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# Design and synthesis of novel opioid ligands with an azabicyclo[2.2.2]octane skeleton having a 7-amide side chain and their pharmacologies

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ABSTRACT

Several derivatives with an azabicyclo[2.2.2]octane skeleton having a 7-amide side chain were synthesized. Compounds that had an electron-donating group exhibited high affinity for the μ opioid receptor while those with a bulky substituent at the 8-nitrogen atom had low affinities for all receptor types. High affinities and selectivities for the κ receptor resulted from the introduction of the longer amide side chain at the 7α-position. Our studies indicate that the orientation of the amide side chain at the 7-position within the azabicyclo[2.2.2]octane skeleton is related to selectivity for the κ receptor.



## 1. Introduction

Three types of opioid receptors (μ, δ, κ) are now well established not only by pharmacological studies but also by molecular biological characterization.[1] Narcotic addiction is believed to be derived from the μ receptor type, and therefore κ and δ types are expected to be promising drug targets for analgesia 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[2,3] and have reported selective ligands for the δ and κ receptors.[4,5] Quite recently, the crystal structures of all three receptor types in complex with their corresponding selective antagonists have been elucidated[6–8] and these would further facilitate the development of the ideal selective ligands.

In 2009, one of the our designed κ selective agonist nalfurafine[4a,b,e] (Fig. 1) was launched in Japan as an antipruritic for patients undergoing dialysis. In previous reports,[4c,d,g] we postulated that the C-ring in the κ agonist was in the boat form in its active conformation and the amide side chain in the nalfurafine would be oriented toward the upper side of the C-ring in the morphinan skeleton by an interaction between the 14-OH group and the amide group (Fig. 1). On the basis of our working hypothesis that the amide orientation in the active conformation of the agonist would significantly influence the affinity and selectivity for the κ receptor, we designed and synthesized KNT-63 having a novel oxabicyclo[2.2.2]octane skeleton (Fig. 1).[4d] The orientation of the amide side chain in KNT-63 is fixed toward the upper side of the C-ring by the oxabicyclo[2.2.2]octane skeleton similar to the postulated amide orientation in the active conformation of nalfurafine. This orientation of the amide side chain may account for the improved affinity of KNT-63 for the κ receptor ($K_i$ = 0.11 nM) even over that of the nalfurafine ($K_i$ = 0.23 nM). The higher affinity of KNT-63 for the κ receptor supported our hypothesis that the C-ring may assume the boat form in the active conformation of the agonist, induced by an interaction between the 14-OH and the amide group.

Quite recently we have reported that azabicyclo[2.2.2]octane derivative **2** showed higher affinity for the μ receptor than **1** with an oxabicyclo[2.2.2]octane skeleton (Fig. 1).[9] Furthermore, the introduction of an electron donating group (e.g., **3**: Me; **4**: CPM) at the 8-nitrogen atom significantly increased the affinity for the μ receptor. Based on this background, we designed novel derivatives **5a** and **5b** having an amide side chain at the 7-position within an azabicyclo[2.2.2]octane skeleton (Fig. 1). Because derivatives **2–4** showed high affinity for all receptor types, that is, no single type selectivity, the derivatives **5a** with a 7-amide side chain (the κ ad-

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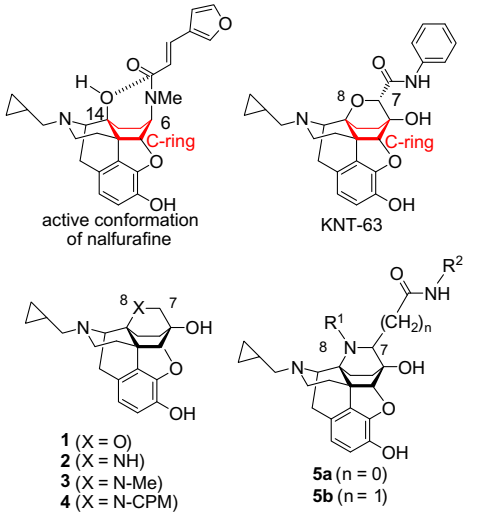



**Figure 1.** Structures of nalfurafine, KNT-63 and derivatives having an oxa or an azabicyclo[2.2.2]octane skeleton.

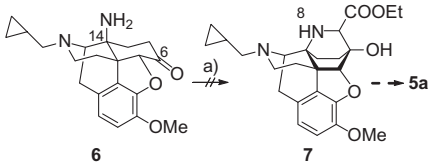
dress part), which would play an important role in improving affinity and selectivity for the κ receptor, would expectedly exhibit stronger agonistic activities for the κ receptor than KNT-63. As the length of the address part would affect the affinity and selectivity for the receptor type according to the message-address concept,[10] we also designed **5b** with a longer amide side chain ($n = 1$) at the 7-position. Furthermore, we attempted to investigate the influence of the configuration of the 7-amide chain (the α- or β-orientation against the F-ring) on the binding properties for the κ receptor (Fig. 2).[11] In this report, we describe the design and synthesis of novel azabicyclo[2.2.2]octane derivatives **5** having an amide side chain at the 7-position and their analogues. We also present an investigation of their pharmacologies.

## 2. Results

### 2.1. Chemistry

In the previous paper,[9] we reported the failure of our attempt to prepare ester **7** as an intermediate for target derivatives **5a** from 14-aminonaltrexone derivative **6** using Darzens reaction[12,13] (Scheme 1). We supposed that the reaction of ethyl chloroacetate with the primary 14-amino group in **6** would lead to a complex mixture.

Alternatively, the synthesis of esters **10a** and **10b** having a Me group at the 8-position was attained through the Darzens condensation of 14-methylaminonaltrexone derivative **8**[9] via epoxy ester intermediate **9** in good yield (**10a**: 40%, **10b**: 27%) (Scheme 2). Contrary to the reaction with the primary amine **6**, the steric bulkiness of the 14-methylamino group in **8** would disturb the reaction with ethyl chloroacetate and could selectively lead to the expected Darzens condensation.




**Scheme 1.** Reagents and conditions: (a) ethyl chloroacetate, NaH, THF, 0 °C to rt.

We next attempted Darzens condensation of 14-(2,2,2-trifluoroethyl)aminonaltrexone derivative **12** or 14-benzylaminonaltrexone derivative **13** under the same reaction conditions as the synthesis of **10a** and **10b** to prepare azabicyclo[2.2.2]octane derivatives **16** and **17** (Scheme 3). *N*-Trifluoroethyl derivative **12** was obtained by trifluoroacetylation of amine **11**[9] with trifluoroacetic anhydride (TFAA), subsequent reduction of the resulting amide with $LiAlH_4$, and hydrolysis of the 6-acetal group. *N*-Benzyl derivative **13** was prepared by benzylation of amine **11** with benzylbromide and subsequent hydrolysis of the 6-acetal group. The Darzens condensation of **12** and **13** at 0 °C to rt did not go to completion and some amounts of the epoxy precursors **14** and **15** were recovered. It was assumed that the steric hindrance between the 6′α-ethoxycarbonyl group and the 2,2,2-trifluoroethyl (**14**) or benzyl (**15**) group on the 14-nitrogen atom would retard the cyclization (Fig. 3). On the other hand, the cyclization of 6′β-epoxyester **15b** into azabicyclo[2.2.2]octane **17b** readily proceeded, which supports the notion of the aforementioned possible steric hindrance (Fig. 3). Furthermore, the lesser nucleophilicity of the 14-amino group with the electron-withdrawing 2,2,2-trifluoroethyl group would further disturb the cyclization. Therefore, the subsequent reflux of the remained epoxy esters **14** and **15** in EtOH[14,15] led the completion of the cyclization to provide esters **16a**, **16b**, **17a** and **17b** in good yield (Scheme 3). The structures of azabicyclo[2.2.2]octane derivatives **10a**, **10b**, **16a**, **16b**, **17a** and **17b**, including the configuration at the 7-position, were determined by 2D NMR (Fig. 4). The obtained esters **17a** and **17b** were respectively debenzylated with Pd-catalyzed hydrogenation to afford the desired esters **7a** and **7b**, which were subsequently treated with (bromomethyl)cyclopropane to give the corresponding 8-cyclopropylmethyl (CPM) derivatives **18a** and **18b**.

The obtained esters **7a**, **10a**, **10b**, **16a**, **16b**, **17b** and **18b** were respectively treated with LiOH, and subsequent condensation with aniline in the presence of EDCI or DMT-MM[16] in MeOH gave the corresponding amides **19a**, **20a**, **20b**, **21a**, **21b**, **22b** and **23b**. The *O*-demethylation of these amides with $BBr_3$ afforded **24a**, **25a**, **25b**, **26a**, **26b**, **27b** and **28b** (Scheme 4). The amidation of **17a** and **18a** did not proceed and starting **17a** and **18a** were recovered. The steric hindrance between the 8-benzyl group in **17a** or the 8-CPM group in **18a** and the 7α-carboxyl group derived by the hydrolysis of 7α-ester group may also inhibit the amidation. Therefore, 8-CPM **23a** was prepared by 8-alkylation of amide **19a**. The demethylation of the methoxy group in **23a** afforded **28a** (Scheme 5). To acetylate the 8-amino group, **27b** was debenzylated by Pd-catalyzed hydrogenation to afford **24b**, followed by acetylation to give **29b** (Scheme 6). Compound **31a** having the *N*-benzylc-

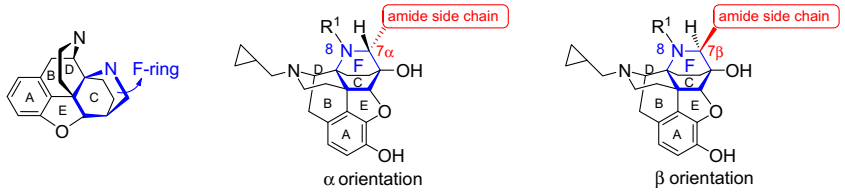



**Figure 2.** The F-ring in the morphinan skeleton with an azabicyclo[2.2.2]octane skeleton and the orientation of the amide side chain at the 7-position.