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

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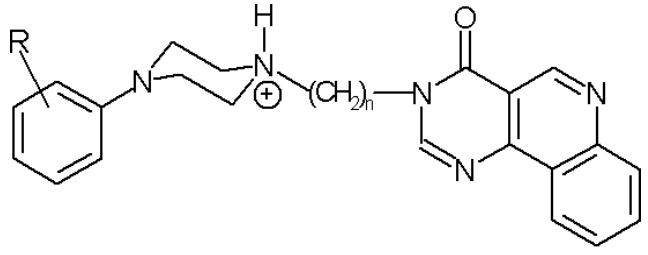
Long-Chain ArylPiperazines (LCAPs) are well known serotonin receptor ligands. Several of them are used as active ingredients of marketed drugs, *i.e.* aripiprazole, buspirone, tandospirone. LCAPs consist of three main structural units: the aryl at N1 of the piperazine ring, the aliphatic chain (called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

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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.

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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