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Influence of partially hydrogenated pyridines (derivatives of cyanothioacetamide) on blood indicators of rats with acute tetrachloromethane hepatitis

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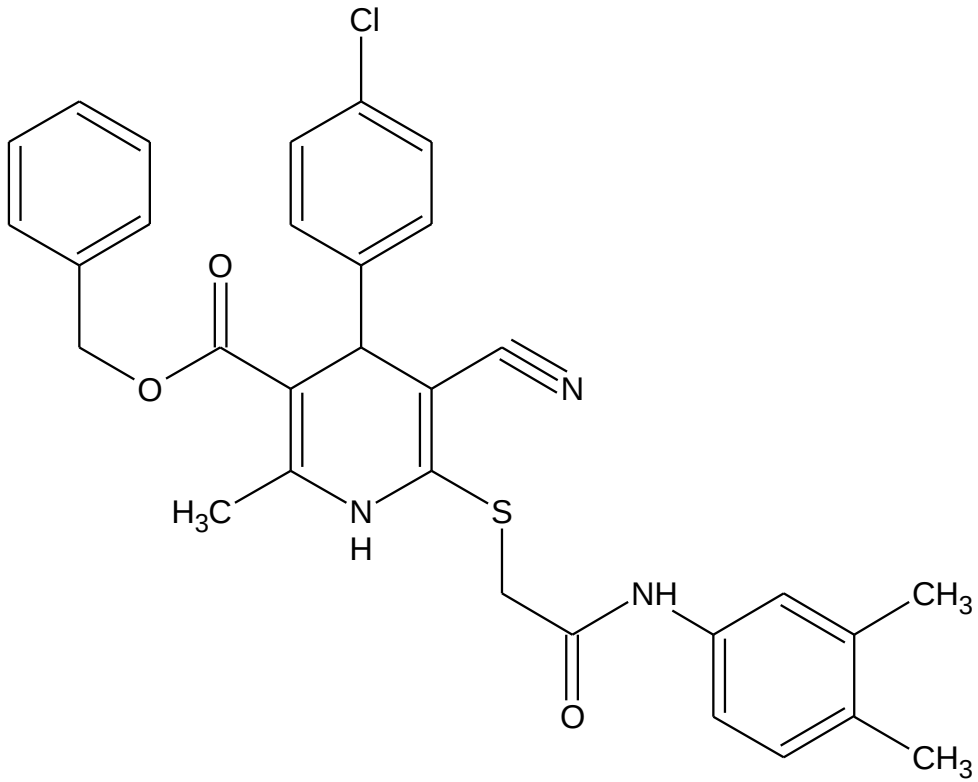
Constitutional formula of substance CV146. This substance showed antitoxic and hepatoprotective activity in an acute toxic tetrachloromethane hepatitis model.

CV146



Abstract:

Currently, a focused search for new and safe hepatoprotective agents is highly relevant. An experimental study was conducted on 80 male rats after intragastric infiltration of carbon tetrachloride (CCl_4) in a 50% solution of refined sunflower oil intragastrically once a day at a dose of 4 ml/kg for 3 days. Screening researches of six partially hydrogenated pyridines, derivatives of cyanothioacetamide, on a model of acute tetracycline hepatitis at a dose of 5 mg/kg showed a high hepatoprotective and detoxifying activity in all compounds. They stabilize the level of biochemical blood parameters, keeping them at the normal level in terms of hepatotoxicity induced by the use of high dosages of CCl_4 in vivo. A compound CV146 (benzyl 4- (4-chlorophenyl) -5-cyano-6 - ({2 - [(3,4-dimethylphenyl) amino] -2-oxoethyl} thio) -2-methyl-1,4-dihydropyridine -3-carboxylate) should be considered as an perspective in terms of further preclinical studies in order to find new highly effective and safe agents for the pharmacocorrection of acute toxic liver damages.

Keywords: Hepatoprotective agents, carbon tetrachloride, hydrogenated pyridines, cyanothioacetamide

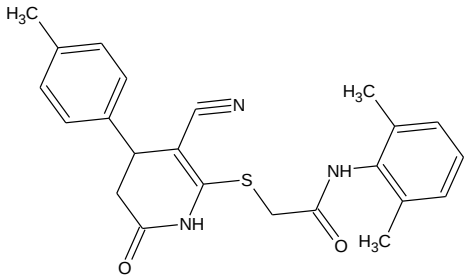
Introduction

50 new derivatives of partially hydrogenated pyridines synthesized in NIL “Chemex” of LNU named Vladimir Dahl were subjected to virtual bioscreening. That made it possible to select 6 compounds whose biological activity may be associated with an effect on the protein synthesizing and detoxifying liver functions. The aim of the study was to screen new partially hydrogenated pyridines, derivatives of cyanothioacetamide, with potential antitoxic and hepatoprotective activity in an acute toxic tetrachloromethane hepatitis model.

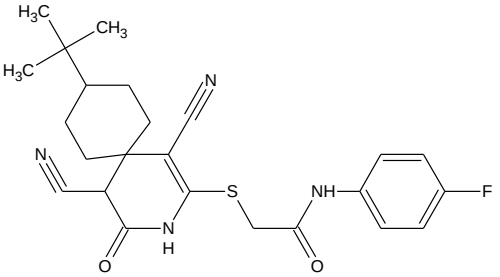
Materials and methods

The present pharmacological studies were carried out on 80 white mature male rats weighing 170-240 g in the autumn period at the certified pharmacological laboratory of GI of the Lugansk People's Republic "Lugansk State Medical University named after St. Luke. An experimental model of acute toxic liver damage was the pathological process that develops in animals after the introduction of carbon tetrachloride (CCl4) in a 50% solution of refined sunflower oil intragastrically once a day at a dose of 4 ml/kg for 3 days. For research, we used substituted di- and tetrahydropyridines with the codes CV042, CV043, CV046, CV047, CV080, CV146

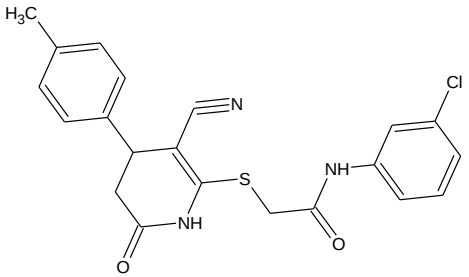
CV146



CV047



CV043



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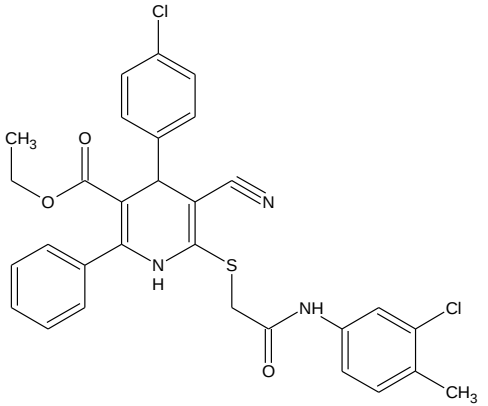

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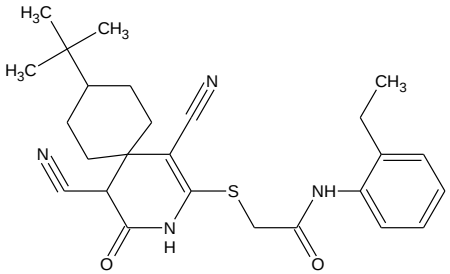
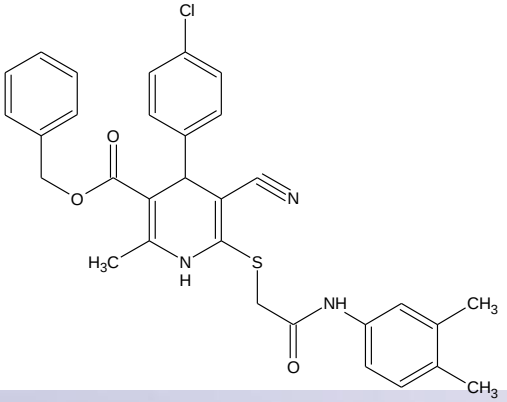


CV042



Results and discussion

• The level of total bilirubin in the biochemical analysis of blood of rats in the control group significantly ($p < 0.03$) increases by 3.37 times compared with indicators recorded in experimental animals of the intact group.

• the activity of liver enzymes – ALT by 169,8% and AST by 221,6%

• alkaline phosphatase at rats of the control group is 167% higher than that registered in animals of the intact group.

Results and discussion

• Comparison rats treated with carlsil for prophylactic and pharmacotherapeutic purposes showed a 2.11-fold decrease in bilirubin compared with animals in the control group, but this indicator was 1.6 times greater than in intact rats.
• A similar results were observed with respect to ALT. The activity indicators of alkaline phosphatase and AST at rats of the comparison group are close to the values recorded at animals of the intact group.

Results and discussion

• The significant differences with the indices in the control group according to the level of bilirubin. were found at animals of the experimental groups treated with samples CV043 and CV042. ALT activity is reduced by 25.5% and 30.9%, respectively, in comparison with the indicators in the control group. The AST values at the rat blood of experimental groups have no significant differences compared with those in intact animals. The activity of alkaline phosphatase at the blood of rats with an acute tetrachloromethane hepatitis, treated with CV043 and CV042 are at the level of intact values.

Results and discussion

• Comparing the values of the total bilirubin in the blood of rats with simulated toxic hepatitis and pharmacocorrection compound CV146 with those in intact animals, a decrease of 25.6% is seen. The activity of transaminases in the blood of rats of this experimental group was reduced by 25.5% (ALT) and 39.2% (AST) compared with the control group. Alkaline phosphatase activity was at the level recorded in the group of intact animals.

Results and discussion

• When comparing the level of total bilirubin in the biochemical analysis of blood of rats treated with CV047 with the parameters of the control group, the maximum decrease in this indicator (by 7.56 times) is noted. In this experimental group of rats, ALT transaminase activity is high, exceeding that in rats of the control group.

Conclusions

The conducted researches of the hepatoprotective and detoxifying properties of 6 partially hydrogenated pyridines, derivatives of cyanothioacetamide at a dose of 5 mg / kg on a model of acute tetrachloromethane hepatitis, determined the presence of these properties in the five studied samples. A compound CV146 (benzyl 4- (4-chlorophenyl) -5-cyano-6 - ({2 - [(3,4-dimethylphenyl) amino] -2-oxoethyl} thio) -2-methyl-1,4-dihydropyridine -3-carboxylate) should be considered as an perspective in terms of further preclinical studies in order to find new highly effective and safe agents for the pharmacocorrection of acute toxic liver damages.