Silva, F.T. Martins, S.B. Honorato, N.B. Boechat, A.P. Ayala, J. Ellena, *Crystal Growth & Design* ***2010****, 10 (7)*, 3094-3101.

Keywords: pseudopolymorphism, solid-state characterization, diethylcarbamazine

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Spacer geometry and 5-HT_{1A} receptor affinity of LCAPs

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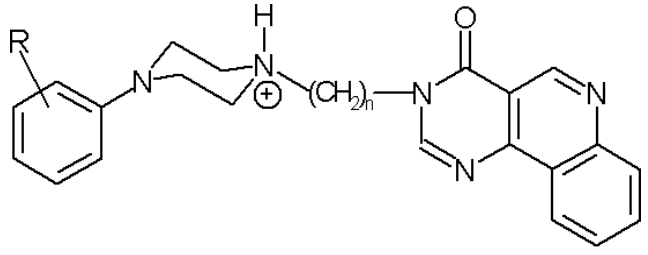
Long-Chain ArylPiperazines (LCAPs) are well known serotonin receptor ligands. Several of them are used as active ingredients of marketed drugs, *i.e.* aripiprazole, buspirone, tandospirone. LCAPs consist of three main structural units: the aryl at N1 of the piperazine ring, the aliphatic chain (called either spacer or linker) at N4, joining the ring with the terminal aromatic system of variable size through amide or imide group.

There is a vast literature concerning SAR of 5-HT_{1A} receptors ligands. Well established are influence of the aryl substitution and the spacer length of the aliphatic chain, most often tri- or tetramethylene, on 5-HT receptors affinities. Less is known on active conformation of the spacer and the role of the terminal moiety. In most models of the 5-HT_{1A} receptor and interactions with its ligands, protonation of piperazine N4 atom is assumed.

In our latest study a series of the new LCAPs hydrochlorides with pyrimido[5,4-c]quinolin-4(*3H*)-ones as the terminal group and a range of methylene units in the spacer (*n*=2-4) have been obtained and their activity determined *in vitro* (project no. NN405165633 from Ministry of Science and Higher Education, Poland) [1]. Unexpected observation was that 5-HT_{1A} receptor affinities of LCAPs with *n*=2 and 4 were similar and generally much higher than those for analogous compounds with *n*=3.



In efforts for structural explanation of the phenomenon, we have search CSD and were surprised by finding only several similar LCAP hydrochlorides, two with *n*=2 and three with *n*=3, which was not enough for SAR study. Solving twelve crystal structures of pirimidoquinolone type LCAPs with *n*=2-4 by ourselves enlarged significantly the structural data available and enabled us to point out a simple structural explanation. Namely, affinities of the LCAPs are related not only to the distance between the aromatic terminal group and the piperazine ring but also to their relative orientation, which critically depends on parity of *n*.

[1] W. Lewgowd, A.J. Bojarski, M. Szczesio, A. Olczak, M.L. Główka, S. Mordalski, A. Stańczak, *Eur. J. Med. Chem.* **2011**, accepted.

Keywords: LCAP, molecular structure, SAR

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A Generic Method to Increase Throughput and Efficiency of Crystallization Optimization

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Crystallization optimization, from a possible hit condition to producing a crystal of diffraction quality, is a critical but time consuming step in the macromolecular crystallization process. Major challenges include: 1) insufficient protein samples; 2) unrealistic experiments and/or conditions set up by hand; 3) eliminating false positives, such as salt crystals, and false negatives, such as protein micro crystals in a drop that is difficult to see with human eyes; 4) reproducibility due to human pipetting variations; and 5) organization and iteration of experiments. With new technology built into robotic instruments and software applications, many of the challenges mentioned above can be significantly reduced or completely eliminated. One such example is to consolidate various conventional crystallization optimization plates into one standard 96-well plate and to replace hand pipetting with robots [1], thereby increasing the throughput by multiple times while eliminating dispense variability issues. UV fluorescence imaging in addition to traditional bright field microscopy [2], [3] drastically improves efficiency by eliminating false positives and false negatives, especially during the initial screening and early stages of optimization. A user-centric software application further organizes both experiments and data in order to present the results clearly and to make suggestions systematically and strategically for follow-up experiments. We introduce here a generic method of combining new and existing technology with robots to overcome the majority of these challenges during optimization and, hence, increase throughput and efficiency. We will analyze the crystallization process of glucose isomerase, compare this method with traditional pathway by hand, and illustrate how this method can improve throughput and efficiency of crystallization optimization.

[1] J. Xu, M. Lundy, M. Willis, *ACA* **2011** poster presentation, New Orleans, USA. [2] J. Xu M. Willis, *ACA* **2009** oral presentation, Toronto, Canada. [3] M. Mickley, C. Boarman, G. Mullen, M. Petersen, *ACA* **2011** poster presentation, New Orleans, USA.

Keywords: crystallization, optimization, automation

MS53.P07

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On the Crystal Structure of the Common Antihistaminic Dexchlorpheniramine Maleate

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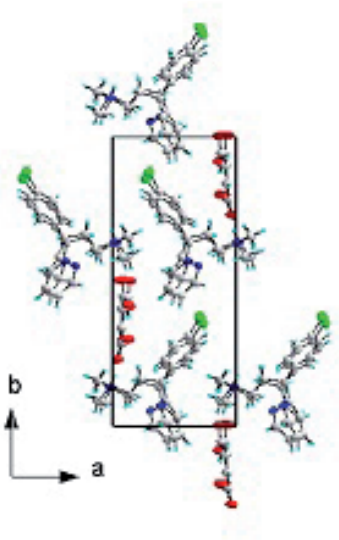
As part of the work being done at the *Laboratorio de Cristalografia*, ULA, on the characterization of Active Pharmaceutical Ingredients (APIs), a study by X-ray diffraction, FT-IR and NMR spectroscopy, and thermal analysis (TGA-DSC) of dexchlorpheniramine maleate (DexChlor) was carried out.

DexChlor is the dextrorotatory isomer of chlorpheniramine. Both forms are active pharmaceutical ingredients (APIs) used to

treat symptoms of allergic conditions such as rhinitis and urticara. In the Cambridge Structural Database (*CSD*) there is one report for the dextro isomer (REFCODE: CPHMAL10) and three reports in the Powder Diffraction File (PDF-4+: 00-041-1599, 00-042-1792, 00-050-2420). Similarly, there is one report in *CSD* and five in the PDF-4 for the racemic mixture. In an attempt to obtain polymorphic modifications of DexChlor, crystallization experiments were carried by slow evaporation and vapour diffusion using water, ethanol, methanol, acetone, dichloromethane and DMSO, among other solvents. The crystallization of DexChlor in acetone, by slow evaporation at 4-5 ºC, produced colourless prisms. The ***c*** parameter of the unit cell of this phase is twice the corresponding value for CPHMAL10. The asymmetric unit has two crystallographically independent molecules. The geometry of one of the molecules is such that it overlaps with the molecule obtained in the previous report but the second independent molecule has a different conformation. In the new dataset, the reflections with *l*=2n+1 are systematically weak but nevertheless present. Transformation of the atomic positions of CPHMAL10 and re-indexing of data in the smaller cell resulted in a non-satisfactory refinement of the structure. This indicated that the small cell does not represent correctly the structure of DexChlor. Thus, DexChlor crystallizes in the monoclinic system, space group $P2_1$ with unit cell parameters *a*=8.8872(6), *b*=20.3157(14), *c*=11.4666(7)Å, β=104.032(4)°, V=2008.5(2) $Å^3$, $Z=4$. A detailed description will be presented.



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Keywords: dexchlorpheniramine maleate, crystal structure, antihistaminic

MS53.P08

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Rapid Monitoring Polymorphism of Clopidogrel (Plavix)

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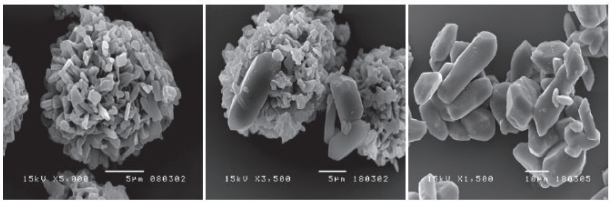
Polymorphic stability of drugs towards heat, moisture, oxidation and light is of great interest in pharmaceutical industry. Rapid monitoring of drug polymorphism in pharmaceutical processes by X-ray powder diffraction is a challenging task especially when the peaks of the different polymorphs overlapped [1]. Clopidogrel (PLAVIX) is a potent oral antiplatelet agent commercially and widely used in the treatment of diseases related to coronary artery, peripheral vascular and cerebrovascular.

Clopidogrel bisulfate (CPL^+ HSO_4^-) exists in many polymorphic forms (Form I to VII). Only Form I (monoclinic) and Form II (orthorhombic) are used in pharmaceutical formulation [2]. This work presents the rapid monitoring polymorphic change in the case of Clopidogrel and its formulations under various conditions of temperature, moisture and storage time under FDA regulations (Clopidogrel is given by Silom Medical Co. Ltd. Thailand).



0 day, Form I 1 month, Form I+II 3 months, Form II

[1] D. Giron *American Pharmaceutical Reviews* **2008,**. *11(1)*, 66-71, [2] *US patent No. 20070037842A1*, Polymorphs and amorphous form of (s)-(+)-clopidogrel bisulfate.

Keywords: rapid monitor, polymorph, pharmaceutical process

MS53.P09

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A Monoclinic Polymorph of the Ticlopidine Hydrochloride

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Antiplatelet therapy prevents ischemic events in patients with high risk of arterial-occlusive thrombosis and myocardial infarction. Ticlopidine hydrochloride (TICLID®) [1] is a platelet antiaggregating agent whose use as a potent antithrombotic pharmaceutical ingredient is widespread [2]. Only the crystal phase used for drug product manufacturing (form I) is known [3]. Here, a new polymorph of ticlopidine hydrochloride (form II) is discrebed for the first time.

A sample of raw ticlopidine hydrochloride powder was dissolved in MeOH by shaking the mixture at room temperature. This solution was allowed to stand in the dark for 5 days at 28 ºC within a crystal growth chamber. After this period, the solvent was completely evaporated and colorless prisms were grown on the bottom of the glass crystallizer. A clear crystal with dimensions of 0.55 x 0.09 x 0.07 mm was chosen for the single crystal X-ray diffraction experiment that was performed at room temperature using an Enraf-Nonius Kappa-CCD diffractometer. The X-ray beam was the graphite-monochromated MoKα line.

While the previous polymorph crystallizes in the triclinic space group *P-1* [3], the new crystal phase was solved in the monoclinic space group $P2_1/c$. Both polymorphs crystallize as racemic mixtures of enantiomeric $(ticlopidine)^+$ cations. Detailed geometrical and packing comparisons between the crystal structures of the two polymorphs have allowed us to understand how different supramolecular architectures are assembled. It was possible to conclude that the main difference between the two polymorphs is a rotation of about 120º on the bridging bond between the thienopyridine and *o*-chlorobenzyl moieties. The differential *o*-chlorobenzyl conformation alters the pattern of weak intermolecular contacts involving this moiety, leading to the change in crystal assembly and increasing the symmetry in the ticlopidine hydrochloride solid state form described for the first time in this study. Other conformational features are slightly different between the two polymorphs, as the thienopyridine puckerings and the *o*-chlorophenyl orientations. These conformational characteristics were also correlated to the crystal packing patterns.

The finding of a new polymorph of this important platelet