Synthesis and structure-activity relationship analysis of 5-HT$_7$ receptor antagonists: piperazin-1-yl substituted unfused heterobiaryls

Jarosław Sączewski$^{1}$, Elizabeth A. Raux$^{2}$, Nilm T. Fernando$^{2}$, Jeff Klenc$^{2}$, Shirish Paranjpe$^{2}$, Aldona Raszkiewicz$^{2}$, Ava L. Blake$^{2}$, Adam J. Ehalt$^{2}$, Samuel Barnes$^{2}$, Andrzej J. Bojarski$^{3}$, Lucjan Strekowski$^{2}$

$^1$Department of Chemical Technology of Drugs, Medical University of Gdańsk, Al. Gen. J. Hallera 107, 80-416 Gdańsk, Poland; $^2$Department of Chemistry, Georgia State University, Atlanta, Georgia 30302, USA; $^3$Department of Medicinal Chemistry, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, 31-343 Kraków, Poland

Serotonin (5-hydroxytryptamine or 5-HT) is involved in cognitive and behavioral functions. Activation of the 5-HT$_7$ receptor plays a role in smooth muscle relaxation, thermoregulation, circadian rhythm, learning, memory, and sleep. On the other hand, the 5-HT$_7$ antagonism has been linked to diverse antidepressant-like behavioral effects [1, 2].

Many amino-substituted heterobiaryls are CNS antagonists [2, 3]. More than 1000 such compounds were synthesized and assayed for binding to different 5-HT receptors in our laboratories. The binding results of a variety of heterobiaryl antagonists with the 5-HT$_7$ receptor, expressed by inhibition constants ($K_i$), are discussed in this presentation. The representative molecules are shown below for illustration. These agents were selected to show how a small alteration of the structure has a profound effect on the binding to the 5-HT$_7$ receptor. For example, 4-(furan-3-yl)pyrimidines are much more active than their furan-2-yl analogs.

\[ R = H, \text{Me, Et, Pr} \quad K_i = 7-13 \text{ nM} \]
\[ R = \text{Me, Et, Bu, Hexyl} \quad K_i = 1.6-7 \text{ nM} \]
\[ K_i > 10,000 \text{ nM} \]
\[ K_i = 148 \text{ nM} \]
\[ K_i = 1021 \text{ nM} \]
\[ K_i = 632 \text{ nM} \]
\[ K_i = 209 \text{ nM} \]
\[ K_i = 11 \text{ nM} \]
\[ K_i = 17 \text{ nM} \]
\[ X = \text{O: } K_i = 31 \text{ nM} \]
\[ X = \text{S: } K_i = 342 \text{ nM} \]
\[ X = \text{O: } K_i = 914 \text{ nM} \]
\[ X = \text{S: } K_i = 542 \text{ nM} \]
\[ K_i > 10,000 \text{ nM} \]