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

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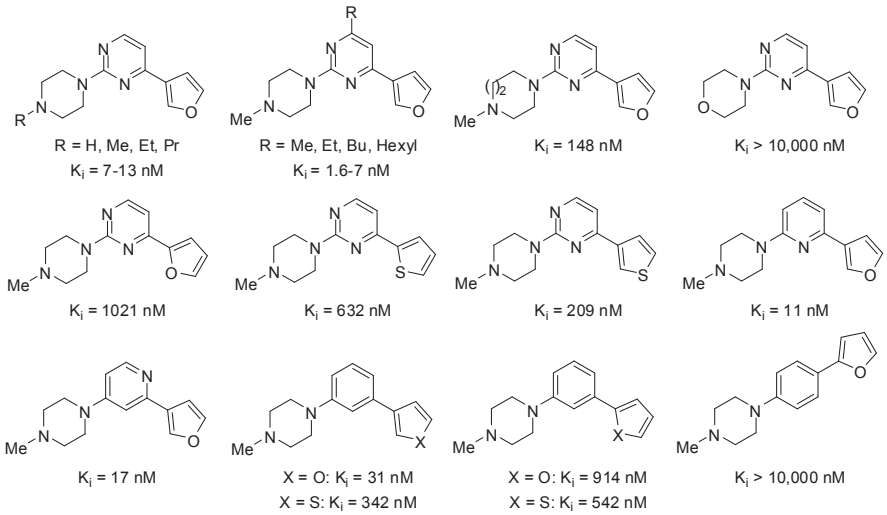
Serotonin (5-hydroxytryptamine or 5-HT) is involved in cognitive and behavioral functions. Activation of the 5-HT$_7$ receptor plays a role in smooth muscle relaxation, thermoregulation, circadian rhythm, learning, memory, and sleep. On the other hand, the 5-HT$_7$ antagonism has been linked to diverse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



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