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An Impact of Halogen Position in 4-Phenylpiperazine of LCAPs with Spirohydantoins on the 5-HT_{1A}/5-HT_7 Receptor Selectivity.

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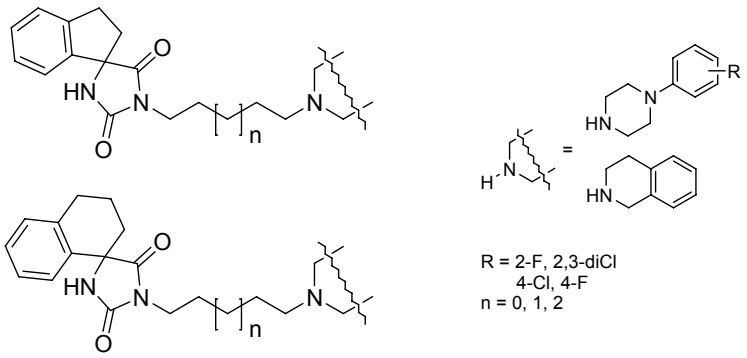
Long-chain arylpiperazines (1-aryl-4-alkylpiperazines, LCAPs) have been extensively studied as 5-HT_{1A} receptor ligands. Due to the structural similarity between the 5-HT_{1A} and 5-HT_7 receptors, LCAPs were also extensively modified, in order to identify selective 5-HT_7 receptor ligands [1]. Differently substituted, in position 5, hydantoin derivatives of LCAP were previously evaluated in order to study the effect of the amide part on the affinity for 5-HT_{1A} receptors [2].
Continuing our studies, in this work aimed at verification of structural features determining 5-HT_{1A}/5-HT_7 receptor affinity and selectivity, we selected indene and tetralin substituted spirohydantoins as core imide fragments. Further modification consisted in diversification of halogen position in the phenylpiperazine fragment, and variation of the length of an alkylene spacer (C4–C6). Additionally, we replaced arylpiperazine moiety with its tetrahydroisoquinoline bioisostere.



The tested compounds were obtained in a three-step synthesis starting from cyclisation of spiro-[imidazolidine-4,1'-indene/naphthalene]-2,5-diones from corresponding ketone followed by alkylation with the halogenoalkanes and coupling with differently substituted phenylpiperazines. Herein, we discuss the relationship between structural modifications applied on compounds affinity and selectivity for 5-HT_{1A} and 5-HT_7 receptors.

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[2] Czopek A., Byrtus H., Kołaczkowski M., Pawłowski M., Dybała M., Nowak G., Tatarczyńska E., Wesołowska A., Chojnacka-Wójcik E.: *Eur J Med Chem.* **45** (4) (2010),1295-303.

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