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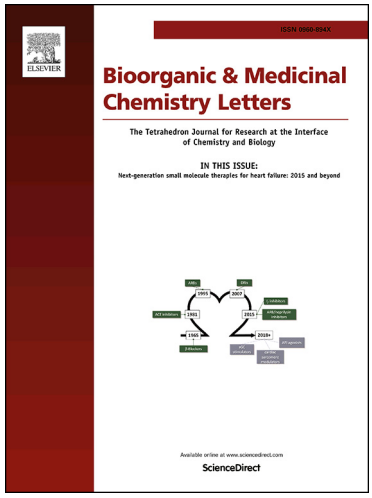

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Discovery of naldemedine: A potent and orally available opioid receptor antagonist for treatment of opioid-induced adverse effects

Masanao Inagaki[a,*], Masaharu Kume[a], Yoshinori Tamura[a], Shinichiro Hara[a], Yoshihisa Goto[b], Haga Nobuhiro[a], Tsuyoshi Hasegawa[a], Takashi Nakamura[c], Katsumi Koike[d], Shuuichi Oonishi[e], Toshiyuki Kanemasa[d], Hiroyuki Kai[a].

[a] *Medicinal Chemistry Research Laboratory, Shionogi Co., Ltd. 3-1-1 Futaba-cho, Toyonaka, Osaka 561-0825, Japan.*

[b] *Production Technology Department, Shionogi Co. & Ltd. 2-1-3 Kuise Terajima, Amagasaki, Hyogo 660-0813, Japan*

[c] *Shionogi TechnoAdvance Research Co., Ltd. 1405 Koga-cho Gotanda, Koga, Shiga 520-3423, Japan.*

[d] *Drug Discovery & Disease Research Laboratory, Shionogi & Co., Ltd, 3-1-1 Futaba-cho, Toyonaka, Osaka 561-0825, Japan.*

[e] *Research Laboratory for Development, Shionogi & Co., Ltd, 3-1-1 Futaba-cho, Toyonaka, Osaka 561-0825, Japan.*

* Corresponding author. Tel.: +81-6-6331-6194; fax: +81-6-6332-6385; E-mail address: masanao.inagaki@shionogi.co.jp

Key words: μ- and δ-opioid receptor antagonist, peripherally selective, morphinan, opioid-induced constipation, opioid-induced emesis/vomiting

Abbreviation: methanesulfonic acid: MsOH, aqueous: aq., room temperature: rt, saturated: sat., *N*-hydroxybenzotriazole: HOBt, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride: WSCD·HCl, ethyl acetate: AcOEt, subcutaneous injection: sc, per os: po.

Abstract: Structure-activity relationship studies of several morphinan derivatives were conducted to obtain dual antagonists for μ- and δ-opioid receptors. We discovered peripherally restricted dual antagonists for μ/δ-opioid receptors as a new chemotype with a morphinan scaffold, which are orally available and do not easily pass the blood–brain barrier. As we expected, some of these compounds inhibit opioid-induced constipation and emesis/vomiting with limited potential to interfere the analgesic effects of morphine. Among them, naldemedine was selected as a potential drug candidate.

Opioid analgesics such as morphine and oxycodone have long played a critical role in chronic and acute pain control.[1] Opioids are potent analgesic agents and, therefore, widely used for pain management in cancer and non-cancer patients.[2] Conversely, opioids are associated with adverse events, such as analgesic tolerance, physical dependence, addiction, sedation, respiratory depression, constipation, and nausea/vomiting.[3] Among them, the most common adverse effects are constipation and nausea/vomiting.[4] These adverse effects of opioids are among the main reasons why patients discontinue their therapeutic use. Opioid-induced constipation (OIC) is thought to be caused by activation of μ-opioid receptors in the gastrointestinal tract.[5] Additionally, δ-opioid receptor antagonism is reported to decrease opioid-induced nausea/vomiting (OINV).[6] Thus, μ- and δ-opioid dual antagonists would be desirable drugs for alleviation of certain side-effects of opioids. Indeed, naltrexone and naloxone have been reported to be effective to reduce the frequency of constipation, but these antagonists also block desirable analgesic effects.[7] Therefore, we sought to design peripheral opioid antagonists. Methylnaltrexone[8] and naloxegol[9] are the only such drugs currently approved for the treatment of OIC. These drugs were designed to act peripherally by modification of naltrexone and naloxone. They have characteristic structures, including a quaternary nitrogen atom and a polyethylene glycol (PEG) side chain. These characteristic moieties restrict these drugs to act peripherally and limit their ability to penetrate the BBB.

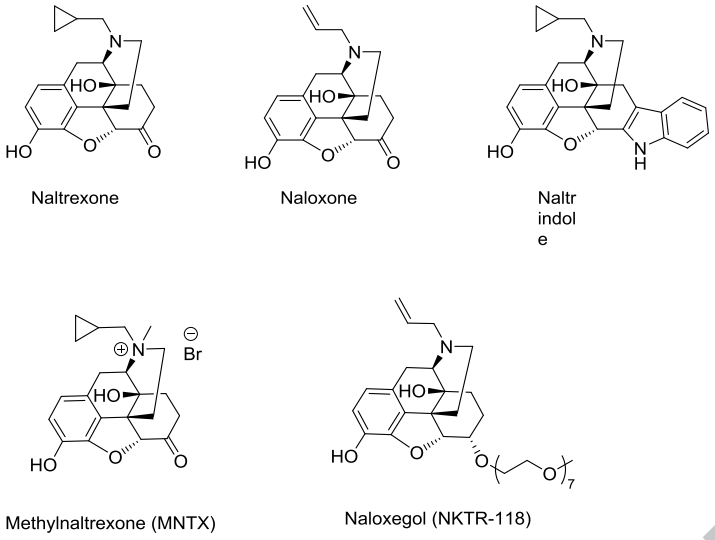
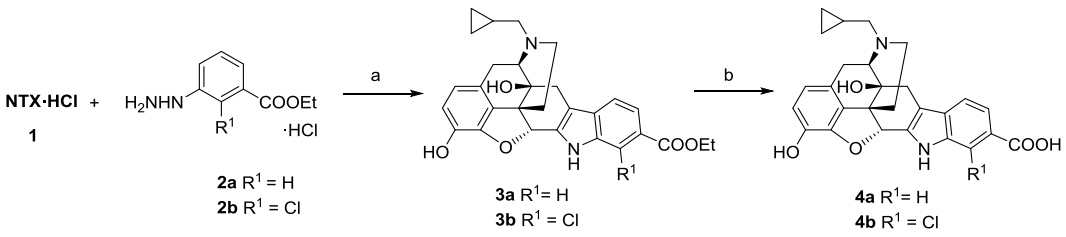


Figure 1. Known opioid receptor antagonists

Our design strategies were different from these. Our first strategy involved introduction of a highly polar moiety such as a carboxylic acid moiety to known opioid antagonists, such as naltrindole[10] derivatives (Toray's patent compounds[11]) to confer peripheral selectivity, because compounds with highly polar functions are known to not easily cross the blood–brain barrier (BBB).[12] Our second strategy was to design new chemotypes with morphinan scaffolds, which were expected to minimize the penetration of the BBB.

First, we introduced carboxylic acid moieties to known opioid receptor antagonists. Indole carboxylic acids **4** were synthesized by Fischer indole synthesis from naltrexone hydrochloride (NTX·HCl; **1**) as a starting material and the corresponding arylhydrazine (**2**) in acidic conditions and following hydrolysis, according to the known method[11] described in scheme 1.

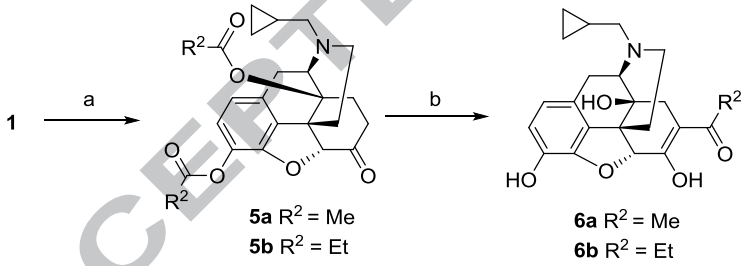


Scheme 1. Reagents and conditions for the synthesis of indole carboxylic acids **4**: (a) MsOH, EtOH,

reflux, R^1= H 57%, R^1= Cl 78%; (b) 2M NaOH, MeOH, rt, R^1= H 97%, R^1= Cl 98%.

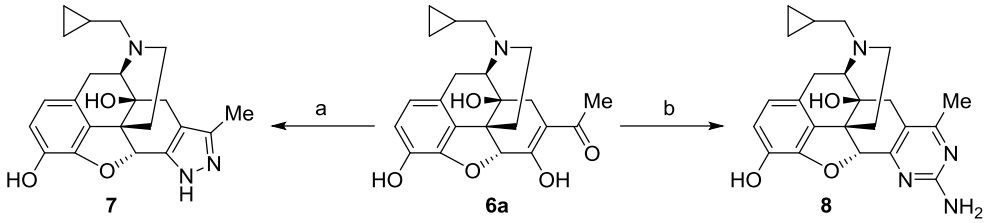
Next, we designed new chemotypes that could be synthesized starting from naltrexone. We focused upon 7-acetyl-morphinan, which had been reported previously,[13] because: 1) only 7-acetyl-morphinan was known, and its biological activities have not been studied; 2) β-diketones are easily converted to various heterocyclic compounds, such as pyrazoles, and pyrimidines. Moreover, these derivatives are predicted to not easily penetrate the BBB because of their higher polar surface area (PSA) values compared with naltrexone.

Indeed, the heterocyclic compounds described above were synthesized from 7-acyl morphinans. The intermediate 7-acyl morphinans were synthesized using previously reported methods.[13] Free naltrexone (prepared from **1**) was treated with acyl anhydride at 130 °C to yield the 3,14-di-*O*-acyl derivative **5**. Next, compound **5** was treated with aqueous NaOH, and deprotection / acyl rearrangement to the 7-position proceeded smoothly to yield the 7-acyl derivatives **6** (Scheme 2).



Scheme 2. Reagents and conditions for the synthesis of the 7-acyl derivatives **6**: (a) 1) sat. $NaHCO_3$; 2) $(R^2CO)_2O$, 100 °C; (b) 2M NaOH, MeOH, rt, R^2 = Me 80%, R^2 = Et 92% (2 steps).

6,7-Fused heterocyclic compounds were synthesized as follows (Scheme 3). Pyrazole **7** was simply obtained by treatment with the corresponding hydrazine and compound **6a**. Pyrimidine **8** was synthesized from guanidine and the intermediate (**6a**).



Scheme 3. Reagents and conditions for the synthesis of compounds **7** and **8**: (a) hydrazine·2HCl, EtOH, reflux, 46%; (b) guanidine carbonate, AcOH, EtOH, reflux, 20%.

The preliminary SAR results are shown in Table 1. The indole carboxylic acid **4a** along with the naltrindole derivatives had dual affinities to opioid receptors, but showed slight δ-receptor selectivity. Compound **4a** was metabolically stable and showed a low brain Kp value but was not orally bioavailable. This extremely low bioavailability of compound **4a** was thought to result from its zwitterion structure. Introduction of a chlorine substituent onto the indole ring produced no improvement in bioavailability (**4b**). The other indole carboxylic acid derivatives were all orally inactive (data not shown). We concluded that introduction of a carboxylic acid moiety on the morphinan scaffold was an ineffective strategy for development of opioid antagonists in light of the poor oral bioavailability of this series of compounds.

Next, the 7-acyl derivatives **6** also had dual affinities for opioid receptors but were slightly μ-selective, unlike the indole carboxylic acids. These derivatives showed extremely high clearance and poor bioavailability. Additionally, they had high brain Kp values (**6a**: 1.1, **6b**: 1.7).

The results of the 6,7-fused heterocycles are shown in Table 1. Pyrazole **7** showed moderate bioavailability and a comparatively low brain Kp value, but its value was not lower than our preriminary criteria (brain Kp value: <0.1). Pyrimidine **8** showed good bioavailability and a moderately low brain Kp value. The 6,7-Fused heterocycles were all slightly δ-selective antagonists. The compounds shown in Table 1 did not achieve both bioavailability and low brain Kp.

Table 1. SAR study of morphinan derivatives

Comp.No	μ (Ki:nM)*1	δ (Ki:nM)*2	MS h, r (%) *3	CL *4	BA *5	brain Kp *6	Conc. in brain (ng/mL) *7	PSA*8
4a	18	0.62	98, 97	71.8	0.1	0.03	0.023	106
4b	19	1	97, 100	18.1	0.2	0.03	0.032	106
6a	0.95	31	95, 80	233	4	1.1	5.8	83
6b	1.4	9.9	85, 46	313	6.4	1.7	6.5	83
7	24	1.2	98, 81	199	26.9	0.25	2.2	82
8	8.6	2.1	92, 58	220	42.5	0.31	4.6	105

*[1, 2] Recombinant human μ-opioid receptors (produced in CHO-K1 cells) and δ-opioid receptors (produced in HEK-293 cells); the radioligands [^{3}H]- [D-Ala2, *N*-MePhe4, Gly-ol]-enkephalin (DAMGO) (for μ-opioid receptors), [^{3}H]- [D-Ala2, D-Leu5]-enkephalin (DADLE) (for δ-opioid receptors). *[3]Metabolic stabilities were evaluated by measuring the remaining % of substrates (0.5uM) after 0.5 hour incubation with human or rat microsomes. *[4, 5, 6]Compounds were evaluated in cassette dosing. Usually 2 to 5 compounds (1mg/kg) were orally administered simultaneously and, then evaluated. CL: total clearance (mL/min/kg); BA: bioavailability (%); brain Kp: ratio of the concentrations in brain tissue and in the blood. *[7]Concentrations in brain at Cmax in oral adiministration. *[8]PSA: polar surface area (Å^2) calculated by MOE. PSA value of NTI is 62.

We found that the 7-Acyl derivatives **6a** and **6b** were chemically unstable and easily converted to a mixture of the 14-*O*-acyl form and the 7-acyl form. They were produced from intramolecular rearrangement (Figure 2). In compound **10**, polar hydroxy group on 14 position was masked by acyl group. So, compound **10** could pass BBB more easily than naltrexone and compound **6**. This would be the reason why 7-acyl derivatives **6a** and **6b** have much higher brain Kp values than we expected. Next, we designed chemically stable 7-carboxamide derivatives, **9**, because acyl rearrangements are well-known reactions in some chemistries,[14] especially sugar chemistry,[14a] but carboxamide rearrangements are uncommon.[15] More importantly, carboxamides have larger PSA values than corresponding acyl derivatives.

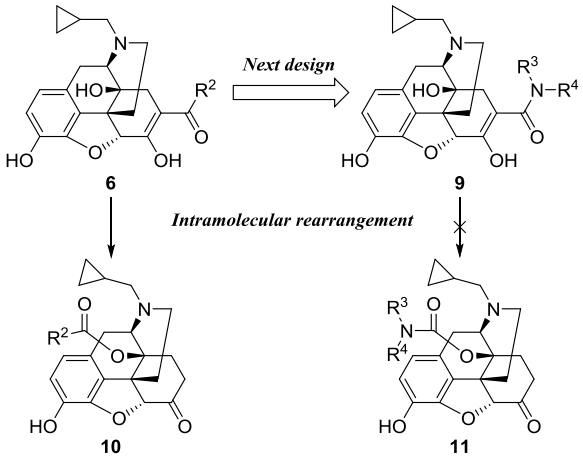
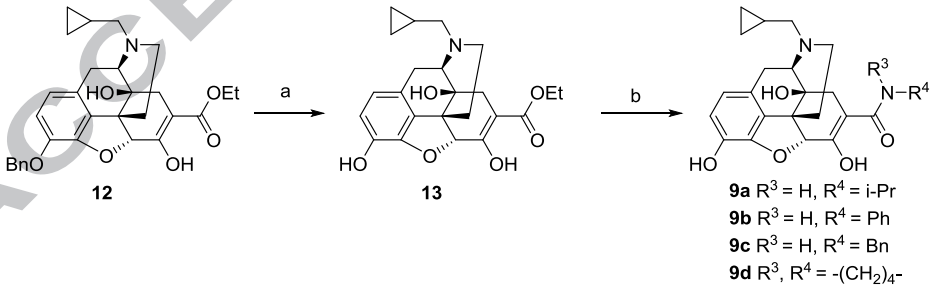


Figure 2. Structure-based design of 7-carboxamide derivatives **9**

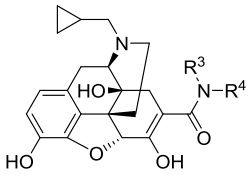
The 7-carboxamide derivatives, **9,** were synthesized from the 7-ethoxycarbonylnaltrexone **13** derived from **12,**[16] and excess amines with microwave irradiation following acidic hydrolysis of intermediates, enamino-carboxamides (method A). These 7-carboxamide derivatives were revealed to be chemically stable, as we expected. After 24 hour incubation in plasma at 37 °C, 7-acyl derivatives were unstable (remaining % values were <20%) but 7-carboxamides were generally stable (remaining % values were >80%).



Scheme 4. Reagents and conditions for the synthesis of the 7-carboxamide derivatives **9** (method A): (a) H_2, Pd/C, EtOH, rt, 96%; (b) 1) R^3NHR^4, Et_3N, methoxyethanol, 180 °C, microwave irradiation; 2) 2M HCl, rt, 1h, **9a**: 68%, **9b**: 34%, **9c**: 11%, **9d**: 41%.

The results for the 7-carboxamide derivatives (**9a**–**d**) are shown in Table 2. Compounds **9a** and **9b** showed high affinities to opioid receptors and good metabolic stabilities, moderate clearances, good bioavailability, and especially, low brain Kp values. (In both cases, neither compound was detected in brain tissues.) Lipophilic amines, such as the benzylamine (**9c**) and the secondary cyclic amine (**9d**) showed poorer metabolic stability, slightly higher clearance, and higher brain Kp values than those of **9a** and **9b**.

Table 2. Preliminary SAR results of morphinan-7-carboxamide derivatives



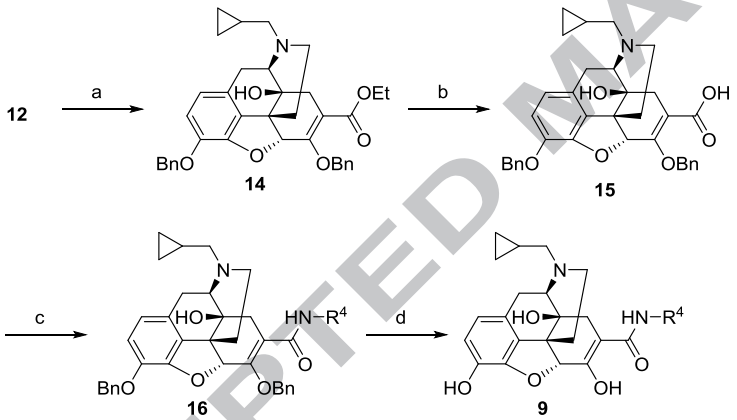
Comp. No	R^3	R^4	μ (Ki:nM)	δ (Ki:nM)	MS h, r (%)	CL	BA	brain Kp	Conc. in brain (ng/mL)	PSA
9a	H	i-Pr	5.2	7.4	95, 88	41	50	NC[*1]	ND[*2]	90
9b	H	Ph	4.1	20	89, 78	36	57	NC	ND	90
9c	H	Bn	1.1	16	94, 14	61	46	0.17	12	90
9d	-$(CH_2)_4$-		4	7.4	99, 24	102	18	0.22	3.0	83

See footnotes of Table 1.

[*1] NC: not calculated. [*2] ND: not detected.

Exploratory structure-activity relationship studies of the morphinans led to discovery of a new chemotype, the 7-carboxamide derivatives **9**, which showed high affinities for μ- and δ-opioid receptors, good pharmacokinetics profiles, and most importantly, extremely low brain Kp values.

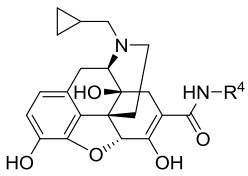
Encouraged by these results, we began further optimization of the 7-carboxamide derivatives **9**. We designed compounds which had larger PSA values than those of **9a** and **9b**. In further modification studies, another useful synthetic method (method B) for 7-carboxamide derivatives had to be developed, as described in Scheme 5. The enol OH of **12** was protected with a benzyl group by the Mitsunobu reaction to give a dibenzyl ether **14**. The dibenzyl ether **14** was hydrolyzed to afford the carboxylic acid **15**. The acid **15** was treated with amines under general amidation conditions to give protected amides **16.** Finally, the protecting groups were removed by hydrogenation or treatment with BBr_3 to give the 7-carboxamide derivatives **9**.

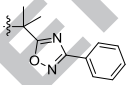


Scheme 5. Reagents and conditions for the synthesis of the 7-carboxamide derivatives **9** (method B): (a) benzyl alcohol, ADDP, $^{n}Bu_3P$, THF, -10 °C, quant; (b) 4M KOH aq., MeOH, 50 °C, 77%; (c) R^4-NH_2, WSCD·HCl, HOBt, DMF, rt, 38 to 83%; (d) H_2, $Pd(OH)_2$, MeOH, rt, (or BBr_3, CH_2Cl_2, rt to 40 °C); 30 to 86%.

The results from the 7-carboxamide derivatives (**9e**–**n**) are shown in Table 3. Several compounds with nanomolar affinity for μ- and δ-opioid receptors were obtained, which showed good to moderate pharmacokinetics profiles and very low brain Kp values.

Table 3. Optimizations of 7-carboxamide derivatives



Comp. No	R^4	μ (Ki:nM)	δ (Ki:nM)	MS h, r (%)	CL	BA	brain Kp	Conc. in brain (ng/mL)	PSA
9e		16.5	3.99	101, 103	25	68	0.08	5.1	119
9f		46.1	11.8	NT[*1]	28	0.52	0.04	0.055	130
9g		1.6	9.8	100, 103	30	11	0.06	1.3	125
9h		93.6	5.5	104, 99	15	0.77	0.01	0.018	157
9i		19.4	18	NT	27	3.4	0.05	0.21	115
9j		7.3	5.8	92, 99	29	11	0.04	0.29	130
9k		1.1	0.91	73, 76	20	29	0.03	1.3	130
9l		5.1	11.1	103, 92	8.5	12	0.03	1.3	116
9m		9.8	6.8	98, 97	25	55	0.05	5.6	102
9n		2.4	18.9	93, 86	28	13	0.04	0.56	105

See footnotes of Table 1.

[*1] NT: not tested.

Among these 7-carboxamide derivatives, four compounds (**9a**, **9b**, **9g**, and **9k**)[17] were selected for

further evaluation. They were evaluated for *in vivo* antagonism of opioid-induced emesis/vomiting in the ferret,[18] against opioid-induced constipation in the rat[19], and against the analgesic effects of morphine in the rat[20]. The results are shown in Table 4. All compounds reversed constipation and reduced emetic effects. Two compounds produced no antagonism of opioid analgesic activity. Among those examined further, compound **9k** antagonized both emetic effect and constipation effect at 0.03mg/kg (po), and its safety margin was quite large. These efforts led to the discovery of clinical candidate **9k**, naldemedine (S-297995), for the treatment of opioid-induced adverse effects.

Table 4. Evaluation studies of selected compounds

Compound No.	**9a**	**9b**	**9g**	**9k**	**MNTX**
Binding affinity (Ki: nM)	μ: 3.4 δ: 2.0	μ: 1.0 δ: 6.8	μ: 1.6 δ: 9.8	μ: 1.13 δ: 0.91	μ: 5.48 δ: 3460
Functional activity (Ke: nM)[*1]	μ: 6.2 δ: 3.8	μ: 3.2 δ: 3.6	μ: 4.1 δ: 7.6	μ: 0.05 δ: 0.37	μ: 56 δ: 1080
Anti emetic effect (ED_{50}: mg/kg)[18]	0.04	0.04	0.026	0.03	0.69 (SC[*2])
Anti constipation effect (ED_{50}: mg/kg)[19]	0.57	0.99	0.57	0.03	4.5 (SC)
Anti analgegic effect (ED_{50}: mg/kg)[20]	10.65	16.54	>100	>30	NT[*3]
Margin between anti emetic and anti analgesic activity	266	413	>3846	>1000	-
Margin between anti constipation and anti analgegic activity	19	17	>175	>500	-

[*1] Antagonist activities were evaluated by [^{35}S]- guanosine 5'-*O*-[gamma-thio]triphosphate (GTPγS) binding assay. [*2] SC: subcutaneous injection [*3] NT: not tested.

Acknowledgements

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17) NMR data of compound **9a** : ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.12-0.15 (m, 2H), 0.44-0.53 (m, 2H), 0.83 (m, 1H), 1.02 (d, J = 6.6 Hz, 3H), 1.08 (d, J = 6.6 Hz, 3H), 1.41 (d, J = 11.4 Hz, 1H), 1.85 (d, J = 15.6 Hz, 1H), 2.04-2.62 (m, 7H), 3.04 (d, J = 18.6 Hz, 1H), 3.24 (m, 1H), 3.96 (m, 1H), 4.71 (s, 1H), 4.74 (s, 1H), 6.51 (d, J = 8.4 Hz, 1H), 6.56 (d, J = 8.4 Hz, 1H), 7.40 (br d, J = 7.2 Hz, 1H), 9.16 (s, 1H), 14.50 (s, 1H).

NMR data of compound **9b**: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.10-0.24 (m, 2H), 0.45-0.60 (m, 2H), 0.89 (m, 1H), 1.45 (d, J = 11.1 Hz, 1H), 1.70-3.40 (m, 10H), 4.78 (s, 1H), 4.82 (s, 1H), 6.54 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 8.4 Hz, 1H), 7.05 (m, 1H), 7.29 (t, J = 7.8 Hz, 2H), 7.51 (d, J = 8.7 Hz, 2H), 9.14 (s, 1H), 9.24 (br s, 1H), 13.90 (br s, 1H).

NMR data of compound **9g**: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.12-0.14 (m, 2H), 0.46-0.51 (m, 2H), 0.85 (m, 1H), 1.06-1.09 (m, 2H), 1.35-1.36 (m, 2H), 1.41 (d, J = 11.7 Hz, 1H), 1.86 (d, J = 15.6 Hz, 1H), 2.17-2.61 (m, 7H), 3.03 (d, J = 18.3 Hz, 1H), 3.17 (d, J = 6.0 Hz, 1H), 3.56 (s, 3H), 4.74 (s, 1H), 4.77 (brs, 1H), 6.51 (d, J = 8.1 Hz, 1H), 6.56 (d, J = 8.1 Hz, 1H), 9.17 (brs, 1H), 14.1 (brs, 1H). A proton (OH) was

not observed.

Experimental procedure for preparation of compound **9k**: The synthetic method and NMR data are as follows. Acid **15** (500 mg, 0.884 mmol) was dissolved in CH_2Cl_2 (5 mL). To this solution, WSCD·HCl (203 mg, 1.06 mmol), HOBt (143 mg, 1.06 mmol), 2-(3-phenyl-1,2,4-oxadiazol-5-yl)propan-2-amine (212 mg, 0.884 mmol), and Et_3N (0.308 mL, 2.21 mmol) were added, and the mixture was stirred at rt overnight. The reaction mixture was poured into cold saturated aqueous $NaHCO_3$. The product was extracted by AcOEt twice. The combined organic layer was washed with brine. The organic layer was separated and dried over Na_2SO_4, filtered and evaporated to give a crude residue. The residue was purified using silica gel chromatography by eluting with $CHCl_3$: MeOH = 100:1~30:1 to give the precursor of **9k** as a yellow foam (431 mg, 64.9%). The precursor (430 mg, 0.573 mmol) was dissolved in CH_2Cl_2 (4 mL). To this solution was added BBr_3 (1.0M solution in CH_2Cl_2; 1.72 mL) at rt. The mixture was stirred at rt for 2 hours and treated with BBr_3 (1.0M solution in CH_2Cl_2; 1.72 mL) again. The reaction was stirred at rt for 1 hour, and then at 40 °C for 1 hour. After cooling to rt, the reaction mixture was poured into cold saturated aqueous $NaHCO_3$. The products were extracted twice with EtOAc. The combined organic layer was washed with brine. The organic layer was separated and dried over Na_2SO_4, filtered and evaporated to give a crude residue. The residue was purified using silica gel chromatography by eluting with $CHCl_3$: MeOH = 50:1~20:1 to yield compound **9k** as a colorless solid (98 mg, 30%). NMR data of *p*-TsOH salt of **9k**; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.35-0.55 (2H, m), 0.55-0.80 (2H, m), 0.95-1.15 (1H, m), 1.60-1.75 (1H, m), 1.70 (6H, s), 2.10 (1H, d, J=14.7 Hz), 2.29 (3H, s), 2.40-2.60 (2H, m), 2.60-2.75 (1H, m), 2.90-3.00 (1H, m), 3.07 (2H, br d, J=12 Hz), 3.25-3.50 (2H, m), 3.95 (1H, d, J=5.1 Hz), 4.94 (1H, s), 6.56 (1H, s), 6.69 (2H, ABq.), 7.11 (2H, d, J=8.4 Hz), 7.45-7.49 (2H, m), 7.53-7.60 (3H, m), 7.96-7.99 (2H, m), 8.12 (1H, s), 8.95 (1H, br s), 9.44 (1H, s), 13.37 (1H, s).

18) Evaluation of the test compound antagonism of morphine-induced emesis/vomiting in the ferret.

19) Evaluation of the test compound antagonism of constipation produced by morphine-induced

inhibition of small intestinal transit in the rat.

20) Evaluation of test compound antagonism of morphine analgesia in the rat tail-flick test.

- We discovered a new chemotype, 7-carboxamide morphinan derivatives as opioid antagonist.
- This chemotype is suitable for acting on peripherally.
- From our results, compounds which have over 100 of PSA values are difficult to pass BBB.
- Naldemedine showed dual actions in one dose, inhibiting constipation and nausea/vomiting induced by opioids.

Graphical Abstract

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Discovery of naldemedine: A potent and orally available opioid receptor antagonist for treatment of opioid-induced adverse effects

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