Synthesis and Structure–Activity Relationships in a Series of Ethenesulfonamide Derivatives, a Novel Class of Endothelin Receptor Antagonists

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In the previous paper, we described a series of the 2-arylethenesulfonamide derivatives, a novel class of ET_A-selective endothelin (ET) receptor antagonists, including the compounds 1a, b. Compound 1a showed excellent oral antagonistic activities and pharmacokinetic profiles, and the monopotassium salt of 1 (YM-598 monopotassium) is in clinical trials. In this paper, we wish to report the investigation of the further details of structure–activity relationships (SARs) of the 2-phenylethenesulfonamide region in 1a. It was found that methyl substitutions at the 2-, 4- and 6-positions of the phenyl group in 1a led to the discovery of the ET_A/ET_B mixed antagonist (6s) with an IC_{50} of 2.2 nM for the ET_A receptor. We also found that introduction of an ethyl group to the 1-position of the ethenyl group in 1a gave the ET_A selective antagonist (6u) with an oral endothelin antagonistic activity in rats.

Key words endothelin antagonist; endothelin-A/endothelin-B mixed antagonist; ethenesulfonamide; endothelin-A selective antagonist

Endothelin (ET), isolated from the conditioned medium of cultured porcine vascular endothelial cells in 1988, is a highly potent vasoconstrictive 21-amino acid peptide.[3)] There are three isoforms (ET-1, ET-2, ET-3). ET-1 is the predominant component of the three ET-isopeptides and is derived from precursor big ET-1.[4)] ET-1 has been believed to be implicated in the pathogenesis of various diseases, largely because of its ability to constrict vascular and nonvascular smooth muscle.[5)]

Two subtypes of receptors for ETs , termed the ET_A receptor and ET_B receptor, have been cloned and stably expressed in mammals. ET_A receptor appears to exhibit affinity for ET-1 and ET-2 over ET-3, whereas the ET_B receptor has nearly equipotent affinity for these three ETs.[6)]

A number of ET_A-selective and ET_A/ET_B mixed antagonists have been reported for a decade,[7)] and some of these ET antagonists are currently in clinical trials.

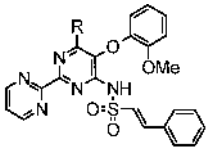
In the previous paper,[8)] we described a series of the 2-arylethenesulfonamide derivatives, a novel class of ET_A-selective ET receptor antagonists, including the compounds (**1a, b**) (Fig. 1). Among these, the potassium salt of **1a** (YM598 monopotassium) is in clinical trials. Compound **1a** showed an IC_{50} value of 3.1 nM for the ET_A receptor and 1200 nM for the ET_B receptor (ET_B/ET_A ratio=390). In the *in vivo* study, it showed a potent oral inhibitory activity of pressor response to big ET-1-treated rats and excellent pharmacokinetic profiles in rats and dogs. In this paper, we wish to report the investigation of the further details of the structure–activity relationships (SARs) of the 2-phenylethenesulfonamide region in **1a**.

In the previous study,[8b)] replacement of the phenyl group of the 2-phenylethenesulfonmamide moiety in compound **1a** with another aryl or heteroaryl groups was explored. This exercise revealed that these modifications were well tolerated in the ET_A binding affinity and remarkably led to various ET_B/ET_A ratios in the 50—820 range. Intrigued by these observations, we became interested in the effect of the further modification of the phenyl group in the phenylethenesulfonamide moiety of **1a** on both ET_A and ET_B binding affinities and the ET_A/ET_B ratio. We also investigated modification of the ethenyl group in the phenylethenesulfonamide moiety.

Chemistry

Charts 1 and 2 show the syntheses of alkenesulfonamide derivatives.

The starting compound (**3**) was prepared according to the method reported by Burri and his coworkers.[9)] Nucleophilic substitution of the pyrimidine derivative **3** with (*E*)-alkenesulfonamide (**4**) resulted in the chloropyrimidine (**5a**—**j**, **m**—**x**). The chloropyrimidine **5** was treated with sodium methoxide in *N*,*N*-dimethylformamide (DMF) or methanol to give the methoxy analogues (**6a**, **c**—**j**, **m**—**x**). Compound **3** was also treated with the methyl ester (**4k**) to give a mixture of the benzoic acid analogue (**5l**) and the methyl ester (**5k**). This mixture was treated with concentrated sulfuric acid in methanol to give **5k** as a sole product. Treatment of **5k** with sodium methoxide in methanol gave the benzoic acid analogue (**6l**). Under these reaction conditions, *in situ* hydrolysis of the esters was observed. Esterification of **6l** gave the methyl ester **6k**. The chloropyrimidine **5b** was treated with sodium and ethyleneglycol to afford the hydroxyethoxy derivative **6b**. The (*E*) form of all screened compounds **6** was



1a : R = MeO

YM598 monopotassium :potassium salt of **1a**

1b : R = $HOCH_2CH_2O$

Fig. 1

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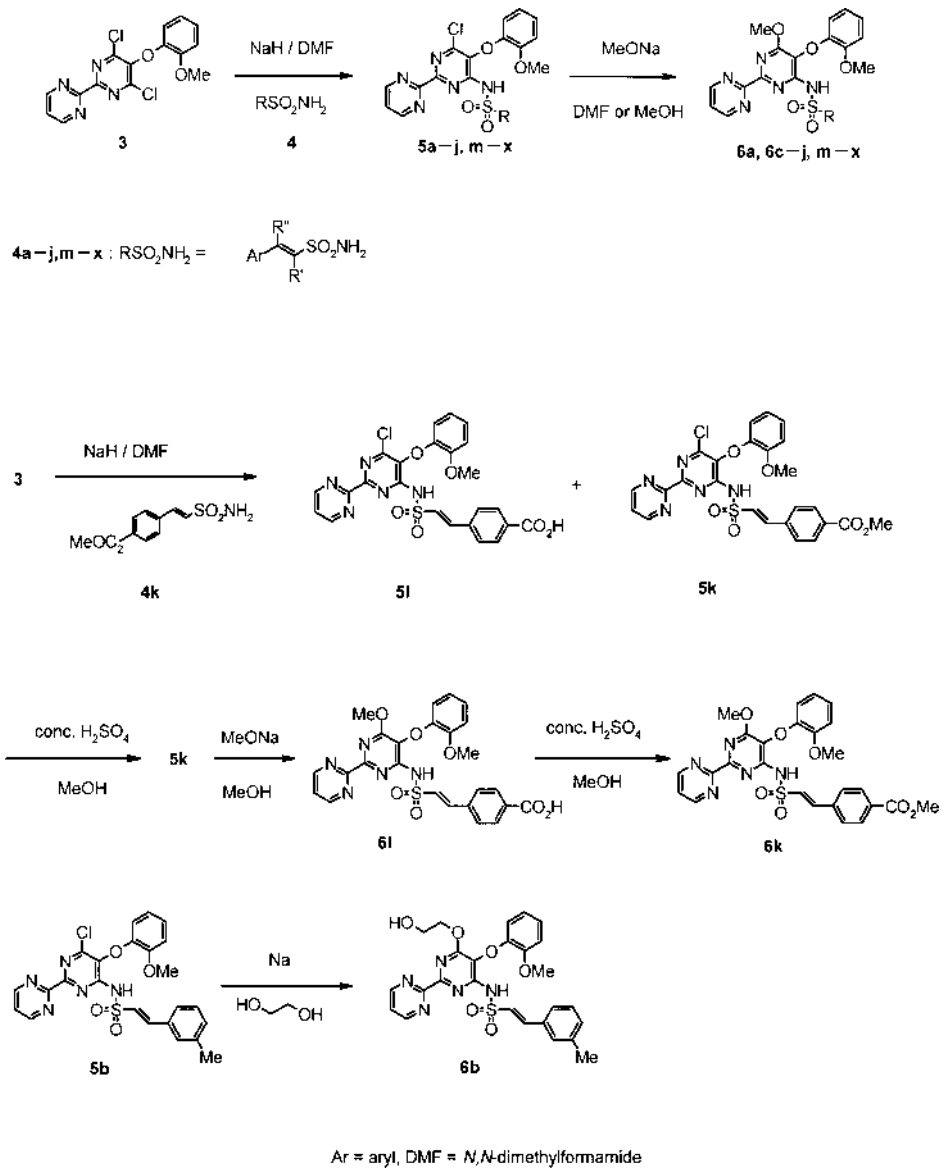


Chart 1

confirmed by the coupling constant between the vinyl protons ($J>14$ Hz) in the ^{1}H-NMR spectrum except for **6t**—**x**.

In Chart 2, an outline of the synthesis of the key intermediates **4** is given.

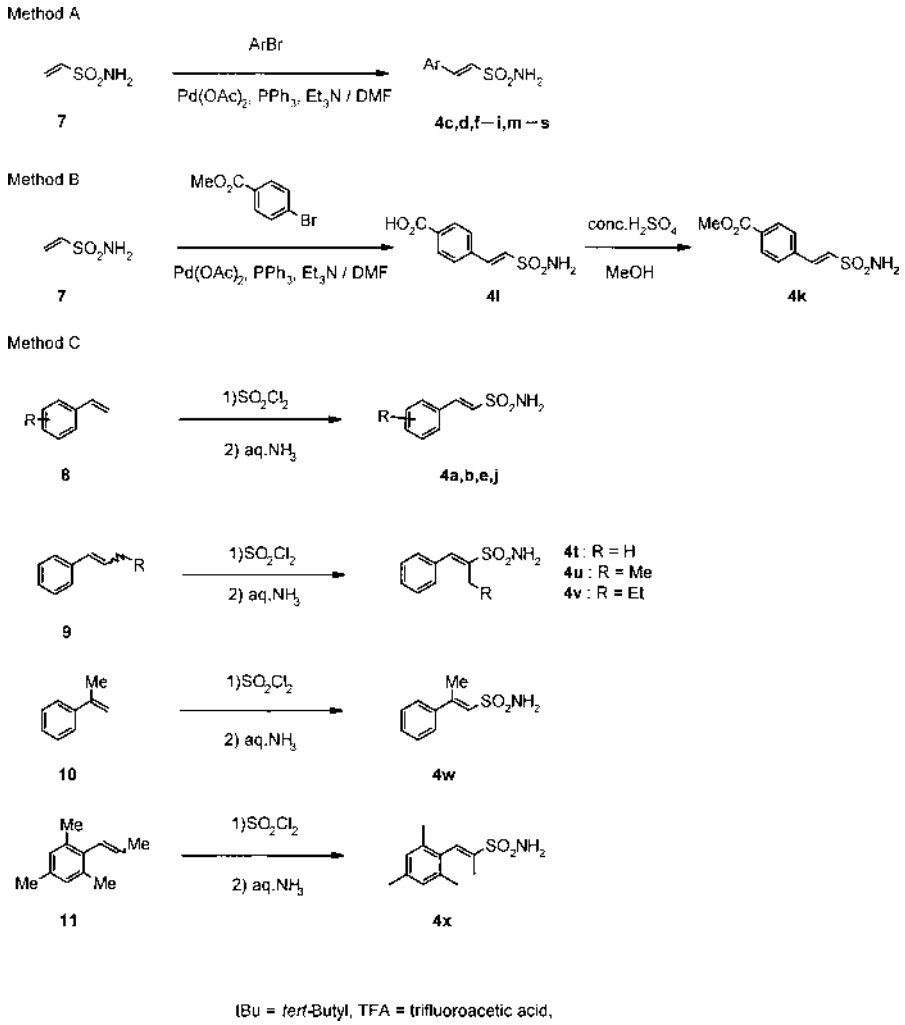
A palladium-catalyzed Heck reaction between ethenesulfonamide (**7**) and arylbromide afforded the (*E*)-2-phenylethenesulfonamide derivatives (**4c**, **d**, **f**—**i**, **m**—**s**) (method A).[10] Under the same condition, methyl 4-bromobenzoate was reacted with **7** to afford the benzoic acid analogue (**4l**). Esterification of **4l** gave the methyl ester **4k**. (method B)

Other (*E*)-2-arylethenesulfonamide derivatives (**4a**, **b**, **e**, **j**, **t**—**x**) have been synthesized *via* the route shown in method C.[11] The styrene derivatives (**8**) were treated with sulfuryl chloride and followed by the treatment with aqueous ammonia to give the ethenesulfonamide derivatives **4a**, **b**, **e**, **j**. The (*E*)-form of the disubstituted (*E*)-2-phenylethenesulfonamide derivatives **4a**—**k**, **m**—**s** was confirmed by the coupling constant between the vinyl protons ($J>14$ Hz) in the ^{1}H-NMR spectrum. The trisubstituted (*E*)-2-phenylethenesulfonamide derivatives (**4t**—**x**) were also synthesized according to the same procedure. The (*E*)-form of these derivatives was confirmed by the NMR spectra (Fig. 2). A nuclear Overhauser effect (NOE) between the allyl proton and aromatic protons was observed, but an NOE between the allyl proton and vinyl proton was not observed. The structure of **4x** was confirmed by using a heteronuclear multiple-bond correlation spectrum (HMBC), a heteronuclear multiple quantum coherence spectrum (HMQC) and an NOE study. The chemical shifts (ppm) in the ^{1}H- and ^{13}C-NMR spectra of **4x** are shown in Fig. 2.

Results and Discussion

Compounds have been evaluated *in vitro* for their affinity toward cloned human ET_A and ET_B receptors expressed in COS-1 cells employing receptor-binding assays. Some compounds were further examined *in vivo* for their ability after oral or intravenous administration to inhibit an increase in mean arterial blood pressure (MABP) due to the administration of exogenous big ET-1 to pithed or conscious rats.

The SARs of our novel series of ET receptor antagonists



tBu = *tert*-Butyl, TFA = trifluoroacetic acid,

Chart 2

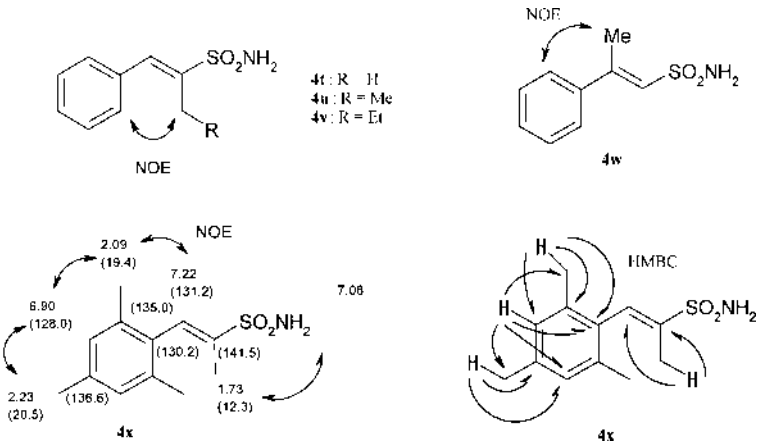


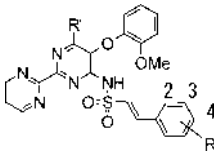
Fig. 2. Confirmation of the Structure of **4t**—**x**

The arrow shows that the NOE between the two protons was observed. The values in the structure **4x** show the chemical shifts (ppm) in ^{1}H-NMR spectrum and the values in parentheses show the chemical shifts (ppm) in ^{13}C-NMR spectrum.

are summarized in Tables 1—4.

Mono-substitution at the 2—4 position of the phenyl ring was investigated (Table 1). Introduction of a methyl group into the phenyl ring of the 2-phenylethenesulfonamide moiety (**6a**—**c**) retained the same order of the affinity for the ET_A receptor compared with **1a** and **b**. On the other hand, the 2-methyl derivative **6a** and the 4-methyl derivative **6c** resulted in an increase in the ET_B binding affinity over the compound **1a** by 4-fold and 6-fold respectively. For the chlorine substitution, the 2- and 4-positions (**6d**, **f**) also showed

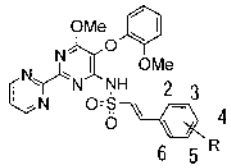
Table 1. ET_A and ET_B Receptor Binding Affinities for Ethenesulfonamide Derivatives



Compound	R	R′	IC_{50} (nM)[a]		Selectivity for ET_A[c]
			ET_A[b]	ET_B[b]	
1a[d]	H	MeO	3.1	1200	390
1b[d]	H	$HO(CH_2)_2O$–	1.6	370	231
6a	2-Me	MeO	1.9	320	170
6b	3-Me	$HO(CH_2)_2O$–	7.6	360	50
6c	4-Me	MeO	2.8	190	68
6d	2-Cl	MeO	2.3	270	120
6e	3-Cl	MeO	2.2	770	330
6f	4-Cl	MeO	13	280	22
6g	4-Et	MeO	11	580	52
6h[e]	4-*tert*-Bu	MeO	120	350	2.9
6i	4-MeO	MeO	13	320	25
6j[e]	4-CF_3	MeO	38	350	9.2
6k	4-COOMe	MeO	12	650	54
6l	4-COOH	MeO	140	>1000	

a) Experiments were performed twice except **1a** for ET_A and ET_B, **6w** for ET_A. *b*) Cloned human receptor binding. *c*) Expressed as ET_B IC_{50}/ET_A IC_{50}. *d*) The biological data of compound was previously reported (see ref. 8). *e*) Potassium salt.

Table 2. ET_A and ET_B Receptor Binding Affinities for Ethenesulfonamide Derivatives



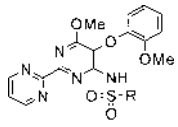
Compound	R	IC_{50} (nM)[a]		Selectivity for ET_A[c]
		ET_A[b]	ET_B[b]	
1a[d]	H	3.1	1200	390
6a	2-Me	1.9	320	170
6m	2,3-di-Me	3.6	290	81
6n	2,4-di-Me	2.2	93	42
6o	2,5-di-Me	37	340	9.1
6p	2,6-di-Me	8.7	74	8.5
6q	2,6-di-Et	26	180	6.9
6r	2,6-di-Cl	4.6	160	35
6s	2,4,6-tri-Me	2.2	30	14

a—*d*) See footnotes in Table 1.

an increase in the ET_B binding affinity by 4-fold.

Realizing the effectiveness of 4-substitution in increasing the ET_B binding affinity, we then synthesized and evaluated a series of compounds with another substitutions at the 4-position. The ethyl, *tert*-butyl, methoxy, trifluoromethyl and methoxycarbonyl derivatives (**6g**—**k**) were more potent in ET_B binding affinity than **1a** by 2- to 4-fold. On the other hand, the ET_A binding affinities of these 4-substituted analogues (**6f**—**k**) were less potent than that of **1a** by 4- to 40-fold. These results suggested that substituents at the 4-position larger than a methyl group were not well tolerated in the ET_A binding affinity, probably due to the steric factors. The

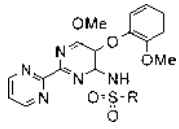
Table 3. ET_A and ET_B Receptor Binding Affinities for Ethenesulfonamide Derivatives

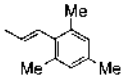
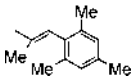


Compound	R	IC_{50} (nM)[a]		Selectivity for ET_A[c]
		ET_A[b]	ET_B[b]	
1a[d]		3.1	1200	390
6t		1.6	310	190
6u[e]		3.3	790	240
6v[e]		170	>1000	
6w		11	760	69

a—*e*) See footnotes in Table 1.

Table 4. ET_A and ET_B Receptor Binding Affinities for Ethenesulfonamide Derivatives



Compound	R	IC_{50} (nM)[a]		Selectivity for ET_A[c]
		ET_A[b]	ET_B[b]	
1a[d]		3.1	1200	390
6s		2.2	30	14
6x		6.2	130	21

a—*d*) See footnotes in Table 1.

acid derivative **6l** was much less potent in both ET_A and ET_B binding affinity than **1a**, indicating that acidic groups may not be tolerated at this position.

Because 2-methyl derivative **6a** showed a potent ET_A binding affinity and an increased ET_B binding affinity, we decided to investigate additional methyl substitutions to 2-methyl derivative **6a** (Table 2). Methyl substitution at the 3- and 5-positions (**6m**, **o**) had no effect on the ET_B binding affinity, while an additional methyl substitution at the 4- and 6-positions (**6n**, **p**) increased the ET_B binding affinity compared to **6a** by 3- and 4-fold, respectively. The 2,4- and 2,6-dimethyl derivatives **6n** and **6p** retained reasonable ET_A binding affinity. The ET_A selectivity of **6p** was 8.5 and lower than that of **1a** by 49-fold. Replacement of the methyl groups in **6p** with ethyl groups (**6q**) or chlorine atoms (**6r**) led to a slight decrease in the ET_B binding affinity. The ET_A binding affinities of **6q** and **6r** were lower than that of **6a** by about 14-fold and 2-fold, respectively. Introduction of the third methyl group at

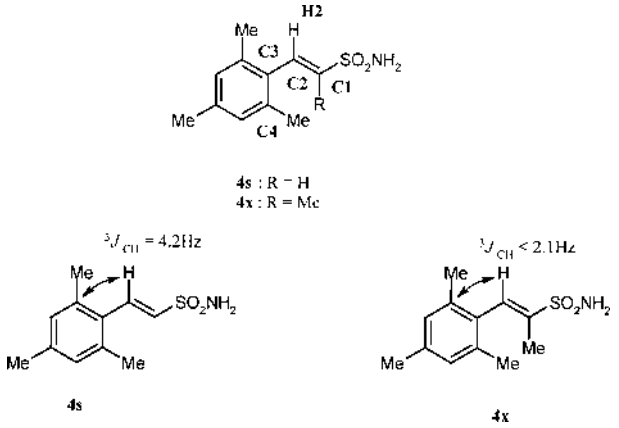


Fig. 3. The NMR Studies of **4s** and **4x**

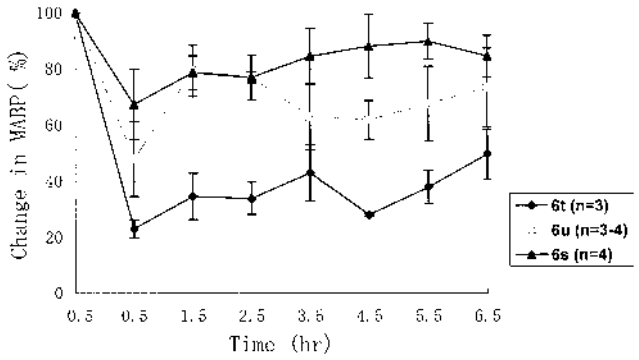


Fig. 4. Effect of oral Administration of **6s** (10 mg/kg), **6t** (3 mg/kg) and **6u** (0.3 mg/kg) on Pressor Response to Big ET-1 in Conscious Normotensive Rats

Change in MABP (%): increase in MABP in conscious rats elicited by intravenous administration of big ET-1 (0.5 nmol/kg).

the 4-position of **6p** afforded the trimethyl derivative **6s** and resulted in an increase in both ET_A and ET_B binding affinity by *ca.* 4-fold and 2-fold, respectively. Compound **6s** had a potent ET_A binding affinity and a low ET_A selectivity, with an IC_{50} value of 2.2 nM for the ET_A receptor and an ET_B/ET_A ratio of 14. It was found that 2,4,6-trimethyl substitution of **1a** increased the ET_B binding affinity by 40-fold.

We were then curious to explore the introduction of alkyl groups into the ethenyl moiety in the 2-phenylethenesulfonamide (Table 3).

Methyl substitution at the 1-position of the ethenyl moiety (**6t**) increased the both ET_A and ET_B binding affinity compared to **1a** by about 2-fold and 4-fold, respectively. Replacement of the methyl group in **6t** with the ethyl group (**6u**) led to *ca.* a 2-fold decrease in both ET_A and ET_B binding affinities. The 1-propyl derivative (**6v**) was significantly less active than **1a** in both ET_A and ET_B binding affinities. The 2-methyl derivative (**6w**) was found to be almost equally potent to **1a** in the ET_B binding affinity but was about 4-fold less potent than **1** in the ET_A binding affinity.

Compounds in Table 4 exemplify combination of the groups from two sites of the 2-phenylethenesulfonamide moiety.

Introduction of a methyl group at the 1-position of the ethenesulfonamide in the trimethyl derivative **6s** gave the compound **6x** with *ca.* a 3-fold decrease in the ET_A binding affinity and a 4-fold decrease in the ET_B binding affinity. We assumed that these decreases might be due to the changes in the conformation in the 2-phenylethenesulfonamide region in **6s** and **6x**.

In order to investigate the differences in the stable conformation of the 2-phenylethenesulfonamide region between **6s** and **6x**, molecular mechanics studies and NMR studies were performed using **4s** and **4x** as simple models (Fig. 3). A conformational analysis using a systematic search in which the torsion angle of the C1–C2–C3–C4 bond was rotated in 1° increments revealed that the torsion angles (C1–C2–C3–C4) of the most energetically favored conformations of **4s** and **4x** were 59° and 90°, respectively (Windows CAChe version 4.4 MM2, Fujitsu Limited). In the NMR studies, the coupling constants ($^3J_{CH}$) between H2 and C4 obtained by long-range selective proton decoupling (LSPD) experiments were 4.2 Hz for **4s** and <2.1 Hz for **4x**. The value of the coupling constant <2.1 Hz indicated that the torsion angle (H2–C2–C3–C4) in **4x** was about 90°, and the value 4.2 Hz indicated that the torsion angle in **4s** was smaller than 90°.[12] These two studies suggested that the stable conformation of the 2-phenylethenesulfonamide region in **6s** and **6x** might be different in each compound.

Table 5. Comparison of the Effects of Oral Administration of the 2-Phenylethenesulfonamide Derivatives on Pressor Response to Big ET-1 in Pithed Rats

Compound	ID_{50} (mg/kg)[a]
	p.o.
6t	6.6 (3.4—16.1)
6u	1.7 (1.1—3.0)
1a	1.1 (0.70—2.4)[b]

a) ID_{50} value was defined as the dose of test compounds which caused a 50% inhibition of the pressor response to big ET-1 in DBP. n=3—8, ID_{50} values are expressed as the mean with 95% confidence limits. *b*) The biological data of compound was previously reported (see ref. 8).

We have discovered the ET_A/ET_B mixed antagonist **6s** and the ET_A selective antagonists **6t** and **6u** through the SAR study around the 2-phenylethenesulfonamide region in **1a**. These compounds were further evaluated in the *in vivo* studies (Fig. 4, Table 5).

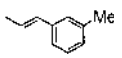
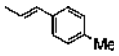
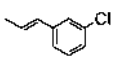
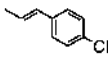
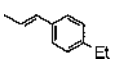
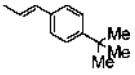
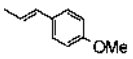
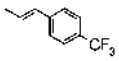
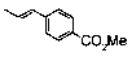
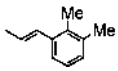
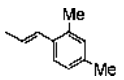
The trimethyl derivative **6s**, the 1-methyl derivative **6t** and the 1-ethyl derivative **6u** were tested for their antihypertensive activity in conscious rats after oral administration (Fig. 4). Though **6s** showed potent binding affinity for the ET_A receptor, it showed poor oral antagonistic activity. Compound **6s** also showed weak antagonistic activity after intravenous administration at 10 mg/kg, and the maximum inhibition of the pressor effect of big ET-1 was 45±7.6%. Additional ET_B antagonism might weaken the inhibitory activity against the pressor effect of big ET-1,[13] but the reason for the poor *in vivo* potency of **6s** was not clear.

On the other hand, **6t** and **6u** showed potent activities (Fig. 4). Maximum inhibition of the pressor effect of big ET-1 after oral administration was 77% for **6t** (3 mg/kg) and 52% for **6u** (0.3 mg/kg).

Compounds **6t** and **6u** also inhibited the increase in MABP due to the administration of exogenous big ET-1 to anesthetized pithed rats after oral administration (Table 5). In this study, the ID_{50} value was defined as the dose of test com-

Table 6. Physical Data for Compounds **4**

RSO_2NH_2

No.	R[a]	mp (°C) (Solvent)	Yield (%)	Method	400 MHz[b] ^{1}H-NMR (DMSO-d_6)[c] δ	FAB[d] MS m/z
4a		125—126 (Toluene)	24	C	2.38 (3H, s), 7.00—7.46 (7H, m, containing, 7.09, d, J=15.5 Hz), 7.62—7.72 (1H, m)	197 (M^+)
4b		149—150 (EtOH)	28	C	2.33 (3H, s), 7.01 (2H, s), 7.19 (1H, d, J=15.0 Hz), 7.22—7.39 (3H, m), 7.45 (1H, d, J=10.0 Hz), 7.48 (1H, d, J=15.0 Hz)	197 (M^+)
4c					See ref. 14	
4d					See ref. 11	
4e		139—140 (EtOAc–Hex)	36	C	5.84 (2H, s), 7.89 (1H, d, J=16.0 Hz), 7.31—7.51 (5H, m).	218 (M^++1)
4f					See ref. 14	
4g		100—101 (Et_2O)	73	A	1.18 (3H, t, J=4.1 Hz), 2.67 (2H, q, J=4.1 Hz), 7.00—7.35 (6H, m, containing, 7.14, d, J=16.1 Hz), 7.60 (2H, d, J=8.1 Hz)	212 (M^++1)
4h					See ref. 11	
4i		130—131 (EtOAc–Hex)	39	A	3.80 (3H, s), 6.80—7.15 (5H, m), 7.29 (1H, d, J=15.9 Hz), 7.62 (2H, d, J=8.8 Hz)	214 (M^+)
4j		121—122 (EtOAc–Hex)	35	C	7.04 (1H, d, J=16.0 Hz), 7.39 (2H, d, J=7.7 Hz), 7.50—7.80 (5H, m)	251 (M^+)
4k		74—75 (EtOAc–Hex)	29	B	3.94 (3H, s), 6.99 (1H, d, J=15.5 Hz), 7.50—7.66 (5H, m), 8.07 (2H, d, J=6.9 Hz)	242 (M^++1)
4m		58—59 (Et_2O)	37	A	2.26 (3H, s), 2.27 (3H, s), 7.03 (1H, d, J=14.8 Hz), 7.10—7.16 (3H, m), 7.22 (1H, d, J=6.8 Hz), 7.45 (1H, d, J=7.6 Hz), 7.61 (1H, d, J=14.8 Hz)	212 (M^++1)
4n		94—95 (Et_2O)	95	A	2.29 (3H, s), 2.34 (3H, s), 7.03—7.10 (5H, m), 7.48 (1H, d, J=15.6 Hz), 7.57 (1H, d, J=7.8 Hz)	212 (M^++1)

a) The (*E*) form of all compounds was confirmed by the coupling constant between vinyl protons (J>14 Hz) in the ^{1}H-NMR spectrum. *b*) 90 MHz for **4e**, **g**, **k**. *c*) $CDCl_3$ for **4j**, **k**. *d*) EI-MS for **4a**, **b**, **j**.

pounds which caused a 50% inhibition of the pressor response to big ET-1 in diastolic blood pressure (DBP) (details are described in the Experimental section). Compounds **6t** and **6u** showed excellent inhibitory activities after oral administration with ID_{50} values of 6.6 and 1.7 mg/kg, respectively. The oral activity of compound **6u** was almost the same potent as that of **1a**, calculated from these ID_{50} values.

Conclusions

Investigation of the further details of SARs of the ethenesulfonamide derivative **1a** led to the discovery of compounds with various ET_A selectivities. Introduction of methyl groups to the phenyl group in the 2-phenylethensulfonamide moiety in **1a** increased the affinity for the ET_B receptor and led to the discovery of ET_A/ET_B mixed ET antagonists, the trimethylphenyl derivative **6s** (YM-95562). Unfortunately, **6s** lacked potent *in vivo* activity. However, it could be used as a valuable tool for *in vitro* study. We also found that the introduction of the ethyl group at the 1-position of the ethenyl group in the 2-phenylethensulfonamide moiety afforded **6u** (YM-91746) and retained both ET_A binding affinity and ET_A selectivity. Compound **6u** had a potent oral activity in the inhibition of the pressor response caused by a big ET-1 infusion in both pithed and conscious rats.

Experimental

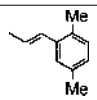
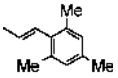
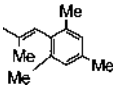
Melting points were determined on a Yanagimoto micro melting point apparatus without correction. ^{1}H-NMR spectra were recorded on a JNM-LA400, LA500, and A500 spectrometers using tetramethylsilane as an internal standard. MS spectra were determined with an Hitachi M-80 or JEOL JMS-DX300 spectrometer. High resolution (HR)-MS spectra were recorded using a JEOL JMS-700T mass spectrometer. Elemental analysis data were within±0.4% of the calculated values. All organic extracts were dried over anhydrous $MgSO_4$. Chromatographic purification was performed on Merck KGaA Silica gel 60 (0.040—0.063 mm).

The ethenesulfonamide derivatives (**4a**—**x**) were prepared according to the procedures described in method A—C. The physical data and the synthetic methods for **4a**—**x** are shown in Tables 6 and 7.

Method A. (*E*)-2-(4-Ethylphenyl)ethenesulfonamide (4g) To a solution of triphenylphosphine (86 mg, 0.328 mmol) in DMF (10 ml) was added palladium acetate ($Pd(OAc)_2$, 35 mg, 0.154 mmol) at room temperature under an argon atmosphere. After stirring for 5 min, to the mixture was added a solution of 1-bromo-4-ethylbenzene (1.48 g, 8.00 mmol), ethenesulfonamide (1.00 g, 9.35 mmol) and triethylamine (3.0 ml, 21.6 mmol) in DMF (5 ml). The mixture was stirred at 130 °C for 12 h and poured into 1 M aqueous HCl. The mixture was extracted with EtOAc, and the organic layer was

Table 7. Physical Data for Compounds **4**

RSO_2NH_2

No.	R[a]	mp (°C) (Solvent)	Yield (%)[a]	Method	400 MHz[b] ^{1}H-NMR (DMSO-d_6)[c] δ	FAB[d] MS m/z
4o		128—129 (Et_2O)	93	A	2.28 (3H, s), 2.32 (3H, s), 7.09 (1H, d, J=15.6 Hz), 7.10—7.16 (4H, m), 7.48 (1H, d, J=15.6 Hz), 7.49 (1H, s)	211 (M^+)
4p		124—125 (Et_2O)	83	A	2.23 (6H, s), 6.74 (1H, d, J=15.6 Hz), 7.08—7.18 (5H, m), 7.38 (1H, d, J=15.6 Hz)	211 (M^+)
4q		Yellow oil	100	A	1.13 (6H, t, J=7.3 Hz), 2.61 (4H, q, J=7.3 Hz), 6.64 (1H, d, J=15.6 Hz), 7.08—7.18 (4H, m), 7.20—7.26 (1H, m), 7.44 (1H, d, J=15.6 Hz)	238 (M^+-1)
4r		202—203 (EtOAc–Hex)	13	A	7.15 (1H, d, J=14.8 Hz), 7.25—7.40 (2H, m), 7.43—7.66 (4H, m)	252 (M^++1)
4s		171—172 (EtOAc–Hex)	45	A	2.29 (3H, s), 2.34 (6H, s), 4.68 (2H, br s), 6.59 (1H, d, J=16.2 Hz), 6.96 (2H, s), 7.65 (1H, d, J=16.2 Hz)	224 (M^+-1)
4t		143—144 (EtOH)	12	C	2.41 (3H, d, J=2.8 Hz), 6.85 (1H, s), 7.12 (2H, s), 7.40—7.46 (3H, m), 7.48—7.54 (2H, m)	198 (M^++1)
4u		127—128 (Et_2O)	43	C	1.21 (3H, t, J=7.6 Hz), 2.65 (2H, q, J=7.6 Hz), 7.11 (2H, s), 7.36 (1H, s), 7.37—7.49(5H, m)	211 (M^+)
4v		Brown oil	59	C	0.92 (3H, t, J=7.2 Hz), 1.58—1.67 (2H, m), 2.55—2.62 (2H, m), 7.07—7.11 (2H, m), 7.37 (1H, s), 7.39—7.49 (5H, m)	226 (M^++1)
4w		85—86 (Toluene)	6.3	C	2.41 (3H, s), 7.12 (2H, s), 7.40—7.46 (3H, m), 7.50—7.54 (2H, m)	198 (M^++1)
4x		173—174 (Toluene)	36	C	1.73 (3H, s), 2.09 (6H, s), 2.23 (3H, s), 6.90 (2H, s), 7.08 (2H, s), 7.22 (1H, s)	240 (M^++1)

a) The (*E*) form of all compounds was confirmed by the coupling constant between vinyl protons (J>14 Hz) in the ^{1}H-NMR spectrum except for **4t**—**x**. *b*) 90 MHz for **4s**. *c*) $CDCl_3$ for **4s**. *d*) EI-MS for **4o**, **p**, **u**.

washed with brine and concentrated *in vacuo.* The residue was chromatographed over silica gel using 40 : 1 $CHCl_3$–MeOH to give a solid. The solid was washed with Et_2O to give **4g** (1.24 g, 73%) as a yellow solid.

Method B. Methyl (*E*)-4-(2-Sulfamoylethenyl)benzoate (4k) To a solution of triphenylphosphine (100 mg, 0.381 mmol) in DMF (10 ml) was added palladium acetate ($Pd(OAc)_2$, 41 mg, 0.183 mmol) at room temperature under an argon atmosphere. After stirring for 5 min, to the mixture was added a solution of methyl 4-bromobenzoate (2.00 g, 9.30 mmol), ethenesulfonamide (1.10 g, 10.3 mmol) and triethylamine (3.5 ml, 21.6 mmol) in DMF (5 ml). The mixture was stirred at 140 °C for 23 h and concentrated *in vacuo.* To the residue was added water and the mixture was acidified with 1 M aqueous HCl. It was extracted with EtOAc. The organic layer was washed with brine and concentrated *in vacuo* to give 4-(2-sulfamoylethenyl)benzoic acid (**4l**). The solution of **4l** and concentrated sulfuric acid (0.1 ml, 1.88 mmol) in MeOH (30 ml) was stirred at 70 °C for 3 d. The mixture was concentrated *in vacuo.* To the residue was added water and the mixture was extracted with EtOAc. The organic layer was washed with brine and concentrated *in vacuo.* The residue was chromatographed over silica gel using hexane (Hex)–EtOAc (1 : 1) to give a solid. It was recrystallized from Hex–EtOAc to give **4k** (0.65 g, 29% in 2 steps) as colorless crystals.

Method C. (*E*)-2-(2-Methylphenyl)ethenesulfonamide (4a) To 6 ml (77.5 mmol) of DMF was added dropwise sulfurylchloride (5.3 ml, 66.1 mmol) at 0 °C. To the solution was added (2-methylphenyl)ethene (5 ml, 38.8 mmol) at room temperature and the mixture was stirred at 80 °C for 30 min. The mixture was poured into ice and extracted with $CHCl_3$, and the organic layer was washed with brine and concentrated *in vacuo* to give 2-(2-methylphenyl)ethenesulfonyl chloride as a yellow oil (6.17 g). To an ice-cooled solution of 2-(2-methylphenyl)ethenesulfonyl chloride (6.17 g) in tetrahydrofuran (THF) (25 ml) was added 29% aqueous ammonium hydroxide (7.6 ml), and the mixture was stirred at room temperature at 12 h. The mixture was acidified with 0.5 M aqueous HCl and extracted with EtOAc. The organic layer was washed with brine and concentrated *in vacuo* to give a solid. It was recrystallized from toluene to give **4a** (1.80 g, 24%) as colorless crystals.

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(2-methylphenyl)ethenesulfonamide (5a) To an ice-cooled solution of (*E*)-2-(2-methylphenyl)ethenesulfonamide (**4a**) (571 mg, 2.90 mmol) in DMF (6 ml) was added 60% sodium hydride in mineral oil (281 mg, 7.03 mmol) and the mixture was stirred for 10 min at room temperature. To the mixture 4,6-dichloro-5-(2-methoxyphenoxy)pyrimidine (**3**) (1.01 g, 2.89 mmol) was added, and the mixture was stirred for 2 h at room temperature. It was poured into ice-water and acidified with 1 M aqueous HCl. The mixture was extracted with EtOAc, and the organic layer was washed with brine and concentrated *in vacuo* to give a brown residue. It was crystallized from EtOH to give **5a** (1.16 g, 78%), mp 192—193 °C, 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.36 (3H, s), 3.81 (3H, s), 6.83 (1H, dd, J=1.6, 8.1 Hz), 6.85—6.90 (1H, m), 7.06—7.12 (1H, m), 7.14 (1H, dd, J=1.1, 8.1 Hz), 7.25—7.30 (2H, m), 7.32—7.37 (1H, m), 7.70 (1H, t, J=3.9 Hz), 7.75 (1H, d, J=7.0 Hz), 7.83—7.87 (1H, m), 7.92 (1H, d, J=16.1 Hz), 9.04 (2H, d, J=3.9 Hz). FAB-MS m/z: 510 (M^++1).

The chloropyrimidine derivatives (**5b**—**j**, **m**—**x**) were prepared according to the same procedure as **5a** using the corresponding ethenesulfonamide derivatives (**4b**—**j**, **m**—**x**).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(3-methylphenyl)ethenesulfonamide (**5b**): 780 mg (53%), mp 190—191 °C (EtOH), 500 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.32 (3H, s), 3.80 (3H, s), 6.82 (1H, d, J=8.0 Hz), 6.85—6.89 (1H, m), 7.07—7.10 (1H, m), 7.13 (1H, d, J=8.0 Hz), 7.26 (1H, d, J=8.0 Hz), 7.31—7.35 (1H, m), 7.51—7.54 (2H, m), 7.60 (1H, t, J=5.0 Hz), 7.80—7.90 (2H, m), 9.10 (2H, d, J=4.0 Hz). FAB-MS m/z: 510 (M^++1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(4-methylphenyl)ethenesulfonamide (**5c**): 830 mg (64%), mp 257—

258 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.33 (3H, s), 3.80 (3H, s), 6.82 (1H, d, J=6.8 Hz), 6.85—6.89 (1H, m), 7.06—7.16 (2H, m), 7.26 (2H, d, J=7.2 Hz), 7.63 (2H, d, J=7.2 Hz), 7.72 (1H, t, J=4.8 Hz), 7.76—7.90 (2H, m), 9.10 (2H, d, J=4.8 Hz). FAB-MS m/z: 510 (M^++1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(2-chlorophenyl)ethenesulfonamide (**5d**): 2.98 g (74%), mp 196—197 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 3.81 (3H, s), 6.81—6.90 (2H, m), 7.06—7.11 (1H, m), 7.12—7.16 (1H, m), 7.42—7.50 (2H, m), 7.56—7.59 (1H, m), 7.69 (1H, t, J=4.8 Hz), 7.94 (1H, dd, J=1.0, 7.5 Hz), 7.97—8.03 (2H, m), 9.02 (2H, d, J=4.8 Hz). FAB-MS m/z: 528 (M^+−1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(3-chlorophenyl)ethenesulfonamide (**5e**): 1.27 g (84%), mp 208—210 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 3.81 (3H, s), 6.82 (1H, dd, J=1.6, 8.0 Hz), 6.84—6.89 (1H, m), 7.06—7.11 (1H, m), 7.13 (1H, dd, J=1.6, 8.0 Hz), 7.46—7.52 (2H, m), 7.69—7.75 (2H, m), 7.85—7.89 (2H, m), 7.98 (1H, d, J=15.6 Hz), 9.09 (2H, d, J=4.8 Hz). FAB-MS m/z: 530 (M^++1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(4-chlorophenyl)ethenesulfonamide (**5f**): 1.11 g (73%), mp 244—245 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 3.80 (3H, s), 6.81—6.83 (1H, m), 6.84—6.89 (1H, m), 7.06—7.15 (2H, m), 7.53 (2H, d, J=8.4 Hz), 7.71 (1H, t, J=4.8 Hz), 7.79 (2H, d, J=8.4 Hz), 7.85—7.95 (2H, m), 9.09 (2H, d, J=4.8 Hz). FAB-MS m/z: 530 (M^++1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(4-ethylphenyl)ethenesulfonamide (**5g**): 1.11 g (62%), mp 258—259 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 1.17 (3H, t, J=7.7 Hz), 2.62 (2H, q, J=7.7 Hz), 3.80 (3H, s), 6.79—6.91 (2H, m), 7.05—7.16 (2H, m), 7.29 (2H, d, J=8.1 Hz), 7.65 (2H, d, J=8.1 Hz), 7.72 (1H, t, J=4.5 Hz), 7.79—7.91 (2H, m), 9.11 (2H, d, J=4.5 Hz). FAB-MS m/z: 524 (M^++1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(4-*tert*-butylphenyl)ethenesulfonamide (**5h**): 1.05 g (67%), mp 259—260 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 1.27 (9H, s), 3.80 (3H, s), 6.82 (1H, d, J=7.6 Hz), 6.85—6.91 (1H, m), 7.06—7.16 (2H, m), 7.47 (2H, d, J=8.8 Hz), 7 .68 (2H, d, J=8.8 Hz), 7.74 (1H, t, J=4.8 Hz), 7.83 (1H, d, J=14.4 Hz), 7.91 (1H, d, J=14.4 Hz), 9.13 (2H, d, J=4.8 Hz). FAB-MS m/z: 552 (M^++1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)ethenesulfonamide (**5i**): 1.02 g (68%), mp 227—230 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 3.80 (6H, s), 6.81 (1H, d, J=8.0 Hz), 6.84—6.89 (1H, m), 7.01 (2H, d, J=8.8 Hz), 7.06—7.11 (1H, m), 7.12—7.16 (1H, m), 7.68—7.75 (4H, m), 7.81—7.88 (1H, m), 9.11 (2H, d, J=4.8 Hz). FAB-MS m/z: 526 (M^++1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(4-trifluoromethylphenyl)ethenesulfonamide (**5j**): 2.18 g (70%), mp 212—213 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 3.81 (3H, s), 6.83 (1H, dd, J=1.6, 8.0 Hz), 6.84—6.90 (1H, m), 7.03—7.12 (1H, m), 7.13—7.16 (1H, m), 7.72 (1H, t, J=4.8 Hz), 7.83 (2H, d, J=8.0 Hz), 7.92—8.01 (3H, m), 8.05 (1H, d, J=15.6 Hz), 9.11 (2H, d, J=4.8 Hz). FAB-MS m/z: 564 (M^++1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(2,3-dimethylphenyl)ethenesulfonamide (**5m**): 954 mg (64%), mp 211—212 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.22 (3H, s), 2.26 (3H, s), 3.80 (3H, s), 6.82 (1H, dd, J=1.4, 8.4 Hz), 6.84—6.90 (1H, m), 7.06—7.18 (3H, m), 7.24 (1H, d, J=7.4 Hz), 7.55 (1H, d, J=7.4 Hz), 7.69 (1H, t, J=4.4 Hz), 7.76 (1H, d, J=15.1 Hz), 8.01 (1H, d, J=15.1 Hz), 9.02 (2H, d, J=4.4 Hz). FAB-MS m/z: 524 (M^++1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(2,4-dimethylphenyl)ethenesulfonamide (**5n**): 985 mg (66%), mp 222—223 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.28 (3H, s), 2.32 (3H, s), 3.80 (3H, s), 6.83 (1H, dd, J=1.6, 8.0 Hz), 6.88 (1H, dt, J=1.6, 8.0 Hz), 7.06—7.16 (4H, m), 7.65 (1H, d, J=8.0 Hz), 7.71 (1H, t, J=4.8 Hz), 7.80—7.90 (2H, m), 9.04 (2H, d, J=4.8 Hz). FAB-MS m/z: 524 (M^++1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(2,5-dimethylphenyl)ethenesulfonamide (**5o**): 930 mg (62%), mp 144—145 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.26 (3H, s), 2.30 (3H, s), 3.80 (3H, s), 6.81—6.89 (2H, m), 7.06—7.11 (1H, m), 7.12—7.17 (1H, m), 7.55 (1H, s), 7.71 (1H, t, J=5.2 Hz), 7.81—7.90 (2H, m), 9.04 (2H, d, J=5.2 Hz). FAB-MS m/z: 524 (M^++1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(2,6-dimethylphenyl)ethenesulfonamide (**5p**): 1.02 g (68%), mp 214—215 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.26 (6H, s), 3.80 (3H, s), 6.80—6.84 (1H, m), 6.86—6.91 (1H, m), 7.06—7.19 (5H, m), 7.54 (1H, d, J=16.0 Hz), 7.64 (1H, t, J=4.8 Hz), 7.87 (1H, d, J=16.0 Hz), 8.95 (2H, d, J=4.8 Hz). FAB-MS m/z: 524 (M^++1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(2,6-diethylphenyl)ethenesulfonamide (**5q**): 560 mg (35%), mp 181—182 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 0.98 (6H, t, J=7.6 Hz), 2.53 (4H, q, J=7.6 Hz), 3.81 (3H, s), 6.85—6.90 (1H, m), 6.77 (1H, d, J=7.6 Hz), 7.23 (1H, t, J=7.6 Hz), 7.36 (1H, d, J=15.6 Hz), 7.63 (1H, t, J=4.8 Hz), 7.95 (1H, d, J=15.6 Hz), 8.94 (2H, d, J=4.8 Hz). FAB-MS m/z: 552 (M^++1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(2,6-dichlorophenyl)ethenesulfonamide (**5r**): 369 (76%), mp 197—199 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 3.81 (3H, s), 6.79 (1H, dd, J=1.6, 8.0 Hz), 6.84—6.89 (1H, m), 7.06—7.11 (1H, m), 7.13 (1H, dd, J=1.8, 8.0 Hz), 7.39—7.44 (1H, m), 7.55 (1H, d, J=8.0 Hz), 7.63 (1H, t, J=4.8 Hz), 7.87 (1H, d, J=15.2 Hz), 7.94 (1H, d, J=15.2 Hz), 8.93 (2H, d, J=4.8 Hz). FAB-MS m/z: 564 (M^++1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(2,4,6-trimethylphenyl)ethenesulfonamide (**5s**): 1.23 g (80%), mp 212—214 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.23 (3H, s), 2.25 (6H, s), 3.80 (3H, s), 6.80—6.83 (1H, m), 6.85—6.90 (1H, m), 6.92 (2H, s), 7.07—7.12 (1H, m), 7.13—7.16 (1H, m), 7.54 (1H, d, J=16.0 Hz), 7.65 (1H, t, J=4.8 Hz), 7.84 (1H, d, J=16.0 Hz), 8.97 (2H, d, J=4.8 Hz). FAB-MS m/z: 538 (M^++1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-1-methyl-2-phenylethenesulfonamide (**5t**): 1.05 g (81%), mp 203—204 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.20 (3H, s), 3.81 (3H, s), 6.82 (1H, d, J=7.6 Hz), 6.85—6.91 (1H, m), 7.08 (1H, d, J=8.0 Hz), 7.10—7.16 (1H, m), 7.36—7.47 (6H, m), 7.65 (1H, s), 7.97 (1H, br s), 8.91—9.00 (2H, m). FAB-MS m/z: 510 (M^++1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-1-ethyl-2-phenylethenesulfonamide (**5u**): 886 mg (59%), mp 194—195 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 1.12—1.22 (3H, m), 2.60—2.74 (2H, m), 3.81 (3H, s), 6.79 (1H, d, J=7.2 Hz), 6.88 (1H, t, J=7.6 Hz), 7.09 (1H, t, J=7.6 Hz), 7.14 (1H, d, J=7.6 Hz), 7.36—7.46 (5H, m), 7.65 (1H, s), 7.90—8.10 (1H, m), 8.91—9.02 (2H, m), 11.99 (1H, br s). FAB-MS m/z: 524 (M^++1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-phenyl-1-propylethenesulfonamide (**5v**): 1.11 g (72%), mp 156—157 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 0.85 (3H, t, J=7.6 Hz), 1.55—1.63 (2H, m), 2.54—2.66 (2H, m), 3.81 (3H, s), 6.78 (1H, d, J=7.6 Hz), 6.87 (1H, t, J=7.6 Hz), 7.07—7.11 (1H, m), 7.14 (1H, d, J=8.0 Hz), 7.38—7.43 (5H, m), 7.65 (1H, s), 8.02 (1H, br s), 8.89—9.01 (2H, m). FAB-MS m/z: 538 (M^++1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-methyl-2-phenylethenesulfonamide (**5w**): 915 mg (71%), mp >300 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.48 (3H, s), 3.80 (3H, s), 6.81—6.90 (3H, m), 7.05—7.15 (2H, m), 7.20—7.35 (1H, m), 7.40—7.45 (2H, m), 7.61—7.68 (3H, m), 9.08 (2H, d, J=4.8 Hz). FAB-MS m/z: 510 (M^++1).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-1-methyl-2-(2,4,6-trimethylphenyl)ethenesulfonamide (**5x**): 1.35 g (86%), mp 204—205 °C (EtOH), 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 1.84 (6H, s), 2.19 (3H, s), 2.35 (3H, s), 3.80 (3H, s), 6.80—6.92 (4H, m), 7.05—7.17 (2H, m), 7.62 (1H, s), 7.71—7.81 (1H, m), 8.86—9.02 (2H, m). FAB-MS m/z: 552 (M^++1).

Methyl (*E*)-4-(2-{*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(2-pyrimidinyl)pyrimidin-4-yl]sulfamoyl}ethenyl)benzoate (5k) To an ice-cooled solution of methyl (*E*)-4-(2-sulfamoylethenyl)benzoate (**4k**) (650 mg, 2.69 mmol) in DMF (10 ml) was added 60% sodium hydride in mineral oil (220 mg, 5.50 mmol), and the mixture was stirred for 10 min at room temperature. To the mixture 4,6-dichloro-5-(2-methoxyphenoxy)pyrimidine (**3**) (900 mg, 2.58 mmol) was added, and the mixture was stirred for 15 h at room temperature. To the mixture was added 60% sodium hydride in mineral oil (60 mg, 1.50 mmol), and the mixture was stirred at room temperature for 4 h. It was poured into ice-water and acidified with 1 M aqueous HCl. The resulting precipitate was collected by filtration to give a mixture of **5k** and (*E*)-4-(2-{*N*-[6-chloro-5-(2-methoxyphenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]sulfamoyl}ethenyl)benzoic acid (**5l**). All of the obtained mixture (**5k**, **l**) and concentrated sulfuric acid (0.2 ml, 3.76 mmol) in MeOH (30 ml) were heated under reflux for 24 h. It was then concentrated *in vacuo* and water was added to the residue. The resulting precipitate was collected by filtration. It was recrystallized from MeOH to give **5k** (925 mg, 65%), mp 135—138 °C, 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 3.81 (3H, s), 3.87 (3H, s), 6.82 (1H, dd, J=1.6, 8.0 Hz), 6.86 (1H, dt, J=1.6, 8.0 Hz), 7.06—7.11 (1H, m), 7.13 (1H, dd, J=1.2, 8.0 Hz), 7.72 (1H, t, J=5.2 Hz), 7.88—7.92 (2H,

m), 7.91 (1H, d, J=8.0 Hz), 7.98—8.05 (3H, m), 9.10 (2H, d, J=5.2 Hz). FAB-MS m/z: 552 (M^+-1).

The ethenesulfonamide derivatives (**6a**—**j**, **6m**—**x**) were prepared according to the procedures described in methods D—G using the corresponding chloropyrimidine derivatives (**5a**—**j**, **5m**—**x**).

Method D. (*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(2-methylphenyl)ethenesulfonamide (6a) Sodium (230 mg, 10.0 mmol) was added to methanol (10 ml), and the mixture was stirred at room temperature until all sodium was dissolved. (*E*)-*N*-[6-chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(2-methylphenyl)ethenesulfonamide (**5a**) (514 mg, 1.01 mmol) was added to the solution and stirred at room temperature for 2 h. It was poured into ice-water and acidified with 1 M aqueous HCl. The mixture was extracted with EtOAc, and the organic layer was washed with brine and concentrated *in vacuo.* The residue was recrystallized from EtOAc–Et_2O–Hex to give **6a** (243 mg. 48%) as colorless crystals: mp 232—233 °C. 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.27 (3H, s), 3.81 (3H, s), 3.84 (3H, s), 6.41 (1H, d, J=7.5 Hz), 6.73 (1H, t, J=7.5 Hz), 6.88 (1H, t, J=7.5 Hz), 7.02 (1H, d, J=7.5 Hz), 7.17—7.27 (3H, m), 7.31 (1H, d, J=15.5 Hz), 7.59—7.72 (2H, m), 7.95—8.15 (1H, m), 9.00 (2H, d, J=4.3 Hz). FAB-MS m/z: 506 (M^++1). HR-MS Calcd for $C_{25}H_{24}N_5O_5S$ m/z 506.1498 (M^++1), Found 506.1478.

Method E. (*E*)-*N*-[6-(2-Hydroxyethoxy)-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(3-methylphenyl)ethenesulfonamide (6b) Sodium (315 mg, 13.7 mmol) was added to ethyleneglycol (7.7 ml, 137 mmol), and the mixture was stirred at 60 °C until all sodium was dissolved. (*E*)-*N*-[6-chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(3-methylphenyl)ethenesulfonamide (**5b**) (700 mg, 1.37 mmol) was added to the solution and stirred at 80 °C for 2.5 h. It was poured into ice-water and 1 M HCl, and the resulting precipitate was collected by filtration. The solid was chromatographed over silica gel using 20 : 1 $CHCl_3$–MeOH to give an oil. It was crystallized from Et_2O to give **6b** (533 mg, 73%): mp 167—169 °C. 500 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.33 (3H, s), 3.20—3.60 (2H, m), 3.83 (3H, s), 4.30—4.45 (2H, m), 4.69 (1H, br s), 6.70—6.83 (2H, m), 7.04—7.11 (2H, m), 7.26 (1H, d, J=7.5 Hz), 7.32—7.34 (1H, m), 7.50—7.60 (2H, m), 7.57 (1H, d, J=15.5 Hz), 7.96 (1H, d, J=15.5 Hz), 9.08 (2H, d, J=4.0 Hz), 11.34 (1H, s). FAB-MS m/z: 536 (M^++1). *Anal.* Calcd for $C_{26}H_{25}N_5O_6S$: C, 58.31; H, 4.70; N, 13.08; S, 5.99. Found: C, 58.33; H, 4.59; N, 13.08; S, 6.09.

Method F. (*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(4-methylphenyl)ethenesulfonamide (6c) To the solution of *N*-[6-chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(4-methylphenyl)ethenesulfonamide (**5c**) (450 mg, 0.882 mmol) in DMF (5 ml) was added sodium methoxide (477 mg, 8.82 mmol), and the mixture was stirred at room temperature for 12 h. It was poured into ice-water and acidified with 1 M HCl. The resulting precipitate was collected by filtration. It was chromatographed over silica gel using $CHCl_3$–MeOH (40 : 1) to give a solid. It was recrystallized from EtOH to give **6c** (335 mg, 75%): mp 165—166 °C. 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.33 (3H, s), 3.83 (3H, s), 3.89 (3H, s), 6.66 (1H, d, J=8.0 Hz), 6.78—6.86 (1H, m), 7.03 (1H, t, J=8.0 Hz), 7.09 (1H, d, J=8.0 Hz), 7.27 (2H, d, J=7.8 Hz), 7.62 (2H, d, J=7.8 Hz), 7.69 (1H, 7, J=4.0 Hz), 7.73 (1H, d, J=15.2 Hz), 7.91 (1H, d, J=15.2 Hz), 9.09 (2H, d, J=4.0 Hz). FAB-MS m/z: 506 (M^++1). *Anal.* Calcd for $C_{25}H_{23}N_5O_5S$: C, 59.40; H, 4.59; N, 13.85; S, 6.34. Found: C, 59.25; H, 4.46; N, 13.89; S, 6.44.

Method G. Potassium (*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-1-ethyl-2-phenylethenesulfonamidate (6u) To the solution of *N*-[6-chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-1-ethyl-2-phenylethenesulfonamide (**5u**) (480 mg, 0.916 mmol) in DMF (5 ml) was added sodium methoxide (495 mg, 9.16 mmol), and the mixture was stirred at room temperature for 5 h. It was poured into ice-water and acidified with 1 M HCl. The resulting precipitate was collected by filtration. It was chromatographed over silica gel using $CHCl_3$–MeOH (40 : 1) to give (*E*)-*N*-[6-methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-1-ethyl-2-phenylethenesulfonamide as a yellow amorphous solid (375 mg, 79%). To a solution of potassium hydroxide (0.1 M, 7.22 ml, 0.722mmol) was added (*E*)-*N*-[6-methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-1-ethyl-2-phenylethenesulfonamide (375 mg). The mixture was stirred at room temperature for 30 min and concentrated *in vacuo.* The residue was crystallized from Et_2O to give **6u** (321 mg, 60%) as yellow crystals. mp 146—150 °C (Et_2O). 400 Hz ^{1}H-NMR (DMSO-d_6) δ: 1.00 (3H, t, J=7.2 Hz), 2.39 (2H, q, J=7.2 Hz), 3.78 (3H, s), 3.83 (3H, s), 6.41 (1H, d, J=8.0 Hz), 6.70—6.75 (1H, m), 6.85—6.90 (1H, m), 7.00 (1H, d, J=7.2 Hz), 7.15—7.20 (2H, m), 7.22—7.28 (1H, m), 7.29—7.36 (3H, m), 7.54 (1H, t, J=4.8 Hz), 8.88 (2H, d, J=4.8 Hz). FAB-MS m/z: 596 (M^++K). *Anal.* Calcd for $C_{26}H_{24}N_5O_5SK\cdot1.0H_2O$: C, 54.25; H, 4.55; N, 12.17; S, 5.57. Found: C, 54.41; H, 4.44; N, 12.15; S, 5.52.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(2-chlorophenyl)ethenesulfonamide (**6d**) (Method D): 370 mg (74%): mp 97—98 °C (EtOAc–Et_2O–Hex). 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 3.83 (3H, s), 3.91 (3H, s), 6.68 (1H, d, J=8.4 Hz), 6.77—6.86 (1H, m), 7.03 (1H, t, J=7.6 Hz), 7.09 (1H, d, J=7.6 Hz), 7.42—7.51 (2H, m), 7.54—7.60 (1H, m), 7.62—7.69 (1H, m), 7.89—7.99 (2H, m), 8.14 (1H, d, J=14.0 Hz), 8.97—9.07 (2H, m), 11.63 (1H, s). FAB-MS m/z: 526 (M^++1). HR-MS Calcd for $C_{24}H_{21}ClN_5O_5S$ m/z 526.0952 (M^++1), Found 526.0953.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(3-chlorophenyl)ethenesulfonamide (**6e**) (Method D): 267 mg (90%): mp 95—100 °C (EtOAc–Hex). 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 3.83 (3H, s), 3.90 (3H, s), 6.67 (1H, d, J=7.2 Hz), 6.73—6.86 (1H, m), 7.03 (1H, t, J=7.6 Hz), 7.09 (1H, d, J=8.0 Hz), 7.46—7.54 (2H, m), 7.67—7.91 (4H, m), 8.11 (1H, d, J=15.6 Hz), 9.08 (2H, d, J=3.2 Hz), 11.59 (1H, s). FAB-MS m/z: 526 (M^++1). FAB-MS m/z: (M^++1). *Anal.* Calcd for $C_{24}H_{20}ClN_5O_5S$: C, 54.81; H, 3.83; N, 13.32; S, 6.40; Cl, 6.74. Found: C, 54.57; H, 3.69; N, 13.21; S, 6.08; Cl, 6.79.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(4-chlorophenyl)ethenesulfonamide (**6f**) (Method F): 413 mg (83%): mp 63—64 °C (Et_2O). 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 3.83 (3H, s), 3.89 (3H, s), 6.67 (1H, d, J=7.6 Hz), 6.80—6.84 (1H, m), 7.03 (1H, t, J=8.0 Hz), 7.09 (1H, d, J=8.0 Hz), 7.54 (2H, d, J=8.0 Hz), 7.63—7.72 (1H, m), 7.74—7.85 (3H, m), 8.02 (1H, d, J=15.6 Hz), 9.09 (2H, d, J=4.0 Hz), 11.52 (1H, br s). FAB-MS m/z: 526 (M^++1). *Anal.* Calcd for $C_{24}H_{20}N_5O_5SCl\cdot0.40H_2O$: C, 53.70; H, 4.37; N, 13.59; S, 5.56; Cl, 6.14. Found: C, 53.85; H, 4.32; N, 13.43; S, 5.47; Cl, 6.32.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(4-ethylphenyl)ethenesulfonamide (**6g**) (Method F): 203 mg (45%): mp 104—107 °C (MeOH–EtOH). 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 1.18 (3H, t, J=7.6 Hz), 2.63 (2H, q, J=7.6 Hz), 3.83 (3H, s), 3.89 (3H, s), 6.66 (1H, d, J=7.6 Hz), 6.78—6.86 (1H, m), 7.03 (1H, t, J=7.6 Hz), 7.09 (1H, d, J=8.4 Hz), 7.30 (2H, d, J=8.0 Hz), 7.62—7.72 (3H, m), 7.77 (1H, d, J=15.6 Hz), 7.93 (1H, d, J=15.6 Hz), 9.09 (2H, d, J=4.8 Hz), 11.44 (1H, br s). FAB-MS m/z: 520 (M^++1). *Anal.* Calcd for $C_{26}H_{25}N_5O_5S\cdot0.50H_2O$: C, 59.08; H, 4.96; N, 13.25; S, 6.07. Found: C, 59.38; H, 4.72; N, 13.53; S, 6.16.

Potassium (*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)-pyrimidin-4-yl]-2-(4-*tert*-butylphenyl)ethenesulfonamidate (**6h**) (Method G): 318 mg (60%): mp 155—156 °C (Et_2O). 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 1.28 (9H, s), 3.80 (3H, s), 3.84 (3H, s), 6.37—6.41 (1H, m), 6.70—6.76 (1H, m), 6.84—6.90 (1H, m), 6.98—7.03 (1H, m), 7.09 (1H, d, J=15.6 Hz), 7.41 (2H, d, J=8.0 Hz), 7.50 (2H, d, J=8.0 Hz), 7.63 (1H, t, J=4.8 Hz), 8.13 (1H, d, J=15.6 Hz), 9.05 (2H, d, J=4.8 Hz). FAB-MS m/z: 624 (M^++K). *Anal.* Calcd for $C_{28}H_{28}N_5O_5SK\cdot2.0H_2O$: C, 54.09; H, 5.19; N, 11.26; S, 5.16. Found: C, 54.17; H, 5.02; N, 11.46; S, 5.02.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(4-methoxyphenyl)ethenesulfonamide (**6i**) (Method D): 248 mg (100%): mp 117—123 °C (EtOAc–Hex). 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 3.80 (3H, s), 3.83 (3H, s), 3.89 (3H, s), 6.66 (1H, d, J=8.0 Hz), 6.78—6.85 (1H, m), 6.99—7.06 (3H, m), 7.09 (1H, d, J=8.2 Hz), 7.64—7.72 (3H, m), 7.76 (1H, d, J=15.6 Hz), 7.82 (1H, d, J=15.6 Hz), 9.09 (2H, d, J=4.8 Hz), 11.36 (1H, s). FAB-MS m/z: 520 (M^+−1). HR-MS Calcd for $C_{25}H_{24}N_5O_6S$ m/z 522.1447 (M^++1), Found 522.1467.

Potassium (*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(4-trifluoromethylphenyl)ethenesulfonamidate (**6j**) (Method G): 270 mg (85%): mp 180—185 °C (Et_2O–Hex). 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 3.80 (3H, s), 3.85 (3H, s), 6.39 (1H, d, J=8.0 Hz), 6.71—6.77 (1H, m), 6.85—6.91 (1H, m), 7.01 (1H, d, J=7.6 Hz), 7.19 (1H, d, J=16.4 Hz), 7.62 (1H, t, J=4.8 Hz), 7.78 (2H, d, J=8.0 Hz), 7.82—7.87 (2H, d, J=8.0 Hz), 8.42 (1H, d, J=16.4 Hz), 9.06 (2H, d, J=4.8 Hz). FAB-MS m/z: 636 (M^++K). *Anal.* Calcd for $C_{25}H_{19}F_3N_5O_5SK\cdot1.0H_2O$: C, 48.78; H, 3.44; N, 11.38; S, 5.21; F, 9.26. Found: C, 48.95; H, 3.32; N, 11.47; S, 5.21; F, 9.45.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(2,3-dimethylphenyl)ethenesulfonamide (**6m**) (Method F): 230 mg (58%): mp 96—99 °C (MeOH). 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.21 (3H, s), 2.27 (3H, s), 3.83 (3H, s), 3.90 (3H, s), 6.67 (1H, d, J=7.4 Hz), 6.83 (1H, t, J=7.4 Hz), 7.03 (1H, t, J=7.7 Hz), 7.10 (1H, d, J=7.7 Hz), 7.12—7.20 (1H, m), 7.24 (1H, d, J=7.3 Hz), 7.54 (1H, d, J=7.3 Hz), 7.62—7.70 (1H, m), 7.86 (1H, d, J=20.0 Hz), 7.94 (1H, d, J=20.0 Hz), 9.02 (2H, d,

J=4.4 Hz), 11.43 (1H, br s). FAB-MS m/z: 520 (M^++1). *Anal.* Calcd for $C_{26}H_{25}N_5O_5S \cdot 1.0H_2O$: C, 58.09; H, 5.06; N, 13.03; S, 5.96. Found: C, 58.15; H, 5.00; N, 12.96; S, 5.86.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(2,4-dimethylphenyl)ethenesulfonamide (**6n**) (Method F): 210 mg (53%): mp 165—166 °C (MeOH–EtOH). 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.27 (3H, s), 2.30 (3H, s), 3.83 (3H, s), 3.90 (3H, s), 6.67 (1H, d, J=7.7 Hz), 6.76—6.88 (1H, m), 6.98—7.16 (4H, m), 7.60—7.72 (2H, m), 7.78 (1H, d, J=15.3 Hz), 7.92 (1H, d, J=15.3 Hz), 9.03 (2H, d, J=4.4 Hz), 11.40 (1H, br s). FAB-MS m/z: 520 (M^++1). *Anal.* Calcd for $C_{26}H_{25}N_5O_5S$: C, 60.10; H, 4.85; N, 13.48; S, 6.17 Found: C, 59.92; H, 4.90; N, 13.62; S, 6.15.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(2,5-dimethylphenyl)ethenesulfonamide (**6o**) (Method F): 435 mg (84%): mp 93—95 °C (MeOH–EtOH). 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.27 (3H, s), 2.92 (3H, s), 3.83 (3H, s), 3.90 (3H, s), 6.67 (1H, d, J=8.4 Hz), 6.82 (1H, t, J=7.6 Hz), 7.00—7.06 (1H, m), 7.09 (1H, d, J=8.4 Hz), 7.13—7.18 (2H, m), 7.54 (1H, s), 7.69 (1H, t, J=4.0 Hz), 7.79 (1H, d, J=15.6 Hz), 7.97 (1H, d, J=15.6 Hz), 9.03 (2H, d, J=4.0 Hz), 11.47 (1H, s). FAB-MS m/z: 520 (M^++1). *Anal.* Calcd for $C_{26}H_{25}N_5O_5S \cdot 0.5H_2O$: C, 59.08; H, 4.96; N, 13.25; S, 6.07. Found: C, 58.80; H, 5.07; N, 13.00; S, 5.94.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(2,6-dimethylphenyl)ethenesulfonamide (**6p**) (Method F): 265 mg (51%): mp 91—92 °C (MeOH). 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.27 (6H, s), 3.82 (3H, s), 3.91 (3H, s), 6.66 (1H, d, J=8.0 Hz), 6.79—6.87 (1H, m), 7.01—7.06 (1H, m), 7.07—7.12 (3H, m), 7.14—7.19 (1H, m), 7.56—7.65 (2H, m), 7.81 (1H, d, J=16.0 Hz), 8.93 (2H, d, J=4.4 Hz), 11.46 (1H, s,). FAB-MS m/z: 520 (M^++1). *Anal.* Calcd for $C_{26}H_{25}N_5O_5S \cdot 0.60H_2O$: C, 58.88; H, 4.98; N, 13.20; S, 6.05. Found: C, 58.59; H, 4.81; N, 13.07; S, 5.85.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(2,6-diethylphenyl)ethenesulfonamide (**6q**) (Method F): 265 mg (51%): mp 142—143 °C (MeOH–EtOH). 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 0.98 (6H, d, J=7.6 Hz), 2.54 (4H, q, J=7.6 Hz), 3.83 (3H, s), 3.91 (3H, s), 6.62 (1H, d, J=7.2 Hz), 6.80—6.85 (1H, m), 7.00—7.14 (4H, m), 7.23 (1H, t, J=7.6 Hz), 7.42 (1H, d, J=16.0 Hz), 7.56—7.63 (1H, m), 7.90 (1H, d, J=16.0 Hz), 8.91 (2H, d, J=3.6 Hz), 11.60 (1H, br s). FAB-MS m/z: 548 (M^++1). *Anal.* Calcd for $C_{28}H_{29}N_5O_5S \cdot 0.50H_2O$: C, 60.42; H, 5.43; N, 12.58; S, 5.76. Found: C, 60.57; H, 5.46; N, 12.74; S, 5.88.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(2,6-dichlorophenyl)ethenesulfonamide (**6r**) (Method D): 220 mg (89%): mp 114—115 °C (EtOH). 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 3.82 (3H, s), 3.91 (3H, s), 6.65 (1H, d, J=7.6 Hz), 6.82 (1H, t, J=7.6 Hz), 7.03 (1H, t, J=7.6 Hz), 7.09 (1H, d, J=7.6 Hz), 7.40—7.45 (1H, m), 7.56 (2H, d, J=8.0 Hz), 7.59—7.65 (1H, m), 7.87 (1H, d, J=15.2 Hz), 8.07 (1H, d, J=15.2 Hz), 8.90—8.97 (2H, m), 11.69 (1H, br s). FAB-MS m/z: 560 (M^++1). *Anal.* Calcd for $C_{24}H_{19}Cl_2N_5O_5S \cdot 1.0H_2O$: C, 49.84; H, 3.66; N, 12.11; S, 5.54; Cl, 12.26. Found: C, 49.62; H, 3.63; N, 12.10; S, 5.55; Cl, 12.41.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(2,4,6-trimethylphenyl)ethenesulfonamide (**6s**) (Method D): 291 mg (84%): mp. 167—168 °C (EtOH). 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.23 (3H, s), 2.50 (6H, s), 3.82 (3H, s), 3.90 (3H, s), 6.65 (1H, d, J=8.0 Hz), 6.80—6.85 (1H, m), 6.92 (2H, s), 7.01—7.05 (1H, m), 7.09 (1H, d, J=8.0 Hz), 7.57—7.65 (2H, m), 7.77 (1H, d, J=16.0 Hz), 8.95 (2H, d, J=4.8 Hz), 11.44 (1H, s). FAB-MS m/z: 534 (M^++1). *Anal.* Calcd for $C_{27}H_{27}N_5O_5S \cdot 0.25H_2O$: C, 60.27; H, 5.15; N, 13.01; S, 5.96. Found: C, 60.16; H, 5.01; N, 12.93; S, 5.87.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-1-methyl-2-phenylethenesulfonamide (**6t**) (Method F): 340 mg (67%): mp 148—149 °C (Et_2O–EtOH). 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.22 (3H, s), 3.83 (3H, s), 3.87 (3H, s), 6.65 (1H, d, J=7.2 Hz), 6.81—6.86 (1H, m), 7.04 (1H, t, J=7.6 Hz), 7.09 (1H, d, J=8.0 Hz), 7.34—7.43 (5H, m), 7.61 (1H, t, J=4.0 Hz), 7.87 (1H, s), 8.91 (2H, d, J=4.0 Hz), 11.29 (1H, s). FAB-MS m/z: 506 (M^++1). *Anal.* Calcd for $C_{25}H_{23}N_5O_5S$: C, 59.40; H, 4.59; N, 13.85; S, 6.34. Found: C, 59.30; H, 4.56; N, 13.75; S, 6.29.

Potassium (*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-phenyl-1-propylethenesulfonamidate (**6v**) (Method G): 325 mg (68%): mp 93—96 °C (Et_2O). 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 0.70 (3H, t, J=7.2 Hz), 1.41—1.51 (2H, m), 2.31—2.37 (2H, m), 3.77 (3H, s), 3.84 (3H, s), 6.39 (1H, dd, J=1.8, 8.4 Hz), 6.69—6.75 (1H, m), 6.84—6.90 (1H, m), 6.98—7.02 (1H, m), 7.13—7.18 (2H, m), 7.21—7.26 (1H, m), 7.29—7.35 (2H, m), 7.37 (1H, s), 7.53 (1H, t, J=4.8 Hz), 8.66 (2H, d, J=4.8 Hz). FAB-MS m/z: 610 (M^++K). HR-MS Calcd for $C_{27}H_{27}N_5O_5SK$ m/z 572.1370 (M^++1), Found 572.1355.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-methyl-2-phenylethenesulfonamide (**6w**) (Method F): 33 mg (3.0%): mp >300 °C (Et_2O). 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 2.23 (3H, d, J=0.8 Hz), 3.79 (3H, s), 3.85 (3H, s), 6.39 (1H, dd, J=1.6, 8.0 Hz), 6.70—6.75 (1H, m), 6.85—6.90 (1H, m), 7.01 (1H, dd, J=1.6, 8.0 Hz), 7.18 (1H, d, J=0.8 Hz), 7.26—7.34 (3H, m), 7.52—7.56 (2H, m), 7.61 (1H, t, J=4.8 Hz), 8.98 (2H, d, J=4.8 Hz). FAB-MS m/z: 506 (M^++1). HR-MS Calcd for $C_{25}H_{24}N_5O_5S$ m/z 506.1498 (M^++1), Found 506.1484.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-1-methyl-2-(2,4,6-trimethylphenyl)ethenesulfonamide (**6x**) (Method F): 169 mg (43%): mp 190—192 °C (MeOH–EtOH). 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 1.77 (3H, s), 1.83 (6H, s), 2.19 (3H, s), 3.83 (3H, s), 4.03 (3H, s), 6.65 (1H, d, J=7.6 Hz), 6.78—6.88 (3H, m), 7.05 (1H, t, J=7.6 Hz), 7.11 (1H, d, J=7.6 Hz), 7.56 (1H, t, J=4.8 Hz), 7.71 (1H, s), 8.88 (2H, d, J=4.8 Hz), 11.28 (1H, s). FAB-MS m/z: 546 (M^+−1). *Anal.* Calcd for $C_{28}H_{29}N_5O_5S$: C, 61.41; H, 5.34; N, 12.79; S, 5.86. Found: C, 61.27; H, 5.32; N, 12.93; S, 5.86.

(*E*)-4-(2-{*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)-pyrimidin-4-yl]sulfamoyl}ethenyl)benzoic Acid (6l) Sodium (170 mg, 7.39 mmol) was added to methanol (10 ml) and stirred at room temperature until all sodium was dissolved. Methyl (*E*)-4-(2-{*N*-[6-chloro-5-(2-methoxyphenoxy)-2-(2-pyrimidinyl)-4-pyrimidinyl]sulfamoyl}ethenyl)benzoate (**5k**) (410 mg, 0.740 mmol) was added to the solution, and the mixture was stirred at 50 °C for 4 h. The mixture was concentrated *in vacuo.* 1 M aqueous HCl was added to the residue, and the resulting precipitate was collected by filtration. The solid was washed with EtOH to give **6l** (350 mg 88%) as a yellow solid: mp >250 °C (EtOH). 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 3.83 (3H, s), 3.90 (3H, s), 6.67 (1H, d, J=8.4 Hz), 6.82 (1H, t, J=7.2 Hz), 7.03 (1H, t, J=7.6 Hz), 7.09 (1H, d, J=7.6 Hz), 7.65—7.74 (1H, m), 7.82—7.92 (3H, m), 8.00 (2H, d, J=8.0 Hz), 8.11 (1H, d, J=15.6 Hz), 9.10 (2H, d, J=4.4 Hz), 11.59 (1H, s), 13.15 (1H, s). FAB-MS m/z: 536 (M^++1). *Anal.* Calcd for $C_{25}H_{21}N_5O_7S$: C, 56.07; H, 3.95; N, 13.08; S, 5.99. Found: C, 55.83; H, 3.80; N, 13.18; S, 6.01.

Methyl (*E*)-4-(2-{*N*-[6-methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]sulfamoyl}ethenyl)benzoate (6k) To the solution of **6l** (150 mg, 0.280 mmol) in MeOH (10 ml) was added concentrated sulfuric acid (0.1 ml, 1.88 mmol) and the solution was heated under reflux for 18 h. The mixture was concentrated *in vacuo*, and water was added to the residue. It was extracted with $CHCl_3$. The organic layer was washed with brine and concentrated *in vacuo.* The residual solid was recrystallized from EtOAc to give **6k** (102 mg, 66%) as colorless crystals: mp 178—179 °C. 400 MHz ^{1}H-NMR (DMSO-d_6) δ: 3.83 (3H, s), 3.87 (3H, s), 3.89 (3H, s), 6.67 (1H, d, J=7.6 Hz), 6.75—6.85 (1H, m), 6.96—7.06 (1H, m), 7.09 (1H, d, J=7.6 Hz), 7.66—7.74 (1H, m), 7.80—7.95 (3H, m), 8.03 (2H, d, J=7.6 Hz), 8.13 (1H, d, J=15.2 Hz), 9.09 (2H, d, J=4.8 Hz), 11.60 (1H, s, Hz). FAB-MS m/z: 550 (M^++1). *Anal.* Calcd for $C_{26}H_{23}N_5O_7S$: C, 56.82; H, 4.22; N, 12.74; S, 5.83. Found: C, 56.51; H, 4.21; N, 12.56; S, 5.71.

Binding Assay For competition studies, [^{125}I]ET-1 (200 pM) was added to each membrane preparation, which was incubated with various concentrations of compounds in 250 μl of assay buffer containing 50 mM Tris–HCl, pH 7.4, 10 mM $MgCl_2$ and 0.01% Bovine Serum Albumin (BSA). Binding reactions were initiated by the addition of the membrane preparations. After the incubation period (180 min, room temperature), the reaction was terminated by the addition of 3 ml of ice-cold Tris buffer (50 mM Tris–HCl, pH 7.4, 10 mM $MgCl_2$ and 0.01% BSA) followed by rapid filtration through Whatman GF/C filters. The filters were rinsed twice and the radioactivity retained on the filters was counted using a gamma counter at 60% efficiency. Each assay was performed in duplicate and nonspecific binding was assessed in the presence of 100 nM unlabeled ET-1. The IC_{50} values were calculated with a non-linear regression analysis.

Functional Assay *in Vivo* (Inhibition of Pressor Response to Big ET-1): Conscious Normotensive Rats Male Wistar rats were anesthetized with sodium pentobarbital (60 mg/kg i.p.). The right common carotid artery and the left jugular vein were cannulated with a polyethylene tube for determination of blood pressure and heart rate, and for i.v. administration of big ET-1 (0.5 nmol/kg). The animals were allowed to recover for 2 to 3 d after the operation, during which time they were housed in individual cages with free access to rat chow and water. After an appropriate equilibration period, bolus i.v. doses of big ET-1 were administered to determine control responses and patency of catheters. Each rat was treated with a single *p.o.* dose of antagonist or vehicle (0.5% methyl cellulose) and any changes in blood pressure were noted. The percentage of the pressor responses to big ET-1 challenges during the subsequent 6.5 h and at 24 h were used as a measure of big ET-1 inhibition.

Functional Assay *in Vivo* (Inhibition of Pressor Response to Big ET-1): Pithed Rats *In vivo* antagonistic activity in pithed rats was evaluated according to the method of Clozel *et al.* described previously.[7g] Briefly, male Wistar rats were pithed under sodium pentobarbital anesthesia and artificially ventilated with room air. The right common carotid artery and the left femoral vein were cannulated for blood pressure measurements and i.v. injection of drugs, respectively. After stabilization of blood pressure, various doses of (1 ml/kg) test compounds or vehicle (distilled water) were injected. Five minutes later, the first dose of big ET-1 was injected intravenously. In another series of experiments, the oral activities of test compounds were assessed. Varying doses of (5 ml/kg) test compounds or vehicle (0.5% methyl cellulose) were administered by gastric gavage with a cannula. About 20 min later, the rats were anesthetized with sodium pentobarbital, and 30 min later, pithed and ventilated. After stabilization of blood pressure, the first dose of big ET-1 was injected intravenously. In this study, the DR_2 value was defined as the dose of test compounds which was required to produce a 2-fold rightward shift of the dose–response curves of big ET-1 in DBP.

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References and Notes

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