Design and synthesis of orexin receptor agonists with a tetralin skeleton and MRGPRX2 agonists with a morphinan skeleton

Keita Iio

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Keita Iio
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List of abbreviation

Ac	acetyl
ANOVA	analysis of variance
aq.	aqueous solution
BBB	blood-brain barrier
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Cbz	benzyloxycarbonyl
COCA	cocaine
COMU	1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminooxy) dimethylaminomorpholino)] uronium hexafluorophosphate
CPM	cyclopropylmethyl
CPP	conditioned place preference
CSA	camphorsulfonic acid
DAMGO	[D-Ala^2, *N*-Me-Phe^4, Gly^5-ol]-enkephalin
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	diisopropylethylamine
DMEM	Dulbecco's modified Eagle medium
DMAP	4-dimethylaminopyridine
DMF	*N*, *N*-dimethylformamide
DMSO	dimethyl sulfoxide
DOR	δ opioid receptor
DPDPE	[D-Phe^{2,5}]-enkephalin
dppf	1,1′-bis(diphenylphosphino)ferrocene
EC_{50}	median effective concentration
ED_{50}	median effective dose
E_{max}	maximum effect
eq.	equivalent

ESI	electrospray ionization
Et	ethyl
FBS	fetal bovine serum
FDA	food and drug administration
GDP	guanosine diphosphate
GPCR	G-protein-coupled receptor
GTP	guanosine triphosphate
HATU	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate
HBSS	Hank's balanced salt solution
HEK	human embryonic kidney
HPLC	high-performance liquid chromatography
i.c.v.	intracerebroventricular
i.d.	intradermal
IgE	immunoglobulin E
i.t.	intrathecal
IR	infrared
K_i	inhibition constant
KO	knockout
KOR	κ opioid receptor
Me	methyl
MOR	μ opioid receptor
MRGPR(Mrgpr)	Mas-related G-protein-coupled receptor
NanoBiT	NanoLuc Binary Technology
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
OX_1R	orexin 1 receptor
OX_2R	orexin 2 receptor
OXA	orexin A

OXR	orexin receptor
PDA	photo diode array
ppm	parts per million
Pr	propyl
QWF	Boc-Gln-D-Trp (Formyl)-Phe benzyl ester trifluoroacetate
r.t.	room temperature
REM	rapid eye movement
s.c.	subcutaneous
SAL	saline
SEM	standard error of the mean
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
Troc	2,2,2-trichlotoethoxycarbonyl
UPLC	ultra-performance liquid chromatography
UV	ultraviolet
VEH	vehicle
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Chapter 1. General introduction

1.1 Overview of the functions and structures of G-protein-coupled receptors

Overall, G-protein-coupled receptors (GPCRs) are seven-transmembrane receptors that comprise the largest protein family (composed of approximately 800 members, half of which are olfactory receptors) in the human genome.[1,2] They trigger various physiological responses by converting extracellular stimuli, e.g., photons, neurotransmitters, and hormones, into intracellular signals. Their *N*-terminal amino acid residues are located extracellularly and are connected to the intracellular *C*-terminal amino acid residues via three intracellular loops, three extracellular loops, and seven transmembrane domains (Figure 1).

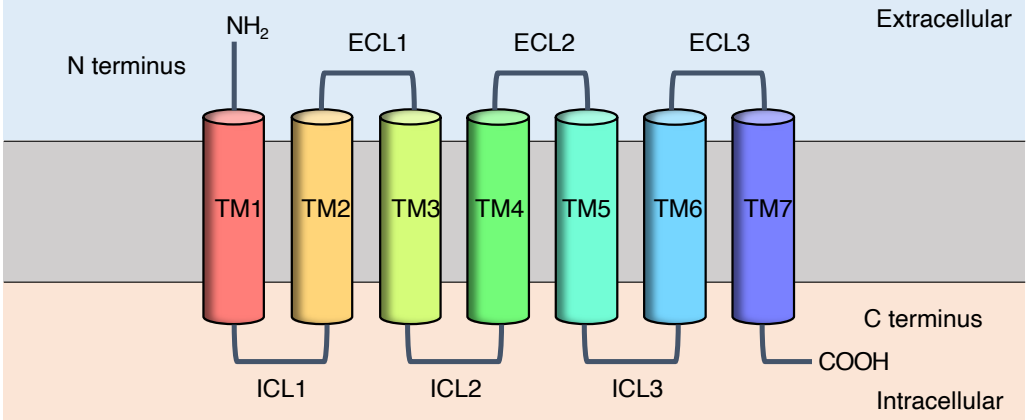


Figure 1. The structure of a GPCR. Here, ICL stands for intracellular loops, ECL stands for extracellular loops, and TM stands for transmembrane.

The dynamic character of GPCRs results in equilibrium between various structures, including their active or inactive forms, in the cell membrane (Figure 2). Agonists are ligands that bind to GPCRs and shift the equilibrium to the active form ($\alpha > 0$), whereas antagonists do not shift the equilibrium ($\alpha = 0$), contributing to the regulation of various physiological effects. Cells contain three types of G proteins, i.e., G_α (further divided into $G_{\alpha s}$, $G_{\alpha i/o}$, $G_{\alpha q}$, etc.), G_β, and G_γ. When a GPCR is transformed to the active form, it binds to these G proteins (Figure 3). Subsequently, a guanosine diphosphate (GDP) to guanosine triphosphate (GTP) exchange reaction occurs to dissociate the G_α and $G_{\beta\gamma}$ units, which are further converted into intracellular signals through their action on downstream effectors.[3]

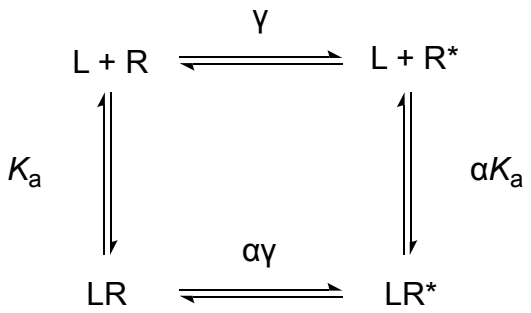


Figure 2. Equilibrium between ligands and GPCRs. L: ligand, R: GPCR (inactive form), R*: GPCR (active form), K_a: equilibrium constant, γ: R*/R, α : ratio of the affinity of L to R and R*

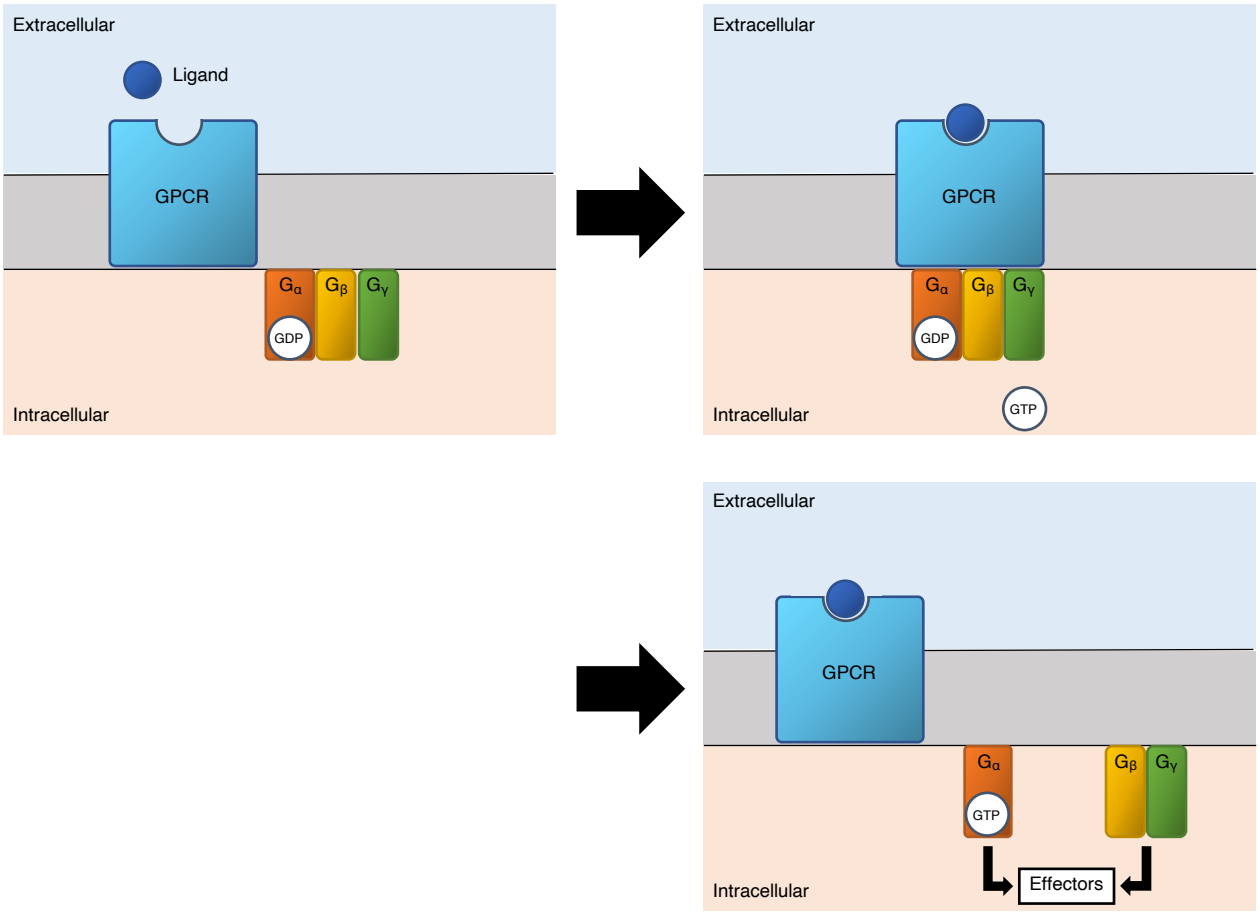


Figure 3. Outline of the activation mechanism of GPCRs

1.2 G-protein-coupled receptors as a drug target

Since many chemicals generally have difficulty penetrating cell membranes, GPCRs, which transmit various external stimuli inside cells, are important drug targets. Drugs that target GPCRs accounted for about 30% of all drugs approved by the United States Food and Drug Administration (FDA) as of 2017.[4,5] Recent remarkable developments in structural biology and computational chemistry have allowed for more detailed analyses and predictions of ligand–receptor binding modes, enabling more efficient drug discovery. Nevertheless, only 108 GPCRs (27% of the non-olfactory GPCRs) are currently targeted by FDA-approved drugs (Figure 4).

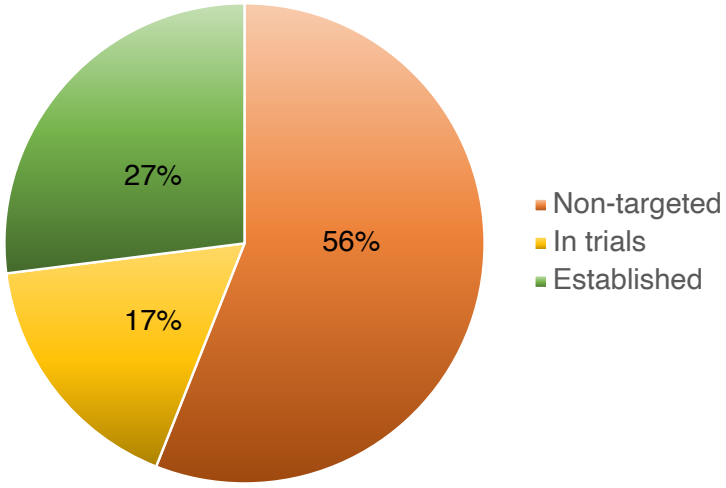


Figure 4. The status of non-olfactory GPCRs in drug discovery[4]

Thus, a large portion of the non-olfactory GPCRs remain untargeted receptors for marketed drugs. It is still important to identify the ligands that act on such receptors or have new properties to uncover new lead compounds for therapeutic agents. In particular, in the field of drug discovery, determining the compounds acting on specific receptors helps reduce the risk of side effects and explore receptor functions. Thus, this doctoral thesis describes the molecular design and structural optimization for the discovery of agonists of orexin 2 receptor (OX_2R) in Chapter 2, orexin 1 receptor (OX_1R) in Chapter 3, and Mas-related G-protein-coupled receptor X2 (MRGPRX2) in Chapter 4 to create lead compounds for pharmaceuticals and chemical tools to explore receptor functions.

Chapter 2. Design and synthesis of orexin 2 receptor agonists with a tetralin skeleton

2.1 Orexins and orexin receptors

Orexin A (OXA) and B (also known as hypocretin 1 and 2, respectively) are hypothalamic neuropeptides independently identified as ligands for orphan GPCRs by Sakurai et al. and de Lecea et al. in 1998.[6,7] These endogenous peptides are produced in specific neurons in the lateral hypothalamic area via proteolytic cleavage from prepro-orexin. They act on OX_1R (coupled with G_q protein) and OX_2R (coupled with $G_{i/o}$ or G_q protein).[8,9] When orexins were first discovered, the orexin/orexin receptor system was considered to regulate feeding behavior and was later revealed to play important roles in sleep/wakefulness,[10–15] reward-seeking,[16,17] and stress responses as well.[18–20]

Many studies regarding the relationship between orexin and sleep/wakefulness have been conducted within the last 20 years. For instance, Chemelli et al. showed that lack of prepro-orexin causes narcolepsy in mice, i.e., a chronic sleep disorder characterized by excessive daytime sleepiness and cataplexy, and Lin et al. reported that canine narcolepsy is caused by OX_2R disruption.[10,11] In a rescue experiment, intracerebroventricular (i.c.v.) administration of OXA attenuated narcoleptic symptoms in orexin neuron–ablated mice,[21] indicating the orexin/orexin receptor system's involvement in narcolepsy. Moreover, in a study focused on the function of each receptor subtype, the OX_2R knockout (KO) mice showed a decrease in wakefulness and an increase in non-rapid-eye-movement (REM) sleep, while OX_1R KO had little effect on the sleep or awake states of the mice.[14,22,23] Furthermore, the i.c.v. administration of OXA was shown to significantly increase wakefulness and decrease non-REM sleep in wild-type and OX_2R KO mice compared with OX_1R KO mice.[24] Therefore, OX_2R is closely involved in the regulation of arousal/sleepiness and the pathophysiology of narcolepsy.

The relationship between narcolepsy and the orexin/orexin receptor system has also been observed in human subjects. In the early 2000s, several pathological studies revealed that an orexin peptide deficiency and a decreased number of orexin neurons were observed in patients with human narcolepsy type I (narcolepsy with cataplexy).[25–28]

2.2 The history of the development of orexin 2 receptor agonists for narcolepsy treatment

Narcolepsy is caused by an orexin deficiency, and only symptomatic drugs with considerable side effects are currently available for its treatment.[29,30] Although i.c.v. administration of orexin peptides can improve narcolepsy symptoms, such an invasive administration method is not practical. In addition, it is difficult to develop orexin peptides with low blood–brain barrier (BBB) permeability as drugs for peripheral administration since orexin receptors are specifically expressed in the brain. Thus, orally available selective small molecule OX_2R agonists are expected to be attractive chemotherapeutic agents for narcolepsy.

In 2010, benzimidazole-type OX_2R agonist Yan 7874 was reported in the patent,[31] but a later study showed that this compound has weak potency for both receptors and cytotoxicity (Figure 5).[32] In 2015, the first non-peptidic OX_2R selective agonist, YNT-185 (median effective concentration [EC_{50}] = 2,750 nM for OX_1R, 28 nM for OX_2R, OX_1R/OX_2R = 98), which has a diarylsulfonamide group, was identified via optimization of hit compound obtained via screening.[33] A subsequent study showed that i.c.v. and intraperitoneal administration of YNT-185 increased the wake time in wild-type mice but not in $OX_{1/2}R$ double KO mice and ameliorated narcolepsy symptoms in orexin KO mice.[34] These results demonstrate the usefulness of OX_2R selective small molecule agonists for treating narcolepsy, but further clinical studies have yet to be conducted due to the agonists' limited *in vivo* efficacy. Several OX_2R agonists have since been reported,[35–40] including piperidine-type agonist TAK-925 (which has excellent potency and selectivity for OX_2R) and TAK-994 (whose chemical structure has not yet been disclosed).[37] These compounds have been clinically developed for the indication of narcolepsy type I; TAK-925 has completed Phase I clinical trials, but research on TAK-994 has been halted at Phase II clinical trials due to safety concerns. Diarylsulfonamide-type agonist **1** has also shown remarkable potency and selectivity for OX_2R.[38] Although copious effort has gone into the development of novel OX_2R agonists with a new chemotype with the desired chemical and pharmacological properties for use in narcolepsy treatment, none have been introduced to the market yet.

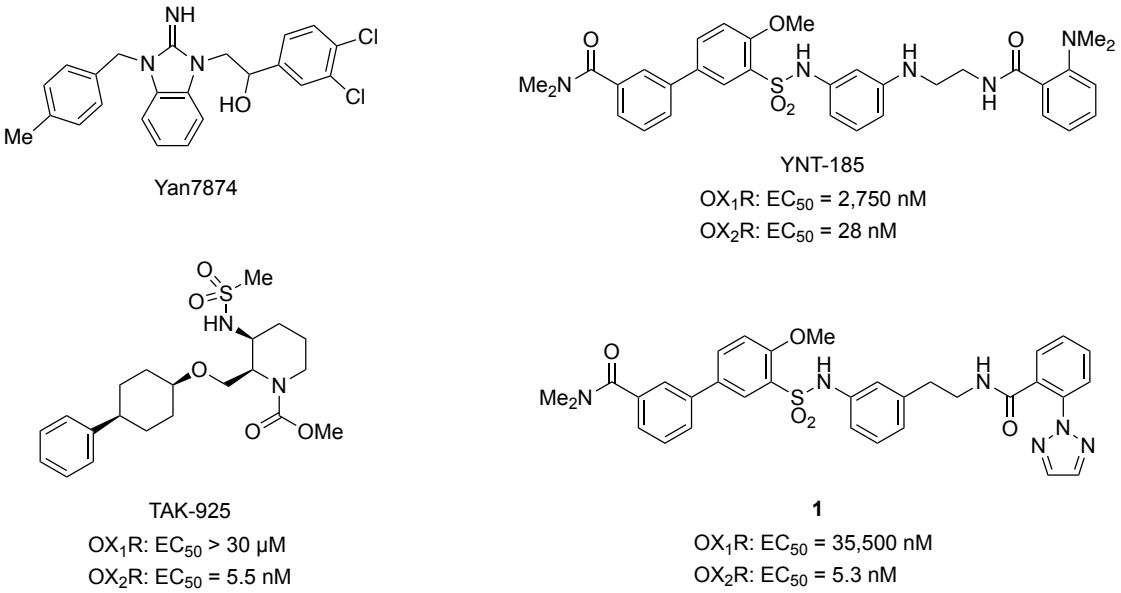


Figure 5. The structure of OX_2R agonists

2.3 The drug design of tetralin ligands toward potent OX_2R agonists

Naphthalene-type OX_2R agonists are designed based on the chemical structure of YNT-185, which can take on two conformation types, i.e., the extension form and bending form (Figure 6).[40] During the discovery of naphthalene ligand **4**, Nagase et al. restricted the rotation of the C1-N1 bond of YNT-185 to imitate both forms. As a result, 1,7-naphthalene derivative **3** (similar to the bending form) is more potent for OX_2R than 2,7-naphthalene derivative **2** (similar to the extension form), implying that the bending form of YNT-185 is preferable for OX_2R agonistic activity. The subsequent optimization of 1,7-naphthalene derivative **3** led to the discovery of potent naphthalene-type OX_2R agonist **4**.

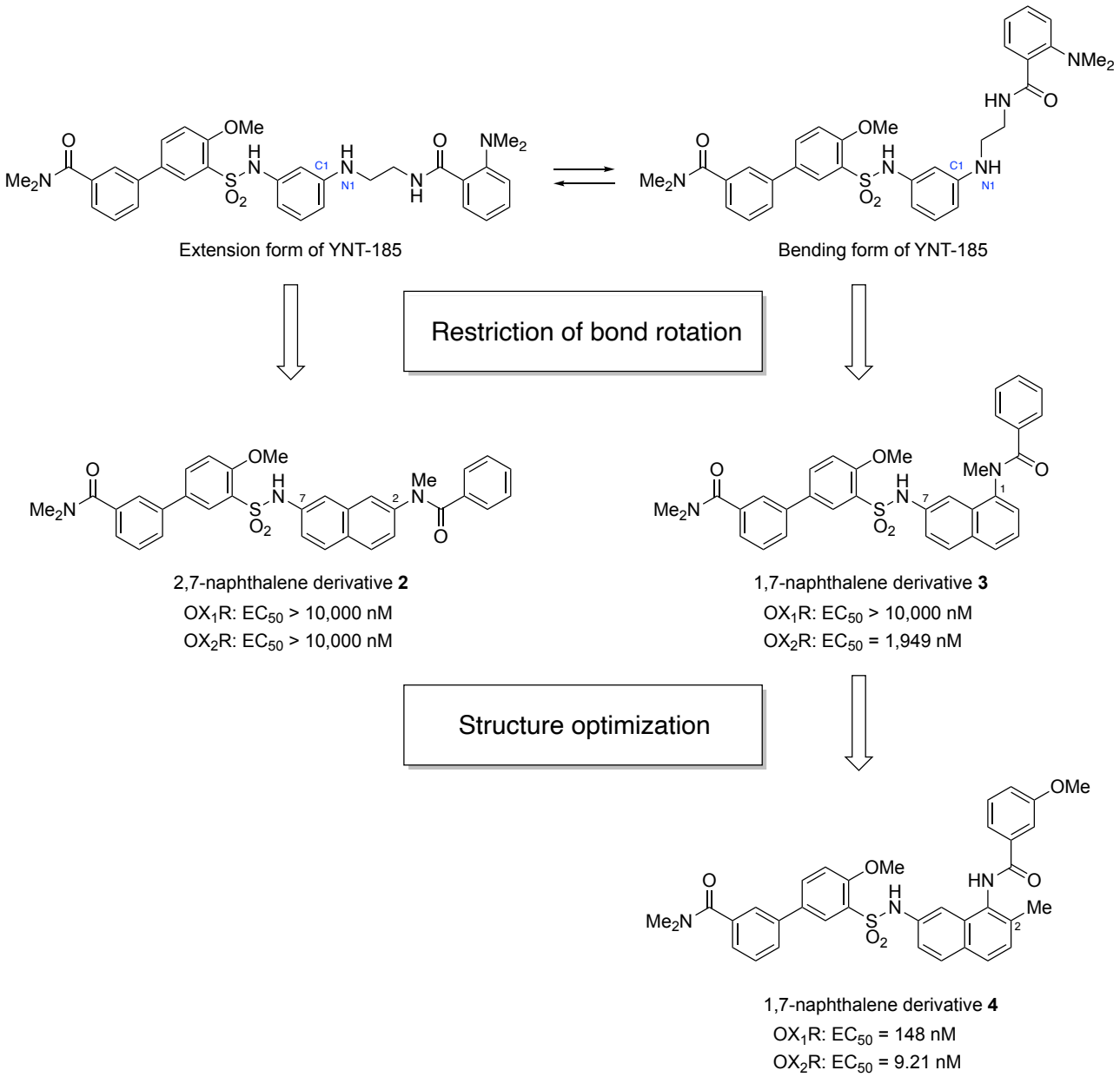


Figure 6. The restriction of the bond rotation of YNT-185 and the discovery of naphthalene-type agonists

In a docking study with OX_2R, naphthalene-type agonist **4** extended the amide chain to the vertical orientation against the naphthalene ring to form a hydrogen bond with histidine 350 (Figure 7). The study's conformational analysis suggested that the 2-methyl group contributed to the amide unit's vertical orientation by steric repulsion, which was supported by the difference in potency between 2-desmethyl derivative **3** and 2-methyl derivative **4**. As such, in the current study, it was hypothesized that a more flexible skeleton with an sp^3 carbon at C1 would be able to arrange the amide side chain to interact with the histidine residue more efficiently (Scheme 1). Thus, a series of tetralin derivatives were designed and synthesized to identify OX_2R agonists more potent than those already reported.

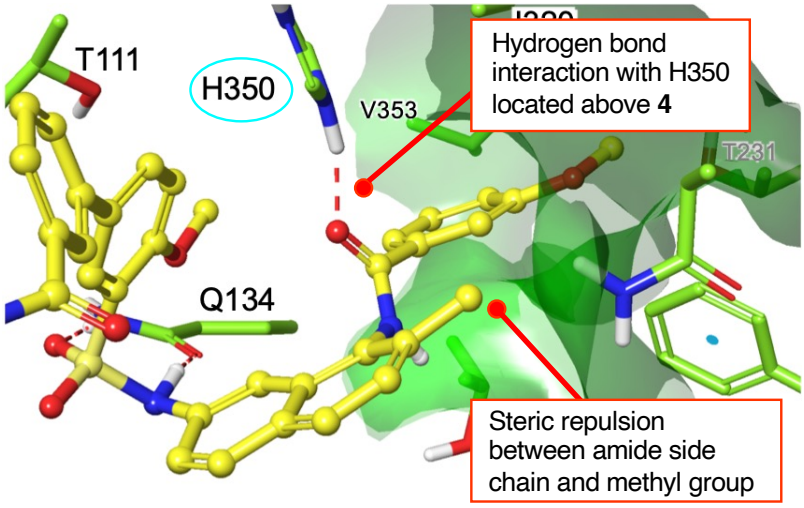
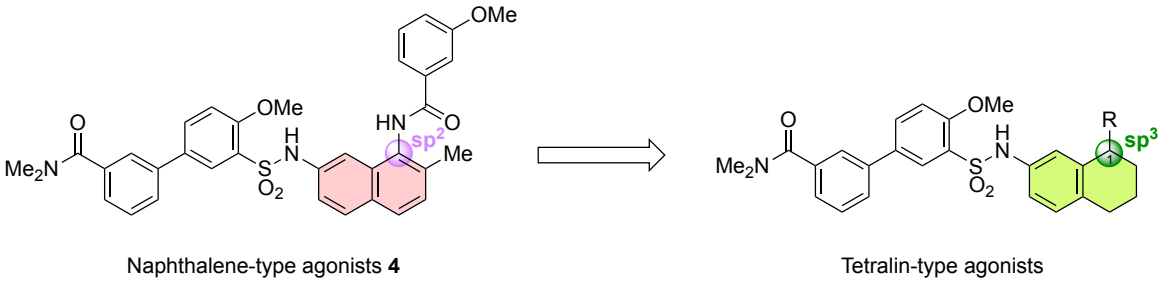


Figure 7. The docking simulation between naphthalene agonist **4** and OX_2R



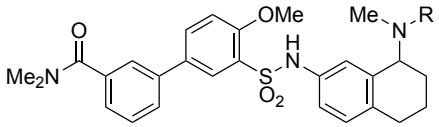
Scheme 1. The molecular design of tetralin-type agonists based on naphthalene-type agonist **4**

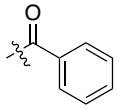
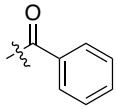
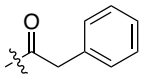
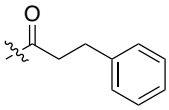
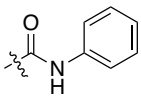
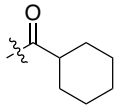
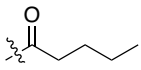
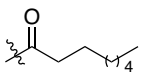
2.4 The discovery of 5j

To start, the amide side chain of the tetralin skeleton was investigated (Table 1). The racemic derivatives' agonistic activity was evaluated by a calcium influx assay utilizing the fact that the orexin receptors were coupled with G_q protein. Naphthalene-type agonist **3** was listed as a control compound. Compound **5a**, which has the same benzoyl group as naphthalene derivative **3,** showed 3.2-fold stronger OX_2R agonistic activity than the derivative. The insertion of one carbon atom between the carbonyl and phenyl groups drastically increased the agonistic activity for both receptors (**5b**), but the introduction of the phenethyl group led to decreased activity, especially for OX_2R (**5c**). Urea-type derivative **5d**, in which the benzylic methylene carbon of **5b** was substituted for a nitrogen, had weak agonistic activity for both receptors, implying that conformation of the carbonyl unit affected the interaction between the ligand and orexin receptor (OXR). To examine the effect of the terminal aromatic ring, alkyl amide derivatives were also evaluated. The cyclohexyl (**5e**) and *n*-butyl derivatives (**5f**) showed moderate activity, while the *n*-octyl derivative (**5g**) showed almost no activity, suggesting that the terminal aromatic ring and its arrangement are significant for tetralin derivatives' agonistic activity for OXRs. The most potent tetralin derivative in Table 1 (**5b**) exhibited more potent OX_1R agonistic activity than YNT-185 and naphthalene-type agonist **4**, implying that a moderately flexible tetralin skeleton is preferable for the development of $OX_{1/2}R$ dual agonists, which may be distinct from reported OX_2R agonists.

Next, the substituents on the terminal aromatic ring in **5b**, which had the best potency (Table 2), were explored. To start, the methoxy group used in naphthalene agonist **4** was introduced into the *ortho*, *para*, and *meta* positions, and the agonistic activity toward OX_2R was enhanced in all cases (**5h–j**). As the *meta*-methoxy derivative showed the most potent OX_2R agonistic activity among these regioisomers, other substituents were introduced to the *meta* position. The hydroxy group's (**5k**) introduction substantially reduced the activity for both receptors, suggesting that this group's placement at the *meta* position is not preferable for agonistic activity enhancement. Conversion of the methoxy group to the ethoxy (**5l**), dimethylamino (**5m**), and fluoro (**5n**) groups resulted in a slight decrease in activity, but no significant difference was observed between the derivatives with electron-donating and electron-withdrawing groups. However, the pyridine derivative (**5o**) showed greatly decreased agonistic activity for both receptors.

Table 1. Orexin receptor agonist activities of **3** and, **5a**–**g**

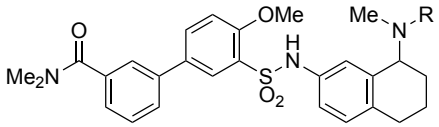


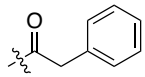
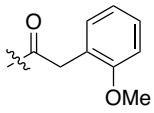
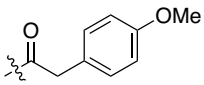
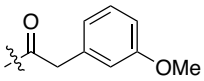
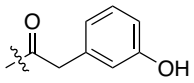
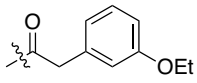
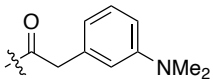
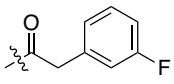
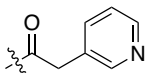
Compounds	R	EC$_{50}$ (nM) [E_{max} (%)[a]]		Selectivity (OX$_1$R/OX$_2$R)
		OX$_1$R	OX$_2$R	
3[b]		> 10,000 [50.8]	1,949 [119]	–
5a		> 10,000 [8.61[c]]	618 [114]	–
5b		112 [83.7]	10.7 [100]	10.5
5c		372 [88.4]	126 [108]	2.95
5d		3,252 [69.7[c]]	140 [110]	23.2
5e		>10,000 [44.3[c]]	837 [113]	–
5f		4,180 [89.5[d]]	1,918 [125]	2.18
5g		_[d] [–[d]]	_[d] [–[d]]	–

[a] E_{max} is expressed as a percentage of OXA maximum. [b] **3** has a naphthalene skeleton instead of a tetralin skeleton.

[c] The value obtained at 10 μM was used. [d] Not tested due to the weak potency.

Table 2. Orexin receptor agonist activities of **5b** and **5h**–**o**



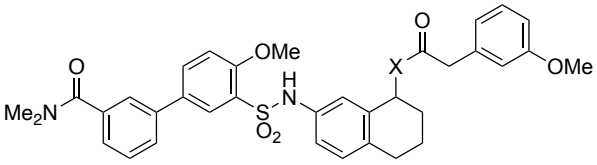
Compounds	R	EC$_{50}$ (nM) [E_{max} (%)[a]]		Selectivity (OX$_1$R/OX$_2$R)
		OX$_1$R	OX$_2$R	
5b		112 [83.7]	10.7 [100]	10.5
5h		92.2 [81.7]	3.59 [90.4]	25.7
5i		120 [94.3]	3.63 [112]	33.1
5j		30.7 [99.6]	1.51 [104]	20.3
5k		713 [96.3]	57.0 [99.9]	12.5
5l		55.3 [106]	2.14 [96.3]	25.8
5m		89.0 [79.2]	5.59 [96.9]	15.9
5n		86.3 [90.8]	6.50 [99.5]	13.3
5o		1,182 [122]	151 [108]	7.83

[a] E_{max} is expressed as a percentage of OXA maximum.

As shown in Tables 1 and 2, the *N*-methyl amide unit was fixed as the spacer linking the backbone to the terminal aromatic ring, so its effects were investigated (Table 3). The conversion of the amide moiety to ester **6a** significantly lowered the agonistic activity for both receptors. A decrease in the activity was also observed when tertiary amides (**5j**) were converted to secondary amides (**6b**), indicating that esters and secondary

amides, which tend to take the *trans* conformation, are unlikely to adopt the desired active conformation. The activity was also decreased when bulky substituents, such as the ethyl (**6c**), *n*-propyl (**6d**), and cyclopropylmethyl (**6e**) groups, were introduced into the nitrogen atom at the amide unit instead of the methyl group. This suggested that tertiary amides with small substituents, such as methyl groups (**5j**), are more likely to adopt a favorable conformation for the expression of agonistic activity for OXR. When the spacer unit was modified, the potency for OXR changed significantly (Table 3), indicating the importance of either the spacer itself or the difference in conformation depending on the spacer.

Table 3. Orexin receptor agonist activities of **5j** and **6a**–**e**



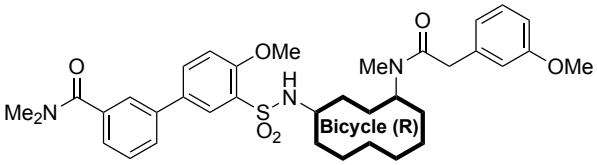
Compounds	X	EC_{50} (nM) [E_{max} (%)[a]]		Selectivity (OX_1R/OX_2R)
		OX_1R	OX_2R	
5j	NMe	30.7 [99.6]	1.51 [104]	20.3
6a	O	5,782 [13.7]	413 [117]	14.0
6b	NH	229 [124]	26.6 [100]	8.61
6c	NEt	356 [118]	19.3 [92.6]	18.4
6d	N^{n}Pr	3,917 [113]	43.7 [93.2]	89.6
6e	NCPM	> 10,000 [18.7[b]]	78.1 [101]	–

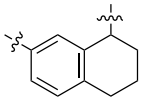
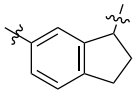
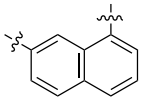
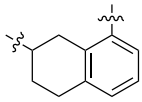
[a] E_{max} expressed as a percentage of OXA maximum. [b] The value obtained at 10 μM was used.

As highly potent derivative **5j** was successfully obtained by optimizing the amide side chain, a skeleton comparison was conducted (Table 4). The tetralin skeleton was converted to an indane skeleton (**7a**) which also has an sp^3 carbon. As a result, the potency of **7a** for OX_2R was slightly decreased—although its selectivity for OX_2R was improved. In contrast, naphthalene derivative **7b** and 2,8-substituted tetralin derivative **7c**, in

which the amide side chain is attached to the sp^2 carbon, showed a remarkable decrease in agonistic activity for both receptors, while their selectivity toward OX_1R tended to increase. This indicated that the amide side chain's vertical orientation to the backbone by the sp^3 carbon is important for the potency for both subtypes and that its horizontal orientation to the backbone by the sp^2 carbon could contribute to the interaction with OX_1R. In summary, the tetralin skeleton with the *N*-methyl amide linker was most suitable for the potent OX_2R agonist. Further pharmacological evaluation may elucidate the compound **5j**'s therapeutic potential.

Table 4. Orexin receptor agonist activities of **5j** and **7a**–**c**

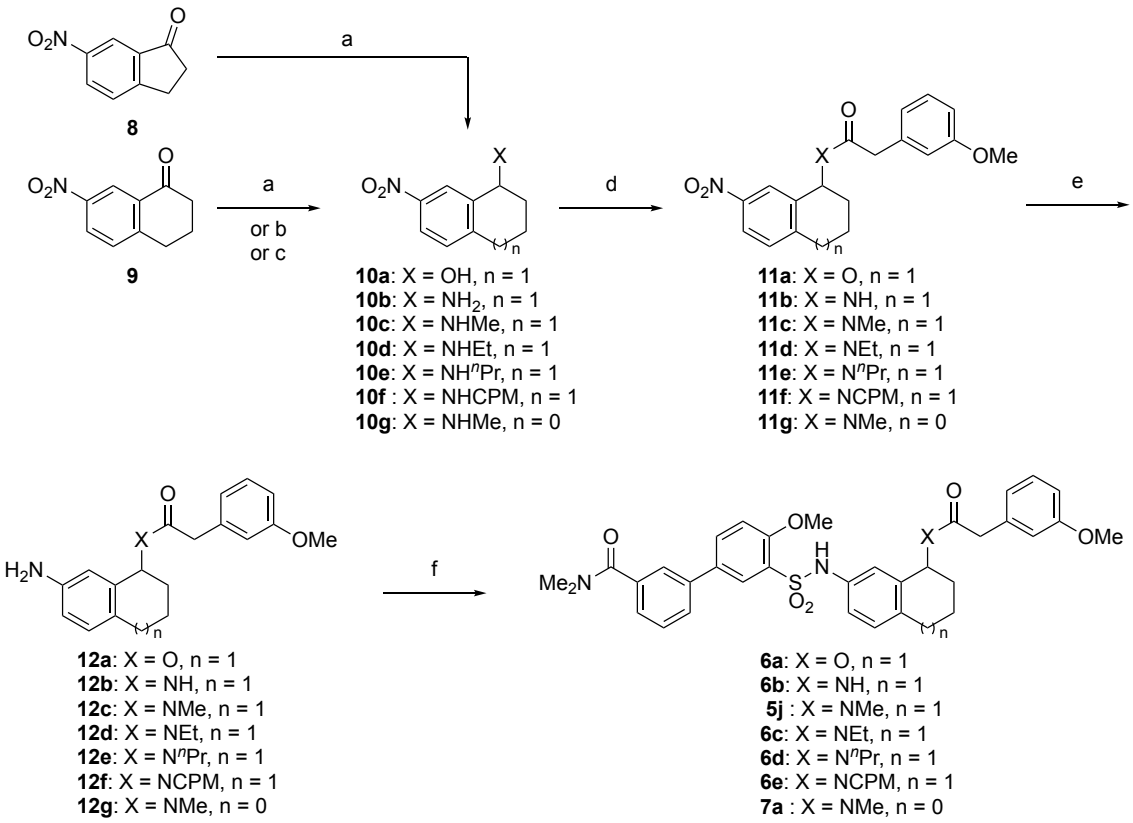


Compounds	R	EC_{50} (nM) [E_{max} (%)[a]]		Selectivity (OX_1R/OX_2R)
		OX_1R	OX_2R	
5j		30.7 [99.6]	1.51 [104]	20.3
7a		287 [92.1]	3.27 [86.6]	87.8
7b		402 [92.1]	224 [86.6]	1.79
7c		5,485 [75.3[b]]	> 10,000 [39.9[b]]	–

[a] E_{max} expressed as a percentage of OXA maximum. [b] The value obtained at 10 μM was used.

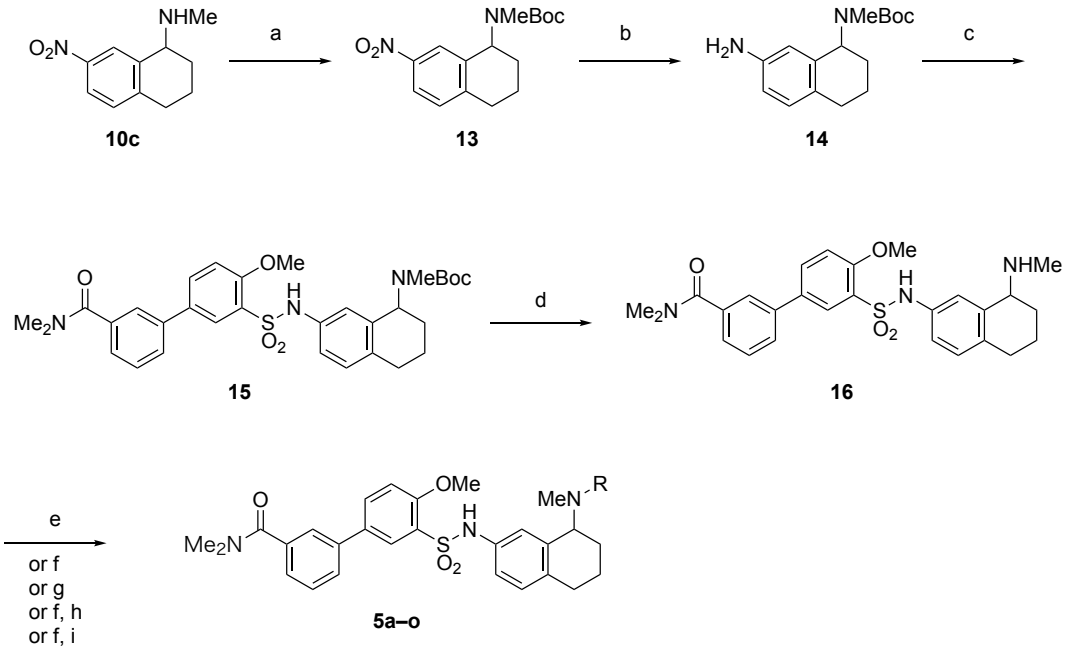
2.5 Synthesis

The reductive amination of 6-methoxy-1-indanone (**8**) and 7-nitro-1-tetralone (**9**) with the corresponding amines yielded **10b–g**. Alcohol **10a** was obtained as a by-product in the synthesis of **10c**. The condensation of alcohol **10a** and amines **10b–g** with 3-methoxyphenylacetic acid, followed by the Bechamp reduction of the nitro group, yielded anilines **12a–g**, which were reacted with 3'-(dimethylcarbamoyl)-4-methoxy-[1,1'-biphenyl]-3-sulfonyl chloride[41] to generate **5j**, **6a–e**, and **7a** (Scheme 2).



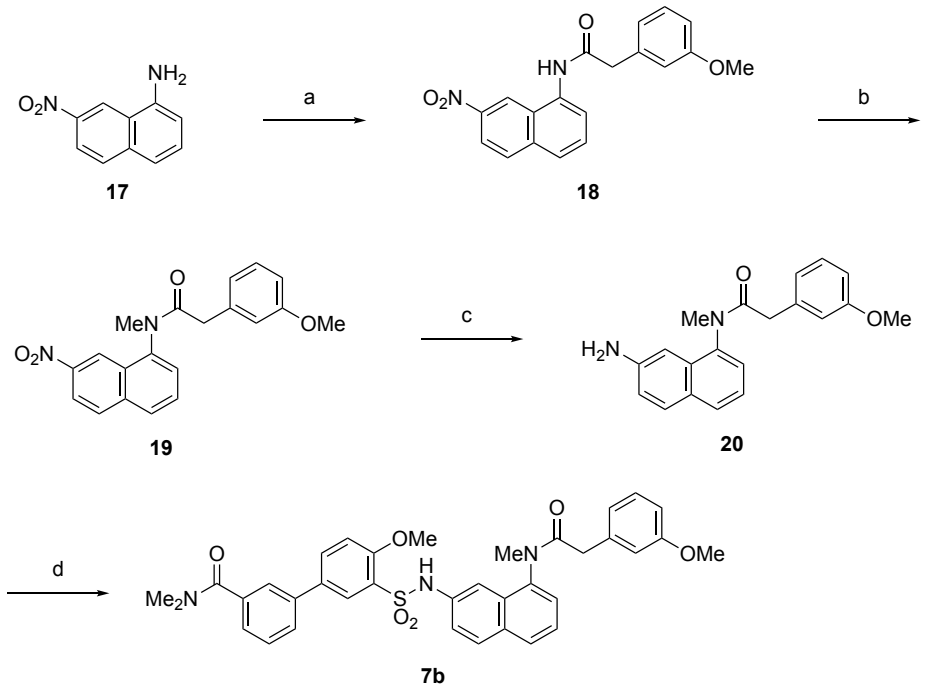
Scheme 2. Reagents and conditions for the synthesis of compound **5j**, **6a–e**, and **7a**: (a) $MeNH_2 \cdot HCl$, $NaBH_3CN$, MeOH or MeOH/THF, reflux, 17–72%; (b) NH_4OAc, $NaBH_3CN$, MeOH, r.t., 37%; (c) RNH_2 ($\cdot HCl$), $NaBH_3CN$, AcONa, AcOH, MeOH, reflux, 51–84%; (d) 3-methoxyphenylacetic acid, HATU, DIPEA or Et_3N, DMF or CH_2Cl_2, r.t.; (e) Fe, NH_4Cl, EtOH, H_2O, 60 or 90 ˚C, 42–96% in 2 steps, (f) 3'-(dimethylcarbamoyl)-4-methoxy-[1,1'-biphenyl]-3-sulfonyl chloride[41], pyridine, CH_2Cl_2, r.t., 84%–quant.

Amine **10c** was protected by the *tert*-butoxycarbonyl (Boc) group, and the reduction of the nitro group yielded aniline **14**. Condensation with 3'-(dimethylcarbamoyl)-4-methoxy-[1,1'-biphenyl]-3-sulfonyl chloride, followed by deprotection of the Boc group, gave amine **16**, which was converted to corresponding derivatives **5a–o** (Scheme 3).



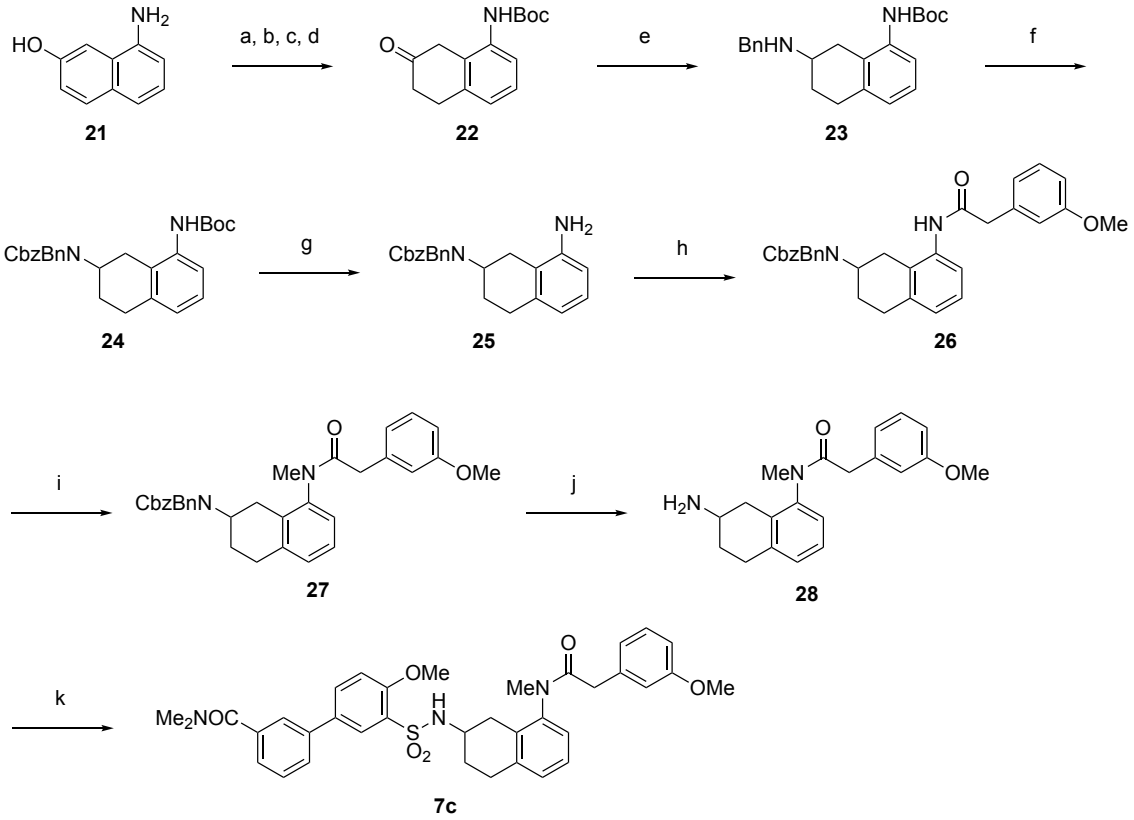
Scheme 3. Reagents and conditions for the synthesis of compound **5a**–**o**: (a) Boc_2O, Et_3N, CH_2Cl_2, r.t., 97%; (b) Fe, NH_4Cl, EtOH, H_2O, 60 ˚C, 87%; (c) 3'-(dimethylcarbamoyl)-4-methoxy-[1,1'-biphenyl]-3-sulfonyl chloride, pyridine, CH_2Cl_2, r.t., 94%; (d) TFA, CH_2Cl_2, r.t., 82%; (e) RCOOH, HATU, Et_3N or DIPEA, DMF or CH_2Cl_2, r.t., 63–96%; (f) RCOCl, pyridine or Et_3N, CH_2Cl_2, r.t., 50%–quant.; (g) benzoic acid, DPPA, Et_3N, benzene, reflux, 82%; (h) K_2CO_3, MeOH, r.t., 93%; (i) 6 M NaOH aq., THF, r.t., 86%. The detailed R groups for **5a–o** are shown in experimental section.

The condensation of aniline **17**[40] with 3-methoxyphenylacetic acid, followed by methylation, yielded compound **19**. After the reduction of the nitro group in **19**, **7b** was obtained via sulfonamidation with 3'-(dimethylcarbamoyl)-4-methoxy-[1,1'-biphenyl]-3-sulfonyl chloride (Scheme 4).



Scheme 4. Reagents and conditions for the synthesis of compound **7b**: (a) 3-methoxyphenylacetic acid, HATU, DIPEA, CH_2Cl_2, r.t., 89%; (b) MeI, NaH, THF, r.t., 53%; (c) Fe, NH_4Cl, EtOH, H_2O, 60 ˚C, 78%; (d) 3'-(dimethylcarbamoyl)-4-methoxy-[1,1'-biphenyl]-3-sulfonyl chloride, pyridine, CH_2Cl_2, r.t., quant.

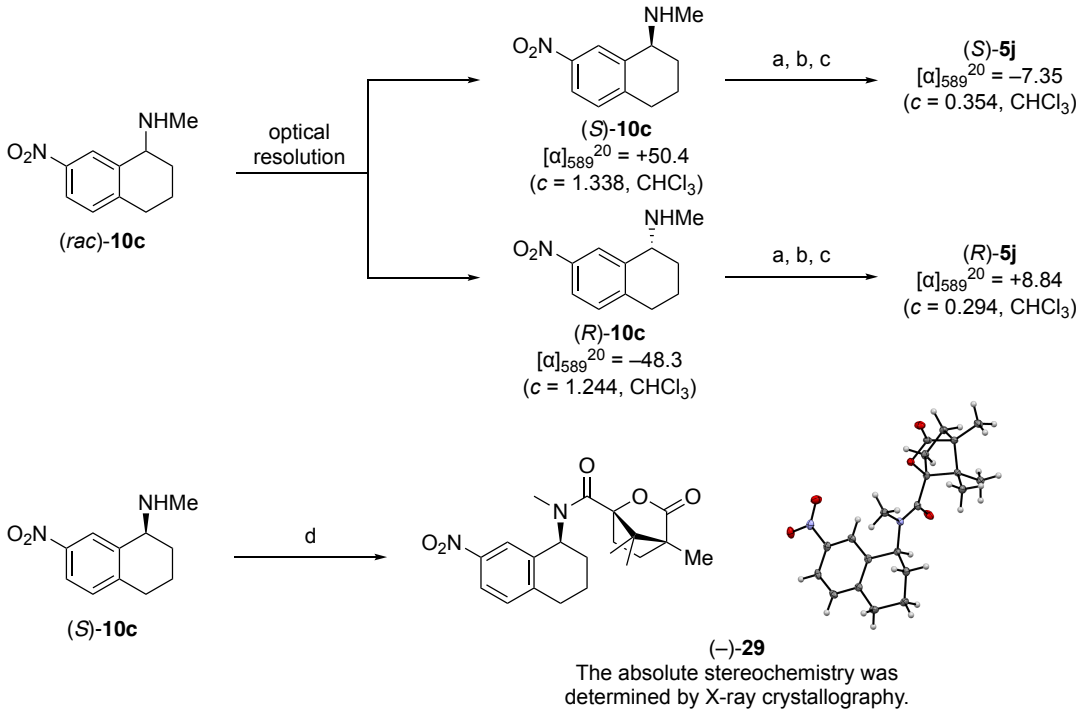
Ketone **22** was synthesized in four steps from commercially available 8-amino-2-naphthol (**21**), referring to previous reports.[42] The reductive amination of **22** with benzylamine and protection with the benzyloxycarbonyl group gave **24**. After deprotection of the Boc group in **24**, resulting aniline **25** was converted to **27** using a similar method as the synthesis of **19**. The benzyl and benzyloxycarbonyl groups of **27** were simultaneously deprotected by hydrogenation, and resulting amine **28** was reacted with 3'-(dimethylcarbamoyl)-4-methoxy-[1,1'-biphenyl]-3-sulfonyl chloride to yield **7c** (Scheme 5).



Scheme 5. Reagents and conditions for the synthesis of compound **7c**: (a) EtI, Cs_2CO_3, DMF, r.t.; (b) Li, ^{t}BuOH, liq. NH_3. –33 ˚C; (c) 2 M HCl aq., r.t.; (d) Boc_2O, sat. $NaHCO_3$ aq., THF, r.t., 24% in 4 steps; (e) $BnNH_2$, $NaBH_3CN$, AcOH, THF, 60 ˚C, 97%; (f) CbzCl, sat. $NaHCO_3$ aq., THF, r.t.; (g) TFA, CH_2Cl_2, r.t.; (h) 3-methoxyphenylacetic acid, HATU, Et_3N, DMF, r.t., 86% in 3 steps; (i) MeI, NaH, THF, r.t., 81%; (j) H_2, Pd/C, THF, r.t.; (k) 3'-(dimethylcarbamoyl)-4-methoxy-[1,1'-biphenyl]-3-sulfonyl chloride, pyridine, CH_2Cl_2, r.t., 62% in 2 steps.

2.6 Evaluation of the optical isomers of (*rac*)-5j

Tetralin derivative **5j** has a pair of optical isomers because C1 is an asymmetric carbon. Each enantiomer of (*rac*)-**5j** was prepared as follows (Scheme 6): (*S*)-**10c** and (*R*)-**10c** were obtained by the optical resolution of (*rac*)-**10c** using preparative high-performance liquid chromatography (HPLC) (Figures 8–10) because optical resolution via various diastereomeric salts was unsuccessful. The absolute configuration of (*S*)-**10c** was determined by X-ray crystallography of (–)-**29** (Figure 33 and Table 11 in experimental section), which was synthesized by condensation via (–)-camphanic acid with (*S*)-**10c**. Then, (*S*)-**5j** and (*R*)-**5j** were synthesized from (*S*)-**10c** and (*R*)-**10c**, respectively, using the same procedure as Scheme 2 (Scheme 15 and 16 in experimental section), and their optical purities were confirmed by chiral HPLC (Figures 11–13).



Scheme 6. Reagents and conditions for the synthesis of (*S*)-**5j**, (*R*)-**5j**, and (–)-**29**: (a) 3-methoxyphenylacetic acid, HATU, Et_3N, DMF, r.t., 95% for (*S*)-**11c**, 98% for (*R*)-**11c**; (b) Fe, NH_4Cl, EtOH, H_2O, 90 ˚C, 51% for (*S*)-**12c**, 87% for (*R*)-**12c**; (c) 3'-(dimethylcarbamoyl)-4-methoxy-[1,1'-biphenyl]-3-sulfonyl chloride, pyridine, CH_2Cl_2, r.t., 96% for (*S*)-**5j**, 93% for (*R*)-**5j**; (d) (–)-camphanic acid, HATU, Et_3N, DMF, r.t., 91%. The optical resolution was conducted using chiral HPLC (DAICEL CHIRALPAK AD-H, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 98/2). The absolute stereochemistry of the optical isomers of (*S*)-**10c** was determined by X-ray crystallography for (–)-**29**.

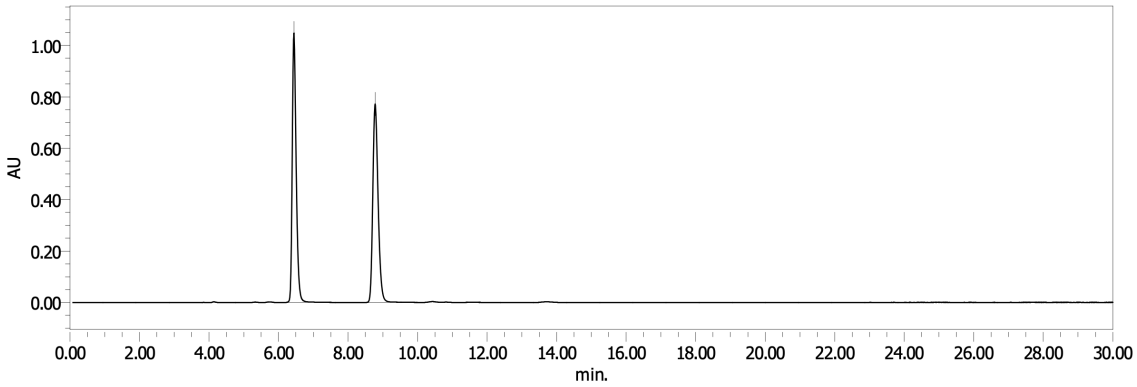


Figure 8. Chiral HPLC chromatogram for (*rac*)-**10c** (DAICEL CHIRALPAK AD-H, 4.6 mm I.D.×250 mmL, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 90/10, flow rate: 1.0 mL/min., λ = 254 nm)

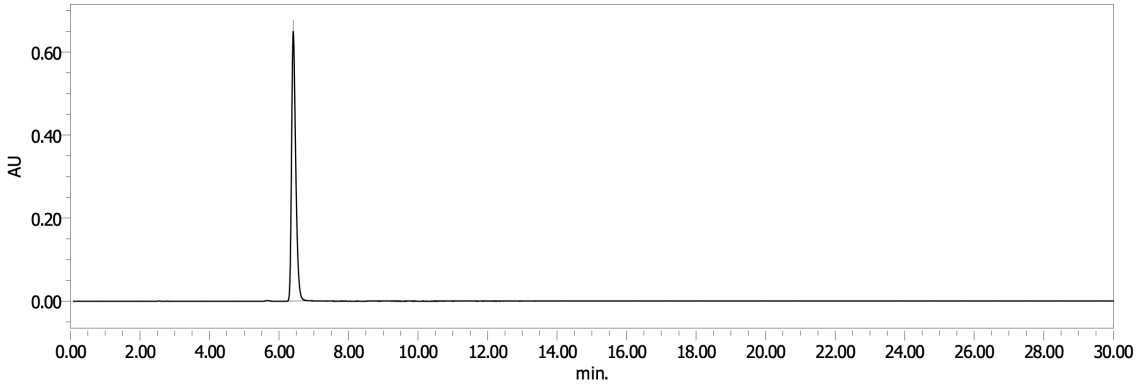


Figure 9. Chiral HPLC chromatogram for (*S*)-**10c** (DAICEL CHIRALPAK AD-H, 4.6 mm I.D.×250 mmL, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 90/10, flow rate: 1.0 mL/min., λ = 254 nm)

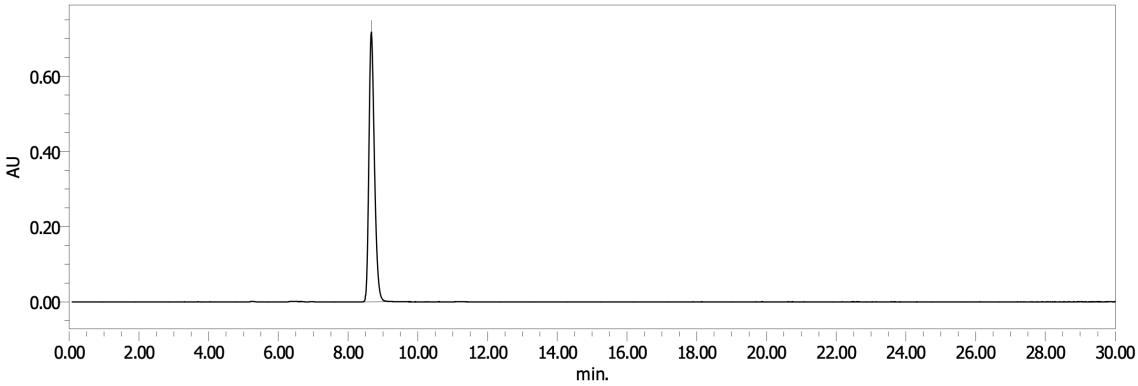


Figure 10. Chiral HPLC chromatogram for (*R*)-**10c** (DAICEL CHIRALPAK AD-H, 4.6 mm I.D.×250 mmL, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 90/10, flow rate: 1.0 mL/min., λ = 254 nm)

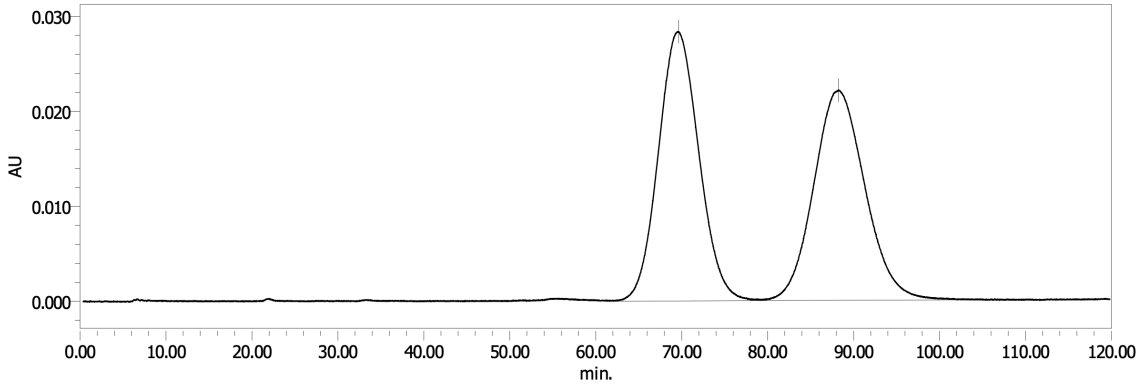


Figure 11. Chiral HPLC chromatogram for (*rac*)-**5j** (DAICEL CHIRALPAK AD-H, 4.6 mm I.D.×250 mmL, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 50/50, flow rate: 1.0 mL/min., λ = 254 nm)

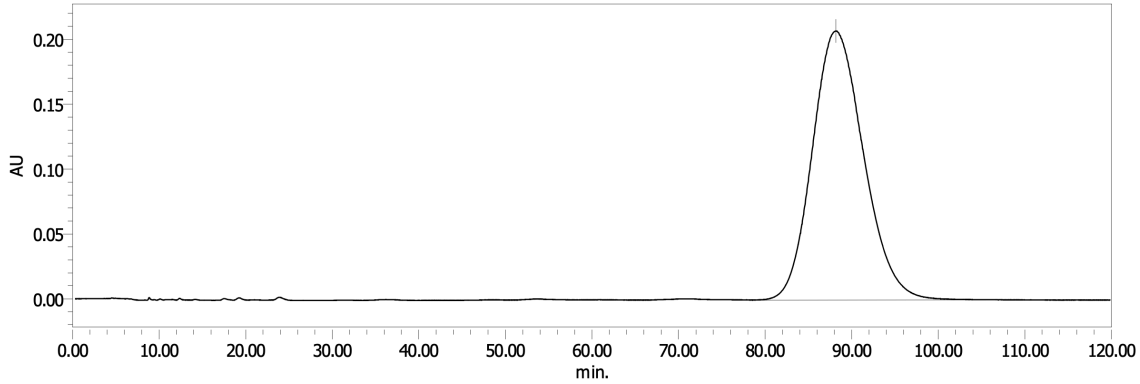


Figure 12. Chiral HPLC chromatogram for (*S*)-**5j** (DAICEL CHIRALPAK AD-H, 4.6 mm I.D.×250 mmL, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 50/50, flow rate: 1.0 mL/min., λ = 254 nm)

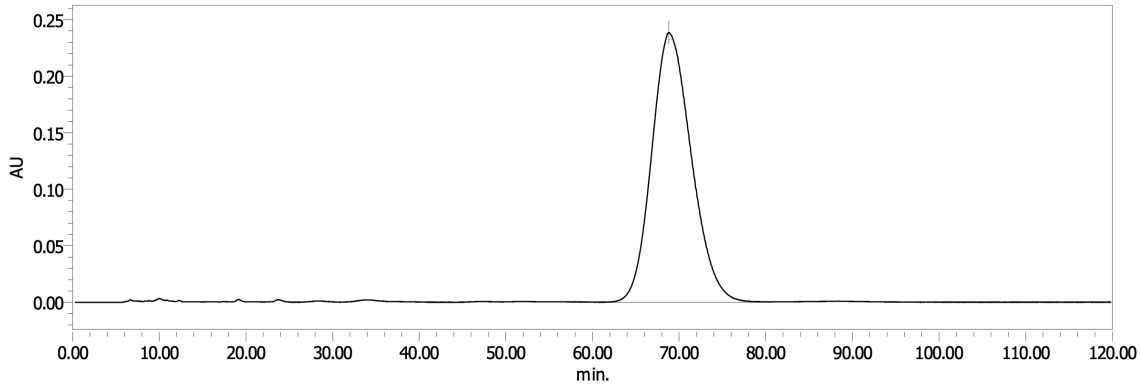


Figure 13. Chiral HPLC chromatogram for (*R*)-**5j** (DAICEL CHIRALPAK AD-H, 4.6 mm I.D.×250 mmL, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 50/50, flow rate: 1.0 mL/min., λ = 254 nm)

To examine the effect of chiral carbons on OXR agonistic activity, the racemate and each optical isomer of **5j** were evaluated in the same system (Figure 14). Overall, (*S*)-**5j** (EC_{50} = 1,240 nM for OX_1R, 2.69 nM for OX_2R, OX_1R/OX_2R = 461) exhibited potent OX_2R agonistic activity 3.4 times stronger than that of naphthalene-type agonist **4**, as expected as well as excellent selectivity for OX_2R owing to its reduced potency for OX_1R. However, its enantiomer, (*R*)-**5j**, showed much more potent OX_2R agonistic activity (EC_{50} = 13.5 nM for OX_1R, 0.579 nM for OX_2R, OX_1R/OX_2R = 23.3). Thus, OX_2R agonist (*R*)-**5j** (approximately 10 times more potent than representative OX_2R ligands TAK-925 and compound **1**) was successfully identified. Interestingly, it also had relatively potent agonistic activity against OX_1R, making it the most potent OXR dual agonist compound reported to date. These results indicated that the aminotetralin skeleton of (*S*)-**5j** is useful for the discovery of OX_2R selective agonists and that the aminotetralin skeleton of (*R*)-**5j** is important for the discovery of dual agonists that act on both OX_2R and OX_1R.

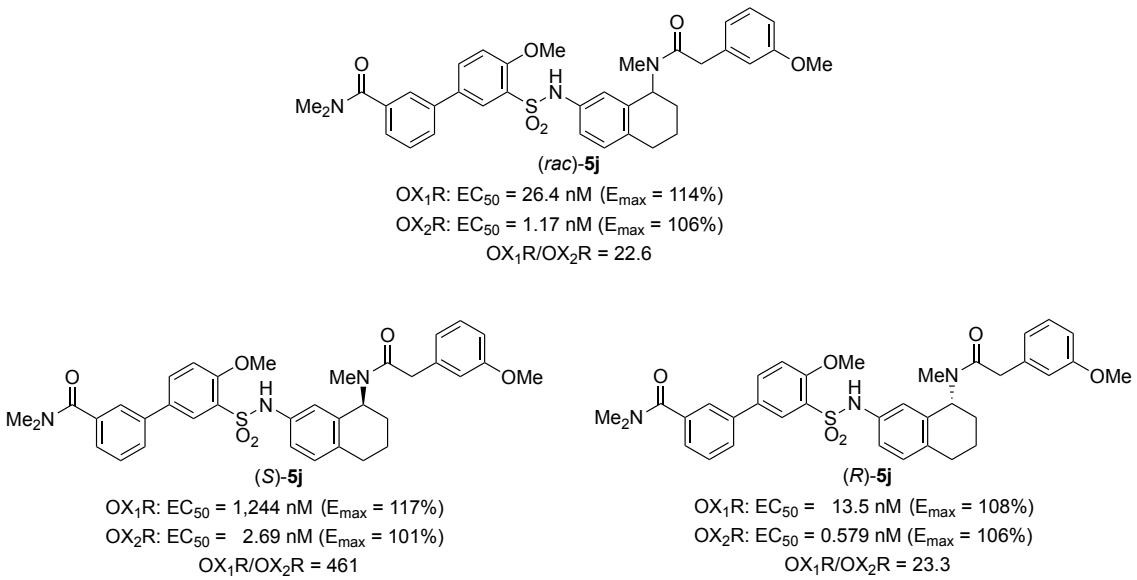


Figure 14. Orexin receptor agonist activities of (*rac*)-**5j**, (*S*)-**5j**, and (*R*)-**5j**

2.7 Conclusion

This chapter explored OX_2R agonists with a higher potency than existing ligands that could serve as lead compounds for narcolepsy treatment. Based on the putative active conformation of naphthalene-type agonist **4** (obtained from the docking simulations), a structural optimization study was performed with the tetralin skeleton, resulting in the successful identification of OX_2R agonist **5j**, which is more potent than YNT-185, compound **1**, TAK-925, and naphthalene-type agonist **4**. This improvement in potency can be attributed to the fixation of the side chain in the desired position by the tetralin skeleton of **5j**. Interestingly, each enantiomer of **5j** exhibited distinct pharmacological activity. For instance, (*S*)-**5j** showed potent agonistic activity and excellent selectivity for OX_2R, while (*R*)-**5j** showed much stronger OX_2R agonistic activity than (*S*)-**5j** and relatively higher agonistic activity for OX_1R. The fact that a single carbon stereocenter in the tetralin skeleton controls the OXR selectivity is highly intriguing. These results will not only encourage future pharmacological evaluation of tetralin ligands but also provide insight into OX_1R agonist development.

Chapter 3. Design and synthesis of orexin 1 receptor agonists with a tetralin skeleton

3.1 Functional overview of orexin 1 receptor

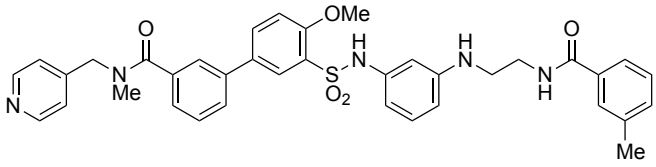
As mentioned in Chapter 2, OX_2R is involved in the regulation of wakefulness and sleep, for which OX_1R is also presumed to play a certain role.[14] Moreover, $OX_{1/2}R$ dual antagonists are known to be more effective at promoting sleep than OX_2R selective antagonists.[43] In addition, OXA-induced increase in wakefulness is decreased not only in OX_2R KO mice but also in OX_1R KO mice.[24] However, OX_1R KO mice exhibit normal sleep/wake phenotype, whereas OX_2R KO mice distinctly exhibit narcoleptic phenotype such as cataplexy-like episodes and fragmentation of wakefulness, albeit more mildly than $OX_{1/2}R$ KO mice.[14,22,23] These evidence suggest that OX_2R is crucial for stability of wakefulness, whereas OX_1R has only marginal roles on the regulation of sleep/wake state when OX_2R-mediated signaling is intact.

OX_1R is thought to have emerged later than OX_2R in terms of evolution.[44] Phylogenetically, OX_1R is present only in the genomes of mammals, whereas OX_2R is present in all vertebrates. This suggests that OX_1R may contribute to the higher level of brain function than OX_2R. Orexin neurons have several roles such as regulation of feeding behavior,[6,45] analgesia,[46] energy homeostasis,[47,48] emotion,[19,20,49,50] autonomic function,[51,52] other than regulation of sleep and wakefulness. Interestingly, these physiological functions are massively regulated by OX_1R. However, the methods of these studies are mainly limited to phenotype analysis in OX_1R KO mice or the mice administered with both orexin peptides and selective OX_1R antagonists. In addition, the administration of the orexin peptides requires surgical invasion to the animal brain because peripherally administered peptides cannot transfer to the brain. Therefore, small-molecule selective OX_1R agonists can be another important tool for addressing those problems and allow for a more direct investigation of function of OX_1R under physiological condition by systemic administration.

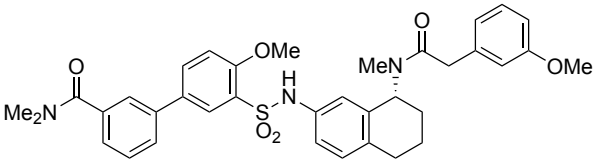
3.2 The drug design of tetralin ligands toward potent OX_1R agonists

Receptor selective ligands may not only be important chemical tools in the elucidation of receptor functions and receptor-related biological phenomena but could also be lead compounds for the drug discovery research that follows. As discussed in Chapter 2, there are several reports on OX_2R selective agonists, including YNT-185, TAK-925, and compound **1**. However, there have been no reports on OX_1R selective agonists in either small molecules or peptides—although $OX_{1/2}R$ dual agonist RTOXA-43 (EC_{50} = 24 nM for OX_1R, 24 nM for OX_2R) was reported quite recently (Figure 15).[39] In this context, the creation of OX_1R selective agonists is invaluable for pharmacology, biology, and drug discovery.

In Chapter 2, compound (*R*)-**5j**, which has selectivity for OX_2R but shows highly potent agonistic activity against both OXR subtypes (EC_{50} = 13.5 nM for OX_1R, 0.579 nM for OX_2R), was identified. In the process, it was found that the aminotetralin skeleton of (*R*)-**5j** is important for its agonistic activity for OX_1R, while its biphenylsulfonamide moiety is an extraordinarily effective substructure for OX_2R agonistic activity enhancement in various ligands (Figure 16). Given these results, optimization of the biphenylsulfonamide moiety with the aminotetralin skeleton of (*R*)-**5j** could lead to a decrease in OX_2R agonistic activity, thereby providing a novel selective OX_1R agonist. Thus, a structural optimization study of the biphenylsulfonamide unit was conducted here to obtain the first selective OX_1R agonist.



RTOXA-43
OX_1R: EC_{50} = 24 nM
OX_2R: EC_{50} = 24 nM



(*R*)-**5j**
OX_1R: EC_{50} = 13.5 nM
OX_2R: EC_{50} = 0.579 nM

Figure 15. OXR ligands that show potent OX_1R agonistic activity

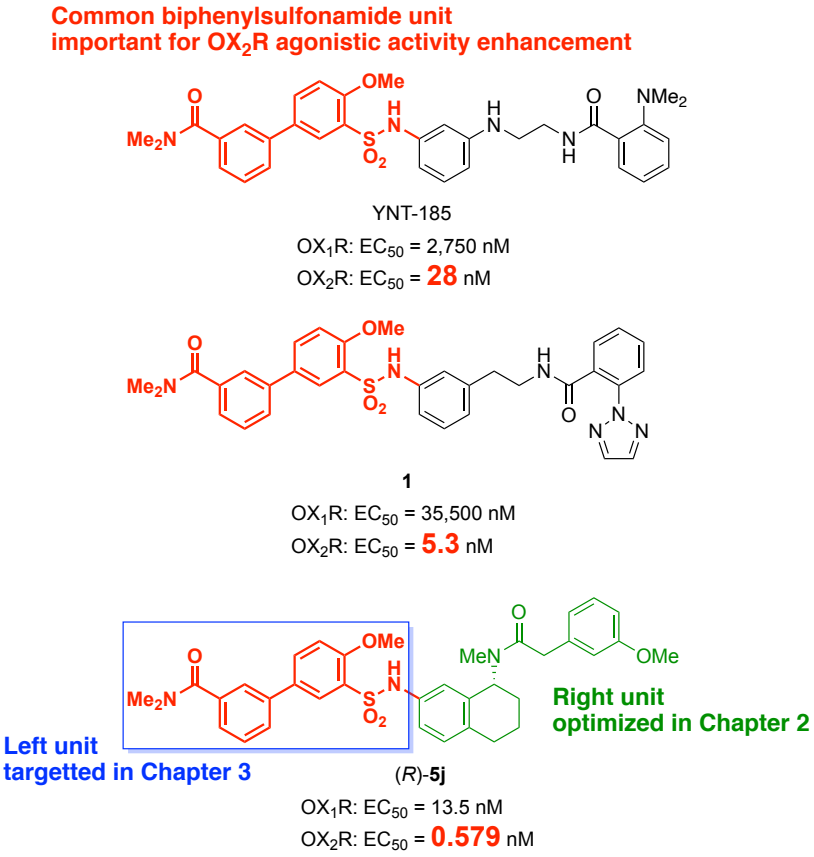


Figure 16. The common biphenylsulfonamide unit in OX_2R agonists

3.3 Structural optimization study

The structure of the active form of OX_2R in complex with OX_2R selective agonist **1** has recently been reported.[38] This previously reported paper demonstrated that a bidentate hydrogen bond interaction between the sulfonamide moiety of **1** and OX_2R significantly contributes to OX_2R agonistic activity expression. A limited number of ligands act on OX_1R, and accordingly, the interaction between OX_1R and its ligands has not been clarified in as much detail as that between OX_2R and its agonists. Thus, to investigate the structure–activity relationships of OX_1R, tetralin-type OXR agonist (*R*)-**5j**, which has relatively potent OX_1R agonistic activity, was highlighted. To start, methylsulfonamide derivative **30** and carboxamide derivative **31** of **5j** were prepared. Unfortunately, the slight structural changes in these compounds caused a complete loss of potency (Figure 17), indicating that the sulfonamide moiety plays an important role in interactions with both OX_2R and OX_1R and is essential for the discovery of OX_1R agonists.

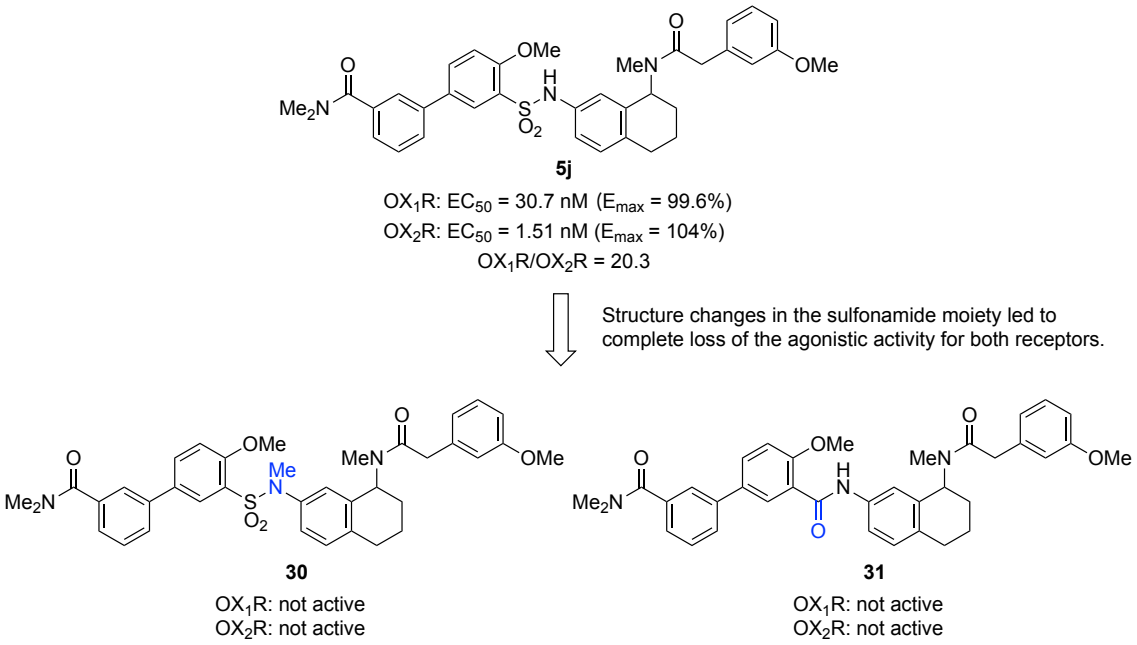
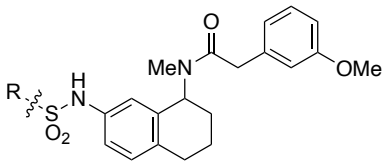
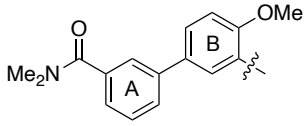
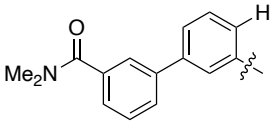
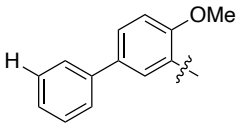
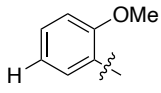


Figure 17. The structure–activity relationship in the sulfonamide moiety of **5j**

Subsequently, derivatives **32a–d** were evaluated to uncover the vital moieties in the biphenyl structure (Table 5). Desmethoxy derivative **32a** showed a significant decrease in potency for both subtypes, indicating that the methoxy group is essential as well. Compound **32b**, in which the dimethylcarbamoyl group was removed, also showed decreased agonistic activity for both receptors but improved selectivity for OX_1R, suggesting that the dimethylcarbamoyl group contributes to the interaction with both receptors but is particularly significant for OX_2R. Next, to explore the biphenyl ring, its two rings were defined as the A- and B-rings. Interestingly, compound **32c**, composed of only the B-ring, exhibited approximately four-fold higher activity for OX_1R, with seven-fold lower activity for OX_2R than **32b**. Moreover, to the best of the author's knowledge, **32c** was the first small molecule agonist to exhibit greater agonistic activity toward OX_1R than OX_2R. Finally, **32d**, in which the B-ring was removed, had no potency. These results suggested that the biphenyl structure plays an important role in OX_2R agonistic activity enhancement, while the structure consisting of only the B-ring is preferred for OX_1R agonistic activity.

Table 5. Orexin receptor agonist activities of **5j** and **32a**–**d**

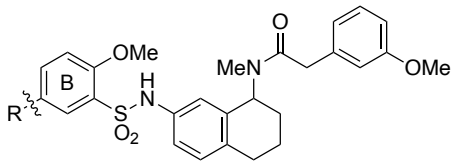


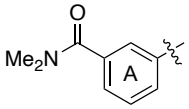
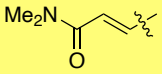
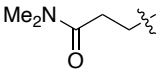
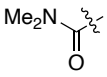
Compounds	R	EC_{50} (nM) [E_{max} (%)[a]]		Selectivity (OX_2R/OX_1R)
		OX_1R	OX_2R	
5j		30.7 [99.6]	1.51 [104]	0.0493
32a		–[c] [–[c]]	–[c] [–[c]]	–
32b		5,925 [39.9[b]]	1,289 [125]	0.218
32c		1,496 [75.9]	8,551 [67.0[b]]	5.72
32d		–[c] [–[c]]	–[c] [–[c]]	–

[a] E_{max} is expressed as a percentage of OXA maximum. [b] The value obtained at 10 μM was used. [c] Not tested due to the weak potency.

Based on the results in Table 5, optimization of the A-ring, which seems to be favorable for OX_2R agonistic activity and unfavorable for OX_1R agonistic activity, was performed to lower the potency for OX_2R and, thereby, improve the selectivity for OX_1R (Table 6). Replacing the A-ring with a *trans*-double bond successfully led to a drastic decrease in the OX_2R agonistic activity, yielding selective OX_1R agonist **32e**. Next, **32f** was synthesized by reducing the double bond of **32e** and showed decreased OX_1R agonistic activity, while **32g**, in which the carbamoyl group was directly connected to the B-ring, showed improved potency for both subtypes compared with **32e** and **32f** but greatly diminished selectivity for OX_1R. These results suggested that the dimethylcarbamoyl group's position and orientation are crucial in modulating the activity and selectivity for both receptors. Among these derivatives, **32e** is the most suitable as an OX_1R agonist. Thus, the substituent of the carbamoyl group was explored next (Table 7).

Table 6. Orexin receptor agonist activities of **5j** and **32e**–**g**

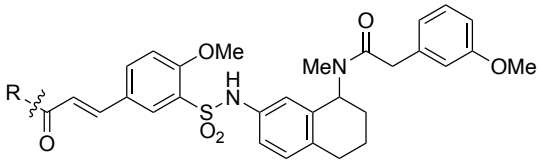


Compounds	R	EC_{50} (nM) [E_{max} (%)[a]]		Selectivity (OX_2R/OX_1R)
		OX_1R	OX_2R	
5j		30.7 [99.6]	1.51 [104]	0.0493
32e		1,279 [111]	> 10,000 [70.1[b]]	–
32f		1,759 [113]	6,410 [88.0[b]]	3.64
32g		606 [98.0]	146 [121]	0.241

[a] E_{max} is expressed as a percentage of OXA maximum. [b] The value obtained at 10 μM was used. [c] Not tested due to the weak potency.

Converting the tertiary amide moiety of **32e** to either the secondary (**33a**) or primary (**33b**) amide resulted in more than a two-fold increase in OX_1R agonistic activity (Table 7), which disappeared upon converting the amide derivatives to carboxylic acid derivative **33c** and ester derivatives **33d** and **33e**, indicating that the heteroatom adjacent to the carbonyl group has a significant effect on the potency. Introducing ethylenediamine units resulted in a further increase in activity for both the secondary (**33g**) and tertiary (**33f**) amide derivatives, implying that their terminal nitrogen atoms act as additional pharmacophores.

Table 7. Orexin receptor agonist activities of **32e** and **33a**–**g**



Compounds	R	EC_{50} (nM) [E_{max} (%)[a]]		Selectivity (OX_2R/OX_1R)
		OX_1R	OX_2R	
32e	Me_2N	1,279 [111]	> 10,000 [70.1[b]]	–
33a	MeHN	501 [102]	> 10,000 [48.5[b]]	–
33b	H_2N	581 [97.2]	7,010 [74.5[b]]	12.1
33c	HO	–[c] [–[c]]	–[c] [–[c]]	–
33d	MeO	–[c] [–[c]]	–[c] [–[c]]	–
33e	EtO	–[c] [–[c]]	–[c] [–[c]]	–
33f	Me_2N Me N	368 [129]	> 10,000 [73.1[b]]	–
33g	Me_2N H N	271 [155]	2,411 [92.0[b]]	8.90

[a] E_{max} is expressed as a percentage of OXA maximum. [b] The value obtained at 10 μM was used. [c] Not tested due to the weak potency.

Since introducing additional nitrogen atoms improved the potency for OX_1R, bond rotation restrictions were adopted to fix the flexible ethylenediamine units in a favorable conformation to effectively interact with OX_1R. The two *trans*-amide conformations (A and B) shown in Figure 18 were presumed to be somewhat stable among the several conformations **33g** can take. Then, structural optimization with different cyclization patterns (types A and B) was performed to fix the molecule similarly to conformation A or B (Tables 8 and 9).

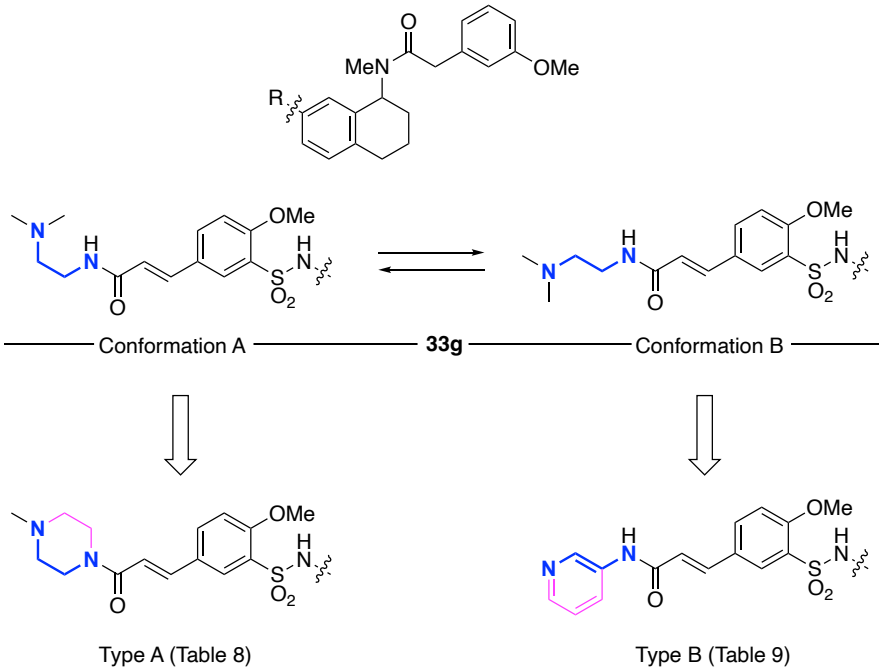
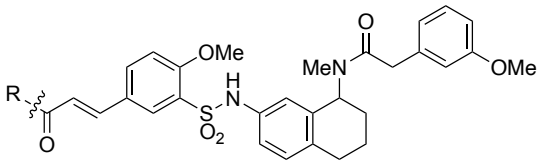
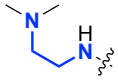
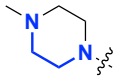
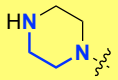
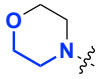


Figure 18. Comparison of the conformational isomers of **33g**

The methylpiperazine ring was used to fix the ligand to conformation A (Table 8), but methylpiperazine derivative **33h** showed weak OXR agonistic activity. Meanwhile, the potency of piperazine **33i**, which lacked the methyl group, was enhanced compared with that of **33g**. Replacing the piperazine ring with a morpholine ring caused a nearly three-fold decrease in the potency (**33j**), indicating that the terminal basic nitrogen atom contributes to potency enhancement. Unfortunately, the fixation of **33g** to conformation A led only to weak potency improvement.

Table 8. Orexin receptor agonist activities of **33g** and **33h–j**

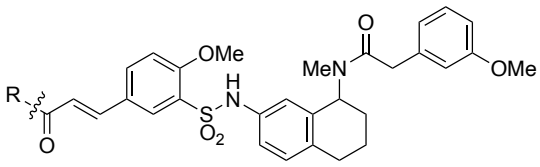


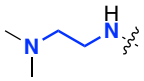
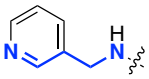
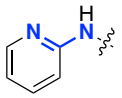
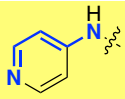
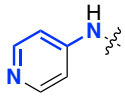
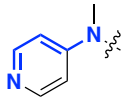
Compounds	R	EC_{50} (nM) [E_{max} (%)[a]]		Selectivity (OX_2R/OX_1R)
		OX_1R	OX_2R	
33g		271 [155]	2,411 [92.0[b]]	8.90
33h		_[c] [–[c]]	_[c] [–[c]]	–
33i		160 [84.6]	1,870 [91.3[b]]	11.7
33j		484 [79.8]	2,520 [84.4[b]]	5.21

[a] E_{max} is expressed as a percentage of OXA maximum. [b] The value obtained at 10 μM was used. [c] Not tested due to the weak potency.

Next, **33g** was fixed to conformation B using pyridine rings (Table 9), and 3-aminopyridine derivative **33k** showed 6.2-fold higher agonistic activity for OX_1R than flexible **33g**. Inserting a methylene carbon between the pyridine ring and nitrogen atom of the amide unit resulted in a slight potency decrease and improved OX_1R selectivity (**33l**). Meanwhile, 2-aminopyridine derivative **33m** showed the same degree of OX_1R agonistic activity as 3-pyridyl derivatives **33l**. Fortunately, however, 4-aminopyridine derivative **33n** showed 17-fold higher OX_1R agonistic activity than **33g**. The reduction of the double bond in **33n** (**33o**) decreased the potency for OX_1R as in the case of **32f**, and methylation of the nitrogen atom of amide **33n** (**33p**) resulted in a decrease in the potency, consistent with the trends for the secondary (**33a** and **33g**) and tertiary (**32e** and **33f**) amide derivatives.

Table 9. Orexin receptor agonist activities of **33g** and **33k**–**p**

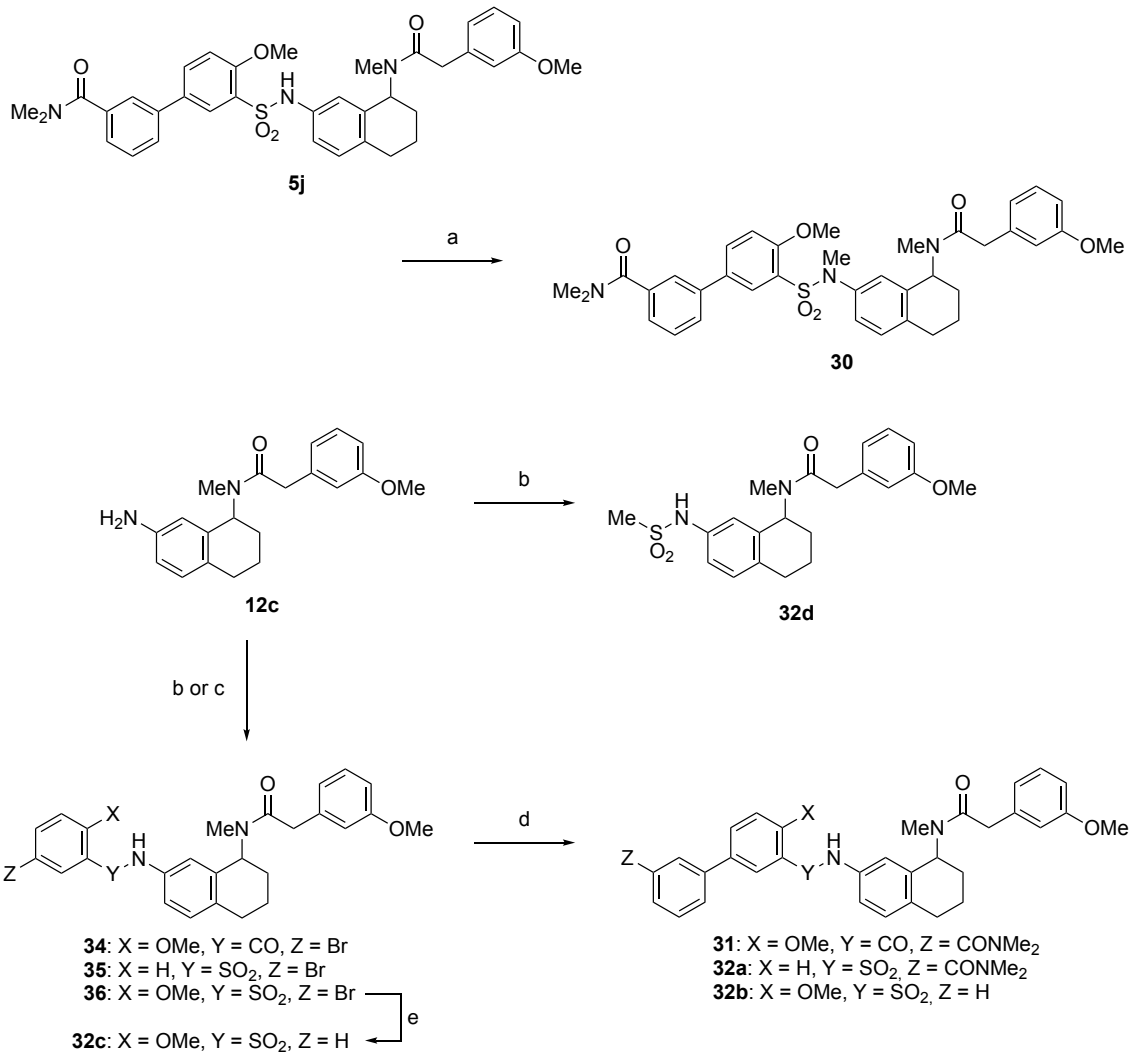


Compounds	R	EC$_{50}$ (nM) [E_{max} (%)[a]]		Selectivity (OX$_2$R/OX$_1$R)
		OX$_1$R	OX$_2$R	
33g		271 [155]	2,411 [92.0[b]]	8.90
33k		43.4 [156]	295 [130]	6.80
33l		231 [96.8]	3,223 [71.0[b]]	14.0
33m		201 [83.8]	955 [101]	4.75
33n		15.3 [87.4]	229 [104]	15.0
33o[c]		72.8 [142]	673 [108]	9.24
33p		187 [112]	275 [115]	1.47

[a] E_{max} is expressed as a percentage of OXA maximum. [b] The value obtained at 10 μM was used. [c] **33o** has α, β-saturated amide instead of α, β-unsaturated amide.

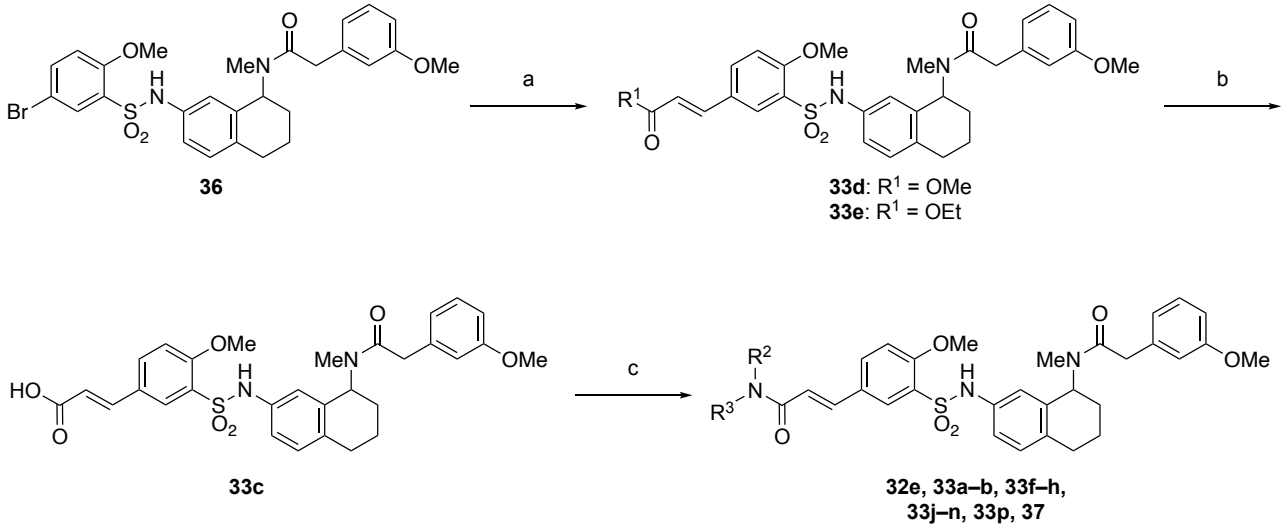
3.4 Synthesis

Compound **30** was synthesized from **5j** using methyl iodide and sodium hydride (Scheme 7). Sulfonamide derivatives **32d**, **35**, and **36** and carboxamide derivative **34** were obtained from condensation with the corresponding carboxylic acid and sulfonyl chlorides. Aryl bromides **34**, **35**, and **36** were converted to **31**, **32a**, and **32b,** respectively, via the Suzuki–Miyaura reaction with the corresponding phenylboronic acids, and anisole **32c** was obtained by the hydrogenation of **36**.

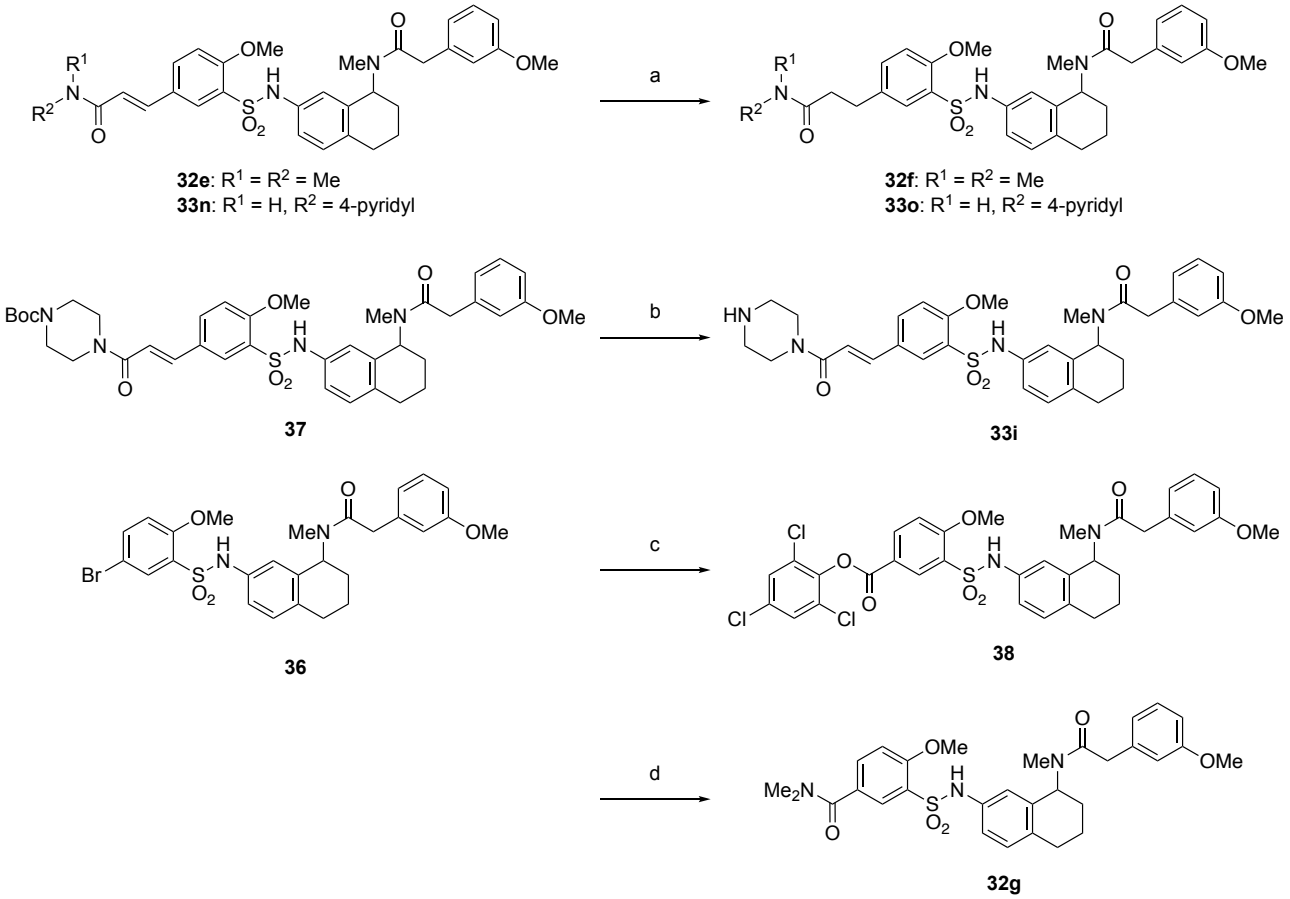


Scheme 7. Reagents and conditions for the synthesis of compound **30**, **31**, and **32a–d**: (a) MeI, NaH, THF, r.t., 96%; (b) the corresponding sulfonyl chlorides, pyridine, CH_2Cl_2, r.t., 81% for **32d**, 98% for **35**, 99% for **36**; (c) 5-bromo-2-methoxybenzoic acid, HATU, Et_3N, DMF, r.t., 86% for **34**; (d) 3-(dimethylcarbamoyl)phenylboronic acid or phenylboronic acid, $Pd(PPh_3)_4$ or $Pd(dppf)Cl_2$, 2.5 M Na_2CO_3 aq., DME, reflux, 74% for **31**, 82% for **32a**, and 55% for **32b**; (e) H_2, Pd/C, MeOH/EtOAc, r.t., 78%.

Ester derivatives **33d** and **33e** were synthesized by the Mizoroki–Heck reaction with the corresponding alkyl acrylates (Scheme 8). The basic hydrolysis of methyl ester **33d** led to carboxylic acid **33c,** and condensation with the corresponding amines yielded amide derivatives **32e**, **33a–b**, **33f–h**, **33j–n**, **33p**, and **37**. Then, **32f** and **32o** were synthesized by the hydrogenation of **32e** and **33n,** respectively (Scheme 9). Finally, *N*-Boc-piperazine derivative **37** was deprotected by trifluoroacetic acid (TFA) to give piperazine **33i**, and **32g** was obtained by the condensation of ester **38**, which was prepared according to the literature.[53]



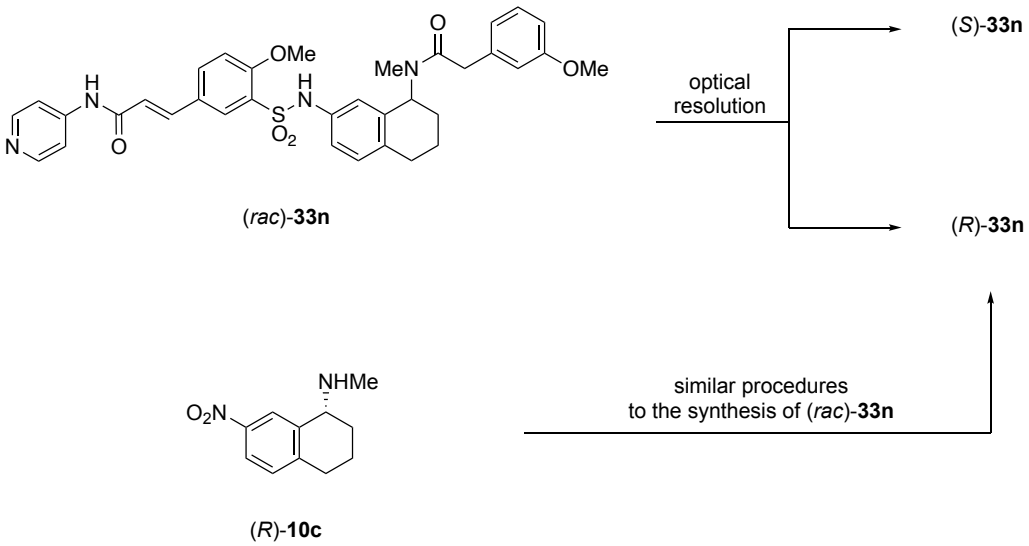
Scheme 8. Reagents and conditions for the synthesis of compound **32e**, **33a–b**, **33f–h**, **33j–n**, **33p**, and **37**: (a) methyl acrylate or ethyl acrylate, $Pd(PPh_3)_4$, DIPEA, DMF, 100 ºC, 73% for **33d**, 53% for **33e**; (b) NaOH aq., THF, r.t., 98%; (c) the corresponding amines, COMU, DIPEA, DMF, r.t., 40–98%. The detailed R^1 and R^2 groups for **32e**, **33a–b**, **33f–h**, **33j–n**, **33p**, and **37** are shown in experimental section.



Scheme 9. Reagents and conditions for the synthesis of compound **32f**, **32o**, **33i**, and **32g**: (a) H_2, Pd/C, MeOH, r.t., 82% for **32f**, 25% for **33o**; (b) TFA, CH_2Cl_2, r.t., 56%; (c) 2,4,6-trichlorophenyl formate, $Pd(OAc)_2$, Xantphos, DBU, toluene, 80 ºC; (d) dimethylamine hydrochloride, Et_3N, DMAP, THF, r.t. 30% in 2 steps.

3.5 Evaluation of the optical isomers of (*rac*)-33n

Upon the successful identification of potent OX_1R agonist **33n,** which shows selectivity for OX_1R over OX_2R, each enantiomer of (*rac*)-**33n** was synthesized considering the fact that the aminotetralin skeleton of (*R*)-**5j** is favorable for OX_1R agonistic activity (Figure 14). The preparation of (*R*)-**33n** and (*S*)-**33n** is shown in Scheme 10. Each stereoisomer of (*rac*)-**33n** was obtained by optical resolution with the chiral HPLC system (Figures 19–21), and the absolute stereochemistry was confirmed by resynthesizing (*R*)-**33n** from (*R*)-**10c** using the similar procedures as in the synthesis of (*rac*)-**33n** (Scheme 17 in experimental section).



Scheme 10. The optical resolution was conducted using chiral HPLC (DAICEL CHIRALPAK AD-H, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 50/50). (*R*)-**33n** was also synthesized from (*R*)-**10c** by the similar procedures to the synthesis of (*rac*)-**33n** to confirm its absolute stereochemistry.

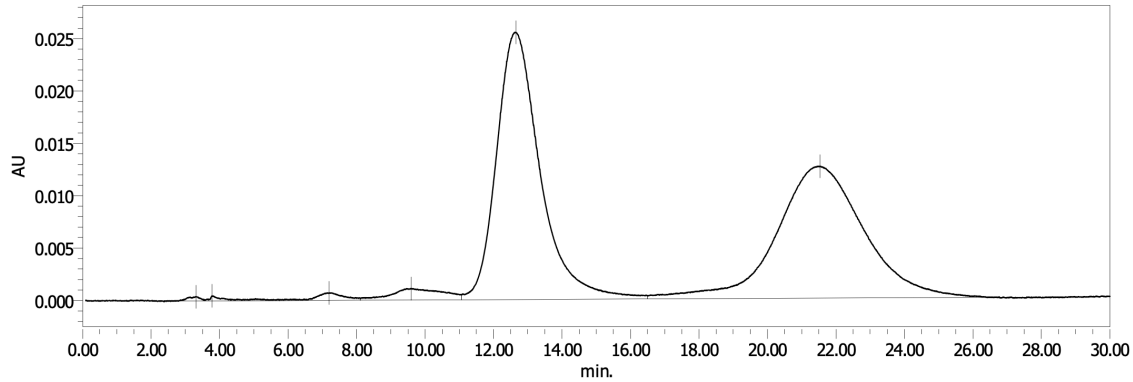


Figure 19. Chiral HPLC chromatogram for (*rac*)-**33n** (DAICEL CHIRALPAK AD-H, 4.6 mm I.D.×250 mmL, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 50/50, flow rate: 1.0 mL/min., λ = 254 nm)

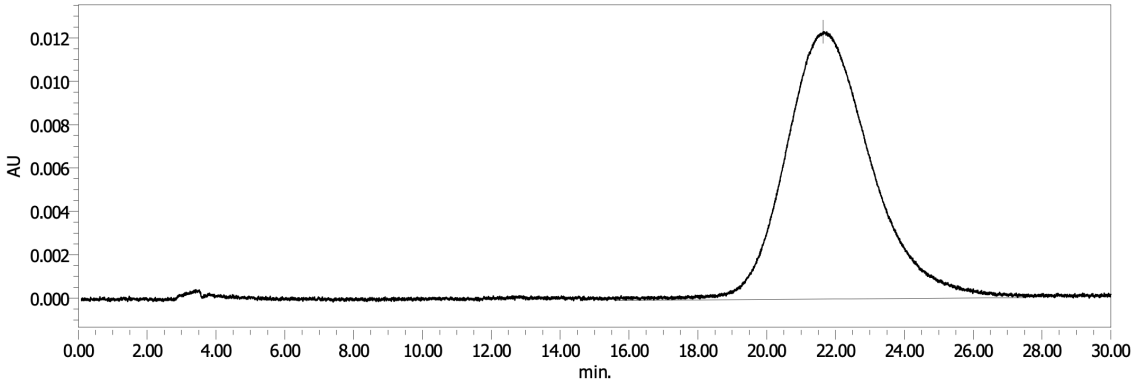


Figure 20. Chiral HPLC chromatogram for (*S*)-**33n** (DAICEL CHIRALPAK AD-H, 4.6 mm I.D.×250 mmL, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 50/50, flow rate: 1.0 mL/min., λ = 254 nm)

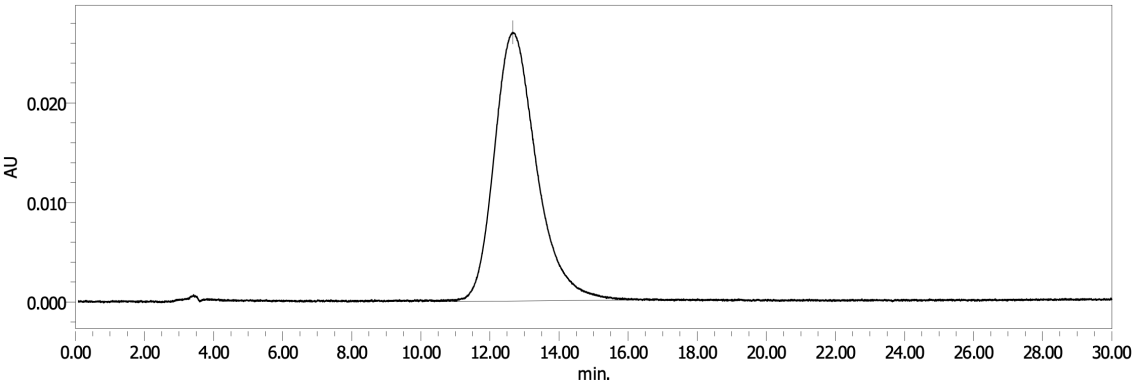
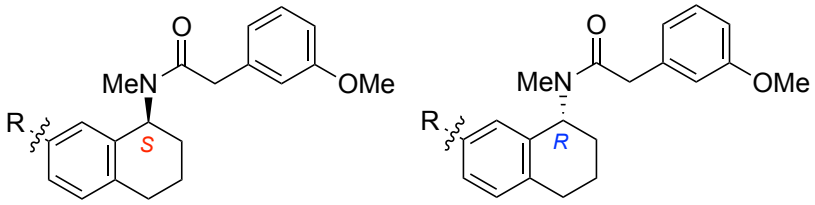
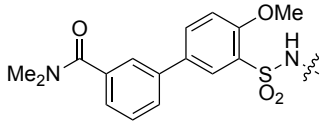
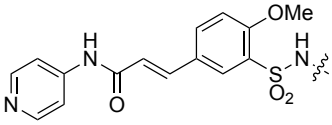


Figure 21. Chiral HPLC chromatogram for (*R*)-**33n** (DAICEL CHIRALPAK AD-H, 4.6 mm I.D.×250 mmL, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 50/50, flow rate: 1.0 mL/min., λ = 254 nm)

As in the case of **5j**, (*R*)-**33n** had much more potent OX_1R agonistic activity than (*S*)-**33n** (Table 10). Introducing the sulfonamide unit identified in Chapter 3 to the aminotetralin skeleton of (*S*)-**5j**, an OX_2R selective agonist, did not produce potent OX_2R agonistic activity, demonstrating the difference between the sulfonamide unit included in **33n** and the biphenyl sulfonamide unit included in YNT-185, **1**, and **5j**. In contrast, (*R*)-**33n** showed an approximately two-fold increase in OX_1R agonistic activity compared with the racemate and was the most potent OX_1R agonist among the tetralin derivatives. In the end, potent OX_1R selective agonist (*R*)-**33n** (EC_{50} = 7.47 nM for OX_1R, 168 nM for OX_2R, OX_2R/OX_1R = 22.5) was successfully identified via structurally optimizing the existing biphenyl sulfonamide unit of (*R*)-**5j**.

Table 10. Orexin receptor agonist activities of stereoisomers of **5j** and **33n**



Compounds	R	EC_{50} (nM) [E_{max} (%)[a]]		Selectivity (OX_2R/OX_1R)
		OX_1R	OX_2R	
(*rac*)-**5j**		26.4 [114]	1.17 [106]	0.0442
(*S*)-**5j**		1,244 [117]	2.69 [101]	0.00217
(*R*)-**5j**		13.5 [108]	0.579 [106]	0.0429
(*rac*)-**33n**		15.0 [104]	277 [98.6]	18.5
(*S*)-**33n**		3,595 [71.2[b]]	1,661 [47.4[b]]	0.462
(*R*)-**33n**		7.47 [101]	168 [105]	22.5

[a] E_{max} is expressed as a percentage of OXA maximum. [b] The value obtained at 10 μM was used.

3.6 The conditioned place preference test

To assess the potential of OX_1R selective small molecule agonist (*R*)-**33n** as a chemical tool for *in vivo* experiments, this section focused on the involvement of OX_1R in the reward system, and a CPP test was performed. This test is a Pavlovian conditioning method used to measure drug-induced motivational effects or experiences and can verify the rewarding or reinforcing effects of drugs by measuring the time spent in an area associated with a drug stimulus. It involves pre-test, conditioning, and post-test sessions, and the CPP score is defined as the time spent in the drug-associated box side after drug conditioning subtracted from the time spent there before drug conditioning. For example, cocaine (COCA), a typical addictive drug, shows a high CPP score in this test. As mentioned in Section 3.1, it has already been reported that COCA-induced place preference is suppressed by selective OX_1R antagonists and that orexin peptides induce place preference in this test.

Here, the CPP test was performed for selective OX_2R agonist (*S*)-**5j**, dual OXR agonist (*R*)-**5j**, and selective OX_1R agonist (*R*)-**33n** by subcutaneous (s.c.) administration. Overall, (*S*)-**5j** did not produce place preference (Figure 22A), while (*R*)-**5j** and (*R*)-**33n**, which have OX_1R agonistic activity, produced significant dose-dependent place preference (Figure 22B and 22C). In addition, the (*R*)-**33n**-induced place preference in wild-type mice was reduced in mice lacking OX_1R, indicating that (*R*)-**33n** induces place preference via OX_1R activation and is a selective OX_1R agonist that can be systematically administered in mice (Figure 22D).

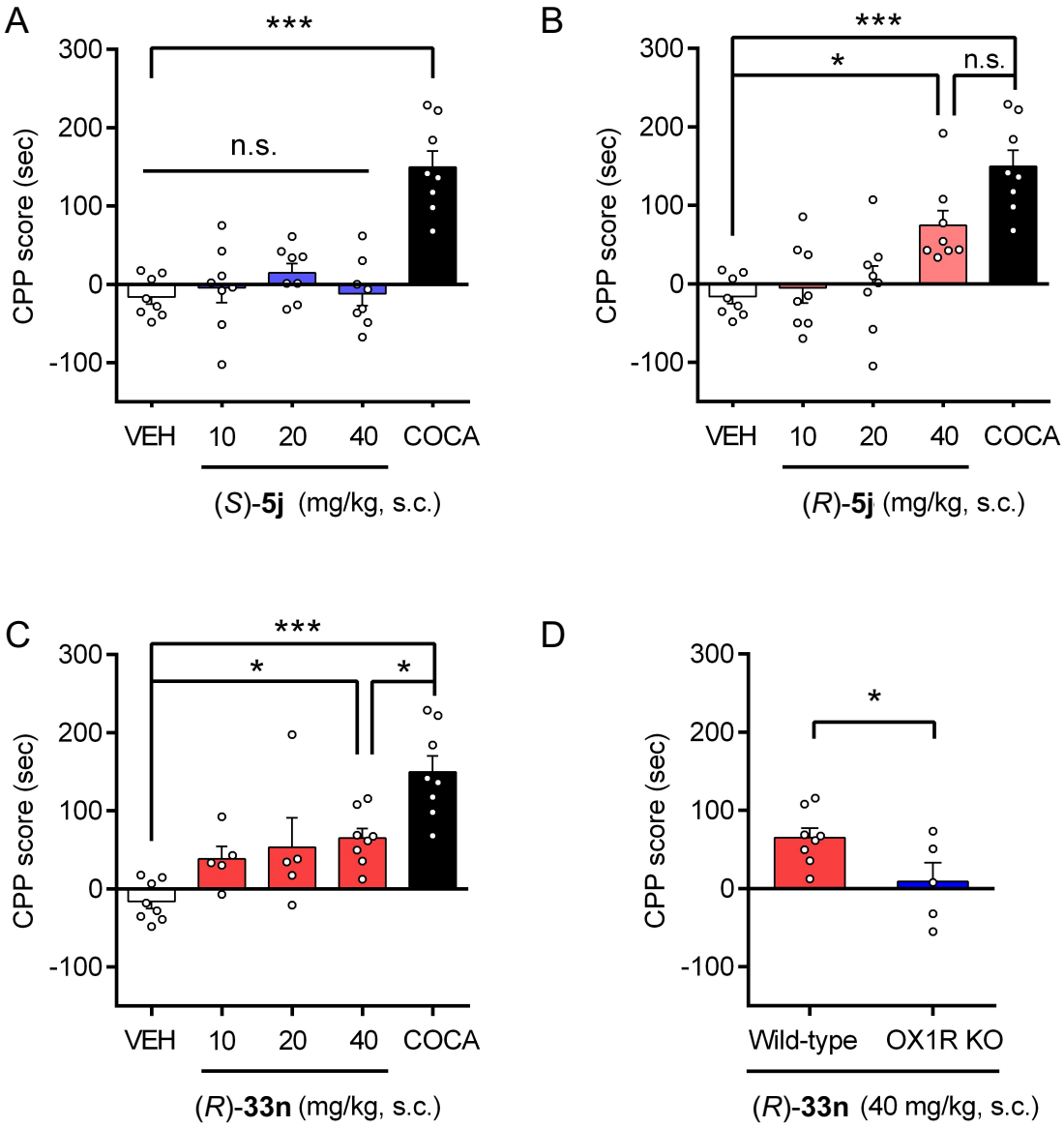


Figure 22. The results of the CPP test for (*S*)-**5j**, (*R*)-**5j**, and (*R*)-**33n**

3.7 Conclusion

Thus far, there have been several reports of selective OX_2R and dual $OX_{1/2}R$ agonists but no reports of selective OX_1R agonists. In this chapter, structural optimization of the biphenyl sulfonamide unit of **5j** identified in Chapter 2 was performed, yielding a novel sulfonamide unit that preferentially shows OX_1R agonistic activity. The initial investigations suggested that the sulfonamide moiety and methoxy group in the biphenylsulfonamide unit of **5j** are essential for the OX_1R agonistic activity, while the A-ring is unfavorable for OX_1R agonistic activity enhancement and favorable for OX_2R agonistic activity enhancement. Substitution of the A-ring with a different spacer yielded **32e**, which showed weak potency but OX_1R selectivity. The structural optimization of the carbamoyl group's substituents in **32e** based on bond rotation regulation led to the discovery of potent OX_1R agonist (*rac*)-**33n** (EC_{50} = 15.0 nM for OX_1R, 277 nM for OX_2R, OX_2R/OX_1R = 18.5). Considering the stereochemistry of the aminotetralin skeleton and the potency obtained in Chapter 2, optical isomers of (*rac*)-**33n** were prepared, and highly potent selective OX_1R agonist (*R*)-**33n** (EC_{50} = 7.47 nM for OX_1R, 168 nM for OX_2R, OX_2R/OX_1R = 22.5) was obtained. Since OX_1R agonistic activity of (*S*)-**33n** was quite weak, the sulfonamide unit and tetralin skeleton of (*R*)-**33n** seem to concertedly contribute to the enhancement of OX_1R agonistic activity. To the best of the author's knowledge, this is the first report of a selective small molecule OX_1R agonist. Moreover, (*R*)-**33n** was demonstrated to be effective in *in vivo* studies (via the CPP test) when administered systemically. Therefore, its future application in both *in vitro* and *in vivo* experiments targeting OX_1R is expected. In addition, even more selective OX_1R agonists will be explored for applications in drug discovery research based on the results of the structure–activity relationship of the compound **33n** derivatives to OX_1R in this study.

Chapter 4. Design and synthesis of Mas-related G-protein-coupled receptor X2 agonists with a morphinan skeleton

4.1 The discovery of δ opioid receptor selective agonists (–)-TAN-67 and (–)-KNT-127

Opioid receptors are a group of GPCRs comprising the μ (MOR), δ (DOR), and κ (KOR) opioid receptor types; β-Endorphin,[54,55] enkephalin,[56] and dynorphin[57] are endogenous peptides for MOR, DOR, and KOR, respectively. These endogenous peptides and opioid receptors contribute to various functions, including analgesia, stress, dependence, learning and memory, and eating, under physiological conditions.[58,59] Morphine is a representative opioid receptor agonist isolated in 1806 from opium, and its unique ring-fused structure is called the morphinan skeleton (Figure 23).[60] It is one of the most potent analgesics used in pain treatment but causes drug dependence as a severe side effect. Genetic experiments have demonstrated that morphine-induced dependence is predominantly mediated by MOR rather than DOR or KOR.[61] Thus, DOR and KOR are expected to be targets for pain treatment with relatively weak dependence liability, and several studies have been conducted to develop selective agonists for them.[62,63]

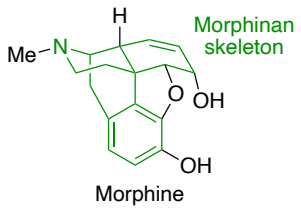


Figure 23. The chemical structure of morphine

Of these selective agonists, (±)-TAN-67 (a DOR selective agonist discovered by Nagase et al. in 1992)[64] has potent agonistic activity but, contrary to expectations, shows weak analgesic activity *in vivo*.[65,66] Thus, in the previous study, each of its enantiomers was synthesized to understand its pharmacological properties, and (–)-TAN-67 showed high affinity for DOR (inhibition constant [K_i] = 1.44 nM). Moreover, intrathecal (i.t.) administration of (–)-TAN-67 to mice produced a dose-dependent analgesic effect (Figure 24).[67–69] In a subsequent study, the phenol ring, which has been proposed as a pharmacophore of (–)-TAN-67, was fixed by a 10-methylene carbon, leading to the 10-fold more potent SN-28 (K_i = 0.14 nM for DOR),[70] which displayed a stronger analgesic effect than (–)-TAN-67 when administered by i.t. injection (median effective dose [ED_{50}] = 0.095 nM) but no analgesic effect when administered by s.c. injection, even at a dose of 30 mg/kg. Based on these results, it was proposed that SN-28 cannot readily reach the central nervous system due to its low BBB

permeability. Nagase et al. postulated that the 17-nitrogen atom, which can be protonated under physiological conditions, is one of the causes of the decrease in BBB permeability. To address this problem, they applied the fact that the 14-hydroxy group forms an intramolecular hydrogen bond with the lone pair of the 17-nitrogen atom to improve the BBB permeability and synthesized (–)-KNT-127 (14-hydroxy SN-28),[71] which shows a comparable binding affinity to DOR as SN-28 (K_i = 0.16 nM), an analgesic effect upon i.t. administration (ED_{50} = 0.149 nM), and a potent analgesic effect by s.c. administration, as expected (ED_{50} = 1.2 mg/kg). These results implied that (–)-KNT-127 has sufficient BBB permeability to produce analgesic effects by systemic administration. In addition, it does not produce the side effects (e.g., catalepsy and convulsions) induced by representative DOR agonist SNC-80.[72,73] Recently, DOR has attracted attention for its contribution to chronic pain modulation and its involvement in emotional processes and the peripheral immune system, and several studies related to (–)-KNT-127, which has excellent pharmacological properties, have been performed regarding its applications in drug discovery.[74,75]

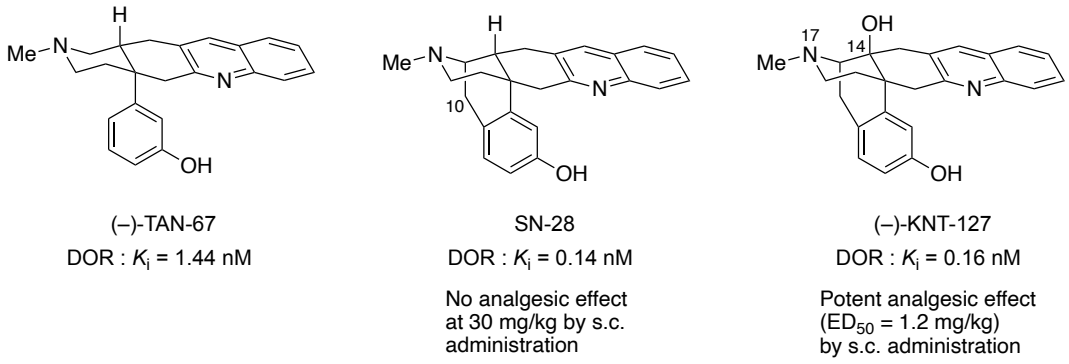
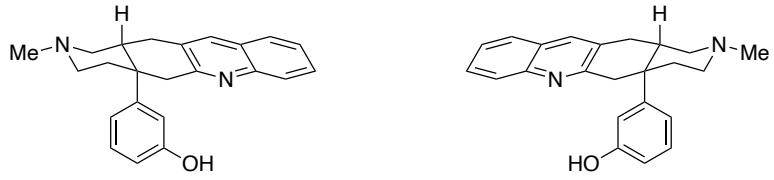


Figure 24. The structures and pharmacological properties of (–)-TAN-67, SN-28, and (–)-KNT-127[71]

4.2 The pharmacology of (+)-TAN-67

The tail-flick test is a method used to evaluate the analgesic effect of compounds. In this test, a light beam is irradiated on a mouse's tail, and the latency until the mouse flicks its tail upon feeling pain is measured. A short latency indicates an increased pain threshold, and a long latency indicates a decreased pain threshold. Here, (–)-TAN-67 exhibited analgesic effects and increased the latency of the tail-flick response when administered to mice via i.t. injection (Figure 25).[67] In contrast, the other enantiomer, (+)-TAN-67, decreased the latency, implying that it causes hyperalgesia. Additionally, i.t. administration of (+)-TAN-67 to the mice induced pain-like nociceptive responses, e.g., biting, licking, and scratching, whereas the administration of (–)-TAN-67 caused no remarkable behavioral changes. These behaviors were inhibited by γ-aminobutyric acid type B receptor agonist baclofen, *N*-methyl-D-aspartic acid receptor antagonist dizocilpine, or neurokinin 1 receptor antagonist GR82334, raising the possibility that they are mediated by nociception-associated receptors.[76,77] However, the detailed mechanism behind the phenomena associated with (+)-TAN-67 has yet to be elucidated. Recently, (+)-TAN-67 has been reported to act on MRGPRX2 (which is associated with pain and itchiness) in addition to DOR.[78]



(–)-TAN-67
Potent DOR agonist
Analgesic effect

(+)-TAN-67
DOR agonist
MRGPRX2 agonist
Nociceptive effect

Figure 25. The structures and pharmacological properties of (–)-TAN-67and (+)-TAN-67

4.3 Mas-related G-protein-coupled receptors

Mas-related GPCRs (Mrgprs) constitute a GPCR family comprising nine subfamilies and around 40 members.[79] These receptors are expressed on sensory neurons or mast cells in primates and rodents.[80] The family includes MRGPRX2 and its murine ortholog, Mrgprb2, which are associated with the pathogenesis of inflammation and itchiness. The murine ortholog, which is expressed in mast cells in mice, is activated by basic secretagogues such as substance P, causing degranulation through an immunoglobulin E (IgE)-independent mechanism. Through this mechanism, Mrgprb2 is involved in pseudo-allergic reactions, immune cell recruitment, and neurogenic inflammation.[81,82] Moreover, the type and amount of chemical mediators released by Mrgprb2-mediated degranulation differ from those released by IgE-mediated degranulation. Thus, a distinct sensory neuron population is excited by Mrgprb2-mediated degranulation, inducing non-histaminergic pruritus.[83]

In humans, MRGPRX2 is expressed in dorsal root ganglia, trigeminal ganglia, and mast cells.[79,84,85] Since it is an ortholog of Mrgprb2, MRGPRX2 has been proposed to serve similar functions in human mast cells and sensory neurons.[78,83,85,86] Mast cells are found in close proximity to nerves in many tissues, and both are suggested to play an important role in the neuroimmune interaction that induces an itch.[87] However, mast cells' detailed contribution to chronic itch remains unclear. Thus, MRGPRX2 and Mrgprb2 are not only important factors for understanding the close relationship between mast cells and nerves but also potential therapeutic targets for treating chronic itch and inflammation.[82,88–92] Several endogenous peptides, e.g., cortistatin-14, proadrenomedullin *N*-terminal 20 Peptide (9-20), and substance P, have been reported to activate MRGPRX2/Mrgprb2, but many also show an affinity to other receptors.[78,81,89,93] The small molecule compounds that activate MRGPRX2 or Mrgprb2 include tetracyclic benzimidazoles, complanadine A, (*R*)-ZINC-3573, opioids (e.g., morphine), antibiotics (e.g., ciprofloxacin), and muscle relaxants (e.g., atracurium); however, some of them are weak agonists or have not been validated in other literature works (Figure 26).[78,81,94–97]

Since (+)-TAN-67 is the most potent compound among the small molecule MRGPRX2 agonists (EC_{50} = 290 nM), in this study, it was postulated that the behavior it induced in the mice in Section 4.2 is associated with the MRGPRX2/Mrgprb2 system. However, the compound's DOR affinity is an obstacle to validating this hypothesis. Thus, here, a novel MRGPRX2/Mrgprb2 agonist with no DOR affinity was created based on the structure of (+)-TAN-67, and the agonist-induced behavior of mice was examined.

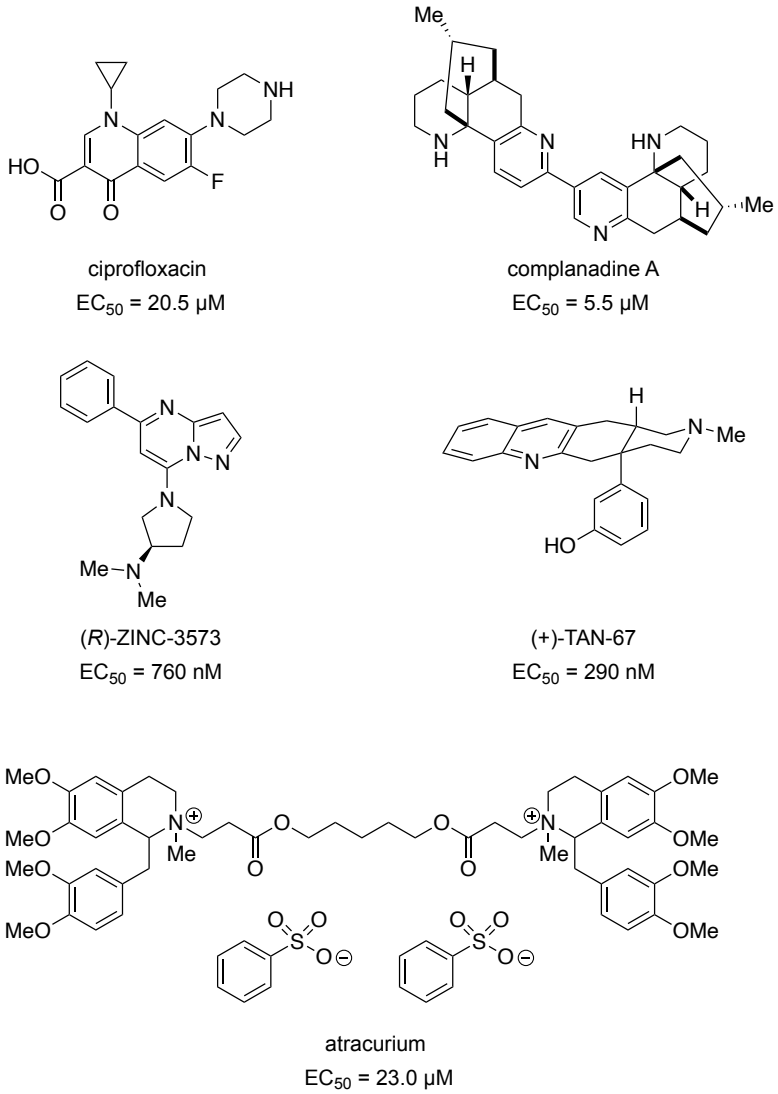


Figure 26. Small molecule MRGPRX2 agonists

4.4 The molecular design of (+)-KNT-127

Analgesic DOR agonist (–)-TAN-67 has a similar stereochemical skeleton to morphine, which is isolated from poppy, and the 17-nitrogen atom and the phenol ring are considered to be pharmacophores for opioid receptors (Figure 27). In contrast, the other enantiomer, (+)-TAN-67, has mirror-image structure **A**. Since its phenol ring can rotate freely, it can adopt conformation **B,** with the pharmacophores in a relatively similar arrangement as those of (–)-morphine and (–)-TAN-67. Thus, in this study, it was hypothesized that conformation **B** contributes to the expression of the DOR agonistic activity of (+)-TAN-67 and that suppression of the phenol ring's free rotation will reduce its DOR affinity. In this context, (+)-KNT-127, in which 10-methylene carbon was introduced to inhibit the phenol ring's rotation, was synthesized.

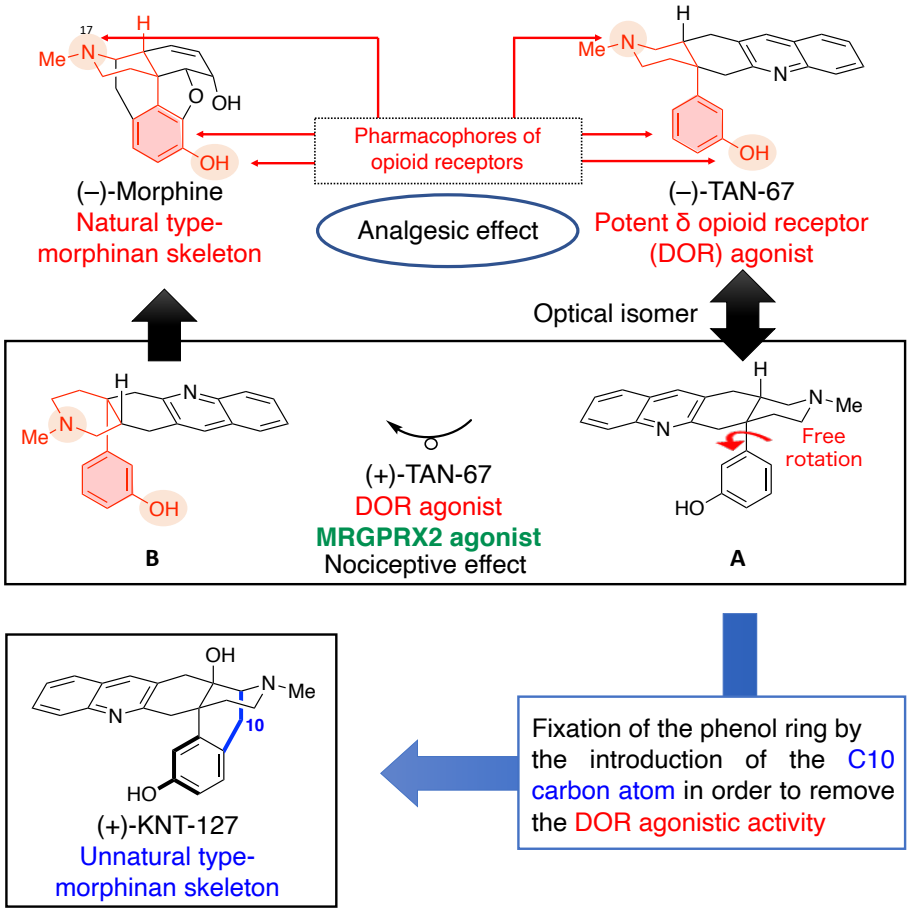
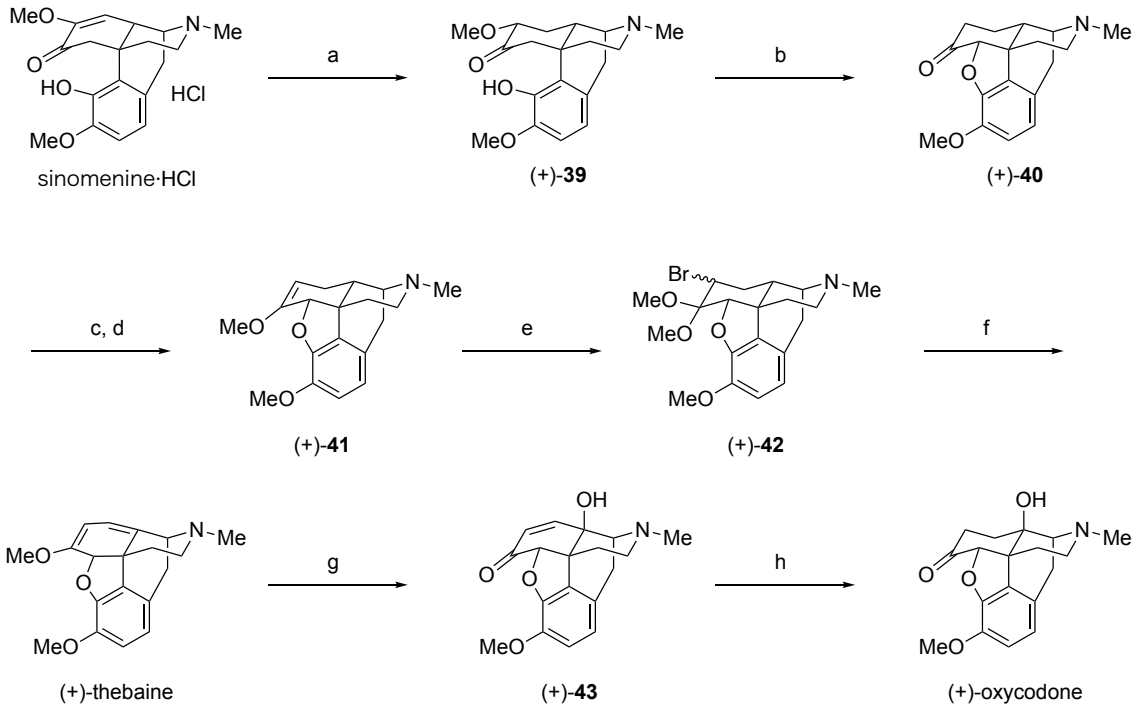


Figure 27. The working hypothesis used to design (+)-KNT-127

4.5 Synthesis

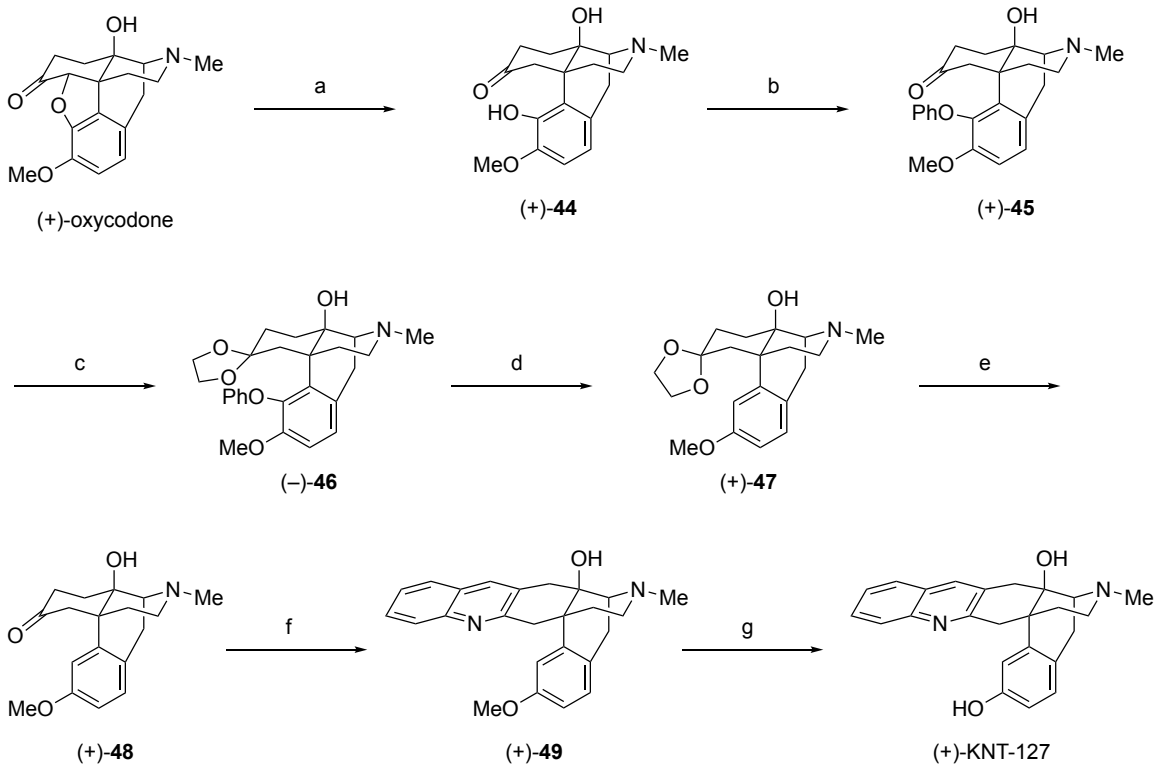
Here, (+)-oxycodone, the synthetic intermediate of (+)-KNT-127, was synthesized referring to previous reports (Scheme 11).[98] To start, the hydrogenation of commercially available sinomenine hydrochloride and subsequent cyclization utilizing Eaton's reagent[99] (10% P_2O_5 in $MeSO_3H$) yielded (+)-**40**. This compound was then converted to methyl enol ether (+)-**41**, which was reacted with *N*-bromosuccinimide (NBS) in methanol to give (+)-**42**. Diastereomixture (+)-**42** was exposed to potassium *tert*-butoxide, and the thebaine produced was oxidized to yield (+)-**43**, which was hydrogenated to obtain (+)-oxycodone.



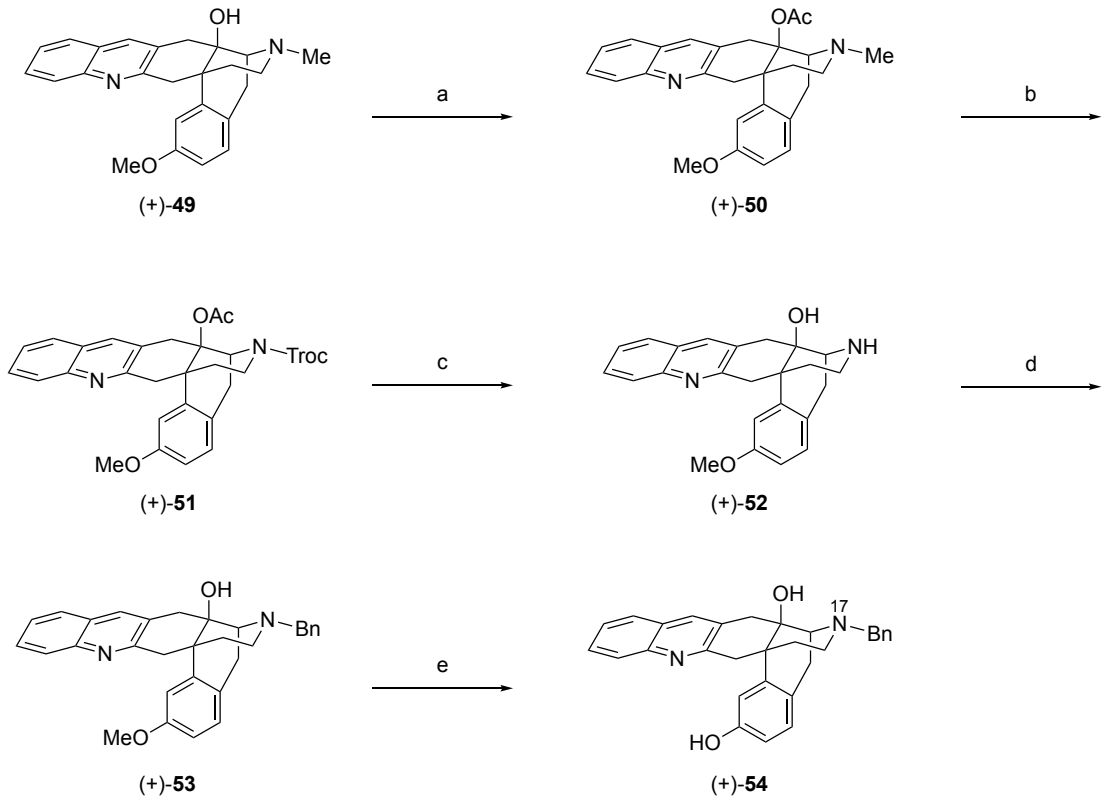
Scheme 11. Reagents and conditions for the synthesis of (+)-oxycodone: (a) H_2, Pd/C, MeOH, r.t.; (b) Eaton's reagent, r.t., 79% in 2 steps; (c) 5-sulfosalicyclic acid dihydrate, trimethyl orthoformate, reflux; (d) CSA, toluene, reflux, 94% in 2 steps; (e) NBS, MeOH, r.t.; (f) *tert*-BuOK, DMSO, 80 ºC, 88% in 2 steps; (g) H_2O_2 aq., H_2SO_4, HCO_2H, 40 ºC, 95%; (h) H_2, Pd/C, AcOH, 84%.

Reducing (+)-oxycodone via zinc powder in acetic acid and introducing the phenyl group by Ullmann condensation yielded (+)-**45** (Scheme 12). After acetal protection of (+)-**45**, Birch reduction and deprotection gave ketone (+)-**48**. Finally, (+)-KNT-127 was obtained via cyclization with 2-aminobenzaldehyde and the subsequent demethylation of (+)-**48**.

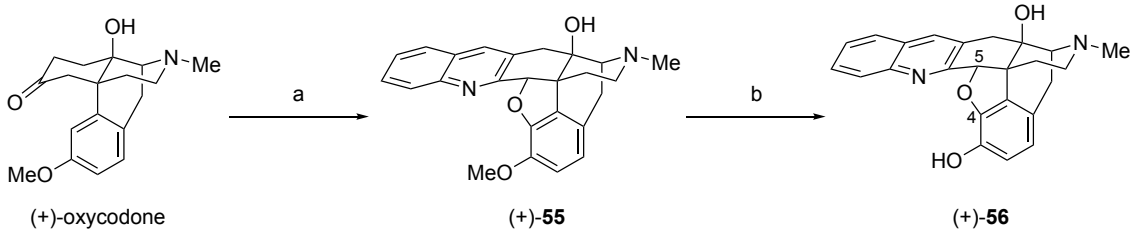
Additionally, 17*N*-benzyl derivative (+)-**54** and 4,5-epoxy derivative (+)-**56** of (+)-KNT-127 were synthesized. Compound (+)-**49** was protected with an acetyl group and 2,2,2-trichlotoethoxycarbonyl (Troc) group (Schemes 13). Basic hydrolysis of the resulting (+)-**51** yielded 17*N*-desmethyl derivative (+)-**52**, which was reacted with benzyl bromide and demethylated with boron tribromide to obtain desired 17*N*-benzyl derivative (+)-**54**. Then, 4,5-epoxy derivative (+)-**56** was synthesized in two steps from (+)-oxycodone using the same methods as the synthesis of (+)-KNT-127 and 17*N*-benzyl derivative (+)-**54** (Schemes 14).



Scheme 12. Reagents and conditions for the synthesis of (+)-KNT-127: (a) Zn, AcOH, reflux; (b) PhBr, Cu, K_2CO_3, pyridine, reflux, 98% in 2 steps; (c) ethylene glycol, *p*-toluenesulfonic acid monohydrate, toluene, reflux, 87%; (d) Na, liq. NH_3, –33 ºC, 88%; (e) HCl aq., r.t., 98%; (f) 2-aminobenzaldehyde, $MeSO_3H$, EtOH, reflux, 86%; (g) BBr_3, CH_2Cl_2, r.t., 86%.



Scheme 13. Reagents and conditions for the synthesis of (+)-**54**: (a) Ac_2O, reflux, 95%; (b) TrocCl, K_2CO_3, $(CHCl_2)_2$, 140 ºC, 98%; (c) LiOH aq., THF, 60 ºC; (d) benzyl bromide, DMF, r.t., 51% in 2 steps; (e) BBr_3, CH_2Cl_2, r.t., 89%.



Scheme 14. Reagents and conditions for the synthesis of (+)-**56**: (a) 2-aminobenzaldehyde, $MeSO_3H$, EtOH, reflux, quant.; (b) BBr_3, CH_2Cl_2, r.t., 94%.

4.6 The pharmacological evaluation of (+)-KNT-127

To evaluate the affinity of (+)-KNT-127 and its derivatives, i.e., (+)-**49**, (+)-**54**, and (+)-**56,** to the opioid receptors, a receptor binding assay was performed following a previously described procedure (Figure 28).[100] Tritium-labeled MOR agonist [D-Ala^2, *N*-Me-Phe^4, Gly^5-ol]-enkephalin (DAMGO), DOR agonist [D-Phe^{2,5}]-enkephalin (DPDPE), and KOR agonist U-69593 were used as radioligands. Overall, (+)-KNT-127 and its derivatives showed almost no affinity for each opioid receptor type, suggesting that compounds with an unnatural morphinan skeleton, in which a methylene carbon is introduced to (+)-TAN-67, are less likely to show such an affinity.

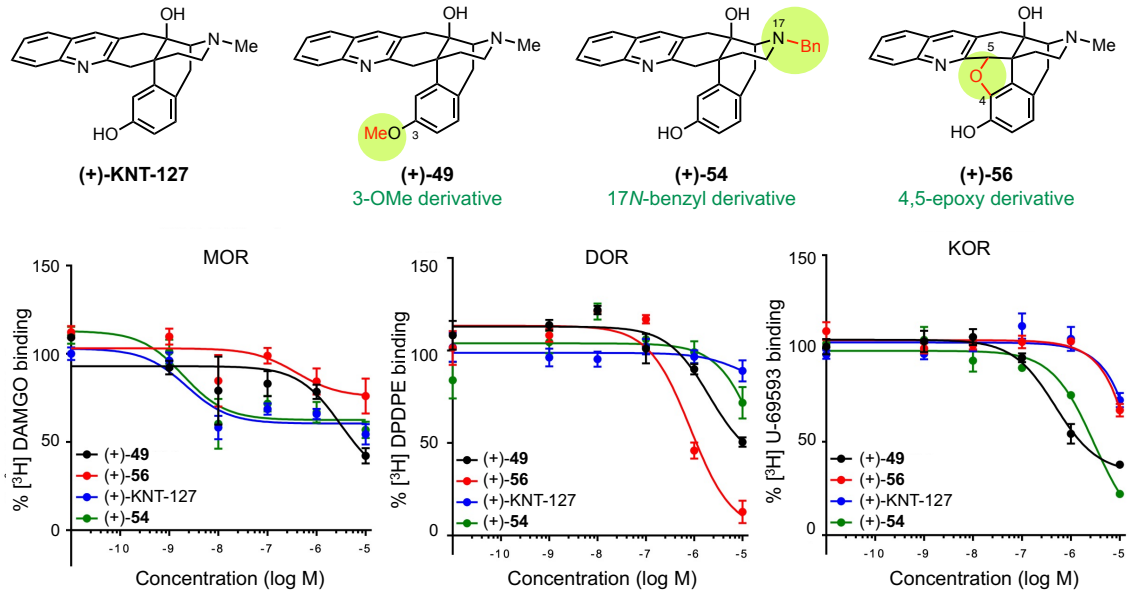


Figure 28. Results of binding assay for opioid receptors

Next, a NanoLuc Binary Technology (NanoBiT) G-protein dissociation assay was performed to evaluate the agonistic activity of (+)-KNT-127 for MRGPRX2 and Mrgprb2 (Figure 29),[101] which were suggested to be coupled with $G_{i/o}$ or $G_{q/11}$ proteins in the cell.[102–104] Cortistatin-14 and (+)-TAN-67, which are MRGPRX2/Mrgprb2 agonists,[78,81] also showed agonistic activity for both receptor types in this assay, as did (+)-KNT-127 under the same conditions, indicating that it is an MRGRPX2/Mrgprb2 agonist with no DOR affinity.

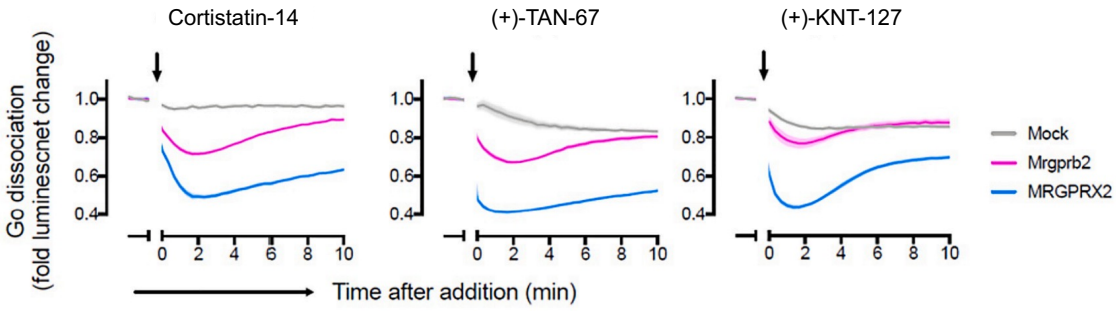


Figure 29. G-protein-dissociation assay for MRGPRX2 and Mrgprb2

Kinetics of G-protein dissociation responses after test compound application in HEK293 cells transiently expressing MRGPRX2 or Mrgprb2. Note that due to time lag between manual compound addition (arrows) and start of measurement, G-protein dissociation had been induced at the first reading. Also note that (+)-TAN-67 and (+)-KNT-127 induced apparent dissociation signals in mock-transfected cells presumably due to its unspecific effect on luciferase. Measurement was recorded at 20-sec interval and data were merged from three independent experiments with shades representing SEM. Concentrations of compounds were 10 μM for Cortistatin-14 and 32 μM for (+)-TAN-67 and (+)-KNT-127.

Since the agonistic activity of (+)-KNT-127 was confirmed in *in vitro*, its *in vivo* pharmacological effects were evaluated in mice. The i.t. administration of (+)-TAN-67 induced nociceptive behaviors such as biting, licking, and scratching, as previously reported (Figure 30A, left).[77] Here, the i.t. administration of (+)-KNT-127 also induced such behaviors in mice in a dose-dependent manner (Figure 30A, right). However, these effects were inhibited by the i.t. pre-treatment of Boc-Gln-D-Trp(Formyl)-Phe benzyl ester trifluoroacetate (QWF), an MRGPRX2/Mrgprb2 antagonist (Figure 30B).[88] These results indicated that synthesized (+)-KNT-127 induces *in vivo* pharmacological effects via MRGPRX2/Mrgprb2 activation. Furthermore, fewer nociceptive behaviors were induced with 17*N*-benzyl derivative (+)-**54**, 4,5-epoxy derivative (+)-**56**, and 3-OMe derivative (+)-**49** than with (+)-KNT-127 (Figure 31). These structural changes could affect the interaction between (+)-KNT-127 and Mrgprs.

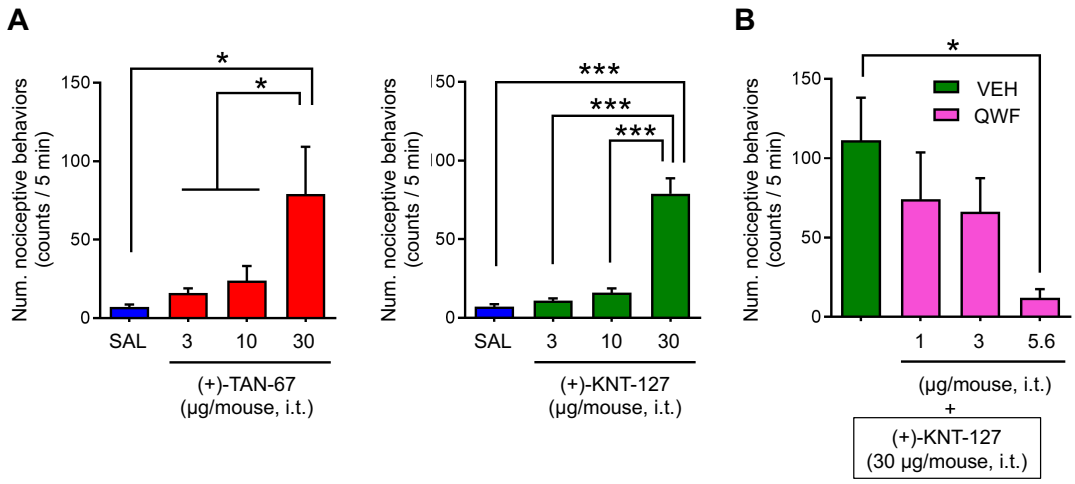


Figure 30. Evaluation of nociceptive behaviors in mice

SAL: saline, VEH: vehicle; (A) Summary bar graphs showing the dose-dependent increase in nociceptive behaviors of (+)-TAN-67 (left: 3–30 μg/mouse, i.t.) and (+)-KNT-127 (right: 3–30 μg/mouse, i.t.) in mice. The number of nociceptive behaviors (itch and pain) was counted after test compound injection for 5 min. (B) The effect of QWF, an MRGPRX2/Mrgprb2 antagonist, on (+)-KNT-127 (30 μg/mouse, i.t.)-induced nociceptive behaviors. QWF (1–5.6 μg/mouse) was intrathecally pretreated 5 min before i.t. injection of (+)-KNT-127. Data represent the mean ± SEM from 5–27 mice. *p < 0.05, ***p < 0.001 by one-way ANOVA followed by Tukey test.

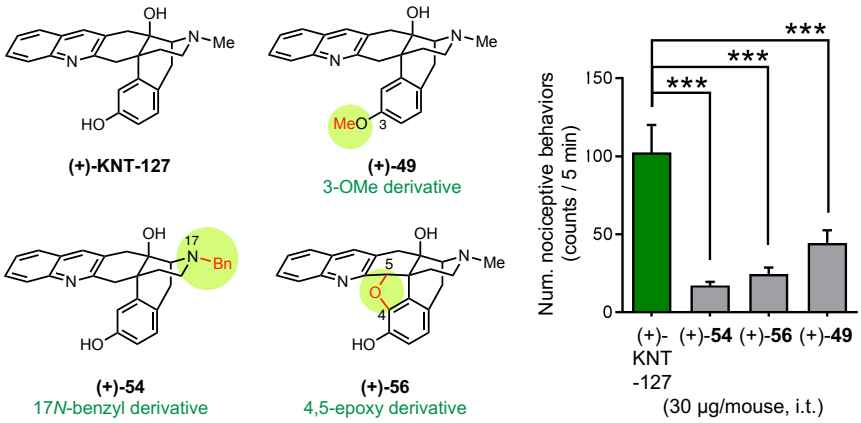


Figure 31. Evaluation of nociceptive behaviors induced by (+)-KNT-127 derivatives in mice

Data represent the mean ± SEM from 9–11 mice. ***p < 0.001 by one-way ANOVA followed by Tukey test.

Both MRGPRX2 and Mrgprb2 are expressed in mast cells and associated with host defense and allergic inflammation. Based on their expression patterns and roles, their activation is considered to contribute to the induction of itch-related scratching behaviors.[88] Thus, this study investigated whether intradermal (i.d.) administration of (+)-KNT-127 induces scratching behaviors in mice. The compound was found to significantly increase the number of scratching behaviors in a dose-dependent manner (Figure 32A). Furthermore, these increased scratching behaviors were significantly attenuated by pre-treatment with nalfurafine, an antipruritic KOR agonist (Figure 32B), suggesting that MRGPRX2/Mrgprb2 agonist (+)-KNT-127 peripherally induces an itch sensation.

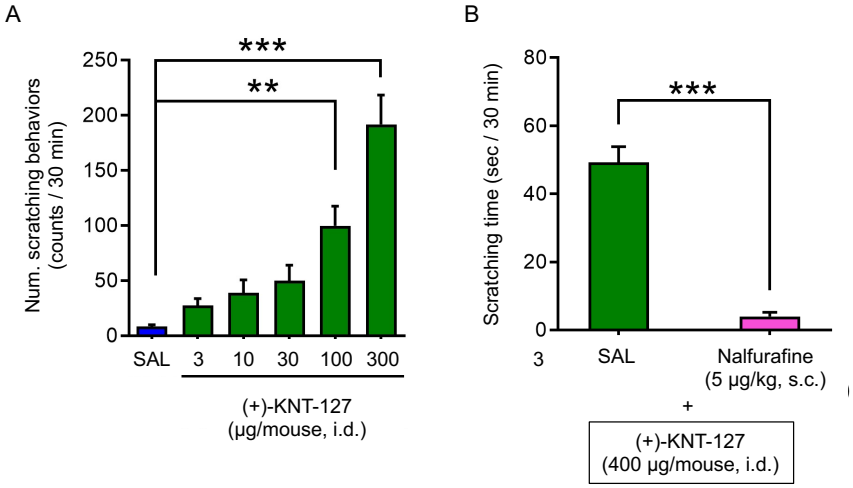


Figure 32. Evaluation of scratching behaviors in mice

(A) Summary bar graph showing the dose-dependent scratching behaviors of (+)-KNT-127 (3–300 μg/mouse, i.d.) in mice. The number of itch-related scratching behaviors was counted 30 min after injection of (+)-KNT-127. Data represent the mean ± SEM from 7 mice. $^{**}p < 0.01$, $^{***}p < 0.001$ by one-way ANOVA followed by Tukey test. (B) The effect of nalfurafine (5 μg/kg, s.c.) on the (+)-KNT-127 (400 μg/mouse, i.d.)-induced increase in total scratching time. Nalfurafine, a clinical antipruritic medication, was subcutaneously administered 20 min before i.d. injection of (+)-KNT-127. Data represent the mean ± SEM from 8 mice. $^{***}p < 0.001$ by unpaired Student's *t*-test.

4.7 Conclusion

In this chapter, an MRGPRX2/Mrgprb2 agonist without DOR affinity was synthesized via the structural optimization of (+)-TAN-67 to determine the mechanism behind the nociceptive behavior it induces in mice. Based on the hypothesis that the DOR affinity of (+)-TAN-67 is attributed to its phenol ring's free rotation, unnatural morphinan derivative (+)-KNT-127, which has a methylene carbon that inhibits the phenol ring's rotation, was synthesized. The i.t. administration of the synthesized compound to mice induced nociceptive behaviors just as (+)-TAN-67 does. These behaviors were inhibited by QWF, which has antagonistic effects on MRGPRX2 and Mrgprb2, implying that (+)-KNT-127 exhibits its effects by acting on Mrgprb2. Fewer nociceptive behaviors were induced by the 17*N*-benzyl derivative, 4,5-epoxy derivative, and 3-methoxy derivative. When administered by s.c. injection, (+)-KNT-127 induced scratching behaviors that were inhibited by antipruritic nalfurafine, indicating that it induces such behaviors derived from itchiness by acting on peripheral Mrgprs. MRGPRX2/Mrgprb2 agonist (+)-KNT-127, which has a morphinan skeleton without affinity for opioid receptors, will be a useful ligand for future development of therapeutics targeting Mrgprs.

Chapter 5. Conclusion

In this research, structural optimization studies and pharmacological evaluations were performed to discover ligands with selective agonistic activity for OX_1R, OX_2R, or MRGPRX2.

In Chapter 2, to develop potent OX_2R agonists that could be used as lead compounds for narcolepsy treatment, a structural optimization study was performed with a tetralin skeleton inspired by the putative binding mode of naphthalene-type agonist **4**, subsequently identifying tetralin-type agonist (*S*)-**5j** (which has high selectivity for OX_2R) and (*R*)-**5j** (which has potent agonistic activity for both receptors). These results indicated that the stereochemistry differences in the tetralin skeleton significantly affect the binding mode of tetralin-type agonists, especially for OX_1R.

In Chapter 3, to create the first selective OX_1R agonist for use in identifying receptor functions, the diarylsulfonamide unit in (*R*)-**5j** was optimized. The results indicated that the B-ring and carbamoyl group play important roles in OX_1R agonistic activity, whereas the A-ring is preferred for OX_2R agonistic activity. Substitution of the A-ring for a *trans*-double bond and modification of the carbamoyl group led to selective OX_1R agonist (*rac*)-**33n**. Finally, the more potent selective OX_1R agonist (*R*)-**33n** was identified by optical resolution utilizing the insights obtained in Chapter 2. This compound is the first selective small molecule OX_1R agonist, and its utility as a chemical tool was demonstrated via an *in vivo* assay.

In Chapter 4, to understand the mechanism of how (+)-TAN-67 induces nociceptive behaviors in mice, (+)-KNT-127, a selective MRGPRX2/Mrgprb2 agonist with almost no affinity for opioid receptors, was created. It was demonstrated that the nociceptive behaviors in mice induced by this compound are inhibited by MRGPRX2/Mrgprb2 antagonist QWF and antipruritic KOR agonist nalfurafine, indicating that these behaviors are induced by an itch sensation through Mrgprs activation.

In the future, these receptor-selective ligands will contribute to the development of novel lead compounds targeting OXR or MRGPRX2 and the elucidation of receptor functions.

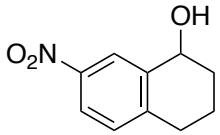
Experimental section

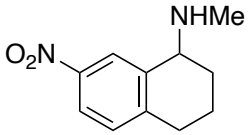
Chemistry

General

All reagents and solvents were purchased from the following commercial suppliers: Tokyo Chemical Industry Co., Ltd., Sigma-Aldrich Co., Kanto Chemical Co., Inc., FUJIFILM Wako Pure Chemical Co., and Nacalai Tesuque, Inc. All commercially available chemicals and solvents were used without further purification. In general, reaction mixtures were magnetically stirred at the respective temperature under argon atmosphere. The synthetic compounds described in this study were checked with analytical thin-layer chromatography (TLC, Merck Co., Ltd., Kieselgel 60 F_{254}, 0.25 mm), visualized under UV light at 254 nm and phosphomolybdic acid in a sulfuric acid aqueous solution, Hanessian stain, ninhydrin or *p*-anisaldehyde followed by heating. Column chromatography was carried out on silica gel (a: spherical, neutral, 40–50 μm, Kanto Chemical Co., Japan; b: spherical, neutral, CHROMATOREX PSQ60B, 60 μm, Fuji Silysia Chemical Ltd.). Preparative TLC was performed on Kieselgel 60 F_{254} (0.50 mm) plates (Merck Co., Ltd.). Infrared (IR) spectra were recorded on a JASCO FT/IR-4100Plus. Nuclear magnetic resonance (NMR) spectra were obtained on a JEOL JNM-ECS 400 at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. NMR chemical shifts are quoted in ppm using tetramethylsilane (δ 0 ppm) as the reference for ^{1}H NMR spectroscopy and $CDCl_3$ (δ 77.16 ppm) for ^{13}C NMR spectroscopy. Some compounds were observed as a mixture of rotamers. Mass spectra (MS) were obtained on a JEOL JMS-T100LP spectrometer. Elemental analysis was performed with a J-SCIENCE MICRO CORDER JM10. The purity (≥95%) of the assayed compounds was determined by analytical HPLC. Analytical HPLC was performed on ACQUITY UPLC system (Waters Co., Ltd) equipped with ACQUITY UPLC BEH C18 column (1.7 μm, 50 mm × 2.1 mm), with PDA detection at 254 nm, at column temperature of 40 ºC. The chiral resolution was performed using SSC-8200-25 recycling preparative HPLC system (Senshu Scientific Co., Ltd.) with a DAICEL CHIRALPAK AD-H (5 μm, 20 mm I.D.×250 mmL), with PDA detection at 254 nm at 25 °C. The optical purity was analyzed using ACQUITY UPLC system (Waters Co., Ltd) with a DAICEL CHIRALPAK AD-H (5 μm, 4.6 mm I.D. × 250 mmL), with PDA detection at 254 nm at 25 °C. Optical rotations were measured with Anton Paar MCP 100 Polarimeter. X-ray crystallographic data were collected by Rigaku R-AXIS RAPID II diffractometer.

7-Nitro-1,2,3,4-tetrahydronaphthalen-1-ol (10a) and *N*-methyl-7-nitro-1,2,3,4-tetrahydronaphthalen-1-amine (10c)





A mixture of 7-nitro-1-tetralone (**9**, 20.8 g, 0.109 mol), $MeNH_2 \cdot HCl$ (22.1 g, 0.327 mol) and $NaBH_3CN$ (10.3 g, 0.164 mol) in MeOH (250 mL) and THF (250 mL) was refluxed for 41 h under an argon atmosphere. After cooling to room temperature, the reaction mixture was quenched by the addition of sat. $NaHCO_3$ aq. (300 mL) and H_2O (300 mL), and extracted with $CHCl_3$ (500, 400, 300, 200 mL). The organic layer was washed with brine (300 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (50% EtOAc in hexane to 5% MeOH in $CHCl_3$). The residue with impurities was dissolved in EtOAc (400 mL). The organic layer was extracted with 2 M HCl aq. (200, 50, 50 mL). The aqueous layer was basified with NaOH and then extracted with CH_2Cl_2 (300, 300, 100, 100 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford *N*-methyl-7-nitro-1,2,3,4-tetrahydronaphthalen-1-amine (18.7 g, 60%) as a yellow oil. 7-Nitro-1,2,3,4-tetrahydronaphthalen-1-ol (**10c**, 3.58g, 17%) was also obtained from the EtOAc layer.

10a: The spectral data were described in the previous report.[105]

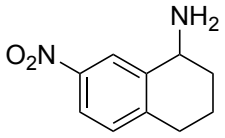
10c: IR (neat): 2937, 1518, 1341 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.73–2.06 (m, 4H), 2.53 (s, 3H), 2.73–2.97 (m, 2H), 3.64–3.78 (m, 1H), 7.22 (d, J = 8.2 Hz, 1H), 7.98 (dd, J = 8.2, 2.3 Hz, 1H), 8.27 (d, J = 2.3 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 18.7, 27.3, 29.7, 33.9, 57.0, 121.6, 124.1, 130.0, 140.8, 145.6, 146.3.

HR-MS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{15}N_2O_2$: 207.11335, found: 207.11246.

7-Nitro-1,2,3,4-tetrahydronaphthalen-1-amine (10b)



To a solution of 7-nitro-1-tetralone (**9**, 100 mg, 0.523 mmol) in MeOH (5.2 mL) were added ammonium acetate (416 mg, 5.23 mmol) and sodium cyanoborohydride (104 mg, 1.57 mmol), and the mixture was stirred for 24 h at room temperature under an argon atmosphere. The reaction mixture was quenched by the addition of sat. $NaHCO_3$ aq. (6 mL), and extracted with $CHCl_3$ (20, 10, 5 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (0–10% MeOH in $CHCl_3$) to afford **10b** (36.9 mg, 37%) as a colorless solid.

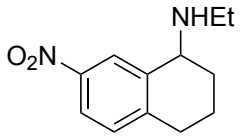
IR (neat): 3371, 1583, 1514, 1339 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.66−1.76 (m, 1H), 1.77−1.90 (m, 1H), 1.93−2.18 (m, 2H), 2.73−2.94 (m, 2H), 4.02 (t, J = 6.0 Hz, 1H), 7.22 (d, J = 8.7 Hz, 1H), 7.96 (dd, J = 8.7, 2.3 Hz, 1H), 8.34 (d, J = 2.3 Hz, 1H). The NH_2 peaks were not observed.

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 19.4, 29.8, 33.4, 49.5, 121.4, 123.3, 129.9, 142.8, 144.9, 146.5.

HR-MS (ESI): m/z $[M+H]^+$ calcd for $C_{10}H_{13}N_2O_2$: 193.0977, found: 193.0983.

***N*-Ethyl-7-nitro-1,2,3,4-tetrahydronaphthalen-1-amine (10d)**



To a solution of 7-nitro-1-tetralone (**9**, 50.0 mg, 0.262 mmol), ethylamine hydrochloride (218 mg, 2.62 mmol), acetic acid (50.0 μL) and sodium acetate (129 mg, 1.57 mmol) in MeOH (2.5 mL) was added sodium cyanoborohydride (49.1 mg, 0.785 mmol). The mixture was stirred for 18 h at 90 °C under an argon atmosphere. After cooling to room temperature, the reaction mixture was quenched by the addition of sat. $NaHCO_3$ aq. (2 mL), and extracted with $CHCl_3$ (20, 10, 5 mL). The organic layer was washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 99:1 to 92:8) and preparative TLC (5% MeOH in $CHCl_3$) to afford **10d** (48.3 mg, 84%) as a colorless oil.

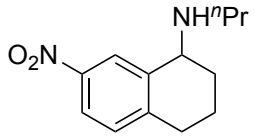
IR (neat): 3584, 3327, 1516, 1341 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.17 (t, *J* = 7.3 Hz, 3H), 1.72−2.10 (m, 4H), 2.63−3.03 (m, 4H), 3.81 (t, *J* = 5.0 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 1H), 7.98 (dd, *J* = 8.7, 2.3 Hz, 1H), 8.28 (d, *J* = 2.3 Hz, 1H). The NH peak was not observed.

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 15.5, 18.8, 27.9, 29.7, 41.5, 55.3, 121.7, 124.1, 130.1, 140.7, 145.6, 146.4.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{12}H_{17}N_2O_2$: 221.1290, found: 221.1293.

7-Nitro-*N*-propyl-1,2,3,4-tetrahydronaphthalen-1-amine (10e)



To a solution of 7-nitro-1-tetralone (**9**, 100 mg, 0.523 mmol), propylamine (429 μL, 5.23 mmol), acetic acid (0.10 mL), sodium acetate (257 mg, 3.14 mmol) in MeOH (5.0 mL) was added sodium cyanoborohydride (98.3 mg, 1.57 mmol). The mixture was stirred for 16 h at 90 °C under an argon atmosphere. After cooling to room temperature, the reaction mixture was quenched by the addition of sat. $NaHCO_3$ aq. (4 mL) and extracted with $CHCl_3$ (20, 10, 5 mL). The organic layer was washed with brine (4 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (8–66% EtOAc in hexane) and preparative TLC ($CHCl_3$/MeOH/28% NH_3 aq. = 100:10:1) to afford **10e** (66.5 mg, 54%) as a colorless oil.

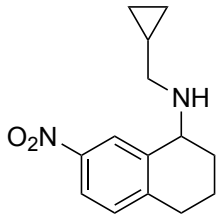
IR (neat): 3584, 3331, 1519, 1342 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.97 (t, J = 7.3 Hz, 3H), 1.40−2.16 (m, 6H), 2.50−3.03 (m, 4H), 3.80 (t, J = 5.0 Hz, 1H), 7.21 (d, J = 8.7 Hz 1H), 7.97 (dd, J = 8.7, 2.3 Hz, 1H), 8.30 (d, J = 2.3 Hz, 1H). The NH peak was not observed.

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 12.0, 18.9, 23.8, 28.1, 29.7, 49.3, 55.4, 121.5, 124.0, 129.9, 141.5, 145.5, 146.4.

HR-MS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{19}N_2O_2$: 235.1447, found: 235.1442.

***N*-(Cyclopropylmethyl)-7-nitro-1,2,3,4-tetrahydronaphthalen-1-amine (10f)**



To a solution of 7-nitro-1-tetralone (**9**, 100 mg, 0.523 mmol), cyclopropylmethylamine (448 μL, 6.29 mmol), acetic acid (0.10 mL) and sodium acetate (257 mg, 3.14 mmol) in MeOH (5.0 mL) was added sodium cyanoborohydride (98.3 mg, 1.57 mmol). The mixture was stirred for 16 h at 90 °C under an argon atmosphere. After cooling to room temperature, the reaction mixture was quenched by the addition of sat. $NaHCO_3$ aq. (4 mL) and extracted with $CHCl_3$ (20, 10, 5 mL). The organic layer was washed with brine (4 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (8–66% EtOAc in hexane and 0–50% EtOAc in hexane) to afford **10f** (65.7 mg, 51%) as a yellow oil.

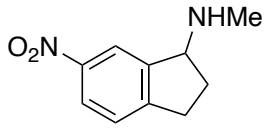
IR (neat): 3330, 1520, 1343 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.06−0.24 (m, 2H), 0.44−0.60 (m, 2H), 0.92−1.09 (m, 1H), 1.66−2.18 (m, 4H), 2.47−2.70 (m, 2H), 2.74−3.02 (m, 2H), 3.84 (t, J = 5.0 Hz 1H), 7.21 (d, J = 8.7 Hz, 1H), 7.97 (dd, J = 8.7, 2.3 Hz, 1H), 8.30 (d, J = 2.3 Hz, 1H). The NH peak was not observed.

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 3.4, 3.7, 11.7, 18.8, 28.0, 29.7, 52.4, 55.2, 121.5, 124.0, 129.9, 141.4, 145.5, 146.3.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{14}H_{19}N_2O_2$: 247.1447, found: 247.1439.

***N*-Methyl-6-nitro-2,3-dihydro-1*H*-inden-1-amine (10g)**



A mixture of 6-nitro-1-indanone (**8**, 263 mg, 1.48 mmol), $MeNH_2 \cdot HCl$ (999 mg, 14.8 mmol) and $NaBH_3CN$ (279 mg, 4.44 mmol) in MeOH (8 mL) was refluxed for 14 h under an argon atmosphere. After cooling to room temperature, the reaction mixture was quenched by the addition of sat. $NaHCO_3$ aq. (10 mL) and H_2O (20 mL) and extracted with 25% MeOH in $CHCl_3$ (40, 30, 20, 10 mL). The organic layer was concentrated under reduced pressure and the crude residue was dissolved in EtOAc (400 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (2–5% MeOH in $CHCl_3$) to afford **10g** (205 mg, 72%) as a black oil.

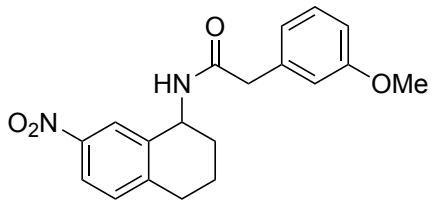
IR (neat): 3324, 2942, 2852, 1519, 1346 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.89−1.98 (m, 1H), 2.47–2.56 (m, 4H), 2.90 (ddd, *J* = 16.9, 7.8, 7.8 Hz, 1H), 3.09 (ddd, *J* = 16.9, 8.7, 5.0 Hz, 1H), 4.23 (t, *J* = 6.6 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 8.10 (dd, *J* = 8.2, 2.1 Hz, 1H), 8.19 (d, *J* = 2.1 Hz, 1H). The NH peak was not observed.

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 30.7, 33.4, 34.0, 64.4, 119.7, 123.4, 125.4, 147.0, 147.4, 151.7.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{10}H_{13}N_2O_2$: 193.09770, found: 193.09740.

2-(3-Methoxyphenyl)-*N*-(7-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide (11b)



A mixture of **10b** (34.9 mg, 0.182 mmol), DIPEA (63.4 µL, 0.363 mmol), 3-methoxy phenylacetic acid (40.0 mg, 0.236 mmol) and HATU (106 mg, 0.272 mmol) in dry CH_2Cl_2 (1.8 mL) was stirred for 1 h at room temperature under an argon atmosphere. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (8–66% EtOAc in hexane) to afford **11b** (52.0 mg, 84%) as a white solid.

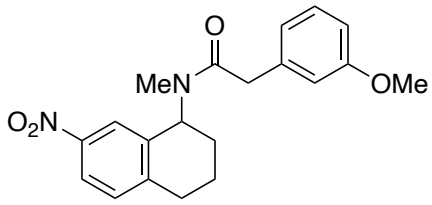
IR (KBr): 3419, 3258, 1642, 1584, 1519, 1344 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.54−1.70 (m, 1H), 1.77−1.89 (m, 2H), 2.05−2.17 (m, 1H), 2.74−2.89 (m, 2H), 3.62 (d, *J* = 16.0 Hz, 1H), 3.69 (d, *J* = 16.0 Hz, 1H), 3.79 (s, 3H), 5.13−5.32 (m, 1H), 5.74 (d, *J* = 8.7 Hz, 1H), 6.77−6.86 (m, 2H), 6.89 (d, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.94 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.98 (d, *J* = 2.3 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 20.3, 29.5, 29.9, 44.1, 47.7, 55.3, 113.2, 114.9, 121.6, 122.0, 122.9, 130.2, 130.4, 136.1, 138.7, 145.3, 146.5, 160.2, 170.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{19}H_{20}N_2NaO_4$: 363.1321, found: 363.1316.

2-(3-Methoxyphenyl)-*N*-methyl-*N*-(7-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide (11c)



A mixture of **10c** (199 mg, 0,965 mmol), 3-methoxyphenylacetic acid (483 mg, 2.91 mmol), Et_3N (1.00 mL, 7.19 mmol), and HATU (1.10 g, 2.89 mmol) in DMF (5 mL) was stirred for 4 h at room temperature under an argon atmosphere. The reaction mixture was diluted with sat. $NaHCO_3$ aq. (5 mL) and H_2O (10 mL) and extracted with $CHCl_3$ (20, 10, 10 mL). The organic layer was washed with 1 M HCl aq. (5 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (18–50% EtOAc in hexane and hexane:EtOAc:MeOH:28% NH_3 aq.=20:10:0.9:0.1) and preparative TLC (33% EtOAc in hexane) to afford **11c** (321 mg, 93%) as a yellow oil.

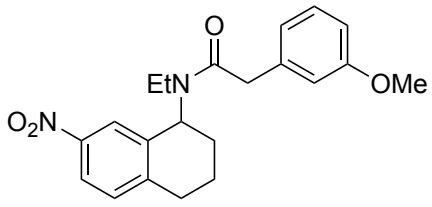
IR (neat): 2938, 1639, 1520, 1341 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.66–2.14 (m, 4H), 2.62 (s, 0.9H), 2.72 (s, 2.1H), 2.76–3.00 (m, 2H), 3.78 (s, 0.9H), 3.83 (s, 2.1H), 3.83–3.90 (m, 2H), 5.06–5.16 (m, 0.3H), 5.96–6.00 (m, 0.7H), 6.77 (dd, *J* = 8.2, 2.3 Hz, 0.3H), 6.85 (dd, *J* = 8.2, 2.3 Hz, 0.7H), 6.87–6.92 (m, 1.3H), 6.96 (d, *J* = 7.3 Hz, 0.7H), 7.16–7.26 (m, 1.3H), 7.33 (t, *J* = 7.8 Hz, 0.7H), 7.66 (s, 0.3H), 7.80 (s, 0.7H), 7.90–8.05 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.6, 21.7, 26.6, 27.9, 29.5, 29.6, 29.8, 31.5, 42.0, 42.2, 52.8, 55.4, 57.3, 112.7, 112.8, 114.0, 114.4, 120.9, 121.0, 121.8, 121.9, 122.1, 122.2, 130.2, 130.4, 130.5, 136.1, 136.5, 136.7, 137.5, 146.4, 146.9, 160.2, 171.7, 172.2.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{20}H_{22}N_2NaO_4S$: 377.14773, found: 377.14866.

***N*-Ethyl-2-(3-methoxyphenyl)-*N*-(7-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide (11d)**



A mixture of **10d** (30.1 mg, 0.137 mmol), DIPEA (47.7 μL, 0.273 mmol), 3-methoxyphenylacetic acid (30.1 mg, 0.178 mmol) and HATU (79.5 mg, 0.205 mmol) in dry CH_2Cl_2 (1.4 mL) was stirred for 2 h at room temperature under an argon atmosphere. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (12–100% EtOAc in hexane) and preparative TLC (50% EtOAc in hexane) to afford **11d** (55.5 mg, quant.) as a colorless oil.

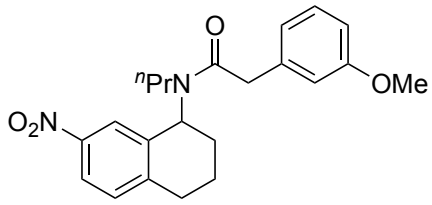
IR (neat): 1639, 1520, 1340 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.16 (t, *J* = 6.9 Hz, 1.2H), 1.22 (t, *J* = 6.9 Hz, 1.8H), 1.54−2.20 (m, 4H), 2.61−2.78 (m, 0.4H), 2.80−2.97 (m, 2H), 2.98−3.16 (m, 0.6H), 3.33−3.53 (m, 1H), 3.74−3.91 (m, 5H), 5.04 (t, *J* = 7.8 Hz, 0.4H), 5.53 (br s, 0.6H), 6.72−6.91 (m, 2.4H), 6.95 (d, *J* = 7.8 Hz, 0.6H), 7.16−7.25 (m, 1.4H), 7.32 (t, *J* = 7.8 Hz, 0.6H), 7.68 (d, *J* = 1.4 Hz, 0.4H), 7.76 (d, *J* = 1.4 Hz, 0.6H), 7.87−7.99 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 14.1, 16.3, 21.8, 22.1, 27.9, 28.9, 29.6, 29.8, 39.3, 41.1, 41.2, 41.6, 42.6, 54.8, 55.3, 58.1, 112.5, 112.7, 112.8, 113.7, 114.5, 115.0, 120.8, 121.0, 121.5, 121.8, 121.9, 122.1, 129.6, 130.1, 130.2, 130.4, 136.4, 136.5, 137.3, 138.5, 145.8, 146.6, 160.1, 160.2, 171.4, 171.6.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{21}H_{24}N_2NaO_4$: 391.1634, found: 391.1628.

2-(3-Methoxyphenyl)-*N*-(7-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-propylacetamide (11e)



A mixture of **10e** (43.4 mg, 0.185 mmol), DIPEA (64.7 μL, 0.370 mmol), 3-methoxyphenylacetic acid (40.8 mg, 0.241 mmol) and HATU (108 mg, 0.278 mmol) in dry CH_2Cl_2 (1.9 mL) was stirred for 5 h at room temperature under an argon atmosphere. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (0–50% EtOAc in hexane) to afford **11e** (67.0 mg, 95%) as a colorless oil.

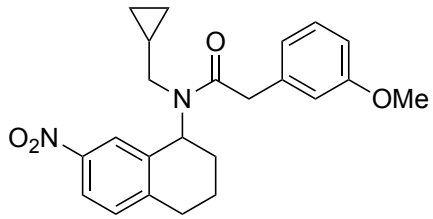
IR (neat): 1640, 1521, 1340 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.79 (t, *J* = 7.3 Hz, 1H), 0.87 (t, *J* = 7.3 Hz, 2H), 1.36−2.22 (m, 6H), 2.42−2.61 (m, 0.3H), 2.75−3.07 (m, 2.7H), 3.20−3.41 (m, 1H), 3.70−3.91 (m, 5H), 5.03 (t, *J* = 7.8 Hz, 0.3H), 5.44 (br s, 0.7H), 6.71−7.04 (m, 3H), 7.15−7.25 (m, 1.3H), 7.31 (t, *J* = 7.8 Hz, 0.7H), 7.68 (d, *J* = 2.3 Hz, 0.3H), 7.76 (d, *J* = 2.3 Hz, 0.7H), 7.84−8.03 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 11.5, 11.7, 21.9, 22.0, 22.1, 24.3, 27.8, 29.0, 29.5, 29.8, 41.7, 42.6, 46.6, 48.8, 55.0, 55.3, 58.0, 112.6, 112.8, 113.7, 114.4, 120.8, 121.0, 121.3, 121.4, 121.8, 122.1, 130.0, 130.1, 130.2, 130.4, 136.4, 136.6, 137.4, 138.6, 145.7, 145.8, 146.5, 146.6, 160.1, 160.1, 171.4, 171.5.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{22}H_{26}N_2NaO_4$: 405.1790, found: 405.1783.

***N*-(Cyclopropylmethyl)-2-(3-methoxyphenyl)-*N*-(7-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide (11f)**



A mixture of **10f** (30.0 mg, 0.122 mmol), DIPEA (42.5 µL, 0.244 mmol), 3-methoxyphenylacetic acid (26.8 mg, 0.158 mmol) and HATU (70.9 mg, 0.183 mmol) in dry CH_2Cl_2 (1.2 mL) was stirred for 4 h at room temperature under an argon atmosphere. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (0–50% EtOAc in hexane) to afford **11f** (41.0 mg, 85%) as a colorless oil.

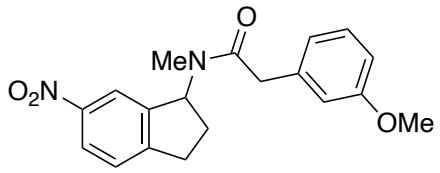
IR (neat): 1642, 1520, 1340 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.00−0.20 (m, 2H), 0.32−0.66 (m, 2H), 0.77−1.11 (m, 1H), 1.55−2.32 (m, 4H), 2.76−3.40 (m, 4H), 3.70−3.96 (m, 5H), 4.89−5.60 (m, 1H), 6.69−6.98 (m, 3H), 7.14−7.36 (m, 2H), 7.69−8.02 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 4.7, 4.9, 5.3, 5.4, 10.8, 11.8, 22.0, 22.3, 27.2, 29.2, 29.7, 29.9, 42.0, 42.6, 48.6, 52.0, 55.3, 55.8, 56.0, 57.7, 112.5, 112.8, 113.8, 114.4, 120.9, 121.0, 121.3, 121.6, 121.8, 122.0, 122.5, 130.0, 130.4, 136.4, 136.6, 137.5, 138.8, 145.6, 145.7, 146.5, 160.1, 171.1, 171.9.

HR-MS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{23}H_{26}N_2NaO_4$: 417.1790, found: 417.1789.

2-(3-Methoxyphenyl)-*N*-methyl-*N*-(6-nitro-2,3-dihydro-1*H*-inden-1-yl)acetamide (11g)



A mixture of **10g** (185 mg, 0.962 mmol), 3-methoxyphenylacetic acid (480 mg, 2.89 mmol), Et_3N (1.35 mL, 9.71 mmol) and HATU (1.10 g, 2.89 mmol) in DMF (5 mL) was stirred for 5 h at room temperature under an argon atmosphere. The reaction mixture was concentrated under reduced pressure and diluted with $CHCl_3$ (30 mL). The mixture was washed with sat. $NaHCO_3$ aq. (20 mL), and the aqueous layer was extracted with $CHCl_3$ (20, 20, 10 mL). The organic layer was washed with 1 M HCl aq. (20 mL) and H_2O (80, 80 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (0–15% EtOAc in Hexane) to afford **11g** (320 mg, 98%) as a yellow oil.

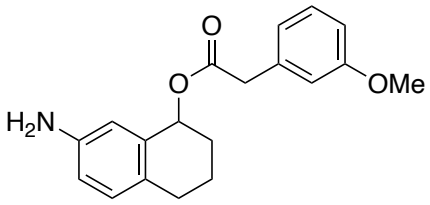
IR (neat): 3002, 2946, 1644, 1519, 1347, 1257, 757 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.89–2.12 (m, 1H), 2.12–2.25 (m, 0.3H), 2.43–2.56 (m, 0.7H), 2.63 (s, 2.1H), 2.70 (s, 0.9H), 2.80–2.99 (m, 1H), 3.00–3.13 (m, 1H), 3.79 (s, 0.9H), 3.80 (s, 1.4H), 3.84 (s, 2.1H), 3.91 (s, 0.6H), 5.53 (t, *J* = 8.2 Hz, 0.3H), 6.38 (t, *J* = 8.5 Hz, 0.6H), 6.75–6.84 (m, 1H), 6.84–6.96 (m, 2H), 7.36–7.26 (m, 2H), 7.50 (s, 0.3H), 7.87 (s, 0.7H), 8.10–8.07 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 28.6, 29.0, 29.6, 30.4, 30.6, 30.9, 41.9, 42.2, 55.4, 55.4, 58.5, 62.9, 112.5, 112.7, 114.3, 114.4, 119.3, 119.5, 120.9, 121.1, 123.6, 124.0, 125.7, 125.8, 130.0, 130.2, 136.2, 136.7, 142.6, 143.6, 147.7, 147.8, 150.5, 151.3, 160.1, 160.3, 171.3, 172.0.

HR-MS (ESI): *m*/*z* [M+Na]+ calcd for $C_{19}H_{20}N_2NaO_4$: 363.13208, found: 363.13175.

7-Amino-1,2,3,4-tetrahydronaphthalen-1-yl 2-(3-methoxyphenyl)acetate (12a)



A mixture of **10a** (1.01 g, 5.23 mmol), 3-methoxyphenylacetic acid (2.61 g, 15.7 mmol), Et_3N (7.30 mL, 52.5 mmol), and HATU (5.97 g, 15.7 mmol) in DMF (25 mL) was stirred for 2 h at room temperature under an argon atmosphere. The reaction mixture was concentrated under reduced pressure and diluted with 25% EtOAc in hexane (100 mL). The mixture was washed with sat. $NaHCO_3$ aq. (50 mL), and the aqueous layer was extracted with 25% EtOAc in hexane (50, 50, 50 mL). The organic layer was washed with 1 M HCl aq. (50, 50 mL), H_2O (100, 100 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (0–20% EtOAc in Hexane) to afford a yellow oil (1.72g) with inseparable impurities. To a stirred solution of the obtained yellow oil in EtOH (16 mL) and H_2O (8.0 mL) were added ammonium chloride (839 mg, 15.7 mmol) and Iron powder (876 mg, 15.7 mmol). The mixture was heated to 90 ˚C for 2 h, and then Iron powder (1.46 g, 26.1 mmol) was added to the reaction mixture. After heating at 90 ˚C for 6 h, Iron powder (1.46 g, 26.1 mmol) and ammonium chloride (2.92 g, 54.6 mmol) were added to the reaction mixture, and then the mixture was stirred for another 2 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The mixture was diluted with sat. $NaHCO_3$ aq. (100 mL) and H_2O (100 mL) and extracted with $CHCl_3$ (200, 100, 100, 50 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (0–20% EtOAc in Hexane) to afford **12a** (683 mg, 42% in 2 steps) as a pale yellow solid.

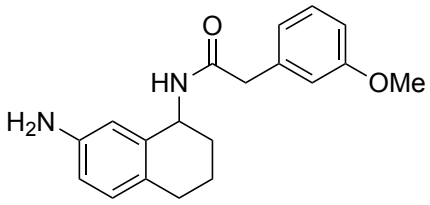
IR (neat): 3451, 3369, 2939, 1724, 1625, 1600, 1508, 1492, 1263, 1149 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.69–2.03 (m, 4H), 2.53–2.79 (m, 2H), 3.50 (br s, 2H), 3.62 (s, 2H), 3.80 (s, 3H), 5.90 (t, J = 4.6 Hz, 1H), 6.48 (d, J = 2.5 Hz, 1H), 6.59 (dd, J = 8.2, 2.5 Hz, 1H), 6.82 (dd, J = 8.0, 2.3 Hz, 1H), 6.85–6.93 (m, 3H), 7.23 (t, J = 8.0 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 19.4, 28.3, 29.3, 42.1, 55.3, 70.9, 112.9, 114.9, 115.4, 115.9, 121.9, 128.0, 129.6, 130.0, 135.3, 135.8, 144.5, 159.8, 171.4.

HR-MS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{19}H_{21}NNaO_3$: 334.14191, found: 334.14124.

***N*-(7-Amino-1,2,3,4-tetrahydronaphthalen-1-yl)-2-(3-methoxyphenyl)acetamide (12b)**



A mixture of **11b** (52.0 mg, 0.153 mmol), iron powder (42.7 mg, 0.764 mmol) and ammonium chloride (40.9 mg, 0.764 mmol) in EtOH (1.5 mL) and H_2O (0.30 mL) was stirred for 4 h at 60 °C under an argon atmosphere. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude residue was purified by preparative TLC (5% MeOH in $CHCl_3$) to afford **12b** (45.4 mg, 96%) as an orange oil.

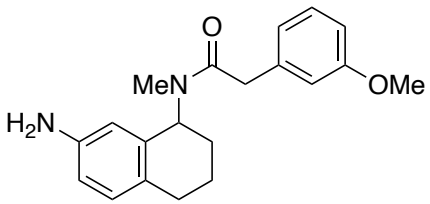
IR (KBr): 3341, 1642 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.52−1.81 (m, 3H), 1.91−2.09 (m, 1H), 2.53−2.68 (m, 2H), 3.52 (br s, 2H), 3.56 (s, 2H), 3.78 (s, 3H), 5.00−5.13 (m, 1H), 5.76 (d, J = 8.7 Hz, 1H), 6.43 (d, J = 2.3 Hz, 1H), 6.49 (dd, J = 8.2, 2.3 Hz, 1H), 6.76−6.90 (m, 4H), 7.23 (t, J = 7.8 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 20.6, 28.4, 30.4, 44.1, 47.8, 55.3, 112.8, 114.2, 114.9, 115.0, 121.7, 127.4, 129.96, 130.05, 136.6, 137.5, 144.7, 160.0, 170.3.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{19}H_{22}NaN_2O_2$: 333.1579, found: 333.1574.

***N*-(7-Amino-1,2,3,4-tetrahydronaphthalen-1-yl)-2-(3-methoxyphenyl)-*N*-methylacetamide (12c)**



A mixture of **11c** (310 mg, 0.875 mmol), ammonium chloride (467 mg, 8.73 mmol), and iron powder (490 mg, 8.77 mmol) in EtOH (6 mL) and H_2O (6 mL) was heated to 90 ˚C for 2 h under an argon atmosphere. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The mixture was diluted with sat. $NaHCO_3$ aq. (10 mL) and H_2O (10 mL) and extracted with $CHCl_3$ (30, 10, 5 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (hexane:EtOAc:MeOH:28% NH_3 aq.=20:10:0.9:0.1) to afford **12c** (263 mg, 93%) as a yellow amorphous.

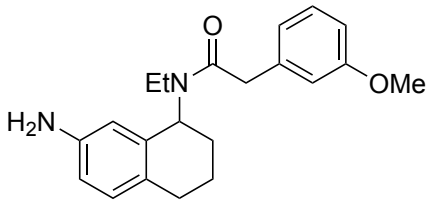
IR (neat): 3440, 3348, 2934, 1629 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.51–2.05 (m, 4H), 2.58–2.69 (m, 5H), 3.32–3.63 (m, 2H), 3.75–3.87 (m, 5H), 5.00 (dd, *J* = 11.0, 5.5 Hz, 0.4H), 5.87 (dd, *J* = 10.3, 5.7 Hz, 0.6H), 6.14–6.31 (m, 1H), 6.48 (dd, *J* = 7.8, 2.3 Hz, 0.6H), 6.52 (dd, *J* = 8.2, 2.3 Hz, 0.4H), 6.76–6.84 (m, 1H), 6.84–6.97 (m, 3H), 7.23 (t, *J* = 8.2 Hz, 0.4H), 7.27 (t, *J* = 7.6 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 22.3, 22.5, 27.3, 28.3, 28.6, 28.8, 29.5, 31.4, 41.9, 42.0, 52.8, 55.4, 57.7, 112.4, 112.6, 112.7, 113.2, 114.2, 114.5, 114.6, 114.8, 121.2, 121.5, 128.1, 128.8, 129.8, 129.9, 130.1, 130.3, 135.5, 136.1, 136.7, 137.1, 144.6, 144.9, 160.0, 160.0, 171.7, 171.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{20}H_{24}N_2NaO_2$: 347.17355, found: 347.17300.

***N*-(7-Amino-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-ethyl-2-(3-methoxyphenyl)acetamide (12d)**



A mixture of **11d** (48.5 mg, 0.132 mmol), iron powder (36.8 mg, 0.658 mmol) and ammonium chloride (35.2 mg, 0.658 mmol) in EtOH (1.3 mL) and H_2O (0.27 mL) was stirred for 21 h at 60 °C under an argon atmosphere. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude residue was purified by preparative TLC (5% MeOH in $CHCl_3$) to afford **12d** (29.5 mg, 66%) as a white solid.

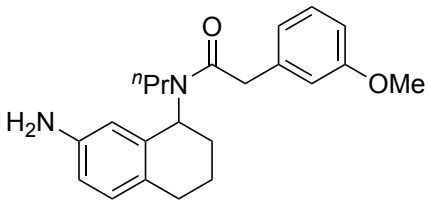
IR (neat): 3445, 3349, 1630 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.15 (t, *J* = 7.3 Hz, 1.8H), 1.21 (t, *J* = 7.3 Hz, 1.2H), 1.44−2.13 (m, 4H), 2.50−2.99 (m, 3H), 3.22−3.68 (m, 3H), 3.70−3.93 (m, 5H), 4.83−5.00 (m, 0.6H), 5.66−5.87 (m, 0.4H), 6.10 (d, *J* = 2.3 Hz, 0.4H), 6.25 (d, *J* = 2.3 Hz, 0.6H), 6.44 (dd, *J* = 8.2, 2.3 Hz, 0.4H), 6.51 (dd, *J* = 8.2, 2.3 Hz, 0.6H), 6.73−7.09 (m, 4H), 7.17−7.32 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 14.2, 16.8, 22.7, 28.5, 28.8, 28.9, 29.4, 39.3, 39.7, 41.6, 42.3, 53.8, 55.3, 55.4, 58.6, 112.4, 112.5, 112.8, 112.9, 113.8, 114.3, 114.7, 114.8, 121.1, 121.7, 128.0, 128.4, 129.7, 129.8, 130.0, 130.3, 136.3, 137.0, 137.2, 137.2, 144.4, 144.8, 159.9, 160.0, 171.4, 171.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{21}H_{26}N_2NaO_2$: 361.1892, found: 361.1879.

***N*-(7-Amino-1,2,3,4-tetrahydronaphthalen-1-yl)-2-(3-methoxyphenyl)-*N*-propylacetamide (12e)**



A mixture of **11e** (61.0 mg, 0.159 mmol), iron powder (44.5 mg, 0.797 mmol) and ammonium chloride (42.7 mg, 0.797 μmol) in EtOH (1.7 mL) and H_2O (0.33 mL) was stirred for 6 h at 60 °C under an argon atmosphere. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude residue was purified by preparative TLC (5% MeOH in $CHCl_3$) to afford **12e** (47.9 mg, 85%) as a pale orange oil.

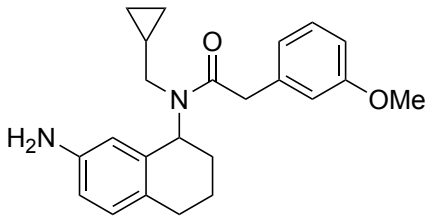
IR (neat): 3447, 3349, 1631 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.72−0.94 (m, 3H), 1.31−2.12 (m, 6H), 2.32−2.86 (m, 3H), 3.07−3.64 (m, 3H), 3.68−3.98 (m, 5H), 4.78−5.01 (m, 0.6H), 5.61−5.87 (m, 0.4H), 6.08 (d, *J* = 2.3 Hz, 0.4H), 6.26 (d, *J* = 2.3 Hz, 0.6H), 6.45 (dd, *J* = 8.2, 2.3 Hz, 0.4H), 6.52 (dd, *J* = 8.2, 2.3 Hz, 0.6H), 6.73−7.11 (m, 4H), 7.15−7.34 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 11.7, 11.8, 22.0, 22.7, 24.9, 28.5, 28.7, 28.9, 29.5, 41.7, 42.3, 46.5, 47.3, 53.9, 55.3, 55.4, 58.5, 112.4, 112.5, 112.8, 113.9, 114.3, 114.7, 114.8, 121.1, 121.7, 127.9, 128.3, 129.7, 129.7, 130.0, 130.3, 136.4, 137.0, 137.2, 137.3, 144.4, 144.8, 159.9, 159.9, 171.7, 171.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{22}H_{28}N_2NaO_2$: 375.2049, found: 375.2050.

***N*-(7-Amino-1,2,3,4-tetrahydronaphthalen-1-yl)-s*N*-(cyclopropylmethyl)-2-(3-methoxyphenyl)acetamide (12f)**



A mixture of **11f** (41.0 mg, 0.104 mmol), iron powder (29.0 mg, 0.520 mmol) and ammonium chloride (27.8 mg, 0.520 mmol) in EtOH (1.1 mL) and H_2O (0.22 mL) was stirred for 6 h at 60 °C under an argon atmosphere. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude residue was purified by preparative TLC (5% MeOH in $CHCl_3$) to afford **12f** (36.2 mg, 95%) as an orange oil.

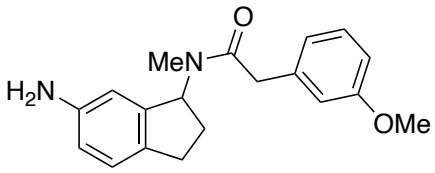
IR (neat): 3449, 3350, 1632 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.02−0.65 (m, 4H), 0.76−0.93 (m, 0.4H), 0.99−1.18 (m, 0.6H), 1.45−2.17 (m, 4H), 2.41−2.90 (m, 3H), 3.10−4.05 (m, 8H), 4.77−5.06 (m, 0.6H), 5.54−5.84 (m, 0.4H), 6.15 (d, *J* = 2.3 Hz, 0.4H), 6.27 (br s, 0.6H), 6.44 (dd, *J* = 8.2, 2.3 Hz, 0.4H), 6.50 (dd, *J* = 8.2, 2.3 Hz, 0.6H), 6.70−7.09 (m, 4H), 7.14−7.34 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 4.9, 5.6, 5.8, 10.8, 12.2, 22.9, 28.6, 28.7, 28.9, 29.9, 41.8, 42.4, 49.8, 54.1, 55.3, 55.4, 58.4, 112.4, 112.7, 112.8, 113.1, 114.0, 114.2, 114.7, 114.8, 121.2, 121.6, 127.9, 128.5, 129.7, 130.0, 130.2, 136.9, 137.2, 137.3, 144.4, 144.8, 159.9, 171.8, 172.2.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{23}H_{28}N_2NaO_2$: 387.2049, found: 387.2038.

***N*-(6-Amino-2,3-dihydro-1*H*-inden-1-yl)-2-(3-methoxyphenyl)-*N*-methylacetamide (12g)**



A mixture of **11g** (286 mg, 0.840 mmol), ammonium chloride (450 mg, 8.41 mmol) and Iron powder (469 mg, 8.40 mmol) in EtOH (6 mL) and H_2O (6 mL) was heated to 90 ˚C for 1 h under an argon atmosphere. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The mixture was diluted with sat. $NaHCO_3$ aq. (10 mL) and H_2O (10 mL) and extracted with $CHCl_3$ (50, 30, 20, 20 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford **12g** (256 mg, 98%) as a pale yellow amorphous.

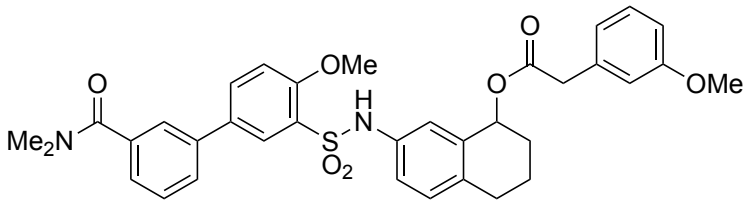
IR (neat): 3445, 3349, 2940, 1632, 1495, 1257 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.76–1.95 (m, 1H), 1.99–2.07 (m, 0.5H), 2.34–2.43 (m, 0.5H), 2.61–2.91 (m, 5H), 3.58 (br s, 2H), 3.77 (s, 1H), 3.79 (s, 1.5H), 3.82 (s, 1.5H), 3.87 (s, 1H), 5.39 (t, *J* = 8.0 Hz, 0.5H), 6.16 (s, 0.5H), 6.25 (t, *J* = 7.8 Hz, 0.5H), 6.38 (s, 0.5H), 6.56 (d, *J* = 7.5 Hz, 1H), 6.77–6.84 (m, 1H), 6.84–6.94 (m, 2H), 6.99 (t, *J* = 7.5 Hz, 1H), 7.21–7.30 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 28.6, 29.2, 29.4, 29.7, 29.8, 30.6, 42.0, 55.4, 55.4, 58.9, 63.6, 110.4, 110.8, 112.5, 112.6, 114.3, 114.4, 115.4 115.7, 121.2, 121.3, 125.5, 125.7, 129.8, 129.9, 133.0, 133.9, 136.8, 137.2, 141.8, 142.7, 145.5, 145.6, 160.0, 160.1, 171.3, 171.6.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{19}H_{22}N_2NaO_2$: 333.15790, found: 333.15706.

7-((3'-(Dimethylcarbamoyl)-4-methoxy-[1,1'-biphenyl])-3-sulfonamido)-1,2,3,4-tetrahydronaphthalen-1-yl 2-(3-methoxyphenyl)acetate (6a)



A mixture of **12a** (15.4 mg, 0.0495 mmol) and 3'-(dimethycarbamoyl)-4-methoxy-[1,1'-biphenyl]-3-sulfonyl chloride (27.0 mg, 0.0763 mmol) in CH_2Cl_2 (0.9 mL) and pyridine (0.3 mL) was stirred for 1 h at room temperature under an argon atmosphere. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (50–80% EtOAc in hexane) to afford **6a** (30.5 mg, 98%) as a colorless oil.

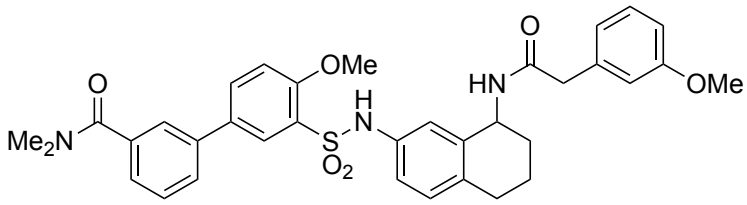
IR (neat): 2940, 1728, 1621, 1503, 1279, 1159 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.61–2.01 (m, 4H), 2.49–2.82 (m, 2H), 2.99 (s, 3H), 3.12 (s, 3H), 3.53 (s, 2H), 3.82 (s, 3H), 3.92–4.05 (3H), 5.82 (t, *J* = 4.6 Hz, 1H), 6.78 (d, *J* = 2.3 Hz, 1H), 6.82–6.89 (m, 3H), 6.97 (d, *J* = 8.2 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 1H), 7.03–7.08 (m, 1H), 7.15 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.23–7.27 (m, 1H), 7.33 (d, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.49–7.58 (m, 2H), 7.68 (dd, *J* = 8.7, 2.3 Hz, 1H), 8.01 (d, *J* = 2.3 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 18.8, 28.4, 28.8, 35.5, 39.7, 41.8, 55.4, 56.6, 70.2, 112.4, 112.7, 115.3, 121.8, 122.2, 122.5, 125.5, 126.0, 126.8, 127.8, 129.0, 129.3, 129.7, 130.2, 133.1, 133.1, 134.4, 135.4, 135.5, 135.6, 137.2, 139.3, 155.7, 159.7, 171.2, 171.4.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{35}H_{36}N_2NaO_7S$: 651.21409, found: 651.21313.

4'-Methoxy-3'-(*N*-(8-(2-(3-methoxyphenyl)acetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide (6b)



A mixture of **12b** (10.0 mg, 32.2 μmol) and 3'-(dimethycarbamoyl)-4-methoxy-[1,1'-biphenyl]-3-sulfonyl chloride (12.5 mg, 35.4 μmol) in CH_2Cl_2 (0.50 mL) and pyridine (0.10 mL) was stirred for 1 h at room temperature under an argon atmosphere. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by preparative TLC (5% MeOH in $CHCl_3$) to afford **6b** (22.2 mg, quant.) as a colorless oil.

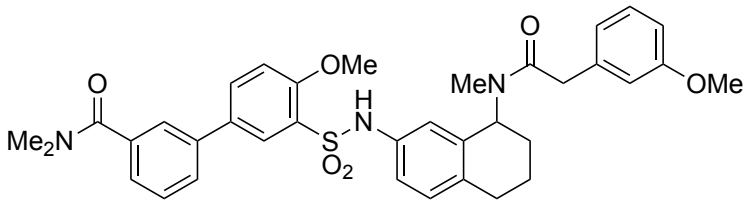
IR (KBr): 3279, 1646, 1620, 1503, 1279, 1161 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.45−2.05 (m, 4H), 2.49−2.70 (m, 2H), 2.99 (s, 3H), 3.12 (s, 3H), 3.54 (s, 2H), 3.82 (s, 3H), 4.02 (s, 3H), 4.92−5.15 (m, 1H), 5.75 (d, *J* = 8.7 Hz, 1H), 6.72−6.93 (m, 5H), 6.99−7.38 (m, 5H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.48−7.62 (m, 2H), 7.70 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.99 (d, *J* = 2.3 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 20.4, 28.6, 30.0, 35.5, 39.7, 44.0, 47.4, 55.5, 56.7, 112.4, 112.8, 115.4, 121.1, 121.4, 121.8, 123.9, 125.5, 126.0, 126.9, 127.9, 129.0, 129.2, 130.1, 130.2, 133.0, 133.1, 136.5, 137.2, 138.0, 139.3, 149.9, 155.8, 160.0, 170.3, 171.4.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{35}H_{37}N_3NaO_6S$: 650.2301, found: 650.2304.

4'-Methoxy-3'-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide (5j)



A mixture of **12c** (211 mg, 650 μmol) and 3'-(dimethycarbamoyl)-4-methoxy-[1,1'-biphenyl]-3-sulfonyl chloride (277 mg, 0.783 μmol) in CH_2Cl_2 (2.7 mL) and pyridine (0.9 mL) was stirred for 22 h at room temperature under an argon atmosphere. The reaction mixture was diluted with sat. $NaHCO_3$ aq. (10 mL) and extracted with $CHCl_3$ (20, 20, 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (80–100% EtOAc in hexane) to afford **5j** (417 mg, quant.) as a colorless amorphous.

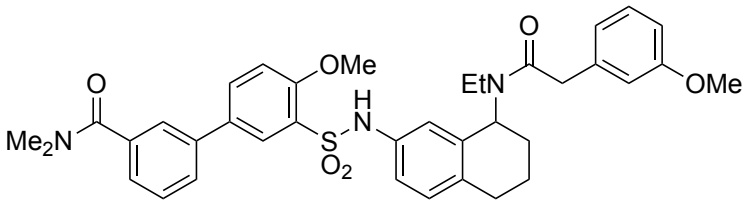
IR (neat): 2935, 1624, 1503, 1397, 1317, 1280, 1161, 751 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.51–1.99 (m, 4H), 2.23 (s, 1.2H), 2.46 (s, 1.8H), 2.63 (d, *J* = 8.5 Hz, 2H), 2.99 (s, 3H), 3.12 (s, 3H), 3.68–3.79 (m, 2H), 3.81 (s, 1.2H), 3.89 (s, 1.8H), 4.00 (s, 1.8H), 4.06 (s, 1.2H), 4.87–4.96 (m, 0.4H), 5.81 (dd, *J* = 10.3, 5.8 Hz, 0.6H), 6.19–6.26 (m, 0.4H), 6.53–6.61 (m, 0.6H), 6.74–7.33 (m, 9H), 7.38–7.46 (m, 1H), 7.46–7.56 (m, 2H), 7.71 (dt, *J* = 8.7, 2.4 Hz, 1H), 7.91 (d, *J* = 2.4 Hz, 0.4H), 8.00 (d, *J* = 2.4 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.0, 26.9, 27.8, 28.7, 28.9, 28.9, 31.2, 35.5, 39.8, 41.7, 41.8, 52.4, 55.5, 55.6, 56.8, 56.9, 57.5, 111.7, 112.1, 112.8, 112.9, 115.0, 115.1, 120.2, 120.4, 121.2, 121.5, 123.1, 125.5, 125.5, 126.0, 126.1, 127.0, 127.8, 127.9, 129.1, 129.1, 129.3, 129.4, 130.0, 130.1, 130.4, 130.7, 133.1, 133.2, 134.6, 134.8, 135.5, 136.1, 136.3, 136.4, 136.6, 136.8, 137.3, 139.2, 139.3, 155.6, 155.9, 160.0, 160.1, 171.4, 171.5, 171.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{36}H_{39}N_3NaO_6S$: 664.24573, found: 664.24479.

3'-(*N*-(8-(*N*-Ethyl-2-(3-methoxyphenyl)acetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-4'-methoxy-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide (6c)



A mixture of **12d** (10.0 mg, 29.5 μmol) and 3'-(dimethycarbamoyl)-4-methoxy-[1,1'-biphenyl]-3-sulfonyl chloride (11.5 mg, 32.5 μmol) in CH_2Cl_2 (0.80 mL) and pyridine (0.20 mL) was stirred for 1 h at room temperature under an argon atmosphere. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by preparative TLC (5% MeOH in $CHCl_3$) to afford **6c** (18.0 mg, 93%) as a colorless oil.

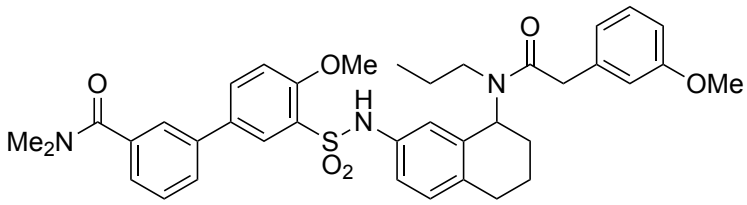
IR (neat): 1627, 1608, 1502, 1279, 1162 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.96 (t, *J* = 6.9 Hz, 1.8H), 1.06 (t, *J* = 6.9 Hz, 1.2H), 1.43−2.31 (m, 5H), 2.53−3.31 (m, 9H), 3.49−4.20 (m, 8H), 4.66−4.98 (m, 0.6H), 5.65 (br s, 0.4H), 6.27 (s, 0.6H), 6.55 (d, *J* = 2.3 Hz, 0.4H), 6.69−7.84 (m, 13H), 7.93 (d, *J* = 2.3 Hz, 0.6H), 8.02 (d, *J* = 2.3 Hz, 0.4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 14.2, 16.6, 22.3, 28.4, 28.7, 29.0, 29.8, 35.5, 38.7, 39.7, 39.9, 41.3, 42.2, 55.4, 55.6, 56.7, 56.9, 58.3, 111.4, 112.2, 112.8, 112.9, 114.6, 115.5, 119.8, 119.9, 120.3, 121.1, 121.7, 123.2, 125.4, 126.0, 126.6, 127.0, 127.7, 127.8, 129.0. 129.2, 129.4, 129.9, 130.0, 130.2, 130.2, 130.6, 132.9, 132.9, 133.0, 133.1, 134.4, 134.7, 135.5, 136.2, 136.4, 136.9, 137.2, 137.3, 137.3, 137.4, 139.2, 139.3, 155.6, 155.7, 155.9, 159.9, 160.0, 171.1, 171.3, 171.4, 171.7.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{37}H_{41}N_3NaO_6S$: 678.2614, found: 678.2629.

4'-Methoxy-3'-(*N*-(8-(2-(3-methoxyphenyl)-*N*-propylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide (6d)



A mixture of **12e** (10.0 mg, 28.4 μmol) and 3'-(dimethycarbamoyl)-4-methoxy-[1,1'-biphenyl]-3-sulfonyl chloride (11.0 mg, 31.2 μmol) in CH_2Cl_2 (0.80 mL) and pyridine (0.20 mL) was stirred for 1 h at room temperature under an argon atmosphere. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by preparative TLC (5% MeOH in $CHCl_3$) to afford **6d** (17.6 mg, 93%) as a colorless oil.

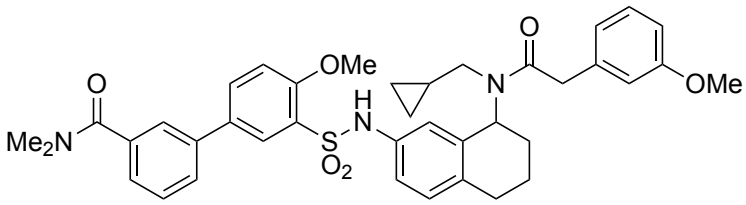
IR (neat): 1627, 1608, 1502, 1279, 1162 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.64 (t, *J* = 7.3 Hz, 1.8H), 0.72 (t, *J* = 7.3 Hz, 1.2H), 1.38−2.11 (m, 7H), 2.55−2.76 (m, 2H), 2.86−3.28 (m, 7H), 3.52−4.20 (m, 8H), 4.57−5.03 (m, 0.6H), 5.61 (br s, 0.4H), 6.25 (br s, 0.6H), 6.53 (d, *J* = 2.3 Hz, 0.4H), 6.71−7.80 (m, 13H), 7.93 (d, *J* = 2.3 Hz, 0.6H), 8.04 (d, *J* = 2.3 Hz, 0.4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 11.6, 11.8, 22.0, 22.3, 22.3, 24.6, 28.4, 28.7, 28.9, 29.0, 29.6, 35.5, 39.7, 41.4, 42.1, 42.2, 55.4, 55.6, 56.6, 56.9, 58.3, 111.4, 112.1, 112.7, 112.9, 114.6, 114.7, 115.4, 115.6, 119.5, 119.6, 120.3, 121.2, 121.8, 123.4, 125.4, 125.5, 126.0, 126.6, 127.0, 127.7, 127.9, 129.0. 129.1, 129.4, 129.9, 130.0, 130.2, 130.7, 132.9, 133.0, 133.1, 134.4, 134.7, 135.4, 136.4, 136.9, 137.2, 137.3, 137.3, 137.4, 139.1, 139.3, 155.6, 155.9, 159.9, 160.0, 171.3, 171.7.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{38}H_{44}N_3O_6S$: 670.2951, found: 670.2959.

3'-(*N*-(8-(*N*-(Cyclopropylmethyl)-2-(3-methoxyphenyl)acetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-4'-methoxy-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide (6e)



A mixture of **12f** (10.0 mg, 27.4 μmol) and 3'-(dimethycarbamoyl)-4-methoxy-[1,1'-biphenyl]-3-sulfonyl chloride (10.7 mg, 30.2 μmol) in CH_2Cl_2 (0.80 mL) and pyridine (0.20 mL) was stirred for 1 h at room temperature under an argon atmosphere. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by preparative TLC (5% MeOH in $CHCl_3$) to afford **6e** (15.7 mg, 84%) as a colorless oil.

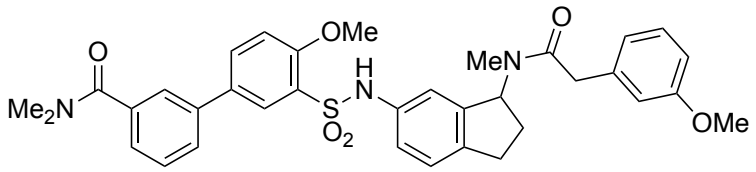
IR (neat): 1627, 1608, 1502 1279, 1162 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.22−1.01 (m, 5H), 1.44−2.11 (m, 5.6H), 2.53−2.82 (m, 2.4H), 2.86−3.30 (m, 7H), 3.46−4.21 (m, 8H), 4.83 (br s, 0.6H), 5.57 (br s, 0.4H), 6.24 (br s, 0.6H), 6.60 (s, 0.4H), 6.67−7.78 (m, 12H), 7.91 (d, *J* = 2.3 Hz, 0.6H), 8.00 (d, *J* = 2.3 Hz, 0.4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 4.7, 5.3, 10.7, 12.0, 22.4, 28.0, 28.8, 29.1, 29.4, 35.5, 39.7, 39.7, 41.7, 42.2, 55.4, 55.6, 56.7, 56.9, 57.9, 111.4, 112.2, 112.7, 113.0, 114.7, 115.4, 119.7, 119.9, 120.5, 121.2, 121.7, 125.4, 125.4, 126.0, 126.1, 126.6, 127.1, 127.7, 127.9, 129.1. 129.3, 129.9, 130.0, 130.2, 130.6, 133.0, 133.0, 133.1, 134.4, 134.4, 134.6, 135.5, 136.3, 136.9, 137.1, 137.3, 137.3, 139.1, 139.2, 155.6, 155.8, 159.9, 171.3, 171.4, 171.9.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{39}H_{43}N_3NaO_6S$: 704.2770, found: 704.2788.

4'-Methoxy-3'-(*N*-(3-(2-(3-methoxyphenyl)-*N*-methylacetamido)-2,3-dihydro-1*H*-inden-5-yl)sulfamoyl)-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide (7a)



A mixture of **12g** (10.1 mg, 0.0325 mmol) and 3'-(dimethycarbamoyl)-4-methoxy-[1,1'-biphenyl]-3-sulfonyl chloride (18.0 mg, 0.0509 mmol) in CH_2Cl_2 (0.9 mL) and pyridine (0.3 mL) was stirred for 16 h at room temperature under an argon atmosphere. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (0–2% MeOH in $CHCl_3$) to afford **7a** (19.4 mg, 96%) as a colorless oil.

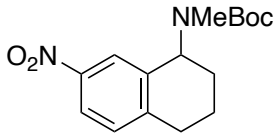
IR (neat): 2934, 1626, 1491, 1279, 1159 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.70–1.89 (m, 1H), 1.95–2.08 (m, 0.4H), 2.29–2.41 (m, 1.8H), 2.46 (s, 1.8H), 2.58–2.89 (m, 2H), 2.98 (s, 3H), 3.14 (s, 3H), 3.67–3.91 (m, 5H), 3.99 (s, 1.8H), 4.07 (s, 1.2H), 5.37 (t, *J* = 8.2 Hz, 0.4H), 6.19 (t, *J* = 8.2 Hz, 0.6H), 6.45 (s, 0.4H), 6.69 (s, 0.6H), 6.77–6.94 (m, 3.4H), 6.94–7.14 (m, 3.6H), 7.20–7.38 (m, 2H), 7.39–7.47 (m, 1H), 7.47–7.57 (m, 2H), 7.65–7.74 (m, 1H), 7.94 (d, *J* = 2.3 Hz, 0.4H), 7.96 (d, *J* = 2.3 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 28.3, 29.0, 29.7, 30.0, 30.5, 35.5, 39.8, 41.8, 41.8, 55.5, 56.8, 56.9, 58.8, 63.4, 112.2, 112.3, 112.7, 112.8, 114.6, 114.7, 118.0, 118.1, 121.1, 121.3, 122.5, 123.2, 125.5, 125.8, 126.0, 126.1, 126.6, 126.8, 127.8, 129.1, 129.4, 130.0, 130.0, 133.2, 133.2, 133.2, 133.3, 135.3, 135.4, 136.6, 136.9, 137.3, 139.2, 139.2, 140.9, 141.6, 141.7, 142.7, 155.6, 155.7, 160.0, 160.1, 171.2, 171.3, 171.7.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{35}H_{37}N_3NaO_6S$: 650.23008, found: 650.23264.

***tert*-Butyl methyl(7-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)carbamate (13)**



A mixture of **10c** (395 mg, 1.91 mmol), di-*tert*-butyl dicarbonate (1.30 mL, 5.66 mmol) and Et_3N (800 μL, 5.74 mmol) in CH_2Cl_2 (4.0 mL) were stirred for 4 h at room temperature under an argon atmosphere. The reaction mixture was diluted with $CHCl_3$ (10 mL) and washed with sat. $NaHCO_3$ aq. (10 mL), H_2O (5 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (25–33% EtOAc in hexane) to afford **13** (568 mg, 97%) as a white solid.

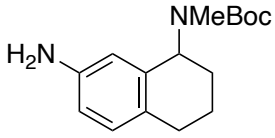
IR (KBr): 2951, 1681, 1514, 1342 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.52–1.59 (m, 9H), 1.69–2.20 (m, 4H), 2.62 (s, 1.8H), 2.69 (s, 1.2H), 2.82–2.93 (m, 2H), 5.06–5.20 (m, 0.4H), 5.46 (dd, J = 10.1, 5.0 Hz, 0.6H), 7.24 (d, J = 8.7 Hz, 1H), 7.92–8.04 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.7, 21.8, 26.9, 27.4, 28.6, 29.8, 30.0, 30.7, 54.5, 56.0, 80.4, 121.7, 122.2, 130.3, 138.2, 138.5, 145.8, 146.3, 146.8, 156.0, 156.7.

HR-MS (ESI): m/z $[M+Na]^+$ calcd for $C_{16}H_{22}N_2NaO_4$: 329.14773, found: 329.14626.

***tert*-Butyl (7-amino-1,2,3,4-tetrahydronaphthalen-1-yl)(methyl)carbamate (14)**



A mixture of **13** (552 mg, 1.80 mmol), Iron powder (1.00 g, 18.0 mmol), and ammonium chloride (1.00 g, 18.7 mmol) in EtOH (6.0 mL) and H_2O (2.0 mL) was heated to 60 ˚C for 1 h under an argon atmosphere. The reaction mixture was filtered through a pad of Celite, and the filtrate was extracted with $CHCl_3$ (25, 10, 5 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (20–50% EtOAc in hexane) to afford **14** (433 mg, 87%) as an orange oil.

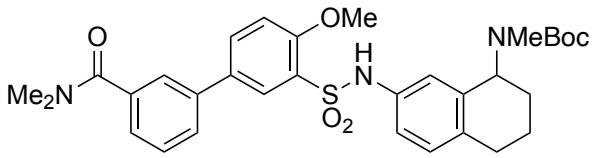
IR (neat): 3454, 3359, 2975, 2932, 1681, 1505, 1392, 1153, 1133 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.46 (s, 4.5H), 1.52 (s, 4.5H), 1.60–2.03 (m, 4H), 2.56 (s, 1.5H), 2.62 (s, 1.5H), 2.64–2.77 (m, 2H), 5.13–5.11 (m, 0.5H), 5.39–5.36 (m, 0.5H), 6.56 (s, 0.5H), 6.61 (s, 0.5H), 6.66 (d, *J* = 8.0 Hz, 0.5H), 6.69 (d, *J* = 8.0 Hz, 0.5H), 6.91 (d, *J* = 8.0 Hz, 0.5H), 6.93 (d, *J* = 8.0 Hz, 0.5H). The NH_2 peaks were not observed.

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 22.4, 22.6, 27.7, 28.1, 28.7, 28.9, 29.9, 54.4, 56.0, 79.5, 79.7, 113.4, 113.8, 114.8, 114.8, 128.7, 129.2, 130.0, 130.1, 136.8, 137.1, 144.0, 144.0, 156.6, 156.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{16}H_{24}N_2NaO_2$: 299.17355, found: 299.17273.

***tert*-Butyl (7-((3'-(dimethylcarbamoyl)-4-methoxy-[1,1'-biphenyl])-3-sulfonamido)-1,2,3,4-tetrahydronaphthalen-1-yl)(methyl)carbamate (15)**



A mixture of **14** (322 mg, 1.17 mmol) and 3'-(dimethycarbamoyl)-4-methoxy-[1,1'-biphenyl]-3-sulfonyl chloride (454 mg, 1.28 mmol) in CH_2Cl_2 (4.0 mL) and pyridine (1.0 mL) was stirred for 12 h at room temperature under an argon atmosphere. The reaction mixture was diluted with $CHCl_3$ (15 mL) and washed with sat. $NaHCO_3$ aq. (10 mL), H_2O (5 mL), and brine (5 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (0–10% MeOH in $CHCl_3$) to afford **15** (656 mg, 94%) as a white solid.

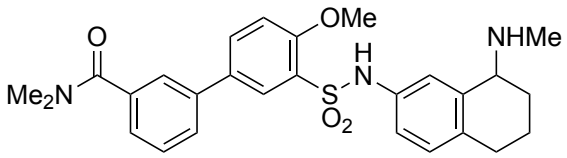
IR (neat): 2933, 1686, 1628, 1501, 1394, 1161 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.45 (s, 4.5H), 1.54 (s, 4.5H), 1.57–1.79 (m, 2H), 1.83–2.02 (m, 2H), 2.19 (s, 1.5H), 2.30 (s, 1.5H), 2.55–2.71 (m, 2H), 3.06 (br s, 6H), 4.08 (s, 3H), 4.99–5.18 (m, 0.5H), 5.22–5.39 (m, 0.5H), 6.55 (s, 0.5H), 6.66 (s, 0.5H), 6.85–7.21 (m, 4H), 7.30–7.38 (m, 1H), 7.38–7.47 (m, 1H), 7.47–7.57 (m, 2H), 7.65–7.78 (m, 1H), 7.90–8.02 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.1, 27.1, 27.5, 28.6, 28.7, 29.0, 29.3, 29.5, 54.2, 55.5, 56.7, 79.7, 79.9, 112.7, 112.8, 120.7, 121.4, 122.4, 125.5, 126.0, 126.8, 127.0, 127.8, 127.9, 129.0, 129.3, 129.4, 130.3, 130.4, 133.1, 133.2, 133.2, 134.5, 136.3, 136.9, 137.1, 137.3, 139.2, 139.3, 155.7, 156.6, 171.4.

HR-MS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{32}H_{39}N_3NaO_6S$: 616.24573, found: 616.24301.

4'-Methoxy-*N*,*N*-dimethyl-3'-(*N*-(8-(methylamino)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-[1,1'-biphenyl]-3-carboxamide (16)



A mixture of **15** (150 mg, 0.253 mmol) and TFA (400 μL, 5.23 mmol) in CH_2Cl_2 (2.0 mL) was stirred for 10 min at room temperature under an argon atmosphere. The reaction mixture was quenched by the addition of sat. $NaHCO_3$ aq. (10 mL), and extracted with CH_2Cl_2 (15, 10, 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (15–25% MeOH in $CHCl_3$) to afford **16** (103 mg, 82%) as a colorless oil.

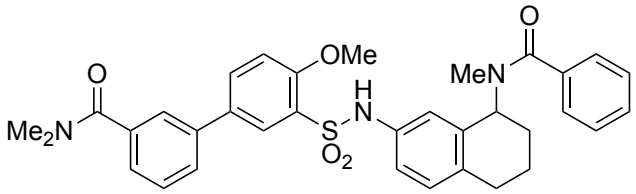
IR (neat): 3449, 2931, 1627, 1500, 1160 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.58-1.99 (m, 4H), 2.34 (s, 3H), 2.52–2.84 (m, 2H), 2.98 (s, 3H), 3.14 (s, 3H), 3.49 (s, 1H), 3.56–3.68 (m, 1H), 4.08 (s, 3H), 6.93 (s, 2H), 7.04–7.14 (m, 2H), 7.34 (d, J = 7.8 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.48–7.56 (m, 2H), 7.70 (d, J = 9.6 Hz, 1H), 8.03 (s, 1H). The NH peak was not observed.

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 18.9, 27.5, 28.7, 33.4, 35.4, 39.7, 50.6, 56.7, 56.8, 112.7, 120.7, 122.2, 125.4, 126.0, 127.1, 127.8, 129.0, 129.3, 130.0, 133.0, 133.1, 134.2, 134.9, 137.2, 139.3, 139.3, 155.9, 171.4.

HR-MS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{32}N_3O_4S$: 494.21135, found: 494.20912.

4'-Methoxy-*N*,*N*-dimethyl-3'-(*N*-(8-(*N*-methylbenzamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-[1,1'-biphenyl]-3-carboxamide (5a)



A mixture of **16** (10.5 mg, 0.0213 mmol), benzoyl chloride (3.7 µl, 0.0321 mmol) and triethylamine (14.8 µl, 0.107 mmol) in CH_2Cl_2 (1.0 mL) was stirred for 2 h at room temperature under an argon atmosphere. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (0–2% MeOH in $CHCl_3$) and preparative TLC (3% MeOH in $CHCl_3$) to afford **5a** (12.5 mg, 98%) as a colorless amorphous.

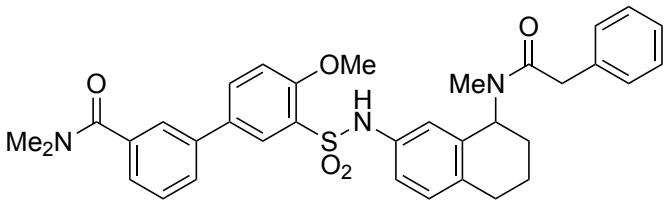
IR (neat): 2935, 1624, 1502, 1399, 1162, 752 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.41–2.14 (m, 4H), 2.45 (s, 3H), 2.53–2.77 (m, 2H), 2.88–3.24 (m, 6H), 4.07 (s, 1.2H), 4.19 (s, 1.8H), 4.72–4.84 (m, 0.6H), 5.84–5.97 (m, 0.4H), 6.76 (s, 0.6H), 6.90 (s, 0.4H), 6.94–7.00 (m, 1.4H), 7.03 (d, *J* = 8.7 Hz, 0.4H), 7.08–7.16 (m, 1.6H), 7.19 (d, *J* = 8.7 Hz, 0.6H), 7.28–7.58 (m, 9H), 7.62 (dd, *J* = 8.2, 2.3 Hz, 0.4H), 7.76 (dd, *J* = 8.7, 2.3 Hz, 0.6H), 7.96 (d, *J* = 2.3 Hz, 0.4H), 7.99 (d, *J* = 2.3 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.0, 26.7, 28.0, 28.7, 28.7, 29.0, 32.9, 35.5, 39.8, 52.8, 56.9, 57.0, 58.6, 112.9, 113.1, 120.3, 120.5, 121.1, 123.0, 125.4, 125.5, 126.0, 126.1, 126.2, 126.9, 127.0, 127.2, 127.8, 127.9, 128.7, 128.9, 129.1, 129.3, 129.7, 129.8, 130.4, 130.7, 133.2, 133.2, 133.3, 134.8, 134.8, 135.9, 136.1, 136.3, 136.4, 136.6, 136.7, 137.3, 137.3, 139.2, 155.7, 155.8, 171.4, 171.4, 172.5, 172.7.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{34}H_{35}N_3NaO_5S$: 620.21951, found: 620.21747.

4'-Methoxy-*N*,*N*-dimethyl-3'-(*N*-(8-(*N*-methyl-2-phenylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-[1,1'-biphenyl]-3-carboxamide (5b)



The title compound was synthesized in 50% according to a method similar to that described for **5a**.

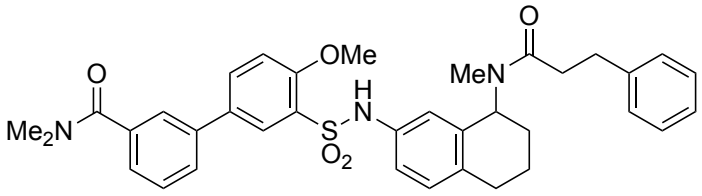
IR (neat): 2936, 1624, 1502, 1397, 1279, 1161 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.49–1.96 (m, 4H), 2.22 (s, 2H), 2.48 (s, 1.5H), 2.58–2.68 (m, 1.5H), 2.98 (s, 3H), 3.12 (s, 3H), 3.62–3.85 (m, 2H), 4.00 (s, 1.5H), 4.03 (s, 1.5H), 4.87–4.99 (m, 0.5H), 5.80 (dd, *J* = 10.7, 5.7 Hz, 0.5H), 6.19–6.26 (m, 0.5H), 6.71 (s, 0.5H), 6.55–6.62 (m, 0.5H), 6.78 (s, 0.5H), 6.89–7.19 (m, 3H), 7.27–7.45 (m, 7H), 7.48–7.55 (m, 2H), 7.68–7.75 (m, 1H), 7.89–8.00 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 22.0, 26.9, 27.7, 28.7, 28.9, 29.0, 31.2, 35.5, 39.7, 41.5, 41.6, 52.7, 56.8, 57.4, 112.8, 112.9, 120.3, 120.6, 121.0, 123.2, 125.4, 125.5, 126.0, 126.1, 126.5, 127.0, 127.1, 127.2, 127.8, 127.9, 128.8, 128.9, 128.9, 129.0, 129.1, 129.1, 129.2, 129.3, 130.4, 130.7, 133.1, 133.2, 134.6, 135.0, 135.3, 135.5, 136.3, 136.3, 136.4, 137.3, 139.2, 139.2, 155.6, 155.7, 171.4, 171.6, 171.9.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{35}H_{37}N_3NaO_5S$: 634.23516, found: 634.23407.

4'-Methoxy-*N*,*N*-dimethyl-3'-(*N*-(8-(*N*-methyl-3-phenylpropanamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-[1,1'-biphenyl]-3-carboxamide (5c)



The title compound was synthesized in 60% (in 2 steps) according to a method similar to that described for **5f**.

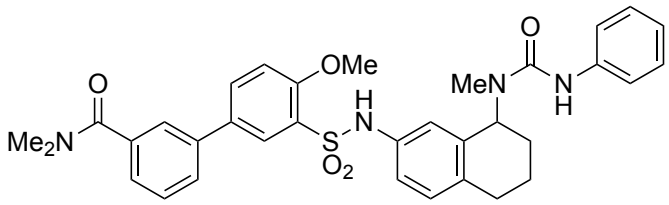
IR (neat): 2933, 1624, 1503, 1397, 1279, 1161, 750 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.50–1.98 (m, 4H) , 2.28 (s, 1.2H), 2.36 (s, 1.8H), 2.59–2.74 (m, 4H), 2.94–3.08 (m, 5H), 3.12 (s, 3H), 4.01 (s, 1.8H), 4.01 (s, 1.2H), 4.76–4.85 (m, 0.4H), 5.79 (dd, *J* = 10.8, 5.4 Hz, 0.6H), 6.29–6.35 (m, 0.4H), 6.48–6.54 (m, 0.6H), 6.83 (d, *J* = 2.1 Hz, 1H), 6.90–7.11 (m, 3H), 7.15–7.37 (m, 6H), 7.37–7.44 (m, 1H), 7.45–7.53 (m, 2H), 7.64–7.71 (m, 1H), 7.93 (d, *J* = 2.4 Hz, 0.4H), 7.96 (d, *J* = 2.4 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 22.0, 26.9, 28.0, 28.7, 28.8, 28.9, 30.7, 31.5, 31.8, 35.1, 35.5, 35.8, 39.7, 52.5, 56.7, 56.8, 56.9, 112.7, 112.8, 120.2, 120.8, 121.3, 122.9, 125.4, 125.4, 126.0, 126.1, 126.4, 126.4, 126.5, 127.1, 127.8, 127.8, 128.6, 128.7, 129.0, 129.1, 129.213, 129.3, 130.3, 130.7, 133.1, 133.1, 134.5, 134.7, 135.7, 136.2, 136.4, 136.5, 137.3, 139.1, 139.2, 141.3, 141.5, 155.5, 155.7, 171.3, 171.4, 172.5, 173.0.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{36}H_{39}N_3NaO_5S$: 648.25081, found: 648.25330.

4'-Methoxy-*N*,*N*-dimethyl-3'-(*N*-(8-(1-methyl-3-phenylureido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-[1,1'-biphenyl]-3-carboxamide (5d)



A mixture of diphenylphosphoryl azide (8.0 μL, 0.0372 mmol), benzoic acid (5.0 mg, 0.0409 mmol), and Et_3N (20.0 μL, 0.143 mmol) in benzene (1.0 mL) was refluxed for 1 h under an argon atmosphere. To the reaction mixture were added a solution of **16** (9.3 mg, 0.0188 mmol) in benzene (0.8 mL). After being stirred for 1 h, the reaction mixture was quenched by the addition of sat. $NaHCO_3$ aq. (5 mL), and extracted with EtOAc (15, 10, 3 mL). The organic layer was washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by preparative TLC (5% MeOH in $CHCl_3$) to afford **5d** (9.5 mg, 82%) as a colorless amorphous.

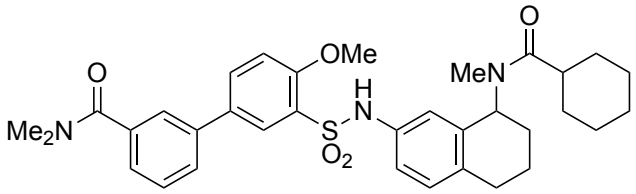
IR (KBr): 3388, 2932, 1624, 1502, 1279, 1161 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.53–2.06 (m, 4H), 2.42 (s, 3H), 2.59–2.74 (m, 2H), 2.99 (s, 3H), 3.12 (s, 3H), 3.98 (s, 3H), 5.39–5.53 (m, 1H), 6.43 (s, 1H), 6.68–6.73 (m, 1H), 6.94–7.01 (m, 3H), 7.02–7.10 (m, 2H), 7.26–7.35 (m, 3H), 7.36–7.46 (m, 3H), 7.46–7.51 (m, 1H), 7.52 (t, J = 1.7 Hz, 1H), 7.64 (dd, J = 8.6, 2.4 Hz, 1H), 7.95 (d, J = 2.4 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 21.9, 26.6, 27.5, 28.0, 28.6, 28.7, 28.9, 29.8, 30.2, 32.9, 35.5, 39.8, 52.9, 54.2, 56.6, 56.8, 56.8, 58.6, 112.7, 112.8, 113.0, 119.4, 120.1, 120.3, 121.2, 122.5, 122.6, 123.2, 125.3, 125.3, 125.4, 125.9, 126.0, 126.1, 126.7, 127.1, 127.8, 128.7, 128.9, 129.0, 129.0, 129.1, 129.7, 129.9, 130.4, 130.6, 132.7, 133.0, 133.3, 134.5, 134.8, 135.7, 135.8, 136.1, 136.4, 136.5, 136.7, 136.8, 136.9, 137.1, 139.2, 139.2, 139.3, 153.4, 155.8, 156.3, 171.5, 172.8.

HR-MS (ESI): m/z $[M+Na]^+$ calcd for $C_{34}H_{36}N_4NaO_5S$: 635.23041, found: 635.22954.

4'-Methoxy-*N*,*N*-dimethyl-3'-(*N*-(8-(*N*-methylcyclohexanecarboxamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-[1,1'-biphenyl]-3-carboxamide (5e)



The title compound was synthesized in 92% according to a method similar to that described for **5h**.

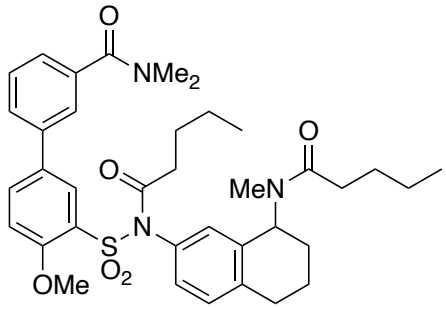
IR (neat): 2931, 1625, 1503, 1279, 1161, 750 cm^{-1}

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.26-2.04 (m, 14H), 2.22 (s, 1.2H), 2.45-2.54 (m, 2.8H), 2.61-2.70 (m, 2H), 2.97 (s, 3H), 3.13 (s, 3H), 4.05 (s, 1.8H), 4.10 (s, 1.2H), 4.92-4.92 (m, 0.4H), 5.76-5.80 (m, 0.6H), 6.48 (s, 0.4H), 6.59 (s, 0.6H), 6.92-7.04 (m, 2.6H), 7.09 (d, *J* = 8.7 Hz, 0.6H), 7.15 (d, *J* = 8.2 Hz, 0.4H), 7.21 (d, *J* = 8.2 Hz, 0.4H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.41-7.47 (m, 1H), 7.52-7.55 (m, 2H), 7.71-7.73 (m, 1H), 7.93 (d, *J* = 2.3 Hz, 0.4H), 7.97 (d, *J* = 2.3 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.1, 25.9, 26.0, 26.0, 26.0, 26.2, 26.9, 28.5, 28.8, 28.9, 29.0, 29.2, 29.7, 29.8, 30.0, 30.3, 30.5, 35.5, 39.8, 41.0, 41.3, 52.2, 56.5, 56.8, 56.9, 112.8, 112.9, 120.4, 120.6, 121.2, 123.3, 125.5, 125.5, 126.0, 126.1, 126.6, 127.1, 127.8, 127.9, 129.0, 129.1, 129.2, 129.3, 130.3, 130.8, 133.1, 133.2, 133.2, 134.5, 134.7, 136.2, 136.4, 136.5, 136.8, 137.3, 139.2, 139.3, 155.5, 155.8, 171.4, 176.7, 177.0.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{34}H_{41}N_3NaO_5S$: 626.26646, found: 626.26339.

4'-Methoxy-*N*,*N*-dimethyl-3'-(*N*-(8-(*N*-methylpentanamido)-5,6,7,8-tetrahydronaphthalen-2-yl)-*N*-pentanoylsulfamoyl)-[1,1'-biphenyl]-3-carboxamide (57)



A mixture of **16** (17.3 mg, 0.0350 mmol) and valeryl chloride (8.5 µl, 0.0702 mmol) in CH_2Cl_2 (0.9 mL) and pyridine (0.3 mL) was stirred for 8 h at room temperature under an argon atmosphere. Additional valeryl chloride (42.5 µl, 0.351 mmol) was added to the mixture, and then the mixture was stirred for another 1 h. The reaction mixture was quenched by the addition of sat. $NaHCO_3$ aq. (5.0 mL) and H_2O (5.0 mL), and extracted with $CHCl_3$ (20, 10, 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by preparative TLC (3% MeOH in $CHCl_3$) to afford **57** (23.1 mg, quant.) as a colorless oil.

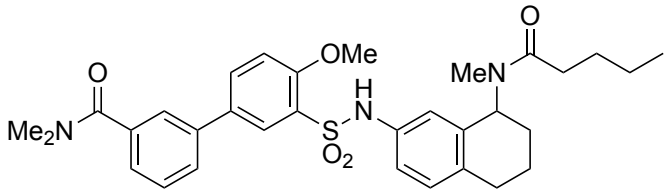
IR (neat): 2956, 1633, 1281, 1166 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.73–0.84 (m, 3H), 0.88–0.99 (m, 3H), 1.08–1.58 (m, 6.7H), 1.58–1.96 (m, 4H), 1.98–2.23 (m, 3.3H), 2.27–2.46 (m, 2H), 2.46–2.62 (m, 0.9H), 2.70 (s, 2.1H), 2.80–2.92 (m, 2H), 3.02 (s, 3H), 3.16 (s, 3H), 3.89 (s, 2.1H), 4.00 (s, 0.9H), 4.96–5.14 (m, 0.3H), 6.03 (dd, J = 10.8, 5.3 Hz, 0.7H), 6.96–7.26 (m, 4H), 7.32–7.42 (m, 1H), 7.43–7.54 (m, 1H), 7.62 (t, J = 8.5 Hz, 2H), 7.76–7.86 (m, 1H), 8.34 (d, J = 2.3 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 13.9, 14.1, 21.8, 22.0, 22.1, 22.2, 22.4, 22.8, 22.8, 26.5, 26.6, 26.9, 27.4, 28.0, 28.3, 29.0, 29.3, 29.5, 31.0, 33.5, 33.9, 35.5, 36.4, 36.6, 39.8, 52.4, 56.4, 56.4, 57.0, 112.9, 113.0, 125.5, 125.6, 126.1, 128.1, 128.2, 128.8, 129.1, 129.5, 129.6, 130.5, 130.8, 131.0, 131.3, 133.2, 133.3, 133.7, 134.0, 134.1, 136.6, 137.2, 139.2, 139.4, 140.2, 140.8, 156.2, 156.3, 171.5, 171.5, 173.3, 173.7, 174.2

HR-MS (ESI): m/z $[M+Na]^+$ calcd for $C_{37}H_{47}N_3NaO_6S$: 684.30833, found: 684.30551.

4'-Methoxy-*N*,*N*-dimethyl-3'-(*N*-(8-(*N*-methylpentanamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-[1,1'-biphenyl]-3-carboxamide (5f)



A mixture of **57** (18.0 mg, 0.0272 mmol) and potassium carbonate (37.6 mg, 0.0272 mmol) in MeOH (2.0 mL) was stirred for 2 h at room temperature under an argon atmosphere. The reaction mixture was quenched by the addition of sat. $NaHCO_3$ aq. (10 mL) and H_2O (10 mL), and extracted with $CHCl_3$ (40, 20, 10 mL). The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by preparative TLC (3% MeOH in $CHCl_3$) to afford **5f** (14.6 mg, 93%) as a colorless amorphous.

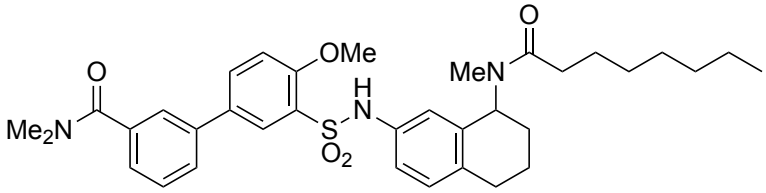
IR (neat): 2934, 1627, 1503, 1399, 1279, 1162, 752 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.87–1.07 (m, 3H), 1.31–2.05 (m, 8H), 2.24 (s, 1.2H), 2.30–2.40 (m, 2H), 2.46 (s, 1.8H), 2.58–2.78 (m, 2H), 2.99 (s, 3H), 3.15 (s, 3H), 4.02–4.27 (m, 3H), 4.77–4.95 (m, 0.4H), 5.71–5.88 (m, 0.6H), 6.48 (s, 0.4H), 6.58 (s, 0.6H), 6.83–7.07 (m, 2.6H), 7.09 (d, J = 8.7 Hz, 0.6H), 7.15 (d, J = 8.7 Hz, 0.4H), 7.19 (dd, J = 8.0, 2.1 Hz, 0.4H), 7.31–7.59 (m, 4H), 7.66–7.79 (m, 1H), 7.93 (d, J = 2.3 Hz, 0.4H), 7.97 (d, J = 2.3 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 14.1, 14.2, 21.9, 22.1, 22.8, 27.0, 27.5, 28.1, 28.1, 28.6, 28.8, 29.0, 30.8, 33.4, 33.8, 35.5, 39.8, 52.3, 56.8, 56.9, 112.7, 112.9, 120.5, 121.0, 121.6, 123.5, 125.5, 125.5, 126.0, 126.1, 126.6, 127.1, 127.8, 127.9, 129.1, 129.1, 129.2, 129.3, 130.4, 130.8, 133.1, 133.2, 133.2, 133.3, 134.5, 134.7, 136.0, 136.5, 136.6, 136.7, 137.3, 139.2, 139.3, 155.5, 155.7, 171.4, 173.6, 174.0.

HR-MS (ESI): m/z $[M+Na]^+$ calcd for $C_{32}H_{39}N_3NaO_5S$: 600.25081, found: 600.25044.

4'-Methoxy-*N*,*N*-dimethyl-3'-(*N*-(8-(*N*-methyloctanamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-[1,1'-biphenyl]-3-carboxamide (5g)



A mixture of **16** (12.1 mg, 0.0245 mmol) and *n*-octanoyl chloride (9.5 µl, 0.0488 mmol) in CH_2Cl_2 (0.9 mL) and pyridine (0.3 mL) was stirred for 8 h at room temperature under an argon atmosphere. Additional *n*-octanoyl chloride (47.5 µl, 0.244 mmol) was added, and then the mixture was stirred for another 18 h. Futhermore, additional *n*-octanoyl chloride (47.5 µl, 0.244 mmol), CH_2Cl_2 (0.9 mL) and pyridine (0.3 mL) were added, and then the mixture was stirred for another 4 h. The reaction mixture was quenched by the addition of sat. $NaHCO_3$ aq. (5.0 mL) and H_2O (5.0 mL), and extracted with $CHCl_3$ (20, 10, 10 mL). The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by preparative TLC (80% EtOAc in Hexane) to afford **5g** (10.0 mg, 66%) as a white solid.

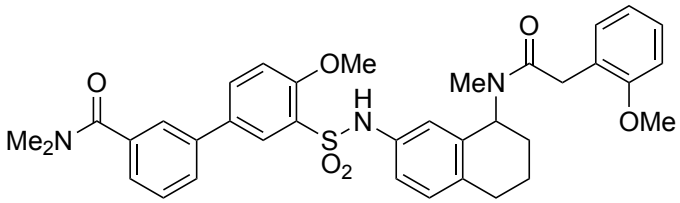
IR (neat): 2930, 1626, 1503, 1279, 1162 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 0.79–0.99 (m, 3H), 1.19–2.10 (m, 14H), 2.22 (s, 1.2H), 2.27–2.40 (m, 2H), 2.45 (s, 1.8H), 2.58–2.77 (m, 2H), 2.99 (s, 3H), 3.14 (s, 3H), 3.99–4.16 (m, 3H), 4.78–4.95 (m, 0.4H), 5.73–5.88 (m, 0.6H), 6.47 (s, 0.4H), 6.59 (s, 0.6H), 6.81–7.06 (m, 2.6H), 7.09 (d, J = 8.7 Hz, 0.6H), 7.15 (d, J = 8.7 Hz, 0.4H), 7.20 (dd, J = 8.2, 2.3 Hz, 0.4H), 7.30–7.38 (m, 1H), 7.38–7.48 (m, 1H), 7.48–7.58 (m, 2H), 7.66–7.79 (m, 1H), 7.93 (d, J = 2.3 Hz, 0.4H), 7.97 (d, J = 2.3 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 14.3, 21.9, 22.1, 22.8, 22.8, 25.4, 26.0, 27.0, 28.1, 28.6, 28.8, 29.0, 29.3, 29.4, 29.7, 30.8, 31.9, 31.9, 33.7, 34.1, 35.5, 39.8, 52.3, 56.8, 56.9, 112.7, 112.9, 120.5, 121.1, 121.7, 123.5, 125.5, 125.5, 126.0, 126.1, 126.6, 127.1, 127.8, 127.9, 129.1, 129.1, 129.2, 129.3, 130.4, 130.8, 133.1, 133.2, 133.2, 133.3, 134.4, 134.7, 136.0 136.6, 136.6, 136.7, 137.3, 139.2, 139.3, 155.5, 155.7, 171.4, 173.6, 174.0.

HR-MS (ESI): m/z $[M+Na]^+$ calcd for $C_{35}H_{45}N_3NaO_5S$: 642.29776, found: 642.29680.

4'-Methoxy-3'-(*N*-(8-(2-(2-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide (5h)



A mixture of **16** (12.0 mg, 0.0240 mmol), 2-methoxyphenylacetic acid (4.6 mg, 0.0277 mmol), DIPEA (20.0 μL, 0.115 mmol) and HATU (10.2 mg, 0.0268 μmol) in DMF (0.5 mL) was stirred for 3 h at room temperature under an argon atmosphere. The reaction mixture was diluted with $CHCl_3$ (15 mL) and washed with sat. $NaHCO_3$ aq. (5 mL), 2 M HCl aq. (5 mL), H_2O (10 mL), and brine (5 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by preparative TLC (3% MeOH in $CHCl_3$) to afford **5h** (12.2 mg, 79%) as a colorless amorphous.

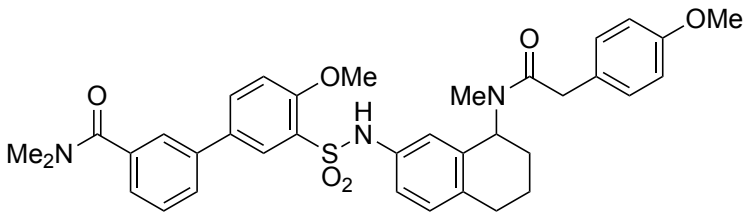
IR (neat): 2936, 1626, 1502, 1396, 1279, 1247, 1161, 753 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.51–1.98 (m, 4H), 2.19 (s, 1.5H), 2.46 (s, 1.5H), 2.68–2.59 (m, 2H), 2.91–3.02 (m, 3H), 3.11 (s, 3H), 3.62–3.75 (m, 3.5H), 3.88 (s, 1.5H), 4.03 (s, 1.5H), 4.03 (s, 1.5H), 5.01–5.10 (m, 0.5H), 5.80 (dd, *J* = 10.5, 5.7 Hz, 0.5H), 6.14–6.18 (m, 0.5H), 6.63 (dd, *J* = 2.4, 1.0 Hz, 0.5H), 6.72 (s, 0.5H), 6.80 (dd, *J* = 8.3, 1.1 Hz, 0.5H), 6.87–7.03 (m, 3.5H), 7.09 (d, *J* = 8.1 Hz, 0.5H), 7.13 (d, *J* = 8.7 Hz, 0.5H), 7.16 (dd, *J* = 8.3, 2.3 Hz, 0.5H), 7.23–7.35 (m, 2.5H), 7.36–7.43 (m, 1.5H), 7.46–7.53 (m, 2H), 7.67–7.75 (m, 1H), 7.90 (d, *J* = 2.4 Hz, 0.5H), 7.98 (d, *J* = 2.4 Hz, 0.5H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 22.2, 26.9, 27.8, 28.7, 28.8, 29.0, 30.9, 34.4, 35.2, 35.5, 39.7, 52.6, 55.4, 55.6, 56.8, 57.1, 110.5, 110.7, 112.8, 112.9, 120.4, 120.8, 120.9, 121.0, 121.3, 123.1, 123.8, 124.0, 125.4, 125.4, 126.0, 126.0, 126.4, 127.0, 127.8, 127.9, 128.4, 128.6, 128.8, 129.0, 129.1, 129.2, 129.3, 130.2, 130.3, 130.4, 130.5, 133.0, 133.1, 133.2, 134.5, 134.6, 136.0, 136.2, 136.5, 136.5, 137.2, 139.2, 139.2, 155.5, 155.8, 156.4, 157.1, 171.4, 172.3, 172.4.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{36}H_{39}N_3NaO_6S$: 664.24573, found: 664.24588.

4'-Methoxy-3'-(*N*-(8-(2-(4-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide (5i)



The title compound was synthesized in 84% according to a method similar to that described for **5h**.

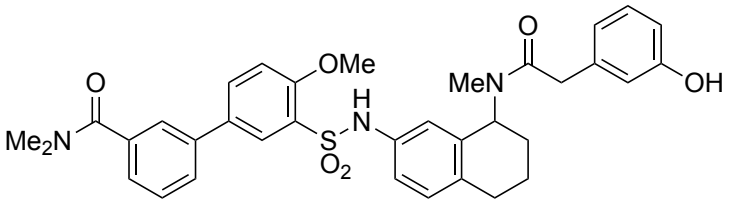
IR (neat): 2935, 1623, 1504, 1397, 1279, 1248, 1162, 752 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.52–1.97 (m, 4H), 2.23 (s, 1.5H), 2.47 (s, 1.5H), 2.64 (d, *J* = 6.6 Hz, 2H), 2.98 (s, 3H), 3.12 (s, 3H), 3.61–3.78 (m, 2H), 3.81 (s, 1.5H), 3.82 (s, 1.5H), 4.02 (s, 1.5H), 4.04 (s, 1.5H), 4.90–4.97 (m, 0.5H), 5.79 (dd, *J* = 10.8, 5.6 Hz, 0.5H), 6.28 (s, 0.5H), 6.60 (s, 0.5H), 6.73–6.95 (m, 4H), 6.96–7.06 (m, 1H), 7.11–7.25 (m, 3H), 7.33 (m, 1H), 7.37–7.46 (m, 1H), 7.48–7.55 (m, 2H), 7.72 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.92 (d, *J* = 2.4 Hz, 0.5H), 7.98 (d, *J* = 2.4 Hz, 0.5H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 22.0, 26.8, 27.8, 28.7, 28.9, 31.2, 35.5, 39.7, 41.7, 41.7, 52.4, 55.4, 55.5, 56.7, 56.8, 57.4, 111.6, 112.1, 112.7, 112.8, 114.9, 115.0, 120.1, 120.3, 121.2, 121.5, 123.0, 125.4, 125.5, 126.0, 126.0, 126.5. 126.9, 127.7, 127.8, 129.0, 129.1, 129.2, 129.4, 130.0, 130.0, 130.3, 130.6, 133.0, 133.0, 133.1, 134.6, 134.8, 135.4, 136.0, 136.2, 136.3, 136.6, 136.7, 137.3, 139.2, 139.3, 155.6, 155.8, 160.0, 160.0, 171.4, 171.4, 171.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{36}H_{39}N_3NaO_6S$: 664.24573, found: 664.24499.

3'-(*N*-(8-(2-(3-Hydroxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-4'-methoxy-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide (5k)



The title compound was synthesized in 63% according to a method similar to that described for **5h**.

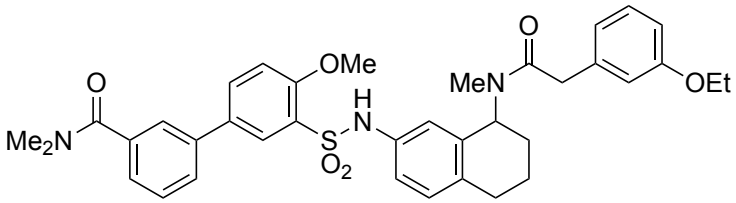
IR (neat): 3235, 2935, 1621, 1503, 1279, 1158 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.38–2.06 (m, 4H), 2.24 (s, 1.8H), 2.37 (s, 1.2H), 2.52–2.63 (m, 2H), 3.01 (s, 3H), 3.13 (s, 1.2H), 3.15 (s, 1.8H), 3.43–3.80 (m, 2H), 3.96 (s, 1.8H), 4.02 (s, 1.2H), 4.79 (t, *J* = 8.1 Hz, 0.4H), 5.76 (dd, *J* = 10.4, 5.9 Hz, 0.6H), 6.43 (d, *J* = 2.3 Hz, 0.4H), 6.62–6.79 (m, 3.6H), 6.85–6.98 (m, 1.4H), 7.03 (d, *J* = 8.7 Hz, 0.6H), 7.07–7.18 (m, 2H), 7.29–7.50 (m, 3H), 7.50–7.58 (m, 1.4H), 7.61 (t, *J* = 1.9 Hz, 0.6H), 7.67–7.76 (m, 1H), 7.93 (d, *J* = 2.4 Hz, 0.4H), 8.05 (d, *J* = 2.4 Hz, 0.6H), 8.46–8.66 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.7, 21.9, 26.8, 27.7, 28.7, 29.0, 29.2, 31.1, 35.7, 35.7, 39.9, 41.9, 42.1, 52.7, 56.8, 56.9, 57.6, 113.0, 113.0, 114.4, 114.6, 115.2, 115.5, 119.4, 119.6, 120.0, 120.3, 121.1, 123.6, 125.1, 125.8, 125.9, 126.4, 126.6, 127.2, 128.1, 129.1, 129.2, 129.3, 129.5, 130.2, 130.3, 130.7, 132.6, 132.9, 133.2, 133.4, 134.6, 134.7, 135.5, 135.8, 136.1, 136.3, 136.4, 136.9, 139.1, 139.5, 155.9, 156.1, 157.5, 157.6, 171.7, 171.7, 172.2.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{35}H_{37}N_3NaO_6S$: 650.23008, found: 650.23161.

3'-(*N*-(8-(2-(3-Ethoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-4'-methoxy-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide (5l)



The title compound was synthesized in 96% according to a method similar to that described for **5h**.

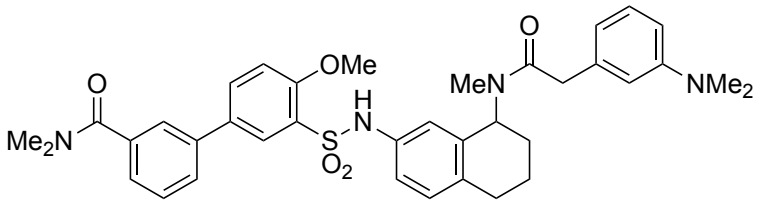
IR (neat): 3026, 2937, 1622, 1490, 1455, 1399, 1316, 1150 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.38–1.48 (m, 3H), 1.50–2.02 (m, 4H), 2.22 (s, 1.2H), 2.48 (s, 1.8H), 2.57–2.68 (m, 2H), 2.98 (s, 3H), 3.14 (s, 3H), 3.61–3.84 (m, 2H), 3.90–4.15 (m, 5H), 4.84–4.98 (m, 0.4H), 5.80 (dd, *J* = 10.3, 5.7 Hz, 0.6H), 6.26 (s, 0.4H), 6.59 (s, 0.6H), 6.74–7.10 (m, 6.4H), 7.10–7.24 (m, 1.6H), 7.25–7.38 (m, 1H), 7.38–7.47 (m, 1H), 7.47–7.58 (m, 2H), 7.70 (t, *J* = 2.4 Hz, 0.6H), 7.72 (t, *J* = 2.5 Hz, 0.4H), 7.92 (d, *J* = 2.3 Hz, 0.4H), 7.99 (d, *J* = 2.7 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 14.9, 14.9, 21.8, 22.0, 26.8, 27.8, 28.7, 28.8, 28.9, 31.2, 35.5, 39.7, 41.6, 41.8, 52.5, 56.8, 56.9, 57.4, 63.7, 112.6, 112.7, 112.8, 115.5, 120.4, 120.4, 120.8, 121.1, 121.2, 123.1, 125.4, 125.5, 126.0, 126.0, 126.4, 126.9, 127.8, 127.8, 129.0, 129.1, 129.2, 129.3, 129.9, 130.0, 130.3, 130.6, 133.0, 133.1, 134.6, 134.7, 135.4, 136.2, 136.2, 136.3, 136.5, 136.7, 137.3, 139.2, 155.6, 155.8, 159.4, 171.4, 171.5, 171.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{37}H_{41}N_3NaO_6S$: 678.26138, found: 678.25913.

3'-(*N*-(8-(2-(3-(Dimethylamino)phenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-4'-methoxy-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide (5m)



The title compound was synthesized in 72% according to a method similar to that described for **5h**.

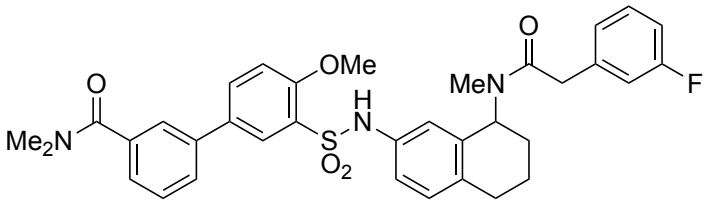
IR (neat): 2936, 1624, 1503, 1397, 1279, 1161, 751 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.51–2.00 (m, 4H), 2.22 (s, 1.2H), 2.47 (s, 1.8H), 2.57–2.66 (m, 2H), 2.84–3.07 (m, 9H), 3.12 (s, 3H), 3.64–3.83 (m, 2H), 3.89 (s, 1.8H), 4.01 (s, 1.2H), 4.94–5.04 (m, 0.4H), 5.81 (dd, *J* = 10.5, 5.7 Hz, 0.6H), 6.16 (d, *J* = 2.3 Hz, 0.4H), 6.47 (d, *J* = 2.3 Hz, 0.6H), 6.59–6.78 (m, 3.4H), 6.88–7.04 (m, 2.6H), 7.09–7.25 (m, 2H), 7.29–7.37 (m, 1H), 7.37–7.47 (m, 1H), 7.48–7.56 (m, 2H), 7.67–7.73 (m, 1H), 7.92 (d, *J* = 2.4 Hz, 0.4H), 8.01 (d, *J* = 2.4 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.1, 26.9, 27.8, 28.7, 28.8, 28.9, 31.2, 35.5, 39.8, 40.7, 41.0, 42.3, 52.5, 56.7, 56.8, 57.5, 111.4, 111.6, 112.8, 112.8, 113.2, 113.2, 117.1, 117.6, 120.1, 120.3, 120.5, 123.0, 125.4, 125.5, 126.0, 126.1, 127.1, 127.8, 127.9, 129.1, 129.1, 129.3, 129.5, 129.6, 130.3, 130.6, 133.1, 134.5, 134.8, 135.6, 135.9, 136.0, 136.2, 136.5, 137.3, 139.2, 139.3, 151.2, 151.3, 155.6, 155.8, 171.4, 171.9, 172.3.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{37}H_{42}N_4NaO_5S$: 677.27736, found: 677.27542.

3'-(*N*-(8-(2-(3-Fluorophenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-4'-methoxy-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide (5n)



The title compound was synthesized in 87% according to a method similar to that described for **5h**.

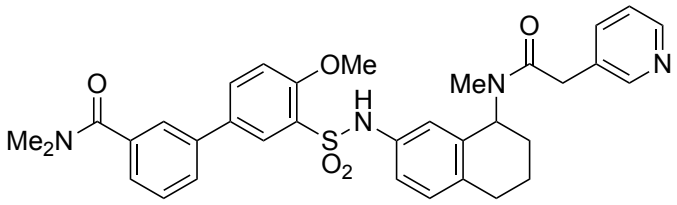
IR (neat): 2937, 1627, 1503, 1279, 1161 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.47–2.02 (m, 4H), 2.27 (s, 1.2H), 2.50 (s, 1.8H), 2.57–2.75 (m, 2H), 3.06 (br s, 6H), 3.66–3.86 (m, 2H), 3.99–4.10 (m, 3H), 4.91–4.87 (m, 0.4H), 5.81–5.77 (m, 0.6H), 6.40 (s, 0.4H), 6.69 (s, 0.6H), 6.88–7.19 (m, 7H), 7.28–7.38 (m, 2H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.47–7.58 (m, 2H), 7.67–7.79 (m, 1H), 7.93 (d, *J* = 2.3 Hz, 0.4H), 7.98 (d, *J* = 2.3 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 21.9, 26.9, 27.9, 28.7, 28.9, 29.0, 31.2, 41.0, 52.9, 56.8, 57.5, 112.8, 112.9, 114.0 (d, *J* = 21.1 Hz), 114.1 (d, *J* = 21.1 Hz), 115.8 (d, *J* = 21.1 Hz), 116.1 (d, *J* = 21.1 Hz), 120.2, 120.6, 120.9, 123.2, 124.6 (d, *J* = 1.9 Hz), 124.8 (d, *J* = 1.9 Hz), 125.5, 125.5, 126.0, 126.1, 126.6, 127.0, 127.8, 127.8, 129.1, 129.1, 129.2, 129.3, 130.2 (d, *J* = 7.7 Hz), 130.4 (d, *J* = 7.7 Hz), 130.8, 133.1, 133.2, 134.7, 134.7, 135.3, 136.1, 136.3, 136.3, 137.2, 137.5 (d, *J* = 7.7 Hz), 137.7 (d, *J* = 7.7 Hz), 139.2, 139.2, 155.6, 155.8, 163.0 (d, *J* = 246.3 Hz), 170.9, 171.3.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{35}H_{36}FN_3NaO_5S$: 652.22574, found: 652.22593.

4'-Methoxy-*N*,*N*-dimethyl-3'-(*N*-(8-(*N*-methyl-2-(pyridin-3-yl)acetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-[1,1'-biphenyl]-3-carboxamide (5o)



The title compound was synthesized in 70% according to a method similar to that described for **5h**.

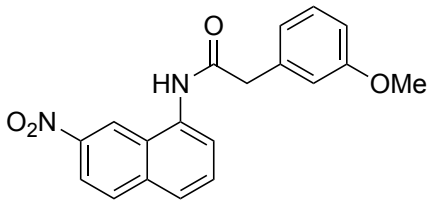
IR (neat): 2936, 1628, 1503, 1279, 1160 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.49–2.06 (m, 4H), 2.32 (s, 1.2H), 2.53 (s, 1.8H), 2.59–2.78 (m, 2H), 2.98 (s, 3H), 3.14 (s, 3H), 3.60–3.82 (m, 2H), 4.01 (s, 3H), 4.86–5.00 (m, 0.4H), 5.80 (dd, *J* = 10.3, 5.7 Hz, 0.6H), 6.48 (s, 0.4H), 6.75 (s, 0.6H), 6.86–6.96 (m, 1.2H), 7.00 (d, *J* = 8.2 Hz, 0.4H), 7.03–7.19 (m, 1.4H), 7.28–7.46 (m, 4H), 7.47–7.58 (m, 2H), 7.64–7.78 (m, 2H), 7.94 (d, *J* = 2.3 Hz, 0.4H), 7.99 (d, *J* = 2.3 Hz, 0.6H), 8.47–8.60 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8, 22.0, 26.9, 28.1, 28.7, 28.9, 29.1, 31.2, 35.5, 38.0, 38.2, 39.7, 53.0, 56.7, 56.8, 57.4, 112.8, 112.9, 120.2, 120.5, 120.8, 123.0, 123.8, 125.4, 125.5, 126.0, 126.1, 126.7, 127.1, 127.7. 127.8, 129.0, 129.1, 129.2, 129.3, 130.4, 130.8, 131.0, 131.2, 133.1, 134.8, 134.9, 135.2, 136.0, 136.1, 136.2, 137.0, 137.1, 137.3, 139.2, 139.2, 148.4, 148.5, 150.0, 150.3, 155.7, 155.8, 170.5, 170.9, 171.3, 171.3.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{34}H_{36}N_4NaO_5S$: 635.23041, found: 635.22938.

2-(3-Methoxyphenyl)-*N*-(7-nitronaphthalen-1-yl)acetamide (18)



A mixture of **17**[40] (20.0 mg, 0.106 mmol), 3-methoxyphenylacetic acid (23.0 mg, 0.138 mmol), DIPEA (54.6 µL, 0.319 mmol) and HATU (67.3 mg, 0.189 mmol) in dry CH_2Cl_2 (1.1 mL) was stirred for 8 h at room temperature under an argon atmosphere. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (4–50% EtOAc in hexane) to afford **S11** (31.9 mg, 89%) as a yellow solid.

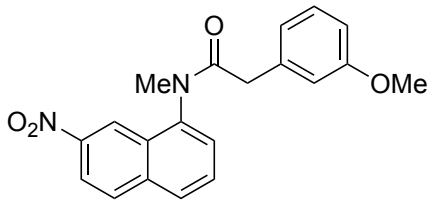
IR (KBr): 3435, 1660, 1525, 1491, 1336 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 3.82–4.00 (m, 5H), 6.93–7.04 (m, 2H), 7.07 (d, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.79 (br s, 1H), 7.89 (d, *J* = 8.7 Hz, 1H), 8.07 (d, *J* = 7.3 Hz, 1H), 8.16 (dd, *J* = 8.7, 1.8 Hz, 1H), 8.30 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 44.9, 55.5, 113.6, 115.6, 117.8, 119.4, 121.8, 122.1, 125.5, 125.7, 130.0, 130.4, 131.1, 134.2, 135.8, 136.4, 145.6, 160.7, 170.0.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{19}H_{16}N_2NaO_4$: 359.1008, found: 359.1005.

2-(3-Methoxyphenyl)-*N*-methyl-*N*-(7-nitronaphthalen-1-yl)acetamide (19)



To a suspension of sodium hydride (5.1 mg, 0.12 mmol) in dry THF (1.5 mL) was added a solution of **18** (30 mg, 0.090 mmol) in dry THF (1.5 mL) at 0 °C under an argon atmosphere. After being stirred for 10 min, iodomethane (17.0 μL, 0.27 mmol) was added to the mixture. The mixture was stirred for 1 h at room temperature under an argon atmosphere. The reaction mixture was quenched by the addition of H_2O (2 mL) and extracted with EtOAc (10, 5, 3 mL). The organic layer was washed with brine (2 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (5–50% EtOAc in hexane) to afford **19** (17.0 mg, 53%) as a yellow amorphous.

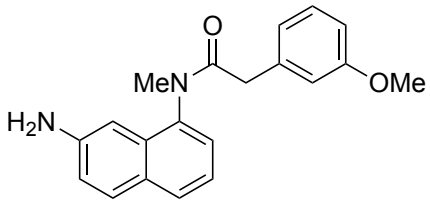
IR (neat): 1659, 1601, 1499, 1344, 1257 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 3.82–4.00 (m, 5H), 6.93–7.04 (m, 2H), 7.07 (dd, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.79 (br s, 1H), 7.89 (d, *J* = 8.7 Hz, 1H), 8.07 (d, *J* = 7.3 Hz, 1H), 8.16 (dd, *J* = 8.7, 1.8 Hz, 1H), 8.30 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 38.0, 42.1, 55.1, 112.1, 114.2, 119.4, 120.1, 121.0, 128.0, 128.9, 129.3, 129.7, 129.7, 130.2, 136.1, 136.8, 142.2, 146.3, 159.5, 171.4.

HR-MS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{20}H_{18}N_2NaO_4$: 373.1164, found: 373.1159.

***N*-(7-Aminonaphthalen-1-yl)-2-(3-methoxyphenyl)-*N*-methylacetamide (20)**



A mixture of **19** (16.1 mg, 46.0 μmol), iron powder (12.8 mg, 230 μmol) and ammonium chloride (12.3 mg, 230 μmol) in EtOH (0.50 mL) and H_2O (0.10 mL) was stirred for 11 h at 60 °C under an argon atmosphere. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude residue was purified by preparative TLC (3% MeOH in $CHCl_3$) to afford **20** (11.5 mg, 78%) as an orange oil.

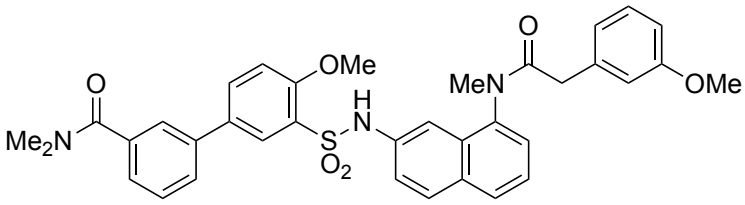
IR (neat): 3457, 3351, 1644, 1600, 1513, 1380, 1283, 1257 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 3.27–3.39 (m, 5H), 3.69 (s, 3H), 3.99 (br s, 2H), 6.49 (t, *J* = 1.8 Hz, 1H), 6.56 (d, *J* = 7.8 Hz, 1H), 6.69 (ddd, *J* = 8.2, 2.8, 0.9 Hz, 1H), 6.78 (d, *J* = 2.3 Hz, 1H), 6.98 (d, *J* = 8.7, 2.3 Hz, 1H), 7.08 (t, *J* = 7.8 Hz, 1H), 7.12–7.22 (m, 2H), 7.67–7.78 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 37.1, 41.0, 55.2, 102.7, 112.5, 114.6, 118.9, 121.7, 122.0, 126.5, 128.6, 129.1, 129.1, 130.1, 132.0, 137.1, 138.0, 145.9, 159.5, 172.0.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{20}H_{20}N_2NaO_2$: 343.1423, found: 343.1418.

4'-Methoxy-3'-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)naphthalen-2-yl)sulfamoyl)-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide (7b)



A mixture of **20** (11.1 mg, 34.6 μmol) and 3'-(dimethycarbamoyl)-4-methoxy-[1,1'-biphenyl]-3-sulfonyl chloride (13.5 mg, 38.1 μmol) in CH_2Cl_2 (0.80 mL) and pyridine (0.20 mL) was stirred for 2 h at room temperature under an argon atmosphere. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by preparative TLC (3% MeOH in $CHCl_3$) to afford **7b** (23.4 mg, quant.) as a colorless oil.

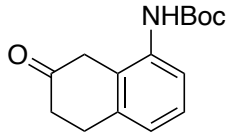
IR (neat): 1628, 1603, 1503, 1280, 1152 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 2.93 (s, 3H), 3.09 (s, 3H), 3.12 (s, 3H), 3.14 (s, 2H), 3.68 (s, 3H), 4.09 (s, 3H), 6.32–6.44 (m, 2H), 6.66 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 1.8 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 1H), 7.18 (dd, *J* = 7.3, 0.9 Hz, 1H), 7.28–7.50 (m, 6H), 7.55 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.69 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 1H), 8.00 (d, *J* = 2.3 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 35.4, 37.2, 39.7, 41.1, 55.2, 56.9, 112.1, 112.8, 113.8, 114.8, 121.4, 123.4, 125.4, 125.5, 126.1, 126.5, 126.7, 127.8, 128.7, 129.1, 129.2, 129.3, 130.2, 130.6, 132.6, 133.3, 133.3, 135.9, 136.6, 137.2, 139.0, 139.4, 155.6, 159.5, 171.3, 171.6.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{36}H_{35}N_3NaO_6S$: 660.2144, found: 660.2140.

***tert*-Butyl (7-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)carbamate**[42] **(22)**



To a solution of 8-aminonaphthalen-2-ol (**21**, 5.10 g, 32.0 mmol) and cesium carbonate (20.8 g, 63.8 mmol) in DMF (150 mL) was added ethyl iodide (3.10 ml, 38.6 mmol) at 0 ˚C, and the mixture was stirred for 19 h at room temperature under an argon atmosphere. The reaction mixture was diluted with H_2O (100 mL) and extracted with $CHCl_3$ (200, 100, 100, 100 mL). The organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford a crude product as a black oil. To a solution of the crude product in liquid ammonia (100 mL) and ^{t}BuOH (18.2 mL) was added lithium (1.30 g, 187 mmol) at –33 ˚C, and the mixture was stirred for 30 min at –33 ˚C under nitrogen flow. After evaporating liquid ammonia, the solution was diluted with sat. NH_4Cl aq. (200 mL) and extracted with $CHCl_3$ (200, 200, 100, 100 mL). The organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford a crude product (5.73 g) as a dark purple oil. A mixture of the crude product in THF (90 mL) and 1 M HCl aq. (30 mL) was stirred for 17 h at room temperature under an argon atmosphere. The reaction mixture was concentrated under reduced pressure, basified with sat. $NaHCO_3$ aq. (100 mL) and extracted with $CHCl_3$ (200, 100, 100, 100 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford a crude product (4.89 g) as a dark purple oil. To a solution of the crude product in THF (100 mL) was added sat. $NaHCO_3$ aq. (50 mL) and Boc_2O (22.1 mL, 96.2 mmol), and the mixture was stirred at room temperature under an argon atmosphere. After the 4 h, another Boc_2O (11.9 mL, 51.8 mmol) was added to the mixture, and the solution was stirred for 49 h. The reaction mixture was diluted with H_2O (100 mL) and extracted with $CHCl_3$ (200, 100, 100, 100 mL). The organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (20–50% EtOAc in hexane and 0–11% acetone in hexane) to afford **22** (2.03 g, 24% in 4 steps) as a brown amorphous.

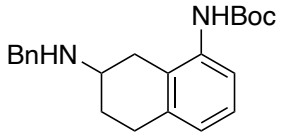
IR (neat): 3329, 2978, 1718, 1524, 1241, 1159 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.51 (s, 9H), 2.57 (t, J = 6.9 Hz, 2H), 3.07 (t, J = 6.9 Hz, 2H), 3.49 (s, 2H), 6.29 (br s, 1H), 7.03 (d, J = 7.8 Hz, 1H), 7.19 (t, J = 7.8 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 28.4, 28.6, 29.0, 38.4, 39.9, 80.9, 121.9, 124.5, 125.8, 127.2, 135.3, 137.3, 153.5, 210.0.

HR-MS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{19}NNaO_3$: 284.12626, found: 284.12599.

***tert*-Butyl (7-(benzylamino)-5,6,7,8-tetrahydronaphthalen-1-yl)carbamate (23)**



A mixture of **22** (17.4 mg, 0.0666 mmol), benzylamine (72.0 µl, 0.0662 mmol), acetic acid (4.0 µL, 0.0699 mmol) and $NaBH_3CN$ (12.8 mg, 0.203 mmol) in THF (3 mL) was heated to 60 ˚C for 14 h under an argon atmosphere. After cooling to room temperature, the reaction mixture was quenched by the addition of sat. $NaHCO_3$ aq. (5 mL) and H_2O (10 mL) and extracted with $CHCl_3$ (15, 15, 10 mL). The organic layer was concentrated under reduced pressure and the crude residue was dissolved in EtOAc (400 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (0–2% MeOH in $CHCl_3$) to afford **23** (22.7 mg, 97%) as a brown oil.

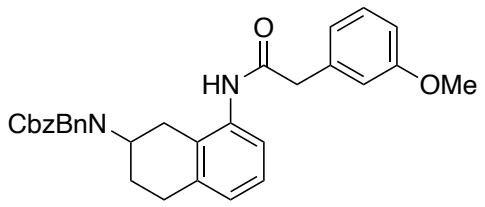
IR (neat): 2977, 2927, 1730, 1523, 1238, 1160 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.47–1.68 (m, 11H), 2.01–2.22 (m, 1H), 2.32 (dd, *J* = 15.6, 9.2 Hz, 1H), 2.72–3.06 (m, 4H), 3.88 (d, *J* = 12.8 Hz, 1H), 3.96 (d, *J* = 12.8 Hz, 1H), 6.19 (br s, 1H), 6.85 (d, *J* = 7.3 Hz, 1H), 7.10 (t, *J* = 7.3 Hz, 1H), 7.30–7.37 (m, 5H), 7.62 (d, *J* = 7.3 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 28.5, 28.7, 28.9, 32.4, 51.4, 53.2, 53.3, 80.5, 118.8, 124.4, 125.3, 126.2, 127.8, 127.2, 128.3, 128.5, 128.7, 136.2, 137.1, 140.4, 140.6, 153.2.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{22}H_{28}N_2NaO_2$: 375.20485, found: 375.20422.

Benzyl benzyl(8-(2-(3-methoxyphenyl)acetamido)-1,2,3,4-tetrahydronaphthalen-2-yl)carbamate (26)



A mixture of **23** (17.0 mg, 0.0482 mmol) and benzyl chloroformate (10.0 µl, 0.0711 mmol) in THF (1 mL) and sat. $NaHCO_3$ aq. (1 mL) was stirred for 19 h at room temperature under an argon atmosphere. The reaction mixture was diluted with H_2O (100 mL) and extracted with $CHCl_3$ (15, 15, 10 mL). The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure to afford a crude product (23.7 mg) as a dark brown oil. To a solution of the crude product in CH_2Cl_2 (2 mL) was added TFA (0.5 mL), and the mixture was stirred for 30 min at room temperature under an argon atmosphere. The reaction mixture was quenched by the addition of sat. $NaHCO_3$ aq. (6 mL) and extracted with $CHCl_3$ (15, 15, 10, 10 mL). The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure to afford a crude product (18.9 mg) as a brown oil. A mixture of the crude product, 3-methoxyphenylacetic acid (16.3 mg, 0.0981 mmol), Et_3N (67.0 µl, 0.482 mmol), and HATU (36.3 mg, 0.0955 mmol) in DMF (1 mL) was stirred for 12 h at room temperature under an argon atmosphere. The reaction mixture was diluted with sat. $NaHCO_3$ aq. (10 mL) and extracted with $CHCl_3$ (15, 15, 10, 10 mL). The organic layer was washed with H_2O (10, 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (0–33% EtOAc in hexane) to afford **26** (22.2 mg, 86% in 3 steps) as a brown oil.

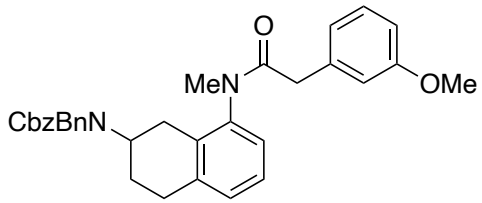
IR (neat): 3278, 3031, 2938, 1693, 1468, 1258 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.68–1.94 (m, 2H), 2.13–2.54 (m, 2H), 2.60–2.92 (m, 2H), 3.62 (s, 2H), 3.85 (s, 3H), 3.97–4.75 (m, 3H), 5.27 (s, 2H), 6.62–6.98 (m, 5H), 7.09 (t, J = 7.8 Hz, 1H), 7.14–7.45 (m, 11H), 7.53–7.73 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 27.1, 27.7, 29.9, 44.9, 47.4, 53.8, 55.4, 67.4, 120.3, 121.9, 125.8, 126.5, 126.9, 127.2, 127.4, 128.1, 128.2, 128.6, 130.5, 135.3, 136.3, 136.5, 136.7, 139.4, 160.4, 169.0.

HR-MS (ESI): m/z $[M+Na]^+$ calcd for $C_{34}H_{34}N_2NaO_4$: 557.24163, found: 557.23981.

Benzyl benzyl(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-1,2,3,4-tetrahydronaphthalen-2-yl)carbamate (27)



A mixture of **26** (18.2 mg, 0.0340 mmol), sodium hydride (55% dispersion in paraffin liquid, 7.8 mg, 0.179 mmol) and methyl iodide (11.2 µl, 0.180 mmol) in dry. THF (1 mL) was stirred for 2 h at room temperature under an argon atmosphere. The reaction mixture was quenched by the addition of H_2O (5 mL) and extracted with $CHCl_3$ (15, 15, 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (20–33% EtOAc in hexane) to afford **27** (15.2 mg, 81%) as a colorless oil.

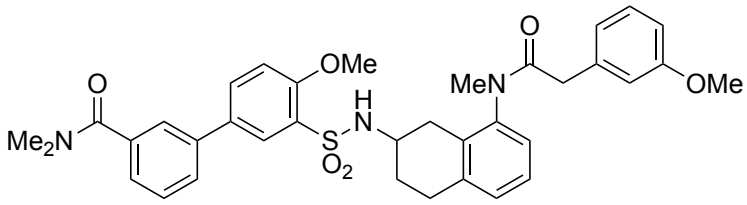
IR (neat): 2937, 1695, 1652, 1455, 1256 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.76–2.17 (m, 2H), 2.26–2.66 (m, 1H), 2.70–3.08 (m, 4H), 3.08–3.18 (m, 1H), 3.18–3.48 (m, 2H), 3.56–4.88 (m, 7H), 4.95–5.49 (m, 2H), 6.37–6.58 (m, 2H), 6.58–6.81 (m, 1H), 6.81–6.98 (m, 1H), 7.00–7.26 (m, 6H), 7.26–7.38 (m, 7H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 27.1, 28.7, 29.8, 29.9, 35.8, 36.5, 41.2, 46.8, 53.2, 54.1, 55.1, 67.3, 112.4, 112.6, 114.5, 114.6, 121.4, 121.6, 125.9, 126.0, 126.7, 126.8, 127.0, 127.1, 127.2, 127.9, 128.0, 128.5, 128.6, 128.9, 129.0, 129.2, 133.6, 134.1, 136.3, 136.5, 136.6, 137.8, 139.1, 139.3, 142.3, 142.5, 159.4, 159.5, 170.7, 170.9.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{35}H_{36}N_2NaO_4$: 571.25728, found: 571.25471.

4'-Methoxy-3'-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-1,2,3,4-tetrahydronaphthalen-2-yl)sulfamoyl)-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide (7c)



A mixture of **27** (19.3 mg, 0.0352 mmol) and 5% Pd/C (77.4 mg) in dry. THF (2.5 mL) was stirred for 1 h at room temperature under a hydrogen atmosphere. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to afford a crude product as a colorless oil. To a solution of the crude product in CH_2Cl_2 (0.9 mL) and pyridine (0.3 mL) was added 3'-(dimethycarbamoyl)-4-methoxy-[1,1'-biphenyl]-3-sulfonyl chloride (125 mg, 0.353 mmol), and the mixture was stirred for 42 h at room temperature under an argon atmosphere. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (80% EtOAc in hexane and 5% MeOH in $CHCl_3$) to afford **7c** (14.0 mg, 62% in 2 steps) as a colorless oil.

IR (neat): 2926, 1634, 1466, 1279, 1159 cm^{-1}.

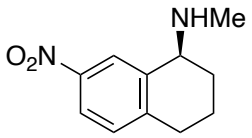
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.40–1.78 (m, 1.4H), 1.86–2.13 (m, 2H), 2.17–2.41 (m, 1.6H), 2.73–2.94 (m, 4H), 2.95–3.21 (m, 8H), 3.40–3.55 (m, 1H), 3.69 (s, 1.2H), 3.75 (s, 1.8H), 3.96 (s, 1.8H), 4.01 (s, 1.2H), 4.78 (d, *J* = 7.8 Hz, 0.6H), 5.02 (d, *J* = 7.8 Hz, 0.4H), 6.24–6.35 (m, 0.4H), 6.39–6.48 (m, 1H), 6.56 (d, *J* = 7.3 Hz, 0.6H), 6.64 (dd, *J* = 8.0, 2.5 Hz, 0.4H), 6.78 (dd, *J* = 8.0, 2.5 Hz, 0.6H), 6.86–6.94 (m, 1H), 7.00 (t, *J* = 8.0 Hz, 0.4H), 7.07–7.22 (m, 3.6H), 7.29–7.50 (m, 2H), 7.56–7.74 (m, 2H), 7.81 (td, *J* = 8.2, 2.3 Hz, 1H), 8.14 (d, *J* = 2.3 Hz, 0.6H), 8.17 (d, *J* = 2.3 Hz, 0.4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 18.6, 27.1, 28.6, 29.1, 29.8, 30.0, 31.1, 31.6, 31.7, 35.5, 36.2, 39.8, 41.3, 49.3, 50.0, 55.2, 55.3, 56.7, 58.6, 112.3, 112.3, 113.1, 114.8, 115.4, 121.3, 121.6, 125.5, 125.6, 126.1, 126.1, 126.2, 126.3, 127.4, 127.5, 127.9, 128.0, 128.6, 129.0, 129.1, 129.2, 129.3, 131.9, 132.5, 133.1, 133.2, 133.5, 136.1, 136.4, 137.3, 137.7, 139.3, 142.2, 142.4, 155.6, 155.8, 159.5, 159.6, 170.8, 171.4.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{36}H_{39}N_3NaO_6S$: 664.24573, found: 664.24347.

Chiral resolution of (*rac*)-10c and synthesis of (–)-29

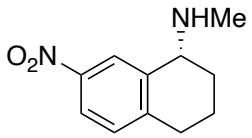
(*S*)-*N*-Methyl-7-nitro-1,2,3,4-tetrahydronaphthalen-1-amine ((*S*)-10c)



The racemic mixture (*rac*)-**10c** was separated by HPLC (DAICEL CHIRALPAK AD-H, 20 mm I.D.×250 mmL, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 98/2, flow rate: 15 mL/min., λ = 254 nm, tR = 14 min.). The optical purity was confirmed by HPLC (DAICEL CHIRALPAK AD-H, 4.6 mm I.D.×250 mmL, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 90/10, flow rate: 1.0 mL/min., λ = 254 nm, tR = 6.4 min., > 95% ee.).

$[\alpha]_{589}^{20}$ = +50.4 (*c* = 1.34, $CHCl_3$)

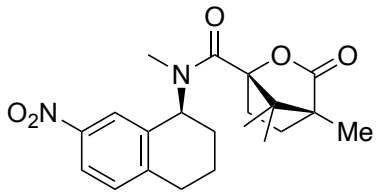
(*R*)-*N*-Methyl-7-nitro-1,2,3,4-tetrahydronaphthalen-1-amine ((*R*)-10c)



The racemic mixture (*rac*)-**10c** was separated by HPLC (DAICEL CHIRALPAK AD-H, 20 mm I.D.×250 mmL, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 98/2, flow rate: 15 mL/min., λ = 254 nm, tR = 22 min.). The optical purity was confirmed by HPLC (DAICEL CHIRALPAK AD-H, 4.6 mm I.D.×250 mmL, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 90/10, flow rate: 1.0 mL/min., λ = 254 nm, tR = 8.7 min., > 95% ee.).

$[\alpha]_{589}^{20}$ = –48.3 (*c* = 1.24, $CHCl_3$)

(1*S*)-*N*,4,7,7-Tetramethyl-*N*-((*S*)-7-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxamide ((–)-29)



A mixture of (*S*)-*N*-methyl-7-nitro-1,2,3,4-tetrahydronaphthalen-1-amine ((*S*)-**10c**) (20.0 mg, 0.0970 mmol), (–)-camphanic acid (57.7 mg, 0.0291 mmol), Et_3N (130 μL, 0.970 mmol) and HATU (10.2 mg, 0.0268 μmol) in DMF (1.0 mL) was stirred for 1 h at room temperature under an argon atmosphere. The reaction mixture was diluted with sat. $NaHCO_3$ aq. (30 mL) and extracted with EtOAc (30, 20, 10 mL). The organic layer was washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (33–67% EtOAc in hexane) to afford (–)-**29** (37.0 mg, 91%) as a pale yellow amorphous.

$[\alpha]_{589}^{20}$ = –71.1 (*c* = 0.204, $CHCl_3$).

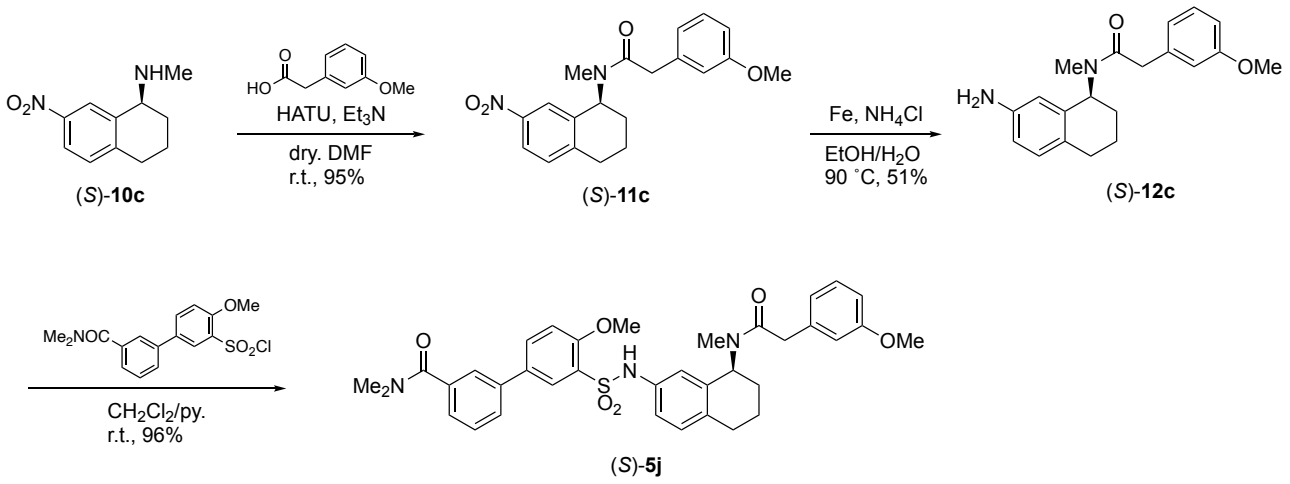
IR (KBr): 2938, 1783, 1626, 1516, 1340 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.06 (s, 1.8H), 1.11 (s, 1.2H), 1.13 (s, 1.8H), 1.16 (s, 1.2H), 1.25 (s, 1.8H), 1.28 (s, 1.2H), 1.67–1.82 (m, 1H), 1.82–2.16 (m, 5.4H), 2.16–2.32 (m, 0.6H), 2.42–2.62 (m, 1H), 2.66 (s, 1.2H), 2.81–2.92 (m, 2H), 2.96 (s, 1.8H), 5.74 (dd, *J* = 10.1, 5.5 Hz, 0.4H), 5.81–6.00 (m, 0.6H), 7.26–7.33 (m, 1H), 7.74–7.85 (m, 1H), 7.95–8.08 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 9.7, 16.8, 16.9, 18.0, 18.0, 21.7, 26.4, 28.6, 29.5, 29.6, 29.7, 30.7, 31.0, 32.2, 53.8, 53.9, 54.1, 55.5, 55.6, 56.3, 92.8, 92.9, 121.6, 121.9, 122.1, 122.5, 130.3, 130.5, 137.0, 137.1, 145.8, 146.5, 146.8, 146.9, 168.2, 168.3, 178.4, 178.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{21}H_{26}N_2NaO_5$: 409.17394, found: 409.17207.

Synthesis of (*S*)-5j



Scheme 15. Synthesis of (*S*)-**5j**

(*S*)-2-(3-Methoxyphenyl)-*N*-methyl-*N*-(7-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide ((*S*)-11c)

The title compound was synthesized in 95% according to a method similar to that described for (*rac*)-**11**.

(*S*)-12): $[\alpha]_{589}^{20}$ = –41.2 (*c* = 1.17, $CHCl_3$)

(*S*)-*N*-(7-Amino-1,2,3,4-tetrahydronaphthalen-1-yl)-2-(3-methoxyphenyl)-*N*-methylacetamide ((*S*)-12c)

The title compound was synthesized in 51% according to a method similar to that described for (*rac*)-**12c**.

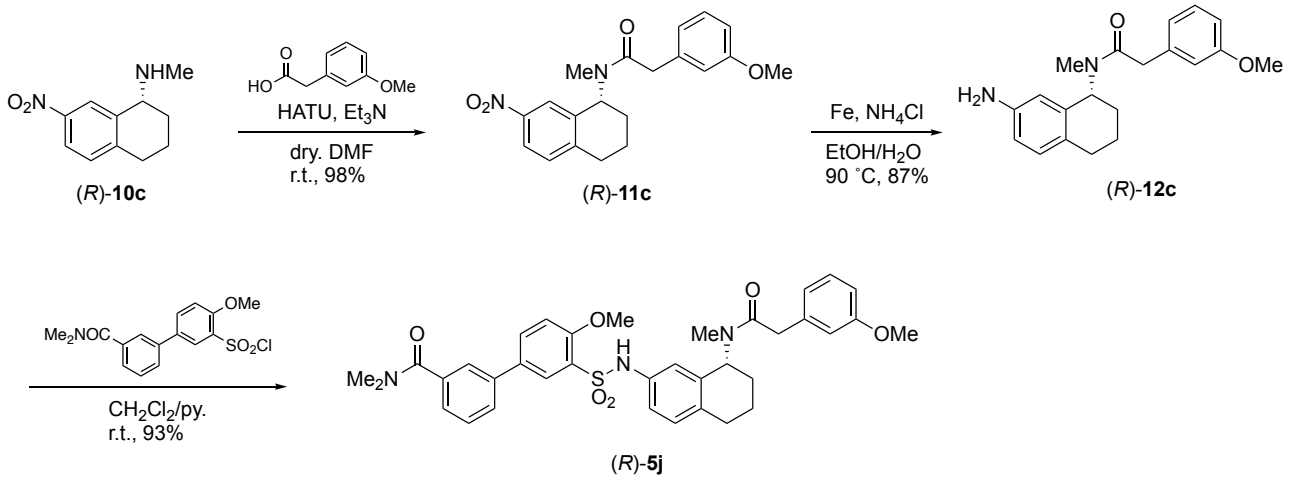
$[\alpha]_{589}^{20}$ = –56.0 (*c* = 0.584, $CHCl_3$)

(*S*)-4'-Methoxy-3'-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide ((*S*)-5j)

The title compound was synthesized in 96% according to a method similar to that described for (*rac*)-**5j**. The optical purity was confirmed by HPLC (DAICEL CHIRALPAK AD-H, 4.6 mm I.D.×250 mmL, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 50/50, flow rate: 1.0 mL/min., λ = 254 nm, tR = 88 min., > 95% ee.).

$[\alpha]_{589}^{20}$ = –7.35 (*c* = 0.354, $CHCl_3$)

Synthesis of (*R*)-5j



Scheme 16. Synthesis of (*R*)-**5j**

(*R*)-2-(3-Methoxyphenyl)-*N*-methyl-*N*-(7-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide ((*R*)-11c)

The title compound was synthesized in 98% according to a method similar to that described for (*rac*)-**11c**.
$[\alpha]_{589}^{20}$ = +43.5 (*c* = 1.13, $CHCl_3$)

(*R*)-*N*-(7-Amino-1,2,3,4-tetrahydronaphthalen-1-yl)-2-(3-methoxyphenyl)-*N*-methylacetamide ((*R*)-12c)

The title compound was synthesized in 87% according to a method similar to that described for (*rac*)-**12c**.
$[\alpha]_{589}^{20}$ = +53.9 (*c* = 0.686, $CHCl_3$)

(*R*)-4'-Methoxy-3'-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide ((*R*)-5j)

The title compound was synthesized in 93% according to a method similar to that described for (*rac*)-**5j**. The optical purity was confirmed by HPLC (DAICEL CHIRALPAK AD-H, 4.6 mm I.D.×250 mmL., hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 50/50, flow rate: 1.0 mL/min., λ = 254 nm, tR = 69 min., > 95% ee.).
$[\alpha]_{589}^{20}$ = +8.84 (*c* = 0.294, $CHCl_3$)

X-ray Crystallographic Analysis

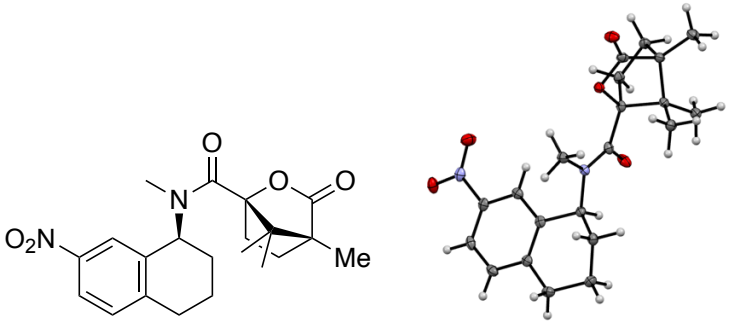
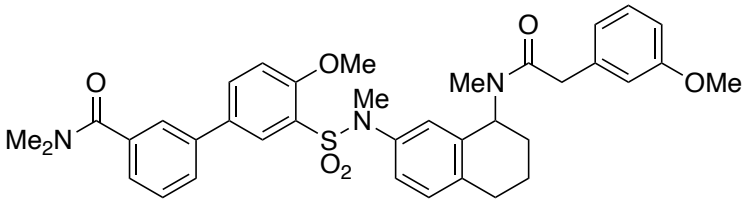


Figure 33. X-ray ORTEP drawing of (–)-**29**

Table 11. Crystal data and structural refinement parameters for (–)-**29**.

Compound		(–)-**29**
Data deposition		CCDC2117019
Empirical formula		$C_{21}H_{26}N_2O_5$
Formula weight		386.44
Temperature		93(2) K
Wavelength		1.54187 Å
Crystal system		orthorhombic
Space group		P 21 21 21
Unit cell dimensions	*a*	6.77450(10) Å
	b	10.9311(2) Å
	c	25.3233(5) Å
	α	90 º
	β	90 º
	γ	90 º
Volume		1875.26(6) Å^3
Z		4
Density (calculated)		1.369 g/m^3
Absorption coefficient Mu		0.804 mm^{-1}
F(000)		824
Crystal size		0.130×0.100×0.080 mm^3
Theta range for data collection		3.49 º to 68.11 º
Index ranges		–7<=*h*<=7
		–13<=*k*<=13
		–30<=*l*<=30
Reflections collected		21565
Data/restraints/parameters		3388/0/257
Goodness-of-fit on F^2		1.035
Final *R* indices		R_1 = 0.0271 [I>2σ(I)]
		wR_2 = 0.0708 (all data)

4'-Methoxy-3'-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)-*N*-methylsulfamoyl)-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide (30)



A mixture of **5j** (5.9 mg, 0.00961 mmol), sodium hydride (55% dispersion in paraffin liquid, 4.9 mg, 0.112 mmol) and methyl iodide (20.0 µl, 0.321 mmol) in dry. THF (1 mL) was stirred for 1 h at room temperature under an argon atmosphere. The reaction mixture was quenched by the addition of H_2O (5 mL) and extracted with $CHCl_3$ (15, 10, 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by preparative TLC (5% MeOH in $CHCl_3$) to afford **30** (5.8 mg, 96%) as a colorless amorphous.

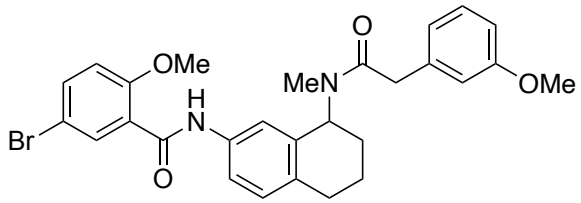
IR (neat): 1633, 1503, 1397, 1337, 1280, 1148, 751 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.38–2.02 (m, 4H), 2.24 (s, 1.2H), 2.47 (s, 1.8H), 2.64–2.73 (m, 2H), 2.98 (s, 3H), 3.12 (s, 3H), 3.24 (s, 1.8H), 3.29 (s, 1.2H), 3.63–3.74 (m, 2H), 3.77 (s, 3H), 3.85 (s, 1.8H), 3.95 (s, 1.2H), 4.90–4.98 (m, 0.4H), 5.85 (dd, *J* = 10.9, 5.6 Hz, 0.6H), 6.52–6.55 (m, 0.4H), 6.71–6.74 (m, 0.6H), 6.74–6.86 (m, 3H), 7.13–6.96 (m, 2.6H), 7.16–7.23 (m, 1.4H), 7.29–7.37 (m, 1H), 7.37–7.46 (m, 1H), 7.46–7.55 (m, 2H), 7.69–7.77 (m, 1H), 7.91 (d, *J* = 2.4 Hz, 0.4H), 7.99 (d, *J* = 2.4 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 14.3, 21.9, 22.0, 22.8, 26.9, 27.8, 28.9, 29.1, 29.8, 31.2, 31.7, 32.9, 35.5, 39.0, 39.7, 41.7, 52.8, 55.3, 56.3, 56.4, 57.5, 112.3, 112.8, 112.9, 114.5, 114.6, 121.0, 121.1, 123.9, 124.7, 125.3, 125.4, 125.5, 125.9, 126.0, 127.1, 127.8, 127.8, 129.1, 129.1, 129.9, 129.9, 130.0, 130.3, 132.6, 132.8, 132.9, 135.5, 136.0, 136.5, 136.8, 137.3, 137.3, 137.4, 137.6, 139.4, 139.6, 139.7, 156.5, 156.6, 160.0, 160.0, 171.3, 171.4, 171.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{37}H_{41}N_3NaO_6S$: 678.26138, found: 678.26003.

5-Bromo-2-methoxy-*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)benzamide (34)



A mixture of **12c** (57.9 mg, 0.178 mmol), 5-bromo-2-methoxybenzoic acid (123 mg, 0.532 mmol), Et_3N (0.247 mL, 1.78 mmol) and HATU (203 mg, 0.534 mmol) in DMF (2 mL) was stirred for 7 h at room temperature under an argon atmosphere. The reaction mixture was diluted with EtOAc (30 mL) and washed with sat. $NaHCO_3$ aq. (10 mL), 1 M HCl aq. (10 mL) and H_2O (10, 10, 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (33–50% EtOAc in hexane). The resulting residue was dissolved in EtOAc (30 mL) and washed with H_2O (30, 30, 30 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford **34** (82.3 mg, 86%) as a colorless amorphous.

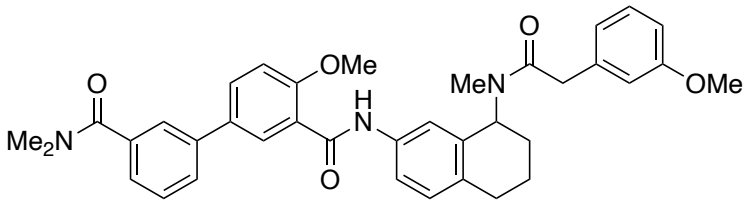
IR (neat): 3357, 2938, 1632, 1594, 1540, 1479, 1269 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.57–2.11 (m, 4H), 2.68 (s, 1.2H), 2.71 (s, 1.8H), 2.73–2.79 (m, 2H), 3.72–3.93 (m, 5H), 4.00 (s, 1.8H), 4.04 (s, 1.2H), 5.09 (dd, *J* = 10.8, 5.7 Hz, 0.4H), 5.95 (dd, *J* = 10.0, 6.1 Hz, 0.6H), 6.77 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.94–6.92 (m, 3.4H), 7.06–7.14 (m, 1.6H), 7.22 (t, *J* = 8.2 Hz, 0.4H), 7.24 (t, *J* = 8.2 Hz, 0.6H), 7.52 (dd, *J* = 8.2, 2.3 Hz, 0.6H), 7.58 (dd, *J* = 8.7, 2.8 Hz, 0.6H), 7.60 (dd, *J* = 8.7, 2.8 Hz, 0.4H), 7.70 (dd, *J* = 8.2, 2.3 Hz, 0.4H), 8.36 (d, *J* = 2.8 Hz, 0.6H), 8.37 (d, *J* = 2.8 Hz, 0.4H), 9.42 (s, 0.6H), 9.47 (s, 0.4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 22.1, 22.2, 27.2, 28.3, 29.0, 29.2, 29.6, 31.6, 41.8, 41.9, 53.0, 55.3, 55.4, 56.8, 56.9, 57.7, 112.5, 112.7, 113.6, 114.3, 114.4, 118.6, 119.6, 120.2, 120.7, 121.2, 121.3, 123.6, 123.8, 129.8, 129.9, 130.0, 130.3, 134.6, 135.2, 135.2, 135.4, 135.8, 135.9, 136.1, 136.5, 136.7, 137.0, 156.4, 160.0, 160.1, 162.0, 162.0, 171.7, 172.0.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{28}H_{29}BrN_2NaO_4$: 559.12084, found: 559.12168.

4-Methoxy-N^3-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)-$N^{3'}$,$N^{3'}$-dimethyl-[1,1'-biphenyl]-3,3'-dicarboxamide (31)



A mixture of **34** (11.1 mg, 0.0207 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (7.6 mg, 0.0104 mmol), 3-(dimethylcarbamoyl)phenylboronic acid (7.9 mg, 0.0409 mmol) and 2.5 M Na_2CO_3 aq. (82.8 μL, 0.207 mmol) in 1,2-dimethoxyethane (2 mL) was refluxed for 7 h under an argon atmosphere. The reaction mixture was filtered, diluted with $CHCl_3$ (30 mL), and washed with sat. $NaHCO_3$ aq. (10 mL). The aqueous layer was extracted with $CHCl_3$ (20, 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by preparative TLC (5% MeOH in $CHCl_3$) to afford **31** (9.3 mg, 74%) as a yellow oil.

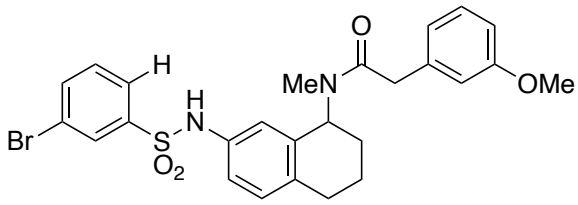
IR (neat): 3356, 2934, 1631, 1504, 752 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.53–2.13 (m, 4H), 2.69 (s, 1.2H), 2.72 (s, 1.8H), 2.74–2.83 (m, 2H), 3.02 (s, 3H), 3.14 (s, 3H), 3.74 (s, 1.8H), 3.77 (s, 1.2H), 3.78–3.94 (m, 2H), 4.06 (s, 1.8H), 4.12 (s, 1.2H), 5.02–5.22 (m, 0.4H), 5.87–6.08 (m, 0.6H), 6.70–6.84 (m, 1H), 6.87–6.99 (m, 2.4H), 7.05–7.19 (m, 2.6H), 7.18–7.25 (m, 1H), 7.36–7.42 (m, 1H), 7.44–7.52 (m, 1H), 7.56–7.78 (m, 4H), 8.47–8.60 (m, 1H), 9.57 (s, 0.6H), 9.59 (s, 0.4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 22.1, 22.2, 27.2, 28.3, 29.0, 29.2, 29.6, 29.8, 31.6, 35.5, 39.8, 41.9, 41.9, 53.0, 55.3, 55.4, 56.7, 56.8, 57.7, 112.3, 112.5, 112.7, 114.2, 114.4, 118.5, 119.5, 120.2, 120.6, 121.2, 121.3, 122.1, 122.3, 125.5, 125.9, 128.0, 129.0, 129.1, 129.8, 129.9, 129.9, 130.2, 131.1, 131.2, 131.6, 131.7, 133.9, 133.9, 134.3, 135.0, 135.3, 135.8, 136.4, 136.7, 137.0, 137.2, 140.0, 140.0, 157.0, 160.0, 160.1, 163.2, 163.2, 171.6, 171.7, 171.9.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{37}H_{39}N_3NaO_5$: 628.27874, found: 628.28014.

***N*-(7-((3-Bromophenyl)sulfonamido)-1,2,3,4-tetrahydronaphthalen-1-yl)-2-(3-methoxyphenyl)-*N*-methylacetamide (35)**



The title compound was synthesized in 98% according to a method similar to that described for **6a**.

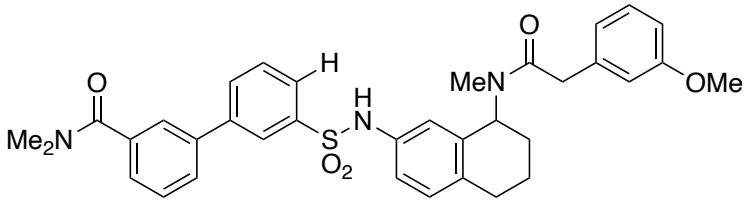
IR (KBr): 3117, 2937, 1618, 1165 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.43–2.08 (m, 4H), 2.39 (s, 1.8H), 2.52 (s, 1.2H), 2.58–2.79 (m, 2H), 3.66–3.84 (m, 3.2H), 3.89 (s, 1.8H), 4.84–5.02 (m, 0.4H), 5.74–5.92 (m, 0.6H), 6.40 (s, 0.6H), 6.52 (s, 0.4H), 6.78 (dd, *J* = 8.2, 2.3 Hz, 0.4H), 6.81–6.94 (m, 2.6H), 6.98 (d, *J* = 5.5 Hz, 0.4H), 7.00 (d, *J* = 5.5 Hz, 0.6H), 7.11 (dd, *J* = 8.2, 2.3 Hz, 0.6H), 7.17–7.33 (m, 1.8H), 7.30 (t, *J* = 8.0 Hz, 0.6H), 7.54 (s, 0.6H), 7.57–7.65 (m, 1.6H), 7.65–7.79 (m, 0.4H), 7.85 (t, *J* = 1.8 Hz, 0.6H), 7.92 (t, *J* = 1.8 Hz, 0.4H), 8.62 (s, 0.4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 22.0, 22.0, 26.8, 27.8, 28.6, 28.9, 29.6, 31.1, 41.8, 41.9, 52.7, 55.5, 55.7, 57.7, 112.0, 112.8, 114.3, 115.1, 119.2, 120.5, 120.6, 121.1, 121.1, 121.6, 122.8, 126.0, 130.0, 130.1, 130.2, 130.3, 130.4, 130.5, 130.5, 130.5, 134.5, 134.9, 135.4, 135.5, 135.7, 135.7, 136.2, 136.3, 136.4, 136.5, 141.2, 141.5, 159.9, 160.1, 172.1, 172.1.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{26}H_{27}BrN_2NaO_4S$: 565.07726, found: 565.07642.

3'-(*N*-(8-(2-(3-Methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-*N*,*N*-dimethyl-[1,1'-biphenyl]-3-carboxamide (32a)



A mixture of **35** (15.4 mg, 0.0283 mmol), $Pd(PPh_3)_4$ (17.2 mg, 0.0149 mmol), 3-(dimethylcarbamoyl)phenylboronic acid (11.2 mg, 0.0580 mmol) and 2.5 M Na_2CO_3 aq. (58.0 μL, 0.145 mmol) in 1,2-dimethoxyethane (2 mL) was refluxed for 16 h under an argon atmosphere. The reaction mixture was diluted with $CHCl_3$ (20 mL) and H_2O (10 mL) and washed with sat. $NaHCO_3$ aq. (5 mL). The aqueous layer was extracted with $CHCl_3$ (15, 10 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by preparative TLC (9% hexane in EtOAc and 3% (28% NH_3 aq./MeOH = 1/9) in $CHCl_3$) to afford **32a** (14.2 mg, 82%) as a colorless oil.

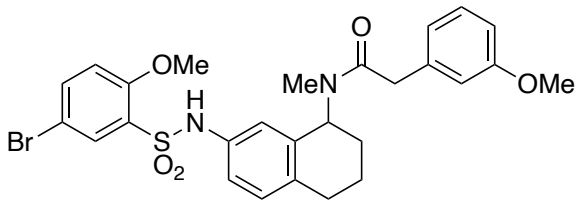
IR (neat): 2936, 1622, 1162 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.46–1.79 (m, 2.3H), 1.80–1.97 (m, 1.7H), 2.34 (s, 2.1H), 2.35 (s, 0.9H), 2.61–2.72 (m, 2H), 2.98 (s, 3H), 3.12 (s, 3H), 3.62–3.76 (m, 2H), 3.77 (s, 0.9H), 3.88 (s, 2.1H),4.88 (dd, *J* = 10.1, 5.4 Hz, 0.3H), 5.76 (dd, *J* = 11.2, 5.3 Hz, 0.7H), 6.37–6.43 (m, 1H), 6.73–6.90 (m, 3H), 6.95–7.05 (m, 1.7H), 7.10–7.20 (m, 1.3H), 7.23–7.29 (m, 0.7H), 7.37–7.54 (m, 5.3H), 7.63 (ddd, *J* = 7.9, 1.7, 1.0 Hz, 0.7H), 7.68 (ddd, *J* = 7.9, 1.7, 1.0 Hz, 0.7H), 7.71 (ddd, *J* = 6.9, 1.7, 1.0 Hz, 0.3H), 7.74 (ddd, *J* = 6.9, 1.7, 1.0 Hz, 0.3H), 7.82 (dd, *J* = 1.7, 1.7 Hz, 0.7H), 7.89 (dd, *J* = 1.7, 1.7 Hz, 0.3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 22.0, 22.0, 26.8, 27.9, 28.7, 28.8, 29.3, 31.0, 35.5, 39.7, 41.8, 41.9, 52.6, 55.5, 55.8, 57.5, 111.7, 112.5, 114.4, 115.2, 119.9, 120.5, 121.0, 121.1, 121.5, 121.7, 125.9, 126.0, 126.2, 126.3, 126.8, 128.3, 129.2, 129.6, 129.8, 130.0, 130.1, 130.4, 130.5, 131.4, 131.4, 134.7, 135.2, 135.4, 135.7, 136.1, 136.6, 136.6, 136.8, 137.4, 139.6, 139.6, 139.8, 140.1, 141.2, 141.3, 159.9, 160.0, 171.2, 171.6, 171.9.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{35}H_{37}N_3NaO_5S$: 634.23516, found: 634.23611.

***N*-(7-((5-Bromo-2-methoxyphenyl)sulfonamido)-1,2,3,4-tetrahydronaphthalen-1-yl)-2-(3-methoxyphenyl)-*N*-methylacetamide (36)**



The title compound was synthesized in 99% according to a method similar to that described for **6a**.

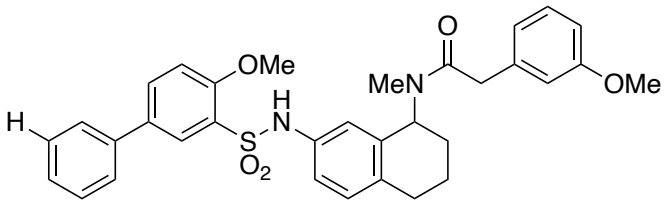
IR (KBr): 2937, 1628, 1479, 1275, 1163, 587 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.52–2.02 (m, 4H), 2.28 (s, 1.2H), 2.50 (s, 1.8H), 2.59–2.71 (m, 2H), 3.65–3.84 (m, 3.2H), 3.88 (s, 1.8H), 3.94 (s, 1.8H), 4.02 (s, 1.2H), 4.85–4.99 (m, 0.4H), 5.75–5.90 (dd, *J* = 10.5, 5.5 Hz, 0.6H), 6.26 (s, 0.4H), 6.58 (s, 0.6H), 6.77–7.04 (m, 6H), 7.07–7.16 (m, 1H), 7.23 (t, *J* = 7.8 Hz, 0.4H), 7.31 (t, *J* = 8.0 Hz, 0.6H), 7.52–7.61 (m, 1H), 7.81 (d, *J* = 2.3 Hz, 0.4H), 7.87 (d, *J* = 2.3 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.0, 26.8, 27.8, 28.7, 28.9, 28.9, 31.2, 41.7, 41.8, 52.4, 55.5, 55.6, 56.8, 57.0, 57.4, 111.6, 112.1, 112.7, 112.9, 114.0, 114.1, 114.9, 115.0, 120.1, 120.3, 120.3, 121.2, 121.5, 123.0, 127.7, 128.1, 130.0, 130.1, 130.4, 130.7, 133.3, 133.4, 134.3, 134.5, 135.6, 136.3, 136.4, 136.5, 136.6, 136.7, 137.5, 137.6, 155.2, 155.4, 160.0, 160.0, 171.5, 171.9.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{27}H_{29}BrN_2NaO_5S$: 595.08782, found: 595.08758.

***N*-(7-((4-Methoxy-[1,1'-biphenyl])-3-sulfonamido)-1,2,3,4-tetrahydronaphthalen-1-yl)-2-(3-methoxyphenyl)-*N*-methylacetamide (32b)**



A mixture of **36** (19.3 mg, 0.0337 mmol), $Pd(PPh_3)_4$ (19.9 mg, 0.0172 mmol), phenylboronic acid (8.4 mg, 0.0689 mmol) and 2.5 M Na_2CO_3 aq. (68.0 μL, 0.170 mmol) in 1,2-dimethoxyethane (2 mL) was refluxed for 3 h under an argon atmosphere. The reaction mixture was diluted with H_2O (10 mL) and sat. $NaHCO_3$ aq. (5 mL). The aqueous layer was extracted with $CHCl_3$ (20, 15, 15, 10 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by preparative TLC (33% toluene in EtOAc) to afford **32b** (10.5 mg, 55%) as a yellow oil.

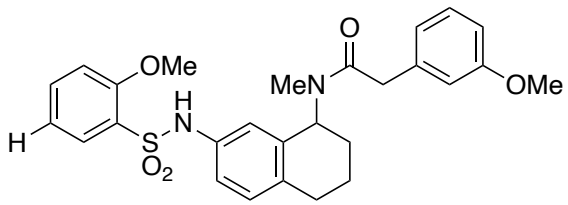
IR (neat): 2937, 1627, 1606, 1482, 1277, 1162, 762 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.48–2.00 (m, 4H), 2.23 (s, 1.2H), 2.43 (s, 1.8H), 2.56–2.69 (m, 2H), 3.60–3.79 (m, 2H), 3.80 (s, 1.2H), 3.88 (s, 1.8H), 4.00 (s, 1.8H), 4.06 (s, 1.2H), 4.85–4.98 (m, 0.4H), 5.81 (dd, *J* = 10.5, 5.5 Hz, 0.6H), 6.25 (d, *J* = 1.8 Hz, 0.4H), 6.59 (d, *J* = 1.8 Hz, 0.6H), 6.77–6.99 (m, 4.4H), 7.01–7.08 (m, 1.6H), 7.13 (d, *J* = 8.7 Hz, 0.4H), 7.17 (dd, *J* = 8.2, 1.8 Hz, 0.4H), 7.23 (t, *J* = 8.0 Hz, 0.4H), 7.27–7.36 (m, 1.6H), 7.36–7.44 (m, 2.2H), 7.44–7.51 (m, 2H), 7.68–7.75 (m, 1H), 7.93 (d, *J* = 2.3 Hz, 0.4H), 8.02 (d, *J* = 2.5 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.0, 26.9, 27.8, 28.7, 28.9, 28.9, 31.2, 41.7, 41.8, 52.5, 55.5, 55.6, 56.8, 56.9, 57.5, 111.7, 112.1, 112.7, 112.8, 114.9, 115.1, 120.1, 120.4, 120.5, 121.2, 121.5, 123.3, 126.4, 126.8, 126.8, 127.7, 128.1, 129.1, 129.1, 129.2, 129.4, 130.0, 130.1, 130.3, 130.6, 133.1, 133.1, 133.8, 133.9, 134.0, 134.7, 134.9, 135.4, 135.8, 136.0, 136.2, 136.3, 136.6, 136.7, 138.8, 138.9, 155.3, 155.6, 160.0, 160.0, 171.5, 171.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{33}H_{34}N_2NaO_5S$: 593.20861, found: 593.20624.

2-(3-Methoxyphenyl)-*N*-(7-((2-methoxyphenyl)sulfonamido)-1,2,3,4-tetrahydronaphthalen-1-yl)-*N*-methylacetamide (32c)



A mixture of **36** (18.6 mg, 0.0324 mmol) and 5% Pd/C (18.4 mg) in MeOH (1.0 mL) and EtOAc (1.0 mL) was stirred for 3 h at room temperature under a hydrogen atmosphere. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to afford a crude product as a colorless amorphous. The crude residue was purified by preparative TLC (50% hexane in acetone) to afford **32c** (12.5 mg, 78%) as a colorless amorphous.

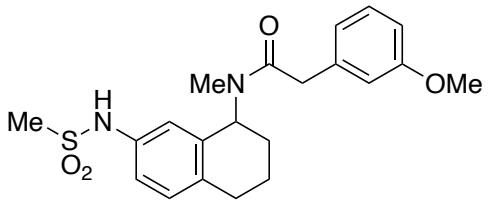
IR (neat): 2939, 1628, 1593, 1480, 1281, 1159 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.49–2.01 (m, 4H), 2.20 (s, 1.2H), 2.45 (s, 1.8H), 2.54–2.70 (m, 2H), 3.61–3.84 (m, 3.2H), 3.89 (s, 1.8H), 3.96 (s, 1.8H), 4.02 (s, 1.2H), 4.84–4.97 (m, 0.4H), 5.74–5.89 (dd, *J* = 10.5, 5.5 Hz, 0.6H), 6.27 (s, 0.4H), 6.56 (s, 0.6H), 6.72–7.08 (m, 7.6H), 7.11 (dd, *J* = 8.2, 2.3 Hz, 0.4H), 7.24 (t, *J* = 8.0 Hz, 0.4H), 7.31 (t, *J* = 7.8 Hz, 0.6H), 7.43–7.56 (m, 1H), 7.71 (dd, *J* = 7.8, 1.4 Hz, 0.4H), 7.75 (dd, *J* = 7.8, 1.4 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.0, 26.9, 27.9, 28.7, 28.8, 28.9, 31.2, 41.7. 41.8, 52.5, 55.5, 55.6, 56.5, 56.6, 57.4, 111.7, 112.1, 112.2, 112.3, 114.9, 115.0, 119.9, 120.2, 120.7, 120.9, 121.2, 121.5, 122.7, 126.0, 126.4, 130.0, 130.1, 130.2, 130.5, 131.1, 131.1, 134.9, 134.9, 135.0, 135.0, 135.4, 135.8, 136.3, 136.6, 136.8, 156.1, 156.3, 160.0, 171.4, 171.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{27}H_{30}N_2NaO_5S$: 517.17731, found: 517.17587.

2-(3-Methoxyphenyl)-*N*-methyl-*N*-(7-(methylsulfonamido)-1,2,3,4-tetrahydronaphthalen-1-yl)acetamide (32d)



The title compound was synthesized in 81% according to a method similar to that described for **6a**.

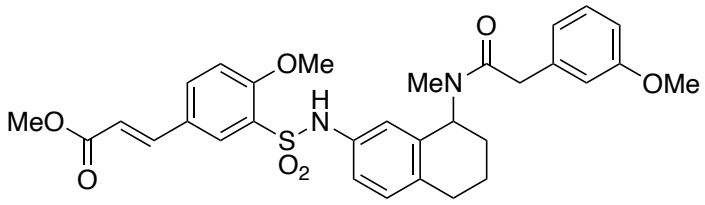
IR (neat): 2936, 1622, 1492, 1322, 1152 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.51–2.10 (m, 4H), 2.62 (s, 2.1H), 2.63 (s, 0.9H), 2.67–2.76 (m, 2H), 2.84 (s, 2.1H), 2.91 (s, 0.9H), 3.73–3.91 (m, 5H), 4.98–5.13 (m, 0.4H), 5.86–5.98 (dd, *J* = 11.0, 5.5 Hz, 0.6H), 6.54–6.81 (m, 2H), 6.83–6.96 (m, 2H), 6.96–7.02 (m, 1H), 7.02–7.11 (m, 1H), 7.16 (dd, *J* = 8.2, 2.3 Hz, 0.7H), 7.19–7.25 (m, 0.6H), 7.30 (t, *J* = 7.8 Hz, 0.7H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 22.0, 22.1, 26.8, 28.0, 28.7, 28.8, 29.6, 31.2, 39.0, 39.2, 41.8, 42.0, 52.6, 55.7, 57.6, 111.7, 112.6, 114.4, 115.3, 118.9, 119.5, 120.1, 121.1, 121.8, 130.0, 130.1, 130.6, 130.7, 135.1, 135.8, 136.0, 136.6, 136.7, 136.8, 159.9, 160.1, 172.1.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{21}H_{26}N_2NaO_4S$: 425.15110, found: 425.15078.

Methyl (*E*)-3-(4-methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)acrylate (33d)



A mixture of **36** (73.9 mg, 0.129 mmol), $Pd(PPh_3)_4$ (29.4 mg, 0.0254 mmol), methyl acrylate (174 μL, 1.93 mmol) and DIPEA (441 μL, 2.58 mmol) in DMF (2 mL) was heated for 3 h at 100 ºC under an argon atmosphere. Another methyl acrylate (174 μL, 1.93 mmol) was added to the reaction mixture. After 17 h from reaction start, $Pd(PPh_3)_4$ (29.4 mg, 0.0254 mmol), methyl acrylate (174 μl, 1.93 mmol) and DIPEA (441 μL, 2.58 mmol) were added to the reaction mixture. After 20 h from reaction start, methyl acrylate (500 μL, 5.56 mmol) was added to the reaction mixture and heated for another one hour. The reaction mixture was diluted with sat. $NaHCO_3$ aq. (10 mL). The aqueous layer was extracted with $CHCl_3$ (20, 10, 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (50–67% EtOAc in hexane) and preparative TLC (50% toluene in acetone) to afford **33d** (54.7 mg, 73%) as a colorless amorphous.

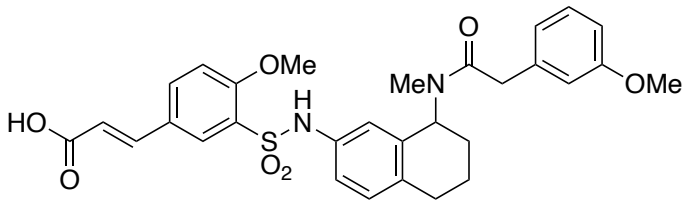
IR (neat): 2938, 1649, 1600, 1496, 1155, 754 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.51–1.99 (m, 4H), 2.21 (s, 1.2H), 2.47 (s, 1.8H), 2.57–2.71 (m, 2H), 3.04 (s, 1.2H), 3.04 (s, 1.8H), 3.15 (s, 3H), 3.67–3.84 (m, 3.2H), 3.90 (s, 1.8H), 3.98 (s, 1.8H), 4.04 (s, 1.2H), 4.84–4.99 (m, 0.4H), 5.80 (dd, *J* = 10.1, 5.0 Hz, 0.6H), 6.24 (d, *J* = 2.1 Hz, 0.4H), 6.56 (d, *J* = 1.4 Hz, 0.6H), 6.74 (s, 0.4H), 6.78 (d, *J* = 15.6 Hz, 0.4H), 6.79 (d, *J* = 15.6 Hz, 0.6H), 6.81–6.99 (5.2H), 7.01 (dd, *J* = 8.2, 1.4 Hz, 0.6H), 7.05 (d, *J* = 8.7 Hz, 0.4H), 7.12 (dd, *J* = 8.2, 2.1 Hz, 0.4H), 7.23 (t, *J* = 7.8 Hz, 0.4H), 7.31 (t, *J* = 7.8 Hz, 0.6H), 7.48 (d, *J* = 15.6 Hz, 0.4H), 7.52 (d, *J* = 15.6 Hz, 0.6H), 7.57 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.90 (d, *J* = 2.1 Hz, 0.4H), 7.99 (d, *J* = 2.1 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.0, 26.8, 27.8, 28.7, 28.8, 28.9, 31.2, 36.1, 37.6, 41.7, 41.8, 52.3, 55.5, 55.6, 56.8, 56.9, 57.4, 111.6, 112.1, 112.5, 112.6, 115.0, 115.1, 117.7, 117.8, 120.1, 120.4, 121.2, 121.6, 122.9, 126.6, 127.0, 128.4, 128.5, 129.2, 129.3, 130.0, 130.1, 130.3, 130.6, 134.5, 134.7, 135.2, 135.2, 135.6, 136.2, 136.3, 136.5, 136.6, 136.8, 139.9, 140.1, 156.6, 156.8, 160.0, 166.4, 171.4, 171.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{32}H_{37}N_3NaO_6S$: 614.23008, found: 614.23272.

(*E*)-3-(4-Methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)acrylic acid (33c)



A mixture of compound **33d** (61.8 mg, 0.107 mmol), 1 M NaOH aq. (2.0 mL) and THF (2.0 mL) was stirred for 6 h at room temperature under an argon atmosphere. The reaction mixture was quenched by the addition of 1 M HCl aq. (3.0 mL) and extracted with 20% MeOH in $CHCl_3$ (20, 10, 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (2–5% MeOH in $CHCl_3$) to afford **33c** (59.4 mg, 98%) as a colorless amorphous.

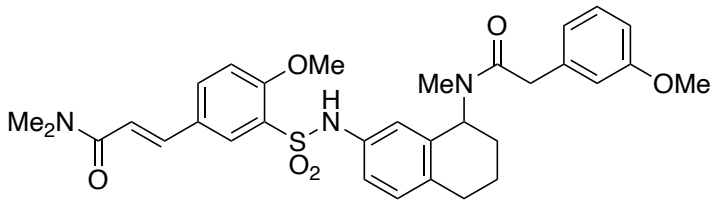
IR (neat): 2942, 1694, 1601, 1496, 1262, 1160, 756 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.50–2.02 (m, 4H), 2.26 (s, 1.2H), 2.53 (s, 1.8H), 2.58–2.71 (m, 2H), 3.69–3.84 (m, 3.2H), 3.88 (s, 1.8H), 3.97 (s, 1.8H), 4.02 (s, 1.2H), 4.88–5.00 (m, 0.4H), 5.76–5.87 (dd, *J* = 9.6, 5.5 Hz, 0.6H), 6.28 (d, *J* = 16.0 Hz, 1H), 6.33 (d, *J* = 16.0 Hz, 1H), 6.33 (s, 1H), 6.64 (s, 0.6H), 6.79 (s, 7.4H), 7.22 (t, *J* = 8.0 Hz, 0.4H), 7.31 (t, *J* = 7.8 Hz, 0.6H), 7.48–7.69 (m, 2H), 7.90 (s, 0.4H), 7.94 (s, 0.6H). The OH peak was not observed.

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.0, 26.8, 27.8, 28.7, 28.9, 29.0, 31.3, 41.6, 41.7, 52.6, 55.5, 55.6, 56.9, 57.0, 57.6, 111.8, 112.2, 112.7, 112.8, 114.9, 115.2, 117.7, 117.8, 119.2, 119.7, 119.8, 121.2, 121.6, 122.4, 126.9, 127.1, 127.2, 130.1, 130.2, 130.4, 130.7, 134.6, 134.8, 134.9, 135.4, 135.9, 136.0, 136.3, 136.4, 136.6, 144.1, 157.6, 157.8, 160.0, 170.2, 170.5, 171.9, 172.3.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{30}H_{32}N_2NaO_7S$: 587.18279, found: 587.18274.

(*E*)-3-(4-Methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)-*N*,*N*-dimethylacrylamide (32e)



A mixture of **33c** (9.3 mg, 0.0165 mmol), dimethylamine hydrochloride (6.8 mg, 0.0834 mmol), DIPEA (28.2 μL, 0.165 mmol), and DIPEA (28.2 μL, 0.165 mmol) in DMF (1.0 mL) was stirred for 17 h at room temperature under an argon atmosphere. The reaction mixture was diluted with sat. $NaHCO_3$ aq. (10 mL) and extracted with $CHCl_3$ (20, 10, 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (0–9% MeCN in $CHCl_3$) and preparative TLC (5% MeOH in $CHCl_3$ and 9% MeOH in $CHCl_3$) to afford **32e** (5.5 mg, 56%) as a colorless amorphous.

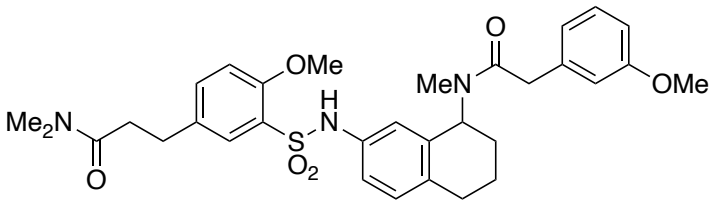
IR (neat): 2938, 1649, 1600, 1496, 1155, 754 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.51–1.99 (m, 4H), 2.21 (s, 1.2H), 2.47 (s, 1.8H), 2.57–2.71 (m, 2H), 3.04 (s, 1.2H), 3.04 (s, 1.8H), 3.15 (s, 3H), 3.67–3.84 (m, 3.2H), 3.90 (s, 1.8H), 3.98 (s, 1.8H), 4.04 (s, 1.2H), 4.84–4.99 (m, 0.4H), 5.80 (dd, *J* = 10.1, 5.0 Hz, 0.6H), 6.24 (d, *J* = 2.1 Hz, 0.4H), 6.56 (d, *J* = 1.4 Hz, 0.6H), 6.74 (s, 0.4H), 6.78 (d, *J* = 15.6 Hz, 0.4H), 6.79 (d, *J* = 15.6 Hz, 0.6H), 6.81–6.99 (5.2H), 7.01 (dd, *J* = 8.2, 1.4 Hz, 0.6H), 7.05 (d, *J* = 8.7 Hz, 0.4H), 7.12 (dd, *J* = 8.2, 2.1 Hz, 0.4H), 7.23 (t, *J* = 7.8 Hz, 0.4H), 7.31 (t, *J* = 7.8 Hz, 0.6H), 7.48 (d, *J* = 15.6 Hz, 0.4H), 7.52 (d, *J* = 15.6 Hz, 0.6H), 7.57 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.90 (d, *J* = 2.1 Hz, 0.4H), 7.99 (d, *J* = 2.1 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.0, 26.8, 27.8, 28.7, 28.8, 28.9, 31.2, 36.1, 37.6, 41.7, 41.8, 52.3, 55.5, 55.6, 56.8, 56.9, 57.4, 111.6, 112.1, 112.5, 112.6, 115.0, 115.1, 117.7, 117.8, 120.1, 120.4, 121.2, 121.6, 122.9, 126.6, 127.0, 128.4, 128.5, 129.2, 129.3, 130.0, 130.1, 130.3, 130.6, 134.5, 134.7, 135.2, 135.2, 135.6, 136.2, 136.3, 136.5, 136.6, 136.8, 139.9, 140.1, 156.6, 156.8, 160.0, 166.4, 171.4, 171.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{32}H_{37}N_3NaO_6S$: 614.23008, found: 614.23272.

3-(4-Methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)-*N*,*N*-dimethylpropanamide (32f)



A mixture of **32e** (5.1 mg, 0.00862 mmol) and 5% Pd/C (11.3 mg) in MeOH (1.6 mL) was stirred for 13 h at room temperature under a hydrogen atmosphere. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to afford a crude product as a colorless amorphous. The crude residue was purified by preparative TLC (5% MeOH in $CHCl_3$) to afford **32f** (4.2 mg, 82%) as a colorless oil.

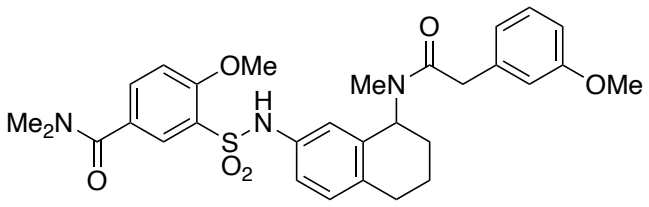
IR (neat): 2935, 1632, 1495, 1156, 755 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.48–2.03 (m, 4H), 2.24 (s, 1.2H), 2.47 (s, 1.8H), 2.48–2.58 (m, 2H), 2.58–2.73 (m, 2H), 2.81–2.96 (m, 8H), 3.63–3.84 (m, 3.2H), 3.89 (s, 1.8H), 3.93 (s, 1.8H), 3.98 (s, 1.2H), 4.83–5.00 (m, 0.4H), 5.81 (dd, *J* = 10.2, 5.8 Hz, 0.6H), 6.28 (d, *J* = 1.4 Hz, 0.4H), 6.57 (d, *J* = 1.4 Hz, 0.6H), 6.68–6.78 (m, 0.4H), 6.78–7.05 (m, 6.2H), 7.11 (dd, *J* = 8.2, 1.4 Hz, 0.4H), 7.23 (t, *J* = 7.8 Hz, 0.4H), 7.31 (t, *J* = 8.0 Hz, 0.6H), 7.37 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.53 (d, *J* = 2.3 Hz, 0.4H), 7.60 (d, *J* = 2.3 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.1, 26.9, 27.9, 28.7, 28.9, 28.9, 29.8, 30.1, 30.2, 31.2, 34.7, 34.9, 35.6, 37.3, 41.7, 41.8, 52.5, 55.5, 55.6, 56.6, 56.7, 57.4, 111.7, 112.1, 112.3, 112.4, 114.9, 115.1, 120.1, 120.3, 121.2, 121.5, 122.7, 125.8, 126.2, 130.0, 130.1, 130.2, 130.4, 130.5, 134.1, 134.2, 134.9, 135.0, 135.3, 135.5, 135.9, 136.3, 136.6, 136.8, 154.4, 154.6, 160.0, 171.4, 171.7, 171.7, 171.78.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{32}H_{39}N_3NaO_6S$: 616.24573, found: 616.24432.

4-Methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)-*N*,*N*-dimethylbenzamide (32g)



A mixture of **36** (19.6 mg, 0.0342 mmol), $Pd(OAc)_2$ (5.1 mg, 0.0227 mmol), Xantphos (20.3 mg, 0.0351 mmol), 2,4,6-trichlorophenyl formate (15.2 mg, 0.0674 mmol) and DBU (10.0 μL, 0.0670 mmol) in toluene (2.0 mL) was heated for 23 h at 80 ºC under an argon atmosphere. $Pd(OAc)_2$ (26.7 mg, 0.119 mmol), Xantphos (101 mg, 0.175 mmol), 2,4,6-trichlorophenyl formate (75.5 mg, 0.335 mmol) and DBU (50.0 μL, 0.335 mmol) were added to the reaction mixture. After 30 h from reaction start, $Pd(PPh_3)_4$ (29.4 mg, 0.0254 mmol), methyl acrylate (174 μl, 1.93 mmol) and DIPEA (441 μL, 2.58 mmol) were added to the reaction mixture. After 20 h from reaction start, the reaction mixture was diluted with 10% (*w*/*v*) citric acid aq. (5.0 mL), H_2O (10 mL) and extracted with $CHCl_3$ (20, 10, 10 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (20–50% acetone in hexane) to afford **38** with inseparable impurities (16.1 mg) as a yellow oil. To a stirred solution of the obtained yellow oil in THF (1 mL) were added Et_3N (8.0 μL, 0.0576 mmol), dimethylamine hydrochloride (4.8 mg, 0.0589 mmol), and DMAP (6.7 mg, 0.0548 mmol). The mixture was stirred for 25 h at room temperature under an argon atmosphere. The mixture was diluted with $CHCl_3$ (3.0 mL) and 1 M HCl aq. (5.0 mL) and extracted with $CHCl_3$ (20, 10, 10 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (11–14% MeOH in $CHCl_3$) to afford **32g** (5.7 mg, 30% in 2 steps) as a colorless oil.

IR (neat): 2937, 1626, 1604, 1488, 1397, 1264, 1160, 755 cm^{-1}.

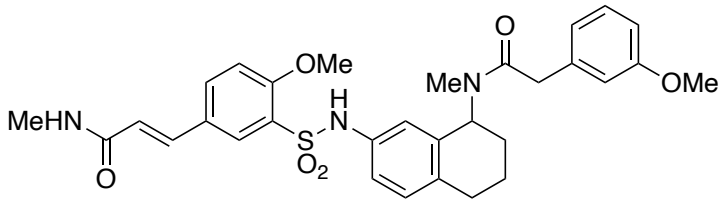
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.47–2.02 (m, 4H), 2.30 (s, 1.2H), 2.49 (s, 1.8H), 2.56–2.70 (m, 2H), 2.91 (s, 3H), 3.05 (s, 3H), 3.69–3.85 (m, 3.2H), 3.90 (s, 1.8H), 3.99 (s, 1.8H), 4.06 (s, 1.2H), 4.83–4.99 (m, 0.4H), 5.74–5.86 (dd, *J* = 10.1, 6.0 Hz, 0.6H), 6.21 (d, *J* = 1.8 Hz, 0.4H), 6.56 (d, *J* = 1.4 Hz, 0.6H), 6.73 (s, 0.4H), 6.78–7.13 (m, 6.6H), 7.23 (t, *J* = 8.0 Hz, 0.4H), 7.31 (t, *J* = 7.8 Hz, 0.6H), 7.60–7.68 (m, 1H), 7.76 (d, *J* = 2.3 Hz, 0.4H), 7.82 (d, *J* = 2.3 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.1, 26.8, 27.8, 28.7, 28.9, 28.9, 31.2, 35.7, 39.8, 41.7, 41.8,

52.3, 55.5, 55.6, 56.8, 57.0, 57.5, 111.5, 112.1, 112.5, 115.0, 115.1, 120.1, 120.1, 120.3, 121.3, 121.6, 122.4, 125.5, 125.7, 128.6, 128.7, 130.0, 130.1, 130.1, 130.4, 130.7, 134.4, 134.6, 134.8, 134.9, 135.6, 136.3, 136.3, 136.5, 136.7, 136.8, 156.9, 157.2, 160.0, 160.0, 169.6, 169.6, 171.5, 171.9.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{30}H_{35}N_3NaO_6S$: 588.21443, found: 588.21181.

(*E*)-3-(4-Methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)-*N*-methylacrylamide (33a)



The title compound was synthesized in 98% according to a method similar to that described for **32e**.

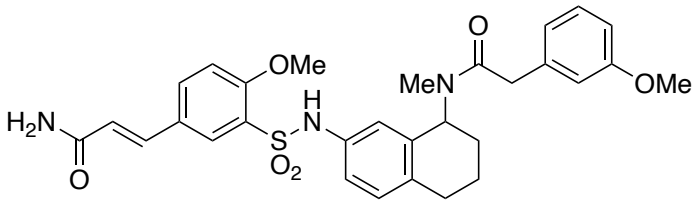
IR (neat): 3295, 2927, 1624, 1603, 1495, 1155, 756 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.49–2.03 (m, 4H), 2.28 (s, 0.9H), 2.55–2.69 (m, 2H), 2.70–2.77 (m, 4.2H), 2.88 (d, *J* = 4.6 Hz, 0.9H), 3.71–4.04 (m, 8H), 4.88–5.05 (m, 0.3H), 5.78 (dd, *J* = 10.5, 5.5 Hz, 0.7H), 6.25 (d, *J* = 15.6 Hz, 0.7H), 6.41–6.61 (m, 1.3H), 6.66 (dd, *J* = 8.0, 2.1 Hz, 0.7H), 6.71 (d, *J* = 1.8 Hz, 0.3H), 6.80–7.06 (m, 7H), 7.24–7.29 (m, 0.3H), 7.32 (t, *J* = 7.8 Hz, 0.7H), 7.39 (d, *J* = 15.6 Hz, 0.7 H), 7.41 (d, *J* = 15.6 Hz, 0.3 H), 7.44 (dd, *J* = 8.2, 2.3 Hz, 0.7 H), 7.52 (dd, *J* = 8.7, 1.8 Hz, 0.3H), 8.00–8.06 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.0, 26.5, 26.6, 27.0, 28.0, 28.8, 31.3, 41.3, 41.4, 53.0, 55.4, 56.8, 56.9, 57.4, 112.1, 112.3, 112.5, 112.6, 114.8, 115.6, 117.2, 117.9, 120.2, 121.2, 121.9, 122.4, 123.3, 126.3, 126.9, 128.5, 128.7, 129.0, 129.0, 130.1, 130.2, 130.4, 130.6, 134.7, 134.9, 135.2, 135.3, 135.5, 135.6, 136.4, 136.7, 136.8, 136.9, 137.2, 156.8, 156.9, 160.1, 166.4, 166.7, 171.6, 172.5.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{31}H_{35}N_3NaO_6S$: 600.21443, found: 600.21535.

(*E*)-3-(4-Methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)acrylamide (33b)



The title compound was synthesized in 68% according to a method similar to that described for **32e**.

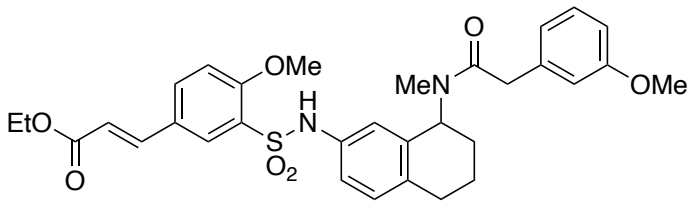
IR (neat): 3426, 3351, 3195, 2940, 1672, 1631, 1599, 1496, 1154, 755 cm^{-1}.

^{1}H-NMR (400 MHz, CD_3OD): δ (ppm) 1.47–1.99 (m, 4H), 2.34 (s, 1.2H), 2.53 (s, 1.8H), 2.57–2.75 (m, 2H), 3.75–3.79 (m, 1.2H), 3.79–3.82 (m, 1.8H), 3.82–3.88 (m, 2H), 3.93–3.97 (m, 1.8H), 3.97–4.02 (m, 1.2H), 5.01–5.15 (m, 0.4H), 5.66–5.77 (m, 0.6H), 6.50 (d, *J* = 16.0 Hz, 0.6H), 6.55 (d, *J* = 16.0 Hz, 0.4H), 6.72–7.02 (m, 6H), 7.06–7.19 (m, 1H), 7.20–7.35 (m, 1H), 7.41 (d, *J* = 16.0 Hz, 0.6H), 7.42 (d, *J* = 15.6 Hz, 0.4H), 7.62–7.74 (m, 1H), 7.87–7.98 (m, 1H). The NH and NH_2 peak were not observed.

^{13}C-NMR (100 MHz, CD_3OD): δ (ppm) 22.9, 23.0, 27.8, 28.6, 29.5, 29.7, 31.7, 42.0, 42.0, 54.5, 55.7, 57.0, 58.9, 113.4, 113.6, 114.0, 114.0, 115.4, 115.8, 119.8, 119.9, 121.1, 121.3, 121.6, 122.1, 122.4, 128.2, 128.3, 128.6, 128.6, 130.6, 130.8, 130.9, 131.1, 131.3, 135.9, 136.0, 136.3, 136.4, 136.4, 136.6, 136.9, 137.0, 137.8, 138.0, 140.4, 158.9, 159.0, 161.5, 161.5, 170.5, 170.6, 174.1, 174.5.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{30}H_{33}N_3NaO_6S$: 586.19878, found: 586.19956.

Ethyl (*E*)-3-(4-methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)acrylate (33e)



The title compound was synthesized in 53% according to a method similar to that described for **33d**.

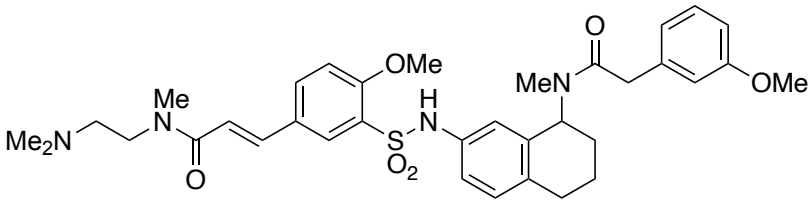
IR (neat): 2940, 1708, 1634, 1601, 1496, 1261, 1160, 756 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.23–1.35 (m, 3H), 1.50–2.03 (m, 4H), 2.22 (s, 1.2H), 2.48 (s, 1.8H), 2.57–2.68 (m, 2H), 3.64–3.84 (m, 3.2H), 3.89 (s, 1.8H), 3.98 (s, 1.8H), 4.05 (s, 1.2H), 4.18–4.28 (m, 2H), 4.86–5.01 (m, 0.4H), 5.80 (dd, *J* = 9.8, 5.7 Hz, 0.6H), 6.24 (s, 0.4H), 6.31 (d, *J* = 16.0 Hz, 0.4H), 6.32 (d, *J* = 16.0 Hz, 0.6H), 6.56 (s, 0.6H), 6.76–7.18 (m, 7H), 7.23 (t, *J* = 8.0 Hz, 0.4H), 7.31 (t, *J* = 7.8 Hz, 0.6H), 7.51 (d, *J* = 16.0 Hz, 0.4H), 7.53 (d, *J* = 16.0 Hz, 0.6H), 7.58–7.66 (m, 1H), 7.86 (d, *J* = 2.3 Hz, 0.4H), 7.94 (d, *J* = 1.8 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 14.4, 21.9, 22.0, 26.8, 27.8, 28.7, 28.8, 28.9, 31.2, 41.7, 41.8, 52.4, 55.4, 55.6, 56.8, 57.0, 57.4, 60.7, 111.6, 112.1, 112.7, 112.8, 115.0, 115.1, 118.4, 118.5 120.1, 120.2, 120.3, 121.2, 121.5, 123.0, 126.8, 127.1, 127.4, 127.5, 130.0, 130.1, 130.3, 130.4, 130.6, 130.6, 134.4, 134.4, 134.5, 134.7, 135.5, 136.1, 136.2, 136.4, 136.6, 136.7, 142.2, 142.3, 157.2, 157.4, 160.0, 160.0, 166.7, 166.8, 171.5, 171.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{32}H_{36}N_2NaO_7S$: 615.21409, found: 615.21346.

(*E*)-*N*-(2-(Dimethylamino)ethyl)-3-(4-methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)-*N*-methylacrylamide (33f)



The title compound was synthesized in 71% according to a method similar to that described for **32e**.

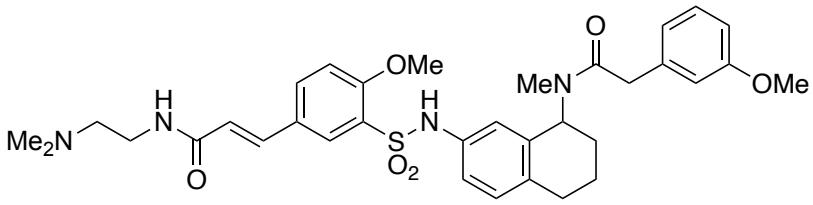
IR (neat): 2939, 1647, 1600, 1496, 1157, 755 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.49–2.03 (m, 4H), 2.22 (s, 1.2H), 2.25–2.36 (m, 6H), 2.47 (s, 1.8H), 2.48–2.57 (m, 2H), 2.57–2.72 (m, 2H), 2.98–3.11 (m, 1.2H), 3.15 (s, 1.8H), 3.45–3.79 (m, 4H), 3.81 (s, 1.2H), 3.89 (s, 1.8H), 3.97 (s, 1.8H), 4.04 (s, 1.2H), 4.83–5.01 (m, 0.4H), 5.80 (dd, *J* = 10.1, 6.0 Hz, 0.6H), 6.18–6.34 (m, 0.4H), 6.52–6.61 (m, 0.6H), 6.69–7.17 (m, 8H), 7.23 (t, *J* = 7.8 Hz, 0.4H), 7.31 (t, *J* = 8.0 Hz, 0.6H), 7.41–7.64 (m, 2H), 7.89–7.89 (m, 0.4H), 7.98–7.95 (m, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.0, 26.8, 27.8, 28.7, 28.8, 28.9, 29.8, 31.2, 34.8, 36.2, 41.7, 41.8, 45.7, 45.9, 46.3, 48.5, 52.4, 55.5, 55.6, 56.7, 56.8, 56.9, 57.4, 58.2, 58.2, 111.6, 112.1, 112.5, 112.6, 115.0, 115.1, 117.8, 117.8, 117.9, 120.2, 120.4, 121.2, 121.6, 122.9, 126.6, 127.0, 128.4, 128.5, 128.6, 129.3, 129.4, 129.6, 129.8, 130.0, 130.1, 130.3, 130.6, 134.6, 134.7, 134.7, 135.1, 135.2, 135.5, 136.2, 136.2, 136.4, 136.6, 136.8, 139.9, 140.1, 140.2, 140.3, 156.7, 156.9, 160.0, 160.0, 166.2, 166.5, 171.4, 171.8.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{35}H_{45}N_4O_6S$: 649.30598, found: 649.30365.

(*E*)-*N*-(2-(Dimethylamino)ethyl)-3-(4-methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)acrylamide (33g)



The title compound was synthesized in 65% according to a method similar to that described for **32e**.

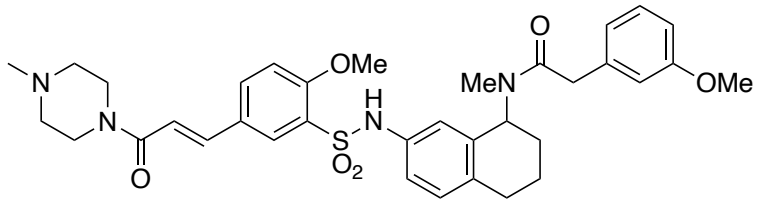
IR (neat): 3286, 2942, 1624, 1602, 1496, 1156, 755 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.48–1.99 (m, 4H), 2.23 (s, 1.2H), 2.26 (s, 6H), 2.43–2.52 (m, 2H), 2.54 (s, 1.8H), 2.57–2.71 (m, 2H), 3.28–3.52 (m, 2H), 3.68–3.87 (m, 5H), 3.95 (s, 1.8H), 4.00 (s, 1.2H), 4.84–4.99 (m, 0.4H), 5.78 (dd, *J* = 10.3, 5.7 Hz, 0.6H), 6.33 (d, *J* = 15.6 Hz, 0.6H), 6.40 (d, *J* = 15.6 Hz, 0.4H), 6.43–6.47 (m, 0.4H), 6.71–7.04 (m, 7.6H), 7.22 (t, *J* = 8.0 Hz, 0.4H), 7.29 (t, *J* = 8.0 Hz, 0.6H), 7.41 (d, *J* = 15.6 Hz, 0.4H), 7.43 (d, *J* = 15.6Hz, 0.6H), 7.48 (dd, *J* = 8.7, 2.3 Hz, 0.6H), 7.52 (dd, *J* = 8.5, 2.1 Hz, 0.4H), 7.92 (d, *J* = 2.1 Hz, 0.4H), 7.95 (d, *J* = 2.3 Hz, 0.6H). The NH peak was not observed.

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.0, 26.9, 27.9, 28.7, 28.9, 29.0, 31.2, 37.0, 41.6, 45.2, 52.7, 55.4, 55.5, 56.8, 56.9, 57.4, 57.9, 111.8, 112.2, 112.5, 112.6, 114.9, 115.3, 118.4, 118.4, 118.9, 119.4, 121.2, 121.6, 121.6, 121.8, 121.8, 122.1, 126.7, 126.8, 128.3, 128.4, 129.2, 129.4, 130.0, 130.1, 130.3, 130.6, 134.9, 135.0, 135.1, 135.1, 135.5, 135.5, 135.6, 136.4, 136.7, 136.8, 137.8, 137.8, 156.7, 156.9, 160.0, 160.0, 165.8, 165.8, 171.5, 172.1.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{34}H_{43}N_4O_6S$: 635.29033, found: 635.28949.

(*E*)-*N*-(7-((2-Methoxy-5-(3-(4-methylpiperazin-1-yl)-3-oxoprop-1-en-1-yl)phenyl)sulfonamido)-1,2,3,4-tetrahydronaphthalen-1-yl)-2-(3-methoxyphenyl)-*N*-methylacetamide (33h)



The title compound was synthesized in 81% according to a method similar to that described for **32e**.

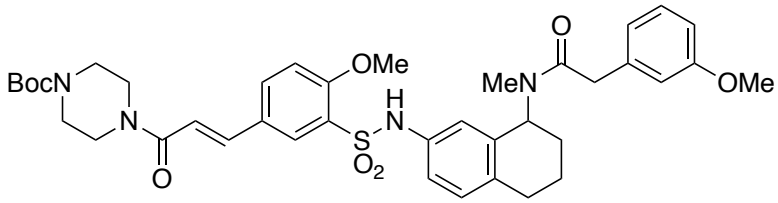
IR (neat): 2940, 1645, 1600, 1496, 1154, 754 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.51–2.06 (m, 4H), 2.21 (s, 1.2H), 2.32 (s, 1.8 H), 2.32 (s, 1.2H), 2.38–2.47 (m, 4H), 2.50 (s, 1.8H), 2.57–2.70 (m, 2H), 3.59–3.79 (m, 6H), 3.82 (s, 1.2H), 3.89 (s, 1.8H), 3.97 (s, 1.8H), 4.04 (s, 1.2H), 4.86–4.97 (m, 0.4H), 5.80 (dd, *J* = 10.1, 6.0 Hz, 0.6H), 6.30 (s, 0.4H), 6.59 (d, *J* = 1.8 Hz, 0.6H), 6.74–7.14 (m, 8H), 7.23 (t, *J* = 7.8 Hz, 0.4H), 7.31 (t, *J* = 8.0 Hz, 0.6H), 7.45–7.61 (m, 2H), 7.92 (d, *J* = 2.3 Hz, 0.4H), 7.99 (d, *J* = 2.3 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.0, 26.8, 27.8, 28.7, 28.8, 28.9, 31.2, 41.6, 41.8, 42.1, 45.7, 46.0, 52.4, 54.8, 55.3, 55.5, 55.6, 56.8, 56.9, 57.4, 111.6, 112.1, 112.5, 112.6, 115.0, 115.1, 117.3, 117.4, 119.9, 120.0, 120.3, 121.2, 121.6, 122.6, 126.7, 127.0, 128.3, 128.4, 129.1, 129.2, 130.0, 130.1, 130.3, 130.6, 134.6, 134.7, 135.2, 135.3, 135.3, 135.6, 136.1, 136.2, 136.4, 136.6, 136.6, 136.8, 140.4, 140.6, 156.7, 156.9, 160.0, 165.2, 171.4, 171.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{35}H_{42}N_4NaO_6S$: 669.27227, found: 669.26977.

***tert*-Butyl (*E*)-4-(3-(4-methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)acryloyl)piperazine-1-carboxylate (37)**



The title compound was synthesized in 51% according to a method similar to that described for **32e**.

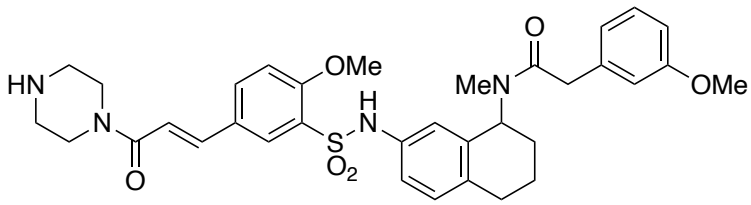
IR (neat): 2935, 1692, 1645, 1600, 1495, 1163, 755 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.47 (s, 9H), 1.53–2.01 (m, 4H), 2.21 (s, 1.2H), 2.49 (s, 1.8H), 2.54–2.79 (m, 2H), 3.38–3.80 (m, 10H), 3.83 (s, 1.2H), 3.90 (s, 1.8H), 3.98 (s,1. 2H), 4.06 (s, 1.8H), 4.82–5.02 (m, 0.4H), 5.80 (dd, *J* = 10.5, 6.0 Hz, 0.6H), 6.30 (s, 0.4H), 6.59 (s, 0.6H), 6.72–7.14 (m, 8H), 7.23 (t, *J* = 7.8 Hz, 0.4H), 7.31 (t, *J* = 7.8 Hz, 0.6H), 7.45–7.66 (m, 2H), 7.93 (d, *J* = 2.3 Hz, 0.4H), 8.00 (d, *J* = 2.3 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.0, 26.8, 27.8, 28.5, 28.7, 28.8, 28.9, 31.2, 41.7, 41.8, 42.2, 43.7, 45.8, 52.4, 55.5, 55.6, 56.8, 56.9, 57.4, 80.5, 111.6, 112.1, 112.5, 112.7, 115.0, 115.2, 117.0, 117.1, 119.8, 120.0, 120.2, 121.2, 121.6, 122.6, 126.7, 127.1, 128.2, 128.3, 129.2, 129.3, 130.0, 130.1, 130.3, 130.6, 134.6, 134.7, 135.3, 135.4, 135.6, 136.1, 136.5, 136.6, 136.8, 140.8, 141.0, 154.7, 156.8, 157.0, 160.0, 165.4, 171.4, 171.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{39}H_{48}N_4NaO_8S$: 755.30905, found: 755.30536.

(*E*)-*N*-(7-((2-Methoxy-5-(3-oxo-3-(piperazin-1-yl)prop-1-en-1-yl)phenyl)sulfonamido)-1,2,3,4-tetrahydronaphthalen-1-yl)-2-(3-methoxyphenyl)-*N*-methylacetamide (33i)



A mixture of **37** (10.6 mg, 0.0145 mmol) in TFA (0.5 mL) and MeOH (2.0 mL) was stirred for 1 h at room temperature under an argon atmosphere. The reaction mixture was quenched by the addition of sat. $NaHCO_3$ aq. (10 mL) and extracted with $CHCl_3$ (20, 10, 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (3–5% MeOH in $CHCl_3$) to afford **33i** (7.7 mg, 84%) as a colorless amorphous.

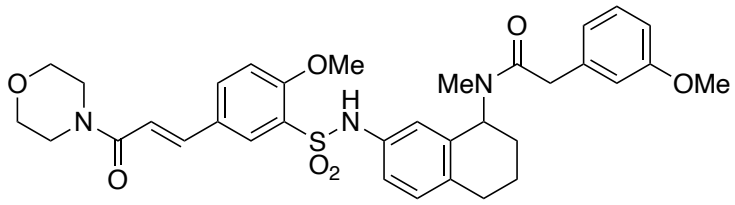
IR (neat): 2936, 1644, 1600, 1495, 1155, 754 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.51–2.07 (m, 4H), 2.21 (s, 1.2H), 2.48 (s, 1.8H), 2.50–2.68 (m, 2H), 2.80–3.01 (m, 4H), 3.55–3.80 (m, 6H), 3.81 (s, 1.2H), 3.89 (s, 1.8H), 3.97 (s, 1.8H), 4.04 (s, 1.2H), 4.82–5.01 (m, 0.4H), 5.80 (dd, *J* = 10.3, 5.7 Hz, 0.6H), 6.29 (d, *J* = 2.3 Hz, 0.4H), 6.58 (d, *J* = 1.8 Hz, 0.6H), 6.77–6.81 (m, 6.2H), 7.04 (d, *J* = 8.7 Hz, 0.4H), 7.10 (dd, *J* = 8.2, 2.3 Hz, 0.4H), 7.23 (t, *J* = 7.8 Hz, 0.4H), 7.31 (t, *J* = 8.0 Hz, 0.6H), 7.47–7.55 (m, 2H), 7.92 (d, *J* = 2.3 Hz, 0.4H), 7.99 (d, *J* = 2.3 Hz, 0.6H). The NH peaks were not observed.

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.0, 26.8, 27.8, 28.7, 28.8, 28.9, 29.8, 31.2, 41.7, 41.8, 43.2, 45.9, 46.5, 47.0, 52.4, 55.5, 55.6, 56.8, 56.9, 57.4, 111.6, 112.1, 112.5, 112.6, 115.0, 115.2, 117.3, 117.4, 119.9, 120.1, 120.3, 121.2, 121.6, 122.7, 126.7, 127.1, 128.4, 128.4, 129.1, 129.2, 130.0, 130.1, 130.3, 130.6, 134.6, 134.7, 135.2, 135.3, 135.6, 136.2, 136.5, 136.6, 136.8, 140.3, 140.6, 156.7, 156.9, 160.0, 160.0, 165.3, 171.4, 171.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{34}H_{40}N_4NaO_6S$: 655,25662, found: 655.25406.

(*E*)-*N*-(7-((2-Methoxy-5-(3-morpholino-3-oxoprop-1-en-1-yl)phenyl)sulfonamido)-1,2,3,4-tetrahydronaphthalen-1-yl)-2-(3-methoxyphenyl)-*N*-methylacetamide (33j)



The title compound was synthesized in 71% according to a method similar to that described for **32e**.

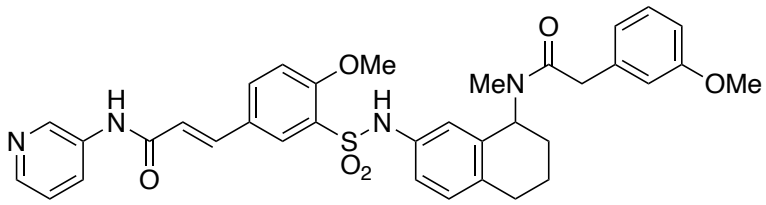
IR (neat): 2937, 1645, 1600, 1496, 1156, 755 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.49–2.01 (m, 4H), 2.21 (s, 1.2H), 2.49 (s, 1.8H), 2.55–2.69 (m, 2H), 3.57–3.84 (m, 11.2H), 3.89 (s, 1.8H), 3.98 (s, 1.8H), 4.04 (s, 1.2H), 4.85–4.99 (m, 0.4H), 5.80 (dd, *J* = 10.1, 6.0 Hz, 0.6H), 6.33 (d, *J* = 1.6 Hz, 0.4H), 6.60 (d, *J* = 1.6 Hz, 0.6H), 6.77 (d, *J* = 15.6 Hz, 0.6H), 6.78 (d, *J* = 15.1 Hz, 0.4H), 6.81–7.12 (m, 7H), 7.23 (t, *J* = 7.8 Hz, 0.4H), 7.31 (t, *J* = 7.8 Hz, 0.6H), 7.48–7.61 (m, 2H), 7.94 (d, *J* = 2.3 Hz, 0.4H), 8.00 (d, *J* = 2.3 Hz, 0.6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.0, 26.8, 27.8, 28.7, 28.8, 28.9, 31.2, 41.6, 41.8, 42.7, 46.4, 52.4, 55.5, 55.6, 56.8, 56.9, 57.4, 111.6, 112.1, 112.5, 112.7, 115.0, 115.2, 116.8, 117.0, 119.7, 119.9, 120.2, 121.2, 121.6, 122.5, 126.7, 127.1, 128.2, 128.3, 129.1, 129.3, 130.0, 130.1, 130.3, 130.6, 134.6, 134.7, 135.3, 135.5, 135.6, 136.1, 136.1, 136.5, 136.6, 136.8, 140.7, 140.9, 156.8, 157.0, 160.0, 160.0, 165.3, 165.4, 171.4, 171.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{34}H_{39}N_3NaO_7S$: 656.24064, found: 656.23778.

(*E*)-3-(4-Methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)-*N*-(pyridin-3-yl)acrylamide (33k)



The title compound was synthesized in 53% according to a method similar to that described for **32e**.

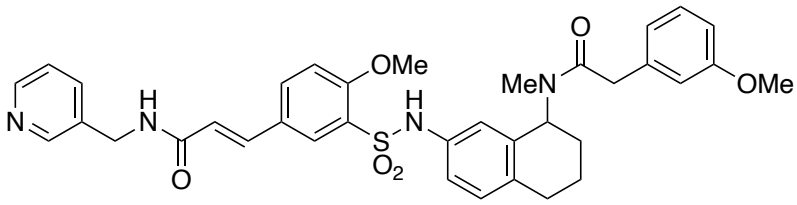
IR (neat): 2939, 1626, 1601, 1495, 1155, 754 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.47–2.09 (m, 4H), 2.37 (s, 0.6H), 2.53–2.76 (m, 2H), 2.86 (s, 2.4H), 3.51–4.13 (m, 8H), 5.00–5.13 (m, 0.2H), 5.74–5.91 (m, 0.8H), 6.34 (d, *J* = 15.6 Hz, 0.8H), 6.55–7.05 (m, 6.2H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.19–7.31 (m, 1.8H), 7.31–7.38 (m, 0.2H), 7.38–7.58 (m, 2H), 8.05–8.39 (m, 3H), 8.51 (s, 0.8H), 8.73 (s, 0.2H), 9.58 (s, 0.8H), 9.84 (s, 0.2H). The NH peak was not observed.

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 22.0, 27.0, 28.2, 28.7, 28.8, 31.1, 31.5, 41.0, 41.1, 53.6, 55.1, 55.4, 56.8, 57.5, 112.3, 112.6, 112.6, 112.7, 113.7, 114.9, 115.9, 117.0, 118.3, 121.3, 121.9, 123.6, 123.8, 124.1, 126.3, 127.1, 127.2, 127.4, 128.3, 128.4, 128.8, 130.2, 130.3, 130.5, 130.6, 134.0, 134.1, 135.5, 135.6, 135.7, 136.1, 136.2, 136.5, 136.5, 136.6, 138.2, 138.4, 140.5, 157.4, 160.0, 164.5, 165.0, 172.1, 173.3.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{35}H_{36}N_4O_6S$: 663.22532, found: 663.22250.

(*E*)-3-(4-Methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)-*N*-(pyridin-3-ylmethyl)acrylamide (33l)



The title compound was synthesized in 66% according to a method similar to that described for **32e**.

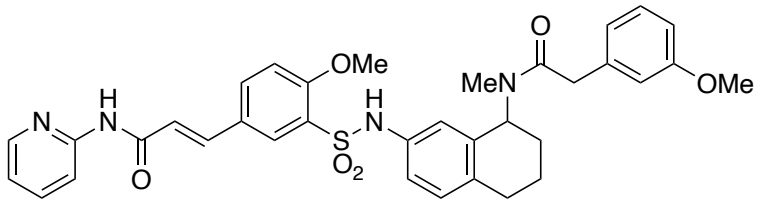
IR (neat): 3282, 2939, 1625, 1602, 1496, 1155, 755 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.49–2.01 (m, 4H), 2.28 (s, 0.9H), 2.52–2.66 (m, 2H), 2.69 (s, 2.1H), 3.64–4.02 (m, 8H), 4.26 (dd, *J* = 15.3, 5.3 Hz, 0.6H), 4.49–4.61 (m, 1.4H), 4.88–5.01 (m, 0.3H), 5.75 (dd, *J* = 10.1, 4.6 Hz, 0.7H), 6.37 (d, *J* = 15.6 Hz, 0.7H), 6.59 (d, *J* = 15.6 Hz, 0.3H), 6.70 (dd, *J* = 8.2, 1.8 Hz, 0.7H), 6.75–7.01 (m, 5.6H), 7.04 (d, *J* = 1.8 Hz, 0.7H), 7.16–7.26 (m, 2H), 7.31–7.62 (m, 4H), 7.65 (d, *J* = 7.8 Hz, 0.7H), 7.70 (d, *J* = 7.3 Hz, 0.3H), 8.04 (d, *J* = 2.1 Hz, 0.7H), 8.08 (d, *J* = 1.8 Hz, 0.3H), 8.41–8.62 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 27.0, 28.0, 28.8, 29.3, 31.3, 40.9, 41.1, 41.2, 41.3, 53.1, 55.4, 56.7, 56.8, 57.4, 112.1, 112.3, 112.5, 112.7, 114.8, 115.5, 115.6, 116.5, 118.0, 119.7, 121.2, 121.7, 122.2, 122.6, 124.1, 126.3, 127.0, 128.2, 128.5, 128.7, 129.0, 130.0, 130.1, 130.4, 130.6, 134.6, 134.6, 135.4, 135.4, 135.5, 135.6, 135.7, 136.2, 136.7, 136.8, 137.0, 137.2, 137.9, 147.0, 147.8, 157.1, 157.1, 159.9, 166.2, 166.4, 171.7, 172.5.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{36}H_{38}N_4NaO_6S$: 677.24097, found: 677.23885.

(*E*)-3-(4-Methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)-*N*-(pyridin-2-yl)acrylamide (33m)



The title compound was synthesized in 40% according to a method similar to that described for **32e**.

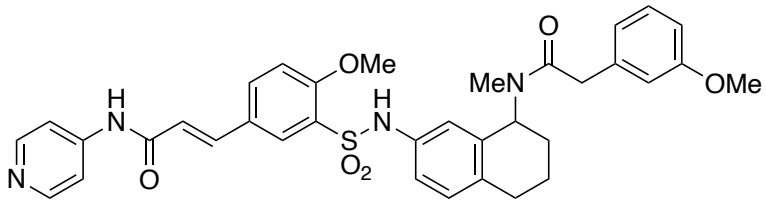
IR (neat): 3258, 2938, 1628, 1601, 1496, 1434, 1154, 755 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.53–2.09 (m, 4H), 2.31 (s, 0.9H), 2.55–2.66 (m, 2H), 2.69 (s, 2.1H), 3.61–4.06 (m, 8H), 4.89–5.08 (m, 0.3H), 5.78–5.95 (m, 0.7H), 6.53 (s, 0.3H), 6.56 (s, 0.7H), 6.65–6.85 (m, 2H), 6.85–7.14 (m, 6H), 7.15–7.26 (m, 1H), 7.50–7.88 (m, 3H), 8.00 (s, 1H), 8.22–8.45 (m, 2H), 9.98 (br s, 1H). The NH peak was not observed.

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 22.0, 22.0, 26.9, 27.9, 28.7, 28.8, 29.2, 31.4, 41.5, 52.9, 55.4, 56.9, 56.9, 57.5, 112.0, 112.3, 112.6, 112.8, 114.8, 115.3, 115.6, 116.9, 118.2, 118.5, 119.5, 119.7, 121.1, 121.3, 121.6, 121.9, 122.3, 126.6, 127.1, 127.8, 128.2, 128.6, 128.7, 130.0, 130.0, 130.1, 130.2, 130.4, 130.6, 132.1, 132.2, 132.3, 134.9, 135.1, 135.1, 135.2, 135.3, 135.7, 136.6, 136.7, 139.7, 139.9, 140.2, 140.5, 146.0, 151.6, 151.7, 157.3, 157.4, 159.9, 160.0, 164.8, 171.7, 172.6.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{35}H_{36}N_4NaO_6S$: 663.22532, found: 663.22393.

(*E*)-3-(4-Methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)-*N*-(pyridin-4-yl)acrylamide (33n)



The title compound was synthesized in 81% according to a method similar to that described for **32e**.

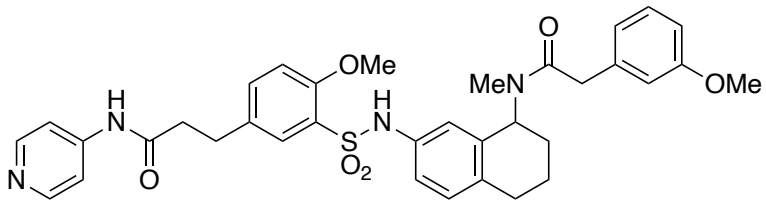
IR (neat): 2936, 1629, 1599, 1496, 1156 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.45–2.11 (m, 4H), 2.36 (s, 0.9H), 2.52–2.79 (m, 2H), 2.86 (s, 2.1H), 3.51–4.12 (m, 8H), 5.00–5.17 (m, 0.3H), 5.71–5.92 (m, 0.7H), 6.34 (d, *J* = 15.6 Hz, 0.7H), 6.55–6.83 (m, 2.3H), 6.83–7.05 (m, 4H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.25–7.29 (m, 1H), 7.38–7.60 (m, 4H), 8.13 (d, *J* = 2.3 Hz, 0.7H), 8.24 (d, *J* = 1.8 Hz, 0.3H), 8.32–8.53 (m, 2H), 9.70 (s, 0.7H), 10.01 (s, 0.3H). The NH peak was not observed.

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 22.0, 27.0, 28.2, 28.7, 28.8, 31.6, 40.9, 40.9, 53.7, 55.1, 55.4, 56.8, 57.5, 112.0, 112.4, 112.6, 112.8, 113.7, 113.9, 114.0, 114.6, 115.3, 116.2, 117.1, 118.2, 121.5, 121.9, 123.4, 123.7, 126.3, 127.5, 128.0, 128.5, 128.6, 128.9, 130.1, 130.3, 130.5, 130.7, 133.9, 134.1, 135.4, 135.7, 135.8, 136.1, 136.2, 136.2, 136.5, 136.6, 138.9, 139.4, 146.9, 146.9, 149.1, 149.5, 157.6, 160.0, 164.9, 165.3, 172.2, 173.4.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{35}H_{37}N_4O_6S$: 641.24338, found: 641.24228.

3-(4-Methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)-*N*-(pyridin-4-yl)propenamide (33o)



The title compound was synthesized in 25% according to a method similar to that described for **32f**.

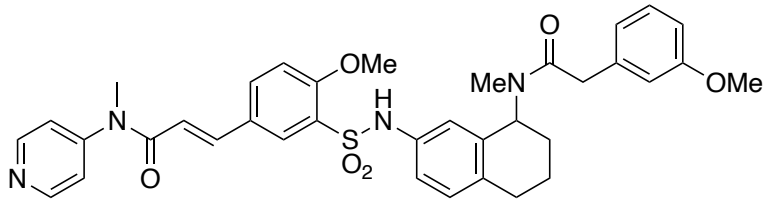
IR (neat): 2927, 1596, 1508, 1496, 1154, 756 cm^{-1}.

^{1}H-NMR (400 MHz, DMSO-D6): δ (ppm) 1.48–1.90 (m, 4H), 2.08 (s, 1.2H), 2.46 (s, 1.8H), 2.49–2.66 (m, 4H), 2.77–2.89 (m, 2H), 3.68–3.85 (m, 8H), 5.04–5.13 (m, 0.4H), 5.53–5.60 (m, 0.6H), 6.69–6.91 (m, 6H), 7.05 (t, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 7.79 Hz, 0.4H), 7.25 (t, *J* = 7.79 Hz, 0.6H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.47–7.56 (m, 2H), 7.57–7.61 (m, 1H), 8.35–8.43 (m, 2H), 9.41–10.37 (br s, 1H), 10.28–10.39 (m, 1H).

^{13}C-NMR (100 MHz, DMSO-d6): δ (ppm) 21.5, 21.6, 26.4, 27.4, 28.0, 28.1, 29.2, 29.2, 30.5, 30.7, 37.9, 38.0, 40.4, 40.6, 52.1, 54.9, 55.0, 56.0, 56.1, 56.4, 111.8, 112.0, 112.8, 113.1, 114.7, 115.0, 117.6, 117.8, 119.0, 119.1, 121.3, 121.4, 129.3, 129.4, 129.6, 129.6, 129.8, 129.9, 132.6, 134.5, 135.4, 135.6, 137.2, 137.6, 145.6, 150.3, 154.6, 154.7, 159.3, 170.7, 171.1, 171.4, 171.4.

HR-MS (ESI): *m*/*z* $[M+H]^{+}$ calcd for $C_{35}H_{39}N_4O_6S$: 643.25903, found: 643.25622.

(*E*)-3-(4-Methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)-*N*-methyl-*N*-(pyridin-4-yl)acrylamide (33p)



The title compound was synthesized in 73% according to a method similar to that described for **32e**.

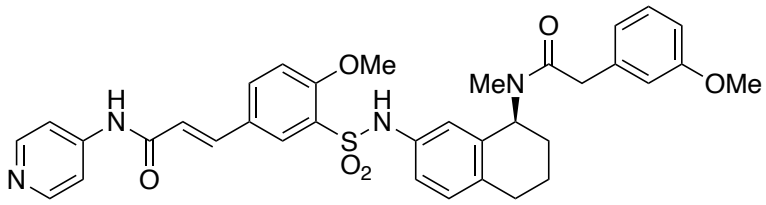
IR (neat): 2930, 1629, 1479, 1162, 755 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.50–2.03 (m, 4H), 2.20 (s, 1.2H), 2.48 (s, 1.8H), 2.56–2.70 (m, 2H), 3.44 (s, 3H), 3.60–3.80 (m, 2H), 3.80 (s, 1.2H), 3.89 (s, 1.8H), 3.95 (s, 1.8H), 4.02 (s, 1.2H), 4.83–4.99 (m, 0.4H), 5.79 (dd, *J* = 10.3, 5.7 Hz, 0.6H), 6.21 (d, *J* = 1.8 Hz, 0.4H), 6.40 (d, *J* = 15.6 Hz, 0.4H), 6.41 (d, *J* = 15.6 Hz, 0.6H), 6.54 (d, *J* = 2.3 Hz, 0.6H), 6.75–7.06 (m, 6H), 7.07–7.15 (m, 1H), 7.15–7.25 (m, 2.4H), 7.30 (t, *J* = 8.0 Hz, 0.6H), 7.43–7.54 (m, 1H), 7.58 (d, *J* = 15.6 Hz, 0.4H), 7.62 (d, *J* = 15.6 Hz, 0.6H), 7.74 (d, *J* = 1.8 Hz, 0.4H), 7.82 (d, *J* = 1.4 Hz, 0.6H), 8.64 (br s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 22.0, 26.8, 27.8, 28.7, 28.8, 28.9, 31.2, 36.9, 41.7, 41.8, 52.3, 55.4, 55.6, 56.8, 57.0, 57.4, 111.5, 112.0, 112.6, 112.7, 115.0, 115.2, 118.2, 118.3, 119.9, 120.0, 120.1, 120.7, 121.2, 121.6, 122.8, 126.7, 127.1, 127.7, 127.8, 130.0, 130.1, 130.3, 130.5, 130.6, 130.7, 134.3, 134.4, 134.5, 134.7, 135.5, 136.0, 136.2, 136.4, 136.6, 136.7, 141.3, 141.4, 150.7, 151.3, 151.3, 157.0, 157.3, 159.9, 160.0, 165.9, 166.0, 171.4, 171.8.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{36}H_{38}N_4NaO_6S$: 677.24097, found: 677.23910.

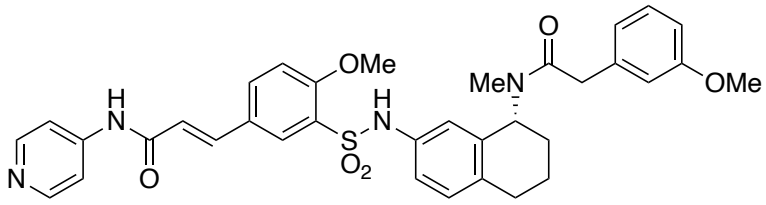
(*S*,*E*)-3-(4-Methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)-*N*-(pyridin-4-yl)acrylamide ((*S*)-33n)



The racemic mixture was separated by HPLC (DAICEL CHIRALPAK AD-H, 20 mm I.D.×250 mmL, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 50/50, flow rate: 15 mL/min., λ = 254 nm, tR = 34 min.). The optical purity was confirmed by HPLC (DAICEL CHIRALPAK AD-H, 4.6 mm I.D.×250 mmL, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 50/50, flow rate: 1.0 mL/min., λ = 254 nm, tR = 21.6 min., > 95% ee.).

$[\alpha]_{589}^{20}$ = –47.115 (*c* =0.312, $CHCl_3$)

(*R*,*E*)-3-(4-Methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)-*N*-(pyridin-4-yl)acrylamide ((*R*)-33n)



The racemic mixture was separated by HPLC (DAICEL CHIRALPAK AD-H, 20 mm I.D.×250 mmL, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 50/50, flow rate: 15 mL/min., λ = 254 nm, tR = 23 min.). The optical purity was confirmed by HPLC (DAICEL CHIRALPAK AD-H, 4.6 mm I.D.×250 mmL, hexane/0.1% $^{i}Pr_2NH$ in $^{i}PrOH$ = 50/50, flow rate: 1.0 mL/min., λ = 254 nm, tR = 12.7 min., > 95% ee.).

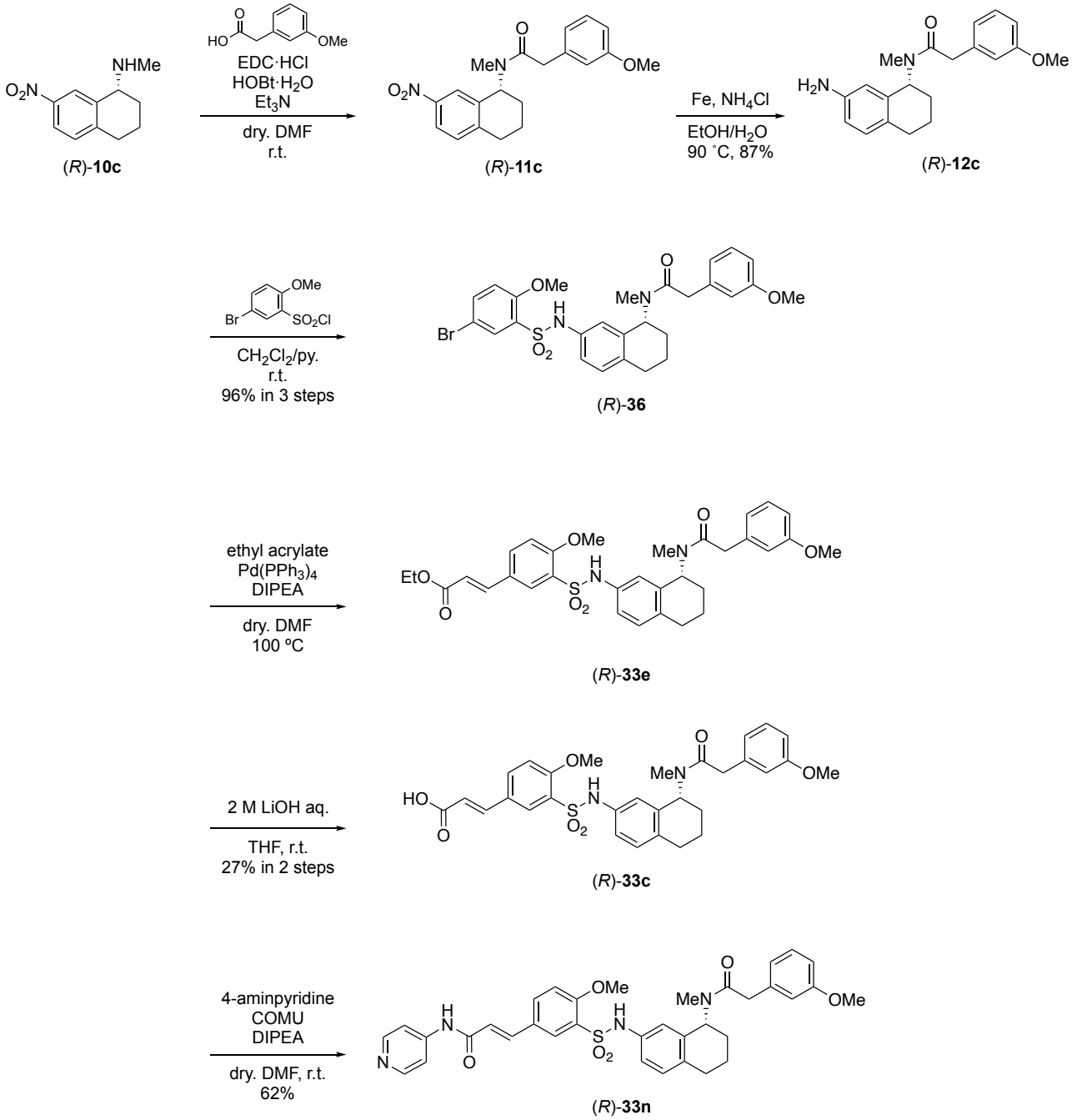
$[\alpha]_{589}^{20}$ = +46.131 (*c* = 0.336, $CHCl_3$)

To improve the solubility in aqueous solution for *in vivo* assay, (*R*)-**33n** was converted into hydrochloric acid salt according to the known methods.[33]

Monohydrochloride

Anal. Calcd for $C_{35}H_{36}N_4O_6 \cdot HCl \cdot 3.4H_2O$: C, 56.93; H, 5.98; N, 7.59. Found: C, 56.90; H, 5.78; N, 7.45.

Synthesis of (*R*)-33n



Scheme 17. Synthesis of (*R*)-**33n**

(*R*)-*N*-(7-((5-Bromo-2-methoxyphenyl)sulfonamido)-1,2,3,4-tetrahydronaphthalen-1-yl)-2-(3-methoxyphenyl)-*N*-methylacetamide ((*R*)-36)

The title compound was synthesized in 96% in 3 steps from (*R*)-**10c** according to a method similar to that described for (*rac*)-**36**.

$[\alpha]_{589}^{20}$ = +18.421 (*c* = 0.304, $CHCl_3$)

(*R*,*E*)-3-(4-Methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)acrylic acid ((*R*)-33c)

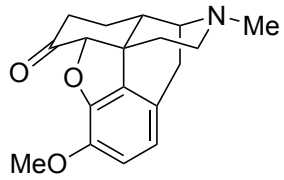
The title compound was synthesized in 27% in 2 steps from (*R*)-**36** according to a method similar to that described for (*rac*)-**33c.**

$[\alpha]_{589}^{20}$ = +1.724 (*c* = 0.058, $CHCl_3$)

(*R*,*E*)-3-(4-Methoxy-3-(*N*-(8-(2-(3-methoxyphenyl)-*N*-methylacetamido)-5,6,7,8-tetrahydronaphthalen-2-yl)sulfamoyl)phenyl)-*N*-(pyridin-4-yl)acrylamide ((*R*)-33n)

The title compound was synthesized in 62% from (*R*)-**33c** according to a method similar to that described for (*rac*)-**33n**. The compound data were already listed above.

(4*S*,4a*S*,7a*S*,12b*R*)-9-Methoxy-3-methyl-2,3,4,4a,5,6-hexahydro-1*H*-4,12-methanobenzofuro[3,2-e]isoquinolin-7(7a*H*)-one ((+)-40)



To a suspension of sinomenine·HCl (31.9 g, 87.2 mmol) in MeOH (400 mL) was added 5% Pd/C (8.53 g), and the mixture was stirred for 5 h at room temperature under a hydrogen atmosphere. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. After the addition of sat. $NaHCO_3$ aq. (300 mL) and water (100 mL), the mixture was extracted with $CHCl_3$ (300, 200, 100, 100, 100 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was used for the next reaction without further purification. A mixture of the crude residue and Eaton's reagent (200 mL) was stirred for 4 h at room temperature under an argon atmosphere. The reaction mixture was poured into 28% NH_3 aq. (1000 mL) at 0 °C. The mixture was filtered through a pad of Celite, and the filtrate was extracted with a mixed solvent (MeOH/$CHCl_3$ = 1/4, 300, 200, 200, 200, 200 mL). The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography [2–3% (28% NH_3 aq./MeOH = 1/9) in $CHCl_3$] to afford (+)-**40** (13.9 g, 79% in 2 steps) as a pale red solid.

$[\alpha]_{589}^{20}$ = +137.1 (*c* = 0.302, $CHCl_3$).

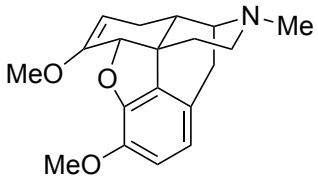
IR (KBr): 1716, 1500, 1443, 1270, 1058, 746 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.20–1.32 (m, 1H), 1.78–1.89 (m, 2H), 2.08 (ddd, *J* = 12.2, 12.1, 4.8 Hz, 1H), 2.20 (ddd, *J* = 12.1, 12.1, 3.2 Hz, 1H), 2.31 (dd, *J* = 18.3, 5.0 Hz, 1H), 2.36–2.44 (m, 2H), 2.44 (s, 3H), 2.53–2.61 (m, 2H), 3.03 (d, *J* = 18.3 Hz, 1H), 3.19 (dd, *J* = 5.0, 2.8 Hz, 1H), 3.91 (s, 3H), 4.66 (s, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 20.0, 25.7, 35.6, 40.3, 42.8, 43.0, 46.9, 47.0, 56.8, 59.3, 91.5, 114.5, 119.9, 126.4, 127.3, 142.9, 145.5, 208.0.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{22}NO_3$: 300.15997, found: 300.15896.

(4*S*,4a*S*,7a*S*,12b*R*)-7,9-Dimethoxy-3-methyl-2,3,4,4a,5,7a-hexahydro-1*H*-4,12-methanobenzofuro[3,2-e]isoquinoline ((+)-41)



A mixture of compound (+)-**40** (28.2 g, 70.6 mmol), 5-sulfosalicylic acid (26.9 g, 0.106 mmol), and trimethyl orthoformate (90 mL) in MeOH (470 mL) was refluxed for 6 h under an argon atmosphere. After cooling to room temperature, the reaction mixture was basified with K_2CO_3 (19.8 g), sat. $NaHCO_3$ aq. (200 mL), and water (300 mL). The mixture was extracted with $CHCl_3$ (300, 300, 300, 200 mL) and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was used for the next reaction without further purification. A solution of the crude residue in toluene (700 mL) was stirred under reflux for 2 h with a Dean–Stark apparatus under an argon atmosphere. To the reaction mixture was added CSA (39.4 g, 170 mmol), and the mixture was refluxed for 3 h with a Dean–Stark apparatus under an argon atmosphere. After cooling to room temperature, the reaction mixture was basified with K_2CO_3 (23.4 g) and sat. $NaHCO_3$ aq. (200 mL), and extracted with $CHCl_3$ (300 mL×3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography [5–10% (28% NH_3 aq./MeOH = 1/9) in $CHCl_3$] to afford (+)-**40** (20.8 g, 94% in 2 steps) as a pale yellow solid.

$[\alpha]_{589}^{20}$ = +213.0 (*c* = 0.378, $CHCl_3$).

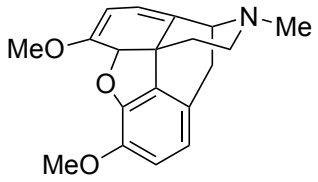
IR (KBr): 1657, 1499, 1445, 1214, 1057, 903 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.57 (dddd, *J* = 16.0, 11.9, 1.8, 1.4 Hz, 1H), 1.82 (ddd, *J* = 12.6, 3.8, 1.4 Hz, 1H), 1.93 (ddd, *J* = 12.6, 12.1, 4.8 Hz, 1H), 1.97 (ddd, *J* = 16.0, 6.9, 6.0 Hz, 1H), 2.23 (ddd, *J* = 12.1, 12.1, 3.8 Hz, 1H), 2.32 (ddd, *J* = 11.9, 6.0, 2.8 Hz, 1H), 2.38 (dd, *J* = 18.8, 6.0 Hz, 1H), 2.41 (s, 3H), 2.52 (ddd, *J* = 12.1, 4.8, 1.4 Hz, 1H), 3.02 (d, *J* = 18.8 Hz, 1H), 3.13 (dd, *J* = 6.0, 2.8 Hz, 1H), 3.49 (s, 3H), 3.85 (s, 3H), 4.73 (dd, *J* = 6.9, 1.8 Hz, 1H), 4.84 (d, *J* = 1.4 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 20.3, 23.8, 35.9, 40.0, 42.6, 43.2, 46.6, 54.5, 56.6, 59.1, 88.7, 98.2, 113.7, 118.7, 127.2, 129.4, 143.2, 145.3, 152.4.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{24}NO_3$: 314.17562, found: 314.17560.

(4*S*,7a*S*,12b*R*)-7,9-Dimethoxy-3-methyl-2,3,4,7a-tetrahydro-1*H*-4,12-methanobenzofuro[3,2-e]isoquinoline ((+)-thebaine)



To a solution of compound (+)-**41** (3.35 g, 10.7 mmol) in MeOH (30 mL) was added a suspension of NBS (1.91 mg, 10.7 mmol) in MeOH (3.0 mL) dropwise at 0 °C over 15 minutes. Under light shielding, the reaction system was gradually warmed to room temperature and stirred for 2 h. After the addition of sat. $Na_2S_2O_3$ aq. (50 mL), the mixture was extracted with $CHCl_3$ (300, 100, 50, 50 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography [2–3% (28% NH_3 aq./MeOH = 1/9) in $CHCl_3$] to afford impure mixture. This mixture was used for the next reaction without further purification. To a solution of the mixture in DMSO (100 mL) was added ^{t}BuOK (6.27 g, 55.9 mmol) and the mixture was stirred for 4 h at 80 ℃ under an argon atmosphere. After cooling to room temperature, water (300 mL) was added to the reaction mixture. The mixture was extracted with benzene (300, 100, 100, 50 mL) and the organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography [2–5% (28% NH_3 aq./MeOH = 1/9) in $CHCl_3$] to afford (+)-thebaine (2.94 g, 88% in 2 steps) as a colorless solid.

$[\alpha]_{589}^{20}$ = +194.1 (*c* = 0.270, $CHCl_3$).

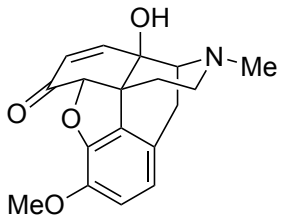
IR (KBr): 1604, 1503, 1443, 1232, 1029, 906 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.73 (ddd, *J* = 12.5, 3.7, 1.0 Hz, 1H), 2.21 (ddd, *J* = 12.8, 12.5, 5.0 Hz, 1H), 2.46 (s, 3H), 2.63 (ddd, *J* = 12.8, 5.0, 1.0 Hz, 1H), 2.66 (dd, *J* = 18.3, 6.9 Hz, 1H), 2.82 (ddd, *J* = 12.8, 12.8, 3.7 Hz, 1H), 3.31 (d, *J* = 18.3 Hz, 1H), 3.60 (s, 3H), 3.61 (d, *J* = 6.9 Hz, 1H), 3.85 (s, 3H), 5.04 (d, *J* = 6.4 Hz, 1H), 5.30 (s, 1H), 5.56 (d, *J* = 6.4 Hz, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 6.66 (d, *J* = 8.2 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 29.9, 36.7, 42.3, 46.0, 46.1, 55.1, 56.5, 61.1, 89.2, 96.0, 112.3, 113.0, 119.4, 127.5, 131.6, 133.2, 143.0, 144.8, 152.8.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{22}NO_3$: 312.15997, found: 312.15945.

(4*S*,4a*R*,7a*S*,12b*R*)-4a-Hydroxy-9-methoxy-3-methyl-2,3,4,4a-tetrahydro-1*H*-4,12-methanobenzofuro[3,2-e]isoquinolin-7(7a*H*)-one ((+)-43)



A mixture of (+)-thebaine (2.94 g, 9.44 mmol), H_2O_2 aq. (30%, 2.50 mL, 24.5 mmol), and formic acid (98%, 14 mL) in H_2SO_4 aq. (0.7%, 42 mL) was heated for 2 h at 40 °C under an argon atmosphere. After cooling to room temperature, the reaction mixture was basified with 28% NH_3 aq., and then extracted with $CHCl_3$ (300, 200, 100, 100 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give (+)-**43** (2.81 g, 95%) as a colorless solid.

$[\alpha]_{589}^{20}$ = +162.1 (*c* = 0.074, $CHCl_3$).

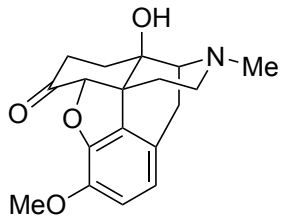
IR (KBr): 3316, 1673, 1498, 1259. 1047, 799 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.69 (ddd, *J* = 11.9, 5.0, 0.9 Hz, 1H), 2.28 (ddd, *J* = 12.0, 11.9, 3.7 Hz, 1H), 2.43 (ddd, *J* = 12.4, 12.0, 5.0 Hz, 1H), 2.44 (s, 3H), 2.52 (ddd, *J* = 12.4, 3.7, 0.9 Hz, 1H), 2.55 (dd, *J* = 18.8, 6.0 Hz, 1H), 3.04 (d, *J* = 6.0 Hz, 1H), 3.24 (d, *J* = 18.8 Hz, 1H), 3.84 (s, 3H), 4,71 (s, 1H), 5.12 (br s, 1H), 6.19 (d, *J* = 10.1 Hz, 1H), 6.62 (d, *J* = 10.1 Hz, 1H), 6.62 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 22.5, 29.6, 42.7, 45.3, 46.8, 56.9, 64.3, 67.9, 87.2, 115.1, 119.7, 125.1, 130.6, 134.8, 142.8, 144.5, 147.5, 194.4.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{20}NO_4$: 314.13923, found: 314.14001.

(4*S*,4a*R*,7a*S*,12b*R*)-4a-Hydroxy-9-methoxy-3-methyl-2,3,4,4a,5,6-hexahydro-1*H*-4,12-methanobenzofuro[3,2-e]isoquinolin-7(7a*H*)-one ((+)-oxycodone)



A mixture of (+)-**43** (2.81 g, 8.97 mmol) and 5% Pd/C (1.00 g) in AcOH (100 mL) was stirred for 4 h at room temperature under a hydrogen atmosphere. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. After the addition of 28% NH_3 aq. (30 mL), the mixture was extracted with $CHCl_3$ (300, 100, 100, 50 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography [0.5–5% (28% NH_3 aq./MeOH = 1/9) in $CHCl_3$] to afford (+)-oxycodone (2.38 g, 84%) as a colorless solid.

$[\alpha]_{589}^{20}$ = +196.6 (*c* = 0.296, $CHCl_3$).

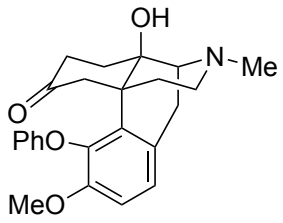
IR (KBr): 3311, 1728, 1500, 1445, 1259, 1038, 937 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.53–1.59 (m, 1H), 1.63 (ddd, *J* = 14.4, 13.7, 3.2 Hz, 1H), 1.87 (ddd, *J* = 13.7, 5.0, 3.2 Hz, 1H), 2.11–2.21 (m, 1H), 2.29 (ddd, *J* = 14.2, 3.2, 3.2 Hz, 1H), 2.36–2.49 (m, 2H), 2.40 (s, 3H), 2.56 (dd, *J* = 18.3, 6.0 Hz, 1H), 2.87 (d, *J* = 6.0 Hz, 1H), 3.02 (ddd, *J* = 14.4, 14.2, 5.0 Hz, 1H), 3.16 (d, *J* = 18.3 Hz, 1H), 3.89 (s, 3H), 4.66 (s, 1H), 4.99 (br s, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 21.9, 30.5, 31.4, 36.2, 42.8, 45.3, 50.3, 56.8, 64.6, 70.4, 90.4, 114.8, 119.5, 125.0, 129.4, 143.0, 145.0, 208.6.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{22}NO_4$: 316.15488, found: 316.15333.

(4b*S*,8a*R*,9*S*)-8a-Hydroxy-3-methoxy-11-methyl-4-phenoxy-8,8a,9,10-tetrahydro-5*H*-9,4b-(epiminoethano)phenanthren-6(7*H*)-one ((+)-45)



A mixture of (+)-oxycodone (301 mg, 0.954 mmol) and Zn powder (3.10 g, 47.4 mmol) in AcOH (10 mL) was refluxed for 8 h under an argon atmosphere. After cooling to room temperature, the reaction mixture was through a pad of Celite and the filtrate was extracted with $CHCl_3$ (40, 30, 20, 20 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography [2–3% (28% NH_3 aq./MeOH = 1/9) in $CHCl_3$] to afford impure mixture. This mixture was used for the next reaction without further purification. To a solution of the mixture in pyridine (4.0 mL) was added K_2CO_3 (301 mg, 2.18 mmol), PhBr (430 µl, 4.09 mmol), and Cu (34.6 mg, 544 µmol). This solution was refluxed for 4 h under an argon atmosphere. After cooling to room temperature, the reaction mixture was through a pad of Celite and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography [2–3% (28% NH_3 aq./MeOH = 1/9) in $CHCl_3$] to afford (+)-**45** (364 mg, 98% in 2 steps) as a pale yellow amorphous.

$[\alpha]_{589}^{20}$ = +14.2 (*c* = 0.120, $CHCl_3$).

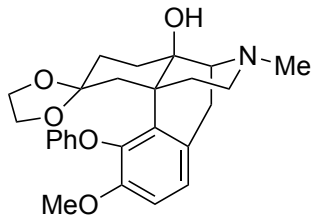
IR (neat): 3423, 1713, 1481, 1433, 1279, 1046, 752 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.23 (ddd, *J* = 12.8, 3.2, 1.8 Hz, 1H), 1.81 (ddd, *J* = 13.3, 7.3, 1.4 Hz, 1H), 1.91 (ddd, *J* = 13.3, 12.8, 5.0 Hz, 1H), 1.96 (ddd, *J* = 14.2, 13.3, 5.5 Hz, 1H), 2.09 (ddd, *J* = 13.3, 11.9, 3.2 Hz, 1H), 2.16 (dddd, *J* = 14.7, 5.5, 1.8, 1.4 Hz, 1H), 2.31 (ddd, *J* = 11.9, 5.0, 1.8 Hz, 1H), 2.37 (s, 3H), 2.75 (ddd, *J* = 14.7, 14.2, 7.3 Hz, 1H), 2.81 (d, *J* = 6.6 Hz, 1H), 2.88 (d, *J* = 13.7 Hz, 1H), 2.90 (dd, *J* = 18.3, 6.6 Hz, 1H), 3.14 (d, *J* = 18.3 Hz, 1H), 3.61 (s, 3H), 3.63 (dd, *J* = 13.7, 1.8 Hz, 1H), 4.50 (br s, 1H), 6.70 (d, *J* = 7.8 Hz, 2H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.94 (m, 2H), 6.96 (d, *J* = 8.2 Hz, 1H), 7.22 (dd, *J* = 7.8, 7.8 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 24.7, 31.9, 34.3, 37.5, 42.8, 45.1, 45.4, 45.5, 56.3, 62.1, 69.4, 112.2, 114.8 (×2), 121.5, 124.7, 129.4 (×2), 129.8, 133.4, 142.4, 151.4, 158.1, 210.1.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{24}H_{28}NO_4$: 394.20183, found: 394.20030.

(4b'*S*,8a'*R*,9'*S*)-3'-Methoxy-11'-methyl-4'-phenoxy-7',8',9',10'-tetrahydro-5'*H*,8a'*H*-spiro[[1,3]dioxolane-2,6'-[9,4b](epiminoethano)phenanthren]-8a'-ol ((–)-46)



A mixture of compound (+)-**45** (350 mg, 0.889 mmol), *p*-TsOH·H_2O (254 mg, 1.34 mmol), and ethylene glycol (300 μL, 5.39 mmol) in toluene (9.0 mL) was refluxed for 3 h with a Dean–Stark apparatus under an argon atmosphere. After cooling to room temperature, the reaction mixture was basified with K_2CO_3 (378 mg) and sat. $NaHCO_3$ aq. (5.0 mL), and then extracted with toluene (40, 30, 20, 20 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography [1–9% (28% NH_3 aq./MeOH = 1/9) in $CHCl_3$] to afford (–)-**46** (340 mg, 87%) as a colorless amorphous.

$[\alpha]_{589}^{20}$ = –1.2 (*c* = 0.162, $CHCl_3$).

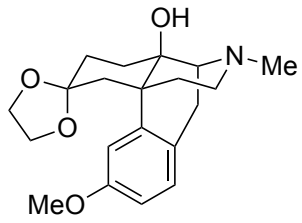
IR (KBr): 3433, 1483, 1280, 1051, 753 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.15 (ddd, *J* = 12.4, 3.2, 1.4 Hz, 1H), 1.49–1.89 (m, 2H), 1.76–1.88 (m, 2H), 1.98 (d, *J* = 13.7 Hz, 1H), 2.05 (ddd, *J* = 12.1, 11.9, 3.2 Hz, 1H), 2.13–2.23 (m, 1H), 2.25 (ddd, *J* = 11.9, 5.0, 1.4 Hz, 1H), 2.33 (s, 3H), 2.68 (d, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 18.3, 6.0 Hz, 1H), 3.08 (d, *J* = 18.3 Hz, 1H), 3.21 (dd, *J* = 13.7, 1.8 Hz, 1H), 3.64 (s, 3H), 3.76 (ddd, *J* = 7.3, 6.4, 6.4 Hz, 1H), 3.87 (ddd, *J* = 7.3, 6.4, 6.4 Hz, 1H), 3.93 (ddd, *J* = 7.3, 6.4, 6.4 Hz, 1H), 4.09 (ddd, *J* = 7.3, 6.4, 6.4 Hz, 1H), 4.29 (br s, 1H), 6.65 (d, *J* = 7.8 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 1H), 6.93 (t, *J* = 7.3 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 1H), 7.02 (dd, *J* = 7.8, 7.3 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 24.9, 30.4, 31.5, 33.7, 36.7, 41.8, 42.7, 46.0, 56.4, 62.5, 64.2, 65.1, 69.1, 109.4, 111.7, 114.7 (× 2), 121.2, 124.6, 129.3 (× 2), 129.8, 135.5, 142.7, 150.7, 158.1.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{26}H_{32}NO_5$: 438.22805, found: 438.22750.

(4b'*S*,8a'*R*,9'*S*)-3'-Methoxy-11'-methyl-7',8',9',10'-tetrahydro-5'*H*,8a'*H*-spiro[[1,3]dioxolane-2,6'-[9,4b](epiminoethano)phenanthren]-8a'-ol ((+)-47)



To liquid ammonia (50 mL) at –33 °C (produced from an ammonia tank) was added a solution of (–)-**46** in anhydrous toluene (2.0 mL) under nitrogen flow. To the solution was added sodium (187 mg, 11 eq.) in small pieces and the mixture was stirred for 30 min at –33 °C under nitrogen flow. After evaporating liq. NH_3, the solution was mixed with toluene (27 mL) and EtOH (2.0 mL), washed with 1 M NaOH aq. (6.0 mL) and the aqueous phase was extracted with toluene (30, 20, 20 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduce pressure. The crude residue was purified by silica gel column chromatography [2–3% (28% NH_3 aq./MeOH = 1/9) in $CHCl_3$] to afford (+)-**47** (229 mg, 88%) as a colorless solid.

$[\alpha]_{589}^{20}$ = +60.7 (*c* = 0.122, $CHCl_3$).

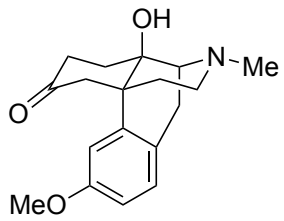
IR (KBr): 3416, 1614, 1498, 800, 741 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.02–1.11 (m, 1H), 1.47–1.59 (m, 2H), 1.69–1.79 (m, 1H), 1.95–2.09 (m, 2H), 2.14 (d, *J* = 14.2 Hz, 1H), 2.14–2.24 (m, 1H), 2.25–2.32 (m, 2H), 2.35 (s, 3H), 2.68 (d, *J* = 5.5 Hz, 1H), 2.78 (dd, *J* = 17.9, 5.5 Hz, 1H), 3.08 (d, *J* = 17.9 Hz, 1H), 3.74–3.82 (m, 4H), 3.83–3.89 (m, 2H), 3.92–3.99 (m, 1H), 4.52 (br s, 1H), 6.71 (dd, *J* = 8.2, 2.8 Hz, 1H), 6.84 (d, *J* = 2.8 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 24.1, 30.0, 31.0, 37.5, 37.8, 41.9, 42.7, 45.7, 55.4, 62.9, 64.0, 64.4, 69.0, 109.2, 111.5, 112.7, 127.2, 128.1, 142.1, 157.3.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{20}H_{28}NO_4$: 346.20183, found: 346.20138.

(4b*S*,8a*R*,9*S*)-8a-Hydroxy-3-methoxy-11-methyl-8,8a,9,10-tetrahydro-5*H*-9,4b-(epiminoethano)phenanthren-6(7*H*)-one ((+)-48)



A solution of compound (+)-**47** (215 mg, 0.622 mmol) in 1 M HCl aq. (6.0 mL) was heated for 3 h at 60 °C under an argon atmosphere. After cooling to room temperature, the reaction mixture was basified with sat $NaHCO_3$ aq. (8.0 mL), then extracted with $CHCl_3$ (30, 20, 10, 10 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography [hexane/EtOAc/(28% NH_3 aq./MeOH = 1/9) = 8/2/1] to afford (+)-**48** (184 mg, 98%) as a colorless solid.

$[\alpha]_{589}^{20}$ = +114.8 (*c* = 0.838, $CHCl_3$).

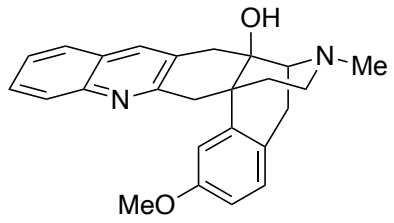
IR (KBr): 3430, 1717, 1610, 1506, 940, 819 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.12–1.24 (m, 1H), 1.78 (ddd, *J* = 13.3, 7.3, 1.8 Hz, 1H), 1.85 (ddd, *J* = 13.3, 13.3, 5.0 Hz, 1H), 2.07–2.29 (m, 3H), 2.32–2.39 (m, 1H), 2.40 (s, 3H), 2.73 (dd, *J* = 18.8, 6.4 Hz, 1H), 2.78 (ddd, *J* = 13.7, 13.3, 7.3 Hz, 1H), 2.81 (d, *J* = 14.2 Hz, 1H), 2.82 (d, *J* = 6.4 Hz, 1H), 3.04 (d, *J* = 14.2 Hz, 1H), 3.16 (d, *J* = 18.8 Hz, 1H), 3.77 (s, 3H), 4.73 (br s, 1H), 6.70 (dd, *J* = 8.2, 2.8 Hz, 1H), 6.80 (d, *J* = 2.8 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 23.9, 31.9, 37.0, 37.7, 42.9, 45.1, 45.2, 46.5, 55.4, 62.2, 69.3, 111.1, 112.7, 127.2, 128.6, 140.6, 158.5, 210.3.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{24}NO_3$: 302.17562, found: 302.17478.

(6*S*,6a*R*,14a*S*)-2-Methoxy-17-methyl-5,6,7,14-tetrahydro-6a*H*-6,14a-(epiminoethano)naphtho[2,1-b]acridin-6a-ol ((+)-49)



A mixture of compound (+)-**48** (76.1 mg, 0.252 mmol), $MeSO_3H$ (70 μL, 1.08 mmol), and 2-aminobenzaldehyde (316 mg, 2.60 mmol) in EtOH (2.5 mL) was refluxed for 19 h under an argon atmosphere. After cooling to room temperature, the reaction was quenched by the addition of sat. $NaHCO_3$ aq. (2.0 mL) and extracted with $CHCl_3$ (20, 10, 10 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography [1–5% (28% NH_3 aq./MeOH = 1/9) in $CHCl_3$] to afford (+)-**49** (82.8 mg, 86%) as a colorless solid.

$[\alpha]_{589}^{20}$ = +279.6 (*c* = 0.250, $CHCl_3$).

IR (KBr): 3441, 1497, 1273, 1044, 767 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.36–1.47 (m, 1H), 2.18–2.29 (m, 2H), 2.40–2.47 (m, 1H), 2.43 (s, 3H), 2.89–2.99 (m, 3H), 3.09 (d. *J* = 17.4 Hz, 1H), 3.26 (d. *J* = 17.9 Hz, 1H), 3.58 (d, *J* = 17.4 Hz, 1H), 3.63 (s, 3H), 3.71 (d, *J* = 17.4 Hz, 1H), 4.74 (br s, 1H), 6.61 (dd, *J* = 8.2, 2.8 Hz, 1H), 6.91 (d, *J* = 2.8 Hz, 1H), 7.00 (d, *J* = 8.7 Hz, 1H), 7.38 (ddd, *J* = 7.3, 6.8, 0.9 Hz, 1H), 7.58 (ddd, *J* = 7.3, 6.8, 1.4 Hz, 1H), 7.60 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.66 (s, 1H), 7.98 (dd, *J* = 7.3, 0.9 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 24.1, 36.2, 36.9, 39.6, 40.8, 43.2, 45.7, 55.3, 61.8, 69.6, 111.0, 112.3, 125.5, 126.9, 127.4, 127.7, 128.2, 128.4, 128.5, 128.6, 135.4, 141.3, 146.7, 157.4, 158.3.

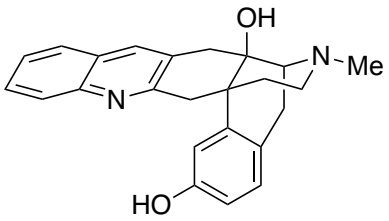
HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{25}H_{27}N_2O_2$: 387.20725, found: 387.20615.

To improve the solubility in aqueous solution for *in vivo* assay, (+)-**49** was converted into hydrochloric acid salt according to the known methods.[33]

Dihydrochloride

Anal. Calcd for $C_{25}H_{26}N_2O_2 \cdot 2HCl \cdot 4.5H_2O$: C, 55.56; H, 6.90; N, 5.18. Found: C, 55.47; H, 6.62; N, 5.12.

(6*S*,6a*R*,14a*S*)-17-Methyl-5,6,7,14-tetrahydro-6a*H*-6,14a-(epiminoethano)naphtho[2,1-b]acridine-2,6a-diol ((+)-KNT-127)



To a solution of compound (+)-**49** (61.1 mg, 0.158 mmol) in CH_2Cl_2 (1.0 mL) was added 1.0 M BBr_3 in CH_2Cl_2 solution (1.9 mL, 1.90 mmol) at 0 °C under an atmosphere. After being stirred for 1 h at room temperature, the reaction was quenched by the addition of 28% NH_3 aq. (7.0 mL) at 0 °C. The reaction mixture was extracted with $CHCl_3$ (30, 20, 10 mL) and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by preparative TLC [$CHCl_3$/(28% NH_3 aq./MeOH = 1/9) = 10/1] to afford (+)-KNT-127 (50.6 mg, 86%) as a colorless solid.

$[\alpha]_{589}^{20}$ = +246.8 (*c* = 0.252, $CHCl_3$).

IR (KBr): 3397, 1609, 762 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.34–1.41 (m, 1H), 2.15 (ddd, *J* = 12.8, 12.8, 5.5 Hz, 1H), 2.31 (ddd, *J* = 12.8, 12.1, 3.2 Hz, 1H), 2.39–2.49 (m, 1H), 2.44 (s, 3H), 2.92 (dd, *J* = 17.9, 6.9 Hz, 1H), 2.95 (d, *J* = 17.9 Hz, 1H), 2.98 (d, *J* = 6.9 Hz, 1H), 3.10 (d, *J* = 17.9 Hz, 1H), 3.28 (d, *J* = 17.9 Hz, 1H), 3.61 (d, *J* = 16.9 Hz, 1H), 3.70 (d, *J* = 16.9 Hz, 1H), 4.75 (br s, 1H), 6.64 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 7.04 (d, *J* = 2.3 Hz, 1H), 7.15 (ddd, *J* = 8.2, 8.2, 1.4 Hz, 1H), 7.21 (ddd, *J* = 8.2, 8.2, 0.9 Hz, 1H), 7.36 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.49 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.65 (s, 1H). The OH peak was not observed.

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 24.1, 36.1, 36.4, 38.9, 40.6, 43.2, 45.7, 61.9, 69.9, 113.0, 114.9, 125.7, 126.7, 126.8, 127.0, 127.3, 128.4, 128.7, 129.0, 136.1, 140.8, 145.6, 155.6, 157.4.

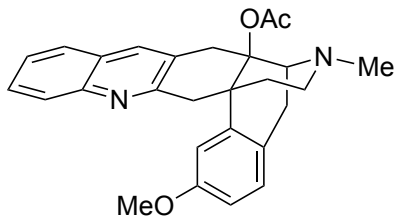
HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{24}H_{25}N_2O_2$: 373.19160, found: 373.19062.

To improve the solubility in aqueous solution for *in vivo* assay, (+)-KNT-127 was converted into hydrochloric acid salt according to the known methods.[33]

Dihydrochloride

Anal. Calcd for $C_{24}H_{24}N_2O_2 \cdot 2HCl \cdot 4.5H_2O$: C, 54.76; H, 6.70; N, 5.32. Found: C, 54.69; H, 6.46; N, 5.36.

(6*S*,6a*R*,14a*S*)-2-Methoxy-17-methyl-5,6,7,14-tetrahydro-6a*H*-6,14a-(epiminoethano)naphtho[2,1-b]acridin-6a-yl acetate ((+)-50)



A solution of compound (+)-**49** (200 mg, 0.517 mmol) in Ac_2O (10 mL) was refluxed for 30 min under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography [$CHCl_3$/(28% NH_3 aq./MeOH = 1/9) = 30/1] to afford (+)-**50** (212 mg, 95%) as a pale yellow amorphous.

$[\alpha]_{589}^{20}$ = +218.9 (*c* = 0.704, $CHCl_3$).

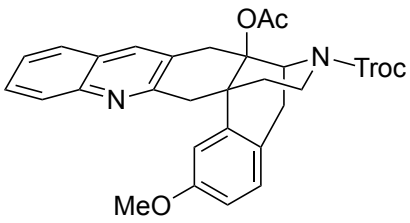
IR (KBr): 3423, 1725, 1496, 1244, 1030, 751 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.35–1.43 (m, 1H), 1.98 (s, 3H), 2.15–2.24 (m, 1H), 2.33–2.48 (m, 2H), 2.38 (s, 3H), 2.83 (dd, *J* = 18.8, 6.4 Hz, 1H), 3.07 (d, *J* = 18.3 Hz, 1H), 3.29 (d, *J* = 18.8 Hz, 1H), 3.55 (d, *J* = 17.9 Hz, 1H), 3.65 (s, 3H), 3.80 (d, *J* = 17.9 Hz, 1H), 3.91 (d, *J* = 18.3 Hz, 1H), 4.26 (d, *J* = 6.4 Hz, 1H), 6.63 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.93 (d, *J* = 2.8 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 7.41 (ddd, *J* = 8.0, 8.0, 0.9 Hz, 1H), 7.61 (ddd, *J* =8.0, 8.0, 1.4 Hz, 1H), 7.62 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.66 (s, 1H), 7.99 (dd, *J* = 8.0, 0.9 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 22.6, 24.6, 32.0, 36.6, 39.4, 40.8, 43.0, 45.8, 55.3, 55.3, 81.6, 111.0, 112.4, 125.8, 127.0, 127.4, 127.6, 128.4, 128.4, 128.5, 128.8, 135.6, 140.3, 146.8, 156.9, 158.4, 171.0.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{27}H_{29}N_2O_3$: 429.21782, found: 429.21627.

2,2,2-Trichloroethyl (6*S*,6a*R*,14a*S*)-6a-acetoxy-2-methoxy-6,6a,7,14-tetrahydro-5*H*-6,14a-(epiminoethano)naphtho[2,1-b]acridine-17-carboxylate ((+)-51)



A mixture of compound (+)-**50** (203 mg, 0.474 mmol), TrocCl (0.64 mL, 4.77 mmol), and K_2CO_3 (655 mg, 4.74 mmol) in $(CHCl_2)_2$ (5.0 mL) was heated for 3 h at 140 °C under an argon atmosphere. After cooling to room temperature, sat. $NaHCO_3$ aq. (20 mL) was added to the reaction mixture. The mixture was extracted with $CHCl_3$ (40, 20, 20 mL), and then the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (0.5–9% MeOH in $CHCl_3$) to afford (+)-**51** (275 mg, 98%) as a pale yellow amorphous.

$[\alpha]_{589}^{20}$ = +218.5 (*c* = 0.966, $CHCl_3$).

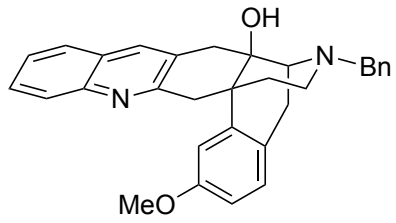
IR (KBr): 3423, 1743, 1714, 1432, 1246, 1035, 753 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.49–1.60 (m, 1H), 1.92 (s, 1.65H), 1.95 (s, 1.35H), 2.39–2.48 (m, 1H), 2.82–2.90 (m, 0.45H), 2.91–3.02 (m, 0.55H), 3.09 (d, *J* = 18.8 Hz, 1H), 3.12 (d, *J* = 18.3 Hz, 1H), 3.49 (dd, *J* = 18.8, 6.4 Hz, 1H), 3.60 (d, *J* = 18.3 Hz, 1H), 3.71 (s, 3H), 4.04–4.27 (m, 2H), 4.31 (d, *J* = 18.3 Hz, 1H), 4.72 (d, *J* = 11.9 Hz, 1H), 4.92 (d, *J* = 11.9 Hz, 1H), 5.77 (d, *J* = 6.4 Hz, 0.55H), 5.80 (d, *J* = 6.4 Hz, 0.45H), 6.70 (d, *J* = 8.2 Hz, 1H), 7.02 (s, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 7.49–7.56 (m, 1H), 7.70–7.75 (m, 2H), 7.85 (s, 0.45H), 7.90 (s, 0.55H), 8.21–8.33 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 22.2, 30.8, 30.9, 33.5, 33.9, 34.7, 35.2, 37.4, 37.4, 41.3, 41.5, 49.1, 49.3, 55.5, 75.1, 75.2, 79.3, 79.5, 95.7, 95.9, 111.0, 111.1, 113.6, 125.9, 126.1, 127.2, 127.4, 129.1, 129.2, 138.5, 153.9, 154.0, 155.3, 155.4, 159.1, 170.0, 170.3.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{29}H_{28}Cl_3N_2O_5$: 589.10638, found: 589.10534.

(6*S*,6a*R*,14a*S*)-17-Benzyl-2-methoxy-5,6,7,14-tetrahydro-6a*H*-6,14a-(epiminoethano)naphtho[2,1-b]acridin-6a-ol ((+)-53)



A mixture of compound (+)-**51** (48.8 mg, 82.7 μmol), 2 M LiOH aq. (1.0 mL) and THF (2.0 mL) was heated for 54 h at 60 °C under an argon atmosphere. The reaction mixture was cooled to toom temperature and concentrated under reduced pressure. The crude residue was used for the next reaction without further purification. To a stirred solution of the crude residue in DMF (1.0 mL) was added BnBr (70 μl, 0.589 mmol), and the mixture was stirred for 20 h under an argon atmosphere. The reaction mixture was quenched by the addition of sat. $NaHCO_3$ aq. (5.0 mL) and H_2O (5.0 mL), and extracted with $CHCl_3$ (20, 10, 10 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by preparative TLC [$CHCl_3$/(28% NH_3 aq./MeOH = 1/9) = 30/1] to afford (+)-**53** (19.5 mg, 51% in 2 steps) as a colorless solid.

$[\alpha]_{589}^{20}$ = +221.8 (*c* = 0.390, $CHCl_3$).

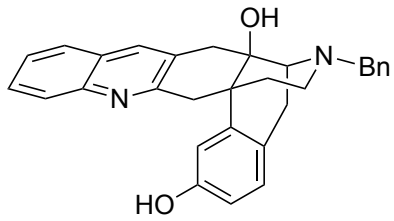
IR (neat): 3423, 1609, 1496, 1271, 1043, 750 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.42 (ddd, *J* = 12.8, 2.5, 2.3 Hz, 1H), 2.21 (ddd, *J* = 12.8, 12.6, 5.0 Hz, 1H), 2.39 (ddd, *J* = 12.6, 12.0, 2.5 Hz, 1H), 2.54 (ddd, *J* = 12.0, 5.0, 2.3 Hz, 1H), 2.89 (d, *J* = 17.4 Hz, 1H), 2.98 (dd, *J* = 18.8, 6.4 Hz, 1H), 3.06 (d, *J* = 17.4 Hz, 1H), 3.09 (d, *J* = 6.4 Hz, 1H), 3.34 (d, *J* = 18.8 Hz, 1H), 3.59 (d, *J* = 17.4 Hz, 1H), 3.63 (s, 3H), 3.70 (s, 2H), 3.72 (d, *J* = 17.4 Hz, 1H), 4.62 (br s, 1H), 6.62 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.92 (d, *J* = 2.8 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 7.27–7.40 (m, 6H), 7.58 (dd, *J* = 8.7, 8.7 Hz, 1H), 7.59–7.64 (m, 2H), 7.99 (d, *J* = 8.7 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 25.0, 36.2, 36.8, 39.5, 41.4, 43.7, 55.3, 59.4, 59.8, 69.6, 111.0, 112.4, 125.6, 126.9, 127.4, 127.6 (×2), 128.2, 128.3, 128.6, 128.6, 128.7 (×2), 129.0 (×2), 135.4, 138.3, 141.3, 146.6, 157.3, 158.4.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{31}H_{31}N_2O_2$: 463.23855, found: 463.23693.

(6*S*,6a*R*,14a*S*)-17-Benzyl-5,6,7,14-tetrahydro-6a*H*-6,14a-(epiminoethano)naphtho[2,1-b]acridine-2,6a-diol ((+)-54)



To a solution of compound (+)-**53** (4.2 mg, 19.1 μmol) in CH_2Cl_2 (1.0 mL) was added 1.0 M BBr_3 in CH_2Cl_2 solution (185 μl, 185 μmol) at 0 °C under an atmosphere. After being stirred for 1 h at room temperature, the reaction was quenched by the addition of H_2O (1.0 mL) and 28% NH_3 aq. (2.0 mL) at 0 °C. The aqueous layer was extracted with $CHCl_3$ (20, 10, 10, 10 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by preparative TLC [$CHCl_3$/(28% NH_3 aq./MeOH = 1/9) = 30/1] to afford (+)-**54** (3.6 mg, 89%) as a colorless solid.

$[\alpha]_{589}^{20}$ = +221.2 (*c* = 0.066, $CHCl_3$).

IR (neat): 3418, 1609, 1496, 1281, 750 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.38 (dd, *J* = 12.4, 3.2 Hz, 1H), 2.14 (ddd, *J* = 12.5, 12.4, 4.6 Hz, 1H), 2.36 (ddd, *J* = 12.5, 11.9, 3.2 Hz, 1H), 2.53 (dd, *J* = 11.9, 4.6 Hz, 1H), 2.90 (d, *J* = 17.9 Hz, 1H), 2.97 (dd, *J* = 18.8, 6.9 Hz, 1H), 3.09 (d, *J* = 17.9 Hz, 1H), 3.10 (d, *J* = 6.9 Hz, 1H), 3.37 (d, *J* = 18.8 Hz, 1H), 3.64–3.70 (m, 2H), 3.71 (d, *J* = 16.0 Hz, 1H), 3.73 (d, *J* = 16.0 Hz, 1H), 4.77 (br s, 1H), 6.64 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 7.03 (d, *J* = 2.3 Hz, 1H), 7.17 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H), 7.22 (ddd, *J* = 8.2, 6.9, 0.9 Hz, 1H), 7.28–7.40 (m, 6H), 7.49 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.62 (s, 1H). The OH peak was not observed.

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 25.0, 36.1, 36.4, 38.9, 41.3, 43.7, 59.5, 59.8, 69.6, 113.1, 114.9, 125.7, 126.7, 126.9, 127.1, 127.3, 127.6, 128.4, 128.7 (×3), 129.0, 129.1 (×2), 136.0, 138.3, 140.9, 145.7, 155.5, 157.4.

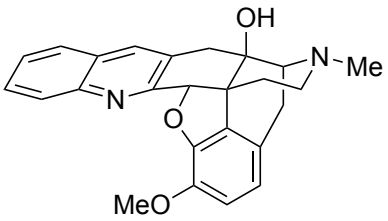
HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{30}H_{29}N_2O_2$: 449.22290, found: 449.22275.

To improve the solubility in aqueous solution for *in vivo* assay, (+)-**54** was converted into hydrochloric acid salt according to the known methods.[33]

Dihydrochloride

Anal. Calcd for $C_{30}H_{28}N_2O_2 \cdot 2HCl \cdot 4.5H_2O$: C, 59.80; H, 6.52; N, 4.65. Found: C, 59.66; H, 6.27; N, 4.60.

(4b*R*,8*S*,8a*R*,15b*S*)-1-Methoxy-7-methyl-5,6,7,8,9,15b-hexahydro-8a*H*-4,8-methanobenzofuro[3,2-c]pyrido[3,4-b]acridin-8a-ol ((+)-55)



A mixture of compound (+)-oxycodone (72.6 mg, 0.230 mmol), $MeSO_3H$ (20 µl, 0.309 mmol), and 2-aminobenzaldehyde (83.2 mg, 0.687 mmol) in EtOH (2.0 mL) was refluxed for 20 h under an argon atmosphere. After cooling to room temperature, the reaction was quenched by the addition of sat. $NaHCO_3$ aq. (5.0 mL) at 0 °C and extracted with $CHCl_3$ (30, 10, 10 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography [hexane/EtOAc/(28% NH_3 aq./MeOH = 1/9) = 1/1/0.1] to afford compound (+)-**55** (91.9 mg, quant.) as a pale red solid.

$[\alpha]_{589}^{20}$ = +560.1 (*c* = 0.306, $CHCl_3$).

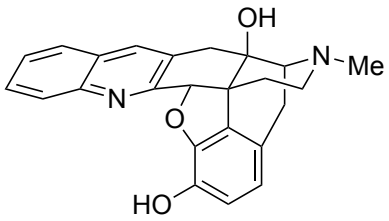
IR (KBr): 3442, 1607, 1502, 1277, 1054, 905, 790 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.82–1.91 (m, 1H), 2.38–2.46 (m, 2H), 2.45 (s, 3H), 2.50–2.58 (m, 1H), 2.70 (dd, *J* = 18.8, 6.4 Hz, 1H), 2.77 (d, *J* = 15.9 Hz, 1H), 2.89 (d, *J* = 15.9 Hz, 1H), 3.00 (d, *J* = 6.4 Hz, 1H), 3.31 (d, *J* = 18.8 Hz, 1H), 3.79 (s, 3H), 4.80 (br s, 1H), 5.70 (s, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 6.67 (d, *J* = 8.2 Hz, 1H), 7.47 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H), 7.64 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H), 7.68 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.81 (s, 1H), 8.15 (dd, *J* = 8.2, 1.4 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 22.4, 32.3, 36.5, 43.1, 45.2, 46.6, 56.8, 64.3, 71.8, 91.2, 114.6, 118.8, 125.8, 126.9, 126.9, 128.0, 128.1, 128.8, 129.6, 131.1, 136.1, 142.9, 145.6, 147.7, 154.2.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{25}H_{25}N_2O_3$: 401.18652, found: 401.18655.

(4b*R*,8*S*,8a*R*,15b*S*)-7-Methyl-5,6,7,8,9,15b-hexahydro-8a*H*-4,8-methanobenzofuro[3,2-c]pyrido[3,4-b]acridine-1,8a-diol ((+)-56)



To a solution of compound (+)-**55** (81.9 mg, 0.205 mmol) in CH_2Cl_2 (2.0 mL) was added 1.0 M BBr_3 in CH_2Cl_2 solution (2.5 mL, 2.5 mmol) at 0 °C under an atmosphere. After being stirred for 1 h at room temperature, the reaction was quenched by the addition of 28% NH_3 aq. (10 mL) at 0 °C. The reaction mixture was extracted with $CHCl_3$ (30, 20, 10, 10 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by preparative TLC [hexane/EtOAc/(28% NH_3 aq./MeOH = 1:9) = 0.5:1:0.1] to afford (+)-**56** (74.6 mg, 94%) as a colorless solid.

$[\alpha]_{589}^{20}$ = +548.7 (*c* = 0.236, $CHCl_3$).

IR (KBr): 3387, 3211, 1614, 1496, 1108 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 1.80–1.90 (m, 1H), 2.37–2.50 (m, 2H), 2.45 (s, 3H), 2.53–2.69 (m, 1H), 2.70 (dd, *J* = 18.8, 6.4 Hz, 1H), 2.78 (d, *J* = 16.0 Hz, 1H), 2.88 (d, *J* = 16.0 Hz, 1H), 3.01 (d, *J* = 6.4 Hz, 1H), 3.29 (d, *J* = 18.8 Hz, 1H), 5.70 (s, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 7.47 (dd, *J* = 7.8, 7.3 Hz, 1H), 7.62 (dd, *J* = 8.7, 7.3 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.82 (s, 1H), 8.09 (d, *J* = 8.7 Hz, 1H). The OH peaks were not observed.

^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 22.5, 32.0, 36.3, 43.2, 45.3, 46.8, 64.4, 71.8, 91.1, 117.5, 119.4, 125.0, 127.0, 128.0, 128.2, 128.4, 129.1, 129.2, 130.5, 136.6, 139.0, 144.0, 147.3, 154.2.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_3$: 387.17087, found: 387.17068.

To improve the solubility in aqueous solution for *in vivo* assay, (+)-**56** was converted into hydrochloric acid salt according to the known methods.[33]

Dihydrochloride

Anal. Calcd for $C_{24}H_{22}N_2O_3 \cdot 2HCl \cdot 4H_2O$: C, 54.24; H, 6.07; N, 5.27. Found: C, 54.29; H, 5.88; N, 5.32.

Pharmacology

Evaluation of compounds (*in vitro*)

Calcium mobilization assay[33]

Chinese hamster ovary K1 cells stably expressing human OX_1R or OX_2R were seeded in a 96-well-plate (10,000 cells/well) and then were incubated with 5% fetal bovine serum (FBS) / Dulbecco's modified Eagle medium (DMEM) at 37 °C for 48 h. After the incubation, cells were loaded with 5 μM fluorescent calcium indicator Fura 2-AM (Cayman Chemical, Michigan, USA) in Hank's balanced salt solution (HBSS) including 20 mM HEPES, 2.5 mM Probenecid, 0.04% Cremophor EL, and 0.1% BSA at 37 °C for 1 h. The cells were washed once and added with 75 μL of HBSS buffer. Then, cells were treated with 25 μL of various concentrations of test compounds or orexin A. The increase of the intracellular Ca^{2+} concentration was measured from the ratio of emission fluorescence of 510 nm by excitation at 340 or 380 nm using the Functional Drug Screening System 7000 system (Hamamatsu Photonics, Shizuoka, Japan). Sigmoidal concentration-response curves were produced by GraphPad Prism software (version 6.05; GraphPad Software Inc., La Jolla, CA, USA). Agonist stimulation of all test compounds was determined by normalizing all values to the maximum response (E_{max}) of sigmoidal curve produced by orexin A. The values of E_{max} and half maximal effective concentration (EC_{50}) for all test compounds were obtained from the average of 1–2 independent experiments. For comparison of the stereoisomers of **5j** and **33n**, the values of E_{max} and EC_{50} were obtained from the individual experiments (Figure 14 and Table 10).

Opioid receptor binding assay

Membrane suspension obtained from Human Embryonic Kidney (HEK) 293 cells stably expressing opioid receptors (MOR, DOR, or KOR) was incubated in 250 μL of assay buffer (50 mM Tris, 1 mM ethylenediaminetetraacetic acid (EDTA), 5 mM $MgCl_2$) with various concentrations of the tested compound and 2 nM tritiated opioid radioligand ([^{3}H]-DAMGO for the MOR, [^{3}H]-DPDPE for the DOR or [^{3}H]-U69,593 for the KOR: PerkinElmer Co., Ltd., Waltham, MA, USA) at 25 °C for 2 h with gentle shaking at 300 rpm. The reaction was terminated by filtration using Filtermat B glass filter (PerkinElmer Co., Ltd.) with a FilterMate cell harvester (PerkinElmer Co., Ltd.). The filters were washed four times with 50 mM Tris buffer, and then dried for 60 min at 60 °C. Finally, MeltiLex B/HS (PerkinElmer Co., Ltd.) was melted on the dried filter for 5 min at 90 °C. The radioactivity in the filter was determined with a Microbeta scintillation counter (PerkinElmer Co., Ltd.). Nonspecific binding was measured in the presence of 10 μM unlabeled opioid ligand

(DAMGO for the MOR, DPDPE for the DOR, U-69,593 for the KOR). Sigmoidal concentration-response curve and K_i values were calculated according to the Cheng–Prusoff equation using Prism software (version 8.4.3; GraphPad Software Inc., La Jolla, CA, USA).

G-protein dissociation assay

NanoBiT-based G-protein dissociation assay was performed as described previously with minor modifications (A. Inoue *et al. Cell*, **2019**, *177*, 1933.).[101] HEK293A cells were seeded in a 6-well culture plate at a concentration of 2 x 10^5 cells mL^{-1} (2 mL per well in DMEM supplemented with 10 % FBS, glutamine, penicillin, and streptomycin), one day before transfection. Plasmid transfection was performed in a 6-well plate with a mixture of 100 ng Gαo-Lg-encoding plasmid, 500 ng untagged Gβ1-encoding plasmid, 500 ng Sm-Gγ2 (C68S)-encoding plasmid, 200 ng GPCR-encoding plasmid (per well, hereafter). After 1 day culture, the transfected cells were harvested with 1 mL of 0.53 mM EDTA-containing Dulbecco's PBS (D-PBS), followed by addition of 2 mL the HEPES-containing HBSS. The cells were pelleted by centrifugation at 190 g for 5 min and resuspended in 2 mL of the 0.01% BSA- and 5 mM HEPES (pH 7.4)-containing HBSS (assay buffer). The cell suspension was seeded in a 96-well culture white plate (Greiner Bio-One, Kremsmünster, Austria) at a volume of 80 μL (per well hereafter) and loaded with 20 μL of 50 μM coelenterazine (Carbosynth, Illinois, USA) solution diluted in the assay buffer. After 2 h incubation with coelenterazine at room temperature, background luminescent signals were measured using a luminescent microplate reader (SpectraMax L, Molecular Devices). Test compound (6X, diluted in the assay buffer) was manually added to the cells (20 μL). Luminescent signals were measured 0-10 min after ligand addition and divided by the initial count. The ligand-induced signal ratio was normalized to that treated with vehicle.

Behavioral experiments (*in vivo*)

Chemicals

(*R*)-**5j**, (*S*)-**5j**, hydrochloride of (*R*)-**33n**, and cocaine (Takeda Pharmaceutical Co. Ltd., Tokyo, Japan) were dissolved in the solution composed of 5% DMSO, 5% Cremophor® EL (Kolliphor® EL), 20% PEG400, 70% Soluplus® (BASF, Ludwigshafen, Germany) aqueous solution. QWF and Cortistatin-14 were purchased from Tocris Bioscience (Bristol, UK). Hydrochlorides of (+)-TAN-67, (+)-KNT-127, (+)-**49**, (+)-**54**, (+)-**56**, and nalfurafine were dissolved in saline for *in vivo* experiments. QWF was dissolved in DMSO at 10 mM and diluted into PBS at 1.4 μg/μL (5.6 μg/mouse). Furthermore, this solution was diluted to the concentration of 0.75 and 0.25 μg/μL with 20% DMSO in PBS (3.0 and 1.0 μg/mouse).

Animals

Male ICR mice (25–35 g) were purchased from Japan SLC, Inc. (Hamamatsu, Japan) and housed at a room temperature of 23 °C with 12 h light/dark cycle. To obtain OX_1R KO mice homozygotes, male and female OX_1R KO mice homozygotes (gift from Prof. Masashi Yanagisawa) were crossed.

Conditioned place pleference (CPP) test

Conditioned place preference test was performed referring the previous reports as described previously.[106,107] The measuring vessel was divided into two compartments of equal size. The surface of one compartment was white and rough, and that of the other was black and smooth. The test involved three phases: pre-test session, conditioning session, and post-test session. In the pre-test session, mice that had not been treated with either test compounds or vehicle were placed in the measuring vessel, and the time spent by the mice in each compartment during 15 minutes was measured. Next conditioning sessions included six days, and test compounds and vehicle were alternately administered by s.c. injection for each day. After administration of test compounds, these animals were placed in the compartment opposite that in which they had spent the most time in the pre-test session for 1 h. On alternative days, these animals received vehicle and were placed in the other compartment for 1 h. In the next day, the post-test session was conducted under the same conditions as the pre-test session. The CPP score was defined as the time spent in the drug-associated box side after drug conditioning subtracted from the time spent there before drug conditioning

Evaluation of nociceptive behaviors by intrathecal administration

Before starting behavioral test, mice were habituated for 10 min in the clear plastic cage. Then, mice were intrathecally (i.t.) administrated saline or several dose of test compounds. 5 min after the injection, mice were recorded by digital video for 5 min. The number of nociceptive behaviors (scratching, biting, and licking) was counted for 5 min. In the inhibition experiment, QWF (1-5.6 μg/4 μL, i.t.) was given to mice 10 min before (+)-KNT-127 (30 μg/4 μL, i.t.) injection.

Evaluation of itch-like scratching behaviors

Before starting behavioral test, mice were habituated for 30 min in the clear plastic cage. Then, the mice were intradermally (i.d.) administrated saline or several dose of the test compounds. After the injection, mice were recorded by digital video for 30 min. Total counts or total time of scratching behaviors were collected for 30 min. In the inhibition experiment, nalfurafine (5 μg/kg, s.c.) was given to mice 20 min before (+)-**2a** (400 μg/50 μL, i.d.) injection.

Statistical analysis

All data are presented as the mean ± SEM. Statistical significance was determined by unpaired Student's t-test or one-way ANOVA followed by Tukey test in GraphPad Prism software (version 8.4.3; GraphPad Software Inc.).

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List of publications

1) **Iio, K.**; Kutsumura, N.; Nagumo, Y.; Saitoh, T.; Tokuda, A.; Hashimoto, K; Yamamoto, N.; Kise, R.; Inoue, A.; Mizoguchi, H.; Nagase, H. Synthesis of Unnatural Morphinan Compounds to Induce Itch-like Behaviors in Mice: Towards the Development of MRGPRX2 Selective Ligands. *Bioorg. Med. Chem. Lett.* **2022**, *56*, 128485.

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Supplementary list of publications

1) Watanabe, R.; Hu, Y.; **Iio, K.**; Yoneda, K.; Hattori, A.; Arai, A.; Kigoshi, H.; Kita, M. Specific protein-labeling and ligand-binding position analysis with amidopyrene probes as LDI MS tags. *Org. Biomol. Chem.* **2018**, *16*, 7883.

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