Bioorganic & Medicinal Chemistry 16 (2008) 10001–10012

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Design, synthesis, and pharmacological evaluation of *N*-bicyclo-5-chloro-1*H*-indole-2-carboxamide derivatives as potent glycogen phosphorylase inhibitors

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ARTICLE INFO

Article history:
Received 5 September 2008
Revised 8 October 2008
Accepted 9 October 2008
Available online 12 October 2008

Keywords:
Glycogen phosphorylase
Hepatic glucose output
Docking study
Hypoglycemic activity

ABSTRACT

As a result of the various *N*-bicyclo-5-chloro-1*H*-indole-2-carboxamide derivatives with a hydroxy moiety synthesized in an effort to discover novel glycogen phosphorylase (GP) inhibitors, 5-chloro-*N*-(5-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-1*H*-indole-2-carboxamide (**5b**) was found to have potent inhibitory activity. The introduction of fluorine atoms both at a position adjacent to the hydroxy group and in the central benzene moiety lead to the optically active derivative 5-chloro-*N*-[(5*R*)-1,3,6,6-tetrafluoro-5-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl]-1*H*-indole-2-carboxamide (**25eα**, which was the most potent compound in this series (IC_{50} = 0.020 μM). This compound inhibited glucagon-induced glucose output in cultured primary hepatocytes with an IC_{50} value of 0.69 μM, and showed oral hypoglycemic activity in diabetic db/db mice at 10 mg/kg. Compound **25eα** also had an excellent pharmacokinetic profile, with high oral bioavailability and a long plasma half-life, in male SD rats. The binding mode of **25eα** to this molecule and the role of fluorine atoms in that binding were speculated in an enzyme docking study.

1. Introduction

According to the International Diabetes Federation's report in 2007, diabetes currently affects 246 million people worldwide and is expected to affect 380 million by 2025.[1] This disease and its complications result in serious economic consequences for both individuals and society (the total cost attributable to diabetes in the US in 2007 was estimated to be $174 billion[2]).

Over 90% of these cases are type 2 diabetes, which is characterized by insulin resistance in target tissues and progressive insulin secretory dysfunction. This metabolic disease often leads to microvascular and macrovascular complications, such as retinopathy, neuropathy, nephropathy, atherosclerosis, and heart disease. Current approaches for treatment of type 2 diabetes usually consist of a combination of diet, physical exercise, and drug therapies. However, gaining tight control of the plasma glucose level is often difficult with current oral hypoglycemic agents because of weak effectiveness, increasing tolerance, and side effects, including hypoglycemia, weight gain, and edema. Therefore, safer and more effective hypoglycemic agents are urgently needed.

High blood glucose levels in type 2 diabetic patients are caused in part by an increase in hepatic glucose output (HGO), which consists of gluconeogenesis (de novo synthesis of glucose from 2- and 3-carbon precursors), and glycogenolysis (phosphorolysis of α-(1,4)-linkages within glycogen molecules).[3–6] Several studies have suggested that glycogenolysis is an important contributor to HGO in type 2 diabetes patients,[3,7] and glycogen phosphorylase (GP) is known to be its regulatory enzyme. In the liver, glucose-1-phosphate produced by GP from glycogen is converted by phosphoglucomutase and glucose-6-phosphatase to glucose, which is released from the liver to other tissues as fuel.[8] Thus, inhibition of glycogenolysis by GP inhibitors has recently attracted a lot of interest as a therapeutic target for this disease.

The GP molecule is a homodimeric enzyme that can be regulated by ligand binding at four sites, including an allosteric site, a catalytic site, a caffeine-binding site, and a dimer interface site; in fact, the binding of several types of GP inhibitors at these sites has been reported.[9–16] In a prior paper, we reported that a series of *N*-aryl-5-chloro-1*H*-indole-2-carboxamide derivatives with a side-chain containing hydroxy groups, such as **1**, derived from CP-320626 showed human liver GPa (hLGPa; active form of hLGP) inhibitory activity. X-ray crystallographic imaging of the complex of **1** with hLGPa showed that the 5-chloro-1*H*-indole-2-carboxam-

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doi:10.1016/j.bmc.2008.10.021

ide moiety had appropriate interactions with hLGPa at the dimer interface site. In addition, two hydroxy groups interacted electrostatically with the enzyme in which the primary and secondary hydroxy groups also made direct electrostatic connections with the imidazole ring of Tyr185 and the backbone of His57, respectively (Fig. 1).[17]

We then attempted to generate new derivatives by introducing a conformationally restricted structure with hydroxy moiety(ies) into a 5-chloro-*N*-phenyl-1*H*-indole-2-carboxamide template as a side chain. In our previous study, compound **2** inhibited hLGPa with an IC_{50} of 1.6 μM. This molecule also has a hydroxy group in a position appropriate for interacting with GP; therefore, it seemed to be a suitable lead compound. In hLGPa, the pocket around the hydroxy moiety of this molecule can afford to be occupied by a hydrophobic moiety, such as a 4-fluorophenyl ring, which was observed in an X-ray crystallographic study of CP-320626.[16,17] Therefore, it seemed possible to obtain inhibitory activity by modifying **2** into a bicyclic system via fixation of the hydroxy methyl side chain.

To that end, we first evaluated the 5-membered ring derivative (**3**). This compound exhibited hLGPa inhibitory activity with an IC_{50} value of 0.44 μM, which was about four times more potent than **2**. This result prompted us to investigate further modification of **3** via ring expansion, introduction of substituents to the central benzene moiety or to adjacent position to the hydroxy group, and synthesis of optically active compounds (Fig. 2).

In the present article, we wish to report both the structure–activity relationships (SARs) of the compounds derived from **3** as a new class of GP inhibitor, and their modes of binding to the enzyme, which were elucidated a docking study.

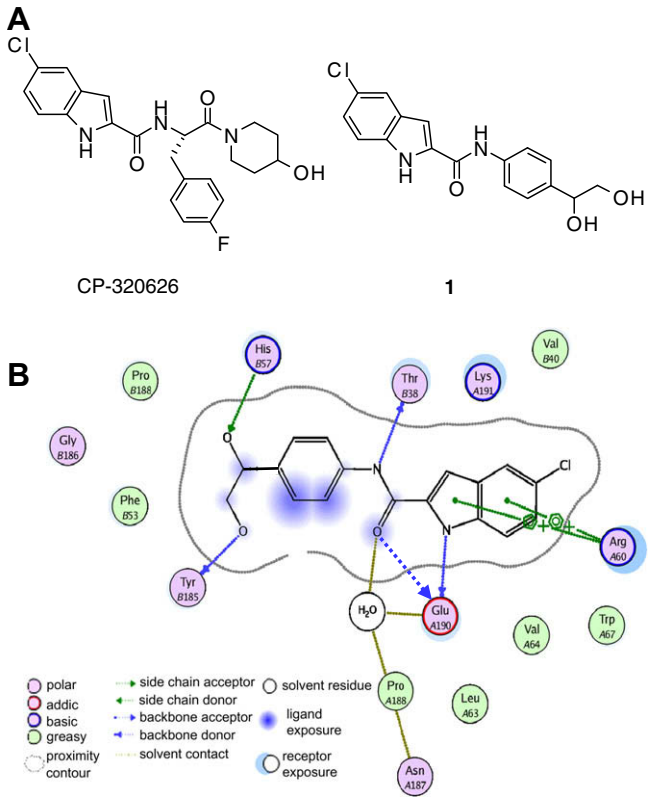


Figure 1. (A) Structure of CP-320626 and an example of *N*-aryl-1*H*-indole-2-carboxamide derivative (**1**). (B) Schematic diagram of the interactions made by **1** with hLGPa revealed by crystallographic analysis. Protein residues of the two hLGPa molecules in the dimer are distinguished with labels (A) and (B), respectively. The figure was prepared using the Ligand Interactions application in MOE .[18]

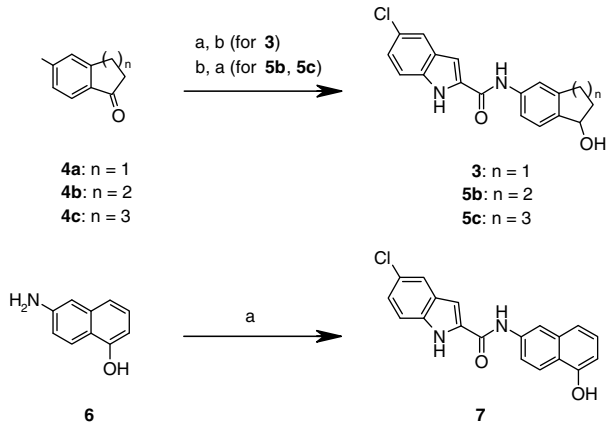
2. Chemistry

5-Chloro-*N*-(1-hydroxy-2,3-dihydro-1*H*-inden-5-yl)-1*H*-indole-2-carboxamide (**3**) was prepared via a coupling reaction between 5-aminoindan-1-one (**4a**) and 5-chloro-1*H*-indole-2-carboxylic acid. A carbonyl moiety on this compound was reduced because that on **4a** was not successful. Six- or 7-membered ring derivatives (**5b**, **c**) were obtained by the reduction of a carbonyl moiety and a successive coupling reaction with 5-chloro-1*H*-indole-2-carboxylc acid.[19] The naphthol derivative (**7**) was also obtained via the coupling reaction (Scheme 1).

A derivative with a *cis* 5,6-diol moiety (**9a**) was obtained by the dehydration of **5b** followed by dihydroxylation using osmium tetroxide and *N*-methylmorpholine-*N*-oxide. A *trans* analogue (**9b**) was synthesized from **9a** by isomerization under acidic conditions (Scheme 2).[20]

A dimethyl analogue (**12**) was obtained via the series of reactions described in Scheme 3. An amino moiety of **4b** was protected as a 2,5-dimethylpyrrole ring, after which dimethyl groups were introduced at the α position of a carbonyl moiety. Ozonolysis of the pyrrole ring and reduction of the carbonyl moiety in **10**, followed by a coupling reaction with 5-chloro-1*H*-indole-2-carboxylc acid led to the desired product.[21,22]

The preparation of tetrahydronaphthalene-5-ol derivatives with difluoro groups (**15**) are shown in Scheme 4. The protection of an amino group in **4b** with a trifluoroacetyl group, followed by difluorination, afforded intermediate **13**. Conversion of **13** to **14** was



Scheme 1. Syntheses of compounds **3**, **5b**, **5c**, and **7**. Reagents: (a) 5-Chloro-1*H*-indole-2-carboxylic acid, WSC·HCl, HOBt, DMF; (b) $NaBH_4$, MeOH.

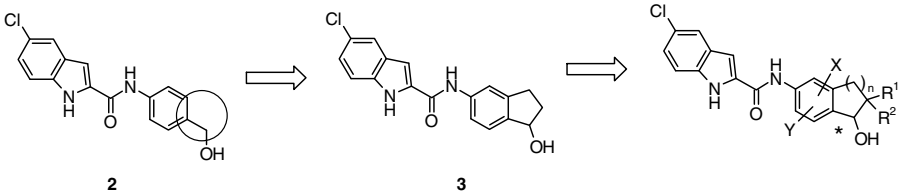
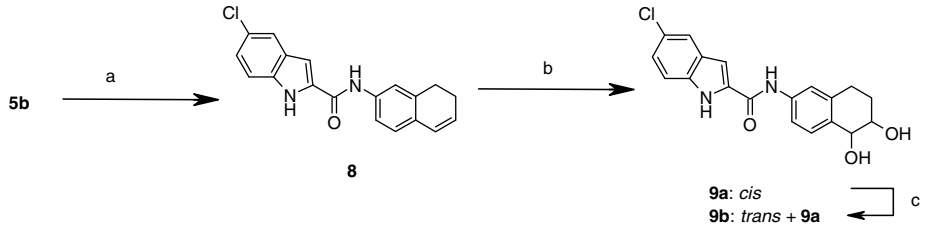
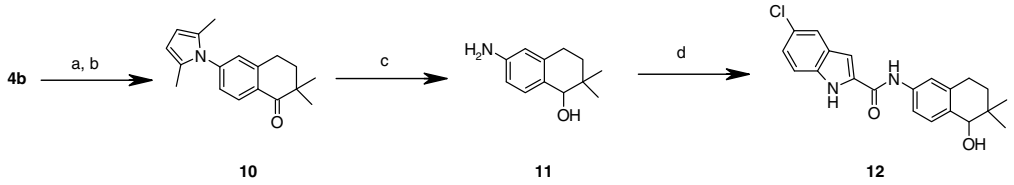


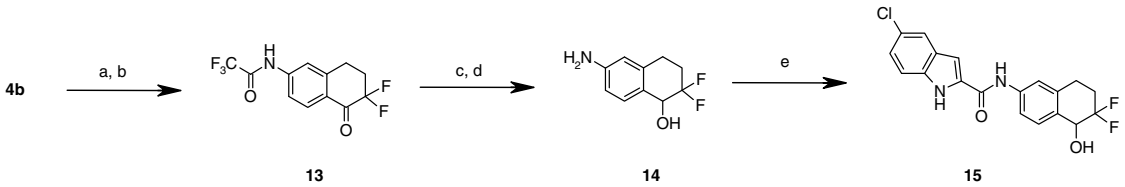
Figure 2. Structure of compound **2** and the modification route.



Scheme 2. Syntheses of compounds **9a**, **9b**. Reagents and conditions: (a) AcOH, 80 °C; (b) OsO_4, NMO, THF-H_2O; (c) 1% H_2SO_4, H_2O-1,4-dioxane, 80 °C.



Scheme 3. Synthesis of compound **12**. Reagents and conditions: (a) 2,5-hexanedione, AcOH, PhH, reflux; (b) MeI, NaH, DMF; (c) O_3, EtOH–$CHCl_3$, −78 °C then $NaBH_4$, 0 °C, then 2 M HCl, reflux; (d) 5-Chloro-1*H*-indole-2-carboxylic acid, $SOCl_2$, then **11**, pyridine.



Scheme 4. Synthesis of compound **15**. Reagents and conditions: (a) $(CF_3CO)_2O$, $CHCl_3$; (b) $(C_6H_5SO_2)_2NF$, NaHMDS, THF, −78 °C to rt; (c) K_2CO_3, MeOH–H_2O, 60 °C; (d) $NaBH_4$, MeOH; (e) 5-Chloro-1*H*-indole-2-carboxylic acid, $SOCl_2$, then **14**, pyridine.

achieved by deprotecting the trifluoroacetyl moiety and reducing a carbonyl group. Finally, a coupling reaction between **14** and 5-chloro-1*H*-indole-2-carbonyl chloride afforded the desired compound.

The serial preparation of substituted analogues on the tetrahydronaphthalene ring of **15** is shown in Scheme 5. For the methoxy analogues, intermediates **18a** and **18b** were obtained from benzoic acid derivatives (**16a**, **b**) via Curtius rearrangement (via bromination for **16a**).[23] The fluoro analogue intermediates (**18c–e**) were prepared from **17a–c** via carboxylation[24] followed by Curtius rearrangement. Intermediates **18a–e** were converted to 1-hydroxybutyl derivatives **20a–e** via a Pd-catalyzed coupling reaction[25] followed by catalytic hydrogenation. Jones oxidation of **20a–e** yielded the corresponding carboxylic acid derivatives (**21a–e**), which were cyclized under acidic conditions using PPA for **22a–e**. These products were difluorinated after protection of their amino groups to yield **23a–e**. The precursors of the desired products were obtained by deprotecting the trifluoroacetamide moiety and reducing the carbonyl group with $NaBH_4$ (**24a**, **b**). Compounds **24c–e** were prepared via an improved one-step procedure using the $NaBH_4$–LiCl system instead of two successive reactions. Finally, a coupling reaction with 5-chloro-1*H*-indole-2-carbonyl chloride afforded the desired products **25a–e**.

Compound **25e** was separated via chiral HPLC (CHIRALPAK AD®, EtOH) into the corresponding enantiomers, **25eα** and **25eβ**. The *R* configuration of the carbon atom that bound to the hydroxy group of **25eα** was determined using single-crystal X-ray analysis (Fig. 3A and B).

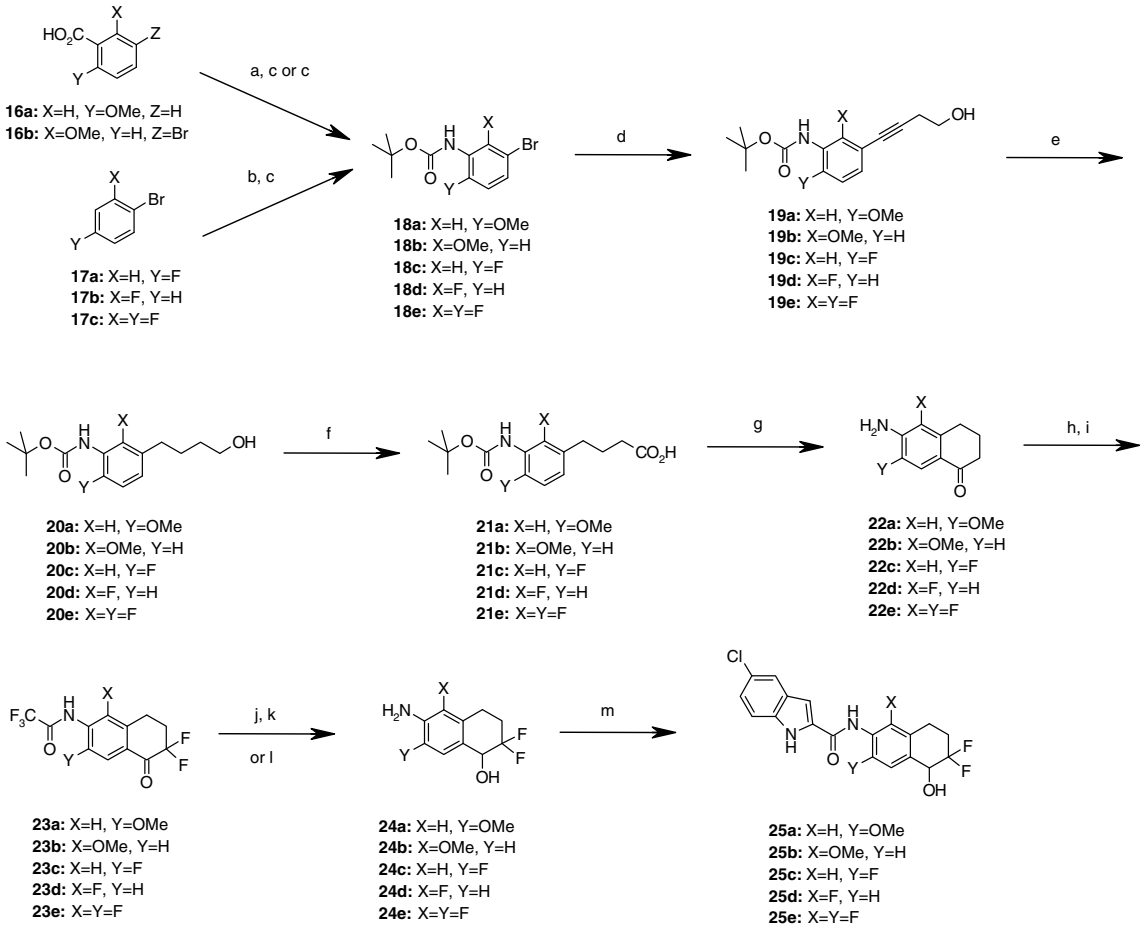
Another route for obtaining the optically active isomer of compound **25e** is described in Scheme 6. Condensation of **25e** with *N*-(*p*-toluenesulfonyl)-L-phenylalanyl chloride yielded a diastereometric mixture (**26**). Stirring the mixture in $CHCl_3$ at room temperature precipitated only a single diastereomer (**27**), and then hydrolysis of **27** afforded **25eα** with >99% ee.

3. Results and discussion

The structures of synthesized compounds and their in vitro hLGPa inhibitory activities are summarized in Tables 1 and 2.

As for the size of the ring fused to the central benzene moiety, the 5-membered ring derivative (**3**) had almost the same level of inhibitory activity as the 6-membered compound (**5b**), but the 7-membered ring derivative (**5c**) exhibited lower activity (IC_{50} = 0.44 μM for **3**, 1.2 μM for **5c** vs 0.32 μM for **5b**). The difference in activity among these compounds seemed to be due to steric hindrance of the 7-membered ring, which occurs when the hydroxy group binds to His57 in the enzyme. The reason why the naphthol ring analogue (**7**) was less active than **5b** was not clear; however, the character of the phenolic hydroxy group and/or the sterically restricted structure of **7** may be related.

To investigate the influence of the substituents around the hydroxy group in **5b**, another hydroxy group, methyl groups, and fluorine atoms were introduced into the moiety next. When the second hydroxy group was introduced, the potency of the *trans* diol (**9b**) decreased slightly (IC_{50} = 0.80 μM), and the *cis* diol (**9a**) was 10 times less potent (IC_{50} = 8.5 μM) than the *trans* analogue. The difference in potency can be attributed to the intramolecular hydrogen bonding of the *cis* diol, which may inhibit the benzylic hydroxy group from properly binding to the His57 in hLGPa. In addition, the two methyl moieties at this position in **12** detracted from its inhibitory activity. It was speculated that the hydroxy group in this molecule could not approach the binding site on hLGPa due to the existence of these two methyl groups. Interest-



Scheme 5. Syntheses of compounds **25a**–**e**. Reagents and conditions: (a) 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione, aq NaOH (for **18a**); (b) LDA, THF, then CO_2, −78 °C to rt; (c) DPPA, *t*-BuOH–toluene, reflux; (d) 3-Butyn-1-ol, $Pd(PPh_3)_4$, CuI, *i*-Pr_2NH, reflux; (e) H_2, 10% Pd–C, MeOH; (f) Jones reagent, acetone, 0 °C; (g) PPA, 110 °C; (h) $(CF_3CO)_2O$, $CHCl_3$; (i) $(C_6H_5SO_2)_2NF$, NaHMDS, THF, −78 °C to rt; (j) K_2CO_3, MeOH–H_2O, 60 °C; (k) $NaBH_4$, MeOH (two steps for **24a**, **b**); (l) $NaBH_4$, LiCl, MeOH–H_2O (for **24c**–**e**); (m) 5-chloro-1*H*-indole-2-carboxylic acid, $SOCl_2$, then **24a**–**e**, pyridine.

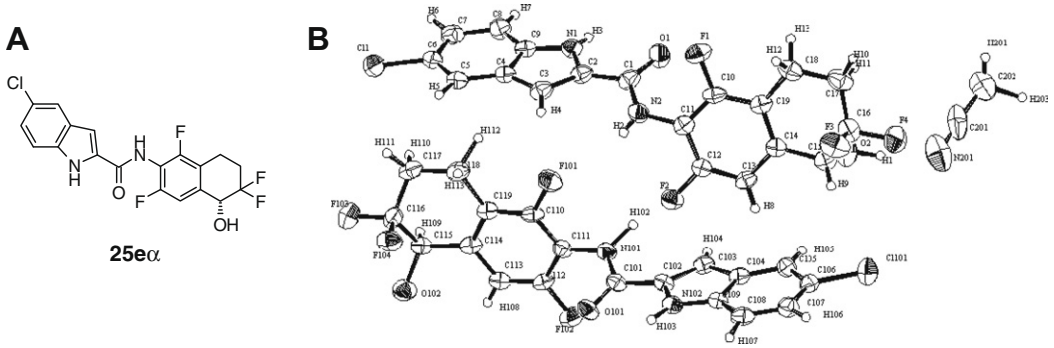
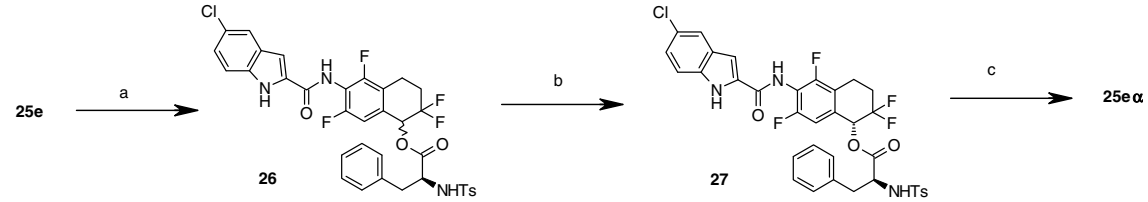
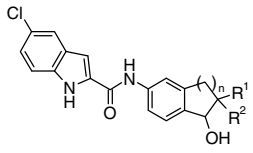


Figure 3. (A) Structure of compound **25eα.** (B) The molecular structure of **25eα** hemiacetonitrilate with the crystallographic numbering scheme.

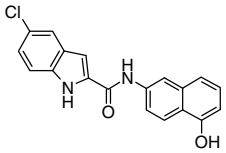


Scheme 6. Synthesis of compound **25eα**. Reagents: (a) *n*-BuLi, *N*-(*p*-toluenesulfonyl)-L-phenylalanyl chloride, THF; (b) stirring in $CHCl_3$ then filtration; (c) 2 M KOH, EtOH.

Table 1
SARs of *N*-aryl-5-chloro-1*H*-indole-2-carboxamide derivatives



3, 5b, 5c, 9a, 9b, 12, 15



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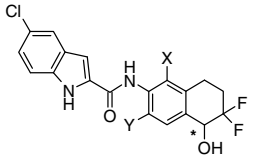
Entry	Compound	*n*	R^1	R^2	hLGPa IC_{50} (μM)
1	**3**	1	H	H	0.44
2	**5b**	2	H	H	0.32
3	**5c**	3	H	H	1.2
4	**7**		—	—	0.90
5	**9a**	2	H	OH (*cis*)	8.5
6	**9b**	2	OH (*trans*)	H	0.80
7	**12**	2	Me	Me	>10
8	**15**	2	F	F	0.068
9	CP-320626				0.92

Table 2
SARs of 5-chloro-*N*-(5-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-1*H*-indole-2-carboxamide derivatives



Entry	Compound	X	Y	hLGPa IC_{50} (μM)
1	**15**	H	H	0.068
2	**25a**	H	OMe	0.81
3	**25b**	OMe	H	0.59
4	**25c**	H	F	0.063
5	**25d**	F	H	0.048
6	**25e**	F	F	0.036
7	**25eβ** (*S*-isomer)	F	F	0.16
8	**25eα** (*R*-isomer)	F	F	0.020
9	CP-320626			0.92

ingly, the presence of the two fluorine atoms at this position (**15**) enhanced inhibitory activity by fivefold over the parent compound (IC_{50} = 0.068 μM for **15** vs 0.32 μM for **5b**), which, next to the hydroxy moiety, was the best result obtained out of all the substituents.

Next, the effects of substituents on a central benzene moiety in **15** were examined. Since X-ray crystallographic observation indicated that the steric allowance around the moiety in the enzyme would be low,[17] only small substituents were introduced.

As shown in Table 2, the introduction of a methoxy group at positions Y or X on the benzene moiety resulted in 0.81 μM and 0.59 μM of IC_{50} values, respectively, which were one-order of magnitude lower in inhibitory activity compared to **15**. On the other hand, introduction of a fluorine atom at the same positions resulted in the retention of or a slight increase in activity (IC_{50} = 0.063 μM for **25c**, 0.048 μM for **25d**, respectively). Incorporation of a fluorine atom at **25c** and **25d**, resulted in an X,Y-difluoro substituted derivative (**25e**), which was about twofold more potent than **15** (IC_{50} = 0.036 μM for **25** vs 0.068 μM for **15**). The discovery of the potent hLGPa inhibitor **25e** inspired us to divide this compound into enantiomers. Compound **25eβ**, which had an absolute configuration of *S*, had an IC_{50} value of 0.16 μM, whereas compound **25eα** (*R*-isomer) exhibited the most potent inhibitory activity (IC_{50} = 0.020 μM) in a series of synthesized compounds.

Next, the ability of the most potent hLGPa inhibitor, **25eα**, to inhibit glycogenolysis in cultured rat hepatocytes and to have hypoglycemic activity in diabetic model mice was investigated (Table 3). Compound **25eα** inhibited glucagon-induced glucose output from hepatocytes dose-dependently with an IC_{50} value of 0.69 μM, which was an improvement of more than twofold over CP-320626. In addition, oral administration of 10 mg/kg **25eα** to diabetic db/db mice lowered plasma glucose at the 2 h time point. This hypoglycemic activity was almost equal to that of 30 mg/kg CP-320626.

Compound **25eα** also exhibited an excellent pharmacokinetic profile, with high oral bioavailability (F = 100%) and a long plasma half-life ($t_{1/2}$ = 12 h), in male SD rats (Table 4).

Compound **25eα** had two kinds of fluorine atoms, 'aliphatic' and 'aromatic,' both of which were thought to be important to high inhibitory activity. To understand the role of these fluorine atoms, a docking study of **25eα** to hLGPa was carried out. The locations of the indole ring, the amide moiety, and the hydroxy group of **25eα**, all of which were thought to be key parts of activity, were assigned to the same dimer interface site as the complex between **1** and hLGPa, as follows: first, the dimer interface site was occupied by two inhibitor molecules; second, the 5-chloroindole group was buried in a hydrophobic pocket composed of lipophilic amino acid side chains; third, the indole NH, the amide NH, and the carbonyl O moiety made polar contact with the enzyme; and last, the hydroxy group interacted electrostatically with the imidazole ring of His57.[17]

The predicted binding model for **25eα** is shown in Figure 4.

The hydrophobic residues, such as Phe53, Pro188, and Gly186, around the two aliphatic fluorine atoms strongly suggested that the lipophilic contact among them was an important driver of activity increases. The fact that the hydrophobic residues Leu39 and Lys191 are close to one of the aromatic fluorine atoms (the position 3 in Figure 4A), suggests that hydrophobic interactions could be an indicating factor for good potency. The other aromatic fluorine atom (position 1 in Figure 4A) seemed to be in hydrophobic

Table 3
Inhibition of glucagon-induced glucose output in cultured primary hepatocytes and oral hypoglycemic activity in diabetic db/db mice

Entry	Compound	hLGPa IC_{50} (μM)	HGO inh. IC_{50} (μM)	db/db Mice hypoglycemic activity[a]	
				Dose (mg/kg, po)	% Glucose lowering
1	**25eα**	0.020	0.69	3	14
2				10	26**
3	CP-320626	0.92	1.7	30	24##

[a] Percent decrease in drug-treated plasma glucose concentration at 2 h post-dose, relative to the vehicle-treated control in db/db mice.
** $P < 0.01$ versus control (Dunnett's test).
$P < 0.01$ versus control (Student's *t*-test).

Table 4
Pharmacokinetic data for **25eα** in male SD rats following intravenous and oral administration

Route	$AUC_{0\to\infty}$ (ng h/mL)	CL_{tot} (mL/h/kg)	Vd (mL/kg)	$t_{1/2}$ (h)	C_{max} (ng/mL)	T_{max} (h)	F (%)
Intravenous[a]	930	1075	18067	12			
Oral[b]	2785				785	0.5	100

[a] Administered at 1 mg/kg in 5% propylene glycol–5% Tween 80.
[b] Administered at 3 mg/kg in 5% propylene glycol–5% Tween 80.

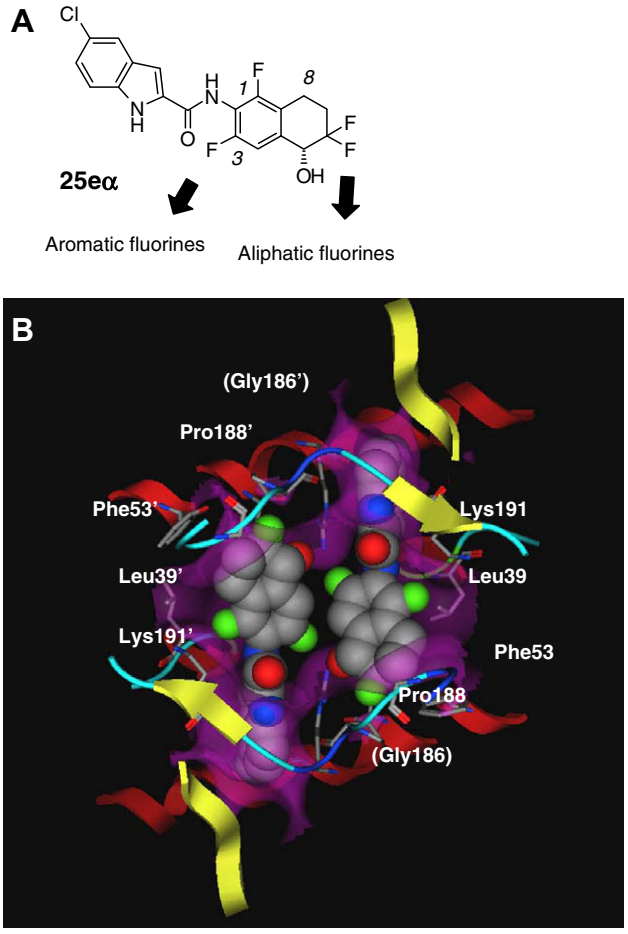


Figure 4. (A) Two kinds of fluorine atoms on compound **25eα.** (B) Predicted binding model for compound **25eα** with hLGPa. Gly186 was situated on the back side of the tetrahydronaphthalene ring of **25eα**. The protein residues of the two hLGPa molecules in the dimer are labeled (').

contact with an aromatic CH moiety in the tetrahydronaphthalene ring of the other **25eα** molecule in the enzyme.

A large difference in the activity between optical isomers (**25eβ** and **25eα** may be due to the following reasons: assuming that the indole ring, the amide moiety, and the hydroxy group of the less active isomer **25eβ** occupied the same regions in the enzyme as the more active isomer **25eα**, the fluorine atom at position 1 on the tetrahydronaphthalene ring of one molecule of **25eβ** and the methylene chain in position 8 of the other molecule would be too close each other at the dimer interface site. This unfavorable steric hindrance could cause **25eβ** to have lower activity than **25eα**.

4. Conclusion

In summary, a novel series of *N*-bicyclo-5-chloro-1*H*-indole-2-carboxamide derivatives containing a hydroxy moiety was synthesized, and the derivatives were evaluated for their inhibition of hLGPa. Of the compounds evaluated, the optically active 5-hydroxy-5,6,7,8-tetrahydronaphthalene derivative **25eα**, which has four fluorine atoms, proved to be the most potent hLGPa inhibitor in this series. Compound **25eα** inhibited glucose output from hepatocytes and hypoglycemic activity in diabetic mice. In rats, this compound also exhibited an excellent pharmacokinetic profile, with high oral bioavailability and a long plasma half-life.

5. Experimental

5.1. Chemistry

^{1}H NMR spectra were recorded on a JEOL JNM-LA300 or a JEOL JNM-EX400 spectrometer, and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard (in NMR description, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad peak). Mass spectra were recorded on a JEOL JMS-700T or micromass Q-Tof Ultima API spectrometer.

The elemental analyses were performed with a Yanaco MT-5 microanalyzer (C, H, N) and were within ±0.4% of theoretical values. The drying of organic solutions during work-up was done over anhydrous $MgSO_4$ or Na_2SO_4.

5.1.1. 5-Chloro-*N*-(1-hydroxy-2,3-dihydro-1*H*-inden-5-yl)-1*H*-indole-2-carboxamide (3)

1-Ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (1.43 g, 7.46 mmol) and 1-hydroxybenzotriazole hydrate (1.11 g, 7.25 mmol) were added to a solution of 5-aminoindan-1-one (1.00 g, 6.79 mmol) and 5-chloro-1*H*-indole-2-carboxylic acid (1.30 g, 6.65 mmol) in DMF (10 mL), and then the mixture was stirred at room temperature for 40 h. H_2O (100 mL) was added to the reaction mixture and the resulting precipitate was collected and washed with $CHCl_3$/MeOH (5:1, 90 mL) to yield 5-chloro-*N*-(1-oxo-2,3-dihydro-1*H*-inden-5-yl)-1*H*-indole-2-carboxamide as a colorless solid (1.09 g, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.60–2.65 (2H, m), 3.08–3.14 (2H, m), 7.25 (1H, dd, J = 1.9, 8.8 Hz), 7.47–7.51 (2H, m), 7.66 (1H, d, J = 8.3 Hz), 7.78–7.84 (2H, m), 8.12 (1H, br s), 10.59 (1H, s), 12.02 (1H, s). FABMS *m/z*: 325 $(M+1)^+$. $NaBH_4$ (70 mg, 1.85 mmol) was added to a solution of the product obtained above (200 mg, 0.62 mmol) in THF/MeOH (2:1, 15 mL) at 0 °C, and the mixture was stirred at room temperature for 6 h. H_2O was added to this reaction mixture and extracted with AcOEt. The AcOEt layer was washed with satd NaCl, and then dried and concentrated in vacuo. The obtained solid was washed with $CHCl_3$–MeOH to yield **3** (120 mg, 59%) as a colorless powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.75–1.85 (1H, m), 2.28–2.39 (1H, m), 2.66-2.78 (1H, m), 2.88-2.98 (1H, m), 5.03 (1H, q, J = 6.4 Hz), 5.16 (1H, d, J = 6.4 Hz), 7.22 (1H, dd, J = 8.8, 2.4 Hz), 7.31 (1H, d, J = 7.8 Hz), 7.38–7.42 (1H, m), 7.47 (1H, d, J = 8.8 Hz), 7.55–7.60 (1H, m), 7.69 (1H, br s), 7.77 (1H, d, J = 2.0 Hz), 10.22 (1H, s), 11.91 (1H, s). FABMS *m/z*: 325 $(M-1)^-$.

5.1.2. 5-Chloro-*N*-(5-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-1*H*-indole-2-carboxamide (5b)

$NaBH_4$ (680 mg, 18.0 mmol) was added to a solution of 6-amino-3,4-dihydronaphthalen-1(2*H*)-one (970 mg, 6.02 mmol) in MeOH (50 mL) at 0 °C, and the mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated in vacuo, and the residue was partitioned between AcOEt (200 mL) and H_2O (80 mL), and the AcOEt layer was washed with satd NaCl, and then dried and concentrated in vacuo to yield 6-amino-1,2,3,4-tetrahydronaphthalen-1-ol (985 mg, quant.) as a colorless solid. ^{1}H NMR (400 MHz, CDCl3) δ: 1.61–2.00 (5H, m), 2.50–2.85 (2H, m), 3.61 (2H, br s), 4.67–4.75 (1H, m), 6.42 (1H, d, J = 2.4 Hz), 6.55 (1H, dd, J = 8.1, 2.4 Hz), 7.20 (1H, d, J = 8.3 Hz). FABMS *m/z*: 146 $(M-H_2O+1)^+$. 1-Ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (1.27 g, 6.62 mmol) and 1-hydroxybenzotriazole hydrate (1.01 g, 6.60 mmol) were added to a mixture of the product obtained above (980 mg, 6.00 mmol) and 5-chloro-1*H*-indole-2-carboxylic acid (1.17 g, 5.98 mmol) in DMF (40 mL), and then the mixture was stirred at room temperature for 12 h. The resulting mixture was concentrated in vacuo, the residue was partitioned between AcOEt (200 mL) and H_2O (100 mL), and the AcOEt layer

was washed with 1 M NaOH, H_2O and satd NaCl, and then dried and concentrated in vacuo. The residue was purified via column chromatography on silica gel ($CHCl_3$/MeOH = 20:1) to yield **5b** (610 mg, 30%) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.64–1.73 (2H, m), 1.88–1.92 (2H, m), 2.62–2.77 (2H, m), 4.51–4.58 (1H, m), 5.03 (1H, d, J = 5.8 Hz), 7.22 (1H, dd, J = 8.7, 2.0 Hz), 7.34–7.41 (2H, m), 7.45–7.51 (2H, m), 7.55–7.60 (1H, m), 7.76 (1H, d, J = 1.9 Hz), 10.16 (1H, s), 11.89 (1H, s). FABMS m/z: 339 $(M-1)^-$.

5.1.3. 5-Chloro-*N*-(5-hydroxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-2-yl)-1*H*-indole-2-carboxamide (5c)

The title compound was prepared in the same manner as described for **5b** using **4c** instead of **4b**, which resulted in a 9% yield (for 2 steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.25–1.43 (1H, m), 1.44–1.61 (1H, m), 1.64–2.05 (4H, m), 2.62–2.90 (2H, m), 4.73 (1H, d, J = 5.9 Hz), 5.15 (1H, d, J = 3.9 Hz), 7.22 (1H, d, J = 8.3 Hz), 7.34–7.54 (4H, m), 7.78 (1H, d, J = 7.8 Hz), 8.31 (1H, s), 10.15 (1H, s), 11.89 (1H, s). FABMS m/z: 355 $(M+1)^+$.

5.1.4. 5-Chloro-*N*-(5-hydroxy-2-naphthyl)-1*H*-indole-2-carboxamide (7)

The title compound was prepared via the same coupling reaction as described for **3** using 6-amino-1-naphthol instead of **4a**, which resulted in a 58% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.70–6.85 (1H, m), 7.24 (1H, dd, J = 8.8, 1.9 Hz), 7.29 (2H, d, J = 4.4 Hz), 7.46–7.52 (2H, m), 7.78–7.83 (2H, m), 8.12 (1H, d, J = 8.8 Hz), 8.33 (1H, d, J = 1.9 Hz), 10.07 (1H, s), 10.44 (1H, s), 11.96 (1H, s). FABMS m/z: 337 $(M+1)^+$.

5.1.5. 5-Chloro-*N*-(7,8-dihydronaphthalen-2-yl)-1*H*-indole-2-carboxamide (8)

A solution of **5b** (570 mg, 1.67 mmol) in AcOH (40 mL) was stirred at 80 °C for 21 h. The reaction mixture was concentrated in vacuo, and then the residue was purified via column chromatography on silica gel (*n*-hexane/AcOEt = 1:1) to yield **8** (370 mg, 69%) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.23–2.33 (2H, m), 2.75 (2H, t, J = 8.3 Hz), 5.97–6.02 (1H, m), 6.47 (1H, d, J = 10.1 Hz), 7.05 (1H, d, J = 10.1 Hz), 7.20–7.25 (1H, m), 7.38–7.65 (4H, m), 7.77 (1H, s), 10.21 (1H, s), 11.91 (1H, s). FABMS m/z: 323 $(M+1)^+$.

5.1.6. *cis*-5-Chloro-*N*-(5,6-dihydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-1*H*-indole-2-carboxamide (9a)

Osmium tetroxide (0.08 Mt-*t*-BuOH solution; 1.20 mL, 0.096 mmol) and *N*-methylmorpholine-*N*-oxide (220 mg, 1.88 mmol) were added to a solution of **8** (395 mg, 1.22 mmol) in THF (20 mL), and then the mixture was stirred at room temperature for 2.5 h. The resulting mixture was concentrated in vacuo, and the residue was washed with H_2O (50 mL) and dried at 50 °C. The crude product was washed with AcOEt–ether to yield **9a** (333 mg, 76%) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.71–1.75 (1H, m), 1.90–1.97 (1H, m), 2.65–2.73 (1H, m), 2.83–2.91 (1H, m), 3.78–3.83 (1H, m), 4.43–4.47 (1H, m), 4.52 (1H, d, J = 4.9 Hz), 4.79 (1H, d, J = 5.9 Hz), 7.22 (1H, dd, J = 8.8, 1.9 Hz), 7.33 (1H, d, J = 8.3 Hz), 7.39–7.41 (1H, m), 7.47 (1H, d, J = 8.3 Hz), 7.47–7.54 (1H, m), 7.57–7.62 (1H, m), 7.75–7.77 (1H, m), 10.18 (1H, s), 11.89 (1H, s). FABMS m/z: 355 $(M-1)^-$.

5.1.7. *trans*-5-Chloro-*N*-(5,6-dihydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-1*H*-indole-2-carboxamide (9b)

A solution of **9a** (325 mg, 0.91 mmol) in 1% H_2SO_4 (5 mL) and 1,4-dioxane (15 mL) was stirred at 80 °C for 1 h. The resulting mixture was concentrated in vacuo, and the residue was partitioned between AcOEt (150 mL) and H_2O (70 mL). The AcOEt layer was washed with satd NaCl and dried, and then the solvent was evaporated off, and the residue was purified via column chromatography on silica gel ($CHCl_3$/MeO = 10:1) to yield **9b** (98 mg, 30%) as a colorless solid (15% recovery of **9a**). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.65–1.72 (1H, m), 1.85–2.00 (1H, m), 2.68–2.75 (1H, m), 2.80–2.85 (1H, m), 3.66–3.70 (1H, m), 4.26 (1H, t, J = 2.4 Hz), 4.81 (1H, d, J = 8.4 Hz), 5.20 (1H, d, J = 6.0 Hz), 7.22 (1H, dd, J = 9.0, 1.8 Hz), 7.36–7.40 (2H, m), 7.46–7.49 (2H, m), 7.57–7.59 (1H, m), 7.76 (1H, d, J = 1.8 Hz), 10.17 (1H, s), 11.88 (1H, s). FABMS m/z: 355 $(M-1)^-$.

5.1.8. 6-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-2,2-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (10)

Hexane-2,5-dione (1.5 mL, 12.6 mmol) was added to a solution of **4b** (2.00 g, 12.4 mmol) in benzene/AcOH (10:1, 22 mL), and the mixture was stirred under reflux for 21 h. 1 M HCl (50 mL) was added to the resulting mixture and extracted with AcOEt (2× 100 mL). The organic layer was washed with satd $NaHCO_3$ (50 mL) and satd NaCl, and then dried and concentrated in vacuo. The residue was purified via column chromatography on silica gel (*n*-hexane/AcOEt = 10:1) to yield 6-(2,5-dimethyl-1*H*-pyrrol-1-yl)-3,4-dihydronaphthalen-1(2*H*)-one as a colorless solid (3.00 g, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.06 (6H, s), 2.18–2.24 (2H, m), 2.71 (2H, t, J = 6.8 Hz), 3.01 (2H, t, J = 6.4 Hz), 5.92 (2H, s), 7.09–7.12 (1H, m), 7.15 (1H, dd, J = 8.4, 2.0 Hz), 8.13 (1H, d, J = 8.0 Hz). FABMS m/z: 240 $(M+1)^+$. NaH (60% in oil, 1.52 g, 38.0 mmol) was added to a solution of the product obtained above (3.00 g, 12.5 mmol) in DMF (60 mL), and then the mixture was stirred at room temperature for 10 min. MeI (2.4 mL, 38.6 mmol) was added to the resulting mixture, and then the mixture was stirred at room temperature for 2.5 h. The reaction was quenched by adding H_2O (150 mL) and extracted with AcOEt (3× 150 mL). The organic layer was washed with satd NaCl, and then dried and concentrated in vacuo. The residue was purified via column chromatography on silica gel (*n*-hexane/AcOEt = 10:1) to yield **10** (1.44 g, 43%) as a light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26 (6H, s), 2.02 (2H, t, J = 6.4 Hz), 2.06 (6H, s), 3.02 (2H, t, J = 6.4 Hz), 5.91 (2H, s), 7.07 (1H, d, J = 1.2 Hz), 7.14 (1H, dd, J = 8.4, 1.5 Hz), 8.13 (1H, d, J = 8.4 Hz). FABMS m/z: 268 $(M+1)^+$.

5.1.9. 6-Amino-2,2-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (11)

A solution of **10** (1.40 g, 5.24 mmol) in MeOH/$CHCl_3$ (4:1, 150 mL) was stirred under an O_3 atmosphere at −78 °C for 45 min. $NaBH_4$ (0.99 g, 26.2 mmol) was added to the reaction mixture, and then the mixture was stirred at 0 °C for 2 h. The reaction mixture was concentrated in vacuo, and then 2 M HCl (50 mL) and MeOH (50 mL) were added. The mixture was stirred under reflux for 2 h, and then concentrated in vacuo. The residue was treated with 1 M NaOH to pH 9.0 and extracted with $CHCl_3$ (2× 100 mL). The organic layer was washed with satd NaCl, and then dried and concentrated in vacuo. The residue was purified via column chromatography on silica gel (*n*-hexane/AcOEt = 4:1) to yield **11** (167 mg, 17%) as a colorless amorphous compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.85 (6H, s), 1.50–1.60 (1H, m), 1.62–1.73 (1H, m), 2.50–2.65 (2H, m), 3.92 (1H, d, J = 6.4 Hz), 4.57 (1H, d, J = 6.4 Hz), 4.76 (2H, s), 6.24 (1H, d, J = 2.0 Hz), 6.37 (1H, dd, J = 8.0, 2.0 Hz), 6.99 (1H, d, J = 8.4 Hz). EIMS m/z: 191 $(M)^+$.

5.1.10. 5-Chloro-*N*-(6,6-dimethyl-5-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-1*H*-indole-2-carboxamide (12)

A mixture of 5-chloro-1*H*-indole-2-carbonyl chloride (453 mg, 2.12 mmol) and **11** (162 mg, 0.85 mmol) in pyridine (20 mL) was stirred at room temperature for 12 h. The reaction mixture was concentrated in vacuo and EtOH (100 mL) and 1 M NaOH (20 mL) were added to the residue, after which the mixture was stirred at room temperature for 30 min. The solvent was evaporated in

vacuo, and the residue was diluted with H_2O (100 mL), and then extracted with $CHCl_3$/*i*-PrOH (4:1, 2× 100mL). The organic layer was washed with satd NaCl, and then dried and concentrated in vacuo. The residue was purified via column chromatography on silica gel (*n*-hexane/AcOEt = 4:1) to yield **12** (107 mg, 34%) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.87 (3H, s), 0.93 (3H, s), 1.43–1.52 (1H, m), 1.69–1.78 (1H, m), 2.64–2.82 (2H, m), 4.07 (1H, d, J = 6.3 Hz), 5.00 (1H, d, J = 6.3 Hz), 7.22 (1H, dd, J = 8.8, 1.9 Hz), 7.34–7.40 (2H, m), 7.45–7.52 (2H, m), 7.57 (1H, dd, J = 8.3, 1.9 Hz), 7.76 (1H, d, J = 1.9 Hz), 10.16 (1H, s), 11.88 (1H, s). FABMS *m/z*: 369 $(M+1)^+$.

5.1.11. *N*-(6,6-Difluoro-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)-2,2,2-trifluoroacetamide (13)

A mixture of **4b** (3.68 g, 22.8 mmol) and trifluoroacetic anhydride (7.36 g, 35.0 mmol) in $CHCl_3$ (30 mL) was stirred at room temperature for 1.5 h. The reaction mixture was concentrated in vacuo, and the residue was purified via column chromatography on silica gel ($CHCl_3$). The obtained solid was recrystallized from MeOH to yield *N*-(5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)-2,2,2-trifluoroacetamide as a brownish solid (3.41 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.10–2.20 (2H, m), 2.66 (2H, t, J = 7.0 Hz), 2.99 (2H, t, J = 6.1 Hz), 7.38 (1H, dd, J = 8.4, 2.2 Hz), 7.72 (1H, d, J = 0.9 Hz), 8.05 (1H, d, J = 8.6 Hz), 8.46 (1H, s). FABMS *m/z*: 258 $(M+1)^+$. NaHMDS-THF solution (1.0 M, 14 mL) was added to a solution of this material (1.00 g, 3.89 mmol) in THF (40 mL) at −78 °C under an argon atmosphere, and then the mixture was stirred at 0 °C for 30 min. After cooling at −78 °C, a solution of *N*-fluorobenzenesulfonimide (5.0 g, 15.9 mmol) in THF (20 mL) was added to the mixture and stirred at room temperature for 3.5 h. HCl (1 M, 20 mL) was added to the reaction mixture and concentrated in vacuo. The residue was diluted with AcOEt (100 mL), and washed with 1 M HCl (2× 30 mL) and satd NaCl, and then the organic layer was dried and concentrated in vacuo. The residue was purified via column chromatography on silica gel (*n*-hexane/AcOEt = 3:1), and the material obtained was washed with $CHCl_3$ to yield **13** (744 mg, 65%) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.62–2.73 (2H, m), 3.16 (2H, t, J = 6.3 Hz), 7.75 (1H, dd, J = 8.3, 2.2 Hz), 7.81 (1H, d, J = 1.9 Hz), 8.04 (1H, d, J = 8.3 Hz), 11.65 (1H, s). FABMS *m/z*: 294 $(M+1)^+$.

5.1.12. 6-Amino-2,2-difluoro-1,2,3,4-tetrahydronaphthalen-1-ol (14)

A mixture of **13** (335 mg, 1.14 mmol) and K_2CO_3 (200 mg, 1.45 mmol) in MeOH (3 mL) and H_2O (2 mL) was stirred at room temperature for 19 h. H_2O (30 mL) was added to the reaction mixture, and the precipitate was collected, washed with H_2O, and dried at 60 °C to yield *N*-(6,6-difluoro-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)-2,2,2-trifluoroacetamide as a colorless powder (179 mg, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.40–2.55 (2H, m), 2.92 (2H, t, J = 6.4 Hz), 6.37 (1H, d, J = 2.2 Hz), 6.54–6.57 (3H, m), 7.68 (1H, d, J = 8.8 Hz). FABMS *m/z*: 198 $(M+1)^+$. $NaBH_4$ (100 mg, 2.64 mmol) was added to the product obtained above (175 mg, 0.887 mmol) dissolved in a solution of MeOH (5 mL), and then the mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated in vacuo, and the residue was partitioned between AcOEt (50 mL) and H_2O (20 mL), and the AcOEt layer was washed with satd NaCl, and then dried and concentrated in vacuo. The residue was purified via column chromatography on silica gel ($CHCl_3$/MeOH = 10:1) to yield **14** (165 mg, 93%) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.98–2.12 (1H, m), 2.20–2.37 (1H, m), 2.65–2.84 (2H, m), 4.38–4.46 (1H, m), 5.03 (2H, s), 5.64 (1H, d, J = 6.6 Hz), 6.29 (1H, d, J = 2.0 Hz), 6.44 (1H, dd, J = 8.2, 2.2 Hz), 6.99 (1H, d, J = 8.2 Hz). EIMS *m/z*: 199 $(M)^+$.

5.1.13. 5-Chloro-*N*-(6,6-difluoro-5-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-1*H*-indole-2-carboxamide (15)

The title compound was prepared in the same manner as described for **12** using **14** instead of **11**, which resulted in a 57% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.15–2.42 (2H, m), 2.89–3.01 (2H, m), 4.63 (1H, dt, J = 6.9, 11.7 Hz), 6.03 (1H, d, J = 6.9 Hz), 7.23 (1H, dd, J = 8.8, 2.0 Hz), 7.38 (1H, d, J = 8.8 Hz), 7.41 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 7.62 (1H, s), 7.67 (1H, dd, J = 8.8, 2.0 Hz), 7.77 (1H, d, J = 2.0 Hz), 10.26 (1H, s), 11.91 (1H, s). FABMS *m/z*: 377 $(M+1)^+$.

5.1.14. *tert*-Butyl (5-bromo-2-methoxyphenyl)carbamate (18a)

1,3-Dibromo-5,5-dimethylimidazolidine-2,4-dione (7.86 g, 27.5 mmol) was added to a solution of **16a** (7.61 g, 50.0 mmol) in aq NaOH (2.8%, 80 mL), and then the mixture was stirred at room temperature for 31 h. H_2O (200 mL) was added to the resulting mixture and washed with AcOEt (200 mL). The water layer was acidified (pH 3) by adding 1 M HCl, and then extracted with $CHCl_3$ (2× 200 mL). The AcOEt layer was washed with satd NaCl, and then dried and concentrated in vacuo to yield 5-bromo-2-methoxybenzoic acid as a colorless solid (8.74 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.07 (3H, s), 6.96 (1H, d, J = 9.2 Hz), 7.66 (1H, dd, J = 8.8, 2.8 Hz), 8.28 (1H, d, J = 2.4 Hz), 10.66 (1H, s). *i*-Pr_2NEt (7.90 mL, 45.3 mmol) and DPPA (9.80 mL, 45.4 mmol) were added to a solution of the product obtained above (8.72 g, 37.7 mmol) in *t*-BuOH/toluene (1:1, 200 mL), and then the mixture was stirred under reflux for 33 h. The resulting mixture was concentrated in vacuo, and the residue was partitioned between $CHCl_3$ (2× 200 mL) and 1 M NaOH (200 mL), and the $CHCl_3$ layer was washed with satd NaCl, and then dried and concentrated in vacuo. The residue was purified via column chromatography on silica gel (*n*-hexane/AcOEt = 9:1) to yield **18a** as an oily product (13.6 g, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52 (9H, s), 3.83 (3H, s), 6.68 (1H, d, J = 8.8 Hz), 7.03–7.07 (2H, m), 8.28 (1H, s). FABMS *m/z*: 300 $(M-1)^-$.

5.1.15. *tert*-Butyl (3-bromo-2-methoxyphenyl)carbamate (18b)

The title compound was prepared in the same manner as described for the later part in **18a** using **16b** which resulted in an 89% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.47 (9H, s), 3.73 (3H, s), 7.02 (1H, t, J = 7.8 Hz), 7.30 (1H, dd, J = 1.4, 7.8 Hz), 7.50 (1H, dd, J =1.5, 7.8 Hz), 8.52 (1H, s). EIMS *m/z*: 302 $(M)^+$.

5.1.16. *tert*-Butyl (5-bromo-2-fluorophenyl)carbamate (18c)

n-BuLi (1.55 M, 90 mL, 140 mmol) was added to a solution of *N*,*N*-diisopropylamine (21.6 mL, 154 mmol) in THF (100 mL) at 0 °C, and the mixture was stirred under an Ar atmosphere for 30 min. After cooling at −78 °C a solution of **17a** (24.5 g, 140 mmol) in THF (150 mL) was added to the mixture and stirred at the same temperature for 1 h. The mixture obtained above was added to a stirred suspension of CO_2 (solid) in THF (250 mL), and the resulting mixture was warmed to room temperature and quenched by adding 0.5 M HCl (200 mL). This mixture was then concentrated and 0.5 M NaOH was added (pH 8), after which it was washed with AcOEt. The aqueous layer was acidified by adding 1 M HCl, and then extracted with $CHCl_3$ (2× 200 mL). The organic layer was washed with satd NaCl and dried, and then concentrated in vacuo to yield 5-bromo-2-fluorobenzoic acid as a colorless solid (29.0 g, 86%). ^{1}H NMR (DMSO-d_6) δ: 7.30–7.36 (1H, m), 7.80–7.86 (1H, m), 7.96 (1H, dd, J = 6.0, 2.4 Hz), 13.52 (1H, s). FABMS *m/z*: 217 $(M-1)^-$. *i*-Pr_2NEt (9.54 mL, 54.8 mmol), and DPPA (10.0 mL, 57.1 mmol) were added to a suspension of the product obtained above (10.0 g, 45.7 mmol) in *t*-BuOH/toluene (1:1, 120 mL), and then the mixture was stirred under reflux for 2 d. The resulting mixture was concentrated in vacuo, the residue was partitioned between $CHCl_3$ (500 mL) and H_2O (500 mL), and the organic layer was washed with satd NaCl, after which it was dried and concentrated in vacuo. The residue was purified via column chromatogra-

phy on silica gel (*n*-hexane/AcOEt = 20:1) to yield **18c** (4.48 g, 34%) as a colorless solid. ^{1}H NMR (DMSO-d_6) δ: 1.46 (9H, s), 7.16–7.29 (2H, m), 7.85–7.92 (1H, m), 9.22 (1H, s). FABMS *m/z*: 288 $(M-1)^-$.

5.1.17. *tert*-Butyl (3-bromo-2-fluorophenyl)carbamate (18d)

The title compound was prepared in the same manner as described for **18c** using **17b** instead of **17a**, which resulted in a 68% yield (for two steps). ^{1}H NMR (DMSO-d_6) δ: 1.46 (9H, s), 7.09 (1H, t, J = 8.0 Hz), 7.35–7.42 (1H, m), 7.55–7.65 (1H, m), 9.16 (1H, s).

5.1.18. *tert*-butyl (3-bromo-2,6-difluorophenyl)carbamate (18e)

The title compound was prepared in the same manner as described for **18c** using **17c** instead of **17a**, which resulted in an 85% yield (for two steps). NMR (DMSO-d_6) δ: 1.43 (9H, s), 7.17 (1H, dd, J = 9.3, 2.0 Hz), 7.64 (1H, ddd, J = 9.3, 7.8, 5.9 Hz), 9.03 (1H, s). FABMS *m/z*: 307 $(M-1)^-$.

5.1.19. *tert*-Butyl [5-(4-hydroxybut-1-yn-1-yl)-2-methoxyphenyl]-carbamate (19a)

$Pd(PPh_3)_4$ (13.5 g, 11.7 mmol), CuI (4.46 g, 23.4 mmol), and 3-butyn-1-ol (17.7 mL, 234 mmol) were added to a solution of **18a** (35.4 g, 117 mmol) in *i*-Pr_2NH (260 mL) under an argon atmosphere, and then the mixture was stirred under reflux for 3 h. After cooling to room temperature, the precipitate was removed via filtration and washed with AcOEt (200 mL), after which the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel (*n*-hexane/AcOEt = 3:1) to yield **19a** (14.0 g, 41%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52 (9H, s), 1.90–2.00 (1H, m), 2.65 (2H, t, J = 6.0 Hz), 3.78 (2H, q, J = 6.0 Hz), 3.86 (3H, s), 6.74 (1H, d, J = 8.0 Hz), 7.00–7.06 (2H, m), 8.18 (1H, s). FABMS *m/z*: 290 $(M-1)^-$.

5.1.20. *tert*-Butyl [3-(4-hydroxybut-1-yn-1-yl)-2-methoxyphenyl]-carbamate (19b)

The title compound was prepared in the same manner as described for **19a** using **18b** instead of **18a**, which resulted in a 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 (9H, s), 2.03 (1H, t, J = 6.2 Hz), 2.74 (2H, t, J = 6.4 Hz), 3.81–3.86 (2H, m), 3.98 (3H, s), 6.99 (1H, t, J = 8.0 Hz), 7.02 (1H, dd, J = 2.2, 8.0 Hz), 7.10 (1H, s), 8.06 (1H, d, J = 8.0 Hz). FABMS *m/z*: 292 $(M+1)^+$.

5.1.21. *tert*-Butyl [5-(4-hydroxybut-1-yn-1-yl)-2-fluorophenyl]-carbamate (19c)

The title compound was prepared in the same manner as described for **19a**, using **18c** instead of **18a**, which resulted in a 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 (9H, s), 1.87 (1H, t, J = 6.0 Hz), 2.65 (2H, t, J = 6.4 Hz), 3.79 (2H, q, J = 6.0 Hz), 6.68 (1H, s), 6.93–7.05 (2H, m), 8.20 (1H, d, J = 7.2 Hz). FABMS *m/z*: FABMS *m/z*: 278 $(M-1)^-$.

5.1.22. *tert*-Butyl [3-(4-hydroxybut-1-yn-1-yl)-2-fluorophenyl]carbamate (19d)

The title compound was prepared in the same manner as described for **19a** using **18d** instead of **18a**, in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 (9H, s), 2.73 (2H, t, J = 6.2 Hz), 3.83 (2H, q, J = 6.2 Hz), 4.12 (1H, q, J = 7.1 Hz), 6.69 (1H, s), 7.00–7.07 (2H, m), 7.98–8.08 (1H, m). EIMS *m/z*: 279 (M^+).

5.1.23. *tert*-Butyl [2,6-difluoro-3-(4-hydroxybut-1-yn-1-yl)phenyl]carbamate (19e)

The title compound was prepared in the same manner as described for **19a** using **18e** instead of **18a**, which resulted in an 88% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.50 (9H, s), 2.71 (2H, t, J = 6.2 Hz), 3.82 (2H, q, J = 6.3 Hz), 5.97 (1H, s), 7.12 (1H, dt, J = 1.4, 8.8 Hz), 7.19–7.28 (1H, m). FABMS *m/z*: 296 $(M-1)^-$.

5.1.24. *tert*-Butyl [5-(4-hydroxybutyl)-2-methoxyphenyl]-carbamate (20a)

A mixture of **19a** (14.0 g, 48.0 mmol) and Pd/C (10 w/w%, 2.80 g) in EtOH/MeOH/THF (10:10:1, 220 mL) was stirred under a hydrogen atmosphere at room temperature for 12 h. The catalyst was filtered through celite, and the filtrate was concentrated in vacuo to yield **20a** (12.3 g, 87%) as a light brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52 (9H, s), 1.55–1.70 (5H, m), 2.58 (2H, t, J = 7.6 Hz), 3.62 (2H, t, J = 6.8 Hz), 3.83 (3H, s), 6.74–6.78 (2H, m), 7.07 (1H, s), 7.93 (1H, s). FABMS *m/z*: 296 $(M+1)^+$.

5.1.25. *tert*-Butyl [3-(4-hydroxybutyl)-2-methoxyphenyl]-carbamate (20b)

The title compound was prepared in the same manner as described for **20a** using **19b** instead of **19a**, which resulted in a 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 (9H, s), 1.55–1.74 (5H, m), 2.66 (2H, t, J = 7.4 Hz), 3.67 (2H, t, J = 6.4 Hz), 3.74 (3H, s), 6.84 (1H, dd, J = 1.4, 8.0 Hz), 6.98 (1H, s), 7.02 (1H, t, J = 8.0 Hz), 7.90 (1H, d, J = 8.0 Hz). FABMS *m/z*: 296 $(M+1)^+$.

5.1.26. *tert*-Butyl [5-(4-hydroxybutyl)-2-fluorophenyl]-carbamate (20c)

The title compound was prepared in the same manner as described for **20a** using **19c** instead of **19a**, in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 (9H, s), 1.55–1.70 (4H, m), 2.60 (2H, t, J = 7.2 Hz), 3.64 (2H, t, J = 6.4 Hz), 6.70 (1H, s), 6.74–6.78 (1H, m), 6.91–6.97 (1H, m), 7.91 (1H, d, J = 7.2 Hz). FABMS *m/z*: 284 $(M+1)^+$.

5.1.27. *tert*-Butyl [3-(4-hydroxybutyl)-2-fluorophenyl]-carbamate (20d)

The title compound was prepared in the same manner as described for **20a** using **19d** instead of **19a**, in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40–1.75 (13H, m), 2.67 (2H, t, J = 7.1 Hz), 3.60–3.73 (2H, m), 6.70 (1H, s), 6.82 (1H, t, J = 7.1 Hz), 7.01 (1H, t, J = 7.9 Hz), 7.85–7.97 (1H, m).

5.1.28. *tert*-Butyl [2,6-difluoro-3-(4-hydroxybutyl)phenyl]-carbamate (20e)

The title compound was prepared in the same manner as described for **20a** using **19e** instead of **19a**, which resulted in an 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.50 (9H, s), 1.52–1.72 (4H, m), 2.64 (2H, t, J = 7.2 Hz), 3.63–3.70 (2H, m), 5.93 (1H, s), 6.84 (1H, dt, J = 1.7, 8.8 Hz), 6.95–7.04 (1H, m). FABMS *m/z*: 302 $(M+1)^+$.

5.1.29. 4-{3-[(*tert*-Butoxycarbonyl)amino]-4-methoxyphenyl}-butanoic acid (21a)

2.67 M Jones reagent (27.8 mL) was added to a solution of **20a** (12.2 g, 41.3 mmol) in acetone (300 mL) at 0 °C, and the mixture was stirred at the same temperature for 1.5 h. *i*-PrOH (200 mL) was added to the reaction mixture, and the precipitate was removed via filtration. The filtrate was then concentrated in vacuo. NaOH (1 M, 500 mL) was added to the residue and washed with $CHCl_3$ (300 mL), after which the aqueous layer was neutralized by adding 1 M HCl and extracted with $CHCl_3$ (3× 500 mL). The organic layer was washed with satd NaCl, dried, and then concentrated in vacuo to yield **21a** (10.0 g, 79%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52 (9H, s), 1.90–2.00 (2H, m), 2.35 (2H, t, J = 7.2 Hz), 2.62 (2H, t, J = 8.0 Hz), 3.84 (3H, s), 6.74–6.78 (2H, m), 7.07 (1H, s), 7.92 (1H, s). FABMS *m/z*: 310 $(M+1)^+$.

5.1.30. 4-{3-[(*tert*-Butoxycarbonyl)amino]-2-methoxyphenyl}-butanoic acid (21b)

The title compound was prepared in the same manner as described for **21a** using **20b** instead of **20a**, which resulted in a 91%

yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 (9H, s), 1.96 (2H, q, J = 7.6 Hz), 2.39 (2H, t, J = 7.6 Hz), 2.69 (2H, t, J = 7.6 Hz), 3.74 (3H, s), 6.83 (1H, dd, J = 0.8, 7.6 Hz), 7.01 (1H, s), 7.03 (1H, t, J = 7.6 Hz), 7.91 (1H, d, J = 7.6 Hz). FABMS m/z: 310 $(M+1)^+$.

5.1.31. 4-{3-[(*tert*-Butoxycarbonyl)amino]-4-fluorophenyl}-butanoic acid (21c)

The title compound was prepared in the same manner as described for **21a** using **20c** instead of **20a**, which resulted in a 91% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.46 (9H, s), 1.72–1.80 (2H, m), 2.21 (2H, t, J = 7.2 Hz), 2.54 (2H, t, J = 7.2 Hz), 6.85–6.92 (1H, m), 7.04–7.10 (1H, m), 7.43 (1H, d, J = 6.4 Hz), 8.84 (1H, s), 11.99 (1H, s). FABMS m/z: 298 $(M+1)^+$.

5.1.32. 4-{3-[(*tert*-Butoxycarbonyl)amino]-2-fluorophenyl}-butanoic acid (21d)

The title compound was prepared in the same manner as described for **21a** using **20d** instead of **20a**, which resulted in a 64% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.45 (9H, s), 1.73–1.81 (2H, m), 2.23 (2H, t, J = 7.3 Hz), 2.61 (2H, t, J = 7.8 Hz), 6.94–7.06 (2H, m), 7.43 (1H, t, J = 7.4 Hz), 8.84 (1H, s), 12.07 (1H, s). FABMS m/z: 296 $(M-1)^-$.

5.1.33. 4-{3-[(*tert*-Butoxycarbonyl)amino]-2,4-difluorophenyl}-butanoic acid (21e)

The title compound was prepared in the same manner as described for **21a** using **20e** instead of **20a**, which resulted in a 55% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.42 (9H, s), 1.71–1.79 (2H, m), 2.22 (2H, t, J = 7.3 Hz), 2.59 (2H, t, J = 7.6 Hz), 7.03 (1H, t, J = 8.8 Hz), 7.16 (1H, dt, J = 6.4, 8.8 Hz), 8.73 (1H, br s), 12.08 (1H, br s). FABMS m/z: 314 $(M-1)^-$.

5.1.34. 6-Amino-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (22a)

A mixture of P_2O_5 (120 g) and phosphoric acid (60 mL) was heated at 150 °C for 1 h, and then **21a** (10.0 g, 32.3 mmol) was added at 120 °C. The mixture was stirred at the same temperature for 1 h, and then H_2O (500 mL) was added slowly at room temperature and extracted with $CHCl_3$ (3× 500 mL). The $CHCl_3$ layer was washed with 1 M NaOH (500 mL), H_2O (500 mL), and satd NaCl, and then dried and concentrated in vacuo. The residue was purified via column chromatography on silica gel (*n*-hexane/AcOEt = 4:1) to yield **22a** (2.60 g, 41%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.03–2.10 (2H, m), 2.56 (2H, t, J = 6.8 Hz), 2.79 (2H, t, J = 6.0 Hz), 3.88 (3H, s), 4.31 (2H, s), 6.85 (1H, s), 7.44 (1H, s). FABMS m/z: 192 $(M+1)^+$.

5.1.35. 6-Amino-5-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (22b)

The title compound was prepared in the same manner as described for **22a** using **21b** instead of **21a**, which resulted in a 46% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.03–2.10 (2H, m), 2.56 (2H, t, J = 6.4 Hz), 2.93 (2H, t, J = 6.4 Hz), 3.75 (3H, s), 4.28 (2H, s), 6.64 (1H, d, J = 8.6 Hz), 7.74 (1H, d, J = 8.6 Hz). FABMS m/z: 192 $(M+1)^+$.

5.1.36. 6-Amino-7-fluoro-3,4-dihydronaphthalen-1(2*H*)-one (22c)

The title compound was prepared in the same manner as described for **22a** using **21c** instead of **21a**, which resulted in a 37% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.90–2.00 (2H, m), 2.42 (2H, t, J = 6.0 Hz), 2.73 (2H, t, J = 6.0 Hz), 6.12 (2H, s), 6.55 (1H, d, J = 8.4 Hz), 7.37 (1H, d, J = 12.4 Hz). EIMS m/z: 179 (M^+).

5.1.37. 6-Amino-5-fluoro-3,4-dihydronaphthalen-1(2*H*)-one (22d)

The title compound was prepared in the same manner as described for **22a** using **21d** instead of **21a**, which resulted in an 89% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.93–2.02 (2H, m), 2.43 (2H, t, J = 7.1 Hz), 2.81 (2H, t, J = 6.1 Hz), 6.08 (2H, s), 6.66 (1H, t, J = 8.6 Hz), 7.48 (1H, d, J = 8.3 Hz). FABMS m/z: 180 $(M+1)^+$.

5.1.38. 6-Amino-5,7-difluoro-3,4-dihydronaphthalen-1(2*H*)-one (22e)

The title compound was prepared in the same manner as described for **22a** using **21e** instead of **21a**, which resulted in a 66% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.96–2.02 (2H, m), 2.33–2.47 (2H, m), 2.80 (2H, t, J = 6.1 Hz), 6.21 (2H, br s), 7.33 (1H, dd, J = 11.5, 1.2 Hz). FABMS m/z: 198 $(M+1)^+$.

5.1.39. *N*-(6,6-Difluoro-3-methoxy-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)-2,2,2-trifluoroacetamide (23a)

Trifluoroacetic anhydride (3.79 mL, 27.1 mmol) was added to a solution of **22a** (2.59 g, 13.5 mmol) in $CHCl_3$ (100 mL) at 0 °C and the mixture was stirred at room temperature for 1 h. This reaction mixture was concentrated in vacuo, and the residue was purified via column chromatography on silica gel (*n*-hexane/AcOEt = 4:1) to yield 2,2,2-trifluoro-*N*-(3-methoxy-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)acetamide as a colorless solid (3.56 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.10–2.18 (2H, m), 2.64 (2H, t, J = 7.2 Hz), 2.94 (2H, t, J = 6.0 Hz), 3.97 (3H, s), 7.57 (1H, s), 8.27 (1H, s), 8.71 (1H, s). FABMS m/z: 288 $(M+1)^+$. NaHMDS (43 mL, 1.0 M in THF) was added to a solution of this material in THF (150 mL) at −78 °C under an argon atmosphere, and the mixture was stirred at 0 °C for 1 h, and then *N*-fluorobenzenesulfonimide (15.6 g, 49.4 mmol) was added at −78 °C. After stirring for 1 h at 0 °C, the reaction was quenched by adding 1 M HCl (60 mL), and then concentrated. The residue was partitioned between $CHCl_3$ (200 mL) and 1 M HCl (100 mL), and the $CHCl_3$ layer was washed with H_2O (100 mL) and satd NaCl, after which it was dried and concentrated in vacuo. The residue was purified via column chromatography on silica gel (*n*-hexane/AcOEt = 5:1) to yield **23a** as a colorless solid, which included inseparable materials; therefore, further purification was not attempted. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.50–2.65 (2H, m), 3.16 (2H, t, J = 6.0 Hz), 4.01 (3H, s), 7.60 (1H, s), 8.33 (1H, s), 8.76 (1H, s). FABMS m/z: 324 $(M+1)^+$.

5.1.40. *N*-(6,6-Difluoro-1-methoxy-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)-2,2,2-trifluoroacetamide (23b)

The title compound was prepared in the same manner as described for **23a** using **22b** instead of **22a**, which resulted in a 73% yield (for 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.50–2.65 (2H, m), 3.21 (2H, t, J = 6.3 Hz), 3.88 (3H, s), 8.01 (1H, d, J = 8.7 Hz), 8.41 (1H, d, J = 8.7 Hz), 8.66 (1H, s). FABMS m/z: 324 $(M+1)^+$.

5.1.41. 2,2,2-Trifluoro-*N*-(3,6,6-trifluoro-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)acetamide (23c)

The title compound was prepared in the same manner as described for **23a** using **22c** instead of **22a**, which resulted in a 13% yield (for two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.54–2.64 (2H, m), 3.21 (2H, t, J = 6.0 Hz), 7.88 (1H, d, J = 10.8 Hz), 8.30 (1H, s), 8.37 (1H, d, J = 7.2 Hz). FABMS m/z: 310 $(M-1)^-$.

5.1.42. 2,2,2-Trifluoro-*N*-(1,6,6-trifluoro-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)acetamide (23d)

The title compound was prepared in the same manner as described for **23a** using **22d** instead of **22a**, which resulted in an 82% yield (for two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.68–2.81 (2H, m), 3.14 (2H, t, J = 6.3 Hz), 7.70 (1H, t, J = 7.4 Hz), 7.90 (1H, d, J = 8.8 Hz), 11.67 (1H, s). FABMS m/z: 312 $(M+1)^+$.

5.1.43. 2,2,2-Trifluoro-*N*-(1,3,6,6-tetrafluoro-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)acetamide (23e)

The title compound was prepared in the same manner as described for **23a** using **22e** instead of **22a**, which resulted in a 71%

yield (for two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.71–2.83 (2H, m), 3.11 (2H, t, J = 6.2 Hz), 7.82 (1H, dd, J = 9.2, 1.4 Hz), 11.92 (1H, s). FABMS m/z: 328 $(M-1)^-$.

5.1.44. 6-Amino-2,2-difluoro-7-methoxy-3,4-dihydronaphthalen-1-ol (24a)

A mixture of crude **23a** and K_2CO_3 (5.10 g, 36.9 mmol) in MeOH/H_2O (5:2, 70 mL) was stirred at 70 °C for 2 h. The mixture was concentrated in vacuo and H_2O (100 mL) was added, followed by extraction with AcOEt (2× 100 mL). The AcOEt layer was washed with H_2O (50 mL) and satd NaCl, and then dried and concentrated in vacuo to yield 6-amino-2,2-difluoro-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one as a colorless solid (1.10 g, 36% for 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.42–2.57 (2H, m), 3.00 (2H, t, J = 6.6 Hz), 3.90 (3H, s), 4.56 (2H, s), 6.43 (1H, s), 7.45 (1H, s). EIMS m/z: 227 $(M)^+$. $NaBH_4$ (98 mg, 2.59 mmol) was added to a solution of this material (490 mgl) in MeOH (40 mL), and the mixture was stirred at room temperature for 12 h. The resulting mixture was concentrated in vacuo, and the residue was partitioned between $CHCl_3$/*i*-PrOH (3:1, 80 mL) and satd NaCl (50 mL), and the organic layer was dried and concentrated in vacuo to yield **24a** (480 mg, 16% from **22a**) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.05–2.25 (1H, m), 2.30–2.55 (2H, m), 2.77–2.97 (2H, m), 3.86 (3H, s), 4.63–4.75 (1H, m), 6.46 (1H, s), 6.84 (1H, s). EIMS m/z: 229 $(M)^+$.

5.1.45. 6-Amino-2,2-difluoro-5-methoxy-3,4-dihydronaphthalen-1-ol (24b)

The title compound was prepared in the same manner as described for **24a** using **23b** instead of **23a**, which resulted in an 82% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.03–2.15 (1H, m), 2.20–2.36 (1H, m), 2.70–2.79 (1H, m), 2.85–2.93 (1H, m), 3.60 (3H, s), 4.41–4.47 (1H, m), 4.88 (2H, s), 5.70 (1H, d, J = 6.9 Hz), 6.61 (1H, d, J = 8.3 Hz), 6.84 (1H, d, J = 8.3 Hz). FABMS m/z: 230 $(M+1)^+$.

5.1.46. 6-Amino-2,2,7-trifluoro-3,4-dihydronaphthalen-1-ol (24c)

$NaBH_4$ (109 mg, 2.89 mmol) and LiCl (123 mg, 2.89 mL) were added to a solution of **23c** (180 mg, 0.578 mmol) in MeOH/H_2O (4:1, 10 mL), and then the mixture was stirred at room temperature for 1 h. The mixture was concentrated in vacuo and H2O (50 mL) was added. The resulting precipitate was collected and washed with H_2O, and then dried to yield **24c** (80 mg, 64%) as a colorless solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.00–2.40 (2H, m), 2.70–2.81 (2H, m), 4.42–4.52 (1H, m), 5.13 (2H, s), 5.83 (1H, d, J = 6.7 Hz), 6.49 (1H, d, J = 9.0 Hz), 6.93 (1H, d, J = 12.2 Hz). FABMS m/z: 216 $(M+1)^+$.

5.1.47. 6-Amino-2,2,5-trifluoro-3,4-dihydronaphthalen-1-ol (24d)

The title compound was prepared in the same manner as described for **24c** using **23d** instead of **23c**, which resulted in a 63% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.06–2.20 (1H, m), 2.22–2.40 (1H, m), 2.68–2.78 (1H, m), 2.82–2.91 (1H, m), 4.44–4.53 (1H, m), 5.09 (2H, s), 5.83 (1H, d, J = 6.4 Hz), 6.67 (1H, t, J = 8.3 Hz), 6.88 (1H, d, J = 8.3 Hz). FABMS m/z: 216 $(M+1)^+$.

5.1.48. 6-Amino-2,2,5,7-tetrafluoro-1,2,3,4-tetrahydronaphthalen-1-ol (24e)

The title compound was prepared in the same manner as described for **24a** using **23e** instead of **23a**, which resulted in a 65% yield (for two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.11–2.38 (2H, m), 2.67–2.86 (2H, m), 4.53 (1H, dd, J = 12.0, 7.1 Hz), 5.19 (2H, s), 5.99 (1H, s), 6.89 (1H, d, J = 11.2 Hz). FABMS m/z: 234 $(M-1)^-$.

5.1.49. 5-Chloro-*N*-(6,6-difluoro-5-hydroxy-3-methoxy-5,6,7,8-tetrahydronaphthalen-2-yl)-1*H*-indole-2-carboxamide (25a)

The title compound was prepared in the same manner as described for **12** using **24a** instead of **11**, which resulted in a 66% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.15–2.42 (2H, m), 2.82–2.98 (2H, m), 3.85 (3H, s), 4.61–4.70 (1H, m), 6.11 (1H, d, J = 6.8 Hz), 7.08 (1H, s), 7.22 (1H, dd, J = 8.8, 2.0 Hz), 7.34 (1H, s), 7.47 (1H, d, J = 8.8 Hz), 7.57 (1H, s), 7.73 (1H, d, J = 2.0 Hz), 9.52 (1H, s), 11.94 (1H, s). FABMS m/z: 407 $(M+1)^+$.

5.1.50. 5-Chloro-*N*-(6,6-difluoro-5-hydroxy-1-methoxy-5,6,7,8-tetrahydronaphthalen-2-yl)-1*H*-indole-2-carboxamide (25b)

The title compound was prepared in the same manner as described for **12** using **24b** instead of **11**, which resulted in a 73% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.18–2.40 (2H, m), 2.86–3.02 (2H, m), 3.70 (3H, s), 4.66 (1H, dt, J = 6.8, 12.2 Hz), 6.14 (1H, d, J = 6.8 Hz), 7.22 (1H, d, J = 8.3 Hz), 7.23 (1H, dd, J = 8.7, 2.0 Hz), 7.41 (1H, d, J = 1.4 Hz), 7.47 (1H, d, J = 8.7 Hz), 7.60 (1H, d, J = 8.3 Hz), 7.75 (1H, d, J = 2.0 Hz), 9.82 (1H, s), 11.98 (1H, s). FABMS m/z: 407 $(M+1)^+$.

5.1.51. 5-Chloro-*N*-(3,6,6-trifluoro-5-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-1*H*-indole-2-carboxamide (25c)

The title compound was prepared in the same manner as described for **12** using **24c** instead of **11**, which resulted in an 85% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.18–2.40 (2H, m), 2.86–3.02 (2H, m), 4.65–4.75 (1H, m), 6.25 (1H, d, J = 6.9 Hz), 7.23 (1H, dd, J = 8.8, 2.4 Hz), 7.28 (1H, d, J = 11.2 Hz), 7.38 (1H, s), 7.40–7.49 (2H, m), 7.77 (1H, d, J = 2.0 Hz), 10.22 (1H, s), 11.97 (1H, s). FABMS m/z: 395 $(M+1)^+$.

5.1.52. 5-Chloro-*N*-(1,6,6-trifluoro-5-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-1*H*-indole-2-carboxamide (25d)

The title compound was prepared in the same manner as described for **12** using **24d** instead of **11**, which resulted in a 39% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.20–2.48 (2H, m), 2.82–3.03 (2H, m), 4.67–4.77 (1H, m), 6.27 (1H, d, J = 6.8 Hz), 7.26 (1H, dd, J = 8.8, 2.0 Hz), 7.29 (1H, d, J = 8.8 Hz), 7.39 (1H, d, J = 1.9 Hz), 7.47 (1H, d, J = 8.8 Hz), 7.54 (1H, t, J = 8.3 Hz), 7.77 (1H, d, J = 1.4 Hz), 10.20 (1H, s), 11.97(1H,s). FABMS m/z: 395 $(M+1)^+$.

5.1.53. 5-Chloro-*N*-(1,3,6,6-tetrafluoro-5-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl)-1*H*-indole-2-carboxamide (25e)

The title compound was prepared in the same manner as described for **12** using **24e** instead of **11**, which resulted in a 76% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.25–2.44 (2H, m), 2.84–2.94 (2H, m), 4.74–4.81 (1H, m), 6.43 (1H, d, J = 6.9 Hz), 7.24 (2H, d, J = 8.8 Hz), 7.38 (1H, s), 7.47 (1H, d, J = 8.8 Hz), 7.79 (1H, d, J = 1.5 Hz), 10.27 (1H, s), 11.99 (1H, s). FABMS m/z: 413 $(M+1)^+$.

5.1.54. (1*R*)-6-{[(5-Chloro-1*H*-indol-2-yl)carbonyl]amino}-2,2,5,7-tetrafluoro-1,2,3,4-tetrahydronaphthalen-1-yl *N*-[(4-methylphenyl)sulfonyl]-L-phenylalaninate (27)

n-BuLi (0.35 mL, 0.55 mmol, 1.56 M *n*-hexane solution) was added dropwise to a solution of **25e** (140 mg, 0.34 mmol) in THF (6 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. *N*-(*p*-Toluenesulfonyl)-L-phenylalanyl chloride (270 mg, 0.80 mmol) was added to the mixture at 0 °C, and then stirring was continued at room temperature for 27.5 h. After concentration of the reaction mixture, H_2O (20 mL) was added to the residue and extracted with AcOEt (50mL). The AcOEt layer was washed with satd NaCl, and then dried and concentrated in vacuo. The residue was purified via column chromatography on silica gel (*n*-hexane/AcOEt = 2:1) to yield **26** (92 mg, 38%) as a colorless foam. A solu-

tion of **26** (90 mg, 0.13 mmol) in $CHCl_3$ (5 mL) was stirred at room temperature, and the resulting precipitate was collected by filtration to yield **27** (35mg, 39%, 99% de). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.20–2.50 (5H, m), 2.75–2.95 (4H, m), 4.11 (1H, q, J = 3.4 Hz), 6.01–6.08 (1H, m), 6.78 (1H, d, J = 3.7 Hz), 7.02–7.06 (2H, m), 7.15–7.20 (3H, m), 7.23–7.29 (3H, m), 7.40 (1H, s), 7.45–7.53 (3H, m), 7.80 (1H, d, J = 0.8 Hz), 8.61 (1H, d, J = 3.3 Hz), 10.36 (1H, s), 12.03 (1H, s). FABMS m/z: 714 $(M+1)^+$.

5.1.55. 5-Chloro-*N*-[(5*R*)-1,3,6,6-tetrafluoro-5-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl]-1*H*-indole-2-carboxamide (25eα)

2 M KOH (1.5 mL) was added to a solution of **27** (30 mg, 0.042 mmol) in EtOH (5 mL), and the mixture was stirred at 40 °C for 2 h. After concentration of the reaction mixture, H_2O (20 mL) was added to the residue and extracted with AcOEt (2× 50 mL). The AcOEt layer was washed with satd NaCl, and then dried and concentrated in vacuo to yield **25eα** (19mg, quant. 99% ee) as a colorless solid.

Acknowledgments

The authors wish to thank Ms. Akiko Matsuyama-Yokono and Ms. Fumie Narazaki for helpful support in the preparation of this manuscript, and the staff of the Division of Analytical Science Laboratories for the elemental analysis and spectral measurements. The authors also wish to thank Dr. Hitoshi Sakashita, Dr. Hideaki Nakahara, and Mr. Tatsuya Maruyama, for their support of this work.

Supplementary data

Combustion analysis data, single-crystal X-ray diffraction analysis data, and biological protocols. This material is available free of charge via the Internet at http://pubs.acs.org. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2008.10.021.

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