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Synthesis and Structure–Activity Relationships of Potent and Orally Active Sulfonamide ET_B Selective Antagonists

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Abstract—The synthesis and structure–activity relationships of a series of *N*-pyrimidinyl benzenesulfonamides as ET_B selective antagonists are described. *N*-Isoxazolyl benzenesulfonamide **1a**, previously reported,[1] was selected as a lead compound, and isosteric replacement of the isoxazole ring of **1a** with a pyrimidine ring led to the discovery of the highly potent ET_B selective antagonist **6e** with oral bioavailability. Modification of the terminal aldehyde group at the 6-position of the pyrimidine ring was investigated, and malonate **15b** and acylhydrazone **16f** were found to be equipotent to aldehyde **6e**. Compound **6e** showed ET_B antagonistic activity on in vivo evaluation.

Introduction

Endothelins (ET-1, ET-2, ET-3), 21-amino acid bicyclic peptides, are the most potent known vasoconstrictors.[2,3] Two distinct G-protein coupled receptors, ET_A and ET_B, were cloned and characterized with respect to their affinity for each endothelin.[4,5] The ET_A receptor on vascular smooth muscle cells has high affinity for ET-1 and ET-2, and mediates vasoconstriction and smooth muscle cell proliferation. The ET_B receptor on vascular endothelial and smooth muscle cells has high affinities for all three endothelins. It mediates both vasodilatation and vasoconstriction. As these two subtypes of receptors are widely distributed in human tissues, selective or non-selective endothelin receptor antagonists have been envisioned to be useful for the treatment of various vascular diseases, including hypertension, congestive heart failure, myocardial infarction, vasospasm, and renal failure.[6]

A number of groups have reported the discovery of non-peptide endothelin antagonists since 1994. Most of them were ET_A selective or non-selective antagonists,[7,8] which were valuable in exploring the role of the ET_A receptor in the pathological conditions. However, only recently have non-peptide ET_B selective antagonists been reported,[9] and the roles of the ET_B receptor in both normal physiological and pathological conditions are poorly understood.

Recently, we have described the identification of non-peptide ET_B selective antagonists aldehyde **1a** and oxime **1b**[1] by modification of sulfamethoxazole[10] and its iodo derivative. Although isoxazole aldehyde **1a** showed sufficient activity and high selectivity for the ET_B receptor, it had low oral bioavailability. Therefore, in order to elucidate the role of the ET_B receptor, ET_B antagonists with better pharmacokinetic profiles had been required. Since almost all the sulfonamide ET antagonists reported at that time had an isoxazole or pyrimidine ring as the heterocycle part,[7a,8a,11] we replaced the isoxazole ring of **1a** with a pyrimidine ring and conducted modification to find better ET_B selective antagonists. Our modification strategy is shown in Scheme 1. First, we investigated the effect of heterocycle parts and optimized the substituents on the pyrimidine ring. Second, we sought other functional groups to replace the terminal aldehyde group. Substituents at the 5 and 6 position of the pyrimidine ring were tethered via the oxygen atom in a same manner as Ro 47-0203 (Bosentan).[8a]

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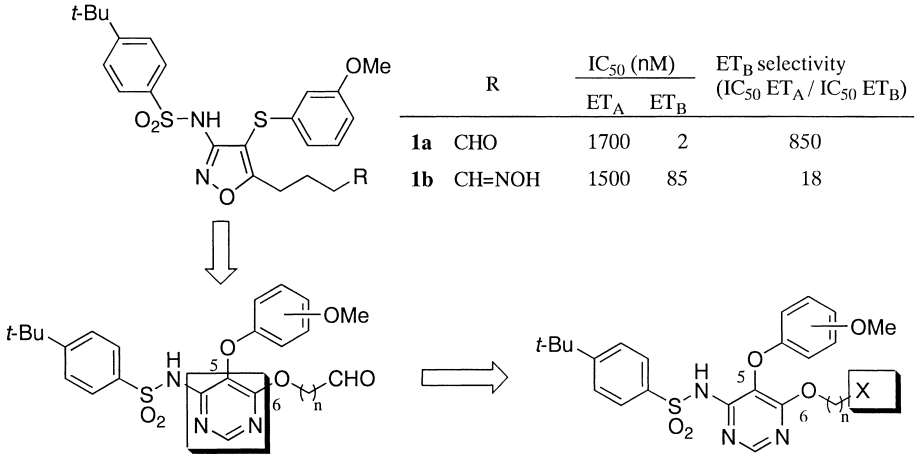


	R	IC_{50} (nM) ET_A	IC_{50} (nM) ET_B	ET_B selectivity (IC_{50} ET_A / IC_{50} ET_B)
1a	CHO	1700	2	850
1b	CH=NOH	1500	85	18

Scheme 1. Modification strategy of *N*-pyrimidinyl benzenesulfonamide derivatives.

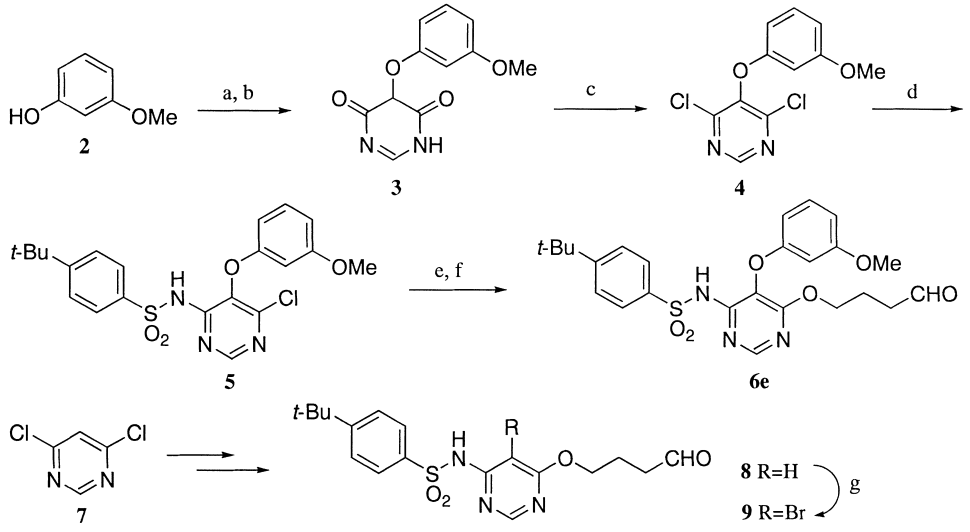
In this paper, we describe the synthesis and structure–activity relationships of this class of compounds and the discovery of orally active ET_B selective antagonists **6b** and **6e** with higher activity and selectivity than those of **1a**. The pharmacokinetic and pharmacological profiles of these compounds are also presented.

Chemistry

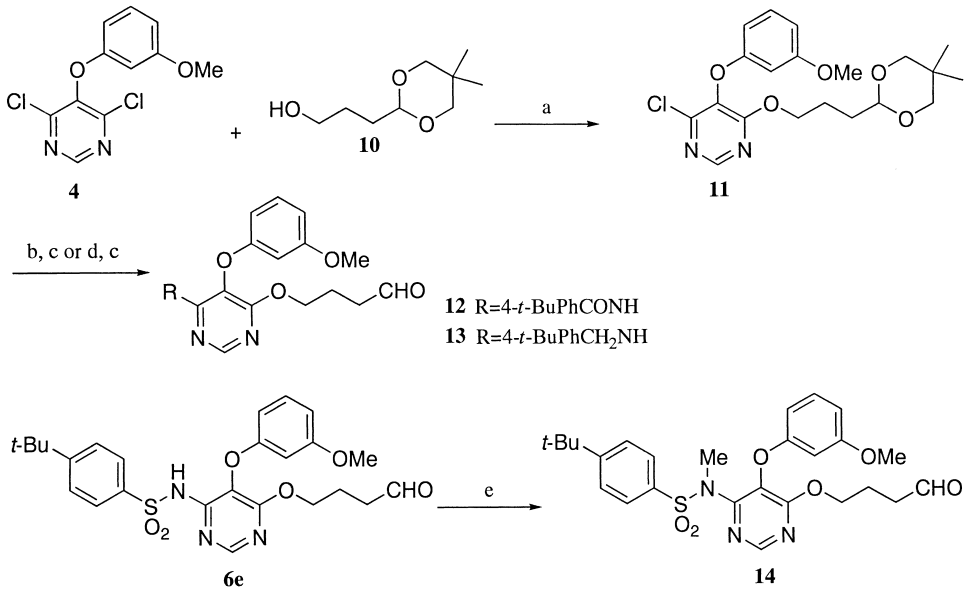
N-Pyrimidinyl benzenesulfonamide derivatives **6a–g**, **8**, **9** (Table 1) were synthesized as shown in Scheme 2. As a typical example of **6a–g**, the synthesis of **6e** is discussed. Alkylation of 3-methoxyphenol **2** with dimethyl chloromalonate and subsequent condensation with formamidine acetate gave 4,6-pyrimidinedione **3**. It was chlorinated with phosphorous oxychloride in the presence of collidine to produce dichloride **4**. Condensation of **4** with potassium 4-*tert*-butylbenzenesulfonamide gave sulfonamide **5**.[12] Chloride displacement of **5** with alkoxide of 1,4-butanediol followed by oxidation with PCC afforded aldehyde **6e**. 5-Unsubstituted compound **8** was also synthesized from commercially available 4,6-dichloropyrimidine **7** by a similar procedure. Bromination of the 5-position in the pyrimidine ring of **8** with NBS gave 5-bromo derivative **9**.

Compounds **12–14** (Table 1) bearing various nitrogen spacers at the 4-position of the pyrimidine ring were prepared as follows (Scheme 3). Displacement of the chloride at the 6-position of the pyrimidine ring of **4** with alkoxide of γ-hydroxy butyraldehyde acetal **10**[13] gave **11**. Next, chloride **11** was converted to the corresponding benzamide or benzylamine derivative, whose acetal groups were hydrolyzed in the aqueous formic acid solution to give aldehyde **12** and **13**, respectively. Methylation of the sulfonamide nitrogen of **6e** with iodomethane gave **14**.

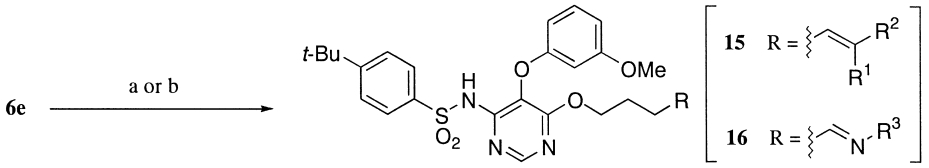
Compounds **15a–e** (Table 2) were synthesized by condensation of aldehyde **6e** with malonic acid, dimethyl and di-*tert*-butyl malonate, acetylacetone or ethyl cyanoacetate. Compounds **16a–g** were also prepared similarly from



Scheme 2. Synthesis of *N*-pyrimidinyl benzenesulfonamide derivatives **6e**, **8**, **9**. (a) Dimethyl chloromalonate, NaOMe, MeOH, rt; (b) HC(=NH)-NH_2·AcOH, NaOMe, MeOH, 0 °C; (c) $POCl_3$, collidine, 135 °C; (d) 4-*t*-Bu-$PhSO_2NHK$, DMSO, 120 °C; (e) NaH, $HO(CH_2)_4OH$, 100 °C; (f) PCC, CH_2Cl_2, rt; (g) NBS, DMF, 0 °C.



Scheme 3. Synthesis of pyrimidine derivatives **12**–**14**. (a) NaH, THF, reflux; (b) 4-*t*-BuPhCONH$_2$, NaH, DMF, 100 °C; (c) HCO_2Na, HCO_2H, 70 °C; (d) 4-*t*-BuPhCH$_2$NH$_2$, 120 °C; (e) MeI, K_2CO_3, DMF, rt.



Scheme 4. Synthesis of pyrimidine derivatives **15** and **16**. (a) $R^1CH_2R^2$, piperidine, EtOH, (b) R^3NH_2, EtOH.

6e by treatment with hydroxylamine, *O*-ethylhydroxylamine or acylhydrazines (Scheme 4).

Results and Discussion

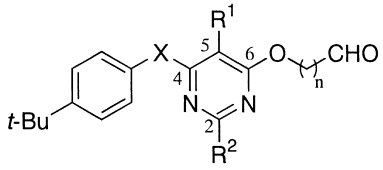
Structure–activity relationships are discussed using IC_{50} values obtained from radioreceptor binding studies (Tables 1 and 2). IC_{50} is the concentration of the antagonist required to cause 50% inhibition of [^{125}I]ET-1 binding to the ET_A receptor and [^{125}I]ET-3 binding to the ET_B receptor. Selectivity for the ET_B receptor was shown as the ratio of the IC_{50} value for ET_A over that for ET_B.

The substitution effect on the pyrimidine ring is summarized in Table 1. We designed pyrimidine aldehyde **6a**–**c** and optimized the alkyl chain length (n = 2–4) at the 6-position of the pyrimidine ring as shown in Scheme 1. Among these compounds, **6b** (n = 3) showed highly ET_B selective antagonistic activity. The binding affinity of **6b** was in the subnanomolar range (0.15 nM), which was 13-fold potent than isoxazole aldehyde **1a**. ET_B selectivity also increased 7-fold as compared to **1a**. This demonstrates that pyrimidine derivatives also have potent binding affinity for the ET_B receptor and that the aldehyde group at the 6-position of the pyrimidine ring plays a crucial role in the ET_B receptor binding as with the isoxazole derivative **1a**.

We next investigated the influence of other substituents in the pyrimidine ring. As for R^1 at the 5-position, unsubstituted derivative **8** and 5-bromo derivative **9** had extremely lower binding affinity for the ET_B receptor compared with **6b**, indicating that introduction of a large hydrophobic aromatic substituent is necessary for the ET_B receptor binding. The binding affinity for the ET_A receptor also increased by introducing aromatic substituent at the 5-position of the pyrimidine ring. Compounds **6d** and **6e** were prepared to optimize the position of the methoxy group in the phenoxy group of **6b**. Among them, *ortho*-substituted **6b** showed the highest ET_B selectivity (6100), and *meta*-substituted **6e** showed the highest affinity for the ET_B receptor (0.06 nM). In fact, **6e** is the most potent non-peptide ET_B receptor antagonist reported so far. Introduction of the substituent R^2 at the 2-position of the pyrimidine ring slightly decreased the ET_B affinity (**6f**, **6g**). The sulfonamide group at the 4-position of the pyrimidine ring was important for the ET_B receptor binding as well as ET_A receptor binding.[14] Replacement of the sulfonamide group of **6e** with carboxamide group greatly decreased the ET_B affinity (**12**). The more basic benzylamine derivative **13** and *N*-methylated sulfonamide derivative **14** showed diminished activity. This implies that the acidic NH proton of the sulfonamide group is necessary for the high affinity binding to the ET_B receptor.

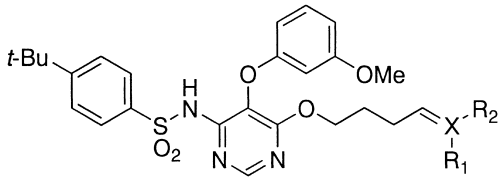
A conformation of **6e** in a crystalline form was determined by X-ray crystallography. Figure 1 shows a superimposition of the crystal structure of **6e** on the modeled **1a**. Key functional groups of **1a** and **6e** such as the aromatic ring, sulfonamide group and aldehyde

Table 1. Structure–activity relationships of the pyrimidine derivatives



Compound	n	R^1	R^2	X	IC_{50} (nM)		ETB selectivity (IC_{50} ET_A/IC_{50} ET_B)
					ET_A	ET_B	
6a	2	2-MeO-PhO	H	$-SO_2NH-$	3000	680	4.4
6b	3	2-MeO-PhO	H	$-SO_2NH-$	910	0.15	6100
6c	4	2-MeO-PhO	H	$-SO_2NH-$	590	42	11
8	3	H	H	$-SO_2NH-$	21,000	3300	6.4
9	3	Br	H	$-SO_2NH-$	>100,000	150	>670
6d	3	4-MeO-PhO	H	$-SO_2NH-$	2300	4.6	500
6e	3	3-MeO-PhO	H	$-SO_2NH-$	180	0.06	3000
6f	3	3-MeO-PhO	Me	$-SO_2NH-$	190	0.56	340
6g	3	3-MeO-PhO	Ph	$-SO_2NH-$	880	0.64	1400
12	3	3-MeO-PhO	H	$-CONH-$	>10,000	510	>20
13	3	3-MeO-PhO	H	$-CH_2NH-$	>10,000	>10,000	—
14	3	3-MeO-PhO	H	$-SO_2NMe-$	>1000	>1000	—

Table 2. Effects of modifying the aldehyde group in the 6-position of the pyrimidine ring of **6e**



Compound	X	R^1	R^2	IC_{50} (nM)		ETB selectivity (IC_{50} ET_A/IC_{50} ET_B)
				ET_A	ET_B	
15a	C	CO_2H	CO_2H	11,000	71	160
15b	C	CO_2Me	CO_2Me	430	0.32	1300
15c	C	CO_2L^tBu	$CO_2{}^tBu$	2400	3.7	650
15d	C	COMe	COMe	160	0.26	620
15e	C	CN	CO_2Et	260	0.68	380
16a	N	—	OH[a]	71	8.0	8.9
16b	N	—	OEt	280	56	5.0
16c	N	—	$NHCONH_2$	160	1.8	89
16d	N	—	NHCOMe	730	1.0	730
16e	N	—	NHCOPh	390	0.29	1300
16f	N	—	NHCO-4-pyridyl	340	0.15	2300
16g	N	—	$NHSO_2Ph$	440	0.22	2000

[a]Mixture of *E*- and *Z*-isomers (1:1).

group occupy similar spatial positions, thus supporting the effectiveness of our first modification strategy.

Having discovered the potent ET_B selective antagonist **6e**, we further modified the aldehyde group at the 6-position of the pyrimidine ring (Table 2). Since the electrophilic carbonyl carbon seemed to play an important role in interacting with the ET_B receptor,[1] we introduced other electrophilic functional groups. We designed malonic acid derivatives (**15a**–**c**), which were synthesized from aldehyde **6e**. Malonic acid **15a** showed greatly reduced binding affinity for the ET_B receptor compared with **6e**. However, the dimethyl ester of **15a** had potent binding affinity in the subnanomolar range (**15b**, 0.32 nM). The introduction of a bulkier di-*tert*-butyl ester decreased the activity (**15c**). Acetylacetone derivative **15d** and cyano acetic acid derivative **15e** were equipotent to **15b** although ET_B selectivity decreased.

Oxime **16a** was designed as a pyrimidine analogue of isoxazole oxime **1b**. Although **16a** had better binding affinity for the ET_B receptor (8.0 nM) than **1b**, ET_B selectivity was low. Oxime ether **16b** showed decreased affinity for ET_A and ET_B receptors than **16a**. This indicates that the hydrogen bond-donating oxime hydroxyl group is effective for the ET_B receptor binding. Therefore, we synthesized derivatives which had other hydrogen bond-donating groups. For this purpose, acylhydrazone derivatives (**16c**–**g**) were tested because a variety of compounds were easily prepared from acylhydrazine

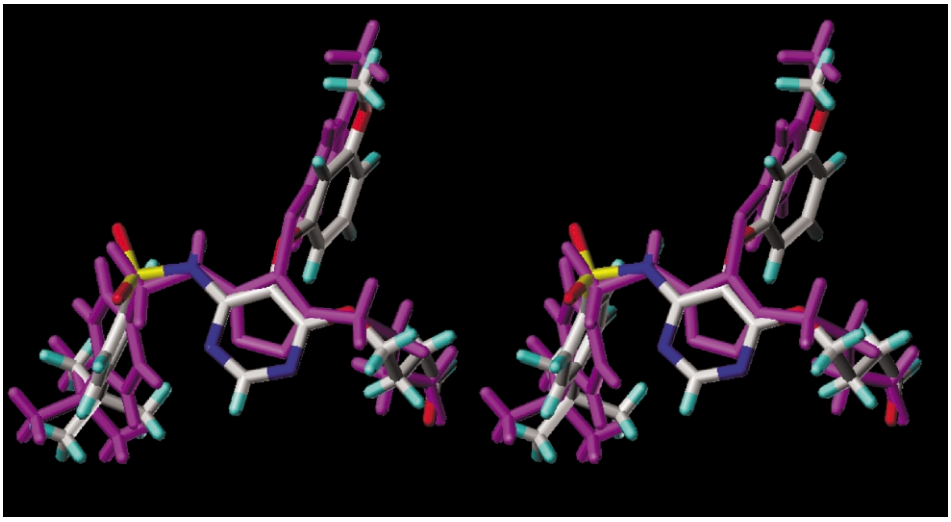


Figure 1. Stereo-view of a superimposition of the crystal structure of **6e** (colored by atom type) on the modeled **1a** (magenta).

and aldehyde **6e**. Semicarbazone **16c** had a potent ET_B affinity, but ET_B selectivity was insufficient. Then, the amino group at the terminal part of the acylhydrazone group of **16c** was replaced with more hydrophobic methyl group to give **16d**, which had better affinity and selectivity for the ET_B receptor than **16c**. Introduction of larger phenyl and pyridyl groups further enhanced ET_B affinity to the subnanomolar range (**16e**, 0.29 nM and **16f**, 0.15 nM) while the orders of magnitude of ET_A affinity were maintained. Sulfonylhydranone **16g** was equipotent to **16f**. This result suggests that there is a hydrophobic binding site on the ET_B receptor which is occupied by the terminal part of the substituent in the 6-position of the pyrimidine ring.

Pharmacokinetic profiles of the selected compounds **6b** and **6e** were evaluated in rats (Table 3). Plasma concentrations of **6b** and **6e** after intravenous (5 mg/kg) or oral (30 mg/kg) administration were measured by HPLC analysis of the plasma samples taken over time. As an iv dose, **6b** and **6e** had similar half-life time ($T_{1/2}$) and AUC values. As an oral dose, **6b** showed more rapid absorption and higher peak plasma concentration (C_{max}) of 12.7 μg/mL than **6e**, resulting in a higher AUC value. The calculated oral bioavailabilities (B.A.) of **6b** and **6e** were 57% and 39%, respectively.

Compound **6e** was evaluated for the ET_B antagonistic activity in vivo. Figure 2 shows the change of blood pressure induced by ET-1 administration (0.1 nmol/kg) at 1-h intervals before and after the administration of **6e** (30 mg/kg, po) in conscious rats. As shown in Figure 2a, an intravenous bolus injection of ET-1 induced a biphasic response consisting of a sharp and transient decrease in blood pressure followed by a sustained pressor response.[9c] On the other hand, after **6e** treatment, the depressor response disappeared and the subsequent pressor response was enhanced, which resulted from removal of the early depressor component (the chart at 1 h after administration of **6e** is shown). Because the depressor response is mediated via ET_B-induced release of nitric oxide and the pressor response is mediated via the ET_A receptor,[9c] this result suggests that **6e** has ET_B selective antagonistic activity in vivo. From the chart as shown in Figure 2a, the depressor and pressor responses were quantified as the maximum change of mean artery blood pressure (MABP) relative to the baseline blood pressure before ET-1 treatment (Fig. 2b). Before the treatment with **6e**, the depressor and pressor responses induced by ET-1 were $-11.7\pm$ 1.7 mmHg and $+11.7\pm1.7$ mmHg, respectively (Fig. 2b, open and solid circles at 0 h). After the oral administration of **6e**, the depressor response was completely blocked (Fig. 2b, open circles at 1 to 5 h), and the pressor response was enhanced 4- to 5-fold (Fig. 2b, solid circles at 1 to 5 h). These effects were sustained for at least 5 h, but disappeared at 24 h after administration of **6e** (data not shown). Based on the above discussion, we conclude that **6e** is a potent and orally active ET_B selective antagonist.

Table 3. Pharmacokinetic profiles of compounds **6b** and **6e** in rats

Compound	iv (5mg/kg)		po (30 mg/kg)		
	$T_{1/2}$ (h)	AUC (μg-h/mL)	C_{max}/T_{max} (μg/mL; h)	AUC (μg-h/mL)	BA (%)
6b	0.58	11.4	12.7/0.8	38.9	57
6e	0.87	11.1	7.7/1.3	26.2	39

Conclusion

We discovered a highly potent ET_B selective antagonist **6e** with subnanomolar IC_{50} value by modifying the amino heterocycle part of **1a**. Modification of the terminal aldehyde group at the 6-position of the pyrimidine ring led to the discovery of malonic acid derivatives and acylhydrazone derivatives equipotent to aldehyde **6e**. Compound **6e** had an oral bioavailability of 39% and displayed ET_B antagonistic activity in vivo. This compound is being evaluated as a potential therapeutic reagent and useful tool for understanding the role of the ET_B receptor in pathological conditions.

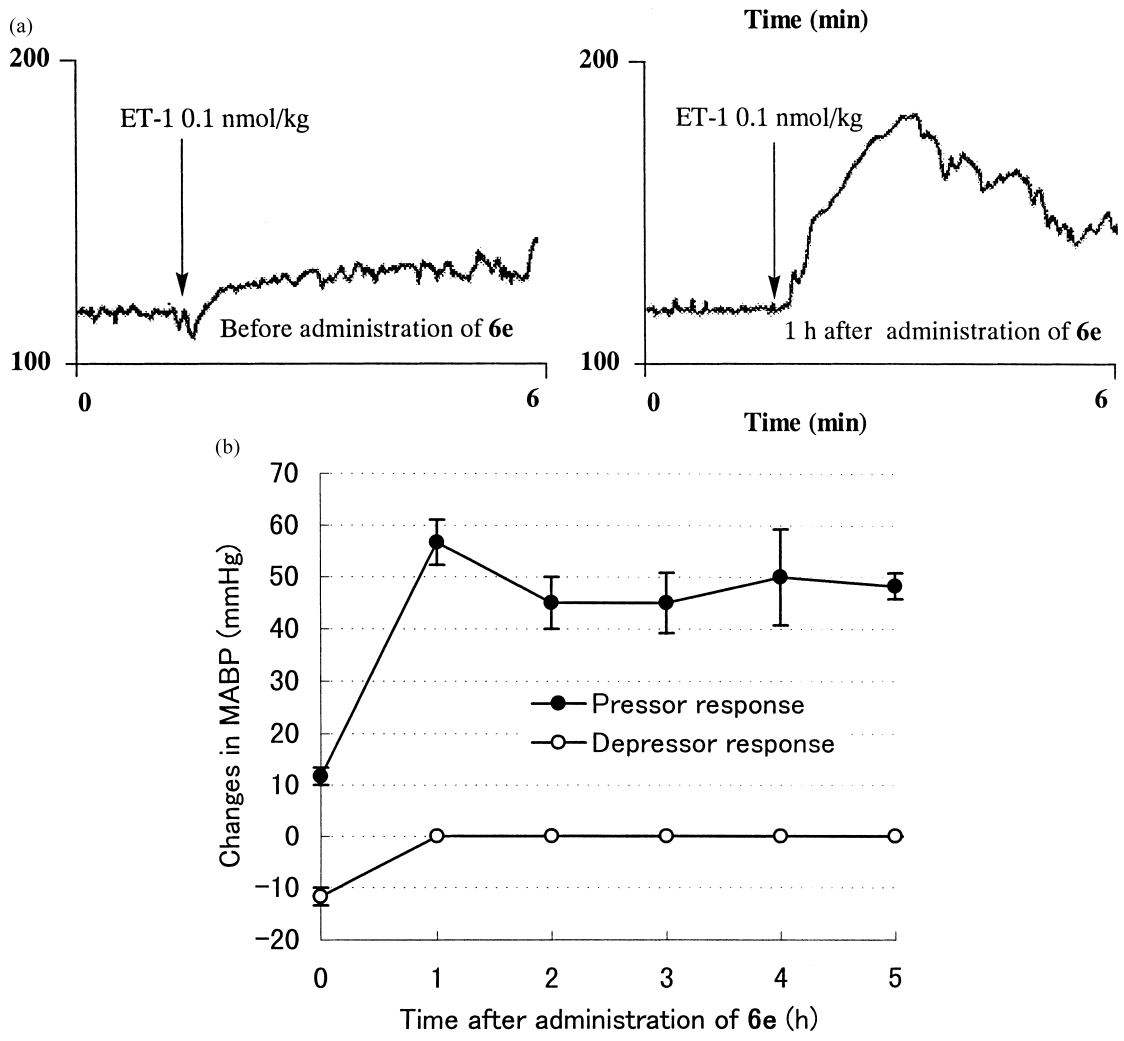


Figure 2. (a) Effects on mean artery blood pressure (MABP) of the ET-1 administered (0.1 nmol/kg) at 1-h intervals in conscious rats (data before and at 1 h after administration of **6e** is shown). After the first treatment of ET-1, compound **6e** (30 mg/kg) was administered orally. (b) Effects on the depressor and pressor responses induced by ET-1 administration of **6e**. The depressor (open circles) and pressor (solid circles) responses were quantified as the maximum change of MABP relative to the baseline blood pressure before ET-1 treatment. Values expressed as mean±S.E.M.

Experimental

Chemistry

Reactions were carried out under a nitrogen atmosphere in anhydrous solvents (dried over molecular sievses type 4A). Organic extracts were dried over anhydrous $MgSO_4$. Solvent removal was accomplished under aspirator pressure using a rotary evaporator. TLC was performed with Merck precoated TLC plates silica gel 60 F_{254}, and compound visualization was made by UV light. Silica gel chromatography was done with Merck silica gel 60 (70–230 mesh). ^{1}H NMR and ^{13}C NMR were determined as $CDCl_3$ solution at 300 and 75.5 MHz, respectively. *J* values are given in hertz.

5-(3-Methoxyphenoxy)-1*H*-pyrimidin-4,6-dione (3). *m*-Methoxyphenol (49.0 g, 0.40 mol) was added dropwise over 15 min to a sodium methoxide solution (1.0 M methanol solution, 395 mL) at 0 °C. After being stirred for 15 min, dimethyl chloromalonate (75.0 g, 0.45 mol) was added dropwise over 15 min at the same temperature. The reaction mixture was stirred for 20 h at rt and concentrated. Water was added to the mixture, and the aqueous layer was extracted with toluene. The organic layer was washed with 1% aqueous NaOH solution and saturated NaCl, dried and concentrated. The residue was distilled under reduced pressure (bp. 155 °C/0.5 mmHg) to give crude dimethyl-3-methoxyphenoxymalonate (67.3 g, 67%), which was used in a following reaction without further purification: ^{1}H NMR δ 3.78 (3H, s), 3.85 (3H, s), 6.46–6.63 (3H, m), 7.19 (1H, t, $J=8.0$). Formamidine acetate (8.6 g, 82.6 mmol) and the malonate (14.0 g, 55.1 mmol) from the preceding reaction were added to a sodium methoxide solution (1.0 M methanol solution, 165 mL) at 0 °C. The reaction mixture was stirred for 2.5 h at rt and concentrated. Water was added to the mixture, and the aqueous layer was extracted with toluene. The aqueous layer was acidified with 1 N HCl. The resulting precipitate was collected, washed with water and dried to give **3** (10.8 g, 84%): mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 3.71 (3H, s), 6.38–6.41 (2H, m), 6.54–6.57 (1H, m), 7.11–7.17 (1H, m), 8.01 (1H, s). Anal. calcd for $C_{11}H_{10}N_2O_4$ 0.1 H_2O: C, 55.98; H, 4.36; N, 11.87. Found: C, 56.08; H, 4.36; N, 11.83.

4,6-Dichloro-5-(3-methoxyphenoxy)pyrimidin (4). To a mixture of **3** (10.8 g, 46.1 mmol) and collidine (15.0 mL, 113.5 mmol) was added phosphorous oxychloride (62.6 mL, 6.7 mol) portionwise at 0 °C. The reaction mixture was stirred at 135 °C for 4 h. The cooled reaction mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed with aqueous $NaHCO_3$ solution and saturated NaCl solution, dried and concentrated. The residue was purified by silica gel chromatography eluting with hexane/AcOEt (4/1 to 2/1) to give **4** (9.7 g, 78%): mp 113–114 °C (hexane/AcOEt); ^{1}H NMR δ 3.81 (3H, s), 6.33–6.38 (2H, m), 6.45 (1H, t, J = 2.4), 6.66–6.71 (1H, m), 7.23 (1H, t, J = 8.2), 8.69 (1H, s). Anal. calcd for $C_{11}H_8Cl_2N_2O_2$ 0.1 H_2O: C, 48.41; H, 3.03; Cl, 25.98; N, 10.26. Found: C, 48.37; H, 2.94; Cl, 25.89; N, 10.27.

4-*tert*-Butyl-*N*-[6-chloro-5-(3-methoxyphenoxy)pyrimidin-4-yl]benzenesulfonamide (5). A solution of **4** (5.3 g, 19.5 mmol) and potassium 4-*tert*-butyl-benzenesulfonate (9.8 g, 40.0 mmol) in DMSO (25 mL) was stirred at 120 °C for 30 min. 1 N HCl was added, and the mixture was extracted with AcOEt. The organic layer was washed with water, dried and concentrated. The residue was crystallized with MeOH to give **5** (7.5 g, 77%): mp 152 °C (MeOH); ^{1}H NMR δ 1.34 (9H, s), 3.78 (3H, s), 6.29–6.39 (1H, m), 6.40–6.42 (1H, m), 6.66–6.71 (1H, m), 7.20 (1H, t, J = 8.2), 7.54, 8.03 (4H, A_2B_2, J = 8.2), 8.49 (1H, s). Anal. calcd for $C_{21}H_{22}ClN_3O_4S$: C, 56.31; H, 4.95; Cl, 7.91; N, 9.38; S, 7.16. Found: C, 56.25; H, 4.99; Cl, 7.52; N, 9.29; S, 7.13.

4-*tert*-Butyl-*N*-[5-(3-methoxyphenoxy)-6-(4-oxobutoxy)-pyrimidin-4-yl]benzenesulfonamide (6e). Sodium hydride (60% dispertion in mineral oil, 2.0 g, 50.0 mmol) was added to 1,4-butandiol (40 mL), and the mixture was stirred at rt for 30 min. Compound **5** (7.5 g, 16.7 mmol) was added, and the reaction mixture was stirred at 100 °C for 6.5 h. 1 N HCl was added, and the mixture was extracted with AcOEt. The organic layer was washed with water and saturated NaCl solution, dried and concentrated. The residue was purified by silica gel chromatography eluting with hexane/AcOEt (1/2 to 1/3) to give 4-*tert*-butyl-*N*-[6-(4-hydroxybutoxy)-5-(3-methoxy-phenoxy)-pyrimidin-4-yl]-benzenesulfonamide (6.0 g, 71%), which was immediately used in a following reaction: ^{1}H NMR δ 1.32 (9H, s), 1.59–1.68 (4H, m), 3.34–3.48 (2H, m), 3.73 (3H, s), 4.24–4.48 (2H, m), 6.34–6.41 (2H, m), 6.61–6.66 (1H, m), 7.17 (1H, t, J = 8.2), 7.52, 8.04 (4H, A_2B_2, J = 8.6,), 8.29 (1H, s). To a solution of the alcohol (6.0 g, 12.0 mmol) from the preceding reaction in CH_2Cl_2 (120 mL) was added PCC (3.0 g, 13.9 mmol) at 0 °C, and the mixture was stirred at rt for 2 h. The reaction mixture was concentrated, and the residue was purified by silica gel chromatography eluting with hexane/AcOEt (1/1) to give **6e** (5.0 g, 84%): TLC (hexane/AcOEt (1/1)) R_f 0.53; mp 110–111 °C (hexane/AcOEt); IR (Nujol) 3267, 1717, 1581, 1490, 1453, 1341, 1079 cm^{-1}; ^{1}H NMR δ 1.34 (9H, s), 1.82–1.90 (2H, m), 2.18 (2H, dt, J = 1.2, 7.2), 3.77 (3H, s), 4.29 (2H, t, J = 6.0), 6.32–6.41 (2H, m), 6.62–6.66 (1H, m), 7.16 (1H, t, J = 8.1), 7.52, 8.03 (4H, A_2B_2, J = 8.4), 8.28 (1H, s), 9.53 (1H, t, J = 1.2); ^{13}C NMR δ 21.26, 31.06, 35.26, 39.88, 55.49, 65.96, 102.27, 107.38, 108.97, 121.55, 125.83, 128.34, 130.22, 136.21, 150.29, 152.91, 157.43, 157.50, 160.87, 161.04, 201.01. Anal. calcd for $C_{25}H_{29}N_3O_6S$: C, 60.10; H, 5.85; N, 8.41; S, 6.41. Found: C, 59.90; H, 5.95; N, 8.66; S, 6.41.

The following compounds were prepared using a similar procedure described for **6e**.

4-*tert*-Butyl-*N*-[5-(2-methoxyphenoxy)-6-(4-oxopropoxy) pyrimidin-4-yl]benzenesulfonamide (6a). Mp 130–132 °C (hexane/AcOEt); ^{1}H NMR δ 1.33 (9H, s), 2.77 (2H, dt, J = 1.5, 6.0), 3.95 (3H, s), 4.66 (2H, t, J = 6.0), 6.82–6.90 (1H, m), 6.95–7.02 (2H, m), 7.08–7.16 (1H, m), 7.48, 8.00 (4H, A_2B_2, J = 9.0), 8.24 (1H, s), 8.77 (1H, s), 9.65 (1H, t, J = 1.5). Anal. calcd for $C_{24}H_{27}N_3O_6S$: C, 59.37; H, 5.60; N, 8.65; S, 6.60. Found: C, 59.38; H, 5.64; N, 8.64; S, 6.85.

4-*tert*-Butyl-*N*-[5-(2-methoxyphenoxy)-6-(4-oxobutoxy)-pyrimidin-4-yl]benzenesulfonamide (6b). TLC (hexane/AcOEt (1/1)) R_f 0.43; mp 88–89 °C (hexane/AcOEt); IR (Nujol) 3201, 1722, 1711, 1585, 1499, 1170, 1078 cm^{-1}; ^{1}H NMR δ 1.33 (9H, s), 1.88–2.01 (2H, m), 2.33 (2H, dt, J = 0.9, 7.2), 3.94 (3H, s), 4.34 (2H, t, J = 6.3), 6.80–6.90 (1H, m), 6.93–7.02 (2H, m), 7.08–7.16 (1H, m), 7.49, 8.01 (4H, A_2B_2, J = 9.0), 8.23 (1H, s), 8.60 (1H, s), 9.64 (1H, t, J = 0.9); ^{13}C NMR δ 21.35, 31.05, 35.21, 40.03, 56.03, 65.97, 112.47, 119.00, 121.17, 124.21, 125.18, 125.74, 128.21, 136.47, 145.86, 149.79, 151.04, 152.43, 157.27, 160.91, 200.98. Anal. calcd for $C_{25}H_{29}N_3O_6S$: C, 60.10; H, 5.85; N, 8.41; S, 6.41. Found: C, 59.90; H, 6.01; N, 8.20; S, 6.14.

4-*tert*-Butyl-*N*-[5-(2-methoxyphenoxy)-6-(4-oxopentoxy)-pyrimidin-4-yl]benzenesulfonamide (6c). Obtained as oil, ^{1}H NMR δ 1.33 (9H, s), 1.50–1.74 (2H, m), 2.37 (2H, dt, J = 1.5, 7.2), 3.96 (3H, s), 4.33 (2H, t, J = 6.0), 6.82–6.89 (1H, m), 6.96–7.02 (4H, m), 7.07–7.14 (1H, m), 7.49, 8.01 (4H, A_2B_2, J = 8.7), 8.24 (1H, s), 8.67 (1H, s), 9.68 (1H, t, J = 1.5). Anal. calcd for $C_{26}H_{31}N_3O_6S$: C, 60.80; H, 6.08; N, 8.18; S, 6.24. Found: C, 60.52; H, 6.15; N, 8.14; S, 6.41.

4-*tert*-Butyl-*N*-[5-(4-methoxyphenoxy)-6-(4-oxobutoxy)-pyrimidin-4-yl]benzenesulfonamide (6d). Mp 125 °C (hexane/AcOEt); ^{1}H NMR δ 1.34 (9H, s), 1.82–1.90 (2H, m), 2.17 (2H, t, J = 8.0), 3.78 (3H, s), 4.27 (2H, t, J = 6.0), 6.71–6.83 (4H, m), 7.52, 8.05 (4H, A_2B_2, J = 8.8), 8.27 (1H, s), 9.54 (1H, s). Anal. calcd for $C_{25}H_{29}N_3O_6S$: C, 60.10; H, 5.85; N, 8.41; S, 6.41. Found: C, 59.95; H, 5.69; N, 8.39; S, 6.44.

4-*tert*-Butyl-*N*-[5-(3-methoxyphenoxy)-2-methyl-6-(4-oxo-butoxy)pyrimidin-4-yl]benzenesulfonamide (6f). Mp 127 °C (hexane/AcOEt); ^{1}H NMR δ 1.34 (9H, s), 1.78–1.91 (2H, m), 2.19 (2H, t, J = 7.0), 2.47 (3H, s), 3.77 (3H, s), 4.27 (2H, t, J = 6.2), 6.32–6.41 (2H, m), 6.60–6.65 (1H, m), 7.15 (1H, d, J = 8.0), 7.51 (2H, d, J = 8.8), 8.05 (2H, t, J = 8.6), 9.54 (1H, s). Anal. calcd for $C_{26}H_{31}N_3O_6S$: C, 60.80; H, 6.08; N, 8.18; S, 6.24. Found: C, 60.77; H, 6.16; N, 8.14; S, 6.17.

4-*tert*-Butyl-*N*-[5-(3-methoxyphenoxy)-6-(4-oxobutoxy)-2-phenylpyrimidin-4-yl]benzenesulfonamide (6g). Mp 124 °C (hexane/AcOEt); ^{1}H NMR δ 1.31 (9H, s), 1.84–1.98 (2H, m), 2.23 (2H, t, J = 7.0), 3.78 (3H, s), 4.42 (2H, t, J = 6.0), 6.62–6.68 (1H, m), 7.18 (1H, t, J = 8.0), 7.43–7.47 (3H, m), 7.51, 8.08 (4H, A_2B_2, J = 8.8), 8.22–8.27 (2H, m), 9.56 (1H, s). Anal. calcd for $C_{31}H_{33}N_3O_6S$: C, 64.68; H, 5.78; N, 7.30; S, 5.57. Found: C, 64.52; H, 5.76; N, 7.36; S, 5.50.

4-*tert*-Butyl-*N*-[6-(4-oxobutoxy)pyrimidin-4-yl]benzenesulfonamide (8). Mp 185–186 °C (hexane/AcOEt); ^{1}H NMR δ 1.33 (9H, s), 2.07–2.15 (2H, m), 2.62 (2H, t, J = 6.9), 4.42 (2H, t, J = 6.3), 7.53, 8.03 (4H, A_2B_2, J = 9.0), 7.86 (1H, s), 9.82 (1H, s). Anal. calcd for $C_{18}H_{23}N_3O_4S$: C, 57.28; H, 6.14; N, 11.13; S, 8.50. Found: C, 57.10; H, 6.10; N, 11.01; S, 8.43.

***N*-[5-Bromo-6-(4-oxobutoxy)pyrimidin-4-yl]-4-*tert*-butylbenzenesulfonamide (9).** To a solution of **8** (2.0 g, 5.3 mmol) in DMF (10 mL) was added *N*-bromosuccinimide (1.23 g, 6.9 mmol) at 0 °C, and the mixture was stirred for 30 min at the same temperature. Aqueous Na_2SO_3 solution was added, and the mixture was extracted with AcOEt. The organic layer was washed with water, dried and concentrated. The residue was purified by silica gel chromatography eluting with hexane/AcOEt (2/1) to give **9** (1.33 g, 55%): mp 164–165 °C (hexane/AcOEt); ^{1}H NMR δ 1.34 (9H, s), 2.05–2.15 (2H, m), 2.63 (2H, t, J = 7.5), 4.38 (2H, t, J = 6.3), 6.66 (s, 1H), 7.53, 7.85 (4H, A_2B_2, J = 8.4), 8.63 (1H, s), 9.84 (1H, s). Anal. calcd for $C_{18}H_{22}BrN_3O_4S$ 0.2H_2O 0.1AcOEt: C, 47.14; H, 4.99; Br, 17.05; N, 8.96; S, 6.84. Found: C, 47.23; H, 4.81; Br, 16.90; N, 8.98; S, 7.01.

4-Chloro-6-[3-(5,5-dimethyl-1,3-dioxinan-2-yl-propoxy]-5-(3-methoxyphenoxy)pyrimidine (11). Sodium hydride (60% dispersion in mineral oil, 4.65 g, 0.12 mol) was added to a solution of **10**[12] (20.3 g, 0.12 mol) in THF (300 mL) at 0 °C, and the mixture was refluxed for 30 min. After cooling, **4** (30.0 g, 0.11 mol) was added and the reaction mixture was refluxed for 3 h. Water was added, and the reaction mixture was extracted with toluene. The organic layer was washed with water, dried and concentrated. The residue was purified by silica gel chromatography eluting with hexane/AcOEt (4/1 to 2/1) to give **11** as oil (40.2 g, 89%): ^{1}H NMR δ 0.70 (3H, s), 1.16 (3H, s), 1.50–1.60 (2H, m), 1.72–1.86 (2H, m), 3.35 (2H, d, J = 10.6), 3.55 (2H, d, J = 10.6), 3.78 (3H, s), 4.33–4.43 (3H, m), 6.36–6.41 (1H, m), 6.47 (1H, t, J = 2.2), 6.60–6.65 (1H, m), 7.17 (1H, t, J = 8.2), 8.41 (1H, s). Anal. calcd for $C_{20}H_{25}ClN_2O_5$: C, 58.75; H, 6.16; Cl, 8.67; N, 6.85. Found: C, 58.71; H, 6.16; Cl, 8.59; N, 6.93.

4-*tert*-Butyl-*N*-[5-(3-methoxyphenoxy)-6-(4-oxobutoxy)-pyrimidin-4-yl]benzamide (12). Sodium hydride (60% dispersion in mineral oil, 148 mg, 3.70 mmol) was added to a solution of 4-*tert*-butyl-benzamide (654 mg, 3.70 mmol) in DMF (6.5 mL) at 0 °C, and the mixture was stirred at rt for 30 min. Compound **11** (503 mg, 1.23 mmol) in DMF (0.5 mL) was added, and the reaction mixture was stirred at 100 °C for 4 h. Ice-water was added, and the mixture was extracted with AcOEt. The organic layer was washed with water, dried and concentrated. The residue was purified by silica gel chromatography eluting with hexane/AcOEt (2/1) to give benzamide (34 mg, 4.9%), which was immediately used in a following reaction: ^{1}H NMR δ 0.70 (3H, s), 1.16 (3H, s), 1.47–1.57 (2H, m), 1.70–1.81 (2H, m), 3.36 (2H, d, J = 11.4), 3.56 (2H, d, J = 11.4), 3.77 (3H, s), 4.34 (1H, t, J = 4.8), 4.38 (2H, t, J = 6.6), 6.45–6.54 (2H, m), 6.61–6.68 (1H, m), 7.19 (1H, t, J = 8.1), 7.45, 7.70 (4H, A_2B_2, J = 8.7), 8.41 (1H, s), 8.55 (1H, s). To a solution of benzamide (34 mg, 0.06 mmol) from the preceding reaction in formic acid (0.7 mL) was added sodium formate (21 mg, 0.31 mmol), and the mixture was stirred at 70 °C for 1.5 h. Water was added, and the mixture was extracted with AcOEt. The organic layer was washed with water, dried and concentrated. The residue was purified by silica gel chromatography eluting with hexane/AcOEt (2/1 to 1/1) to give **12** as oil (19 mg, 65%): ^{1}H NMR δ 1.32 (9H, s), 1.89–1.98 (2H, m), 2.25 (2H, t, J = 6.9), 3.77 (3H, s), 4.39 (2H, t, J = 6.0), 6.46–6.53 (2H, m), 6.61–6.66 (1H, m), 7.20 (1H, t, J = 8.1), 7.46, 7.72 (4H, A_2B_2, J = 8.1), 8.43 (1H, brs), 8.55 (1H, brs), 9.53 (1H, s). Anal. calcd for $C_{26}H_{29}N_3O_5$ 0.2 H_2O: C, 66.85; H, 6.34; N, 9.00. Found: C, 66.86; H, 6.26; N, 8.97.

4-[6-(4-*tert*-Butylbenzylamino)-5-(3-methoxyphenoxy)-pyrimidin-4-yloxy]butyraldehyde (13). This compound was prepared as oil using a similar procedure described for **12**. ^{1}H NMR δ 1.30 (9H, s), 1.87–1.96 (2H, m), 2.26 (2H, t, J = 7.2), 3.76 (3H, s), 4.32 (2H, t, J = 6.0), 4.64 (2H, d, J = 5.7), 6.37–6.61 (3H, m), 7.13–7.22 (3H, m), 7.30–7.35 (2H, m), 8.19 (1H, s), 9.58 (1H, s). Anal. calcd for $C_{26}H_{31}N_3O_4$ 0.3 H_2O: C, 68.64; H, 7.00; N, 9.35. Found: C, 68.58; H, 7.12; N, 9.26.

4-*tert*-Butyl-*N*-[5-(3-methoxyphenoxy)-6-(4-oxobutoxy)-pyrimidin-4-yl]-*N*-methylbenzenesulfonamide (14). To a solution of **6e** (20 mg, 0.04 mmol) in DMF (0.3 mL) was added K_2CO_3 (6.6 mg, 0.048 mmol) and iodomethane (25 μL, 0.40 mmol), and the mixture was stirred at rt for 12 h. Ice-water and 1 N HCl were added, and the mixture was extracted with AcOEt. The organic layer was washed with water, dried and concentrated. The residue was purified by silica gel chromatography eluting with hexane/AcOEt (2/1 to 1/1) to give **14** as oil (19 mg, 93%): ^{1}H NMR δ 1.34 (9H, s), 1.85–1.98 (2H, m), 2.23 (2H, t, J = 7.0), 3.15 (3H, s), 3.78 (3H, s), 4.37 (2H, t, J = 6.2), 6.41–6.50 (2H, m), 6.60–6.65 (1H, m), 7.17 (1H, t, J = 8.2), 7.50, 7.89 (4H, A_2B_2, J = 8.6), 8.43 (1H, s), 9.59 (1H, s). Anal. calcd for $C_{26}H_{31}N_3O_6S$ 0.1 H_2O: C, 60.59; H, 6.10; N, 8.15; S, 6.22. Found: C, 60.44; H, 6.12; N, 8.03; S, 5.98.

2-{4-[6-(4-*tert*-Butylbenzenesulfonylamino)-5-(3-methoxyphenoxy)pyrimidin-4-yloxy]butylidene}malonic acid dimethyl ester (15b). To a solution of **6e** (142 mg, 0.28 mmol) in EtOH (3 mL) was added dimethy malonate (113 mg, 0.86 mmol) and piperidine (14 μL, 0.14 mmol) at rt. The reaction mixture was stirred at 90 °C for 2 h. Ice-water and 1 N HCl were added, and the mixture was extracted with AcOEt. The organic layer was washed with water, dried and concentrated. The residue was purified by silica gel chromatography eluting with hexane/AcOEt

(2/1) to give **15b** as oil (46 mg, 26%): ^{1}H NMR δ 1.34 (9H, s), 1.65–1.79 (2H, m), 2.05–2.18 (2H, m), 3.75–3.78 (9H, m), 4.27 (2H, t, J = 6.4), 6.31–6.41 (2H, m), 6.59–6.65 (1H, m), 6.86 (1H, t, J = 7.8), 7.15 (1H, t, J = 8.2), 7.51, 8.03 (4H, A_2B_2, J = 8.6), 7.72 (1H, brs), 8.29 (1H, s). Anal. calcd for $C_{30}H_{35}N_3O_9S$: C, 58.71; H, 5.75; N, 6.85; S, 5.23. Found: C, 58.43; H, 5.77; N, 6.87; S, 4.94.

The following compounds were prepared using a similar procedure described for **15b**.

2-{4-[6-(4-*tert*-Butylbenzenesulfonylamino)-5-(3-methoxyphenoxy)pyrimidin-4-yloxy]butylidene}malonic acid (15a). Obtained as oil, ^{1}H NMR δ 1.33 (9H, s), 1.60–1.80 (2H, m), 2.48–2.68 (2H, m), 3.72 (3H, s), 4.21–4.34 (2H, m), 6.28–6.45 (2H, m), 6.52–6.64 (1H, m), 7.12 (1H, t, J = 7.8), 7.25 (1H, brs), 7.52, 7.90 (4H, A_2B_2, J = 8.6), 8.11 (1H, s). Anal. calcd for $C_{28}H_{31}N_3O_9S$: C, 57.43; H, 5.34; N, 7.18; S, 5.48. Found: C, 57.55; H, 5.66; N, 7.29; S, 5.40.

2-{4-[6-(4-*tert*-Butylbenzenesulfonylamino)-5-(3-methoxyphenoxy)pyrimidin-4-yloxy]butylidene}malonic acid di-*tert*-butyl ester (15c). Obtained as oil, ^{1}H NMR δ 1.34 (9H, s), 1.47 (18H, s), 1.63–1.76 (2H, m), 2.02–2.13 (2H, m), 3.78 (3H, s), 4.27 (2H, t, J = 6.3), 6.31–6.41 (2H, m), 6.60–6.66 (1H, m), 6.61 (1H, t, J = 7.8), 7.16 (1H, t, J = 8.1), 7.51, 8.03 (4H, A_2B_2, J = 8.7), 8.29 (1H, s). Anal. calcd for $C_{36}H_{47}N_3O_9S$: C, 61.96; H, 6.79; N, 6.02; S, 4.60. Found: C, 61.86; H, 6.72; N, 6.12; S, 4.66.

***N*-[6-(5-Acetyl-6-oxohept-4-enyloxy)-5-(3-methoxyphenoxy)pyrimidin-4-yl]-4-*tert*-butylbenzenesulfonamide (15d).** Obtained as oil, ^{1}H NMR δ 1.33 (9H, s), 1.70–1.79 (2H, m), 2.02–2.09 (2H, m), 2.22 (3H, s), 2.26 (3H, s), 3.77 (3H, s), 4.29 (2H, t, J = 5.7), 6.32–6.40 (2H, m), 6.50 (1H, t, J = 7.8), 6.61–6.65 (1H, m), 7.16 (1H, t, J = 8.1), 7.72 (1H, brs), 7.51, 8.03 (4H, A_2B_2, J = 8.7), 8.29 (1H, s). Anal. calcd for $C_{30}H_{35}N_3O_7S$ 0.3 H_2O: C, 61.38; H, 6.11; N, 7.16; S, 5.46. Found: C, 61.34; H, 6.20; N, 7.16; S, 5.33.

{4-[6-(4-*tert*-Butylbenzenesulfonylamino)-5-(3-methoxyphenoxy)pyrimidin-4-yloxy]butylidene}-2-cyanoacetic acid ethyl ester (15e). Mp 124 °C; ^{1}H NMR δ 1.30–1.39 (3H, m), 1.35 (9H, s), 1.75–1.85 (2H, m), 2.29–2.37 (2H, m), 3.79 (3H, s), 4.27–4.34 (4H, m), 6.35–6.43 (2H, m), 6.62–6.67 (1H, m), 7.18 (1H, t, J = 8.1), 7.46 (1H, t, J = 9.0), 7.66 (1H, s), 7.53, 8.05 (4H, A_2B_2, J = 9.0), 8.30 (1H, s). Anal. calcd for $C_{30}H_{34}N_4O_7S$: C, 60.59; H, 5.76; N, 9.42; S, 5.39. Found: C, 60.45; H, 5.80; N, 9.32; S, 5.36.

4-*tert*-Butyl-*N*-[6-(4-hydroxyiminobutoxy)-5-(3-methoxyphenoxy)pyrimidin-4-yl]benzenesulfonamide (16a). To a solution of **6e** (200 mg, 0.40 mmol) and hydroxylamine hydrochloride (36 mg, 0.52 mmol) in EtOH (1 mL) was added pyridine (42 μL, 0.52 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 30 min. Ice-water and 1 N HCl were added, and the mixture was extracted with AcOEt. The organic layer was washed with water, dried and concentrated. The residue was purified by silica gel chromatography eluting with hexane/AcOEt (1/1) to give **16a** as oil (77 mg, 38%): ^{1}H NMR δ 1.29 (9H, s), 1.55–1.70 (2H, m), 1.86–2.12 (2H, m), 3.72 (3H, s), 4.25 (2H, t, J = 6.3), 6.28–6.36 (1H, m), 6.42 (1H, t, J = 2.4), 6.52 (t, J = 5.7), 6.60–6.68 (1H, m), 7.17 (t, J = 5.7), 7.13–7.14 (1H, m), 7.61, 7.91 (4H, A_2B_2, J = 8.4), 8.27 (1H, s). Anal. calcd for $C_{25}H_{30}N_4O_6S$ 0.2 H_2O: C, 58.09; H, 5.96; N, 10.75; S, 6.15. Found: C, 57.96; H, 5.84; N, 10.64; S, 6.04.

4-*tert*-Butyl-*N*-[6-(4-ethoxyiminobutoxy)-5-(3-methoxyphenoxy)pyrimidin-4-yl]benzenesulfonamide (16b). This compound was prepared as oil using a similar procedure described for **16a**. ^{1}H NMR δ 1.19 (3H, t, J = 7.2), 1.34 (9H, s), 1.67–1.78 (2H, m), 2.14 (2H, dt, J = 5.4, 8.1), 3.76 (3H, s), 4.04 (2H, q, J = 7.2), 4.28 (2H, t, J = 6.3), 6.35 (1H, dt, J = 2.4,8.4), 6.41 (1H, t, J = 2.4), 6.47 (1H, t, J = 5.4), 6.63 (1H, dt, J = 2.4, 8.4), 7.16 (1H, t, J = 8.4), 7.52, 8.04 (4H, A_2B_2, J = 9.0), 7.66 (1H, s), 8.29 (1H, s). Anal. calcd for $C_{27}H_{34}N_4O_6S$ 0.1 H_2O: C, 59.56; H, 6.33; N, 10.29; S, 5.89. Found: C, 59.45; H, 6.36; N, 10.26; S, 5.94.

4-*tert*-Butyl-*N*-(5-(3-methoxyphenoxy)-6-{4-[(1-phenylmethanoyl)hydrazono]butoxy}pyrimidin-4-yl)benzenesulfonamide (16e). To a solution of **6e** (567 mg, 1.13 mmol) in EtOH (9 mL) was added benzoylhydrazine (186 mg, 1.36 mmol) at rt, and the reaction mixture was stirred at 90 °C for 1 h. Ice-water and 1 N HCl were added, and the mixture was extracted with AcOEt. The organic layer was washed with water, dried and concentrated. The residue was purified by silica gel chromatography eluting with $CHCl_3$/MeOH (20/1) to give **16e** (110 mg, 26%): mp 155–156 °C (AcOEt); ^{1}H NMR δ 1.33 (9H, s), 1.74–1.88 (2H, m), 2.10–2.24 (2H, m), 3.72 (3H, s), 4.32 (2H, t, J = 6.3), 6.30–6.39 (2H, m), 6.57–6.62 (1H, m), 7.12 (1H, t, J = 8.1), 7.41 (2H, t, J = 6.9), 7.45–7.55 (1H, m), 7.50, 8.01 (4H, A_2B_2, J = 8.4), 7.77 (2H, d, J = 7.2), 8.26 (1H, s), 9.12 (1H, s). Anal. calcd for $C_{32}H_{35}N_5O_6S$ 0.5 H_2O: C, 61.33; H, 5.79; N, 11.17; S, 5.12. Found: C, 61.44; H, 5.74; N, 11.04; S, 5.09.

The following compounds were prepared using a similar procedure described for **16e**.

4-*tert*-Butyl-*N*-[5-(3-methoxyphenoxy)-6-(4-semicabazonobutoxy)pyrimidin-4-yl]benzenesulfonamide (16c). Obtained as oil, ^{1}H NMR δ 1.33 (9H, s), 1.70–1.79 (2H, m), 1.95–2.04 (2H, m), 3.74 (3H, s), 4.29 (2H, t, J = 6.0), 6.33–6.36 (1H, m), 6.40–6.42 (1H, m), 6.59–6.62 (1H, m), 6.90 (1H, t, J = 4.8), 7.13 (1H, t, J = 8.4), 7.50, 8.02 (4H, A_2B_2, J = 9.0), 8.26 (1H, s), 9.16 (1H, s). Anal. calcd for $C_{26}H_{32}N_6O_6S$ 0.3 H_2O: C, 55.56; H, 5.85; N, 14.95; S, 5.71. Found: C, 55.62; H, 5.55; N, 14.76; S, 5.76.

N-{6-[4-(Acetylhydrazono)butoxy]-5-(3-methoxyphenoxy)pyrimidin-4-yl}-4-tert-butylbenzenesulfonamide (16d). Obtained as oil, ^{1}H NMR δ 1.34 (9H, s), 1.78–1.86 (2H, m), 2.00–2.10 (2H, m), 2.17 (3H, s), 3.78 (3H, s), 4.33 (2H, t, J = 6.3), 6.34–6.41 (2H, m), 6.62–6.66 (1H, m), 6.83 (1H, t, J = 5.4), 7.18 (1H, t, J = 8.1), 7.52, 8.04 (4H, A_2B_2, J = 8.7), 8.17 (1H, s), 8.29 (1H, s). Anal. calcd for $C_{27}H_{33}N_5O_6S$ 0.3 H_2O: C, 57.80; H, 6.04; N, 12.48; S, 5.72. Found: C, 57.67; H, 5.92; N, 12.31; S, 5.68.

4-*tert*-Butyl-*N*-(5-(3-methoxyphenoxy)-6-{4-[(1-pyridin-4-ylmethanoyl)hydrazono]butoxy}pyrimidin-4-yl)benzenesulfonamide (16f). Mp 118–119 °C; ^{1}H NMR δ 1.33

(9H, s), 1.70–1.90 (2H, m), 2.02–2.24 (2H, m), 3.72 (3H, s), 4.30 (2H, t, $J = 5.6$), 6.26–6.38 (2H, m), 6.54–6.63 (1H, m), 7.12 (1H, t, $J = 8.2$), 7.51–7.72 (3H, m), 7.50, 8.00 (4H, A_2B_2, $J = 8.6$), 8.25 (1H, s), 8.67 (1H, s). Anal. calcd for $C_{31}H_{34}N_6O_6S$ 0.3 H_2O: C, 59.66; H, 5.59; N, 13.47; S, 5.14. Found: C, 59.87; H, 5.61; N, 13.16; S, 4.97.

***N*-{6-[4-(Benzenesulfonylhydrazono)butoxy]-5-(3-methoxyphenoxy)pyrimidin-4-yl}-4-*tert*-butylbenzenesulfonamide (16g).** Obtained as oil, ^{1}H NMR δ 1.33 (9H, s), 1.65–1.76 (2H, m), 1.93–2.04 (2H, m), 3.74 (3H, s), 4.16 (2H, t, $J = 5.7$), 6.27–6.35 (2H, m), 6.58–6.62 (1H, m), 6.87 (1H, t, $J = 5.1$), 7.12 (1H, t, $J = 8.1$), 7.36–7.90 (6H, m), 7.52, 8.04 (4H, A_2B_2, $J = 8.7$), 8.25 (1H, s). Anal. calcd for $C_{31}H_{35}N_5O_7S_2$ 0.2 H_2O: C, 56.64; H, 5.43; N, 10.65; S, 9.76. Found: C, 56.61; H, 5.41; N, 10.53; S, 9.56.

Molecular modeling

Molecular modeling and other graphical manipulation were performed using the SYBYL 6.6.1 software package.[15] A three-dimensional model of compound **1a** was built from the crystal structure of hydroxymethyl derivative of **1a** (R = CH_2OH in Scheme 1) by replacing the terminal hydroxymethyl group with an aldehyde group. The points used for fitting the modeled **1a** on the crystal structure of **6e** were carbon 4 in the phenyl ring of the benzenesulfonamide group, the N and H atoms of the sulfonamide group, and the C and O atoms of the aldehyde group.

Receptor binding studies. ET_A: Rat aortic smooth muscle A7r5 cells expressing only ET_A receptors were obtained from Dainippon Seiyaku (Osaka) and cultured in Dulbecco's modified Eagle's medium (GIBCO, Grand Island, NY) supplemented with 10% fetal calf serum (GIBCO), 10 mM HEPES buffer (pH 7.4), 50 μg/mL of streptomycin, and 50 U/mL of penicillin G (GIBCO) in a 5% CO_2-95% air incubator at 37 °C in 48-well culture plates. After 3 to 5 days, the culture medium was aspirated and the cells were washed twice with ice-cold HEPES (20 mM)-buffered Hanks' solution (pH 7.4). Each well was incubated with 8.3 pM [^{125}I]endothelin-1 in 0.2 mL of ice-cold HEPES-buffered Hanks' solution containing 0.1 mM phenylmethylsulfonyl fluoride (PMSF), 10 μg/mL aprotonin, 10 μg/mL leupeptin, pepstatatin A, 250 μg/mL bacitracin, and 10 μg/mL soybean trypsin inhibitor in the absence and presence of various concentrations of compounds. Equilibrium binding studies were performed at 37 °C for 60 min. The incubation was terminated by rapid removal of the incubation medium and addition of 0.25 mL of ice-cold HEPES-buffered Hanks' solution. Free ligand was removed by washing the intact attached cells with ice-cold HEPES-buffered Hanks' solution. The cells were then resolved in 0.1 N NaOH and transferred to a test tube, then the radioactivity was counted. Nonspecific binding was determined in the presence of 0.1 μM endothelin-1.

ET_B: for ET_B receptor binding assay, we employed COS-7 cells transfected with porcine ET_B receptors. After the cells were washed with HEPES (20 mM)-buffered Hanks' solution (pH 7.4), each well was incubated with 25 pM [^{125}I]endothelin-3 in 0.1 mL of HEPES-buffered Hanks' solution containing protease inhibitors in the absence and presence of various concentrations of compounds. Equilibrium binding studies were performed at 37 °C for 60 min. The incubation was terminated by filtering through Whatman GF/C glass fiber filters. The filters were washed 4 times with 2.5 mL each of 50 mM Tris–HCl (pH 7.4), and the radioactivity was counted. Nonspecific binding was determined in the presence of 0.1 μM endothelin-3.

Pharmacokinetic analysis

The pharmacokinetics of **6b** and **6e** were evaluated in Jcl-Sprague–Dawley rats. The test compound was formulated as a 2.5 mg/mL solution in an *N*,*N*-dimethylacetamide : PEG400 : saline (10:50:40, by volume) for the intravenous route and as a 15.0 mg/mL solution/suspension in 0.5% methyl cellulose/saline for the oral route. Three individual rats were dosed by slow bolus injection into the jugular vein at 5 mg/kg (2 mL/kg) or by gavage at 30 mg/kg (2 mL/kg). Serial blood samples (200 μL) were taken from the jugular vein using a heparin-coated syringe at 0.03, 0.17, 0.5, 1, 2, 4, 8, and 24 h postdose for the intravenous groups and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 24 h postdose for the oral groups. Plasma samples obtained from blood by centrifugation were analyzed by reverse-phase HPLC following methanol precipitation of the plasma proteins. Assuming dose proportionality and correcting for the difference in dosing, comparison of the area under the curve (AUC) value after an oral dosing with that obtained after an intravenous dose provided an estimate of the bioavailability (BA).

In vivo antagonistic activities to ET-1 induced responses

Male Wistar rats were anesthetized with 2% halothane. Polyethylene catheters (SP31; Natsume Seisakusho, Japan) were implanted in the femoral artery and vein, which were passed subcutaneously and held at the back of the neck. After the rats were allowed to recover overnight, blood pressure (mm Hg) was measured under conscious conditions via a catheter inserted into the femoral artery by connection to a pressure transducer (TP-200T; Nihon Kohden). ET-1 (0.1 nmol/kg) was administered via the femoral vein after the blood pressure had been stable for about 1 h. We first confirmed the effects of the ET-1 treatment on mean artery blood pressure (MABP) in conscious rats. After the ET-1 treatment, compound **6e** (30 mg/kg) was administered orally. Next, ET-1 (0.1 nmol/kg) was administered from 1 to 5 h at 1-h intervals, and the ET-1 induced responses on MABP were monitored repeatedly.

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