Hong Liu, Expert Opin Environ Biol 2018, Volume 7
DOI: 10.4172/2325-9655-C3-025

Hong Liu

Shanghai Institute of Materia Medica, China

Design, synthesis and bioactivity evaluation of multi-targeted tetrahydroprotoberberine derivatives (THPBs)

Tetrahydroprotoberberines (THPBs) belong to a class of tetrahydroisoquinoline alkaloids with multiple bioactivities derived mainly from Chinese medicinal herbs. An effective and rapid method for the microwave-assisted preparation of the key intermediate for the total synthesis of THPBs including l-stepholidine (l-SPD) was developed. A series of new THPB derivatives were designed, synthesized, and tested for their binding affinity towards dopamine (D1 and D2) and serotonin (5-HT1A and 5-HT2A) receptors. Many of the THPB compounds exhibited high binding affinity and activity at the dopamine D1 receptor, as well as high selectivity for the D1 receptor over the D2, 5-HT1A, and 5-HT2A receptors. On the basis of the pharmacophore model of the marketed drug silodosin, THPBs were modified by introducing an indole segment into their core scaffolds. In calcium assays, 7 compounds displayed excellent antagonistic activities against α1A-ARs, with IC50 less than 250 nM. In the functional assay using isolated rat tissues, compound (S)-27 inhibited norepinephrineinduced urethra smooth muscle contraction potently, without inhibiting the aortic contraction, displaying a better tissue selectivity than the marketed drug silodosin. Additional results of preliminary safety studies and pharmacokinetics studies indicated the potential druggability for compound (S)-27 which is a promising lead for the development of selective α1A-AR antagonists for the treatment of Benign Prostatic Hyperplasia (BPH).

Biography

Hong Liu received her M.S. and Ph.D. in medicinal chemistry from the China Pharmaceutical University in 1996 and 1999. After a postdoctoral at Shanghai Institute of Materia Medica, Chinese Academy of Sciences, she was appointed to the faculty of Shanghai Institute of Materia Medica in 2001. As a visiting scientist, she stayed at University of Texas Medical Branch at Galveston for two years. Dr. Liu's efforts mainly dedicate to the research of pharmaceutical chemistry and drug design and discovery. She is also focusing on the development of new organic synthetic methodologies, building focused combinatorial libraries, and the discovery and optimization of lead compounds for new drugs.

hliu@simm.ac.cn

Notes: