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Ethenesulfonamide and Ethanesulfonamide Derivatives, a Novel Class of Orally Active Endothelin-A Receptor Antagonists

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Abstract—In the previous paper, we described a series of 2-phenylethenesulfonamide derivatives, a novel class of ET_A-selective endothelin (ET) receptor antagonists, including the 2-methoxyethoxy derivative **2a** and the 2-fluoroethoxy derivative (**2b**). In this paper, we wish to report further details of structure–activity relationships (SARs) of the two regions of the molecule in compound **2b**, which were the alkoxy region at the 6-position of the core pyrimidine ring and the 2-phenylethenesulfonamide region. In these modifications, replacement of the 2-fluoroethoxy group with a methoxy group (**6e**) and replacement of the 2-phenylethenesulfonamide group with a 2-(pyridin-3-yl)ethenesulfonamide group (**6l**) or 2-phenylethanesulfonamide group (**6q**) were well tolerated both in the ET_A binding affinity and ET_A selectivity. Among them, compound **6e** showed further improvement in oral activity compared to **2b**. After oral administration, compound **6e** inhibited the big ET-1 induced pressor response in conscious rats at 0.3 mg /kg with a duration of >6.5 h. Compound **6e** also exhibited a potent antagonistic activity in the pithed rats. © 2001 Elsevier Science Ltd. All rights reserved.

Introduction

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

Two subtypes of receptors for ETs, termed ET_A receptor and ET_B receptor, have been cloned and stably expressed in mammals, and the 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.[4]

A number of ET_A- selective and ET_A/ET_B non-selective or mixed non-peptide antagonists have been reported for decades,[5] some literature sources indicated that the ET_A-selective antagonists were the promising candidates for the treatments of cardiovascular diseases such as hypertension and heart failure.[6] So we decided that our first goal was to discover the ET_A-selective antagonists.

In the previous paper,[7] we reported on a series of 2-phenylethenesulfonamide derivatives which have a hydrogen-bond accepting or donating group in the side chain at the 6-position of the pyrimidine ring and the discovery of potent and ET_A-selective antagonists (**2a**–**c**) through the modification of the ET_A/ET_B mixed antagonist, Ro47-0203 (Bosentan, **1**) (Fig. 1).

Although **2b** showed high ET_A-selectivity in vitro and potent oral antagonistic activity in vivo, we further

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investigated the structure–activity relationships (SARs) of the alkoxy region at the 6-position of the core pyrimidine ring in compound **2b,** partly because the toxicity of the 2-fluoroethanol had been reported.[8] We were concerned that metabolism of **2b** might give toxic 2-fluoroethanol or 2-fluoroacetic acid, and we considered that we should avoid using the toxic 2-fluoroethanol for the large scale synthesis. We were also curious to explore the effect of a hydrogen-bond acceptor, such as a fluorine atom or a methoxy group, in the alkoxy side chain at the 6-position. So we started examining compounds that have a simple alkoxy group at the 6-position without hydrogen-bond acceptor or donor in the alkyl moiety.

After we discovered an alternative substituent of a 2-fluoroethoxy group at the 6-position, we further explored the details of the SARs of the 2-phenylethensulfonamide region of the molecule in our class of compounds.

Chemistry

Schemes 1 and 2 show the syntheses of alkenesulfonamide or alkanesulfonamide derivatives.

The starting compound (**3**) was prepared according to the method reported by Burri et al.[9] Nucleophilic substitution of the pyrimidine derivative **3** with (*E*)-alkenesulfonamide (**4a–g and 4k**) or alkanesulfonamide (**4h–j**) resulted in the chloropyrimidines (**5a–k**). The chloropyrimidine **5** was treated with alkoxide in DMF or the corresponding alcohol to give alkoxy analogues (**6a–e, 6i–r**). Treatment **5** with sodium thioalkoxide in DMF gave the alkysulfanyl analogue **6f**. Compound **5k** was heated with methylamine in aqueous dioxane to give the methylamino derivative (**6g**). The hydroxy analogue (**6h**) was synthesized by treatment **5k** with sodium hydroxide in aqueous DMF.

In Scheme 2, an outline of the synthesis of the key intermediates (**4a–j**) is given.

A Palladium-catalyzed Heck reaction between ethenesulfonamide (**7**) and arylbromide afforded the (*E*)-2-arylethenesulfonamide derivatives **4a**, **b**, **f**, **g** (method A).[10]

(*E*)-2-Arylethenesulfonamide derivatives **4c–e** also have been synthesized via the route shown in method B.[11] The aldehyde (**8**) was reacted with the dianion of *N*-*tert*-butyl methanesulfonamide to give the alcohol (**9**). Compound **9** was then mesylated with methanesufonylchloride, followed by elimination of methanesulfonic acid to give the *N*-*tert*-butyl ethenesulfonamide (**10**). The *tert*-butyl group in **10** was removed using TFA to give the (*E*)-2-arylethenesulfonamide derivatives **4c–e**.

The alkanesulfonamide derivative **4h–j** was prepared in three steps (method C).[12] The chloride (**11**) was converted to the sulfonic acid (**12**) with Na_2SO_3. Compound **12** was treated with thionyl chloride, followed by aqueous annmonia to give the alkanesulfonamide derivative **4h–j.**

The (*E*) form of all compounds with an ethenyl group was confirmed by the coupling constant between vinyl protons ($J > 14$ Hz) in the ^{1}H NMR spectrum except **5c, 5e**. **5f** (see Experimental).

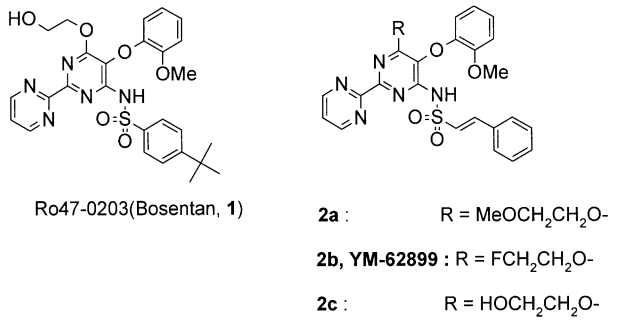


Figure 1.

Results and Discussion

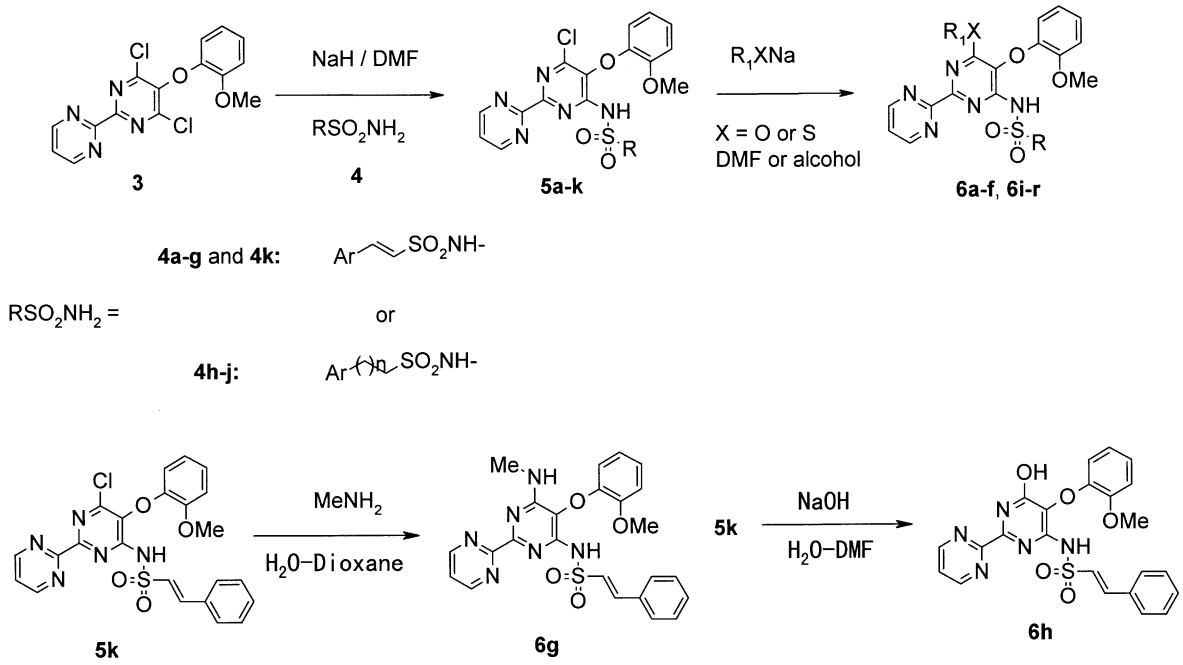
Compounds have been evaluated in vitro for their affinity toward cloned human ET_A and ET_B receptors expressed in COS-1 cells by employing receptor-binding assays. Functional vascular ET-1 antagonism was determined in vitro for the ability to inhibit the ET-1 induced contraction of a ring preparation sample of rat aorta. Some compounds were further examined in vivo for their ability after intravenous or oral 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 endothelin receptor antagonists are summarized in Tables 1–3.

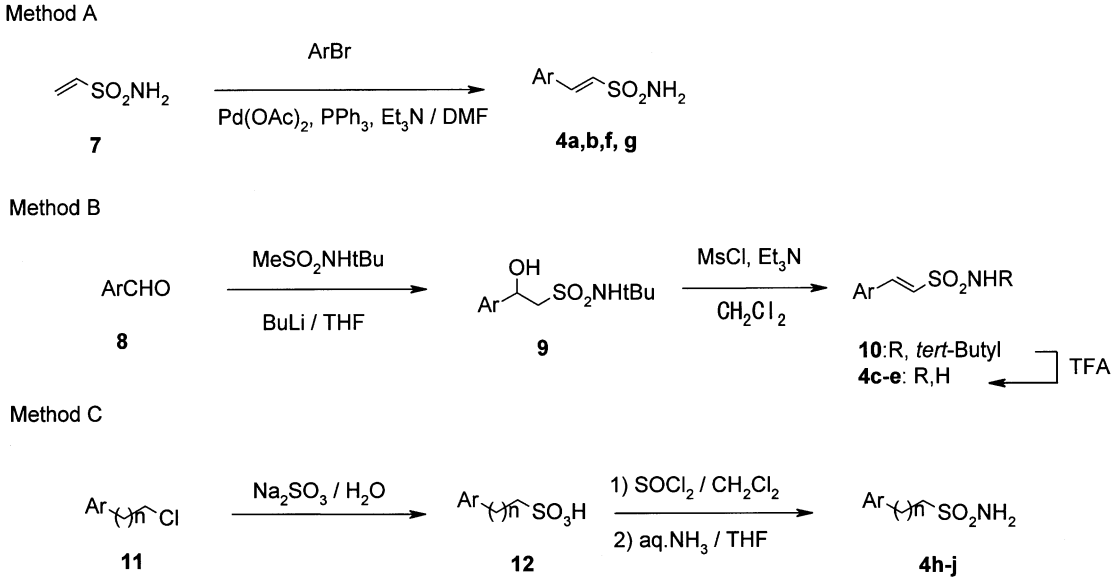
Table 1 shows the SARs of the alkoxy region at the 6-position of the core pyrimidine ring.

Removal of a fluorine atom from the 2-fluoroethoxy derivative **2b** afforded the ethoxy derivative **6a** and resulted in a 7-fold loss of affinity for the ET_A receptor. Increasing the size of the *O*-ethyl on **6a** to propyl (**6b**), isopropyl (**6c**), and cyclopropylmethyl (**6d**) led to a large decrease in the ET_A binding affinity. It was suggested to us that a hydrogen-acceptor such as a fluorine atom might be important for the binding affinity, but unexpectedly the methoxy derivative **6e** was found to be equally potent to the 2-fluoroethoxy derivative **2b**, with an IC_{50} at the ET_A receptor of 3.1 nM. In this simple unsubstituted alkoxy series, the groups larger than a methoxy group were not well tolerated, probably due to steric factors.

There was a difference in the steric limitations of the alkoxy group at the 6-position between two series (**2a–c** vs **6a–e**). These results suggest that the alkoxy side chains with a hydrogen-acceptor in **2a–c** may interact with the hydrogen-bonding pocket on the ET_A receptor that the simple alkoxy side chains with no substituent in **6a–e** cannot interact, and this hydrogen bonding led to an increase in the binding affinity for ET_A receptor. In



Scheme 1. Ar = aryl, DMF = *N*,*N*-dimethylformamide.



Scheme 2. tBu = *tert*-Butyl, TFA = trifluoroacetic acid, Ms = methanesulfonyl.

contrast to the ET_A receptor binding affinity, the affinities for the ET_B receptor of two series, except **2c**, were weak and almost of the same order (IC_{50} = 2000 nM for **2a**, 2500 nM for **2b** and 2500 nM for **6a**), indicating that such a hydrogen bonding binding site may not exist on the ET_B receptor. The relatively high potency of **2c** for the ET_B receptor suggested that the hydroxyl group in the alkoxy side chain might be playing an important role in the ET_B binding affinty.

Although the ET_A selectivity of **6e** was lower than that of **2b**, it was still considerably high (390-fold vs the ET_B receptor). Compound **6e** also blocked the contractions caused by ET-1 in isolated rat aorta in a concentration dependent fashion. The pA_2 value of **6e** was 7.4±0.3 (n = 16) and slightly larger than that of **2b** (pA_2 = 6.9)[7] (pA_2; see Experimental).

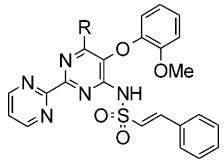
We also examined alkylamino and alkylsulfanyl substitutions at 6-position. The methylsulfanyl derivative **6f** had a slightly decreased affinity for the ET_A binding. The methylamino analogue **6g** was also less potent by 30-fold than **6e.** The hydroxy analogue **6h** was inactive. These results indicated the importance of the alkoxy groups for the ET_A binding affinity in this series of compounds. We then focused our attention on investigating the SARs of the 2-phenylethensulfonamide region of **6e** (Tables 2 and 3).

Replacement of the phenyl group with another aryl or heteoaryl groups was investigated (Table 2). Replacement of the phenyl group with a naphtyl group (**6i** and **6j**) decreased in the ET_A binding affinity by ca. 2- to 4-fold and led to an increase in ET_B binding affinity. The 2-naphtyl derivative **6j** showed 8-fold lower ET_A selectivity than **6e**. A series of pyridine derivatives (**6k**, **6l** and **6m**) were synthesized, and the rank of order of potency in ET_A binding was found to be 3-Py (**6l**) > 2-Py (**6k**) > 4-Py (**6m**). The 3-pyridyl derivative **6l** was the most potent of the 6-methoxy analogues in the ET_A binding affinity and ET_A selectivity, with an IC_{50} of 1.2 nM for the ET_A receptor and an ET_B/ET_A ratio of 820-fold. Replacement of the phenyl group with a thienyl group (**6n** and **6o**) was also well tolerated both in the ET_A binding affinity and ET_A selectivity. This exercise revealed that aryl and heteroaryl substitutions, except for the 4-pyridyl group,were well tolerated in the ET_A binding affinity.

Next, replacement of the ethenyl group in the 2-phenylethensulfonamide region of **6e** with alkyl groups was investigated (Table 3). The benzyl derivative **6p** significantly lost in activity. Though the phenylpropyl derivative **6r** also showed 14-fold less potent ET_A binding affinity compared to **6e**, the phenylethyl derivative **6q** was almost equipotent to **6e** both in the ET_A binding affinity and ET_A selectivity. It is suggested that the distance between the sulfonamide group and the aromatic ring is important and that two carbon units are optimal.

The X-ray crystal structures of Bosentan (**1**) and **6e** are shown in Figures 2 and 3. Superimposition of **1** and **6e** in Figure 4(a) revealed that the key functional groups of **1** and **6e** occupied nearly similar spatial positions, except for the 2-methoxyphenyl group. Although the methoxyphenyl ring of **6e** was almost orthogonal to the plane of the core pyrimidine ring, it was in the opposite direction to the corresponding methoxyphenyl ring of **1**. In order to find stable conformations of the 2-methoxyphenyl group in **6e**, molecular mechanics studies of **6e** were performed using the software SYBYL 6.6 (Tripos, Inc., MO, USA) for modeling on the basis of X-ray data. Rotating the C4–C3–O3-C13 by 1°, two energetically favored conformations, A and B, were observed. The torsion angle (C4–C3–O3–C13) of conformations A and B were 56.0 and −97.0°, respectively. There was no substantial difference between the two conformation energetically, because conformation A was preferred by only 0.67 kcal/mol. As shown in Figure 4(b), good superimposition of the 2-methoxy phenyl groups of conformation B and the crystal structure of **1**, is observed. Therefore, though crystal structures of **1** and **6e** did not show good alignment of the methoxyphenyl

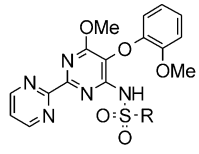
Table 1. ET_A and ET_B receptor binding affinities for ethenesulfonamide derivatives

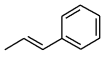
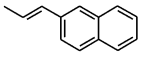
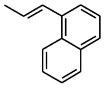
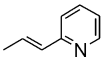
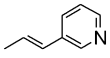
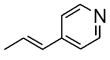
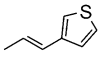
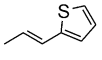


Compound	R	IC_{50} (nM)[a]		Selectivity for ET_A[c]
		ET_A[b]	ET_B[b]	
1[d]		7.3± 1.4	260±33	36
2a[e,h]	–OCH_2CH_2OMe	4.8±2.5	2000 (140)	420
2b[f,h]	–OCH_2CH_2F	2.1	2500±900	1200
2c[g,h]	–OCH_2CH_2OH	1.6 (0.42)	370 (85)	230
6a[e]	–OEt	14±4.0	2500±190	180
6b	–OPr	120 (108)		
6c	–OisoPr	170 (68)		
6d		270 (123)		
6e[e]	–OMe	3.1±1.0	1200±250	390
6f	–SMe	7.0 (0.6)	900 (220)	130
6g	–NHMe	96 (80)	7700 (1350)	81
6h	–OH	>1000		

[a]Experiments were performed twice and the difference between the two values obtained are shown in parentheses unless otherwise noted.
[b]Cloned human receptor binding.
[c]Expressed as ET_B IC_{50}/ET_A IC_{50}.
[d]Sodium salt, values are means±SEM, $n=11$.
[e]Values are means±SEM, $n=3$.
[f]Values are means±SEM, $n=3$ for ET_B, $n=1$ for ET_A.
[g]Potassium salt.
[h]The biological data of compounds **2a**, **2b** and **2c** were previously reported.[7]

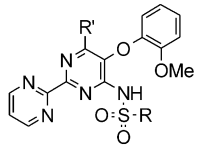
Table 2. ET_A and ET_B receptor binding affinities for ethenesulfonamide derivatives

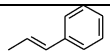
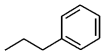
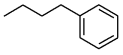


Compound	R	IC_{50} (nM)[a]		Selectivity for ET_A[c]
		ET_A[b]	ET_B[b]	
6e[e]		3.1±1.0	1200±250	390
6i		7.4 (6.0)	640 (560)	86
6j		6.2 (2.7)	310 (270)	50
6k		8.5 (4.5)	730 (210)	86
6l		1.2 (0.48)	980 (55)	820
6m		38 (16)	>1000	>26
6n		1.3 (0.5)	640 (211)	490
6o		1.7 (0.4)	1100 (12)	650

[a–e]See footnotes in Table 1.

Table 3. ET_A and ET_B receptor binding affinities for ethanesulfonamide derivatives



Compound	R	R′	IC_{50} (nM)[a]		Selectivity for ET_A[c]
			ET_A[b]	ET_B[b]	
6e[e]		MeO–	3.1 ± 1.0	1200 ± 250	390
6p		$HO(CH_2)_2O$–	> 1000		
6q		MeO–	3.1 (1.4)	740 (108)	240
6r		MeO–	42 (0.2)	> 1000	> 24

[a–c]See footnotes to Table 1.

groups, it is thought that all key functional groups of **1** and **6e** including the methoxyphenyl group align well.

The *tert*-butyl group in **1** was important for ET_A binding affinity because removal of the *tert*-butyl group led to ca. a 20-fold loss in the ET_A binding affinity.[9] It is noteworthy that the *tert*-butyl group in **1** corresponds to the phenyl group of **6e** in our superimposition [Fig. 4(b)]. This result indicated that a hydrophobic group such as alkyl or aryl group at a certain distance from sulfonamide group might be important for the ET_A binding affinity, corresponding to the result in which the compounds with two carbon units between the aryl group and the sulfonamide group (**6e**, **6i**–**l**, **6n**, **6o** and **6q**) showed potent ET_A binding affinities, but the compounds with one or three carbon units as the linker (**6p** or **6r**) showed much lower binding affinities.

Though the key functional groups of **1** such as methoxyphenoxy, pyrimidinyl and sulfonamide groups correspond to these of **6e**, the selectivity for ET_A receptor in our series was generally higher than that of **1**. These results suggested that (a) an aryl group such as a phenyl group may be more beneficial to ET_A binding than a

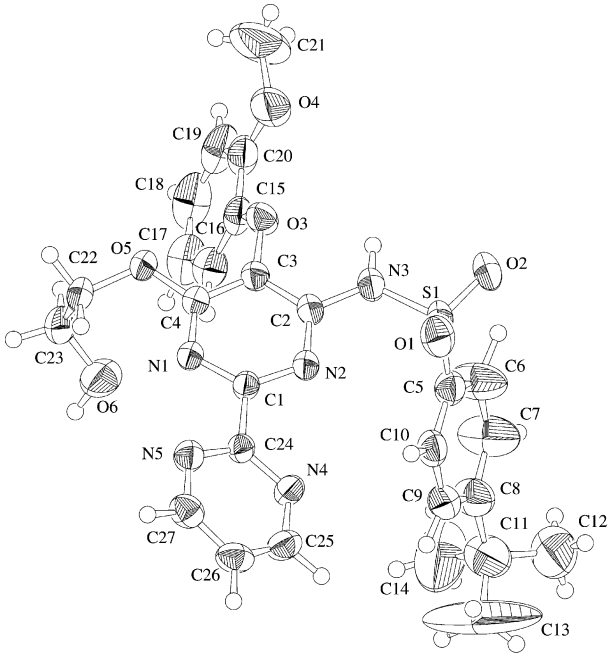


Figure 2. X-ray crystal structure of Bosentan (**1**) (a hydrate molecule was eliminated to simplify the figure).

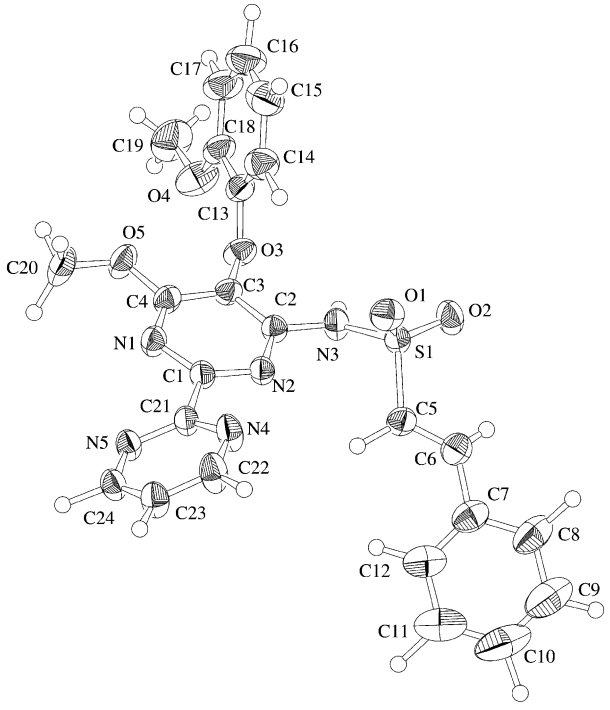


Figure 3. X-ray crystal structure of **6e** (a ethanol solvent of crystallization was eliminated to simplify the figure).

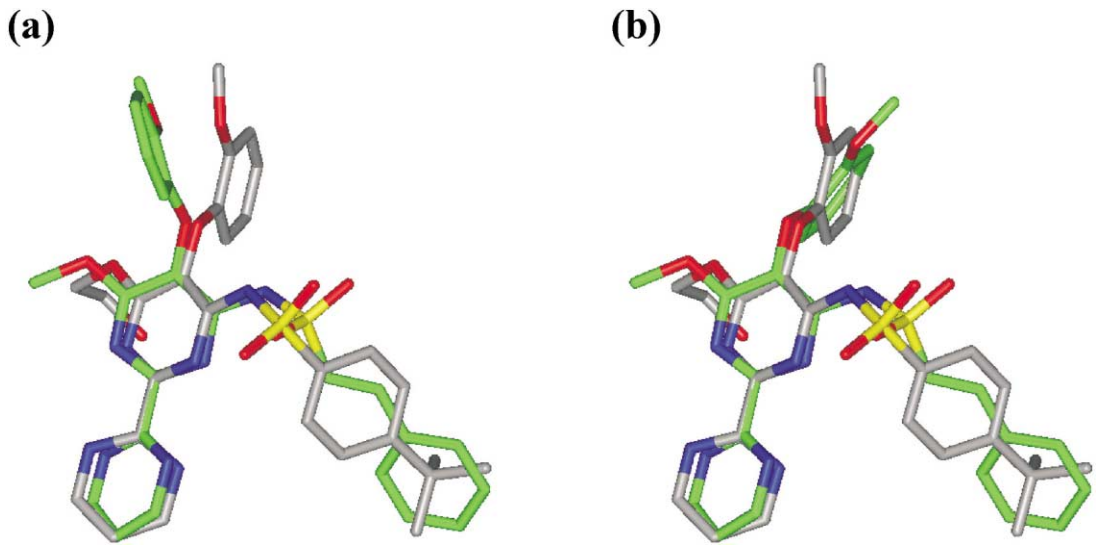


Figure 4. (a) Superimposition of the crystal structures of Bosentan **1** (gray) and **6e**; (b) superimposition of the crystal structure of Bosentan **1** (gray) and conformation B of **6e** (green).

tert-butyl group and be similar to a *tert*-butyl group for ET_B binding(**1** versus **2c**), and (b) the hydroxyethoxy group at the 6-position of pyrimidine may be more beneficial to ET_B binding than other alkoxy groups such as a methoxy group (**2c** vs **6e**). These two factors may contribute to the ET_A selectivity of our series of compounds.

Figure 5(a) and (b) and Table 4 highlight our in vivo studies of the selected compounds.

Compounds with a 2-phenylethenesulfonamide moiety (**6e** and **6l**) and a 2-phenylethanesulfonamide moiety (**6q**) inhibited the increase in MABP due to the administration of exogenous big ET-1 to conscious rats after oral administration [Fig. 5(a)]. These all showed excellent inhibitory activities at 0.3 mg/kg. Maximum inhibition of the pressor effect of big ET-1 was 82% for **6e,** 76% for **6l** and 81% for **6q** (0.3 mg/kg). Though the duration of action of the pyridylethenesulfonamide **6l** was short (<2.5 h), the phenylethenesulfonamide **6e** and the phenylethanesulfonamide **6q** showed a longer duration of action (>6.5 h).

Figure 5(b) and Table 4 show the comparison of the in vivo activity of **1** (Bosentan), **2b** and **6e**.

As shown in Figure 5(b), the oral antagonistic activity of **6e** at 1 mg/kg was more potent than that of **1** at 10 mg/kg, and equipotent to that of **2b** at 3 mg/kg.

Compounds **1**, **2b** and **6e** also inhibited the increase in MABP due to the administration of exogenous big ET-1 to anesthetized pithed rats after intravenous administration or oral administration (Table 4). In this study, the 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 diastolic blood pressure (DBP). (details are described in the Experimental). Compound **6e** showed excellent inhibitory activities after oral

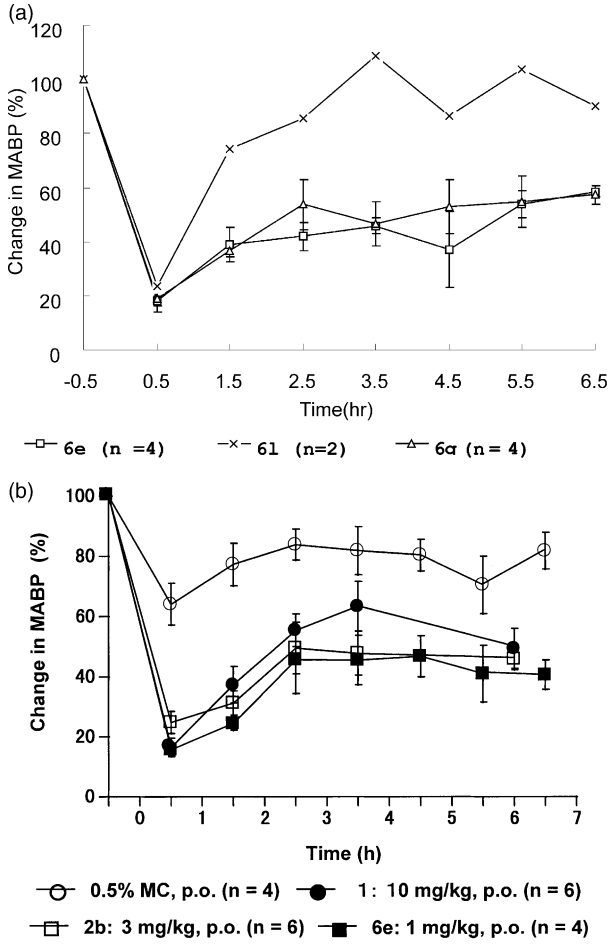


Figure 5. (a) Effect of po administration (0.3 mg/kg) of **6e**, **6l** and **6q** on pressor response to big ET-1 in conscious normotensive rats: (b) comparison of the effect of po administration of **1**, **2b** and **6e** on pressor response to big ET-1 in conscious normotensive rats: Change in MABP (%): increase in mean arterial blood pressure (MABP) in conscious rats elicited by iv administration of big ET-1 (0.5 nmol/kg). **1**: sodium salt.

administration with an ID_{50} value of 1.1 mg /kg. The oral activity of compound **6e** was 32-fold more potent than that of **1** and 4-fold more potent than that of **2b**, calculated from these ID_{50} values.

Figures 6 and 7 show the pharmacokinetic data for **6e** expressed as mean plasma concentration plotted against hours after dosing of the monopotassium salt of **6e** for rats and dogs. At an oral dose of 0.3 mg/kg for the rat, **6e** had an area under the curve of 2.12 μg/h/mL, a half-life of 2.52 h, a peak plasma concentration of 0.50 μg/mL, and the time of peak plasma concentration = 0.50 h. At an oral dose of 0.3 mg/kg for the dog, **6e** had an area under the curve of 18.75 ± 1.22 μg h/mL, a half-life of 7.42 ± 0.92 h, a peak plasma concentration of 1.43 ± 0.08 μg/mL, and the time of peak plasma concentration = 0.69 ± 0.38 h. The bioavailability in the oral administration was estimated to be 89% in the rat and 97 ± 9% in the dog.

Conclusion

Investigation of the details of the SARs of our ethenesulfonamide derivative **2b** led to the discovery of some potent ET_A selective endothelin antagonists, the 2-arylethenesulfonamide derivatives and the 2-phenylethanesulfonamide derivative, including **6e** and **6q** (YM-119836). Among this series, the 2-phenylethenesulfonamide **6e** showed a potent affinity for the ET_A receptor with high ET_A selectivity. Compound **6e** also had a long acting oral activity in the inhibition of the pressor response caused by a big ET-1 infusion in both pithed and conscious rats. The monopotassium salt of **6e** showed an excellent pharmacokinetic profile with bioavailabilities of 89% in the rat and 97% in the dog (0.3 mg/kg). The monopotassium salt of **6e** (YM598 monopotassium salt) is now in clinical trials.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus without correction. ^{1}H NMR spectra were recorded on JNM-LA400, LA500, and A500 spectrometers using tetramethylsilane as an internal standard. MS spectra were determined with a Hitachi M-80 or JEOL JMS-DX300 spectrometer. High resolution mass 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.

Table 4. Comparison of the effects of po and iv administration of the 2-phenyethenesulfonamide derivatives on pressor response to big ET-1 in pithed rats

Compound	ID_{50} (mg/kg)[a]	
	iv	Po
6e	0.76 (0.63–0.94)	1.1 (0.70–2.4)
2b	2.0 (1.5–3.2)	4.1 (3.0–6.6)
1[b]	6.1 (4.9–8.0)	35 (19–220)

[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 diastolic blood pressure (DBP). $n = 3$–8, ID_{50} values are expressed as the mean with 95% confidence limits.
[b]Sodium salt.

4,6-Dichloro-5-(2-methoxyphenoxy)pyrimidine (3). Sodium (12.7 g, 551 mmol) was added to ethanol (700 mL) and stirred at room temperature until all sodium was dissolved. Diethyl 2-(2-methoxyphenoxy)-malonate (51.8 g, 184 mmol) and 2-amidinopyrimidine[13] (benznesulfonic acid salt, 51.4 g, 184 mmol) was added to the solution and heated under reflux for 2.75 h. It was poured into ice-water. The mixture was acidified with 3 M HCl, and the resulting precipitate was collected by filtration. The solid was washed with water and ethanol to give 4,6-dihydroxy-5-(2-methoxyphenoxy)pyrimidine (32.6 g, 57%): mp. 276–277 °C. ^{1}H NMR (DMSO-d_6) δ

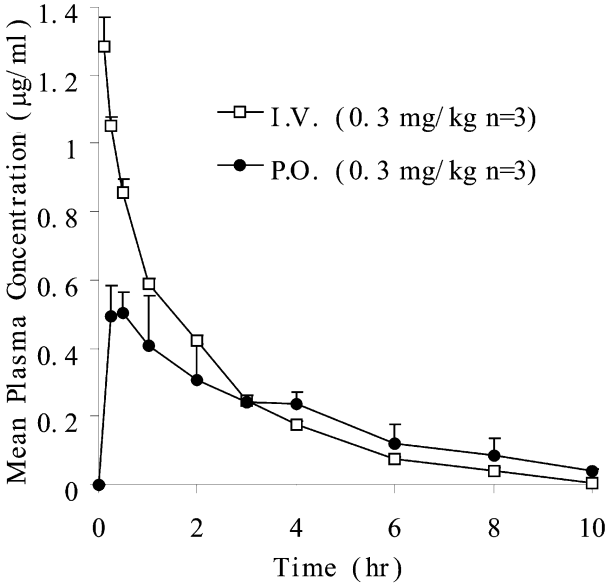


Figure 6. Pharmacokinetics of **6e** in rats.

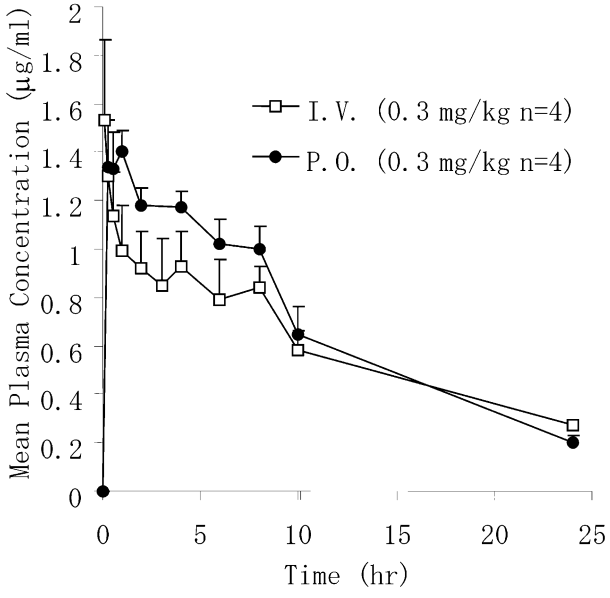


Figure 7. Pharmacokinetics of **6e** in dogs.

3.86 (3H, s), 6.67 (1H, dd, $J=1.2$, 8.0 Hz), 6.76–6.81 (1H, m), 6.93 (1H, dt, $J=1.6$, 8.0 Hz), 7.03 (1H, dd, $J=1.6$, 8.0 Hz), 7.73 (1H, t, $J=4.8$ Hz), 9.07 (2H, d, $J=4.8$ Hz), 12.25 (2H, m). FAB-MS m/z: 313 ($M^+ + 1$). To phosphorous oxychloroide (90 mL) was added 4,6-dihydroxy-5-(2-methoxyphenoxy)pyrimidine (30.0 g, 96.1 mmol) and 2, 4, 6-trimethylpyridine (12.7 mL, 96.1 mmol). The mixture was stirred at 90 °C for 17.5 h, and it was poured into ice-water. The resulting precipitate was collected by filtration. The solid was recystallized from ethanol to give **3** (25.1 g, 75%): mp. 153–154 °C. ^{1}H NMR (DMSO-d_6) δ 3.85 (3H, s), 6.85–6.91 (1H, m), 6.98 (1H, dd, $J=1.6$, 8.0 Hz), 7.11–7.16 (1H, m), 7.17–7.21 (1H, m), 7.72 (1H, t, $J=4.8$ Hz), 9.08 (2H, d, $J=4.8$ Hz). EI–MS m/z 348 (M^+).

The syntheses of the intermediate ethenesulfonamide derivatives **4a**–**g** and alkanesulfonamide derivatives **4h**–**j** were previously reported[10,14,15] except for the compounds described bellow.

(*E*)-2-(Thiophen-3-yl)ethenesulfonamide (4f). To a solution of triphenylphosphine (130 mg, 0.496 mmol) in *N*,*N*-dimethylformamide (DMF) (10 mL) was added palladium acetate [$Pd(OAc)_2$, 55 mg, 0.245 mmol] at room temperature under an argon atmosphere. After stirring for 5 min, to the mixture was added a solution of 3-bromothiophen (1.2 mL, 12.7 mmol), ethenesulfonamide **7** (1.50 g, 14.0 mmol) and triethylamine (5.0 mL, 35.9 mmol) in DMF (5 mL). The mixture was stirred at 140 °C for 7 h and then concentrated in vacuo. To the residue was added diluted HCl and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was chromatographed over silica gel using 1:1 ethyl acetate (AcOEt)/hexane (Hex) to give a solid. The solid was recystallized from AcOEt/Hex to give **4f** (0.75 g, 31%): mp 152–153 °C. 90 MHz ^{1}H NMR (DMSO-d_6) δ:7.03(1H,d, $J=15.5$ Hz), 7.04 (2H,s), 7.34 (1H, d, $J=15.5$ Hz), 7.50–7.97 (3H, m). FAB-MS m/z 190 ($M^+ + 1$).

(*E*)-2-(Naphthalen-2-yl)ethenesulfonamide (4b). Compound **4b** was prepared in the same manner as **4f** in 74% yield as a yellow solid: mp 189–190 °C. 90 MHz ^{1}H NMR (DMSO-d_6) δ 7.05–7.70 (6H, m, containing 7.27, d, $J=15.5$ Hz, 7.55, d, $J=15.5$ Hz), 7.80–8.30 (5H, m). EI–MS m/z: 233 (M^+).

(*E*)-2-(Pyridin-4-yl)ethenesulfonamide (4e). Step 1: To a solution of *N*-*tert*-butylmethanesulfonamide (1.50 g, 9.92 mmol) in tetrahydrofuran (THF) (10 mL) was added a hexane solution of *n*-butyl lithium (12.0 mL, 19.56 mmol) at −78 °C under an argon atmosphere. After stirring for 10 min at 0 °C, 4-pyridinecarboxyaldehyde **8a** (0.9 mL, 9.58 mmol) in THF (10 mL) was added to the mixture at −78 °C. The mixture was stirred at room temperature for 45 min and poured into water. The mixture was extracted with EtOAc added to the mixture. The organic layer was washed with brine and concentrated in vacuo. The residue was chromatographed over silica gel using 7% methanol (MeOH) in chloroform ($CHCl_3$) to give *N*-*tert*-butyl 2-hydroxy-2-(pyridin-4-yl)-ethanesulfonamide (**9a**) (1.61 g, 65%) as an oil: 90 MHz ^{1}H NMR ($CDCl_3$) δ 1.41 (9H, s), 3.29–3.37 (2H, m), 3.90–4.20(1H, m), 4.62 (1H, s), 5.29 (1H, t, $J=6.3$ Hz), 7.26–7.37 (2H, m), 8.50–8.65 (2H, m). FAB-MS m/z 259 ($M^+ + 1$).

Step 2: To a ice-cooled solution of the alcohol **9a** (1.58 g, 6.14 mmol) in dichloromethane (CH_2Cl_2) was added triethylamine (2.6 mL, 18.7 mmol) and methanesulfonylcholoride (0.7 mL, 9.04 mmol). The mixture was stirred at room temperature for 1 h and then concentrated in vacuo. To the residue was added water and extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residue was chromatographed over silica gel using 3% MeOH in $CHCl_3$ to give (*E*)-*N*-*tert*-butyl 2-(pyridin-4-yl)-ethenesulfonamide (**10a**) (1.41 g, 96%) as a yellow oil: 90 MHz ^{1}H NMR ($CDCl_3$) δ 1.38 (9H, s), 4.39 (1H, s), 6.97 (1H, d, $J=15.7$ Hz), 7.26–7.49 (3H, m), 8.64–8.71 (2H, m). FAB-MS m/z 241 ($M^+ + 1$).

Step 3: To **10a** (1.36 g, 5.66 mmol) was added trifluoroacetic acid (TFA) (20 mL) and the solution was stirred at room temperature for 24 h. The solution was then concentrated in vacuo. To the residue was added water and neutralized with 1 N aqueous NaOH. It was extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residual solid was washed with EtOAc/Hex to give **4e** (0.73 g, 70%): mp 197–198 °C (decomp). 90 MHz ^{1}H NMR ($CDCl_3$) δ 7.33 (2H, s), 7.35 (1H, d, $J=16.9$ Hz), 7.68 (1H, d, $J=16.9$ Hz), 7.84–8.00 (2H, m), 8.66–8.90 (2H, m). FAB-MS m/z 185 ($M^+ + 1$).

(*E*)-2-(Pyridin-2-yl)ethenesulfonamide (4c). Compound **4c** was prepared in the same manner as **4f**. Mp 111–112 °C (EtOAc/Hex), 400 MHz ^{1}H NMR (DMSO-d_6) δ 7.20 (2H, brs), 7.34 (1H, d, $J=15.2$ Hz), 7.33–7.45 (1H, m), 7.44 (1H, d, $J=15.2$ Hz), 7.73 (1H, d, $J=18.0$ Hz), 7.85–7.90 (1H, m), 8.63–8.65 (1H, m). FAB-MS m/z 185 ($M^+ + 1$).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(naphtalen-1-yl) ethenesulfonamide (5a). To an ice-cooled solution of (*E*)-2-(naphtalen-1-yl)ethenesulfonamide (**4a**)[10] (670 mg, 2.87 mmol) in DMF (10 mL) was added 60% sodium hydride in mineral oil (230 mg, 5.75 mmol) and the mixture was stirred for 10 min at room temperature. To the mixture 4,6-dichloro-5-(2-methoxyphenoxy)pyrimidine (**3**) (950 mg, 2.72 mmol) was added, and the mixture was stirred for 4 h at room temperature. It was poured into ice-water and acidified with 1 N aqueous HCl, and the resulting precipitate was collected by filtration. The solid was recrystallized from ethanol (EtOH) to give **5a** (1.19 g, 80%): mp 175–177 °C. ^{1}H NMR (DMSO-d_6) δ 3.80 (3H, s), 6.83–6.90 (2H, m), 7.06–7.16 (2H, m), 7.54–7.65 (4H, m), 7.91(1H, d, $J=19.3$ Hz), 7.98–8.03 (2H, m), 8.05 (1H, d, $J=10.0$ Hz), 8.16 (1H, d, $J=10.0$ Hz), 8.59 (1H, d, $J=19.3$ Hz), 8.94 (2H, d, $J=6.0$ Hz). FAB-MS m/z 544 ($M^+ - 1$).

The chloropyrimidine derivatives (**5b**–**j**) were prepared in the same manner as **5a**.

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(naphtalen-2-yl) ethenesulfonamide (5b). Compound **5b** was prepared from (*E*)-2-(naphthalen-2-yl)ethenesulfonamide (**4b**) in 47% yield: mp 203–208 °C (EtOH): ^{1}H NMR (DMSO-d_6) δ 3.83 (3H, s), 6.68–6.79 (1H, m), 6.80–6.89 (1H, m), 7.00–7.08 (1H, m), 7.12 (1H, d, J = 9.0 Hz), 7.54–7.60 (2H, m), 7.72 (1H, t, J = 6.5 Hz), 7.88–8.00 (5H, m), 8.50 (1H, d, J = 20 Hz), 8.13–8.20 (1H, m), 9.13 (2H, d, J = 6.0 Hz). FAB-MS m/z 544 ($M^+ - 1$).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(pyridin-2-yl) ethenesulfonamide (5c). Compound **5c** was prepared from (*E*)-2-(pyridine-2-yl)ethenesulfonamide (**4c**) in 68% yield: mp 189–190 °C (EtOH). ^{1}H NMR (DMSO-d_6) δ 3.80 (3H, s), 6.79–6.90 (2H, m), 7.04–7.17 (2H, m), 7.39–7.46 (1H, m), 7.70 (1H, t, J = 6.0 Hz), 7.78 (1H, d, J = 10.0 Hz), 7.83–7.98 (3H, m), 8.65 (1H, d, J = 10.0 Hz), 9.07 (2H, d, J = 6.5 Hz). FAB-MS m/z: 497 ($M^+ + 1$).

(E)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(pyridin-3-yl)ethenesulfonamide (5d). Compound **5d** was prepared from (*E*)-2-(pyridine-3-yl)ethenesulfonamide (**4d**)[10] in 62% yield: mp 189–190 °C (EtOH), ^{1}H NMR (DMSO-d_6) δ 3.81 (3H, s), 6.81 (1H, d, J = 10.0 Hz), 6.83–6.89 (1H, m), 7.05–7.10 (1H, m), 7.13 (1H, d, J = 10.0 Hz), 7.53 (1H, dd, J = 6.0, 10.0 Hz), 7.71 (1H, t, J = 10.0 Hz), 7.92 (1H, d, J = 19.5 Hz), 7.97 (1H, d, J = 19.5 Hz), 8.21–8.25 (1H, m), 8.62 (1H, dd, J = 2.0, 6.0 Hz), 8.91 (1H, d, J = 2.0 Hz), 9.07 (2H, d, J = 6.0 Hz). FAB-MS m/z 497 ($M^+ + 1$).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(pyridin-4-yl)ethenesulfonamide (5e). Compound **5e** was prepared from (*E*)-2-(pyridine-4-yl)ethenesulfonamide (**4e**)[10] in 21% yield: mp 173–174 °C (decomp) (EtOH). ^{1}H NMR (DMSO-d_6) δ 3.85 (3H, s), 6.66 (1H, dd, J = 2.0, 7.0 Hz), 6.83–6.87 (1H, m), 7.05–7.09 (1H, m), 7.12–7.16 (1H, m), 7.54–7.77 (3H, m), 8.62 (1H, d, J = 7.5 Hz), 8.68–8.77 (1H, m), 8.95 (2H, d, J = 6.5 Hz), 9.02–9.08 (2H, m). FAB-MS m/z 497 ($M^+ + 1$).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)-pyrimidin-4-yl]-2-(thiophen-3-yl) ethenesulfonamide (5f). Compound **5f** was prepared from (*E*)-2-(thiophen-3-yl)ethenesulfonamide (**4f**) in 69% yield: mp 181–182 °C (EtOH). ^{1}H NMR (DMSO-d_6) δ 3.80 (3H, s), 6.81 (1H, d, J = 9.5 Hz), 6.84–6.91 (1H, m), 7.06–7.16 (2H, m), 7.44–7.56 (1H, m), 7.57–7.68 (2H, m), 7.71(1H, t, J = 6.0 Hz), 7.84–8.02 (1H, m), 8.04 (1H, d, J = 3.1 Hz), 9.10 (2H, d, J = 6.0 Hz), 12.08 (1H, brs). FAB-MS m/z 502 ($M^+ + 1$).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)-pyrimidin-4-yl]-2-(thiophen-2-yl) ethenesulfonamide (5g). Compound **5g** was prepared from (*E*)-2-(thiophen-2-yl)ethenesulfonamide (**4g**)[10] in 38% yield: mp 166–167 °C (EtOH). ^{1}H NMR (DMSO-d_6) δ 3.80 (3H, s), 6.82 (1H, d, J = 7.8 Hz), 6.84–6.90 (1H, m), 7.05–7.19 (3H, m), 7.52–7.60 (2H, m), 7.73 (1H, t, J = 4.9 Hz), 7.77 (1H, d, J = 4.9 Hz), 8.10 (1H, d, J = 14.1 Hz), 9.12 (2H, d, J = 4.9 Hz), 12.01 (1H, brs). FAB-MS m/z 502($M^+ + 1$).

***N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-1-phenylmethanesulfonamide (5h).** Compound **5h** was prepared from 1-phenylmethanesulfonamide **4h** (prepared from 1-phenylmethanesulfonylchloride, Aldrich Co., Ltd.) in 96% yield: mp 105–106 °C (Et_2O). ^{1}H NMR (DMSO-d_6) δ 3.78 (3H, s), 5.28 (2H, s), 6.50–6.64 (1H, m), 6.75–6.86 (1H, m), 6.98–7.06 (1H, m), 7.09 (1H, d, J = 8.5 Hz), 7.25–7.46 (5H, m), 7.71 (1H, t, J = 5.0 Hz), 9.09 (2H, d, J = 5.0 Hz). FAB-MS m/z 484 ($M^+ + 1$).

***N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-phenylethanesulfonamide (5i).** Compound **5i** was prepared from 2-phenylethanesulfonamide (**4i**)[14] in 82% yield: mp 198–199 °C (EtOH). ^{1}H NMR (DMSO-d_6) δ 3.00–3.10 (2H, m), 3.82 (3H, s), 4.16–4.38 (2H, m), 6.82 (1H, d, J = 9.5 Hz), 6.85–6.91 (1H, m), 7.05–7.30 (7H, m), 7.69 (1H, t, J = 6.0 Hz), 9.04 (2H, d, J = 6.0 Hz), 11.88(1H, s). FAB-MS m/z 496 ($M^+ - 1$).

***N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-3-phenylpropanesulfonamide (5j).** Compound **5j** was prepared from 2-phenylpropanesulfonamide (**4j**)[15] in 82% yield: mp 194–195 °C (EtOH). ^{1}H NMR (DMSO-d_6) δ 1.90–2.10 (2H, m), 2.70 (2H, t, J = 7.0 Hz), 3.79 (3H, s), 3.82–4.00 (2H, m), 6.80 (1H, d, J = 8.0 Hz), 6.83–6.90 (1H, m), 7.05–7.17 (7H, m), 7.68 (1H, t, J = 4.4 Hz), 9.02 (2H, d, J = 4.4 Hz), 11.76 (1H, s). FAB-MS m/z 512 ($M^+ + 1$).

(*E*)-*N*-[6-Chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-phenylethenesulfonamide (5k). See ref 7.

(*E*)-*N*-[6-Ethoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-phenylethenesulfonamide (6a). Sodium (181 mg, 8.07 mmol) was added to ethanol (10 mL) and stirred at room temperature until all sodium was dissolved. (*E*)-*N*-[6-chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-phenylethenesulfonamide (**5k**) (400 mg, 0.807 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 concentrated in vacuo. The residue was chromatographed over silica gel using 40:1 $CHCl_3$/MeOH to give an oil. It was crystallized from ether (Et_2O) to give **6a** (310 mg, 76%): mp 173–174 °C. ^{1}H NMR (DMSO-d_6) δ 1.05–1.11 (3H, m), 3.82 (3H, s), 4.36–4.38 (2H, m), 6.74 (1H, d, J = 7.9 Hz), 6.83 (1H, t, J = 7.3 Hz), 7.03–7.06 (1H, m), 7.09 (1H, d, J = 7.3 Hz), 7.40–7.55 (3H, m), 7.55–7.80 (3H, m), 7.82 (1H, d, J = 15.0 Hz), 7.99 (1H, d, J = 15.0 Hz), 9.08 (2H, d, J = 5.0 Hz), 11.43 (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, 59.29; H, 4.51; N, 13.68; S, 6.31.

The compounds **6**(**b**–**e**) were prepared in the same manner as **6a**.

(*E*)-*N*-[5-(2-Methoxyphenoxy)-6-propoxy-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-phenylethenesulfonamide (6b). 330 mg (79%), crystallized from Et_2O: mp 161–162 °C. ^1H NMR (DMSO-d_6) δ 0.62 (3H, t, $J=7.5$ Hz), 1.40–1.54 (2H, m), 3.81 (3H, s), 4.18–4.34 (2H, m), 6.76 (1H, d, $J=7.5$ Hz), 6.82–6.85 (1H, m), 7.02–7.06 (1H, m), 7.09 (1H, d, $J=7.5$ Hz), 7.36–7.54 (3H, m), 7.60–7.78 (3H, m), 7.82 (1H, d, $J=15.0$ Hz), 8.98 (1H, d, $J=15.0$ Hz), 9.07 (2H, d, $J=4.0$ Hz), 11.45 (1H, 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, 59.89; H, 4.87; N, 13.25; S, 6.09.

(*E*)-*N*-[6-Isopropyloxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-phenylethenesulfonamide (6c). 57 mg (14%), crystallized from Et_2O: mp 145–147 °C. ^1H NMR (DMSO-d_6) δ: 1.05 (6H, d, $J=7.0$ Hz), 3.81 (3H, s), 5.24–5.42 (1H, m), 6.70–6.94 (2H, m), 6.98–7.16 (2H, m), 7.36–7.55 (3H, m), 7.60–7.88 (4H, m), 7.98 (1H, d, $J=2.0$ Hz), 9.07 (2H, d, $J=5.5$ Hz), 11.38 (1H, s). FAB-MS m/z 520 ($M^+ + 1$). Anal. calcd for $C_{25}H_{23}N_5O_5S\cdot 0.25H_2O$: C, 59.59; H, 4.90; N, 13.36; S, 6.12. Found: C, 59.30; H, 4.97; N, 13.33; S, 6.14.

(*E*)-*N*-[6-Cyclopropylmethoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-phenylethenesulfonamidate (6d). 336 mg (78%), crystallized from Et_2O: mp 134–135 °C ^1H NMR (DMSO-d_6) δ 0.10–0.20 (2H, m), 0.30–0.42 (2H, m), 0.96–1.08 (1H, m), 3.82 (3H, s), 4.19 (2H, d, $J=6.0$ Hz), 6.76 (1H, d, $J=8.0$ Hz), 6.82–6.90 (1H, m), 6.98–7.08 (1H, m), 7.10 (1H, d, $J=7.0$ Hz), 7.38–7.52 (3H, m), 7.60–7.76 (3H, m), 7.81 (1H, d, $J=15.0$ Hz), 7.98 (1H, d, $J=15.0$ Hz), 9.07 (2H, d, $J=4.0$ Hz), 11.39 (1H, s). FAB-MS m/z 532 ($M^+ + 1$). Anal. calcd for $C_{27}H_{25}N_5O_5S\cdot 0.25H_2O$: C, 60.49; H, 4.79; N, 13.06; S, 5.98. Found: C, 60.45; H, 4.52; N, 12.97; S, 5.89.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2 - yl)pyrimidin - 4 - yl] - 2 - phenylethenesulfonamide (6e). 273 mg (69%). recrystallized from MeOH: mp 101–102 °C. ^1H NMR (DMSO-d_6) δ 3.83 (3H, s), 3.89 (3H, s), 6.67 (1H, d, $J=7.3$ Hz), 6.77–6.86 (1H, m), 6.99–7.06 (1H, m), 7.09 (1H, d, $J=7.3$ Hz), 7.40–7.50 (3H, m), 7.65–7.77 (3H, m), 7.81 (1H, d, $J=19.0$ Hz), 7.98 (1H, d, $J=19.0$ Hz), 9.08 (2H, d, $J=6.0$ Hz), 11.48 (1H, s). FAB-MS m/z 492 ($M^+ + 1$). Anal. calcd for $C_{24}H_{21}N_5O_5S$: C, 58.65; H, 4.31; N, 14.25; S,6.52. Found: C, 58.53; H, 4.28; N, 14.21; S, 6.40.

Preparation of monopotassium salt of 6e. A mixture of **6e** (50.05 g, 100 mmol) and 85%KOH (6.6 g, 100 mmol) in EtOH (1 L) was heated under reflux for 2 h. Water (100 mL) was added to the mixture. After the mixture was heated for 1 h, it was filtered. The filtrate was stirred at room temperature for 12 h, then the resulting crystal was collected by filtration to give 49.35 g (93%) of monopotassium salt of **6e**: mp 198–201 °C. ^1H NMR (DMSO-d_6) δ 3.80 (3H, s), 3.85 (3H, s), 6.40 (1H, dd, $J=1.6$, 8.0 Hz), 6.73 (1H, dt, $J=1.6$, 8.0 Hz), 6.75 (1H, dt, $J=1.6$, 8.0 Hz), 7.01 (1H, dd, $J=1.6$, 8.0 Hz), 7.12 (1H, d, $J=16.0$ Hz), 7.29–7.34 (1H, m), 7.38–7.44 (2H, m), 7.56–7.61 (2H, m), 7.62 (1H, t, $J=4.8$ Hz), 8.18 (1H, d, $J=16.0$ Hz), 9.03 (2H, d, $J=4.8$ Hz), FAB-MS m/z 530 ($M^+ + 1$). Anal. calcd for $C_{24}H_{20}N_5O_5SK$: C, 54.43; H, 3.81; N, 13.22; S,6.05; K, 7.38. Found: C, 54.45; H, 3.81; N, 13.31; S, 6.08.

(*E*)-*N*-[5-(2-methoxyphenoxy)-6-methylsulfanyl-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-phenylethenesulfonamide (6f). A 15% solution of sodium thiomethoxide in water (10 mL, 21.4 mmol) was added to **5k** (992 mg, 2.00 mmol) in DMF (10 mL), and the mixture was stirred at room temperature for 2 h. It was poured into ice-water and acidified with 1 N aqueous HCl. The mixture was extracted with EtOAc and the organic layer was concentrated in vacuo. The residue was chromatographed over silica gel using 40:1 $CHCl_3$/MeOH to give an oil. It was crystallized from MeOH to give **6f** (790 mg. 78%): mp 173–174 °C. ^1H NMR (DMSO-d_6) δ 2.56 (3H, s), 3.87 (3H, s), 6.71 (1H, d, $J=7.4$ Hz), 6.82–6.85 (1H, m), 7.04–7.08 (1H, m), 7.20 1H, d, $J=7.4$ Hz), 7.40–7.50 (3H, m), 7.67–7.78 (4H, m), 7.82 (1H, d, $J=15.2$ Hz), 9.13 (2H, d, $J=4.9$ Hz). FAB-MS m/z 508 ($M^+ + 1$). Anal. calcd for $C_{24}H_{21}N_5O_4S_2\cdot 1.2H_2O$: C, 54.47; H, 4.46; N, 13.23; S, 12.12. Found: C, 54.69; H, 4.55; N, 13.10; S, 12.34.

(*E*)-*N*-[5-(2-methoxyphenoxy)-6-methylamino-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-phenylethenesulfonamide (6g). A mixture of **5k** (1.00 g, 2.02 mmol) and methylamine (40% in water, 30 mL) and dioxane (20 mL) was stirred at 60 °C for 8 days. It was concentrated in vacuo, and the residue was chromatographed over silica gel using 40:1 $CHCl_3$/MeOH to give an oil. It was crystallized from MeOH to give **6g** (730 mg. 74%): mp 203–206 °C. ^1H NMR (DMSO-d_6) δ 2.88 (0.78H, d, $J=5.5$ Hz), 3.01 (2.22H, d, $J=5.5$ Hz), 3.84 (2.22H, s), 3.89 (0.78H, s), 6.60–7.20 (5H, m), 7.30–7.85 (7.74H, m), 8.20 (0.26H, d, $J=20.0$ Hz), 9.04 (0.52H, d, $J=6.0$ Hz), 9.16 (1.48H, d, $J=6.0$ Hz), 10.64 (0.26H, s), 13.33 (0.74H, s). FAB-MS m/z 491 ($M^+ + 1$). Anal. calcd. for $C_{24}H_{22}N_6O_4S$: C, 58.76; H, 4.52; N, 17.13; S, 6.54. Found: C, 58.49; H, 4.47; N, 17.04; S, 6.34.

(*E*)-*N*-[6-Hydroxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-phenylethenesulfonamide (6h). A mixture of **5k** (500 mg, 1.01 mmol) and 1 N sodium hydroxide in water (5.0 mL) and DMF (10 mL) was stirred at 110 °C for 2 days. It was poured into ice-water and acidified with 1 N aqueous HCl. The resulting precipitate was collected by filtration and chromatographed over silica gel using 40:1 $CHCl_3$/MeOH to give a solid. It was washed with EtOH to give **6h** (214 mg, 44%): mp 221–223 °C. ^1H NMR (DMSO-d_6) δ 3.84 (3H, s), 6.75–6.97 (2H, m), 6.98–7.01 (1H, m), 7.06 (1H, d, $J=7.0$ Hz), 7.36–7.54 (3H, m), 7.68–7.84 (4H, m), 7.91 (1H, d, $J=16.0$ Hz), 9.11 (2H, d, $J=5.0$ Hz), 11.30 (1H, s), 12.78 (1H, s). FAB-MS m/z: 478 ($M^+ + 1$). Anal. calcd for $C_{23}H_{19}N_5O_5S\cdot 0.2H_2O$: C, 57.46; H, 4.06; N, 14.56; S, 6.67. Found: C, 57.35; H, 3.98; N, 14.62; S, 6.49.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(naphthalen-2-yl)ethenesulfonamide (6i). Sodium (110 mg, 4.78 mmol) was added to methanol (10 mL) and stirred at room temperature until all sodium was dissolved. (*E*)-*N*-[6-chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(naphthalen-2-yl)ethenesulfonamide (**5b**) (260 mg, 0.476 mmol) was added to the solution. The mixture was stirred at room temperature for 1 day and at 80 °C for 3 days. It was poured into ice-water and acidified with 1 N aqueous HCl. The mixture was extracted with EtOAc. The organic layer was washed with brine and concentrated in vacuo. The residual solid was recrystallized from EtOH to give **6i** (147 mg, 57%): mp 164–168 °C. ^{1}H NMR (DMSO-d_6) δ 3.83 (3H, s), 3.89 (3H, s), 6.68 (1H, d, J = 9.5 Hz), 6.78–6.86 (1H, m), 6.99–7.06 (1H, m), 7.09 (1H, d, J = 10.0 Hz), 7.56–7.62 (2H, m), 7.69–7.76 (1H, m), 7.88–8.03 (5H, m), 8.08 (1H, d, J = 20.0 Hz), 8.21 (1H, brs), 9.13 (2H, d, J = 6.0 Hz), 11.52 (1H, s). FAB-MS m/z 540 ($M^+ - 1$). Anal. calcd for $C_{28}H_{23}N_5O_5S \cdot 0.1H_2O$: C, 61.89; H, 4.30; N, 12.89; S, 5.90. Found: C, 61.76; H, 4.16; N, 12.81; S, 5.92.

The (*E*)-2-arylethenesulfonamide derivatives (**6j–n**) were prepared in the same manner as **6i** using the corresponding chloropyrimidines (**5a**, **5c–g**).

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(naphthalen-1-yl)ethenesulfonamide (6j). 300 mg (quant). recrystallized from EtOH: mp 110–113 °C. ^{1}H NMR (DMSO-d_6) δ 3.83 (3H, s), 3.89 (3H, s), 6.69 (1H, d, J = 9.5 Hz), 6.78–6.86 (1H, m), 6.99–7.06 (1H, m), 7.10 (1H, d, J = 10.0 Hz), 7.53–7.64 (4H, m), 7.96–8.07 (4H, m), 8.13 (1H, d, J = 10.0 Hz), 8.52 (1H, d, J = 19.0 Hz), 8.93 (2H, d, J = 6.0 Hz), 11.51 (1H, s). FAB-MS m/z 540 ($M^+ - 1$). Anal. calcd for $C_{28}H_{23}N_5O_5S \cdot 1.2H_2O$: C, 59.71; H, 4.55; N, 12.43; S, 5.69. Found: C, 61.04; H, 4.77; N, 12.07; S, 5.54.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(pyridin-2-yl)ethenesulfonamide (6k). 235 mg (79%), crystallized from EtOH: mp 176–177 °C. ^{1}H NMR (DMSO-d_6) δ 3.83 (3H, s), 3.89 (3H, s), 6.67 (1H, d, J = 9.5 Hz), 6.77–6.86 (1H, m), 6.99–7.05 (1H, m), 7.09 (1H, d, J = 9.0 Hz), 7.42 (1H, dd, J = 1.5, 9.0 Hz), 7.62–7.71 (1H, m), 7.75 (1H, d, J = 8.5 Hz), 7.82–7.93 (2H, m), 7.97 (1H, d, J = 17.5 Hz), 8.65 (1H, d, J = 4.5 Hz), 9.06 (2H, d, J = 4.0 Hz), 11.52 (1H, s). FAB-MS m/z 493 ($M^+ + 1$). Anal. calcd for $C_{23}H_{20}N_6O_5S$: C, 56.09; H, 4.09; N, 17.06; S, 6.51. Found: C, 56.04; H, 4.05; N, 17.19; S, 6.64.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(pyridin-3-yl)ethenesulfonamide (6l). 264 mg (83%), recrystallized from EtOH**,:** mp 135–137 °C. ^{1}H NMR (DMSO-d_6) δ 3.83 (3H, s), 3.90 (3H, s), 6.68 (1H, d, J = 9.5 Hz), 6.78–6.85 (1H, m), 6.89–7.06 (1H, m), 7.09 (1H, dd, J = 2.0, 10.0 Hz), 7.50 (1H, dd, J = 6.0, 10.0 Hz), 7.70 (1H, t, J = 6.0 Hz), 7.86 (1H, d, J = 20.0 Hz), 8.02 (1H, d, J = 20.0 Hz), 8.18 (1H, d, J = 10.0 Hz), 8.61 (1H, dd, J = 2.0, 6.0 Hz), 8.89 (1H, brs), 9.06 (2H, d, J = 6.0 Hz), 11.66 (1H, s). FAB-MS m/z 493 ($M^+ + 1$). Anal. calcd for $C_{23}H_{20}N_6O_5S \cdot 0.5H_2O$: C, 55.08; H, 4.22; N, 16.76; S, 6.39. Found: C, 55.27; H, 4.14; N, 16.39; S, 6.39.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(pyridin-4-yl)ethenesulfonamide (6m). 76 mg (51%), crystallized from Et_2O: mp 150–160 °C. ^{1}H NMR (DMSO-d_6) δ 3.82 (3H, s), 3.90 (3H, s), 6.68 (1H, d, J = 10.0 Hz), 6.77–6.84 (1H, m), 6.98–7.05 (1H, m), 7.06–7.11 (1H, m), 7.67–7.80 (4H, m), 8.16 (1H, d, J = 20.0 Hz), 8.67 (2H, d, J = 7.0 Hz), 9.08 (2H, d, J = 6.0 Hz). FAB-MS m/z: 491 ($M^+ - 1$). HRMS calcd for $C_{23}H_{21}N_6O_5S$ m/z 493.1294 ($M^+ + 1$), found 493.1306.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(thiophen-3-yl)ethenesulfonamide (6n). 243 mg (88%), recrystallized from EtOAc: mp 128–133 °C. ^{1}H NMR (DMSO-d_6) δ 3.82 (3H, s), 3.88 (3H, s), 6.65 (1H, d, J = 9.5 Hz), 6.82 (1H, t, J = 9.5 Hz), 7.02 (1H, t, J = 9.5 Hz), 7.09 (1H, d, J = 9.5 Hz), 7.53 (1H, d, J = 6.0 Hz), 7.62–7.78 (3H, m), 7.88 (1H, d, J = 20.0 Hz), 8.00 (1H, brs), 9.09 (2H, d, J = 6.0 Hz), 9.09 (2H, d, J = 6.0 Hz), 11.41 (1H, s). FAB-MS m/z: 510 ($M^+ + 1$). HRMS calcd for $C_{25}H_{24}N_5O_6S$ m/z 498.0906 ($M^+ + 1$), found 498.0889.

(*E*)-*N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(thiophen-2-yl)ethenesulfonamide (6o). To the solution of *N*-[6-chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-(thiophen-2-yl)ethanesulfonamide (**5g**) (502 mg, 1.00 mmol) in DMF (10 mL) was added sodium methoxide (540 mg, 10.0 mmol), and the mixture was stirred at room temperature for 1 h. It was poured into ice-water and acidified with 1 N HCl. The resulting precipitate was collected by filtration and recrystallized from MeOH to give **6o** (219 mg, 44%): mp 145–146 °C. ^{1}H NMR (DMSO-d_6) δ 3.83 (3H, s), 3.90 (3H, s), 6.66 (1H, d, J = 9.5 Hz), 6.82 (1H, t, J = 9.5 Hz), 7.03 (1H, t, J = 9.5 Hz), 7.09 (1H, d, J = 9.5 Hz), 7.16 (1H, t, J = 5.0 Hz), 7.56–7.61 (1H, m), 7.65–7.81 (3H, m), 8.03 (1H, d, J = 19.0 Hz), 9.10 (2H, d, J = 6.5 Hz), 11.48 (1H, s). FAB-MS m/z: 498 ($M^+ + 1$). HRMS calcd for $C_{25}H_{24}N_5O_6S$ m/z 498.0906 ($M^+ + 1$), found 498.0923.

***N*-[6-(2-Hydroxyethoxy)-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-1-phenylmethanesulfonamide (6p).** Sodium (380 mg, 16.5 mmol) was added to ethylene glycol (9.2 mL, 165 mmol) and stirred at 60 °C until all sodium was dissolved. *N*-[6-chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-phenylmethanesulfonamide (**5h**) (800 mg, 1.065 mmol) was added to the solution and stirred at 80 °C for 2.5 h. It was poured into ice-water. The mixture was acidified with 1 N HCl, and the resulting precipitate was collected by filtration. The solid was chromatographed over silica gel using 40:1 $CHCl_3$/MeOH to give an oil. It was crystallized from Et_2O to give **6p** (430 mg, 51%): mp 194–196 °C. ^{1}H NMR (DMSO-d_6) δ 3.45–3.60 (2H, m), 3.76 (3H, s), 4.41 (2H, t, J = 5.0 Hz), 4.62–4.82 (1H, m), 5.32

(2H, s), 6.64 (1H, d, $J=8.0$ Hz), 6.80 (1H, t, $J=8.0$ Hz), 6.91–7.08 (2H, m), 7,24–7.48 (5H, m), 7.67 (1H, t, $J=5.0$ Hz), 9.07 (2H, d, $J=5.0$ Hz), 11.04 (1H, s). FAB-MS m/z 510 ($M^+ + 1$). Anal. calcd for $C_{25}H_{23}N_5O_6S \cdot 0.2H_2O$: C, 56.57; H, 4.55; N, 13.74; S, 6.29. Found: C, 56.21; H, 4.52; N, 13.76; S, 6.33.

***N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)-pyrimidin-4-yl]-2-phenylethanesulfonamide (6q).** To the solution of *N*-[6-chloro-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)pyrimidin-4-yl]-2-phenylethanesulfonamide (**5i**) (450 mg, 0.904 mmol) in DMF (10 mL) was added sodium methoxide (488 mg, 9.04 mmol), and the mixture was stirred at room temperature for 16 h. It was poured into ice-water. The mixture was acidified with 1 N HCl, and the resulting precipitate was collected by filtration. The solid was chromatographed over silica gel using 40:1 $CHCl_3$/MeOH to give an oil. It was crystallized from Et_2O/EtOH to give **6q** (294 mg, 66%): mp 147–149 °C. ^{1}H NMR (DMSO-d_6) δ 3.00–3.10 (2H, m), 3.83 (3H, s), 3.91 (3H, s), 4.20–4.28 (2H, m), 6.67 (1H, d, $J=8.0$ Hz), 6.80–6.87 (1H, m), 7.01–7.06 (1H, m), 7.11 (1H, d, $J=7.5$ Hz), 7.16–7.22 (1H, m), 7.26 (2H, t, $J=7.0$ Hz), 7.26–7.34 (2H, m), 7.65 (1H, t, $J=5.0$ Hz), 9.02 (2H, d, $J=5.0$ Hz), 11.20 (1H, s). FAB-MS m/z 492 ($M^+ - 1$). Anal. calcd for $C_{24}H_{23}N_5O_5S$: C, 58.41; H, 4.70; N, 14.19; S, 6.50. Found: C, 58.28; H, 4.54; N, 14.26; S, 6.59.

The propanesulfonamide derivative (**6r**) was synthesized according to the same procedure as for **6q**.

***N*-[6-Methoxy-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl)-pyrimidin-4-yl]-3-phenylpropanesulfonamide (6r).** 290 mg (73%) crystallized from Et_2O: mp 186–187 °C. ^{1}H NMR (DMSO-d_6) δ 1.96–2.07 (2H, m), 2.71 (2H, t, $J=7.4$ Hz), 3.82 (3H, s), 3.84–3.92 (5H, m), 6.65 (1H, d, $J=7.8$ Hz), 6.83 (1H, t, $J=7.8$ Hz), 7.00–7.06 (1H, m), 7.07–7.20 (6H, m), 7.64 (1H, t, $J=4.9$ Hz), 9.01 (2H, d, $J=4.9$ Hz), 11.10 (1H, s). FAB-MS m/z 508 ($M^+ + 1$). Anal. calcd for $C_{25}H_{25}N_5O_6S$: C, 59.16; H, 4.96; N, 13.80; S, 6.32. Found: C, 58.91; H, 4.84; N, 13.83; S, 6.36.

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% 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 nonlinear regression analysis.

Vessel contraction (inhibition of big ET-1 induced contraction of ring preparation sample of rat aorta)

Male Wistar rats were anesthetized with sodium pentobarbital (60 mg/kg ip) and the thoracic aorta was quickly removed and placed in a Krebs–Henseleit solution (118.4 mM NaCl, 4.7 mM KCl, 1.2 mM $MgCl_2$, 1.2 mM KH_2PO_4, 25 mM $NaHCO_3$, 2.5 mM $CaCl_2$, 11.1 mM glucose). The endothelium was removed by gentle rubbing of the intimal surface using a small cotton ball, and each ring was suspended in a 10 mL isolated organ chamber (siliconized) containing gassed (95% O_2–5% CO_2) and warmed (37 °C) Krebs–Henseleit solution. Vessel segments were attached to an isometric force transducer linked to a physiographic recorder for monitoring tension change. Baseline tension was set at 1.0 g and the tissues were allowed to equilibrate for 60 min. The tissues were contracted with phenylephrine (1 μM) followed by challenge with acetylcholine (1 μM). A negative relaxant response to acetylcholine confirmed the absence of the endothelium. The rings were stimulated to contract with 60 mM KCl repeatedly until the contractile response to KCl became stable before starting the experiments. Cumulative concentration–response curves to ET-1 were performed in the presence or absence of test compounds after a 30-min pretreatment period. Contractile responses were expressed as a percentage of the response elicited by 60 mM KCl. The effective concentration of ET-1 causing a 50% maximum response (EC_{50}) in the presence or absence of test compounds was determined by regression analysis. Dose ratios were determined, and the results analyzed for competitiveness. The pA_2 value was estimated by plotting the log of (dose ratio − 1) as a function of the negative log of concentration of the test compounds.

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.[5g] Briefly, male Wistar rats were pithed by inserting a steel rod 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 iv injection of drugs, respectively. After stabilization of the blood pressure, various doses of (1 mL/kg) the test compounds or vehicle (distilled water) were injected. Five min later, big ET-1 (1.6 nmol/kg) was injected intravenously. In another series of experiments, the oral activities of the 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 the blood pressure, a dose of 1.6 nmol/kg of big ET-1 was injected intravenously. In this study, the ID_{50} value was defined as the dose of the test compounds which caused a 50% inhibition of the pressor response to big ET-1 in diastolic blood pressure (DBP).

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 ip). 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 iv administration of big ET-1 (0.5 nmol/kg). The animals were allowed to recover for 2–3 days 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 iv doses of big ET-1 were administered to determine control responses and patency of the catheters. Each rat was treated with a single po dose of antagonist or vehicle (0.5% methyl cellulose), and any changes in blood pressure were noted. The percentage of the pressor response 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.

Pharmacokinetics

The pharmacokinetic behavior of **6e** was evaluated in male rats and dogs. Compound **6e** was administered as its potassium salt. Groups of rats ($n=3$ per group) and dogs ($n=4$ per group) received either a 0.3 mg/kg iv dose administered as a bolus in the vein or a 0.3 mg/kg oral dose administered by gavage. Heparinized blood samples were obtain from a vein of each rat 0.1 (iv only) 0.25, 0.5, 1, 2, 3, 4, 6, 8 and 10 h after dosing and dog 0.1 (iv only) 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10 and 24 h after dosing. The samples were analyzed by reverse-phase HPLC following liquid–liquid extraction and solid-phase extraction from the plasma. For the calculation of pharmacokinetic parameters, the WinNonlin Standard Network Edition Version 1.5 was used as software. (Plasma sample) blood was collected from the vein using a heparinized syringe. The blood sample was centrifuged to obtain plasma. (Analytical condition for HPLC) column: TSKgel, ODS-80Ts (4.6×250 mm, Tosoh), Column temperature: 35 °C, Mobile phase: 50 mM phosphate buffered solution (pH 2.0)/acetonitrile (45:55), Flow rate: 1.0 mL/min, Detection: UV (270 nm).

X-ray crystallographic analysis. The reflection data for **1** were collected on a Rigaku AFC-7R diffractometer with graphite-monochromated MoK_α radiation ($\lambda=0.7107$ Å) and the reflection data for **6e** were collected on a Rigaku AFC-5R diffractometer with graphite-monochromated CuK_α radiation. ($\lambda=1.5418$ Å). The structures were solved by direct methods using the SIR92 program. The structures were then refined by a full-matrix least-squares procedure with anisotropic temperature factors for the non-hydrogen atoms and isotropic temperature factors for the hydrogen atoms. Crystal data for **6e**: Suitable crystals ($C_{24}H_{21}N_5O_5S{\cdot}C_2H_6O$) for X-ray diffraction studies were formed from EtOH/H_2O. crystal system, triclinic; space group, P1, a = 11.976 (1) Å, b = 12.493 (1) Å, c = 10.3458 (6) Å, $\alpha=98.753$ (6)°, $\beta=105.243$ (6)°, $\gamma=113.538(6)$°, $V=1310.0(2)$ Å^3; $D_c=1.363$ g/cm^3; $Z=2$, $R=0.048$, $R_W=0.096$ for 4408 reflections with $I>3\sigma$ (*I*). Crystal data for **1**: Suitable crystals ($C_{27}H_{29}N_5O_6S{\cdot}H_2O$) for X-ray diffraction studies were formed from EtOH/H_2O. crystal system, monoclinic; space group, $P2_1/a$, a = 15.030(1) Å, b = 15.047(2) Å, c = 12.420(1) Å, $\beta=95.153(6)$°, $V=2797.4(4)$ Å^3; $D_c=1.352$ g/cm^3; $Z=4$, $R=0.050$, $R_W=0.081$ for 3886 reflections with $I>3\sigma$ (*I*). We will deposit the crystallographic data for these structure with the Cambridge Crystallographic Data Centre after this manuscript is accepted.

Molecular modeling study. Molecular modeling studies were performed using the software SYBYL 6.6 (Tripos, Inc., MO, USA) and displayed using the software insightII (Biosym/MSI, CA, USA) on a Silicon Graphics O2 R12000 workstation.

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