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Conformational Analysis of Flexible Long Chain Arylpiperazines Using Semiempirical Calculations with Solvent Effects

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Conformational flexibility is the hallmark feature of the Long chain arylpiperazines (LCAPs), the most numerous and thoroughly studied class of 5-HT_{1A} receptor ligands.[1]

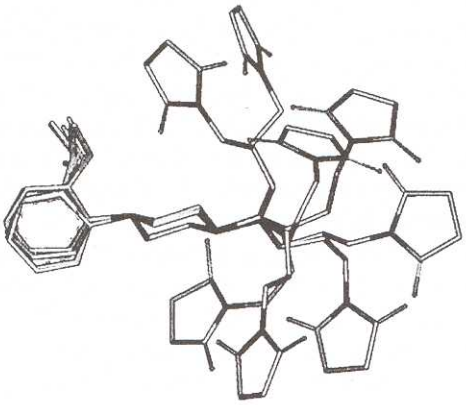

Fig. Several examples of LCAP' low energy conformations displaying its conformational freedom.

Determination of LCAPs' active conformations is of great importance for accurate pharmacophore modelling and investigation of correct ligand binding mode. A lot of crystallographic, NMR-spectroscopic and molecular modeling studies were therefore devoted to characterization of LCAPs' conformational behaviour. The main drawback of computational methods was lack of apropriate simulation of solvent effects.

In the present study we performed systematic conformational analysis of LCAPs, focusing mainly on 4-unit alkyl spacer. Calculations were held using 6 quantum semiempirical methods (including new PM5 hamiltonian) in vacuum and in solvent environment, simulated by COnductorlike Screening MOdel (COSMO) [2]. All methods are implemented in CAChe's MOPAC 2002.

The results obtained *in silico* were compared to conformations determined on the basis of 2D NOESY NMR spectra in both polar and nonpolar solvents.

1. Lopez-Rodriguez, M.L.; Ayala, D.; Benhamu, B.; Morcillo, M.J.; Viso, A. Arylpiperazine Derivatives Acting at 5-HT_{1A} Receptors. *Curr. Med. Chem.* **2002**, *9*, 443-469.
2. Klamt A.; Schümann G. COSMO: A New Approach to Dielectric Screening in Solvents with Explicit Expressions for the Screening Energy and its Gradient. *J. Chem. Soc. Perkin Transactions 2*, **1993**, 799-805.

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