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DESIGN AND SYNTHESIS OF NOVEL OREXIN ANTAGONISTS VIA STRUCTURAL SIMPLIFICATION OF THE MORPHINAN SKELETON

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Abstract – Herein, we report novel orexin antagonists with a *spiro*-type piperidine skeleton designed and synthesized via removal of the unnecessary sites of orexin 1 receptor (OX_1R) antagonists with a morphinan skeleton for binding to OX_1R. In addition, while decahydroisoquinoline compounds with an A-ring did not show antagonistic activity for OX_1R, *spiro*-type piperidine compounds with a dihydroindene structure showed antagonistic activities. This suggests that the lipophilic site corresponding to the A-ring of the morphinan skeleton is important for determining the antagonistic activity toward OX_1R.

INTRODUCTION

Orexins (orexin A and orexin B, also known as hypocretin-1 and -2, respectively) are endogenous neuropeptides that were first reported by two independent research groups in 1998.[1] Both peptides bind to two subtypes of orexin receptors, orexin 1 (OX_1R) and orexin 2 (OX_2R), which are G-protein coupled receptors.[2] The orexin system is important for the regulation of sleep/wake cycles and arousal, as well as feeding behavior, energy homeostasis, addiction, and stress responses.[3] Many research groups have reported orexin antagonists,[4] particularly dual OX_1R/OX_2R antagonists for the treatment of insomnia;[5] to date, two therapeutic agents (Suvorexant[6] and Lemborexant[7]) have been approved by the FDA. OX_1R, on the other hand, has been reported to regulate reward and motivation; thus, OX_1R antagonists are expected to be applicable for treating addiction.[8]

Recently, we found that the κ opioid receptor agonist nalfurafine showed a moderate activity and high selectivity toward OX_1R, and we also synthesized the more potent OX_1R antagonist YNT-707 (**1**) (Figure 1).[9] In these studies, we focused on how the specific character of the 4,5-epoxy-morphinan skeleton contributes to the remarkable OX_1R selectivity and studied the essential structural sites required for binding to OX_1R in the morphinan compounds based on **1**. Our analyses showed that the specific conformation of the N17 functional group and C6 amide side chain are essential for the OX_1R activity (Figure 1).[10-12] Moreover, neither the E-ring (4,5-epoxy ring) nor the C14 OH group were essential for binding to OX_1R.[12] The C3 OMe group and the aromaticity of the A-ring were not essential for the 6α-amide isomer; however, in the 6β-amide isomer, the removal of these groups reduced the resulting activity.[12] It has also been reported that the OX_1R activity was lost when the E-ring and D-rings were removed at the same time.[13,14]

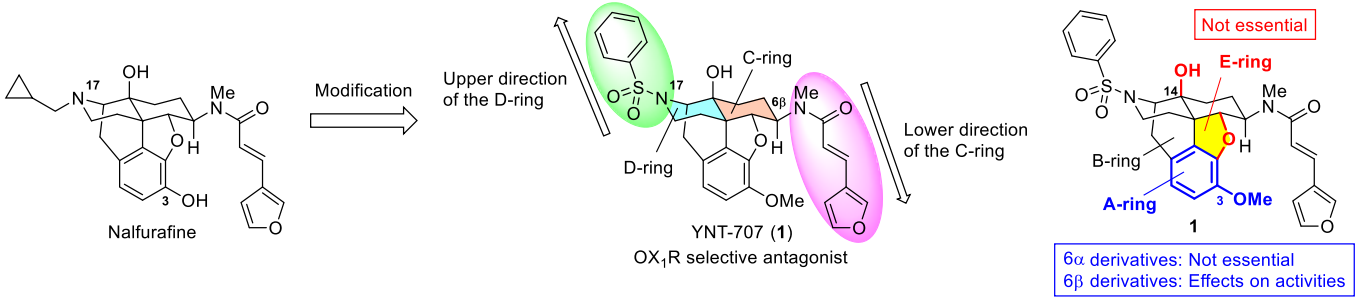


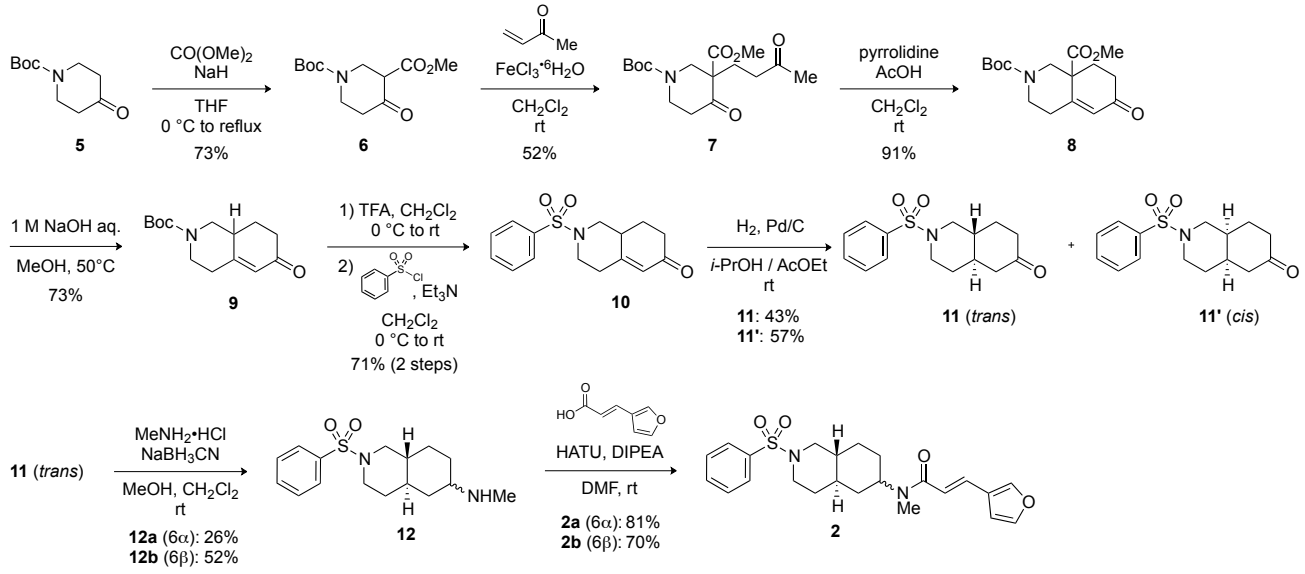
Figure 1. Essential structural requirements for OX_1R selective antagonistic activity

Although the 4,5-epoxy-morphinan compounds are characterized by their high selectivity toward OX_1R, their medicinal use is hindered by their high molecular weight and high lipophilicity.[15] Therefore, based on current knowledge regarding the essential structural sites of the morphinan compounds, we expected that it would be possible to develop a new lead compound with a simpler skeleton by removing the lipophilic sites from the morphinan skeleton. In this paper, we disclose the necessity for a lipophilic site corresponding to the A-ring of the morphinan skeleton for binding to OX_1R and also report a novel OX_1R antagonist with a simpler skeleton.

RESULTS AND DISCUSSION

First, we designed decahydroisoquinoline compounds **2**, **3**, and **4** (Schemes 1–3) to determine whether the A-ring of the morphinan skeleton is required for binding to OX_1R. Scheme 1 shows the synthetic route to designed compound **2**. 1-Boc-4-piperidone (**5**) was condensed with dimethyl carbonate to give **6**[16] and then reacted with methyl vinyl ketone to synthesize **7**.[17] Robinson annulation of **7** was carried out in the presence of pyrrolidine and acetic acid,[17] following which demethoxycarbonylation was performed via

hydrolysis of the resulting ester **8** with a 1 M aqueous NaOH solution to obtain **9**. Removal of the Boc group from **9** followed by *N*-sulfonylation of the resulting amine gave sulfonamide **10**. Then, **10** was hydrogenated with Pd/C under a hydrogen atmosphere to yield the *trans*-fused **11** and *cis*-fused **11′**, which were separated (**11**: 43%, **11′**: 57%). The relative configurations of **11** and **11′** were determined by the vicinal coupling constants $J_{1,8a}$ and $J_{5,4a}$ (Figure 2). Reductive amination of **11** with $MeNH_2 \cdot HCl$ and $NaBH_3CN$ gave C6α-methylamine **12a** and C6β-methylamine **12b**, whose relative configurations were determined by the vicinal coupling constants $J_{6,5}$ and $J_{6,7}$ (Figure 2). Then, each amine was acylated to afford the designed compounds **2a** and **2b**, respectively.



Scheme 1. Synthetic route to decahydroisoquinoline compounds **2a** and **2b**

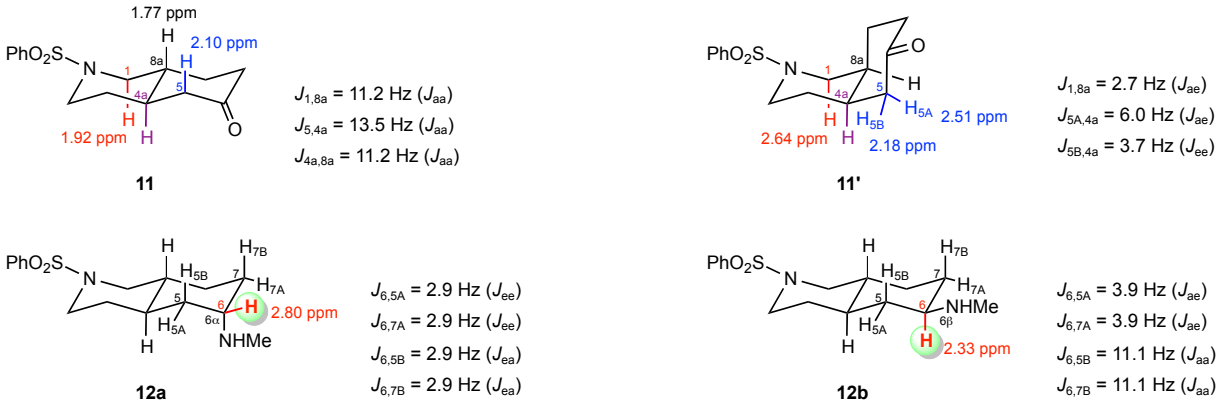
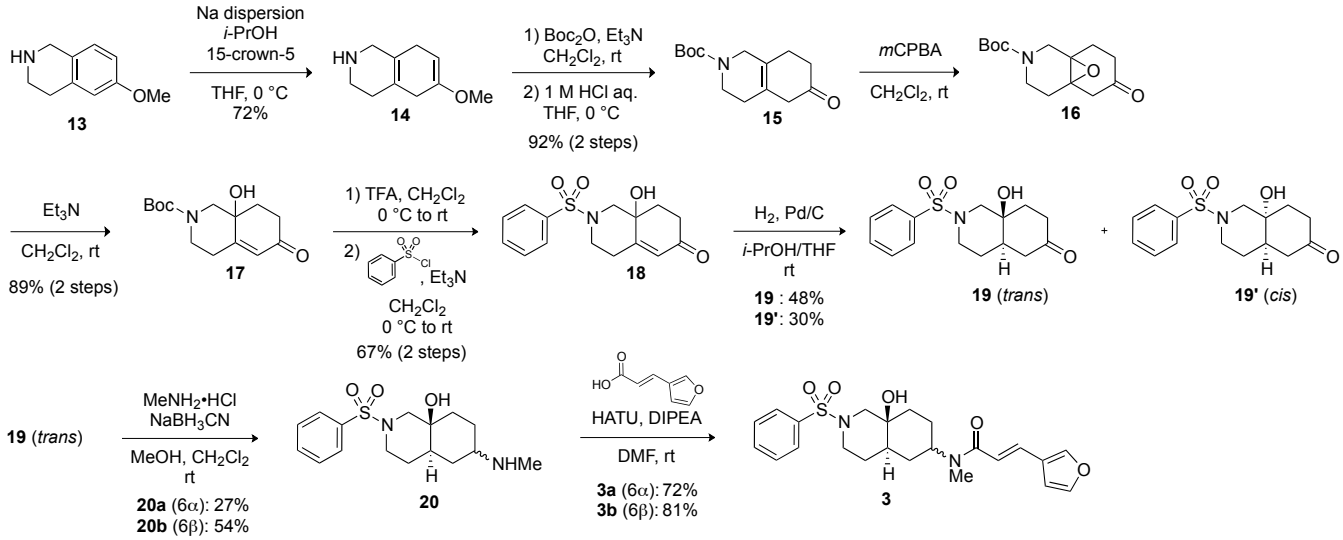


Figure 2. Relative configurations of **11**, **11′**, **12a**, and **12b**

The synthetic route to designed compound **3** is depicted in Scheme 2.[18] The ammonia-free Birch reduction[19] of **13** gave enol ether **14**; subsequently, Boc-protection of the amine in **14** followed by hydrolysis of the enol ether afforded ketone **15**. Epoxidation of **15** was performed using *m*CPBA,

followed by treatment with triethylamine to cleave the epoxide ring via α-deprotonation of the keto carbonyl, which yielded *α,β*-unsaturated ketone **17** with an angular hydroxy group. The removal of the Boc group, sulfonylation, and hydrogenation were performed in the same manner as described in Scheme 1 to obtain *trans*-fused **19** and *cis*-fused **19′**. The relative configurations of **19** and **19′** were determined by the vicinal coupling constant $J_{5,4a}$ and the ROESY correlation between H_4 and H_8, respectively (Figure 3). The designed compounds **3a** and **3b** were obtained from *trans*-fused **19** by reductive amination to afford **20a** and **20b** followed by acylation. The relative configurations of **20a** and **20b** were determined by the vicinal coupling constants $J_{6,5}$ and $J_{6,7}$ (Figure 3).



Scheme 2. Synthetic route to decahydroisoquinoline compounds **3a** and **3b** with an angular OH group

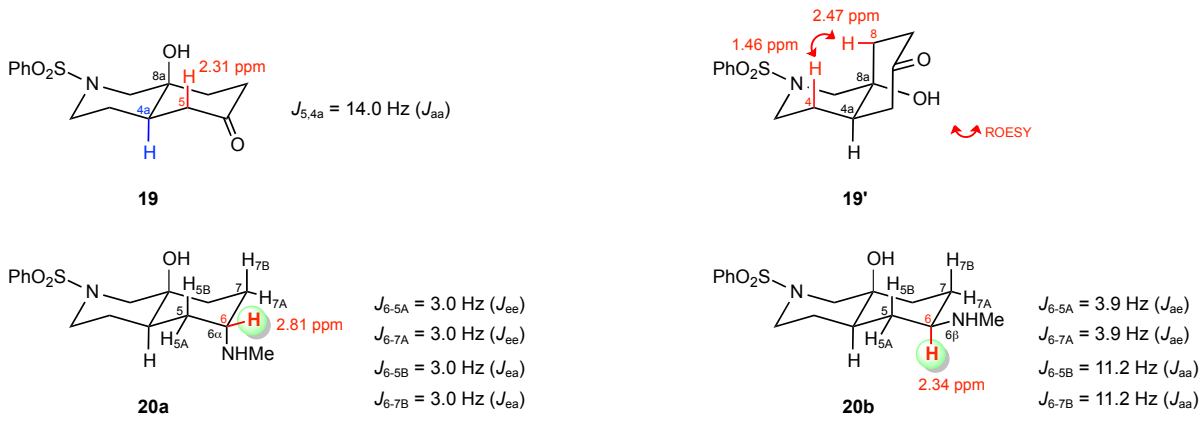
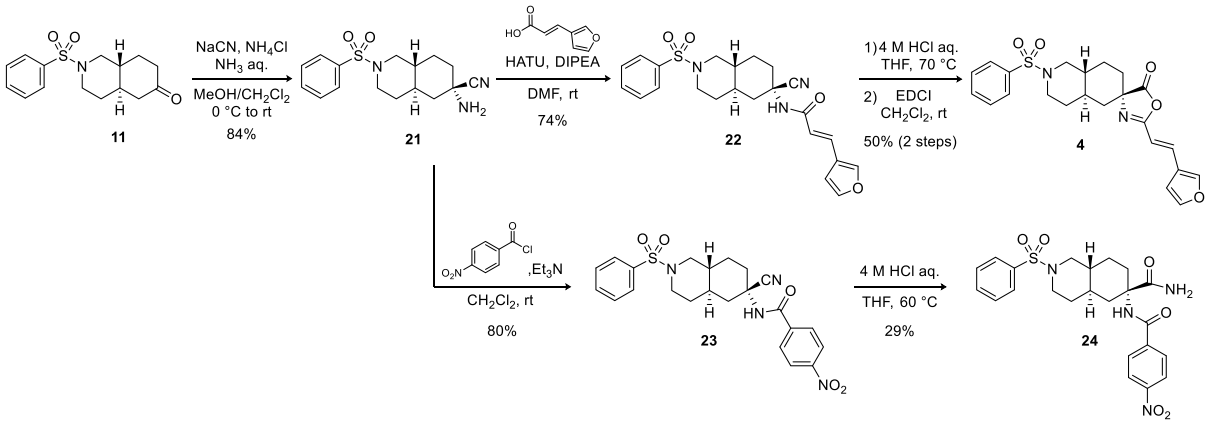


Figure 3. Relative configurations of **19**, **19′**, **20a**, and **20b**

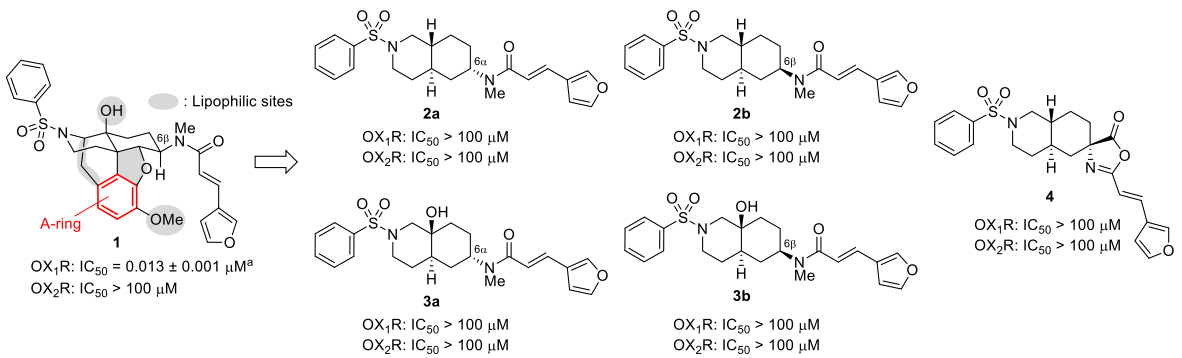
The decahydroisoquinoline derivative is expected to have an increased degree of free rotation of the C-N bond in the C6 amide side chain due to the removal of the B-ring and E-ring that fixed the C- and D-rings

in the 4,5-epoxy-morphinan derivative. Therefore, it may not be able to interact with orexin receptors, leading to a decrease in activity. To control the orientation of the C6 amide side chain, we designed *spiro*-type compound **4** with a side chain fixed below the C-ring. The synthetic route to **4** is shown in Scheme 3. The aforementioned **11** was converted to aminonitrile **21** using the Strecker reaction, and then acylation of **21** gave amide **22**. Hydrolysis of **22** followed by intramolecular cyclization of the resulting carboxylic acid afforded **4**. The relative configuration of **21** was determined by X-ray crystal structure analysis of **24**,[20] which was derived from **21** by acylation followed by hydrolysis.



Scheme 3. Synthetic route to *spiro*-compound **4**

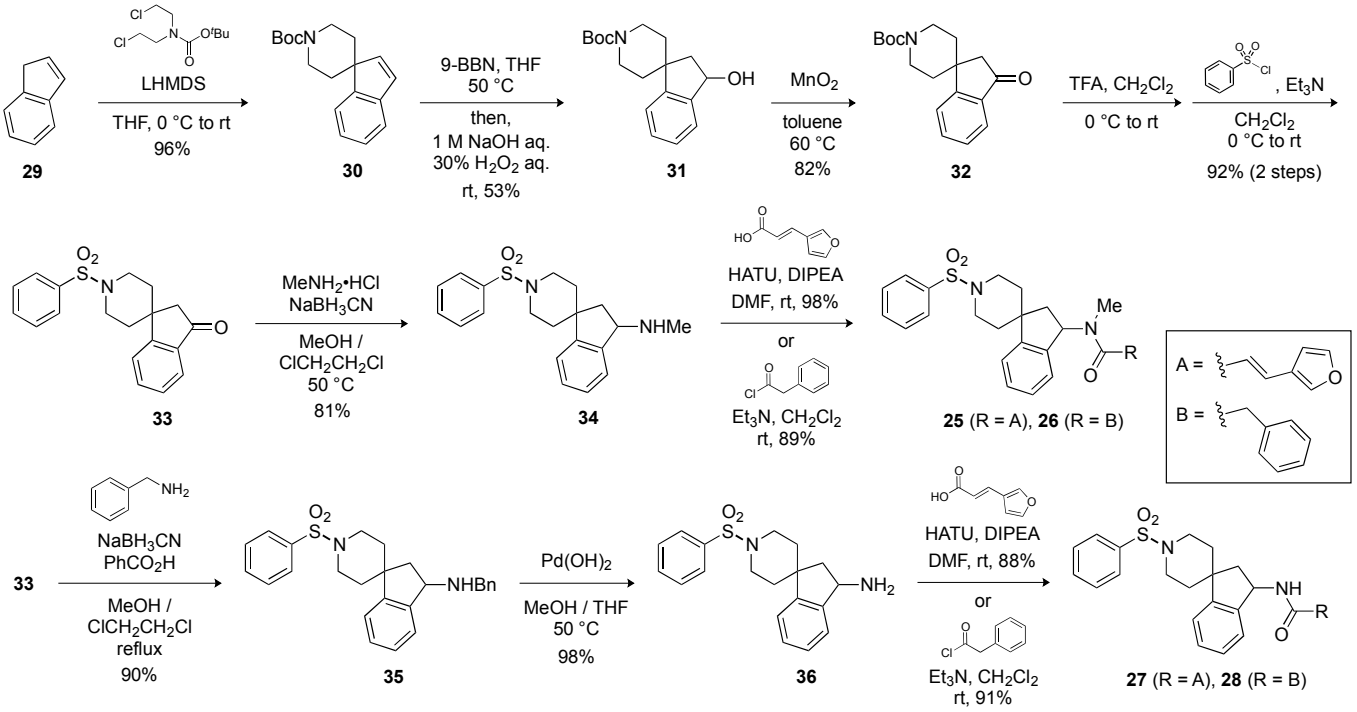
We evaluated the antagonistic activities of synthetic compounds **2**, **3**, and **4** toward OX_1R and OX_2R (Figure 4). Although morphinan compounds with the A-ring showed selective antagonistic activities toward OX_1R, **2a**, **2b**, **3a**, and **3b**, all lacking the A-ring, showed a significant loss of activity. Moreover, **4** with a side chain fixed below the C-ring showed no antagonistic activity. These results suggested that the lipophilic site corresponding to the A-ring plays an important role in binding to OX_1R.



These IC_{50} values were obtained by at least three independent calcium assays (n = 12). [a]The IC_{50} value represents the mean ± standard error of the mean (SEM).

Figure 4. Antagonistic activities for OXRs of **1**, **2**, **3**, and **4**

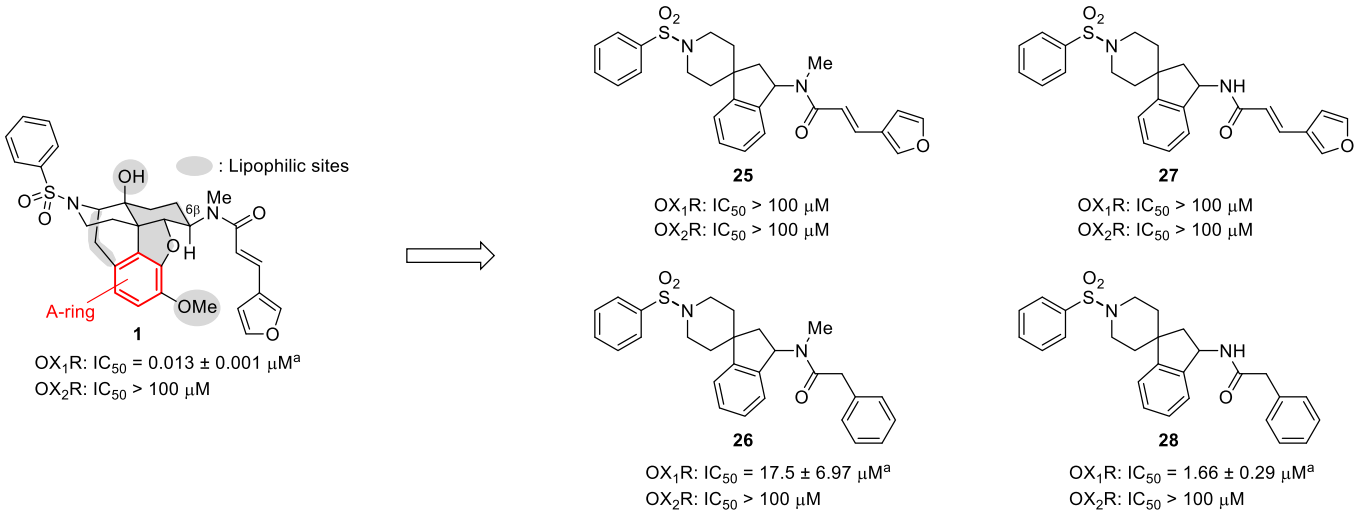
We next designed *spiro*-type piperidine compounds **25–28** with a dihydroindene structure. The synthetic route of these compounds is shown in Scheme 4. Condensation of indene (**29**) with *tert*-butyl bis(2-chloroethyl)carbamate yielded **30**, following which successive hydroboration of **30** with 9-BBN, H_2O_2 treatment, and oxidation with MnO_2 gave ketone **32**.[21] Removal of the Boc group from **32** followed by sulfonylation of the resulting amine afforded sulfonamide **33**. Reductive amination of cyclopentanone in **33** with $MeNH_2 \cdot HCl$ and $NaBH_3CN$ gave *N*-methylamine **34**, which was then acylated to afford designed compounds **25** and **26**. On the other hand, reductive amination of **33** with benzylamine, $NaBH_3CN$, and benzoic acid gave *N*-benzylamine **35**. Removal of the benzyl group of **35** with $Pd(OH)_2$ under a hydrogen atmosphere followed by acylation of the resulting amine **36** with two different acyl chlorides afforded **27** and **28**.



Scheme 4. Synthetic route to *spiro*-type piperidine derivatives **25–28**

Figure 5 shows the antagonistic activities of synthetic compounds **25–28**. Compounds **26** and **28** showed moderate antagonistic activities for OX_1R, whereas **25** and **27** showed diminished activities. These results suggested that the length or conformation of the amide side chain is important for determining the antagonistic activity. Additionally, considering that *N*-H amide **28** has a stronger activity than *N*-Me amide **26**, it is possible that the hydrogen bond (N-H) may be important. Moreover, compound **26** has a tertiary amide which occurs *cis-trans* isomerization. In the future, we would like to elucidate the effect of the amide conformation on antagonistic activities. Furthermore, no activity was observed for the

decahydroisoquinoline derivative **2–4** without the A-ring (Figure 4), whereas the *spiro*-type piperidine derivatives with the A-ring showed antagonistic activities. This suggested that the lipophilic site corresponding to the A-ring is important for binding to OX_1R.



These IC_{50} values were obtained by at least three independent calcium assays (n = 12). [a]The IC_{50} values represent the mean ± SEM.

Figure 5. Antagonistic activities of *spiro*-type piperidine derivatives **25–28**

In conclusion, we succeeded in developing new, simpler orexin ligands based on the idea of removing the unnecessary sites from the morphinan skeleton for binding to OX_1R. We found that the two *spiro*-type piperidine derivative **26** and **28** showed moderate antagonistic activities for OX_1R. Furthermore, while the decahydroisoquinoline compounds did not show antagonistic activities for OX_1R, antagonistic activities were observed for the *spiro*-type piperidine compounds, indicating that the lipophilic site corresponding to the A-ring of the morphinan skeleton plays an important role in binding to OX_1R. There have been no previous studies on orexin ligands with a *spiro*-type piperidine skeleton, and thus this report may offer important information for the further study of orexin ligands. We are exploring further optimization based on compound **28** and will report more details in the future.

EXPERIMENTAL

Chemistry

General methods. NMR spectra were recorded on a JEOL ECZ 400S spectrometer (400 MHz for ^{1}H-NMR, 100 MHz for ^{13}C-NMR). Chemical shifts were reported in ppm on the δ scale relative to Me_4Si (δ = 0 for ^{1}H NMR), $CDCl_3$ (δ = 77.0 for ^{13}C NMR), CD_3OD (δ = 49.0 for ^{13}C NMR), and DMSO-d_6 (δ = 2.50 for ^{1}H NMR, δ = 39.7 for ^{13}C NMR). IR spectra were measured with a JASCO FT/IR-4600 spectrometer. High-resolution mass spectra (HRMS) were recorded on a Thermo Fisher Scientific

Exactive Plus. Preparative HPLC was performed with a Yamazen EPCLC W-Prep 2XY equipped with Fuji Silysia CHROMATOREX Q-PACK SI 30. Thin layer chromatography was performed on TLC (Merck Ltd.; Silica gel 60 F254, 0.25 mm). Preparative thin layer chromatography was performed on PLC (Merck Ltd.; Silica gel 60 F254, 0.5 mm). Visualization was accomplished by UV light (254 nm), anisaldehyde, and phosphomolybdic acid. NH_3 aq. was 28% aqueous ammonia solution.

***tert*-Butyl 6-oxo-3,4,6,7,8,8a-hexahydroisoquinoline-2(1*H*)-carboxylate (9).** To a solution of **8** (13.0 g, 42.0 mmol) in MeOH (130 mL) was added 1 M aqueous NaOH solution (50 mL) and the mixture was stirred for 6.5 h at 50 °C under an argon atmosphere. The reaction mixture was added with 1 M aqueous HCl solution (60 mL) and the mixture was extracted with $CHCl_3$ (300 mL, 200 mL, 150 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 (*n*-hexane : EtOAc = 2 : 1 → 1 : 1) to afford **9** (7.74 g, 73%) as a white solid. IR (film): 1673 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.49 (s, 9H), 1.53–1.66 (m, 1H), 2.04–2.13 (m, 1H), 2.29–2.59 (m, 6H), 2.76–2.93 (m, 1H), 4.08–4.40 (m, 2H), 5.89–5.93 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 25.6, 28.4, 34.0, 36.3, 36.8, 43.8, 49.3, 80.2, 125.9, 154.3, 162.1, 199.0. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{21}NO_3Na$: 274.1419, found: 274.1410.

2-(Phenylsulfonyl)-1,3,4,7,8,8a-hexahydroisoquinolin-6(2*H*)-one (10). To a solution of **9** (1.50 g, 5.97 mmol) in CH_2Cl_2 (17 mL) was added TFA (3 mL) at 0 °C and the mixture was stirred for 3 h at room temperature under an argon atmosphere. The reaction mixture was basified with saturated aqueous $NaHCO_3$ solution (100 mL) at 0 °C and added with H_2O (50 mL). The mixture was extracted with *i*-PrOH/$CHCl_3$ (1/3) (200 mL, 150 mL, 100 mL × 5). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. To a mixture of the obtained crude product and Et_3N (2.08 mL, 14.9 mmol) in CH_2Cl_2 (30 mL) was added benzenesulfonyl chloride (920 μL, 7.17 mmol) at 0 °C and the mixture was stirred for 1 h at room temperature under an argon atmosphere. After the reaction mixture was diluted with $CHCl_3$ (30 mL) and washed with saturated aqueous $NaHCO_3$ solution (30, 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 (*n*-hexane : EtOAc = 1 : 1) to afford **10** (1.24 g, 71%) as a white amorphous material. IR (film): 1671, 1336, 1165 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.52 (dddd, *J* = 13.6, 13.6, 10.5, 5.0 Hz, 1H), 2.02 (dd, *J* = 11.4, 11.4 Hz, 1H), 2.05–2.14 (m, 1H), 2.29–2.48 (m, 4H), 2.61–2.79 (m, 2H), 3.94–4.03 (m, 2H), 5.84–5.86 (m, 1H), 7.52–7.59 (m, 2H), 7.60–7.66 (m, 1H), 7.76–7.81 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 25.6, 33.6, 36.2, 36.6, 46.0, 51.5, 126.1, 127.5, 129.2, 133.0, 136.2, 159.4, 198.5. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{17}NO_3SNa$: 314.0827, found: 314.0819.

Procedure for the synthesis of *trans*-fused 11 and *cis*-fused 11'. To a solution of **10** (329 mg, 1.13 mmol) in *i*-PrOH (7 mL)/ EtOAc (7 mL) was added Pd/C (type STD, Pd 5%, wetted with water) (277

mg) and the mixture was stirred for 18 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 (*n*-hexane : EtOAc = 2 : 1 → 3 : 2) to afford **11** (142 mg, 43%) as a white solid and **11'** (189 mg, 57%) as a colorless oil.

(4a*R,8a*R**)-2-(Phenylsulfonyl)octahydroisoquinolin-6(2*H*)-one (11).** IR (film): 1712, 1338, 1168 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.21–1.36 (m, 2H), 1.54 (dddd, *J* = 12.6, 12.6, 12.6, 4.3 Hz, 1H), 1.67–1.75 (m, 1H), 1.77 (dddd, *J* = 11.2, 11.2, 11.2, 3.4, 3.4 Hz, 1H), 1.92 (dd, *J* = 11.2, 11.2 Hz, 1H), 1.93–2.01 (m, 1H), 2.10 (dd, *J* = 13.5, 13.5 Hz, 1H), 2.23 (ddd, *J* = 12.6, 12.6, 2.7 Hz, 1H), 2.31–2.47 (m, 3H), 3.85–3.92 (m, 2H), 7.52–7.58 (m, 2H), 7.59–7.64 (m, 1H), 7.75–7.79 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 29.5, 32.3, 39.6, 40.6, 40.8, 45.9, 47.1, 50.9, 127.6, 129.1, 132.8, 136.2, 209.4. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{20}NO_3S$: 294.1164, found: 294.1156.

(4a*R,8a*S**)-2-(Phenylsulfonyl)octahydroisoquinolin-6(2*H*)-one (11').** IR (film): 1710, 1336, 1167 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.52–1.72 (m, 2H), 1.87–1.95 (m, 1H), 2.03–2.13 (m, 1H), 2.18 (ddd, *J* = 14.2, 3.7, 1.4 Hz, 1H), 2.18–2.40 (m, 4H), 2.42 (ddd, *J* = 11.4, 11.4, 3.2 Hz, 1H), 2.51 (dd, *J* = 14.2, 6.0 Hz, 1H), 2.64 (dd, *J* = 11.7, 2.2 Hz, 1H), 3.54–3.60 (m, 1H), 3.61–3.69 (m, 1H), 7.51–7.57 (m, 2H), 7.58–7.64 (m, 1H), 7.73–7.78 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 25.5, 26.6, 34.0, 36.3, 39.7, 45.6, 45.7, 49.6, 127.5, 129.0, 132.7, 136.3, 210.2. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{19}NO_3SNa$: 316.0983, found: 316.0977.

Procedure for the synthesis of α-methylamine 12a and β-methylamine 12b. A mixture of **11** (56 mg, 0.191 mmol), methylamine hydrochloride (64 mg, 0.948 mmol), and sodium cyanoborohydride (24 mg, 0.382 mmol) in MeOH (3 mL)/CH_2Cl_2 (2 mL) was stirred for 14.5 h at room temperature under an argon atmosphere. After addition of saturated aqueous $NaHCO_3$ solution (5 mL) and H_2O (10 mL), the mixture was extracted with $CHCl_3$ (25, 20, 15 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 [$CHCl_3$: (NH_3 aq./MeOH = 1/9) = 10 : 1] to afford **12a** (15.5 mg, 26%) as a colorless oil and **12b** (30.4 mg, 52%) as a colorless oil.

(4a*R,6*S**,8a*R**)-*N*-Methyl-2-(phenylsulfonyl)decahydroisoquinolin-6-amine (12a).** IR (film): 3355, 1343, 1169 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.12–1.41 (m, 6H), 1.43–1.56 (m, 2H), 1,62–1.68 (m, 1H), 1.74–1.82 (m, 1H), 1.91 (dd, *J* = 11.0, 11.0 Hz, 1H), 2.21 (ddd, *J* = 11.7, 11.7, 2.7 Hz, 1H), 2.33 (s, 3H), 2.80 (dddd, *J* = 2.9, 2.9, 2.9, 2.9 Hz, 1H), 3.65 (ddd, *J* = 11.0, 3.2, 1.8 Hz, 1H), 3.79–3.85 (m, 1H), 7.48–7.55 (m, 2H), 7.56–7.62 (m, 1H), 7.71–7.77 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 23.9, 29.0, 32.0, 34.2, 34.3, 36.0, 41.2, 46.8, 51.7, 54.3, 127.6, 128.8, 132.5, 136.0. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{25}N_2O_2S$: 309.1637, found: 309.1626.

(4a*R,6*R**,8a*R**)-*N*-Methyl-2-(phenylsulfonyl)decahydroisoquinolin-6-amine (12b).** IR (film): 3345, 1337, 1164 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.77–0.99 (m, 3H), 1.08 (dddd, *J* = 12.9, 12.9, 11.1, 3.5 Hz, 1H), 1.28 (ddddd, *J* = 11.2, 11.2, 11.2, 3.7, 3.7 Hz, 1H), 1.40 (dddd, *J* = 12.1, 12.1, 12.1, 4.1 Hz, 1H), 1.58–1.69 (m, 2H), 1.80–1.90 (m, 2H), 1.86 (dd, *J* = 11.2, 11.2 Hz, 1H), 1.93–2.01 (m, 1H), 2.23 (ddd, *J* = 12.1, 12.1, 2.5 Hz, 1H), 2.33 (dddd, *J* = 11.1, 11.1, 3.9, 3.9 Hz, 1H), 2.40 (s, 3H), 3.73 (ddd, *J* = 11.2, 3.7, 1.8 Hz, 1H), 3.81–3.87 (m, 1H), 7.50–7.56 (m, 2H), 7.57–7.63 (m, 1H), 7.74–7.79 (m, 2H).^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.4, 31.9, 32.1, 33.4, 38.8, 39.3, 40.8, 46.5, 51.5, 58.1, 127.5, 128.9, 132.5, 136.4. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{25}N_2O_2S$: 309.1637, found: 309.1620.

(*E*)-3-(Furan-3-yl)-*N*-methyl-*N*-((4a*R,6*S**,8a*R**)-2-(phenylsulfonyl)decahydroisoquinolin-6-yl)acrylamide (2a).** To a mixture of 3-(3-furyl)acrylic acid (10.4 mg, 0.0753 mmol), HATU (29.0 mg, 0.0763 mmol), and (*i*-Pr)$_2$NEt (22 μL, 0.128 mmol) in DMF (2 mL) was added a solution of **12a** (15.5 mg, 0.0503 mmol) in DMF (1 mL) and the mixture was stirred for 0.5 h at room temperature under an argon atmosphere. After addition of H_2O (10 mL), the mixture was extracted with EtOAc (15, 10, 10 mL). The organic layer was washed with H_2O (10 mL×2) and brine (10 mL×2), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane : EtOAc = 1 : 1 → 3 : 7) and PLC ($CHCl_3$: MeOH = 20 : 1) to afford **2a** (17.4 mg, 81%) as a white amorphous material. IR (film): 1652, 1601, 1338, 1169 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.08–1.51 (m, 5H), 1.59–1.69 (m, 2H), 1.70–2.01 (m, 3H), 1.91 (dd, *J* = 11.3, 11.3 Hz, 1H), 2.25 (ddd, *J* = 12.0, 12.0, 2.7 Hz, 1H), 3.08 (s, 3H), 3.77 (ddd, *J* = 11.3, 3.8, 1.6 Hz, 1H), 3.82–3.89 (m, 1H), 4.36–4.61 (m, 1H), 6.52–6.59 (m, 2H), 7.39–7.44 (m, 1H), 7.50–7.58 (m, 3H), 7.58–7.64 (m, 2H), 7.74–7.80 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.0, 27.7, 32.1, 32.3, 36.0, 36.1, 39.5, 46.6, 49.1, 51.8, 107.4, 117.9, 123.1, 127.6, 129.0, 132.4, 132.6, 136.3, 143.9, 144.1, 166.9. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{28}N_2O_4S$: 451.1667, found: 451.1652.

(*E*)-3-(Furan-3-yl)-*N*-methyl-*N*-((4a*R,6*R**,8a*R**)-2-(phenylsulfonyl)decahydroisoquinolin-6-yl)acrylamide (2b).** To a mixture of 3-(3-furyl)acrylic acid (17.2 mg, 0.125 mmol), HATU (56.2 mg, 0.148 mmol), and (*i*-Pr)$_2$NEt (42 μL, 0.244 mmol) in DMF (2 mL) was added a solution of **12b** (30.4 mg, 0.0986 mmol) in DMF (1.5 mL) and the mixture was stirred for 1 h at room temperature under an argon atmosphere. After addition of H_2O (10 mL), the mixture was extracted with EtOAc (25, 20, 15 mL). The organic layer was washed with H_2O (20 mL×2) and brine (20 mL×2), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane : EtOAc = 2 : 1 → 1 : 1 → 1 : 3) to afford **2b** (29.5 mg, 70%) as a white amorphous material. IR (film): 1653, 1600, 1337, 1166 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.99–1.94 (m, 11H), 2.16–2.28 (m, 1H), 2.89 (s, 0.9H), 2.96 (s, 2.1H), 3.69–3.91 (m, 2.3H), 4.50–4.63 (m, 0.7H), 6.46–6.63 (m, 2H), 7.37–7.44 (m, 1H), 7.49–7.65 (m, 5H), 7.72–7.81 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 27.7, 28.6,

29.7, 29.9, 31.8, 31.9, 35.2, 36.5, 39.6, 39.8, 40.1, 40.4, 46.4, 51.3, 51.4, 51.7, 55.9, 76.7, 77.0, 77.2, 77.3, 107.3, 117.2, 117.7, 123.0, 127.5, 129.0, 132.3, 132.5, 132.6, 136.1, 143.9, 144.1, 166.2, 166.5. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{29}N_2O_4S$: 429.1848, found: 429.1830.

6-Methoxy-1,2,3,4,5,8-hexahydroisoquinoline (14). To a suspension of Na dispersion in oil (25 wt%, 6.0 g, 65.2 mmol) in THF (30 mL) was added 15-crown-5 (11.7 mL, 61.1 mmol) at 0 °C under an argon atmosphere and the mixture was stirred for 5 min. A solution of **13** (1.65 g, 10.1 mmol) in THF (20 mL) and *i*-PrOH (4.7 mL, 61.0 mmol) were added and the mixture was stirred for 1 h at the same temperature. The reaction was quenched saturated aqueous $NaHCO_3$ solution (40 mL) and H_2O (30 mL), the mixture was extracted with Et_2O (150, 100, 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 ($CHCl_3$: (NH_3 aq./MeOH = 1/9) = 100 : 0 → 5 : 1, gradient) to afford **14** (1.20 g, 72%) as a yellow oil. IR (film): 3398, 1221 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.94–2.01 (m, 2H), 2.11 (s, 1H), 2.57–2.68 (m, 4H), 3.00 (t, *J* = 6.0 Hz, 2H), 3.18–3.24 (m, 2H), 3.55 (s, 3H), 4.61–4.66 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 29.0, 29.6, 33.5, 43.3, 48.1, 53.8, 90.1, 123.8, 125.8, 152.8. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{16}NO$: 166.1232, found: 166.1225.

***tert*-Butyl 6-oxo-3,4,5,6,7,8-hexahydroisoquinoline-2(1*H*)-carboxylate (15).** To a mixture of **14** (1.06 g, 6.42 mmol) and Et_3N (2.2 mL, 15.8 mmol) in CH_2Cl_2 (20 mL) was added Boc_2O (1.75 mL, 7.62 mmol) and the mixture was stirred for 0.5 h at room temperature under an argon atmosphere. After the reaction mixture was concentrated under reduced pressure, 1 M aqueous HCl solution (7 mL) was added to a solution of the obtained crude product in THF (15 mL) at 0 °C and the mixture was stirred for 9 h at the same temperature under an argon atmosphere. After the reaction mixture was basified with saturated aqueous $NaHCO_3$ solution (20 mL) at 0 °C and added with H_2O (20 mL), the mixture was extracted with $CHCl_3$ (50 mL, 40 mL, 30 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane : EtOAc = 7 : 3) to afford **15** (1.49 mg, 92%, 2 steps) as a white solid. IR (film): 1719, 1697 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.48 (s, 9H), 2.04 (brs, 2H), 2.32–2.40 (m, 2H), 2.52 (t, *J* = 6.9 Hz, 2H), 2.80 (brs, 2H), 3.52 (t, *J* = 5.8 Hz, 2H), 3.82 (brs, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 27.4, 28.4, 29.1, 38.4, 39.3, 40.6, 43.7, 46.1, 79.7, 125.1, 126.5, 154.7, 209.5. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{21}NO_3Na$: 274.1419, found: 274.1406.

***tert*-Butyl 8a-hydroxy-6-oxo-3,4,6,7,8,8a-hexahydroisoquinoline-2(1*H*)-carboxylate (17).** To a solution of **15** (1.47 g, 5.85 mmol) in CH_2Cl_2 (20 mL) was added *m*CPBA (1.78 g, 10.3 mmol) at 0 °C and the mixture was stirred for 1.5 h at room temperature under an argon atmosphere. The reaction mixture was quenched with 2-methyl-2-butene (1.3 mL, 12.3 mmol) and stirred for 5 min. After addition of saturated aqueous Na_2SO_3 solution (30 mL) and saturated aqueous $NaHCO_3$ solution (30 mL), the

mixture was extracted with $CHCl_3$ (100 mL, 70 mL, 50 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. To a mixture of the obtained crude product in CH_2Cl_2 (20 mL) was added Et_3N (1.65 mL, 11.8 mmol) and the mixture was stirred for 0.5 h at room temperature under an argon atmosphere. After the mixture was concentrated under reduced pressure, the crude residue was purified by column chromatography on silica gel (*n*-hexane : EtOAc = 1 : 1 → 2 : 3) to afford **17** (1.39 g, 89%, 2 steps) as a white amorphous material. IR (film): 3429, 1671 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.49 (s, 9H), 1.96 (ddd, *J* = 13.7, 13.7, 4.4 Hz, 1H), 2.07 (ddd, *J* = 13.7, 5.2, 3.4 Hz, 1H), 2.22–2.30 (m, 1H), 2.40 (ddd, *J* = 16.5, 4.4, 3.4 Hz, 1H), 2.54 (brs, 1H), 2.70–2.93 (m, 4H), 4.15–4.34 (m, 2H), 5.82 (brs, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.3, 30.8, 32.6, 33.1, 44.2, 55.1, 67.8, 80.6, 126.0, 155.6, 158.4, 198.9. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{21}NO_4Na$: 290.1368, found: 290.1354.

8a-Hydroxy-2-(phenylsulfonyl)-1,3,4,7,8,8a-hexahydroisoquinolin-6(2*H*)-one (18). To a solution of **17** (1.02 g, 3.82 mmol) in CH_2Cl_2 (20 mL) was added TFA (6 mL) at 0 °C and the mixture was stirred for 2.5 h at room temperature under an argon atmosphere. The reaction mixture was basified with 1 M aqueous NaOH solution (30 mL) and saturated aqueous $NaHCO_3$ solution (30 mL) and then extracted with *i*-PrOH/$CHCl_3$ (1/3) (100 mL, 70 mL, 50 mL × 7). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. To a mixture of the obtained crude product and Et_3N (1.33 mL, 9.54 mmol) in CH_2Cl_2 (30 mL) was added benzenesulfonyl chloride (540 μL, 4.21 mmol) at 0 °C and the mixture was stirred for 1.5 h at room temperature under an argon atmosphere. After the reaction mixture was diluted with $CHCl_3$ (30 mL) and washed with saturated aqueous $NaHCO_3$ solution (30, 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 (*n*-hexane : EtOAc = 1 : 1 → 1 : 3) to afford **18** (787 mg, 67%) as a white solid. IR (film): 3468, 1670, 1336, 1167 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.86 (ddd, *J* = 13.7, 13.7, 4.6 Hz, 1H), 2.14 (ddd, *J* = 13.7, 5.3, 3.4 Hz, 1H), 2.33 (d, *J* = 12.4 Hz, 1H), 2.33–2.45 (m, 3H), 2.78 (ddd, *J* = 16.5, 13.7, 5.3 Hz, 1H), 2.90–3.03 (m, 1H), 3.21 (s, 1H), 3.87 (dd, *J* = 12.4, 2.3 Hz, 1H), 3.97–4.04 (m, 1H), 5.77 (d, *J* = 1.8 Hz, 1H), 7.54–7.60 (m, 2H), 7.61–7.67 (m, 1H), 7.76–7.82 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 30.4, 32.4, 33.2, 46.3, 57.4, 66.6, 126.2, 127.5, 129.4, 133.3, 135.9, 156.0, 198.4. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{17}NO_4SNa$: 330.0776, found: 330.0764.

Procedure for the synthesis of *trans*-fused 19 and *cis*-fused 19'. To a solution of **18** (770 mg, 2.51 mmol) in *i*-PrOH (7 mL)/THF (15 mL) was added Pd/C (type STD, Pd 5%, wetted with water) (570 mg) and the mixture was stirred for 23 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 (*n*-hexane : EtOAc = 1 : 1) and

column chromatography on silica gel ($CHCl_3$: EtOAc = 5 : 1 → 3 : 1) to afford **19** (370 mg, 48%) as a white solid and **19'** (230 mg, 30%) as a white amorphous solid.

(4a*R,8a*S**)-8a-Hydroxy-2-(phenylsulfonyl)octahydroisoquinolin-6(2*H*)-one (19).** IR (film): 3491, 1709, 1342, 1168 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.30–1.37 (m, 1H), 1.50–1.60 (m, 2H), 1.70 (dddd, *J* = 12.7, 12.7, 12.7, 4.1 Hz, 1H), 1.79 (ddd, *J* = 13.5, 6.9, 1.8 Hz, 1H), 1.89 (ddd, *J* = 14.0, 3.9, 1.8 Hz, 1H), 2.00–2.08 (m, 1H), 2.08–2.17 (m, 1H), 2.11 (d, *J* = 11.4 Hz, 1H), 2.31 (dd, *J* = 14.0, 14.0 Hz, 1H), 2.58 (ddd, *J* = 14.2, 14.2, 6.9 Hz, 1H), 3.56 (dd, *J* = 11.4, 1.8 Hz, 1H), 3.61–3.69 (m, 1H), 4.89 (s, 1H), 7.59–7.66 (m, 2H), 7.66–7.76 (m, 3H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 26.7, 34.8, 36.6, 40.9, 42.6, 45.7, 55.8, 66.0, 127.5, 129.5, 133.1, 136.0, 209.7. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{19}NO_4SNa$: 332.0932, found: 332.0922.

(4a*R,8a*R**)-8a-Hydroxy-2-(phenylsulfonyl)octahydroisoquinolin-6(2*H*)-one (19').** IR (film): 3486, 1705, 1341, 1166 cm^{-1}. ^{1}H-NMR (400 MHz, CD_3OD): δ 1.46 (dddd, *J* = 13.3, 13.3, 12.0, 4.6 Hz, 1H), 1.63–1.71 (m, 1H), 1.80 (dddd, *J* = 14.1, 7.1, 2.1, 2.1 Hz, 1H), 1.84–1.92 (m, 1H), 1.90–1.97 (m, 1H), 2.13–2.21 (m, 1H), 2.18 (d, *J* = 11.2 Hz, 1H), 2.25 (ddd, *J* = 12.0, 12.0, 2.7 Hz, 1H), 2.47 (ddd, *J* = 14.1, 14.1 5.0 Hz, 1H), 2.76 (ddd, *J* = 14.1, 14.1, 7.1 Hz, 1H), 3.01 (dd, *J* = 14.2, 6.2Hz, 1H), 3.57 (dd, *J* = 11.2, 1.6 Hz, 1H), 3.73–3.78 (m, 1H), 7.58–7.65 (m, 2H), 7.65–7.71 (m, 1H), 7.74–7.79 (m, 2H). ^{13}C-NMR (100 MHz, CD_3OD): δ 30.2, 32.1, 37.3, 43.1, 44.6, 47.4, 57.3, 69.3, 128.7, 130.4, 134.2, 137.4, 213.3. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{19}NO_4SNa$: 332.0932, found: 332.0921.

Procedure for the synthesis of α-methylamine 20a and β-methylamine 20b. A mixture of **19** (101 mg, 0.326 mmol), methylamine hydrochloride (221 mg, 3.27 mmol), and sodium cyanoborohydride (62 mg, 0.987 mmol) in MeOH (6 mL)/CH_2Cl_2 (2 mL) was stirred for 18.5 h at room temperature under an argon atmosphere. After addition of saturated aqueous $NaHCO_3$ solution (5 mL) and H_2O (15 mL), the mixture was extracted with $CHCl_3$ (30, 20, 15 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 [$CHCl_3$: (NH_3 aq./MeOH = 1/9) = 40 : 7] to afford **20a** (28.3 mg, 27%) as a colorless oil and **20b** (57.5 mg, 54%) as a colorless oil.

(4a*R,6*S**,8a*S**)-6-(Methylamino)-2-(phenylsulfonyl)octahydroisoquinolin-8a(1*H*)-ol (20a).** IR (film): 3315, 1341, 1170 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.29–1.44 (m, 3H), 1.49–1.68 (m, 5H), 1.88–1.99 (m, 1H), 2.15 (d, *J* = 11.4 Hz, 1H), 2.21 (ddd, *J* = 11.8, 11.8, 2.9 Hz, 1H), 2.34 (s, 3H), 2.81 (dddd, *J* = 3.0, 3.0, 3.0, 3.0 Hz, 1H), 3.49 (dd, *J* = 11.4, 1.6 Hz, 1H), 3.79–3.85 (m, 1H), 7.49–7.57 (m, 2H), 7.57–7.64 (m, 1H), 7.71–7.77 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 24.5, 27.0, 29.6, 31.0, 34.3, 35.2, 47.0, 54.3, 57.3, 67.8, 127.6, 129.0, 132.9, 135.6. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{25}N_2O_3S$: 325.1586, found: 325.1568.

(4a*R,6*R**,8a*S**)-6-(Methylamino)-2-(phenylsulfonyl)octahydroisoquinolin-8a(1*H*)-ol (20b).** IR (film): 3314, 1337, 1166 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.07–1.30 (m, 3H), 1.41–1.73 (m, 5H), 1.77–1.85 (m, 1H), 1.92 (brs, 1H), 2.08 (d, *J* = 11.4 Hz, 1H), 2.22 (ddd, *J* = 12.0, 12.0, 3.0 Hz, 1H), 2.34 (dddd, *J* = 11.2, 11.2, 3.9, 3.9 Hz, 1H), 2.41 (s, 3H), 3.59 (dd, *J* = 11.4, 1.8 Hz, 1H), 3.81–3.88 (m, 1H), 7.52–7.58 (m, 2H), 7.59–7.65 (m, 1H), 7.74–7.79 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 27.2, 27.6, 33.4, 33.8, 34.3, 40.7, 46.6, 57.2, 58.0, 67.2, 127.6, 129.1, 132.9, 136.0. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{25}N_2O_3S$: 325.1586, found: 325.1568.

(*E*)-3-(Furan-3-yl)-*N*-((4a*R,6*S**,8a*S**)-8a-hydroxy-2-(phenylsulfonyl)decahydroisoquinolin-6-yl)-*N*-methylacrylamide (3a).** To a mixture of 3-(3-furyl)acrylic acid (13.0 mg, 0.0941 mmol), HATU (35.0 mg, 0.0920 mmol), and (*i*-Pr)$_2$NEt (33 μL, 0.192 mmol) in DMF (1 mL) was added a solution of **20a** (25.0 mg, 0.0771 mmol) in DMF (2 mL) and the mixture was stirred for 1 h at room temperature under an argon atmosphere. After addition of H_2O (15 mL), the mixture was extracted with EtOAc (25, 20, 15 mL). The organic layer was washed with H_2O (20 mL×3) and brine (20 mL×2), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane : EtOAc = 1 : 2 → 1 : 3 → 1 : 4) to afford **3a** (24.7 mg, 72%) as a white solid. IR (film): 3390, 1652, 1592, 1336, 1166 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.39 (dddd, *J* = 12.1, 12.1, 4.4, 4.4 Hz, 1H), 1.45–1.65 (m, 4H), 1.71 (ddd, *J* = 13.7, 5.0, 5.0 Hz, 1H), 1.75–1.87 (m, 2H), 2.07–2.18 (m, 1H), 2.12 (d, *J* = 11.4 Hz, 1H), 2.24 (ddd, *J* = 11.8, 11.8, 3.2 Hz, 1H), 2.48 (s, 1H), 3.06 (s, 3H), 3.63 (dd, *J* = 11.4, 1.4 Hz, 1H), 3.82–3.91 (m, 1H), 4.38–4.52 (m, 1H), 6.53–6.61 (m, 2H), 7.39–7.43 (m, 1H), 7.50–7.67 (m, 5H), 7.75–7.80 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 23.7, 27.5, 31.2 (×2), 32.3, 37.2, 46.8, 49.5, 57.5, 67.1, 107.4, 117.9, 123.1, 127.6, 129.2, 132.4, 133.0, 135.9, 143.9, 144.1, 166.9. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{28}N_2O_5SNa$: 467.1617, found: 467.1595.

(*E*)-3-(Furan-3-yl)-*N*-((4a*R,6*R**,8a*S**)-8a-hydroxy-2-(phenylsulfonyl)decahydroisoquinolin-6-yl)-*N*-methylacrylamide (3b).** To a mixture of 3-(3-furyl)acrylic acid (28.0 mg, 0.203 mmol), HATU (76.0 mg, 0.200 mmol), and (*i*-Pr)$_2$NEt (72 μL, 0.418 mmol) in DMF (1 mL) was added a solution of **20b** (54.2 mg, 0.167 mmol) in DMF (2 mL) and the mixture was stirred for 1 h at room temperature under an argon atmosphere. After addition of H_2O (15 mL), the mixture was extracted with EtOAc (20, 15, 10 mL). The organic layer was washed with H_2O (20 mL×3) and brine (20 mL×2), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane : EtOAc = 2 : 3 → 1 : 3) to afford **3b** (59.9 mg, 81%) as a white amorphous material. IR (film): 3399, 1652, 1594, 1342, 1169 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.22–1.42 (m, 3H), 1.42–2.03 (m, 6H), 2.06–2.15 (m, 1H), 2.21 (ddd, *J* = 12.0, 12.0, 2.5 Hz, 1H), 2.34–2.46 (m, 1H), 2.93 (s, 0.9H), 2.99 (s, 2.1H), 3.55–3.92 (m, 2.3H), 4.60 (dddd, *J* = 12.2, 12.2, 3.9, 3.9 Hz, 0.7H), 6.47–6.63 (m, 2H), 7.37–7.44 (m, 1H), 7.49–7.67 (m, 5H), 7.74–7.80 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 23.8, 25.2, 27.2, 28.0,

29.7, 30.1, 31.5, 34.3, 38.6, 40.9, 41.1, 46.6, 51.4, 55.9, 56.9, 57.1, 66.4, 66.7, 107.4, 117.4, 117.8, 123.1, 127.6, 129.2, 132.2, 132.5, 133.1, 135.8, 143.9, 144.1, 166.3. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{28}N_2O_5SNa$: 467.1617, found: 467.1592.

(4a*R,6*S**,8a*R**)-6-Amino-2-(phenylsulfonyl)decahydroisoquinoline-6-carbonitrile (21).** To a solution of **11** (50 mg, 0.170 mmol), ammonium chloride (11 mg, 0.206 mmol), and 28% NH_3 solution (2.5 mL) in CH_2Cl_2 (1 mL)/MeOH (2.5 mL) was added sodium cyanide (9.2 mg, 0.188 mmol) at 0 °C and the mixture was stirred for 5 h at room temperature under an argon atmosphere. The reaction mixture was added with H_2O (10 mL) and extracted with $CHCl_3$ (20 mL, 15 mL, 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 (*n*-hexane : EtOAc = 1 : 1 → 1 : 2) to afford **21** (45.5 mg, 84%) as a white solid. IR (film): 3584, 3372, 1337, 1160 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.16–1.57 (m, 6H), 1.60–1.76 (m, 2H), 1.84 (brs, 2H), 1.89–2.00 (m, 2H), 2.07 (ddd, *J* = 13.3, 5.7, 3.0 Hz, 1H), 2.26 (ddd, *J* = 12.0, 12.0, 2.7 Hz, 1H), 3.76 (ddd, *J* = 11.2, 3.4, 1.8 Hz, 1H), 3.84–3.91 (m, 1H), 7.51–7.58 (m, 2H), 7.59–7.65 (m, 1H), 7.73–7.79 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 26.4, 31.2, 37.3, 37.4, 40.0, 43.5, 46.3, 51.0, 51.8, 123.8, 127.5, 129.1, 132.8, 136.0. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{22}N_3O_2S$: 320.1433, found: 320.1415.

(*E*)-*N*-((4a*R,6*S**,8a*R**)-6-Cyano-2-(phenylsulfonyl)decahydroisoquinolin-6-yl)-3-(furan-3-yl)acrylamide (22).** To a mixture of 3-(3-furyl)acrylic acid (27.5 mg, 0.199 mmol), HATU (76.0 mg, 0.200 mmol), and (*i*-Pr)$_2$NEt (81 μL, 0.471 mmol) in DMF (2 mL) was added a solution of **21** (50.0 mg, 0.157 mmol) in DMF (2 mL) and the mixture was stirred for 1 h at room temperature under an argon atmosphere. After addition of H_2O (20 mL), the mixture was extracted with EtOAc (30, 25, 20 mL). The organic layer was washed with H_2O (20 mL×3) and brine (15 mL×2), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane : EtOAc = 1 : 1 → 1 : 2 → 0 : 100) and PLC ($CHCl_3$: MeOH = 20 : 1) to afford **22** (50.8 mg, 74%) as a colorless oil. IR (film): 1670, 1632, 1336, 1159 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.19–1.50 (m, 5H), 1.53–1.64 (m, 1H), 1.66–1.73 (m, 1H), 1.73–1.80 (m, 1H), 1.91–1.99 (m, 1H), 2.21–2.31 (m, 1H), 2.54–2.69 (m, 2H), 3.72–3.81 (m, 1H), 3.83–3.92 (m, 1H), 5.64 (s, 1H), 6.08 (d, *J* = 15.3 Hz, 1H), 6.50–6.56 (m, 1H), 7.39–7.44 (m, 1H), 7.51–7.67 (m, 5H), 7.72–7.79 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 25.9, 31.0, 35.2, 36.8, 40.3, 40.9, 46.3, 51.0, 52.1, 107.3, 118.6, 119.1, 122.3, 127.5, 129.1, 132.9, 133.2, 135.8, 144.4, 144.7, 165.0. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{25}N_3O_4SNa$: 462.1463, found: 462.1455.

***N*-((4a*R**,6*S**,8a*R**)-6-Cyano-2-(phenylsulfonyl)decahydroisoquinolin-6-yl)-4-nitrobenzamide (23).** To a mixture of **21** (50.7 mg, 0.159 mmol) and Et_3N (55 μL, 0.395 mmol) in CH_2Cl_2 (3 mL) was added *p*-nitrobenzoyl choloride (35.4 mg, 0.191 mmol) and the mixture was stirred for 2 h at room temperature

under an argon atmosphere. After addition of saturated aqueous $NaHCO_3$ solution (10 mL), the mixture was extracted with $CHCl_3$ (25, 20, 15 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$: MeOH = 100 : 0 → 97 : 3) to afford **23** (59.3 mg, 80%) as a yellow solid. IR (film): 1675, 1522, 1349, 1330, 1161 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.13–1.46 (m, 5H), 1.65–1.81 (m, 3H), 1.96 (dd, J = 11.2, 11.2 Hz, 1H), 2.24–2.34 (m, 1H), 2.45–2.55 (m, 2H), 3.61–3.68 (m, 1H), 3.68–3.75 (m, 1H), 7.62–7.69 (m, 2H), 7.70–7.78 (m, 3H), 8.05–8.11 (m, 2H), 8.30–8.35 (m,2H), 9.08 (s, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 25.5, 30.4, 33.8, 36.3, 39.6 (×2), 46.0, 50.5, 52.2, 119.6, 123.5, 127.3, 129.2, 129.4, 133.1, 135.6, 139.0, 149.3, 164.8. HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{23}H_{23}N_4O_5S$: 467.1389, found: 467.1379.

(4a*R,6*S**,8a*R**)-6-(4-Nitrobenzamido)-2-(phenylsulfonyl)decahydroisoquinoline-6-carboxamide (24).** To a solution of **23** (39.0 mg, 0.0832 mmol) in THF (4 mL) was added 4 M aqueous HCl solution (3 mL) and the mixture was stirred for 18 h at 60 °C under an argon atmosphere. The reaction mixture was added with saturated aqueous $NaHCO_3$ solution (25 mL) and then extracted with $CHCl_3$ (35 mL, 39 mL, 25 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 (*n*-hexane : EtOAc = 2 : 3 → 1 : 4 → 1 : 9 → 0 : 100) to afford **24** (11.9 mg, 29%) as a white solid. IR (film): 1676, 1655, 1523, 1347, 1328, 1156 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.09–1.41 (m, 5H), 1.45–1.64 (m, 3H), 1.80 (dd, J = 11.0, 11.0 Hz, 1H), 2.14–2.24 (m, 1H), 2.38–2.54 (m, 2H), 3.56–3.64 (m, 1H), 3.65–3.73 (m, 1H), 6.73 (brs, 1H), 7.19 (brs, 1H), 7.61–7.69 (m, 2H), 7.69–7.77 (m, 3H), 8.05–8.11 (m, 2H), 8.26–8.33 (m, 2H), 8.43 (brs, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 25.9, 31.6, 33.7, 36.1, 46.5, 51.4, 59.1, 123.3, 127.5, 129.4, 129.5, 133.2, 135.7, 140.7, 149.1, 164.4, 174.7. Two carbons were overlapped with a peak of DMSO-d_6. HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{23}H_{25}N_4O_6S$: 485.1495, found: 485.1497.

(4a*R,6*S**,8a*R**)-2'-((*E*)-2-(Furan-3-yl)vinyl)-2-(phenylsulfonyl)-1,3,4,4a,5,7,8,8a-octahydro-2*H*,5'*H*-spiro[isoquinoline-6,4'-oxazol]-5'-one (4).** To a solution of **22** (44.1 mg, 0.100 mmol) in THF (3 mL) was added 4 M aqueous HCl solution (3 mL) and the mixture was stirred for 64 h at 70 °C under an argon atmosphere. The reaction mixture was added with saturated aqueous $NaHCO_3$ solution (15 mL) and saturated aqueous NH_4Cl solution (15 mL), and then extracted with *i*-PrOH/$CHCl_3$ (1/3) (30 mL, 25 mL, 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 PLC ($CHCl_3$: MeOH = 20 : 3), but the impurities could not be completely removed, and thus used directly in the next reaction. To a solution of the obtained crude product in CH_2Cl_2 (4 mL) was added EDCI (18.3 mg, 0.0955 mmol) and the mixture was stirred for 0.5 h at room temperature under an argon atmosphere. After the reaction mixture was concentrated under reduced pressure, the crude residue was purified by column chromatography on silica gel ($CHCl_3$: MeOH

= 100 : 0 → 97 : 3) to afford **4** (22.0 mg, 50%, 2 steps) as a white solid. IR (film): 1800, 1658, 1339, 1163 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.35–1.51 (m, 2H), 1.52–1.74 (m, 6H), 1.75–1.94 (m, 2H), 2.02 (dd, *J* = 11.0, 11.0 Hz, 1H), 2.24–2.33 (m, 1H), 3.75–3.82 (m, 1H), 3.83–3.91 (m, 1H), 6.27 (d, *J* = 16.0 Hz, 1H), 6.60 (brs, 1H), 7.34 (d, *J* = 16.0 Hz, 1H), 7.45 (brs, 1H), 7.51–7.59 (m, 2H), 7.59–7.65 (m, 2H), 7.73–7.80 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 24.0, 31.5, 32.8, 34.2, 38.9, 39.8, 46.4, 51.2, 67.3, 107.1, 113.1, 122.7, 127.6, 129.0, 132.7, 132.8, 136.1, 144.3, 144.7, 159.8, 179.0. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{25}N_2O_5S$: 441.1484, found: 441.1471.

1'-(Phenylsulfonyl)spiro[indene-1,4'-piperidin]-3(2*H*)-one (33). To a solution of **32** (1.08 g, 3.58 mmol) in CH_2Cl_2 (20 mL) was added TFA (3 mL) at 0 °C and the mixture was stirred for 2 h at room temperature under an argon atmosphere. The reaction mixture was basified with saturated aqueous $NaHCO_3$ solution (20 mL) and then extracted with *i*-PrOH/$CHCl_3$ (1/3) (30 mL, 30 mL, 20 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. To a mixture of the obtained crude product and Et_3N (1.24 mL, 8.90 mmol) in CH_2Cl_2 (20 mL) was added benzenesulfonyl chloride (550 μL, 4.29 mmol) at 0 °C and the mixture was stirred for 15.5 h at room temperature under an argon atmosphere. After the reaction mixture was diluted with $CHCl_3$ (30 mL) and washed with saturated aqueous $NaHCO_3$ solution (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 (*n*-hexane : EtOAc = 2 : 1) to afford **33** (1.13 g, 92%) as a white solid. IR (film): 1711, 1603, 1353, 1344, 1325, 1168 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.55–1.62 (m, 2H), 2.20 (ddd, *J* = 12.8, 12.8, 4.3 Hz, 2H), 2.37 (s, 2H), 2.40 (ddd, *J* = 12.8, 12.8, 2.1 Hz, 2H), 3.91–3.98 (m, 2H), 7.38–7.44 (m, 1H), 7.46–7.51 (m, 1H), 7.55–7.62 (m, 2H), 7.62–7.69 (m, 2H), 7.68–7.73 (m, 1H), 7.78–7.84 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 37.2, 40.7, 44.2, 46.9, 123.7, 123.9, 127.6, 128.3, 129.2, 133.0, 135.3, 135.6, 136.0, 161.3, 203.8. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{19}NO_3SNa$: 364.0983, found: 364.0973.

***N*-Methyl-1'-(phenylsulfonyl)-2,3-dihydrospiro[indene-1,4'-piperidin]-3-amine (34).** A mixture of **33** (52.6 mg, 0.154 mmol), methylamine hydrochloride (104 mg, 1.54 mmol), and sodium cyanoborohydride (29.6 mg, 0.471 mmol) in MeOH (4 mL)/1,2-dichloroethane (2 mL) was stirred for 14 h at 50 °C under an argon atmosphere. After addition of saturated aqueous $NaHCO_3$ solution (10 mL) and H_2O (10 mL), the mixture was extracted with $CHCl_3$ (30, 25, 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 PLC [$CHCl_3$: (NH_3 aq./MeOH = 1/9) = 20 : 1] to afford **34** (44.3 mg, 81%) as a white solid. IR (film): 1351, 1342, 1324, 1169, 1157 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.44–1.54 (m, 2H), 1.61–1.70 (m, 1H), 1.82–1.92 (m, 1H), 2.18 (ddd, *J* = 13.0, 13.0, 4.4 Hz, 1H), 2.25 (dd, *J* = 13.0, 7.3 Hz, 1H), 2.46 (s, 3H), 2.50 (dddd, *J* = 12.4, 12.4, 12.4, 2.7 Hz, 2H), 3.78–3.88 (m, 2H), 4.15 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.11–7.15 (m, 1H), 7.20–

7.34 (m, 3H), 7.54–7.61 (m, 2H), 7.61–7.67 (m, 1H), 7.79–7.84 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 33.8, 36.5, 37.5, 41.9, 43.7, 44.0, 44.1, 62.3, 122.6, 124.3, 127.5, 127.6, 128.1, 129.1, 132.7, 136.3, 143.7, 149.5. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{25}N_2O_2S$: 357.1637, found: 357.1616.

(*E*)-3-(Furan-3-yl)-*N*-methyl-*N*-(1'-(phenylsulfonyl)-2,3-dihydrospiro[indene-1,4'-piperidin]-3-yl)-acrylamide (25). To a mixture of 3-(3-furyl)acrylic acid (16.4 mg, 0.119 mmol), HATU (45.0 mg, 0.118 mmol), and (*i*-Pr)$_2$NEt (42 μL, 0.244 mmol) in DMF (1 mL) was added a solution of **34** (35.2 mg, 0.0987 mmol) in DMF (3 mL) and the mixture was stirred for 2 h at room temperature under an argon atmosphere. After addition of H_2O (15 mL), the mixture was extracted with EtOAc (25, 20, 15 mL). The organic layer was washed with H_2O (20 mL×4) and brine (20 mL×2), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane : EtOAc = 3 : 2 → 1 : 1) to afford **25** (45.9 mg, 98%) as a white amorphous material. IR (film): 1652, 1605, 1352, 1343, 1325, 1169, 1159 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.42 (dd, *J* = 12.8, 9.2 Hz, 0.7H), 1.54–1.92 (m, 3.3H), 2.24–2.57 (m, 4H), 2.68 (s, 0.9H), 2.77 (s, 2.1H), 3.78–3.93 (m, 2H), 5.57–5.68 (m, 0.3H), 6.26–6.35 (m, 0.7H), 6.50–6.74 (m, 2H), 7.06 (d, *J* = 7.3 Hz, 0.7H), 7.11 (d, *J* = 7.3 Hz, 0.3H), 7.15–7.38 (m, 3H), 7.38–7.46 (m, 1H), 7.52–7.68 (m, 5H), 7.75–7.84 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.8, 30.4, 36.2, 36.5, 37.1, 37.3, 38.0, 39.0, 43.5, 43.9, 44.1, 57.0, 60.5, 107.3, 116.8, 117.0, 122.8, 122.96, 123.02, 124.1, 124.2, 127.5, 127.7, 128.1, 128.4, 128.96, 129.04, 129.1, 132.8, 133.4, 135.8, 136.0, 139.4, 139.9, 144.0, 144.2, 148.9, 149.6, 167.4, 167.5. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{28}N_2O_4SNa$: 499.1667, found: 499.1653.

***N*-Methyl-2-phenyl-*N*-(1'-(phenylsulfonyl)-2,3-dihydrospiro[indene-1,4'-piperidin]-3-yl)acetamide (26).** To a mixture of **34** (26.2 mg, 0.0735 mmol) and Et_3N (26 μL, 0.187 mmol) in CH_2Cl_2 (2 mL) was added phenylacetyl chloride (12 μL, 0.0908 mmol) and the mixture was stirred for 1 h at room temperature under an argon atmosphere. After the reaction mixture was diluted with $CHCl_3$ (15 mL) and washed with saturated aqueous $NaHCO_3$ solution (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 (*n*-hexane : EtOAc = 1 : 1) to afford **26** (30.9 mg, 89%) as a white amorphous material. IR (film): 1639, 1352, 1343, 1325, 1170, 1156 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.23–1.47 (m, 2H), 1.48–1.62 (m, 1.6H), 1.62–1.70 (m, 0.4H), 1.72–1.82 (m, 0.6H), 2.12 (ddd, *J* = 12.2, 12.2, 2.5 Hz, 0.4H), 2.16–2.41 (m, 2.4H), 2.49 (ddd, *J* = 12.2, 12.2, 2.5 Hz, 0.6H), 2.57 (s, 1.2H), 2.61 (s, 1.8H), 3.67–3.74 (m, 0.4H), 3.74–3.94 (m, 3.6H), 5.37 (dd, *J* = 8.6, 8.6 Hz, 0.4H), 6.26 (dd, *J* = 8.6, 8.6 Hz, 0.6H), 6.88–6.92 (m, 0.4H), 6.92–6.96 (m, 0.6H), 7.06–7.13 (m, 0.8H), 7.13–7.17 (m, 0.6H), 7.17–7.36 (m, 6.6H), 7.54–7.67 (m, 2.6H), 7.67–7.73 (m, 0.4H), 7.77–7.82 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.5, 30.5, 35.9, 36.2, 36.8, 37.1, 37.9, 38.1, 41.6, 42.4, 43.3, 43.4, 43.5, 43.9, 43.9, 44.2, 56.7, 61.2, 122.8, 122.80, 123.84, 124.1, 126.7, 126.8, 127.62, 127.64, 127.7, 127.9, 128.4, 128.5, 128.70,

128.72, 128.8, 129.1, 132.8, 134.8, 135.5, 136.0, 136.2, 139.2, 139.9, 148.7, 149.6, 171.4, 172.1. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{31}N_2O_3S$: 475.2055, found: 475.2044.

***N*-Benzyl-1'-(phenylsulfonyl)-2,3-dihydrospiro[indene-1,4'-piperidin]-3-amine (35).** A mixture of **33** (348 mg, 1.02 mmol), benzylamine (555 μg, 5.10 mmol), benzoic acid (150 mg, 1.23 mmol), and sodium cyanoborohydride (192 mg, 3.06 mmol) in MeOH (7 mL)/1,2-dichloroethane (3 mL) was refluxed for 18 h under an argon atmosphere. After cooling to the room temperature, the reaction mixture was added with saturated aqueous $NaHCO_3$ solution (5 mL) and H_2O (10 mL), and then was extracted with $CHCl_3$ (25, 20, 15 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 (*n*-hexane : EtOAc = 2 : 1) and column chromatography on silica gel (*n*-hexane : THF = 2 : 1) afford **35** (398 mg, 90%) as a white amorphous material. IR (film): 3319, 1352, 1343, 1325, 1169, 1156 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.49 (ddd, *J* = 13.0, 4.5, 2.5 Hz, 1H), 1.54 (ddd, *J* = 13.0, 6.9 Hz, 1H), 1.72 (ddd, *J* = 13.0, 4.5, 2.5 Hz, 1H), 1.87 (ddd, *J* = 13.0, 13.0, 4.5 Hz, 1H), 2.17 (ddd, *J* = 13.0, 13.0, 4.5 Hz, 1H), 2.23 (dd, *J* = 13.0, 6.9 Hz, 1H), 2.46 (ddd, *J* = 13.0, 13.0, 2.5 Hz, 1H), 2.49 (ddd, *J* = 13.0, 13.0, 2.5 Hz, 1H), 3.77–3.90 (m, 2H), 3.85 (s, 2H), 4.27 (dd, *J* = 6.9, 6.9 Hz, 1H), 7.11–7.15 (m, 1H), 7.20–7.38 (m, 8H), 7.55–7.61 (m, 2H), 7.62–7.68 (m, 1H), 7.79–7.84 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 36.4, 37.5, 42.5, 43.7, 44.0, 44.3, 51.5, 60.5, 122.6, 124.3, 127.0, 127.5, 127.7, 128.0, 128.1, 128.4, 129.1, 132.7, 136.4, 140.3, 144.1, 149.5. HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{29}N_2O_2S$: 433.1950, found: 433.1931.

1'-(Phenylsulfonyl)-2,3-dihydrospiro[indene-1,4'-piperidin]-3-amine (36). To a solution of **35** (270 mg, 0.624 mmol) in MeOH (6 mL)/THF (4 mL) was added $Pd(OH)_2$ (20 wt.% loading (dry basis), wetted with water) (100 mg) and the mixture was stirred for 14 h at 50 °C under a hydrogen atmosphere. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was added with saturated aqueous $NaHCO_3$ solution (100 mL) and the mixture was extracted with *i*-PrOH/$CHCl_3$ (1/3) (150 mL, 100 mL, 60 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 [$CHCl_3$: (NH_3 aq./MeOH = 1/9) = 100 : 0 → 19 : 1, gradient] to afford **36** (210 mg, 98%) as a white amorphous material. IR (film): 3368, 1352, 1342, 1325, 1170, 1157 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.32(ddd, *J* = 13.0, 7.7, 1.1 Hz, 1H), 1.51 (ddd, *J* = 13.0, 5.0, 2.5 Hz, 1H), 1.62 (ddd, *J* = 13.0, 5.0, 2.5 Hz, 1H), 1.75–1.86 (m, 1H), 2.24 (ddd, *J* = 13.0, 13.0, 4.4 Hz, 1H), 2.38 (ddd, *J* = 13.0, 7.7 Hz, 1H), 2.42–2.56 (m, 2H), 3.76–3.88 (m, 2H), 4.30 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.09–7.15 (m, 1H), 7.23–7.32 (m, 3H), 7.53–7.60 (m, 2H), 7.61–7.67 (m, 1H), 7.78–7.83 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 35.9, 37.3, 43.6, 43.8, 44.1, 46.1, 54.5, 122.4, 123.5, 127.65, 127.68, 127.9, 129.0, 132.8, 136.1, 146.3, 149.0. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{22}N_2O_2SNa$: 365.1300, found: 365.1289.

(*E*)-3-(Furan-3-yl)-*N*-(1'-(phenylsulfonyl)-2,3-dihydrospiro[indene-1,4'-piperidin]-3-yl)acrylamide (27). To a mixture of 3-(3-furyl)acrylic acid (20.9 mg, 0.151 mmol), HATU (58.0 mg, 0.153 mmol), and (*i*-Pr)$_2$NEt (43 μL, 0.250 mmol) in DMF (2 mL) was added a solution of **36** (34.8 mg, 0.101 mmol) in DMF (2 mL) and the mixture was stirred for 1 h at room temperature under an argon atmosphere. After addition of H_2O (15 mL), the mixture was extracted with EtOAc (25, 20, 15 mL). The organic layer was washed with H_2O (20 mL×3) and brine (20 mL×2), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane : EtOAc = 4 : 1 → 2 : 1 → 1 : 1 → 1 : 2) and PLC (*n*-hexane : EtOAc = 1 : 1) to afford **27** (41.4 mg, 88%) as a white amorphous material. IR (film): 1665, 1620, 1531, 1352, 1343, 1324, 1168, 1158 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.50 (dd, *J* = 13.3, 7.8 Hz, 1H), 1.52–1.61 (m, 2H), 1.85 (ddd, *J* = 13.0, 13.0, 4.1 Hz, 1H), 2.21 (ddd, *J* = 12.8, 12.8, 4.1 Hz, 1H), 2.31–2.41 (m, 1H), 2.42–2.51 (m, 1H), 2.51 (dd, *J* = 13.3, 7.8 Hz, 1H), 3.75–3.86 (m, 2H), 5.50 (ddd, *J* = 7.8, 7.8, 7.8 Hz, 1H), 5.91 (d, *J* = 7.8 Hz, 1H), 6.12 (d, *J* = 15.6 Hz, 1H), 6.51 (d, *J* = 1.6 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.22–7.36 (m, 3H), 7.38–7.41 (m, 1H), 7.51 (d, *J* = 15.6 Hz, 1H), 7.52–7.59 (m, 2H), 7.59–7.67 (m, 2H), 7.72–7.78 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 36.1, 37.4, 43.2, 43.6, 44.0, 44.4, 52.6, 107.3, 119.9, 122.5, 122.7, 124.1, 127.5, 127.9, 128.8, 129.1, 131.5, 132.9, 135.9, 141.6, 144.1, 144.2, 149.6, 165.8. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{26}N_2O_4SNa$: 485.1511, found: 485.1493.

2-Phenyl-*N*-(1'-(phenylsulfonyl)-2,3-dihydrospiro[indene-1,4'-piperidin]-3-yl)acetamide (28). To a mixture of **36** (20.0 mg, 0.0584 mmol) and Et_3N (20 μL, 0.143 mmol) in CH_2Cl_2 (1.5 mL) was added phenylacetyl chloride (9.3 μL, 0.0704 mmol) and the mixture was stirred for 1 h at room temperature under an argon atmosphere. After the reaction mixture was diluted with $CHCl_3$ (15 mL) and washed with saturated aqueous $NaHCO_3$ solution (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 (*n*-hexane : EtOAc = 1 : 1) and PLC ($CHCl_3$: MeOH = 40 : 1) to afford **28** (24.6 mg, 91%) as a white amorphous material. IR (film): 1645, 1538, 1352, 1343, 1325, 1169, 1157 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.29 (dd, *J* = 13.2, 7.8 Hz, 1H), 1.45 (ddd, *J* = 12.8, 12.8, 2.5 Hz, 1H), 1.50–1.58 (m, 1H), 1.80 (ddd, *J* = 12.8, 12.8, 4.1 Hz, 1H), 2.18 (ddd, *J* = 12.8, 12.8, 4.1 Hz, 1H), 2.27–2.36 (m, 1H), 2.41–2.51 (m, 2H), 3.57 (d, *J* = 16.0 Hz, 1H), 3.62 (d, *J* = 16.0 Hz, 1H), 3.74–3.84 (m, 2H), 5.37 (ddd, *J* = 7.8, 7.8, 7.8 Hz, 1H), 5.49 (d, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.18–7.36 (m, 7H), 7.54–7.61 (m, 2H), 7.61–7.68 (m, 1H), 7.75–7.81 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 35.9, 37.1, 43.0, 43.5, 43.8, 44.0, 44.2, 52.4, 122.6, 123.7, 127.4, 127.5, 127.9, 128.7, 129.0, 129.1, 129.2, 132.9, 134.6, 136.0, 141.5, 149.5, 171.0. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{28}N_2O_3SNa$: 483.1718, found: 483.1704.

Biology

Materials. Human orexin-A (Peptide Institute) was dissolved in 0.1% bovine serum albumin (BSA: Sigma)/phosphate buffered saline (PBS). Compounds were dissolved in dimethyl sulfoxide (DMSO: Nakarai Tesque) solution and re-adjusted by adding these solutions into each experimental solution (final concentration of DMSO is 1%).

Cell culture and media. CHO-K1 cells stably expressing human OX_1R ($CHOOX_1R$) or OX_2R ($CHOOX_2R$) cells were cultured in Dulbecco's modified Eagle's medium (DMEM:WAKO) supplemented with 5% fetal bovine serum (FBS: Gibco), Puromycin (10 μg/mL: Sigma-Aldrich), G418 (0.5 mg/mL: WAKO), and penicillin/streptomycin (100 units/mL, 100 μg/mL: WAKO). All cells were maintained at 37 °C, 5% CO_2 and passaged every 3 days.

Evaluation of antagonistic activity on human OX_1R and OX_2R. Ca^{2+} elevations were measured by using CHOOX1R and CHOOX2R as described before (Ref 12: Yamamoto et al., BMC, 2019). The cells were exposed to the loading solution composed of 5 μM fluorescent calcium indicator Fura 2-AM (Cayman Chemical). Fifteen minutes after addition of compounds, 0.3 nM of orexin-A was added to the cell. The intracellular Ca^{2+} levels were measured as the ratio of fluorescence emission at of 510 nm by excitation at 340 or 380 nm using the Functional Drug Screening System 7000 system (Hamamatsu Photonics). The IC_{50} values of compounds were calculated using Graph Pad Prism 7 (Graph Pad).

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20. CCDC 2045897 (**24**) contain the supplementary crystallographic data for this paper. Free copies of the data can be obtained via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (þ 44) 1223-336-033; or deposit@ccdc.cam.ac.uk). Crystal Data for $C_{25}H_{32}N_4O_7S$ (M =532.60 g/mol): triclinic, space group P-1 (no. 2), a = 6.0312(2) A, b = 12.6934(3) A, c = 17.0392(3) A, α = 97.977(2)°, β = 95.600(2)°, γ = 92.771(2)°, V = 1283.14(6) A3, Z = 2, T = 100.15 K, μ(CuKα) = 1.568 mm-1, Dcalc = 1.379 g/cm^3, 29437 reflections measured (2θ = 5.266°–147.734°), 5032 unique (Rint = 0.0441, Rsigma = 0.0284) which were used in all calculations. The final R1 was 0.0652 (I > 2σ(I)) and wR 2 was 0.1741 (all data).
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