Hepatoprotective effect of the N-alkylated isobornylamine on CCl_4 - induced liver injury in mice

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Introduction

Type 2 diabetes (T2D) is known to be closely associated with the development of non-alcoholic fatty liver disease (NAFLD). Therefore, it is necessary to improve liver condition concomitant to blood glucose level reduction. Previously, N-alkylated isobornylamine (compound **1**) at a dose of 30 mg/kg in C57Bl/6^{Ay} mice (impaired glucose tolerance mice) was shown to resolve of fatty liver degeneration improving glucose tolerance. In this work, we carried out a study of the hepatoprotective effect of the compound **1** on CCl4 - induced hepatotoxicity in mice.

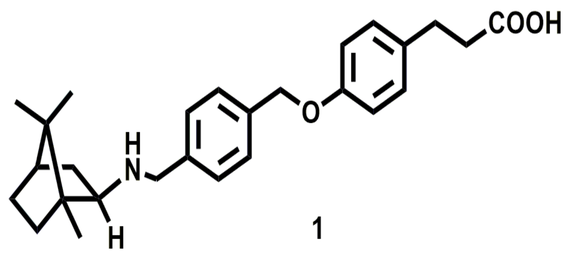

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Figure 1. N-alkylated isobornylamine

Materials & methods

Animals: male CD-1 mice weighting 25-30 g.

Experimental method

Animals of groups № 1-4 received *per os* the following compounds daily for 3 weeks:

№	Injected compound
1 (intact control)	Distilled water + Tween 80
2 (negative control)	Distilled water + Tween 80
3	Compound **1** 30 mg/kg
4	Compound **1** 60 mg/kg

Groups 2-4 were injected with a 0.5% solution of CCl_4 in oil twice a week one hour after the test compounds. Instead of water, groups 2-4 received a 5% solution of ethyl alcohol for 3 weeks.

Results

Blood biochemical parameters in treated CD-1 mice at the end of the experiment

	TC, g/L	ALT (U/l)	AST (U/l)	ALP (U/l)
Intact control	61.78 ± 2.25	65.29 ± 3.32	243.29 ± 29.40	108 ± 7.98
Negative control	52.77 ± 1.72*	73.29 ± 4.06	287.33 ± 71.09	144.88 ± 8.26*
Compound 1 30 mg/kg	51.24 ± 1.34*	100 ± 5.55 *#	582.4 ± 33.67 *#	134 ± 8.61*
Compound 1 60 mg/kg	58.27 ± 1.41#	93.67 ± 5.79 *#	470.16 ± 148.59	195 ± 21.06 *#

Table 1. *p ≤ 0.05 as compared to Intact control, #p < 0.05 as compared to Negative control. TC: total cholesterol, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase.

*At the end of experiment, a biochemical blood assay was carried out, which showed that the compound **1** at both doses increased in ALT, AST and ALP. However, total protein concentration was increased indicating a preservation of the synthetic liver function.*

Histological examination

Histological examination of the liver of an untreated CD-1 mice

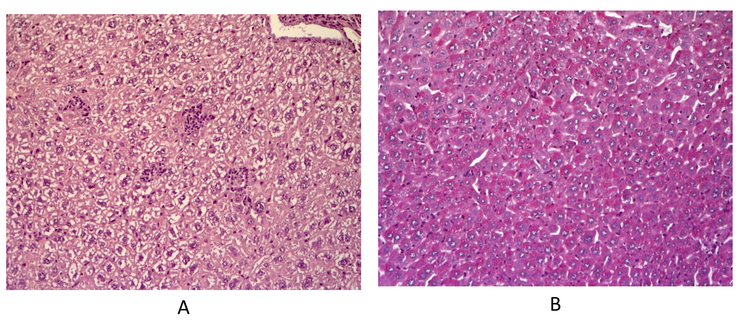

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Figure 2. ***A.*** Intact animal liver. The liver architectonics was preserved, the bile capillaries, veins and arteries had a typical structure. Small focal necrosis of hepatocytes. Staining with hematoxylin and eosin, magnification ×200. ***B.*** Intact animal liver. Hepatocytic glycogen in the form of dusty granularity. Staining: periodic acid-Schiff, hematoxylin, and orange G; magnification ×100.

Histological examination of the liver of CD-1 mice treated with a only 0.5% solution CCl4

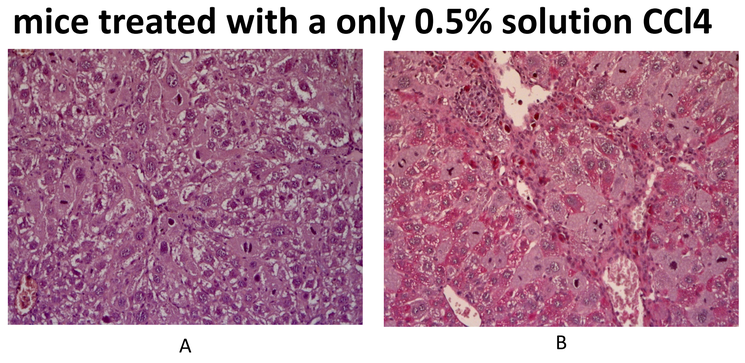

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Figure 3. ***A.*** Negative control liver. Revealed signs of chronic toxic liver damage. Hydropic and balloon dystrophy of hepatocytes, their nuclear and cellular polymorphism. Staining with hematoxylin and eosin, magnification ×200. ***B.*** Negative control liver. Mixed fibrosis, hemosiderosis, nuclear polymorphism of hepatocytes. Mitoses in hepatocytes, lack of glycogen. Staining: periodic acid-Schiff, hematoxylin, and orange G; magnification ×200.

Histological examination of the liver of CD-1 mice treated with a compound 1 at a dose of 30 mg/kg

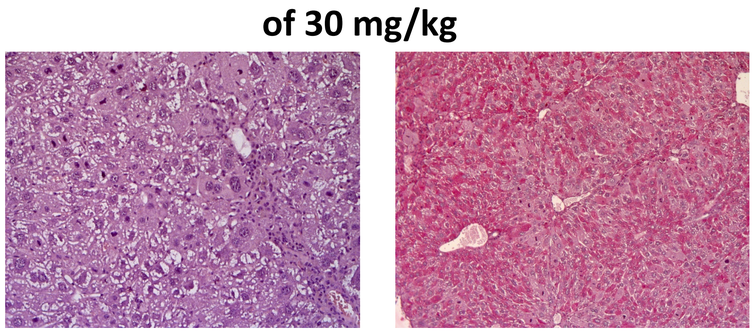

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Figure 4. ***A.*** Mouse liver after treatment of a 0.5% solution CCl4 and compound **1** 30 mg/kg. A slight decrease of degenerative-necrotic changes in hepatocytes. Hydropic and balloon dystrophy of hepatocytes, their nuclear and cellular polymorphism, mixed fibrosis. Staining with hematoxylin and eosin, magnification ×200. ***B.*** Mouse liver after treatment of a 0.5% solution CCl4 and compound **1** 30 mg/kg. Mixed fibrosis, hepatocytic polymorphism, the appearance of glycogen. Staining: periodic acid-Schiff, hematoxylin, and orange G; magnification ×200.

Histological examination of the liver of CD-1 mice treated with a compound 1 at a dose of 60 mg/kg

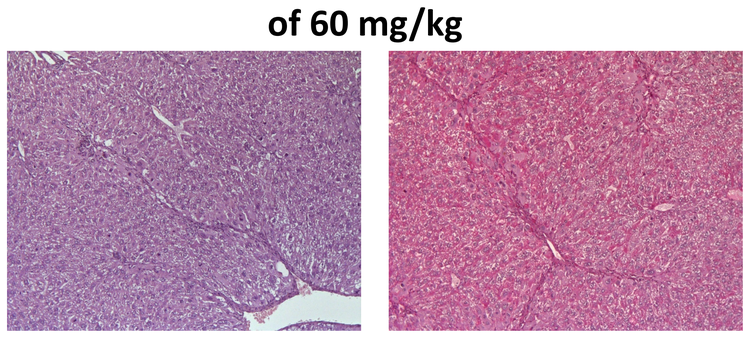

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Figure 5. ***A.*** Mouse liver after treatment of a 0.5% solution CCl4 and compound **1** 60 mg/kg. A decrease of degenerative-necrotic changes in hepatocytes. Hepatocytic polymorphism is less pronounced, the appearance of glycogen. Staining with hematoxylin and eosin, magnification ×200. ***B.*** Mouse liver after treatment of a 0.5% solution CCl4 and compound **1** 60 mg/kg. Mixed fibrosis, the appearance of glycogen. Staining: periodic acid-Schiff, hematoxylin, and orange G; magnification ×200.

*According to the results of histological liver examination, administration of the compound **1** at doses of 30 and 60 mg/kg was found to reduce the severity of degenerative-necrotic changes in hepatocytes, while the changes at a dose of 60 mg/kg were more significant. There was a less significant polymorphism of hepatocytes and appearance of glycogen at a dose of 60 mg/kg, which may be evidence of an increased liver regeneration.*

Conclusion

These results indicate that N-alkylated isobornylamine exhibit a hepatoprotective effect not only in metabolic liver injury, but also in CCl_4 - induced liver damage.

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