Communications to the Editor

[Chem. Pharm. Bull. 34(10)4439—4442(1986)]

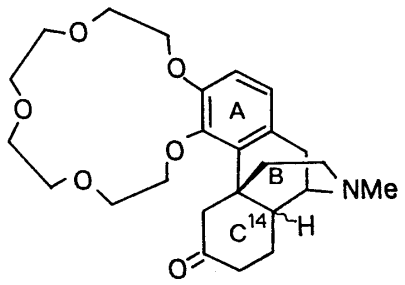
SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF MORPHINE CONGENERS HAVING PENDANT CROWN ETHER AS AN OPIOID RECEPTOR PROBE

Ikuo Fujii, Hiroko Togame, and Ken Kanematsu*
Institute of Synthetic Organic Chemistry, Faculty of Pharmaceutical Sciences, Kyushu University 62, Fukuoka 812, Japan

Morphine congeners (5a, 5b, and 10) with pendant benzo[15-crown-5]crown ether at C-6 were synthesized. Their pharmacological properties were evaluated on ^{3}H-naloxone binding, analgesic, and antitussive tests.

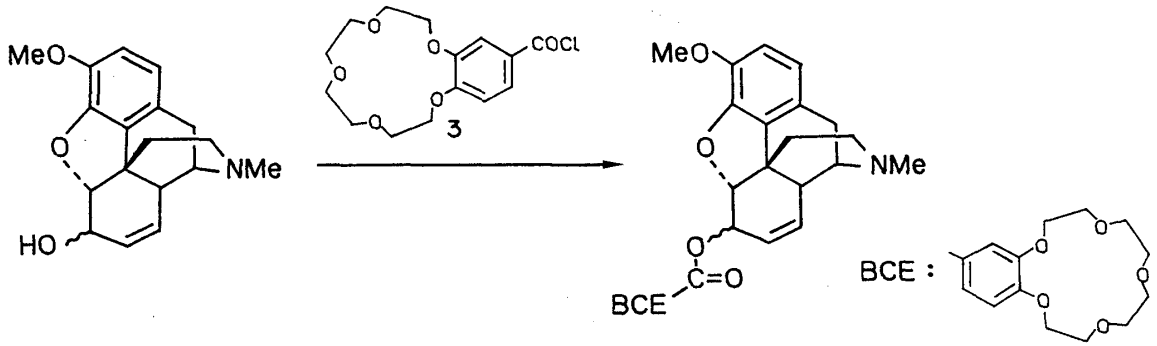
KEYWORDS ——crowned morphine; benzo[15-crown-5]crown ether; opioid receptor probe; sodium effect; ^{3}H-naloxone binding test; analgesic test; antitussive test

It has been advanced by Snyder et al. that the mechanisms of action of opioids and the transmission of pain are closely related to sodium ion transport processes in opioid receptor membranes.[1-3] The role of the sodium ion in the opioid receptor could be directly tested by introducing the ionophore function into opiate molecules by the intramolecular incorporation of crown ether. In our previous paper,[4] we described the first and expedient synthesis of crowned morphinanones (1a and 1b) bearing a crown ether moiety in the A-ring (Chart 1). In the subsequent biological assay, however, these ligands gave inconclusive results: they retained no analgesic activity but had antitussive activity nearly equal to dextromethorphan. This may be because 1a and 1b have markedly less affinity for the receptor than codeine.[5] Further examination of this receptor probe may lead to the design of new analogues of the crown ether moiety to the morphine skeleton at C-6.[6] In this communication, we wish to report the synthesis and pharmacological properties of morphine congeners with pendant crown ether.



1a : α-H14 (B/C trans)
1b : β-H14 (B/C cis)

Chart 1



2a : C(6)α
2b : C(6)β

5a : C(6)α
5b : C(6)β

Chart 2

Compounds (5a) and (5b) were synthesized respectively from codeine (2a) and isocodeine (2b) with acid chloride (3),[7] (Chart 2). The reaction of 2a with 3 in the presence of 4-dimethylaminopyridine under refluxing temperature in toluene gave compound (5a) (mp 68-69.5°C, 59%),[8] and the reaction of 2b proceeded readily in the presence of triethylamine at 80°C to afford 5b (mp 72.5-73.0°C, 83%).[9] Next, the crown ether moiety was linked to the morphine molecule by an amide bond which is relatively resistant to metabolic breakdown (Chart 3). Silylation (tert-butyldimethylsilyl chloride/NaH/THF, 7, 92.7%)[10] of dihydromorphinone (6) followed by reductive amination ($NaCNBH_3/NH_4OAc/MeOH$)[11] gave the crude amine (8), which was condensed with acid (4)[7] by esterification (1-hydroxybenzotriazole / 1-(3-dimethylaminopropyl)-3-ethylcarbodiimido hydrochloride/ CH_2Cl_2) to afford the 6α isomer (9a) (15.0% overall yield from 7) along with a small amount of the 6β isomer (9b). The stereochemical assignment at the C-6 position in both 9a and 9b was deduced on the basis of NMR spectral analogy with naltrexamines and closely related congeners.[12] The 5β-hydrogen of 9a (δ 4.69) showed a signal downfield from that of 9b (δ 4.65), and the coupling constant ($J_{5\beta-6\beta}$) for 9a (4.5 Hz) was smaller than that ($J_{5\beta-6\alpha}$) for 9b (8.0 Hz). Next, the treatment of 9a with 1N HCl in EtOH gave the crystalline product (10)[13] in 93% yield.

Compounds (5a), (5b), and (10) were evaluated with regard to ^{3}H-naloxone binding, and their analgesic, and antitussive effects. These results may be summarized as follows. i) Compound (10) greatly inhibited ^{3}H-naloxone binding (IC_{50} = 21.4 nM vs. codeine IC_{50} = 140 nM) and (5b) did so moderately (IC_{50} = 146 nM). Their respective sodium indices,[2] IC_{50} ($+Na^+$)/IC_{50} ($-Na^+$), were 14.5 for 10 and 8.6 for 5b. Thses are slightly lower than the index of codeine (sodium index: 20) and markedly lower than that of morphine (sodium index: 110).[14]

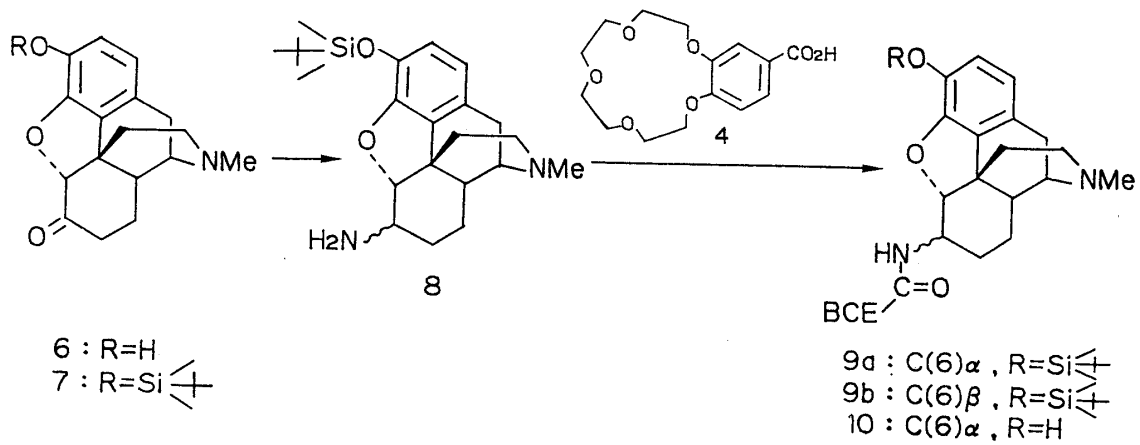


Chart 3

ii) Only compound (10) exerted analgesic effects both at 30 mg/kg s.c. and at 10 nmol/animal intracisternally as indicated by hot-plate and tail-flick tests in mice. The analgesic effect was less than that of codeine. However, 10 showed neither potentiation nor antagonism of morphine analgesia in mice at 30 mg/kg s.c.[15] iii) In cats lightly anesthetized with sodium pentobarbital, both compounds (10) and (5a) inhibited the cough reflex elicited by a mechanical stimulation of the tracheal muscle 2.3 and 1.3 times more potently than codeine.[16]

In summary, it is most noteworthy that compound (10) has 2.3 time more antitussive and less analgesic activities than codeine, while retaining potent affinity for the opioid receptor. Although the molecular mechanisms and a satisfactory explanation of the dramatic antitussive activity of these ligands must await further study, it may be possible to modify the pharmacological properties of morphine molecules by incorporating the crown ether ring into them.

ACKNOWLEDGEMENT We thank Dr. Keiji Nakamura and his associates, Department of Pharmacology Nippon Roche Research Center, for doing the pharmacological screening.

REFERENCES AND NOTES

1) S. H. Snyder, Scientific American, 236, No.3, 44 (1977); idem, Chemical & Eng. News, Nov.28, 26 (1977).
2) C. B. Pert and S. H. Snyder, Mol. Pharmacol., 10, 868 (1974).

3) A. P. Feinberg, I. Creese, and S. H. Snyder, Proc. Natl. Acad. Sci. U.S.A., 73, 4215 (1976).
4) I. Fujii, K. Hayakawa, and K. Kanematsu, Tetrahedron Lett., 25, 3335 (1984).
5) I. Fujii, K. Hayakawa, and K. Kanematsu, unpublished results.
6) P. S. Portoghese, D. L. Larson, J. B. Jiang, T. P. Caruso, and A. T. Takemori, J. Med. Chem., 22, 168 (1979) and references cited therein.
7) Acid chloride (3) was prepared from 4-formylbenzocrown ether obtained by the method of Smid et al. in two steps, i) CrO_3-H_2SO_4/ acetone and ii) $SOCl_2$/pyridine, [J. Smid, B. E. Haj, T. Majewicz, A. Nonni, and R. Sinta, Org. Prep. and Proced. Int., 8, 193, (1976)].
8) Compound (5a)·HCl: mp 183.5°C; Anal. Calcd for $C_{33}H_{39}NO_9$·HCl·1.5 H_2O: C, 60.31; H, 6.60; N, 2.13. Found: C, 60.56; H, 6.66; N, 1.95.
9) Compound (5b)·HCl: mp 116.7°C; Anal. Calcd for $C_{33}H_{39}NO_9$·HCl·H_2O: C, 61.15; H, 6.53; N, 2.16. Found: C, 61.27; H, 6.68; N, 2.13.
10) S. Fang, A. E. Takemori, and P. S. Portoghese, J. Med. Chem., 27, 1361 (1984).
11) J. B. Jiang, R. N. Hanson, P. S. Portoghese, and A. E. Takemori, J. Med. Chem., 20, 1100 (1977).
12) L. M. Sayre and P. S. Portoghese, J. Org. Chem., 45, 3366 (1980).
13) Compound (10): mp 205.8-206.3°C; Anal. Calcd for $C_{32}H_{40}N_2O_8$·H_2O: C, 64.20; H, 7.07; N, 4.68. Found: C, 64.44; H, 7.17; N, 4.49.
14) ^{3}H-Naloxone binding to the crude membrane preparation of rat whole brain minus cerebellum was measured at a radioligand concentration of 2 nM in the presence or absence of 100 mM NaCl according to the method of Childers et al. [S. R. Childers, I. Creese, A. M. Snowman, and S. H. Snyder, Eur. J. Pharmacol., 55, 11, (1979)].
15) Intracisternal analgesic experiments were carried out in male ICR mice weighing 25 - 30 g. Compounds were dissolved in distilled water containing Evans blue for monitoring intracisternal injection. Five μg of vehicle solution or solution containing either compound was slowly injected into the cisterna magma of conscious mice with a microsyringe attached to a J-shaped stainless needle, according to the method of Ueda et al. [H. Ueda, H. Amano, H. Shiomi, and H. Takagi, Eur. J. Pharmacol., 56, 265, (1979)]. Analgesic activity was evaluated by both hot-plate and tail flick methods at 5, 10, 20, 30, and 60 min after the intracisternal injection.
16) ED_{50} values were calculated from the dose-response relationship 0 - 30 min after the intravenous administration; ED_{50} value (mg/kg), 10: 0.90, 5a: 1.29, 5b: 2.45, codeine: 1.56, and dextromethorphan: 2.86.

(Received September 1, 1986)