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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

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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, **10l** and **18b** (YM-228855), combinations of 2-cyanophenyl and 4-methyl-5-isopropylthiazole moieties, showed extremely potent anti-HIV-1 activity. The EC_{50} values of **101** and **18b** were 0.0017 and 0.0018 μM, 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 IC_{50} values of 0.043 and 0.013 μM, respectively.

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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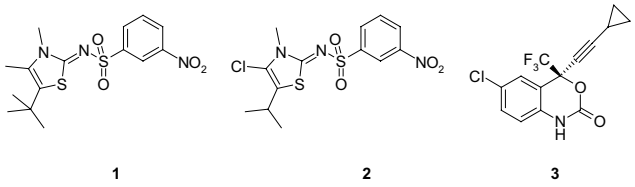


Figure 1. Structures of thiazolidenebenzenesulfonamide derivatives (**1**, **2**) and efavirenz (**3**).

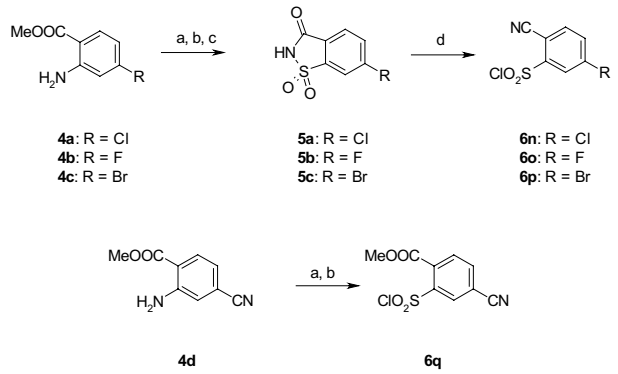
carrying the amino acid mutations surrounding the NNRTI binding pocket.

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 PCl_5 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 derivatives (**10f–h**, **j**, **k**, **o**, **p**) using BBr_3 provided the corresponding phenol analogues (**11a–g**).



Scheme 1. Reagents and conditions: (a) $NaNO_2$, HCl/AcOH; (b) SO_2, CuCl, $CuCl_2$/AcOH–H_2O; (c) NH_3 aq; (d) PCl_5.

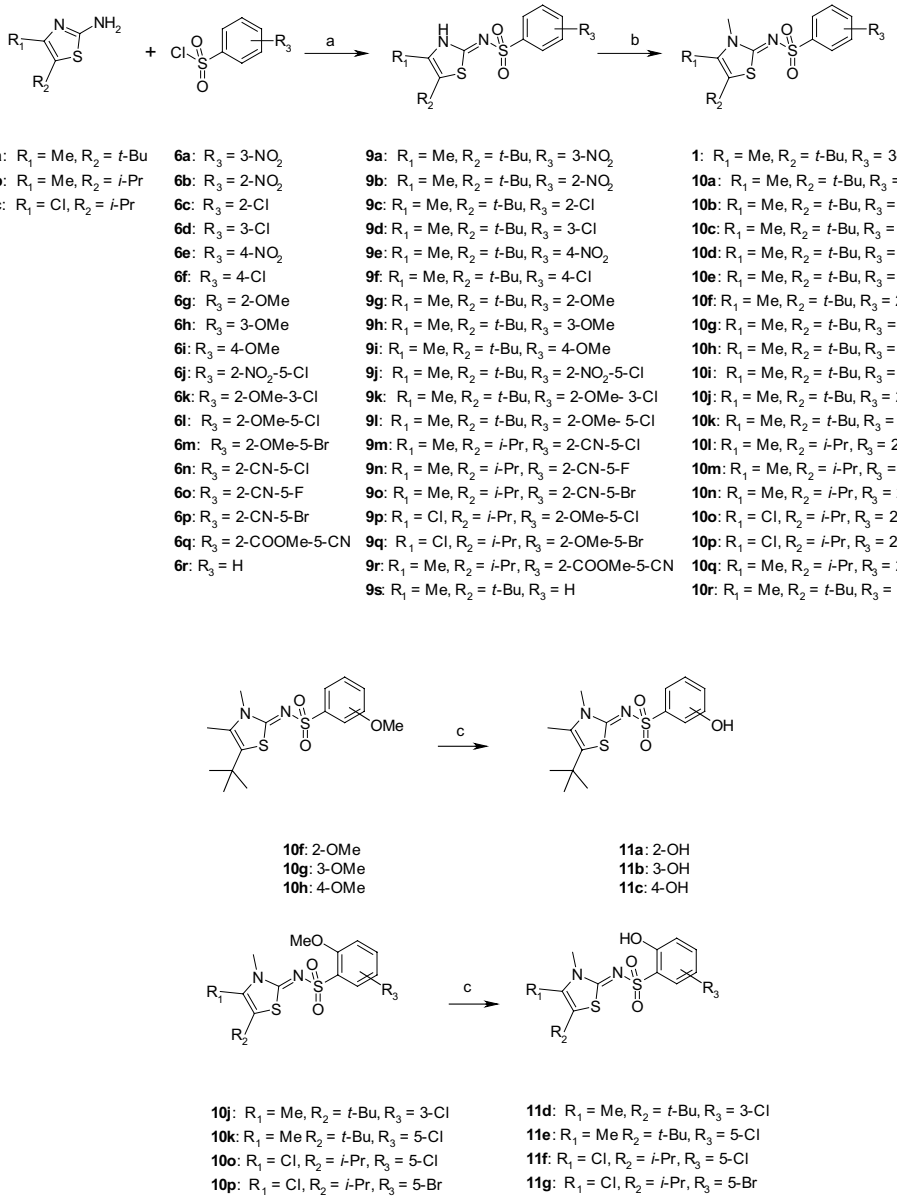
As shown in Scheme 3, the nitro compound **10i** was converted into aniline **12** by catalytic hydrogenation. Aniline **12** was reacted with acetyl chloride or methanesulfonyl chloride to provide acetamide **13** and methanesulfonamide **14**, respectively. The triflates **15a** and **15b** were prepared from the corresponding phenol analogues (**11e**,**f**). A palladium-catalyzed carbon monoxide insertion with triflate **15a** afforded the methoxycarbonyl 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 4-position 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



8a: R_1 = Me, R_2 = *t*-Bu
8b: R_1 = Me, R_2 = *i*-Pr
8c: R_1 = Cl, R_2 = *i*-Pr

6a: R_3 = 3-NO_2
6b: R_3 = 2-NO_2
6c: R_3 = 2-Cl
6d: R_3 = 3-Cl
6e: R_3 = 4-NO_2
6f: R_3 = 4-Cl
6g: R_3 = 2-OMe
6h: R_3 = 3-OMe
6i: R_3 = 4-OMe
6j: R_3 = 2-NO_2-5-Cl
6k: R_3 = 2-OMe-3-Cl
6l: R_3 = 2-OMe-5-Cl
6m: R_3 = 2-OMe-5-Br
6n: R_3 = 2-CN-5-Cl
6o: R_3 = 2-CN-5-F
6p: R_3 = 2-CN-5-Br
6q: R_3 = 2-COOMe-5-CN
6r: R_3 = H

9a: R_1 = Me, R_2 = *t*-Bu, R_3 = 3-NO_2
9b: R_1 = Me, R_2 = *t*-Bu, R_3 = 2-NO_2
9c: R_1 = Me, R_2 = *t*-Bu, R_3 = 2-Cl
9d: R_1 = Me, R_2 = *t*-Bu, R_3 = 3-Cl
9e: R_1 = Me, R_2 = *t*-Bu, R_3 = 4-NO_2
9f: R_1 = Me, R_2 = *t*-Bu, R_3 = 4-Cl
9g: R_1 = Me, R_2 = *t*-Bu, R_3 = 2-OMe
9h: R_1 = Me, R_2 = *t*-Bu, R_3 = 3-OMe
9i: R_1 = Me, R_2 = *t*-Bu, R_3 = 4-OMe
9j: R_1 = Me, R_2 = *t*-Bu, R_3 = 2-NO_2-5-Cl
9k: R_1 = Me, R_2 = *t*-Bu, R_3 = 2-OMe- 3-Cl
9l: R_1 = Me, R_2 = *t*-Bu, R_3 = 2-OMe- 5-Cl
9m: R_1 = Me, R_2 = *i*-Pr, R_3 = 2-CN-5-Cl
9n: R_1 = Me, R_2 = *i*-Pr, R_3 = 2-CN-5-F
9o: R_1 = Me, R_2 = *i*-Pr, R_3 = 2-CN-5-Br
9p: R_1 = Cl, R_2 = *i*-Pr, R_3 = 2-OMe-5-Cl
9q: R_1 = Cl, R_2 = *i*-Pr, R_3 = 2-OMe-5-Br
9r: R_1 = Me, R_2 = *i*-Pr, R_3 = 2-COOMe-5-CN
9s: R_1 = Me, R_2 = *t*-Bu, R_3 = H

1: R_1 = Me, R_2 = *t*-Bu, R_3 = 3-NO_2
10a: R_1 = Me, R_2 = *t*-Bu, R_3 = 2-NO_2
10b: R_1 = Me, R_2 = *t*-Bu, R_3 = 2-Cl
10c: R_1 = Me, R_2 = *t*-Bu, R_3 = 3-Cl
10d: R_1 = Me, R_2 = *t*-Bu, R_3 = 4-NO_2
10e: R_1 = Me, R_2 = *t*-Bu, R_3 = 4-Cl
10f: R_1 = Me, R_2 = *t*-Bu, R_3 = 2-OMe
10g: R_1 = Me, R_2 = *t*-Bu, R_3 = 3-OMe
10h: R_1 = Me, R_2 = *t*-Bu, R_3 = 4-OMe
10i: R_1 = Me, R_2 = *t*-Bu, R_3 = 2-NO_2-5-Cl
10j: R_1 = Me, R_2 = *t*-Bu, R_3 = 2-OMe-3-Cl
10k: R_1 = Me, R_2 = *t*-Bu, R_3 = 2-OMe- 5-Cl
10l: R_1 = Me, R_2 = *i*-Pr, R_3 = 2-CN-5-Cl
10m: R_1 = Me, R_2 = *i*-Pr, R_3 = 2-CN-5-F
10n: R_1 = Me, R_2 = *i*-Pr, R_3 = 2-CN-5-Br
10o: R_1 = Cl, R_2 = *i*-Pr, R_3 = 2-OMe-5-Cl
10p: R_1 = Cl, R_2 = *i*-Pr, R_3 = 2-OMe-5-Br
10q: R_1 = Me, R_2 = *i*-Pr, R_3 = 2-COOMe-5-CN
10r: R_1 = Me, R_2 = *t*-Bu, R_3 = H

10f: 2-OMe
10g: 3-OMe
10h: 4-OMe

11a: 2-OH
11b: 3-OH
11c: 4-OH

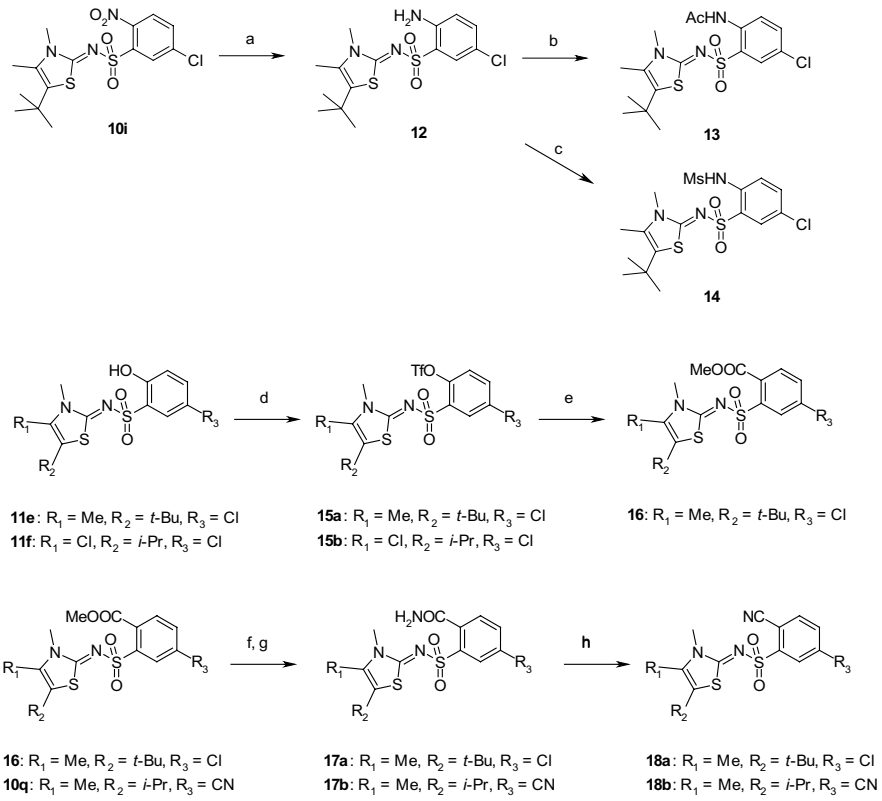
10j: R_1 = Me, R_2 = *t*-Bu, R_3 = 3-Cl
10k: R_1 = Me R_2 = *t*-Bu, R_3 = 5-Cl
10o: R_1 = Cl, R_2 = *i*-Pr, R_3 = 5-Cl
10p: R_1 = Cl, R_2 = *i*-Pr, R_3 = 5-Br

11d: R_1 = Me, R_2 = *t*-Bu, R_3 = 3-Cl
11e: R_1 = Me R_2 = *t*-Bu, R_3 = 5-Cl
11f: R_1 = Cl, R_2 = *i*-Pr, R_3 = 5-Cl
11g: R_1 = Cl, R_2 = *i*-Pr, R_3 = 5-Br

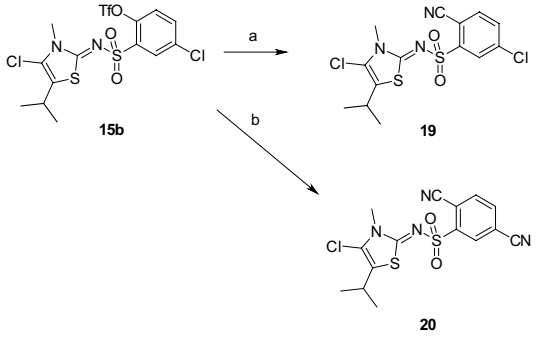
Scheme 2. Reagents and conditions: (a) Py; (b) MeI, NaH/THF; (c) BBr_3/CH_2Cl_2.

nitro and chloro substituents also resulted in more potent anti-HIV-1 activity, and compounds **1** and **10c** showed anti-HIV-1 activity with EC_{50} values of 0.085 and 0.20 μM, 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 IC_{50} value than that of the unsubstituted compound **10r**. Compound **11a** also exhibited moderate anti-HIV-1 activity (EC_{50} = 2.3 μM). 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 μM), 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 μM) 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) H_2, Pd–C/EtOH–THF; (b) AcCl, DMAP/Py; (c) MsCl, Et_3N/THF; (d) Tf_2O, 2,6-lutidine/CH_2Cl_2; (e) CO, MeOH, $Pd(OAc)_2$, dppp, Et_3N/DMF; (f) NaOH aq, THF/MeOH, (g) NH_4Cl, WSC·HCl, *i*-Pr_2NEt, HOBt/DMF; (h) $POCl_3$/DMF.



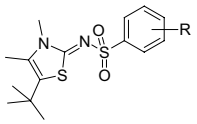
Scheme 4. Reagents and conditions: (a) $Zn(CN)_2$ (0.6 equiv), Zn, $Pd(dba)_2$, dppf/DMA; (b) $Zn(CN)_2$ (1.6 equiv), Zn, $Pd(dba)_2$, dppf/DMA.

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 EC_{50} value of 0.037 μM, and the TI value of **11g** exceeded 680. With the exception of compound **10m**, the 2-cyanophenyl derivatives (**10l**, **10n**, and **18b**), which all have 5-isopropyl-4-methylthiazolidene moieties, exhibited extremely potent anti-HIV-1 activity (EC_{50} = 0.0017–0.0021 μM), with TIs ranging from 6100 to >15,000. Interestingly,

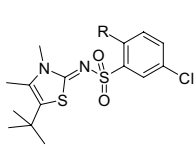
Table 1. In vitro activities of mono-substituted benzenesulfonamide derivatives

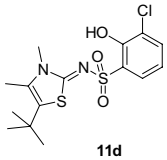


Compounds	R	IC_{50}[a] (μM)			EC_{50}[b] (μM)	CC_{50}[c] (μM)	TI[d]
		WT	K103N	Y181C			
1	3-NO_2	0.27	13	0.066	0.085	>25	>290
10a	2-NO_2	>50	>50	36	>25	>25	—
10b	2-Cl	>10	>10	>10	NT[e]	NT[e]	—
10c	3-Cl	0.30	11	0.044	0.20	>25	>125
10d	4-NO_2	>10	>10	>10	NT[e]	NT[e]	—
10e	4-Cl	>10	>10	>10	NT[e]	NT[e]	—
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	H	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 (CC_{50}/EC_{50}).
[e] NT: not tested.

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





11d

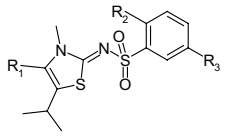
Compounds	R	IC_{50}[a] (μM)			EC_{50}[b] (μM)	CC_{50}[c] (μM)	TI[d]
		WT	K103N	Y181C			
10c	H	0.30	11	0.044	0.20	>25	>125
10i	NO_2	2.4	>50	NT[e]	0.36	22	61
11d		6.3	>50	NT[e]	11	>25	>2
11e	OH	0.032	1.1	0.011	0.026	>25	>960
12	NH_2	0.19	17	0.11	0.025	>25	>1000
13	NHCOMe	>50	>50	>50	2.7	>25	>9
14	$NHSO_2$ 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, **10l** and **18b** (YM-228855), exhibited strong anti-HIV-1 activity, with EC_{50} values of 0.0017 and 0.0018 μM, respectively, both of which were more potent than that of efavirenz (EC_{50} = 0.0027 μM). 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 **10l** 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 IC_{50} values of 0.0043, 0.043, and 0.013 μM, 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] (μM)	CC_{50}[c] (μM)	TI[d]
				WT	K103N	Y181C			
10l	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 (CC_{50}/EC_{50}).

accompanying potent anti-HIV-1 activity (EC_{50}: 0.037 μM). 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 (**10l** and **18b**) showed extremely potent anti-HIV-1 activity, with EC_{50} 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 IC_{50} values of 0.0043, 0.043, and 0.013 μM, respectively. This compound also strongly inhibited HIV-1 replication in cell cultures (EC_{50} = 0.037 μM). 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 (^{1}H NMR) spectra were obtained in $CDCl_3$ 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), SO_2 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. ^{1}H 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; ^{1}H NMR (DMSO-d_6) δ: 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; ^{1}H 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 ice-water. 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 (6o). 54% yield; ^{1}H 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), SO_2 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. ^{1}H NMR (DMSO-d_6) δ: 3.75 (3H, s, CH_3 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. ^{1}H 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; ^{1}H NMR (DMSO-d_6) δ: 1.30 (9H, s, CH_3 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; ^{1}H NMR (DMSO-d_6) δ: 1.29 (9H, s, CH_3 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; ^{1}H NMR (DMSO-d_6) δ: 1.30 (9H, s, CH_3 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*-Butyl-4-methyl-1,3-thiazol-2-yl)-4-chlorobenzenesulfonamide (9f). 78% yield; ^{1}H NMR (DMSO-d_6) δ: 1.29 (9H, s, CH_3 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; ^{1}H NMR (DMSO-d_6) δ: 1.31 (9H, s, CH_3 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; ^{1}H NMR (DMSO-d_6) δ: 1.29 (9H, s, CH_3 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)-5-chloro-2-nitrobenzenesulfonamide (9j). 41% yield; ^{1}H NMR (DMSO-d_6) δ: 1.30 (9H, s, CH_3 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)-5-chloro-2-methoxybenzenesulfonamide (9l). 94% yield; ^{1}H NMR (DMSO-d_6) δ: 1.32 (9H, s, CH_3 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. ^{1}H NMR (DMSO-d_6) δ: 1.14 (6H, d, J = 6.8 Hz, CH_3 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 *m*/*z*: 356 (M^++1).

5.1.20. 5-Fluoro-2-cyano-*N*-(5-isopropyl-4-methyl-1,3-thiazol-2-yl)benzenesulfonamide (9n). 20% yield; ^{1}H NMR (DMSO-d_6) δ: 1.14 (6H, d, J = 6.9 Hz, CH_3 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 (9o). 27% yield from **8b**; ^{1}H NMR (DMSO-d_6) δ: 1.14 (6H, d, J = 6.8 Hz, CH_3 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)-5-chloro-2-methoxybenzenesulfonamide (9p). 22% yield; ^{1}H NMR ($CDCl_3$) δ: 1.25 (6H, d, J = 7.0 Hz, CH_3 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)-5-bromo-2-methoxybenzenesulfonamide (9q). 59% yield;. ^{1}H NMR (DMSO-d_6) δ: 1.20 (6H, d, J = 6.8 Hz, CH_3 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; ^{1}H NMR (DMSO-d_6) δ: 1.15 (6H, d, J = 6.9 Hz, CH_3 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, CH_3 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; ^{1}H NMR (DMSO-d_6) δ: 1.28 (9H, s, CH_3 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).

5.1.26. *N*-(5-*tert*-Butyl-3,4-dimethyl-1,3-thiazol-2(3*H*)-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. ^{1}H NMR ($CDCl_3$) δ: 1.36 (9H, s, CH_3 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).^{1}H NMR ($CDCl_3$) δ: 1.33 (9H, s, CH_3 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 $C_{15}H_{19}ClN_2O_2S_2$: 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(3*H*)-ylidene)-3-chlorobenzenesulfonamide (10c). 90% yield;

mp 138–139 °C (chloroform). ^{1}H NMR (DMSO-d_6) δ: 1.31 (9H, s, CH_3 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 $C_{15}H_{19}ClN_2O_2S_2Cl$: 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). ^{1}H NMR ($CDCl_3$) δ: 1.37 (9H, s, CH_3 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 $C_{15}H_{19}N_3O_4S_2$: 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). ^{1}H NMR ($CDCl_3$) δ: 1.36 (9H, s, CH_3 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 $C_{15}H_{19}ClN_2O_2S_2$: 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). ^{1}H NMR (DMSO-d_6) δ: 1.33 (9H, s, CH_3 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 $C_{16}H_{22}N_2O_3S_2{\cdot}0.1CHCl_3$: 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). ^{1}H NMR (DMSO-d_6) δ 1.31 (9H, s, CH_3 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 $C_{16}H_{22}N_2O_3S_2$: 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). ^{1}H NMR ($CDCl_3$) δ: 1.34 (9H, s, CH_3 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 $C_{16}H_{22}N_2O_3S_2$: 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). ^{1}H NMR (DMSO-d_6) δ: 1.33 (9H, s, CH_3 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 $C_{15}H_{18}ClN_3O_4S_2$: 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**; ^{1}H NMR (DMSO-d_6) δ: 1.22 (9H, s, CH_3 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; ^{1}H NMR (DMSO-d_6) δ: 1.34 (9H, s, CH_3 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. ^{1}H NMR (DMSO-d_6) δ: 1.15 (6H, d, J = 6.9 Hz, CH_3 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 $C_{15}H_{16}ClN_3O_2S_2$: 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). ^{1}H NMR (DMSO-d_6) δ: 1.14 (6H, d, J = 6.8 Hz, CH_3 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 $C_{15}H_{16}FN_3O_2S_2$: 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). ^{1}H NMR (DMSO-d_6) δ: 1.15 (6H, d, J = 6.9 Hz, CH_3 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 $C_{15}H_{16}BrN_3O_2S_2$: 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; ^{1}H NMR (DMSO-d_6) δ: 1.23 (6H, d, J = 6.8 Hz, CH_3 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; ^{1}H NMR ($CDCl_3$) δ: 1.26 (6H, d, J = 6.8 Hz, CH_3 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). ^{1}H NMR (DMSO-d_6) δ: 1.15 (6H, d, J = 6.9 Hz, CH_3 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 $C_{17}H_{19}N_3O_4S_2$: 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).^{1}H NMR (DMSO-d_6) δ: 1.31 (9H, s, CH_3 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 $C_{15}H_{20}N_2O_2S_2$: 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(3*H*)-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. ^{1}H NMR (DMSO-d_6) δ: 1.31 (9H, s, CH_3 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 $C_{15}H_{20}N_2O_3S_2 \cdot 0.2H_2O$: 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). ^{1}H NMR (DMSO-d_6) δ: 1.32 (9H, s, CH_3 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 $C_{15}H_{20}N_2O_3S_2$: 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). ^{1}H NMR (DMSO-d_6) δ: 1.31 (9H, s, CH_3 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 $C_{15}H_{20}N_2O_3S_2$: 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). ^{1}H NMR (DMSO-d_6) δ: 1.32 (9H, s, CH_3 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 $C_{15}H_{19}ClN_2O_3S_2$: 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). ^{1}H NMR (DMSO-d_6) δ: 1.32 (9H, s, CH_3 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 $C_{15}H_{19}ClN_2O_3S_2$: 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). ^{1}H NMR (DMSO-d_6) δ: 1.21 (6H, d, J = 6.8 Hz, CH_3 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 $C_{13}H_{14}Cl_2N_2O_3S_2$: 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). ^{1}H

NMR (DMSO-d_6) δ: 1.21 (6H, d, J = 6.8 Hz, CH_3 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 $C_{13}H_{14}ClBrN_2O_3S_2$: 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(3*H*)-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. ^{1}H NMR (DMSO-d_6) δ: 1.31 (9H, s, CH_3 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 $C_{15}H_{20}ClN_3O_2S_2$: 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(3*H*)-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. ^{1}H NMR (DMSO-d_6) δ: 1.28 (9H, s, CH_3 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 $C_{17}H_{22}ClN_3O_3S_2$: 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. ^{1}H NMR (DMSO-d_6) δ: 1.32 (9H, s, CH_3 of *t*-Bu), 2.29 (3H, s, 4-Me), 3.24 (3H, s, CH_3 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 $C_{16}H_{22}ClN_3O_4S_3$: 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(3*H*)-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. ^{1}H NMR (DMSO-d_6) δ: 1.18 (6H, d, J = 6.8 Hz, CH_3 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 mmol), 1,3-bis(diphenylphosphino)propane (1.74 g, 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 °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 acetate–toluene) and recrystalized from isopropanol–diethyl ether to give **16** (7.32 g, 42%) as a colorless powder. Mp 142–143 °C. ^{1}H NMR (DMSO-d_6) δ: 1.32 (9H, s, CH_3 of *t*-Bu), 2.30 (3H, s, 4-Me), 3.43 (3H, s, 3-Me), 3.78 (3H, s, CH_3 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 $C_{17}H_{21}ClN_2O_4S_2$: 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(3*H*)-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, 0.372 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (WSC·HCl, 71 mg, 0.372 mmol), *N*,*N*-diisopropylethylamine (0.17 mL, 0.992 mmol), and ammonium chloride (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. ^{1}H NMR (DMSO-d_6) δ: 1.31 (9H, s, CH_3 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, NH_2), 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. ^{1}H NMR (DMSO-d_6) δ: 1.15 (6H, d, $J = 6.8$ Hz, CH_3 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, NH_2), 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(3*H*)-ylidene)benzenesulfonamide (18b). Phosphorous oxychloride (0.3 mL, 3.3 mmol) and *N*,*N*-dimethylformamide (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. ^{1}H NMR (DMSO-d_6) δ: 1.15 (6H, d, $J = 6.8$ Hz, CH_3 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 $C_{16}H_{16}N_4O_2S_2$: 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. ^{1}H NMR (DMSO-d_6) δ: 1.32 (9H, s, CH_3 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 $C_{16}H_{18}ClN_3O_2S_2$: 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.

5.1.61. 5-Chloro-*N*-(4-chloro-5-isopropyl-3-methyl-1,3-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). ^{1}H NMR (DMSO-d_6) δ: 1.20 (6H, d, $J = 6.8$ Hz, CH_3 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 $C_{14}H_{13}Cl_2N_3O_2S_2$: 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(3*H*)-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). ^{1}H NMR ($CDCl_3$): 1.27 (6H, d, $J = 6.8$ Hz, CH_3 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 $C_{15}H_{13}ClN_4O_2S_2$: 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 Quikchange™ 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 $MgCl_2$, 0.1% Triton X-100, 2 mM dithiothreitol, 0.01 OD_{260} of poly(rC)/oligo$(dG)_{12–18}$, and 1 μCi of [1′,2′-^{3}H]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 cells[14] 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 flat-bottomed 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-$1_{IIIB\text{-}R}$.[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 EC_{50}.

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