S31-4 Discovery of selective antagonists for prostaglandin E2 receptor subtype EP1

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It has been well known that prostaglandin E_2 (PGE_2) has many physiological actions, which are mediated through four receptor subtypes (EP1, EP2, EP3 and EP4). These receptor subtypes are distributed over various tissues. Nonselective receptor agonist/antagonist causes both of the favorable and unfavorable actions because of the diversity of the biological activities of PGE_2. Thus, identification of subtype-selective agonist/antagonist has been thought to be one of the promising approaches to develop new drugs without unfavorable actions. Among the four receptor subtypes, EP1 has been considered to be a promising therapeutic target for the treatment of overactive bladder (OAB) because direct administration of PGE_2 into bladder causes OAB-like symptom in animal experiments.

Based on the information described above, we started the project to find subtype-selective EP1 receptor antagonists as a new drug for OAB. Starting from a hit compound **1** found in our in-house chemical library, we have resulted in the highly potent and highly subtype-selective EP1 antagonist **2** through the study of the chemical optimization.