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Studies of non-nucleoside HIV-1 reverse transcriptase inhibitors. Part 2: Synthesis and structure–activity relationships of 2-cyano and 2-hydroxy thiazolidenebenzenesulfonamide derivatives

Naoyuki Masuda,^{a,*} Osamu Yamamoto,^a Masahiro Fujii,^a Tetsuro Ohgami,^a Jiro Fujiyasu,^a Toru Kontani,^a Ayako Moritomo,^a Masaya Orita,^a Hiroyuki Kurihara,^a Hironobu Koga,^a Shunji Kageyama,^a Mitsuaki Ohta,^a Hiroshi Inoue,^a Toshifumi Hatta,^a Masafumi Shintani,^a Hiroshi Suzuki,^a Kenji Sudo,^a Yasuaki Shimizu,^a Eiichi Kodama,^b Masao Matsuoka,^b Masatoshi Fujiwara,^c Tomoyuki Yokota,^c Shiro Shigeta^d and Masanori Baba^e

^aInstitute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd, 21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan ^bLaboratory of Virus Immunology, Institute for Virus Research, Kyoto University, 53 Syogoin, Kawaramachi, Sakyo-ku, Kyoto 606-8507, Japan

^cRational Drug Design Laboratories, 4-1-1, Misato, Matsukawa-Machi, Fukushima 960-1242, Japan

^dDepartment of Microbiology, School of Medicine, Fukushima Medical University, 1 Hikarigaoka, Fukushima 960-1295, Japan

^eDivision of Antiviral Chemotherapy, Center for Chronic Viral Diseases, Graduate School of Medical and Dental Sciences,

Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima 890-8544, Japan

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Abstract—In a previous study, we described the structure–activity relationships (SARs) for a series of thiazolidenebenzenesulfonamide derivatives. These compounds were found to be highly potent inhibitors of the wild type (WT) and Y181C mutant reverse transcriptases (RTs) and modest inhibitors of K103N RT. These molecules are thus considered to be a novel class of non-nucleoside HIV-1 RT inhibitors (NNRTIs). In this paper, we have examined the effects of substituents on both the thiazolidene and benzenesulfonamide moieties. Introduction of a 2-cyanophenyl ring into these moieties significantly enhanced anti-HIV-1 activity, whereas a 2-hydroxyphenyl group endowed potent activity against RTs, including K103N and Y181C mutants. Among the series of molecules examined, **101** and **18b** (YM-228855), combinations of 2-cyanophenyl and 4-methyl-5-isopropylthiazole moieties, showed extremely potent anti-HIV-1 activity. The EC₅₀ values of **101** and **18b** were 0.0017 and 0.0018 μ M, respectively. These values were lower than that of efavirenz (**3**). Compound **11g** (YM-215389), a combination of 2-hydroxyphenyl and 4-chloro-5-isopropylthiazole moieties, proved to be the most active against both K103N and Y181C RTs with IC₅₀ values of 0.043 and 0.013 μ M, respectively. © 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Reverse transcriptase (RT) is a key enzyme, which plays an essential and multifunctional role in the replication of human immunodeficiency virus type 1 (HIV-1) and thus considered to be an attractive target for inhibition of HIV-1 replication.¹ Non-nucleoside reverse transcriptase inhibitors (NNRTIs), a group of structurally diverse compounds, have been reported to directly inhibit the enzyme in an allosteric fashion by binding to a pocket near the polymerase active site.² To date, many classes of NNRTIs have been identified, and three inhibitors, nevirapine, delavirdine, and efavirenz, have been approved for the treatment of HIV-1 infection. However, NNRTI-containing regimens are compromised by rapid emergence of drug-resistant strains

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^{*} Corresponding author. Tel.: +81 298 63 6752; fax: +81 298 52 2971; e-mail: masuda.naoyuki@yamanouchi.co.jp

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Figure 1. Structures of thiazolidenebenzenesulfonamide derivatives (1, 2) and efavirenz (3).

carrying the amino acid mutations surrounding the NNRTI binding pocket.

The mutation of tyrosine to cysteine at position 181 in HIV-1 RT (Y181C) following treatment with nevirapine or delavirdine has been documented in cell culture experiments.³ Furthermore, the mutation of lysine to asparagine at position 103 (K103N) is frequently observed in patients who do not respond to the treatment with either NNRTI alone or in combination with other inhibitors.⁴ The newest NNRTI, efavirenz (**3**) has been shown significant clinical efficacy in combination with both protease-containing and protease-sparing regimens.⁵ Although the majority of patients receiving efavirenz-containing regimens show a sustained antiviral response, more than 90% of the viruses isolated from the patients whose viral loads have rebounded after an initial drug response have the K103N mutation.⁶

Our previously determined structure–activity relationships (SARs) for a series of thiazolidenebenzenesulfonamide derivatives and docking studies have suggested the importance of a bulky 5-alkyl group on the thiazolidene ring for potent inhibitory activity against Y181C RT.⁷ In addition, we found that 3-nitrobenzenesulfonamide derivatives (1, 2) possess potent activity against the wild type (WT) and Y181C RTs, but that their activity against K103N RT was not satisfactory. In this study, we have explored the SARs of substituents in a series of thiazolidenebenzenesulfonamides, in order to identify novel NNRTIs that are capable of inhibiting both K103N and Y181C RT activity and HIV-1 replication (Fig. 1).

2. Chemistry

A series of benzenesulfonamide derivatives (1, 10a–q, 11a–g, 16a, 17a, 18a,b, 19, 20) was synthesized as shown in Schemes 1–4. Cyanobenzenesulfonylchlorides 6n-p were prepared from their corresponding substituted methyl anthranilates (Scheme 1). Sandmeyer reactions of anthranilates 4a-c with ammonia provided saccharins 5a-c.⁸ Treatment of saccharins 5a-c with PCl₅ afforded 2-cyanobenzenesulfonylchlorides 6n-p. Compound 4d was converted to the methoxycarbonyl-substituted sulfonylchloride by a one-pot reaction (6q). Condensation of 2-aminothiazoles 8a-c with the substituted sulfonylchlorides 6a-r, followed by selective methylation on the thiazolidene ring of compounds 9a-s, afforded the desired thiazolidenesulfonamide derivatives 1 and 10a-r (Scheme 2).⁷ The demethylation of the methoxy deri-



Scheme 1. Reagents and conditions: (a) NaNO₂, HCl/AcOH; (b) SO₂, CuCl, CuCl₂/AcOH–H₂O; (c) NH₃ aq; (d) PCl₅.

vatives (10f-h, j, k, o, p) using BBr₃ provided the corresponding phenol analogues (11a-g).

As shown in Scheme 3, the nitro compound 10i was converted into aniline 12 by catalytic hydrogenation. Aniline 12 was reacted with acetyl chloride or methanesulfonyl chloride to provide acetamide 13 and methanesulfonamide 14, respectively. The triflates 15a and 15b were prepared from the corresponding phenol analogues (11e,f). A palladium-catalyzed carbon monoxide insertion with triflate 15a afforded the methoxy-carbonyl derivative 16.⁹ Hydrolysis of the ester derivatives (16, 10q) followed by amidation gave the carbamoyl derivatives (17a,b). The cyano derivatives 18a and 18b were obtained by dehydration of compounds 17a and 17b, respectively.

For the synthesis of 2-cyanobenzenesulfonamide derivatives (**19**, **20**), we have efficiently applied palladium-catalyzed cyanation of the aryl triflates with a combination of Pd(dba)₂, dppf, Zn(CN)₂ and Zn powder (Scheme 4).¹⁰ Mono- and di-cyano compounds (**19**, **20**) were obtained by controlling the amount of Zn(CN)₂. Use of 0.6 mol equiv of Zn(CN)₂, which provided 1.2 equiv of cyanide anion, gave the mono-cyano compound **19** through reaction at the triflate group only. With use of 1.6 mol equiv of Zn(CN)₂, the major product was the di-cyano compound **20**.

3. Results and discussion

Tables 1–3 summarize the inhibitory activities against the WT, Y181C, and K103N RTs and HIV-1 replication of thiazolidenebenzenesulfonamide derivatives carrying different substituents on the phenyl ring, or at the 4position on the thiazolidene ring, or both.

We first investigated the effect on the inhibitory activity of substituents on the benzene ring, as shown in Table 1. The RT inhibitory activity of the substituted benzenesulfonamide analogues varied considerably with different substituents. Substituents at the *meta*-position were favorable for the inhibition of RT and HIV-1 replication, and compounds that had a nitro (1) or chloro (10c) group were most potent against all RTs. These







Scheme 2. Reagents and conditions: (a) Py; (b) MeI, NaH/THF; (c) BBr₃/CH₂Cl₂.

nitro and chloro substituents also resulted in more potent anti-HIV-1 activity, and compounds **1** and **10c** showed anti-HIV-1 activity with EC₅₀ values of 0.085 and 0.20 μ M, respectively. In contrast, *ortho-* and *para*substituted compounds were essentially inactive against the WT RT, with an exception of the *ortho*-hydroxy compound **11a**, which showed a lower IC₅₀ value than that of the unsubstituted compound **10r**. Compound **11a** also exhibited moderate anti-HIV-1 activity (EC₅₀ = 2.3 μ M). Therefore, we concluded that the substitution of a chloro or nitro group at the *meta*-position or a hydroxy group at the *ortho*-position on the benzene ring was favorable for RT inhibition.

We next focused on combinations of an *ortho*-substituent and a *meta*-chloro group, as shown in Table 2. Although the 2-hydroxy-3-chloro derivative (**11d**) was somewhat less active against the WT RT ($IC_{50} =$ $6.3\,\mu\text{M}$), substitution at the 2-position on a 5-chlorophenyl ring (11e, 12, 18a), resulted in an enhancement of activity against the RTs. The introduction of an amino group at the 2-position of the phenyl ring (12) resulted in a significant improvement of anti-HIV-1 activity but reduced activity against K103N and Y181C RTs, when compared with 10c. On the other hand, compound 11e was about 10-fold more potent against the WT and K103N RTs, and 4-fold more potent against Y181C RT, as compared to compound 10c. The cyano derivative 18a possessed the most potent antiviral activity $(EC_{50} = 0.0083 \,\mu\text{M})$ with a therapeutic index (TI) of >960, but it showed no inhibition of K103N RT. Although the amino and cyano compounds (12, 18a) showed less potent activity against WT RT than the hydroxy compound 11e, these compounds possessed more potent anti-HIV-1 activity than 11e. We cannot explain the exact reason for this phenomenon. One possibility,



Scheme 3. Reagents and conditions: (a) H₂, Pd–C/EtOH–THF; (b) AcCl, DMAP/Py; (c) MsCl, Et₃N/THF; (d) Tf₂O, 2,6-lutidine/CH₂Cl₂; (e) CO, MeOH, Pd(OAc)₂, dppp, Et₃N/DMF; (f) NaOH aq, THF/MeOH, (g) NH₄Cl, WSC·HCl, *i*-Pr₂NEt, HOBt/DMF; (h) POCl₃/DMF.



Scheme 4. Reagents and conditions: (a) $Zn(CN)_2$ (0.6 equiv), Zn, Pd(dba)₂, dppf/DMA; (b) $Zn(CN)_2$ (1.6 equiv), Zn, Pd(dba)₂, dppf/DMA.

however, is that the increase in lipophilicity caused by the substitution of the hydroxy group to the amino or cyano group potentiated their cell membrane permeability, which resulted in the increase of anti-HIV-1 activity. We also have to consider other possibilities, such as that the introduction of these groups allow compound stability to be maintained under the assay conditions, or that they acquire the other anti-viral mechanism (inhibition of HIV-protease, integrase, RNaseH, or virus adsorption).

On the other hand, replacement of the cyano group with other electron-withdrawing groups, such as nitro (10i), methoxycarbonyl (16) and carbamoyl (17a), led to loss of RT inhibition. Substitution of the cyano group with an acetamide or methanesulfonamide group (13, 14), which are known to be bioisosteres of the phenolic hydroxy group, was also detrimental to inhibition with all RTs. Thus, concerning the 5-chlorophenyl derivatives, the introduction of a hydroxy, amino, or cyano group at the 2-position markedly enhanced the inhibition of HIV-1 replication.

We previously reported that compounds with 5-isopropyl-4-methyl- and 4-chloro-5-isopropyl-substituted thiazolidene moieties had increased activity against the WT and Y181C RTs.⁷ On the basis of the SARs described in Table 2, we synthesized new compounds with a combination of 2-cyanophenyl or 2-hydroxyphenyl moiety and 5-isopropyl-4-methyl or 4-chloro-5-isopropyl thiazolidene moiety (10l-n, 11f,g, 18b, 19, 20; Table 3). Among these, compound 11f, having both 2-hydroxy-5-chlorophenyl and 4-chlorothiazolidene moieties, was a more potent inhibitor of all the RT enzymes, compared to compound 11e. In addition, compound 11g (YM-215389), which has 5-bromophenyl ring, showed significantly more potent activity against all the RTs, compared to compound 11f. Compound 11g also exhibited strong anti-HIV-1 activity, with an EC₅₀ value of $0.037 \,\mu\text{M}$, and the TI value of **11g** exceeded 680. With the exception of compound 10m, the 2-cyanophenyl derivatives (101, 10n, and 18b), which all have 5-isopropyl-4-methylthiazolidene moieties, exhibited extremely potent anti-HIV-1 activity (EC₅₀ = $0.0017 - 0.0021 \,\mu$ M), with TIs ranging from 6100 to >15,000. Interestingly,

Table 1. In vitro activities of mono-substituted benzenesulfonamide derivatives



Compounds	R	IC_{50}^{a} (μ M)			$EC_{50}^{b}(\mu M)$	CC ₅₀ ^c (µM)	TI^d
		WT	K103N	Y181C			
1	3-NO ₂	0.27	13	0.066	0.085	>25	>290
10a	$2-NO_2$	>50	>50	36	>25	>25	
10b	2-C1	>10	>10	>10	NT ^e	NT ^e	_
10c	3-C1	0.30	11	0.044	0.20	>25	>125
10d	$4-NO_2$	>10	>10	>10	NT ^e	NT ^e	
10e	4-C1	>10	>10	>10	NT ^e	NT ^e	
10f	2-OMe	50	>50	NT ^e	10	>25	>3
10g	3-OMe	8.8	>50	NT ^e	11	>25	>2
10h	4-OMe	>10	>10	>10	>25	>25	
10r	Н	4.9	>50	5.1	>25	>25	
11a	2-OH	1.6	30	0.41	2.3	>25	>11
11b	3-OH	8.8	>50	14	>25	>25	
11c	4-OH	>10	>10	>10	>25	>25	

^a Compound concentration required to achieve 50% inhibition of recombinant HIV-1 RT activities.

^b Compound concentration required to achieve 50% protection of MT-4 cells from HIV-1 induced CPE, as determined by the MTT method.

^c Compound concentration required to reduce the viability of mock-infected MT-4 cells, as determined by the MTT method.

^d Therapeutic index (CC₅₀/EC₅₀).

^eNT: not tested.

Table 2. In vitro activities of 2-substituted 5-chlorobenzenesulfonamide derivatives



Compounds	R	IC_{50}^{a} (μM)			$EC_{50}^{b}(\mu M)$	CC ₅₀ ^c (µM)	TI ^d
		WT	K103N	Y181C			
10c	Н	0.30	11	0.044	0.20	>25	>125
10i	NO_2	2.4	>50	NT ^e	0.36	22	61
11d		6.3	>50	NT ^e	11	>25	>2
11e	OH	0.032	1.1	0.011	0.026	>25	>960
12	NH_2	0.19	17	0.11	0.025	>25	>1000
13	NHCOMe	>50	>50	>50	2.7	>25	>9
14	NHSO ₂ Me	>50	>50	>50	>25	>25	
16	COOMe	>10	>10	10	>25	>25	
17a	$CONH_2$	>10	>10	>10	NT ^e	NT ^e	
18a	CN	0.18	>50	0.069	0.0083	8	>960

^a Compound concentration required to achieve 50% inhibition of recombinant HIV-1 RT activities.

^b Compound concentration required to achieve 50% protection of MT-4 cells from HIV-1 induced CPE, as determined by the MTT method.

^c Compound concentration required to reduce the viability of mock-infected MT-4 cells, as determined by the MTT method.

^d Therapeutic index (CC_{50}/EC_{50}).

^e NT: not tested.

the 2-cyanophenyl and 5-isopropyl-4-methylthiazolidene derivatives, **101** and **18b** (YM-228855), exhibited strong anti-HIV-1 activity, with EC₅₀ values of 0.0017 and 0.0018 μ M, respectively, both of which were more potent than that of efavirenz (EC₅₀ = 0.0027 μ M). The replacement of the 5-chloro or 5-cyano group on the phenyl ring with a 5-bromo group (**10n**) was tolerable for anti-HIV-1 activity, but this derivative was found to be a modest inhibitor of K103N RT. We also investigated the substitution of the methyl group at the 4-position of **10I** with a chloro group (**19**, **20**), anticipating further increase in RT inhibitory activity and anti-HIV-1 activity. However, this attempt gave slightly less potent compounds than their methyl counterparts. Among the compounds shown in Table 3, compound **11g** was the most potent inhibitor against the WT, Y181C, and K103N RTs, with IC₅₀ values of 0.0043, 0.043, and 0.013 μ M, respectively, and

Table 3. In vitro activities of 5-isopropylthiazolidenesulfonamide derivatives



Compounds	R_1	R_2	R ₃	IC ₅₀ ^a (µM)			$EC_{50}^{b}(\mu M)$	CC ₅₀ ^c (µM)	TI ^d
				WT	K103N	Y181C			
101	Me	CN	Cl	0.011	5.9	0.20	0.0017	>25	>15000
10m	Me	CN	F	0.092	>10	2.1	0.0077	>25	>3200
10n	Me	CN	Br	0.018	3.9	0.26	0.0021	>25	>12,000
11f	Cl	OH	Cl	0.0094	0.17	0.021	0.027	>25	>930
11g (YM-215389)	Cl	OH	Br	0.0043	0.043	0.013	0.037	>25	>680
18b (YM-228855)	Me	CN	CN	0.012	4.1	0.47	0.0018	11	6100
19	Cl	CN	Cl	0.0090	3.7	0.091	0.0047	3.8	810
20	Cl	CN	CN	0.0095	3.0	0.21	0.0036	22	6100
1				0.27	13	0.066	0.085	>25	>290
2				0.077	6.9	0.13	0.048	24	500
Efavirenz (3)				0.0069	0.021	0.0040	0.0027	8.5	3200

^a Compound concentration required to achieve 50% inhibition of recombinant HIV-1 RT activities.

^b Compound concentration required to achieve 50% protection of MT-4 cells from HIV-1 induced CPE, as determined by the MTT method.

^c Compound concentration required to reduce the viability of mock-infected MT-4 cells, as determined by the MTT method.

^d Therapeutic index (CC₅₀/EC₅₀).

accompanying potent anti-HIV-1 activity (EC₅₀: 0.037 μ M). Consequently, the discovery of an effective compound against the WT, K103N, and Y181C mutant RTs as well as HIV-1 replication has been made by the exploration of the optimum combination of substituents on both the thiazole and phenyl rings. This compound is referred to as YM-215389. Further improvement of anti-HIV-1 properties in this series of compounds and their potential use as anti-HIV-1 agents will be reported in due course.

4. Conclusion

In this paper, the synthesis and SARs of thiazolidenebenzenesulfonamide derivatives have been described. An interesting aspect of this study is that both potency and spectrum of thiazolidenebenzenesulfonamides varied, depending on the number and position of the substituents on the phenyl ring. It was found that the combination of a hydroxy or cyano group at the 2-position on the phenyl ring with a 5-isopropylthiazolidene ring improved the inhibitory activities against RT enzymes and HIV-1 replication. The cyano derivatives (101 and 18b) showed extremely potent anti-HIV-1 activity, with EC₅₀ values of 0.0017 and 0.0018 µM, respectively. These values were significantly better than that of efavirenz (3). However, the activity of the cyano derivatives against the K103N mutant RT was insufficient. Compound 11g (YM-215389) possessed the most potent activity against the WT, K103N, and Y181C RTs, with IC₅₀ values of 0.0043, 0.043, and 0.013 μ M, respectively. This compound also strongly inhibited HIV-1 replication in cell cultures (EC₅₀ = $0.037 \,\mu$ M). Because of their excellent potency, these thiazolidenebenzenesulfonamide derivatives may have potential and should be further pursued as next-generation NNRTIs.

5. Experimental

5.1. Chemistry

Melting points were determined on a Yanaco micromelting apparatus or Büchi B-545 melting point apparatus and are uncorrected. Proton magnetic resonance (¹H NMR) spectra were obtained in CDCl₃ or dimethylsulfoxide- d_6 (DMSO- d_6) using a JEOL JNM-EX90, JNM-EX400, JNM-GX500, or JNM-A500 spectrometer. Chemical shifts were expressed in δ (ppm) values with tetramethylsilane as an internal standard (in NMR description, s: singlet, d: doublet, t: triplet, m: multiplet, br: broad peak). Mass spectra (MS) were recorded on a JEOL JMS-DX300 or a HITACHI M-80 mass spectrometer. Elemental analysis was carried out on Yanaco MT-3 or MT-5 CHN analyzer and a Yokogawa IC7000S Ion Chromatoanalyzer. Chromatographic separations were performed using a silica gel column (Merck Kieselgel 60). Analytical thin-layer chromatography (TLC) was carried out on precoated glass plates (Merck Kieselgel 60F254).

The following known materials were prepared as described in the literature: $(6j)^{11}$ or obtained from commercial suppliers (6a-i, 6r). And the preparation of 1, **8a–c**, **9a** was described in our previous report.⁷

5.1.1. 6-Chloro-1,2-benzisothiazol-3(2*H*)-one-1,1-dioxide (5a). To solution of 4a (7.42 g, 40 mmol) in acetic acid (45 mL) and concentrated hydrochloric acid (90 mL) was added sodium nitrite (2.90 g, 42 mmol) in water (12 mL) at -5 °C and the solution was stirred at -5 °C for 1 h. To a mixture of copper(II) chloride (5.38 g, 40 mmol) and copper(I) chloride (3.96 g, 40 mmol) in acetic acid (120 mL) and concentrated hydrochloric acid (15 mL), SO₂ gas was bubbled at -5 °C. The suspension of prepared diazonium salt was added dropwise to the mixture at -10 °C and stirred at room temperature for 3 h. The reaction mixture was poured into water and 28% aqueous ammonia solution (500 mL) was added under ice-bath cooling. The resulting mixture was extracted with chloroform and washed with saturated aqueous sodium hydrogen carbonate solution. The organic layer was dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to give **5a** (3.90 g, 45%) as a colorless powder. ¹H NMR (DMSO- d_6) δ : 7.97 (3H, m, benzene), 8.43 (1H, br s, NH); FAB-MS *m*/*z*: 218 (M⁺+1).

The following compounds were obtained in the same manner.

5.1.2. 6-Fluoro-1,2-benzisothiazol-3(2*H***)-one-1,1-dioxide (5b). 31% yield; ¹H NMR (DMSO-d_6) \delta: 7.57 (1H, m, benzene), 7.82 (2H, m, benzene), 7.90 (1H, m, NH); FAB-MS** *m***/***z***: 200 (M⁻-1).**

5.1.3. 6-Bromo-1,2-benzisothiazol-3(2*H*)-one-1,1-dioxide (5c). 56% yield; ¹H NMR (DMSO- d_6) δ : 7.80 (1H, br s, NH), 7.87 (1H, d, J = 8.3 Hz, benzene), 8.09 (1H, dd, J = 1.5, 8.3 Hz, benzene), 8.51 (1H, d, J = 1.5 Hz, benzene); FAB-MS m/z: 263 (M⁺+1).

5.1.4. 5-Chloro-2-cyanobenzenesulfonyl chloride (6n). A mixture of **5a** (3.90 g, 18.0 mmol) and phosphorus pentachloride (22.4 g, 90.0 mmol) was heated to 120 °C and stirred for 7 h. The reaction mixture was poured into icewater. The resulting mixture was extracted with ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate solution. The organic layer was dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to give **6n** (2.89 g, 68%) as a pale yellow powder. This crude product was used for next step without further purification.

The following compounds were obtained in the same manner.

5.1.5. 5-Fluoro-2-cyanobenzenesulfonyl chloride (60). 54% yield; ¹H NMR (DMSO- d_6) δ : 7.40 (1H, dt, J = 3.6, 11.2 Hz, benzene), 7.59 (1H, dd, J = 3.6, 12.0 Hz, benzene), 7.92 (1H, dd, J = 6.8, 11.2 Hz, benzene); EI-MS m/z: 219 (M⁺).

5.1.6. 5-Bromo-2-cyanobenzenesulfonyl chloride (6p). Without isolation.

5.1.7. Methyl 2-chlorosulfonyl-4-cyanobenzoate (6q). Sodium nitrite (5.10 g, 73.5 mmol) in water (25 mL) was added to solution of 4d (12.3 g, 70 mmol) in concentrated hydrochloric acid (120 mL) at -5 °C and the solution was stirred at -5 °C for 1.5 h. To a mixture of copper(II) chloride dihydrate (2.60 g, 15.0 mmol) in acetic acid (200 mL), SO₂ gas was bubbled at -5 °C. The suspension of prepared diazonium salt was added dropwise to the mixture at -10 °C and stirred at room temperature for 3 h. The reaction mixture was poured into water. The resulting precipitate was collected by filtration and washed with water. The precipitate was dried under reduced pressure to give **6q** (19.0 g, quantitative) as a colorless powder. ¹H NMR (DMSO- d_6) δ : 3.75 (3H, s, CH₃ of COOMe), 7.52 (1H, d, J = 8.1 Hz, benzene), 7.87 (1H, dd, J = 1.5, 8.1 Hz, benzene), 8.03 (1H, d, J = 1.5 Hz, benzene); EI-MS m/z: 259 (M⁺).

5.1.8. N-(5-tert-Butyl-4-methyl-1,3-thiazol-2-yl)-2-nitrobenzenesulfonamide (9b). A solution of 8a. hydrochloride (8.00 g, 38.7 mmol) in pyridine (100 mL) was added **6b** (10.3 g, 46.4 mmol) and the solution was stirred at room temperature for 12 h. The reaction mixture was poured into water. The resulting mixture was extracted with ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate solution, 1 M hydrochloric acid and brine. The organic layer was dried over anhydrous sodium sulfate and solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate-hexane) to give **9b** (10.89 g, 79%) as an orange solid. ¹H NMR (DMSO- d_6) δ : 1.30 (9H, s, t-Bu), 2.18 (3H, s, 4-Me), 7.80 (2H, m, benzene), 7.87 (1H, m, benzene), 8.03 (1H, m, benzene), 12.65 (1H, br s, NH); FAB-MS m/z: $356 (M^++1).$

The following compounds were obtained in the same manner.

5.1.9. *N*-(5-*tert*-Butyl-4-methyl-1,3-thiazol-2-yl)-2-chlorobenzenesulfonamide (9c). 34% yield; ¹H NMR (DMSO- d_6) δ : 1.30 (9H, s, CH₃ of *t*-Bu), 2.16 (3H, s, 4-Me), 8.03 (2H, d, J = 8.8 Hz, benzene), 8.36 (2H, d, J = 8.8 Hz, benzene), 12.58 (1H, br s, NH); FAB-MS *m*/*z*: 345 (M⁺+1).

5.1.10. *N*-(5-*tert*-Butyl-4-methyl-1,3-thiazol-2-yl)-3-chlorobenzenesulfonamide (9d). 99% yield; ¹H NMR (DMSO- d_6) δ : 1.29 (9H, s, CH₃ of *t*-Bu), 2.16 (3H, s, 4-Me), 7.58 (1H, t, J = 7.8 Hz, benzene), 7.67 (1H, br d, J = 7.8 Hz, benzene), 7.74 (1H, br s, benzene), 7.75 (1H, br d, J = 7.8 Hz, benzene), 12.46 (1H, br s, NH); FAB-MS *m*/*z*: 345 (M⁺+1).

5.1.11. *N*-(5-*tert*-Butyl-4-methyl-1,3-thiazol-2-yl)-4-nitrobenzenesulfonamide (9e). 85% yield; ¹H NMR (DMSO- d_6) δ : 1.30 (9H, s, CH₃ of *t*-Bu), 2.16 (3H, s, 4-Me), 8.03 (2H, d, J = 8.8 Hz, benzene), 8.36 (2H, d, J = 8.8 Hz, benzene), 12.58 (1H, br s, NH); FAB-MS *m*/*z*: 356 (M⁺+1).

5.1.12. *N*-(**5**-*tert*-**Buty**]-**4**-methyl-**1**,**3**-thiazol-**2**-yl)-**4**-chlorobenzenesulfonamide (9f). 78% yield; ¹H NMR (DMSO- d_6) δ : 1.29 (9H, s, CH₃ of *t*-Bu), 2.15 (3H, s, 4-Me), 7.60 (2H, d, J = 7.5 Hz, benzene), 7.78 (2H, d, J = 7.5 Hz, benzene), 12.42 (1H, br s, NH); FAB-MS m/z: 345 (M⁺+1).

5.1.13. *N*-(5-*tert*-Butyl-4-methyl-1,3-thiazol-2-yl)-2-methoxybenzenesulfonamide (9g). 50% yield; ¹H NMR (DMSO- d_6) δ : 1.31 (9H, s, CH₃ of *t*-Bu), 2.15 (3H, s, 4-Me), 3.73 (3H, s, MeO), 7.03 (1H, t, *J* = 7.5 Hz, benzene), 7.13 (1H, d, *J* = 7.5 Hz, benzene), 7.50 (2H, m, benzene), 12.14 (1H, br s, NH); FAB-MS *m*/*z*: 341 (M⁺+1). **5.1.14.** *N*-(5-*tert*-Butyl-4-methyl-1,3-thiazol-2-yl)-3-methoxybenzenesulfonamide (9h). 61% yield; ¹H NMR (DMSO- d_6) δ : 1.29 (9H, s, CH₃ of *t*-Bu), 1.98 (3H, s, 4-Me), 3.80 (3H, s, MeO), 7.14 (1H, dd, J = 2.5, 8.3 Hz, benzene), 7.26 (1H, t, J = 2.5 Hz, benzene), 7.36 (1H, br d, J = 7.8 Hz, benzene), 7.45 (1H, t, J = 7.8 Hz, benzene), 12.34 (1H, br s, benzene); FAB-MS *m*/*z*: 341 (M⁺+1).

5.1.15. *N*-(5-*tert*-Butyl-4-methyl-1,3-thiazol-2-yl)-4-methoxybenzenesulfonamide (9i). Without isolation.

5.1.16. *N*-(5-*tert*-Butyl-4-methyl-1,3-thiazol-2-yl)-5chloro-2-nitrobenzenesulfonamide (9j). 41% yield; ¹H NMR (DMSO- d_6) δ : 1.30 (9H, s, CH₃ of *t*-Bu), 2.20 (3H, s, 4-Me), 7.91 (1H, dd, J = 2.0, 8.3 Hz, benzene), 7.98 (1H, d, J = 2.0 Hz, benzene), 7.99 (1H, d, J = 8.8 Hz, benzene), 12.76 (1H, br s, NH); FAB-MS *m*/*z*: 390 (M⁺+1).

5.1.17. *N*-(**5**-*tert*-**Butyl**-**4**-methyl-**1**,**3**-thiazol-**2**-yl)-**3**-**chloro-2**-methoxybenzenesulfonamide (9k). Without isolation.

5.1.18. *N*-(5-*tert*-Butyl-4-methyl-1,3-thiazol-2-yl)-5chloro-2-methoxybenzenesulfonamide (9l). 94% yield; ¹H NMR (DMSO- d_6) δ : 1.32 (9H, s, CH₃ of *t*-Bu), 2.17 (3H, s, 4-Me), 3.74 (3H, s, MeO), 7.18 (1H, d, J = 8.8 Hz, benzene), 7.59 (1H, dd, J = 2.9, 8.8 Hz, benzene), 7.73 (1H, d, J = 2.9 Hz, benzene), 12.30 (1H, br s, NH); FAB-MS *m*/*z*: 375 (M⁺+1).

5.1.19. 5-Chloro-2-cyano-*N***-(5-isopropyl-4-methyl-1,3-thiazol-2-yl)benzenesulfonamide (9m).** 13% yield. ¹H NMR (DMSO- d_6) δ : 1.14 (6H, d, J = 6.8 Hz, CH₃ of *i*-Pr), 2.06 (3H, s, 4-Me), 3.11 (1H, heptet, J = 6.8 Hz, CH of *i*-Pr), 7.88 (1H, dd, J = 2.5, 8.3 Hz, benzene), 8.00 (1H, d, J = 2.5 Hz, benzene), 8.09 (1H, d, J = 8.3 Hz, benzene), 12.83 (1H, br s, NH); FAB-MS *mlz*: 356 (M⁺+1).

5.1.20. 5-Fluoro-2-cyano-*N***-(5-isopropyl-4-methyl-1,3-thiazol-2-yl)benzenesulfonamide (9n).** 20% yield; ¹H NMR (DMSO- d_6) δ : 1.14 (6H, d, J = 6.9 Hz, CH₃ of *i*-Pr), 2.06 (3H, s, 4-Me), 3.11 (1H, heptet, J = 6.9 Hz, CH of *i*-Pr), 7.67 (1H, dt, J = 1.9, 8.8 Hz, benzene), 7.82 (1H, dd, J = 1.9, 8.8 Hz, benzene), 8.16 (1H, dd, J = 5.4, 8.8 Hz, benzene), 12.82 (1H, br s, NH); FAB-MS m/z: 340 (M⁺+1).

5.1.21. 5-Bromo-2-cyano-*N***-(5-isopropyl-4-methyl-1,3-thiazol-2-yl)benzenesulfonamide (90).** 27% yield from **8b**; ¹H NMR (DMSO-*d*₆) δ : 1.14 (6H, d, J = 6.8 Hz, CH₃ of *i*-Pr), 2.06 (3H, s, 4-Me), 3.11 (1H, heptet, J = 6.8 Hz, CH of *i*-Pr), 8.01 (2H, m, benzene), 8.13 (1H, d, J = 1.4 Hz, benzene), 12.84 (1H, br s, NH).; FAB-MS *m/z*: 400 (M⁺+1).

5.1.22. *N*-(4-Chloro-5-isopropyl-1,3-thiazol-2-yl)-5chloro-2-methoxybenzenesulfonamide (9p). 22% yield; ¹H NMR (CDCl₃) δ : 1.25 (6H, d, J = 7.0 Hz, CH₃ of *i*-Pr), 2.67 (1H, br s, NH), 3.16 (1H, heptet, J = 7.0 Hz, CH of *i*-Pr), 3.87 (3H, s, MeO), 6.94 (1H, d, J = 8.8 Hz, benzene), 7.46 (1H, dd, J = 2.4, 8.8 Hz, benzene), 7.94 (1H, d, J = 2.4 Hz, benzene); FAB-MS m/z: 381 (M⁺+1).

5.1.23. *N*-(4-Chloro-5-isopropyl-1,3-thiazol-2-yl)-5bromo-2-methoxybenzenesulfonamide (9q). 59% yield;. ¹H NMR (DMSO- d_6) δ : 1.20 (6H, d, J = 6.8 Hz, CH₃ of *i*-Pr), 3.12 (1H, heptet, J = 6.8 Hz, CH of *i*-Pr), 3.76 (3H, s, MeO), 7.14 (1H, d, J = 9.0 Hz, benzene), 7.79 (1H, dd, J = 2.6, 9.0 Hz, benzene), 7.87 (1H, d, J = 2.6 Hz, benzene); FAB-MS *m*/*z*: 427 (M⁺+1).

5.1.24. Methyl 4-cyano-2-{[(5-isopropyl-4-methyl-1,3-thiazol-2-yl)amino]sulfonyl}benzoate (9r). 68% yield; ¹H NMR (DMSO- d_6) δ : 1.15 (6H, d, J = 6.9 Hz, CH₃ of *i*-Pr), 2.07 (3H, s, 4-Me), 3.11 (1H, heptet, J = 6.9 Hz, CH of *i*-Pr), 3.80 (3H, s, CH₃ of COOMe), 7.78 (1H, d, J = 7.8 Hz, benzene), 8.14 (1H, dd, J = 1.4, 7.8 Hz, benzene), 8.28 (1H, d, J = 1.4 Hz, benzene), 12.59 (1H, br s, NH); FAB-MS m/z: 380 (M⁺+1).

5.1.25. *N*-(5-*tert*-Butyl-4-methyl-1,3-thiazol-2-yl)benzenesulfonamide (9s). 61% yield; ¹H NMR (DMSO- d_6) δ : 1.28 (9H, s, CH₃ of *t*-Bu), 2.14 (3H, s, 4-Me), 7.54 (3H, m, benzene), 7.78 (2H, m, benzene), 12.32 (1H, br s, NH); FAB-MS *m*/*z*: 311 (M⁺+1).

N-(5-tert-Butyl-3,4-dimethyl-1,3-thiazol-2(3H)-5.1.26. ylidene)-2-nitrobenzenesulfonamide (10a). To a solution of 9b (10.89 g, 30.6 mmol) in tetrahydrofuran (100 mL) was added sodium hydride (60% dispersion in mineral oil: 1.47 g, 36.8 mmol) and iodomethane (5.7 mL, 91.8 mmol) under ice-bath cooling. The solution was warmed to room temperature and stirred for 12 h. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with brine, and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (chloroform) and recrystalized from methanol to give 10a (7.01 g, 62%) as a yellow powder. Mp 138-139 °C. ¹H NMR (CDCl₃) δ: 1.36 (9H, s, CH₃ of t-Bu), 2.28 (3H, s, 4-Me), 3.45 (3H, s, 3-Me), 7.61 (3H, m, benzene), 8.25 (1H, m, benzene); FAB-MS m/z: 370 (M^++1) . Anal. Calcd for $C_{15}H_{19}N_3O_4S_2$: C, 48.76; H, 5.18; N, 11.37; S, 17.36. Found: C, 48.76; H, 4.99; N, 11.38; S, 17.69.

The following compounds were obtained in the same manner.

5.1.27. *N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)ylidene)-2-chlorobenzenesulfonamide (10b). 86% yield; mp 153–155 °C (ethyl acetate–benzene).¹H NMR (CDCl₃) δ: 1.33 (9H, s, CH₃ of *t*-Bu), 2.27 (3H, s, 4-Me), 3.47 (3H, s, 3-Me), 7.46 (3H, m, benzene), 8.23 (1H, m, benzene); FAB-MS *m*/*z*: 359 (M⁺+1). Anal. Calcd for C₁₅H₁₉ClN₂O₂S₂: C, 50.20; H, 5.34; N, 7.81; S, 17.87; Cl, 9.88. Found: C, 50.15; H, 5.17; N, 7.82; S, 17.80; Cl, 9.75.

5.1.28. N-(5-tert-Butyl-3,4-dimethyl-1,3-thiazol-2(3H)ylidene)-3-chlorobenzenesulfonamide (10c). 90% yield; mp 138–139 °C (chloroform). ¹H NMR (DMSO- d_6) δ : 1.31 (9H, s, CH₃ of *t*-Bu), 2.28 (3H, s, 4-Me), 3.42 (3H, s, 3-Me), 7.57 (1H, dd, J = 7.8, 8.3 Hz, benzene), 7.66 (1H, ddd, J = 1.0, 2.0, 8.3 Hz, benzene), 7.79 (1H, br s, benzene), 7.80 (1H, br d, J = 7.8 Hz, benzene); FAB-MS m/z: 359 (M⁺+1). Anal. Calcd for C₁₅H₁₉ClN₂O₂S₂Cl: C, 50.20; H, 5.34; N, 7.81; S, 17.87; Cl, 9.88. Found: C, 50.01; H, 5.26; N, 7.76; S, 18.00; Cl, 10.04.

5.1.29. *N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)-ylidene)-4-nitrobenzenesulfonamide (10d). 50% yield; mp 184–185 °C (ethyl acetate–hexane). ¹H NMR (CDCl₃) δ : 1.37 (9H, s, CH₃ of *t*-Bu), 2.27 (3H, s, 4-Me), 3.46 (3H, s, 3-Me), 8.15 (2H, dt, *J* = 2.4, 8.8 Hz, benzene), 8.29 (2H, dt, *J* = 2.4, 8.8 Hz, benzene); FAB-MS *m/z*: 370 (M⁺+1). Anal. Calcd for C₁₅H₁₉N₃O₄S₂: C, 48.76; H, 5.18; N, 11.37; S, 17.36. Found: C, 48.70; H, 4.98; N, 11.51; S, 17.43.

5.1.30. *N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)ylidene)-4-chlorobenzenesulfonamide (10e). 50% yield; mp 157–158 °C (ethyl acetate–hexane). ¹H NMR (CDCl₃) δ : 1.36 (9H, s, CH₃ of *t*-Bu), 2.26 (3H, s, 4-Me), 3.43 (3H, s, 3-Me), 7.41 (2H, dt, *J* = 2.4, 8.8 Hz, benzene), 7.91 (2H, dt, *J* = 2.4, 8.8 Hz, benzene); FAB-MS *m*/*z*: 359 (M⁺+1). Anal. Calcd for C₁₅H₁₉ClN₂O₂S₂: C, 50.20; H, 5.34; N, 7.81; S, 17.87; Cl, 9.88. Found: C, 50.01; H, 5.10; N, 7.87; S, 17.86; Cl, 9.89.

5.1.31. *N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)ylidene)-2-methoxybenzenesulfonamide (10f). 20% yield; mp 197–198 °C (diethyl ether–hexane). ¹H NMR (DMSO- d_6) δ : 1.33 (9H, s, CH₃ of *t*-Bu), 2.28 (3H, s, 4-Me), 3.37 (3H, s, 3-Me), 3.73 (3H, s, MeO), 7.03 (1H, t, *J* = 7.9 Hz, benzene), 7.14 (1H, d, *J* = 8.3 Hz, benzene), 7.52 (1H, dt, *J* = 1.5, 7.9 Hz, benzene), 7.79 (1H, dd, *J* = 1.5 Hz, benzene); FAB-MS *m*/*z*: 355 (M⁺+1). Anal. Calcd for C₁₆H₂₂N₂O₃S₂·0.1CHCl₃: C, 52.77; H, 6.08; N, 7.65; S, 17.50; Cl, 2.90. Found: C, 52.84; H, 5.98; N, 7.59; S, 17.56; Cl, 2.50.

5.1.32. *N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)-ylidene)-3-methoxybenzenesulfonamide (10g). 76% yield; mp 192–193 °C (diethyl ether). ¹H NMR (DMSO-*d*₆) δ 1.31 (9H, s, CH₃ of *t*-Bu), 2.27 (3H, s, 4-Me), 3.40 (3H, s, 3-Me), 3.81 (3H, s, MeO), 7.14 (1H, ddd, *J* = 1.0, 2.5, 7.8 Hz, benzene), 7.29 (1H, t, *J* = 2.5 Hz, benzene), 7.39 (1H, br d, *J* = 7.8 Hz, benzene), 7.44 (1H, t, *J* = 7.8 Hz, benzene); FAB-MS *m*/*z*: 355 (M⁺+1). Anal. Calcd for C₁₆H₂₂N₂O₃S₂: C, 54.21; H, 6.26; N, 7.90; S, 18.09. Found: C, 54.31; H, 6.25; N, 7.86; S, 18.17.

5.1.33. *N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)-ylidene)-4-methoxybenzenesulfonamide (10h). 81% yield from 8a; mp 181–183 °C (ethyl acetate–hexane). ¹H NMR (CDCl₃) δ : 1.34 (9H, s, CH₃ of *t*-Bu), 2.24 (3H, s, 4-Me), 3.42 (3H, s, 3-Me), 3.87 (3H, s, MeO), 6.92 (2H, d, *J* = 8.6 Hz, benzene), 7.91 (2H, d, *J* = 8.6 Hz, benzene); FAB-MS *m*/*z*: 355 (M⁺+1). Anal. Calcd for C₁₆H₂₂N₂O₃S₂: C, 54.21; H, 6.26; N, 7.90; S, 18.09. Found: C, 54.23; H, 6.18; N, 7.89; S, 17.98.

5.1.34. *N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)ylidene)-5-chloro-2-nitrobenzenesulfonamide (10i). 49% yield; mp 204–205 °C (acetonitrile). ¹H NMR (DMSO d_6) δ : 1.33 (9H, s, CH₃ of *t*-Bu), 2.31 (3H, s, 4-Me), 3.45 (3H, s, 3-Me), 7.91 (1H, dd, J = 1.9, 8.3 Hz, benzene), 7.98 (1H, d, J = 8.3 Hz, benzene), 8.01 (1H, d, J = 1.9 Hz, benzene); FAB-MS *m*/*z*: 404 (M⁺+1). Anal. Calcd for C₁₅H₁₈ClN₃O₄S₂: C, 44.60; H, 4.49; N, 10.40; S, 15.88; Cl, 8.78. Found: C, 44.44; H, 4.41; N, 10.34; S, 16.03; Cl, 8.82.

5.1.35. *N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)ylidene)-3-chloro-2-methoxybenzenesulfonamide (10j). 60% yield from 8a; ¹H NMR (DMSO- d_6) δ : 1.22 (9H, s, CH₃ of *t*-Bu), 2.22 (3H, s, 4-Me), 3.35 (3H, s, 3-Me), 3.73 (3H, s, MeO), 7.38 (1H, dd, *J* = 7.8, 8.3 Hz, benzene), 7.77 (1H, dd, *J* = 1.5, 8.3 Hz, benzene), 7.88 (1H, dd, *J* = 1.5, 7.8 Hz, benzene); FAB-MS *m*/*z*: 388 (M⁺+1).

5.1.36. *N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)ylidene)-5-chloro-2-methoxybenzenesulfonamide (10k). 81% yield; ¹H NMR (DMSO-*d*₆) δ : 1.34 (9H, s, CH₃ of *t*-Bu), 2.29 (3H, s, 4-Me), 3.38 (3H, s, 3-Me), 3.73 (3H, s, MeO), 7.19 (1H, d, *J* = 8.8 Hz, benzene), 7.59 (1H, dd, *J* = 2.5, 8.8 Hz, benzene), 7.73 (1H, d, *J* = 2.5 Hz, benzene); FAB-MS *m*/*z*: 388 (M⁺+1).

5.1.37. 5-Chloro-2-cyano-*N*-(**5-isopropyl-3,4-dimethyl-1,3-thiazol-2(3***H***)-ylidene)benzenesulfonamide (10l). 63% yield; mp 180–182 °C. ¹H NMR (DMSO-***d***₆) \delta: 1.15 (6H, d,** *J* **= 6.9 Hz, CH₃ of** *i***-Pr), 2.19 (3H, s, 4-Me), 3.22 (1H, heptet,** *J* **= 6.9 Hz, CH of** *i***-Pr), 3.48 (3H, s, 3-Me), 7.88 (1H, dd,** *J* **= 1.9, 8.3 Hz, benzene), 8.02 (1H, d,** *J* **= 1.9 Hz, benzene), 8.10 (1H, d,** *J* **= 8.3 Hz, benzene); FAB-MS** *m***/***z***: 370 (M⁺+1). Anal. Calcd for C₁₅H₁₆ClN₃O₂S₂: C, 48.71; H, 4.36; N, 11.36; S, 17.34; Cl, 9.58. Found: C, 48.43; H, 4.24; N, 11.33; S, 17.45; Cl, 9.38.**

5.1.38. 5-Fluoro-2-cyano-*N***-(5-isopropyl-3,4-dimethyl-1,3-thiazol-2(3***H***)-ylidene)benzenesulfonamide** (10m). 81% yield; mp 184–186 °C (methanol–chloroform). ¹H NMR (DMSO-*d*₆) δ : 1.14 (6H, d, *J* = 6.8 Hz, CH₃ of *i*-Pr), 2.19 (3H, s, 4-Me), 3.20 (1H, heptet, *J* = 6.8 Hz, CH of *i*-Pr), 3.49 (3H, s, 3-Me), 7.66 (1H, dt, *J* = 2.9, 8.3 Hz, benzene), 7.85 (1H, dd, *J* = 2.5, 8.3 Hz, benzene), 8.16 (1H, dd, *J* = 5.3, 8.8 Hz, benzene); FAB-MS *m*/*z*: 354 (M⁺+1). Anal. Calcd for C₁₅H₁₆-FN₃O₂S₂: C, 50.97; H, 4.56; N, 11.89; S, 18.15; F, 5.38. Found: C, 51.05; H, 4.60; N, 11.76; S, 18.09; F, 5.63.

5.1.39. 5-Bromo-2-cyano-*N*-(**5-isopropyl-3,4-dimethyl-1,3-thiazol-2(3***H***)-ylidene)benzenesulfonamide (10n). 56% yield; mp 179–181 °C (isopropanol). ¹H NMR (DMSO-d_6) \delta: 1.15 (6H, d, J = 6.9 Hz, CH₃ of** *i***-Pr), 2.18 (3H, s, 4-Me), 3.22 (1H, heptet, J = 6.9 Hz, CH of** *i***-Pr), 3.48 (3H, s, 3-Me), 8.01 (2H, m, benzene), 8.14 (1H, d, J = 1.0 Hz, benzene); FAB-MS m/z: 414 (M⁺+1). Anal. Calcd for C₁₅H₁₆BrN₃O₂S₂: C, 43.48; H, 3.89; N, 10.14; S, 15.48; Br, 19.28. Found: C, 43.50; H, 3.70; N, 10.07; S, 15.51; Br, 18.91.**

5.1.40. 5-Chloro-*N*-(**4-chloro**-**5-isopropyl-3-methyl-1, 3-thiazol-2(3***H***)-ylidene)-2-methoxybenzenesulfonamide (10o**). 60% yield; ¹H NMR (DMSO-*d*₆) δ : 1.23 (6H, d, J = 6.8 Hz, CH₃ of *i*-Pr), 3.20 (1H, heptet, J = 6.8 Hz, CH of *i*-Pr), 3.43 (3H, s, 3-Me), 3.74 (3H, s, MeO), 7.22 (1H, d, J = 8.8 Hz, benzene), 7.63 (1H, dd, J = 2.5, 8.8 Hz, benzene), 7.76 (1H, d, J = 2.4 Hz, benzene); FAB-MS *m*/*z*: 395 (M⁺+1).

5.1.41. 5-Bromo-*N***-(4-chloro-5-isopropyl-3-methyl-1, 3-thiazol-2(3***H***)-ylidene)-2-methoxybenzenesulfonamide (10p**). 73% yield; ¹H NMR (CDCl₃) δ : 1.26 (6H, d, J = 6.8 Hz, CH₃ of *i*-Pr), 3.22 (1H, heptet, J = 6.8 Hz, CH of *i*-Pr), 3.51 (3H, s, 3-Me), 3.82 (3H, s, MeO), 6.85 (1H, d, J = 8.8 Hz, benzene), 7.55 (1H, dd, J = 2.4, 8.8 Hz, benzene), 8.16 (1H, d, J = 2.4 Hz, benzene); FAB-MS *m*/*z*: 439 (M⁺+1).

5.1.42. Methyl 4-cyano-2-{[(5-isopropyl-3,4-dimethyl-1,3-thiazol-2(3*H*)-ylidene)amino]sulfonyl}benzoate (10q). 37% yield; mp 224–226 °C (isopropanol–diethyl ether). ¹H NMR (DMSO- d_6) δ : 1.15 (6H, d, J = 6.9 Hz, CH₃ of *i*-Pr), 3.22 (1H, heptet, J = 6.9 Hz, CH of *i*-Pr), 2.19 (3H, s, 4-Me), 3.44 (3H, s, 3-Me), 3.81 (3H, s, MeO), 7.78 (1H, d, J = 7.8 Hz, benzene), 8.14 (1H, dd, J = 1.5, 7.8 Hz, benzene), 8.33 (1H, d, J = 1.5 Hz, benzene); FAB-MS m/z: 394 (M⁺+1). Anal. Calcd for C₁₇H₁₉N₃O₄S₂: C, 51.89; H, 4.87; N, 10.68; S, 16.30. Found: C, 51.65; H, 4.79; N, 10.72; S, 16.03.

5.1.43. *N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)-ylidene)benzenesulfonamide (10r). 95% yield; mp 188–189 °C (ethyl acetate–hexane).¹H NMR (DMSO- d_6) δ : 1.31 (9H, s, CH₃ of *t*-Bu), 2.26 (3H, s, 4-Me), 3.40 (3H, s, 3-Me), 7.54 (3H, m, benzene), 7.82 (2H, m, benzene); FAB-MS *m*/*z*: 325 (M⁺+1). Anal. Calcd for C₁₅H₂₀N₂O₂S₂: C, 55.53; H, 6.21; N, 8.63; S, 19.77. Found: C, 55.38; H, 6.32; N, 8.55; S, 19.79.

5.1.44. N-(5-tert-Butyl-3,4-dimethyl-1,3-thiazol-2(3H)ylidene)-2-hydroxybenzenesulfonamide (11a). Under argon atmosphere, boron tribromide (0.17 mL, 1.71 mmol) was added dropwise to a solution of 10f (200 mg, 0.57 mmol) in dichloromethane (20 mL) at -78 °C and stirred at the same temperature for 30 min. The mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate solution and extracted with chloroform. The organic layer was washed with brine, then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was recrystalized from methanol to give **11a** (167 mg, 86%) as a colorless crystals. Mp 201–202 °C. ¹H NMR (DMSO- d_6) δ : 1.31 (9H, s, CH₃ of t-Bu), 2.27 (3H, s, 4-Me), 3.39 (3H, s, 3-Me), 6.93 (1H, dd, J = 2.5, 7.8 Hz, benzene), 7.21 (1H, m, benzene), 7.23 (1H, br d, J = 7.8 Hz, benzene), 7.31 (1H, t, J = 8.3 Hz, benzene), 9.95 (1H, s, OH); FAB-MS m/z: 341 (M⁺+1). Anal. Calcd for C₁₅H₂₀N₂O₃₋ S2.0.2H2O: C, 52.36; H, 5.98; N, 8.14; S, 18.64. Found: C, 52.45; H, 5.83; N, 7.94; S, 18.34.

The following compounds were obtained in the same manner.

5.1.45. *N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)ylidene)-3-hydroxybenzenesulfonamide (11b). 87% yield; mp 145–146 °C (diethyl ether–hexane). ¹H NMR (DMSO- d_6) δ : 1.32 (9H, s, CH₃ of *t*-Bu), 2.27 (3H, s, 4-Me), 3.38 (3H, s, 3-Me), 6.88 (2H, m, benzene), 7.36 (1H, dt, *J* = 1.4, 7.3 Hz, benzene), 7.70 (1H, dd, *J* = 1.4, 7.8 Hz, benzene), 10.12 (1H, s, OH); FAB-MS *m*/*z*: 341 (M⁺+1). Anal. Calcd for C₁₅H₂₀N₂O₃S₂: C, 52.92; H, 5.92; N, 8.23; S, 18.84. Found: C, 52.78; H, 5.70; N, 8.16; S, 18.84.

5.1.46. *N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)-ylidene)-4-hydroxybenzenesulfonamide (11c). 60% yield; mp 234–236 °C (ethyl acetate–hexane). ¹H NMR (DMSO- d_6) δ : 1.31 (9H, s, CH₃ of *t*-Bu), 1.99 (3H, s, 4-Me), 3.37 (3H, s, 3-Me), 6.84 (2H, d, J = 8.6 Hz, benzene), 7.63 (1H, d, J = 8.6 Hz, benzene), 10.22 (1H, br s, OH); FAB-MS *m*/*z*: 341 (M⁺+1). Anal. Calcd for C₁₅H₂₀N₂O₃S₂: C, 52.92; H, 5.92; N, 8.23; S, 18.84. Found: C, 52.68; H, 5.70; N, 8.02; S, 18.45.

5.1.47. *N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)-ylidene)-3-chloro-2-hydroxybenzenesulfonamide (11d). 64% yield; mp 147–148 °C (methanol). ¹H NMR (DMSO- d_6) δ : 1.32 (9H, s, CH₃ of *t*-Bu), 2.29 (3H, s, 4-Me), 3.41 (3H, s, 3-Me), 6.98 (1H, t, *J* = 7.8 Hz, benzene), 7.59 (1H, dd, *J* = 1.5, 7.8 Hz, benzene), 7.69 (1H, dd, *J* = 1.5, 7.8 Hz, benzene), 9.93 (1H, br s, OH); FAB-MS *m*/*z*: 375 (M⁺+1). Anal. Calcd for C₁₅H₁₉ClN₂O₃S₂: C, 48.05; H, 5.11; N, 7.47; S, 17.11; Cl, 9.46. Found: C, 47.94; H, 5.07; N, 7.32; S, 17.16; Cl, 9.38.

5.1.48. *N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)ylidene)-5-chloro-2-hydroxybenzenesulfonamide (11e). 71% yield; mp 147–149 °C (ethyl acetate–hexane). ¹H NMR (DMSO- d_6) δ : 1.32 (9H, s, CH₃ of *t*-Bu), 2.28 (3H, s, 4-Me), 3.38 (3H, s, 3-Me), 6.92 (1H, d, J = 8.7 Hz, benzene), 7.41 (1H, dd, J = 3.0, 8.7 Hz, benzene), 7.65 (1H, d, J = 3.0 Hz, benzene), 10.56 (1H, br s, OH); FAB-MS *m*/*z*: 375 (M⁺+1). Anal. Calcd for C₁₅H₁₉CIN₂O₃S₂: C, 48.05; H, 5.11; N, 7.47; S, 17.11; Cl, 9.46. Found: C, 48.04; H, 5.09; N, 7.61; S, 17.24; Cl, 9.23.

5.1.49. 5-Chloro-*N***-(4-chloro-5-isopropyl-3-methyl-1, 3-thiazol-2(3***H***)-ylidene)-2-hydroxybenzenesulfonamide (11f).** 53% yield; mp 132–133 °C (diethyl ether). ¹H NMR (DMSO- d_6) δ : 1.21 (6H, d, J = 6.8 Hz, CH₃ of *i*-Pr), 3.18 (1H, heptet, J = 6.8 Hz, CH of *i*-Pr), 3.43 (3H, s, 3-Me), 6.88 (1H, d, J = 8.8 Hz, benzene), 7.56 (1H, dd, J = 2.4, 8.8 Hz, benzene), 7.79 (1H, d, J = 2.4 Hz, benzene), 10.86 (1H, br s, OH); FAB-MS *m*/*z*: 381 (M⁺+1). Anal. Calcd for C₁₃H₁₄Cl₂N₂O₃S₂: C, 40.95; H, 3.70; N, 7.35; S, 16.82; Cl, 18.60. Found: C, 40.94; H, 3.49; N, 7.36; S, 16.75; Cl, 18.39.

5.1.50. 5-Bromo-*N*-(4-chloro-5-isopropyl-3-methyl-1, 3-thiazol-2(3*H*)-ylidene)-2-hydroxybenzenesulfonamide (11g). 41% yield; mp 135–137 °C (diethyl ether). ¹H

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NMR (DMSO- d_6) δ : 1.21 (6H, d, J = 6.8 Hz, CH₃ of *i*-Pr), 3.18 (1H, heptet, J = 6.8 Hz, CH of *i*-Pr), 3.43 (3H, s, 3-Me), 6.93 (1H, d, J = 8.8 Hz, benzene), 7.44 (1H, dd, J = 2.9, 8.8 Hz, benzene), 7.67 (1H, d, J = 2.9 Hz, benzene), 10.85 (1H, br s, OH); FAB-MS *m*/*z*: 425 (M⁺+1). Anal. Calcd for C₁₃H₁₄ClBrN₂O₃S₂: C, 36.67; H, 3.31; N, 6.58; S, 15.06; Cl, 8.33; Br, 18.77. Found: C, 36.67; H, 3.36; N, 6.54; S, 15.04; Cl, 8.49; Br, 18.53.

5.1.51. 2-Amino-N-(5-tert-butyl-3,4-dimethyl-1,3-thiazol-2(3H)-ylidene)-5-chlorobenzenesulfonamide (12). To a suspension of 10i (960 mg, 2.38 mol) in ethanol (10 mL) and tetrahydrofuran (30 mL) was added 10% palladium-charcoal. The reaction mixture was stirred at room temperature for 1.5 h under hydrogen atmosphere. The suspension was filtered through the Celite pad and evaporated. The residue was purified with recrystalization from isopropanol-diethyl ether to give **12** (548 mg, 62%) as a brown powder. Mp 163–164 °C. ¹H NMR (DMSO- d_6) δ : 1.31 (9H, s, CH₃ of t-Bu), 2.27 (3H, s, 4-Me), 3.41 (3H, s, 3-Me), 5.94 (2H, br s, NH2), 6.79 (1H, d, J = 8.8 Hz, benzene), 7.24 (1H, dd, J = 2.4, 8.8 Hz, benzene), 7.49 (1H, d, J = 2.4 Hz, benzene); FAB-MS m/z: 374 (M⁺+1). Calcd for C₁₅H₂₀ClN₃O₂S₂: C, 48.18; H, 5.39; N, 11.24; S, 17.15; Cl, 9.48. Found: C, 48.43; H, 5.36; N, 11.10; S, 17.05; Cl, 9.19.

5.1.52. N-(2-{[(5-tert-Butyl-3,4-dimethyl-1,3-thiazol-2(3H)-ylidene)amino|sulfonyl}-4-chlorophenyl)acetamide (13). A solution of 12 (330 mg, 0.88 mmol), N,N-dimethylaminopyridine (110 mg, 0.88 mmol) and acetyl chloride (0.13 mL, 1.76 mmol) in pyridine (7 mL) was stirred at room temperature for 5 h. The reaction mixture was evaporated and diluted with ethyl acetate. The solution was washed with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate solution and brine, then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (chloroform-methanol) and recrystalized from acetonitrile to give 13 (92 mg, 25%) as a colorless powder. Mp 194–195 °C. ¹H NMR (DMSO- d_6) δ : 1.28 (9H, s, CH₃ of t-Bu), 2.12 (3H, s, 4-Me), 2.28 (3H, s, CH_3 of Ac), 3.41 (3H, s, 3-Me), 7.63 (1H, dd, J = 2.5, 8.8 Hz, benzene), 7.81 (1H, d, J = 2.5 Hz, benzene), 8.11 (1H, d, J = 8.8 Hz, benzene), 9.24 (1H, br s, NH); FAB-MS m/z: 416 (M⁺+1). Calcd for C₁₇H₂₂ClN₃O₃S₂: C, 49.09; H, 5.23; N, 10.10; S, 15.42; Cl, 8.52. Found: C, 49.10; H, 5.25; N, 10.06; S, 15.49; Cl, 8.46.

5.1.53. *N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)-ylidene)-5-chloro-2-[(methylsulfonyl)amino]benzenesulfonamide (14). A solution of 12 (200 mg, 0.54 mmol), triethylamine (0.15 mg, 1.08 mmol), and methanesulfonyl chloride (0.062 mL, 0.83 mmol) in tetrahydrofuran (4 mL) was stirred at room temperature for 1 h. The reaction mixture was evaporated and diluted with ethyl acetate. The solution was washed with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate solution and brine, then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate-toluene) and recrystalized from methanol to give **14** (135 mg, 56%) as a colorless powder. Mp 165–166 °C. ¹H NMR (DMSO-*d*₆) δ : 1.32 (9H, s, CH₃ of *t*-Bu), 2.29 (3H, s, 4-Me), 3.24 (3H, s, CH₃ of Ms), 3.44 (3H, s, 3-Me), 7.62 (1H, d, J = 8.8 Hz, benzene), 7.69 (1H, dd, J = 2.4, 8.8 Hz, benzene), 7.82 (1H, d, J = 2.4 Hz, benzene), 8.68 (1H, br s, NH); FAB-MS *m*/*z*: 452 (M⁺+1). Calcd for C₁₆H₂₂ClN₃O₄S₃: C, 42.51; H, 4.91; N, 9.30; S, 21.28; Cl, 7.84. Found: C, 42.51; H, 4.87; N, 9.29; S, 21.41; Cl, 7.66.

5.1.54. 2-{[(5-tert-Butyl-3,4-dimethyl-1,3-thiazol-2(3H)ylidene)amino|sulfonyl}-4-chlorophenyl trifluoromethanesulfonate (15a). A solution of 11e (1.00 g, 2.67 mmol), 2,6-lutidine (0.47 mL, 4.01 mmol), and N,N-dimethylaminopyridine (33 mg, 0.27 mmol) in dichloromethane (15 mL) was added trifluoromethanesulfonic anhydride (0.68 mL, 4.01 mmol) under ice-bath cooling. The solution was stirred at the same temperature for 30 min. The reaction mixture was poured into water and extracted with chloroform. The organic layer was washed with saturated aqueous potassium hydrogen sulfate and brine, then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was recrystalized from diethyl ether to give 15a (877 mg, 64%) as a colorless powder. This crude product was used for next steps without further purification.

5.1.55. 4-Chloro-2-{[(4-chloro-5-isopropyl-3-methyl-1,3-thiazol-2(3*H*)-ylidene)amino]sulfonyl}phenyl trifluoromethanesulfonate (15b). Compound 15b was obtained from 11f in the same manner as described in the synthesis of 15a quantitative. ¹H NMR (DMSO- d_6) δ : 1.18 (6H, d, J = 6.8 Hz, CH₃ of *i*-Pr), 3.17 (1H, heptet, J = 6.8 Hz, CH of *i*-Pr), 3.48 (3H, s, 3-Me), 7.60 (1H, s, J = 8.8 Hz, benzene), 7.88 (1H, dd, J = 2.4, 8.8 Hz, benzene), 8.01 (1H, d, J = 2.4 Hz, benzene); FAB-MS m/z: 513 (M⁺+1).

5.1.56. Methyl 2-{[(5-tert-butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)-ylidene)amino|sulfonyl}-4-chlorobenzoate (16). Under argon atmosphere, **15a** (25.4 g, 50.1 mmol) was dissolved in N,N-dimethylformamide (280 mL) and methanol (140 mL). Triethylamine (12.9 mL, 92.6 1,3-bis(diphenylphosphino)propane (1.74 g, mmol). 4.2 mmol), palladium acetate (0.95 g, 4.2 mmol) was added and carbon monoxide gas was bubbled. The reaction mixture was stirred at 70 $^{\circ}\mathrm{C}$ for 2.5 h under carbon monoxide atmosphere. The mixture was evaporated and diluted with ethyl acetate. The organic layer was washed with 1 M hydrochloric acid and brine, then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetatetoluene) and recrystalized from isopropanol-diethyl ether to give 16 (7.32 g, 42%) as a colorless powder. Mp 142–143 °C. ¹H NMR (DMSO- d_6) δ : 1.32 (9H, s, CH₃ of t-Bu), 2.30 (3H, s, 4-Me), 3.43 (3H, s, 3-Me), 3.78 (3H, s, CH₃ of COOMe), 7.61 (d, J = 8.3 Hz, benzene), 7.75 (1H, dd, J = 2.0, 8.3 Hz, benzene), 7.91 (1H,

d, J = 2.0 Hz, benzene); FAB-MS m/z: 417 (M⁺+1). Calcd for C₁₇H₂₁ClN₂O₄S₂: C, 48.97; H, 5.08; N, 6.72; S, 15.38; Cl, 8.50. Found: C, 49.02; H, 4.95; N, 6.78; S, 15.43; Cl, 8.47.

5.1.57. 2-{[(5-tert-Butyl-3,4-dimethyl-1,3-thiazol-2(3H)ylidene)amino|sulfonyl}-4-chlorobenzamide (17a). To a solution of 16 (100 mg, 0.248 mmol) in N,N-dimethylformamide (2 mL), 1-hydroxybenzotriazole (50 mg, 1-[3-(dimethylamino)propyl]-3-ethylcar-0.372 mmol), bodiimide hydrochloride (WSC·HCl, 71 mg, 0.372 mmol), *N*,*N*-diisopropylethylamine (0.17 mL, ammonium chloride 0.992 mmol), and (27 mg, 0.496 mmol) was added. The solution was stirred at room temperature for 2.5 h. The reaction mixture was poured into water and extracted with chloroform. The organic layer was washed with 1 M hydrochloric acid and brine, then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (methanol-chloroform) and recrystalized from diethyl ether to give 17a (71 mg, 71%) as a colorless powder. Mp 196–198 °C. ¹H NMR (DMSO-*d*₆) δ: 1.31 (9H, s, CH₃ of t-Bu), 2.28 (3H, s, 4-Me), 3.42 (3H, s, 3-Me), 7.47 (1H, d, J = 8.3 Hz, benzene), 7.61 (2H, br s, NH₂), 7.68 (1H, dd, J = 2.0, 8.3 Hz, benzene), 7.87 (1H, d, J = 2.0 Hz, benzene); FAB-MS m/z: 402 (M^++1) . Anal. Calcd for $C_{16}H_{20}ClN_3O_3S_2$: C, 47.81; H, 5.02; N, 10.45; S, 15.96; Cl, 8.82. Found: C, 47.72; H, 4.78; N, 10.42; S, 15.82; Cl, 8.91.

5.1.58. 4-Cyano-2-{[(5-isopropyl-3,4-dimethyl-1,3-thiazol-2(3*H*)-ylidene)amino]sulfonyl}benzamide (17b). Compound 17b was obtained from 10q in the same manner as described in the synthesis of 17a. 68% yield. ¹H NMR (DMSO- d_6) δ : 1.15 (6H, d, J = 6.8 Hz, CH₃ of *i*-Pr), 2.17 (3H, s, 4-Me), 3.21 (1H, heptet, J = 6.8 Hz, CH of *i*-Pr), 3.43 (3H, s, 3-Me), 7.61 (1H, d, J = 8.3 Hz, benzene), 7.72 (2H, br d, J = 6.3 Hz, NH₂), 8.02 (1H, dd, J = 1.9 Hz, benzene), 8.27 (1H, d, J = 1.9 Hz, benzene); FAB-MS *m*/*z*: 379 (M⁺+1).

5.1.59. 2,5-Dicyano-N-(5-isopropyl-3,4-dimethyl-1,3-thiazol-2(3H)-ylidene)benzenesulfonamide (18b). Phosphorous oxychloride (0.3 mL, 3.3 mmol) and N,Ndimethylformamide (50 µL, 0.66 mmol) was added to a solution of 17b (250 mg, 0.66 mmol) in chloroform (30 mL). The reaction mixture was refluxed for 24 h. The reaction mixture was poured into ice-water and extracted with chloroform. The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (methanol-chloroform) to give **18b** (52 mg, 22%) as a yellow powder. Mp 222–224 °C. ¹H NMR (DMSO- d_6) δ : 1.15 (6H, d, J = 6.8 Hz, CH₃ of *i*-Pr), 2.19 (3H, s, 4-Me), 3.22 (1H, heptet, J = 6.8 Hz, CH of *i*-Pr), 3.49 (3H, s, 3-Me), 8.28 (2H, m, benzene), 8.42 (1H, br s, benzene); FAB-MS m/z : 361 (M⁺+1). Anal. Calcd for C₁₆H₁₆N₄O₂S₂: C, 53.31; H, 4.47; N, 15.54; S, 17.79. Found: C, 53.15; H, 4.39; N, 15.70; S, 17.74.

5.1.60. *N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)ylidene)-5-chloro-2-cyanobenzenesulfonamide (18a). Compound 18a was obtained from 17a in the same manner as described in the synthesis of 18b. 67% yield; mp 160–162 °C. ¹H NMR (DMSO- d_6) δ : 1.32 (9H, s, CH₃ of *t*-Bu), 2.30 (3H, s, 4-Me), 3.49 (3H, s, 3-Me), 7.88 (1H, dd, J = 2.0, 8.3 Hz, benzene), 8.02 (1H, d, J = 2.0 Hz, benzene), 8.09 (1H, d, J = 8.3 Hz, benzene); FAB-MS *m*/*z*: 384 (M⁺+1). Anal. Calcd for C₁₆H₁₈ClN₃O₂S₂: C, 50.06; H, 4.73; N, 10.95; S, 16.70; Cl, 9.23. Found: C, 49.84; H, 4.63; N, 10.75; S, 16.67; Cl, 9.15.

5-Chloro-N-(4-chloro-5-isopropyl-3-methyl-1,3-5.1.61. thiazol-2(3*H*)-ylidene)-2-cyanobenzenesulfonamide (19). Under argon atmosphere, 15b (3.64 g, 7.1 mmol) was dissolved in N,N-dimethylformamide (100 mL) and palladium tris(dibenzylideneacetone)dipalladium (408 mg, 0.71 mmol), 1,1'-bis(diphenylphosphino)ferrocene (787 mg, 14.2 mmol), zinc powder (56 mg, 0.85 mmol), and zinc(II) cyanide (500 mg, 4.3 mmol) was added. The reaction mixture was stirred at 130 °C for 2.5 h under argon atmosphere. The mixture was evaporated and diluted with ethyl acetate. The organic layer was washed with 2 M aqueous ammonia solution, water, and brine, then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate-toluene) and recrystalized from isopropanol to give 19 (1.38 g, 50%) as a pale yellow powder. Mp 181–182 °C (isopropanol). ¹H NMR (DMSO- d_6) δ : 1.20 (6H, d, J = 6.8 Hz, CH₃ of *i*-Pr), 3.18 (1H, heptet, J = 6.8 Hz, CH of *i*-Pr), 3.32 (3H,s, 3-Me), 7.92 (1H, dd, J = 1.9, 8.3 Hz, benzene), 8.04 (1H, d, J = 1.9 Hz, benzene), 8.12 (1H, d, J = 8.3 Hz, benzene); FAB-MS m/z: 390 (M⁺+1). Anal. Calcd for C₁₄H₁₃Cl₂N₃O₂S₂: C, 43.08; H, 3.36; N, 10.77; S, 16.43; Cl, 18.17. Found: C, 43.03; H, 3.23; N, 10.70; S, 16.34; Cl, 18.21.

5.1.62. *N*-(4-Chloro-5-isopropyl-3-methyl-1,3-thiazol-2(*3H*)-ylidene)-2,5-dicyanobenzenesulfonamide (20). Compound 20 was obtained from 15b in the same manner as described in the synthesis of 19 with 1.6 mol equiv of Zn(CN)₂. 60% yield. Mp 205–207 °C (isopropanol). ¹H NMR (CDCl₃): 1.27 (6H, d, J = 6.8 Hz, CH₃ of *i*-Pr), 3.22 (1H, heptet, J = 6.8 Hz, CH of *i*-Pr), 3.60 (3H, s, 3-Me), 7.87 (1H, dd, J = 1.9, 8.3 Hz, benzene), 7.92 (1H, d, J = 8.3 Hz, benzene), 8.47 (1H, d, J = 1.9 Hz, benzene); FAB-MS *m*/*z*: 381 (M⁺+1). Anal. Calcd for C₁₅H₁₃ClN₄O₂S₂: C, 47.30; H, 3.44; N, 14.71; S, 16.84; Cl, 9.31. Found: 47.15; H, 3.52; N, 15.00; S, 16.65; Cl, 9.35.

5.2. Pharmacology

5.2.1. In vitro RT inhibition assay. A expression plasmide, pG280, encoding HIV-1 RT proteins as LacZ fusion proteins were used for the expression of the WT RT and mutated RTs.¹² The single amino acid-substituted RTs (K103N RT and Y181C RT) were constructed using pG280 from a QuikchangeTM Site-Directed Mutagenesis Kit (Stratagene, La Jolla, CA). Recombinant

RT enzymes were expressed in *E. coli.* UTX81 and purified by the scheme described by Saitoh et al.¹² In vitro RT assays were conducted according to the previously described method with the following modifi cations.¹³ Test compounds and 0.01 unit of recombinant HIV-1 RT (either wild type or mutant) were incubated in a reaction mixture (50 µL), containing 50 mM Tris– HCl (pH 8.4), 100 mM KCl, 10 mM MgCl₂, 0.1% Triton X-100, 2 mM dithiothreitol, 0.01 OD₂₆₀ of poly(rC)/oligo(dG)_{12–18}, and 1 µCi of [1',2'-³H]dGTP (33 Ci/mmol) at 37 °C for 1 h. The reaction was stopped with 200 µL of 5% cold trichloroacetic acid. The precipitated materials were analyzed for radio activity using a scintillation counter (Aloka Co., Ltd., Tokyo, Japan).

5.2.2. Cells and viruses. MT-4 cells¹⁴ and HIV-1_{IIIB} were used for the anti-HIV-1 assays. MT-4 cells were grown and maintained in RPMI-1640 medium supplemented with 10% heat-inactivated fetal bovine serum (FBS), penicillin G (100 units/mL), and gentamicin (20 mg/mL). MT-4 cells and HIV-1_{IIIB} were obtained from Rational Drug Design Laboratories (Fukushima, Japan).

5.2.3. Anti-HIV-1 assay. Determination of the antiviral activity of the test compounds against HIV-1_{IIIB} replication was based on the inhibition of virus-induced cytopathicity in MT-4 cells. Briefly, MT-4 cells were suspended in culture medium at 1×10^5 cells/mL and infected with virus at a multiplicity of infection (MOI) of 0.02. Immediately after virus infection, the cell suspension (100 µL) was brought into each well of a flatbottomed microtiter tray containing various concentrations of the test compounds. After a 5-day incubation at 37 °C, the number of viable cells was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method.¹⁵ The HTS of our compound library was also performed using the MTT assay against HIV-1_{IIIB-R}.¹⁴ The anti-HIV-1 activity and cytotoxicity of test compounds were expressed as EC_{50} and CC_{50} , respectively. EC_{50} is the concentration of a test compound that was able to achieve 50%protection of MT-4 cells from HIV-1 induced CPE. CC_{50} is the concentration of a test compound that reduced viable cell number by 50% in mock-infected cells. The therapeutic index (TI) is the ratio of CC_{50} to EC₅₀.

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