Project 7: Crystal Transformations and Crystallisation Methodologies Date: **19/08/2010**	Author: **John Hayes** Strand : **2** Institute: **University College Cork**

Title: Crystallisation and solid state investigations of glucuronides and their intermediates**.**
Principal Focus: The crystallisation and crystal forms of the biologically important metabolite, paracetamol-*O*-glucuronide **4**. We aim to investigate the crystal habit and morphology of this API like model compound. The main synthetic intermediates in the synthesis of the glucuronide series, methyl tetra-*O*-acetyl-β-D-glucopryranuronate **2**, and methyl 2,3,4-tri-*O*-acetyl-1-*O*-(trichloroacetimidoyl)-α-D-glucopyranouronate **3** will be investigated and any solid state forms reported. We will report on structure solutions for both anomers of **2** along with crystal habit and morphology. Crystallisation methodologies using meta-stable zone width diagrams and seeding experiments will be reported on for methyl tetra-*O*-acetyl-β-D-glucopryranuronate **2**.

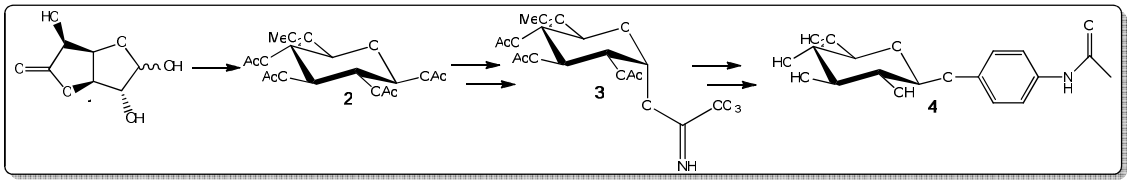

Figure 1: Synthetic Scheme for paracetamol-*O*-glucuronide **4**

Discussion: The synthesis and crystal structure solution for the target paracetamol-*O*-glucuronide **4** has been elucidated. This represents the first structural solution for this important biological metabolite. As expected this compound crystallised with molar equivalent of solvent of crystallisation, a result due to the ratio of hydrogen bond donor/acceptor ratio.

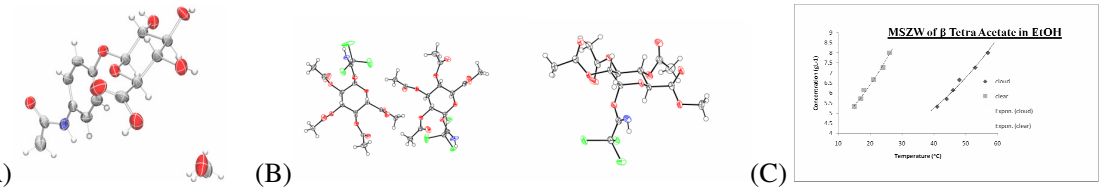

Figure 2: (A) Crystal Structure of paracetamol-O-glucuronide **4** (B) the polymorphic forms of methyl 2,3,4-tri-*O*-acetyl-1-*O*-(trichloroacetimidoyl)-α-D-glucopyranouronate **3**.

The glycoside donor **3** has been found to be polymorphic, and full solid state characterisation of these polymorphs has been conducted. MSZW diagrams for **2** in THF and EtOH were conducted. These were used in seeding experiments and the resulting crystal form, habit and particle size distributions were investigated. No change in habit or morphology was observed but, it was found that nucleation was the predominant factor and growth was difficult to control.

Future Work: To investigate the relationships between crystallisation parameters such as solvent/antisolvent interactions, cooling rates, seeding techniques and the resulting crystal habit and morphology. To investigate desupersauration curves for the crystallisation of **2**, and to use this data in conjunction with MSZW diagrams in order to further control growth over nucleation.

References:
(1) Bollenback, G. N.; *et al*; *The Synthesis of Aryl-D-glucopyranosiduronic Acids*, *Journal of the American Chemical Society* ***1955***, 77, 3310-3315.
(2) Stachulski A.V.; Jenkins G., *The Synthesis of O-Glucuronides, Nat. Prod. Rep.* ***1998***, 15, 173-186.
(3) Nudelman, A.; Herzig, J.; Gottlieb, H. E.; Keinan, E.; Sterling, J. *Carbohydrate Research* ***1987***, 162, 145-152**.**