RESEARCH ARTICLE

Synthesis and Biological Activity of few Pyrimidines Derivatives against Hepatic Injury Stimulated by Carbon Tetrachloride in Male Rats

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ABSTRACT

In the presence of sodium hydroxide, substituted chalcones are reacted with cyanoguandine in ethanol, and some chalcone compounds are used as a nucleus in the preparation of some five-, hexa-, and hepta-, heterocyclic compounds pyrimidine (pyrimidines derivatives), pyrimidine derivatives (A1, A2, and A3). Contains therapeutic properties and bioactivity, and has been used to treat various ailments. This study aimed to learn more about how pyrimidine derivatives could help mitigate the undesirable implications of carbon tetrachloride. a group of 50 male rats were separated into 5 groups: healthy control (no treated), CCl_4 group, and the rest. A1 (N-(6-(5-methylthiophen-2yl)-4-phenyl-3,4-dihydropyrimidin- (1H)-ylidene) cyanamide), A2 (N-(6-(5-methylthiophen-2yl)-4-(4-nitrophenyl)-3,4-dihydropyrimidin -2(1H)-ylidene)cyanamide), A3 (N-(4-(Melting points, (FTIR) spectroscopy, ^{1}HNMR spectroscopy, and thin layer chromatography method (TLC) were used to describe compounds [A1, A2 and A3] to monitor the impacted liver function. Pyrimidines derivatives compounds reduced CCl_4 toxicity while increasing the levels of aspartate transaminase, alanine transaminase, gamma-glutamyltransferase, and alkaline phosphatase, unlike the CCl_4 group and the CCl_4 groups containing pyrimidines derivatives. The quantities of total lipids, protein, globulin, and albumin in the control group were substantially different (P0.05). Lipid peroxidation produced a considerable quantity of malondialdehyde compared to the control group, the CCl_4 group. However, pyrimidines derivatives components reduced the quantity CCl_4, lowering oxidative stress. The levels of catalase, glutathione, and glutathione peroxidase were higher in individuals who were given just CCl_4 elevated in groups of pyrimidines derivatives component. There were substantial disparities in superoxide dismutase levels throughout the groups studied.

Keywords: Antioxidant, Carbon Tetrachloride, Lipid peroxidation, Pyrimidines Derivatives, reactive oxygen species (ROS).

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INTRODUCTION

Liver disease is quite widespread, and it is the biggest cause of mortality in the globe. Steatosis is the most frequent hepatocellular malignancy, followed by chronic hepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma.[1] Viruses, alcohol abuse, metabolism disorders, narcotics autoimmune attack triggered by an overabundance of iron or copper on liver tissue, anomalies of the hepatic duct epithelium, or hereditary hepatic duct epithelium can all lead to long-term illnesses of damage to the liver.[2] In recent decades, pyrimidine, a nitrogen-containing heterocyclic ring system that is both synthetically and physiologically relevant, has been discovered to have characteristics of biological and pharmacological. Also, six heterocyclic aromatics containing one and three N atoms at the band to be categorized.[3] The relevance of pyrimidine preparation by various techniques may be found in the disciplines of chemistry in healthcare. Pyrimidines and their derivatives are organic compounds synthesized from pyrimidines. They have anti-inflammatory properties, extreme anti-malaria properties, anti-cancer, cardiovascular health, prophylactic properties of neoplastic, known to inhibit tubercular, antiviral of human immunodeficiency virus (HIV), antihypertensive, anti-bacterial, and therapeutic properties. This review discusses the pyrimidine nucleus's biological and pharmacological functions. This research is part of the use of chalcone compounds as a nucleus in the creation of five-, hexa-, and hepta-heterocyclic compounds. Different intrinsic biological features of pyrimidine (pyrimidines derivatives),[4] pyrimidines derivatives pyrimidines are utilized as *Mycobacterium tuberculosis*, antioxidants, and antidiabetics,

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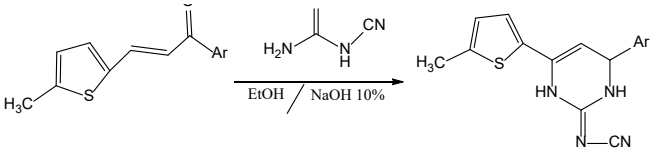

Figure 1: Preparation of pyrimidine derivatives.

making them appealing to medicinal chemistry researchers.[5] Antiallergic, antioxidant, antiviral, antihistaminic,[6] cytostatic, immunomodulating, herbicidal, and anticonvulsant effects are all found in heterocycles containing pyrimidopyrimidine.[3] Antimicrobial properties of pyrimidines include fungicidal, antitoxoplasma, antimalarial, antibacterial1, antifilerial, and antileishmanial.[7] Pyrimidines are an important class of antibacterial medicines that have significantly influenced antibacterial chemotherapy in recent years. Pyrimidine nuclei are chemotherapeutic drugs that also have anticancer properties.[8]

MATERIALS AND METHODS

Chemicals and Materials

The CCl_4 was given by SISCO Research PVT LTD's Laboratories (Mumbai, India). The majority of chemicals, except ethanol (Sigma–Aldrich), have been donated by (Merck group, BDH and Fluke Company, Germany). BioLab Diagnostics (India Private Limited) provided kits and other substances for analytical grade.

Synthesis Pyrimidines Derivatives

Adam *et al*., 2019 synthesized pyrimidines derivatives.[9] By reacting the modified galcon with thiourea in ethanol as a solvent, we made several pyrimidine alternatives.

Diagnosis of Prepared Compounds (A1, A2 and A3):

The legitimacy of the chemical structures was established using spectroscopic techniques such as FTIR (infrared), nuclear magnetic resonance of protons, and nuclear magnetic resonance of carbon (C-NMR). Physical methods are also utilized, such as color change, melting point, and yield ratio calculation.[10]

Animals Experimentation

The Laboratory Animal Center of the College of Veterinary Medicine, University of Tikrit, provided the wistar male rats utilized in this study, which weighed on average 200 ± 25 g. The animals were kept in regular circumstances (23–25°C, 12 hours/12 hours light/dark cycle). The experimentation Ethics Committee on Animal Use of the College of Veterinary Medicine, University of Tikrit, authorized the study's protocol, which followed the US National Institutes of Health Guidelines for the Care and Use of Laboratory Animals in Biomedical Research (NRC, 1985).

Experiment Determination

The 50 rats were utilized to see if pyrimidine derivatives (A1, A2, and A3) might prevent them from CCl_4-induced hepatotoxicity. The effects of mixing CCl_4 and olive oil 1 to 1 (w/w) on hepatoprotection against CCl_4-induced liver damage were tested. Four groups of rats were created of 10 rats for each one, with every group receiving different treatment conditions. For four weeks, rats in group one were fed a common manufactured food. Rats in 2nd Group include: For 30 days from the date, the rats were given an equal amount of CCl_4 and olive oil (1 mL/kg) orally through Gavage of the stomach (bw). 3rd Groups through 5th were given 100 mg/kg body weight of A1, A2, and A3, which are pyrimidine derivatives, from day 15 to day 30.

Analytical Biochemistry

Using an automatic serum biochemical analyzer (Hitachi 7180, Hitachi, Tokyo, Japan), biochemistry analysis was performed to estimate the levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total cholesterol, total protein, albumin, triglycerides, high density lipoprotein (HDL), and low density lipoprotein (LDL).

Estimating Lipid Peroxidation and Antioxidant Enzymes

Using reactions with thiobarbituric acid, malondialdehyde concentrations were determined (MDA). The derivative of thiobarbituric acid (TBARS) content was found in the tissue determined employing the Halliwell and Chirico method.[11] The Mohammed and Kakey technique was used to determine GSH concentration.[12] Other methods were used to evaluate the activity of CAT, SOD, and GPx (antioxidant enzymes).[13]

Analytical Statistics

SPSS v.12.0 statistical analysis software was used for the statistical studies (IBM Corp., Armonk, NY, USA). The statistical analyses of biochemical parameters were conducted using one-way analysis of variance (ANOVA) and Dunnett's multiple comparison test. For the analysis of particular biochemical tests, the chi-square test and the Kruskal-Wallis test were utilized. For *p-values* less than 0.05, the results were considered statistically significant.

Table 1: (A1-A3) Infrared IR spectrum values for vehicles.

Comp. No.	*Ar*	*FTIR υ cm^{-1} (KBr)*				*Others*
		Ar-H	*C=N*	C=C	*NH*	
A1	C_6H_5	3035	1676	1522	3201	
A2	$C_6H_4NO_2$	3012	1622	1517	3419	1350 for NO_2
A3	C_4H_2SBr	3078	1596	1517	3153	669 for C-S 584 for C-Br

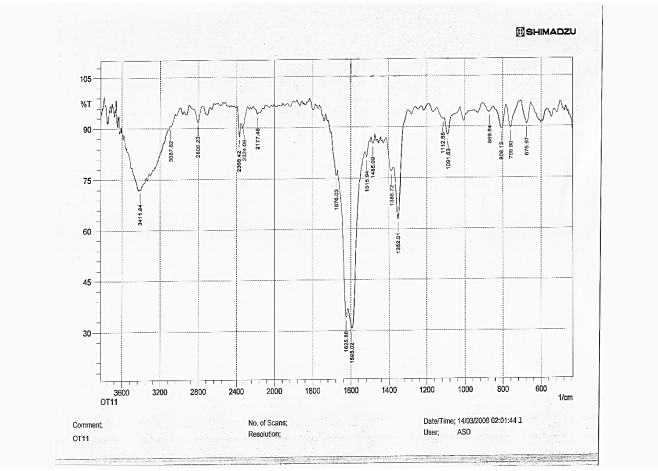

Figure 2: FT spectrum. IR of the compound A1

RESULTS

The effect of CCl_4 and pyrimidine derivatives (A1, A2, and A3) chemicals on the lipid profile of male rats was shown in Table 2. Levels of cholesterol, triglycerides, LDL-c, and of VLDL-c in male rats were lower in groups control (1.660.14, 5.11 ± 1.12, 3.51 ± 0.39, and 0.351 ± 0.010) than in the CCL_4 group (1.98 ± 0.63, 5.88 ± 1.02, 4.48 ± 1.17, and 0.396 ± 0.12), respectively, while HDL-c results in the control group were slightly higher (1.25 ± 0.22) than in the CCl_4 group (1.04 ± 0.12). Table 2 shows the results.

The comparison results among the control group and the CCl_4 groups with pyrimidines derivatives compounds (A1, A2, and A3) indicated that the CCl_4 group with A1 (1.89 ± 0.42, 5.60 ± 0.33, 4.14 ± 0.11, and 0.369 ± 0.08) had higher levels of triglycerides, cholesterol, LDL-c, and VLDL-c, while the CCl_4 group with A2 (1.87 ± 0.37, 5.77 ± 0.10, 4.31 ± 0.1, 1.25 ± 0.22), respectively (Table 2).

Table 3 shows the findings of the influence of CCl_4 and pyrimidines derivatives substances on activated liver enzymes in male rats. The results showed that the levels of alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl tansferase (GGT), and Globulin (g/dL) in the control group of male rats were lower (30.19 ± 0.10, 39.16 ± 1.5, 98.52, 28.79 ± 1.59, 2.08 ± 0.07) than those in the CCl_4 group (47.14 ± 0.14, 44.87 ± 1.20, 158.1 ± 1.8, 58.26 ± 1.17, 2.36 ± 0.28), whereas the albumin (g/dL) and Table 3 shows the results. The comparison of the control group with the CCl_4 groups with pyrimidines derivatives compounds (A2, A3, and A1) revealed that the control group had lower levels of ALT, AST, GGT, ALP, and Globulin (g/dL) than the CCl_4 group with A1. The results revealed that ALT (U/L), AST (U/L), Total protein (g/dL), and albumin (g/dL) were higher in the controls than in the CCl_4 group with A1 (27.22 ± 1.28, 34.53 ± 1.57, 6.24 ± 0.48, and 3.94 ± 0.38), respectively, while GGT (U/L), ALP (U/L), and Globulin (g/dL) were lower in the controls than in the CCl_4 group.

AST, GGT, ALP, total protein (g/dL), and globulin (g/dL) in the CCl_4 group with A2 were lower in the controls group than in the CCl_4 group with A2 (41.19 ± 1.12, 1364.5, 31.52 ± 1.33, and 6.39 ± 0.44), respectively, while ALT and albumin (g/dL) were higher in the controls group than in the CCl_4 group with A2 (29.79 ± 1.11, 3.65 ± 0.12). Finally, the findings revealed that the CCl_4 group with A3 had higher levels of ALT, AST, Total Protein (g/dL), and Albumin (g/dL) than the controls group (28.99 ± 0.34, 31.16 ± 1.5, 6.08 ± 0.19, and 3.28 ± 0.09). GGT, ALP, and Globulin (g/dL) levels in the control group were lower than in the CCl_4 groups, with A3 (1285.2, 37.71 ± 1.59, and 2.67 ± 0.07), respectively (Table 3).

Table 4 also included the results of antioxidant enzymes such Adult Muscular Dystrophy (MDA) (lipid peroxidation), GSH, CAT, GPx, and SOD, which were used to assess the influence on the liver function of male rats. The control group's MDA level (0.790.04) was lower than that of the CCl_4 group, CCl_4 group with A1, CCl_4 group with A2 group, and CCl_4 group with A3 group (1.56 ± 0.02, 1.06 ± 0.02, 1.41 ± 0.02, and 1.46 ± 0.02), respectively. The control group's GSH level (87 ± 1.13) was higher (51 ± 2.9, 62 ± 2.9, 65 ± 2.1) than that of the CCl_4 group, CCl_4 (Table 4). Furthermore, the control group's CAT (mmol/L) level (0.180.02) was greater than the CCl_4 group, CCl_4 group with A1, CCl_4 group with A2, and CCl_4 group with A3 (0.08 ± 0.01, 0.16 ± 0.05, 0.16 ± 0.06, and 0.16 ± 0.01), respectively. The results indicated that the control group's GpX (U/mg protein) level was higher than the GpX (U/mg protein) level. Finally, the findings showed that SOD levels in the control group (2.800.3) were greater than those in the CCl_4 group, CCl_4 group with A1, CCl_4 group with A2,

Table 2: The effects of carbon tetrachloride and derivatives of pyrimidines on the lipid profile of male rats

Groups Parameters	*Control group (mean ± SD)*	*CCl_4 group (mean ± SD)*	*CCl_4+ A1 group (mean ± SD)*	*CCl_4+ A2 group (mean ± SD)*	*CCl_4+A3 group (mean ± SD)*
TG(mmol/l)	1.66 ± 0.14	1.98 ± 0.63	1.89 ± 0.42	1.87 ± 0.37	1.74 ± 0.42
Cho (mmol/l)	5.11 ± 1.12	5.88 ± 1.02	5.50 ± 0.33	5.77 ± 0.10	5.60 ± 0.89
HDL-c(mmol/l)	1.25 ± 0.22	1.04 ± 0.12	1.17 ± 0.19	1.16 ± 0.12	1.14 ± 0.08
LDL-c(mmol/l)	3.51 ± 0.39	4.48 ± 1.17	4.14 ± 0.11	4.31 ± 0.10	4.11 ± 0.86
VLDL-c(mmol/l)	0.351 ± 0.10	0.396 ± 0.12	0.369 ± 0.08	0.354 ± 0.07	0.378 ± 0.08

Table 3: The effect of carbon tetrachloride and its derivatives on male rats' activated liver enzymes

Groups Parameters	*Control group (mean ± SD)*	*CCl_4 group (mean ± SD)*	*CCl_4+ A1 group (mean ± SD)*	*CCl_4+ A2 group (mean ± SD)*	*CCl_4+A3 group (mean ± SD)*
ALT (U/L)	30.19 ± 0.10	47.14 ± 0.14	27.22 ± 1.28	29.79 ± 1.11	28.99 ± 0.34
AST (U/L)	39.16 ± 1.5	44.87 ± 1.20	34.53 ± 1.57	41.19 ± 1.12	31.16 ± 1.5
GGT (U/L)	98 ± 5.2	158 ± 11.8	156 ± 3.4*	136 ± 4.5	128 ± 5.2
ALP (U/L)	28.79 ± 1.59	58.26 ± 1.17	34.39 ± 1.22	31.52 ± 1.31	37.71 ± 1.59
Total Protein ($_{g/dL}$)	6.08 ± 0.32	5.17 ± 0.51	6.24 ± 0.48	6.39 ± 0.44	6.08 ± 0.09
Albumin ($_{g/dL}$)	4.08 ± 0.09	2.90 ± 0.20	3.94 ± 0.38	3.65 ± 0.12	3.28 ± 0.09
Globulin ($_{g/dL}$)	2.08 ± 0.07	2.36 ± 0.28	2.86 ± 0.16	2.61 ± 0.15	2.67 ± 0.07

Table 4: The effect of carbon tetrachloride and derivatives of pyrimidines on antioxidant enzymes in male rats

Groups Parameters	*Control group (mean ± SD)*	*CCL_4 group (mean ± SD)*	*CCL_4+ A1 group (mean ± SD)*	*CCL_4+ A2 group (mean ± SD)*	*CCL_4+A3 group (mean ± SD)*
MDA (mM/100 g tissue)	0.69 ± 0.14	1.56 ± 0.02	1.06 ± 0.02	1.41 ± 0.02	1.46 ± 0.02
GSH (mM/100 g tissue)	87 ± 1.13	51 ± 2.9	89 ± 2.9	62 ± 2.9	65 ± 2.1
CAT (mmol/L)	0.18 ± 0.02	0.08 ± 0.01	0.16 ± 0.05	0.18 ± 0.06	0.16 ± 0.01
GpX (U/mg protein)	6.98 ± 0.47	3.75 ± 0.31	5.95 ± 0.37	5.71 ± 0.10	5.45 ± 0.11
SOD	2.80 ± 0.3	2.11 ± 0.2	2.52 ± 0.2	2.40 ± 0.1	2.84 ± 0.2

and CCl_4 group with A3 (2.11 ± 0.2, 2.52 ± 0.2, 2.40 ± 0.1, and 2.84 ± 0.2, respectively) (Table 4).

DISCUSSION

This study investigated the effects of pyrimidine derivatives on CCl_4- adult male rats subjected to hepatotoxicity. This problem also looks at the effects of the A1, A2, and A3 on the hepatic function and oxidation-emphasized markers (malondialdehyde levels and glutathione reductase activity in the liver). Pyrimidine derivatives (A1,A2, and A3) were found to have significant antioxidant action, perhaps protecting the liver from harm. Pyrimidine derivatives with various substituents such as Cl, Br, CF_3, and NO_2 improved lipid membrane penetration, resulting in higher antioxidant activity.[13] Mondal and colleagues synthesized 1-(2-mercapto-6-indoline-2-one and 1-(2-amino-6-(substituted phenyl)pyrimidine-4-yl)pyrimidine-4-yl)pyrimidine-4-yl)pyrimidine-4-yl)pyrimidine-4-yl)pyrimidine-4-yl)pyrimidine-4-yl)pyrimidine-4-yl)pyrimidine-4-y To produce -3-(2-substituted phenylimino) indolin-2-one, several substituted chalconised indole-2,3-diones were utilized. The substitution of SH and NH_2 groups in the pyrimidine ring's second position,[14] by scavenging nitric oxide radicals and scavenging hydrogen peroxide, Pyrimidines Derivatives have shown excellent antioxidant activity similar to that of ascorbic acid.[15] The current study's findings demonstrated an increase in serum of metabolic enzymes (ALT, AST, GGT, and ALP) activity along with a consequence of CCl_4 poisoning, which is consistent as for Wang *et al.,* for example, reported previous research, which found an increase in activated liver function markers as a result of toxication.[16] Scavengers of oxygen radicals (antioxidants and phytochemicals) have being suggested as a potential process of hepatoprotection.[17] Fraisse and his colleagues discovered that the periodically retreatment through pyrimidine derivatives to act as antioxidants could considerably reduce GPT, GOT, TC, and TG levels in mouse given alcohol.[18] In this investigation, the CCl_4-treated group saw significant alterations in plasma lipoprotein levels. high and low concentration of serum lipoproteins are associated to healthy hepatic functionality. Both density lipoproteins low and high are essential for the transit of lipoproteins. The hepatic tissue was affected via CCl_4 because it raised LDL, T.C, and T,G, whereas decreased High density lipoprotein. The results additionally demonstrated the impact of substances generated by pyrimidine derivatives (A1, A2, and A3) on lipidemic in the study groups. Many epidemiological studies demonstrate that consuming a diet high in natural foods high in antioxidants like pyrimidines increases the oxidative inhibitor capacity of the body and reduces the risk of several diseases. pyrimidine chemical therapy or getting more popular dietary supplements increases to avoid or treat increases of lipid in blood, especially in those with borderline concentration of serum cholesterol.[19] According to others, This might be related to its ability to survive oxidative stress by eliminating free radicals created by the HFD in the body. When contrasted to pyrimidines derivatives, the amount of total polyphenols in the pyrimidines derivatives a tincture that has been examined might be linked to antioxidative properties, as there showed considerably significant levels.[20] According to Olorunnisola *et al.,* pyrimidines in conjunction with flavonoids enhanced liver

function test results and decreased liver injury.[21] Furthermore, Saleh *et al.* observed that phenolics and sesquiterpenes, which might also prevent hepatic against injury, may reduce transaminase enzyme levels in the blood.[22] One mechanism for protection against pyrimidines derivatives-induced liver damage might be the components of A1, A2, and A3 acting as free radical scavengers and intercepting those free radicals.[23]

Ramesh and his colleagues discovered that phenolic compounds in the diet can lower the risk of cardiovascular disease by reducing LDL oxidation. Pyrimidines are a polyphenolic molecule with antioxidant capabilities that appear to restrict the formation of reactive oxygen and nitrogen species while also sustaining the antioxidant defense system. Pyrimidines may also aid liver cells in more efficiently removing LDL from the circulation.[24]

Pyrimidine derivatives do this through elevation a number of receptors of low density L in the liver and apolipoprotein B binding.[25] These findings suggest that phenolic chemicals might be the cause of these reactions. A lowering in the solubilization of cholesterol micellars in the digestive system, an elevated flow of bile, and bile cholesterol concentrations, and fecal steroid excretion all lead to a decrease in cholesterol.[26] According to current research, pyrimidine derivatives had the best antioxidant effect opposing oxidation of low density Lipoprotein and hyperlipidemia. Secondary metabolites like phenolic compounds have a wide range of biologic functions, involving antioxidants, improved endothelial function, anti-atherosclerosis, and cardiovascular protection.

The antioxidant action of phenolics is due mostly to their redox properties, which enable them to serve as reduction agents or solubilizing and neutralizing reactive free radicals. hydrogen donors are significant in the catalysis peroxidation of lipids also have been considered as a possible treatment for relating to free radicals diseases.[27] In the CCl_4 group, catalase, glutathione, and superoxide dismutase (SOD) levels, in addition to GSH-Px, were considerably lower than in the controls, although MDA levels increased. When the GSH, SOD, GSH-Px, and CAT levels in the CCl_4 group were compared to the catalase, glutathione, and superoxide dismutase (SOD), and GSH-Px, levels in the CCl_4 with pyrimidines derivatives compounds (A1, A2, and A3) group, it was discovered that catalase, glutathione, and superoxide dismutase (SOD), and GSH-Px levels were greater while MDA levels were lower.

The considerable decline MDA in plasma and rise in the levels of antioxidant enzymes in rats with hyperlipidemia, Withstanding their ability to rebound to near-normal levels after therapy, revealed pyrimidines derivatives' effective antioxidant properties. Cells are protected from reactive oxygen species stress by antioxidants through interrupting the antioxidant chain, that inhibits the spread of free radicals. Increased lipid and protein alterations, as well as immediate, lowers in both enzyme-mediated and non-enzymatic antioxidants, were discovered to be caused by the ethanol diet. Surprisingly, after eating pyrimidines derivatives such as A1, A2 and A3, partially restored enzyme functionality and concentrations of non-enzymatic antioxidant properties, and also fat and protein byproducts.[30]

CONCLUSION

In the current investigation, pyrimidines derivatives were shown to play a critical role in inhibiting CCl_4's harmful effects. pyrimidines derivatives may boost antioxidative enzymes and accelerate or diminish lipid peroxidation. pyrimidines derivatives have a significant hepatoprotective impact, and antioxidant activity, according to the present data. Active ingredients in pyrimidines derivatives might be used to treat a range of acute liver ailments in the future.

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