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6-Carboxy-5,7-diarylcyclopenteno[1,2-*b*]pyridine Derivatives: A Novel Class of Endothelin Receptor Antagonists

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Abstract—Compounds (**2**–**5**) with a 6-carboxy-5,7-diarylcyclopentenopyridine skeleton were designed, synthesized, and identified as a new class of potent non-peptide endothelin receptor antagonists. The regio-isomer **2** was found to show potent inhibitory activity with an IC_{50} value of 2.4 nM against ^{125}I-labeled ET-1 binding to human ET_A receptors and a 170-fold selectivity for ET_A over ET_B receptors. Furthermore, **2** displayed more potent in vivo activity than did the indan-type compound **1** in a mouse ET-1 induced lethality model, suggesting the potential of **2** as a new lead structure. Derivatization on substituted phenyl groups at the 5- and 7-positions of **2** revealed that a 3,4-methylenedioxyphenyl group at the 5-position and a 4-methoxyphenyl group at the 7-position were optimal for binding affinity. Further derivatization of **2** by incorporating a substituent into the 2-position of the 4-methoxyphenyl group led to the identification of a more potent ET_A selective antagonist **2p** with an IC_{50} value of 0.87 nM for ET_A receptors and a 470-fold selectivity. In addition, **2p** showed highly potent in vivo efficacy (AD_{50}: 0.04 mg/kg) in the lethality model.

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-1 selective ET_A receptors are primarily found on vascular smooth muscle and mediate vasoconstriction and vascular smooth muscle proliferation. The non-selective ET_B receptors are primarily found in vascular endothelium and can 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 such as renal failure, cerebral vasospasm, pulmonary hypertension, and congestive heart failure. Elevated levels of endothelins have been observed in many of these disease states. Therefore, endothelin receptor antagonists are expected to have clinical potential in the endothelin-mediated disorders mentioned above.[3]

We initiated exploration of peptide endothelin antagonists immediately after the discovery of the endothelins and identified ET_A selective BQ-123[4] and ET_B selective BQ-788,[5] which have greatly contributed to elucidation of the physiological roles of endothelin receptors. In addition, we simultaneously looked for a novel non-peptide pharmacophore to develop as an orally active endothelin receptor antagonist.

There are a number of non-peptide endothelin antagonists including ET_A selective,[6] ET_B selective,[7] and ET_A/ET_B mixed agents[8] known to date. The common feature of these antagonists is an acidic functional group such as carboxylic acid or sulfonamide positioned between two aromatic rings. Among them, we had an interest in the highly rigid structure of **1** (Fig. 1) with nano-molar binding affinity for ET_A receptors.[8b] We speculated that incorporation of a nitrogen atom into the indan skeleton of **1** would change the physicochemical properties, in particular its hydrophilicity, leading to a new pharmacophore with a different biological profile from **1**.

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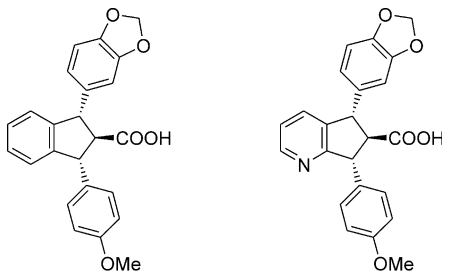


Figure 1.

Based on this speculation, we designed and synthesized four regio-isomers of cyclopentenopyridines (**2**–**5**) as racemates, and compared their biological properties with that of **1**.

In this paper, we describe the synthesis of cyclopentenopyridines and their in vitro binding affinity for ET_A and ET_B receptors. We also describe the structure–activity relationships of some derivatives of the selected pharmacophore **2** to optimize the substituents on the cyclopentenopyridine skeleton. In addition, we refer to the identification of a highly potent ET_A selective antagonist through further modification.

Chemistry

The synthetic procedure of 6-carboxy-7-(4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine **2** is summarized in Scheme 1. Pyridine-2,3-dicarboxylic anhydride **6** was reacted with a 4-methoxyphenyl Grignard reagent to provide a mixture of regioisomers **7** and **8** (**7**:**8** = 1:1) in 65% yield,[9,10] which was separated by chromatography to give **8** in 33% yield. Transformation of **8** to an enone **9** was achieved by the following reaction steps: (1) $SOCl_2$, (2) $EtOMgCH(CO_2Et)_2$, and (3) 5% Na_2CO_3,[11] though the yield was not reproducible (15–63%). The enone **9** was converted to a tertiary alcohol **10** in 91% yield by treatment with a 3,4-methylenedioxyphenyl Grignard reagent. Conversion of **10** to the desired *cis–cis* isomer **12** was accomplished in 47% yield by catalytic hydrogenation in the presence of sulfuric acid, while **11** was obtained in 33% yield as a major by-product. Epimerization and hydrolysis of the ester moiety was simultaneously achieved by treatment with NaOH in MeOH to give **2** in 93% yield. The regio-isomer **5** was obtained in a similar manner by using the 3,4-methylenedioxyphenyl Grignard reagent in place of 4-methoxyphenyl Grignard reagent in the initial step of the synthesis of **2**.

Synthesis of 6-carboxy-5-(4-methoxyphenyl)-7-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*c*]pyridine **4** was initiated from the addition reaction of 4-methoxyphenyl Grignard reagent to pyridine-3,4-dicarboxylic anhydride **13** (Scheme 2). This reaction proceeded regioselectively to yield **14** in 65% yield.[10] Transformation of **14** to **4** was achieved in a manner similar to that described for the preparation of **2**. The regio-isomer **3** was obtained in a similar manner by using the 3,4-methylenedioxyphenyl Grignard reagent in place of 4-methoxyphenyl Grignard reagent in the initial step of the synthesis of **4**.

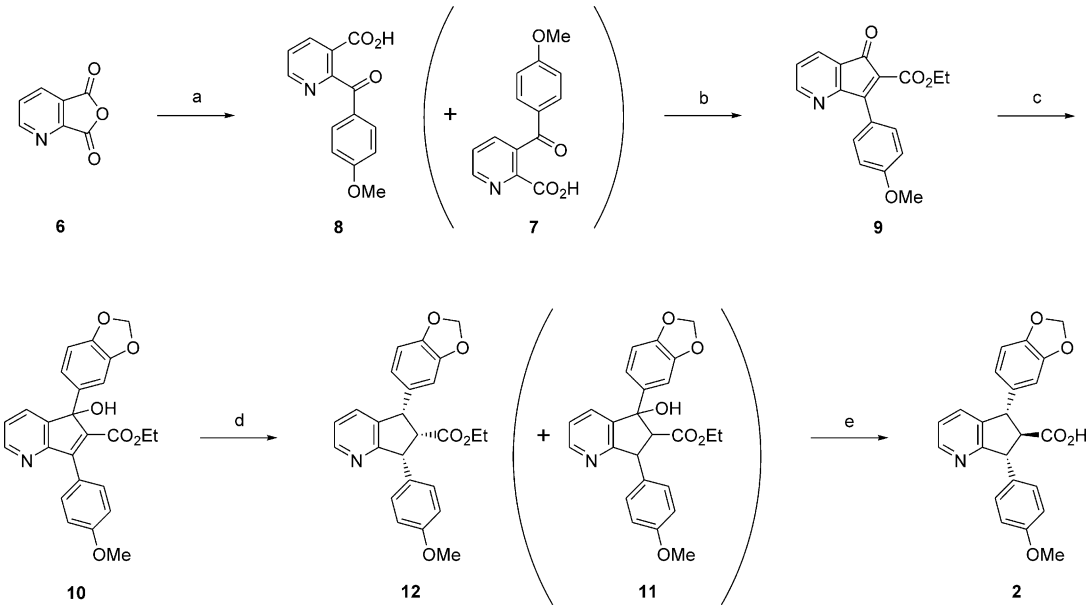
For the synthesis of derivatives that have a 2-substituted phenyl group at the 7-positon of **2**, an intermediate **18** was prepared as the starting material from **6** in an analogous fashion to the synthesis of **2**. Transformation of **18** to substituted derivatives was achieved in a similar manner to the reported procedure.[11] 2-*O*-Alkoxy-4-methoxyphenyl derivatives (**2k**–**2n**) were obtained by alkylation of **18** with a alkyl bromide followed by hydrolysis (Scheme 3). Trifluoromethanesulfonylation of **18** followed by a Heck reaction gave an intermediate **21**, which was hydrolyzed to afford the cinnamic acid analogue **2o**. Hydrogenation of **21** followed by hydrolysis gave the propionic acid analogue **2p**.

Results and Discussion

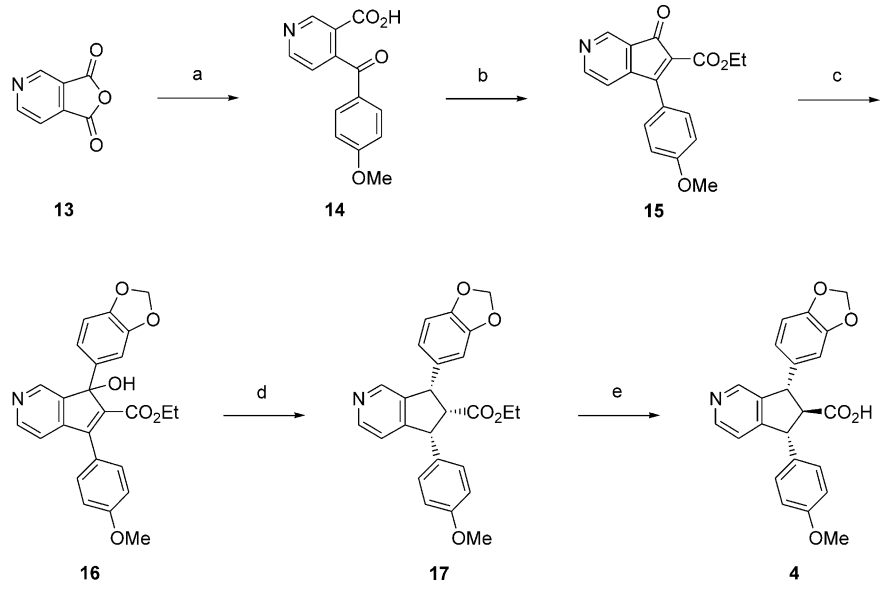
The synthesized compounds were evaluated in binding assays (inhibitory activity against ^{125}I-labeled ET-1 binding to both human ET_A and ET_B receptors).[12] Selected compounds were further assessed in isolated tissue assays using rabbit iliac arteries[13] and in an in vivo assay using a mouse lethality model.[13] A rat in situ intestinal absorption study was also conducted to estimate the oral absorption of the compounds.

At first, the binding affinities of the cyclopentenopyridine analogues (**2**–**5**) were compared with that of the indan-type compound **1** (Table 1). It is interesting to note that large differences in the binding affinities were observed among these four regio-isomers (**2**–**5**). The isomer **2** was most potent and had an IC_{50} value of 2.4 nM for ET_A receptors, which is comparable to that of **1**. The rank order of the binding affinities of the isomers for ET_A receptors was as follows: **2** > **3** > **4** > > **5**. The least potent isomer **5** showed a 200-fold decreased affinity (IC_{50}: 460 nM) compared with **2**. On the other hand, **2** showed a 7-fold reduction in the ET_B binding affinity compared with **1**. Thus, the selectivity of **2** for ET_A over ET_B receptors was 10-fold greater than that of **1**. These results not only indicated that the replacement of a benzene ring with a pyridine ring was tolerated but also implied the interaction of the nitrogen atom in the molecule with the both receptors. Since **2** would have another interaction site, analogues of **2** were expected to have different binding profiles from the analogues of **1**, which has no site to interact with the receptors on the indan ring.

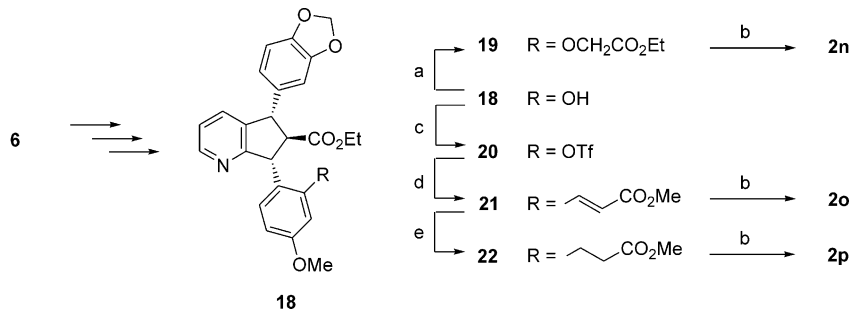
In the mouse lethality model, **2** was effective (AD_{50}: 6 mg/kg iv), while **1** was not effective even at 10 mg/kg in spite of having comparable binding affinities. From physicochemical analysis, it was revealed that logP values of the two compounds were largely different (**1**: 2.1, **2**: 0.12). Judging from a much lower logP value of **2**, improvement in the in vivo efficacy was considered to be due to the increased hydrophilic character of **2**. These results suggested that cyclopentenopyridine analogues



Scheme 1. Synthesis of a cyclopenteno[1,2-*b*]pyridine derivative **2**. Reagents: (a) 4-methoxyphenylmagnesium bromide, THF, −78 °C; (b) (1) $SOCl_2$, reflux; (2) $EtOMgCH(CO_2Et)_2$, rt; (3) 5% aq Na_2CO_3, reflux; (c) 3,4-(methylenedioxy)phenylmagnesium bromide, THF, −78 °C; (d) H_2, Pd/C, H_2SO_4, EtOH, rt; (e) NaOH, MeOH, rt.



Scheme 2. Synthesis of a cyclopenteno[1,2-*c*]pyridine derivative **4**. Reagents: (a) 4-methoxyphenylmagnesium bromide, THF, −78 °C; (b) (**1**) $SOCl_2$, reflux; (2) $EtOMgCH(CO_2Et)_2$, rt; (3) 5% aq Na_2CO_3, reflux; (c) 3,4-(methylenedioxy)phenylmagnesium bromide, THF, −78 °C; (d) H_2, Pd/C, H_2SO_4, EtOH, rt; (e) NaOH, MeOH, rt.



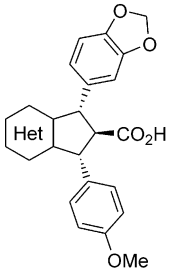
Scheme 3. Synthesis of 2-substituted 4-methoxyphenylderivatives **2n**, **2o** and **2p**. Reagents: (a) NaH, $BrCH_2CO_2Et$, THF; (b) 4 N NaOH, MeOH, rt; (c) Tf_2O, DMAP, CH_2Cl_2; (d) methyl acrylate, $PdCl_2(PPh_3)_2$, $NaHCO_3$, 120 °C; (e) H_2, Pd/C, MeOH.

had different biological as well as physicochemical properties from indan analogues than were expected. Therefore, the cyclopenteno[1,2-*b*]pyridine analogue **2** was selected as a novel pharmacophore for a non-peptide antagonist, and further derivatization of this structure was performed.

In order to optimize the substituents on the phenyl groups at the 5- and 7-positions of **2**, we prepared analogues (**2a**–**2i**) and evaluated them in the binding assay (Table 2). Replacement of the 3,4-methylenedioxyphenyl group at the 5-position with a phenyl group (**2a**) resulted in substantial loss of potency for both ET_A and ET_B receptors. Introduction of a methoxy group into the 2-, 3-, and 4-position of the phenyl group [(**2b**), (**2c**), (**2d**), respectively] resulted in partial recovery of the binding affinity for ET_A receptors. Although **2c** was the most potent analogue of the three, its ET_A binding affinity was approximately 10-fold less than that of **2**. From the results, we assumed that an electron-donating group at the 3-position was necessary for retaining the potent ET_A binding affinity. Based on this assumption, an indole moiety was introduced in place of the methylenedioxyphenyl group, however, the resulting analogues (**2e** and **2f**) showed unexpectedly low binding affinity (**2e**: $IC_{50} > 1100$ nM, **2f**: $IC_{50} = 3500$ nM) for ET_A receptors. With respect to a substituent on the phenyl group at the 7-position, it is evident that a 4-methoxy group in **2** makes a significant contribution to the high binding affinity for ET_A receptors compared to the affinity of unsubstituted (**2g**), 4-fluoro (**2h**), and 4-hydroxy (**2i**) analogues. These derivatives indicated, based upon the limited SAR performed, that a 3,4-methylenedioxyphenyl group at the 5-position and a 4-methoxyphenyl group at the 7-position of the cyclopenteno[1,2-*b*]pyridine were optimal.

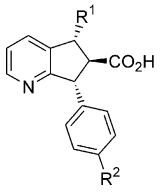
From the report of indan-type compounds,[8b] we expected that introduction of a substituent into the 2-position of the 4-methoxyphenyl group would lead to identification of a compound that had different biological properties without losing in vitro potency. Therefore, we performed derivatization of **2** based on this strategy, and characterized their biological properties (Table 3). Introduction of a hydroxyl group (**2j**) resulted in moderate binding affinity (IC_{50}: 5.3 nM) for ET_A receptors. The ET_A receptor affinity of the 2-(2-hydroxyethoxy) analogue **2k** was comparable to that of **2**. Replacement of the hydroxylethyl moiety of **2k** with a carbamoylmethyl (**2m**)

Table 1. In vitro potency of indan and cyclopentenopyridine derivatives



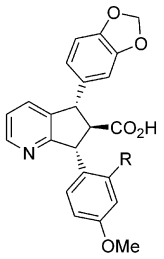
Compound	Het	IC_{50}, nM (*n*)		Selectivity ET_B/ET_A
		ET_A	ET_B	
1		3.3±0.2 (2)	56±6 (3)	17
2	N	2.4±0.5 (1)	410±110 (3)	170
3	N	6.8±0.3 (2)	270±37 (2)	40
4	N	30 (1)	690 (1)	23
5	N	460±15 (2)	83000 (1)	180

Table 2. In vitro potency of cyclopenteno[1,2-*b*]pyridine derivatives



Compound	R^1	R^2	IC_{50}, nM (*n*)		Selectivity ET_B/ET_A
			ET_A	ET_B	
2	3,4-Metylenedioxyphenyl	OMe	2.4±0.5 (11)	410±110 (3)	170
2a	Phenyl	OMe	1500 (1)	>100000 (1)	>67
2b	2-Methoxyphenyl	OMe	310 (1)	300000 (1)	97
2c	3-Methoxyphenyl	OMe	42 (1)	7000 (1)	170
2d	4-Methoxyphenyl	OMe	270 (1)	4400 (1)	16
2e	Indol-4-yl	OMe	1100 (1)	>100000 (1)	—
2f	Indol-6-yl	OMe	3500 (1)	28000 (1)	8
2g	3,4-Methylenedioxyphenyl	H	19 (1)	2400 (1)	130
2h	3,4-Methylenedioxyphenyl	F	39 (1)	2700 (1)	69
2i	3,4-Methylenedioxyphentl	OH	96 (1)	11000 (1)	110

Table 3. Biological properties of cyclopenteno[1,2-*b*]pyridine derivatives



Compound	R	IC_{50}, nM (*n*)		Selectivity ET_B/ET_A	AD_{50}[a] (mg/kg, iv)	pA_2[b]	Absorption[c] (%)
		ET_A	ET_B				
2	H	2.4±0.5 (11)	410±110 (3)	170	6	8.0	100
2j	OH	5.3±1.6 (3)	680±77 (2)	130			
2k	OCH_2CH_2OH	2.5±0.3 (3)	540±32 (3)	220	>3		47
2l	OCH_2CH_2NHMe	28 (1)	6600 (1)	240			
2m	OCH_2CONH_2	2.0 (1)	660 (1)	330	>3		17
2n	OCH_2CO_2H	1.2±0.02 (3)	200±24 (3)	170	0.2	8.2	12
2o	$CH{=}CHCO_2H$	1.9±0.4 (2)	470±160 (2)	250	2		16
2p	$CH_2CH_2CO_2H$	0.87±0.35 (2)	410±84 (2)	470	0.04	8.8	7

[a]ET-1 induced mouse lethality.
[b]Isolated rabbit iliac artery.
[c]In situ rat intestinal loop.

or a carboxymethyl group (**2n**) resulted in maintenance of the ET_A binding affinity, while replacement with a basic (*N*-methyamino)ethyl (**2l**) group reduced the affinity. It is worthy of note that the carboxymethoxy analogue **2n** showed much improved in vivo efficacy (AD_{50}: 0.2 mg/kg) in the mouse lethality model as compared with **2**, although the intrinsic antagonistic activity of **2n** was comparable to **2**. Taken together, we assumed that incorporating an additional carboxylic moiety to the 4-methoxyphenyl group contributed to improvement in in vivo efficacy. Based on the structure of **2n**, we also designed and synthesized carbon linked analogues (**2o** and **2p**). The cinnamic acid analogue **2o** showed potent binding affinity comparable to **2n**, but was 10-fold less active in the lethality model. In contrast, the propionic acid analogue **2p** showed the highest in vitro potency (IC_{50}: 0.87 nM) for the ET_A receptors in this class of compounds and a 470-fold selectivity for the ET_A over the ET_B receptors. In addition, **2p** displayed 5-fold higher in vivo efficacy (AD_{50}: 0.04 mg/kg) than did **2n** in the mouse model. **2p** also showed greater antagonistic activity than **2n** in the rabbit isolated tissue assay (pA_2: **2p** = 8.8, **2n** = 8.2). These results suggested that **2p** had great potential for a highly potent non-peptide endothelin receptor antagonist. However, the rat in situ intestinal absorption study indicated that the dicarboxylic acid analogues (**2n** and **2p**) showed low absorption (**2n**: 12%, **2p**: 7%), while the monocarboxylic acid **2** showed good absorption (100%). We considered that the poor absorption was caused from highly hydrophilic character of these compounds. Therefore, further derivatization of this class to identify an orally active antagonist is focused on increasing the hydrophobicity of the dicarboxylic acid analogues.

Conclusion

In summary, we have discovered 6-carboxy-7-(4-methoxyphenyl)-5-(3,4-methylenedioxypheny)cyclopenteno[1,2-*b*]pyridine **2** with an IC_{50} value of 2.4 nM for ET_A receptors as a novel pharmacophore of a non-peptide endothelin antagonist. This compound **2** showed highly potent antagonistic activity (pA_2: 8.0) in the rabbit isolated tissue assay. In addition, **2** had higher in vivo efficacy in the mouse lethality model than that of the indan-type compound **1**. Derivatization of **2** by introducing a substituent into the 4-methoxyphenyl group led to the identification of **2p**, which possessed high binding affinity (IC_{50}: 0.87 nM) for ET_A receptors with a 470-fold selectivity for ET_A over ET_B receptors. In addition, **2p** showed not only greater intrinsic antagonistic activity (pA_2: 8.8) in the tissue assay but also greater in vivo efficacy (AD_{50}: 0.04 mg/kg) in comparison with **2** (AD_{50}: 6 mg/kg). These biological properties indicated that **2p** has great potential as a novel potent non-peptide ET_A selective endothelin receptor antagonist. In spite of highly potent biological activities, its intestinal absorption was poor. Therefore, we will focus our effort on improving absorbability. Further derivatization of **2** directed toward an orally active ET_A/ET_B mixed or ET_A selective antagonist will be described in the near future.

Experimental

General

All reagents and solvents were of commercial quality and were used without further purification unless

otherwise noted. Melting points were determined with a Yanaco MP micromelting point apparatus and were not corrected. ^{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 with fast atom bombardment (FAB) ionization on a JEOL JMS-SX 102A spectrometer. Thin layer chromatography was performed with E. Merck Kieselgel 60 F_{254} plates (0.25 mm) and visualized with UV light or phosphomolybdic acid. Column chromatography was performed on Wako gel C-300.

2-(4-Methoxybenzoyl)pyridine-3-carboxylic acid (8). A solution of pyridine-2,3-dicaboxylic anhydride 6 (7.46 g, 50.0 mmol) in anhydrous THF (80 mL) was treated with 4-methoxyphenyl Grignard reagent prepared from 4-bromoanisole (6.57 mL, 52.5 mmol), magnesium turnings (1.34 g, 55.1 mmol), and anhydrous THF (100 mL) at −78 °C. After 30 min of stirring at the same temperature, the reaction mixture was quenched with 1 N HCl (55 mL), and was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was triturated with Et_2O (50 mL) and the resulting insoluble material was collected by filtration. The crude product was purified by column chromatography on silica gel to give **8** as a white foam (4.28 g, 33%). ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 6.92 (d, J = 9.0 Hz, 2H), 7.51 (dd, J = 4.9 and 8.1 Hz, 1H), 7.76 (d, J = 9.0 Hz, 2H), 8.37 (dd, J = 1.8 and 8.1 Hz, 1H), 8.82 (dd, J = 1.8 and 4.9 Hz, 1H); MS m/z 258 $(M+H)^+$.

6-Ethoxycarbonyl-7-(4-methoxyphenyl)-5-oxocyclopenta-1,3-dieno[2,1-*b*]pyridine (9). A mixture of **8** (4.12 g, 16.0 mmol) and thionyl chloride (29.2 mL, 400 mmol) was refluxed for 2 h. After cooling to room temperature, the mixture was concentrated under reduced pressure, and the residue was azeotroped with toluene to remove the residual thionyl chloride and hydrogen chloride to give the crude acid chloride (4.02 g) as a pale yellow powder. The powder was dissolved in THF (25 mL) and Et_2O (25 mL) and treated with $EtOMgCH(CO_2Et)_2$ prepared from diethyl malonate (5.03 mL, 33.1 mmol), magnesium turnings (875 mg, 36.0 mmol), EtOH (4 mL), and Et_2O (16 mL). After 1 h of stirring at room temperature, the reaction mixture was quenched with 10% H_2SO_4 (100 mL) at 0 °C, and was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a pale brown oil. To the residue was added 5% Na_2CO_3 solution (100 mL) and the mixture was refluxed for 10 min. After cooling to room temperature, the mixture was neutralized with 1 N HCl, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give **9** as an orange foam (3.11 g, 63%). ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 7.0 Hz, 3H), 3.90 (s, 3H), 4.33 (q, J = 7.0 Hz, 2H), 7.03 (d, J = 9.0 Hz, 2H), 7.28 (dd, J = 5.1 and 7.3 Hz, 1H), 7.83 (dd, J = 1.8 and 7.3 Hz, 1H), 7.96 (d, J = 9.0 Hz, 2H), 8.62 (dd, J = 1.8 and 5.1 Hz, 1H); MS m/z 310 $(M+H)^+$.

6-Ethoxycarbonyl-5-hydroxy-7-(4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenta-1,3-dieno[2,1-*b*]pyridine (10). A solution of **9** (1.55 g, 5.01 mmol) in anhydrous THF (50 mL) was treated with 3,4-methylenedioxypheny Grignard reagent prepared from 4-bromo-1,2-methylenedioxybenzene (1.21 g, 6.01 mmol), magnesium turnings (153 mg, 6.29 mmol), and anhydrous THF (12 mL) at −78 °C. After 30 min of stirring at the same temperature, the reaction mixture was quenched with 1 N HCl (8 mL), and was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was triturated with Et_2O to give **10** as a pale yellow powder (1.96 g, 91%).^{1}H NMR ($CDCl_3$) δ 1.09 (t, J = 7.0 Hz, 3H), 3.88 (s, 3H), 4.02–4.24 (m, 2H), 4.51 (s, 1H), 5.92 (d, J = 1.5 Hz, 1H), 5.94 (d, J = 1.5 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.98 (d, J = 1.7 Hz, 1H), 7.03 (d, J = 8.9 Hz, 2H), 7.04 (dd, J = 1.7 and 8.1 Hz, 1H), 7.15 (dd, J = 4.8 and 7.6 Hz, 1H), 7.56 (dd, J = 1.4 and 7.6 Hz, 1H), 7.68 (d, J = 8.9 Hz, 2H), 8.54 (dd, J = 1.4 and 4.8 Hz, 1H); HRMS calcd for $C_{25}H_{22}NO_6$ $(M+H)^+$: 432.1447. Found 432.1453.

(5*RS*,6*RS*,7*SR*)-6-Ethoxycarbonyl-7-(4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine (12). To a solution of **10** (457 mg, 1.06 mmol) and H_2SO_4 (0.29 mL) in EtOH (20 mL) was added 10% palladium on carbon (914 mg) and the mixture was hydrogenated at atmospheric pressure at room temperature for 70 h. The catalyst was removed by filtration and washed with EtOAc (50 mL). The filtrate and washings were combined, washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give **12** as a pale yellow foam (206 mg, 47%) together with a by-product **11** (150 mg, 33%). **11**: ^{1}H NMR ($CDCl_3$) δ 1.04 (t, J = 7.0 Hz, 3H), 3.63 (d, J = 9.7 Hz, 1H), 3.79 (s, 3H), 3.85–3.95 (m, 2H), 4.90 (d, J = 9.7 Hz, 1H), 5.93 (d, J = 1.5 Hz, 1H), 5.94 (d, J = 1.5 Hz, 1H), 6.63 (dd, J = 1.7 and 8.2 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 6.73 (d, J = 1.7 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H), 7.22 (dd, J = 4.9 and 7.9 Hz, 1H), 7.58 (dd, J = 1.8 and 7.9 Hz, 1H), 8.59 (dd, J = 1.8 and 4.9 Hz, 1H); HRMS calcd for $C_{25}H_{24}NO_6$ $(M+H)^+$: 434.1604. Found 434.1598. 12: ^{1}H NMR ($CDCl_3$) δ 0.69 (t, J = 7.2 Hz, 3H), 3.46 (q, J = 7.2 Hz, 2H), 3.78 (s, 3H), 3.88 (t, J = 7.6 Hz, 1H), 4.70 (d, J = 7.6 Hz, 1H), 4.79 (d, J = 7.6 Hz, 1H), 5.94 (d, J = 1.5 Hz, 1H), 5.95 (d, J = 1.5 Hz, 1H), 6.76–6.88 (m, 5H), 7.17 (dd, J = 4.8 and 7.6 Hz, 1H), 7.34 (d, J = 8.9 Hz, 2H), 7.52 (d, J = 7.6 Hz, 1H), 8.51 (d, J = 4.8 Hz, 1H); MS m/z 418 $(M+H)^+$.

(5*RS*,6*SR*,7*SR*)-6-Carboxy-7-(4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2 - *b*]pyridine (2). To a solution of **12** (271 mg, 0.65 mmol) in MeOH (4.9 mL) was added 4 N NaOH (1.63 mL) and the mixture was stirred at room temperature for 16.5 h. The mixture was neutralized with 4 N HCl (1.63 mL) and concentrated under reduced pressure. To the residue was added water (3 mL), the insoluble material was collected by filtration, washed with Et_2O, and dried in vacuo to give **2** (236 mg, 93%) as a white solid. Mp 230–233 °C

(dec.); ^{1}H NMR (DMSO-d_6) δ 3.15 (t, J = 10.2 Hz, 1H), 3.74 (s, 3H), 4.51 (d, J = 10.2 Hz, 1H), 4.53 (d, J = 10.2 Hz, 1H), 6.01 (s, 2H), 6.77 (dd, J = 1.5 and 8.0 Hz, 1H), 6.84 (d, J = 1.5 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.7 Hz, 2H), 7.14–7.26 (m, 2H), 8.30–8.34 (m, 1H); HRMS calcd for $C_{23}H_{20}NO_5$ $(M+H)^+$: 390.1341. Found 390.1366.

(5*RS*,6*SR*,7*SR*)-6-Carboxy-5-(4-methoxyphenyl)-7-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine (5). This compound was prepared by a similar procedure as described for the preparation of **2**. White foam; ^{1}H NMR ($CDCl_3$) δ 3.30 (t, J = 9.9 Hz, 1H), 3.82 (s, 3H), 4.61 (d, J = 9.9 Hz, 1H), 4.69 (d, J = 9.9 Hz, 1H), 5.92 (s, 2H), 6.68 (d, J = 1.3 Hz, 1H), 6.74 (dd, J = 1.3 and 7.7 Hz, 1H), 6.79 (d, J = 7.7 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 7.13 (dd, J = 4.9 and 7.7 Hz, 1H), 7.18 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 7.7 Hz, 1H), 8.48 (d, J = 4.9 Hz, 1H); HRMS calcd for $C_{23}H_{20}NO_5$ $(M+H)^+$: 390.1341. Found 390.1338.

4-(4-Methoxybenzoyl)pyridine-3-carboxylic acid (14). This compound was prepared from pyridine-3,4-dicarboxylic anhydride **13** by a similar procedure as described for the preparation of **8**. White foam; ^{1}H NMR (DMSO-d_6) δ 3.83 (s, 3H), 7.03 (d, J = 9.1 Hz, 2H), 7.45 (dd, J = 1.2 and 4.8 Hz, 1H), 7.61 (d, J = 9.1 Hz, 2H), 8.87 (d, J = 4.8 Hz, 1H), 9.13 (d, J = 1.2 Hz, 1H), MS m/z 258 $(M+H)^+$.

6-Ethoxycarbonyl-5-(4-methoxyphenyl)-7-oxocyclopenta-1,3-dieno[1,2-*c*]pyridine (15). This compound was prepared from **14** by a similar procedure as described for the preparation of **9**. Yellow foam; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H), 3.91 (s, 3H), 4.29 (q, J = 7.1 Hz, 2H), 7.05 (d, J = 8.9 Hz, 2H), 7.31 (d, J = 4.9 Hz, 1H), 7.57 (d, J = 8.9 Hz, 2H), 8.77 (d, J = 4.9 Hz, 1H), 8.79 (s, 1H); MS m/z 310 $(M+H)^+$.

6-Ethoxycarbonyl-7-hydroxy-5-(4-methoxyphenyl)-7-(3,4-methylenedioxyphenyl)cyclopenta-1,3-dieno[1,2-*c*]pyridine (16). This compound was prepared from **15** by a similar procedure as described for the preparation of **10**. Yellow foam; ^{1}H NMR ($CDCl_3$) δ 1.05 (t, J = 7.1 Hz, 3H), 3.90 (s, 3H), 4.00–4.21 (m, 2H), 4.42 (s, 1H), 5.93 (d, J = 1.5 Hz, 1H), 5.95 (d, J = 1.5 Hz, 1H), 6.76 (d, J = 8.6 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H), 7.02–7.07 (m, 1H), 7.03 (d, J = 8.9 Hz, 2H), 7.20 (dd, J = 0.9 and 5.2 Hz, 1H), 7.47 (d, J = 8.9 Hz, 2H), 8.52 (d, J = 0.9 Hz, 1H), 8.56 (d, J = 5.2 Hz, 1H); MS m/z 432 $(M+H)^+$.

(5*RS*,6*RS*,7*SR*)-6-Ethoxycarbonyl-5-(4-methoxyphenyl)-7-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*c*]pyridine (17). This compound was prepared from **15** by a similar procedure as described for the preparation of **12**. Pale yellow foam; ^{1}H NMR ($CDCl_3$) δ 0.70 (t, J = 7.2 Hz, 3H), 3.47 (q, J = 7.2 Hz, 2H), 3.81 (s, 3H), 3.83 (t, J = 7.5 Hz, 1H), 4.71 (d, J = 7.5 Hz, 1H), 4.78 (d, J = 7.5 Hz, 1H), 5.94 (d, J = 1.7 Hz, 1H), 5.95 (d, J = 1.7 Hz, 1H), 6.78 (d, J = 8.7 Hz, 1H), 6.84–6.89 (m, 2H), 6.87 (d, J = 8.4 Hz, 2H), 7.19 (dd, J = 1.4 and 5.2 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 8.47 (d, J = 1.4 Hz, 1H), 8.53 (d, J = 5.2 Hz, 1H); MS m/z 418 $(M+H)^+$.

(5*RS*,6*SR*,7*SR*)-6-Carboxy-5-(4-methoxyphenyl)-7-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*c*]pyridine (4). This compound was prepared from **17** by a similar procedure as described for the preparation of **2**. White solid; mp 190–192 °C; ^{1}H NMR (DMSO-d_6) δ 3.18 (t, J = 10.2 Hz, 1H), 3.75 (s, 3H), 4.54 (d, J = 10.2 Hz, 1H), 4.60 (d, J = 10.2 Hz, 1H), 6.02 (s, 2H), 6.79–6.82 (m, 2H), 6.88–6.94 (m, 2H), 6.93 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 8.00 (s, 1H), 8.38 (d, J = 4.8 Hz, 1H); HRMS calcd for $C_{23}H_{20}NO_5$ $(M+H)^+$: 390.1341. Found 390.1354.

(5*RS*,6*SR*,7*SR*)-6-Carboxy-7-(4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*c*]pyridine (3). This compound was prepared by a similar procedure as described for the preparation of **4**. Pale brown solid; mp 187 °C (dec.); ^{1}H NMR (DMSO-d_6) δ 3.18 (t, J = 10.6 Hz, 1H), 3.76 (s, 3H), 4.55 (d, J = 10.6 Hz, 1H), 4.59 (d, J = 10.6 Hz, 1H), 6.01 (s, 2H), 6.79 (dd, J = 1.7 and 8.1 Hz, 1H), 6.82–6.90 (m, 3H), 6.93 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 7.96 (s, 1H), 8.38 (d, J = 4.6 Hz, 1H); HRMS calcd for $C_{23}H_{20}NO_5$ $(M+H)^+$: 390.1341. Found 390.1347.

The following compounds (**2a**–**2i**) were prepared in a similar manner to that described for the preparation of **2**.

(5*RS*,6*SR*,7*SR*)-6-Carboxy-7-(4-methoxyphenyl)-5-phenylcyclopenteno[1,2-*b*]pyridine (2a). White solid; mp 164–165 °C; ^{1}H NMR ($CDCl_3$) δ 3.38 (t, J = 9.8 Hz, 1H), 3.78 (s, 3H), 4.68 (d, J = 9.8 Hz, 1H), 4.73 (d, J = 9.8 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 7.12 (dd, J = 4.9 and 7.5 Hz, 1H), 7.19 (d, J = 8.8 Hz, 2H), 7.20–7.40 (m, 6H), 8.47 (d, J = 4.9 Hz, 1H); HRMS calcd for $C_{22}H_{20}NO_3$ $(M+H)^+$: 346.1443. Found 346.1444.

(5*RS*,6*SR*,7*SR*)-6-Carboxy-5-(2-methoxyphenyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-*b*]pyridine (2b). White solid; mp 194–197 °C; ^{1}H NMR ($CDCl_3$) δ 3.48 (t, J = 9.6 Hz, 1H), 3.67 (s, 3H), 3.75 (s, 3H), 4.73 (d, J = 9.6 Hz, 1H), 4.94 (d, J = 9.6 Hz, 1H), 6.84 (d, J = 9.1 Hz, 2H), 6.87–6.97 (m, 2H), 7.09 (dd, J = 5.0 and 7.6 Hz, 1H), 7.15 (d, J = 9.1 Hz, 2H), 7.15–7.20 (m, 1H), 7.24–7.31 (m, 2H), 8.43 (d, J = 5.0 Hz, 1H); HRMS calcd for $C_{23}H_{22}NO_4$ $(M+H)^+$: 376.1549. Found 376.1547.

(5*RS*,6*SR*,7*SR*)-6-Carboxy-5-(3-methoxyphenyl)-7-(4-methoxyphenyl)cyclopenteno[1,2-*b*]pyridine (2c). White solid; mp 193–195 °C; ^{1}H NMR ($CDCl_3$) δ 3.36 (t, J = 9.6 Hz, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 4.65 (d, J = 9.6 Hz, 1H), 4.72 (d, J = 9.6 Hz, 1H), 6.80–6.90 (m, 3H), 6.88 (d, J = 8.8 Hz, 2H), 7.11–7.15 (m, 1H), 7.17 (d, J = 8.8 Hz, 2H), 7.28–7.33 (m, 2H), 8.47 (d, J = 4.8 Hz, 1H); HRMS calcd for $C_{23}H_{22}NO_4$ $(M+H)^+$: 376.1549. Found 376.1541.

(5*RS*,6*SR*,7*SR*)-6-Carboxy-5,7-bis(4-methoxyphenyl)cyclopenteno[1,2-*b*]pyridine (2d). Pale yellow solid; mp 185–187 °C; ^{1}H NMR ($CDCl_3$) δ 3.33 (t, J = 9.8 Hz, 1H), 3.79 (s, 3H), 3.82 (s, 3H), 4.63 (d, J = 9.8 Hz, 1H), 4.71 (d, J = 9.8 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 6.90

(d, $J=8.8$ Hz, 2H), 7.12 (dd, $J=4.8$ and 7.7 Hz, 1H), 7.19 (d, $J=8.8$ Hz, 2H), 7.20 (d, $J=8.8$ Hz, 2H), 7.21–7.30 (m, 1H), 8.46 (d, $J=4.8$ Hz, 1H); HRMS calcd for $C_{23}H_{22}NO_4$ $(M+H)^+$: 376.1549. Found 376.1536.

(5*RS*,6*SR*,7*SR*)-6-Carboxy-5-(indol-4-yl)-7-(4-methoxyphenyl)cyclopenteno[1,2-*b*]pyridine (2e). White foam; ^1H NMR (CD_3OD) δ 3.51 (t, $J=10.1$ Hz, 1H), 3.79 (s, 3H), 4.75 (d, $J=10.1$ Hz, 1H), 5.04 (d, $J=10.1$ Hz, 1H), 6.12–6.18 (m, 1H), 6.90–6.96 (m, 1H), 6.93 (d, $J=8.8$ Hz, 2H), 7.10 (dd, $J=7.3$ and 8.1 Hz, 1H), 7.16–7.25 (m, 2H), 7.20 (d, $J=8.8$ Hz, 2H),7.30–7.34 (m, 1H), 7.36 (d, $J=8.1$ Hz, 1H), 8.32–8.36 (m, 1H); HRMS calcd for $C_{24}H_{21}N_2O_3$ $(M+H)^+$: 385.1552. Found 385.1540.

(5*RS*,6*SR*,7*SR*)-6-Carboxy-5-(indol-6-yl)-7-(4-methoxyphenyl)cyclopenteno[1,2-*b*]pyridine (2f). White foam mp; ^1H NMR (CD_3OD) δ 3.27–3.35 (m, 1H), 3.79 (s, 3H), 4.69 (d, $J=9.8$ Hz, 1H), 4.73 (d, $J=9.6$ Hz, 1H), 6.43 (dd, $J=0.9$ and 3.2 Hz, 1H), 6.90 (dd, $J=1.6$ and 8.1 Hz, 1H), 6.93 (d, $J=8.8$ Hz, 2H), 7.18 (d, $J=8.8$ Hz, 2H), 7.22–7.28 (m, 1H), 7.22 (d, $J=3.2$ Hz, 1H), 7.33 (s, 1H), 7.37–7.43 (m, 1H), 7.55 (d, $J=8.1$ Hz, 1H), 8.30–8.34 (m, 1H); HRMS calcd for $C_{24}H_{21}N_2O_3$ $(M+H)^+$: 385.1552. Found 385.1570.

(5*RS*,6*SR*,7*SR*)-6-Carboxy-5-(3,4-methylenedioxyphenyl)-7-phenylcyclopenteno[1,2-*b*]pyridine (2g). White solid; mp 243–245 °C; ^1H NMR ($CDCl_3$) δ 3.35 (t, $J=9.7$ Hz, 1H), 4.63 (d, $J=9.7$ Hz, 1H), 4.75 (d, $J=9.7$ Hz, 1H), 5.97 (d, $J=1.5$ Hz, 1H), 5.98 (d, $J=1.5$ Hz, 1H), 6.72 (d, $J=1.7$ Hz, 1H), 6.77 (dd, $J=1.7$ and 7.8 Hz, 1H), 6.81 (d, $J=7.8$ Hz, 1H), 7.14 (dd, $J=5.1$ and 8.2 Hz, 1H), 7.25–7.40 (m, 6H), 8.48 (d, $J=5.1$ Hz, 1H); HRMS calcd for $C_{22}H_{18}NO_4$ $(M+H)^+$: 360.1236. Found 360.1225.

(5*RS*,6*SR*,7*SR*)-6-Carboxy-7-(4-fluorophenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine (2h). White solid; mp 234–236 °C; ^1H NMR ($CDCl_3$) δ 3.29 (t, $J=10.0$ Hz, 1H), 4.62 (d, $J=10.0$ Hz, 1H), 4.75 (d, $J=10.0$ Hz, 1H), 5.98 (s, 2H), 6.71 (d, $J=1.3$ Hz, 1H), 6.77 (dd, $J=1.3$ and 7.9 Hz, 1H), 6.81 (d, $J=7.9$ Hz, 1H), 7.03–7.30 (m, 5H), 7.33 (d, $J=7.6$ Hz, 1H), 8.49 (d, $J=4.7$ Hz, 1H); HRMS calcd for $C_{22}H_{17}FNO_4$ $(M+H)^+$: 378.1142. Found 378.1139.

(5*RS*,6*SR*,7*SR*)-6-Carboxy-7-(4-hydroxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine (2i). White solid; mp 226 °C (dec.); ^1H NMR ($CDCl_3$) δ 3.25 (t, $J=9.9$ Hz, 1H), 4.60 (d, $J=9.9$ Hz, 1H), 4.65 (d, $J=9.9$ Hz, 1H), 5.96 (s, 2H), 6.71–6.82 (m, 3H), 6.73 (d, $J=8.5$ Hz, 2H), 7.04 (d, $J=8.5$ Hz, 2H), 7.15 (dd, $J=5.0$ and 7.6 Hz, 1H), 7.34 (d, $J=7.6$ Hz, 1H), 8.42 (d, $J=5.0$ Hz, 1H); HRMS calcd for $C_{22}H_{18}NO_5$ $(M+H)^+$: 376.1185. Found 376.1201.

(5*RS*,6*SR*,7*SR*)-6-Ethoxycarbonyl-7-(2-hydroxy-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine (18). This compound was prepared from **6** and 2-benzyloxy-4-methoxy-1-bromobenzene in a similar manner to that described for the preparation of **2**. White powder; ^1H NMR ($CDCl_3$) δ 1.20 (t, $J=7.1$ Hz, 3H), 3.68 (t, $J=9.8$ Hz, 1H), 3.78 (s, 3H), 4.17 (q, $J=7.1$ Hz, 2H), 4.62 (d, $J=9.8$ Hz, 1H), 5.08 (d, $J=9.8$ Hz, 1H), 5.98 (s, 2H), 6.45 (dd, $J=2.7$ and 8.6 Hz, 1H), 6.66 (d, $J=1.8$ Hz, 1H), 6.67 (d, $J=2.7$ Hz, 1H), 6.71 (dd, $J=1.8$ and 7.9 Hz, 1H), 6.80 (d, $J=7.9$ Hz, 1H), 7.07 (d, $J=8.6$ Hz, 1H), 7.18 (dd, $J=5.0$ and 7.6 Hz, 1H), 7.36 (d, $J=7.6$ Hz, 1H), 8.38 (d, $J=5.0$ Hz, 1H); MS m/z 434 $(M+H)^+$.

The following compounds (**2j**–**2p**) were prepared from the intermediate **18** in a similar manner to that described in the literature.[11]

(5*RS*,6*SR*,7*SR*)-6-Carboxy-7-(2-hydroxy-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine (2j). White solid; mp 128–130 °C; ^1H NMR ($CDCl_3$) δ 3.64 (t, $J=9.3$ Hz, 1H), 3.73 (s, 3H), 4.62 (d, $J=9.3$ Hz, 1H), 5.10 (d, $J=9.3$ Hz, 1H), 5.97 (s, 2H), 6.46 (dd, $J=2.5$ and 8.6 Hz, 1H), 6.59 (d, $J=2.5$ Hz, 1H), 6.67 (d, $J=1.4$ Hz, 1H), 6.73 (dd, $J=1.4$ and 8.1 Hz, 1H), 6.79 (d, $J=8.1$ Hz, 1H), 7.01 (d, $J=8.6$ Hz, 1H), 7.19 (dd, $J=5.1$ and 8.0 Hz, 1H), 7.37 (d, $J=8.0$ Hz, 1H), 8.38 (d, $J=5.1$ Hz, 1H); HRMS calcd for $C_{23}H_{20}NO_6$ $(M+H)^+$: 406.1291. Found 406.1302.

(5*RS*,6*SR*,7*SR*)-6-Carboxy-7-[2-(2-hydroxyethoxy)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine (2k). White; mp 125–128 °C; ^1H NMR ($CDCl_3$) δ 3.26 (t, $J=9.9$ Hz, 1H), 3.71–4.04 (m, 4H), 3.77 (s, 3H), 4.58 (d, $J=9.9$ Hz, 1H), 5.16 (d, $J=9.9$ Hz, 1H), 5.95 (d, $J=1.5$ Hz, 1H), 5.96 (d, $J=1.5$ Hz, 1H), 6.44 (d, $J=2.4$ Hz, 1H), 6.49 (dd, $J=2.4$ and 8.4 Hz, 1H), 6.70 (d, $J=1.3$ Hz, 1H), 6.74 (dd, $J=1.3$ and 8.0 Hz, 1H), 6.78 (d, $J=8.0$ Hz, 1H), 7.04 (d, $J=8.4$ Hz, 1H), 7.13 (dd, $J=4.8$, and 7.8 Hz, 1H), 7.32 (d, $J=7.8$ Hz, 1H), 8.46 (d, $J=4.8$ Hz, 1H); HRMS calcd for $C_{25}H_{24}NO_7$ $(M+H)^+$: 450.1553. Found 450.1555.

(5*RS*,6*SR*,7*SR*)-6-Carboxy-7-[2-[2-(methylamino)ethoxy]-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine (2l). White solid; mp 130–132 °C; ^1H NMR ($CDCl_3$) δ 2.58 (s, 3H), 2.84 (t, $J=9.9$ Hz, 1H), 3.00–3.13 (m, 2H), 3.75 (s, 3H), 4.01–4.19 (m, 2H), 4.61 (d, $J=9.9$ Hz, 1H), 5.17 (d, $J=9.9$ Hz, 1H), 5.92 (d, $J=1.4$ Hz, 1H), 5.94 (d, $J=1.4$ Hz, 1H), 6.33 (d, $J=2.3$ Hz, 1H), 6.50 (dd, $J=2.3$ and 8.4 Hz, 1H), 6.68–6.79 (m, 3H), 7.00 (d, $J=8.4$ Hz, 1H), 7.10 (dd, $J=5.0$ and 7.5 Hz, 1H), 7.33 (d, $J=7.5$ Hz, 1H), 8.47 (d, $J=5.0$ Hz, 1H); HRMS calcd for $C_{26}H_{27}N_2O_6$ $(M+H)^+$: 463.1869. Found 463.1881.

(5*RS*,6*SR*,7*SR*)-7-(2-Carbamoylmethoxy-4-methoxyphenyl)-6-carboxy-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine (2m). White solid; mp 138–140 °C; ^1H NMR (DMSO-d_6) δ 3.37 (t, $J=10.0$ Hz, 1H), 3.74 (s, 3H), 4.40 (s, 2H), 4.53 (d, $J=10.0$ Hz, 1H), 4.90 (d, $J=10.0$ Hz, 1H), 6.00 (s, 2H), 6.51 (d, $J=2.9$ Hz, 1H), 6.52 (dd, $J=2.9$ and 8.2 Hz, 1H), 6.77 (dd, $J=1.6$ and 7.8 Hz, 1H), 6.83 (d, $J=1.6$ Hz, 1H), 6.89 (d, $J=7.8$ Hz, 1H), 7.10 (d, $J=8.2$ Hz, 1H), 7.17 (dd, $J=4.6$ and 7.5

Hz, 1H), 7.23 (dd, $J=1.9$ and 7.5 Hz, 1H), 7.26 (br s, 1H), 7.41 (br s, 1H), 8.25 (dd, $J=1.9$ and 4.6 Hz, 1H); HRMS calcd for $C_{25}H_{23}N_2O_7$ $(M+H)^+$: 463.1505. Found 463.1501.

(5*RS*,6*SR*,7*SR*)-6-Carboxy-7-(2-carboxymethoxy-4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine (2n). White solid; mp 154–156 °C; ^{1}H NMR (CD_3OD) δ 3.64 (t, $J=10.3$ Hz, 1H), 3.77 (s, 3H), 4.37 (d, $J=16.1$ Hz, 1H), 4.58 (d, $J=16.1$ Hz, 1H), 4.66 (d, $J=10.3$ Hz, 1H), 4.91 (d, $J=10.3$ Hz, 1H), 5.93 (s, 2H), 6.50 (d, $J=2.3$ Hz, 1H), 6.56 (dd, $J=2.3$ and 8.1 Hz, 1H), 6.75–6.86 (m, 3H), 7.18 (d, $J=8.1$ Hz, 1H), 7.31 (dd, $J=5.4$ and 7.5 Hz, 1H), 7.48 (d, $J=7.5$ Hz, 1H), 8.27 (d, $J=5.5$ Hz, 1H); HRMS calcd for $C_{25}H_{22}NO_8$ $(M+H)^+$: 464.1345. Found 464.1356.

(5*RS*,6*SR*,7*SR*)-6-Carboxy-7-[2-(2-carboxyethenyl)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine (2o). Pale yellow solid; mp 180 °C (decomp.); ^{1}H NMR ($CDCl_3$) δ 3.03 (t, $J=10.2$ Hz, 1H), 3.83 (s, 3H), 4.77 (d, $J=10.2$ Hz, 1H), 5.27 (d, $J=10.2$ Hz, 1H), 5.95 (d, $J=1.9$ Hz, 1H), 5.96 (d, $J=1.9$ Hz, 1H), 6.29 (d, $J=15.4$ Hz, 1H), 6.68 (d, $J=1.8$ Hz, 1H), 6.76 (dd, $J=1.8$ and 7.9 Hz, 1H), 6.79 (d, $J=7.9$ Hz, 1H), 7.00 (dd, $J=2.3$ and 8.9 Hz, 1H), 7.03 (d, $J=8.9$ Hz, 1H), 7.12 (d, $J=2.3$ Hz, 1H), 7.20 (dd, $J=4.9$ and 7.9 Hz, 1H), 7.38 (d, $J=7.9$ Hz, 1H), 8.32 (d, $J=15.4$ Hz, 1H), 8.54 (d, $J=4.9$ Hz, 1H); HRMS calcd for $C_{26}H_{22}NO_7$ $(M+H)^+$: 460.1397. Found 460.1393.

5*RS*,6*SR*,7*SR*)-6-Carboxy-7-[2-(2-carboxyethyl)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine (2p). White foam; ^{1}H NMR ($CDCl_3$) δ 2.60–2.80 (m, 2H), 2.98–3.26 (m, 2H), 3.43 (t, $J=9.9$ Hz, 1H), 3.76 (s, 3H), 4.64 (d, $J=9.9$ Hz, 1H), 5.04 (d, $J=9.9$ Hz, 1H), 5.98 (d, $J=2.3$ Hz, 1H), 5.99 (d, $J=2.3$ Hz, 1H), 6.72–6.83 (m, 5H), 6.90 (d, $J=8.2$ Hz, 1H), 7.19 (dd, $J=5.0$ and 8.1 Hz, 1H), 7.39 (d, $J=8.1$ Hz, 1H), 8.38 (d, $J=5.0$ Hz, 1H); HRMS calcd for $C_{26}H_{24}NO_7$ $(M+H)^+$: 462.1553. Found 462.1549.

Endothelin receptor binding assay. According to the reported method,[12] binding affinities were determined 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.[5]

Antagonism of ET-1-induced contractile response in rabbit iliac artery. The antagonism study was conducted according to the reported experimental protocol[13] using isolated rabbit iliac arteries. The pA_2 values were obtained by analysis of Schild plots.[14]

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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.; Suga, S.; Ogawa, Y.; Mukoyama, M.; Shirakami, G.; Saito, Y.; Nakanishi, S.; Imura, H. *FEBS Lett*. **1991**, *287*, 23.
3. (a) Ferro, C. J.; Webb, D. J. *Drugs* **1996**, *51*, 12. (b) Webb, D. J.; Strachan, F. E. *Am. J. Hypertens*. **1998**, *11*, 71S.
4. Ishikawa, K.; Fukami, T.; Nagase, T.; Fujita, K.; Hayama, T.; Niiyama, K.; Mase, T.; Ihara, M.; Yano, M. *J. Med. Chem*. **1992**, *35*, 2139.
5. Ishikawa, K.; Ihara, M.; Noguchi, K.; Mase, T.; Mino, N.; Saeki, T.; Fukuroda, T.; Fukami, T.; Ozaki, S.; Nagase, T.; Nishikibe, M.; Yano, M. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4892.
6. (a) Stein, P. D.; Hunt, J. T.; Floyd, D. M.; Moreland, S.; Dickenson, K. E. J.; Mitchell, C.; Liu, E. C.-K.; Webb, M. L.; Murugesan, N.; Dickey, J.; McMullen, D.; Zhang, R.; Lee, V. G.; Serafino, R.; Delaney, C.; Schaeffer, T. R.; Kozlowsky, M. *J. Med. Chem*. **1994**, *37*, 329. (b) Doherty, A. M.; Patt, W. C.; Edmunds, J. J.; Berryman, K. A.; Reisdorph, B. R.; Plummer, M. S.; Shahripour, A.; Lee, C.; Cheng, X.-M.; Walker, D. M.; Haleen, S. J.; Keiser, J. A.; Flynn, M. A.; Welch, K. M.; Hallak, H.; Taylor, D. G.; Reynolds, E. E. *J. Med. Chem*. **1995**, *38*, 1259. (c) Winn, M.; von Geldern, T. W.; Opgenorth, T. J.; Jae, H.-S.; 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. (d) Wu, C.; Chan, M. F.; Stavros, F.; Raju, B.; Okun, I.; Mong, S.; Keller, K. M.; Brock, T.; Kogan, T. P.; Dixon, R. A. F. *J. Med. Chem*. **1997**, *40*, 1690.
7. (a) Breu, V.; Clozel, M.; Burri, K.; Hirth, G.; Neidhart, W.; Ramuz, H. *FEBS Lett*. **1996**, *383*, 37. (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.
8. (a) Clozel, M.; Breu, V.; Gray, G. A.; Kalina, B.; Löffler, B.-M.; Burri, K.; Cassal, J.-M.; Hirth, G.; Müller, 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., Jr.; 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 Papers*, 208th National Meeting of the American Chemical Society, Washington DC, Aug 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.
9. Canonne, P.; Belley, M. *Can. J. Chem*. **1987**, *65*, 1885.
10. Potts, K. T.; Bhattacharjee, D.; Walsh, E. B. *J. Org. Chem*. **1986**, *51*, 2011.
11. Cousins, R. D.; Elliott, J. D.; Lago, M. A.; Leber, J. D.;

Peishoff, C. E. PCT Patent WO 9308799, 1993; *Chem. Abstr.* **1992**, *120*, 106563.
12. Ihara, M.; Fukuroda, T.; Saeki, T.; Nishikibe, M.; Kojiri, K.; Suda, H.; Yano, M. *Biochem. Biophys. Res. Commun.* **1991**, *178*, 132.
13. Ihara, M.; Noguchi, K.; Saeki, T.; Fukuroda, T.; Tsuchida, S.; Kimura, S.; Fukami, T.; Ishikawa, K.; Nishikibe, M.; Yano, M. *Life Sci.* **1992**, *50*, 247.
14. Arunlakshana, O.; Shild, H. O. *Br. J. Pharmacol.* **1959**, *14*, 48.