Design and synthesis of selective orexin 1 receptor antagonists with a morphinan skeleton and novel rearrangement reaction of morphinan skeleton

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List of abbreviation

1-SORA	selective orexin 1 receptor antagonist
Ac	acetyl
anal	analysis
aq	aqueous solution
BBB	blood-brain barrier
BNTX	7-benzylidenenaltrexone
Boc	tert-butoxycarbonyl
calcd	calculated
CAMDAS	Conformational Analyzer with Molecular Dynamics And Sampling
CHO cell	Chinese hamster ovary cell
CNS	central nervous system
conc	concentrated
CPM	cyclopropylmethyl
CPME	cyclopentyl methyl ether
dec	decomposition
DIPEA	diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DOR	δ opioid receptor
DORA	dual orexin receptor antagonist
eq.	equivalent
ESI	electrospray ionization
HATU	1-[bis(dimethylamino)-methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HEK cell	Human embryonic kidney cell
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectra
IC_{50}	inhibitory concentration 50%
i.p.	intraperitoneal

IR	infrared
KOR	κ opioid receptor
Me	methyl
MOR	μ opioid receptor
Mp	melting point
NMR	nuclear magnetic resonance
NOESY	nuclear overhauser enhanced spectroscopy
nor-BNI	nor-binaltorphimine
NTB	naltriben
NTI	naltrindole
OX_1R	orexin 1 receptor
OX_2R	orexin 2 receptor
OX-A	orexin-A
PDB	Protein Data Bank
Ph	phenyl
PLC	preparative thin layer chromatography
ppm	parts per million
quant	quantitative
rt	room temperature
s.c.	subcutaneously
SEM	standard error of the mean
temp.	temperature
THF	tetrahydrofuran
TM	transmembrane
Troc	2,2,2-trichloroethoxycarbonyl

1. General introduction

1.1 Overview of morphinan derivatives

Morphinan is a general name for compounds containing a heterocyclic skeleton **1** composed of A-, B-, C-, and D-rings (**Figure 1**). Natural products with the morphinan skeleton include morphine (**2**) and thebaine (**3**), which are extracted from the unripe seed pods of opium poppy.[1] These morphinan compounds with an oxygen-containing ring (E-ring) are called 4,5-epoxymorphinans. Morphinan derivatives typically bind with opioid receptors, which are classified into μ, δ, and κ opioid receptor types abbreviated MOR, DOR, and KOR, respectively.[2] For example, **2**, which shows agonistic activity for MOR, is a clinically used analgesic drugs. Naltrexone (**4**), a semi-synthetic opioid, shows antagonistic activity for MOR and is used as a therapeutic agent for drug addiction to morphine and their related drugs.

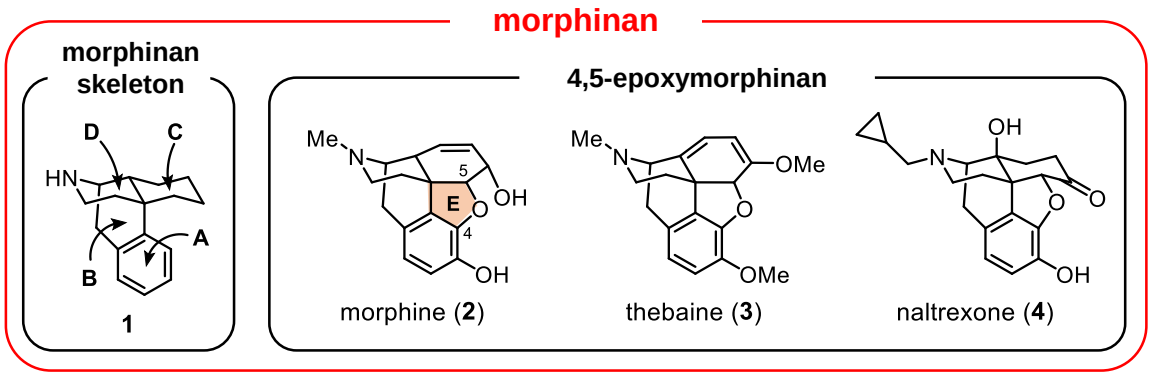


Figure 1. Structures of the morphinan skeleton and derivatives

Other examples include hydromorphone (**5**), oxymorphone (**6**), and levorphanol (**7**), which are MOR agonists used as opioid analgesics. Naloxone (**8**), an MOR antagonist, is used to improve respiratory depression caused by overdose of opioid analgesics (**Figure 2**). These drugs exert pharmacological effects by acting on opioid receptors in the central nervous system (CNS).

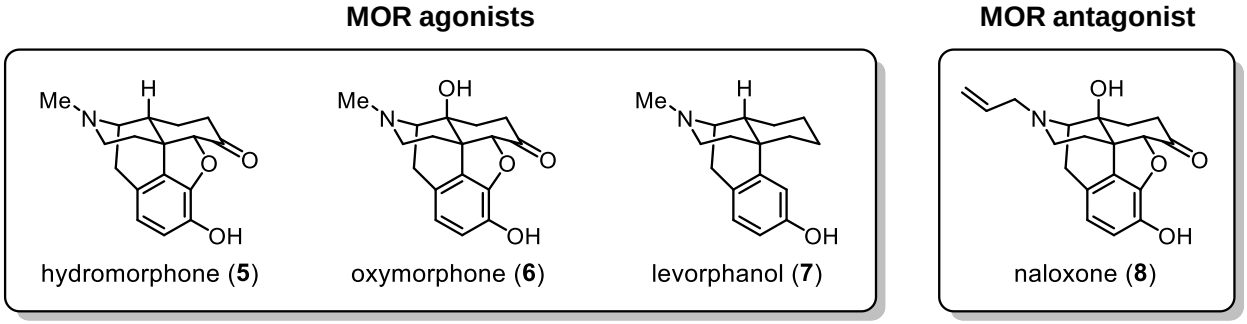


Figure 2. Structures of typical selective MOR ligands

Unlike drugs acting on the peripheral nervous system, CNS drugs must have proper physicochemical and pharmacokinetic properties to penetrate the blood–brain barrier (BBB).[3] Thus, morphinan derivatives can be applied to study and develop CNS drugs.

The unique structures of morphinan derivatives can be utilized in organic synthesis and medicinal chemistry. For instance, naltrexone (**4**) has four consecutive asymmetric centers and five reactive functional groups: 3-phenolic hydroxy, 4,5-epoxy, 6-carbonyl, 14-hydroxy, and 17-basic tertiary amino groups (**Figure 3**). These structural features enable to arrange the functional groups to proper three-dimensional directions, which are essential for an adequate interaction with target receptors and enzymes. Thus, **4** is often used as an starting material or intermediate for the synthesis of drugs with the morphinan skeleton.

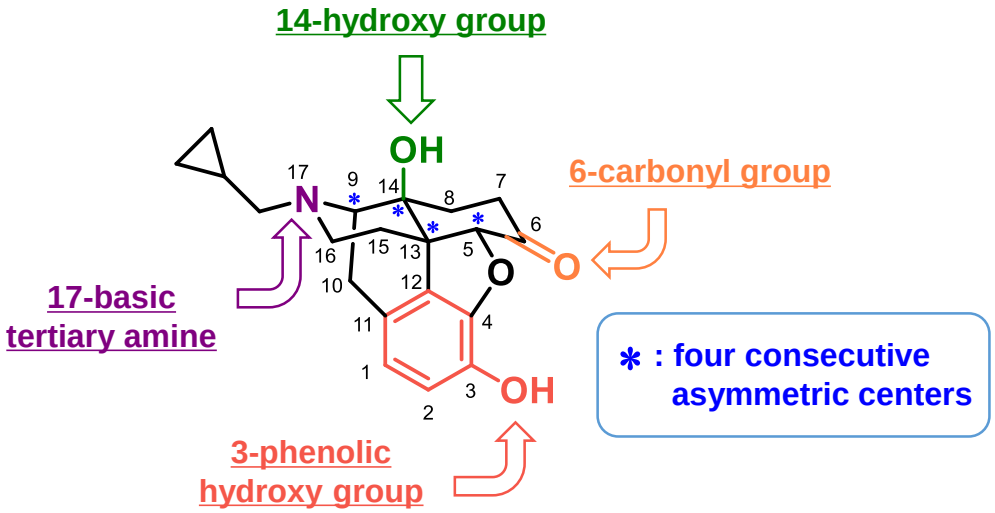


Figure 3. Structural features of **4**

For the above reasons, various researchers reported the conversion of the naltrexone into other morphinan derivatives.[4–10]

1.2 Application studies on morphinan derivatives

1.2.1 Type-selective opioid receptor ligands with a morphinan skeleton

Opioid drugs with the morphinan skeleton can act through three different types of opioid receptors. All clinically used opioids are MOR agonists, which are effective in alleviating chronic and cancer pains. However, MOR agonists cause serious side effects including nausea, respiratory depression, constipation, and dependence.[11] Therefore, selective DOR and KOR agonists are expected to be analgesic drugs without these side effects. From these research background, many selective DOR and KOR ligands with the morphinan skeleton have been reported to study the pharmacological actions of each opioid receptor types in detail. **Figures 4** and **5** show representative DOR and KOR ligands.

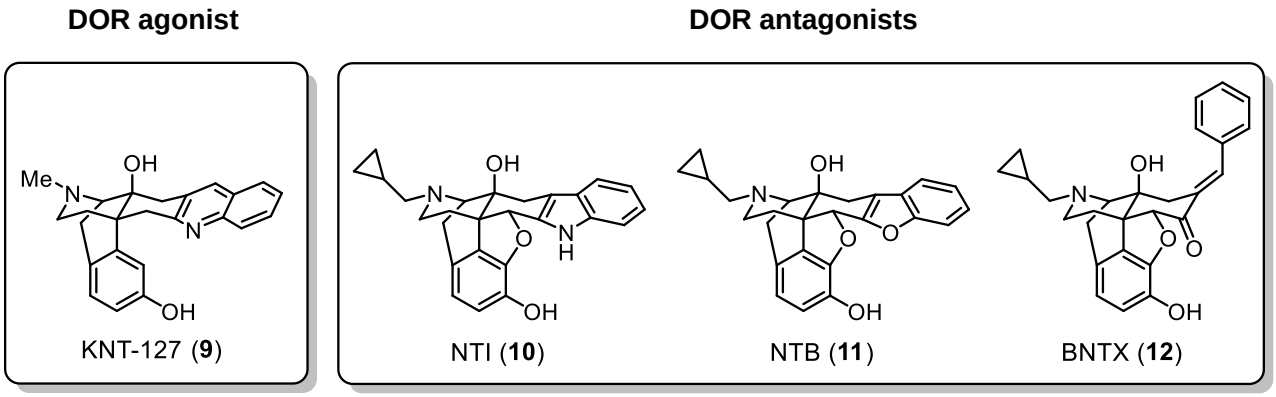


Figure 4. Structures of representative DOR ligands

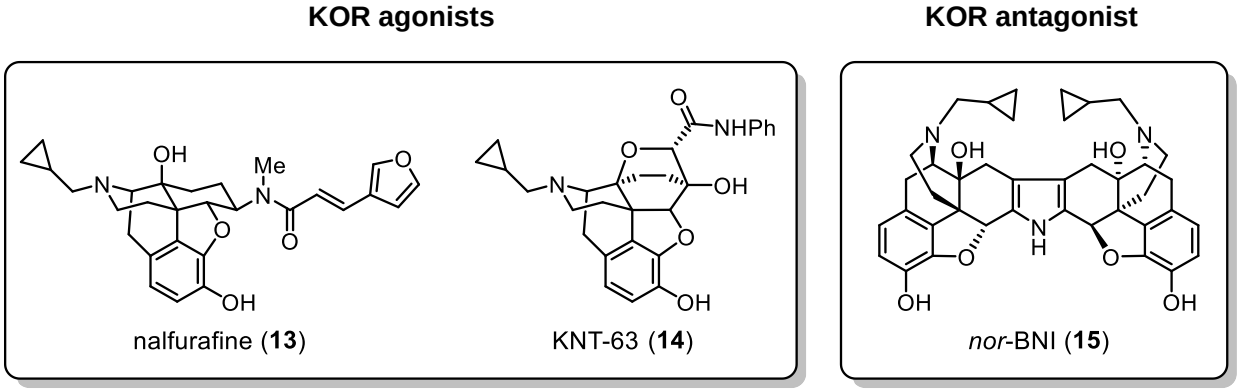


Figure 5. Structures of representative KOR ligands

KNT-127 (**9**)[4] is a selective DOR agonist that showed analgesic, anti-anxiety and anti-depressant effects in mice without convulsion and catalepsy, which are side effects of other representative DOR agonists. Naltrindole (NTI, **10**),[5] naltriben (NTB, **11**),[6] and 7-benzylidenenaltrexone (BNTX, **12**)[7] are DOR antagonists used in basic research of opioid receptors. Nalfurafine (**13**)[8] and KNT-63 (**14**)[9] are selective KOR agonists with analgesic and antipruritic effects. **13** is the only clinically used KOR agonist as a treatment drug of severe itch for kidney dialysis patients. *nor*-Binaltorphimine (*nor*-BNI, **15**)[10] is a KOR antagonist used in basic research of opioid receptors.

The *in vivo* effects of these ligands suggested the effective BBB permeability and the usefulness of the morphinan derivatives as the drug-likeness ligands.

1.2.2 Unique rearrangement reaction of morphinan derivatives

The intramolecular interactions in the morphinan derivatives are caused by the rigid skeleton to induce unusual rearrangement reactions (**Figure 6**).

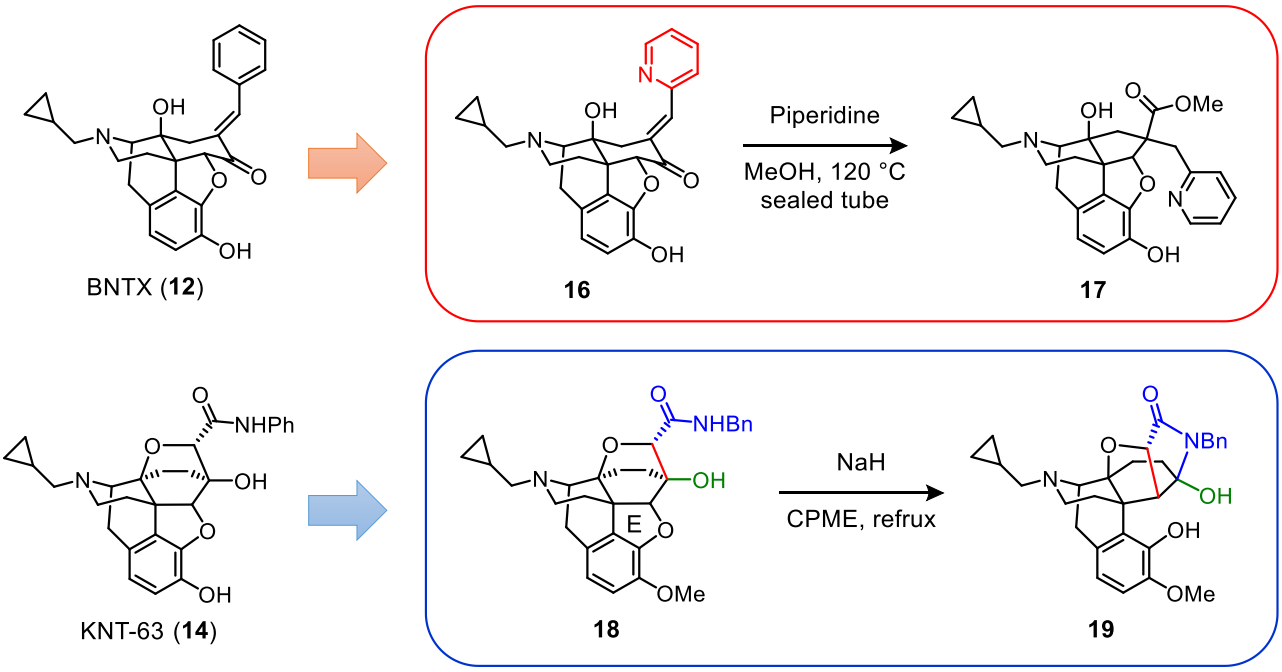


Figure 6. Unique rearrangement reaction of morphinan derivatives

For instance, a BNTX (**12**) derivative **16** underwent a Favorskii-type rearrangement reaction and produced a novel C-ring-contracted morphinan derivative **17**.[12] Compound **17** showed selective affinity for KOR, whereas BNTX derivatives typically showed selective DOR antagonistic activity.[12,13] Furthermore, an unusual rearrangement reaction of the KNT-63 derivative **18** afforded **19** with a new fused ring system.[14] The morphinan derivatives derived from **19** showed selective DOR agonistic activities, whereas the parent compounds KNT-63 derivatives are selective KOR agonists.[15] Similar to these examples, novel compounds obtained by rearrangement reactions of morphinan derivatives have the potential to be lead compounds for the development of type-selective opioid receptor ligands.

Based on this background, the author applied the morphinan skeleton to construct the ligands for other than opioid receptors. In this thesis, the design and synthesis of potent and highly selective orexin 1 receptor antagonists with a morphinan skeleton and their pharmacologies are discussed in Chapter 2. Furthermore, a novel rearrangement reaction of morphinan to arylmorphan skeletons was discovered. Therefore, the pharmacological activity of the rearrangement products and their derivatives are discussed in Chapter 3. Finally, conclusions are summarized in Chapter 4.

2. Design and synthesis of potent and highly selective orexin 1 receptor antagonists with a morphinan skeleton and their pharmacologies

2.1 Introduction of orexin receptors

Orexin (orexin-A and -B[16a], also known as hypocretin-1 and -2[16b], respectively) is a pair of lateral hypothalamic neuropeptides originally identified as the endogenous ligands for orphan G-protein-coupled receptors, orexin 1 receptor (OX_1R) and orexin 2 receptor (OX_2R). OX_1R is a Gq-coupled receptor with a selective affinity for orexin-A, whereas OX_2R is a Gq or Gi/o-coupled receptor with nearly equal affinity for both orexin peptides (**Figure 7**).[17] An essential role of the orexin system in sleep/wakefulness regulation was first demonstrated by discovering that OX_2R-deficient dogs[18a] and prepro-orexin knockout mice[18b] exhibited symptoms highly similar to the sleep disorder narcolepsy/cataplexy. On the other hand, OX_1R/OX_2R double-null mice exhibit a severe narcoleptic phenotype indistinguishable from that seen in prepro-orexin knockout mice, whereas OX_2R-null mice show a somewhat milder narcolepsy phenotype. Moreover, OX_1R-null mice exhibit no appreciable sleep/wakefulness-related phenotype, suggesting that OX_2R rather than OX_1R plays a predominant role in sleep/wake regulation and that an intact OX_2R-mediated signaling is sufficient to prevent the symptoms of narcolepsy/cataplexy.[19]

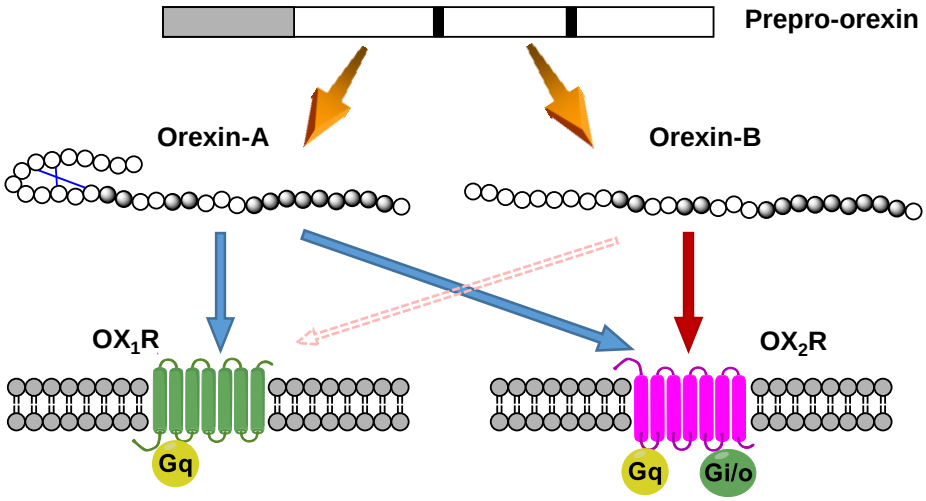


Figure 7. Overview of orexins and orexin receptors

This pharmacological activity of orexin receptors (OXRs) encouraged many researchers to investigate the possibility of developing non-peptidic orexin antagonists to elucidate the role of OXRs, especially in the context of sleep/wake cycle.[20] As a results, selective OX_1R antagonists (1-SORAs), such as SB-334867 (**23**),[21] SB-408124 (**24**),[22] SB-674042 (**25**),[22] and GSK-1059865 (**26**),[23] as well as selective OX_2R antagonists, such as TCS-OX2-29 (**27**),[24] and MK-3697 (**28**),[25] along with dual OX_1R/OX_2R antagonists (DORAs), such as suvorexant (**20**),[26] almorexant (**21**),[27] and SB-649868 (**22**),[28] were reported (**Figure 8**).

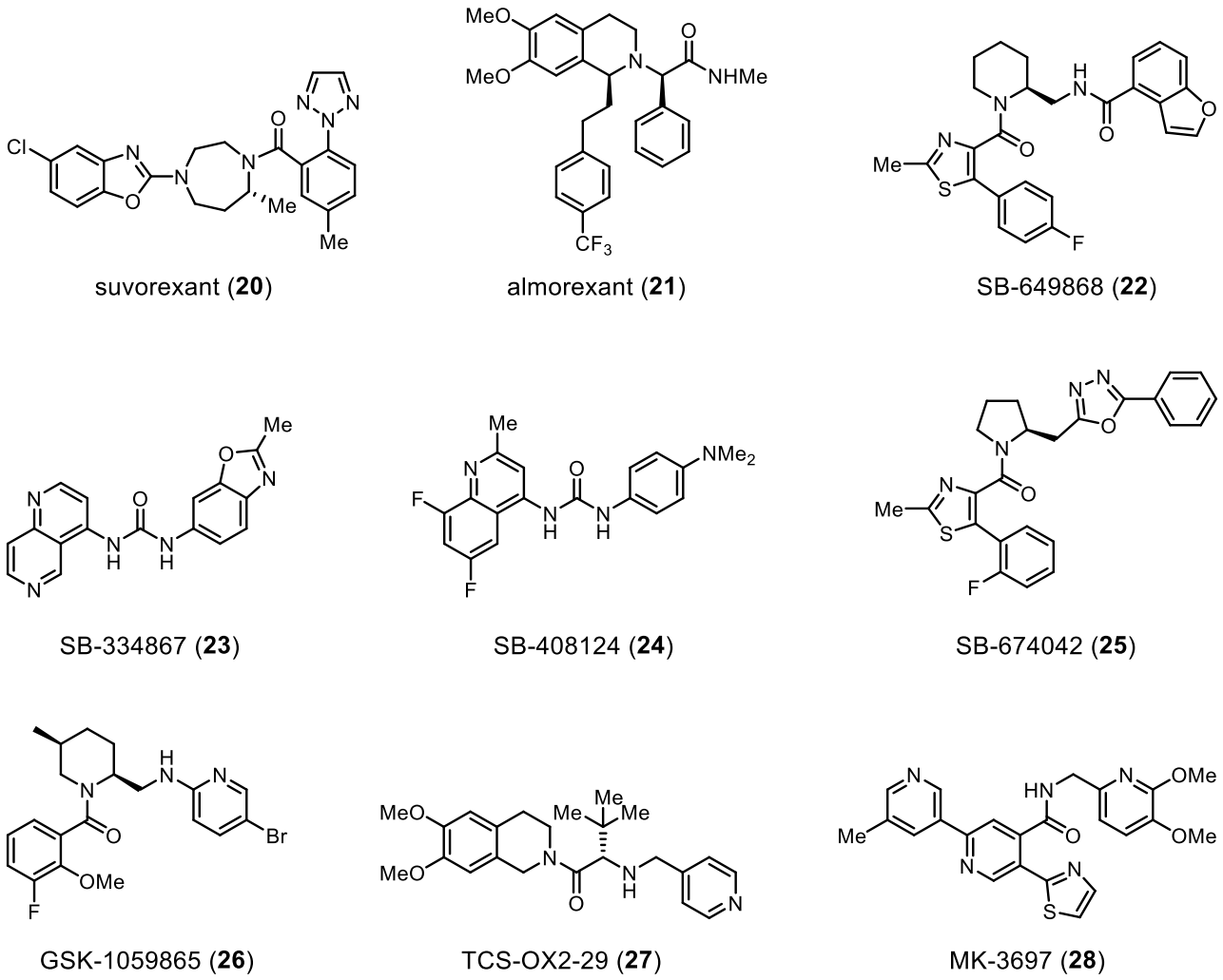


Figure 8. Structures of the dual orexin receptor antagonists **20**–**22**, selective OX_1R antagonists **23**–**26**, and selective OX_2R antagonists **27** and **28**.

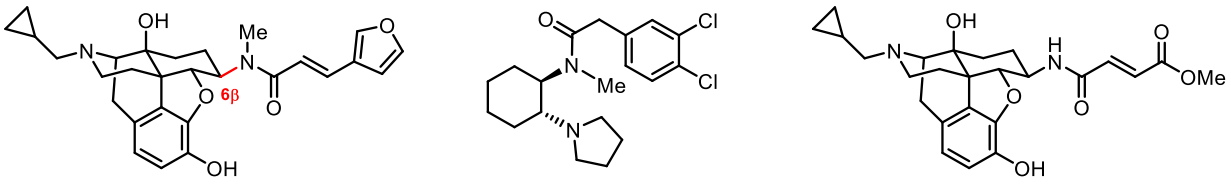
Recently, Merck released **20** (DORA) in Japan and the United States as a treatment for insomnia.[26] As mentioned, the relationship between OXRs and "sleep" was actively studied, and many OXRs antagonists were investigated for developing sleep-inducing agents.

OXRs were found to be involved in regulating a wide range of behaviors other than sleep/wake, e.g., hedonic feeding behavior and reward seeking.[29a,30] Especially, OX_1R was found to regulate reward-related behaviors. Several studies indicate that orexin neurons play a part in the behavioral presentation of addiction to morphine,[31a,32] cocaine,[31b,c] amphetamine,[33] heroin,[34] nicotine,[35] ethanol,[36] and cannabinoids.[37] Blockade of the OX_1R using 1-SORAs **23**[38] and **26**[23] were found to attenuate the expression of conditioned place preference induced by cocaine and amphetamine in rats. Furthermore, 1-SORA **23** was found to prevent morphine withdrawal in mice.[39] Therefore, 1-SORAs can be effective drugs for the treatment of addiction.

Despite this widely reported effect of 1-SORAs, still this is no clinical use of it, because of its low selectivity for OX_1R and/or undesired pharmacokinetic profiles.[40] Accordingly, it is required to develop 1-SORAs with a novel skeleton different from existing ligands. Under such background, a study on the subject by Nagase *et al*. revealed that nalfurafine (**13**), a KOR agonist, showed affinity for OX_1R.[48] Herein, the author attempted to develop new 1-SORAs by structural optimization of the morphinan derivative **13**.

2.2 Discovery of the 1-SORAs with a morphinan skeleton

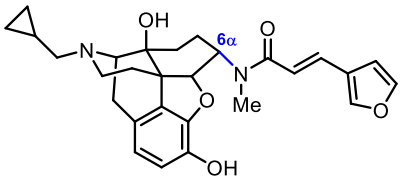
Coexpression of orexin peptide and dynorphin (**31**, endogenous KOR agonist) with excitatory and inhibitory effects, respectively, within the same vesicle in orexin-producing neurons was reported.[41] Moreover, research on the heterodimerization of the OX_1R and KOR was conducted.[42] These reports shed further light on the potential colocalization function of the corresponding two peptides with opposite effects,[41,43] which were shown in the endogenous peptide and exogenous alkaloids. For example, 1-SORA **23** attenuated drug addiction,[31b,35b,44] and most KOR agonists represented by U-50488H (**29**, **Figure 9**)[45] induced severe aversion (e.g., psychotomimetic effect) and dysphoria,[46] which was an ample reason to eliminate the derivatives of **29** at an early stage of the clinical trials. Intriguingly, among all KOR agonists, only **13** caused no addiction or drug aversion and was released as an antipruritic agent for kidney dialysis patients in Japan in 2009.[8,47] Currently, several researchers are investigating why only **13** caused no aversion. Here, it was postulated that **13** binds with the OX_1R–KOR dimer to prevent aversion, whereas **29** binds with pure KOR to produce an intrinsic aversive effect. Furthermore, it was hypothesized that, if **13** could show affinity for the receptor heterodimer, it would bind with OX_1R in addition to KOR.



H-Tyr-Gly-Gly-Phe-Leu-Arg-Arg-X

dynorphine (**31**)

dynorphine A: X = Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln-OH
dynorphine B: X = Gln-Phe-Lys-Val-Val-Thr-OH



32

Figure 9. Structures of the selective KOR agonists **13** and **29**, MOR antagonist **30**, endogenous KOR agonist **31**, and nalfurafine 6-α-isomer **32**.

On the basis of these assumptions, **13** was evaluated with a calcium transient assay in Chinese hamster ovary (CHO) cells expressing human OX_1R or OX_2R to examine the possible activity for OXRs. The results indicated that **13** showed specific antagonistic activity for OX_1R (OX_1R, K_i = 250 nM; OX_2R, not active).[48] Interestingly, only **13** showed antagonistic activity for the OX_1R contrary to the MOR antagonist, β-funaltrexamine (**30**);[49] the selective DOR agonist, KNT-127 (**9**); the antagonist, NTI (**10**); and the selective KOR antagonist, *nor*-BNI (**15**). Furthermore, the KOR agonist, **29**,[50] without morphinan skeleton showed no affinity for OX_1R. The structure of **13** contains a tyrosine moiety similar to the N-terminal structure of dynorphin (**31**), while **29** does not. The fact that only **13**, with a structure partially similar to the **31**, showed activity for OX_1R might be a clue for clarifying the role of the aforementioned coexistence of dynorphin and orexin.

The antagonists illustrated in **Figure 8** have flexible structures that consist of aromatic or alicyclic rings connected to each other with amide or urea bonds. In contrast, **13** has a characteristic rigid morphinan skeleton with a tyrosine moiety, which is partially similar to the **31** structure. Thus, it can be assumed that a structural modification of **13** would easily improve its antagonistic activity and selectivity for OX_1R. To the best of my knowledge, no OXRs ligand with a morphinan skeleton has been reported. First results of evaluating the OX_1R antagonistic activity of the nalfurafine derivatives showed that the 6-α-amide isomer **32** had almost no activity for OXRs.[51] Therefore, in this study, the structure of **13** was modified by focusing on 6-β-amide isomers.

2.3 Design and synthesis of morphinan derivatives and pharmacological evaluation of their derivatives

2.3.1 Design of morphinan derivatives based on the structure of nalfurafine

The objectives of the structural optimization of **13** for developing novel 1-SORAs (**Figure 10**) are as follows: (1) to improve the antagonistic activity while maintaining specific selectivity for OX_1R, (2) to eliminate the affinity for opioid receptors to remove side effects derived from opioid receptors, and (3) to develop water-soluble compounds for investigating pharmacological effects *in vivo*. In particular, the elimination of the affinity for opioid receptors is important because the parent compound **13** is a potent KOR agonist.

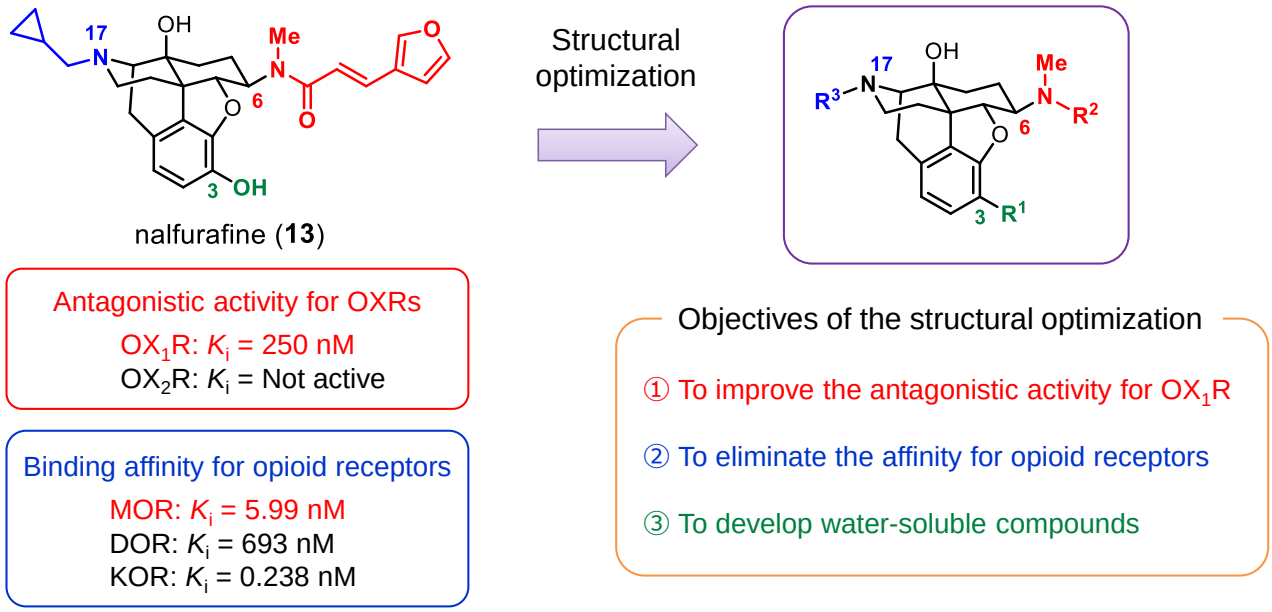


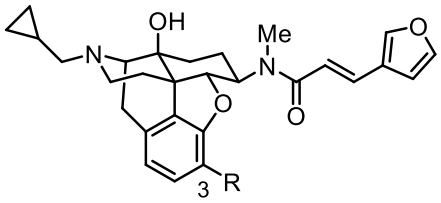
Figure 10. Pharmacological effects of nalfurafine (**13**) and objectives of the structural optimization

The binding mode of **13** with opioid receptors was previously reported.[47,52] The essential functional groups are the 3-phenolic hydroxy group, 6-amide side chain, and 17-basic nitrogen substituent denoted R_1, R_2, and R_3, respectively, (**Figure 10**). Hence, the optimization of **13** was performed by focusing on these essential functional groups.

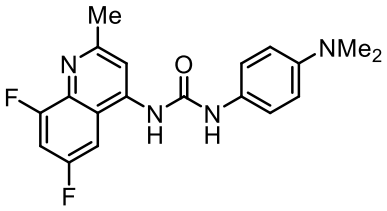
2.3.2 Structural optimization to obtain potent and highly selective OX_1R antagonists

First, the modification of functional group at the 3-position in **13** was performed to investigate the influence of the 3-phenolic hydroxy group. 3-Methyl ether derivative **33** and 3-dehydroxy derivative **34** were synthesized using conventional method.[53] The assay results of these compounds for OXRs antagonism are listed in **Table 1**.

Table 1. Assay results of nalfurafine derivatives (**13**, **33**, and **34**) and SB-408124 (**24**) for OXRs antagonism



13 (R = OH)
33 (R = OMe)
34 (R = H)



SB-408124 (**24**)

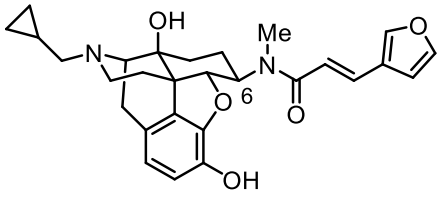
Compounds	R	K_i (nM)[a]	
		OX_1R	OX_2R
nalfurafine (**13**)	OH	250 ± 37.1	–[b]
33	OMe	22.5 ± 2.56	–[b]
34	H	1245 ± 132	–[b]
SB-408124 (**24**)		18.9 ± 0.688	2070 ± 482

[a] K_i values represent the mean ± SEM. These values were calculated by Cheng–Prusoff equation using EC_{50} values of OX-A and IC_{50} values of nalfurafine derivatives. IC_{50} values were obtained from at least three independent calcium assays. [b] K_i value was not calculated. IC_{50} value was over 10,000 nM (cut off value) or was not obtain from concentration–response curve.

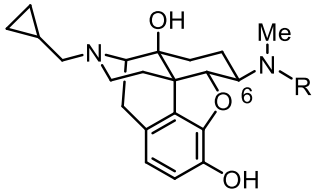
The results showed that 3-methyl ether **33** had a potent antagonistic activity for OX_1R 11 times higher than that of nalfurafine (**13**). Furthermore, **33** exhibited antagonistic activity for OX_1R equivalent to that of SB-408124 (**24**) but did not exhibit antagonistic activity for OX_2R. On the other hand, the 3-dehydroxy derivative **34** showed very weak activity for OXRs. These results reflect the necessity of the oxygen atom at the 3-position for the expression of antagonistic activity for OXRs and that the methylation of the 3-phenolic hydroxy group was important for enhancing the antagonistic activity.

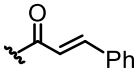
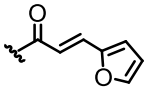
Next, the 3-furylacryl group on the 6-side chain in **13** was converted to benzyl, phenylacryl, and 2-furylacrylamide groups.[47a,53b] The derivatives **35–37** did not improve the antagonistic activities (**Table 2**). Then, the methyl ether at the 3-position and 3-furyl acrylamide group at the 6-position were fixed for optimization of the 17-basic nitrogen substituent.

Table 2. Assay results of nalfurafine derivatives (**35**–**37**) for OXRs antagonism



nalfurafine (**13**)

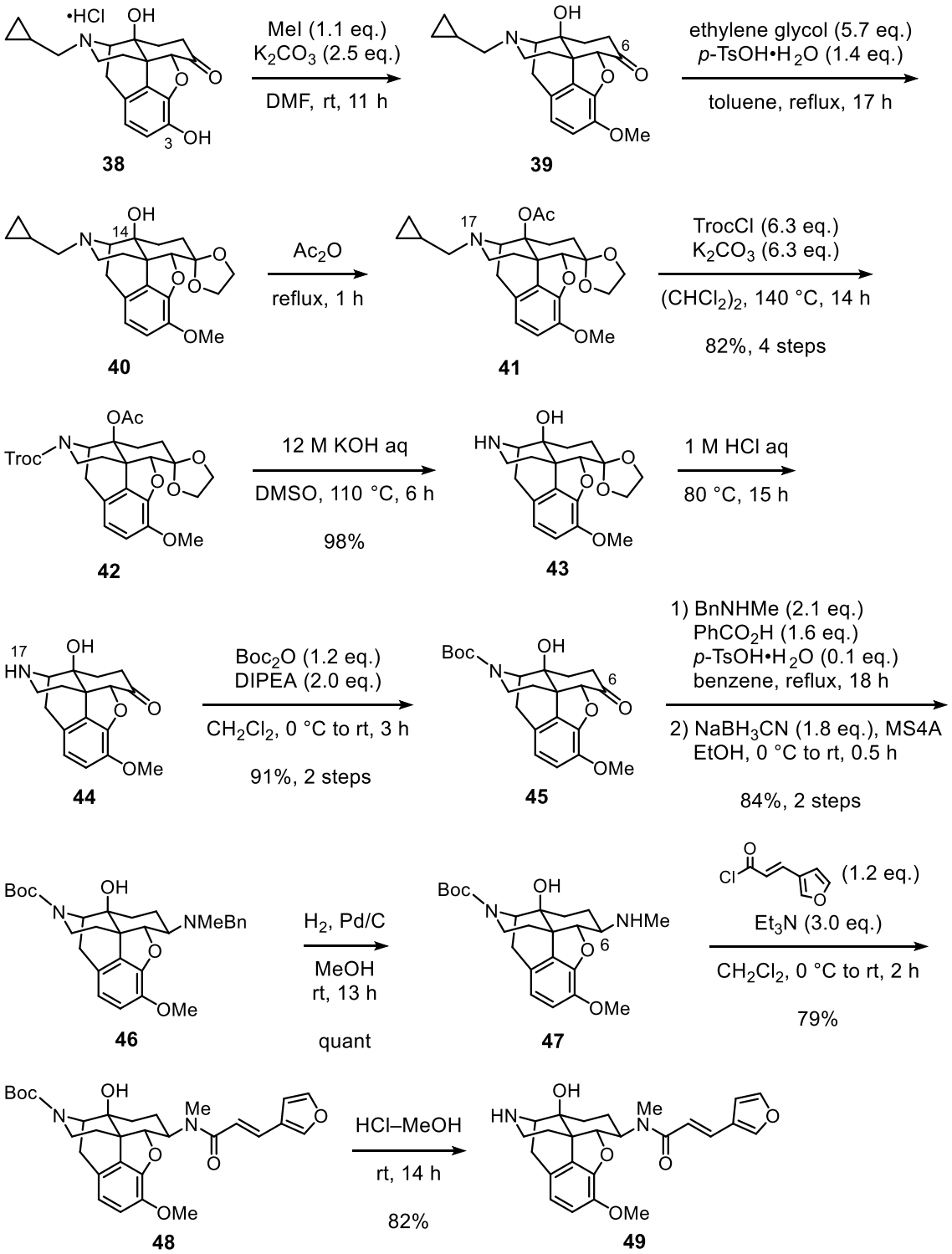


Compounds	R	K_i (nM)[a]	
		OX_1R	OX_2R
nalfurafine (**13**)		250 ± 37.1	–[b]
35		–[b]	–[b]
36		389 ± 88.8	–[b]
37		751 ± 178	–[b]

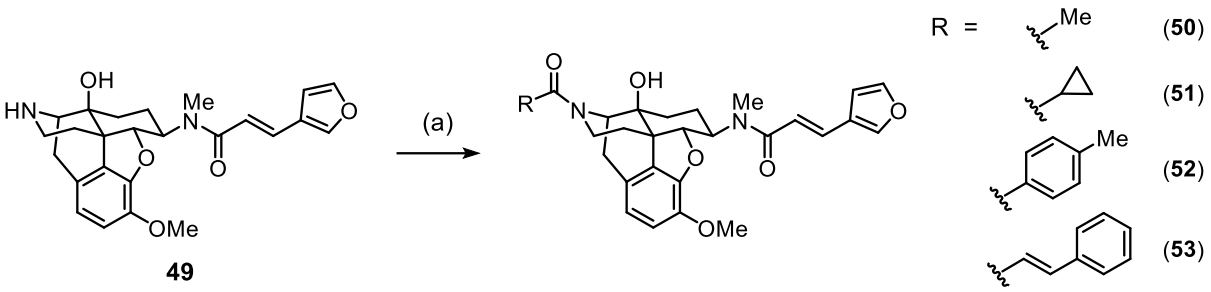
[a] K_i values represent the mean ± SEM. These values were calculated by Cheng–Prusoff equation using EC_{50} values of OX-A and IC_{50} values of nalfurafine derivatives. IC_{50} values were obtained from at least three independent calcium assays. [b] K_i value was not calculated. IC_{50} value was over 10,000 nM (cut off value) or was not obtain from concentration–response curve.

To further improve the antagonistic activity for OX_1R, the replacement of the 17-cyclopropylmethyl (CPM) group in **33** with various acyl-substituents was investigated (**Scheme 1**). The phenolic hydroxy group in naltrexone hydrochloride (**38**) was methylated, and the 6-ketone group was protected as 1,3-dioxolane. This was followed by an acetylation of the 14-hydroxy group under refluxing in acetic anhydride. The CPM group of the resulting acetate was exchanged for a 2,2,2-trichloroethoxycarbonyl (Troc) group at 140 °C with an excess amount of TrocCl to produce carbamate **42**. The carbamate and the acetyl groups in **42** were hydrolyzed with aqueous potassium hydroxide at 110 °C. After removing the 1,3-dioxolane group from **43**, the resultant secondary amine was protected with the *tert*-butoxycarbonyl (Boc) group to give high yield of a ketone **45**.

The imine formation of **45** with *N*-benzylmethylamine, followed by a reduction with sodium cyanoborohydride afforded β-amine **46**. Hydrogenolysis of **47** and amidation of the resulting amine with (*E*)-3-(furan-3-yl)acryloyl chloride resulted in 17-carbamate derivative **48**.[54] Deprotection of the Boc group in **48** resulted in the key intermediate **49**, which was converted to 17-amide derivatives **50–53** (**Scheme 2**).



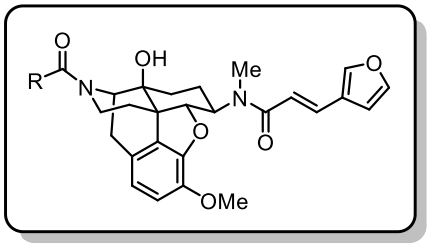
Scheme 1. Synthesis of key intermediate **49** from naltrexone hydrochloride (**38**)

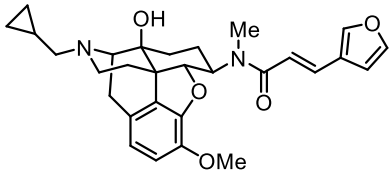


Scheme 2. Synthesis of 17-carbonyloxy compounds **50**–**53**. (a) Ac_2O, pyridine, rt, 97% for **50**; cyclopropanecarbonyl chloride, pyridine, 0 °C to rt, 82% for **51**; *p*-toluoyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt, 85% for **52**; cinnamoyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt, 77% for **53**.

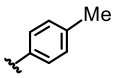
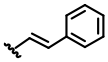
Table 3 shows the antagonistic activities of the obtained 17-carbamate and amide derivatives for OXRs. The carbamate derivative **48** and amide derivatives **51**–**53** exhibited potent antagonistic activities for OX_1R compared with 17-alkyl derivative **33**. However, 17-amide derivatives, especially **52,** tended to decrease the selectivity for OX_1R.

Table 3. Assay results of the 17-carbamate and amide derivatives for OXRs antagonism



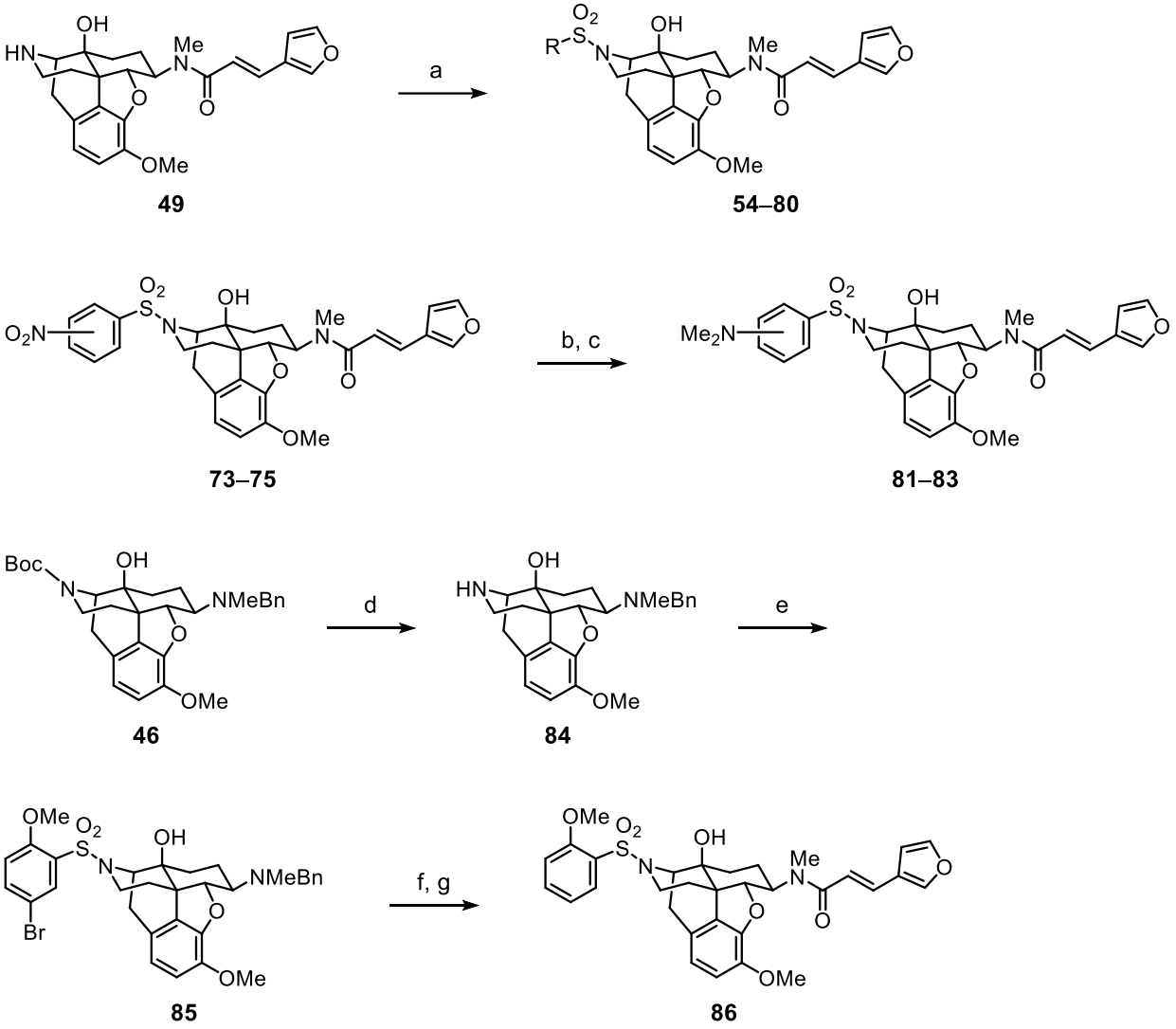


33

Compounds	R	K_i (nM)[a]	
		OX_1R	OX_2R
33		22.5 ± 2.56	–[b]
48		4.15 ± 0.235	–[b]
50		541 ± 59.9	–[b]
51		12.0 ± 0.715	–[b]
52		14.0 ± 1.98	725 ± 41.5
53		14.0 ± 2.20	–[b]

[a] K_i values represent the mean ± SEM. These values were calculated by Cheng–Prusoff equation using EC_{50} values of OX-A and IC_{50} values of nalfurafine derivatives. IC_{50} values were obtained from at least three independent calcium assays. [b] K_i value was not calculated. IC_{50} value was over 10,000 nM (cut off value) or was not obtain from concentration–response curve.

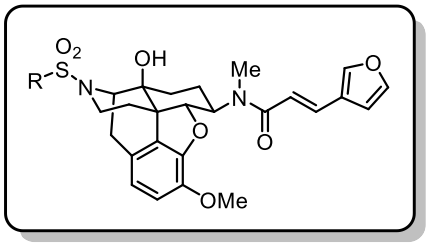
Next, 17-sulfonamide derivatives were synthesized (**Scheme 3**). The syntheses of the alkyl and aryl sulfonamide derivatives **54**–**80** were attained by sulfonamidation of the amine **49**. Dimethylamino-benzenesulfonamide derivatives **81**–**83** were synthesized from the corresponding nitrobenzenesulfonamide derivatives **73**–**75** by nitro group reduction and reductive amination with paraformaldehyde. Deprotection of the Boc group in **46** and sulfonamidation with 5-bromo-2-methoxybenzenesulfonyl chloride produced sulfonamide **85**. The benzyl group and bromine atom were removed by hydrogenation followed by amidation with (*E*)-3-(furan-3-yl)acyloyl chloride to produce high yield of *o*-methoxybenzenesulfonamide derivative **86**.

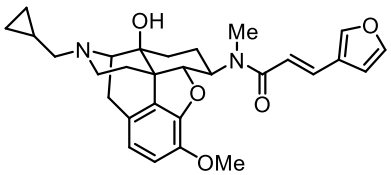


Scheme 3. Synthesis of 17-sulfonamide derivatives. (a) RSO_2Cl, Et_3N, CH_2Cl_2, 0 °C to rt, 66–99%; (b) $SnCl_2$, conc HCl, CH_2Cl_2, EtOH, 40 °C; (c) paraformaldehyde, $NaBH_3CN$, AcOH, 40 °C, 73–90% (2 steps); (d) HCl–MeOH, rt, 99%; (e) 5-bromo-2-methoxybenzenesulfonyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt, 84%; (f) H_2, Pd/C, MeOH, rt; (g) (*E*)-3-(furan-3-yl)acyloyl chloride, Et_3N, CH_2Cl_2, 0 °C to rt, 77% (2 steps).

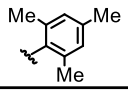
The activities of the 17-alkyl and aryl sulfonamide derivatives **54**–**57** were evaluated (**Table 4**). The alkyl sulfonamide derivatives **54** and **55** were found to exhibit potent antagonistic activities for OX_1R compared with the 17-alkyl derivative **33**. The aryl sulfonamide derivatives **56** and **57** also exhibited potent antagonistic activities. Among these, the tri-substituted aryl sulfonamide derivative **57** exhibited more potent antagonistic activities for OX_1R. As the introduction of substituents onto the aromatic ring was effective in improving the activity, the effects of introducing various halogen groups, electron-withdrawing groups, and electron-donating groups were subsequently examined (**Table 5**). Almost all substituted aryl sulfonamide derivatives showed higher activities compared with non-substituted aryl sulfonamide derivative **56**. The observed tendency for the highest potency for the *o*-substituted derivatives suggested that the *o*-substituent group might introduce a steric hindrance to the B-ring of the morphinan skeleton to direct the phenyl ring into an adequate ligand-binding site for OX_1R. Furthermore, small differences were observed in the antagonistic activities of mono-substituted derivatives, independent of the electron-donating (Me and NMe_2, except for OMe) or electron-withdrawing (CF_3, CN, and NO_2) character of the substituents. These results suggested that the effect of the steric hindrance was more important for improving the antagonistic activities compared with the electronic effects.

Table 4. Assay results of 17-sulfonamide derivatives **54–57** for OXRs antagonism



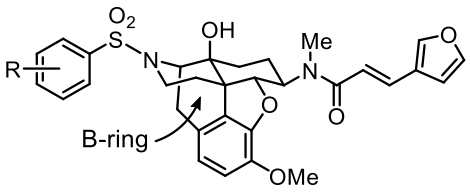


33

Compounds	R	K_i (nM)[a]	
		OX_1R	OX_2R
33		22.5 ± 2.56	–[b]
54		12.1 ± 1.14	–[b]
55		5.94 ± 0.237	–[b]
56		8.14 ± 0.606	–[b]
57		4.16 ± 0.696	–[b]

[a] K_i values represent the mean ± SEM. These values were calculated by Cheng–Prusoff equation using EC_{50} values of OX-A and IC_{50} values of nalfurafine derivatives. IC_{50} values were obtained from at least three independent calcium assays. [b] K_i value was not calculated. IC_{50} value was over 10,000 nM (cut off value) or was not obtain from concentration–response curve.

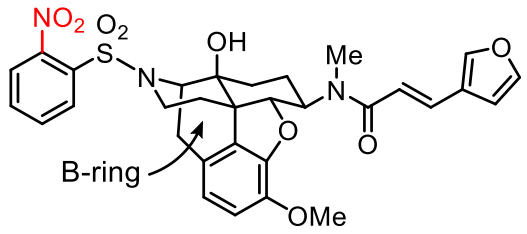
Table 5. Assay results of mono-substituted aryl sulfonamide derivatives for OXRs antagonism



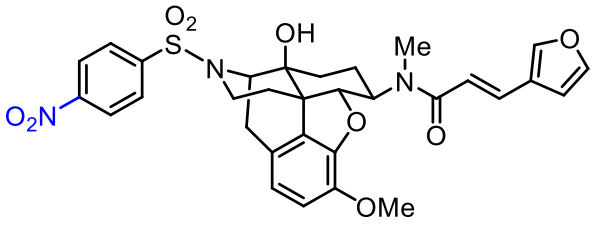
R	K_i (nM)[a]		R	K_i (nM)[a]		R	K_i (nM)[a]	
	OX_1R	OX_2R		OX_1R	OX_2R		OX_1R	OX_2R
2-F (**58**)	2.07 ± 0.222	–[b]	2-CF_3 (**67**)	2.05 ± 0.209	–[b]	2-NMe_2 (**81**)[c]	1.92 ± 0.190	–[b]
3-F (**59**)	7.60 ± 0.570	–[b]	3-CF_3 (**68**)	6.19 ± 0.934	–[b]	3-NMe_2 (**82**)[c]	7.25 ± 0.557	–[b]
4-F (**60**)	4.05 ± 0.471	–[b]	4-CF_3 (**69**)	12.6 ± 0.790	–[b]	4-NMe_2 (**83**)[c]	12.9 ± 1.26	–[b]
2-Cl (**61**)	1.93 ± 0.138	–[b]	2-CN (**70**)	1.96 ± 0.359	–[b]	2-OMe (**86**)	6.37 ± 0.921	–[b]
3-Cl (**62**)	3.47 ± 0.274	–[b]	3-CN (**71**)	7.30 ± 0.748	–[b]	3-OMe (**76**)	2.44 ± 0.388	–[b]
4-Cl (**63**)	5.13 ± 1.02	–[b]	4-CN (**72**)	13.9 ± 0.451	–[b]	4-OMe (**77**)	8.99 ± 1.22	–[b]
2-Br (**64**)	2.10 ± 0.184	–[b]	2-NO_2 (**73**)	1.81 ± 0.142	–[b]	2-Me (**78**)	1.70 ± 0.194	–[b]
3-Br (**65**)	2.27 ± 0.204	–[b]	3-NO_2 (**74**)	5.05 ± 0.343	–[b]	3-Me (**79**)	2.98 ± 0.364	–[b]
4-Br (**66**)	6.21 ± 0.655	–[b]	4-NO_2 (**75**)	12.5 ± 1.26	–[b]	4-Me (**80**)	5.85 ± 0.794	–[b]

[a] K_i values represent the mean ± SEM. These values were calculated by Cheng–Prusoff equation using EC_{50} values of OX-A and IC_{50} values of nalfurafine derivatives. IC_{50} values were obtained from at least three independent calcium assays. [b] K_i value was not calculated. IC_{50} value was over 10,000 nM (cut off value) or was not obtain from concentration–response curve. [c] Its HCl salt was assayed.

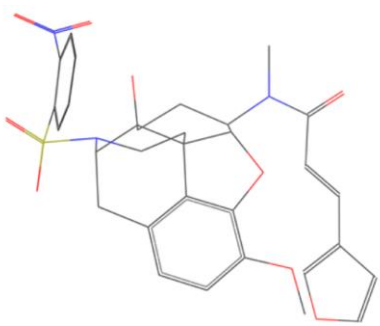
Next, the conformation of the aryl sulfonamide derivatives was analyzed to investigate the steric effects of substituent groups. Conformational analyses of an *o*-nitrobenzenesulfonamide derivative **73** and a *p*-nitrobenzene sulfonamide derivative **75** were performed using Conformational Analyzer with Molecular Dynamics And Sampling (CAMDAS).[55] **Figure 11** shows that the spatial arrangements of *o*-nitro and *p*-nitrobenzene sulfonamides were quite different in the most stable conformers of **73** and **75**. Further, the superimpositions of the most stable conformers upon lower energy conformers within 2.0 kcal/mol from the most stable indicated that the *o*-nitrobenzenesulfonamide group of **73** could be widely spread out, whereas the *p*-nitrobenzenesulfonamide group of **75** was spatially restricted. These results also suggested the *o*-substituent group might cause a steric hindrance to the B-ring of the morphinan skeleton.



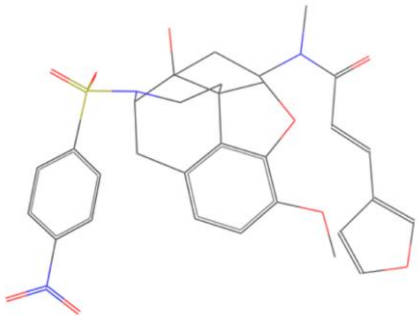
73, K_i = 1.81 nM (OX_1R)



75, K_i = 12.5 nM (OX_1R)

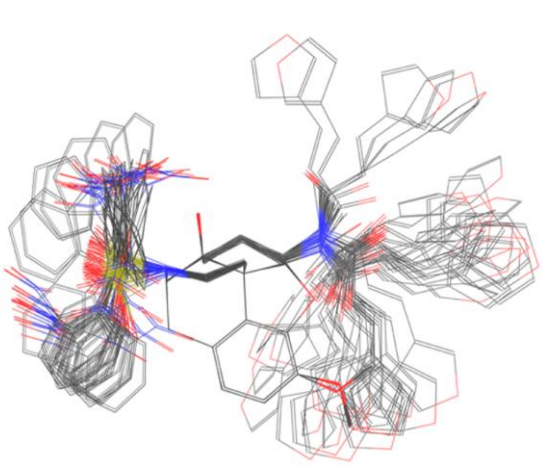


144.31 kcal/mol



139.28 kcal/mol

within 2.0 kcal/mol



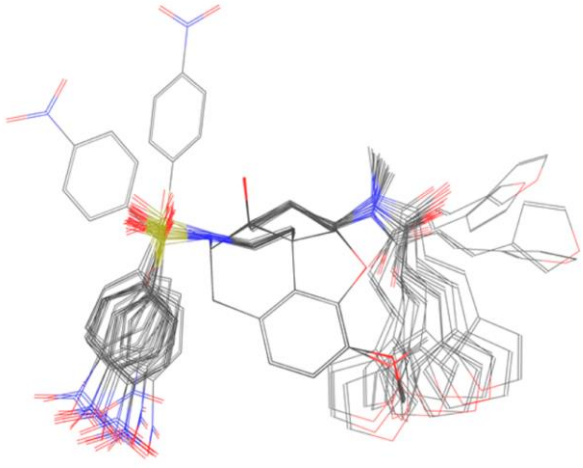
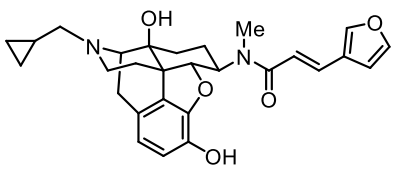


Figure 11. The most stable conformations and the superimpositions of the low-energy conformers of **73** and **75** (Adapted with permission from *J. Med. Chem.* **2017**, *60*, 1018-1040. Copyright 2017 American Chemical Society.)

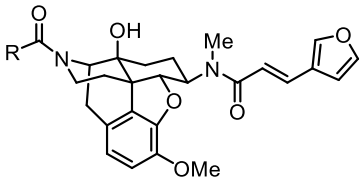
2.3.3 Opioid receptor binding assay of morphinan derivatives

As nalfurafine derivatives that can improve the antagonistic activity for OX_1R were obtained, opioid receptor binding assay was performed next. 17-Amide and sulfonamide derivatives **51**, **56**, and **83** with a 3-methoxy group showed extremely lower affinity for opioid receptors compared with that of **13** (**Table 6**). These results were in accordance with previous studies, which reported that the morphinan derivatives protecting the 3-phenolic hydroxy group markedly decrease the affinity for opioid receptors.[56] On the other hand, although the 17-carbamate derivative **48** contains the 3-methoxy group, it showed a relatively weak affinity for the KOR. Additionally, a sulfonamide derivative **87** with a 3-phenolic hydroxy group was synthesized by demethylation of **83** and binding affinity of **87** for opioid receptors was evaluated (**Scheme 4**). As expected, the phenolic compound **87** showed affinity for opioid receptors, whereas the methyl ether **83** did not.

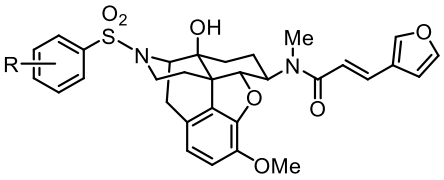
Table 6. Assay results of the nalfurafine (**13**), morphinan derivatives **48**, **51**, **56**, **83**, and **87**



nalfurafine (**13**)



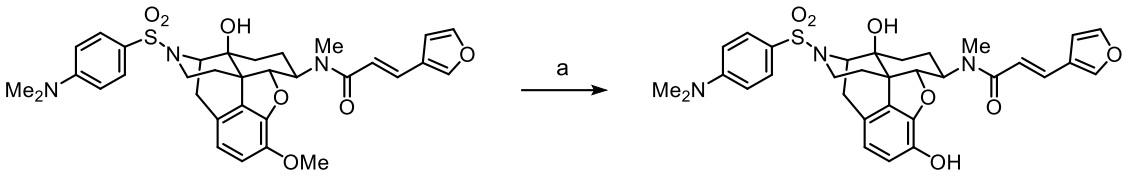
48 (R = O*t*Bu)
51 (R = cyclopropyl)



56 (R = H)
83 (R = 4-NMe_2)

Compounds	K_i (nM)[a]		
	μ ([^{3}H]DAMGO)	δ ([^{3}H]DPDPE)	κ ([^{3}H]U-69,593)
nalfurafine (**13**)[b]	5.99 (3.4–10.6)	693 (223–2154)	0.238 (0.147–0.385)
48	>1000	>1000	184
51	>1000	>1000	>1000
56	>1000	>1000	>1000
83[b]	>1000	>1000	>1000
87[c]	971 (654–1441)	>1000	200 (35–295)

[a] K_i values with 95% confidential intervals were obtained from radioligand-based competitive receptor binding assay using CHO cells stably expressing human μ, δ, or κ opioid receptors. [b] Its HCl salt was assayed. [c] Its $MeSO_3H$ salt was assayed.



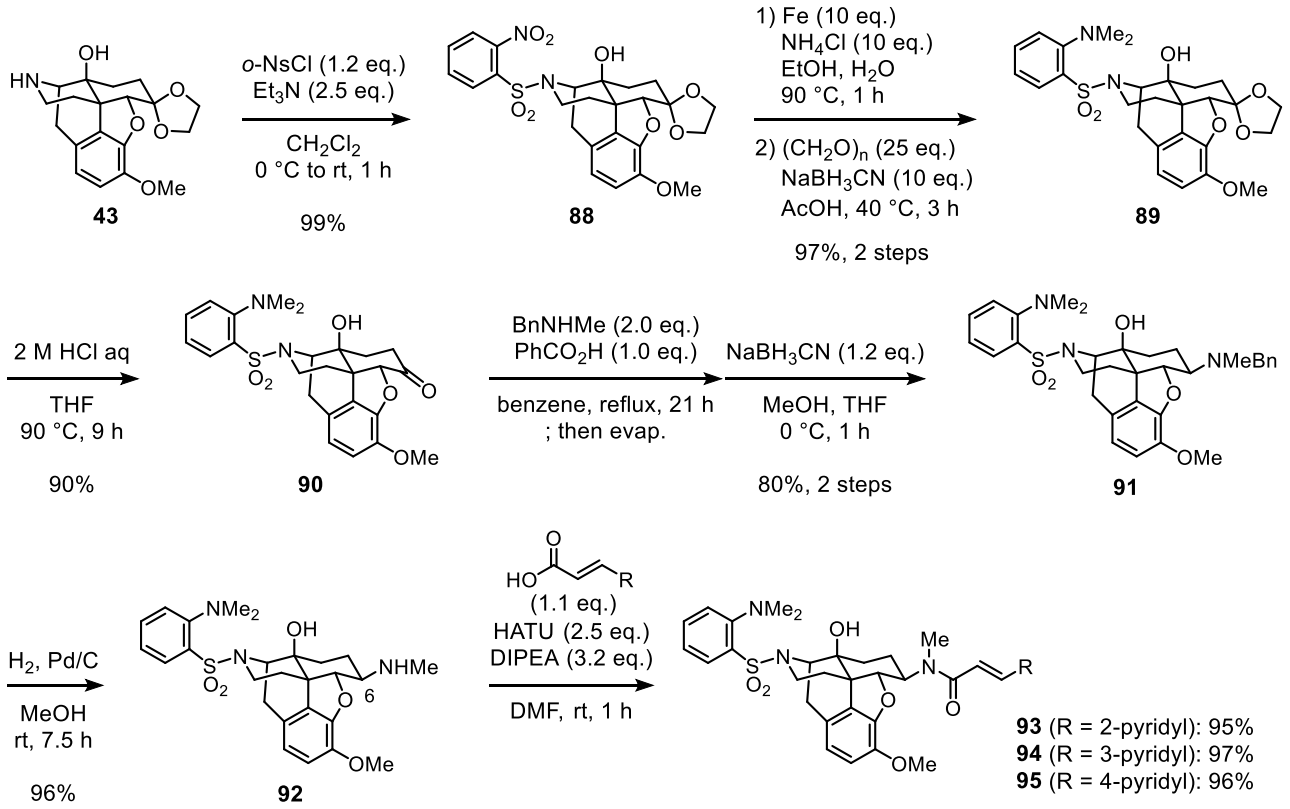
83 **87**

Scheme 4. Demethylation of the 3-methoxy group in **83**. (a) BBr_3, CH_2Cl_2, –78 °C to rt, 51%.

These results suggest that, although the structures of the obtained 17-amide and sulfonamide derivatives with the 3-methoxy group were derived from the potent KOR agonist **13**, they could eliminate the serious side effects caused by opioid receptors (i.e., addiction, constipation, and respiratory depression from MOR; catalepsy from DOR; and sedation and aversion from KOR).

2.3.4 Structural optimization for the development water-soluble compounds

As described earlier, nalfurafine derivatives, which showed the potent and highly selective antagonistic activity for OX_1R without affinity for opioid receptors, were obtained. Subsequently, obtaining water-soluble compounds was investigated. Salt formations of **81** with hydrochloric, sulfuric, methanesulfonic, and 10-camphorsulfonic acids were performed. However, these salts were not soluble in water or saline. Therefore, introduction of an additional basic amine moiety to **81** to obtain a diprotonated salt was studied (**Scheme 5**).

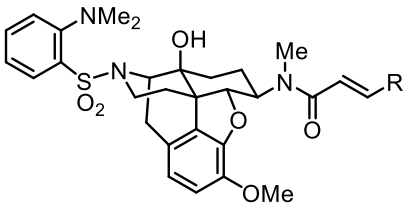


Scheme 5. Synthesis of pyridyl derivatives **93**–**95**

The sulfonamide derivative **88** was attained by sulfonamidation of the amine **43**. The reduction of the nitro group of **88** followed by reductive amination with paraformaldehyde and removal of the 1,3-dioxolane group of **89** resulted in ketone **90**. The imine formation of **90** with *N*-benzylmethylamine followed by reduction with sodium cyanoborohydride yielded 6β-amine **91**. The hydrogenation of **91** and amidation of the resulting amine **92** with corresponding acrylic acid derivatives afforded 2-, 3-, and 4-pyridyl derivatives **93**, **94**, and **95**, respectively.

Table 7 shows the antagonistic activities of the obtained pyridyl derivatives for OXRs. The 2-pyridyl derivative **93** exhibited the most potent antagonistic activity in all the obtained morphinans. On the other hand, the 3-pyridyl derivative **94** showed weaker antagonistic activity for OX_1R compared with **93**. Furthermore, the 4-pyridyl derivative **95** exhibited little antagonistic activity for OX_1R. These results indicate that the basic nitrogen in the pyridine ring played an important role in the expression of antagonistic activities for OX_1R.

Table 7. Assay results of the pyridyl derivatives **93**–**95** for OXRs antagonism



Compounds	R	K_i (nM)[a]	
		OX_1R	OX_2R
81[c]		1.92 ± 0.190	–[b]
93		1.36 ± 0.174	–[b]
94		42.3 ± 2.25	–[b]
95		–[b]	–[b]

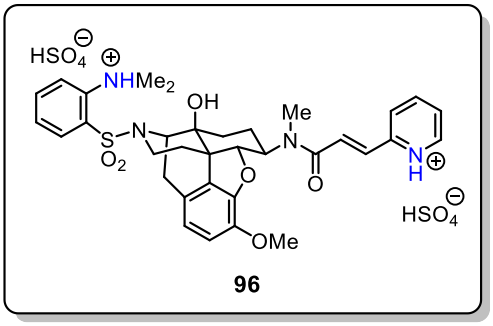
[a] K_i values represent the mean ± SEM. These values were calculated by Cheng–Prusoff equation using EC_{50} values of OX-A and IC_{50} values of nalfurafine derivatives. IC_{50} values were obtained from at least three independent calcium assays. [b] K_i value was not calculated. IC_{50} value was over 10,000 nM (cut off value) or was not obtain from concentration–response curve. [c] Its HCl salt was assayed.

In addition, salt formations of the 2-pyridyl derivative **93** with various acids were carried out. The result showed that a dihydrosulfate **96**, which could be easily dissolved in water (solubility: 10 mg in 50 μL of saline) was obtained. Furthermore, **96** did not show affinity for opioid receptors (K_i > 1000 nM for MOR, DOR, and KOR). Therefore, this nalfurafine derivative **96** was the required final compound, which has highly selective and potent antagonistic activity for OX_1R, no affinity for opioid receptors, and good water solubility.

2.3.5 Evaluation of attenuation effects on morphine withdrawal

The effect of **96** on morphine (**2**) withdrawal was evaluated. Generally, opioid abuse develops opioid-induced physical dependence, and discontinuation of opioid intake induces severe opioid withdrawal in animals and humans. **Table 8** and **Figure 12** show that naloxone (**8**)-precipitated withdrawal in mice with chronic morphine injection induced several classic behavioral signs of morphine withdrawal. Among these signs, naloxone-precipitated body weight loss, diarrhea, and jumping behavior were significantly suppressed by intraperitoneal (i.p.) pretreatment with **96** before naloxone challenge injection, indicating that the 1-SORA **96** attenuated the expression of naloxone-precipitated morphine withdrawal. Therefore, the synthesized novel 1-SORA would be a useful tool for understanding the physiological significance of the orexinergic system and may be useful as a treatment for drug dependence.

Table 8. Effect of **96** on naloxone-precipitated withdrawal signs in morphine-dependent mice[a]



96

withdrawal signals	positive animals/total animals	
	saline	**96**
jumping	9/13	2/13**
body shakes	9/13	7/13
ptosis	6/13	3/13
forepaw tremor	12/13	11/13
rearing	12/13	11/13

[a] The morphine dose was increased progressively from 8 to 45 mg/kg, subcutaneously (s.c.) over a period of 5 days. Saline or **96** was intraperitoneally (i.p.) injected 30 min before naloxone treatment. Withdrawal signs were induced by naloxone (3 mg/kg, s.c.) 2 h after the final morphine treatment and then were observed for 60 min. **$p < 0.01$ by χ^2 test.

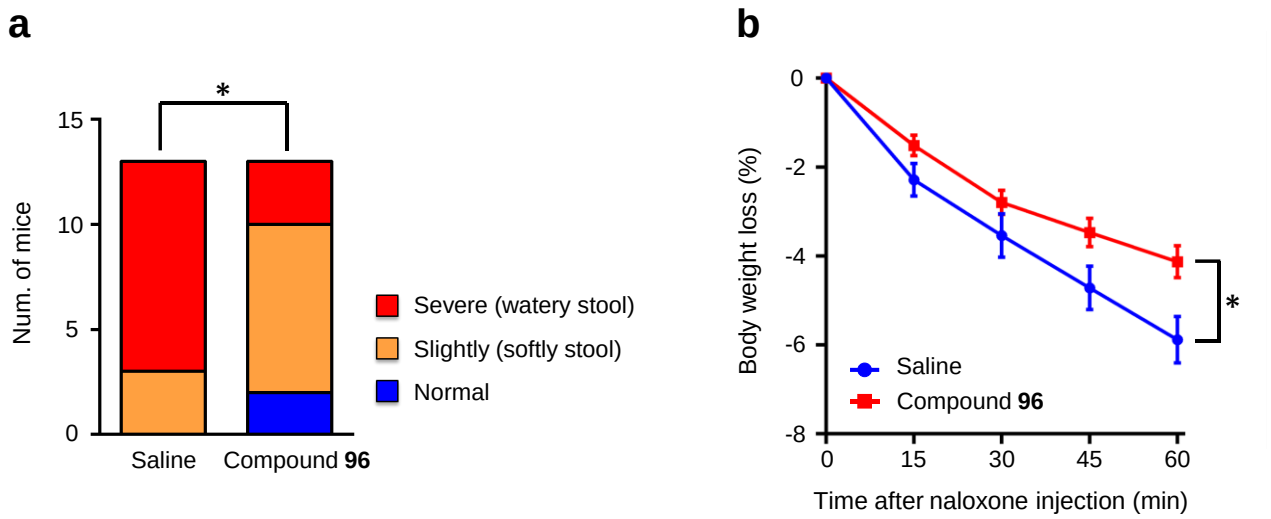


Figure 12. Morphine withdrawal signs were suppressed by **96**. Naloxone-precipitated diarrhea (a) and body weight loss (b) were suppressed by pretreatment with **96** (10 mg/kg, i.p.) at 30 min before naloxone challenge injection. **96** was dissolved in saline. Each point in (b) represents the mean body weight loss of 13 mice with SEM: *p < 0.05 by χ^2 test (a) or two-way ANOVA (b). (Adapted with permission from *J. Med. Chem.* **2017**, *60*, 1018-1040. Copyright 2017 American Chemical Society.)

2.4 Analysis of binding mode between the morphinan derivatives and OX_1R

Recently, two X-ray crystal structures of the human OX_1R bound to suvorexant (**20**) (PDB code 4ZJ8) and SB-674042 (**25**) (PDB code 4ZJC) were reported.[57] By use of these X-ray structures, the binding mode of **93** with OX_1R was investigated by molecular docking calculations. The resulting binding mode of **93** is shown in **Figure 13**. The morphinan skeleton of **93** was suggested to be located in the middle of the ligand-binding site of OX_1R. The 17-*o*-dimethylaminobenzene group of **93** was oriented toward transmembrane helixes 2 and 3 (TM2 and TM3) to form hydrophobic interactions with A102 (TM2), V106 (TM2), W112 (loop between TM2 and TM3), I122 (TM3), and P123 (TM3) of OX_1R. On the other hand, the 2-pyridyl group of **93** was oriented to the opposite direction and made hydrophobic interactions with F219 (TM5), F220 (TM5), I314 (TM6), and I319 (TM6). The compound **93** also used an ether oxygen of the morphinan skeleton and a nitrogen atom of the 2-pyridyl group to form two hydrogen bonds with N318 (TM6) of OX_1R. This configuration might indicate the importance of the nitrogen atom on the pyridyl group for interactions with OX_1R.

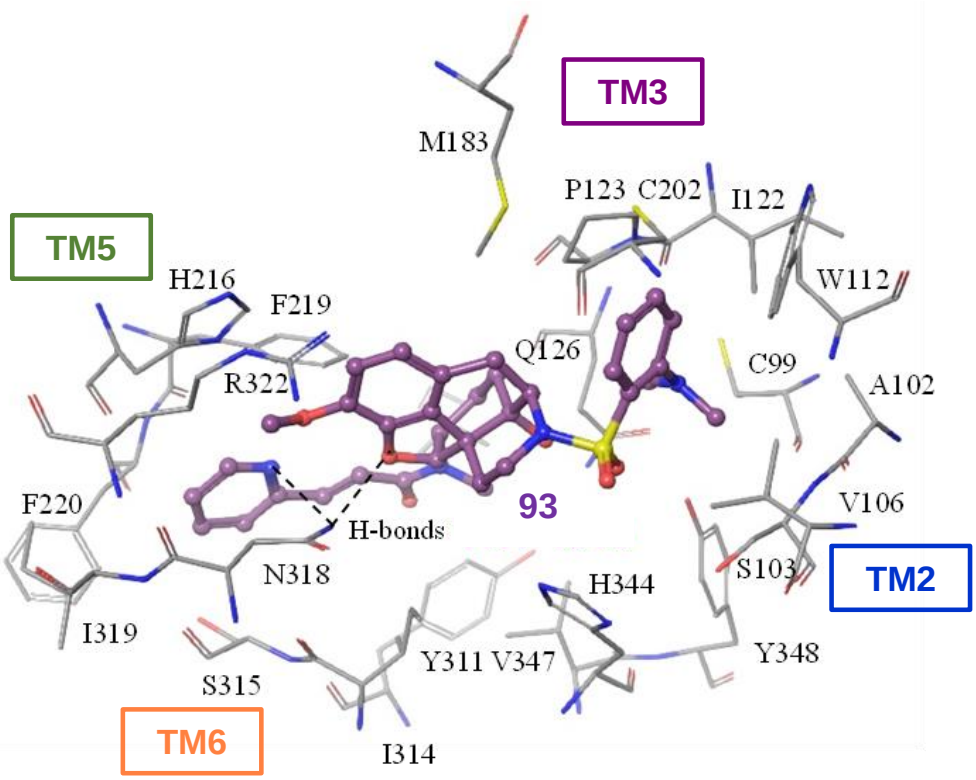


Figure 13. Binding mode of **93** with the OX_1R determined by docking procedure. Hydrogen-bonding interactions are indicated by dashed lines. (Adapted with permission from *J. Med. Chem.* **2017**, *60*, 1018-1040. Copyright 2017 American Chemical Society.)

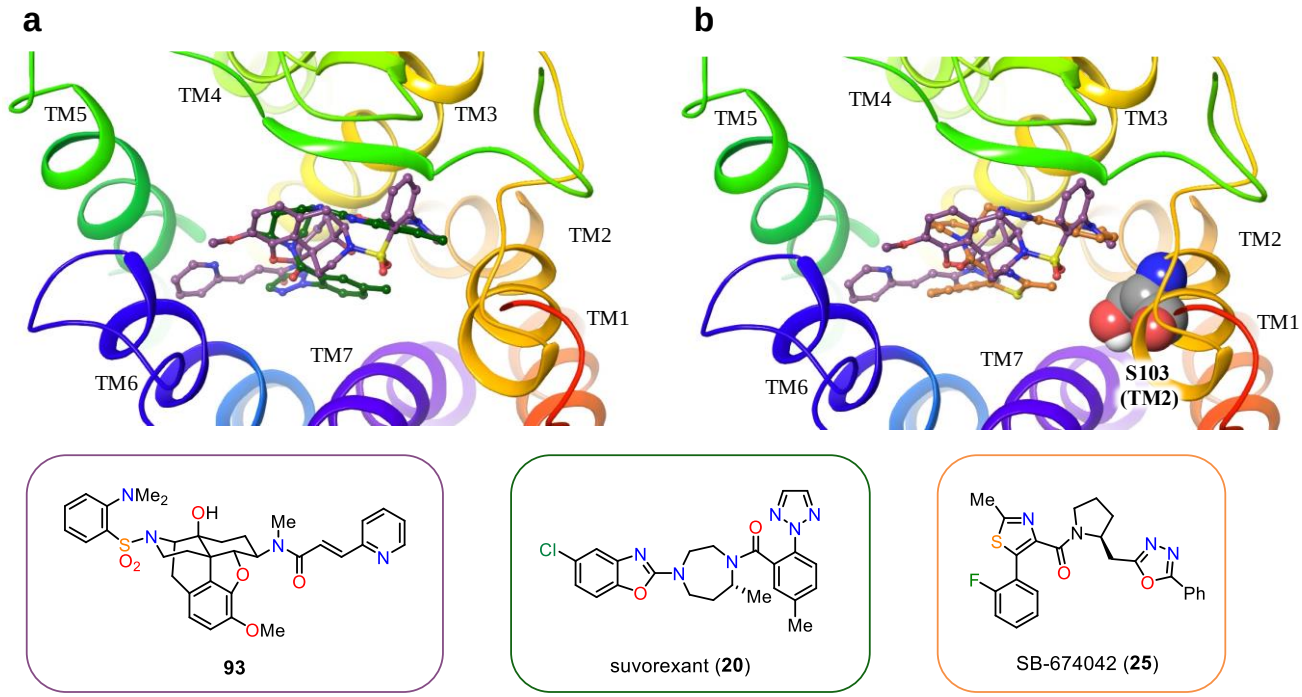


Figure 14. (a) Superimposition of **93** (purple) and **20** (green) in the ligand-binding site of OX_1R. (b) Superimposition of **93** (purple) and **25** (orange) in the ligand-binding site of OX_1R. (Adapted with permission from *J. Med. Chem.* **2017**, *60*, 1018-1040. Copyright 2017 American Chemical Society.)

Figure 14 compares the binding modes of **93**, **20** (DORA), and **25** (1-SORA representing a 117-fold selectivity[22]). The position of the morphinan skeleton of **93** corresponds to the seven-membered ring of **20** and the 2-pyrrolidyl methylene part of **25**, which were proposed to inhibit inward movements of TM5 and TM6 relative to the rest of the TM bundle (Figures **14a** and **14b**). The 17-*o*-dimethylaminobenzene group of **93** corresponds to the 5-chloro-1,3-benzoxazol-2-yl group of **20** and the 5-phenyl-1,3,4-oxadiazol-2-yl group of **25**. Recently, the selective OX_1R antagonistic activity of **25** was examined from the structural point of view.[57] Comparing the binding sites of OX_1R and OX_2R, there are only two substitutions. S103 (TM2) and A127 (TM3) of OX_1R were mutated to T111 (TM2) and T135 (TM3) of OX_2R. As both residues of OX_2R are larger than those of OX_1R, the volume of the pocket of OX_2R is somewhat smaller than OX_1R. In the literature, when the experimentally observed pose of **25** in complex with OX_1R was placed into the OX_2R structure by superimposition of the pockets, some clashes with T111 (TM2) and T135 (TM3) of OX_2R were observed,[57] suggesting that the volume of the pocket of OX_1R was a much better fit to **25** than that of OX_2R. When the 1-SORA **93** was also placed into the pocket of OX_2R, a clash between the 17-*o*-dimethylaminobenzene group of **93** and T111 (TM2) of OX_2R was observed. This observation might be a source of the selective OX_1R antagonistic activity of **93** and may well explain these experimental results that the 17-sulfonamide motif is a key pharmacophore to afford selective OX_1R antagonistic activity.

2.5 Conclusion

In this study, nalfurafine (**13**) with a potent KOR agonistic activity was proved to have antagonistic activity for OX_1R (K_i = 250 nM). Structural optimization of the substituent groups at the 3-, 6-, and 17-positions of **13** improved the K_i value from 250 to 1.36 nM. The obtained morphinan derivatives, especially 17-sulfonamide compounds, showed potent and highly selective antagonistic activities for OX_1R. The *o*-substituted benzenesulfonamide derivatives tended to show more potent antagonistic activities compared with *m*- and *p*-substituted benzenesulfonamide derivatives. Conformational analysis of **81** and **83** suggested that the presence of the *o*-substituent group introduces steric hindrance to B-ring of the morphinan skeleton and directs the phenyl ring into an adequate ligand-binding site of OX_1R. The 17-sulfonamide derivatives with the 3-methoxy group exhibited almost no affinity for the opioid receptors. This suggested that these morphinan-type OX_1R antagonists would induce few side effects resulting from opioid receptors. Structural optimization to improve the water solubility afforded a highly water-soluble compound **93** with the most potent antagonistic activity for OX_1R. The dihydrosulfate **96** derived from **93** could be easily dissolved in water (solubility: 10 mg in 50 μL of saline) and exhibited almost no affinity for opioid receptors. The dihydrosulfate **96** attenuated the physical dependence of morphine *via* i.p. injection, which suggested that **96** could have BBB permeability. Therefore, the nalfurafine derivatives could be lead compounds to develop 1-SORAs, which would provide important information for many researchers in the field of orexin research.

3. A novel rearrangement reaction of morphinan to arylmorphan skeletons and the pharmacologies of arylmorphan derivatives

3.1 Discovery of a novel rearrangement reaction of morphinan to arylmorphan skeletons

Chapters 1 and 2 discussed the utility of the 4,5-epoxymorphinan derivatives in drug discovery research. This chapter discusses a novel rearrangement reaction for **97** (without 4,5-epoxy ring) to produce arylmorphan derivatives. This rearrangement reaction was discovered during the synthesis of bicyclo[2.2.2]octane derivatives **98** from diene **97** by the Diels–Alder reaction (**Figure 15**). The Diels–Alder reaction of the thebaine (**3**) and a dienophile has been reported to produce a bicyclo [2.2.2]octane derivative (representative derivative: buprenorphine (**99**)).[58] On the other hand, the Diels–Alder reaction of a morphinan derivative **97** without 4,5-epoxy ring was not previously reported. Therefore, the author attempted to investigate the reaction of **97** with dienophile and the pharmacological effects of the cycloadducts.

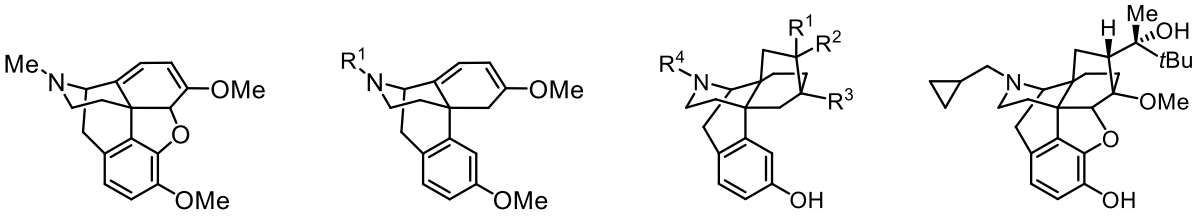
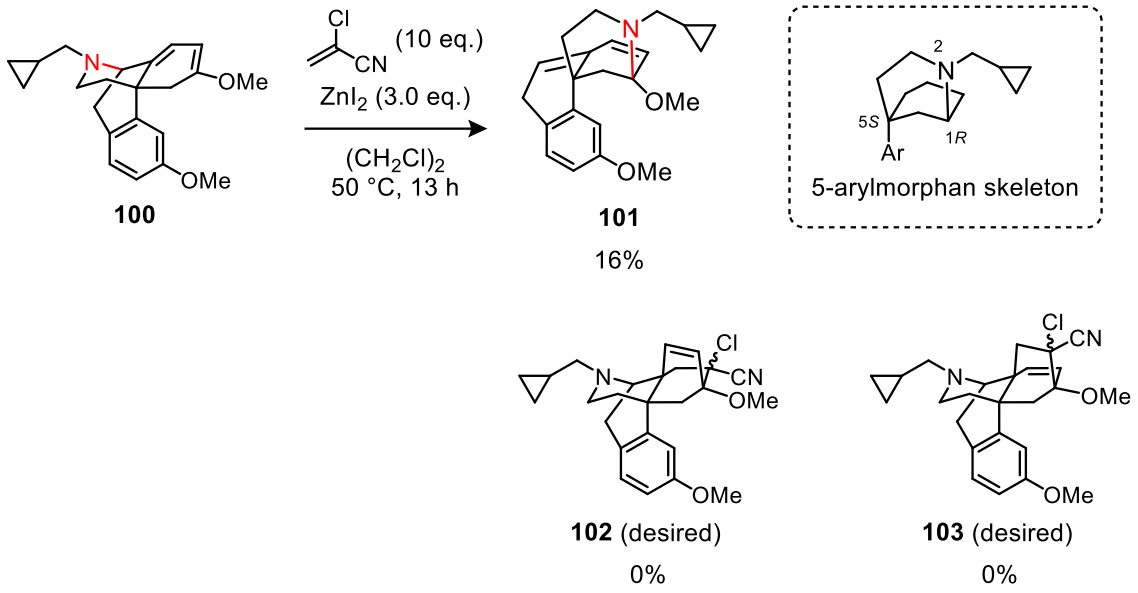


Figure 15. Structures of thebaine (**3**), morphinan derivatives **97** and **98**, and buprenorphine (**99**)

In the context of this research background, an unexpected novel rearrangement occurred and yielded 5-arylmorphan derivative **101** when a morphinan derivative **100** was treated with 2-chloroacrylonitrile in the presence of zinc iodide (**Scheme 6**).[59] However, bicyclo[2.2.2]octane derivatives **102** or **103** were not obtained. **Figure 16** shows the rearrangement reactions of a propellane alkaloid to the corresponding 5-arylmorphan derivative recently reported by Reisman and co-workers (the reported reactant and product were enantiomeric forms of **100** or **101**).[60] Previously, 5-arylmorphan derivatives **104** and **105** with a similar structure to the resulting 5-arylmorphan derivative **101** have been reported as selective MOR ligands.[61] On the basis of these reports,[60,61] the novelty of the rearrangement of morphinan to arylmorphan skeletons and the structural similarity between **101** and the known MOR ligands **104** and **105** encouraged the author to carry out a detailed study on the serendipitous rearrangement.



Scheme 6. Reaction of **100** with 2-chloroacrylonitrile in the presence of zinc iodide

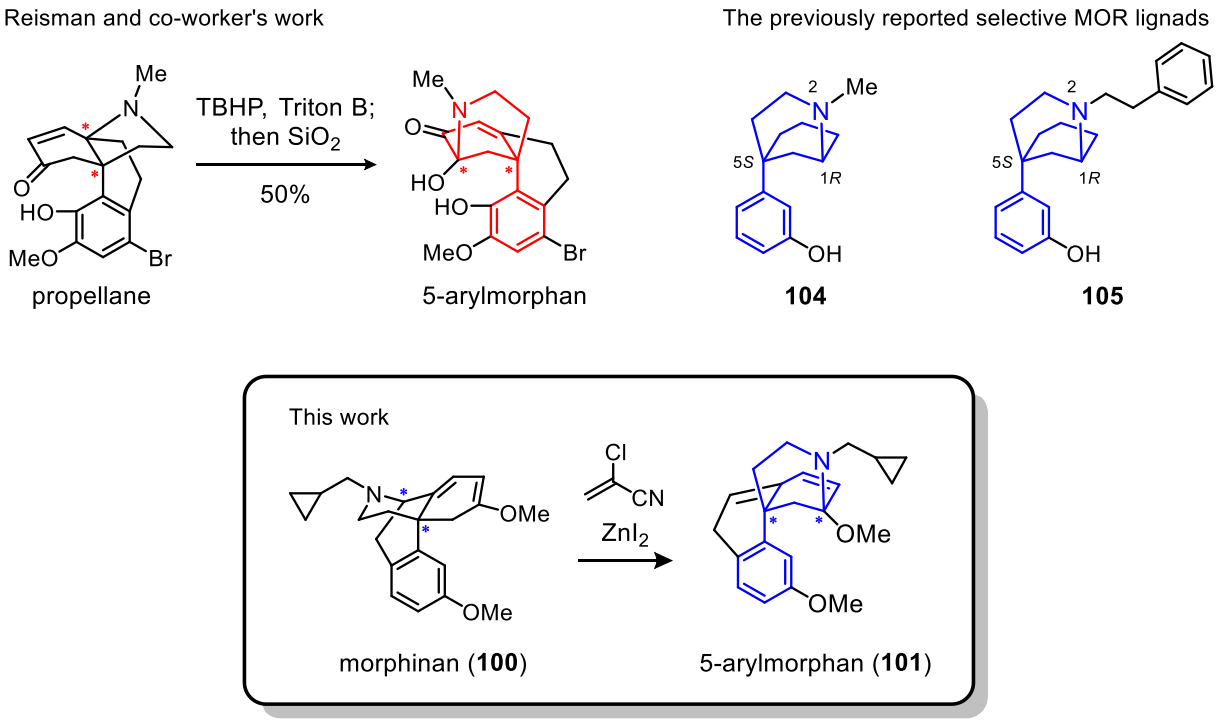
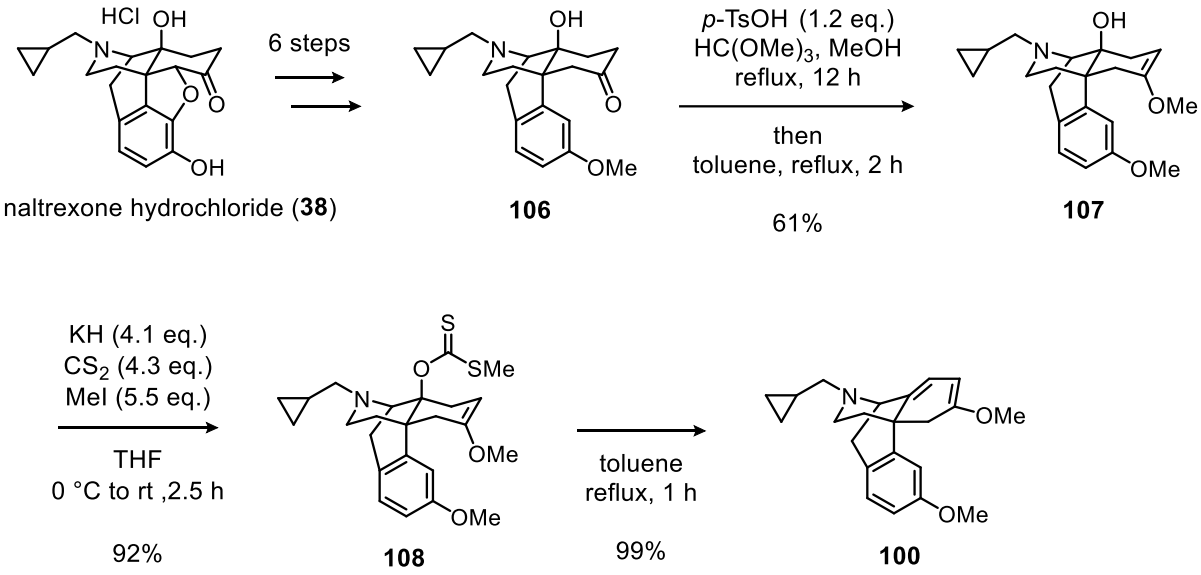


Figure 16. Comparison between the previously reported rearrangement and that discovered in this work, and the structural similarity between the previously reported selective MOR ligands **104** and **105** and the obtained 5-arylmorphan derivative **101**

3.2 Investigation of the rearrangement reaction conditions

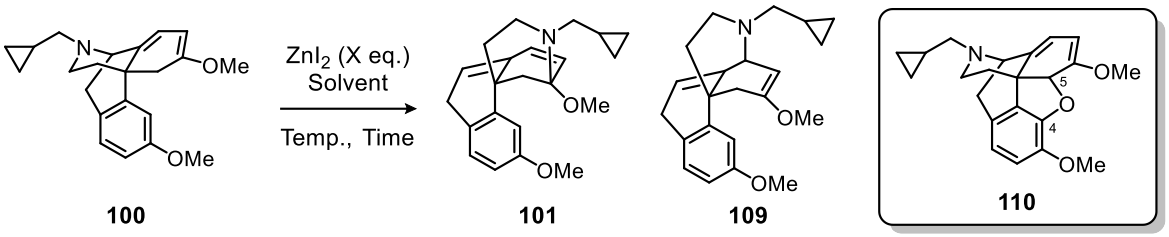
The starting dienol ether **100** was obtained from the known morphinan **106**, which was easily transformed from naltrexone hydrochloride (**38**) in six steps,[62] through the following process: enolization of the ketone in **106**, formation of xanthate **108** from methyl enol ether **107**, and Chugaev elimination of **108** (**Scheme 7**).



Scheme 7. Synthesis of **100** from the commercially available **38** *via* the known morphinan **106**

The essential reaction conditions were investigated by examining the reaction of **100** without 2-chloroacrylonitrile, because 2-chloroacrylonitrile was not embedded in the structure of the rearrangement product **101** (**Table 9**). The rearrangement reaction without 2-chloroacrylonitrile in 1,2-dichloroethane mainly afforded another novel arylmorphan isomer **109** with low yield of **101** (**Table 9**, Entry 2). Changing the solvent to tetrahydrofuran (THF) was found to improve the yield of **101** (**Table 9**, Entry 3). Moreover, the reaction was conducted under microwave (MW) irradiation (**Table 9**, Entry 4). This was found to increase the total yields of the rearrangement products **101** and **109**, suggesting that the reaction time shown in entries 2 and 3 might have been insufficient for reaching equilibrium. The use of other Lewis acids, such as boron trifluoride diethyl ether complex, titanium(IV) chloride, and ytterbium(III) trifluoromethanesulfonate, under the same condition yielded complex mixtures. The author confirmed that the isolated **109** was gradually converted into another product **101** along with the starting morphinan **100** under the condition of entry 4. On the other hand, the rearrangement reaction of the dienol ether **110** with 4,5-epoxy ring did not progress, and 94% of the **110** was recovered under similar condition to entry 4. This result suggested that the ring rigidity arising from the 4,5-epoxy ring moiety might prevent the progress of the rearrangement.

Table 9. Rearrangement reaction of **100** in the presence of zinc iodide



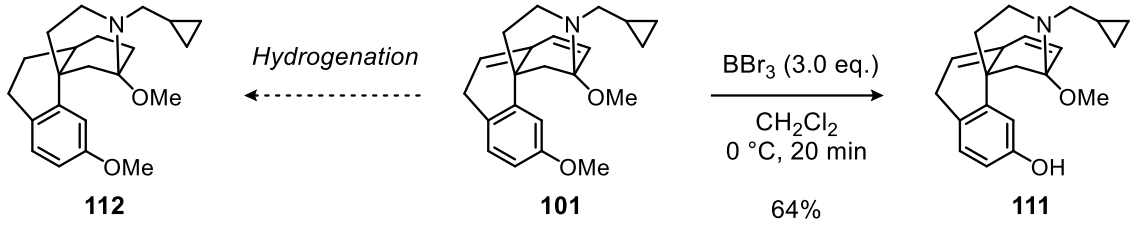
100 **101** **109** **110**

Entry	X (eq.)	Solvent	Temp. (°C)	Time (h)	Yield (%)	
					101	**109**
1[a]	3.0	$(CH_2Cl)_2$	50	13	16	0
2	2.5	$(CH_2Cl)_2$	50	9.0	8	36
3	3.0	THF	60	13	32	43
4	3.0	THF	60 (MW)[b]	9.0	31	65

[a] 2-chloroacrylonitrile (10 eq.) was added.; [b] Under microwave (MW) irradiation.

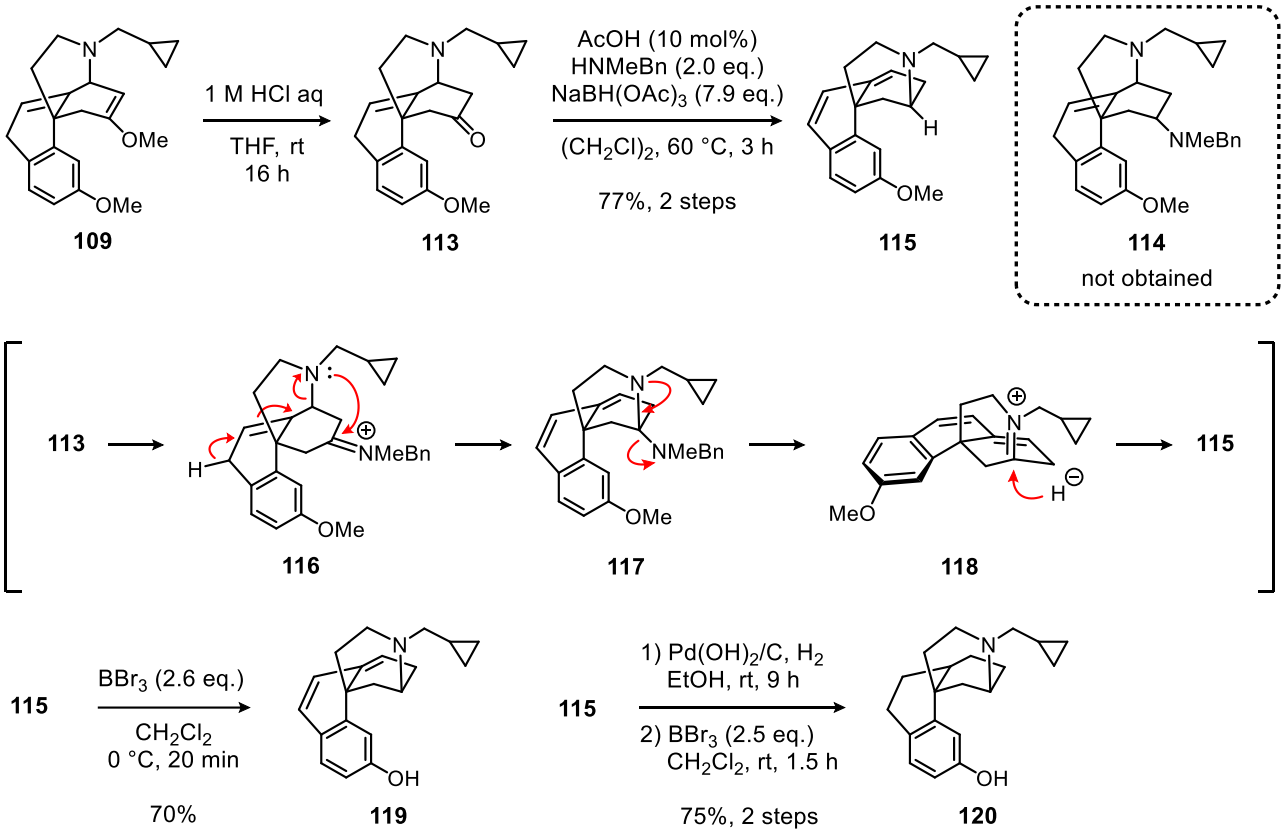
3.3 Synthesis of arylmorphan derivatives

Next, a variety of 5-arylmorphan derivatives derived from **101** or **109** were designed and synthesized to evaluate their pharmacological effects. First, demethylation of **101** using boron tribromide produced **111** (**Scheme 8**). However, all attempts for the hydrogenation of **101** to obtain the corresponding saturated arylmorphan derivative **112** were unsuccessful under a variety of reaction conditions (Pd/C, Pd/Fib, Pd/C(en), $Rh(PPh_3)_3Cl$, Crabtree's catalyst, and PtO_2 under H_2 atmosphere) and yielded an unidentified complex mixture. These failures were probably due to the unstable moiety of the amino ether at the allylic position in **101**.

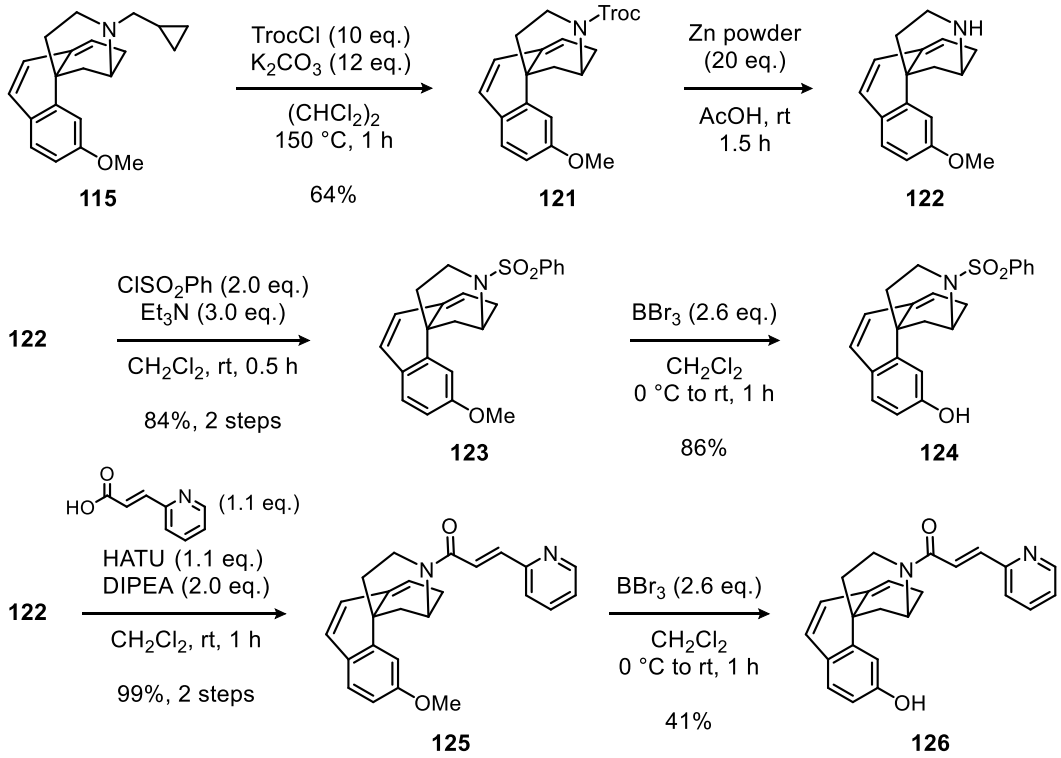


Scheme 8. Transformation of **101** into **111**

As shown in **Scheme 9**, **119** and **120** were prepared from arylmorphan **109**. Originally, the author attempted to synthesize **114** by reductive amination of the ketone **113** derived from **109**. However, an unanticipated rearrangement was found to yield **115** with a skeleton similar to that of **101**. The compound **115** can be obtained by the reduction of the iminium intermediate **118** with sodium cyanoborohydride *via* the aminal **117**, which was rearrangement product of **116**. Demethylation of **115** with boron tribromide yielded **119**. Hydrogenation of **115** by using 40 mol% of Pearlman's catalyst followed by demethylation produced **120** (approximately 5:1 diastereomixture by ^{1}H NMR).[63] **Scheme 10** shows the preparation of the derivatives **124** and **126** from arylmorphan **115**. After replacing the CPM group with the Troc group, **121** was treated with zinc powder to produce the desired secondary amine **122**. Reaction of **122** with benzenesulfonyl chloride and (*E*)-3-(pyridin-2-yl)acrylic acid[64] yielded **123** and **125**, respectively. Finally, demethylation of **123** and **125** produced **124** and **126**, respectively.



Scheme 9. Transformation of **109** into **119** and **120**

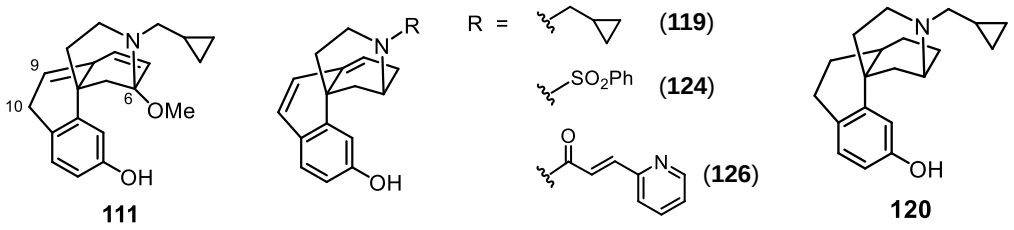


Scheme 10. Transformation of **115** into **124** and **126**

3.4 Pharmacologies of the obtained arylmorphan derivatives

First, the binding affinities of the obtained compounds **111**, **119**, **120**, **124**, and **126** were evaluated for opioid receptors using the opioid receptor binding assay (**Table 10**). Although most of the known arylmorphan derivatives were reported to show selective affinity for MOR[64], all the obtained arylmorphan derivatives showed affinity for KOR. This may be attributed to the presence of a C9–C10 bridge in the morphinan skeleton moiety, which could fix the conformation of the phenol ring, unlike many reported 5-arylmorphans. The presence or absence of the methoxy group at the C6 position was found to significantly affect the binding affinity of opioid receptors despite the presence of the same functional group (CPM group) on the nitrogen (**111** vs **119** and **120**). The sulfonamide and amide derivatives **124** and **126** showed weaker binding affinities for opioid receptors compared with **119**. This result suggested that the basic nitrogen in these novel 5-arylmorphan derivatives as well as the general morphinan derivatives are essential for opioid receptor binding.[65] Next, the functional activity of **111** with the most potent affinity for KOR was assessed using the [^{35}S]GTPγS-binding assays. The results revealed that **111** has antagonistic activity for KOR (IC_{50} = 8.18 nM). This result suggested that the obtained 5-arylmorphan derivatives are expected to be lead compounds for developing selective KOR antagonists.

Table 10. Results of the opioid receptor binding assay of the compounds **111**, **119**, **120**, **124**, and **126**

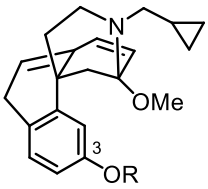


Compounds	Binding affinity K_i (nM)[b]			Selectivity
	μ ([^{3}H]DAMGO)	δ ([^{3}H]DPDPE)	κ ([^{3}H]U-69,593)	μ/κ
111	58.5	978	16.6	3.52
119	552	306	1770	0.31
120[a]	–[c]	–[c]	460	–
124	–[c]	–[c]	705	–
126	–[c]	–[c]	2120	–

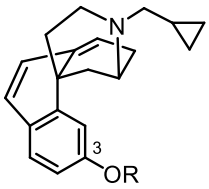
[a] The binding assay of **120** was carried out as a 5:1 mixture of diastereomers due to the infeasible separation. [b] K_i values were obtained from radioligand-based competitive receptor binding assay using Human embryonic kidney (HEK) cells stably expressing human μ, δ, or κ opioid receptors. [c] Not detected.

Moreover, the activities of the obtained arylmorphan derivatives for OXRs were evaluated. Both **101** and **115** were found to show dual antagonistic activities for the OXRs (**Table 11**). On the other hand, the 5-arylmorphan derivatives **111** and **119** with 3-phenolic hydroxy group showed no OXRs antagonistic activities, which reflected the importance of the methoxy group at the C3 position for the antagonistic activity for OXRs. These results are the first examples of arylmorphan derivatives with antagonistic activities for OXRs.

Table 11. Assay results of the arylmorphan derivatives **101**, **111**, **115**, and **119** for OXRs antagonism



101 (R = Me)
111 (R = H)



115 (R = Me)
119 (R = H)

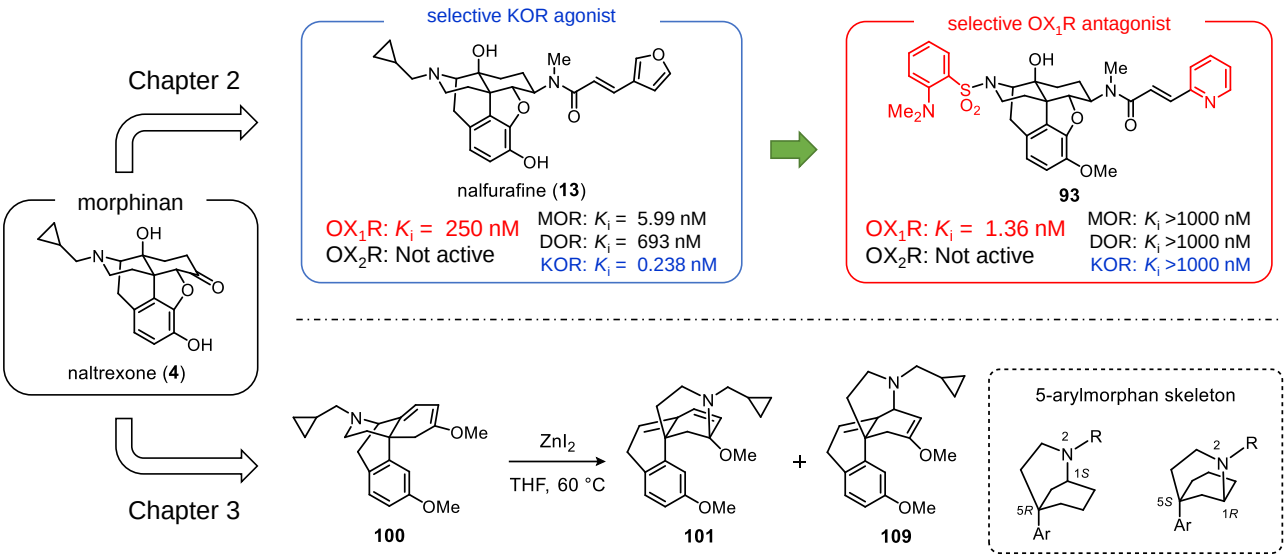
Compounds	IC_{50} (μM)[a]	
	OX_1R	OX_2R
101	4.87	3.73
111	–[b]	–[b]
115	5.48	3.46
119	–[b]	–[b]

[a] IC_{50} values were obtained from at least three independent calcium assays. [b] Not detected.

3.5 Conclusion

In this study, a novel rearrangement reaction of morphinan derivative **100** using zinc iodide to produce 5-arylmorphan derivatives **101** and **109** was discovered. The investigation of this reaction revealed that the flexibility of the morphinan skeleton would be important for this rearrangement, because the reaction of a more rigid 4,5-epoxy-morphinan **110** did not occur under the same conditions. Moreover, the rearrangement products were converted to various 5-arylmorphan derivatives, which showed affinities for KOR. Among these, **111** showed selective and potent affinity for KOR (K_i = 16.6 nM, binding selectivity: μ/κ = 3.52) and antagonistic activities for KOR (IC_{50} = 8.18 nM). The basicity of nitrogen in 5-arylmorphane derivatives plays an important role in its binding with opioid receptors as well as that in morphinan derivatives. In addition, the arylmorphans **101** and **115** showed dual antagonistic activities for OXRs. These results are promising and encouraging for continuing the exploration of more effective orexin ligands. This study can provide useful information for medicinal chemists working in the field of opioid receptors and OXRs.

4. Conclusion



In this thesis, the studies of a morphinan skeleton for developing ligands that act on receptors other than opioid receptors as well as of specific rearrangement reaction of morphinan skeleton were described.

In Chapter 2, structural optimization of nalfurafine (**13**) with potent KOR agonistic activity resulted in the development of the highly selective and potent OX_1R antagonist **93**. The dihydrosulfate **96** was highly soluble in water and did not show any affinity for opioid receptors. Additionally, the salt **96** attenuated the physical dependence of morphine *via* i.p. injection in mice. These results provide useful information to medicinal chemists and pharmacologists in the study of OX_1R.

In Chapter 3, the novel rearrangement reaction of the morphinan **100** to produce the corresponding 5-arylmorphan derivatives **101** and **109**, synthesis of the arylmorphan derivatives derived from **101** and **109**, and evaluation of their pharmacological effects were investigated. The results indicated that the obtained 5-arylmorphan derivatives showed selective KOR affinity and antagonistic activity, although the known arylmorphan derivatives were reported to be MOR ligands. In addition, DORAs with a 5-arylmorphan skeleton were discovered. These findings would contribute to the development of novel selective KOR and OXRs ligands.

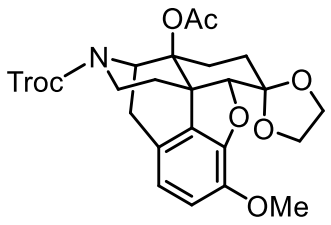
Experimental section

Chemistry.

General.

All melting points were determined on a Yanaco MP melting point apparatus and are uncorrected. Infrared spectra were recorded with a JASCO FT/IR 4100 spectrophotometer. ^{1}H and ^{13}C NMR spectral data were obtained with JEOL JNM-ECS 400 instruments. Chemical shifts are quoted in ppm using tetramethylsilane (δ = 0 ppm) as the reference for ^{1}H NMR spectroscopy, $CDCl_3$ (δ = 77.0 ppm) and pyridine-d_5 (δ = 135.5 ppm) for ^{13}C NMR spectroscopy. Mass spectra were measured with a JEOL JMS-T100LP spectrometer. Compound names were determined using ChemBioDraw Ultra version 13.0. The purity (≥95%) of the assayed compounds was determined by analytical HPLC or elemental analysis. Analytical HPLC was performed on a Shimadzu LC-2040C 3D instrument equipped with Xbridge-C18 3.5 μm, 4.6 mm × 150 mm column, with PDA detection at 254 nm, at column temperature of 40 °C. Elemental analyses were performed with a J-SCIENCE LAB microcorder JM10. Column chromatography was carried out on silica gel (spherical, neutral, 40–50 μm, Kanto Chemical Co. or packed column, 40 μm, Yamazen Co.), NH-silica gel (40–75 μm, Fuji Silysia Chemical Ltd.), and DIOL-silica gel (40–75 μm, Fuji Silysia Chemical Ltd).

2,2,2-Trichloroethyl (4′*R*,4a′*S*,7a′*R*,12b′*S*)-4a′-acetoxy-9′-methoxy-1′,2′,4′,4a′,5′,6′-hexahydro-3′*H*,7a′*H*-spiro[[1,3]-dioxolane-2,7′-[4,12]methanobenzofuro[3,2-*e*]isoquinoline]-3′-carboxylate (**42**).



42

To a suspension of naltrexone hydrochloride (**38**) (20 g, 52.9 mmol) in DMF (150 mL) were added K_2CO_3 (18.3 g, 132 mmol) and MeI (3.65 mL, 58.5 mmol), and the mixture was stirred at room temperature for 11 h under an argon atmosphere. The reaction was quenched with H_2O (200 mL), and the mixture was extracted with Et_2O (300, 300, 200 mL). The organic layer was washed with H_2O (200 mL) and brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford a crude product as a colorless solid. To a solution of the crude product in toluene (150 mL) were added *p*-TsOH·H_2O (14.3 g, 75.2 mmol) and ethylene glycol (16.7 mL, 299 mmol), and the mixture was refluxed with a Dean–Stark apparatus for 17 h under an argon atmosphere. After cooling to room temperature, the reaction mixture was basified with K_2CO_3 (12 g) and saturated $NaHCO_3$ aq (80 mL) and extracted with $CHCl_3$ (300, 200, 100 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford a crude product as a colorless solid. The crude product was suspended in Ac_2O (200 mL), and the mixture was refluxed for 1 h under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and azeotropically dried with toluene three times, then $CHCl_3$ three times to afford a crude product as a brown amorphous. To a solution of the crude product in 1,1,2,2-tetrachloroethane (200 mL) were added K_2CO_3 (46 g, 333 mmol) and 2,2,2-trichloroethyl chloroformate (45.8 mL, 333 mmol), and the mixture was stirred at 140 °C for 14 h under an argon atmosphere. The reaction mixture was cooled to room temperature, and H_2O (200 mL) was added. The mixture was extracted with $CHCl_3$ (200, 100, 100 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (EtOAc/hexane = 1/3 to 3/1) to afford compound **42** (24.3 g, 82% in 4 steps) as a yellow amorphous.

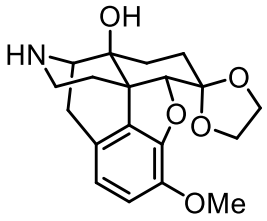
IR (KBr): 1744, 1713 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.46–1.59 (m, 3H), 1.76–1.87 (m, 1H), 2.05 (s, 1.5H), 2.07 (s, 1.5H), 2.33–2.45 (m, 1H), 2.73–3.00 (m, 3H), 3.10 (ddd, *J* = 18.4, 5.6, 5.6 Hz, 1H), 3.77–3.84 (m, 1H), 3.87–3.95 (m, 1H), 3.89 (s, 3H), 3.97–4.08 (m, 2H), 4.17–4.24 (m, 1H), 4.60 (s, 1H), 4.66 (d, *J* = 12.0 Hz, 0.5H), 4.68 (d, *J* = 12.0 Hz, 0.5H), 4.87 (d, *J* = 12.0 Hz, 0.5H), 4.91 (d, *J* = 12.0 Hz, 0.5 H), 5.60–5.66 (m, 1H), 6.65 (d, *J* = 8.4 Hz, 0.5H), 6.67 (d, *J* = 8.4 Hz, 0.5H), 6.80 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.95, 22.0, 12.5, 23.5, 28.5, 28.6, 29.0, 31.5, 31.9, 37.6, 37.9, 48.0, 18.2, 51.7, 51.8, 56.5, 74.9, 75.0, 81.0, 81.2, 93.2, 95.5, 95.8, 108.0, 114.3, 118.9, 123.5, 123.7, 128.6, 128.7, 142.77, 142.8, 146.2, 146.2, 153.8, 154.0, 169.3, 169.5.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{24}H_{26}Cl_3NO_8Na$, 584.0622; found, 584.0638.

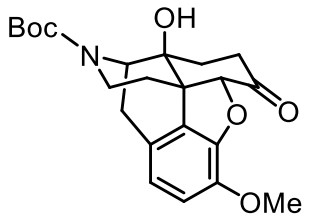
(4′*R*,4a′*S*,7a′*R*,12b′*S*)-9′-Methoxy-1′,2′,3′,4′,5′,6′-hexahydro-4a′*H*,7a′*H*-spiro[[1,3]dioxolane-2,7′-[4,12]methanobenzofuro[3,2-*e*]isoquinolin]-4a′-ol (43).



43

To a suspension of compound **42** (10 g, 17.8 mmol) in DMSO (100 mL) was added 12 M KOH aq solution (50 mL), and the mixture was stirred for 6 h at 110 °C under an argon atmosphere. After cooling to room temperature, the reaction mixture was adjusted to pH 10 with saturated NH_4Cl aq (100 mL) and extracted with a mixed solution, *i*-PrOH/$CHCl_3$ = 1/3 (150, 125, 100 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (5–15% (28% NH_3 aq/MeOH = 1/9) in $CHCl_3$) to afford compound **43** (6.0 g, 98%) as a colorless solid. The spectral data of compound **43** were as reported.[65]

***tert*-Butyl (4*R*,4a*S*,7a*R*,12b*S*)-4a-hydroxy-9-methoxy-7-oxo-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (45).**

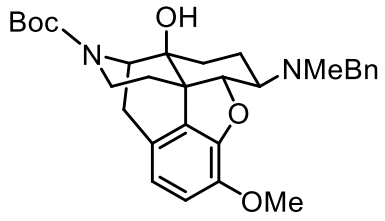


45

Compound **45** was synthesized by the modified procedure of the reported method.[54] The spectral data were also as reported.

A mixture of compound **43** (5.59 g, 16.2 mmol) in 1 M HCl aq (50 mL) was stirred for 15 h at 80 °C under an argon atmosphere. After cooling to room temperature, the reaction mixture was basified with K_2CO_3 (5 g) and extracted with a mixed solution, *i*-PrOH/$CHCl_3$ = 1/3 (50, 40, 30, 30 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (5–15% (28% NH_3 aq/MeOH = 1/9) in $CHCl_3$) to afford a colorless amorphous (4.88 g) with inseparable impurities. To a stirred solution of the obtained amorphous in CH_2Cl_2 (80 mL) were added (*i*-Pr)$_2$NEt (5.6 mL, 32.2 mmol) and $(Boc)_2O$ (4.5 mL, 19.6 mmol) at 0 °C under an argon atmosphere. After stirring for 3 h at room temperature, the reaction mixture was washed with saturated $NaHCO_3$ aq (80 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (40–60% EtOAc in hexane) to afford compound **45** (5.93 g, 91%) as a colorless amorphous.

***tert*-Butyl (4*R*,4a*S*,7*R*,7a*R*,12b*S*)-7-[benzyl(methyl)amino]-4a-hydroxy-9-methoxy-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (46).**

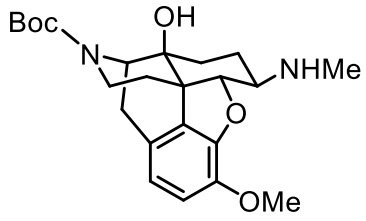


46

Compound **46** was synthesized by the modified procedure of the reported method.[54] The spectral data were also as reported.

To a solution of compound **45** (875 mg, 2.18 mmol) in benzene (22 mL) were added *N*-benzylmethylamine (580 μL, 4.49 mmol), $PhCO_2H$ (426 mg, 3.49 mmol), and *p*-TsOH·H_2O (32 mg, 0.168 mmol), and the mixture was refluxed for 18 h with a Dean–Stark apparatus under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and MS4A (1.3 g) was added. The mixture was dissolved in absolute EtOH (26 mL) under an argon atmosphere, cooled with an ice–salt (NaCl) bath, and a solution of $NaBH_3CN$ (247 mg, 3.92 mmol) in THF (4.0 mL) was added. After 0.5 h, the ice–salt (NaCl) bath was removed. The reaction mixture was stirred for 2 h at room temperature, and then MeOH (20 mL) and saturated $NaHCO_3$ aq (30 mL) were added. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure and extracted with $CHCl_3$ (30, 20, 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 column chromatography on silica gel (0–5% MeOH in $CHCl_3$) to afford compound **46** (927 mg, 84%) as a colorless amorphous.

***tert*-Butyl (4*R*,4a*S*,7*R*,7a*R*,12b*S*)-4a-hydroxy-9-methoxy-7-(methylamino)-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (47).**



47

Compound **47** was synthesized by the modified procedure of the reported method.[54]

To a solution of compound **46** (285 mg, 0.563 mmol) in MeOH (3 mL) was added 5% Pd/C, Degussa type (95 mg), and the mixture was stirred for 13 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. The crude residue was purified by column chromatography on silica gel (5–15% (28% NH_3 aq/MeOH = 1/9) in $CHCl_3$) to afford compound **47** (240 mg, quant) as a colorless amorphous.

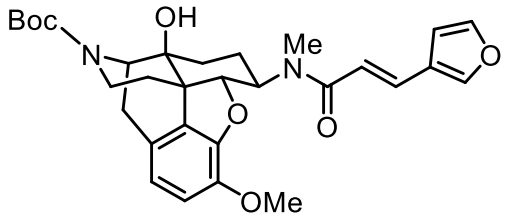
IR (film): 3372, 1681 cm^{-1}

^1H NMR (400 MHz, pyridine-d_5): δ (mixture of rotamers) = 1.30–1.57 (m, 2H), 1.49 (s, 5.4H), 1.51 (s, 3.6H), 1.62–1.89 (m, 1H), 2.08–2.22 (m, 1H), 2.53–2.92 (m, 3H), 2.86 (s, 1.2H), 2.87 (s, 1.8H), 2.94–3.16 (m, 3H), 3.85 (s, 3H), 4.08 (dd, *J* = 12.8, 4.0 Hz, 0.6H), 4.34 (dd, *J* = 12.8, 4.0 Hz, 0.4H), 4.63 (d, *J* = 4.0 Hz, 0.4H), 4.90 (d, *J* = 4.0 Hz, 0.6H), 5.25 (d, *J* = 6.8 Hz, 0.4H), 5.27 (d, *J* = 6.8 Hz, 0.6H), 6.78 (d, *J* = 8.4 Hz, 0.6H), 6.82 (d, *J* = 8.4 Hz, 0.4H), 6.97 (d, *J* = 8.4 Hz, 1H). Two protons (NH, OH) were not observed.

^{13}C NMR (100 MHz, pyridine-d_5): δ (mixture of rotamers) = 22.0, 28.4, 28.7, 29.0, 30.5, 32.0, 32.1, 32.3, 37.5, 38.4, 47.9, 56.8, 58.2, 60.9, 70.0, 79.1, 79.8, 91.3, 91.4, 115.5, 120.1, 125.6, 131.8, 144.0, 144.5, 155.8, 155.9.

HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{23}H_{33}N_2O_5$, 417.2390; found, 417.2381.

***tert*-Butyl (4*R*,4a*S*,7*R*,7a*R*,12b*S*)-7-[(*E*)-3-(furan-3-yl)-*N*-methylacrylamido]-4a-hydroxy-9-methoxy-1,2,4,4a,5,6,7,7aoctahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (48).**



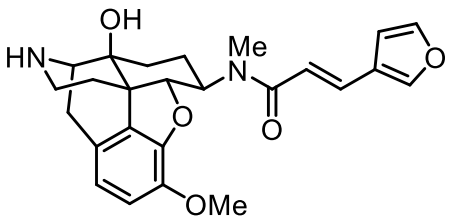
48

Compound **48** was synthesized by the modified procedure of the reported method.[54] The spectral data were also as reported.

To a stirred solution of compound **47** (240 mg, 0.576 mmol) in CH_2Cl_2 (5.8 mL) were added Et_3N (240 µL, 1.72 mmol) and (*E*)-3-(furan-3-yl)acryloyl chloride (108 mg, 0.690 mmol) at 0 °C under an argon atmosphere. After stirring for 2 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with saturated $NaHCO_3$ aq (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 column chromatography on silica gel (80–100% EtOAc in hexane) to afford compound **48** (245 mg, 79%) as a colorless amorphous.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-3-(Furan-3-yl)-*N*-[(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl]-*N*-methylacrylamide (49).



49

A mixture of compound **48** (64 mg, 0.119 mmol) in 10% hydrogen chloride–methanol solution (3.0 mL) was stirred for 14 h at room temperature under an argon atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was basified with saturated $NaHCO_3$ aq (20 mL) and extracted with a mixed solution, *i*-PrOH/$CHCl_3$ = 1/3 (10 mL × 4). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by PLC (28% NH_3 aq/MeOH/$CHCl_3$ = 1/9/200) to afford compound **49** (42.8 mg, 82%) as a colorless amorphous.

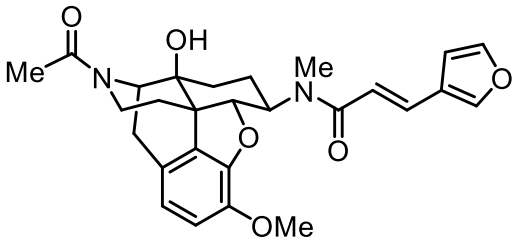
IR (film): 3323, 1651 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.38–1.73 (m, 4H), 2.12–2.36 (m, 2H), 2.65–2.78 (m, 2H), 2.94–3.20 (m, 3.6H), 3.02 (s, 2.4H), 3.70–3.90 (m, 0.8H), 3.81 (s, 2.4H), 3.85 (s, 0.6H), 4.25–4.45 (m, 0.2H), 4.61 (d, *J* = 7.6 Hz, 0.8H), 4.74 (d, *J* = 7.6 Hz, 0.2H), 6.42–6.66 (m, 2.2H), 6.69 (d, *J* = 8.4 Hz, 0.8H), 6.74 (d, *J* = 8.4 Hz, 0.2H), 6.81 (d, *J* = 8.4 Hz, 0.8H), 7.33–7.63 (m, 3H). Two protons (NH and OH) were not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.6, 23.2, 29.9, 30.4, 30.7, 32.8, 32.9, 37.5, 37.6, 47.9, 56.8, 57.3, 57.5, 58.4, 69.8, 70.1, 89.2, 89.9, 107.4, 107.7, 115.0, 115.4, 118.1, 118.4, 118.6, 119.2, 123.1, 123.4, 125.6, 125.9, 131.6, 131.9, 132.5, 143.0, 143.5, 143.6, 143.8, 143.9, 144.1, 166.8, 167.6.

HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{25}H_{29}N_2O_5$, 437.2077; found, 437.2068.

(*E*)-*N*-[(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-Acetyl-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl]-3-(furan-3-yl)-*N*-methylacrylamide (50).



50

A mixture of compound **49** (30 mg, 0.0687 mmol) in Ac_2O (0.5 mL) and pyridine (0.25 mL) was allowed to stand for 3 h at room temperature under an argon atmosphere. The reaction mixture was concentrated under reduced pressure and azeotropically dried with toluene (1 mL × 3) and then $CHCl_3$ (2 mL × 2). The crude product was purified by PLC (MeOH/$CHCl_3$ = 1/10) to afford compound **50** (32 mg, 97%) as a colorless amorphous.

IR (film): 3365, 1651 cm^{-1}

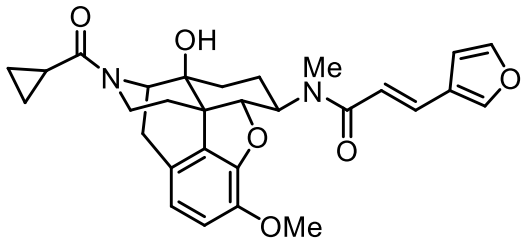
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.38–1.82 (m, 4H), 1.93–2.58 (m, 3H), 2.14 (s, 2.1H), 2.21 (s, 0.9H), 2.79–3.26 (m, 5.7H), 3.37 (brs, 0.3H), 3.53–3.67 (m, 0.7H), 3.71–4.36 (m, 4.3H), 4.45 (dd, *J* = 14.0, 4.8 Hz, 0.3H), 4.65 (d, *J* = 8.0 Hz, 0.7H), 4.75–4.87 (m, 0.3H), 4.91–5.03 (m, 0.7H), 6.39–6.52 (m, 1.4H), 6.54–6.62 (m, 0.6H), 6.65 (d, *J* = 8.0 Hz, 0.3H), 6.72 (d, *J* = 8.0 Hz, 0.7H), 6.77 (d, *J* = 8.0 Hz, 0.3H), 6.81–6.89 (m, 0.7H), 7.35–7.66 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.2, 22.1, 22.8, 28.2, 28.5, 28.8, 29.0, 30.3, 30.7, 31.0, 31.2, 31.4, 32.1, 34.9, 40.3, 47.3, 53.8, 53.9, 56.8, 57.1, 57.2, 58.1, 59.95, 60.0, 70.4, 70.6, 70.7, 88.8, 89.1, 89.4, 107.4, 107.7, 115.3, 115.5, 115.7, 117.8, 117.9, 118.1, 119.3, 119.9, 123.1, 123.3, 123.8, 124.4, 124.6, 130.8, 131.1, 132.1, 132.6, 132.8, 143.1, 143.6, 143.9, 144.1, 144.2, 144.3, 166.8, 167.6, 170.9, 171.0, 171.1.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{27}H_{30}N_2O_6Na$, 501.2002; found, 501.1989.

The purity was >98% as assessed by HPLC (254 nm).

(*E*)-*N*-[(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-(Cyclopropanecarbonyl)-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl]-3-(furan-3-yl)-*N*-methylacrylamide (51).



51

To a stirred solution of compound **49** (30 mg, 0.0687 mmol) in pyridine (0.5 mL) was added cyclopropanecarbonylchloride (7.5 μL, 0.0827 mmol) at 0 °C, and the reaction mixture was stirred for 21 h at room temperature under an argon atmosphere. The reaction was quenched with saturated $NaHCO_3$ aq (5 mL), and the mixture was extracted with $CHCl_3$ (10, 7, 5 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by PLC (MeOH/$CHCl_3$ = 1/10) to afford compound **51** (28.6 mg, 82%) as a colorless amorphous.

IR (film): 3375, 1651 cm^{-1}

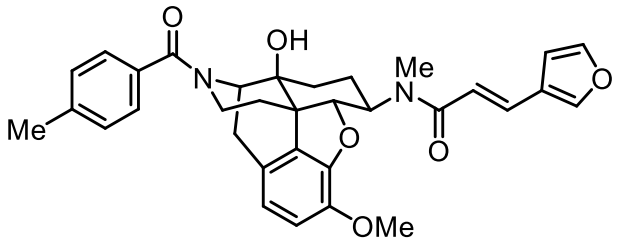
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 0.72–0.92 (m, 2H), 0.93–1.18 (m, 2H), 1.38–2.01 (m, 5H), 2.10–2.66 (m, 2H), 2.76–3.34 (m, 7H), 3.61–3.95 (m, 3.9H), 3.96–4.13 (m, 0.7H), 4.17–4.54 (m, 0.7H), 4.59–4.72 (m, 0.7H), 4.74–4.88 (m, 0.3H), 4.88–5.04 (m, 0.7H), 6.41–6.53 (m, 1.4H), 6.55–6.91 (m, 2.6H), 7.36–7.67 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 7.5, 7.8, 11.8, 21.2, 22.8, 28.3, 28.8, 29.1, 29.3, 29.7, 30.6, 31.0, 31.3, 32.2, 35.6, 39.4, 47.5, 47.6, 54.4, 56.7, 57.2, 58.1, 59.1, 70.8, 71.0, 88.8, 89.4, 107.4, 107.6, 115.2, 115.5, 115.6, 117.9, 118.1, 119.2, 119.8, 123.1, 123.3, 124.5, 124.7, 131.2, 132.1, 132.6, 143.0, 143.6, 143.8, 144.0, 144.3, 166.8, 167.6, 174.1, 174.2, 174.4.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{29}H_{32}N_2O_6Na$, 527.2158; found, 527.2138.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-3-(Furan-3-yl)-*N*-[(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-4a-hydroxy-9-methoxy-3-(4-methylbenzoyl)-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl]-*N*-methylacrylamide (52).



52

To a stirred solution of compound **49** (30 mg, 0.0687 mmol) in CH_2Cl_2 (0.7 mL) were added Et_3N (30 μL, 0.215 mmol) and *p*-toluoyl chloride (11 μL, 0.0832 mmol) at 0 °C under an argon atmosphere. The mixture was stirred for 2 h at room temperature, and then additional *p*-toluoyl chloride (11 μL, 0.0832 mmol) was added. After stirring for 3 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated $NaHCO_3$ aq (5 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by PLC (MeOH/$CHCl_3$ = 1/20) to afford compound **52** (32.2 mg, 85%) as a colorless amorphous.

IR (film): 3374, 1651 cm^{-1}

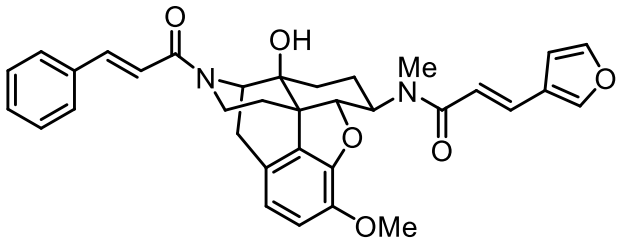
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.23–1.75 (m, 4H), 1.86–2.12 (brs, 1H), 2.17–2.75 (m, 2H), 2.38 (s, 3H), 2.84–3.37 (m, 3H), 2.98 (s, 2.1H), 3.13 (m, 0.9H), 3.42–3.68 (m, 1H), 3.68–3.91 (m, 0.7H), 3.81 (s, 2.1H), 3.85 (s, 0.9H), 3.93–4.19 (m, 0.3H), 4.24–4.83 (m, 1.4H), 4.97–5.12 (m, 0.6H), 6.37–6.90 (m, 4H), 7.15–7.26 (m, 2H), 7.29–7.66 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.2, 21.4, 22.7, 28.8, 29.2, 29.4, 30.4, 31.0, 31.3, 32.3, 35.5, 41.9, 42.0, 47.5, 54.5, 56.7, 57.2, 58.1, 60.7, 70.9, 71.2, 71.4, 88.9, 89.4, 107.4, 107.6, 115.3, 115.7, 117.9, 118.2, 119.2, 119.8, 123.1, 123.3, 124.3, 124.6, 127.2, 129.1, 131.0, 131.3, 132.1, 132.7, 132.8, 133.1, 140.2, 143.0, 143.6, 143.8, 144.0, 144.1, 144.3, 166.8, 167.6, 172.6, 172.8.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{33}H_{34}N_2O_6Na$, 577.2315; found, 577.2303.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-*N*-[(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-Cinnamoyl-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl]-3-(furan-3-yl)-*N*-methylacrylamide (53).



53

To a stirred solution of compound **49** (30 mg, 0.0687 mmol) in CH_2Cl_2 (0.7 mL) were added Et_3N (30 μL, 0.215 mmol) and cinnamoyl chloride (14 mg, 0.0840 mmol) at 0 °C under an argon atmosphere. After stirring for 2 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated $NaHCO_3$ aq (5 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by PLC (MeOH/$CHCl_3$ = 1/20) to afford compound **53** (30.1 mg, 77%) as a colorless amorphous.

IR (film): 3366, 1646 cm^{-1}

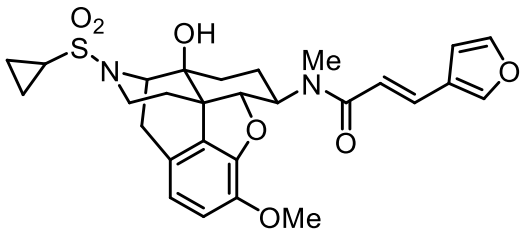
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.39–1.88 (m, 4H), 2.18–2.57 (m, 1.8H), 2.58–2.74 (m, 0.2H), 2.87–3.25 (m, 6H), 3.52 (brs, 1H), 3.73–3.95 (m, 4.7H), 4.15–4.40 (m, 0.3H), 4.43–4.70 (m, 0.3H), 4.66 (d, *J* = 7.6 Hz, 0.7H), 4.80 (d, *J* = 7.6 Hz, 0.3H), 5.03–5.14 (m, 0.7H), 6.39–7.07 (m, 5H), 7.31–7.70 (m, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.3, 22.8, 28.4, 28.8, 29.1, 29.3, 30.8, 31.1, 31.3, 31.5, 32.5, 35.8, 39.9, 47.5, 54.5, 56.7, 57.1, 57.2, 58.1, 59.6, 70.7, 71.0, 88.8, 89.4, 107.4, 107.7, 115.3, 115.5, 115.7, 117.8, 117.9, 118.1, 119.2, 119.9, 123.1, 123.3, 123.9, 124.4, 124.6, 127.7, 128.8, 129.7, 129.8, 130.9, 131.1, 132.1, 132.6, 135.0, 135.1, 142.9, 143.06, 143.12, 143.3, 143.6, 143.9, 144.1, 144.3, 166.8, 167.6, 167.7, 167.9.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{34}H_{34}N_2O_6Na$, 589.2315; found, 589.2314.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-*N*-[(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-(Cyclopropylsulfonyl)-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl]-3-(furan-3-yl)-*N*-methylacrylamide (54).



54

To a stirred solution of compound **49** (30 mg, 0.0687 mmol) in CH_2Cl_2 (0.7 mL) were added Et_3N (30 μL, 0.215 mmol) and cyclopropanesulfonyl chloride (8.5 μL, 0.0834 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 2 h at room temperature, and then additional Et_3N (30 μL, 0.215 mmol) and cyclopropanesulfonyl chloride (8.5 μL, 0.0834 mmol) were added. After stirring for 22 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated $NaHCO_3$ aq (5 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by PLC (MeOH/$CHCl_3$ = 1/20) to afford compound **54** (24.4 mg, 66%) as a colorless solid.

IR (KBr): 3393, 1650, 1325, 1154 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 0.98–1.13 (m, 2H), 1.16–1.30 (m, 2H), 1.39–1.78 (m, 4H), 2.15–2.54 (m, 3H), 2.87–2.98 (m, 1H), 3.01 (s, 2.1H), 3.09–3.27 (m, 3H), 3.16 (s, 0.9H), 3.58–3.69 (m, 1H), 3.72–3.91 (m, 0.7H), 3.82 (s, 2.1H), 3.86 (s, 0.9H), 4.03–4.15 (m, 1H), 4.19–4.35 (m, 0.3H), 4.63 (d, *J* = 8.4 Hz, 0.7H), 4.78 (d, *J* = 8.4 Hz, 0.3H), 6.43 (d, *J* = 15.6 Hz, 0.7H), 6.43–6.50 (m, 0.7H), 6.55–6.70 (m, 0.6H), 6.67 (d, *J* = 8.4 Hz, 0.3H), 6.74 (d, *J* = 8.4 Hz, 0.7H), 6.77 (d, *J* = 8.4 Hz, 0.3H), 6.86 (d, *J* = 8.4 Hz, 0.7H), 7.34–7.67 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 5.4, 5.7, 21.3, 22.9, 28.9, 29.2, 29.3, 29.7, 30.2, 30.5, 31.2, 31.4, 32.8, 39.1, 39.2, 47.2, 47.2, 56.8, 57.1, 58.0, 59.1, 70.0, 70.2, 89.0, 89.5, 107.4, 107.6, 115.5, 115.7, 117.8, 118.0, 19.2, 119.8, 123.0, 123.2, 123.8, 124.0, 130.5, 130.8, 132.2, 132.7, 143.1, 143.6, 143.9, 144.0, 144.1, 144.2, 144.4, 166.8, 167.6.

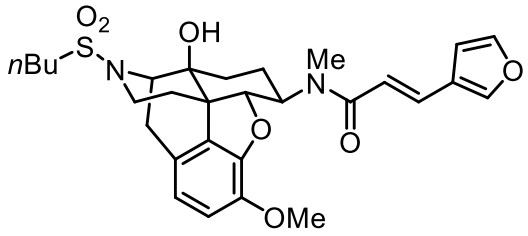
HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{28}H_{32}N_2O_7SNa$, 563.1828; found, 563.1804.

The purity was >99% as assessed by HPLC (254 nm).

General procedure for sulfonamidation.

To a stirred solution of compound **49** (30 mg, 0.0687 mmol) in CH_2Cl_2 (0.7 mL) were added Et_3N (30 μL, 0.215 mmol) and alkyl- or arylsulfonyl chloride (1.2 eq.) at 0 °C under an argon atmosphere. After stirring for 2 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated $NaHCO_3$ aq (5 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by PLC (MeOH/$CHCl_3$ = 1/20) to afford the desired 17-sulfonamide derivative.

(*E*)-*N*-[(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-(Butylsulfonyl)-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl]-3-(furan-3-yl)-*N*-methylacrylamide (55).



55

The title compound was synthesized in 75% yield according to the general procedure for sulfonamidation.

IR (film): 3357, 1651, 1320, 1154 cm^{-1}

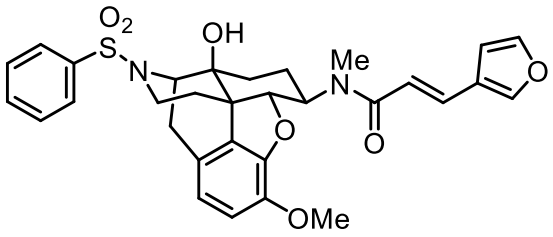
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 0.96 (t, *J* = 7.6 Hz, 3H), 1.37–1.92 (m, 8H), 2.18–2.45 (m, 2H), 2.84–3.28 (m, 6H), 3.00 (s, 2.1H), 3.17 (s, 0.9H), 3.52–3.69 (m, 1H), 3.70–3.91 (m, 0.7H), 3.82 (s, 2.1H), 3.86 (s, 0.9H), 3.99–4.17 (m, 1.3H), 4.64 (d, *J* = 7.6 Hz, 0.7H), 4.83 (d, *J* = 7.6 Hz, 0.3H), 6.42–6.91 (m, 0.7H), 6.43 (d, *J* = 15.2 Hz, 0.7H), 6.54–6.62 (m, 0.3H), 6.58 (d, *J* = 15.2 Hz, 0.3H), 6.67 (d, *J* = 8.4 Hz, 0.3H), 6.74 (d, *J* = 8.4 Hz, 0.7H), 6.77 (d, *J* = 8.4 Hz, 0.3H), 6.86 (d, *J* = 8.4 Hz, 0.7H), 7.32–7.67 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 13.6, 21.8, 21.6, 22.9, 25.5, 29.0, 29.1, 30.3, 30.8, 31.9, 32.2, 37.2, 47.2, 52.6, 56.8, 57.0, 58.0, 58.6, 58.7, 70.0, 70.2, 89.3, 89.4, 107.4, 107.6, 115.5, 117.7, 118.0, 119.2, 119.9, 123.0, 123.2, 124.0, 130.4, 130.7, 132.3, 132.8, 143.1, 143.7, 143.8, 144.07, 144.14, 144.2, 144.3, 166.8, 167.6.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{29}H_{36}N_2O_7SNa$, 579.2141; found, 579.2148.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-3-(Furan-3-yl)-*N*-[(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-4a-hydroxy-9-methoxy-3-(phenylsulfonyl)-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl]-*N*-methylacrylamide (56).



56

The title compound was synthesized in 89% yield according to the general procedure for sulfonamidation.

IR (film): 3377, 1651, 1323, 1160 cm^{-1}

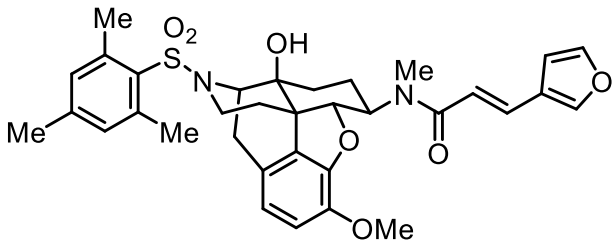
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.37–1.77 (m, 4H), 2.13–2.40 (m, 2H), 2.56 (d, *J* = 18.4 Hz, 0.3H), 2.58 (d, *J* = 18.4 Hz, 0.7H), 2.73 (ddd, *J* = 12.4, 12.4, 3.6 Hz, 1H), 2.86 (dd, *J* = 18.4, 5.2 Hz, 1H), 2.99 (s, 2.1H), 3.05 (s, 1H), 3.13 (s, 0.9H), 3.64–3.87 (m, 1.7H), 3.78 (s, 2.1H), 3.82 (s, 0.9H), 4.11–4.23 (m, 1H), 4.24–4.38 (m, 0.3H), 4.60 (d, *J* = 8.0 Hz, 0.7H), 4.74 (d, *J* = 8.0 Hz, 0.3H), 6.40 (d, *J* = 14.8 Hz, 0.7H), 6.40–6.49 (m, 1H), 6.52 (d, *J* = 8.4 Hz, 0.7H), 6.54–6.62 (m, 0.6H), 6.70 (d, *J* = 8.4 Hz, 0.3H), 6.77 (d, *J* = 8.4 Hz, 0.7H), 7.34–7.70 (m, 6H), 7.79–7.90 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.3, 22.9, 28.8, 29.2, 29.3, 29.4, 29.5, 30.2, 30.4, 32.3, 38.9, 47.1, 47.2, 53.4, 56.3, 56.8, 57.2, 58.0, 59.0, 59.1, 88.8, 89.4, 107.4, 107.6, 115.5, 115.7, 117.8, 118.0, 119.0, 119.7, 123.0, 123.2, 123.6, 123.9, 127.1, 129.35, 129.43, 130.3, 130.6, 132.2, 132.7, 132.9, 133.1, 139.6, 139.7, 143.0, 143.6, 143.8, 143.9, 144.1, 144.4, 166.8, 167.5.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{31}H_{32}N_2O_7SNa$, 599.1828; found, 599.1824.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-3-(Furan-3-yl)-*N*-[(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-4a-hydroxy-3-(mesitylsulfonyl)-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl]-*N*-methylacrylamide (57).



57

The title compound was synthesized in 99% yield according to the general procedure for sulfonamidation.

IR (film): 3374, 1651, 1312, 1156 cm^{-1}

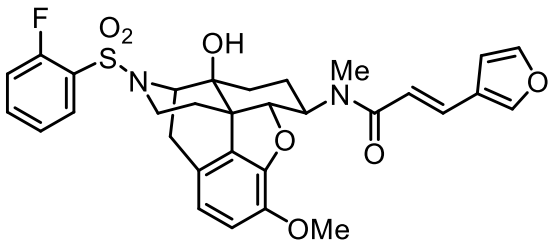
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.38–1.77 (m, 4H), 2.12–2.35 (m, 2H), 2.33 (s, 3H), 2.63 (s, 6H), 2.91 (ddd, *J* = 12.8, 12.8, 3.6 Hz, 1H), 2.87–3.06 (m, 1H), 2.98 (s, 2.1H), 3.07–3.34 (m, 2.9H), 3.47–3.58 (m, 1H), 3.71–3.90 (m, 1.7H), 3.81 (s, 2.1H), 3.85 (s, 0.9H), 4.22–4.37 (m, 0.3H), 4.59 (d, *J* = 7.6 Hz, 0.7H), 4.75 (d, *J* = 7.6 Hz, 0.3H), 6.43 (d, *J* = 15.2 Hz, 0.7H), 6.43–6.49 (m, 0.7H), 6.53–6.61 (m, 0.6H), 6.64 (d, *J* = 8.0 Hz, 0.3H), 6.70 (d, *J* = 8.0 Hz, 0.7H), 6.76 (d, *J* = 8.0 Hz, 0.3H), 6.83 (d, *J* = 8.0 Hz, 0.7H), 6.96–7.02 (m, 2H), 7.34–7.62 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.0, 21.3, 22.8, 23.0, 28.8, 29.0, 29.2, 30.4, 30.6, 30.6, 32.4, 38.5, 47.4, 56.8, 57.2, 58.0, 58.2, 58.3, 70.2, 70.4, 88.8, 89.5, 107.4, 107.6, 115.5, 115.7, 117.9, 118.1, 119.3, 119.9, 123.1, 123.3, 124.1, 124.4, 130.4, 130.7, 132.0, 132.1, 132.2, 132.3132.6, 140.0, 143.0, 143.1, 143.6, 143.8, 143.9, 144.1, 144.3, 166.7, 167.5.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{34}H_{38}N_2O_7SNa$, 641.2297; found, 641.2281.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-*N*-{(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-[(2-Fluorophenyl)sulfonyl]-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl}-3-(furan-3-yl)-*N*-methylacrylamide (58).



58

The title compound was synthesized in 85% yield according to the general procedure for sulfonamidation.

IR (film): 3364, 1651, 1325, 1159 cm^{-1}

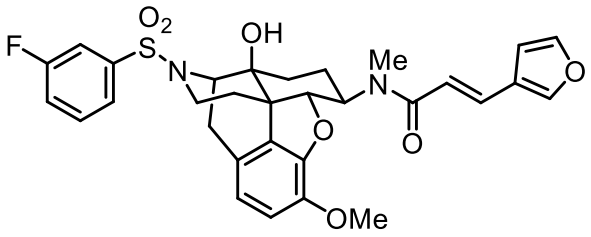
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.39–1.78 (m, 4H), 2.13–2.39 (m, 1H), 2.32 (ddd, *J* = 12.8, 12.8, 5.6 Hz, 1H), 2.80–2.96 (m, 3H), 2.97–2.38 (m, 1H), 2.99 (s, 2.1H), 3.13 (s, 0.9H), 3.67–3.86 (m, 1.7H), 3.81 (s, 2.1H), 3.84 (s, 0.9H), 4.12 (d, *J* = 5.2 Hz, 0.3H), 4.16 (d, *J* = 5.2 Hz, 0.7H), 4.22–4.36 (m, 0.3H), 4.61 (d, *J* = 8.0 Hz, 0.7H), 4.76 (d, *J* = 8.0 Hz, 0.3H), 6.42 (d, *J* = 15.6 Hz, 0.7H), 6.42–6.49 (m, 0.7H), 6.53–6.62 (m, 0.9H), 6.65 (d, *J* = 8.4 Hz, 0.7H), 6.74 (d, *J* = 8.4 Hz, 0.3H), 6.82 (d, *J* = 8.4 Hz, 0.7H), 7.19–7.69 (m, 6H), 7.89–7.98 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.3, 22.8, 28.8, 29.1, 29.2, 30.4, 30.6, 30.7, 32.5, 39.1, 47.2, 56.8, 57.2, 57.9, 59.0, 59.1, 70.1, 70.2, 88.8, 89.4, 107.4, 107.6, 115.5, 115.7, 117.2, 117.4, 118.1, 119.2, 119.8, 123.0, 123.2, 123.7, 123.9, 124.7, 127.6, 127.7, 130.3, 130.6, 130.9, 132.2, 132.7, 135.2, 135.4, 135.5, 143.0, 143.6, 143.8, 143.9, 144.1, 144.2, 144.4, 158.7 (d, $J_{C–F}$ = 255.0 Hz), 166.7, 167.5.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{31}H_{31}N_2O_7SFNa$, 617.1734; found, 617.1717.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-*N*-{(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-[(3-Fluorophenyl)sulfonyl]-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl}-3-(furan-3-yl)-*N*-methylacrylamide (59).



59

The title compound was synthesized in 80% yield according to the general procedure for sulfonamidation.

IR (film): 3349, 1651, 1323, 1158 cm^{-1}

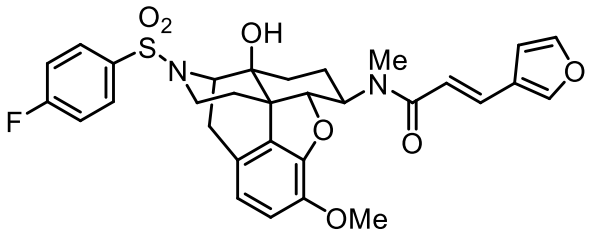
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.40–1.78 (m, 4H), 2.15–2.38 (m, 2H), 2.57–2.65 (m, 0.3H), 2.61 (d, *J* = 18.4 Hz, 0.7H), 2.71–2.84 (m, 1H), 2.84–2.98 (m, 2H), 2.99 (s, 2.1H), 3.14 (s, 0.9H), 3.64–3.86 (m, 1.7H), 3.79 (s, 2.1H), 3.83 (s, 0.9H), 4.17 (d, *J* = 5.2 Hz, 1H), 4.14–4.31 (m, 0.3H), 4.61 (d, *J* = 7.6 Hz, 0.7H), 4.76 (d, *J* = 7.6 Hz, 0.3H), 6.40 (d, *J* = 15.6 Hz, 0.7H), 6.41–6.46 (m, 0.7H), 6.50 (d, *J* = 8.4 Hz, 0.3H), 6.53–6.61 (m, 0.6H), 6.55 (d, *J* = 8.4 Hz, 0.7H), 6.71 (d, *J* = 8.4 Hz, 0.3H), 6.79 (d, *J* = 8.4 Hz, 0.7H), 7.29–7.68 (m, 7H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.2, 22.8, 28.8, 29.0, 29.1, 29.8, 30.0, 30.2, 30.5, 32.6, 39.1, 47.1, 56.8, 57.1, 57.9, 59.2, 70.1, 70.3, 88.8, 89.4, 107.4, 107.6, 114.4, 114.6, 115.5, 115.7, 117.8, 118.0, 119.1, 119.7, 120.0, 120.1, 120.3, 122.8, 123.0, 123.2, 123.4, 123.7, 130.2, 130.5, 131.2, 131.3, 132.2, 132.7, 141.7, 141.8, 141.9, 143.0, 143.6, 143.8, 144.0, 144.2, 144.4. 162.5 (d, $J_{C–F}$ = 252.0 Hz), 166.8, 167.6.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{31}H_{31}N_2O_7SFNa$, 617.1734; found, 617.1713.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-*N*-{(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-[(4-Fluorophenyl)sulfonyl]-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl}-3-(furan-3-yl)-*N*-methylacrylamide (60).



60

The title compound was synthesized in 74% yield according to the general procedure for sulfonamidation.

IR (film): 3365, 1651, 1324, 1157 cm^{-1}

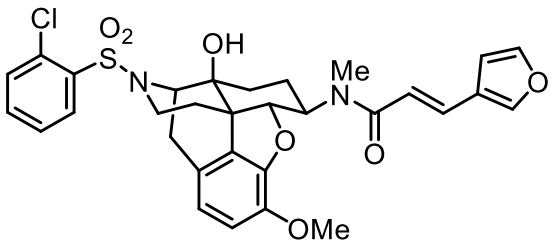
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.40–1.78 (m, 4H), 2.15–2.37 (m, 2H), 2.61 (d, *J* = 18.4 Hz, 0.7H), 2.62 (d, *J* = 18.4 Hz, 0.3H), 2.68–2.83 (m, 1H), 2.86–3.04 (m, 2H), 2.99 (s, 2.1H), 3.14 (s, 0.9H), 3.60–3.86 (m, 1.7H), 3.79 (s, 2.1H), 3.83 (s, 0.9H), 4.16 (d, *J* = 4.8 Hz, 1H), 4.13–4.32 (m, 0.3H), 4.60 (d, *J* = 8.0 Hz, 0.7H), 4.76 (d, *J* = 8.0 Hz, 0.3H), 6.40 (d, *J* = 15.2 Hz, 0.7H), 6.40–6.46 (m, 0.7H), 6.50 (d, *J* = 8.0 Hz, 0.3H), 6.53–6.61 (m, 0.6H), 6.56 (d, *J* = 8.4 Hz, 0.7H), 6.71 (d, *J* = 8.0 Hz, 0.3H), 6.79 (d, *J* = 8.0 Hz, 0.7H), 7.18–7.29 (m, 2H), 7.33–7.63 (m, 3H), 7.82–7.91 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.3, 22.9, 28.8, 29.1, 29.2, 29.6, 29.9, 30.2, 30.5, 38.9, 47.1, 56.8, 57.1, 58.0, 59.1, 70.1, 70.2, 88.9, 89.4, 107.4, 107.6, 115.5, 115.7, 116.4, 116.6, 116.7, 116.8, 117.8, 118.0, 119.1, 119.7, 123.0, 123.2, 123.5, 123.7, 129.8, 129.9, 130.3, 130.5, 132.2, 132.7, 135.7, 135.9, 143.0, 143.6, 143.8, 144.0, 144.1, 144.2, 144.4, 165.2 (d, $J_{C–F}$ = 255.9 Hz), 166.8, 167.5.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{31}H_{31}N_2O_7SFNa$, 617.1734; found, 617.1721.

The purity was >98% as assessed by HPLC (254 nm).

(*E*)-*N*-{(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-[(2-Chlorophenyl)sulfonyl]-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl}-3-(furan-3-yl)-*N*-methylacrylamide (61).



61

The title compound was synthesized in 87% yield according to the general procedure for sulfonamidation.

IR (film): 3365, 1651, 1323, 1160 cm^{-1}

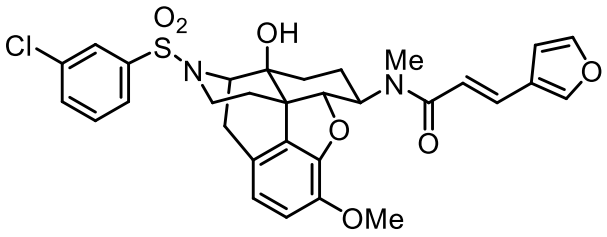
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.37–1.76 (m, 4H), 2.10–2.35 (m, 1H), 2.33 (ddd, *J* = 12.8, 12.8, 5.6 Hz, 1H), 2.89–3.24 (m, 7H), 3.69–3.80 (m, 0.7H), 3.73 (dd, *J* = 13.6, 4.8 Hz, 1H), 3.81 (s, 2.1H), 3.85 (s, 0.9H), 3.90 (d, *J* = 4.8 Hz, 0.3H), 3.94 (d, *J* = 4.8 Hz, 0.7H), 4.25–4.41 (m, 0.3H), 4.61 (d, *J* = 8.0 Hz, 0.7H), 4.75 (d, *J* = 8.0 Hz, 0.3H), 6.42 (d, *J* = 15.2 Hz, 0.7H), 6.45–6.48 (m, 0.7H), 6.54–6.61 (m, 0.6H), 6.64 (d, *J* = 8.0 Hz, 0.3H), 6.71 (d, *J* = 8.0 Hz, 0.7H), 6.76 (d, *J* = 8.0 Hz, 0.3H), 6.84 (d, *J* = 8.0 Hz, 0.7H), 7.35–7.62 (m, 6H), 8.13–8.19 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.3, 22.8, 28.8, 29.0, 29.2, 30.3, 30.5, 31.0, 32.2, 39.4, 39.5, 47.3, 47.3, 56.2, 56.8, 57.2, 57.9, 58.8, 59.0, 70.3, 70.5, 88.7, 89.4, 107.4, 107.6, 115.5, 115.8, 117.9, 118.1, 119.3, 119.9, 123.1, 123.2, 123.8, 124.1, 127.26, 127.33, 130.3, 130.5, 132.16, 132.19, 132.4, 134.1, 134.3, 143.0, 143.6, 143.8, 143.9, 144.08, 144.12, 144.4, 166.8, 167.5.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{31}H_{31}N_2O_7SClNa$, 633.1438; found, 633.1421.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-*N*-{(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-[(3-Chlorophenyl)sulfonyl]-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl}-3-(furan-3-yl)-*N*-methylacrylamide (62).



62

The title compound was synthesized in 83% yield according to the general procedure for sulfonamidation.

IR (film): 3356, 1651, 1324, 1160 cm^{-1}

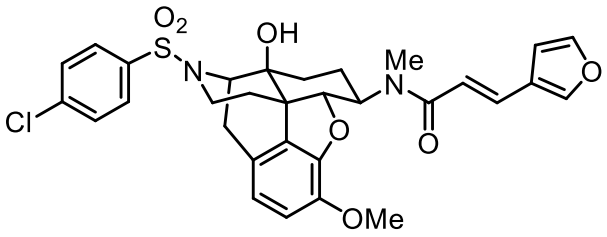
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.40–1.83 (m, 4H), 2.15–2.38 (m, 2H), 2.63 (d, *J* = 18.4 Hz, 1H), 2.71–2.83 (m, 1H), 2.89–3.02 (m, 2H), 2.99 (s, 2.1H), 3.14 (s, 0.9H), 3.62–3.81 (m, 1.7H), 3.79 (s, 2.1H), 3.83 (s, 0.9H), 4.14–4.28 (m, 1.3H), 4.61 (d, *J* = 8.0 Hz, 0.7H), 4.77 (d, *J* = 8.0 Hz, 0.3H), 6.40 (d, *J* = 14.8 Hz, 0.7H), 6.41–6.47 (m, 0.7H), 6.52 (d, *J* = 8.4 Hz, 0.3H), 6.57 (d, *J* = 8.4 Hz, 0.7H), 6.57–6.62 (m, 0.6H), 6.72 (d, *J* = 8.4 Hz, 0.3H), 6.79 (d, *J* = 8.4 Hz, 0.7H), 7.34–7.63 (m, 5H), 7.68–7.76 (m, 1H), 7.82–7.87 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.3, 22.8, 28.9, 29.0, 29.1, 29.8, 30.1, 30.2, 30.5, 39.1, 47.1, 47.1, 56.8, 57.1, 57.9, 59.2, 70.1, 70.3, 88.9, 89.4, 107.4, 107.6, 115.5, 115.7, 117.8, 118.0, 119.1, 119.8, 123.0, 123.2, 123.4, 123.6, 125.1, 127.1, 130.2, 130.5, 130.6, 130.7, 132.2, 132.7, 133.0, 133.1, 135.4, 135.6, 141.5, 141.7, 143.0, 143.6, 143.8, 144.0, 144.1, 144.2, 144.4, 166.8, 167.6.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{31}H_{31}N_2O_7SClNa$, 633.1438; found, 633.1423.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-*N*-{(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-[(4-Chlorophenyl)sulfonyl]-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl}-3-(furan-3-yl)-*N*-methylacrylamide (63).



63

The title compound was synthesized in 86% yield according to the general procedure for sulfonamidation.

IR (film): 3357, 1651, 1324, 1160 cm^{-1}

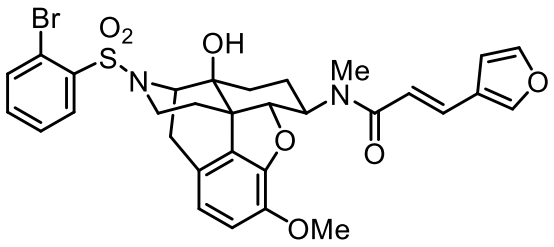
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.40–1.77 (m, 4H), 2.15–2.37 (m, 2H), 2.63 (d, *J* = 18.4 Hz, 0.7H), 2.64 (d, *J* = 18.4 Hz, 0.3H), 2.69–2.82 (m, 1H), 2.88–3.04 (m, 2H), 2.99 (s, 2.1H), 3.14 (s, 0.9H), 3.60–3.87 (m, 1.7H), 3.79 (s, 2.1H), 3.83 (s, 0.9H), 4.12–4.28 (m, 1.3H), 4.60 (d, *J* = 8.0 Hz, 0.7H), 4.76 (d, *J* = 8.0 Hz, 0.3H), 6.40 (d, *J* = 15.6 Hz, 0.7H), 6.40–6.47 (m, 0.7H), 6.52 (d, *J* = 8.0 Hz, 0.3H), 6.54–6.61 (m, 0.6H), 6.57 (d, *J* = 8.0 Hz, 0.7H), 6.72 (d, *J* = 8.0 Hz, 0.3H), 6.79 (d, *J* = 8.0 Hz, 0.7H), 7.34–7.63 (m, 5H), 7.75–7.83 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.3, 22.8, 28.8, 29.0, 29.1, 29.8, 30.1, 30.2, 30.5, 39.0, 47.1, 47.1, 56.8, 57.1, 58.0, 59.1, 70.1, 70.3, 88.9, 89.4, 107.4, 107.6, 115.5, 115.6, 117.8, 118.0, 119.1, 119.8, 123.0, 123.2, 123.5, 123.7, 128.5, 129.6, 129.7, 130.3, 130.5, 132.2, 132.8, 138.3, 138.5, 139.3, 139.5, 143.0, 143.6, 143.8, 144.0, 144.1, 144.2, 144.4, 166.8, 167.6.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{31}H_{31}N_2O_7SClNa$, 633.1438; found, 633.1420.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-*N*-{(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-[(2-Bromophenyl)sulfonyl]-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl}-3-(furan-3-yl)-*N*-methylacrylamide (64).



64

The title compound was synthesized in 87% yield according to the general procedure for sulfonamidation.

IR (film): 3365, 1651, 1323, 1160 cm^{-1}

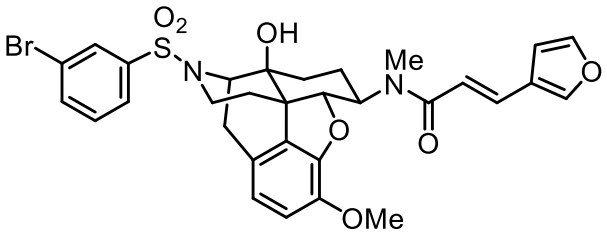
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.37–1.68 (m, 4H), 2.08–2.40 (m, 1H), 2.35 (ddd, *J* = 12.8, 12.8, 4.8 Hz, 1H), 2.92–3.32 (m, 4.9H), 2.99 (s, 2.1H), 3.66–3.97 (m, 2.7H), 3.82 (s, 2.1H), 3.85 (s, 0.9H), 4.26–4.44 (m, 0.3H), 4.61 (d, *J* = 8.0 Hz, 0.7H), 4.75 (d, *J* = 8.0 Hz, 0.3H), 6.42 (d, *J* = 15.6 Hz, 0.7H), 6.42–6.50 (m, 0.7H), 6.53–6.61 (m, 0.6H), 6.65 (d, *J* = 8.4 Hz, 0.3H), 6.72 (d, *J* = 8.4 Hz, 0.7H), 6.76 (d, *J* = 8.4 Hz, 0.3H), 6.84 (d, *J* = 8.4 Hz, 0.7H), 7.33–7.63 (m, 5H), 7.75–7.86 (m, 1H), 8.21 (dd, *J* = 7.6, 1.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.2, 22.8, 28.8, 29.0, 29.2, 30.3, 30.5, 31.0, 32.1, 39.4, 39.6, 47.2, 56.1, 56.8, 57.2, 57.9, 58.8, 59.0, 70.4, 70.6, 88.7, 89.4, 107.4, 107.6, 115.5, 115.8, 117.9, 118.1, 119.3, 119.9, 120.1, 123.0, 123.2, 123.8, 124.2, 127.9, 130.3, 130.5, 132.1, 132.8, 132.8, 134.1, 134.3, 135.7, 137.8, 138.0, 143.0, 143.6, 143.8, 143.9, 144.1, 144.4, 166.7, 167.5.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{31}H_{31}N_2O_7SBrNa$, 677.0933; found, 677.0920.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-*N*-{(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-[(3-Bromophenyl)sulfonyl]-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl}-3-(furan-3-yl)-*N*-methylacrylamide (65).



65

The title compound was synthesized in 86% yield according to the general procedure for sulfonamidation.

IR (film): 3357, 1651, 1324, 1160 cm^{-1}

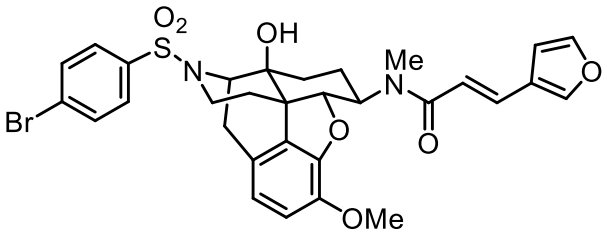
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.41–1.76 (m, 4H), 2.14–2.38 (m, 2H), 2.63 (d, *J* = 18.4 Hz, 0.7H), 2.64 (d, *J* = 18.4 Hz, 0.3H), 2.71–2.83 (m, 1H), 2.86–3.02 (m, 2H), 2.99 (s, 2.1H), 3.14 (s, 0.9H), 3.60–3.86 (m, 1.7H), 3.79 (s, 2.1H), 3.83 (s, 0.9H), 4.12–4.29 (m, 1.3H), 4.61 (d, *J* = 7.6 Hz, 0.7H), 4.77 (d, *J* = 7.6 Hz, 0.3H), 6.40 (d, *J* = 14.8 Hz, 0.7H), 6.41–6.48 (m, 0.7H), 6.52 (d, *J* = 8.4 Hz, 0.3H), 6.54–6.62 (m, 0.6H), 6.57 (d, *J* = 8.4 Hz, 0.7H), 6.72 (d, *J* = 8.4 Hz, 0.3H), 6.79 (d, *J* = 8.4 Hz, 0.7H), 7.34–7.63 (m, 4H), 7.71–7.81 (m, 2H), 7.97–8.02 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.3, 22.8, 28.7, 28.8, 29.0, 29.1, 29.9, 30.1, 30.2, 30.5, 32.7, 39.1, 47.1, 47.1, 56.8, 57.1, 57.9, 59.2, 70.1, 70.3, 88.8, 89.4, 107.4, 107.6, 115.5, 115.7, 117.8, 118.0, 119.1, 119.8, 123.0, 123.2, 123.3, 123.4, 123.7, 125.5, 130.0, 130.3, 130.5, 130.8, 130.9, 132.2, 132.7, 135.8, 136.0, 141.7, 141.8, 143.0, 143.6, 143.8, 144.0, 144.1, 144.2, 144.4, 166.8, 167.6.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{31}H_{31}N_2O_7SBrNa$, 677.0933; found, 677.0920.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-*N*-{(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-[(4-Bromophenyl)sulfonyl]-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl}-3-(furan-3-yl)-*N*-methylacrylamide (66).



66

The title compound was synthesized in 79% yield according to the general procedure for sulfonamidation.

IR (film): 3364, 1651, 1324, 1159 cm^{-1}

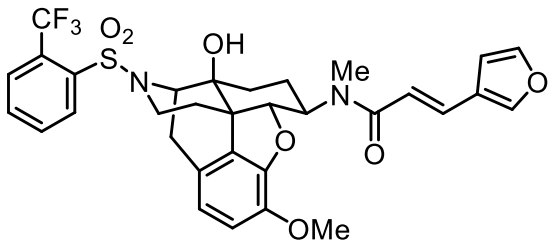
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.40–1.80 (m, 4H), 2.15–2.37 (m, 2H), 2.64 (d, *J* = 18.4 Hz, 0.7H), 2.65 (d, *J* = 18.4 Hz, 0.3H), 2.69–2.84 (m, 1H), 2.88–3.05 (m, 2H), 2.99 (s, 2.1H), 3.14 (s, 0.9H), 3.60–3.86 (m, 1.7H), 3.79 (s, 2.1H), 3.83 (s, 0.9H), 4.11–4.27 (m, 1.3H), 4.60 (d, *J* = 8.0 Hz, 0.7H), 4.76 (d, *J* = 8.0 Hz, 0.3H), 6.40 (d, *J* = 15.6 Hz, 0.7H), 6.41–6.46 (m, 0.7H), 6.50–6.62 (m, 1.6H), 6.72 (d, *J* = 8.4 Hz, 0.3H), 6.79 (d, *J* = 8.4 Hz, 0.7H), 7.34–7.64 (m, 3H), 7.65–7.75 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.3, 22.8, 28.8, 29.0, 29.1, 29.8, 30.1, 30.2, 30.5, 32.7, 39.0, 47.1, 47.1, 56.8, 57.1, 57.9, 59.1, 70.1, 70.3, 88.9, 89.4, 107.4, 107.6, 115.5, 115.6, 117.7, 118.0, 119.2, 119.8, 123.0, 123.2, 123.4, 123.7, 127.8, 128.0, 128.6, 130.2, 130.5, 132.2, 132.5, 132.7, 132.8, 138.8, 139.0, 143.0, 143.6, 143.8, 144.0, 144.1, 144.2, 144.4, 166.8, 167.6.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{31}H_{31}N_2O_7SBrNa$, 677.0933; found, 677.0915.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-3-(Furan-3-yl)-*N*-((4*R*,4a*S*,7*R*,7a*R*,12b*S*)-4a-hydroxy-9-methoxy-3-{[2-(trifluoromethyl)phenyl] sulfonyl}-2,3,4,4a,5,6,7,7aoctahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl)-*N*-methyl-acrylamide (67).



67

The title compound was synthesized in 86% yield according to the general procedure for sulfonamidation.

IR (film): 3349, 1651, 1338, 1161 cm^{-1}

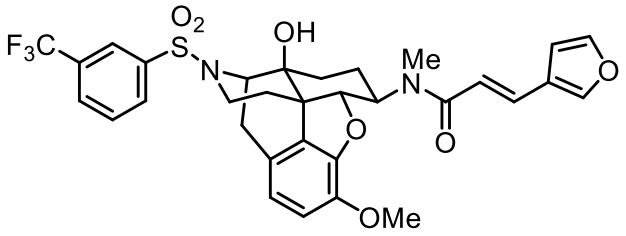
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.37–1.72 (m, 4H), 2.12–2.40 (m, 2H), 2.83–3.08 (m, 4H), 2.98 (s, 2.1H), 3.14 (s, 0.9H), 3.62–3.88 (m, 1.7H), 3.80 (s, 2.1H), 3.84 (s, 0.9H), 4.01–4.12 (m, 1H), 4.17–4.35 (m, 0.3H), 4.61 (d, *J* = 8.0 Hz, 0.7H), 4.77 (d, *J* = 8.0 Hz, 0.3H), 6.41 (d, *J* = 15.2 Hz, 0.7H), 6.42–6.50 (m, 0.7H), 6.53–6.63 (m, 0.9H), 6.66 (d, *J* = 8.0 Hz, 0.7H), 6.74 (d, *J* = 8.0 Hz, 0.3H), 6.82 (d, *J* = 8.0 Hz, 0.7H), 7.34–7.63 (m, 3H), 7.69–7.80 (m, 2H), 7.88–7.99 (m, 1H), 8.22–8.32 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.2, 22.8, 28.9, 29.0, 30.4, 30.7, 30.9, 31.0, 39.3, 39.4, 47.1, 56.6, 56.8, 57.1, 57.9, 58.9, 59.0, 70.2, 70.4, 88.8, 89.4, 107.4, 107.6, 115.5, 115.7, 117.8, 118.0, 119.2, 119.9, 121.2, 123.0, 123.2, 123.7, 123.9, 124.0, 126.9, 127.3, 127.6, 127.9, 128.77, 128.8, 130.3, 130.5, 132.2, 132.3, 132.5, 132.7, 132.9, 133.1, 138.3, 138.6, 143.0, 143.6, 143.8, 144.0, 144.1, 144.2, 144.4, 166.8, 167.6.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{32}H_{31}N_2O_7SF_3Na$, 667.1702; found, 667.1697.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-3-(Furan-3-yl)-*N*-((4*R*,4a*S*,7*R*,7a*R*,12b*S*)-4a-hydroxy-9-methoxy-3-{[3-(trifluoromethyl)phenyl] sulfonyl}-2,3,4,4a,5,6,7,7aoctahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl)-*N*-methyl-acrylamide (68).



68

The title compound was synthesized in 82% yield according to the general procedure for sulfonamidation.

IR (film): 3357, 1651, 1327, 1160 cm^{-1}

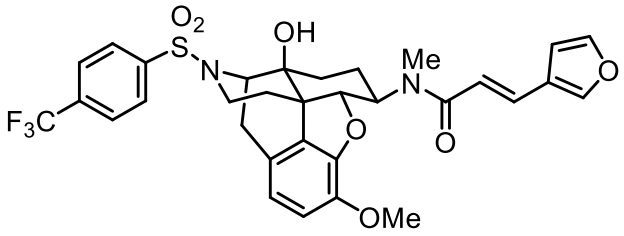
^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) =1.40–1.80 (m, 4H), 2.17–2.38 (m, 2H), 2.62 (d, *J* = 18.0 Hz, 0.7H), 2.66 (d, *J* = 18.0 Hz, 0.3H), 2.71–2.91 (m, 1.7H), 2.92–3.03 (m, 1.3H), 2.99 (s, 2.1H), 3.15 (s, 0.9H), 3.61–3.86 (m, 1.7H), 3.79 (s, 2.1H), 3.83 (s, 0.9H), 4.09–4.24 (m, 0.3H), 4.21 (d, *J* = 5.6 Hz, 1H), 4.61 (d, *J* = 8.0 Hz, 0.7H), 4.79 (d, *J* = 8.0 Hz, 0.3H), 6.40 (d, *J* = 15.2 Hz, 0.7H), 6.40–6.47 (m, 0.7H), 6.49–6.61 (m, 1.6H), 6.72 (d, *J* = 8.0 Hz, 0.3H), 6.79 (d, *J* = 8.0 Hz, 0.7H), 7.34–7.43 (m, 1H), 7.47 (d, *J* = 15.2 Hz, 0.7H), 7.52 (d, *J* = 15.2 Hz, 0.3H), 7.54–7.63 (m, 1H), 7.66–7.75 (m, 1H), 7.84–7.92 (m, 1H), 8.01–8.09 (m, 1H), 8.10–8.17(m,1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.2, 22.8, 28.9, 28.9, 30.1, 30.3, 30.5, 30.6, 39.1, 47.1, 47.1, 53.4, 56.8, 57.1, 57.9, 59.2, 70.1, 70.3, 89.0, 89.3, 89.5, 107.4, 107.6, 115.5, 117.7, 118.0, 119.2, 119.8, 121.7, 123.0, 123.2, 123.4, 123.5, 124.2, 124.4, 127.2, 129.5, 130.0, 130.2, 130.3, 130.5, 131.5, 131.7, 131.8, 132.0, 132.2, 132.3, 132.8, 141.2, 141.4, 143.1, 143.7, 143.8, 144.0, 144.1, 144.2, 144.4, 166.8, 167.6.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{32}H_{31}N_2O_7SF_3Na$, 667.1702; found, 667.1677.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-3-(Furan-3-yl)-*N*-((4*R*,4a*S*,7*R*,7a*R*,12b*S*)-4a-hydroxy-9-methoxy-3-{[4-(trifluoromethyl)phenyl] sulfonyl}-2,3,4,4a,5,6,7,7aoctahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl)-*N*-methyl-acrylamide (69).



69

The title compound was synthesized in 79% yield according to the general procedure for sulfonamidation.

IR (film): 3357, 1651, 1324, 1162 cm^{-1}

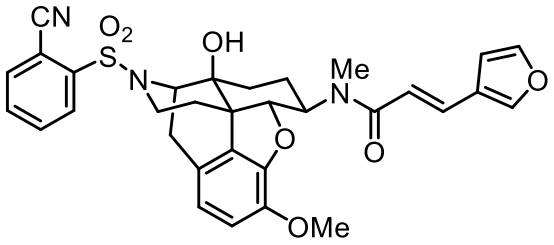
^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.39–1.85 (m, 4H), 2.15–2.40 (m, 2H), 2.63 (d, *J* = 18.4 Hz, 0.7H), 2.67 (d, *J* = 18.4 Hz, 0.3H), 2.80 (dddd, *J* = 13.2, 13.2, 13.2, 3.6 Hz, 1H), 2.88–3.10 (m, 2H), 2.99 (s, 2.1H), 3.15 (s, 0.9H), 3.61–3.81 (m, 1.7H), 3.79 (s, 2.1H), 3.83 (s, 0.9H), 4.07–4.24 (m, 0.3H), 4.22 (d, *J* = 4.8 Hz, 1H), 4.61 (d, *J* = 8.0 Hz, 0.7H), 4.78 (d, *J* = 8.0 Hz, 0.3H), 6.40 (d, *J* = 15.2 Hz, 0.7H), 6.40–6.47 (m, 0.7H), 6.49–6.63 (m, 1.6H), 6.72 (d, *J* = 8.4 Hz, 0.3H), 6.79 (d, *J* = 8.4 Hz, 0.7H), 7.34– 7.44 (m, 1H), 7.47 (d, *J* = 15.2 Hz, 0.7H), 7.52 (d, *J* = 15.2 Hz, 0.3H), 7.54–7.63 (m, 1H), 7.76–7.87 (m, 2H), 7.94–8.05 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.2, 22.8, 28.9, 29.0, 30.2, 30.6, 39.1, 47.0, 56.8, 57.1, 57.9, 59.2, 70.1, 70.3, 89.0, 89.3, 107.4, 107.5, 115.5, 117.6, 117.9, 119.2, 119.8, 121.8, 123, 123.2, 123.4, 123.5, 124.5, 126.4, 126.5, 127.6, 127.7, 130.2, 130.5, 132.3, 132.8, 134.2, 134.4, 134.5, 134.7, 143.0, 143.5, 143.7, 144.06, 144.1, 144.3, 144.4, 166.8, 167.6.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{32}H_{31}N_2O_7SF_3Na$, 667.1702; found, 667.1674.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-*N*-{(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-[(2-Cyanophenyl)sulfonyl]-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl}-3-(furan-3-yl)-*N*-methylacrylamide (70).



70

The title compound was synthesized in 85% yield according to the general procedure for sulfonamidation.

IR (film): 3357, 2231, 1651, 1324, 1162 cm^{-1}

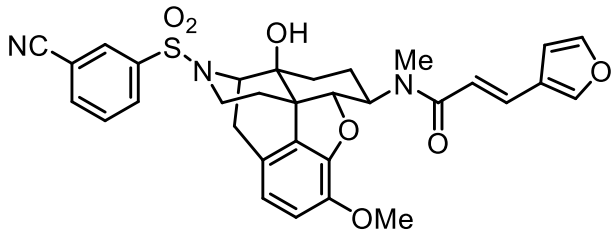
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.38–1.83 (m, 4H), 2.14–2.37 (m, 1H), 2.41 (ddd, *J* = 12.8, 12.8, 5.6 Hz, 1H), 2.72–2.87 (m, 1H), 2.88–3.03 (m, 1H), 2.98 (s, 2.1H), 3.04–3.20 (m, 2.9H), 3.62 (dd, *J* = 13.6, 4.8 Hz, 0.7H), 3.65–3.90 (m, 0.7H), 3.69 (dd, *J* = 13.6, 4.8 Hz, 0.3H), 3.80 (s, 2.1H), 3.85 (s, 0.9H), 4.12–4.30 (m, 1.3H), 4.62 (d, *J* = 8.0 Hz, 0.7H), 4.79 (d, *J* = 8.0 Hz, 0.3H), 6.11 (d, *J* = 15.2 Hz, 0.7H), 6.42–6.48 (m, 0.7H), 6.53–6.61 (m, 0.6H), 6.63 (d, *J* = 8.0 Hz, 0.3H), 6.69 (d, *J* = 8.0 Hz, 0.7H), 6.75 (d, *J* = 8.0 Hz, 0.3H), 6.83 (d, *J* = 8.0 Hz, 0.7H), 7.35–7.43 (m, 1H), 7.46 (d, *J* = 15.2 Hz, 0.7H), 7.51 (d, *J* = 15.2 Hz, 0.3H), 7.54–7.64 (m, 1H), 7.67–7.83 (m, 2H), 7.86–7.96 (m, 1H), 8.12–8.20 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.1, 22.7, 28.5, 28.7, 30.6, 31.0, 31.5, 33.0, 39.6, 47.0, 47.1, 56.8, 57.1, 57.9, 59.2, 70.5, 70.6, 88.9, 89.3, 107.4, 107.6, 110.1, 110.2, 115.5, 115.6, 116.7, 117.8, 118.0, 119.3, 120.0, 123.0, 123.2, 123.7, 123.9, 130.3, 130.5, 132.2, 132.7, 132.9, 132.9, 133.1, 135.46, 135.5, 142.5, 142.8, 143.0, 143.6, 143.8, 144.0, 144.1, 144.2, 144.4, 166.8, 167.5.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{32}H_{31}N_3O_7SNa$, 624.1780; found, 624.1768.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-*N*-{(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-[(3-Cyanophenyl)sulfonyl]-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl}-3-(furan-3-yl)-*N*-methylacrylamide (71).



71

The title compound was synthesized in 75% yield according to the general procedure for sulfonamidation.

IR (KBr): 3375, 2232, 1655, 1323, 1157 cm^{-1}

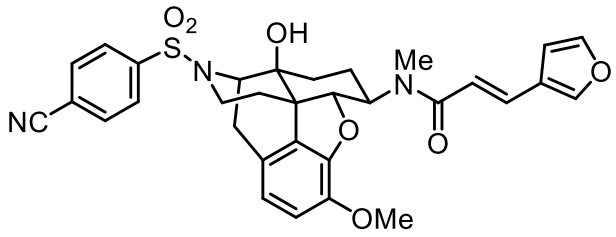
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.39–1.87 (m, 4H), 2.17–2.40 (m, 2H), 2.67 (d, *J* = 18.4 Hz, 0.7H), 2.73 (d, *J* = 18.4 Hz, 0.3H), 2.74–2.91 (m, 1H), 2.93–3.21 (m, 2H), 2.98 (s, 2.1H), 3.16 (s, 0.9H), 3.58–3.90 (m, 1.7H), 3.79 (s, 2.1H), 3.84 (s, 0.9H), 3.95–4.13 (m, 0.3H), 4.22 (d, *J* = 5.2 Hz, 1H), 4.61 (d, *J* = 7.6 Hz, 0.7H), 4.81 (d, *J* = 7.6 Hz, 0.3H), 6.39 (d, *J* = 15.2 Hz, 0.7H), 6.40–6.45 (m, 0.7H), 6.52–6.64 (m, 1.6H), 6.73 (d, *J* = 8.4 Hz, 0.3H), 6.81 (d, *J* = 8.4 Hz, 0.7H), 7.35–7.45 (m, 1H), 7.46 (d, *J* = 14.8 Hz, 0.7H), 7.52 (d, *J* = 14.8 Hz, 0.3H), 7.54–7.64 (m, 1H), 7.65–7.73 (m, 1H), 7.84–7.93 (m, 1H), 8.05–8.14 (m, 1H), 8.16–8.22 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.1, 22.8, 28.6, 28.7, 30.2, 30.6, 31.1, 39.3, 39.4, 47.0, 56.8, 57.0, 57.9, 58.1, 59.2, 59.3, 70.2, 70.3, 89.1, 89.3, 107.3, 107.5, 113.6, 113.8, 115.5, 117.1, 117.2, 117.6, 117.9, 119.3, 119.9, 123.0, 123.2, 123.5, 130.2, 130.3, 130.7, 130.8, 131.0, 131.1, 132.3, 132.9, 135.7, 135.9, 141.9, 142.1, 143.0, 143.7, 144.1, 144.3, 144.4, 166.8, 167.6.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{32}H_{31}N_3O_7SNa$, 624.1780; found, 624.1762.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-*N*-{(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-[(4-Cyanophenyl)sulfonyl]-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl}-3-(furan-3-yl)-*N*-methylacrylamide (72).



72

The title compound was synthesized in 77% yield according to the general procedure for sulfonamidation.

IR (KBr): 3391, 2233, 1655, 1331, 1153 cm^{-1}

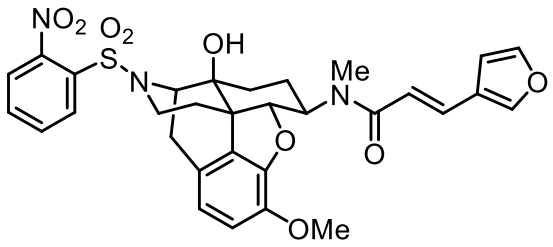
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.40–1.85 (m, 4H), 2.17–2.40 (m, 2H), 2.64 (d, *J* = 18.0 Hz, 0.7H), 2.71 (d, *J* = 18.0 Hz, 0.3H), 2.75–3.05 (m, 3H), 2.98 (s, 2.1H), 3.16 (s, 0.9H), 3.59–3.89 (m, 1.7H), 3.79 (s, 2.1H), 3.84 (s, 0.9H), 3.93–4.10 (m, 0.3H), 4.20 (d, *J* = 5.6 Hz, 1H), 4.61 (d, *J* = 8.0 Hz, 0.7H), 4.80 (d, *J* = 8.0 Hz, 0.3H), 6.39 (d, *J* = 15.6 Hz, 0.7H), 6.39–6.46 (m, 0.7H), 6.53–6.62 (m, 1.6H), 6.73 (d, *J* = 8.0 Hz, 0.3H), 6.80 (d, *J* = 8.0 Hz, 0.7H), 7.35–7.65 (m, 3H), 7.80–7.88 (m, 2H), 7.93–8.03 (m, 2H).

^{13}C NMR (100 MHz, pyridine-d_5): δ (mixture of rotamers) = 21.8, 23.3, 28.4, 28.7, 31.0, 31.6, 32.2, 39.9, 47.6, 56.1, 56.6, 57.6, 58.3, 60.2, 60.3, 70.1, 70.3, 89.3, 90.0, 108.3, 115.5, 115.8, 117.1, 118.2, 119.5, 119.9, 120.4, 124.1, 125.0, 128.2, 131.6, 131.7, 132.2, 132.6, 133.3, 143.8, 144.3, 144.5, 144.6, 144.7, 144.8, 144.9, 145.9, 166.7, 167.3.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{32}H_{31}N_3O_7SNa$, 624.1780; found, 624.1758.

The purity was >96% as assessed by HPLC (254 nm).

(*E*)-3-(Furan-3-yl)-*N*-{(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-4a-hydroxy-9-methoxy-3-[(2-nitrophenyl)sulfonyl]-2,3,4, 4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl}-*N*-methylacrylamide (73).



73

The title compound was synthesized in 93% yield according to the general procedure for sulfonamidation.

IR (KBr): 3422, 1654, 1543, 1373, 1162 cm^{-1}

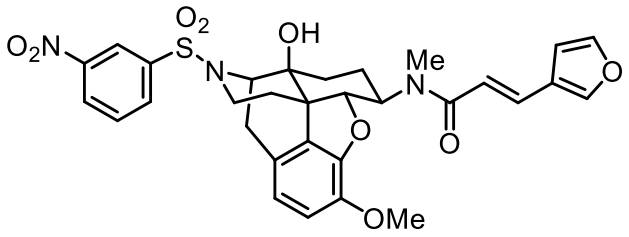
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.34–1.71 (m, 4H), 2.07–2.31 (m, 1H), 2.40 (ddd, *J* = 12.8, 12.8, 5.6 Hz, 1H), 2.91–3.05 (m, 1H), 2.96 (s, 2.1H), 3.06–3.26 (m, 3.9H), 3.70–3.80 (m, 1.7H), 3.81 (s, 2.1H), 3.85 (s, 0.9H), 3.95–4.01 (m, 1H), 4.19–4.36 (m, 0.3H), 4.60 (d, *J* = 7.6 Hz, 0.7H), 4.76 (d, *J* = 7.6 Hz, 0.3H), 6.41 (d, *J* = 15.2 Hz, 0.7H), 6.42–6.48 (m, 0.7H), 6.53– 6.61 (m, 0.6H), 6.65 (d, *J* = 8.4 Hz, 0.3H), 6.71 (d, *J* = 8.4 Hz, 0.7H), 6.78 (d, *J* = 8.4 Hz, 0.3H), 6.85 (d, *J* = 8.4 Hz, 0.7H), 7.35–7.62 (m, 3H), 7.66–7.81 (m, 3H), 8.11–8.17 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.2, 22.8, 28.7, 28.9, 30.4, 30.6, 31.5, 39.3, 47.0, 56.8, 57.2, 57.9, 59.3, 59.5, 70.4, 70.6, 88.7, 89.3, 107.4, 107.6, 115.6, 115.8, 117.8, 118.0, 119.3, 120.0, 123.2, 124.0, 124.5, 130.4, 131.5, 132.1, 132.2, 132.9, 133.8, 134.0, 143.0, 143.6, 144.1, 144.2, 147.5, 166.8, 167.6.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{31}H_{31}N_3O_9SNa$, 644.1679; found, 644.1661.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-3-(Furan-3-yl)-*N*-{(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-4a-hydroxy-9-methoxy-3-[(3-nitrophenyl)sulfonyl]-2,3,4, 4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl}-*N*-methylacrylamide (74).



74

The title compound was synthesized in 97% yield according to the general procedure for sulfonamidation.

IR (KBr): 3372, 1654, 1531, 1350, 1324, 1161 cm^{-1}

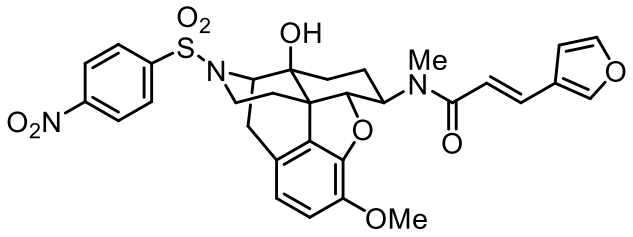
^1H NMR (400 MHz, pyridine-d_5): δ (mixture of rotamers) = 1.31–1.55 (m, 3H), 1.69–1.78 (m, 1H), 2.43–2.57 (m, 1H), 2.64–2.76 (m, 1H), 3.01 (s, 0.9H), 3.05–3.17 (m, 3H), 3.07 (s, 2.1H), 3.80 (s, 2.1H), 3.90–3.98 (m, 1.3H), 3.92 (s, 0.9H), 4.04–4.18 (m, 0.7H), 4.59–4.66 (m, 1H), 4.89–4.97 (m, 0.7H), 5.02–5.12 (m, 0.3H), 6.67–6.96 (m, 3H), 7.00–7.08 (m, 1H), 7.61–7.68 (m, 2H), 7.83–7.91 (m, 1.3H), 7.96 (d, J = 14.8 Hz, 0.7H), 8.30 (d, J = 8.4, 1.6 Hz, 1H), 8.49–8.53 (m, 1H), 9.04–9.07 (m, 1H). One proton (OH) was not observed.

^{13}C NMR (100 MHz, pyridine-d_5): δ (mixture of rotamers) = 21.8, 23.3, 28.3, 28.8, 31.0, 31.5, 32.6, 39.9, 47.6, 56.0, 56.6, 57.6, 58.3, 60.3, 60.4, 70.2, 70.3, 79.7, 89.3, 89.9, 108.3, 115.5, 117.1, 119.1, 119.4, 119.9, 120.4, 122.6, 124.2, 124.96, 125.0, 126.9, 130.8, 131.5, 131.6, 132.1, 132.6, 133.3, 143.76, 143.8, 144.3, 144.5, 144.6, 144.7, 144.8, 144.9, 148.4, 166.6, 167.3.

HRMS–ESI (m/z): $[M + Na]^+$ calcd for $C_{31}H_{31}N_3O_9SNa$, 644.1679; found, 644.1666.

The purity was >96% as assessed by HPLC (254 nm).

(*E*)-3-(Furan-3-yl)-*N*-{(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-4a-hydroxy-9-methoxy-3-[(4-nitrophenyl)sulfonyl]-2,3,4, 4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl}-*N*-methylacrylamide (75).



75

The title compound was synthesized in 95% yield according to the general procedure for sulfonamidation.

IR (film): 3356, 1651, 1529, 1349, 1325, 1161 cm^{-1}

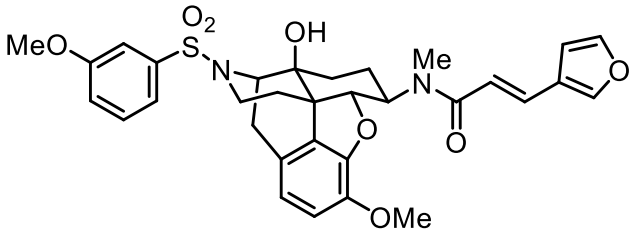
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.38–1.78 (m, 4H), 2.17–2.40 (m, 2H), 2.69 (d, *J* = 18.4 Hz, 0.7H), 2.76 (d, *J* = 18.4 Hz, 0.3H), 2.76–3.28 (m, 3H), 2.97 (s, 2.1H), 3.16 (s, 0.9H), 3.61–3.89 (m, 1.7H), 3.78 (s, 2.1H), 3.84 (s, 0.9H), 3.90–4.09 (m, 0.3H), 4.20–4.28 (m, 1H), 4.61 (d, *J* = 7.6 Hz, 0.7H), 4.82 (d, *J* = 7.6 Hz, 0.3H), 6.38 (d, *J* = 15.6 Hz, 0.7H), 6.33–6.47 (m, 0.7H), 6.52–6.64 (m, 1.6H), 6.73 (d, *J* = 8.4 Hz, 0.3H), 6.80 (d, *J* = 8.4 Hz, 0.7H), 7.34–7.45 (m, 1H), 7.46 (d, *J* = 15.2 Hz, 0.7H), 7.51 (d, *J* = 15.2 Hz, 0.3H), 7.54–7.65 (m, 1H), 8.02–8.12 (m, 2H), 8.32–8.42 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.1, 22.7, 28.6, 28.7, 28.8, 30.2, 30.6, 30.8, 31.3, 39.3, 47.0, 47.0, 56.7, 56.9, 57.9, 59.2, 59.4, 70.2, 70.3, 89.2, 107.3, 107.5, 115.4, 117.5, 117.8, 119.3, 119.9, 122.9, 123.1, 123.4, 124.3, 124.5, 128.3, 128.4, 130.1, 130.3, 132.4, 133.0, 143.0, 143.67, 143.7, 144.3, 144.4, 145.9, 146.2, 149.9, 150.0, 166.8, 167.6.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{31}H_{31}N_3O_9SNa$, 644.1679; found, 644.1678.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-3-(Furan-3-yl)-*N*-{(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-4a-hydroxy-9-methoxy-3-[(3-methoxyphenyl)sulfonyl] 2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl}-*N*-methylacrylamide (76).



76

The title compound was synthesized in 84% yield according to the general procedure for sulfonamidation.

IR (film): 3365, 1651, 1314, 1158 cm^{-1}

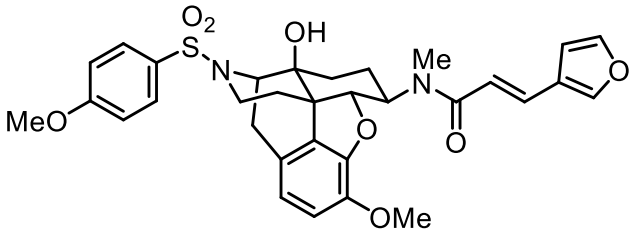
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.39–1.82 (m, 4H), 2.13–2.37 (m, 2H), 2.61 (d, *J* = 18.4 Hz, 0.3H), 2.63 (d, *J* = 18.4 Hz, 0.7H), 2.75 (ddd, *J* = 13.2, 13.2, 3.2 Hz, 1H), 2.89 (dd, *J* = 18.4, 5.6 Hz, 1H), 2.96–3.04 (m, 1H), 2.99 (s, 2.1H), 3.12 (s, 0.9H), 3.63–3.93 (m, 1.7H), 3.79 (s, 2.1H), 3.83 (s, 0.9H), 3.87 (s, 3H), 4.12–4.19 (m, 1H), 4.24–4.37 (m, 0.3H), 4.60 (d, *J* = 7.6 Hz, 0.7H), 4.74 (d, *J* = 7.6 Hz, 0.3H), 6.41 (d, *J* = 15.2 Hz, 0.7H), 6.41–6.51 (m, 1H), 6.52–6.61 (m, 1.3H), 6.70 (d, *J* = 8.0 Hz, 0.3H), 6.78 (d, *J* = 8.0 Hz, 0.7H), 7.11–7.18 (m, 1H), 7.32–7.62 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.4, 22.9, 28.9, 29.2, 29.3, 29.4, 29.6, 30.2, 30.4, 32.3, 38.9, 39.0, 47.1, 47.2, 55.7, 56.8, 57.2, 58.0, 59.0, 59.1, 70.1, 70.2, 88.8, 89.4, 107.4, 107.6, 112.0, 115.5, 115.7, 117.8, 118.0, 119.1, 119.7, 123.1, 123.2, 123.6, 123.9, 130.3, 130.45, 130.5, 130.6, 132.2, 132.7, 140.7, 140.9, 143.0, 143.6, 143.8, 143.9, 144.1, 144.4, 160.1, 166.8, 167.5.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{32}H_{34}N_2O_8SNa$, 629.1934; found, 629.1957.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-3-(Furan-3-yl)-*N*-{(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-4a-hydroxy-9-methoxy-3-[(4-methoxyphenyl)sulfonyl] 2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl}-*N*-methylacrylamide (77).



77

The title compound was synthesized in 84% yield according to the general procedure for sulfonamidation.

IR (film): 3371, 1651, 1323, 1157 cm^{-1}

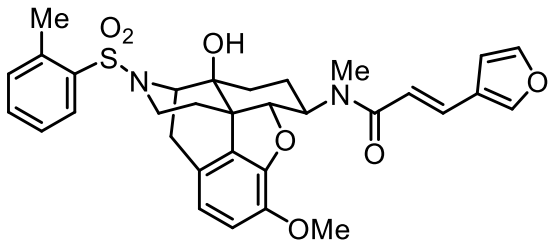
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.39–1.77 (m, 4H), 2.13–2.37 (m, 2H), 2.63 (d, *J* = 18.4 Hz, 0.3H), 2.66 (d, *J* = 18.4 Hz, 0.7H), 2.66–2.76 (m, 1H), 2.88 (dd, *J* = 18.4, 5.2 Hz, 1H), 2.99 (s, 2.1H), 3.12 (brs, 1H), 3.13 (s, 0.9H), 3.59–3.84 (m, 1.7H), 3.79 (s, 2.1H), 3.83 (s, 0.9H), 3.90 (s, 3H), 4.10–4.17 (m, 1H), 4.26–4.38 (m, 0.3H), 4.60 (d, *J* = 7.6 Hz, 0.7H), 4.74 (d, *J* = 7.6 Hz, 0.3H), 6.41 (d, *J* = 14.8 Hz, 0.7H), 6.41–6.46 (m, 0.7H), 6.49 (d, *J* = 8.4 Hz, 0.3H), 6.55 (d, *J* = 8.4 Hz, 0.7H), 6.53–6.61 (m, 0.6H), 6.70 (d, *J* = 8.4 Hz, 0.3H), 6.78 (d, *J* = 8.4 Hz, 0.7H), 6.98–7.04 (m, 2H), 7.35–7.62 (m, 3H), 7.77–7.80 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.4, 22.9, 28.8, 29.2, 29.3, 30.2, 30.4, 32.2, 38.7, 38.8, 47.1, 47.2, 55.6, 56.2, 56.8, 57.2, 58.0, 58.9, 59.0, 70.0, 70.2, 88.8, 89.4, 107.4, 107.6, 114.5, 115.4, 115.7, 117.8, 118.0, 119.0, 119.7, 123.0, 123.2, 123.7, 124.0, 129.3, 130.4, 130.7, 130.9, 131.1, 132.1, 132.7, 143.0, 143.6, 143.8, 143.9, 144.1, 144.3, 163.0, 163.1, 166.8, 167.5.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{32}H_{34}N_2O_8SNa$, 629.1934; found, 629.1938.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-3-(Furan-3-yl)-*N*-[(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-4a-hydroxy-9-methoxy-3-(*o*-tolylsulfonyl)-2,3,4,4a,5,6,7, 7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl]-*N*-methylacrylamide (78).



78

The title compound was synthesized in 86% yield according to the general procedure for sulfonamidation.

IR (film): 3375, 1651, 1313, 1158 cm^{-1}

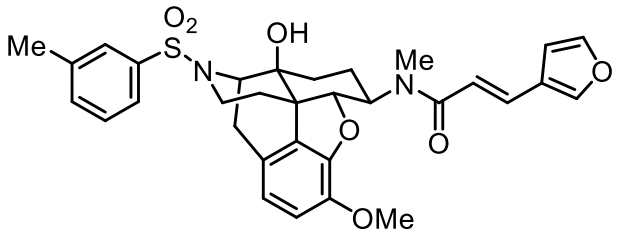
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.38–1.82 (m, 4H), 2.13–2.37 (m, 1H), 2.32 (ddd, *J* = 12.8, 12.8, 5.6 Hz, 1H), 2.64 (s, 3H), 2.84–3.17 (m, 4H), 2.99 (s, 2.1H), 3.14 (s, 0.9H), 3.60–3.89 (m, 1.7H), 3.80 (s, 2.1H), 3.84 (s, 0.9H), 3.94–4.04 (m, 1H), 4.19–4.37 (m, 0.3H), 4.60 (d, *J* = 8.0 Hz, 0.7H), 4.76 (d, *J* = 8.0 Hz, 0.3H), 6.37–6.49 (m, 1.4H), 6.53–6.63 (m, 0.9H), 6.66 (d, *J* = 8.4 Hz, 0.7H), 6.74 (d, *J* = 8.4 Hz, 0.3H), 6.82 (d, *J* = 8.4 Hz, 0.7H), 7.30–7.65 (m, 6H), 7.97–8.03 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 20.5, 21.2, 22.8, 28.8, 29.1, 29.2, 30.4, 30.6, 30.7, 32.5, 38.98, 39.0, 47.3, 56.6, 56.8, 57.2, 58.0, 58.4, 58.5, 70.1, 70.3, 88.9, 89.4, 107.4, 107.6, 115.5, 115.7, 117.8, 118.1, 119.2, 119.8, 123.0, 123.2, 123.8, 124.1, 126.3, 126.4, 130.3, 130.6, 132.1, 132.87, 132.9, 133.2, 137.0, 137.2, 137.3, 137.4, 143.0, 143.6, 143.8, 143.9, 144.08, 144.1, 144.4, 166.8, 167.6.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{32}H_{34}N_2O_7SNa$, 613.1984; found, 613.1989.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-3-(Furan-3-yl)-*N*-[(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-4a-hydroxy-9-methoxy-3-(*m*-tolylsulfonyl)-2,3,4,4a,5,6,7, 7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl]-*N*-methylacrylamide (79).



79

The title compound was synthesized in 92% yield according to the general procedure for sulfonamidation.

IR (film): 3366, 1651, 1323, 1158 cm^{-1}

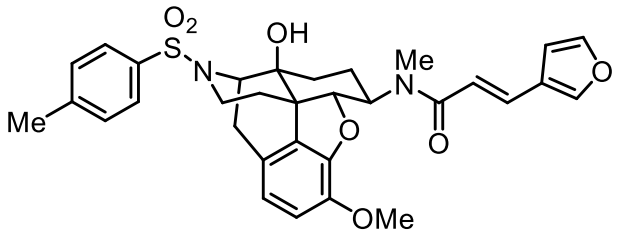
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.38–1.81 (m, 4H), 2.13–2.38 (m, 2H), 2.45 (s, 3H), 2.59 (d, *J* = 18.4 Hz, 0.3H), 2.62 (d, *J* = 18.4 Hz, 0.7H), 2.73 (ddd, *J* = 12.8, 12.8, 3.6 Hz, 1H), 2.88 (dd, *J* = 18.4, 5.2 Hz, 1H), 2.96–3.07 (m, 1H), 3.01 (brs, 2.1H), 3.14 (brs, 0.9H), 3.63–3.88 (m, 1.7H), 3.79 (s, 2.1H), 3.83 (s, 0.9H), 4.11–4.20 (m, 1H), 4.25–4.43 (m, 0.3H), 4.60 (d, *J* = 7.6 Hz, 0.7H), 4.73 (d, *J* = 7.6 Hz, 0.3H), 6.35–6.65 (m, 3H), 6.70 (d, *J* = 8.4 Hz, 0.3H), 6.77 (d, *J* = 8.4 Hz, 0.7H), 7.34–7.69 (m, 7H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.4, 22.9, 28.8, 29.2, 29.4, 29.6, 30.2, 30.4, 32.2, 38.9, 39.0, 47.1, 47.2, 56.2, 56.8, 57.2, 57.7, 58.0, 58.9, 59.1, 70.0, 70.2, 88.8, 89.5, 107.4, 107.6, 115.4, 115.7, 117.9, 118.1, 119.0 119.7, 123.0, 123.2, 123.6, 123.9, 124.2, 127.4, 129.3, 130.4, 130.6, 132.1, 132.6, 133.7, 133.9, 139.4, 139.5, 139.6, 139.7, 143.0, 143.6, 143.8, 143.9, 144.1, 144.4, 166.7, 167.6.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{32}H_{34}N_2O_7SNa$, 613.1984; found, 613.1993.

The purity was >99% as assessed by HPLC (254 nm).

(*E*)-3-(Furan-3-yl)-*N*-[(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-4a-hydroxy-9-methoxy-3-(*p*-tolylsulfonyl)-2,3,4,4a,5,6,7, 7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl]-*N*-methylacrylamide (80).



80

The title compound was synthesized in 90% yield according to the general procedure for sulfonamidation.

IR (film): 3365, 1651, 1323, 1159 cm^{-1}

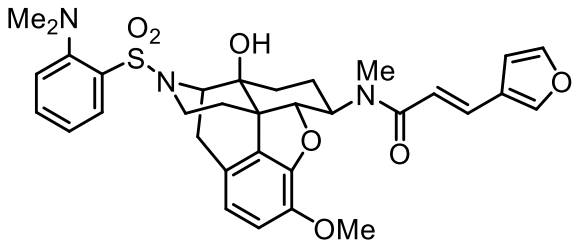
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.37–1.77 (m, 4H), 2.13–2.37 (m, 2H), 2.46 (s, 3H), 2.61 (d, *J* = 18.4 Hz, 0.3H), 2.64 (d, *J* = 18.4 Hz, 0.7H), 2.72 (ddd, *J* = 12.8, 12.8, 3.6 Hz, 1H), 2.88 (dd, *J* = 18.4, 5.2 Hz, 1H), 2.97 (s, 2.1H), 3.04 (s, 0.9H), 3.14 (s, 1H), 3.62–3.85 (m, 1.7H), 3.78 (s, 2.1H), 3.82 (s, 0.9H), 4.11–4.20 (m, 1H), 4.24–4.39 (m, 0.3H), 4.60 (d, *J* = 8.0 Hz, 0.7H), 4.73 (d, *J* = 8.0 Hz, 0.3H), 6.41 (d, *J* = 15.2 Hz, 0.7H), 6.41–6.63 (m, 2.3H), 6.69 (d, *J* = 8.0 Hz, 0.3H), 6.77 (d, *J* = 8.0 Hz, 0.7H), 7.30–7.62 (m, 5H), 7.68–7.76 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.4, 21.6, 22.9, 28.8, 29.2, 29.4, 29.5, 30.2, 30.4, 32.3, 38.8, 47.1, 56.8, 57.2, 58.0, 58.9, 59.0, 70.0, 70.2, 88.8, 89.4, 107.4, 107.6, 115.5, 115.8, 117.9, 119.0, 119.7, 123.1, 123.2, 123.7, 124.0, 127.1, 130.0, 130.4, 130.7, 132.1, 132.6, 136.6, 136.7, 143.0, 143.6, 143.9, 144.1, 144.4, 166.7, 167.5.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{32}H_{34}N_2O_7SNa$, 613.1984; found, 613.1986.

The purity was >98% as assessed by HPLC (254 nm).

(*E*)-*N*-((4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-{[2-(Dimethylamino)phenyl]-sulfonyl}-4a-hydroxy-9-methoxy-2,3,4,4a, 5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl)-3-(furan-3-yl)-*N*-methylacryl-amide (81).



81

A mixture of compound **73** (107 mg, 0.172 mmol), $SnCl_2$ (326 mg, 1.72 mmol) and conc HCl (57 μL) in CH_2Cl_2 (1.8 mL) and EtOH (1.8 mL) was heated to 40 °C with stirring under an argon atmosphere. After 4 h, the reaction mixture was basified with 1 M NaOH aq (10 mL) and extracted with CH_2Cl_2 (15, 12, 9, 6, 3 mL). The combined organic layer was washed with H_2O (30 mL) and then brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was dissolved in acetic acid (2.9 mL), and paraformaldehyde (110 mg, 3.68 mmol) and $NaBH_3CN$ (92 mg, 1.46 mmol) were added. After stirring for 1.5 h at 40 °C under an argon atmosphere, the reaction mixture was concentrated under reduced pressure, basified with saturated $NaHCO_3$ aq, and extracted with $CHCl_3$ (10, 8, 6 mL). The organic layer was washed with brine and concentrated under reduced pressure. The crude residue was purified by PLC (28% NH_3 aq/MeOH/$CHCl_3$ = 1/9/200) to afford compound **81** (96.2 mg, 90% in 2 steps) as an off-white amorphous. The product (64.6 mg) was dissolved in a mixture of MeOH (0.5 mL) and $CHCl_3$ (1.0 mL), and 10% hydrogen chloride in MeOH (200 μL) was added. The mixture was concentrated under reduced pressure and azeotropically dried with MeOH four times. The residue was dissolved in MeOH (several drops), and Et_2O (3 mL) was added. The precipitate was collected by filtration to afford hydrochloride (48.6 mg) as a brown solid.

IR (film): 3323, 1652, 1316, 1154 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.38–1.59 (m, 3H), 1.60–1.75 (m, 1H), 2.12 (ddd, *J* = 12.8, 12.8, 5.6 Hz, 1H), 2.19–2.38 (m, 1H), 2.83 (s, 1.8H), 2.84 (s, 4.2H), 2.91 (ddd, *J* = 12.8, 12.8, 3.6 Hz, 1H), 3.00 (s, 2.1H), 2.97–3.24 (m, 3H), 3.13 (s, 0.9H), 3.71–3.86 (m, 0.7H), 3.80 (s, 2.1H), 3.84 (s, 0.9H), 4.10–4.16 (m, 0.3H), 4.19 (d, *J* = 4.4 Hz, 0.7H), 4.25–4.40 (m, 0.3H), 4.58 (d, *J* = 8.4 Hz, 0.7H), 4.69–4.78 (m, 0.6H), 4.92–4.97 (m, 0.7H), 6.37–6.50 (m, 1.7H), 6.53–6.62 (m, 0.3H), 6.62 (d, *J* = 8.4 Hz, 0.3H), 6.70 (d, *J* = 8.4 Hz, 0.7H), 6.74 (d, *J* = 8.4 Hz, 0.3H), 6.82 (d, *J* = 8.4 Hz, 0.7H), 7.21–7.29 (m, 1H), 7.35–7.65 (m, 5H), 8.07–8.19 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 14.1, 21.4, 22.6, 22.9, 28.9, 29.1, 29.2, 29.7, 30.6, 30.8, 31.1, 31.2, 31.5, 32.3, 39.2, 39.4, 46.5, 47.5, 47.6, 56.6, 57.1, 58.0, 58.1, 58.3, 69.9, 70.1, 88.8, 89.5, 107.4, 107.6, 115.1, 115.5, 118.0, 118.2, 119.2, 119.9, 122.4, 123.1, 123.3, 124.2, 124.4, 124.5, 125.2, 128.2, 129.0, 130.5, 130.8, 132.1, 132.5, 132.7, 132.9, 133.0, 134.4, 134.6, 142.9, 143.6, 143.8, 143.86, 143.9, 144.0, 144.2, 152.9, 153.0, 166.8, 167.6.

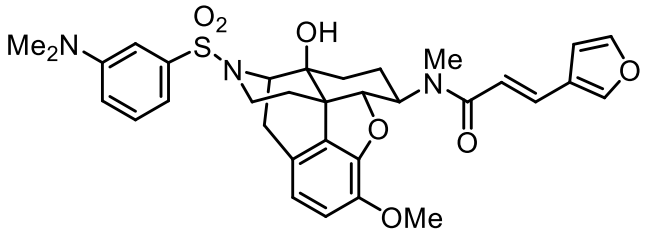
HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{33}H_{38}N_3O_7S$, 620.2430; found, 620.2407.

Hydrochloride

Mp (dec): 124–126 °C.

Anal. Calcd for $C_{33}H_{37}N_3O_7S \cdot HCl \cdot 1.5H_2O \cdot 0.5Et_2O$: C, 58.30; H, 6.36; N, 5.89. Found: C, 58.28; H, 6.65; N, 5.66.

(*E*)-*N*-((4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-{[3-(Dimethylamino)phenyl]-sulfonyl}-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl)-3-(furan-3-yl)-*N*-methylacrylamide (82).



82

The title compound was synthesized from compound **74** in 73% yield according to the procedure described for compound **81**. The product was converted to the hydrochloride.

IR (film): 3375, 1651, 1311, 1157 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.37–1.77 (m, 4H), 2.12–2.37 (m, 2H), 2.61–2.80 (m, 2H), 2.81–2.94 (m, 1H), 2.94–3.15 (m, 4H), 2.99 (s, 1.8H), 3.02 (s, 4.2H), 3.63–3.85 (m, 1.7H), 3.79 (s, 2.1H), 3.83 (s, 0.9H), 4.08–4.21 (m, 1H), 4.26–4.45 (m, 0.3H), 4.60 (d, *J* = 7.6 Hz, 0.7H), 4.72 (d, *J* = 7.6 Hz, 0.3H), 6.41(d, *J* = 15.6 Hz, 0.7H), 6.42–6.48 (m, 0.7H), 6.48 (d, *J* = 8.4 Hz, 0.3H), 6.50–6.62 (m, 0.6H), 6.55 (d, *J* = 8.4 Hz, 0.7H), 6.70 (d, *J* = 8.4 Hz, 0.3H), 6.78 (d, *J* = 8.4 Hz, 0.7H), 6.89 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.05–7.12 (m, 2H), 7.32–7.65 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 14.2, 21.1, 21.4, 28.9, 29.3, 29.4, 30.2, 30.4, 38.9, 39.0, 40.5, 47.2, 56.8, 57.2, 58.1, 59.0, 59.1, 60.4, 70.1, 70.3, 88.8, 89.5, 107.4, 107.6, 110.0, 114.2, 114.3, 115.4, 115.7, 116.2, 117.9, 118.1, 119.1, 119.7, 123.1, 123.3, 123.8, 124.2, 130.1, 130.4, 130.7, 132.2, 132.7, 140.1, 143.0, 143.6, 143.8, 144.0, 144.1, 144.3, 150.5, 166.8, 167.6.

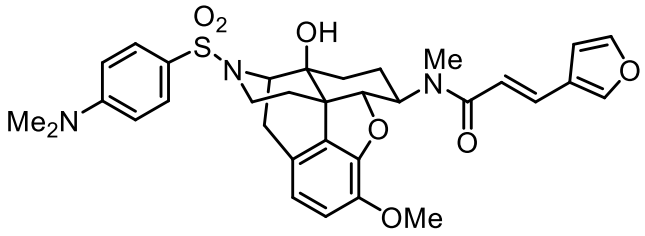
HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{33}H_{37}N_3O_7SNa$, 642.2250; found, 642.2248.

Hydrochloride

Mp (dec): 127–129 °C.

Anal. Calcd for $C_{33}H_{37}N_3O_7S \cdot HCl \cdot 1.4H_2O \cdot 0.3Et_2O$: C, 58.38; H, 6.27; N, 5.97. Found: C, 58.47; H, 6.57; N, 5.85.

(*E*)-*N*-((4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-{[4-(Dimethylamino)phenyl]-sulfonyl}-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl)-3-(furan-3-yl)-*N*-methylacrylamide (83).



83

The title compound was synthesized from compound **75** in 76% yield according to the procedure described for compound **81**. The product was converted to the hydrochloride.

IR (film): 3407, 1651, 1312, 1153 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.38–1.61 (m, 3H), 1.62–1.77 (m, 1H), 2.14–2.36 (m, 2H), 2.64–2.92 (m, 3H), 2.96–3.17 (m, 3H), 2.99 (s, 1.8H), 3.08 (s, 4.2H), 3.19–3.27 (m, 1H), 3.57–3.67 (m, 1H), 3.68–3.85 (m, 0.7H), 3.79 (s, 2.1H), 3.82 (s, 0.9H), 4.06–4.17 (m, 1H), 4.25–4.46 (m, 0.3H), 4.59 (d, *J* = 8.0 Hz, 0.7H), 4.71 (d, *J* = 8.0 Hz, 0.3H), 6.42 (d, *J* = 15.2 Hz, 0.7H), 6.43–6.61 (m, 2.3H), 6.65–6.72 (m, 2.3H), 6.75–6.80 (m, 0.7H), 7.32–7.69 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.5, 23.0, 28.9, 29.1, 29.4, 29.6, 30.1, 30.3, 32.0, 38.5, 38.6, 40.1, 47.2, 47.3, 56.0. 56.8, 57.3, 58.2, 58.7, 58.9, 70.0, 70.2, 88.7, 89.5, 107.4, 107.6, 111.0, 115.4, 115.7, 117.9, 118.1, 119.0, 119.7, 123.1, 123.3, 124.0, 124.2, 124.4, 129.0, 130.5, 130.8, 132.1 132.6, 143.0, 143.6, 143.8, 143.9, 144.0, 144.1, 144.3, 153.0, 166.8, 167.6.

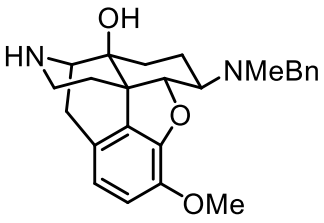
HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{33}H_{37}N_3O_7SNa$, 642.2250; found, 642.2246.

Hydrochloride

Mp (dec): 142–144 °C.

Anal. Calcd for $C_{33}H_{37}N_3O_7S \cdot HCl \cdot 0.2H_2O \cdot 0.5Et_2O$: C, 60.32; H, 6.28; N, 6.03. Found: C, 60.58; H, 6.56; N, 5.96.

(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-7-[Benzyl(methyl)amino]-9-methoxy-1,2,3,4,5,6,7,7a-octahydro-4a*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-4a-ol (84).



84

A mixture of compound **46** (1.92 g, 3.79 mmol) in 10% hydrogen chloride methanol solution (10 mL) was stirred for 37 h at room temperature and then 7 h at 50 °C under an argon atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was basified with saturated $NaHCO_3$ aq (20 mL) and extracted with a mixed solution, *i*-PrOH/$CHCl_3$ = 1/3 (20, 15, 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 column chromatography on silica gel (5–15% (28% NH_3 aq/MeOH = 1/9) in $CHCl_3$) to afford compound **84** (1.53 g, 99%) as a colorless amorphous.

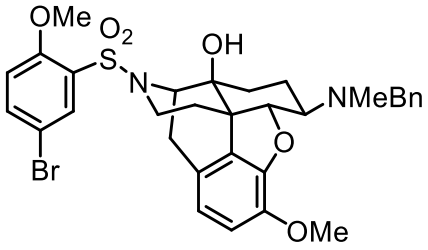
IR (film): 3289 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 (ddd, *J* = 13.6, 11.6, 3.6 Hz, 1H), 1.46–1.57 (m, 2H), 1.68 (ddd, *J* = 13.6, 4.0, 4.0 Hz, 1H), 1.91–2.04 (m, 1H), 2.26–2.39 (m, 1H), 2.32 (s, 3H), 2.60 (ddd, *J* = 11.6, 6.8, 4.4 Hz, 1H), 2.74 (ddd, *J* = 12.8, 12.8, 4.0 Hz, 1H), 2.90 (dd, *J* = 12.8, 4.8 Hz, 1H), 3.08 (dd, *J* = 18.4, 5.6 Hz, 1H), 3.14 (d, *J* = 18.4 Hz, 1H), 3.37 (d, *J* = 4.0 Hz, 1H), 3.70 (d, *J* = 14.0 Hz, 1H), 3.77 (d, *J* = 14.0 Hz, 1H), 3.88 (s, 3H), 4.76 (d, *J* = 6.8 Hz, 1H), 6.61 (d, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 7.17–7.23 (m, 1H), 7.24–7.31 (m, 2H), 7.33–7.39 (m, 2H). Two protons (OH and NH) were not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3, 29.9, 30.3, 31.5, 37.5, 37.9, 47.2, 56.7, 57.5, 59.1, 63.2, 70.0, 90.0, 114.4, 118.5, 124.9, 126.7, 128.1 (×2), 128.7 (×2), 131.5, 139.6, 143.6, 144.3.

HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{25}H_{31}N_2O_3$, 407.2335; found, 407.2319.

(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-7-[Benzyl(methyl)amino]-9-methoxy-1,2,3,4,5,6,7,7a-octahydro-4a*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-4a-ol (85).



85

To a stirred solution of compound **84** (50 mg, 0.123 mmol) in CH_2Cl_2 (1.2 mL) were added Et_3N (52 μL, 0.373 mmol) and 5-bromo-2-methoxysulfonyl chloride (42 mg, 0.147 mmol) at 0 °C under an argon atmosphere. After stirring for 1.5 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated $NaHCO_3$ aq (5 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by PLC (MeOH/$CHCl_3$ = 1/20) to afford compound **85** (68 mg, 84%) as a colorless amorphous.

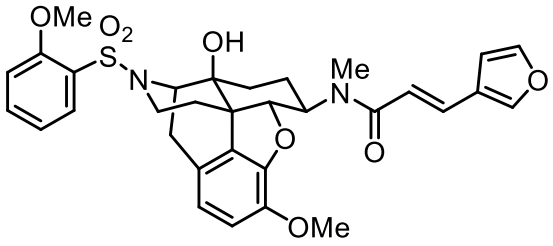
IR (film): 3499, 1335, 1322, 1159 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 1.33 (ddd, *J* = 12.8, 12.8, 2.4 Hz, 1H), 1.50–1.64 (m, 3H), 1.94 (dddd, *J* = 12.8, 12.8, 12.8, 2.4 Hz, 1H), 2.14 (ddd, *J* = 12.8, 12.8, 5.2 Hz, 1H), 2.32 (s, 3H), 2.58 (ddd, *J* = 12.8, 7.6, 4.8 Hz, 1H), 2.94 (ddd, *J* = 12.8, 12.8, 3.6 Hz, 1H), 3.02 (dd, *J* = 18.4, 4.8 Hz, 1H), 3.09 (d, *J* = 18.4 Hz, 1H), 3.41 (brs, 1H), 3.50 (dd, *J* = 12.8, 5.2 Hz, 1H), 3.67 (d, *J* = 13.6 Hz, 1H), 3.78 (d, *J* = 13.6 Hz, 1H), 3.88 (s, 3H), 3.98 (s, 3H), 4.00 (d, *J* = 4.8 Hz, 1H), 4.70 (d, *J* = 7.6 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 1H), 7.16–7.23 (m, 1H), 7.23–7.30 (m, 2H), 7.33–7.38 (m, 2H), 7.66 (dd, *J* = 8.8, 2.8 Hz, 1H), 8.09 (d, *J* = 2.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 29.4, 30.3, 31.4, 37.8, 39.2, 47.2, 56.7, 56.9, 58.9, 59.1, 63.1, 70.5, 89.8, 113.0, 114.5, 114.6, 118.8, 124.0, 126.6, 128.1 (× 2), 128.6 (× 2), 129.0, 130.8, 134.1, 137.6, 139.9, 144.0, 155.4. One quaternary carbon was not observed.

HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{32}H_{36}N_2O_6SBr$, 655.1477; found, 655.1483.

(*E*)-3-(Furan-3-yl)-*N*-{(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-4a-hydroxy-9-methoxy-3-[(2-methoxyphenyl)sulfonyl] 2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl}-*N*-methylacrylamide (86).



86

To a solution of compound **85** (50 mg, 0.0763 mmol) in MeOH (5 mL) was added 5% Pd/C, degussa type (100 mg), and the mixture was stirred for 6 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 to afford a crude residue as a colorless solid. To a solution of the residue in CH_2Cl_2 (7.6 mL) were added Et_3N (106 μL, 0.761 mmol) and (*E*)-3-(furan-3-yl)acryloyl chloride (36 mg, 0.230 mmol) at 0 °C. After stirring for 1.5 h at room temperature, the reaction mixture was washed with saturated $NaHCO_3$ aq (10 mL) and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by PLC (MeOH/$CHCl_3$ = 1/20) to afford compound **86** (35.4 mg, 77% in 2 steps) as a colorless amorphous.

IR (film): 3483, 1652, 1320, 1158 cm^{-1}

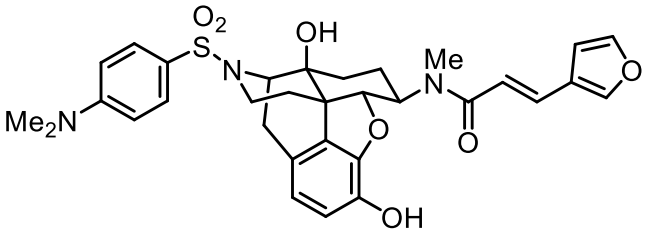
^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.39–1.73 (m, 4H), 2.18 (ddd, *J* = 12.8, 12.8, 5.6 Hz, 1H), 2.26 (dddd, *J* = 12.8, 12.8, 12.8, 5.6 Hz, 1H), 2.94 (ddd, *J* = 12.8, 12.8, 3.6 Hz, 1H), 2.99 (s, 2.4H), 3.04–3.20 (m, 1.2H), 3.13 (s, 0.6H), 3.20 (d, *J* = 18.4 Hz, 0.8H), 3.40–3.51 (m, 0.2H), 3.44 (dd, *J* = 12.8, 4.4 Hz, 0.8H), 3.58 (brs, 0.2H), 3.64–3.90 (m, 1H), 3.70 (brs, 0.8H), 3.81 (s, 2.4H), 3.85 (s, 0.6H), 3.97–4.14 (m, 0.8H), 4.00 (s, 0.6H), 4.02 (s, 2.4H) 4.24–4.38 (m, 0.2H), 4.58 (d, *J* = 8.0 Hz, 0.8H), 4.75 (d, *J* = 8.0 Hz, 0.2H), 6.39–6.51 (m, 1.6H), 6.51–6.61 (m, 0.4H), 6.64 (d, *J* = 8.0 Hz, 0.2H), 6.71 (d, *J* = 8.0 Hz, 0.8H), 6.76 (d, *J* = 8.0 Hz, 0.2H), 6.84 (d, *J* = 8.0 Hz, 0.8H), 7.06–7.65 (m, 2H), 7.36–7.65 (m, 4H), 7.98 (d, *J* = 7.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.4, 22.9, 28.8, 29.1, 29.3, 30.4, 30.6, 31.3, 32.4, 38.8, 39.0, 47.4, 47.5, 56.5, 56.6, 56.7, 57.2, 58.0, 58.3, 58.6, 70.1, 70.3, 88.7, 89.4, 107.4, 107.6, 112.8, 112.9, 115.3, 115.7, 118.0, 118.1, 119.2, 119.9, 120.9, 121.0, 123.1, 123.3, 124.2, 124.5, 126.7, 126.9, 130.4, 130.7, 131.86, 131.9, 132.1, 132.6, 135.2, 135.3, 143.0, 143.59, 143.6, 143.8, 143.9, 144.0, 144.3, 156.3, 166.7, 167.6.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{32}H_{34}N_2O_8SNa$, 629.1934; found, 629.1910.

The purity was >97% as assessed by HPLC (254 nm).

(*E*)-*N*-((4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-{[4-(Dimethylamino)phenyl]-sulfonyl}-4a,9-dihydroxy-2,3,4,4a,5,6,7, 7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl)-3-(furan-3-yl)-*N*-methylacrylamide (87).



87

To a stirred solution of compound **83** (160 mg, 0.258 mmol) in CH_2Cl_2 (5.2 mL) was added 1.0 M BBr_3 in CH_2Cl_2 solution (1.3 mL, 1.30 mmol) at –78 °C under an argon atmosphere. The mixture was gradually warmed to room temperature over 20 min and stirred for 1 h. The reaction mixture was quenched with 28% NH_3 aq (15 mL) at 0 °C and vigorously stirred for 3 h at room temperature and extracted with CH_2Cl_2 (15, 10, 5 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (0–5% (28% NH_3 aq/MeOH = 1/9) in $CHCl_3$) and then PLC (MeOH/$CHCl_3$ = 1/20) to afford compound **87** (80.1 mg, 51%) as a colorless solid. To a stirred solution of compound **87** (47.4 mg, 0.0783 mmol) in absolute EtOAc (2 mL) was added 1.0 M $MeSO_3H$ in EtOAc solution (78 μL, 0.0780 mmol). The mixture was stirred for 5 min at room temperature and then for 5 min at 0 °C. The precipitate was collected by filtration to give methanesulfonate (32.8 mg) as a colorless solid.

IR (KBr): 1650, 1314, 1153 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.10–1.50 (m, 2H), 1.53–1.71 (m, 2H), 2.16–2.34 (m, 2H), 2.55 (d, *J* = 18.4 Hz, 0.8H), 2.60–2.82 (m, 2.2H), 2.99–3.12 (m, 3H), 3.01 (s, 1.2H), 3.09 (s, 4.8H), 3.38 (brs, 1H), 3.60–3.72 (m, 2H), 4.04–4.11 (m, 0.2H), 4.07 (d, *J* = 5.2 Hz, 0.8H), 4.53–4.65 (m, 0.2H), 4.61 (d, *J* = 7.6 Hz, 0.8H), 6.30 (d, *J* = 15.2 Hz, 0.8H), 6.41 (d, *J* = 8.4 Hz, 0.2H), 6.45 (d, *J* = 8.4 Hz, 0.8H), 6.57 (d, *J* = 15.2 Hz, 0.2H), 6.65–6.74 (m, 3H), 6.81 (d, *J* = 8.0 Hz, 0.8H), 7.22–7.31 (m, 3.2H), 7.58–7.65 (m, 2H), 9.33 (brs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.6, 22.9, 28.4, 28.7, 29.0, 29.3, 30.1, 31.1, 37.5, 38.7, 40.1, 47.3, 47.4, 54.9, 58.1, 58.8, 70.2, 70.4, 89.2, 89.7, 107.4, 108.0, 111.1, 117.1, 117.5, 118.7, 118.9, 119.4, 120.0, 122.6, 123.0, 123.1, 124.0, 128.9, 130.2, 133.4, 133.6, 140.9, 141.9, 143.1, 143.5, 143.9, 144.2, 144.3, 153.0, 167.6, 168.9.

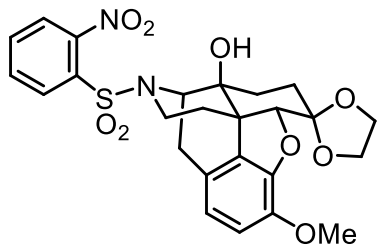
HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{32}H_{35}N_3O_7SNa$, 628.2093; found, 628.2113.

Methanesulfonate

Mp (dec): 140–144 °C.

Anal. Calcd for $C_{32}H_{35}N_3O_7S \cdot CH_3SO_3H \cdot 3.5H_2O$: C, 51.82; H, 6.06; N, 5.49. Found: C, 51.75; H, 5.91; N, 5.40.

(4′*R*,4a′*S*,7a′*R*,12b′*S*)-9′-Methoxy-3′-[(2-nitrophenyl)-sulfonyl]-1′,2′,3′,4′,5′,6′-hexahydro-4a′*H*,7a′*H*-spiro[[1,3]-dioxolane-2,7′-[4,12]methanobenzofuro[3,2-*e*]isoquinolin]-4a′-ol (88).



88

To a stirred solution of compound **43** (5.94 g, 17.2 mmol) in CH_2Cl_2 (100 mL) were added Et_3N (6.0 mL, 43.0 mmol) and 2-nitrobenzenesulfonyl chloride (4.57 g, 20.6 mmol) at 0 °C, and the reaction mixture was stirred for 1 h at room temperature under an argon atmosphere. The reaction was quenched with saturated $NaHCO_3$ aq (80 mL), and the mixture was extracted with $CHCl_3$ (70, 30 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (0–5% MeOH in $CHCl_3$) to afford compound **88** (9.06 g, 99%) as a yellow amorphous.

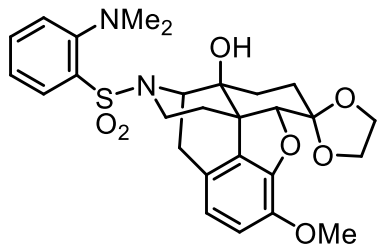
IR (film): 3538, 1543, 1372, 1341, 1162 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 1.47 (ddd, *J* = 13.6, 3.6, 3.6 Hz, 1H), 1.52–1.63 (m, 3H), 2.11 (ddd, *J* = 13.2, 9.2, 6.8 Hz, 1H), 2.40 (ddd, *J* = 12.8, 12.8, 5.6 Hz, 1H), 3.03 (ddd, *J* = 13.2, 13.2, 4.0 Hz, 1H), 3.06–3.15 (m, 2H), 3.19 (d, *J* = 18.4 Hz, 1H), 3.74 (dd, *J* = 13.2, 5.6 Hz, 1H), 3.79 (dd, *J* = 12.8, 6.8 Hz, 1H), 3.87 (s, 3H), 3.89 (dd, *J* = 13.2, 6.8 Hz, 1H), 3.96 (d, *J* = 4.8 Hz, 1H), 4.01 (dd, *J* = 13.2, 6.8 Hz, 1H), 4.17 (dd, *J* = 12.8, 6.8 Hz, 1H), 4.51 (s, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 7.66–7.78 (m, 3H), 8.14 (dd, *J* = 6.8, 2.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.5, 28.9, 29.6, 31.5, 39.3, 47.6, 56.5, 59.5, 65.0, 66.4, 70.3, 92.9, 108.2, 114.2, 118.8, 123.4, 124.5, 129.3, 131.5, 132.1, 133.1, 133.9, 142.7, 146.2, 147.6.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{25}H_{26}N_2O_9SNa$, 553.1257; found, 553.1253.

(4′*R*,4a′*S*,7a′*R*,12b′*S*)-3′-{[2-(Dimethylamino)phenyl]-sulfonyl}-9′-methoxy-1′,2′,3′,4′,5′,6′-hexahydro-4a′*H*,7a′*H*-spiro[[1,3]dioxolane-2,7′-[4,12]methanobenzofuro[3,2-*e*]-isoquinolin]-4a′-ol (89).



89

To a suspension of compound **88** (9.06 g, 17.1 mmol) in EtOH (180 mL) were added H_2O (36 mL), saturated NH_4Cl aq (25 mL), and iron powder (9.6 g, 172 mmol), and the mixture was stirred for 1 h at 90 °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 reduced pressure. To the residue was added saturated $NaHCO_3$ aq (50 mL), and the mixture was extracted with $CHCl_3$ (150, 100, 100 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. To a stirred solution of the crude product in acetic acid (200 mL) were added paraformaldehyde (12.8 g, 426 mmol) and $NaBH_3CN$ (10.7 g, 170 mmol). After stirring for 3 h at 40 °C under an argon atmosphere, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was basified with saturated $NaHCO_3$ aq (300 mL) and extracted with $CHCl_3$ (400, 200, 100 mL). The organic layer was washed with brine, 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 compound **89** (9.33 g, 97% in 2 steps) as a colorless amorphous.

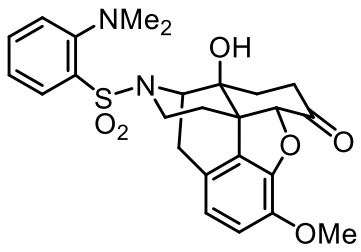
IR (film): 3305, 1317, 1152 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 1.42–1.63 (m, 4H), 2.10 (ddd, *J* = 12.8, 12.8, 5.6 Hz, 1H), 2.24 (ddd, *J* = 13.6, 13.6, 3.6 Hz, 1H), 2.83 (s, 6H), 2.93 (ddd, *J* = 12.8, 12.8, 3.6 Hz, 1H), 3.02 (dd, *J* = 18.4, 4.8 Hz, 1H), 3.07–3.14 (m, 1H), 3.14 (d, *J* = 18.4 Hz, 1H), 3.78 (dd, *J* = 12.8, 6.8 Hz, 1H), 3.87 (s, 3H), 3.89 (dd, *J* = 13.6, 6.8 Hz, 1H), 4.01 (dd, *J* = 13.6, 6.8 Hz, 1H), 4.12–4.22 (m, 2H), 4.53 (s, 1H), 4.92 (brs, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 7.21–7.28 (m, 1H), 7.37 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.58 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H), 8.13 (dd, *J* = 8.0, 1.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.9, 29.0, 29.8, 31.4, 39.3, 46.6 (× 2), 48.1, 56.5, 58.5, 65.1, 66.6, 70.0, 93.7, 108.8, 114.0, 118.9, 122.5, 124.0, 124.4, 129.8, 133.0, 133.2, 134.6, 142.7, 146.3, 153.0.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{27}H_{32}N_2O_7SNa$, 551.1828; found, 551.1832.

(4*R*,4a*S*,7a*R*,12b*S*)-3-{[2-(Dimethylamino)phenyl]sulfonyl}-4a-hydroxy-9-methoxy-2,3,4,4a,5,6-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7(7a*H*)-one (90).



90

To a solution of compound **89** (6.56 g, 12.4 mmol) in THF (100 mL) was added 2 M HCl aq (100 mL), and the mixture was stirred for 9 h at 90 °C under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was basified with saturated $NaHCO_3$ aq (120 mL) and extracted with $CHCl_3$ (200, 100, 100 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on DIOL-silica gel (EtOAc/hexane = 1/5 to 1/2) to afford compound **90** (5.41 g, 90%) as a colorless amorphous.

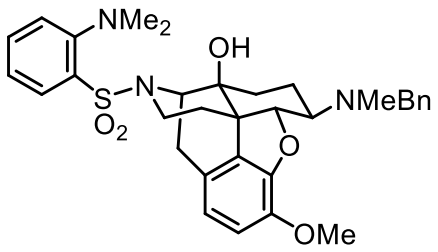
IR (film): 3289, 1728, 1316, 1152 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 1.53–1.69 (m, 2H), 1.92 (ddd, *J* = 13.2, 4.8, 3.2 Hz, 1H), 2.26 (ddd, *J* = 12.8, 12.8, 5.2 Hz, 1H), 2.30 (ddd, *J* = 14.0, 2.8, 2.8 Hz, 1H), 2.86 (s, 6H), 2.92 (ddd, *J* = 12.8, 12.8, 3.6 Hz, 1H), 2.99–3.17 (m, 3H), 3.17 (d, *J* = 18.8 Hz, 1H), 3.87 (s, 3H), 4.29 (d, *J* = 5.2 Hz, 1H), 4.64 (s, 1H), 5.38 (s, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 7.23–7.30 (m, 1H), 7.41 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.62 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H), 8.15 (dd, *J* = 8.0, 1.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.2, 31.3, 31.5, 35.9, 38.9, 46.6, 46.6, 50.7, 56.6, 57.7, 70.2, 90.0, 115.0, 120.0, 122.4, 123.8, 124.5, 128.3, 132.5, 133.2, 134.7, 143.2, 145.0, 152.8, 207.9.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{25}H_{28}N_2O_6SNa$, 507.1566; found, 507.1566.

(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-7-[Benzyl(methyl)amino]-3-{[2-(dimethylamino)phenyl]sulfonyl}-9-methoxy-1,2,3,4,5,6,7,7a-octahydro-4a*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-4a-ol (91).



91

To a solution of compound **90** (1.07 g, 2.20 mmol) in benzene (30 mL) were added $PhCO_2H$ (273 mg, 2.24 mmol) and *N*-benzylmethylamine (0.57 mL, 4.42 mmol), and the mixture was refluxed with a Dean–Stark apparatus for 21 h under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. To a solution of the residue in absolute MeOH (13 mL) and absolute THF (20 mL) was added $NaBH_3CN$ (167 mg, 2.65 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 1 h, and saturated $NaHCO_3$ aq (20 mL) and brine (20 mL) were added. The mixture was extracted with $CHCl_3$ (30 mL × 2). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on NH-silica gel (EtOAc/hexane = 1/3) to give compound **91** (1.04 g, 80% in 2 steps) as a colorless amorphous.

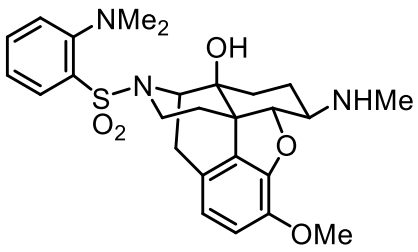
IR (KBr): 3313, 1317, 1152 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 1.27–1.38 (m, 1H), 1.47 (dd, *J* = 12.8, 2.4 Hz, 1H), 1.52–1.66 (m, 2H), 1.92–2.11 (m, 2H), 2.32 (s, 3H), 2.57 (ddd, *J* = 12.4, 7.6, 4.8 Hz, 1H), 2.83 (s, 6H), 2.89 (ddd, *J* = 12.8, 12.8, 3.6 Hz, 1H), 2.99 (dd, *J* = 18.4, 5.2 Hz, 1H), 3.09 (d, *J* = 18.4 Hz, 1H), 3.09–3.17 (m, 1H), 3.67 (d, *J* = 13.6 Hz, 1H), 3.79 (d, *J* = 13.6. Hz, 1H), 3.87 (s, 3H), 4.11 (d, *J* = 4.8 Hz, 1H), 4.68 (d, *J* = 8.0 Hz, 1H), 4.73 (s, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 7.16–7.32 (m, 4H), 7.31–7.40 (m, 3H), 7.55–7.61 (m, 1H), 8.12 (dd, *J* = 7.6, 1.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 29.4, 30.6, 31.2, 37.9, 39.4, 46.5, 47.5, 56.7, 58.4, 59.0, 63.5, 70.3, 90.2, 114.5, 118.7, 122.3, 124.2, 124.3, 126.6, 128.1 (× 2), 128.6 (× 2), 131.1, 133.0, 134.4, 140.0, 143.9, 153.0.

HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{33}H_{40}N_3O_5S$, 590.2689; found, 590.2660.

(4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-{[2-(Dimethylamino)phenyl]-sulfonyl}-9-methoxy-7-(methylamino)-1,2,3,4,5,6,7,7a-octahydro-4a*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-4a-ol (92).



92

To a solution of compound **91** (698 mg, 1.18 mmol) in MeOH (20 mL) and THF (10 mL) was added 5% Pd/C, degussa type (678 mg), and the mixture was stirred at room temperature under a hydrogen atmosphere. After stirring for 7.5 h, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (2–20% (28% NH_3 aq/MeOH = 1/9) in $CHCl_3$) to give compound **92** (570 mg, 96%) as a colorless amorphous.

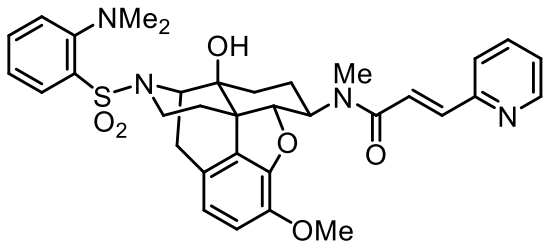
IR (KBr): 3318, 1318, 1153 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (ddd, *J* = 12.8, 12.8, 3.2 Hz, 1H), 1.45 (dd, *J* = 12.8, 1.6 Hz, 1H), 1.58–1.67 (m, 1H), 1.68–1.89 (m, 2H), 2.08 (ddd, *J* = 12.8, 12.8, 5.6 Hz, 1H), 2.45–2.53 (m, 1H), 2.51 (s, 3H), 2.82 (s, 6H), 2.89 (ddd, *J* = 12.8, 12.8, 3.2 Hz, 1H), 3.04 (dd, *J* = 18.4, 5.2, 1H), 3.06–3.14 (m, 1H), 3.15 (d, *J* = 18.4 Hz, 1H), 3.86 (s, 3H), 4.15 (d, *J* = 5.2 Hz, 1H), 4.46 (d, *J* = 6.8 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 7.20–7.26 (m, 1H), 7.34–7.39 (m, 1H), 7.55–7.61 (m, 1H), 8.10–8.14 (m, 1H). Two protons (OH and NH) were not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 29.2, 29.8, 33.5, 39.2, 46.4, 47.1, 56.4, 58.1, 60.6, 70.1, 93.4, 114.1, 119.1, 122.3, 124.2, 124.3, 130.8, 132.8, 132.9, 134.4, 143.69, 143.7, 152.8.

HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{26}H_{34}N_3O_5S$, 500.2219; found, 500.2198.

(*E*)-*N*-((4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-{[2-(Dimethylamino)phenyl]-sulfonyl}-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl)-*N*-methyl-3-(pyridin-2-yl)acrylamide (93).



93

To a solution of compound **92** (230 mg, 0.461 mmol) in DMF (8.0 mL) were added 3-(2-pyridyl)acrylic acid (75.7 mg, 0.508 mmol), HATU (437 mg, 1.15 mmol), and (*i*-Pr)$_2$NEt (0.25 mL, 1.46 mmol), and the mixture was stirred for 1 h at room temperature under an argon atmosphere. The reaction mixture was poured into EtOAc (70 mL) and washed with water (100 mL × 4). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1–2% (28% NH_3 aq/MeOH = 1/9) in $CHCl_3$) to give compound **93** (277 mg, 95%) as a colorless amorphous. To a stirred solution of compound **93** (180 mg, 0.284 mmol) in MeOH (4 mL) were added 1 M H_2SO_4 in MeOH solution (568 μL, 0.568 mmol) and then Et_2O (4 mL). The mixture was stirred for 0.5 h at 0 °C under an argon atmosphere. The precipitate was collected by filtration to give dihydrosulfate **96** (180 mg) as a light yellow solid.

IR (film): 3418, 1650, 1317, 1153 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.41–1.59 (m, 3H), 1.62–1.75 (m, 1H), 2.04–2.37 (m, 2H), 2.75–2.97 (m, 1H), 2.83 (s, 2.4H), 2.84 (s, 3.6H), 2.98–3.24 (m, 3H), 3.04 (s, 1.8H), 3.20 (s, 1.2H), 3.50 (s, 1.8H), 3.81–3.92 (m, 0.6H), 3.85 (s, 1.2H), 4.14 (d, *J* = 4.0 Hz, 0.4H), 4.18 (d, *J* = 4.0 Hz, 0.6H), 4.30–4.33 (m, 0.4H), 4.57 (d, *J* = 7.6 Hz, 0.6H), 4.71–4.80 (m, 0.8H), 4.93 (s, 0.6H), 6.60–6.71 (m, 1.6H), 6.75 (d, *J* = 8.4 Hz, 0.4H), 7.15 (d, *J* = 15.2 Hz, 0.6H), 7.16–7.28 (m, 2H), 7.31–7.41 (m, 2H), 7.48 (d, *J* = 15.2 Hz, 0.4H), 7.55–7.72 (m, 3H), 8.13 (d, *J* = 7.6 Hz, 1H), 8.52 (d, *J* = 4.4 Hz, 0.6H), 8.62 (d, *J* = 4.4 Hz, 0.4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.4, 22.9, 28.9, 29.1, 29.3, 30.7, 30.8, 31.2, 31.2, 32.4, 39.2, 39.4, 46.5, 47.5, 47.6, 55.9, 57.3, 58.1, 58.3, 70.0, 70.1, 88.8, 89.2, 114.3, 115.8, 119.3, 119.7, 122.4, 122.5, 122.6, 123.3, 123.8, 124.1, 124.27, 124.3, 124.4, 124.8, 130.4, 130.6, 132.7, 133.0, 133.1, 134.5, 134.6, 136.4, 136.8, 140.7, 140.9, 142.9, 143.8, 144.2, 144.3, 149.5, 149.9, 152.9, 153.0, 153.5, 154.2, 166.6, 167.3.

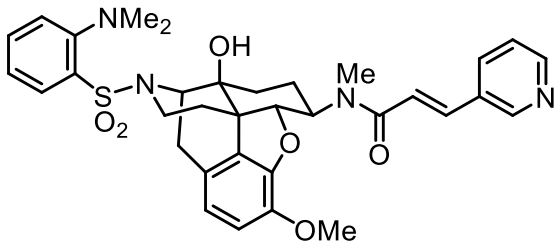
HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{34}H_{39}N_4O_6S$, 631.2590; found, 631.2578.

The purity was >99% as assessed by HPLC (254 nm).

Dihydrosulfate 96

Mp (dec): 217–220 °C. Anal. Calcd for $C_{34}H_{38}N_4O_6S \cdot 2H_2SO_4 \cdot 4H_2O$: C, 45.43; H, 5.61; N, 6.23. Found: C, 45.49; H, 5.52; N, 6.10.

(*E*)-*N*-((4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-{[2-(Dimethylamino)phenyl]-sulfonyl}-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl)-*N*-methyl-3-(pyridin-3-yl)acrylamide (94).



94

To a solution of compound **92** (32 mg, 0.0640 mmol) in DMF (1.5 mL) were added 3-(3-pyridyl)acrylic acid (10.5 mg, 0.0704 mmol), HATU (61 mg, 0.160 mmol), and (*i*-Pr)$_2$NEt (35 μL, 0.204 mmol), and the mixture was stirred for 1 h at room temperature under an argon atmosphere. The reaction mixture was poured into EtOAc (20 mL) and washed with water (20 mL × 4). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1–2% (28% NH_3 aq/MeOH = 1/9) in $CHCl_3$) to give compound **94** (39.6 mg, 97%) as a colorless amorphous.

IR (film): 3399, 1649, 1317, 1154 cm^{-1}

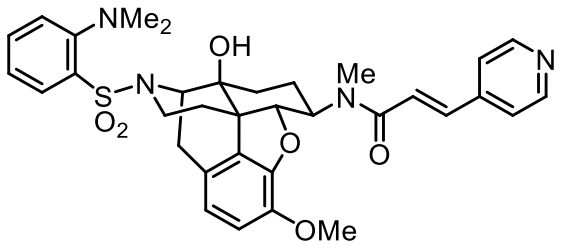
^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.42–1.77 (m, 4H), 2.13 (ddd, *J* = 12.8, 12.8, 5.2 Hz, 1H), 2.21–2.40 (m, 1H), 2.80–2.97 (m, 1H), 2.83 (s, 1.2H), 2.84 (s, 4.8H), 3.03 (s, 2.4H), 3.05–3.23 (m, 3.6H), 3.70–3.82 (m, 0.8H), 3.75 (s, 2.4H), 3.85 (s, 0.6H), 4.11–4.17 (m, 0.2H), 4.19 (d, *J* = 4.4 Hz, 0.8H), 4.26–4.38 (m, 0.2H), 4.60 (d, *J* = 7.6 Hz, 0.8H), 4.72–4.81 (m, 0.4H), 4.97 (brs, 0.8H), 6.64 (d, *J* = 8.4 Hz, 0.2H), 6.71 (d, *J* = 8.4 Hz, 0.8H), 6.76 (d, *J* = 8.4 Hz, 0.2H), 6.80 (d, *J* = 16.0 Hz, 0.8H), 6.84 (d, *J* = 8.4 Hz, 0.8 H), 6.94 (d, *J* = 16.0 Hz, 0.2H), 7.20–7.34 (m, 2H), 7.36–7.43 (m, 1H), 7.52 (d, *J* = 15.6 Hz, 0.8H), 7.56–7.70 (m, 2H), 7.78–7.85 (m, 0.2H), 8.13 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.53 (dd, *J* = 4.8, 1.6 Hz, 0.8H), 8.55–8.63 (m, 1H), 8.73–8.77 (m, 0.2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 21.1, 22.9, 28.9, 29.0, 29.2, 29.6, 30.6, 30.8, 31.2, 32.4, 39.2, 39.4, 46.5, 47.6, 56.3, 57.0, 58.0, 58.3, 59.9, 70.1, 88.7, 89.5, 114.3, 115.3, 119.3, 120.0, 120.7, 121.0, 122.4, 123.3, 123.6, 124.2, 124.38, 124.4, 130.5, 130.6, 131.1, 131.3, 132.7, 132.9, 133.0, 134.2, 134.5, 134.6, 138.2, 138.8, 142.8, 143.7, 144.0, 144.3, 148.9, 149.2, 149.7, 149.8, 150.2, 152.9, 153.0, 166.1, 167.1.

HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{34}H_{39}N_4O_6S$, 631.2590; found, 631.2573.

The purity was >95% as assessed by HPLC (254 nm).

(*E*)-*N*-((4*R*,4a*S*,7*R*,7a*R*,12b*S*)-3-{[2-(Dimethylamino)phenyl]-sulfonyl}-4a-hydroxy-9-methoxy-2,3,4,4a,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl)-*N*-methyl-3-(pyridin-4-yl)acrylamide (95).



95

To a solution of compound **92** (31 mg, 0.0620 mmol) in DMF (1.5 mL) were added 3-(4-pyridyl)acrylic acid (10.3 mg, 0.0691 mmol), HATU (59.3 mg, 0.156 mmol), and (*i*-Pr)$_2$NEt (40 μL, 0.234 mmol), and the mixture was stirred for 1 h at room temperature under an argon atmosphere. The reaction mixture was poured into EtOAc (20 mL) and washed with water (20 mL × 4). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1–2% (28% NH_3 aq/MeOH = 1/9) in $CHCl_3$) to give compound **95** (37.7 mg, 96%) as a colorless amorphous.

IR (film): 3410, 1651, 1316, 1154 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.41–1.84 (m, 4H), 2.06–2.40 (m, 2H), 2.78–2.97 (m, 1H), 2.83 (s, 1.2H), 2.84 (s, 4.8H), 2.98–3.23 (m, 3.6H), 3.03 (s, 2.4H), 3.66–3.79 (m, 0.8H), 3.41 (s, 2.4H), 3.85 (s, 0.6H), 4.14 (d, *J* = 3.2 Hz, 0.2H), 4.20 (d, *J* = 4.8 Hz, 0.8H), 4.26–4.39 (m, 0.2H), 4.59 (d, *J* = 7.6 Hz, 0.8H), 4.71–4.80 (m, 0.4H), 4.95–4.51 (brs, 0.8H), 6.64 (d, *J* = 8.4 Hz, 0.2H), 6.72 (d, *J* = 8.4 Hz, 0.8H), 6.76 (d, *J* = 8.4 Hz, 0.2H), 6.81 (d, *J* = 8.4 Hz, 0.8H), 6.89 (d, *J* = 15.6 Hz, 0.8H), 7.03 (d, *J* = 15.6 Hz, 0.2H), 7.18–7.30 (m, 2.8H), 7.33–7.43 (m, 1.2H), 7.44 (d, *J* = 15.6 Hz, 0.8H), 7.53 (d, *J* = 15.6 Hz, 0.2H), 7.56–7.64 (m, 1H), 8.10–8.16 (m, 1H), 8.54–8.65 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 14.1, 21.4, 22.6, 22.9, 28.9, 29.1, 29.2, 29.7, 30.7, 30.8, 31.1, 31.0, 31.5, 31.9, 32.4, 39.1, 39.4, 46.5, 47.6, 56.3, 57.0, 58.0, 58.3, 58.5, 59.9, 70.1, 88.6, 89.46, 114.3, 115.3, 119.3, 120.0, 121.7, 122.4, 123.1, 123.6, 124.2, 124.4, 124.6, 130.4, 130.6, 132.7, 132.9, 133.1, 134.5, 134.6, 138.9, 139.6, 142.6, 142.8, 142.9, 143.7, 143.9, 144.3, 150.1, 150.4, 152.9, 160.0, 165.9, 166.7.

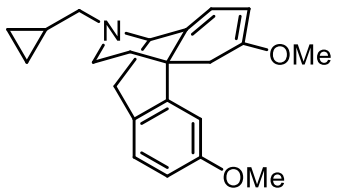
HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{34}H_{39}N_4O_6S$, 631.2590; found, 631.2561.

The purity was >95% as assessed by HPLC (254 nm).

Typical procedure (Table 9, entry 3) of rearrangement reaction

A mixture of **100** (3.16 g, 9.36 mmol) and zinc iodide (8.96 g, 28.1 mmol) in THF (30 mL) was stirred at 60 °C for 13 h. After the addition of saturated $NaHCO_3$ aq (30 mL) at 0 °C, the mixture was extracted with EtOAc (200, 100 mL), washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on NH-silica gel (EtOAc/hexane = 1/12 to 1/5) to afford **101** (1.02 g, 32%) as a pale brown oil and **109** (1.35 g, 43%) as a pale brown oil.

(4b*R*,9*R*)-11-(Cyclopropylmethyl)-3,6-dimethoxy-9,10-dihydro-5*H*-9,4b(epiminoethano)phenanthrene (100).



100

A mixture of compound **108** (4.19 g, 9.41 mmol) in toluene (50 mL) was refluxed for 1 h under an argon atmosphere. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure, and the crude residue was purified by column chromatography on silica gel (1–3% MeOH in $CHCl_3$) to afford compound **100** (3.16 g, 99%) as a pale yellow oil.

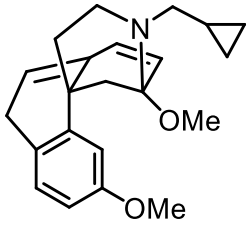
IR (film): 2909, 1666, 1607 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 0.08–0.19 (m, 2H), 0.46–0.57 (m, 2H), 0.83–0.95 (m, 1H), 1.31–1.38 (m, 1H), 2.25 (ddd, *J* = 12.4, 12.4, 4.4 Hz, 1H), 2.32–2.41 (m, 2H), 2.50 (dd, *J* = 12.4, 6.4 Hz, 1H), 2.62 (d, *J* = 17.6 Hz, 1H), 2.78 (ddd, *J* = 12.4, 4.4, 2.0 Hz, 1H), 2.88 (dd, *J* = 17.2, 6.0 Hz, 1H), 3.04 (d, *J* = 17.2 Hz, 1H), 3.17 (d, *J* = 17.2 Hz, 1H), 3.57 (s, 3H), 3.71 (d, *J* = 5.6 Hz, 1H), 3.78 (s, 3H), 4.88 (d, *J* = 6.4 Hz, 1H), 5.75 (d, *J* = 6.4 Hz, 1H), 6.69 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.8, 4.2, 9.8, 31.8, 38.6, 41.3, 41.9, 46.0, 54.7, 55.4, 58.9, 59.3, 91.2, 109.9, 111.5, 115.7, 128.6, 129.6, 131.8, 145.0, 156.3, 158.4.

HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{22}H_{28}NO_2$, 338.2120; found, 338.2123.

(4*R*,12b*S*)-3-(Cyclopropylmethyl)-4,11-dimethoxy-2,3,4,8-tetrahydro-1*H*-4,12b-methanonaphtho[1,2-*d*]azocine (101).



101

The title compound was synthesized according to the typical procedure of rearrangement reaction.

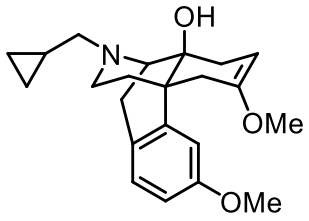
IR (film): 2954, 1614, 1498, 1146, 1105 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 0.05–0.16 (m, 2H), 0.39–0.50 (m, 1H), 0.50–0.60 (m, 1H), 0.78–0.90 (m, 1H), 1.50–1.61 (m, 2H), 1.66 (ddd, *J* = 12.4, 12.4, 5.2 Hz, 1H), 1.83 (dd, *J* = 11.2, 2.8, Hz, 1H), 2.12 (ddd, *J* = 12.4, 12.4, 4.0 Hz, 1H), 2.59 (d, *J* = 10.8 Hz, 1H), 3.14 (dd, *J* = 12.8, 6.0 Hz, 1H), 3.28–3.35 (m, 1H), 3.37 (d, *J* = 5.6 Hz, 1H), 3.42 (d, *J* = 3.2 Hz, 1H), 3.47 (s, 3H), 3.81 (s, 3H), 5.43 (d, *J* = 9.6 Hz, 1H), 5.99 (dd , *J* = 5.6, 3.2 Hz, 1H), 6.41 (d, *J* = 9.6 Hz, 1H), 6.74 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.99 (d, *J* = 2.4 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 2.6, 5.8, 9.8, 30.1, 38.1, 39.6, 40.4, 47.9, 48.4, 53.5, 55.5, 87.6, 109.8, 111.0, 125.3, 126.1, 127.6, 128.8, 131.8, 138.8, 144.9, 158.6.

HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{22}H_{28}NO_2$, 338.2120; found, 338.2125.

(4b*R*,8a*S*,9*R*)-11-(Cyclopropylmethyl)-3,6-dimethoxy-5,8,9,10-tetrahydro-8a*H*-9,4b-(epiminoethano)-phenanthren-8a-ol (107).



107

A mixture of compound **106** (31.19 g, 91.35 mmol) and *p*-TsOH·H_2O (21.05 g, 109.62 mmol) in MeOH (100 mL) and trimethyl orthoformate (200 mL) was refluxed for 12 h under an argon atmosphere. After cooling to room temperature, the mixture was concentrated under reduced pressure. The crude residue was dissolved in absolute toluene (200 mL), and the mixture was refluxed with a Dean–Stark apparatus for 2 h under an argon atmosphere. After cooling to room temperature, the reaction mixture was filtered and the residual solid was washed with toluene (50 mL). The obtained residual solid was dissolved in mixed solution, MeOH/$CHCl_3$ = 1/4 (500 mL), and washed with saturated $NaHCO_3$ aq (200 mL). The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was dissolved in hot EtOH (65 °C), and cool to room temperature. The obtained white solid was filtered and dried under reduced pressure at room temperature. The crude filtrate was concentrated under reduced pressure, and the recrystallization was performed twice with the same operation as above to afford compound **107** (19.80 g, 61%) as a white solid.

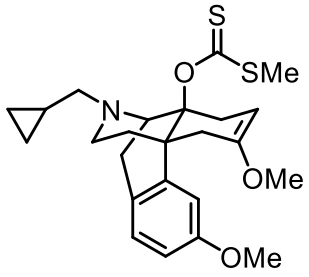
IR (KBr): 3381, 2916, 1673 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 0.07–0.17 (m, 2H), 0.47–0.57 (m, 2H), 0.81–0.91 (m, 1H), 1.16–1.26 (m, 1H), 1.98–2.13 (m, 3H), 2.19 (ddd, *J* = 16.8, 2.4, 2.4 Hz, 1H), 2.37 (d, *J* = 6.4 Hz, 2H), 2.53 (d, *J* = 16.4 Hz, 1H), 2.60 (d, *J* = 6.8 Hz, 1H), 2.65 (ddd, *J* = 16.4, 4.4, 2.4 Hz, 1H), 2.87 (dd, *J* = 18.8, 6.4 Hz, 1H), 3.06 (d, *J* = 18.8 Hz, 1H), 3.09 (d, *J* = 6.4 Hz, 1H), 3.46 (s, 3H), 3.76 (s, 3H), 4.32 (ddd, *J* = 4.8, 2.4, 2.4 Hz, 1H), 4.67 (brs, 1H), 6.70 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.84 (d, *J* = 2.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.9, 4.1, 9.6, 24.8, 31.9, 34.2, 36.6, 41.0, 43.9, 54.0, 55.3, 59.5, 59.7, 68.8, 89.7, 110.3, 111.6, 128.0, 128.4, 142.3, 152.9, 158.3.

HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{22}H_{30}NO_3$, 356.2226; found, 356.2222.

***O*-[(4b*R*,8a*S*,9*R*)-11-(Cyclopropylmethyl)-3,6-dimethoxy-5,8,9,10-tetrahydro-8a*H*-9,4b-(epiminoethano)phenanthren-8a-yl] *S*-methyl carbonodithioate (108).**



108

An oven dried separable flask was charged with KH (1.89 g, 47.12 mmol) and absolute THF (30 mL) under an argon atmosphere. To the stirred slurry at 0 °C was added a solution of **107** (4.13 g, 11.61 mmol) in absolute THF (70 mL), and the mixture was stirred at room temperature for 0.5 h followed by addition of CS_2 (3.00 mL, 49.68 mmol). After stirring for 1 h, the reaction mixture was added MeI (4.00 mL, 64.22 mmol), and stirred for 1 h, followed by slowly addition of mixed solution, *i*-PrOH/hexane = 1/1 (20 mL) at 0 °C. After that, the reaction mixture was added saturated NH_4Cl aq (20 mL) and water (50 mL), and extracted with EtOAc (200, 100, 50 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 (8–23% EtOAc in hexane) to afford compound **108** (4.75 g, 92%) as a pale yellow amorphous.

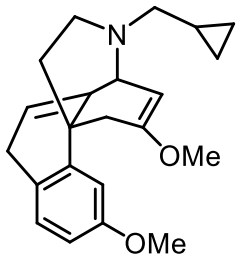
IR (film): 2917, 1677, 1238, 1030 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 0.01–0.13 (m, 2H), 0.39–0.52 (m, 2H), 0.73–0.85 (m, 1H), 1.21–1.29 (m, 1H), 2.06–2.21 (m, 3H), 2.31 (ddd, *J* = 12.4, 12.4, 5.2, Hz, 1H), 2.49 (dd, *J* = 12.4, 5.6 Hz, 1H), 2.53 (s, 3H), 2.56–2.62 (m, 1H), 2.64 (d, *J* = 17.4 Hz, 1H), 2.68–2.75 (m, 1H), 2.80 (dd, *J* = 18.4, 6.8 Hz, 1H), 3.11 (d, *J* = 18.4 Hz, 1H), 3.45 (s, 3H), 3.77 (s, 3H), 3.83 (dd, *J* = 18.4, 4.8 Hz, 1H), 4.23–4.27 (m, 1H), 5.16 (d, *J* = 6.4 Hz, 1H), 6.73 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.86 (d, *J* = 2.4 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.7, 4.3, 9.8, 19.2, 25.4, 26.4, 33.9, 36.3, 42.1, 44.1, 51.9, 54.1, 55.3, 59.5, 89.1, 91.5, 110.3, 111.9, 128.3, 128.4, 141.2, 152.6, 158.4, 213.6.

HRMS–ESI (*m*/*z*): $[M + H - X]^+$ calcd for $C_{22}H_{28}NO_2$, 338.2120; found, 338.2129. A peak without xanthic acid was observed (X = $C_2H_4OS_2$).

(1*S*,4a*R*)-13-(Cyclopropylmethyl)-3,6-dimethoxy-1,9-dihydro-4*H*-1,4a-(epiminoethano)phenanthrene (109).



109

The title compound was synthesized according to the typical procedure of rearrangement reaction.

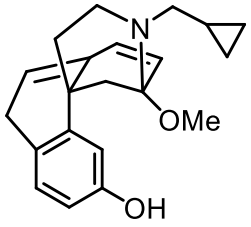
IR (film): 2909, 1612, 1504, 1156, 1044 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 0.08–0.19 (m, 2H), 0.48–0.59 (m, 2H), 0.87–1.01 (m, 1H), 1.87–2.00 (m, 2H), 2.17 (dd, *J* = 12.4, 6.4 Hz, 1H), 2.37–2.46 (m, 2H), 2.62 (d, *J* = 17.2 Hz, 1H), 2.77 (ddd, *J* = 12.0, 12.0, 5.6 Hz, 1H), 2.89 (ddd, *J* = 12.8, 4.8, 2.0 Hz, 1H), 3.37 (dd, *J* = 22.0, 3.2 Hz, 1H), 3.45 (dd, *J* = 22.0, 3.6 Hz, 1H), 3.57 (s, 3H), 3.79 (s, 3H), 3.98 (d, *J* = 6.0 Hz, 1H), 4.69 (d, *J* = 6.0 Hz, 1H), 5.80 (dd, *J* = 3.6, 3.2 Hz, 1H), 6.70 (d, *J* = 2.8 Hz, 1H), 6.74 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.9, 4.2, 9.6, 28.6, 37.1, 41.4, 43.7, 45.1, 54.6, 55.3, 59.5, 59.9, 88.9, 110.5, 112.2, 115.0, 123.7, 129.6, 136.6, 143.6, 158.3, 159.4.

HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{22}H_{28}NO_2$, 338.2120; found, 338.2132.

(4*R*,12b*S*)-3-(Cyclopropylmethyl)-4-methoxy-2,3,4,8-tetrahydro-1*H*-4,12b-methanonaphtho[1,2-*d*]azocin-11-ol (111).



111

A mixture of **101** (28.9 mg, 0.0856 mmol) in CH_2Cl_2 (2 mL) was stirred at 0 °C under an argon atmosphere. The reaction mixture was added 1.0 M BBr_3 in CH_2Cl_2 solution (0.26 mL, 0.260 mmol), and stirred for 20 min. After the addition of saturated $NaHCO_3$ aq (6 mL) at 0 °C, the mixture was extracted with $CHCl_3$ (15 mL, 10 mL, 5 mL), 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 compound **111** (17.7 mg, 64%) as a pale yellow oil.

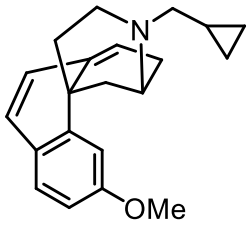
IR (film): 3330, 3007, 2933, 1611, 1292, 1143, 1105 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 0.07–0.15 (m, 2H), 0.41–0.48 (m, 1H), 0.52–0.62 (m, 1H), 0.80–0.95 (m, 1H), 1.49–1.67 (m, 3H), 1.85 (dd, *J* = 11.2, 2.8 Hz, 1H), 2.14 (ddd, *J* = 12.4, 12.4, 4.0 Hz, 1H), 2.63 (d, *J* = 11.2 Hz, 1H), 3.17 (dd, *J* = 12.8, 6.0 Hz, 1H), 3.28–3.43 (m, 3H), 3.49 (s, 3H), 5.44 (d, *J* = 10.4 Hz, 1H), 5.99 (dd, *J* = 5.2, 2.8 Hz, 1H), 6.42 (d, *J* = 10.4 Hz, 1H), 6.69 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H). One proton (OH) was not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 2.7, 5.9, 9.6, 30.1, 37.8, 39.3, 40.2, 47.9, 48.7, 53.6, 88.0, 111.1, 113.6, 125.66, 125.74, 127.2, 129.0, 132.4, 138.7, 144.7, 155.0.

HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{21}H_{26}NO_2$, 324.1964; found, 324.1957.

(4*R*,12b*S*)-3-(Cyclopropylmethyl)-11-methoxy-2,3,4,5-tetrahydro-1*H*-4,12b-methanonaphtho[1,2-*d*]azocine (115).



115

A mixture of **109** (337.7 mg, 1.00 mmol) in THF (6 mL) was added 1 M HCl aq (4 mL), and stirred for 16 h at room temperature under an argon atmosphere. After the addition of saturated $NaHCO_3$ aq (10 mL), the mixture was extracted with $CHCl_3$ (50, 30, 20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was dissolved in 1,2-dichloroethane (10 mL), and added acetic acid (5.7 μL, 0.100 mmol), *N*-benzylmethylamine (258 μL, 2.00 mmol) and $NaBH(OAc)_3$ (1.67 g, 7.86 mmol). The mixture was stirred for 3 h at 60 °C under an argon atmosphere. After the addition of saturated $NaHCO_3$ aq (15 mL), the mixture was extracted with $CHCl_3$ (40, 30, 20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on NH silica gel (EtOAc/hexane = 1/9) to afford compound **115** (236.8 mg, 77% in 2 steps) as a pale yellow oil.

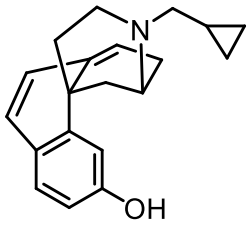
IR (film): 2912, 1600 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 0.07–0.19 (m, 2H), 0.48–0.58 (m, 2H), 0.83–0.94 (m, 1H), 1.62–1.73 (m, 2H), 1.88–1.95 (m, 1H), 2.10 (ddd, *J* = 20.4, 4.8, 3.2 Hz, 1H), 2.28–2.50 (m, 4H), 2.58 (dd, *J* = 12.4, 3.6 Hz, 1H), 2.73 (ddd, *J* = 12.0, 3.2, 3.2 Hz, 1H), 3.46–3.52 (m, 1H), 3.80 (s, 3H), 5.83 (dd, *J* = 3.6, 3.6 Hz, 1H), 5.97 (d , *J* = 9.6 Hz, 1H), 6.19 (d, *J* = 9.6 Hz, 1H), 6.68 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 2.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.9, 4.1, 9.4, 24.0, 35.1, 37.4, 38.7, 44.0, 51.6, 55.4, 60.0, 111.1, 111.2, 124.3, 125.6, 126.2, 127.9, 128.1, 137.7, 145.2, 159.4.

HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{21}H_{26}NO$, 308.2014; found, 308.2009.

(4*R*,12b*S*)-3-(Cyclopropylmethyl)-2,3,4,5-tetrahydro-1*H*-4,12b-methanonaphtho[1,2-*d*]azocin-11-ol (119).



119

A mixture of **115** (20.3 mg, 0.0660 mmol) in CH_2Cl_2 (2 mL) was stirred at 0 °C under an argon atmosphere. The reaction mixture was added 1.0 M BBr_3 in CH_2Cl_2 solution (0.17 mL, 0.170 mmol), and stirred for 20 min. After the addition of 28% NH_3 aq (0.5 mL) and saturated $NaHCO_3$ aq (2 mL) at 0 °C, the mixture was extracted with $CHCl_3$ (20, 15, 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by PLC (28% NH_3 aq/MeOH/$CHCl_3$ = 1/9/100) to afford compound **119** (13.6 mg, 70%) as a pale yellow oil.

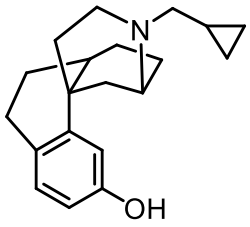
IR (film): 3333, 3006, 2918, 1601, 1470, 1300, 1123, 1093 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 0.10–0.20 (m, 2H), 0.49–0.59 (m, 2H), 0.90–1.01 (m, 1H), 1.51–1.62 (m, 2H), 1.78–1.86 (m, 1H), 2.10 (ddd, *J* = 20.4, 4.0, 3.6 Hz, 1H), 2.29 (dd, *J* = 20.4, 4.4 Hz, 1H), 2.36–2.47 (m, 3H), 2.65 (dd, *J* = 12.4, 3.2 Hz, 1H), 2.73 (ddd, *J* = 12.4, 3.2, 3.2 Hz, 1H), 3.49–3.55 (m, 1H), 5.74 (dd, *J* = 3.6, 3.6 Hz, 1H), 5.89 (d, *J* = 9.6 Hz, 1H), 6.15 (d, *J* = 9.6 Hz, 1H), 6.59 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 2.0 Hz, 1H). One proton (OH) was not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 4.2, 4.4, 8.3, 23.7, 33.8, 36.8, 37.8, 43.8, 51.7, 59.6, 113.8, 114.8, 124.4, 124.9, 125.0, 126.5, 128.4, 137.9, 144.6, 157.2.

HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{20}H_{24}NO$, 294.1858; found, 294.1844.

(4*R*,12b*S*)-3-(Cyclopropylmethyl)-2,3,4,5,6,6a,7,8-octahydro-1*H*-4,12b-methanonaphtho[1,2-*d*]azocin-11-ol (120).



120

A mixture of **115** (61.3 mg, 0.199 mmol) and 20 wt % $Pd(OH)_2/C$ (50% H_2O, 58.6 mg, 0.0417 mmol) in EtOH (3 mL) was stirred for 9 h at room temperature under a hydrogen atmosphere. The reaction mixture was filtered through a sheet of filter paper, and the filtrate was concentrated under reduced pressure. The crude residue was dissolved in CH_2Cl_2 (2 mL), and stirred at 0 °C under an argon atmosphere. The reaction mixture was added 1.0 M BBr_3 in CH_2Cl_2 solution (0.50 mL, 0.500 mmol), and stirred for 1.5 h at room temperature. After the addition of 28% NH_3 aq (0.5 mL) and saturated $NaHCO_3$ aq (2 mL) at 0 °C, the mixture was extracted with $CHCl_3$ (20, 10, 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by PLC (28% NH_3 aq/MeOH/$CHCl_3$ = 1/9/100) to afford compound **120** (41.5 mg, 75% in 2 steps) as a colorless solid.

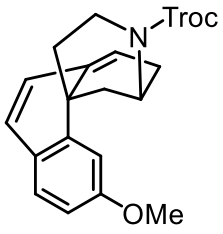
IR (film): 3378, 3001, 2922, 1606, 1450, 1253, 1105 cm^{-1}

^1H NMR (400 MHz, pyridine-d_5): δ (5:1 mixture of diastereomers) = 0.11–0.21 (m, 2H), 0.41–0.52 (m, 2H), 0.87–1.00 (m, 1H), 1.29–1.41 (m, 1H), 1.47–1.85 (m, 6H), 1.90–2.01 (m, 1H), 2.02–2.19 (m, 2H), 2.28 (dd, *J* = 12.4, 7.2 Hz, 1H), 2.46 (dd, *J* = 12.4, 6.0 Hz, 0.17H), 2.55 (dd, *J* = 12.8, 6.0 Hz, 0.83H), 2.65–2.91 (m, 4H), 2.92–3.01 (m, 1H), 3.04–3.09 (m, 0.17H), 3.15–3.25 (m, 0.83H), 7.01–7.11 (m, 2H), 7.37–7.43 (m, 1H), 11.12 (brs, 1H).

^{13}C NMR (100 MHz, pyridine-d_5): δ (major isomer) = 3.9, 4.9, 10.1, 26.1, 26.6, 29.5, 30.6, 36.1, 36.2, 40.7, 42.8, 49.7, 53.6, 60.9, 112.7, 114.5, 126.9, 130.7, 148.7, 157.2.

HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{20}H_{28}NO$, 298.2171; found, 298.2162.

2,2,2-Trichloroethyl (4*R*,12b*S*)-11-methoxy-1,2,4,5-tetrahydro-3*H*-4,12b-methanonaphtho[1,2-*d*]azocine-3-carboxylate (121).



121

To a solution of compound **115** (84.0 mg, 0.273 mmol) in 1,1,2,2-tetrachloroethane (10 mL) were added K_2CO_3 (484.5 mg, 3.28 mmol) and 2,2,2-trichloroethyl chloroformate (367 μL, 2.73 mmol), and the mixture was stirred at 150 °C for 1 h under an argon atmosphere. After cooling to room temperature, the reaction mixture was added saturated $NaHCO_3$ aq (8 mL), extracted with $CHCl_3$ (30, 20, 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (10–20% EtOAc in hexane) to afford compound **121** (74.9 mg, 64%) as a colorless solid.

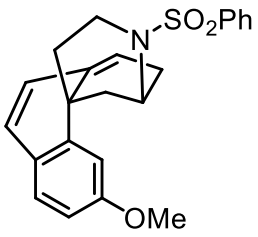
IR (KBr): 2876, 1718, 1600, 1411, 1222, 1123 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.45–1.56 (m, 1H), 1.70–1.82 (m, 1H), 1.90–1.97 (m, 1H), 2.19 (dd, *J* = 10.4, 4.8 Hz, 0.45H), 2.24 (dd, *J* = 10.4, 4.8 Hz, 0.55H), 2.39–2.46 (m, 1H), 2.61–2.72 (m, 1H), 3.22 (ddd, *J* = 13.2, 3.6, 3.6 Hz, 0.45H), 3.30 (ddd, *J* = 13.2, 3.6, 3.6 Hz, 0.55H), 3.81 (s, 3H), 3.93–4.03 (m, 1H), 4.75 (d, *J* = 12.0 Hz, 0.55H), 4.74–4.82 (m, 0.9H), 4.78 (d, *J* = 2.4 Hz, 1H), 4.86 (d, *J* = 12.0 Hz, 0.55H), 5.83–5.90 (m, 1H), 6.017 (d, *J* = 9.2 Hz, 0.55H), 6.022 (d, *J* = 9.6 Hz, 0.45H), 6.25 (d, *J* = 9.2 Hz, 0.55H), 6.26 (d, *J* = 9.6 Hz, 0.45H), 6.70 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.85 (d, *J* = 2.4 Hz, 1H), 6.999 (d, *J* = 8.4 Hz, 0.55H), 7.001 (dd, *J* = 8.4 Hz, 0.45H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 32.0, 32.3, 33.3, 33.5, 36.8, 37.0 (×2), 37.2, 37.7, 38.1, 46.9 (×2), 55.4 (×2), 75.2 (×2), 95.9 (×2), 110.8, 110.9, 111.40, 111.44, 124.95, 125.00, 125.25, 125.27, 126.0 (×2), 126.3, 126.5, 128.4 (×2), 137.0 (×2), 144.00, 144.02, 153.6, 153.7, 159.5 (×2).

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{20}H_{20}Cl_3NNaO_3$, 450.0407; found, 450.0412.

(4*R*,12b*S*)-11-Methoxy-3-(phenylsulfonyl)-2,3,4,5-tetrahydro-1*H*-4,12b-methanonaphtho[1,2-*d*]azocine (123).



123

A mixture of **121** (43.7 mg, 0.102 mmol) and zinc powder (133.3 mg, 2.04 mmol) in acetic acid (4 mL) was stirred for 1.5 h at room temperature under an argon atmosphere. The reaction mixture was filtered through a pad of Celite, washed with MeOH (60 mL), and the filtrate was concentrated under reduced pressure. After the addition of saturated $NaHCO_3$ aq (10 mL), the mixture was extracted with a mixed solution, *i*-PrOH/$CHCl_3$ = 1/4 (30, 20, 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. To a stirred solution of the crude residue in CH_2Cl_2 (5.0 mL) was added Et_3N (42.6 μL, 0.306 mmol) and benzenesulfonyl chloride (26.0 μL, 0.204 mmol) at room temperature under an argon atmosphere. After stirring for 0.5 h, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (15–25% EtOAc in hexane) to afford compound **123** (33.7 mg, 84% in 2 steps) as a colorless solid.

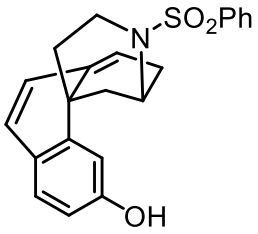
IR (KBr): 2916, 1600, 1499, 1446, 1342, 1311, 1164 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 1.48 (ddd, *J* = 12.8, 12.8, 4.8 Hz, 1H), 1.64–1.71 (m, 1H), 1.83 (ddd, *J* = 12.4, 2.4, 2.4 Hz, 1H), 1.92 (dd, *J* = 20.4, 4.4 Hz, 1H), 2.36 (dd, *J* = 12.4, 3.2 Hz, 1H), 2.39–2.49 (m, 1H), 3.18 (ddd, *J* = 12.8, 12.8, 3.2 Hz, 1H), 3.71 (dd, *J* = 12.8, 4.4 Hz, 1H), 3.79 (s, 3H), 4.48–4.56 (m, 1H), 5.69 (dd, *J* = 3.6, 3.6 Hz, 1H), 5.93 (d, *J* = 9.6 Hz, 1H), 6.20 (d, *J* = 9.6 Hz, 1H), 6.64–6.72 (m, 2H), 6.96 (d, *J* = 8.8 Hz, 1H), 7.50–7.65 (m, 3H), 7.84–7.90 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.6, 33.7, 36.7, 37.6, 37.8, 48.5, 55.5, 111.2, 111.3, 125.0 (×2), 125.8, 126.3, 127.2 (×2), 128.5, 129.4 (×2), 132.6, 137.0, 140.9, 143.7, 159.5.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{23}H_{23}NNaO_3S$, 416.1296; found, 416.1312.

(4*R*,12b*S*)-3-(Phenylsulfonyl)-2,3,4,5-tetrahydro-1*H*-4,12b-methanonaphtho[1,2-*d*]azocin-11-ol (124).



124

A mixture of **123** (24.3 mg, 0.0614 mmol) in CH_2Cl_2 (2.5 mL) was stirred at 0 °C under an argon atmosphere. The reaction mixture was added 1.0 M BBr_3 in CH_2Cl_2 solution (0.16 mL, 0.160 mmol), and stirred for 1 h at room temperature. After the addition of 28% NH_3 aq (0.5 mL) and saturated $NaHCO_3$ aq (2 mL) at 0 °C, the mixture was extracted with $CHCl_3$ (20, 15, 10 mL), 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 compound **124** (20.1 mg, 86%) as a pale colorless solid.

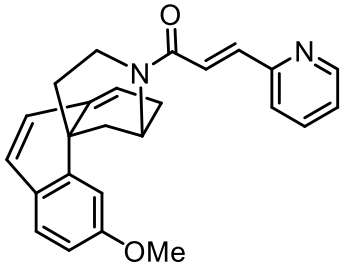
IR (KBr): 3389, 2916, 1601, 1569, 1446, 1328, 1156, 1115, 1091 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 1.49 (ddd, *J* = 12.8, 12.8, 4.8 Hz, 1H), 1.65–1.72 (m, 1H), 1.84 (ddd, *J* = 12.4, 2.4, 2.4 Hz, 1H), 1.91 (dd, *J* = 20.8, 4.4 Hz, 1H), 2.36 (dd, *J* = 12.4, 3.6 Hz, 1H), 2.43 (ddd, *J* = 20.8, 5.6, 3.6 Hz, 1H), 3.17 (ddd, *J* = 12.8, 12.8, 3.6 Hz, 1H), 3.66–3.73 (m, 1H), 4.48–4.54 (m, 1H), 4.97 (brs, 1H), 5.69 (dd, *J* = 3.6, 3.6 Hz, 1H), 5.92 (d, *J* = 9.6 Hz, 1H), 6.19 (d, *J* = 9.6 Hz, 1H), 6.61 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.67 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 7.52–7.64 (m, 3H), 7.84–7.89 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.5, 33.8, 36.7, 37.6, 37.7, 48.5, 112.1, 113.5, 124.9, 125.0, 125.9, 126.3, 127.2 (×2), 128.7, 129.4 (×2), 132.7, 136.9, 140.8, 144.0, 155.6.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{22}H_{21}NNaO_3S$, 402.1140; found, 402.1137.

(*E*)-1-[(4*R*,12b*S*)-11-Methoxy-1,2,4,5-tetrahydro-3*H*-4,12b-methanonaphtho[1,2-*d*]azocin-3-yl]-3-(pyridin-2-yl)prop-2-en-1-one (125).



125

A mixture of **121** (44.1 mg, 0.103 mmol) and zinc powder (134.5 mg, 2.06 mmol) in acetic acid (4 mL) was stirred for 1.5 h at room temperature under an argon atmosphere. The reaction mixture was filtered through a pad of Celite, washed with MeOH (60 mL), and the filtrate was concentrated under reduced pressure. After the addition of saturated $NaHCO_3$ aq (10 mL), the mixture was extracted with a mixed solution, *i*-PrOH/$CHCl_3$ = 1/4 (30, 20, 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. To a stirred solution of the crude residue in CH_2Cl_2 (4 mL) was added (*i*-Pr)$_2$NEt (35.8 μL, 0.206 mmol), 3-(2-pyridyl)acrylic acid (16.9 mg, 0.113 mmol) and HATU (43.1 mg, 0.113 mmol) at room temperature under an argon atmosphere. After stirring for 1 h, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (20–40% Acetone in hexane) to afford compound **125** (39.3 mg, 99% in 2 steps) as a colorless amorphous.

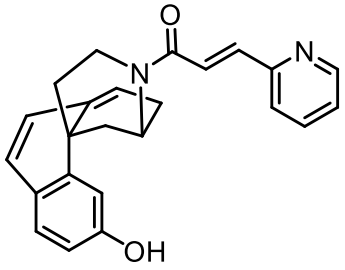
IR (KBr): 2931, 1650, 1600, 1435, 1219, 1106, 1036 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.52 (ddd, *J* = 13.2, 4.8 Hz, 1H), 1.74–1.85 (m, 1H), 1.93–2.01 (m, 1H), 2.14–2.27 (m, 1H), 2.43 (ddd, *J* = 12.0, 3.6 Hz, 1H), 2.66–2.80 (m, 1H), 3.05–3.16 (m, 0.45H), 3.48–3.58 (m, 0.55H), 3.80 (s, 3H), 3.95 (dd, *J* = 14.0, 4.4 Hz, 0.55H), 4.55 (dd, *J* = 14.0, 4.4 Hz, 0.45H), 4.73–4.79 (m, 0.45H), 5.33–5.40 (m, 0.55H), 5.85–5.89 (m, 0.45H), 5.89–5.93 (m, 0.55H), 6.04 (d, *J* = 9.2 Hz, 1H), 6.26 (d, *J* = 9.2 Hz, 0.55H), 6.27 (d, *J* = 9.2 Hz, 0.45H), 6.68–6.72 (m, 1H), 6.84 (d, *J* = 10.0 Hz, 0.45H), 6.85 (d, *J* = 10.0 Hz, 0.55H), 6.98–7.02 (m, 1H), 7.20–7.28 (m, 1H), 7.34–7.39 (m, 1H), 7.53–7.74 (m, 3H), 8.59–8.66 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 31.9, 32.7, 33.4, 34.3, 34.6, 37.2, 37.3, 38.0, 38.5, 38.9, 44.0, 48.6, 55.4 (×2), 111.0, 111.2, 111.25, 111.28, 122.1, 122.2, 123.88, 123.93, 124.8, 124.9, 124.98, 125.01, 125.2, 125.3, 125.9 (×2), 126.0, 126.9, 128.37, 128.44, 136.98, 137.03 (×2), 137.4, 140.9, 141.0, 143.8 (×2), 145.0 (×2), 153.6 (×2), 159.5 (×2), 165.3, 165.4.

HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{25}H_{24}N_2NaO_2$, 407.1736; found, 407.1736.

(*E*)-1-((4*R*,12b*S*)-11-Hydroxy-1,2,4,5-tetrahydro-3*H*-4,12b-methanonaphtho[1,2-*d*]azocin-3-yl)-3-(pyridin-2-yl)prop-2-en-1-one (126)



126

A mixture of **125** (33.1 mg, 0.0861 mmol) in CH_2Cl_2 (3 mL) was stirred at 0 °C under an argon atmosphere. The reaction mixture was added 1.0 M BBr_3 in CH_2Cl_2 solution (0.22 mL, 0.220 mmol), and stirred for 1 h at room temperature. After the addition of 28% NH_3 aq (0.5 mL) and saturated $NaHCO_3$ aq (2 mL) at 0 °C, the mixture was extracted with $CHCl_3$ (20, 15, 10 mL), 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 compound **126** (13.0 mg, 41%) as a pale yellow oil.

IR (film): 3418, 1650, 1614, 1446, 1298, 1225, 1128, 1025, 1128, 1025 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ (mixture of rotamers) = 1.33–1.50 (m, 1H), 1.52–1.60 (m, 0.7H), 1.81–1.95 (m, 1H), 2.07–2.20 (m, 1.3H), 2.28–2.38 (m, 1H), 2.57–2.73 (m, 1H), 3.09 (ddd, *J* = 13.2, 13.2, 3.6 Hz, 0.3H), 3.39 (ddd, *J* = 13.2, 13.2, 3.6 Hz, 0.7H), 3.79 (dd, *J* = 13.2, 4.0 Hz, 0.7H), 4.45 (dd, *J* = 13.2, 4.0 Hz, 0.3H), 4.63–4.69 (m, 0.3H), 5.28–5.34 (m, 0.7H), 5.81 (dd, *J* = 4.0, 4.0 Hz, 0.3H), 5.84 (dd, *J* = 4.0, 4.0 Hz, 0.7H), 5.93–6.01 (m, 1H), 6.21 (d, *J* = 9.6 Hz, 0.7H), 6.22 (d, *J* = 9.6 Hz, 0.3H), 6.64 (dd, *J* = 8.4, 2.4 Hz, 0.3H), 6.69 (dd, *J* = 8.4, 2.4 Hz, 0.7H), 6.79 (d, *J* = 1.6 Hz, 0.3H), 6.87–6.92 (m, 1.7H), 7.27–7.31 (m, 1H), 7.32–7.36 (m, 0.3H), 7.36–7.40 (m, 0.7H), 7.56 (d, *J* = 14.8 Hz, 0.7H), 7.60–7.66 (m, 1.3H), 7.70–7.77 (m, 1H), 8.58–8.62 (m, 0.7H), 8.62–8.66 (m, 0.3H). One proton (OH) was not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ (mixture of rotamers) = 31.8, 32.8, 33.4, 34.3, 35.0, 37.0, 37.1, 38.0, 38.57, 38.63, 44.4, 48.8, 112.2, 112.3, 113.5, 113.6, 122.5, 122.7, 124.2, 124.3, 124.6, 124.7, 125.0, 125.1, 125.2, 125.3, 125.5, 125.6 (×2), 126.2, 128.6, 128.7, 137.2, 137.4, 137.5, 137.6, 140.7 (×2), 143.8, 143.9, 149.68, 149.73, 153.3, 153.4, 156.8, 157.3, 165.4, 165.7.

HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{24}H_{23}N_2O_2$, 371.1760; found, 371.1754.

Computational calculation

Conformational analysis of 73 and 75

The initial structures for **73** and **75** were prepared using SYBYL6.91 (Tripos, St Louis, MO, USA). Conformational analysis of these two compounds was performed using the Conformational Analyzer with Molecular Dynamics And Sampling (CAMDAS) 2.1 program.[55] CAMDAS generates the energetically accessible conformers of a target molecule by performing an MD calculation and sampling conformers along the trajectory. The procedure for the CAMDAS calculation was similar to that described previously.[67] In total, 23 dihedral angles were used to cluster similar conformations for both **73** and **75**. From the CAMDAS calculation, 7056 and 9158 different conformers were obtained for **73** and **75**, respectively.

Modeling of binding mode of 93 with OX_1R

All calculations were performed using the Schrödinger suite 2015-4 (Schrödinger, LLC, New York, NY, 2015). First, the 3D structure of **93** was constructed using the LigPrep 3.6 program, and its protonation state was predicted using Epik 3.4 program.[68] The resulting conformer was used in the following docking calculations. Two X ray structures of the OX_1R were available in the Protein Data Bank (PDB).[57] One is in complex with suvorexant (**20**; PDB ID: 4ZJ8), and the other is in complex with SB-674042 (**25**; PDB ID: 4 ZJC). These two structures were used as receptors for docking. Both structures were prepared using the Protein Preparation Wizard in Maestro 10.4 and minimized using force field OPLS3. The docking calculation of **93** against OX_1R receptors was performed using the Induced Fit Docking protocol as implemented in Schrödinger suite 2015-4.[69] Box center for the "Receptor Grid Generation" protocol was set to a centroid of **20** or **25** binding to OX_1R. Prime 4.2 program[70] was used to refine residues within 4.0 Å of ligand poses. The generated poses were ranked according to IFDScore to select the top 10% docked complexes. Then, the binding free energies of these complexes (ΔG_{bind}s) were estimated by the molecular mechanics generalized Born surface area (MM-GBSA) method using Prime 4.2 program, and a docked complex with the lowest ΔG_{bind}s was finally selected as the interaction model.

Pharmacology

Calcium assay for OXRs

Chinese hamster ovary (CHO)-K1 cells stably expressing human OX_1R ($CHOOX_1R$)[66] or OX_2R ($CHOOX_2R$)[66] were seeded in a 96-well-plate (10 000 cells per 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 4 μM fluorescent calcium indicator Fura 2-AM (Cayman Chemical) in Hanks' balanced salt solution (HBSS, GIBCO) including 20 mM HEPES (Sigma-Aldrich), 2.5 mM Probenecid (WAKO), 5% CremophorEL (Fluka), and 0.1% bovine serum albumin (BSA) (Sigma-Aldrich) at 37 °C for 1 h. The cells were washed once and added with 50 μL of HBSS buffer. Cells were pretreated with 25 μL of various concentrations of test compounds for 15 min. After that, submaximal concentration of human orexin-A (OX-A, 0.3 nM, Peptide Institute, Inc.) at 25 μL was added to the cells. 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). The IC_{50} values and pA_2 of compound to orexin A were calculated using GraphPad Prism 5J (MDF). K_i values were calculated by using the Cheng–Prusoff formula $K_i = IC_{50}/[1 + (L/EC_{50})]$, where IC_{50} is IC_{50} value of each test compound, L is orexin A concentration at IC_{50} experiments, EC_{50} is the half-maximal effective concentration of orexin A.

Solutions and materials

Human orexin-A was dissolved 0.1% BSA/phosphate buffered saline. Compounds were dissolved in dimethyl sulfoxide (DMSO, Nacalai Tesque) solution and readjusted by adding these solutions into each experimental solution (final concentration of DMSO is 1%).

Binding and [^{35}S]GTPγS assays for opioid receptor

Chinese hamster ovary (CHO) cells stably expressing human μ, δ, or κ opioid receptors were purchased from ChanTest Co., and Human embryonic kidney (HEK) cells stably expressing human μ, δ, or κ opioid receptors were gifted from Drs. Uezono and Miyano (National Cancer Center Research Institute); these cell membranes were used for opioid receptor binding assay and GTPγS binding assay. Binding affinity for μ, δ, or κ opioid receptor in test compounds was measured by displacement of [^{3}H]-DAMGO, [^{3}H]-DPDPE, or [^{3}H]-U69,593 (each 2 nM), respectively. Nonspecific binding was measured in the presence of 10 μM unlabeled DAMGO, DPDPE, or U-69,593. Radioactivity in the test samples was determined by a MicroBeta scintillation counter with 96-well microplate (PerkinElmer). In GTPγS binding assay, various concentrations of test compounds were incubated with cell membrane, 30 μM GDP and 0.1 nM [^{35}S]GTPγS in 96-well microplate. In case of IC_{50} calculation in test compounds (antagonistic activity test), 10^{-6} M U-69,593 (approximately EC_{80}), a standard κ receptor agonist, was added to incubating solution. Nonspecific binding was measured in the presence of 10 μM unlabeled GTPγS. Radioactivity in the test samples was determined by a MicroBeta scintillation counter. The value of each test compounds was calculated as $[(T_1 – T_0)/(T_2 – T_0)] \times 100$, where T_0 is the nonspecific binding, T_1 is the radioligand binding in the presence of various concentrations of test compounds ($10^{–5}$–$10^{–11}$ M), and T_2 is the radioligand binding in the absence of respective test compounds. For IC_{50} calculation, T_2 is the radioligand binding in the presence of 10^{-6} M U-69,593 without test compounds. Sigmoidal concentration–response curve and values of K_i and IC_{50} were calculated by Prism software (version 6.05).

Behavioral Assay

Animals

Male ICR mice (25–30 g) were housed in a room maintained at 23 ± 1 °C with a 12 h light–dark cycle (lights on 8:00 to 20:00). Food and water were available ad libitum. Animal experiments were carried out in a humane manner after receiving approval from the Institutional Animal Care and Use Committee of the University of Tsukuba and in accordance with the Regulation for Animal Experiments in our university and Fundamental Guidelines for Proper Conduct of Animal Experiments and Related Activities in Academic Research Institutions under the jurisdiction of the Ministry of Education, Culture, Sports, Science, and Technology.

Chronic treatment with morphine

Mice were given subcutaneously (s.c.) morphine hydrochloride (Daiichi-Sankyo Co., Tokyo, Japan) every 12 h according to the schedule as described previously. The morphine dose was increased progressively from 8 to 45 mg/kg over a period of 5 days. The doses of morphine (mg/kg) injected in the morning and evening were the following: first day (8, 15), second day (20, 25), third day (30, 35), fourth day (40, 45), fifth day (45 in the morning only). Newly synthesized selective OX_1R antagonist **96** (10 mg/kg, dissolved in saline) was intraperitoneally (i.p.) injected 30 min before the first morphine injection of each day.

Morphine withdrawal signs

Morphine withdrawal signs were precipitated by injecting naloxone (3 mg/kg, s.c.) 2 h after the final injection of morphine. After the naloxone injection, mice were immediately placed on a circular platform (30 cm in diameter × 70 cm in height). Naloxone-precipitated morphine withdrawal signs, which are jumping, body shakes, ptosis, forepaw tremor, rearing, diarrhea, and body weight loss, were observed for 60 min, as described previously.[71] Diarrhea was evaluated by scoring as follows: Normal, normal stool; Slightly, softly stool; Severe, watery stool. Body weight was measured at 15, 30, 45, and 60 min after naloxone injection.

Statistical analysis

All statistical analyses were performed using Prism software (version 6.05, GraphPad Software). For body weight loss, the statistical significance of differences between groups was assessed by two-way ANOVA. For other withdrawal signs, the incidence of withdrawal signs was statistically analyzed by χ^2 test.

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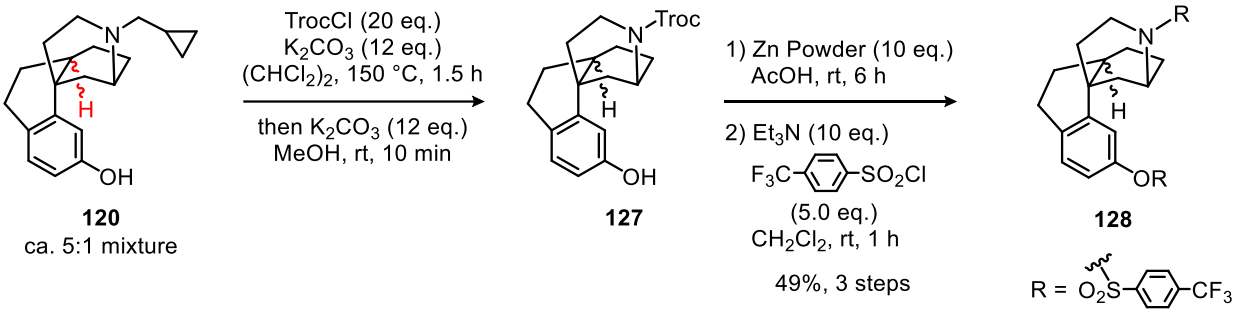
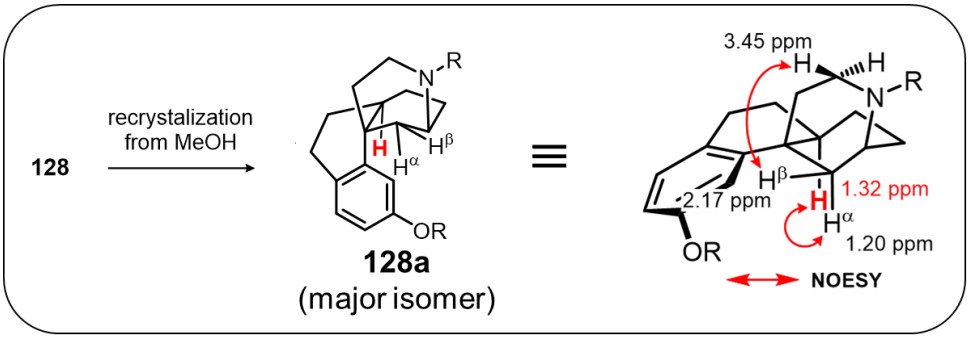
63. Synthesis of **128** was performed to determine the stereochemistry of the major diastereomer of the compound **120** as follows. The recrystallization of the approximately 5:1 diastereomixture of **128** (12.3 mg) from refluxing MeOH afforded only **128a** (5.0 mg) as a needle-like crystal and the stereochemistry of the **128a** was determined by the NOESY experiments. As a result, the stereochemistry of the major isomer of **128** should be the same as that of **128a**.





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List of publications

1. Nagase, H.; Yamamoto, N.; **Yata, M.**; Ohrui, S.; Okada, T.; Saitoh, T.; Kutsumura, N.; Nagumo, Y.; Irukayama-Tomobe, Y.; Ishikawa, Y.; Ogawa, Y.; Hirayama, S.; Kuroda, D.; Watanabe, Y.; Gouda, H.; Yanagisawa, M.

   "Design and Synthesis of Potent and Highly Selective Orexin 1 Receptor Antagonists with a Morphinan Skeleton and Their Pharmacologies"

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2. **Yata, M.;** Kutsumura, N.; Nagumo, Y.; Yamamoto, N.; Saitoh, T.; Ishikawa, Y.; Irukayama-Tomobe, Y.; Yanagisawa, M.; Nagase, H.

   "A novel rearrangement reaction of morphinan to arylmorphan skeletons and the pharmacologies of arylmorphan derivatives"

   Heterocycles **2019**, *99*, 134–144.

Supplementary list of publications

1. Yamamoto, N.; Ohrui, S.; Okada, T.; **Yata, M.**; Saitoh, T.; Kutsumura, N.; Nagumo, Y.; Irukayama-Tomobe, Y.; Ogawa, Y.; Ishikawa, Y.; Watanabe, Y.; Hayakawa, D.; Gouda, H.; Yanagisawa, M.; Nagase, H.

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