26G-ISMS36 **Synthesis and Evaluation of Potent, Orally Available, Well-balanced EP2 and EP3 Dual Agonists**

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Our purpose was to develop PGE2 analogs possessing highly potent dual EP2 and EP3 agonist activity with selectivity against the other two subtypes (EP1 and EP4), because a dual EP2 and EP3 agonist is expected as an effective therapeutics addressing unmet medical needs for treatment of a underactive bladder (UAB). While no dual EP2 and EP3 agonist has been reported, a dual EP2 and EP4 agonist with selectivity against the EP1 and EP3 receptor subtypes was reported in 2012[1]. At first, we synthesized cyclic carbamate derivatives having cyclobutyl group and terminal fluorine atom in order to reduce EP4 agonist activity and add EP3 agonist activity, and then replaced the core structure with cyclopentanone for enhancement of orally absorption. The resulting compound, **ONO-8055,** showed excellent potency (human EC_{50} EP2 = 0.67 nM, EP3 = 0.7 nM), EP1 and EP4 subtype selectivity (>400-fold) and good pharmacokinetic profiles. Regarding *in vivo* efficacy, **ONO-8055** improved the lower urinary tract dysfunctions of neurogenic underactive bladder in a rat lumber spinal stenosis (LCS) model[2]. Furthermore, as a result of Phase I trial in Europe, there was no safety or PK concern. **ONO-8055** is currently under development as a new highly promising UAB drug.

[1)] Kambe, T.; Maruyama, T; Nakai, Y; Oida H.; Maruyama T.; Abe N.; Nishiura, A.; Nakai, H.; Toda, M. *Bioorganic & Medicinal Chemistry*, **2012**, *20*, 3502.

[2)] Sekido N.; Kida J.; Mashimo H.; Wakamatsu D.; Okada H.; Matsuya H.; *J Urol,* **2016**, *196*, 609.