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Investigation of Beckett–Casy model 1: Synthesis of novel 16,17-*seco*-naltrexone derivatives and their pharmacology

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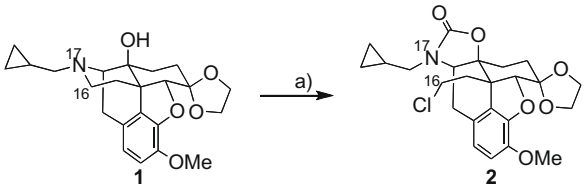
ABSTRACT

Novel 16,17-*seco*-naltrexone derivatives **3** were synthesized using a 16–17 bond cleavage reaction of naltrexone as the key reaction to examine the Beckett–Casy model. All the prepared 16,17-*seco*-naltrexone derivatives **3** showed lower affinities for opioid receptors than naltrexone. Although the results of binding assay seem to support the existence of a cavity in the model, further investigation using 15,16-nornaltrexone derivatives **26** will be needed to confirm the model.

Opioid receptors have been generally classified as μ, δ, and κ types not only by pharmacological studies but also by molecular biological characterization.[1] Narcotic addiction is believed to be derived from the μ receptor type, and therefore δ and κ receptor 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 type of opioid receptor and numerous pharmacological studies support its existence.[2] To obtain ideal analgesics without addiction and other side effects derived from the μ receptor, we have synthesized various naltrexone derivatives and selective ligands for κ, δ, and the putative ε receptors.[3–9] We especially focused our recent investigations on modification of the 4,5-epoxymorphinan skeleton that is believed to be the structural feature that is essential for binding to the opioid receptor.[10–15] In the course of our investigation, we observed the 16–17 bond cleavage reaction of the naltrexone derivative **1** to afford oxazolidinone derivative **2** (Scheme 1).[12] Our interest in the pharmacology of 16,17-*seco*-naltrexone derivatives **3** (Fig. 1) derived from compound **2** led us to study their structure–activity relationships (SAR). Herein, we report synthesis of the 16,17-*seco*-naltrexone derivatives **3** and their pharmacology.

Our first attempts to reduce the oxazolidinone ring in compound **2** with LAH provided ring closure product **4** in 88% yield. Compound **4** was hydrolyzed and subsequently demethylated with BBr_3 to afford **5** (KNT-5) (Scheme 2). On the other hand, when compound **7**, prepared by the 16–17 cleavage reaction of **6**, was treated



Scheme 1. Reagents and conditions: (a) ACE–Cl, K_2CO_3, 1,1,2,2-tetrachloroethane, 150 °C, 93%.

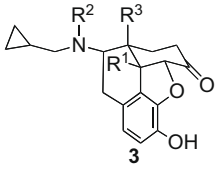
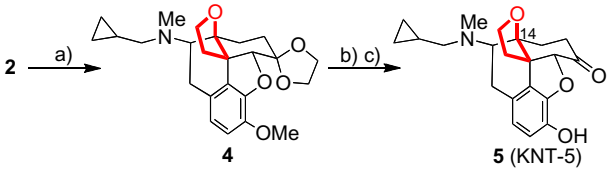


Figure 1. Structure of 16,17-*seco*-naltrexone derivatives **3**.



Scheme 2. Reagents and conditions: (a) LAH, THF, rt, 88%; (b) 1 M HCl, 80 °C, 98%; (c) BBr_3, CH_2Cl_2, rt, 47%.

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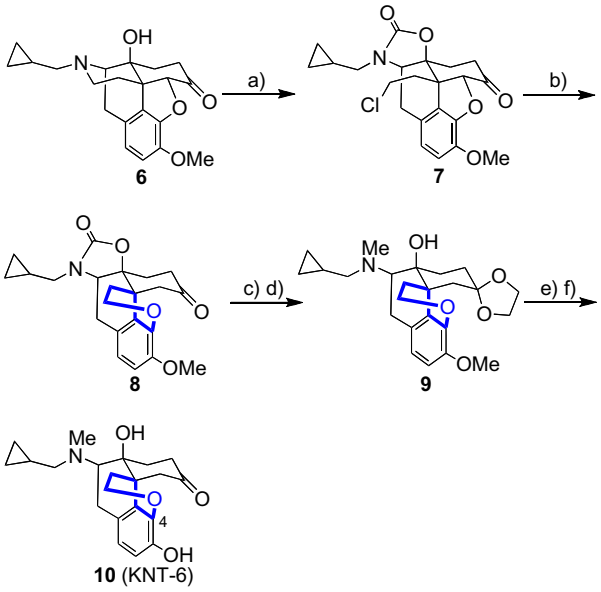
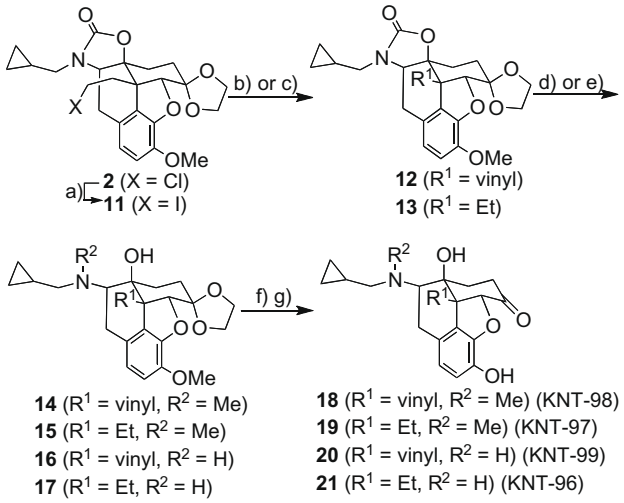


Scheme 3. Reagents and conditions: (a) ACE–Cl, K_2CO_3, 1,1,2,2-tetrachloroethane, 150 °C, 92%; (b) Zn, AcOH, reflux, 87%; (c) ethylene glycol, *p*-TsOH·H_2O, toluene, azeotropy, 89%; (d) LAH, THF, rt, 87%; (e) 1 M HCl, reflux, 54%; (f) BBr_3, CH_2Cl_2, rt, 71%.



Scheme 4. Reagents and conditions: (a) NaI, DMF, 130 °C, 94%; (b) *t*-BuOK, THF, 0 °C, 95%; (c) Zn, AcOH, rt, 93%; (d) LAH, THF, rt; (e) 12 M NaOH, DMSO, 110 °C, **16**: 53%, **17**: 89%; (f) 2 M HCl, MeOH, reflux; (g) BBr_3, CH_2Cl_2, rt, **18**: 11% from **12**, **19**: 42% from **13**, **20**: 33% from **16**, **21**: 24% from **17**.

with Zn-AcOH, ring closure product **8** was isolated in 87% yield. The keto group of compound **8** was protected by converting it to the acetal which was subsequently reduced with LAH to provide amine **9** in 87% yield. Deacetalyzation with 1 M HCl (54%) was followed by subsequent demethylation with BBr_3 to afford **10** (KNT-6) in 71% yield (Scheme 3).

The binding abilities of the thus obtained KNT-5 and KNT-6 for opioid receptors were estimated. Surprisingly, the affinities of KNT-6 for the μ, δ, and κ receptors were very poor (K_i values: not determined). In contrast, the affinities of KNT-5 for μ and κ receptors were better than those of KNT-6 (K_i (μ) = 24 nM, K_i (δ): not determined, K_i (κ) = 43.2 nM), but were worse than those of naltrexone (K_i (μ) = 0.335 nM, K_i (δ) = 44.2 nM, K_i (κ) = 0.373 nM). KNT-5 and KNT-6 may have lower affinities than naltrexone because the newly formed ring produces steric hindrance that disrupts binding with the receptor site. Although the dihydropyran ring in KNT-6, which was located at the lower side of the molecule (indicated by blue color in Scheme 3), seemed to hinder the binding with the receptor, the tetrahydrofuran ring in KNT-5, which lay in the upper side of the molecule (indicated by red color in Scheme 2), did not show as much hindrance. This indication of steric hindrance reminded us of the Beckett–Casy binding model (Fig. 2).[16,17] This model has been applied to morphinan derivatives whose structures have a basic nitrogen, a phenol group, and a 15–16 ethylene unit in the piperidine moiety, that is, D ring. The 15–16 ethylene unit in morphinans is perceived to lie in front of the plane containing the aromatic ring (A ring) and the basic nitrogen to accommodate in the cavity moiety in the model. The bond between C16 and N17 were cleaved and the resulting C16 unit was bound with the 14-OH in KNT-5 or 4-OH in KNT-6, respectively. As a result of the bond change, the dihydropyran moiety in KNT-6 and the tetrahydrofuran moiety in KNT-5 might exhibit severe steric hindrance that would prevent a good fit into the cavity. Although the credibility of the Beckett–Casy model has been under discussion for a long time, a decisive conclusion has not yet been obtained.[16,17] Many structural skeletons have been applied to the model, resulting in confusing interpretations and no clear outcome. The model was originally applied to morphine, 4,5-epoxymorphinan skeleton, and at most, morphinans and benzomorphans. Therefore, we tried to examine precisely the Beckett–Casy model using a series of 4,5-epoxymorphinan derivatives to obtain coherent results. In the present study, since we obtained the 16,17-*seco*-derivatives **3**, the compounds **3** were utilized to examine the Beckett–Casy model.

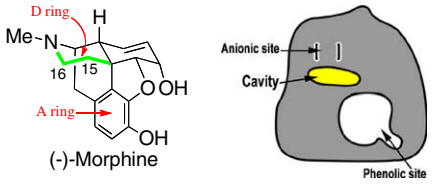
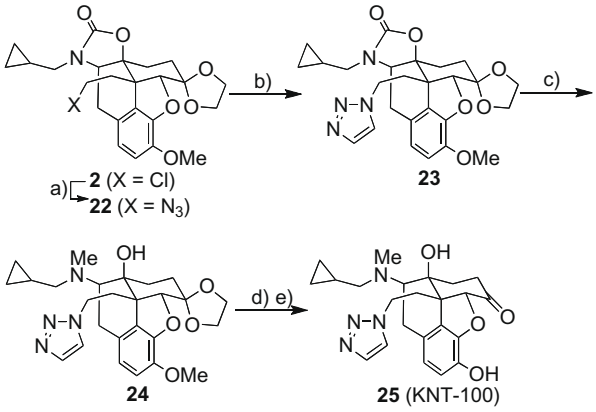


Figure 2. (−)-Morphine and the Beckett–Casy binding model. (−)-Morphine can bind the opioid receptor site by use of three pharmacophoric interactions; ionic, π–π (aromatic ring) interactions, and hydrogen bonding. Furthermore, the 15–16 bond (green line) projecting in front of and to the side of the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

Chloride **2** was converted to iodide **11** with NaI in 94% yield (Scheme 4). The resulting iodide **11** was treated with *t*-BuOK to give unsaturated compound **12**. Saturated compound **13** was obtained by reduction of iodide **11** with Zn–AcOH. Compounds **12** and **13** were converted to compounds **14** and **16** or to **15** and **17** by LAH reduction or basic hydrolysis, respectively. Acetals of compounds **14**–**17** were deprotected with 2 M HCl, followed by demethylation with BBr_3 to give compounds **18**–**21** (KNT-96-99).

Synthesis of triazole **25** (KNT-100) started with azidation of chloride **2** (Scheme 5). Azide **22** was converted to triazole **23** in 75% yield by Huisgen 1,3-dipolar cycloaddition using 2,5-norbornadiene.[18] The oxazolidinone ring of **23** was reduced by LAH, followed by deacetalyzation with 1 M HCl and subsequent demethylation with BBr_3 to give KNT-100.

The results of the opioid receptor binding assays of the prepared compounds are shown in Table 1. The binding affinities of all the synthesized compounds for each type of opioid receptor were much weaker than for naltrexone. Particularly, KNT-6, 97, and 100 showed almost no binding affinity for all three receptor types. KNT-5, 96, 98, and 99 showed some binding affinity. The projection of the dihydropyran ring in KNT-6 in front of and to the lower side of the molecule may disturb the fit of the molecule to the receptor. Similarly, the location of the triazole ring in KNT-100 in front of



Scheme 5. Reagents and conditions: (a) NaN_3, DMSO, 150 °C, 95%; (b) 2,5-norbornadiene, 1,4-dioxane, reflux, 75%; (c) LAH, THF, rt, 46%; (d) 1 M HCl, reflux, 91%; (e) BBr_3, CH_2Cl_2, rt, 46%.

and to the lower side of the molecule may cause severe steric hindrance. On the other hand, in KNT-5, the tetrahydrofuran ring protrudes in front of, but to the upper side of the molecule, and this structure may not severely disturb the fit of the molecule to the receptor. The ethyl group in KNT-97 is smaller than the triazole ring in KNT-100 and the modest binding to only the κ receptor, as indicated by an intermediate value of K_i, may reflect less steric hindrance. KNT-96, which differs from KNT-97 by the absence of the *N*-methyl group, showed satisfactory K_i values for all the three receptor types. Perhaps the presence of the methyl group of KNT-97 forces the ethyl substituent to the lower side of the molecule and increases the steric hindrance. The disruption of binding affinity caused by this displacement of the methyl group may account for the poorer binding of KNT-97, as compared to that of KNT-96. Likewise, KNT-99, which also lacks the *N*-methyl group, showed higher affinity than that of corresponding KNT-98 with an *N*-methyl group. The presence of the vinyl group, which is smaller than the ethyl group, may account for the improved affinities of KNT-98 or KNT-99 as compared to KNT-96 or KNT-97. The 15–16 ethylene unit in naltrexone forms the D ring and has no rotation. This unit may fit into the cavity to result in excellent affinity. These

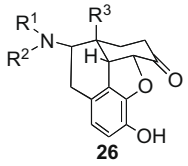


Figure 3. Structure of 15–16 nornaltrexone derivatives **26**.

results seem to support the existence of a cavity structure, as proposed in the Beckett–Casy model. However, the confirmation of the model will require further experiments and discussion. Toward this goal, an examination of the binding of the molecules **26**, which do not have the 15–16 bond (Fig. 3), would be needed to clarify the importance of steric hindrance of the 15–16 ethylene unit. We are presently investigating the methodology for removing the 15–16 bond to give a 15–16 nornaltrexone.

In conclusion, we have synthesized novel 16,17-*seco*-naltrexone derivatives **3** to examine the Beckett–Casy model. All of the synthesized compounds showed poorer K_i values than naltrexone. These results seem to support the existence of a cavity moiety to accommodate the 15–16 ethylene unit in the 4,5-epoxymorphinan skeleton, as proposed in the Beckett–Casy model. However, further experiments will be needed to determine the importance of the cavity. Especially, an investigation of the binding of the molecules **26** without the 15–16 bond is needed to estimate the influence of the steric hindrance of 15–16 bond.

Acknowledgments

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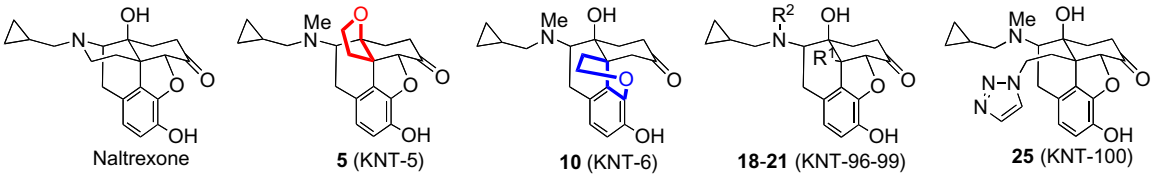
Table 1
Binding affinities of 16–17 cleaved compounds for opioid receptors[a]



Compound [b]	R^1	R^2	K_i (μ)[c] (nM)	K_i (κ)[d] (nM)	K_i (δ)[e] (nM)
Naltrexone	—	—	0.335	0.373	44.2
KNT-5	—	—	24	43.2	ND[f]
KNT-6	—	—	ND[f]	ND[f]	ND[f]
KNT-96	Et	H	26.3	24.1	275
KNT-97	Et	Me	ND[f]	77.6	ND[f]
KNT-98	Vinyl	Me	26.4	39.7	200
KNT-99	Vinyl	H	8.6	4.73	193
KNT-100	—	—	ND[f]	ND[f]	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 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.

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