Articles

Potent and Selective ET-A Antagonists. 1. Syntheses and Structure−Activity Relationships of *N*-(6-(2-(Aryloxy)ethoxy)-4-pyrimidinyl)sulfonamide Derivatives

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Modifications to the $ET_{A/B}$ mixed type compounds **1** (Ro. 46-2005) and **2** (bosentan) were performed. Introduction of a pyrimidine group into **1** resulted in a dramatic increase in affinity for the ET_A receptor, and the subsequent optimization of substituents on the pyrimidine ring led us to the discovery of *N*-(6-(2-((5-bromo-2-pyrimidinyl)oxy)ethoxy)-5-(4-methylphenyl)-4-pyrimidinyl)-4-*tert*-butylbenzenesulfonamide (**7k**), which showed an extremely high affinity for the human cloned ET_A receptor ($K_i = 0.0042 \pm 0.0038$ nM) and an $ET_{A/B}$ receptor selectivity up to 29 000 ($K_i = 130 \pm 50$ nM for the human cloned ET_B receptor). The compound was designed on the hypothesis that the hydrogen atom of the hydroxyl group in **1** and **2** played a role not as a proton donor but as an acceptor in the possible hydrogen bonding with Tyr129. Since the incorporation of a pyrimidinyl group into the hydroxyethoxy side chain of the nonselective antagonist (**1**) dramatically enhanced both the ET_A receptor affinity and selectivity, and since similar results were obtained from the benzene analogues, we put forward the hypothesis that a "pyrimidine binding pocket" might exist in the ET_A receptor.

Introduction

Endothelin (ET)-1 was first isolated from cultured porcine vascular endothelial cells in 1988 and has been found to be the most potent and long-lasting vasoconstrictor peptide.[1] Subsequent studies revealed the existence of two additional isopeptides, ET-2 and ET-3, and of two distinct ET receptor subtypes, ET_A (binding affinity: ET-1 = ET-2 > ET-3) and ET_B (binding affinity: ET-1 = ET-2 = ET-3).[2] ETs have been implicated as pathogenic factors for a variety of disease states, including essential hypertension, congestive heart failure, pulmonary hypertension, subarachnoid hemorrhage, cerebral ischemia, vasospasm, cyclosporin-induced renal failure, atherosclerosis, and asthma.[3] It has been suggested that an ET antagonist may be effective in the treatment of these disorders.[4]

The Roche group disclosed the first orally active sulfonamide derivatives, Ro.46-2005 (**1**)[5] in 1993 and bosentan (**2**)[6] in 1994, as nonpeptidic $ET_{A/B}$ mixed type antagonists (Figure 1). Although the relative merits of selective vs nonselective antagonist therapy are still under debate, it was reported that the effect of ET-1 on the cardiovascular system (smooth muscle contraction, cell proliferation, hypertrophy of cardiac myocytes, and positive inotropic and chronotropic effects) was mainly mediated by ET_A receptors.[3] Therefore, the selective ET_A antagonist is expected to be a useful therapeutic agent for these cardiovascular diseases. On the other hand, the pathophysiological role[7] of the ET_B receptor is still unclear. Aiming to develop a potent and selective ET_A antagonist, we started to modify Roche's sulfonamide derivatives (**1** and **2**), which are thought to be insufficient in terms of selectivity and potency.

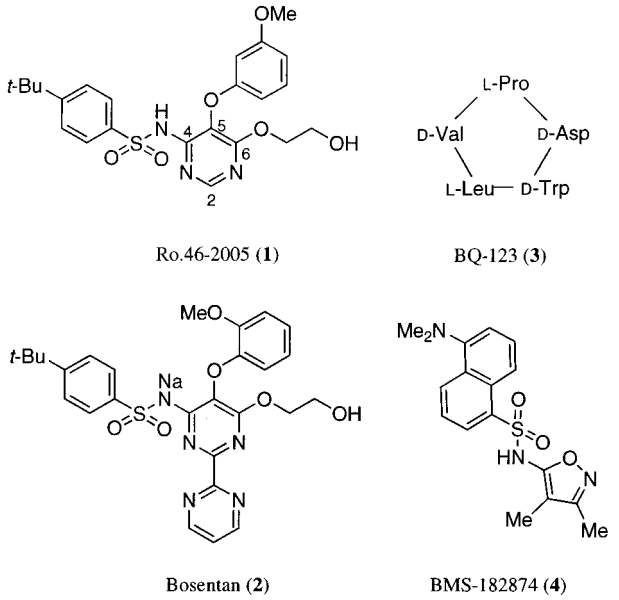

Figure 1. Roche's sulfonamide derivatives (**1**, **2**) and ET_A-selective antagonist BQ-123 (**3**) and BMS-182874 (**4**).

Breu et al. mentioned that the hydroxyl group at the 6-position in Roche's sulfonamide derivatives is important for hydrogen bonding to ET receptors.[6b,c] To verify their hypothesis and to discover more potent and ET_A-selective compounds, we performed introduction of alkyl, aryl, and heteroaryl groups into the 2-hydroxyethoxy

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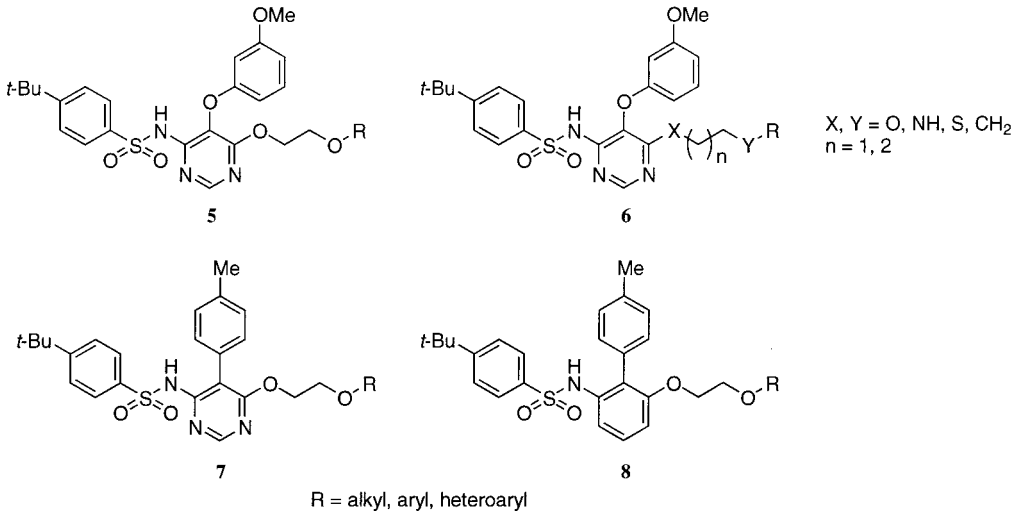


Figure 2. Prepared compounds.

moiety (compound **5**) and modification of the moiety (compound **6**) at the 6-position of **1** (Figure 2). The effect of substituting the *p*-tolyl group at the 5-position for the aryloxy group of **1** was also investigated (compound **7**). For rapid and efficient optimization at the 4- and 5-position, we developed new synthetic routes that allowed us to prepare the diverse sulfonamidopyrimidines. In addition, the benzene analogues **8**, shown in Figure 2, were synthesized to evaluate the role of the pyrimidine nucleus and of the side chain for the receptor binding. This report describes the syntheses, inhibitory activities, structure−activity relationships (SAR), and pharmacological effects of our potent, ET_A-selective antagonists.

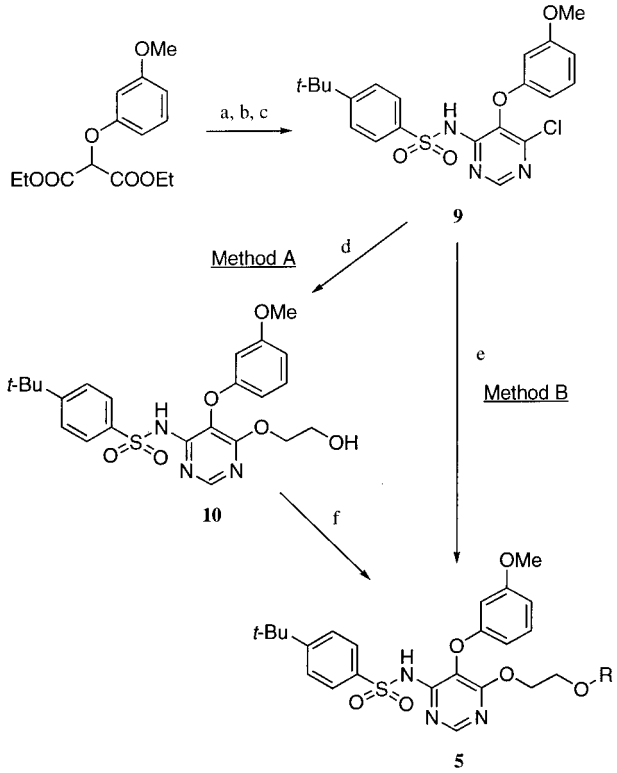
Chemistry

1. General Synthetic Method (Methods A and B). The general synthetic method of pyrimidine-4-sulfonamide derivatives **5** is shown in Scheme 1. The 2-hydroxyethoxy derivatives **10** were synthesized by the reported method.[8] The following arylations of **10** (method A) or direct substitution of the 6-chloropyrimidine **9**[8] with appropriate alcohols (method B) afforded **5**. Modification of the ethylene glycol moiety (compound **6**), and syntheses of the 5-*p*-tolyl derivatives **7** were performed in a manner similar to methods A and B.

2. Modification of the Sulfonamide Part at the 4-Position (Methods C and D). Scheme 2 shows the preparation of the sulfonamidopyrimidines containing a variety of substituents at the 4-position of the nucleus pyrimidine. The 4-aminopyrimidine derivative **15** was prepared from dichloride **11**[8] in four steps. The reaction of **15** to sulfonamide did not proceed by the usual methods, such as treatment with arylsulfonyl chloride in pyridine. We found, however, that **16** could be efficiently prepared by reactions with arylsulfonyl chlorides using NaH in tetrahydrofuran with NaI when necessary (method C), or KOH in the presence of *n*-Bu_4NHSO_4 in toluene (method D).

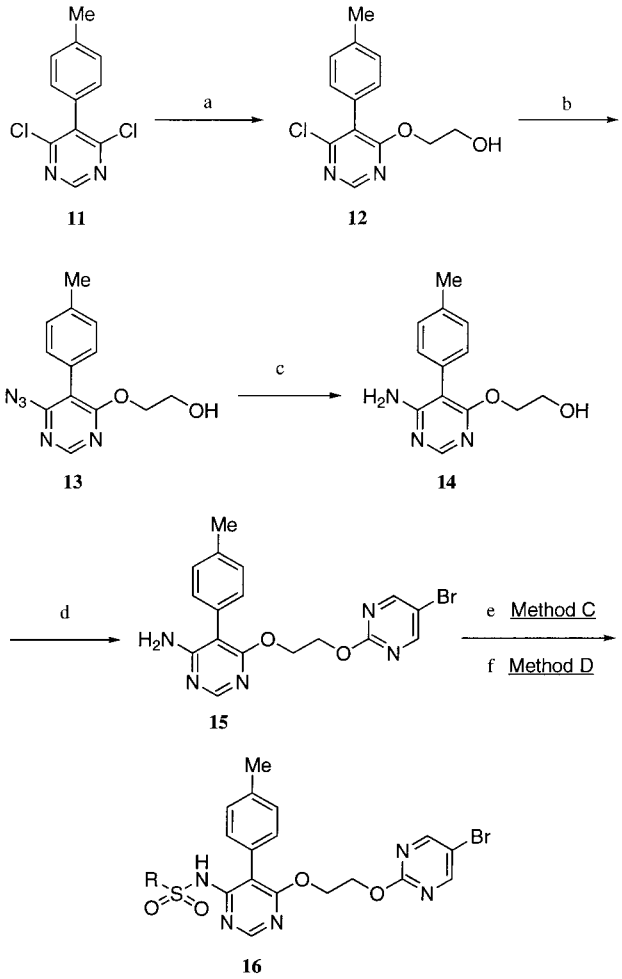
3. Modification at the 5-Position (Method E). In the SAR study at the 5-position of the nucleus pyrimidine, 5-(methylthio)pyrimidin-2-yl derivative **7s**, which exhibited an inhibitory activity for ET_A receptor as high as that exhibited by **7k** (see below), was modified due to high reactivity of the bromine atom of **7k** under palladium-catalyzed cross-coupling conditions. The modification was performed as shown in Scheme 3 (method E). Bromination of **18**, derived from 4,6-dichloropyrimidine (**17**) in two steps, with *N*-bromosuccinimide (NBS) and following introduction of the side chain into the pyrimidine gave the 5-bromo-2-(5-methylthio)pyrimidinyl derivative **20**. Various aryl groups were introduced into **20** by palladium-catalyzed cross-coupling[9] to afford the 5-aryl compounds **21**. The synthetic routes to the 5-(2-methoxyphenyl)thio derivative are shown in Scheme 4. 2-Methoxyphenylsulfenyl chloride (**23**), derived from bis(2-methoxyphenyl) disulfide[10] (**22**), was reacted with pyrimidine-4,6-diol to give the sulfide **24**.[11]

Scheme 1. General Modification Methods at the 6-Position of Pyrimidine (Methods A and B)[a]



[a] Reagents: (a) formamidine acetate, NaOMe; (b) $POCl_3$; (c) *p-tert*-butylbenzenesulfonamide, NaH or K_2CO_3; (d) ethylene glycol, NaH; (e) HO-$(CH_2)_2$-OR, NaH; (f) R-Cl or R-Br, NaH.

Scheme 2. Modification at the Sulfonamide Part (Methods C and D)[a]



[a] Reagents: (a) ethylene glycol, NaH; (b) NaN_3; (c) H_2, Pd/C; (d) 5-bromo-2-chloropyrimidine, NaH; (e) R-SO_2Cl, NaH (+NaI) in THF; (f) R-SO_2Cl, *n*-Bu_4NHSO_4, KOH in toluene.

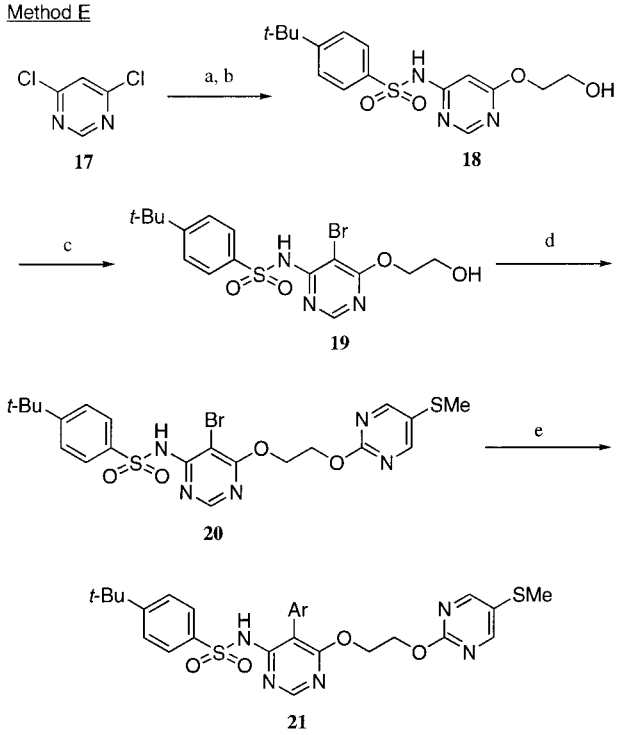
Conversion of **24** to the dichloride **25** followed by substitution at the 4- and 6-positions according to the method A afforded the targeted compound **27**.

4. Syntheses of Benzene Analogues. The preparation of the benzene nucleus analogues **8k** and **8w** is shown in Scheme 5. The compound **29** was prepared from 2-chloro-3-nitrophenol[12] (**28**) by Mitsunobu reaction. Palladium-catalyzed cross-coupling of **29** with tributyl-*p*-tolyltin afforded the tolyl derivative **30**, which was modified to the sulfonamide **31** by subsequent reduction of the nitro group, sulfonylation, and hydrogenolysis of the benzyl group. The 5-bromopyrimidin-2-yl group was introduced by the described method A to give the benzene analogue **8k**. Compound **8k** was converted to 5-(3-thienyl)pyrimidin-2-yl derivative **8w** by palladium-catalyzed cross-coupling with tributyl-3-thienyltin.

Results

1. SAR of the Side Chain at the 6-Position (Compounds 5 and 6). The introduction of phenyl (**5a**) and the methyl group (**5b**) into the side chain at the 6-position increased the affinity for the ET_A receptor compared to **1**. Furthermore, the introduction of pyridine and pyrimidine groups resulted in a large increase

Scheme 3. Modification at the 5-Position (Method E)[a]



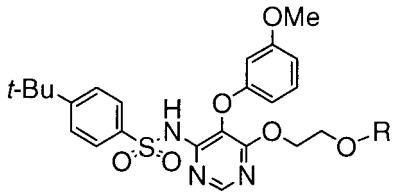
[a] Reagents: (a) *p-tert*-butylbenzenesufonamide, NaH; (b) ethylene glycol, NaH; (c) NBS; (d) 2-chloro-5-(methylthio)pyrimidine, NaH; (e) Ar-$SnBu_3$, $PdCl_2(PPh_3)_2$, PPh_3, CuBr.

in affinity. The SARs of the heteroaryl derivatives **5** and **6** are shown in Tables 1 and 2. Generally, the following relationship was observed with respect to the side chain at the 6-position. (1) Heteroaryl groups (**5d**−**i**) increased the affinity much more than the phenyl group did. (2) Pyrimidinyl groups (**5e**,**h**) exhibited the highest affinity. (3) Introduction of substituents into the pyrimidine at the 5′-position (**5j**−**m**) increased the affinity dramatically. (4) Introduction of substituents into the pyrimidine at the 4′-position (**5n**,**o**) diminished the affinity. (5) Monocyclic heteroaryl groups exhibited higher affinity than bicyclic ones (**5p**−**r**). (6) Conversion of one of the oxygens in ethylene glycol to other atoms in **5**, such as NH, CH_2, or S, reduced the affinity (**5e** vs **6a**−**d**). (7) Elongation of the carbon chain also resulted in a drop of the affinity (**5j** vs **6e**).

2. Comparative Study of the 5-Position of the Nucleus Pyrimidine (Compounds 5 and 7). As shown in Table 3, conversion of the *m*-methoxyphenoxy group in **5** to a *p*-tolyl group (compound **7**) increased the affinity for ET_A. The affinities of the *p*-tolyl derivatives **7** were much higher than that of **5**. Introduction of thienyl or furyl groups into the 5-position of the side chain pyrimidine (**7u**−**w**) maintained the extremely high affinity with IC_{50} values of smaller than 1 pM.

3. SAR of the Side Chain at the 4-Position (Compound 16). SARs of the sulfonamide part in the compounds **16** are shown in Table 4. Replacement of the *tert*-butyl group at the para position of the benzene ring with other bulky ones (**16a**,**b**) preserved the high affinity for the ET_A receptor. However, introduction of a halogen or a trifluoromethyl group (**16c**−**f**) and replacement of the benzene ring with naphthalene (**16i**,**j**) or with heteroaryl groups (**16k**,**l**) tended to

Table 1. Modification Effect at the 6-Position of Pyrimidine

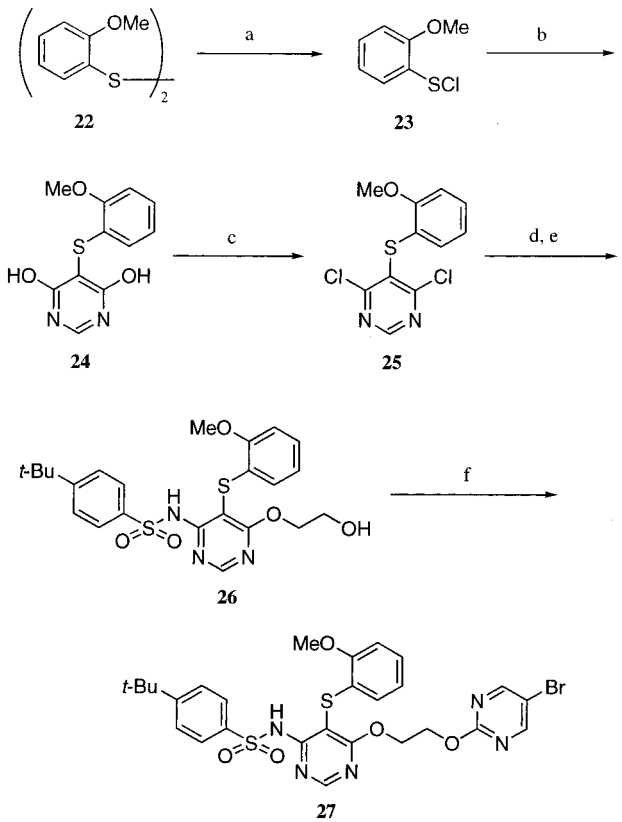


1, 5a–r

compd	R	IC_{50} (nM)[a]	method	mp (°C)	mol. formula[b]
5a	phenyl	65	B	129–130	$C_{29}H_{31}N_3O_6S$
5b	methyl	92	B	143–144	$C_{24}H_{29}N_3O_6S$
5c	benzyl	170	B	158.5–159	$C_{30}H_{33}N_3O_6S$
5d	2-pyridyl	8.8	A	130.5–132	$C_{28}H_{30}N_4O_6S$
5e	2-pyrimidinyl	1.9	A	128–129.5	$C_{27}H_{29}N_5O_6S$
5f	2-pyrazinyl	24.5	A	140.5–141.5	$C_{27}H_{29}N_5O_6S$
5g	3-pyridazinyl	51.4	A	169.5–170	$C_{27}H_{29}N_5O_6S$
5h	4-pyrimidinyl	1.2	A	149–150.5	$C_{27}H_{29}N_5O_6S$
5i	2-thiazolyl	12	A	100.5–101	$C_{26}H_{28}N_4O_6S_2$
5j	5-Me-2-pyrimidinyl	0.86	A	142–142.5	$C_{28}H_{31}N_5O_6S$
5k	5-Br-2-pyrimidinyl	0.051	A	168–168.5	$C_{27}H_{28}BrN_5O_6S$
5l	5-Cl-2-pyrimidinyl	0.059	A	153.5–154.5	$C_{27}H_{28}ClN_5O_6S$
5m	5-(OMe)-2-pyrimidinyl	0.015	A	122–125	$C_{28}H_{31}N_5O_7S$
5n	4-Me-2-pyrimidinyl	39.4	A	132–134.5	$C_{28}H_{31}N_5O_6S$
5o	4-(OMe)-2-pyrimidinyl	>100	A	122–123	$C_{28}H_{31}N_5O_7S$
5p	2-quinolyl	15.2	A	160–161	$C_{32}H_{32}N_4O_6S \cdot H_2O$
5q	2-quinoxalinyl	45.4	A	156–157	$C_{31}H_{31}N_5O_6S$
5r	1-isoquinolyl	>100	A	147.5–148.5	$C_{32}H_{32}N_4O_6S \cdot 0.3H_2O$
1	H (Ro.46-2005)	160			

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

Scheme 4. Synthetic Route of the 5-(2-Methoxy)phenylthio Derivative[a]



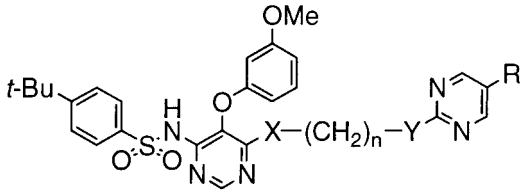
[a] Reagents: (a) SO_2Cl_2, Et_3N, CCl_4; (b) 4,6-dihydroxypyrimidine; (c) $POCl_3$; (d) *p-tert*-butylbenzenesufonamide, NaH; (e) ethylene glycol, NaH; (f) 5-bromo-2-chloropyrimidine, NaH.

diminish the affinity. These results indicated that the benzene ring possessing a bulky alkyl group such as *tert*-butyl was preferable in terms of high affinity for the ET_A receptor.

4. SAR of the Side Chain at the 5-Position (Compound 21). Table 5 shows the effect of substituents at the 5-position. Substitution of the *p*-tolyl group of **7s** with 4-chlorophenyl (**21c**) and 4-methoxyphenyl (**21f**) groups preserved the high activity for the ET_A receptor. The 3-methoxyphenyl compound **21e** was less potent than **21f**. Introduction of more bulky substituents at the para position of the phenyl group, such as ethyl (**21a**) and isopropyl (**21b**), resulted in loss of activity. The 3,4-disubstituted phenyl compounds (**21g**,**h**) were slightly less potent than **7s**. However, replacement with the 2-naphthyl group (**21j**) and heteroaryl groups (**21k**–**n**) resulted in drastic loss of activity. The 5-bromopyrimidin-2-yl derivatives possessing a 2-methoxyphenylthio group (**27**) and a 2-methoxyphenoxy group (**32**) at the 5-position of the nucleus pyrimidine preserved the higher activity but not to the same degree as **7k**. Overall, among the compounds made by modification at the 5-position, **7k** resulted in one of the most potent affinities for the ET_A receptor.

5. Binding Potency and Selectivities for $ET_{A/B}$ Receptor Subtypes. Table 6 shows the binding potency of the Na salts of the compounds **7k**, **7l**, **7m**, **7s**, **7u**, and **7v** to ET receptor subtypes on cultured cells. Our compounds exhibited higher affinity for the ET_A receptor than did **1** or **2**. Moreover, it was found that the binding potency and the selectivity for ET_A/ET_B receptors varied depending on the 5′-substituents on the side chain pyrimidine. Halogen, methoxy, or methylthio substituents (**7k**, **7l**, **7m**, **7s**) showed much higher selectivity for the ET_A receptor than did heteroaryl substituents (**7u**, **7v**). Among these, **7k** proved to be the most potent (IC_{50} = <0.001 nM in porcine aortic

Table 2. Modification Effect of the Ethylene Glycol Part

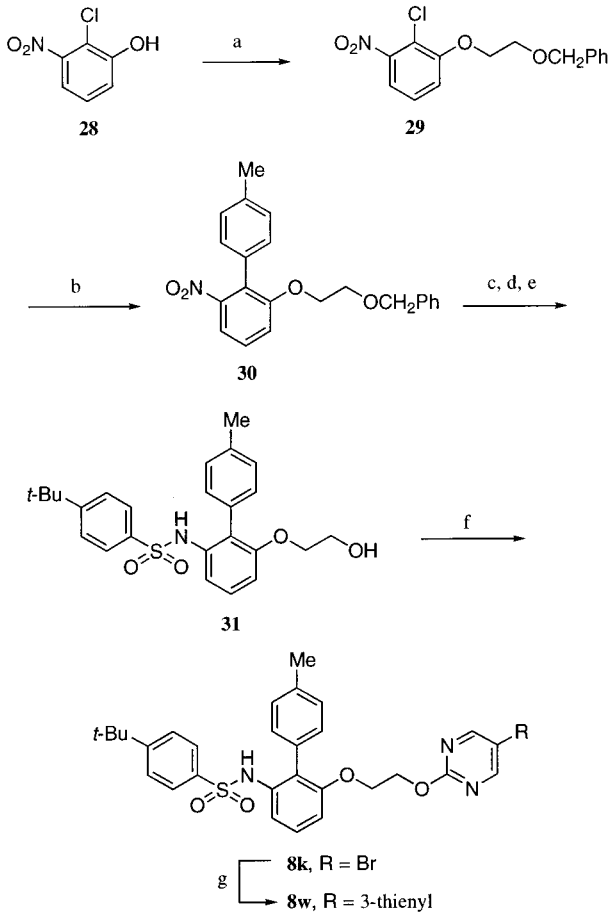


6

compd	X	*n*	Y	R	IC_{50} (nM)[a]	method	mp (°C)	mol. formula[b]
6a	O	2	NH	H	>100	A	101−102 (dec)	$C_{27}H_{30}N_6O_5S\cdot H_2O\cdot 0.2EtOAc$
6b	O	2	CH_2	H	>100	B	148−149.5	$C_{28}H_{31}N_5O_5S\cdot 0.5H_2O$
6c	S	2	O	H	25.8	A	167.5−168	$C_{27}H_{29}N_5O_5S_2$
6d	NH	2	O	H	6.2	A	147.5−149	$C_{27}H_{30}N_6O_5S\cdot 0.2H_2O$
6e	O	3	O	Me	93.5	A	117−118.5	$C_{29}H_{33}N_5O_6S$

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

Scheme 5. Synthetic Route of the Benzene Analogues[a]



[a] Reagents: (a) HO-$(CH_2)_2$-OCH_2Ph, PPh_3, DEAD; (b) tributyl-*p*-tolyltin, $PdCl_2(PPh_3)_2$; (c) Fe, HCl; (d) *p*-*tert*-butylbenzenesulfonyl chloride, pyridine; (e) H_2, Pd/C; (f) 5-bromo-2-chloropyrimidine, NaH; (g) tributyl-3-thienyltin, $PdCl_2(PPh_3)_2$.

membrane), showing 970-fold higher affinity for the ET_A receptor (IC_{50} = 0.039 nM in rat A10 cells) than for the ET_B receptor (IC_{50} = 38 nM in human GH cells). The ET_A-selectivity of **1** and **2** on cultured cells (A10 and GH cells) were 5 and 220, respectively.

The binding potencies (K_i values) of **7k** and bosentan on human cloned ET receptor subtypes expressed in CHO cells were 0.0042 ± 0.0038 nM and 81 ± 26 nM for ET_A and 130 ± 50 nM and 140 ± 26 nM for ET_B, respectively. The ET_A-selectivity of **7k** and bosentan were 29 000 and 1.7, respectively. The reason for these discrepancies in the affinity and selectivity between cultured cells and human cloned cells is uncertain.

6. Binding Affinity of the Benzene Analogues. The benzene analogues **8k** and **8w** showed a markedly lower affinity for the ET_A receptor (IC_{50} **8k**, 16 nM; **8w**, 61 nM in porcine aortic membrane) than their corresponding pyrimidine counterparts (IC_{50} **7k**, <0.001 nM; **7w**, <0.001 nM). Nevertheless, the IC_{50} values of **8k** and **8w** were smaller than that of the hydroxyethoxy derivative **31** (IC_{50} > 100 nM). Although the conversion of the nucleus pyrimidine to benzene caused a drop in affinity, the introduction of the pyrimidine moieties into the side chain increased the affinity.

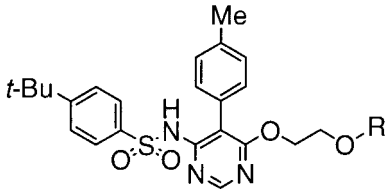
7. Functional Study of 7k.[13] Compound **7k** shifted the concentration−response curve of ET-1-induced contraction in the isolated rat aorta (endothelium denuded) to the right (ET_A receptors, pA_2 = 9.3 ± 0.4). In anesthetized rats, **7k** at doses of 0.01−1 mg/kg, iv, inhibited the pressor response to the exogenous big ET-1 (1 nmol/kg, iv). The hypotensive response to exogenous ET_B-selective agonist sarafotoxin S6c (0.3 nmol/kg, iv) was also reduced by a high dose of **7k** (1 mg/kg, iv).

Discussion

In an effort to develop more potent and ET_A-selective compounds, and in order to confirm the hypothesis of the Roche group that the hydroxyl group at the 6-position in the sulfonamide derivatives is important for hydrogen bonding to ET receptors,[6c] we modified the hydroxyethoxy moiety of **1** and **2**. The introduction of heteroaryl groups, such as pyridyl or pyrimidinyl groups, resulted in much higher affinity for the ET_A receptor than was exhibited by Roche's compounds. In particular, 5′-substituted pyrimidin-2-yl derivatives showed extremely high affinity and selectivity. Our SAR study also suggested that a para-substituted benzene ring with a bulky hydrophobic group at the sulfonamide moiety and a para-substituted benzene ring with a compact group at the 5-position of the nucleus pyrimidine were conducive to higher affinity for the ET_A receptor.

Several studies have shown that Tyr129 in the ET_A receptor is important for binding of ET_A-selective antagonists. (1) With respect to BQ-123 (**3**), the peptidic ET_A-selective antagonist, Lee et al. reported that the

Table 3. SAR between the Compounds **7**

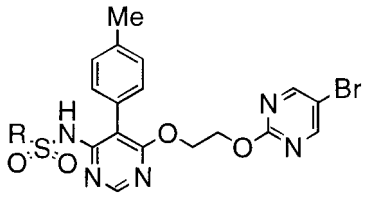


7

compd[a]	R	IC_{50} (nM)[b]	mp (°C)	mol. formula[c]
7e	2-pyrimidinyl	0.11	169−170	$C_{27}H_{29}N_5O_4S$
7k	5-Br-2-pyrimidinyl	<0.001	167−168	$C_{27}H_{28}BrN_5O_4S$
7l	5-Cl-2-pyrimidinyl	<0.001	169.5−170.5	$C_{27}H_{28}ClN_5O_4S$
7m	5-(OMe)-2-pyrimidinyl	0.0017	188.5−189	$C_{28}H_{31}N_5O_5S$
7s	5-(SMe)-2-pyrimidinyl	<0.001	194.5−195.5	$C_{28}H_{31}N_5O_4S_2$
7t	5-(2-pyridyl)-2-pyrimidinyl	0.036	185.5−186.5	$C_{32}H_{32}N_6O_4S\cdot0.3H_2O$
7u	5-(2-furyl)-2-pyrimidinyl	<0.001	193−195	$C_{31}H_{31}N_5O_5S$
7v	5-(2-thienyl)-2-pyrimidinyl	<0.001	180.5−182	$C_{31}H_{31}N_5O_4S_2\cdot0.5H_2O$
7w	5-(3-thienyl)-2-pyrimidinyl	<0.001	151.5−153	$C_{33}H_{33}N_3O_4S_2$
14	H	>100	167.5−168.5[d]	$C_{23}H_{27}N_3O_4S$
bosentan (**2**)		7.5		

[a] All the compounds were prepared by the method A in Scheme 1. [b] Inhibition of [^{125}I]ET-1 binding in vitro to ET_A receptors in porcine aortic membrane. Values are from a single experiment. [c] Analyses (C, H, N) were within ±0.4% of theoretical values. [d] Lit.; EP 510526 (1992), mp 169−170 °C.

Table 4. SAR of the 4-Substituted Derivatives



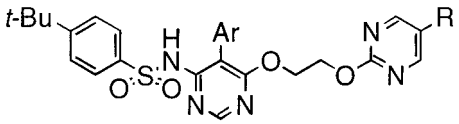
16

compd	R	IC_{50} (nM)[a]	method	mp (°C)	mol. formula[b]
7k	4-*tert*-Bu-phenyl	<0.001			
16a	4-*tert*-pentyl-phenyl	<0.001	D	153.5−154.5	$C_{28}H_{30}BrN_5O_4S$
16b	4-*i*-Pr-phenyl	0.16	A	143−144	$C_{26}H_{26}BrN_5O_4S\cdot0.1H_2O$
16c	4-Cl-phenyl	1.9	C	208−209	$C_{23}H_{19}BrClN_5O_4S\cdot0.2THF$
16d	4-Br-phenyl	2.8	C	217−218	$C_{23}H_{19}Br_2N_5O_4S$
16e	4-I-phenyl	1.0	D	207.5−208	$C_{23}H_{19}BrIN_5O_4S$
16f	4-CF_3-phenyl	1.4	D	191.5−192.5	$C_{24}H_{19}BrF_3N_5O_4S$
16g	4-(OMe)-phenyl	0.76	D	216.5−217.5	$C_{24}H_{22}BrN_5O_5S$
16h	3,4-$(OMe)_2$-phenyl	0.64	D	180.5−182	$C_{25}H_{24}BrN_5O_6S$
16i	1-naphthyl	22	D	169.5−170.5	$C_{27}H_{22}BrN_5O_4S\cdot0.2H_2O$
16j	2-naphthyl	1.0	D	204−204.5	$C_{27}H_{22}BrN_5O_4S$
16k	2-thienyl	3.1	D	152−155	$C_{21}H_{18}BrN_5O_4S_2$
16l	5-(2-pyridyl)-2-thienyl	3.4	D	226−227	$C_{26}H_{21}BrN_6O_4S_2$

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

presence of Tyr129 in the transmembrane (TM)-2 region was the most important modification in terms of enhancing ET_A binding, based on point mutation analyses of the ET_A receptor. These authors further reported that a point mutation of Tyr129 to Ala129 caused a more dramatic reduction of the binding affinity of BQ-123 to the ET_A receptor than to other amino acids such as Phe129.[14] (2) Krystek, Jr., et al. described the importance of interactions between the nonpeptidic ET_A-selective antagonist BMS-182874 (**4**) and Tyr129.[15] Affinity of **4** was decreased drastically in Tyr129Ala, Tyr129Ser, and Tyr129His ET_A mutants. However, the substitution of Tyr129 with Phe or Trp caused a smaller decrease in affinity. These authors pointed out that the binding to the ET_A receptor may have been partially enhanced through aromatic interaction between the naphthalene ring of **4** and the phenyl ring of Tyr129, as well as through hydrogen bonding between the dimethylamino group of **4** and the hydroxyl group of Tyr129. They also found that **1** did not interact with this site.[15] (3) Breu et al. found that point mutations of Lys159 and Gln165 in TM-3, of Tyr263 in TM-5, of Arg326 in TM-6, and of Asp351 in TM-7 influenced the binding of the $ET_{A/B}$ mixed type antagonist bosentan, while point mutations of Asp126 and Tyr129 in TM-2, of Arg326 in TM-6, and of Asp351 in TM-7 influenced the binding of **3**.[16] Together, the above findings suggest that Tyr129 plays a more important role than other

Table 5. SAR of the 5-Substituted Derivatives

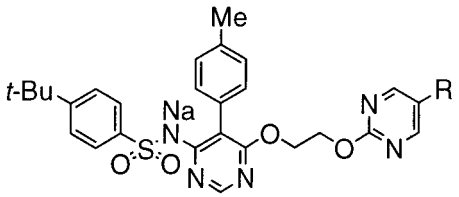


7s, **21a–n**; R = SMe
5k, **27**, **32**; R = Br

compd	Ar	IC_{50} (nM)[a]	method	mp (°C)	mol. formula[b]
7s	4-Me-phenyl	<0.001			
21a	4-Et-phenyl	0.013	E	157.5−159.5	$C_{29}H_{33}N_5O_4S_2$
21b	4-*i*-Pr-phenyl	1.2	E	144.5−145.5	$C_{30}H_{35}N_5O_4S_2$
21c	4-Cl-phenyl	<0.001	E	180.5−181.5	$C_{27}H_{28}ClN_5O_4S_2$
21d	4-CF_3-phenyl	0.0017	E	170−171	$C_{28}H_{28}F_3N_5O_4S_2$
21e	3-(OMe)-phenyl	0.028	E	126−129	$C_{28}H_{31}N_5O_5S_2$
21f	4-(OMe)-phenyl	<0.001	E	166−167	$C_{28}H_{31}N_5O_5S_2$
21g	3,4-$(OMe)_2$-phenyl	0.0085	E	170.5−171.5	$C_{29}H_{33}N_5O_6S_2$·0.2EtOAc
21h	3,4-(OCH_2O)-phenyl	0.0011	E	150−151	$C_{28}H_{29}N_5O_6S_2$
21i	2-(OMe)-phenoxy	0.37	A	156−157	$C_{28}H_{31}N_5O_6S_2$
32	2-(OMe)-phenoxy	0.0039	A	181.5−182.5	$C_{27}H_{28}BrN_5O_6S$
5k	3-(OMe)-phenoxy	0.051			
27	2-(OMe)-phenylthio	0.018		141−142	$C_{27}H_{28}BrN_5O_5S_2$
21j	2-naphthyl	0.29	E	187−189	$C_{31}H_{31}N_5O_4S_2$
21k	2-thienyl	0.89	E	182−184	$C_{25}H_{27}N_5O_4S_3$
21l	5-Me-2-thienyl	0.16	E	160−162	$C_{26}H_{29}N_5O_4S_3$
21m	2-furyl	2.9	E	175.5−177	$C_{25}H_{27}N_5O_5S_2$
21n	4-pyridyl	9.9	E	182.5−184	$C_{26}H_{28}N_6O_4S_2$

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

Table 6. Binding Potency of Na Salts of **7k−m**,**s**,**u**,**v** on ET Receptor Subtypes



7k–m, **s**, **u**, **v**

		IC_{50} (nM)[a]				
compd	R	ET_A (A10 cell)	ET_B (GH cell)	ET_A-selectivity[b]	mp (°C)	mol. formula[c]
7k·Na salt	Br	0.039	38	970	238−242 (dec)	$C_{27}H_{27}BrN_5NaO_4S$
7l·Na salt	Cl	0.08	28	350	218- (dec)	$C_{27}H_{27}ClN_5NaO_4S$
7m·Na salt	OMe	0.56	240	430	148	$C_{28}H_{30}N_5NaO_4S$·1.3EtOH
7s·Na salt	SMe	0.42	220	520	165- (dec)	$C_{28}H_{30}N_5NaO_4S_2$·0.5H_2O
7u·Na salt	2-furyl	0.48	7	15	254−257.5 (dec)	$C_{31}H_{30}N_5NaO_5S$·0.3H_2O
7v·Na salt	2-thienyl	0.25	3.8	15	244−250 (dec)	$C_{31}H_{30}N_5NaO_4S_2$·0.5H_2O
Ro.46-2005 (**1**)		230	1100	5		
bosentan (**2**)		1.4	310	220		

[a] IC_{50} for inhibition of specific binding of [^{125}I]ET-1 (20 pM) to A 10 cells which express ET_A receptors or GH cells which express ET_B receptors. Values are the average from two experiments. [b] IC_{50} for ET_B/IC_{50} for ET_A. [c] Analyses (C, H, N) were within ±0.4% of theoretical values.

amino acids in the higher binding affinity for the ET_A. On the basis of these data, we speculated that the poor $ET_{A/B}$ subtype selectivity of **1** and **2** would result from the lack of interaction with Tyr129.

Our data led to the hypothesis that the pyrimidin-2-yloxy group at the 6-position in our compounds would interact with Tyr129 via aromatic interaction and/or hydrogen bonding in a manner similar to that of **4** as reported by Krystek, Jr., et al. Our hypothesis is supported by the following: (1) the phenoxy derivative (**5a**), which would interact with Tyr129 via aromatic interaction, showed higher affinity for ET_A receptor than the methoxy derivative (**5b**); (2) conversion of the oxygen atom to amine (compound **6a**) or methylene (compound **6b**) reduced the affinity; and (3) 2-pyridyloxy and 2-pyrimidinyloxy groups acted as stronger hydrogen bonding acceptors than did methoxy or phenoxy groups. Our proposed interaction would cause extremely high affinity and selectivity for the ET_A receptor. Figure 3 shows our putative interaction model between the pyrimidin-2-yloxy group and Tyr129.

Derivatives with 4′-substituted pyrimidinyl groups (**5n**,**o**) showed a drastic reduction of affinity. This may have been caused by steric repulsion between the

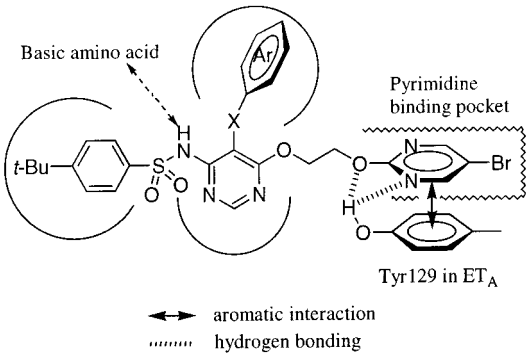


Figure 3. A putative binding model.

substituents at the 4′-position of the pyrimidine and the binding pocket in the ET_A receptor. As for the 5′-position of the side chain pyrimidine, introduction of a 2-furyl or 2-thienyl group (**7u**,**v**) diminished the ET_A-selectivity (Table 6). These groups are likely to cause some interaction with the ET_B receptor, thereby maintaining an extremely high affinity for the ET_A receptor. The binding pocket in the ET_A receptor may preferentially accept 5′-substituted pyrimidine.

With respect to the benzene analogues, both **8k** and **8w** showed a drop of affinity probably because their sulfonamide group had lower acidity than did that of **7k** and **7w**. At the same time, however, incorporation of the 2-pyrimidinyl moiety into the 2-hydroxyethoxy moiety of **31** resulted in a large increase in the affinity.

These results suggested that the pyrimidine in the side chain played a very important role in the increased affinity by interacting with the so-called, "pyrimidine binding pocket" in ET_A receptor. Further studies, including investigation into the point mutations of the receptor, will be needed to obtain experimental evidence in support of our hypothesis.

Conclusion

Chemical modifications of **1** and **2** at the 6-position were performed based on the fact that conversion of hydroxyl group on the side chain to phenyl or methoxy groups have been shown to improve affinity for the ET_A receptor. Our data led to the hypothesis that our compounds would interact with Tyr129 in the ET_A receptor, which does not exist in the ET_B receptor, via aromatic interaction and/or hydrogen bonding. The modifications of the moiety led to production of a potent and selective ET_A receptor antagonist, **7k**, which we will examine further in future studies.

Experimental Section

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

Halo-heteroaryl Compounds. 2-Bromopyridine, 2-chloropyrimidine, 2-chloropyrazine, 3,6-dichloropyridazine, 4-chloro-2-methylthiopyrimidine, 2-bromothiazole, 2-bromoquinoline, 2-chloroquinoxaline, and 1-chloroisoquinoline were commercially available. 2-Chloro-5-methylpyrimidine,[17] 2,5-dichloropyrimidine,[18] 5-bromo-2-chloropyrimidine,[18,19] 2-chloro-5-methoxypyrimidine,[20] 2-chloro-4-methylpyrimidine,[21] 2-chloro-4-methoxypyrimidine,[22] and 2-chloro-5-methylthiopyrimidine[23,24] were prepared by the reported methods.

Arylbenzenesulfonyl Chlorides. 4-*tert*-Butylbenzenesulfonyl chloride, 4-isopropylbenzenesulfonyl chloride 4-*tert*-pentylbenzenesulfonyl chloride, 3,4-dimethoxybenzenesulfonyl chloride, 4-methoxybenzenesulfonyl chloride, 2-naphthalenesulfonyl chloride, 4-iodobenzenesulfonyl chloride, 4-(trifluoromethyl)benzenesulfonyl chloride, 4-chlorobenzenesulfonyl chloride, 4-bromobenzenesulfonyl chloride, 2-thiophenesulfonyl chloride, 5-(2-pyridyl)-2-thiophenesulfonyl chloride, and 1-naphthalenesulfonyl chloride were commercially available.

Tributyl-aryltins. Tributyl-(4-methylphenyl)tin, tributyl-(4-chlorophenyl)tin, tributyl-(3,4-methylenedioxyphenyl)tin, tributyl-(4-trifluoromethylphenyl)tin, tributyl-(3,4-dimethoxyphenyl)tin, and tributyl-4-pyridyltin were prepared by Method 1. Tributyl-(5-methyl-2-thienyl)tin, tributyl-2-thienyltin, and tributyl-2-furyltin were prepared by Method 2. Tributyl-(4-methoxyphenyl)tin, tributyl-(4-ethylphenyl)tin, tributyl-(3-methoxyphenyl)tin, tributyl-2-naphthyltin, and tributyl-(4-isopropylphenyl)tin were prepared by Method 3.

a. Method 1. Under Ar atmosphere, *n*-BuLi in hexane (1 equiv) was added to arylbromide in THF dropwise at −78 °C. After 1 h, *n*-tributylstannyl chloride (1 equiv) was added dropwise at the same temperature, then the whole was allowed to warm to room temperature over 1 h. The reaction mixture was diluted with 10% aqueous KF and extracted with EtOAc. The organic extract was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on alumina (eluted with hexane) to afford the corresponding tributyl-aryltin.

b. Method 2. Under Ar atmosphere, *n*-BuLi in hexane (1 equiv) was added to arene in Et_2O dropwise at −78 °C. After 1 h, *n*-tributylstannyl chloride (1 equiv) was added dropwise at the same temperature, then the whole was allowed to warm to room temperature over 1 h. The same work up as in method 1 afforded the corresponding tributyl-aryltin.

c. Method 3. Under Ar atmosphere, to a stirred mixture of Mg (1.2 equiv) in THF was added a catalytic amount of 1,2-dibromoethane. After the mixture was stirred at room temperature for 15 min, arylbromide was added dropwise, and then the mixture was stirred at the same temperature for 1 h. After cooling to −78 °C, *n*-tributylstannyl chloride (1 equiv) was added dropwise, and then the whole was allowed to warm to room temperature over 1 h. The same work up as in method 1 afforded the corresponding tributyl-aryltin.

4-*tert*-Butylbenzenesulfonamide. A solution of 4-*tert*-butylbenzenesulfonyl chloride (60.00 g, 0.258 mol) in EtOAc (200 mL) was added to ice-cooled concentrated NH_4OH (300 mL), and the mixture was stirred at room temperature for 1 h. NH_3 and EtOAc were evaporated in vacuo, and the residue was acidified with 10% aqueous HCl and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residual powder was recrystallized from EtOAc−hexane to afford 4-*tert*-butylbenzenesulfonamide as colorless leaflets (52.52 g, 95%): mp 138−138.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86 (2H, d, J = 8.8 Hz), 7.53 (2H, d, J = 8.8 Hz), 4.92 (2H, br s), 1.35 (9H, s); IR (Nujol) cm^{-1} 3360, 3270, 3110, 1600, 1570, 1495, 1465; EI-MS m/z 213 (M^+), 198.

Representative Procedure for Compounds 5 (Method A). 4-*tert*-Butyl-*N*-(5-(3-methoxyphenoxy)-6-(2-((5-methoxy-2-pyrimidinyl)oxy)ethoxy)-4-pyrimidinyl)benzenesulfonamide (5m). To a stirred suspension of 4-*tert*-butyl-*N*-(6-(2-hydroxyethoxy)-5-(3-methoxyphenoxy)-4-pyrimidinyl)-benzenesulfonamide[8] (**10**) (200 mg, 0.422 mmol) and 60% NaH in mineral oil dispersion (58 mg, 1.48 mmol) in dry *N*,*N*-dimethylacetamide (DMAc) (4 mL) was added 2-chloro-5-methoxypyrimidine[20] (122 mg, 0.844 mmol), and the mixture was stirred at room temperature for 2 days, diluted with saturated aqueous NH_4Cl, and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in

vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 30:1, v/v), and recrystallized from EtOAc−*i*-Pr_2O to afford **5m** as colorless crystals (127 mg, 52%): mp 122−125 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.27 (1H, s), 8.11 (2H, s), 8.02 (2H, d, J = 8.7 Hz), 7.61 (1H, br s), 7.51 (2H, d, J = 8.8 Hz), 6.56 (1H, ddd, J = 0.8, 2.4, 8.2 Hz), 5.37 (1H, t, J = 2.4 Hz), 6.30 (1H, ddd, J = 0.8, 2.4, 8.2 Hz), 4.63−4.69 (2H, m), 4.41−4.47 (2H, m), 3.85 (3H, s), 3.74 (3H, s), 1.34 (9H, s); IR (Nujol) cm^{-1} 3090, 1610, 1595, 1585; FAB-MS *m*/*z* 582 (M+H$^+$), 456, 259, 153; Anal. ($C_{28}H_{31}N_5O_7S$) C, H, N.

Representative Procedure for Compounds 5 (Method B). 4-*tert*-Butyl-*N*-(5-(3-methoxyphenoxy)-6-(2-phenoxy)-ethoxy-4-pyrimidinyl)benzenesulfonamide (5a). To a solution of 2-phenoxyethanol (231 mg, 1.67 mmol) in dry DMSO (3 mL) was added 60% NaH in mineral oil dispersion (52 mg, 1.35 mmol), and the mixture was stirred at 100 °C for 10 min. 4-*tert*-butyl-*N*-(6-chloro-5-(3-methoxyphenoxy)-4-pyrimidinyl)-benzenesulfonamide[8] (**9**) (150 mg, 0.325 mmol) was added, and the mixture was stirred at 100 °C for 40 min, diluted with 10% aqueous HCl, and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane:EtOAc, 4:1, v/v), and recrystallized from EtOAc−hexane to afford **5a** as colorless needles (149 mg, 81%): mp 129−130 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32 (1H, s), 8.04 (2H, d, J = 8.7 Hz), 7.68 (1H, br s), 7.52 (2H, d, J = 8.8 Hz), 7.19−7.27 (2H, m), 7.07 (1H, t, J = 8.3 Hz), 6.90−6.97 (1H, m), 6.71−6.78 (2H, m), 6.58 (1H, ddd, J = 0.8, 2.3, 8.1 Hz), 6.41 (1H, t, J = 2.4 Hz), 6.33 (1H, ddd, J = 0.8, 2.3, 8.1 Hz), 4.64 (2H, t, J = 4.9 Hz), 4.08 (2H, t, J = 4.9 Hz), 1.35 (9H, s); IR (Nujol) cm^{-1} 3230, 1610, 1590, 1580, 1495; EI-MS *m*/*z* 549 (M$^+$), 485; Anal. ($C_{29}H_{31}N_3O_6S$) C, H, N.

4-*tert*-Butyl-*N*-(5-(3-methoxyphenoxy)-6-(2-((2-pyridazinyl)-oxy)ethoxy)-4-pyrimidinyl)benzenesulfonamide (5g). A mixture of 4-*tert*-butyl-*N*-(5-(3-methoxyphenoxy)-6-(2-((6-chloro-3-pyridazinyl)oxy)ethoxy)-4-pyrimidinyl)benzenesulfonamide (150 mg, 0.256 mmol), prepared by the same procedure as for **5m**, 10% palladium on activated carbon (50% water wet) (30 mg), and triethylamine (52 mg, 0.514 mmol) in MeOH (8 mL)−THF (6 mL) was stirred at room temperature under H_2 atmosphere for 5 h. The catalyst was filtered off and washed with MeOH, and the combined filtrate and washings were concentrated in vacuo. The residue was dissolved in $CHCl_3$, washed with 10% aqueous citric acid, H_2O, and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The obtained amorphous was crystallized from EtOAc−*i*-Pr_2O to afford **5g** as slight yellow prisms (111 mg, 79%): mp 169.5−170 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.80 (1H, dd, J = 1.5, 4.5 Hz), 8.29 (1H, s), 8.01−8.05 (2H, m), 7.60 (1H, s), 7.49−7.54 (2H, m), 7.32 (1H, dd, J = 4.5, 5.0 Hz), 7.16 (1H, t, J = 8.0 Hz), 6.78 (1H, dd, J = 2.5, 8.0 Hz), 6.52−6.58 (1H, m), 6.37 (1H, t, J = 2.5 Hz), 6.29−6.34 (1H, m), 4.68−4.71 (2H, m), 4.62−4.65 (2H, m), 3.70 (3H, s), 1.34 (9H, s); IR (Nujol) cm^{-1} 1610, 1600; FAB-MS *m*/*z* 552 (M+H$^+$), 456, 123; Anal. ($C_{27}H_{29}N_5O_6S$) C, H, N.

4-*tert*-Butyl-*N*-(5-(3-methoxyphenoxy)-6-(2-((4-pyrimidinyl)-oxy)ethoxy)-4-pyrimidinyl)benzenesulfonamide (5h). A mixture of 4-*tert*-butyl-*N*-(5-(3-methoxyphenoxy)-6-(2-((2-methylthio-4-pyrimidinyl)oxy)ethoxy)-4-pyrimidinyl)benzenesulfonamide (150 mg, 0.256 mmol), prepared by the same procedure as for **5m**, and activated Raney-Ni (W-2) in EtOH dispersion (2 mL) was stirred at 50 °C for 4 h, then refluxed for 4 h. The catalyst was removed by filtration and washed with EtOH then AcOH. The filtrate and washings were concentrated in vacuo, and the residual oil was dissolved in EtOAc−H_2O. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 100:1, v/v), and recrystallized from EtOAc−hexane to afford **5h** as colorless needles (96 mg, 33%): mp 149−150.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.68 (1H, s), 8.38 (1H, d, J = 5.8 Hz), 8.29 (1H, s), 8.03 (2H, d, J = 8.7 Hz), 7.6−7.8 (1H, br), 7.51 (2H, d, J = 8.8 Hz), 7.06 (1H, t, J = 8.2 Hz), 6.53−6.59 (1H, br), 6.54 (1H, dd, J = 1.2, 5.8 Hz), 6.35 (1H, t, J = 2.4 Hz), 6.30 (1H, ddd, J = 0.8, 2.3, 8.2 Hz), 4.61−4.66 (2H, m), 4.47−4.58 (2H, m), 3.72 (3H, s), 1.34 (9H, s); IR (Nujol) cm^{-1} 3200−2400, 1615, 1590, 1580, 1565, 1495; EI-MS *m*/*z* 552 (M$^+$), 456, 123; Anal. ($C_{27}H_{29}N_5O_6S$) C, H, N.

4-*tert*-Butyl-*N*-(5-(3-methoxyphenoxy)-6-(2-(2-pyrimidinyl)-aminoethoxy)-4-pyrimidinyl)benzenesulfonamide (6a). (1) A mixture of **9**[8] (6.08 g, 13.5 mmol), 2-hydroxyethylamine (25 mL), and 60% NaH in mineral oil dispersion (2.60 g, 67.5 mmol) was stirred at 80 °C for 30 min, cooled to room temperature, and neutralized with 10% aqueous HCl and saturated aqueous NH_4Cl. The resulting precipitate was collected, washed with H_2O, and air-dried. The obtained powder was dissolved in 14% HCl−EtOH, concentrated in vacuo, and recrystallized from EtOH to afford *N*-(6-(2-aminoethoxy)-5-(3-methoxyphenoxy)-4-pyrimidinyl)-4-*tert*-butylbenzenesulfonamide hydrochloride as colorless crystals (5.94 g, 86%): mp 201.5−202 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.50 (1H, br), 8.32 (1H, s), 8.10−8.26 (2H, br), 7.91 (2H, d, J = 7.7 Hz), 7.61 (2H, d, J = 8.3 Hz), 7.20 (1H, t, J = 8.2 Hz), 6.67 (1H, dd, J = 2.2, 8.1 Hz), 6.46 (1H, t, J = 2.4 Hz), 6.37 (1H, dd, J = 2.2, 8.1 Hz), 4.69 (2H, t, J = 5.6 Hz), 3.74 (3H, s), 2.98−3.06 (2H, br), 1.30 (9H, s); IR (Nujol) cm^{-1} 3380, 3110, 3060, 1630, 1595, 1560, 1485, 1460; FAB-MS *m*/*z* 473 (M+H$^+$), 430, 309, 233, 154, 137, 119.

(2) A mixture of the obtained aminoethoxy derivative (150 mg, 0.295 mmol), 2-chloropyrimidine (61 mg, 0.533 mmol), and K_2CO_3 (122 mg, 0.885 mmol) in DMAc (1.5 mL) was stirred at 70−100 °C for 3 days, diluted with saturated aqueous NH_4Cl, and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 100:1, v/v), and recrystallized from EtOAc−hexane to afford **6a** as colorless prisms (135 mg, 81%): dec 101−102 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.28 (1H, s), 8.11 (2H, s), 8.22 (2H, d, J = 4.8 Hz), 8.03 (2H, d, J = 8.9 Hz), 7.51 (2H, d, J = 8.9 Hz), 7.17 (1H, t, J = 8.2 Hz), 6.64 (1H, ddd, J = 0.8, 2.4, 8.2 Hz), 6.54 (1H, t, J = 4.9 Hz), 6.41 (1H, t, J = 2.4 Hz), 6.34 (1H, ddd, J = 0.8, 2.4, 8.2 Hz), 5.5−5.6 (1H, br), 4.45 (2H, t, J = 5.2 Hz), 3.78 (3H, s), 3.62 (2H, q, J = 5.5 Hz), 1.34 (9H, s); IR (Nujol) cm^{-1} 3150, 1600, 1580, 1550, 1495; EI-MS *m*/*z* 550 (M$^+$), 429, 365, 350; Anal. ($C_{27}H_{30}N_6O_5S\cdot H_2O\cdot 0.2EtOAc$) C, H, N.

3-(2-Pyrimidinyl)propanol.[25] (1) To a stirred solution of 2-(2-propynyloxy)tetrahydropyran (3.10 g, 22.1 mmol) in THF (30 mL) was added 1.6 M *n*-BuLi in hexane (12.5 mL, 20.0 mmol) dropwise at 0 °C. After 30 min, the whole was cooled to −78 °C, and 4,6-dichloro-5-(3-methoxy)phenoxypyrimidine (5.00 g, 18.4 mmol), prepared by the reported method,[8] in THF (20 mL) was added dropwise. The mixture was stirred at the same temperature for 1 h, then at 0 °C for 2 h, diluted with H_2O, and extracted with EtOAc. The extract was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane:EtOAc, 10:1, v/v) to afford 4,6-dichloro-2-(3-(tetrahydropyran-2-yloxy)-1-propynyl)pyrimidine as brown oil (5.09 g, 96%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (1H, s), 4.86−4.90 (1H, m), 4.51 (2H, s), 3.80−3.90 (1H, m), 3.52−3.61 (1H, m), 1.49−1.91 (6H, m); IR (Neat) cm^{-1} 3100, 2240, 1520; FAB-MS *m*/*z* 287 (M+H$^+$), 203, 185, 85.

(2) A mixture of the obtained oil (2.50 g, 8.71 mmol), 10% palladium on activated carbon (50% water wet) (0.50 g), and triethylamine (1.94 g, 19.2 mmol) in EtOH (25 mL) was stirred at room temperature under H_2 atmosphere for 7 h. The catalyst was filtered off and washed with EtOH, and the combined filtrate and washings were concentrated in vacuo. The residue was dissolved in EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford 2-(3-(tetrahydropyran-2-yloxy)propyl)pyrimidine as brown oil (1.28 g, 66%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.67 (2H, d, J = 4.9 Hz), 7.12 (1H, t, J = 4.9 Hz), 4.59−4.63 (1H, m), 3.79−3.90 (2H, m), 3.44−3.54 (2H, m), 3.04−3.11 (2H, m),

2.10−2.21 (2H, m), 1.44−1.90 (6H, m); IR (Neat) cm^{-1} 3040, 1575, 1560, 1425; FAB-MS *m/z* 223 ($M+H^+$), 139, 121, 85.

(3) A mixture of the obtained oil (1.24 g, 5.58 mmol) and *p*-toluenesulfonic acid hydrate (1.11 g, 5.84 mmol) in MeOH (20 mL) was stirred at room temperature for 13 h and concentrated in vacuo. The residue was diluted with $CHCl_3$ and saturated aqueous $NaHCO_3$, and the separated aqueous layer was extracted three times with $CHCl_3$. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 10:1, v/v) to afford 3-(2-pyrimidinyl)propanol as slight brown oil (0.71 g, 93%): ^1H NMR ($CDCl_3$, 300 MHz) δ 8.67 (2H, d, J = 4.9 Hz), 7.16 (1H, t, J = 4.9 Hz), 3.71−3.78 (2H, m), 3.32 (1H, t, J = 5.7 Hz), 3.15 (2H, t, J = 6.9 Hz), 2.05−2.14 (2H, m); IR (Neat) cm^{-1} 3360, 1575, 1560, 1425, 1060; FAB-MS *m/z* 137 ($M-H^+$), 119, 107, 94.

4-*tert*-Butyl-*N*-(5-(3-methoxyphenoxy)-6-(3-(2-pyrimidinyl)-propyloxy)-4-pyrimidinyl)benzenesulfonamide(6b). To a stirred solution of **9**[8] (150 mg, 0.335 mmol) and 3-(2-pyrimidinyl)propanol[25] (379 mg, 2.74 mmol) in dry DMSO (5 mL) was added 60% NaH in mineral oil dispersion (120 mg, 3.00 mmol), and the mixture was stirred at 100 °C for 4 h, diluted with saturated aqueous NH_4Cl, and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was separated by preparative TLC ($CHCl_3$:MeOH, 30:1, v/v), and recrystallized from EtOAc−*i*-Pr_2O to afford **6b** as slightly brown crystalline powder (38 mg, 21%): mp 148−149.5 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.60 (2H, d, J = 4.9 Hz), 8.28 (1H, s), 8.03 (2H, d, J = 8.3 Hz), 7.61 (1H, br s), 7.51 (2H, d, J = 8.3 Hz), 7.06−7.20 (2H, m), 6.60 (1H, dd, J = 2.3, 8.4 Hz), 6.41 (1H, t, J = 2.4 Hz), 6.34 (1H, dd, J = 2.3, 8.4 Hz), 4.38 (2H, t, J = 6.6 Hz), 3.75 (3H, s), 2.81 (2H, t, J = 7.5 Hz), 2.02−2.20 (2H, m), 1.34 (9H, s); IR (Nujol) cm^{-1} 1610, 1580, 1565, 1490; FAB-MS *m/z* 550 ($M+H^+$), 121; Anal. ($C_{28}H_{31}N_5O_5S\cdot0.5H_2O$) C, H, N.

4-*tert*-Butyl-*N*-(5-(3-methoxyphenoxy)-6-(2-(2-pyrimidinyl)-ethylthio)-4-pyrimidinyl)benzenesulfonamide(6c). (1) To a solution of 2-mercaptoethanol (1.31 g, 16.7 mmol) in dry DMAc (15 mL) was added 60% NaH in mineral oil dispersion (0.52 g, 13.4 mmol) on an ice bath. After 5 min, **9**[8] (1.50 g, 3.35 mmol) was added, and the mixture was stirred at 130 °C for 2 h, diluted with 10% aqueous HCl, and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:MeOH, 70:1, v/v), and recrystallized from EtOAc−hexane to afford 4-*tert*-butyl-*N*-(6-(2-hydroxyethylthio)-5-(3-methoxyphenoxy)-4-pyrimidinyl)benzenesulfonamide as colorless fine needles (1.14 g, 70%): mp 149.5−150.5 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.45 (1H, s), 8.00 (2H, d, J = 8.7 Hz), 7.57 (1H, s), 7.52 (2H, d, J = 8.8 Hz), 7.19 (1H, t, J = 8.2 Hz), 6.68 (1H, ddd, J = 0.8, 2.3, 8.3 Hz), 6.41 (1H, t, J = 2.4 Hz), 6.32 (1H, ddd, J = 0.8, 2.4, 8.2 Hz), 3.82 (2H, q, J = 5.6 Hz), 3.79 (3H, s), 3.28 (1H, t, J = 5.6 Hz), 3.09 (1H, t, J = 5.6 Hz), 1.34 (9H, s); IR (Nujol) cm^{-1} 3450, 3370, 3250, 1610, 1570, 1490; EI-MS *m/z* 489 (M^+), 471, 425.

(2) The same procedure as for **5m** started from the obtained alcohol (200 mg, 0.408 mmol), 2-chloropyrimidine (61 mg, 0.531 mmol), and 60% NaH in mineral oil dispersion (47 mg, 1.23 mmol) afforded **6c** as colorless fine needles (191 mg, 83%): mp 167.5−168.0 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.46 (1H, s), 8.46 (2H, d, J = 4.9 Hz), 8.00 (2H, d, J = 8.7 Hz), 7.51−7.53 (1H, br), 7.51 (2H, d, J = 8.7 Hz), 7.17 (1H, t, J = 8.2 Hz), 6.92 (1H, t, J = 4.9 Hz), 6.65 (1H, dd, J = 2.4, 8.2 Hz), 6.40 (1H, t, J = 2.4 Hz), 6.31 (1H, ddd, J = 0.8, 2.4, 8.2 Hz), 4.51 (2H, t, J = 6.7 Hz), 3.78 (3H, s), 3.55 (2H, t, J = 6.7 Hz), 1.34 (9H, s); IR (Nujol) cm^{-1} 3230, 1615, 1590, 1570, 1535, 1490; EI-MS *m/z* 567 (M^+), 503, 471, 407, 274; Anal. ($C_{27}H_{29}N_5O_5S_2$) C, H, N.

Representative Procedure for Compounds 7. *N*-(6-(2-((5-Bromo-2-pyrimidinyl)oxy)ethoxy)-5-(4-methylphenyl)-4-pyrimidinyl)-4-*tert*-butylbenzenesulfonamide (7k). To a stirred solution of 4-*tert*-butyl-*N*-(6-(2-hydroxyethoxy)-5-(4-methylphenyl)-4-pyrimidinyl)benzenesulfonamide[8] (3.00 g, 6.79 mmol) in dry DMAc (30 mL) was added 60% NaH in mineral oil dispersion (815 mg, 20.4 mmol) on an ice bath. After 20 min, 5-bromo-2-chloropyrimidine[18,19] (1.84 g, 9.51 mmol) was added, and the mixture was stirred at room temperature for 7 h, poured into ice-cooled saturated aqueous NH_4Cl, and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:EtOAc, 10:1, v/v), and recrystallized from EtOAc−*i*-Pr_2O to afford **7k** as colorless prisms (3.57 g, 88%): mp 167−168 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.44 (2H, s), 8.38 (1H, s), 8.01 (2H, d, J = 8.8 Hz), 7.51 (2H, d, J = 8.8 Hz), 7.23 (2H, d, J = 7.8 Hz), 7.15 (1H, br s), 7.10 (2H, d, J = 8.2 Hz), 4.62−4.68 (2H, m), 4.56−4.61 (2H, m), 2.41 (3H, s), 1.34 (9H, s); IR (Nujol) cm^{-1} 3250, 1575, 1545; FAB-MS *m/z* 598 ($M+H^+$), 424, 203, 201; Anal. ($C_{27}H_{28}BrN_5O_4S$) C, H, N.

***N*-(6-(2-((5-Bromo-2-pyrimidinyl)oxy)ethoxy)-5-(4-methylphenyl)-4-pyrimidinyl)-4-*tert*-butylbenzenesulfonamide Sodium Salt (Na Salt of 7k).** To a solution of **7k** (4.50 g, 7.52 mmol) in $CHCl_3$ (25 mL)−EtOH (25 mL) was added 28% NaOMe in MeOH (1.44 g, 7.46 mmol) dropwise over 10 min at 0 °C. The mixture was concentrated in vacuo and chased twice with EtOH. The residual powder was triturated with Et_2O, collected, and washed with Et_2O to afford Na salt of **7k** as colorless crystalline powder (4.62 g, 99%): mp 238−242 (dec); Anal. ($C_{27}H_{27}BrN_5NaO_4S$) C, H, N, Na.

Representative Procedure for Compounds 7t−w from 7k. 4-*tert*-Butyl-*N*-(5-(4-methylphenyl)-6-(2-((5-(2-thienyl)-2-pyrimidinyl)oxy)ethoxy)-4-pyrimidinyl)-benzenesulfonamide (7v). Under Ar atmosphere, to a stirred solution of **7k** (201 mg, 0.336 mmol) in dry 1,4-dioxane (5 mL) were added tributyl-2-thienyltin (185 mg, 0.496 mmol) and $PdCl_2(PPh_3)_2$ (12 mg, 0.0171 mmol), and the mixture was refluxed for 18 h. After cooling, the reaction mixture was diluted with EtOAc and 10% aqueous KF, and the mixture was stirred at room temperature for 1 h. Insoluble materials were removed by filtration, and the filtrate was extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was separated by preparative TLC ($CHCl_3$:EtOAc, 30:1, v/v), and recrystallized from EtOAc−*i*-Pr_2O to afford **7v** as colorless crystalline powder (137 mg, 68%): mp 180.5−182 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.64 (2H, s), 8.39 (1H, s), 8.01 (2H, d, J = 8.8 Hz), 7.51 (2H, d, J = 8.8 Hz), 7.37 (1H, dd, J = 1.3, 5.2 Hz), 7.08−7.30 (7H, m), 4.52−4.76 (4H, m), 2.35 (3H, s), 1.34 (9H, s); IR (Nujol) cm^{-1} 3230, 1735, 1600, 1570, 1560, 1545; FAB-MS *m/z* 602 ($M+H^+$), 424, 226, 205; Anal. ($C_{31}H_{31}N_5O_4S_2\cdot0.5H_2O$) C, H, N.

4-Chloro-6-(2-hydroxyethoxy)-5-(4-methylphenyl)pyrimidine (12). NaH (60%) in mineral oil dispersion (0.53 g, 13.2 mmol) was added to ethylene glycol (50 mL) on an ice bath. After 5 min, 2,6-dichloro-5-(4-methylphenyl)pyrimidine[8] (3.00 g, 12.5 mmol) was added, and the mixture was allowed to stir at room temperature for 2.5 h, acidified with 10% aqueous HCl, diluted with H_2O, and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane:EtOAc, 2:1, v/v), and triturated with *i*-Pr_2O−hexane to afford **12** as colorless crystalline powder (3.01 g, 91%): mp 62−64 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.53 (1H, s), 7.21−7.30 (4H, m), 4.48−4.53 (2H, m), 3.83−3.89 (2H, m), 2.42 (3H, s), 2.19 (1H, t, J = 6.2 Hz); IR (Nujol) cm^{-1} 3340, 3180, 1560, 1545; EI-MS *m/z* 264 (M^+), 220, 193, 158.

4-Azido-6-(2-hydroxyethoxy)-5-(4-methylphenyl)pyrimidine (13). A mixture of **12** (2.52 g, 9.52 mmol) and NaN_3 (1.23 g, 18.9 mmol) in DMF (30 mL) was stirred at 80 °C for 19 h, diluted with H_2O, and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography

(hexane:EtOAc, 5:1−2:1, v/v), and triturated with hexane to afford **13** as colorless crystalline powder (2.17 g, 84%): mp 83.5−85 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.49 (1H, s), 7.25 (4H, s), 4.49−4.53 (2H, m), 3.84−3.90 (2H, m), 2.66 (1H, t, J = 6.0 Hz), 2.40 (3H, s); IR (Nujol) cm^{-1} 3360, 3080, 2130, 1610, 1540, 1510, 1460; EI-MS m/z 271 (M^+), 243, 199.

4-Amino-6-(2-hydroxyethoxy)-5-(4-methylphenyl)pyrimidine (14). A mixture of **13** (2.17 g, 8.01 mmol) and 10% palladium on activated carbon (50% water wet) (0.78 g) in EtOH (40 mL) was stirred at room temperature under H_2 atmosphere for 2 h. The catalyst was filtered off and washed with EtOH, and the combined filtrate was concentrated in vacuo. The residue was dissolved in EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residual powder was recrystallized from EtOAc−hexane to afford **14** as pale yellow needles (1.87 g, 95%): mp 95−96 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.21 (1H, s), 7.22−7.29 (4H, m), 4.84 (2H, br s), 4.41−4.45 (2H, m), 3.75−3.85 (3H, m), 2.40 (3H, s); IR (Nujol) cm^{-1} 3390, 3310, 3160, 1645, 1585, 1560; EI-MS m/z 245 (M^+), 214, 201.

4-Amino-6-(2-((5-bromo-2-pyrimidinyl)oxy)ethoxy)-5-(4-methylphenyl)pyrimidine (15). To a solution of **14** (7.54 g, 30.7 mmol) in dry THF (150 mL) was added 60% NaH in mineral oil dispersion (1.47 g, 36.8 mmol) at room temperature. After 5 min, 5-bromo-2-chloropyrimidine[18,19] (7.73 g, 39.9 mmol) was added, and the mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with aqueous NH_4Cl, and the volatile was removed in vacuo. The resulting precipitate was collected, washed with H_2O, air-dried, and purified by silica gel column chromatography ($CHCl_3$:MeOH, 100:1−80:1, v/v) to afford **15** as faintly yellow crystalline powder (11.27 g, 91%): mp 178.5−179.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.46 (2H, s), 8.21 (1H, s), 7.19 (4H, s), 4.70−4.78 (2H, br), 4.60−4.70 (4H, m), 2.38 (3H, s); IR (Nujol) cm^{-1} 3400, 3300, 3130, 1640, 1580, 1570, 1550; EI-MS m/z 401 (M^+), 322, 201.

Representative Procedure for Compounds 16 (Method C). 4-Bromo-*N*-(6-(2-((5-bromo-2-pyrimidinyl)-oxy)ethoxy)-5-(4-methylphenyl)-4-pyrimidinyl)benzenesulfonamide (16d). A mixture of **15** (150 mg, 0.373 mmol), 4-bromobenzenesulfonyl chloride (382 mg, 1.49 mmol), NaI (112 mg, 0.747 mmol), and 60% NaH in mineral oil dispersion (90 mg, 2.24 mmol) in dry THF (5 mL) was refluxed for 16 h. After cooling, the reaction mixture was diluted with aqueous NH_4Cl, and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative TLC ($CHCl_3$:EtOAc, 10:1, v/v), and crystallized from THF-*i*-Pr_2O to afford **16d** as pale yellow crystalline powder (85 mg, 37%): mp 217−218 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (2H, s), 8.36 (1H, s), 7.97 (2H, d, J = 8.6 Hz), 7.65 (2H, d, J = 8.7 Hz), 7.24 (2H, d, J = 7.8 Hz), 7.16 (1H, br s), 7.10 (2H, d, J = 8.1 Hz), 4.55−4.70 (4H, m), 2.41 (3H, s); IR (Nujol) cm^{-1} 1575, 1560; FAB-MS m/z 620 ($M+H^+$); Anal. ($C_{23}H_{19}Br_2N_5O_4S$) C, H, N.

Representative Procedure for Compounds 16 (Method D). *N*-(6-(2-((5-Bromo-2-pyrimidinyl)oxy)-ethoxy)-5-(4-methylphenyl)-4-pyrimidinyl)-4-*tert*-pentylbenzenesulfonamide (16a). A mixture of **15** (150 mg, 0.373 mmol), 4-*tert*-pentylbenzenesulfonyl chloride (184 mg, 0.476 mmol), 96% KOH powder (300 mg, 5.14 mmol), and tetrabutylammonium hydrogen sulfate (34 mg, 0.10 mmol) in dry THF (10 mL) was stirred at room temperature for 16 h, diluted with aqueous NH_4Cl, and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:EtOAc, 5:1, v/v), and recrystallized from EtOAc−hexane to afford **16a** as colorless needles (188 mg, 82%): mp 153.5−154.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (2H, s), 8.37 (1H, s), 8.00 (2H, d, J = 8.7 Hz), 7.45 (2H, d, J = 8.8 Hz), 7.23 (2H, d, J = 7.8 Hz), 7.15 (1H, br s), 7.10 (2H, d, J = 8.1 Hz), 4.61−4.68 (2H, m), 4.56−4.61 (2H, m), 2.41 (3H, s), 2.41 (6H, s), 1.67 (2H, q, J = 7.4 Hz), 0.67 (3H, t, J = 7.5 Hz); IR (Nujol) cm^{-1} 3270, 1570, 1550; FAB-MS m/z 612 ($M+H^+$), 438, 412; Anal. ($C_{28}H_{30}BrN_5O_4S$) C, H, N.

4-*tert*-Butyl-*N*-(6-(2-hydroxyethoxy)-4-pyrimidinyl)-benzenesulfonamide (18). (1) To a stirred solution of 2,4-dichloropyrimidine (13.30 g, 89.2 mmol) and 4-*tert*-butylbenzenesulfonamide (19.60 g, 91.9 mmol) in dry DMSO (200 mL) was added 60% NaH in mineral oil dispersion (7.14 g, 179 mmol) in some portions, and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with 10% aqueous HCl and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residual powder was recrystallized from EtOAc to afford 4-*tert*-butyl-*N*-(6-chloro-4-pyrimidinyl)benzenesulfonamide as slightly brown prisms (17.80 g, 61%): mp 225−226.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.54 (1H, br s), 8.78 (1H, d, J = 0.7 Hz), 7.85 (2H, d, J = 8.8 Hz), 7.56 (2H, d, J = 8.8 Hz), 7.39 (1H, d, J = 0.7 Hz), 1.34 (9H, s); IR (Nujol) cm^{-1} 3035, 3200, 1630, 1595, 1575; EI-MS m/z 325 (M^+), 310, 260.

(2) 60% NaH in mineral oil dispersion (10.18 g, 255 mmol) was added to stirred ethylene glycol (200 mL) in some portions at room temperature. After 30 min, the obtained sulfonamide (16.61 g, 50.9 mmol) was added, and the mixture was stirred at 60 °C for 20 h. After cooling, the reaction mixture was acidified with 10% aqueous HCl, diluted with H_2O, and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residual powder was triturated with EtOAc to afford **18** as colorless needles (15.79 g, 88%): mp 169−170.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.68 (1H, d, J = 0.9 Hz), 7.81−7.86 (2H, m), 7.49−7.55 (2H, m), 6.72, (1H, s), 4.47−4.52 (2H, m), 3.92−3.98 (2H, m), 2.53 (1H, br s), 1.33 (9H, s); IR (Nujol) cm^{-1} 3440, 1600, 1570; FAB-MS m/z 352 ($M+H^+$), 308, 154, 137, 119.

***N*-(5-Bromo-6-(2-hydroxyethoxy)-4-pyrimidinyl)-4-*tert*-butylbenzenesulfonamide (19).** To a stirred solution of **18** (5.00 g, 14.2 mmol) in dry DMF (50 mL) was added *N*-bromosuccinimide (2.66 g, 14.9 mmol), and the mixture was stirred at room temperature for 1 h. 10% aqueous $Na_2S_2O_3$ and 10% aqueous HCl were added to the mixture, and the product was extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was crystallized from EtOAc−hexane and recrystallized from EtOAc to afford **19** as colorless crystalline powder (5.46 g, 89%): mp 146−148 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.30 (1H, s), 8.05−8.10 (2H, m), 7.83 (1H, br s), 7.50−7.56 (2H, m), 4.51−4.55 (2H, m), 3.91−3.97 (2H, m), 2.40 (1H, t, J = 6.0 Hz), 1.34 (9H, s); IR (Nujol) cm^{-1} 3360, 3200, 1620, 1575; FAB-MS m/z 430 ($M+H^+$), 388, 386.

***N*-(5-Bromo-6-(2-((5-methylthio-2-pyrimidinyl)oxy)-ethoxy)-4-pyrimidinyl)-4-*tert*-butylbenzenesulfonamide (20).** To a stirred solution of **19** (3.10 g, 7.20 mmol) in dry DMAc (30 mL) was added 60% NaH in mineral oil dispersion (720 mg, 18.0 mmol). After stirring at room temperature for 30 min, 2-chloro-5-methylthiopyrimidine[23,24] (1.51 g, 9.40 mmol) was added, and the mixture was stirred at room temperature for 12 h, diluted with 10% aqueous NH_4Cl and 10% aqueous HCl, and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:EtOAc, 10:1, v/v), and crystallized from EtOAc−hexane to afford **20** as colorless crystalline powder (3.34 g, 84%): mp 87 °C-; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.47 (2H, s), 8.28 (1H, s), 8.04−8.10 (2H, m), 7.78 (1H, br s), 7.50−7.55 (2H, m), 4.67−4.78 (4H, m), 2.45 (3H, s), 1.33 (9H, s); IR (Nujol) cm^{-1} 1620, 1570, 1540; FAB-MS m/z 554 ($M+H^+$), 412, 307, 169.

Representative Procedure for Compounds 21 (Method E). 4-*tert*-Butyl-*N*-(5-(4-chlorophenyl)-6-(2-((5-methylthio-2-pyrimidinyl)oxy)ethoxy)-4-pyrimidinyl)-benzenesulfonamide (21c). Under Ar atmosphere, a mixture of **20** (300 mg, 0.541 mmol), tributyl-(4-chlorophenyl)-tin (650 mg, 1.62 mmol), $PdCl_2(PPh_3)_2$ (76 mg, 0.108 mmol),

CuBr (31 mg, 0.216 mmol), PPh_3 (57 mg, 0.217 mmol), and 2,6-di-*tert*-butylcresol (a few crystals) in dry dioxane (10 mL) was stirred at reflux for 4 h, cooled to room temperature, diluted with EtOAc and 10% aqueous KF, and stirred at room temperature for 30 min. Insoluble material was removed by filtration, and the separated organic layer of the filtrate was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane:EtOAc, 1:1, v/v), and recrystallized from EtOAc−hexane to afford **21c** as colorless crystalline powder (138 mg, 44%): mp 180.5−181.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (2H, s), 8.41 (1H, s), 7.99−8.05 (2H, m), 7.49−7.55 (2H, m), 7.38−7.43 (2H, m), 7.17−7.22 (2H, m), 7.07 (1H, br s), 4.61−4.68 (2H, m), 4.55−4.69 (4H, m), 2.45 (3H, s), 1.34 (9H, s); IR (Nujol) cm^{-1} 3230, 1590, 1565, 1535, 1460, 1435, 1425; FAB-MS *m*/*z* 586 ($M+H^+$), 444, 308, 169; Anal. ($C_{27}H_{28}ClN_5O_4S_2$) C, H, N.

5-(2-Methoxyphenyl)thiopyrimidine-4,6-diol (24).[11] To a stirred suspension of bis(*o*-methoxyphenyl) disulfide[10] (**22**) (800 mg, 2.87 mmol) and one drop of triethylamine in dry CCl_4 (4 mL) was added SO_2Cl_2 (0.23 mL, 2.87 mmol), and the mixture was stirred at room temperature for 30 min. The resulting solution was added to a suspension of pyrimidine-4,6-diol (584 mg, 5.21 mmol) in dry DMF (8 mL) dropwise over 5 min at room temperature, and the whole was stirred at the same temperature for 3 h. The reaction mixture was diluted with H_2O, and the resulting precipitate was collected and washed with H_2O and Et_2O, then air-dried to afford **24** as colorless powder (1.26 g, 97%): mp >300 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12−13 (2H, br), 8.45 (1H, s), 6.99−7.06 (1H, m), 6.92 (1H, dd, J = 1.2, 8.1 Hz), 6.75−6.82 (1H, m), 6.63 (1H, dd, J = 1.6, 7.7 Hz), 3.82 (3H, s); IR (Nujol) cm^{-1} 3080, 1675, 1640, 1595, 1575, 1535, 1460; EI-MS *m*/*z* 250 (M^+), 137, 125, 108.

4,6-Dichloro-5-(2-methoxyphenyl)thiopyrimidine (25). A mixture of **24** (1.23 g, 4.91 mmol) in $POCl_3$ (5 mL) was refluxed for 1 h, cooled to room temperature, poured into H_2O, and extracted with EtOAc. The extract was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was separated by silica gel column chromatography (hexane:$CHCl_3$, 1:2, v/v) to afford **25** as colorless crystalline powder (10.2 g, 72%): mp 105−110 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.69 (1H, s), 7.25−7.31 (1H, m), 7.13 (1H, dd, J = 1.6, 7.7 Hz), 6.85−6.94 (2H, m), 3.80 (3H, s); IR (Nujol) cm^{-1} 1580, 1500, 1460, 1395, 1375; EI-MS *m*/*z* 286 (M^+), 237, 235.

4-*tert*-Butyl-*N*-(6-(2-hydroxyethoxy)-5-(2-methoxyphenyl)thio-4-pyrimidinyl)benzenesulfonamide (26). (1) A mixture of **25** (951 mg, 3.31 mmol), 4-*tert*-butylbenzenesulfonamide (776 mg, 3.64 mmol), and K_2CO_3 (1.37 g, 9.91 mmol) in dry DMSO (10 mL) was stirred at 80 °C for 1 h, cooled to room temperature, diluted with H_2O, acidified with 10% aqueous HCl, and extracted with EtOAc. The organic extract was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was recrystallized from EtOAc−hexane to afford 4-*tert*-butyl-*N*-(6-chloro-5-(2-methoxyphenyl)thio-4-pyrimidinyl)benzenesulfonamide as colorless crystalline powder (1.30 g, 85%): mp 186−190 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.53 (1H, br s), 8.46 (1H, s), 7.95−8.00 (2H, m), 7.46−7.54 (3H, m), 7.34−7.41 (1H, m), 6.95−7.00 (1H, m), 6.92 (1H, dd, J = 1.2, 7.5 Hz), 4.00 (3H, s), 1.32 (9H, s); IR (Nujol) cm^{-1} 3170, 1590, 1580, 1535, 1475, 1460; FAB-MS *m*/*z* 464 ($M+H^+$), 291, 235, 177, 154.

(2) NaH (60%) in mineral oil dispersion (538 mg, 13.45 mmol) was added to stirred ethylene glycol (13 mL) in some portions at room temperature. After 30 min, the obtained sulfonamide (1.25 g, 2.69 mmol) was added, and the mixture was stirred at 100 °C for 4 h. After cooling, the reaction mixture was acidified with 10% aqueous HCl, diluted with H_2O, and extracted with EtOAc. The organic extract was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was separated by silica gel column chromatography ($CHCl_3$:EtOAc, 5:1, v/v), and recrystallized from EtOAc−hexane to afford **26** as colorless plates (1.21 g, 92%): mp 165−166.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.20 (1H, s), 8.34, (1H, s), 7.99−8.05 (2H, m), 7.47−7.52 (2H, m), 7.27−7.35 (2H, m), 6.90−6.95 (1H, m), 6.87 (1H, dd, J = 1.2, 7.5 Hz), 4.44−4.49 (2H, m), 3.95 (3H, s), 3.82−3.88 (2H, m), 2.32 (1H, t, J = 6.2 Hz), 1.33 (9H, s); IR (Nujol) cm^{-1} 3200, 1560, 1460; FAB-MS *m*/*z* 490 ($M+H^+$), 394, 350, 293.

***N*-(6-(2-((5-Bromo-2-pyrimidinyl)oxy)ethoxy)-5-(2-methoxyphenyl)thio-4-pyrimidinyl)-4-*tert*-butylbenzenesulfonamide (27).** To a stirred solution of **26** (674 mg, 1.37 mmol) in dry THF (10 mL)−dry DMAc (1 mL) was added 60% NaH in mineral oil dispersion (165 mg, 4.13 mmol) at room temperature. After 5 min, 5-bromo-2-chloropyrimidine[18,19] (397 mg, 2.05 mmol) was added, and the mixture was stirred at room temperature for 1 h, diluted with 10% aqueous NH_4Cl, and extracted with EtOAc. The extract was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was separated by silica gel column chromatography (hexane:EtOAc, 1:1, v/v), and recrystallized from EtOAc−hexane to afford **27** as colorless crystalline powder (897 mg, 86%): mp 141−142 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.38 (1H, s), 8.50 (2H, s), 8.31 (1H, s), 7.96−8.01 (2H, m), 7.45−7.50 (2H, m), 7.43 (1H, dd, J = 1.7, 7.7 Hz), 7.23−7.30 (1H, m), 6.90 (1H, dd, J = 1.2, 8.4 Hz), 6.78−6.85 (1H, m), 4.65−4.75 (4H, m), 3.99 (3H, s), 1.32 (9H, s); IR (Nujol) cm^{-1} 1555, 1460, 1445, 1415, 1375; FAB-MS *m*/*z* 646 ($M+H^+$), 472, 446, 203, 201; Anal. ($C_{27}H_{28}BrN_5O_5S_2$) C, H, N.

1-(2-Benzyloxyethoxy)-2-chloro-3-nitrobenzene (29). To a solution of 2-chloro-3-nitrophenol[12] (**28**) (2.34 g, 13.5 mmol), 2-benzyloxyethanol (2.26 g, 14.9 mmol), and PPh_3 (5.30 g, 20.3 mmol) in dry THF (100 mL) was added diethyl azodicarboxylate (3.52 g, 20.3 mmol) at 0 °C, and the mixture was stirred at the same temperature for 2 h. After addition of H_2O (1 mL), the mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$, then hexane:EtOAc, 3:1−1:1, v/v) to afford **29** as yellow crystalline powder (3.54 g, 85%): mp 51−52 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26−7.40 (7H, m), 7.15 (1H, dd, J = 1.6, 8.1 Hz), 4.66 (2H, s), 4.25−4.30 (2H, m), 3.88−3.93 (2H, m); IR (Nujol) cm^{-1} 1595, 1535, 1500, 1470, 1450, 1360; EI-MS *m*/*z* 307 (M^+), 290, 272, 91.

2-(2-Benzyloxyethoxy)-4′-methyl-6-nitrobiphenyl (30). Under Ar atmosphere, a mixture of **29** (3.24 g, 10.5 mmol), tributyl-(4-methylphenyl)tin (8.03 g, 21.0 mmol), and $PdCl_2(PPh_3)_2$ (0.37 g, 0.525 mmol) in dry dioxane (100 mL) was refluxed for 16 h. After cooling, 10% aqueous KF (20 mL) was added, and the mixture was stirred at room temperature for 4 h, filtered through Celite, and the precipitate was washed with EtOAc. The separated organic layer of the filtrate and washings were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane:EtOAc, 5:1, v/v) to afford **30** as yellow oil (3.41 g, 89%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.14−7.40 (12H, m), 4.40 (2H, s), 4.11−4.15 (2H, m), 3.67−3.72 (2H, m), 2.37 (3H, s); IR (Nujol) cm^{-1} 1605, 1580, 1530, 1495, 1475, 1450; EI-MS *m*/*z* 363 (M^+), 346, 91.

4-*tert*-Butyl-*N*-(3-(2-hydroxyethoxy)-2-(4-methylphenyl)-phenyl)benzenesulfonamide (31). (1) A mixture of **30** (3.39 g, 9.33 mmol) and Fe powder (5.20 g, 93.3 mmol) in THF (60 mL), H_2O (30 mL), EtOH (90 mL), and 10% aqueous HCl (5 mL) was refluxed for 3.5 h. After cooling, the precipitate was filtered off and washed with EtOH. The combined filtrate and washings were concentrated in vacuo, basified with saturated aqueous $NaHCO_3$, and extracted twice with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting solid was recrystallized from EtOAc−hexane to afford 6-(2-benzyloxyethoxy)-4′-methylbiphenyl-2-amine as colorless needles (2.71 g, 87%): mp 88−89 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.15−7.32 (9H, m), 7.07 (1H, t, J = 8.1 Hz), 6.38−6.44 (2H, m), 4.38 (2H, s), 4.03−4.08 (2H, m), 3.62−3.68 (2H, m), 3.58 (2H, br s), 2.37 (3H, s); IR (Nujol) cm^{-1} 3450, 3370, 1620, 1600, 1585, 1495; EI-MS *m*/*z* 333 (M^+), 199, 91.

(2) A mixture of the obtained aniline derivative (1.84 g, 5.52 mmol) and 4-*tert*-butylbenzenesulfonyl chloride (1.61 g, 6.90 mmol) in pyridine (20 mL) was stirred at room temperature for 2 h, concentrated in vacuo, and dissolved in a mixture of 10% aqueous HCl and EtOAc. The separated aqueous layer was extracted with EtOAc. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane:EtOAc, 6:1, v/v) to afford *N*-((6-(2-benzyloxyethoxy)-4′-methylbiphenyl)-2-yl)-4-*tert*-butylbenzenesulfonamide as light yellow oil (2.94 g, 100%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.60−7.55 (16H, m), 6.33 (1H, s), 4.30 (2H, s), 3.97−4.03 (2H, m), 3.54−3.60 (2H, m), 2.37 (3H, s), 1.33 (9H, s); IR (Nujol) cm^{-1} 3340, 1595, 1590, 1495, 1465, 1455; FAB-MS *m*/*z* 530 (M+H$^+$), 333, 91.

(3) A mixture of the obtained sulfonamide derivative (2.92 g, 5.51 mmol), 10% aqueous HCl (5 mL) and 10% palladium on activated carbon (50% water wet) (400 mg) in EtOH (50 mL) was stirred at room temperature under H_2 atmosphere for 3 h. The catalyst was filtered off and washed with EtOH, and the combined filtrate and washings were concentrated in vacuo. The residue was dissolved in EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residual powder was recrystallized from EtOAc−hexane to afford **31** as colorless fine needles (2.26 g, 93%): mp 114−115.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.53 (2H, d, J = 8.8 Hz), 7.40−7.46 (3H, m), 7.27 (1H, t, J = 8.2 Hz), 7.13 (2H, d, J = 8.4 Hz), 6.77 (1H, dd, J = 1.1, 8.3 Hz), 6.32 (1H, br s), 3.92 (2H, t, J = 4.6 Hz), 3.60−3.67 (2H, m), 2.39 (3H, s), 1.45 (1H, t, J = 6.6 Hz), 1.34 (9H, s); IR (Nujol) cm^{-1} 3590, 3540, 3320, 3220, 1595, 1585, 1470, 1460; EI-MS *m*/*z* 439 (M$^+$), 242, 198.

***N*-(3-(2-((5-Bromo-2-pyrimidinyl)oxy)ethoxy)-2-(4-methylphenyl)phenyl)-4-*tert*-butylbenzenesulfonamide(8k).** The same procedure as for **7k** started from **31** afforded **8k** as colorless needles (92%): mp 124.5−125.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.42 (2H, s), 7.49−7.54 (2H, m), 7.38−7.44 (3H, m), 7.25 (1H, t, J = 8.3 Hz), 7.02 (2H, d, J = 7.7 Hz), 6.74 (1H, dd, J = 1.1, 8.3 Hz), 6.54−6.59 (2H, m), 6.30 (1H, s), 4.47 (2H, t, J = 5.0 Hz), 4.17 (2H, t, J = 5.0 Hz), 2.36 (3H, s), 1.33 (9H, s); IR (Nujol) cm^{-1} 3260, 1590, 1565, 1545, 1465, 1430; FAB-MS *m*/*z* 596 (M+H$^+$), 399, 201; Anal. ($C_{29}H_{30}BrN_3O_4S$) C, H, N.

4-*tert*-Butyl-*N*-(2-(4-methylphenyl)-3-(2-((5-(3-thienyl-2-pyrimidinyl)oxy)ethoxy)phenyl)benzenesulfonamide (8w). The same procedure as for **7w** started from **8k** and tributyl-3-thienyltin afford **8w** as colorless needles (219 mg, 87%): mp 151.5−153 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.64 (2H, s), 7.49−7.55 (2H, m), 7.48 (1H, dd, J = 2.9, 4.8 Hz), 7.45 (1H, dd, J = 1.5, 2.9 Hz), 7.38−7.45 (3H, m), 7.31 (1H, dd, J = 1.5, 4.8 Hz), 7.26 (1H, t, J = 8.3 Hz), 7.02 (2H, d, J = 7.7 Hz), 6.78 (1H, dd, J = 1.0, 8.3 Hz), 6.58−6.62 (2H, m), 4.51 (2H, t, J = 5.2 Hz), 4.22 (2H, t, J = 5.2 Hz), 2.29 (3H, s), 1.34 (9H, s); IR (Nujol) cm^{-1} 3350, 3120, 3110, 3000, 1600, 1585, 1560, 1530; FAB-MS *m*/*z* 600 (M+H$^+$), 205; Anal. ($C_{33}H_{33}N_3O_4S_2$) C, H, N.

ET_A Receptor Binding Assay on Porcine Aortic Membrane. These binding experiments were performed in a manner similar to Ihara et al.[26] with minor modification: Porcine aorta (known to contain ET_A receptors) from which endothelium was removed was homogenized in 10 mM 3-[*N*-morpholino]propane sulfonic acid (MOPS) buffer (pH 7.4) containing 20% sucrose. The homogenate was centrifuged under cooling for 15 min at 1000*g*. The supernatant was centrifuged under cooling for 45 min at 90000*g*. The precipitate was resuspended in 5 mM HEPES-Tris buffer to obtain a membrane preparation. A total of 50 μL of the diluted membrane preparation (2 mg/mL), 50 μL of ^{125}I-labeled endothelin-1 (final concentration of ^{125}I-labeled endothelin-1: 20 pM, specific activity: 74 TBq/mmol, Amersham Japan), and 50 μL of a test compound solution in various concentrations were admixed. The mixture was added to 150 μL of assay buffer (50 mM Tris-HCl buffer (pH 7.4) containing 0.1% BSA, 0.1 mM phenylmethylsulfonyl fluoride, 1 μM pepstatin A, 2 μM leupeptin, 1 mM 1, 10-phenanethrorine and 1 mM EDTA), and incubated for 2 h at 25 °C. The incubation was terminated by rapid filtration through a Whatman GF/B grass fiber filters. The filters were washed with ice-cooled 5 mM HEPES-Tris buffer (pH 7.4) containing 0.1% BSA and the radioactivity was counted by a gamma counter (ARC-360, Aloka Ltd.). The antagonistic activity of the test compound (inhibitory effect on ^{125}I-labeled endothelin-1 binding to porcine aortic mebranes) was estimated as IC_{50} which is the concentration (M) required to inhibit the specific binding of ^{125}I-labeled endothelin-1 by 50%. Meanwhile, the nonspecific binding of endothelin was estimated in the presence of 2×10^{-7} M endothelin-1.

Binding Studies on Cultured Cells (rat A10 cells for ET_A receptors and human GH cells for ET_B receptors) and on Membranes of CHO Cells (expressing cloned human ET_A and ET_B receptors). These binding studies were carried out as reported.[27]

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