LTB_4 12-hydroxydehydrogenase/15-oxo-PG 13-reductase and Indomethacin Complex

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The bi-functional leukotriene B_4 12-hydroxydehydrogenase/15-oxo-prostaglandin 13-reductase (LTB_4 12-HD/PGR) is essential for eicosanoid inactivation. It catalyzes the first irreversible reactions in each eicosanoid inactivation and the activity may be regulated by a protein with SH3 domain. LTB_4 is oxidized to 12-oxo-LTB_4, and 15-oxo-PGE_2 are reduced to 13,14-dihydro 15-oxo-PGE_2. Some none steroidal anti-inflammatory drugs inhibit LTB_4 12-HD/PGR activity. Here we report the structure of LTB_4 12-HD/PGR with $NADP^+$ and indomethacin. The indomethacin binds to the 15-oxo-PGE_2 binding site, indicating that the indomethacin competitively inhibits LTB_4 12-HD/PGR. The chloro-benzene moiety of indomethacin enters into the hydrophobic pore that is the recognition site of ω-chain of 15-oxo-PGE_2, and the carboxyl group of indomethacin interacts with Arg56 and Tyr262. The architecture is identical to those of indomethacin and cyclooxygenase complexes. The result may be useful for further development of cyclooxygenase inhibitor.

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