Chiral inversion of NSAID-CoA esters by human α-methylacyl-CoA racemase 1A

T. J. Woodman, P. J. Wood, A. S. Thompson, T. Hutchings, P. Jiao, G. R. Steel, M. D. Threadgill, **M. D. Lloyd**

Medicinal Chemistry, Department of Pharmacy & Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, United Kingdom; M.D.Lloyd@bath.ac.uk

Ibuprofen and other 2-arylpropanoic acids (2-APAs) are non-steroidal anti-inflammatory drugs (NSAIDs) and the 2*S*- enantiomers act by inhibition of cyclo-oxygenase 1 and 2 (COX-1 and -2). 2-APA drugs are given as racemic mixtures and chiral inversion is essential for pharmacological activity. This pathway for 2*R*-ibuprofen consists of conversion to the 2*R*-acyl-CoA ester, chiral inversion to the 2*S*-epimer, and hydrolysis to 2*S*-ibuprofen. The chiral inversion reaction is catalysed by α-methylacyl-CoA racemase (AMACR; P504S). AMACR is increased ~10-fold in prostate and other cancers, and is a novel cancer drug target. Other 2-APAs undergo chiral inversion *in vivo*, but it is unclear if AMACR is involved.

The present study investigates whether AMACR catalyses chiral inversion of other 2-APA-CoA esters. Substrates were incubated with human AMACR 1A in $^{2}H_{2}O$-containing buffer and all exchanged the 2-proton, an obligatory step for chiral inversion. Derivatization of products from chiral substrates showed a *ca.* 1:1 epimeric mixture of products, consistent with the proposed deprotonation/reprotonation mechanism. Steady state kinetic analysis showed that most substrates were converted with similar efficiency (k_{cat}/K_m = 100-150 M^{-1} s^{-1}). Fenoprofenoyl-CoA was converted much more efficiently (k_{cat}/K_m = ~1426 M^{-1} s^{-1}), due to its low K_m value (~2.3 μM *cf.* 26-74 μM).

The results suggest that all 2-APA drugs undergo the same chiral inversion pathway. 2-APAs may be useful for treatment of cancers with increased AMACR levels.

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