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The effect of 17-N substituents on the activity of the opioid κ receptor in nalfurafine derivatives

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ABSTRACT

We have previously reported the essential structure of the opioid κ receptor agonist nalfurafine hydrochloride (TRK-820) for binding to the κ receptor. In the course of this study, we focused on the effect of the substituent at 17-N in nalfurafine on the binding affinity for the κ receptor. The exchange of the 17-N substituent in nalfurafine from cyclopropylmethyl to fluoro-substituted alkyl groups, which are strong electron withdrawing substituents, almost completely diminished the binding affinities for the μ and δ opioid receptors, but the binding affinity for the κ receptor was still maintained. As a result, nalfurafine derivatives with 17-fluoro-substituted alkyl groups showed higher selectivities for the κ receptor than did nalfurafine itself. With regard to the κ agonistic activities, the conversion of the 17-N substituent in nalfurafine from cyclopropylmethyl to fluoro-substituted alkyl groups led to the gradual decrease of the agonistic activities in the order corresponding to their binding affinities for the κ receptor. In contrast, the derivative with the bulky 17-isobutyl group showed lower affinity and agonistic activity for the κ receptor than the derivatives with the smaller functional groups. This research suggested that both the electronic property and the steric characteristics of the 17-N substituent would have a great influence on the binding property for the κ receptor.

Three types of opioid receptors (μ, δ, κ) are now well established not only by pharmacological studies, but also through molecular biological studies.[1] For the past three decades, considerable effort has been expended on obtaining an opioid κ selective agonist to eliminate undesirable morphine-like side effects like addiction. In 1982, U-50,488H was discovered to be a highly selective κ agonist by researchers at Upjohn (now merged with Pfizer).[2–4] Since then, numerous research groups have modified its structure and succeeded in preparing more selective and potent κ agonists. These compounds had potent antinociceptive effects in animal models and also succeeded in eliminating the morphine-like side effects. However, all these compounds have structures similar to that of U-50,488H, with arylacetamide skeleton (Fig. 1), and showed severe aversion like psychotomimetic effects. We recently reported a novel κ agonist, TRK-820 (nalfurafine hydrochloride),[5–9] which has a structure quite different from U-50,488H. Unlike U-50,488H, TRK-820 bears a tyrosine-glycine dipeptide unit which is a structural motif commonly found in endogenous opioid peptides (Fig. 1).

Our compound, which was launched in Japan as an antipruritic agent for kidney dialysis patients in 2009,[7–9] is the first opioid drug that caused neither addiction nor aversion. Our interest in the differences in the pharmacological effects between nalfurafine and arylacetamide derivatives led us to examine the structure–activity relationship of nalfurafine derivatives. Recently, we have reported the essential structure of nalfurafine for binding to the κ receptor.[10–12] In the course of this study, we paid attention to the effect of the 17-substituent in nalfurafine on the binding affinity and the agonistic activity to the κ receptor.

The 4,5-epoxymorphinan structure (message site) in nalfurafine (Fig. 2) is believed to influence the intrinsic activity of the ligand for the opioid receptor and the substituents (address site) would help the drug distinguish among the opioid receptor types.[13] The message structure contributed to three points of association between the drug molecule and the receptor site, which included an ionic interaction (formed by the 17-nitrogen (17-N) atom), a π–π interaction (formed by the benzene ring), and formation of a hydrogen bond (contributed by the 3-hydroxy group) in Figure 2.[14,15] On the other hand, we concluded in a previous report that the phenol ring in nalfurafine increased its binding affinity to the κ receptor, but was not indispensable for binding.[10–12] We next attempted to investigate the importance of the ionic interaction, which was believed to be the strongest of the three actions,

Abbreviation: CPM, cyclopropylmethyl; CHO, Chinese hamster ovary.

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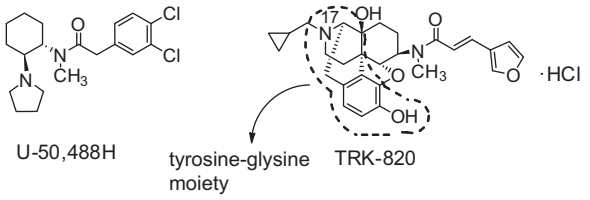


Figure 1. The structures of U-50,488H and TRK-820.

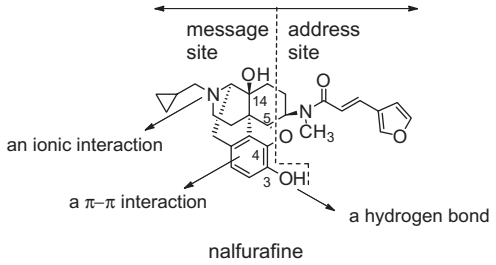


Figure 2. The message site and address site of nalfurafine.

for binding to the κ receptor. Generally speaking, in morphinan derivatives the 17-N substituent plays an important role in distinguishing between the agonist and antagonist. With regard to peptide κ ligands, dynorphin A is a potent κ agonist while *N*-acetylated dynorphin A derivatives like JVA-901 and arodyn are κ antagonists (Fig. 3).[16,17] These compounds maintained sufficient binding affinities for the κ receptor despite the decrease of the basicity of nitrogen. The basicity of nitrogen may affect the agonist property of dynorphin A. On the basis of the hypothesis that the loss of the basicity of the terminal nitrogen in peptide κ ligands may convert the property of the ligand from agonist to antagonist, Schiller co-worker prepared dynantin (Fig. 3), a selective κ antagonist derived from dynorphin A.[18] However, this structure–activity relationship concerning the nature of the substituent on the nitrogen has not yet been applied to non-peptide κ agonists. Therefore, we examined the effect of the 17-N substituent, especially 17-N electron-withdrawing substituents, in nalfurafine on the agonistic activities for the κ receptor. We designed the *N*-fluoroalkylated delivatives **1**–**3** (Fig. 4). We also designed nalfurafine derivatives **4**–**7** with 17-alkyl substituents, some of which were similar in size to fluoro-substituted alkyl groups of derivatives **1**–**3**. Herein, we report the synthesis of these compounds and their pharmacological effects.

The 17-NH-morphinan **8** was synthesized from noroxycodone by the reported method.[19] The compound **8** was converted to compounds **10a–c** with a 17-fluoro-substituted alkyl group by amidation[20] and subsequent reduction with BH_3·THF (Scheme 1). The hydrolysis of compounds **10a–c** provided ketones **11a–c**, followed by the reductive amination with *N*-methylbenzylamine and subsequent hydrogenolysis in the presence of 10%Pd-C to give 6β-amine **13a–c**.[11] Compounds **13a–c** were converted to amides **14a**–**c** by amidation with 3-(furan-3-yl)acryloyl chloride.[6] The resulting compounds **14a–c** were demethylated with BBr_3 to afford objective compounds **1–3** (Scheme 1).[21]

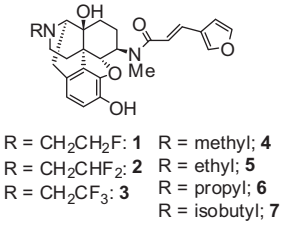


Figure 4. The structures of compounds **1**–**7**.

To synthesize the compounds with ethyl or propyl group on the 17-nitrogen atom, compound **8** was *N*-ethylated with ethyl iodide, or was *N*-propylated by amidation with propionyl chloride, followed by reduction with $LiAlH_4$. Compounds **15a** and **15b** were converted to the objective compounds **5** and **6** in a similar manner as shown in Scheme 1 (Scheme 2). Compound **20**[22] was converted to compound **21**, bearing a 17-isobutyl group, by hydrogenation in the presence of PtO_2 catalyst.[23,24] Compound **21** was converted to the objective compound **7** by the reported method (Scheme 3).[6] Compound **4** with a 17-methyl group was synthesized by the reported method.[6] To evaluate the pharmacological profiles of the thus synthesized compounds for the opioid receptors, the resulting compounds **1**–**7** were converted into the respective hydrochlorides (SYK-52, 53, 60, 305, 235, 304, 463: Table 1).

We evaluated the binding affinities of the synthesized compounds toward opioid μ, δ, and κ receptors (Table 1). For the purpose of comparison, the results of the standard κ agonist U-69,593 and κ agonist TRK-820 were also shown. The assays were performed for each receptor type by previously reported procedures.[21] The evaluated compounds except SYK-53 (**2**) and SYK-60 (**3**) showed high affinities and selectivities for the κ receptor. TRK-820 showed the highest κ affinity, whereas all compounds except SYK-305 (**4**) with a 17-methyl group showed higher selectivities for the κ receptor than did TRK-820. With the exception of SYK-463 (**7**) and SYK-52 (**1**), the general trend was the stronger the electron-donating properties of the 17-N substituents, the higher the κ affinities. The binding affinities for the μ and δ receptor of the derivatives with 17-fluoro-substituted alkyl substituents [SYK-52 (**1**), SYK-53 (**2**), and SYK-60 (**3**)], declined markedly, while their binding affinities for the κ receptor were reasonably maintained.

We also evaluated the functional activities of the synthesized compounds toward the opioid κ receptor in the [^{35}S]GTPγS binding assay (Table 2). The assays were performed by procedures similar to those previously reported.[25] The standard ligand U-69,593 was

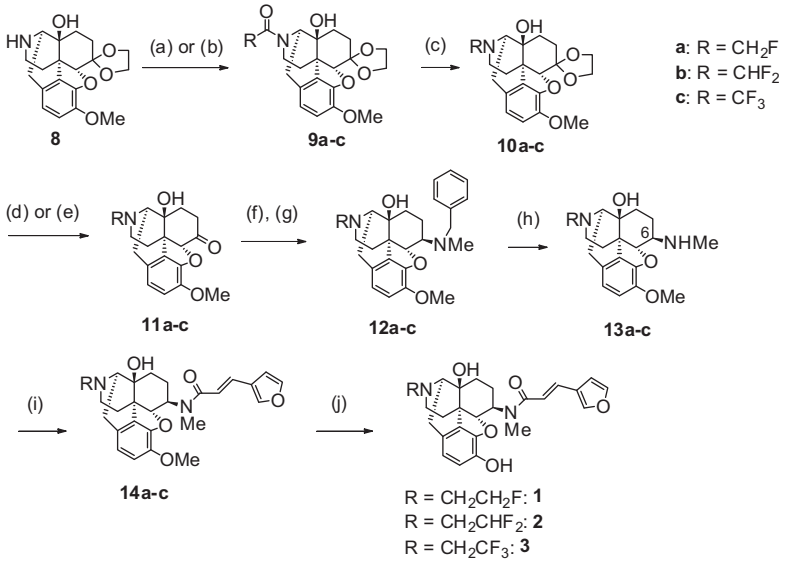
dynorphin A (1-11) NH_2: Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-NH_2

JVA-901: Ac-Tyr-Lys-Trp-Trp-Leu-Arg-Arg-D-Ala-Arg-Pro-Lys-NH_2

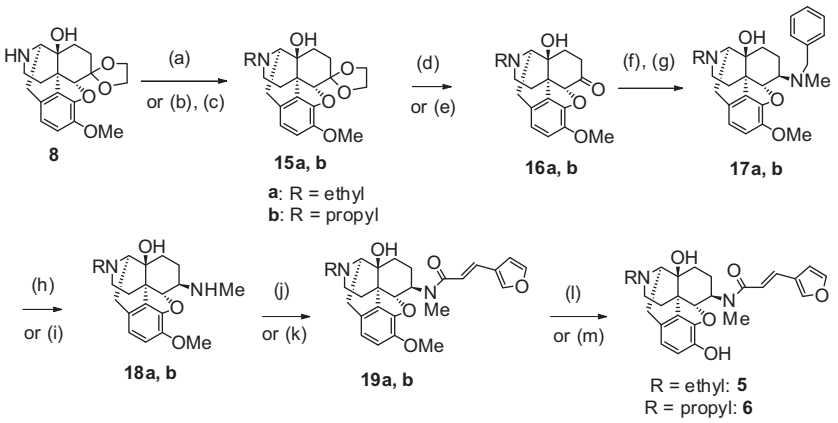
arodyn: Ac-Phe-Phe-Phe-Arg-Leu-Arg-Arg-D-Ala-Arg-Pro-Lys-NH_2

dynantin: [(2*S*)-Mdp[1]]Dynorphin A (1-11) NH_2[a]

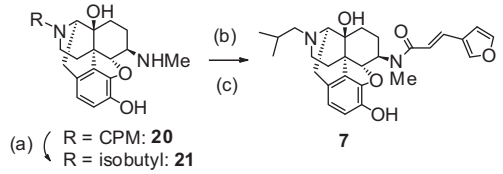
Figure 3. The structures of dynorphin A (1-11) NH_2 and *N*-acetylated dynorphin A derivatives (JVA-901 and arodyn), and dynantin.
[a]Mdp: 2-methyl-3-(2′,6′-dimethyl-4-hydroxyphenyl)propanoic acid.



Scheme 1. Reagents and conditions: (a) RCOOEt, Me_3Al, CH_2Cl_2, 0 °C to rt; 70% (**9a**), 51% (**9b**); (b) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, rt; (c) BH_3·THF, THF, 0 °C to rt, 70% (**10c**: 2 steps from **8**); (d) 6 M HCl, 0 °C to 50 °C, 72% (**11a**: 2 steps from **9a**),76% (**11b**: 2 steps from **9b**); (e) 2 M HCl, THF, 50 °C, 96% (**11c**); (f) *p*-TsOH·H_2O, *N*-methylbenzylamine, benzoic acid, toluene, reflux; (g) $NaCNBH_3$, EtOH, MS3A, 0 °C to rt, 59% (**12c**: 3 steps from **10c**); (h) 10%Pd-C, H_2, MeOH, rt, 98% (**13a**: 3 steps from **11a**), 98% (**13b**: 3 steps from **11b**), 61% (**13c**), (i) 3-(furan-3-yl)acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt, 69% (**14a**), 79% (**14b**), 87% (**14c**); (j) BBr_3, CH_2Cl_2, 0 °C to rt, 90% (**1**), 23% (**2**), 82% (**3**).



Scheme 2. Reagents and conditions: (a) EtI, K_2CO_3, DMF, rt, 100%; (b) EtCOCl, Et_3N, CH_2Cl_2, 0 °C to rt, quant.; (c) $LiAlH_4$, THF, 0 °C to 50 °C, 96%; (d) 2 M HCl, THF, reflux, 84% (**16a**); (e) 2 M HCl, MeOH, 80 °C, 96% (**16b**); (f) *p*-TsOH·H_2O, *N*-methylbenzylamine, benzoic acid, benzene, reflux; (g) $NaCNBH_3$, EtOH, 0 °C to rt, 63% (**17a**; 2 steps from **16a**), 42% (**17b**: 2 steps from **16b**); (h) 10%Pd-C, H_2, MeOH, rt, 76% (**18a**); (i) 5%Pd-C, H_2, MeOH, rt, 50% (**18b**); (j) 3-(furan-3-yl)acryloyl chloride, CH_2Cl_2, 0 °C to rt, 83% (**19a**); (k) 3-(furan-3-yl)acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt, 44% (**19b**); (l) BBr_3, CH_2Cl_2, −78 °C to rt, 83% (**5**); (m) BBr_3, CH_2Cl_2, 0 °C to rt, 100% (**6**).

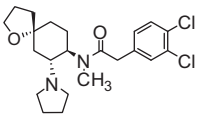


Scheme 3. Reagents and conditions: (a) 1 M HCl, PtO_2, rt, quant.; (b) 3-(furan-3-yl)acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt; (c) 2 M NaOH, MeOH, 86% (2 steps from **21**).

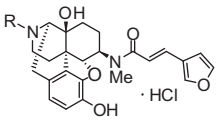
included for comparison. All compounds showed almost full agonistic activities equipotent to the standard κ agonist U-69,593. Among them, the conversion of 17-substituent in TRK-820 from CPM to fluoro-substituted alkyl groups led to a decrease in the potency of agonistic activities, consistent with our observations regarding the binding affinity for the κ receptor. The affinity and the agonistic potency for the κ receptor of SYK-52 (**1**) (with a 2-fluoroethyl group) were similar to those of SYK-235 (**5**) (with an ethyl group) and SYK-304 (**6**) (with a propyl group).

Earlier, we reported that high affinities for the opioid receptors would arise from 17-N substituents with strong electron-donating properties.[19,26] Indeed, our results in that investigation showed that the greater the electron-donating property of the 17-N substituent, the higher the affinity for the κ receptor. This tendency was also observed in the agonistic activity for the κ receptor. However, SYK-52 (**1**) and SYK-463 (**7**) did not follow this predicted trend. Interestingly, SYK-52 (**1**) with the electron-withdrawing 2-fluoroethyl group showed higher affinity and agonistic activity for the κ receptor than did SYK-235 (**5**) with the electron-donating ethyl group, which was of similar size to the 2-fluoroethyl group. Perhaps the fluorine atom of the 2-fluoroethyl group in SYK-52 (**1**) interacts with the κ receptor, affording high affinity and agonistic activity toward the κ receptor. On the other hand, SYK-463 (**7**) (with an isobutyl group) showed lower affinity and activity than SYK-305 (**4**), SYK-235 (**5**), and SYK-304 (**6**) despite its strong

Table 1
The binding affinities and selectivities of U-69,593, TRK-820, and SYK-compounds for opioid μ, δ, and κ receptors[a]



U-69,593



Compounds	R	Affinity (K_i, nM)			Selectivity	
		μ	δ	κ	μ/κ	δ/κ
U-69,593		548	391	1.37	400.0	285.4
TRK-820	CPM	0.431	51.3	0.178	2.42	288
SYK-305 (**4**)	Me	2.767	35.67	0.7346	3.77	48.6
SYK-235 (**5**)	Et	10.99	511.6	0.6252	17.6	818
SYK-304 (**6**)	Propyl	19.17	176.2	0.3283	58.4	537
SYK-463 (**7**)	Isobutyl	46.22	513.8	0.5895	78.4	871.6
SYK-52 (**1**)	$-CH_2CH_2F$	8.394	>1000	0.507	16.6	—
SYK-53 (**2**)	$-CH_2CHF_2$	>1000	>1000	2.192	—	—
SYK-60 (**3**)	$-CH_2CF_3$	>1000	>1000	4.584	—	—

[a] Evaluated by ability of each compound to displace [^{3}H]DAMGO (μ), [^{3}H]DPDPE (δ), or [^{3}H]U-69,593 (κ) binding from membranes of mouse whole brain without cerebellum (μ and δ) or the guinea pig cerebellum (κ). The data represent means of three samples.

Table 2
κ-Agonist activities of U-69,593, TRK-820, and SYK-compounds[a]

Compounds	17-substituents	EC_{50} (nM)	Emax (%)
U-69,593		28.1	100.0
TRK-820	CPM	0.05	98.1
SYK-305 (**4**)	Me	11.26	90.44
SYK-235 (**5**)	Et	3.787	97.38
SYK-304 (**6**)	Propyl	2.721	86.47
SYK-463 (**7**)	Isobutyl	8.071	99.53
SYK-52 (**1**)	$-CH_2CH_2F$	2.231	95.24
SYK-53 (**2**)	$-CH_2CHF_2$	22.41	101.4
SYK-60 (**3**)	$-CH_2CF_3$	32.21	89

[a] Membranes were incubated with [^{35}S] GTPγS and GDP with the compound. The κ human recombinant cell membrane (CHO) was used in this assay. U-69,593 was used as the standard κ agonist. The data represent means of four samples.

electron-donating property. The larger size of the isobutyl group may be responsible for the lower affinities and activities for the κ receptor. These results suggested that not only the basicity of nitrogen but also the bulkiness of the 17-N substituent could contribute to the binding affinity and agonist properties and that the favorable balance between the two factors would lead to the improved affinity and agonistic activity for the κ receptor. Therefore, the noticeable decrease in the affinities and agonistic activities of SYK-53 (**2**) and SYK-60 (**3**) with the fluoro-substituted alkyl group may be derived from the bulkiness[26] as well as the strong electron-withdrawing property of this functional group.

Although the binding affinities of 17-fluoro-substituted alkyl derivatives SYK-52 (**1**), SYK-53 (**2**), and SYK-60 (**3**) for the κ receptor decreased, they remained reasonable. In contrast, their affinities for the μ and δ receptors were extremely decreased. As a result, TRK-820 derivatives with the 17-fluoro-substituted ethyl groups showed markedly higher selectivities for the κ receptor than did TRK-820 itself. To account for these observations, we proposed that the κ address part (Fig. 2), which adequately interacts with the κ receptor, can compensate for the binding to the κ receptor despite the fact that the binding affinity that stemmed from the message site was greatly reduced due to the decrease in the electron density on the nitrogen. In addition, SYK-53 (**2**) with the 17-difluoroethyl substituent showed more selectivity than U-69,593 and almost the same activity as that of U-69,593 for the κ receptor while TRK-820 with the 17-CPM group (a strong electron-donating group) showed low μ/κ selectivity and very potent κ agonistic activity. On the basis of these results, the selectivity and agonistic activity for the κ receptor was controlled by the introduction of the 17-fluoro-substituted groups. These findings are expected to be useful for designing novel κ selective and potent agonists.

As mentioned above, the peptide κ ligand dynorphin A is a potent κ agonist while the *N*-acetylated dynorphin A derivatives are κ antagonist (Fig. 3).[16,17] In contrast, nalfurafine derivatives maintained agonistic activities toward the κ receptor despite the decrease in the basicity of the nitrogen. It is difficult to explain why nalfurafine derivatives with the morphinan skeleton showed a different tendency from that of the peptide κ ligands. It may be that peptides and nonpeptides bind to different binding sites of the κ receptor,[17] a possibility that requires further investigation.

Of the synthesized compounds, SYK-304 (**6**) with a 17-propyl substituent showed the highest κ affinity, the most balanced and highest selectivity, and an elevated agonistic activity for the κ receptor. These favorable properties of SYK-304 (**6**) could be attributed to the electron-donating property and the appropriate size of the 17-propyl group.

In conclusion, 17-N electron-donating substituents increased the binding affinity and agonistic activities for the κ receptor. Electron-withdrawing substituents at 17-N (fluorinated substituents) in nalfurafine derivatives significantly increased the receptor type selectivity while they decreased the κ agonistic activities. SYK-463 (**7**), with a bulky isobutyl group, exhibited low affinity and κ agonistic activity. Therefore, not only the electronic properties but also the steric characteristics of the 17-N substituent would have a great influence on the binding ability and the agonistic activity for the κ receptor. As a result, SYK-304 (**6**) with a propyl group showed high affinity and agonistic potency for the κ receptor. These findings are expected to be useful for designing novel κ selective agonists. We are currently examining the effects of fluorinated substituents in opioid δ ligands.

Acknowledgments

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