Bioorganic & Medicinal Chemistry 23 (2015) 6271–6279

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis of new opioid derivatives with a propellane skeleton and their pharmacologies: Part 5, novel pentacyclic propellane derivatives with a 6-amide side chain

Ryo Nakajima [a], Naoshi Yamamoto [b], Shigeto Hirayama [c], Takashi Iwai [c], Akiyoshi Saitoh [d], Yasuyuki Nagumo [b], Hideaki Fujii [c], Hiroshi Nagase [a,b,*]

[a] Graduate School of Pure and Applied Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8571, Japan
[b] International Institute for Integrative Sleep Medicine (WPI-IIIS), University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan
[c] School of Pharmacy, Kitasato University, 5-9-1, Shirokane, Minato-ku, Tokyo 108-8641, Japan
[d] Department of Neuropsychopharmacology, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo 187-8553, Japan

ARTICLE INFO

Article history:
Received 5 August 2015
Revised 24 August 2015
Accepted 26 August 2015
Available online 28 August 2015

Keywords:
Opioid
Propellane
KOR selectivity
Analgesic
Nalfurafine

ABSTRACT

We designed and synthesized pentacyclic propellane derivatives with a 6-amide side chain to afford compounds with higher MOR/KOR ratio and lower sedative effects than nalfurafine. The obtained etheno-bridged derivative with a β-amide side chain, YNT-854, showed a higher MOR/KOR ratio than nalfurafine. YNT-854 also exhibited a higher dose ratio between the sedative effect and the analgesic effect than observed with nalfurafine, which may guide the future design of useful analgesics with a weaker sedative effect than nalfurafine.

1. Introduction

Three types of opioid receptors (μ (MOR), δ (DOR), and κ (KOR)) are now well established not only by pharmacological studies but by molecular biological studies.[1] Narcotic addiction is believed to be derived from MOR type, and therefore KOR and DOR types are promising drug targets for analgesics without addiction. A putative ε receptor, which has not yet been cloned, has also been proposed as another opioid receptor type and much pharmacological data support its existence.[2] To obtain ideal analgesics without addiction and other side effects derived from the MOR, we have synthesized various kinds of naltrexone derivatives and have reported selective ligands for KOR,[3–9] DOR,[10–13] and the putative ε[14] receptors. Recently, one of our designed KOR selective agonists, nalfurafine (TRK-820, Fig. 1),[3,4,7,9] was launched in Japan as an antipruritic for patients undergoing dialysis. Although many arylacetamide derivatives such as U-50,488H[15,16] and U-69,593[17] (Fig. 2) have been synthesized and developed as KOR 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] On the other hand, nalfurafine has neither aversive nor addictive effects. We proposed that, in its binding to the KOR, 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. 1).[5,6,20,21] Based on the proposed active conformation, we investigated the essential nalfurafine structure for binding to the KOR.[22–24]

Recently, we reported the synthesis and the pharmacologies of novel KOR ligands KNT-42 (Fig. 3) with a propellane skeleton. In comparison with nalfurafine, KNT-42 displayed greater selectivity for KOR while simultaneously exhibiting much lower affinity for KOR.[25] We assumed that the reason for the weak affinity of KNT-42 for KOR would derive from the conformational flexibility of the compound. KNT-42 could have two canonical structures; we termed them the bent form and the extended form (Fig. 3).[27] Compared to the proposed active conformation of nalfurafine, the bent form would play an important role for KOR binding. Therefore, we designed and synthesized pentacyclic derivatives (SYK-347 and SYK-393, Fig. 3) with the bent form fixed by etheno- and ethano-bridge.[27] As expected, etheno-bridged and ethano-bridged pentacyclic derivatives SYK-347 (K_i = 1.92 nM, K_i ratio MOR/KOR = 9.17) and SYK-393 (K_i = 0.84 nM, K_i ratio

* Corresponding author. Tel./fax: +81 29 853 6437.
E-mail address: nagase.hiroshi.gt@u.tsukuba.ac.jp (H. Nagase).

http://dx.doi.org/10.1016/j.bmc.2015.08.036
0968-0896/

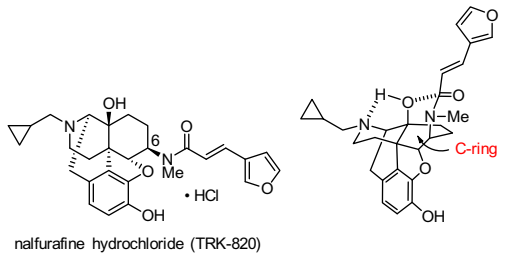


Figure 1. Structure of nalfurafine hydrochloride (TRK-820) and its proposed active conformation binding to the KOR.

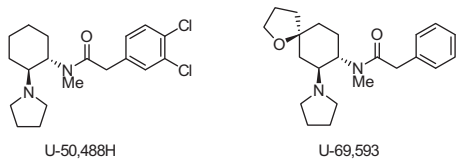


Figure 2. Structures of arylacetamide derivatives U-50,488H and U-69,593.

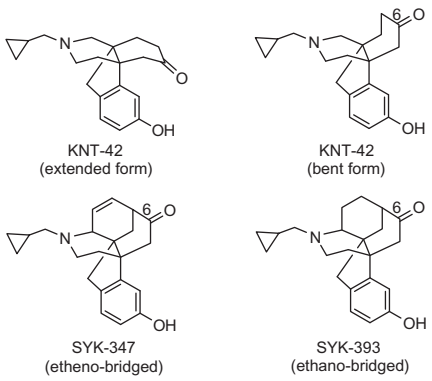


Figure 3. Two canonical conformations of KNT-42 (bent and extended forms) and pentacyclic propellane derivatives SYK-347 and SYK-393.[26]

MOR/KOR = 3.82) showed higher affinity and selectivity for KOR than did KNT-42.[28] As we have reported for KOR agonists, the 6-amide side chains would be an important pharmacophore for binding to the KOR.[5,6,20,21] In the course of the conversion of the 17-alkylsubstituents, we found that the methyl group did not show sufficient KOR selectivity. Therefore, we focused on using the cyclopropylmethyl group as the 17-nitrogen substituent. Next, we introduced a 6-amide side chain to the pentacyclic derivatives SYK-347 and SYK-393 to afford compounds **6**, **7**, **12**, and **13**. Compared with the range of orientations of the amide side chain of nalfurafine, the amide side chains in the pentacyclic compounds **6**, **7**, **12** and **13** could be constrained into more limited space with the rigid pentacyclic structure, which would be expected to lead to enhanced KOR activity and selectivity for KOR. Herein, we report the design and synthesis of the novel KOR selective pentacyclic derivatives with a 6-amide side chain.

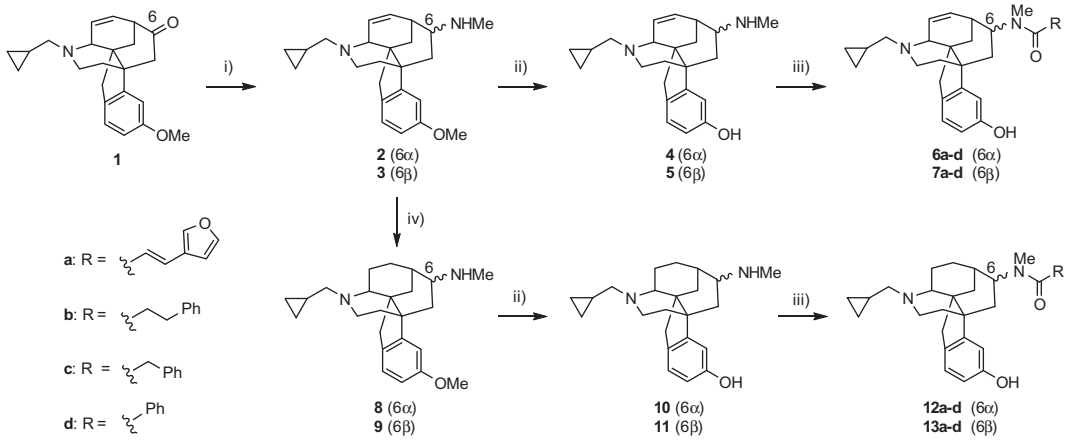
2. Results and discussion

2.1. Chemistry

All of the 6-amide derivatives **6a–d**, **7a–d**, **12a–d** and **13a–d** were synthesized from pentacyclic ketone **1**[27] (Scheme 1). Reductive amination of **1** gave methylamines **2** and **3** in 51% and 24%, respectively.[29] At first, we converted methylamines **2** and **3** to the corresponding amide derivatives by use of acyl chloride. However, the yields of the *O*-demethylation reaction in the obtained amide derivatives with boron tribromide were very low (0–28%), which may have resulted from the decomposition of the amide group.[30] Therefore, the *O*-methyl group in **2** and **3** were removed with pyridinium hydrochloride before acylation of the amine groups. The obtained phenolic compounds **4** and **5** were treated with acyl chlorides to successfully give the etheno-bridged amides **6a–d** and **7a–d**. The ethano-bridged compounds **8** and **9** were obtained by catalytic hydrogenation of **2** and **3** with Pd/C in MeOH. The demethylation of **8** and **9**, followed by amidation of the resulting phenols **10** and **11** afforded the amide derivatives **12a–d** and **13a–d**. To evaluate the binding profiles of the thus synthesized compounds for opioid receptors, the resulting compounds **6a–d**, **7a–d**, **12a–d**, and **13a–d** were converted into their respective hydrochlorides or camphorsulfonates.

2.2. Pharmacology

The results of binding assays of the obtained 6-amide derivatives for the opioid receptors are shown in Table 1. The affinities for the KOR of the etheno- and ethano-bridged compounds **6** and **12** with the 6α-amide side chain were higher than those of



Scheme 1. Reagents and conditions: (i) $NaBH_3CN$, $MeNH_2$·HCl, MeOH, rt, **2**: 51%, **3**: 24%; (ii) HCl·pyridine, 180 °C, **4**: 77% from **2**, **5**: 85% from **3**, **10**: 96% from **8**, **11**: 55% from **9**; (iii) RCOCl, Et_3N, CH_2Cl_2, rt then K_2CO_3, MeOH, rt, **6a**: 98% from **4**, **6b**: 91% from **4**, **6c**: 89% from **4**, **6d**: 99% from **4**, **7a**: 73% from **5**, **7b**: 74% from **5**, **7c**: 74% from **5**, **7d**: 92% from **5**, **12a**: 70% from **10**, **12b**: 85% from **10**, **12c**: 96% from **10**, **12d**: 96% from **10**, **13a**: 73% from **11**, **13b**: 68% from **11**, **13c**: 66% from **11**, **13d**: 83% from **11**; (iv) H_2, 10% Pd/C, MeOH, rt, **8**: 69% from **2**, **9**: 88% from **3**.