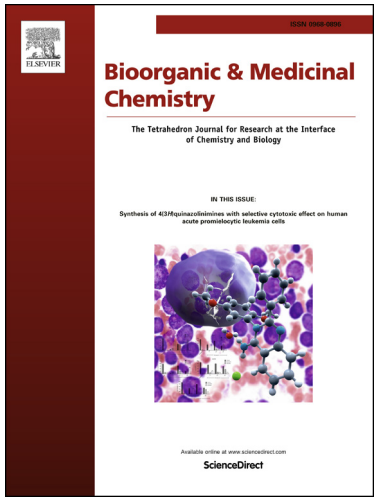
# Accepted Manuscript




Discovery, synthesis, and structure-activity relations of 3,4-dihydro-1*H*-spiro(naphthalene-2,2'-piperidin)-1-ones as potassium-competitive acid blockers

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**Discovery, synthesis, and structure-activity relations of**

**3,4-dihydro-1*H*-spiro(naphthalene-2,2'-piperidin)-1-ones as potassium-competitive acid blockers**

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Keywords: $H^+$,$K^+$-ATPase; potassium-competitive acid blockers; docking analysis; 3,4-dihydro-1*H*-spiro[naphthalene-2,2′-piperidin]-1-one derivatives; S-enantiomer

Abbreviations: 1,1′-bis(diphenylphosphino)ferrocene (dppf), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos), *N*,*N*-dimethylformamide (DMF), gastroesophageal reflux disease (GERD), high-performance liquid chromatography (HPLC), lithium diisopropylamide (LDA), potassium-competitive acid blockers (P-CABs), proton pump inhibitors (PPIs), room temperature (rt), structure–activity relationship (SAR), tetrahydrofuran (THF)

**Abstract**

With the aim to discover a gastric antisecretory agent more potent than the existing proton pump inhibitors, novel 3,4-dihydro-1*H*-spiro(naphthalene-2,2′-piperidin)-1-one derivatives, which could

occupy two important lipophilic pockets (described as LP-1 and LP-2) of $H^+$,$K^+$-ATPase and can strongly bind to the $K^+$-binding site, were designed based on a docking model. Among the compounds synthesized, compound **4d** showed a strong $H^+$,$K^+$-ATPase-inhibitory activity and a high stomach concentration in rats, resulting in potent inhibitory action on histamine-stimulated gastric acid secretion in rats. Furthermore, **4d** exerted significant inhibitory action on histamine-stimulated gastric-acid secretion in rats with a rapid onset and moderate duration of action after the administration. These findings may lead to a new insight into the drug design of potassium-competitive acid blockers.

## 1. Introduction

Gastroesophageal reflux disease (GERD) is the most common disorder of the gastrointestinal tract in the general population and is increasing in prevalence worldwide. There is acid suppression therapy with proton pump inhibitors (PPIs), which is associated with well-established benefits in the management of GERD and other acid-related disorders.[1] As a new class of acid suppressant, the so called potassium-competitive acid blockers (P-CABs)[2] are expected to have some therapeutic advantages over PPIs' shortcoming such as delayed onset of action, the influence of cytochrome P450 (CYP) polymorphism, and insufficient inhibition of nocturnal acid breakthrough.[3] Although PPIs have a unique mechanism of action based on their chemistry, the P-CABs have a structural specificity for their target, the $K^+$-binding region of the $H^+$,$K^+$-ATPase where a P-CAB can bind in or near the $K^+$ binding site and prevent access of the cation to the site.

In one study on P-CABs, novel pyrrole derivatives showing a great potential as unprecedented gastric antisecretory agents were found,[4] and then **TAK-438** (vonoprazan fumarate) was discovered as a drug candidate for the treatment of GERD, peptic ulcer, and other acid-related diseases.[5] Taking advantage of the research on pharmacology and structure-based drug design (SBDD) studies in pursuit of novel and potent P-CABs, we continued to explore a new chemotype, for example, having a docking mode

different from that of **TAK-438**: our SBDD research has been focused on the two lipophilic pockets (described as LP-1, LP-2 in Figure 2) to be occupied for strong binding to the $K^+$-binding site.

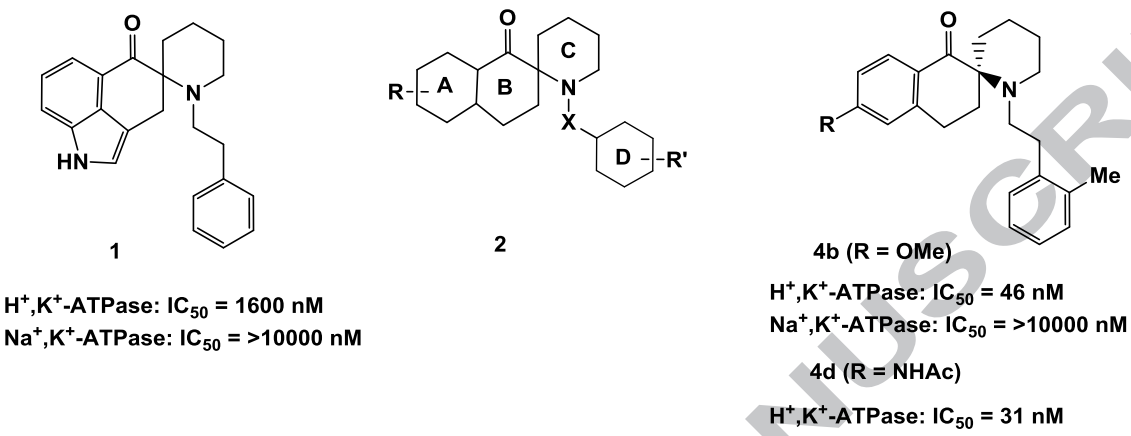



**Figure 1. 1**: Selected as a hit compound by in-house screening for $H^+$,$K^+$-ATPase-inhibitory activities at pH 6.5. **2**: The general structure of 3,4-dihydro-1*H*-spiro(naphthalene-2,2′-piperidin)-1-one derivatives after modification for P-CAB designed from hit compound **1** based on the docking model. **4b** and **4d**: Found as potent P-CABs showing significant in vivo acid suppression in rats.

During the screening of our in-house chemical library, 1,3-dihydro-5*H*-spiro(benzo[*cd*]indole-4,2′-piperidin)-5-one derivative **1** was found as a reversible $H^+$,$K^+$-ATPase inhibitor with a possibility of occupying both LP-1 and LP-2 according to the docking analysis. The compound showed inhibition of $H^+$,$K^+$-ATPase activity in pig gastric microsomes with $IC_{50}$ of 1600 nM and more than 100-fold lower affinity for $Na^+$, $K^+$-ATPase in vitro, and then showed an inhibitory effect on histamine-stimulated acid secretion in anesthetized rats: 71% inhibition at 10 mg/kg (intravenous injection). We, in particular, utilized its 4-dihydro-1*H*-spiro(naphthalene-2,2′-piperidin)-1-one skeleton as a pharmacophore for activity based on the docking analysis, which suggested that the pyrrole moiety of **1** may be removed, whereas the

benzene moiety must be necessary to occupy one key lipophilic pocket (described as LP-2 in Figure 2). We also focused on its *N*-phenethyl side chain, whose benzene moiety should be necessary to occupy another key lipophilic pocket (LP-1).

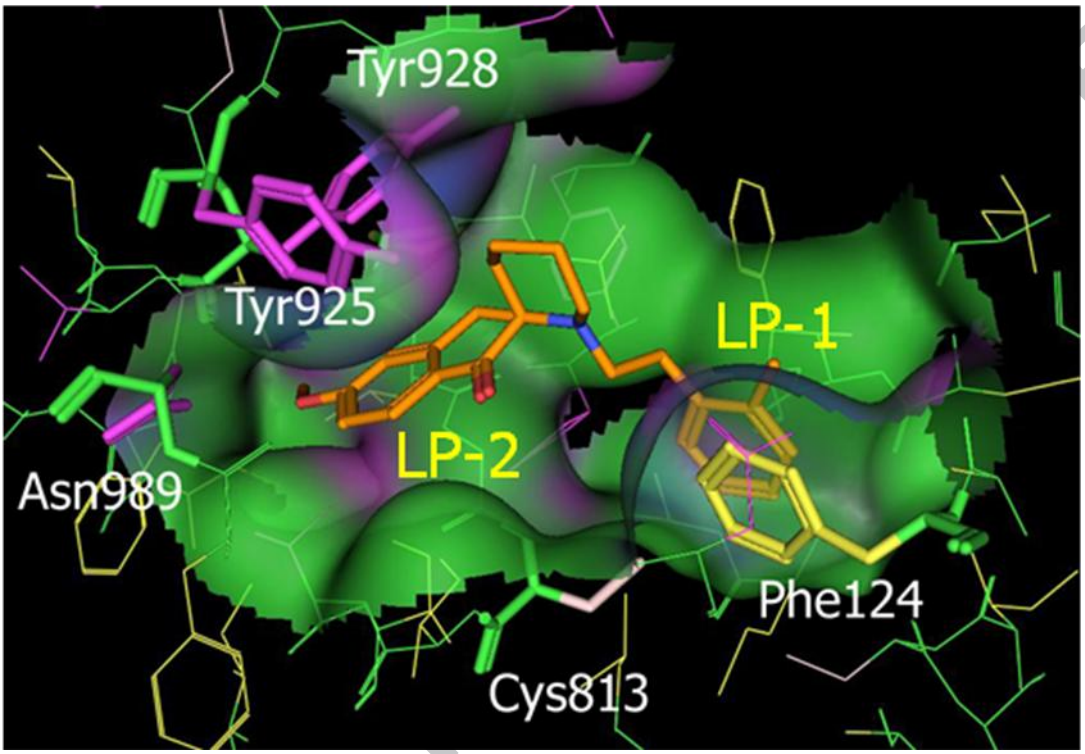



**Figure 2.** Docking analysis of **4b** having the S-configuration at position 2 using a homology model of the luminal region of $H^+,K^+$-ATPase, which was constructed from the crystal structure of $Ca^{2+}$-ATPase. Both lipophilic pockets LP-1 and LP-2 were sufficiently occupied by the substituted phenethyl side chain and 1,3-dihydro-5*H*-dihydronaphthalene-5-one skeleton, respectively.

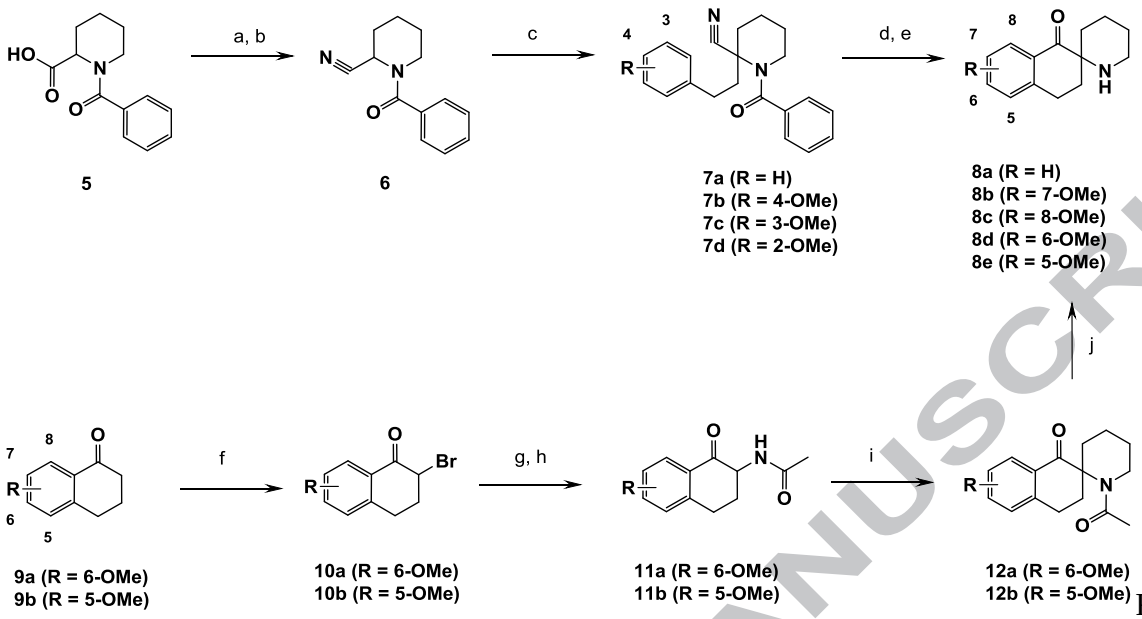
We then designed general structure **2**, which consists of core bicyclic scaffold AB, piperizine ring C, and side chain's ring D with linkage X. The analysis of linkage X, substitutes (R, R'), and absolute configuration led to compound **4b**, which could occupy both lipophilic pockets very well, as a potent P-CAB with $IC_{50}$ of 46 nM. We then discovered acetamide derivative **4d** having the strongest in vitro activity (31 nM) with significant inhibition of acid secretion: by 95% at 1 mg/kg (rats, intravenous

injection). Herein, we report the discovery, synthesis, and structure–activity relations of 3,4-dihydro-1*H*-spiro(naphthalene-2,2′-piperidin)-1-one derivatives.

## 2. Chemistry

The key intermediates of 3,4-dihydro-1*H*-spiro(naphthalene-2,2′-piperidin)-1-one derivatives (**8a**–**e**) were synthesized starting from 1-benzoylpiperidine-2-carboxylic acid **5** or 1-tetralone **9** as outlined in Scheme 1. Nitrile derivative **6** prepared from carboxylic acid **5** in a usual manner was reacted with phenethyl iodides,[6] which were synthesized from alcohols in a usual manner, to obtain alkylated compounds **7a**–**d**. The cyano group in **7a,b** was activated with a Lewis acid to promote intramolecular cyclization at position 2 on the benzene ring of the phenethyl group, and then the benzoyl group on the piperizine ring was removed by basic hydrolysis to produce piperidines **8a** and **8b**, respectively. 3-Methoxy derivative **7c** has two reaction points at the second and sixth position on the benzene ring, resulting in two products: **8c** and **8d**. The reaction for 2-methoxy derivative **7d** produced such a complex mixture that the desired product (**8e**) was not obtained.

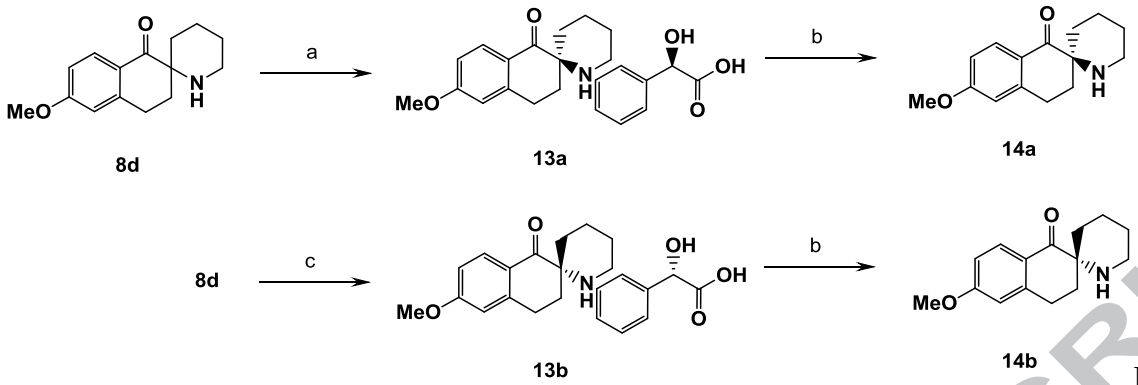
**Scheme 1**




Reagents and conditions: (a) $ClCO_2Et$, $Et_3N$, aq. $NH_3$, THF; (b) $POCl_3$, pyridine, THF, DMF; (c) LDA, R-$C_6H_4$-I, THF; (d) $AlCl_3$ or $CF_3CO_2H$ or $CF_3SO_3Si(CH_3)_3$, toluene or $CF_3Ph$; (e) 8N NaOH; (f) $PhNMe_3Br$-$Br_2$, THF; (g) $NaN_3$, AcOH, DMF; (h) $H_2$/Pd-C, AcOH, THF; (i) NaH, $Br(CH_2)_4Br$, DMF; (j) cHCl.

Stepwise functionalization at position 2 of 1-tetralone **9a**,**b** using trimethylphenylammonium tribromide and subsequently sodium azide followed by catalytic hydrogen reduction with acetic anhydride yielded acetylamido derivatives **11a,b** via **10a,b**. These compounds were alkylated at position 2 with 1,4-dibromobutane, leading to immediate internal cyclization with formation of *N*-acylpiperidine derivatives **12a,b**,[7] and then the acyl group was removed by acid hydrolysis to obtain piperidines **8d** and **8e**, respectively. These intermediates (**8a–e**) were used in the following steps in a free form or as a HCl salt, which was prepared by a typical method from a free form to store the oily intermediates as a solid (a scheme and spectral data are not shown).

**Scheme 2**

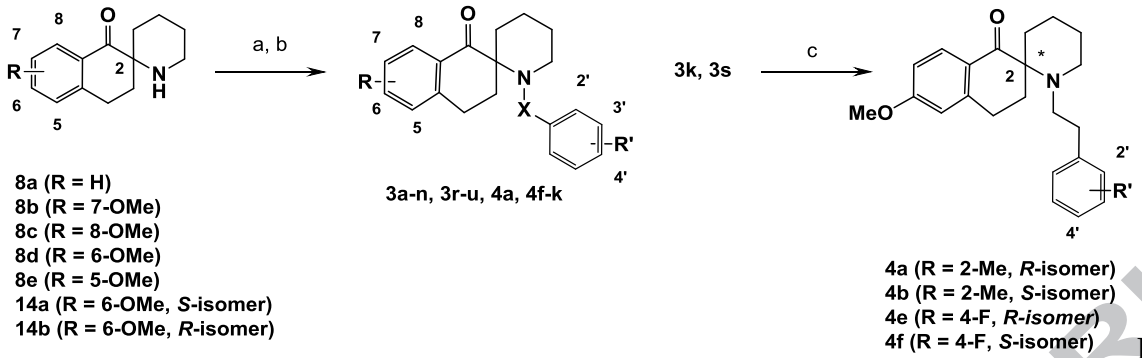



Reagents and conditions: (a) D-(*R*)-(–)-mandelic acid, EtOH; (b) aq. NaOH; (c) L-(*S*)-(+)-mandelic acid, EtOH.

Preparation of both enantiomeric intermediates **14a** and **14b** is shown in Scheme 2; this procedure was conducted by optical resolution using D-(*R*)-(–)- and L-(*S*)-(+)-mandelic acids from racemate **8d** and following basic hydrolysis. The absolute configuration of **14a** as an S-enantiomer was determined by X-ray analysis of the optical salt **13a** (data not shown).

These intermediates **8a–e** and **14a,b** were converted to *N*-alkyl or *N*-acyl derivatives **3a–n**, **3r–u**, **4a**, and **4f–k** as a free form or HCl salt by treatment with alkyl halides or an acyl halide in the presence of base reagents (Scheme 3). Both enantiomers of 2-methylphenethyl products **4a,b** and 4-fluorophenethyl derivatives **4e,f** were obtained from corresponding racemic derivatives **3k** and **3s** by standard preparative chiral high-performance liquid chromatography (HPLC). Their absolute configurations were determined by comparing their retention time during chiral HPLC with the corresponding optical derivative compounds (**4a, 4f**), which were synthesized from the corresponding intermediates (**14b,a**) using the *R* or *S* absolute configuration information.

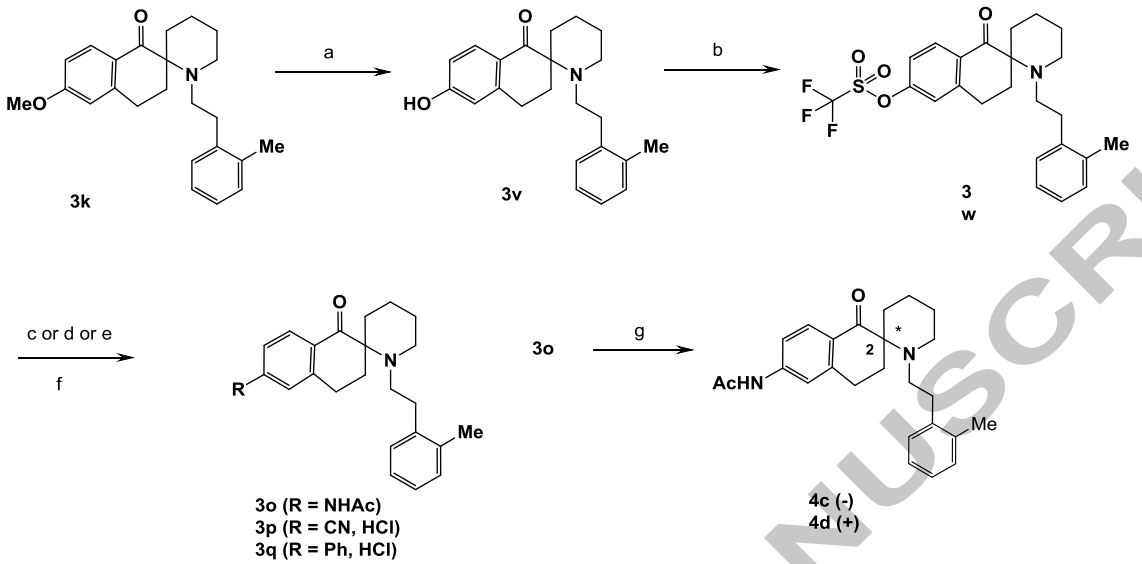
**Scheme 3**




Reagents and conditions: (a) R′-$C_6H_4$-X-Y (Y = Cl, Br, I), $iPr_2NEt$, toluene; (b) 4N HCl/EtOAc, $Et_2O$; (c) preparative chiral HPLC.

Further conversion of the methoxy group of **3k** into acetylamido (**3o**), cyano (**3p**), or phenyl (**3q**) groups via a coupling reaction with a trifluorosulfonyloxy derivative (**3w**), which was obtained from demethyl derivative **3v**, is shown in Scheme 4. The enantiomers of acetamide derivatives **4c** and **4d** were separated from racemate **3o** by standard preparative chiral HPLC, with estimation of their absolute configuration by referring to the order of the retention time values during chiral HPLC and the minus or plus sign of the specific optical rotation for similar methoxy derivatives **4a** and **4b** and then by confirming their in vitro activity.

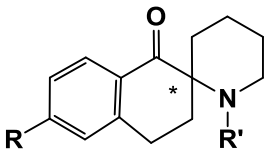
**Scheme 4**[a]




Reagents and conditions: (a) 46% HBr; (b) $(CF_3SO_2)_2O$, pyridine; (c) $AcNH_2$, $PhB(OH)_2$ (cat.), $Pd(OAc)_2$, Xphos, $K_2CO_3$, DMA; (d) $Zn(CN)_2$, $Pd_2(dba)_3$, dppf, DMF; (e) $PhB(OH)_2$, $Pd(OAc)_2$, Xphos, $K_2CO_3$, DMA; (f) 4N HCl/EtOAc, $Et_2O$; (g) preparative chiral HPLC.

Table 1 summarized the optical active derivatives with enantiomeric excess (ee) measured by chiral HPLC and specific optical rotation in MeOH.

**Table 1** A summary of optical active intermediates **14a,b** and derivatives **4a**–**k** with enantiomeric excess (ee) measured by chiral HPLC and specific optical rotation in MeOH.




**14a, 14b, 4a-k**

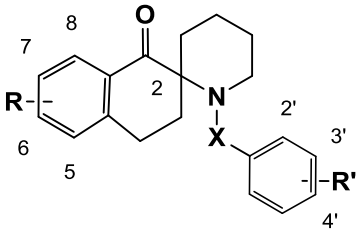
| compd. | R | R' | salt | config. | ee (%)[a] | specific optical rotation $[\alpha]_D^{20}$ (MeOH) |
|---|---|---|---|---|---|---|
| **14a** | MeO | H | HCl | S | 98.3 | +31.0 (c = 0.500) |
| **14b** | MeO | H | HCl | R | 99.7 | –32.7 (c = 0.505) |
| **4a** | MeO | $CH_2CH_2$(2-Me)Ph | HCl | R | 99.9[b] | –69.9 (c = 0.500) |
| **4b** | MeO | $CH_2CH_2$(2-Me)Ph | HCl | S | 99.4[b] | +70.4 (c = 0.505)[c] |
| **4c** | AcNH | $CH_2CH_2$(2-Me)Ph | free | R[d] | 99.9 | –62.1 (c = 0.383) |
| **4d** | AcNH | $CH_2CH_2$(2-Me)Ph | free | S[d] | 99.4 | +66.3 (c = 0.500) |
| **4e** | MeO | $CH_2CH_2$(4-F)Ph | HCl | R | 99.8[b] | NT[e] |
| **4f** | MeO | $CH_2CH_2$(4-F)Ph | HCl | S | 96.7 | +41.6 (c = 0.505) |
| **4g** | MeO | $CH_2CH_2$(3-F)Ph | HCl | S | NT[e] | +40.8 (c = 0.250) |
| **4h** | MeO | $CH_2CH_2$(2-F)Ph | HCl | S | NT[e] | +42.6 (c = 0.250) |
| **4i** | MeO | $CH_2CH_2$(2-OMe)Ph | HCl | S | NT[e] | +63.5 (c = 0.250) |
| **4j** | MeO | $CH_2CH_2$(3-OMe)Ph | HCl | S | NT[e] | +42.0 (c = 0.250) |
| **4k** | MeO | $CH_2CH_2$(4-OMe)Ph | HCl | S | NT[e] | +35.9 (c = 0.250) |

[a] Calculated from the area in chiral HPLC, whose retention time was compared with that of the racemate. [b] Measured for their free forms. [c] Its free form was also analyzed: $[\alpha]_D^{20}$ +68.7 (c = 0.44, MeOH). There was almost no difference between the HCl salt and free form in specific optical rotation. [d] Estimated based on retention time order, specific optical rotation, and in vitro activity in a comparison with **4a** and **4b**. [e] Not tested.

## 3. Results and Discussion

The compounds synthesized were evaluated for their $H^+,K^+$-ATPase-inhibitory activities at pH 6.5 by their $IC_{50}$ values (in vitro); the results of in vitro evaluation are shown in Table 2.

**Table 2** $H^+,K^+$-ATPase inhibitory activities at pH 6.5 of spirodihydronaphthalene derivatives **3a**–**u** and **4a–k**.




**3a-u, 4a-k**

| compd. | R | Y | R' | config. | salt | in vitro $H^+,K^+$-ATP-inhibitory activity ($IC_{50}$, nM) |
|---|---|---|---|---|---|---|
| **3a** | H | $CH_2CH_2$ | H | R/S | HCl | 1000 |
| **3b** | H | $CH_2CH_2$ | 2′-Me | R/S | HCl | 290 |
| **3c** | 6-OMe | $CH_2CH_2$ | H | R/S | HCl | 290 |
| **3d** | 6-OMe | none | H | R/S | HCl | >10000 |
| **3e** | 6-OMe | $CH_2$ | H | R/S | HCl | >10000 |
| **3f** | 6-OMe | $CH_2CH_2CH_2$ | H | R/S | HCl | 890 |
| **3g** | 6-OMe | $CH_2CH_2CH_2CH_2$ | H | R/S | HCl | >10000 |
| **3h** | 6-OMe | $COCH_2$ | H | R/S | free | >10000 |
| **3i** | 6-OMe | $CH_2CO$ | H | R/S | free | >10000 |
| **3j** | 6-OMe | $CH_2C(CH_3)H$ | H | R/S | HCl | 300 |
| **3k** | 6-OMe | $CH_2CH_2$ | 2′-Me | R/S | HCl | 82 |
| **3l** | 5-OMe | $CH_2CH_2$ | 2′-Me | R/S | HCl | 300 |
| **3m** | 7-OMe | $CH_2CH_2$ | 2′-Me | R/S | HCl | 270 |
| **3n** | 8-OMe | $CH_2CH_2$ | 2′-Me | R/S | HCl | 290 |
| **3o** | 6-NHAc | $CH_2CH_2$ | 2′-Me | R/S | free | 45 |
| **3p** | 6-CN | $CH_2CH_2$ | 2′-Me | R/S | HCl | >10000 |
| **3q** | 6-Ph | $CH_2CH_2$ | 2′-Me | R/S | HCl | >10000 |
| **3r** | 6-OMe | $CH_2CH_2$ | 2′-Cl | R/S | HCl | 170 |
| **3s** | 6-OMe | $CH_2CH_2$ | 4′-F | R/S | HCl | 87 |
| **3t** | 6-OMe | $CH_2CH_2$ | 2′-Me,4′-F | R/S | HCl | 57 |
| **3u** | 6-OMe | $CH_2CH_2$ | 2′,4′,6′-Me | R/S | HCl | 140 |
| **4a** | 6-OMe | $CH_2CH_2$ | 2′-Me | R | HCl | >10000 |
| **4b** | 6-OMe | $CH_2CH_2$ | 2′-Me | S | HCl | 46 |
| **4c** | 6-NHAc | $CH_2CH_2$ | 2′-Me | R[a] | free | >10000 |
| **4d** | 6-NHAc | $CH_2CH_2$ | 2′-Me | S[a] | free | 31 |
| **4e** | 6-OMe | $CH_2CH_2$ | 4′-F | R | HCl | >10000 |
| **4f** | 6-OMe | $CH_2CH_2$ | 4′-F | S | HCl | 64 |
| **4g** | 6-OMe | $CH_2CH_2$ | 3′-F | S | HCl | 370 |
| **4h** | 6-OMe | $CH_2CH_2$ | 2′-F | S | HCl | 160 |
| **4i** | 6-OMe | $CH_2CH_2$ | 2′-OMe | S | HCl | 83 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **4j** | 6-OMe | $CH_2CH_2$ | 3′-OMe | S | HCl | 1100 |
| **4k** | 6-OMe | $CH_2CH_2$ | 4′-OMe | S | HCl | 1800 |

[a] Estimated based on retention time order, specific optical rotation, and in vitro activity in a comparison with **4a** and **4b**.

First of all, the 1,3-dihydro-5*H*-benzo[*cd*]indole-5-one skeleton of **1** was replaced by a 1,3-dihydro-5*H*-dihydronaphthalene-5-one skeleton to simplify its chemical structure for SAR analysis based on a docking analysis of **1** and the $H^+$,$K^+$-ATPase model. The result revealed that such a conversion maintained the enzymatic inhibitory potency of **1** (**1**: $IC_{50}$ = 1600 nM, **3a**: $IC_{50}$ = 1000 nM). The introduction of a methyl group at position 2 on the benzene ring of the phenethyl side chain (R') or a methoxy group at position 6 on the benzene ring of 1,3-dihydro-5*H*-dihydronaphthalene-5-one (R) increased the activity (**3b**: $IC_{50}$ = 290 nM, **3c**: $IC_{50}$ = 290 nM). On the other hand, the modification of the ethylene linker (X) between the skeleton and phenyl of the side chain caused a big loss of activity irrespective of length, type, and other parameters (**3d, 3e, 3g–j** vs. **3c**) except for propylene linkers (**3f**). The combination of the methoxy group at the sixth position on the benzene ring of 1,3-dihydro-5*H*-dihydronaphthalene-5-one, ethylene linker (X), and a methyl group at position 2′ on the benzene ring of the phenethyl side chain had a synergistic effect on the in vitro inhibitory activity (**3k**: $IC_{50}$ = 82 nM).

As for the optimization of the R moiety of **3k**, the shift of the methoxy group at position 6 of **3k** to position 5, 7, or 8 decreased the activity, and the conversion of the methoxy group at position 6 of **3k** to an acetylamide group yielded stronger potency (**3o**: $IC_{50}$ = 45 nM) whereas both the cyano group and phenyl group led to a big loss of activity (**3p** and **3q**: $IC_{50}$ = >10000 nM). As for the substituent (R) on the benzene ring of the 1,3-dihydro-5*H*-dihydronaphthalene-5-one skeleton, introduction of small substituents at position 6 (except for electron-withdrawing groups, which could directly affect the role of the carbonyl group in the activity by electronic effects) seems to be the most favorable for a potent activity. As a matter of fact, the reduction of carbonyl group at position 1 to a hydroxyl group or methylene caused a big loss of activity (data were not shown); hence, the carbonyl group must play an

important role in the interaction with the enzyme via a water molecule and stabilization of active conformation although the docking analysis could not explain the reason very well.

On the other hand, regarding the substituent (R'), the conversion of the methyl group at position 2′ on the benzene ring of the phenethyl side chain of **3k** into a chloro group at position 2′ or a fluoro group at position 4′ also maintained the potency (**3r**: $IC_{50}$ = 170 nM, **3s**: $IC_{50}$ = 87 nM). The compounds with these multiple substituents on the benzene ring of the phenethyl side chain such as 2′-methyl-4′-fluoro or 2′,4′,6′-trimethyl derivatives also showed the similar activity (**3t**: $IC_{50}$ = 57 nM, **3u**: $IC_{50}$ = 140 nM).

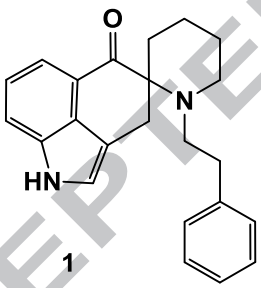
For the purpose of determining the absolute configuration of the eutomer, we synthesized both enantiomers of the key compounds. As a result, the optical derivatives having the *S* absolute configuration at position 2 in the 3,4-dihydro-1*H*-spiro(naphthalene-2,2′-piperidin)-1-one skeleton (**4b**, **4d**, and **4f**) had approximately twice stronger inhibitory activities than their racemates did (**3k**, **3o**, and **3s**), whereas the enantiomers having the R absolute configuration (**4a**, **4c**, and **4e**) showed a (complete) big loss of activity. Therefore, we continued the optimization of substituents (R') by synthesizing optical active derivatives having the *S* absolute configuration. The shift of fluoro group at position 4′ on the benzene ring of phenethyl side chain of **4f** to the 3′ and 2′ positions (**4g, 4h**) yielded a slight loss of activity. The conversion of the methyl group at the 2′ position on the benzene ring of phenethyl side chain of **3k** into a methoxy group maintained the activity (**4i**), but the shift of the methoxy group at the 2′ position on the benzene ring to the 3′ and 4′ positions decreased the potency (**4j, 4k**). As for the substituent (R') on the benzene ring of the phenethyl side chain, introduction of substituents at the 2′ position seems to be the most favorable for the activity.

The docking analysis of compound **4b** using a homology model of the luminal region of $H^+$,$K^+$-ATPase, which was constructed from the crystal structure of $Ca^{2+}$-ATPase (PDB ID, 1IWO[8]) by means of SCWRL ver. 2.9,[9] is shown in Figure 2. Both lipophilic pockets LP-1 and LP-2 were sufficiently occupied by the substituted phenethyl side chain and 1,3-dihydro-5*H*-dihydronaphthalene-5-one

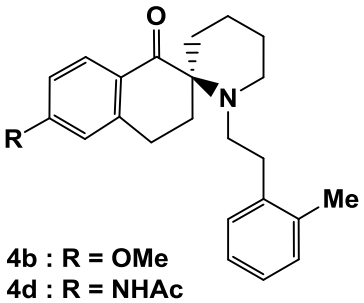
skeleton, respectively. The docking analysis of both configurations at position 2 also indicated that the *S*-configuration can be more favorable than the R-configuration (data not shown).

Some representative compounds were studied regarding their inhibitory effects on histamine-induced gastric acid secretion in anesthetized rats (Table 3). The in vivo experiment was conducted by intravenous administration of the compound at 1, 3, or 10 mg/kg, and the total acid output for 3 h after the histamine injection was compared with that obtained after administration of the vehicle. In addition, their concentrations were measured in the rat plasma and stomach after intravenous administration at a dose of 0.2 mg/kg as free compounds.

**Table 3** Inhibitory effects of compounds **1**, **4b**, and **4d** on histamine-induced gastric acid secretion in anesthetized rats (in vivo) and concentrations in rat plasma and stomach after intravenous administration at a dose of 0.2 mg/kg as free compounds.




**1**




**4b : R = OMe**
**4d : R = NHAc**

| compd. | $AUC_{0-24h}$[a] (plasma, ng·h/mL) | $AUC_{0-24h}$[a] (stomach, ng·h/g) | in vitro $H^+,K^+$-ATP inhibitory activity ($IC_{50,}$ nM) | in vivo acid secretion in rats (1 mg/kg, i.v., % inhibition) |
|---|---|---|---|---|
| **1** | 71 | 1171 | 1600 | 71 (10 mg/kg, i.v.) |
| **4b** | 74 | 3035 | 46 | 87 |
| **4d** | 68 | 15131 | 31 | 95 |

[a] Calculated from the concentration at 10 min, 1 h, 4 h, and 24 h after administration.

Optically active compound **4b**, which had more than 30-fold stronger in vitro activity and twofold higher concentration in the stomach than those of racemic compound **1**, showed considerably higher potency of the in vivo inhibitory activity (87% inhibition at 1 mg/kg) than that of **1** (71% inhibition at 10 mg/kg). Furthermore, the conversion of the methoxy group at position 6 on the benzene ring of the 1,3-dihydro-5*H*-dihydronaphthalene-5-one skeleton of **4b** into an acetylamide group (**4d**) improved not only in vitro activity 1.5-fold but also the concentration in the stomach fivefold. As expected, **4d** showed a significantly more potent in vivo inhibitory activity (95% inhibition at 1 mg/kg) than **4b** did.

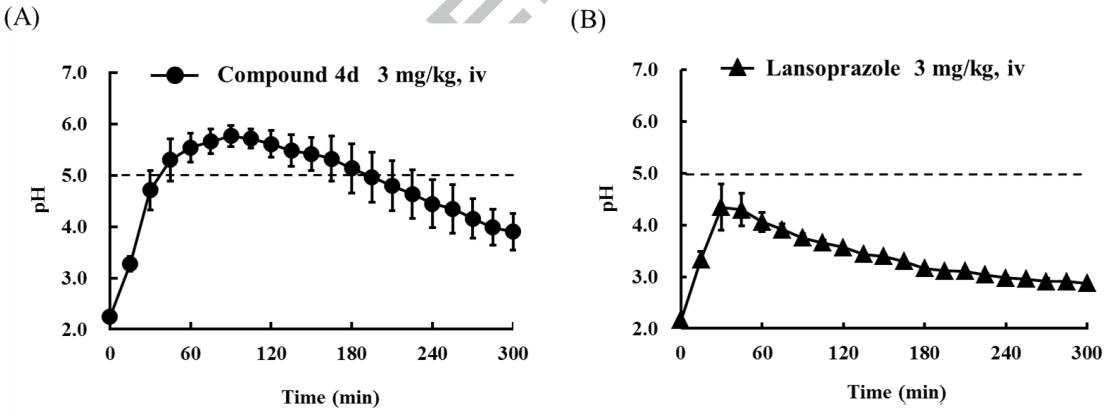



**Figure 3.** Effects of intravenous administration of compound **4d** (A) and lansoprazole (B)[11] on pH of a gastric perfusate under conditions of histamine stimulation in anesthetized rats. Intravenous administration of **4d** at 3 mg/kg increased pH to ~6.0 in anesthetized rats with a rapid onset and moderate duration after the administration.

Intravenous administration of lansoprazole, as a representative PPI, at 3 mg/kg increased pH of the

gastric perfusate to ~4.5 during histamine stimulation in anesthetized rats as reported in our previous paper (Figure 3B[11]), whereas intravenous administration of **4d** at 3 mg/kg increased pH of the gastric perfusate to ~6.0 as shown in Figure 3A. In addition to the effectiveness at pH elevation in the gastric perfusate, **4d** showed a rapid onset of action and its effect was sustained until 5 h after the administration (Figure 3). Although **4d** (log D = 3.56) showed not only much lower ligand-lipophilicity efficiency but also lower potency as compared to **TAK-438** did (log D = 0.4, $IC_{50}$ = 19 nM, 98% inhibition at 1 mg/kg)[5], these findings suggested that our 3,4-dihydro-1*H*-spiro[naphthalene-2,2′-piperidin]-1-one derivatives could be further optimized as a P-CAB for the treatment of GERD, peptic ulcer, or other acid-related diseases.

The docking analysis using a homology model of the luminal region of $H^+$,$K^+$-ATPase indicated that any significant interactions except for lipophilic pockets LP-1 and LP-2 can not be observed (Figure 2). Therefore, it might be able to find a more excellent P-CAB by introducing polar groups aimed for new ionic interactions.

## 4. Conclusion

We synthesized a series of 3,4-dihydro-1*H*-spiro[naphthalene-2,2′-piperidin]-1-one derivatives and evaluated their SAR for inhibitory activities on $H^+$,$K^+$-ATPase in vitro. Our results show that the *N*-phenethyl side chain is the most suitable for potency; introduction of both substituents into the benzene ring of 1,3-dihydro-5*H*-dihydronaphthalene-5-one (R) and into the benzene ring of the phenethyl side chain (R') dramatically increased in vitro activity. As shown in a docking model of **4b** with $H^+$,$K^+$-ATPase, 3,4-dihydro-1*H*-spiro[naphthalene-2,2′-piperidin]-1-one derivatives can occupy both important lipophilic pockets (LP-1 and LP-2) very well and the absolute configuration of 3,4-dihydro-1*H*-spiro[naphthalene-2,2′-piperidin]-1-one derivatives with the *S*-enantiomer should be related to the active conformation. In addition, acetamide derivative **4d** showed not only a stronger in

vitro activity but also a much higher concentration in the stomach than enantiomer **4b** did, resulting in potent inhibitory actions on histamine-stimulated gastric acid secretion in rats. Intravenous administration of **4d** at 3 mg/kg increased pH of the gastric perfusate to ~6.0 in anesthetized rats with a rapid onset and moderate duration after the administration. These findings may lead to a new insight into the drug design of P-CABs.

## 5. Experimental Section

### *5.1. General*

Melting points (mp) were determined on a Yanagimoto micro melting point apparatus or Buchi melting point apparatus and are uncorrected. Proton nuclear magnetic resonance ($^1$H-NMR) spectra were recorded on a Varian Mercury-300, a Jeol JNM-AL400 or a Bruker AV-300 M spectrometer. Chemical shifts were reported in δ value (ppm) with tetramethylsilane as an internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; dd, double doublet; br s, broad singlet; m, multiplet. Coupling constants (*J*) are reported in hertz (Hz). Elemental analyses (C, H, N) and specific optical rotation were carried out by Takeda Analytical Research Laboratories, Ltd, and the results were within 0.4% of theoretical values. Thin-layer chromatography (TLC) analyses were performed with silica gel 60 $F_{254}$ plate (Merck Art. 5715), alumina 60 $F_{254}$ plate (Type E) and NH TLC plates (Fuji Silysia Chemical Ltd.). Chromatographic separations were performed with Merck Aluminium oxide 90 (basic, activity III) and NH silica gel (Fuji Silysia Chemical Ltd.).

### *5.2. (2RS)-1-Benzoylpiperidine-2-carbonitrile (**6**)*

To a solution of **5** (10.0 g, 42.9 mmol) in THF (90 mL) were added $Et_3N$ (6.70 mL, 47.2 mmol) and a solution of ethyl chloroformate (5.28 g, 47.2 mmol) at –20 to –15 °C. After stirring at –20 to –15 °C for 30 min, 28–30% aqueous $NH_3$ (20.2 mL, 300 mmol) was added to the mixture. This mixture was stirred

at rt for 3 h, and then, concentrated under reduced pressure. The residue was partitioned between $H_2O$ (30 mL) and EtOAc (100 mL). The separable aqueous layer was extracted with EtOAc (100 mL x 2). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was washed with $Et_2O$ to obtain (2*RS*)-1-Benzoylpiperidine-2-carboxamide (6.11 g, 61%) as white powder. Furthermore, the recrystallization from n-hexane/EtOAc gave colorless prism: mp 172 °C (n-hexane/EtOAc); $^1$H-NMR ($CDCl_3$) δ 1.24–1.97 (5H, m), 2.33 (1H, d, *J* = 12.9 Hz), 3.07 (1H, dd, *J* = 13.3 Hz), 3.72 (1H, d, *J* = 12.9 Hz), 5.27 (1H, brs), 5.43 (1H, brs), 6.44 (1H, brs), 7.44 (5H, s); IR (KBr) cm$^{-1}$ 3331, 3198, 3061, 2939, 2862, 1691, 1682, 1668, 1653, 1622, 1599, 1578, 1495, 1445, 1435, 1393, 1369, 1352, 1313, 1285, 1271, 1238, 1184, 1142, 1099, 1076, 1038, 1007, 926, 907; Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.76; H, 7.02; N, 12.04.

To a solution of (2*RS*)-1-Benzoylpiperidine-2-carboxamide (5.90 g, 25.4 mmol) in THF (110 mL) were added pyridine (3.50 mL, 43.2 mmol) and $POCl_3$ (3.60 mL, 38.1 mmol) at 0 °C. The mixture was stirred at rt for 10 h, and then, DMF (100 mL) was added to the mixture. After stirring at rt for 13 h and at 80 °C for 4 h, the reaction was quenched by the addition of 1 N NaOH (100 mL). This mixture was extracted with EtOAc (100 mL). The separable organic layer was washed with 2 N HCl (100 mL), $H_2O$ (50 mL), brine (50 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was purified by column chromatography ($SiO_2$, n-hexane/EtOAc = 1/0–4/1) to obtain **6** (1.86 g, 34%) as yellow oil: $^1$H-NMR ($CDCl_3$) δ 1.33–2.27 (6H, m), 3.12–3.44 (1H, m), 3.88 (1H, brs), 5.79 (1H, brs), 7.36–7.56 (5H, m); IR (KBr) cm$^{-1}$ 3510, 3061, 3028, 3000, 2943, 2862, 2237, 1651, 1601, 1578, 1493, 1464, 1447, 1408, 1371, 1354, 1339, 1319, 1273, 1234, 1177, 1144, 1134, 1103, 1076, 1032, 999, 928, 901; LC/MS (ESI) *m/z* 216 $(M+H)^+$.

### *5.3. (2RS)-1-Benzoyl-2-(2-phenylethyl)piperidine-2-carbonitrile (**7a**)*

To a solution of **6** (9.40 g, 43.9 mmol) and phenethyl iodide (15.58 g, 65.8 mmol) in THF (2200 mL)

was added LDA (42.7 mL, 76.8 mmol) at –78 °C under $N_2$ atmosphere for 15 min. After stirring at –78 to 0 °C for 1.5 h and at rt for 1.5 h, the reaction was quenched by the addition of $H_2O$ (100 mL). This mixture was extracted with EtOAc (200 mL). The separable organic layer was washed with sat. $Na_2S_2O_3$ (20 mL)/$H_2O$ (100 mL), $H_2O$ (100 mL), brine (50 mL), and dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was purified by column chromatography ($SiO_2$, *n*-hexane/EtOAc = 1/0–4/1) to produce **7a** (11.48 g, 82%) as pale yellow oil. $^1$H-NMR ($CDCl_3$) δ 1.56–1.99 (4H, m), 2.15–2.23 (2H, m), 2.38–2.54 (1H, m), 2.54–2.70 (1H, m), 2.76 (1H, ddd, *J* = 12.9, 12.1, 4.9 Hz), 2.89 (1H, ddd, *J* = 12.9, 12.1, 4.5 Hz), 3.37 (1H, ddd, *J* = 14.0, 8.3, 4.2 Hz), 3.49 (1H, ddd, *J* = 14.0, 6.4, 4.5 Hz), 7.13–7.33 (5H, m), 7.34–7.48 (3H, m), 7.48–7.56 (2H, m).

*5.4. (2RS)-1-Benzoyl-2-[2-(4-methoxyphenyl)ethyl]piperidine-2-carbonitrile (**7b**)*

**6** (5.00 g, 23.3 mmol), *p*-methoxyphenethyl iodide (9.17 g, 35.0 mmol), LDA (20.5 mL, 40.8 mmol) and THF (120 mL) were used as previously described for **7a**. The crude product was purified by column chromatography ($SiO_2$, n-hexane/EtOAc = 1/0–4/1) to produce **7b** (7.02 g, 85%) as pale yellow oil. $^1$H-NMR ($CDCl_3$) δ 1.49–2.00 (4H, m), 2.08–2.23 (2H, m), 2.43 (1H, ddd, *J* = 13.2, 12.2, 5.3 Hz), 2.58 (1H, ddd, *J* = 13.2, 11.7, 4.9 Hz), 2.70 (1H, ddd, *J* = 13.0, 11.7, 5.3 Hz), 2.83 (1H, ddd, *J* = 13.0, 12.2, 4.9 Hz), 3.36 (1H, ddd, *J* = 13.9, 8.5, 4.3 Hz), 3.49 (1H, ddd, *J* = 13.9, 6.4, 4.5 Hz), 3.77 (3H, s), 6.82 (2H, ddd, *J* = 9.4, 2.8, 2.3 Hz), 7.14 (2H, ddd, *J* = 9.4, 2.8, 2.1 Hz), 7.38–7.48 (3H, m), 7.48–7.55 (2 H, m); IR (KBr) cm$^{-1}$ 3061, 3028, 2999, 2947, 2866, 2835, 2233, 1659, 1651, 1645, 1612, 1582, 1514, 1493, 1464, 1447, 1404, 1394, 1354, 1302, 1267, 1248, 1115, 1074, 1034, 1001, 978, 953, 928, 914; LC/MS (ESI) *m/z* 349 $(M+H)^+$.

*5.5. (2RS)-1-Benzoyl-2-[2-(3-methoxyphenyl)ethyl]piperidine-2-carbonitrile (**7c**)*

**6** (5.00 g, 23.3 mmol), *p*-methoxyphenethyl iodide (9.17 g, 35.0 mmol), LDA (20.5 mL, 40.8 mmol)

and THF (50 mL) were used as previously described for **7a**. The crude product was purified by column chromatography ($SiO_2$, n-hexane/EtOAc = 3/1–2/1) to obtain **7c** (6.02 g, 73%) as yellow brown oils. $^1$H-NMR ($CDCl_3$) δ 1.40–2.00 (4H, m), 2.15–2.21 (2H, m), 2.40–2.95 (4H, m), 3.34–3.55 (2H, m), 3.79 (3H, s), 5.73–5.90 (2H, m), 7.16–7.52 (7H, m).

*5.6. (2RS)-1-Benzoyl-2-[2-(2-methoxyphenyl)ethyl]piperidine-2-carbonitrile (**7d**)*

**6** (5.00 g, 23.3 mmol), *o*-methoxyphenethyl iodide (9.17 g, 35.0 mmol), LDA (20.5 mL, 40.8 mmol) and THF (120 mL) were used as previously described for **7a**. The crude product was purified by column chromatography ($SiO_2$, n-hexane /EtOAc = 1/0–4/1) to obtain **7d** (6.30 g, 78%) as pale yellow oil. $^1$H-NMR ($CDCl_3$) δ 1.59–1.95 (4H, m), 2.13–2.34 (2H, m), 2.36–2.60 (2H, m), 2.70–2.96 (2H, m), 3.34 (1H, ddd, *J* = 13.8, 9.2, 4.5 Hz), 3.50 (1H, ddd, *J* = 13.8, 5.7, 4.7 Hz), 3.81 (3H, s), 6.84 (1H, d, *J* = 8.3 Hz), 6.84–6.92 (1H, m), 7.18 (1H, d, *J* = 7.3 Hz), 7.18–7.23 (1 H, m), 7.37–7.49 (3H, m), 7.50–7.55 (2H, m); IR (KBr) $cm^{-1}$ 3061, 2999, 2943, 2868, 2837, 2233, 1663, 1651, 1601, 1587, 1580, 1495, 1462, 1454, 1447, 1394, 1385, 1350, 1339, 1269, 1244, 1204, 1177, 1161, 1115, 1074, 1049, 1028, 1001, 978, 953, 912; LC/MS (ESI) *m/z* 349 $(M+H)^+$.

*5.7. (2RS)-3,4-Dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one (**8a**)*

To a solution of **7a** (1.07 g, 3.36 mmol) in toluene (16 mL) was added $AlCl_3$ (1.14 g, 8.40 mmol) at rt. After stirring at 85 °C for 5 h, the reaction was quenched by the addition of 1 N HCl (50 mL). The precipitate was collected off, and washed with 1 N HCl (20 mL × 3), $H_2O$ (20 mL × 3), $Et_2O$ (20 mL × 3) to obtain white powder (686 mg). This powder was dissolved in MeOH/THF = 1/1 (64 mL), and 8 N NaOH (16 mL) was added to the mixture. After stirring at 85 °C for 2 days, the reaction mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc (50 mL) and $H_2O$ (30 mL). The separable organic layer was washed with $H_2O$ (50 mL), brine (50 mL), and dried over $MgSO_4$,

filtered, concentrated under reduced pressure. The residue was purified by column chromatography ($NHSiO_2$, n-hexane /EtOAc = 1/0–9/1) to obtain **8a** (245 mg, 34%) as pale yellow oil. $^1$H-NMR ($CDCl_3$) δ 1.35–1.90 (7H, m), 2.04 (1H, ddd, *J* = 13.8, 9.2, 6.4 Hz), 2.42 (1H, ddd, *J* = 13.8, 5.1 Hz), 2.86 (1H, ddd, *J* = 13.1, 9.1, 3.9 Hz), 2.95–3.04 (2H, m), 3.07 (1H, ddd, *J* = 13.1, 4.9, 4.7 Hz), 7.22 (1H, d, *J* = 7.5 Hz), 7.30 (1H, dd, *J* = 7.7, 7.5 Hz), 7.46 (1H, ddd, *J* = 7.7, 7.5, 1.4 Hz), 8.02 (1H, dd, *J* = 7.7, 1.4 Hz); IR (KBr) $cm^{-1}$ 3319, 3063, 3024, 2930, 2862, 1682, 1601, 1483, 1454, 1435, 1356, 1339, 1327, 1306, 1286, 1271, 1223, 1198, 1167, 1155, 1128, 1101, 1082, 1055, 995, 978, 949, 932, 901; LC/MS (ESI) *m/z* 216 $(M+H)^+$.

*5.8. (2RS)-7-Methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one (**8b**)*

**7b** (7.02 g, 2.01 mmol), $AlCl_3$ (6.85 g, 50.4 mmol), toluene (100 mL), 8 N NaOH (100 mL), THF (50 mL), and MeOH (100 mL) were used as previously described for **8a**. The crude product was purified by column chromatography ($NHSiO_2$, n-hexane/EtOAc = 1/0–4/1%) to obtain **8b** (260 mg, 5%) as red oil. $^1$H-NMR ($CDCl_3$) δ 1.37–1.62 (3H, m), 1.62–1.84 (3H, m), 1.93–2.07 (1H, m), 2.41 (1H, ddd, *J* = 13.8, 4.9, 4.9 Hz), 2.80–2.87 (1H, m), 2.88–2.96 (2H, m), 3.07 (1H, ddd, *J* = 13.4, 4.9, 4.7 Hz), 3.83 (3H, s), 7.04 (1H, dd, *J* = 8.3, 2.8 Hz), 7.13 (1H, d, *J* = 8.3 Hz), 7.49 (1H, d, *J* = 2.8 Hz); LC/MS (ESI) *m/z* 246 $(M+H)^+$.

*5.9. (2RS)-8-Methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one (**8c**)*

To a solution of **7c** (1.0 g, 2.9 mmol) in toluene (10 mL) was added $CF_3CO_2H$ (3 mL) at rt, and the mixture was stirring at rt for 4 h and concentrated under reduced pressure. The residue was dissolved in MeOH (10 mL), and 8 N NaOH (1 mL) was added to the mixture. After stirring at 120 °C for 18 h, the mixture was partitioned between EtOAc and $H_2O$. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, and dried over $Na_2SO_4$, filtered, concentrated under

reduced pressure. The residue was purified by column chromatography ($NHSiO_2$, n-hexane /EtOAc = 10/1–5/1) to obtain **8c** (0.05 g, 7%) as pale brown oil and **8d** (0.27 g, 35%). $^1$H-NMR ($CDCl_3$) δ 1.45–1.67 (4H, m), 1.75–1.81 (1H, m), 1.95–2.05 (3H, m), 2.18–2.26 (1H, m), 2.81–3.13 (4H, m), 3.89 (3H, s), 6.76–6.83 (2H, m), 7.36 (1H, d, *J* = 8.1 Hz).

*5.10. (2RS)-6-Methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one (**8d**)*

To a solution of **7c** (1.0 g, 2.9 mmol) in trifluorobenzene (10 mL) was added trimethylsilyl trifluoromethanesulfonate (2 g) in an ice-bath, and the mixture was stirring at rt for 18 h and concentrated under reduced pressure. The residue was dissolved in MeOH (30 mL), and 8 N NaOH (20 mL) was added to the mixture. After stirring at 130 °C for 48 h, the mixture was partitioned between EtOAc and $H_2O$. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, and dried over $Na_2SO_4$, filtered, concentrated under reduced pressure. The residue was purified by column chromatography ($NHSiO_2$, n-hexane /EtOAc = 10/1–5/1) to obtain **8d** (0.34 g, 48%) as pale brown oil. $^1$H-NMR ($CDCl_3$) δ 1.31–1.61 (3H, m), 1.61–1.85 (3H, m), 2.02 (2H, ddd, *J* = 13.8, 9.2, 6.6 Hz), 2.42 (1H, ddd, *J* = 13.8, 4.9, 4.9 Hz), 2.84 (1H, ddd, *J* = 13.4, 9.7, 3.8 Hz), 2.91–3.00 (2H, m), 3.07 (1H, ddd, *J* = 13.4, 4.6, 4.6 Hz), 3.84 (3H, s), 6.67 (1H, d, *J* = 2.4 Hz), 6.83 (1H, dd, *J* = 8.7, 2.5 Hz), 7.99 (1H, d, *J* = 8.7 Hz); IR (KBr) $cm^{-1}$ 3319, 3001, 2926, 2860, 1672, 1599, 1572, 1495, 1462, 1450, 1356, 1340, 1304, 1258, 1227, 1157, 1130, 103, 1082, 1053, 1030, 997, 980. 963, 905; LC/MS (ESI) *m/z* 246 $(M+H)^+$.

*5.11. (2RS)-2-Bromo-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (**10a**)*

To a solution of 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**9a**, 35.6 g, 200 mmol) in THF (600 mL) was added a solution of phenyltrimethylammonium tribromide (76.4 g, 200 mmol) in THF (400 mL) at –78 °C for 1 h under $N_2$ atmosphere. After stirring at –78 °C to room temperature (rt) for 4 h and at rt for 12 h., the precipitation was collected off and washed with EtOAc. The filtrate was concentrated under

reduced pressure. The residue was cooled with refrigerator. The precipitation was collected off and washed with $iPr_2O$ to obtain **10a** (42.9 g, 84%) as white powder. Furthermore, the recrystallization form n-hexane/$iPr_2O$ gave colorless plate. $^1$H-NMR ($CDCl_3$) δ 2.33–2.60 (2H, m), 2.87 (1H, ddd, *J* = 17.0 Hz, 4.5 Hz, 4.2 Hz), 3.30 (1H, ddd, *J* = 17.0 Hz, 9.8 Hz, 6.1 Hz), 3.87 (3H, s), 4.69 (1H, dd, *J* = 4.2 Hz, 4.2 Hz), 6.72 (1H, d, *J* = 2.7 Hz), 6.87 (1H, dd, *J* = 9.1 Hz, 2.7 Hz), 8.07 (1H, d, *J* = 9.1 Hz); IR (KBr) $cm^{-1}$ 3007, 2943, 2909, 2839, 1680, 1599, 1568, 1495, 1462, 1454, 1443, 1435, 1429, 1352, 1319, 1302, 1261, 1215, 1194, 1159, 1124, 1113, 1086, 1034, 1016, 995, 930; Anal. Calcd for $C_{11}H_{11}O_2Br$: C, 51.79; H, 4.35. Found: C, 51.75; H, 4.28.

*5.12. (2RS)-2-Bromo-5-methoxy-3,4-dihydronaphthalen-1(2H)-one (**10b**)*

To a solution of **9b** (4.96 g, 27.3 mmol) in THF (140 mL) were added phenyltrimethylammonium tribromide (11.00 g, 28.7 mmol) at rt under $N_2$ atmosphere. After stirring at rt for 2 h, the precipitate was collected off, and washed with EtOAc. The filtrate was washed with sat. $Na_2S_2O_3$ (20 mL)/$H_2O$ (100 mL), $H_2O$ (50 mL), brine (50 mL), and dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was washed with $iPr_2O$ to obtain **10b** (3.99 g, 57%) as white powder. Furthermore, the recrystallization from with $iPr_2O$ gave white powder: mp 93 °C (n-hexane/$iPr_2O$); $^1$H-NMR ($CDCl_3$) δ ppm 2.45–2.54 (2H, m), 3.02 (2H, dd, *J* = 6.1, 6.1 Hz), 3.88 (3H, s), 4.71 (1H, dd, *J* = 4.5, 4.2 Hz), 7.06 (1H, d, *J* = 8.0 Hz), 7.32 (1H, dd, *J* = 8.0, 8.0 Hz), 7.70 (1H, d, *J* = 8.0 Hz); IR (KBr) $cm^{-1}$ 3003, 2949, 2901, 2837, 1688, 1597, 1582, 1474, 1456, 1437, 1346, 1315, 1300, 1283, 1261, 1211, 1196, 1186, 1151, 1123, 1082, 1063, 1032, 995, 922; LC/MS (ESI) *m/z* 255 $M^+$, 257 $(M+2)^+$.

*5.13. (2RS)-N-(6-Methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (**11a**)*

To a solution of **10a** (42.9 g, 168 mmol) in DMF (850 mL) were added AcOH (21.2 mL, 370 mmol) and a solution of $NaN_3$ (22.3 g, 336 mmol) in $H_2O$ (70 mL) at from –15 °C to –5 °C. After stirring at

from –15 °C to 0 °C for 6 h, the reaction was quenched by the addition of $H_2O$ (1 L). Precipitation was collected off and washed with EtOAc. The filtrate was concentrated under reduced pressure. The residue was cooled with refrigerator to produce precipitation, which was collected off and washed with $iPr_2O$ to obtain crude azide compound (38.1 g) as white powder.

This material was dissolved in THF (850 mL). To the solution were added $Ac_2O$ (24.6 mL, 252 mmol) and 10% Pd/C (15.2 g, 40 %w/w) at 0 °C. After stirring at rt for 16 h under $H_2$ atmosphere, the mixture was filtered with Celite. To the filtrate was added 10% Pd/C (15.2 g, 40 %w/w) at rt. After stirring at rt for 8 h under $H_2$ atmosphere, the mixture was filtered with Celite. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on $SiO_2$ with n-hexane/EtOAc (1/5–0/1) as eluent to obtain **11a** (13.54 g, 35% in 2 steps) as white powder. Furthermore, the recrystallization form n-hexane/EtOAc gave white needle: mp 151.2–151.3 °C; $^1$H-NMR ($CDCl_3$) δ 1.85 (1H, dddd, *J* = 14.0 Hz, 13.4 Hz, 12.4 Hz, 4.3 Hz), 2.09 (3H, s), 2.80 (1H, dddd, *J* = 12.4 Hz, 4.9 Hz, 4.5 Hz, 2.5 Hz), 2.95 (1H, ddd, *J* = 17.1 Hz, 4.3 Hz, 2.5 Hz), 3.24 (1H, ddd, *J* = 17.1 Hz, 13.0 Hz, 4.5 Hz), 3.87 (3H, s), 4.57 (1H, ddd, *J* = 13.4 Hz, 5.1 Hz, 4.9 Hz), 6.63 (1H, brs), 6.71 (1H, d, *J* = 2.4 Hz), 6.85 (1H, dd, *J* = 8.9 Hz, 2.5 Hz), 7.99 (1H, d, *J* = 8.9 Hz); IR (KBr) cm$^{-1}$ 3277, 3069, 2943, 2839, 1680, 1651, 1601, 1568, 1551, 1537, 1497, 1464, 1454, 1447, 1433, 1373, 1335, 1319, 1250, 1213, 1155, 1109, 1097, 1051, 1028, 924, 910; LC/MS (ESI) m/z 234 $(M+H)^+$; Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.86; H, 6.42; N, 6.00.

*5.14. (2RS)-1'-Acetyl-6-methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one (**12a**)*

To a solution of **11a** (6.94 g, 29.8 mmol) in DMF (150 mL) were added 1,4-dibromobutane (18.9 mL, 155 mmol) and NaH (40%, 3.14 g, 65.5 mmol) at –78 °C under $N_2$ atmosphere. After stirring at from –78 °C to rt for 2 h and rt for 3 h, the reaction was quenched by the addition of $H_2O$ (100 mL). This mixture was extracted with EtOAc (100 mL × 4) and $CHCl_3$ (100 mL ×2). The combined organic layers

were dried order $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography ($SiO_2$, n-hexane/EtOAc) to obtain **12a** (6.53 g, 76%) as white powder. Furthermore, the recrystallization form n-hexane/EtOAc gave pale purple plate: mp 122–126 °C; $^1$H-NMR ($CDCl_3$) δ 1.50–1.66 (1H, m), 1.71–1.86 (3H, m), 1.89–2.01 (1H, m), 2.06 (3H, s), 2.07–2.16 (1H, m), 2.58 (1H, ddd, *J* = 13.0 Hz, 12.8 Hz, 5.1 Hz), 2.72–3.06 (2H, m), 3.16–3.40 (1H, m), 3.69–3.80 (1H, m), 3.83 (3H, s), 6.63 (1H, d, *J* = 2.4 Hz), 6.84 (1H, dd, *J* = 8.7 Hz, 2.5 Hz), 8.09 (1H, d, *J* = 8.7 Hz); IR (KBr) cm$^{-1}$ 3015, 2941, 2866, 1682, 1651, 1634, 1601, 1574, 1495, 1470, 1462, 1454, 1445, 1435, 1427, 1416, 1402, 1398, 1356, 1346, 1337, 1273, 1250, 1225, 1194, 1163, 1142, 1128, 1113, 1105, 1074, 1030, 1001, 972, 941, 908; LC/MS (ESI) *m/z* 288 $(M+H)^+$; Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 71.01; H, 7.31; N, 4.85.

*5.15. (2RS)-1'-Acetyl-5-methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one (**12b**)*

To a solution of **10b** (3.90 g, 15.3 mmol) in DMF (150 mL) were added AcOH (1.95 mL, 33.6 mmol) and a solution of $NaN_3$ (2.03 g, 30.6 mmol) in $H_2O$ (14 mL) at –15 to –10 °C under $N_2$ atmosphere. After stirring at –15 to 0 °C for 4 h, the reaction was quenched by the addition of ice. The precipitate was collected off, and washed with $H_2O$ (20 mL ×3) and $iPr_2O$ (20 mL × 3) to obtain crude azide (2.98 g, 90%) as white powder. This material was used on next step without further purification.

To a solution of crude azide (2.83 g, 13.0 mmol) in THF (60 mL) were added $Ac_2O$ (2.55 mL, 26.1 mmol) and 10% Pd/C (849 mg, 30 %w/w) at rt. After stirring at rt for 1 day under $H_2$ atmosphere, the mixture was filtered with Celite®. The filtrate was concentrated under reduced pressure. The residue was washed with $iPr_2O$ (10 mL × 2) to produce red power. Furthermore, recrystallization from n-hexane/EtOAc gave (2*RS*)-*N*-(5-Methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (**11b**) as red powder (1.84 g).

To a suspension of 50–72% NaH (788 mg, 16.4 mmol) in DMF (30 mL) were added 1,4-dibromobutane

(4.75 mL, 38.8 mmol) and a solution of **11b** (1.74 g, 7.46 mmol) in DMF (10 mL) at 0 ℃ under $N_2$ atmosphere. After stirring at 0 ℃ to rt for 1 h and at rt for 3 h, the reaction was quenched by the addition of 1 N HCl (50 mL). This mixture was extracted with EtOAc (100 mL × 2). The combined organic layers were washed with $H_2O$ (50 mL), brine (50 mL), and dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was by column chromatography ($SiO_2$, n-hexane/EtOAc = 3/2–2/3) to obtain **12b** (1.03 g, 48%) as white powder. Furthermore, recrystallization from n-hexane/EtOAc gave colorless prism: mp 130–133 °C (n-hexane/EtOAc); $^1$H-NMR ($CDCl_3$) δ 1.54–1.68 (1H, m), 1.70–1.86 (4H, m), 1.90–2.20 (2H, m), 2.05 (3H, s), 2.40–2.70 (2H, m), 2.93–3.16 (1H, m), 3.22–3.33 (1H, m), 3.69–3.79 (1H, m), 3.84 (3H, s), 6.97 (1H, d, *J* = 7.6 Hz), 7.28 (1H, dd, *J* = 7.6, 7.6 Hz), 7.74 (1H, d, *J* = 7.6 Hz); IR (KBr) cm$^{-1}$ 3071, 2941, 2864, 1691, 1682, 1643, 1634, 1583, 1470, 1439, 1414, 1402, 1344, 1315, 1288, 1259, 1225, 1184, 1167, 1146, 1119, 1101, 1057, 1036, 1005, 970, 951, 908; LC/MS (ESI) *m/z* 288 $(M+H)^+$; Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.56; H, 7.32; N, 4.65.

*5.16. (2RS)-6-Methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one (**8d**)*

To a solution of **12a** (6.53 g, 22.7 mmol) in EtOH (150 mL) was added cHCl (50.0 mL) at rt. After stirring under reflux for 3 days, the reaction mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc (200 mL) and 1 N NaOH (200 mL). The separable organic layer was washed with brine (100 mL), dried over, $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography ($SiO_2$ , n-hexane/EtOAc = 1/0–0/1) to obtain **8d** (3.58 g, 64%) as yellow oil, and to recover **12a** (1.84 g, 28%).

*5.17. 5-Methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one (**8e**)*

To a solution of **12b** (850 mg, 2.96 mmol) in EtOH (30 mL) was added *c*HCl (10 mL) at rt. After

stirring under reflux for 1 week, the reaction was quenched by the addition of 8 N NaOH (50 mL). This mixture was extracted with EtOAc (200 mL × 4). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was by column chromatography ($NHSiO_2$, n-hexane/EtOAc = 50/1–2/1) to obtain **8e** (297 mg, 41%) as yellow oil. $^1$H-NMR ($CDCl_3$) δ 1.36–1.62 (3H, m), 1.62–1.79 (3H, m), 1.90–2.02 (1H, ddd, *J* = 13.8, 10.0, 5.5 Hz), 2.42 (1H, ddd, *J* = 13.8, 5.1, 4.9 Hz), 2.67–2.81 (1 H, ddd, *J* = 18.5, 10.0, 5.5 Hz), 2.81–2.92 (1H, m), 2.94–3.05 (1H, m), 3.01–3.12 (1H, m), 3.86 (3H, s), 7.00 (1H, dd, *J* = 7.9, 0.9 Hz), 7.28 (1H, dd, *J* = 7.9, 7.9 Hz), 7.62 (1H, dd, *J* = 7.9, 0.9 Hz); LC/MS (ESI) *m/z* 246 $(M+H)^+$.

*5.18. (2S)-6-Methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one D-(R)-mandelate (**13a**).*

**8d** hydrochloride (5.2 g, 18.3 mmol) was partitioned between ethyl acetate and 0.1 N NaOH (400 mL), and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. to produce brown oils (4.73 g). To a solution of the oils in ethanol (100 mL) was added a solution of D-(*R*)-(-)-mandelic acid (2.78g, 18.3 mmol) in ethanol (100 mL) and diisopropylether (800 mL), and the mixture was stirred at rt for 18 h. The precipitation was filtered off to obtain **13a** (2.89 g, 40%) as white crystals: $^1$H-NMR ($CDCl_3$) δ 1.40–1.80 (6H, m), 2.12 (1H, dt, *J* = 5.7 Hz, 12.9 Hz), 2.30–2.36 (1H, m), 2.79–2.86 (1H, m), 2.92–3.04 (2H, m), 3.55–3.63 (1H, m), 3.87 (3H, s), 4.85 (1H, s), 5.71 (3H, brs), 6.64 (1H, d, *J* = 2.7 Hz), 6.86 (1H, dd, *J* = 2.4 Hz, 8.7 Hz), 7.05–7.15 (3H, m), 7.37 (2H, dd, *J* = 1.5 Hz, 7.5 Hz), 7.97 (1H, d, *J* = 8.4 Hz); Anal. Calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.46; H, 6.85; N, 3.54.

*5.19. (2R)-6-methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one L-(S)-mandelate (**13b**)*

The mother liquid of **13a** was partitioned between ethyl acetate and 0.1 N NaOH (300 mL), and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. to produce brown oils (2.71 g). To a solution of the oils in ethanol (50 mL) was added a solution of L-(*S*)-(+)-mandelic acid (1.68 g, 11.1 mmol) in ethanol (50 mL) and diisopropylether (400 mL), and the mixture was stirred at rt for 5 h. The precipitation was filtered off to obtain **13b** (3.02 g, 42%) as white crystals: $^1$H-NMR ($CDCl_3$) δ 1.40–1.80 (6H, m), 2.12 (1H, dt, *J* = 5.7 Hz, 12.9 Hz), 2.30–2.36 (1H, m), 2.79–2.86 (1H, m), 2.92–3.04 (2H, m), 3.55–3.63 (1H, m), 3.87 (3H, s), 4.85 (1H, s), 5.71 (3H, brs), 6.64 (1H, d, *J* = 2.7 Hz), 6.86 (1H, dd, *J* = 2.4 Hz, 8.7 Hz), 7.05–7.15 (3H, m), 7.37 (2H, dd, *J* = 1.5 Hz, 7.5 Hz), 7.97 (1H, d, *J* = 8.4 Hz); Anal. Calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.50; H, 6.83; N, 3.54.

*5.20. (2S)-6-Methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one (**14a**)*

**13a** (2.82 g, 7.10 mmol) was portioned between EtOAc and 0.2N NaOH, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed washed with brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to produce **14a** (1.8 g, ~100%) as pale brown oil. $[\alpha]_D^{20}$ +31.0° (c = 0.500, MeOH); 98.3% ee [colimm: CHIRALPAK OJ; mobile phase: n-hexane/EtOH/diethylamine (95/5/01)(v/v/v)].

*5.21. (2R)-6-Methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one (**14b**)*

**13b** (2.96 g) was portioned between EtOAc and 0.33N NaOH, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed washed with brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to produce **14a** (1.88 g, ~100%) as pale brown oil. $[\alpha]_D^{20}$ –32.7° (c = 0.505, MeOH); 99.7% ee [colimm: CHIRALPAK OJ; mobile phase: n-hexane/EtOH/diethylamine (95/5/01)(v/v/v)].

*5.22. 1'-(2-Phenylethyl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**3a**)*

A mixture of **8a** hydrochloride (0.35 g, 1.4 mmol), *N*-ethyldisopropylamine (0.54 g, 4.2 mmol) and potassium carbonate (0.67 g, 4.9 mmol) in DMF (20 mL) was stirred for 1h at rt. To the mixture was added (2-iodoethyl)benzene (0.97 g, 4.2 mmol) in an ice-bath, and the mixture was stirred at 100 °C for 24 h and concentrated in vacuo. The residue was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography on basic silica gel (n-hexane/EtOAc = 10/1– 6/1) to produce brown oils (0.34 g), to a solution of which in ether (5 mL) was added 4N HCl/EtOAc (0.30 mL, 1.2 mmol) dropwise in an ice-bath, and the precipitaion was filtered off to obtain **3a** (0.32 g, 65%) as white crystals: mp 116–117 °C; $^1$H-NMR (DMSO-$d_6$) δ 1.50–2.80 (6H, m), 3.07–3.74 (10H, m), 7.20–7.34 (5H, m), 7.43–7.48 (2H, m), 7.69 (1H, t, *J* = 7.5 Hz), 8.03 (1H, d, *J* = 5.7 Hz), 9.92 (1H, brs); Anal. Calcd for $C_{22}H_{25}NO{\cdot}HCl{\cdot}0.5H_2O$: C, 72.41; H, 7.46; N, 3.84. Found: C, 73.01; H, 7.73; N, 3.76; LC/MS (ESI) *m/z* 320 $(M+H)^+$.

*5.23. (2RS)-1'-[2-(2-Methylphenyl)ethyl]-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**3b**)*

To a solution of **8a** (225 mg, 1.05 mmol) and 1-(2-iodoethyl)-2-methylbenzene (386 mg, 1.57 mmol) in toluene (5 mL) were added $iPr_2NEt$ (740 μL, 4.18 mmol) at rt with silica gel blue tube. After stirring under reflux for 1.5 days, a solution of 1-(2-iodoethyl)-2-methylbenzene (386 mg, 1.57 mmol) in toluene (5 mL) was added to the mixture. This mixture was stirred under reflux for 1 day, and then, the reaction was quenched by the addition of $H_2O$ (20 mL). This mixture was extracted with EtOAc (50 mL). The separated organic layer was washed with sat. $Na_2S_2O_3$ (5 mL)/$H_2O$ (20 mL), $H_2O$ (20 mL), brine (20 mL), and dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was by column chromatography ($NHSiO_2$, n-hexane /EtOAc = 1/0–19/1) to obtain free form of **3b** as a pale yellow oil

(324 mg, 93%). To a solution of the oil (324 mg, 973 μmol) in $Et_2O$ (5 mL) were added 4N HCl/EtOAc (365 μL, 1.60 mmol) at 0 °C with silica gel blue tube. After stirring at 0 °C for 30 min, the precipitate was collected off, and washed with $Et_2O$ to obtain **3b** (362 mg, quant) as a white powder: mp 98–104 °C (EtOAc/$Et_2O$); $^1$H-NMR ($CDCl_3$) δ 1.30–1.51 (1H, m), 1.74–1.85 (1H, m), 1.91 (1H, brd, *J* = 13.4 Hz), 2.34 (1H, brd, *J* = 11.5 Hz), 2.38 (3H, s), 2.43–2.81 (3H, m), 2.99–3.12 (1H, m), 3.14–3.48 (5H, m), 3.52–3.66 (1H, m), 3.84 (1H, brd, *J* = 10.7 Hz), 3.98–4.17 (1H, m), 7.08–7.19 (4H, m), 7.26 (1H, d, *J* = 7.5 Hz), 7.35 (1H, dd, *J* = 7.5, 7.2 Hz), 7.55 (1H, ddd, *J* = 7.5, 7.5, 1.3 Hz), 7.97 (1H, d, *J* = 7.2 Hz), 12.31 (1H, brs); IR (KBr) $cm^{-1}$ 3377, 3051, 3013, 2949, 2870, 2804, 2689, 2619, 2525, 2195, 1692, 1684, 1601, 1489, 1468, 1460, 1456, 1427, 1373, 1354, 1312, 1283, 1236, 1209, 1157, 1126, 1020, 982, 957, 935, 924, 908; LC/MS (ESI) *m/z* 334 $(M+H)^+$.

*5.24. 6-Methoxy-1'-(2-phenylethyl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**3c**)*

A mixture of **8d** hydrochloride (0.30 g, 1.0 mmol), N-ethyldisopropylamine (0.27 g, 2.1 mmol) and potassium carbonate (0.17 g, 1.2 mmol) in DMF (5 mL) was stirred for 1h at rt. To the mixture was added (2-iodoethyl)benzene (0.36 g, 1.5 mmol) in an ice-bath, and the mixture was stirred for 24 h at 60 °C and for 1h at 100 °C, and concentrated in vacuo. The residue was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography on basic silica gel (n-hexane/EtOAc = 10/1–5/1) to produce pale brown oils (0.17 g), to a solution of which in ether (5 mL) was added 4N HCl/EtOAc (0.15 mL, 0.60 mmol) dropwise in an ice-bath, and the precipitate was filtered off to obtain **3c** (0.08 g, 22%) as white crystals. mp 131–132 °C; $^1$H-NMR (DMSO-$d_6$) δ 1.48–2.00 (6H, m), 2.18–2.66 (4H, m), 3.07–3.39 (5H, m), 3.66–3.70 (1H, m), 3.85 (3H, s), 6.97–7.01 (2H, m), 7.20–7.38 (5H, m), 7.97 (1H, d, *J* = 8.7 Hz), 9.83

(1H, brs); Anal. Calcd for $C_{23}H_{27}NO \cdot HCl \cdot 0.5H_2O$: C, 69.95; H, 7.40; N, 3.55. Found: C, 69.69; H, 7.46; N, 3.46; LC/MS (ESI) *m/z* 350 $(M+H)^+$.

*5.25. 6-Methoxy-1'-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**3d**)*

A mixture of **8d** hydrochloride (0.14 g, 0.50 mmol), iodobenzene (1.02 g, 5.05 mmol), sodium tert-butoxide (1.15 g, 12.0 mmol), tri-tert-butylphosphine (0.016 g, 0.08 mmol) and tris(dibenzylideneacetone)dipalladium (0) (0.092 g, 0.1 mmol) in toluene (30 mL) was stirred for 18 h at 100 °C. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography on basic silica gel (n-hexane/EtOAc = 25/1) to produce pale brown oils, to a solution of which in ether (5 mL) was added 4N HCl/EtOAc (0.15 mL, 0.6 mmol) dropwise in an ice-bath, and the precipitate was filtered off to obtain **3d** (0.055 g, 31%) as pale brown crystals: mp 119–120 °C; $^1$H-NMR (DMSO-$d_6$) δ 1.60–2.50 (8H, m), 2.90–3.10 (2H, m), 3.40–3.90 (2H, m), 3.81 (3H, s), 4.45 (1H, brs), 6.85 (1H, s), 6.91 (1H, dd, *J* = 2.4 Hz, 8.7 Hz), 7.10–7.60 (5H, m), 7.85 (1H, d, *J* = 8.7 Hz); Anal. Calcd for $C_{21}H_{23}NO_2 \cdot HCl$: C, 70.48; H, 6.76; N, 3.91. Found: C, 70.23; H, 7.01; N, 3.74; LC/MS (ESI) *m/z* 322 $(M+H)^+$.

*5.26. 1'-Benzyl-6-methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**3e**)*

A mixture of **8d** hydrochloride (0.11 g, 0.45 mmol) and N-ethyldisopropylamine (0.29 g, 2.2 mmol) in toluene (5 mL) was added benzyl bromide (0.085 g, 0.50 mmol), and the mixture was stirred at rt for 48h. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated

in vacuo. The residue was purified by column chromatography on basic silica gel (n-hexane/EtOAc = 20/1) to produce pale brown oils, to a solution of which in ether (5 mL) was added 4N HCl/EtOAc (0.11 mL, 0.44 mmol) dropwise in an ice-bath, and the precipitate was filtered off to obtain **3e** (0.08 g, 47%) as white crystals: $^1$H-NMR (DMSO-$d_6$) δ 1.50–2.78 (8H, m), 3.10–3.95 (4H, m), 3.88 (3H, s), 3.94–4.38 (2H, m), 7.01–7.04 (2H, m), 7.48–7.57 (5H, m), 8.04 (1H, d, *J* = 8.4 Hz), 9.64 (1H, brs); LC/MS (ESI) *m/z* 336 $(M+H)^+$.

*5.27. 6-Methoxy-1'-(3-phenylpropyl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**3f**)*

A mixture of **8d** hydrochloride (0.30 g, 1.06 mmol), N-ethyldisopropylamine (0.68 g, 5.3 mmol) and sodium hydride (0.15 g, 3.7 mmol) in DMF (10 mL) was stirred for 0.5h at rt. To the mixture was added 1-iodo-3-phenylpropane (0.86 g, 3.5 mmol) in an ice-bath, and the mixture was stirred for 5h at 120 °C. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography on basic silica gel (n-hexane/EtOAc = 10/1–5/1) to produce pale brown oils, to a solution of which in ether (5 mL) was added 4N HCl/EtOAc (0.30 mL, 1.2 mmol) dropwise in an ice-bath, and the precipitation was filtered off to obtain **3f** (0.32 g, 76%) as white crystals: $^1$H-NMR (DMSO-$d_6$) δ 1.40–2.75 (12H, m), 2.80–3.60 (6H, m), 3.87 (3H, s), 6.98–7.02 (2H, m), 7.16–7.37 (5H, m), 7.95 (1H, d, *J* = 8.4 Hz), 9.59 (1H, brs); Anal. Calcd for $C_{24}H_{29}NO\cdot HCl\cdot 0.5H_2O$: C, 70.49; H, 7.64; N, 3.42. Found: C, 70.53; H, 7.86; N, 3.32; LC/MS (ESI) *m/z* 364 $(M+H)^+$.

*5.28. 6-Methoxy-1'-(4-phenylbutyl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**3g**)*

A mixture of **8d** hydrochloride (0.15 g, 0.53 mmol), N-ethyldisopropylamine (0.34 g, 2.7 mmol) and sodium hydride (0.07 g, 1.8 mmol) in DMF (5 mL) was stirred for 0.5h at rt. To the mixture was added 4-phenylbutylbromide (0.50 g, 2.35 mmol) in an ice-bath, and the mixture was stirred for 2 h at 120 °C. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography on basic silica gel (n-hexane/EtOAc = 15/1–10/1) to produce pale brown oils, to a solution of which in ether (5 mL) was added 4N HCl/EtOAc (0.15 mL, 0.6 mmol) dropwise in an ice-bath, and the precipitate was filtered off to obtain **3g** (0.15 g, 66%) as pale brown crystals. $^1$H-NMR (DMSO-$d_6$) δ 1.40–2.73 (14H, m), 2.80–3.40 (6H, m), 3.87 (3H, s), 6.99–7.03 (2H, m), 7.16–7.32 (5H, m), 7.97 (1H, d, *J* = 8.4 Hz), 9.45 (1H, brs); Anal. Calcd for $C_{25}H_{32}NO_2Cl{\cdot}HCl{\cdot}0.5H_2O$: C, 70.99; H, 7.86; N, 3.31. Found: C, 71.75; H, 8.26; N, 3.32; LC/MS (ESI) *m/z* 378 $(M+H)^+$.

*5.29. 6-Methoxy-1'-(phenylacetyl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one (**3h**)*

A mixture of **8d** hydrochloride (0.30 g, 1.06 mmol), N-ethyldisopropylamine (0.68 g, 5.3 mmol) and sodium hydride (0.15 g, 3.7 mmol) in DMF (10 mL) was stirred for 0.5h at rt. To the mixture was added phenylacetyl chloride (0.54 g, 3.5 mmol) in an ice-bath, and the mixture was stirred for 3h at rt. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography on basic silica gel (n-hexane/EtOAc = 1/1) to obtain **3h** (0.25 g, 65%) as pale brown amorphous. $^1$H-NMR ($CDCl_3$) δ 1.48–2.10 (7H, m), 2.64 (1H, dt, *J* = 5.1 Hz, 12.9 Hz), 2.69–3.15 (1H, d, *J* = 2.4 Hz), 3.66–3.74 (3H, m), 3.83 (3H, s), 3.62 (1H, d, *J* = 2.4 Hz), 6.84 (1H, dd, *J* = 2.4 Hz, 8.7 Hz), 7.14–7.32 (5H, m), 8.11 (1H, d, *J* = 8.7 Hz); IR (KBr) $cm^{-1}$ 2940, 1674, 1636, 1601, 1495, 1454, 1399, 1254, 1157, 1138, 1030; LC/MS (ESI) *m/z* 364 $(M+H)^+$.

*5.30. 6-Methoxy-1'-(2-oxo-2-phenylethyl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one (**3i**)*

To a solution of **8d** (0.046 g, 0.17 mmol) in toluene (0.5 mL) was added 2-bromo-1-phenylehtanone (0.044 g, 0.22 mmol) and *N*-ethyldisopropylamine (0.086 mL, 0.50 mmol). After being stirred at rt for 0.5 h, the mixture was concentrated in vacuo. The residue was purified by column chromatography on basic silica gel (n-hexane/EtOAc = 3/1–2/3) to obtain **3i** (0.060 g, 82%) as pale yellow powder: mp 119–120 °C; $^1$H-NMR ($CDCl_3$) δ 1.42–3.35 (13H, m), 3.53–3.77 (1H, m), 3.78–3.97 (3H, m), 6.59–6.74 (1H, m), 6.77–6.95 (1H, m), 7.33–7.69 (3H, m), 7.92–8.23 (3H, m).

*5.31. 6-Methoxy-1'-(2-phenylpropyl)-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**3j**)*

A mixture of **8d** (0.06 g, 0.25 mmol), *N*-ethyldisopropylamine (1.56 g, 12.0 mmol) and sodium hydride (0.030 g, 0.74 mmol) in DMF (2 mL) was stirred for 0.5h at rt. To the mixture was added 1-bromo-2-phenylpropane (1.0 g, 5.0 mmol) in an ice-bath, and the mixture was stirred for 24 h at 120 °C. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography on basic silica gel (n-hexane/EtOAc = 20/1) to produce pale brown oils. To the solution of the oils in ether (2 mL) was added 4N HCl/EtOAc (0.02 mL, 0.080 mmol) dropwise in an ice-bath, and the precipitate was filtered off to obtain **3j** (0.015 g, 15%) as pale brown crystals: $^1$H-NMR (DMSO-$d_6$) δ 1.36 (3H, d, $J$ = 6.6 Hz), 1.50–2.80 (9H, m), 3.00–3.70 (6H, m), 3.85 (3H, s), 3.85, 3.87 (each 1.5H, s), 6.95–7.03 (2H, m), 7.23–7.33 (5H, m), 7.91–8.02 (1H, m), 9.38–9.51 (1H, m); Anal. Calcd for $C_{24}H_{29}NO_2 \cdot HCl \cdot H_2O$: C, 68.97; H, 7.72; N, 3.35. Found: C, 68.37; H, 7.95; N, 3.25; LC/MS (ESI) *m/z* 364 $(M+H)^+$.

*5.32. 6-Methoxy-1'-[2-(2-methylphenyl)ethyl]-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**3k**)*

A mixture of **8d** (0.15 g, 0.53 mmol), N-ethyldisopropylamine (0.34 g, 2.7 mmol) and sodium hydride (0.07 g, 1.8 mmol) in DMF (5 mL) was stirred for 0.5h at rt. To the mixture was added 1-(2-iodoethyl)-2-methylbenzene (1.0 g, 5.0 mmol) and sodium iodide (0.78 g, 5.2 mmol) in an ice-bath, and the mixture was stirred for 9 h at 120 °C. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography on basic silica gel (n-hexane/EtOAc = 15/1) to produce pale brown oils, to a solution of which in ether (5 mL) was added 4N HCl/EtOAc (0.15 mL, 0.6 mmol) dropwise in an ice-bath, and the precipitate was filtered off to obtain **3k** (0.05 g, 22%) as white crystals: mp 125–127 °C; $^1$H-NMR (DMSO-$d_6$) δ 1.45–2.80 (13H, m), 2.90–3.75 (6H, m), 3.85 (3H, s), 6.96–7.01 (2H, m), 7.10–7.25 (4H, m), 7.97 (1H, d, *J* = 8.4 Hz), 9.83 (1H, brs); Anal. Calcd for $C_{24}H_{29}NO_2 \cdot HCl \cdot 0.5H_2O$: C, 70.49; H, 7.64; N, 3.42. Found: C, 69.90; H, 8.09; N, 3.24; LC/MS (ESI) *m/z* 364 $(M+H)^+$.

*5.33. 5-Methoxy-1'-[2-(2-methylphenyl)ethyl]-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**3l**)*

**8e** (178 mg, 726 μmol), 1-(2-iodoethyl)-2-methylbenzene (268 mg, 1.09 mmol), $iPr_2NEt$ (515 μL, 2.90 mmol), and toluene (3 mL) were used as previously described for **3a**. The residue was purified by column chromatography ($NHSiO_2$, n-hexane/EtOAc = 1/0–19/1) to obtain free form of **3b** as yellow oil (118 mg, 45%).

The free form of **3b** (111 mg, 305 μmol), 4N HCl/EtOAc (155 μL, 610 μmol) and $Et_2O$ (5 mL) were used as previously described for **3a**. The precipitate was collected off, and washed with $Et_2O$ to produce

**3l** (124 mg, quant) as white powder: mp 173–180 $^{0}$C (EtOAc/$Et_2O$); $^{1}$H NMR ($CDCl_3$) δ 1.27–1.48 (1H, m), 1.77 (1H, d, *J* = 13.9 Hz), 1.89 (1H, d, *J* = 14.1 Hz), 2.32 (1H, d, *J* = 14.5 Hz), 2.38 (3H, s), 2.50–2.71 (3H, m), 2.92 (1H, ddd, *J* = 18.3, 12.6, 5.3 Hz), 3.13–3.35 (4H, m), 3.36–3.51 (1H, m), 3.52–3.69 (1H, m), 3.73–3.91 (1H, m), 3.87 (3H, s), 3.98–4.18 (1H, m), 7.06 (1H, d, *J* = 7.9 Hz), 7.09–7.19 (4H, m), 7.32 (1H, dd, *J* = 7.9, 7.9 Hz), 7.55 (1H, dd, *J* = 7.9, 0.8 Hz), 12.27 (1H, s); IR (KBr) $cm^{-1}$ 3393, 2953, 2837, 2619, 2534, 1693, 1593, 1583, 1493, 1470, 1450, 1441, 1371, 1346, 1319, 1296, 1267, 1236, 1215, 1182, 1161, 1113, 1097, 1082, 1061, 1022, 984, 843, 924; LC/MS (ESI) *m/z* 364 $(M+H)^{+}$.

*5.34. (2RS)-7-Methoxy-1'-[2-(2-methylphenyl)ethyl]-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**3m**)*

**8b** (260 mg, 1.06 mmol), 1-(2-iodoethyl)-2-methylbenzene (391 mg, 1.59 mmol) $iPr_2NEt$ (750 μL, 4.23 mmol) and toluene (5 mL) were used as previously described for **3a** (reaction was performed under reflex for 1.5 days). The crude product was purified by column chromatography ($NHSiO_2$, n-hexane/EtOAc = 1/0–19/1) to produce free form of **3m** (295 mg, 77%) as pale yellow oil. The free form of **3m** (283 mg, 844 μmol), 4N HCl/EtOAc (250 μL, 1.27 mmol) and $Et_2O$ (5 mL) were used as previously described for **3a**. The precipitate was collected off, and washed with $Et_2O$ to obtain **3m** (342 mg, quant) as pale yellow powder: mp 116–119 °C (EtOAc/$Et_2O$); $^{1}$H-NMR ($CDCl_3$) δ 1.42 (1H, dddd, *J* = 13.8, 13.8, 3.4, 3.4 Hz), 1.80 (1H, ddd, *J* = 14.3, 3.0, 2.9 Hz), 1.91 (1H, brd, *J* = 14.3 Hz), 2.27–2.43 (1H, m), 2.38 (3H, s), 2.46–2.66 (2H, m), 2.64–2.77 (1H, m), 2.94–3.07 (1H, m), 3.14–3.32 (4H, m), 3.34–3.49 (1H, m), 3.53–3.69 (1H, m), 3.76–3.91 (1H, m), 3.82 (3H, s), 3.95–4.19 (1H, m), 7.06–7.22 (6H, m), 7.41 (1H, d, *J* = 2.4 Hz), 12.31 (1H, brs); IR (KBr) $cm^{-1}$ 3408, 2949, 2837, 2625, 2529, 1682, 1611, 1497, 1466, 1456, 1427, 1373, 1348, 1337, 1327, 1296, 1281, 1259, 1204, 1178, 1157, 1030, 982, 955, 922; LC/MS (ESI) *m/z* 364 $(M+H)^{+}$.

*5.35. 8-Methoxy-1'-[2-(2-methylphenyl)ethyl]-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**3n**)*

A mixture of **8c** (0.05 g, 0.20 mmol), 1-(2-iodoethyl)-2-methylbenzene (0.50 g, 2.0 mmol) and N-ethyldisopropylamine (0.52 g, 4.0 mmol) in toluene (5 mL) was stirred under reflux at 120 °C for 72 h. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography on basic silica gel (n-hexane/EtOAc = 10/1) to produce pale brown oils. To the solution of the oils in ether (2 mL) was added 4N HCl/EtOAc (0.030 mL, 0.12 mmol) dropwise in an ice-bath, and the precipitate was filtered off to obtain **3n** (0.028 g, 35%) as pale brown crystals: $^1$H-NMR (DMSO-$d_6$) δ 1.50–2.50 (10H, m), 2.31 (3H, s), 2.90–3.80 (6H, m), 3.85 (3H, s), 6.91–6.94 (1H, m), 7.02–7.05 (1H, m), 7.10–7.20 (4H, m), 7.55–7.59 (1H, m), 9.69 (1H, brs); Anal. Calcd for $C_{24}H_{29}NO_2 \cdot HCl \cdot 2H_2O$: C, 66.12; H, 7.86; N, 3.21. Found: C, 65.77; H, 7.61; N, 2.95; LC/MS (ESI) *m/z* 364 $(M+H)^+$.

*5.36. 1'-[2-(2-Chlorophenyl)ethyl]-6-methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**3r**)*

A mixture of **8d** hydrochloride (0.15 g, 0.53 mmol), N-ethyldisopropylamine (0.34 g, 2.7 mmol) and sodium hydride (0.07 g, 1.8 mmol) in DMF (5 mL) was stirred for 0.5h at rt. To the mixture was added 1-(2-iodoethyl)-2-chlorobenzene (1.0 g, 4.6 mmol) and sodium iodide (0.78 g, 5.2 mmol) in an ice-bath, and the mixture was stirred for 8 h at 120 °C. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography on basic silica gel (n-hexane/EtOAc = 20/1) to produce pale brown oils, to a solution of

which in ether (5 mL) was added 4N HCl/EtOAc (0.15 mL, 0.6 mmol) dropwise in an ice-bath, and the precipitate was filtered off to obtain **3r** (0.06 g, 27%) as white crystals: mp 148–149 °C; $^1$H-NMR (DMSO-$d_6$) δ 1.45–2.80 (10H, m), 2.95–3.74 (6H, m), 3.85 (3H, s), 6.97–7.01 (2H, m), 7.27–7.44 (4H, m), 7.97 (1H, d, $J$ = 9.0 Hz), 9.92 (1H, brs); Anal. Calcd for $C_{23}H_{26}NO_2Cl{\cdot}HCl{\cdot}0.5H_2O$: C, 64.34; H, 6.57; N, 3.26. Found: C, 63.70; H, 6.89; N, 3.13; LC/MS (ESI) *m/z* 384 $(M+H)^+$.

*5.37. 1'-[2-(4-Fluorophenyl)ethyl]-6-methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**3s**)*

A mixture of **8d** (0.30 g, 1.06 mmol), N-ethyldisopropylamine (0.68 g, 5.3 mmol) and sodium hydride (0.15 g, 3.7 mmol) in DMF (10 mL) was stirred for 0.5 h at rt. To the mixture was added 1-fluoro-4-(2-iodoethyl)benzene (2.5 g, 10.0 mmol) in an ice-bath, and the mixture was stirred for 6h at 120 °C. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography on basic silica gel (n-hexane/EtOAc = 15/1–10/1) to produce pale brown oils, to a solution of which in ether (5 mL) was added 4N HCl/EtOAc (0.30 mL, 1.2 mmol) dropwise in an ice-bath, and the precipitate was filtered off to obtain **3s** (0.35 g, 82%) as white crystals: mp 116–117 °C; $^1$H-NMR (DMSO-$d_6$) δ 1.45–2.00 (6H, m), 2.17–2.80 (4H, m), 3.06–3.65 (6H, m), 3.85 (3H, s), 6.97–7.00 (2H, m), 7.13 (2H, t, $J$ = 8.7 Hz), 7.27 (2H, dd, $J$ = 8.7 Hz, 5.4 Hz), 7.97 (1H, d, $J$ = 8.1 Hz), 9.80 (1H, brs); Anal. Calcd for $C_{23}H_{26}NO_2{\cdot}HCl{\cdot}H_2O$: C, 65.47; H, 6.93; N, 3.32. Found: C, 66.03; H, 7.31; N, 3.21; LC/MS (ESI) *m/z* 368 $(M+H)^+$.

*5.38. 1'-[2-(4-Fluoro-2-methylphenyl)ethyl]-6-methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**3t**)*

To a solution of **8d** (0.031 g, 0.11 mmol) in toluene (0.5 mL) was added 4-fluoro-1-(2-iodoethyl)-2-methylbenzene (0.165 g, 0.62 mmol) and *N*-ethyldisopropylamine (0.162 mL, 0.95 mmol). After being stirred at 100 °C for 18 h, the mixture was cooled to rt, and the precipitation was filtered off. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on basic silica gel (n-hexane/EtOAc = 3/2– 0/1) to produce pale yellow oils, to a solution of which in ether (1 mL) was added 4N HCl/EtOAc (0.128 mL, 0.5 mmol) dropwise at 5 °C, and the mixture was stirred at the temperature for 0.5 h and concentrated in vacuo. to obtain **3t** (0.037 g, 86%) as white powder: $^1$H-NMR (DMSO-$d_6$) δ 1.40–2.06 (4H, m), 2.13–2.25 (1H, m), 2.29 (3H, s), 2.54–2.75 (2H, m), 2.88–3.28 (7H, m), 3.63–3.80 (1H, m) 3.86 (3H, s), 6.86–7.07 (4H, m), 7.20 (1H, dd, *J* = 8.4 Hz, 6.1 Hz), 7.98 (1H, d, *J* = 8.7 Hz), 9.88 (1H, brs).

*5.39. 1'-(2-Mesitylethyl)-6-methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**3u**)*

A mixture of **8d** hydrochloride (0.30 g, 1.06 mmol), *N*-ethyldisopropylamine (0.68 g, 5.3 mmol) and sodium hydride (0.15 g, 3.7 mmol) in DMF (10 mL) was stirred at rt for 0.5 h. To the mixture was added 2-(2-iodoethyl)-1,3,5-trimethylbenzene (3.84 g, 14.0 mmol) in an ice-bath, and the mixture was stirred for 8 h at 120 °C. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography on basic silica gel (n-hexane/EtOAc, 10/1– 7.5/1) to produce pale brown oils, to a solution of which in ether (5 mL) was added 4N HCl/EtOAc (0.30 mL, 1.2 mmol) dropwise in an ice-bath, and the precipitate was filtered off to obtain **3u** (0.16 g, 34%) as pale brown crystals: mp 140–141 °C; $^1$H-NMR (DMSO-$d_6$) δ 1.45–2.56 (19H, m), 2.70–3.80 (6H, m), 3.85 (3H, s), 6.79–6.83 (2H, m), 6.95–7.00 (2H, m), 7.97 (1H, d, *J* = 8.7 Hz), 9.86 (1H, brs); Anal. Calcd for $C_{26}H_{33}NO\cdot HCl\cdot 0.5H_2O$: C, 71.45; H, 8.07; N, 3.21. Found: C,

70.90; H, 8.26; N, 3.03; LC/MS (ESI) *m/z* 392 $(M+H)^+$.

*5.40. (2RS)-6-Hydroxy-1'-[2-(2-methylphenyl)ethyl]-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one (**3v**)*

A mixture of **3k** (5.20 g, 14.9 mmol) in 46% HBr (75 mL) was heated under reflux for 1.5 days, and then, this mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc (200 mL) and 1 N NaOH (400 mL). The separable aqueous layer was extracted with EtOAc (100 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was by column chromatography ($NHSiO_2$, n-hexane/EtOAc = 1/0–0/1) to obtain **3v** (4.46 g, 86%) as a pale yellow amorphous: $^1$H-NMR ($CDCl_3$) δ 1.42–1.89 (6H, m), 2.08–2.26 (2H, m), 2.29 (3H, s), 2.41 (1H, ddd, *J* = 12.5, 11.4, 5.3 Hz), 2.58 (1H, ddd, *J* = 12.5, 11.4, 5.3 Hz), 2.64–3.07 (5H, m), 3.16–3.29 (1H, m), 6.62 (1H, d, *J* = 2.7 Hz), 6.76 (1H, dd, *J* = 8.7, 2.7 Hz), 6.96–7.16 (4H, m), 7.99 (1H, d, *J* = 8.7 Hz); IR (KBr) $cm^{-1}$ 2941, 2862, 1666, 1595, 1574, 1489, 1464, 1429, 1350, 1335, 1281, 1259, 1234, 1219, 1155, 1119, 1099, 1080, 1059, 1036, 1020, 993, 937, 908; LC/MS (ESI) *m/z* 350 $(M+H)^+$.

*5.41. (2RS)-1'-[2-(2-Methylphenyl)ethyl]-1-oxo-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-6-yl (**3w**)*

To a solution of **3v** (2.00 g, 5.73 mmol) in pyridine (10 mL) was added $Tf_2O$ (1.50 mL, 8.58 mmol) at 0 °C under $N_2$ atmosphere. After stirring at rt for 14 h, the reaction was quenched by the addition of $H_2O$ (50 mL). This mixture was extracted with EtOAc (150 mL). The separable organic layer was washed with $H_2O$ (50 mL × 2), brine (50 mL), and dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was purified by column chromatography ($SiO_2$, n-hexane/EtOAc = 1/0–9/1) to obtain **3w** (2.65 g, 96%) as a yellow oil: $^1$H-NMR ($CDCl_3$) δ 1.49–1.86 (6H, m), 2.09–2.20 (1H, m), 2.21–2.33 (1H, m), 2.29 (3H, s), 2.43 (1H, ddd, *J* = 12.8, 10.9, 5.7 Hz), 2.58 (1H, ddd, *J* = 12.8, 10.9,

5.7 Hz), 2.68–2.81 (2H, m), 2.89 (1H, ddd, *J* = 12.8, 10.7, 5.3 Hz), 2.91–3.14 (2H, m), 3.16–3.27 (1H, m), 7.03–7.14 (4H, m), 7.14–7.21 (2H, m), 8.14 (1H, d, *J* = 8.7 Hz); IR (KBr) $cm^{-1}$ 3013, 2939, 2860, 1693, 1682, 1605, 1582, 1483, 1468, 1462, 1452, 1427, 1252, 1213, 1140, 1103, 1084, 993, 930; LC/MS (ESI) *m/z* 482 $(M+H)^+$.

*5.42. (2RS)-N-{1'-[2-(2-Methylphenyl)ethyl]-1-oxo-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin ]-6-yl}acetamide (**3o**)*

A mixture of **3w** (241 mg, 0.50 mmol), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol), X-Phos (12.3 mg, 0.025 mmol), $K_2CO_3$ (174 mg, 1.25 mmol), $PhB(OH)_2$ (3.1 mg, 0.025 mmol), acetamide (75.3 mg, 1.25 mmol), and t-BuOH (1 mL) was heated at 110 °C for 24 h, and then, the reaction mixture was filtered through Celite with aid of EtOAc. The filtrate was concentrated under pressure. The crude product was purified by column chromatography ($NHSiO_2$, n-hexane/EtOAc = 9/1–3/2) to obtain **3o** (179 mg, 97%) as pale yellow powder. Furthermore, the recrystallization from n-hexane/EtOAc gave **3o** (123 mg, 63%) as colorless cotton: mp 128–136 °C; $^1$H-NMR ($CDCl_3$) δ 1.47–1.89 (6H, m), 2.20 (3H, s), 2.29 (3H, s), 2.14–3.11 (9H, m), 3.24 (1H, brs), 6.98–7.13 (4H, m), 7.17 (1H, brd, *J* = 8.5 Hz), 7.38 (1H, brs), 7.66 (1H, brs), 8.00 (1H, d, *J* = 8.5 Hz); IR (KBr) $cm^{-1}$ 3342, 3034, 2937, 2860, 1693, 1682, 1666, 1601, 1585, 1545, 1537, 1529, 1520, 1504, 14951487, 1472, 1466, 1454, 1443, 1435, 1425, 1416, 1371, 1352, 1337, 1315, 1277, 1256, 1234, 1221, 1132, 1121, 1101, 1084, 1015, 937, 908; LC/MS (ESI) *m/z* 391 $(M+H)^+$.

*5.43. (2RS)-1'-[2-(2-Methylphenyl)ethyl]-1-oxo-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidine]-6 -carbonitrile hydrochloride (**3p**)*

A test tube was charged with **3w** (912 mg, 1.89 mmol), $Zn(CN)_2$ (170 mg, 1.42 mmol), $Pd_2dba_3$ (86.7 mg, 0.095 mmol), dppf (111 mg, 0.19 mmol). This tube was evacuated and backfilled with Ar three

times. DMF (10 mL) was added to the mixture, which was again evacuated and backfilled with Ar three times. This reaction mixture was heated at 120 °C for 1.5 h, and then, the reaction was quenched by the addition of $H_2O$ (30 mL). The mixture was extracted with EtOAc (50 mL). The separable organic layer was washed with $H_2O$ (30 mL × 2), brine (30 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was purified by column chromatography ($NHSiO_2$, n-hexane/ EtOAc = 1/0-7/3) to produce yellow gum (561 mg), to a solution of which (60.7 mg, 0.169 mmol) in ether (5 mL) was added 4N HCl/EtOAc (0.085 mL, 0.34 mmol) dropwise in an ice-bath, and the precipitate was filtered off to obtain **3p** (65.2 mg, quant) as white powder: mp 226–231 °C; $^1$H-NMR ($CDCl_3$) δ 1.26–1.47 (1H, m), 1.76–1.99 (2H, m), 2.26 (1H, d, *J* = 15.1 Hz), 2.38 (3H, s), 2.45–2.82 (3H, m), 3.02–3.47 (6H, m), 3.53–3.70 (1H, m), 3.72–3.91 (1H, m), 3.91–4.10 (1H, m), 7.14 (4H, brs), 7.63 (1H, d, *J* = 7.9 Hz), 7.61 (1H, s), 8.08 (1H, d, *J* = 8.0 Hz), 12.65 (1H, brs); IR (KBr) cm$^{-1}$ 3393, 2953, 2808, 2969, 2617, 2548, 2363, 2232, 1693, 1607, 1566, 1493, 1464, 1445, 1425, 1412, 1375, 1354, 1308, 1283, 1234, 1177, 1159, 1132, 1119, 1018, 986, 957, 937, 922; LC/MS (ESI) *m/z* 359 $(M+H)^+$.

*5.44. (2RS)-1'-[2-(2-Methylphenyl)ethyl]-6-phenyl-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin] -1-one hydrochloride (**3q**)*

A test tube was charged with 3w (241 mg, 0.50 mmol), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol), X-Phos (12.3 mg, 0.025 mmol), $PhB(OH)_2$ (126 mg, 1.00 mmol) and $K_3PO_4 \cdot H_2O$ (364 mg, 1.50 mmol). This tube was evacuated and backfilled with Ar three times. Dry THF (1 mL) was added to the mixture, which was again evacuated and backfilled with Ar three times. This reaction mixture was heated at 80 °C for 3 h, and then, the reaction was quenched by the addition of $H_2O$ (10 mL). The mixture was extracted with EtOAc (30 mL). The separable organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was purified by column chromatography ($SiO_2$, n-hexane/EtOAc = 1/0–19/1) to produce colorless gum (168 mg,), to a solution of which (161

mg,) in ether (5 mL) was added 4N HCl/EtOAc (0.085 mL, 0.34 mmol) dropwise in an ice-bath, and the precipitate was filtered off to obtain **3q** (183 mg) as a white powder. mp 210–213 °C; $^1$H-NMR ($CDCl_3$) δ 1.35–1.59 (1H, m), 1.83 (1H, brd, *J* = 14.1 Hz), 1.94 (1H, brd, *J* = 13.0 Hz), 2.39 (3H, s), 2.27–2.48 (1H, m), 2.49–2.87 (3H, m), 3.02–3.55 (6H, m), 3.54–3.73 (1H, m), 3.87 (1H, d, *J* = 10.5 Hz), 3.98–4.23 (1H, m), 7.14 (4H, brs), 7.36–7.53 (4H, m), 7.53–7.69 (3H, m), 8.04 (1H, d, *J* = 8.3 Hz), 11.81 (1H, brs); IR (KBr) $cm^{-1}$ 3393, 3024, 2955, 2864, 2808, 2617, 2523, 1682, 1605, 1493, 1472, 1462, 1450, 1420, 1408, 1371, 1352, 1310, 1279, 1238, 1180, 1159, 1134, 1117, 1076, 1055, 1040, 1020, 982, 959, 937, 924, 908; LC/MS (ESI) *m/z* 410 $(M+H)^+$.

*5.45. (2R)-6-Methoxy-1'-[2-(2-methylphenyl)ethyl]-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin ]-1-one hydrochloride (**4a**)*

A mixture of **14b** (0.05 g, 0.18 mmol), *N*-ethyldisopropylamine (0.34 g, 1.1 mmol) and sodium hydride (0.07 g, 0.8 mmol) in DMF (2 mL) was stirred at rt for 0.5h. To the mixture was added 1-(2-iodoethyl)-2-methylbenzene (0.5 g, 2.5 mmol) in an ice-bath, and the mixture was stirred for 5 h at 120 °C. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography on basic silica gel (n-hexane/EtOAc = 20/1) to produce pale brown oils, to a solution of which in ether (5 mL) was added 4N HCl/EtOAc (0.10 mL, 0.4 mmol) dropwise in an ice-bath, and the precipitate was filtered off to obtain **4a** (0.053 g, 66%) as white crystals, 98.1% ee [colimm: CHIRALPAK AD; mobile phase: n-hexane/EtOH/diethylamine (95/5/01)(v/v/v)].

*5.46. (2R)-6-Methoxy-1'-[2-(2-methylphenyl)ethyl]-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin ]-1-one hydrochloride (**4a**)*

**3k** (400 mg) was partitioned between ethyl acetate and 1 N NaOH (400 mL), and the aqueous layer

was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. to produce yellow brown oils (367 mg). The free form of **3k** (367 mg) was purified by standard preparative chiral high-performance liquid chromatography (HPLC [colimm: CHIRALPAK AD; mobile phase: n-hexane/EtOH/diethylamine (95/5/01)(v/v/v)]) to produce free form of **4a** (162 mg, small retention time, 99.9% ee [colimm: CHIRALPAK AD; mobile phase: n-hexane/EtOH/diethylamine (95/5/01)(v/v/v)]) as colorless oils and free form of **4b** (159 mg, large retention time, 99.4% ee [colimm: CHIRALPAK AD; mobile phase: n-hexane/EtOH/diethylamine (95/5/01)(v/v/v)]) as colorless oils. To a solution of free form of **4a** (159 mg, small retention time) in ether (10 mL) was added 4N HCl/EtOAc (0.20 mL, 0.8 mmol) dropwise in an ice-bath, and the precipitate was filtered off to abtain **4a** (159 g) as white crystals: $[\alpha]_D^{20}$ –69.9° (c = 0.500, MeOH).

*5.47. (2S)-6-Methoxy-1'-[2-(2-methylphenyl)ethyl]-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin] -1-one hydrochloride (**4b**)*

To a solution of free form of **4b** (158 mg, large retention time) in ether (10 mL) was added 4N HCl/EtOAc (0.20 mL, 0.8 mmol) dropwise in an ice-bath, and the precipitate was filtered off to obtain **4a** (168 mg) as white crystals: mp 138–139 °C; $[\alpha]_D^{20}$ +70.4° (c = 0.505, MeOH).

*5.48. (-)-N-{1'-[2-(2-Methylphenyl)ethyl]-1-oxo-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-6-yl}acetamide (**4c**)*

**3o** (594 mg) was purified by standard preparative chiral high-performance liquid chromatography (HPLC [colimm: CHIRALPAK AD; mobile phase: n-hexane/EtOH/diethylamine (95/5/01)(v/v/v)]) to **4c** (275 mg, small retention time) as colorless oils. $[\alpha]_D^{20}$ –62.1° (c = 0.383, MeOH); 99.9% ee [colimm: CHIRALPAK AD; mobile phase: n-hexane/EtOH/diethylamine (95/5/01)(v/v/v)].

*5.49. (+)-N-{1'-[2-(2-Methylphenyl)ethyl]-1-oxo-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-6-yl}acetamide (**4d**)*

**3o** (594 mg) was purified by standard preparative chiral high-performance liquid chromatography (HPLC [colimm: CHIRALPAK AD; mobile phase: n-hexane/EtOH/diethylamine (95/5/01)(v/v/v)]) to **4d** (271 mg, large retention time) as colorless oils: $[\alpha]_D^{20}$ +66.3° (c = 0.500, MeOH); 99.4% ee [colimm: CHIRALPAK AD; mobile phase: n-hexane/EtOH/diethylamine (95/5/01)(v/v/v)].

*5.50. (2R)-1'-[2-(4-fluorophenyl)ethyl]-6-methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**4e**)*

**3s** (233 mg) was partitioned between ethyl acetate and 1 N NaOH (400 mL), and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. to produce yellow brown oils (205 mg). The free form of **3s** (100 mg) was purified by standard preparative chiral high-performance liquid chromatography (HPLC [colimm: CHIRALPAK AD; mobile phase: n-hexane/EtOH/diethylamine (95/5/01)(v/v/v)]) to free form of **4e** (42 mg, small retention time, 99.8% ee [colimm: CHIRALPAK AD; mobile phase: n-hexane/EtOH/diethylamine (95/5/01)(v/v/v)]) as colorless oils and free form of **4f** (41 mg, large retention time, 99.7% ee [colimm: CHIRALPAK AD; mobile phase: n-hexane/EtOH/diethylamine (95/5/01)(v/v/v)]) as colorless oils. To a solution of free form of **4e** (42 mg, small retention time) in ether (4 mL) was added 4N HCl/EtOAc (0.05 mL, 0.2 mmol) dropwise in an ice-bath, and the precipitate was filtered off to obtain **4e** (45 g) as pale brown powder.

*5.51. (2S)-1'-[2-(4-fluorophenyl)ethyl]-6-methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**4f**)*

To a solution of free form of **4f** (41 mg, large retention time) in ether (4 mL) was added 4N HCl/EtOAc

(0.05 mL, 0.2 mmol) dropwise in an ice-bath, and the precipitate was filtered off to obtain **4f** (45 mg) as white crystals.

*5.52. (2S)-1'-[2-(4-fluorophenyl)ethyl]-6-methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**4f**)*

To a mixture of **14a** (0.25 g, 1.0 mmol) and *N*-ethyldisopropylamine (0.65 g, 5.0 mmol) in toluene (10 mL) was added 1-fluoro-4-(2-iodoethyl)benzene (1.0 g, 4.0 mmol), and the mixture was stirred under reflux at 120 °C for 72 h. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography on basic silica gel (n-hexane/EtOAc = 10/1) to produce pale brown oils, to a solution of which in ether (10 mL) was added 4N HCl/EtOAc (0.30 mL, 1.2 mmol) dropwise in an ice-bath, and the precipitate was filtered off to obtain **4f** (0.34 g, 83%) as white crystals: mp 131–133 °C; 1H-NMR (DMSO-$d_6$) δ 1.45–2.80 (10H, m), 2.95–3.75 (6H, m), 3.86 (3H, s), 6.98–7.31 (6H, m), 7.98 (1H, d, $J$ = 8.7 Hz), 9.82 (1H, brs); LC/MS (ESI) *m/z* 368 $(M+H)^+$; $[\alpha]_D^{20}$ +41.6° (c = 0.505, MeOH); 96.7% ee [column: CHIRALPAK AD; mobile phase: n-hexane/EtOH/diethylamine (95/5/01)(v/v/v)].

*5.53. (2S)-1'-[2-(3-Fluorophenyl)ethyl]-6-methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**4g**)*

**14a** (245 mg, 1.00 mmol), 1-fluoro-3-(2-iodoethyl)benzene (750 mg, 3.00 mmol) $iPr_2NEt$ (710 μL, 4.00 mmol) and toluene (5 mL) were used as previously described for **3a** (reaction was performed under reflex for 3 days). The crude product was purified by column chromatography ($NHSiO_2$, n-hexane /EtOAc = 1/0–19/1) to produce free from of **4g** (324 mg, 88%) as a yellow oil. The free from of **4g** (305 mg, 830 μmol), 4N HCl/EtOAc (310 μL, 1.25 mmol) and $Et_2O$ (5 mL) were used as previously

described for **3a**. The precipitate was collected off, and washed with $Et_2O$ to obtain **4g** (316 mg, quant) as a white powder: mp 92–100 °C (EtOAc/$Et_2O$); $^1$H-NMR ($CDCl_3$) δ 1.35–1.55 (1H, m), 1.77 (1H, brd, *J* = 14.4 Hz), 1.88 (1H, brd, *J* = 12.9 Hz), 2.32 (1H, brd, *J* = 14.4 Hz), 2.42–2.63 (2H, m), 2.63–2.78 (1H, m), 2.91–3.09 (1H, m), 3.16–3.39 (4H, m), 3.40–3.64 (2H, m), 3.73 (1H, brd, *J* = 11.4 Hz), 3.86 (3H, s), 3.98–4.24 (1H, m), 6.69 (1H, d, *J* = 1.9 Hz), 6.81–6.97 (3H, m), 7.02 (1H, d, *J* = 7.6 Hz), 7.18–7.36 (1H, m), 7.95 (1H, d, *J* = 8.7 Hz), 12.23 (1H, brs); IR (KBr) $cm^{-1}$ 3389, 2949, 2841, 2617, 2550, 2363, 2195, 1674, 1599, 1495, 1489, 1447, 1371, 1352, 1308, 1563, 1236, 1209, 1157, 1144, 1126, 1119, 1088, 1074, 1028, 986, 961, 939, 924, 903; LC/MS (ESI) *m/z* 368 $(M+H)^+$; $[\alpha]_D^{20}$ +40.8° (c = 0.250, MeOH).

*5.54. (2S)-1'-[2-(2-fluorophenyl)ethyl]-6-methoxy-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**4h**)*

To a mixture of **14a** (0.25 g, 1.0 mmol) and N-ethyldisopropylamine (0.65 g, 5.0 mmol) in toluene (10 mL) was added 1-fluoro-2-(2-iodoethyl)benzene (1.0 g, 4.0 mmol), and the mixture was stirred under reflux at 120 ℃ for 72 h. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography on basic silica gel (n-hexane/EtOAc = 10/1) to produce pale brown oils, to a solution of which in ether (10 mL) was added 4N HCl/EtOAc (0.30 mL, 1.2 mmol) dropwise in an ice-bath, and the precipitate was filtered off to obtain **4h** (0.33 g, 82%) as white crystals: 1H-NMR (DMSO-$d_6$) δ 1.45–2.80 (10H, m), 2.90–3.72 (6H, m), 3.85 (3H, s), 6.96–7.01 (2H, m), 7.12–7.37 (4H, m), 7.97 (1H, d, *J* = 8.4 Hz), 9.90 (1H, brs); LC/MS (ESI) *m/z* 368 $(M+H)^+$; $[\alpha]_D^{20}$ +42.6° (c = 0.250, MeOH).

*5.55. (2S)-6-Methoxy-1'-[2-(2-methoxyphenyl)ethyl]-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidi*

*n]-1-one hydrochloride (**4i**)*

To a solution of **14a** (245 mg, 1.00 mmol) and 35a (524 mg, 2.00 mmol) in toluene (5 mL) were added $iPr_2NEt$ (0.71 mL, 4.00 mmol) at rt with silica gel blue tube. After stirring under reflux for 2 days, the reaction was quenched by the addition of $H_2O$ (10 mL). This mixture was extracted with EtOAc (30 mL). The separated organic layer was washed with sat. $Na_2S_2O_3$ (5 mL)/$H_2O$ (20 mL), $H_2O$ (20 mL), brine (20 mL), and dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was by column chromatography ($NHSiO_2$, n-hexane/EtOAc = 1/0–9/1) to produce pale yellow oil (354 mg), to a solution of which in ether (5 mL) was added 4N HCl/EtOAc (0.27 mL, 1.09 mmol) dropwise in an ice-bath, and the precipitate was filtered off to obtain **4i** (382 mg) as a white powder: mp 123–124 °C; $^1$H-NMR ($CDCl_3$) δ 1.32–1.55 (1H, m), 1.77 (1H, d, *J* = 14.0 Hz), 1.86 (1H, d, *J* = 14.8 Hz), 2.28 (1H, d, *J* = 14.0 Hz), 2.45–2.85 (3H, m), 3.02 (1H, dd, *J* = 16.3, 5.3 Hz), 3.15–3.53 (6H, m), 3.73–3.92 (1H, m), 3.79 (3H, s), 3.86 (3H, s), 3.96–4.24 (1H, m), 6.69 (1H, d, *J* = 2.3 Hz), 6.76–6.93 (3H, m), 7.11–7.25 (1H, m), 7.18 (1H, d, *J* = 8.7 Hz), 7.94 (1H, d, *J* = 8.7 Hz), 11.91 (1H, brs); IR (KBr) $cm^{-1}$ 3393, 2947, 2839, 2619, 2527, 1674, 1599, 1574, 1495, 1464, 1456, 1447, 1369, 1352, 1310, 1261, 1240, 1207, 1177, 1159, 1124, 1086, 1074, 1028, 984, 959, 937, 924, 905; LC/MS (ESI) *m/z* 380 $(M+H)^+$; $[\alpha]_D^{20}$ +63.5° (c = 0.250, MeOH).

*5.56. (2S)-6-Methoxy-1'-[2-(3-methoxyphenyl)ethyl]-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidi n]-1-one hydrochloride (**4j**)*

**14a** (245 mg, 1.00 mmol), 1-(2-iodoethyl)-3-methoxybenzene (393 mg, 1.50 mmol) $iPr_2NEt$ (710 μL, 4.00 mmol) and toluene (5 mL) were used as previously described for **3a** (reaction was performed under reflex for 2.5 days). The crude product was purified by column chromatography ($NHSiO_2$, n-hexane/EtOAc = 1/0–19/1) to obtain free form of **4j** (327 mg, 86%) as a yellow oil. The free form of **4j** (327 mg, 861 μmol), 4N HCl/EtOAc (322 μL, 1.29 mmol) and $Et_2O$ (5 mL) were used as previously

described for **3a**. The precipitate was collected off, and washed with $Et_2O$ to obtain **4j** (362 mg, quant) as a white powder: mp 102–104 °C (EtOAc/$Et_2O$); $^1$H-NMR ($CDCl_3$) δ 1.30–1.55 (1H, m), 1.72–1.82 (1H, m), 1.88 (1H, brd, *J* = 13.9 Hz), 2.21–2.36 (1H, m), 2.42–2.63 (2H, m), 2.64–2.78 (1H, m), 2.94–3.08 (1H, m), 3.14–3.39 (4H, m), 3.42–3.60 (2H, m), 3.69–3.81 (1H, m), 3.78 (3H, s), 3.86 (3H, s), 3.98–4.19 (1H, m), 6.69 (1H, d, *J* = 2.5 Hz), 6.75 (1H, dd, *J* = 7.5, 2.5 Hz), 6.77 (1H, s), 6.80 (1H, d, *J* = 7.9 Hz), 6.86 (1H, dd, *J* = 8.9, 2.4 Hz), 7.20 (1H, ddd, *J* = 7.9, 7.5, 2.5 Hz), 7.94 (1H, d, *J* = 8.9 Hz), 12.11 (1H, brs); IR (KBr) $cm^{-1}$ 3339, 2947, 2837, 2619, 2546, 2359, 2341, 2195, 1674, 1599, 1495, 1468, 1454, 1371, 1352, 1306, 1263, 1236, 1209, 1190, 1155, 1126, 1117, 1088, 1074, 1030, 986, 961, 939, 924, 907; LC/MS (ESI) *m/z* 380 $(M+H)^+$; $[\alpha]_D^{20}$ +42.0° (c = 0.250, MeOH).

*5.57. (2S)-6-Methoxy-1'-[2-(4-methoxyphenyl)ethyl]-3,4-dihydro-1H-spiro[naphthalene-2,2'-piperidin]-1-one hydrochloride (**4k**)*

**14a** (245 mg, 1.00 mmol), 35b (393 mg, 1.50 mmol), $iPr_2NEt$ (710μL, 4.00 mmol) and toluene (5 mL) were used as previously described for **4i** (reaction was performed under reflex for 3 days). The crude product was purified by column chromatography ($NHSiO_2$, n-hexane/EtOAc = 1/0–4/1) to produce free form of **4k** (336 mg, 88%) as a pale yellow oil. The free form of **4k** (329 mg, 867 μmol), 4N HCl/EtOAc (325 μL, 1.30 mmol) and $Et_2O$ (5 mL) were used as previously described for **4i**. The precipitate was collected off, and washed with $Et_2O$ to obtain **4k** (370 mg, quant) as pale yellow powder: mp 143–149 °C; $^1$H-NMR ($CDCl_3$) δ 1.32–1.56 (1H, dddd, *J* = 13.9, 13.4, 3.1, 2.9 Hz), 1.77 (1H, dd, *J* = 13.8, 2.7 Hz), 1.87 (1H, d, *J* = 15.3 Hz), 2.30 (1H, d, *J* = 14.5 Hz), 2.40–2.63 (2H, m), 2.63–2.78 (1H, m), 2.96–3.07 (1H, m), 3.10–3.35 (4H, m), 3.36–3.55 (2H, m), 3.69–3.80 (1H, m), 3.76 (3H, s), 3.86 (3H, s), 4.01–4.18 (1H, m), 6.69 (1H, d, *J* = 2.4 Hz), 6.74–6.84 (2H, m), 6.86 (1H, dd, *J* = 8.9, 2.5 Hz), 7.10–7.18 (2H, m), 7.94 (1H, d, *J* = 8.9 Hz), 12.06 (1H, s); IR (KBr) $cm^{-1}$ 3340, 2949, 2837, 2619, 2527, 1674, 1599, 1574, 1514, 1497, 1464, 1456, 1447, 1371, 1352, 1304, 1263, 1250, 1238, 1178, 1159, 1126,

1120, 1086, 1076, 1030, 956, 959, 937, 924, 905; LC/MS (ESI) *m/z* 380 $(M+H)^+$; $[\alpha]_D^{20}$ +35.9° (c = 0.250, MeOH).

*5.58. Preparation of 1-Fluoro-3-(2-iodoethyl)benzene and related compounds*

*5.58.1 Step1*

To a solution of 3-fluorophenylacetic acid (24.85 g, 158 mmol) in MeOH (200 mL) was added $SOCl_2$ (4.00 mL, 52.2 mmol) at 0 °C with silica gel blue tube. After stirring at rt for 3 h, the reaction mixture was concentrated under reduced pressure. The residue was partitioned between 1 N NaOH (250 mL) and EtOAc (250 mL). The separable organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure to obtain methyl (3-fluorophenyl)acetate (25.81 g, 97%) as colorless oil. $^1$H-NMR ($CDCl_3$) δ 3.62 (2H, s), 3.71 (3H, s), 6.92–7.09 (3H, m), 7.29 (1H, ddd, *J* = 7.9, 7.7, 6.0 Hz); IR (KBr) $cm^{-1}$ 3065, 3024, 3001, 2955, 2845, 1740, 1616, 1593, 1489, 1450, 1437, 1342, 1258, 1200, 1165, 1144, 1076, 1015, 955, 930.

*5.58.2 Step2*

To a suspension of $LiAlH_4$ (14.56 g, 307 mmol) in THF (150 mL) was added a solution of (3-fluorophenyl)acetate (25.80 g, 153 mmol) at 0 °C for 30 min under $N_2$ atmosphere. This mixture was stirred at 0 °C for 1 h and at rt 3 h, and then, the reaction was quenched by the addition of saturated Rochel's salt until participating. This precipitate was collected off, and washed with THF (500 mL). The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography ($SiO_2$, n-hexane/EtOAc = 5/1–3/1) to obtain 2-(3-fluorophenyl)ethanol (19.74 g, 92%) as colorless oil. $^1$H-NMR ($CDCl_3$) δ 1.45 (1H, brs), 2.87 (2H, t, *J* = 6.4 Hz), 3.87 (2H, dt, *J* = 6.3, 6.4 Hz), 6.87–6.98 (2H, m), 7.01 (1H, d, *J* = 7.7 Hz), 7.17–7.39 (1H, m); IR (KBr) $cm^{-1}$ 3337, 3071, 3042, 2949, 2880, 1614, 1589, 1487, 1450, 1377, 1337, 1250, 1140, 1045, 982, 939.

*5.58.3 Step3*

To a solution of 2-(3-fluorophenyl)ethanol (25.26 g, 180 mmol) in pyridine (180 mL) was added TsCl

(36.49 g, 186 mmol) at 0 °C with silica gel blue tube. After stirring at rt for 4 h, the reaction was quenched by the addition of 2 N HCl (750 mL) at 0 °C. This mixture was extracted with EtOAc (300 mL). The separable organic layer was washed with 2 N HCl (250 mL), $H_2O$ (200 mL), brine (100 mL), and dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was purified by column chromatography ($SiO_2$, n-hexane/EtOAc = 10/1–5/1) to obtain 2-(3-fluorophenyl)ethyl 4-methylbenzenesulfonate (38.54 g, 73%) as a colorless oil. $^1$H-NMR ($CDCl_3$) δ 2.43 (3H, s), 2.94 (2H, t, *J* = 6.8 Hz), 4.21 (2H, t, *J* = 6.8 Hz), 6.77 (1H, ddd, *J* = 9.8, 2.1, 1.9 Hz), 6.84–6.98 (2H, m), 7.21 (1H, ddd, *J* = 7.9, 7.9, 6.0, Hz), 7.28 (2H, ddd, *J* = 8.7, 2.1, 1.7 Hz), 7.68 (2H, ddd, *J* = 8.5, 2.1, 1.9 Hz); IR (KBr) cm$^{-1}$ 3065, 3045, 2963, 2926, 2901, 2878, 1620, 1614, 1591, 1489, 1470, 1462, 1452, 1418, 1400, 1360, 1308, 1292, 1254, 1211, 1188, 1177, 1142, 1121, 1097, 1055, 1020, 972, 912.

*5.58.4 Step 4*

To a solution of 2-(3-fluorophenyl)ethyl 4-methylbenzenesulfonate (38.54 g, 131 mmol) in acetone (130 mL) was added NaI (39.45 g, 262 mmol) at rt with silica gel blue tube. After stirring under reflux for 3 h, the reaction mixture was concentrated under reduced pressure. The residue was partitioned between $H_2O$ (200 mL) and EtOAc (300 mL). The separable organic layer was washed with sat. $Na_2S_2O_3$ (50 mL)/$H_2O$ (200 mL), $H_2O$ (100 mL), brine (100 mL), and dried over $MgSO_4$, filtered, concentrated under reduced pressure. The residue was purified by column chromatography ($SiO_2$, n-hexane) to obtain 1-fluoro-3-(2-iodoethyl)benzene (30.67 g, 94%) as a pale red oil. $^1$H-NMR ($CDCl_3$) δ 3.17 (2H, t, *J* = 7.6 Hz), 3.34 (2H, t, *J* = 7.6 Hz), 6.83–7.04 (3H, m), 7.28 (1H, ddd, *J* = 8.0, 8.0, 6.1 Hz); IR (KBr) cm$^{-1}$ 3045, 3040, 2961, 2895, 2862, 2841, 1616, 1589, 1518, 1487, 1450, 1337, 1310, 1275, 1252, 1234, 1173, 1140, 1115, 1069, 1015, 1003, 970, 947, 918.

*5.58.5 Related compounds*

1-(2-iodoethyl)-2-methxybenzene,1-chloro-2-(2-iodoethyl)benzene,1-fluoro-1-(4-iodoethyl)-3-methxy benzene,2-(2-iodoethyl)-1,3,5-trimethylbenzene,1-fluoro-4-(2-iodoethyl)benzene,1-fluoro-2-(2-iodoethy

l)benzene,1-(2-iodoethyl)-2-methoxybenzene,1-(2-iodoethyl)-3-methoxybenzene, and 1-(2-iodoethyl)-4-methoxybenzene were prepared from commercial available intermediates according to the preparation of 1-fluoro-3-(2-iodoethyl)benzene.

*5.59. Homology Modeling and Ligand Docking*

The homology model of the luminal region of $H^+,K^+$-ATPase was constructed from the crystal structure of $Ca^{2+}$-ATPase (PDB code 1IWO[8]) by using SCWRL, version 2.9.[9] Compounds **4d** was docked into the cavity affirmed in the $H^+,K^+$-ATPase model by using GOLD, version 2.1.2.[10]

*5.60. Measurement of $H^+,K^+$-ATPase activity*

This procedure was performed using an approach similar to a previously reported method.[4] A gastric mucosal microsomal fraction was prepared from the stomach of porcine. The inhibitory effects of the test compounds were expressed as percentage inhibition with respect to the $K^+$-stimulated $H^+,K^+$-ATPase activity in the control. The values of $IC_{50}$ were calculated using sigmoidal dose response equation in GraphPad Prism (GraphPad Software Inc., San. Diego, CA, USA).

*5.61. Measurement of $Na^+,K^+$-ATPase inhibitory activity*

This procedure was performed using an approach similar to a previously reported method.[4] The activity of $Na^+,K^+$-ATPase from porcine cerebral cortex (Sigma) was measured.

*5.62. An assay of inhibition of acid secretion in anesthetized rats by intravenous administration*

This procedure was performed using an approach similar to a previously reported method.[4] The gastric contents were collected and centrifuged at 3000 rpm for 10 min. The volume of each sample was measured and the acid concentration was determined by automatic titration to pH 7.0 with 0.1 mol/L

NaOH, and the total acid output during the 3 h period (μEq/3 h) was calculated.

*5.63. Measurement of pH of a gastric perfusate under conditions of histamine stimulation in anesthetized rats*

This procedure was performed using an approach similar to a previously reported method.[11] Histamine 2 HCl (8 mg/kg/h) was infused intravenously via the cervical vein. When pH stabilized, a test compound or vehicle was administered intravenously. The pH level of the perfusate was measured for 5 h after administration of the drug or vehicle.

*5.64. A pharmacokinetic experiment in rats*

This procedure was performed using an approach similar to a previously reported method.[12] The blood and stomach samples were collected 10 min, 1, 4 and 24 h after administration. The concentrations of compounds were determined by high performance liquid chromatography / tandem mass spectrometry (LC/MS/MS).

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**Disclosure**

The authors declare that they have no conflicts of interest.

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**Graphical Abstract**

**Discovery, synthesis, and structure-activity relations of 3,4-dihydro-1H-spiro(naphthalene-2,2'-piperidin)-1-ones as potassium-competitive acid blockers**

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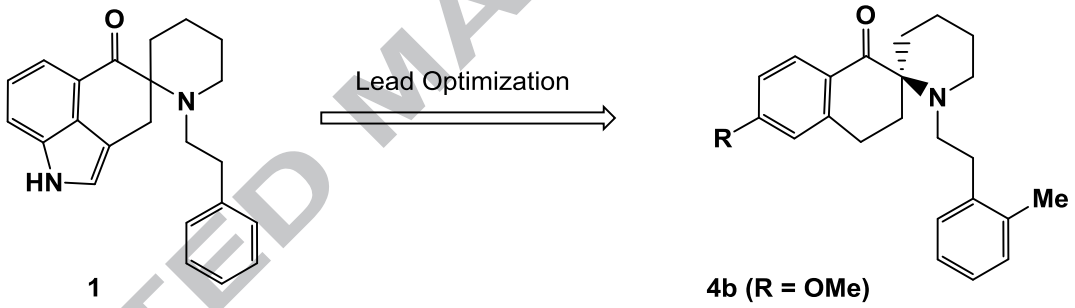


**1** **4b (R = OMe)**