P43

2-Aminoimidazole-based antagonists of a serotonin receptor, a new concept in aminergic GPCR ligand design

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Until now, the chemical space of ligands of aminergic G protein-coupled receptors (GPCR) has been expanding mainly by the employment of novel bioisosteric building blocks, resulting in a large diversity of core scaffolds, aromatic systems, linkers, hydrogen bond donors and acceptors. This is in sharp contrast to the very narrow pool of amine-like groups that have been used to replace the aminoalkyl chains of endogenous neurotransmitters and classical ligands. Interestingly, hardly any attempts have been made to employ aromatic basic groups in the design of aminergic GPCR ligands. 2-Aminoimidazole (2-AI) remains an unexplored highly basic scaffold, and it has been found to be a common molecular framework of numerous marine alkaloids[1] and synthetic antibacterial (antibiofilm) agents.[2]

Highly selective 5-HT_6 receptor antagonists of various basicities were designed by employing 2-AI and 2-aminothiazole moieties as the amine-like fragment of the ligand. Considering the multiple functionalization sites of the embedded guanidine fragment, a diverse library was constructed, and the relationships between the structure and activity, metabolic stability, and solubility were established.
The lead compound in the series 4-methyl-5-[1-(naphthalene-1-sulfonyl)-1*H*-indol-3-yl]-1*H*-imidazol-2-amine (AHN-208) was shown to reverse the cognitive impairment caused by the administration of scopolamine in rats indicating procognitive potential.

[1] Nakamura, H.; Ohizumi, Y.; Kobayashi, J.; Hirata, Y. *Tetrahedron Lett*. 1984, *25* (23), 2475-2478
[2] Ermolat'ev, D. S.; Van der Eycken, E. V. *J. Org. Chem*. 2008, *73* (17), 6691-6697

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