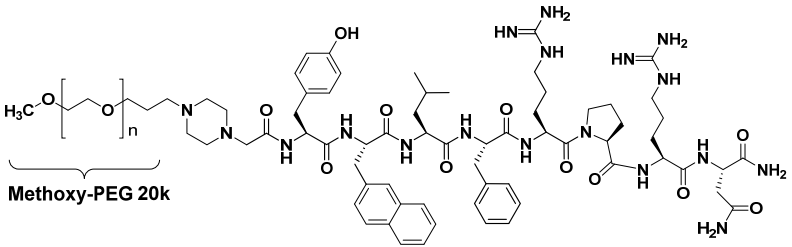
27O-ISMS18 **Design and Synthesis of a Neuromedin U Receptor 2-selective PEGylated Peptide with Potent Body Weight-Lowering Effect**

○Yoko KANEMATSU[1], Naoki NISHIZAWA[1], Tomoko KAISHO[1], Hiroaki NAGAI[1], Taisuke MOCHIDA[1], Tomoko ASAKAWA[1], Hiroshi INOOKA[1], Katsuko DOTE[1], Hisashi FUJITA[1], Kouta MATSUMIYA[1], Hideaki HIRABAYASHI[1], Junichi SAKAMOTO[1], Tetsuya OHTAKI[1], Shiro TAKEKAWA[1], Taiji ASAMI[1]
[1]Pharmaceutical Research Division, Takeda Pharmaceutical Company, Ltd.

Neuromedin U (NMU) is a neuropeptide that has been reported to have a wide variety of peripheral and central activities via its receptors; NMUR1 and NMUR2. Recently, there has been increased attention to NMU as a promising new treatment for obesity. Human NMU octapeptide (NMU-8) is the minimum requirement for agonist activity, however, the low metabolic stability of NMU-8 in biological fluids has limited its use in biomedical applications. Therefore, we designed and synthesized NMU-8 analogues covalently attached to polyethylene glycol (PEG; molecular weight, 20 kDa; PEG20k) via a linker. We found that the replacement of Phe with 3-(2-Naphthyl)alanine at position 19 increased NMUR2 selectivity with retaining high agonist activity. An NMUR2-selective analogue **1**, which has piperazin-1-ylacetyl linker and PEG20k, showed a potent anoretic and body weight-lowering effect by the repeated once-daily administration for 2 weeks in diet-indued obese mice.



1