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Structure–activity relationships of a novel class of endothelin receptor selective antagonists; 6-carboxy-2-isopropylamino-5,7-diarylcyclopenteno[1,2-*b*]pyridines

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Abstract—The synthesis and structure–activity relationships of 6-carboxy-2-isopropylamino-5,7-diarylcyclopenteno[1,2-*b*]pyridine class of ET_A receptor selective antagonists were described. These derivatives were prepared from the optically active key intermediates (**3**, **4**, **10**, and **13**). Optimization of the substituent at the 2-position of the bottom 4-methoxyphenyl ring of the lead compound **1** led to identification of 2-hydroxy-1-methylethoxy (**2g** and **h**), hydroxyalkyl (**2i**, **m**, and **p**), 3-methoxy-2-methylpropyl (**2t** and **u**), *N*-acetyl-*N*-methylaminomethyl (**2v**), and 2-(dimethylcarbamoyl)propyl (**2w**) derivatives that showed greater than 1000-fold selectivity for the ET_A receptor over the ET_B receptor with excellent binding affinity ($IC_{50} < 0.10$ nM). Further screening of these compounds by assessing the plasma exposures at 1 h, 4 h, and 8 h after oral administration (3 or 10 mg/kg) in rats led to identification of the hydroxymethyl (**2i**) and 3-methoxy-2-methylpropyl (**2u**) derivatives exhibiting good oral bioavailability in rats.

1. Introduction

Endothelins (ET-1, ET-2, and ET-3) were discovered as highly potent endogenous vasoconstrictor peptides and are known to possess a variety of additional biological activities.[1] The actions of these endothelins are mediated through two distinct G-protein coupled receptors (ET_A and ET_B).[2] The ET_A receptor is expressed predominantly in vascular smooth muscle cells and mediates vasoconstrictive and proliferative responses. The ET_B receptor is the major receptor on endothelial cells, but the functions remain to be clearly understood. While the ET_B receptor mediates constriction in some tissue beds, it has been linked to vasodilation and the clearance of endogenous endothelins.[3]

A number of ET_A[4] and ET_B[5] receptor selective as well as ET_A- and ET_B-balanced receptor antagonists[6] have been described in the literatures, and these endothelin receptor antagonists are currently being investigated as to the roles of endothelins and their receptors in mediating various phathophysiology. Previously, we described a new class of endothelin receptor antagonists with a 6-carboxy-2-substitued-5,7-diarylcyclopenteno[1,2-*b*]pyridine skeleton, in which the selectivity of compounds for the ET_A receptor over the ET_B receptor was depended mainly on the substituent at the 2-position of the cyclopenteno[1,2-*b*]pyridine core.[7] Particularly, an isopropylamino moiety at this position was identified as one of the most effective functional groups in terms of enhancing the selectivity for the ET_A over the ET_B receptor. Our efforts focusing on the optimization of the

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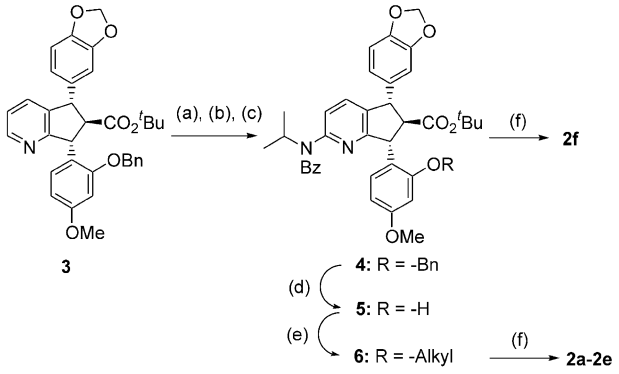
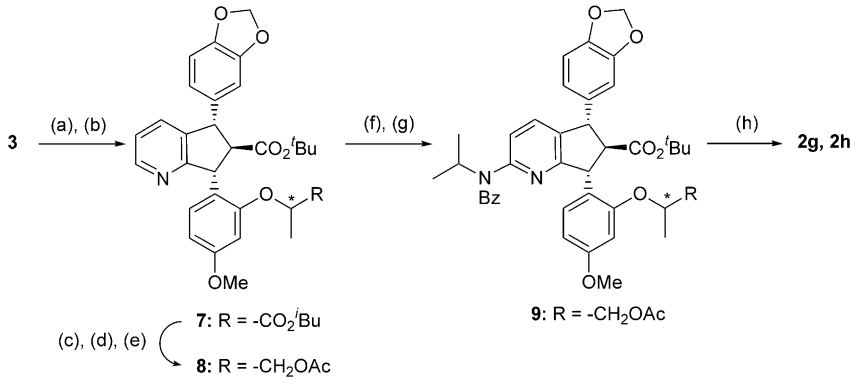
substituent at the 2-position of the 4-methoxyphenyl ring attached at the cyclopenteno[1,2-*b*]pyridine core have been made to identify potent and orally bioavailable ET_A receptor selective antagonists. Herein, we wish to describe the synthesis and the structure–activity relationships (SARs) of these cyclopenteno[1,2-*b*]pyridine derivatives.



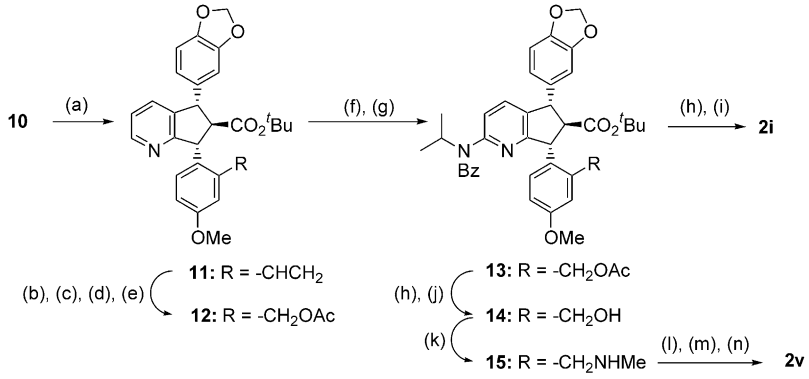
Scheme 1. Synthesis of the 2-alkoxy-4-methoxyphenyl derivatives (**2a–f**). Reagents: (a) mCPBA, $CHCl_3$, 0 °C, 87%; (b) ^{i}PrN=C(Cl)Ph, Et_3N, $CHCl_3$, reflux, 87%; (c) CHIRALPAK AD, Hexane–^{i}prOH (7:3), 45%; (d) H_2, Pd–C, MeOH, rt, quant.; (e) 60% NaH, iodoalkane, DMF, rt; (f) 4N NaOH, MeOH, reflux.

2. Chemistry

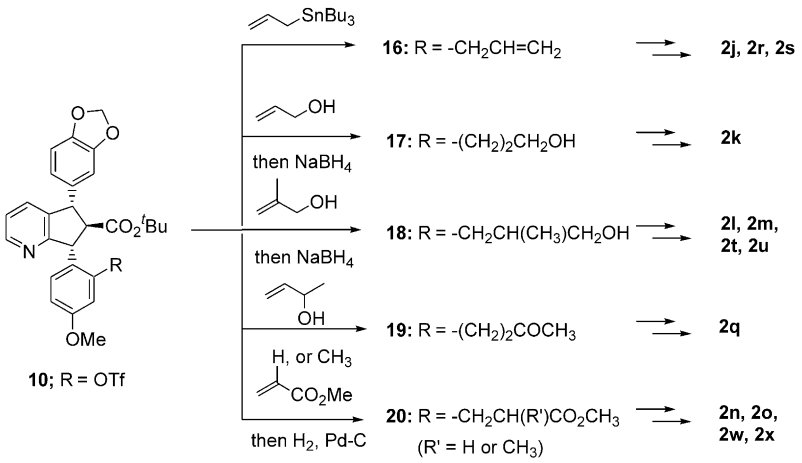
Robust synthetic methods of the novel class of the optically active 6-carboxy-2-isopropylamino-5-(3,4-methylenedioxyphenyl)-7-(4-methoxy-2-substituted-phenyl)cyclopenteno[1,2-*b*]pyridines (**2a–x**) via the key intermediates (**3**, **4**, **10**, and **13**) have been developed as shown in Schemes 1–4.[8] Synthesis of the 7-(2-alkyloxy-4-methoxyphenyl)cyclopenteno[1,2-*b*]pyridine derivatives (**2a–h**) was started from *N*-oxidation of the pyridine nitrogen of **3** with *m*-chloroperbenzoic acid (Scheme 1). The resulting *N*-oxide was treated with *N*-isopropylbenzimidoyl chloride in the presence of triethylamine (NEt_3) to produce the migrated product, 2-(*N*-isopropyl-*N*-benzoylamino)pyridine **4** in 87% yield.[9] Optical resolution of **4** was achieved by CHIRALPAK AD® to produce the optically active **4** in 45% yield. Debenzylation of **4** followed by alkylation of the resulting phenol moiety gave **6**, which were hydrolyzed with 4N NaOH to afford the desired derivatives (**2a–f**) in good yields. Compound (**2g**) or (**2h**) was prepared from the optically active intermediate **3** by the 8 step reaction sequence, in which the *N*-isopropyl-*N*-benzoylamino moiety at the 2-position of the cyclopentenopyridine core was introduced after the functionalization of the phenol moiety (Scheme 2).[10]



Scheme 2. Synthesis of the 2-alkoxy-4-methoxyphenyl derivatives (**2g** and **h**). Reagents for **2g**: (a) (1) CHIRALPAK AD, Hexane–^{i}PrOH (7:3), 42%; (2) H_2, Pd–C, THF, rt, quant.; (b) (*S*)-BrCH(Me)$CO_2{}^i$Bu, K_2CO_3, KI, MEK, reflux, 40%; (c) 4N NaOH, MeOH, rt, 92%; (d) BH_3–THF complex, THF, 0 °C to rt, 52%; (e) Ac_2O, pyridine, rt, 91%; (f) *m*CPBA, $CHCl_3$, 0 °C, 60%; (g) ^{i}PrN=C(Cl)Ph, CsF, MS3A, $(ClCH_2)_2$, reflux, 57%; (h) 6N NaOH, reflux, 66%.



Scheme 3. Synthesis of the 2-substituted-4-methoxyphenyl derivatives (**2i** and **v**). Reagents: (a) $(CH_2=CH)Bu_3Sn$, $PdCl_2(PPh_3)_2$, LiCl, DMF, 110 °C, 92%; (b) OsO_4, *N*-methylmorphine-*N*-oxide, CH_3CN–H_2O, rt; (c) $NaIO_4$, THF–H_2O, 0 °C; (d) $NaBH_4$, MeOH, 0 °C, 56% for 3 steps; (e) Ac_2O, Et_3N, DMAP, $CHCl_3$, rt, 65%; (f) *m*CPBA, $CHCl_3$, 0 °C; (g) ^{i}PrN=C(Cl)Ph, Et_3N, $CHCl_3$, reflux, 91% for 2 steps; (h) Optical resolution by CHIRALPAK AD, Hexane–^{i}PrOH (7:3), 47%; (i) 4N NaOH, MeOH reflux, 88%; (j) 1N NaOH, MeOH, rt, 88%; (k) NaI, TMSCl, CH_3CN, then 40% $MeNH_2$, MeOH, rt, 81%; (l) 9-BBN, THF, rt; (m) Ac_2O, Et_3N, $CHCl_3$, rt, 39% for 2 steps; (n) TFA, rt, 93%.



Scheme 4. Synthesis of the 2-substituted-4-methoxyphenyl derivatives via Pd-catalyzed Stille or Heck reaction. Stille reaction: Tin reagent (1.2 equiv), $PdCl_2(PPh_3)_2$ (5.5 mol%), LiCl (3 equiv), DMF (0.1M), 130 °C. Heck reaction: olefin (5–10 equiv), $PdCl_2(PPh_3)_2$ (10–20 mol%), $NaHCO_3$ (3 equiv), DMF, 130 °C.

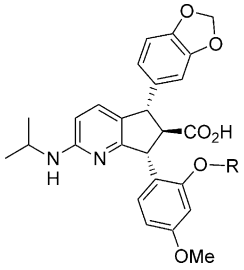
Scheme 3 shows the synthesis of hydroxymethyl (**2i**) and *N*-acetyl-*N*-methylaminomethyl (**2v**) derivatives. Stille coupling of the triflate **10** with tributyl(vinyl)tin in the presence of lithium chloride provided **11** in 92% yield.[11] Transformation of the vinyl moiety to the acetoxymethyl group (**12**) was achieved by the conventional 4 reaction steps; (1) cat. OsO_4, *N*-methylmorphorine-*N*-oxide (NMO)/CH_3CN–H_2O, (2) $NaIO_4$/THF–H_2O, (3) $NaBH_4$/MeOH, (4) Ac_2O, NEt_3, 4-dimethylaminopyridine (DMAP)/$CHCl_3$. Introduction of the *N*-isopropyl-*N*-benzoylamino moiety into the 2-position of the cyclopentenopyridine core in **12** and the subsequent optical resolution produced the optically active intermediate **13**. Basic hydrolysis of both the benzoylamino and *tert*-butyl ester moieties in **13** produced **2i** in 88% yield. With regard to the synthesis of **2v**, the acetoxy group of the optically active **13** was selectively hydrolyzed under a mild basic condition (1N NaOH/MeOH) to afford the hydroxymethyl derivative **14**, which was converted to the corresponding *N*-methylaminomethyl group (**15**). Selective deprotection of the benzoyl group by treatment with 9-BBN[12] followed by acetylation of the *N*-methylaminomethyl moiety and deprotection of the *tert*-butyl ester with trifluoroacetic acid (TFA) yielded the compound **2v** in 36% yield. The 2-isopropylamino-7-(2-substituted alkyl-4-methoxyphenyl)cyclopenteno [1,2-*b*]pyridines (**2j–u**,**w**,**x**) were prepared via Stille coupling[11] or Heck reaction[13] of the optically active triflate **10** with an appropriate reagent such as allyltributyltin or allyl alcohol. Subsequent functionalization of the C-2 side chain produced the derivatives (**2j–u**) in moderate to good yields (Scheme 4).[14]

3. Biological properties

Compounds synthesized above were primarily evaluated in the binding assay (inhibitory activity against ^{125}I-labled ET-1 binding to both the human ET_A and ET_B receptors).[15] Selected compounds were tested in the isolated tissues assay using rabbit iliac artery in the presence of 3% human serum albumin to examine their functional antagonist activity toward the ET_A receptor.[16] Furthermore, the rat plasma exposures at 1 h, 2 h, and 8 h after oral administration (3 or 10 mg/kg) were examined to predict a compounds oral bioavailability and duration of their plasma exposures.

The binding affinity of the 2-isopropylamino-7-(2-substituted-4-methoxyphenyl)cyclopenteno[1,2-*b*]pyridine derivatives (**1**, **2a–x**) toward the ET_A and ET_B receptors and their selectivity for the ET_A receptor over the ET_B receptor are shown in Tables 1 and 2. The 7-(2-hydroxy-4-methoxyphenyl) derivative **1** was a potent ET_A receptor selective antagonist. Methylation (**2a**) of the phenol moiety of **1** improved the binding affinity for the ET_A receptor, while the other alkylated derivatives (**2b–f**) except for **2d** resulted in decreasing the binding affinity for the ET_A receptor.

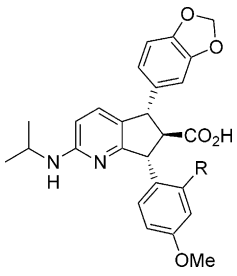
Table 1. In vitro potency of the cyclopenteno[1,2-*b*]pyridine derivatives (**1**, **2a–h**)



Compd	R	IC_{50}[a] (nM)		Selectivity
		ET_A	ET_B	ET_B/ET_A
1	H	0.22	290	1300
2a	Methyl	0.047	25	530
2b	Ethyl	0.74	45	61
2c	*n*-Propyl	0.41	100	240
2d	*i*-Propyl	0.11	88	800
2e	*i*-Butyl	0.86	420	490
2f	Benzyl	0.80	480	600
2g	2-Hydroxy-1-methylethyl[b]	0.057	78	1400
2h	2-Hydroxy-1-methylethyl[b]	0.036	61	1700

[a] Values are the mean of the two or more independent assay.
[b] Each of the two diastereomers on the side chain (R).

Table 2. In vitro potency of cyclopenteno[1,2-*b*]pyridine derivatives (**2i–x**)



Compd	R	IC_{50}[a] (nM)		Selectivity
		ET_A	ET_B	ET_B/ET_A
2i	Hydroxymethyl	0.062	62	1000
2j	2-Hydroxyethyl	0.031	19	610
2k	3-Hydroxypropyl	0.022	20	910
2l	3-Hydroxy-2-methylpropyl[b]	0.059	51	860
2m	3-Hydroxy-2-methylpropyl[b]	0.041	54	1300
2n	3-Hydroxy-2-ethylpropyl[c]	0.011	11	910
2o	3-Hydroxy-2-ethylpropyl[c]	0.045	15.7	350
2p	2-Hydroxy-2-methylpropyl	0.014	14	1000
2q	3-Hydroxy-3-methylbutyl	0.065	23	350
2r	2,3-Dihydroxypropyl[d]	0.011	6.0	550
2s	2,3-Dihydroxylpropyl[d]	0.048	5.6	120
2t	3-Methoxy-2-methylpropyl[e]	0.011	25	2300
2u	3-Methoxy-2-methylpropyl[e]	0.025	48	1900
2v	*N*-Acetyl-*N*-methylaminomethyl	0.027	43	1600
2w	2-(*N*,*N*-Dimethylcarbamoyl)propyl[f]	0.024	43	1800
2x	2-(*N*,*N*-Dimethylcarbamoyl)propyl[f]	0.014	9.5	680

[a] Values are the mean of the two or more independent assay.
[b–f] Each of the two diastereomers on the side chain (R).

The previous SARs on the prototype 7-[2-substituted-4-methoxyphenyl]cyclopenteno[1,2-*b*]pyridine derivatives[7] suggested that incorporation of a hydroxyalkyloxy-substituent at the C-2 side chain was tolerated in terms of the ET_A binding affinity and the selectivity for the ET_A over ET_B receptor. In fact, incorporation of a hydroxyl group into the isopropyl moiety of **2d** improved the potency (**2g**: IC_{50}: 0.057 nM, **2h**: IC_{50}: 0.036 nM) for the ET_A receptor and the selectivity for the ET_A receptor over the ET_B receptor (**2g**: $ET_B/ET_A = 1400$-fold, **2h**: $ET_B/ET_A = 1700$-fold). These results prompted us to further investigate the SARs of the hydroxylated alkyl derivatives (**2i–u**) on the ET_A binding affinity and the selectivity for the ET_A receptor over the ET_B receptor. These derivatives showed excellent binding affinity (IC_{50}: 0.011 ~ 0.065 nM) for the ET_A receptor. Comparison of the ET_A selectivity of the two diastereomers on the side chain at the 2-position of the bottom phenyl ring [2-methyl- (**2l** and **m**), 2-ethyl- (**2n** and **o**) and 2-hydroxyl- (**2r** and **s**) 3-hydroxypropyl derivatives] suggested that the stereochemical structures of the side chain affected the selectivity for the ET_A over the ET_B receptor.

The biological properties of the derivatives exhibiting greater than 1000-fold selectivity for the ET_A over ET_B receptor were further characterized (Table 3). The isolated tissue assays of these derivatives using the rabbit iliac artery were performed in the presence of 3% human serum albumin (HSA) to predict a compounds

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

Compd	PK_B[a]	Mouth lethality	Rat plasma exposure (nM)[b]		
		AD_{50} (mpk, iv)	1 h	4 h	8 h
2g	7.46	NT	440	20	69
2h	8.00	0.046	160	47	62
2i	7.76	0.12	(130	94	19)[c]
2m	8.33	0.034	(110	22	11)[c]
2p	NT	0.042	460	48	110
2t	NT	0.042	810	130	120
2u	8.33	0.039	(220	81	52)[c]
2v	8.97	NT	(2	3	0.4)[c]
2w	NT	0.017	65	7	10

[a] Assays were performed in the presence of 3% human serum albumin. Values are the mean of three or more independent assays.
[b] Compounds (10 mg/kg) were orally administered to rats ($n = 2$–3), otherwise noted.
[c] Compounds (3 mg/kg) were orally administered to rats ($n = 2$–3).

functional antagonist activity in humans. The 3-hydroxy-2-methylpropyl derivative **2m** showed sub nano-molar order of the intrinsic antagonist activity (PK_B: 10.0), while **2m** showed decreased antagonist activity (PK_B: 8.33) in the presence of 3% HSA, suggesting that **2m** showed the considerable protein-binding shift. However, it was clear that all the tested compounds retained high antagonist activity even in the presence of 3% HSA (Table 3). In addition, these derivatives showed excellent in vivo efficacy (AD_{50}: 0.017–0.12 mg/kg after intravenous administration) in the mouse lethality model. These results suggested that the high functional antagonist activity of these compounds in the tissue assay well reflected their in vivo efficacy in mice.

Improvement of the oral bioavailability of this class is a key to success for the development of ET_A receptor selective antagonists, because the prototype dicarboxylic acid derivatives[7] showed poor oral absorption in the rat in situ intestinal absorption study. Therefore, screening of compounds by assessing their plasma levels at 1 h, 4 h and 8 h after oral administration (3 or 10 mg/kg) to rats was performed to identify ET_A receptor selective antagonists with high orally bioavailability. Among the hydroxyalkoxy and hydroxyalkyl derivatives, the 2-hydroxy-1-methylethoxy (**2g**) and hydroxyalkyl (**2i**,**m**, and **2p**) derivatives showed moderate plasma exposures at 1 h after oral administration, if the plasma exposures of the compounds (**2i** and **m**) at 3 mg/kg were extrapolated to 10 mg/kg. However, these derivatives had different characteristics in terms of the duration of the plasma exposures. The hydroxymethyl derivative **2i** had relatively high plasma exposure at 4 h, while the 3-hydroxy-2-methylpropyl derivative **2m** showed approximately 4-fold lower plasma exposure at 4 h than **2i**. These results suggested that **2i** would have higher bioavailability in rats than **2m**. Indeed, the bioavailability of these derivatives (**2i** and **m**) in rats (3 mpk, po and 1 mpk, iv) were 57% and 7.6%, respectively.

The 3-methoxy-2-methylpropyl derivatives (**2t** and **u**) showed higher plasma exposure levels at 1 h, 4 h, and 8 h

after oral administration when compared with those of the 3-hydroxy-2-methylpropyl derivative **2m**. Particularly, the bioavailability of **2u** in rats (3 mpk, po and 1 mpk, iv) was 70%. In contrast, the 2-(dimethylcarbamoyl)propyl derivatives (**2v** and **w**) showed extremely lower plasma exposure levels at 1 h than the above hydroxyalkyl and methoxypropyl derivatives, probably due to their more hydrophilic natures.

In conclusion, we have extensively derivatized the substituent at the 2-position of the bottom 4-methoxyphenyl ring on the cyclopenteno[1,2-*b*]pyridine core to identify potent, orally bioavailable ET_A receptor selective antagonists in this class. As a result, the 2-hydroxy-1-methylethoxy (**2g** and **h**), hydroxyalkyl (**2i**, **m**, and **p**), *N*-acetyl-*N*-methylaminomethyl (**2v**), and 2-(dimethylcarbamoyl)propyl (**2w**) derivatives that showed greater than 1000-fold selectivity for the ET_A receptor over the ET_B receptor with excellent binding affinity ($IC_{50} < 0.10$ nM) have been identified. Furthermore, the rat plasma exposure screening of the compounds at 1 h, 4 h, and 8 h after oral administration led to identification of the hydroxymethyl (**2i**) and 3-methoxy-2-methylpropyl (**2u**) derivatives as having good oral bioavailability (**2i**: 57%, **2u**: 70%) in rats. The 3-methoxy-2-methylpropyl derivative **2u** showed the interesting in vivo efficacy in rats.[17] The in vivo efficacy of the hydroxymethyl derivative **2i** will be reported in the near future.

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