Synthesis, hepatoprotective and radical-scavenging properties of novel hydrazone derivatives of the N,N'-disubstituted benzimidazole-2-thione containing chloro and methyl moieties

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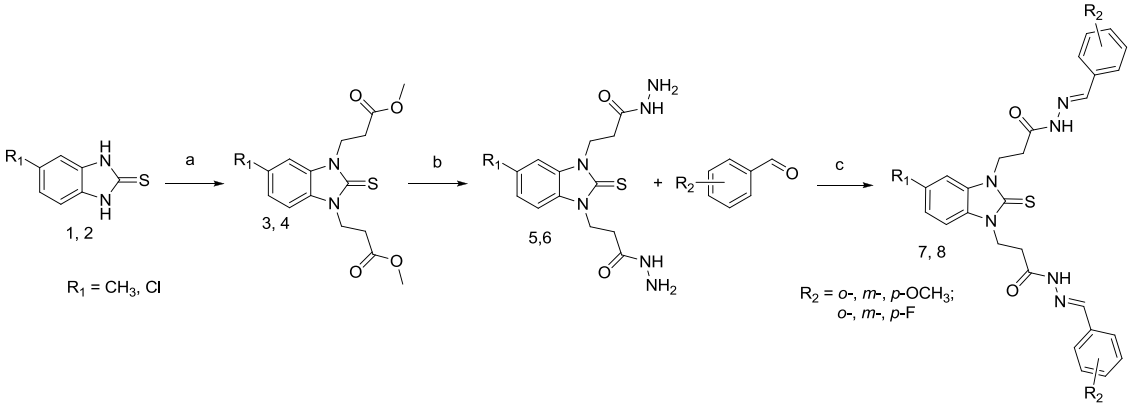
Abstract

Redox imbalance in liver is the cause for numerous liver disorders: alcoholic and nonalcoholic fatty liver disease, hepatic encephalopathy, liver fibroproliferative diseases and hepatitis C [1, 2]. The application of antioxidants is a good therapeutic strategy to prevent and cure such conditions. Our recently studies on the cytoprotective effects of ester and hydrazide derivatives of benzimidazole-2-thione on tBuOOH-induced oxidative stress in rat hepatocytes showed promising results and motivated us to design and synthesize new modified derivatives of benzimidazole-2-thione continuing in order to improve further their hepatoprotective capacity. 3,3'-(2-thioxo-1H-benzo[d]imidazole-1,3(2H)-diyl)bis(N'-substituted-methoxybenzylidene)propanehydrazides and 3,3'-(5-benzoyl-2-thioxo-1H-benzo[d]imidazole-1,3(2H)-diyl)bis(N'-substituted-methoxybenzylidene)propane-hydrazides have been synthesized and showed cytoprotective and antioxidant effects superior to those of the ester and hydrazide derivatives. Herein we report a series of novel hydrazine derivatives of the benzimidazole-2-thione synthesized as analogues of the famous antioxidant melatonin in the search of hepatoprotectors with antioxidant action. The novel derivatives have methyl and chloro substituents at position 5 of the benzimidazole ring.



The chloro derivatives exhibited the highest toxicological potential compared to the previously reported unsubstituted and benzoyl substituted benzimidazole-2-thiones. The methyl substituted benzimidaozle-2-thiones are amongst one of the least toxic hydrazones and were further subjected to inhibition of tert-butyl hydroperoxide (tert-BOOH)-dependent lipid peroxidation in induced oxidative stress. They preserved the cell viability and GSH level of isolated rad hepatocytes and decrease LDH leakage and MDA production similar to the reference compound Quercetin. which could be due to their radical scavenging properties. This assumption was confirmed with DFT analysis and the most probable mechanism of action was established.

Key words: antioxidants, benzimidazoles, lipid peroxidation, hepatoprotectors

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