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Investigation of Beckett–Casy model 2: Synthesis of novel 15–16 nornaltrexone derivatives and their pharmacology

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ABSTRACT

We synthesized novel 15–16 nornaltrexone derivatives **9**, **11** and **22** to examine the importance of the cavity in the Beckett–Casy model, which was proposed to interact with the 15–16 ethylene moiety in the morphine structure. All the synthesized compounds showed lower affinities for the opioid receptor than did the naltrexone (**10**). The binding affinities of 14-OH derivatives **11**, in which the rotation of the 9–17 bond would be restricted by an intramolecular hydrogen bond, was improved compared to the corresponding 14-H derivatives **9**. Compound **22** whose 9–17 bond was strictly fixed by the ethylene bridge hardly bound to the opioid receptor. Compound **26** also showed very weak binding affinity in spite of the existence of the 15–16 ethylene unit. We proposed an important role for the orientation of the lone electron pair on the 17-nitrogen rather than the significance of the cavity in the Beckett–Casy model.

Three types of opioid receptors (μ, δ, and κ) are now well established not only by pharmacological studies but also by molecular biological studies.[1] The μ receptor type is believed to be involved in narcotic addiction, and therefore δ and κ types are promising drug targets for analgesics without addiction. To obtain ideal analgesics free of addictive properties and other side effects derived from the μ receptor, we have focused our investigation on δ and κ receptor ligands to develop selective δ and κ agonists[2–6] and to discover other new reactions using naltrexone derivatives.[7–18] Recently, we have reported synthesis of 16,17-*seco*-naltrexone derivatives **1** (Fig. 1)[19] and have discussed the importance of the putative cavity in the Beckett–Casy model[20–22] based on their binding affinities for the opioid receptor.[19] This model proposes that a cavity would exist on the opioid receptor site and interact with the 15–16 ethylene moiety in the morphine structure (Fig. 2). Although the investigation using 16,17-*seco*-naltrexone derivatives **1** seemed to support the existence of such a cavity structure, the confirmation of the model required further experiments using 15–16 nornaltrexone derivatives **2** (Fig. 1) which lacked the 15–16 bond. Herein, we report synthesis 15–16 nornaltrexone derivatives **2** and discuss the importance of the cavity in the Beckett–Casy model, based on the binding affinities of these new structures.

Synthesis of 15–16 nornaltrexones **9** commenced from hydrogenation of **3** prepared by a reported method using a double decarboxylation reaction[18] as the key reaction (Scheme 1). The stereochemistry of **4** was determined by 2D NMR experiments.[23] Selective dealkylation of the cyclopropylmethyl (CPM) group[12] in

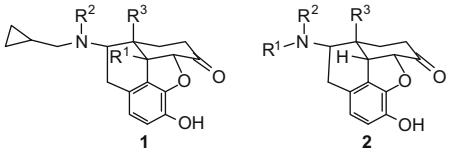

Figure 1. Structures of 16,17-*seco*-naltrexone derivatives **1** and 15–16 nornaltrexone derivatives **2**.

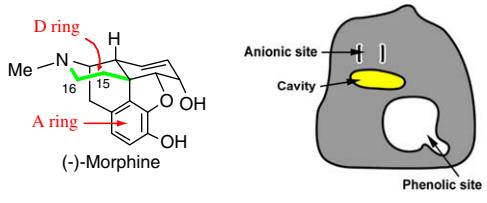

Figure 2. (−)-Morphine and the Beckett–Casy binding model. (−)-Morphine can bind the opioid receptor site by use of three pharmacophoric interactions; ionic, π–π (aromatic ring) interactions, and hydrogen bonding. Furthermore, the 15–16 bond (green line) projecting in front of and to the side of the line between the center of A-ring and the basic nitrogen in morphine is proposed to fit into the cavity moiety in this model.

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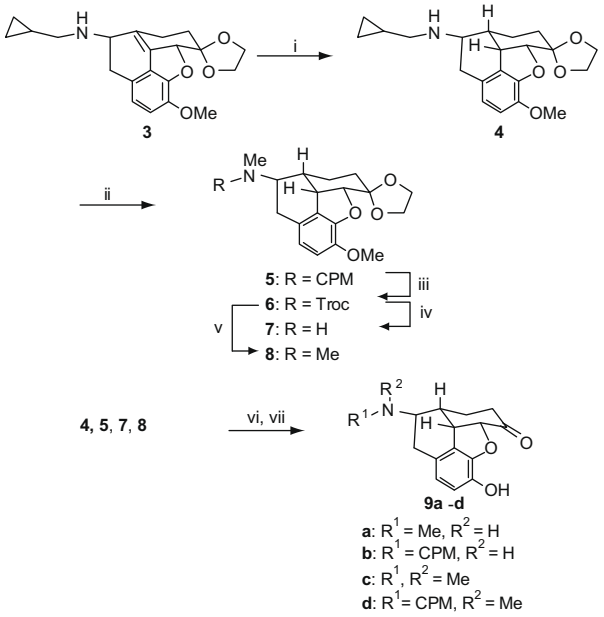


Scheme 1. Reagents and conditions: (i) H_2, Pd/C, MeOH, rt, quant.; (ii) $(CH_2O)_n$, $NaBH_3CN$, AcOH, rt, 90%; (iii) Troc-Cl, proton-sponge, CH_2Cl_2, rt, 61%; (iv) Zn, AcOH, rt, 89%; (v) $LiAlH_4$, THF, rt, quant.; (vi) HCl, MeOH, reflux, 88%—quant.; (vii) BBr_3, CH_2Cl_2, rt, 16–27%.

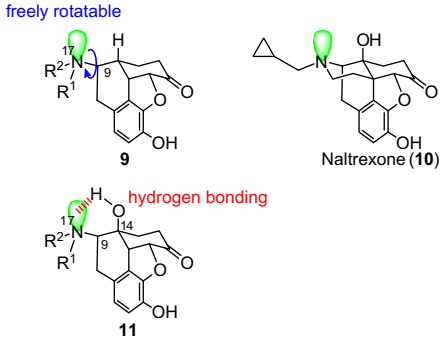


Figure 3. Structures of compounds **9**–**11** and their lone electron pairs.

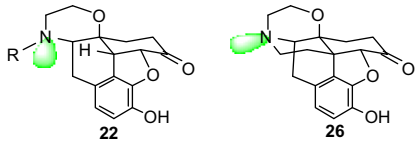
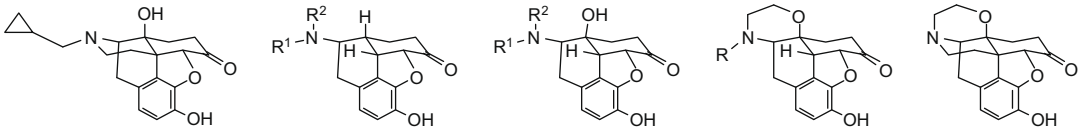


Figure 4. Structures of compounds **22** and **26** and their lone electron pairs.

5, prepared by reductive methylation of **4**, gave compound **6**, which was converted into **7** and **8**. Deprotection of compounds **4**, **5**, **7**, and **8** afforded the objective compounds **9**. In binding assays,[17] the tertiary amines **9c** and **9d** showed significant affinities for the μ receptor compared to the corresponding secondary amines **9a** and **9b**, respectively (Table 1). Furthermore, the compounds **9b** and **9d** with the 17-CPM group had better affinities than the corresponding **9a** and **9c** with the methyl substituent, which may arise from strong electron releasing effects by the CPM group.[14] However, the binding affinities of all the synthesized compounds **9** were 10- to 500-fold weaker than naltrexone (**10**). These results were consistent with the existence of the cavity described in the Beckett–Casy model.

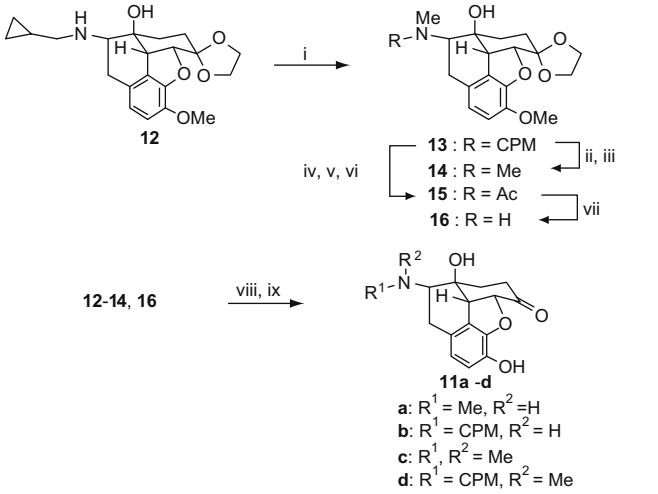
The 9–17 bond of **9** can freely rotate around the axis, whereas that of μ antagonist naltrexone (**10**) was fixed (Fig. 3). Perhaps some of the rotamers of **9** may prevent the compound from approaching the receptor, leading compounds **9** to show weaker affinities. So, we next attempted to prevent rotation by fixing the 9–17 bond through formation of hydrogen bonds between the 17-nitrogen and the 14-hydroxy groups[24] (compounds **11** in Fig. 3) or via incorporation of tethering structures (compounds **22** and **26** in Fig. 4). 15–16 Nornaltrexone derivatives **11** having the 14-OH group were synthesized as shown in Scheme 2. Compound **12**, prepared from **3** by the reported method,[18] was converted into **13** by reductive methylation. Treatment of **13** with α-chloroethyl chloroformate (ACE-Cl) gave the oxazolidinone,[12]

Table 1
Binding affinities of compounds **9**–**11**, **22**, and **26** for opioid receptors[a]

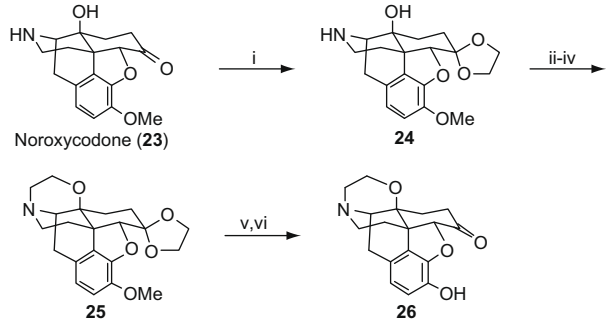


Compound [b]	R^1 or R	R^2	K_i (μ)[c] (nM)	K_i (κ)[d] (nM)	K_i (δ)[e] (nM)
Naltrexone (**10**)	—	—	0.335	0.373	44.2
9a	Me	H	164	ND[f]	ND[f]
9b	CPM[g]	H	30.3	32.2	ND[f]
9c	Me	Me	50.9	ND[f]	ND[f]
9d	CPM[g]	Me	3.36	8.81	272
11a	Me	H	118	ND[f]	ND[f]
11b	CPM[g]	H	24.7	68.4	ND[f]
11c	Me	Me	8.95	ND[f]	ND[f]
11d	CPM[g]	Me	1.17	5.1	55.2
22a	CPM[g]	—	294	ND[f]	ND[f]
22b	Me	—	ND[f]	ND[f]	ND[f]
26	—	—	86.0	72.6	ND[f]

[a] Binding assay was carried out in duplicate using homogenate of guinea pig brain (κ, cerebellum; μ and δ, forebrain).
[b] All compounds were evaluated after being converted to their HCl salts.
[c] [^{3}H] DAMGO was used.
[d] [^{3}H] U-69593 was used.
[e] [^{3}H] NTI was used.
[f] ND: the K_i value was not determined because the IC_{50} value was over 1000 nM.
[g] Cyclopropylmethyl.



Scheme 2. Reagents and conditions: (i) $(CH_2O)_n$, $NaBH_3CN$, AcOH, rt, 88%; (ii) ACE-Cl, K_2CO_3, 1,1,2,2-tetrachloroethane, 150 °C, 78%; (iii) $LiAlH_4$, THF, rt, 56%; (iv) Ac_2O, Et_3N, 60 °C, quant.; (v) Troc-Cl, K_2CO_3, 1,1,2,2-tetrachloroethane, 150 °C, quant.; (vi) Zn, AcOH, rt, 97%; (vii) 6 M NaOH, DMSO, 80 °C, 75%; (viii) HCl, MeOH, reflux, 93%—quant.; (ix) BBr_3, CH_2Cl_2, rt, 26–53%.

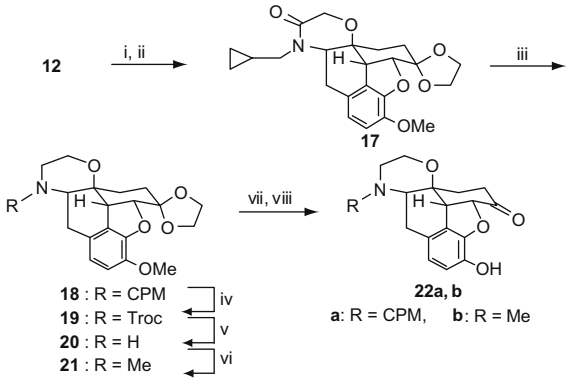


Scheme 4. Reagents and conditions: (i) ethylene glycol, camphorsulfonic acid, benzene, azeotropy, 96%; (ii) 2-bromoethanol, K_2CO_3, DMF, rt, 70%; (iii) MsCl, *i*-Pr_2EtN, CH_2Cl_2, rt, 44%, (iv) KI, NaH, THF, reflux, 78%; (v) HCl, MeOH, reflux, 99%; (vi) BBr_3, CH_2Cl_2, rt, 12%.

which was reduced by LAH to afford **14**. After acetylation of **13**, reaction of the resulting 14-acetate with trichloroethyl chloroformate (Troc-Cl) and subsequent deprotection of the Troc group provided acetamide **15**, which was then hydrolyzed to give **16**. Deprotection of compounds **12**–**14** and **16** afforded the objective compounds **11**. Tethered compounds **22** were prepared from **12** via lactam formation with chloroacetyl chloride and subsequent reduction as key reactions (Scheme 3). Another tethered compound **26** having the D-ring (see Fig. 4) was synthesized by morpholine ring construction as a key reaction (Scheme 4).

The binding affinities[17] of all the synthesized compounds were determined and compared with that of naltrexone (**10**) (Table 1). Tertiary amines **11c** and **11d** with 14-OH group also showed stronger binding affinities than the corresponding secondary amines **11a** and **11b**, suggesting that the higher electron density on the 17-N in the tertiary amines than the secondary amines would increase in the binding abilities to the opioid receptor.

The binding affinities of the 14-OH derivatives **11** were improved compared to those of the corresponding 14-H derivatives **9**. Given that this improvement was derived from the expected hydrogen bond between the 17-N and 14-OH groups (Fig. 3), the decrease in the binding affinities of compounds **9** may result



Scheme 3. Reagents and conditions: (i) chloroacetyl chloride, Et_3N, CH_2Cl_2, rt, quant.; (ii) NaH, THF, rt, 66%; (iii) $LiAlH_4$, THF, rt, 95%; (iv) Troc-Cl, K_2CO_3, 1,1,2,2-tetrachloroethane, 150 °C, quant.; (v) Zn, AcOH, rt, 85%; (vi) $(CH_2O)_n$, $NaBH_3CN$, AcOH, rt, 76%; (vii) HCl, MeOH, reflux, 69%—quant.; (viii) BBr_3, CH_2Cl_2, rt, 49–62%.

mainly from the hindrance arising from some rotamers rather than from the absence of interaction with the proposed cavity. Even compound **11d** having the strongest affinity among the 14-OH derivatives **11** more weakly bound to the μ receptor than naltrexone (**10**), suggesting that simply restricting bond rotation by the hydrogen bond may be insufficient for optimum interaction with the μ opioid receptor. The binding abilities of compounds **22** were expected to be further improved because the rotation of the 9–17 bond in the compounds was strictly fixed by the ethylene bridge between the 17-N and 14-OH groups. However, compounds **22** hardly bound to the opioid receptor. Moreover, another tethered compound **26** bound to the opioid receptor, but its affinity was very weak in spite of the presence of the 15–16 ethylene unit.

It is difficult to explain these outcomes by only the existence of the cavity and/or by the steric hindrance arising from some rotamers. A possible alternative explanation is that the orientation of the lone electron pair on the 17-N may play an important role in the interaction between a ligand and the opioid receptor. Ion–ion interaction between the ligand and the receptor has been generally proposed to be the most important pharmacophore.[25] The orientations of the lone electron pairs in compounds **9**–**11**, **22**, and **26** are shown in Figures 3 and 4.[26] The orientation of the lone electron pair in naltrexone (**10**) is firmly fixed in the axial orientation by the hydrogen bonding with the 14-OH group[24] and the 15–16 bond in the D-ring. Therefore, of the compounds in Table 1, the affinity of naltrexone for the opioid receptor would be the strongest. Due to hydrogen bonding between the 17-N and 14-OH group, the lone electron pairs in compounds **11** would tend to take an axial direction as opposed to those in compounds **9** with only the 14-H. The difference of orientational tendency would influence the binding affinities: 14-OH compounds **11** exhibited higher affinities than the corresponding compounds **9** without the intramolecular hydrogen bond. In compound **26**, an ethylene bridge would restrict the orientation of the lone electron pair to the equatorial position. As a result, despite the fact that the compound has the 15–16 ethylene moiety, compound **26** would show weaker affinity than compounds **11** whose lone electron pair would be located in the axial position. On the other hand, the lone electron pairs in compounds **22** were predicted to project in front of the plane consisting of the 17-N and the phenol ring, and not to be arrayed in an axial orientation, leading to the very low affinity. On the basis of the above discussion, we propose that the cavity of the Beckett–Casy model might not exist and that the 15–16 bond in the D-ring may play a role in fixation of the lone electron pair on the 17-N in the desired axial orientation. However, a steric hindrance resulted from the methylene moiety in compounds **22** and **26** may decrease in the binding abilities of these compounds. To confirm our proposal, the further

investigations using compounds which have lone electron pair projecting in various directions without steric hindrance are carried out and will be reported in due course.

In conclusion, we have synthesized novel 15–16 nornaltrexone derivatives **9**, **11**, and **22** to examine the importance of the proposed cavity in the Beckett–Casy model. All the synthesized compounds showed lower affinities for the opioid receptor than naltrexone (**10**). The binding affinities of 14-OH derivatives **11**, in which the rotation of the 9–17 bond would be restricted by the intramolecular hydrogen bond, were improved compared to the corresponding 14-H derivatives **9**. Compounds **22** whose 9–17 bonds were strictly fixed by the ethylene bridge hardly bound to the opioid receptor. Compound **26** also showed very weak binding affinity in spite of the existence of the 15–16 ethylene unit. We proposed an important role for the orientation of the lone electron pair on the 17-N rather than the significance of the cavity in the Beckett–Casy model based on the intimate comparisons of the binding affinities of 15–16 nornaltrexone derivatives.

Acknowledgments

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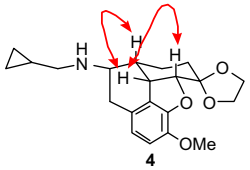
23. NOEs were observed between protons indicated by arrows.



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26. The B ring (cyclohexene ring) in compounds **9** and **11** are estimated to adopt the same conformation as that in naltrexone (**10**), that is, a chair-like conformation. If the B ring were in a boat-like conformation, perhaps the compounds may hardly bound to the opioid receptor because the 17-N group would protrude in a spatially different direction from that of the compounds with the B ring in a chair-like conformation.