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# Novel Delta Opioid Receptor Agonists with Oxazatricyclodecane Structure

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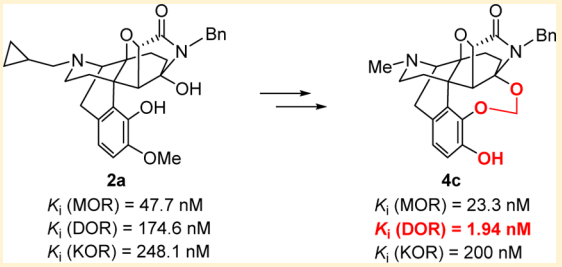
Supporting Information

**ABSTRACT:** We synthesized compounds **4a,c−f,h,i** containing the oxazatricyclodecane structure from a novel rearrangement reaction product **2a**. All the prepared compounds **4a,c−f,h,i** exhibited full agonistic activities for the $\delta$ opioid receptor (DOR). Among them, the *N*-methyl derivative **4c** was highly selective, and the most effective DOR agonist in functional assays. Subcutaneous administration of **4c** produced dose-dependent and NTI (selective DOR antagonist)-reversible antinociception lacking any convulsive behaviors in the mice acetic acid writhing tests. The *N*-methyl derivative **4c** is expected to be a promising lead compound for selective DOR agonists with a novel chemotype.




**KEYWORDS:** *Opioid, DOR, oxazatricyclodecane structure, CellKey*

The $\delta$ opioid receptor (DOR) is one of the three opioid receptor types ($\mu$ (MOR), DOR, and $\kappa$ (KOR)), and activation of this receptor is associated with various pharmacological effects such as antinociceptive, antidepressive, anxiolytic, and cardioprotective effects.[1−3] In contrast to the undesirable effects mediated by the MOR such as dependence, constipation, emesis, and respiratory depression or the aversive effects mediated by the KOR,[4,5] the DOR is a promising medical target because it seems to induce neither addictive nor aversive effects. Since the first nonpeptidic DOR agonist TAN-67[6,7] (Figure 1) emerged,[3] various nonpeptidic DOR agonists have been reported.[1−3] Several investigations revealed that the DOR agonists like BW373U86[8] and SNC80[9] (Figure 1) exerted convulsive behaviors.[3] However, some DOR agonists such as ADL5747[10] and KNT-127[11,12] (Figure 1) have recently been reported to induce no convulsion. Although SNC80 has been reported to induce the internalization of the DORs and to develop tolerance toward the analgesic, locomotor, and anxiolytic effects, ARM390[13] (Figure 1) induced hardly any internalization of the DORs and showed tolerance to analgesia but not to locomotor or anxiolytic responses.[14,15] Thus, a distinct DOR agonist interacting with the same DOR sometimes exerted different pharmacological responses. Recently, SNC80, a well-known representative selective DOR agonist, was reported to activate the MOR/DOR heteromer more selectively than the DOR homomer.[16] It is not yet clear why the various DOR agonists mentioned above elicit different pharmacological responses, but the structure of the DOR agonist may account, in part, for their distinct activities. For example, a structural feature of DOR agonists may influence the induction of convulsive behaviors: the DOR agonists that do not cause convulsion had a structure distinct from diarylmethylpiperazine and its related structures such as BW373U86 and SNC80.[3] However, diarylmethylpiperazine derivative AZD2327 (Figure 1) reportedly produced no convulsion.[17] The synthesis and pharmacological characterization of DOR agonists with different chemotypes will help to better understand the different pharmacological profiles of distinct DOR agonists. We have recently reported the synthesis and binding affinities for the MOR, DOR, and KOR of an oxazatricyclodecane derivative **2a**, which was obtained from endoethanotetrahydrothebaine derivative **1** by a novel rearrangement reaction[18] (Scheme 1). This new compound exhibited moderate affinities for the opioid receptors ($K_i$ (MOR) = 47.7 nM, $K_i$ (DOR) = 174.6 nM, and $K_i$ (KOR)

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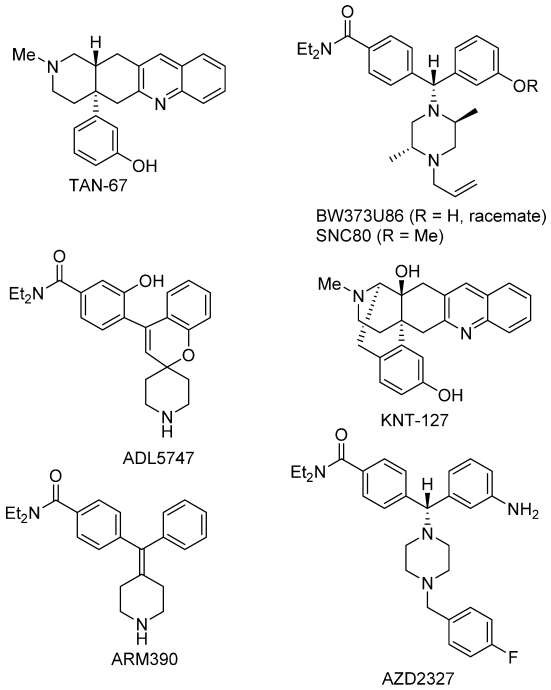
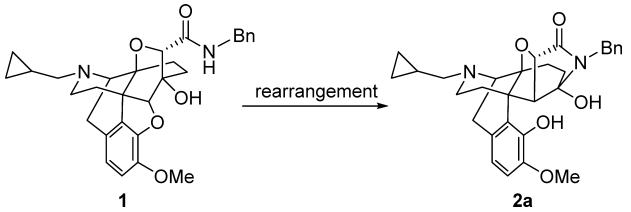
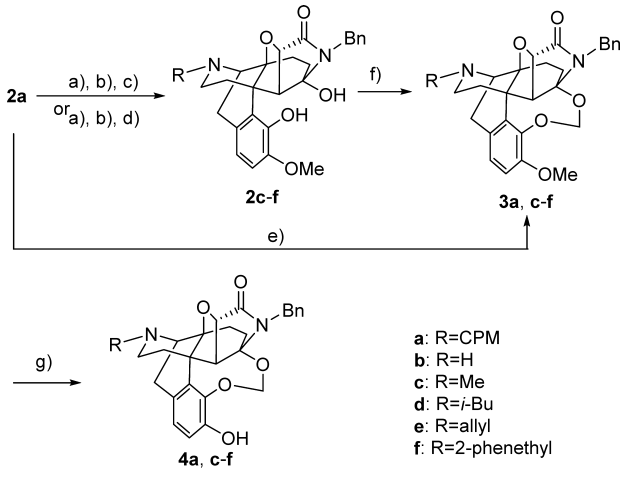



**Figure 1.** Structures of DOR agonists, TAN-67, BW373U86, SNC80, ADL5747, KNT-127, ARM390, and AZD2327.

**Scheme 1. Potential Opioid Ligand 2a**

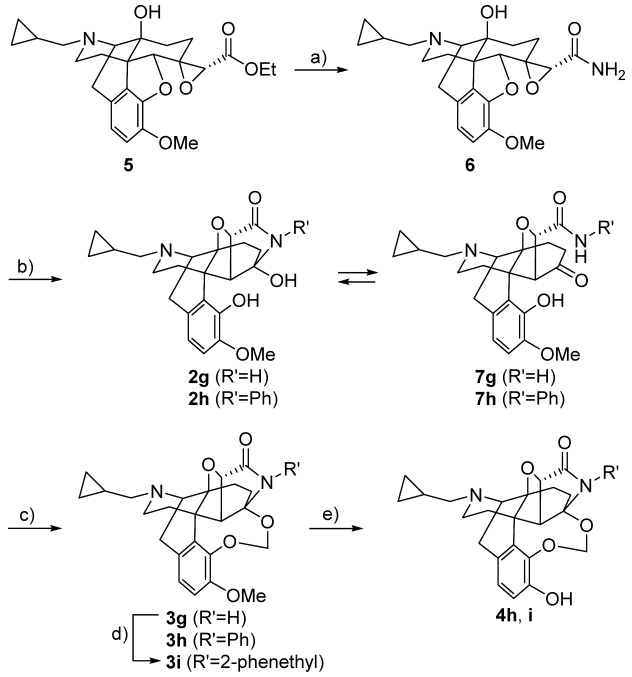



**Scheme 2. Synthesis of 4a,c–f**[a]




[a]Reagents and conditions: (a) Troc-Cl, $K_2CO_3$, 1,1,2,2-tetrachloroethane, 150 °C; (b) Zn, AcOH, rt, 80% from **2a**; (c) aldehyde, AcOH, $NaB(OAc)_3H$, 1,2-dichloroethane, rt, 74%-quant. (for *R* = Me, 2-phenethyl); (d) alkyl bromide, $NaHCO_3$, DMF, rt, 48–92% (for *R* = allyl, *i*-Bu); (e) $CH_2Br_2$, $K_2CO_3$, DMF (0.0005 M), rt, 66%; (f) $CH_2ClBr$, $K_2CO_3$, DMF (0.0004 M), rt, a solution of **2c–f** in DMF was added portion-wise. 69–98%; (g) $BBr_3$, $CH_2Cl_2$, 0 °C, 76–95%.

**Scheme 3. Synthesis of 4h and 4i**[a]




[a]Reagents and conditions: (a) 12 M $NH_3$aq, EtOH, rt, 73%; (b) *t*-BuOK, *t*-BuOH, reflux, quant.; (c) $CH_2ClBr$, $K_2CO_3$, DMF (0.0004 M), rt, a solution of **2g** and **7g** or **2h** and **7h** in DMF was added portion-wise. 73–93%; (d) 60% NaH, $PhCH_2CH_2Br$, DMF, rt, 83%; (e) $BBr_3$, $CH_2Cl_2$, 0 °C, 61–89%.

**Table 1. Binding Affinities of 4a,c–f,h,i for the Opioid Receptors**[a]

| | $K_i$ (nM) | | | selectivity | |
|---|---|---|---|---|---|
| compd | MOR[b] | DOR[c] | KOR[d] | MOR/DOR | KOR/DOR |
| SNC80 | 695 | 1.04 | >1000 | 668 | 962 |
| **2a**[e] | 47.7 | 175 | 248 | 0.27 | 1.4 |
| **4a** | 3.14 | 0.313 | 5.14 | 10.0 | 16.4 |
| **4c** | 23.3 | 1.94 | 200 | 12.0 | 103 |
| **4d** | 186 | 7.00 | 119 | 26.6 | 17.0 |
| **4e** | 68.4 | 1.23 | 56.6 | 55.8 | 46.2 |
| **4f** | 45.9 | 2.59 | 588 | 17.7 | 227 |
| **4h** | 4.61 | 0.534 | 1.69 | 8.6 | 3.2 |
| **4i** | 1.75 | 1.16 | 1.94 | 1.5 | 1.7 |

[a]Binding assays were carried out in duplicate using mouse whole brain without cerebellum membranes for MOR and DOR or guinea pig cerebellum membranes for KOR. [b][$^3$H] DAMGO was used. [c][$^3$H] DPDPE was used. [d][$^3$H] U-69,593 was used. [e]Ref 18.

=248.1 nM). The potential opioid ligand **2a** was expected to lead to other ligands selective for an opioid receptor type with a unique core structure. Herein, we report the synthesis of novel DOR agonists **4a,c–f,h,i** with oxazatricyclodecane structure derived from **2a** and their pharmacological properties.

The synthesis of the objective compounds **4a,c–f** commenced with compound **2a**[18] (Scheme 2). The treatment of **2a** with 2,2,2-trichloroethyl chloroformate (Troc-Cl) in the presence of $K_2CO_3$ and the subsequent zinc/AcOH treatment gave norcompound **2b**.[19] Various *N*-substituents were introduced by reductive alkylation of **2b** or the alkylation of **2b** with an alkyl bromide to provide **2c–f**. Compound **2a** reacted with $CH_2Br_2$ in the presence of $K_2CO_3$ under high dilution


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**Table 2. Functional Activities of 4a,c−f,h,i for the Opioid Receptors Assessed by [$^{35}$S]GTPγS Binding Assays[a]**

| | MOR | | DOR | | KOR | |
|---|---|---|---|---|---|---|
| compd | $EC_{50}$ (nM) | $E_{max}$ (%)[b] | $EC_{50}$ (nM) | $E_{max}$ (%)[c] | $EC_{50}$ (nM) | $E_{max}$ (%)[d] |
| SNC80 | NT[e] | NT[e] | 1.9 | 100 | NT[e] | NT[e] |
| **4a** | 2.8 | 13.7 | 1.1 | 92.8 | 80.5 | 69.1 |
| **4c** | 113 | 110 | 11 | 112 | 478 | 83.6 |
| **4d** | 223 | 8.4 | 15.6 | 96.4 | 760 | 65.6 |
| **4e** | 2.7 | 5.4 | 6.5 | 94.6 | 231 | 74.0 |
| **4f** | 2.3 | 83.0 | 9.2 | 115 | ND[f] | ND[f] |
| **4h** | 9.0 | 25.6 | 0.98 | 118 | 6.5 | 42.9 |
| **4i** | 2.1 | 19.7 | 0.41 | 103 | 3.9 | 51.2 |

[a][$^{35}$S]GTPγS binding assays were carried out in duplicate using human MOR, DOR, or KOR expressed CHO cells. [b]$E_{max}$ was calculated as the % of the response obtained with DAMDO. [c]$E_{max}$ was calculated as the % of the response obtained with SNC80. [d]$E_{max}$ was calculated as the % of the response obtained with U-69,593. [e]Not tested. [f]Not determined.

**Table 3. Functional Activities of 4a,c−f,h,i for the Opioid Receptors Assessed by CellKey Assays[a]**

| | MOR | | DOR | | KOR | |
|---|---|---|---|---|---|---|
| compd | $EC_{50}$ (nM) | $E_{max}$ (%)[b] | $EC_{50}$ (nM) | $E_{max}$ (%)[c] | $EC_{50}$ (nM) | $E_{max}$ (%)[d] |
| SNC80 | 0.14 | 6.8 | 1.7 | 100 | 5264 | 5.9 |
| **4a** | 1.8 | 9.6 | 1.54 | 88.7 | 39.8 | 50.5 |
| **4c** | 1350 | 36.1 | 141 | 138 | 307 | 79.2 |
| **4d** | 400 | 12.2 | 140 | 130 | 333 | 57.9 |
| **4e** | 5.1 | 11.3 | 2.0 | 77.2 | ND[e] | ND[e] |
| **4f** | 639 | 40.2 | 20.5 | 108 | 12530 | 22.6 |
| **4h** | 1.2 | 8.8 | 0.39 | 123 | 1.2 | 80.4 |
| **4i** | 5.2 | 4.8 | 0.62 | 90.6 | 2.4 | 75.8 |

[a]CellKey assays were carried out in duplicate using human MOR, DOR, or KOR expressed HEK293 cells. [b]$E_{max}$ was calculated as the % of the response obtained with DAMGO. [c]$E_{max}$ was calculated as the % of the response obtained with SNC80. [d]$E_{max}$ was calculated as the % of the response obtained with (−)-U-50,488H. [e]Not determined.

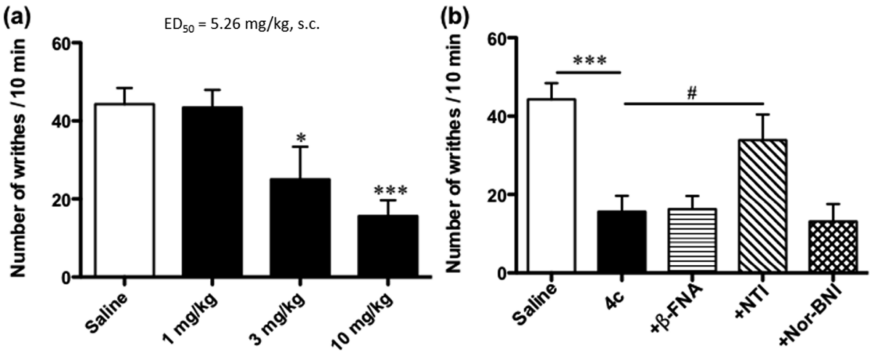


**Figure 2.** (a) Antinociceptive effect of **4c** administered subcutaneously in the mice acetic acid writhing tests. The statistical significance of differences between the groups was assessed with one-way ANOVA followed by Bonferroni's test. *$p < 0.05$ and ***$p < 0.001$ versus saline treated mice. (b) Effects of opioid receptor antagonists on the antinociception induced by subcutaneous treatment of **4c** in the mice acetic acid writhing tests. The statistical significance of differences between the groups was assessed with one-way ANOVA followed by Bonferroni's test. ***$p < 0.001$ versus saline treated mice. #$p < 0.05$ versus **4c** treated mice.

conditions (0.0005 M) to provide dioxymethylene compound **3a** in 66% yield concomitantly with a dimer in 30% yield in which two **2a** units were tethered with a methylene group (see the Supporting Information for details). A portion-wise addition of a solution of **2c−f** markedly improved the yields of **3c−f** and prevented formation of the dimer. Finally, the *O*-methyl group in **3a,c−f** was removed by a treatment with $BBr_3$ to give **4a,c−f**. Compounds **4h** and **4i** with respective phenyl and 2-phenethyl groups as the lactam nitrogen substituents were prepared as shown in Scheme 3. After a conversion of ester **5** into **6**, the treatment of **6** with *t*-BuOK in *t*-BuOH provided an equilibrium mixture of **2g** and **7g**. An equilibrium mixture of **2h** and **7h** was prepared from **5** by a previously reported method.[18] The mixture of **2g** and **7g** or **2h** and **7h** was reacted with $CH_2ClBr$ in the same manner shown in Scheme 2 to afford dioxymethylene compounds **3g,h**. The 2-phenethyl group was introduced on the lactam nitrogen in **3g** by alkylation to give **3i**.

The affinities of the prepared compounds **4a,c−f,h,i** were evaluated by competitive binding assays (Table 1). All the compounds **4a,c−f,h,i** bound to the opioid receptors. The phenolic hydroxy group at the 3-position appeared to play an important role in improving the binding affinities for the opioid receptors compared to the parent compound **2a**.[20] Except for *N*-(2-phenethyl)lactam **4i**, compounds **4a,c−f,h** showed selectivities for the DOR, suggesting that the phenyl group of


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the substituent on the lactam nitrogen would function as a DOR address such as the phenyl moiety in NTI.[21,22] The binding affinities of **4a** and **4h** for the DOR were better than that of SNC80. Compounds **4c** and **4f** with respective *N*-methyl and *N*-(2-phenethyl) substituents were over 100-fold more selective for the DOR as compared to the KOR. The functional activities of **4a,c−f,h,i** were determined by [$^{35}$S]GTP$\gamma$S binding and CellKey assays (Tables 2 and 3).[23] The CellKey system utilizes impedance biosensors for detection of cell behaviors and is a functional cell-based assay technology enabling label-free analysis of cell surface receptor activity.[24,25] It is noteworthy that the [$^{35}$S]GTP$\gamma$S and CellKey assays differed in the observed output, even though giving similar results. All the compounds **4a,c−f,h,i** were full agonists for the DOR. The agonistic activities for the DOR of **4c,f,h** were more efficacious than that of SNC80 in both of the functional assays. Compounds **4h** and **4i** were also potent KOR agonists, whereas compounds **4c** and **4f** exhibited agonistic activities for the MOR. Although *N*-methyl derivative **4c** had moderate to high efficacy for the MOR and KOR, the potencies for these receptors were poor, which suggested that **4c** was highly selective and the most efficacious DOR agonist among the tested compounds. Derivatives **4a,e,f** with respective cyclopropylmethyl (CPM), allyl, and 2-phenethyl substituents on the basic nitrogen were more potent agonists for the DOR than *N*-methyl derivative **4c** in both functional assays; however, their functional selectivities for the DOR were lower than that of **4c** in [$^{35}$S]GTP$\gamma$S binding assays and lower or comparable to that of **4c** in CellKey assays. Therefore, the *N*-methyl substituent on the basic nitrogen appeared to be the optimal group among the tested compounds.

We next assessed the antinociceptive effects of **4c** in mice by acetic acid writhing tests. Subcutaneously administered **4c** significantly exhibited antinociception in a dose-dependent manner and its $EC_{50}$ value was 5.26 mg/kg (Figure 2a). No convulsive behaviors were observed. The antinociceptive effects induced by **4c** were attenuated by the selective DOR antagonist NTI but not by the selective MOR antagonist $\beta$-FNA or the selective KOR antagonist nor-BNI (Figure 2b). Taken together, these results indicate that compound **4c** could be a promising lead compound for selective DOR agonists with a novel chemotype, the oxazatricyclodecane structure

In conclusion, we synthesized novel DOR agonists **4a,c−f,h,i** with oxazatricyclodecane structure. Among the synthesized compounds, *N*-methyl derivative **4c** was highly selective and the most effective DOR agonist. Subcutaneous administration of **4c** produced dose-dependent and NTI-reversible antinociception without any convulsive behaviors. *N*-Methyl derivative **4c** is expected to be a promising lead compound for selective DOR agonists containing the novel oxazatricyclodecane structure.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Experimental procedures for the synthesis and characterization of the compounds, the in vitro activity assay, the in vivo mice acetic acid writhing assay, and the spectral data of the reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.


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### Notes

The authors declare no competing financial interest.

## ■ ABBREVIATIONS

Bn, benzyl; CHO, chinese hamster ovary; CPM, cyclopropylmethyl; DAMGO, [D-Ala$^2$, *N*-Me-Phe$^4$, Gly-ol$^5$]-enkephalin; DOR, $\delta$ opioid receptor; DPDPE, [D-Pen$^2$, D-Pen$^5$]-enkephalin; $\beta$-FNA, $\beta$-funaltrexamine; HEK, human embryonic kidney; KOR, $\kappa$ opioid receptor; MOR, $\mu$ opioid receptor; nor-BNI, nor-binaltorphimine; NTI, naltrindole; Troc, 2,2,2-trichloroethoxycarbonyl

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