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Naltrindole derivatives with fluorinated ethyl substituents on the 17-nitrogen as δ opioid receptor inverse agonists

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ABSTRACT

We synthesized derivatives of the δ opioid receptor (DOR) antagonists naltrindole (NTI) and compound **1** that were modified with small alkyl or fluorinated ethyl substituents on the 17-nitrogen. Although the derivatives showed decreased binding affinities for the opioid receptors, their selectivities for the DOR were higher than the parent compounds NTI and compound **1**. Surprisingly, 17-fluoroethyl NTI derivatives exerted DOR inverse agonistic activities. The DOR inverse agonism of compounds **4c–e** was less efficacious but significant, as compared with a standard DOR inverse agonist ICI-174864. On the other hand, compound **1** and its derivatives with small alkyl or monofluoroethyl substituents were partial agonists, but the derivatives having di- or trifluoroethyl group showed neither agonistic nor inverse agonistic activities.

The opioid receptor is one of the most important medicinal target proteins and a representative opioid, morphine, is a prescribed drug for severe pain such as cancer pain and postoperative pain. The opioid receptor is classified into three types (μ (MOR), δ (DOR), and κ (KOR)) and selective ligands for each receptor type have been developed.[1–4] The morphinan and 4,5-epoxymorphinan skeletons, which are included in the morphine structure, are very important chemical classes as opioid ligands. The substituent on the 17-nitrogen is well-known to be a determinant of functional properties of ligands, agonists or antagonists. For example, most MOR agonists have a small alkyl group like methyl or ethyl on the 17-nitrogen, whereas 17-substituents of most MOR antagonists are larger groups such as allyl or cyclopropylmethyl (CPM).[5] KOR agonists are reported to prefer the CPM group.[6–8] Concerning the DOR ligands, the influence of the 17-substituents appears to be more complicated. Although early investigation showed the 17-methyl and CPM derivatives were DOR partial agonists and antagonists, respectively,[9] DOR agonists seem to tolerate the 17-substituents.[10] Indeed, some KNT-127 derivatives with larger 17-substituents such as propyl, 2-hydroxypropyl, and 3-ethoxypropyl groups showed full DOR agonist activities.[10] Therefore, intense effort has been made to investigate 17-substituents, but only a few compounds possessing the 17-fluoroalkyl have been reported. We recently synthesized 17-fluoroalkyl derivatives of the selective KOR agonist nalfurafine (Fig. 1)[6,11–13] and the selective DOR agonist KNT-127 (Fig. 1),[14] and reported that these substitutions led to increased selectivities for the KOR or DOR, respectively, but decreased the binding affinities compared with the parent compounds.[10,15] The agonistic activities of 17-fluoroalkyl derivatives also decreased.[10,15] As our previous investigation dealt with agonists, we next attempted to apply these substitutions to DOR antagonist, naltrindole (NTI)[9,16] and compound **1**.[17] Herein, we report the synthesis of derivatives of NTI and compound **1** with the 17-fluoroethyl and 17-alkyl substituents, which were of similar size to the introduced fluorinated ethyl groups. We also evaluated their binding and functional properties.

Indole derivatives **3a–e** and quinolone derivatives **5a–e** were synthesized from ketones **2a–e**[10] by Fischer indole synthesis and Friedländer quinoline synthesis, respectively. *O*-Demethylation with boron tribromide provided the NTI derivatives **4a–e** and compound **1** derivatives **6a–e** (Scheme 1).

The binding affinities of the prepared NTI derivatives **4a–e** and compound **1** derivatives **6a–e** for the opioid receptors were evaluated by previously reported procedures[18] (Table 1). Among the tested compounds, the parent compounds NTI and compound **1** with 17-CPM group showed the highest affinities for the opioid receptors, whereas their selectivities for the DOR were lowest.

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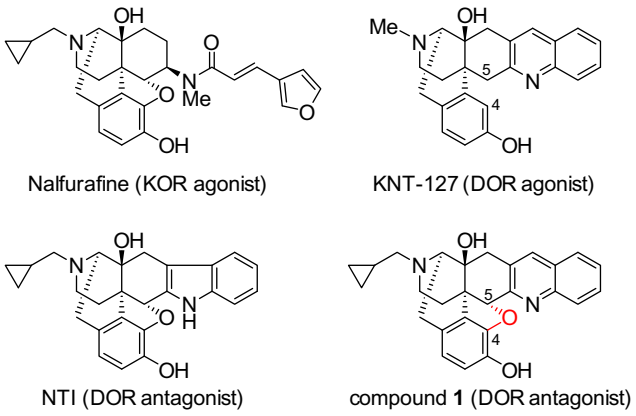
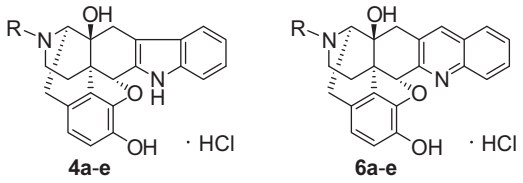


Figure 1. Structures of nalfurafine, KNT-127, NTI, and compound **1**. The 4,5-epoxy bridge in **1** was indicated by red color.

The binding affinity of 2-fluoroethyl derivative **4c** for the DOR was comparable to those of compounds **4a** and **4b** with respective 17-ethyl and 17-propyl substituents, which were of similar sizes to the fluoroethyl groups. Meanwhile 2,2-difluoroethyl and 2,2,2-trifluoroethyl derivatives **4d** and **4e** showed lower affinities. Similar tendencies were observed in the compound **1** derivatives (**6a**–**e**). The introduction of fluorine atoms in the 17-substituent decreased the affinities for the DOR, but these modifications markedly lowered the affinities for the MOR and KOR. As a result, the prepared 17-fluoroalkyl derivatives **4c**–**e** and **6c**–**e** exhibited higher selectivities for the DOR than did NTI and compound **1** themselves. Such tendencies as mentioned above were observed with both nalfurafine and KNT-127 derivatives.[10,15] The tendencies obtained in nalfurafine and KNT-127 derivatives were explained from the viewpoint of the message-address concept.[9,16,19] In a similar way, these observations on **4c**–**e** and **6c**–**e** could be explained. The electron density on the 17-nitrogen, which is well-known to be one of the important pharmacophores, was decreased by the electron-withdrawing properties of the fluoroalkyl substituents, which would weaken the binding affinities for all the types of the opioid receptors. However, NTI and compound **1** derivatives had the appropriate structural determinants, the indole and quinolone parts, to interact with the DOR, that is, the δ address moiety. The δ address moiety could compensate the binding ability to the DOR. Therefore, 17-fluoroalkyl NTI and compound **1** derivatives exhibited higher selectivities toward the DOR. On the other hand,

Table 1
The binding affinities and selectivities of NTI, compound **1**, and their derivatives **4a**–**e** and **6a**–**e** for the opioid receptors[a]

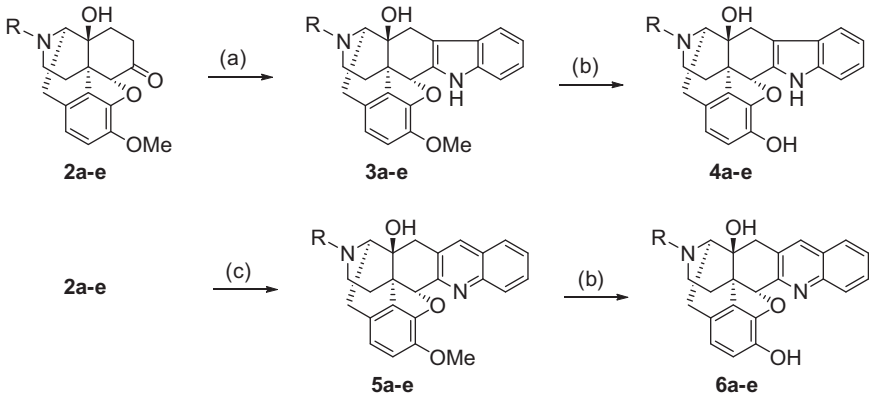


Compounds	R	Affinity (K_i, nM)			Selectivity	
		MOR	DOR	KOR	MOR/DOR	KOR/DOR
NTI	CPM	30.7	0.457	14.7	67.1	32.2
4a	Et	788	2.71	468	291	172
4b	Propyl	133	1.11	74.3	120	66.9
4c	$-CH_2CH_2F$	675	1.94	397	348	204
4d	$-CH_2CHF_2$	>1000	15.5	>1000	—[b]	—[b]
4e	$-CH_2CF_3$	>1000	134	>1000	—[b]	—[b]
1	CPM	20.8	0.407	11.0	51.1	27.1
6a	Et	670	8.89	477	75.4	53.7
6b	Propyl	123	2.77	313	44.5	113
6c	$-CH_2CH_2F$	422	5.58	854	75.7	153
6d	$-CH_2CHF_2$	>1000	18.2	>1000	—[b]	—[b]
6e	$-CH_2CF_3$	>1000	37.8	>1000	—[b]	—[b]

[a] Evaluated by ability of each compound to displace [^{3}H]DAMGO (MOR), [^{3}H]DPDPE (DOR), or [^{3}H]U-69,593 (KOR) binding to the CHO cells expressing human MOR, DOR, or KOR. The data represent means of three samples.
[b] Not calculated because K_i values for MOR or KOR were over 1000 nM.

although the alkyl groups are electron-donating groups, the electron-donating property of the methyl or propyl groups was weaker than that of the CPM group,[20–22] which would lead to higher comparable selectivities for **4a**, **b** and **6a**, **b** as compared with their respective parent compounds NTI and compound **1**.

We next evaluated the functional activities of the prepared compounds for the DOR by the [^{35}S]GTPγS binding assays (Table 2). The assays were performed by procedures similar to those previously reported.[23] With respect to NTI derivatives, compounds **4a** and **4b** as well as NTI had no agonistic activities. Surprisingly, derivatives **4c**–**e** with fluorinated ethyl substituents on the 17-nitrogen exhibited inverse agonist activities. Compared with a standard DOR inverse agonist ICI-174864,[24] the efficacies of **4c**–**e** as the DOR inverse agonist were lower but significant (Table 2). Although constitutively active mutant (CAM) receptors



a: R = Et, **b**: R = propyl, **c**: R = -CH_2CH_2F, **d**: R = -CH_2CHF_2, **e**: R = -CH_2CF_3

Scheme 1. Reagents and conditions: (a) phenylhydrazine hydrochloride, AcOH, reflux, **3a**: 87%, **3b**: 74%, **3c**: 66%, **3d**: 87%, **3e**: 90%; (b) BBr_3, CH_2Cl_2, 0 °C to rt, **4a**: 34%, **4b**: 52%, **4c**: 16%, **4d**: 27%, **4e**: 45%, **6a**: 40%, **6b**: 43%, **6c**: 56%, **6d**: 79%, **6e**: 85%; (c) 2-aminobenzaldehyde, CH_3SO_3H, EtOH, reflux, **5a**: 96%, **5b**: 97%, **5c**: 72%, **5d**: 88%, **5e**: quant.