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Discovery of highly selective κ-opioid receptor agonists: 10α-Hydroxy TRK-820 derivatives

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ABSTRACT

κ-Opioid receptor agonists with high selectivity over the μ-opioid receptor are attractive targets in the development of drugs for pain and pruritus. We previously reported the synthesis of 10α-hydroxy TRK-820 (**1**). In this study, we elucidated the biological properties of **1** and optimized its 6-acyl unit by modifying our synthetic route. Among the 10α-hydroxy TRK-820 derivatives prepared, **26** showed the most potent κ-opioid agonist activity (EC_{50} = 0.00466 nM) and excellent selectivity and **22** was the most κ-selective agonist.

The μ-opioid receptor (MOR) is deeply involved in the analgesic effect of morphine, and thus various MOR agonists are used as analgesics. However, MOR agonists cause drug dependence and respiratory depression. Therefore, analgesics that avoid these adverse effects are strongly desired in the clinical setting. The κ-opioid receptor (KOR) has attracted interest because its activation produces an analgesic effect with minimal physical dependence and respiratory depression.[1] Nalbuphine is a KOR agonist/MOR antagonist used as an analgesic (Fig. 1).[2] In addition, KOR agonists are useful for treating pruritus. We previously developed TRK-820 (nalfurafine hydrochloride: a 4,5-epoxymorphinan derivative that is a KOR agonist/MOR partial agonist) as an antipruritic agent for uremic pruritus.[3] TRK-820 is a strong KOR agonist (EC_{50}: 0.0082 nM) and moderate MOR agonist (EC_{50}: 1.7 nM).[4] Because these 4,5-epoxymorphinan KOR agonists affect also MOR to some extent, the intrinsic potential of a pure KOR agonist as medication is not known. Pure KOR agonists are attractive targets and a challenging theme for drug development. Accordingly, several pharmaceutical companies are conducting research on KOR agonists; in particular, CR-845 is highly KOR-selective peptide that is currently in clinical trials for treatment of pain by intravenous administration.[5]

We previously reported 10α-hydroxy TRK-820 (**1**), which was obtained as a degradation product in the development of a TRK-820 formulation (Fig. 2).[6] We confirmed **1** has strong KOR agonist activity (EC_{50}: 0.025 nM) and excellent selectivity for KOR over MOR (44,000 fold). Therefore, we expected that **1** could serve as a starting point for developing a pure KOR agonist for use as an orally available drug. In this letter, we report a synthetic method and the pharmacological properties of 10α-hydroxy TRK-820 derivatives.

First, we tested the pharmacological effects of **1** in rats after partial sciatic nerve ligation (Fig. 3).[7] **1** was administered 7 days after ligation. The anti-allodynic effect of **1** was evaluated at 30 min after intravenous administration. Allodynia was assessed using the 50% withdrawal threshold measured according to the up-down method with von Frey filaments. A significant reduction of allodynia was observed in the 3 and 5 mg/kg groups compared with the vehicle group.

We also tested the antipruritic effect of **1** on substance P (SP)-induced scratching behavior in mice (Fig. 4).[8] **1** was administered by intraperitoneal injection to mice, and 15 min later, SP (250 nmol/site) was administered by intradermal injection into the nape of the neck. Immediately after the injection of SP, the number of scratching behavior was recorded for 30 min by using MicroAct® (Neuroscience, Tokyo, Japan). Scratching behavior was significantly inhibited in the 3 mg/kg groups compared with the vehicle group.

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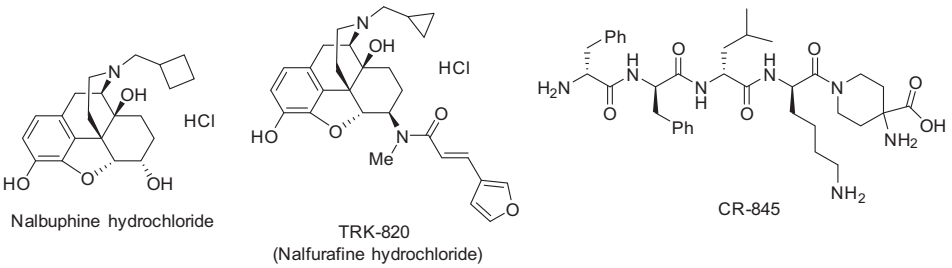

Fig. 1. Chemical structures of known κ-opioid receptor agonists.

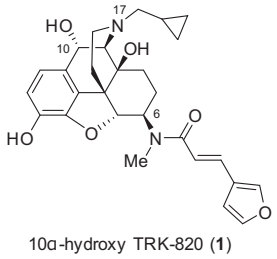

Fig. 2. Structure of 10α-hydroxy TRK-820 (**1**).

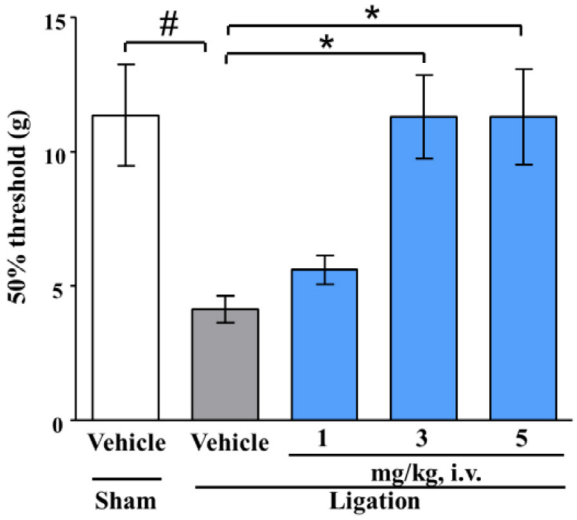

Fig. 3. Anti-allodynic effect of **1** in rats after partial sciatic nerve ligation. i.v., intravenous. *: $P < 0.025$ versus Ligation-vehicle-treated group (Shirley-Williams test), #: $P < 0.05$ versus sham-vehicle-treated group (t-test).

In these *in vivo* experiments, **1** showed good *anti*-allodynic and antipruritic effects, both of which appear promising for therapeutic use. To date, although no structure–activity relationship (SAR) study of 10α-hydroxy-4,5-epoxymorphinan has not been conducted, Portoghese and co-worker demonstrated that the subtype selectivity of 4,5-epoxymorphinan could be controlled through the message-address concept.[9–11] Additionally, we reported that changing the address site of norbinaltorphimine (C6 position of 4,5-epoxymorphinan) to flexible a substituent based on the same concept afforded a KOR-selective ligand.[12] Therefore, we modified the 6-amide unit of **1** to clarify the SAR of 6-amide-10α-hydroxy-4,5-epoxymorphinans.

We have previously reported the synthesis of **1**, which required multiple steps and introduction of the 10α-hydroxy group after the 6-acyl group.[13] However, this route is not suitable for modifying the 6-amide unit. Thus, we developed an effective intermediate for acylation of the 6-amino group in the last step.

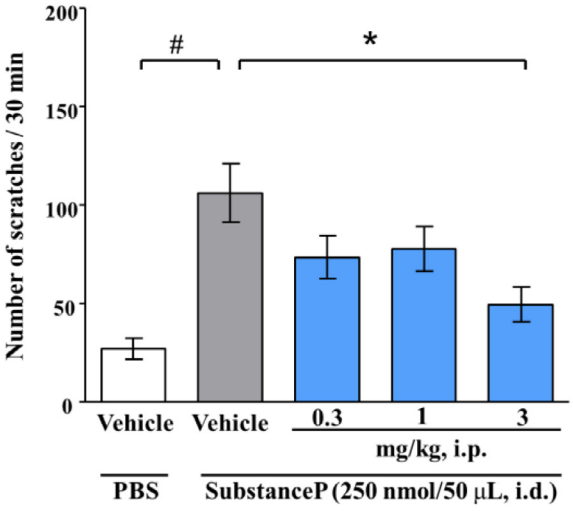

Fig. 4. Effects of **1** on substance P-induced scratching behavior in mice. i.d., intradermal; i.p., intraperitoneal; PBS, phosphate-buffered saline. *: $P < 0.05$ versus substance P-vehicle-treated group (Dunnett's multiple comparison), #: $P < 0.05$ versus PBS-vehicle-treated group (Welch's test).

First, we considered how to easily introduce the 10α-hydroxy group and then to derivatize the acyl group in the last step. In our previous study, the 10-oxo compound was reduced with $NaBH_4$ to selectively give 10β-hydroxy compound, which was converted into the 10α-hydroxy compound by mesylation and the subsequent S_N2 inversion with sodium acetate and hydrolysis.[13,14] Because of the steric effect of the 17-cyclopropylmethyl group, the hydride's approach from the α-face (front side) is tightly restricted. Hence, we attempted to use ceric ammonium nitrate (CAN) as an oxidant. CAN induces one-electron oxidization and provides a carbon radical. After the susequent one-electron oxidation of the carbon radical, the resulting carbon cation reacts with water from the back side to provide a secondary alcohol forms. Because of the steric hindrance of the tri-substituted benzylic carbon, we expected that further oxidation would not occur. In our strategy, we selected naltalimide (TRK-130) as a starting material.[15,16] Thus, we established a kilogram-scale synthesis of TRK-130 and can easily derivatize the 6-amide part in the last step.

The 10α-hydroxy derivatives were synthesized by the route shown in Scheme 1. The phenolic hydroxyl group of TRK-130 was protected with a benzyl group. Using CAN, oxidation of the 10α position proceeded in moderate yield.[17–19] Deprotection of the phthalimide by treatment with hydrazine monohydrate gave amine **9**. Two-step reductive amination by treatment with benzaldehyde followed by formalin gave **10**. Removal of the two benzyl groups in **10** gave *N*-methyl amine **11** as a common intermediate. Finally, amidation with various carboxylic acids (**A**) or acyl chlorides (**B**) gave the desired compounds.