MS9-P15 Polymorphism and phase stability of ketoprofen salts

M. Ben Nasr[1], A. Doudouh[1], P. Durand[1], A. Gansmuller[1], E. Aubert[1], E. Espinosa[1]

1. Laboratoire CRM2 Université de Lorraine

email: mahjouba.ben-nasr@univ-lorraine.fr

Ketoprofen is a Non-Steroidal Anti-Inflammatory Drug (NSAID) of propionic acid class having analgesic and antipyretic effects [1]. It exhibits poor water solubility and dissolution rate [2]. To enhance its solubility, ketoprofen has been formulated and marketed as a trometamol salt [3].

Up to now the structures of ketoprofen salts were unknown. Recently, we have succeeded to obtain single crystals of a salt of racemic ketoprofen with trometamol, as well as two polymorphs of S-ketoprofen-trometamol salts (Fig.1). The prepared salts were characterized by using single-crystal and powder X-ray diffraction, DSC, FT-IR and 13C CP-MAS NMR, coupled with Density Functional Theory calculations. The structures and properties of these salts, which show enhanced aqueous solubility as compared to pure ketoprofen, will be discussed.

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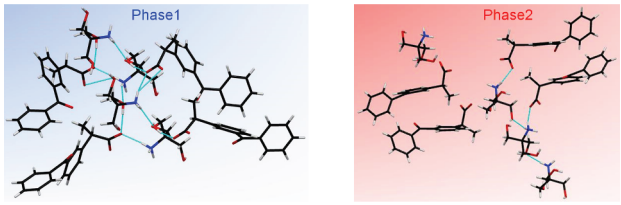

Figure 1. Crystal structures of two polymorphs of S-ketoprofen-trometamol salts. N-H…O and O-H…O hydrogen bonds are shown as blue lines

Keywords: Crystallization, ketoprofen, trometamol, salt, hydrogen bonding, solubility.

MS9-P16 Conserved hydrogen bonding in tetrahydrocarbazolone derivatives: Influence of solution-state assembly on crystal form nucleation

Katharina Fucke[1], Robert M. Edkins[2,3], Elliott Hayden[1]

1. School of Medicine, Pharmacy and Health, Durham University Queen's Campus, University Boulevard, Stockton-on-Tees, TS17 6BH, United Kingdom
2. Institut fuer Anorganische Chemie, Julius-Maximilians-Universitaet Wuerzburg, Am Hubland, 97074 Wuerzburg, Germany
3. Department of Chemistry, Durham University, South Road, Durham, DH1 3LE, United Kingdom

email: katharina.fucke@durham.ac.uk

Different crystal forms (polymorphs) may vary substantially in their physico-chemical characteristics, including melting point, chemical and physical stability, solubility and dissolution rate, the latter of which represents both a challenge and an opportunity for the pharmaceutical industry.[1] Bioactive molecules typically have multiple functional groups, enabling them to interact with receptors and thus show pharmacological action. Furthermore, as drug molecules become ever larger, they tend to show increased flexibility. These two factors make investigations and predictions of the crystallisation behaviour of most drug molecules inherently difficult.[2] In this study, we investigate two tetrahydrocarbazolone derivatives, as they represent core fragments of many antibacterial and antiviral drugs and prodrugs,[3] whilst having a rigid core with only one hydrogen-bond (HB) donor and one HB acceptor functionality, enabling us to deconvolute the influence of specific functional groups. In addition, the influence of the position of methylation on the existence of supramolecular synthons is probed. *Ortho*-methylated tetrahydrocarbazolone (OCB) can exist in four polymorphs, three of which show the anticipated dimer formation, a synthon proved to exist in the pre-crystallisation solution. The thermodynamically stable polymorph, however, crystallises in a catemer motif but has a considerably longer nucleation time. When moving the methyl group from the *ortho*- to the *para*-position (PCB), only dimer formation was observed, while the different polymorphs become very close in energy and concomitant crystallisation occurred. Thus, subtle changes in molecular structure can have profound influences on crystallisation behaviour. It is also predicted that a bio-isosteric replacement of the CH_3 group of OCB with CF_3 will further stabilise the catemer, highlighting a potential problem for the design and subsequent formulation of new drugs.

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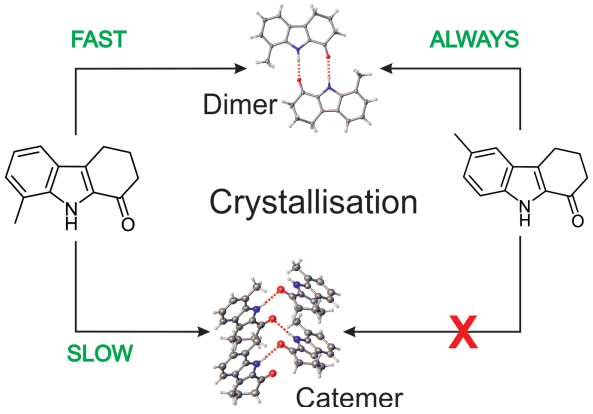

Figure 1. How subtle changes in substitution pattern can effect massive changes in crystallisation behaviour.

Keywords: pharmaceuticals, polymorphism, aggregation in solution

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

Olivera R. Klisurić[1], Edward T. Petri[2], Anđelka S. Ćelić[2], Katarina M. Penov Gaši[3], Marija N. Sakač[3], Jovana J. Ajduković[3], Andrea R. Nikolić[3], Aleksandar M. Oklješa[3], Marina P. Savić[3], Dimitar S. Jakimov[4], Evgenija A. Đurendić[3]

1. Department of Physics, Faculty of Sciences, University of Novi Sad, Trg Dositeja Obradovića 4, 21000 Novi Sad, Serbia
2. Department of Biology and Ecology, Faculty of Sciences, University of Novi Sad, Trg Dositeja Obradovića 4, 21000 Novi Sad, Serbia
3. Department of Chemistry, Biochemistry and Environmental Protection, Faculty of Sciences, University of Novi Sad, Trg Dositeja Obradovića 3, 21000 Novi Sad, Serbia
4. Oncology Institute of Vojvodina, Institutski put 4, 21204 Novi Sad, Serbia

email: olivera.klisuric@df.uns.ac.rs

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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