Potent and Selective ET-A Antagonists. 2. Discovery and Evaluation of Potent and Water Soluble *N*-(6-(2-(Aryloxy)ethoxy)-4-pyrimidinyl)sulfonamide Derivatives

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In the preceding article,[1] we outlined the discovery and structure−activity relationship of a potent and selective ET_A receptor antagonist **1** and its related compounds. Metabolites of **1** having potent selective ET_A receptor antagonist activity were identified. This study suggested the metabolic pathways of **1** were considerably affected by species. Consequently, structural modification of **1** intended to improve the complexity of the metabolic pathway, and water solubility was performed. The subsequent introduction of a hydroxyl group into the *tert*-butyl moiety of **1** led to the discovery of our new clinical candidate, **6b**, which showed a higher water solubility, a uniform metabolic pathway among species, and very high affinity and selectivity for the human ET_A receptor (K_i for ET_A receptor: 0.015 ± 0.004 nM; for ET_B receptor: 41 ± 21 nM).

Introduction

In the preceding article,[1] we described the preparation and evaluation of a potent ET_A-selective inhibitor, 4-*tert*-butyl-*N*-(6-(2-((5-bromo-2-pyrimidinyl)oxy)ethoxy)-5-(4-methylphenyl)-4-pyrimidinyl)benzenesulfonamide (**1**), exhibiting extremely high affinity and selectivity for the cloned human ET_A receptor (K_i for human ET_A: 0.0042 ± 0.0038 nM; for ET_B: 130 ± 50 nM). However, it showed low bioavailability resulting from its lower water solubility (0.0016 mg/mL at pH 7.5) and a significant difference of metabolic pathways among animal species.

It is known that lipophilic compounds are converted to the hydrophilic forms by metabolic reactions to be excreted into urine or bile, and some active metabolites are often better therapeutic candidates than the parent compounds[2] from the standpoint of water solubility and pharmacokinetic characteristics. Therefore, it was expected that some of the more hydrophilic derivatives of **1**, including the metabolites of **1**, might show good water solubility and that they would show a smaller difference in metabolic pathways among animal species than did **1** because of the higher oxidized functional groups, such as carboxylic acid and hydroxyl groups, in the former. The functional groups would reduce the number of sites susceptible to metabolism and direct the metabolic pathway. On the basis of the expectation, we identified the metabolites and synthesized more hydrophilic compounds than **1**. As shown in Figure 1, carboxylic acid and hydroxyl groups were introduced into each end of the three side chains on the nucleus pyrimidine of **1** and the 5-(methylthio)pyrimidin-2-yl derivative **2**, which showed extremely high antagonistic activity for the ET_A receptor.[1]

We here report a study of the metabolic pathway of **1** over species and the discovery of a potent and highly water soluble ET_A-selective antagonist, **6b**.

Chemistry

A structural modification of **1** intended to improve its bioavailability by increasing its water solubility was performed in the following steps: (1) replacement of the bromo group on the side chain pyrimidine with carboxylic acid or hydroxymethyl groups (compounds **3a**,**b**); (2) conversion of the methyl moiety into the two groups above in the tolyl group (compounds **4a**,**b** and **5b**); and (3) conversion of the methyl moiety into the two groups above in the *tert*-butyl group in the sulfonamide part (compounds **6a**,**b**). Methods of introduction of carboxylic acid and alcohol into the side chain pyrimidine (compounds **3a**,**b**) and the tolyl group (compounds **4a**,**b** and **5b**) are shown in Scheme 1. 5-Pyrimidinecarboxylic acid moiety was introduced into the reported compound **7**[3] by the method described in the preceding article[1] to afford the intended compound **3a**. Formylation at the 5-position of the side chain pyrimidine of **1** and following reduction to alcohol gave the hydroxymethyl derivative **3b**. Palladium-catalyzed cross-coupling of the 5-bromopyrimidine derivative **10**, prepared from **9** by the method described in the preceding article,[1] with methyl 4-tributylstannylbenzoate[4] and 4-tributylstannybenzaldehyde diethyl acetal[5] afforded the methyl ester **11** and the diethyl acetal **12**, respectively, which were converted to the carboxylic acid **4a** by alkali hydrolysis and to the alcohol **4b** by treatment with acid and subsequent reduction. Palladium-catalyzed cross-coupling of **9** with 4-tributylstannylbenzaldehyde diethyl acetal, followed by introduction of a 5-bromopyrimidinyl group, deacetalization, and reduction of the aldehyde, afforded **5b**.

Introduction of carboxylic acid and alcohol into the sulfonamide moiety (compounds **6a**,**b**) was performed

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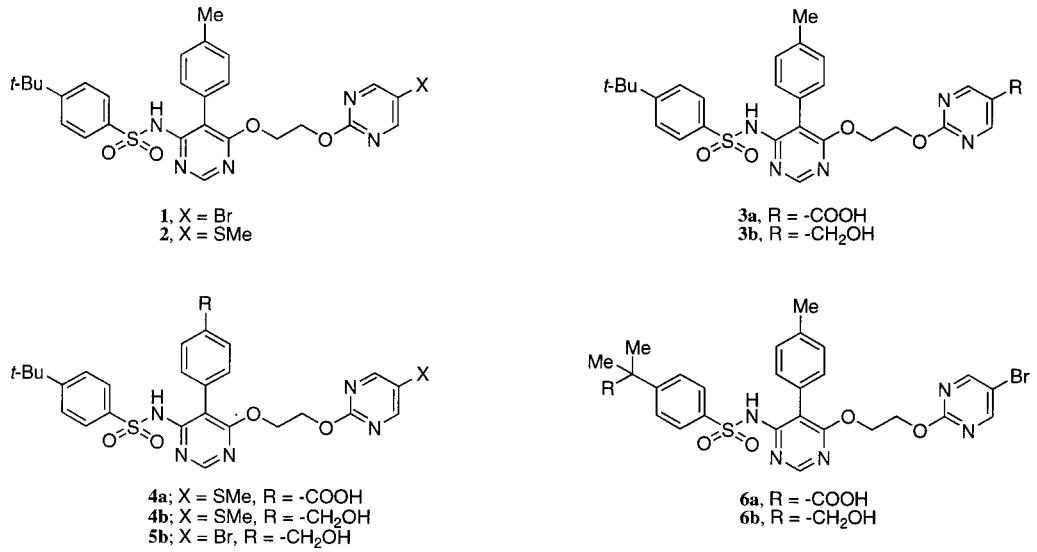
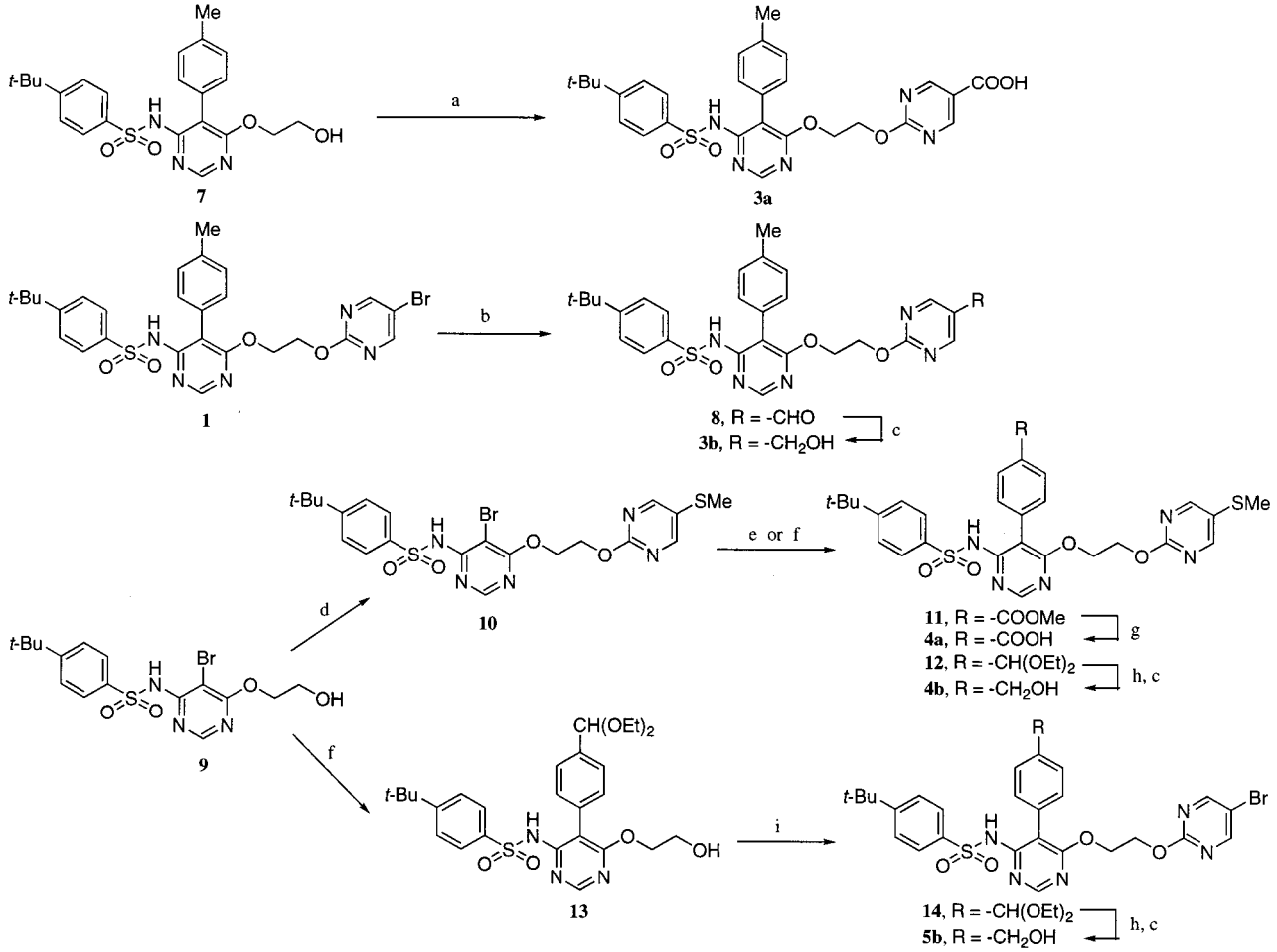


Figure 1. Structures of compound **1** and designed compounds.

Scheme 1. Introduction of Carboxylic Acid and Alcohol into the Side Chain Pyrimidine and the Tolyl Group[a]

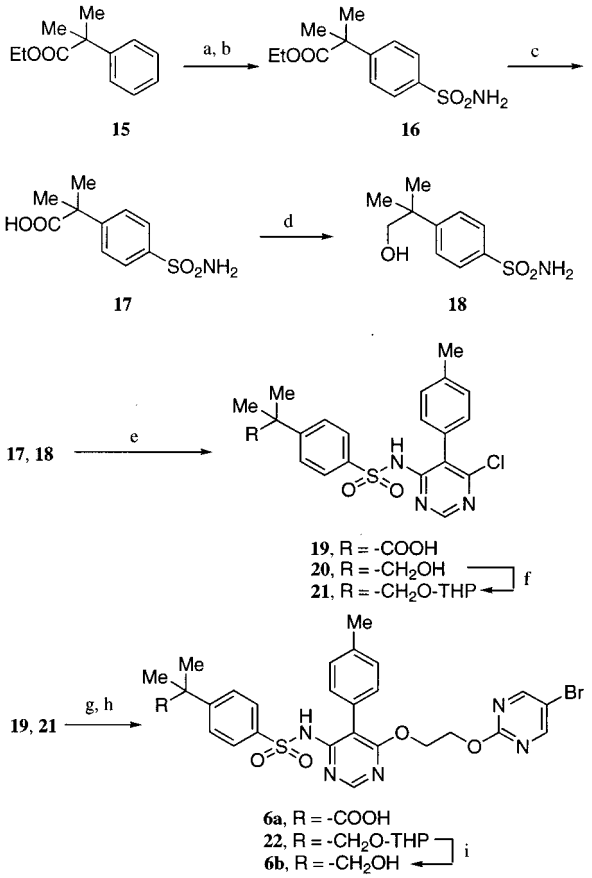


[a] Reagents: (a) NaH, 2-chloro-5-pyrimidinecarboxylic acid; (b) *n*-BuLi, *N*,*N*-dimethylformamide; (c) $NaBH_4$; (d) NaH, 2-chloro-5-methylthiopyrimidin; (e) methyl 4-tributylstannylbenzoate, $PdCl_2(PPh_3)_2$, PPh_3, CuBr, 2,6-di-*tert*-butylcresol; (f) 4-tributylstannylbenzaldehyde diethyl acetal, $PdCl_2(PPh_3)_2$, PPh_3, CuBr, 2,6-di-*tert*-butylcresol; (g) aq NaOH; (h) *p*-toluenesulfonic acid; (i) NaH, 5-bromo-2-chloropyrimidin.

as shown in Scheme 2. The sulfonamides **17** and **18**, synthesized from ethyl 1-methyl-1-phenylpropionate (**15**), were reacted with 4,6-dichloro-5-(4-methylphenyl)-pyrimidine[1] in the presence of K_2CO_3 to afford **19** and **20**, respectively. Protection of the alcohol of **20** with a tetrahydropyranyl group provided **21**. The standard transformations[1] led to **6a** and **6b**.

The diol form **26**, one of the metabolites of **1** (mentioned below), was prepared as in Scheme 3. Acetylation of **6b** and followed by bromination of the methyl moiety

Scheme 2. Introduction of Carboxylic Acid and Alcohol into the Sulfonamide Part[a]



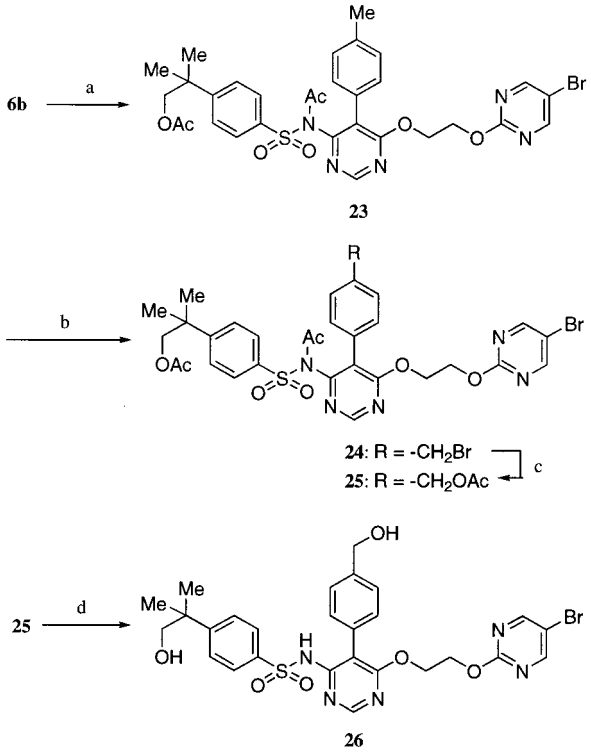
[a] Reagents: (a) $ClSO_3H$, $SOCl_2$; (b) NH_4OH; (c) aq NaOH; (d) $NaBH_4$, $BF_3{\cdot}Et_2O$; (e) 5-*p*-tolyl-4,6-dichloropyrimidine, K_2CO_3; (f) 3,4-dihydro-2*H*-pyran, 10-camphorsulfonic acid; (g) NaH, ethylene glycol; (h) NaH, 5-bromo-2-chloropyrimidine; (i) *p*-toluenesulfonic acid.

in the tolyl group with *N*-bromosuccinimide (NBS) in the presence of a catalytic amount of azobis(isobutyronitrile) (AIBN) in CCl_4 afforded the compound **24**. The bromo group of **24** was substituted by an acetyloxy group (compound **25**), and all the acetyl groups were removed by alkali hydrolysis to give the diol derivative **26**.

Results and Discussion

ESI mass chromatograms of unchanged **1** and its metabolites in the plasma 4 h after oral administration of **1** (0.3 mg/kg) to rats and dogs are shown in Figure 2. The $[M+H]^+$ peaks of the compounds were observed at *m*/*z* 598 (unchanged form), *m*/*z* 614 (M1), *m*/*z* 614 (M2), *m*/*z* 628 (M3), and *m*/*z* 630 (M4). The structures of these metabolites were identified as being in the hydroxylated form at the methyl group of the tolyl moiety (M1, **5b**), in the hydroxylated and carboxylic acid form at the *tert*-butyl groups (M2, **6b** and M3, **6a**), and in the dihydroxylated form at the *tert*-butyl and the methyl part of the tolyl moiety (M4, **26**) by comparison with the synthesized authentic samples using LC-MS/MS. As shown in Figure 2, the hydroxylated forms M1 and M2 were found to be major metabolites in plasma. In rats, hydroxylation at the *tert*-butyl group seemed to be dominant; the hydroxylation of the tolyl group seemed to be slightly faster than that of the *tert*-butyl in dogs (data not shown).

Scheme 3. Synthetic Route of the Diol Form, One of the Metabolites of **1**[a]



[a] Reagents: (a) Ac_2O, pyridine; (b) NBS, AIBN, CCl_4; (c) AcOK, NaI; (d) aq NaOH.

The metabolic experiment in vivo was supported by a metabolic study in vitro using hepatic microsomal fractions of several animals, including humans (Figure 3). Metabolic rates from **1** to M1 were 48 ± 13, 176 ± 53, and 64 ± 49 ng/mg protein/min in rats, dogs, and humans, respectively, and those from **1** to M2 were calculated as 67 ± 15, 49 ± 7, and 60 ± 15 ng/mg protein/min, respectively. The level of the dihydroxylated form (M4) was below the detectable limit. From these results, it was estimated that the main metabolic pathways in dogs and rats were hydroxylation at the tolyl and at the *tert*-butyl moiety, respectively. The proposed metabolic pathway of **1** is shown in Figure 4.

Table 1 shows the binding affinities of the synthesized derivatives **3a,b**−**6a,b** for the ET_A receptor. Introduction of carboxylic acid drastically diminished the affinity (**3a**, **4a**, **6a**). On the other hand, introduction of a hydroxymethyl group, especially **3b** or **6b**, maintained the high affinity for the ET_A receptor (**3b**: IC_{50} = 2.6 pM; **6b**: IC_{50} = 6.2 pM). The binding potency of Na salts of **3b** and **6b** on ET receptor subtypes are shown in Table 2 (ET_A on rat A10 cells vs ET_B on human GH cells). Both of these compounds showed high ET_A-selectivity. Since Na salt of **6b** exhibited higher water solubility (5.8 mg/mL at pH 7.5 and more than 120 mg/mL at pH 9.5), the potency on the human cloned ET_A and ET_B receptor subtypes expressed on the CHO cell membrane was evaluated[6] (Table 2). Compound **6b** showed very high affinity and selectivity for the human ET_A receptor (K_i = 0.015 ± 0.004 nM for human ET_A receptor and K_i = 41 ± 21 nM for human ET_B receptor). The K_i values of bosentan were 81 ± 26 nM for human ET_A and 140 ± 26 nM for human ET_B.[6] Because these

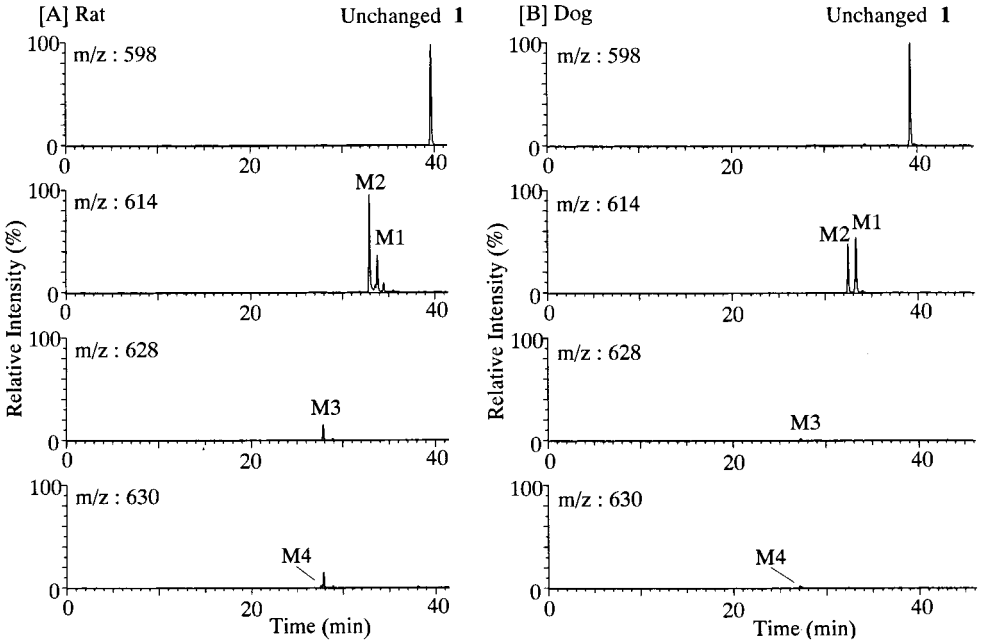


Figure 2. ESI mass chromatograms of metabolites in plasma from rats [A] and dogs [B] 4 h after oral administration of compound **1** (0.3 mg/kg).

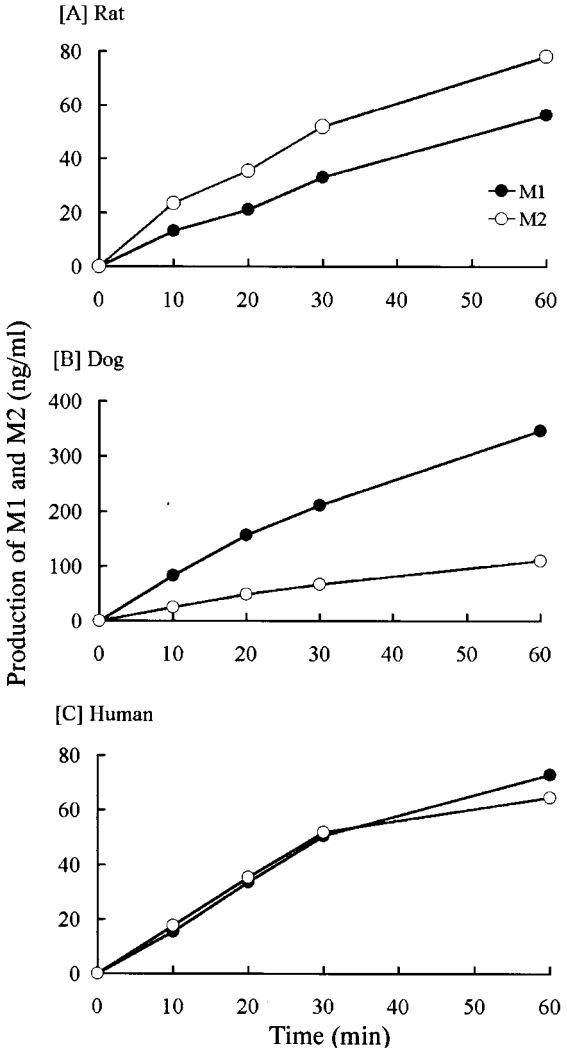


Figure 3. Time course of the hydroxyl metabolites M1 (●) and M2 (○) from compound **1** in rat [A], dog [B], and human liver microsomes [C]. All data points were from a single experiment.

Table 1. Binding Affinity of Carboxylic Acid and Hydroxymethyl Derivatives for the ET_A Receptor

compd	IC_{50} (nM)[a]	mp (°C)	mol. formula[b]
3a	>10	222−225	$C_{28}H_{29}N_5O_6S \cdot 0.6H_2O$
4a	>10	226−227	$C_{28}H_{29}N_5O_6S_2 \cdot H_2O$
6a	1.4	130−137 (dec)	$C_{27}H_{26}BrN_5O_6S \cdot CH_2Cl_2$
3b	0.0026	172−173	$C_{28}H_{31}N_5O_5S$
4b	0.040	172−173	$C_{28}H_{31}N_5O_5S_2$
5b	0.040	194−195	$C_{27}H_{28}BrN_5O_5S$
6b	0.0062	179.5−180	$C_{27}H_{28}BrN_5O_5S$
1	<0.001		
2	<0.001		
bosentan	7.5		

[a] Inhibition of [^{125}I]-ET-1 binding in vitro to ET_A receptors in porcine aortic membrane. Values are from a single experiment. [b] Analyses (C, H, N) were within ±0.4% of theoretical values.

results indicated that **6b** was preferable to **1**, **6b** was further studied.

The metabolism and pharmacokinetics of **6b** were investigated in rats. The main metabolite of **6b** was in carboxylic acid form (M3), the minor one was in dihydroxylated form (M4) in rats,[7] and the species difference of metabolic pathway was not observed between rats and dogs (data not shown). The bioavailability after oral administration of **6b** (0.3 mg/kg) was calculated as 60% higher than that of **1**.[7] The plasma concentration of **6b** declined with an elimination half-life ($t_{1/2}$) of 1.8 h (1−8 h after dosing),[7] but a long duration of action was observed in vivo.[6] From the measurement of concentration in target tissues after oral administration, it was considered that the pharmacological effects of **6b** were not mirrored in the concentration in plasma but rather in the concentration in tissues.[8]

In previously published pharmacological studies, **6b**, code named TA-0201, inhibited the ET-1-induced contraction of the isolated endothelium-denuded rabbit pulmonary artery and also the pressor response to exogenous big ET-1 in the anesthetized rats in a dose-dependent manner after both iv and po administration.[6] In cardiomyopathic hamsters with chronic heart failure, chronic ET_A receptor blockade by **6b** greatly ameliorated

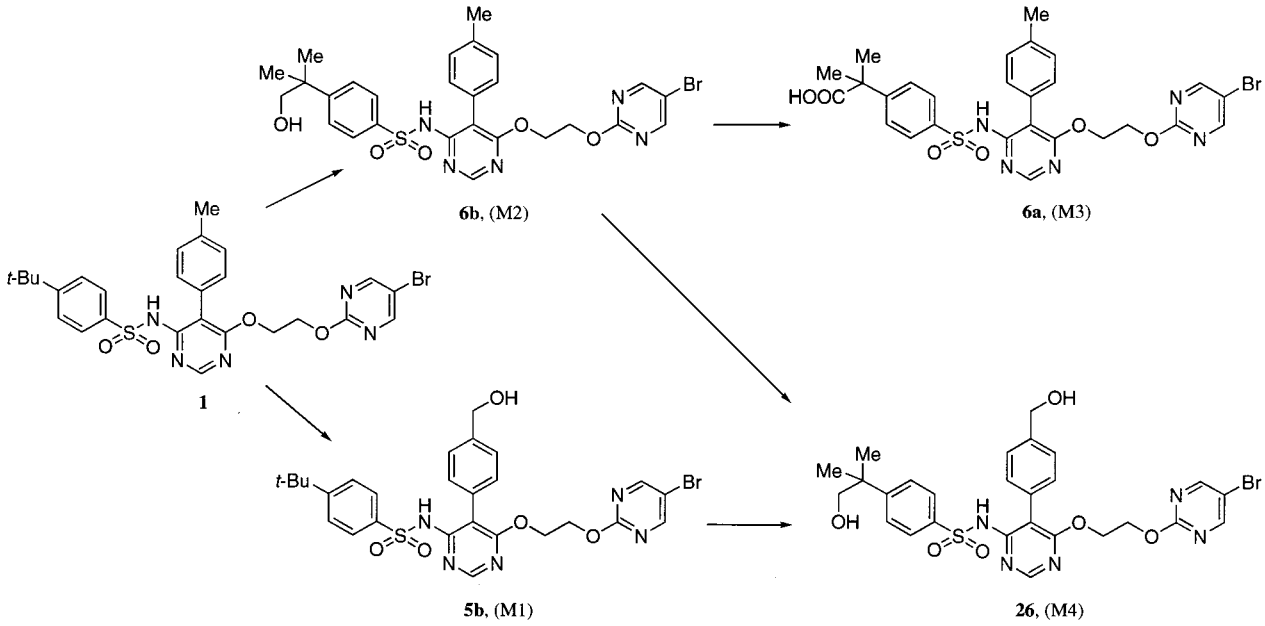


Figure 4. Proposed metabolic pathway of compound **1**.

Table 2. Binding Potencies of **3b**, **6b**, **1**, and Bosentan on ET Receptor Subtypes

compd	ET_A (A 10 cell) IC_{50} (nM)[a]	ET_B (GH cell) IC_{50} (nM)[b]	human ET_A K_i (nM)[c]	human ET_B K_i (nM)[c]	ET_A-selectivity[d]
3b·Na salt	0.034 ± 0.009	31 ± 3			
6b·Na salt	0.33 ± 0.09	8.3 ± 0.9	0.015 ± 0.004[e]	41 ± 21[e]	2700
1	0.039 ± 0.011	38 ± 3	0.0042 ± 0.0038[f]	130 ± 50[f]	29000
bosentan			81 ± 26[e]	140 ± 26[e]	1.7

[a] IC_{50} for inhibition of specific binding of [^{125}I]-ET-1 (20 pM) to rat A 10 cells which express ET_A receptors ($n = 3$, means ± SEM). [b] IC_{50} for inhibition of specific binding of [^{125}I]-ET-1 (20 pM) to human GH cells which express ET_B receptors ($n = 3$, means ± SEM). [c] K_i values on [^{125}I]-ET-1 binding to human cloned ET receptors expressed on CHO cell membrane, means ± SEM. [d] IC_{50} for human ET_B/IC_{50} for human ET_A. [e] $n = 6$. [f] $n = 3$.

the cardiac dysfunction and improved the survival rate.[9] Further, oral administration of **6b** to hypoxic rats inhibited the hypoxia-induced right ventricular hypertrophy.[10]

Conclusion

Modification of **1** to improve its lower water solubility and metabolic problems led to a new potent and ET_A-selective antagonist **6b**. This orally active ET_A antagonist is so potent and selective that it is expected to constitute a new class of drugs for treatment of various cardiovascular diseases, such as chronic heart failure. The clinical trial of **6b** is now underway.

Experimental Section

All melting points were determined on a Büchi 535 digital melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on an Analect RFX-65 or an Analect FX-6200 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL JNM-FX200, a Varian Gemini 300 spectrometer, or a JEOL JNM-GSX400. Mass spectra were recorded on a JEOL JMS-HX100 mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400 C, H, N analyzer and a HITACHI Z-7000 atomic absorption spectrophotometer for Na, and values were within ±0.4% of the calculated values.

2-Chloropyrimidine-5-carboxylic Acid. To a solution of 5-bromo-2-chloropyrimidine[11,12] (3.00 g, 15.5 mmol) in dry THF (200 mL) was added *n*-BuLi (1.63 M in hexane) (10.0 mL, 16.3 mmol) dropwise over 10 min at −90 °C, and the mixture was stirred at the same temperature for 15 min. The solution was poured onto solid carbon dioxide, and the whole was allowed to warm to −20 °C, acidified with 10% aqueous HCl, and extracted three times with $CHCl_3$. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was separated by silica gel column chromatography ($CHCl_3$:MeOH, 100:1, v/v then $CHCl_3$:MeOH:AcOH, 30:1:1, v/v) and recrystallized from CH_2Cl_2−*i*-Pr_2O to afford 2-chloropyrimidine-5-carboxylic acid as colorless solid (640 mg, 26%): mp 126−131 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 14.01 (1H, br s), 9.16 (2H, s); IR (Nujol) cm^{-1} 3330, 1700, 1570, 1545, 1460; EI-MS *m*/*z* 158 (M^+), 141, 130, 123.

2-(2-((6-(4-*tert*-Butyl)benzenesulfonamido-5-(4-methylphenyl)-4-pyrimidinyl)oxy)ethoxy)pyrimidine-5-carboxylic Acid (3a). To a stirred solution of 4-*tert*-butyl-*N*-(6-(2-hydroxyethoxy)-5-(4-methylphenyl)-4-pyrimidinyl)-benzenesulfonamide[3] (**7**) (840 mg, 1.90 mmol) in dry THF (10 mL)−dry *N*,*N*-dimethylacetamide (DMAc) (2 mL) was added 60% NaH in mineral oil dispersion (380 mg, 9.50 mmol). After 10 min, 2-chloropyrimidine-5-carboxylic acid (453 mg, 2.86 mmol) was added, and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with aqueous NH_4Cl and 10% aqueous HCl, extracted with EtOAc. The organic extracts was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:AcOEt, 3:1, v/v then $CHCl_3$:MeOH, 50:1−10:1, v/v), and recrystallized from EtOH−EtOAc to afford **3a** as colorless crystalline powder (199 mg, 19%): mp 222−225 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.95 (2H, s), 8.32 (1H, s), 7.81−7.90 (2H, m), 7.52−7.59 (2H, m), 7.07−7.16 (4H, m), 4.57−4.69 (4H, m), 2.32 (3H, s), 1.29 (9H, s); IR (Nujol) cm^{-1} 3380, 1705, 1595, 1565, 1460, 1450, 1430, 1410; FAB-MS *m*/*z* 564 ($M+H^+$), 424, 307, 257, 154; Anal. ($C_{28}H_{29}N_5O_6S$·0.6H_2O) C, H, N.

4-*tert*-Butyl-*N*-(6-(2-((5-formyl-2-pyrimidinyl)oxy)-ethoxy)-5-(4-methylphenyl)-4-pyrimidinyl)benzenesulfonamide (8). To a stirred solution of 4-*tert*-butyl-*N*-(6-

(2-((5-bromo-2-pyrimidinyl)oxy)ethoxy)-5-(4-methylphenyl)-4-pyrimidinyl)benzenesulfonamide[1] (**1**) (700 mg, 1.17 mmol) in dry THF (15 mL) was added 1.6 M *n*-BuLi in hexane (1.46 mL, 2.34 mmol) dropwise over 10 min at −78 °C. After 15 min, DMF (3.9 mL, 50.4 mmol) was added dropwise over 50 min, and the mixture was stirred at −78 °C for 15 min. Aqueous NH_4Cl (3 mL) was added dropwise, and the mixture was allowed to warm to room temperature over 1 h, acidified with aqueous HCl, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was separated by silica gel column chromatography ($CHCl_3$:EtOAc, 100:1−30:1, v/v) to afford **8** as colorless crystalline powder (198 mg, 31%): mp 184−187 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.00 (1H, s), 8.89 (2H, s), 8.38 (1H, s), 8.01 (2H, d, J = 8.8 Hz), 7.51 (2H, d, J = 8.8 Hz), 7.22 (2H, d, J = 7.7 Hz), 7.10 (2H, d, J = 8.1 Hz), 4.66−4.76 (4H, m), 2.38 (3H, s), 1.34 (9H, s); IR (Nujol) cm^{-1} 1695, 1600, 1570, 1460, 1445, 1340; FAB-MS m/z 548 (M+H$^+$).

4-*tert*-Butyl-*N*-(6-(2-((5-hydroxymethyl-2-pyrimidinyl)-oxy)ethoxy)-5-(4-methylphenyl)-4-pyrimidinyl)benzene-sulfonamide (3b). To a suspension of **8** (143 mg, 0.261 mmol) in THF (4 mL)−2-propanol (4 mL) was added $NaBH_4$ (13 mg, 0.344 mmol) at 0 °C, and the mixture was stirred at 0 °C for 2 h, diluted with aqueous NH_4Cl (20 mL) and H_2O (50 mL), and extracted EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:EtOAc, 20:1, v/v then $CHCl_3$:MeOH, 200:1−50:1, v/v) and recrystallized from EtOAc−hexane to afford **3b** as colorless crystalline powder (96 mg, 67%): mp 172−173 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.46 (2H, s), 8.38 (1H, s), 8.01 (2H, d, J = 8.7 Hz), 7.52 (2H, d, J = 8.7 Hz), 7.25 (2H, d, J = 7.9 Hz), 7.13 (2H, d, J = 8.2 Hz), 7.17 (1H, br s), 4.65 (2H, d, J = 5.5 Hz), 4.65−4.70 (2H, m), 4.58−4.62 (2H, m), 2.40 (3H, s), 1.89 (1H, t, J = 5.5 Hz), 1.34 (9H, s); IR (Nujol) cm^{-1} 3400, 1560, 1465, 1450; FAB-MS m/z 550 (M+H$^+$), 424, 153; Anal. ($C_{28}H_{31}N_5O_5S$) C, H, N.

4-*tert*-Butyl-*N*-(6-(2-((5-hydroxymethyl-2-pyrimidinyl)-oxy)ethoxy)-5-(4-methylphenyl)-4-pyrimidinyl)benzene-sulfonamide Sodium Salt (Na Salt of 3b). To a solution of **3b** (3.05 g, 5.54 mmol) in dry THF (60 mL) was added 28% NaOMe in MeOH (1.05 g, 5.54 mmol) dropwise over 10 min at 0 °C, and the mixture was concentrated in vacuo. The residue was dissolved in EtOH, then Et_2O was added. The resulting precipitate was collected, washed with Et_2O, and dried in vacuo at 60 °C for 12 h to afford Na salt of **3b** as colorless crystalline powder (3.14 g, 98%): mp 175 °C-. Anal. ($C_{28}H_{31}N_5NaO_5S\cdot0.5H_2O$) C, H, N, Na.

Methyl 4-(4-(4-*tert*-Butylbenzenesulfonamido)-6-(2-((5-methylthio-2-pyrimidinyl)oxy)ethoxy)-5-pyrimidinyl)-benzoate (11). Under Ar atmosphere, a mixture of 4-*tert*-butyl-*N*-(6-(2-((5-methylthio-2-pyrimidinyl)oxy)ethoxy)-5-bromo-4-pyrimidinyl)benzenesulfonamide[1] (**10**) (509 mg, 0.917 mmol), $PdCl_2(PPh_3)_2$ (256 mg, 0.365 mmol), PPh_3 (48 mg, 0.182 mmol), CuBr (26 mg, 0.182 mmol), 2,6-di-*tert*-butylcresol (a few crystals), and methyl 4-tributylstannylbenzoate[4] (1.17 g, 2.75 mmol) in dry dioxane (15 mL) was refluxed for 8 h, cooled to room temperature, and diluted with EtOAc and 10% aqueous KF, and the mixture was stirred at room temperature for 15 min. Insoluble materials were removed by filtration on Celite. The organic layer of the filtrate was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:EtOAc, 5:1, v/v) and preparative TLC ($CHCl_3$:EtOAc, 4:1, v/v), and recrystallized from EtOAc−hexane to afford **11** as colorless crystalline powder (201 mg, 36%): mp 171−172 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.42 (3H, s), 8.06−8.11 (2H, m), 7.99−8.04 (2H, m), 7.49−7.55 (2H, m), 7.32−7.37 (2H, m), 7.06 (1H, br s), 4.63−4.69 (2H, m), 4.54−4.60 (2H, m), 3.96 (3H, s), 2.44 (3H, s), 1.34 (9H, s); IR (Nujol) cm^{-1} 3250, 1715, 1570, 1460, 1440, 1425; FAB-MS m/z 610 (M+H$^+$), 468, 169.

4-(4-(4-*tert*-Butylbenzenesulfonamido)-6-(2-((5-methylthio-2-pyrimidinyl)oxy)ethoxy)-5-pyrimidinyl)benzoic Acid (4a). A mixture of **11** (142 mg, 0.232 mmol) and 1 N aqueous NaOH (0.46 mL, 0.46 mmol) in THF (3 mL)−H_2O (1 mL) was stirred at room temperature for 8 h, diluted with H_2O, acidified with 10% aqueous HCl, and extracted twice with $CHCl_3$. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was separated by preparative TLC ($CHCl_3$:MeOH, 10:1 v/v), and recrystallized from EtOAc−hexane to afford **4a** as colorless crystalline powder (56 mg, 41%): mp 226−227 °C; ^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz) δ 8.43 (2H, s), 8.38 (1H, s), 8.05−8.10 (2H, m), 7.95−8.01 (2H, m), 7.48−7.53 (2H, m), 7.34−7.39 (2H, m), 4.63−4.69 (2H, m), 4.56−4.60 (2H, m), 2.45 (3H, s), 1.34 (9H, s); IR (Nujol) cm^{-1} 3180, 1690, 1610, 1580, 1560, 1540; FAB-MS m/z 596 (M+H$^+$), 454, 309, 155, 137, 119; Anal. ($C_{28}H_{29}N_5O_6S_2\cdot H_2O$) C, H, N.

4-*tert*-Butyl-*N*-(5-(4-diethoxymethyl)phenyl-6-(2-((5-methylthio-2-pyrimidinyl)oxy)ethoxy)-4-pyrimidinyl)-benzenesulfonamide (12). Under Ar atmosphere, a mixture of **10** (1.50 g, 2.70 mmol), $PdCl_2(PPh_3)_2$ (386 mg, 0.550 mmol), PPh_3 (283 mg, 1.08 mmol), CuBr (155 mg, 1.08 mmol), 2,6-di-*tert*-butylcresol (a few crystals), and 4-tributylstannybenzaldehyde diethyl acetal[5] (3.80 g, 8.10 mmol) in dry dioxane (20 mL) was refluxed for 4 h, cooled to room temperature, and diluted with EtOAc and 10% aqueous KF. The mixture was stirred at room temperature for 30 min, and the insoluble materials were removed by filtration on Celite. The filtrate was extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:EtOAc, 5:1, v/v) and recrystallized from EtOAc−hexane to afford **12** as colorless crystalline powder (650 mg, 37%): mp 165.5−166.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (2H, s), 8.39 (1H, s), 7.99−8.04 (2H, m), 7.49−7.58 (4H, m), 7.22−7.28 (2H, m), 7.15 (1H, br s), 5.53 (1H, s), 4.64−4.69 (2H, m), 4.54−4.59 (2H, m), 3.55−3.75 (4H, m), 2.44 (3H, s), 1.34 (9H, s), 1.28 (6H, t, J = 7.1 Hz); IR (Nujol) cm^{-1} 1590, 1570, 1560, 1540, 1460, 1450, 1430, 1375, 1335; FAB-MS m/z 654 (M+H$^+$), 608, 438, 169.

4-*tert*-Butyl-*N*-(5-(4-hydroxymethyl)phenyl-6-(2-((5-methylthio-2-pyrimidinyl)oxy)ethoxy)-4-pyrimidinyl)-benzenesulfonamide (4b). (1) A mixture of **12** (558 mg, 0.853 mmol) and *p*-toluenesulfonic acid monohydrate (50 mg, 0.263 mmol) in THF (18 mL)−H_2O (6 mL) was stirred at room temperature for 1 h, diluted with EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:EtOAc, 2:1, v/v), and recrystallized from CH_2Cl_2−EtOAc to afford 4-*tert*-butyl-*N*-(5-(4-formyl)phenyl-6-(2-((5-methylthio-2-pyrimidinyl)oxy)ethoxy)-4-pyrimidinyl)benzenesulfonamide as colorless crystalline powder (345 mg, 70%): mp 223−224 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (1H, s), 8.41 (2H, s), 7.99−8.05 (2H, m), 7.91−7.96 (2H, m), 7.50−7.56 (2H, m), 7.43−7.48 (2H, m), 7.06 (1H, br s), 4.65−4.71 (2H, m), 4.55−4.61 (2H, m), 2.44 (3H, s), 1.34 (9H, s); IR (Nujol) cm^{-1} 1680, 1665, 1600, 1580, 1560, 1540, 1460; FAB-MS m/z 580 (M+H$^+$), 309, 273, 257.

(2) To a stirred solution of the obtained formyl derivative (120 mg, 0.207 mmol) in THF (6 mL)−2-propanol (3 mL) was added $NaBH_4$ (12 mg, 0.317 mmol) at 0 °C, and the mixture was stirred at the same temperature for 15 min. The reaction mixture was diluted with 10% aqueous HCl and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was separated by preparative TLC ($CHCl_3$:EtOAc, 1:1 v/v), and recrystallized from EtOAc−hexane to afford **4b** as colorless crystalline powder (79 mg, 66%): mp 172−173 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.42 (2H, s), 8.40 (1H, s), 7.98−8.04 (2H, m), 7.49−7.55 (2H, m), 7.41−7.46 (2H, m), 7.21−7.26 (2H, m), 7.14 (1H, br s), 4.75 (2H, d, J = 5.9 Hz), 4.64−4.69 (2H, m), 4.56−4.61 (2H, m), 2.44 (3H, s), 1.87 (1H, t, J = 6.0 Hz), 1.34 (9H, s); IR (Nujol) cm^{-1} 3470, 1570, 1550, 1460, 1440, 1430, 1375; FAB-MS m/z 582 (M+H$^+$), 440, 309, 242, 169; Anal. ($C_{28}H_{31}N_5O_5S_2$) C, H, N.

4-*tert*-Butyl-*N*-(5-(4-diethoxymethyl)phenyl-6-(2-hydroxyethoxy)-4-pyrimidinyl)benzenesulfonamide (13). The same method as for compound **11** started from *N*-(5-bromo-6-(2-hydroxyethoxy)-4-pyrimidinyl)-4-*tert*-butylbenzenesulfonamide[1] (**9**) afforded **13** as pale yellow foam (61%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.42 (1H, s), 8.02 (2H, d, J = 8.6 Hz), 7.62 (2H, d, J = 8.6 Hz), 7.56 (2H, d, J = 8.2 Hz), 7.28 (2H, d, J = 8.2 Hz), 7.20 (1H, s), 4.37−4.42 (2H, m), 3.67−3.72 (6H, m), 1.34 (3H, s), 1.34 (9H, s), 1.30 (3H, s); IR (Nujol) cm^{-1} 3380, 3240, 1365, 1170; ESI-MS m/z 530 (M+H$^+$).

***N*-(6-(2-((5-Bromo-2-pyrimidinyl)oxy)ethoxy)-5-(4-diethoxymethyl)phenyl-4-pyrimidinyl)-4-*tert*-butylbenzenesulfonamide (14).** To a suspension of 60% NaH in mineral oil dispersion (81 mg, 2.01 mmol) in THF (2 mL) was added a solution of **13** (355 mg, 0.672 mmol) in dry DMAc (1 mL)−dry THF (5 mL) dropwise over 5 min at room temperature. 5-Bromo-2-chloropyrimidine[11,12] (195 mg, 1.01 mmol) was added. The mixture was stirred at room temperature for 2.5 h, diluted with ice-saturated aqueous NH_4Cl, and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:EtOAc, 5:1, v/v), and recrystallized from Et_2O−hexane to afford **14** as colorless crystalline powder (303 mg, 66%): mp 200−201.5 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.67 (2H, s), 8.40 (1H, s), 7.90 (2H, d, J = 7.8 Hz), 7.58 (2H, d, J = 7.7 Hz), 7.39 (2H, d, J = 7.9 Hz), 7.23 (2H, d, J = 7.8 Hz), 5.50 (1H, s), 4.58−4.63 (4H, m), 3.52−3.58 (4H, m), 1.30 (9H, s), 1.19 (6H, t, J = 7.2 Hz); IR (Nujol) cm^{-1} 1340, 1160; ESI-MS m/z 686 (M+H$^+$).

***N*-(6-(2-((5-Bromo-2-pyrimidinyl)oxy)ethoxy)-5-(4-hydroxymethyl)phenyl-4-pyrimidinyl)-4-*tert*-butylbenzenesulfonamide (5b).** The same method as for compound **4b** started from **14** afforded **5b** as colorless crystalline powder (76%): mp 194−195 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.38 (1H, br s), 8.70 (1H, s), 8.36 (1H, s), 7.90 (2H, d, J = 8.4 Hz), 7.58 (2H, d, J = 8.4 Hz), 7.32 (2H, d, J = 7.7 Hz), 7.19 (2H, d, J = 7.7 Hz), 5.32 (1H, s), 4.58−4.63 (2H, m), 4.52−4.58 (4H, m), 1.29 (9H, s); IR (Nujol) cm^{-1} 3497, 1568, 1549, 1461, 1447, 1431; ESI-MS m/z 612(M−H$^-$); Anal. ($C_{27}H_{28}BrN_5O_5S$) C, H, N.

Ethyl 2-Methyl-2-(4-sulfamoylphenyl)propionate (16). (1) To a solution of ethyl 2-methyl-2-phenylpropionate (**15**) (2.00 g, 10.4 mmol) in CH_2Cl_2 (20 mL) was added $ClSO_3H$ (1.73 mL, 26.0 mmol) dropwise over 3 min at 0 °C, and the mixture was allowed to stir at room temperature for 22 h. After evaporation of the volatile, $SOCl_2$ (20 mL) was added, and the reaction mixture was stirred at 60 °C for 3 h. The volatile was evaporated. The residue was poured into ice−water and extracted with ether. The organic extract was washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford crude ethyl 2-(4-chlorosulfonylphenyl)-2-methylpropionate as pale brown oil (2.33 g).

(2) To a solution of the obtained sulfonyl chloride (2.33 g) in ice-H_2O (25 mL)−EtOAc (25 mL) was added concentrated NH_4OH (4 mL). The mixture was stirred at room temperature for 2 h and acidified with 10% aqueous HCl. The organic layer was separated, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residual oil was crystallized from *i*-Pr_2O−hexane to afford **16** as colorless crystalline powder (1.56 g, 42%): mp 73−78 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88 (2H, d, J = 8.8 Hz), 7.49 (2H, d, J = 8.9 Hz), 5.01 (2H, br s), 4.13 (2H, q, J = 7.2 Hz), 1.59 (6H, s), 1.19 (3H, t, J = 7.2 Hz); IR (Nujol) cm^{-1} 3360, 3275, 1720, 1550, 1460, 1330; EI-MS m/z 271 (M$^+$), 227, 198.

2-Methyl-2-(4-sulfamoylphenyl)propionic Acid (17). To a solution of **16** (2.23 g, 8.22 mmol) in MeOH (10 mL) was added a solution of NaOH (1.14 g, 28.5 mmol) in H_2O (10 mL) at 0 °C. The mixture was allowed to stir at room temperature for 22 h, acidified with 10% aqueous HCl, saturated with NaCl, and extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 20:1−10:1, v/v) to afford **17** as colorless crystalline powder (1.77 g, 94%): mp 134 °C-; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.51 (1H, br s), 7.78 (2H, d, J = 8.7 Hz), 7.53 (2H, d, J = 8.7 Hz), 7.30 (2H, s), 1.50 (6H, s); IR (Nujol) cm^{-1} 3330, 3260, 1730, 1715, 1460, 1315; FAB-MS m/z 243 (M+H$^+$), 198, 170.

4-(2-Hydroxy-1,1-dimethylethyl)benzenesulfonamide (18). To a suspension of $NaBH_4$ (2.34 g, 61.8 mmol) in dry THF (50 mL) was added BF_3·Et_2O (0.84 mL, 68.3 mmol) dropwise at 0 °C over 5 min, and the mixture was stirred at the same temperature for 30 min. A solution of **17** (5.00 g, 20.6 mmol) in dry THF (25 mL) was added dropwise at the same temperature over 30 min, and the mixture was stirred at room temperature for 3 h. MeOH was added to the reaction mixture until H_2 gas generation stopped. The mixture was diluted with 10% aqueous HCl and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 100:1−10:1, v/v), and crystallized from $CHCl_3$ to afford **18** as colorless prisms (4.61 g, 98%): mp 102−104 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.73 (2H, d, J = 8.6 Hz), 7.26 (2H, br s), 7.54 (2H, d, J = 8.7 Hz), 4.75 (1H, t, J = 5.3 Hz), 3.44 (2H, d, J = 5.3 Hz), 1.24 (6H, s); IR (Nujol) cm^{-1} 3500, 3340, 3260, 3080, 1325; FAB-MS m/z 230 (M+H$^+$), 213, 195.

2-(4-(*N*-(6-Chloro-5-(4-methylphenyl)-4-pyrimidinyl)-sulfamoyl)phenyl)-2-methylpropionic Acid (19). To a solution of 4,6-dichloro-5-(4-methylphenyl)pyrimidine[3] (2.95 g, 12.3 mmol) and **17** (3.00 g, 12.3 mmol) in dry DMSO (21 mL) was added 60% NaH in mineral oil dispersion (1.58 g, 39.5 mmol) in some portions over 10 min at room temperature, and the mixture was stirred at the same temperature for 22 h, diluted with ice−10% aqueous HCl, and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 100:1, v/v), and the residual solid was triturated with *i*-Pr_2O to afford **19** as colorless crystalline powder (1.54 g, 28%): dec 239−241 °C; ^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz) δ 8.52 (1H, s), 8.02 (2H, d, J = 8.4 Hz), 7.55 (2H, d, J = 8.7 Hz), 7.36 (2H, d, J = 8.1 Hz), 7.19 (2H, d, J = 8.1 Hz), 2.46 (3H, s), 1.59 (6H, s); IR (Nujol) cm^{-1} 3250, 1695, 1540, 1445, 1345; FAB-MS m/z 446 (M+H$^+$).

***N*-(6-Chloro-5-(4-methylphenyl)-4-pyrimidinyl)-4-(2-hydroxy-1,1-dimethylethyl)benzenesulfonamide (20).** A mixture of **18** (3.06 g, 13.3 mmol), 4,6-dichloro-5-(4-methylphenyl)pyrimidine[3] (3.19 g, 13.3 mmol), and K_2CO_3 (5.51 g, 39.9 mmol) in dry DMSO (60 mL) was stirred at 80 °C for 1.5 h, cooled to room temperature, poured into ice−aqueous HCl, and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residual solid was recrystallized from EtOAc−hexane to afford **20** as colorless crystalline powder (4.11 g, 71%): mp 228−229 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.56 (1H, s), 8.06 (2H, d, J = 8.8 Hz), 7.56 (2H, d, J = 8.8 Hz), 7.37 (2H, d, J = 7.8 Hz), 7.21 (1H, br s), 7.15 (2H, d, J = 8.1 Hz), 3.66 (2H, d, J = 6.2 Hz), 1.37 (1H, t, J = 6.2 Hz), 1.36 (6H, s); IR (Nujol) cm^{-1} 3540, 1540, 1455, 1380, 1335; FAB-MS m/z 432 (M+H$^+$), 220, 154, 137, 119.

***N*-(6-Chloro-5-(4-methylphenyl)-4-pyrimidinyl)-4-(1,1-dimethyl-2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)-benzenesulfonamide (21).** A mixture of **20** (500 mg, 1.15 mmol), 3,4-dihydro-2*H*-pyran (125 mg, 1.49 mmol), and 10-camphorsulfonic acid (13 mg, 0.0560 mmol) in CH_2Cl_2 (60 mL) was stirred at room temperature for 1.5 h, diluted with 10% aqueous $NaHCO_3$, and extracted twice with $CHCl_3$. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:EtOAc, 15:1, v/v), and recrystallized from CH_2Cl_2−EtOAc to afford **21** as colorless crystalline powder (444 mg, 83%): mp 182−183 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.55 (1H, s), 8.00−8.05 (2H, m), 7.54−7.60 (2H, m), 7.35−7.40 (2H, m), 7.12−7.18 (3H, m), 4.48−4.52 (1H, m), 3.79 (1H, d, J = 9.4

Hz), 3.55−3.64 (1H, m), 3.37−3.45 (1H, m), 3.33 (1H, d, J = 9.4 Hz), 2.46 (3H, s), 1.25−1.75 (6H, m), 1.38 (6H, s); IR (Nujol) cm^{-1} 3240, 1540, 1445, 1375, 1345; FAB-MS m/z 516 ($M+H^+$), 432, 414, 350, 220, 154, 137, 119.

2-(4-(*N*-(6-(2-((5-Bromo-2-pyrimidinyl)oxy)ethoxy)-5-(4-methylphenyl)-4-pyrimidinyl)sulfamoyl)phenyl)-2-methylpropionic Acid (6a). (1) To ethylene glycol (30 mL) was added 60% NaH in mineral oil dispersion (0.78 g, 19.5 mmol) in some portions at room temperature over 30 min, and **19** (1.50 g, 3.25 mmol) was added. The mixture was stirred at 110 °C for 2 days, cooled to room temperature, diluted with ice−10% aqueous HCl, and extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 100:1−10:1, v/v) to afford 2-(4-(*N*-(6-(2-hydroxyethoxy)-5-(4-methylphenyl)-4-pyrimidinyl)sulfamoyl)phenyl)-2-methylpropionic acid as pale yellow crystalline powder (1.28 g, 84%): mp 189−191 °C; ^{1}H NMR (DMSO-d_6+D_2O+TFA*, 200 MHz) δ 8.37 (1H, s), 7.92 (2H, d, J = 8.3 Hz), 7.52 (2H, d, J = 8.8 Hz), 7.26 (2H, d, J = 8.8 Hz), 7.21 (2H, d, J = 8.8 Hz), 4.27−4.33 (2H, m), 3.53−3.59 (2H, m), 2.37 (3H, s), 1.50 (6H, s) (*The peaks observed were broad without addition of D_2O and TFA.); IR (Nujol) cm^{-1} 3480, 3270, 3250, 1720, 1560, 1435, 1305; FAB-MS m/z 472 ($M+H^+$), 428, 308, 154.

(2) To a suspension of 60% NaH in mineral oil dispersion (344 mg, 8.59 mmol) in dry DMAc (3 mL)−dry THF (3 mL) was added the obtained hydroxyethoxy derivative (900 mg, 1.91 mmol) in dry DMAc (5 mL)−dry THF (5 mL) dropwise over 10 min at room temperature. 5-Bromo-2-chloropyrimidine[11,12] (1.48 g, 7.63 mmol) was added. The mixture was stirred at room temperature for 3 h, diluted with ice−10% aqueous HCl, and extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 100:1−20:1, v/v), and recrystallized from CH_2Cl_2−i-Pr_2O to afford **6a** as colorless prisms (988 mg, 73%): dec 130−137 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.54 (1H, br s), 10.39 (1H, br s), 8.69 (2H, s), 8.36 (1H, s), 7.94 (2H, d, J = 7.9 Hz), 7.52 (2H, d, J = 8.1 Hz), 7.18 (2H, d, J = 8.0 Hz), 7.11 (2H, d, J = 7.9 Hz), 4.58−4.64 (2H, m), 4.52−4.58 (2H, m), 2.35 (3H, br s), 1.49 (6H, s); IR (Nujol) cm^{-1} 3240, 1720, 1570, 1560, 1460, 1430, 1420, 1340; FAB-MS m/z 630 ($M+H^+$); Anal. ($C_{27}H_{26}BrN_5O_6S$·CH_2Cl_2) C, H, N.

***N*-(6-(2-((5-Bromo-2-pyrimidinyl)oxy)ethoxy)-5-(4-methylphenyl)-4-pyrimidinyl)-4-(1,1-dimethyl-2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)benzenesulfonamide (22).** The same procedure as for **6a** started from **21** afforded **22** as colorless foam (395 mg, 76%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (2H, s), 8.37 (1H, s), 8.01 (2H, d, J = 8.7 Hz), 7.55 (2H, d, J = 8.7 Hz), 7.24 (2H, d, J = 8.3 Hz), 7.15 (1H, br s), 7.09 (2H, d, J = 8.1 Hz), 4.62−4.67 (2H, m), 4.56−4.61 (2H, m), 4.50 (1H, t, J = 3.3 Hz), 3.78 (1H, d, J = 9.4 Hz), 3.54−3.63 (1H, m), 3.35−3.43 (1H, m), 3.32 (1H, d, J = 9.4 Hz), 2.41 (3H, s), 1.20−1.76 (6H, m), 1.37 (6H, s); IR (Nujol) cm^{-1} 3360, 1565, 1455, 1420; FAB-MS m/z 698 ($M+H^+$), 524, 414, 203, 201.

***N*-(6-(2-((5-Bromo-2-pyrimidinyl)oxy)ethoxy)-5-(4-methylphenyl)-4-pyrimidinyl)-4-(2-hydroxy-1,1-dimethylethyl)benzenesulfonamide (6b).** A mixture of **22** (200 mg, 0.286 mmol) and *p*-toluenesulfonic acid monohydrate (50 mg, 0.0263 mmol) in MeOH (4 mL)−THF (2 mL) was stirred at room temperature for 16 h, diluted with EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was separated by preparative TLC ($CHCl_3$:EtOAc, 5:1, v/v), and recrystallized from EtOAc−hexane to afford **6b** as colorless crystalline powder (153 mg, 87%): mp 179.5−181 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (2H, s), 8.37 (1H, s), 8.02−8.08 (2H, m), 7.50−7.56 (2H, m), 7.21−7.26 (2H, m), 7.17 (1H, br s), 7.08−7.13 (2H, m), 4.63−4.68 (2H, m), 4.56−4.61 (2H, m), 3.65 (1H, d, J = 6.3 Hz), 2.41 (3H, s), 1.36 (6H, s), 1.33 (1H, t, J = 6.3 Hz); IR (Nujol) cm^{-1} 3500, 3240, 1565, 1550, 1460, 1440, 1430; FAB-MS m/z 614 ($M+H^+$), 461, 309; Anal. ($C_{27}H_{28}BrN_5O_5S$) C, H, N.

***N*-(6-(2-((5-Bromo-2-pyrimidinyl)oxy)ethoxy)-5-(4-methylphenyl)-4-pyrimidinyl)-4-(2-hydroxy-1,1-dimethylethyl)benzenesulfonamide Sodium Salt (Na Salt of 6b).** To a solution of **6b** (10.20 g, 16.4 mmol) in THF (100 mL)−MeOH (20 mL) was added 28% NaOMe in MeOH (3.10 g, 16.1 mmol) dropwise over 15 min at 0 °C, and the solvent was evaporated. The residue was dissolved in MeOH, then concentrated in vacuo. *i*-PrOH was added, and the resulting precipitate was collected, washed with *i*-Pr_2O, and dried in vacuo at 60 °C for 18 h to afford Na salt of **6b** as colorless crystalline powder (10.40 g, 96%): mp 182 °C− (dec); Anal. ($C_{27}H_{28}BrN_5NaO_5S$·$1.5H_2O$) C, H, N, Na.

2-(4-(*N*-Acetyl-*N*-(6-(2-((5-bromo-2-pyrimidinyl)oxy)-ethoxy)-5-(4-methylphenyl)-4-pyrimidinyl)sulfamoyl)-phenyl)-2-methylpropyl Acetate (23). To a solution of **6b** (500 mg, 0.814 mmol) in dry pyridine (3 mL) was added acetic anhydride (0.23 mL, 2.44 mmol) at 0 °C. The mixture was stirred at room temperature for 18 h, diluted EtOAc, washed with 10% aqueous HCl, H_2O, and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane:EtOAc, 2:1, v/v) to afford **23** as colorless foam (498 mg, 88%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.77 (1H, s), 8.48 (2H, s), 8.09 (2H, d, J = 8.7 Hz), 7.52 (2H, d, J = 8.6 Hz), 7.29 (2H, d, J = 8.2 Hz), 7.20 (2H, d, J = 7.9 Hz), 4.82 (2H, m), 4.72 (2H, m), 4.15 (2H, s), 2.40 (3H, s), 2.01 (3H, s), 1.83 (3H, s), 1.38 (6H, s); IR (Nujol) cm^{-1} 1740, 1718, 1375, 1315; FAB-MS m/z 722 ($M+Na^+$), 700 ($M+H^+$).

2-(4-(*N*-(5-((4-Acetoxymethyl)phenyl)-6-(2-((5-bromo-2-pyrimidinyl)oxy)ethoxy)-4-pyrimidinyl)-*N*-acetylsulfamoyl)phenyl)-2-methylpropyl Acetate (25). (1) A mixture of **23** (200 mg, 0.286 mmol), NBS (60 mg, 0.336 mmol), and AIBN (3 mg, 0.0153 mmol) in CCl_4 (2 mL) was refluxed for 2 h. After cooling, the precipitate was removed by filtration, and the filtrate was concentrated in vacuo. The residue was separated by silica gel column chromatography (hexane:EtOAc, 2:1−1:1, v/v) to afford crude 2-(4-(*N*-acetyl-*N*-(5-((4-bromomethyl)phenyl)-6-(2-((5-bromo-2-pyrimidinyl)oxy)ethoxy)-4-pyrimidinyl)sulfamoyl)phenyl)-2-methylpropyl acetate (**24**) as colorless foam (218 mg).

(2) A mixture of crude **24** (200 mg, 0.286 mmol), potassium acetate (267 mg, 2.72 mmol), and sodium iodide (4 mg, 0.0272 mmol) in dry DMF (2 mL) was stirred at 60 °C for 3 h. The reaction mixture was poured into ice−water and extracted with EtOAc. The extract was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane:EtOAc, 3:1−1:1, v/v) to afford **25** as colorless foam (106 mg, 52% from **23**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.46 (2H, s), 8.40 (1H, s), 8.06 (2H, d, J = 8.4 Hz), 7.51 (2H, d, J = 8.8 Hz), 7.45 (2H, d, J = 7.8 Hz), 7.26 (2H, d, J = 8.4 Hz), 7.12 (1H, br), 5.16 (2H, s), 4.67 (2H, m), 4.58 (2H, m), 4.13 (2H, s), 2.17 (3H, s), 1.99 (3H, s), 1.38 (6H, s); IR (Nujol) cm^{-1} 1735, 1377, 1227; FAB-MS m/z 716 ($M+H^+$).

***N*-(6-(2-((5-Bromo-2-pyrimidinyl)oxy)ethoxy)-5-((4-hydroxymethyl)phenyl)-4-pyrimidinyl)-4-(2-hydroxy-1,1-dimethylethyl)benzenesulfonamide (26).** To a solution of **25** (91 mg, 0.127 mmol) in THF (1 mL)−MeOH (1 mL) was added 1 N aqueous NaOH (0.5 mL) at 0 °C, and the mixture was stirred at the same temperature for 1 h. The reaction mixture was neutralized with saturated aqueous NH_4Cl, and the volatile was evaporated. The residue was dissolved in EtOAc−H_2O, and the separated organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 30:1, v/v), and recrystallized from Et_2O−hexane to afford **26** as colorless crystalline powder (70 mg, 87%): mp 199−201 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.45 (2H, s), 8.39 (1H, s), 8.05 (2H, d, J = 8.6 Hz), 7.54 (2H, d, J = 8.6 Hz), 7.44 (2H, d, J = 8.1 Hz), 7.25 (2H, d, J = 8.4 Hz), 7.19 (1H, br), 4.75 (2H, d, J = 5.3 Hz), 4.66 (2H, m), 4.58 (2H, m), 3.67 (2H, d, J = 5.7 Hz), 1.85 (1H, br), 1.36 (6H, s); IR (Nujol) cm^{-1} 3489, 1571, 1336; FAB-MS m/z 632 ($M+H^+$); Anal. ($C_{27}H_{28}BrN_5O_6S$·$0.2H_2O$) C, H, N.

ET_A Receptor Binding Assay on Porcine Aortic Membrane. These binding experiments were performed in a manner similar to Ihara et al.[13] with minor modification.[1]

Binding Studies on Cultured Cells (rat A10 cells for ET_A receptors and human GH cells for ET_B receptors) and on Membranes of CHO Cells (expressing cloned human ET_A and ET_B receptors). These binding studies were carried out as reported.[6]

Metabolic and Pharmacokinetic Studies of Compound 1. (1) In vivo study (determination of **1** and its major metabolites): Compound **1** (0.3 mg/kg/10 mL in 0.25% CMC) was administered to three rats and dogs. Blood samples were collected with a heparinized syringe 4 h after administration (Cmax point). Sample preparation and analyses were carried out as reported.[7,8] (2) In vitro study (analyses of metabolic pathway in species): The species difference of metabolic activities and formation of the metabolites from **1** were studied using the liver microsome of rat, dog, and human. The experiments were carried out as reported.[7]

Metabolic and Pharmacokinetic Studies of 6b. These studies were described in the reported articles.[7,8]

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