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Article

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

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KEYWORDS

Orexin, Opioid, OX_1R antagonist, Morphinan skeleton

ABSTRACT

Nalfurafine, a κ-selective opioid receptor agonist, unexpectedly showed a selective antagonist activity toward the orexin 1 receptor (OX_1R) (K_i = 250 nM). Modification of the 17-amino side chain of the opioid ligand to an arylsulfonyl group and the 6-furan acrylamide chain to 2-pyridyl acryl amide led to compound **71** with improvement of the antagonist activity (OX_1R: K_i = 1.36 nM, OX_2R: Not active) without any detectable affinity for the opioid receptor. The dihydrosulfate salt of **71**, freely soluble in water, attenuated the physical dependence of morphine. Furthermore, all of the active nalfurafine derivatives in this study had almost no activity for OX_2R, which led to high OX_1R selectivity. These results suggest that nalfurafine derivatives could be a useful series of lead compounds to develop highly selective OX_1R antagonists.

INTRODUCTION

Orexin (orexin-A and -B,[1] also known as hypocretin-1 and -2[2]) are a pair of lateral hypothalamic neuropeptides originally identified as the endogenous ligands for two previously orphan G protein-coupled receptors, orexin 1 receptor (OX_1R) and orexin 2 receptor (OX_2R). An essential role of the orexin system in regulation of sleep and wakefulness was initially demonstrated by the discoveries that OX_2R-deficient dogs[3a] and prepro-orexin knockout mice[3b] both exhibited symptoms highly similar to the sleep disorder narcolepsy/cataplexy. Whereas OX_1R/OX_2R double null mice exhibit a severe narcoleptic phenotype indistinguishable from that seen in prepro-orexin knockout mice, 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 an intact OX_2R-mediated signaling is sufficient to prevent the symptoms of narcolepsy/cataplexy.[4]

Many researchers have attempted to develop non-peptide orexin antagonists to evaluate the role of orexin receptors (OXRs), especially focused on sleep indications.[5] Many selective OX_1R antagonists (1-SORAs); **4** (SB-334867),[6] **5** (SB-408124),[7] **6** (SB-674042),[7] **7** (GSK-1059865),[8] and selective OX_2R antagonists (2-SORAs); **8** (TCS-OX2-29),[9] **9** (MK-3697)[10], as well as dual OX_1R/OX_2R antagonists (DORAs); suvorexant (**1**)[11], almorexant (**2**)[12], **3** (SB-649868)[13], have been reported (Figure 1).

Quite recently, Merck released suvorexant (**1**) (DORA) in Japan and the United States for treatment of insomnia.[11] However, no orexin agonist had been reported until recently. In 2015, we reported the design and synthesis of the first non-peptide OX_2R agonists; one of the agonists, compound **10**, showed potent and selective agonistic activity for OX_2R (OX_1R: EC_{50} = 2,750 nM; OX_2R: EC_{50} = 28 nM, E_{max} = 94%) (Figure 1).[14] Central injection of dihydrochloride of compound **10** (260 nmol) in mice increased wake time to a similar degree achieved with 3 nmol orexin-A.

Orexins have been reported to be also involved in regulation of a wide range of behaviors other than sleep/wake, e.g., hedonic feeding behavior and reward seeking.[15,16] Especially, OX_1R was reported to contribute to regulating reward-related behaviors. An increasing body of work shows that orexin neurons play a part in the behavioral presentation of addiction to morphine,[17a,18] cocaine,[17b,17c] amphetamine,[19] heroin,[20] nicotine,[21] ethanol,[22] and cannabinoids.[23] Generally, orexin seems to be involved in the modulation of highly motivated reward seeking, especially when the seeking is triggered by external cues. 1-SORAs, **4**[24] and **7**[8] were reported to attenuate

the expression of conditioned place preference induced by cocaine and amphetamine in rats. Orexin might also be involved in opioid addiction; for example, orexin knockout mice, as well as wild type mice treated with the 1-SORA, **4**, reduced morphine withdrawal.[25]

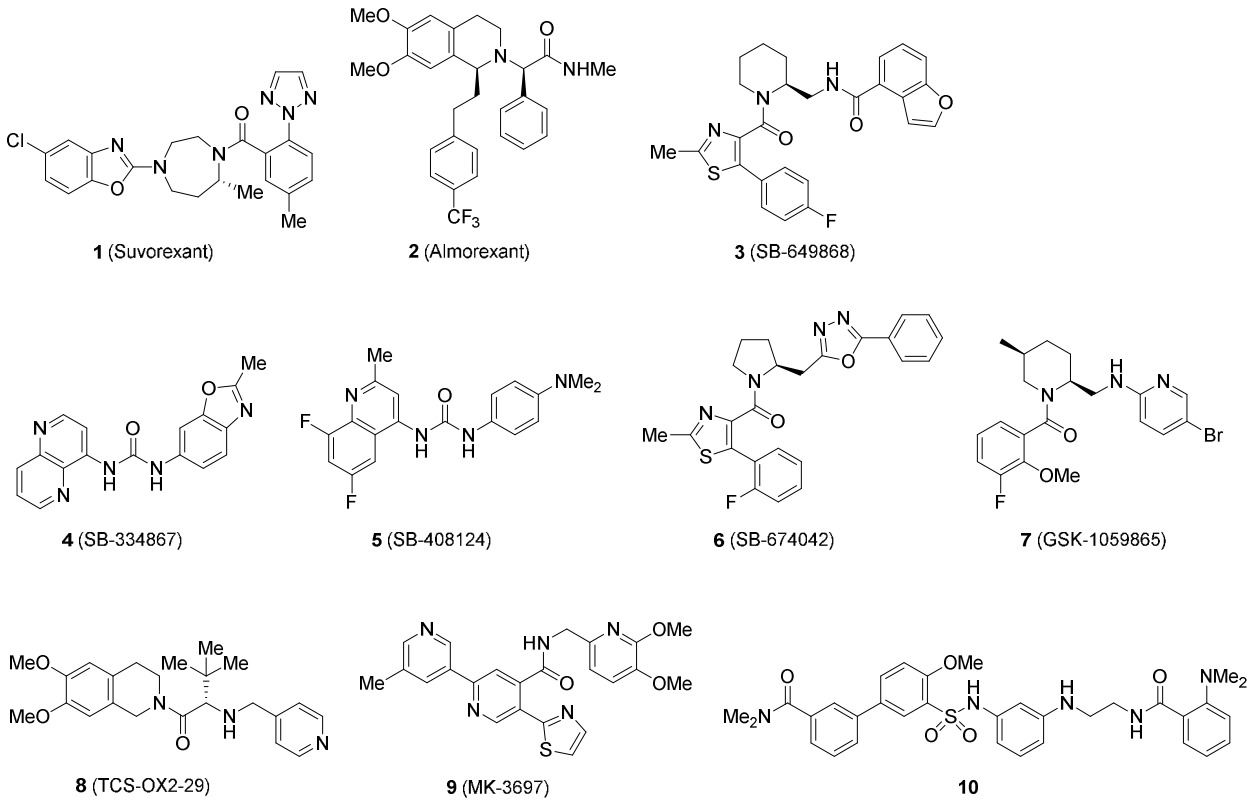


Figure 1. The structures of the dual orexin receptor antagonists **1**–**3**, selective OX_1R antagonists **4**–**7**, selective OX_2R antagonists **8**–**9**, and selective OX_2R agonist **10**.

We have been interested in the interaction of the OX_1R with opioid receptors on the basis of our long history in the opioid research field,[26] and also intrigued by the biological relevance for the coexpression of excitatory orexin and inhibitory dynorphin (**11**, endogenous κ opioid agonist) and the coexistence of their opposing effects within the same vesicle in the orexin neuron.[27] To obtain specific ligands for clarifying the potential role for their coexistence, we attempted to design and synthesize OX_1R antagonists derived from κ opioid receptor (KOR) ligands.

Quite recently, the heterodimerization of the OX_1R and KOR has been reported,[28] shedding further light on the potential function for the colocalization of the corresponding two peptides with opposite effects,[27,29] which were shown in not only the endogenous peptide, but also with exogenous alkaloids. For example, as we mentioned above, OX_1R antagonist **4** attenuated drug addiction[17b,21b,30] and most KOR agonists represented by **16** (U-50488H)[31] induced severe aversion (like the psychotomimetic effect) and dysphoria,[32] which was ample reason to eliminate the derivatives of **16** at the early stage of the clinical trials. Intriguingly, only nalfurafine (**12**) among all of the KOR agonists showed neither addiction nor drug aversion and was released as an antipruritic agent for kidney dialysis patients in Japan in 2009.[26a−e] Even now, many researchers have been interested in and are investigating why only nalfurafine (**12**) caused no aversion. We postulated that nalfurafine (**12**) might bind with the OX_1R-KOR dimer to prevent aversion, but **16** binds with pure KOR to afford an intrinsic aversive effect. Furthermore, we expected that nalfurafine (**12**) would also bind with OX_1R in addition to binding with KOR, if the nalfurafine could show affinity for the receptor heterodimer. Based on these considerations, we evaluated nalfurafine (**12**) with a calcium transient assay in CHO cells expressing human OX_1R or OX_2R, to examine the possible activity of nalfurafine for orexin receptors. As we expected, nalfurafine (**12**) showed antagonistic activity for OX_1R (OX_1R: K_i = 250 nM, OX_2R: Not active) (Figure 2).[33]

Interestingly, only nalfurafine (**12**) showed activity for the OX_1R, but no effect was noted with the μ opioid receptor (MOR) antagonist β-funaltrexamine (β-FNA),[34] the δ opioid receptor (DOR) selective agonist (6*R*,6a*S*,14a*R*)-17-methyl-5,6,7,14-tetrahydro-6a*H*-6,14a-(epiminoethano)naphtho[2,1-*b*]acridine-2,6a-diol (KNT-127),[35] the antagonist naltrindole (NTI),[36] and the KOR selective antagonist *nor*-binaltorphimine (nor-BNI).[37] Furthermore, the

Upjohn-type KOR agonist **16**[38] showed no activity for OX_1R. The structure of nalfurafine (**12**) contains a tyrosine moiety as the *N*-terminal structure of dynorphin (**11**), while **16** does not. The fact that only nalfurafine (**12**), with the partial structure of dynorphin (**11**), showed activity for OX_1R in our opioid chemical library, might be a clue for clarifying the role of the aforementioned coexistence of dynorphin and orexin.

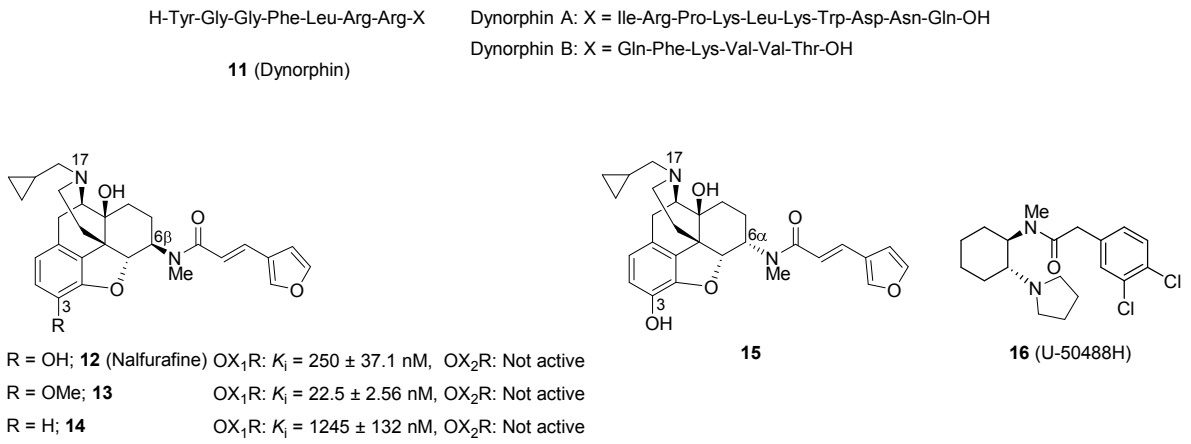


Figure 2. The structures of dynorphin (**11**), nalfurafine (**12**), nalfurafine derivatives **13**–**15**, and **16**.

The above described antagonists in Figure 1 have rather simple flexible structures which consist of aromatic or alicyclic rings connected to each other with amide or urea bonds. In contrast, nalfurafine (**12**) has a characteristic rigid morphinan skeleton with a tyrosine moiety which is a partial structure of dynorphin (**11**) (Figure 2). So, we expected that the antagonistic activity and selectivity of nalfurafine for OX_1R could be easily improved by using our modification techniques developed over the long course of our opioid research.

To the best of our knowledge, no OXR ligand with a morphinan skeleton has been reported. First results of testing nalfurafine derivatives for OX_1R antagonism showed that the 6-α-amide isomer **15** of nalfurafine had almost no activity for OXRs.[39] Therefore, we focused our modification on

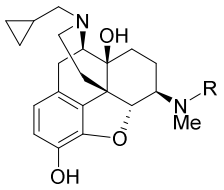
the 6-β-amide isomers. Herein, we report the results of the modification of nalfurafine (**12**) and the pharmacological effects of the resulting selective and potent antagonists of OX_1R.

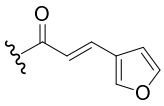
RESULTS AND DISCUSSIONS

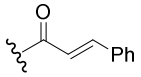
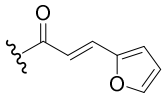
We started with the methylation of 3-OH in nalfurafine (**12**) to afford 3-methyl ether **13** which showed 11 times more potent antagonistic activity for OX_1R than nalfurafine (Figure 2). We also synthesized 3-dehydroxynalfurafine **14**[40] which showed very weak activity for OXRs. These facts led us to use the 3-methyl ether as a lead compound for succeeding modifications of the nalfurafine derivatives.

Next the 3-furylacryl group of the 6-amide side chain in nalfurafine methyl ether **13**[26b,41] was converted to benzyl, phenylacryl and 2-furylacryl amide groups. These derivatives **17**–**19** gave no improved activities (Table 1). Then we decided to hold the 6-amide side chain on the 3-furylacryloyl group in the following modification.

Table 1. Assay results of the 6-substituted nalfurafine derivatives for orexin receptor antagonism



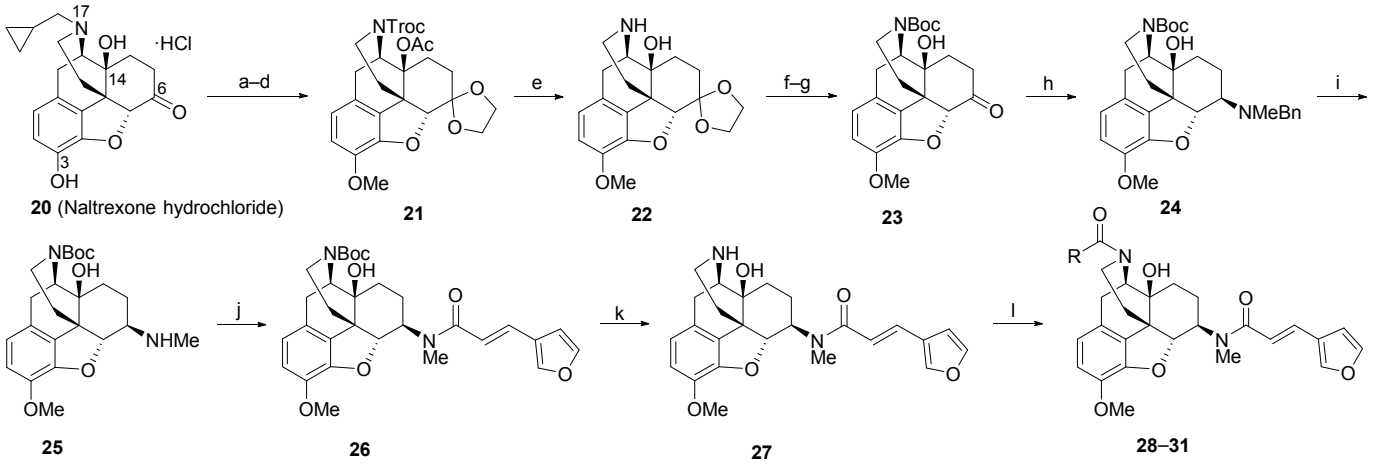
		K_i (nM)	
Compound	R	OX_1R	OX_2R
5[a]	–	18.9 ± 0.688	2070 ± 482
nalfurafine (**12**)[a]		250 ± 37.1	–[b]
17[a]		–[b]	–[b]

18[a]		389 ± 88.8	–[b]
19[a]		751 ± 178	–[b]

K_i values represented the mean ± SEM. These values were calculated using IC_{50} values of nalfurafine derivatives at least three independent calcium assays performed in triplicate (Cheng-Prusoff equation). [a]Its HCl salt was assayed. [b]K_i value was not calculated, IC_{50} value was over than 10,000 nM (cut off value) or was not obtain from concentration-response curve.

We then replaced the 17-cyclopropylmethyl (CPM) group in nalfurafine methyl ether **13** by various acyl substituents to improve the activity for OX_1R (Scheme 1). The phenolic hydroxyl group in naltrexone hydrochloride (**20**) was methylated and the 6-ketone group was protected as 1,3-dioxolane, followed by acetylation of the 14-OH under refluxing in Ac_2O. The CPM group of the resulting acetate was exchanged for a Troc group at 140 °C with an excess amount of TrocCl to afford carbamate **21**. The carbamate and the acetate group in **21** were hydrolyzed with aqueous KOH at 110 °C. After removing the 1,3-dioxolane group in amine **22**, the secondary amine was protected with Boc to give ketone **23** in good yield. The imine formation of **23** with *N*-benzylmethylamine, followed by reduction with $NaBH_3CN$ afforded β-amine **24**. Hydrogenation of **24** and amidation of the resulting amine with (*E*)-3-(furan-3-yl)acryloyl chloride afforded 17-Boc nalfurafine derivative **26**.[42] Deprotection of the Boc group in compound **26** gave key intermediate **27**, which was converted to 17-amide nalfurafine derivatives **28**–**31**. The antagonistic activities for OXRs of the obtained 17-Boc and amide derivatives were estimated in the Ca^{2+} assays.

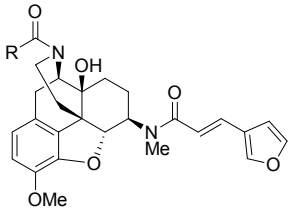
Scheme 1. Synthesis of 17-carbonyloxy compounds **28**–**31** from naltrexone hydrochloride (**20**).

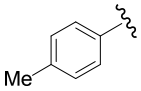
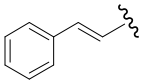


Reagents and conditions: a) MeI, K_2CO_3, DMF, rt; b) ethylene glycol, *p*-TsOH·H_2O, toluene, reflux; c) Ac_2O, reflux; d) TrocCl, K_2CO_3, 1,1,2,2-tetrachloroethane, 140 °C, 82% (4 steps); e) KOH aq., DMSO, 110 °C, 98%; f) HCl aq., 80 °C; g) $(Boc)_2O$, $(i\text{-Pr})_2NEt$, CH_2Cl_2, rt, 91%; h) BnNHMe, $PhCO_2H$, *p*-TsOH·H_2O, PhH, reflux; evap.; $NaBH_3CN$, MS4A, EtOH, 0 °C to rt, 84%; i) H_2, Pd/C, MeOH, rt, quant; j) (*E*)-3-(furan-3-yl)acryloyl chloride, Et_3N, CH_2Cl_2, rt, 79%; k) HCl–MeOH, rt, 82%; l) Ac_2O, pyridine, rt, 97% for **28**; cyclopropanecarbonyl chloride, pyridine, rt, 82% for **29**; *p*-toluoyl chloride, Et_3N, CH_2Cl_2, rt, 85% for **30**; cinnamoyl chloride, Et_3N, CH_2Cl_2, rt, 77% for **31**.

Unexpectedly, the 17-Boc nalfurafine derivative **26** showed the strongest antagonist activity (OX_1R: K_i = 4.15 nM) among the resulting amide derivatives shown in Table 2. However, the OX_1R selectivity over OX_2R was not as high as those of the acetamide and cyclopropylamide derivatives (**28** and **29**) (Table 2).

Table 2. Assay results of the 17-Boc and amide derivatives for orexin receptor antagonism



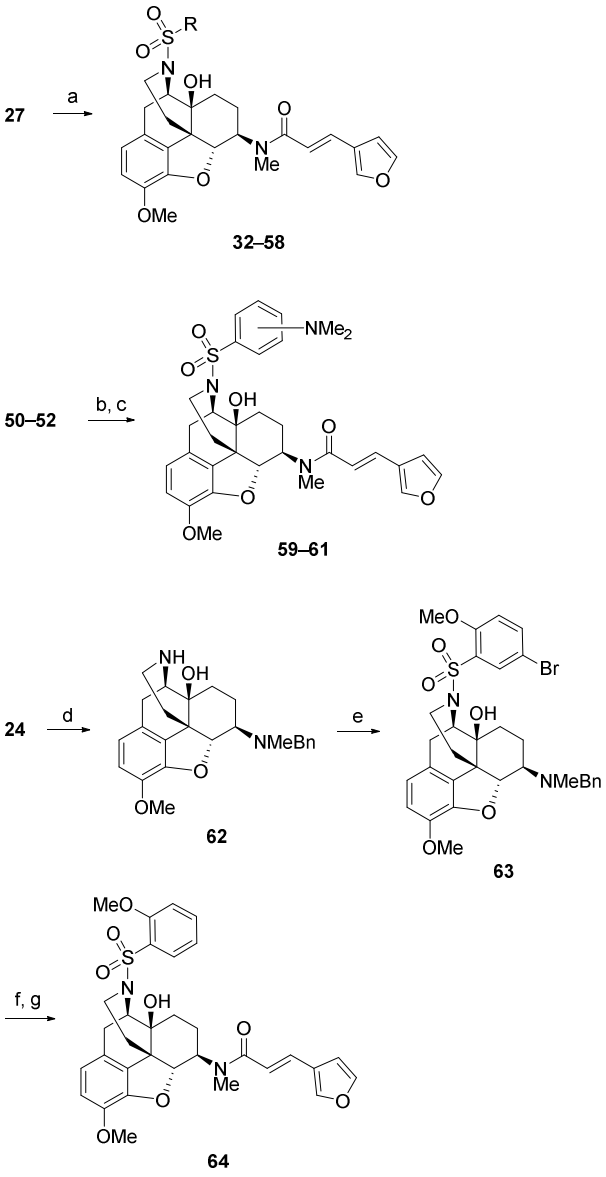
Compound	R	K_i (nM) OX_1R	K_i (nM) OX_2R
26		4.15 ± 0.235	–[a]
28		541 ± 59.9	–[a]
29		12.0 ± 0.715	–[a]
30		14.0 ± 1.98	725 ± 41.5
31		14.0 ± 2.20	–[a]

K_i values represented the mean ± SEM. These values were calculated using IC_{50} values of nalfurafine derivatives at least three independent calcium assays performed in triplicate (Cheng-Prusoff equation). [a]K_i value was not calculated, IC_{50} value was over than 10,000 nM (cut off value) or was not obtain from concentration-response curve.

The key functional group in the aforementioned first selective OX_2R agonists reported in 2015 were sulfonamides,[14a] which led us to synthesize 17-sulfonamide nalfurafine derivatives. The synthetic route for the 17-sulfonamide derivatives are shown in Scheme 2. The syntheses of the alkyl- and arylsulfoamide derivatives **32**–**58** were attained by sulfoamidation of the amine **27**. Dimethylaminobenzenesulfonamide derivatives **59**–**61** were synthesized from the corresponding nitrobenzenesulfonamide derivatives **50**–**52** by reduction of the nitro group and reductive amination of the resulting amine. Deprotection of the Boc group in **24** and sulfonamidation with

5-bromo-2-methoxybenzensulfonyl chloride afforded sulfonamide **63**. The benzyl group and bromine atom were removed by hydrogenation, followed by amidation with (*E*)-3-(furan-3-yl)acyloyl chloride to give the *o*-MeO derivative **64** in good yield.

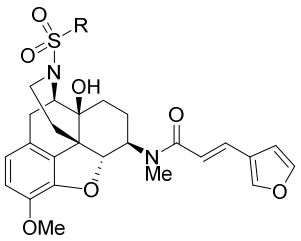
Scheme 2. Synthesis of the 17-sulfonamide derivatives

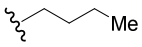
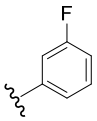
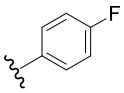
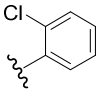


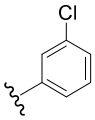
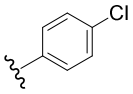
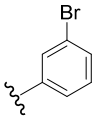
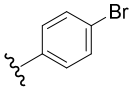
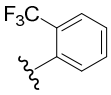
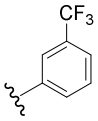
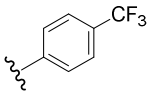
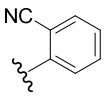
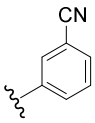
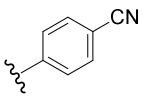
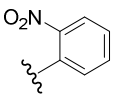
Reagents and Conditions: a) RSO_2Cl, Et_3N, CH_2Cl_2, rt, 66–99%; b) $SnCl_2$, HCl, CH_2Cl_2, 40 °C; c) paraformaldehyde, $NaBH_3CN$, AcOH, 40 °C, 73–90% (2 steps); d) HCl–MeOH, rt, 99%;

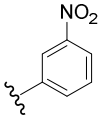
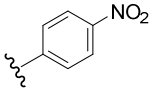
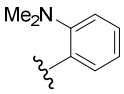
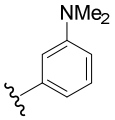
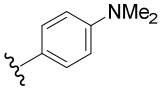
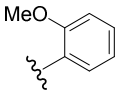
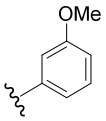
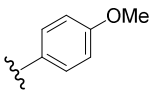
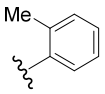
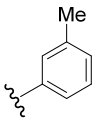
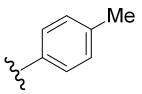
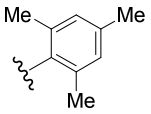
e) 5-bromo-2-methoxybenzensulfonyl chloride, Et_3N, CH_2Cl_2, rt, 84%; f) H_2, Pd/C, MeOH, rt; g) (*E*)-3-(furan-3-yl)acyloyl chloride, Et_3N, CH_2Cl_2, rt, 77% (2 steps).

Table 3. Assay results of the 17-sulfonamide derivatives for orexin receptor antagonism



		K_i (nM)	
Compound	R	OX_1R	OX_2R
32		12.1 ± 1.14	–[b]
33		5.94 ± 0.237	–[b]
34		8.14 ± 0.606	–[b]
35		2.07 ± 0.222	–[b]
36		7.60 ± 0.570	–[b]
37		4.05 ± 0.471	–[b]
38		1.93 ± 0.138	–[b]

39		3.47 ± 0.274	–[b]
40		5.13 ±1.02	–[b]
41		2.10 ± 0.184	–[b]
42		2.27 ± 0.204	–[b]
43		6.21 ± 0.655	–[b]
44		2.05 ± 0.209	–[b]
45		6.19 ± 0.934	–[b]
46		12.6 ± 0.790	–[b]
47		1.96 ± 0.359	–[b]
48		7.30 ± 0.748	–[b]
49		13.9 ± 0.451	–[b]
50		1.81 ± 0.142	–[b]

51		5.05 ± 0.343	–[b]
52		12.5 ± 1.26	–[b]
59[a]		1.92 ± 0.190	–[b]
60[a]		7.25 ± 0.557	–[b]
61[a]		12.9 ± 1.26	–[b]
64		6.37 ±0.921	–[b]
53		2.44 ± 0.388	–[b]
54		8.99 ± 1.22	–[b]
55		1.70 ± 0.194	–[b]
56		2.98 ± 0.364	–[b]
57		5.85 ± 0.794	–[b]
58		4.16 ± 0.696	–[b]

K_i values represented the mean ± SEM. These values were calculated using IC_{50} values of nalfurafine derivatives at least three independent calcium assays performed in triplicate (Cheng-Prusoff equation). [a]Its HCl salt was assayed. [b]K_i value was not calculated, IC_{50} value was over than 10,000 nM (cut off value) or was not obtain from concentration-response curve.

The activities of the sulfonamides are shown in Table 3. The activities of the two alkyl sulfonamide derivatives **32** and **33** were lower than that of the 17-Boc derivative **26**. Almost all the substituted sulfonamide derivatives showed high activities in the single digit nM range and high selectivities for OX_1R, with only minor differences among the respective *o*-, *m*-, *p*-substitutions. We observed only small differences in activities and selectivities between the substituted derivatives, independent of the electron donating (Me, NMe_2, except for OMe) or electron withdrawing (CF_3, CN, NO_2) character of the substitutents.

The observed tendency for the highest potency for the *o*-substituted derivatives suggests that the *o*-substituent group might induce a rotation around the Ar–SO_2NR_2 single bond by steric hindrance with the *o*-substituents or by dipole-dipole interaction between the F group and the sulfonamide group forcing the phenyl ring into an adequate fitting position at the receptor site, thus increasing the activity.

We carried out conformational analyses of **50** (*o*-nitrobenzenesulfonamide) and **52** (*p*-nitrobenzenesulfonamide) to compare their most stable conformations. As shown in Figure 3, we found that the spatial dispositions of *o*-nitro- and *p*-nitrobenzenesulfonamides were quite different between the most stable conformers of **50** and **52**. Further, from the superimpositions of lower energy conformers of **50** and **52**, we found that the *o*-nitrobenzenesulfonamide of **50** could be widely spread out, but the *p*-nitrobenzenesulfonamide of **52** was spatially restricted. These results again suggested the *o*-substituent group might facilitate the rotation around Ar-SO_2NR_2.

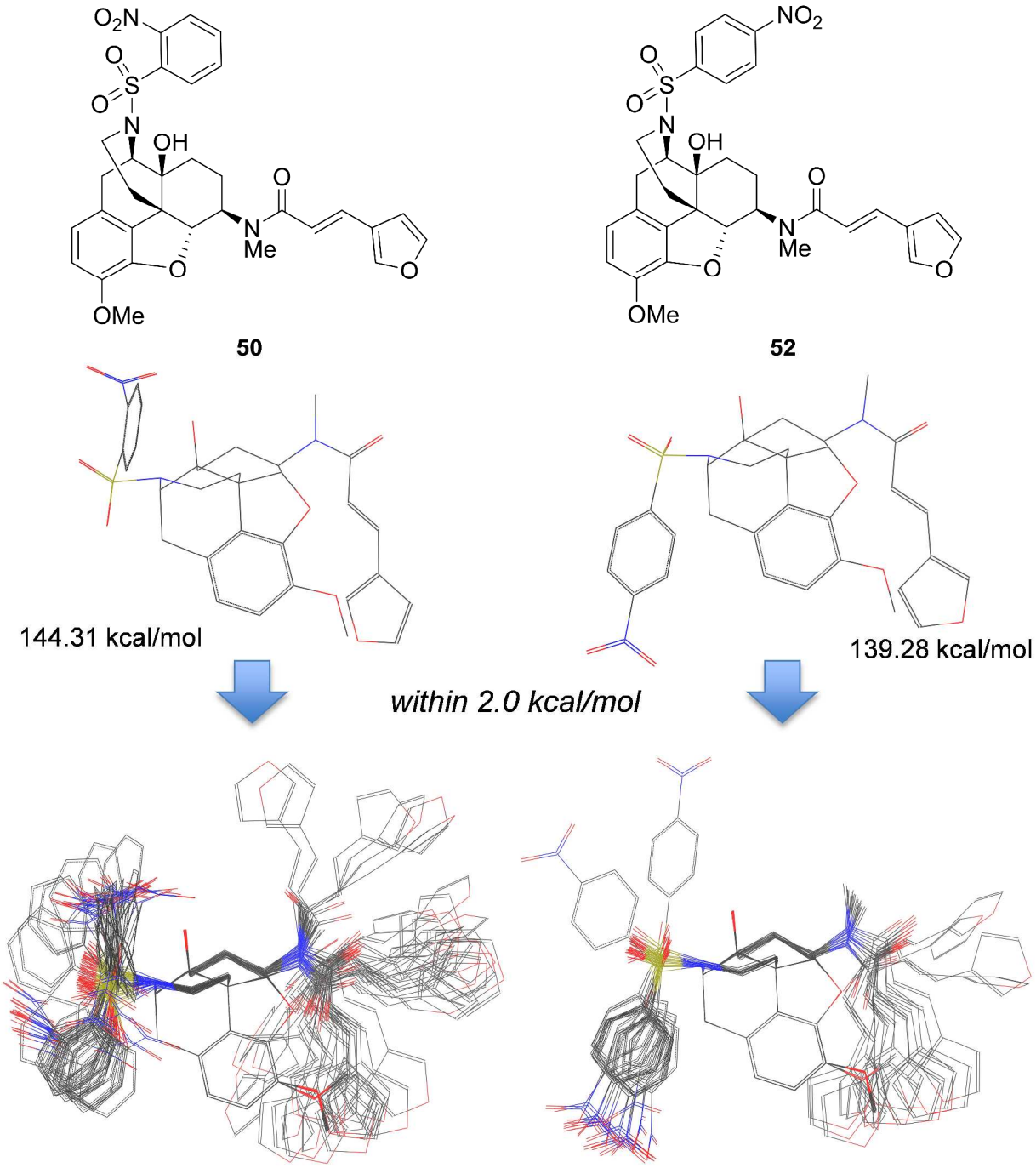
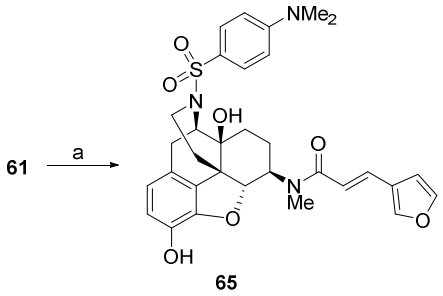


Figure 3. The most stable conformations and the superimpositions of the low-energy conformers of **50** and **52**.

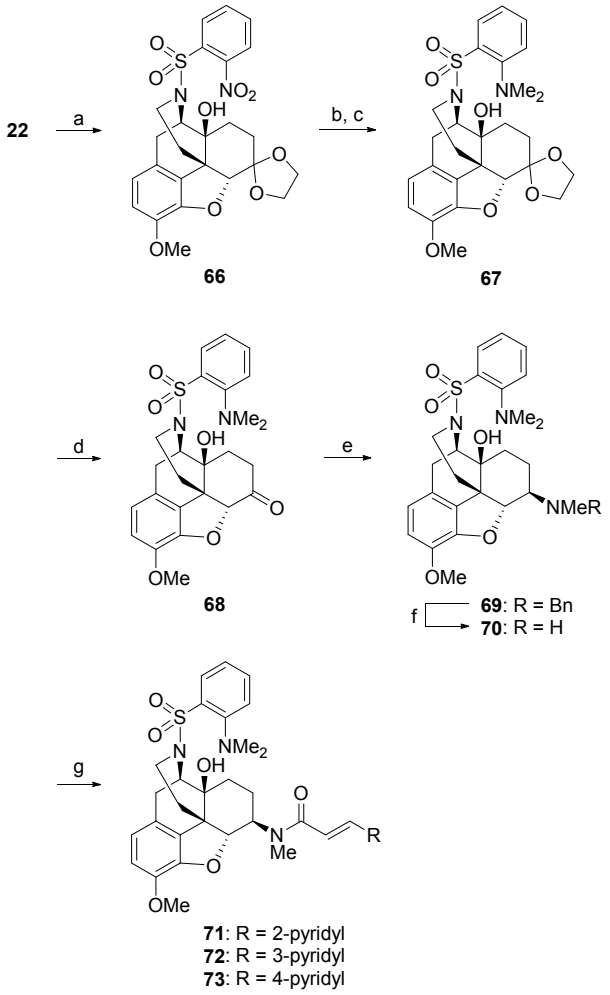
The activities of *p*-substituted sulfonamide derivatives with electron donating groups (including halogen) were slightly higher than those of the electron deficient group (the $NHMe_2^+$ group resulted from protonation under physiological condition and would become an electron withdrawing group), quite a different observation from *o*-substituted derivatives. As the *p*-substituted derivatives would provide neither steric nor dipole-dipole interaction to the sulfonamide group, the activity may directly be affected by the electron effect of the substituent on the aromatic ring.

Scheme 3. Demethylation of the 3-OMe group in compound **61**



Reagents and Conditions: a) BBr_3, CH_2Cl_2, –78 °C to rt, 51%.

Scheme 4. Synthesis of the compounds with pyridyl moiety



Reagents and Conditions: a) *o*-nitrobenzenesulfonyl chloride, Et_3N, CH_2Cl_2, rt, 99%; b) Fe, NH_4Cl, EtOH, H_2O, 90 °C; c) $(CH_2O)_n$, $NaBH_3CN$, AcOH, 40 °C, 97% (2 steps); d) HCl aq., THF, 90 °C, 90%; e) BnNHMe, $PhCO_2H$, PhH, reflux; evap.; $NaBH_3CN$, MeOH, THF, 0 °C, 80%; f) H_2, Pd/C, MeOH, rt, 96%; g) $RCH{=}CHCO_2H$, HATU, $(i\text{-}Pr)_2NEt$, DMF, rt, 95–97%.

Table 4. Assay results of the **65**, **71**–**73** for orexin receptor antagonism

	K_i (nM)	
Compound	OX_1R	OX_2R
65	320 ± 72.1	–[a]

71	1.36 ± 0.174	–[a]
72	42.3 ± 2.25	–[a]
73	–[a]	–[a]

K_i values represented the mean ± SEM. These values were calculated using IC_{50} values of nalfurafine derivatives at least three independent calcium assays performed in triplicate (Cheng-Prusoff equation). [a]K_i value was not calculated, IC_{50} value was over than 10,000 nM (cut off value) or was not obtain from concentration-response curve.

Table 5. Assay results for opioid receptors

Compound	K_i (nM)		
	μ ([^{3}H]DAMGO)	δ ([^{3}H]DPDPE)	κ ([^{3}H]U-69593)
5	>1,000	>1,000	>1,000
nalfurafine (**12**)[a]	5.99 (3.4–10.6)	693 (223–2154)	0.238 (0.147–0.385)
26	>1,000	>1,000	184 (130–261)
29	>1,000	>1,000	>1,000
31	>1,000	>1,000	>1,000
34	>1,000	>1,000	>1,000
61	>1,000	>1,000	>1,000
65[b]	971	>1,000	200

	(654–1441)		(35–295)
71[c]	>1,000	>1,000	>1,000

K_i values with 95% confidential intervals were obtained from radioligand-based competitive receptor binding assay. [a]Its HCl salt was assayed. [b]Its $MeSO_3H$ salt was assayed. [c]Its $2H_2SO_4$ salt was assayed.

The activity of 2,4,6-trimethylbenzenesulfonamide derivative **58** was almost equivalent with that of *o*-Me-substituted derivative **55**. These results also support the idea that steric hindrance on the aromatic ring could induce a favorable rotation around the SO_2–Ar bond.

The 6-NH carboxyamide derivatives of the *o*-dimethylaminosulfonamide-6-pyridylacrylamide derivatives showed markedly lower activity (about 100 times lower) for OXRs than the corresponding 6-NMe amide derivative.

Intriguingly, the above obtained 17-carboxyamide and sulfonamide derivatives with a 3-methoxy group showed extremely lower affinity for opioid receptors (MOR, DOR, and KOR: K_i = >1,000 nM) compared with that of nalfurafine (MOR: K_i = 5.99 nM, DOR: K_i = 693 nM, KOR: K_i = 0.238 nM) (Table 5). Even the *p*-dimethylaminobenzenesulfonamide derivative with a 3-hydroxy group **65** showed very low affinity for the opioid receptor (MOR: K_i = 971 nM, DOR: K_i = >1,000 nM, KOR: K_i = 200 nM). The only 17-Boc derivative **26** had a rather higher affinity for the KOR (K_i = 184 nM) despite containing the 3-methoxy group. These data from the binding assays suggest that the above obtained 3-methoxy-sulfonamide derivatives could remove the serious side effects derived from the opioid receptors (addiction, constipation, respiratory depression from MOR, and catalepsy from DOR and especially, sedation and aversion from KOR) although the structures of these OX_1R antagonists were derived from the potent KOR agonist, nalfurafine (**12**).[26]

The opioid ligands bind with opioid receptors with three main types of pharmacophore bonds: ionic attraction, π–π interaction, and hydrogen bonding, termed the message site.[26] The above obtained potent OX_1R antagonists were hardly bound with the opioid receptors because of the absence of the basic nitrogen and the phenolic hydroxy group.[26a,26b,43] The ion formed by the protonation on the basic 17-nitrogen and the acidic hydrogen derived from the 3-phenolic hydroxyl group seemed to disrupt the fitting to the orexin receptor. This information could be an important clue for designing OX_1R ligands with a morphinan skeleton without affinity for opioid receptors. Quite recently, Perrey *et al*. reported improved antagonists for OX_1R and the most potent and selective compound in their paper showed promising K_e values for OX_1R (K_e = 8.50 ± 1.0 nM) and for OX_2R (K_e = >10,000 nM).[44] On the other hand, one of our antagonists, compound **50** showed almost equivalent activity and selectivity for OX_1R (OX_1R: K_e = 3.69 ± 0.0376 nM, OX_2R: Not active).[45]

Although the above antagonists were sufficiently potent and selective for OX_1R, even the salts were not soluble in water or saline. Therefore, we tried to introduce an additional basic moiety to the antagonists to obtain di-protonated salts. The obtained di-hydrosulfate of 17-*o*-dimethylaminosulfonamide-6-(2-pyridyl)-acrylamide derivative **71** could be easily dissolved in water (solubility: 10 mg in 50 μL saline).

Table 6. Effect of compound **71** on naloxone-precipitated withdrawal signs in morphine-dependent mice

	Positive animals / Total animals	
Withdrawal signals	Saline	Compound **71**
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

The morphine dose was increased progressively from 8 to 45 mg/kg, subcutaneously (*s.c.*) over a period of 5 days. Saline or compound **71** was intraperitoneally injected 30 min before naloxone treatment. Withdrawal signs were induced by injecting naloxone (3 mg/kg, s.c.) 2 hr after the final morphine treatment and then were observed for 60 min. ** $p<0.01$ vs. Saline.

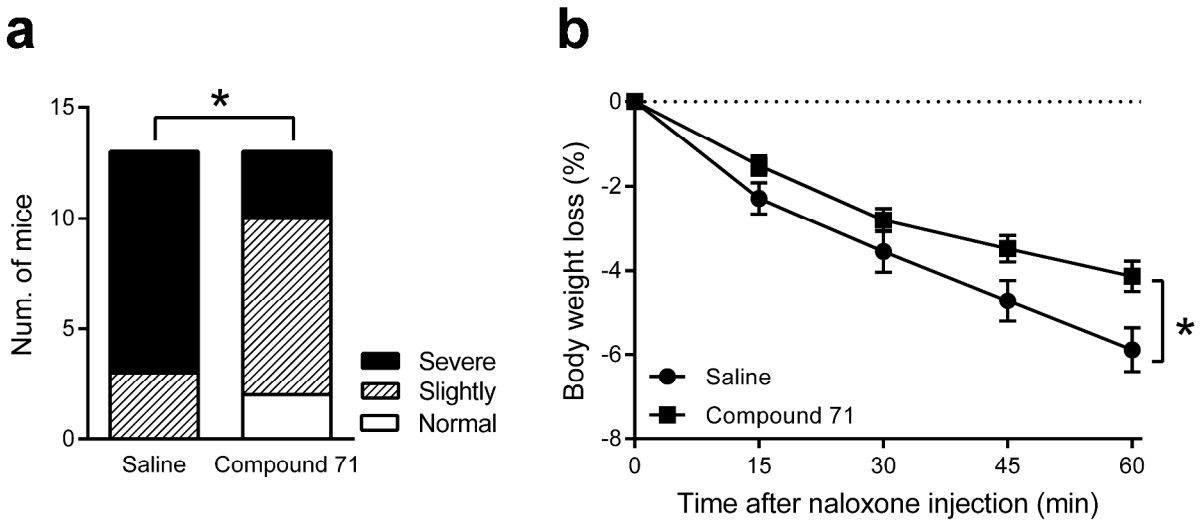


Figure 4. Morphine withdrawal is suppressed by compound **71**. Naloxone-precipitated diarrhea (a) and body weight loss (b) were suppressed by *i.p.* pretreatment with compound **71** (10 mg/kg) at 30 min before naloxone challenge injection. Compound **71** was dissolved in saline. Each point represents the mean body weight loss of 13 mice with SEM. *$p<0.05$: saline vs compound **71**.

We evaluated the effect of compound **71** on morphine withdrawal. As shown Table 6 and Figure 4, naloxone-precipitated withdrawal in mice with chronic morphine injection induced several classic behavioral signs of morphine withdrawal. Of these several signs, naloxone-precipitated body weight loss, diarrhea, and jumping behavior were significantly suppressed by *i.p.* pretreatment with compound **71** before naloxone challenge injection, indicating that the OX_1R antagonist attenuated the expression of naloxone-precipitated morphine withdrawal. Therefore, the newly synthesized selective OX_1R antagonist would be a useful tool for understanding the physiological significance of the orexinergic system, and may be useful as a medicine to treat drug dependence.

Finally, we found that all antagonists derived from nalfurafine showed high selectivity for OX_1R (as OX_2R/OX_1R selectivity from IC_{50} value; at least 88.4-fold) as shown in Tables 1–3, although many extremely low selective derivatives for OX_1R (some derivatives showed rather selective for OX_2R) were observed in the course of structure-activity relationship study of the other known antagonists shown in Scheme 1. This result indicates that nalfurafine derivatives with the morphinan skeleton would be specific lead compounds for developing selective OX_1R antagonists, which would provide important information for many researchers in the field of orexin research.

Recently, two X-ray crystal structures of the human OX_1R bound to suvorexant (**1**) (PDB: 4ZJ8) and **6** (PDB: 4ZJC) were reported.[46] Using these X-ray structures, the binding mode of **71** with OX_1R was investigated by molecular-docking calculations. The resulting binding mode of **71** is shown in Figure 5. The morphinan skeleton of **71** was suggested to be located in the middle of the ligand-binding site of OX_1R (Figure 5A). The 17-*o*-dimethylaminobenzene group of **71** 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 (Figure 5B). On the other hand, the 2-pyridyl group of **71** was oriented in the opposite direction, and made hydrophobic interactions with F219 (TM5), F220 (TM5), I314 (TM6), and I319 (TM6). Compound **71** 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 (Figure 5B). This configuration might indicate the importance of the nitrogen atom on the pyridyl group for interactions with OX_1R.

Figure 6 compares the binding modes of **71**, suvorexant (**1**) (DORA), and **6** (1-SORA representing a 117-fold selectivity[7]). The position of the morphinan skeleton of **71** corresponds to the 7-membered ring of **1** and the 2-pyrrolidyl methylene part of **6**, which were proposed to inhibit inward movements of TM5 and TM6 relative to the rest of the TM bundle (Figures 6B and C). The 17-*o*-dimethylaminobenzene group of **71** corresponds to the 5-chloro-1,3-benzoxazol-2-yl group of **1** and the 5-phenyl-1,3,4-oxadiazol-2-yl group of **6**. Recently, the selective OX_1R antagonist activity of **6** was examined from the structural point of view.[46] 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 **6** 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,[46] suggesting that the volume of the pocket of OX_1R was a much better fit to **6** than that of OX_2R. When we also placed **71** bound to OX_1R into the pocket of OX_2R, a clash between the 17-*o*-dimethylaminobenzene group of **71** and T111 (TM2) of OX_2R was observed. This observation might be a source of the selective

OX_1R antagonist activity of **71** and may well explain our experimental results that the 17-sulfonamide motif is a key pharmacophore to afford selective OX_1R antagonist activity.

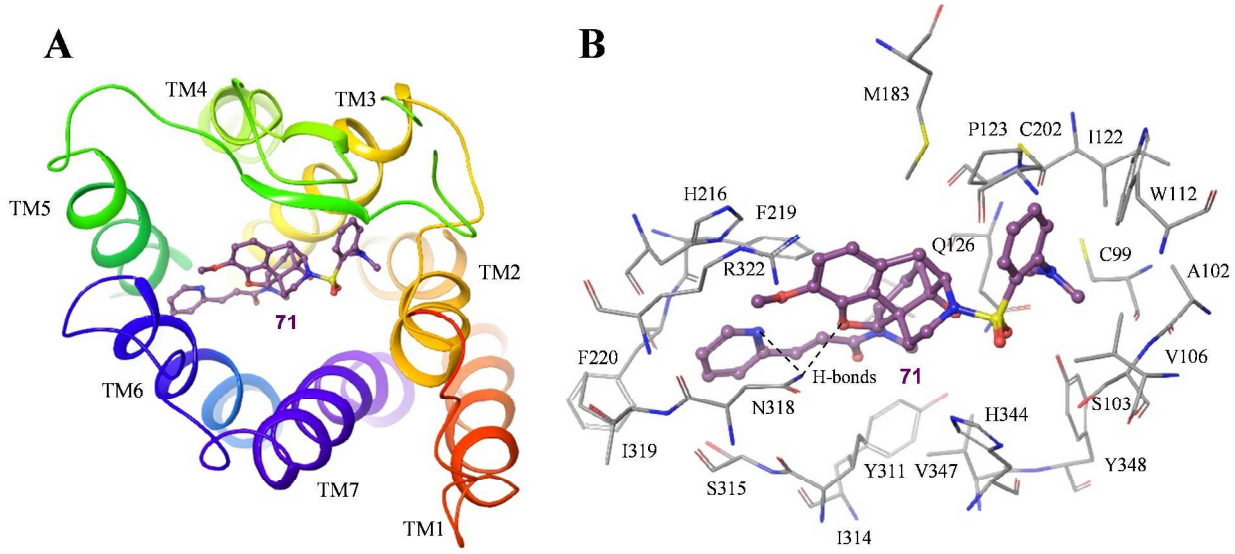


Figure 5. The binding mode of **71** with the OX_1R determined by our docking procedure. Hydrogen-bonding interactions are indicated by dashed lines.

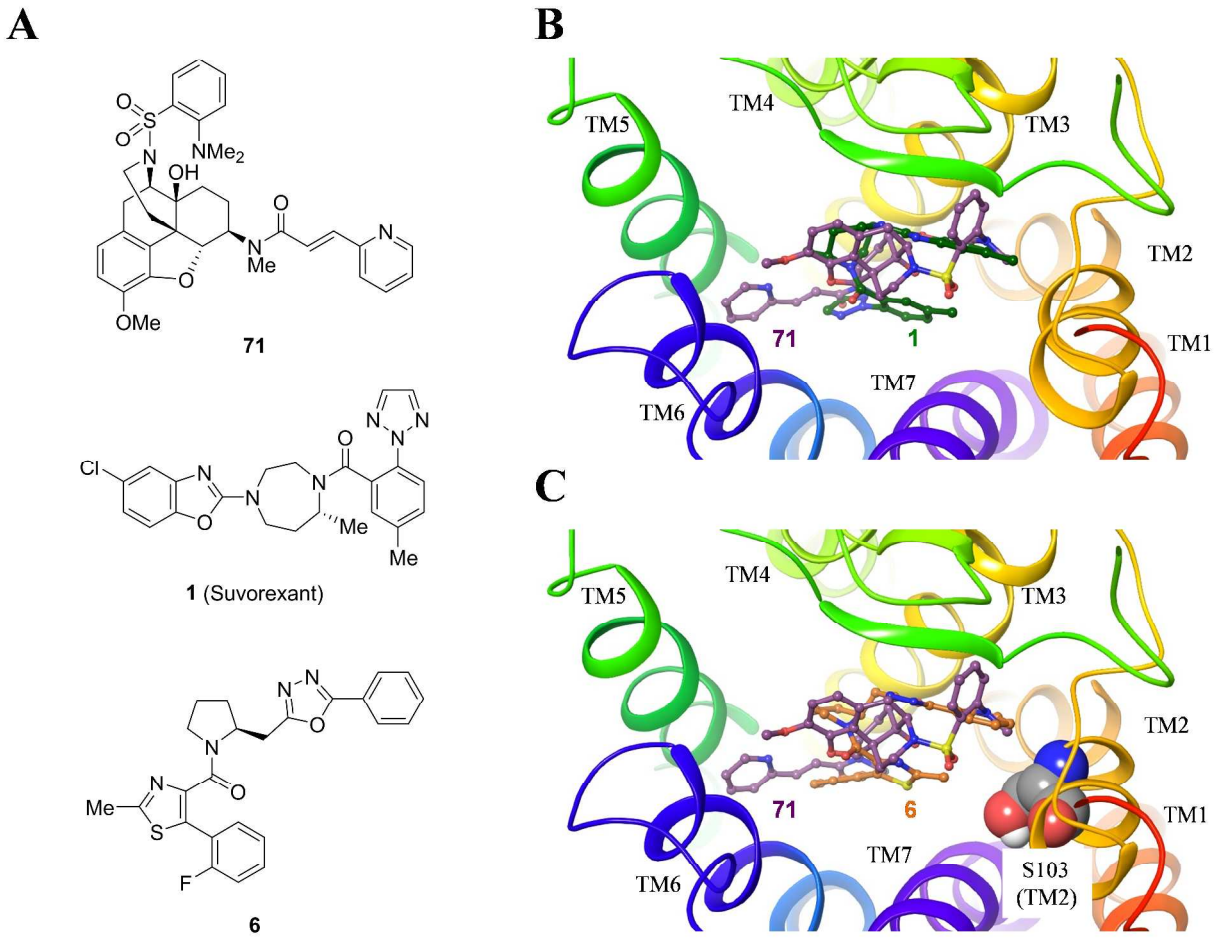


Figure 6. (A) Chemical structures of **71**, suvorexant (**1**), and **6**. (B) Superimposition of **71** (purple) and **1** (green) in the ligand-binding site of OX_1R. (C) Superimposition of **71** (purple) and **6** (orange) in the ligand-binding site of OX_1R.

CONCLUSIONS

The antagonistic activity of nalfurafine (**12**) for OX_1R was discovered and improved from K_i value: 250 to 1.36 nM by modification of the 17-nitrogen substituent and the 3-hydroxy group, and the selectivities of the obtained derivatives were not active for OX_2R. The *o*-substituted benzenesulfonamide derivatives showed tendency for more potent antagonistic activities than *m*- and *p*-substituted benzenesulfonamide derivatives. The most stable conformations of **50** and **52**

and the superimpositions of the low-energy conformers of **50** and **52** were performed. Interestingly, thus obtained 17-sulfonamide derivatives shown in Table 5 showed almost no affinity to opioid receptors which means that the OX_1R antagonists would be expected to have few side effects derived from opioid receptors. One of the most potent OX_1R antagonists attenuated the physical dependence of morphine via *i.p.* injection and would be expected to clarify the pharmacological activities of OX_1R. Furthermore, the antagonists could be applied to the treatment of opioid addiction.

Finally, the nalfurafine derivatives with the morphinan skeleton could serve as specific lead compounds to develop OX_1R selective antagonists, which would provide important information for many researchers in the field of orexin research.

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. ^1H 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 ^1H 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. The purity (≥95%) of the assayed compounds was determined by analytical HPLC or elemental analysis. Analytical HPLC were performed on a Shimadzu LC-2040C 3D instrument, equipped with Xbridge-C18 3.5 μm, 4.6 x 150 mm column, with PDA detection at 254 nm, at column

temperature of 40 °C. Elemental analyses were performed with a J-SCIENCE LAB micro corder 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 (21)

To a suspension of naltrexone hydrochloride (**20**) (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 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 mL × 2, 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 aqueous $NaHCO_3$ solution (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 (200mL) was added. The mixture was extracted with $CHCl_3$ (200 mL, 100 mL × 2). 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 : *n*-hexane = 3 : 1 to 1 : 3) to afford compound **21** (24.3 g, 82% in 4 steps) as a yellow amorphous.

IR (film) 1744, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 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 = 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 (22)

To a suspension of compound **21** (10 g, 17.8 mmol) in DMSO (100 mL) was added 12 M aqueous KOH 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 aqueous NH_4Cl solution (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 **22** (6.0 g, 98%) as a colorless solid.

The spectral data of compound **22** were as reported[47].

***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 (23)**

Compound **23** was synthesized by the modified procedure of the reported method.[42] The spectral data were also as reported.

A mixture of compound **22** (5.59 g, 16.2 mmol) in 1 M HCl (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 mL, 30 mL×2). 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 aqueous $NaHCO_3$ solution (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 *n*-hexane) to afford compound **23** (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 (24)

Compound **24** was synthesized by the modified procedure of the reported method.[42] The spectral data were also as reported.

To a solution of compound **23** (875 mg, 2.18 mmol) in benzene (22 mL) were added benzylmethylamine (580 μL, 4.49 mmol), $PhCO_2H$ (426 mg, 3.49 mmol), and *p*-$TsOH \cdot H_2O$ (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 aqueous $NaHCO_3$ solution (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 **24** (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 (25)

Compound **25** was synthesized by the modified procedure of the reported method.[42]

To a solution of compound **24** (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 **25** (240 mg, quant) as a colorless amorphous.

IR (film) 3372, 1681 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ = 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* = 6.8Hz, 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 = 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,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (26)**

Compound **26** was synthesized by the modified procedureof the reported method.[42] The spectral data were also as reported.

To a stirred solution of compound **25** (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 aqueous $NaHCO_3$ solution (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 *n*-hexane) to afford compound **26** (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 (27)

A mixture of compound **26** (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 aqueous $NaHCO_3$ solution (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 **27** (42.8 mg, 82%) as a colorless amorphous.

IR (film) 3323, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 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 = 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 (28)

A mixture of compound **27** (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) then $CHCl_3$ (2 mL × 2). The crude product was purified by PLC (MeOH : $CHCl_3$ = 1 : 10) to afford compound **28** (32 mg, 97%) as a colorless amorphous.

IR (film) 3365, 1651cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 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 = 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 (29)

To a stirred solution of compound **27** (30 mg, 0.0687 mmol) in pyridine (0.5 mL) was added cyclopropanecarbonyl chloride (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 aqueous $NaHCO_3$ solution (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 **29** (28.6 mg, 82%) as a colorless amorphous.

IR (film) 3375, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 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 = 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 (30)

To a stirred solution of compound **27** (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 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 aqueous $NaHCO_3$ solution (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 **30** (32.2 mg, 85%) as a colorless amorphous.

IR (film) 3374, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 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 = 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 (31)

To a stirred solution of compound **27** (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 aqueous $NaHCO_3$ solution (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 **31** (30.1 mg, 77%) as a colorless amorphous.

IR (film) 3366, 1646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 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 = 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 (32)

To a stirred solution of compound **27** (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 aqueous $NaHCO_3$ solution (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 **32** (24.4 mg, 66%) as a colorless solid.

IR (KBr) 3393, 1650, 1325, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 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 = 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 **27** (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 equiv) 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 aqueous $NaHCO_3$ solution (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 (33)

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 = 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 = 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 (34)

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 = 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 = 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*)-*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 (35)

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

IR (film) 3364, 1651, 1325, 1159 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 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 = 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, 157.4, 159.9, 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 (36)

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 = 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 = 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.; 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 (37)

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 = 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 = 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, 163.9, 166.5, 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 (38)

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 = 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 = 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 (39)

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

IR (film) 3356, 1651, 1324, 1160 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 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 = 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 (40)

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 = 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 = 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 (41)

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

IR (film) 3365, 1651, 1323, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 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 = 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 (42)

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 = 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 = 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 (43)

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

IR (film) 3364, 1651, 1324, 1159 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 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 = 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,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl)-*N*-methylacrylamide (44)

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 = 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 = 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,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl)-*N*-methylacrylamide (45)

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

IR (film) 3357, 1651, 1327, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 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 = 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,5,6,7,7a-octahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-yl)-*N*-methylacrylamide (46)

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

IR (film) 3357, 1651, 1324, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 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 = 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 (47)

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

IR (film) 3357, 2231, 1651, 1324, 1162 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 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, 4.8Hz, 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 = 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 (48)

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

IR (KBr) 3375, 2232, 1655, 1323, 1157 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 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 = 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 (49)

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 = 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 = 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 (50)

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 = 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 = 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 (51)

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 = 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 = 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 (52)

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 = 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 = 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 (53)

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 = 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 = 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 (54)

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 = 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 = 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 (55)

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 = 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 = 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 (56)

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

IR (film) 3366, 1651, 1323, 1158 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 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 = 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 (57)

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

IR (film) 3365, 1651, 1323, 1159 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 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 = 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*)-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 (58)

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 = 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 = 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-(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 (59)

To a mixture of compound **50** (107 mg, 0.172 mmol), $SnCl_2$ (326 mg, 1.72 mmol) and conc. HCl (57 μL) in CH_2Cl_2 (1.75 mL) and EtOH (1.75 mL) was heated to 40 °C with stirring under an argon atmosphere. After 4 h, the reaction mixture was basified with 1 M aqueous NaOH solution (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 aqueous $NaHCO_3$ solution 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 **59** (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}; ^1H NMR (400 MHz, $CDCl_3$) δ = 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 = 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 (60)

The title compound was synthesized from compound **51** in 73% yield according to the procedure described for compound **59**. The product was converted to the hydrochloride.

IR (film) 3375, 1651, 1311, 1157cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 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 = 14.2, 21.1, 21.4, 2.9, 28.9, 29.3, 29.4, 30.2, 30.4, 38.9, 39.0, 40.5, 47.2, 17.2, 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 (61)

The title compound was synthesized from compound **52** in 76% yield according to the procedure described for compound **59**. The product was converted to the hydrochloride.

IR (film) 3407, 1651, 1312, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 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 = 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 (62)

A mixture of compound **24** (1.92g, 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 aqueous $NaHCO_3$ solution (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 **62** (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) was 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 (two carbons), 128.7 (two carbons), 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]-3-[(5-bromo-2-methoxyphenyl)sulfonyl]-9-methoxy-1,2,3,4,5,6,7,7a-octahydro-4a*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-4a-ol (63)

To a stirred solution of compound **62** (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 aqueous $NaHCO_3$ solution (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 **63** (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 (two carbons), 128.6 (two carbons), 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 (64)

To a solution of compound **63** (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 aqueous $NaHCO_3$ solution (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 **64** (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 = 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 = 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 (65)

To a stirred solution of compound **61** (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 25% aqueous ammonia solution (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 **65** (80.1 mg, 51%) as a colorless solid. To a stirred solution of compound **65** (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 = 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 = 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 (66)

To a stirred solution of compound **22** (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 aqueous $NaHCO_3$ solution (80 mL) and the mixture was extracted with $CHCl_3$ (30, 70 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 **66** (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 (67)

To a suspension of compound **66** (9.06 g, 17.1 mmol) in EtOH (180 mL) were added H_2O (36 mL), saturated aqueous NH_4Cl solution (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 aqueous $NaHCO_3$ solution (50 mL) and the mixture was extracted with $CHCl_3$ (150 mL, 100 mL × 2). 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 aqueous $NaHCO_3$ solution (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 **67** (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, 6.8Hz, 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 (two carbons), 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 (68)

To a solution of compound **67** (6.56 g, 12.4 mmol) in THF (100 mL) was added 2 M HCl (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 aqueous $NaHCO_3$ solution (120 mL) and extracted with $CHCl_3$ (200 mL, 100 mL × 2). 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 : *n*-hexane = 1 : 5 to 1 : 2) to afford compound **68** (5.41 g, 90%) as a colorless amorphous.

IR (film) 3289, 1728, 1316, 1152 cm^{-1}; ^{1}H 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, 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 (69)

To a solution of compound **68** (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 45 min and saturated aqueous $NaHCO_3$ solution (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 : *n*-hexane = 1 : 3) to give compound **69** (1.04 g, 80%) as a colorless amorphous.

IR (KBr) 3313, 1317, 1152 cm^{-1}; ^{1}H 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 (two carbons), 128.6 (two carbons), 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 (70)

To a solution of compound **69** (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 **70** (570 mg, 96%) as a colorless amorphous.

IR (KBr) 3318, 1318, 1153 cm^{-1}; ^{1}H 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 (71)

To a solution of compound **70** (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 2 h at room temperature under an argon atmosphere. The reaction mixture was poured to 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 **71** (277 mg, 95%) as a colorless amorphous. To a stirred solution of compound **71** (180 mg, 0.284 mmol) in MeOH (4 mL) was added 1.0 M H_2SO_4 in MeOH solution (568 μL, 0.568 mmol) and then Et_2O (4 mL). The mixture was stirred for for 30 min at 0 °C under an argon atmosphere. The precipitate was collected by filtration to give dihydrosulfate (180 mg) as a light yellow solid.

IR (film) 3418, 1650, 1317, 1153cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 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 = 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

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 (72)

To a solution of compound **70** (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 $(i\text{-Pr})_2$NEt (35 μL, 0.204 mmol), and the mixture was stirred for 0.5 h at room temperature under an argon atmosphere. The reaction mixture was poured to 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 **72** (39.6 mg, 97%) as a colorless amorphous.

IR (KBr) 3399, 1649, 1317, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 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 = 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 (73)

To a solution of compound **70** (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 $(i\text{-Pr})_2$NEt (40 μL, 0.234 mmol), and the mixture was stirred for 0.5 h at room temperature under an argon atmosphere. The reaction mixture was poured to 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 **73** (37.7 mg, 96%) as a colorless amorphous.

IR (film) 3410, 1651, 1316, 1154 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 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 = 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).

Biology.

Calcium imaging. Chinese hamster ovary (CHO)-K1 cells stably expressing human OX1R (CHOOX1R)[14a] or OX2R (CHOOX2R)[14a] 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 pre-treated with 25 μL of various concentrations of test compounds for 15 min. After that, submaximal concentration of human orexin-A (OXA, 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 Graph Pad Prism5J (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. Orexin A was made and purified by Peptide institute, Inc. Orexin A was dissolved 0.1% BSA/Phosphate buffered saline. Compounds were dissolved in dimethyl sulfoxide (DMSO, Nacalai tesque) solution and re-adjusted by adding these solution into each experimental solution (final concentration of DMSO is 1%).

Opioid receptor binding. CHO cells stably expressing human μ, δ or κ opioid receptor were purchased from ChanTest Co., these cell membranes were used for opioid receptor 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 micro plate (PerkinElmer). The value of each test sample was calculated as: $(T_1 - T_0)/(T_2 - T_0) \times 100$, where T_0 is the non-specific binding, T_1 is the [^{3}H]-labeled ligand binding in the presence of various concentrations of test compounds (10^{-5}-10^{-11} M) and T_2 is the [^{3}H]-labeled ligand binding in the absence of respective test compounds. Sigmoidal concentration-response curve and K_i values 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 hr 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 Guideline 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 hr according to the schedule as described previously.[50] 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: 1st day (8, 15), 2nd day (20, 25), 3rd day (30, 35), 4th day (40, 45), 5th day (45 in the morning only). Newly synthesized selective OX_1R antagonist **71**·$2H_2SO_4$ (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 hr 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.[48] Diarrhea was evaluated by scoring as follows: Normal, normal stool; Slightly, soft 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 Chi-square test.

Supporting Information. General information and detailed experimental procedures, synthetic protocols, and chemical data. The Supporting Information is available free of charge via the Internet at http://pubs.acs.org."

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ABBREVIATIONS

OX_1R, orexin 1 receptor; OX_2R, orexin 2 receptor; DORA, dual orexin antagonist; Boc, *tert*-butoxycarbonyl; MP, melting point; KOR, κ opioid receptor; MOR, μ opioid receptor; DOR, δ

opioid receptor; β-FNA, beta-funaltrexamine; NTI, naltindole; nor-BNI, nor-binaltorphimine; CPM, cyclopropylmethyl; Troc, 2,2,2-trichoroethoxycarbonyl; HATU, 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate; SEM, standard error of the mean; CHO, Chinese hamster ovary.

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45. Perrey *et al*. reported only K_e value for their antagonists.[46] Therefore, we would measured the K_e value of compound **50** to directly compare with the most potent compound in Perrey's paper.

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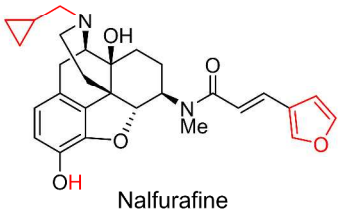
Table of Contents Graphic

κ Opioid Receptor Agonist
with orexin 1 receptor antagonistic activity

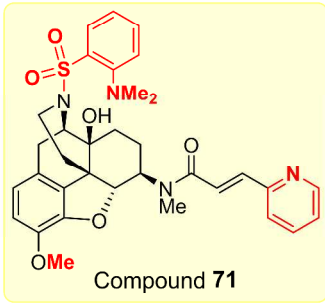


Nalfurafine

OX_1R: K_i = 250 nM
OX_2R: Not active

MOR: K_i = **5.99** nM
DOR: K_i = **693** nM
KOR: K_i = **0.238** nM

Selective Orexin 1 Receptor Antagonist



Compound **71**

OX_1R: K_i = 1.36 nM
OX_2R: Not active

MOR: K_i = **>1,000** nM
DOR: K_i = **>1,000** nM
KOR: K_i = **>1,000** nM