Essential Structure of Opioid κ Receptor Agonist Nalfurafine for Binding to κ Receptor 1: Synthesis of Decahydroisoquinoline Derivatives and Their Pharmacologies

Hiroshi Nagase,* Satomi Imaide, Takaaki Yamada, Shigeto Hirayama, Toru Nemoto, Noriyuki Yamaotsu, Shuichi Hirono, and Hideaki Fujii

School of Pharmacy, Kitasato University; 5–9–1 Shirokane, Minato-ku, Tokyo 108–8641, Japan.
Received April 13, 2012; accepted May 14, 2012

On the basis of the three-dimensional pharmacophore model of opioid κ agonists, we simplified the structure of nalfurafine (selective κ agonist) to find the essential structural moieties for binding the opioid receptors, especially κ receptor type. As a result, we found that the *trans*-fused decahydroisoquinoline derivatives without a phenol ring bound the opioid receptor in micromolar order and that both the amide side chain and the nitrogen substituted by the cyclopropylmethyl group were indispensable moieties for eliciting the κ selectivity. The simple decahydroisoquinoline without amide side chain also bound the opioid receptor without receptor type selectivity, suggesting that the message-address concept would be applicable to even these simple derivatives. These findings that the simple decahydroisoquinoline derivatives showed the affinities for the opioid receptors, especially some of the compounds showed κ selectivity, are the first example in the opioid field.

Key words opioid; κ receptor; decahydroisoquinoline; nalfurafine; three-dimensional pharmacophore model

Three types of opioid receptors (μ, δ, κ) are now well established not only by 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. To obtain ideal analgesics without addiction and other side effects derived from the μ receptor, we have synthesized various kinds of naltrexone derivatives and have reported selective ligands for κ[2–9)] and δ[10–14)] receptors. Quite recently, one of our designed κ selective agonists, nalfurafine hydrochloride (TRK-820,[2,3,6,8,9)] Fig. 1), was launched in Japan as an antipruritic for patients undergoing dialysis.[6,8,9)]

Although many arylacetamide derivatives such as U-50,488H[15,16)] (Fig. 1) and U-69,593[17)] were synthesized and developed as κ agonists, all of these derivatives were eliminated from clinical trials as not only analgesics but also as antipruritics because of their serious side effects like psychotomimetic and aversive reactions.[18,19)] In contrast, nalfurafine has neither aversive nor addictive effects.[20)] Our interest in the differences in the pharmacological effects between nalfurafine and the arylacetamide derivatives led us to conduct a detailed structure activity relationship investigation of nalfurafine derivatives. From these studies, we developed the hypothesis that in the active conformation of nalfurafine (Fig. 2), the C-ring would assume the boat form, thereby elevating the amide side chain to bind the κ receptor.[4,5,21,22)] Based on this hypothesis, we designed and synthesized KNT-63 with an oxabicyclo[2.2.2]octane skeleton (Fig. 1), and confirmed its high affinity for the κ receptor.[5)] We also proposed a new three-dimensional pharmacophore model applicable to some κ agonists with various chemotypes.[21,22)] Our new pharmacophore model of κ agonists supported the proposed active conformation of nalfurafine and indicated that the binding modes of κ agonists to the κ receptor could be classified into four types. Nalfurafine belongs to binding mode type I, whereas U-50,488H represents binding mode types II or III (Fig. 3). On the basis of the model, we attempted to identify the essential structural features of nalfurafine required for binding to the κ receptor. From the view point of the message-address concept,[23–26)] which is a useful guideline for designing selective ligands for the opioid receptor types, the binding mode type II seemed to resemble a binding pattern for the message part, *i.e.*, the μ antagonist naltrexone. So, we focused on the binding mode type III and compared the conformations of nalfurafine and U-50,488H (Fig. 3B) to identify two common structural moieties: a basic nitrogen and an amide side chain. These observations prompted us to design simple decahydroisoquinoline derivatives **1** (Fig. 4) which contain the same structures as nalfurafine, but without the phenol ring moiety. Herein, we report the synthesis of the designed decahydroisoquinoline derivatives and the evaluation of their binding affinities for the opioid receptor types.

The designed compound **1** (X=H) was prepared from piperidone **2** (Chart 1). Piperidone **2** was converted to α,β-unsaturated ketone **5** by condensation with dimethyl carbonate and subsequent Robinson annulation.[27,28)] Birch reduction of **5** afforded *trans*-fused decahydroisoquinolinone **6**.[28)] The target compounds **9** were obtained from **6** as a mixture of 6α- and 6β-amides *via* exchange of *N*-substituent, deacetalyzation reductive amination, and following acylation. The corresponding *N*-methyl derivatives **10** (Fig. 5) were also synthesized by the same manner from **6**. The synthesis of the designed compounds **1** with an angular hydroxy group (X= OH) commenced with tetrahydroisoquinoline **11** prepared by the reported method[29)] (Chart 2). Enol ether **12** prepared from **11** by Birch reduction was acylated and hydrolyzed to give

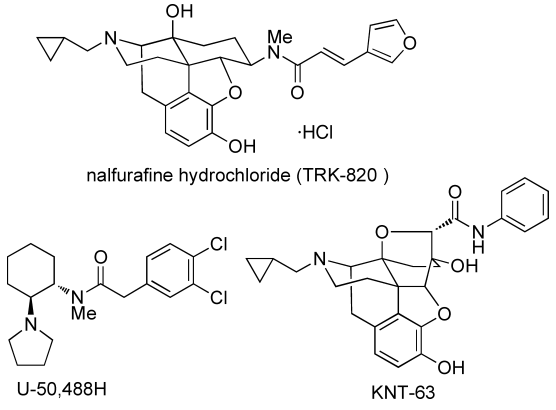


Fig. 1. Structures of Nalfurafine Hydrochloride, U-50,488H, and KNT-63

The authors declare no conflict of interest.

* To whom correspondence should be addressed. e-mail: nagaseh@pharm.kitasato-u.ac.jp

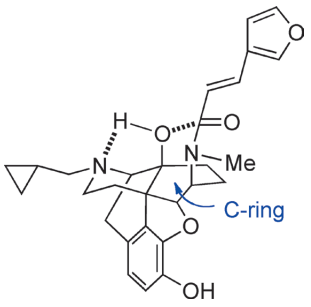


Fig. 2. Proposed Active Conformation of Nalfurafine Binding to the κ Receptor

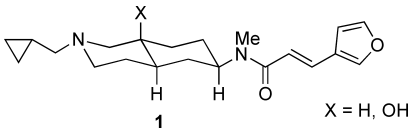


Fig. 4. Structure of the Designed Decahydroisoquinoline **1**

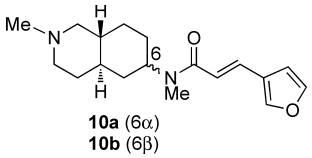


Fig. 5. Structure of *N*-Methyldecahydroisoquinoline Derivatives **10**

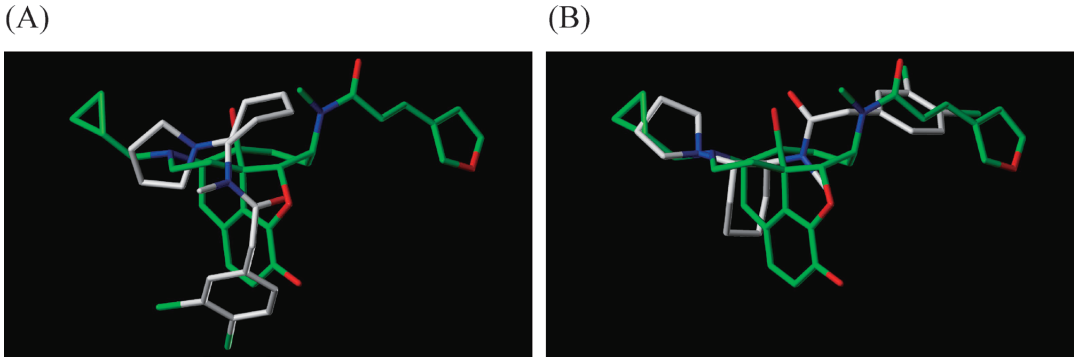
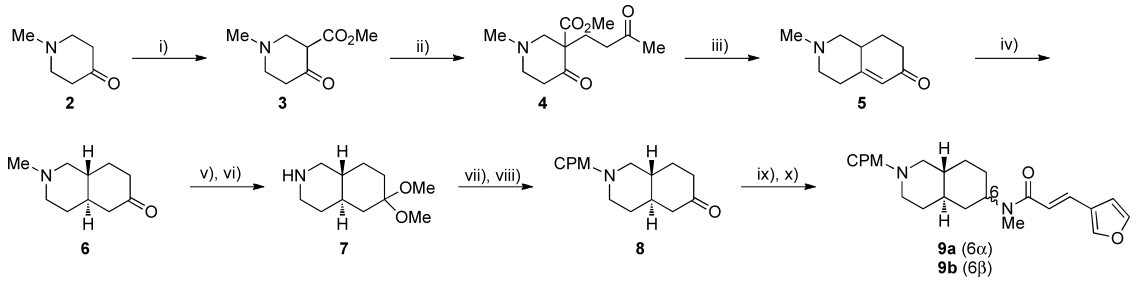


Fig. 3. (A) Superimposition of Active Conformation of Nalfurafine (Binding Mode Type I, Green) and U-50,488H (Binding Mode Type II, White) and (B) Superimposition of Active Conformation of Nalfurafine (Binding Mode Type I, Green) and U-50,488H (Binding Mode Type III, White)



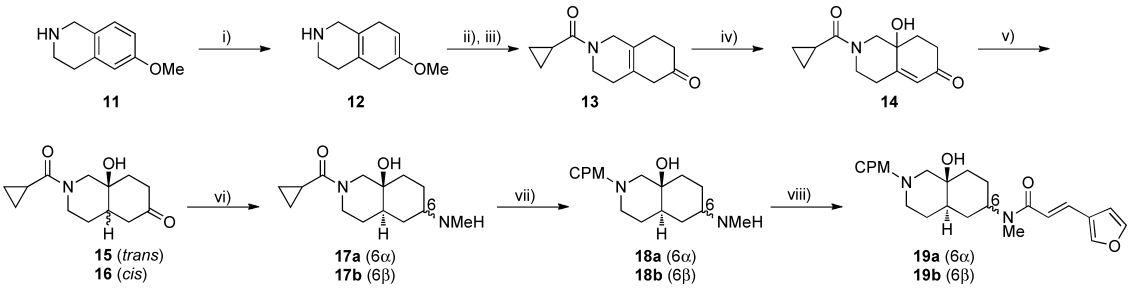
Reagents and conditions: i) NaH, $CO(OMe)_2$, toluene, reflux, 57%; ii) methyl vinyl ketone, H_2O, rt, 63%; iii) K_2CO_3, H_2O, reflux, 34%; iv) Li, NH_3 (liq.), EtOH, −78°C, 40%; v) α-chloroethyl chloroformate, K_2CO_3, $(CHCl_2)_2$, reflux; vi) MeOH, reflux, 53% from **6**; vii) *c*-PrCHO, $NaBH_3CN$, AcOH, CH_2Cl_2, 0°C to rt; viii) 1 M HCl, 100°C, 36% from **7**; ix) $MeNH_2$·HCl, $NaBH_3CN$, MeOH, reflux; x) 3-(furan-3-yl)acryloyl chloride, Et_3N, CH_2Cl_2, 0°C, **9a**: 14% from **8**, **9b**: 26% from **8**. CPM: cyclopropylmethyl.

Chart 1

β,γ-unsaturated ketone **13**.[28] The treatment of **13** with *m*CPBA provided α,β-unsaturated ketone **14** with an angular hydroxy group, and following hydrogenation of **14** afforded *trans*- and *cis*-fused decahydroisoquinolinones **15** and **16**. The target compounds **19** were obtained from *trans*-fused **15** *via* reductive amination, reduction of amide, and subsequent acylation.

The binding affinities of the prepared compounds for the opioid receptor types were evaluated with competitive binding assays (Table 1). The assays were performed by a modification of a previously reported procedure.[14]

Although all the synthesized compounds showed weak binding affinities for the opioid receptors (micromolar order affinities), *N*-cyclopropylmethyl (CPM) derivatives **9** and **19** had significant affinities and selectivities for the κ receptor. To the best of our knowledge, this was the first result that such simple *trans*-decahydroisoquinoline derivatives without an angular aryl group exhibited κ opioid receptor affinities and selectivities.[30–32] The angular hydroxy group in nalfurafine significantly influenced the κ selectivity,[3,8] whereas the angular substituent (H or OH) in decahydroisoquinoline derivatives **9** and **19** had minimal influence in the κ selectivity. Despite the presence of the same amide side chain with the same configuration as that of nalfurafine, the 6β-amide isomers **9b** and **19b** showed worse affinities and selectivities for the κ receptor than the corresponding 6α-amide compounds **9a** and **19a**. This improved binding might result from the participation of the boat conformer **A**′ of the 6α-amides which is favored over the chair conformer **A** by a steric repulsion due to 1,3-interaction in **A** (Fig. 6). The amide side chain in the conformer **A**′ could be oriented toward the upper side to more effectively bind to the κ receptor and this orientation is not possible in the stable chair conformer **B** of the 6β-amides. The



Reagents and conditions: i) Li, NH_3 (liq.), EtOH, THF, −78°C, 80%; ii) *c*-PrCOCl, Et_3N, CH_2Cl_2, rt; iii) 0.5 M HCl, THF, rt, 75% from **12**; iv) *m*CPBA, CH_2Cl_2, rt, 70%; v) H_2, Pd/C, THF, rt, **15**: 49%, **16**: 47%; vi) $MeNH_2$·HCl, $NaBH_3CN$, MeOH; vii) $LiAlH_4$, THF, rt, **18a**: 24% from **15**, **18b**: 19% from **15**; viii) 3-(furan-3-yl)acryloyl chloride, Et_3N, CH_2Cl_2, 0°C, **19a**: 93% from **18a**, **19b**: 93% from **18b**. CPM: cyclopropylmethyl.

Chart 2

Table 1. Binding Affinities of Decahydroisoquinolines **9**, **10**, **18**, and **19** for Opioid Receptor Types[a)]

Compound	K_i (μM)		
	μ[b)]	δ[c)]	κ[d)]
9a	45.7	>100	11.0
9b	>100	>100	19.2
10a	>100	12.2	>100
10b	9.82	85.2	15.3
18a	20.6	32.1	36.3
18b	>100	36.1	>100
19a	>100	>100	11.4
19b	>100	>100	19.1

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.

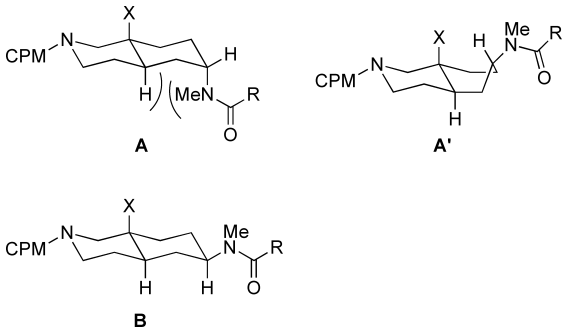


Fig. 6. Conformers **A** and **A′** of *trans*-Fused Decahydroisoquinoline-6α-amides **9a** and **19a**, and Conformer **B** of *trans*-Fused Decahydroisoquinoline-6β-amides **9b** and **19b**

trans-decahydroisoquinolines **9** and **19** showed noteworthy affinities for the κ receptor, however their affinities were lower than that of nalfurafine which displayed subnanomolar order affinity.[9)] These observations suggest that the phenol moiety plays an important role in elicitation of high affinity for the opioid receptor types but that it is not an indispensable part for binding to the κ receptor.[33–37)] The phenol functionality in nalfurafine would force the C-ring to assume a boat form and effectively increase the population of the active conformation. *trans*-Decahydroisoquinoline **18a** without the amide side chain showed binding affinities for the all opioid receptor types but no selectivity for the κ receptor was observed. It is remarkable that even the simple decahydroisoquinoline without amide side chain exhibited affinity for each of the opioid receptor types and that the message-address concept would also be applicable to the decahydroisoquinoline derivatives. This result would support the importance of the amide side chain for conferring selectivity to the κ receptor binding. Compared to the *N*-CPM derivatives **9**, *N*-methyl derivatives **10** lost κ selectivities, confirming that the *N*-CPM substituent is preferable for elicitation of the κ selectivity.

In conclusion, on the basis of the three-dimensional pharmacophore model of κ agonists, we simplified the structure of nalfurafine to find the essential structural determinants for binding the opioid receptor, especially the κ receptor type. As a result, we found that the *trans*-fused decahydroisoquinoline derivatives without a phenol ring bound the opioid receptor in the micromolar order and that both the amide side chain and the nitrogen substituted by the CPM group were indispensable moieties for eliciting the κ selectivity. The simple decahydroisoquinoline without an amide side chain could also bind the opioid receptor without receptor type selectivity, suggesting that the message-address concept would be applicable to even these simple derivatives. These findings that the simple decahydroisoquinoline derivatives showed the affinities for the opioid receptor, especially with some of the compounds showing κ selectivity, are unprecedented in opioid research. The outcomes are expected to contribute to the design of new κ opioid selective ligands.

Acknowledgements We acknowledge the financial supports from Shorai Foundation for Science, Uehara Memorial Foundation, and JSPS KAKENHI (23590133) [Grant-in-Aid for Scientific Research (C)]. We also acknowledge the Institute of Instrumental Analysis of Kitasato University, School of Pharmacy for its facilities.

References and Notes

1) Dhawan B. N., Cesselin F., Raghubir R., Reisine T., Bradley P. B., Portoghese P. S., Hamon M., *Pharmacol. Rev.*, **48**, 567–592 (1996).
2) Nagase H., Hayakawa J., Kawamura K., Kawai K., Takezawa Y., Matsuura H., Tajima C., Endo T., *Chem. Pharm. Bull.*, **46**, 366–369 (1998).
3) Kawai K., Hayakawa J., Miyamoto T., Imamura Y., Yamane S., Wakita H., Fujii H., Kawamura K., Matsuura H., Izumimoto N., Kobayashi R., Endo T., Nagase H., *Bioorg. Med. Chem.*, **16**, 9188–9201 (2008).
4) Nemoto T., Fujii H., Narita M., Miyoshi K., Nakamura A., Suzuki T., Nagase H., *Bioorg. Med. Chem. Lett.*, **18**, 6398–6401 (2008).
5) Nagase H., Watanabe A., Nemoto T., Yamaotsu N., Hayashida K., Nakajima M., Hasebe K., Nakao K., Mochizuki H., Hirono S., Fujii H., *Bioorg. Med. Chem. Lett.*, **20**, 121–124 (2010).
6) Nakao K., Mochizuki H., *Drugs Today* (Barc.), **45**, 323–329 (2009).

7) Nemoto T., Yamamoto N., Watanabe A., Fujii H., Hasebe K., Nakajima M., Mochizuki H., Nagase H., *Bioorg. Med. Chem.*, **19**, 1205–1221 (2011).
8) Nagase H., Fujii H., *Top. Curr. Chem.*, **299**, 29–62 (2011).
9) Nagase H., Hirayama S., Fujii H., "Pharmacology," ed. by Luca G., InTech, 2012, pp. 81–98.
10) Nagase H., Kawai K., Hayakawa J., Wakita H., Mizusuna A., Matsuura H., Tajima C., Takezawa Y., Endoh T., *Chem. Pharm. Bull.*, **46**, 1695–1702 (1998).
11) Nagase H., Yajima Y., Fujii H., Kawamura K., Narita M., Kamei J., Suzuki T., *Life Sci.*, **68**, 2227–2231 (2001).
12) Nagase H., Osa Y., Nemoto T., Fujii H., Imai M., Nakamura T., Kanemasa T., Kato A., Gouda H., Hirono S., *Bioorg. Med. Chem. Lett.*, **19**, 2792–2795 (2009).
13) Nagase H., Nemoto T., Matsubara A., Saito M., Yamamoto N., Osa Y., Hirayama S., Nakajima M., Nakao K., Mochizuki H., Fujii H., *Bioorg. Med. Chem. Lett.*, **20**, 6302–6305 (2010).
14) Ida Y., Nemoto T., Hirayama S., Fujii H., Osa Y., Imai M., Nakamura T., Kanemasa T., Kato A., Nagase H., *Bioorg. Med. Chem.*, **20**, 949–961 (2012).
15) Lahti R. A., VonVoigtlander P. F., Barsuhn C., *Life Sci.*, **31**, 2257–2260 (1982).
16) Szmuszkovicz J., Von Voigtlander P. F., *J. Med. Chem.*, **25**, 1125–1126 (1982).
17) Lahti R. A., Mickelson M. M., McCall J. M., Von Voigtlander P. F., *Eur. J. Pharmacol.*, **109**, 281–284 (1985).
18) Mucha R. F., Herz A., *Psychopharmacology* (Berl.), **86**, 274–280 (1985).
19) Millan M. J., *Trends Pharmacol. Sci.*, **11**, 70–76 (1990).
20) Tsuji M., Takeda H., Matsumiya T., Nagase H., Narita M., Suzuki T., *Life Sci.*, **68**, 1717–1725 (2001).
21) Yamaotsu N., Fujii H., Nagase H., Hirono S., *Bioorg. Med. Chem.*, **18**, 4446–4452 (2010).
22) Yamaotsu N., Hirono S., *Top. Curr. Chem.*, **299**, 277–307 (2011).
23) According to the message-address concept, opioid ligands can be divided into the message and address sites. The message site is the essential structure for binding to the opioid receptor, whereas the address site relates to the receptor type selectivity. See refs. 24–26.
24) Portoghese P. S., *Trends Pharmacol. Sci.*, **10**, 230–235 (1989).
25) Portoghese P. S., Sultana M., Takemori A. E., *J. Med. Chem.*, **33**, 1714–1720 (1990).
26) Portoghese P. S., *J. Med. Chem.*, **34**, 1757–1762 (1991).
27) Hajos Z. G., Parrish D. R., *J. Org. Chem.*, **39**, 1612–1615 (1974).
28) Ornstein P. L., Arnold M. B., Augenstein N. K., Paschal J. P., *J. Org. Chem.*, **56**, 4388–4392 (1991).
29) Dalence-Guzmán M. F., Berglund M., Skogvall S., Sterner O., *Bioorg. Med. Chem.*, **16**, 2499–2512 (2008).
30) There are some reports of 4a-aryl-*trans*-decahydroisoquinoline derivatives showing binding affinities for the opioid receptor types. For example, see refs. 31, 32.
31) Zimmerman D. M., Cantrell B. E., Swartzendruber J. K., Jones N. D., Mendelsohn L. G., Leander J. D., Nickander R. C., *J. Med. Chem.*, **31**, 555–560 (1988).
32) Nagase H., Fujii H., *Top. Heterocycl. Chem.*, **8**, 99–125 (2007), and references cited therein.
33) Opioid ligands are generally known to include three important interactions with the opioid receptor: an ionic interaction with the 17-nitrogen, a π–π interaction with the phenol ring, and a hydrogen bond with the phenolic hydroxy group. See the refs. 34–36.
34) Beckett A. H., Casy A. F., *J. Pharm. Pharmacol.*, **6**, 986–1001 (1954).
35) Beckett A. H., *J. Pharm. Pharmacol.*, **8**, 848–859 (1956).
36) Fries D. S., "Foye's Principles of Medicinal Chemistry," 6th ed., ed. by Lemke T. L., Williams D. A., Lippincott Williams & Wilkins, Philadelphia, 2008, pp. 652–678.
37) Very recently, the crystal structure of the κ receptor binding with a non-morphinan κ antagonist JDTic has been elaborated. In this report, the interactions between the κ receptor binding pocket and a morphinan κ antagonist nor-BNI were investigated. The investigation indicated that a hydrogen bond is formed between the phenolic hydroxy group in nor-BNI and the Tyr residue in the binding pocket. Wu H., Wacker D., Mileni M., Katritch V., Han G. W., Vardy E., Liu W., Thompson A. A., Huang X.-P., Carroll F. I., Mascarella S. W., Westkaemper R. B., Mosier P. D., Roth B. L., Cherezov V., Stevens R. C., *Nature* (London), **485**, 327–332 (2012).