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Selective Irreversible Inhibitors of Aldose Reductase.

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A series of 5-substituted-1,3-dioxo-1H-benz[de]isoquinoline-2(3H)-acetic acid analogues have been examined as irreversible inhibitors of aldose reductase. The 5-α-bromoacetamide and 5-α-iodoacetamide analogues 5 and 6 gave irreversible inhibition of aldose reductase while the 5-α-chloroacetamide analogue 3 did not show this type of inhibition. Protection studies indicate that irreversible inhibitions are occurring at the inhibitor binding site. Comparative irreversible inhibition studies with rat lens aldose reductase and rat kidney aldehyde reductase indicate that 5-α-haloacetamide analogues 5 and 6 are much more effective inhibitors of rat lens aldose reductase.

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Chemical Modification of Cysteinyl, Lysyl and Histidyl Residues of Mouse Liver 17β-Hydroxysteroid Dehydrogenase.

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Monomeric 17β-hydroxysteroid dehydrogenase from mouse liver was rapidly inactivated by 5,5'-dithiobis (2-nitrobenzoic acid) and 2,4,6-trinitrobenzene-1-sulfonate. The inactivation by the two reagents was protected by $NADP^+$ but not by a steroid substrate. Chemical modification by diethyl pyrocarbonate also produced a pseudo-first-order kinetic inactivation of the enzyme, and the inactivation was completely protected in the presence of both the coenzyme and substrate. The results suggest the presence of essential cysteine and lysine residues at or near the coenzyme-binding site and that of essential histidine residue(s) in the catalytic region of the active site.

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Modification of Pig Liver Dimeric Dihydrodiol Dehydrogenase with Diethylpyrocarbonate and by Rose Bengal-Sensitized Photooxidation-Evidence for an Active-Site Histidine Residue.

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Pig liver dihydrodiol dehydrogenase was inactivated by diethylpyrocarbonate and by rose bengal-sensitized photooxidation. The kinetics of inactivation of the modified residues suggested that complete inactivation was caused by modification of one histidine residue per active site. The inactivation was partially prevented by NADP (H) and completely prevented in the presence of both $NADP^+$ and a competitive inhibitor. The results suggest the presence of essential histidine residues in the catalytic region of the active site of pig liver dihydrodiol dehydrogenase.