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Essential structure of opioid κ receptor agonist nalfurafine for binding to the κ receptor 2: Synthesis of decahydro(iminoethano)phenanthrene derivatives and their pharmacologies

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ABSTRACT

To clarify the essential structures of an opioid κ receptor selective agonist, nalfurafine, for binding to the κ receptor, we designed and synthesized some nalfurafine derivatives and the decahydro(iminoethano)phenanthrene derivatives with a cyclohexene moiety as a surrogate for the phenol ring. In addition to the 6-amide side chain and the 17-nitrogen substituted by a cyclopropylmethyl group, the 4,5-epoxy ring, phenolic hydroxy group, and angular hydroxy group played important roles in eliciting the binding properties of nalfurafine but these three moieties were not indispensable for binding to the κ receptor. Moreover, the phenol ring was also not essential for the binding to the κ receptor, and the cyclohexene moiety would play an important role in fixing the conformation of decahydro(iminoethano)phenanthrene derivatives to effectively raise the amide side chain, rendering a conformation that resembled the active one of nalfurafine.

Opioid receptors are now classified into three types (μ, δ, and κ) based on not only pharmacological studies, but also by molecular biological studies.[1] Narcotic addiction is believed to be derived from the μ receptor type, and therefore δ and κ types are promising drug targets for analgesics without addiction. Recently, one of our designed κ selective agonists, nalfurafine hydrochloride (TRK-820, Fig. 1),[2–6] was launched in Japan as an antipruritic for patients undergoing dialysis.[4,5] Although prototypical κ agonists with an arylacetamide structure such as U-50,488H[7,8] and U-69,593 (Fig. 1)[9] had serious side effects like psychotomimetic and aversive reactions,[10,11] nalfurafine showed neither aversive nor addictive effects.[12] This disparity of properties between nalfurafine and arylacetamide κ agonists was proposed to stem from the differences in κ receptor subtypes[13–16] that each compound interacted with: arylacetamide κ agonists would interact with the κ_1 receptor subtype,[14,15] whereas nalfurafine may interact with the κ_3 receptor subtype.[17–21] We were interested in the differences in the pharmacological effects between nalfurafine and the arylacetamide derivatives. We therefore designed and synthesized decahydroisoquinoline derivatives lacking the phenol ring moiety to clarify the essential structural features of nalfurafine that mediate binding to the κ receptor on the basis of the new three-dimensional pharmacophore model of κ agonists.[22,23] The *trans*-fused decahydroisoquinoline derivatives **1** with a 6-amide side chain and a cyclopropylmethyl substituent at the nitrogen (Fig. 2)

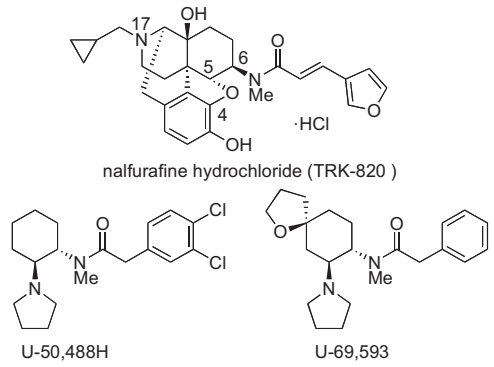

Figure 1. Structures of nalfurafine hydrochloride, U-50,488H, and U-69,593.

exhibited binding affinities and selectivities for the κ receptor, indicating that these two functional groups should be essential for the binding to the κ receptor.[24] Moreover, the subnanomolar K_i values of nalfurafine as opposed to the micromolar order binding affinity of **1** for the κ receptor suggested that the phenol moiety in nalfurafine could force the C-ring into the boat form and effectively increase the population of nalfurafine molecules in the most favorable conformation for binding to the κ receptor (Fig. 3).[24] Therefore, we attempted to elucidate the role of the phenol ring in nalfurafine in binding. In general, the phenol ring moiety in the morphinan derivatives is thought to be the most important pharmacophoric unit to provide a π–π interaction and a hydrogen bond

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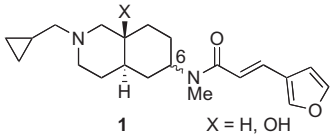


Figure 2. Structures of decahydroisoquinoline derivatives.

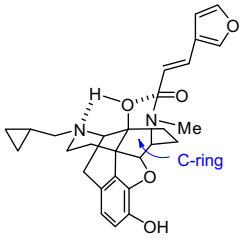


Figure 3. Proposed active conformation of nalfurafine binding to the κ receptor.

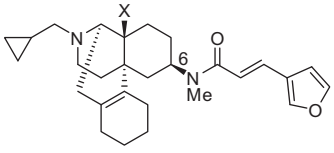
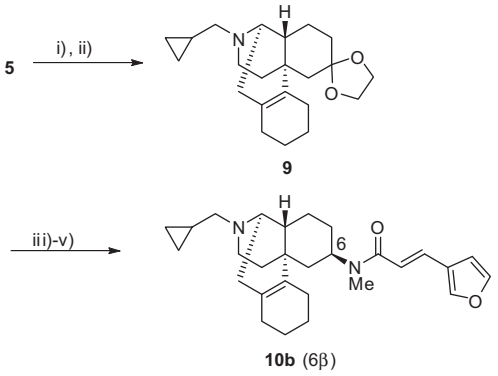


Figure 4. Structures of designed decahydro(iminoethano)phenanthrene derivatives.

with the opioid receptor.[25–27] So, to examine the role of the phenol ring, we designed decahydro(iminoethano)phenanthrene derivatives **2** (Fig. 4) whose cyclohexene moiety would mimic the phenol part in nalfurafine, but could not provide either a π–π interaction or a hydrogen bond with the receptor. The olefin moiety in **2** would fix the cyclohexene moiety in a position resembling that of the phenol ring in nalfurafine. Herein, we report the synthesis of some nalfurafine derivatives and the designed decahydro(iminoethano)phenanthrene derivatives **2**. We also evaluate their binding affinities for the opioid receptors.

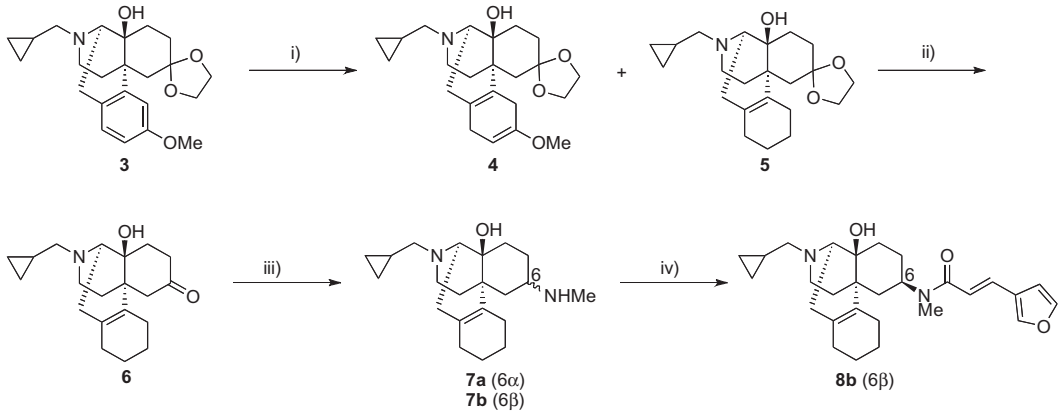
We attempted to synthesize the designed compound **8b** (X = OH, Fig. 4) (Scheme 1) starting from morphinan **3** prepared by a reported method.[28,29] Morphinan **3** was reduced under the Birch conditions to give cyclohexadiene **4** and cyclohexene **5**. The



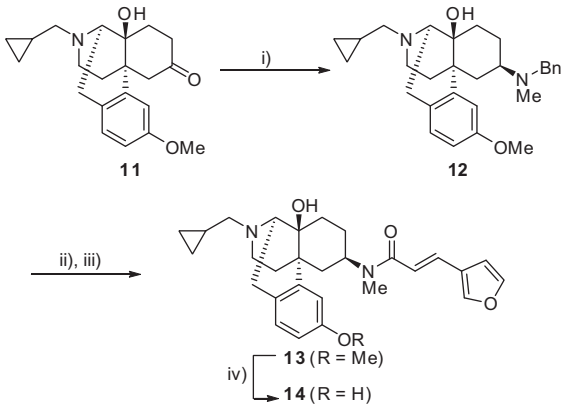
Scheme 2. Reagents and conditions: (i) $SOCl_2$, pyridine, rt, 46%; (ii) H_2, Pd/C, MeOH, rt, 40%; (iii) 2 M HCl, MeOH, 80 °C, 82%; (iv) $MeNH_2$·HCl, $NaBH_3CN$, MeOH, 70 °C, then separation of 6α- and 6β-amines; (v) (2*E*)-3-(furan-3-yl)prop-2-enoyl chloride, Et_3N, CH_2Cl_2, rt, 20% from **9** via 6β-amine.

olefin moiety in **5** was resistant to hydrogenation under various conditions. Ketone **6**, obtained by hydrolysis of **5**, was submitted to reductive amination to provide amines **7**,[30] of which 6β-isomer **7b** was converted into **8b** by acylation. The other designed compound **10b**[30] (X = H, Fig. 4) was synthesized by a similar manner as shown in Scheme 1. Preparation of compound **9** (Scheme 2) was accomplished by dehydration of **5** using thionyl chloride and subsequent catalytic hydrogenation.[31] The synthesis of nalfurafine derivative **14** without a 4,5-epoxy ring commenced with morphinan **11** (Scheme 3). The reductive amination of **11**[32] with benzylmethylamine stereoselectively gave 6β-amine **12** in the same manner as for 4,5-epoxymorphinans.[33,34] Nalfurafine derivative **14** was obtained from 6β-amine **12** by debenzylation, acylation, and subsequent demethylation. The key reaction in the synthesis of nalfurafine derivative **18**, which lacked the phenolic hydroxy group, was deoxygenation via 1-phenyltetrazol-5-yl ether **16** (Scheme 4).[35,36] Ether **16** prepared from naltrexone (**15**) was treated under hydrogenolysis conditions to afford 3-dehydroxynaltrexone (**17**).[36] Compound **17** was converted to nalfurafine derivative **18** by similar methods shown in Scheme 3. Nalfurafine derivative **20**, without an angular hydroxy group, was prepared from 14-dehydroxynaltrexone (**19**)[31] by methods similar to those shown in Scheme 3 (Fig. 5).

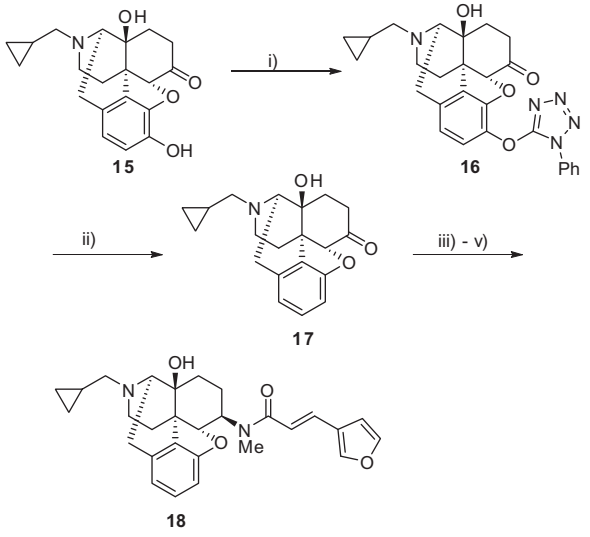
The binding affinities of the prepared compounds for the opioid receptors were evaluated with competitive binding assays. The results were shown in Table 1 with the affinities of nalfurafine and



Scheme 1. Reagents and conditions: (i) Li, NH_3 (liq.), EtOH, THF, −33 °C, **4**: 53%, **5**: 46%; (ii) 2 M HCl, MeOH, 80 °C, 92% from **5**; (iii) $MeNH_2$·HCl, $NaBH_3CN$, MeOH, 60 °C, **7a**: 64%, **7b**: 22%; (iv) (2*E*)-3-(furan-3-yl)prop-2-enoyl chloride, Et_3N, CH_2Cl_2, rt, 99% from **7b**.



Scheme 3. Reagents and conditions: (i) *p*-TsOH·H_2O, MeNHBn, $PhCO_2H$, PhH, reflux, then $NaBH_3CN$, EtOH, MS4A, 0 °C to rt, 36%; (ii) H_2, Pd/C, MeOH, rt, 60%; (iii) (2*E*)-3-(furan-3-yl)prop-2-enoyl chloride, Et_3N, CH_2Cl_2, rt, 74%; (iv) BBr_3, CH_2Cl_2, 0 °C to rt, 83%.



Scheme 4. Reagents and conditions: (i) 5-chloro-1-phenyl-1*H*-tetrazole, K_2CO_3, DMF, rt, 89%; (ii) H_2, Pd/C, AcOH, 50 °C, 89%; (iii) *p*-TsOH·H_2O, MeNHBn, $PhCO_2H$, PhH, reflux, then $NaBH_3CN$, EtOH, MS4A, 0 °C to rt, 74%; (iv) H_2, Pd/C, MeOH, rt, 71%; (v) (2*E*)-3-(furan-3-yl)prop-2-enoyl chloride, Et_3N, CH_2Cl_2, rt, 99%.

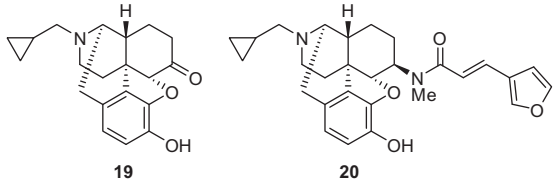


Figure 5. Structures of 14-dehydroxynaltrexone (**19**) and nalfurafine derivative **20**.

decahydroisoquinoline **1** (X = OH, 6β) for comparison. The assays were performed by previously reported procedures.[37]

Nalfurafine derivative **14** without the 4,5-epoxy ring showed affinities for the μ and κ receptors comparable to nalfurafine itself, but higher affinity to the δ receptor than nalfurafine. The 4,5-epoxy ring may hardly facilitate nalfurafine to acquire an active conformation as shown in Figure 3, which would result in the affinity of **14** for the κ receptor comparable to that of nalfurafine. The affinities of nalfurafine derivative **18** without the phenolic hydroxy group were lower for all three types of the opioid receptors (especially for the μ receptor, with 290-fold lower affinity than that of nalfurafine), but **18** had acceptable affinity for the κ receptor. As a result, the κ selectivity of **18** over the μ receptor increased markedly. This observation indicates that the phenolic hydroxy group, which is believed to be one of the most important pharmacophores to bind with the opioid receptor, would not be an essential pharmacophore for binding to the κ receptor. Nalfurafine derivative **20** without an angular hydroxy group maintained its affinities to the μ receptor compared to nalfurafine, whereas the affinity of **20** for the δ receptor increased. While the decrease in the affinity of **20** for the κ receptor would result from lacking the interaction between 6-amide side chain and 14-hydrogen. These outcomes indicated that the 4,5-epoxy ring, phenolic hydroxy group, and angular hydroxy group played important roles in eliciting the binding properties of nalfurafine but these structural features were not indispensable for binding to the κ receptor. Surprisingly, the designed compounds **8b** and **10b**, which have a cyclohexene moiety as a surrogate for the phenol ring, showed high affinity for the κ receptor and low affinities to the μ and δ receptors. These outcomes indicated that the benzene ring, which is believed to be one of the most important pharmacophores for binding with the opioid receptor, was not essential for binding to the κ receptor. The affinities of **8b** and **10b** for the κ receptor were about 3400- and 1500-fold higher than that of decahydroisoquinoline derivatives **1** (X = OH, 6β), respectively.[24] This result would stem from the ability of the cyclohexene moiety to force the conformation of **8b** and **10b** to effectively raise the amide side chain, a conformation in which the amide side chain at the upper side would resemble the active conformation of nalfurafine (Fig. 3). On the other hand, decahydro(iminoethano)phenanthrene derivatives **6** and **7b** lacking the 6-amide side chain showed low affinities for the κ receptor, supporting the idea that the amide side chain would play an important role in binding to the κ receptor.

In conclusion, to clarify the essential structures of nalfurafine for binding to the κ receptor, we designed and synthesized some nalfurafine derivatives and the decahydro(iminoethano)phenanthrene derivatives with the cyclohexene moiety serving as a surrogate for the phenol ring. In addition to the 6-amide side chain and the 17-nitrogen bearing the cyclopropylmethyl substituent, the 4,5-epoxy ring, phenolic hydroxy group, and angular hydroxy group played important roles in eliciting the binding properties

Table 1
Binding affinities of **6**–**8b**, **10b**, **14**, **18**, **20**, nalfurafine, and decahydroisoquinoline derivative **1** (X = OH, 6β) for opioid receptors[a]

compound	*Ki* (nM)			Selectivity	
	μ[b]	δ[c]	κ[d]	μ/κ	δ/κ
Nalfurafine	0.582	96.5	0.195	2.6	456
1[e]	>100,000	>100,000	19,130	—[f]	—[f]
6	391	939	787	0.50	1.19
7b	>1000	>1000	352	—[g]	—[g]
8b	83.2	308	5.64	14.7	54.5
10b	24.6	204	12.7	1.94	16.1
14	0.43	2.09	0.18	2.42	11.8
18	169	>1000	2.82	59.8	—[g]
20	0.51	8.82	0.35	1.47	25.3

[a] Binding assays were carried out in duplicate (κ: cerebellum of guinea pig, μ and δ: whole brain without cerebellum of mouse).
[b] [^{3}H] DAMGO was used.
[c] [^{3}H] DPDPE was used.
[d] [^{3}H] U-69,593 was used.
[e] Ref. 24.
[f] Selectivity was not calculated due to the K_i value for the μ or δ receptor was over 100,000 nM.
[g] Selectivity was not calculated due to the K_i value for the μ or δ receptor was over 1000 nM.

of nalfurafine, but these three moieties were not indispensable for binding to the κ receptor. Moreover, the decahydro(iminoethano)phenanthrene derivatives permitted us to determine that the phenol ring of nalfurafine was not essential for binding to the κ receptor as pharmacophores providing the hydrogen bond and the π–π interaction, but rather one of its key roles would be to effectively locate the amide side chain in a favorable conformation for the κ receptor binding.

Acknowledgments

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