26G-ISMS28 **Design, Synthesis and Biological Evaluation of a Novel Series of Peripheral-selective Noradrenaline Reuptake Inhibitor, Part II -Lead Optimization with Avoiding P-gp Substrate and Genetic Polymorphism-**

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Peripherally selective inhibition of noradrenaline reuptake is a novel mechanism for the treatment of stress urinary incontinence to overcome adverse effects associated with central action. Herein, we describe our medicinal chemistry approach to discover peripheral-selective noradrenaline reuptake inhibitors to avert the risk of P-gp-mediated DDI at the blood–brain barrier. We observed that steric shielding of the HBA and HBD reduced the multidrug resistance protein 1 (MDR1) efflux ratio; however, the resulting compound was mainly metabolized by CYP2D6 and CYP2C19 in the in vitro phenotyping study, implying the risk of PK variability based on the genetic polymorphism. Replacement of the hydrogen atom with a deuterium atom in a strategic, metabolically hot spot led to compound, which was mainly metabolized by CYP3A4. To our knowledge, this study represents the first report of the effect of deuterium replacement for a major metabolic enzyme.