CONFORMATIONAL FLEXIBILITY OF BUSPIRONE ANALOGUES
FROM X-RAY IN THE SOLIDS AND NMR IN SOLUTION

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Bioactive molecular conformation of a drug is one of the key points for understanding the ligand-receptor interactions. N-substituted arylpiperazines are important class of 5-HT receptor ligands (particularly 5-HT1A, 5-HT2A and 5-HT7) widely used in the treatment of anxiety, depression, schizophrenia, sleep and memory disorders. Majority of compounds of this group possess hydrocarbon linker of different length and type, which connects the arylpiperazine moiety with the second terminal group, e. g. cyclic imide. According to SAR (structure-activity relationship) analyses, the presence of an aryl group at N4 atom of the piperazine ring is critical in respect to the biological activity of these compounds. The protonated nitrogen atom forms the hydrogen bond with the carboxyl oxygen of the Asp 3.32 side chain, that is crucial for the interaction with the 5-HT receptors. In addition, the aromatic ring stabilizes the ligand binding by a CH…π interaction with the Phe 6.52 residue. Nowak et al. claimed that ω-methoxy-phenyl moieties of a ligand form a hydrogen bond with the hydroxyl group of Ser 5.42 [1]. Some authors have underlined also a role of the terminal hydrophobic imide part in a stabilization of the ligand-receptor complex by π…π and/or dipole…dipole interactions [2].

Approved anxiolytic drugs in a group of N1-alkyl-N4-pyrimidynylpiperazines, such as buspirone or gepirone, contain flexible butyl linker. Various modifications increasing the rigidity of the n-alkyl chain were reported including alkoxyl, thioalkyl, alkenyl or cycloalkyl spacers [3]. In general, in vivo and in vitro functional assays reveal that flexible ligands of the arylpiperazine type have features of postsynaptic 5-HT1A receptor agonists or partial agonists (as buspirone), whereas their rigid analogues act rather as antagonists of these receptors [4].

In the group of conformations classified as extended, the terminal imide moiety is located near the axis determined by the arylpiperazine part. If an imide part is rotated away from the axis of an arylpiperazine, this kind of conformations are known bent or folded. An extensive conformational search indicated that extended conformations are predominant in vacuum, in solutions and during interactions with 5-HT1A receptor [5]. However another proposed binding mode assumes the folded conformation of buspirone analogues using three-point pharmacophore model developed by Chilmonczyk et al.

In order to determine conformations of hydrocarbon chains adopted in solid by known alkyl- and alkoxypiperazinyl cyclic imide derivatives, structural data from the Cambridge Structural Database were analyzed [6]. The search of the CSD revealed: 24 structures containing butylarylpirperazine moiety, 7 having propylpiperazine fragment and 5 structures with hydroxypropyl unit. Only two examples of propoxy derivatives were found.

In a group of butyl derivatives, the chain is flexible and adopts one of two main conformations: folded (for 9 compounds) or extended (15 derivatives). The observed N4imide…N1piperazine distances vary from 5.0 to 6.30 Å; this value is lower than 6 Å for conformers with a folded four-unit chain.
The basic question whether the conformations occurring in the solid state are maintained in solutions, and, when so, to what extent, appears again and again and should be considered individually for various classes of compounds. In order to elucidate this problem for investigated buspirone analogues, a comparative study comprising eight 4-membered chain derivatives with different imide and arylpiperazine moieties has been performed. The geometry of butyl and propoxy chains was analyzed in the solid state by X-ray crystallography and in solution by NMR spectroscopy. Apparently in solutions the chain remains flexible, therefore, diverse populations of rotamers and dynamic conformational equilibria should be taken into account.

Presenting our preliminary results, crystal structures of molecules 1 and 2 are shown below. Both compounds contain propoxy-linker, which in 1 is folded and in 2 extended. The observed N4imide…N1piperazine distances are 4.87 and 5.40 Å in 1 and 2, respectively.

For solutions, the NMR NOESY method was applied in order to find contacts within the linking chain and surrounding space. Following NOE proton contacts were found for 1: C2\textsubscript{chain}-C2,6\textsubscript{piperazine} and C2\textsubscript{chain}-C8,9, whereas for 2 generally no noticeable NOE interactions have been observed. These results confirm stabilization of the linking chain in distinct conformations in solution. Moreover, the type of conformation observed in the solid state was preserved in solution.

According to in vitro pharmacological evaluation [7], both compounds 1 and 2 show affinity for 5-HT\textsubscript{1A} receptor, which is preferential for 1.