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Synthesis of new opioid derivatives with a propellane skeleton and their pharmacology. Part 2: Propellane derivatives with an amide side chain

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ABSTRACT

We designed and synthesized propellane derivatives with a 6- or 7-amide side chain on the basis of the active conformation of the κ selective agonist nalfurafine. The 6-amides showed high affinities for the κ receptor, and one of the 6β-amides showed higher κ selectivity than nalfurafine. On the other hand, although the affinities of the 7-amides decreased compared to the 6-amides, some 7α-amides showed the highest selectivities for the κ receptor among the tested compounds. The affinities of 7β-isomers were extremely low, which was postulated to result from the shielding effect of the 7β-amide side chain against the lone electron pair on the 17-nitrogen. This is the first conformational information about the 7-amide side chain in propellane derivatives.

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 the 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 the κ[2–8] or δ[9–13] receptors. Recently, one of our designed κ selective agonists, nalfurafine hydrochloride (TRK-820, Fig. 1),[2,3,6,8] was launched in Japan as an antipruritic for patients undergoing dialysis.[6,8] Although many arylacetamide derivatives such as U-50,488H[14,15] and U-69,593 (Fig. 1)[16] have been synthesized and developed as κ agonists, all of these derivatives were eliminated from clinical trials not only as analgesics but also as antipruritics because of their serious side effects like psychotomimetic and aversive reactions.[17,18] On the other hand, nalfurafine has neither aversive nor addictive effects.[19] We have been interested in the pharmacological differences between nalfurafine and arylacetamide derivatives with or without aversion side effects. We postulated that the differences in pharmacological effects between these two classes of compounds may derive from the differences in their affinities for κ receptor subtypes (κ_1 and κ_3)[20–22] (arylacetamide derivatives: κ_1[21,22] and nalfurafine: κ_3[23–27]). We were also interested in the pharmacological effects of the κ_2 subtype for which benzomorphans like (−)-pentazocine and bremazocine[20,22] are proposed to show high affinity.

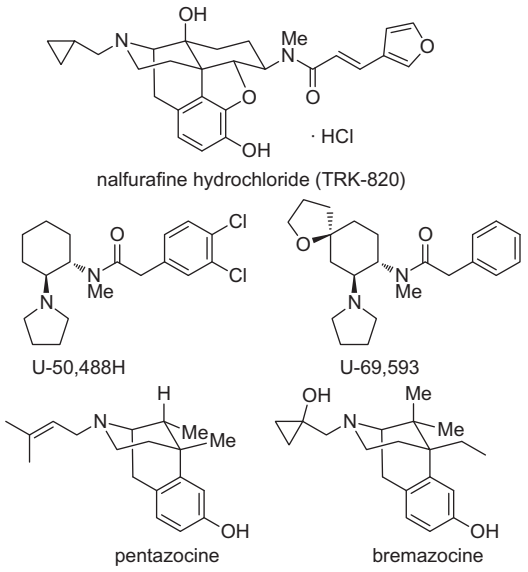

Figure 1. Structures of nalfurafine hydrochloride, U-50,488H, U-69,593, pentazocine, and bremazocine.

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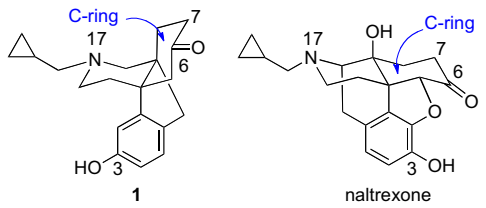


Figure 2. Structures of propellane **1**[29] and naltrexone.

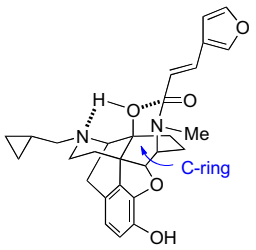
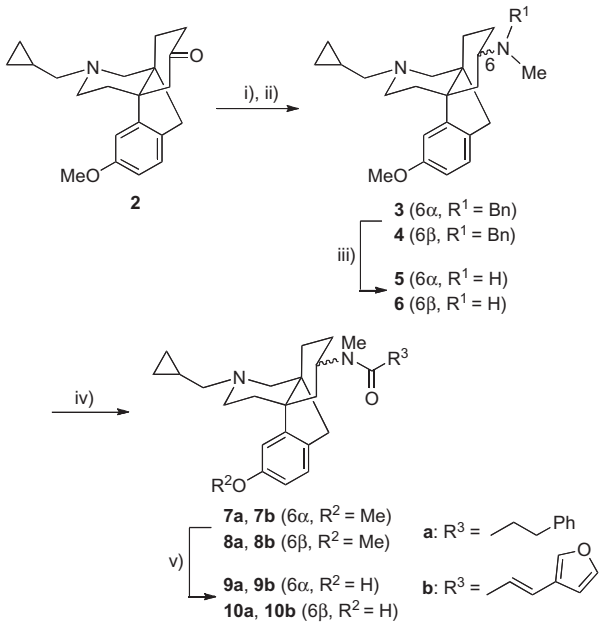


Figure 3. Proposed active conformation of nalfurafine binding to the κ receptor.

In the course of our synthetic and pharmacological studies with naltrexone derivatives, we discovered the synthesis of propellane derivatives.[28] In contrast to nalfurafine, the propellane derivative **1** (Fig. 2) lacks an amide side chain, thought to be a crucial structural determinant for binding to the κ receptor (κ address). Surprisingly, **1** showed κ agonist activity,[30] indicating that the propellane skeleton would have a potential to bind to the κ receptor. We also proposed that in its binding to the κ receptor, nalfurafine would acquire an active conformation in which the C-ring assumes the boat form to orient the 6-side chain toward the upper side of the C-ring (Fig. 3).[4,5,31,32] The 6-keto group in the C-ring of propellane **1** could therefore exist in a relatively higher position than that observed for naltrexone (Fig. 2). If an amide group could be introduced in the 6- or 7-position of **1**, the amide group would be expected to orient at a position that was closer to the upper side as compared to that of nalfurafine. Therefore, we attempted to synthesize propellane derivatives with an amide side chain in the 6- or 7-position. Herein, we report the synthesis of more κ selective propellane derivatives with an amide side chain and their pharmacologies.



Scheme 1. Reagents and conditions: (i) BnMeNH, $PhCO_2H$, *p*-TsOH·H_2O, PhH reflux; (ii) $NaBH_3CN$, MeOH, 0 °C, **3**: 40%, **4**: 25%; (iii) H_2, Pd/C, MeOH, rt; (iv) R^3COCl, Et_3N, CH_2Cl_2, 0 °C to rt, **7a**: 88% from **3**, **7b**: 76% from **3**, **8a**: 77% from **4**, **8b**: 80% from **4**; (v) BBr_3, CH_2Cl_2, −78 °C to rt, **9a**: 70%, **9b**: 35%, **10a**: 43%, **10b**: 56%.

As the 17-cyclopropylmethyl (CPM) group was known to promote κ selectivity,[30] we synthesized only the derivatives with a 17-CPM substituent. The synthesis of 6-amide derivatives commenced with propellane **2** (Scheme 1). Propellane **2** was converted to methylamines **5** and **6** by reductive amination followed by debenzylation. Obtained methylamines **5** and **6** were treated with acyl chlorides to provide **7** and **8** and then the *O*-methyl group in **7** and **8** was removed by boron tribromide treatment.

The 7-amides **18** and **19** were synthesized from propellane **2** (Scheme 2). Condensation of **2** with dimethyl carbonate gave ketoesters **11** and **12**. The keto group in **11** and **12** was removed by reduction, and then subsequent dehydration and hydrogenation gave 7-esters **14** and **15** as a diastereomixture. 7-Esters **14** and **15** were alternatively prepared from **13** by reduction using magnesium.[33] The epimerization of the major 7β-isomer **15** gave the minor 7α-isomer **14** in 24% yield. 7-Amides **18** and **19** were prepared by ester-amide exchange reaction of **14** and **15** followed by demethylation. α,β-Unsaturated amides **21** were provided from the intermediate **13** by the same method shown in Scheme 2 (Scheme 3).

The binding affinities of the prepared propellane derivatives for the opioid receptors were evaluated with a competitive binding assay (Table 1). The assays were performed by a previously reported procedure.[13]

All the 6-amide derivatives **9** and **10** showed higher affinities for all three receptor types than did propellane **1** which lacked the amide side chain. The κ selectivity over the μ receptor of **10b** was improved as compared to those of nalfurafine and propellane **1**. Interestingly, 6β-isomers **10** were more κ selective over the μ receptor than the corresponding 6α-isomers **9**. This result with the 6β-isomers may be caused by the orientation of the side chain toward the upper side of the C-ring, as opposed to the orientation of the side chain in the 6α-isomers. Meanwhile, the affinities of 7-amide derivatives **18**, **19**, and **21** were lower than those of the 6-amide derivatives **9** and **10**. Especially, the affinities of 7β-isomers **19** were low and **19b** showed almost no interaction with the δ and κ receptors. On the other hand, 7α-isomers **18** and α,β-unsaturated amides **21** exhibited somewhat higher affinities for the three receptor types as compared to the β-isomers **19**. The α,β-unsaturated amides **21** showed μ selectivity, whereas the α-isomers **18** except for **18c** exhibited κ selectivity. The κ selectivities of **18a** and **18b** were higher than those of nalfurafine and 6β-amide **10b**. These outcomes may result from the different orientation of the amide side chain (Fig. 4). The amide side chain of **18** may be able to locate in a direction that enhances binding to the κ receptor, whereas that of **21** cannot. The extreme decrease in the affinities of the 7β-isomer **19** is difficult to explain by an unfavorable orientation of the amide side chain, that is, the side chain is incapable of functioning as the κ address. So, we postulated that the flexible 7β-side chain could locate over the 17-nitrogen to interfere with the ionic interaction between the 17-nitrogen and the opioid receptor. The ionic interaction of the 17-nitrogen, along with a π–π interaction with the phenol ring and formation of a hydrogen bond with the phenolic hydroxy group are three important processes that have been identified in opioid ligand–receptor binding.[35–37]

To confirm our hypothesis, we carried out conformational analyses of three 7-amides **18b**, **19b**, and **21b** using Conformational Analyzer with Molecular Dynamics And Sampling (CAMDAS) 2.1 program[38] (Fig. 5). The benzene ring of the 7β-amide side chain