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α-Methylacyl-CoA racemase (AMACR): Chemical biology approaches to novel prostate cancer drugs

Matthew D Lloyd
University of Bath, UK

α-Methylacyl-CoA racemase (AMACR; P504S) catalyses a key step in the degradation of branched-chain fatty acids and is important for the pharmacological activation of Ibuprofen and related drugs. Over-expression of AMACR correlates with tumorigenesis of many cancer types, including prostate cancer. Therefore, inhibition of AMACR is a promising chemotherapeutic strategy. Development of AMACR as a drug target has been hampered by the lack of a convenient biochemical assay for enzymatic activity, and therefore few inhibitors have been identified to date. We have developed a new, continuous colorimetric assay based on the elimination of 2,4-dinitrophenolate from a novel acyl-CoA substrate. Our fully developed enzyme assay can be performed in a high-throughput screening format using a microtitre plate. Our assay has been used to determine the kinetic parameters for the substrate, determine IC_{50} and K_i values for known inhibitors, reversibility of inhibition, and characterise irreversible inhibitors. IC_{50} values for ~30 known substrates and inhibitors were determined to reveal the first structure-activity relationship study against AMACR in which potency was related to the lipophilicity of the acyl-CoA side-chain. The most potent inhibitor was *N*-dodecyl-*N*-methylcarbamoyl-CoA (IC_{50} vs. AMACR = 400 pM). High-throughput screening and IC50 determination of drug-like molecule libraries identified several new classes of inhibitors of AMACR. Our colorimetric assay now allows for screening and rational drug design approaches and full characterization of AMACR inhibitors as new agents against prostate cancer.

Biography

Matthew D Lloyd graduated with a DPhil from Oxford on clavulanic acid biosynthesis. Following Post-Doctoral Research at Brown University, USA and Oxford, he took up a Lectureship at the University of Bath in 2002. He is currently a Senior Lecturer (Associate Professor) in Pharmacy & Pharmacology. His research interests include prostate cancer, chemical biology, lipid metabolism, enzymes and inhibitors as drugs. He has published >70 research papers and is an Editorial Board Member of *The Journal of Enzyme Inhibition and Medicinal Chemistry and The World Journal of Biological Chemistry*.

M.D.Lloyd@bath.ac.uk

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