Hong Liu et al., Organic Chem Curr Res 2018, Volume:7
DOI: 10.4172/2161-0401-C1-022

Structural modification and bioactivity evaluation of multi-targeted Tetrahydroprotoberberine Derivatives (THPBs)

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Tetrahydroprotoberberines (THPBs) belong to a class of tetrahydroisoquinoline alkaloids with multiple bioactivities derived mainly from Chinese medicinal herbs. In the 1960, tetrahydropalmatine (THP) and its analogs were tested as new types of central depressants. Subsequent investigations focused on the effect of THP on the dopaminergic system. 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-HT_{1A} and 5-HT_{2A}) receptors. Many of the THPB compounds exhibited high binding affinity and activity at the dopamine D1 receptor, as well as high selectivity for the D_1 receptor over the D_2, 5-HT_{1A}, and 5-HT_{2A} 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 α_{1A}-ARs, with IC50 less than 250 nM. In the functional assay using isolated rat tissues, compound (*S*)-27 inhibited norepinephrine induced 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).

Recent publications

1. Guo D, Li J, Lin H, Zhou Y, Chen Y, et al. (2016) Design, synthesis, and biological evaluation of novel tetrahydroprotoberberine derivatives (THPBs) as selective α1A-adrenoceptor antagonists. J Med Chem 59:9489-9502.
2. Zhou S, Duan Y, Wang J, Zhang J, Sun H, et al. (2017) Design, synthesis and biological evaluation of 4,7,12,12a-tetrahydro-5H-thieno[3',2':3,4]pyrido[1,2-b]isoquinolines as novel adenosine 5'-monophosphate-activated protein kinase (AMPK) indirect activators for the treatment of type 2 diabetes. Eur J Med Chem 140:448-464
3. Li Z, Huang J, Sun H, Zhou S, Guo L, et al. (2014) Design, synthesis and evaluation of benzo[a]thieno[3,2-g]quinolizines as novel l-SPD derivatives possessing dopamine D_1, D_2 and serotonin 5-HT_{1A} multiple action profiles. Bioorg Med Chem 22:5838-5846.

Biography

Hong Liu received her MS and PhD in Medicinal Chemistry from the China Pharmaceutical University in 1996 and 1999. After her Postdoctoral studies at Shanghai Institute of Materia Medica, Chinese Academy of Sciences, she was appointed at 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. Her 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.

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