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Design and synthesis of novel delta opioid receptor agonists and their pharmacologies

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ABSTRACT

We re-examined the accessory site of the 4,5-epoxymorphinan skeleton by CAMDAS conformational analysis in an effort to deign novel δ opioid receptor antagonists. We synthesized three novel compounds (SN-11, 23 and 28) with a 10-methylene bridge and without a 4,5-epoxy ring. Among them, compounds SN-23 (17-isobutyl derivative) and SN-28 (17-methyl derivative) showed very strong agonist activity (over 10 times more than TAN-67). SN-28 also showed high δ selectivity. The δ agonist activity of SN-23 was weaker than that of SN-28, but in terms of the δ selectivity, SN-23 was higher than that of SN-28. These unexpected results indicated that the 4,5-epoxy ring, but not the 10-methylene bridge, was an accessory site in δ opioid receptor agonists.

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Three types of opioid receptors (μ, δ, κ) are now well established not only by pharmacological studies but by molecular biological studies.[1] Recently, nonpeptide δ opioid receptor agonists BW373U86,[2] SNC80,[3] OMI,[4,5] and SIOM[6] were described. We have also reported the highly selective δ agonist, TAN-67,[7,8] which was designed from δ selective antagonist, Naltrindole (NTI)[5,9] by removing postulated accessory sites,[10] that is, the 4,5-epoxy ring and 10-methylene bridge and converting the indole ring to a quinoline ring (Fig. 1).

The key structural features of TAN-67 are a freely rotatable phenol ring and a quinoline nitrogen. The phenol ring of TAN-67 can rotate to a suitable position by induced fit and the quinoline nitrogen can form a hydrogen bond with the δ opioid receptor, thereby inducing agonist activity.[7,8] This time we tried to confirm if both of the postulated two accessory sites would be necessary to be removed to afford full agonist activity. This trial gave us the conclusion which only 4,5-epoxy ring would be an accessory site.

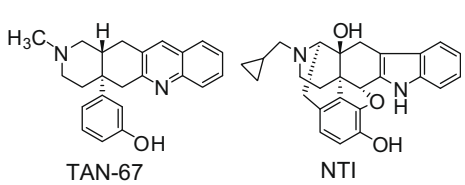

Figure 1. The structures of TAN-67 and NTI.

NTI is a potent and selective nonpeptide δ antagonist. The rationale for the design of this antagonist was based on the 'message-address' concept.[11] In the binding model of NTI with the δ opioid receptor, we considered the three pharmacophore binding modes (ionic, π–π and hydrogen bonds) at the morphinan moiety (message part) and the single delta opioid receptor specific interaction (π–π interaction) at the address part (Fig. 2).

This binding model for NTI led us to the design of the novel selective δ receptor agonist, TAN-67. In general, when an agonist binds a receptor, the receptor changes its structure to accommodate the structure of the agonist (induced fit). This change leads to the next signal transduction, and thus, the agonist produces a pharmacological effect. On the other hand, since an antagonist

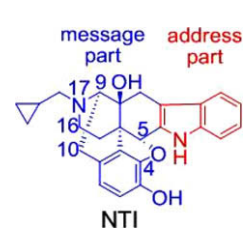

Figure 2. The message part and the address part of NTI.

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has some extra structural parts (accessory site) that interfere with the structural change of the receptor, the ligand does not cause pharmacologic effect even if it binds the receptor. Agonists have no accessory sites,[10] and therefore their binding with the receptor is sufficient to induce a structural change of the receptor.

On the basis of these ideas, we proposed to remove the possible accessory sites of NTI to afford a δ agonist. Previously, we hypothesized that the accessory sites of NTI were the 4,5-epoxy ring and the 10-methylene bridge which were removed to give TAN-57. However, TAN-57 was still an antagonist. We then substituted the quinoline or quinoxaline rings for the indole ring as the address site. Both quinoline or quinoxaline rings have a lone pair electron on the nitrogen, but the indole ring does not. The lone pair electron would be required to afford agonist activity by additional pharmacophore binding with the δ receptor. The resulting compound TAN-67 showed a potent and highly selective δ agonist activity, as well as strong analgesic activity (ED_{50} = 31.4 mg/kg in the acetic acid writhing assay).[7,8] *N*-Cyclopropylmethyl (CPM) derivative **1** of TAN-67 was also δ agonist.[7]

Figure 3 shows the drug design from NTI to TAN-67 and **1**. We postulated that if the 4,5-epoxy ring and the 10-methylene bridge were removed from NTI, the phenol ring would be able to freely rotate to a suitable position by induced fit and permit the agonistic interaction with the receptor. On the other hand, compound **2** with both the 4,5-epoxy ring and the 10-methylene bridge has already been reported as δ antagonist (Fig. 4).[12] We questioned if the 4,5-epoxy ring and the 10-methylene bridge were truly accessory sites. To clarify this point, we performed conformational analysis of TAN-67 and model compounds **3** and **4** (Fig. 4).

The conformational analysis of TAN-67 and compounds **3**, **4** was performed using Conformational Analyzer with Molecular Dynamics And Sampling (CAMDAS) 2.1 program.[13] The CAMDAS calculations furnished twelve, four, and two distinct conformers for TAN-67 and compounds **3** and **4**, respectively.

Figure 5 shows stereopairs of superimpositions of conformers of TAN-67, and compounds **3** and **4**. The superimpositions correspond to the best-fit of the quinoline ring. As expected, compound **4** had the least number of conformers, that is, only two conformers, which differed slightly in structure around C16 and N17 (Fig. 5C). On the other hand, both TAN-67 and compound **3** possessed two kinds of different spatial orientations (O-I and O-II) with respect

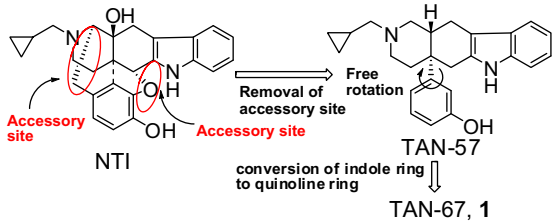


Figure 3. The drug design from NTI to TAN-67.

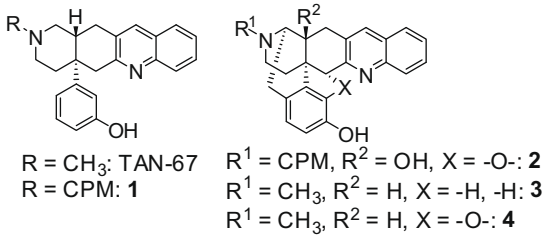


Figure 4. The structures of TAN-67 and compounds **2**–**4**.

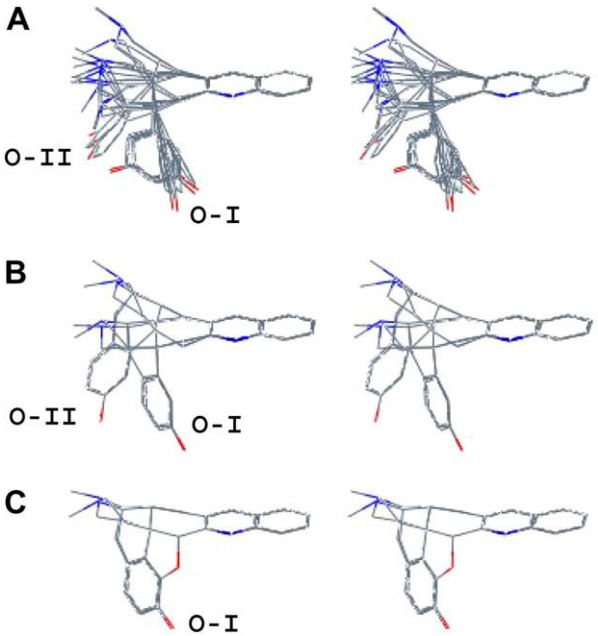


Figure 5. The stereopairs of superimpositions of the CAMDAS conformers of TAN-67 (A), and compounds **3** (B), **4** (C).

to the phenol ring (Fig. 5A and B). These two dispositions are related to the variations of the two torsion angles (T-I and T-II) indicated in Figure 6.

All three compounds can adopt conformers corresponding to O-I (Fig. 6). On the other hand, conformers corresponding to O-II are possible only for TAN-67 and compound **3**, but not for compound **4**. These results clearly suggest that TAN-67 and compound **3** can undergo significant conformational changes between O-I and O-II, but compound **4** cannot.

TAN-67 has neither the 4,5-epoxy ring nor the 10-methylene bridge, and compound **3** has only the 10-methylene bridge. The range of conformations available to compound **3** is almost the same as for TAN-67 (Fig. 5A and B). Therefore, we can consider that the presence of the 10-methylene bridge would not disturb the structural change of the receptor related to the agonistic effect, because of the ligand's ability to undergo conformational change (Fig. 7A). On the other hand, the presence of the 4,5-epoxy ring may be responsible for preventing the receptor from undergoing the structural change due to steric repulsion (Fig. 7B).

These results indicate that only the 4,5-epoxy ring may be an accessory site, but not the 10-methylene bridge. Taking these considerations into account, we designed and synthesized a morphinan derivative **3** (SN-28) to obtain a potent and selective δ agonist.

New two compounds with different 17-substituent groups (isobutyl, and CPM groups) were also designed and synthesized. The morphinan structure **5** was synthesized from naltrexone by the reported method.[14–16] 14-H Morphinan structure **7** was synthesized from **5** in 3 steps (Scheme. 1),[17] and 17-isobutyl derivative **9** was obtained by the reductive cleavage of the 17-cyclopropylmethyl substituent in compound **7**.[18] Compounds **8** and **10** were synthesized from the respective morphinan derivatives **7** and **9** with 2-aminobenzaldehyde in the presence of a catalytic amount of CH_3SO_3H in C_2H_5OH.[7] The resulting compounds **8** and **10** were demethylated with BBr_3 in CH_2Cl_2 to afford SN-11 and SN-23 respectively (Scheme 1).[19] The 17-CPM group of compound **7** was converted to a 17-methyl group by a previously reported method.[20,21] The resulting 17-methyl derivative **12** was converted to SN-28 (compound **3**) as shown in Scheme 2.[7,19]

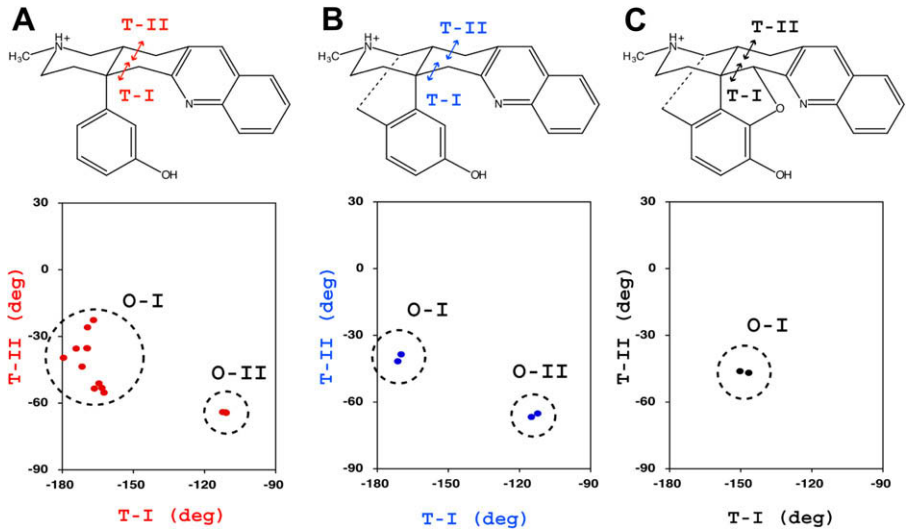


Figure 6. The two-dimensional plots of two selected torsion angles for TAN-67 (A), compounds **3** (B), and **4** (C).

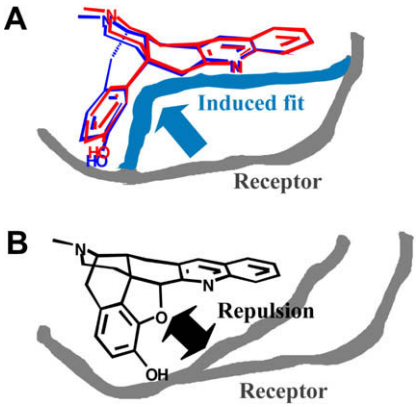
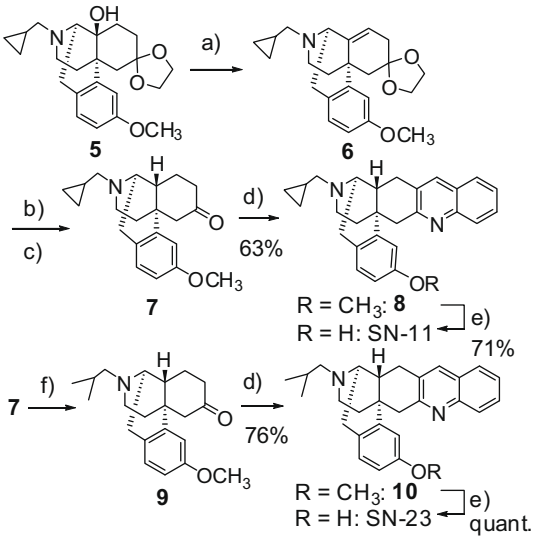
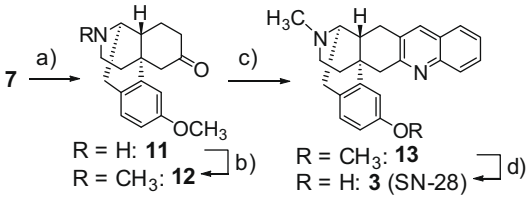


Figure 7. The interaction models of three compounds with the receptor. (A) TAN-67 (red) and compound **3** (blue). (B) compound **4**.



Scheme 1. Reagents and conditions: (a) $SOCl_2$, pyridine, 0 °C to rt, 95%; (b) PtO_2, H_2, CH_3OH, rt; (c) 1 M HCl, 50 °C, 65% (2 steps from compound **6**); (d) 2-aminobenzaldehyde, CH_3SO_3H, C_2H_5OH, 100 °C; (e) BBr_3, CH_2Cl_2, 0 °C to rt; (f) 5 M HCl, PtO_2, H_2, rt, 73%.



Scheme 2. Reagents and conditions: (a) $ClCO_2CHClCH_3$, $Cl_2CHCHCl_2$, 100 °C, then CH_3OH, reflux, 80%; (b) 37% HCHO, CH_3COONa, 2 M AcOH, rt, 10% Pd–C, H_2, rt, 66%; c) 2-aminobenzaldehyde, CH_3SO_3H, C_2H_5OH, 100 °C, 61%; (d) BBr_3, CH_2Cl_2, 0 °C to rt, 48%.

Table 1 shows the binding affinity and selectivity toward opioid μ, δ, and κ receptors of the three compounds. For purposes of comparison, NTI and TAN-67 are also presented as standard compounds. SN-11, 23, and 28 showed high affinities and full agonist activities (Table 2) for the δ receptor. The standard δ antagonist, NTI (μ/δ = 81.5, κ/δ = 48.3) and agonist, TAN-67 (μ/δ = 197, κ/δ = 509) showed also high selectivity for δ receptor in this binding assay. As shown in Table 2, SN-11, 23 and 28 displayed better than over 10 times stronger δ agonist activities (EC_{50} = 0.018, 0.06 and 0.047 nM, respectively) than TAN-67 (EC_{50} = 0.70 nM) and SNC80 (EC_{50} = 15.7 nM), which is widely used as a nonpeptide δ agonist. Among these compounds, SN-11 was the strongest agonist, but its δ selectivity was not sufficient. This tendency of CPM derivative was also observed in the series of TAN-67 derivatives.[7] The low selectivity and strong ago-

Table 1
The binding affinity and selectivity of SN-11, 23, and 28 for opioid μ, δ and κ receptors[a]

Compounds	Affinity (K_i, nM)			Selectivity	
	μ	δ	κ	μ/δ	κ/δ
NTI	23.64	0.29	14.01	81.5	48.3
(−)TAN-67	284.14	1.44	732.45	197.3	508.7
SN-11	0.77	0.19	0.36	4.1	1.9
SN-23	23.61	0.19	4.41	124.3	23.2
SN-28	11.53	0.14	10.2	82.4	72.9

[a] Evaluated by ability of each compound to displace [^{3}H]DAMGO (μ), [^{3}H]DADLE (δ), and [^{3}H]U-69,593 (κ) binding to membranes of rat cerebellum (μ and δ) or the guinea pig cerebellum (κ).

Table 2
δ Agonist activities of SN-11, 23 and 28[a]

Compounds	EC_{50} (nM)
(−)TAN-67	0.7
(−)TAN-67	1.4[b]
SNC80	15.7[b]
Met-enk	1.03
SN-11	0.018
SN-23	0.06
SN-28	0.047

[a] Membranes were incubated with [^{35}S] GTPγS and GDP with the compound. Human recombinant cell membrane (HEK-293) was used in this assay. TAN-67 and [Met^5]-enkephalin were used as the standard δ agonists.
[b] Ref. 23.

nist activity of CPM derivatives may result from the electron-donating property of CPM group.[22]

The more potent activities for δ receptor of three compounds, SN-11, 23, 28 than TAN-67 might be derived from restriction of rotation of the phenol ring, compared with that of TAN-67. The phenol ring of TAN-67 may be able to rotate away from the receptor site to form hydrogen bond. On the other hand, the phenol ring of the three compounds may rotate only within area where could effectively form hydrogen bond with the receptor (entropy effect).

In summary, to confirm which of the accessory sites of the δ antagonist NTI were required to effect a conformational change in the receptor, we performed conformational analysis. Based on the results of these studies, we designed δ agonists to confirm the accessory sites of NTI in comparison with TAN-67. We synthesized three compounds with three types of 17-substituents (methyl, isobutyl, and CPM groups) and compared them with NTI and TAN-67 for δ selectivity and agonist activity. SN-11, bearing a 17-CPM group showed the strongest agonist among these three compounds but the selectivity was not satisfactory. Compounds SN-23 and 28 with the 10-methylene bridge showed satisfactory δ selectivities and over 10 times stronger agonist activities than TAN-67, suggesting that the 17-methyl and 17-isobutyl substituents were almost equally effective for both agonist activity and δ selectivity. From the outcome of these studies, we concluded that only the 4,5-epoxy ring was an accessory site in NTI, and not the 10-methylene bridge. Currently, we are examining the structure activity relationships for the above novel derivatives as well as their in vivo analgesic potency. These results will appear in an extensive report in the future.

Acknowledgements

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