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[Lab. of Biochemistry]

Reduction of Drug Ketones by Dihydrodiol Dehydrogenases, Carbonyl Reductase and Aldehyde Reductase of Human Liver.

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We compared the enzymatic reduction of 10 drugs with a ketone group by homogeneous carbonyl reductase, aldehyde reductase and three dihydrodiol dehydrogenases. At least one and in some cases all of the three dihydrodiol dehydrogenases reduced each of the ten drugs. Among these naloxone, naltrexone, buprenorphine, ethacrynic acid and ketoprofen were substrates specific for the dehydrogenases. The dihydrodiol dehydrogenases also showed lower K_m values for haloperidol and loxoprofen than did carbonyl reductase. The results indicate that the three dihydrodiol dehydrogenases are implicated in the reduction of ketone-containing drugs in human liver cytosol.

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[Lab. of Biochemistry]

Inhibition of Oral Carcinogenesis by the Arotinoid Mofarotene (Ro 40-8757) in Male F344 Rats.

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The chemopreventive effect of dietary administration of a new arotinoid, mofarotene (Ro 40-8757), which contains a morpholine structure in the polar end group, during the initiation phase of 4-nitroquinoline 1-oxide-induced oral carcinogenesis was investigated in male F344 rats. Feeding of Ro 40-8757 caused a 78 % reduction in incidence of tongue neoplasms. Similarly, expression of three biomarkers (polyamine levels, the 5-bromodeoxyuridine-labeling index and the number of AgNORs) was also decreased significantly by dietary treatment with Ro 40-8757. These results might suggest the possible application of Ro 40-8757 for cancer chemoprevention in the oral cavity.

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**Expression and Kinetic Properties of a Recombinant 3 α -Hydroxysteroid/
Dihydrodiol Dehydrogenase Isoenzyme of Human Liver.**

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Human liver cytosol contains multiple forms of 3 α -hydroxysteroid dehydrogenase with dihydrodiol dehydrogenase activity, and multiple cDNAs for the enzymes have been cloned from human liver cDNA libraries. The recombinant enzyme derived from a cDNA encoding an isoenzyme or DD4 showed structural and functional properties almost identical to those of native DD4. The steady-state kinetic data for NADP⁺-linked (S)-1-indanol oxidation by the recombinant enzyme was consistent with a sequential ordered mechanism in which NADP⁺ binds first. Phenolphthalein inhibited this enzyme much more potently than it did the other human liver dihydrodiol dehydrogenases.