Thiolactomycin is an inhibitor of type II dissociable fatty acid synthases from plants and bacteria [1]. The three β-ketoacyl acyl carrier protein (ACP) synthases in peas are all inhibited by thiolactomycin [2]. Condensing enzyme II (KAS II), which catalyses the elongation of palmitoyl-ACP to stearoyl-ACP is the most sensitive and the short chain condensing enzyme (KAS III), which catalyses the initial condensation of acetyl-CoA with malonyl-ACP, the least sensitive [2]. There is some evidence that acetyl-CoA: ACP transacylase activity is also inhibited but the other enzymes of fatty acid synthesis appear to be unaffected [2, 3].

Table 1 shows that several of the analogues produce greater inhibition of fatty acid synthesis than thiolactomycin itself. Thiolactomycin has a polar head group and a 5 carbon hydrophobic side chain (see legend to Table 1). Apart from analogue 7, which contains a nitrile group and gave rather inconsistent results, the most effective analogue structures are 5 and 6, both of which are more hydrophobic than thiolactomycin. Analogue 4 which is a straight-chain hydrocarbon but less hydrophobic than thiolactomycin itself, appears to give an inhibition, though not so much as thiolactomycin. The shorter side chain of analogue 2 and the epoxy side-group of analogue 3 produced no inhibition at all. Hydrophobicity and length of the side chain therefore appear to affect the inhibitory action. These results are interesting as the fatty acid synthase inhibitor cerulenin has an 8 carbon hydrophobic side chain. However, the condensing enzymes have different susceptibilities to cerulenin compared with their susceptibility to thiolactomycin, KAS I is irreversibly inhibited by covalent binding of cerulenin to the active site cysteine at 10μM cerulenin [5, 6]. KAS II is less susceptible [7] and KAS III unaffected by cerulenin [3]. Cerulenin is also an irreversible inhibitor of multifunctional fatty acid synthases which are insensitive to thiolactomycin [6]. The action of thiolactomycin appears to be reversible [7] and it has been suggested to be a competitive inhibitor with respect to malonyl-ACP.

Thiolactomycin produces a distinct change in the pattern of fatty acids labelled from [1-14C]acetate by chloroplasts, giving an increase in the proportion of labelling of short-chain fatty acids [Jones and Harwood, unpublished data]. There is some indication that the inhibitory analogues also have this effect, implying that they too inhibit KAS II more than KAS I and both to a greater degree than KAS III. The analogues that produced no inhibition did not change the labelling of fatty acids. In some cases analogues that inhibited at one concentration actually appeared to produce increases in lipid labelling at lower concentrations - this occurred with analogues 6 and 7.

We are also using molecular modelling software to model thiolactomycin, cerulenin and the analogues to see if this yields any interesting comparisons which will explain the mechanism of condensing enzyme inhibition.

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