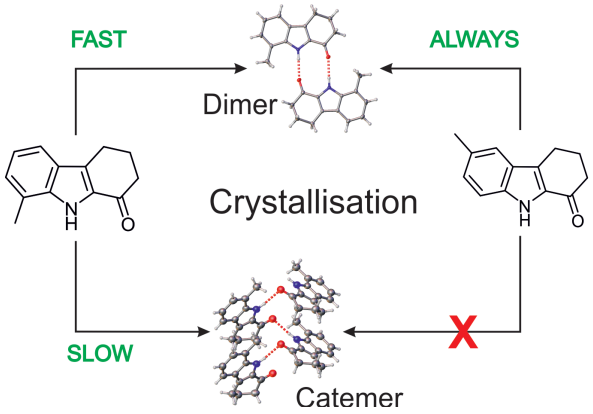

Figure 1. How subtle changes in substitution pattern can effect massive changes in crystallisation behaviour.

Keywords: pharmaceuticals, polymorphism, aggregation in solution

MS9-P17 Structural analysis and molecular docking studies of nitrogen containing steroidal compounds as potential antitumor agents

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Nitrogen containing steroidal compounds target a variety of biological processes, and are potential candidates for the treatment of a wide-range of diseases, including breast and prostate cancer. Prostate cancer is the second most common cancer among men worldwide, while among women, breast cancer is the second leading cause of cancer deaths today. Breast tumors with a relatively high concentration of estrogen receptors can often be treated successfully with steroid-based anti-hormonal therapy. Similarly, several nitrogen containing steroidal compounds have been developed for the treatment of prostate cancer, including Abiraterone, VN/124-1 (galeterone) and VN/85-1 which reduce circulating androgen levels through inhibition of 17α-hydroxylase/17,20-lyase (CYP17).

Building on our previous work [1-3], in the present study we present more than 20 nitrogen containing androstane derivatives. Synthesized products were validated by spectroscopy and X-ray crystallography, and screened for antitumor potential by in silico molecular docking and anti-proliferation studies. Molecular docking simulations were performed against known clinical targets of steroidal chemotherapeutic drugs currently used in the treatment of breast and prostate cancer: estrogen receptor α (ERα), androgen receptor (AR), Aromatase (CYP19A1) and 17,20-lyase/17α-hydroxylase (CYP17A1). Virtual screening and in vitro anti-proliferation studies suggest that A-modified 17(E)-picolinylidene androstane derivatives represent promising candidates for the development of a new series of steroid-based compounds for the treatment of prostate cancer, indicating the need for more detailed future studies.

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MS9-P18 Human LLT1, a ligand for NKR-P1, and its variability under various conditions

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Natural killer cells (NK cells) are large granular lymphocytes able to kill virally infected, stressed or tumor cells. Unlike T-cells, the activity of NK cells is innate.

NKR-P1 (CD161) is a receptor on a surface of human NK cells. LLT1 is a ligand for NKR-P1 receptor, expressed primarily on activated lymphocytes and antigen presenting cells. The interaction of the ligand with the receptor inhibits NK cell cytotoxicity; however, it may have also activation effects in some cases. Extracellular domains of both binding partners, NKR-P1 and LLT1, have C-type lectin like (CTL) fold.

Using X-ray diffraction, we determined four structures of LLT1 [1] from protein produced in HEK293S GnTI- cells [2]. The protein with $GlcNAc_2Man_5$ glycosylation packs into hexamers (consisting of three dimers) in crystals. The protein deglycosylated after the first N-acetylglucosamine was found in our crystal structures in forms of dimers (in pH 7.0) and monomers (in pH 3.5).

The LLT1 structures show that LLT1 follows the “classical” mode of dimerization known from other structures with the same fold (CD69 [3], Clr-g [4]). The series of the LLT1 structures (PDB codes 4QKG, 4QKH, 4QKI, 4QKJ) bring insight into variability of the dimerization interface, flexibility of the outer long loop of the CTL domain and influence of glycosylation on the structure.

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