P11

Studies on 5-HT_7 /α_1 -AR/ D_2 -dopamine receptors discrimination for novel (hydroxy)propylpiperazine derivatives of 5,5-dimethylhydantoin

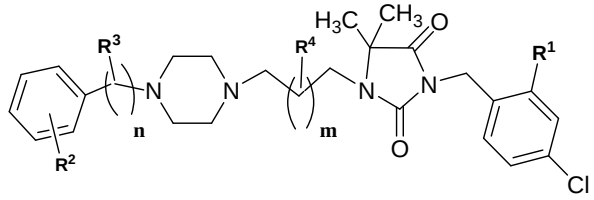
Aleksandra Janik,[a] Maria Gloma,[a] Agata Siwek,[a] Grzegorz Satała,[b] Andrzej Bojarski,[b] Katarzyna Kieć-Kononowicz,[a] Jadwiga Handzlik[a]

[a]Faculty of Pharmacy, Jagiellonian University, Medical College, Medyczna 9, 30-688 Cracow, Poland
[b]Institute of Pharmacology, Polish Academy of Sciences, Smetna 12, 31-343 Cracow, Poland

e-mail: aleksandraaa.janik@gmail.com

The 5-HT_7, α_1 -AR/, D_2 -dopamine receptors are important GPCRs biological targets involving in various diseases of peripheral or central nervous systems. The dopamine D_2 and 5-HT_7 receptors play an important role in neurodegenerative diseases like schizophrenia and Parkinson's disease as well as they can be used in depression and insomnia. The selective α_1-adrenergic receptor antagonists have important therapeutic perspectives as they are able to improve the urodynamic parameters and reduces the symptoms of benign prostatic hypertrophy. In this context, the search for GPCRs has been, and still is, an important topic in medicinal chemistry.

In the previous studies we investigated a number of phenylpiperazine derivatives of 5,5-diphenyllhydantoin [1], which possessed two additional aromatic fragments at position 5. The compounds were selective in respect to dopaminergic and serotonin receptor 5-HT_7 but their affinity for α_1-AR was moderate only. Thus, we decided to reduce the number of aromatic moieties and moved it from position 5 into position 3 of hydantoin [2]. The current study is concentrated on design and synthesis of new arylpiperazine derivatives of 3-benzyl-5,5-dimethylhydantoin (Fig.1).



1-24

R^1 = H; Cl
R^2 = H, 2-MeO, 2-CN, 2,4-diF, 2-F, 4-F, 2,5-diMe, 3-MeO, 3,4-diMe, 2,3-diCl, 3,4-diCl,
R^3 = Ph
R^4 = H, OH
n = 0,1
m= 3,4

Fig. 1

The final products were obtained within three-step synthesis, using two-phase alkylation processes. The new compounds were tested on their affinity for 5-HT_7 receptor in comparison to other closely related GPCRs: α_1-AR and dopamine D_2 receptors. SAR analysis indicates that the chemical modifications significantly improved the affinity for α_1-AR comparing to that of 5,5-diphenylhydantoin analogues. The best activity was found for the 2-fluorophenylpiperazine derivative with hexyl linker. 4-chlorobenzyl derivative with 2-metoxy substituent at phenylpiperazine phenyl ring and pentyl linker have shown high affinity for 5-HT_7 and D_2 receptors. Compounds were evaluated on their "drugability" and toxic effects using OSIRIS program.

[1] J. Handzlik, D. Maciąg, M. Kubacka, et al. Bioorg. Med. Chem., 16 (2008) 5982-5998.
[2] J. Handzlik, M. Bajda, M. Zygmunt, et al. Bioorg. Med. Chem. 20 (2012) 2290-2303.

Acknowledgements:
Partly supported by project K/ZDS/005593.