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DESIGN AND SYNTHESIS OF 10-OXO DERIVATIVE OF *N*-CYCLOPROPYLMETHYL (-)-6β-ACETYLTHIODIHYDRO-NORMORPHINE, A POTENTIALLY κ-SELECTIVE OPIOID RECEPTOR LIGAND

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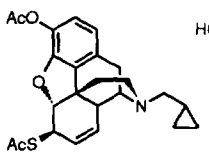
Abstract. The design and synthesis of 10-oxo derivative of *N*-cyclopropylmethyl-(-)-6β-acetylthio dihydronormorphine (**4**) are described. The result of pharmacological assays indicate that compound **4** acts as a μ-opioid receptor antagonist and κ-opioid receptor agonist which is suggested to be more potent analgesic action than that of **1** and morphine through an activation of κ-opioid receptors.

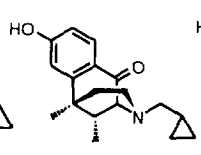
Introduction

The existence of three major opioid receptor types, namely, μ, δ, and κ, in the brain and the peripheral tissues has been documented in biochemical and pharmacological studies. Especially the κ-opioid receptor has been of most interest because its activation produces analgesia with minimum physical dependence and respiratory depression.[1] Thus, highly selective κ-opioid agonists may provide useful analgesics free from the abuse potential and the adverse side effects of μ-agonists like morphine.[1,2]

Recently, we have described the synthesis of (-)-3-acetyl-6β-acetylthio-*N*-cyclopropylmethyl normorphine **1** and its pharmacological activities.[3] Analgesic actions of **1** were mediated through an activation of κ-opiooid receptors and about 10 times as potent as morphine. Furthermore, **1** was free from undesirable physical and psychic dependence liabilities, because **1** acted as κ-agonist, but at the same time, behaved as strong antagonist for μ and δ-opioid receptors. Thus the ligand acting as both the κ-agonist and μ–antagonist, may be a useful prototype for the clinical analgesics of low-side effect liability or without producing physical dependence. The objective of this work is to develop more highly κ-selective agonists than **1**.



1



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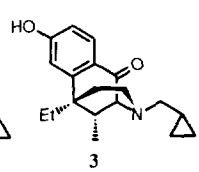

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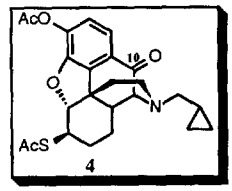


4

Some κ-selective ligands like ketocyclazocine (**2**) and ethylketocyclazocine (**3**)[4] have the oxo group in common on their benzylic positions. It appears that the benzylic oxo group might contribute to their high

affinity and κ-selectivity as the additional first recognition sites for κ-opioid receptors. Recently, we have reported the molecular model building of multiple opioid receptor subtypes.[5] A comparison of our 3D models of the three opioid receptor subtypes defined variant amino acid residues, which are different in charge and hydrophobic properties. At the top of the TM 6 helix in the putative ligand-binding sites, the μ-, δ-, and κ-opioid receptors possess Lys_{303}, Trp_{284}, and Glu_{297} respectively (Fig. 1). When the ligands which have the benzylic oxo group were manually docked into the κ-opioid receptor model, the positions of Glu_{297} and the benzylic oxo group of the ligands are close enough to interact each other (data not shown). It is likely that the variant amino acid residues are able to participate in the mechanism that controls the type selectivity of the ligand binding. This hypothesis may also account for the high κ-selectivity of **2** and **3**.

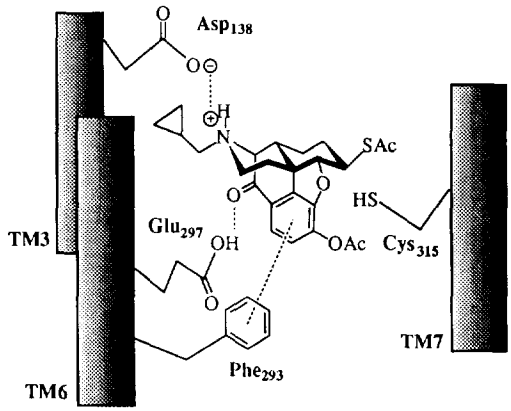


Figure 1. Schematic representation of the interaction between κ-opioid receptor recognition sites and compound **4**.

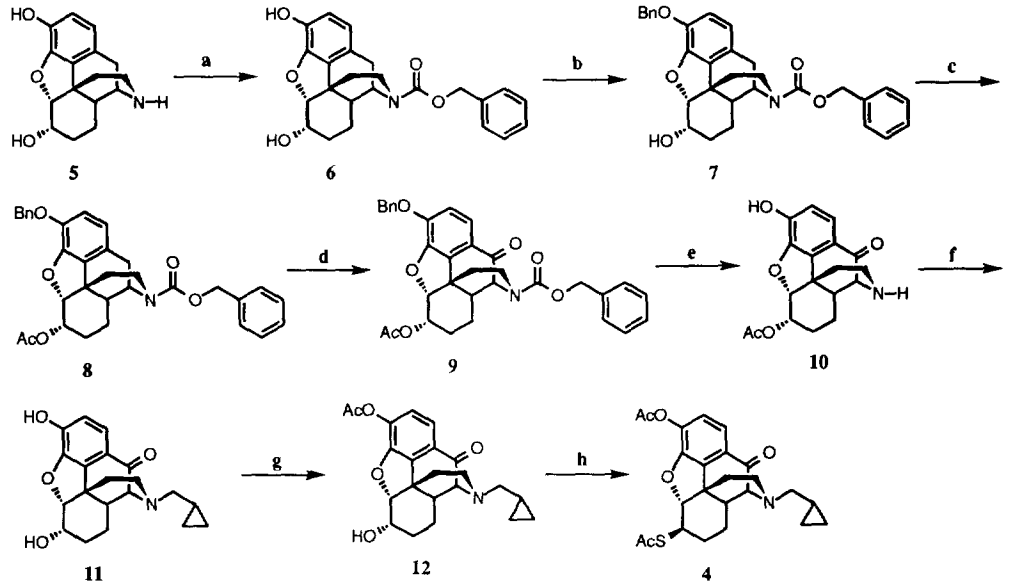
As a part of our research programs on the design of opioid receptor probes, we designed the ligand **4**, the 10-oxo derivative of **1**, aiming to recognize the Glu_{297} in the κ-opioid receptor and to evaluate the pharmacological effect of a benzylic oxo group. We describe here the synthesis of (-)-3-acetyl-6β-acetylthio-10-oxo-*N*-cyclopropylmethyl dihydronormorphine **4** as the potentially κ-selective opioid ligand and its biological properties.

Results and Discussion

Chemistry

The target compound **4** was prepared by the route shown in Scheme 1. The amino group of well-known dihydronormorphine (**5**) was protected as benzyloxycarbamate, because the carbamate moiety on this position is necessary for the following oxidation step. Treatment of dihydronormorphine (**5**) with benzyl chloroformate in the presence of sodium carbonate produced the *N*-carbobenzyloxy dihydronormorphine (**6**). Then the phenolic hydroxyl group of the carbamate (**6**) was protected selectively as benzyl ether, because protecting the phenolic hydroxyl group as acetate instead of benzyl ether seriously reduced the yield of the following oxidation step (< 3%). Thus, the carbamate (**6**) was treated with benzyl bromide in the presence of potassium carbonate in DMF to give benzyl ether (**7**) in 80% yield. Benzyl ether (**7**) was readily treated with acetic anhydride in the presence of a catalytic amount of pyridine to give fully protected dihydronormorphine (**8**) in 90% yield. There are few examples of benzylic oxidation of opiates.[6]

Scheme 1



Reagents: a) benzyl chloroformate, Na_2CO_3 (80%); b) benzyl bromide, K_2CO_3, DMF (90%); c) Ac_2O, pyridine, 90 °C (quant.); d) SeO_2(3 eq.), 1,4-dioxane, 180 °C, 24 h (quant.); e) $Pd(OH)_2$, H_2, 6Kgf/cm^2, EtOH (quant.); f) cyclopropylmethyl bromide, K_2CO_3, DMF; 25% H_2SO_4, reflux (85%); g) Ac_2O, aq.$NaHCO_3$ (quant.); h) PPh_3, diisopropyl azodicarboxylate, THF; AcSH, 0 °C (70%)

However, most of the methods were highly specific for substrates and not of general applicability. Our strategies for introduction of oxygen at benzylic position of (**8**) were according to the method described by Uyeda *et.al*,[6] slightly modified in our laboratory. Heating the fully protected dihydronormorphine (**8**) with three equivalents of selenium dioxide in dioxane at 180 °C in a sealed tube for 24 h gave 10-keto-dihydronormorphine derivative (**9**) in quantitative yields, surprisingly, in contrast to the low yield reported by Uyeda *et.al*.[6] According to our knowledge, this is the most efficient method of benzylic oxidation of morphine-like structure. The detail of the structure-reactivity of this reaction will be discussed elsewhere. The 10-keto-dihydromorphine derivative (**9**) was then converted into the target ligand as following steps. First, removing the phenolic benzyl ether and benzyloxy carbonyl group at the same time by hydrogenolysis in the presence of a catalytic amount of palladium dihydroxide gave 6-acetoxy-10-oxo-dihydronormorphine (**10**) in quantitative yields. Alkylation of an amine group with cyclopropylmethyl bromide in the presence of potassium carbonate in DMF, and subsequently hydrolysis in aqueous H_2SO_4 gave 10-oxo-*N*-cyclopropylmethyl-dihydronormorphine (**11**) in 85% overall yield. Selective acetylation of the phenolic hydroxyl group by acetic anhydride in the presence of sodium bicarbonate in water gave 3-acetoxy-10-oxo-*N*-cyclopropylmethyl-dihydronormorphine (**12**) in high yields. Finally, treatment of compound (**12**) with thioacetic acid in the presence of triphenylphosphine and diisopropyl azodicarboxylate in dry THF at 0 °C (Mitsunobu reaction) produced stereoselectively 3-acetoxy-6β-acetylthio-10-oxo-*N*-cyclopropylmethyl-dihydronormorphine (**4**) in 70% yields. The target compound (**4**) was then converted

into HCl salt: mp 154 °C; $[\alpha]_D$ -67° (c 1.2, MeOH); IR 1760, 1675, 1595 cm^{-1}; Anal. Calcd for $C_{24}H_{27}O_5NS \cdot HCl \cdot 0.5H_2O$: C, 59.18; H, 5.91; N, 2.93. Found : C, 59.19; H, 6.00; N, 2.88.

Biological results

The opioid receptors in the cholinergic nerves of the guinea-pig ileum are similar to those in the central nervous system, and the electrically stimulated ileal strip from guinea-pig is used as a model to investigate the mode of action of narcotic and antinarcotic analgesics in the central nervous system. We studied actions of **4** on the electrically stimulated ileal strip of guinea-pig as described previously.[3]

Compound **4** as well as **1** and morphine (reference drugs) inhibited the twitch response of the longitudinal muscle strip to electrical stimulation in a concentration-dependent manner. The pD_2 value (a negative logarithm of the concentration (M) to produce 50% of the maximum response) was 7.23±0.11 for morphine, 8.40 ± 0.10 for **1** and 9.03 ± 0.04 for **4**. Each value is presented as a mean ± S.E. of 3 experiments. These results suggest that in analgesic activity, **4** is about 60 times as potent as morphine and about 4 times as potent as **1**. The twitch response of ileal strip to electrical stimulation is inhibited by an activation of μ- or κ-opioid receptors. The concentration response curve of morphine, a μ-agonist, is significantly shifted by a low concentration (3×10^{-10} M) of **4** in a competitive manner suggesting that **4** has μ-receptor blocking action. Higher concentration ($> 3 \times 10^{-10}$ M) of **4** was not used in this experiment, because **4** inhibit the twitch in high concentrations. Norbinaltorphimine, a κ-receptor antagonist shifted the concentration response curve of **4** toward a higher concentration. The pA_2 value (a negative logarithm of dissociation constant) calculated from the parallel shift of the curve was 10.45 ± 0.14 (a mean ± S.E. of 3 experiments), which was practically equal to that described.[7] The results mentioned above indicate that **4** is a μ-antagonist and κ-agonist and the possibility that **4** has potent analgesic action, which is mediated through an activation of κ-opioid receptors. Introduction of an oxo group at the 10 position of **1** might increase analgesic activity or affinity to κ-opioid receptors. Further studies on the dependence and the development of tolerance produced by **4** are in progress in our laboratories.

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References and Notes

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