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A histochemical study to evaluate the role of some isoindoline-1-one compounds γ-lactam compounds on the biological functions of adult laboratory rabbits

Dr. Adeeb Abdulally Abdulhussien[1*], MSC. Noor .R. Ali[2] , MSC. Zainab M. Farhan[3] and Adnan Shait Khalaf [4]

[1] Alayen University College of Medicine, Thi-Qar, Iraq.
[2] College of Science, Thi-Qar University, Iraq.
[3,4] Ministry of Health, Immam Hussein teaching hospital ,Thi-Qar, Iraq.

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ABSTRACT

This study is concerned with the synthesis and characterization of derivatives of the isoindoline-1-one γ-lactams (c-d), were prepared by reacting Phenyl succinic anhydirde with the appropriate Schiff base (a-b), in the presence of γ-lactam compounds were prepared from the reaction between 2-chloro benzoyl chloride with imines (a-b) in the prescence Phenyl lithium under (N2) atm (-5) in THF solvent to yielded product γ-lactams. reaction was verified by thin layer chromatography (TLC), and the formed compounds were identified by NMR, IR, mass spectra. The proposed reaction for their formations . In the current study, 30 white male rabbits with an average weight of 250 g were used, they were randomly divided into three groups as follows, group (1) includes 10 untreated rabbits as a control group, group (2) consists of 10 rabbits treated with the first compound. A) at a concentration of 30 mg | kg | day, group (3) consisted of 10 rabbits that were treated with the second compound (B) at a concentration of 30 mg | kg | day. The dose was determined based on body weight and all animals received the doses by oral administration for thirty days Blood samples were taken at the end of the experiment by a direct heart stab and the samples were centrifuged, and they were kept in special tubes at 4°C until the start of measuring the industrial and enzyme functions of the kidney. % of all mice until the start of preparing the tissue sections and studying the effect of the two compounds. The two compounds varied in their effect on some biochemical parameters related to the manufacturing and enzyme function of the kidney. Histologically, the results indicated that treatment with compound A did not show any histological changes, while the results of treatment with compound B showed enlargement of some kidney cells and atrophy of the nuclei of other cells with cases of fibrosis, blood congestion and infiltration of inflammatory cells compared to control group.

1. Introduction

The γ-lactams are five-membered ring lactams, which are known as γ-lactams or isoindoline-1-one oxo pyrrolidines or 2-Pyrrolidone, are important structural motifs in biologically active natural products that are also found in medicinal leads and approved drugs figure. 1 (Damdom, W. K., & Magtoof, 2013).

The Structural motifs including a C5 quaternary stereocenter are prevalent in physiologically significant compounds, including neooxazolomycin and salinosporamide. Adysibetaine and lactacystin possessing a C5 quaternary stereocenter are prevalent structural motifs

* Corresponding author.
E-mail address: zainab.farhan@nust.edu.iq

found in numerous biologically significant compounds, including lactacystin2,(-)-dysibetaine, and as neooxazolomy cinsalinosporamide (Lettan, R. B., Galliford, Woodward, & Scheidt, K. A. , 2009).

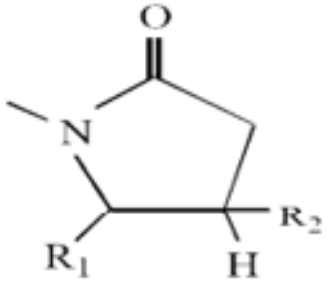


Figure.1 five-membered ring lactams.

2. The Experimental

All solvents were distilled/dried before use. All solvents were dried over anhydrous sodium sulfate unless otherwise specified. ^{13}C NMR; $^{1}HNMR$ Spectroscopy were recorded using Bruker DRX system AL 500 (500 mhz). IR spectra were recorded, using a shimadzu FT-IR affinity spectrophotometer, as kbr disks. Only principal absorption bands of interest are reported and expressed in cm^{-1}.

1 - General Procedure for the preparation of imines

In general, the Schiff bases were prepared by heating the mixture of 0.01-mole amine with 0.01-mole aldehyde,10 ml of ethanol, and one drop of glacial acetic acid was heated in the water bath at (70-80˚C) for 30 min. The progress of the reaction was checked by TLC. After completion, the solvent evaporated more than recrystallized from a suitable solvent. The following are methods of imine preparation.

1.1: N-(p-methoxyphenyl)-4-florobenzylidine (a)

The compound was prepared from (0.01 mole) *p*-methoxy aniline and (0.01mole) of 4-florobenzaldehyde

1.2: N-(4-methyl phenyl)-4-florobenzylidine (b)

The compound was prepared from (0.01 mole) *4-di*methylaniline and (0.01 mole) of 4- florobenzaldehyde.

2- Preparation of γ-lactam (Tietz, N. W. (1999)

2.1: Preparation of 2-Chlorobenzoyl chloride

To a well stirred solution of 2-chloro benzoic acid (3 g ,1.9mmole) in dry methelene chloride (50 ml), and added drop wiseasolution of phosphorus trichloride (pcl3), (7.9g, 5.02 ml, 3mmole) the reaction mixture heated upto become clear ,the progress of the reaction was checed by TLC and contents were stirred for 20 min ,solvent evaporator under redused pressure.

2.2:3-(4-fluorophenyl)-2-(4-methoxyphenyl)isoindolin-1-one.(c)

To a suspension of 2-chlorobenzoylchloride (0.81g, 1.2mmole), with N-(p-methoxyphenyl)-4-florobenzylidine (a) (1.0g,3.33mmole) in 35 ml of dry THF under nitrogen atm at -5˚C to(10 minut) and then was added dropwise under nitrogen at (-10˚C) was solution phli (phenyllithium) of (0.35g,0.42ml,1.1mmole) with stirring at less -10˚C, the reaction was checked by TLC and contents were stirred for (60min), thereafter, the contents let it at room temperature

(60min), After completion, the solvent evaporated more than recryastalized from ethanole to give the pur -γ- lactam (c) table. 2

2.3:3-(4-fluorophenyl)-2-p-tolylisoindolin-1-one.(d)

To a suspension of 2-chlorobenzoylchloride (0.84g,1.2mmole), N-(4–chlorophenyl)-4-chlorobenzylidine (b) (1.0g,3.17mmole) in 35 ml of dry THF under nitrogen at -5˚C to(10 min), and then was added drop wise under nitrogen at(- 10˚C) was solution of phli (0.35g ,0.42ml , 1.1 mmol) with stirring at less -10˚C. The reaction was checked by TLC and contents were stirred for (60min). Thereafter, the contents let it at room temperature(1h), After completion, the solvent evaporated more than recryastalized from ethanole to give the pure γ- lactam (d) table. 2.

Table.1 The symbol a and b.

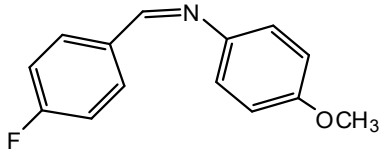
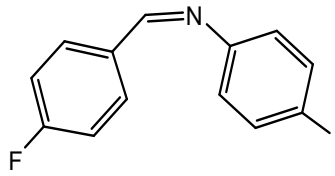
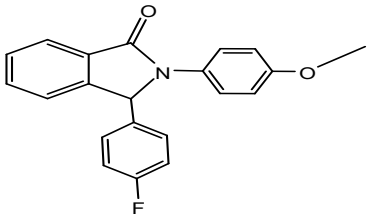
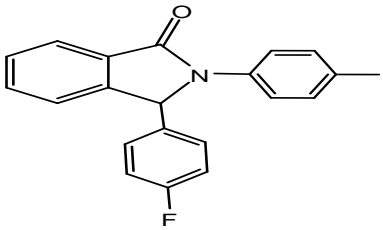
Symbol	Imines
a	
b	

Table.2 The symbol c and d**.**

Symbol	γ-lactams
c	 3-(4-fluorophenyl)-2-(4-methoxyphenyl)isoindolin-1-one
d	 3-(4-fluorophenyl)-2-*p*-tolylisoindolin-1-one

3. The biological efficacy method

The primary organs of adult laboratory rabbits were evaluated for this study work between early October 2022 and late July 2023 in the anatomical medical laboratories and laboratories of Al-Hussein Teaching Hospital in Dhi Qar Governorate. Here, we see the appearance of the nuclei and the shrinkage of the glomeruli, or the epithelial lining, of the renal tubules. Moreover, it is demonstrated that a portion of the inner lining of the renal tubules has broken apart and become invaded. Data, such as age, sex, and other details, were collected on each animal involved in the experiment. A total of thirty mature albino rabbits, ranging in age from three to nine months, were chosen. 3-(4-fluorophenyl)-2-(4-methoxyphenyl)isoindolin-1-one (c) was administered to ten rabbits. Additionally, there is 3-(4-fluorophenyl)-2-(4-methoxyphenyl) isoindolin-1-one (d). 3-(4-fluorophenyl)-2-(4-methoxyphenyl)isoindolin-1-one (c) was administered to ten rabbits. Moreover, 3-(4-fluorophenyl)-2-(4-methoxyphenyl) isoindolin-1-one (d) was administered to ten additional rabbits. Unlike the control group, which included 10 exclusively male rabbits, the other group received epolactaene. Five milliliters of blood, as well as separated serum and the appropriate measurements, including the quantity of thyroid hormone (thyroxine), were obtained.

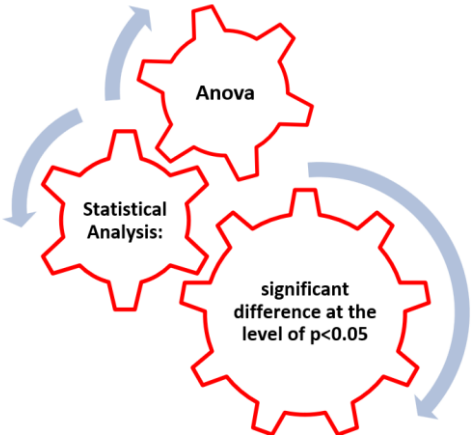


Figure. 2 The biological efficacy method

4. Results and discussion

Equine quantities of suitable aromatic aldehydes and aromatic amines were reacted with refluxing ethanol to prepare the various Schiff's bases (imines)a-b needed for the γ-lactam synthesis c-d. Based on their spectral data (IR), the structures of these imines a–b were verified. Are cyclic amide heterocyclic compounds with one nitrogen atom and five membered rings.

The γ-lactams are also widely distributed natural products and physiologically active molecules. Many γ-lactams are synthesized through formal [2+3] annulations of β-lactam derivatives.

Figure. 3 shows the general reaction sequence. It is a reaction in the precipitation between 2-chloro benzoyl chloride and imines 2 d-e. Figure. 4 illustrate the reaction between 2-chloro benzoyl chloride and imines (a–b) in the presence Phenyl lithium at (N2) atm at -10 in THF solvent, which produces the product γ-lactams.

The ^{13}C NMR spectrum of the c showed resonance between 114.90 -163.61 ppm which assigned to the carbon30,31,32group were belonged to the aromatic, carbons C-5 was appeared at 60.88 and carbon of methoxy group showed singlet peak at 114.90, whereas

the resonance at 166.65 ppm were assigned to the C=O carbonyl group figure. 4.
Figure. 4 shows the ^{1}H-NMR spectrum of (d) showing a singlet peak C5-H (6.42), the 1H-NMR spectrum of (d) showing a peak methyl group (CH3) at 2.20 ppm, and finally the 1H-NMR spectrum of (d) showing aromatic protons integrated 8H at (7.30- 7.44) ppm.

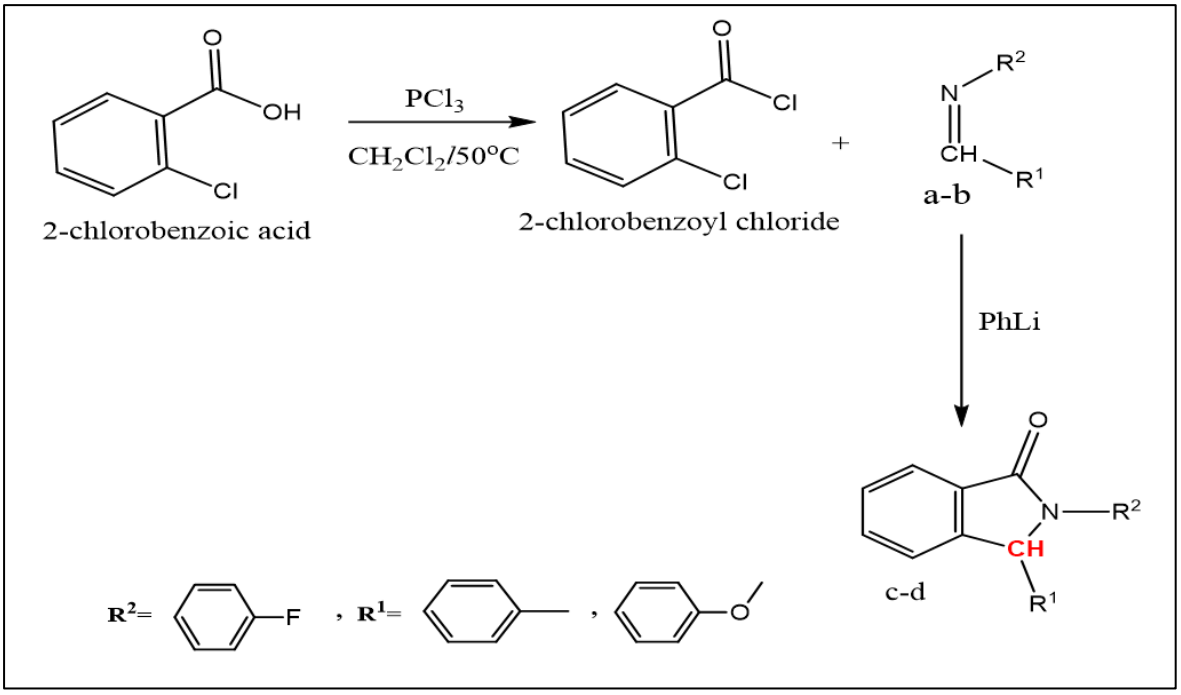


Figure. 3 The general reaction sequence

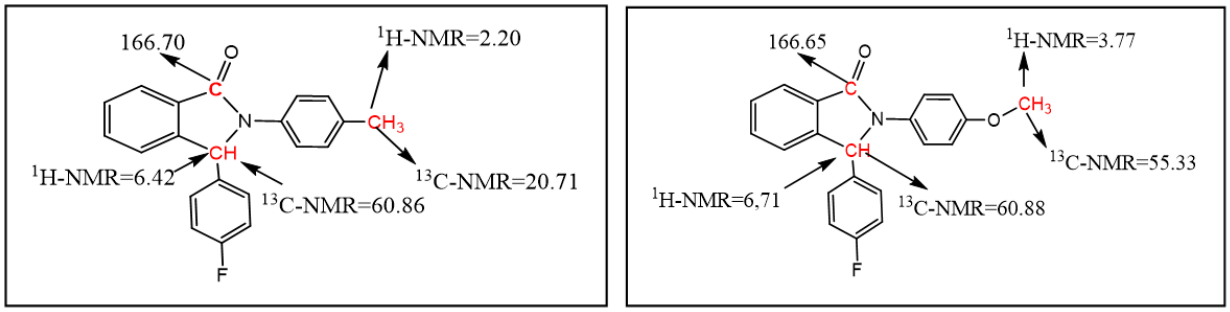


Figure. 4 The carbon -13 NMR spectroscopy.

The ^{13}C NMR spectrum of the c showed resonance between 116.81 -164.64 ppm which assigned to the carbon[30,31,32]group which belonged to the aromatic, carbons C-5 appeared at 60.86 and carbon of methyl group showed singlet peak at 20.71, while the resonance at 166.70 ppm was assigned to the C=O carbonyl group figure. 6.

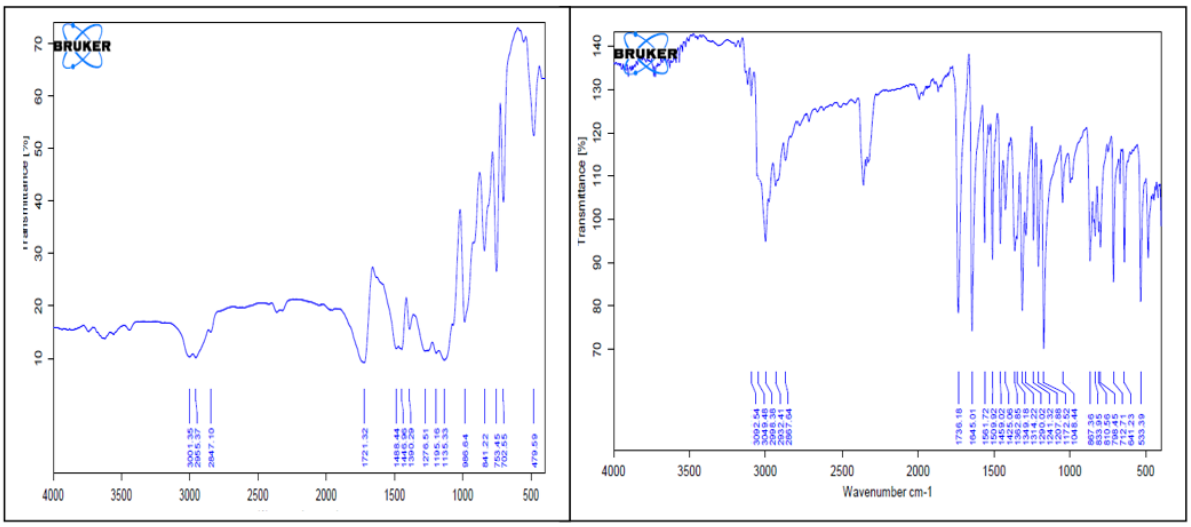


Figure. 5 The enhanced 13 C NMR signals.

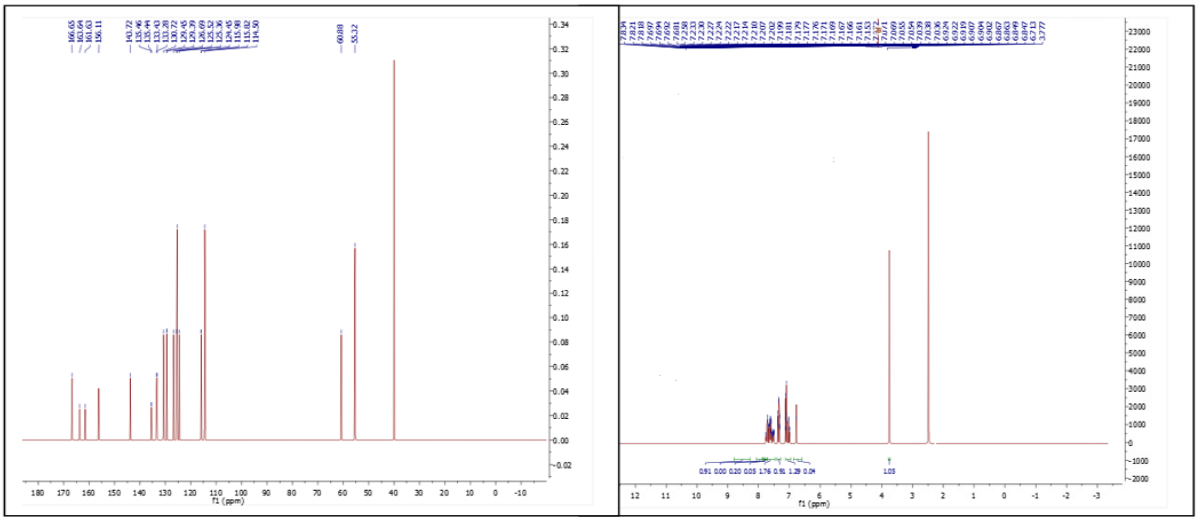


Figure. 6 (a) The 13 C-NMR spectrum of compound (d).

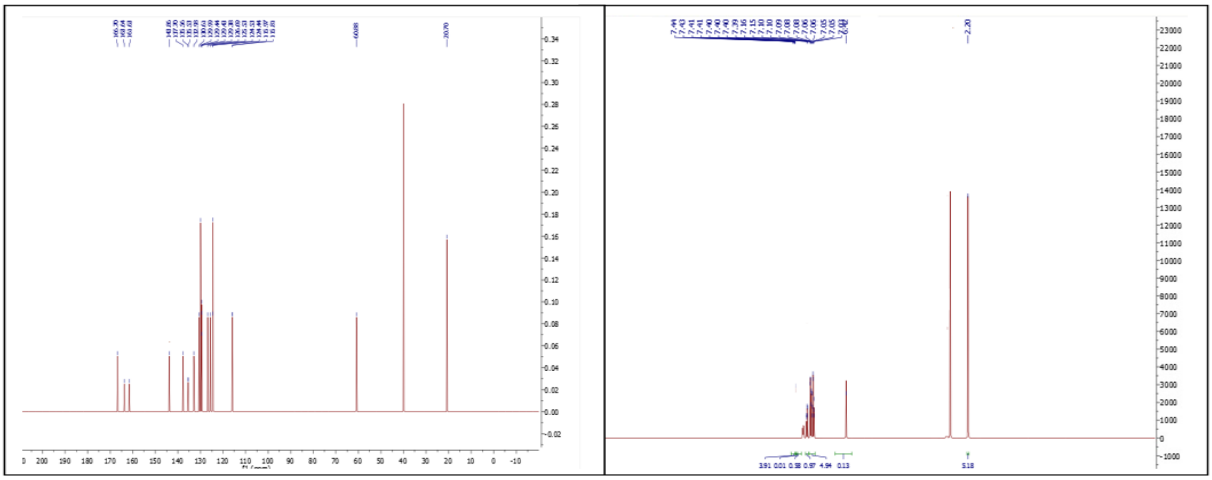


Figure. 6 (b) 13 C -NMR spectrum of compound (C).

Table .3 The effect of treatments on the level of urea and creatinine in blood serum compared to the Control group

Parameter Groups	Blood urea Mg|dl	S.creatin in Mg|dl
C	18.20	0.74
T1	22.4	0.83
T2	25.3*	1.26*
LSD	3.2	0.08

Table.4 The effect of treatments on the level of thyroid hormones in blood serum compared to the control group.

Parameter Groups	T3 nmol|l	T4 nmol|l	TSH Mu|l
C	1,20	12.86	0.048
T1	1.46*	18.20*	0.032
T2	1.38*	34.32*	0.018*
LSD	0.06	4.34	0.018

Significant ($p<0.05$)

The Bio-efficacy discussion

The impact of interventions on blood serum levels of creatinine and urea in relation to the control group. The groups treated with 3-(4-fluorophenyl)-2-(4-methoxyphenyl)isoindolin-1-one.(c),(d) and the control group in table. 1, which shows the impact of medications on the levels of urea and creatinine in blood serum, differ significantly from one another. Conversely, it was shown that when comparing the mean creatinine expression with the average T1 expression (22.41±8.20, respectively), significant differences were discovered between the blood urea groups. The mean T1 expression level and the mean T2 creatinine expression level, however, varied significantly throughout the blood creatinine groups. For both the mean T1 expression and creatinine and the mean T1 expression and urea, there were no discernible

The effect of therapies on the level of thyroid hormones in blood serum in comparison to the control group ANOVA analysis revealed significant differences in creatinine levels, T1 expression levels, and T2 expression levels in relation to thyroid hormone levels (T3, T4) and TSH levels at p 0.05, according to the conclusions of this study:

Our data reveal that there are no statistically significant differences between the average level of creatinine expression and the levels of T1, T2 expression for the thyroid hormones T3, T4, and TSH. Gornall, A. G., bardawilc. J., & David, M. M. (1949) Reitman, S., & Frankel, S. (1957).

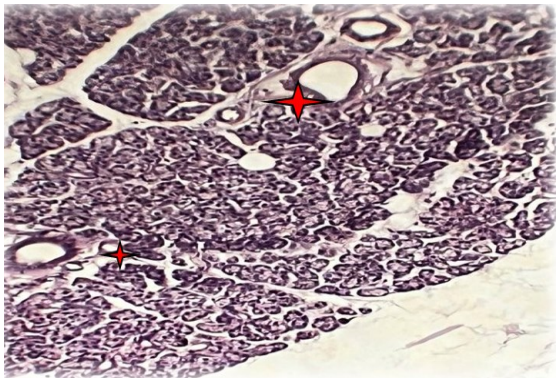


Figure. 7 The lobules thyroid units and channels between the separator shall lobules in

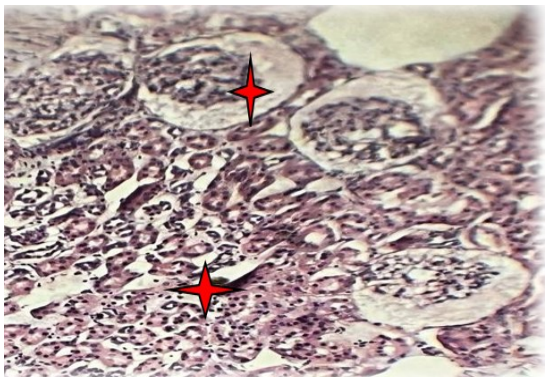
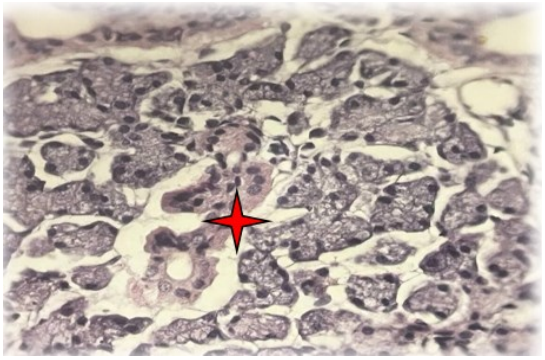


Figure. 8 The glomeruli, Bowman's capsule, and renal tubules in the control group 40x.



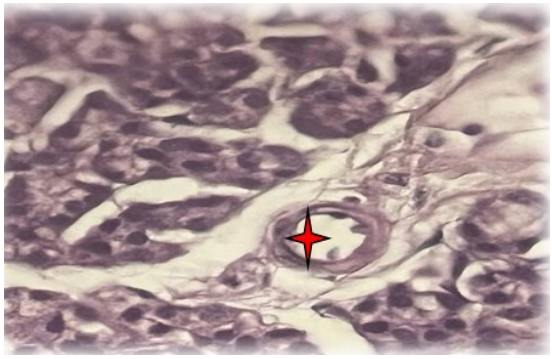


Figure. 9 (a) The units in the thyroid separator shall with the presence of edema and inflammatory infiltration in the control group 40x, (b) the units in the thyroid separator shall with the presence of edema and inflammatory infiltration in the control group 40x.

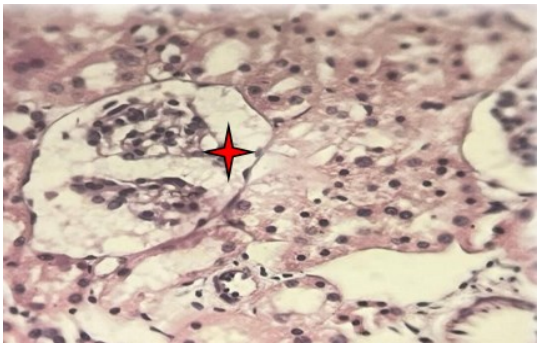


Figure. 10 The Nuclei contraction glomerulus epithelial lining of the renal tubules in the first treatment group 40x.

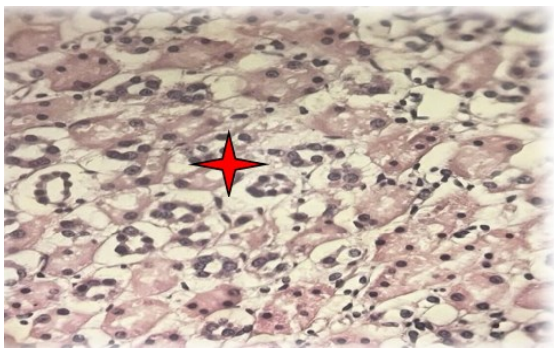


Figure. 11 The Shows the separation of some of the inner lining of the renal tubules and infiltration in the first treatment group 40x.

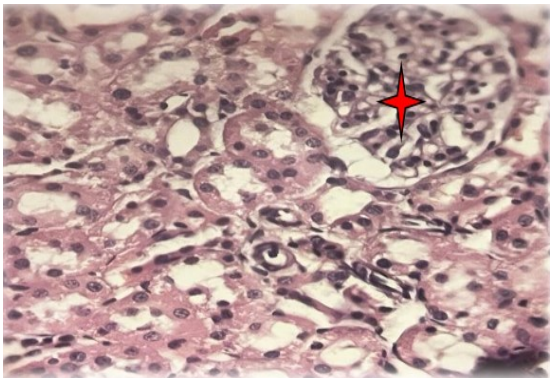


Figure. 12 the bombing of the glomerulus and renal tubule with the presence of inflammatory infiltration in the second treatment group.

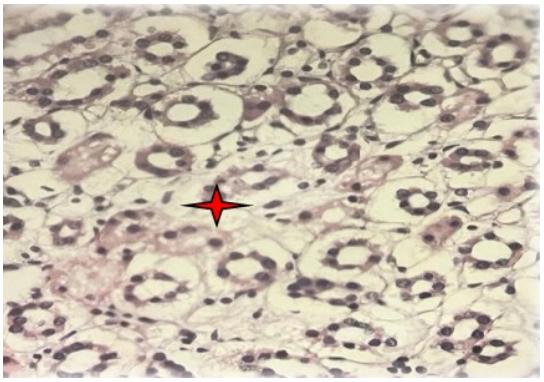


Figure. 13 The separation some of the inner lining of the renal tubules and loss episodes ,and inflammatory infiltration second

5. Conclusion

The study's findings, which were attained through one-way Anova statistical analysis, demonstrated how medications affect body functions such as the thyroid gland and kidneys in a beneficial way. The thyroid gland is one of the organs that is affected by drug dosages as well as thyroid gland changes, whether high or low. According to the findings of the current study, abnormalities in thyroid gland functioning have a considerable and positive impact on the development of kidney problems. This is attributable, in our opinion, to the study's findings, because changes in thyroid hormone output primarily affect the physiological activities of the kidneys. Kind, P. R. N., & King, E. (1954) Bancroft, J. D., & Gamble, M. (2008).

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