## FA4-MS09-P06

**One Instrument to Answer to All Your Challenges? Cu/Mo, Small Crystals and More…** Claire Wilson[a], Masataka Maeyama[b], Kimiko Hasegawa[b], Kazuaki Aburaya[b]. [a]*Rigaku Europe, Sevenoaks, Kent UK.* [b]*Rigaku Corporation, Tokyo, Japan.*
E-mail: claire.wilson@rigaku.com

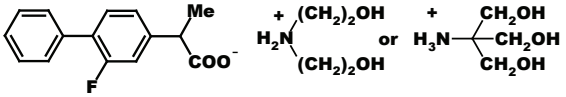
Today's most interesting samples rarely make our jobs easy for us. Unfortunately many of the systems that we want to study crystallise as very tiny crystals. This can be particularly true of pharmaceuticals but is a widespread difficulty in many areas of chemistry and materials where we repeatedly face these challenges. Constant pressure to deliver high quality results and extract as much information as possible are coupled with pressures to do so both cost and time efficiently.
The combination of the Rigaku MicroMax 007HF generator with the RAPID II unique curved, large area image plate detector already provides a hugely flexible tool to address many of these challenges. Advances in optics now mean that this powerful combination of generator and detector can be used with both Mo and Cu radiation (or Cu and Cr) on the same instrument, just by swapping the rapidly interchangeable targets. The image plate is highly sensitive for all these wavelengths providing for high quality data without compromise. The extremely large active area of the detector (-60 to 144°) allows a massive solid angle of data to be collected in a single exposure; ideal for fast high resolution Cu data for absolute configuration determination and equally for very high resolution data with Mo radiation. The exceptional low noise and wide dynamic range also suit the long exposure times often necessary for very tiny crystals – even with a brilliant source - without saturation or excessive noise problems. This single instrument is so versatile that it can replace several others – for single crystal diffraction studies (both small and macromolecular) at both wavelengths as well as powder diffraction. Results of studies using this new dual wavelength capability system will be presented.

**Keywords: instrument development; chemical crystallography; absolute configuration**

## FA4-MS09-P07

**Hydrogen Bonding in Flurbiprofen Salts.** Carl H. Schwalbe[a], Miren Ramirez[a], Chris J. Bache[a], Simon J. Coles[b], Barbara R. Conway[a], Peter Timmins[c]. [a]*School of Life and Health Sciences, Aston University, Birmingham B4 7ET, UK.* [b]*School of Chemistry, University of Southampton, Southampton SO17 1BJ, UK.* [c]*Bristol-Myers Squibb, Reeds Lane, Moreton CH46 1QW, UK.*
E-mail: C.H.Schwalbe@aston.ac.uk

Flurbiprofen (F) is a valuable anti-inflammatory drug, but its aqueous solubility is only 0.03 mg $mL^{-1}$. Its salts with cyclohexylammonium or adamantylammonium ions still have limited solubility; in both structures N-H…O hydrogen bonds form ladders [1]. In a series of $H_2NC(CH_3)_{3-n}(CH_2OH)_n$ salts of the carboxylic acid drug gemfibrozil [2] the members with n = 0, 1 and 2 also form ladders; but when n = 3, these change to layers [2]. Hoping that counter ions with OH groups would enhance the solubility of F through hydrophilicity and would improve its mechanical properties by greater hydrogen bonding, we have studied the diethanolamine (DEA) and tris(hydroxymethyl) aminomethane (TRIS) salts.




FDEA forms no ladders, nor any other extended motif. Two anions and two cations use their $NH_2^+$ and $COO^-$ functionality to form a discrete $R_4^4(12)$ ring. Instead of linking adjacent rings, one ethanolamine OH donates a hydrogen bond to the same carboxylate O atom already accepting from NH, thus appending another $R_2^1(7)$ ring to either side of the main ring. The other ethanolamine OH can link to a carboxylate O atom across the large ring, but its disorder suggests limited importance. Hydroxyl O atoms accept no hydrogen bonds from NH or OH donors. Instability of the crystals due to disorder and the lack of any hydrogen-bonded spine are consistent with the low melting point of 63°C, density of 1.284 g $cm^{-3}$ and the high solubility of >200 mg $mL^{-1}$.

FTRIS appears to exist as more than one polymorph. The one examined does have hydrogen-bonded motifs extending throughout the crystal. The ammonium ion of TRIS donates a hydrogen bond to each of two carboxylate ions, forming C(6) chains along *x*, and another to OH, while its three OH groups donate to two different $COO^-$ and one OH. Thereby dimeric $R_2^2(10)$ and $R_4^4(18)$ rings link adjacent chains, and conjoined $R_2^2(9)$ and $R_3^2(9)$ rings are appended to each chain. The resulting stability is reflected in the melting point of 148°C, density of 1.345 g $cm^{-3}$ and solubility of 16.34 mg $mL^{-1}$.

[1] C.H. Schwalbe, S.J. Teat, S.E. David, W.J. Irwin, B.R. Conway, P. Timmins, *Acta Cryst.,* **2005**, A61, C350. [2] E.Y. Cheung, S.E. David, K.D.M. Harris, B.R. Conway, P. Timmins, *J. Solid State Chem.*, **2007**, 180, 1068-1075.

**Keywords: pharmaceutical crystallography; hydrogen bonds in organic crystals; solubility**

## FA4-MS09-P08

**Fragment-based Discovery of S100B Inhibitors Combining Computational and Biophysical Approaches.** Stefano Mangani[c], Lucia Cesari[b,c], Matteo Andreini[b], Daniela Lalli[d], Rebecca del Conte[d], Paola Turano[d], Alessandro Padova[b], Mariangela Agamennone[a]. [a]*Dipartimento di Scienze del Farmaco, Università "G. d'Annunzio", Chiet.* [b]*Drug Design Technologies Unit, Siena Biotech S.p.A., Siena.* [c]*Dipartimento di Chimica, Università di Siena.* [d]*Magnetic Resonance Center CERM, Università di Firenze - Italy.*
E-mail : mangani@unisi.it

S100B belongs to the highly conserved S100 family, a subclass of the EF-hand $Ca^{2+}$-binding proteins, constituted by 21 known members implicated in intracellular and extracellular regulatory activity[1]. It has been demonstrated that the binding of S100B and the C-terminal domain of p53, a well known tumor-suppressor protein, prevents p53 phosphorylation and tetramerization, blocking its anticancer activity [2]. This inhibitory activity has been related with S100B overexpression in some malignant tumors. This interaction between an anphypatic α-helix on a protein and a hydrophobic cleft on its partner is similar to other therapeutically relevant interactions suggesting the possibility to design small molecules inhibitors of protein-protein interaction. Few inhibitors have been identified so far by using a NMR-based screening [3,4]. Our objective is the identification of small molecules able to block the protein-protein interaction between S100B and p53, through the SAR by NMR approach, successfully developed and applied by Fesik and coworkers [5]. The biophysical screening was preceded from a computational screening aimed to filter fragments to be screened in the following assays. Siena Biotech's fragment collection was used for a virtual screening campaign based on docking and pharmacohore approaches, leading to the selection of 280 molecules. NMR-based screening (WaterLOGSY) was performed in order to identify interacting fragments and $^{15}N$-HSQC analysis confirmed the interaction of the strongest binders. Co-crystallization trials have been set up for one of the most active molecules. Crystals of protein-ligand complexes grow in few days and the analysis of diffraction data provides good-quality electron density maps at about 1.9 Å resolution. The binding site of the fragment has been clearly identified and corresponds to p53 binding site, as it was previously determined by the above mentioned NMR experiments. Structure-based library design has started in order to increase the potency of the fragments, through fragment evolution. Crystallization trials to obtain binary complexes of S100B with all the identified fragments are still on going.

[1]Microscopy research and technique **2003**, 60, 540-551; *Frontiers in bioscience* **2002**, 7, 1356-1368; [2]*Mol. Cell. Biol.* **1998**, 18, 4272-4281; *J. Biol. Chem.* **2001**, 276, 35037-35041; *PNAS*, **2005**, 102, 4735-4740;[3] *J. Med. Chem*., **2004**, 47, 5085-5093, *Curr Top Med Chem*, **2005**, 5, 1093-1108, *Mini Rev Med Chem*, **2007**, 7, 609-616;[4] *ChemMedChem,* **2007***,* 2, 1648-1654 ;[5]*Science*, **1996**, 274, 1531-1534;*J. Am. Chem. Soc.*, **1997**, 119, 5818–5827; *Molecular Interventions*, **2006**, 6, 266-272.

**Keywords: structure and function of protein; NMR spectroscopic investigations; X-ray structure determination**

## FA4-MS09-P09

**Electronic Structure of $[RuCl_3(indazole)_2NO]$.** Jozef Kožíšek[a], Marek Fronc[a], Marin Breza[a], Katharina Schiessl[b], Vladimir B. Arion[b]. [a]*Department of Physical Chemictry, Slovak Technical University, Radlinského 9, SK-812 37 Bratislava, Slovak Republic.* [b]*Institute of Inorganic Chemistry, University of Vienna, Währingerstr. 42, A-1090 Vienna, Austria.*
E-mail: jozef.kozisek@stuba.sk

The development of metallopharmaceuticals is a frontier area in bioinorganic chemistry where both the Ru(II) and Ru(III) coordination compounds play an important role [1]. We have synthesized a novel ruthenium nitrosyl compound, $[RuCl_3(indazole)_2NO]$ and studied its geometric and electronic structure.
An experimental data set (GEMINI R diffractometer, 100K, 47 runs, 147 740 diffractions, resolution 0.54Å) was measured. Data reduction was done by CrysAlis171.33.31 and an average redundancy of 12.8 gives $R_{int}$ of 0.045.
After the multipole refinement the topological analysis was performed using XD package. Theoretical calculation was done using CRYSTAL06 and TOPOND software.
Comparison of experimental and theoretical results will be disscussed.
This work has been supported by Slovak Grant Agency APVV and VEGA (APVV-0093-07, SK-AT-0018-08 and 1/0817/08).

[1] Sebrián-Losantos B., Reisner E, Kowol Ch.R., Roller A. Shova S. Arion V.B., Keppler K., *Inorg.Chem*, **2008**, 47, 6513. [2] Grirrane, A.; Pastor, A.; Galindo, A.; Ienco, A.; Mealli, C. *Chemm. Commun.* **2003**, 512.

**Keywords: charge density; ruthenium; electronic structure**

## FA4-MS09-P10

**Analysis of Organic Molecular Compounds and Pharmaceuticals from Their X-Ray Powder Diffraction Patterns.** Pauline Martinetto[a], Michel Anne[a], Pierre Bordet[a], Julie Linol[b], Gérard Coquerel[b], Eric Dooryhée[a], Pierre Terech[c]. [a]*Institut Néel, CNRS-UJF, Grenoble, France.* [b]*IMR, Université de Rouen, Mont Saint Aignan, France.* [c]*INAC, CEA, Grenoble, France.*
E-mail: pauline.martinetto@grenoble.cnrs.fr

Pharmaceutical developers are more and more concerned by solid form of drugs because it dictates their properties, including stability, hygroscopicity, dissolution rate, solubility, and bioavaibility. These solids can be molecular crystals (often prepared as polycrystalline powders) or noncrystalline solids (less stable but often with desirable pharmaceuticals properties, such as faster dissolution rates). In the recent years, advances in methodology have enabled to characterize both solid forms using only X-ray powder diffraction data. We have already reported structural studies carried out on a special steroid derivative molecule (STNH) which exhibits spectacular properties of an efficient organogelator of saturated alkanes [1]. Here, the crystallographic behavior of different xerogel forms are now observed ex- and in-situ using laboratory and synchrotron X-ray powder diffraction together with conventional and global optimization methods. We also present the study carried out on the molecular compound (±) modafinil, known to crystallise in five pure polymorphic forms [2, 3]. Under high energy milling, a new phase is obtained, which is a defective phase likely related to the original forms I and III. We are currently studying the total scattering signal