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Significance of absolute configuration in the search for serotonin 5-HT$_7$ receptor antagonists among hydantoin derivatives

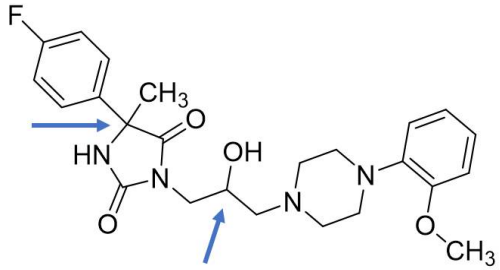
Katarzyna Kucwaj-Brysz,[a] *Grzegorz Satała,*[b] *Katarzyna Kieć-Kononowicz,*[a] *Jadwiga Handzlik*[a]

[a]*Department of Technology and Biotechnology of Drugs, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Cracow, Poland*
[b]*Department of Medicinal Chemistry, Institute of Pharmacology, Polish Academy of Science, Smętna 12, 31-343 Cracow, Poland*

e-mail: k.kucwaj@wp.pl

According to literature 5-HT$_7$R antagonists may have particular activity in depression treatment and coexisting cognitive impairment and anxiety [1]. Our previous studies led to synthesis and pharmacological evaluation of ~50 hydantoin derivatives, of which more than 20 bind to 5-HT$_7$R with K_i<20 nM. Among the most active ones, 6 compounds turned up to cause antidepressant effect in Porsolt's test [2-4]. Worth noting that all the above-mentioned hydantoin derivatives were synthesized as racemic mixture. It is proved that stereoisomers may differ from each other in terms of both biological activity and pharmacokinetic properties [5]. Hence, isolation, biological characterization and finally selection of the stereoisomer with the most desired properties seems to be necessary task within preclinical studies.

The aim of this work was to synthesis, separation and evaluation in radioligand binding assay of 4 stereoisomers of lead structure (compound MF-8) as a representative of the whole series. The resulted data enabled to analyze the influence of particular absolute configuration on 5-HT$_7$R affinity and selectivity over 5-HT$_{1A}$R.



The representative compound (MF-8) with indicated stereogenic centers.

[1] Nikiforuk A. *CNS Drugs.* 29 (2015) 265-275
[2] Kucwaj-Brysz et al. *Eur. J. Med. Chem*. 112 (2016) 258-269
[3] Kucwaj-Brysz et al. *Eur. J. Med. Chem*. 147 (2018) 102-114
[4] Kucwaj-Brysz et al. *MedChemComm*. 9 (2018) 1033-1044
[5] Brooks W.H. et al. *Curr. Top. Med. Chem*. 11 (2011) 760-770