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Potent and orally active ET_A selective antagonists with 5,7-diarylcyclopenteno[1,2-*b*]pyridine-6-carboxylic acid structures

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Abstract—The synthesis and structure–activity relationships of a series of 5,7-diarylcyclopenteno[1,2-*b*]pyridine-6-carboxylic acids are described. Our efforts have been focused on modification of the aryl ring at the 5-position and the alkyl substituent at the 2-position of the bottom 4-methoxyphenyl ring in an effort to develop orally available ET_A selective antagonists with safer profiles in terms of the P-450 enzyme inhibitory activity. Incorporation of a hydroxymethyl group as an alkyl substituent in methylenedioxyphenyl and 6-dihydrobenzofuran derivatives led to the identification of orally bioavailable ET_A selective antagonists **1f** and **7f**. These compounds also showed not only excellent binding affinity ($IC_{50} < 0.10$ nM, more than 800-fold selectivity for the ET_A receptor over the ET_B receptor) but also sufficient oral bioavailability, 48% and 56%, respectively, in rats. Furthermore, these compounds did not exhibit either competitive or mechanism-based inhibition of human cytochrome P450 enzymes.

1. Introduction

Endothelin-1 (ET-1)[1] and its closely related isopeptides (ET-2, ET-3) were identified as potent vasoconstrictor peptides consisting of 21 amino acids. The endothelins exert their diverse biological actions through distinct cell surface G-protein coupled receptors (GPCR), termed ET_A and ET_B.[2] The ET_A receptor subtype mediates vasoconstriction and vascular smooth muscle proliferation, whereas the ET_B receptor subtype is thought to mediate either vasodilation or vasoconstriction. The diversity of physiological effects elicited by the endothelins has been implicated in the pathogenesis of a variety of disease states including renal failure, cerebral vasospasm, pulmonary hypertension, and congestive heart failure. Since elevated levels of endothelins have been observed in a number of these disease states, endothelin receptor antagonists are expected to possess clinical potential against endothelin-mediated disorders.[3]

Several ET_A selective[4], ET_B selective,[5] and ET_A/ET_B mixed[6] nonpeptide endothelin antagonists have been disclosed. We have recently reported, both an ET_A/ET_B mixed antagonist[7] and an ET_A selective antagonist (**1b**)[8] from the series of the 5,7-diarylcyclopenteno[1,2-*b*]pyridine-6-carboxylic acids. However, our ET_A selective antagonist lead, 3-hydroxy-2-methylpropyl derivative (**1b**), had poor oral bioavailability (7.6%) in rats, while the oral bioavailability of the advanced lead, 3-methoxy-2-methylpropyl group derivative (**1d**) was significantly higher (70%).

CYPs inhibition is known to be due to oxidation of a methylenedioxyphenyl ring, forming reactive species such as a catechol, formate, and carbon monoxide.[9] Indeed, the orally bioavailable derivative (**1d**) with a methylenedioxyphenyl moiety showed significant inhibitory activity against CYP3A4 isozyme (vide infra). The mechanism of this inhibition assumes the methylenedioxyphenyl moiety is metabolized. Therefore, the effects of the SARs of the 5-aryl rings and the 2-substituent on the 7-(4-methoxyphenyl) ring on CYP3A4 inhibition were investigated in order to identify a safer ET_A selective antagonist.

Herein, we describe the SARs of the 5-aryl ring and alkyl substituent of the 7-aryl ring on the binding affinity for the ET_A and ET_B receptors, and the inhibitory

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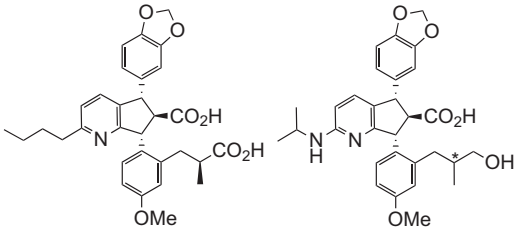


	ET_A/ET_B mixed	ET_A selective (1b: polar diastereomer)
IC_{50}	ET_A: 0.11 nM	ET_A: 0.041 nM
	ET_B: 0.60 nM	ET_B: 54 nM
	ET_B/ET_A: 5.6	ET_B/ET_A: 1300

Figure 1.

activities on testosterone 6β-hydroxylation in human CYP3A4 (Fig. 1).

2. Chemistry

The general synthesis of 5,7-diarylcyclopenteno[1,2-*b*]pyridine-6-carboxylic acids with a variety of 5-aryl rings was highlighted by the 2,3-dihydrobenzo[*b*]furan derivative (**7f**).[8] The addition of a 2,3-dihydrobenzo[*b*]furan moiety[10] to the enone **12**[11] via a Grignard reaction yielded the corresponding *tert*-alcohol **13** in an 89% yield. Acetylation of **13** and subsequent stereoselective reduction by heterogeneous hydrogenation ($Pd(OH)_2$ in THF/EtOH) produced the corresponding *cis–cis* isomer (**14**).[11] Thermodynamic epimerization of **14** (*tert*-BuOK in dioxane–*tert*-BuOH) followed by trifluoromethanesulfonylation (Tf_2O, DMAP) afforded the *trans–trans* triflate (**15**). This triflate **15** was transformed into the vinyl analog via Stille coupling (cat. $PdCl_2[(PPh_3)_2]$ in DMF at 125 °C). The subsequent stepwise oxidative cleavage of the vinyl moiety (OsO_4–NMO and $NaIO_4$ system in THF–H_2O) yielded an aldehyde, which was subsequently reduced using $NaBH_4$ in MeOH to hydroxymethyl analog **16** (75% overall yield from **15**). Protection of the primary alcohol as an acetate followed by oxidation with *m*-CPBA produced the corresponding pyridine N-oxide, which was treated with *N*-isopropylbenzimidoyl chloride in the presence of triethylamine to yield **17**.[12] Optical resolution of **17** was achieved by liquid chromatography using a Chiralpak AD column to yield **18**. The protecting groups (*N*-benzoyl, *O*-acetyl, and *tert*-butyl ester) of **18** were removed in two steps: (1) reduction with diisobutylaluminum hydride (DIBAL)[13] and (2) treatment with trifluoroacetic acid (TFA) to give optically pure **7f** (Scheme 1).[14]

The 2-alkyl substituents in compounds (**1b**–**f**) were introduced using either a Heck reaction or Stille coupling of the triflate (**20**) with an appropriate reagent such as allyltri-*n*-butyltin or allyl alcohol.[8] The 3-hydroxyl-2-methylpropyl derivatives (**1a**–**b**) were prepared via the Heck reaction using a methallyl alcohol and the subsequent reduction of the resulting aldehyde by $NaBH_4$. The two diastereomers were separated by column chromatography. Further modification of these intermediates (**21a**–**b**) based on the similar methods described above gave **1a** and **1b**, respectively (Scheme 2).

3. Results and discussion

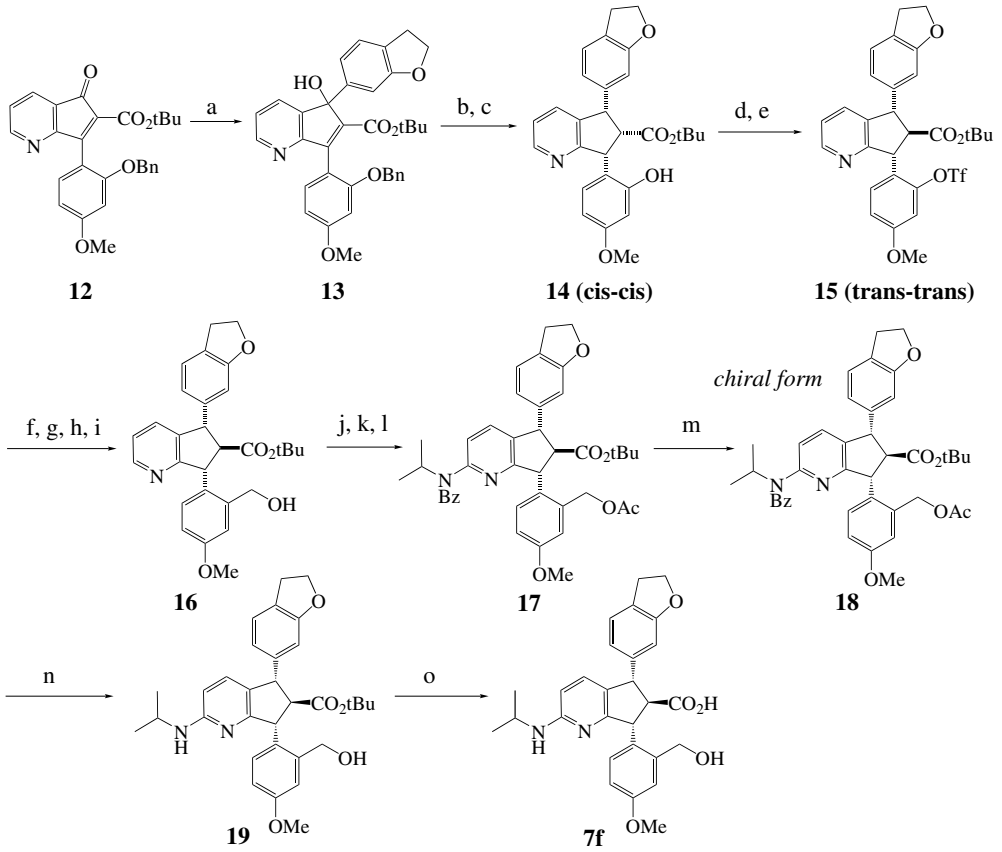
The synthesized compounds were evaluated in binding assays (inhibitory activity against ^{125}I-labeled ET-1 binding to both human ET_A and ET_B receptors).[15] Selected compounds were further evaluated in CYP3A4 inhibition assays (inhibitory activities on testosterone 6β-hydroxylation after 60-min preincubation with 20 μM of test compounds) and in pharmacokinetic studies (oral bioavailability in rats).

The effects of the 5-aryl ring in the 7-[2-(3-hydroxy-2-methylpropyl)-4-methoxyphenyl]cyclopenteno[1,2-*b*]pyridine core on the binding affinity for the ET_A and ET_B receptors and ET_A selectivity over the ET_B receptor were first investigated (Table 1).

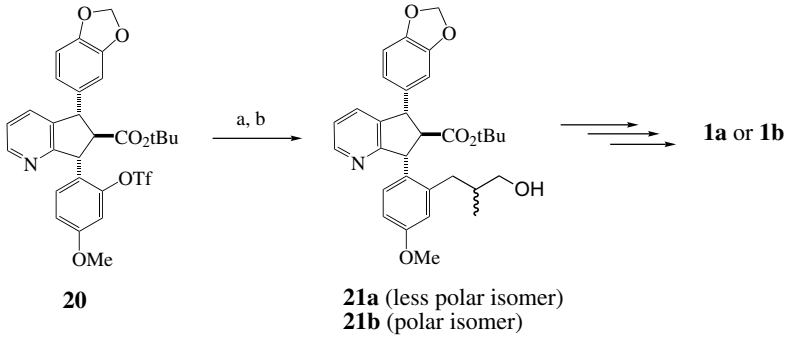
Replacement of methylenedioxyphenyl with a 3,4-dimethoxyphenyl group (**2a**–**b**) resulted in a more than 20-fold reduction in the binding affinity for the ET_A and ET_B receptors, suggesting that the bicyclic structure at the 5-aryl ring is important for retaining ET_A and ET_B binding affinity. The 5-indan group (**3a**–**b**) clearly retained its binding affinity comparable with **1a**–**b**. Interestingly, these compounds possessed higher selectivity for the ET_A than the ET_B receptor relative to **1a**–**b**. The 5- and 6-benzofurans (**4a**–**b** and **6a**–**b**) and the corresponding dihydrobenzofuran (**5a**–**b** and **7a**–**b**) were acceptable in terms of ET_A binding affinity and ET_A selectivity over ET_B receptors. It is interesting to note that a difluoromethylenedioxyphenyl moiety (**11a**–**b**) dramatically improved the ET_A selectivity over ET_B ($ET_B/ET_A = >10{,}000$ fold) without loss of the ET_A binding affinity (**11a**: IC_{50}=0.11 nM).

Selected compounds (**1a**–**b**, **3a**–**b**, **4a**–**b**, **5a**–**b**, **6a**–**b**, **7a**–**b**, **11a**–**b**) were tested in human CYP3A4 inhibition assays (Table 2). Prior to derivatization, the replacement of the methylenedioxyphenyl ring or the blockade of the methylene spacer was expected to decrease the inhibitory activity on CYP3A4.

Comparison of the two diastereomers of the methylenedioxyphenyl derivative (**1a**–**b**) indicated that the less polar diastereomer (**1a**) had weaker CYP3A4 inhibition than that of the polar diastereomer (**1b**).[16] Unexpectedly, replacement of the methylenedioxyphenyl ring with indan (**3b**), 5-benzofuran (**4a**–**b**), 5-dihydrobenzofuran (**5a**–**b**), 6-benzofuran (**6a**–**b**) or difluoromethylenedioxyphenyl ring (**11a**–**b**) resulted in increasing CYP3A4 inhibitory activity, when compared with those of **1a**–**b**. In contrast, the 6-dihydrobenzofuran ring (**7a**–**b**) retained or slightly decreased the CYP3A4 inhibition (**7a**: 22%, **7b**: 35%).



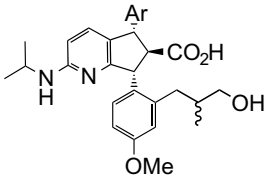
Scheme 1. The representative synthetic route: synthesis of **7f**. Reagents and conditions: (a) 5-bromo-2,3-dihydrobenzo[*b*]furan, Mg, THF, −78 °C, 89%; (b) Ac_2O, DMAP, $CHC1_3$; (c) H_2, $Pd(OH)_2$, $NaHCO_3$, THF–EtOH, rt, 82% in two steps; (d) ^{t}BuOK, ^{t}BuOH–THF, 0 °C; (e) Tf_2O, DMAP, $CHCl_3$, 0 °C, 72% in two steps; (f) vinyl(tributyl)tin, $PdCl_2(PPh_3)_2$, DMF, 125 °C, quant.; (g) OsO_4, NMO, THF–H_2O, rt; (h) $NaIO_4$, THF–H_2O, rt; (i) $NaBH_4$, THF–H_2O, 75% in three steps; (j) Ac_2O, DMAP, THF, rt; (k) *m*-CPBA, $CHCl_3$ 0 °C; (l) *i*PrN=C(Cl)Ph, Et_3N, $CHC1_3$, 70 °C; (m) optical resolution using Chiralpak AD, hexane-2-propanol, 33% from **16**; (n) DIBAL, THF, −78 °C, 91%; (o) TFA, rt, 92%.

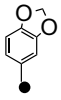
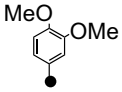
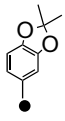
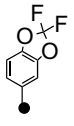


Scheme 2. Introduction of 3-hydroxy-2-methylpropyl group. Reagents and conditions: (a) methallyl alcohol (10 equiv), $PdCl_2(PPh_3)_2$ (10 mol%), $NaHCO_3$ (2 equiv), DMF, 130 °C, 12 h; (b) $NaBH_4$, MeOH, rt.

Since several alkyl side chains at the 2-position of the 7-aryl ring were acceptable in terms of the ET_A binding affinity and the selectivity for the ET_A receptor over the ET_B receptor,[8] the effects of these side chains on CYP3A4 inhibition were also investigated (Table 2). Interestingly, the more lipophilic side chains [2-ethyl-3-hydroxypropyl (**1c**) and 2-methyl-3-methoxypropyl (**1d**)] had stronger inhibitory activity (58% and 57%) for human CYP3A4 than **1b**, whereas the more hydrophilic side chains [3-hydroxypropyl (**1e**) and hydroxymethyl (**1f**)] reduced the CYP3A4 inhibition (**1e**: 27%, **1f**: 19%). These results suggested that the side chain at the 2-position of the 7-aryl ring plays a key role in reducing the CYP3A4 inhibitory activity. Among them, the hydroxy- methyl group was determined to be one of the most effective functional groups in terms of CYP3A4 inhibition. Incorporation of the hydroxymethyl group in 6-dihydrobenzofuran and difluoromethylenedioxyphenyl derivatives (**7f** and **11f**) was clearly effective in reducing the CYP3A4 inhibition without causing a

Table 1. Structure–activity relationship and CYP3A4 inhibition of a series of cyclopenteno [1,2-*b*]pyridine with a variety of aryl groups at 5-position



Compound[a]	Ar	IC_{50} (nM)		B/A ratio[b]	CYP3A4 inh. (%)[c]
		ET_A	ET_B		
1a		0.059	51	860	26
b		0.041	54	1300	45
2a		2.6	2300	890	NT[d]
b		1.1	1100	1000	NT[d]
3a		0.12	310	2600	71
b		0.21	300	1400	58
4a		0.067	77	1200	79
b		0.041	210	1900	75
5a		0.20	180	900	52
b		0.12	290	2400	54
6a		0.085	75	880	78
b		0.16	270	690	77
7a		0.094	240	2600	22
b		0.11	56	510	35
8a		2.4	950	400	NT[d]
b		4.4	2100	480	NT[d]
9a		0.70	1100	1600	NT[d]
b		3.8	3400	890	NT[d]
10a		5.2	>10000	>1900	NT[d]
b		4.3	>10000	>2300	NT[d]
11a		0.11	>1100	>10000	59
b		0.16	>1100	>6900	63

[a] The less polar diastereomer and the polar diastereomer were shown in the symbols **a** and **b**.
[b] $IC_{50}(ET_B)/IC_{50}(ET_A)$.
[c] Inhibitory activities on testosterone 6b-hydroxylation activities for human CYP3A4.
[d] Not tested.

significant loss in the ET_A potency and ET_A selectivity over the ET_B receptor.

The oral bioavailability of the hydroxymethyl derivatives (**1f** and **7f**) was examined and compared with that of the other alkyl derivatives (**1b** and **1d**). In contrast to the low oral bioavailability of **1b**, the hydroxymethyl derivatives (**1f** and **7f**) showed excellent oral bioavailability (**1f**: 48%,**7f**: 56%) in rats.

Finally, the inhibitory activity of **1f** and **7f** on the marker activities for human CYPs were also evaluated in an effort to clarify whether they showed competitive and mechanism-based inhibition of human P450s (CYP1A2, 2A6, 2C9, 2C19, 2D6, and 3A4). The data shown in Table 3 clearly indicates that these compounds were neither competitive inhibitors nor mechanism-based inactivators of human P450s.

4. Conclusion

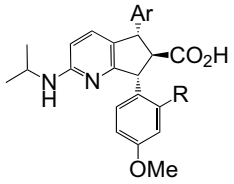
In conclusion, we have derivatized the 5-aryl rings and the alkyl side chain of the 7-aryl ring of the 5,7-diarylcyclopenteno[1,2-*b*]pyridine-6-carboxylic acids in order to identify orally bioavailable ET_A selective antagonists without significant CYPs inhibitory activity. As a result, 6-dihydrobenzofuran was determined to be a replaceable 5-aryl ring of the cyclopenteno[1,2-*b*]pyridine core in place of the methylenedioxyphenyl ring. Moreover, the SARs of the alkyl side chains at the 7-aryl ring on CYP3A4 inhibitory activity suggested that the hydroxymethyl group was effective in reducing the CYP3A4 inhibitory activity. Among the test compounds, the hydroxymethyl derivatives (**1f** and **7f**) showed excellent ET_A binding affinity with more than 800-fold selectivity for the ET_A receptor over the ET_B receptor. In addition, they had excellent oral bioavailability in rats. These compounds were determined to be neither competitive inhibitors of P450 marker activities (even at 100 μM) nor mechanism-based inactivators of P450s (up to 10 μM).

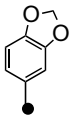
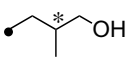
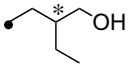
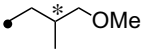
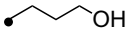
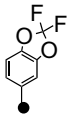
5. Experimental

5.1. General

All reagents and solvents were of commercial quality and were used without further purification unless otherwise noted. Melting points were determined using a Yanako MP micromelting point apparatus and were not corrected. Optical rotations were determined on a JASCO P-1020 polarimeter. ^{1}H NMR spectra were recorded on a Varian Gemini-300 instrument at 300 MHz. Chemical shifts were reported in parts per million as δ units relative to tetramethylsilane as an internal standard. Mass spectra were recorded using fast atom bombardment (FAB) ionization on a JEOL JMS-SX 102A spectrometer. Thin layer chromatography was performed using E-Merck Kieselgel 60 F_{254} plates (0.25 mm) and visualized using either UV light or phosphomolybdic acid. Column chromatography was performed using Wako gel C-300.

Table 2. Biological profiles of cyclopenteno[1,2-*b*]pyridine analogs with several kinds of alkyl substituents



Compound	Ar	R	IC_{50} (nM)		B/A ratio	CYP3A4 inh. (%)[a]	B/A (%)[b]
			ETA	ETB			
1b[c]			0.041	54	1300	45	7.6
1c[c]			0.045	16	340	58	NT[d]
1d[c]			0.025	48	1900	57	70
1e			0.022	20	910	27	NT[d]
1f			0.062	62	1000	19	48
7f			0.10	80	800	18	56
11f			0.23	430	1900	25	NT[d]

[a] The inhibitory activities on testosterone 6β-hydroxylation activity for human CYP3A4 after 60 min preincubation of compounds, $N = 2$.
[b] Bioavailability in rats (3mpk, po and 1 mpk, iv).
[c] Polar diastereomer.
[d] Not tested.

Table 3. Competitive inhibition (IC_{50s}) of P450 marker activities and mechanism-based inactivation (%inh.) of P450 by **1f** and **7f** in human liver microsomes

P450 marker metabolism (P450)	Competitive inhibition		Mechanism-based inactivation	
	1f	**7f**	**1f**	**7f**
	IC_{50} (μM)		% inhibition @ 10μM	
7-Ethoxyresorufin O-deethylation (CYP1A2)	>100	>100	None	None
Coumarin 7-hydroxylation (CYP2A6)	>100	>100	None	None
Tolbutamide methylhydroxylation (CYP2C9)	>100	>100	None	None
S-Mephenytoin 4′-hydroxylation (CYP2C19)	>100	>100	None	None
Bufurolol 1′-hydroxylation (CYP2D6)	>100	>100	None	None
Testosterone 6β-hydroxylation(CYP3A4)	>100	>100	None	None

5.1.1. 7-(2-Benzyloxy-4-methoxyphenyl)-6-*tert*-butoxycarbonyl-5-(2,3-dihydrobenzo[*b*]furan-6-yl)-5-hydroxy-cyclopenta-1,3-dieno[2,1-*b*]pyridine (13). A suspension of Mg (28.7 g, 1.18 mol) in a 30 mL aliquot of a solution of 5-bromo-2,3-dihydrobenzo[*b*]furan (224 g, 1.13 mol) in dry THF (1.1 L) was heated under a N_2 atmosphere. Upon initiation of the exothermic reaction, the remainder of the solution was added at a rate in which the reflux was maintained. Following the addition, the mixture was stirred at ambient temperature for 30 min. The resulting Grignard reagent mixture was added to a solution of enone **12**[11] (250 g, 564 mmol) in dry THF (2.5 L) at −78 °C under N_2 atmosphere over 40 min, and subsequently maintained at the same temperature with stirring

for 20 min. The reaction mixture was quenched with NH_4Cl (saturated, 2 L), then extracted with EtOAc (4 L). The organic layer was washed with water (4 L), brine (1 L), and concentrated. The residue was washed with diisopropyl ether and dried in vacuo to yield **13** as a pale yellow crystal (282 g, 89% yield). mp: 183–184 °C; ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 9H), 3.15 (t, $J = 8.7$ Hz, 2H), 3.87 (s, 3H), 4.41 (s, 1H), 4.54 (t, $J = 8.7$ Hz, 2H), 5.10 (s, 2H), 6.67–6.70 (m, 2H), 6.80–6.96 (br, 2H), 7.08 (dd, $J = 5.0$, 7.5 Hz), 7.11–7.16 (m, 1H), 7.22–7.47 (m, 6H), 7.53 (dd, $J = 1.5$, 7.5 Hz, 1H), 8.48 (dd, $J = 1.5$, 5.0 Hz, 1H); HRMS calcd for $C_{35}H_{33}NO_6$ $(M+H)^+$: 564.2386. Found 564.2387.

5.1.2. (5*RS*,6*RS*,7*SR*)-7-(2-Hydroxy-4-methoxyphenyl)-6-*tert*-butoxycarbonyl-5-(2,3-dihydrobenzo[*b*]furan-6-yl)-cyclopenteno[1,2-*b*]pyridine (14). To a solution of **13** (282 g, 500 mmol) and DMAP (183 g, 1.50 mol) in chloroform (2.0 L) was added acetic anhydride (189 mL, 2.00 mol), and the mixture was stirred at ambient temperature for 1 h. The reaction mixture was diluted with EtOAc (8 L) and hexane (1.5 L), and then washed with 0.5 M HCl (3 L), 10% $KHSO_4$ (2 L), $NaHCO_3$ (saturated, 2 L), and brine (1 L). The organic layer was dried over $MgSO_4$ and concentrated, and the resulting crude product was used for the next step without further purification.

The crude product was dissolved in THF (1.6 L) and EtOH (1.2 L), followed by the addition of 20% palladium hydroxide on carbon (160 g) and $NaHCO_3$ (50.4 g, 600 mmol). After stirring the mixture under an H_2 atmosphere (1 atm) at room temperature for 45 h, the reaction mixture was filtered through a pad of Celite and the cake was washed with THF (2 L). The combined filtrates were concentrated, and the resulting solid was washed with diisopropyl ether (1.5 L), and dried in vacuo to give **14** as a white powder (189 g, 82% in two steps). mp: 178–181 °C; ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 9H), 3.21 (t, $J = 8.6$ Hz, 2H), 3.77 (s, 3H), 3.94 (dd, $J = 5.9$, 7.3 Hz, 1H), 4.58 (t, $J = 8.6$ Hz, 2H), 4.73 (d, $J = 7.3$ Hz, 1H), 4.97 (d, $J = 5.9$ Hz, 1H), 6.37 (dd, $J = 2.4$, 8.5 Hz, 1H), 6.52 (d, $J = 2.4$ Hz, 1H), 6.73 (s, 1H), 6.84 (d, $J = 7.0$ Hz, 1H), 7.08 (d, $J = 8.5$ Hz, 1H), 7.18 (dd, $J = 5.0$, 7.8 Hz, 1H), 7.21 (d, $J = 7.0$ Hz, 1H), 7.58 (d, $J = 7.8$ Hz, 1H), 8.36 (d, $J = 5.0$ Hz, 1H); HRMS calcd for $C_{28}H_{29}NO_5$ $(M+H)^+$: 460.2124. Found 460.2122.

5.1.3. (5*RS*,6*SR*,7*SR*)-7-(2-Trifluoromethanesulfonyloxy-4-methoxyphenyl)-6-*tert*-butoxycarbonyl-5-(2,3-dihydrobenzo[*b*]furan-6-yl)cyclopenteno [1,2-*b*]pyridine (15). A solution of **14** (185 g, 403 mmol) and potassium *tert*-butoxide (90.3 g, 805 mmol) in dry THF (1.5 L) and *tert*-butyl alcohol (1.0 L) was stirred at 0 °C under N_2 atmosphere for 20 min. The reaction mixture was quenched using AcOH (69.2 mL, 1.21 mol), then extracted with EtOAc/hexane (1/1, 4 L). The organic layer was washed with $NaHCO_3$ (saturated) and brine, then dried over $MgSO_4$ and concentrated to afford the crude *trans–trans* isomer. To the crude product dissolved in dry $CHCl_3$ (1.5 L) was added DMAP (197 g, 1.76 mol) and trifluoromethanesulfonic anhydride (Tf_2O, 102 mL, 606 mmol) at 0 °C under a N_2 atmosphere. After maintaining the mixture at 0 °C with stirring for 30 min, the reaction mixture was diluted with hexane (1.5 L) and EtOAc (4.5 L), washed with 0.5 M HCl (2 L), 10% $KHSO_4$ (2 L), $NaHCO_3$ (saturated, 2 L), and brine (2 L). The organic layer was dried over $MgSO_4$, concentrated, and subsequently treated with diisopropyl ether (400 mL). The resulting crystalline material was collected, washed with diisopropyl ether, and dried in vacuo to give **15** as a white solid (172 g, 72% in two steps). mp: 145–146 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 9H), 3.22 (t, $J = 8.8$ Hz, 2H), 3.25 (dd, $J = 9.9$, 10.5 Hz, 1H), 3.83 (s, 3H), 4.60 (t, $J = 8.8$ Hz, 2H), 4.65 (d, $J = 9.9$ Hz, 1H), 4.91 (d, $J = 10.5$ Hz, 1H), 6.68 (s, 1H), 6.78 (d, $J = 7.6$ Hz, 1H), 6.91 (s, 1H), 6.93 (d, $J = 7.6$ Hz, 1H), 7.13 (dd, $J = 4.9$, 7.7 Hz), 7.15–7.20 (m, 2H), 7.32 (d, $J = 7.7$ Hz), 8.45 (d, $J = 4.9$ Hz, 1H); HRMS calcd for $C_{29}H_{28}F_3NO_7S$ $(M+H)^+$: 592.1617. Found 592.1619.

5.1.4. (5*RS*,6*SR*,7*SR*)-7-(2-Hydroxymethyl-4-methoxyphenyl)-6-*tert*-butoxycarbonyl-5-(2,3-dihydrobenzo[*b*]-furan-6-yl)cyclopenteno[1,2-*b*]pyridine (16). A mixture of **15** (140 g, 237 mmol), vinyl(tributyl)tin (90.2 g, 284 mmol), dichloro[bis(triphenylphosphine)]palladium (16.6 g, 23.7 mmol), and LiCl (30.1 g, 710 mmol) in DMF (1.1 L) was stirred at 125 °C under a N_2 atmosphere for 4 h. After cooling to ambient temperature, EtOAc (1.0 L) and 20% aqueous KF (1.5 L) was added, and the resulting mixture was vigorously stirred for 30 min. The mixture was filtered through a pad of Celite, and the organic and aqueous layers of the filtrate were separated. The organic layer was washed with 20% aqueous KF (0.5 L), and the combined aqueous layers were extracted with EtOAc (0.5 L). The combined organic layers were washed with water (2 L) and brine (1.5 L), dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography eluted with hexane/EtOAc to give the vinyl analog as a pale green oil (112 g): ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9H), 3.23 (t, $J = 8.6$ Hz, 2H), 3.28 (dd, $J = 9.7$, 10.8 Hz, 1H), 3.83 (s, 3H), 4.59 (t, $J = 8.6$ Hz, 2H), 4.60 (1H, d, $J = 4.6$ Hz, 1H), 4.99 (d, $J = 9.7$ Hz, 1H), 5.28 (d, $J = 10.8$ Hz, 1H), 5.63 (d, $J = 17.3$ Hz, 1H), 6.68 (s, 1H), 6.77 (d, $J = 7.5$ Hz, 1H), 6.83 (dd, $J = 2.7$, 8.6 Hz, 1H), 6.91–7.04 (br s, 1H), 6.98 (d, $J = 8.6$ Hz, 1H), 7.05 (d, $J = 2.7$ Hz, 1H), 7.09 (dd, $J = 4.8$, 7.6 Hz, 1H), 7.17 (d, $J = 7.5$ Hz, 1H), 7.31 (dd, $J = 1.2$, 7.6 Hz, 1H), 8.45 (dd, $J = 1.2$, 4.8 Hz, 1H); HRMS calcd for $C_{30}H_{31}NO_4$ $(M+H)^+$: 470.2331. Found 470.2325.

To a solution of this vinyl compound (112 g, 237 mmol) in THF (800 mL) was added 4-methylmorpholine-*N*-oxide (41.9 g, 358 mmol) and 0.05 M OsO_4 in water (158 mL, 7.9 mmol). After stirring the mixture at ambient temperature for 12 h, the reaction mixture was quenched using 10% $Na_2S_2O_3$ (1.5 L). The mixture was extracted with EtOAc (1.6 L), then the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. To the crude residue dissolved in THF (300 mL)

was added a solution of $NaIO_4$ (34.1 g, 159 mmol) in water (300 mL) over 10 min at 0 °C. After stirring for an additional 10 min, $NaBH_4$ (9.04 g, 239 mmol) was added in small portions, and the mixture was stirred at ambient temperature for 20 min. To the mixture was added water (0.6 L) and EtOAc (0.9 L). The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified using silica gel column chromatography eluted with hexane/EtOAc to give hydroxymethyl analog **16** as an oil (84.2 g, 75% in four steps). ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9H), 3.26 (t, $J = 8.7$ Hz, 2H), 3.62 (dd, $J = 9.6$, 11.8 Hz, 1H), 3.84 (s, 3H), 4.59–4.61 (m, 2H), 4.63 (t, $J = 8.7$ Hz, 2H), 4.95 (d, $J = 11.8$ Hz, 1H), 5.14 (d, $J = 9.6$ Hz, 1H), 6.73 (d, $J = 1.5$ Hz, 1H), 6.80 (dd, $J = 1.5$, 7.5 Hz, 1H), 6.85 (dd, $J = 2.8$, 8.6 Hz, 1H), 7.06 (d, $J = 2.8$ Hz, 1H), 7.08 (dd, $J = 4.8$, 7.7 Hz, 1H), 7.12 (d, $J = 8.6$ Hz, 1H), 7.22 (d, $J = 7.5$ Hz, 1H), 7.35 (dd, $J = 1.3$, 7.7 Hz, 1H), 8.34 (dd, $J = 1.3$, 4.8 Hz, 1H); HRMS calcd for $C_{29}H_{31}NO_5$ $(M+H)^+$: 474.2280. Found 474.2274.

5.1.5. (5*RS*,6*SR*,7*SR*)-7-(2-Acetoxymethyl-4-methoxyphenyl)-6-*tert*-butoxycarbonyl-5-(2,3-dihydrobenzo[*b*]-furan-6-yl)-2-(*N*-benzoyl-isopropylamino)cyclopenteno-[1,2-*b*]pyridine (17). To a solution of **16** (84.1 g, 178 mmol) in THF (420 mL) were added DMAP (65.2 g, 534 mmol) and acetic anhydride (67.0 mL, 710 mmol). After stirring the mixture at ambient temperature for 20 min, the reaction mixture was diluted with EtOAc (1.2 L), washed with 10% $KHSO_4$ (1.5 L), $NaHCO_3$ (saturated, 1 L), and brine (1 L), then dried over $MgSO_4$, and concentrated. The residue was passed through a short column using a silica gel, and the resulting crude product was used in the next step without further purification.

To a solution of this acetoxy analog (74.2 g, 144 mmol) in $CHCl_3$ (700 mL) was added *m*-CPBA (74.5 g, 432 mmol) in small portions at 0 °C. After stirring the mixture at 0 °C for 15 h, the reaction mixture was quenched with 15% $Na_2S_2O_3$ (1.5 L), and extracted with hexane (1.4 L)-EtOAc (0.7 L). The organic layer was washed with $NaHCO_3$ (saturated, 1.5 L) and brine, dried over $MgSO_4$, and concentrated to give the corresponding pyridine N-oxide, which was used in the next step without further purification.

A mixture of this pyridine N-oxide, *N*-isopropylbenzimidoyl chloride (78.5 g, 432 mmol), and triethylamine (141 mL, 1.01 mol) in dry $CHCl_3$ (600 mL) was refluxed under a N_2 atmosphere for 17 h. After cooling to ambient temperature, $NaHCO_3$ (saturated, 1.5 L) was added and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography with hexane/EtOAc as an eluent to give **17** as a pale green oil (72.9 g, 61% from **16**). ^{1}H NMR ($CDCl_3$) δ 1.12 (d, $J = 7.7$ Hz, 3H), 1.17 (d, $J = 7.7$ Hz, 3H), 1.35 (s, 9H), 2.10 (s, 3H), 3.21 (t, $J = 8.7$ Hz, 2H), 3.29 (dd, $J = 9.6$, 9.9 Hz, 1H), 3.85 (s, 3H), 4.48 (d, $J = 9.6$ Hz, 1H), 4.59 (t, $J = 8.7$ Hz, 2H), 4.94–5.02 (m, 1H), 4.96 (d, $J = 9.9$ Hz, 1H), 5.21–5.32 (m, 2H), 6.52 (d, $J = 1.2$ Hz, 1H), 6.57 (d, $J = 7.9$ Hz, 1H), 6.63–6.99 (m, 4H), 7.03 (dd, $J = 1.2$, 7.9 Hz, 1H), 7.12–7.25 (m, 6H); HRMS calcd for $C_{41}H_{44}N_2O_7$ $(M+H)^+$: 677.3227. Found 677.3228.

5.1.6. Optically pure compound 18. Racemic **17** (72.9 g) was optically resolved using chiral HPLC (Chiralpak AD, 50 × 500 mm, hexane/2-propanol (70:30), flow rate=100 mL/min) to give chiral compound **18** (32.2 g, 44%). Chiral analytical HPLC indicated that enantiomeric excess (ee) of **18** was >99.9%; $[\alpha]_D^{27}$ +22.8 (*c* 1.00, EtOH).

5.2. *tert*-Butyl

5.2.1. (5*S*,6*R*,7*R*)-(+)-5-(2,3-dihydrobenzo[*b*]furan-6-yl)-7-(2-hydroxylmethyl-4-methoxyphenyl)-2-(*N*-isopropylamino)cyclopenteno[1,2-*b*]pyridine-6-carboxylate (19). To a solution of **18** (30.0 g, 44.3 mmol) in THF (300 mL) was added 1.01 M diisobutylaluminum hydride in toluene (175 mL, 177 mmol) over 30 min at −78 °C. The mixture was maintained at the same temperature with stirring for 1.5 h. To the reaction mixture was added NH_4Cl (saturated, 1.0 L), EtOAc (0.90 L), water (0.50 L), and 10% $KHSO_4$ (0.10 L). The layers were separated and the organic layer was washed with 10% $KHSO_4$ (0.60 L) and brine (0.60 L), dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography with hexane/EtOAc as the mobile phase to give **19** as an off-white solid (21.5 g, 91%). mp: 89–92 °C; ^{1}H NMR (DMSO-d_6) δ 0.97 (d, $J = 6.4$ Hz, 3H), 1.04 (d, $J = 6.4$ Hz, 3H), 3.00 (dd, $J = 8.3$, 8.9 Hz, 1H), 3.15 (t, $J = 8.9$ Hz, 2H), 3.39–3.47 (m, 1H), 3.60–3.71 (m, 1H), 3.73 (s, 3H), 4.32 (d, $J = 8.3$ Hz, 1H), 4.46–4.57 (m, 1H), 4.51 (t, $J = 8.9$ Hz, 2H), 4.62 (d, $J = 8.9$ Hz, 1H), 4.59–4.64 (m, 1H), 6.25 (d, $J = 8.5$ Hz, 1H), 6.59 (d, $J = 1.4$ Hz, 1H), 6.70 (dd, $J = 1.4$, 7.6 Hz, 1H), 6.74 (dd, $J = 2.8$, 8.5 Hz, 1H), 6.89 (d, $J = 7.9$ Hz, 1H), 6.92 (d, $J = 7.9$ Hz, 1H), 7.00 (d, $J = 2.8$ Hz, 1H), 7.17 (d, $J = 7.6$ Hz, 1H); $[\alpha]_D^{27}$ +20.9 (*c* 1.00, EtOH); HRMS calcd for $C_{32}H_{38}N_2O_5$ $(M+H)^+$: 531.2859. Found 531.2858.

5.2.2. (5*S*,6*R*,7*R*)-(+)-5-(2,3-Dihydrobenzo[*b*]furan-6-yl)-7-(2-hydroxylmethyl-4-methoxyphenyl)-2-(*N*-isopropylamino)cyclopenteno[1,2-*b*]pyridine-6-carboxylic acid (7f)[14]. A solution of **19** (21.0 g, 39.6 mmol) in TFA (63 mL) was stirred at room temperature for 1 h, then concentrated. Water (100 mL) adjusted to pH 6.5 using $NaHCO_3$ (saturated) was added to the residue dissolved in EtOAc (200 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were concentrated, and the residue was washed with EtOAc (200 mL) then dried in vacuo to give **7f** as a colorless crystal (15.7 g). The washings were concentrated and purified by silica gel column chromatography to afford a second crop (1.6 g) for a combined total yield of 17.3 g (92%). mp: 220–222 °C; ^{1}H NMR (DMSO-d_6) δ 0.98 (d, $J = 6.4$ Hz, 3H), 1.04 (d, $J = 6.4$ Hz, 3H), 3.01 (dd, $J = 8.6$, 8.8 Hz, 1H), 3.15 (t, $J = 8.8$ Hz, 2H), 3.60–3.71 (m, 1H), 3.73 (s, 3H),

4.32 (d, $J = 8.6$ Hz, 1H), 4.44–4.56 (m, 3H), 4.60–4.72 (m, 2H), 6.25 (d, $J = 8.5$ Hz, 1H), 6.60 (s, 1H), 6.70 (d, $J = 7.7$ Hz, 1H), 6.75 (dd, $J = 2.9$, 8.6 Hz, 1H), 6.89 (d, $J = 7.7$ Hz, 1H), 6.92 (d, $J = 7.6$ Hz, 1H), 7.02 (d, $J = 2.9$ Hz, 1H), 7.18 (d, $J = 7.6$ Hz, 1H); $[\alpha]_D^{20}$ +71.9 (*c* 1.00, 1 M NaOH); HRMS calcd for $C_{28}H_{30}N_2O_5$ $(M+H)^+$: 475.2233. Found 475.2239.

5.2.3. (5*RS*,6*SR*,7*SR*)-7-[2-(3-Hydroxy-2-methylpropyl)-4-methoxyphenyl]-6-*tert*-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine (21a,b). The mixture of $PdCl_2(PPh_3)_2$ (7.70 g, 0.011 mol), $NaHCO_3$ (18.4 g, 0.22 mol), methallyl alcohol (93.1 mL, 1.10 mol) and **20** (64.9 g, 0.11 mol) in DMF (650 mL) was heated with stirring at 130 °C for 12 h under N_2. After cooling to room temperature, the reaction mixture was diluted with EtOAc and H_2O, and the organic layer was washed with water and brine, dried over Na_2SO_4 and then concentrated. The residue was dissolved in MeOH and $NaBH_4$ (8.32 g, 0.22 mol) was added to the solution in small portions at 0 °C. After an additional stirring for 15 min, the mixture was quenched using saturated NH_4Cl and diluted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography eluted with hexane/EtOAc to give less polar diastereomer **21a** as a colorless solid (9.91 g, 18% yield) and polar diastereomer **21b** as an oil (8.62 g, 15% yield). **21a**; ^{1}H NMR ($CDCl_3$) δ 8.37 (d, $J = 5.0$ Hz, 1H), 7.27 (d, $J = 7.3$ Hz 1H), 7.07 (dd, $J = 7.3$ and 5.0 Hz, 1H), 6.87 (d, $J = 7.7$ Hz, 1H), 6.62–6.83 (m, 5H), 5.97 (s, 2H), 5.04 (d, $J = 9.9$ Hz, 1H), 4.51 (d, $J = 9.9$ Hz, 1H), 3.78 (s, 3H), 3.40–3.63 (m, 2H), 3.27 (t, $J = 9.9$ Hz, 1H), 2.66–2.98 (m, 2H), 1.88–2.07 (m, 1H), 1.32 (s, 9H), 1.00 (d, $J = 6.6$ Hz, 3H). HRMS calcd for $C_{31}H_{36}NO_6$ $(M+H)^+$ 518.2543. Found 518.2540.

21b; ^{1}H NMR ($CDCl_3$) δ 8.35 (d, $J = 5.0$ Hz, 1H), 7.33 (d, $J = 7.7$ Hz, 1H), 7.10 (dd, $J = 7.7$ and 5.0 Hz, 1H), 6.86 (d, $J = 8.4$ Hz, 1H), 6.69–6.83 (m, 5H), 5.98 (s, 2H), 5.13 (d, $J = 9.7$ Hz, 1H), 4.57 (d, $J = 9.7$ Hz, 1H), 3.78 (s, 3H), 3.53 (dd, $J = 11.4$ and 3.1 Hz, 1H), 3.43 (dd, $J = 11.4$ and 4.4 Hz, 1H), 3.26 (t, $J = 9.7$ Hz, 1H), 3.00–3.17 (m, 1H), 2.46–2.61 (m, 1H), 2.04–2.19 (m, 1H), 1.34 (s, 9H), 1.09 (d, $J = 6.6$ Hz, 3H). HRMS calcd for $C_{31}H_{36}NO_6$ $(M+H)^+$ 518.2543, found 518.2543.

The preparation of methylenedioxyphenyl derivatives (**1a**–**f**) was previously reported.[8] Compounds **2a**–**7b** and **8a**–**11b** were prepared from intermediate **12** in a similar manner using the corresponding arylbromide. The synthesis of **11f** was analogous to the method used for the synthesis of **7f**.

5.2.4. (5*S*,6*R*,7*R*)-5-(2,3-Dimethoxyphenyl)-7-[2-(3-hydroxy-2-methylpropyl)-4-methoxyphenyl]-2-(*N*-isopropylamino)cyclopenteno[1,2-*b*]pyridine-6-carboxylic acid (2a,b). **2a**; White solid; mp 124–127 °C; ^{1}H NMR ($CDCl_3$) δ 0.75 (d, $J = 6.4$ Hz, 3H), 1.14 (d, $J = 6.3$ Hz, 3H), 1.18 (d, $J = 6.3$ Hz, 3H), 1.79–1.91 (m, 1H), 2.00–2.14 (m, 1H), 2.99 (dd, $J = 6.5$, 6.6 Hz, 1H), 3.08–3.12 (m, 1H), 3.20–3.35 (m, 2H), 3.58–3.65 (m, 1H), 3.70 (s, 3H), 3.77 (s, 3H), 3.83 (s, 3H), 4.25 (d, $J = 6.5$ Hz, 1H), 4.99 (d, $J = 6.6$ Hz, 1H), 6.34 (d, $J = 8.8$ Hz, 1H), 6.52 (br s, 1H), 6.62–6.83 (m, 5H), 7.24–7.26 (m, 1H); HRMS calcd for $C_{31}H_{38}N_2O_6$ $(M+H)^+$: 535.2808. Found 535.2803.

2b; White solid; mp 114–116 °C; ^{1}H NMR ($CDCl_3$) δ 1.07 (d, $J = 6.5$ Hz, 3H), 1.12 (d, $J = 6.3$ Hz, 3H), 1.18 (d, $J = 6.3$ Hz, 3H), 2.06–2.09 (m, 1H), 2.49–2.57 (m, 1H), 2.95–3.04 (m, 1H), 3.23 (dd, $J = 7.7$, 8.1 Hz, 1H), 3.35–3.45 (m, 2H), 3.61–3.66 (m, 1H), 3.76 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 4.49 (d, $J = 7.7$ Hz, 1H), 5.07 (d, $J = 8.1$ Hz, 1H), 6.22 (d, $J = 8.9$ Hz, 1H), 6.67–6.91 (m, 6H), 7.12 (d, $J = 8.2$ Hz, 1H); $[\alpha]_D^{27}$ +21.0 (*c* 1.00, EtOH); HRMS calcd for $C_{31}H_{38}N_2O_6$ $(M+H)^+$: 535.2808. Found 535.2816.

5.2.5. (5*S*,6*R*,7*R*)-(+)-5-(Indan-5-yl)-7-[2-(3-hydroxy-2-methylpropyl)-4-methoxyphenyl]-2-(*N*-isopropylamino)-cyclopenteno[1,2-*b*]pyridine-6-carboxylic acid (3a,b). 3a; White solid; mp 122–125 °C; ^{1}H NMR ($CDCl_3$) δ 1.06 (d, $J = 7.6$ Hz, 3H), 1.09 (d, $J = 6.4$ Hz, 3H), 1.14 (d, $J = 6.4$ Hz, 3H), 2.03–2.13 (m, 3H), 2.52–2.57 (m, 1H), 2.87–3.02 (m, 5H), 3.25 (dd, $J = 8.6$, 8.9 Hz, 1H), 3.33–3.51 (m, 2H), 3.54–3.68 (m, 1H), 3.75 (s, 3H), 4.49 (d, $J = 8.6$ Hz, 1H), 5.05 (d, $J = 8.9$ Hz, 1H), 6.19 (d, J = 8.2 Hz, 1H), 6.63–6.74 (m, 2H), 6.85–7.21 (m, 5H); $[\alpha]_D^{29}$ +23.3 ($c = 1.00$, EtOH); HRMS calcd for $C_{32}H_{38}N_2O_4$ $(M+H)^+$: 515.2910. Found 515.2914.

3b; White solid; mp 117–121 °C; ^{1}H NMR ($CDCl_3$) δ 0.93 (d, $J = 6.4$ Hz, 3H), 1.12 (d, $J = 6.3$ Hz, 3H), 1.14 (d, $J = 6.3$ Hz, 3H), 1.92–2.10 (m, 3H), 2.60–2.72 (m, 2H), 2.84–2.93 (m, 4H), 3.20 (dd, $J = 8.7$, 8.9 Hz, 1H), 3.30–3.49 (m, 2H), 3.58–3.67 (m, 1H), 3.73 (s, 3H), 4.47 (d, $J = 8.7$ Hz, 1H), 4.87 (d, $J = 8.9$ Hz, 1H), 6.18 (d, $J = 8.8$ Hz, 1H), 6.64–6.73 (m, 2H), 6.90–7.20 (m, 5H); $[\alpha]_D^{29}$ +40.3 ($c = 1.00$, EtOH); HRMS calcd for $C_{32}H_{38}N_2O_4$ $(M+H)^+$: 515.2910. Found 515.2915.

5.2.6. (5*S*,6*R*,7*R*)-(+)-5-(Benzofuran-5-yl)-7-[2-(3-hydroxy-2-methylpropyl)-4-methoxyphenyl]-2-(*N*-isopropylamino)cyclopenteno[1,2-*b*]pyridine-6-carboxylic acid (4a,b). 4a; White solid; mp 116–119 °C; ^{1}H NMR ($CDCl_3$) δ 1.00 (d, $J = 6.5$ Hz, 3H), 1.08 (d, $J = 6.2$ Hz, 3H), 1.13 (d, $J = 6.2$ Hz, 3H), 1.95–2.10 (m, 1H), 2.49 (dd, $J = 4.9$, 13.8 Hz, 1H), 2.93 (d, $J = 13.8$ Hz, 1H), 3.22 (dd, $J = 8.2$, 8.3 Hz, 1H), 3.30–3.50 (m, 2H), 3.52–3.65 (m, 1H), 3.70 (s, 3H), 4.60 (d, $J = 8.2$ Hz, 1H), 5.04 (d, $J = 8.3$ Hz, 1H), 6.19 (d, $J = 8.6$ Hz, 1H), 6.63–6.75 (m, 3H), 6.90 (d, $J = 9.2$ Hz, 1H), 7.07 (d, $J = 8.6$ Hz, 1H), 7.20 (d, $J = 8.5$ Hz, 1H), 7.44 (d, $J = 8.5$ Hz, 1H), 7.56 (s, 1H), 7.60 (s, 1H); $[\alpha]_D^{30}$ +32.4 (*c* 1.00, EtOH); HRMS calcd for $C_{31}H_{34}N_2O_5$ $(M+H)^+$: 515.2546. Found 515.2549.

4b; White crystals; mp 219–221 °C; ^{1}H NMR ($CDCl_3$) δ 0.90 (d, $J = 6.3$ Hz, 3H), 1.12 (d, $J = 6.5$ Hz, 3H), 1.14 (d, $J = 6.5$ Hz, 3H), 1.90–2.05 (m, 1H), 2.50–2.65 (m, 1H), 2.65–2.75 (m, 1H), 3.21 (dd, $J = 8.3$, 8.4 Hz, 1H), 3.30–3.50 (m, 2H), 3.55–3.65 (m, 1H), 3.69 (s, 3H), 4.58

(d, $J = 8.3$ Hz, 1H), 4.89 (d, $J = 8.4$ Hz, 1H), 6.20 (d, $J = 8.2$ Hz, 1H), 6.60–6.75 (m, 3H), 6.94 (d, $J = 8.2$ Hz, 1H), 7.07 (d, $J = 8.8$ Hz, 1H), 7.19 (d, $J = 8.5$ Hz, 1H), 7.44 (d, $J = 8.5$ Hz, 1H), 7.49 (s, 1H), 7.61 (s, 1H); $[\alpha]_D^{30}$ +48.5 (*c* 0.30, EtOH); HRMS calcd for $C_{32}H_{38}N_2O_4$ $(M+H)^+$: 515.2546. Found 515.2526.

5.2.7. (5*S*,6*R*,7*R*)-(+)-5-(2,3-Dihydrobenzo[*b*]furan-5-yl)-7-[2-(3-hydroxy-2-methylpropyl)-4-methoxyphenyl]-2-(*N*-isopropylamino)cyclopenteno[1,2-*b*]pyridine-6-carboxylic acid (5a,b). 5a; White solid; mp 199–201 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (d, $J = 6.2$ Hz, 3H), 1.09 (d, $J = 6.2$ Hz, 3H), 1.14 (d, $J = 6.2$ Hz, 3H), 1.98–2.12 (m, 1H), 2.48–2.57 (m, 1H), 2.91–3.02 (m, 1H), 3.15–3.25 (m, 3H), 3.32–3.50 (m, 2H), 3.56–3.65 (m, 1H), 3.74 (s, 3H), 4.45 (d, $J = 8.5$ Hz, 1H), 4,56 (t, $J = 8.6$ Hz, 2H), 5.02 (d, $J = 8.7$ Hz, 1H), 6.18 (d, $J = 8.4$ Hz, 1H), 6.65–6.78 (m, 3H), 6.89 (d, $J = 8.2$ Hz, 1H), 7.02 (d, $J = 7.7$ Hz, 1H), 7.07 (d, $J = 8.4$ Hz, 1H), 7.12 (s, 1H); $[\alpha]_D^{31}$ +18.6 (*c* 0.44, EtOH); HRMS calcd for $C_{31}H_{36}N_2O_5$ $(M+H)^+$: 517.2702. Found 517.2698.

5b: White solid; mp 212–215 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (d, $J = 6.4$ Hz, 3H), 1.12 (d, $J = 5.9$ Hz, 3H), 1.17 (d, $J = 5.9$ Hz, 3H), 1.84–1.98 (m, 1H), 2.40–2.52 (m, 1H), 2.64–2.78 (m, 1H), 3.08 (dd, $J = 8.2$, 8.3 Hz, 1H), 3.16 (t, $J = 8.6$ Hz, 2H), 3.25–3.40 (m, 2H), 3.52–3.65 (m, 1H), 3.68 (s, 3H), 4.39 (d, $J = 8.2$ Hz, 1H), 4,54 (t, $J = 8.6$ Hz, 2H), 4.83 (d, $J = 8.3$ Hz, 1H), 6.23 (d, $J = 8.6$ Hz, 1H), 6.65 (s, 1H), 6.67 (d, $J = 8.8$ Hz, 1H), 6.71 (d, $J = 8.3$ Hz, 1H), 6.88 (d, $J = 8.8$ Hz, 1H), 6.97 (d, $J = 8.3$ Hz, 1H), 7.06 (s, 1H), 7.10 (d, $J = 8.6$ Hz, 1H); $[\alpha]_D^{20}$ +35.9 (*c* 0.92, EtOH); HRMS calcd for $C_{31}H_{36}N_2O_5$ $(M+H)^+$: 517.2702. Found 517.2693.

5.2.8. (5*S*,6*R*,7*R*)-5-(Benzofuran-6-yl)-7-[2-(3-hydroxy-2-methylpropyl)-4-methoxyphenyl]-2-(*N*-isopropylamino)-cyclopenteno[1,2-*b*]pyridine-6-carboxylic acid (6a,b). 6a; White solid; ^{1}H NMR ($CDCl_3$) δ 1.00 (d, $J = 6.6$ Hz, 3H), 1.09 (d, $J = 6.3$ Hz, 3H), 1.14 (d, $J = 6.3$ Hz, 3H), 1.95–2.07 (m, 1H), 2.43–2.55 (m, 1H), 2.88–2.99 (m, 1H), 3.22 (dd, $J = 8.1$, 8.4 Hz, 1H), 3.32–3.48 (m, 2H), 3.55–3.66 (m, 1H), 3.70 (s, 3H), 4.62 (d, $J = 8.4$ Hz, 1H), 5.04 (d, $J = 8.1$ Hz, 1H), 6.20 (d, $J = 8.4$ Hz, 1H), 6.62–6.69 (m, 2H), 6.74 (d, $J = 1.5$ Hz, 1H), 6.89 (d, $J = 8.4$ Hz, 1H), 7.08 (d, $J = 8.4$ Hz, 1H), 7.17 (d, $J = 8.4$ Hz, 1H), 7.43 (s, 1H), 7.53 (d, $J = 8.4$ Hz, 1H), 7.60 (d, $J = 1.5$ Hz, 1H); HRMS calcd for $C_{31}H_{34}N_2O_5$ $(M+H)^+$: 515.2546. Found 515.2523.

6b; White solid; ^{1}H NMR ($CDCl_3$) δ 0.86 (d, $J = 6.9$ Hz, 3H), 1.13 (d, $J = 6.9$ Hz, 3H), 1.15 (d, $J = 6.9$ Hz, 3H), 1.83–1.96 (m, 1H), 2.40–2.52 (m, 1H), 2.65–2.77 (m, 1H), 3.18 (dd, $J = 8.3$, 8.2 Hz, 1H), 3.28–3.42 (m, 2H), 3.55–3.65 (m, 1H), 3.67 (s, 3H), 4.58 (d, $J = 8.3$ Hz, 1H), 4.89 (d, $J = 8.2$ Hz, 1H), 6.22 (d, $J = 8.4$ Hz, 1H), 6.60 (d, $J = 2.4$ Hz, 1H), 6.66 (dd, $J = 2.4$, 8.4 Hz, 1H), 6.73 (d, $J = 2.4$ Hz, 1H), 6.90 (d, $J = 8.4$ Hz, 1H), 7.10 (d, $J = 8.4$ Hz, 1H), 7.15 (d, $J = 8.4$ Hz, 1H), 7.40 (s, 1H), 7.52 (d, $J = 8.4$ Hz, 1H), 7.59 (d, $J = 2.4$ Hz, 1H); HRMS calcd for $C_{31}H_{34}N_2O_5$ $(M+H)^+$: 515.2546. Found 515.2539.

5.2.9. (5*S*,6*R*,7*R*)-5-(2,3-Dihydrobenzo[*b*]furan-6-yl)-7-[2-(3-hydroxy-2-methylpropyl)-4-methoxyphenyl]-2-(*N*-isopropylamino)cyclopenteno[1,2-*b*]pyridine-6-carboxylic acid (7a,b). 7a; white solid; ^{1}H NMR ($CDCl_3$) δ 1.06 (d, $J = 6.9$ Hz, 3H), 1.10 (d, $J = 6.3$ Hz, 3H), 1.14 (d, $J = 6.3$ Hz, 3H), 2.10–2.12 (m, 1H), 2.49–2.62 (m, 1H), 3.01 (dd, $J = 8.9$, 9.0 Hz, 1H), 3.15–3.25 (m, 1H), 3.21 (t, $J = 8.7$ Hz, 2H), 3.37–3.42 (m, 2H), 3.56–3.67 (m, 1H), 3.75 (s, 3H), 4.49 (d, $J = 9.0$ Hz, 1H), 4,58 (t, $J = 8.7$ Hz, 2H), 5.05 (d, $J = 8.9$ Hz, 1H), 6.19 (d, $J = 8.5$ Hz, 1H), 6.66–6.77 (m, 3H), 6.81 (d, $J = 7.3$ Hz, 1H), 6.91 (d, $J = 8.5$ Hz, 1H), 7.09 (d, $J = 8.5$ Hz, 1H), 7.15 (d, $J = 7.3$ Hz, 1H); $[\alpha]_D^{26}$ +14.1 (*c* 1.00, EtOH); HRMS calcd for $C_{31}H_{36}N_2O_5$ $(M+H)^+$: 517.2702. Found 517.2682.

7b; White solid; ^{1}H NMR ($CDCl_3$) δ 0.92 (d, $J = 6.6$ Hz, 3H), 1.12 (d, $J = 6.3$ Hz, 3H), 1.14 (d, $J = 6.3$ Hz, 3H), 1.90–2.03 (m, 1H), 2.53–2.75 (m, 2H), 3.12–3.23 (m, 3H), 3.32–3.46 (m, 2H), 3.56–3.66 (m, 1H), 3.72 (s, 3H), 4.45 (d, $J = 8.4$ Hz, 1H), 4,56 (t, $J = 8.4$ Hz, 2H), 4.87 (d, $J = 8.4$ Hz, 1H), 6.20 (d, $J = 8.6$ Hz, 1H), 6.62–6.72 (m, 3H), 6.76 (d, $J = 7.2$ Hz, 1H), 6.90 (d, $J = 8.6$ Hz, 1H), 7.07–7.18 (m, 2H); HRMS calcd for $C_{31}H_{36}N_2O_5$ $(M+H)^+$: 517.2702. Found 517.2706.

5.2.10. (5*S*,6*R*,7*R*)-5-(Benzofuran-4-yl)-7-[2-(3-hydroxy-2-methylpropyl)-4-methoxyphenyl]-2-(*N*-isopropylamino)-cyclopenteno[1,2-*b*]pyridine-6-carboxylic acid (8a,b). 8a; White solid; mp 124–126 °C; ^{1}H NMR ($CDCl_3$) δ 0.98 (d, $J = 6.7$ Hz, 3H), 1.09 (d, $J = 6.3$ Hz, 3H), 1.15 (d, $J = 6.3$ Hz, 3H), 1.98–2.08 (m, 1H), 2.41–2.52 (m, 1H), 2.88–3.01 (m, 1H), 3.26 (dd, $J = 7.3$, 8.4 Hz, 1H), 3.32–3.48 (m, 2H), 3.58–3.66 (m, 1H), 3.69 (s, 3H), 4.87 (d, $J = 7.3$ Hz, 1H), 5.07 (d, $J = 8.4$ Hz, 1H), 6.22 (d, $J = 8.5$ Hz, 1H), 6.60–6.72 (m, 2H), 6.89 (d, $J = 8.5$ Hz, 1H), 7.07–7.53 (m, 4H); $[\alpha]_D^{31}$ −0.75 (*c* 1.00, EtOH); HRMS calcd for $C_{31}H_{34}N_2O_5$ $(M+H)^+$: 515.2546. Found 515.2517.

8b; White solid; mp 126–127 °C; ^{1}H NMR ($CDCl_3$) δ 0.85 (d, $J = 6.5$ Hz, 3H), 1.12 (d, $J = 6.5$ Hz, 3H), 1.15 (d, $J = 6.5$ Hz, 3H), 1.85–1.95 (m, 1H), 2.37–2.49 (m, 1H), 2.67–2.81 (m, 1H), 3.23 (dd, $J = 8.2$, 8.8 Hz, 1H), 3.29–3.40 (m, 2H), 3.52–3.65 (m, 1H), 3.65 (s, 3H), 4.83 (d, $J = 8.8$ Hz, 1H), 4.90 (d, $J = 8.2$ Hz, 1H), 6.23 (d, $J = 8.5$ Hz, 1H), 6.55–6.70 (m, 3H), 6.89 (d, $J = 8.5$ Hz, 1H), 7.06 (d, $J = 7.5$ Hz, 1H), 7.03–7.14 (m, 2H), 7.40 (d, $J = 8.2$ Hz, 1H), 7.51 (d, $J = 2.1$ Hz, 1H); $[\alpha]_D^{31}$ +15.9 (*c* 0.94, EtOH); HRMS calcd for $C_{31}H_{34}N_2O_5$ $(M+H)^+$: 515.2546. Found 515.2533.

5.2.11. (5*S*,6*R*,7*R*)-5-(2,3-Dihydrobenzo[*b*] furan-4-yl)-7-[2-(3-hydroxy-2-methylpropyl)-4-methoxyphenyl]-2-(*N*-isopropylamino)cyclopenteno[1,2-*b*]pyridine-6-carboxylic acid (9a,b). 9a; White solid; mp 128–130 °C. ^{1}H NMR ($CDCl_3$) δ 1.06 (d, $J = 6.9$ Hz, 3H), 1.10 (d, $J = 6.3$ Hz,

3H), 1.14 (d, $J = 6.3$ Hz, 3H), 2.10–2.12 (m, 1H), 2.49–2.62 (m, 1H), 3.01 (dd, $J = 8.9$, 9.0 Hz, 1H), 3.15–3.25 (m, 1H), 3.21 (t, $J = 8.7$ Hz, 2H), 3.37–3.42 (m, 2H), 3.56–3.67 (m, 1H), 3.75 (s, 3H), 4.49 (d, $J = 9.0$ Hz, 1H), 4,58 (t, $J = 8.7$ Hz, 2H), 5.05 (d, $J = 8.9$ Hz, 1H), 6.19 (d, $J = 8.5$ Hz, 1H), 6.66–6.77 (m, 3H), 6.81 (d, $J = 7.3$ Hz, 1H), 6.91 (d, $J = 8.5$ Hz, 1H), 7.09 (d, $J = 8.5$ Hz, 1H), 7.15 (d, $J = 7.3$ Hz, 1H); $[\alpha]_D^{32}$ −8.0 (*c* 1.00, EtOH); HRMS calcd for $C_{31}H_{36}N_2O_5$ $(M+H)^+$: 517.2702. Found 517.2690.

9b; White solid; mp 127–129 °C. ^{1}H NMR ($CDCl_3$) δ 0.87 (d, $J = 6.5$ Hz, 3H), 1.12 (d, $J = 6.6$ Hz, 3H), 1.15 (d,$J = 6.6$ Hz, 3H), 1.82–1.95 (m, 1H), 2.40–250 (m, 1H), 2.83–2.95 (m, 1H), 3.05–3.17 (m, 2H), 3.18 (dd, $J = 8.2, 8.8$ Hz), 3.25–3.40 (m, 2H), 3.53–3.66 (m, 1H), 3.68 (s, 3H), 4.40–4.53 (m, 2H), 4.53 (d, $J = 8.2$ Hz, 1H), 4.83 (d, $J = 8.8$ Hz, 1H), 6.22 (d, $J = 8.5$ Hz, 1H), 6.55–6.70 (m, 4H), 6.87 (d, $J = 8.5$ Hz, 1H), 7.03–7.18 (m, 2H); $[\alpha]_D^{32}$ +6.3 (*c* 1.00, EtOH); HRMS calcd for $C_{31}H_{36}N_2O_5$ $(M+H)^+$: 517.2702. Found 517.2689.

5.2.12. (5*S*,6*R*,7*R*)-(+)-5-(2,2-Dimethylbenzo[1,3]dioxol-5-yl)-7-[2-(3-hydroxy-2-methylpropyl)]-4-methoxyphenyl-2-(*N*-isopropylamino)cyclopenteno[1,2-*b*]pyridine-6-carboxylic acid (10a,b). 10a; White solid; mp 126–127 °C. ^{1}H NMR ($CDCl_3$) δ 0.98 (d, $J = 6.7$ Hz, 3H), 1.12 (d, $J = 6.7$ Hz, 3H), 1.15 (d, $J = 6.7$ Hz, 3H), 1.66 (s, 6H), 1.98–2.10 (m, 1H), 2.40–2.52 (m, 1H), 2.90–3.00 (m, 1H), 3.15 (t, $J = 9.0$ Hz, 1H), 3.30–3.50 (m, 2H), 3.55–3.66 (m, 1H), 3.73 (s, 3H), 4.43 (d, $J = 9.0$ Hz, 1H), 5.02 (d, $J = 9.0$ Hz, 1H), 6.20 (d, $J = 8.2$ Hz, 1H), 6.52–6.72 (m, 4H), 6.86 (d, $J = 8.2$ Hz, 1H), 7.08–7.17 (m, 2H); $[\alpha]_D^{26}$ +22.7 (*c* 2.16, EtOH); HRMS calcd for $C_{32}H_{38}N_2O_6$ $(M+H)^+$: 547.2808. Found 547.2813.

10b; White solid; mp 122–124 °C. ^{1}H NMR ($CDCl_3$) δ 0.93 (d, $J = 6.3$ Hz, 3H), 1.14 (d, $J = 6.6$ Hz, 3H), 1.16 (d, $J = 6.6$ Hz, 3H), 1.66 (s, 6H), 1.91–2.06 (m, 1H), 2.55–2.83 (m, 2H), 3.17 (t, $J = 8.4$ Hz, 1H), 3.32–3.52 (m, 2H), 3.56–3.67 (m, 1H), 3.72 (s, 3H), 4.45 (d, $J = 8.4$ Hz, 1H), 4.90 (d, $J = 8.4$ Hz, 1H), 6.22 (d, $J = 8.7$ Hz, 1H), 6.60–6.75 (m, 4H), 6.90 (d, $J = 8.7$ Hz, 1H), 7.08–7.17 (m, 2H). $[\alpha]_D^{26}$ +38.3 (*c* 2.46, EtOH); HRMS calcd for $C_{32}H_{38}N_2O_6$ $(M+H)^+$: 547.2808. Found 547.2805.

5.2.13. (5*S*,6*R*,7*R*)-(+)-5-(2,2-Difluorobenzo[1,3]dioxol-5-yl)-7-[2-(3-hydroxy-2-methylpropyl)-4-methoxyphenyl]-2-(*N*-isopropylamino)cyclopenteno[1,2-*b*]pyridine-6-carboxylic acid (11a,b). 11a; White form; mp 121–124 °C. ^{1}H NMR ($CDCl_3$) δ 1.05 (d, $J = 6.0$ Hz, 3H), 1.10 (d, $J = 6.3$ Hz, 3H), 1.15 (d, $J = 6.3$ Hz, 3H), 1.98–2.10 (m, 1H), 2.48–2.56 (m, 1H), 2.99 (dd, $J = 8.2$, 10.2 Hz, 1H), 3.10–3.19 (m, 1H), 3.30–3.50 (m, 2H), 3.54–3.70 (m, 1H), 3.76 (s, 3H), 4.50 (d, $J = 8.2$ Hz, 1H), 5.04 (d, $J = 10.2$ Hz, 1H), 6.20 (d, $J = 8.5$ Hz, 1H), 6.68–6.73 (m, 2H), 6.83 (d, $J = 8.5$ Hz, 1H), 7.01–7.09 (m, 4H). $[\alpha]_D^{20}$ +17.8 (*c* 1.0, EtOH); HRMS calcd for $C_{30}H_{32}F_2N_2O_6$ $(M+H)^+$: 555.2307. Found 555.2291.

11b; White form; mp 119–120 °C. ^{1}H NMR ($CDCl_3$) δ 0.90 (d, $J = 6.8$ Hz, 3H), 1.13 (d, $J = 6.9$ Hz, 3H), 1.15 (d, $J = 6.9$ Hz, 3H), 1.86–2.01 (m, 1H), 2.47–2.72 (m, 2H), 3.06 (dd, $J = 8.8$,9.2 Hz, 1H), 3.28–3.47 (m, 2H), 3.59–3.70 (m, 1H), 3.71 (s, 3H), 4.46 (d, $J = 8.8$ Hz, 1H), 4.87 (d, $J = 9.2$ Hz, 1H), 6.24 (d, $J = 8.6$ Hz, 1H), 6.61–6.70 (m, 2H), 6.84 (d, $J = 8.6$ Hz, 1H), 6.93–7.02 (m, 3H), 7.08 (d, $J = 8.7$ Hz, 1H); $[\alpha]_D^{32}$ +27.7 (*c* 1.00, EtOH). HRMS calcd for $C_{30}H_{32}F_2N_2O_6$ $(M+H)^+$: 555.2307. Found 555.2280.

5.2.14. (5*S*,6*R*,7*R*)-(+)-5-(2,2-Difluorobenzo[1,3]dioxol-5-yl)-7-(2-hydroxymethyl-4-methoxyphenyl)-2-(*N*-isopropylamino)cyclopenteno[1,2-*b*]pyridine-6-carboxylic acid (11f). 11f; Pale yellow solid; mp 139–142 °C. 1H NMR (CDCl3) δ 1.24–1.28 (m, 6H), 3.86 (dd, $J = 8.9$, 9.2 Hz, 1H), 3.59–3.70 (m, 1H), 3.76 (s, 3H), 4.60 (d, $J = 9.2$ Hz, 1H), 4.62 (d, $J = 12.8$ Hz, 1H), 4.98 (d, $J = 12.8$ Hz, 1H), 5.50 (d, $J = 8.9$ Hz, 1H), 6.56 (d, $J = 9.0$ Hz, 1H), 6.81–7.10 (m, 6H), 7.39 (d, $J = 9.0$ Hz, 1H); $[\alpha]_D^{20}$ +37.8 (*c* 1.00, EtOH); HRMS calcd for $C_{27}H_{27}F_2N_2O_6$ $(M+H)^+$: 513.1837. Found 513.1812.

5.3. Endothelin receptor binding assay

The binding affinities were determined according to the reported method[15] by inhibition of specific binding of [^{125}I]ET-1 using membranes prepared from human neuroblastoma-derived SK-N-MC cells and Girardi heart cells that were reported to possess only ET_A and ET_B receptors, respectively.[17]

5.4. Screening assay for CYP3A4 inhibition

Human liver microsome (1.0 mg/mL) in buffer A [consisting of 0.1 M phosphate buffer (pH 7.4), 3.0 mM $MgCl_2$, 0.4 μ/mL glucose-6-phosphate dehydrogenase, 3.3 mM glucose-6-phosphate and 1.3 mM NADP] was incubated with tested compound (20 μM) at 37 °C for 60 min. Testosterone (0.2 mM) in buffer A at was subsequently incubated for 5 min at 37 °C. After the addition of a 2-fold volume of methanol, the amount of 6β-hydroxytestosterone was measured by HPLC (column: Capcelpak AG 120 C18, Mobile Phase: MeOH/10 mM $AcONH_4$ (3:2), flow rate: 1.0 mL/min).

5.5. Competitive inhibition of human CYPs marker activities

Human liver microsomes were preincubated for 5 min at 37 °C in the presence of a NADPH-generating system (10 mM glucose-6-phosphate, 1 unit/mL glucose-6-phosphate dehydrogenase, 3 mM $MgCl_2$, 1 mM β-$NADP^+$ in 100 mM potassium phosphate buffer pH 7.4). The reaction was initiated by adding test compound (**1f** or **7f** up to 100 μM) and a CYP marker substrate at a concentration similar to its K_m value.[18] The reaction was terminated by adding 2 vol of an actonitrile–methanol mixture (2:1, v/v) except that

0.1 vol of 60% $HClO_{4aq}$ was used for bufuralol. The amount of metabolite formation specific for the CYP activity was measured by either HPLC-UV or HPLC-fluorescence method. The percent inhibition of the CYP activity was calculated from the ratio of metabolite formation with or without the test compound.

5.6. Mechanism-based inactivation of human CYPs

Mechanism-based inactivation was examined by preincubating with human liver microsomes and 10 μM of either **1f** or **7f** in the presence of a NADPH-generating system. After the 30-min preincubation, a CYP marker substrate at a concentration similar to its K_m value[18] was added to the mixture. The reaction was terminated by adding 2 vol of an actonitrile–methanol mixture (2:1, v/v) except that 0.1 vol of 60% $HClO_{4aq}$ was used for bufuralol. The amount of metabolite formation specific for the CYP activity was measured by either HPLC-UV or HPLC-fluorescence method. The percent inhibition of the CYP activity was calculated from the ratio of metabolite formation with or without the test compound.

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References and notes

1. Yanagisawa, M.; Kurihara, H.; Kimura, S.; Tomobe, Y.; Kobayashi, M.; Mitsui, Y.; Yazaki, Y.; Goto, K.; Masaki, T. *Nature* **1988**, *332*, 411.
2. Hosoda, K.; Nakao, K.; Arai, H.; Nagakawa, O.; Suga, S.; Nakanishi, S.; Imura, H. *FEBS Lett.* **1991**, *287*, 23.
3. (a) Ferro, C. J.; Webb, D. J. *Drugs* **1996**, *51*, 12–27; (b) Webb, D. J.; Strachan, F. E. *Am. J. Hypertens.* **1998**, *11*, 71S.
4. (a) Winn, M.; Geldern, T. W.; Opgenorth, T. J.; Jae, H.; Tasker, A. S.; Boyd, S. A.; Kester, J. A.; Mantei, R. A.; Bal, R.; Sorensen, B. K.; Wu-Wong, J. R.; Chiou, W. J.; Dixon, D. B.; Novosad, E. I.; Hernadez, L.; Marsh, K. C. *J. Med. Chem.* **1996**, *38*, 1039; (b) Wu, C.; Chan, M. F.; Stavros, F.; Okun, I.; Mong, S.; Keller, K. M.; Brock, T.; Kogan, T. P.; Dixon, R. A. F. *J. Med. Chem.* **1997**, *40*, 1690; (c) Liu, G.; Henry, K. J., Jr.; Szczepankiewicz, B. G.; Winn, M.; Kozmina, N. S.; Boyd, S. A.; Wasicak, J.; von Geldern, T. W.; Wu-Wong, J. R.; Chiou, W. J.; Dixon, D. B.; Nguyen, B.; Marsh, K. C.; Opgenorth, T. J. *J. Med. Chem.* **1998**, *41*, 3261; (d) Astles, P. C.; Brown, T. J.; Halley, F.; Handscombe, C. M.; Harris, N. V.; Majid, T. N.; McCarthy, C.; McLay, A.; Porter, B.; Roach, A. G.; Sargent, C.; Smith, C.; Walsh, R. J. A. *J. Med. Chem.* **2000**, *43*, 900; (e) Wu, C.; Decker, E. R.; Blok, N.; Li, J.; Bourgoyne, A. R.; Bui, H.; Keller, K. M.; Knowles, V.; Li, W.; Stavros, F. D.; Holland, G. W.; Brock, T. A.; Dixon, R. A. F. *J. Med. Chem.* **2001**, *44*, 1211; (f) Morimoto, H.; Ohashi, N.; Shimadzu, H.; Kushiyama, E.; Kawanishi, H.; Hosaka, T.; Kawase, Y.; Yasuda, K.; Kikkawa, K.; Yamauchi-Kohno, R.; Yamada, K. *J. Med. Chem.* **2001**, *44*, 3369; (g) Ishizuka, N.; Matsumura, K.; Sakai, K.; Fujimoto, M.; Mihara, S.; Yamamori, T. *J. Med. Chem.* **2002**, *45*, 2041; (h) Murugesan, N.; Gu, Z.; Spergel, S.; Young, M.; Chen, P.; Mathur, A.; Leith, L.; Hermsmeier, M.; Liu, E. C.-K.; Zhang, R.; Bird, E.; Waldron, T.; Marino, A.; Koplowitz, B.; Humphreys, W. G.; Chong, S.; Morrison, R. A.; Webb, M. L.; Moreland, S.; Trippodo, N.; Barrish, J. C. *J. Med. Chem.* **2003**, *46*, 125.
5. (a) Balwierczak, J. L.; Bruseo, C. W.; Del Grande, D.; Jeng, A. Y.; Savage, P.; Shetty, S. S. *J. Cardiovasc. Pharmacol.* **1995**, *26*, S393; (b) Chan, M. F.; Kois, A.; Verner, E. J.; Raju, B. G.; Castillo, R. S.; Wu, C.; Okun, I.; Stavros, F. D.; Balaji, V. N. *Bioorg. Med. Chem.* **1998**, *6*, 2301; (c) Liu, G.; Kozmina, N. S.; Winn, M.; von Geldern, T. W.; Chiou, W. J.; Dixon, D. B.; Nguyen, B.; Marsh, K. C.; Opgenorth, T. J. *J. Med. Chem.* **1999**, *42*, 3679; (d) Mederski, W. W. K. R.; Osswald, M.; Dorsch, D.; Christadler, M.; Schmitges, C.-J.; Wilm, C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 619.
6. (a) Clozel, M.; Breu, V.; Gray, G. A.; Kalina, B.; Loffler, B.; Burri, K.; Cassal, J.; Hirth, G.; Muller, M.; Neidhart, W.; Ramuz, H. *J. Pharmacol. Exp. Ther.* **1994**, *270*, 228; (b) Elliot, J. D.; Lago, M. A.; Cousins, R. D.; Gao, A.; Leber, J. D.; Erhard, K. F.; Nambi, P.; Elshourbagy, N. A.; Kumar, C.; Lee, J. A.; Bean, J. W.; Debrosse, C. W.; Eggleston, D. S.; Brooks, D. P.; Feuerstein, G.; Ruffolo, R. R.; Weinstock, J.; Gleason, J. G.; Peishoff, C. E.; Ohlstein, E. *J. Med. Chem.* **1994**, *37*, 1553; (c) Walsh, T. F.; Fitch, K. J.; Chakravarty, P. K.; Williams, D. L.; Murphy, K. A.; Nolan, N. A.; O'Brien, J. A.; Lis, E. V.; Pettibone, D. J.; Kivlighn, S. D.; Gabel, R. A.; Zingaro, G. J.; Krause, S. M.; Siegl, P. K. S.; Clineschmidt, B. V.; Greenlee, W. J. Abstracts of American Chemical Society National Meeting, Washington, DC, August 21–25, 1994, American Chemical Society: Washington, DC, 1994; MEDI 145; (d) Jae, H.-S.; Winn, M.; Dixon, D. B.; Marsh, K. C.; Nguyen, B.; Opgenorth, T. J.; von Geldern, T. W. *J. Med. Chem.* **1997**, *40*, 3217; (e) Amberg, W.; Hergenröder, S.; Hillen, H.; Jansen, R.; Kettschau, G.; Kling, A.; Klinge, D.; Raschack, M.; Riechers, H.; Unger, L. *J. Med. Chem.* **1999**, *42*, 3026.
7. Nishikibe, M.; Ohta, H.; Okada, M.; Ishikawa, K.; Hayama, T.; Fukuroda, T.; Noguchi, K.; Saito, M.; Kanoh, T.; Ozaki, S.; Kamei, T.; Hara, K.; William, D.; Kivlighn, S.; Krause, S.; Gabel, R.; Zingaro, G.; Nolan, N.; O'brien, J.; Clayton, F.; Lynch, J.; Pettibone, D.; Siegl, P. *J. Pharmacol. Exp. Ther.* **1999**, *289*, 1262.
8. Takahashi, H.; Ohtake, N.; Sakamoto, T.; Iino, T.; Kawanishi, N.; Nakamura, M.; Yoshizumi, T.; Niiyama, K.; Ozaki, S.; Okada, H.; Kano, A.; Takahashi, H.; Ishii, Y.; Okada, M.; Saito, M.; Sawazaki, Y.; Hayama, T.; Nishikibe, M. *Bioorg. Med. Chem. Lett.*, **2004**, *14*, 1503.
9. Kumagai, Y.; Fukuto, J. M.; Cho, A. K. *Curr. Med. Chem.* **1994**, *4*, 254.
10. Song, Z. J.; Zhao, M.; Frey, L.; Li, J.; Tan, L.; Chen, C. Y.; Tschaen, D. M.; Tillyer, R.; Grabowski, E. J. J.; Volante, R. P.; Reider, P. J.; Kato, Y.; Okada, S.; Nemoto, T.; Sato, H.; Akao, A.; Mase, T. *Org. Lett.* **2001**, *3*, 3357.
11. Stereoselective reduction of allylalochol into *cis–cis* isomer using Zn powder under acidic conditions has also been reported. Niiyama, K.; Yoshizumi, T.; Takahashi, H.; Naya, A.; Ohtake, N.; Fukami, T.; Mase, T.; Hayama, T.; Ishikawa, K. *Bioorg, Med. Chem.* **2002**, *10*, 3437.
12. A variety of *N*-alkyl benzamide can also be introduced using this method. Takahashi, H.; Fukami, T.; Yamakawa, T. unpublished results.
13. Gutzwiller, J.; Uskokovic, M. *J. Am. Chem. Soc.* **1970**, *92*, 204.

14. An efficient asymmetric synthesis of **7f** has been reported. Kato, Y.; Niiyama, K.; Nemoto, T.; Jona, H.; Akao, A.; Okada, S.; Song, Z. J.; Zhao, M.; Tsuchiya, Y.; Tomimoto, K.; Mase, T. *Tetrahedron* **2002**, *58*, 3409.
15. Ihara, M.; Fukuroda, T.; Saeki, T.; Nishikibe, M.; Kojiri, K.; Suda, H.; Yano, M. *Biochem. Biophys. Res. Commun.* **1991**, *178*, 132.
16. Oral bioavailability in rats of **1a** was found to be poor (less than 10%).
17. Ishikawa, K.; Ihara, M.; Noguchi, K.; Mase, T.; Mino, M.; Seaki, T.; Fukuroda, T.; Fukami, T.; Ozaki, S.; Nagase, T.; Nishikibe, M.; Yano, M. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 4892.
18. Concentration of marker substrates, incubation time and microsomal protein concentration used in this study are as follows: 7-Ethoxyresorufin (CYP1A2): 0.2 μM, 10 min (0.25 mg/mL microsomal protein concentration), Coumarin (CYP2A6): 0.3 μM, 25 min (0.005 mg/mL), tolbutamide (CYP2C9): 100 μM, 60 min (0.25 mg/mL), *S*-Mephenytoin (CYP2C19): 100 μM, 60 min (1.0 mg/mL), Bufurolol (CYP2D6): 20 μM, 20 min (0.25 mg/mL), Testosterone (CYP3A4): 100 μM, 10 min (0.25 mg/mL).