

Design, Synthesis and Biological Evaluation of a Novel Series of Peripheral-selective Noradrenaline Reuptake Inhibitor, Part I -Lead Series Discovery and Biological Concept Validation-

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Centrally acting noradrenaline reuptake inhibitor (NRI) is reportedly effective for patients with stress urinary incontinence (SUI) by increasing urethral closure in the clinical Phase IIa study with esreboxetine. Noradrenaline transporters are expressed in both central and peripheral nervous systems and the contribution of each site to efficacy has not been clarified. This poster describes the development of a series of peripheral-selective 7-phenyl-1,4-oxazepane NRIs to investigate the contribution of the peripheral site to increasing urethral resistance in rats. An acetamide derivative which showed high peripheral NET selectivity in rats increased urethral resistance in a dose-dependent manner and exhibited a maximal effect on par with esreboxetine. These results indicate that the urethral resistance-increasing effects of NRI in rats are fully achieved by the peripheral selective NET inhibition.