Crystallographic Studies on Acyl Ureas, a New Class of Inhibitors of Glycogen Phosphorylase

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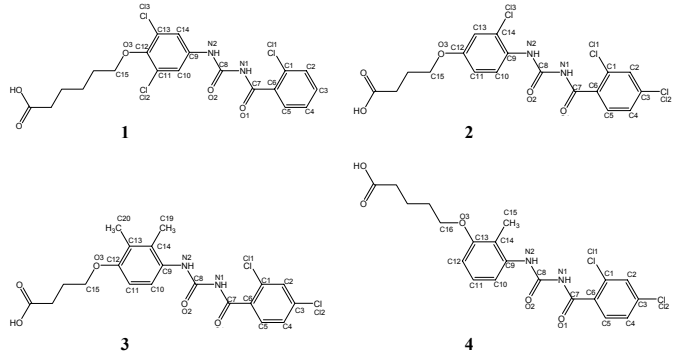
Acyl ureas were discovered as a novel class of inhibitors for glycogen phosphorylase, a molecular target to control hyperglycemia in type 2 diabetics [1]. This series is exemplified by 6-{2,6-Dichloro-4-[3-(2-chloro-benzoyl)-ureido]-phenoxy}-hexanoic acid (1), which inhibits human liver glycogen phosphorylase with an IC_{50} of 2.0 μM. Here we report on four crystal structures of acyl urea derivatives (1-4) in complex with rabbit muscle glycogen phosphorylase b to elucidate the mechanism of inhibition of these inhibitors. The structures were determined and refined to 2.26 Å resolution and demonstrate, that the inhibitors bind at the allosteric activator site, where the physiological activator AMP binds. Acyl ureas induce conformational changes in the vicinity of the allosteric site. The induced conformational changes are characteristic of the T' state conformation, and the key rearrangement is probably the backbone displacement of the loop 193-196 that allows for van der Waals interactions with the ligands similar to those observed with W1807 [2]. Our findings suggest that acyl ureas inhibit glycogen phosphorlyase by direct inhibition of AMP binding and by indirect inhibition of substrate binding through stabilization of the T' state. The structural results with the acyl ureas can be further exploited by means of chemical modification to produce new potential antidiabetic agents.

Scheme I. Chemical structures of the acyl ureas compounds **1-4**



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