**Keywords: hydrogen bonding, conformation, crystal engineering**

## MS53.P03

*Acta Cryst.* (2011) A**67,** C559

**Polymorphism of a model arylboronic azaester – combined experimental and computational studies**

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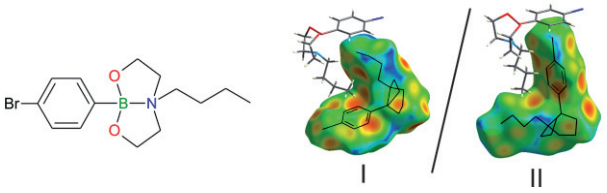
Arylboronic acids and their esters are very important reagents in synthetic chemistry and in medicine. Protection of boronic acids with appropriate diethanolamines leads to so-called azaesters, and enables their further functionalization. Azaesters of arylboronic acids exibit anti-cance, anti-hyperlidemic, anti-inflammatory and anti-neoplastic activities. Recently azaesters of arylboronic acids were found to show anti-microbial activity against *Streptococcus mutants* mainly responsible for tooth decay.




We have performed combined $^{13}C$ CP/MAS solid-state NMR, single-crystal X-ray diffraction and theoretical studies of two polymorphic structures of model arylboronic azaester (form **I** and **II**). It has been shown that the crystallization conditions determine the phase which is formed. Clear differences are visible in the solid-state NMR spectra, where the chemical shifts for the carbon atoms of form **I** are systematically shifted to higher frequency values, in comparison to form **II**. This can be correlated with the overall crystal field strength suggesting that structure **I** is more compact. This is confirmed by the X-ray diffraction results including crystal structure analysis (packing and Hirshfeld surfaces). Molecular geometries of both forms are fairly similar. Some discrepancies have been found in the conformations of the bicyclic moieties, especially for the lengths of the B–N bonds. The most striking differences between the molecules of different polymorphic forms are observed in Hirshfeld surfaces and fingerprint plots. Thermal-expansion tensor and multi-temperature unit-cell X-ray analysis show significant differences between the forms **I** and **II**. This is especially clear when comparing the thermal expansion of crystals in different crystal directions. Our analysis of molecular dipole moments in crystals provides a clear picture of differences for both polymorphs, however, according to computations the dispersion contributions plays a very important role. Theoretical calculations, using *PIXEL* and *CRYSTAL09* programs, are in perfect agreement. They show that the proper handling of the dispersion correction is extremely important for molecular crystals. Calculated lattice energies suggest that the form **I** is slightly more stable than the form **II**. This is also reflected in the crystallization kinetics and melting point temperatures. The higher lattice energy in form **II** seems to be partially compensated by the lower conformational energy of the independent molecules in this form.

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**Keywords: polymorphism, boron, theoretical**

## MS53.P04

*Acta Cryst.* (2011) A**67,** C559-C560

**Crystal structure of the drug diethylcarbamazine and a new maleate salt**

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The Drugs for Neglected Diseases Initiative (DNDi) was created to improve the quality of life for people affected by disease such as lymphatic filariasis (LF). Although the drugs used to treat this disease were developed long ago, little is known about their mechanisms of action. Diethylcarbamazine (DEC-CIT) citrate is one of the most widely used drugs in the treatment of FL. However, very little information about its solid-state characteristics can be found in the literature[1-3]. In a previous study we crystallized and analyzed DEC-CIT by thermal methods, vibrational and X-ray diffraction, revealing three phase transitions at low temperatures, resulting in changes in its molecular structure[4]. In the current study, we crystallized and analyzed the solid state properties of DEC in its pure form and in a new salt form with maleic acid, in order to establish relationships concerning their behavior under different molecular crystals arrangements.

DEC crystallizes in the monoclinic space group $P2_1/n$ with four molecules per unit cell. The pattern of molecular interactions is composed only of weak interactions of types C-H•••O and C-H•••N, forming trimers, unlike what occurs for the citrate salt (DEC-CIT), where citrate molecules form strong bonds with the drug molecules and each other. These weak interactions result in a low density arrangement, which dissolves as the temperature increases. Studies of single crystal X-ray diffraction at different temperatures showed the absence of phase transitions. Above 250K the crystal diffraction stops due to a slow amorphyzation process that leads to a loss of crystallinity, and evolves into a completely amorphous state at room temperature. DSC experiments confirmed the fusion of DEC around 320K, while the one for DEC-CIT was around 410K. IR and Raman spectra were recorded and were consistent with the structural features shown by DSC.

Diethylcarbamazine maleate (DEC-M) crystallizes in the triclinic space group P-1 with two very similar conformations of DEC molecule and two molecules of maleic acid per asymmetric unit. In this new salt, we observed a *cis* conformation for both ethyl chains of the DEC molecules at room temperature. This conformation was only observed in DEC-CIT under 100K, and are *anti* related in the other structures. The crystal structure is stabilized by N-H•••O interactions between the DEC and maleic acid molecules. Besides these interactions, there is a complex network of C-H•••O interactions, which stabilize the compound in a sandwich-like arrangement, interspersed with layers of DEC over bilayers of maleic acid. This new arrangement keeps the compound stable at room temperature. Studies as function of temperature by DSC, IR and Raman spectroscopy confirmed the absence of phase transitions as observed for DEC-CIT. Although solubility tests are still necessary, it is believed that the new crystal packing releases DEC molecules more quickly in solution, making this new compound a strong candidate for active pharmaceutical ingredient (API), while the weak interactions and low melting point disqualify the DEC in its pure form as an API.

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**Keywords: pseudopolymorphism, solid-state characterization, diethylcarbamazine**

## MS53.P05

*Acta Cryst.* (2011) A**67,** C560

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

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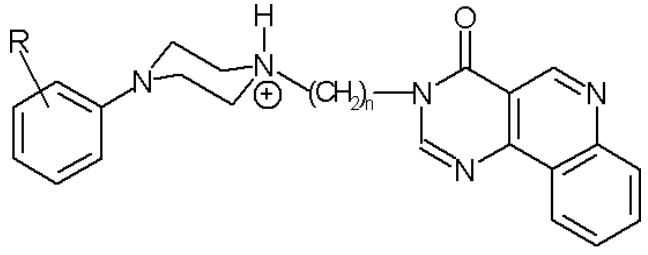
Long-Chain ArylPiperazines (LCAPs) are well known serotonin receptor ligands. Several of them are used as active ingredients of marketed drugs, *i.e.* aripiprazole, buspirone, tandospirone. LCAPs consist of three main structural units: the aryl at N1 of the piperazine ring, the aliphatic chain (called 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**

## MS53.P06

*Acta Cryst.* (2011) A**67,** C560

**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.

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**Keywords: crystallization, optimization, automation**

## MS53.P07

*Acta Cryst.* (2011) A**67,** C560-C561

**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