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High-throughput screening to identify novel inhibitors of human α-methylacyl-CoA racemase 1A (AMACR; P504S)

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α-Methylacyl-CoA racemase (AMACR; P504S) catalyzes a key step in the degradation of branched-chain fatty acids and is important for the pharmacological activation of Ibuprofen and related drugs. Both the concentration and activity of AMACR are increased in prostate and other cancer cells, and the enzyme is a recognized drug target. However, all the reported inhibitors are acyl-CoA esters (which do not comply with Lipinski guidelines) or non-specific protein modifying agents. Libraries of ~20,000 drug-like compounds were screened using a novel colorimetric assay; Incubation of *R*, *S*-2-3-(2,4-dinitrophenoxy)-2-methylpropanoyl-CoA with active AMACR resulted in the elimination of the strongly yellow 2,4-dinitrophenoxide and allows continuous measurement of activity in a microtiter plate format. Inhibitors were identified by a reduction in the rate of reaction in the presence of the library compound vs. the control. Several novel reversible inhibitors were identified and their potency determined using dose-response curves. The results demonstrate the utility of the assay for the discovery and characterization of AMACR inhibitors as anti-cancer agents.

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.*

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