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# Design and synthesis of piperidine farnesyltransferase inhibitors with reduced glucuronidation potential

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**Abstract**—The design and synthesis of a novel piperidine series of farnesyltransferase (FTase) inhibitors with reduced potential for metabolic glucuronidation are described. The various substitution and exchange of the phenyl group at the C-2 position of the previously described 2-(4-hydroxy)phenyl-3-nitropiperidine **1a** (FTase $IC_{50}$ = 5.4 nM) resulted in metabolically stable compounds with potent FTase inhibition (**14a** $IC_{50}$ = 4.3 nM, **20a** $IC_{50}$ = 3.0 nM, and **50a** $IC_{50}$ = 16 nM). Molecular modeling studies of these compounds complexed with FTase and farnesyl pyrophosphate are also described.


## 1. Introduction

Ras protein plays a key role in cell growth and cell proliferation in the MAP kinase signal transduction pathway. Protein farnesyltransferase (FTase), an enzyme that catalyzes farnesylation of proteins ending with the CAAX motif (C, cystein; A, aliphatic amino acid; and X, C-terminal amino acid), is one of the crucial enzymes involved in the signal transduction pathway. FTase inhibitors inhibit anchorage-independent growth of a variety of transformed cells. A survey of cancer cell lines has shown that >70% of cells are sensitive to FTase inhibitors.[1] In addition, FTase inhibitors have been shown to inhibit the growth of tumors in a number of animal model studies.[2,3] Therefore, FTase inhibitors have emerged as promising anti-cancer drugs.[1] Some FTase inhibitors, such as R115777 (tipifarnib) and SCH66336 (lonafarnib), are currently being assessed in clinical trials and have demonstrated clinical efficacy for the treatment of human cancers.[4]

The 3-nitro piperidine derivatives **1a** and **2a** have already been described as FTase inhibitors (Chart 1).[5] Although the compounds have potent FTase inhibitory activity (**1a** $IC_{50}$ = 5.4 nM and **2a** $IC_{50}$ = 3.7 nM), rapid clearance of these compounds limits their application. Preliminary pharmacokinetic studies suggested that glucuronidation of the phenolic groups on the benzene ring at the C-2 position of the piperidine core could be one of the responsible factors for the rapid clearance. Here we describe our efforts to identify potent piperidine inhibitors of FTase with reduced potential for glucuronidation.

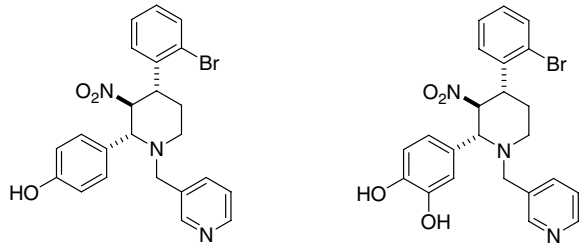


**Chart 1.**

*Keywords*: Farnesyltransferase (FTase) inhibitors; Piperidine derivatives; Reduced glucuronidation; Design and synthesis.
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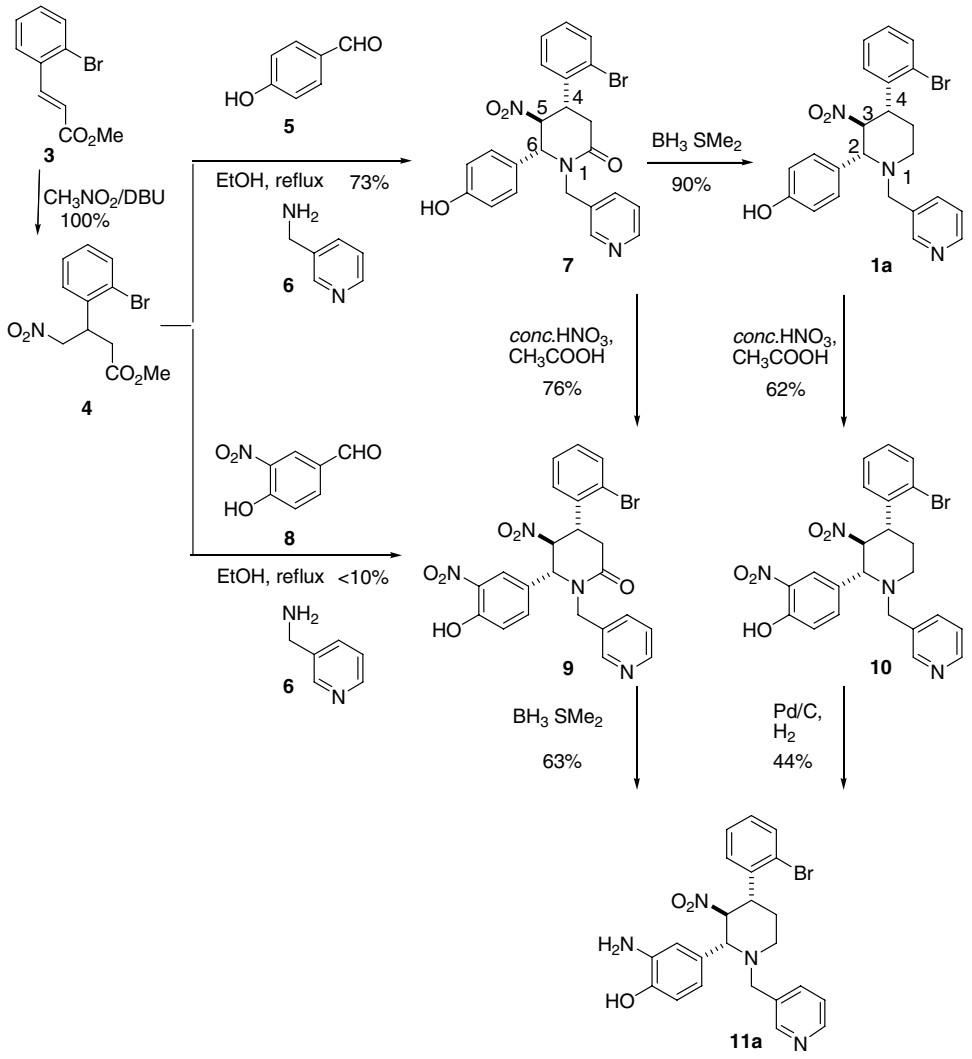


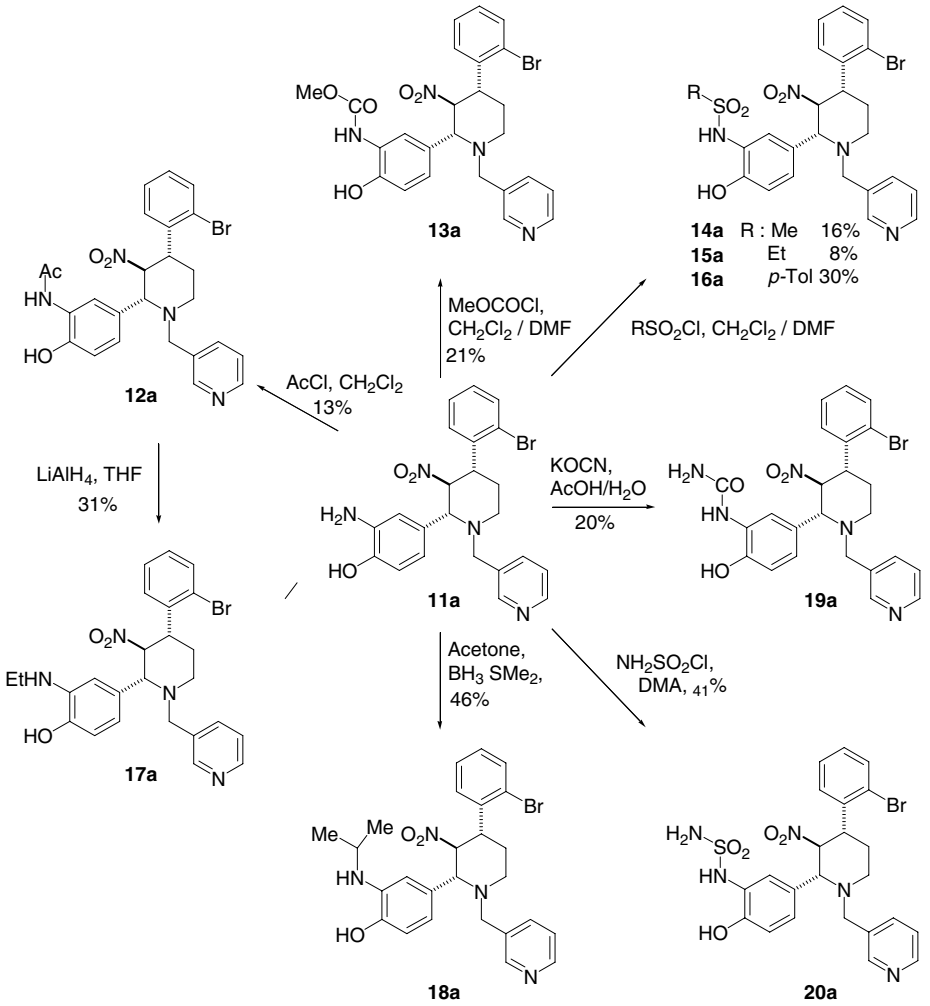

**Scheme 1.** Synthesis of 3-nitropiperidine derivatives at 2 position (1).

## 2. Chemistry

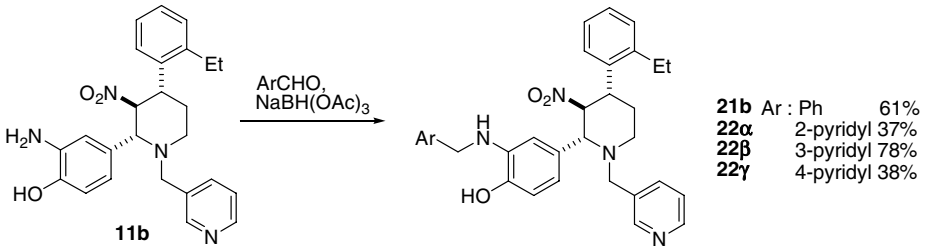
In Scheme 1, key intermediate **11a** was synthesized as described in two previous papers.[5,6] The relative stereochemistry of the piperidine core was determined by NMR analysis as described in the previous paper.[5] Although the 3-component coupling reaction of 4-nitrobutyrate **4**, which was synthesized from the cinnamate **3** by the Michael addition of nitromethane[7] in quantitative yield, 3-nitro-4-hydroxybenzaldehyde **8**, and amine **6** resulted in a low yield of the desired piperidin-2-one **9**, nitration of **7** gave desired **9** in 76% yield. Reduction of piperidin-2-one **9** with borane–methyl sulfide complex gave the desired key intermediate **11a** in 63% yield. Alternatively, nitration of piperidine **1a** followed by hydrogenation of the nitro group gave **11a** in moderate yields.

Compound **11a** was used as a starting material for the modification of the amino group ortho to the hydroxy group at the C-2 phenyl (Scheme 2). Treatment of **11a** with acetyl chloride, methyl chloroformate, sulfonyl chlorides, potassium cyanate, or sulfamoyl chloride[8] afforded acetamide **12a**, carbamate **13a**, sulfonamides **14a**–**16a**, or sulfamide **20a**, respectively. Reductive alkylation of **11a** with acetone and borane dimethyl sulfide complex gave isopropyl amino derivative **18a**. $LiAlH_4$ reduction of **12a** afforded ethyl amino derivative **17a**. Since replacement of the bromo substituent on the C-4 phenyl ring with ethyl had proven to be acceptable, 4-(2-ethylphenyl)piperidine **11b** was also used as starting material. Reductive alkylation of **11b** with aryl or heteroaryl aldehyde in the presence of sodium triacetoxyborohydride afforded **21b** and **22α**–**γ** by parallel solution-phase synthesis (Scheme 3).

Although the corresponding three-component coupling reactions using 4-aminomethylimidazole or 4-aminomethyl-1-trityl-1*H*-imidazole did not proceed to give 3-nitropiperidine derivative **24**, reductive alkylation of *N*-unsubstituted 3-nitropiperidine **23** with sodium triacetoxyborohydride and 4-imidazolecarboxaldehyde did give **24**. Compound **23** was synthesized by the coupling reaction of 4-nitrobutyrate **4** with benzaldehyde and ammonium acetate, followed by the reduction of the carbonyl group with borane-methyl sulfide complex. Methylation of **24** with iodomethane and potassium carbonate afforded a 2:1 mixture of **25** and




**Scheme 2.** Synthesis of 3-nitropiperidine derivatives at 2 position (2).



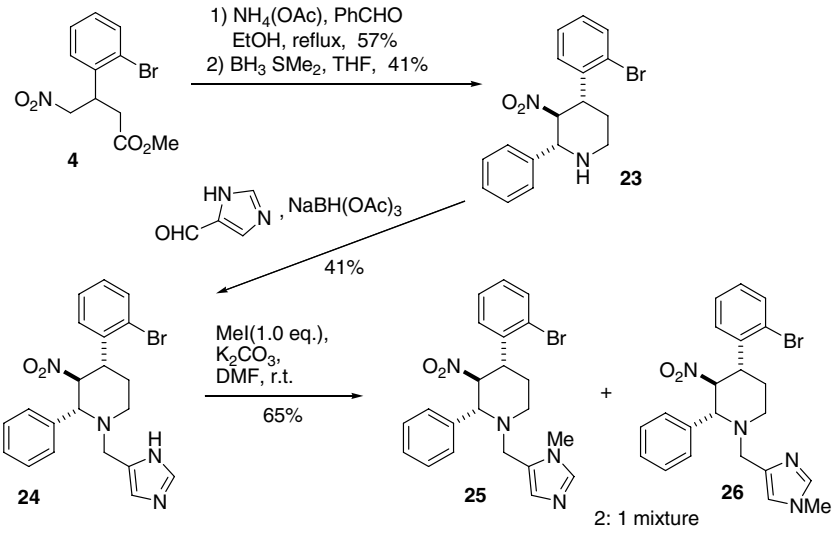

**Scheme 3.** Synthesis of 3-nitropiperidine derivatives at 2 position (3).

**26** (Scheme 4). The regiochemistry of methylation was determined by the NOE of $^1$H NMR.

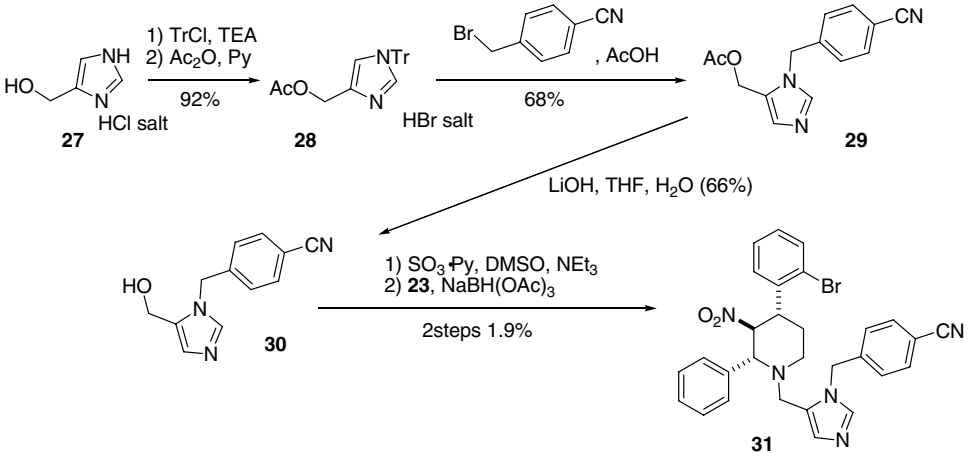
Reductive alkylation of **23** with 3-(4-cyanobenzyl)-3*H*-imidazol-4-ylcarboxaldehyde afforded imidazole derivative **31**. Synthesis of 3-(4-cyanobenzyl)-3*H*-imidazol-4-ylcarboxaldehyde from 4-(hydroxymethyl) imidazole hydrochloride is shown in Scheme 5.

The syntheses of 2-phenyl-3-carboxypiperidine derivatives are summarized in Scheme 6. Addition of allyl benzoylacetate **32** to 2-ethylcinnamaldehyde **33** afforded aldehyde **34**. Treatment of aldehyde **34** with 3-(aminomethyl)pyridine **6** and sodium triacetoxyborohydride followed by the reduction with sodium cyanoborohydride gave desired 3-allyloxycarbonylpiperidine **36**. The isomerization of the C-3 position of **36** with sodium allyloxide proceeded to give the 2,3-*trans*-3,4-*trans* isomer **38** along with 3-carboxypiperidine **37**.

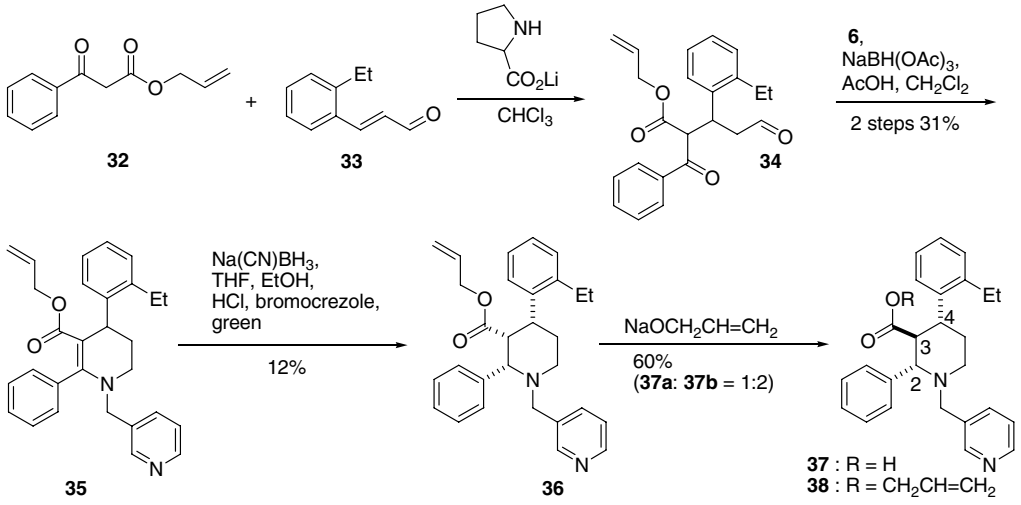
Acid chloride **39**, prepared from **37** with thionyl chloride, was used for the preparation of many kinds of novel 3-substituted piperidine derivatives (Scheme 7). 3-Hydroxymethylpiperidine **41** was prepared by $LiAlH_4$ reduction. Treatment of **39** with methylamine, methionine methyl ester, and methanol




**Scheme 4.** Synthesis of imidazole derivatives.

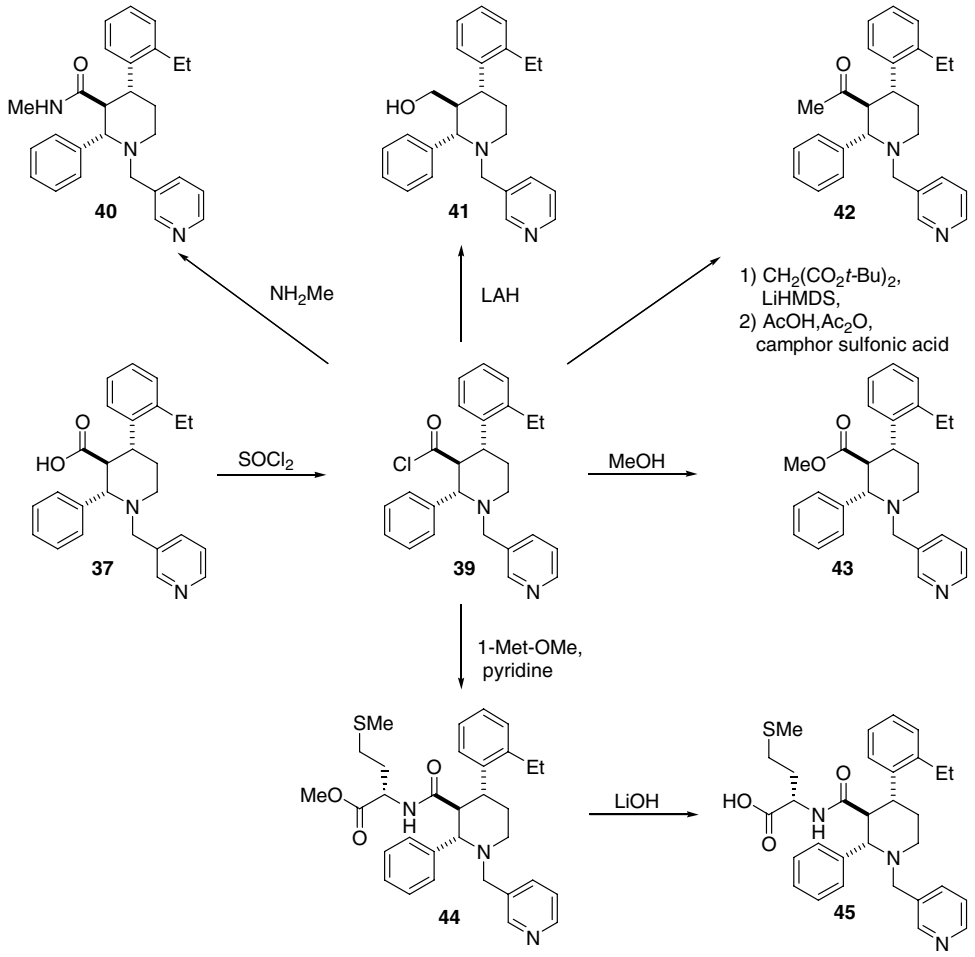



**Scheme 5.** Synthesis of 1-(4-cyanobenzyl)imidazolylmethyl derivative **31**.




**Scheme 6.** Synthesis of 3-carboxypiperidine derivatives.

afforded amides **40**, **43**, and methyl ester **44**, respectively. Methionine amide **45** was prepared from **43** by hydrolysis with LiOH. Treatment of acid chloride **39** with the lithium enolate of di-*tert*-butylmalonate followed by decarboxylation afforded 3-acetylpiperidine **42**.




**Scheme 7.** Synthesis of piperidine derivatives at 3 position.

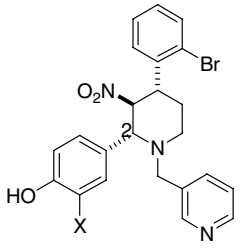
## 3. Results and discussion

Although **1a** and **2a** show potent FTase inhibition, the metabolic stability of these compounds needs to be improved. We hypothesized that the glucuronidation of phenolic hydroxy groups might be the cause of metabolic instability. Our strategy for designing compounds includes incorporation of substituents at the *ortho*-position of the phenolic hydroxy group and removal of the groups themselves.

FTase enzyme inhibition was determined by inhibition of farnesylation of human K-Ras by human FTase, as previously described.[9] In vitro metabolic stability of selected compounds was evaluated by mouse liver microsome assay.

Our previous studies[5] suggest that the *para*-hydroxy group on the C-6 benzene ring may be important for FTase inhibition, since changing the *para*-hydroxy group to a methoxy, amino or amide group resulted in significantly reduced activity. In order to avoid glucuronidation while maintaining FTase inhibition, we therefore evaluated the introduction of substituents ortho to the hydroxy group of the C-2 benzene ring (Table 1). Although introduction of nitro or iodo groups (compounds **10** and **47a**) reduced activity, methoxy derivative **46a** showed some activity against FTase ($IC_{50}$ = 180 nM). Interestingly, *ortho*-amino derivatives (**11a** $IC_{50}$ = 13 nM and **11b** $IC_{50}$ = 46 nM) retained FTase inhibition potency.

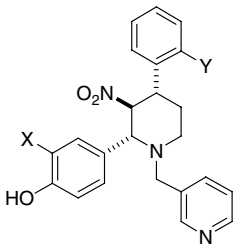
**Table 1.** Modification of the *ortho*-position of the hydroxyl group at the C-2 benzene ring on the 3-nitropiperidine (**1**)




| Compound | X | FTase $IC_{50}$ (nM) |
|---|---|---|
| **1a** | H | 5.4 |
| **2a** | –OH | 3.7 |
| **46a** | $–OCH_3$ | 180 |
| **10** | $–NO_2$ | >500 |
| **47a** | I | >500 |
| **11a** | $–NH_2$ | 13 |

We hypothesized that introduction of substituents into the amino group ortho to the phenolic hydroxy group

**Table 2.** Modification of the *ortho*-position of the hydroxyl group at the C-2 benzene ring on the 3-nitropiperidine (**2**)



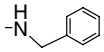
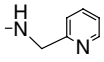
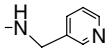
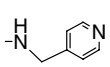
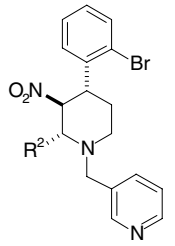
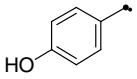
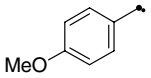
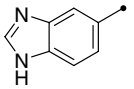
| Compound | X | FTase $IC_{50}$ (nM) | |
|---|---|---|---|
| | | **a** Y = Br | **b** Y = Et |
| **1** | H | 5.4 | 20 |
| **11** | $-NH_2$ | 13 | 46 |
| **17** | –NHEt | 50 | |
| **18** | $-NHCH(Me)_2$ | 98 | |
| **21** |  | | 121 |
| **22α** |  | | 23 |
| **22β** |  | | 24 |
| **22γ** |  | | 12 |
| **12** | –NHCOMe | 27 | |
| **13** | $-NHCO_2Me$ | 14 | |
| **14** | $-NHSO_2Me$ | 4.3 | 4.6 |
| **15** | $-NHSO_2Et$ | 5.9 | |
| **16** | $-NHSO_2Tol$ | 270 | |
| **19** | $-NHCONH_2$ | 15 | 6.2 |
| **20** | $-NHSO_2NH_2$ | 3.0 | 4.5 |

**Table 3.** Modification at 2-position on the 3-nitropiperidine



| Compound | $R^2$ | FTase $IC_{50}$ (nM) |
|---|---|---|
| **1a** |  | 5.4 |
| **48a** |  | >500 |
| **49a** |  | >500 |
| **50a** |  | 16 |
| **51a** |  | 36 |
| **52a** |  | 25 |
| **53a** |  | >500 |

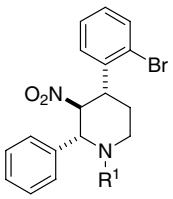
of **11a** may further reduce the rate of glucuronidation (Table 2). Simple alkylation of the amino group resulted in decreased potency (**17a**, **18a**, and **21b**), however, 2-pyridylmethylamino derivative **22α** ($IC_{50}$ = 23 nM), 3-pyridylmethylamino derivative **22β** ($IC_{50}$ = 24 nM), and 4-pyridylmethylamino derivative **22γ** ($IC_{50}$ = 12 nM) retained FTase inhibition. It is possible that the nitrogen of the pyridine may have a direct interaction with the enzyme, however, molecular modeling studies of **22γ** with FTase did not provide support for this hypothesis. Although the methyl or ethyl sulfonamide series showed potent FTase inhibition (**14a** $IC_{50}$ = 4.3 nM, **15a** $IC_{50}$ = 5.9 nM), *p*-tosyl derivative **16a** did not ($IC_{50}$ = 270 nM). In this case, the bulk of the substituent may affect FTase inhibition. Urea derivative **19a** ($IC_{50}$ = 15 nM) and sulfamoylamino derivative **20a** ($IC_{50}$ = 3.0 nM) also showed potent FTase inhibition. Ethyl analogues such as **14b** ($IC_{50}$ = 4.6 nM), **19b** ($IC_{50}$ = 6.2 nM), and **20b** ($IC_{50}$ = 4.5 nM) were also potent inhibitors.

In an alternative strategy to avoid glucuronidation, we tried to change the C-2 phenyl group into the other aromatic rings without involvement of the phenolic hydroxy group (Table 3). Although the methoxy derivative **48a** lost FTase inhibition, the simple phenyl derivative **50a** showed potent FTase inhibition ($IC_{50}$ = 16 nM). Other heterocycles such as 3-thiophene **51a** ($IC_{50}$ = 36 nM) or 2-pyridine **52a** ($IC_{50}$ = 25 nM) also showed FTase inhibition. Interestingly, the 2-pyridine derivative **53a** showed no FTase inhibition.

With the identification of non-phenolic replacements for the R2 group, alternative substituents at N-1 of the piperidine core (Table 4) and replacement of the C-3 nitro group were also reexamined (Table 5). Although most of the N-1 modified derivatives lost FTase inhibition (data not shown), substituted 4-imidazolylmethyl compounds, such as **25** ($IC_{50}$ = 17 nM) and **31** ($IC_{50}$ = 44 nM), showed potent FTase inhibition comparable to that of 3-pyridylmethyl compounds. On the contrary, compound **26**, a regio-isomer of **25**, and N-unsubstituted imidazole derivative **24** showed no FTase inhibitory activity ($IC_{50}$ > 500 nM).

Modification of the nitro group of 3-nitropiperidines, such as compound **50a**, is important to change the physical and biological character of these series. Table 5 summarizes the structures and FTase inhibition of the piperidine derivatives at the C-3 position. The compounds with carboxylic acid or hydroxymethyl group at the C-3 position showed no FTase inhibitory activity (**37** or **41** $IC_{50}$ > 500 nM). However, 3-acetylpiperidine **42** was found to have potent activity ($IC_{50}$ = 42 nM)

**Table 4.** Modification at 1-position on the 3-nitropiperidine



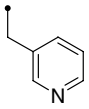
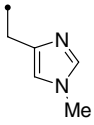
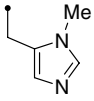
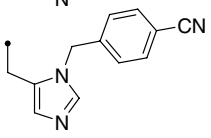
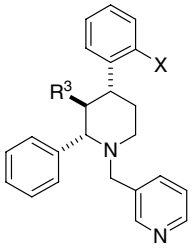
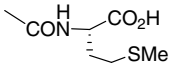
| Compound | $R^1$ | FTase $IC_{50}$ (nM) |
|---|---|---|
| **50a** |  | 16 |
| **24** |  | >500 |
| **26** |  | >500 |
| **25** |  | 17 |
| **31** |  | 44 |

**Table 5.** Modification of 3-position on the piperidine



| Compound | X | $R^3$ | FTase $IC_{50}$ (nM) |
|---|---|---|---|
| **50a** | Br | $-NO_2$ | 16 |
| **37** | Et | $-CO_2H$ | >500 |
| **41** | Et | $-CH_2OH$ | >500 |
| **42** | Et | –COMe | 42 |
| **43** | Et | $-CO_2Me$ | 95 |
| **38** | Et | $-CO_2CH_2CH{=}CH_2$ | >500 |
| **40** | Et | –CONHMe | >500 |
| **45** | Me |  | 19 |

and 3-methoxycarbonylpiperidine **43** also showed FTase inhibition ($IC_{50}$ = 95 nM). Changing the methyl ester to allyl ester or *N*-methyl amide resulted in the loss of FTase inhibitory activity (**38** or **40** $IC_{50}$ > 500 nM). Interestingly, the L-methionine amide retained potent inhibition **45** ($IC_{50}$ = 19 nM). Since the nitropiperidine inhibitors were shown to be Ras competitive, we hypothesized that the methionine residue may interact with the FTase like the C-terminal region of Ras peptide, but this hypothesis could not be confirmed by molecular modeling.

### 3.1. Proposed binding model of the piperidine derivatives for FTase

The binding model of the piperidine derivatives in the Ras protein-binding site of FTase was developed using the crystal structure of rat FTase, CAAX peptide, and Farnesyl diphosphate analogue complex.[9] Figure 1 shows the proposed binding mode of **1a** in the Ras protein-binding pocket.

In this model, there are three hydrogen bonds. One was between the O of 3-nitro group and OH of Ser98, Another was between N of the C-1 pyridine and Zinc cation of the protein involved water, and last one is between OH on the C-2 phenyl group and O of Asp359. This suggests that the direction of the proton in this phenolic hydroxyl group might be important to forming the hydrogen bond.

Binding models of **19b** and **22γ**, with potent FTase inhibitory activity, are shown in Figure 2. The three hydrogen bonds, described above, also exist, and importantly, the direction of the proton in this phenolic hydroxyl group may be fixed to ASP359 by intermolecular hydrogen bond between 4′-OH and 3′-NH. As expected, the substituents on the position are outside this binding pocket of protein, but the model predicted that bulky substituents on this position could not be acceptable.

The binding models also suggest that the *ortho*-position of the phenolic hydroxyl group may be near to the edge of the binding pocket and directly outside of the protein. Some substituents on this position are possible to retain binding ability because these would be outside this binding pocket.

### 3.2. In vitro metabolic stability of C-2 modified piperidine derivatives

Since **1a** was eliminated immediately in mouse in vivo, in vitro metabolic stability studies of **1a** and some other derivatives using mouse liver microsome were conducted. Compound **1a** was metabolized in mouse liver microsome mainly as the glucuronide conjugate and the contribution of P450 to the metabolism was found to be very small. To assess the contribution of oxidative metabolism by cytochrome P450, and glucuronidation to the elimination of the compounds, NADPH and UDPGA, co-enzymes of each metabolic reaction, were utilized. The residual ratio was calculated by dividing the concentration of compounds in the metabolized samples by those in the initial samples. We checked the metabolic stabilities of several compounds in mouse microsome in the presence of NADPH and/or UDPGA. Our preliminary results suggest that the bromo and ethyl group at C-4 phenyl ring did not greatly affect glucuronidation, therefore we

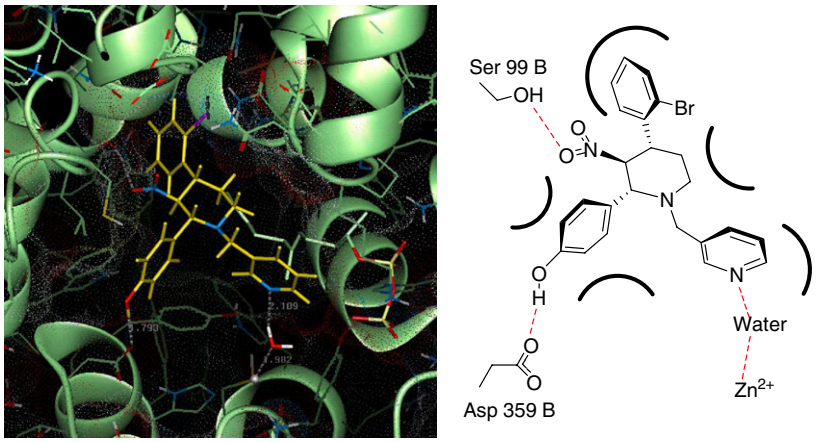



**Figure 1.** Proposed binding model of **1a** for FTase.

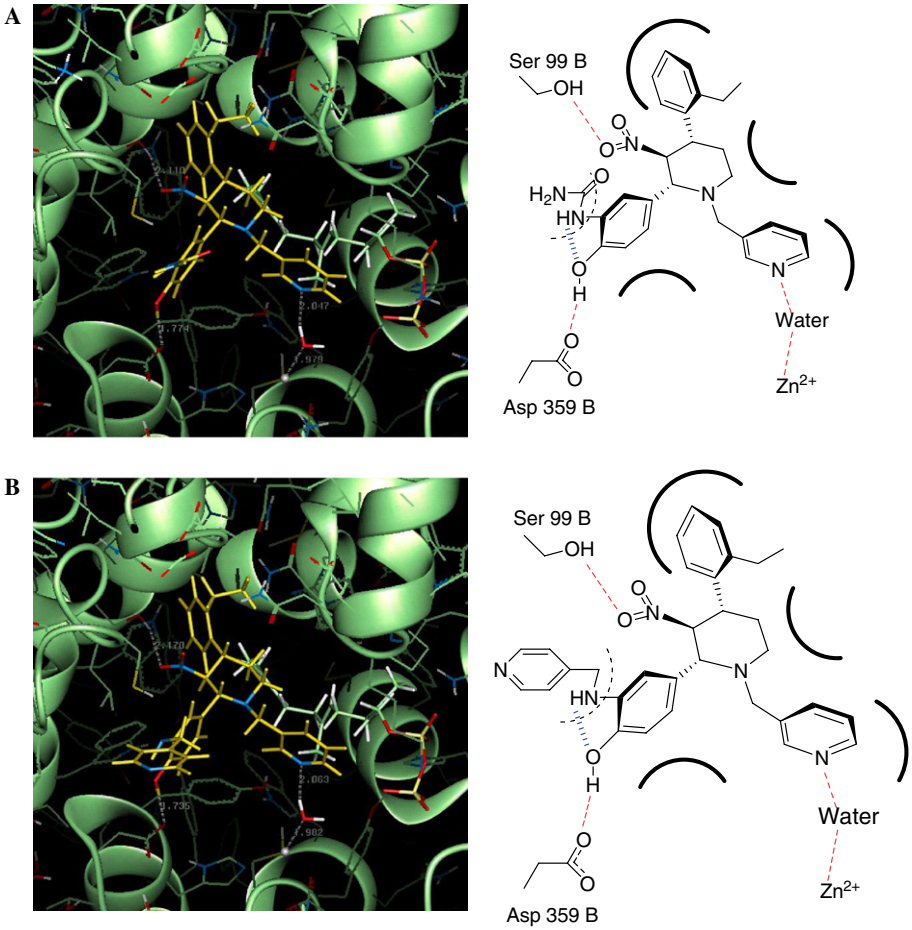



**Figure 2.** (A) Proposed binding model of **19b** for FTase. (B) Proposed binding model of **22γ** for FTase.

used either substituent for the stability tests. As expected, introduction of a substitution ortho to the phenolic hydroxy group of C-2 phenyl ring in **1a** or **1b** resulted in compounds with reduced propensity for glucuronidation (UDPGA system, uridine 5′-diphosphoglucuronic acid). Although *ortho*-methoxy compound **48a** was still prone to glucuronidation, amino compound **11a** (data not shown, ca. 40%), 4-pyridylmethylamino compound **22γ**, acetamido compound **12a**, urea compound **19b**, and sulfamide compound **20b** were found to be more stable than the simple phenol compound **1a**. In particular, **20b** showed the best stability in assays of the *ortho*-substituted phenol compounds (Fig. 3).

Figure 4 shows the metabolic stability of the C-2 phenyl, thienyl, and pyridyl compounds in the mouse liver microsome assay. Since there are no phenolic hydroxy

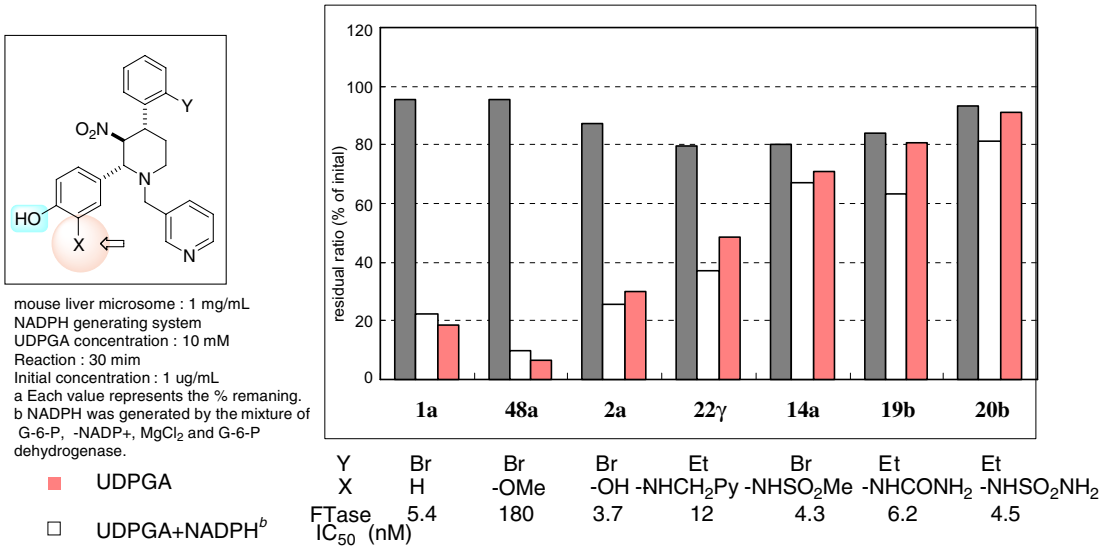



**Figure 3.** Metabolic studies of piperidine derivatives with C-2 substituted phenol parts.

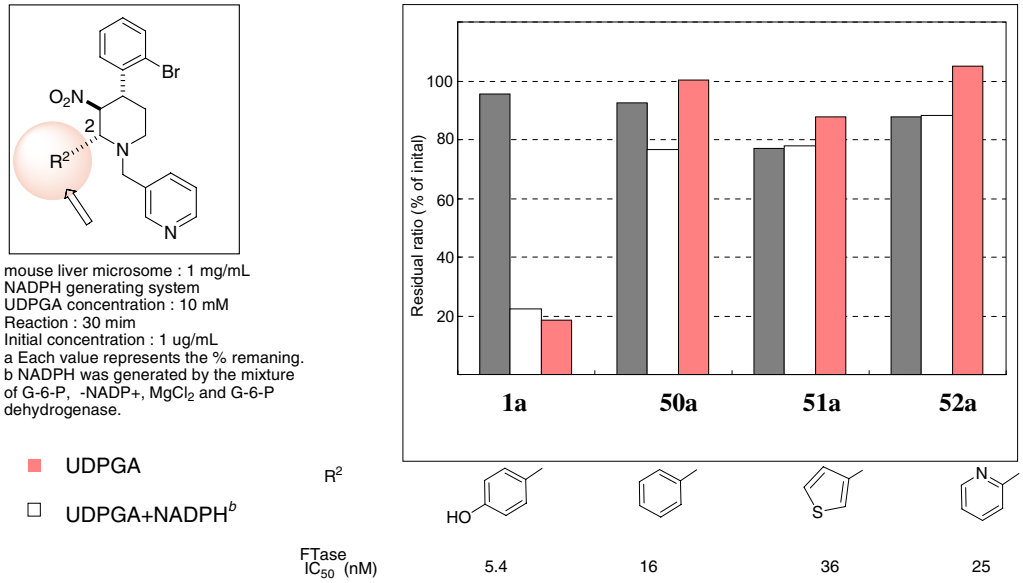



**Figure 4.** Metabolic studies of C-2 modified piperidine derivatives.

groups in their structures, dramatic improvement in metabolic stability was observed in each compound.

Based on the results of in vitro metabolic studies, in vivo pharmacokinetic and efficacy studies of the selected compounds such as **20b** or **50a** are now in progress. Details of these results will be published elsewhere.

## 4. Conclusion

SAR studies around the novel and potent piperidine inhibitors of FTase, such as **1a** and **2a**, were carried out in order to improve their metabolic stability. In vitro metabolic stability assays suggested that the glucuronide conjugation of phenolic hydroxy group could be a primary metabolic pathway.

In order to improve the metabolic stability by steric effect for glucuronidation, insertion of substituents to the *ortho*-position of phenolic hydroxy group was examined. Some substituents, such as methanesulfonylamino (**14a** $IC_{50}$ = 4.3 nM), urea (**19b** $IC_{50}$ = 6.2 nM), and sulfamoylamino (**20a** $IC_{50}$ = 3.0 nM) groups, showed good metabolic stability in vitro with potent FTase inhibition. In addition, the simple phenyl compound (**50a** $IC_{50}$ = 16 nM), 3-thiophene compound (**51a** $IC_{50}$ = 36 nM), and 2-pyridine compound (**52a** $IC_{50}$ = 25 nM) retained the FTase inhibition with good metabolic stability in vitro. Modifications to the 2-nitro and *N*-3-pyridylmethyl groups of compound **50a** were further examined in this series. Exchange of the nitro group to acetyl group (**42** $IC_{50}$ = 42 nM) or to methionine amide group (**45** $IC_{50}$ = 19 nM) resulted in potent FTase inhibitors. In addition, exchange of the *N*-3-pyridylmethyl

group to substituted imidazolylmethyl group resulted in the potent FTase inhibitors, such as **25** ($IC_{50}$ = 17 nM) or **31** ($IC_{50}$ = 44 nM). Further studies of these compounds will be reported in due course.

## 5. Experimental

### 5.1. General methods

NMR spectra were recorded on a JEOL Lambda 300 (300 MHz), JEOL GX-270 (270 MHz), JEOL EX-270 (270 MHz) or a JEOL JNM 400 (400 MHz) NMR spectrometer. Mass spectra were recorded on a JEOL JMS HX/HX110 mass spectrometer and Micromass Quattro mass spectrometer.

Elemental analyses were performed on a Perkin-Elmer Series II Analyzer 2400 elemental analyzer or a Yamato MT-5 analyzer.

### 5.2. *rac*-(4*R*,5*R*,6*S*)-4-(2-Bromophenyl)-6-(4-hydroxyphenyl)-5-nitro-1-*N*-(3-pyridylmethyl)-piperidin-2-one (7)

Methyl 3-(2-bromophenyl)-4-nitrobutylate **4** (61 g, 0.20 mol), 4-hydroxybenzaldehyde **5** (25 g, 0.21 mol), and 3-(aminomethyl)pyridine **6** (42 mL, 0.41 mol) in EtOH (1.0 L) were heated under reflux for 20 h. After removal of EtOH under reduced pressure, the residue was chromatographed on silica gel, eluted with $CHCl_3$/MeOH, 19:1, to afford 7 (69 g, 73% yield). Analytically pure **7** was afforded by recrystallization from hot EtOH. $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 9.62 (s, 1H), 8.38 (d, $J$ = 4.8 Hz, 1H), 8.11 (s, 1H), 7.78 (d, $J$ = 7.9 Hz, 1H), 7.61 (d, $J$ = 7.9 Hz, 1H), 7.39–7.46 (m, 2H), 7.22–7.27 (m, 2H), 7.14 (d, $J$ = 8.0 Hz, 2H), 6.64 (d, $J$ = 8.0 Hz, 2H), 5.89 (dd, $J$ = 11.0, 9.5 Hz, 1H), 4.94 (d, $J$ = 9.5 Hz, 1H), 4.47 (d, $J$ = 15.8 Hz, 1H), 4.38 (m, 1H), 4.18 (d, $J$ = 15.8 Hz, 1H), 3.05 (dd, $J$ = 16.8, 11.0 Hz, 1H), 2.74 (dd, $J$ = 16.8, 4.7 Hz, 1H). FAB-MS (*m*/*z*): 484, 482 $(M+H)^+$. Anal. ($C_{23}H_{20}BrN_3O_4$): C, H, N. (C, 57.27; H, 4.19; N, 8.71%. Found: C, 57.12; H, 4.21; N, 8.67%).

### 5.3. *rac*-(2*R*,3*S*,4*S*)-4-(2-Bromophenyl)-2-(4-hydroxyphenyl)-3-nitro-1-*N*-(3-pyridylmethyl)-piperidine (1a)

To a solution of **7** (40 g, 83 mmol) in THF (2.0 L) was added borane–methyl sulfide complex (30 mL, 320 mmol) and the mixture was refluxed for 10 h. After cooling to 4 °C, the reaction was quenched by the addition of water (50 mL) and the mixture was concentrated. The resulting residue was heated with aqueous HCl (3.0 mol/L, 400 mL) and neutralized with aqueous NaOH (3.5 mol/L, 300 mL) after cooling to room temperature. The solid formed was recrystallized from EtOH to give analytically pure **1a** (35 g, 90% yield). mp 229–230 °C. IR (KBr) 2823, 1614, 1560, 1554, 1473, 1373, 1280, 1250, 1022, 761 $cm^{-1}$. $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 9.53 (s, 1H), 8.44 (m, 1H), 8.16 (br s, 1H), 7.73 (m, 1H), 7.65–7.56 (m, 2H), 7.40–7.31 (m, 4H), 7.18 (m, 1H), 6.78 (br s, 1H), 6.75 (br s, 1H), 5.34 (dd, $J$ = 9.4, 11.7 Hz, 1H), 3.87 (dt, $J$ = 4.0, 11.7 Hz, 1H), 3.73 (d, $J$ = 9.4 Hz, 1H), 3.59 (d, $J$ = 13.9 Hz, 1H), 3.08 (d, $J$ = 13.9 Hz, 1H), 2.90 (m, 1H), 2.39 (m, 1H), 1.89–1.67 (m, 2H). FAB-MS (*m*/*z*): 470, 468 $(M+H)^+$.

### 5.4. *rac*-(2*R*,3*S*,4*S*)-4-(2-Bromophenyl)-2-[3-nitro-4-hydroxy]-3-nitro-1-*N*-(3-pyridylmethyl)-piperidine (10)

To a solution of **1a** (300 mg, 0.69 mmol) in acetic acid (10 mL) was added concentrated nitric acid (0.055 mL, 1.4 mmol) under cooling with ice. After stirred for 1.5 h while elevating the temperature to room temperature, the reaction solution was poured into water, and the mixture was neutralized with a dilute aqueous solution of sodium hydroxide and extracted with a $CHCl_3$/MeOH, 9:1, mixed solvent. The extract was dried over sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was chromatographed on silica gel, eluted with $CHCl_3$/MeOH, 98:2, to afford **10** (220 mg, 62% yield). $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 10.61 (br s, 1H), 8.51 (dd, $J$ = 4.8, 1.2 Hz, 1H), 8.47 (d, $J$ = 1.7 Hz, 1H), 8.23 (br s, 1H), 7.72 (d, $J$ = 8.3 Hz, 1H), 7.56–7.53 (m, 2H), 7.37–7.15 (m, 4H), 7.10 (m, 1H), 4.93 (dd, $J$ = 10.8, 9.9 Hz, 1H), 4.08 (m, 1H), 3.90 (d, $J$ = 9.4 Hz, 1H), 3.73 (d, $J$ = 13.6 Hz, 1H), 3.11–3.06 (m, 2H), 2.46 (td, 1H, $J$ = 12.3, 2.0 Hz, 1H), 2.06 (d, $J$ = 11.2 Hz, 1H), 1.71 (m, 1H). FAB-MS (*m*/*z*): 515, 513 $(M+H)^+$.

### 5.5. *rac*-(2*R*,3*S*,4*S*)-4-(2-Bromophenyl)-2-(3-amino-4-hydroxyphenyl)-3-nitro-1-*N*-(3-pyridylmethyl) piperidine (11a)

To a solution of the nitro compound **10** (210 mg, 0.41 mmo1) in MeOH (20 mL) was added palladium on carbon (21 mg) in a nitrogen atmosphere at room temperature. After the mixture was refluxed for 5 h, the catalyst was removed by Celite filtration, and the solvent was evaporated under reduced pressure. The resulting residue was chromatographed on silica gel, eluted with $CHCl_3$/MeOH, 19:1, to afford **11a** (87 mg, 44% yield). $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 9.14 (br s, 1H), 8.46 (m, 2H), 7.71 (d, $J$ = 6.6 Hz, 1H), 7.65 (d, $J$ = 7.9 Hz, 1H), 7.57 (dd, $J$ = 8.1, 1.1 Hz, 1H), 7.40–7.29 (m, 2H), 7.17 (m, 1H), 6.77 (br s, 1H), 6.63 (d, $J$ = 7.7 Hz, 1H), 6.53 (m, 1H), 5.19 (dd, $J$ = 11.0, 9.6 Hz, 1H), 4.60 (br s, 2H), 3.86 (m, 1H), 3.67 (d, $J$ = 13.8 Hz, 1H), 3.56 (d, $J$ = 9.1 Hz, 1H), 3.04 (d, $J$ = 13.8 Hz, 1H), 2.87 (dd, $J$ = 11.6, 3.3 Hz, 1H), 2.34 (m, 1H), 1.90 (m, 1H), 1.73 (m, 1H). FAB-MS (*m*/*z*): 485, 483 $(M+H)^+$.

### 5.6. *rac*-Aceto-5-[{(3*R*,4*R*)-4-(2-bromophenyl)-3-nitro-1-*N*-(3-pyridylmethyl)piperidin}-(2*S*)-2-yl]-2-hydroxyanilide (12a)

To a solution of **11a** (24 mg, 0.050 mmol) in $CH_2Cl_2$ (5.0 mL) was added acetyl chloride (0.0036 mL, 0.050 mol) at room temperature. After stirred for 1 h, the reaction solution was poured into water and the mixture was extracted with $CHCl_3$/MeOH, 9:1. The extract was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was chromatographed on silica gel, eluted with $CHCl_3$,

and re-precipitated in diethyl ether/hexane to afford **12a** (7.2 mg, 13% yield). $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.51–8.49 (m, 2H), 7.97 (m, 1H) 7.69 (d, $J$ = 7.9 Hz, 1H), 7.53 (d, $J$ = 9.0 Hz, 1H), 7.38–7.11 (m, 4H), 7.10 (d, $J$ = 7.3 Hz, 1H), 7.01 (d, $J$ = 7.5 Hz, 1H), 4.97 (dd, $J$ = 10.8, 8.8 Hz, 1H), 4.05 (m, 1H), 3.80 (d, $J$ = 13.6 Hz, 1H), 3.76 (d, $J$ = 8.8 Hz, 1H), 3.07-3.05 (m, 2H), 2.42 (m, 1H), 2.27 (s, 3H), 2.03 (d, $J$ = 15.2 Hz, 1H), 1.80 (m, 1H). FAB-MS (*m*/*z*): 527, 525 $(M+H)^+$.

### 5.7. *rac*-*N*-(5-[{(3*R*,4*R*)-4-(2-Bromophenyl)-3-nitro-1-*N*-(3-pyridylmethyl)piperidin}-(2*S*)-2-yl]-2-hydroxyphenyl)-*N*′-methyl-carbamate (13a)

To a solution of **11a** (48 mg, 0.10 mmol) in $CH_2Cl_2$/DMF (2:1, 3.0 mL) was added methyl chlorocarbonate (0.0036 mL, 0.050 mmol) at room temperature. After stirred for 30 min, the reaction solution was poured into water and the mixture was extracted with a $CHCl_3$/MeOH, 9:1. The extract was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was chromatographed on silica gel, eluted with $CHCl_3$, re-precipitated in diethyl ether/hexane to afford **13a** (12 mg, 21% yield). $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.51 (br s, 1H), 8.47 (d, $J$ = 3.3 Hz, 1H), 7.67 (d, $J$ = 7.7 Hz, 1H), 7.52 (d, $J$ = 7.7 Hz, 1H), 7.35 (d, $J$ = 7.3 Hz, 1H), 7.27–7.23 (m, 3H), 7.08 (d, $J$ = 7.2 Hz, 1H), 7.04 (br s, 1H), 6.85 (d, $J$ = 7.3 Hz, 1H), 5.01 (dd, $J$ = 10.8, 8.8 Hz, 1H), 4.04 (m, 1H), 3.94–3.76 (m, 5H), 3.13 (d, $J$ = 13.6 Hz, 1H), 3.02 (d, $J$ = 12.3 Hz, 1H), 2.47 (m, 1H), 2.03 (d, $J$ = 12.3 Hz, 1H), 1.69 (m, 1H). FAB-MS (*m*/*z*): 543, 541 $(M+H)^+$.

### 5.8. *rac*-*N*-([5-{(3*R*,4*R*)-4-(2-Bromophenyl)-3-nitro-1-*N*-(3-pyridylmethyl)piperidin}-(2*S*)-2-yl]-2-hydroxyphenyl) methanesulfonamide (14a)

To a solution of **11a** (48 mg, 0.10 mmol) in $CH_2Cl_2$/DMF (2:1, 3.0 mL) was added methanesulfonyl chloride (0.0077 mL, 0.10 mmol) at room temperature. After stirred for 30 min, the reaction solution was poured into water and the mixture was extracted with $CHCl_3$/MeOH, 9:1. The extract was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was chromatographed on silica gel, eluted with $CHCl_3$, re-precipitated in diethyl ether/hexane to afford **14a** (8.9 mg, 16% yield). $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.54 (br s, 1H), 8.45 (d, $J$ = 4.0 Hz, 1H), 7.69 (d, $J$ = 7.6 Hz, 1H), 7.69 (m, 1H), 7.53 (d, $J$ = 8.1 Hz, 1H), 7.34–7.21 (m, 4H), 7.08 (d, $J$ = 7.0 Hz, 1H), 6.92 (d, $J$ = 8.1 Hz, 1H), 4.98 (dd, $J$ = 10.7, 9.8 Hz, IH), 4.06 (m, 1H), 3.90 (d, $J$ = 14.1 Hz, 1H), 3.82 (d, $J$ = 9.0 Hz, 1H), 3.18 (d, $J$ = 14.1 Hz, 1H), 3.05 (dd, $J$ = 13.4,l.6 Hz, 1H), 2.51 (m, 1H), 2.04 (m, 1H), 1.76 (m, 1H), 1.43 (s, 3H). FAB-MS (*m*/*z*): 563, 561 $(M+H)^+$.

### 5.9. *rac*-*N*-([5-{(3*R*,4*R*)-4-(2-Bromophenyl)-3-nitro-1-*N*-(3-pyridylmethyl)piperidin}-(2*S*)-2-yl]-2-hydroxyphenyl) ethanesulfonamide (15a)

To a solution of **11a** (24 mg, 0.05 mmol) in $CH_2Cl_2$ (10 mL) were added ethanesulfonyl chloride (0.0094 mL, 0.10 mmol) and pyridine (0.10 mL) at room temperature. After stirred at room temperature for 30 min, the reaction solution was poured into water and the mixture was extracted with $CHCl_3$/MeOH, 9:1. The extract was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was chromatographed on silica gel, eluted with $CHCl_3$, re-precipitated in diethyl ether/hexane to afford **15a** (2.3 mg, 8.0% yield). $^1$H NMR (DMSO-$d_6$, 270 MHz) $\delta$ 9.04 (s, 1H), 8.71 (s, 1H) 8.56 (d, $J$ = 4.6 Hz, 1H), 8.44–8.30 (m, 2H), 7.75 (d, $J$ = 8.9 Hz, 1H), 7.68 (d, $J$ = 7.6 Hz, 1H), 7.55 (d, $J$ = 7.9 Hz, 1H), 7.49 (m, 1H), 7.38–7.29 (m, 2H), 7.16 (m, 1H), 6.83 (d, $J$ = 8.3 Hz, 1H), 5.27 (dd, $J$ = 10.6, 9.3 Hz, 1H), 3.86 (m, 1H), 3.70 (d, $J$ = 9.2 Hz, 1H), 3.60 (d, $J$ = 13.5 Hz, 1H), 3.05 (d, $J$ = 13.5 Hz, 1H), 3.00 (q, $J$ = 7.4 Hz, 2H), 2.86 (d, $J$ = 12.2 Hz, 1H), 2.33 (m, 1H), 1.80–1.70 (m, 2H), 1.18 (t, $J$ = 7.4 Hz, 3H). FAB-MS (*m*/*z*): 577, 575 $(M+H)^+$.

### 5.10. *rac*-*N*-(5-{[(3*R*,4*R*)-4-(2-Bromophenyl)-3-nitro-1-*N*-(3-pyridylmethyl)piperidin]-(2*S*)-2-yl}-2- hydroxyphenyl) *p*-toluenesulfonamide (16a)

To a solution of **11a** (24 mg, 0.050 mmol) in $CH_2Cl_2$ (2.0 mL) was added *p*-toluenesulfonyl chloride (9.5 mg, 0.050 mmol) at room temperature. After stirred at room temperature for 2 h, the reaction solution was poured into water and the mixture was extracted with $CHCl_3$/MeOH, 9:1. The extract was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was purified by preparative silica plate with $CHCl_3$/MeOH, 9:1, to afford **16a** (9.5 mg, 30% yield). $^1$H NMR (DMSO-$d_6$, 270 MHz) $\delta$ 9.73 (br s, 1H), 9.11 (br s, 1H), 8.46 (br s, 1H), 7.72 (m, 1H), 7.56 (d, $J$ = 4.0 Hz, 1H), 7.37–7.33 (m, 2H), 7.18 (d, $J$ = 8.2 Hz, 4H), 7.20–7.13 (m, 3H), 6.66 (d, $J$ = 7.9 Hz, 1H), 5.20 (dd, $J$ = 10.9, 10.2 Hz, 1H), 3.87 (m, 1H), 3.67 (d, $J$ = 9.2 Hz, 1H), 3.50 (d, $J$ = 14.2 Hz, 1H), 3.04 (d, $J$ = 14.2 Hz, 1H), 2.86 (d, $J$ = 10.9 Hz, 1H), 2.41 (m, 1H), 2.24 (s, 3H), 1.82–1.70 (m, 2H). FAB-MS (*m*/*z*): 638, 636 $(M+H)^+$.

### 5.11. *rac*-(2*R*,3*S*,4*S*)-4-(2-Bromophenyl)-2-(3-ethylamino-4-hydroxyphenyl)-3-nitro-1-*N*-(3-pyridylmethyl)piperidine (17a)

To a suspension of lithium aluminum hydride (20 mg, 0.50 mmol) in THF (100 mL) was added an ice-cold solution (10 mL) of **12a** (52 mg, 0.10 mmol). After stirred for 12 h while elevating the temperature to room temperature, the reaction mixture was poured into dilute aqueous HCl, followed by stirring for 10 min. The mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$/MeOH, 9:1. The extract was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was purified by preparative silica plate with $CHCl_3$ and re-precipitated in diethyl ether/hexane to afford **17a** (15 mg, 31% yield). $^1$H NMR (DMSO-$d_6$, 270 MHz) $\delta$ 9.45 (br s, 1H), 8.65 (br s, 1H), 8.48 (dd, $J$ = 4.8, 1.5 Hz, 1H), 7.80 (br s, 1H), 7.59–7.52 (m, 2H), 7.37–7.06 (m, 7H), 4.99 (dd, $J$ = 10.8, 9.9 Hz, 1H),

4.05 (m, 1H), 3.89–3.83 (m, 2H), 3.08–3.03 (m, 2H), 2.45 (m, 1H), 2.04 (m, 1H), 1.66 (m, 1H). FAB-MS (*m*/*z*): 513, 511 $(M+H)^+$.

### 5.12. *rac*-(2*R*,3*S*,4*S*)-4-(2-Bromophenyl)-2-(3-isopropylamino-4-hydroxyphenyl)-5-nitro-1-*N*-(3-pyridylmethyl)piperidine (18a)

To a solution of **11a** (48 mg, 0.1 mmo1) in THF (10 mL) were added acetone (0.015 mL, 0.20 mmol) and borane–methyl sulfide complex (0.010 mL, 0.11 mmol) at room temperature. After stirred for 12 h, the solvent was evaporated under reduced pressure. The resulting residue was dissolved in MeOH (10 mL), and to the solution was added aqueous HCl (1.0 mol/L, 2.0 mL). After stirred at 50 °C for 1 h, the mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was chromatographed on silica gel, eluted with $CHCl_3$/MeOH, 9:1, to afford **18a** (24 mg, 46% yield). $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 8.52 (s, 1H), 8.47 (d, $J$ = 6.9 Hz, 1H), 7.75 (d, $J$ = 8.6 Hz, 1H), 7.53 (d, $J$ = 7.6 Hz, 1H), 7.42–7.28 (m, 3H), 7.13 (m, 1H), 6.74–6.64 (m, 3H), 4.99 (dd, $J$ = 10.9, 9.5 Hz, 1H), 4.11 (m, 1H), 3.90 (d, $J$ = 14.2 Hz, 1H), 3.74 (d, $J$ = 9.5 Hz, 1H), 3.63 (m, 1H), 2.96 (m, 2H), 2.47 (m, 1H), 2.05 (m, 1H), 1.73 (m, 1H), 1.25 (d, $J$ = 6.2 Hz, 3H), 1.17 (d, $J$ = 6.2 Hz, 3H). FAB-MS (*m*/*z*): 527, 525 $(M+H)^+$.

### 5.13. *rac*-*N*-([5-{(3*R*,4*R*)-4-(2-Bromophenyl)-3-nitro-1-*N*-(3-pyridylmethyl)piperidin}-(2*S*)-2-yl]-2-hydroxyphenyl) urea (19a)

To a solution of **11a** (96 mg, 0.20 mmol) in THF (10 mL) were added acetic acid (1.0 mL) and potassium cyanate (160 mg, 2.0 mmol) at room temperature. After stirred for 1 h, the reaction solution was poured into water and the mixture was extracted with $CHCl_3$/MeOH, 9:1. The extract was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was chromatographed on silica gel, eluted with $CHCl_3$, and re-precipitated in diethyl ether/hexane to afford **19a** (21 mg, 20% yield). $^1H$ NMR (DMSO-$d_6$, 270 MHz) $\delta$ 10.08 (s, 1H), 8.48 (d, $J$ = 1.3 Hz, 1H), 8.44 (dd, $J$ = 4.8, 1.4 Hz, 1H), 8.12 (br s, 1H), 8.03 (s, 1H), 7.76–7.71 (m, 2H), 7.57 (dd, $J$ = 7.9, 1.0 Hz, 1H), 7.39–7.29 (m, 2H), 7.17 (m, 1H), 6.89 (br s, 1H), 6.67 (d, $J$ = 7.9 Hz, 1H), 6.24 (br s, 2H), 5.19 (dd, $J$ = 10.9, 9.9 Hz, 1H), 3.88 (m, 1H), 3.69–3.65 (m, 2H), 3.04 (d, $J$ = 13.5 Hz, 1H), 2.95 (m, 1H), 2.38 (m, 1H), 1.88–1.68 (m, 2H). FAB-MS (*m*/*z*): 528, 526 $(M+H)^+$.

### 5.14. *rac*-*N*-([5-{(3*R*,4*R*)-4-(2-Bromophenyl)-3-nitro-1-*N*-(3-pyridylmethyl)piperidin}-(2*S*)-2-yl]-2-hydroxyphenyl) sulfamide (20a)

To a solution of **11a** (48 mg, 0.10 mmol) in *N*,*N*-dimethylacetamide solution (1.0 mL) was added sulfamoyl chloride (12 mg, 0.10 mmol) at room temperature. After stirred for 15 min, the reaction solution was poured into water, and the powder formed was collected by filtration. The resulting crude product was chromatographed on silica gel, eluted with chloroform/methanol, 98:2, and re-precipitated in diethyl ether/hexane to obtain **20a** (23 mg, 41% yield). $^1H$ NMR (DMSO-$d_6$, 270 MHz) $\delta$ 9.87 (br s, 1H), 8.45 (br s, 2H), 7.87 (br s, 1H), 7.75 (d, $J$ = 6.9 Hz, 1H), 7.68 (m, 1H), 7.62–7.59 (m, 2H), 7.39 (m, 1H), 7.31 (m, 1H), 7.21–7.18 (m, 3H), 6.98 (br s, 1H), 6.79 (d, $J$ = 7.9 Hz, 1H), 5.38 (dd, $J$ = 10.9, 9.6 Hz, 1H), 3.87 (m, 1H), 3.69 (d, $J$ = 9.6 Hz, 1H), 3.65 (d, $J$ = 14.2 Hz, 1H), 3.03 (d, $J$ = 14.2 Hz, 1H), 2.88 (m, 1H), 2.37 (m, 1H), 1.88 (m, 1H), 1.65 (m, 1H). FAB-MS (*m*/*z*): 564, 562 $(M+H)^+$.

### 5.15. *rac*-(2*R*,3*S*,4*S*)-4-(2-Ethylphenyl)-2-(3-benzylamino-4-hydroxyphenyl)-3-nitro-1-*N*-(3-pyridylmethyl)piperidine (21b)

To a solution of **11b** (48 mg, 0.10 mmol) in THF (10 mL) were added benzaldehyde (0.010 mL, 0.10 mmol), and sodium triacetoxyborane hydride (210 mg, 1.0 mmol) at room temperature. After stirred for 12 h, the reaction mixture was poured into water, and the mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was chromatographed on silica gel, eluted with $CHCl_3$/MeOH, 9:1, to afford **21b** (16 mg, 61% yield). $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 8.55 (br s, 1H), 8.45 (d, $J$ = 4.0 Hz, 1H), 7.50 (d, $J$ = 7.9 Hz, 1H), 7.43–7.11 (m, 10H), 6.87–6.66 (m, 3H), 4.92 (dd, $J$ = 10.5, 9.9 Hz, 1H), 4.38 (s, 2H), 3.85 (d, $J$ = 13.5 Hz, 1H), 3.67–3.64 (m, 2H), 3.06–2.97 (m, 2H), 2.80–2.52 (m, 2H), 2.37 (m, 1H), 1.90–1.85 (m, 2H), 1.18 (t, $J$ = 7.6 Hz, 3H). FAB-MS (*m*/*z*): 523 $(M+H)^+$.

### 5.16. *rac*-(2*R*,3*S*,4*S*)-4-(2-Ethylphenyl)-2-[3-(2-pyridyl)methylamino-4-hydroxyphenyl]-3-nitro-1-*N*-(3-pyridylmethyl)piperidine (22α)

According to the procedure for the synthesis of **21b**, **11b** (48 mg, 0.10 mmol), 2-pyridinecarboxaldehyde (0.010 mL, 0.10 mmol), and sodium triacetoxyborane hydride (210 mg, 1.0 mmol) afforded **22α** (9.7 mg, 37% yield). ESI-MS (*m*/*z*): 524 $(M+H)^+$.

### 5.17. *rac*-(2*R*,3*S*,4*S*)-4-(2-Ethylphenyl)-2-[3-(3-pyridyl)methylamino-4-hydroxyphenyl]-3-nitro-1-*N*-(3-pyridylmethyl)piperidine (22β)

According to the procedure for the synthesis of **21b**, **11b** (48 mg, 0.10 mmol), 4-pyridinecarboxaldehyde (0.010 mL, 0.10 mmol) and sodium triacetoxyborane hydride (210 mg, 1.0 mmol) afforded **22β** (20 mg, 78% yield). ESI-MS (*m*/*z*): 524 $(M+H)^+$.

### 5.18. *rac*-(2*R*,3*S*,4*S*)-4-(2-Ethylphenyl)-2-[3-(4-pyridyl)methylamino-4-hydroxyphenyl]-3-nitro-1-*N*-(3-pyridylmethyl)piperidine (22γ)

According to the procedure for the synthesis of **21b**, **11b** (48 mg, 0.10 mmol), 4-pyridinecarboxaldehyde (0.010 mL, 0.10 mmol), and sodium triacetoxyborane

hydride (210 mg, 1.0 mmol) afforded **22γ** (9.4 mg, 36% yield). ESI-MS (*m*/*z*): 524 $(M+H)^+$.

### 5.19. *rac*-(2*R*,3*S*,4*S*)-4-(2-Bromophenyl)-3-nitro-2-phenyl-piperidine (23)

**Step 1** Methyl 3-(2-bromophenyl)-4-nitrobutyrate (1.8 g, 6.0 mmol), benzaldehyde (0.61 mL, 6.0 mmol), and ammonium acetate (920 mg, 12 mmol) were heated under reflux in ethanol for 20 h. The solvent was evaporated under reduced pressure, and the resulting residue was chromatographed on silica gel, eluted with $CHCl_3$/MeOH, 98:2, to afford a piperidin-2-one derivative (1.4 g, 57% yield). ESI-MS (*m*/*z*): 440 $(M+H)^+$. **Step 2** According to the procedure for the synthesis of **1a**, the resulting piperidin-2-one derivative and borane-methyl sulfide complex (2.7 mL, 30 mmol) afforded **23** (890 mg, 41% yield). $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 8.62 (d, $J = 2.6$ Hz, 1H), 7.56 (d, $J = 8.2$ Hz, 1H), 7.37–7.21 (m, 5H), 7.22 (d, $J = 7.6$ Hz, 1H), 7.13–7.08 (m, 2H), 6.27 (d, $J = 5.6$ Hz, 1H), 5.56 (m, 1H), 4.40 (m, 1H), 4.20 (m, 1H), 3.83 (m, 1H), 2.45 (m, 1H), 1.92 (m, 1H). ESI-MS (*m*/*z*): 426 $(M+H)^+$.

### 5.20. *rac*-(2*R*,3*S*,4*S*)-4-(2-Bromophenyl)-1-(3*H*-imidazol-4-ylmethyl)-3-nitro-2-phenyl-piperidine (24)

To a solution of **23** (720 mg, 2.0 mmol) in acetic acid (5.0 mL) were added 4-imidazolecarboxaldehyde (190 mg, 2.0 mmol) and sodium triacetoxyborohydride (2.1 g, 10 mmol) at room temperature. After stirred for 12 h, the reaction solution was poured into water, and the mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was chromatographed on silica gel, eluted with $CHCl_3$/MeOH, 9:1, to afford **24** (360 mg, 41% yield). $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 7.71 (br s, 1H), 7.52 (d, $J = 7.9$ Hz, 1H), 7.45–7.26 (m, 7H), 7.07 (m, 1H), 6.82 (br s, 1H), 6.01 (br s, 1H), 4.98 (dd, $J = 11.2$, 9.9 Hz, 1H), 3.97 (m, 1H), 3.78 (d, $J = 9.3$ Hz, 1H), 3.65 (d, $J = 14.5$ Hz, 1H), 3.28 (d, $J = 14.5$ Hz, 1H), 3.17 (m, 1H), 2.53 (m, 1H), 2.05 (m, 1H), 1.75 (m, 1H). ESI-MS (*m*/*z*): 444, 442 $(M+H)^+$.

### 5.21. *rac*-(2*R*,3*S*,4*S*)-4-(2-Bromophenyl)-1-[(1-*N*-methylimidazol)-4-yl-methyl]-3-nitro-2-phenyl-piperidine (25) and *rac*-(2*R*,3*S*,4*S*)-4-(2-bromophenyl)-1-[(3-*N*-methylimidazol)-4-yl-methyl]-3-nitro-2-phenyl-piperidine (26)

To an ice-cold solution of **24** (160 mg, 0.37 mmol) in DMF (5.0 mL) were added methyl iodide (0.023 mL, 0.37 mmol) and potassium carbonate (50 mg, 0.36 mmol). After the mixture was stirred for 1 h, the reaction solution was poured into water and the mixture was extracted with $CHCl_3$. The extract was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The resulting residue was purified by preparative silica plate with $CHCl_3$/MeOH, 9:1, to afford **25** (6.7 mg, 4.2% yield), **26** (19 mg, 12% yield), and a mixture of **25** and **26** (110 mg, 69% yield). Compound **25**: $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 8.00 (br s, 1H), 7.53 (d, $J = 8.3$ Hz, 1H), 7.43–7.24 (m, 7H), 7.08 (m, 1H), 6.88 (br s, 1H), 5.03 (dd, $J = 10.9$, 9.6 Hz, 1H), 4.05 (m, 1H), 3.73 (d, $J = 9.6$ Hz, 1H), 3.63(s, 3H), 3.55 (d, $J = 14.0$ Hz, 1H), 3.14–3.02 (m, 2H), 2.27 (m, 1H), 2.05 (m, 1H), 1.61 (m, 1H). ESI-MS (*m*/*z*): 458, 456 $(M+H)^+$. Compound **26**: $^1H$ NMR ($CDCl_3$, 270 MHz) $\delta$ 8.02 (br s, 1H), 7.52 (dd, $J = 7.9$, 1.0 Hz, 1H), 7.43–7.24 (m, 7H), 7.06 (m, 1H), 6.58 (br s, 1H), 4.97 (dd, $J = 11.2$, 9.6 Hz, 1H), 3.99 (m, 1H), 3.79 (d, $J = 9.6$ Hz, 1H), 3.65 (s, 3H), 3.62 (d, $J = 14.0$ Hz, 1H), 3.36–3.24 (m, 2H), 2.61 (m, 1H), 2.04 (m, 1H), 1.78 (m, 1H). FAB-MS (*m*/*z*): 458, 456 $(M+H)^+$.

### 5.22. 1-Trityl-1*H*-imidazol-4-ylmethyl acetate (28)

**Step 1** To a solution of 4-(hydroxymethyl)-imidazole hydrochloride salt (880 mg, 6.5 mmol) in DMF (20 mL) was added triethylamine (2.3 mL, 16.0 mmol) which immediately caused a white precipitate to form. After stirred for 10 min, a solution of chlorotriphenylmethane (2.0 g, 7.2 mmol) in DMF (15 mL) was added dropwise. After stirred overnight under a nitrogen atmosphere, the reaction mixture was poured into ice water and the mixture was filtered. The solid was washed with cold dioxane and dried under vacuum to afford (1-trityl-1*H*-imidazol-4-yl)-methanol as a white powder (2.2 g, 100% yield). $^1H$ NMR ($CD_3CO_2D$, 250 MHz) $\delta$ 8.56 (d, 1H), 7.57–7.40 (m, 7H), 7.38–7.18 (m, 9H), 4.78 (s, 2H). EI-MS (*m*/*z*): 363 $(M+Na)^+$. **Step 2** To a suspension of (1-trityl-1*H*-imidazol-4-yl)-methanol (2.3 g, 6.5 mmol) in pyridine (15 mL) was added acetic anhydride (2.0 mL, 20 mmol) in 5 portions at room temperature over 30 min. After stirred under a nitrogen atmosphere overnight, the reaction mixture had become homogeneous and was diluted with EtOAc (30 mL) and this mixture was washed with water, aqueous HCl (5%), and saturated aqueous $NaHCO_3$. The organic layer was then dried over $MgSO_4$ and the solvent evaporated to afford **28** (2.3 g, 93% yield) as a white solid. $^1H$ NMR ($CDCl_3$, 250 MHz) $\delta$ 8.61 (d, 1H), 7.38–7.26 (m, 9H), 7.18–7.07 (m, 7H), 5.05 (s, 2H), 2.07 (s, 3H). EI-MS (*m*/*z*): 405 $(M+Na)^+$.

### 5.23. 3-(4-Cyano-benzyl)-3*H*-imidazol-4-ylmethyl acetate (29)

To a solution of **28** (2.3 g, 6.1 mmol) in EtOAc (20 mL) was added α-bromo-*p*-tolunitrile (1.30 g, 6.70 mmol) at room temperature and heated at 60 °C. After stirred at 60 °C overnight, a white precipitate had formed. The reaction mixture was filtered and the solid material dissolved in MeOH (20 mL) and heated at 60 °C, again. After stirred at 60 °C for 2 h, the reaction mixture was cooled and the solvent evaporated. The remaining solid was triturated with hexane to afford **29** (1.38 g, 68% yield) as a white powder. $^1H$ NMR (250 MHz, $CD_3OD$) $\delta$ 7.80–7.75 (m, 2H), 7.75–7.62 (m, 1H), 7.56–7.47 (m, 2H), 7.30–7.23 (m, 1H), 5.72 (s, 2H), 5.20 (s, 2H), 1.90 (s, 3H). EI-MS (*m*/*z*): 256 $(M+H)^+$.

### 5.24. 4-(5-Hydroxymethyl-imidazol-1-ylmethyl)-benzonitrile (30)

To a solution of **29** (1.4 g, 4.1 mmol) in THF/water (3:1, 20 mL) was added lithium hydroxide (520 mg, 12 mmol)

at room temperature. After stirred for 1 h, the reaction mixture was diluted with EtOAc (30 mL) and washed with water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over sodium sulfate, and the solvent was evaporated under reduced pressure to afford **30** (530 mg, 60% yield) as a yellow brown solid. $^1H$ NMR ($CD_3OD$, 250 MHz) $\delta$ 7.68–7.55 (m, 3H), 7.22 (d, 2H), 6.89 (s, 1H), 5.30 (s, 2H), 4.76 (s, 2H), 4.34 (s, 1H). EI-MS (*m*/*z*): 213 $(M+)^+$.

### 5.25. *rac*-4-(5-{[(2*R*,3*S*,4*S*)-4-(2-Bromophenyl)-3-nitro-2-phenyl-piperidin]-1-ylmethyl}-imidazol-1-ylmethyl) benzonitrile (31)

To a solution of 4-(5-hydroxymethyl-imidazol-1-ylmethyl)-benzonitrile **30** (130 mg, 0.61 mmol) in DMSO (5.0 mL), triethylamine (0.34 mL, 2.4 mmol) was added followed by the sulfur trioxide pyridine complex (240 mg, 1.5 mmol) at room temperature under a nitrogen atmosphere. After stirred for 40 min, the reaction mixture was diluted with EtOAc (20 mL) and washed with water and saturated aqueous $NaHCO_3$. The organic layer was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. This residue was then dissolved in $CH_2Cl_2$ (2.0 mL) and cooled to 0 °C under a nitrogen atmosphere. To this solution was added (220 mg, 0.61 mmol) along with sodium triacetoxyborohydride (190 mg, 0.92 mmol) and the reaction mixture left to warm to room temperature overnight. After this time the reaction mixture was diluted in EtOAc (20 mL) and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. This residue was chromatographed on silica gel, to afford **31** (6.4 mg, 1.9% yield). $^1H$ NMR ($CD_3OD$, 250 MHz) $\delta$ 7.58 (t, 3H); 7.45 (d, 1H), 7.38–7.10 (m, 7H), 7.04 (dt, 1H), 6.95 (d, 2H), 6.81 (s, 1H), 4.78 (s, 4H), 3.91 (td, 1H), 3.56 (d, 1H), 2.92 (dt, 1H), 2.21 (td, 2H), 1.55–1.32 (m, 2H). EI-MS (*m*/*z*): 558, 556 $(M+H)^+$, EI-MS (*m*/*z*): 556, 554 $(M-H)^-$.

### 5.26. 3-Allyl benzoylacetate (32)

Ethyl benzoylacetate (50 mL, 0.29 mol), allyl alcohol (300 mL, 4.4 mol), and dimethylaminopyridine (11 g, 0.090 mol) were mixed and heated at reflux for 3 days. The solution was evaporated and NMR indicated approximately 15% starting material remained. Allyl alcohol (300 mL, 4.4 mol) was added and the solution was refluxed for 18 h. The solution was evaporated and no starting material was observed by NMR. The resulting residue was dissolved in EtOAc and the solution washed with saturated ammonium chloride solution until all dimethylaminopyridine was removed. The organic layer was dried over sodium sulfate and evaporated under reduced pressure. Compound **32** (32 g, 54% yield) was isolated by vacuum distillation (0.02 torr, 130–135 °C). $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.90 (d, $J$ = 7.8 Hz, 2H), 7.55 (m, 1H), 7.40 (m, 2H), 5.85 (m, 1H), 5.26 (d, $J$ = 17.0 Hz, 1H), 5.18 (d, $J$ = 10 Hz, 1H), 4.61 (d, $J$ = 5.9 Hz, 2H), 3.99 (s, 2H).

### 5.27. 2-Ethyl-cinnamaldehyde (33)

To a suspension of $NaHCO_3$ (63 g, 0.75 mol) and tetrabutylammonium chloride hydrate (83 g, 0.30 mol) in DMF (300 mL), 1-ethyl-2-iodobenzene (43 mL, 0.30 mol) and acrolein (47 mL, 0.60 mol) were added and the mixture was stirred for 15 min. Palladium acetate (3.4 g, 15 mmol) was added and the mixture was stirred under nitrogen for 2 days. Additional palladium acetate (2.0 g, 8.8 mmol) was added at 23 h. An aqueous extraction with EtOAc failed to give separable layers and the organic/aqueous mixture was evaporated. The resulting residue was loaded directly onto a silica plug and eluted with hexane/$CH_2Cl_2$, 1:1 to 0:1. The recovered product was dissolved in EtOAc (800 mL) and the solution was washed with water. The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was chromatographed on silica gel, eluted with hexane/$CH_2Cl_2$, 1:1, to afford **33** (6.1 g, 13% yield). $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 9.70 (d, $J$ = 7.3 Hz, 1H), 7.77 (d, $J$ = 16.0 Hz, 1H), 7.56 (d, $J$ = 8.3 Hz, 1H), 7.33 (m, 1H), 7.22 (m, 2H), 6.64 (dd, $J$ = 15.6, 7.8 Hz, 1H), 2.78 (q, $J$ = 7.6, 15.0 Hz, 2H), 1.21 (t, $J$ = 7.6 Hz, 3H).

### 5.28. *rac*-3-Allyl [4-(2-ethylphenyl)-2-phenyl-1-*N*-(3-pyridylmethyl)-2,3-dehydro-piperidin]-3-ylcarboxylate (35)

**Step 1** Proline lithium salt (0.26 g, 2.2 mmol) was placed in a 2-necked flask and evacuated and flushed with nitrogen 4×. Allyl benzoyl acetate **32** (13.2 g, 65 mmol) in $CHCl_3$ (10 mL) was transferred to the reaction flask by cannula. The aldehyde **33** (6.9 g, 43 mmol) in $CHCl_3$ (10 mL) was transferred to the reaction flask by cannula. Total $CHCl_3$ used was 65 mL. After all reagents and solvent were added to the flask, a subsurface nitrogen purge was maintained for 15 min. After stirred under nitrogen for 2 days, the reaction was quenched with aqueous HCl (2.0 mol/L). The product was extracted with $CH_2Cl_2$. The extracts were washed with brine, dried over sodium sulfate, and evaporated under reduced pressure. The resulting residue was chromatographed on silica gel, eluted with hexane/EtOAc, 9:1, to provide a mixture of the product isomers **34** with impurities (9.9 g). **Step 2** To an ice-cold mixture of 3-(aminomethyl)pyridine (3.0 g, 27 mmol), sodium triacetoxyborohydride (12 g, 54 mmol), and acetic acid (0.80 mL, 14 mmol) in $CH_2Cl_2$ (65 mL) was added the aldehyde **34** (9.9 g, 27.0 mmol) in $CH_2Cl_2$ (15 mL) dropwise over 1.3 h. After stirred at 0 °C for an additional 30 min, the ice bath was removed and the reaction mixture was stirred at room temperature, overnight. The reaction mixture was washed with saturated aqueous $NaHCO_3$. The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was chromatographed on silica gel, eluted with $CH_2Cl_2$/EtOAc, 9:1, to afford **35** (5.9 g, 31% yield over 2 steps). $^1H$ NMR ($CDCl_3$, 250 MHz): $\delta$ 8.43 (s, 1H), 8.34 (s, 1H), 7.44–7.05 (m, 13H), 5.25 (m, 1H), 4.77 (dd, $J$ = 11.0, 1.5 Hz, 1H), 4.70 (dd, $J$ = 17.0, 1.6 Hz, 1H), 4.47 (d, $J$ = 5.5 Hz, 1H), 4.14–3.97 (m, 4 H), 3.09 (dt, $J$ = 13.0, 3.1 Hz, 1H), 2.90 (m, 1H), 2.80 (qn, 1H),

2.63 (qn, 1H), 1.96 (m, 1H), 1.65 (m, 1H), 1.24 (t, $J$ = 7.5 Hz, 3H). ESI-MS ($m/z$): 439 $(M+H)^+$.

### 5.29. *rac*-3-Allyl [(2*R*,4*R*)-4-(2-ethylphenyl)-2-phenyl-1-*N*-(3-pyridylmethyl)-piperidin]-(3*S*)-3-ylcarboxylate (36)

Sodium cyanoborohydride (1.0 g, 16 mmol) and bromocresol green (1.0 mg) were added to a solution of the enamine **35** (5.9 g, 14 mmol) in THF (65 mL) and absolute EtOH (130 mL). To the resultant blue solution was added dropwise a solution of concd HCl/EtOH (1:2) to maintain a yellow color over the course of a day. The solution was stirred at room temperature, overnight. Thirty minutes prior to workup, concd HCl/EtOH solution (10 mL) was added to the reaction mixture. Aqueous HCl (5.0 mol/L) was then added at a rate such that with ice bath cooling, the mixture was kept at 25 °C. A clear yellow solution formed after 80 mL was added and a total of 100 mL was added. The solution was basified with aqueous NaOH (5.0 mol/L) cooling with ice bath to keep the mixture below 26 °C. The product was extracted with EtOAc. The extract was dried over sodium sulfate and evaporated under reduced pressure. The resulting residue, a blue foam, 5.2 g, was chromatographed on silica gel, eluted with $CH_2Cl_2$/EtOAc, 9:1 to 1:1, to afford **36** as a yellow solid (3.6 g, 61%) and a borane-complexed product (0.93 g). *Decomposition of borane-complex*. To a solution of the borane-complexed product (0.89 g) in MeOH (20 mL) was added Amberlyst A-21 resin (9.0 g) and the slurry was refluxed for 48 h. The mixture was cooled to room temperature and filtered. After evaporation, the residue was dissolved in $CH_2Cl_2$. The solution was dried over sodium sulfate and evaporated under reduced pressure to afford **36** as an oil which crystallized upon standing (0.74 g, 13% yield). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.13 (d, $J$ = 7.8 Hz, 2H), 7.44 (d, $J$ = 7.3 Hz, 1H), 6.93–6.67 (m, 8 H), 4.92–4.82 (m, 1H), 4.46 (dd, $J$ = 11.0, 1.5 Hz, 1H), 4.27 (dd, $J$ = 17.0, 1.7 Hz, 1H), 3.67–3.52 (m, 3H), 3.27 (d, $J$ = 3.9 Hz, 1H), 2.92–2.86 (m, 2H), 2.72–2.62 (m, 3H), 2.44–2.35 (m, 1H), 2.32–2.23 (m, 1H), 1.87 (dt, $J$ = 12.0, 2.4 Hz, 1H), 1.22–1.18 (m, 1H), 0.89 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 63 MHz) $\delta$ 170.11, 149.93, 148.20, 141.50, 140.90, 139.23, 136.38, 134.49, 131.91, 128.76, 128.58, 128.42, 127.72, 127.62, 126.70, 125.91, 123.46, 117.03, 69.93, 63.95, 56.53, 54.15, 53.93, 40.59, 25.84, 25.17, 15.79. ESI-MS ($m/z$): 441 $(M+H)^+$.

### 5.30. *rac*-[(2*R*,4*R*)-4-(2-Ethylphenyl)-2-phenyl-1-*N*-(3-pyridylmethyl)piperidin]-(3*S*)-3-ylcarbonic acid (37) and *rac*-3-allyl [(2*R*,4*R*)-4-(2-ethylphenyl)-2-phenyl-1-*N*-(3-pyridylmethyl)- piperidin]- (3*S*)-3-ylcarboxylate (38)

The ester **11a** (1.0 g, 2.3 mmol) was treated with aqueous sodium allyloxide (10%wt) in allyl alcohol (50 mL). The solution was refluxed for 22 h. After cooling to room temperature, the solution was diluted with $CH_2Cl_2$ and saturated ammonium chloride solution. The aqueous solution was neutralized with HCl (1.0 mol/L). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic extracts were dried over sodium sulfate and evaporated to give an orange oil. The oil was dissolved in EtOAc (25 mL) and the products extracted into aqueous HCl (1.0 mol/L). The combined aqueous fractions were layered with $CH_2Cl_2$ and aqueous NaOH (1.0 mol/L) was added to reach pH 5–6. The products were extracted into $CH_2Cl_2$. The combined organic fractions were washed with aqueous NaOH (1.0 mol/L, $2 \times 20$ mL) to remove the acid **37**. The organic layer was dried over sodium sulfate and evaporated to give the ester **38**. The pH of the aqueous layer was adjusted to 5–6 with HCl (1.0 mol/L) and the acid **37** was extracted with $CH_2Cl_2$. The organic layer was dried over sodium sulfate and evaporated to give the acid **37**. Allyloxy-derived impurities were present in each sample so both the ester and acid **37** were separately extracted into acid or base for further purification. **37** (0.41 g, 40% yield) and **38** (0.23 g, 25% yield) were isolated. Compound **37**: $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.27 (s, 1H), 8.22 (d, $J$ = 3.9 Hz, 1H), 7.52 (d, $J$ = 7.8 Hz, 1H), 7.39–7.37 (m, 2H), 7.23–7.12 (m, 7 H), 7.07 (m, 1H), 7.02 (d, $J$ = 3.9 Hz, 1H), 3.66 (d, $J$ = 13.7 Hz, 1H), 3.46 (d, $J$ = 9.8 Hz, 1H), 3.27–3.20 (m, 1H), 3.00–2.85 (m, 3H), 2.69 (m, 1H), 2.50 (m, 1H), 2.22 (m, 1H), 1.77–1.69 (m, 2H), 1.09 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 63 MHz) $\delta$ 175.57, 148.66, 146.94, 141.68, 140.27, 137.70, 128.77, 128.72, 128.42, 127.99, 126.63, 126.51, 126.15, 123.62, 70.74, 57.51, 55.93, 52.93, 40.35, 33.35, 25.84, 15.89. FD-MS ($m/z$): 401 $(M+H)^+$. Compound **38**: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.42 (s, 2H), 7.54 (d, $J$ = 7.3 Hz, 1H), 7.40 (s, 2H), 7.31–7.17 (m, 5 H), 7.12–7.00 (m, 3H), 5.07 (m, 1H), 4.74 (m, 1H), 4.54 (m, 1H), 3.90 (m, 1H), 3.80 (m, 1H), 3.73 (d, $J$ = 13.7 Hz, 1H), 3.50 (d, $J$ = 9.8 Hz, 1H), 3.27 (m, 1H), 3.04–2.88 (m, 3H), 2.75–2.66 (m, 1H), 2.58–2.48 (m, 1H), 2.26 (s, 1H), 1.75 (s, 2H), 1.12 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 63 MHz) $\delta$ 172.33, 150.18, 148.34, 141.71, 140.82, 140.09, 136.29, 131.61, 128.85, 128.70, 128.27, 127.98, 126.55, 126.46, 126.07, 123.38, 117.30, 70.89, 64.41, 57.92, 56.42, 52.97, 40.45, 33.63, 25.88, 15.83. FD-MS ($m/z$): 441 $(M+H)^+$.

### 5.31. *rac*-Chloro [(2*R*,4*R*)-4-(2-ethylphenyl)-2-phenyl-1-*N*-(3-pyridylmethyl)-piperidin]-(3*S*)-3-ylcarboxylate (39)

The acid **37** (0.37 g, 0.92 mmol) was dissolved in thionyl chloride (5.0 mL) with a drop of DMF and the solution was refluxed for 48 h. After cooling to room temperature, the thionyl chloride was evaporated. Toluene was added and evaporated. The gummy solid was triturated with ether to give an orange powder. The ether was decanted and the trituration repeated twice. The acid chloride **39** was used directly without further purification.

### 5.32. *rac*-*N*-Methyl [(2*R*,4*R*)-4-(2-ethylphenyl)-2-phenyl-1-*N*-(3-pyridylmethyl)-piperidin]-(3*S*)-3-ylcarboxamide (40)

The acid chloride **39** (75 mg, 0.18 mmol) and methylamine hydrochloride (0.10 g, 1.5 mmol) were dissolved in pyridine (1.0 mL) and the mixture was stirred for 48 h. The solvent was evaporated and the residue was dissolved in $CH_2Cl_2$. The solution was treated with

saturated ammonium chloride solution and the pH adjusted to 5–6 with aqueous HCl (1.0 mol/mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The resulting residue, orange oil (72 mg), was chromatographed on silica gel, eluted with $CH_2Cl_2$/EtOAc, 3:1, to provide **40** which was further purified by aqueous NaOH (1.0 mol/mL) washes of an EtOAc solution. Final purification was achieved with a preparative silica plate with $CH_2Cl_2$/EtOAc, 3:1, to afford **40** (20 mg, 27% yield) as a white solid. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.41 (s, 2H), 7.55–7.39 (m, 3H), 7.30–7.15 (m, 5 H), 7.07–7.00 (m, 3H), 4.27 (s, 1H), 3.73 (d, 1H), 3.62 (d, 1H), 3.38 (m, 1H), 3.00–2.75 (m, 3H), 2.62–2.45 (m, 2H), 2.28 (m, 1H), 2.03 (d, 3H), 1.75 (m, 2H), 1.13 (t, 3H). FD-MS (*m*/*z*): 414 $(M+H)^+$.

### 5.33. *rac*-(2*R*,3*S*,4*R*)-4-(2-Ethylphenyl)-3-hydroxymethyl-2-phenyl-1-*N*-(3-pyridylmethyl)piperidine (41)

To a solution of **39** (75 mg, 0.18 mmol) in THF (0.50 mL) was added lithium aluminum hydride (0.020 g, 0.54 mmol) and the mixture was stirred for 24 h. After the reaction was quenched with wet THF, the mixture was filtered through Celite with EtOAc. The filtrate was washed with saturated ammonium chloride solution. The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The resulting residue, orange oil (72 mg), was chromatographed on silica gel, eluted with hexane/EtOAc, 1:1, to provide **41** (12 mg, 17% yield) as a white solid. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.40 (m, 2 H), 7.53–7.45 (m, 3H), 7.30–7.05 (m, 8 H), 3.65 (d, 1H), 3.40 (d, 1H), 3.15–3.00 (m, 2H), 2.96–2.75 (m, 4 H), 2.60 (m, 1H), 2.15 (dt, 1H), 2.00 (m, 1H), 1.85–1.70 (m, 2H), 1.15 (t, 3H). FD-MS (*m*/*z*): 387 $(M+H)^+$.

### 5.34. *rac*-(2*R*,3*S*,4*R*)-4-(2-Ethylphenyl)-3-acetyl-2-phenyl-1-*N*-(3-pyridylmethyl)piperidine (42)

To ice-cold di-*tert*-butylmalonate (2.7 mL, 12 mmol) was added lithium bis(trimethylsilyl)amide (12 mL, 1.0 mol/L in THF). After stirred for 30 min, **39** (0.50 g, 1.2 mmol) was added in one portion as a solid. The solution was stirred for 1 h with the ice bath and then it was stirred for 48 h. Water was added and the solution was acidified to pH 5 with aqueous HCl (0.10 mol/L). The product was extracted with EtOAc. The combined organic layers were dried over sodium sulfate and evaporated to give diester derivative and unreacted di-*tert*-butylmalonate. To a solution of this mixture in acetic anhydride/acetic acid (2:98, 8.0 mL) was added camphorsulfonic acid (42 mg, 0.18 mmol) and refluxed for 3 h. After cooling to room temperature, the solution was evaporated. Toluene was added and evaporated. The resulting residue was dissolved in EtOAc and washed with aqueous NaOH (1.0 mol/L). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified by radial chromatography eluted with hexane/EtOAc, 1:1, to afford **42** (60 mg, 13% yield) as a yellow oil. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.45 (br s, 2H), 7.53 (d, 1H), 7.45 (m, 1H), 7.37–7.00 (m, 9 H), 3.70 (d, 1H), 3.40 (m, 1H), 3.25–3.15 (m, 2H), 2.95 (dt, 1H), 2.85 (d, 1H), 2.75–2.60 (m, 1H), 2.55–2.40 (m, 1H), 2.23 (dt, 1H), 1.90–1.65 (m, 2H), 1.10 (t, 3H). 1.00 (s, 3H). FD-MS (*m*/*z*): 399 $(M+H)^+$.

### 5.35. *rac*-Methyl [(2*R*,4*R*)-4-(2-ethylphenyl)-2-phenyl-1-*N*-(3-pyridylmethyl)- piperidin]-(3*S*)-3-ylcarboxylate (43)

The acid chloride **39** (75 mg, 0.18 mmol) was dissolved in MeOH (5.0 mL) and the solution was stirred for 48 h. The solvent was evaporated and the residue was dissolved in $CH_2Cl_2$. The solution was washed with saturated aqueous $NaHCO_3$, dried over sodium sulfate, and evaporated under reduced pressure. The resulting residue, an orange oil (69 mg), was chromatographed on silica gel, eluted with hexane/EtOAc, 1:1, to provide **43** (38 mg, 51% yield) as an off-white solid. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.41 (s, 2H), 7.54 (d, $J$ = 6.8 Hz, 1H), 7.39 (s, 2H), 7.29–7.14 (m, 5H), 7.09–7.00 (m, 3H), 3.73 (d, $J$ = 13.7 Hz, 1H), 3.50 (d, $J$ = 9.8 Hz, 1H), 3.26 (m, 1H), 2.99–2.87 (m, 6 H), 2.71 (m, 1H), 2.55 (m, 1H), 2.26 (s, 1H), 1.74 (s, 2H), 1.13 (t, $J$ = 7.5 Hz, 3H). FD-MS (*m*/*z*): 415 $(M+H)^+$.

### 5.36. *rac*-*N*-(*O*-Methyl-*l*-Methionine) [(2*R*,4*R*)-4-(2-ethylphenyl)-2-phenyl-1-*N*-(3-pyridylmethyl)-piperidin]-(3*S*)-3-ylcarboxylamide (44)

To a solution of **39** (100 mg, 0.24 mmol) in pyridine (1.0 mL) was added *l*-methionine methyl ester hydrochloride (0.10 g, 0.48 mmol) at room temperature. After stirred for 24 h, the solvent was evaporated and the residue was dissolved in EtOAc. The solution was washed with saturated ammonium chloride solution (2×), aqueous NaOH (1.0 mol/L), and saturated ammonium chloride solution. The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was chromatographed on silica gel, eluted with hexane/acetone/$CH_2Cl_2$, 4:2:1, to afford **44** (49 mg, 37% yield) as a yellow solid. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 8.45 (m, 2H), 7.55–7.40 (m, 3H), 7.30–7.00 (m, 8H), 5.25 (dd, 1H), 4.05 (m, 1H), 3.75–3.55 (m, 2H), 3.45–3.25 (m, 4H), 3.00–2.88 (m, 2H), 2.75 (m, 1H), 2.60–2.45 (m, 2H), 2.28 (m, 1H), 1.85–1.70 (m, 5H), 1.60–1.39 (m, 2H), 1.30–1.05 (m, 5H). FD-MS (*m*/*z*): 546 $(M+H)^+$.

### 5.37. *rac*-*N*-(*l*-methionine) [(2*R*,4*R*)-4-(2-ethylphenyl)-2-phenyl-1-*N*-(3-pyridylmethyl)-piperidin]-(3*S*)-3-ylcarboxylamide (45)

To a solution of **44** (33 mg, 0.06 mmol) in THF (1.0 mL) was added a solution of lithium hydroxide (8.0 mg, 0.19 mmol) in water (1.0 mL). After stirred for 24 h, the mixture was diluted with saturated ammonium chloride solution and neutralized with aqueous HCl (0.10 mol/L). The product was extracted with $CH_2Cl_2$. The combined organic layers were dried over sodium sulfate and evaporated to give **45** (25 mg, 78% yield) of acceptable purity. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.45 (m, 2H), 7.60–7.40 (m, 3H), 7.34–6.85 (m, 8H), 5.60 (m, 1H), 4.00 (m, 1H), 3.85–3.63 (m, 2H), 3.33 (m, 1H), 3.07–2.95 (m, 2H), 2.83–2.68 (m, 2H), 2.53

(m, 1H), 2.35 (m, 1H), 1.90–1.73 (m, 5H), 1.62–1.50 (m, 2H), 1.43–1.35 (m, 2H), 1.18–1.05 (m, 3H). FD-MS (*m*/*z*): 532 $(M + H)^+$.

### 5.38. *rac*-(2*R*,3*S*,4*S*)-4-(2-Bromophenyl)-2-(3,4-dihydroxyphenyl)-3-nitro-1-*N*-(3-pyridylmethyl) piperidine (2a)

**Step 1** According to the procedure for the synthesis of **7**, methyl-3-(2-bromophenyl)-4-nitrobutyrate (81 g, 0.27 mol), 3,4-dihydroxybenzaldehyde (37 g, 0.27 mol), and 3-(aminomethyl)pyridine (54 mL, 0.53 mol) afforded 4-(2-bromophenyl)-6-(3,4-dihydroxyphenyl)-5-nitro-1-(3-pyridylmethyl) piperidin-2-one (78 g, 60% yield). $^1$H NMR (DMSO-$d_6$) $\delta$ 9.23 (s, 1H), 8.95 (s, 1H), 8.43 (dd, $J$ = 4.6, 1.5 Hz, 1H), 8.18 (d, $J$ = 2.0 Hz, 1H), 7.79 (d, $J$ = 7.2 Hz, 1H), 7.61 (dd, $J$ = 7.8, 1.1 Hz, 1H), 7.41–7.47 (m, 2H), 7.29 (dd, $J$ = 7.8, 4.7 Hz, 1H), 7.22 (dt, $J$ = 7.8, 1.5 Hz, 1H), 6.75 (d, $J$ = 2.0 Hz, 1H), 6.64 (d, $J$ = 8.1 Hz, 1H), 6.56 (dd, $J$ = 8.1, 2.0 Hz, 1H), 5.84 (dd, $J$ = 11.3, 9.8 Hz, 1H), 4.80 (d, $J$ = 9.8 Hz, 1H), 4.65 (d, $J$ = 15.6 Hz, 1H), 4.35 (m, 1 H), 3.99 (d, $J$ = 15.6 Hz, 1H), 3.02 (dd, $J$ = 16.9, 12.5 Hz, 1H), 2.72 (dd, $J$ = 16.9, 4.6 Hz, 1H). FAB-MS (*m*/*z*): 500, 498 $(M+H)^+$. **Step 2** To a solution of 4-(2-bromophenyl)-6-(3,4-dihydroxyphenyl)-5-nitro-1-(3-pyridylmethyl)piperidin-2-one (41 g, 82 mmol) in THF (1.6 L) was added borane–methyl sulfide complex (30 mL, 320 mmol) and the mixture was refluxed for 10 h. After cooling to 4 °C, the reaction was quenched by the addition of water (50 mL) and the mixture was concentrated. The resulting residue was heated with aqueous HCl (3.0 mol/L, 400 mL) and neutralized with aqueous NaOH (3.5 mol/L, 300 mL) after cooling to room temperature. The solid formed was recrystallized from EtOH to give analytically pure **2a** (24.7 g, 62% yield). $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 9.05 (s, 1H), 8.97 (s, 1H), 8.44 (m, 2H), 8.42 (m, 1H), 7.75 (m, 1H), 7.66–7.56 (m, 2H), 7.40–7.32 (m, 2H), 7.17 (m, 1H), 6.94 (br s, 1H), 6.72 (m, 1H), 5.25 (dd, $J$ = 9.4, 11.6 Hz, 1H), 3.86 (dt, $J$ = 4.0, 11.6 Hz, 1H), 3.64 (d, $J$ = 13.8 Hz, 1H), 3.63 (d, $J$ = 9.4 Hz, 1H), 3.05 (d, $J$ = 13.8 Hz, 1H), 2.88 (m, 1H), 2.36 (m, 1H), 1.86–1.71 (m, 2H). FAB-MS (*m*/*z*): 486, 484 $(M+H)^+$.

### 5.39. *rac*-(2*R*,3*S*,4*S*)-4-(2-Bromophenyl)-2-(4-hydroxy-3-methoxyphenyl)-3-nitro-1-*N*-(3-pyridylmethyl) piperidine (46a)

**Step 1** According to the procedure for the synthesis of **7**, methyl 3-(2-bromophenyl)-4-nitrobutylate (300 mg, 1.0 mmol), vanilline (150 mg, 1.0 mmol), and 3-aminomethylpyridine (0.20 mL, 2.0 mmol) afforded 4-(2-ethylphenyl)-6-(4-hydroxy-3-methoxyphenyl)-5-nitro-1-(3-pyridyl-methyl)piperidin-2-one (320 mg, 63% yield). FAB-MS (*m*/*z*): 514, 512 $(M+H)^+$. **Step 2** According to the procedure for the synthesis of **1a**, 4-(2-bromophenyl)-6-(4-hydroxy-3-methoxy-phenyl)-5-nitro-1-*N*-(3-pyridylmethyl)piperidin-2-one (135 mg, 0.26 mmol) and borane–methyl sulfide complex (0.95 mL, 10 mmol) afforded **46a** (47 mg, 39% yield). $^1$H NMR ($CD_3OD$, 300 MHz) $\delta$ 8.48 (s, 1H), 8.39 (m, 1H), 7.88 (d, $J$ = 7.9 Hz, 1H), 7.73 (d, $J$ = 6.4 Hz, 1H), 7.53–7.46 (m, 2H), 7.35 (m, 1H), 7.17–7.08 (m, 2H), 6.96–6.86 (m, 2H), 5.13 (dd, $J$ = 11.2, 9.7 Hz, 1H), 3.88–3.71 (m, 7H), 3.31–3.07 (m, 2H), 2.95 (dd, $J$ = 12.1, 3.5 Hz, 1H), 2.02 (td, $J$ = 12.1, 8.9 Hz, 1H). FAB-MS (*m*/*z*): 500, 498 $(M+H)^+$.

### 5.40. *rac*-(2*R*,3*S*,4*S*)-4-(2-Bromophenyl)-2-(4-hydroxy-3-iodophenyl)-3-nitro-1-*N*-(3-pyridylmethyl) piperidine (47a)

**Step 1** According to the procedure for the synthesis of **7**, methyl 3-(2-bromophenyl)-4-nitro-butylate (1.4 g, 4.7 mmol), 4-hydroxy-3-iodobenzaldehyde (1.0 g, 4.7 mmol) and 3-aminomethyl-pyridine (1.0 g, 9.4 mmol) afforded 4-(2-bromophenyl)-6-(4-hydroxy-3-iodophenyl)-5-nitro-1-(3-pyridylmethyl)-piperidin-2-one (1.7 g, 60% yield). FAB-MS (*m*/*z*): 609, 607 $(M+H)^+$. **Step 2** According to the procedure for the synthesis of **1a**, 4-(2-bromophenyl)-6-(4-hydroxy-3-iodophenyl)-5-nitro-1-*N*-(3-pyridylmethyl)-piperidin-2-one (1.3 g, 2.0 mmol) and borane-methyl sulfide complex (1.9 mL, 10 mmol) afforded **47a** (470 mg, 40% yield). $^1$H NMR (DMSO-$d_6$, 300 MHz) $\delta$ 10.45 (br s, 1H), 8.44–8.30 (m, 2H), 7.91 (m, 1H), 7.80 (d, $J$ = 7.91 Hz, 1H), 7.57 (d, $J$ = 9.4 Hz, 1H), 7.55 (dd, $J$ = 8.0, 1.1 Hz, 1H), 7.39–7.30 (m, 3H), 7.16 (m, 1H), 6.85 (d, $J$ = 8.0 Hz, 1H), 5.39 (dd, $J$ = 11.0, 9.5 Hz, 1H), 3.85 (m, 1H), 3.73 (d, $J$ = 9.5 Hz, 1H), 3.55 (d, $J$ = 14.0 Hz, 1H), 3.07 (d, $J$ = 14.0 Hz, 1H), 2.88 (m, 1H), 2.48 (m, 1H), 1.87–1.72 (m, 2H). FAB-MS (*m*/*z*): 595, 593 $(M+H)^+$.

### 5.41. *rac*-(2*R*,3*S*,4*S*)-4-(2-Ethylphenyl)-2-(4-hydroxyphenyl)-3-nitro-1-*N*-(3-pyridylmethyl)piperidine (1b)

**Step 1** According to the procedure for the synthesis of **7**, methyl 3-(2-ethylphenyl)-4-nitrobutylate (1.0 g, 4.0 mmol), 4-hydroxybenzaldehyde (450 mg, 4.0 mmol), and 3-aminomethylpyridine (0.82 mL, 8.0 mmol) afforded 4-(2-ethylphenyl)-6-(4-hydroxyphenyl)-5-nitro-1-*N*-(3-pyridylmethyl)piperidin-2-one (1.4 g, 82% yield). **Step 2** According to the procedure for the synthesis of **1a**, 4-(2-ethylphenyl)-6-(4-hydroxyphenyl)-5-nitro-1-*N*-(3-pyridylmethyl)piperidin-2-one (670 mg, 1.6 mmol) and borane–methyl sulfide complex (0.74 mL, 7.8 mmol) afforded **1b** (420 mg, 64% yield). $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 8.59 (br s, 1H), 8.48 (dd, $J$ = 5.0, 1.6 Hz, 1H), 8.15 (m, 1H), 7.56 (d, $J$ = 7.9 Hz, 1H), 7.37–7.28 (m, 4H), 7.20–7.13 (m, 2H), 6.87 (d, $J$ = 8.6 Hz, 2H), 4.97 (dd, $J$ = 10.9, 9.6 Hz, 1H), 3.85 (d, $J$ = 9.2 Hz, 1H), 3.70 (d, $J$ = 5.9 Hz, 1H), 7.65 (m, 1H), 3.09–3.04 (m, 2H), 2.79–2.57 (m, 2H), 2.43 (m, 1H), 1.90 (m, 2H), 1.20 (t, $J$ = 7.6 Hz, 3H). FAB-MS (*m*/*z*): 434 $(M+H)^+$.

### 5.42. *rac*-(2*R*,3*S*,4*S*)-4-(2-Ethylphenyl)-2-(3-amino-4-hydroxyphenyl)-3-nitro-1-*N*-(3-pyridylmethyl)piperidine (11b)

**Step 1** According to the procedure for the synthesis of **10**, concentrated nitric acid (1.0 mL, 25 mmol) and **1b** (1.7 g, 3.9 mmol) afforded 4-(2-ethylphenyl)-6-(3-amino-4-hydroxyphenyl)-5-nitro-1-*N*-(3-pyridylmethyl)piperidin-2-one (1.3 g, 69% yield). $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 8.51 (d, $J$ = 3.3 Hz, 1H), 8.47 (br s, 1H),

7.72 (d, $J$ = 7.6 Hz, 1H), 7.57 (d, $J$ = 7.6 Hz, 1H), 7.32–7.15 (m, 7H), 4.93 (dd, $J$ = 11.2, 9.8 Hz, 1H), 3.86 (d, $J$ = 9.6 Hz, 1H), 3.76–7.66 (m, 2H), 3.12–3.05 (m, 2H), 2.78–2.57 (m, 2H), 2.43 (m, 1H), 1.95–1.86 (m, 2H), 1.20 (t, $J$ = 7.6 Hz, 3H). FAB-MS ($m/z$): 463 $(M+H)^+$. **Step 2** According to the procedure for the synthesis of **11a**, prepared nitro compound (0.47 g, 1.0 mmol) and palladium on carbon afforded **11b** (0.16 g, 37% yield). $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 8.52 (br s, 1H), 8.43 (d, $J$ = 4.0 Hz, 1H), 7.58 (d, $J$ = 7.9 Hz, 1H), 7.35–7.11 (m, 5H), 6.80–6.61 (m, 3H), 4.98 (dd, $J$ = 10.9, 9.9 Hz, 1H), 3.86 (d, $J$ = 14.2 Hz, 1H), 3.71–3.63 (m, 2H), 3. 07 (d, $J$ = 14.2 Hz, 1H), 3.01 (d, $J$ = 14.5 Hz, 1H), 2.78–2.55 (m, 2H), 2.40 (m, 1H), 1.90–1.50 (m, 2H), 1.18 (t, $J$ = 7.6 Hz, 3H). FAB-MS ($m/z$): 433 $(M+H)^+$.

### 5.43. *rac*-*N*-(5-{[(3*R*,4*R*)-4-(2-Ethylphenyl)-3-nitro-1-*N*-(3-pyridylmethyl)piperidin]-(2*S*)-2-yl}-2-hydroxyphenyl) methanesulfonamide (14b)

According to the procedure for the synthesis of **14a**, **11b** (43 mg, 0.10 mmol) and methanesulfonyl chloride (0.0077 mL, 0.10 mmol) afforded **14b** (23 mg, 45% yield). $^1$H NMR (DMSO-$d_6$, 270 MHz) $\delta$ 10.02 (br s, 1H), 8.76 (br s, 1H), 8.46–8.43 (m, 2H), 7.68 (d, $J$ = 7.6 Hz, 1H), 7.55 (d, $J$ = 6.3 Hz, 1H), 7.45 (m, 1H), 7.32 (dd, $J$ = 7.6, 4.8 Hz, 1H), 7.20–7.12 (m, 4H), 6.87 (d, $J$ = 8.3 Hz, 1H), 5.17 (dd, $J$ = 10.9, 9.6 Hz, 1H), 3.72 (d, $J$ = 9.6 Hz, 1H), 3.65–3.60 (m, 2H), 3.06 (d, $J$ = 13.5 Hz, 1H), 2.92 (s, 3H), 2.85 (m, 1H), 2.69–2.51 (m, 2H), 2.40 (m, 1H), 1.81 (br s, 2H), 1.12 (t, $J$ = 7.6 Hz, 3H). FAB-MS ($m/z$): 511 $(M+H)^+$.

### 5.44. *rac*-*N*-({5-[(3*R*,4*R*)-4-(2-Ethylphenyl)-3-nitro-1-*N*-(3-pyridylmethyl)piperidin]-(2*S*)-2-yl}-2-hydroxy)phenylurea (19b)

According to the procedure for the synthesis of **19a**, **11b** (86 mg, 0.20 mmol), acetic acid (1.0 mL), and potassium cyanate (160 mg, 2.0 mmol) afforded **19b** (30 mg 32% yield). $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 8.44 (br s, 1H), 8.36 (br s, 1H), 7.92 (br s, 1H), 7.52 (m, 1H), 7.25–7.09 (m, 4H), 6.94–6.81 (m, 3H), 5.45 (br s, 2H), 4.96 (dd, $J$ = 10.8, 9.6 Hz, 1H), 3.77–3.66 (m, 4H), 2.95–2.88 (m, 2H), 2.81–2.50 (m, 2H), 2.34 (m, 1H), 1.84–1.82 (m, 2H), 1.16 (t, $J$ = 7.8 Hz, 3H). FAB-MS ($m/z$): 476 $(M+H)^+$.

### 5.45. *rac*-5-[{(3*R*,4*R*)-4-(2-Ethylphenyl)-3-nitro-1-*N*-(3-pyridylmethyl)piperidine}-(2*S*)-yl]-2-hydroxyphenyl sulfamide (20b)

According to the procedure for the synthesis of **20a**, **11b** (200 mg 0.46 mmol), sulfamoyl chloride (79 mg 0.69 mmol), and *N*,*N*-dimethylacetamide solution (5.0 mL) afforded **20b** (62 mg 26% yield). $^1$H NMR (DMSO-$d_6$, 270 MHz) δ 9.84 (br s, 1H), 8.46–8.43 (m, 2H), 7.98 (br s, 1H), 7.73 (d, $J$ = 7.9 Hz, 1H), 7.64–7.53 (m, 2H), 7.32 (dd, $J$ = 7.9, 5.0 Hz, 1H), 7.19–7.13 (m, 4H), 7.00 (br s, 1H), 6.81 (d, $J$ = 8.3 Hz, 1H), 5.25 (dd, $J$ = 10.2, 10.0 Hz, 1H), 3.84–3.72 (m, 2H), 3.16 (d, $J$ = 13.5 Hz, 1H), 3.00 (d, $J$ = 11.2 Hz, 1H), 2.81–2.51 (m, 3H), 1.94-1.85 (m, 2H), 1.26 (t, $J$ = 7.6 Hz, 3H). FAB-MS ($m/z$): 512 $(M+H)^+$. Anal. Calcd For $C_{26}H_{29}Cl_2N_5O_4$: C, 65.67; H, 6.15; N, 14.73%. Found: C, 65.91; H, 6.38; N, 14.45%.

### 5.46. *rac*-(2*R*,3*S*,4*S*)-4-(2-Bromophenyl)-2-(4-methoxyphenyl)-3-nitro-1-*N*-(3-pyridylmethyl)piperidine (48a)

**Step 1** According to the procedure for the synthesis of **7**, methyl 3-(2-bromophenyl)-4-nitrobutylate (300 mg 1.0 mmol), 4-methoxybenzaldehyde (0.10 mL, 0.90 mmol), and 3-aminomethylpyridine (0.20 mL, 2.0 mmol) afforded 4-(2-bromophenyl)-6-(4-methoxyphenyl)-5-nitro-1-*N*-(3-pyridylmethyl)piperidin-2-one (220 mg, 45% yield). FAB-MS ($m/z$): 498, 496 $(M+H)^+$. **Step 2** According to the procedure for the synthesis of **1a**, 4-(2-bromophenyl)-6-(4-methoxyphenyl)-5-nitro-1-*N*-(3-pyridylmethyl)piperidin-2-one (58 mg, 0.12 mmol) and borane–methyl sulfide complex (0.047 mL, 0.50 mmol) afforded **48a** (18 mg, 30% yield). $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.52–8.49 (m, 2 H), 7.61–7.53 (m, 2H), 7.38–7.21 (m, 3H), 7.09 (ddd, $J$ = 8.0, 7.2, 1.9 Hz, 1H), 7.02 (d, $J$ = 8.2 Hz, 2H), 6.84 (d, $J$ = 8.2 Hz, 2H), 4.98 (dd, $J$ = 10.7, 9.7 Hz, 1H), 4.03 (m, 1H), 3.90 (s, 3H), 3.89–3.80 (m, 2H), 3.07–3.03 (m, 2tI), 2.43 (m, 1H), 2.05 (m, 1H), 1.70 (m, 1H). FAB-MS ($m/z$): 484, 482 $(M+H)^+$.

### 5.47. *rac*-(2*R*,3*S*,4*S*)-4-(2-Bromophenyl)-2-(5-benzimidazol)-3-nitro-1-*N*-(3-pyridylmethyl)piperidine (49a)

**Step 1** According to the procedure for the synthesis of **7**, methyl 3-(2-bromophenyl)-4-nitrobutylate (120 mg, 0.40 mmol), 1-*N*-trityl-5-benzimidazolecarboxaldehyde (190 mg, 2.0 mmol), and 3-aminomethylpyridine (0.082 mL, 0.80 mmol) afforded crude 4-(2-bromophenyl)-6-(1-*N*-trityl-5-benzimidazol)-5-nitro-1-*N*-(3-pyridylmethyl)-piperidin-2-one. **Step 2** To a solution of resulting *N*-trityl derivatives in MeOH (10 mL) was added trifluoroacetic acid (0.50 mL), and the mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure, and the residue was purified by preparative silica plate, diluted with $CHCl_3$/MeOH, 9:1, to afford 4-(2-bromo-phenyl)-6-(5-benzimidazol)-5-nitro-1-*N*-(3-pyridylmethyl) piperidin-2-one (32 mg, 2 steps 16% yield). FAB-MS ($m/z$): 508, 506 $(M+H)^+$. **Step 3** According to the procedure for the synthesis of **1a**, 4-(2-bromophenyl)-6-(5-benzimidazol)-5-nitro-1-*N*-(3-pyridylmethyl)piperidin-2-one (8.0 mg, 0.016 mmol) and borane–methyl sulfide complex (0.0047 mL, 0.05 mmol) afforded **49a** (0.7 mg, 8.9% yield). $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 8.49–8.47 (m, 2H), 8.06 (br s, lH), 7.78–7.67 (m, 2H), 7.59–7.48 (m, 3H), 7.35 (m, 1H), 7.28–7.20 (m, 3H), 7.08 (m, 1H), 5.08 (dd, $J$ = 10.8, 9.2 Hz, 1H), 4.09 (m, 1H), 3.99 (d, $J$ = 9.2 Hz, 1H), 3.80 (d, $J$ = 13.9 Hz, 1H), 3.09–3.04 (m, 2H), 2.45 (m, 1H), 2.08 (m, 1H), 1.75 (m, 1H). FAB-MS ($m/z$): 494, 492 $(M+H)^+$.

### 5.48. *rac*-(2*R*,3*S*,4*S*)-4-(2-Bromophenyl)-3-nitro-2-phenyl-1-*N*-(3-pyridylmethyl)piperidine (50a)

**Step 1** According to the procedure for the synthesis of **7**, methyl 3-(2-bromophenyl)-4-nitrobutylate (110 mg

0.50 mmol), benzaldehyde (53 mg, 1.0 mmol), and 3-aminomethylpyridine (0.11 mL, 1.0 mmol) afforded 4-(2-bromophenyl)-5-nitro-6-phenyl-1-*N*-(3-pyridylmethyl)piperidin-2-one (110 mg 47% yield). FAB-MS (*m*/*z*): 468, 466 $(M+H)^+$. **Step 2** According to the procedure for the synthesis of **1a**, 4-(2-bromophenyl)-5-nitro-6-phenyl-1-*N*-(3-pyridylmethyl)piperidin-2-one (33 mg 0.072 mmo1) and borane–methyl sulfide complex (0.025 mL, 0.27 mmol) afforded **50a** (23 mg 69% yield). $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.49 (br s, 2H), 7.56–7.47 (m, 4H) 7.41–7.20 (m, 6H), 6.98 (m, 1H), 5.02 (dd, $J$ = 10.7, 10.1 Hz, 1H), 4.07 (m, 1H), 3.86 (d, $J$ = 9.4 Hz, 1H), 3.75 (d, $J$ = 13.7 Hz, 1H), 3.06–2.95 (m, 2H), 2.43 (m, 1H), 2.04 (d, $J$ = 11.4 Hz, 1H), 1.68 (m, 1H). FAB-MS (*m*/*z*): 454, 452 $(M+H)^+$.

### 5.49. *rac*-(2*R*,3*S*,4*S*)-4-(2-Bromophenyl)-3-nitro-1-*N*-(3-pyridylmethyl)-2-(3-thienyl)piperidine (51a)

**Step 1** According to the procedure for the synthesis of **7**, methyl 3-phenyl-4-nitrobutylate (110 mg, 0.50 mmol), 3-thiophenecarboxaldehyde (0.044 mL 0.50 mmol) and 3-aminomethylpyridine (0.41 mL, 4.0 mmol) afforded 4-(2-bromophenyl)-5-nitro-1-*N*-(3-pyridylmethyl)-6-(3-thienyl)piperidin-2-one (75 mg, 32% yield). FAB-MS (*m*/*z*): 474, 472 $(M+H)^+$. **Step 2** According to the procedure for the synthesis of **1a**, 4-(2-bromo-phenyl)-5-nitro-1-*N*-(3-pyridylmethyl)-6-(3-thiophenyl)piperidin-2-one (30 mg, 0.064 mmol) and borane–methyl sulfide complex (0.025 mL, 0.27 mmol) afforded **51a** (14 mg, 48% yield). $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.51–8.42 (m, 2H), 7.58–7.52 (m, 2H), 7.40–7.18 (m, 6H), 7.10 (m, 1H), 5.00 (dd, $J$ = l.5, 10.8 Hz, 1H), 4.05–3.96 (m, 2H), 3.81 (d, $J$ = 13.8 Hz, 1H), 3.08 (d, $J$ = 13.8 Hz, 1H), 2.98 (m, 1H), 2.40 (m, 1H), 2.03 (m, 1H), 1.68 (m, 1H). Anal. Calcd For $C_{21}H_{20}BrN_3O_2S$: C, 55.03; H, 4.40; N, 9.17%. Found: C, 54.97; H, 4.52; N, 8.77%. FAB-MS (*m*/*z*): 460, 458 $(M+H)^+$.

### 5.50. *rac*-(2*R*,3*S*,4*S*)-4-(2-Bromophenyl)-3-nitro-2-(2-pyridyl)-1-*N*-(3-pyridylmethyl)piperidine (52a)

**Step 1** According to the procedure for the synthesis of **7**, methyl 3-(2-bromophenyl)-4-nitrobutylate (600 mg, 2.0 mmol), 2-pyridinecarboxaldehyde (210 mg, 2.0 mmol) and 3-aminomethylpyridine (0.41 mL, 4.0 mmol) afforded 4-(2-bromophenyl)-6-(2-pyridyl)-5-nitro-1-*N*-(3-pyridylmethyl)-piperidin-2-one (96 mg, 10% yield). FAB-MS (*m*/*z*): 469, 467 $(M+H)^+$. **Step 2** According to the procedure for the synthesis of **1a**, 4-(2-bromophenyl)-6-(2-pyridyl)-5-nitro-1-*N*-(3-pyridylmethyl)-piperidin-2-one (30 mg, 0.064 mmol) and borane–methyl sulfide complex (0.074 mL, 0.78 mmol) afforded **52a** (14 mg, 48% yield). $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 8.72 (d, $J$ = 4.6 Hz, 1H), 8.49 (dd, $J$ = 4.6, 1.8 Hz, 1H), 8.44 (d, $J$ = 1.8 Hz, 1H), 8.11 (td, $J$ = 7.4, 1.8 Hz, 1H), 7.59 (d, $J$ = 7.9 Hz, 1H), 7.52 (dd, $J$ = 8.2, 1.0 Hz, 1H), 7.40 (m, 1H), 7.29–7.21 (m, 4H), 7.08 (m, 1H), 5.37 (dd, $J$ = 11.2, 9.9 Hz, 1H), 4.11–4.03 (m, 2H), 3.61 (d, $J$ = 13.5 Hz, 1H), 3.20 (d, $J$ = 13.5 Hz, 1H), 2.52 (m, 1H), 2.08–2.01 (m, 2H), 1.81 (m, 1H). Anal. Calcd for $C_{22}H_{21}BrN_4O_2$: C, 58.29; H, 4.67; N, 12.36%. Found: C, 58.32; H, 4.90; N, 12.37%. FAB-MS (*m*/*z*): 455, 453 $(M+H)^+$.

### 5.51. *rac*-(2*R*,3*S*,4*S*)-4-(2-Bromophenyl)-3-nitro-2-(3-pyridyl)-1-*N*-(3-pyridylmethyl)piperidine (53a)

**Step 1** According to the procedure for the synthesis of **7**, methyl 3-(2-bromophenyl)-4-nitrobutylate (300 mg, 1.0 mmol), 3-pyridinecarboxaldehyde (100 mg, 1.0 mmol) and 3-aminomethylpyridine (0.20 mL, 2.0 mmol) afforded 4-(2-bromophenyl)-5-nitro-6-(3-pyridyl)-1-*N*-(3-pyridylmethyl)-piperidin-2-one (190 mg, 41% yield). FAB-MS (*m*/*z*): 469, 467 $(M+H)^+$. **Step 2** According to the procedure for the synthesis of **1a**, 4-(2-bromophenyl)-5-nitro-6-(3-pyridyl)-1-*N*-(3-pyridylmethyl)piperidin-2-one (190 mg, 0.41 mmol) and borane–methyl sulfide complex (0.20 mL, 2.1 mmol) afforded **53a** (80 mg, 18% yield). $^1$H NMR ($CDCl_3$, 270 MHz) $\delta$ 8.74 (br s, 1H), 8.61 (m, 1H), 8.52–8.48 (m, 2H), 7.83 (d, $J$ = 7.9 Hz, 1H), 7.54 (d, $J$ = 7.9 Hz, 2H), 7.38–7.22 (m, 4H), 7.09 (m, 1H), 5.01 (dd, $J$ = 10.8, 9.8 Hz, 1H), 4.08 (m, 2H), 3.93 (d, $J$ = 9.5 Hz, 1H), 3.70 (d, $J$ = 13.4 Hz, 1H), 3.11–3.06 (m, 2H), 2.46 (m, 1H), 2.07 (m, 1H), 1.70 (m, 1H). FAB-MS (*m*/*z*): 455, 453 $(M+H)^+$.

### 5.52. Enzyme assay of FTase inhibition

FTase activity with full-length K-Ras substrate was determined by measuring transfer of [$^3$H]farnesyl from [$^3$H]farnesyl diphosphate to trichloroacetic acid-precipitable $His_6$-K-Ras4B, respectively. Typical reaction mixture contained 50 mM Tris–HCl, pH 7.7, $MgCl_2$ (5 mM), $ZnCl_2$ (5 μM), DTT (2 mM), 0.2% octyl-glucoside, [$^3$H]farnesyl diphosphate (500 nM), 50 ng purified enzyme, indicated concentration of piperidine compounds or DMSO vehicle control, and K-Ras4B (1 μM). After 30-min incubation at room temperature, reactions were stopped with 4% SDS and K-Ras protein was precipitated with cold 30% trichloroacetic acid (0.5 mL). Precipitated protein was collected on GF/C filter paper mats using a Brandel harvester. Filter mats were washed once with 6% trichloroacetic acid, 2% SDS and radioactivity was measured in a Wallac 1204 Betaplate BS liquid scintillation counter. Percent inhibition was calculated relatively to the DMSO vehicle control.

### 5.53. Molecular modeling

The crystal structure of rat FTase, CVIM peptide, and farnesyl diphosphate analogue complex (PDB1QBQ)[10] was used for the initial structure of protein. We deleted the CVIM peptide from the complex and added a water molecule at the position of the sulfur atom of cysteine of CVIM peptide.

The initial structures of ligands were built using standard bond lengths and angles, then conformation search calculations were performed using MMFF force field[11] by SPARTAN.[12]

The initial structure of FTase and **1a** complex was selected from the result of the systematic search including the ligand flexibility. Then energy-refinement calculation was performed using MMFF/AMBER force field using AMBER.[13]

The structures of FTase and **19b**, **22γ** complex were built using the structure of FTase and 1a complex as template, then energy-refinement calculations were performed.

### 5.54. Metabolic stability

An NADPH-generating system consisted of 20 IU/mL glucose-6-phosphate dehydrogenase, glucose-6-phosphate (2.0 mmol/L), and β-$NADP^+$ (8.0 mmol/L) in $MgCl_2$ (60 mmol/L) aqueous solution. The compound (0.0010 mg/mL as final concentration) was pre-incubated with mouse liver microsomes [1.0 mg/mL as final concentration in potassium phosphate (100 mmol/L) buffer, pH 7.4] at 37 °C for 5.0 min. The metabolic reaction was initiated by the addition of the NADPH-generating system, NADPH-generating system containing UDPGA (100 mmol/L) or UDPGA (100 mmol/L) alone, to the mixture. Initial sample was obtained by terminating the reaction just after the start of a reaction by the addition of two volumes of internal standard solution in acetonitrile. The reaction mixtures were incubated for 30 min at 37 °C and the reactions were terminated by the addition of two volumes of internal standard solution. The terminated incubation mixtures, as well as standard curve samples, composed of the same matrix materials but without NADPH generating system and UDPGA, were stirred for 0.5 min and centrifuged (20,679*g*, 5.0 min, 4 °C). The supernatants were analyzed by HPLC [YMC-Pack ODS C18 (4.6 × 150 mm, YMC), 30 °C, eluted with 50 mmol/L phosphoric acid (50 mmol/L) buffer solution (pH 3.0)/acetonitrile].

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