

## TOWARDS NOVEL SELECTIVE 5-HT<sub>7</sub> RECEPTOR ANTAGONISTS AMONG HYDANTOIN DERIVATIVES

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The latest discovered serotonergic receptor 5-HT<sub>7</sub> is localized in central nervous system, where plays a crucial role in such processes as learning and memory, thermoregulation or circadian rhythm regulation. Studies on animal models showed that its blockade induces antidepressant mechanisms [1]. Moreover, the recent studies indicates its significant meaning in reduction of Fragile X Syndrom's symptoms [2].

Our previous studies allowed us to select the first potent ( $K_i=3$  nM) and selective 5-HT<sub>7</sub> ligand (MF-8) among hydantoin derivatives (40-fold selectivity with respect to 5-HT<sub>1A</sub>R, 240-fold with respect to D<sub>2</sub>R and 60-fold with respect to  $\alpha_1$ R).<sup>3</sup> The compound MF-8 was selected as a lead structure for further chemical modifications (compounds 1-14). Here, it is presented pharmacological evaluation for the lead modifications 1-14. All the compounds were tested in radioligand binding assays. For selected molecules, concentration-response curves for cAMP production by 5-CT (60 nM) in the absence or presence of different concentrations (from 100 pM to 100  $\mu$ M) of the antagonists were performed. Antagonist potency (expressed as IC<sub>50</sub>, the concentration of compound that causes half-maximal inhibition of cAMP production stimulated by 5-CT) of the compounds in cAMP assays were calculated by fitting the data to a sigmoidal dose-response model.

On the basis of obtained results, structure-activity and structure-selectivity relationship analysis was performed that allowed to identify a II-generation lead structure, useful for further modifications.

Authors participate in the European COST Action CM1207 (GLISTEN).

### REFERENCES

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