ABSTRACT

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Carbonyl reductases are enzymes participating in metabolic pathways of various eobiotics and xenobiotics. Of all known enzymes metabolizing xenobiotics only 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) is found in the microsomal membrane. It also contributes to metabolism of prochiral anticancer drug oracin, which main metabolic pathway is a carbonyl reduction on the position 11 leading to two enantiomers of (+) an (-) 11-dihydrooracin (DHO). Based on the discrepancy between microsomes and 11β-HSD1 stereospecifity of oracin reduction exist a hypothesis of participation an unknown microsomal enzyme in oracin metabolism. The aim of this study is to purify a new microsomal carbonyl reducing enzyme contributing in the biotransformation of oracin.

Human liver microsomes were solubilised and desalted. The prepared sample was used for the first purification step on Q-Sepharose. Captured flow through fraction Q2 was loaded on Phenyl-sepharose. Captured suitable fraction P11 was used for third purification step by gel filtration. All fractions acquired during purification procedure were tested for oracin reducing activity, stereospecifity of the reduction and protein concentration. It was obtained a fraction that reduces oracin with anticipated preferential formation of (+)-DHO about 80%.

It is clear that the significantly purified fraction contains a new microsomal carbonyl reductase that participates in biotransformation of oracin differing from 11β-HSD1. Therefore it is probable that the enzyme will participate in metabolism of similar drugs (e.g. doxorubicin, daunorubicin) and it is necessary to identify it.