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Comparative Study of Some New Naproxen Derivatives on the Liver and Kidney Tissues of Mice

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Abstract: Naproxen is a phenyl propionic acid that has anti-inflammatory, analgesic, and antipyretic effects with confirmed adverse effects on most body organs involve the stomach, intestine, liver, and kidneys. This study aimed to assess the analgesic effects of new naproxen derivatives (synthesized in other studies) and limited side effects by modifying their chemical structure by adding active groups to the parent compounds. We performed analysis of newly synthesized and administered naproxen-derived drugs on male albino mice (30-35 g) distributed into five groups; the first was named the negative control group. Four other groups administered one of the synthesized compounds of naproxen derivatives. The current study reported that the histopathological section of hepatocyte of mice treated orally with 250 mg/kg of naproxen for five days showed severe dilatation and congestion of central vein with necrosis of hepatic tissue with amyloid deposition in necrotic hepatic tissue with lymphocyte and Kupffer cells infiltration. On the other hand, the histopathological section of the liver of mice treated orally with 250 mg/kg of compound 4a for five days showing severe distraction and hemorrhage of hepatic tissue, while compound 5 showed severe necrosis of hepatic tissue with vacuolation, necrosis of hepatic tissue and inflammatory cell infiltration in rats. At the same time, the results revealed clear improvement in the liver of mice who received 4b compound via regeneration of hepatic tissue by the formation of multiple granulomas around the newly formed blood vessels and immune cell stimulation. In addition to naproxen appears amyloid deposition in necrotic renal tissue while 4b orally appears regeneration of malignant tissue by the formation of granuloma around newly formed blood vessels. Our research concludes that 4b related new derivative is a valuable focus for future seeks and potentially clinical implementation due to its relatively high efficacy and minimal adverse effects compared to another tested compound in our study.

Keywords: naproxen, mice, nonsteroidal anti-inflammatory drug.

一些新型萘普生衍生物對小鼠肝腎組織的比較研究

摘要：萘普生是一種苯基丙酸，具有抗炎、鎮痛和解熱作用，已證實對包括胃、腸、肝和腎在內的大多數身體器官產生不利影響。本研究旨在評估新萘普生衍生物（在其他研究中合成）的鎮痛作用和有限的副作用，通過向母體化合物添加活性基團來修改其化學結構。我們對分為五組的雄性白化小鼠進行了新合成和施用的萘普生衍生藥物的分析；第一個被命名為陰性對照組。其他四組給予其中一種合成的萘普生衍生物化合物。目前的研究報導，口服萘普生250毫克/公斤5天的小鼠肝細胞組織病理切片顯示中心靜脈嚴重擴張充血，肝組織壞死，壞死肝組織澱粉樣沉積，淋巴細胞和枯否細胞浸潤。.另一方面，口服250毫克/公斤化合物

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4a五天小鼠肝臟組織病理切片顯示肝組織嚴重牽張和出血，而化合物5顯示肝組織嚴重壞死伴空泡化、肝壞死。大鼠組織和炎症細胞浸潤。同時，結果顯示，通過在新形成的血管周圍形成多個肉芽腫和免疫細胞刺激，肝組織再生，接受4b化合物的小鼠的肝臟明顯改善。除了萘普生外，壞死的腎組織中出現澱粉樣蛋白沉積，而4b口服出現通過在新形成的血管周圍形成肉芽腫來再生惡性組織。我們的研究得出的結論是，與我們研究中的另一種測試化合物相比，4b相關的新衍生物是未來探索和潛在臨床實施的一個有價值的焦點，因為它具有相對較高的功效和最小的副作用。

关键词：萘普生，小鼠，非甾体抗炎药。

1. Introduction

The first use of nonsteroidal anti-inflammatory drugs (NSAIDs) was more than 3,500 years ago. Anti-inflammatory drugs have been used to control pain, and firstly, Salicin was initially identified in 1828, confirming its anti-inflammatory performance [1]. In addition to two years after Clinical trials with small doses, Bayer management determined to begin production and release of aspirin, as a drug has an analgesic for control pain and blood thinner in a hypertensive patient [2]. Many families of cyclooxygenase (COX), also named prostaglandin-endoperoxide synthase enzymes, were first documented by many researchers in the last century. Other studies confirmed two enzymes, including cyclooxygenase-2 (COX-1) and cyclooxygenase-2 (COX-2); in fact, the toxicity and adverse effects related to NSAID use have played a role in COX-1 inhibition [3].

COX-1 is currently) under fundamental conditions in different cells, involving renal marrow collecting ducts Endothelial cells, cells of the mucosal layer in the gastrointestinal tract, platelets, and Interstitial. COX-2 isoform is normally present at minimum concentrations in smooth muscle cells, macrophages, fibroblasts monocytes, and chondrocytes; still, it is also formative in some tissues, such as the duodenal mucosa, kidneys, and brain. Moreover, COX-1 is one of the constituent isoforms overexpression through the physiological state, and expression of COX-2 is stimulated under specific pathological conditions, such as after excitation of IL6, TNFa as inflammatory cytokines or insinuation to a natural toxin such as lipopolysaccharide (LPS) of salmonella [4, 5]. NSAIDs in Veterinary Medicine are considered effective in managing pain and other discomforts related to oral surgery. Thus, it has a curative effect by prohibiting Cyclooxygenase (COX), which blocks prostaglandins output that synergistic interactions with other remedies promoting local inflammatory reactions and huge pain.

Naproxen is one of the derivatives of a phenyl propionic group, has many pharmacological properties as analgesic activity, anti-inflammatory, and control of hyperthermia. The main mechanism by inhibiting complex prostaglandin synthetase enzymes leads to the limitation of the generation of prostaglandins from the arachidonic acid pathway. The exact mechanisms by which NSAIDs induce gastrointestinal ulcer and bleeding by damage of the tissue surface barrier to gastric acid and cytotoxic and NSAIDs reduced mucus, bicarbonate layer, blood flow, and cell renewal that considered as a defensive mechanism. The stomach has a mucus gel layer that possesses hydrophobic character via the synthesis and secretion of surfactant-like phospholipids [6, 7]. Some studies modify the NSAIDS chemical structure to reduce the harmful effect on GIT mucosa. One of them suggested formulated naproxen with phosphatidylcholine and showed a clear reduction in GIT injury and limited hemorrhagic ulcer without anti-inflammatory and COX-inhibitory activity [8-10]. The addition of material assistance to the foundation material may alter the effectiveness of the qualities and material basis. NSAIDs modification may be a positive direction and thus reduces the harmful effect on GIT with potentiating analgesic and anti-inflammatory properties [11-13]. One of the pathways protecting the mucosa of the GIT tract is by conserving the number of prostaglandins that act as cytoprotective [14, 15]. The current study aimed to improve naproxen by increasing its analgesic effect and minimizing its adverse effects by modifying the parent naproxen by adding new compounds to formulate new drugs [16, 17]. The current study was also conducted to evaluate the efficacy of new synthetic chemical agents derived from naproxen by adding chemical groups to standard naproxen and evaluating new compounds' safety on gastrointestinal tissue. Modifying the naproxen is expected to generate new drugs that have better properties clinically than reference naproxen that can produce anti-inflammatory, antipyretic with minimal side effects than NSAIDs.

2. Material and Methods

2.1. Synthesis of the New Compound from Naproxen Interaction Scheme

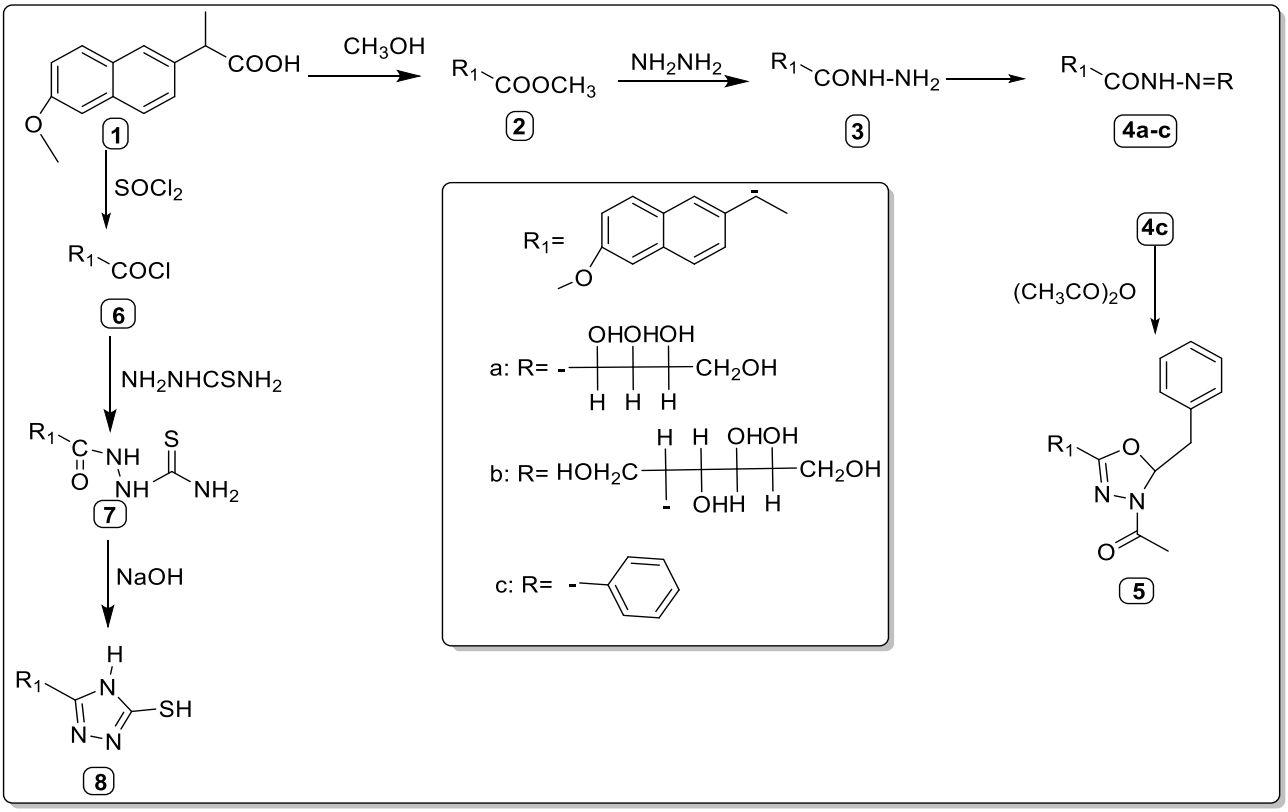

Fig. 1 Show synthesized new compounds (4a-c, 5, and 8) from naproxen drug

2.2. Animals

Groups of new naproxen derivatives (4a-c, 5 and 8) were synthesized in one of our previous studies as in Fig. 1.

Thirty healthy male albino mice weighing 25-30 grams were purchased from the laboratory animal house of the University of Baghdad and randomly divided into six groups, each group containing five mice placed in polypropylene cages. Mice were maintained at room temperature and under environmental conditions for nearly 8–12 h in the light-dark cycle). All animals were acclimatized for two weeks to animal house conditions before beginning the experimental protocol, taking into account the diet in pellets and water were given ad libitum.

2.3. Experiments

After two weeks of days of adaptation, mice were randomly divided into six groups: Group 1: negative representation of the control group, this group was given only distilled water Group 2: positive control group to evaluate induced stomach ulcer of naproxen after an overnight fast. Group 4: after an overnight fast, animals (20 mg/kg) received compound 5 to evaluate induced stomach ulcer Group 5: after an overnight fast, the animals (20 mg/kg) received compound 4b to induced stomach ulcer Group 6: after an overnight fast, the animals received 20 mg/kg of compound 4b to evaluate induced stomach ulcer.

2.4. Histopathological Examination

The stomachs of sacrificed mice were taken, washed with normal saline, and then immersed in 10% formalin solution. The fixed samples were then trimmed, washed, and dried in ascending degrees of alcohol. Samples were then flushed in xylol, embedded in paraffin, cut to 4–6 μm thickness, and stained with (H&E) stain for gastrulation as Carlton described in 1979.

3. Results and Discussion

The present study aimed to evaluate the efficacy of new synthetic chemical agent derived from naproxen by adding a chemical group to standard naproxen for generating new drugs that have properties more preferable than standard naproxen through the ability to prolong sedation and good anti-inflammatory with minimum side effect than the pure drug [18, 19]. Painkillers and anti-inflammatories relieve pain and reduce inflammation and hyperthermia in humans and animals as symptomatic therapy. These agents are effective in joint and muscle pain and headache, but they are not efficient in obvious visceral organ pain [20]. The therapeutic effect returns to the powerful inhibitory prostaglandins transmitter responsible for the sensation of distress and inflammation and control of body temperature. High doses of NSAIDS or long-term therapy enhance the risk of gastroduodenal injury, ulcers, and gastric bleeding [21].

Clinical therapy used to minimize NSAID-injury to duodenal injury by conventional drugs such as omeprazole has been shown to reduce GI damage [22]. However, modern animal studies indicate that block

acid secretion can worsen NSAID-induced gastric injury, liver damage, and kidney dysfunction. The current study reported that the histopathological section of hepatocyte of mice treated orally with 250 mg/kg of naproxen for five days showed severe dilatation and congestion of central vein with necrosis of hepatic tissue with amyloid deposition in necrotic hepatic tissue with lymphocyte and Kupffer cell infiltration. Moreover, the histopathological section of the liver of mice treated orally with 250 mg/kg of 4b for five days showed severe distractions and hemorrhage of hepatic tissue, while damage was shown more prominent in the fifth group with recorded severe necrosis of hepatic tissue and vacuolation. In addition to the tissue of hepatocyte of liver of mice treated orally with 250 mg/kg of 8 for 5 days showing necrosis of hepatic tissue and inflammatory cell infiltration mainly lymphocyte and giant cell, with the presence of Kupffer cell. In addition, our data showed clear improvement in of liver of mice who received 4b compound via regeneration of hepatic tissue by the formation of multiple granulomas around the newly formed blood vessels (Figs. 2-14).

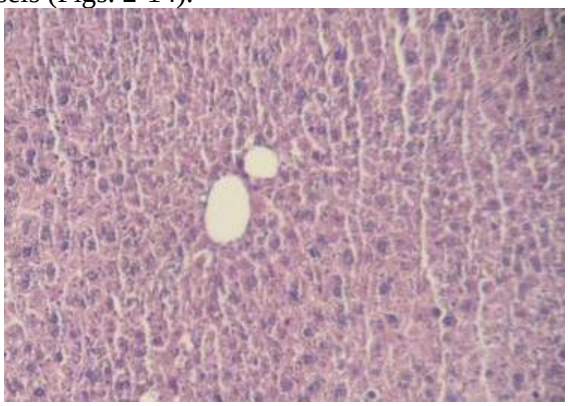

Fig. 2 Histological section of mice liver of the normal histological stricture (control group); (H&E 10 x)

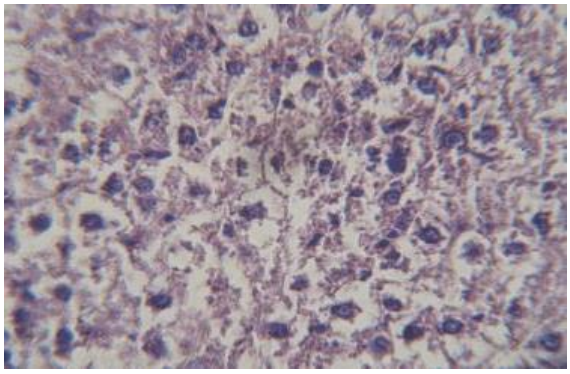

Fig. 3 Histopathological section of liver of mice treated orally with 250 mg/kg for five days showing severe necrosis of hepatic tissue and vacuolation (H&E 400X)

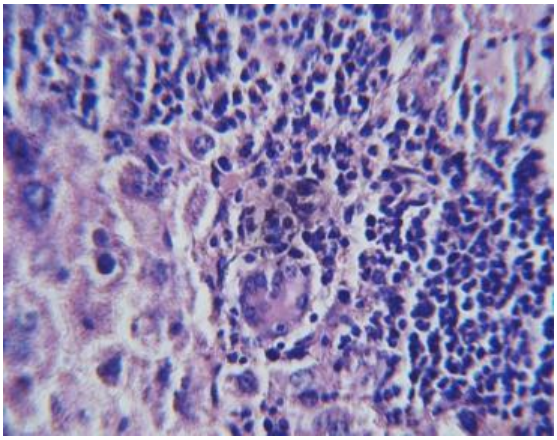

Fig. 4 Histopathological section of liver of mice treated orally with 250 mg/kg for five days showing necrosis of hepatic tissue and inflammatory cell infiltration, mainly lymphocyte and giant cell with the presence of Kupffer cells (H&E 400X)

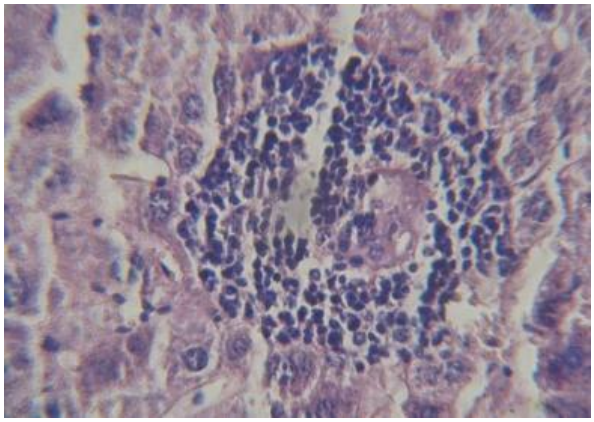

Fig. 5 Histopathological section of liver of mice treated orally with 250 mg/kg of compound 4b for five days showing the formation of early granuloma (H&E 400X)

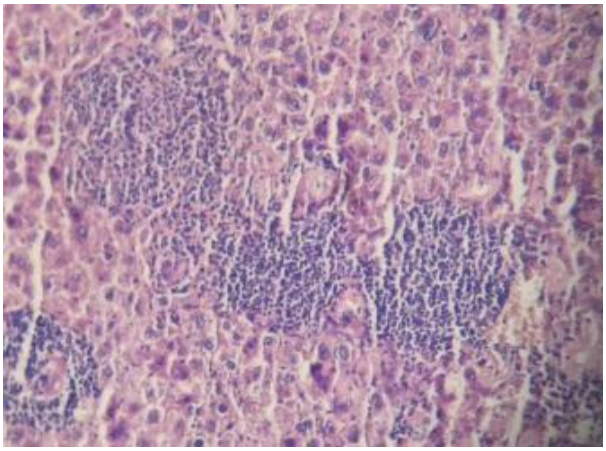

Fig. 6 Histopathological section of liver of mice treated orally with 250 mg/kg of compound 4b for five days showing regeneration of hepatic tissue by the formation of multiple granulomas around newly formed blood vessels (H&E 400X)

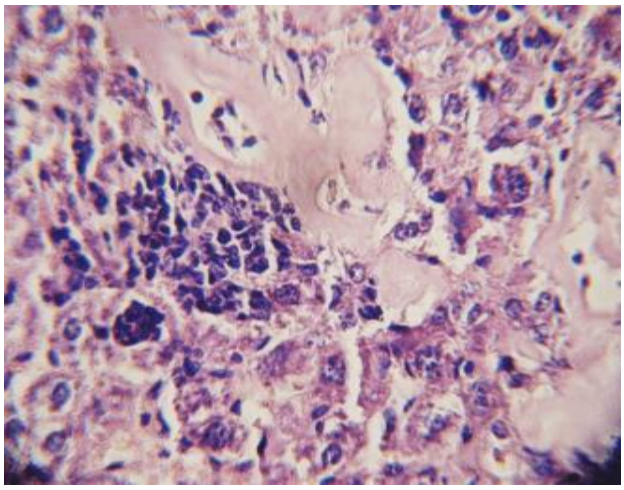

Fig. 7 Histopathological section of liver of mice treated orally with 250 mg/kg of naproxen for five days showing amyloid deposition in nicrotic hepatic tissue with lymphocyte and Kupffer cell infiltration (H&E 400X)

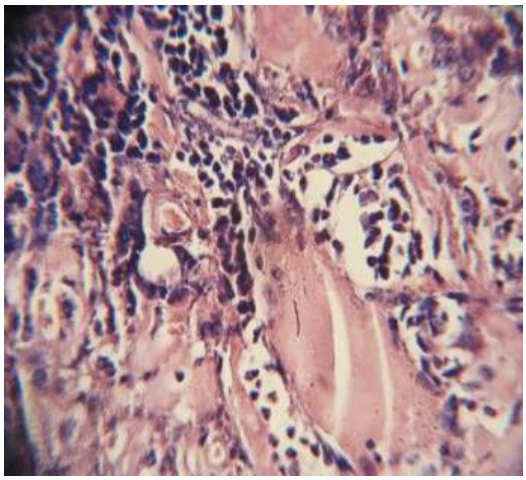

Fig. 8 Histopathological section of liver of mice treated orally with 250 mg/kg of naproxen for five days showing amyloid deposition in necrotic hepatic tissue with lymphocyte and Kupffer cell infiltration (H&E 400X)

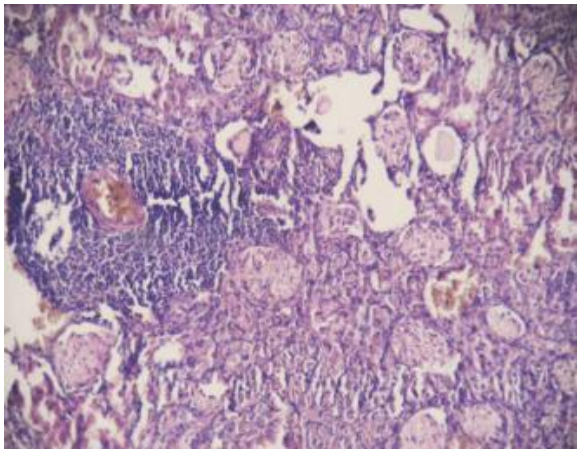

Fig. 9 Histopathological section of kidney of mice treated orally with 250 mg/kg of naproxen for five days showing amyloid deposition in necrotic renal tissue with perivascular Kupffer cell (H&E 100X)

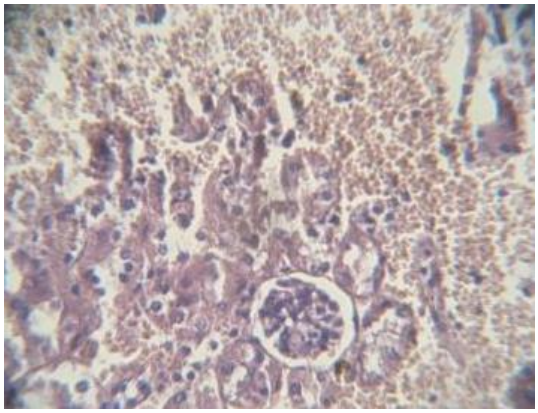

Fig. 10 Histopathological section of kidney of mice treated orally with 250 mg/kg of compound 8 for 5 days showing necrotic and hemorrhages of renal (H&E 400X)

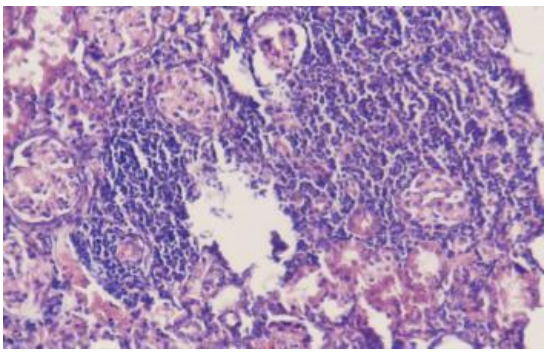

Fig. 11 Histopathological section of kidney of mice treated orally with 250 mg/kg of 4b for five days showing regeneration of malignant tissue by the formation of granuloma around newly formed blood vessels (H&E 100X)

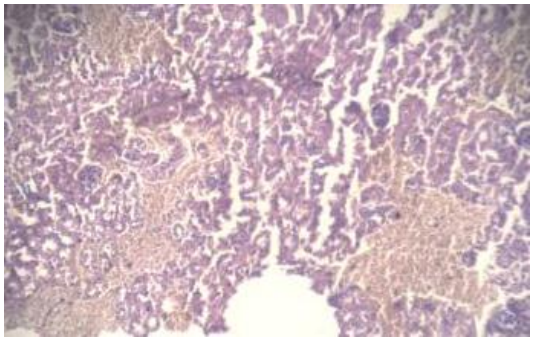

Fig. 12 Histopathological section of kidney of mice treated orally with 250 mg/kg for five days showing severe necrosis and hemorrhage (H&E 100X)

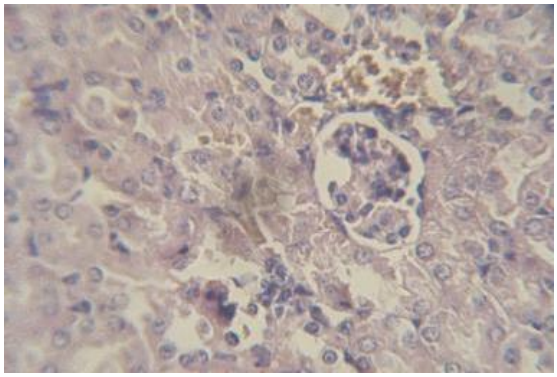

Fig. 13 Histopathological section of kidney of mice treated orally with 250 mg/kg of 4a for five days showing degeneration and necrosis of renal tubules and glomeruli with hemorrhages (H&E 100X)

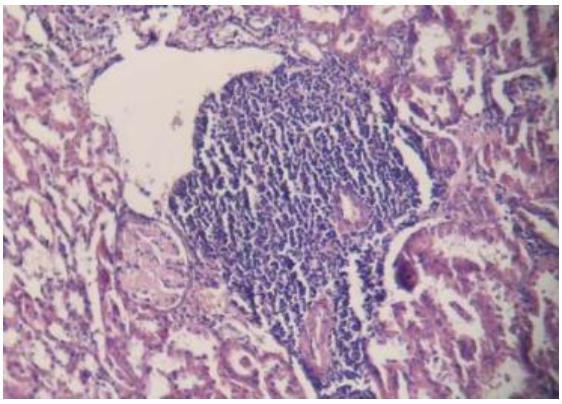

Fig. 14 Histopathological section of kidney of mice treated orally with 250 mg/kg of compound 4b for five days showing regeneration of malignant tissue by the formation of granuloma around newly formed blood vessels (H&E 100X)

The present study is supported by other previous studies showed that 4b group was most clear and revealed a perfect number of goblet cells in the small intestine with the encouragement of secretion the mucin is seen in the lumen with infiltration of mononuclear cell with lymphoid tissue that gives indicating a good chance for boost immune tissue and resistant ulcer [23, 24]. Our data indicate that a new compound synthesis and an active group addition increases analgesic activity agreed with [25], indicating that Naproxen Phosphatidylcholine (Naproxen-PC) showed improvement in anti-inflammatory and COX-block activity and minimized GI injury and ulceration in two rodent models. COX inhibitory activity may be higher for the modified naproxen than the parent naproxen. It may be highly effective in decreasing pain sensation through the strong inhibition of arachidonate cyclooxygenase and thus the inhibition of prostaglandin releasing [26]. Histopathological section of kidney of mice treated orally with 250 mg/kg of naproxen for five days showing amyloid deposition in necrotic renal tissue with perivascular cuff cell. Our data reported that the histopathological section of kidney of mice treated orally with 250 mg/kg of 4b for five days showing regeneration of malignant tissue by the formation of granuloma around newly formed blood vessels. However, very limited information is available on the renal safety of these compounds. The current study indicates that naproxen, using in during a short period of medication, adversely affects renal function via increased release of the renin-angiotensin system [27]. Cyclooxygenases (cox-1 and cox-2) are key enzymes in prostaglandin biosynthesis and the target enzymes for the commonly utilized non-steroidal anti-inflammatory drugs.

4. Conclusion

The current study concluded that new derivatives 4b have perfect anti-inflammatory and antipyretic with very mild influence on liver and kidney tissues.

Ethical Approval

The ethical committee has approved the research of veterinary medicine according to no: 533fd2.

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