallized to give invented drug {3}., which represented (formazan compounds).

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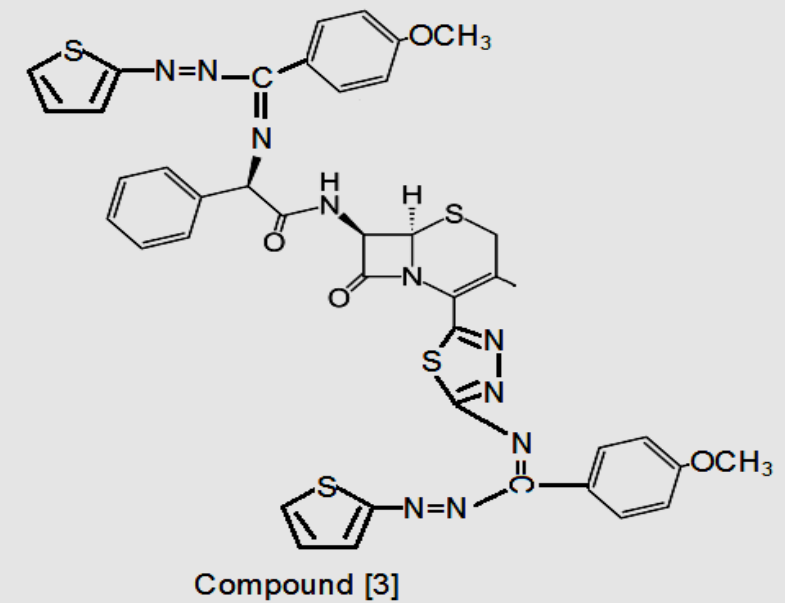
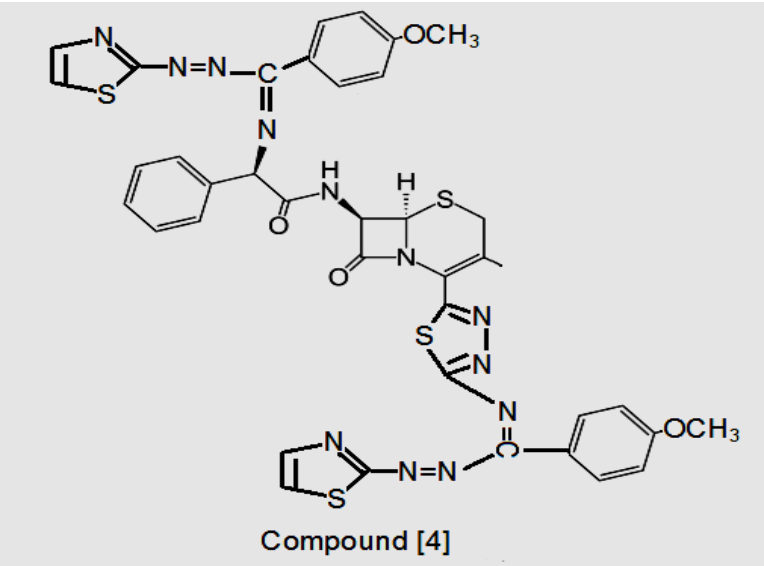


Scheme 3: Preparation of Invented drug derivative {3}

Preparation Invented drug derivative {4}

Invented Drug{1} (0.01 mole) reacted with (0.02 mole) of thiazolyl azo salt in basic medium via many steps and several reactions to yield new invented drug according to procedures[55-60] the formatted precipitation, filtered, dried and re-crystallized to give invented drug {4}., which represented (formazan compounds).



Scheme 4: Preparation of Invented drug derivative {4}

III. RESULTS AND DISCUSSION

The invented drug derivatives tested and investigated with number of spectral techniques act: (FT.IR, H.NMR, C.NMR) spectra with studying of toxicity and resistance of infection:

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Investigation of Invented Drugs

FT.IR- Spectra of invented Drug Derivatives: The spectra of invented drugs appeared various absorption bands at (C=N) imine group: 1635, (C=N-) endocycle: 1658., (CO-N) carbonyl of amide: 1686.,(NH) amide: 3210, (OCH_3): 1212 in Invented drug-derivative {1}, while new absorption bands appeared at (C=N) imine group: 1617, (N=N): azo group: (1498, 1520),, (C=N-) endocycle: 1654., (CO-N) carbonyl of amide: 1688., (NH) amide: 3218, (OCH_3): 1207 in Invented drug -derivative {2}., many bands at (C=N) imine group:1615, (N=N): azo group: (1490, 1518), (C=N-) endocycle: 1649., (CO-N) carbonyl of amide: 1686., (NH) amide: 3221, (OCH_3): 1203 Invented drug-derivative {3}, last bands at (C=N) imine group:1621, (N=N): azo group: (1492, 1526),, (C=N-) endocycle: 1635., (CO-N) carbonyl of amide: 1689, (NH) amide: 3214, (OCH_3): 1213 Invented drug-derivative {4}, all these bands are evidences for our invented drugs.

^{1}H.NMR- Spectra of invented Drug Derivatives: spectra of invented drugs appeared peaks point to prepared invented drugs and new active groups[55-65] in our studying., the spectra of all invented derivatives showed peaks at (2. 5) due to solvent (DMSO), novel invented derivative {1} gave many peaks at ƃ (CH=N) imine group: 8. 34., (N<u>H</u>-CO) Proton of amide group: 9. 30., Protons of aromatic ring: (6. 92-7. 48)., (C<u>H$_3$</u>-) protons: 0. 94., (O-<u>CH$_3$</u>) protons: (2. 21)., but invented derivative {2} sowed many signals at., (N<u>H</u>-CO) Proton of amide group: 9. 33., Protons of aromatic ring: (6. 87-7. 52)., (C<u>H$_3$</u>-) protons: 0. 91., (O-<u>CH$_3$</u>) protons: (2. 25), protons of Pyridyl ring: 7.96., while invented derivative {3} sowed many signals at., (N<u>H</u>-CO) Proton of amide group: 9. 24., Protons of aromatic ring: (6. 81-7. 59)., (C<u>H$_3$</u>-) protons: 0. 76., (O-<u>CH$_3$</u>) protons: (2. 10), protons of thiophene ring: 7.91., but invented derivative {4} sowed many signals at., (N<u>H</u>-CO) Proton of amide group: 9. 23., Protons of aromatic ring: (6. 84-7. 62)., (C<u>H$_3$</u>-) protons: 0. 77., (O-<u>CH$_3$</u>) protons: (2. 09), protons of thiazolyl ring: 7.93.

The ^{13}C.NMR spectral of invented Drug Derivatives: Our spectra indicated to appearance of new peaks in prepared invented derivatives and formatted active groups[46-49] in this study, the spectra of all invented derivatives gave peaks at (40.0) due to solvent (DMSO)., novel invented derivative {1} showed numerous peaks at (158 . 05) for (C, imine group –<u>CH</u>=N)., (111. 03 -131. 06) for (C, Aromatic ring)., (164. 10) for (C, carbonyl of amide CO-N), (140.0, 142. 14) for (C, carbons of thiadiazole ring), (55. 09) carbons of (O-CH_3)., (-CH_3) carbons of methyl group: (18. 11)., while invented derivative {2} showed many peaks at (150 . 00) for (C, imine group –<u>C</u>=N)., (110. 12 -136. 14) for (C, Aromatic ring)., (165. 11) for (C, carbonyl of amide CO-N), (140.12, 143. 18) for (C, carbons of thiadiazole ring), (57. 01) carbons of (O-CH_3)., (-CH_3) carbons of methyl group: (15. 19), (147.11 - 140. 00) for (C, carbons of pyridyl ring)., but invented derivative {3} showed many peaks at (155. 07) for (C, imine group –<u>C</u>=N)., (113. 04 -132. 12) for (C, Aromatic ring)., (162. 02) for (C, carbonyl of amide CO-N), (143.11, 146. 16) for (C, carbons of thiadiazole ring), (53. 00) carbons of (O-CH_3)., (-CH_3) carbons of methyl group: (19. 11), (149.10 - 142. 10) for (C, carbons of thiophene ring)., while invented derivative {4} showed many peaks at (156 . 15) for (C, imine group –<u>C</u>=N)., (114. 05 -140. 00) for (C, Aromatic ring)., (160. 10) for (C, carbonyl of amide CO-N), (145.00, 147. 12) for (C, carbons of thiadiazole ring), (53. 00) carbons of (O-CH_3)., (CH_3) carbons of methyl group: (14. 17), (149.06 - 152. 05) for (C, carbons of thiazolyl ring).

DOI: 10.37200/IJPR/V24I4/PR201489
Received: 16 Jan 2020 | Revised: 17 Feb 2020 | Accepted: 26 Feb 2020

Studying of Cytotoxicity Effect[53,54]

The cytotoxicity Test for the prepared invented derivatives against Breast Cancer (AMJ13) and Hela Cancer cells appears that the invented drug derivatives gave good results for toxicity. Invented derivative {4} which involved thiazole ring in its structure showed 85% inhibition with an (IC50 = 1 µg/ml) against (AMJ13) Breast cell and moiety showed 80% inhibition with an (IC50 = 1 µg/ml) against Hela cell but it not active on Embryonic cell moiety showed 38% inhibition with an (IC50= 1 µg/ml)., Invented derivative {3} which involved thiophene ring in its structure that appeared 70% inhibition with an (IC50 = 1 µg/ml) against (AMJ13) Breast cancer and moiety showed 83% inhibition with an (IC50=1 µg/ml) against Hela cell while it active on Embryonic cell moiety showed 80% inhibition with an (IC50= 1 µ g/ml).

In the present tests we observed that increasing in the concentration leads to increasing in the percentage of inhibition, but concentration of invented derivative {4} that equal (0. 50 µg/ml) gave the percentage of inhibition equal (40%) but noted when the increasing in concentration of Invented derivative {4} to (2 µg/ml) that appeared the percentage of inhibition equal (92%).

Fig. 2: 40 $_{x}$ AMJ13 Cell Control

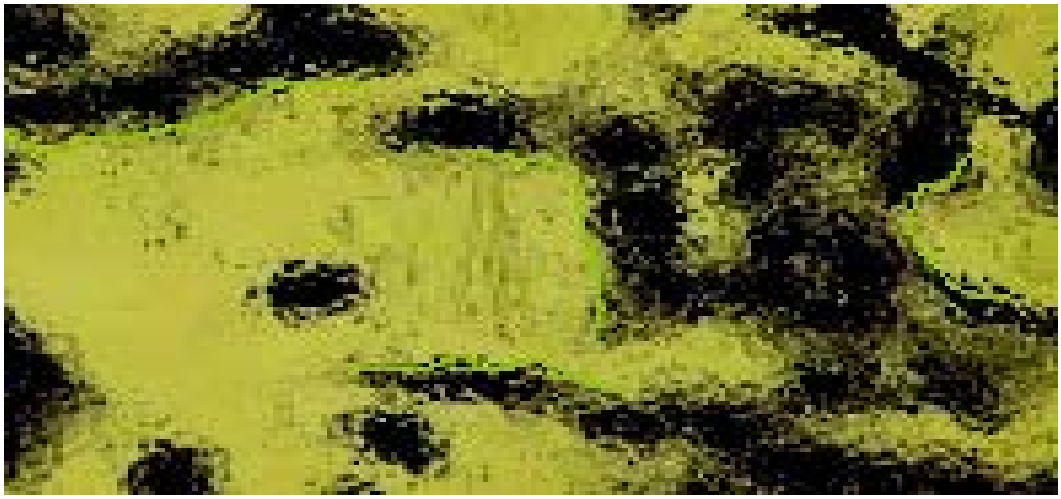

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Fig. 3: 40 $_X$ AMJ13 Cell Treated with Best Conc. of Invented derivative {4}

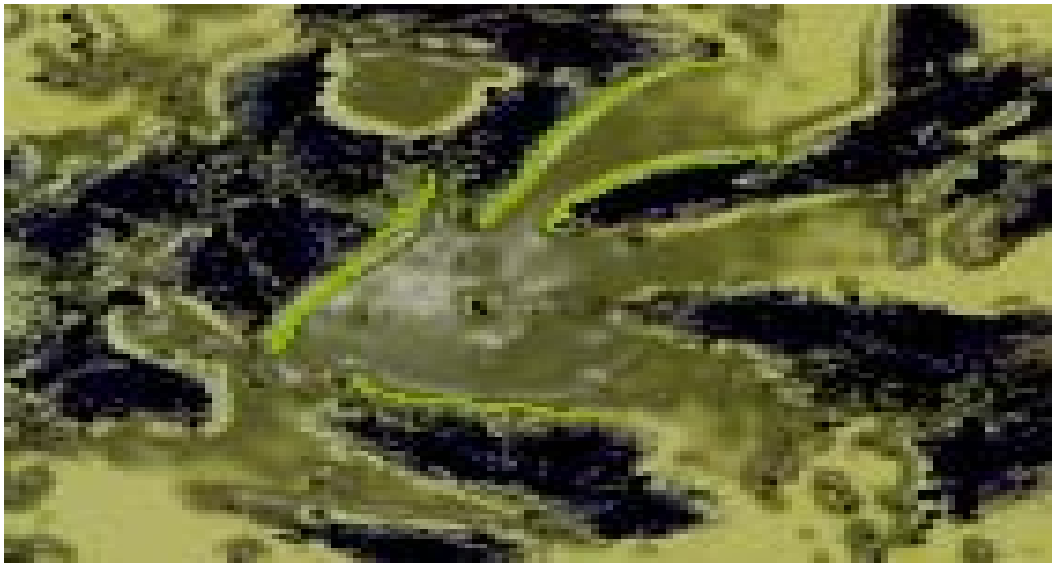

Fig. 4: 40 $_X$ AMJ13 Cell Treated with Best Conc. of Invented derivative {3}

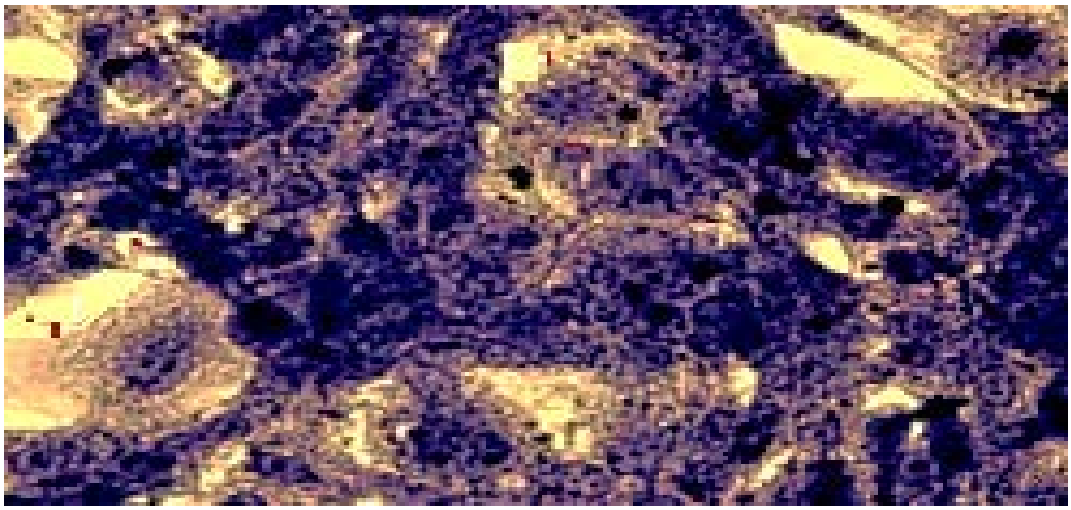

Fig. 5: 40$_X$ Embryonic Cell Control

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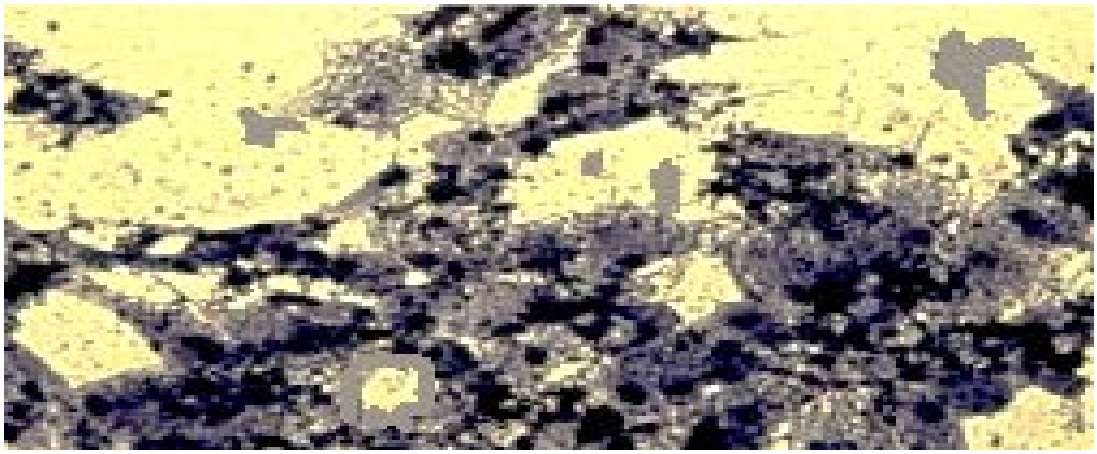

Fig. 6: 40_X Embryonic Cell Treated with Best Conc. of Invented derivative {4}

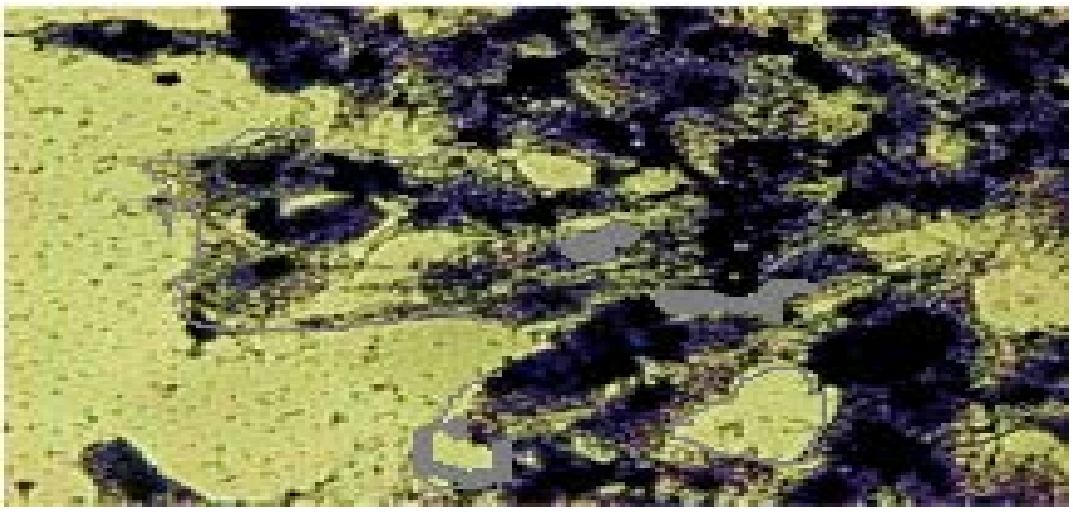

Fig. 7: 40_X Embryonic Cell Treated with Best Conc. of Invented derivative {3}

Selection of Bacteria[(60-65)]

Salmonella. Typhi

Salmonella .typhi is a gram-negative bacterium which is guilty for typhoid infection and has been a liability on increasing nations to generations. While first pronounced in the initial 1800s, it was not till 1880 once the creature for typhoid fever was developed in 1880.

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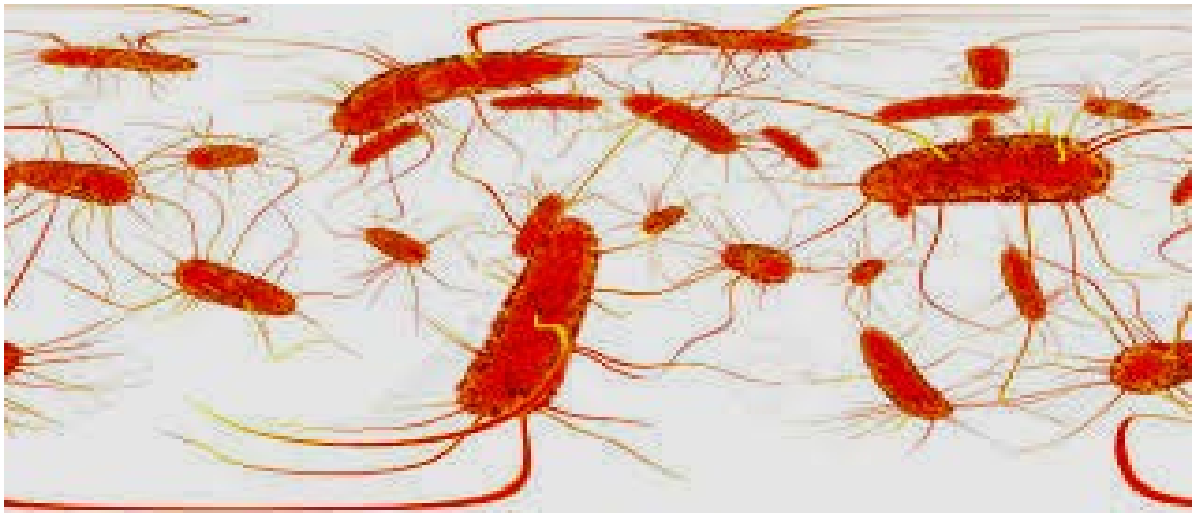
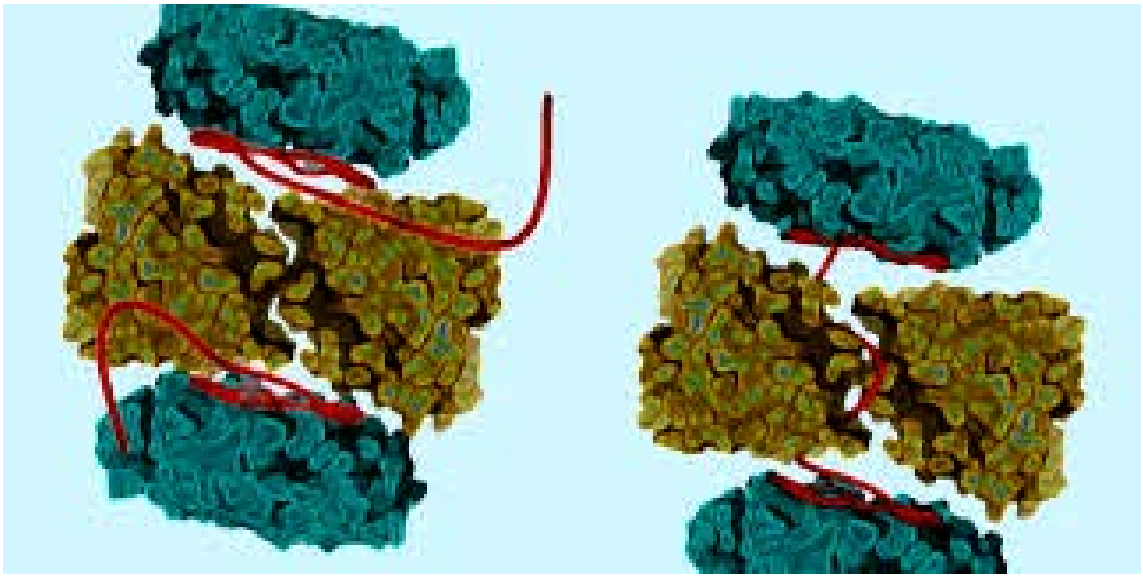


Pict. 1: Salmonella. Typhi

P. aeruginosa

Pseudomonas aeruginosa is a public encapsulated, Gram-negative, rod-shaped bacterium which can source infection and disease in plants and animals, involving humans. A species of significant pharmaceutical importance, Pseudomonas. aeruginosa is a many drug resistant pathogen identified to its ubiquity.



Pict. 2: P. aeruginosa

Streptococcus. Faecalis

S. faecalis is a kind of streptococcus bacteria are a gram positive bacteria fitting to the lactic acid bacteria collection, which grow in pairs or restraints due to their kind of cellular partition which is a separation along a only axis.

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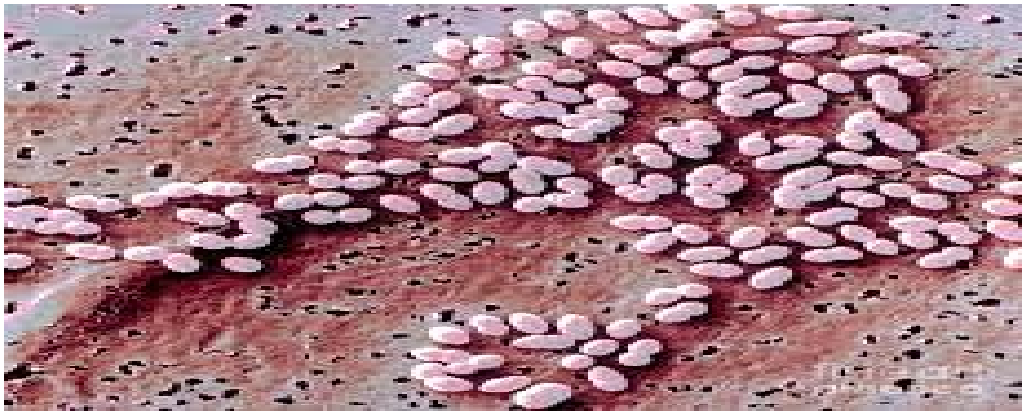
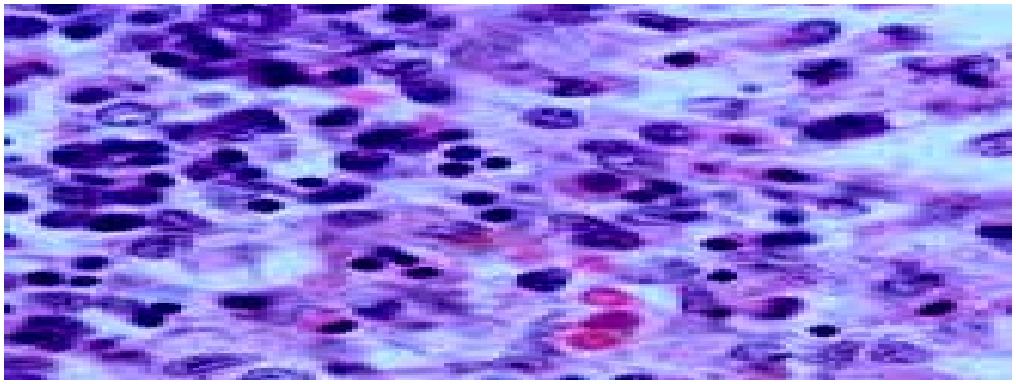


Pict. 3: Streptococcus. Faecalis

Aeromonas .hydrophilia

A. hydrophila is a nonspore-production, Gram-negative, a fermentative, oxidase-positive.



Pict. 4: Aeromonas .hydrophilia

Resistance of Infection Tests[(55-60)]

Resistance investigations for the prepared Invented Cephalexin derivatives have been tested for their antimicrobial assay via agar via several procedures[(65, 66)] .The investigation of microbial inhibition carried out at (three concs) (10, 20, 25 micro gram) concentrations in best solvent (DMSO) with bacteria:***(Salmonella. Typhi, P. aeruginosa, Streptococcus. Faecalis, Aeromonas. hydrophilia)***.These types of bacteria incubated for (24 hr) at (37^{o}C).

The test of resistance of the bacteria, which involved brands of bacteria to screen the biotic action of invented derivatives against selected bacteria., Table (1) indicated to that the diameter of inhibition zone(mm) for invented drug derivatives towards the bacteria.

Table 1: Inhibition test of Invented derivatives in Conc. (20 micro gram)

Cephalexin Derivatives	*Salmonella. typhi*	*Aeromonas .hydrophilia*	*Streptococcus. faecalis*	*P. aeruginosa*
Invented Derivative {1}	+	++	++	++
Invented Derivative {2}	+++	+++	++	+++

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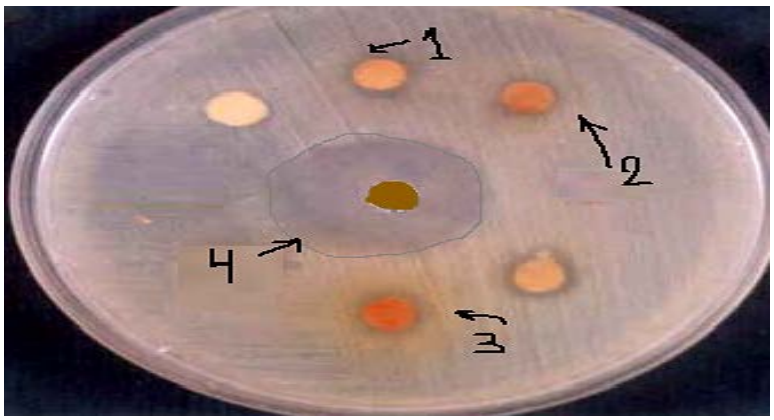
Invented Derivative {3}	+++	+++	+++	+++
Invented Derivative {4}	+++	+++	+++	+++

(+): inhibition (6-9) mm

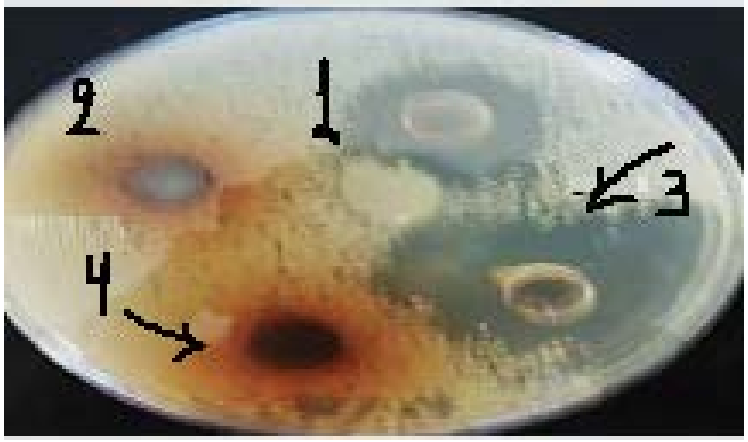
(++): inhibition (10-14) mm

(+++): inhibition (15-20) mm

The evaluations in the present tests indicated that the resistance of the Invented Cephalexin derivatives{4, 3} are higher than remaining Invented derivatives in the inhibition of tested bacteria due to involving thiazole ring, and thiophene ring in their structures which gave high efficiency against tested bacteria[57-60].



Pict. 5: Inhibition Diameter against *Salmonella. Typhi*



Pict. 6: Inhibition Diameter against *P. aeruginosa*

Mechanism of Resistance Action

The Invented drug derivatives involve a beta-lactam in their structure which form the peptidoglycan layer of the cell wall of bacteria. Some Cells of bacteria have the enzyme (β-lactamase) which hydrolyzes the beta-lactam cycle in drugs, that leads to the drug became inactive. The prepared Invented drugs inhibited the infection then fighting bacteria[58-68].

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IV. CONCLUSION

All prepared Invented derivatives indicated to high resistance towered tested bacteria and the efficiency of invented derivatives {4, 3} is higher than the remaining invented derivatives in the inhibition of selected bacteria, and good results in toxicity tests.

REFERENCES

[1] Thornhill TS, Levison ME, Johnson WD, Kaye D: In vitro antimicrobial activity and human pharmacology of cephalexin, a new orally absorbed cephalosporin C antibiotic. *Appl Microbiol.* 1969 Mar; 17(3):457-61.
[2] Sullivan HR, Billings RE, McMahon RE: Metabolism of cephalexin-14C in mice and in rats. *J Antibiot (Tokyo).* 1969 May; 22(5):195-200.
[3] Gower PE, Dash CH: Cephalexin: human studies of absorption and excretion of a new cephalosporin antibiotic. *Br J Pharmacol.* 1969 Nov; 37(3):738-47.
[4] Henning C, Kallings LO, Lidman K, Sterner G: Studies of absorption, excretion, antibacterial and clinical effect of cephalexin. *Scand J Infect Dis.* 1970; 2(2):131-8.
[5] Griffith RS: The pharmacology of cephalexin. *Postgrad Med J.* 1983; 59 Suppl 5:16-27.
[6] Pfeffer M, Jackson A, Ximenes J, de Menezes JP: Comparative human oral clinical pharmacology of cefadroxil, cephalexin, and cephradine. *Antimicrob Agents Chemother.* 1977 Feb; 11(2):331-8.
[7] Tanrisever B, Santella PJ: Cefadroxil. A review of its antibacterial, pharmacokinetic and therapeutic properties in comparison with cephalexin and cephradine. *Drugs.* 1986; 32 Suppl 3:1-16.
[8] Sader HS, Jacobs MR, Fritsche TR: Review of the spectrum and potency of orally administered cephalosporins and amoxicillin/clavulanate. *Diagn Microbiol Infect Dis.* 2007 Mar; 57(3 Suppl):5S-12S.
[9] Fisher JF, Meroueh SO, Mobashery S: Bacterial resistance to beta-lactam antibiotics: compelling opportunism, compelling opportunity. *Chem Rev.* 2005 Feb; 105(2):395-424.
[10] Williamson R, Hakenbeck R, Tomasz A: In vivo interaction of beta-lactam antibiotics with the penicillin-binding proteins of Streptococcus pneumoniae. *Antimicrob Agents Chemother.* 1980 Oct; 18(4): 629-37.
[11] Mitsuoka K, Kato Y, Kubo Y, Tsuji A: Functional expression of stereoselective metabolism of cephalexin by exogenous transfection of oligopeptide transporter PEPT1. *Drug Metab Dispos.* 2007 Mar; 35(3):356-62. Epub 2006 Dec 1.
[12] Bratlid D, Bergan T: Displacement of albumin-bound antimicrobial agents by bilirubin. *Pharmacology.* 1976; 14(5):464-72.
[13] Nerli B, Romanini D, Pico G: Structural specificity requirements in the binding of beta lactam antibiotics to human serum albumin. *Chem Biol Interact.* 1997 May 2; 104(2-3):179-202.
[14] Ganapathy ME, Huang W, Rajan DP, Carter AL, Sugawara M, Iseki K, Leibach FH, Ganapathy V: beta-lactam antibiotics as substrates for OCTN2, an organic cation/carnitine transporter. *J Biol Chem.* 2000 Jan 21; 275(3):1699-707.
[15] Liang R, Fei YJ, Prasad PD, Ramamoorthy S, Han H, Yang-Feng TL, Hediger MA, Ganapathy V, Leibach FH: Human intestinal H+/peptide cotransporter. Cloning, functional expression, and chromosomal localization. *J Biol Chem.* 1995 Mar 24; 270(12):6456-63.
[16] Wenzel U, Gebert I, Weintraut H, Weber WM, Clauss W, Daniel H: Transport characteristics of differently charged cephalosporin antibiotics in oocytes expressing the cloned intestinal peptide transporter PepT1 and in human intestinal Caco-2 cells. *J Pharmacol Exp Ther.* 1996 May; 277(2):831-9.
[17] Covitz KM, Amidon GL, Sadee W: Human dipeptide transporter, hPEPT1, stably transfected into Chinese hamster ovary cells. *Pharm Res.* 1996 Nov; 13(11):1631-4.
[18] Han HK, Rhie JK, Oh DM, Saito G, Hsu CP, Stewart BH, Amidon GL: CHO/hPEPT1 cells overexpressing the human peptide transporter (hPEPT1) as an alternative in vitro model for peptidomimetic drugs. *J Pharm Sci.* 1999 Mar; 88(3):347-50.
[19] Guo A, Hu P, Balimane PV, Leibach FH, Sinko PJ: Interactions of a nonpeptidic drug, valacyclovir, with the human intestinal peptide transporter (hPEPT1) expressed in a mammalian cell line. *J Pharmacol Exp Ther.* 1999 Apr; 289 (1):448-54.
[20] Luckner P, Brandsch M: Interaction of 31 beta-lactam antibiotics with the H+/peptide symporter PEPT2: analysis of affinity constants and comparison with PEPT1. *Eur J Pharm Biopharm.* 2005 Jan; 59(1):17-24.
[21] Terada T, Saito H, Mukai M, Inui K: Recognition of beta-lactam antibiotics by rat peptide transporters, PEPT1 and PEPT2, in LLC-PK1 cells. Am J Physiol. 1997 Nov; 273 (5 Pt 2): F706-11.

DOI: 10.37200/IJPR/V24I4/PR201489
Received: 16 Jan 2020 | Revised: 17 Feb 2020 | Accepted: 26 Feb 2020

[22] Ganapathy ME, Brandsch M, Prasad PD, Ganapathy V, Leibach FH: Differential recognition of beta - lactam antibiotics by intestinal and renal peptide transporters, PEPT 1 and PEPT 2. *J Biol Chem.* 1995 Oct 27; 270 (43): 25672-7.

[23] Tamai I, Nakanishi T, Hayashi K, Terao T, Sai Y, Shiraga T, Miyamoto K, Takeda E, Higashida H, Tsuji A: The predominant contribution of oligopeptide transporter PepT1 to intestinal absorption of beta-lactam antibiotics in the rat small intestine. *J Pharm Pharmacol.* 1997 Aug; 49 (8):796-801.

[24] Liu W, Liang R, Ramamoorthy S, Fei YJ, Ganapathy ME, Hediger MA, Ganapathy V, Leibach FH: Molecular cloning of PEPT 2, a new member of the H+/peptide cotransporter family, from human kidney. Biochim Biophys Acta. 1995 May 4; 1235(2):461-6.

[25] Ganapathy ME, Brandsch M, Prasad PD, Ganapathy V, Leibach FH: Differential recognition of beta - lactam antibiotics by intestinal and renal peptide transporters, PEPT 1 and PEPT 2. *J Biol Chem.* 1995 Oct 27; 270 (43): 25672-7.

[26] Terada T, Saito H, Mukai M, Inui K: Recognition of beta-lactam antibiotics by rat peptide transporters, PEPT1 and PEPT2, in LLC-PK1 cells. Am J Physiol. 1997 Nov; 273 (5 Pt 2): F706-11.

[27] Luckner P, Brandsch M: Interaction of 31 beta-lactam antibiotics with the H+/peptide symporter PEPT2: analysis of affinity constants and comparison with PEPT1. Eur J Pharm Biopharm. 2005 Jan; 59 (1):17-24.

[28] Jung KY, Takeda M, Shimoda M, Narikawa S, Tojo A, Kim DK, Chairoungdua A, Choi BK, Kusuhara H, Sugiyama Y, Sekine T, Endou H: Involvement of rat organic anion transporter 3 (rOAT3) in cephaloridine-induced nephrotoxicity: in comparison with rOAT1. Life Sci. 2002 Mar 8; 70(16):1861-74.

[29] Jariyawat S, Sekine T, Takeda M, Apiwattanakul N, Kanai Y, Sophasan S, Endou H: The interaction and transport of beta-lactam antibiotics with the cloned rat renal organic anion transporter 1. *J Pharmacol Exp Ther*. 1999 Aug; 290(2):672-7.

[30] Uwai Y, Saito H, Inui K: Rat renal organic anion transporter rOAT1 mediates transport of urinary-excreted cephalosporins, but not of biliary-excreted cefoperazone. *Drug Metab Pharmacokinet.* 2002; 17(2):125-9.

[31] Watanabe S, Tsuda M, Terada T, Katsura T, Inui K: Reduced renal clearance of a zwitterionic substrate cephalexin in MATE1-deficient mice. *J Pharmacol Exp Ther.* 2010 Aug; 334(2):651-6.

[32] Motohashi H, Inui K: Organic cation transporter OCTs (SLC22) and MATEs (SLC47) in the human kidney. *AAPS J.* 2013 Apr; 15(2): 581-8.

[33] Jung KY, Takeda M, Shimoda M, Narikawa S, Tojo A, Kim DK, Chairoungdua A, Choi BK, Kusuhara H, Sugiyama Y, Sekine T, Endou H: Involvement of rat organic anion transporter 3 (rOAT3) in cephaloridine-induced nephrotoxicity: in comparison with rOAT1. Life Sci. 2002 Mar 8; 70(16):1861-74.

[34] Thornhill TS, Levison ME, Johnson WD, Kaye D: In vitro antimicrobial activity and human pharmacology of cephalexin, a new orally absorbed cephalosporin C antibiotic. *Appl Microbiol.* 1969 Mar; 17(3):457-61.

[35] Sullivan HR, Billings RE, McMahon RE: Metabolism of cephalexin-14C in mice and in rats. *J Antibiot (Tokyo).* 1969 May; 22(5):195-200.

[36] Gower PE, Dash CH: Cephalexin: human studies of absorption and excretion of a new cephalosporin antibiotic. *Br J Pharmacol.* 1969 Nov; 37(3):738-47.

[37] Henning C, Kallings LO, Lidman K, Sterner G: Studies of absorption, excretion, antibacterial and clinical effect of cephalexin. *Scand J Infect Dis.* 1970; 2(2):131-8.

[38] Griffith RS: The pharmacology of cephalexin. Postgrad Med J. 1983; 59 Suppl 5:16-27. [PMID:6364086]

[39] Pfeffer M, Jackson A, Ximenes J, de Menezes JP: Comparative human oral clinical pharmacology of cefadroxil, cephalexin, and cephradine. *Antimicrob Agents Chemother.* 1977 Feb; 11(2):331-8.

[40] Tanrisever B, Santella PJ: Cefadroxil. A review of its antibacterial, pharmacokinetic and therapeutic properties in comparison with cephalexin and cephradine. *Drugs.* 1986; 32 Suppl 3:1-16.

[41] Sader HS, Jacobs MR, Fritsche TR: Review of the spectrum and potency of orally administered cephalosporins and amoxicillin/clavulanate. Diagn Microbiol Infect Dis. 2007 Mar; 57(3 Suppl):5S-12S. doi: 10.1016/j.diagmicrobio.2006.12.014. Epub 2007 Feb 9. [PMID:17292577]

[42] Fisher JF, Meroueh SO, Mobashery S: Bacterial resistance to beta-lactam antibiotics: compelling opportunism, compelling opportunity. Chem Rev. 2005 Feb; 105(2):395-424.

[43] McPherson, Edwin M. (2007). Pharmaceutical Manufacturing Encyclopedia (3rd ed.). Burlington: Elsevier. p. 915. ISBN 9780815518563. Archived from the original on 2017-09-08.

[44] McEvoy, G.K. (ed.). American Hospital Formulary Service — Drug Information 95. Bethesda, MD: American Society of Hospital Pharmacists, Inc., 1995 (Plus Supplements 1995)., p. 166

[45] Brunton, Laurence L. (2011). "53, Penicillins, Cephalosporins, and Other β-Lactam Antibiotics". Goodman & Gilman's pharmacological basis of therapeutics (12th ed.). New York: McGraw-Hill. ISBN 978-0071624428.

DOI: 10.37200/IJPR/V24I4/PR201489
Received: 16 Jan 2020 | Revised: 17 Feb 2020 | Accepted: 26 Feb 2020

[46] Wendy Jones (2013). Breastfeeding and Medication. Routledge. p. 227 ISBN 9781136178153. Archived from the original on 2017-09-08.
[47] Hey, Edmund, ed. (2007). Neonatal formulary 5 drug use in pregnancy and the first year of life (5th ed.). Blackwell. p. 67. ISBN 9780470750353. Archived from the original on 2017-09-08.
[48] Ravina, Enrique (2011). The evolution of drug discovery: from traditional medicines to modern drugs (1. Aufl. ed.). Weinheim: Wiley-VCH. p. 267. ISBN 9783527326693. Archived from the original on 2017-09-08.
[49] Hanlon, Geoffrey; Hodges, Norman (2012). Essential Microbiology for Pharmacy and Pharmaceutical Science. Hoboken: Wiley. p. 140. ISBN 9781118432433. Archived from the original on 2017-09-08.
[50] Haberfeld, H, ed. (2009). Austria-Codex (in German) (2009/2010 ed.). Vienna: Österreichischer Apothekerverlag. ISBN 3-85200-196-X.
[51] Barrio Lera JP, Alvarez AI, Prieto JG (Jun 1991). "Effects of ethanol on the pharmacokinetics of cephalexin and cefadroxil in the rat". Journal of Pharmaceutical Sciences. 80(6): 511–6.
[52] Jayasagar G, Krishna Kumar M, Chandrasekhar K, Madhusudan Rao C, Madhusudan Rao Y (2002). "Effect of cephalexin on the pharmacokinetics of metformin in healthy human volunteers". Drug Metabolism and Drug Interactions. 19(1): 41–8.
[53] B.H.M. Jayakumar, P.N. Balaji, N. Pramod, E. Jajuri, R.N. Rao, *Int. J. of Pharmacy & Therapeutics*, 3(3), 276-281, (2012) .
[54] Sagheer, O.M., Saour, K.Y., and Ghareeb, M.M. *International Journal of Pharmacy and Pharmaceutical Sciences.*, 5(4) 464-469, (2013).
[55] Nagham Mahmood Aljamali. "Synthesis and Chemical Identification of Macro Compounds of (Thiazol and Imidazol)". *Research J. Pharm. and Tech*, 2015, 8,1, 78-84.
[56] Mieaad, M., Nagham Mahmood Aljamali, WassanAla, S., Sabreen, A., 2018, "New Azomethine- Azo Heterocyclic Ligands Via Cyclization of Ester ", *Research J. Pharm. and Tech.* 11, 6.
[57] Mieaad Mohammed, Nagham Mahmood Aljamali, Sabreen Ali Abdalrahman, Wassan Ala Shubber., "Formation of Oxadiazole Derivatives Ligands from Condensation and Imination Reaction with References To Spectral Investigation, Thermal and Microbial Assay"., Biochem. Cell. Arch., 2018, 18, 1, pp. 847-853.
[58] Nagham Mahmood Aljamali. "Synthesis and Biological Study of Hetero (Atoms and Cycles) Compounds", Der Pharma Chemica, 2016, 8, 6, 40-48.
[59] 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.
[60] Nagham Mahmood Aljamali.; Saher Mahmood Jawd.; Zainab M Jawad.; Intisar, O. Alfatlawi.; 2017, "Inhibition activity of (Azo–acetyl acetone) on bacteria of mouth"., *Research Journal of Pharmacy and Technology* 10(6):1683-1686.
[61] M. Lindsay Grayson (Editor in Chief) (2 October 2017). Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs, Seventh Edition - Three Volume Set. CRC Press. pp. 364. ISBN 978-1-4987-4796-7.
[62] Bothara SS, Kadam KR, Mahadik KG (2006). "Antibiotics". *Principles of Medicinal Chemistry*. 1(14th ed.). Pune: Nirali Prakashan. p. 81. ISBN 8185790043.
[63] Fisher JF, Meroueh SO, Mobashery S (Feb 2005). "Bacterial resistance to beta-lactam antibiotics: compelling opportunism, compelling opportunity". *Chemical Reviews. 105*(2): 395–424.
[64] Drawz SM, Bonomo RA (Jan 2010). "Three decades of beta-lactamase inhibitors". *Clinical Microbiology Reviews* 23 (1): 160–201.
[65] Haidareganum, Saher Mahmood Jawd, Nagham Mahmood Aljamali, Benzothiazol derivatives (synthesis, investigation, bio-studying). *International Journal of Pharmaceutical Research*, Jan-Mar 2019, Vol 11, Issue 1, 1627-1635 .
[66] Linda Skidmore-Roth (16 July 2015). Mosby's Drug Guide for Nursing Students, with 2016 Update. *Elsevier Health Sciences.* pp. 181–. ISBN 978-0-323-17297-4.
[67] Nagham Mahmood Aljamali, Rasha Neama H, Aafaq Jaber Alnajem, Ali Jassim Alzuhairi, Afaq Jaber Kadhium, Afaq JK., Studying of (Chemical, Physical, Biological)–Applications of Oxo- Sulfur Derivatives., *Journal of Natural Sciences Research.*, 6, 7, 2016.
[68] Nagham Mahmood Aljamali, Alaa Jawad Kadhim, Jalal Hasan Mohammed, Rajaa Abdul Ameer Ghafil, Alaa JK, Rajaa AAG. Review on Preparation and Applications of Formazan Compounds. *International Journal of Thermodynamics and Chemical Kinetics.* 2019; 5(2): 23–33p.

DOI: 10.37200/IJPR/V24I4/PR201489
Received: 16 Jan 2020 | Revised: 17 Feb 2020 | Accepted: 26 Feb 2020