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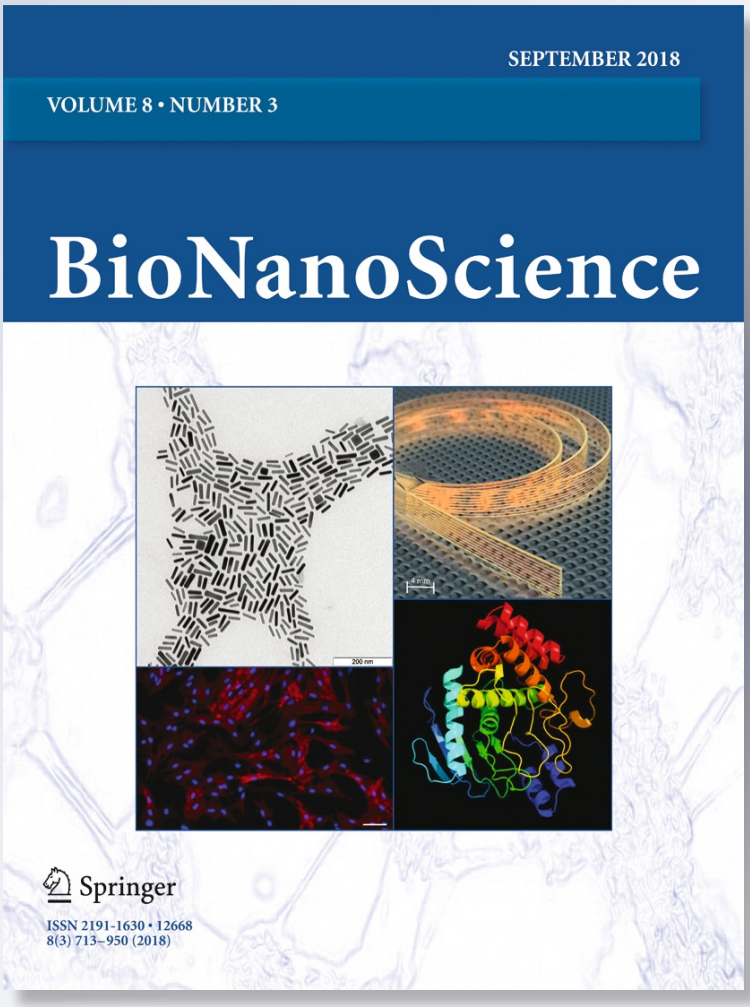

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Hepato-, Nephro- and Pancreatoprotective Effect of Derivatives of Drug Xymedon with Biogenic Acids Under Toxic Influence of Carbon Tetrachloride in Rats

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Abstract

The main purpose of the work is to study pharmacological peculiar properties of effect of pyrimidine derivatives, salt-like conjugates of the pyrimidine-based drug Xymedon (**I**) with biogenic acids (succinic (**II**), L-ascorbic (**III**), *para*-aminobenzoic (**IV**), niacin (**V**), and L-methionine (**VI**)) as well as a compound (**VII**), in which the atom *N* of the pyrimidine ring is alkylated by the methyl group, on the liver, kidney, and pancreas in rats under toxic influence of carbon tetrachloride. The experiment has been carried out on 115 mature outbred white rats of both sexes at the prophylactic scheme. The compounds were studied in doses 1/300 of LD_{50}. The research has studied the structural-morphological changes in the liver, kidneys, and pancreas, as well as biochemical markers: cytolysis (lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase), liver (total, direct, and indirect bilirubin, γ-glutamyl transpeptidase) kidney (urea, creatinine), and pancreas (amylase, lipase) functions. The study has shown that noncovalent conjugates of Xymedon with biogenic acids had a protective effect on the liver as well as on the kidneys and pancreas poisoned by carbon tetrachloride. The derivative with L-ascorbic acid, which had the most pronounced effect on structural-morphological changes in liver among other pyrimidine derivatives, has also proved to be effective in terms of the impact on the kidney and pancreatic cells. The derivative with *p*-aminobenzoic acid, along with improving the structural-morphological organization of kidneys, also results in reduced levels of creatinine and bilirubin in the blood.

Keywords Pyrimidine derivatives · Carbon tetrachloride · Toxic damage · Liver · Kidneys · Pancreas

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1 Introduction

The growing use of various technogenic toxicants is seriously spoiling the natural environment. Moreover, the application of medication is increasing too. All this leads to disruption of the body's systems and the emergence of chronic diseases, especially of such organs as the liver and kidneys, which neutralize and remove toxins from the body. The pancreas is also susceptible to the effects of toxicants, which can lead to disorders such as pancreatitis or diabetes. Therefore, searching for new hepato-, nephro-, and pancreatoprotectors is an actual research field.

The analysis of contemporary literature has shown that many studies are aimed at developing effective hepatoprotectors [1–6]. While some works [4–6] study nephroprotective properties of substances along with their hepatoprotective properties, other works study the protective effect of such substances on kidneys [7–9] and testicles [10] separately. These studies use models of organ pathologies that are induced by the toxic influence of some poisons—CCl_4 [1, 3, 5–10], antitubercular drugs [2], and alcohol [4].

The pyrimidine-based drug Xymedon attracts attention due to its property to stimulate tissue regeneration [11]. We have shown the hepatoprotective properties of one of the pyrimidine derivatives, namely the active ingredient of 1-(beta-hydroxyethyl)-4,6-dimethyl-1,2-dihydro-2-oxopyrimidine and registered in Russia as Xymedon [12], as well as of its derivative with ascorbic acid [13].

According to the results of our previous studies of the primary estimate of hepatoprotective and antitoxic properties of Xymedon derivatives with biogenic acids, Xymedon and its derivatives increase the survival of rats and normalize integrated functional parameters—body mass and temperature—that are reduced under toxic carbon tetrachloride damage. Pathological areas of lesions of steatosis and necrosis in liver were decreased 2–3 times in groups treated with Xymedon and its conjugates with succinic, L-ascorbic, and nicotinic acids [14, 15]. In addition, [16] have shown that the Xymedon derivative with L-ascorbic acid has an ability to increase adaptation reserves of the body under given stress conditions induced by increased exercise in the forced swimming test. In the work of [17], it was shown that derivative of Xymedon with *para*-aminobenzoic acid promotes regeneration of nervous tissue in the spinal cord in the case of contusion.

The main purpose of the work is to study pharmacological peculiar properties of the effect of pyrimidine derivatives, salt-like conjugates of the drug Xymedon (**I**) with biogenic acids (succinic (**II**), L-ascorbic (**III**), *para*-aminobenzoic (**IV**), niacin (**V**), L-2-amino-4-(methylthio)butanoic (L-methionine) (**VI**)) as well as a compound (**VII**), in which the atom *N* of the pyrimidine ring is alkylated by the methyl group on the liver, kidney, and pancreas in rats under toxic damage by carbon tetrachloride.

A number of works has shown that toxic substances attack kidneys along with the liver [4–6]. One of the key mechanisms of CCl_4-induced cell damage is intensification of lipid peroxidation [18]. It was shown that CCl_4 generates the very reactive trichloromethyl (-CCl3) and peroxy-trichloromethyl ($-OOCCl_3$) radicals which form alkoxy (R°) and peroxy radicals (ROO°) that generate lipid peroxides [19]; covalent interactions with critical target molecules such as DNA, lipids, proteins, and carbohydrates including the generation of reactive oxygen species; and alterations of the redox status [20]. It was shown that under the influence of CCl_4, the expression of miRNAs (miR-30, miR-32, miR-101, miR-384) in mouse kidney is increased and miR-1247 is decreased [21]. A reduction in the level of antioxidant enzymes under the influence of CCl_4 has been shown in [22].

2 Methods

2.1 Test Compounds

This paper represents the study of derivatives of the active ingredient (**I**) of the medicinal product Xymedon, its salt-like conjugates with biogenic acids, namely succinic, L-ascorbic, *para*-aminobenzoic, niacin, and L-2-amino-4-(methylthio)butanoic (L-methionine) acids (compounds (**II**)–(**VI**) in Fig. 1, respectively). In addition, the group of substances studied include a compound (**VII**), in which the atom *N* of the pyrimidine ring is alkylated by the methyl group (Fig. 1). The conjugates (**II**)–(**VI**) (Fig. 1) were prepared by heating the mixture of pyrimidine (**I**) and the corresponding acid in alcohol or water. The drug Thiotriazolinum (active substance—morpholine-methyl-triazolyl-thioacetate), purchased in a pharmacy chain, was studied as a reference substance.

1-(Beta-hydroxyethyl)-4,6-dimethyl-1,2-dihydro-2-oxopyrimidine (Xymedon, (**I**)) was synthesized on the basis of 4,6-dimethyl-1,2-dihydro-2-aminopyrine and 2-chloroethanol according to a known procedure [23]. 1-(2-Hydroxyethyl)-1,2-dihydro-3,4,6-trimethyl-2-oxopyrimidinium iodide (**VII**) was also obtained according to a known procedure [24]. We used commercial succinic (Acros Organics), L-ascorbic (OJSC Tatchempharmpreparaty), *p*-aminobenzoic acids (Fisher Chemicals), niacin (Fisher Chemicals), and L-methionine (Acros Organics).

The structure of compounds (**II**)–(**VI**) was established through a series of homo- and hetero-correlation NMR-experiments (2D 1H-1H-COSY, 2D 1H-13C-HSQC/HMBC, 13C, DEPT) and infrared spectroscopy, while their composition was determined using the elemental composition data. The NMR ^{1}H and ^{13}C spectra of compounds (**II**)–(**VI**) include

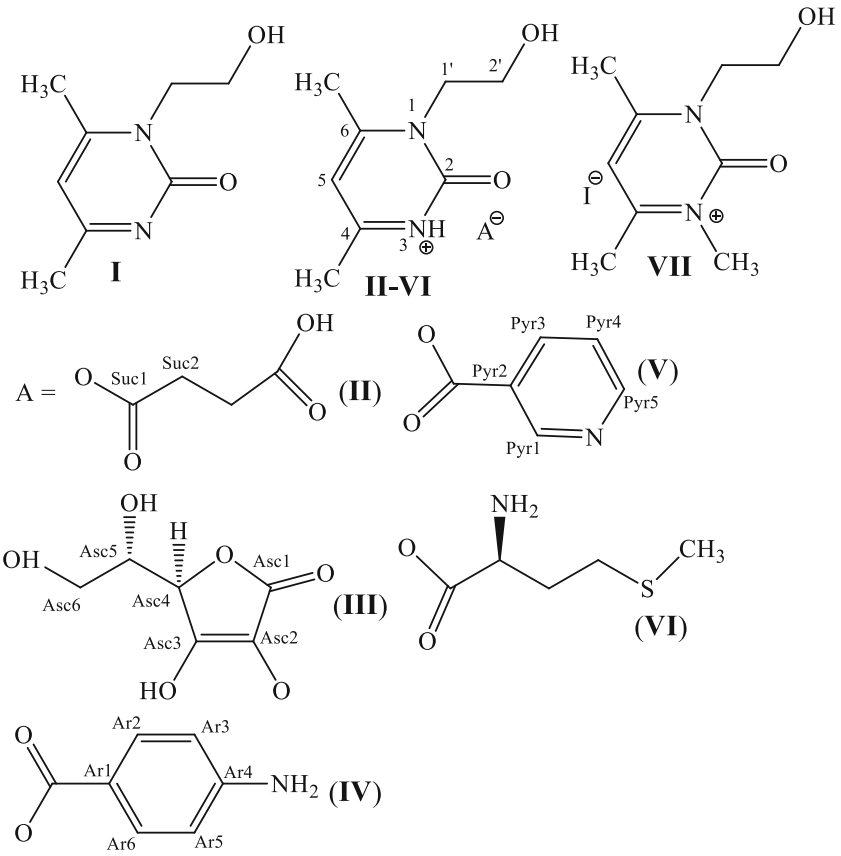


Fig. 1 Xymedon and its derivatives (**II**)–(**VII**). The numbering of the atoms of the compounds is indicated

resonance signals of both the pyrimidine and acid fragments. The IR-spectra of compounds (**II**)–(**VI**) are practically additives to the spectra of pyrimidine (**I**) and the corresponding acid.

2.2 Ethics Statement

Laboratory animal protocols performed in the present study were in compliance with the regulations of the Local Ethics Committee of Kazan Federal University. All animal experimentations and protocols were approved by the Local Ethics Committee of Kazan Federal University (Protocol № 4 dated 18 May 2017).

2.3 The Design of Experiment.

The experiment has been carried out on 115 mature outbred white rats of both sexes weighing 250–400 g, received from vivarium of A.E. Arbuzov Institute of Organic and Physical Chemistry. Using the randomization method, the animals were divided into equal groups of 10–11 rats each (5–6 males and 5–6 females). Conditions of animal husbandry and experiment performance corresponded to the policy on humane care and use of laboratory animals [25, 26]. Animals had constant access to food and water. The diet included complete pellets (raw protein 22%, raw fat max. 5%, raw fiber max. 4%, crude ash max. 9%, moisture max. 13.5%, energy value 295 kcal/100 g) supplemented with oats, dried bread, and vegetables.

Compounds were studied according to the preventive scheme [27] and were injected intraperitoneally for 11 days at doses of 1/300 of LD_{50}, corresponding to Thiotriazolinum 20 mg/kg, Xymedon (**I**) 20 mg/kg, (**II**) 3 mg/kg, (**III**) 20 mg/kg, (**IV**) 6 mg/kg, (**V**) 6 mg/kg, (**VI**) 20 mg/kg, and (**VII**) 6 mg/kg, before modeling the toxic damage by CCl_4. Then, continuing the injection of substances, to induce the toxic damage, the animals were administered with 50% oil solution of carbon tetrachloride CCl_4 subcutaneously once a day at a dose of 2 ml/kg for 3 days in 1–1.5 h after the injection of substances, according to [27]. The control group was injected with H_2O for injection only and not treated by anything preparations but exposed to CCl_4 similarly to experimental groups. The group that was not treated with any preparations and not exposed to CCl_4 was used as intact (normal) control or reference group.

2.4 Sample Preparation

Some of the animals of the intact control group without exposure were sacrificed to set the normal range parameters. At the end of the experiment, the day after the last injection of substances and CCl_4, the animals were sacrificed for sampling of blood and their organs were examined (liver, kidneys and

pancreas). Euthanasia of animals in all groups was carried out in a similar way—by exsanguination through the carotid artery under anesthesia with chloral hydrate. The collected blood was placed in test tubes with gel marked as "coagulation activator" and then was centrifuged. The sampled serum before the blood test was stored in a freezer at a temperature of − 25 °C. The serum samples were unfrozen and stirred immediately prior to the test.

2.5 Histological Studies

After the animals were sacrificed, samples of the liver, kidneys and pancreas for histological examination were fixed with 4% buffered formalin. Fixed samples of examined organs processed in a series of solutions: ethanol in an increasing concentration from 50 up to 100%, xylene and paraffin molten at 58 °C. Then, tissue slices were prepared with thickness of 5–7 μm and colored by hematoxylin and eosin. The tissue specimens were examined with a Nikon upright microscope with a digital camera. The morphometric analysis to measurement areas of liver injury and islets of Langerhans of the pancreas was conducted using the NIS B software.

2.6 Biochemical Examination

Biochemical examination of serum samples was conducted in an automated biochemical analyzer using the ready-made reagent kit. One series of examinations was performed using the Cobas Integra 400 device (manufactured by Roche, Switzerland), and the second series was performed using the ARD 200 device (manufactured by OAO Vitako, Russia). Lactate dehydrogenase (LDH) was determined as nonspecific cytolysis marker, and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined as hepatocytes cytolysis marker. Total bilirubin and γ-glutamyl transpeptidase (gGT) were determined as cholestasis markers, and direct and indirect bilirubin were determined as markers of excretory function of hepatocytes. Changes in the kidney were determined according to urea, urea acid, and creatinine. Functional state of pancreas was determined according to the activity of lipase and amylase.

2.7 Statistical Analysis

Statistical analysis was performed in programs such as SPSS, Origin 6.0, and STATISTICA. The obtained samples were analyzed for normality of distribution according to the Kolmogorov-Smirnov test. In the case of normal distribution, the samples were compared by Student's *t* test and in the case of deviations from normal distribution by the Mann-Whitney test.

3 Results

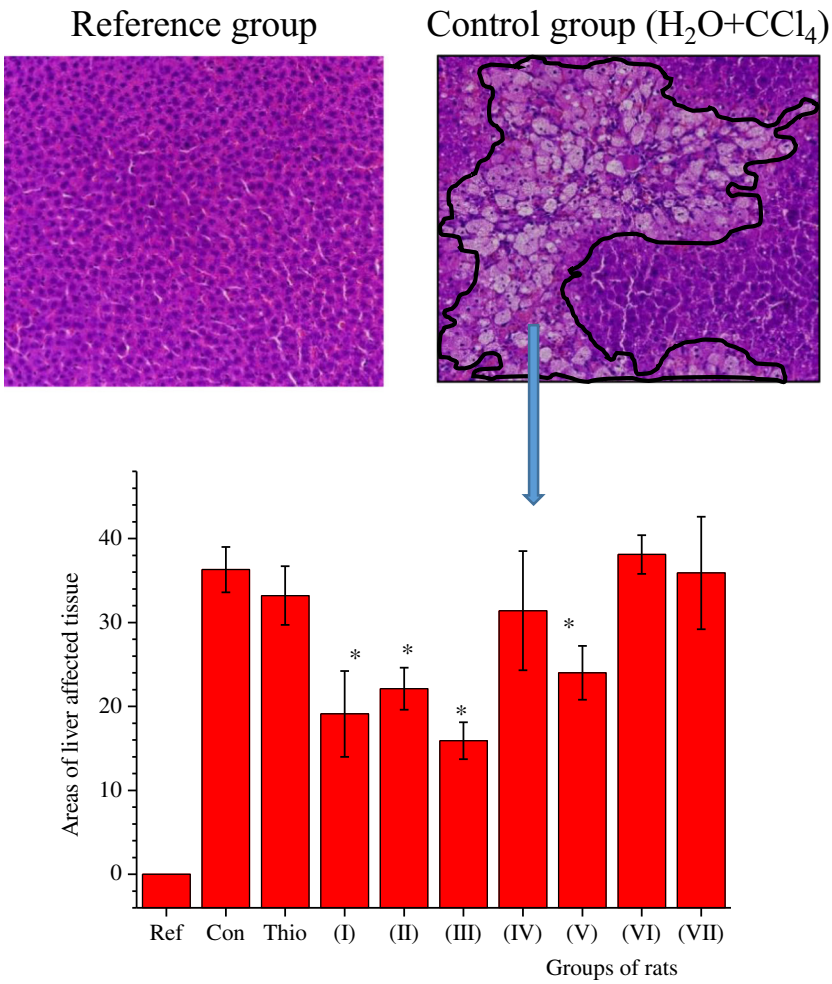
3.1 Antitoxic and Hepatoprotective Effects of Xymedon Derivatives with Biogenic Acids

The results showed that about 16% of animals (3 out of 19) in the control group that did not receive treatment have died under the effect of CCl_4. The studied pyrimidine derivatives have led to increased animal survival, which is evidence of their detoxifying effect in case of toxic injury by carbon tetrachloride. The highest survival rate (100%) in conditions of poisoning by carbon tetrachloride was recorded in the groups of rats that were injected with compound (**V**), Xymedon (**I**), and Thiotriazolinum (reference substance). It was shown that the studied pyrimidine derivatives, under the effect of which the average weight of the body affected by CCl_4 was maintained at the initial values, were reference substances Thiotriazolinum, Xymedon, and compounds (**III**), (**V**), (**VI**), and (**VII**). In addition, a less pronounced temperature decrease as compared to the control group was observed under the effect of the pyrimidine derivatives (in descending order): (**III**), (**VII**), Xymedon (**I**), (**V**), and (**II**). The conducted study proves the antitoxic effect of the two-fragment conjugated pyrimidine derivatives, one of the fragments of which is Xymedon (substance (**I**)) and the other is biogenic acid. The data have been published in [15]. This paper has also shown that pyrimidine derivatives reduce the signs of liver toxicity. Figure 2 shows structural-morphological changes in the liver of rats in the control group and in groups treated with Xymedon, Thiotriazolonum, and derivative (**III**). The group treated with (**III**) has shown the minimum pathological changes in the liver.

Under impact of Xymedon and its derivatives **II**, **III**, and **V**, the affected areas of the liver tissue were decreased by 47.4, 39.2, 56.2, and 33.8%, respectively (the diagram on Fig. 2). The effectiveness of the pyrimidine derivatives was higher than that of the reference substance of the hepatoprotective medication, that is, Thiotriazolinum. Injection of compound **III** resulted in the smallest area of the liver tissue injury (Fig. 2). Compound **IV** that is a pyrimidine derivative with *p*-aminobenzoic acid had no impact on the structural-morphological changes in the liver tissue.

3.1.1 Biochemical Markers of Cytolysis

The toxic influence of CCl_4 caused the strong increase of biochemical cytolysis marker like LDH (in 5.9 times), ALT (in 9–14.5 times), and AST (in 3.5–11 times) in male and female rats (Fig. 3). The statistically significant effect of Xymedon derivatives and Thiotriazolinum on LDH has not been observed. There was only a tendency of LDH being reduced in groups treated with (**II**), (**III**), (**V**), and (**VII**) in males and (**II**) and (**IV**) in females (Fig. 3). The observations



◀ **Fig. 2** Micromorphology of rat liver in the reference (Ref) or intact control group, the control (Con) group, and the method of determining of liver injury areas (selected in black line). On the diagram, it shows results of areas affected, tissue of the liver in tested groups of rats, %: mean and errors of mean, and comparisons between the samples according to the Student's *t* test are given for the area of liver injury (*—differences with the control group are significant at $p < 0.05$). Micromorphology of rat liver in group injected with the most effective derivative (**III**) in comparison with Xymedon (**I**) and Thiotriazolinum (Thio) is shown in the bottom photos. Slices were stained with hematoxylin and eosin. Zoom 300×

showed decrease in ALT activity in groups of rat females and no effect on AST activity. The most effective compounds for action on ALT were (**II**), (**III**), and (**IV**). The results show that the drug Xymedon and its derivatives lead to decrease in cytolysis of hepatocytes.

3.1.2 Biochemical Markers of Cholestasis and Excretory Function of Hepatocytes

g-GT and total bilirubin were determined to assess cholestasis. Determination of direct and indirect bilirubin was performed to assess the hepatocyte excretory function. The results showed a significant increase in activity of g-GT and the levels of total, direct, and indirect bilirubin in both male and female rats (Fig. 4).

Among the studied biochemical markers, the pyrimidine derivatives ((**I**)–(**V**)) had a little effect on the g-GT marker of cholestasis. At the same time, the level of total bilirubin (one of the markers of cholestasis) as well as both its fraction of direct and indirect bilirubin decreased under the influence of Xymedon and its derivatives ((**II**)–(**V**)). The most pronounced effect of compounds on bilirubin level was shown in groups that were injected with (**II**), (**III**), and (**IV**) (Fig. 4).

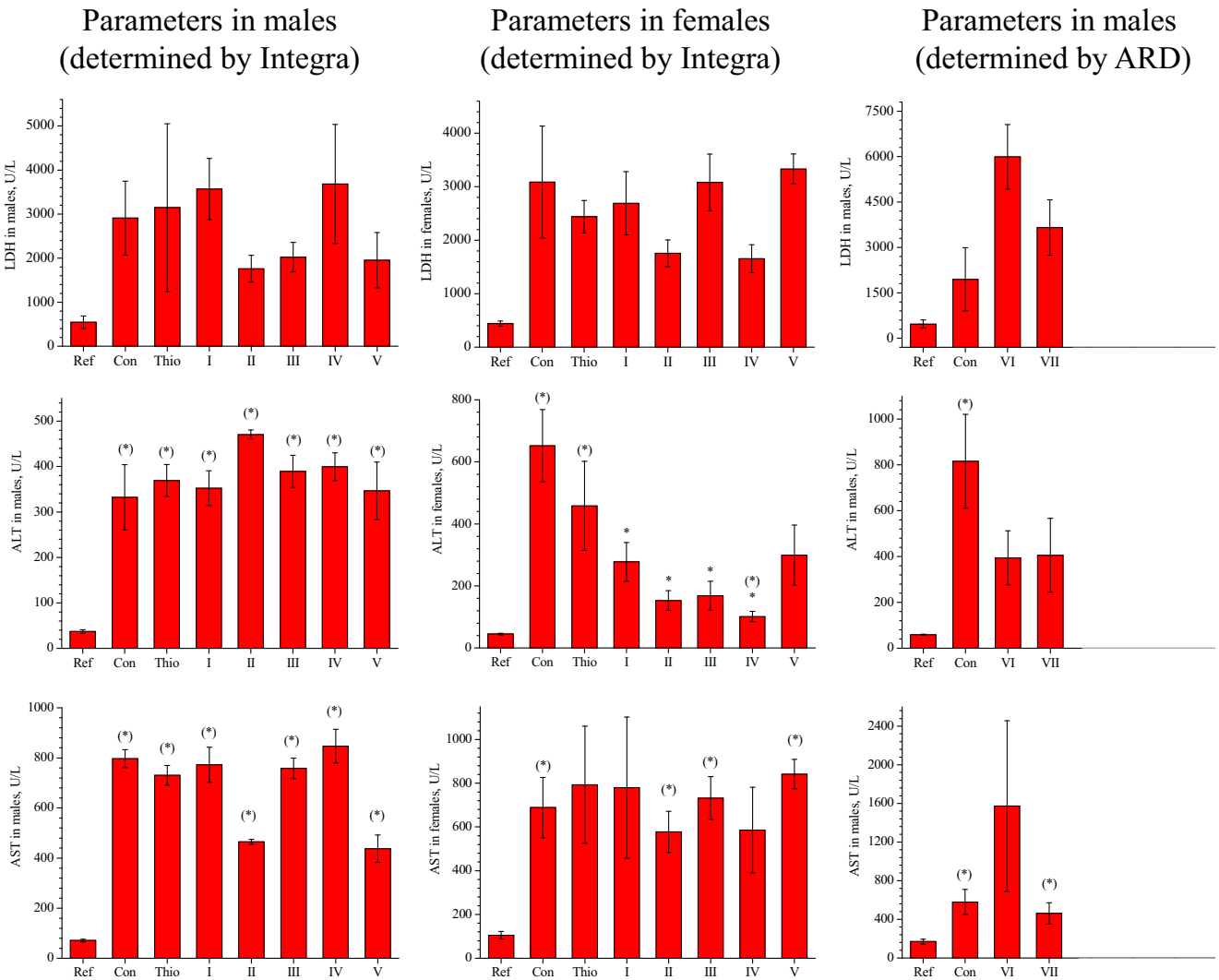


Fig. 3 Biochemical markers of cytolysis. (*)—differences with the reference (intact) control group are statistically significant ($p < 0.05$); *—differences with the control group are statistically significant ($p < 0.05$). Ref, reference group of normal (intact control); Thio, group injected with Thiotriazolinum

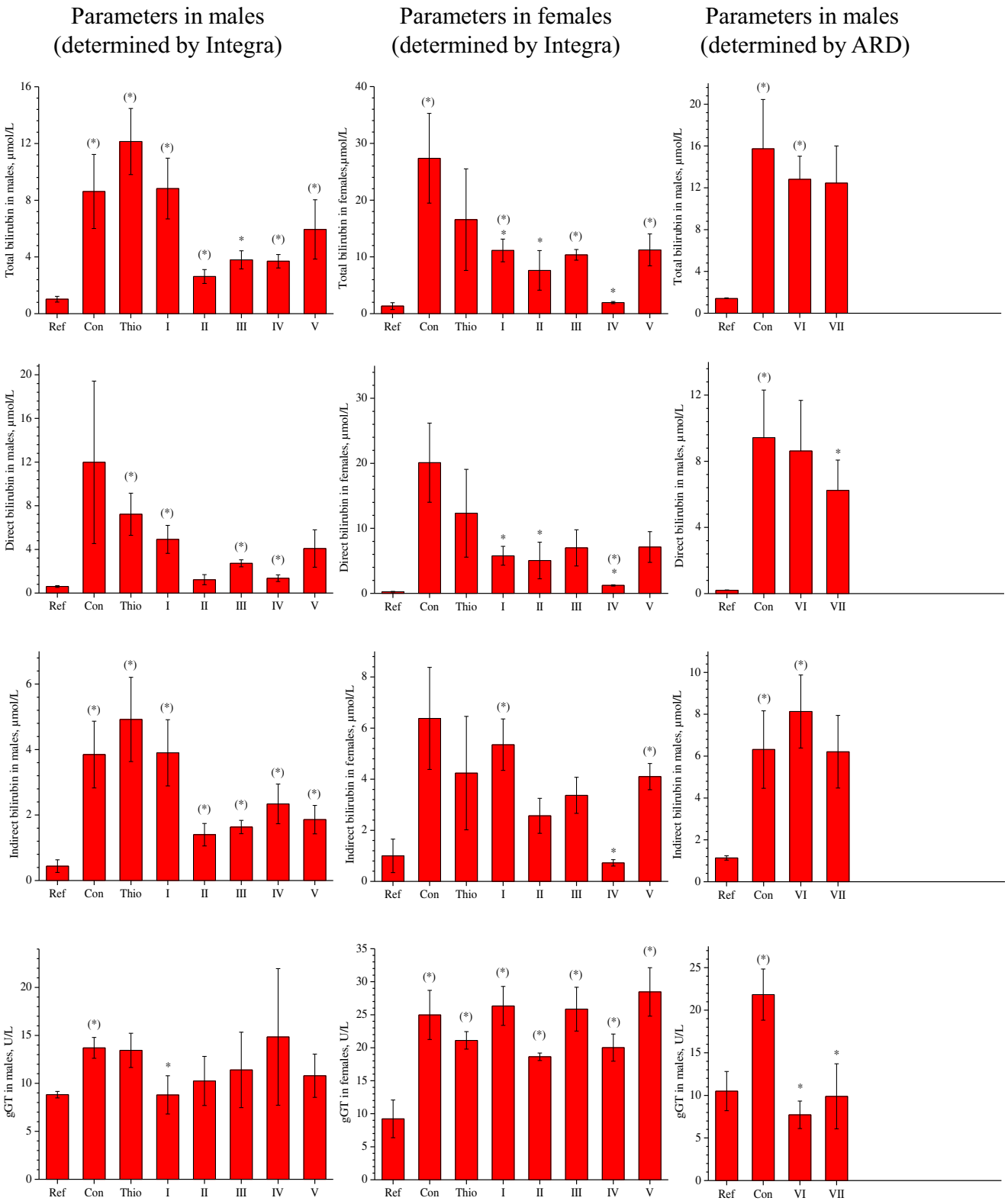


Fig. 4 Biochemical markers of cholestasis and excretory function of hepatocytes. (*)—differences with the reference (intact) control group are statistically significant ($p < 0.05$); *—differences with the control group are statistically significant ($p < 0.05$). Ref, reference group of normal (intact control); Thio, group injected with Thiotriazolinum

The results show that these derivatives of Xymedon improve functions of the biliary system and the excretory function of hepatocytes in conditions of toxic influence of CCl_4. The effect of derivatives (**VI**) and (**VII**) on bilirubin level was less

pronounced. However, both (**VI**) and (**VII**) lead to decrease of g-GT activity, i.e., possessing anticholestatic effect.

3.2 Nephroprotective Effect of Xymedon Derivatives with Biogenic Acids

3.2.1 Pathomorphological Studies of the Kidney

Significant changes were observed in the kidney under the effect of CCl_4, which manifested as an increase of kidney size: mass ratio for the left kidney increased by 56.7% and the right kidney by 61.3%. Increased size of the kidneys may be due to pathological changes such as pyelonephritis or inflammation in response to the toxic effects of CCl_4. With the combined injection of CCl_4 and the pyrimidine derivatives, the mass ratios of kidneys decreased, but the differences with the control group were statistically insignificant.

Histological study of the kidneys of all rats in the control group have shown pronounced signs of destructive and degenerative changes covering the significant part of the organ both in the cortex and the medulla (Fig. 5). The Malpighian glomeruli were deformed and destroyed, and Bowman's capsule cells also showed signs of destructive and degenerative changes. We have discovered extensive zones of tubular necrosis. In the medulla, we have observed ballooning degeneration of tubular cells and widened lumens of proximal tubules and detected erythrocytes in these lumens, which is indicative of hematuria, as well as pink amorphous masses, which is characteristic of proteinosis.

As shown in Fig. 6, derivatives (**I**), (**II**), (**III**), (**IV**), and (**VII**) have reduced degenerative changes in the Malpighian glomeruli and Bowman's capsules in the glomeruli. All the derivatives of pyrimidine have caused reduction of the degenerative and necrotic changes in the renal tubules. Although, there had been such changes, such as the presence of

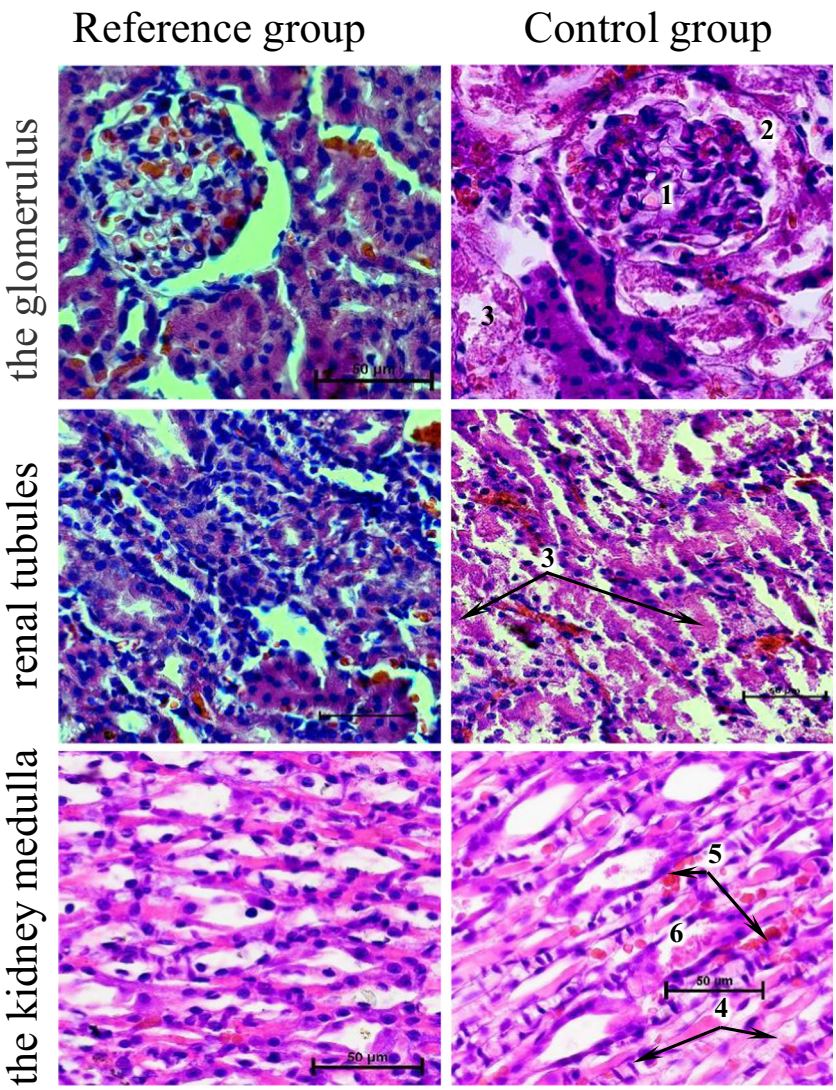


Fig. 5 Pathomorphological changes of the structure of the kidney under the toxic influence of CCl_4. (1) Deformation and destruction of Malpighii ball in the glomerulus. (2) Destructive and necrotic changes in the cells of Bowman's capsule. (3) Necrosis of renal tubules. (4) Balloon degeneration of tubules cells. (5) Erythrocytes in the lumens of the tubules. (6) The amorphous mass colored in pink in the lumens of tubules

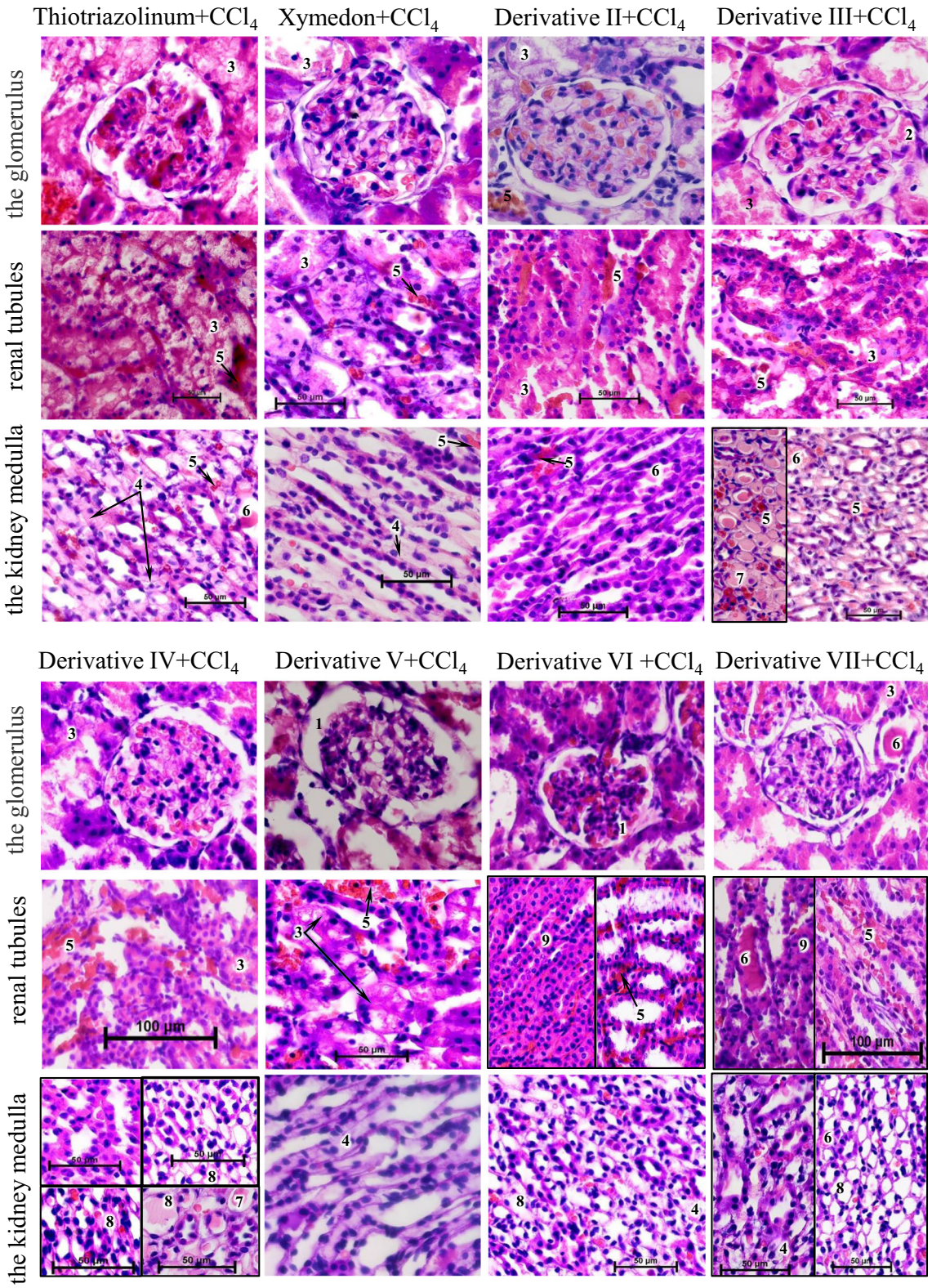


Fig. 6 Pathomorphological changes of structure of kidney in experimental groups. (1) Deformation and destruction of Malpighii ball in the glomerulus. (2) Destructive and necrotic changes in the cells of Bowman's capsule. (3) Necrosis of renal tubules. (4) Balloon degeneration of tubules cells. (5) Erythrocytes in the lumens of tubules. (6) The amorphous mass colored in pink in the lumens of tubules. (7) Areas of "thyroid kidney." (8) The thinning of the tubular epithelium. (9) Narrowing of the clearance of the tubules

erythrocytes (hematuria) or amorphous masses in the lumens of tubules (proteinosis). Some animals treated with the derivative (**III**) did not have erythrocytes in the lumens of tubules of the medulla. In experimental groups of animals, there were such changes in the medulla of their kidneys, such as ballooning degeneration of the epithelial cells, epithelial thinning, and appearance of erythrocytes or amorphous masses in the lumens of tubules in some animals. In other words, the positive impact of the compounds being studied was mainly directed at the renal cortex cells—renal glomeruli and convoluted tubules. The pyrimidine derivatives affected the renal medulla cells to a lesser extent.

3.2.2 Biochemical Markers of Kidney Injury

The study of biochemical indicators has shown differences between male and female species. Females had statistically higher level of urea and magnesium, whereas the level of creatinine was higher inconsistently. CCl_4 had increased the level of urea and creatinine statistically to a greater extent in females, rather than in males. However, uric acid under CCl_4, on the contrary, was decreased (Fig. 7).

The pyrimidine derivatives did not have any effect on the urea level of female animals. The downward tendency in the urea level was observed only in the administration of

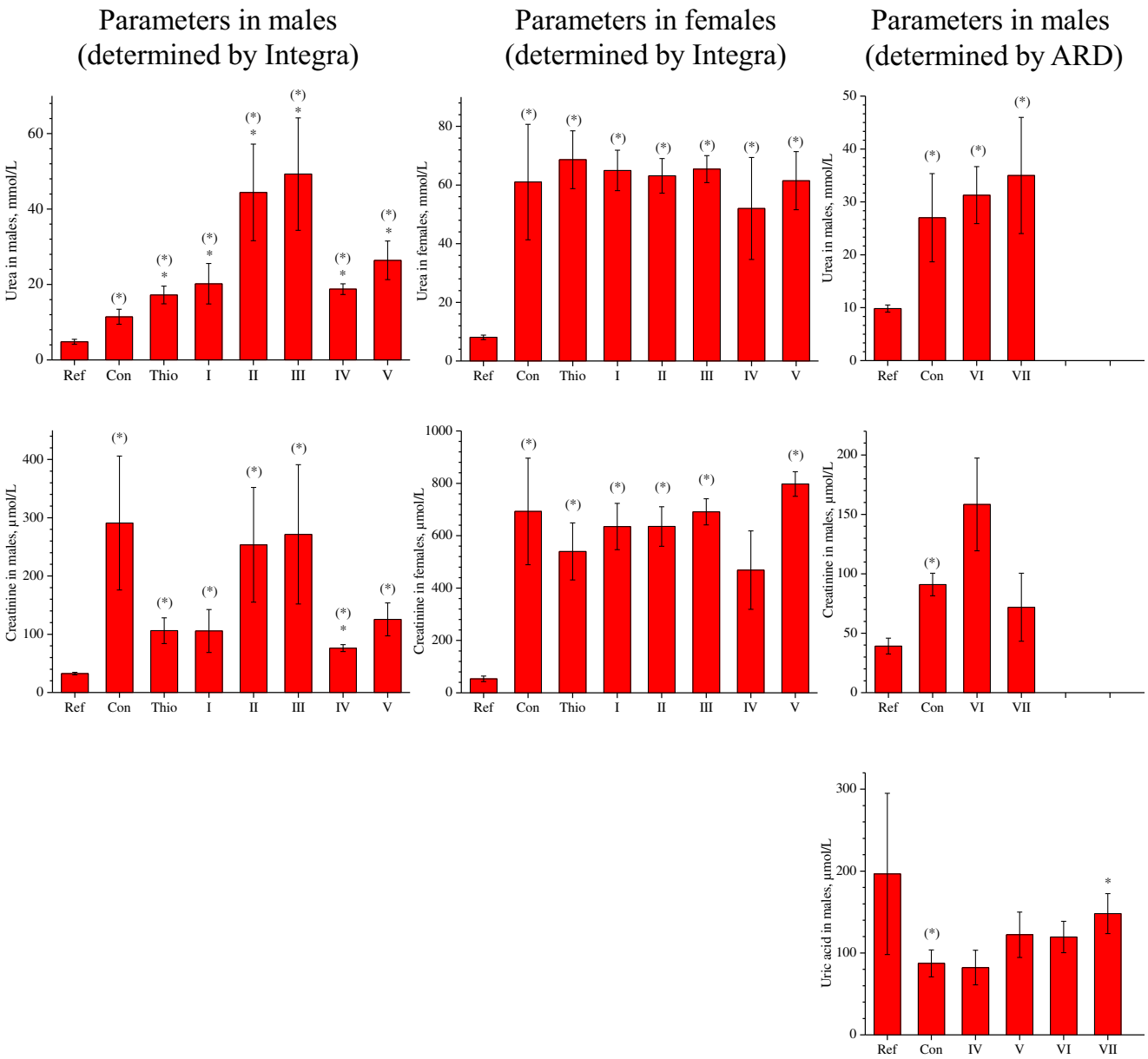


Fig. 7 Biochemical parameters of the blood that are markers of kidney functions. (*)—differences with the intact control group are statistically significant ($p < 0.05$); *—differences with the control group are statistically significant ($p < 0.05$). Ref, reference group of normal (intact control); Thio, group injected with Thiotriazolinum

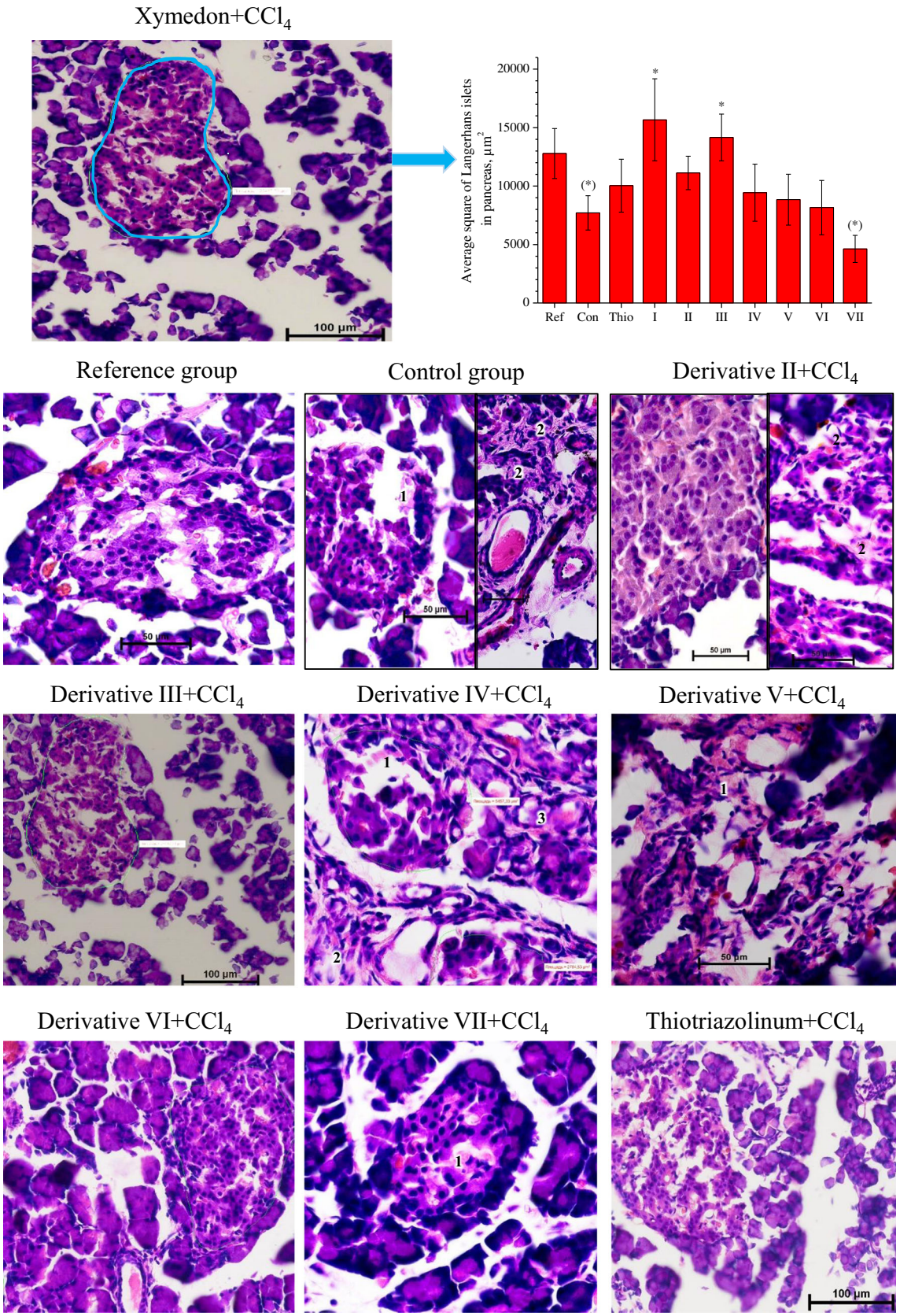


Fig. 8 Pathomorphological changes of islets of Langerhans in pancreas. (1) Necrosis and degeneration. (2) Fibrotic changes. (3) Degeneration of the acinus. (*)—Differences with the intact control group are statistically significant ($p < 0.5$); *—differences with the control group are statistically significant ($p < 0.05$)

derivative (**IV**). Males in the experimental groups had, on the contrary, an increased level of urea, which may be associated with not only a renal excretory system failure but also with higher metabolism in comparison to females. The change in creatinine level of females under the pyrimidine derivatives has proved to be insufficient in comparison to the intact control group. The downward trend has been observed only under the substance (**IV**) and Thiotriazolinum. In males, the derivative (**IV**) has caused positive reduction of the creatinine level, which is indicative of improvement in the renal excretory system. Under Thiotriazolinum, (**I**), (**V**), and (**VI**), the level of creatinine has also reduced, but the results were statistically inconsistent.

The decline in the level of uric acid in the blood serum of the intact control group may have been caused by either liver damage, which had occurred from the administration of CCl_4 and leads to a reduction in production of uric acid, or renal irritation. Reduction of uric acid at renal irritation points at defective renal tubules and impairment of their reabsorption function, which correlates with the results of the histological study. Under (**V**), (**VI**), and (**VII**), the level of uric acid increased, and the differences with the control group were significant in the group treated with (**VII**).

3.3 Pancreatoprotective Effect of Xymedon Derivatives with Biogenic Acids

3.3.1 Pathomorphological Studies of the Pancreas

The results of pathomorphological study of the pancreas have shown significant changes in terms of pancreatic islets (or islets of Langerhans) performing the endocrine function. In the control group, after being exposed to CCl_4, we have observed atrophy, destructive changes of the islet cells, signs of fibroid degeneration, and also positive reduction of the average area of the islets (Fig. 8). In relation to the remaining zones of the pancreas (acini, duct, and stroma), no features of the effects of CCl_4 poison and tested derivatives were revealed.

Under the derivatives of pyrimidine, the destructive and degenerative changes of the islet cells have been significantly decreasing and the area of islets growing to the size of that in

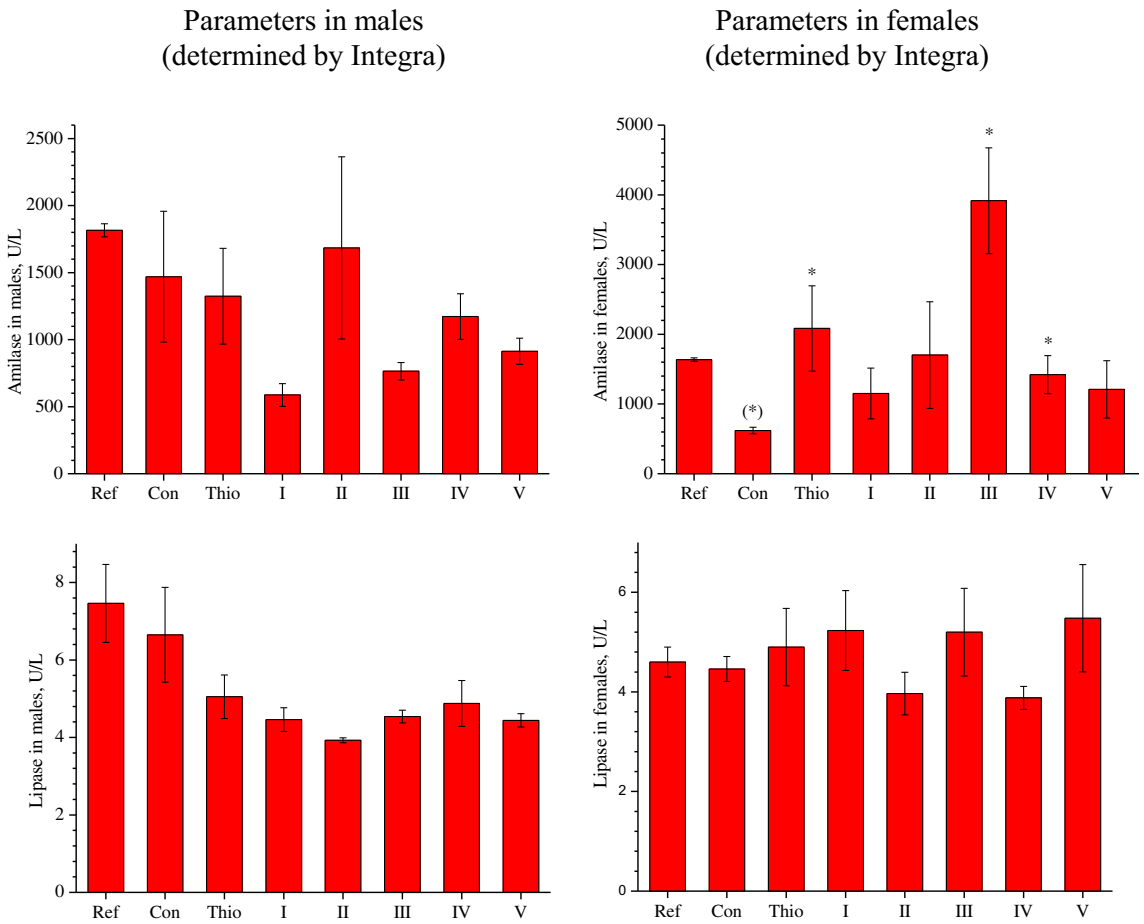


Fig. 9 Biochemical markers of pancreas state—activity of lipase and amylase in rats. (*)—differences with the intact control group are statistically significant ($p < 0.05$); *—differences with the control group are statistically significant ($p < 0.05$). Ref, reference group of normal (intact control); Thio, group injected with Thiotriazolinum

the intact control group. Compounds (**I**) and (**III**) had the most pronounced positive effect on the pancreatic islets.

3.3.2 Biochemical Markers of Pancreatic Injury

Males have been observed to have a higher level of lipase and amylase than females. Under CCl_4, the level of activity of both, lipase and amylase, in males followed the downward trend, whereas in females the activity of lipase did not change, while the activity of amylase reduced significantly (Fig. 9), which is indicative of pancreatic dysfunction. Introduction of pyrimidine derivatives and Thiotriazolinum reduced the activity of lipase: in males, all the substances; in females, only the derivatives (**II**) and (**IV**). Males in the group that was treated with derivatives (**I**) and (**II**) have shown a pronounced downward trend in terms of the activity of amylase. All of the pyrimidine derivatives and Thiotriazolinum affected the females by increasing the activity of amylase, especially when administering the derivative (**III**). The statistically consistent increase of amylase, when compared to the intact control group, was observed in groups that was given Thiotriazolinum, (**III**), and (**IV**).

4 Discussion

Xymedon, a Russian drug based on pyrimidine, is known in the preparation for stimulation of regeneration. This property of Xymedon has been demonstrated in [28, 29] on the test object *Girardia tigrina Planarians* with initiation of regeneration by amputation of the head and in the area of the eyes. According to the literature, Xymedon affects the key biochemical processes at the cellular and sub-cellular levels, such as activating adenylate cyclase, which ultimately leads to cAMP's fast accumulation in a cell, to a better metabolism, first and foremost protein biosynthesis [11].

Our previous studies [12–15] have detected both protective and regeneration-stimulating properties of Xymedon and its derivatives towards the liver. As it was shown [15], derivatives of pyrimidine induce reduction of the signs of destructive and degenerative changes and necrosis of hepatocytes and reduction of the area of tissue invaded by necrosis and steatosis. In this study, we investigated biochemical parameters of the blood that let us to evaluate the liver functions and processes under the toxic influence of CCl_4. Moreover, we have discovered protective effects of pyrimidine derivatives on kidney and pancreatic cells. In kidneys, the effect manifested itself in the cortex cells (glomeruli and convoluted tubules), and in the pancreas, it acted on the islets of Langerhans.

It is thought that the protective effects of studied pyrimidine derivative on the liver, kidneys, and pancreas lies not only in the activity of the pyrimidine fragment but also in the activity of biogenic acid. The obtained results allow estimating the influence of fragments of biogenic acids in the structure of conjugates on the pharmacological efficiency of a Xymedon fragment, leading to its strengthening or weakening. The peculiarities of the action of Xymedon derivatives with biogenic acids on the liver, kidneys, and pancreas depending on the used fragment of biogenic acid are revealed.

5 Conclusion

The study has shown that derivatives of the drug Xymedon based on pyrimidine with biogenic acids had a protective effect on the liver as well as on the kidneys and pancreas when attacked by carbon tetrachloride. The derivative with L-ascorbic acid, which had the most pronounced effect on structural-morphological changes in the liver among the other pyrimidine derivatives, has also proved to be effective in terms of the impact on the kidney and pancreatic cells. The derivative with *p*-aminobenzoic acid, along with improving the structural-morphological organization of kidneys, also results to reduced creatinine as well as bilirubin level in the blood.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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