Polish-Austrian-German-Hungarian-Italian Joint Meeting on Medicinal Chemistry, 15-18 October 2003, Kraków, Poland

The screening of a library of arylpiperazine derivatives for 5-HT_7 receptor affinity

Beata Duszyńska, Krystyna Nędza, Marcin Wasylewski, Andrzej J. Bojarski

Department of Medicinal Chemistry, Institute of Pharmacology of the Polish Academy of Sciences, 12 Smętna Street, 31-343 Kraków, Poland
duszyn@if-pan.krakow.pl

The 5-hydroxytryptamine7 (5-HT_7) receptor is the most recently identified subtype of the serotonin receptor family by molecular cloning technique. The wide distribution of 5-HT_7 receptors throughout the brain suggests that they are engaged in various functions. Preliminary pharmacological evidence indicates that it may be involved in depression, control of circadian rhythms, and relaxation of vascular smooth muscle (1). Thus ligands of 5-HT_7 receptor are now a new target for medicinal chemistry.

To date only a few research groups have focused their interest on the search for new selective 5-HT_7 receptor agents. It has been reported that some high-affinity ligands are present among long-chain arylpiperazines (in particular 1-(2-methoxyphenyl)piperazine derivatives) (2, 3) and tetrahydroisoquinolines (4). Since compounds of this type were investigated in our laboratory as 5-HT_{1A} and 5-HT_{2A} receptor ligands, we decided to launch a new project: the search for novel 5-HT_7 receptor ligands. At the initial stage of investigation, we screened our compound library against the native 5-HT_7 receptor from rat hypothalamic membranes. Preliminary tests were performed at two compound concentrations (1 μM and 0.1 μM), and for the assays in which inhibition was detected, K_i values were then measured by competition binding.

Here we present the results of these experiments and show structures possessing good 5-HT_7 receptor affinity and a diversified selectivity ratio over 5-HT_{1A} and 5-HT_{2A} receptors. Several lead compounds were identified for future structural modifications in order to obtain more potent and selective 5-HT_7 receptor agents.

This study was supported by research grant no. 012/2002 from the Polish Pharmacy and Medicine Development Fundation by POLPHARMA Pharmaceutical Works

(1) Vanhoenacker, P.; Haegeman, G.; Leysen, J.E. *Trends Pharmacol. Sci.* **2000**, *21*, 70-77.
(2) Lopez-Rodriguez, M.L.; Porras, E.; Benhamu, B.; Ramos, J.A.; Morcillo, M.J.; Lavandera, J.L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1097-1100.
(3) Perrone, R.; Berardi, F.; Colabufo, N.A.; Lacivita, E.; Leopoldo, M.; Tortorella, V. J Med. Chem. **2003**, 46, 646-649.
(4) Kikuchi, C.; Hiranuma, T.; Koyama, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2549-2552.