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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

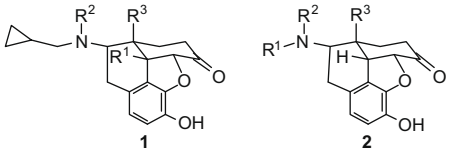

Figure 1. Structures of 16,17-*seco*-naltrexone derivatives **1** and 15–16 nornaltrexone derivatives **2**.

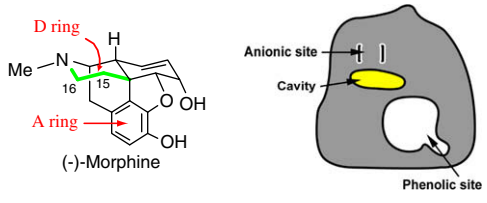

Figure 2. (−)-Morphine and the Beckett–Casy binding model. (−)-Morphine can bind the opioid receptor site by use of three pharmacophoric interactions; ionic, π–π (aromatic ring) interactions, and hydrogen bonding. Furthermore, the 15–16 bond (green line) projecting in front of and to the side of the 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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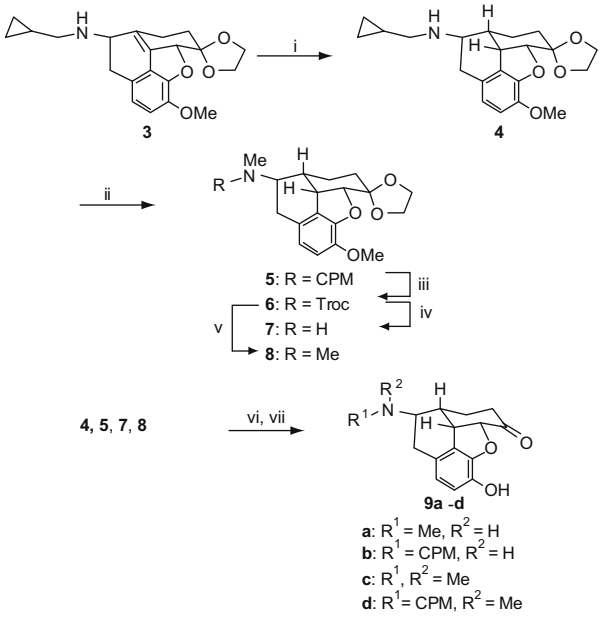


Scheme 1. Reagents and conditions: (i) H_2, Pd/C, MeOH, rt, quant.; (ii) $(CH_2O)_n$, $NaBH_3CN$, AcOH, rt, 90%; (iii) Troc-Cl, proton-sponge, CH_2Cl_2, rt, 61%; (iv) Zn, AcOH, rt, 89%; (v) $LiAlH_4$, THF, rt, quant.; (vi) HCl, MeOH, reflux, 88%—quant.; (vii) BBr_3, CH_2Cl_2, rt, 16–27%.

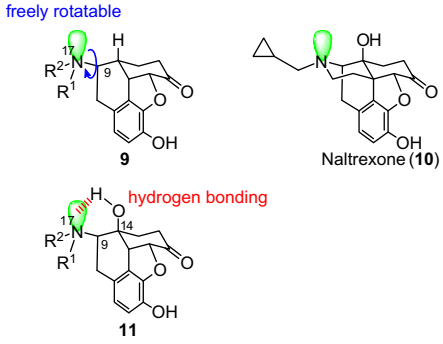


Figure 3. Structures of compounds **9**–**11** and their lone electron pairs.

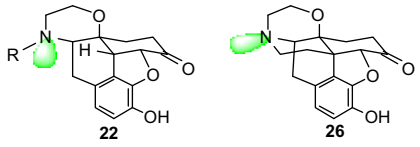
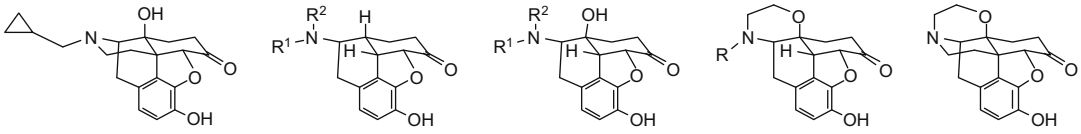


Figure 4. Structures of compounds **22** and **26** and their lone electron pairs.

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.