New Serotonin 5-HT7 Receptor Ligands with 1,2,4-Oxadiazole Fragment

Ryszard Bugno, Anna Stankiewicz, Grzegorz Satała

Department of Medicinal Chemistry, Institute of Pharmacology Polish Academy of Sciences, 12 Smętna Street, 31-343 Kraków, Poland.

The 5-HT7 receptor is the most recently discovered G-protein-coupled receptor from the serotonin family. There are a lot of evidences that these receptors have a significant and unique role in many essential brain functions such as learning, memory, sleep, circadian rhythms, thermoregulation and mood regulation.[1] Many studies show involvement of brain 5-HT7R in different neurological and psychiatric diseases, e.g. anxiety, obsessive compulsive disorder, migraine headaches, chronic pain conditions, schizophrenia. Moreover, the pharmacological blockade the 5-HT7R is recently postulated as a new, fast acting, antidepressant strategy.[1,2] As a part of our ongoing efforts to discover new 5-HT7R ligands, we designed and synthesized a new series of compounds with 1,2,4-oxadiazole moiety. Such heterocyclic ring is important non-classical bioisoster group for esters and amides used previously, e.g. in development of new 5-HT1DR[3] and 5-HT6R[4] ligands. All the new compounds were evaluated for affinity at 5-HT7R, and also selectivity over 5-HT6, and 5-HT1A receptors was checked. It was found that 5-HT7R affinity depends on methylenearomatic substituent at position 3 of central 5-phenyl-1,2,4-oxadiazole fragment, as well as on the length of aliphatic linker between central core and terminal dimethylamine group. 1. Pittalà V. et al. Mini-Reviews in Medicinal Chemistry. 2007, 7, 945-60. 2. Mnie-Filali O. et al. Neuropsychopharmacology 2011, 36, 1275-88. 3. Beer M. S. et al. Br. J. Pharmacol. 1993, 110, 1196-200. 4. Russell M. G. et al. J. Med. Chem. 2001, 44, 3881-95. Acknowledgments This study were partly supported by grant PNRF-103-AI-1/07 from Norway through Norwegian Financial Mechanism