Poster Presentation

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Crystallographic approach to determination of active conformations of LCAPs

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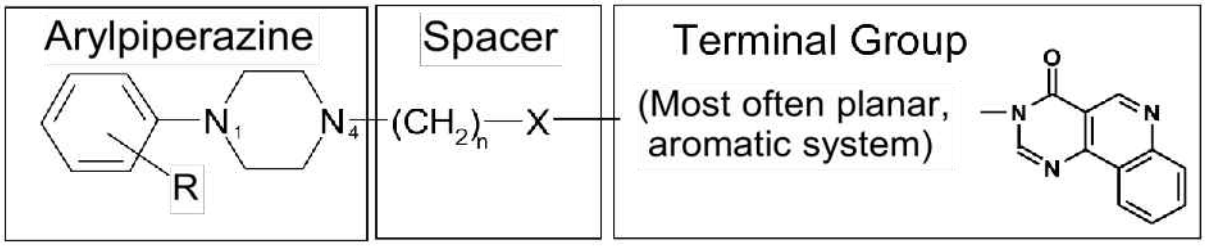
Long-Chain Aryl-Piperazines (LCAPs) are well known serotonin receptor ligands used in several marketed antidepressant drugs. LCAPs consist of three structural units: a terminal group, an arylpiperazine at one N atom and an aliphatic chain (spacer) at the other N atom joining the two former units. Both the arylpiperazine and the terminal groups have rather rigid structures and thus their conformational freedom is limited. The opposite is true for the aliphatic spacer, which allows practically any orientation of the terminal group. The resulting diversity of conformations observed in the crystals of LCAPs is significant, which explains their affinity to many serotonin receptors. There is a vast literature on the subject and some qualitative observations were developed. However, due to the flexible spacer and diversity of the terminal groups, their usefulness is limited. Our X-ray (16 crystal structures) and affinity studies on almost sixty new LCAPs [1], together with the data from CSD, enable us to determine the common conformations of LCAPs and the relationships between structure, affinity and conformation. In the analysis, the following features were considered: (i) - axial/equatorial orientations of the substituents of the piperazine ring; (ii) –N1 protonation possible in the physiological environment; (iii) - a twist of the aryl ring; (iv) –the parity and the number of atoms in the spacer; (v) – the presence of heteroatoms or groups in the spacer; (vi) – the spatial position of the terminal group in relation to the piperazine ring.

[1] *Lewgowd, W., et al. (2011). Eur. J. Med. Chem. 46, 3348-3361.*



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