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Compounds with dual activity: Serotonin transporter inhibitor (SERT) and serotonin 5-HT2C receptor antagonist properties for the treatment of depression

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Abstract

Depression is a common mental disease, which affects 6-7% of the population. Major depressive disorder is treated by talk therapy or medication, usually by antidepressants which are either serotonin selective reuptake inhibitors (SSRI) like fluoxetine and paroxetine, or by serotonin and norepinephrine reuptake inhibitors (SNRI) like duloxetine and venlafaxine. Because of the well-known slow onset and side effects of the antidepressants, there is an unmet medical need for further efficient drugs with more advantageous side effect profiles. Some antidepressants, (e.g. trazodone, nefazodone, mianserin, mirtazapine) act both as SERT inhibitors and 5-HT2C antagonists. The suggestion arose that the compounds with dual activities might be advantageous. The design and synthesis of dually active compounds are more difficult processes than the design and synthesis of selective inhibitors. Éliás and coworkers developed various types of hybrid compounds with serotonin transporter inhibitor (SERT) and serotonin 5-HT2C receptor antagonist activities [O.Éliás et al. Bioorg. Med. Chem. Lett.24, 2118 (2014), ibid 26, 914 (2016)].

We have synthesized a compound family with substituted phenoxy-benzylamine moieties. Our novel compounds showed excellent rSERT Ki and r5-HT2C Ki values and advantageous physico-chemical properties (clogP, solubility). A few structure-activity relationships (SAR) have also been established.

Biography

Bölcskei H has completed her MSc study as a chemical engineer from University of Technology Budapest, Hungary. She received her PhD degree in 1979 from the same university and her scientific degree “candidate of sciences in 1988 from the Hungarian Academy of Sciences. Between 1973 and 2013 she worked as a researcher, later senior research associate at the Hungarian pharmaceutical company Gedeon Richter Plc. in the field of medicinal chemistry and neuroscience. Since 2009 she has been working as the associate professor of University of Technology and Economics, Budapest, Hungary. Her main research interest: Alkaloid chemistry, organic chemistry, medicinal chemistry. She has over 70 publications, and has been serving as a regular reviewer of reputed Journals. She was awarded by Géza Zemplén price in 1990.

Publications

1. Synthesis of Phenyl- and Pyridyl-substituted Benzyloxybenzaldehydes Suzuki-miyaura Coupling Reactions
2. Synthesis of Vinca Alkaloids and Related Compounds XLVIII. Synthesis of (+)-Catharanthine and (+)-Allocatharanthine
3. Synthesis of Spiro[cycloalkane-pyridazinones] with High Fsp3 Character
4. Eredmények a természetes szerves anyagok kutatásában. Új, daganatellenes hatású Vinca alkaloid származékok előállítása és flavon alkaloidok szintézise
5. The synthesis of (Iodobenzyl)oxybenzaldehydes, useful intermediates for biologically active targets
6. Voltage-gated sodium channel blockers, 2001-2006: An overview
7. Blockers of Voltage-Gated Sodium Channels for the Treatment of Central Nervous System Diseases
8. NMR study of 6-azabicyclo[3.2.1]octene derivatives, by-products of catharanthine synthesis
9. Synthesis of Vinca Alkaloids and Related Compounds LVI. 15',20'-Anhydrovinblastine Borane Complex. Structural Invetigations NMR Methods

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