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Identification of an Orally Active Opioid Receptor-like 1 (ORL1) Receptor Antagonist 4-{3-[(2*R*)-2,3-Dihydroxypropyl]-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl}-1-[(1*S*,3*S*,4*R*)-spiro[bicyclo[2.2.1]heptane-2,1′-cyclopropan]-3-ylmethyl]piperidine as Clinical Candidate

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Abstract: Our efforts to optimize prototype opioid receptor-like 1 (ORL1) antagonist **1** led to the discovery of 4-{3-[(2*R*)-2,3-dihydroxypropyl]-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl}-1-[(1*S*,3*S*,4*R*)-spiro[bicyclo[2.2.1]heptane-2,1′-cyclopropan]-3-ylmethyl]piperidine **10**. **10** showed potent ORL1 antagonistic activity, excellent selectivity over other opioid receptors, and in vivo efficacy after oral dosing. Currently clinical trials of **10** are underway.

In 1994, the ORL1[a] receptor was identified as a fourth opioid receptor using a cloning technique.[1] This G-protein-coupled receptor has significant sequence homology with classical opioid receptors (μ, κ, δ); however, none of the classical opioid ligands show significant affinity for the ORL1 receptor. Nociceptin, also named orphanin FQ (NC/OFQ), is a peptide consisting of 17 amino acids that was identified as an endogenous ligand for ORL1 receptor in 1995.[2] Although NC/OFQ is homologous with the classical opioid peptide dynorphin A, it has no significant activity at the classical opioid receptors. NC/OFQ and ORL1 receptors are widely distributed in the central nervous systems, and the physiological roles of the NC/OFQ-ORL1 system have been the focus of intense research. In addition to investigations using NC/OFQ, studies involving ORL1-deficient mice showed that this system may play important roles in pain regulation,[3] learning and memory,[4] food intake,[5] anxiety,[6] and cardiovascular system,[7] among others,[8] thus prompting many pharmaceutical companies to identify small molecules as potent and selective ORL1 agonists and antagonists.[9]

We previously reported the discovery of 1-[(3*R*,4*R*)-1-cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one (**1**, J-113397) as the first potent and selective small molecule ORL1 antagonist.[10] **1** has trisubstituted piperidine and benzimidazolidinone structure and shows high affinity for the ORL1 receptor with greater than 600-fold selectivity over opioid μ, κ, and δ receptors. **1** behaves as an antagonist at the ORL1 receptor in in vitro functional assays and in vivo assays. Therapeutic targets for ORL1 antagonists have been explored with **1**, and blockage of ORL1 demonstrated antihyperalgesic effects in various animal models without analgesic effects in acute pain models.[11] Since wide distribution of NC/OFQ and ORL1 receptors in the brain suggested broad functions of peptide and its receptors, we are conducting clinical trials of **10** for multiple target indications with an experimental medicine approach.

Various classes of ORL1 antagonists have been also reported (Structures are shown in Supporting Information Figure S-1), including *N*-(4-amino-2-methylquinolin-6-yl)-2-(4-ethylphenoxymethyl)benzamide (**2**, JTC-801),[12] phenylpiperidine (**3**, SB612111),[13] spiropiperidines (**4**−**6**),[14] benzimidazole (**7**),[15] cycloalkanopyridine (**8**),[16] and aminoquinazoline (**9**).[17] Among them, **2** has efficacious and potent antinociceptive effects in animal acute pain models and only entered clinical trials as a novel type of analgesic.[12]

1 has become an important pharmacological tool for the elucidation of NC/OFQ-ORL1 systems roles in pain modulation and other physiological functions. Numerous studies have employed **1** as a tool to confirm ORL1 receptor mediated NC/OFQ effects. In our previous report, we demonstrated that subcutaneous injection of **1** inhibited hyperalgesia induced by intracerebroventricular injection of NC/OFQ (0.1 nmol). Further characterization revealed that **1** could not move forward as a preclinical candidate because of its drug metabolism and pharmacokinetics (DMPK) profiles, that is, poor oral bioavailability. Thus, we revisited modification of benzimidazolidinone analogues.

Our goals were to investigate the detailed structure−activity relationships (SAR) of benzimidazolidinone derivatives and to identify potent and orally available ORL1 antagonists. We tried three approaches for the improvement of metabolic stability without loss of ORL1 potency and selectivity: (1) replacement of the cyclooctyl ring with various kinds of cycloalkane groups; (2) introduction of a variety of hydrophilic substituents at the piperidine ring; (3) introduction of a variety of hydrophilic substituents on the benzimidazolidine nitrogen.

In this paper, we report on the characterization of **1** and the SAR of benzimidazolidinone analogues (Figure 1). We identify potent and orally active diol compounds and describe their in vitro and in vivo characterizations.

Synthetic routes are summarized in Scheme 1. Chiral tosylate **19** was prepared from (1*S*,3*R*,6*S*)-2,1′-spirocyclopropane(bicycle[2.2.1]heptane)-1′-norbornylmethanol **18**, which was synthesized by a known procedure reported by Merck Research Laboratories.[18] Alkylation of commercially available piperidine analogue **11** with tosylate **19** in the presence of $^{i}Pr_2NEt$ in *N*-methyl-2-pyrrolidinone (NMP) afforded **12**. The preparation of *N*-isopropylidene protected alkyl diol benzimidizolidinones **13**−**15** was achieved by treating **12** with NaH in *N*,*N*′-dimethylformamide (DMF) followed by corresponding commercially available (*S*)-2,2-dimethyl-1,3-dioxolane-4-methanol *p*-toluenesulfonate,

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[a] Abbreviations: ORL1, opioid receptor-like 1; NC/OFQ, nociceptin/orphanin FQ; SAR, structure−activity relationship; DMPK, drug metabolism and pharmacokinetics; NMP, *N*-methyl-2-pyrrolidinone; TsCl, *p*-toluanesulfonyl chloride; MsCl, methanesulfonyl chloride; P-gp, P-glycoorotein; PK, pharmacokinetics; CHO, Chinese hamster ovary; hERG, human ether-a-go-go related gene.

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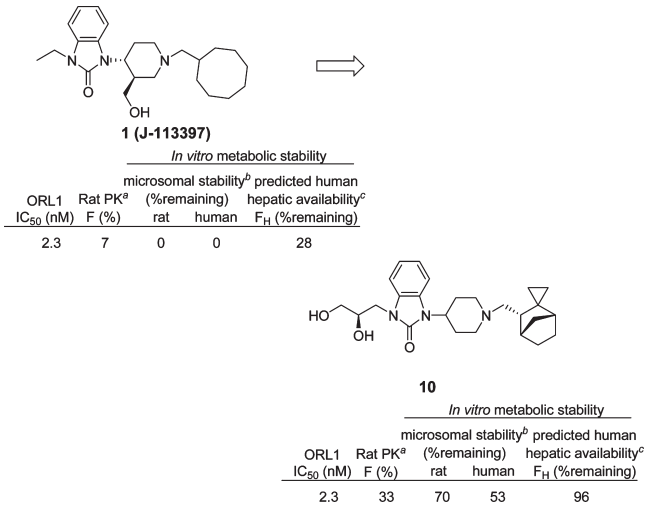
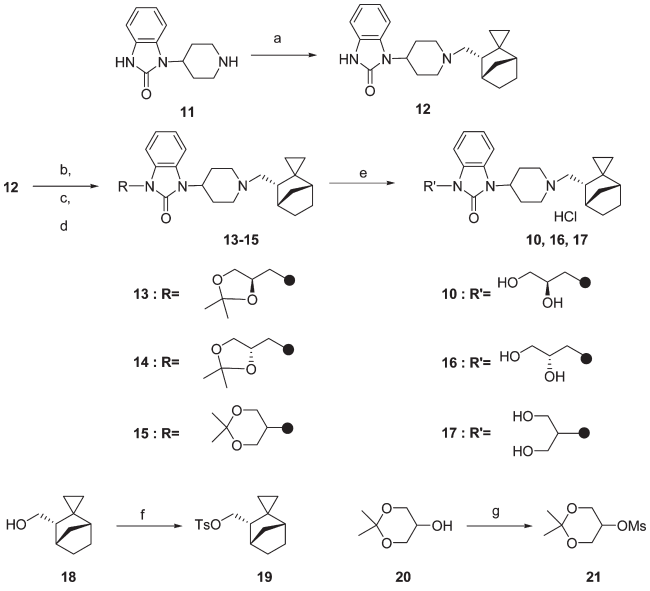


Figure 1. Identification of **10**. Footnote letters indicate the following: (a) Pharmacokinetic study was conducted in fasted Sprague–Dawley rats (n = 3) dosed at 3 mg/kg (**1**) and 1 mg/kg (**10**) for intravenous dosing and dosed at 10 mg/kg (**1**) and 3 mg/kg (**10**) for oral dosing as a solution in water. (b) Rat and human microsomal stabilities were determined by % parent compound (1 μM) remaining after 30 min (37 °C) incubation with rat liver microsomes (0.25 mg protein/mL) or human liver microsomes (0.25 mg protein/mL). (c) Predicted hepatic availability (FH %) in humans was determined by serum incubation method.[21]

Scheme 1. Synthesis of Diol Compounds[a]



[a] Reagents: (a) **19**, $^{i}Pr_2NEt$, NMP, 100 °C, 39%; (b) (*S*)-2,2-dimethyl-1,3-dioxolane-4-methanol *p*-toluenesulfonate, NaH, DMF, 80 °C, 80% (for **13**), 74% (for **14**); (c) (*R*)-2,2-dimethyl-1,3-dioxolane-4-methanol *p*-toluenesulfonate, NaH, DMF, 80 °C, 95%; (d) **21**, NaH, DMF, 120 °C, 55%; (c) aqueous HCl/MeOH, 61% (for **10**), 72% (for **16**), 66% (for **17**); (f) TsCl, Et_3N, AcOEt, quant; (g) MsCl, Et_3N, THF, quant.

(*R*)-2,2-dimethyl-1,3-dioxolane-4-methanol *p*-toluenesulfonate, or 1,3-isopropylidene protected 1,2,3-triol 2-mesylate **21**. Mesylate **21** was prepared from **20**, which was synthesized by a known method.[19] Finally, deprotection of isopropylidenes of **13**–**15** with aqueous HCl in methanol yielded desired compounds **10**, **16**, **17** as hydrochloride salts.

The structure–activity relationship of the benzimidazolidinone class is summarized in Figure 2.

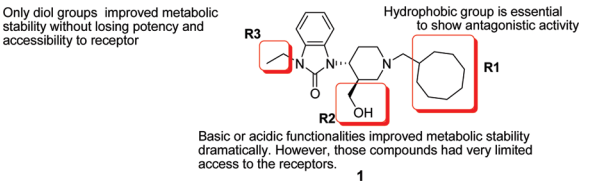


Figure 2. SAR summary of benzimidazolidinone class.

With the replacement of the cyclooctyl ring with various kinds of cycloalkane groups, a metabolite identification study of **1** revealed that oxidation was the major metabolism and the cyclooctyl group was one of the major metabolic sites. Thus, substituent effects at R1 for the improvement of metabolic stability were investigated. Various substituents were tested as a cyclooctyl replacement to obtain detailed SAR. We previously reported that the *N*-methylene linker (nonsubstituted) and alkane group are essential to show full antagonistic activities.[10]

The outline of R1 modification is shown in Supporting Information Figure S-2. Various kinds of cycloalkanes, substituted or nonsubstituted cyclopropyl rings to medium sized rings (such as cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, cyclooctylmethyl, cyclononylmethyl, cyclodecylmethyl), spiroalkane (such as spiro[2.5]octanemethyl, spiro[3.5]nonanemethyl, spiro[4.5]decanemethyl, spiro[2.4]heptanemethyl, spiro[3.4]octanemethyl, spiro[4.4]nonanemethyl), bicycloheptane (such as methylbicyclo[2.2.1]heptylmethyl, dimethylbicyclo[2.2.1]heptylmethyl, spirocyclopropanebicycloheptanemethyl), and branched alkanes (such as 3,3-dimethylbutane, 3,3-dithylbutane, 1-methylcyclobutaneethyl, 1-methylcyclopentaneethyl, 1-methylcyclohexaneethyl) were tested. Unfortunately, cyclooctyl replacement alone could not achieve sufficient levels of metabolic stability without loss of ORL1 potency (data not shown). Among them, the spirocyclopropanebicycloheptane ring was found as the most balanced cyclooctyl replacement in regard to ORL1 binding affinity and metabolic stability.

With the introduction of a variety of hydrophilic substituents at the piperidine ring, the effects of hydrophilic functional group substitution at the R2 position for improvement of metabolic stability were investigated. Unfortunately, introduction of basic or acidic functional groups tended not to improve metabolic stability. Only few functionalities (such as aminomethyl, carboxyl) dramatically improved metabolic stability. However, these compounds did not show any in vivo antagonism in mice even at 10 mg/kg subcutaneous injection because of decreases in brain/receptor accessibility. Meanwhile, insertion of neutral functional groups (hydroxy, dihydroxy, amide, etc.) generally led to metabolically unstable compounds except dihydroxypropylurea derivatives, whereas these functionalities decreased brain penetration. Diolurea derivatives also did not demonstrate in vivo efficacy at 10 mg/kg subcutaneous injection in a mouse locomotor model (data not shown).

Unfortunately, there was no R2 substituent that was consistent with metabolic stability and receptor accessibility, even if R1 was newly identified spirocyclopropanebicycloheptane ring.

With the introduction of a variety of hydrophilic substituents into the benzimidazolidinone nitrogen, the effects of hydrophilic substituents at the urea position were investigated. Introduction of basic functional groups, especially methylaminoethyl group, dramatically improved metabolic stability without losing ORL1 affinity. However, these analogues did not show in vivo efficacy, similar to substituents at R2, because of low receptor accessibility. Although we expected that diol analogues may have low brain penetrability

and may not show in vivo efficacy, surprisingly only neutrally functional diol groups at the R3 position led to metabolically stable analogues with in vivo efficacious profiles.

From these results, diol units were combined with spirocyclopropane-bicycloheptane ring, and three representative diol compounds **10**, **16**, and **17** were identified. Detailed profiles of diol compounds are shown in Table 1−4. Diol analogues **10**, **16**, and **17** showed potent single digit nanomolar binding affinity and full antagonistic activities for ORL1 receptors. Excellent selectivity over other opioid receptors was exhibited by comparing with binding affinity data to μ, κ, and δ (Table 1). In vivo antagonistic activity in an ORL1-driven efficacy model that inhibited reduction of locomotor activity induced by ORL1 agonist was also demonstrated at 30 mg/kg oral dosing in ICR mice. The brain/plasma ratio was comparatively high despite having diol groups, especially for **10** (Table 2). In addition, these analogues had acceptable DMPK profiles, much improved microsomal stabilities compared with that of prototype **1**, and moderate oral bioavailability (F = 17−33%) in rats. Moreover, human hepatic availability (F_H) was predicted by in vitro serum incubation method previously reported by our laboratory.[20] Consequently, these compounds were predicted to have very good hepatic availability (F_H = 83−96%) in humans. In the case of rats, the predicted F_H of these analogues was consistent with in vivo oral bioavailability. These results indicated that **10**, **16**, and **17** can be orally available in human (Table 3).

Demonstrating in vivo efficacy required a relatively high dose (30 mg/kg), since **10**, **16**, and **17** had P-glycoprotein (P-gp) susceptibility in mice but not in humans. Therefore, brain penetrability (brain/plasma ratio) was measured in P-gp deficient CF-1(−/−) mice to predict human brain penetrability. As a result, despite the diol functional group, **10**, **16**, and **17** had much higher brain penetrability than in ICR mice that were used in the in vivo antagonism study. These data suggest that **10**, **16**, and **17** should demonstrate more potent in vivo efficacy in humans than in mice (Table 4).

10 had the most balanced profile and was chosen for further evaluation. **10** was a weak competitive inhibitor for CYP2D6 with an IC_{50} of 16 μM, whereas **10** was not an inhibitor for CYP1A2, CYP2C8, CYP2C9, and CYP3A4 with IC_{50} of $> 100\,\mu$M and low binding affinity to the hERG K^+ channel, as measured in MK-499 binding assay (IC_{50} = 25 μM). Furthermore, excellent genotoxic profiles were exhibited; microbial mutagenesis assay was negative, in vitro alkaline elution assay was negative, and in vitro chromosomal aberration assay was negative (Supporting information Table S-1). In a dog telemetry study for evaluation of cardiovascular effects, no significant changes in cardiovascular variables were detected up to 5 mg/kg. From all in vitro and in vivo data, **10** was moved forward to clinical trial.

In conclusion, our efforts to optimize prototype ORL1 antagonist **1** led to the discovery of 4-{3-[(2*R*)-2,3-dihydroxypropyl]-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl}-1-[(1*S*,3*S*,4*R*)-spiro[bicyclo[2.2.1]heptane-2,1′-cyclopropan]-3-ylmethyl]piperidine **10**. **10** had potent ORL1 antagonistic activity and excellent selectivity over other opioid receptors and showed in vivo efficacy after oral dosing and good brain penetrability. **10** is currently undergoing a clinical trial.

Table 1. In Vitro Profiles of Diol Compounds[a]

	binding affinity IC_{50} (nM)				GTPγS antagonism, IC_{50} (nM)[f]
compd	ORL-1[b]	μ[c]	κ[d]	δ[e]	
10	2.3 ± 0.2	4500 ± 200	10000 ± 900	> 10000	16 ± 7
16	1.9 ± 0.1	2700 ± 100	6800 ± 300	> 10000	29 ± 7
17	2.3 ± 0.2	6200 ± 800	11000 ± 1700	> 10000	15 ± 3

[a] All values are the mean of more than three independent determinations performed in duplicate. [b] Displacement of [^{125}I]Tyr^{14}-nociceptin. [c] [^{3}H]diprenorphin, [d] [^{3}H]U-69593. [e] [^{3}H]Naltrindole binding from CHO cells stably expressing cloned human ORL1, opioid μ, opioid κ, and opioid δ receptors, respectively. [f] IC_{50} values on nociceptin-produced [^{35}S]GTPγS binding to ORL1-expressed in CHO cells.

Table 2. In Vivo Profiles of Diol Compounds

	in vivo antagonism	brain penetrability		
compd	(% reversal)[a]	plasma (nM)[b]	brain levels (nmol/g brain)[b]	brain/plasma ratio
10	85	0.19 ± 0.06	0.19 ± 0.05	1.0
16	77	0.35 ± 0.10	0.28 ± 0.08	0.79
17	69	0.54 ± 0.24	0.25 ± 0.09	0.48

[a] Data show antagonistic activity of analogues (30 mg/kg, po) against the reduction in locomotor activity produced by an ORL1 agonist for 30 min in mice (n = 6−12). Values are expressed as % reversal of the agonist response. [b] Plasma and brains of mice were collected at 3 h after drug administration (30 mg/kg, po), and drug concentrations were measured (n = 3 mice/group). Each value represents mean ± sd of three animals.

Table 4. P-gp Susceptibility and Brain Penetrability in CF-1(−/−) Mice of Diol Compounds

	P-gp substrate assay[a]		brain penetrability in CF-1(−/−) mice[b]		
compd	L-mdr1a (mouse)	L-MDR1 (human)	plasma (nM)	brain levels (nmol/g brain)	brain/plasma ratio
10	4.3	1.4	0.087	0.56	6.4
16	7.3	1.7	0.078	0.42	5.6
17	13.2	2.8	0.10	0.43	4.1

[a] P-gp susceptibility assay was conducted by using human L-MDR1 and mouse L-mdr1a transfected porcine renal epithelial (LLC-PK1) cell monolayers.[21] Transcellular transport ratio of L-MDR1 and L-mdr1a was calculated as basal-to-apical versus apical-to-basal transported amounts. [b] Plasma and brains of CF-1(−/−) mice were collected at 1 h after drug administration (0.3 mg/kg, sc), and drug concentrations were measured (n = 3 mice/group).

Table 3. Drug Metabolism and Pharmacokinetic Profiles of Diol Compounds

	in vitro metabolic stability				rat PK[c]			
	microsomal stability (% remaining)[a]		predicted hepatic availability,[b] F_H (% remaining)		iv			
compd	human	rat	human	rat	CL_p ((mL/min)/kg)	$t_{1/2}$ (h)	Vd_{ss} (L/kg)	F (%)
10	53	70	96	30	56	1.1	4.8	33
16	54	66	91	17	34	1.4	3.7	17
17	45	74	83	17	63	1.3	5.3	22

[a] Rat and human microsomal stabilities were determined by % parent compound (1 μM) remaining after 30 min (37 °C) of incubation with rat liver microsomes (0.25 mg protein/mL) or human liver microsomes (0.25 mg protein/mL) (n = 3). [b] Predicted hepatic availability (F_H, %) in human and rat was determined by serum incubation method. [c] Pharmacokinetic study was conducted in fasted Sprague−Dawley rats (n = 3) dosed at 1 mg/kg for intravenous dosing and dosed at 3 mg/kg for oral dosing as a solution in water.

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Supporting Information Available: Purity results from HPLC analysis for all target compounds, experimental procedures and characterization data for all new compounds, in vitro biological assays, and in vivo pharmacological experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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